NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Daiichi Sankyo
   a. Addendum

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Now.

4. **Evidence Review Group report** prepared by Liverpool review and implementation group (LriG)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Daiichi Sankyo**

7. **Technical engagement responses and statements**
   a. Prof. Peter Schmid, Centre of Experimental Cancer Medicines – clinical expert, nominated by Daiichi Sankyo UK
   b. Holly Heath – patient expert, nominated by Breast Cancer Now *(see item 3a)*
   c. Claire Myerson – patient expert, nominated by Breast Cancer Now

8. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool review and implementation group (LriG)

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 2 or more anti-HER2 therapies [ID2697]

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Abbreviations

Abbreviation	Definition
AC	Adjudication committee
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
BC	Breast cancer
BI	Budget impact
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BSA	Body surface area
CAP	College of American Pathologists
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CG	Clinical guideline
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CM	Low-dose oral cyclophosphamide and methotrexate
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug antibody ratio
DCR	Disease control rate
DoR	Duration of response
DSU	Decision Support Unit
EAS	Enrolled analysis set

Abbreviation	Definition
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen receptor
EPAR	European public assessment report
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
HER2+	Human epidermal growth factor 2 overexpression (positive)
HER2–	Human epidermal growth factor 2 negative
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICR	Independent central review
IHC	Immunohistochemistry
ILD	Interstitial lung disease
ISH	In situ hybridisation
ITT	Intent to treat
IV	Intravenous
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LYG	Life years gained
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
mBC	Metastatic breast cancer
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MRU	Medical resource use
NA	Non-applicable
NCI	National Cancer Institute
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival

Abbreviation	Definition
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PgR	Progesterone receptor
PS	Performance status
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QoL	Quality of life
OR	Odds ratio
QT	QT interval
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended part 2 dose
RR	Relative risk
SACT	Systemic Anti-Cancer Therapy Dataset
SAE	Serious adverse event
SD	Standard deviation
SLR	Systemic literature review
SE	Standard error
SmPC	Summary of product characteristics
SoC	Standard-of-care
TA	Technology appraisal
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse events
TPC	Treatment of physician’s choice
TSD	Technical support document
TTD	Time-to-discontinuation
TTR	Time to response
uBC	Unresectable breast cancer

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.

The submission covers the technology's full anticipated marketing authorisation for trastuzumab deruxtecan (T-DXd) as a treatment for [redacted].

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 two or more prior anti-HER2 therapies.	People with HER2-positive, unresectable or metastatic breast cancer who have received two or more prior anti-HER2 therapies. • This is in line with the anticipated indication.	NA
Intervention	Trastuzumab deruxtecan	Trastuzumab deruxtecan (T-DXd)	NA
Comparator(s)	• Capecitabine • Vinorelbine Eribulin (for people who have had 2 or more chemotherapy regimens)	• Capecitabine • Vinorelbine • Eribulin (or people who have had 2 or more chemotherapy regimens)	NA
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • HRQoL.	The outcome measures from DESTINY-Breast01 (the pivotal clinical trial) that are presented and included in the economic model are: • Progression-free survival • Overall survival • Objective response rate according to ICR (primary endpoint) (to inform progression-free, on treatment utility values) • Adverse effects of treatment. In addition, data from the following key secondary endpoints from the DESTINY-Breast01 trial are also presented: **Key secondary endpoints:** • ORR as confirmed by the Investigator • Disease control rate and clinical benefit rate as confirmed by ICR	NA

		• Duration of response as confirmed by ICR • Best percent change in the sum of the diameter of measurable tumours • Time to response HRQoL data was not collected in DESTINY-Breast01; however, alternative sources of HRQoL data have been used to inform the economic model.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost-utility analysis will be performed, with the key outcome being the incremental cost per QALY gained. 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: HER2, human epidermal growth factor 2; HRQoL, health-related quality of life; ICR, independent central review; mBC, metastatic breast cancer; NA, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; ORR, objective response rate; 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 draft summary of product characteristics (SmPC) is provided in Appendix C. The draft European public assessment report (EPAR) will be provided to NICE once available.

Table 2: Technology being appraised

UK approved name and brand name	Trastuzumab deruxtecan (T-DXd; ENHERTU®).
Mechanism of action	T-DXd is a HER2-directed ADC. It is composed of three components 1) a humanised anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Following binding to HER2 on tumour cells, T-DXd undergoes internalisation and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. ADCs combine the advantage of antibodies in binding to a specific target expressed on cancer cells with cytotoxic capability of a chemotherapeutic drug that is released at the tumour site, thereby improving the efficacy of the chemotherapy while also reducing systemic exposure and toxicity
Marketing authorisation/CE mark status	• T-DXd is being assessed under the EU centralised procedure, [redacted] • The EMA dossier was submitted on [redacted] • CHMP opinion is anticipated on [redacted] • The EC decision is expected by [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]. It is anticipated that the licence wording will be in the public domain by [redacted]. **Restrictions** [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 beyond those routinely conducted in NHS clinical practice.
List price and average cost of a course of treatment	List price: [redacted] per 100 mg vial • Cost per cycle: [redacted] † • Cost per course: [redacted] ‡

Patient access scheme (if applicable)	A simple patient access scheme (PAS) in the form of a fixed price has been proposed for all licensed indications of T-DXd in the United Kingdom. Price with simple PAS: [redacted] per 100 mg vial • Cost per cycle: [redacted]† • Cost per course: [redacted]‡

Abbreviations: ADC, antibody drug conjugate; CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; EMA, European Medicines Agency; EU, European Union; HER2, human epidermal growth factor 2; mAb, monoclonal antibody; NHS, National Health Service; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan.

†Cost per cycle is calculated using the method of moments assuming a normal distribution around mean weight from DESTINY-Breast01, assuming no vial sharing.

‡ Cost per course assuming time to discontinuation as in the cost-effectiveness model; see Section B.3.3.3

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

B.1.3.1 Disease overview

Breast cancer (BC) is the most common cancer in the UK, accounting for 15% of all new cancer cases, and the 4th most common cause of cancer death.[1,2] In the UK, 99% of BC cases are in females, and 1% are in males.[2] The vast majority of cases are diagnosed in the early stages, however a small proportion of cases are diagnosed in the advanced stages, when the tumour has spread significantly within the breast (locally advanced), or to other organs of the body (metastatic breast cancer [mBC]).[3] In addition, a proportion of patients initially diagnosed with early stage BC will subsequently develop either a local recurrence or metastases.[4,5]

For the purpose of prognostication and treatment decision-making, BC is classified according to its type, grade, stage, and the presence of biological markers including oestrogen receptors (ER) and/or progesterone receptors (PgR) (ER-positive and PgR-positive) and human epidermal growth factor receptor 2 (HER2) overexpression (HER2-positive [HER2+]).[6-9]

BC is staged from stage 0 to stage IV using the American Joint Committee on Cancer (AJCC) tumour (T), node (N), metastasis (M) staging system.[10] Unresectable BC (uBC) (inoperable) and mBC are the most advanced forms of BC. Although treatable, u/mBC is generally considered an incurable disease.[11] Symptoms can be severe and debilitating including cancer-related fatigue, along with other complications relating to the organ(s) to which the cancer has spread, most commonly the liver, lungs, lymph nodes, brain and/or bones (Table 3), of which pain is a particularly common and distressing symptom.[12-14]

Table 3: Associated symptoms of metastatic breast cancer

Metastatic site	Associated symptoms
General	Fatigue, difficulty sleeping, depression
Bone	Pain, hypercalcemia, pathologic fracture, loss of mobility
Brain	Headache, confusion, weakness, pain, seizure, altered mentation, cranial nerve palsies, speech impairment
Lymph nodes	Brachial plexopathies, pain
Liver	Discomfort or pain, nausea, swollen abdomen, loss of appetite, jaundice
Lungs	Pain, dyspnea, hemoptysis, cough

Source: Irvin 2011[13]; Cancer Research UK 2017[12]

HER2 is a member of the HER superfamily that initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways.[15,16] Approximately 13–20% of BC tumours are HER2+.[17]

NICE and the UK National Coordinating Committee for Breast Pathology recommend that HER2 status should be routinely assessed in all invasive primary breast carcinomas and in recurrent and metastatic tumours whenever biopsy tissue is available, in order to decide how best to treat and manage the cancer.[17,18] Testing involves immunohistochemistry (IHC) with >10% complete strong membrane staining defining a positive status. In situ hybridisation (ISH) is used either upfront or in IHC borderline cases to detect the presence of *HER2* gene amplification.[17] For IHC scoring, samples scoring 3+ are regarded as unequivocally positive, and those scoring 0/1+ as negative. Borderline scores (2+) are regarded as equivocal and mandate further assessment using ISH.[17]

While one of the main risk factors for BC is older age, patients with HER2+ disease tend to be younger than those with HER2-negative (HER2–) disease.[19] In addition, before the advent of HER2-targeted therapy, HER2+ BCs have historically been associated with more aggressive disease and worse outcomes compared with HER2– BCs.[20,21] However, since 2010, the introduction and expanded use of HER2-targeted treatments (specifically trastuzumab- and pertuzumab-based regimens), along with other advances in care, have provided substantial survival gains for patients with HER2+ mBC.[22] Despite this breakthrough however, nearly all patients eventually progress on currently available anti-HER2 therapies due to de novo or acquired resistance.[23] There is currently no approved HER2-targeted therapy in patients with HER2+ u/mBC who have received two or more prior anti-HER2 therapies,[23] and the prognosis in these patients is extremely poor, with a life expectancy of less than 2 years (Section B.1.3.5. and Section B.2.13.3).

B.1.3.2 Burden on patients, carers and society

Patients with u/mBC face a wide range of medical, practical, and emotional challenges that impact their quality of life (QoL).[24,25] As such, they are also at risk for emotional distress, including symptoms of depression and anxiety as well as existential distress and loneliness.[13,24,25]

The QoL of patients with mBC is particularly poor due to the incurable nature of the disease and burdensome symptom profile.[26,27] In patients with mBC, QoL is lower than those with early BC and the general population,[28,29] and is often adversely affected by a wide range of physical symptoms, including fatigue, insomnia, lack of concentration, neuropathy, and

pain.[25] In a study of 185 HER2+ mBC patients, the symptoms most frequently reported as being experienced “quite a bit” or “very much” on the Rotterdam Symptom Checklist were: tiredness (~52%), decreased sexual interest (~52%), lack of energy (~45%), sore muscles (~36%), worrying (~36%), difficulty sleeping (~33%), and joint pain (~33%).[30] In addition, brain metastases are more common in HER2+ BC than in some of the other subtypes, with up to 50% of women with HER2+ disease developing brain metastases;[31] this further reduces QoL[32] and causes debilitating symptoms such as seizures, stroke and personality changes.[33]

While increasing survival and progression-free survival (PFS) are priorities for patients with mBC and their carers,[26,34] maintaining a good QoL with well-tolerated treatments is also an important treatment goal.[11,25] Disease progression in patients with mBC has a significant negative impact on QoL, emphasising the relevance of delaying progression in order to maintain QoL.[34-36]

There is also a large carer burden associated with mBC; caregivers themselves have persistent unmet needs, based on their reduced physical and psychological well-being, with negative effects on sleep habits, relationships and social life, hobbies and personal time, and financial stability.[37]

mBC is also associated with a substantial economic burden to society and healthcare systems, as well as to individual patients and their families.[38,39] [25,37,40] In England, it was estimated that BC costed £504 million to the health system in 2010 due to hospital care, with a higher clinical stage associated with higher costs.[38] The mean 15-month cumulative health-care costs for BC cases in England were estimated to be £12,595 per-patient, with clinical stage being the most important predictor of costs.[39]

B.1.3.3 Epidemiology

Around 46,109 people were newly diagnosed with BC in England in 2017.[1] According to the National Cancer Registration and Analysis Service there were approximately 2,309 cases of BC in stage IV in the UK in 2016, and 3,881 in stage III.[41] Further to this, it is estimated that approximately 13–20% people with BC will have HER2+ tumours.[17] The indication for T-Dxd is anticipated to predominantly cover patients with stage IV HER2+ BC; some patients with stage III HER2+ BC may have locally advanced BC that is unresectable, although they may receive neoadjuvant treatment to make the tumour operable.

According to the eribulin NICE appraisal, which is the only previous NICE appraisal in third-line u/mBC (TA423)[42,43], the prevalence of mBC is 7.39% (from the Cancer Mpact database, Kantar Health) (3,407 patients), with 34.41% of mBC patients receiving third-line therapy (from: Cancer Mpact database, Kantar Health) (1,173 patients). According to the updated UK recommendations for HER2 assessment in BC, data indicate that the frequency of HER2 positivity is between 13% and 20%;[17] therefore, using a conservative value of 20% of the patients having HER2+ disease, an estimated 235 patients would potentially be eligible for treatment with T-DXd (see the Budget Impact Model for more details).

B.1.3.4 Trastuzumab deruxtecan

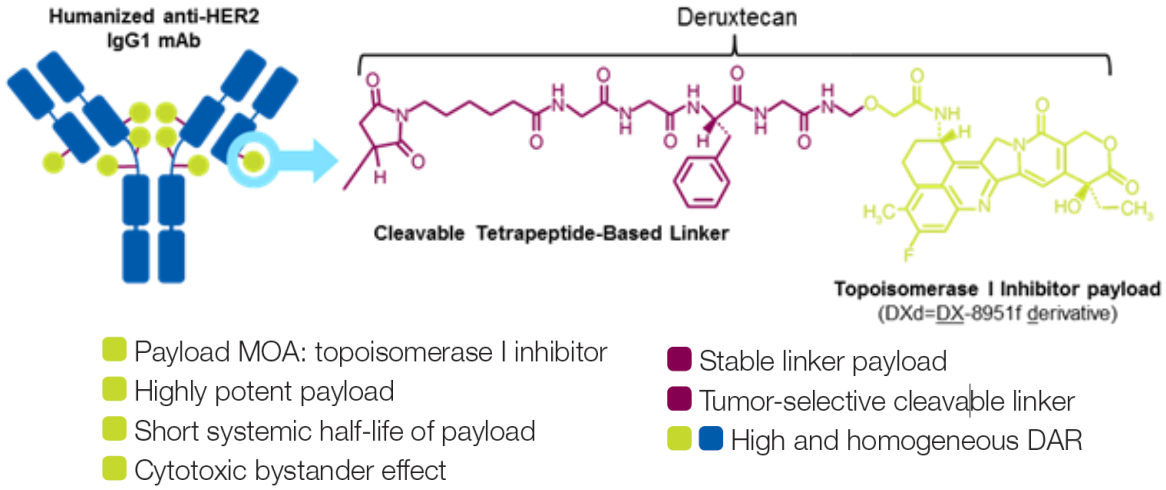
Mechanism of action of T-DXd

Antibody-drug conjugates (ADCs) are molecules consisting of a recombinant monoclonal antibody (mAb) covalently bound to a cytotoxic drug (called drug payload or warheads) via a synthetic linker.[44,45] ADCs combine the advantage of antibodies in binding to a specific target expressed on cancer cells with cytotoxic capability of a chemotherapeutic drug that is released at the tumour site, thereby improving the efficacy of the chemotherapy while also reducing systemic exposure and toxicity. A stable linker between the antibody and the cytotoxic drug is crucial for the ADC integrity in circulation. After antibody binding to the specific antigen on the (cancer) cell surface, the ADC is internalised and the cytotoxic drug released intracellularly where it can exert its effect. ADCs can also be designed to promote drug release from the target cell to the extracellular space. Thereby, neighbouring tumour cells, which may or may not express the ADC target antigen, can be affected by taking up the cytotoxic drug. This is independent of the targeting effect of the antibody and so does not require all of the cancer cells to express the relevant antigen.

T-DXd is a HER2-targeted ADC designed to deliver optimal antitumour effect. T-DXd is composed of a humanised mAb specifically targeting HER2, with the same amino acid sequence as trastuzumab, covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker. Specifically, deruxtecan is composed of the linker and the topoisomerase I inhibitor payload (an exatecan derivative [DXd]).

T-DXd was rationally designed with seven key attributes to overcome the efficacy and toxicity limitations of earlier ADCs[46-49]. Figure 1 presents the structure of T-DXd, highlighting the specific parts of the drug responsible for each of the seven key attributes.

Figure 1: Structure of T-DXd



Abbreviations: DAR, drug-antibody ratio; HER2, human epidermal growth factor receptor 2; mAB, monoclonal antibody; MOA, mechanism of action.
Source: Adapted from Nakada 2019[46]

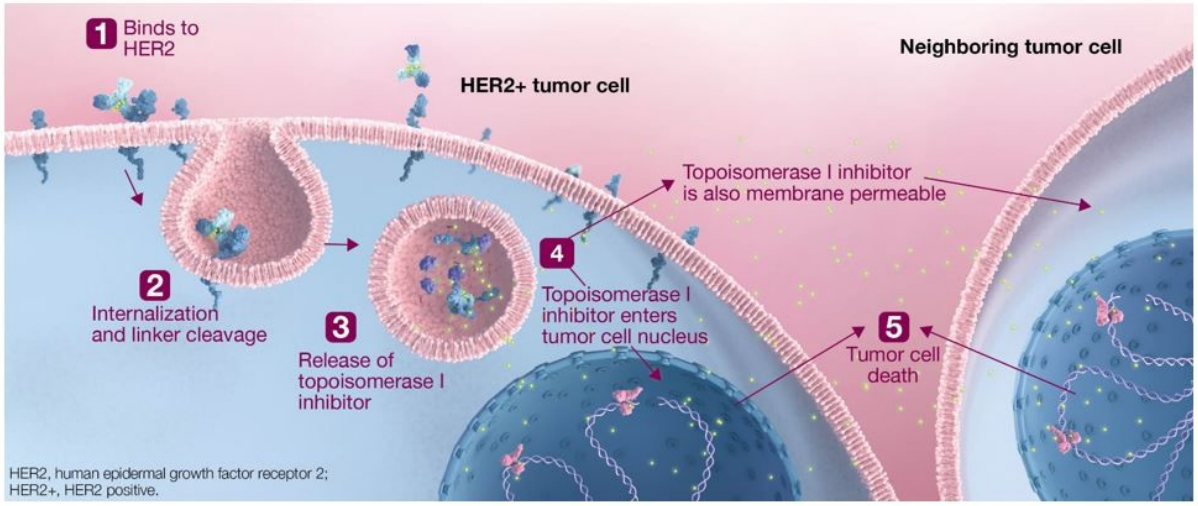
The seven key attributes include:

- Payload mechanism of action (MOA): DXd is a novel analogue of the active metabolite irinotecan, a topoisomerase I inhibitor, that was developed for conjugation with trastuzumab and has a distinct proposed MOA from currently used payloads[46]
- High potency of payload: 10-fold higher potency than the active metabolite (SN-38) of irinotecan[46,48]
- High homogeneous drug-antibody ratio (DAR): The GGFG tetrapeptide–based linker of T-DXd allows for a high DAR of ≈8, with reduced hydrophobicity[46,48]
  - High DAR facilitates delivery of more payload molecules to target cells compared with currently approved ADCs[46,48]
  - The homogeneous[a] DAR results in improved pharmacokinetic (PK) attributes and lower toxicity[48]
- Payload with short systemic half-life: Payload is expected to have a short half-life based on in vivo studies[46,48,50]
  - $t_{1/2}$ of ≈ 1.37 hours in systemic circulation[51]
- Stable linker payload: The GGFG tetrapeptide–based linker reduces the hydrophobicity of T-DXd, resulting in an ADC that is highly stable in plasma with low levels of clearance[50]
- Tumour-selective cleavable linker: The GGFG tetrapeptide–based linker is an enzymatically cleavable peptide and is cleaved by lysosomal proteases once in tumour cells, thus, ensuring stability in systemic circulation and limiting systemic toxicity[46,48]

- Membrane permeable payload: preclinical research demonstrates that DXd has a high-cell membrane permeability that enables elimination of both target tumour cells and the neighbouring tumour cells[46,48]
  - Cytotoxic effect of topoisomerase I inhibitor was detected in the tumour microenvironment only.[48]

Figure 2 presents an overview of the MOA of T-DXd.

Figure 2: Mechanism of action of T-DXd



Abbreviations: HER2, human epidermal growth factor receptor 2.

The proposed 5-step MOA of T-DXd allows for efficient delivery and release of the topoisomerase I inhibitor at the tumour site:

- Step 1**:** the monoclonal antibody component selectively binds to HER2 expressed on the tumour cell surface[48]
- Step 2: T-DXd is internalised by the cell and intracellular lysosomal enzymes upregulated in tumour cells cleave the tetrapeptide-based linker[48]
- Step 3: the topoisomerase I inhibitor payload is released into the cytoplasm of the cell[48]
- Step 4: the released payload enters the tumour cell nucleus and causes damage to the tumour cell's DNA.[48] Because the payload is membrane permeable, it penetrates neighboring tumour cells, enabling the destruction of tumour cells adjacent to those targeted, regardless of HER2 status[52]
- Step 5: the DNA damage caused by payload release results in tumour cell death.[46,48,52]

B.1.3.5 Current treatment pathway and the position of T-DXd

Current pathway of care

NICE has issued a clinical pathway for the management of HER2+ advanced BC, which encompasses relevant technology appraisals.[53] Recommendations for the management and treatment of advanced BC are also provided by the NICE clinical guideline for advanced BC (CG81).[54] The 4th European School of Oncology (ESO) – European Society of Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer also provide clinical guidelines relevant to this submission.[11] A summary of clinical guidelines relevant to this submission is presented in Appendix L.

First and second-line treatment for HER2+ advanced BC

As per the NICE pathway, pertuzumab in combination with trastuzumab and docetaxel is recommended for treating HER2+ metastatic or locally recurrent unresectable BC, in adults who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease.[53,55] Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel) is also recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have not received chemotherapy for mBC and in whom anthracycline treatment is inappropriate.[53,56] For second-line treatment, trastuzumab emtansine (T-DM1) is recommended as an option for treating HER2+ uBC, locally advanced BC or mBC in adults who previously received trastuzumab and a taxane, separately or in combination; patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.[53,57]

The ESO/ESMO guideline for advanced BC states that for HER2+ disease the standard first-line therapy for patients previously untreated with anti-HER2 therapy is the combination of chemotherapy + trastuzumab and pertuzumab, because it has proven to be superior to chemotherapy + trastuzumab in terms of overall survival (OS) in this population.[11] After first-line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER2-based therapies in the second line (versus lapatinib + capecitabine) ‘and beyond’ (versus treatment of physician’s choice).

Third-line treatment for HER2+ advanced BC

Eribulin is the only treatment recommended at this point in the NICE pathway as an option for treating locally advanced BC or mBC in adults only when it has progressed after at least two chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).[42,53] In addition, NICE clinical guideline (CG81) recommends that patients may receive treatment with non-targeted chemotherapies such as capecitabine or vinorelbine for

the treatment of advanced BC in general.[54] Recommendations for use of eribulin, capecitabine and vinorelbine are not specific to HER2+ patients. Of note, there is a paucity of evidence specific to HER2+ u/mBC for these third-line agents (see the clinical SLR in Appendix D, and Section B.2.9)

The ESO/ESMO guideline offers no specific recommendations for standard-of-care for third-line treatment.[11] It states that in case of progression on trastuzumab-based therapy, the combination of trastuzumab + lapatinib is a reasonable treatment option for some patients, however, there are no data on the use of this combination after progression on pertuzumab or T-DM1. In addition, for later lines of therapy, trastuzumab can be administered with several chemotherapy agents, including but not limited to, vinorelbine (if not given in first line), taxanes (if not given in first line), capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine or metronomic CM (cyclophosphamide [C] and methotrexate [M]). The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability. With respect to country availability, some of the ESO/ESMO options are not available on the NHS in England, including trastuzumab + lapatinib and lapatinib + capecitabine, which are not reimbursed in the third-line u/mBC setting.[53,58]

To understand the current management of HER2+ u/mBC in clinical practice in England, an advisory board was conducted in August 2020, involving 4 UK clinical experts in BC and 4 health economics experts.[59] Clinicians agreed that capecitabine was the most frequently used third-line intervention, followed very closely by vinorelbine, with a much smaller proportion of patients treated with eribulin (~10%). In addition, the clinical experts agreed that patients receiving T-DXd are expected to have received at least two or more prior chemotherapy regimens, and so eribulin is a relevant comparator for the full considered population[1].

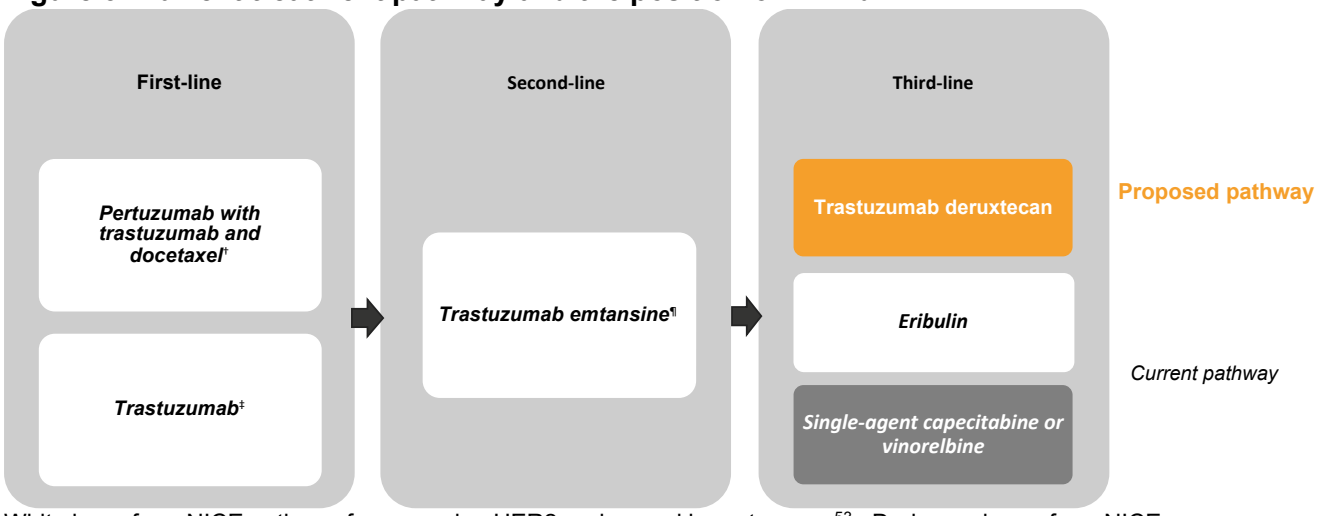
Proposed position of T-DXd

The current treatment pathway and the proposed position of T-DXd is shown in Figure 3. T-DXd is anticipated to be indicated for patients who have received two or more anti-HER2 therapies (i.e. in the third-line setting). Based on the recommended clinical pathway

[1] In the final scope issued by NICE, eribulin was listed as a comparator in patients who have received two or more prior chemotherapy regimens.

described above and in Figure 3, it is anticipated that this would be the majority of HER2+ u/mBC patients at third-line.

Figure 3: Current treatment pathway and the position of T-DXd



White box= from NICE pathway for managing HER2+ advanced breast cancer[53]; Dark grey box = from NICE clinical guideline (CG81): Advanced breast cancer[54]
† NICE [TA509]: Pertuzumab, in combination with trastuzumab and docetaxel is recommended for treating HER2-positive metastatic or locally recurrent unresectable breast cancer, in adults who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease[55]; ‡ NICE [TA34]: Trastuzumab in combination with paclitaxel is recommended as an option for people with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate[56]; ¶ NICE [TA458]: Trastuzumab emtansine is recommended as an option for treating human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination[57]; § NICE [TA423]: Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).[42]

Unmet need

There are no treatments available on the NHS in England that have a modern evidence base in HER2+ patients with u/mBC who have progressed on two or more prior HER2 targeted therapies, and capecitabine, vinorelbine and eribulin remain the only options. While eribulin is the only treatment recommended at this point in the NICE pathway, there is a lack robust efficacy data in HER2+ patients with u/mBC in the third-line setting, and indeed feedback from clinicians suggests that only 10% of these patients receive eribulin, also suggesting a lack of efficacy.[59] Overall, currently available treatments offer BC patients in the third-line metastatic setting limited overall survival (OS) (less than 2 years) and PFS benefit (median PFS of ~3-6 months)[42,60], with patients ultimately progressing and dying of the disease. Patients with HER2+ u/mBC who have progressed on two or more prior HER2 targeted therapies are particularly difficult to treat; as well as having a high symptom burden, they have built up treatment resistance through multiple previous lines of therapy. Overall, there

is a substantial unmet need for a therapy with demonstrated efficacy and tolerability in these patients, with novel mechanisms that can help overcome the treatment resistance.

B.1.4 Equality considerations

No equity or equality issues are anticipated for the appraisal of T-DXd. However, feedback from an advisory board meeting has suggested that some patients with HER2+ u/mBC who have progressed on two or more prior HER2 targeted therapies are able to access treatments through clinical trials or expanded access programmes in some regions in England, but not others.[61] This suggests that the current lack of a standard of care for this patient population may lead to variability in patient outcomes due to a lack of equity in access to treatment.

B.2 Clinical effectiveness

Summary of clinical systematic literature review (SLR)

- An SLR was conducted to identify relevant clinical evidence describing the efficacy and safety of T-DXd and all currently available (as per NICE scope for T-DXd) and investigational therapies used to treat patients with advanced BC or mBC presenting with either HER2+ status, mixed HER2 status, or an unknown HER2 status, who have received two or more prior therapies in a uBC/mBC setting.
- The patient population in the SLR was broad as there are few published data available for currently available treatments solely in HER2+ patients; using these broad criteria 185 relevant publications across 108 studies were identified.
- The SLR identified two key trials for T-DXd in patients with HER2+ uBC or mBC who have received two or more prior anti-HER2 therapies: the pivotal Phase II DESTINY-Breast01 trial (key evidence) and the Phase I DS8201-A-J101 trial (supportive evidence).

Summary of clinical effectiveness of T-DXd

DESTINY-Breast01 (NCT03248492)

DESTINY-Breast01 is a two-part, open-label, single-group, multicentre, Phase II study, evaluating T-DXd in adults with pathologically documented HER2+ uBC or mBC who had received previous treatment with T-DM1. The efficacy and safety of T-DXd were evaluated at the recommended dose of 5.4mg/kg (N=184).

At a data-cut of 1 August 2019 (median duration of follow-up 11.1 months [range, 0.7 to 19.9]) T-DXd demonstrated a consistent high level of clinical activity across a range of endpoints:

- Median PFS was 16.4 months (95% CI: 12.7, not evaluable [NE])
- Median OS had not been reached
  - Estimated OS was 93.9% (95% CI: 89.3, 96.6) at 6 months and 86.2% (95% CI: 79.8, 90.7) at 12 months
- Response to therapy was reported in 112 patients (60.9%; 95% confidence interval [CI]: 53.4, 68.0) based on independent central review (ICR)
- Complete response (CR) was reported in 11 (6%) patients and partial response [PR] in 101 (54.9%) patients
- Most patients had a reduction in tumour size while on treatment
- Prespecified subgroup analyses showed consistent responses across demographic and prognostic subgroups including patients who had received previous pertuzumab

therapy, hormone receptor status, receipt of T-DXd immediately after initial T-DM1 therapy, number of prior regimens, and those who had CNS metastases at baseline

  - Patients achieved a confirmed objective response rate (ORR) >50% regardless of the number of prior lines of systemic therapy they received; however, the highest ORR was observed in those who had received only two prior lines
- Durable activity was demonstrated with a median duration of response (DoR) of 14.8 months (95% CI: 13.8, 16.9)
- Disease control rate (DCR) was 97.3% (95% CI: 93.8, 99.1)
- Clinical benefit rate (CBR) was 76.1% (95% CI: 69.3, 82.1)
- Median time to response (TTR) was 1.6 months (95% CI: 1.4, 2.6)
- T-DXd demonstrated efficacy in patients who had a history of CNS metastases at baseline (n=24) that was similar to the overall population: ORR: 58.3% (95% CI: 36.6, 77.9); median PFS: 18.1 months (95% CI: 6.7, 18.1).

Study DS8201-A-J101 (NCT02564900)

Study DS8201-A-J101 is a two-part (dose-escalation and dose-expansion), first-in-human, non-randomised, open-label, Phase I study. The safety, tolerability, and activity of T-DXd at the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg every 3 weeks) were assessed in cohorts of different solid tumours including a large of cohort of HER2+ uBC or mBC after T-DM1 (N=115).

Of the 115 patients, 111 (97%) were evaluable for confirmed response.

At a median follow-up of 9.9 months:

- ORR was 59.5% (95% CI: 49.7, 68.7)
- Median PFS was 22.1 months (95% CI: NE)
- Median OS had not been reached
- DCR was 93.7% (95% CI: 87.4, 97.4)
- Median DoR was 20.7 months (95% CI: NE)
- Median TTR was 1.6 months (95% CI: 1.4, 2.8).

Summary of matching-adjusted indirect comparisons (MAICs)

- DESTINY-Breast01 is a single group trial; a series of unanchored MAICs were therefore performed to assess the comparative effectiveness of T-DXd vs the comparators listed in the NICE final scope (eribulin, capecitabine and vinorelbine)
- MAICS were conducted for four studies identified for eribulin, two identified for capecitabine and one for vinorelbine; outcomes considered were OS, PFS and response

- All results show T-DXd to be associated with significant improvement in OS, PFS and response.

Comparator	Study	Hazard ratio for T-DXd vs. comparator		Odds ratio for T-DXd vs. comparator		
		OS	PFS	ORR	DCR	CBR
Eribulin	Barni 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cortes 2010	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cortes 2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamucci 204	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	Fumoleau 2004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Blum 2001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	Sim 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Summary of safety of T-DXd

DESTINY-Breast01 (NCT03248492)

- The most common treatment-emergent adverse events (TEAEs) were gastrointestinal and haematologic in nature
- 22.8% had serious TEAEs; 35.3% and 23.4% had a dose interruption or dose reduction, respectively, and 15.2% discontinued treatment due to TEAEs
- No events of cardiac failure with left ventricular ejection fraction (LVEF) decline were reported
  - No patients had an LVEF of <40% or a decrease of ≥20% at any timepoint
- Interstitial lung disease (ILD) was observed in a subgroup of patients and requires attention to pulmonary symptoms and careful monitoring
  - ILD events were independently adjudicated and actively managed by patient monitoring, dose modification, and adherence to the ILD management guidelines
  - ILD related to T-DXd was observed in 25 patients (13.6%), primarily grade 1 or 2 (10.9%). Four deaths (2.2%) were attributed to ILD
- There were 9 (4.9%) TEAE-associated deaths (respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock haemorrhagic; 1 patient had two TEAEs associated with death: acute kidney injury and acute hepatic failure).

Study DS8201-A-J101 (NCT02564900)

The safety profile of DESTINY-Breast01 was consistent with the results from the Phase I DS8201-A-J101 study:

- The most common TEAEs were gastrointestinal and haematologic in nature
- All patients experienced ≥1 TEAE of any grade, 19% experienced ≥1 serious TEAE, and 50% had a TEAE of ≥ Grade 3
- No events of cardiac failure with LVEF decline were reported
- Drug-related TEAEs leading to discontinuation occurred in 11% of patients, which included nine cases of ILD/pneumonitis.

Summary of innovation

T-DXd is a novel therapy that represents a step-change in the treatment of HER2+ mBC:

- For HER2+ u/mBC patients who have progressed on or after two anti-HER2 therapies, currently available therapies offer little benefit, with patients ultimately progressing and dying of the disease.
- These patients, who have built up treatment resistance through multiple previous lines of therapy, are particularly difficult to treat, requiring novel therapeutic strategies .
- T-DXd is a newer ADC designed to deliver optimal antitumour effects
  - It has distinct pharmaceutical properties which may contribute to it retaining efficacy in heavily pre-treated patients, such as the potent topoisomerase I inhibitor payload instead of a microtubule inhibitor, an increased DAR ratio (approximately 8 with T-DXd vs. approximately 3.5 with T-DM1), and the high membrane permeability of the released payload that enables elimination of both target tumour cells and the neighbouring tumour cells.
- Overall, T-DXd, with its novel features designed to overcome resistance mechanisms, represents a step-change in the treatment of HER2+ mBC.
- The innovative nature of T-DXd in an area of high unmet need has been recognised at the regulatory level by [redacted]
  - T-DXd has been approved in the US and in Japan, where it was assessed under the US Food and Drug Administration's (FDA's) Breakthrough Therapy and Priority Review programme and Japan's conditional early approval system.

End-of-life

NICE end-of-life status applies for the current appraisal as:

- T-DXd is indicated for patients with a short life expectancy and high unmet need, with evidence demonstrating that the life expectancy in patients with HER2+ mBC is normally less than 24 months; and

- T-DXd has the prospect of offering an extension to life of more than 3 months versus current treatment in the NHS.

Conclusion

- T-DXd is a novel, innovative, targeted monotherapy with a high level of clinical activity and a manageable safety profile, that is expected to result in significant and substantial improvements in health-related benefits for patients.
- Daiichi Sankyo considers T-DXd for the treatment of adult patients with HER2+ u/mBC who have received two or more prior anti-HER2 therapies to be a candidate for the Cancer Drugs Fund (CDF).
- It is anticipated that the CDF would provide the opportunity to address the clinical uncertainty, with additional evidence from the Phase III active-controlled randomised controlled trial (RCT), while providing timely, managed patient access to an innovative and efficacious treatment in this disease area of high unmet need.

B.2.1 Identification and selection of relevant studies

See Appendix D1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised. A systematic literature review (SLR) was conducted to identify the existing clinical evidence detailing the efficacy, safety, and QoL for currently available and investigational therapies used to treat patients with advanced or mBC presenting with either HER2+ status, mixed HER2 status, or an unknown HER2 status, who have received two or more prior therapies in a u/mBC setting. Please note that the population is broader than the population in the NICE decision problem with regard to HER2+ status; this is because the relevant comparator treatments were not developed specifically for HER2+ BC, and as such there was concern that evidence from these comparators would not be captured if the population was restricted to HER2+ patients. The SLR was conducted in April 2019 (referred to as the original SLR), that was subsequently updated in Jan 2020 (referred to as the first SLR update) and June 2020 (referred to as the second SLR update).

In total, the SLR identified 375 publications; as some studies were associated with multiple publications, secondary publications were combined; this resulted in 174 unique studies identified from the 375 publications. Of these, 190 publications from 66 studies were not relevant for this submission because they did not investigate comparators of interest. Therefore, there were a total of 185 relevant publications across 108 studies.

There were 3 studies from 16 publications that were identified for T-DXd: DESTINY-Breast01, study DS8201-A-J101 and a Phase I study to evaluate the effect of T-DXd on the QT/QTc Interval in HER2-expressing breast cancer (NCT03366428); the latter is not presented in this submission. For the relevant comparators there were 57 studies (109 publications) evaluating eribulin, 23 studies (28 publications) evaluating capecitabine and 25 studies (32 publications) evaluating vinorelbine.

B.2.2 List of relevant clinical effectiveness evidence

The SLR for clinical evidence identified two studies evaluating the efficacy and safety of T-DXd in patients with HER2+, uBC or mBC who had received previous treatment with T-DM1. This submission focuses primarily on the key evidence from the Phase II study, DESTINY-Breast01. A Phase I study (DS8201-A-J101) is provided as supporting evidence. The results of DS8201-A-J101 support the results of DESTINY-Breast01, however, it is not included in the economic model due to the availability of data from the Phase II study. Both studies are summarised in Table 4.

Table 4: Clinical effectiveness evidence

Study	**DESTINY-Breast01 (NCT03248492)**					**Study DS8201-A-J101 (NCT02564900)**				
Study design	Phase II, two-part, multicentre, open-label, single-group study					Phase I, open-label, dose-escalation and dose-expansion study				
Population	Adults with HER2+ uBC or mBC who had received previous treatment with trastuzumab emtansine					Adults with HER2+, uBC or mBC who had received previous treatment with trastuzumab emtansine				
Intervention(s)	T-DXd was evaluated at a dose of 5.4 mg/kg (N=184)					T-DXd was evaluated at a dose of 5.4 mg/kg (N=49) or 6.4 mg/kg (N=66) (Overall N=115)				
Comparator(s)	No comparator					No comparator				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X	Yes	X	Indicate if trial used in the economic model	Yes	
	No			No		No			No	X
Rationale for use/non-use in the model	Pivotal study supporting this indication					Phase I study supporting this indication				
Reported outcomes specified in the decision problem	• **PFS** • **OS** • **ORR** • **AEs**					• PFS • OS • ORR • DoR				

Study	DESTINY-Breast01 (NCT03248492)	Study DS8201-A-J101 (NCT02564900)
	• DoR	• AEs
All other reported outcomes	• DCR • CBR • TTR • Best percent change in the sum of diameters of measurable tumours	• DCR • TTR • Best percent change in the sum of diameters of measurable tumours
Key publication	Modi 2020[62]	Tamura 2019[63]
Secondary sources	Jerusalem 2020[64] Modi 2020[65] Daiichi-Sankyo, Inc., 2019 (CSR)[66] Clinicaltrials.gov (NCT03248492)[67]	-

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CSR, clinical study report; DCR, disease control rate; DoR, duration of response; HER, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; TTR, time to response; uBC, unresectable breast cancer**.** **Bold**=outcomes that are incorporated in the model.

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

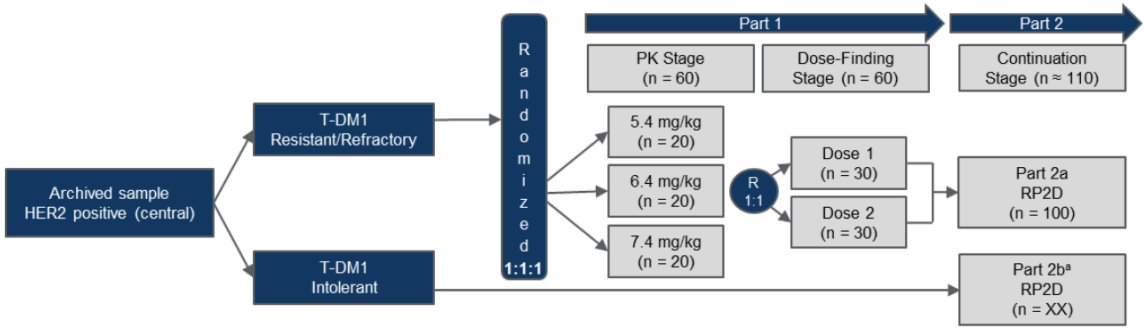
B.2.3.1 Key trial: DESTINY-Breast01

B.2.3.1.1 Study design

The Phase II DESTINY-Breast01 trial (NCT03248492) is an on-going, two-part, open-label, single group, multicentre, study of T-DXd in adults with pathologically documented HER2+, uBC or mBC who had received previous treatment with T-DM1. Positivity for HER2 was defined as a score of 3+ on IHC analysis or as positive results on ISH, as centrally confirmed on archival tissue.

Part 1 of the study consisted of two sequential stages: PKs and dose finding (Figure 4). In the PK stage, patients were randomly assigned in a 1:1:1 ratio to receive T-DXd at a dose of 5.4 mg/kg, 6.4 mg/kg, or 7.4 mg/kg administered by intravenous infusion every 3 weeks.

Figure 4: DESTINY-Breast01 study design



Abbreviations: HER2, human epidermal growth factor receptor 2; PK, pharmacokinetics; RP2D, recommended Part 2 dose; T-DM1, trastuzumab emtansine.
The n values shown in the figure are the planned enrolment numbers. Randomisation for the dose finding stage was based on pharmacokinetics. [a] Approximately 10 to 15 patients were expected to enrol in Part 2b.
Source: Modi 2020 (Supplementary Figure S1)[62]

On the basis of the PK analysis, two doses were identified for evaluation in the dose-finding stage, in which newly enrolled patients were randomly assigned in a 1:1 ratio (Figure 4). The recommended dose was identified using a predicted benefit-risk profile modelled from exposure-response, exposure-safety, and PK analyses as well as clinical data from this study and from the Phase I DS8201-A-J101 study (see Appendix D1.2 for the justification of the recommended dose).[63]

In part 2 of the study, the efficacy and safety of the recommended dose of T-DXd (5.4 mg/kg) was evaluated. Part 2 consisted of two cohorts: one involved patients who had tumour progression during or after the previous administration of T-DM1 and one involved patients who had discontinued T-DM1 for reasons other than progressive disease (e.g. toxicity). Treatment continued until disease progression, the occurrence of unacceptable toxic effects, or withdrawal of consent.

This submission focuses on data from the 5.4 mg/kg cohort from part 1 (n=50) and part 2 (part 2a: n=130; 2b: n=4), which corresponds to the recommended dose of T-DXd (n=184).

Table 5 shows a summary of the methodology of DESTINY-Breast01.

Table 5: Summary of DESTINY-Breast01 methodology

Trial design	Phase II, two-part, open-label, single group, multicentre study.
Location	72 sites in eight countries in Europe (Belgium, France, Italy, Spain, UK), North America (US) and Asia (Japan, South Korea).
Eligibility criteria for participants	**Inclusion criteria** • Men or women ≥18 years old, with the exception of Japan and South Korea (≥20 years old)

	• Pathologically documented BC that: – Is unresectable or metastatic – Has confirmed HER2+ expression (ER/PR positive patients may be enrolled if they are HER2+) according to ASCO-CAP guidelines[68] evaluated at a central laboratory – Patient must have BC that is resistant or refractory to T-DM1 with documented clinical or radiographic progression of disease during or after treatment with T-DM1 – For Part 2b, patients must have discontinued treatment with T-DM1 for reasons other than resistant or refractory disease – Presence of at least one measurable lesion as per RECIST Version 1.1 • LVEF ≥50% • ECOG PS 0 or 1 • Adequate bone marrow function, defined as ANC ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, and haemoglobin level ≥9.0 g/dL • Adequate renal function, defined as creatinine clearance ≥30 mL/min[†] • Adequate hepatic function, including mild–moderate hepatic impairment, defined as total bilirubin ≤3 × ULN (including patients with documented Gilbert's Syndrome or liver metastases or other aetiologies) and AST/ALT ≤5 x ULN • Adequate blood clotting function, defined as international normalised ratio and activated partial thromboplastin time ≤1.5 × ULN • Male and female subjects of reproductive/childbearing potential had to agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study drug
	Exclusion criteria • Myocardial infarction ≤ 6 months before registration, symptomatic CHF (New York Heart Association Class II to IV), unstable angina, or serious cardiac arrhythmia requiring treatment • Corrected QT interval prolongation to >470 ms (women) or >450 ms (men) • History of (noninfectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening • Brain metastases that are untreated, symptomatic, or require therapy to control symptoms • Clinically significant corneal disease in the opinion of the investigator • Prior treatment with an ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor • Unresolved toxicities from previous anticancer therapy • Current treatment with CYP3A4 strong inhibitors (washout period of ≥3 elimination half-lives of the inhibitor is required)
Settings and locations where the data were collected	A total of 253 subjects were enrolled and treated at one of 72 study sites in the following countries: US (24 study sites), Japan (10), France (9), Spain (8), South Korea (7), Belgium (5), UK (5), and Italy (4).[†] Enrolment was proportional across geographic regions: Asia, 56 (22.1%) subjects in Japan and 40 (15.8%) subjects in South Korea; US, 77 (30.4%) subjects; and Europe: 80 (31.6%) subjects.[†]

Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	T-DXd was administered as an IV infusion once every 3 weeks, on Day 1 of each 21 day cycle. • In the part 1 PK stage, subjects were randomised to receive 1 of 3 doses: 5.4 mg/kg, 6.4 mg/kg, or 7.4 mg/kg. • In the part 1 dose finding stage, subjects were randomised to receive 1 of the 2 doses selected in the PK stage (identified as 5.4 mg/kg and 6.4 mg/kg). Once assigned, subjects remained on study in their treatment group and did not change dose groups. • In part 2, all subjects received 5.4 mg/kg, which was determined to be the RP2D. The first dose of T-DXd was to be administered over 90 minutes (± 10 minutes). If there was no infusion-related reaction after the first dose, subsequent doses were to be administered over 30 minutes (± 5 minutes).
Permitted and disallowed concomitant medication	The following medications, treatments, and procedures were prohibited during the treatment period: • Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment. • Other investigational therapeutic agents. • Radiotherapy (except for palliative radiation to known metastatic sites, as long as it did not affect assessment of response or interrupt treatment for more than the maximum time • Radiotherapy to the thorax. • Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications (inhaled steroids or intra-articular steroid injections were permitted). – Subjects with bronchopulmonary disorders who required intermittent use of bronchodilators (such as albuterol) were not excluded from this study. • CYP3A4 strong inhibitors • OATP1B inhibitors • Foods or beverages containing grapefruit Hematopoietic growth factors could be used for prophylaxis or treatment based on the clinical judgment of the investigator. Prophylactic or supportive treatment of study-drug induced AEs were otherwise to be as per investigator's discretion and institutional guidelines. Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments was discouraged, but not prohibited.
Primary outcomes (including scoring methods and timings of assessments)	ORR (CR plus PR; RECIST version1.1) according to ICR (see Section B.2.3.1.2. for further details of outcomes)
Other outcomes used in the economic model/specified in the scope	PFS OS AEs
Other outcomes of interest	ORR according to the investigator, ICR-assessed DCR, CBR, DoR, TTR, and best percent change in the sum of diameters of measurable tumours

Pre-planned subgroups	Subgroups were examined for the primary endpoint of ORR and secondary endpoint of DoR to assess homogeneity of estimate of treatment effect.† Demographic and prognostic subgroups were pre-defined, including previous receipt of pertuzumab, hormone receptor status and receipt of T-DXd immediately after initial T-DM1 therapy.

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; ALT, alanine transaminase; ANC, absolute neutrophil count; ASCO-CAP, American Society of Clinical Oncology – College of American Pathologists; AST, aspartate transaminase; CHF, congestive heart failure; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ILD, interstitial lung disease; IV, intravenous; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PR, progesterone receptor; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended part 2 dose; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTR, time to response; QTc, corrected QT interval; ULN, upper limit of normal.
Source: Modi 2020[62]; Clinical Study Protocol publically available from Clinicaltrials.gov (NCT03248492)[67]; †From Daiichi-Sankyo, Inc., 2019 (CSR)[66]

B.2.3.1.2 Outcomes reported

Trial endpoints, their definitions, and censoring rules are outlined in Table 6.

Table 6: Summary of DESTINY-Breast01 endpoints

Endpoint/assessment	Details	Censoring rules[‡]
Primary endpoint		
ORR assessed by independent central imaging facility review	Defined as the proportion of subjects who achieved a best overall response of CR or PR, based on RECIST 1.1.	-
Secondary endpoints		
PFS	Defined as the time interval between the date of randomisation/registration and the first documentation of disease progression or death due to any cause. Disease progression was determined through an ICR of tumour scans using RECIST 1.1. Clinical progression without objective documentation of disease progression per RECIST 1.1 was not considered to be progression while deriving the PFS endpoint.[†]	• Subjects known to not have progressed or died at the data cut-off date were to be censored at the date of last evaluable tumour assessment. • Subjects who discontinue from the study prior to first post-baseline evaluable tumour assessment for a reason other than death were to be censored at the date of randomisation (the date of registration for not randomised subjects). • Subjects who start other anti-cancer therapy prior to disease progression or death were to be censored at the date of last tumour evaluable assessment prior to starting new anti-cancer therapy. • Subjects who have progressive disease or die after missing ≥2 consecutive scheduled tumour assessments (i.e., more than 14 weeks, allowing for 2 weeks visit window) were to be censored at the date of last evaluable tumour assessment prior to progression. • Subjects without baseline evaluable tumour assessment were to be censored at the date of randomisation or registration, except death within first 2 scheduled tumour assessments (i.e., 14 weeks) were to be considered as a PFS event.

Endpoint/assessment	Details	Censoring rules[‡]
OS	Defined as the time interval between the date of randomisation/registration and the date of death due to any cause. If the analysis subject was not known to have died prior to the data cut-off date, OS was censored at the last contact date at which the subject was known to be alive. Based on ICR.[†]	If analysis patient is not known to have died prior to the data cut-off date, OS was to be censored at the last contact date at which the subject was known to be alive. The last contact date was defined as the last date the subject was known to be alive up-to the data cut-off date. The date was to be the latest date among the dates below. Only assessments up-to the data cut-off date were to be considered in deriving the last contact date. • Last non-missing assessment/onset date captured in the following eCRF pages (or if a date of assessment/onset is not available the “date of visit” for the eCRF page could be used): adverse events, vital signs, physical examination, ECOG PS, ECG, clinical laboratory test, tumour assessment, and PK/biomarker/other specimen sample collection date. • Last dosing date of study drug, last date of concomitant medications, and last date of nondrug treatments/procedures. • Last date of subsequent anti-cancer therapy administered after study treatment discontinuation. • Date of last contact collected on the survival follow up page of the eCRF.
DoR	Defined as the time interval between the date of first documentation of objective response (CR or PR) and the date of the first objective documentation of disease progression or death due to any cause; based on ICR.[†]	• Subjects who are not known to have progressed or died at the data cut-off date were to be censored at the date of last evaluable tumour assessment. An evaluable tumour assessment was defined as an assessment where the overall tumour response was not “Inevaluable (NE)”. • Subjects who start other anti-cancer therapy prior to disease progression or death were to be censored at the date of the last tumour evaluable assessment prior to starting new anticancer therapy. • Subjects who progress or die after missing ≥2 consecutive scheduled tumour assessments were to be

Endpoint/assessment	Details	Censoring rules‡
		censored at the date of the last evaluable tumour evaluation prior to progression or death. In this study, tumour assessment was performed every 6 weeks (±7 days), therefore, progression or death after missing ≥2 consecutive scheduled tumour assessments was defined as progression or death that occurs after more than 14 weeks (two tumour assessment visits plus 2 weeks visit window). This definition was to be applied throughout the study period.
Best percent change in the sum of the diameter of measurable tumours	Defined as the percent change in the smallest sum of diameters from all post-baseline tumour assessments, taking as reference the baseline sum of diameters, based on RECIST Version 1.1; based on ICR.†	-
DCR	Defined as the proportion of subjects who achieved a best overall response of CR, PR or SD; based on ICR.†	-
CBR	Defined as the proportion of subjects who achieved a best overall response of CR or PR or more than 6 months of SD; based on ICR.†	-
ORR based on investigator assessment	Defined as the proportion of subjects who achieved a best overall response of CR or PR based on local radiologists/investigators' tumour assessments using RECIST 1.1.†	-
Exploratory endpoints		
Duration of SD	Defined as the time from the date of randomisation/ registration to the date of first documentation of PD or death due to any cause in subjects with a best overall response of SD.†	Censoring rules were the same as described above for DoR.
TTR	Defined as the time from the date of randomisation/ registration to the date of the first documentation of objective response (CR or PR) in responding subjects.†	-
Safety		

Endpoint/assessment	Details	Censoring rules‡
Assessment of AEs and SAEs	Safety endpoints include SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings, ophthalmologic findings, and ADAs. All AEs were categorised using the MedDRA. AEs and abnormal laboratory test results, if applicable, were graded using NCI-CTCAE Version 4.03.†	-

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CBR, clinical benefit rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; Echo, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report from; ICR, independent central review; MedDRA, Medical Dictionary for Regulatory Activities; MUGA, multigated acquisition scan; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TTR, time to response.
Source: Modi 2020[62]; †From Clinical Study Protocol publically available from Clinicaltrials.gov (NCT03248492)[67]; ‡From Daiichi-Sankyo, Inc., 2019 (SAP)[69]

Enrolment and treatment decisions were made by investigators based on local review of radiographic exams.[66] All on-study images required per protocol were collected by the study sites and submitted to an independent central facility as soon as possible after the scans were performed.[66] A blinded independent central review (ICR) of patient radiographic studies with assessment of response using modified RECIST 1.1 was conducted on an ongoing basis by two independent radiologists, with adjudication as needed by a third independent radiologist.[66]

All lesions (target and non-target) were to be assessed by the investigator at screening.[66] Tumour assessments, based on sites of disease identified at screening and any additional newly suspected sites of progressive disease (PD), were to be conducted every 6 weeks (± 7 days) from Cycle 1 Day 1, independent of treatment cycle. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the suspected sites of disease in the chest, abdomen, and pelvis were mandatory. CT and/or MRI (spiral CT or MRI with ≤ 5 mm cuts) of chest, abdomen, and pelvis were to be used for tumour assessment unless another modality of disease assessment was necessary for the lesions. The same assessment modality was to be used throughout the study for all assessments for each patient unless prior approval was obtained from the sponsor or its designee. Unscheduled tumour assessments could be performed if progression was suspected.

A CT or MRI of the brain was mandatory for all patients included with baseline stable brain metastases. Patients without brain metastases did not need additional brain scans for tumour assessment unless clinically indicated.

Patients were also assessed every 3 months (± 14 days) from the date of the 40-day follow-up visit for survival and subsequent anticancer therapy until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurred first.

B.2.3.1.3 Baseline characteristics

The baseline characteristics of patients who received the recommended dose of 5.4 mg/kg T-DXd is shown in Table 7.

Among the patients who received the recommended dose of 5.4 mg/kg T-DXd, the median age was 55 years (range, 28 to 96); 76% of the patients were younger than 65 years of age. Of the 184 patients, 97 (52.7%) had hormone receptor–positive tumours. All but one subject had an Eastern Cooperative Oncology Group performance status (ECOG PS) of either 0 or 1 as the most recent PS prior to dosing. The patient who had an ECOG of 2 at baseline had originally had an ECOG PS of 1 at screening but then had an ECOG PS of 2 at Cycle 1 Day

1.[66] Per inclusion criteria, as the patient had an ECOG PS of 1 at screening, she was eligible for the study.

Most patients (93.5%) had metastatic disease. Most patients were heavily pretreated; the median number of previous lines of therapy for locally advanced BC or mBC excluding hormone therapy was 6 (range, 2 to 27). All 184 patients had received prior T-DM1, as per protocol. All patients had also received prior trastuzumab, 65.8% of subjects had received prior pertuzumab (this was a global study and pertuzumab was not available in all countries recruiting into the trial), and 54.3% had received additional anti-HER2 therapy (not including trastuzumab, pertuzumab, or T-DM1). The best response to prior T-DM1 (CR or PR) was 21.7%, and 35.9% of patients had PD.

Table 7: DESTINY-Breast01: Baseline characteristics of patients who received 5.4 mg/kg T-DXd (enrolled analysis set)

Characteristic	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Age	
Age, median (range), years	55.0 (28.0–96.0)
<65 years	140 (76.1)
≥65 years	44 (23.9)
Female, n (%)	184 (100)
Race, n (%)	
Asian	70 (38.0)
White	101 (54.9)
Other	9 (4.9)
Missing data	4 (2.2)
Region, n (%)	
Europe	68 (37.0)
Asia	63 (34.2)
North America	53 (28.8)
ECOG performance-status score, n (%)	
0	102 (55.4)
1	81 (44.0)
2	1 (0.5)
Hormone-receptor status, n (%)	
Positive	97 (52.7)
Negative	83 (45.1)
Unknown	4 (2.2)

Characteristic	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
HER2 expression, n (%)	
IHC 3+	154 (83.7)
IHC 1+ or 2+, ISH-positive	28 (15.2)
Missing data‡	2 (1.1)
Median sum of diameters of target lesions (range), cm	5.5 (1.2–24.5)
Subjects with following metastases†, n (%)	
Yes	172 (93.5)
Brain	24 (13.0)
Bone	53 (28.8)
Lung	105 (57.1)
Liver	56 (30.4)
Visceral	169 (91.8)
Median no. of previous cancer regimens (range) (excluding hormone therapy)	6 (2–27)
Previous systemic cancer therapy, n (%)	
Trastuzumab	184 (100)
T-DM1	184 (100)
Pertuzumab	121 (65.8)
Other anti-HER2 therapy	100 (54.3)
Hormone therapy	90 (48.9)
Other systemic therapy	183 (99.5)
Best response to T-DM1 therapy, n (%)	
CR/PR†	40 (21.7)
SD†	39 (21.2)
CR/PR/SD	79 (42.9)
PD	66 (35.9)
Could not be evaluated	39 (21.2)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
‡ HER2 expression was centrally confirmed by analysis of the most recent archival tissue, according to the ASCO-CAP guidelines.[68] According to these guidelines, HER2 positivity was defined as a HER2 IHC analysis score of 1+ (IHC negative) or 2+ (IHC borderline) and positive results on ISH or a score of 3+ (IHC positive). Data for patients with an IHC score indicated as 1+ or 2+ include data for patients for whom the result was equivocal or could not be evaluated. Data regarding HER2 status were missing for a patient who had an IHC 2+ result with equivocal results on ISH and for another patient who had conflicting IHC results during evaluations in 2017 and 2018.
Source: Modi 2020[62]; †From Daiichi-Sankyo, Inc., 2019 (CSR)[66]

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

B.2.4.1 Analysis sets

The main analysis population sets in the DESTINY-Breast01 trial are defined in Table 8, together with the number and percentage of patients in each analysis set.

Table 8: DESTINY-Breast01: Analysis sets

Analysis set	Definition	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) n (%)
Enrolled analysis set (EAS) (intent-to-treat analysis set)	All subjects who signed an ICF and were randomised in part 1 or registered in part 2.	184 (100.0)
Safety analysis set	All subjects enrolled in part 1 or part 2 who received at least 1 dose of study drug. The safety Analysis Set is identical to the Full Analysis Set.	184 (100.0)
Response evaluable set (RES)	All subjects enrolled in part 1 or part 2 who received at least 1 dose of study drug and had measurable tumours assessed by ICR at baseline.	170 (92.4)[†]

Abbreviations: ICF, informed consent form; ICR, independent central review; T-DXd. trastuzumab deruxtecan.
[†]A total of 18 patients were excluded from the RES due to no measurable target lesion at baseline per ICR (used for sensitivity analysis).
Source: Daiichi-Sankyo, Inc., 2019 (CSR)[66] and Daiichi-Sankyo, Inc., 2019 (data on file 90-day update)[70]

The primary endpoint was performed on the enrolled analysis set (EAS, which was the same as the intent-to-treat [ITT] analysis set) and the response evaluable set (RES), and the secondary endpoints were performed on the EAS.[66] Safety analyses were to be performed using the safety analysis set. All other exploratory analyses were to be performed based on the EAS and availability of assessment.

B.2.4.2 Statistical analyses

A summary of the statistical methods used in the DESTINY-Breast01 trial are presented in Table 9.

Table 9: DESTINY-Breast01: Summary of statistical analyses

Hypothesis objective	The study hypothesis was that T-DXd will confer a significant benefit in ORR in subjects with HER2+ BC who are resistant or refractory to T-DM1.†
Statistical analysis	The estimate of ORR (with CR plus PR confirmation) was calculated with the 2-sided 95% exact CI using the Clopper-Pearson method. PFS, OS and DOR were estimated using the Kaplan–Meier method; corresponding two-sided 95% CIs were calculated with the Brookmeyer and Crowley methods.[71]
Sample size, power calculation	It was calculated that a sample of approximately 230 patients would result in approximately 150 patients being treated at the RP2D of T-DXd in both parts of the study, which would provide a 95% CI within 10% of the ORR. Enrolment was designed to continue until at least 100 patients who had received previous treatment with pertuzumab were enrolled at the recommended dose.‡ With 150 patients, the probability that the lower boundary of the 95% CI would be more than 20% was 0.982, and the probability that the estimated response rate would be 30% or more was 0.916, according to the anticipated response rate of 35%.
Data management, patient withdrawals	In general, missing or dropout data were not to be imputed for the purpose of data analysis, unless otherwise specified. The rules for censored data for DoR, PFS, and OS are defined in Table 6.
Data-cuts and statistical analysis timepoints	The primary analysis was performed after all the patients who had received the recommended dose of T-DXd had at least 6 months of follow-up or had discontinued their participation in the study (data cut-off 21 March 2019). 90-day update data-cut was 1 August 2019, corresponding to minimum 10 months of follow-up after last subject enrolled.

Abbreviations: BC, breast cancer; CI, confidence interval; CR, complete response; DoR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RP2D, recommended part 2 dose; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
‡In 2016, US prescribing patterns indicated that a large majority of subjects with HER2-positive BC received pertuzumab in the first- or second-line setting. Slightly lower rates were reported in Europe and Japan. The DESTINY-Breast01 study design attempted to replicate this rate of approximately two-thirds of subjects having received pertuzumab by setting a minimum on the number of such subjects enrolled.[66]
Source: Modi 2020[62]; †From Daiichi-Sankyo, Inc., 2019 (CSR)[66]

The primary data cut-off date was 21 March 2019, corresponding to minimum 6 months of follow-up after last subject enrolled; these data are reported in the CSR. A 90-day update data-cut was performed on 1 August 2019, corresponding to a minimum of 10 months of follow-up after last subject enrolled; the latter data have been reported by Modi 2020[62]; they are not included in the CSR, but are summarised in data-on-file documents.[70,72] The submission, including the data used in the economic analysis, primarily focuses on the most mature data from the 1 August 2019 data-cut.

B.2.4.3 Participant flow

For full details of the participant flow in the DESTINY-Breast01 trial see Appendix D. Overall, 253 patients were enrolled and received at least one dose of T-DXd; 184 patients received the recommended dose of 5.4 mg/kg dose, which is the focus of this submission as this

corresponds to the indicated recommended dosage (i.e. both part 2a and 2b). The dose justification is documented in Appendix D.

At the time of the data cut-off (1 August 2019), 79 of 184 patients (42.9%) who had received the recommended dose were continuing to receive T-DXd. The primary reasons for discontinuation included PD according to RECIST, version 1.1 (28.8%), and treatment-emergent adverse events (TEAEs) (15.2%). The median treatment duration was 10.0 months (range, 0.7 to 20.5), and the median duration of follow-up was 11.1 months (range, 0.7 to 19.9); 128 patients (69.6%) continued to receive T-DXd for more than 6 months.

B.2.4.4 Supportive trial: Study DS8201-A-J101

Study DS8201-A-J101 was an open-label, dose-escalation and dose-expansion Phase I trial conducted at eight hospitals and clinics in the USA and six in Japan.[63] Eligible patients were at least 18 years old in the USA and at least 20 years of age in Japan and had advanced solid tumours (regardless of HER2 expression in dose escalation or HER2 expression or mutation in dose expansion).

In the dose-expansion part (part 2) of the study, the safety, tolerability, and activity of T-DXd at the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg every 3 weeks) were assessed in five patient cohorts (Parts 2a-e), with parts 2a and 2e including a large cohort of patients with advanced, HER2+ uBC or mBC after T-DM1 (defined as IHC 3+ or ISH positive). Data from part 2a and 2e in this patient cohort at the recommended doses for expansion analysed together are presented in this submission.

This study was not used to inform the economic model due to the availability of data from the Phase II study at the recommended dose of 5.4 mg/kg. Nevertheless, it is presented here as a supportive study, to demonstrate the clinical activity and the manageable safety profile of T-DXd in patients with uBC or mBC and previous treatment with T-DM1.

A summary of the study methodology is shown in Table 12, with more details provided in Appendix M, including the patient disposition and patient demographics and baseline characteristics.

Table 10: Summary of the Phase I study DS8201-A-J101

Trial design	A two-part (dose-escalation and dose-expansion), first-in-human, non-randomised, open-label, Phase I study; in the dose-expansion part (part 2) of the study, the safety, tolerability, and activity of T-DXd at the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg every 3 weeks) were assessed.

Population	Advanced, uBC, or mBC HER2+ after T-DM1 (defined as IHC 3+ or ISH-positive).
Outcomes	The primary endpoints of the study were safety and preliminary activity. **Primary efficacy endpoint**: Proportion of patients who achieved an objective response (defined as patients who achieved a complete response or partial response) as assessed by the investigators. **Other efficacy endpoints**: OS, PFS, DCR, percentage change of the sum of target lesion diameters, DoR, TTR, duration of stable disease, time on therapy for T-DXd, and growth modulation index ratio. Activity endpoints were not centrally reviewed for this analysis. A retrospective, blinded, independent review is ongoing.

Abbreviations: CI, confidence interval; DCR, disease control rate; DoR, duration of response; HER2, IHC, immunohistochemistry; ISH, in-situ hybridisation; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTR, time to response; uBC, unresectable breast cancer.
Source: Tamura 2019[63]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the non-RCTs was performed by two independent reviewers using a checklist by Downs and Black.[60,73]

A summary of the quality assessments performed for DESTINY-Breast01 (non-RCT for part 2) and DS8201-A-J101 (non-RCT) are provided in Table 11.

Table 11: Overview of quality assessments for Study DESTINY-Breast01 and DS8201-A-J101

Questions	DESTINY-Breast01 (Modi 2020[62])	Study DS8201-A-J101 (Tamura 2019[63])
Is the hypothesis/aim/objective of the study clearly described?	Y	Y
Are the main outcomes to be measured clearly described in the introduction or methods section?	Y	Y
Are the characteristics of the patients included in the study clearly described?	Y	Y
Are the interventions of interest clearly described?	Y	Y
Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y	Y
Are the main findings of the study clearly described?	Y	Y
Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y

Questions	DESTINY-Breast01 (Modi 2020[62])	Study DS8201-A-J101 (Tamura 2019[63])
Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y
Have the characteristics of patients lost to follow-up been described?	Y	N
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Y	N
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	Y
Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Y	UTD
Was an attempt made to blind study subjects to the intervention they have received?	N	N
Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N
If any of the results of the study were based on 'data dredging', was this made clear?	N	Y
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	NA	Y
Were the statistical tests used to assess the main outcomes appropriate?	Y	Y
Was compliance with the intervention(s) reliable?	Y	Y
Were the main outcome measures used accurate (valid and reliable)?	Y	Y
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Y	NA
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Y	NA
Were study subjects randomised to intervention groups?	Y	NA
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Y	NA
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Y	N
Were losses of patients to follow-up taken into account?	Y	Y

Questions	DESTINY-Breast01 (Modi 2020[62])	Study DS8201-A-J101 (Tamura 2019[63])
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N	Y

Abbreviations: N, No; NA, not applicable; UTD, unable to determine; Y, Yes.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Key trial: DESTINY-Breast01

B.2.6.1.1 Primary efficacy outcome: objective response rate

The efficacy results for the primary outcome of ICR-assessed ORR in the DESTINY-Breast01 trial at the data-cuts of 21 March 2019 (primary analysis) and 1 August 2019 (90-day update) are presented in Table 12. Among the 184 patients who received T-DXd at the recommended dose of 5.4 mg/kg (data-cut of 1 August 2019), the confirmed ORR on ICR was 60.9% (95% CI, 53.4, 68.0); of these 11 patients (6.0%) had a CR, and 101 patients (54.9%) had a PR. Another 3 patients (1.6%) had PD, and 2 (1.1%) could not be evaluated.

Patients achieved a confirmed ORR >50% regardless of the number of prior lines of systemic therapy they received; however, the highest ORR was observed in those who had received only two prior lines (Appendix E). Five patients with a CR had had two prior lines of systemic therapy, three had had four prior lines and three had had five prior lines (Appendix E).

The confirmed ORR based on investigator assessment (secondary endpoint) in the primary 5.4 mg/kg dose cohort was 66.8% (95% CI: 59.5, 73.6), with 8% having a CR and 62.5% having a PR.

Table 12: DESTINY-Breast01: Primary efficacy outcome – ORR by ICR (EAS)

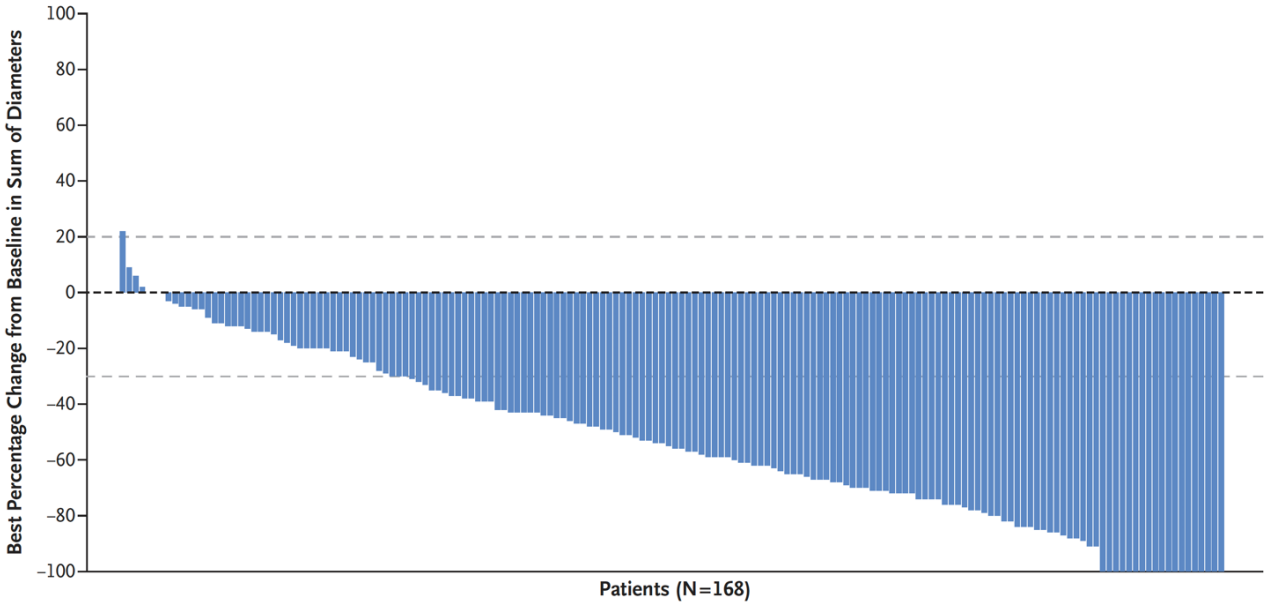
Primary endpoint	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 21 March 2019 (ICR)†‡	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 1 August 2019 (ICR)¶	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 1 August 2019 (INV)§
ORR, n (% [95% CI])	111 (60.3 [52.9, 67.5])	112 (60.9 [53.4, 68.0])	123 (66.8 [59.5, 73.6])
CR, n (%)	8 (4.3)	11 (6.0)	8 (4.3)
PR, n (%)	103 (56.0)	101 (54.9)	115 (62.5)

Primary endpoint	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 21 March 2019 (ICR)†‡	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 1 August 2019 (ICR)¶	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) Data-cut: 1 August 2019 (INV)§
SD, n (%)	68 (37.0)	67 (36.4)	56 (30.4)
PD, n (%)	3 (1.6)	3 (1.6)	4 (2.2)
NE, n (%)	2 (1.1)	2 (1.1)	1 (0.5)

Abbreviations: CI, confidence interval; CR, complete response; EAS, enrolled analysis set; ICR, independent central review; INV, investigator; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan
‡ The data-cut-off for the primary analysis occurred on 21 March 2019 when all subjects had at least 6 months of follow-up or had discontinued from the study. At data-cut-off, the median study duration across all doses was 7.8 months (range, 0.7 to 17.2)
¶ A second data-cut occurred on 1st August 2019 corresponding to minimum >10 months of follow-up after last subject enrolled; the median duration of follow-up in the 5.4 mg/kg dose cohort was 11.1 months (range, 0.7 to 19.9)
§ Key secondary endpoint was ORR based on investigator assessment
Source: Modi 2020[62]; †From Daiichi-Sankyo, Inc., 2019 (CSR)[66]

Most of the patients for whom both baseline and postbaseline data were available had a reduction in tumour size (Figure 5).

Figure 5: DESTINY-Breast01: Waterfall plot of change from baseline in tumour size for the 5.4 mg/kg dose of T-DXd, as measured by ICR (EAS)



Abbreviations: ICR, independent central review.
Data-cut: August 1, 2019
Of the patients in the 5.4 mg/kg cohort (n = 184), 168 patients had both baseline and post-baseline target legion assessments by ICR. The upper dashed horizontal line indicates a 20% increase in tumour size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumour size (partial response).
Source: Modi 2020[62]

B.2.6.1.2 Key secondary outcomes

Progression-free survival

Of the 184 patients receiving the recommended dose of 5.4 mg/kg (data-cut of 1 August 2019), there were 58 PFS events and the median PFS for these patients was 16.4 months (95% CI: 12.7, NE) (Table 13). Of the 184 patients, 48 had PD and 10 had died by 20 months.

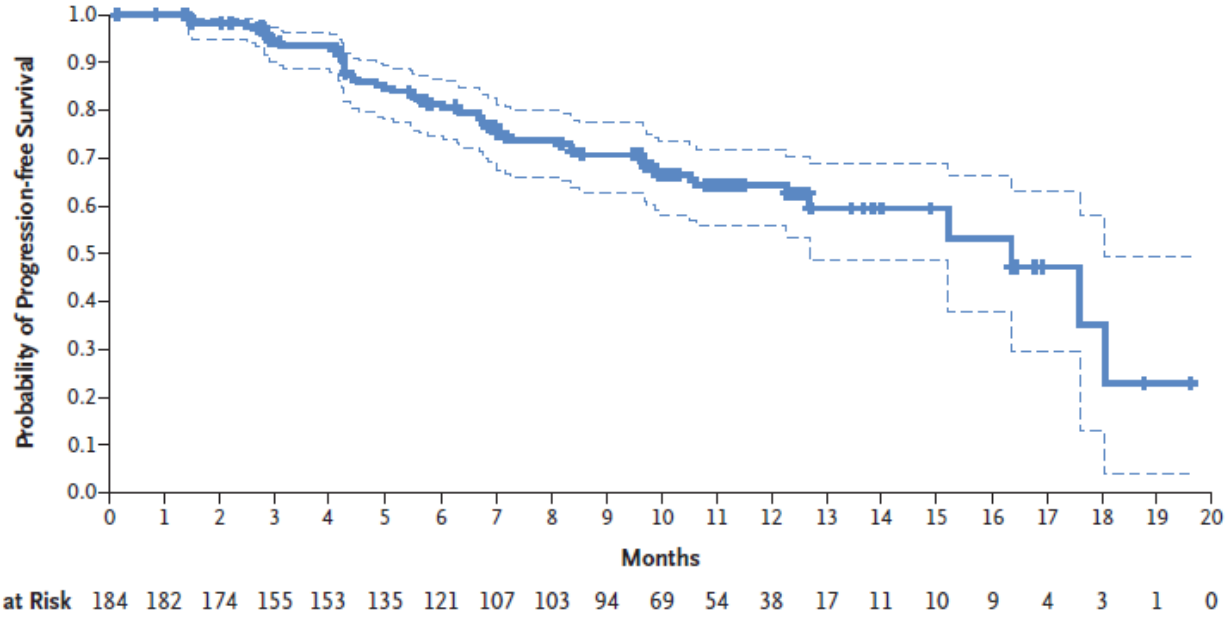
Table 13: DESTINY-Breast01: PFS as assessed by ICR (EAS)

PFS	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Median PFS, months (95% CI)	**16.4 (12.7, NE)**
PFS events, n (%)	58 (31.5)
Progressive disease, n (%)	48 (26.1)
Death, n (%)	10 (5.4)
Censored, n (%)	126 (68.5)

Abbreviations: CI, confidence interval; EAS, Enrolled Analysis Set; ICR, independent central review; ITT, Intent-to-Treat; NE, not evaluable; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Source: Modi 2020[62]

Figure 6 presents a Kaplan–Meier (KM) curve of PFS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b.

Figure 6: DESTINY-Breast01: Kaplan–Meier plot of PFS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)

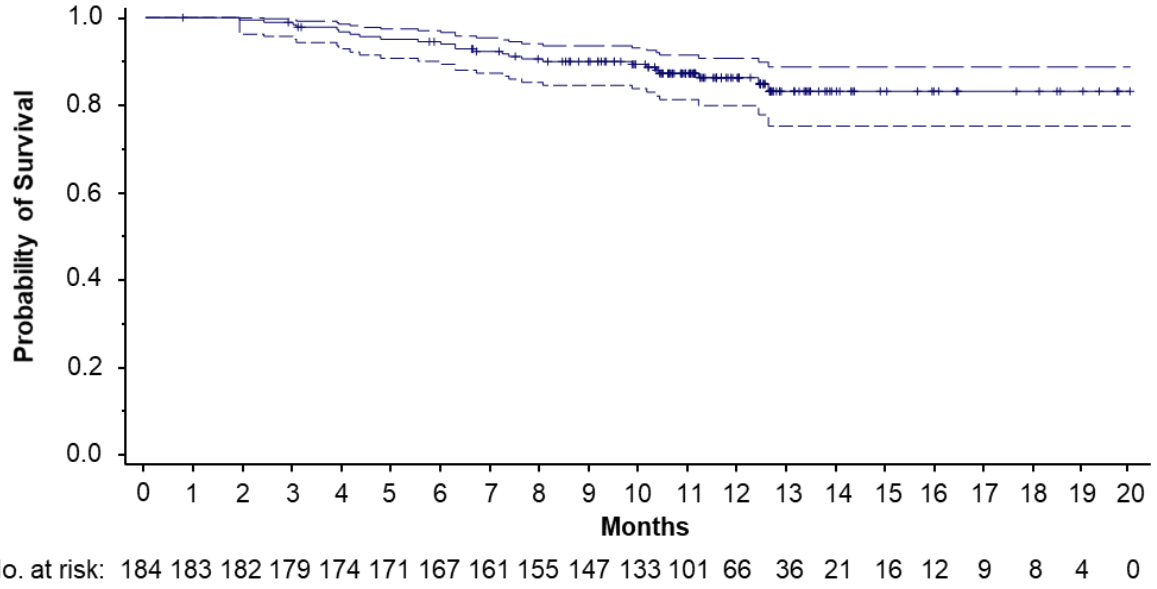


Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Data for 126 patients were censored, as indicated by tick marks. Disease progression was assessed with the use of the modified RECIST version 1.1. The dashed lines indicate the 95% CI.
Source: Modi 2020[62]

Overall survival

The OS data are immature, and the median OS was not reached as of the data-cut of 1 August 2019. Estimated OS was 93.9% (95% CI, 89.3 to 96.6) at 6 months and 86.2% (95% CI, 79.8 to 90.7) at 12 months. Figure 7 presents a KM curve of OS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b. As of the data cut-off, 25 of 184 patients (13.6%) had died and 159 were censored for the OS analysis.

Figure 7: DESTINY-Breast01: Kaplan–Meier plot of OS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)



Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; OS, overall survival; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Data for 159 patients were censored, as indicated by tick marks. The dashed lines indicate the 95% CI.
Source: Modi 2020 (Supplementary Figure S2)[62]

Other secondary endpoints

A summary of the results for other secondary efficacy outcomes assessed in the DESTINY-Breast01 trial are presented in Table 14.

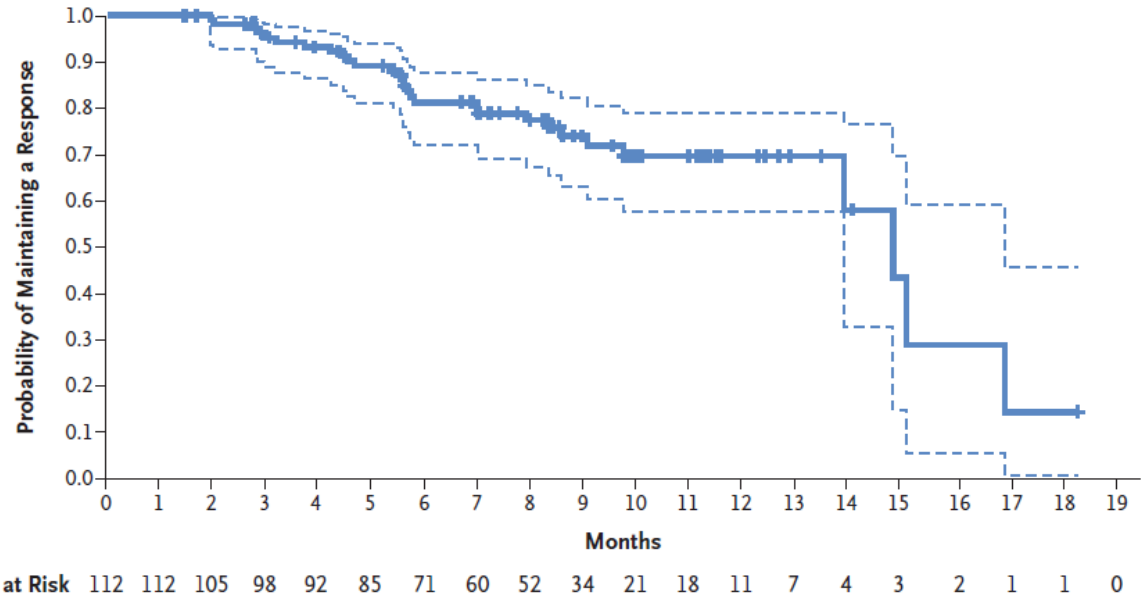
Table 14: DESTINY-Breast01: Summary of other secondary efficacy endpoints as assessed by ICR (EAS)

Secondary endpoints	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Censored, n (%)	83 (74.1)
DCR, n (% [95% CI])	179 (97.3 [93.8, 99.1])
CBR, n (% [95% CI])	140 (76.1 [69.3, 82.1])
Median DoR, months (95% CI)	14.8 (13.8, 16.9)
Median TTR, months (95% CI)	1.6 (1.4, 2.6)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; DoR, duration of response; EAS, Enrolled Analysis Set; ICR, independent central review; TTR, time to response; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Source: Modi 2020[62]

The DCR and CBR for patients receiving the 5.4 mg/kg dose was 97.3% (95% CI: 93.8, 99.1) and 76.1% (69.3, 82.1), respectively. For the 112 patients who achieved a response with the 5.4 mg/kg dose, the median DoR was 14.8 months (95% CI: 13.8, 16.9), and the median TTR was 1.6 months (95% CI: 1.4, 2.6). A KM curve of DoR is presented in Figure 8.

Figure 8: DESTINY-Breast01: Kaplan–Meier plot of DoR for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)



Abbreviations: DoR, duration of response; ICR, independent central review

DoR is shown for the 112 patients who had a complete or partial response among the 184 patients treated with the recommended dose of 5.4 mg/kg T-DXd

Data-cut: August 1, 2019
Source: Modi 2020[62]

B.2.6.2 Supportive trial: Study DS8201-A-J101

A summary of anti-tumour activity outcomes in study DS8201-A-J101 is tabulated in Appendix M. Of the 115 patients, 111 (97%) were evaluable for confirmed response. Of these, 66 (59.5%) achieved a confirmed objective response and 104 (93.7%) achieved confirmed disease control, with a median follow-up of 9.9 months. The median TTR was 1.6 months and the median DoR was 20.7 months. The median PFS was 22.1 months, and the median OS has not been reached. Tumour shrinkage was observed in 102 (93%) of 110 patients with measurable lesions who had at least one postbaseline scan. Of these, 91 (89%) had tumour shrinkage by the first 6-week postbaseline tumour assessment.

B.2.6.3 Efficacy discussion and conclusions

In the key trial, DESTINY-Breast01, T-DXd (at a dose of 5.4 mg/kg) demonstrated robust anti-tumour activity in patients with HER2+ uBC and mBC who had undergone extensive

previous treatment, with a confirmed ORR of 60.9%, a median duration of PFS of 16.4 months, and a median response duration of 14.8 months.

T-DXd demonstrated efficacy in a heavily pre-treated population, including patients who had progressed on T-DM1. While the exact mechanisms of resistance to T-DM1 are unknown, overcoming these processes can be challenging.[23,62] T-DXd has distinct pharmaceutical properties which may contribute to it retaining efficacy in these patients, such as the potent topoisomerase I inhibitor payload instead of a microtubule inhibitor, an increased DAR (approximately 8 with T-DXd vs. approximately 3.5 with T-DM1), and the high membrane permeability of the released payload that enables elimination of both target tumour cells and the surrounding tumour cells (Section B.1.3.4).[62]

Efficacy results were consistent across key subgroups (Section B.2.7), including patients who had received previous pertuzumab therapy, which is important as pertuzumab (in combination chemotherapy and trastuzumab) is generally the standard-of-care for first-line HER2+ advanced BC. Although only a small subgroup (n=24), T-DXd showed efficacy in patients who had stable, treated brain (CNS) metastases at baseline (Section B.2.7); CNS metastasis is a common and devastating complication of HER2+ mBC that can be challenging to treat.[74]

These results validate earlier observations from the Phase I study, which showed a response of 59.5% (95% CI, 49.7 to 68.7) in a similar patient population.

Overall, the efficacy observed with T-DXd is expected to substantially exceed those of currently available treatments in this difficult to treat population with a high unmet need (Section B.2.9).

B.2.7 Subgroup analysis

The methods and results of subgroup analyses in the DESTINY-Breast01 study are presented in Appendix E. Overall, T-DXd demonstrated consistent effectiveness across clinically relevant subgroups including previous receipt of pertuzumab, hormone receptor status, receipt of T-DXd immediately after initial T-DM1 therapy, number of prior regimens (≥3 and <3 prior regimens, excluding hormone therapy) and in patients with CNS (brain) metastases at baseline.[62,64,65] Patients achieved a confirmed ORR >50% regardless of the number of prior lines of systemic therapy they received; however, the highest ORR was observed in those who had received only two prior lines.[65]

B.2.8 Meta-analysis

A meta-analysis to pool the Phase II DESTINY-Breast01 study and the Phase I DS8201-A-J101 study has not been conducted; DS8201-A-J101 evaluated the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg), as opposed to the recommended Phase II dose of 5.4 mg/kg in the DESTINY-Breast01 study. Therefore, pooling the studies would potentially add more complexity without additional benefit.

B.2.9 Indirect and mixed treatment comparisons

The SLR reported in Section B.2.1 and Appendix D identified studies for eribulin, vinorelbine, and capecitabine (the comparators listed in the NICE final scope). However, as DESTINY-Breast01 is a single group study, there was no connected network to enable a network meta-analysis (NMA) or a Bucher indirect comparison. To assess the comparative effectiveness of T-DXd vs comparators and inform the cost-effectiveness model, indirect comparisons for efficacy outcomes (OS, PFS and response outcomes) were made using an unanchored matching-adjusted indirect comparison (MAIC) approach. It was not possible to make comparisons of time to discontinuation (TTD), as Kaplan-Meier (KM) data for TTD were not available for the comparator studies. The MAIC analyses are described in summary below and further details are provided in Appendix D.

B.2.9.1 Brief description of the approach

MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated without individual patient data (IPD) in one of the treatment arms. In this case, individual T-DXd-treated patients are assigned statistical weights that adjust for their over- or underrepresentation relative to that observed in each comparative evidence source.[75]

The premise of MAIC is to adjust for between-trial differences in baseline characteristics. When a common treatment comparator or 'linked network' is unavailable (known as an unanchored comparison), a MAIC assumes that differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and treatment effect modifiers.[76] Under this assumption, every prognostic variable and treatment effect modifier that is imbalanced between the two studies must be available and included in a propensity score logistic regression model. The MAIC method differs from other indirect comparison approaches in that it utilises patient-level data for the treatment of interest along with published aggregate trial level data for the comparator. For the

comparison of T-DXd vs relevant comparators a series of seven MAICs were undertaken to target the key efficacy outcomes of OS, PFS and response (ORR, DCR and CBR):

- Four MAICs for T-DXd vs eribulin
- Two MAICS for T-DXd vs capecitabine
- One MAIC for T-DXd vs vinorelbine.

Estimation of the efficacy of T-DXd vs comparators was conducted using patient-level clinical trial data for T-DXd (from DESTINY-Breast01) along with published, aggregate-level data for other comparators.

All analyses were consistent with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 and Phillippo et al.[77,78]

B.2.9.2 Data sources

The percentage of OS and PFS over time was extracted from the published KM curves, using Engauge Digitizer 10.4, and pseudo individual patient-level data were reconstructed from this (supplemented by the number of patients at risk over time, if reported) using the algorithm published by Guyot et al. 2012.[79] Appendix D provides an additional summary of the available median OS and PFS reported for each included study.

Response data (ORR, DCR and CBR) were extracted from each of the published studies in the form of number of patients with an event, total number of patients in the relevant treatment arm and the percentage of patients with an event (where reported). If the number of patients with a response event was not available, this was calculated from the percentage and the total number in the treatment arm.

B.2.9.2.1 T-DXd

Patient-level data for T-DXd were obtained from DESTINY-Breast01 to provide evidence for T-DXd vs comparators in patients with HER2+ uBC or mBC who have received two or more prior anti-HER2 therapies.

B.2.9.2.2 Comparators

A summary of the reasons for exclusion from the MAIC analyses for the studies identified by the SLR is presented in Appendix D. Table 15 summarises the study characteristics of the seven studies included for the MAICs. A summary of the reasons for exclusion from the MAIC

analyses for the studies identified by the SLR is presented in Appendix D. The quality of two[80,81] of the studies was limited by their study designs, being retrospective chart review/observational studies. Of the remaining five trials, two were randomised and three were single arm prospective studies. The population of interest was HER2+, however only two of the identified studies reported outcome data (OS, PFS and response) for this group of patients.[80,82]

Table 15: Summary of studies included in the MAIC analyses

Comparator	Author (Year)	Study design	Aim of study
Eribulin	Barni (2019)[80]	Multicentre, retrospective cohort	Efficacy of eribulin in patients with mBC in a real-world setting, with HER2+ subgroup data for OS and PFS
	Cortes (2010)[83]	Phase II, single-arm, open-label	Safety and efficacy of eribulin mesylate in patients with locally advanced or mBC who were previously treated with anthracycline, a taxane and capecitabine
	Cortes (2011)[84]	Phase III, randomised controlled, open-label	To compare eribulin mesylate and treatment of physician's choice amongst patients with locally recurrent or mBC who had previous chemotherapies
	Gamucci (2014)[81]	Multi-centre observational	Safety and efficacy of eribulin in real-world patients with advanced breast cancer who have been previously treated by no less than 2 lines of chemotherapy
Capecitabine	Blum (2001)[85]	Multicentre, Phase II single-arm	Efficacy and safety of capecitabine in patients with mBC who failed taxane therapy
	Fumoleau (2004)[86]	Multicentre, Phase II single-arm	To evaluate the capecitabine monotherapy in mBC patients who previously were treated with anthracycline and taxane
Vinorelbine	Sim (2019)[82]	Phase II, randomised controlled, open-label	To compare lapatinib + vinorelbine vs. vinorelbine alone in patients with HER2 + mBC who progressed on both trastuzumab and lapatinib

Abbreviations: mBC: metastatic breast cancer; HER2+, human epidermal growth factor 2 overexpression (positive).

A summary of the baseline characteristics for the included studies is provided in Appendix D.

B.2.9.3 Identification of prognostic factors and treatment effect modifiers

Prognostic variables and treatment-effect modifiers were required for use as covariates in the matching process. These baseline characteristics must be available in the IPD of DESTINY-Breast01, and reported for the comparator studies.

The following list of matching variables was identified based on published evidence of the variable being a prognostic factor in uBC or mBC:

- Prior pertuzumab treatment[87-90]
- Number of lines of prior therapy[91,92]
- Hormone receptor status.[93-96]

Additional matching factors were identified through discussion with the Daiichi Sankyo medical team:

- Visceral disease
- Age
- ECOG-PS
- Brain metastases.

These seven factors were presented to a UK clinical expert (a medical oncologist who specialises in breast cancer). The clinical expert confirmed that the current list of matching variables is appropriate, and suggested the following additions:

- HER2 status
- Number of metastatic sites
- Prior trastuzumab treatment
- Comorbidities (including prior respiratory disease)
- Prior endocrine therapy.

It was also recommended that number of lines of prior therapy be separated into chemotherapy, HER2-targeted therapy, and hormone therapy wherever possible. However, on review of the available data, it would not be possible to match based on prior HER2-targeted therapy, given that all patients in DESTINY-Breast01 had received prior HER2-targeted therapy. The overall number of prior lines of therapy was therefore used; where no other data were available, prior lines of chemotherapy was used as a proxy for the total number of prior lines.

It was not possible to include several of the proposed matching factors (comorbidities, number of metastatic sites, HER2 status, prior trastuzumab treatment) for the following reasons:

- Comorbidities were not reported for any of the seven comparator studies
- Number of metastatic sites was not collected in DESTINY-Breast01
- 100% of patients in DESTINY-Breast01 were HER2+

- 100% of patients in DESTINY-Breast01 had received prior trastuzumab treatment.

Table 16 summarises the included prognostic factors and treatment effect modifiers, and the studies in which these factors were reported.

At an advisory board conducted in August 2020,[59] it was discussed that age may not be a reliable matching factor, given that both extremes of young and old age are associated with worse prognosis in mBC. Removing age from the matching variables was tested in the two study comparisons with the most extreme ages (Sim 2019 and Gamucci 2014) – these studies also resulted in the smallest effective sample sizes (ESS) from the DESTINY-Breast01 study when age was included. Given that the ESS increased in the weighted comparison with Sim 2019, and that there was no impact on ESS for the Gamucci 2014 comparison when age was removed, age was excluded permanently for the Sim 2019 comparison but retained in the matching variables for Gamucci 2014.

Baseline characteristics for all studies are presented in Appendix D.

Table 16: Summary of prognostic factors and treatment effect modifiers

Factor	Prognostic factor or treatment effect modifier	Comparator studies in which factor is reported
Prior treatment with pertuzumab (yes/no)	• Treatment effect modifier	• Sim 2019
Number of lines of prior therapy (<3, ≥3)	• Treatment effect modifier	• Cortes 2010 • Cortes 2011 • Gamucci 2014 • Barni 2019 • Fumoleau 2004 • Blum 2001 • Sim 2019
Hormone receptor (HR) status (positive/negative)	• Prognostic factor	• Cortes 2010 • Cortes 2011 • Gamucci 2014 • Sim 2019
Presence of visceral disease (yes/no)	• Prognostic factor	• Barni 2019 • Blum 2001 • Gamucci 2014 • Sim 2019
Age	• Prognostic factor	• Cortes 2010 • Cortes 2011 • Gamucci 2014

Factor	Prognostic factor or treatment effect modifier	Comparator studies in which factor is reported
		• Barni 2019 • Fumoleau 2004 • Blum 2001 • Sim 2019
ECOG-PS (0/1+)	• Prognostic factor	• Barni 2019 • Cortes 2010 • Cortes 2011 • Fumoleau 2004 • Sim 2019
Brain metastases (yes/no)	• Treatment effect modifer	• Barni 2019
Prior endocrine therapy (yes/no)	• Prognostic factor	• Gamucci 2014 • Blum 2001

Abbreviations: HR: hormone receptor; T-DM1: Trastuzumab emtansine; BC: breast cancer; HER2: Human epidermal growth factor 2; mBC: metastatic breast cancer.

B.2.9.4 Data extraction and variable generation

Individual patient-level data were obtained from DESTINY-Breast01, and relevant characteristics and outcomes were abstracted for the analysis dataset. This included the baseline characteristics that were also available in the comparator studies of interest and their eligibility criteria.

Table 17 shows the baseline characteristics of studies used in the MAICs.

Table 17: Comparison of baseline characteristics used in MAIC

	T-DXd unadjusted (DESTINY-Breast01)	Barni 2019 (eribulin)	Blum 2001 (capecitabine)	Cortes 2010 (eribulin)	Cortes 2011 (EMBRACE) (eribulin)	Fumoleau 2004 (capecitabine)	Gamucci 2014 (eribulin)	Sim 2019 (vinorelbine)
N	184	95	74	269	508	126	133	74
Age Mean/ median <55 years (%)	 56.0 47.8	 59.5 -	 52.5 -	 56 -	 55 -	 54 -	 62 -	 52 -
ECOG-PS = 0 (%)	55.4	40.9†	-	37.2	42.7†	43.7†	-	25.7
Prior pertuzumab treatment = yes (%)	65.8	-	-	-	-	-	-	-
Prior hormone therapy = yes (%)	48.9	-	70.2	-	85.0	-	69.2	-
Prior treatment lines Mean prior lines Prior lines ≥3 (%) Treatment lines prior to T-DM1 <2 (%)	 6.6 91.8 18.5	 - - -	 - - -	 - - -	 - - -	 - - -	 - - -	 - 100 -
Prior chemo lines ≥3 (%)	-	64.6	66.2	89.6	87.0	45.2	50.4	-
HR + ‡ (%)	52.7†	-	-	71.0	64.4†	-	84.0	45.9
Visceral disease = yes (%)	91.8	59.4	79.7	-	-	-	80.5	50.0
Brain metastases = yes (%)	13.0	¶	-	-	-	-	-	-
Other comments	-	-	-	-	-	-	-	100% prior trastuzumab

Abbreviations**:** ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; N, sample size; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; HR+, hormone recptor positive %.

† missing data counted as no/negative in calculation of %

‡oestrogen receptor positive and/or progesterone receptor positive (does not include HER2+/OR-ve/PgR -ve patients)

¶1.2% had brain metastases only, which does not match the variable from DESTINY which includes any brain metastases.

B.2.9.5 Matching average baseline characteristics between T-DXd and comparators

The MAIC approach was applied separately for the comparisons of T-DXd vs each comparator, by study. Average baseline characteristics were matched for the T-DXd patients and trial populations from each relevant comparator study. Individual patients in the DESTINY-Breast01 trial were assigned weights such that a) their weighted mean baseline characteristics match those reported for patients in the comparator trial; b) each individual patients' weight was equal to one's estimated odds of being in the given trial of comparator of interest vs DESTINY-Breast01. Weights were obtained from a logistic regression model, with baseline characteristics used for matching included as predictors in the model. A method of moments was utilised to allow a propensity score logistic regression model to be estimated without IPD for the comparative trial. For each MAIC analysis, outcomes were compared post-matching between T-DXd and the comparator study of interest. The robustness of the analyses was also considered by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate.[77] A small ESS is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable.

To account for the fact that weights are estimated rather than fixed and known, standard errors for the MAIC estimates were calculated using a bootstrap estimator.[77]

The use of a bootstrap estimator is intuitively appealing; weights are estimated and subject to sampling uncertainty, and bootstrapping can quantify this. Bootstrapping was performed using the following algorithm:

- T-DXd treated patients were sampled with replacement (a bootstrap dataset)
- For each bootstrap dataset, a set of weights was derived using the methodology described as above
- For each bootstrap dataset and corresponding set of weights, the relative treatment effect was estimated using a Cox proportional hazards model to estimate a weighted hazard ratio (HR) for T-DXd relative to comparator treatments.

This procedure was repeated a sufficiently large number of times to obtain a distribution of estimates for which the 2.5th and 97.5th percentile was used to generate the limits of a confidence interval.

B.2.9.6 Results from MAIC analyses

B.2.9.6.1 T-DXd vs eribulin

Four separate MAIC comparisons were made to compare T-DXd with eribulin.

Cortes 2011

To compare T-DXd with eribulin, weights were estimated relative to the Cortes 2011 population baseline characteristics. Table 18 presents the DESTINY-Breast01 (unadjusted and weighted) and Cortes 2011 baseline characteristics for the five matching variables. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3), percentage of prior hormone therapy and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a moderate ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had similar mean age, higher proportion of ECOG-PS 0 status, a higher number of prior lines, lower percentage of prior hormone therapy and lower proportion with hormone receptor positive status compared with the Cortes 2011 study.

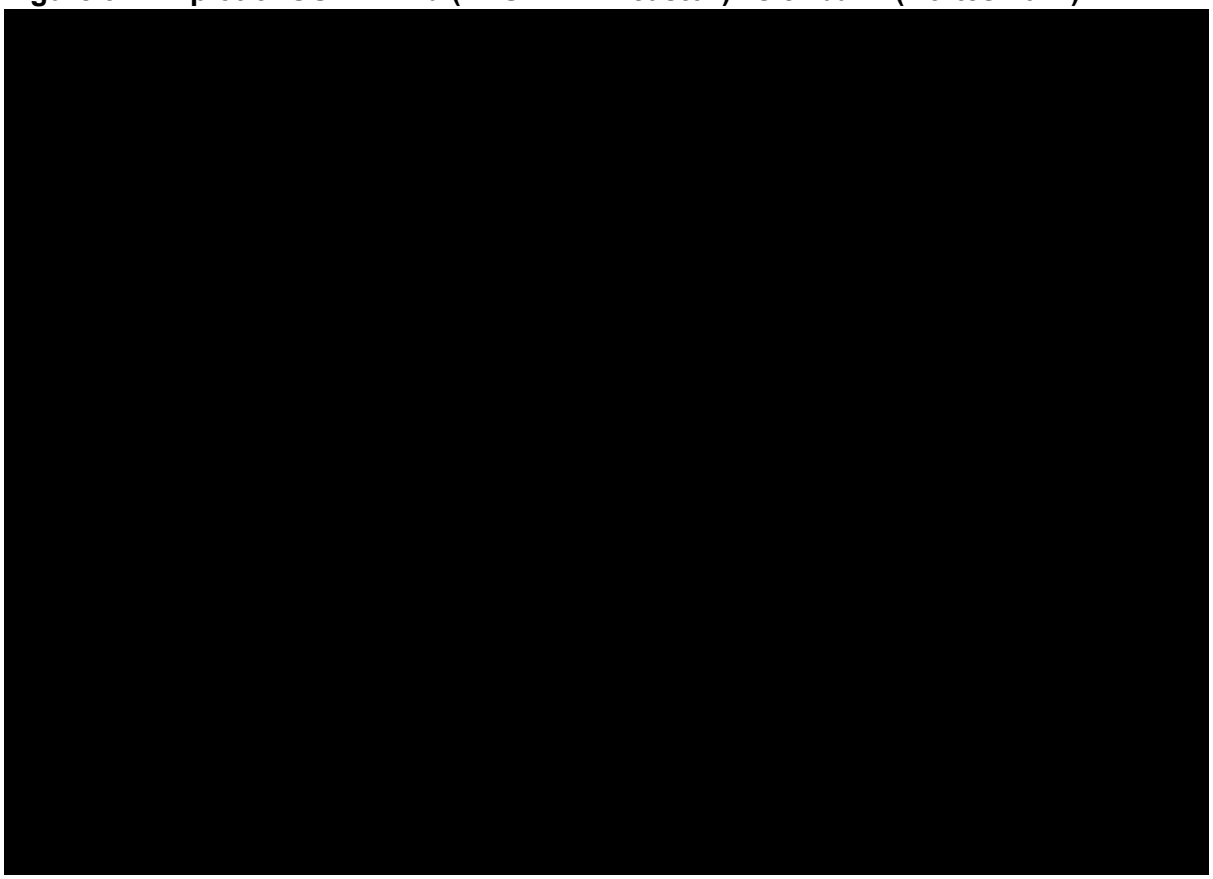
Table 18: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Mean/ median age	Percent ECOG= 0	Percent prior hormone therapy	Percent prior line ≥3	Percent hormone receptor positive
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	48.9	91.8	52.7
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	55.00	42.7	85.0	87.0	64.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 9. The KM plots show that weighting has resulted in only a very small improvement in OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm (Table 19). Table 20 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR [redacted]).

Figure 9: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)



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

Table 19: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	274	13.10 (12.10 to 14.60)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 20: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

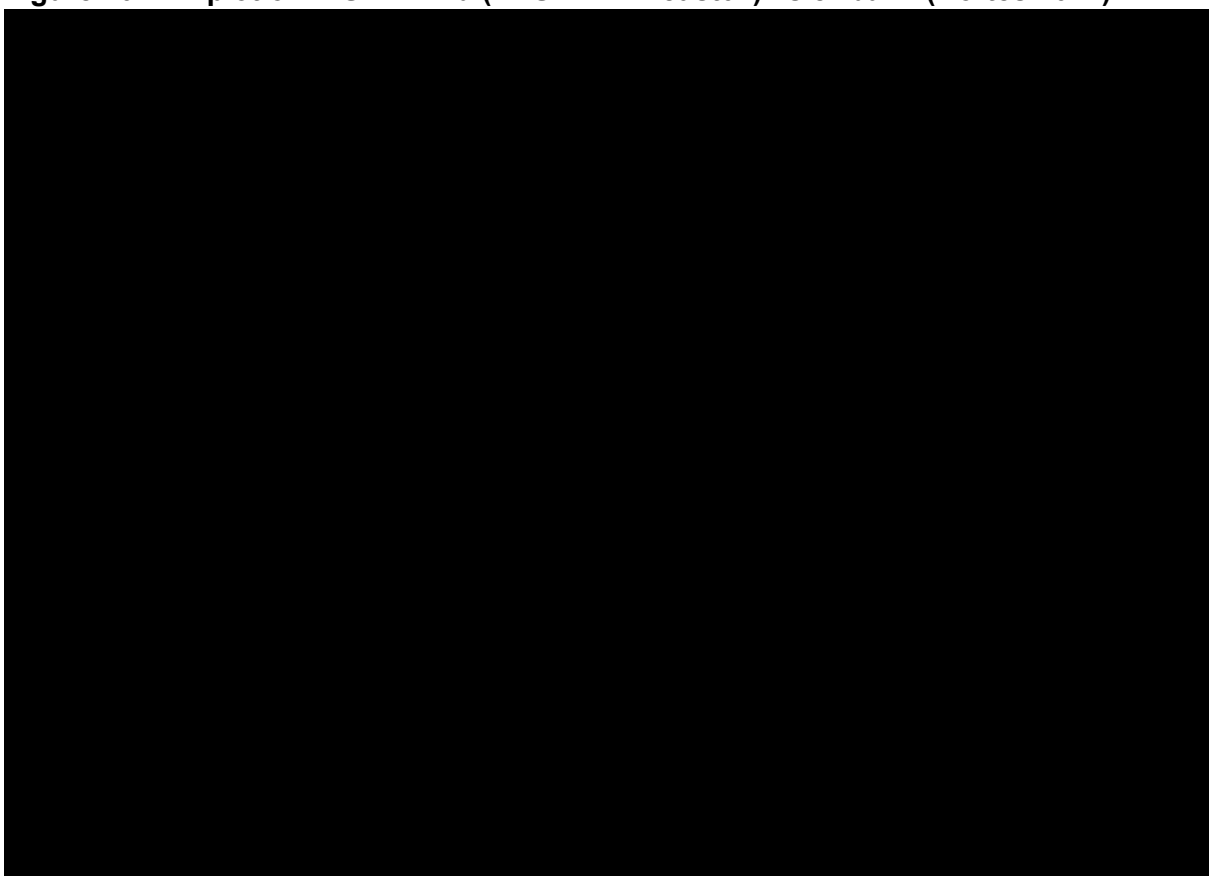
Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 10. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm, the median survival time did not change before and after weighting (Table 21). Table 22 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The proportional

hazard assumption was violated for the matching PFS curves (see Schoenfeld test and residuals plot in Appendix D). The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 10: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)



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

Table 21: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	357	3.66 (3.26 to 3.81)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 22: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 23 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 18. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 23: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Barni 2019

To compare T-DXd with eribulin, weights were estimated relative to the Barni 2019 population baseline characteristics. Table 24 presents the DESTINY-Breast01 (unadjusted and weighted) and Barni 2019 baseline characteristics for the four variables available for matching. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3) and visceral disease status. The ESS after matching was n=[redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had slightly younger mean age, higher proportion of ECOG-PS 0 status, a higher proportion with ≥3 prior lines and higher proportion with visceral disease than those in the Barni 2019 study.

Table 24: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3	Percent visceral Y
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8	91.8

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3	Percent visceral Y
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	95.0	59.50	40.9	64.6	59.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 11. The KM plots show that weighting has resulted in improved OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm as would be expected given that the original DESTINY-Breast01 data did not reach median OS (Table 25). Table 26 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted].

Figure 11: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

[redacted]

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

Table 25: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	100.0	65	10.81 (8.92 to 12.01)

Abbreviations**:** ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

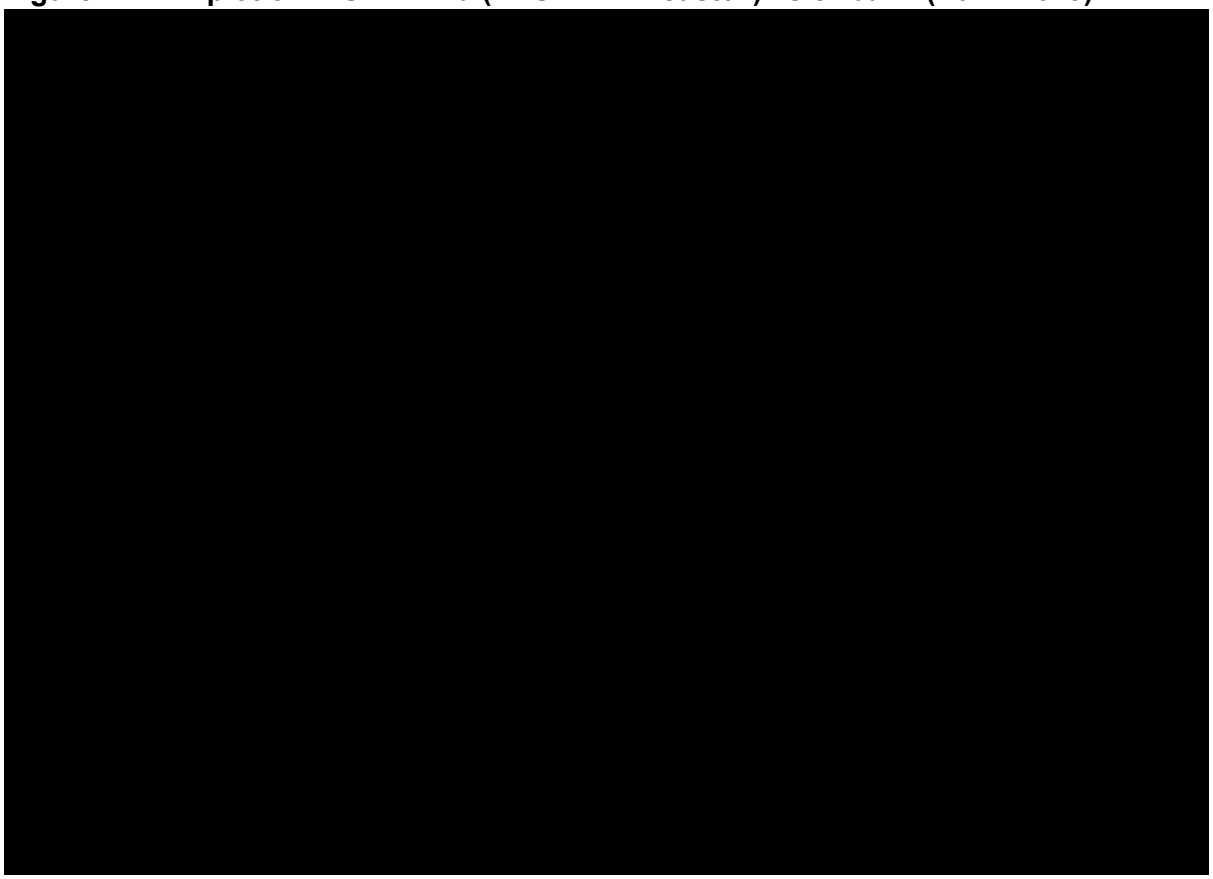
Table 26: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations : T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 12. The KM plots show that weighting has resulted in improved PFS outcomes for the T-DXd arm; the median PFS is not reached for the weighted T-DXd arm (Table 27). Table 28 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 12: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)



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

Table 27: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	95.0	79	3.28 (2.72 to 3.94)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 28: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 29 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 24. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 29: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Cortes 2010

To compare T-DXd with eribulin, weights were estimated relative to the Cortes 2010 population baseline characteristics. Table 30 presents the DESTINY-Breast01 (unadjusted and weighted) and Cortes 2010 baseline characteristics for the four matching variables. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3) and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a relatively large ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had very similar mean age, higher proportion of ECOG-PS 0 status, a similar proportion with ≥3 prior lines and lower proportion with hormone receptor positive status compared with the Cortes 2010 study.

Table 30: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3	Percent hormone receptor positive
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8	52.7
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	56.00	37.2	89.6	71.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 13. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm, with near-identical estimates; the median OS is not reached for the weighted T-DXd arm (Table 31). Table 32

presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 13: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

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

Table 31: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	191	10.40 (9.30 to 11.50)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 32: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 14. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm (Table 33). Table 34 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 14: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

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

Table 33: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	224	2.67 (2.30 to 3.15)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 34: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 35 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 30. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 35: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Gamucci 2014

To compare T-DXd with eribulin, weights were estimated relative to the Gamucci 2014 population baseline characteristics. Table 36 presents the DESTINY-Breast01 (unadjusted and weighted) and Gamucci 2014 baseline characteristics for the five matching variables. Matching was based on mean age, prior treatment lines (<3/≥3), percentage of prior hormone therapy, percentage of visceral disease and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a very small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had a younger mean age, a higher proportion with ≥3 prior lines, lower percentage of prior hormone therapy, lower proportion with hormone receptor positive and a higher percentage of visceral disease compared with the Gamucci 2014 study.

Table 36: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Mean/ median age	Percent prior hormone therapy	Percent prior line ≥3	Percent hormone receptor positive	Percent visceral Y

T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	48.9	91.8	52.7	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	62.00	69.2	50.4	84.0	80.5

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 15. The KM plots show that weighting has resulted in improved OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm and eribulin arm (Table 37). Table 38 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 15: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

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

Table 37: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	46	NA (11.66 to NA)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval

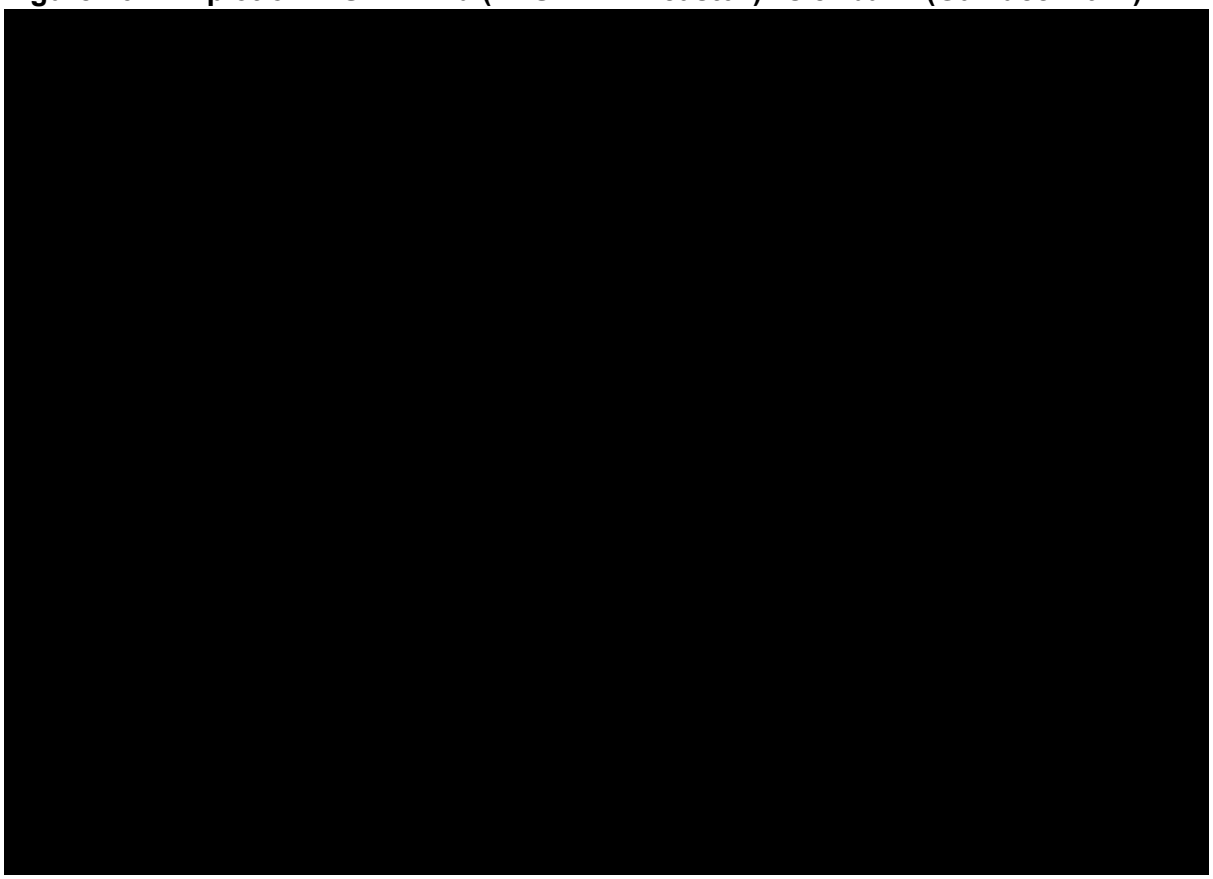
Table 38: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 16. The KM plots show that weighting has resulted in improved PFS outcomes for the T-DXd arm, the median survival time did not change before and after weighting (Table 39). Table 40 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 16: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)



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

Table 39: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	115	4.45 (3.78 to 5.24)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 40: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 41 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 36. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 41: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

B.2.9.6.2 T-DXd vs capecitabine

Fumoleau 2004

To compare T-DXd with capecitabine, weights were estimated relative to the Fumoleau 2004 population baseline characteristics. Table 42 presents the DESTINY-Breast01 (unadjusted and weighted) and Fumoleau 2004 baseline characteristics for the three matching variables. Matching was based on mean age, ECOG-PS and prior treatment lines (<3/≥3). The ESS after matching was [redacted] This is a relatively small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had older mean age, higher proportion of ECOG-PS 0 status and a higher proportion with ≥3 prior lines compared with the Fumoleau 2004 study.

Table 42: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)	126.0	54.00	43.7	45.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 17. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm; the median OS is

not reached for the weighted T-DXd arm (Table 43). Table 44 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 17: KM plot of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

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

Table 43: KM summary of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)	126.0	81	15.80 (13.40 to 19.60)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 44: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]

Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 18. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm; the median PFS is not reached for the weighted T-DXd arm (Table 45). Table 46 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 18: KM plot of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

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

Table 45: KM summary of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]

Capecitabine (Fumoleau 2004)	126.0	110	4.90 (3.96 to 6.48)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 46: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 47 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 42. T-DXd demonstrates significantly improved outcomes for response compared with capecitabine.

Table 47: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
DCR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Blum 2001

To compare T-DXd with capecitabine, weights were estimated relative to the Blum 2001 population baseline characteristics. Table 48 presents the DESTINY-Breast01 (unadjusted and weighted) and Blum 2001 baseline characteristics for the four matching variables. Matching was based on mean age, percentage of prior hormone therapy, percentage of visceral disease and prior treatment lines (<3/≥3). The ESS after matching was [redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial compared with the Blum 2001 study had older mean age, lower proportion of

previous hormone therapy, higher proportion with ≥3 prior lines and higher percentage of visceral Y.

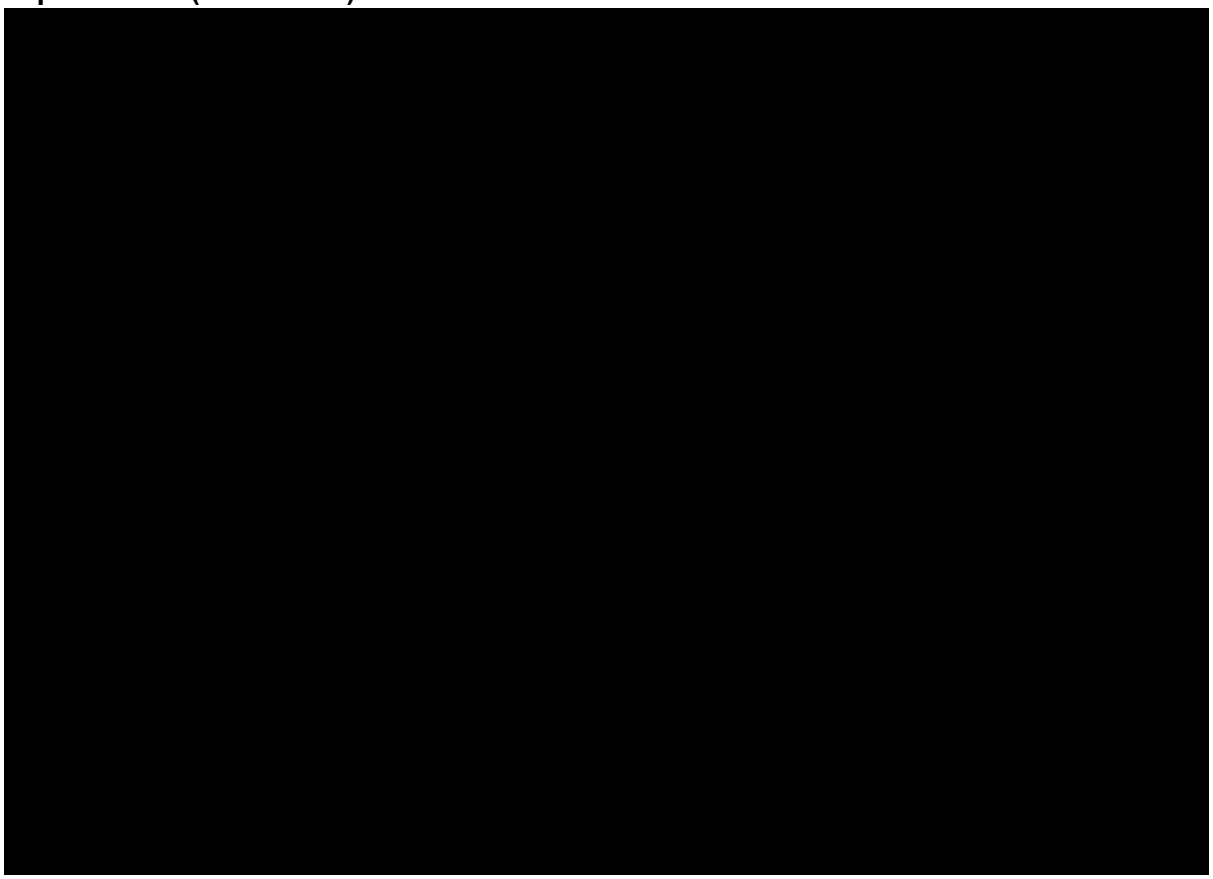
Table 48: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Treatment (study)	N/ ESS	Mean/ median age	Percent prior hormone therapy	Percent prior line ≥3	Percent visceral Y
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	48.9	91.8	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	52.50	70.2	66.2	79.7

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 19. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm (Table 49). Table 50 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 19: KM plot of OS - T-DXd (Destiny Breast 01DESTINY-Breast01) vs capecitabine (Blum 2001)



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

Table 49: KM summary of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	25	NA (NA to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	48	12.19 (7.66 to 15.24)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

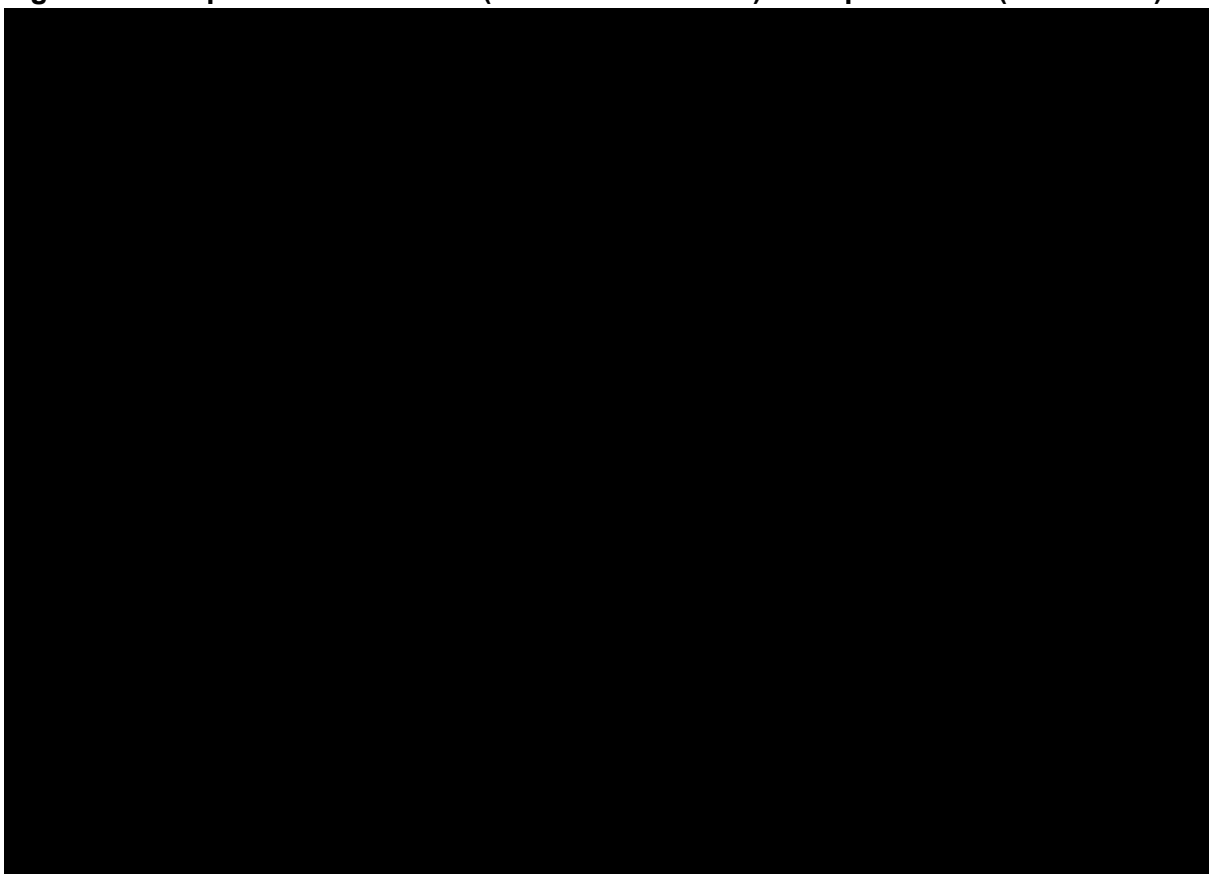
Table 50: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 20. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm; the median PFS is not reached for the weighted T-DXd arm (Table 51). Table 52 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 20: KM plot of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)



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

Table 51: KM summary of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	70	3.20 (2.38 to 4.34)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 52: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 53 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 48. T-DXd demonstrates significantly improved outcomes for response compared with capecitabine.

Table 53: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
DCR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

B.2.9.6.3 T-DXd vs vinorelbine

Sim 2019

To compare T-DXd with vinorelbine, weights were estimated relative to the Sim 2019 population baseline characteristics. Table 54 presents the DESTINY-Breast01 (unadjusted and weighted) and Sim 2019 baseline characteristics for the four matching variables. Matching was based on ECOG-PS, prior treatment lines (<3/≥3), percent hormone receptor positive, and percent visceral. Mean age was available from the Sim study but was removed from the analysis (see Section B.2.9.3). The ESS after matching was [redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had a higher proportion of ECOG-PS 0 status, lower proportion with ≥3 prior lines,

higher percentage of hormone receptor positive and higher percent of visceral disease compared with the Sim 2019 study.

Table 54: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Percent ECOG= 0	Percent prior line ≥3	Percent hormone receptor positive	Percent visceral Y
T-Dxd unadjusted (DESTINY-Breast01)	184.0	55.4	91.8	52.7	91.8
T-Dxd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	25.7	100.0	45.9	50.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in **Figure** 21. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm (Table 55). Table 56 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd did not demonstrate significantly greater improvements in OS compared with patients receiving vinorelbine, with large uncertainty around the point estimate, probably due to the small ESS (weighted HR: [redacted]). Note that from visual inspection of the KM curves the proportional hazards assumption of matching curves is violated.

OS data from the Sim study were presented to clinical experts at an advisory board and were not considered to be clinically plausible (see Section B.3.3.1.2 for further details). These results should therefore be interpreted with caution.

Figure 21: KM plot of OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

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

Table 55: KM summary of OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-Dxd unadjusted (Destiny Breast 01)	184.0	25	NA (NA to NA)
T-Dxd weighted (Destiny Breast 01)	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	53	18.87 (13.29 to 29.13)

Abbreviations: ESS, effective sample size; N, sample size;T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 56: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-Dxd vs Vinorelbine	[redacted]
Weighted standard CI	T-Dxd vs Vinorelbine	[redacted]
Weighted bootstrapped CI	T-Dxd vs Vinorelbine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 22. The KM plots show that weighting has not resulted in significantly improved PFS outcomes for the T-DXd arm (Table

57). Table 58 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving vinorelbine (weighted HR: [redacted]).

Figure 22: KM plot of PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

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

Table 57: KM summary of PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	58	16.36 (15.21 to 18.07)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	65	2.73 (2.51 to 4.22)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 58: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs vinorelbine	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 59 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 61 . T-DXd demonstrates significantly improved outcomes for response compared with vinorelbine.

Table 59: Odds ratio for ORR and CBR – T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs vinorelbine	[redacted]
	Weighted GLM model	T-DXd vs vinorelbine	[redacted]
	Weighted sandwich estimator	T-DXd vs vinorelbine	[redacted]
CBR	Unadjusted	T-DXd vs vinorelbine	[redacted]
	Weighted GLM model	T-DXd vs vinorelbine	[redacted]
	Weighted sandwich estimator	T-DXd vs vinorelbine	[redacted]

Abbreviations: CBR, clinical benefit rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

The above analyses are associated with uncertainty due to small sample sizes, trial heterogeneity and the differences in prognostic factors available from each study. In addition, OS data from DESTINY-Breast01 were immature, with a KM estimator of approximately 80% patients alive at the last data cut. Therefore, the results should be interpreted with caution.

In addition, an unanchored MAIC assumes that the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and treatment effect modifiers, which sometimes can be too strong an assumption. Matching adjustments were limited to data reported in the comparator trials and that collected in DESTINY-Breast01. It was not possible to adjust for differences in HER2 status between the studies, given that 100% of patients in DESTINY-Breast01 were HER2-positive. It was therefore necessary to make subsequent adjustments in the cost-effectiveness model (see Section B.3.3.4). Extensive efforts were sought in this series of MAICs to ensure that as many confounding factors were adjusted for as possible, but the consequence was small sample sizes. In addition, it was noted at the August advisory board that both young and old age are associated with worse prognosis in mBC, and so age may not be a reliable matching factor[59].

In the absence of KM data for TTD in the comparator studies, it was not possible to conduct MAIC analyses on this outcome. The only available data for vinorelbine are from the Sim

2019 study; OS data from this study were considered to be clinically implausible by clinical experts at the August advisory board (see Section B.3.3.1.2 for further details).

In the absence of more robust comparative studies, these data provide a directional indication of the relative benefit of T-DXd with respect to comparators. This technique circumvented existing data limitations for the treatments that prevented construction of network meta-analyses for the outcomes of interest.

B.2.10 Adverse reactions

The safety of T-DXd in patients with HER2+ uBC or mBC after two or more anti-HER2 therapies was evaluated in the DESTINY-Breast01 study and the DS8201-A-J101 study.

B.2.10.1 Key trial: DESTINY-Breast01

The data presented from the DESTINY-Breast01 study are from the 90-day update data-cut (1 August 2019), as reported in the primary publication (Modi 2020).[62] Please note that the safety data in the CSR corresponds to the primary data cut-off date (21 March 2019, minimum 6 months of follow-up after last subject enrolled).[66] Compared with safety data at primary data-cut, safety data at the 90-day safety update showed no significant changes in most of the TEAE parameters, and no new safety signals were observed.[70]

TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Potential episodes of ILD were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE.

B.2.10.1.1 Exposure to study drug

At the data-cut of 1 August 2019 in the overall 5.4 mg/kg dose cohort, 79/184 (42.9%) patients were still on treatment with T-DXd (Table 60). The median treatment duration was 10 months (range, 0.7 to 20.5). The median relative dose intensity (i.e. the ratio of the amount of drug delivered to the planned dose delivered) was 97.6%. The median total number of cycles initiated was 14 (range, 1 to 29).

Table 60: DESTINY-Breast01: Study drug exposure

	T-DXd 5.4 mg/kg (Part 1+2a and 2b) (N=184)
Subjects on treatment, n (%)	79 (42.9)

Median treatment duration, months (range)	10.00 (0.7–20.5)
Mean dose intensity (SD)	5.02 (0.584)
Median relative dose intensity, % (range)	97.60 (46.1–103.7)
Median total number of cycles initiated (range)	14.0 (1–29)
Subjects who completed following treatment period, n (%)	
≤3 months	28 (15.2)
>3 to ≤6 months	28 (15.2)
>6 to ≤9 months	26 (14.1)
>9 to ≤12 months	52 (28.3)
>12 to ≤24 months	50 (27.2)

Abbreviations, SD, standard deviation; T-DXd, trastuzumab deruxtecan.
Data-cut: August 1, 2019
Source: Daiichi-Sankyo, Inc., 2019 (data on file)[70,97]

B.2.10.1.2 Treatment-emergent adverse events

A summary of TEAEs reported in patients who received the recommended dose of T-DXd of 5.4 mg/kg in the DESTINY-Breast01 study are shown in Table 61.

Table 61: DESTINY-Breast01: Summary of treatment-emergent adverse events

Type of TEAE, n (%)[†]	**T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)**
TEAEs	183 (99.5)
Drug-related TEAEs	183 (99.5)
TEAEs Grade ≥3	105 (57.1)
Drug-related TEAEs Grade ≥3	89 (48.4)
Serious TEAEs	42 (22.8)
Drug-related serious TEAEs	23 (12.5)
TEAEs leading to T-DXd discontinuation	28 (15.2)
Drug-related TEAEs leading to T-DXd discontinuation	27 (14.7)
TEAEs leading to dose reduction	43 (23.4)
Drug-related TEAEs leading to dose reduction	40 (21.7)
TEAEs leading to dose interruption	65 (35.3)
Drug-related TEAEs leading to dose interruption	53 (28.8)
TEAEs leading to death	9 (4.9)
Drug-related TEAEs leading to death	2 (1.1)

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan
[†]TEAE relationship to study drug was determined by the treating investigator
Data-cut: August 1, 2019
Source: Modi 2020 (Supplementary Table S3)[62]

Of the 184 patients who received the recommended dose of T-DXd, 183 (99.5%) patients experienced at least one TEAE, with 183 (99.5%) patients reporting at least one study drug-related TEAE per investigator assessment.[62]

Overall, 105 (57.1%) patients experienced ≥Grade 3 TEAEs, with 89 (48.4%) patients having at least one study drug-related ≥Grade 3 TEAE based on investigator assessment.[62]

Treatment-emergent serious adverse events (SAEs) were reported in 42 (22.8%) patients, with 23 (12.5%) patients having at least one study drug-related treatment-emergent SAE based on investigator assessment.[62] The most common treatment-emergent SAEs were vomiting in 4 (2.2%) patients, and nausea, pneumonia, cellulitis, intestinal obstruction, pleural effusion and pneumonitis, which were each reported in 3 (1.6%) of patients.[70]

TEAEs led to a dose interruption in 65 patients (35.3%) and to a dose reduction in 43 patients (23.4%); 28 patients (15.2%) discontinued treatment because of a TEAE. TEAEs that led to discontinuation in at least 2 patients included pneumonitis (in 11 patients) and ILD (in 5 patients).[62]

Overall, 9 (4.9%) patients had TEAEs associated with a fatal outcome on-study (defined as occurring on or after first dose until 47 days after last dose), with 2 (1.1%) patients having at least one study drug-related TEAE associated with a fatal outcome on-study based on investigator assessment. Overall, a total of 25 deaths (any death) were reported in patients treated with 5.4 mg/kg T-DXd, including 7 that occurred during treatment as a result of either disease progression (in 3 patients) or TEAEs (haemorrhagic shock, general physical health deterioration, pneumonia, and acute organ failure in 1 patient each).[62] During survival follow-up (which was defined as 47 days after the end of treatment), 18 of the 25 deaths occurred, 2 of which were caused by events associated with ILD that started during treatment and are among those described below (TEAEs of special interest: Section B.2.10.1.4); the remaining 16 deaths were considered by investigators to be unrelated to T-DXd.[62]

B.2.10.1.3 Most common treatment-emergent adverse events

A summary of TEAEs experienced by ≥10% of patients treated with 5.4 mg/kg T-DXd by CTCAE grade in order of decreasing frequency is presented in Table 62. Select TEAEs by cycle are shown in Table 63.

Table 62: DESTINY-Breast01: Treatment-emergent adverse events according to CTCAE grade experienced by ≥10% of the population treated with T-DXd 5.4 mg/kg

TEAE, n (%)	Any Grade	Grade 3	Grade 4
Any TEAE	**183 (99.5)**	**89 (48.4)**	**7 (3.8)**
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anaemia	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhoea	54 (29.3)	5 (2.7)	0
Decreased white-cell count	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count	26 (14.1)	11 (6.0)	1 (0.5)
Dyspnoea	27 (14.7)	3 (1.6)	0
Stomatitis	27 (14.7)	2 (1.1)	0
Aspartate aminotransferase increased	26 (14.1)	2 (1.1)	0
Asthenia	26 (14.1)	2 (1.1)	0
Dyspepsia	26 (14.1)	0	0
Interstitial lung disease	25 (13.6)	1 (0.5)	0
Epistaxis	24 (13.0)	0	0
Dry eye	21 (11.4)	0	1 (0.5)
Hypokalaemia	21 (11.4)	6 (3.3)	0
Upper respiratory tract infection	20 (10.9)	0	0

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Source: Modi 2020 (Supplementary Table S5)[62]

Table 63: DESTINY-Breast01: Select TEAEs by cycle in patients who received T-DXd 5.4 mg/kg (N=184)

n (%)	Cycle								
	1	2	3	4	5	6	7	≥8	≥18
Nausea	120 (65.2)	51 (27.7)	37 (20.1)	29 (15.8)	17 (9.2)	20 (10.9)	14 (7.6)	30 (16.3)	3 (1.6)
Vomiting	50 (27.2)	27 (14.7)	21 (11.4)	12 (6.5)	13 (7.1)	7 (3.8)	8 (4.3)	23 (12.5)	3 (1.6)
Fatigue	54 (29.3)	21 (11.4)	13 (7.1)	7 (3.8)	8 (4.3)	7 (3.8)	6 (3.3)	23 (12.5)	3 (1.6)
Constipation	29 (15.8)	15 (8.2)	8 (4.3)	7 (3.8)	9 (4.9)	3 (1.6)	3 (1.6)	15 (8.2)	--
Diarrhoea	21 (11.4)	13 (7.1)	4 (2.2)	5 (2.7)	5 (2.7)	2 (1.1)	5 (2.7)	20 (10.9)	2 (1.1)
Decreased appetite	33 (17.9)	9 (4.9)	6 (3.3)	11 (6.0)	3 (1.6)	3 (1.6)	6 (3.3)	9 (4.9)	--

Source: Daiichi-Sankyo, Inc., 2019 (data on file)[98]

Gastrointestinal and haematologic toxic effects were the most common TEAEs. Among the gastrointestinal events, nausea was the most frequently reported TEAE (143 [77.7%] patients at 5.4 mg/kg);[62] events of nausea were mostly Grade 1 (41.3% patients) or Grade 2 (28.8% patients), occurring most frequently in the first 2 cycles (Table 63). [98] The events were manageable under routine medical practice without a need for treatment discontinuation.[66] Available concomitant medications data did not allow for distinction between premedication for and management of nausea.[66] Similarly, most of the events of diarrhoea were Grade 1 (17.4% patients) or Grade 2 (9.2%), and were most commonly reported in the first 2 cycles (Table 63).[98]

Among the haematologic events, neutrophil count decrease, anaemia, white blood cell count decreased, and platelet count decrease were the most frequently reported TEAEs (64 [34.8%], 55 [29.9%], 39 [21.2%], and 39 [21.2%] patients, respectively, at 5.4 mg/kg).[62] They were mostly Grade 1 or Grade 2, occurred most frequently in the first 2 cycles, and were manageable under routine medical practice without a need for treatment discontinuation.[66]

The most common TEAEs of Grade 3 or higher that occurred in more than 5% of the patients were a decreased neutrophil count (in 20.7%), anaemia (in 8.7%), nausea (in 7.6%), a decreased white-cell count (in 6.5%), a decreased lymphocyte count (in 6.5%), and fatigue (in 6.0%); 3 patients (1.6%) had febrile neutropenia.[62]

B.2.10.1.4 Treatment-emergent adverse events of special interest

TEAEs of special interest in patients treated with T-DXd 5.4 mg/kg are shown in Table 64.

Table 64: DESTINY-Breast01: Treatment-emergent adverse events of special interest in patients treated with T-DXd 5.4 mg/kg

TEAE, n (%)	Any Grade	Grade 3	Grade 4
Interstitial lung disease†	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased LVEF‡	3 (1.6)	1 (0.5)¶	0

Abbreviations: LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.
†The presence of interstitial lung disease was determined by an independent adjudication committee, since the condition has been associated with trastuzumab deruxtecan. Four patients who had Grade 5 events are included in the category of any Grade.
‡ The LVEF was measured on echocardiography or multigated acquisition scans every four treatment cycles.
¶ In this patient, the LVEF was more than 55% during treatment.
Data-cut: August 1, 2019
Source: Modi 2020[62]

A decrease in the LVEF occurred in 3 patients (2 with Grade 2 and 1 with Grade 3); all the patients were asymptomatic and had recovered or were recovering after an interruption in the study treatment.[62] No events of cardiac failure associated with the decrease in the ejection fraction were reported. No patients had an ejection fraction of less than 40% or a decrease from baseline of 20% or more, and no patients discontinued treatment because of a decrease in the ejection fraction.

Infusion-related reactions were reported in 4 patients, all of which were Grade 1 or 2. Prolonged QT interval was reported in nine patients, with 2 (1.1%) patients having a grade 3 event (Table 64).

An independent ILD adjudication committee (AC) was responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection was to be conducted for all cases that were brought for adjudication. These additional data collections covered a more in-depth relevant medical history (e.g., smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection was triggered for AEs reported using MedDRA selected preferred terms (PTs) from the ILD standardised MedDRA query (SMQ) that were recommended and approved by the ILD AC; per the ILD AC Charter, a list of 44 PTs in total was selected for adjudication.[66]

Overall, 25 patients (13.6%) had ILD related to the receipt of T-DXd, as determined by an independent adjudication committee.[62] These events were primarily CTCAE Grade 1 or 2 (10.9%); 1 patient (0.5%) had a Grade 3 event, and no patients had a Grade 4 event. Four deaths (2.2% of the patients) were attributed to ILD by independent adjudication and were initially reported as respiratory failure, acute respiratory failure, lymphangitis, and pneumonitis in one patient each by the treating investigators; the primary cause of death was reported as disease progression (in 2 patients) and adverse events during survival follow-up (in 2 patients). Among the investigator-reported cases of ILD of any Grade, the median time until the onset of lung disease was 193 days (range, 42 to 535). At the time of the data cut-off, 7 patients with ILD had recovered, 2 were recovering, 10 had ongoing ILD, and 4 had died; status was unknown for 2 patients. Among the patients with investigator reported ILD, the median duration from the date of onset to the date of recovery was 34 days (range, 3 to 179). Of the 20 patients who were reported to have interstitial lung disease of Grade 2 or higher, 13 received glucocorticoids and 7 were hospitalised.

B.2.10.2 Supportive trial: Study DS8201-A-J101

The safety analysis set included all HER2+ BC patients who received at least one dose of T-DXd at the recommended doses for expansion (5.4 mg/kg and 6.4 mg/kg).

A summary of TEAEs are shown in Table 65.

Table 65: Study DS8201-A-J101: Summary of treatment-emergent adverse events

Type of TEAE, n (%)	T-DXd 5.4 mg/kg (N=49)	T-DXd 6.4 mg/kg (N=66)
TEAEs	49 (100%)	66 (100%)
Drug-related TEAEs	48 (98%)	65 (98%)
TEAEs Grade ≥3	19 (39%)	38 (58%)
Serious TEAEs	8 (16%)	14 (21%)
Drug-related serious TEAEs	4 (8%)	9 (14%)
Grade ≥3	6 (12%)	12 (18%)
TEAEs leading to T-DXd discontinuation	2 (4%)	11 (17%)
Drug-related TEAEs leading to T-DXd discontinuation	2 (4%)	11 (17%)
TEAEs leading to dose reduction	4 (8%)	17 (26%)
Drug-related TEAEs leading to dose reduction	3 (6%)	15 (23%)
TEAEs leading to dose interruption	14 (29%)	20 (30%)
Drug-related TEAEs leading to dose interruption	9 (18%)	16 (24%)

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan

Data-cut: August 10, 2018
Source: Tamura 2019 (Supplementary table, pg 13)[63]

All 115 patients had one or more TEAEs of any Grade, 22 (19%) had one or more treatment emergent SAEs, and 57 (50%) had a TEAE of Grade 3 or worse. Drug-related TEAEs leading to treatment discontinuation occurred in 13 (11%) patients, which included ILD or pneumonitis in nine patients as well as organising pneumonia, radiation pneumonitis, radiation necrosis, and anaemia (each in one patient). Drug-related treatment emergent SAEs occurred for 13 (11%) patients. Drug-related treatment emergent SAEs occurring in more than one patient included ILD or pneumonitis (n=4) and vomiting (n=2). At the time of this analysis, there were three deaths due to TEAEs: one from progressive disease and two from pneumonitis. Both cases of pneumonitis were considered drug-related.

A summary of TEAEs according to CTCAE Grade experienced by ≥10% and TEAEs of special interest are shown in Appendix F. Two of the most common classes of TEAEs were gastrointestinal and haematological. No cases of decreased ejection fraction were recorded. Twenty cases of ILD, pneumonitis, or organising pneumonia were reported, six with 5.4 mg/kg (six [12%] of 49) and 14 with 6.4 mg/kg doses (14 [21%] of 66).

B.2.10.3 Safety conclusions

The safety profile in the Phase II DESTINY-Breast01 study was consistent with results from the Phase I DS8201-A-J101 study. Gastrointestinal and haematologic toxic effects were the most common TEAEs, however they were mostly Grade 1 or Grade 2, occurred most frequently in the first two cycles, and were manageable under routine medical practice without a need for treatment discontinuation events.

Other HER2-targeted therapies, such as trastuzumab, T-DM1, and pertuzumab, have been associated with a risk of cardiomyopathy, particularly left ventricular dysfunction.[99,100] In contrast, clinically significant cardiotoxicity was not observed in DESTINY-Breast01 or in the DS8201-A-J101 study.

T-DXd was associated with a risk of ILD (13.6%), which led to death in some patients. In accordance with the study protocol, investigators managed ILD with dose reductions or discontinuations, the administration of glucocorticoids, and supportive care. Education and close monitoring for signs and symptoms of ILD (including fever, cough, or dyspnoea) is recommended for early detection. Risk Minimisation Materials (RMMs) are in development and will be available in early 2021.

B.2.11 Ongoing studies

DESTINY-Breast02 (NCT03523585) is a Phase III, multicentre, randomised, open-label, active-controlled study of T-DXd versus treatment of investigator's choice for HER2+, uBC and/or mBC patients previously treated with T-DM1.[101] This is a global study, with the comparator arm (treatment of investigator's choice) being trastuzumab or lapatinib, both in addition to capecitabine[2].

The primary outcome is PFS based on blinded ICR. [101] Secondary outcomes include OS, ORR, DoR and CBR based on blinded ICR and investigator assessment, and PFS based on investigator assessment. Exploratory endpoints include best percent change in the sum of the diameter of measurable tumours, time to objective response, duration of stable disease, and time to hospitalisation. HRQoL will be assessed based on the EORTC QLQ-C30 and the EORTC QLQ-BR45, and using the EQ-5D-5L health status self-assessment questionnaire. AEs and SAEs will be assessed.

The trial is currently ongoing and recruiting patients, with an anticipated timeframe for study completion of [redacted]

B.2.12 Innovation

A novel therapy that represents a step-change in the treatment of HER2+ u/mBC

The introduction of the HER2 targeted therapy trastuzumab (Herceptin®) transformed care for people with HER2+ BC when it was approved in 1998, as recognised by the prestigious Lasker Awards in 2019.[102] Subsequently developed anti-HER2 agents have even further improved survival, including another monoclonal antibody (pertuzumab) and more recently the ADC T-DM1. However, for patients who have progressed on or after two anti-HER2 therapies, currently available therapies offer little benefit, with patients ultimately progressing and dying of the disease. These patients, who have built up treatment resistance through multiple previous lines of therapy, are particularly difficult to treat, requiring novel therapeutic strategies.[23] T-DXd is a newer ADC designed to deliver optimal antitumour effects (Section B.1.3.4).); these novel features include the potent topoisomerase I inhibitor payload instead of a microtubule inhibitor, and an increased DAR (approximately 8 with T-DXd vs. approximately 3.5 with T-DM1). In addition, the T-Dxd payload hashigh membrane permeability that effects both target tumour cells and the surrounding tumour cells. This is

[2] Note that these treatment combinations are not currently funded in the UK.

independent of the targeting effect of the antibody and so does not require all of the tumour cells to express HER2; this is particularly pertinent because HER2 intratumoural heterogeneity may be involved in the development of resistance to anti-HER2 therapies in BC, particularly to T-DM1.[103] Furthermore, the T-DXd linker provides stability in systemic circulation, potentially limiting off-target toxicity. Overall, T-DXd, with its novel MOA has demonstrated unprecedented efficacy in this patient population. It is anticipated to be the first HER2-targeted treatment specifically indicated for patients who have received two or more anti-HER2 therapies, representing a step-change in the treatment of HER2+ u/mBC.

An innovative therapy for a life-threatening disease with a high unmet need recognised at the regulatory level

T-DXd is being assessed under the

[redacted][104]

The US Food and Drug Administration approved T-DXd under its Breakthrough Therapy and Priority Review programme 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 in the metastatic setting.[105,106] The Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).[107]

T-DXd was approved in Japan for the treatment of patients with HER2 unresectable or recurrent breast cancer after prior chemotherapy under the conditional early approval system. Since initiation in 2017, this approval represents the third ever under this system,[108] which is designed to approve innovative new products conditionally for life-threatening disease that do not currently have an effective treatment modality if the effectiveness and the safety are reasonably assured by the existing clinical data analysis.[109]

A technologically advanced, unique, and effective ADC, designed to overcome the shortcomings of currently approved ADCs

T-DXd is in clinical development for a variety of HER2+ expressing cancers,[47] with the indication in HER2+ uBC or mBC at third-line anticipated to be the first to be approved, representing the culmination of more than a decade of research.[47] Developing ADC-based

therapies is not a straight-forward task – the development of T-DXd has required many years of research requiring novel and sophisticated approaches.[46,47,49,110] While the tremendous promise of ADCs to treat diseases has been known since the 1980s, progress translating these agents into the clinic has been hampered by technological challenges in the development of linkers and payloads, with only a handful achieving regulatory approval.[46,47,49,110] The research team at Daiichi Sankyo Co., set out to overcome identifiable shortcomings of earlier ADCs by rationally designing a technologically advanced, unique, and effective ADC technology, resulting in the creation of the proprietary linker and payload technology with seven key attributes (Section B.1.3.4). The novel features have translated into an efficacious treatment with a manageable safety profile, with the potential to change the treatment landscape in HER2+ mBC, as well as other HER2+ solid tumours.[46,47] In addition, T-DXd is being evaluated in a trial in patients with mBC and low levels of HER2 expression (HER2 low)[111,112], with promising preliminary antitumour activity demonstrated in a Phase I trial.[111]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence base

T-DXd provided clinically meaningful improvements in ORR and PFS in a difficult-to-treat population of patients with uBC or mBC who had received previous treatment with T-DM1.

Overall, 184 patients (median age: 55.0 years [range, 28.0 to 96.0]) who had undergone a median of six previous treatments, received the recommended dose of T-DXd 5.4 mg/kg. At a data-cut of 1 August 2019 (median duration of follow-up 11.1 months [range, 0.7 to 19.9]) T-DXd demonstrated a consistent high level of clinical activity across a range of endpoints:

- Response to therapy was reported in 112 patients (60.9%; 95% CI: 53.4, 68.0) based on ICR
- CR was reported in 11 (6%) patients and PR in 101 (54.9%) patients
- Most patients had a reduction in tumour size while on treatment
- Prespecified subgroup analyses showed consistent responses across demographic and prognostic subgroups including patients who had received previous pertuzumab therapy, hormone receptor status, receipt of T-DXd immediately after initial T-DM1 therapy, number of regimens (≥3 and <3 prior regimens, excluding hormone therapy) and those who had CNS metastases at baseline

  - Patients achieved a confirmed ORR > 50% regardless of the number of prior lines of systemic therapy they received; however, the highest ORR was observed in those who had received only two prior lines
- Median PFS was 16.4 months (95% CI: 12.7, NE)
- Median OS had not been reached
  - Estimated OS was 93.9% (95% CI: 89.3, 96.6) at 6 months and 86.2% (95% CI: 79.8, 90.7) at 12 months
- Median DoR was 14.8 months (95% CI: 13.8, 16.9)
- DCR was 97.3% (95% CI: 93.8, 99.1)
- CBR was 76.1% (95% CI: 69.3, 82.1)
- Median TTR was 1.6 months (95% CI: 1.4, 2.6).
- T-DXd demonstrated efficacy in patients who had a history of CNS metastases at baseline (n=24) that was similar to the overall population: ORR: 58.3% (95% CI: 36.6, 77.9); median PFS: 18.1 months (95% CI: 6.7, 18.1).
- The results validate earlier observations from the Phase I Study DS8201-A-J101, which showed a response of 59.5% (95% CI, 49.7 to 68.7) in a similar patient population.

The safety profile was consistent with results from the Phase 1 DS8201-A-J101 study:

- The most common TEAEs were gastrointestinal and hematologic in nature
- 22.8% had serious TEAEs; 35.3% and 23.4% had a dose interruption or
- dose reduction, respectively, and 15.2% discontinued treatment due to TEAEs
- No events of cardiac failure with LVEF decline were reported
  - No patients had an LVEF of <40% or a decrease of ≥20% at any timepoint
- ILD was observed in a subgroup of patients and requires attention to pulmonary symptoms and careful monitoring
  - ILD events were independently adjudicated and actively managed by patient monitoring, dose modification, and adherence to the ILD management guidelines
  - ILD related to T-DXd was observed in 25 patients (13.6%), primarily grade 1 or 2 (10.9%). Four deaths (2.2%) were attributed to ILD
- There were 9 (4.9%) TEAE-associated deaths (respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock haemorrhagic; 1 patient had two TEAEs associated with death: acute kidney injury and acute hepatic failure)

The results of the MAICs support that the efficacy of T-DXd provides substantial benefits over eribulin, capecitabine and vinorelbine for response, PFS and OS.

Overall, T-DXd is a novel, innovative, targeted monotherapy with a high level of clinical activity and a manageable safety profile, that is expected to result in significant and substantial improvements in health-related benefits for patients with limited alternative treatments.

B.2.13.2 Strengths and limitations of the evidence base

Internal and external validity

Both the DESTINY-Breast01 and DS8201-A-J101 study enrolled a large number of patients in the context of the disease patient population (i.e. HER2+ [estimated at 13–20% of BC cases] uBC or mBC in the third-line setting), which required multicentre, global trials. The DESTINY-Breast01 study included patients from five centres in England (Modi et al 2020, supplementary appendix)[62], with 68 (37%) patients being from Europe.

Overall, 54.9% of patients in the DESTINY-Breast01 trial were white, which is lower than would be expected in England and Wales.[113] In a real-world cross-sectional review of patients with HER2+ mBC conducted between January and April 2016 that included 750 cases in the UK, as well as Italy (1,270 cases), Spain (957 cases) and the Netherlands (91 cases), the median age of patients in the third-line setting was 58.4 years, and 59% were hormone receptor positive.[114] Patients in the DESTINY-Breast01 had a median age of 55.0 years (range, 28.0 to 96.0), with 52.7% being hormone receptor positive, similar to the patients in the real-world study. In addition, clinicians from the UK advisory board meeting conducted on behalf of Daiichi Sankyo in August 2020, agreed that the patient population in DESTINY-Breast01 generally reflected their patients in the ≥ third-line setting, although DESTINY-Breast01 included a higher proportion of patients with ECOG PS 0 (55.4%) than might be expected in clinical practice, where the majority would have ECOG PS 1.[59]

Most patients were heavily pre-treated, with the median number of previous lines of therapy for locally advanced or mBC excluding hormone therapy being 6 (range, 2 to 27). As per protocol, all patients had received prior T-DM1, which is the standard-of-care for second-line in HER2+ mBC in England. Clinicians from the advisory board meeting agreed that the majority of patients with HER2+ u/mBC patients receive T-DM1 at second-line (80-100% of patients across the 4 clinicians), and it is likely that all/the vast majority of patients who would be suitable for treatment with T-DXd would have been previously treated with T-

DM1.[59] In addition, all patients had also received prior trastuzumab, 65.8% of subjects had received prior pertuzumab, and 54.3% had received additional anti-HER2 therapy (not including trastuzumab, pertuzumab, or T-DM1). With this in mind, subgroup analysis demonstrated a consistent ORR in patients who had received previous pertuzumab therapy; pertuzumab, in combination with trastuzumab and is now the standard-of-care for first-line therapy.

DESTINY-Breast01 collected data on a variety of endpoints that are clinically relevant, and also have importance for patients. While this was an open-label study, the endpoints were assessed by blinded ICR. The efficacy of T-DXd was demonstrated consistently across all the endpoints. ORR was the primary endpoint, demonstrating that a large proportion of patients (61%) showed a response, with 6% of patients demonstrating a CR. The key secondary endpoints included PFS and OS. Studies have reported the importance of these endpoints to patients with mBC. In a survey of 94 patients with mBC and 6 carers, 67% of patients/ carers believed life-extending treatment to be important in order to extend time spent with family and friends.[26] Other studies have also reported on the value that patients place on PFS.[34,36] The majority of patients (63%) from a study of 282 US mBC patients indicated they preferred treatments with a longer PFS. Longer PFS was also associated with better emotional well-being, higher overall QoL, and better physical functioning.[36] Concurring with these studies, MacEwan et al also reported that contiguous periods of stable disease/PFS and OS were important factors in treatment decision making among 299 mBC patients, with stable disease allowing patients to proceed with their daily lives in a predictable way.[34]

Limitations

There are currently areas of clinical uncertainty, especially surrounding the immaturity of the survival data from DESTINY-Breast01: at the data-cut of 1 August 2019 (median duration of follow-up 11.1 months [range, 0.7 to 19.9]) median OS had not been reached.[62] Median PFS in the DESTINY-Breast01 trial was 16.4 months (95% CI: 12.7, NE), and of note, several studies in mBC patients have indicated that PFS correlates strongly with OS, including a review of 144 studies involving more than 43,000 patients.[115-118]

Another limitation is the lack of HRQoL data in patients who are receiving T-DXd; HRQoL data are currently being collected as part of the on-going Phase III DESTINY-Breast02 study (Section B.2.11). However, it should also be noted that improved PFS is considered to result in a delay or prevention of the deterioration of QoL.[35,36]

Furthermore, since currently-available evidence for T-DXd in mBC is from the single group, Phase II study DESTINY-Breast01, there is uncertainty regarding the magnitude of benefit compared with standard-of-care. However, the MAICs have provided evidence that the efficacy observed with T-DXd appears to substantially exceed that of capecitabine, vinorelbine and eribulin.

Overall, data from the Phase II DESTINY-Breast01 suggest that T-DXd is expected to result in substantial improvements in health-related benefits. However, due to the clinical uncertainty Daiichi Sankyo considers T-DXd for the treatment of adult patients with HER2+ u/mBC who have received two or more prior anti-HER2 therapies to be a candidate for the CDF. It is anticipated that the CDF would provide the opportunity to address the clinical uncertainty, while providing timely, managed patient access to an innovative and efficacious treatment in this disease area of high unmet need. DESTINY-Breast02 (NCT03523585) is a Phase III, multicentre, randomised, open-label, active-controlled study of T-DXd versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic BC patients previously treated with T-DM1 (Section B.2.11).[101] This is a global study, with the comparator arm (treatment of investigator's choice) being trastuzumab in addition to capecitabine or lapatinib in addition to capecitabine, and therefore there are some limitations regarding the relevance of the comparator arm to standard-of-care in England. However, it is thought that the comparator arms of this study will be able to provide clinical evidence to support a cost-effectiveness analysis for T-DXd.

The trial is currently ongoing and estimated primary completion date [redacted]. Final OS database lock is expected [redacted]. Daiichi Sankyo would also anticipate a complementary approach of CDF data collection from Public Health England via the SACT dataset.

Additionally, Daiichi Sankyo has initiated a project to obtain real-world patient characteristics, treatment patterns and outcomes in 3L HER2+ mBC. Public Health England's (PHE) Cancer Analysis System (CAS) will be used for this analysis. Daiichi Sankyo proposes to update and provide NHS England/NICE with outputs of this study in order to inform CDF outcomes.

B.2.13.3 End-of-life criteria

NICE end-of-life status applies for the current appraisal (Table 66), as:

- T-DXd is indicated for patients with a short life expectancy and high unmet need, with evidence demonstrating that the life expectancy in patients with HER2+ mBC is normally less than 24 months; and
- T-DXd has the prospect of offering an extension to life of more than 3 months versus current treatment in the NHS.

Table 66: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Mean overall survival estimated in the cost-effectiveness model is as follows: • Eribulin: 11.3 months • Capecitabine: 12.8 months • Vinorelbine: 12.8 months	Section B.3.3.1, page 115
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Mean overall survival estimated in the cost-effectiveness model for T-DXd is 56.4 months, resulting in an estimated extension to life of 45.1, 43.5 and 43.5 months compared with eribulin, capecitabine and vinorelbine, respectively.	Section B.3.3.1, page 115

Abbreviations: T-DXd, trastuzumab deruxtecan.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify relevant economic evaluations of treatments for patients with HER2+ mBC in the third-line or later line setting. A detailed description of the review methods and results is reported in Appendix G.

Three studies from 5 publications were identified as eligible. Table 67 presents a summary of the cost-effectiveness studies identified in the SLR.

A quality assessment of the identified studies is also presented in Appendix G.

Table 67: Summary list of published cost-effectiveness studies

Study	Cost year/ currency	Objective	Summary of model	Patient population characteristics (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Delea 2012[119]	2008/ Pound £	To evaluate the cost-effectiveness of lapatinib plus capecitabine versus capecitabine monotherapy or trastuzumab plus capecitabine, in women with HER2+ mBC who have received prior treatment with trastuzumab, from the UK NHS perspective.	Cost-utility analysis (cost per QALY reported) **Type of Model:** A 'partitioned survival analysis' or 'area-under-the curve' model **Time horizon:** All outcomes were evaluated over a 5-year time horizon from the point of entry into the model approximating a lifetime projection. **Cycle length:** A daily cycle length was employed.	Women with HER2+ mBC previously treated with an anthracycline and a taxane (for adjuvant and/or metastatic disease) and trastuzumab (for metastatic disease) (NR)	Lapatinib + Capecitabine: Expected progression-free life-years = 0.664 Expected post-progression life-years = 0.988 Expected overall life-years = 1.652 Expected QALYs = 0.927 Capecitabine: Expected progression-free life-years = 0.428 Expected post-progression life-years = 0.932 Expected overall life-years = 1.360 Expected QALYs = 0.737 Incremental expected progression-free life-years (Lapatinib + Capecitabine vs. Capecitabine): 0.236 Incremental expected post-progression life-years (Lapatinib + Capecitabine vs. Capecitabine): 0.057 Incremental expected overall life-years (Lapatinib +	Total cost in Pound (£) Lapatinib + Capecitabine: 28,816 Capecitabine: 13,985 Incremental cost (Lapatinib + Capecitabine vs. Capecitabine): 14,831	Cost per life-year gained Lapatinib + Capecitabine vs. Capecitabine: £ 50,772 Cost per QALY gained Lapatinib + Capecitabine vs. Capecitabine: £ 77,993 Note: * The cost per QALY gained with Lapatinib + Capecitabine was £59,734 vs. Capecitabine-only when a utility weight equal to that of a healthy woman of the same age (0.85) was assigned to gains in life expectancy with

					Capecitabine vs. Capecitabine): 0.292 Incremental expected QALYs (Lapatinib + Capecitabine vs. Capecitabine): 0.190		combination therapy consistent with NICE advice for evaluation of life-extending end-of-life treatments.
Le 2016[120]	2013/ US dollar $	To identify the general and common Markov models used in modelling cost-effectiveness for advanced breast cancer (ABC) treatment and to examine the impact of using different Markov model structures on cost-effectiveness results in the context of a combination therapy of lapatinib and capecitabine for the treatment of HER2+ ABC.	Cost-utility analysis (cost per QALY reported) **Type of Model:** Markov model (State transition probability model) **Time horizon:** NR **Cycle length:** All 4 models with a 1.5-month cycle length	Patients with HER2+ advanced mBC receiving 3-line therapy (NR)	Markov model 1: Total QALYs Lapatinib + Capecitabine = 0.984 Capecitabine = 0.916 Markov model 2: Total QALYs Lapatinib + Capecitabine = 1.271 Capecitabine = 1.170 Markov model 3: Total QALYs Lapatinib + Capecitabine = 1.088 Capecitabine = 0.932 Markov model 4: Total QALYs Lapatinib + Capecitabine = 1.228 Capecitabine = 1.106 Markov averaging: Total QALYs Lapatinib + Capecitabine = 1.143 Capecitabine = 1.031	Markov model 1: Total cost, $ Lapatinib + Capecitabine = $132,796 Capecitabine = $98,671 Markov model 2: Total cost, $ Lapatinib + Capecitabine = $170,807 Capecitabine = $125,418 Markov model 3: Total cost, $ Lapatinib + Capecitabine = $149,588 Capecitabine = $102,108 Markov model 4: Total cost, $ Lapatinib + Capecitabine = $168,659 Capecitabine = $121,189 Markov averaging: Total cost, $ Lapatinib + Capecitabine = $155,463 Capecitabine = $111,846 Note: Markov model 4: Stable-disease health state	Markov model 1 (Lapatinib + Capecitabine vs Capecitabine): 495,800/QALY Markov model 2 (Lapatinib + Capecitabine vs Capecitabine): 447,308/QALY Markov model 3 (Lapatinib + Capecitabine vs Capecitabine): 303,909/QALY Markov model 4 (Lapatinib + Capecitabine vs Capecitabine): 390,216/QALY Markov averaging (Lapatinib + Capecitabine vs Capecitabine): 389,270/QALY

						(Estimated cost, $) Lapatinib + Capecitabine = 14,430 (Range 11,544–17,316) Capecitabine Alone = 8414 (Range 6731–10,097) Markov model 2: Respond-to-therapy health state (Estimated cost, $) Lapatinib + Capecitabine = 14,430 (Range 11,544–17,316) Capecitabine Alone = 8414 (Range 6731–10,097) Markov models 1, 2, 3, and 4: Disease-progressing health state (Estimated cost, $) Lapatinib + Capecitabine = 7260 (Range 11,544–17,316) Capecitabine Alone = 7606 (Range 6085–9127) Note: The estimated cost in each health state was assumed to vary within 620% of the average costs Source: Le QA, Hay JW. Cost-effectiveness analysis of lapatinib in HER2-positive advanced breast cancer. Cancer. 2009;115:489–98.	

Diaby 2020[121]	2018/ US dollar $	To simulate the cost and effectiveness associated with first-line THP, followed by T-DM1 and lapatinib/ capecitabine for patients newly diagnosed with HER2+ mBC in Taiwan, compared with three other sequencing modalities.	Cost utility analysis (cost per QALY reported) **Type of Model:** Markov model **Time horizon:** Lifetime **Cycle length:** Weekly cycles with half-cycle correction	Patients with HER2-positive mBC receiving 3rd-line therapy (NR)	Sequence 3 (Trastuz/Docet > T-DM1 > Trastuz/Lapat): 1.275 QALYs Sequence 4 (Trastuz/Docet > Trastuz/Lapat > Trastuz/Cape): 1.407 QALYs Sequence 2 (THP > Trastuz/Lapat > Trastuz/Cape): 1.781 QALYs Sequence 1 (THP > TDM1 > Cape/Lapat): 1.808 QALYs Incremental QALYs vs. Sequence 3 (Trastuz/Docet > T-DM1 > Trastuz/Lapat) Sequence 4 (Trastuz/Docet > Trastuz/Lapat > Trastuz/Cape): 0.132 QALYs Sequence 2 (THP > Trastuz/Lapat > Trastuz/Cape): 0.506 QALYs Sequence 1 (THP > TDM1 > Cape/Lapat): 0.534 QALYs	Sequence 3 (Trastuz/Docet > T-DM1 > Trastuz/Lapat): $79,958.7 Sequence 4 (Trastuz/Docet > Trastuz/Lapat > Trastuz/Cape): $88,392.98 Sequence 2 (THP > Trastuz/Lapat > Trastuz/Cape): $162,393 Sequence 1 (THP > TDM1 > Cape/Lapat): $164,211.4 Incremental costs vs. Sequence 3 (Trastuz/Docet > T-DM1 > Trastuz/Lapat) Sequence 4 (Trastuz/Docet > Trastuz/Lapat > Trastuz/Cape): $8,434.28 Sequence 2 (THP > Trastuz/Lapat > Trastuz/Cape): $82,434.33 Sequence 1 (THP > TDM1 > Cape/Lapat): $84,252.69	Incremental cost effectiveness vs Sequence 3 (Trastuz/Docet > T-DM1 > Trastuz/Lapat) Sequence 4 (Trastuz/Docet > Trastuz/Lapat > Trastuz/Cape): $63,887.71 Sequence 2 (THP > Trastuz/Lapat > Trastuz/Cape): $162,919.8 Sequence 1 (THP > TDM1 > Cape/Lapat): $157,888.1

Abbreviations: HER2, human epidermal growth factor 2; ICER, incremental cost-effectiveness ratio; mBC, metastatic breast cancer; NHS, National Health Service; NR, not reported; T-DM1, trastuzumab emtansine; THP, pertuzumab + trastuzumab + docetaxel; QALYs, quality-adjusted life years.

B.3.2 Economic analysis

No existing economic evaluations of T-DXd were identified in the cost-effectiveness SLR (Section B.3.1); it was therefore necessary to develop a de novo cost-effectiveness model. The economic evaluation presented in the only previous NICE appraisal in third-line uBC or mBC (TA423) was used to inform the de novo model's structure, assumptions, and data sources.[42]

B.3.2.1 Patient population

The population considered in the analysis is individuals with HER2+, uBC, or mBC who have received two or more prior anti-HER2 therapies. This is in line with the population considered in DESTINY-Breast01 (the pivotal clinical trial; Section B.2.2), the anticipated marketing authorisation and the final scope issued by NICE.

B.3.2.2 Model structure

The cost-effectiveness model is structured as a partitioned survival model with four health states:

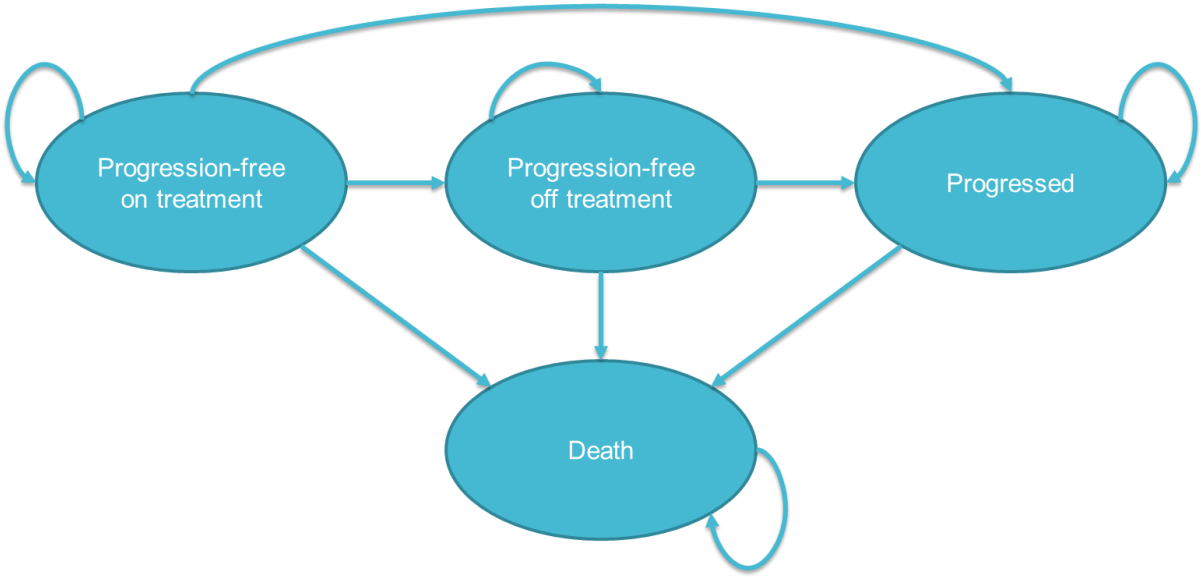
- Progression-free, on treatment
- Progression-free, off treatment
- Progressed
- Dead.

Figure 23 presents the model structure and the permitted flow of patients. All patients enter the model in the 'Progression-free, on treatment' state and receive either T-DXd or a comparator treatment. Individuals can either experience disease progression and transition to the 'Progressed' state or discontinue treatment and transition to the 'Progression-free, off-treatment' state. From the 'Progression-free, off-treatment' health state, individuals can experience disease progression and transition to the 'Progressed' state. Patients can transition to the 'Dead' state from any state in the model; this is an absorbing state.

The PFS curve is used to inform the proportion of individuals in the progression-free health states over time. The time-to-discontinuation (TTD) curve is used to inform the number of individuals who are in the progression-free on and off treatment states. The OS curve is used to inform the proportion of individuals in the 'Dead' health state over time. Long-term OS estimates are constrained by general population mortality informed by life tables for

England and Wales;[122] the probability of death in the model is prevented from falling below that of the general population. In the survival extrapolations, the TTD curve is not permitted to exceed the PFS curve[3], and the PFS curve is not permitted to exceed the OS curve.

Figure 23: Model schematic



Progression-based models are commonly used in economic analyses of oncology treatments because they accurately reflect the progressive nature of the disease, and they separate pre- and post-progression states, which in turn helps to capture differences in patient utility before and after progression and clinical decisions to stop treatment on tumour progression.

B.3.2.2.1 Time-horizon

The model considers a 'lifetime' time horizon. Given a starting age of 56 years, a time horizon of 40 years is expected to adequately capture lifetime costs and outcomes.

B.3.2.2.2 Cycle length

A 1-week cycle length is used to adequately capture transitions and reflect changes in health, while also allowing drug cycles to be appropriately costed. A 1-week cycle length ensures that the model can consider the different dosing schedules across the comparator arms, while also reflecting the trastuzumab deruxtecan 3-week dosing cycle. A half-cycle

[3] In DESTINY-Breast 01, treatment with T-DXd was not permitted beyond progression.

correction is applied using the life table method to account for uncertainty in the timing of transitions within the cycle period[4].

B.3.2.2.3 Discounting

In the base-case, a discount rate of 3.5% per annum is applied in line with current NICE guidelines.[123] Discount rates for costs and health outcomes of 0% and 6% are explored in scenario analyses.

B.3.2.2.4 Perspective

The analysis was conducted from the perspective of the NHS and personal social services (PSS) in England and Wales, in line with current NICE guidelines.[123] The analysis excludes out-of-pocket expenses, carers' costs, and lost productivity derived costs.

B.3.2.3 Features of the economic analysis

Table 68: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA423[43†]	Chosen values	Justification
Cycle length	3 weeks	1 week	A 1-week cycle length was chosen to allow for the different treatment schedules of the comparators in the model to be accurately modelled
Perspective	NHS and PSS	NHS and PSS	This approach is consistent with previous models in mBC and is in line with current NICE guidelines[43,123]
Model type	Partitioned survival analysis	Partitioned survival analysis	This approach is consistent with previous models in mBC and other oncology indications
Time horizon	Lifetime	Lifetime	A lifetime horizon was selected to capture all differences in costs and outcomes between treatments, as per the NICE reference case.[124]
Source of utilities	Mixed model regression based on data from study 301	Progression-free and progressed utility values from TA423, adjusted for response rates as per the method in TA423.	The trial utility data from TA423 were taken from a breast cancer population and generated the utility increment associated with response to treatment. These values were adjusted for response to reflect the difference in treatment

[4] Treatment costs are not half-cycle corrected, given that these costs are frequently incurred at the beginning of a treatment cycle.

Factor	Previous appraisals	Current appraisal	
	TA423[43†]	Chosen values	Justification
		Scenarios are presented which use utility values from Le et al. [120,125] [121,126]	efficacy between comparator treatments.
Source of costs	eMIT BNF NHS reference costs PSSRU NICE Breast Cancer Guidance, Marie Curie report	eMIT BNF NHS reference costs PSSRU NICE Breast Cancer Guidance, Marie Curie report	The sources of cost data are as per the NICE methods guide.[124]

Abbreviations: BNF, British National Formulary; mBC, metastatic breast cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.
† Eribulin for treating local advanced or metastatic breast cancer after 2 or more chemotherapy regimens.

B.3.2.4 Intervention technology and comparators

The intervention modelled in the analysis is T-DXd at a dose of 5.4 mg/kg, administered once per 21-day cycle.

The intervention is compared with the following comparators:

- Eribulin at a dose of 1.23 mg/kg on days one and eight of a 21-day cycle
- Capecitabine at a dose of 1,250 mg/m^2 twice daily for 14 days every 21-day cycle
- Vinorelbine at a dose of 60 mg/m^2 on days one and eight of a 21-day cycle.

The intervention and comparators in the analysis are those listed in the NICE scope.[126] Although the NICE scope states that eribulin is a comparator only in patients who have received two or more prior chemotherapies, clinical experts at an advisory board conducted in August 2020 confirmed that all patients eligible for treatment with T-DXd would have received two or more prior chemotherapies (i.e. eribulin is a relevant comparator in the full modelled population).[59]

B.3.3 Clinical parameters and variables

The principal source of data used to inform the analysis is the DESTINY-Breast01 clinical trial. Patient level-data were used to inform the following outcomes for T-DXd:

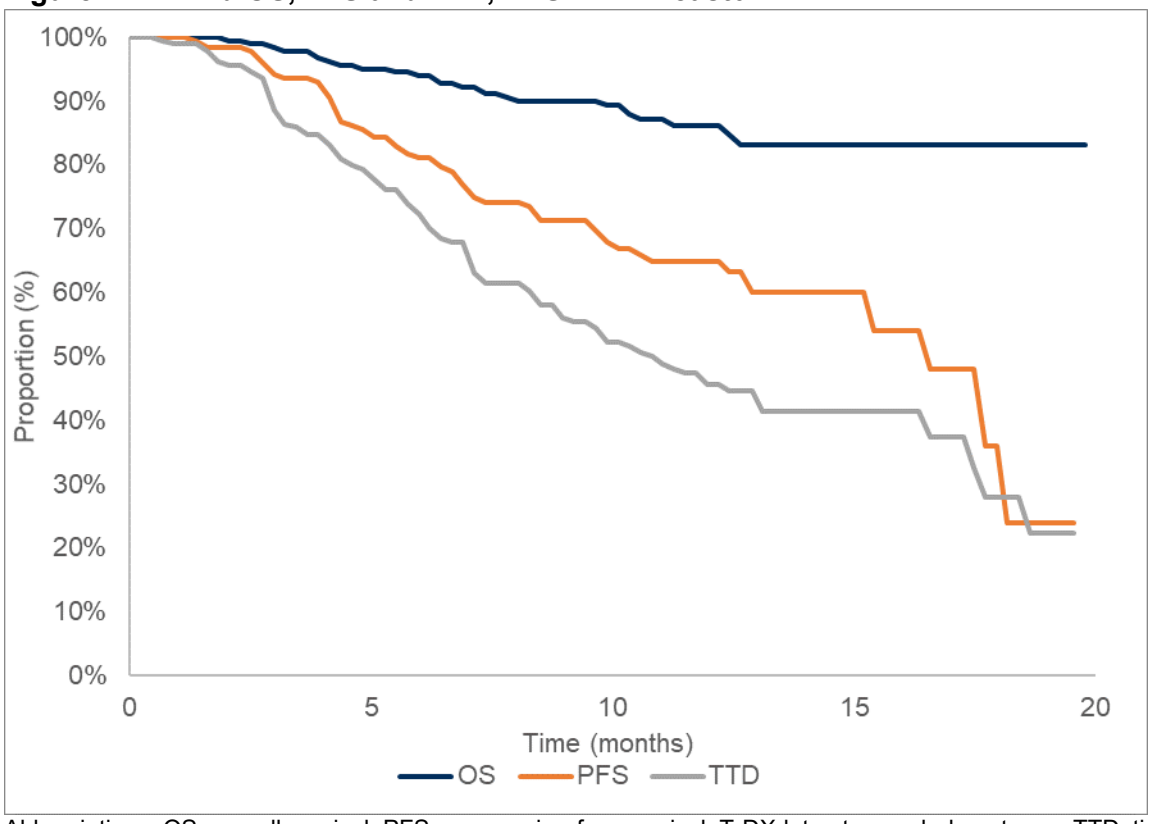
- Extrapolation of TTD
- Extrapolation of PFS

- Extrapolation of OS
- Adverse event (AE) durations and frequencies.

Given that DESTINY-Breast01 is a single group trial, unanchored MAICs have been used to inform comparisons against eribulin, capecitabine and vinorelbine (Section B.2.9). For both eribulin and capecitabine, there were multiple studies available. Of the four eribulin studies available, the Cortes (2011) study was chosen as the model base-case as this was the publication of the pivotal EMBRACE trial and was presented as the primary source of evidence in TA423.[84] Of the two available capecitabine studies, the Fumoleau (2004) study was chosen as the base-case as it was the most recent of the two studies and better outcomes were observed in this study, resulting in a conservative estimate of cost-effectiveness for T-DXd.[86] Only the Sim (2019) study was available to inform the comparison against vinorelbine[82]; however, clinical experts at the August advisory board advised that the OS observed in Sim 2019 (18.9 months) is not plausible following PFS of 12 weeks, and is likely driven by the use of post-progression therapies (see also Section B.3.3.1.2).[59] Given that vinorelbine is associated with similar or worse PFS compared with capecitabine, OS for vinorelbine is assumed to be equivalent to OS for capecitabine; further details are provided in Section B.3.3.1.2.

Kaplan-Meier data for TTD, PFS and OS from DESTINY-Breast01 are presented in Figure 24.

Figure 24: **T-DXd OS, PFS and TTD, DESTINY-Breast01**



Abbreviations: OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.

As PFS data for T-DXd are relatively mature, parametric survival curves are generated for T-DXd and HRs from the MAICs are applied to generate outcomes for the model comparators. TTD data for T-DXd are also relatively mature; however, no KM data are available for the model comparators. Parametric survival curves are therefore generated for T-DXd, with treatment to progression assumed for the model comparators; scenario analyses consider alternative assumptions (see Section B.3.3.3).

OS data are less mature, with a KM estimator of approximately 80% patients alive at the last data cut. Predictions of long-term OS for T-DXd are generated by applying a HR to third-line data for a HER2-targeted treatment (T-DM1) with longer follow-up than observed in DESTINY-Breast01. OS for comparator treatments is estimated by fitting parametric survival curves to the digitized KM data from the relevant studies. For completeness, a scenario is performed in which OS for T-DXd is generated by applying the HR from the MAIC vs. Cortes 2011 (B.2.9[redacted]) to the survival curve for eribulin; see Appendix O for further details.

Outcomes were extrapolated beyond the trial period using parametric survival techniques consistent with NICE DSU TSD 14.[127]All statistical models used in the base-case are presented in Appendix O.

B.3.3.1 Extrapolation of OS

OS data in DESTINY-Breast01 are considered prohibitively immature for informative parametric modelling (Figure 24). Given a lack of mature data, a reasonable approach to extrapolating OS is to apply a HR to OS for existing therapies with similar mechanisms of action in similar patient populations.

As the comparators in scope (eribulin, capecitabine and vinorelbine) are not HER2-targeting agents, there are concerns over whether these would be appropriate analogues to inform the extrapolation of OS for T-DXd. According to clinical experts, it is expected that OS for HER2+ mBC patients treated with T-DXd would be more similar to that seen with other HER2-targeting agents (trastuzumab emtansine, trastuzumab, pertuzumab)[88,89,128] than to OS for non-targeted chemotherapies (eribulin, capecitabine, vinorelbine).

OS data for trastuzumab emtansine (TH3RESA in 3L, EMILIA in 2L) and for trastuzumab and pertuzumab chemotherapy in 1L (CLEOPATRA) indicated that a substantial proportion of patients demonstrate long-term survival; the OS KM curves show more of a 'tail' in long-term follow up compared to the OS data available for eribulin, capecitabine and vinorelbine.

Additional translational research to link the mechanism of action to potential impact on long term overall survival is not available; however, in the published literature there are hypotheses on HER2-targeting mediated effects, including immune responses,[129] that could significantly improve long term survival in HER2+ breast cancer compared to non-HER2-targeting therapies.

As clinical experts stated that long term survival for T-DXd would be better informed by other HER2-targeting therapies, predictions of long-term OS for T-DXd are generated by applying a HR to third-line data for a HER2-targeted treatment (T-DM1) with longer follow-up than observed in DESTINY-Breast01; the TH3RESA data for T-DM1 was considered the most relevant due to similarities in mechanism of action and line of therapy.

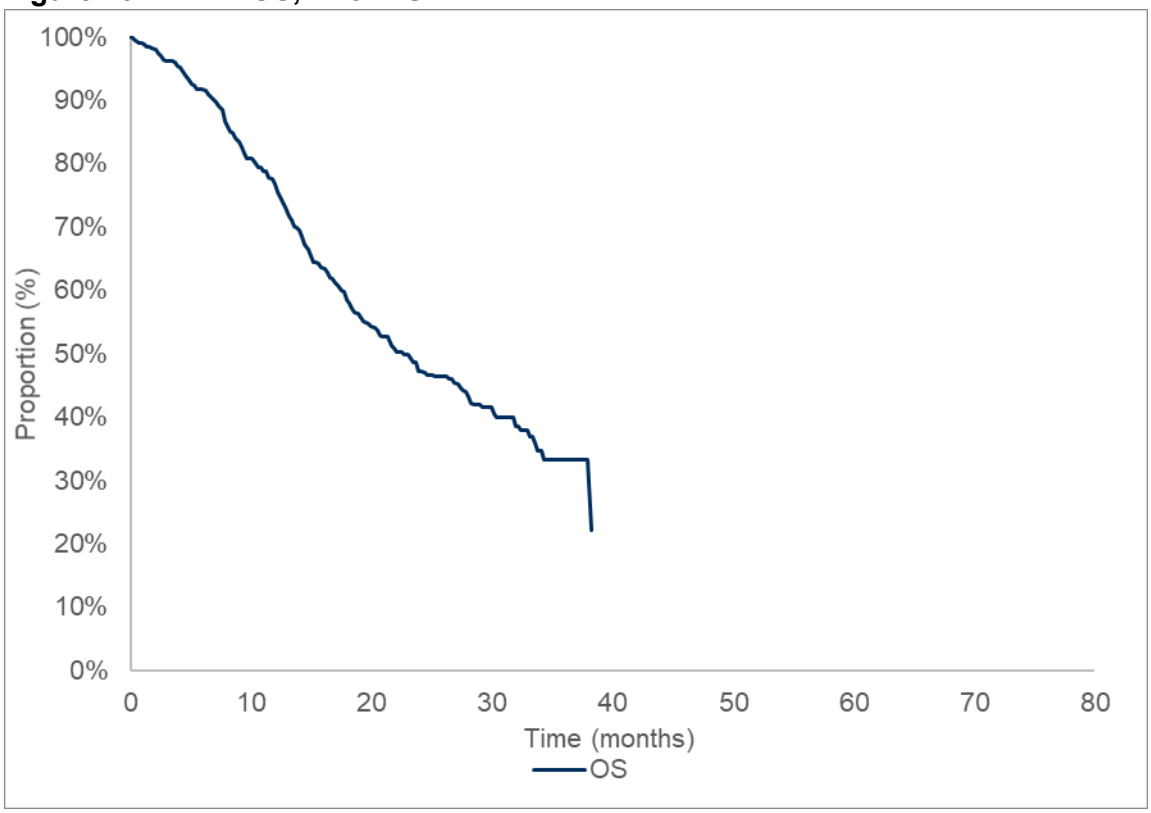
OS for eribulin and capecitabine is estimated by fitting parametric survival curves to the digitized KM data from the relevant studies; given that available OS data for vinorelbine were not considered plausible or reflective of survival outcomes in UK patients in this setting by clinical experts at the August advisory board and PFS estimates for vinorelbine were similar to/lower than for capecitabine, OS for vinorelbine was assumed equivalent to that for capecitabine (see Section B.3.3.1.2).

B.3.3.1.1 T-DXd

In UK clinical practice, T-DM1 is the standard-of-care for second-line HER2-positive patients, and is recommended by NICE for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination.[42,123] To inform the submission to NICE, the company submitted evidence for T-DM1 in both second-line and third-line settings, with the third-line evidence informed by the TH3RESA trial.

In the model base-case, OS for T-DXd is modelled by applying HR to the extrapolated OS curve from TH3RESA; the KM for T-DM1 from TH3RESA is presented in Figure 25.[130]

Figure 25: T-DM1 OS, TH3RESA



Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine

Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including a trastuzumab-like antibody, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or capecitabine. Clinical experts at the August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect the shape of the T-DM1 curve than that of the model comparators; additionally, clinical experts engaged in previous discussions noted that:

- Comparing targeted therapies (i.e. T-DXd) against non-targeted therapies (i.e. eribulin, capecitabine and vinorelbine) may mean that assuming proportional hazards is not reasonable; one of the clinical experts independently suggested the use of TH3RESA as a 'control' arm to apply a HR to

- It is reasonable to expect a 'tail' in T-DXd OS, as observed for T-DM1.

The model diagnostics for the extrapolation of the TH3RESA data are shown in Table 69. A HR was generated for T-DXd vs. T-DM1 using a Cox proportional hazards model (Table 70).

Table 69: Model diagnostics, TH3RESA, OS

Model	AIC	BIC
Exponential	939.05	943.05
Weibull	921.90	929.90
Log-normal	935.65	943.65
Log-logistic*	917.34	925.35
Gompertz	932.01	940.01
Generalised gamma	922.01	934.01

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
* Lowest AIC/BIC scores.

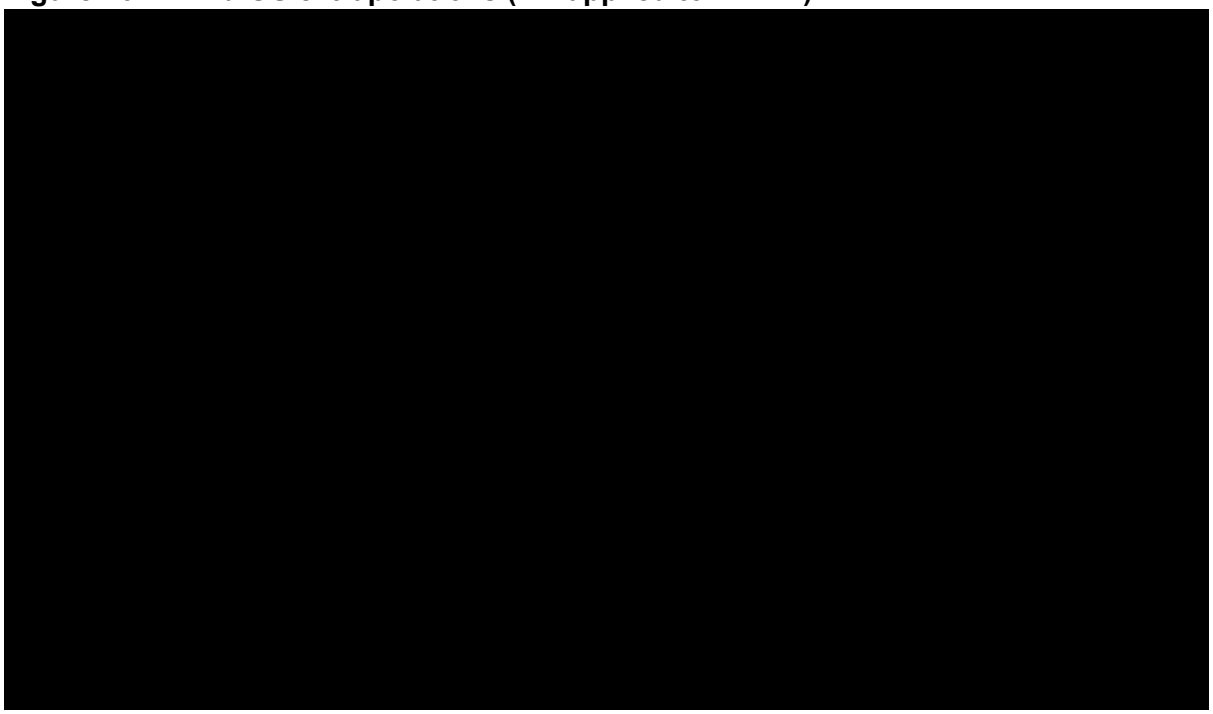
Table 70: OS HR vs. T-DM1

Treatment	Hazard ratio	Standard error	P>z	95% CI (lower)	95% CI (upper)
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; s.e, standard error; T-DM1, trastuzumab emtansine' T-DXd, trastuzumab deruxtecan

The resulting extrapolations of T-DXd OS in Figure 26 were presented to UK clinical experts at the August advisory board[59]; the Weibull and generalised gamma distributions were considered to be most plausible. Both distributions were compared against KM data for other HER2-targetd therapies: T-DM1 in the TH3RESA trial, and T-DM1 and lapatinib plus capecitabine in the EMILIA trial (Figure 27). The generalised gamma distribution was considered to better reflect the shape of the OS curve observed for other HER2-targeted therapies, and was selected for the model base-case; the extrapolation of T-DM1 OS assuming the generalised gamma distribution is presented in Figure 28. All distributions were considered in scenario analyses.

Figure 26: T-DXd OS extrapolations (HR applied to T-DM1)



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

Figure 27: Comparison of OS extrapolations vs. other HER2-targeted therapies

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

Figure 28: Base-case OS extrapolation, T-DM1

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

B.3.3.1.2 Comparators

Overall survival for eribulin and capecitabine were extrapolated from digitized KM data published in studies by Cortes and Fumoleau, respectively.

On review of the available comparator publications, the OS data provided in the only identified vinorelbine publication[82] providing KM data to inform the MAICs was identified to provide highly inconsistent results versus current OS reported in this patient population. Further, reported OS seen in this study is inconsistent when considering observed PFS, and as compared with comparator PFS:OS ratios (Table 71).

Table 71: Ratio of PFS to OS

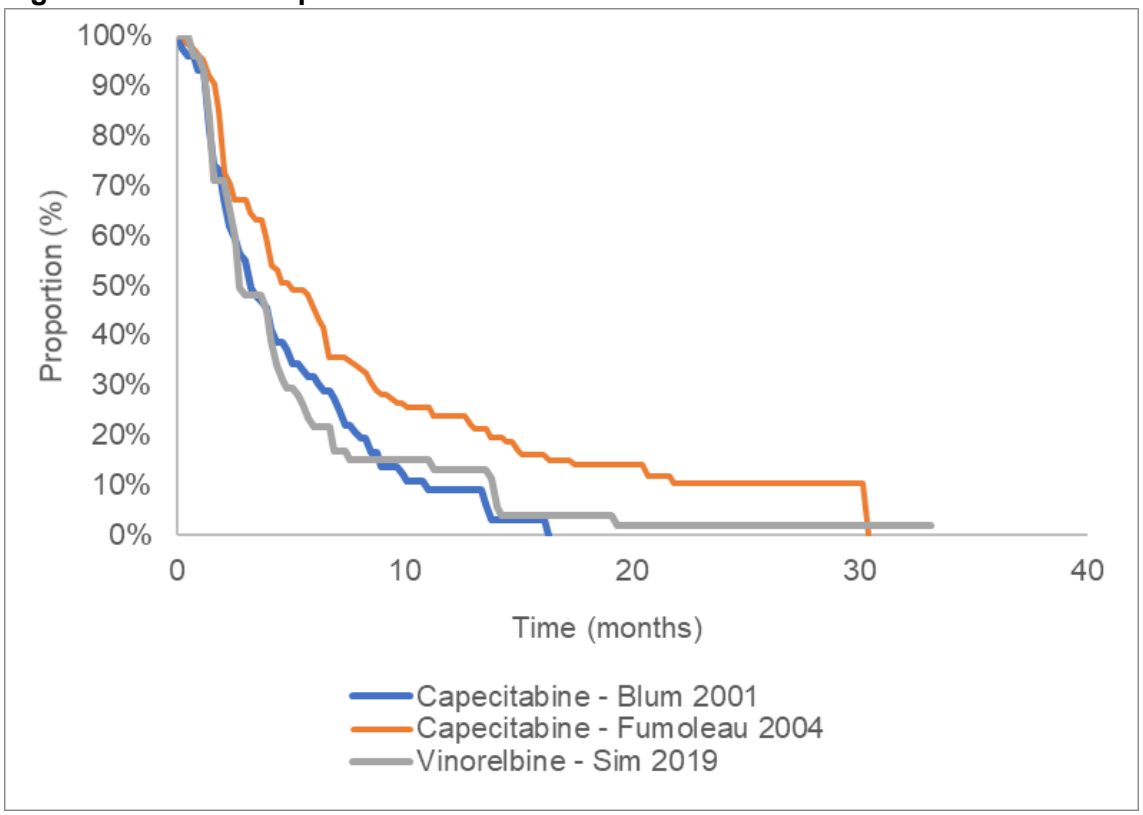
Comparator	Study	Median OS (months)	Median PFS (months)	Ratio of OS to PFS
Eribulin	Cortes 2011	13.2	3.7	3.6
	Barni 2019	10.1	3.2	3.2
	Cortes 2010	10.4	2.6	4.0
	Gamucci 2014	14.3	4.4	3.3
Capecitabine	Fumoleau 2004	15.2	4.9	3.1
	Blum 2001	12.2	3.2	3.8
Vinorelbine	Sim 2019	18.9	2.8	6.8

Abbreviations: OS, overall survival, PFS; progression-free survival

UK clinical expert opinion was sought at an advisory board regarding this study[59]; no clinical

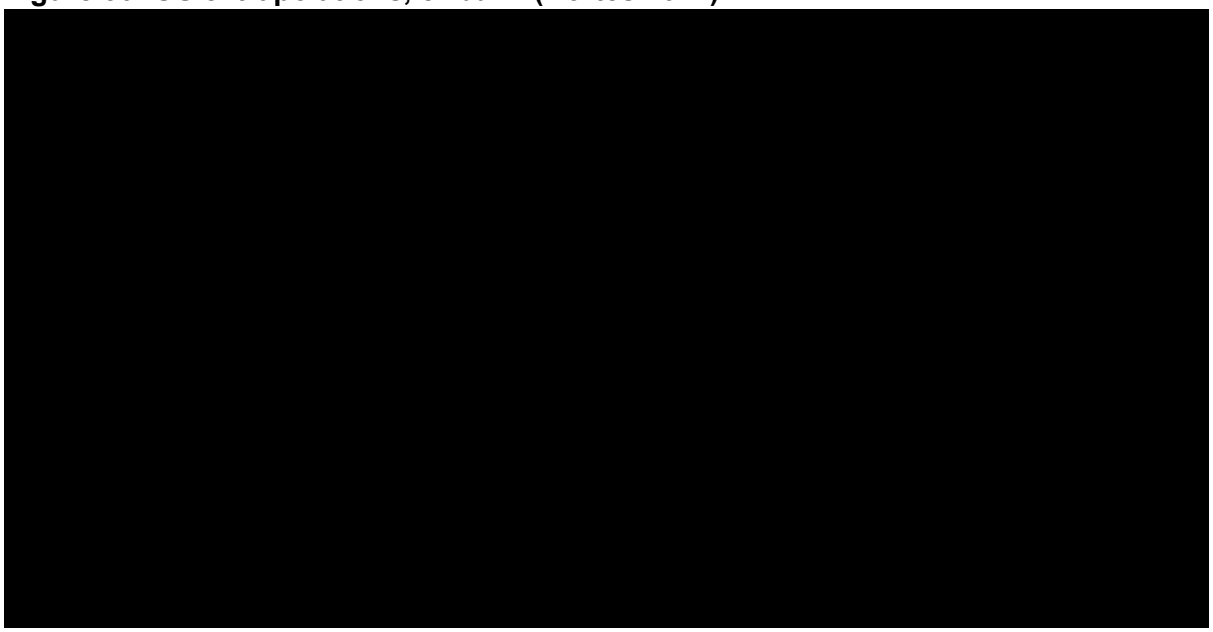
expert was previously aware of this data, and they perceived the reported OS to lack face validity, with expected OS in a UK patient population to be lower. It was anticipated that the reported OS in this study may be driven by subsequent therapies, not reported in the publication and not funded in the UK. Given the highlighted issues and in order to inform economic modelling, vinorelbine OS is assumed to be equal to that of capecitabine OS; this is considered reasonable, given that vinorelbine is associated with similar/lower PFS compared to capecitabine (Figure 29). This approach is consistent with clinical expert expectation regarding survival of UK patients and no identified clinical consensus or guideline which proposes use of one therapy in place of the other due to published clinical data.

Figure 29: PFS for capecitabine and vinorelbine



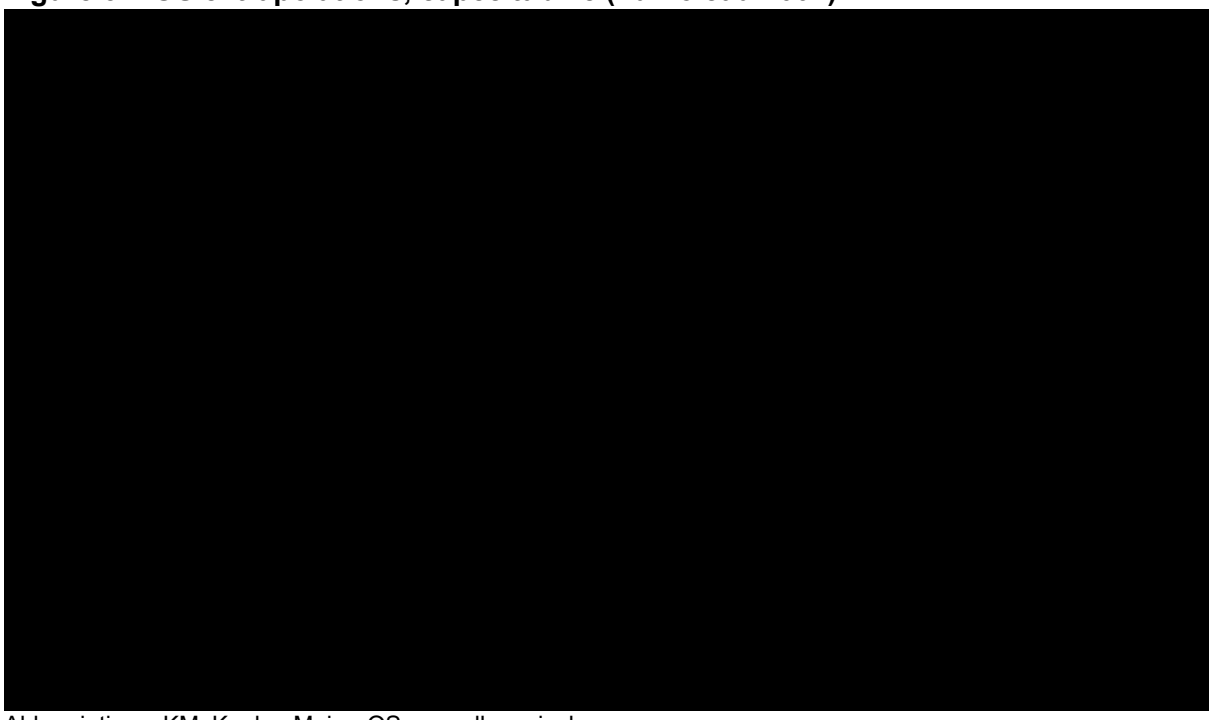
Parametric survival curves were fit to the data for eribulin and capecitabine and used to extrapolate beyond the trial period. All distributions for each comparator are presented in Figure 30 and Figure 31. In the base-case, the distribution for eribulin was selected that gave the most clinically plausible outcomes in T-DXd when a HR vs. eribulin was applied in a scenario analysis (see Appendix O). In the capecitabine arm, the distribution with the lowest AIC/BIC was chosen. The generalised gamma and Gompertz distributions were therefore selected for eribulin and capecitabine, respectively. Model diagnostics are presented in Table 72 and Table 73 and all distributions are presented in scenario analyses.

Figure 30: OS extrapolations, eribulin (Cortes 2011)



Abbreviations: KM, Kaplan Meier; OS, overall survival

Figure 31: OS extrapolations, capecitabine (Fumoleau 2004)



Abbreviations: KM, Kaplan Meier; OS, overall survival

Table 72: Model diagnostics, eribulin

Model	AIC	BIC
Eribulin		
Exponential	1088.95	1093.18

Model	AIC	BIC
Weibull	1022.60	1031.06
Log-normal	1023.71	1032.17
Log-logistic	1017.85	1026.31
Gompertz	1049.83	1058.29
Generalised gamma*	1019.14	1031.83

Table 73: Model diagnostisics, capecitabine

Model	AIC	BIC
Exponential	333.73	336.57
Weibull	332.48	338.15
Log-normal	348.73	354.40
Log-logistic	339.42	345.09
Gompertz*	329.83	335.51
Generalised gamma	331.61	340.12

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Base-case.

B.3.3.1.3 Life tables

Age- and gender-specific probabilities of death were taken from published national life tables for England and Wales, using data for 2019.[122] Life tables are used in the model to ensure the weekly probability of mortality never falls below that of the general population. A mean baseline age of 56 years was assumed, to align with DESTINY-Breast01.

B.3.3.2 Extrapolation of PFS

Median PFS was 16.34 months in T-DXd patients in DESTINY-Breast01. Model diagnostics for alternative survival distributions are presented in Table 74. The extrapolations shown in Figure 32 were presented to UK clinical experts at the August advisory board;[59] the Gompertz and generalised gamma distributions were considered to generate clinically implausible extrapolations, and so were removed from consideration. Of the remaining distributions, the log-normal distribution was associated with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC), and so was selected in the model base-case. Other survival distributions are considered in scenario analyses.

Figure 32: PFS, T-DXd

Table 74: Model diagnostics, PFS - T-DXd

Model	AIC	BIC
Exponential	298.88	302.09
Weibull	288.11	294.54
Log-normal*	283.55	289.98
Log-logistic	286.76	293.19
Gompertz	293.85	300.28
Gen. gamma	284.84	294.48

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; T-DXd, trastuzumab deruxtecan.
*Lowest AIC/BIC scores.

MAICs were conducted (Section B.2.9) for all relevant comparators and HRs were applied to the T-DXd extrapolated survival curve. Table 75 presents the HRs from the MAICs for each model comparator.

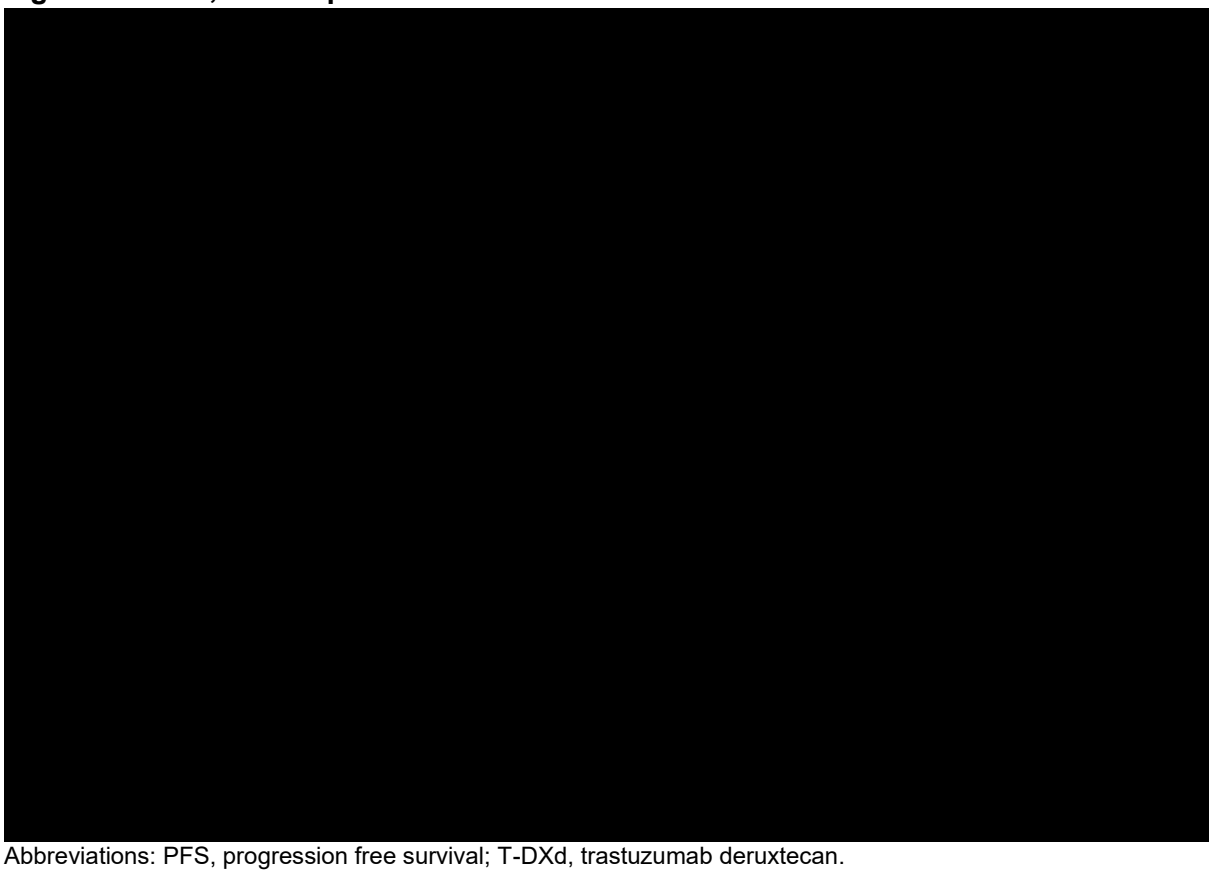
Table 75: PFS HRs

Comparator	Study	HR (95% CI)
Eribulin	EMBRACE (Cortes 2011)*	0.21 (0.15, 0.28)
	Barni 2019	0.08 (0.05, 0.13)
	Cortes 2010	0.13 (0.10, 0.18)
	Gamucci 2014	0.11 (0.06, 0.17)
Capecitabine	Fumoleau 2004*	0.20 (0.12, 0.37)
	Blum 2001	0.16 (0.11, 0.23)
Vinorelbine	Sim 2019	0.15 (0.10, 0.22)

Abbreviations: CI; confidence interval; HR, hazard ratio; PFS, progression free survival.
*Model base-case

Figure 33 presents the extrapolated survival curves for each comparator in the model, given the base-case HRs presented in Table 75 and assuming a log-normal distribution.

Figure 33: PFS, all comparators



Abbreviations: PFS, progression free survival; T-DXd, trastuzumab deruxtecan.

B.3.3.3 Extrapolation of TTD

Median TTD was 10.59 months in T-DXd patients in DESTINY-Breast01. Model diagnostics for alternative survival distributions are presented in Table 76. The extrapolations shown in Figure 34 were presented to UK clinical experts at the August advisory board.[59] Graphically,

two groups of curves were present: one group (log-normal, log-logistic, generalised gamma, exponential) which implies that a proportion of patients would remain on treatment beyond 5 years; and a second group of curves (Gompertz and Weibull) where all patients would discontinue by 5 years. In discussion with clinical experts, it was confirmed that there are some patients who would remain on treatment beyond 5 years, but it was unclear which of the two groups of curves best represented the experience of the overall group of patients. The exponential distribution was therefore selected in the base-case, given that this is the lowest of the first group of curves, and therefore may be considered an approximate midpoint between the two groups. Other survival distributions are considered in scenario analyses.

Figure 34: TTD, T-DXd

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

Table 76: Model diagnostics, TTD - T-DXd

Model	AIC	BIC
Exponential	438.36	441.58
Weibull	426.65	433.08
Log-normal*	419.52	425.95
Log-logistic	422.01	428.44

Model	AIC	BIC
Gompertz	434.86	441.29
Gen. gamma	421.48	431.13

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time-to-discontinuation
*Lowest AIC/BIC scores.

TTD KM data were not available for eribulin, capecitabine or vinorelbine. In the base-case, treatment to progression was assumed for these comparators. A scenario is considered in which a HR is applied to the T-DXd curve such that each curve passes through the observed median TTD in each study. The estimated HR for each study is presented in Table 77. No median TTD was available from the Sim study in vinorelbine, and so treatment to progression was assumed in all scenarios.

Treatment to progression was assumed in the base-case because:

- Applying a HR to TTD data for T-DXd quickly results in the estimated TTD curve crossing the PFS curve; functionality is included in the model to correct for this (i.e. to prevent TTD from exceeding PFS), however, this suggests that the assumption of proportional hazards between T-DXd and the relevant comparators is not valid for TTD.

- PFS for the modelled comparators is relatively short; it is therefore unlikely that discontinuation and progression would occur on different follow-up visits in an NHS setting.

Table 77: TTD HRs (estimated)

Comparator	Study	Observed median TTD	HR
Eribulin	EMBRACE (Cortes 2011)*	3.90	2.50
	Barni 2019	2.76	3.96
	Cortes 2010	2.76	3.51
	Gamucci 2014	3.45	2.85
Capecitabine	Fumoleau 2004*	4.10	2.57
	Blum 2001	3.20	3.41
Vinorelbine	Sim 2019	N/A	N/A

Abbreviations: HR, hazard ratio; n/a; not applicable; TTD, time to discontinuation.
*model base-case.

Figure 35: TTD, all comparators

Abbreviations: SoC, standard-of-care; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.

B.3.3.4 HER2+ efficacy adjustment

In DESTINY-Breast01, all patients in the trial had HER2+ disease, while several comparator studies included a mix of HER2+ and HER2– patients. Two studies were identified that have assessed the difference in survival outcomes between patients with HER2+ and HER2– disease.[80,131] Barni et al. conducted a retrospective cohort study of mBC patients who received eribulin at 39 oncology centres in Italy; no statistically significant difference was observed in either OS or PFS between those with HER2+ and HER2– disease. Lv et al. retrospectively compared clinical outcomes of HER2+ patients with or without trastuzumab vs. HER2– patients treated at six cancer centres in China. Patients were matched on age, histology, tumour grade, tumour/node/metastasis (TNM) stage, HR expression status, initial metastasis location, metastasis number, and treatment regimen. HER2+ patients without trastuzumab experienced poorer OS outcomes when compared with HER2– patients (HR: 1.843, 95% C.I.:1.325 – 2.564).[131]

HER2+ disease is a more agressive phenotype than HER2- disease and has traditionally been associated with poorer outcomes.[132] With the introduction of HER2-targeted therapies,

outcomes in this subgroup are improving. However, in this indication, patients treated in the NHS do not have HER2-targeted treatment options and therefore poorer survival when treated with non-targeted therapies are expected. At the August advisory board, clinical experts advised that outcomes in patients with HER2+ disease are expected to be worse than in those with HER2– disease.[59] The HR reported by Lv et al was therefore used to adjust OS and PFS estimates in studies which included HER2– patients. In the absence of other data, the same HR was assumed for both OS and PFS; a scenario is considered in which no adjustment is made for HER2 status.

The proportions of patients who had HER2+ disease in each study are presented in Table 78. In the base-case, the model uses the proportions from Cortes 2011 (EMBRACE) and Fumoleau for eribulin and capecitabine patients, respectively. Where the survival curves are generated from different studies in scenario analyses (Section B.3.3.1), the proportion from the corresponding study is used. Where there were no data available on HER2 status, 20% of patients were assumed to be HER2+, in line with the proportion observed in clinical practice.[17]

Table 78: Proportion of patients with HER2+ disease

Treatment	Study	Proportion of patients HER2+
Eribulin	EMBRACE (Cortes 2011)	17.80%
	Barni 2019	100.00%
	Cortes 2010	11.00%
	Gamucci 2014	21.10%
Capecitabine	Fumoleau 2004*	20.00%
	Blum 2001*	20.00%
Vinorelbine	Sim 2019	100.00%

Abbreviations: HER2, human epidermal growth factor receptor 2.
*HER2 status not reported; 20% HER2-positive patient population is assumed.

Table 79: HER2+ efficacy adjustment HRs

Comparator	HER2+ adjustment HR, OS	HER2+ adjustment HR, PFS
Eribulin	1.69	1.69
Capecitabine	1.67	1.67
Vinorelbine	N/A	1

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

B.3.3.5 Adverse events

All grade three and above adverse events that occurred in at least 5% of patients were included for each comparator from the respective studies. In addition, any adverse events listed as AEs of special interest in the DESTINY-Breast01 clinical study report or deemed of clinical importance by clinicians were also included. ILD, LVEF decrease, QT prolongation, and infusion-related reactions have been identified as adverse events of special interest in the DESTINY-Breast01 CSR.[66]

AE numbers were assessed during the safety period of DESTINY-Breast01, from Day 1 through to the end of treatment visit or 30-days after the last study treatment, whichever was later. AEs have not been extrapolated beyond the safety period and all costs and quality-adjusted life years (QALY) losses associated with AEs are assumed to occur in the first cycle of the model.

The AE inputs used in the T-DXd arm of the model are presented in Table 80.

Table 80: Adverse events, T-DXd

Pre-matched cohort (N = 184	Number of events	Proportion	Events resulting in hospitalisation	Proportion of events resulting in hospitalisation
Neutrophil count decreased	38	20.56%	0	0.00%
Anaemia	28	15.56%	2	7.14%
Neutropenia	37	20.56%	1	2.70%
Nausea	16	8.33%	4	25.00%
Fatigue	15	7.78%	0	0.00%
White blood cell count decreased	11	6.11%	0	0.00%
Dyspnoea	3	1.67%	0	0.00%
Febrile neutropenia	3	1.67%	0	0.00%
Electrocardiogram QT prolonged	3	1.67%	0	0.00%
Interstitial lung disease	2	1.11%	2	100.00%
Ejection fraction decreased	1	0.56%	0	0.00%
Pneumonitis	1	0.56%	1	100.00%
Vomiting	0	0.00%	0	0.00%

Abbreviations: T-DXd, trastuzumab deruxtecan

In the eribulin arm of the model, adverse event frequencies were taken as a weighted average from all of the studies considered in the model that reported information on adverse events. The proportion of AEs in each study was reweighed to reflect the size of the patient

population. AE data were not available from the Gamucci study. Data were not available on the AEs that resulted in hospitalisation from the Cortes 2010 or Barni studies, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed. AE frequencies are presented in Table 81.

Table 81: Adverse events, eribulin

Adverse event	Proportion of patients – Cortes 2011 (EMBRACE) n=503	Proportion of patients – Barni 2019 n=574	Proportion of patients – Cortes 2010 n=291	Weighted proportion
Neutrophil count decreased	0.00%	0.00%	0.00%	0.00%
Anaemia	1.99%	0.06%	0.15%	0.79%
Neutropenia	14.51%	0.33%	1.46%	5.78%
Nausea	1.19%	0.07%	0.41%	0.55%
Fatigue**	1.90%	0.00%	0.00%	0.70%
White blood cell count decreased*	4.17%	0.00%	0.00%	1.53%
Dyspnoea	3.38%	0.00%	0.00%	1.24%
Febrile neutropenia	1.60%	0.00%	0.00%	0.59%
Electrocardiogram QT prolonged	0.00%	0.00%	0.00%	0.00%
Interstitial lung disease	0.00%	0.00%	0.00%	0.00%
Ejection fraction decreased	0.00%	0.00%	0.00%	0.00%
Pneumonitis	0.00%	0.00%	0.00%	0.00%
Vomiting	0.00%	0.00%	0.00%	0.00%
Palmar-Plantar Erythro-Dysaesthesia Syndrome	6.10%	0.00%	0.00%	2.24%

*Reported as 'Leucopenia'/'Leukopenia'
** Fatigue and/or asthenia
*** Reported as 'Peripheral neuropathy' in EMBRACE

In the capecitabine arm of the model, adverse event frequencies were taken from the data reported in the Blum study only as data were not available from Fumoleau (Table 82).[85] Data were not available on the AEs that resulted in hospitalisation, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed.

Table 82: Adverse events, capecitabine

Adverse event	Number of events	Proportion of patients
Neutrophil count decreased	0	0.0%

Adverse event	Number of events	Proportion of patients
Anaemia	0	0.0%
Neutropenia	1	1.4%
Nausea	7	9.5%
Fatigue*	6	8.1%
White blood cell count decreased	0	0.0%
Dyspnoea	0	0.0%
Febrile neutropenia	0	0.0%
Electrocardiogram QT prolonged	0	0.0%
Interstitial lung disease	0	0.0%
Ejection fraction decreased	0	0.0%
Pneumonitis	0	0.0%
Vomiting	0	0.00%
Diarrhoea	14	18.92%
Palmar-Plantar Erythro-Dysaesthesia Syndrome	16	21.62%
Dehydration	5	6.8%
Stomatitis	9	12.2%

* Fatigue and/or asthenia

In the vinorelbine arm of the model, adverse event frequencies were taken from the data reported in the Sim study and are presented in Table 83.[82] Data were not available on the AEs that resulted in hospitalisation, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed.

Table 83: Adverse events, vinorelbine

Adverse event	Number of events	Proportion of patients
Neutrophil count decreased	0	0.0%
Anaemia	4	5.4%
Neutropenia	45	60.8%
Nausea	0	0.0%
Fatigue*	2	2.7%
White blood cell count decreased	0	0.0%
Dyspnoea	0	0.0%
Febrile neutropenia	5	6.8%
Electrocardiogram QT prolonged	0	0.0%
Interstitial lung disease	0	0.0%
Ejection fraction decreased	0	0.0%

Adverse event	Number of events	Proportion of patients
Pneumonitis	1	1.4%
Vomiting	0	0.00%
Abdominal pain	12	16.22%

B.3.4 Measurement and valuation of health effects

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

HRQoL data were not collected in DESTINY-Breast01.

B.3.4.2 Mapping

HRQoL data were identified from the published literature; there was no requirement for mapping.

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

A SLR to identify relevant HRQoL (utilities) studies was conducted. See Appendix H for full details of the methods of the SLR and the identified studies. The SLR identified 6 studies from 7 publications. An overview of the study details and results from included utility studies, together with the quality assessments, are presented in Appendix H.

B.3.4.4 Adverse reactions

The impact of AEs on HRQoL is captured as a one-off QALY loss in the first cycle of the model. The AE frequencies from the relevant studies for each comparator (see Section B.3.3.5), the durations of each AE reported in DESTINY-Breast01 and disutilities sourced from the literature were used to calculate a one-off QALY loss for each treatment. Where available, AE disutilities were taken directly from Hudgens et al., a health-related quality of life study in patients with locally advanced or metastatic breast cancer treated with eribulin or capecitabine.[133] For AEs that were not reported in the study by Hudgens et al., AE disutilities were sourced from alternative published studies. The AE disutilities and durations used in the model are presented in Table 84.

Table 84: AE disutilities

AE	Disutility	Source	AE duration (days)	QALY decrement
Neutrophil count decreased	0.0070	Hudgens et al.	40.10	0.0008
Anaemia	0.0100	Hudgens et al.	42.90	0.0012
Neutropenia	0.0070	Hudgens et al.	40.10	0.0008

AE	Disutility	Source	AE duration (days)	QALY decrement
Nausea	0.0210	Hudgens et al.	36.20	0.0021
Fatigue	0.0290	Hudgens et al.	58.30	0.0046
White blood cell count decreased	0.0030	Hudgens et al.	42.20	0.0003
Dyspnoea	0.0270	Hudgens et al.	9.6	0.0009
Febrile neutropenia	0.0120	Hudgens et al.	7	0.0002
Electrocardiogram QT prolonged	0.0000	Lachaine et al.[134]	31.40	0.0000
Interstitial lung disease	0.1700	Doyle et al.[135]	51.10	0.0238
Ejection fraction decreased	0.0590	Sandhu et al[136]	31.00	0.0050
Pneumonitis†	0.1700	Doyle et al.[135]	51.10	0.0238
Vomiting	0.1030	Lloyd et al[137]	13.70	0.0039
Diarrhoea	0.0060	TA423	17.00	0.0003
PPE	0.1160	Shlomai et al[138]	14.00	0.0044
Dehydration‡	0.0060	TA423	17.00	0.0003
Stomatitis	0.1510	TA250	10.00	0.0041
Abdominal pain‡	0.0060	TA423	17.00	0.0003
Peripheral neuropathy	0.0140	TA423	40.10	0.0015

Abbreviations: AE, adverse event; QALY, quality-adjusted life year; PPE, palmar-plantar erythrodysesthesia syndrome.
† Another term for Interstitial lung disease
‡ Assumed equal to diarrhoea

The total QALY loss for each treatment arm in the model is presented in Table 85.

Table 85: Total QALY loss

Treatment	QALY loss
T-DXd	0.0013
Blended SoC	0.0006
Eribulin	0.0003
Capecitabine	0.0006
Vinorelbine	0.0006

Abbreviations: QALY, quality-adjusted life year; SoC, standard-of-care; T-DXd, trastuzumab deruxtecan.

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

In TA423, progression free, on-treatment utility values were calculated as a function of objective response rate (ORR; defined as patients experiencing a best overall response of complete response or partial response) and adverse event rates from the eribulin and

treatment of physician's choice (TPC) arms of the EMBRACE clinical trial. In the current model, costs and utility impact of adverse events are modelled in the first cycle only; health state utility values used in the analysis therefore incorporate response only, and adverse event disutilities are modelled separately.

The calculation of progression-free, on-treatment utility values is presented in Table 86. The baseline utility value (0.704), tumour response utility value (0.780) and the incremental utility of response (0.076) were taken from TA423, and progression free, on-treatment utility values were calculated for each treatment using ORR. The ORR from DESTINY-Breast01 (60.9%) was used for T-DXd,[62] and ORR values from the MAIC were used for each comparator (see Section B.2.9).

Table 86: Progression-free, on-treatment utility values

	Eribulin	Capecitabine	Vinorelbine	T-DXd
Baseline	0.704	0.704	0.704	0.704
Tumour response	0.780	0.780	0.780	0.780
Incremental utility of response	0.076	0.076	0.076	0.076
Tumour response rate	Cortes (2011): 14.0% Barni: 17.2% Cortes (2010): 10.0% Gamucci: 26.0%	Fumoleau: 19.0% Blum: 22.5%	31.6%	60.9%
Progression free, on treatment utility value †	Cortes (2011): 0.715 Barni: 0.717 Cortes (2010): 0.712 Gamucci: 0.724	Fumoleau: 0.718 Blum: 0.721	0.728	0.750

Abbreviations: SoC, standard-of-care; T-DXd, trastuzumab deruxtecan.
† Progression free, on treatment utility = baseline + ORR * incremental utility of response
¥Base-case

In the base-case, the progression-free, off treatment utility value is equal to the 'baseline' utility value in Table 86 (0.704). The progressed disease utility value was aligned with the committee's comments from TA423. In TA423, the ERG stated that the value used by the company for progressed disease (0.679) was unrealistic as it did not represent a large enough drop in utility after patients experienced disease progression, and proposed a value of 0.496 from Lloyd et al.[137] The committee stated that the true utility value was likely

somewhere between the company and ERG value, as clinicians stated that the drop-off in utility was likely smaller than suggested by the ERG's recommendation. Therefore, in the base-case, the average from TA423 of the company and ERG values for progressed disease (0.598) is used. Scenarios are presented which model progressed disease assuming each of the ERG and company's proposed values for progressed disease from TA423.

An additional scenario analysis is included using utility values presented by Le et al. (Table 87), a simulation study assessing the cost effectiveness of lapatinib and capecitabine for HER2+ advanced breast cancer.[120]

Table 87: Utility value scenario, Le et al.

Health state	Utility value
Progression-free (all health states and comparators)	0.700
Progressed disease	0.500

B.3.4.5.1 General population utility

Age-specific utility multipliers are derived based on the relationship between age and utility values observed in the general population. The following relationship is presented by Ara and Brazier:[139]

$$General\ population\ EQ-5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

Health state utility values identified in the published literature are assumed to apply at the start of the model; for every year subsequent to this, a multiplier is applied based on the ratio between the general population utility values for current age and starting age. The baseline starting age in the model, based on DESTINY-Breast01 data, is 56 years.

B.3.4.6 Summary of utility values for cost-effectiveness analysis

Table 88: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
Progression-free, T-DXd	0.750	0.68, 0.83	Derived from the 3L mBC submission TA423
Progression-free, eribulin	0.713	0.64, 0.78	Derived from the 3L mBC submission TA423
Progression-free, capecitabine	0.725	0.65, 0.80	Derived from the 3L mBC submission TA423

State	Utility value: mean (standard error)	95% confidence interval	Justification
Progression-free, vinorelbine	0.717	0.64, 0.79	Derived from the 3L mBC submission TA423
Progression-free, blended SoC	0.713	0.64, 0.78	Derived from the 3L mBC submission TA423
Progression-free, off treatment	0.704	0.63, 0.77	Derived from the 3L mBC submission TA423
Progressed	0.588	0.53, 0.65	Derived from the 3L mBC submission TA423

Abbreviations: mBC, metastatic breast cancer; 3L, third line; 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 patients in the third-line or later line setting. For full details on the methods of the SLR and the identified studies, see Appendix I. The SLR identified 7 studies from 11 publications. An overview of the study details and results from included cost and resource use studies is presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Acquisition costs

The acquisition costs for each comparator are presented in Table 89. All costs were sourced from eMIT where available or the BNF.[140,141] All therapies are costed as per the time-on-treatment in each arm as presented in Section B.3.3.1. Costs collected from related technology appraisals were inflated to 2018/2019 using inflation indices provided in the PSSRU Unit Costs of Health and Social Care.[142]

Table 89: Acquisition costs

Drug	Dose	mg/pack	Pack price	Pack size
T-DXd (list price)†	5.4 mg/kg	100 mg	[redacted]	1
T-DXd (PAS price)†	5.4 mg/kg	100 mg	[redacted]	
Eribulin	1.23 mg/m^2	2 ml	£361.00	1
		3 ml	£541.50	
Capecitabine	1250 mg/m^2	150mg	£4.17	60
		300mg	£7.26	
Vinorelbine	60 mg/m^2	1 ml	£36.71	10
		5 ml	£133.28	

† A list price application has been made to the Department of Health and a patient access scheme application has been made to the Patient Access Scheme Liaison Unit (PASLU).
Abbreviations: PAS, patient access scheme; T-DXd, trastuzumab deruxtecan.

B.3.5.1.2 Wastage

In TA523, a clinical expert confirmed that "in clinical practice drug wastage is recognised and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain". In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.

The average body surface area (BSA) in DESTINY-Breast01 was 1.66 m^2 (CI: 1.63,1.69), and average weight was 62.4 kg (CI: 60.4, 64.5). Drug wastage was calculated using the method of moments assuming a normal distribution of patients around the mean weight or BSA. Scenario analyses are presented which assume 0% and 100% vial sharing. The cost per dose without wastage and cost per dose with wastage is combined and weighted by the assumed proportion of vial sharing (Table 90).

Table 90: Primary therapy wastage

Drug	Wastage	Cost per dose with wastage	Cost per dose without wastage	Adjusted cost per dose
T-DXd (list price)	Yes	[redacted]	[redacted]	[redacted]
T-DXd (PAS price)	Yes	[redacted]	[redacted]	[redacted]
Eribulin	Yes	£778.89	£703.16	£741.02
Capecitabine	Yes	£0.75	£0.70	£0.73
Vinorelbine	Yes	£28.11	£22.29	£25.20

Abbreviations: PAS, patient access scheme.

B.3.5.1.3 Relative dose intensity

The mean relative dose intensities (RDIs) of the primary therapies are presented in Table 91. The relative dose intensity for T-DXd is taken from DESTINY-Breast01, the RDI for eribulin was assumed equal to the RDI presented in NICE TA423. The RDI for capecitabine and vinorelbine was conservatively assumed equal to eribulin. An RDI of 100% is assumed for subsequent therapies.

Table 91: Mean RDIs

Treatment	RDI
T-DXd	93.19%
Eribulin	84.00%
Capecitabine	84.00%
Vinorelbine	84.00%

Abbreviations: RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

B.3.5.1.4 Administration costs

The cost of infusion in the outpatient setting was sourced from NHS reference costs 2018/19, as shown in Table 92.[143] The cost of infusion is applied as a single cost per treatment dose. Patients receiving T-DXd received one infusion per 21-day cycle, eribulin and vinorelbine patients received two infusions per 21-day cycle. Capecitabine patients incurred a one-off cost of £92, equivalent to one-hour with a hospital based nurse (band 5).

Table 92: Administration costs

Method	Cost	Source/service code
Oral – one off cost	£92.00	PSSRU 2019 - 13 Hospital-based nurse cost per hour of patient contact (band 5)
IV infusion	£254.14	NHS reference costs 2018/2019/SB12Z - daycase

Abbreviations: IV, intravenous; NHS, National Health Service,

B.3.5.1.5 Subsequent therapies

In the base-case, 60% of patients receive a lifetime cost of subsequent therapies once they transition into the 'Progressed' health state. Subsequent therapies were costed to align with the ERG's preferred assumptions in TA423[42], with drug costs taken from the latest published version of eMIT or the BNF if not available in eMIT (Table 93). The average weekly cost of a treatment was calculated as an average of the weekly cost over three weekly cycles (as this was the maximum treatment cycle length for some of the treatments below) to account for differing treatment cycle lengths.

Table 93: Subsequent therapy costs

Drug	Dose	Administration method	Cost per dose	Frequency	Distribution of treatments
Vinorelbine IV	60.0 mg/kg	IV	£15.02	Weekly	18.4%
Vinorelbine oral	60 mg/m2	Oral	£219.90	Weekly	18.4%

Drug	Dose	Administration method	Cost per dose	Frequency	Distribution of treatments
Gemcitabine	1250.00 mg/m2	IV	£35.55	Day 1 & 8 of 21 day cycle	27.7%
Docetaxel	100 mg/m2	IV	£37.50	q3w	6.0%
Paclitaxel	175.0 mg/kg	IV	£37.76	q3w	15.7%
Doxorubucin	68 mg/m2	IV	£17.21	q3w	13.9%

Abbreviations: IV, intravenous.

A cost of £174.32per week was applied to patients in all arms of the model in the progressed disease state for their lifetime. A scenario analysis is presented that costed subsequent therapy using the same cost per week of subsequent therapies presented in TA423, £10.22.

B.3.5.2 Health-state unit costs and resource use

Medical resource use (MRU) costs and frequencies were informed by the resource use presented in NICE TA423 for pre- and post-progression health states.[42] Different assumptions were made in pre- and post-progression health states to reflect the varying intensities of follow-up care. Medical resource use incurred during an AE is costed separately (Section B.3.5.3). Costs were sourced from NHS Reference Costs 2018/19.[143]

Table 94: Resource use estimates

Resource	Pre-progression	Post-progression	Unit cost	Source/service code
	Frequency (per month)			
Medical Oncologist – follow-up	1.00	1.00	£147.97	NHS reference costs 2018/2019 - service code 370
GP contact	1.00	1.00	£39.23	PSSRU 2019 - 10.3b
CT scan	0.33	0.33	£77.95	NHS reference costs - RD20A

Abbreviations: CT, computerised topography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 95: Resource use costs by health state

Health state	Monthly cost	Weekly cost
Pre-progression	£253.70	£58.34
Post-progression	£253.70	£58.34

B.3.5.3 Adverse reaction unit costs and resource use

The costs of treating an AE were calculated using the NHS reference costs applied in TA423. All costs were updated to 2018/2019 NHS reference costs and 2019 PSSRU

costs.[143,144] The costs of AEs were applied to the proportion of each event that resulted in hospitalisation. For the adverse events reported for the comparators that were also reported for T-DXd, then the proportion of events that resulted in hospitalisation were based on the proportions of hospitalisation reported for T-DXd for each event (as reported in Section B.3.4.4). For events that occurred in the comparator trials that did not occur for T-DXd, then it was assumed in the base case 0% would lead to hospitalisation. This was tested in sensitivity analysis. The unit cost of each event and its relevant code are reported in Table 96. This approach aligns with the method adopted in TA423. The total cost of each adverse event was applied to the proportion of patients experiencing the AEs and a one-off cost was applied in the first cycle of the model. The differences in the costs applied to each comparator in the model are driven primarily by differences in AE frequencies (Section B.3.3.5). Appling AE costs as a one-off upfront cost was considered reasonable because of the short duration of treatment. The costs of AEs applied in each arm are presented in (Table 97).

Table 96: Cost of adverse events

AE	Cost	Reference/service code
Neutrophil count decreased/Neutropenia	£125.88	NHS reference costs 2016/2017/ XD25Z - Neutropenia drugs band 1[1]
Anaemia	£475.29	NHS reference costs 2018/2019/ SA04K - Iron deficiency anaemia with cc score 2-5 non-elective short stay
Nausea	£388.44	NHS reference costs 2018/2019/ JA12L - Malignant breast disorders without Interventions, with CC score 0-1 non-elective short stay
Fatigue	£60	PSSRU 2019/ 1hr community nurse visit (band 5)
White blood cell count decreased	£125.88	Assumed same as neutrophil count decreased
Dyspnoea	£466.30	NHS reference costs 2018/2019/ DZ20E - Pulmonary Oedema without interventions, with CC score 6+
Febrile neutropenia	£3,745.55	NHS reference costs 2016/2017/ PA45Z - Febrile Neutropenia with Malignancy[1]
Electrocardiogram QT prolonged	£783.48	NHS reference costs 2018/2019/ EY51Z: Electrocardiogram monitoring or stress testing non-elective short stay
Interstitial lung disease/Pneumonitis	£1,621.24	Reference costs 2018/2019/ DZ11M, Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8 non-elective short stay
Ejection fraction decreased	£404.73	NHS reference costs 2018/2019/ EB03E, Heart failure or shock, with CC score 0-3, non-elective short stay
Vomiting	£388.44	Assumed the same as nausea

AE	Cost	Reference/service code
Diarrhoea	£388.44	NHS reference costs 2018/2019/ JA12L - Malignant breast disorders without Interventions, with CC score 0-1 non elective short stay
Palmar-plantar erythrodysesthesia syndrome	£391.43	NHS reference costs 2018/2019/ JD07J - Skin disorders without intervention, with cc score 2-5 non-elective inpatient short stay
Dehydration	£399.42	TA515: Malignant Breast Disorders without Interventions, with CC Score 0-1 (Non-elective short stay)
Stomatitis	£518.95	TA423: WA21W Other Procedures and health care problems with CC -- Day Cases HRG
Abdominal pain	£319.73	Weighted average of day case abdominal pain with and without interventions (FD05A and FD05B), NHS reference costs 2018/19
Peripheral neuropathy	£137.35	TA423, inflated from 2015 prices

Abbreviations: AE, adverse event; NHS, national health service; PSSRU, Personal Social Services Research Unit.
1. NHS reference costs 2016/17 is when this HRG code was last available, and therefore this has been used as the source and inflated to 2019.

Table 97: Total adverse event costs by treatment

Treatment	AE cost
T-DXd	£40.73
Eribulin	£43.48
Capecitabine	£9.23
Vinorelbine	£25.81

Abbreviations: AE, adverse event; SoC, standard-of-care; T-DX-d, T-DXd, trastuzumab deruxtecan.

B.3.5.4 Miscellaneous unit costs and resource use

The cost of palliative care was assigned to each patient in the progressed state for 5.5 months before transitioning into the 'Dead' health state, as assumed in TA423.[42] The frequency of resource use for patients who were receiving palliative care was sourced from estimates presented in NICE TA423.[42] All resource use cost estimates were calculated based on 2019 PSSRU costs and 2018/2019 NHS reference costs and are presented in Table 98.[143,144]

Table 98: Palliative care disaggregated costs

Palliative care resources	Frequency (per month)	Unit cost	Source/service code
Medical oncologist – follow-up	1.00	£187.00	NHS reference costs 2018/2019 - service code 370

GP home visit	1.00	£39.23	2019 PSSRU costs – 10.3b
Clinical nurse specialist	1.00	£92.00	2019 PSSRU costs – 13 Hospital-based nurse cost per hour of patient contact (band 5)
Community nurse home visit	0.67	£60.00	2019 PSSRU costs – PSSRU 2019 - 10.1 Nurse Cost per hour of patient related work (band 5)

Abbreviations: GP, general practitioner; NHS, national health service; PSSRU, Personal Social Services Research Unit

A cost of £358.43 per month was applied to patients who were receiving palliative care for 5.5 months (Table 99).

Table 99: Palliative care total costs

Input	Value
Palliative care monthly costs	£358.43
Months of palliative care prior to death	5.50

End of life costs were applied to each patient who transitioned to the 'Dead' health state for 2 weeks before death. The cost of end of life treatment at a hospital or medical institution, hospice or at home, and the proportion of patients who died in each setting was taken from the estimates presented in NICE TA423 Table 100.[42] The total palliative, end of life costs and terminal care costs are presented in Table 101.

Table 100: End of life costs

End of life - care setting	Proportion of patients	Unit cost	Cost year	Uplifted and weighted cost
Hospital/Medical institution	40%	£5,135.25	2015	£2,178.60
Hospice	10%	£6,402.15	2015	£679.02
At home (with community support)	50%	£2,649.47	2015	£1,405.03
			Weighted EoL cost	**£4,262.64**

Abbreviations: EoL, end of life.

Table 101: Total terminal care costs

Type of cost	Cost
Palliative care costs	£1,971.37
EoL costs	£4,262.64
Total terminal care costs	£6,234.00

Abbreviations: EoL, end of life

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

B.3.6.1 Summary of base-case analysis inputs

Table 102: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline characteristics			
Mean age	55.96	CI= 54.26, 57.67 (Normal)	B.3.3.1.3
Mean weight (kg)	62.47	CI= 60.43, 64.51 (Normal)	
Mean BSA	1.66	CI= 1.63, 1.69 (Normal)	B.3.5.1.2
Proportion HER2 positive by study - EMBRACE (Cortes 2011)	18%	N/A	
Proportion HER2 positive by study - Barni 2019	100%	N/A	
Proportion HER2 positive by study - Cortes 2010	11%	N/A	
Proportion HER2 positive by study - Gamucci 2014	21%	N/A	
Proportion HER2 positive by study - Fumoleau 2004	20%	N/A	
Proportion HER2 positive by study - Blum 2001	20%	N/A	
Proportion HER2 positive by study - Sim 2019	100%	N/A	
Proportion HER2 positive by study - TH3RESA	100%	N/A	B.3.3.4
OS/PFS/TTD data			
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	1.84	CI= 1.33, 2.56 (Log-normal)	B.3.3
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	1.84	CI= 1.33, 2.56 (Log-normal)	
Eribulin median treatment duration (months) - EMBRACE (Cortes 2011)	3.9	N/A	
Eribulin median treatment duration (cycles) - Barni 2019	4	N/A	
Eribulin median treatment duration (cycles) - Cortes 2010	4	N/A	
Eribulin median treatment duration (cycles) - Gamucci 2014	5	N/A	
Capecitabine median treatment duration (months) - Fumoleau 2004	4.1	N/A	
Capecitabine median treatment duration (months) - Blum 2001	3.2	N/A	
PFS - Eribulin versus T-DXd - MAIC HR - EMBRACE (Cortes 2011)	[redacted]	[redacted]	
PFS - Eribulin versus T-DXd - MAIC HR - Barni 2019	[redacted]	[redacted]	
PFS - Eribulin versus T-DXd - MAIC HR - Cortes 2010	[redacted]	[redacted]	
PFS - Eribulin versus T-DXd - MAIC HR - Gamucci 2014	[redacted]	[redacted]	
PFS - Capecitabine versus T-DXd - MAIC HR - Fumoleau 2004	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PFS - Capecitabine versus T-DXd - MAIC HR - Blum 2001	[redacted]	[redacted]	
PFS - Vinorelbine versus T-DXd - MAIC HR	[redacted]	[redacted]	
OS - T-DXd versus Eribulin - MAIC HR - EMBRACE (Cortes 2011)	[redacted]	[redacted]	
OS HR - T-DXd versus TH3RESA	[redacted]	[redacted]	
Drug cost inputs			
Pack price - T-DXd - 100mg	[redacted]	N/A	B.3.5.1
Pack price - Vinorelbine - 1ml	£36.71	N/A	
Pack price - Vinorelbine - 5ml	£133.28	N/A	
Pack price - Eribulin - 2ml	£361.00	N/A	
Pack price - Eribulin - 3ml	£541.50	N/A	
Pack price - Capecitabine - 150mg	£4.17	N/A	
Pack price - Capecitabine - 300mg	£7.26	N/A	
Pack price - Capecitabine - 500mg	£25.76	N/A	
T-DXd RDI	93%	N/A	
Eribulin RDI	84%	N/A	
Capecitabine RDI	84%	N/A	
Vinorelbine RDI	84%	N/A	
% vial sharing assumed	50%	CI= 0.45, 0.55 (Beta)	
Administration cost Oral	£0.00	N/A	
Administration cost IV infusion	£254.14	CI= 228.73, 279.55 (Gamma)	
Proportion of progressed patients receiving subsequent therapy	60%	CI= 0.54, 0.66 (Beta)	
TA423 - Monthly average subsequent treatment cost (used in scenario analysis)	44	CI= 39.6, 48.4 (Gamma)	
Weekly subsequent treatment cost (base case)	£174.32	N/A	
Distribution of treatments for subsequent therapy - Vinorelbine IV (used in scenario analysis)	18%	N/A	
Distribution of treatments for subsequent therapy - Vinorelbine oral (used in scenario analysis)	18%	N/A	
Distribution of treatments for subsequent therapy - Gemcitabine (used in scenario analysis)	28%	N/A	
Distribution of treatments for subsequent therapy - Docetaxel (used in scenario analysis)	6%	N/A	
Distribution of treatments for subsequent therapy - Paclitaxel (used in scenario analysis)	16%	N/A	
Distribution of treatments for subsequent therapy - Doxorubucin (used in scenario analysis)	14%	N/A	
Resource use inputs			
Resource use - pre-progression - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	B.3.5.2
Resource use - pre-progression - TA423 - GP Contact - frequency per month	1	CI= 0.9, 1.1 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Resource use - pre-progression - TA423 - CT scan - frequency per month	0.33	CI= 0.3, 0.36 (Gamma)	
Resource use - Medical Oncologist - follow-up - unit cost	£147.97	CI= 133.17, 162.76 (Gamma)	
Resource use - GP Contact - unit cost	£39.23	CI= 35.31, 43.15 (Gamma)	
Resource use - CT scan - unit cost	£77.95	CI= 70.16, 85.75 (Gamma)	
Resource use - post-progression - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - post-progression - TA423 - GP Contact - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - post-progression - TA423 - CT scan - frequency per month	0.33	CI= 0.3, 0.36 (Gamma)	
Resource use - palliative care - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	B.3.5.4
Resource use - palliative care - TA423 - GP Home visit - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - palliative care - TA423 - Clinical nurse specialist - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - palliative care - TA423 - Community nurse home visit - frequency per month	0.67	CI= 0.6, 0.74 (Gamma)	
Resource use - palliative care - TA423 - Medical Oncologist - follow-up - unit cost	£147.97	CI= 133.17, 162.76 (Gamma)	
Resource use - palliative care - TA423 - GP Home visit - unit cost	£39.23	CI= 35.31, 43.15 (Gamma)	
Resource use - palliative care - TA423 - Clinical nurse specialist - unit cost	£92.00	CI= 82.8, 101.2 (Gamma)	
Resource use - palliative care - TA423 - Community nurse home visit - unit cost	£60.00	CI= 54, 66 (Gamma)	
Reource use - palliative care - duration (months)	5.5	CI= 4.95, 6.05 (Gamma)	
Terminal care proportion - Hospital/Medical Institution	40%	N/A	
Terminal care proportion - Hospice	10%	N/A	
Terminal care proportion - At home (with community support)	50%	N/A	
Terminal care cost - Hospital/Medical Institution	£5,135.25	CI= 4621.73, 5648.78 (Gamma)	
Terminal care cost - Hospice	£6,402.15	CI= 5761.94, 7042.37 (Gamma)	
Terminal care cost - At home (with community support)	£2,649.47	CI= 2384.52, 2914.42 (Gamma)	
Adverse events			
AE - T-DXd full cohort - Neutrophil count decreased - events (N)	38	CI= 34.2, 41.8 (Gamma)	B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - T-DXd full cohort - Anaemia - events (N)	28	CI= 25.2, 30.8 (Gamma)	
AE - T-DXd full cohort - Neutropenia - events (N)	37	CI= 33.3, 40.7 (Gamma)	
AE - T-DXd full cohort - Nausea - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - T-DXd full cohort - Fatigue - events (N)	15	CI= 13.5, 16.5 (Gamma)	
AE - T-DXd full cohort - White blood cell count decreased - events (N)	11	CI= 9.9, 12.1 (Gamma)	
AE - T-DXd full cohort - Dyspnoea - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Febrile neutropenia - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Electrocardiogram QT prolonged - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Interstitial lung disease - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Ejection fraction decreased - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Pneumonitis - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Vomiting - events (N)	0	N/A	
AE - T-DXd full cohort - Neutrophil count decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Anaemia - N hospitalised	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Neutropenia - N hospitalised	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Nausea - N hospitalised	4	CI= 3.6, 4.4 (Gamma)	
AE - T-DXd full cohort - Fatigue - N hospitalised	0	N/A	
AE - T-DXd full cohort - White blood cell count decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Dyspnoea - N hospitalised	0	N/A	
AE - T-DXd full cohort - Febrile neutropenia - N hospitalised	0	N/A	
AE - T-DXd full cohort - Electrocardiogram QT prolonged - N hospitalised	0	N/A	
AE - T-DXd full cohort - Interstitial lung disease - N hospitalised	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Ejection fraction decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Pneumonitis - N hospitalised	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Vomiting - N hospitalised	0	N/A	
AE - Eribulin - EMBRACE - Neutrophil count decreased (%)	0%	N/A	
AE - Eribulin - EMBRACE - Anaemia (%)	2%	CI= 0.01, 0.04 (Beta)	
AE - Eribulin - EMBRACE - Neutropenia (%)	15%	CI= 0.12, 0.18 (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Eribulin - EMBRACE - Nausea (%)	1%	CI= 0, 0.03 (Beta)	
AE - Eribulin - EMBRACE - Fatigue** (%)	2%	CI= 0.01, 0.04 (Beta)	
AE - Eribulin - EMBRACE - White blood cell count decreased* (%)	4%	CI= 0.03, 0.06 (Beta)	
AE - Eribulin - EMBRACE - Dyspnoea (%)	3%	CI= 0.02, 0.05 (Beta)	
AE - Eribulin - EMBRACE - Febrile neutropenia (%)	2%	CI= 0.01, 0.03 (Beta)	
AE - Eribulin - EMBRACE - Electrocardiogram QT prolonged (%)	0%	N/A	
AE - Eribulin - EMBRACE - Interstitial lung disease (%)	0%	N/A	
AE - Eribulin - EMBRACE - Ejection fraction decreased (%)	0%	N/A	
AE - Eribulin - EMBRACE - Pneumonitis (%)	0%	N/A	
AE - Eribulin - EMBRACE - Vomiting (%)	0%	N/A	
AE - Eribulin - EMBRACE - Palmar-Plantar Erythro-Dysaesthesia Syndrome1 (%)	6%	CI= 0.04, 0.09 (Beta)	
AE - Eribulin - EMBRACE - Peripheral neuropathy1 (%)	0%	N/A	
AE - Eribulin - Barni 2019 - Neutrophil count decreased - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Anaemia - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Eribulin - Barni 2019 - Neutropenia - events (N)	70	CI= 63, 77 (Gamma)	
AE - Eribulin - Barni 2019 - Nausea - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Barni 2019 - Fatigue** - events (N)	42	CI= 37.8, 46.2 (Gamma)	
AE - Eribulin - Barni 2019 - White blood cell count decreased* - events (N)	4	CI= 3.6, 4.4 (Gamma)	
AE - Eribulin - Barni 2019 - Dyspnoea - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Barni 2019 - Febrile neutropenia - events (N)	15	CI= 13.5, 16.5 (Gamma)	
AE - Eribulin - Barni 2019 - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Interstitial lung disease - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Ejection fraction decreased - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Pneumonitis - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Vomiting - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Palmar-Plantar Erythro-Dysaesthesia Syndrome1 - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Peripheral neuropathy1 - events (N)	0	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Eribulin - Cortes 2010 - Neutrophil count decreased - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Anaemia - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Neutropenia - events (N)	157	CI= 141.3, 172.7 (Gamma)	
AE - Eribulin - Cortes 2010 - Nausea - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Fatigue - events (N)	29	CI= 26.1, 31.9 (Gamma)	
AE - Eribulin - Cortes 2010 - White blood cell count decreased* - events (N)	41	CI= 36.9, 45.1 (Gamma)	
AE - Eribulin - Cortes 2010 - Dyspnoea - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Febrile neutropenia - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Interstitial lung disease - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Ejection fraction decreased - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Pneumonitis - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Vomiting - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Cortes 2010 - Palmar-Plantar Erythro-Dysaesthesia Syndrome - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Peripheral neuropathy1 - events (N)	20	CI= 18, 22 (Gamma)	
AE - Capecitabine - Neutrophil count decreased - events (N)	0	N/A	
AE - Capecitabine - Anaemia - events (N)	0	N/A	
AE - Capecitabine - Neutropenia - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - Capecitabine - Nausea - events (N)	7	CI= 6.3, 7.7 (Gamma)	
AE - Capecitabine - Fatigue - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Capecitabine - White blood cell count decreased - events (N)	0	N/A	
AE - Capecitabine - Dyspnoea - events (N)	0	N/A	
AE - Capecitabine - Febrile neutropenia - events (N)	0	N/A	
AE - Capecitabine - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Capecitabine - Interstitial lung disease - events (N)	0	N/A	
AE - Capecitabine - Ejection fraction decreased - events (N)	0	N/A	
AE - Capecitabine - Pneumonitis - events (N)	0	N/A	
AE - Capecitabine - Vomiting - events (N)	0	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Capecitabine - Diarrhoea - events (N)	14	CI= 12.6, 15.4 (Gamma)	
AE - Capecitabine - Palmar-Plantar Erythro-Dysaesthesia Syndrome - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - Capecitabine - Dehydration - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Capecitabine - Stomatitis - events (N)	9	CI= 8.1, 9.9 (Gamma)	
AE - Vinorelbine - Neutrophil count decreased - events (N)	0	N/A	
AE - Vinorelbine - Anaemia - events (N)	4	CI= 3.6, 4.4 (Gamma)	
AE - Vinorelbine - Neutropenia - events (N)	45	CI= 40.5, 49.5 (Gamma)	
AE - Vinorelbine - Nausea - events (N)	0	N/A	
AE - Vinorelbine - Fatigue - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Vinorelbine - White blood cell count decreased - events (N)	0	N/A	
AE - Vinorelbine - Dyspnoea - events (N)	0	N/A	
AE - Vinorelbine - Febrile neutropenia - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Vinorelbine - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Vinorelbine - Interstitial lung disease - events (N)	0	N/A	
AE - Vinorelbine - Ejection fraction decreased - events (N)	0	N/A	
AE - Vinorelbine - Pneumonitis - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - Vinorelbine - Vomiting - events (N)	0	N/A	
AE - Vinorelbine - Abdominal pain - events (N)	12	CI= 10.8, 13.2 (Gamma)	
Adverse event costs and assumptions			
AE cost - hospitalized - Neutrophil count decreased	£119.49	CI= 107.54, 131.44 (Gamma)	B.3.5.3
AE cost - hospitalized - Anaemia	£475.29	CI= 427.76, 522.82 (Gamma)	
AE cost - hospitalized – Neutropenia (uninflated)	£119.49	CI= 107.54, 131.44 (Gamma)	
AE cost - hospitalized - Nausea	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - Fatigue	£60.00	CI= 54, 66 (Gamma)	
AE cost - hospitalized - White blood cell count decreased (uninflated)	£119.49	CI= 107.54, 131.44 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE cost - hospitalized - Dyspnoea	£466.30	CI= 419.67, 512.93 (Gamma)	
AE cost - hospitalized - Febrile neutropenia (uninflated)	£3,619.00	CI= 3257.1, 3980.9 (Gamma)	
AE cost - hospitalized - Electrocardiogram QT prolonged	£783.48	CI= 705.13, 861.83 (Gamma)	
AE cost - hospitalized - Interstitial lung disease	£1,621.24	CI= 1459.12, 1783.36 (Gamma)	
AE cost - hospitalized - Ejection fraction decreased	£404.73	CI= 364.25, 445.2 (Gamma)	
AE cost - hospitalized - Pneumonitis	£1,621.24	CI= 1459.12, 1783.36 (Gamma)	
AE cost - hospitalized - Vomiting	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - Diarrhoea	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - PPE	£391.43	CI= 352.28, 430.57 (Gamma)	
AE cost - hospitalized - Dehydration	£399.42	CI= 359.48, 439.36 (Gamma)	
AE cost - hospitalized - Stomatitis	£518.95	CI= 467.06, 570.85 (Gamma)	
AE cost - hospitalized - Abdominal pain	£319.73	CI= 287.76, 351.7 (Gamma)	
AE cost - hospitalized - Peripheral neuropathy (uninflated)	£128.67	CI= 115.8, 141.54 (Gamma)	
Proportion hospitalised - Diarrhoea	0%	N/A	
Proportion hospitalised - PPE	0%	N/A	
Proportion hospitalised - Dehydration	0%	N/A	
Proportion hospitalised - Stomatitis	0%	N/A	
Proportion hospitalised - Abdominal pain	0%	N/A	
Proportion hospitalised - Peripheral neuropathy	0%	N/A	
Utilities			
Response rate - T-DXd (U201)	61%	CI= 0.53, 0.68 (Beta)	B.3.4.5
Response rate - Eribulin - EMBRACE	14%	CI= 0.09, 0.21 (Beta)	
Response rate - Eribulin - Barni	17%	CI= 0.1, 0.28 (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Response rate - Eribulin - Cortes 2010	10%	CI= 0.06, 0.16 (Beta)	
Response rate - Eribulin - Gamucci	26%	CI= 0.09, 0.57 (Beta)	
Response rate - Capecitabine - Fumoleau	19%	CI= 0.1, 0.33 (Beta)	
Response rate - Capecitabine - Blum	23%	CI= 0.12, 0.39 (Beta)	
Response rate - Vinorelbine	32%	CI= 0.13, 0.6 (Beta)	
Incremental utility of response	8%	CI= 0.05, 0.1 (Beta)	
Utility: Progression free off treatment, TA423	70%	CI= 0.69, 0.72 (Beta)	
Utility: PFS off treatment, Le et al.	70%	CI= 0.5, 0.8 (Beta)	
Utility: Progressed, TA423	68%	CI= 0.67, 0.69 (Beta)	
Utility: Progressed, Le et a.	50%	CI= 0.45, 0.72 (Beta)	
Utility: Progressed, ERG	50%	CI= 0.45, 0.55 (Beta)	
Utility: Progressed, Average of ERG and company	59%	CI= 0.53, 0.65 (Beta)	
AE disutility - Neutrophil count decreased	0.01	CI= 0, 0.014 (Beta)	B.3.4.4
AE disutility - Anaemia	0.01	CI= -0.015, 0.035 (Beta)	
AE disutility - Neutropenia	0.01	CI= 0, 0.014 (Beta)	
AE disutility - Nausea	0.02	CI= -0.019, 0.061 (Beta)	
AE disutility - Fatigue	0.03	CI= 0.014, 0.044 (Beta)	
AE disutility - White blood cell count decreased	0.00	CI= -0.009, 0.015 (Beta)	
AE disutility - Dyspnoea	0.03	CI= 0.007, 0.047 (Beta)	
AE disutility - Febrile neutropenia	0.01	CI= -0.017, 0.041 (Beta)	
AE disutility - Electrocardiogram QT prolonged	0.00	N/A	
AE disutility - Interstitial lung disease	0.17	CI= 0.153, 0.187 (Beta)	
AE disutility - Ejection fraction decreased	0.06	CI= 0, 0.11 (Beta)	
AE disutility - Pneumonitis	0.17	CI= 0.153, 0.187 (Beta)	
AE disutility - Vomiting	0.10	CI= 0.093, 0.113 (Beta)	
AE disutility - Diarrhoea	0.01	CI= -0.014, 0.026 (Beta)	
AE disutility - PPE	0.12	CI= 0.093, 0.139 (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE disutility - Dehydration	0.01	CI= -0.026, 0.014 (Beta)	
AE disutility - Stomatitis	0.15	CI= 0.11, 0.19 (Beta)	
AE disutility - Abdominal pain	0.01	CI= -0.026, 0.014 (Beta)	
AE disutility - Peripheral neuropathy	0.01	CI= 0.002, 0.03 (Beta)	
AE duration - Neutrophil count decreased	40.10	CI= 31.899, 48.301 (Gamma)	
AE duration - Anaemia	42.90	CI= 33.083, 52.717 (Gamma)	
AE duration - Neutropenia	40.10	CI= 31.899, 48.301 (Gamma)	
AE duration - Nausea	36.20	CI= 23.752, 48.648 (Gamma)	
AE duration - Fatigue	58.30	CI= 46.797, 69.803 (Gamma)	
AE duration - White blood cell count decreased	42.20	CI= 34.188, 50.212 (Gamma)	
AE duration - Dyspnoea	9.60	CI= 8.64, 10.56 (Gamma)	
AE duration - Febrile neutropenia	7.00	CI= 6.3, 7.7 (Gamma)	
AE duration - Electrocardiogram QT prolonged	31.40	CI= 24.847, 37.953 (Gamma)	
AE duration - Interstitial lung disease	51.10	CI= 43.413, 58.787 (Gamma)	
AE duration - Ejection fraction decreased	31.00	CI= 29.33, 32.67 (Gamma)	
AE duration - Pneumonitis	51.10	CI= 43.413, 58.787 (Gamma)	
AE duration - Vomiting	13.70	CI= 8.348, 19.052 (Gamma)	
AE duration - Diarrhoea	17.00	CI= 13.67, 20.33 (Gamma)	
AE duration - PPE	14.00	CI= 12.6, 15.4 (Gamma)	
AE duration - Dehydration	17.00	CI= 13.67, 20.33 (Gamma)	
AE duration - Stomatitis	10.00	CI= 9, 11 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE duration - Abdominal pain	17.00	CI= 13.67, 20.33 (Gamma)	
AE duration - Peripheral neuropathy	40.10	CI= 31.899, 48.301 (Gamma)	
Utility - general population - sex coefficient	0.02121	CI= 0.01599, 0.02644 (Normal)	B.3.4.5.1
Utility - general population - age coefficient	-0.00026	CI= -0.00098, 0.00048 (Normal)	
Utility - general population - age squaredcoefficient	-0.00003	CI= -0.00004, -0.00002 (Normal)	
Utility - general population - constant	0.95	CI= 0.935, 0.965 (Beta)	

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; CT, computed tomography; ERG; evidence review group; gen. gamma, generalised gamma; GP, general practitioner; HR, hazard ratio; IV, itranvenous; MAIC, matched adjusted indirect comparison; N/A, not applicable; OS, overall survival; PFS progression free survival; PPE, Palmar-Plantar Erythro-Dysaesthesia Syndrome; QALYs, quality adjusted life year; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

B.3.6.2 Assumptions

Table 103 provides a summary of assumptions applied in the economic model.

Table 103: Summary of assumptions applied in the economic model

Assumption	Rationale
Extrapolations of T-DXd overall survival were based on applying a HR vs. the T-DM1 OS curve from the TH3RESA trial	OS data in DESTINY-Breast01 are considered prohibitively immature for informative parametric modelling, therefore a HR was applied to T-DM1 OS curve from TH3RESA. Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including trastuzumab, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or capecitabine. Clinical experts at the August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect that of T-DM1 than that of the model comparators, and that a 'tail' should be expected in the T-DXd OS curve; anchoring on non-targeted therapies (such as eribulin) is not expected to provide an accurate estimate of long-term survival. More information is provided in Section B.3.3.1.1
Vinorelbine OS is equivalent to capecitabine OS	Only the Sim (2019) study was available to inform the comparison against vinorelbine[82]; however, clinical experts at the August advisory board advised that the OS observed in Sim 2019 (18.9 months) is not plausible following PFS of 12 weeks, and is likely driven by the use of post-progression therapies.[59] Given that vinorelbine is associated with similar or worse PFS compared with capecitabine, OS for vinorelbine is assumed to be equivalent to OS for capecitabine; further details are provided in Section B.3.3.1.2.
20% HER2-positive patients were	Where information was available on the distribution of HER2-expression in a trial population (Cortes, 2011), an adjustment was made to the trial

assumed in trials with no information regarding HER2-expression in the patient population	outcomes in order to compare outcomes with a 100% HER2-positive population. There was no information on HER2-expression in the data presented by Fumoleau et al, therefore an adjustment was made assuming that 20% of patients in the study were HER2-positive, as observed in clinical practice.[17]
The impact of HER2 status on outcomes is the same between OS and PFS	In the base-case, an adjustment to OS and PFS in the eribulin and capecitabine arms of the model is made to account for the proportion of patients with HER2-positive vs. HER2-negative disease, using the HR presented by Lv et al. Only OS was presented in the study, and therefore the same HR was applied to adjust PFS. At the August advisory board, clinical experts advised that both PFS and OS would be poorer for HER2-positive patients.
Treatment to PFS is assumed for all comparator drugs	For comparator treatments, only median TTD data were available from the studies. When a HR is applied vs. T-DXd TTD for each comparator that passes through the median TTD, the TTD curve quickly passes through the PFS curve. This suggests that the shape of the TTD curves of each comparator is not the same as that of T-DXd. Furthermore, as mean PFS for each comparator is relatively short, it is reasonable to assume that patients would not discontinue treatment before progression in UK clinical practice.
50% drug wastage is assumed	In TA523, a clinical expert confirmed that "in clinical practice drug wastage is recognized and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain". In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.
AE-associated cost and QALY losses accounted for in first cycle of model	Time on treatment is short for all comparators, and therefore there are not expected to be any long-term cost and QALY losses associated with AEs.
The proportion of AEs that resulted in hospitalisation in DESTINY-Breast01 was applied to all comparator AE proportions	There were no data available on the proportion of each AE that resulted in hospitalisation for each comparator, therefore the best available evidence - patient level data from DESTINY-Breast01 - was used.
0% hospitalisation is assumed in AEs with no hospitalisation data	For AEs that did not occur in DESTINY-Breast01, there were no data available on the proportion of AEs that resulted in hospitalisation. A conservative assumption of 0% was applied in the base-case.
The RDI for capecitabine and vinorelbine was assumed equal to eribulin.	In the absence of other data, the RDI for capecitabine and vinorelbine is conservatively assumed to be the same as for eribulin.
Resource use estimates are equal for all treatments	This is consistent with previous TAs

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS progression free survival; QALYs, quality adjusted life year; RDI, relative dose intensity; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TA, technology assessment; TTD, time-to-discontinuation

B.3.7 Base-case results

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

In the base-case analysis, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the base-case, fully incremental results is presented in Table 104.

Table 104: Base-case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted] compared with capecitabine, giving a probabilistic ICER of [redacted] This is highly congruent with deterministic changes in costs of [redacted] and QALYs of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of [redacted] QALY was [redacted]. A summary of the probabilistic, fully incremental results are presented in Table 105. The cost-effectiveness plane vs. each comparator and CEAC are presented in Figure 36, Figure 37, Figure 38**,** and Figure 39.

Table 105: PSA results (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 36: T-DXd vs eribulin scatterplot (list price)

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

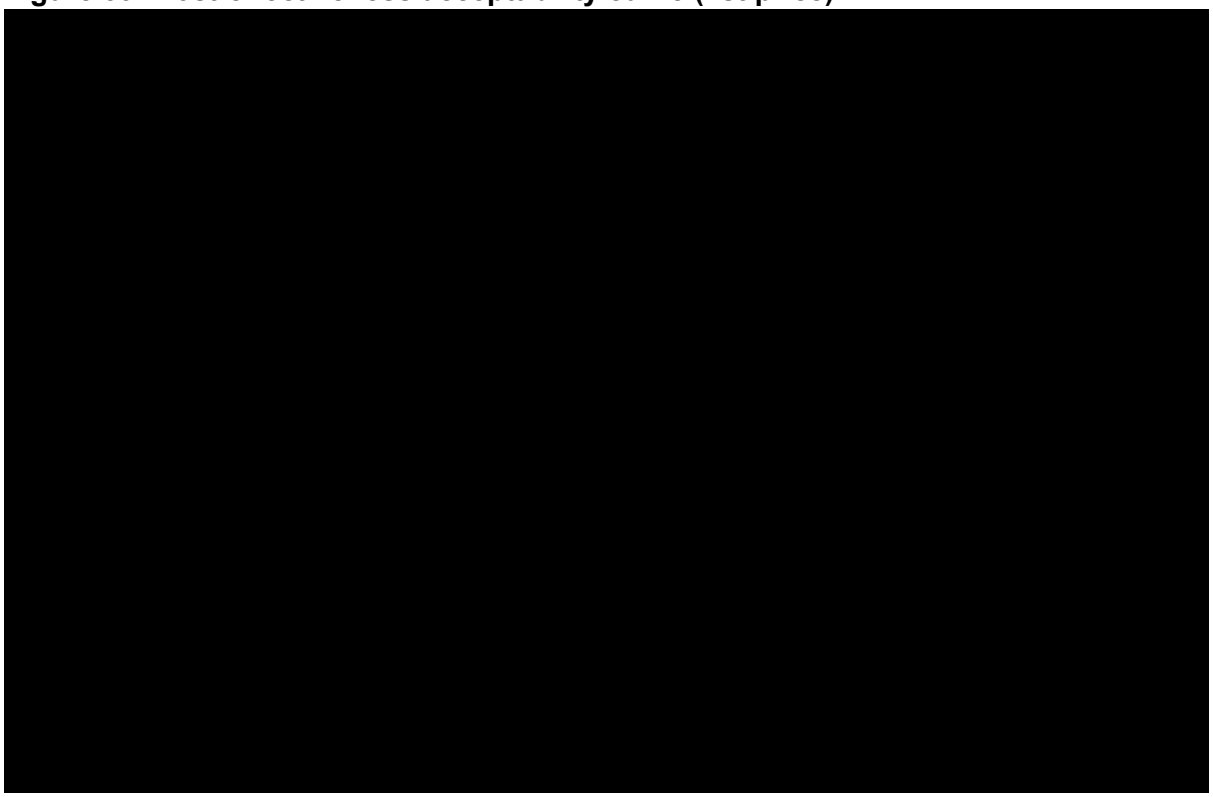
Figure 37: T-DXd vs capecitabine scatterplot (list price)

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 38: T-DXd vs vinorelbine scatterplot (list price)

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 39: Cost-effectiveness acceptability curve (list price)



Abbreviations: T-DXd, trastuzumab deruxtecan.

B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±10% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are reported for each pairwise comparison. For each comparator, the most influential parameter was the HR applied to TH3RESA curve to model T-DXd OS. As the survival gains in the T-DXd arm of the model are the primary driver of results in the model, it is to be expected that the OS HR that informs T-DXd survival would have the largest impact on results. Other influential parameters include the HER2-positive efficacy adjustment HR and health state utility values, although the effect of varying these parameters on results is small.

B.3.8.2.1 T-DXd vs eribulin

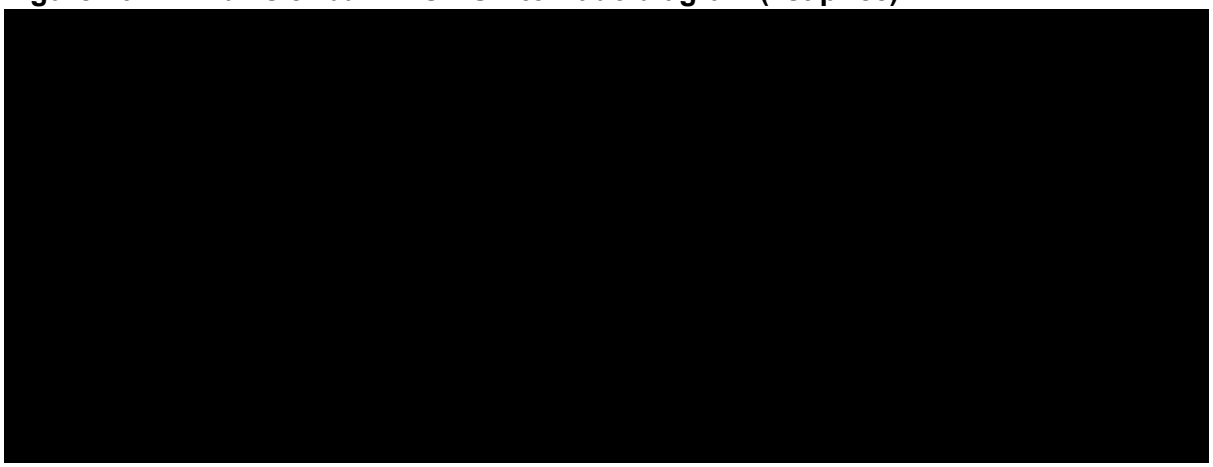
The OWSA results for the comparison of T-DXd vs. eribulin are presented in Table 106; the tornado diagram is presented in Figure 40.

Table 106: OWSA results - T-DXd vs eribulin (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA	[redacted]	[redacted]
T-DXd RDI	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
PFS - Eribulin versus T-DXd - MAIC HR - EMBRACE (Cortes 2011)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	[redacted]	[redacted]
Eribulin RDI	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy	[redacted]	[redacted]
Administration cost IV infusion	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival, OWSA; one-way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan, IV; intravenous

Figure 40: T-DXd vs eribulin - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS; overall survival, OWSA, one-way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan, IV; intravenous

B.3.8.2.2 T-DXd vs capecitabine

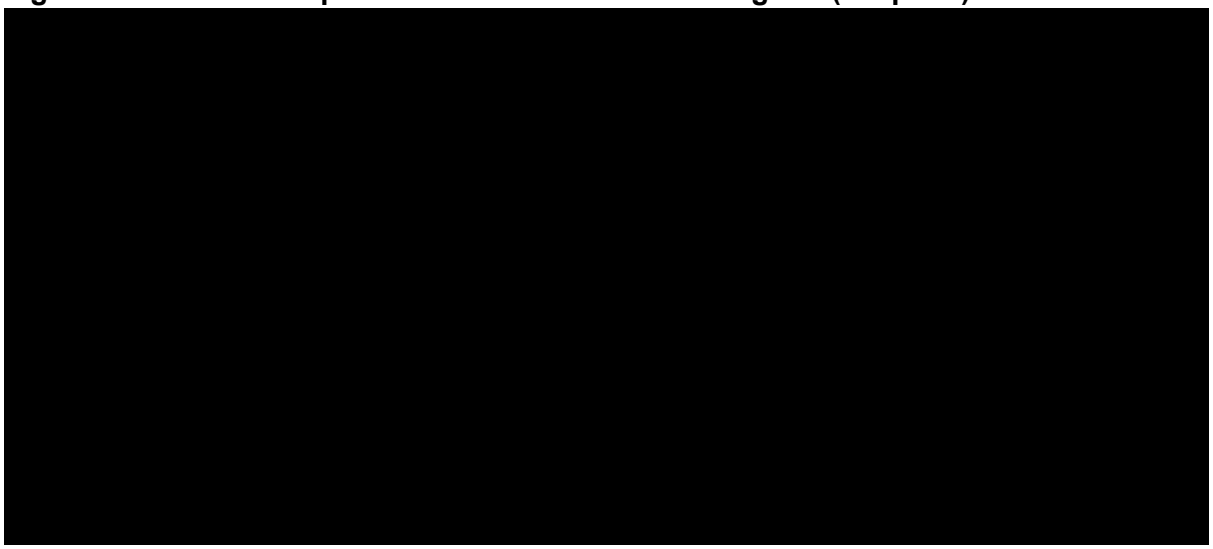
The OWSA results for the comparison of T-DXd vs. capecitabine are presented in Table 107; the tornado diagram is presented in Figure 41.

Table 107: OWSA results - T-DXd vs capecitabine (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA	[redacted]	[redacted]
T-DXd RDI	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
PFS - Capecitabine versus T-DXd - MAIC HR - Fumoleau 2004	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	[redacted]	[redacted]
Utility - general population - age squaredcoefficient	[redacted]	[redacted]
% vial sharing assumed	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan

Figure 41: T-DXd vs capecitabine - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan

B.3.8.2.3 T-DXd vs vinorelbine

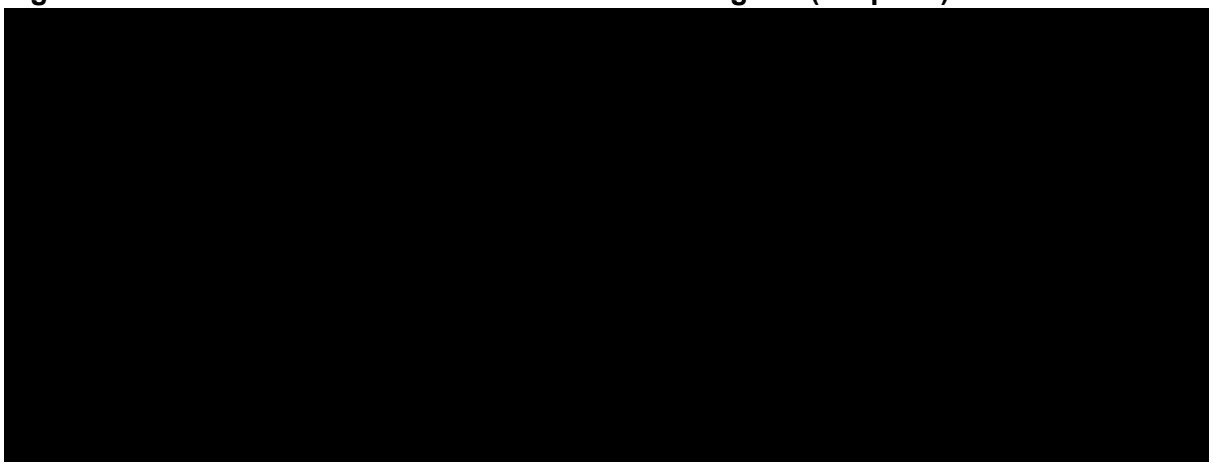
The OWSA results for the comparison of T-DXd vs. vinorelbine are presented in Table 108, and the tornado diagram is presented in Figure 42.

Table 108: OWSA results - T-DXd vs vinorelbine (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA	[redacted]	[redacted]
T-DXd RDI	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy	[redacted]	[redacted]
% vial sharing assumed	[redacted]	[redacted]
Utility - general population - age coefficient	[redacted]	[redacted]
Response rate - Vinorelbine	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan

Figure 42: T-DXd vs vinorelbine - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one-way sensitivity analysis; RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan

B.3.8.3 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied. For all comparators, the scenarios with the biggest impact on the ICER were selection of different distributions for the TH3RESA OS extrapolation, choosing the log-normal or log-logistic distributions decreased the ICER by over 20% in each analysis, and choosing the Gompertz distribution increased the ICER by over 20%. The distribution chosen for TTD also had a large impact on the ICER. Choosing the Weibull and Gompertz distribution decreased the

ICER by over 10% and choosing the log-logistic and generalised gamma distributions increased the ICER. Other influential scenarios included choosing different baseline survival curve sources for each comparator.

B.3.8.3.1 T-DXd vs Eribulin

Scenario analyses for the analysis vs. eribulin are presented in Table 109.

Table 109: T-DXd vs eribulin - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]

Eribulin OS: Using Barni - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median TTD, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

B.3.8.3.2 T-DXd vs capecitabine

Scenario analyses for the analysis vs. capecitabine are presented in Table 110.

Table 110: T-DXd vs capecitabine - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]

Cap OS: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median TTD, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

[†]Note that in the PSA, the incremental costs are rounded to two decimal places, and therefore the base case ICER can differ slightly from that of the base case results in the model.

B.3.8.3.3 T-DXd vs vinorelbine

Scenario analyses for the analysis vs. vinorelbine are presented in Table 111.

Table 111: T-DXd vs vinorelbine - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]

Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median TTD, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]

T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

B.3.8.4 Summary of sensitivity analyses results

The results of sensitivity analyses demonstrate that in all cases T-DXd is expected to provide a significant increase in QALYs vs. each comparator.

Deterministic analyses showed that the most influential parameter was the HR for T-DXd vs. TH3RESA that defined the survival extrapolations in OS; this is to be expected as the cost-effectiveness results are primarily driven by survival gains. Beyond this parameter, the impact of varying other parameters in the model was small.

Scenario analyses showed that the parameters with the most influence on the ICER was the distribution chosen to model TH3RESA OS. Other key assumptions were the distribution used to model TTD for T-DXd and the source of comparator efficacy data.

Probabilistic analysis indicated that there is a [redacted] likelihood of T-DXd being cost-effective at a willingness to pay threshold of £50,000 per QALY.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Quality control of the electronic model was performed both internally by the model developers, and externally by an independent health economist. Validation of the model by both internal and external health economists involved review of:

- Formulae
- Consistency with the model decision problem
- VBA implementation

- Inputs
- Model functionality

Furthermore, model inputs and assumptions were validated at the August Advisory Board involving four UK clinical experts in BC and four independent health economists.[59]

B.3.11 Interpretation and conclusions of economic evidence

In the base-case analysis, eribulin is dominated, vinorelbine is extendedly dominated [redacted]. However, a confidential PAS for T-DXd has been proposed, which would result in a lower ICER compared with capecitabine [redacted] Key drivers of cost-effectiveness are the OS HR for T-DXd vs. T-DM1, and the survival distributions for OS and TTD for all comparators. DS considers T-DXd to be a plausible CDF candidate in this indication.

Mean OS for individuals receiving T-DXd was predicted to be [redacted] months, compared with [redacted] months for eribulin and [redacted] months for capecitabine and vinorelbine. T-DXd is therefore expected to represent a life extending treatment at the end of life, and additional QALY weighting is expected to apply.

The key strengths of the analysis are:

- Key components of the economic model were informed and validated by four clinical experts with specialist knowledge of mBC
- Multiple scenario and sensitivity analyses were conducted, and the results of the analysis were found to be relatively robust to alternative assumptions

The key limitations of the analysis are:

- Single-arm data are available from DESTINY-Breast01; comparative data vs. eribulin, capecitabine and vinorelbine are therefore informed by unanchored MAICs
- OS data from DESTINY-Breast01 were considered prohibitively immature for informative parametric survival modelling; it was therefore necessary to use OS data from other HER2-targeted ADCs in third-line mBC

Despite uncertainties in the analysis, T-DXd has demonstrated the potential to be a cost-effective use of NHS resources at the proposed PAS price; the proposed PAS is expected to result in improved cost-effectiveness. If T-DXd were recommended for use within the CDF,

additional data collected in the Phase III trial is expected to address outstanding areas of uncertainty.

B.4 References

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

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: Checklist of confidential information

Appendix L: Clinical guidelines

Appendix M: Supplementary clinical study

Appendix N: Results using PAS price

Appendix O: Extrapolation of OS, PFS and TTD

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Addendum

Company evidence submission

November 2020

File name	Version	Contains confidential information	Date
Trastuzumab deruxtecan [ID2697]_NICE Addendum [ACIC]	**1.0**	**Yes**	**26th November 2020**

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Abbreviations

Abbreviation	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
BC	Breast cancer
CBR	Clinical benefit rate
CE	Cost-effectiveness
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
EAS	Enrolled analysis set
ECOG	Eastern Cooperative Oncology Group
ER	Oestrogen receptor
HER2+	Human epidermal growth factor 2 overexpression (positive)
HER2–	Human epidermal growth factor 2 negative
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICR	Independent central review
IHC	Immunohistochemistry
ILD	Interstitial lung disease
ISH	In situ hybridisation
IV	Intravenous
LVEF	Left ventricular ejection fraction
mBC	Metastatic breast cancer
NCI	National Cancer Institute
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PSS	Personal social services
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QoL	Quality of life
QT	QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Standard deviation
SLR	Systemic literature review
SE	Standard error
SmPC	Summary of product characteristics
TA	Technology appraisal
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse events
TTR	Time to response

1. Addendum summary

This addendum provides an update to the clinical and cost-effectiveness of trastuzumab deruxtecan (T-DXd) using the latest available clinical data from the DESTINY-Breast01 trial, representing an update from a data-cut of August 1, 2019 (median follow-up 11.1 months [range, 0.7 to 19.9]) to June 8, 2020 (median follow-up 20.5 months [redacted]). Updated responses to ERG clarification questions were incorporated into the relevant sections, and where reporting errors were identified in the original company submission (CS), corrections to these were also made.

The addendum consists of an update to all the clinical efficacy and safety outcomes reported in the original CS, together with respective changes to the results of the matching-adjusted indirect comparison (MAIC) analyses, the cost-effectiveness analyses and the budget impact model (BIM).

Clinical and cost-effectiveness conclusions using the latest June 2020 data cut from DESTINY-Breast01 trial are consistent with those reported in the original company submission.

The key updates include:
Objective response rate (ORR) has changed from 60.9% (95% confidence interval [CI]: 53.4, 68.0) to 61.4% ([redacted])
Median progression-free survival (PFS) has changed from 16.4 months (12.7, not evaluable [NE]) to 19.4 months (14.1, NE)
Preliminary median overall survival (OS) is reported for the first time: 24.6 months (23.1, NE) (estimated at 35% maturity with only 17% patients at risk at 24 months)
Median duration of response (DoR) has changed from 14.8 months (13.8, 16.9) to 20.8 months (15.0, NE)
The results of the updated cost-effectiveness analysis (including the approved patient access scheme for T-DXd) are:
T-DXd vs. capecitabine: £45,216 per QALY gained
T-DXd vs. vinorelbine: £42,473 per QALY gained
T-DXd vs. eribulin: £37,471 per QALY gained

This single addendum comprises the following sections:

Addendum to CS Document A (Section 2)

Addendum to CS Document B (Section 3)

Addendum to the Budget Impact Model (submitted to NICE as a separate document as requested)

Addenda to CS appendices

- Appendix D: Model diagnostics for the 7 MAIC analyses (Section 5.1)
- Appendix J: Clinical outcomes and disaggregated results from the model (Section 5.2)
- Appendix N: Cost-effectiveness results using PAS price (Section 5.3)

Appendix O: Extrapolation of OS, PFS and time to treatment discontinuation (TTD) (Section 5.4)

Please note that the addendum only contains sections that have been updated from the original CS; the corresponding section numbers from the original CS are provided throughout.

2. Addendum to Document A

2.1. Key results of the clinical effectiveness evidence (addendum to Document A, Section A.7)

A summary of the key results of the clinical effectiveness evidence from DESTINY-Breast01 at the June 8, 2020 data-cut are shown in Table 1: Key results of the clinical effectiveness evidence, DESTINY-Breast01.

Table 1: Key results of the clinical effectiveness evidence, DESTINY-Breast01

Endpoints	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)	Section, page in the submission
Primary endpoint		
ORR (ICR assessed), n (% [95% CI])	**113 (61.4 [redacted]†**	Addendum 3.1.1.2, page 55
CR, n (%)	12 (6.5)	
PR, n (%)	101 (54.9)	
SD, n (%)	66 (35.9)	
PD, n (%)	[redacted]	
NE, n (%)	[redacted]	
Secondary endpoints specified in the decision problem		
Median PFS, months (95% CI) (ICR assessed)	**19.4 (14.1, NE)**	Addendum 3.1.1.3, page 57
Events, n (%)	[redacted]	
PD, n (%)	[redacted]	
Death, n (%)	[redacted]	
Censored, n (%)	[redacted]	
Preliminary median OS, months (95% CI) (ICR assessed)	**24.6 (23.1, NE)**	Addendum 3.1.1.3, page 58
Events	[redacted]	
Censored, n (%)	[redacted]	
Median DoR, months (95% CI) (ICR assessed)	**20.8 (15.0, NE)†**	Addendum 3.1.1.3, page 59-60
Events, n/N patients with response, (%)	[redacted]†	
Censored, n/N patients with response (%)	[redacted]	

Endpoints	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)	Section, page in the submission
Other secondary endpoints (ICR assessed)		
DCR, n (% [95% CI])	179 (97.3 [93.8, 99.1])	Addendum 3.1.1.3, pages 59-60
CBR, n (% [95% CI])	[redacted]	
Median TTR, months (95% CI)	[redacted]†	

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; EAS, Enrolled Analysis Set; ICR, independent central review; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response; T-DXd, trastuzumab deruxtecan.

Data-cut: June 8, 2020

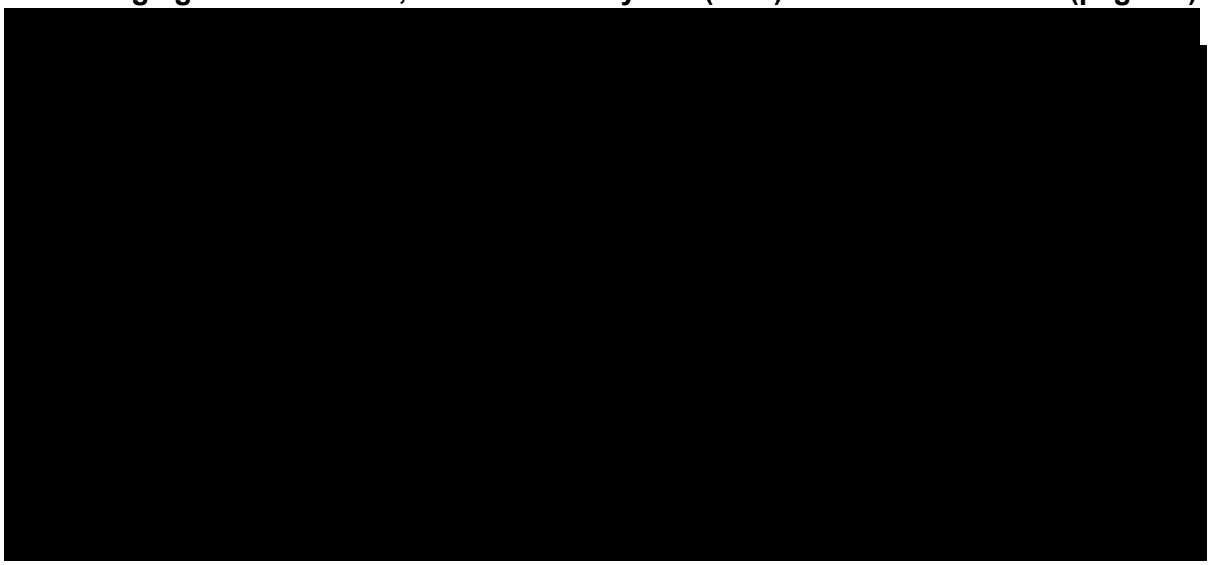
† [redacted]

Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file) [2]

2.1.1. DESTINY-Breast01: Primary efficacy outcome: Objective response rate evidence (addendum to Document A, Section A.7.1)

Among the 184 patients who received T-DXd at the recommended dose of 5.4 mg/kg (data-cut of June 8, 2020), the confirmed objective response rate (ORR) on independent central review (ICR) was 61.4% [redacted] of these 12 patients (6.5%) had a CR, and 101 patients (54.9%) had a PR (Figure 1). [redacted] The confirmed ORR based on investigator assessment (secondary endpoint) in the 5.4 mg/kg dose cohort was [redacted]

Figure 1: **DESTINY-Breast01: Waterfall plot of change from baseline in tumour size for the 5.4 mg/kg dose of T-DXd, as measured by ICR (EAS) - Addendum 3.1.1.2 (page 55)**



Abbreviations: ICR, independent central review.
Data-cut: June 8, 2020

The upper horizontal line indicates a 20% increase in tumour size in the patients who had disease progression, and the lower line indicates a 30% decrease in tumour size (partial response).
Source: Daiichi-Sankyo, Inc., 2020 (data on file) [2]

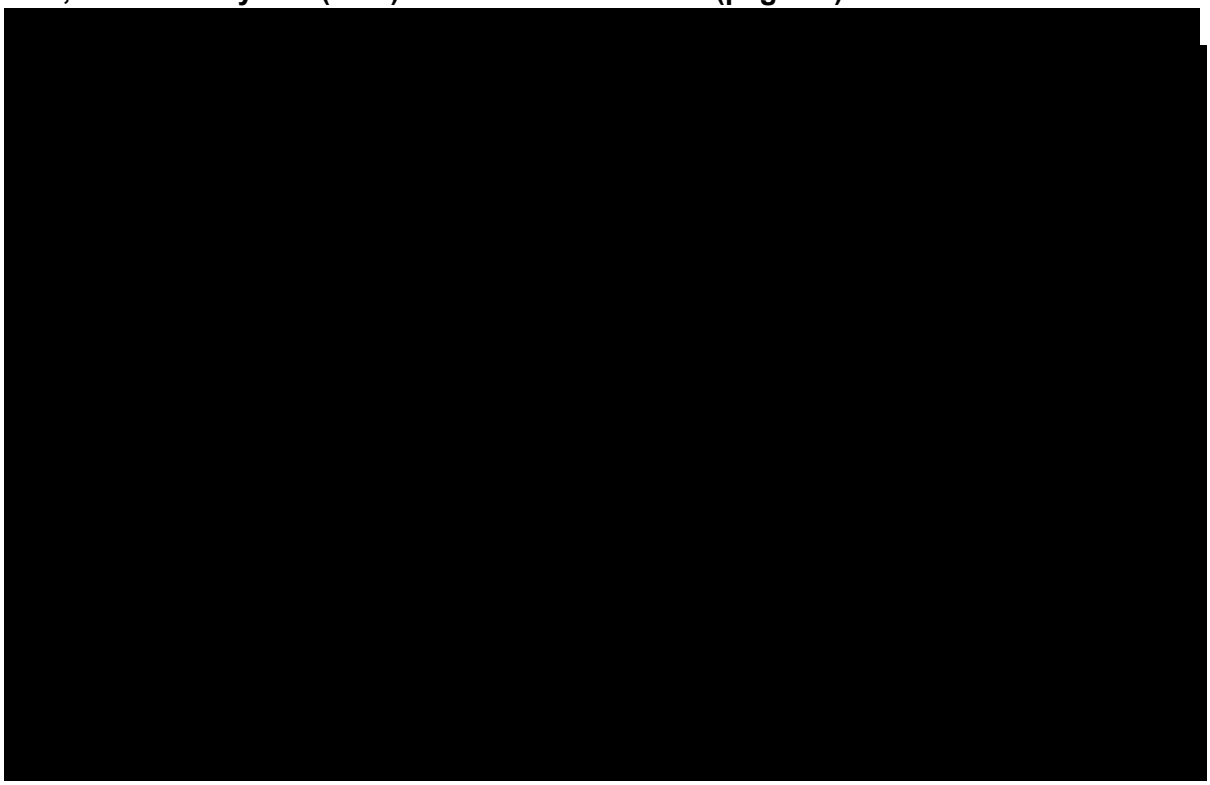
Prespecified subgroup analyses showed consistent responses across demographic and prognostic subgroups including

(Addendum Section 3.1.2).

2.1.2. DESTINY-Breast01: Progression-free survival (addendum to Document A, Section A.7.2)

Of the 184 patients receiving the recommended dose of 5.4 mg/kg (data-cut of June 8, 2020), there were and the median PFS for these patients was 19.4 months (95% CI: 14.1, NE) (Figure 2). Of the 184 patients, had PD and had died. Figure 20 presents a Kaplan–Meier (KM) curve of PFS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b.

Figure 2: DESTINY-Breast01: Kaplan–Meier plot of PFS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS) - Addendum B.2.6.1.2 (page 11)



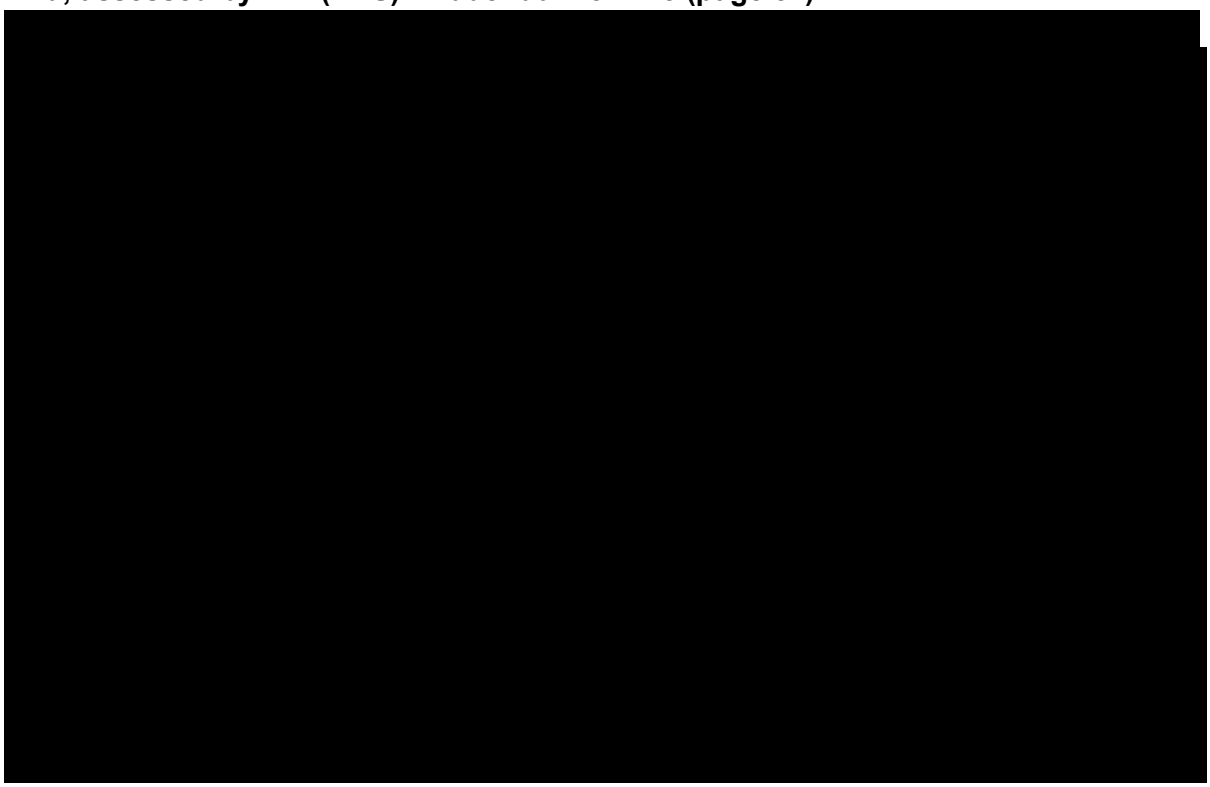
Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
Data-cut: June 8, 2020
Data for [redacted] patients were censored, as indicated by tick marks. Disease progression was assessed with the use of the modified RECIST version 1.1. The dashed lines indicate the 95% CI.
Source: Daiichi-Sankyo, Inc., 2020 (data on file) [2]

2.1.3. DESTINY-Breast01: Overall survival (addendum to Document A, Section A.7.3)

At the data-cut of June 8, 2020 (median follow-up of 20.5 months), median OS was 24.6 months (95% CI: 23.1, NE); [redacted] had died and [redacted] were censored for the OS analysis; the majority of patients were thought to be censored [redacted] (based on an analysis from August 1, 2019). Figure 3 presents a KM curve of OS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b. Please note that the median OS data are preliminary, estimated at 35% maturity.[1] The information provided by a KM curve at a particular time point is dependent on the number of subjects at risk at that time point, and if there are only a few patients at risk, then one single extra event will make a substantial impact on the distance by which the KM curve decreases.[3] Therefore, [redacted] [1] makes this portion of the KM data uninformative for modelling in terms of long-term survival extrapolation. Although the data are preliminary, it is

worth noting that the lower CI for T-DXd (23.1 months) already exceeds the median OS of the comparator treatments, and indeed the upper CI from most of the comparator studies.

Figure 3: DESTINY-Breast01: Kaplan–Meier plot of OS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS) - Addendum 3.1.1.3 (page 57)



Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; OS, overall survival; T-DXd, trastuzumab deruxtecan.
Data-cut: June 8, 2020
Data for [redacted] patients were censored, as indicated by tick marks. The dashed lines indicate the 95% CI.
The reasons for censoring for OS were not collected as part of the analysis. Additional analyses provided to the ERG for the previous data-cut (August 1, 2019; n=159 censored) showed that the majority of patients were censored due to [redacted]
Source: Daiichi-Sankyo, Inc., 2020 (data on file) [2]

2.1.4. DESTINY-Breast01: Duration of response (addendum to Document A, Section A.7.4)

For the 112 patients who achieved a response with the 5.4 mg/kg dose, the median duration of response (DoR) was 20.8 months (95% CI: 15.0, NE). See Addendum 3.1.1.3, page 59-60.

2.1.5. DESTINY-Breast01: Additional key secondary outcomes (addendum to Document A, Section A.7.5)

The disease control rate (DCR) and clinical benefit rate (CBR) was 97.3% (95% CI: 93.8, 99.1) and [redacted], respectively. For the 112 patients who achieved a response with the 5.4 mg/kg dose, the median time to response (TTR) was [redacted]. See Addendum 3.1.1.3, page 59-60.

2.2. Evidence synthesis (addendum to Document A, Section A.8)

An SLR was conducted to identify relevant clinical evidence describing the efficacy and safety of T-DXd and all currently available therapies (as per NICE scope for T-DXd) used to treat patients with advanced BC or mBC presenting with either HER2+ status, mixed HER2 status, or an unknown HER2 status, who have received two or more prior therapies in a uBC/mBC setting (Appendix D). The patient population in the SLR was broad as there are few published data available for currently available treatments solely in HER2+ patients (see Appendix D in the original company submission for details of the SLR, which remains unchanged).

DESTINY-Breast01 is a single-group trial; a series of unanchored MAICs were therefore performed to assess the comparative effectiveness of T-DXd vs the comparators listed in the NICE final scope (eribulin, capecitabine and vinorelbine) (Section B2.9, pages 55-88). MAICs were conducted for four studies identified for eribulin, two identified for capecitabine and one for vinorelbine; outcomes considered were OS, PFS and response (Table 2). Results from the MAICs were used to inform PFS in the cost-effectiveness model; following clinical expert feedback, an alternative approach was taken to modelling OS (Section 2.5

All analyses were consistent with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 and Phillippo et al.[4,5]

Table 2: Summary of studies included in the MAIC analyses – Addendum 3.1 (page 64)

Comparator	Author (Year)	Study design	Aim of study
Eribulin	Barni (2019)[77]	Multicentre, retrospective cohort	Efficacy of eribulin in patients with mBC in a real-world setting, with HER2+ subgroup data for OS and PFS
	Cortes (2010)[80]	Phase II, single-arm, open-label	Safety and efficacy of eribulin mesylate in patients with locally advanced or mBC who were previously treated with anthracycline, a taxane and capecitabine
	Cortes (2011)[81]	Phase III, randomised controlled, open-label	To compare eribulin mesylate and treatment of physician's choice amongst patients with locally recurrent or mBC who had previous chemotherapies
	Gamucci (2014)[78]	Multi-centre observational	Safety and efficacy of eribulin in real-world patients with advanced breast cancer who have been previously treated by no less than 2 lines of chemotherapy
Capecitabine	Blum (2001)[82]	Multicentre, Phase II single-arm	Efficacy and safety of capecitabine in patients with mBC who failed taxane therapy
	Fumoleau (2004)[83]	Multicentre, Phase II single-arm	To evaluate the capecitabine monotherapy in mBC patients who previously were treated with anthracycline and taxane
Vinorelbine	Sim (2019)[79]	Phase II, randomised controlled, open-label	To compare lapatinib + vinorelbine vs. vinorelbine alone in patients with HER2+ mBC who progressed on both trastuzumab and lapatinib

Abbreviations: MAIC, matching-adjusted indirect comparison; mBC, metastatic breast cancer; PFS, progression-free survival; OS, overall survival.

All results show T-DXd to be associated with significant improvement in OS, PFS and response (Table 3).

Table 3: Summary of the MAIC analyses results – Addendum 3.1.3 (pages 64-89)

Comparator	Study	Hazard ratio (95% CI) for T-DXd vs. comparator		Odds ratio for T-DXd vs. comparator		
		OS	PFS	ORR	DCR	CBR
Eribulin	Cortes 2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Barni 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cortes 2010	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamucci 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	Fumoleau 2004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Blum 2001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	Sim 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CBR, clinical benefit rate; DCR, disease control rate; PFS, progression-free survival; ORR, objective response rate; OS, overall survival.

2.3. Key clinical issues (addendum to Document A, Section A.9)

Despite the high quality of DESTINY-Breast01, there were some limitations consistent with conducting clinical trials in an area of very high unmet need (Section B.2.13.2, Company submission pages 100–104 and addendum 3.1.5.2 page 99).

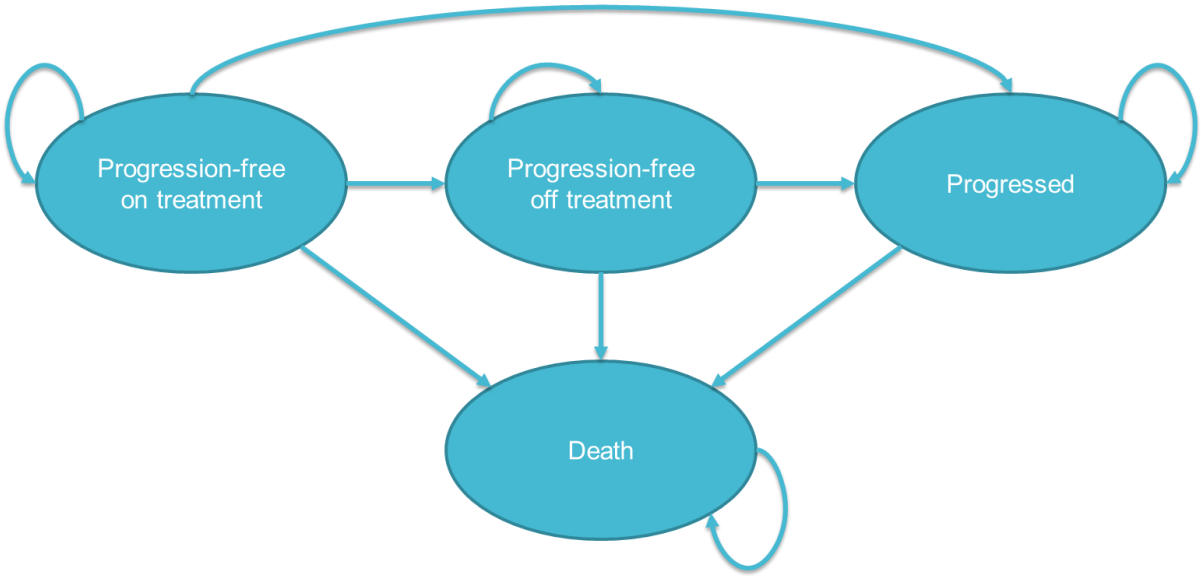
- DESTINY-Breast01 is a single arm study, and therefore there is uncertainty regarding the magnitude of benefit compared with standard-of-care.
- The median OS data are only preliminary, estimated at 35% maturity with only 17 patients at risk at 24 months. In particular, the high number of censorings from 20 months onwards makes this portion of the KM data uninformative for modelling in terms of long-term survival extrapolation.

Health-related quality of life (HRQoL) data were not captured in the DESTINY-Breast01 study.

Daiichi Sankyo considers T-DXd to be a candidate for the CDF. It is anticipated that the CDF would provide the opportunity to address the clinical uncertainty by collecting additional data, while providing timely, managed patient access to an innovative and efficacious treatment in this disease area of high unmet need. Efficacy and safety data, which can be used to inform an indirect treatment comparison, will be obtained from the DESTINY-Breast02 (NCT03523585) Phase III RCT of T-DXd versus treatment of investigator's choice (trastuzumab in addition to capecitabine or lapatinib in addition to capecitabine) in HER2+, u/mBC patients previously treated with T-DM1.

2.4. Overview of the economic analysis (addendum to Document A, Section A.10)

Figure 4: Model diagram – B.3.2 (page 111)



The economic model compares T-DXd against eribulin, capecitabine and vinorelbine in individuals with HER2-positive, unresectable or metastatic breast cancer who have received two or more prior anti-HER2 therapies.

The model considers a 'lifetime' time horizon. A 1-week cycle length is used to adequately capture transitions and reflect changes in health, while also allowing drug cycles to be appropriately costed. A half-cycle correction is applied using the life table method.

The modelled health state distribution is derived based on overall survival (OS), progression-free survival (PFS), and time to discontinuation (TTD) curves for each of the comparators.

2.5. Incorporating clinical evidence into the model (addendum to Document A, Section A.12)

The OS data in DESTINY-Breast01 from the June 2020 data cut are considered prohibitively immature for informative parametric modelling with only 35.3% of patients having an OS event. Extrapolation of the T-DXd OS curve is therefore performed by applying a hazard ratio to third-line data for a HER2-targeted treatment (T-DM1) with longer follow-up than observed in DESTINY-Breast01. Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including a trastuzumab-like antibody, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or

capecitabine. Clinical experts at an August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect the shape of the T-DM1 curve than that of the model comparators. A HR was generated for T-DXd vs. T-DM1 using a cox proportional hazards model based on:

- Only OS data from DESTINY-Breast01 up to 20.5 months (primary analysis)
- All OS data from DESTINY-Breast01 (secondary analysis)

OS data beyond 20.5 months were not considered to be informative given the substantial censoring observed beyond this time point: [redacted] patients ([redacted]% of those remaining) are censored and only [redacted] ([redacted]%) OS events occur after 20.5 months. This results in an implausible trajectory for OS, suggesting that OS and PFS Kaplan-Meier curves would converge shortly after the end of trial follow-up. OS for comparator treatments is estimated by fitting parametric survival curves to the digitized Kaplan-Meier data from the relevant studies.

Parametric survival modelling is used to inform PFS and TTD curves in the model using data from DESTINY-Breast01 for T-DXd patients. The TTD curve represents the individuals in the progression-free, on treatment health state and the difference between the PFS and TTD curves represents the individuals in the progression-free, off-treatment health state. For each comparator, a MAIC was conducted to generate a HR vs. T-DXd for the PFS curve. In the absence of Kaplan-Meier data for TTD in the comparator studies, treatment to progression for comparator treatments is assumed in the base-case.

Patient-level data from DESTINY-Breast01 was used for T-DXd safety data. All grade three and above adverse events that occurred in at least 5% of patients were included for each comparator from the respective base-case studies. In addition, any adverse events listed as AEs of special interest in the DESTINY-Breast01 clinical study report, or those identified by clinicians as AEs of particular significance were also included.

In the base-case, utility weights were calculated using the method applied in TA423.[6] Baseline utility and the incremental utility of response weights were taken from TA423 and adjusted using ORR. For T-DXd, the ORR was taken directly from DESTINY-Breast01. A MAIC was conducted to adjust each comparator ORR based on patient population differences between trials.

2.6. Key model assumptions and inputs (addendum to Document A, Section A.13)

Table 4: Key model assumptions and inputs

Model input and cross-reference	Source/assumption	Justification
Overall survival	Extrapolations of T-DXd overall survival were based on applying a HR vs. the T-DM1 OS curve from the TH3RESA trial	OS data in DESTINY-Breast01 from the June 2020 data cut are not considered sufficiently mature for informative parametric modelling, with only [redacted] of patients having an OS event, therefore a HR was applied to T-DM1 OS curve from TH3RESA. Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including trastuzumab, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or capecitabine. Clinical experts at the August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect that of T-DM1 than that of the model comparators, and that a 'tail' should be expected in the T-DXd OS curve; anchoring on non-targeted therapies (such as eribulin) is not expected to provide an accurate estimate of long-term survival.
	Vinorelbine OS is equivalent to capecitabine OS	Only the Sim (2019) study was available to inform the comparison against vinorelbine[7]; however, clinical experts at the August advisory board advised that the OS observed in Sim 2019 (18.9 months) is not plausible following PFS of 12 weeks, and is likely driven by the use of post-progression therapies.[8] Given that vinorelbine is associated with similar or worse PFS compared with capecitabine, OS for vinorelbine is assumed to be equivalent to OS for capecitabine.
Adjustment for HER2 status	20% HER2-positive patients were assumed in trials with no information regarding HER2-expression in the patient population	Where information was available on the distribution of HER2-expression in a trial population (Cortes, 2011), an adjustment was made to the trial outcomes in order to compare outcomes with a 100% HER2+ population. No adjustment was required for the Barni 2019 study, which evaluates the only NICE-recommended treatment option, eribulin, in a HER2-positive population, or for the Sim 2019 study. There was no information on HER2-expression in the data presented by Fumoleau et al, therefore an

Model input and cross-reference	Source/assumption	Justification
		adjustment was made assuming that 20% of patients in the study were HER2+, as observed in clinical practice.[9] Adjustment for HER2 status was recommended by clinical experts at the August advisory board[9] and is in line with previous published findings[10] demonstrating HER2+ disease to be more aggressive and more likely to recur.
	The impact of HER2 status on outcomes is the same between OS and PFS	In the base-case, an adjustment to OS and PFS in the eribulin and capecitabine arms of the model is made to account for the proportion of patients with HER2+ vs. HER2– disease, using the HR presented by Lv et al. Only OS was presented in the study, and therefore the same HR was applied to adjust PFS. At the August advisory board, clinical experts advised that both PFS and OS would be poorer for HER2-positive patients.
Time on treatment	Treatment to PFS is assumed for all comparator drugs	For comparator treatments, only median TTD data were available from the studies. When a HR is applied vs. T-DXd TTD for each comparator that passes through the median TTD, the TTD curve quickly passes through the PFS curve. This suggests that the shape of the TTD curves of each comparator is not the same as that of T-DXd. Furthermore, as mean PFS for each comparator is relatively short, it is reasonable to assume that patients would not discontinue treatment before progression in UK clinical practice.
Wastage	50% drug wastage is assumed	In TA523, a clinical expert confirmed that "in clinical practice drug wastage is recognised and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain". In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.
Adverse events	AE-associated cost and QALY losses accounted for in first cycle of model	Time on treatment is short for all comparators, and therefore there are not expected to be any long-term cost and QALY losses associated with AEs.

Model input and cross-reference	Source/assumption	Justification
	The proportion of AEs that resulted in hospitalisation in DESTINY-Breast01 was applied to all comparator AE proportions	There were no data available on the proportion of each AE that resulted in hospitalisation for each comparator, therefore the best available evidence - patient level data from DESTINY-Breast01 - was used.
	0% hospitalisation is assumed in AEs with no hospitalisation data	For AEs that did not occur in DESTINY-Breast01, there were no data available on the proportion of AEs that resulted in hospitalisation. A conservative assumption of 0% was applied in the base-case.
Relative dose intensity	The RDI for capecitabine and vinorelbine was assumed equal to eribulin.	In the absence of other data, the RDI for capecitabine and vinorelbine is conservatively assumed to be the same as for eribulin.
Resource use	Resource use estimates are equal for all treatments	This is consistent with previous TAs

Abbreviations: ADC, antibody drug conjugate; AE, adverse event; HER2, human epidermal growth factor 2; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; TA, technology appraisal; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to discontinuation.

2.7. Base-case ICER (deterministic, PAS price results) (addendum to Document A, Section A.14)

In the original company submission, PAS price results were presented in Appendix N. Following the approval of the PAS for T-DXd on 3rd November 2020, the PAS price results are presented in sections 2.7, 2.8, 2.9 and 3.2.5. Results based on the list price for T-DXd are presented in sections 2.10, 2.11, 2.12 and 3.2.8.

2.7.1. Primary analysis, T-DXd PAS price

In the primary analysis, censoring T-DXd OS at 20.5 months, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an incremental cost-effectiveness ratio (ICER) of £45,216 per quality-adjusted life-year (QALY) gained. A summary of the fully incremental results using the PAS price for T-DXd are presented in Table 5.

Table 5: Primary analysis results (censoring T-DXd OS at 20.5 months), T-DXd PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£483,164	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,216	£45,216

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

2.7.2. Secondary analysis, T-DXd PAS price

Secondary analyses are considered in which the full OS Kaplan-Meier data for T-DXd are used, assuming each of the exponential and generalised gamma distributions. Due to the high level of censoring from 20.5 months, the Kaplan Meier data from this point onwards is not considered to be informative. Therefore, this analysis is expected to be a conservative estimate of the cost-effectiveness of T-DXd and it is proposed that the primary analysis is used for decision making purposes.

In the secondary analysis assuming an exponential distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented in Table 6.

Table 6: Secondary analysis results (full use of K-M data), T-DXd OS distribution: exponential (T-DXd PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the secondary analysis assuming a generalised gamma distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented inTable 7 .

Table 7: Secondary analysis results (full use of K-M data), T-DXd OS distribution: generalised gamma (T-DXd PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; K-M, Kaplan-Meier; LYG, life years gained; QALYs, quality-adjusted life years								

2.8. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

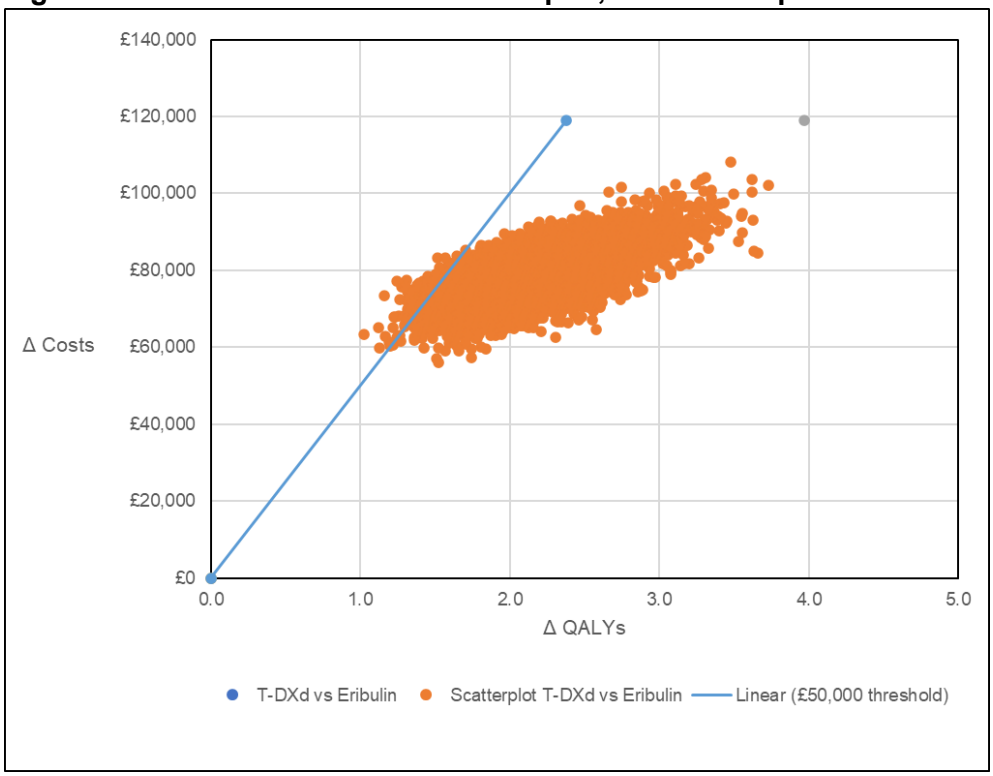
The average incremental costs over the simulated results were xxxxxxx and the average incremental QALYs were xxxx compared with capecitabine, giving a probabilistic ICER of £45,008. This is highly congruent with deterministic changes in costs of xxxxxxx and QALYs of xxxx, respectively. The proportion of simulations considered cost-effective at a threshold of £50,000 per QALY was xx%. A summary of the probabilistic, fully incremental results using the PAS price for T-DXd are presented in Table 8. The cost-effectiveness plane vs. each comparator and CEAC are presented in Figure 5, Figure 6, Figure 7, and Figure 8.

Table 8: PSA results, T-DXd PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	£648,845	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	£45,008	£45,008

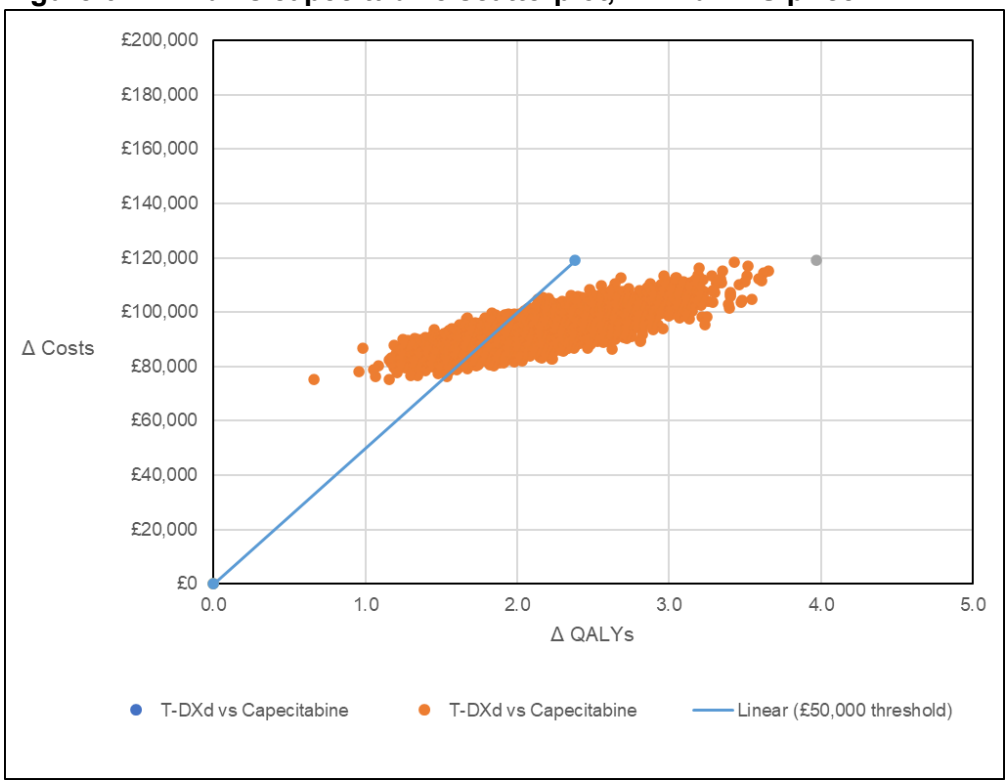
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 5: T-DXd versus eribulin scatterplot, T-DXd PAS price



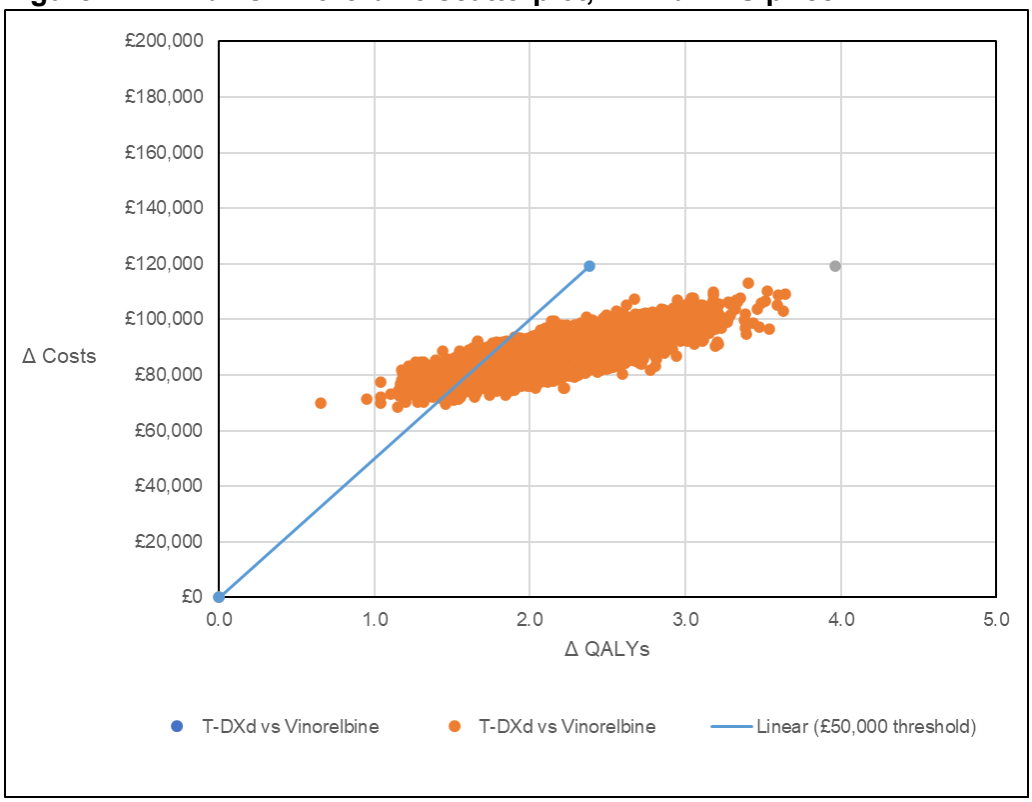
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 6: T-DXd vs capecitabine scatterplot, T-DXd PAS price



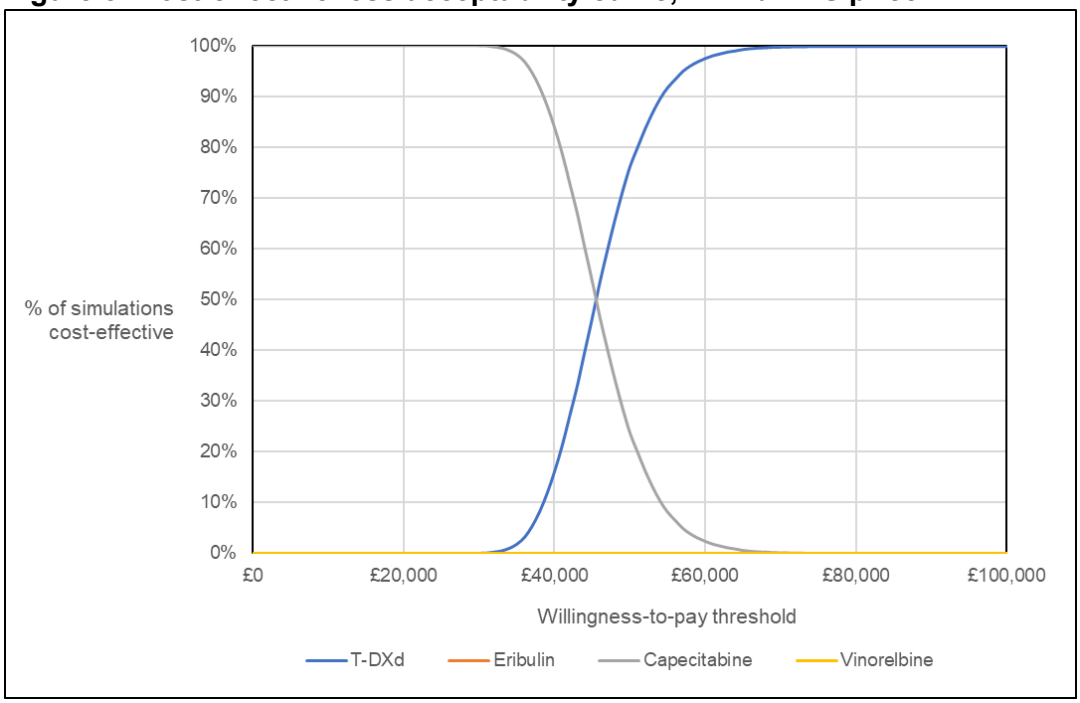
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 7: T-DXd vs vinorelbine scatterplot, T-DXd PAS price



Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 8: Cost-effectiveness acceptability curve, T-DXd PAS price

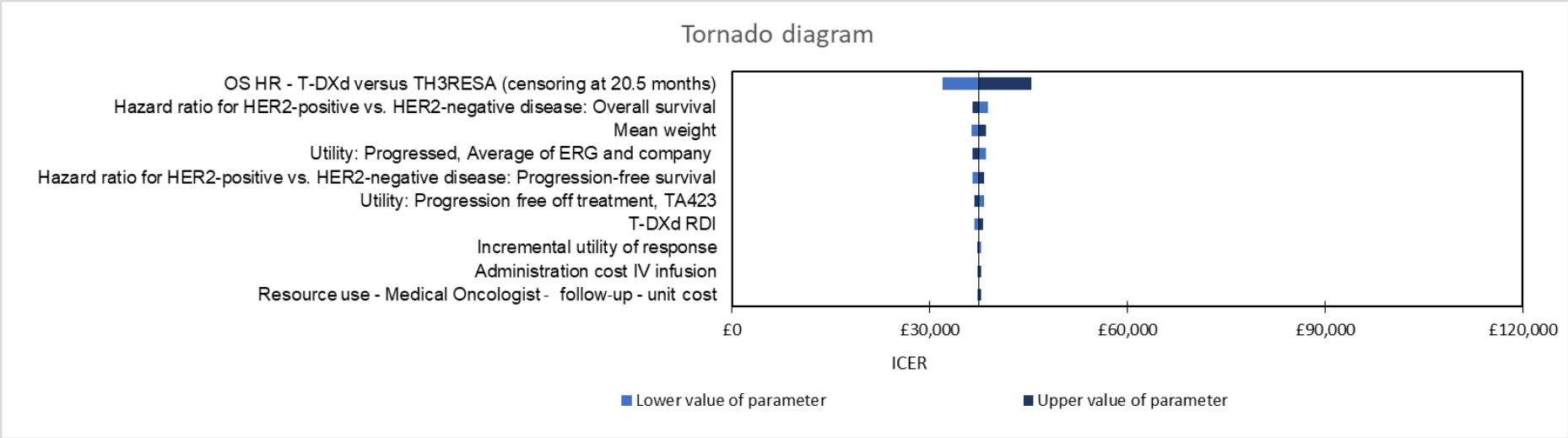


Abbreviations: T-DXd, trastuzumab deruxtecan.

2.9. Key sensitivity and scenario analyses, T-DXd PAS price (addendum to Document A, Section A.16)

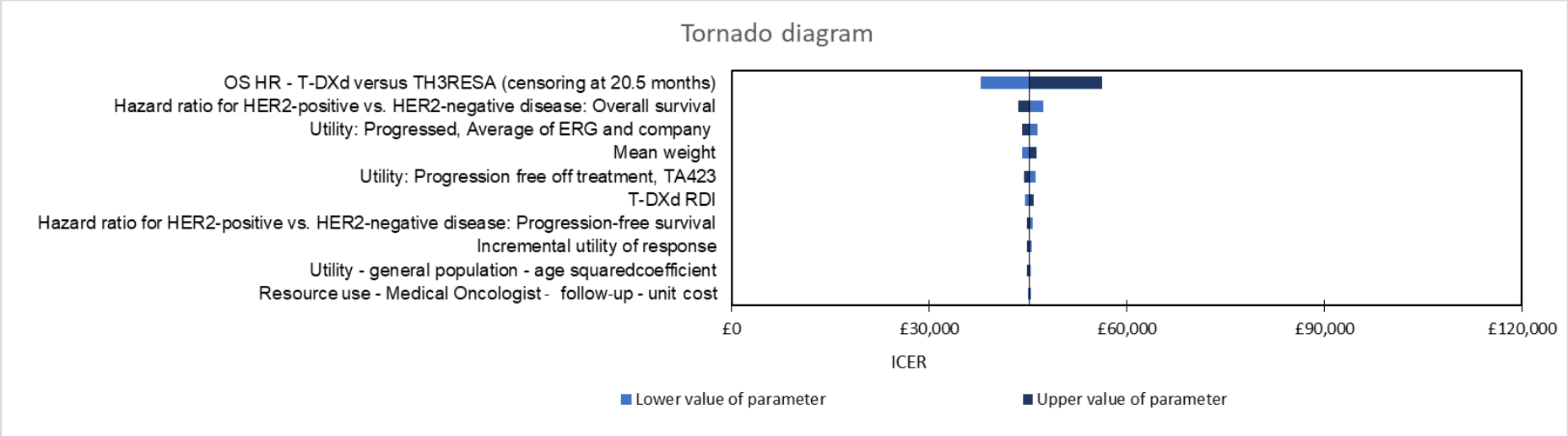
For each analysis, a tornado diagram of one-way sensitivity analysis (OWSA) is presented in Figure 9, Figure 10, and Figure 11. OWSA showed that the most influential parameter was the HR for T-DXd vs. TH3RESA that defined the survival extrapolations in OS; this is to be expected as the cost-effectiveness results are primarily driven by survival gains. Beyond this parameter, the impact of varying other parameters in the model was small.

Figure 9: Tornado diagram, T-DXd vs. Eribulin, PAS price – 3.2.6.2 (page 150)



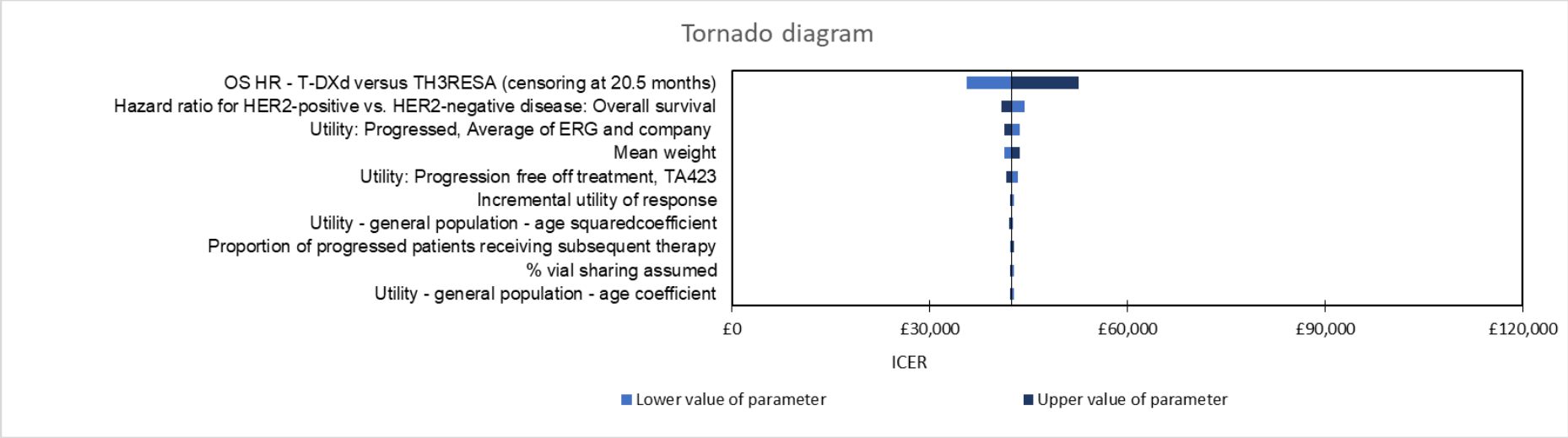
Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

Figure 10: Tornado diagram, T-DXd vs. capecitabine, PAS price – 3.2.6.2 (page 151)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

Figure 11: Tornado diagram, T-DXd vs. vinorelbine, PAS price – B.3.2.6.2 (page 153)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

For each analysis, the scenarios that change the ICER by at least 15% are presented in Table 9, Table 10, and Table 11. The most influential scenarios in each comparison are anchoring T-DXd OS to eribulin; modelling T-DXd based on a no-censoring approach (i.e. Secondary analysis); and scenarios that change the distributions of OS for either T-DXd or a comparator. The main model drivers are the OS gains and treatment costs in the T-DXd arm; therefore, it is reasonable that scenarios that change these parameters have the biggest impact on the ICER. The scenario comparing T-DXd against the only NICE-recommended comparator, eribulin, using the Barni 2019 study (the only identified study of eribulin with data in the HER2-positive population) resulted in a modest change in the ICER to £41,827.

Table 9: Key scenario analyses, T-DXd vs. eribulin, PAS price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative eribulin baseline data source and OS distribution (B.3.3.1.2)	Modelling eribulin OS using data from Gamucci 2014 and the generalised gamma distribution	The ICER is sensitive to the distribution and data source for the comparator OS as it influences the OS gains, which is a key model driver. All alternative distributions and data sources were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Table 10: Key scenario analyses, T-DXd vs. capecitabine, PAS price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Table 11: Key scenario analyses, T-DXd vs. vinorelbine, PAS price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

2.10. Base-case ICER (deterministic, list price results) (addendum to Document A, Section A.14)

2.10.1. Primary analysis, list price

In the base-case analysis, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the base-case, fully incremental results are presented in Table 12. The results presented here are calculated using the list price of T-DXd and therefore do not reflect the incremental costs based on the PAS price of T-DXd.

Table 12: Primary analysis results assuming list price (deterministic) – B.3.2.8.1.1 (page 164)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.10.2. Secondary analysis, list price

In the secondary analysis, assuming a generalised gamma distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results are presented in Table 13. The results presented here are calculated using the list price of T-DXd and therefore do not reflect the incremental costs based on the PAS price of T-DXd.

Table 13: Secondary analysis results, T-DXd OS distribution: gen. gamma, assuming list price (deterministic) – B.3.2.8.1.1 (page 165)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: gen. gamma, generalised gamma; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In the secondary analysis, assuming an exponential distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results are presented in Table 14Table 12. The results presented here are calculated using the list price of T-DXd and therefore do not reflect the incremental costs based on the PAS price of T-DXd. Results based on the PAS price of T-DXd are presented in Appendix N of Document B.

Table 14: Secondary analysis results, T-DXd OS distribution: exponential, assuming list price (deterministic) – B.3.2.8.1.1 (page 165)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.11. Probabilistic sensitivity analysis, list price (addendum to Document A, Section A.15)

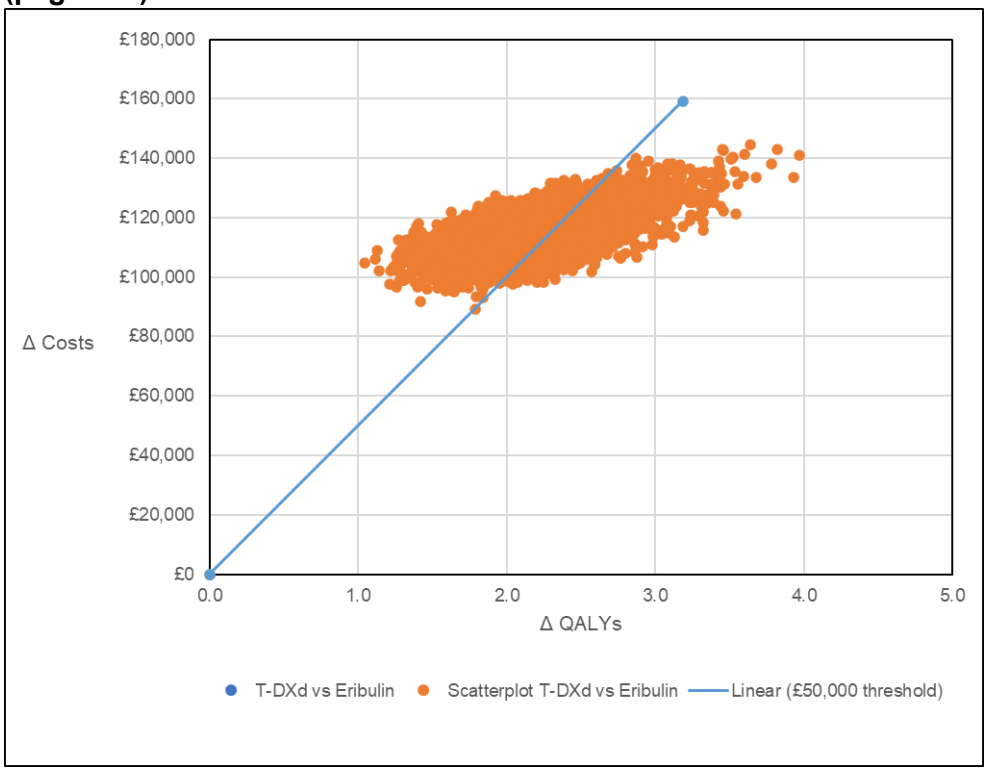
Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted] compared with capecitabine, giving a probabilistic ICER of [redacted]. This is highly congruent with deterministic changes in costs of [redacted] and QALYs of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of £50,000 per QALY was [redacted]. A summary of the probabilistic, fully incremental results are presented in Table 15. The cost-effectiveness plane vs. each comparator and CEAC are presented in Figure 12, Figure 13, Figure 14and Figure 15. Probabilistic results presented here are calculated using the list price of T-DXd and therefore do not reflect the incremental costs based on the PAS price of T-DXd. Probabilistic results based on the PAS price of T-DXd are presented in Appendix N of Document B.

Table 15: Base-case results assuming list price (probabilistic) – Addendum 3.2.9.1 (page 167)

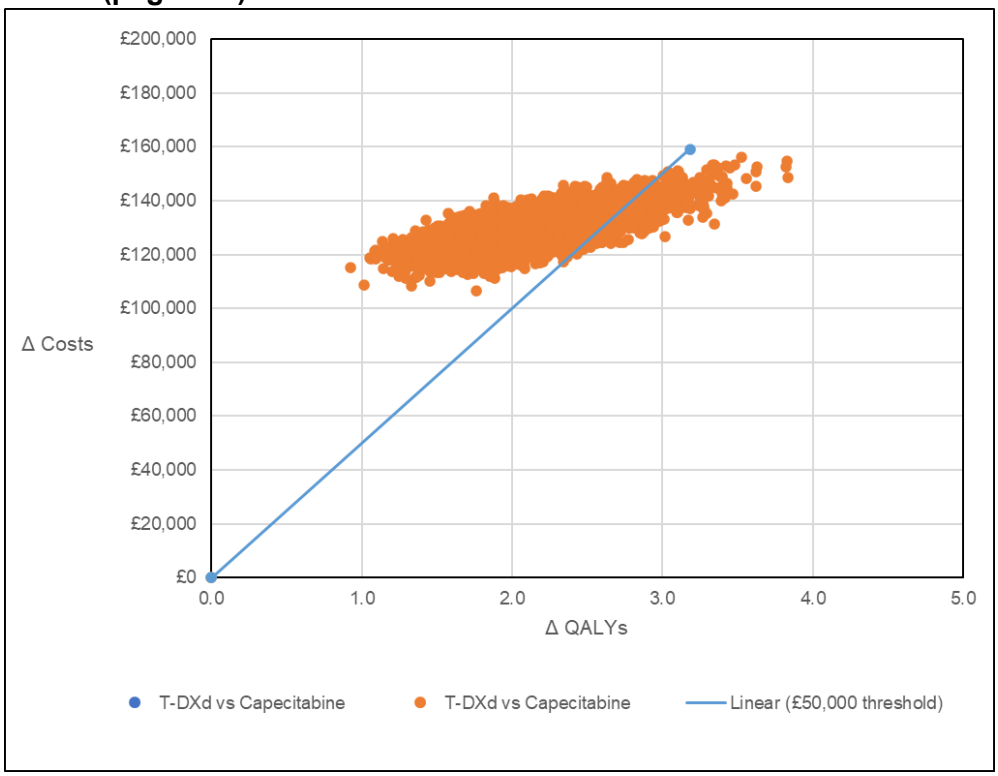
Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12: Scatterplot of probabilistic results, T-DXd vs. eribulin, list price – 3.2.9.1 (page 168)



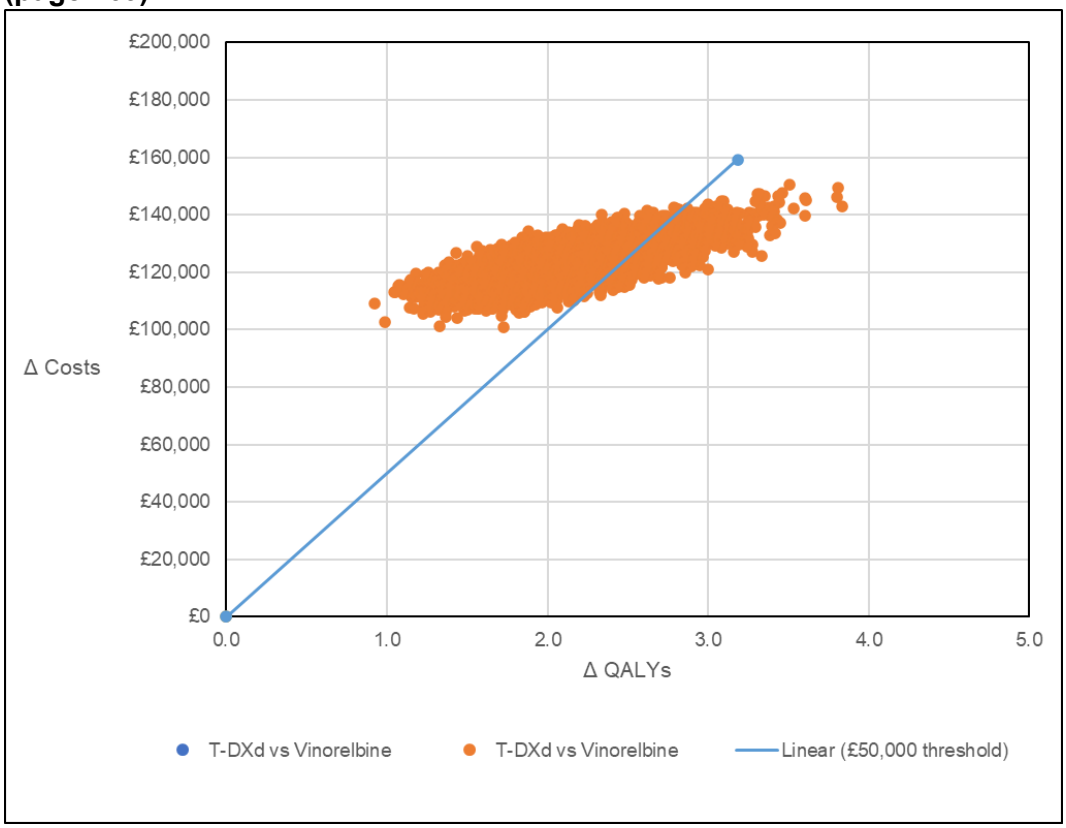
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 13: Scatterplot of probabilistic results, T-DXd vs. capecitabine, list price – 3.2.9.1 (page 168)



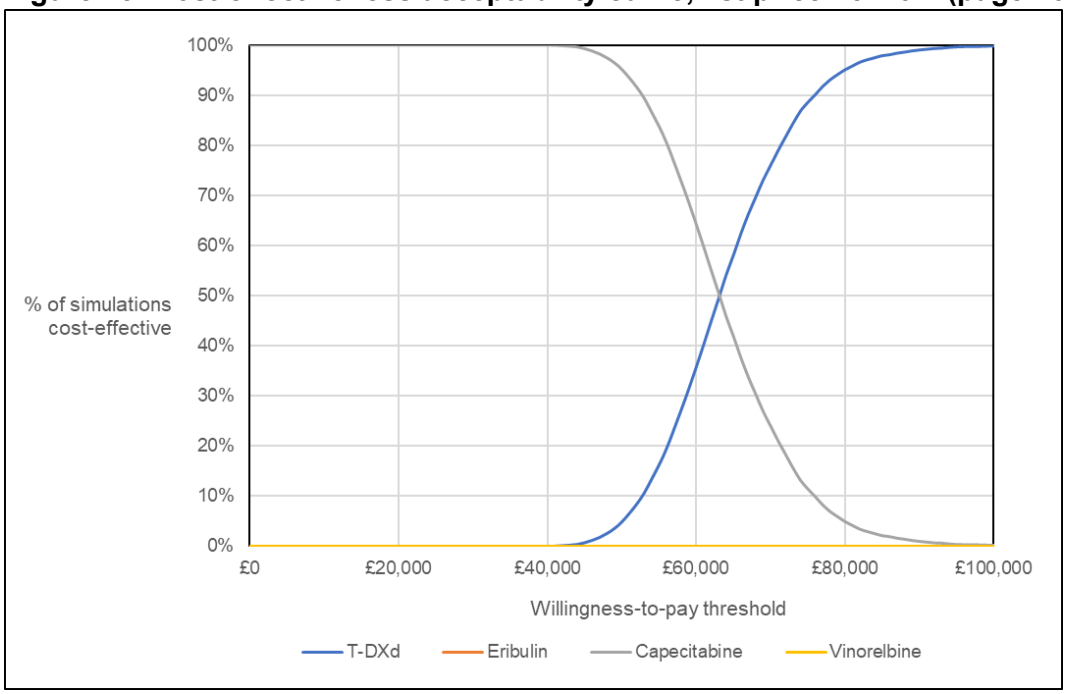
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 14: Scatterplot of probabilistic results, T-DXd vs. vinorelbine, list price – 3.2.9.1 (page 169)



Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 15: Cost-effectiveness acceptability curve, list price - 3.2.9.1 (page 169)

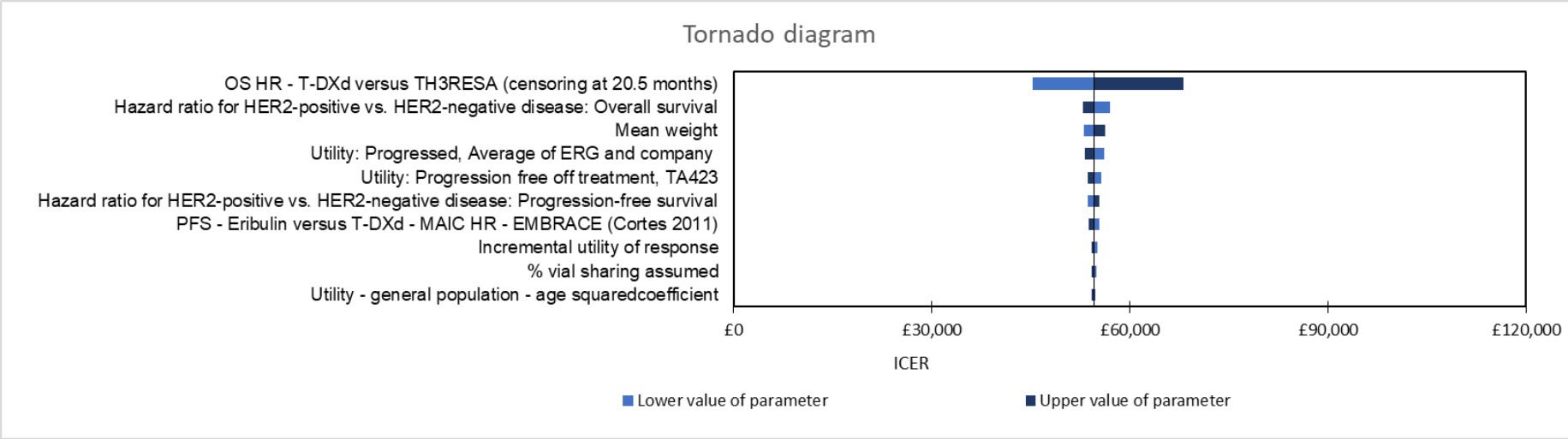


Abbreviations: T-DXd, trastuzumab deruxtecan

2.12. Key sensitivity and scenario analyses, list price (addendum to Document A, Section A.16)

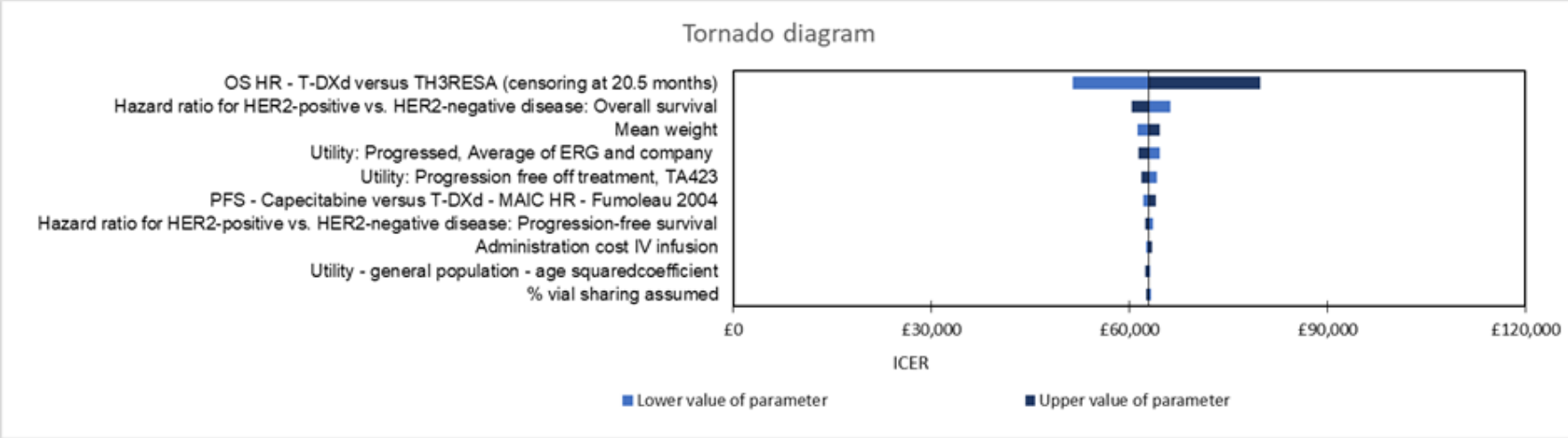
For each analysis, a tornado diagram of one-way sensitivity analysis (OWSA) is presented in Figure 16, Figure 17 and Figure 18. OWSA showed that the most influential parameter was the HR for T-DXd vs. TH3RESA that defined the survival extrapolations in OS; this is to be expected as the cost-effectiveness results are primarily driven by survival gains. Beyond this parameter, the impact of varying other parameters in the model was small.

Figure 16: Tornado diagram, T-DXd vs. eribulin, list price – 3.2.9.2.1 (page 171)



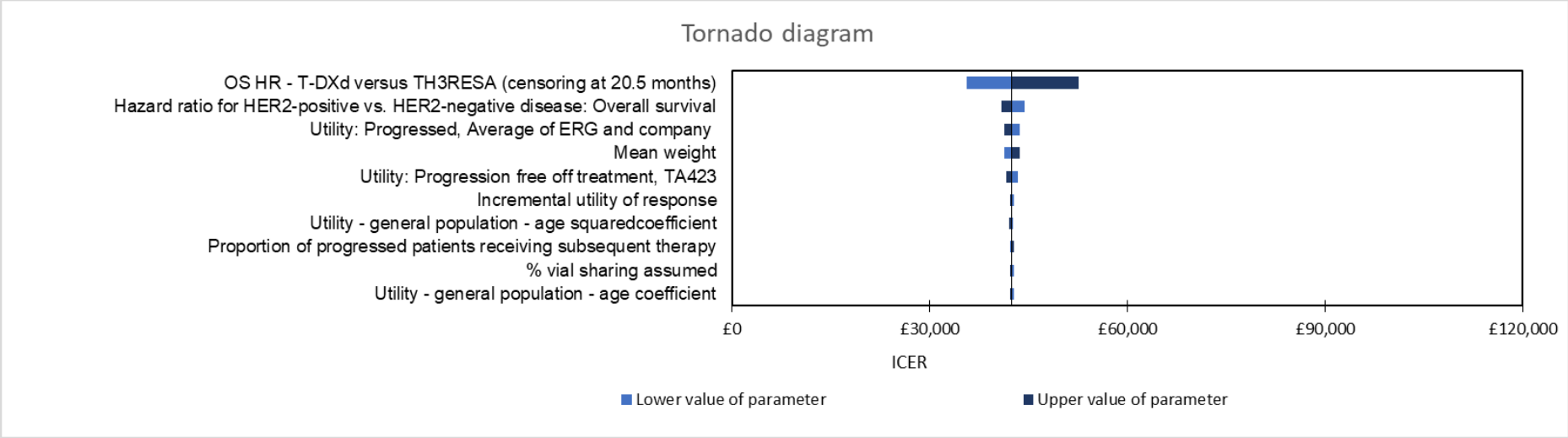
Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

Figure 17: Tornado diagram, T-DXd vs. capecitabine, list price – 3.2.9.2.2 (page 172)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

Figure 18: Tornado diagram, T-DXd vs. vinorelbine, list price – 3.2.9.2.3 (page 173)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

For each analysis, the scenarios that change the ICER by at least 15% are presented in Table 16, Table 17 and Table 18. The most influential scenarios in each comparison are anchoring T-DXd OS to eribulin; modelling T-DXd based on a no-censoring approach; and ones that change the distributions of OS for either T-DXd or a comparator. The main model drivers are the OS gains and treatment costs in the T-DXd arm; therefore, it is reasonable that scenarios that change these parameters have the biggest impact on the ICER. The scenario comparing T-DXd against the only NICE-recommended comparator, eribulin, using the Barni 2019 study (the only identified study of eribulin with data in the HER2-positive population) resulted in a modest change in the ICER to £60,939.

Table 16: Key scenario analyses, T-DXd vs. eribulin, list price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative eribulin baseline data source and OS distribution (B.3.3.1.2)	Modelling eribulin OS using data from Gamucci 2014 and the generalised gamma distribution	The ICER is sensitive to the distribution and data source for the comparator OS as it influences the OS gains, which is a key model driver. All alternative distributions and data sources were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Table 17: Key scenario analyses, T-DXd vs. capecitabine, list price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Table 18: Key scenario analyses, T-DXd vs. vinorelbine, list price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Alternative HR for T-DXd OS vs. TH3RESA	Secondary analysis: Modelling OS using a HR vs. TH3RESA that was calculated using no censoring in the T-DXd KM data.	The ICER is sensitive to the OS HR vs. TH3RESA as modelled T-DXd OS is a key model driver. All clinically plausible distributions were tested in scenario analyses.	[redacted]
Alternative OS anchor for T-DXd	Modelling T-DXd OS by anchoring to eribulin	The ICER is sensitive to the anchor for T-DXd OS as modelled T-DXd OS is a key model driver.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-normal distribution to model TH3RESA OS	The ICER is sensitive to the distribution chosen for TH3RESA OS as it affects T-DXd OS gains which is a key model driver. All alternative distributions were therefore tested in scenario analyses.	[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using log-logistic distribution to model TH3RESA OS		[redacted]
Alternative OS distribution for TH3RESA (B.3.3.1.1.1)	Using Gompertz distribution to model TH3RESA OS		[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

2.13. End-of-life criteria (addendum to Document A, Section A.18)

NICE end-of-life status applies for the current appraisal for T-DXd (Table 19).

Table 19: End-of-life criteria – Addendum 3.1.5.2 (page 99-100)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Mean overall survival estimated in the cost-effectiveness model is as follows: • Eribulin: [redacted] months • Capecitabine: [redacted] months • Vinorelbine: [redacted] months Of note, median PFS for T-DXd is greater than comparator modelled median OS: 19.4 months (95% CI: 14.1, NE).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean overall survival estimated in the cost-effectiveness model for T-DXd is [redacted] months, resulting in an estimated extension to life of [redacted] and [redacted] months compared with eribulin, capecitabine and vinorelbine, respectively. In the DESTINY-Breast01 trial at the June 8, 2020 data-cut, the estimated OS was 85% (95% CI: 79, 90) at 12 months and 74% (67%, 80%) at 18 months. Preliminary median OS was 24.6 months (23.1, NE) (estimated at 35% maturity).

Abbreviations: OS, overall survival.

2.14. Budget impact (addendum to Document A, Section A.19)

The net budget impact for T-DXd in the population under evaluation assuming the PAS price of T-DXd is reported in Table 20 and is not expected to exceed the budget impact test of £20 million per year in any of the first three years of its use in the NHS in England. The budget impact assuming the list price is reported in Table 20.

Table 20: Budget impact assuming PAS price – Budget impact analysis submission

	Company estimate	Cross reference
Number of people in England who would have treatment	Year 1: [redacted][9,11,12] Year 2: [redacted] Year 3: [redacted] Year 4: [redacted] Year 5: [redacted]	Section 3

	Company estimate	Cross reference
Average treatment cost per person	[redacted]	Section 4
Estimated annual budget impact on the NHS in England	[redacted]	Section 7

Table 21: Budget impact assuming list price – Budget impact analysis submission

	Company estimate	Cross reference
Number of people in England who would have treatment	Year 1: [redacted][9,11,12] Year 2: [redacted] Year 3: [redacted] Year 4: [redacted] Year 5: [redacted]	Section 3
Average treatment cost per person	[redacted]	Section 4
Estimated annual budget impact on the NHS in England	[redacted]	Section 7

2.15. Interpretation and conclusions of the evidence (addendum to Document A, Section A.20)

In the key trial, DESTINY-Breast01, T-DXd at a dose of 5.4 mg/kg at the latest data-cut (June 8, 2020; median duration of follow-up: 20.5 months [redacted]) continued to demonstrate robust anti-tumour activity in patients with HER2+ unresectable BC and mBC who had undergone extensive previous treatment, with a confirmed ORR of 61.4%, a median duration of PFS of 19.4 months, a median DoR of 20.8 months, and a median OS, reported for the first time albeit as preliminary results, of 24.6 months.[2] These results validate earlier observations from the Phase I study.[13] T-DXd has distinct pharmaceutical properties which may contribute to it retaining efficacy in these difficult to treat patients.[14] Overall, the efficacy observed with T-DXd is expected to substantially exceed those of currently available treatments in an area of a high unmet need. Given the clinical uncertainty in the evidence base, with only 35.3% of patients having an OS event at the June 2020 data cut off, Daiichi Sankyo considers T-DXd to be a candidate for the CDF, while additional evidence from the Phase III active-controlled RCT (DESTINY-Breast02) and real-world data are collected. Further, DS considers T-DXd to meet the EoL criteria in this setting (Section 2.13). Significant LY gain is expected versus comparator treatments, supported by median PFS from DESTINY-Breast01 being greater than observed comparator median OS.

3. Addendum to Document B

3.1. Clinical effectiveness (addendum to Document B, Section B.2)

Section 3.1 reflects updates to the clinical effectiveness of T-DXd using the most mature clinical data from the DESTINY-Breast01 trial (data-cut June 8, 2020).

DESTINY-Breast01 is a two-part, open-label, single-group, multicentre, Phase II study, evaluating T-DXd in adults with pathologically documented human epidermal growth factor 2 overexpression (HER2+) unresectable breast cancer (uBC) or metastatic breast cancer (mBC) who had received previous treatment with trastuzumab emtansine (T-DM1). The efficacy and safety of T-DXd were evaluated at the recommended dose of 5.4 mg/kg (N=184).

At a data-cut of June 8, 2020 (median duration of follow-up: 20.5 months [redacted]) T-DXd demonstrated a consistent high level of clinical activity across a range of endpoints:

- Response to therapy was reported in 113 patients (61.4%; [redacted] based on independent central review (ICR)
- Complete response (CR) was reported in 12 (6.5%) patients and partial response (PR) in 101 (54.9%) patients
- Most patients had a reduction in tumour size while on treatment
- Median progression-free survival (PFS) was 19.4 months (95% CI: 14.1, not evaluable [NE])
- Preliminary median overall survival (OS) was 24.6 months (95% CI: 23.1, NE) (estimated at 35% maturity with only 17 patients at risk at 24 months); this is the first report of median OS
- Prespecified subgroup analyses showed consistent responses across demographic and prognostic subgroups including patients [redacted]
- Durable activity was demonstrated with a median duration of response (DoR) of 20.8 months (95% CI: 15.0, NE)
- Disease control rate (DCR) was 97.3% (95% CI: 93.8, 99.1)
- Clinical benefit rate (CBR) was [redacted]

- Median time to response (TTR) was [redacted]

Summary of matching-adjusted indirect comparisons (MAICs)

- DESTINY-Breast01 is a single group trial; a series of unanchored MAICs were therefore performed to assess the comparative effectiveness of T-DXd vs the comparators listed in the NICE final scope (eribulin, capecitabine and vinorelbine)
- MAICS were conducted for four studies identified for eribulin, two identified for capecitabine and one for vinorelbine; outcomes considered were OS, PFS and response (ORR, DCR and CBR)
- All results show T-DXd to be associated with significant improvement in OS, PFS and response (ORR, DCR and CBR).

Comparator	Study	Hazard ratio for T-DXd vs. comparator		Odds ratio for T-DXd vs. comparator		
		OS	PFS	ORR	DCR	CBR
Eribulin	Cortes 2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Barni 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cortes 2010	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamucci 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	Fumoleau 2004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Blum 2001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	Sim 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Summary of safety of T-DXd for DESTINY-Breast01

- The most common treatment-emergent adverse events (TEAEs) were gastrointestinal and haematologic in nature
- [redacted]% had serious TEAEs; [redacted]% and [redacted]% had a dose interruption or dose reduction, respectively, and 18.5% discontinued treatment due to TEAEs
- No events of cardiac failure with left ventricular ejection fraction (LVEF) decline were reported
  - No patients had an LVEF of <40% or a decrease of ≥20% at any timepoint
- Interstitial lung disease (ILD) was observed in a subgroup of patients and required attention to pulmonary symptoms and careful monitoring

– ILD events were independently adjudicated and actively managed by patient monitoring, dose modification, and adherence to the ILD management guidelines – ILD related to T-DXd was observed in 28 patients (15.2%), primarily Grade 1 or 2 ([redacted]). Five deaths (2.7%) were attributed to ILD • There were [redacted] TEAE-associated deaths [redacted]
End-of-life NICE end-of-life status applies for the current appraisal as: • T-DXd is indicated for patients with a short life expectancy and high unmet need, with all available evidence demonstrating that the life expectancy in patients with HER2+ mBC is normally less than 24 months; and • T-DXd has the prospect of offering an extension to life of more than 3 months versus current treatment in the NHS. Median PFS for T-DXd is greater than comparator modelled median OS.
Conclusion • T-DXd at a dose of 5.4 mg/kg at the latest data-cut (June 8, 2020) continued to demonstrate robust anti-tumour activity in patients with HER2+ uBC and mBC who had undergone extensive previous treatment, with a confirmed ORR of 61.4%, a median duration of PFS of 19.4 months, a median DoR of 20.8 months, and a median OS, reported for the first time, of 24.6 months.

3.1.1. Key trial: DESTINY-Breast01 (addendum to Document B, Section B.2.6.1)

3.1.1.1. Participant flow (addendum to Document B, Section B.2.4.3)

At the time of the data cut-off (June 8, 2020), 37 of 184 patients (20.1%) who had received the recommended dose were continuing to receive T-DXd. The primary reasons for discontinuation included progressive disease ([redacted] and [redacted] (Table 22). The median treatment duration was [redacted], and the median duration of follow-up was 20.5 months [redacted]; [redacted] continued to receive T-DXd for more than 6 months.

Table 22: DESTINY-Breast01: Patient disposition

	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Subjects enrolled	184
Subjects treated	184
Subjects on treatment, n (%)	37 (20.1)
Subjects discontinued by reasons, n (%)	[redacted]
PD per RECIST	[redacted]
TEAE	[redacted]
Withdrawal by subject	[redacted]
Physician decision	[redacted]
Death	[redacted]
Other	[redacted]
Median duration of follow-up, months (range)	20.5 [redacted]
Median treatment duration, months (range)	[redacted]

Abbreviations, PD, progressive disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Data-cut: June 8, 2020
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.1.1.1 and Table 14.1.5.1[2]

3.1.1.2. Primary efficacy outcome: objective response rate (addendum to Document B, Section B.2.6.1.1)

The efficacy results for the primary outcome of ICR-assessed ORR in the DESTINY-Breast01 trial at the data-cut of June 8, 2020 are presented in Table 23. Among the 184 patients who received T-DXd at the recommended dose of 5.4 mg/kg, the confirmed ORR on ICR was 61.4% [redacted]); of these 12 patients (6.5%) had a CR, and 101 patients (54.9%) had a PR. [redacted]

The confirmed ORR based on investigator assessment (secondary endpoint) in the 5.4 mg/kg dose cohort was [redacted]

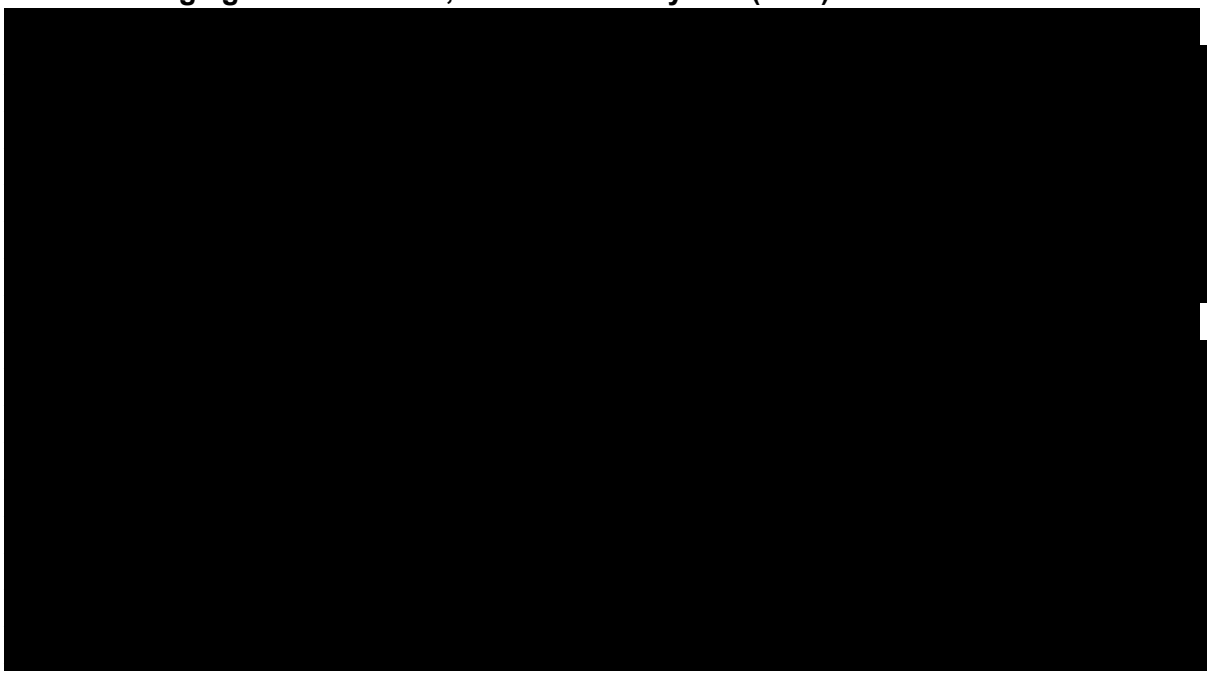
Table 23: DESTINY-Breast01: Primary efficacy outcome – ORR by ICR (EAS)

Primary endpoint	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) (ICR)	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184) (INV)[†]
ORR, n (% [95% CI])	113 (61.4[redacted]	[redacted]
CR, n (%)	12 (6.5)	[redacted]
PR, n (%)	101 (54.9)	[redacted]
SD, n (%)	66 (35.9)	[redacted]
PD, n (%)	[redacted]	[redacted]
NE, n (%)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CR, complete response; EAS, enrolled analysis set; ICR, independent central review; INV, investigator; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan
[†] Key secondary endpoint was ORR based on investigator assessment
Data-cut: June 8, 2020
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.2.1.1 and Table 14.2.1.2[2]

Most of the patients for whom both baseline and postbaseline data were available had a reduction in tumour size (Figure 19).

Figure 19: DESTINY-Breast01: Waterfall plot of change from baseline in tumour size for the 5.4 mg/kg dose of T-DXd, as measured by ICR (EAS)



Abbreviations: ICR, independent central review.
Data-cut: June 8, 2020

The upper horizontal line indicates a 20% increase in tumour size in the patients who had disease progression, and the lower line indicates a 30% decrease in tumour size (partial response).
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Figure 14.2.1.1[2]

3.1.1.3. Key secondary outcomes (addendum to Document B, Section B.2.6.1.2)

Progression-free survival

Of the 184 patients receiving the recommended dose of 5.4 mg/kg (data-cut of June 8, 2020), there were and the median PFS for these patients was 19.4 months (95% CI: 14.1, NE) (Table 24). Of the 184 patients,

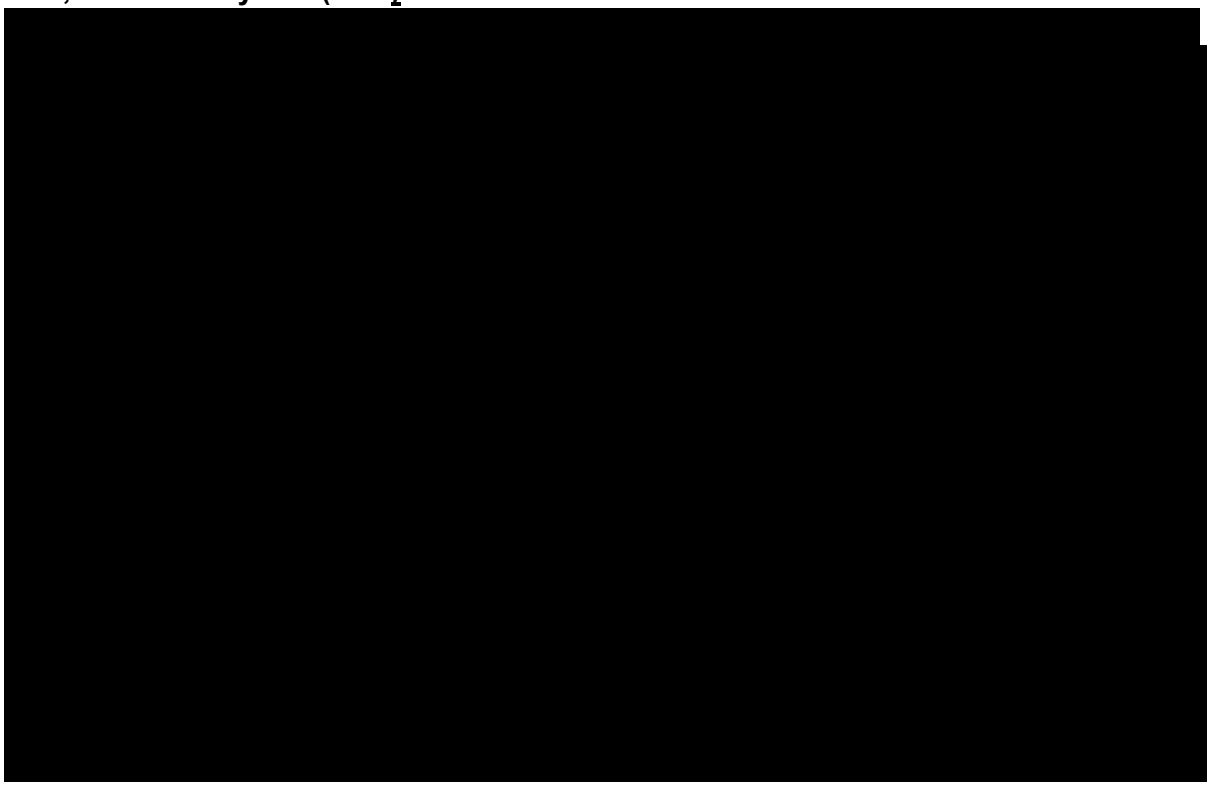
Table 24: DESTINY-Breast01: PFS as assessed by ICR (EAS)

PFS	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Median PFS, months (95% CI)	**19.4 (14.1, NE)**
PFS events, n (%)	[redacted]
Progressive disease, n (%)	[redacted]
Death, n (%)	[redacted]
Censored, n (%)	[redacted]
No PD or death	[redacted]
New anti-cancer therapy	[redacted]
Missed 2 consecutive tumour assessments	[redacted]
No post-baseline tumour assessments	[redacted]

Abbreviations: CI, confidence interval; EAS, Enrolled Analysis Set; ICR, independent central review; ITT, Intent-to-Treat; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Data-cut: June 8, 2020
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.2.2.2

Figure 20 presents a Kaplan–Meier (KM) curve of PFS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b.

Figure 20: DESTINY-Breast01: Kaplan–Meier plot of PFS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)



Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Data-cut: June 8, 2020
Data for [redacted] patients were censored, as indicated by tick marks. Disease progression was assessed with the use of the modified RECIST version 1.1. The dashed lines indicate the 95% CI.
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Figure 14.2.4.1[2]

Overall survival

At the data-cut of June 8, 2020 (median follow-up of 20.5 months), preliminary median OS was 24.6 months (95% CI: 23.1, NE) (estimated at 35% maturity with only 17 patients at risk at 24 months); [redacted] had died and [redacted] were censored for the OS analysis (Table 25). Estimated OS was 85% (95% CI: 79, 90) at 12 months and 74% (67, 80) at 18 months.

Table 25: DESTINY-Breast01: OS as assessed by ICR (EAS)

OS	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Median OS, months (95% CI)	**24.6 (23.1, NE)**
OS events, n (%)	[redacted]
Censored, n (%)	[redacted]

Abbreviations: CI, confidence interval; EAS, Enrolled Analysis Set; ICR, independent central review; ITT, Intent-to-Treat; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan
‡The reasons for censoring for OS were not collected as part of the analysis. Additional analyses provided to the ERG for the previous data-cut (August 1, 2019; n=159 censored) showed that the majority of patients were censored due to being alive (n=144; 78.3%), while 10 (5.4%) were lost to follow-up, and 5 (2.7%) were due to withdrawal by subject.
Data-cut: June 8, 2020
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.2.2.3

Figure 21 presents a KM curve of OS for the 5.4 mg/kg dose in Part 1, Part 2a and Part 2b (data-cut of June 8, 2020).

Figure 21: DESTINY-Breast01: Kaplan–Meier plot of OS for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)

[redacted]

Abbreviations: EAS, Enrolled Analysis Set; ICR, independent central review; OS, overall survival; T-DXd, trastuzumab deruxtecan
Data-cut: June 8, 2020
Data for [redacted] patients were censored, as indicated by tick marks. The dashed lines indicate the 95% CI.
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Figure 14.2.4.2[2]

Other secondary endpoints

A summary of the results for other secondary efficacy outcomes assessed in the DESTINY-Breast01 trial (data-cut of June 8, 2020) are presented in Table 26.

Table 26: DESTINY-Breast01: Summary of other secondary efficacy endpoints as assessed by ICR (EAS)

Secondary endpoints	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
DCR, n (% [95% CI])	179 (97.3 [93.8, 99.1])
CBR, n (% [95% CI])	[redacted]
Median DoR, months (95% CI)	20.8 (15.0, NE)
Events, n/N patients with response, (%)	[redacted]
Censored, n/N patients with response (%)	[redacted]
Median TTR, months (95% CI)	[redacted]

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; DoR, duration of response; EAS, Enrolled Analysis Set; ICR, independent central review; TTR, time to response; T-DXd, trastuzumab deruxtecan
Data-cut: June 8, 2020

DoR and TTR is shown for the 112 patients who had a complete or partial response among the 184 patients treated with the recommended dose of 5.4 mg/kg T-DXd

Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.2.4.1 and Table 14.2.2.1[2]

The DCR and CBR for patients receiving the 5.4 mg/kg dose was 97.3% (95% CI: 93.8, 99.1) [redacted] For the 112 patients who achieved a response with the 5.4 mg/kg dose, the median DoR was 20.8 months (95% CI: 15.0, NE), and the median TTR was [redacted] A KM curve of DoR is presented in Figure 22.

Figure 22: DESTINY-Breast01: Kaplan–Meier plot of DoR for the 5.4 mg/kg dose of T-DXd, assessed by ICR (EAS)

Abbreviations: DoR, duration of response; ICR, independent central review

Data-cut: June 8, 2020

DoR is shown for the 112 patients who had a complete or partial response among the 184 patients treated with the recommended dose of 5.4 mg/kg T-DXd

Source: Daiichi-Sankyo, Inc., 2020 (data on file): Figure 14.2.4.3[2]

3.1.1.4. Efficacy discussion and conclusions (addendum to Document B, Section B.2.6.3)

In the key trial, DESTINY-Breast01, T-DXd at a dose of 5.4 mg/kg at the latest data-cut (June 8, 2020) continued to demonstrate robust anti-tumour activity in patients with HER2+ uBC and mBC who had undergone extensive previous treatment, with a confirmed ORR of 61.4%, a median duration of PFS of 19.4 months, and a median DoR of 20.8 months. In addition,

At this latest data-cut, median OS, reported for the first time, was 24.6 months (95% CI: 23.1-NE), representing an increase in overall survival compared to current treatment in the NHS. However, please note that the median OS data are preliminary, estimated at 35% maturity.[1] The information provided by a KM curve at a particular time point is dependent on

the number of subjects at risk at that time point, and if there are only a few patients at risk, then one single extra event will make a substantial impact on the distance by which the KM curve decreases.[3] Therefore, [redacted] makes this portion of the KM data uninformative for modelling in terms of long-term survival extrapolation. Although the data are preliminary, it is worth noting that the lower CI for T-DXd (23.1 months) already exceeds the median OS of the comparator treatments, and indeed the upper CI from most of the comparator studies.

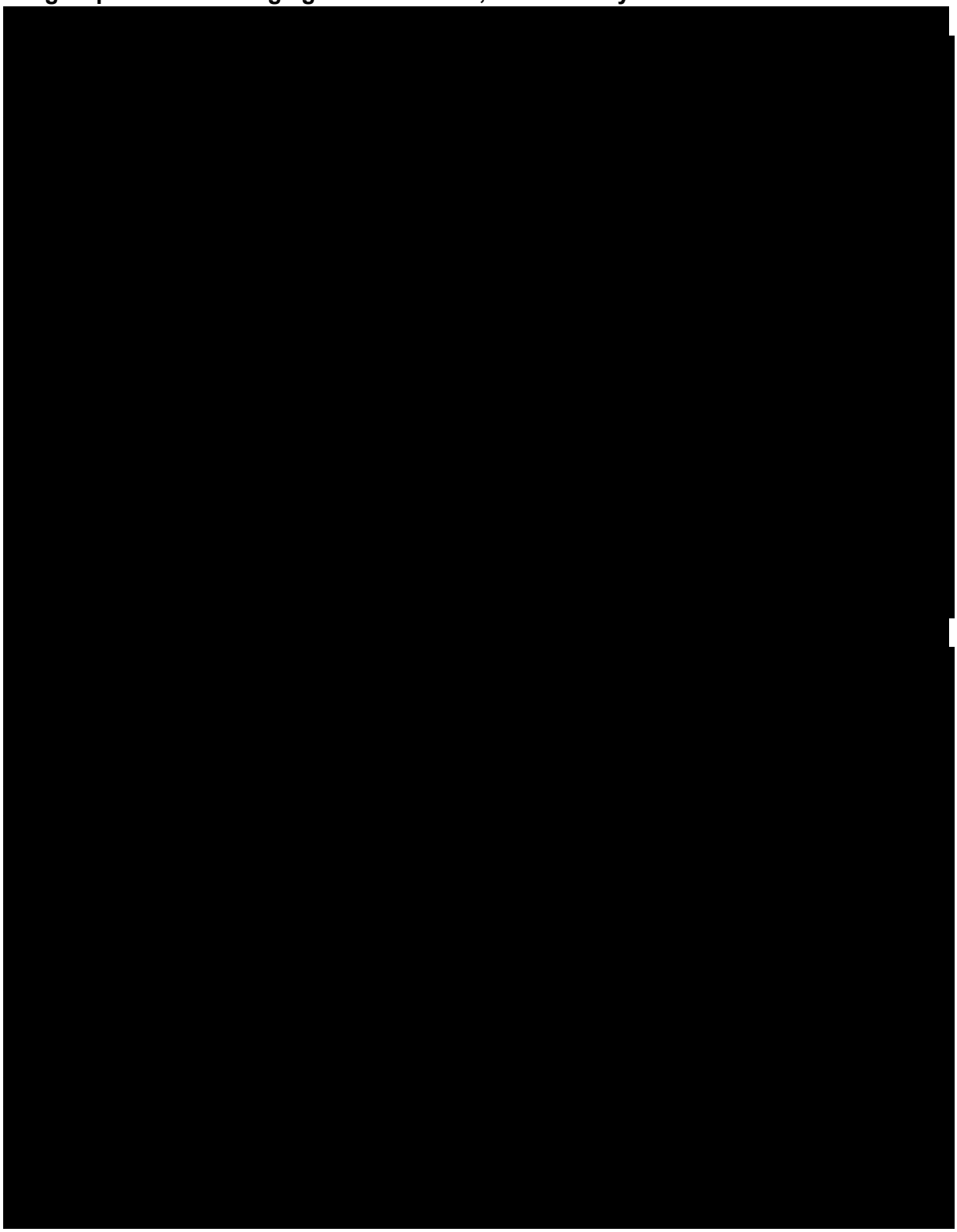
Overall, the efficacy observed with T-DXd is expected to substantially exceed those of currently available treatments in this difficult to treat population with a high unmet need. For further discussion points on efficacy and subgroup analyses that are unchanged since the the original company submission, please see Section B.2.6.3 of the original company submission.

3.1.2. Subgroup analysis (addendum to Document B, Section B.2.7)

Pre-specified demographic and prognostic subgroups were examined for the primary endpoint of ORR to assess homogeneity of estimate of treatment effect (Figure 23). In each of the subgroups, the analysis was carried out using the same methodology and analysis set as described for the overall analysis of the corresponding endpoint.[2] Results of the subgroup analyses are presented using descriptive summaries and results plotted graphically.[2]

In the 5.4 mg/kg dose cohort, a confirmed ORR based on ICR of at [redacted] was observed in most subgroups (data-cut of June 8, 2020) (Figure 23). [redacted]

Figure 23: DESTINY-Breast01: Forest plot for objective response in pre-specified subgroups for the 5.4 mg/kg dose of T-DXd, assessed by ICR



Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; JPN, Japan; KOR, Korea; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridisation; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Data-cut: June 8, 2020
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Figure 14.2.5.1[2]

3.1.3. Indirect and mixed treatment comparisons (addendum to Document B, Section B.2.9)

3.1.3.1. Results from MAIC analyses (addendum to Document B, Section B.2.9.6)

3.1.3.1.1 T-DXd vs eribulin (addendum to Document B, Section B.2.9.6.1)

Four separate MAIC comparisons were made to compare T-DXd with eribulin.

Cortes 2011

To compare T-DXd with eribulin, weights were estimated relative to the Cortes 2011 population baseline characteristics. Table 27 presents the DESTINY-Breast01 (unadjusted and weighted) and Cortes 2011 baseline characteristics for the five matching variables. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3), percentage of prior hormone therapy and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a moderate ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had similar mean age, higher proportion of ECOG-PS 0 status, a higher number of prior lines, lower percentage of prior hormone therapy and lower proportion with hormone receptor positive status compared with the Cortes 2011 study.

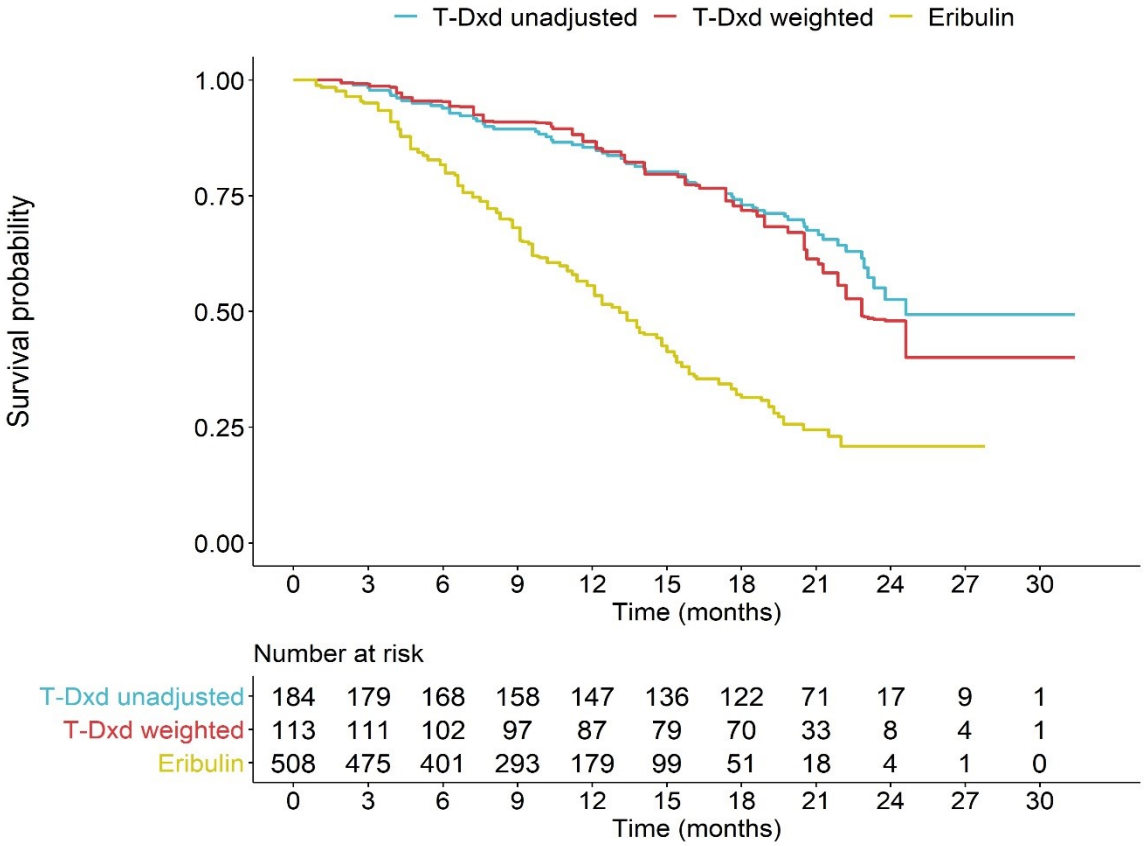
Table 27: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Mean/ median age	Percent ECOG= 0	Percent prior hormone therapy	Percent prior line ≥3	Percent hormone receptor positive
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	48.9	91.8	52.7
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	55.00	42.7	85.0	87.0	64.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 24. The KM plots show that weighting has resulted in only a minor decline in OS outcomes for the T-DXd arm; the median OS is 22.83 months for the weighted T-DXd arm (Table 28). Table 29 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 24: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)



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

Table 28: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	274	13.10 (12.10 to 14.60)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

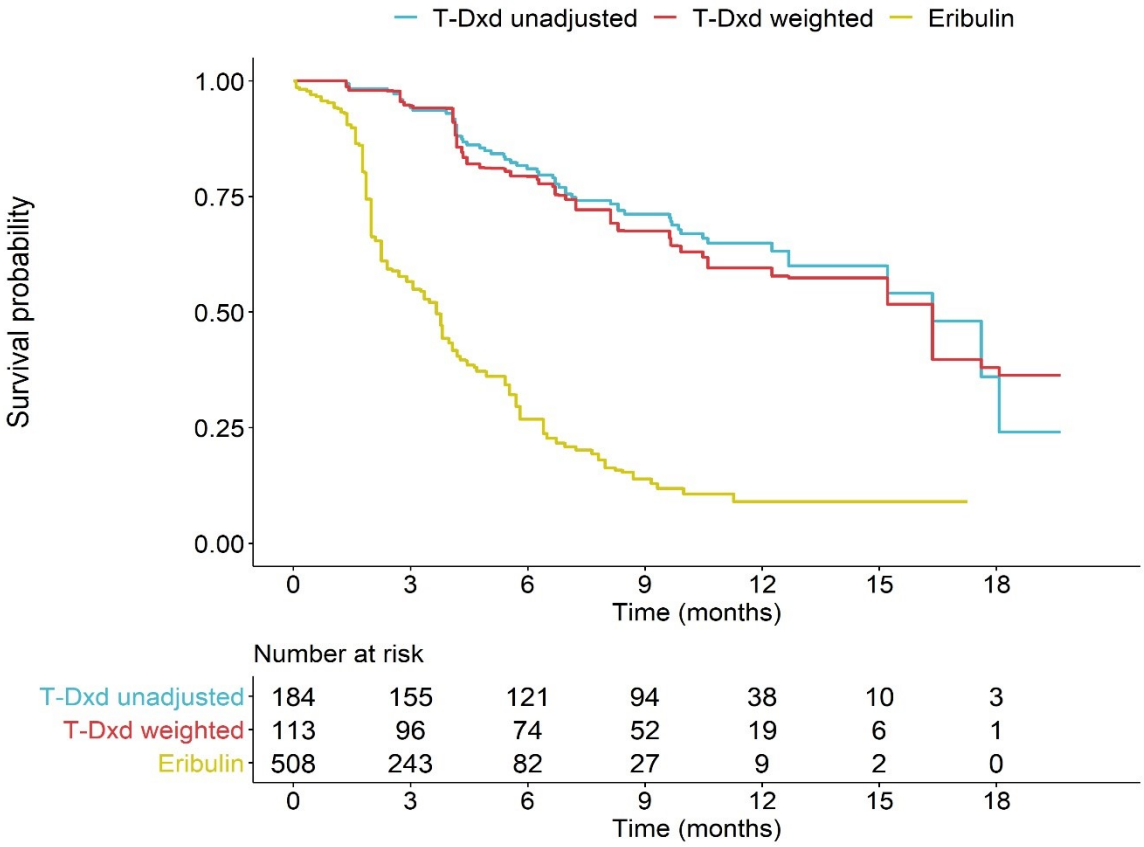
Table 29: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 25. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm, the median survival time decreased to 14.98 months after weighting (Table 30). Table 31 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The proportional hazard assumption was violated for the matching PFS curves (see Schoenfeld test and residuals plot in Appendix D). The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 25: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)



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

Table 30: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2011)	508.0	357	3.66 (3.26 to 3.81)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 31: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 32 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 27. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 32: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Barni 2019

To compare T-DXd with eribulin, weights were estimated relative to the Barni 2019 population baseline characteristics. Table 33 presents the DESTINY-Breast01 (unadjusted and weighted) and Barni 2019 baseline characteristics for the four variables available for matching. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3) and visceral disease status. The ESS after matching was n=[redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had slightly younger mean age, higher proportion of ECOG-PS 0 status, a higher proportion with ≥3 prior lines and higher proportion with visceral disease than those in the Barni 2019 study.

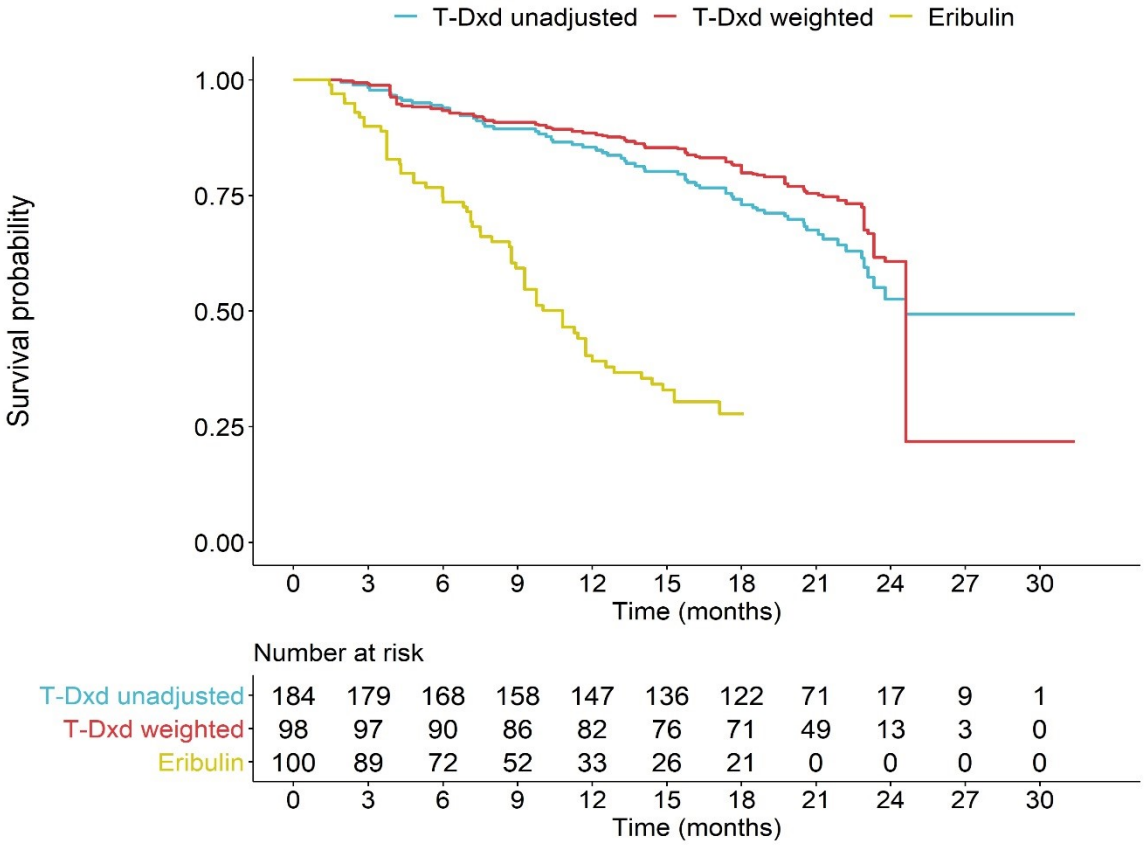
Table 33: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3	Percent visceral Y
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	95.0	59.50	40.9	64.6	59.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 26 for the full DESTINY-Breast01 population and the HER2-positive subgroup of the Barni 2019 study. The KM plots show that weighting has resulted in improved OS outcomes for the T-DXd arm; the median OS point estimate did not change before and after weighting T-DXd arm (Table 34). Table 35 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted].

Figure 26: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)



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

Table 34: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	100.0	65	10.81 (8.92 to 12.01)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 35: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

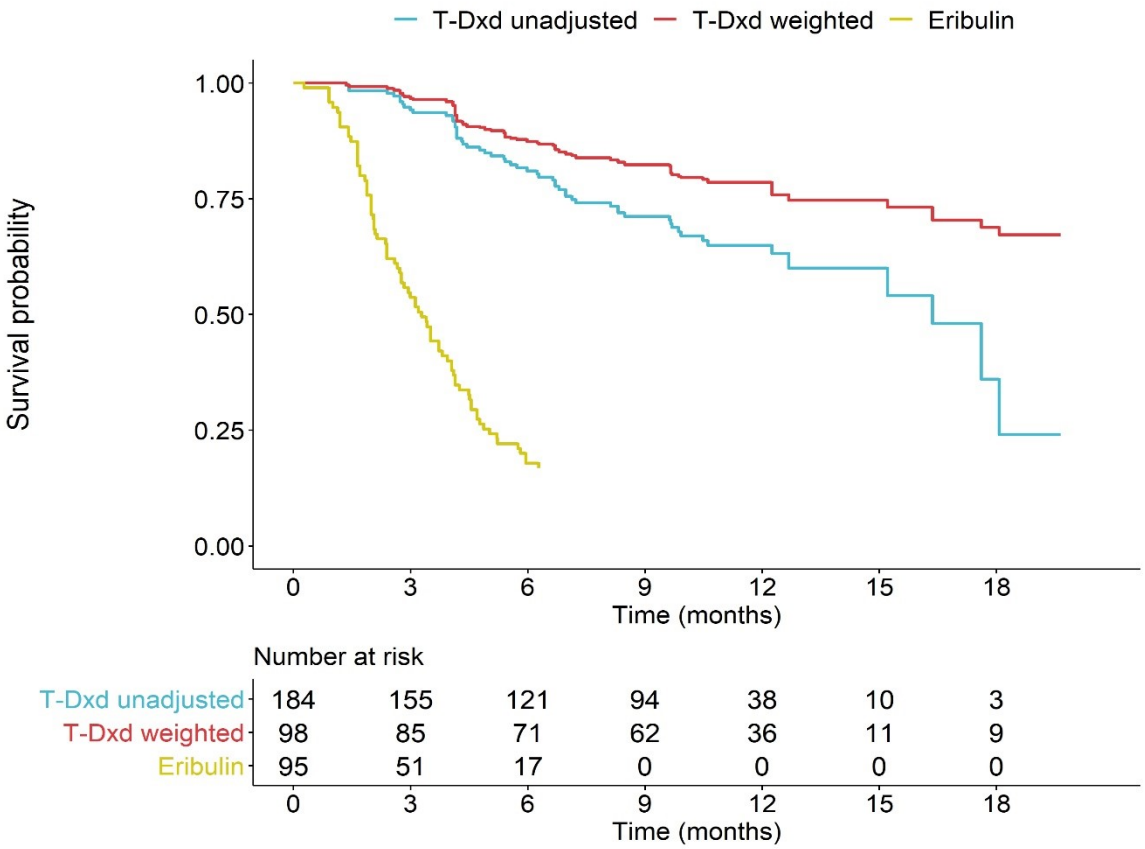
Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations : T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 27. The KM plots show that weighting has resulted in improved PFS outcomes for the T-DXd arm; the median PFS is prolonged in the weighted T-DXd arm (Table 36). Table 37 presents the weighted HR

results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 27: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)



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

Table 36: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)	95.0	79	3.28 (2.72 to 3.94)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 37: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 38 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 33. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 38: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Cortes 2010

To compare T-DXd with eribulin, weights were estimated relative to the Cortes 2010 population baseline characteristics. Table 39 presents the DESTINY-Breast01 (unadjusted and weighted) and Cortes 2010 baseline characteristics for the four matching variables. Matching was based on mean age, ECOG-PS, prior treatment lines (<3/≥3) and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a relatively large ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had very similar mean age, higher proportion of ECOG-PS 0 status, a similar proportion with ≥3 prior lines and lower proportion with hormone receptor positive status compared with the Cortes 2010 study.

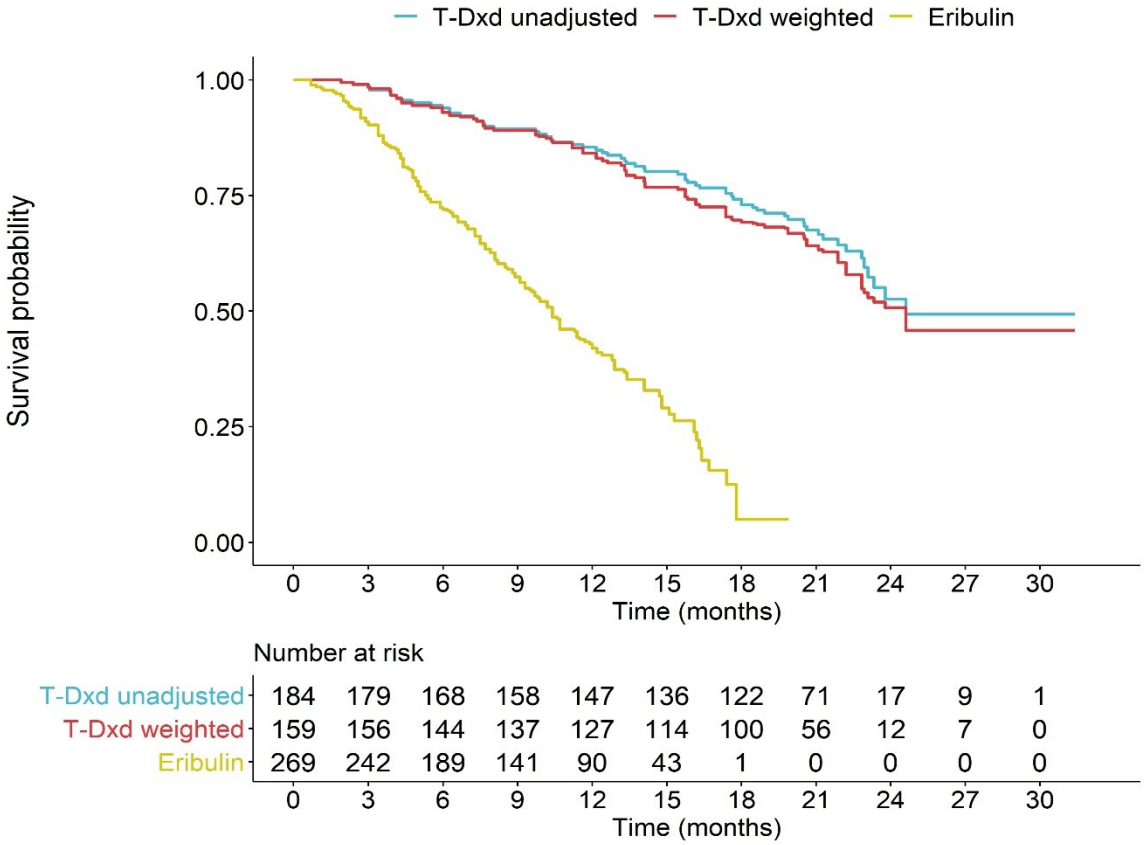
Table 39: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3	Percent hormone receptor positive
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8	52.7
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	56.00	37.2	89.6	71.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 28. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm, with near-identical estimates (Table 40). Table 41 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 28: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)



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

Table 40: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	191	10.40 (9.30 to 11.50)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

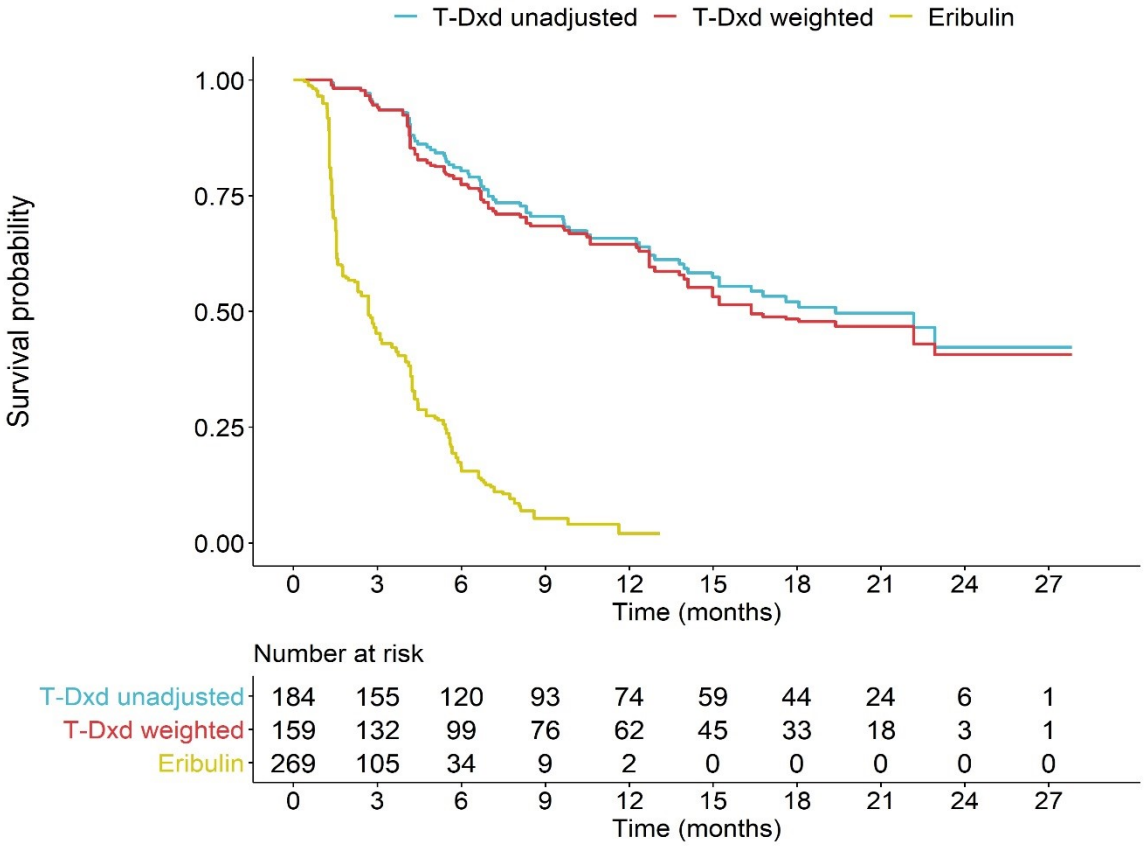
Table 41: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 29. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm (Table 42). Median PFS point estimate decreased after weighting the T-DXd arm. Table 43 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 29: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)



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

Table 42: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Cortes 2010)	269.0	224	2.67 (2.30 to 3.15)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 43: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 44 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 39. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 44: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2010)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Gamucci 2014

To compare T-DXd with eribulin, weights were estimated relative to the Gamucci 2014 population baseline characteristics. Table 45 presents the DESTINY-Breast01 (unadjusted and weighted) and Gamucci 2014 baseline characteristics for the five matching variables. Matching was based on mean age, prior treatment lines (<3/≥3), percentage of prior hormone therapy, percentage of visceral disease and percentage of hormone receptor positive. The ESS after matching was [redacted]. This is a very small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had a younger mean age, a higher proportion with ≥3 prior lines, lower percentage of prior hormone therapy, lower proportion with hormone receptor positive and a higher percentage of visceral disease compared with the Gamucci 2014 study.

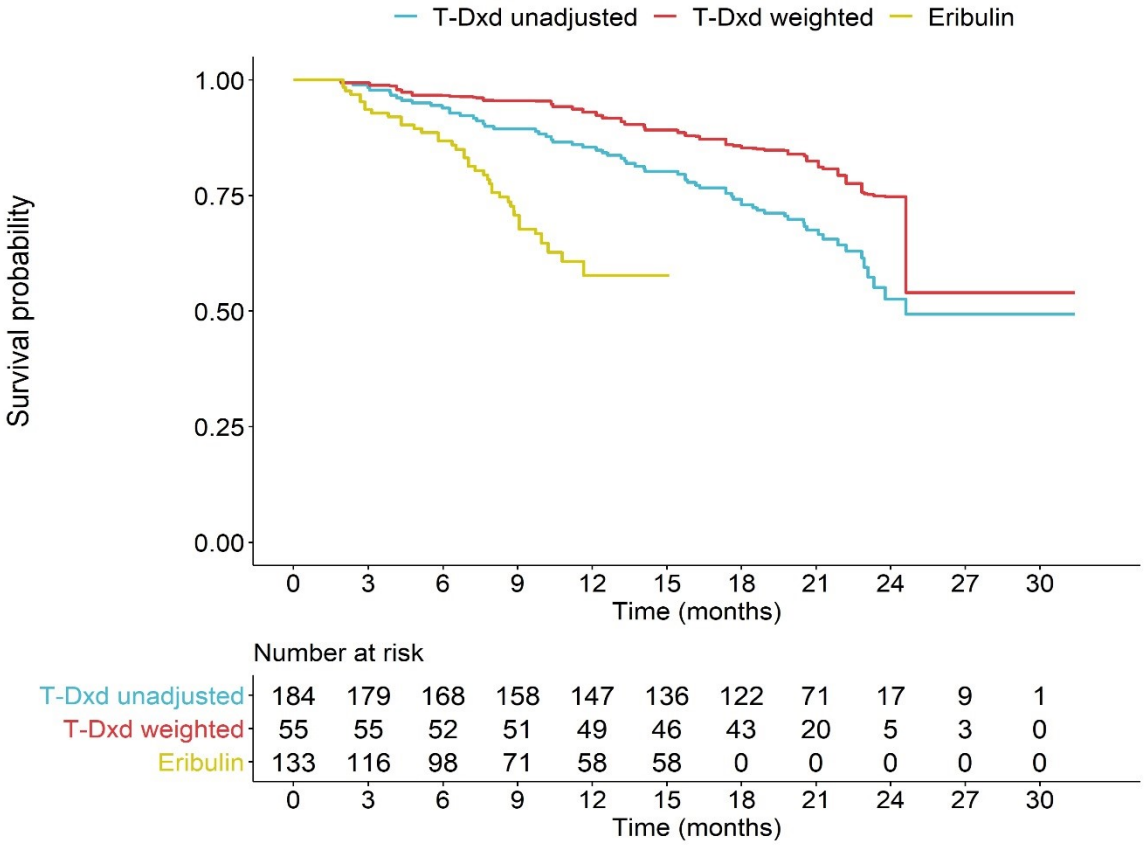
Table 45: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Mean/ median age	Percent prior hormone therapy	Percent prior line ≥3	Percent hormone receptor positive	Percent visceral Y
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	48.9	91.8	52.7	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	62.00	69.2	50.4	84.0	80.5

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 30. The KM plots show that weighting has resulted in improved OS outcomes for the T-DXd arm; the median OS is not reached for the weighted T-DXd arm or eribulin arm (Table 46). Table 47 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 30: KM plot of OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)



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

Table 46: KM summary of OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	46	NA (11.66 to NA)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval

Table 47: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

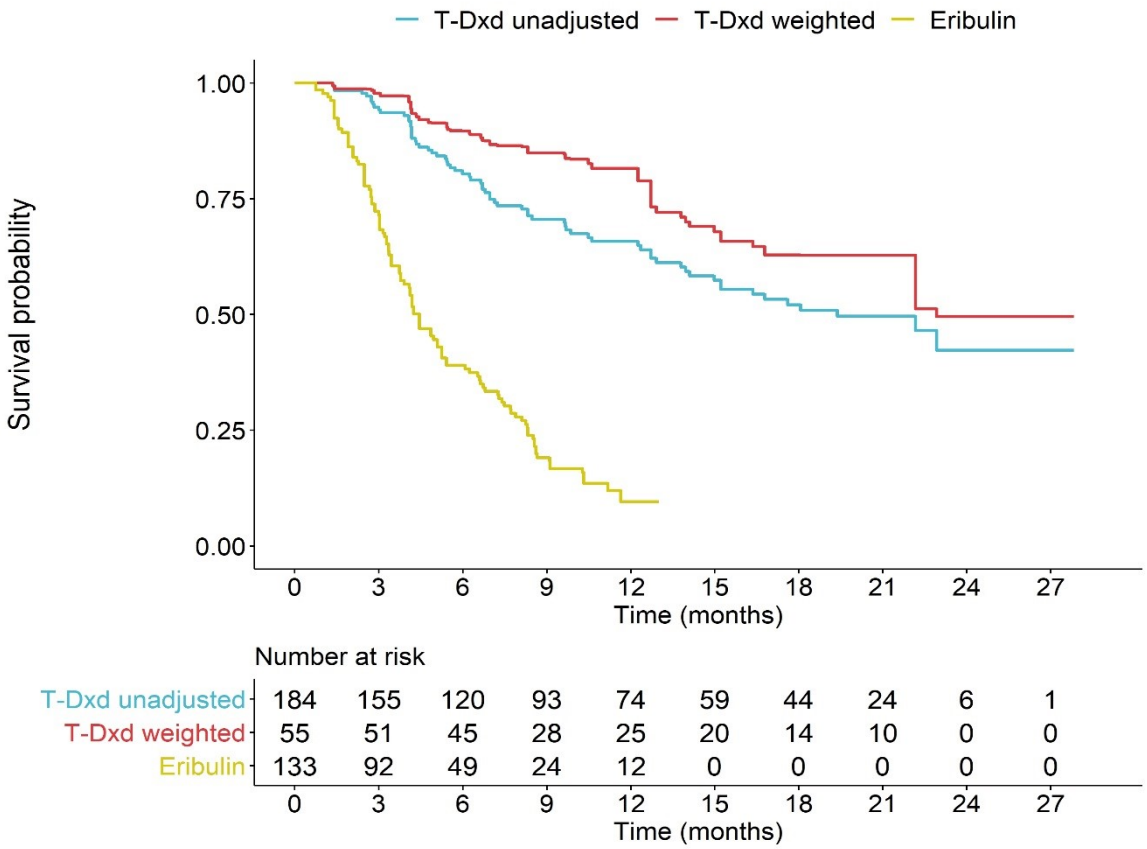
Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 31. The KM plots show that weighting has resulted in improved PFS outcomes for the T-DXd arm, the median survival time prolonged after weighting (Table 48). Table 49 presents the weighted HR results,

alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 31: KM plot of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)



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

Table 48: KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)	133.0	115	4.45 (3.74 to 5.24)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 49: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 50 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 45. T-DXd demonstrates significantly improved outcomes for response compared with eribulin.

Table 50: Odds ratio for ORR, DCR and CBR – T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
DCR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]
CBR	Unadjusted	T-DXd vs eribulin	[redacted]
	Weighted GLM model	T-DXd vs eribulin	[redacted]
	Weighted sandwich estimator	T-DXd vs eribulin	[redacted]

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval

3.1.3.1.2 T-DXd vs capecitabine (addendum to Document B, Section B.2.9.6.2)

Fumoleau 2004

To compare T-DXd with capecitabine, weights were estimated relative to the Fumoleau 2004 population baseline characteristics. Table 51 presents the DESTINY-Breast01 (unadjusted and weighted) and Fumoleau 2004 baseline characteristics for the three matching variables. Matching was based on mean age, ECOG-PS and prior treatment lines (<3/≥3). The ESS after matching was [redacted] This is a relatively small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had older mean age, higher proportion of ECOG-PS 0 status and a higher proportion with ≥3 prior lines compared with the Fumoleau 2004 study.

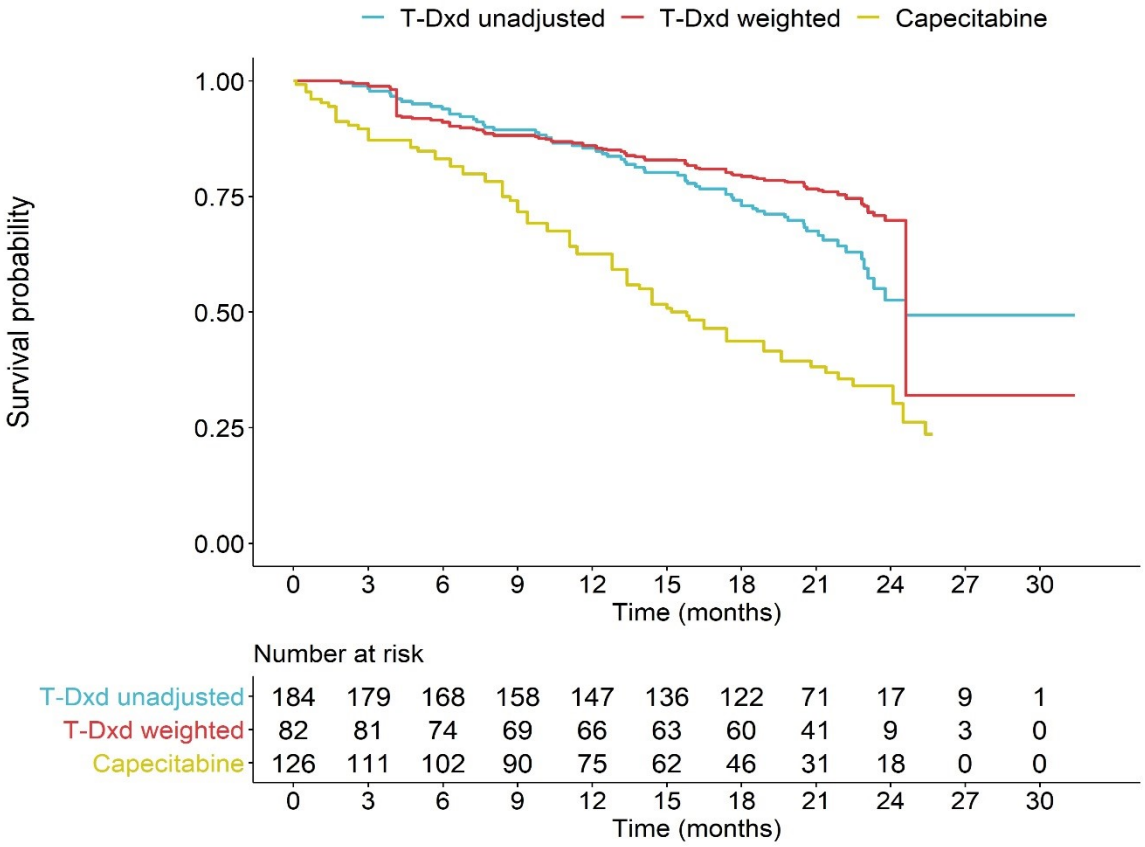
Table 51: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Mean/median age	Percent ECOG= 0	Percent prior line ≥3
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	55.4	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)	126.0	54.00	43.7	45.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 32. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm. (Table 52). Table 53 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 32: KM plot of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)



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

Table 52: KM summary of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)	126.0	81	15.80 (13.40 to 19.60)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

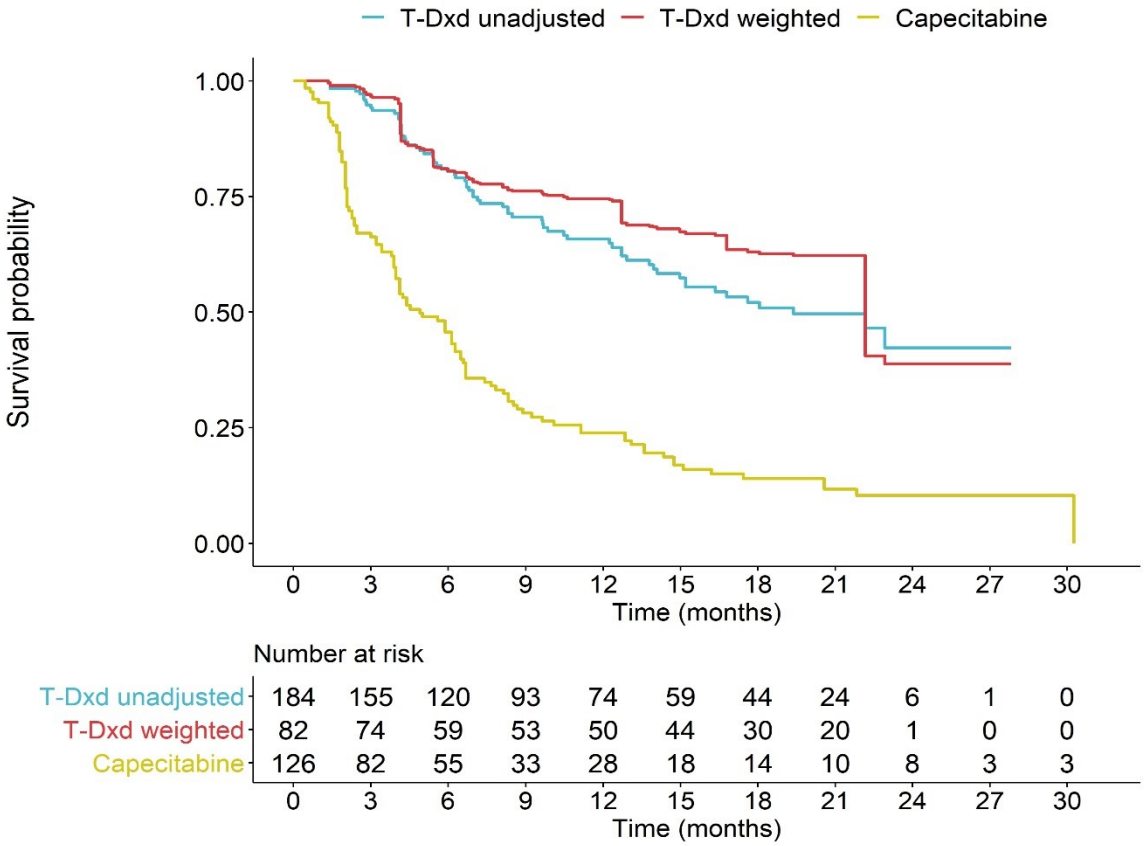
Table 53: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 33. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm (Table 54). Table 55 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 33: KM plot of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)



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

Table 54: KM summary of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)	126.0	110	4.90 (3.96 to 6.48)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 55: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 56 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 51. T-DXd demonstrates significantly improved outcomes for response compared with capecitabine.

Table 56: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
DCR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Blum 2001

To compare T-DXd with capecitabine, weights were estimated relative to the Blum 2001 population baseline characteristics. Table 57 presents the DESTINY-Breast01 (unadjusted and weighted) and Blum 2001 baseline characteristics for the four matching variables. Matching was based on mean age, percentage of prior hormone therapy, percentage of visceral disease and prior treatment lines (<3/≥3). The ESS after matching was [redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial compared with the Blum 2001 study had older mean age, lower proportion of previous hormone therapy, higher proportion with ≥3 prior lines and higher percentage of visceral Y.

Table 57: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

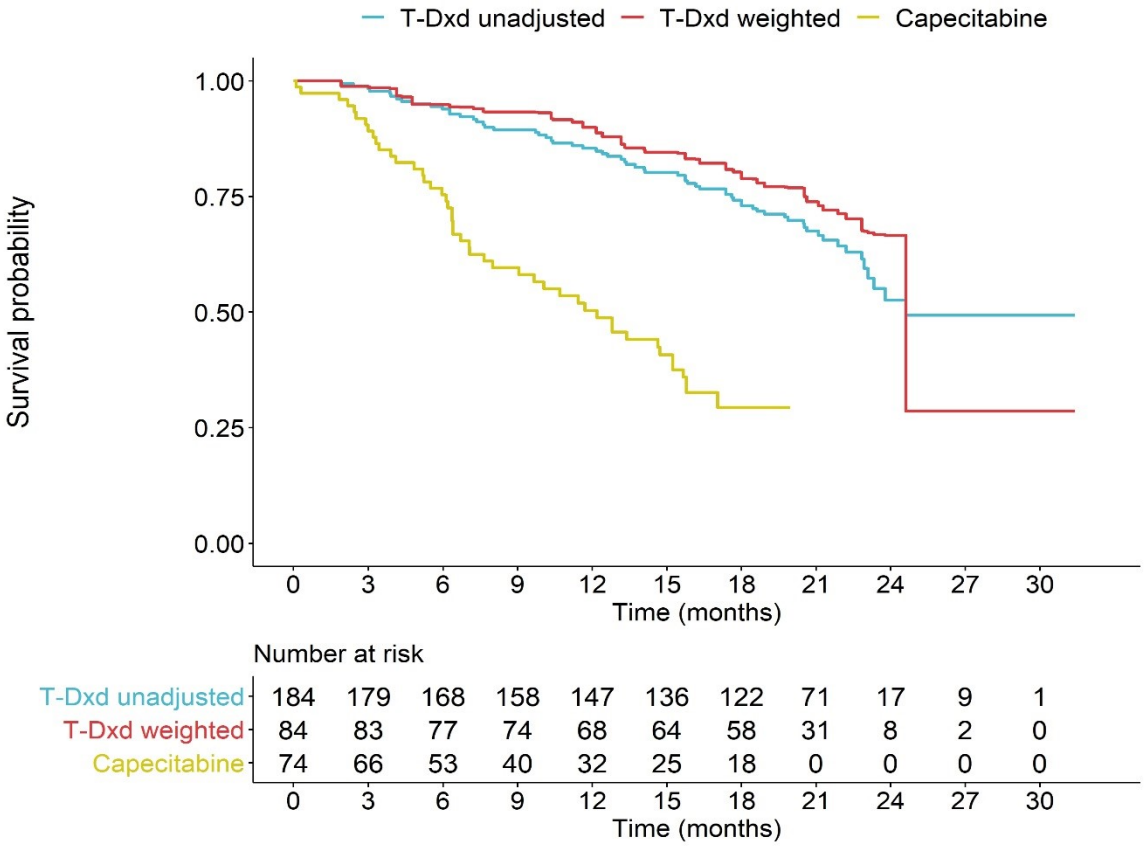
Treatment (study)	N/ ESS	Mean/ median age	Percent prior hormone therapy	Percent prior line ≥3	Percent visceral Y
T-DXd unadjusted (DESTINY-Breast01)	184.0	55.96	48.9	91.8	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	52.50	70.2	66.2	79.7

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in

Figure 34. The KM plots show that weighting has not resulted in improved OS outcomes for the T-DXd arm(Table 58). Table 59 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in OS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 34: KM plot of OS - T-DXd (Destiny Breast 01DESTINY-Breast01) vs capecitabine (Blum 2001)



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

Table 58: KM summary of OS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	48	12.19 (7.66 to 15.24)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

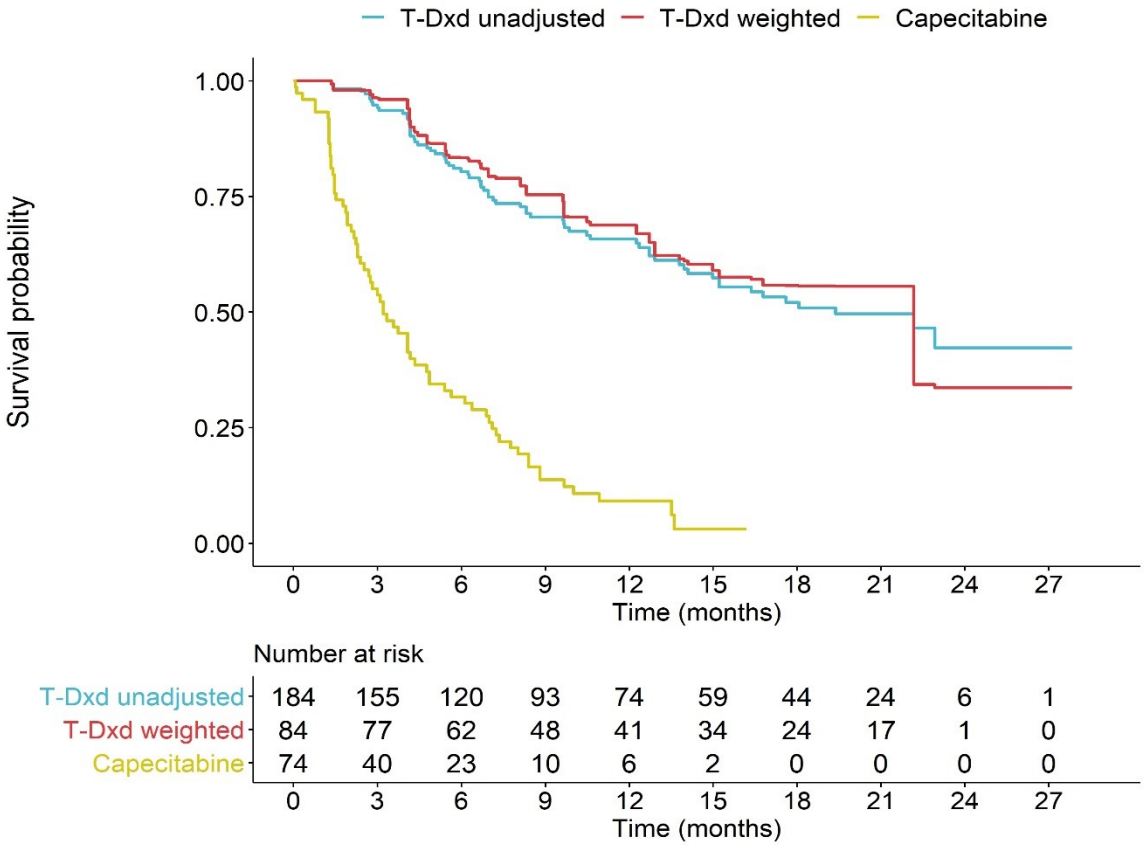
Table 59: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 35. The KM plots show that weighting has not resulted in improved PFS outcomes for the T-DXd arm (Table 60). Table 61 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving capecitabine (weighted HR: [redacted]).

Figure 35: KM plot of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)



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

Table 60: KM summary of PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Blum 2001)	74.0	70	3.20 (2.28 to 4.34)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 61: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs capecitabine	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 62 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 57. T-DXd demonstrates significantly improved outcomes for response compared with capecitabine.

Table 62: Odds ratio for ORR and DCR – T-DXd (DESTINY-Breast01) vs capecitabine (Blum 2001)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
DCR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]

Abbreviations: DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

3.1.3.1.3 T-DXd vs vinorelbine (addendum to Document B, Section B.2.9.6.3)

Sim 2019

To compare T-DXd with vinorelbine, weights were estimated relative to the Sim 2019 population baseline characteristics. Table 63 presents the DESTINY-Breast01 (unadjusted and weighted) and Sim 2019 baseline characteristics for the four matching variables. Matching was based on ECOG-PS, prior treatment lines (<3/≥3), percent hormone receptor positive, and percent visceral. Mean age was available from the Sim study but was removed from the analysis (see Section B.2.9.3 in the main submission). The ESS after matching was [redacted]. This is a small ESS compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had a higher proportion of ECOG-PS 0 status, lower proportion with ≥3 prior lines, higher percentage of hormone receptor positive and higher percent of visceral disease compared with the Sim 2019 study.

Table 63: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

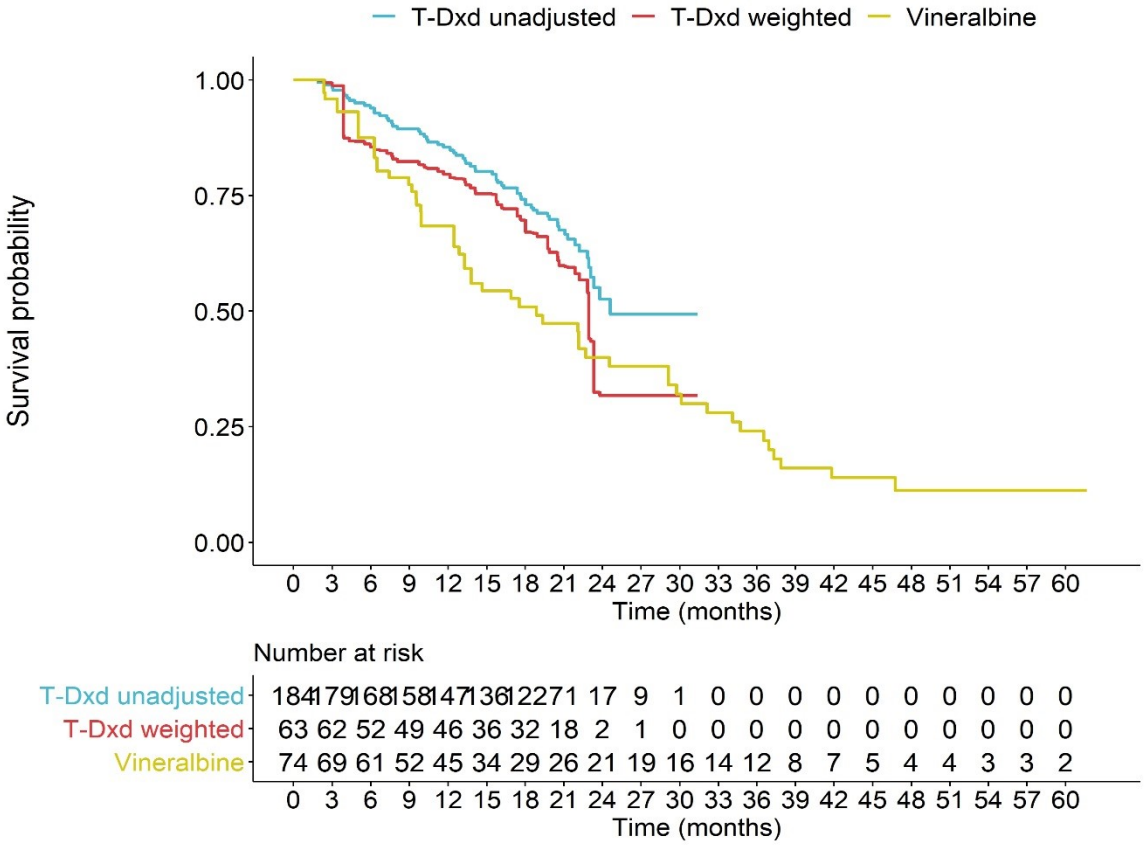
Treatment (study)	N/ ESS	Percent ECOG= 0	Percent prior line ≥3	Percent hormone receptor positive	Percent visceral Y
T-Dxd unadjusted (DESTINY-Breast01)	184.0	55.4	91.8	52.7	91.8
T-Dxd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	25.7	100.0	45.9	50.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.

Unadjusted and weighted KM plots of OS are shown in Figure 36: KM plot of OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019). The KM plots show that weighting has resulted in declining OS outcomes for the T-DXd arm (Table 64). Table 65 presents the weighted HR results, alongside unadjusted naïve HRs for comparison. The weighted patients receiving T-DXd did not demonstrate significantly greater improvements in OS compared with patients receiving vinorelbine, with large uncertainty around the point estimate, probably due to the small ESS (weighted HR: [redacted]). Note that from visual inspection of the KM curves the proportional hazards assumption of matching curves is violated.

OS data from the Sim study were presented to clinical experts at an advisory board and were not considered to be clinically plausible (see Section 3.3.1.2 in the main submission for further details). These results should therefore be interpreted with caution.

Figure 36: KM plot of OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)



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

Table 64: KM summary of OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-Dxd unadjusted (Destiny Breast 01)	184.0	65	24.61 (23.10 to NA)
T-Dxd weighted (Destiny Breast 01)	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	53	18.87 (13.29 to 29.13)

Abbreviations: ESS, effective sample size; N, sample size;T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 65: Hazard ratios for OS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

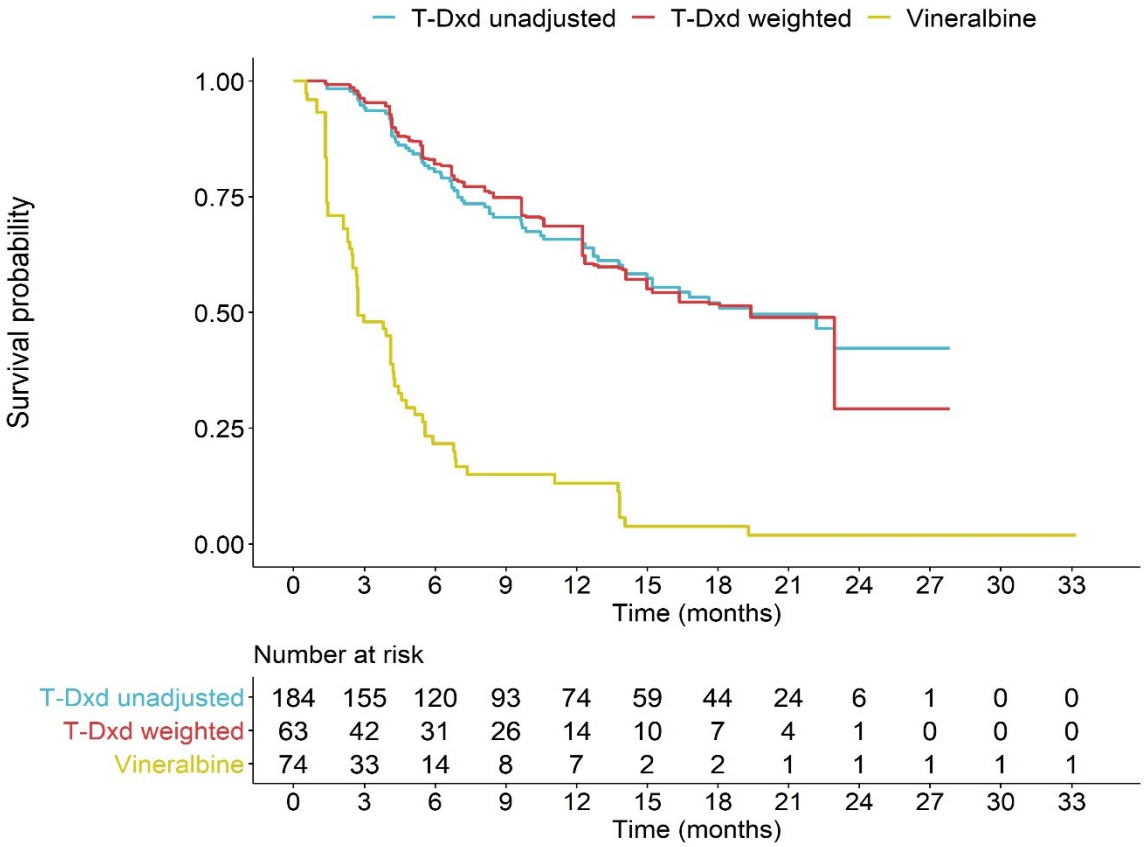
Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-Dxd vs Vinorelbine	[redacted]
Weighted standard CI	T-Dxd vs Vinorelbine	[redacted]
Weighted bootstrapped CI	T-Dxd vs Vinorelbine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Unadjusted and weighted KM plots of PFS are shown in Figure 37. The KM plots show that weighting has not resulted in significantly improved PFS outcomes for the T-DXd arm (Table 66). Table 67 presents the weighted HR results, alongside unadjusted naïve HRs for

comparison. The weighted patients receiving T-DXd demonstrated significantly greater improvements in PFS compared with patients receiving vinorelbine (weighted HR: [redacted]).

Figure 37: KM plot of PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)



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

Table 66: KM summary of PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)	74.0	65	2.73 (2.51 to 4.22)

Abbreviations: ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan; NA, not applicable; CI, confidence interval.

Table 67: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs vinorelbine	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; CI, confidence interval.

Table 68 presents the unadjusted and weighted OR results for the response outcomes. The ESS is the same as that outlined in Table 70 . T-DXd demonstrates significantly improved outcomes for response compared with vinorelbine.

Table 68: Odds ratio for ORR and CBR – T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs vinorelbine	[redacted]
	Weighted GLM model	T-DXd vs vinorelbine	[redacted]
	Weighted sandwich estimator	T-DXd vs vinorelbine	[redacted]
CBR	Unadjusted	T-DXd vs vinorelbine	[redacted]
	Weighted GLM model	T-DXd vs vinorelbine	[redacted]
	Weighted sandwich estimator	T-DXd vs vinorelbine	[redacted]

Abbreviations: CBR, clinical benefit rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; CI, confidence interval.

3.1.3.2. Uncertainties in the indirect and mixed treatment comparisons (addendum to Document B, Section B.2.9.7)

The above analyses are associated with uncertainty due to small sample sizes, trial heterogeneity and the differences in prognostic factors available from each study. In addition, OS data from DESTINY-Breast01 are relatively immature, with the trial only just reaching median survival. Therefore, the results should be interpreted with caution.

In addition, an unanchored MAIC assumes that the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and treatment effect modifiers, which sometimes can be too strong an assumption. Matching adjustments were limited to data reported in the comparator trials and that collected in DESTINY-Breast01. It was not possible to adjust for differences in HER2 status between the studies, given that 100% of patients in DESTINY-Breast01 were HER2-positive; however, data in a HER2-positive population were available from Barni 2019 (eribulin) and Sim 2019 (vinorelbine). It was therefore necessary to make subsequent adjustments in the cost-effectiveness model (see Section B.3.3.4 in the main submission). Extensive efforts were sought in this series of MAICs to ensure that as many confounding factors were adjusted for as possible, but the consequence was small sample sizes. In addition, it was noted at the August advisory board that both young and old age are associated with worse prognosis in mBC, and so age may not be a reliable matching factor[8].

In the absence of KM data for TTD in the comparator studies, it was not possible to conduct MAIC analyses on this outcome. The only available data for vinorelbine are from the Sim 2019 study; OS data from this study were considered to be clinically implausible by clinical experts at the August advisory board (see Section B.3.3.1.2 in the main submission for further details).

In the absence of more robust comparative studies, these data provide a directional indication of the relative benefit of T-DXd with respect to comparators. This technique circumvented existing data limitations for the treatments that prevented construction of network meta-analyses for the outcomes of interest.

3.1.4. Adverse reactions (addendum to Document B, Section B.2.10)

The safety of T-DXd in patients with HER2+ uBC or mBC after two or more anti-HER2 therapies was evaluated in the DESTINY-Breast01 study and the DS8201-A-J101 study. For study DS8201-A-J101, please see the main submission Section B2.10.2 and Appendix F.

3.1.4.1. Key trial: DESTINY-Breast01 (addendum to Document B, Section B.2.10.1)

The data presented from the DESTINY-Breast01 study in this addendum are from the June 8, 2020 data-cut. The data presented in the main submission are from the August 1, 2019 data-cut, as reported in the primary publication (Modi 2020).[14] Please note that the safety data in the CSR corresponds to the primary data cut-off date (March 21, 2019, minimum 6 months of follow-up after last subject enrolled).[15] Compared with safety data at the primary data-cut, and the August 1, 2019 data-cut, the latest safety update showed no significant changes in most of the TEAE parameters, and no new safety signals were observed.

TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities (MeDRA), version 20.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Potential episodes of interstitial lung disease (ILD) were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE.

3.1.4.1.1 Exposure to study drug (addendum to Document B, Section B.2.10.1.1)

At the data-cut of June 8, 2020 in the overall 5.4 mg/kg dose cohort, 37/184 (20.1%) patients were still on treatment with T-DXd (Table 69). The median treatment duration was [redacted]. The median relative dose intensity (i.e. the ratio of the amount

of drug delivered to the planned dose delivered) was [redacted] The median total number of cycles initiated was [redacted]

Table 69: DESTINY-Breast01: Study drug exposure

	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Subjects on treatment, n (%)	37 (20.1)
Median treatment duration, months (range)	[redacted]
Mean dose intensity (SD)	[redacted]
Median relative dose intensity, % (range)	[redacted]
Median total number of cycles initiated (range)	[redacted]
Subjects who completed following treatment period, n (%)	
≤3 months	[redacted]
>3 to ≤6 months	[redacted]
>6 to ≤9 months	[redacted]
>9 to ≤12 months	[redacted]
>12 to ≤24 months	[redacted]
>24 months	[redacted]

Abbreviations, SD, standard deviation; T-DXd, trastuzumab deruxtecan.
Data-cut: June 8, 2020
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.1.5.1[2]

3.1.4.1.2 Treatment-emergent adverse events (addendum to Document B, Section B.2.10.1.2)

A summary of TEAEs reported in patients who received the recommended dose of T-DXd of 5.4 mg/kg in the DESTINY-Breast01 study are shown in Table 70.

Table 70: DESTINY-Breast01: Summary of treatment-emergent adverse events

Type of TEAE, n (%)	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
TEAEs	183 (99.5)
Drug-related TEAEs	[redacted]
TEAEs Grade ≥3	113 (61.4)
Drug-related TEAEs Grade ≥3	[redacted]
Serious TEAEs	[redacted]
Drug-related serious TEAEs	[redacted]
TEAEs leading to T-DXd discontinuation	34 (18.5)
Drug-related TEAEs leading to T-DXd discontinuation	[redacted]
TEAEs leading to dose reduction	[redacted]
Drug-related TEAEs leading to dose reduction	[redacted]
TEAEs leading to dose interruption	[redacted]
Drug-related TEAEs leading to dose interruption	[redacted]
TEAEs leading to death	10 (5.4)
Drug-related TEAEs leading to death	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan
[†]TEAE relationship to study drug was determined by the treating investigator
Data-cut: June 8, 2020
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.3.1.1[2]

Of the 184 patients who received the recommended dose of T-DXd, 183 (99.5%) patients experienced at least one TEAE, with [redacted] patients reporting at least one study drug-related TEAE per investigator assessment.

Overall, 113 (61.4%) patients experienced ≥Grade 3 TEAEs, with [redacted] patients having at least one study drug-related ≥Grade 3 TEAE based on investigator assessment.

Treatment-emergent serious adverse events (SAEs) were reported in [redacted] patients, with [redacted] patients having at least one study drug-related treatment-emergent SAE based on investigator assessment. The most common treatment-emergent SAEs were [redacted] (June 8, 2020 data-cut, Table 14.3.1.3.2).[2]

TEAEs led to a dose interruption in [redacted] and to a dose reduction in [redacted] 34 patients (18.5%) discontinued treatment because of a TEAE. TEAEs that led to discontinuation in at least 2 patients included [redacted] (June 8, 2020 data-cut, Table 14.3.2.2.1).[2]

Overall, [redacted] patients had TEAEs associated with a fatal outcome on-study (defined as occurring on or after first dose until 47 days after last dose), with [redacted] patients having at least one study drug-related TEAE associated with a fatal outcome on-study based on investigator assessment. The three events considered to be drug-related TEAEs based on investigator assessment were: respiratory failure in one patient and pneumonitis in two patients. These events occurred more than 47 days after the last dose of study medication June 8, 2020 data-cut, Listing 16.2.7.6).[2] TEAEs associated with a fatal outcome on-study included [redacted] (June 8, 2020 data-cut, Listing 16.2.7.6).[2]

Overall, a total of [redacted] deaths (any death) were reported in patients treated with 5.4 mg/kg T-DXd, including [redacted] that occurred during treatment as a result of either [redacted] (June 8, 2020 data-cut, Table 14.3.2.1).[2] Please note that disease progression (PD) was reported as a SAE if the subject died from PD with no other immediate causes according to the clinical study protocol for DESTINY-Breast01. Overall, [redacted] were during survival follow-up (which was defined as 47 days after the end of treatment). [redacted] as described below (TEAEs of special interest: Section 3.1.4.1.4); [redacted] (June 8, 2020 data-cut, Table 14.3.1.4.1).[2]

3.1.4.1.3 Most common treatment-emergent adverse events (addendum to Document B, Section B.2.10.1.3)

A summary of TEAEs experienced by ≥10% of patients treated with 5.4 mg/kg T-DXd by CTCAE grade in order of decreasing frequency is presented in Table 71.

Table 71: DESTINY-Breast01: Treatment-emergent adverse events according to CTCAE grade experienced by ≥10% of the population treated with T-DXd 5.4 mg/kg

TEAE, n (%)	Any Grade	Grade 3	Grade 4
Any TEAE	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan
Data-cut: June 8, 2020
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.3.1.2.3 and Table 14.3.1.2.1[2]

Gastrointestinal and haematologic toxic effects were the most common TEAEs. Among the gastrointestinal events, nausea was the most frequently reported TEAE (patients at 5.4 mg/kg); events of nausea were mostly Grade 1 ( ) or Grade 2 ( ), occurring most frequently in the first 2 cycles (Table 72). The events were manageable under routine medical practice without a need for treatment discontinuation. Available concomitant medications data did not allow for distinction between premedication for and management of nausea. Similarly, most of the events of diarrhoea were Grade 1 ( ) or Grade 2 ( ), and were most commonly reported in the first 2 cycles.

Table 72: DESTINY-Breast01: Select TEAEs by cycle in patients who received T-DXd 5.4 mg/kg (N=184)

n (%)	Cycle								
	1	2	3	4	5	6	7	≥8	≥18
Nausea									
Vomiting									
Fatigue									
Constipation									
Diarrhoea									
Decreased appetite									

Data-cut: June 8, 2020
Source: Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.3.1.5.3[2]

Among the haematologic events, ( ],] and], respectively, at 5.4 mg/kg). They were mostly .

The most common TEAEs of Grade 3 or higher that occurred in more than 5% of the patients were

3.1.4.1.4 Treatment-emergent adverse events of special interest (addendum to Document B, Section B.2.10.1.4)

TEAEs of special interest in patients treated with T-DXd 5.4 mg/kg are shown in Table 73.

Table 73: DESTINY-Breast01: Treatment-emergent adverse events of special interest in patients treated with T-DXd 5.4 mg/kg

TEAE, n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adjudicated as drug-related ILD†	28 (15.2)	[redacted]	[redacted]	[redacted]	[redacted]	5 (2.7)
Prolonged QT interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased LVEF‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.
Data-cut: June 8, 2020
†The presence of ILD was determined by an independent adjudication committee, since the condition has been associated with trastuzumab deruxtecan. Adjudicated as drug-related ILD.
‡ The LVEF was measured on echocardiography or multigated acquisition scans every four treatment cycles.
¶ In this patient, the LVEF was more than 55% during treatment.
Source: Modi 2020[1]; Daiichi-Sankyo, Inc., 2020 (data on file): Table 14.3.1.6.1, Listing 16.2.7.7, and Table 14.3.1.8.2[2]

[redacted]

Infusion-related reactions were reported in [redacted] Prolonged QT interval was reported in [redacted] having a Grade 3 event.

An independent ILD adjudication committee (AC) was responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection was to be conducted for all cases that were brought for adjudication. These additional data collections covered a more in-depth relevant medical history (e.g. smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data

collection was triggered for AEs reported using MedDRA selected preferred terms (PTs) from the ILD standardised MedDRA query (SMQ) that were recommended and approved by the ILD AC; per the ILD AC Charter, a list of 44 PTs in total was selected for adjudication.[15]

[redacted] overall 28/184 (15.2%) patients experienced an adjudicated drug-related ILD of [redacted]

[redacted] June 8, 2020 data-cut, [redacted]

Among the investigator-reported cases of ILD of any Grade, the median time until the onset of ILD was [redacted] (June 8, 2020 data-cut, Table 14.3.1.7.1).[2] Among the patients with investigator reported ILD, the median duration from the date of onset to the date of recovery was [redacted] (June 8, 2020 data-cut, Table 14.3.1.7.2).[2]

3.1.4.1.5 Safety conclusions (addendum to Document B, Section B.2.10.3)

At the latest data-cut (June 8, 2020) in the DESTINY-Breast01 study, gastrointestinal and haematologic toxic effects continued to be the most common TEAEs, as reported at the earlier data-cuts; they were mostly Grade 1 or Grade 2, occurred most frequently in the first two cycles, and were manageable under routine medical practice without a need for treatment discontinuation events.

Other HER2-targeted therapies, such as trastuzumab, T-DM1, and pertuzumab, have been associated with a risk of cardiomyopathy, particularly left ventricular dysfunction.[16,17] In contrast, clinically significant cardiotoxicity was not observed in DESTINY-Breast01 or in the DS8201-A-J101 study.

T-DXd was associated with a risk of ILD (15.2%), which led to death in some patients. In accordance with the study protocol, investigators managed ILD with dose reductions or discontinuations, the administration of glucocorticoids, and supportive care. Education and close monitoring for signs and symptoms of ILD (including fever, cough, or dyspnoea) is

recommended for early detection. Risk Minimisation Materials (RMMs) are in development and will be available in early 2021.

3.1.5. Interpretation of clinical effectiveness and safety evidence (addendum to Document B, Section B.2.13)

3.1.5.1. Principal findings from the clinical evidence base (addendum to Document B, Section B.2.13.1)

T-DXd provided clinically meaningful improvements in ORR and PFS in a difficult-to-treat population of patients with uBC or mBC who had received previous treatment with T-DM1.

Overall, 184 patients (median age: 55.0 years [range, 28.0 to 96.0]) who had undergone a median of six previous treatments, received the recommended dose of T-DXd 5.4 mg/kg. At a data-cut of June 8, 2020 (median duration of follow-up: 20.5 months [redacted]) T-DXd demonstrated a consistent high level of clinical activity across a range of endpoints:

- Response to therapy was reported in 113 patients (61.4%; [redacted] based on ICR
- CR was reported in 12 (6.5%) patients and PR in 101 (54.9%) patients
- Most patients had a reduction in tumour size while on treatment
- Median PFS was 19.4 months (95% CI: 14.1, NE)
- Preliminary median OS was 24.6 months (95% CI: 23.1, NE) (estimated at 35% maturity); this is the first report of median OS
- Prespecified subgroup analyses showed consistent responses across demographic and prognostic subgroups including patients [redacted]
- Durable activity was demonstrated with a median duration of response (DoR) of 20.8 months (95% CI: 15.0, NE)
- DCR was 97.3% (95% CI: 93.8, 99.1)
- CBR was [redacted]
- Median TTR was [redacted]

At the latest data-cut (June 8, 2020) in the DESTINY-Breast01 study:

- The most common TEAEs were gastrointestinal and haematologic in nature

- [redacted]% had SAEs; [redacted]% and [redacted]% had a dose interruption or dose reduction, respectively, and 18.5% discontinued treatment due to TEAEs
- No events of cardiac failure with LVEF decline were reported
  - No patients had an LVEF of <40% or a decrease of ≥20% at any timepoint
- ILD was observed in a subgroup of patients and requires attention to pulmonary symptoms and careful monitoring
  - ILD events were independently adjudicated and actively managed by patient monitoring, dose modification, and adherence to the ILD management guidelines
  - ILD related to T-DXd was observed in 28 patients (15.2%), primarily Grade 1 or 2 ([redacted]). Five deaths (2.7%) were attributed to ILD
- There were [redacted] TEAE-associated deaths [redacted]

3.1.5.2. Strengths and limitations of the evidence base (addendum to Document B, Section B.2.13.2)

In the key trial, DESTINY-Breast01, T-DXd at a dose of 5.4 mg/kg at the latest data-cut (June 8, 2020) continued to demonstrate robust anti-tumour activity. In addition, at this latest data-cut, median OS was reported for the first time. Please see Section B.2.13.2 of the original submission for the strengths of the evidence base that remain unchanged.

While the latest data-cut has addressed some of the uncertainty regarding the immaturity of the survival data from DESTINY-Breast01, where median OS had now been reported (24.6 months [95% CI: 23.1, NE]), there are still clinical uncertainties which mean that Daiichi Sankyo considers T-DXd for the treatment of adult patients with HER2+ u/mBC who have received two or more prior anti-HER2 therapies to be a candidate for the CDF. The clinical uncertainties include:

- DESTINY-Breast01 is a single arm study, and therefore there is uncertainty regarding the magnitude of benefit compared with standard-of-care.
- The median OS data are only preliminary, estimated at 35% maturity with only 17 patients at risk at 24 months. In particular, the high number of censorings from 20

months onwards makes this portion of the KM data uninformative for modelling in terms of long-term survival extrapolation.
  - While the OS data are preliminary, it is worth noting that the lower CI for T-DXd (23.1 months) already exceeds the median OS of the comparator treatments, and indeed the upper CI from most of the comparator studies.
- Health-related quality of life (HRQoL) data were not captured in the DESTINY-Breast01 study.

Daiichi Sankyo considers T-DXd to be a candidate for the CDF. It is anticipated that the CDF would provide the opportunity to address the clinical uncertainty by collecting additional data, while providing timely, managed patient access to an innovative and efficacious treatment in this disease area of high unmet need. Efficacy and safety data, which can be used to inform an indirect treatment comparison, will be obtained from the DESTINY-Breast02 (NCT03523585) Phase III RCT of T-DXd versus treatment of investigator's choice (trastuzumab in addition to capecitabine or lapatinib in addition to capecitabine) in HER2+, u/mBC patients previously treated with T-DM1.

3.1.5.3. End-of-life criteria (addendum to Document B, Section B.2.13.3)

NICE end-of-life status applies for the current appraisal (Table 74), as:

- T-DXd is indicated for patients with a short life expectancy, with evidence demonstrating that the life expectancy in patients with HER2+ mBC is normally less than 24 months; and
- T-DXd has the prospect of offering an extension to life of more than 3 months versus current treatment in the NHS.

Table 74: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Mean overall survival estimated in the cost-effectiveness model is as follows: • Eribulin: [redacted] months • Capecitabine: [redacted] months • Vinorelbine: [redacted] months Of note, median PFS for T-DXd is greater than comparator modelled median OS: 19.4 months (95% CI: 14.1, NE).	Section B.3.3.1.2 in the main submission
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean overall survival estimated in the cost-effectiveness model for T-DXd is [redacted] months, resulting in an estimated extension to life of [redacted], [redacted] and [redacted] months compared with eribulin, capecitabine and vinorelbine, respectively. In the DESTINY-Breast01 trial at the June 8, 2020 data-cut, the estimated OS was 85% (95% CI: 79, 90) at 12 months and 74% (67%, 80%) at 18 months. Preliminary median OS was 24.6 months (23.1, NE) (estimated at 35% maturity).	Section B.3.3.1.1

Abbreviations: T-DXd, trastuzumab deruxtecan.

3.2. Cost effectiveness (addendum to Document B, Section B.3)

Economics sections of Document B that did not require updates following availability of the June 2020 data cut include:

- B.3.1 – Published cost-effectiveness studies
- B.3.2 – Economic analysis
- B.3.3.1.2 – Extrapolation of OS, comparators
- B.3.3.1.3 – Extrapolation of OS, life tables
- B.3.3.4 – HER2+ efficacy adjustment
- B.3.4.1 – Health-related quality of life data from clinical trials
- B.3.4.2 – Mapping
- B.3.4.3 – Health-related quality of life studies
- B.3.5.1.4 – Administration costs
- B.3.5.2 – Health-state unit costs and resource use
- B.3.9 – Subgroup analysis
- B.3.10 – Validation

For details of these sections, please refer to the original company submission.

3.2.1. Clinical parameters and variables (addendum to Document B, Section B.3.3)

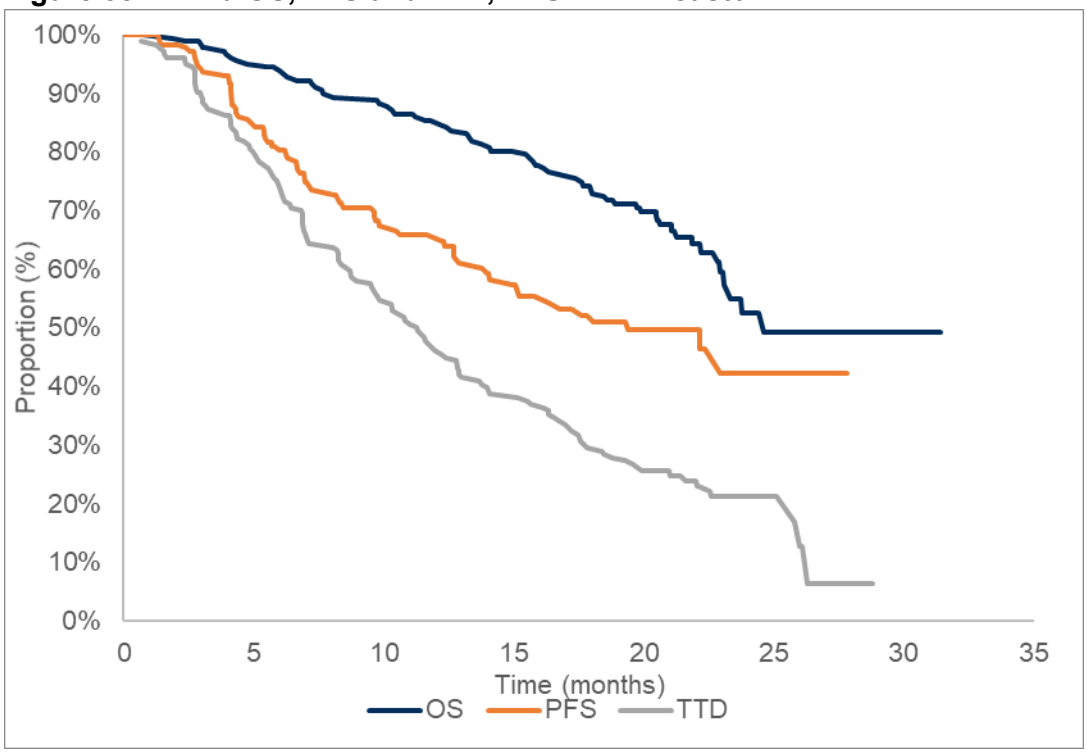
The principal source of data used to inform the analysis is the DESTINY-Breast01 clinical trial. Patient level-data were used to inform the following outcomes for T-DXd:

- Extrapolation of TTD
- Extrapolation of PFS
- Extrapolation of OS
- Adverse event (AE) durations and frequencies.

Given that DESTINY-Breast01 is a single group trial, unanchored MAICs have been used to inform comparisons against the comparators specified by NICE in the final scope for this appraisal, namely eribulin, capecitabine and vinorelbine (Section B.2.9 in the main submission). For both eribulin and capecitabine, there were multiple studies available. Of the four eribulin studies available, the Cortes (2011) study was chosen as the model base-case as this was the publication of the pivotal EMBRACE trial and was presented as the primary source of evidence in TA423.[18] Of the two available capecitabine studies, the Fumoleau (2004) study was chosen as the base-case as it was the most recent of the two studies and better outcomes were observed in this study, resulting in a conservative estimate of cost-effectiveness for T-DXd.[19] Only the Sim (2019) study was available to inform the comparison against vinorelbine[7]; however, clinical experts at the August 2020 advisory board advised that the OS observed in Sim 2019 (18.9 months) is not plausible following PFS of 12 weeks, and is likely driven by the use of post-progression therapies (see also Section B.3.3.1.2 in main submission).[8] Given that vinorelbine is associated with similar or worse PFS compared with capecitabine, OS for vinorelbine is assumed to be equivalent to OS for capecitabine; further details are provided in Section B.3.3.1.2 in main submission.

Kaplan-Meier data for TTD, PFS and OS from DESTINY-Breast01 are presented in Figure 38.

Figure 38: **T-DXd OS, PFS and TTD, DESTINY-Breast01**



Abbreviations: OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.

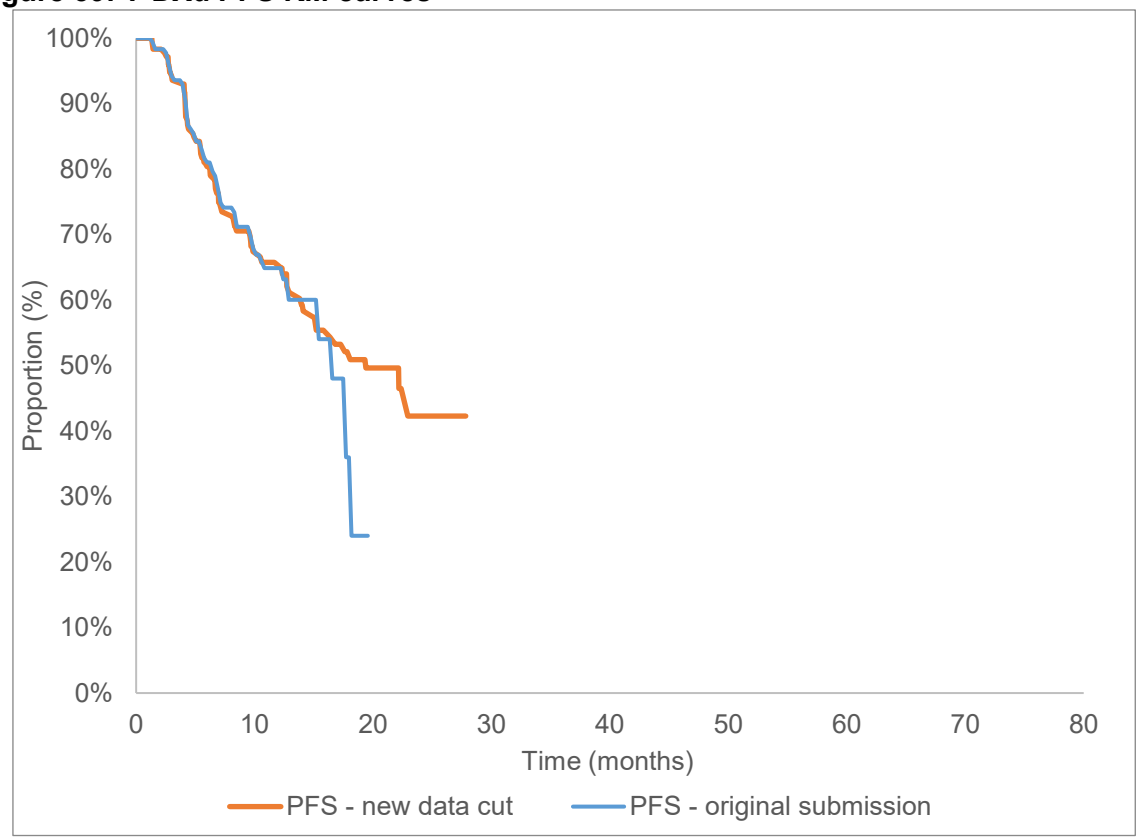
As PFS data for T-DXd are relatively mature, parametric survival curves are generated for T-DXd and HRs from the MAICs are applied to generate outcomes for the model comparators. TTD data for T-DXd are also relatively mature; however, no KM data are available for the model comparators. Parametric survival curves are therefore generated for T-DXd, with treatment to progression assumed for the model comparators; scenario analyses consider alternative assumptions (see Section 3.2.1.3).

OS data for T-DXd are associated with the following challenges:

- OS data are relatively immature, with the trial only just reaching median survival and only [redacted] of patients having an OS event at the June 2020 data cut off
- Substantial censoring is observed after 20.5 months (the median trial follow-up), with [redacted] patients censored and only [redacted] events subsequent to this, resulting in considerable uncertainty in the shape of the OS curve; the shape of the OS curve may change substantially as further follow-up data becomes available, as observed for PFS data between the August 2019 and June 2020 data cuts (see Figure 39).

- The Kaplan-Meier curves for PFS and OS appear to be converging (Figure 38), which is not considered to be clinically plausible given that delayed progression is expected to result in extended survival.

Figure 39: T-DXd PFS KM curves



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

Predictions of long-term OS for T-DXd are therefore generated by applying a HR to third-line data for a HER2-targeted treatment (T-DM1) with longer follow-up than observed in DESTINY-Breast01. In the primary analysis, this HR is generated using data up to 20.5 months (i.e. OS data are censored after 20.5 months); secondary analyses consider a HR in which all observed OS data are used. OS for comparator treatments is estimated by fitting parametric survival curves to the digitized KM data from the relevant studies. For completeness, a scenario is performed in which OS for T-DXd is generated by applying the HR from the MAIC vs. Cortes 2011 (B.2.9 in the main submission) to the survival curve for eribulin; see Appendix O for further details.

Outcomes were extrapolated beyond the trial period using parametric survival techniques consistent with NICE DSU TSD 14.[20]All statistical models used in the base-case are presented in Appendix O.

3.2.1.1. Extrapolation of OS (addendum to Document B, Section B.3.3.1)

OS data in DESTINY-Breast01 from the June 2020 data cut are not considered sufficiently mature for informative parametric modelling (Figure 38). Given a lack of mature data, a reasonable approach to extrapolating OS is to apply a HR to OS for existing therapies with similar mechanisms of action in similar patient populations.

As the comparators in scope (eribulin, capecitabine and vinorelbine) are not HER2-targeting agents, there are concerns over whether these would be appropriate analogues to inform the extrapolation of OS for T-DXd. According to clinical experts, it is expected that OS for HER2+ mBC patients treated with T-DXd would be more similar to that seen with other HER2-targeting agents (trastuzumab emtansine, trastuzumab, pertuzumab)[21-23] than to OS for non-targeted chemotherapies (eribulin, capecitabine, vinorelbine).

OS data for trastuzumab emtansine (TH3RESA in 3L, EMILIA in 2L) and for trastuzumab and pertuzumab chemotherapy in 1L (CLEOPATRA) indicated that a substantial proportion of patients demonstrate long-term survival; the OS KM curves show more of a ‘tail’ in long-term follow up compared to the OS data available for eribulin, capecitabine and vinorelbine.

Additional translational research to link the mechanism of action to potential impact on long term overall survival is not available; however, in the published literature there are hypotheses on HER2-targeting mediated effects, including immune responses,[24] that could significantly improve long term survival in HER2+ breast cancer compared to non-HER2-targeting therapies.

As clinical experts stated that long term survival for T-DXd would be better informed by other HER2-targeting therapies, predictions of long-term OS for T-DXd are generated by applying a HR to third-line data for a HER2-targeted treatment (T-DM1) with longer follow-up than observed in DESTINY-Breast01; the TH3RESA data for T-DM1 was considered the most relevant due to similarities in mechanism of action and line of therapy.

OS for eribulin and capecitabine is estimated by fitting parametric survival curves to the digitized KM data from the relevant studies; given that available OS data for vinorelbine were not considered plausible or reflective of survival outcomes in UK patients in this setting by

clinical experts at the August 2020 advisory board and PFS estimates for vinorelbine were similar to/lower than for capecitabine, OS for vinorelbine was assumed equivalent to that for capecitabine (see Section B.3.3.1.2 in main submission).

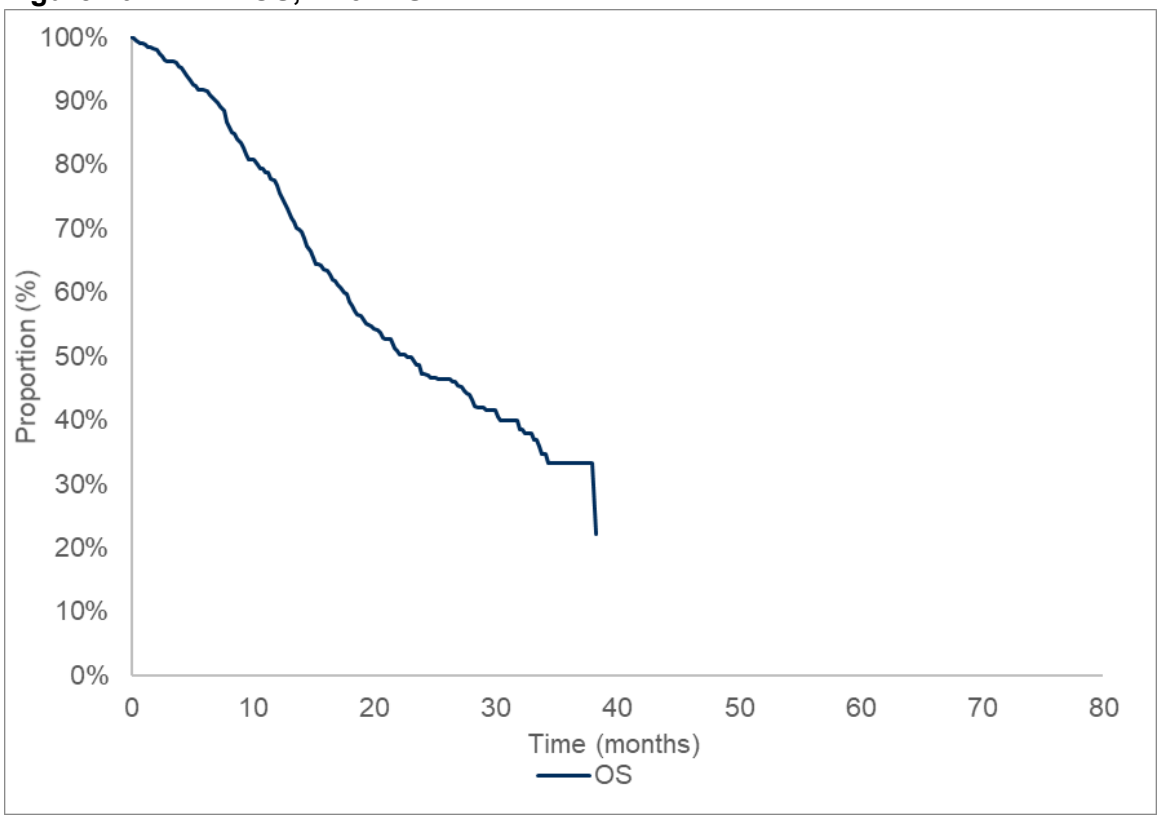
3.2.1.1.1 T-DXd (addendum to Document B, Section B.3.3.1.1)

In UK clinical practice, T-DM1 is the standard-of-care for second-line HER2-positive patients, and is recommended by NICE for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination.[6,25] To inform the submission to NICE, evidence was submitted for T-DM1 in both second-line and third-line settings, with the third-line evidence informed by the TH3RESA trial.

In the model base-case, OS for T-DXd is modelled by applying HR to the extrapolated OS curve from TH3RESA; the KM for T-DM1 from TH3RESA is presented in

Figure 40.[26]

Figure 40: T-DM1 OS, TH3RESA



Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine

Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including a trastuzumab-like antibody, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or capecitabine. Clinical experts at the August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect the shape of the T-DM1 curve than that of the model comparators; additionally, clinical experts engaged in previous discussions noted that:

- Comparing targeted therapies (i.e. T-DXd) against non-targeted therapies (i.e. eribulin, capecitabine and vinorelbine) may mean that assuming proportional hazards is not reasonable; one of the clinical experts independently suggested the use of TH3RESA as a 'control' arm to apply a HR to

It is reasonable to expect a 'tail' in T-DXd OS, as observed for T-DM1.

- The model diagnostics for the extrapolation of the TH3RESA data are shown in Table 75.

Table 75: Model diagnostics, TH3RESA, OS

Model	AIC	BIC

Exponential	939.05	943.05
Weibull	921.90	929.90
Log-normal	935.65	943.65
Log-logistic*	917.34	925.35
Gompertz	932.01	940.01
Generalised gamma	922.01	934.01

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
* Lowest AIC/BIC scores.

A HR was generated for T-DXd vs. T-DM1 using a Cox proportional hazards model based on:

- Only OS data from DESTINY-Breast01 up to 20.5 months (primary analysis)
- All OS data from DESTINY-Breast01 (secondary analysis).

OS data beyond 20.5 months were not considered to be informative given the substantial censoring observed beyond this time point, and the resulting convergence of OS and PFS (see Section 3.2.1).

Primary analysis

The primary analysis was based on a HR generated for T-DXd vs. T-DM1 using the T-DXd OS censored at 20.5 months, as previously described. A Cox proportional hazards model was used (Table 76).

Table 76: OS HR vs. T-DM1 (with T-DXd OS censored at 20.5 months)

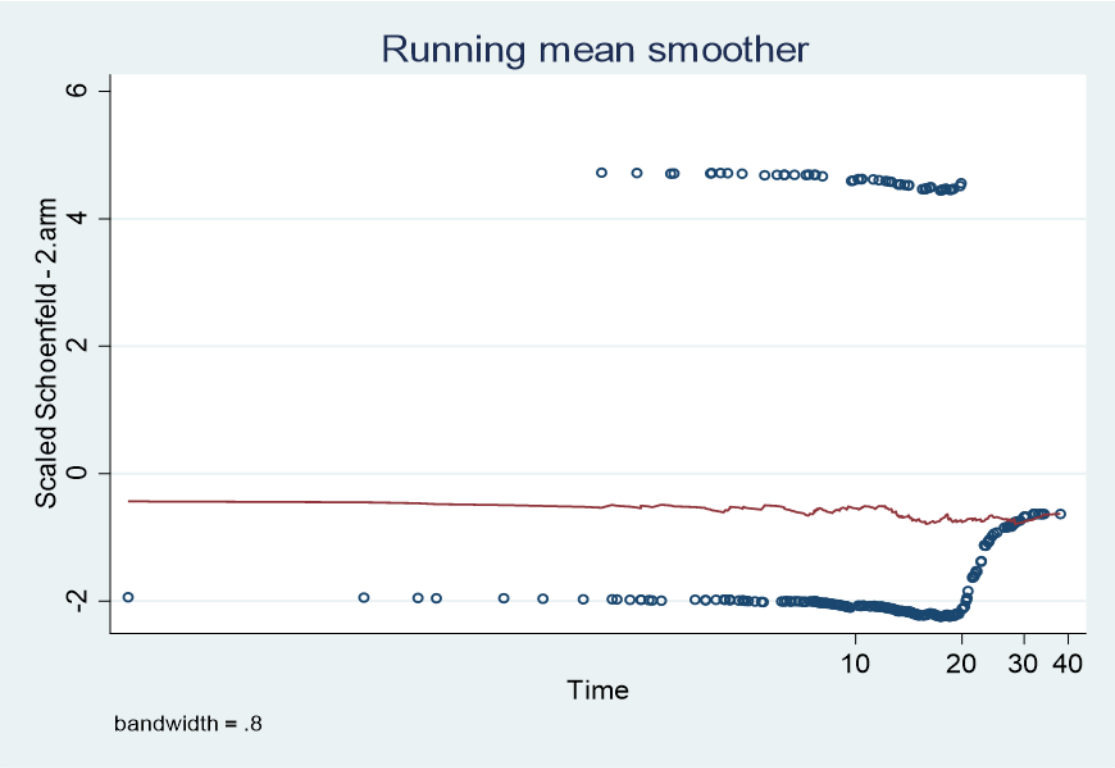
Treatment	Hazard ratio	Standard error	P>z	95% CI (lower)	95% CI (upper)
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; s.e, standard error; T-DM1, trastuzumab emtansine' T-DXd, trastuzumab deruxtecan

The proportional hazards assumption was assessed on the basis of Schoenfeld residuals (Figure 41) and visual inspection of the log-log plot (Figure 42). The assumption of proportional hazards is considered to be valid on the basis that:

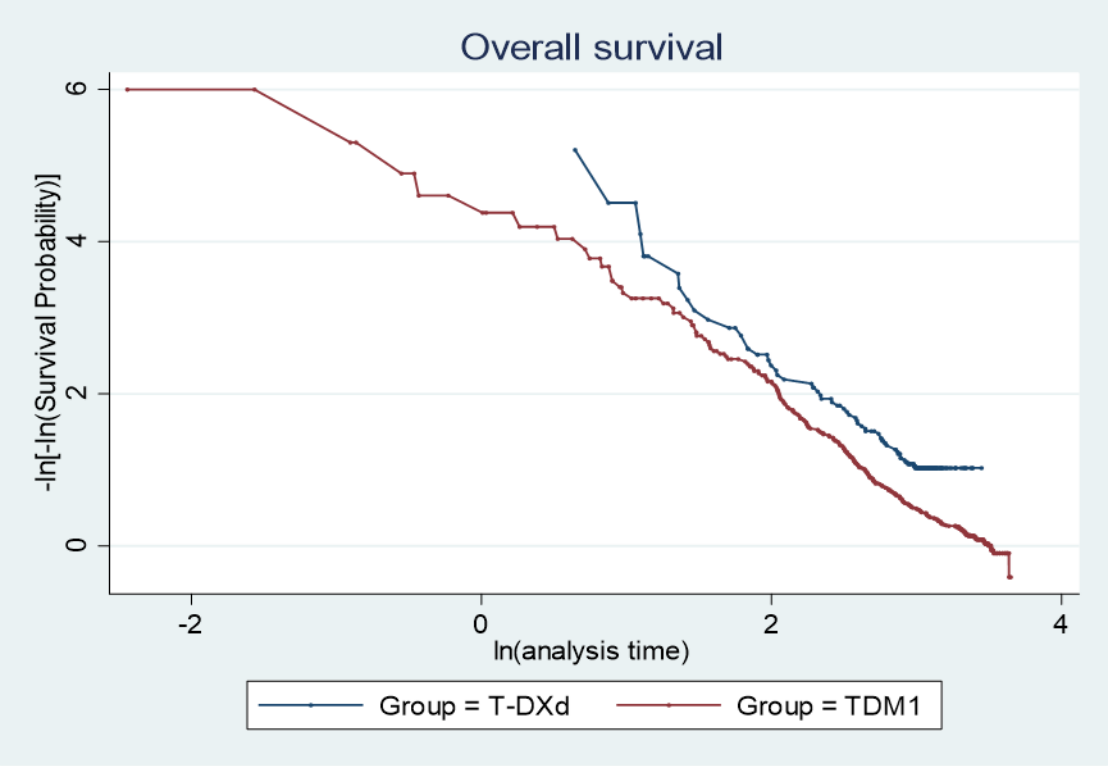
- The locally weighted scatterplot smoothing (LOWESS) curve lies close to the y=0 line
- The assumption of proportional hazards between T-DXd and T-DM1 could not be rejected based on the results of the Schoenfeld residual test (p= 0.4138)
- The log-log plots for each patient group were broadly parallel over time.

Figure 41: Schoenfeld residuals (overall survival), DESTINY-Breast01 vs TH3RESA (with T-DXd OS censored at 20.5 months)



Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 42: Log-log plot (overall survival), DESTINY-Breast01 vs TH3RESA (with T-DXd OS censored at 20.5 months)



Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

The HR in Table 76 derived when using the OS data censored at 20.5 months was very similar (to two decimal places) to the original HR from the main submission (0.5297). The rationale for selecting the generalised gamma distribution in the main submission was therefore considered to still apply given that the resulting survival curves are very similar (34% survival at 5 years in both models); the generalised gamma distribution was therefore used in the base-case. All distributions were considered in scenario analyses.

Secondary analysis

In a secondary analysis, a HR was generated for T-DXd vs. T-DM1 using all observed T-DXd OS data. A Cox proportional hazards model was used (Table 77).

Table 77: OS HR vs. T-DM1

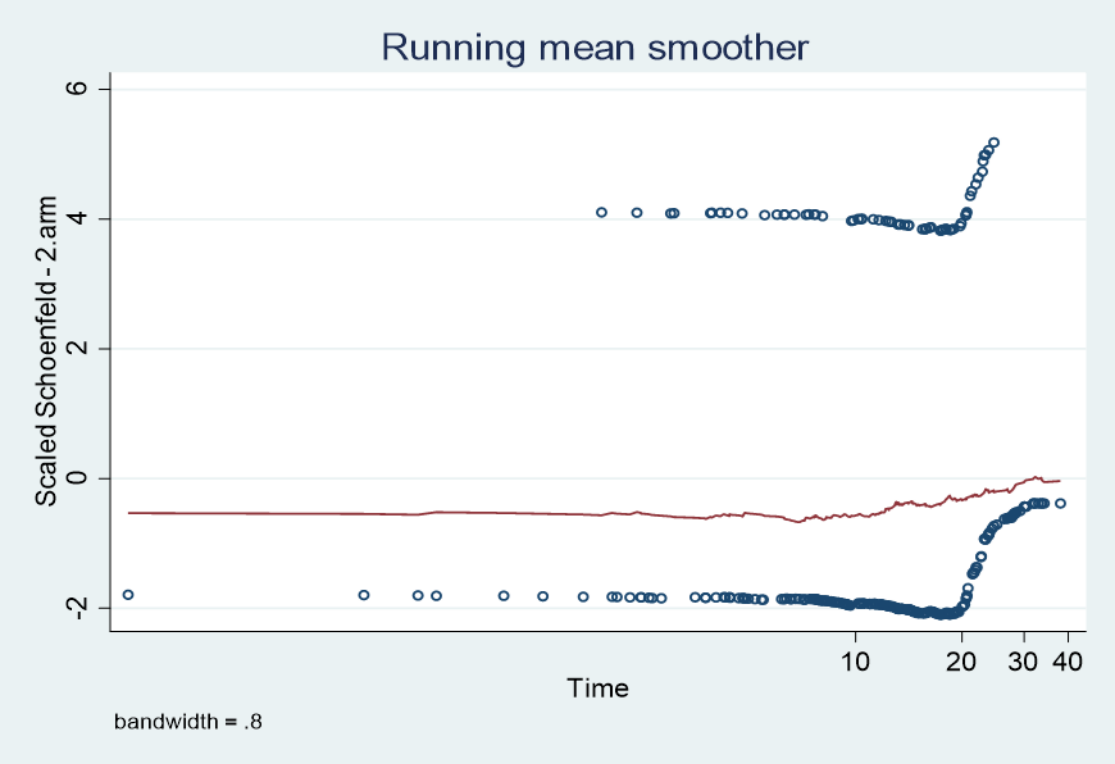
Treatment	Hazard ratio	Standard error	P>z	95% CI (lower)	95% CI (upper)
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; s.e, standard error; T-DM1, trastuzumab emtansine' T-DXd, trastuzumab deruxtecan

The proportional hazards assumption was assessed on the basis of Schoenfeld residuals (Figure 43) and visual inspection of the log-log plot (Figure 44). The assumption of proportional hazards is considered to be valid on the basis that:

- The LOWESS curve lies close to the y=0 line
- The assumption of proportional hazards between T-DXd and T-DM1 could not be rejected based on the results of the Schoenfeld residual test (p= 0.192)
- The log-log plots for each patient group were broadly parallel over time.

Figure 43: Schoenfeld residuals (overall survival), DESTINY-Breast01 vs TH3RESA



Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan

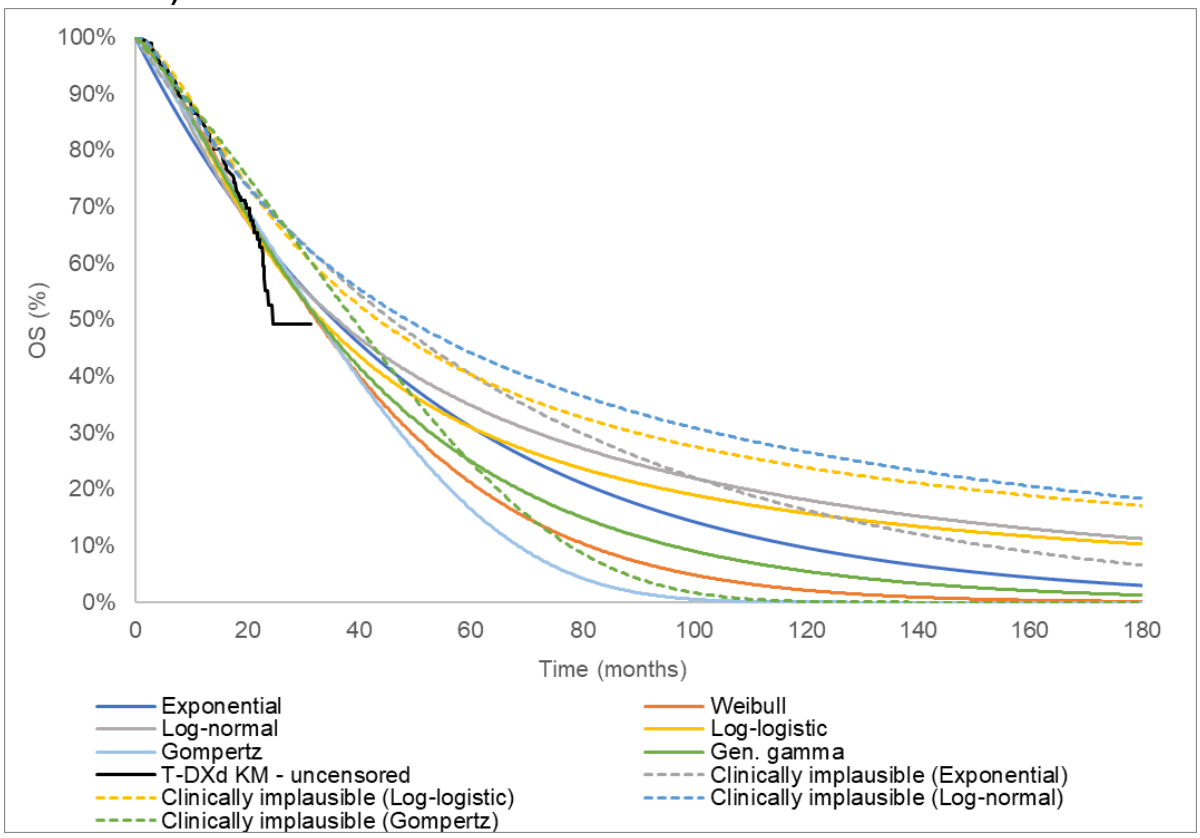
Figure 44: Log-log plot (overall survival), DESTINY-Breast01 vs TH3RESA

Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

In order to select the most appropriate distribution to extrapolate the OS data, the distributions that were judged to be implausible from the August advisory board (which were based on the OS data from the main submission), were compared against the curves based on the new HR vs T-DM1 (Figure 45). The log-logistic and log-normal curves fell above curves previously considered implausibly high, and the Weibull and Gompertz curves fell below those previously considered implausibly low; these distributions were therefore removed from consideration, with the generalised gamma and exponential distribution remaining.

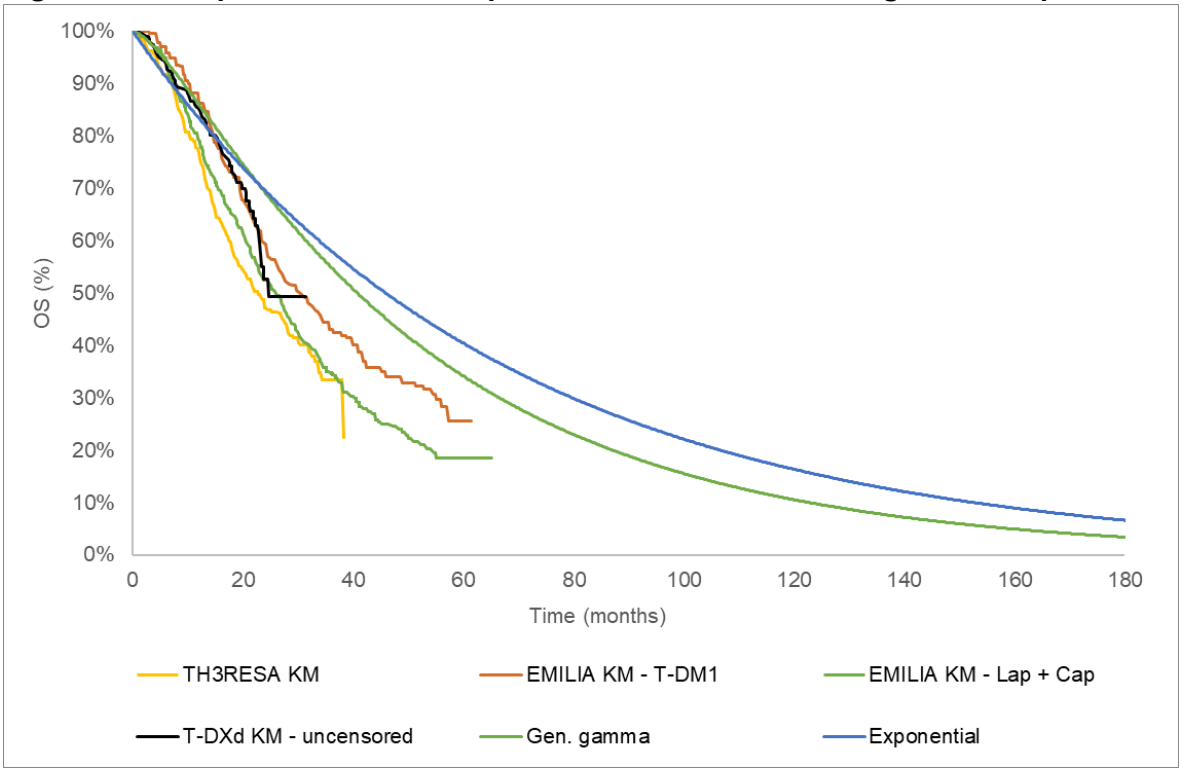
The generalized gamma and exponential distributions were compared against KM data for other HER2-targeted therapies: T-DM1 in the TH3RESA trial, and T-DM1 and lapatinib + capecitabine in the EMILIA trial (Figure 46). However, it should be noted that lapatinib + capecitabine and TDM-1 are not reimbursed for third line treatment in the UK. Both curves were considered to reflect the shape of the OS curves observed for other HER2-targeted therapies, and so both distributions are presented as secondary analyses.

Figure 45: T-DXd OS extrapolations (HR applied to T-DM1) (with T-DXd OS uncensored)



Abbreviations: HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 46: Comparison of OS extrapolations vs. other HER2-targeted therapies

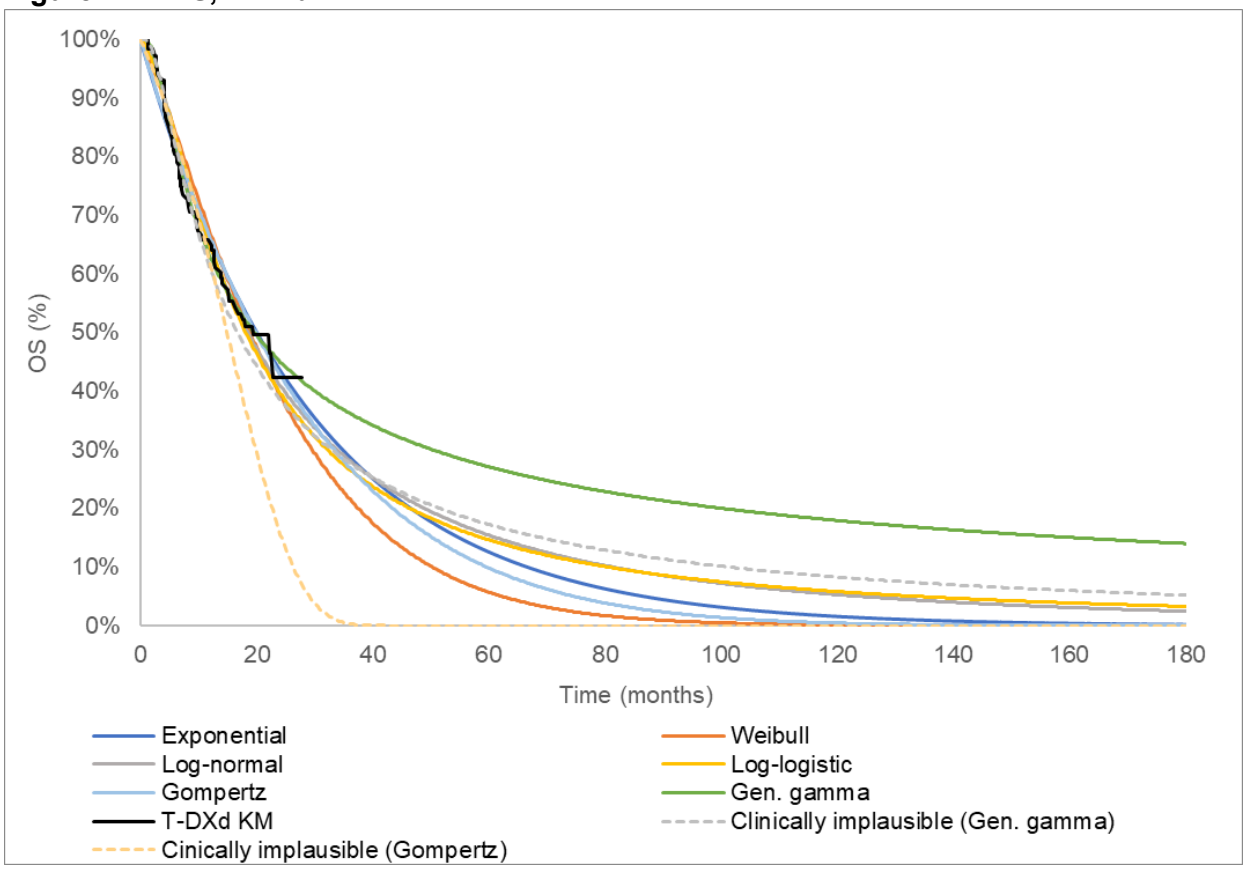


Abbreviations: Gen. gamma, generalised gamma; KM, Kaplan Meier; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

3.2.1.2. Extrapolation of PFS (addendum to Document B, Section B.3.3.2)

Median PFS was 19.4 months in T-DXd patients in DESTINY-Breast01. Model diagnostics for alternative survival distributions are presented in Table 78. As for OS, the extrapolations presented to UK clinical experts at the August advisory board were based on those from the previous data cut;[8] the survival curves for the June 2020 data cut were compared against curves considered implausible at the advisory board (Figure 47). The generalised gamma distribution was removed from consideration because this fell above a distribution that was considered implausible at the advisory board. The distribution used for PFS in the main submission was the log-normal, and this still had the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) score based on the new data cut, therefore this remained the distribution used in the base-case for PFS. Other survival distributions are considered in scenario analyses.

Figure 47: PFS, T-DXd



Abbreviations: Gen. gamma, generalised gamma; KM, Kaplan Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Table 78: Model diagnostics, PFS - T-DXd

Model	AIC	BIC
Exponential	349.21	352.43
Weibull	347.39	353.82
Log-normal*	336.52	342.95
Log-logistic	341.91	348.34
Gompertz	351.15	357.58
Gen. gamma	341.91	348.34

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; T-DXd, trastuzumab deruxtecan.
*Lowest AIC/BIC scores.

MAICs were conducted (Section B.2.9 in main submission) for all relevant comparators and HRs were applied to the T-DXd extrapolated survival curve. Table 79 presents the HRs from the MAICs for each model comparator.

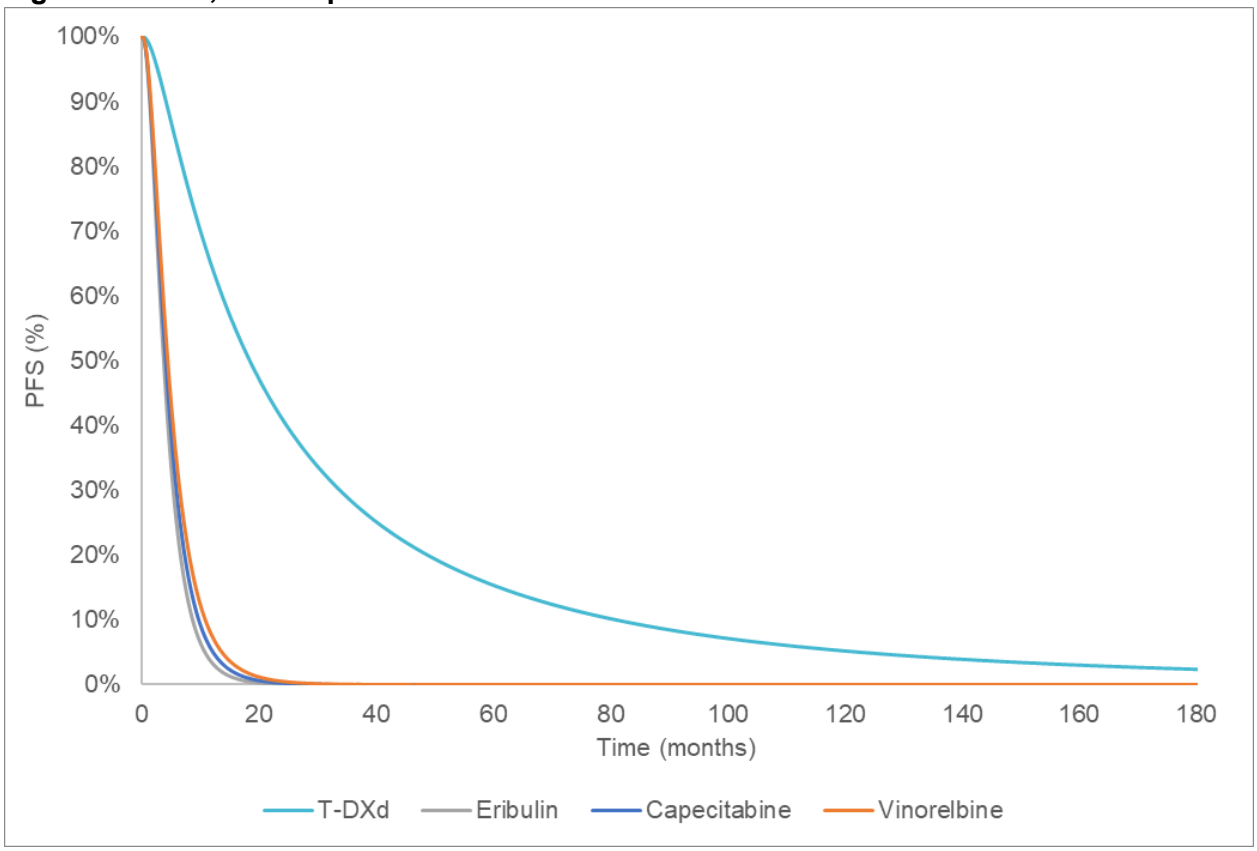
Table 79: PFS HRs

Comparator	Study	HR (95% CI)
Eribulin	EMBRACE (Cortes 2011)*	[redacted]
	Barni 2019	[redacted]
	Cortes 2010	[redacted]
	Gamucci 2014	[redacted]
Capecitabine	Fumoleau 2004*	[redacted]
	Blum 2001	[redacted]
Vinorelbine	Sim 2019	[redacted]

Abbreviations: CI; confidence interval; HR, hazard ratio; PFS, progression free survival.
*Model base-case

Figure 48 presents the extrapolated survival curves for each comparator in the model, given the base-case HRs presented in Table 79 and assuming a log-normal distribution.

Figure 48: PFS, all comparators



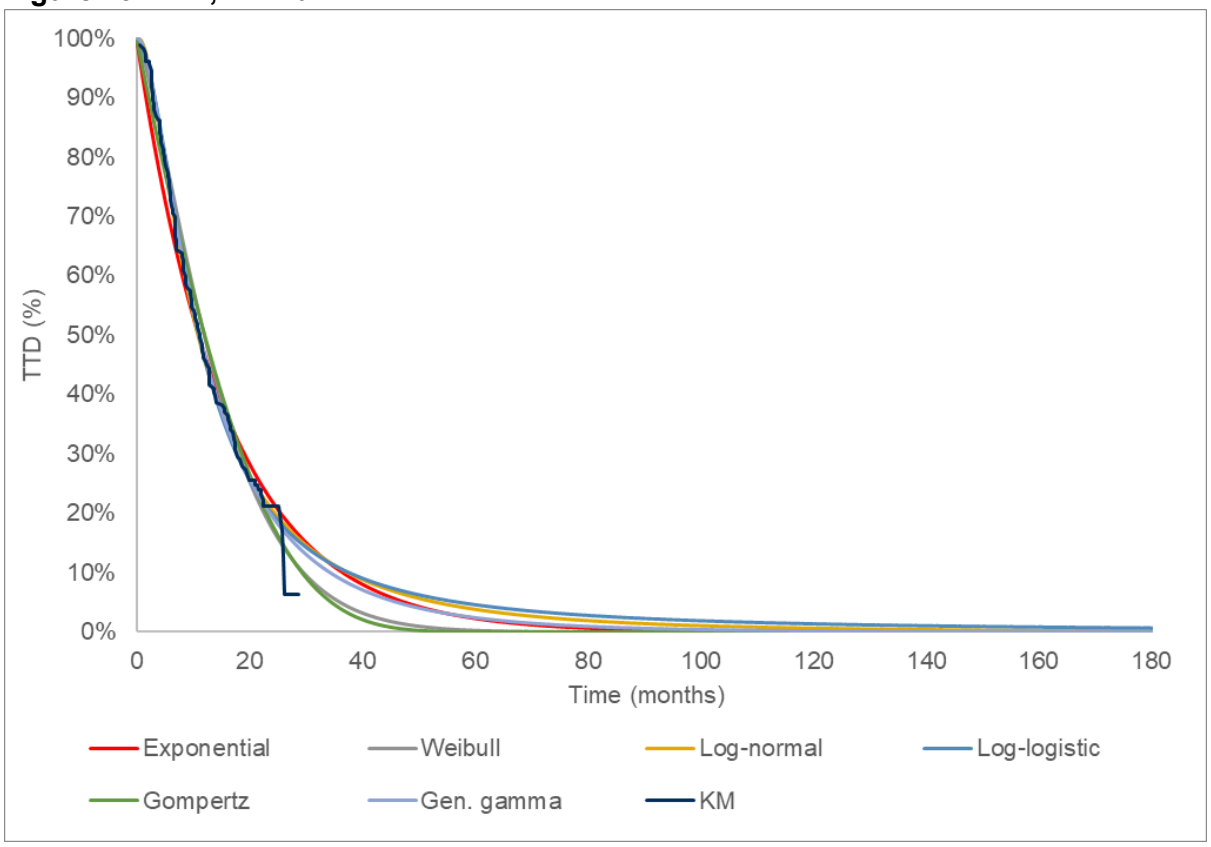
Abbreviations: PFS, progression free survival; T-DXd, trastuzumab deruxtecan.

3.2.1.3. Extrapolation of TTD (addendum to Document B, Section B.3.3.3)

Median TTD was 10.1 months in T-DXd patients in DESTINY-Breast01. Model diagnostics for alternative survival distributions are presented in Table 80. As for OS and PFS, the extrapolations presented to UK clinical experts at the August advisory board were based on those from the previous data cut.[8] Graphically, two groups of curves were present: one group (log-normal, log-logistic, generalised gamma, exponential) which implies that a proportion of patients would remain on treatment beyond 5 years; and a second group of curves (Gompertz and Weibull) where all patients would discontinue by 5 years. In discussion with clinical experts, it was confirmed that there are some patients who would remain on treatment beyond 5 years, but it was unclear which of the two groups of curves best represented the experience of the overall group of patients. The exponential distribution was therefore selected in the base-case in the main submission, given that this is the lowest of the first group of curves, and therefore may be considered an approximate midpoint between the two groups.

In the extrapolations based on the updated data cut, two groups were once again present, with the exponential distribution being the lowest of the first group of curves; the exponential distribution was therefore selected for the model base-case. Other survival distributions are considered in scenario analyses.

Figure 49: TTD, T-DXd



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

Table 80: Model diagnostics, TTD - T-DXd

Model	AIC	BIC
Exponential	485.06	488.27
Weibull	472.66	479.09
Log-normal*	467.40	473.83
Log-logistic	468.06	474.49
Gompertz	480.83	487.26
Gen. gamma	468.06	474.49

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time-to-discontinuation
*Lowest AIC/BIC scores.

TTD KM data were not available for eribulin, capecitabine or vinorelbine. In the base-case, treatment to progression was assumed for these comparators. A scenario is considered in which a HR is applied to the T-DXd curve such that each curve passes through the observed median TTD in each study. The estimated HR for each study is presented in Table 81. No

median TTD was available from the Sim study in vinorelbine, and so treatment to progression was assumed in all scenarios.

Treatment to progression was assumed in the base-case because:

- Applying a HR to TTD data for T-DXd quickly results in the estimated TTD curve crossing the PFS curve; functionality is included in the model to correct for this (i.e. to prevent TTD from exceeding PFS), however, this suggests that the assumption of proportional hazards between T-DXd and the relevant comparators is not valid for TTD.

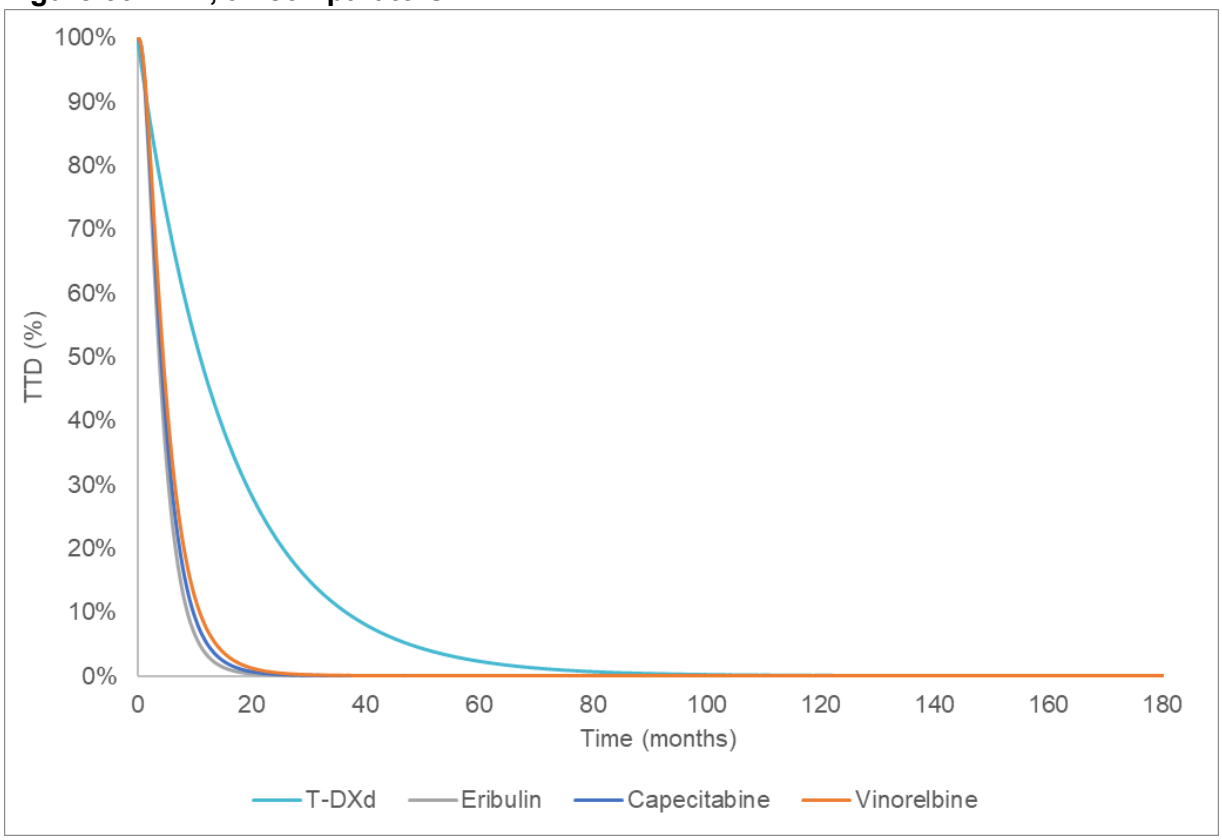
- PFS for the modelled comparators is relatively short; it is therefore unlikely that discontinuation and progression would occur on different follow-up visits in an NHS setting.

Table 81: TTD HRs (estimated)

Comparator	Study	Observed median TTD	HR
Eribulin	EMBRACE (Cortes 2011)*	3.90	[redacted]
	Barni 2019	2.76	[redacted]
	Cortes 2010	2.76	[redacted]
	Gamucci 2014	3.45	[redacted]
Capecitabine	Fumoleau 2004*	4.10	[redacted]
	Blum 2001	3.20	[redacted]
Vinorelbine	Sim 2019	N/A	N/A

Abbreviations: HR, hazard ratio; n/a; not applicable; TTD, time to discontinuation.
*model base-case.

Figure 50: TTD, all comparators



Abbreviations: SoC, standard-of-care; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.

3.2.1.4. Adverse events (addendum to Document B, Section B.3.3.5)

All grade three and above adverse events that occurred in at least 5% of patients were included for each comparator from the respective studies. In addition, any adverse events listed as AEs of special interest in the DESTINY-Breast01 clinical study report or deemed of clinical importance by clinicians were also included. ILD, LVEF decrease, QT prolongation, and infusion-related reactions have been identified as adverse events of special interest in the DESTINY-Breast01 CSR.[15]

AE numbers were assessed during the safety period of DESTINY-Breast01, from Day 1 through to the end of treatment visit or 30-days after the last study treatment, whichever was later. AEs have not been extrapolated beyond the safety period and all costs and quality-adjusted life years (QALY) losses associated with AEs are assumed to occur in the first cycle of the model.

The AE inputs used in the T-DXd arm of the model are presented in Table 82.

Table 82: Adverse events, T-DXd

Pre-matched cohort (N = 184	Number of events	Proportion	Events resulting in hospitalisation	Proportion of events resulting in hospitalisation
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan

In the eribulin arm of the model, adverse event frequencies were taken as a weighted average from all of the studies considered in the model that reported information on adverse events. The proportion of AEs in each study was reweighed to reflect the size of the patient population. AE data were not available from the Gamucci study. Data were not available on the AEs that resulted in hospitalisation from the Cortes 2010 or Barni studies, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed. AE frequencies are presented in Table 83.

Table 83: Adverse events, eribulin

Adverse event	Proportion of patients – Cortes 2011 (EMBRACE) n=503	Proportion of patients – Barni 2019 n=574	Proportion of patients – Cortes 2010 n=291	Weighted proportion
Neutropenia	14.51%	0.33%	1.46%	5.78%
Anaemia	1.99%	0.06%	0.15%	0.79%
White blood cell count decreased*	4.17%	0.00%	0.00%	1.53%
Palmar-Plantar Erythro-Dysaesthesia Syndrome	6.10%	0.00%	0.00%	2.24%
Nausea	1.19%	0.07%	0.41%	0.55%
Fatigue**	1.90%	0.00%	0.00%	0.70%
Dyspnoea	3.38%	0.00%	0.00%	1.24%
Febrile neutropenia	1.60%	0.00%	0.00%	0.59%
Electrocardiogram QT prolonged	0.00%	0.00%	0.00%	0.00%
Interstitial lung disease	0.00%	0.00%	0.00%	0.00%
Ejection fraction decreased	0.00%	0.00%	0.00%	0.00%
Pneumonitis	0.00%	0.00%	0.00%	0.00%
Vomiting	0.00%	0.00%	0.00%	0.00%
Neutrophil count decreased	0.00%	0.00%	0.00%	0.00%

*Reported as 'Leucopenia'/'Leukopenia'
** Fatigue and/or asthenia
*** Reported as 'Peripheral neuropathy' in EMBRACE

In the capecitabine arm of the model, adverse event frequencies were taken from the data reported in the Blum study only as data were not available from Fumoleau (Table 84).[27] Data were not available on the AEs that resulted in hospitalisation, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed.

Table 84: Adverse events, capecitabine

Adverse event	Number of events	Proportion of patients
Palmar-Plantar Erythro-Dysaesthesia Syndrome	16	21.62%
Diarrhoea	14	18.92%
Stomatitis	9	12.2%
Nausea	7	9.5%
Fatigue*	6	8.1%
Dehydration	5	6.8%
Neutropenia	1	1.4%
White blood cell count decreased	0	0.0%
Dyspnoea	0	0.0%
Febrile neutropenia	0	0.0%
Electrocardiogram QT prolonged	0	0.0%
Interstitial lung disease	0	0.0%
Ejection fraction decreased	0	0.0%
Pneumonitis	0	0.0%
Vomiting	0	0.00%
Neutrophil count decreased	0	0.0%
Anaemia	0	0.0%

* Fatigue and/or asthenia

In the vinorelbine arm of the model, adverse event frequencies were taken from the data reported in the Sim study and are presented in Table 85.[7] Data were not available on the AEs that resulted in hospitalisation, therefore the same proportion of AEs resulting in hospitalisation from DESTINY-Breast01 was assumed. For AEs that did not occur in DESTINY-Breast01, a 0% hospitalisation rate was conservatively assumed.

Table 85: Adverse events, vinorelbine

Adverse event	Number of events	Proportion of patients
Neutropenia	45	60.8%
Abdominal pain	12	16.22%
Febrile neutropenia	5	6.8%
Anaemia	4	5.4%
Fatigue*	2	2.7%
Pneumonitis	1	1.4%
Nausea	0	0.0%
White blood cell count decreased	0	0.0%
Dyspnoea	0	0.0%
Electrocardiogram QT prolonged	0	0.0%
Interstitial lung disease	0	0.0%
Ejection fraction decreased	0	0.0%
Vomiting	0	0.00%
Neutrophil count decreased	0	0.0%

3.2.2. Measurement and valuation of health effects (addendum to Document B, Section B.3.4)

Update to CS Section B.3.4

- Updated AE frequencies and durations, and response data from the June 2020 data cut for DESTINY-Breast01.
- Corrections to reporting errors for:
  - The average utility value of the company and ERG values from TA423 for progressed disease
  - The progression-free eribulin utility value in Table 90
  - The confidence interval for the progression-free (off treatment) utility value in Table 90

3.2.2.1. Adverse reactions (addendum to Document B, Section B.3.4.4)

The impact of AEs on HRQoL is captured as a one-off QALY loss in the first cycle of the model. The AE frequencies from the relevant studies for each comparator (see Section 3.2.1.4), the durations of each AE reported in DESTINY-Breast01 and disutilities sourced from the literature were used to calculate a one-off QALY loss for each treatment. Where

available, AE disutilities were taken directly from Hudgens et al., a health-related quality of life study in patients with locally advanced or metastatic breast cancer treated with eribulin or capecitabine.[28] For AEs that were not reported in the study by Hudgens et al., AE disutilities were sourced from alternative published studies. The AE disutilities and durations used in the model are presented in Table 86.

Table 86: AE disutilities

AE	Disutility	Source	AE duration (days)	QALY decrement
Neutrophil count decreased	0.0070	Hudgens et al.	25.30	0.0005
Anaemia	0.0100	Hudgens et al.	12.20	0.0003
Neutropenia	0.0070	Hudgens et al.	16.20	0.0003
Nausea	0.0210	Hudgens et al.	63.50	0.0037
Fatigue	0.0290	Hudgens et al.	53.60	0.0043
White blood cell count decreased	0.0030	Hudgens et al.	45.40	0.0004
Dyspnoea	0.0270	Hudgens et al.	9.60	0.0007
Febrile neutropenia	0.0120	Hudgens et al.	6.30	0.0002
Electrocardiogram QT prolonged	0.0000	Lachaine et al.[29]	13.20	0.0000
Interstitial lung disease	0.1700	Doyle et al.[30]	3.00	0.0014
Ejection fraction decreased	0.0590	Sandhu et al[31]	27.00	0.0044
Pneumonitis†	0.1700	Doyle et al.[30]	3.00	0.0014
Vomiting	0.1030	Lloyd et al[32]	13.40	0.0038
Diarrhoea	0.0060	TA423	17.00	0.0003
PPE	0.1160	Shlomai et al[33]	14.00	0.0044
Dehydration‡	0.0060	TA423	17.00	0.0003
Stomatitis	0.1510	TA250	10.00	0.0041
Abdominal pain‡	0.0060	TA423	17.00	0.0003
Peripheral neuropathy	0.0140	TA423	16.20	0.0006

Abbreviations: AE, adverse event; QALY, quality-adjusted life year; PPE, palmar-plantar erythrodysesthesia syndrome.
† Another term for Interstitial lung disease
‡ Assumed equal to diarrhoea

The total QALY loss for each treatment arm in the model is presented in Table 87.

Table 87: Total QALY loss

Treatment	QALY loss
T-DXd	0.0011
Eribulin	0.0002
Capecitabine	0.0022
Vinorelbine	0.0004

Abbreviations: QALY, quality-adjusted life year; SoC, standard-of-care; T-DXd, trastuzumab deruxtecan.

3.2.2.2. Health-related quality-of-life data used in the cost-effectiveness analysis (addendum to Document B, Section B.3.4.5)

In TA423, progression free, on-treatment utility values were calculated as a function of objective response rate (ORR; defined as patients experiencing a best overall response of complete response or partial response) and adverse event rates from the eribulin and treatment of physician's choice (TPC) arms of the EMBRACE clinical trial. In the current model, costs and utility impact of adverse events are modelled in the first cycle only; health state utility values used in the analysis therefore incorporate response only, and adverse event disutilities are modelled separately.

The calculation of progression-free, on-treatment utility values is presented in Table 88. The baseline utility value (0.704), tumour response utility value (0.780) and the incremental utility of response (0.076) were taken from TA423, and progression free, on-treatment utility values were calculated for each treatment using ORR. The ORR from DESTINY-Breast01 (61.4%) was used for T-DXd,[14] and ORR values from the MAIC were used for each comparator (see Section B.2.9).

Table 88: Progression-free, on-treatment utility values

	Eribulin (95% C.I.)	Capecitabine (95% C.I.)	Vinorelbine (95% C.I.)	T-DXd (95% C.I.)
Baseline	0.704 (0.69, 0.72)	0.704 (0.69, 0.72)	0.704 (0.69, 0.72)	0.704 (0.69, 0.72)
Incremental utility of response	0.076 (0.051, 0.101)	0.076 (0.051, 0.101)	0. 0.076 (0.051, 0.101)	0.076 (0.051, 0.101)
Tumour response rate	Cortes (2011): 14.2% (9.0%, 21.7%) Barni: 16.6% (9.4%%, 27.6%) Cortes (2010): 9.8% (6.0%, 15.6%) Gamucci: 24.8% (7.8%, 56.2%)	Fumoleau: 15.1% (8.6%, 25.2%) Blum: 22.2% (11.3%, 39.0%)	30.8% (14.0%, 55.0%)	61.4% (54%, 68.5%)
Progression free, on treatment utility value †	Cortes (2011): 0.715 Barni: 0.717 Cortes (2010): 0.711 Gamucci: 0.723	Fumoleau: 0.715 Blum: 0.721	0.727	0.751

Abbreviations: SoC, standard-of-care; T-DXd, trastuzumab deruxtecan.
† Progression free, on treatment utility = baseline + ORR * incremental utility of response
¥Base-case

In the base-case, the progression-free, off treatment utility value is equal to the 'baseline' utility value in Table 88 (0.704). The progressed disease utility value was aligned with the committee's comments from TA423. In TA423, the ERG stated that the value used by the company for progressed disease (0.679) was unrealistic as it did not represent a large enough drop in utility after patients experienced disease progression, and proposed a value of 0.496 from Lloyd et al.[32] The committee stated that the true utility value was likely somewhere between the company and ERG value, as clinicians stated that the drop-off in utility was likely smaller than suggested by the ERG's recommendation. Therefore, in the base-case, the average from TA423 of the company and ERG values for progressed disease (0.588, 95% CI: 0.53, 0.65)) is used. Scenarios are presented which model progressed disease assuming each of the ERG and company's proposed values for progressed disease from TA423.

An additional scenario analysis is included using utility values presented by Le et al. (Table 89), a simulation study assessing the cost effectiveness of lapatinib and capecitabine for HER2+ advanced breast cancer.[34]

Table 89: Utility value scenario, Le et al.

Health state	Utility value (95% CI)
Progression-free (all health states and comparators)	0.700 (0.69, 0.72)
Progressed disease	0.500 (0.45, 0.72)

3.2.2.3. Summary of utility values for cost-effectiveness analysis (addendum to Document B, Section B.3.4.6)

Table 90: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Justification
Progression-free, T-DXd	0.751	Derived from the 3L mBC submission TA423
Progression-free, eribulin	0.715	Derived from the 3L mBC submission TA423
Progression-free, capecitabine	0.715	Derived from the 3L mBC submission TA423
Progression-free, vinorelbine	0.727	Derived from the 3L mBC submission TA423
Progression-free, off treatment	0.704	Derived from the 3L mBC submission TA423
Progressed	0.588	Derived from the 3L mBC submission TA423

Abbreviations: mBC, metastatic breast cancer; 3L, third line; T-DXd, trastuzumab deruxtecan

3.2.3. Cost and healthcare resource use identification, measurement and valuation (addendum to Document B, Section B.3.5)

Update to CS Section B.3.5

- Updated RDI and adverse event frequencies from the June 2020 data cut for DESTINY-Breast01
- Updated vinorelbine dose and cost to reflect the ERG report
- Corrections to reporting errors for:
  - Cost per dose for drugs that make up subsequent therapy costs
  - Medical oncologist follow-up cost
  - Palliative monthly care cost
  - End of life costs
  - Total terminal care costs

3.2.3.1. Intervention and comparators' costs and resource use (addendum to Document B, Section B.3.5.1)

3.2.3.1.1 Acquisition costs (addendum to Document B, Section B.3.5.1.1)

The acquisition costs for each comparator are presented in Table 91. All costs were sourced from eMIT where available or the BNF.[35,36] All therapies are costed as per the time-on-treatment in each arm as presented in Section 3.2.1.1. Costs collected from related technology appraisals were inflated to 2018/2019 using inflation indices provided in the PSSRU Unit Costs of Health and Social Care.[37]

Table 91: Acquisition costs

Drug	Dose	mg/pack	Pack price	Pack size
T-DXd (list price)	5.4 mg/kg	100 mg	[redacted]	1
T-DXd (PAS price)	5.4 mg/kg	100 mg	[redacted]	
Eribulin	1.23 mg/m^2	2 ml	£361.00	1
		3 ml	£541.50	
Capecitabine	1250 mg/m^2	150mg	£4.17	60
		300mg	£7.26	
Vinorelbine	30 mg/m^2	1 ml	£36.71	10
		5 ml	£133.28	

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

3.2.3.1.2 Wastage (addendum to Document B, Section B.3.5.1.2)

In TA523, a clinical expert confirmed that "in clinical practice drug wastage is recognised and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain". In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.

The average body surface area (BSA) in DESTINY-Breast01 was 1.66 m^2 (CI: 1.63,1.69), and average weight was 62.4 kg (CI: 60.4, 64.5). Drug wastage was calculated using the method of moments assuming a normal distribution of patients around the mean weight or BSA. Scenario analyses are presented which assume 0% and 100% vial sharing. The cost per dose without wastage and cost per dose with wastage is combined and weighted by the assumed proportion of vial sharing (Table 92).

Table 92: Primary therapy wastage

Drug	Wastage	Cost per dose with wastage	Cost per dose without wastage	Adjusted cost per dose
T-DXd (list price)	Yes	[redacted]	[redacted]	[redacted]
T-DXd (PAS price)	Yes	[redacted]	[redacted]	[redacted]
Eribulin	Yes	£778.89	£703.16	£741.02
Capecitabine	Yes	£0.75	£0.70	£0.73
Vinorelbine	Yes	£14.75	£11.14	£12.95

Abbreviations: PAS, patient access scheme.

3.2.3.1.3 Relative dose intensity (addendum to Document B, Section B.3.5.1.3)

The mean relative dose intensities (RDIs) of the primary therapies are presented in Table 93. The relative dose intensity for T-DXd is taken from DESTINY-Breast01, the RDI for eribulin was assumed equal to the RDI presented in NICE TA423. The RDI for capecitabine and vinorelbine was conservatively assumed equal to eribulin. An RDI of 100% is assumed for subsequent therapies.

Table 93: Mean RDIs

Treatment	RDI
T-DXd	[redacted]%
Eribulin	84.00%
Capecitabine	84.00%
Vinorelbine	84.00%

Abbreviations: RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

3.2.3.1.4 Subsequent therapies (addendum to Document B, Section B.3.5.1.5)

In the base-case, 60% of patients receive a lifetime cost of subsequent therapies once they transition into the 'Progressed' health state. Subsequent therapies were costed to align with the ERG's preferred assumptions in TA423[6], with drug costs taken from the latest published version of eMIT or the BNF if not available in eMIT (Table 94). The average weekly cost of a treatment was calculated as an average of the weekly cost over three weekly cycles (as this was the maximum treatment cycle length for some of the treatments below) to account for differing treatment cycle lengths.

Table 94: Subsequent therapy costs

Drug	Dose	Administration method	Cost per dose	Frequency	Distribution of treatments
Vinorelbine IV	30.0 mg/kg	IV	£11.14	Weekly	18.4%
Vinorelbine oral	60 mg/m2	Oral	£218.89	Weekly	18.4%
Gemcitabine	1250.00 mg/m2	IV	£18.75	Day 1 & 8 of 21 day cycle	27.7%
Docetaxel	100 mg/m2	IV	£21.84	q3w	6.0%
Paclitaxel	175.0 mg/kg	IV	£36.73	q3w	15.7%
Doxorubicin	68 mg/m2	IV	£9.69	q3w	13.9%

Abbreviations: IV, intravenous.

A cost of £172.27 per week was applied to patients in all arms of the model in the progressed disease state for their lifetime. A scenario analysis is presented that costed subsequent therapy using the same cost per week of subsequent therapies presented in TA423, £10.22.

3.2.3.2. Adverse reaction unit costs and resource use (addendum to Document B, Section B.3.5.3)

The costs of treating an AE were calculated using the NHS reference costs applied in TA423. All costs were updated to 2018/2019 NHS reference costs and 2019 PSSRU costs.[38,39] The costs of AEs were applied to the proportion of each event that resulted in hospitalisation. For the adverse events reported for the comparators that were also reported for T-DXd, then the proportion of events that resulted in hospitalisation were based on the proportions of hospitalisation reported for T-DXd for each event (as reported in Section 3.2.2.1). For events that occurred in the comparator trials that did not occur for T-DXd, then it was assumed in the base case 0% would lead to hospitalisation. This was tested in

sensitivity analysis. The unit cost of each event and its relevant code are reported in Table 95. This approach aligns with the method adopted in TA423. The total cost of each adverse event was applied to the proportion of patients experiencing the AEs and a one-off cost was applied in the first cycle of the model. The differences in the costs applied to each comparator in the model are driven primarily by differences in AE frequencies (Section 3.2.1.4). Appling AE costs as a one-off upfront cost was considered reasonable because of the short duration of treatment. The costs of AEs applied in each arm are presented in (Table 96).

Table 95: Cost of adverse events

AE	Cost	Reference/service code
Neutrophil count decreased/Neutropenia	£125.88	NHS reference costs 2016/2017/ XD25Z - Neutropenia drugs band 1[1]
Anaemia	£475.29	NHS reference costs 2018/2019/ SA04K - Iron deficiency anaemia with cc score 2-5 non-elective short stay
Nausea	£388.44	NHS reference costs 2018/2019/ JA12L - Malignant breast disorders without Interventions, with CC score 0-1 non-elective short stay
Fatigue	£60	PSSRU 2019/ 1hr community nurse visit (band 5)
White blood cell count decreased	£125.88	Assumed same as neutrophil count decreased
Dyspnoea	£466.30	NHS reference costs 2018/2019/ DZ20E - Pulmonary Oedema without interventions, with CC score 6+
Febrile neutropenia	£3,745.55	NHS reference costs 2016/2017/ PA45Z - Febrile Neutropenia with Malignancy[1]
Electrocardiogram QT prolonged	£783.48	NHS reference costs 2018/2019/ EY51Z: Electrocardiogram monitoring or stress testing non-elective short stay
Interstitial lung disease/Pneumonitis	£1,621.24	Reference costs 2018/2019/ DZ11M, Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8 non-elective short stay
Ejection fraction decreased	£404.73	NHS reference costs 2018/2019/ EB03E, Heart failure or shock, with CC score 0-3, non-elective short stay
Vomiting	£388.44	Assumed the same as nausea
Diarrhoea	£388.44	NHS reference costs 2018/2019/ JA12L - Malignant breast disorders without Interventions, with CC score 0-1 non elective short stay
Palmar-plantar erythrodysesthesia syndrome	£391.43	NHS reference costs 2018/2019/ JD07J - Skin disorders without intervention, with cc score 2-5 non-elective inpatient short stay

AE	Cost	Reference/service code
Dehydration	£399.42	TA515: Malignant Breast Disorders without Interventions, with CC Score 0-1 (Non-elective short stay)
Stomatitis	£518.95	TA423: WA21W Other Procedures and health care problems with CC -- Day Cases HRG
Abdominal pain	£319.73	Weighted average of day case abdominal pain with and without interventions (FD05A and FD05B), NHS reference costs 2018/19
Peripheral neuropathy	£137.35	TA423, inflated from 2015 prices

Abbreviations: AE, adverse event; NHS, national health service; PSSRU, Personal Social Services Research Unit.
1. NHS reference costs 2016/17 is when this HRG code was last available, and therefore this has been used as the source and inflated to 2019.

Table 96: Total adverse event costs by treatment

Treatment	AE cost
T-DXd	£52.12
Eribulin	£43.48
Capecitabine	£9.22
Vinorelbine	£18.84

Abbreviations: AE, adverse event; SoC, standard-of-care; T-DX-d, T-DXd, trastuzumab deruxtecan.

3.2.3.3. Miscellaneous unit costs and resource use (addendum to Document B, Section B.3.5.4)

The cost of palliative care was assigned to each patient in the progressed state for 5.5 months before transitioning into the 'Dead' health state, as assumed in TA423.[6] The frequency of resource use for patients who were receiving palliative care was sourced from estimates presented in NICE TA423.[6] All resource use cost estimates were calculated based on 2019 PSSRU costs and 2018/2019 NHS reference costs and are presented in Table 97.[38,39]

Table 97: Palliative care disaggregated costs

Palliative care resources	Frequency (per month)	Unit cost	Source/service code
Medical oncologist – follow-up	1.00	£147.97	NHS reference costs 2018/2019 - service code 370
GP home visit	1.00	£39.23	2019 PSSRU costs – 10.3b
Clinical nurse specialist	1.00	£92.00	2019 PSSRU costs – 13 Hospital-based nurse cost per hour of patient contact (band 5)
Community nurse home visit	0.67	£60.00	2019 PSSRU costs – PSSRU 2019 - 10.1 Nurse Cost per hour of patient related work (band 5)

Abbreviations: GP, general practitioner; NHS, national health service; PSSRU, Personal Social Services Research Unit

A cost of £358.43 per month was applied to patients who were receiving palliative care for 5.5 months (Table 98).

Table 98: Palliative care total costs

Input	Value
Palliative care monthly costs	£319.40
Months of palliative care prior to death	5.50

End of life costs were applied to each patient who transitioned to the 'Dead' health state for 2 weeks before death. The cost of end of life treatment at a hospital or medical institution, hospice or at home, and the proportion of patients who died in each setting was taken from the estimates presented in NICE TA423 Table 99.[6] The total palliative, end of life costs and terminal care costs are presented in Table 100.

Table 99: End of life costs

End of life - care setting	Proportion of patients	Unit cost	Cost year	Uplifted and weighted cost
Hospital/Medical institution	40%	£5,135.25	2015	£2,192.66
Hospice	10%	£6,402.15	2015	£683.40
At home (with community support)	50%	£2,649.47	2015	£1,414.09
			Weighted EoL cost	£4,262.64

Abbreviations: EoL, end of life.

Table 100: Total terminal care costs

Type of cost	Cost
Palliative care costs	£1,756.68
EoL costs	£4,290.15
Total terminal care costs	£6,046.83

Abbreviations: EoL, end of life

3.2.4. Summary of base-case analysis inputs and assumptions (addendum to Document B, Section B.3.6)

Update to CS Section B.3.6

- Reflects changes to Sections B.3.3 – B.3.5

3.2.4.1. Summary of base-case analysis inputs (addendum to Document B, Section B.3.6.1)

Table 101: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline characteristics			
Mean age	55.96	CI= 54.26, 57.67 (Normal)	B.3.3.1.3 in main submission
Mean weight (kg)	62.47	CI= 60.43, 64.51 (Normal)	3.2.3.1.2
Mean BSA	1.66	CI= 1.63, 1.69 (Normal)	
Proportion HER2 positive by study - EMBRACE (Cortes 2011)	18%	N/A	B.3.3.4 in main submission
Proportion HER2 positive by study - Barni 2019	100%	N/A	
Proportion HER2 positive by study - Cortes 2010	11%	N/A	
Proportion HER2 positive by study - Gamucci 2014	21%	N/A	
Proportion HER2 positive by study - Fumoleau 2004	20%	N/A	
Proportion HER2 positive by study - Blum 2001	20%	N/A	
Proportion HER2 positive by study - Sim 2019	100%	N/A	
Proportion HER2 positive by study - TH3RESA	100%	N/A	
OS/PFS/TTD data			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	1.84	CI= 1.33, 2.56 (Log-normal)	3.2.1
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	1.84	CI= 1.33, 2.56 (Log-normal)	
Eribulin median treatment duration (months) - EMBRACE (Cortes 2011)	3.9	N/A	
Eribulin median treatment duration (cycles) - Barni 2019	4	N/A	
Eribulin median treatment duration (cycles) - Cortes 2010	4	N/A	
Eribulin median treatment duration (cycles) - Gamucci 2014	5	N/A	
Capecitabine median treatment duration (months) - Fumoleau 2004	4.1	N/A	
Capecitabine median treatment duration (months) - Blum 2001	3.2	N/A	
PFS - Eribulin versus T-DXd - MAIC HR - EMBRACE (Cortes 2011)	[redacted]	[redacted]	
PFS - Eribulin versus T-DXd - MAIC HR - Barni 2019	[redacted]		
PFS - Eribulin versus T-DXd - MAIC HR - Cortes 2010	[redacted]		
PFS - Eribulin versus T-DXd - MAIC HR - Gamucci 2014	[redacted]		
PFS - Capecitabine versus T-DXd - MAIC HR - Fumoleau 2004	[redacted]		
PFS - Capecitabine versus T-DXd - MAIC HR - Blum 2001	[redacted]		
PFS - Vinorelbine versus T-DXd - MAIC HR	[redacted]		
OS - T-DXd versus Eribulin - MAIC HR - EMBRACE (Cortes 2011)	[redacted]		
OS HR - T-DXd versus TH3RESA (T-DXd OS censored at 20.5 months)	[redacted]		
OS HR - T-DXd versus TH3RESA (T-DXd OS uncensored)	[redacted]		
Drug cost inputs			
Pack price - T-DXd - 100mg	[redacted]	N/A	B.3.5.1 in main submission
Pack price - T-DXd - 100mg (with PAS discount)	[redacted]	N/A	
Pack price - Vinorelbine - 1ml	£36.71	N/A	
Pack price - Vinorelbine - 5ml	£133.28	N/A	
Pack price - Eribulin - 2ml	£361.00	N/A	
Pack price - Eribulin - 3ml	£541.50	N/A	
Pack price - Capecitabine - 150mg	£4.17	N/A	
Pack price - Capecitabine - 300mg	£7.26	N/A	
Pack price - Capecitabine - 500mg	£25.76	N/A	
T-DXd RDI	92%	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Eribulin RDI	84%	N/A	
Capecitabine RDI	84%	N/A	
Vinorelbine RDI	84%	N/A	
% vial sharing assumed	50%	CI= 0.45, 0.55 (Beta)	
Administration cost Oral	£0.00	N/A	
Administration cost IV infusion	£254.14	CI= 228.73, 279.55 (Gamma)	
Proportion of progressed patients receiving subsequent therapy	60%	CI= 0.54, 0.66 (Beta)	
TA423 - Monthly average subsequent treatment cost (used in scenario analysis)	£44	CI= 39.6, 48.4 (Gamma)	
Weekly subsequent treatment cost (base case)	£172.27	N/A	
Distribution of treatments for subsequent therapy - Vinorelbine IV (used in scenario analysis)	18%	N/A	
Distribution of treatments for subsequent therapy - Vinorelbine oral (used in scenario analysis)	18%	N/A	
Distribution of treatments for subsequent therapy - Gemcitabine (used in scenario analysis)	28%	N/A	
Distribution of treatments for subsequent therapy - Docetaxel (used in scenario analysis)	6%	N/A	
Distribution of treatments for subsequent therapy - Paclitaxel (used in scenario analysis)	16%	N/A	
Distribution of treatments for subsequent therapy - Doxorubucin (used in scenario analysis)	14%	N/A	
Resource use inputs			
Resource use - pre-progression - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	B.3.5.2 in main submission
Resource use - pre-progression - TA423 - GP Contact - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - pre-progression - TA423 - CT scan - frequency per month	0.33	CI= 0.3, 0.36 (Gamma)	
Resource use - Medical Oncologist - follow-up - unit cost	£147.97	CI= 133.17, 162.76 (Gamma)	
Resource use - GP Contact - unit cost	£39.23	CI= 35.31, 43.15 (Gamma)	
Resource use - CT scan - unit cost	£77.95	CI= 70.16, 85.75 (Gamma)	
Resource use - post-progression - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - post-progression - TA423 - GP Contact - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - post-progression - TA423 - CT scan - frequency per month	0.33	CI= 0.3, 0.36 (Gamma)	
Resource use - palliative care - TA423 - Medical Oncologist - follow-up - frequency per month	1	CI= 0.9, 1.1 (Gamma)	3.2.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Resource use - palliative care - TA423 - GP Home visit - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - palliative care - TA423 - Clinical nurse specialist - frequency per month	1	CI= 0.9, 1.1 (Gamma)	
Resource use - palliative care - TA423 - Community nurse home visit - frequency per month	0.67	CI= 0.6, 0.74 (Gamma)	
Resource use - palliative care - TA423 - Medical Oncologist - follow-up - unit cost	£147.97	CI= 133.17, 162.76 (Gamma)	
Resource use - palliative care - TA423 - GP Home visit - unit cost	£39.23	CI= 35.31, 43.15 (Gamma)	
Resource use - palliative care - TA423 - Clinical nurse specialist - unit cost	£92.00	CI= 82.8, 101.2 (Gamma)	
Resource use - palliative care - TA423 - Community nurse home visit - unit cost	£60.00	CI= 54, 66 (Gamma)	
Reource use - palliative care - duration (months)	5.5	CI= 4.95, 6.05 (Gamma)	
Terminal care proportion - Hospital/Medical Institution	40%	N/A	
Terminal care proportion - Hospice	10%	N/A	
Terminal care proportion - At home (with community support)	50%	N/A	
Terminal care cost - Hospital/Medical Institution	£5,135.25	CI= 4621.73, 5648.78 (Gamma)	
Terminal care cost - Hospice	£6,402.15	CI= 5761.94, 7042.37 (Gamma)	
Terminal care cost - At home (with community support)	£2,649.47	CI= 2384.52, 2914.42 (Gamma)	
Adverse events			
AE - T-DXd full cohort - Neutrophil count decreased - events (N)	42	CI= 37.8, 46.2 (Gamma)	3.2.1.4
AE - T-DXd full cohort - Anaemia - events (N)	30	CI= 27, 33 (Gamma)	
AE - T-DXd full cohort - Neutropenia - events (N)	46	CI= 41.4, 50.6 (Gamma)	
AE - T-DXd full cohort - Nausea - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - T-DXd full cohort - Fatigue - events (N)	18	CI= 16.2, 19.8 (Gamma)	
AE - T-DXd full cohort - White blood cell count decreased - events (N)	17	CI= 15.3, 18.7 (Gamma)	
AE - T-DXd full cohort - Dyspnoea - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Febrile neutropenia - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Electrocardiogram QT prolonged - events (N)	4	CI= 3.6, 4.4 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - T-DXd full cohort - Interstitial lung disease - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Ejection fraction decreased - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Pneumonitis - events (N)	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Vomiting - events (N)	0	N/A	
AE - T-DXd full cohort - Neutrophil count decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Anaemia - N hospitalised	3	CI= 2.7, 3.3 (Gamma)	
AE - T-DXd full cohort - Neutropenia - N hospitalised	1	CI= 0.9, 1.1 (Gamma)	
AE - T-DXd full cohort - Nausea - N hospitalised	4	CI= 3.6, 4.4 (Gamma)	
AE - T-DXd full cohort - Fatigue - N hospitalised	0	N/A	
AE - T-DXd full cohort - White blood cell count decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Dyspnoea - N hospitalised	0	N/A	
AE - T-DXd full cohort - Febrile neutropenia - N hospitalised	0	N/A	
AE - T-DXd full cohort - Electrocardiogram QT prolonged - N hospitalised	0	N/A	
AE - T-DXd full cohort - Interstitial lung disease - N hospitalised	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Ejection fraction decreased - N hospitalised	0	N/A	
AE - T-DXd full cohort - Pneumonitis - N hospitalised	2	CI= 1.8, 2.2 (Gamma)	
AE - T-DXd full cohort - Vomiting - N hospitalised	0	N/A	
AE - Eribulin - EMBRACE - Neutrophil count decreased (%)	0%	N/A	
AE - Eribulin - EMBRACE - Anaemia (%)	2%	CI= 0.01, 0.04 (Beta)	
AE - Eribulin - EMBRACE - Neutropenia (%)	15%	CI= 0.12, 0.18 (Beta)	
AE - Eribulin - EMBRACE - Nausea (%)	1%	CI= 0, 0.03 (Beta)	
AE - Eribulin - EMBRACE - Fatigue** (%)	2%	CI= 0.01, 0.04 (Beta)	
AE - Eribulin - EMBRACE - White blood cell count decreased* (%)	4%	CI= 0.03, 0.06 (Beta)	
AE - Eribulin - EMBRACE - Dyspnoea (%)	3%	CI= 0.02, 0.05 (Beta)	
AE - Eribulin - EMBRACE - Febrile neutropenia (%)	2%	CI= 0.01, 0.03 (Beta)	
AE - Eribulin - EMBRACE - Electrocardiogram QT prolonged (%)	0%	N/A	
AE - Eribulin - EMBRACE - Interstitial lung disease (%)	0%	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Eribulin - EMBRACE - Ejection fraction decreased (%)	0%	N/A	
AE - Eribulin - EMBRACE - Pneumonitis (%)	0%	N/A	
AE - Eribulin - EMBRACE - Vomiting (%)	0%	N/A	
AE - Eribulin - EMBRACE - Palmar-Plantar Erythro-Dysaesthesia Syndrome1 (%)	6%	CI= 0.04, 0.09 (Beta)	
AE - Eribulin - EMBRACE - Peripheral neuropathy1 (%)	0%	N/A	
AE - Eribulin - Barni 2019 - Neutrophil count decreased - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Anaemia - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Eribulin - Barni 2019 - Neutropenia - events (N)	70	CI= 63, 77 (Gamma)	
AE - Eribulin - Barni 2019 - Nausea - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Barni 2019 - Fatigue** - events (N)	42	CI= 37.8, 46.2 (Gamma)	
AE - Eribulin - Barni 2019 - White blood cell count decreased* - events (N)	4	CI= 3.6, 4.4 (Gamma)	
AE - Eribulin - Barni 2019 - Dyspnoea - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Barni 2019 - Febrile neutropenia - events (N)	15	CI= 13.5, 16.5 (Gamma)	
AE - Eribulin - Barni 2019 - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Interstitial lung disease - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Ejection fraction decreased - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Pneumonitis - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Vomiting - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Palmar-Plantar Erythro-Dysaesthesia Syndrome1 - events (N)	0	N/A	
AE - Eribulin - Barni 2019 - Peripheral neuropathy1 - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Neutrophil count decreased - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Anaemia - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Neutropenia - events (N)	157	CI= 141.3, 172.7 (Gamma)	
AE - Eribulin - Cortes 2010 - Nausea - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Fatigue - events (N)	29	CI= 26.1, 31.9 (Gamma)	
AE - Eribulin - Cortes 2010 - White blood cell count decreased* - events (N)	41	CI= 36.9, 45.1 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Eribulin - Cortes 2010 - Dyspnoea - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Febrile neutropenia - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - Eribulin - Cortes 2010 - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Interstitial lung disease - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Ejection fraction decreased - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Pneumonitis - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Vomiting - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Eribulin - Cortes 2010 - Palmar-Plantar Erythro-Dysaesthesia Syndrome - events (N)	0	N/A	
AE - Eribulin - Cortes 2010 - Peripheral neuropathy1 - events (N)	20	CI= 18, 22 (Gamma)	
AE - Capecitabine - Neutrophil count decreased - events (N)	0	N/A	
AE - Capecitabine - Anaemia - events (N)	0	N/A	
AE - Capecitabine - Neutropenia - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - Capecitabine - Nausea - events (N)	7	CI= 6.3, 7.7 (Gamma)	
AE - Capecitabine - Fatigue - events (N)	6	CI= 5.4, 6.6 (Gamma)	
AE - Capecitabine - White blood cell count decreased - events (N)	0	N/A	
AE - Capecitabine - Dyspnoea - events (N)	0	N/A	
AE - Capecitabine - Febrile neutropenia - events (N)	0	N/A	
AE - Capecitabine - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Capecitabine - Interstitial lung disease - events (N)	0	N/A	
AE - Capecitabine - Ejection fraction decreased - events (N)	0	N/A	
AE - Capecitabine - Pneumonitis - events (N)	0	N/A	
AE - Capecitabine - Vomiting - events (N)	0	N/A	
AE - Capecitabine - Diarrhoea - events (N)	14	CI= 12.6, 15.4 (Gamma)	
AE - Capecitabine - Palmar-Plantar Erythro-Dysaesthesia Syndrome - events (N)	16	CI= 14.4, 17.6 (Gamma)	
AE - Capecitabine - Dehydration - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Capecitabine - Stomatitis - events (N)	9	CI= 8.1, 9.9 (Gamma)	
AE - Vinorelbine - Neutrophil count decreased - events (N)	0	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE - Vinorelbine - Anaemia - events (N)	4	CI= 3.6, 4.4 (Gamma)	
AE - Vinorelbine - Neutropenia - events (N)	45	CI= 40.5, 49.5 (Gamma)	
AE - Vinorelbine - Nausea - events (N)	0	N/A	
AE - Vinorelbine - Fatigue - events (N)	2	CI= 1.8, 2.2 (Gamma)	
AE - Vinorelbine - White blood cell count decreased - events (N)	0	N/A	
AE - Vinorelbine - Dyspnoea - events (N)	0	N/A	
AE - Vinorelbine - Febrile neutropenia - events (N)	5	CI= 4.5, 5.5 (Gamma)	
AE - Vinorelbine - Electrocardiogram QT prolonged - events (N)	0	N/A	
AE - Vinorelbine - Interstitial lung disease - events (N)	0	N/A	
AE - Vinorelbine - Ejection fraction decreased - events (N)	0	N/A	
AE - Vinorelbine - Pneumonitis - events (N)	1	CI= 0.9, 1.1 (Gamma)	
AE - Vinorelbine - Vomiting - events (N)	0	N/A	
AE - Vinorelbine - Abdominal pain - events (N)	12	CI= 10.8, 13.2 (Gamma)	
Adverse event costs and assumptions			
AE cost - hospitalized - Neutrophil count decreased	£119.49	CI= 107.54, 131.44 (Gamma)	3.2.3.2
AE cost - hospitalized - Anaemia	£475.29	CI= 427.76, 522.82 (Gamma)	
AE cost - hospitalized – Neutropenia (uninflated)	£119.49	CI= 107.54, 131.44 (Gamma)	
AE cost - hospitalized - Nausea	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - Fatigue	£60.00	CI= 54, 66 (Gamma)	
AE cost - hospitalized - White blood cell count decreased (uninflated)	£119.49	CI= 107.54, 131.44 (Gamma)	
AE cost - hospitalized - Dyspnoea	£466.30	CI= 419.67, 512.93 (Gamma)	
AE cost - hospitalized - Febrile neutropenia (uninflated)	£3,619.00	CI= 3257.1, 3980.9 (Gamma)	
AE cost - hospitalized - Electrocardiogram QT prolonged	£783.48	CI= 705.13, 861.83 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE cost - hospitalized - Interstitial lung disease	£1,621.24	CI= 1459.12, 1783.36 (Gamma)	
AE cost - hospitalized - Ejection fraction decreased	£404.73	CI= 364.25, 445.2 (Gamma)	
AE cost - hospitalized - Pneumonitis	£1,621.24	CI= 1459.12, 1783.36 (Gamma)	
AE cost - hospitalized - Vomiting	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - Diarrhoea	£388.44	CI= 349.6, 427.29 (Gamma)	
AE cost - hospitalized - PPE	£391.43	CI= 352.28, 430.57 (Gamma)	
AE cost - hospitalized - Dehydration	£399.42	CI= 359.48, 439.36 (Gamma)	
AE cost - hospitalized - Stomatitis	£518.95	CI= 467.06, 570.85 (Gamma)	
AE cost - hospitalized - Abdominal pain	£319.73	CI= 287.76, 351.7 (Gamma)	
AE cost - hospitalized - Peripheral neuropathy (uninflated)	£128.67	CI= 115.8, 141.54 (Gamma)	
Proportion hospitalised - Diarrhoea	0%	N/A	
Proportion hospitalised - PPE	0%	N/A	
Proportion hospitalised - Dehydration	0%	N/A	
Proportion hospitalised - Stomatitis	0%	N/A	
Proportion hospitalised - Abdominal pain	0%	N/A	
Proportion hospitalised - Peripheral neuropathy	0%	N/A	
Utilities			
Response rate - T-DXd (U201)	61%	CI= 0.54, 0.69 (Beta)	3.2.2.2
Response rate - Eribulin - EMBRACE	14%	CI= 0.09, 0.22 (Beta)	
Response rate - Eribulin - Barni	17%	CI= 0.09, 0.28 (Beta)	
Response rate - Eribulin - Cortes 2010	10%	CI= 0.06, 0.16 (Beta)	
Response rate - Eribulin - Gamucci	25%	CI= 0.08, 0.56 (Beta)	
Response rate - Capecitabine - Fumoleau	15%	CI= 0.09, 0.25 (Beta)	
Response rate - Capecitabine - Blum	22%	CI= 0.11, 0.39 (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Response rate - Vinorelbine	31%	CI= 0.14, 0.55 (Beta)	
Incremental utility of response	8%	CI= 0.05, 0.1 (Beta)	
Utility: Progression free off treatment, TA423	70%	CI= 0.69, 0.72 (Beta)	
Utility: PFS off treatment, Le et al.	70%	CI= 0.5, 0.8 (Beta)	
Utility: Progressed, TA423	68%	CI= 0.67, 0.69 (Beta)	
Utility: Progressed, Le et al.	50%	CI= 0.45, 0.72 (Beta)	
Utility: Progressed, ERG	50%	CI= 0.45, 0.55 (Beta)	
Utility: Progressed, Average of ERG and company	59%	CI= 0.53, 0.65 (Beta)	
AE disutility - Neutrophil count decreased	0.007	CI= 0, 0.014 (Beta)	3.2.2.1
AE disutility - Anaemia	0.010	CI= -0.015, 0.035 (Beta)	
AE disutility - Neutropenia	0.007	CI= 0, 0.014 (Beta)	
AE disutility - Nausea	0.021	CI= -0.019, 0.061 (Beta)	
AE disutility - Fatigue	0.029	CI= 0.014, 0.044 (Beta)	
AE disutility - White blood cell count decreased	0.003	CI= -0.009, 0.015 (Beta)	
AE disutility - Dyspnoea	0.027	CI= 0.007, 0.047 (Beta)	
AE disutility - Febrile neutropenia	0.012	CI= -0.017, 0.041 (Beta)	
AE disutility - Electrocardiogram QT prolonged	0.000	N/A	
AE disutility - Interstitial lung disease	0.170	CI= 0.153, 0.187 (Beta)	
AE disutility - Ejection fraction decreased	0.059	CI= 0, 0.11 (Beta)	
AE disutility - Pneumonitis	0.170	CI= 0.153, 0.187 (Beta)	
AE disutility - Vomiting	0.103	CI= 0.093, 0.113 (Beta)	
AE disutility - Diarrhoea	0.006	CI= -0.014, 0.026 (Beta)	
AE disutility - PPE	0.116	CI= 0.093, 0.139 (Beta)	
AE disutility - Dehydration	0.006	CI= -0.026, 0.014 (Beta)	
AE disutility - Stomatitis	0.151	CI= 0.11, 0.19 (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE disutility - Abdominal pain	0.006	CI= -0.026, 0.014 (Beta)	
AE disutility - Peripheral neuropathy	0.014	CI= 0.002, 0.03 (Beta)	
AE duration - Neutrophil count decreased	25.3	CI= 20.66, 29.94(Gamma)	
AE duration - Anaemia	12.2	CI= 8.82, 15.58(Gamma)	
AE duration - Neutropenia	16.2	CI= 11.4, 21(Gamma)	
AE duration - Nausea	63.5	CI= 51.35, 75.65(Gamma)	
AE duration - Fatigue	53.6	CI= 40.09, 67.11(Gamma)	
AE duration - White blood cell count decreased	45.4	CI= 36.01, 54.79(Gamma)	
AE duration - Dyspnoea	9.60	CI= 8.64, 10.56 (Gamma)	
AE duration - Febrile neutropenia	6.3	CI= 5.65, 6.95(Gamma)	
AE duration - Electrocardiogram QT prolonged	13.2	CI= 11.71, 14.69(Gamma)	
AE duration - Interstitial lung disease	3.0	CI= 2.7, 3.3(Gamma)	
AE duration - Ejection fraction decreased	27.0	CI= 24.3, 29.7 (Gamma)	
AE duration - Pneumonitis	3.0	CI= 2.7, 3.3(Gamma)	
AE duration - Vomiting	13.4	CI= 8.52, 18.28(Gamma)	
AE duration - Diarrhoea	17.0	CI= 13.67, 20.33	
AE duration - PPE	14.00	CI= 12.6, 15.4 (Gamma)	
AE duration - Dehydration	17.00	CI= 13.67, 20.33 (Gamma)	
AE duration - Stomatitis	10.00	CI= 9, 11 (Gamma)	
AE duration - Abdominal pain	17.00	CI= 13.67, 20.33 (Gamma)	
AE duration - Peripheral neuropathy	16.2	CI= 11.4, 21(Gamma)	
Utility - general population - sex coefficient	0.02121	CI= 0.01599, 0.02644 (Normal)	B.3.4.5.1 in main submission
Utility - general population - age coefficient	-0.00026	CI= -0.00098, 0.00048 (Normal)	
Utility - general population - age squaredcoefficient	-0.00003	CI= -0.00004, -0.00002 (Normal)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utility - general population - constant	0.95	CI= 0.935, 0.965 (Beta)	

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; CT, computed tomography; ERG; evidence review group; gen. gamma, generalised gamma; GP, general practitioner; HR, hazard ratio; IV, itranvenous; MAIC, matched adjusted indirect comparison; N/A, not applicable; OS, overall survival; PFS progression free survival; PPE, Palmar-Plantar Erythro-Dysaesthesia Syndrome; QALYs, quality adjusted life year; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

3.2.4.2. Assumptions (addendum to Document B, Section B.3.6.2)

Table 102 provides a summary of assumptions applied in the economic model.

Table 102: Summary of assumptions applied in the economic model

Assumption	Rationale
Extrapolations of T-DXd overall survival were based on applying a HR vs. the T-DM1 OS curve from the TH3RESA trial	OS data in DESTINY-Breast01 from the June 2020 data cut are not considered sufficiently mature for informative parametric modelling, therefore a HR was applied to T-DM1 OS curve from TH3RESA. Given that T-DXd and T-DM1 are both HER2-targeted therapies and are both ADCs including trastuzumab, long-term survival for T-DXd is expected to be more comparable to T-DM1 than to eribulin, vinorelbine or capecitabine. Clinical experts at the August advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect that of T-DM1 than that of the model comparators, and that a 'tail' should be expected in the T-DXd OS curve; anchoring on non-targeted therapies (such as eribulin) is not expected to provide an accurate estimate of long-term survival. More information is provided in Section 3.2.1.1.1
Vinorelbine OS is equivalent to capecitabine OS	Only the Sim (2019) study was available to inform the comparison against vinorelbine[7]; however, clinical experts at the August advisory board advised that the OS observed in Sim 2019 (18.9 months) is not plausible following PFS of 12 weeks, and is likely driven by the use of post-progression therapies.[8] Given that vinorelbine is associated with similar or worse PFS compared with capecitabine, OS for vinorelbine is assumed to be equivalent to OS for capecitabine; further details are provided in Section B.3.3.1.2.

Assumption	Rationale
20% HER2-positive patients were assumed in trials with no information regarding HER2-expression in the patient population	Where information was available on the distribution of HER2-expression in a trial population (Cortes, 2011), an adjustment was made to the trial outcomes in order to compare outcomes with a 100% HER2-positive population. No adjustment was required for the Barni 2019 study, which evaluates the only NICE-recommended treatment option, eribulin, in a HER2-positive population, or for the Sim 2019 study. There was no information on HER2-expression in the data presented by Fumoleau et al, therefore an adjustment was made assuming that 20% of patients in the study were HER2-positive, as observed in clinical practice.[9]
The impact of HER2 status on outcomes is the same between OS and PFS	In the base-case, an adjustment to OS and PFS in the eribulin and capecitabine arms of the model is made to account for the proportion of patients with HER2-positive vs. HER2-negative disease, using the HR presented by Lv et al. Only OS was presented in the study, and therefore the same HR was applied to adjust PFS. At the August advisory board, clinical experts advised that both PFS and OS would be poorer for HER2-positive patients.
Treatment to PFS is assumed for all comparator drugs	For comparator treatments, only median TTD data were available from the studies. When a HR is applied vs. T-DXd TTD for each comparator that passes through the median TTD, the TTD curve quickly passes through the PFS curve. This suggests that the shape of the TTD curves of each comparator is not the same as that of T-DXd. Furthermore, as mean PFS for each comparator is relatively short, it is reasonable to assume that patients would not discontinue treatment before progression in UK clinical practice.
50% drug wastage is assumed	In TA523, a clinical expert confirmed that “in clinical practice drug wastage is recognized and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain”. In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.
AE-associated cost and QALY losses accounted for in first cycle of model	Time on treatment is short for all comparators, and therefore there are not expected to be any long-term cost and QALY losses associated with AEs.
The proportion of AEs that resulted in hospitalisation in DESTINY-Breast01 was applied to all comparator AE proportions	There were no data available on the proportion of each AE that resulted in hospitalisation for each comparator, therefore the best available evidence - patient level data from DESTINY-Breast01 - was used.
0% hospitalisation is assumed in AEs with no hospitalisation data	For AEs that did not occur in DESTINY-Breast01, there were no data available on the proportion of AEs that resulted in hospitalisation. A conservative assumption of 0% was applied in the base-case.

Assumption	Rationale
The RDI for capecitabine and vinorelbine was assumed equal to eribulin.	In the absence of other data, the RDI for capecitabine and vinorelbine is conservatively assumed to be the same as for eribulin.
Resource use estimates are equal for all treatments	This is consistent with previous TAs

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS progression free survival; QALYs, quality adjusted life year; RDI, relative dose intensity; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TA, technology assessment; TTD, time-to-discontinuation

3.2.5. Base-case results, PAS price (addendum to Document B, Section B.3.7)

Update to CS Section B.3.7
• Reflects changes to Sections B.3.3 – B.3.5

3.2.5.1. Base-case incremental cost-effectiveness analysis results, PAS price (addendum to Document B, Section B.3.7.1)

A simple patient access scheme (PAS) for trastuzumab deruxtecan (T-DXd) in the National Health Service (NHS) has been approved in the form of a fixed price of [redacted] per 100mg vial.

3.2.5.1.1 Primary analysis, PAS price

In the primary analysis, censoring T-DXd OS at 20.5 months, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an incremental cost-effectiveness ratio (ICER) of £45,216 per quality-adjusted life-year (QALY) gained. A summary of the fully incremental results using the PAS price for T-DXd are presented in Table 103.

Table 103: Primary analysis results (censoring T-DXd OS at 20.5 months), T-DXd PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£483,164	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,216	£45,216

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

3.2.5.1.2 Secondary analysis, PAS price

Secondary analyses are considered in which the full OS Kaplan-Meier data for T-DXd are used, assuming each of the exponential and generalised gamma distributions. Due to the high level of censoring from 20.5 months, the Kaplan Meier data from this point onwards is not considered to be informative. Therefore, this analysis is expected to be a conservative estimate of the cost-effectiveness of T-DXd and it is proposed that the primary analysis is used for decision making purposes.

In the secondary analysis assuming an exponential distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented in Table 104.

Table 104: Secondary analysis results, T-DXd OS distribution: exponential (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the secondary analysis assuming a generalised gamma distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented in

Table 105.

Table 105: Secondary analysis results, T-DXd OS distribution: generalised gamma (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

3.2.6. Sensitivity analyses, PAS price (addendum to Document B, Section B.3.8)

3.2.6.1. Probabilistic sensitivity analysis, PAS price (addendum to Document B, Section B.3.8.1)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

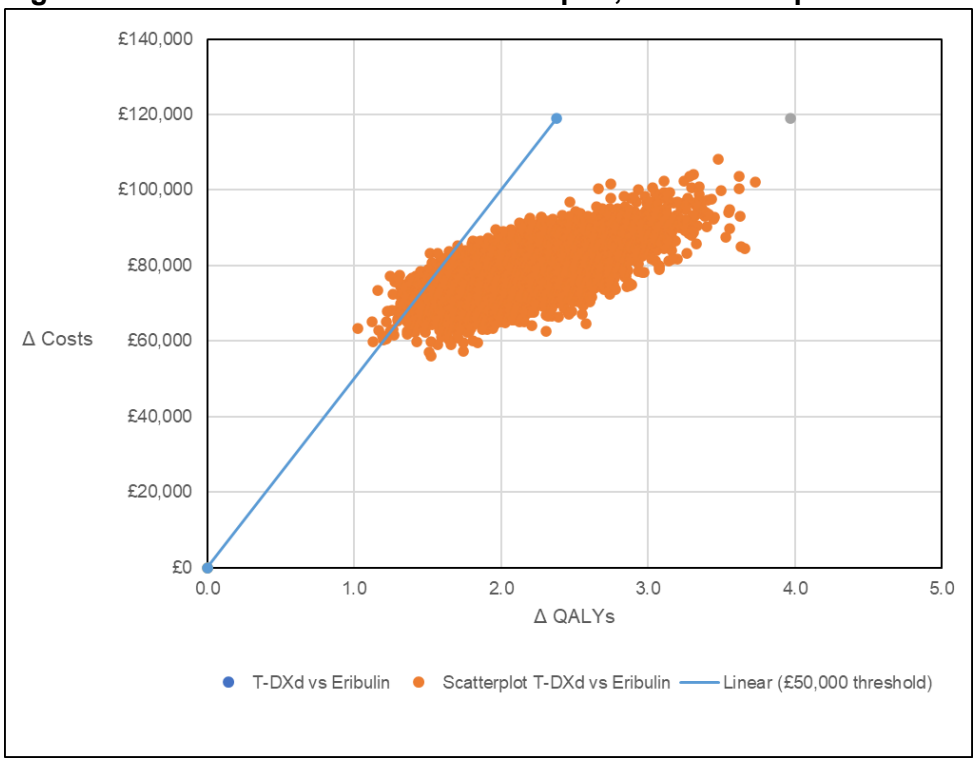
The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted] compared with capecitabine, giving a probabilistic ICER of £45,008. This is highly congruent with deterministic changes in costs of [redacted] and QALYs of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of £50,000 per QALY was [redacted]%. A summary of the probabilistic, fully incremental results using the PAS price for T-DXd are presented in Table 106. The cost-effectiveness plane vs. each comparator and CEAC are presented in Figure 51 – Figure 54.

Table 106: PSA results, T-DXd PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	£648,845	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	£45,008	£45,008

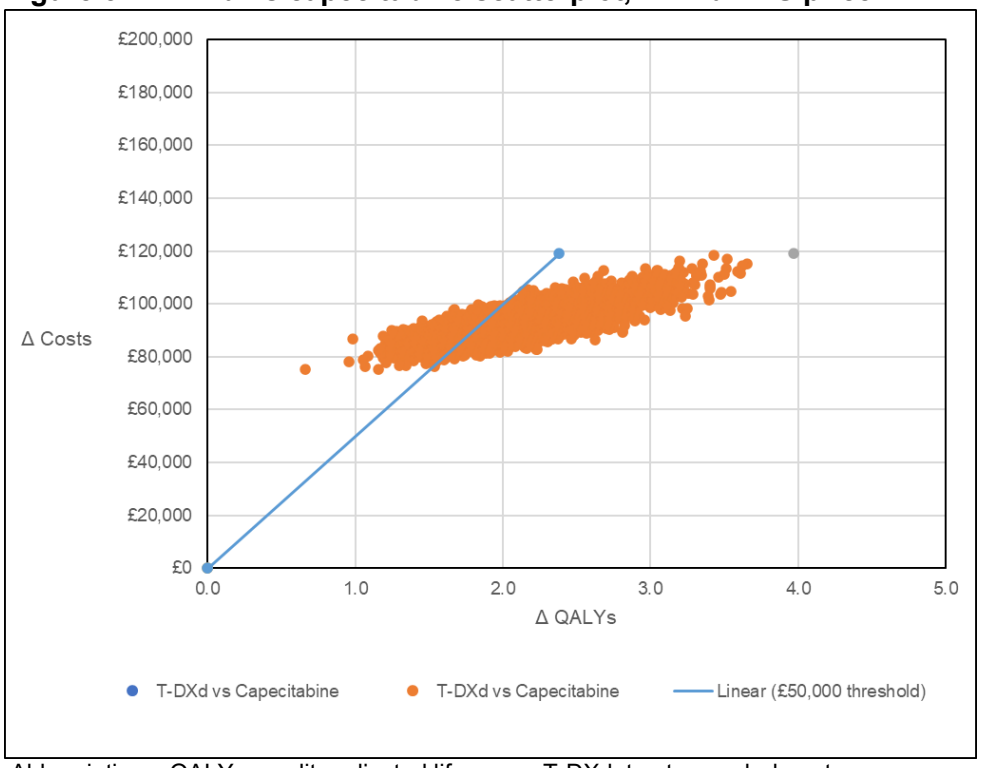
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 51: T-DXd versus eribulin scatterplot, T-DXd PAS price



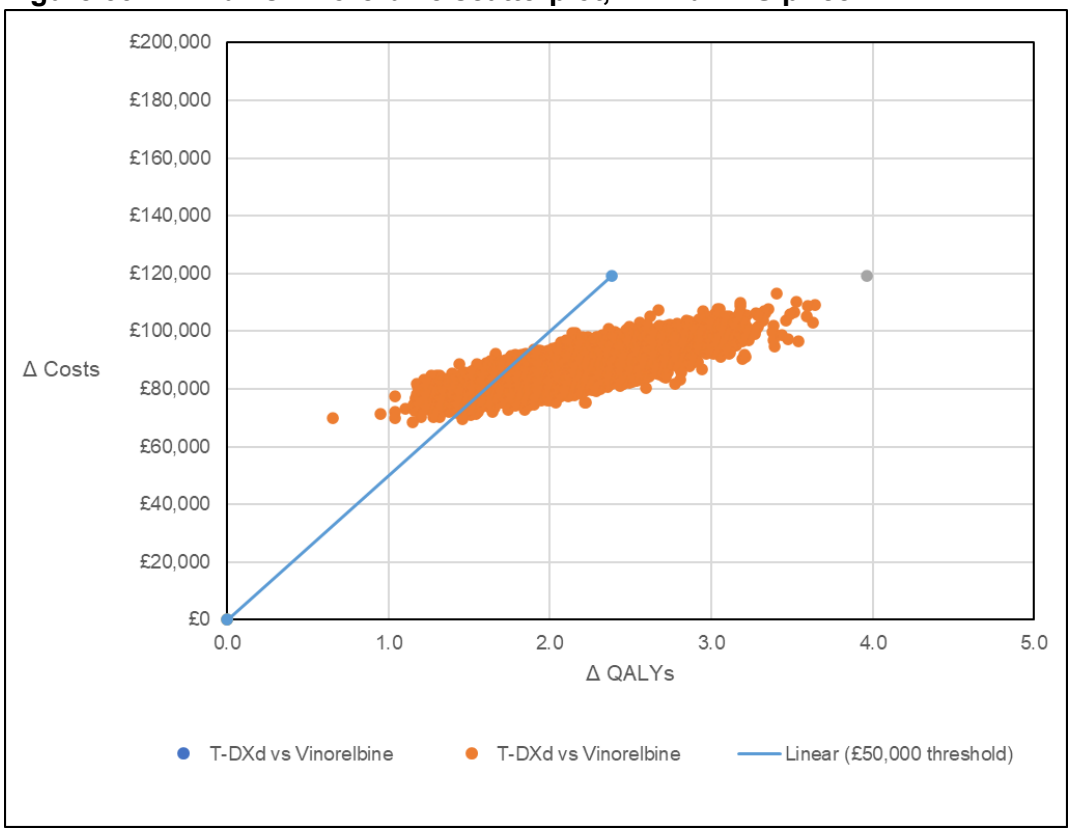
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 52: T-DXd vs capecitabine scatterplot, T-DXd PAS price



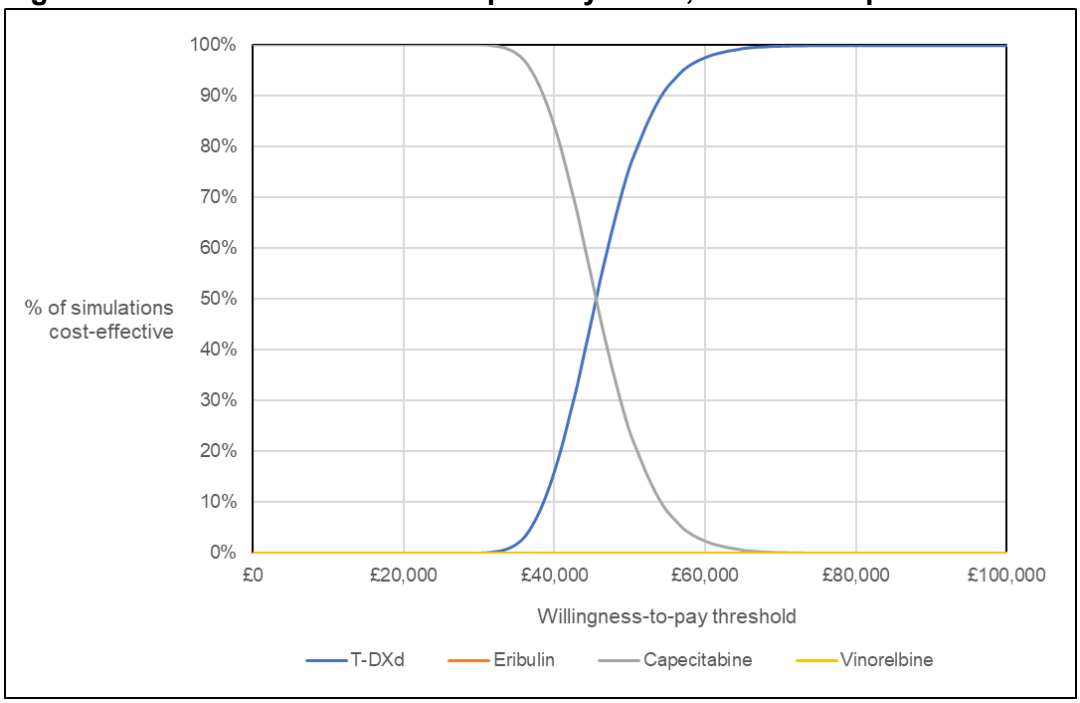
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 53: T-DXd vs vinorelbine scatterplot, T-DXd PAS price



Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 54: Cost-effectiveness acceptability curve, T-DXd PAS price



Abbreviations: T-DXd, trastuzumab deruxtecan.

3.2.6.2. Deterministic sensitivity analysis (addendum to Document B, Section B.3.8.2)

Parameter uncertainty was tested using one-way sensitivity analysis (OWSA), in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±10% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are reported for each pairwise comparison. For each comparator, the most influential parameter was the HR applied to TH3RESA curve to model T-DXd OS. As the survival gains in the T-DXd arm of the model are the primary driver of results in the model, it is to be expected that the OS HR that informs T-DXd survival would have the largest impact on results. Other influential parameters include the HER2-positive efficacy adjustment HR and health state utility values, although the effect of varying these parameters on results is small.

3.2.6.2.1 T-DXd vs eribulin

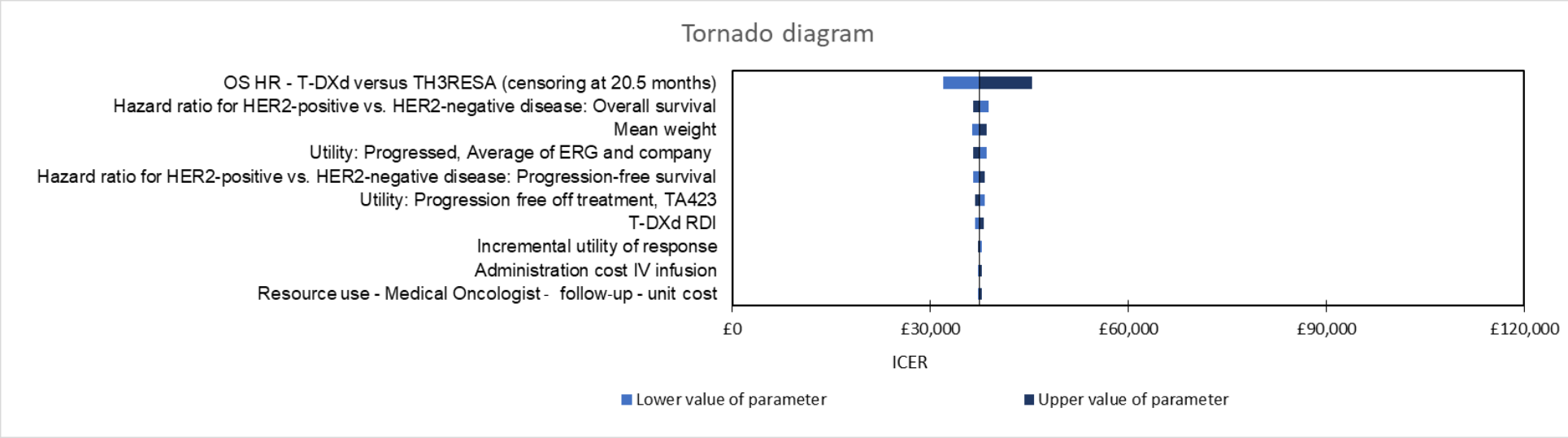
The OWSA results for the comparison of T-DXd vs. eribulin are presented in Table 107; the tornado diagram is presented in Figure 55**Error! Reference source not found.**.

Table 107: OWSA results - T-DXd vs eribulin, T-DXd PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
T-DXd RDI	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Administration cost IV infusion	[redacted]	[redacted]
Resource use - Medical Oncologist - follow-up - unit cost	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan

Figure 55: T-DXd vs Eribulin - OWSA tornado diagram, T-DXd PAS price



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one-way sensitivity analysis; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan

3.2.6.2.2 T-DXd vs capecitabine

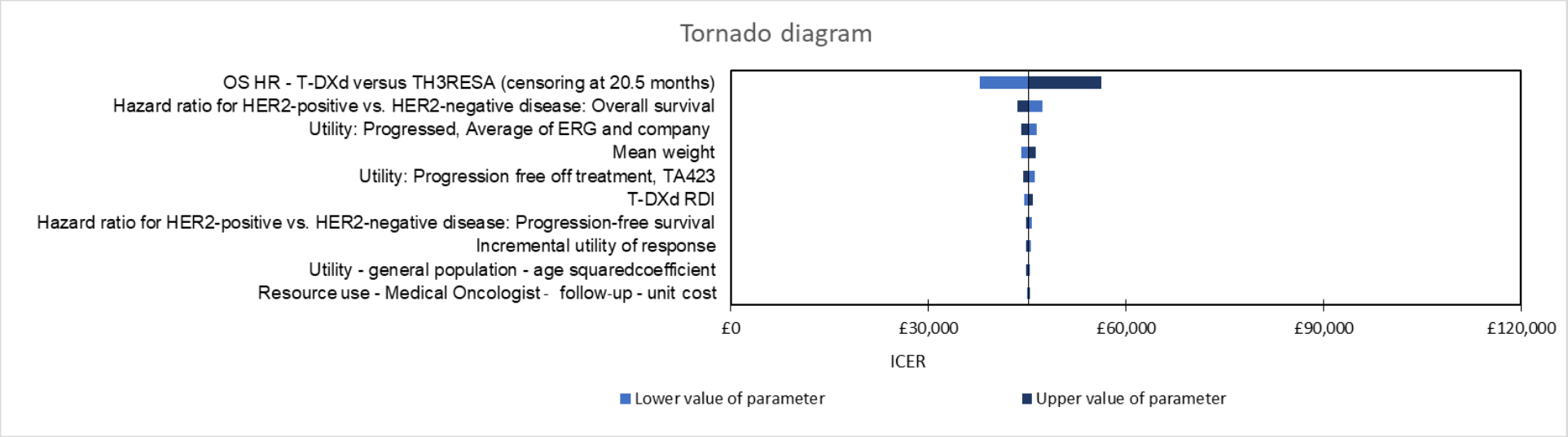
The OWSA results for the comparison of T-DXd vs. capecitabine are presented in Table 108; the tornado diagram is presented in Figure 56.

Table 108: OWSA results - T-DXd vs capecitabine, T-DXd PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
T-DXd RDI	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Utility - general population - age squaredcoefficient	[redacted]	[redacted]
Resource use - Medical Oncologist - follow-up - unit cost	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; RDI; relative dose intensity; T-DXd, trastuzumab deruxtecan

Figure 56: T-DXd vs Capecitabine - OWSA tornado diagram, T-DXd PAS price



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan

3.2.6.2.3 T-DXd vs vinorelbine

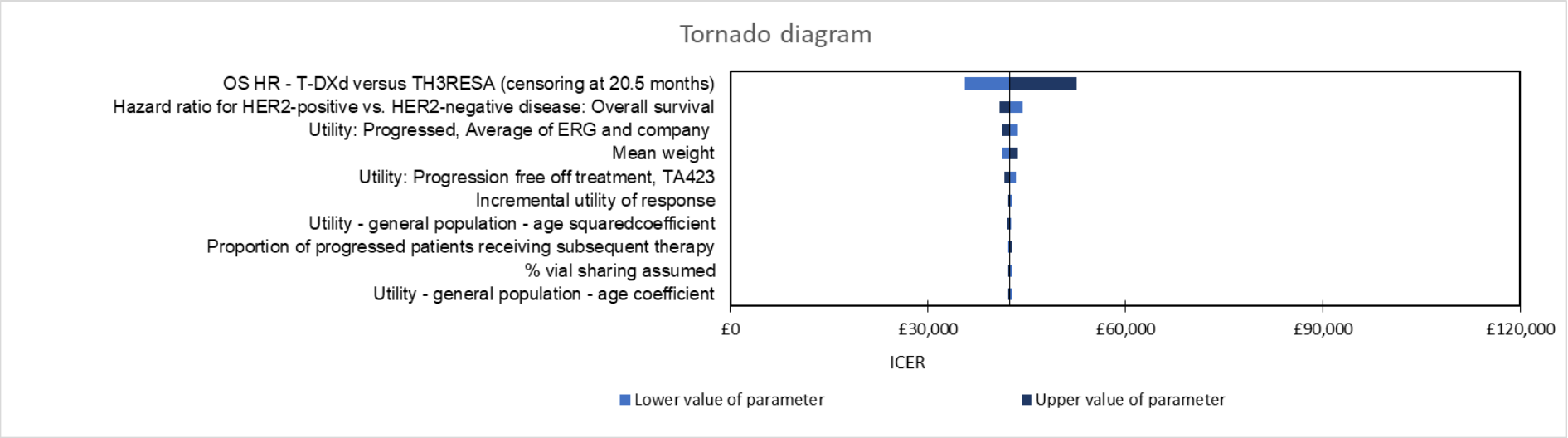
The OWSA results for the comparison of T-DXd vs. vinorelbine are presented in Table 119, and the tornado diagram is presented in Table 109.

Table 109: OWSA results - T-DXd vs Vinorelbine, T-DXd PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Resource use - Medical Oncologist - follow-up - unit cost	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy	[redacted]	[redacted]
% vial sharing assumed	[redacted]	[redacted]
Utility - general population - age coefficient	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan

Figure 57:T-DXd vs Vinorelbine - OWSA tornado diagram, T-DXd PAS price



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan

3.2.6.3. Scenario analysis (addendum to Document B, Section B.3.8.3)

Scenario analyses were performed in which key structural assumptions were varied. For all comparators, the scenarios with the biggest impact on the ICER were modelling T-DXd OS by anchoring to eribulin, or the selection of different distributions for the TH3RESA OS extrapolation. Choosing the log-normal or log-logistic OS distributions decreased the ICER by over 20% in each analysis and choosing the Gompertz distribution increased the ICER by over 20%. Modelling T-DXd OS by using a HR vs. TH3RESA with no additional censoring applied to the T-DXd data also increased the ICER by over 10% when the generalised gamma distribution was selected. The distribution chosen for TTD also had a large impact on the ICER. Choosing the Weibull and Gompertz distribution decreased the ICER by over 10% and choosing the log-logistic and generalised gamma distributions increased the ICER. Other influential scenarios included choosing different baseline survival curve sources for each comparator.

3.2.6.3.1 T-DXd vs eribulin

Scenario analyses for the analysis vs. eribulin are presented in Table 110. Comparing against eribulin data in the HER2-positive population from the Barni 2019 study still resulted in an ICER below £50,000 per QALY.

Table 110: T-DXd vs eribulin - scenario analysis , T-DXd PAS price

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin (Cortes 2011, no censoring)	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using EMBRACE - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Barni - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Eribulin OS: Using Barni - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Cortes 2010 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin OS: Using Gamucci 2014 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

3.2.6.3.2 T-DXd vs capecitabine

Scenario analyses for the analysis vs. capecitabine are presented in Table 111.

Table 111: T-DXd vs capecitabine - scenario analysis, T-DXd PAS price

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

3.2.6.3.3 T-DXd vs vinorelbine

Scenario analyses for the analysis vs. vinorelbine are presented in Table 112.

Table 112: T-DXd vs vinorelbine - scenario analysis, T-DXd PAS price

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Cap OS: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap OS: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PAS, patient access scheme; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

3.2.7. Summary of base-case results and sensitivity analysis

When the proposed PAS for T-DXd is applied, T-DXd is associated with a base-case ICER of £45,216. Given that end-of-life criteria are expected to apply, T-DXd may be considered a cost-effective use of NHS resources. The approach taken to model T-DXd in the base-case was informed by clinical expert opinion and aims to more accurately model OS in a HER2-targeted therapy.

The results of sensitivity analyses demonstrate that in all cases T-DXd is expected to provide a significant increase in QALYs vs. each comparator.

Deterministic analyses showed that the most influential parameter was the HR for T-DXd vs. TH3RESA that defined the survival extrapolations in OS; this is to be expected as the cost-effectiveness results are primarily driven by survival gains. Beyond this parameter, the impact of varying other parameters in the model was small.

Scenario analyses showed that the parameter with the most influence on the ICER was the distribution chosen to model TH3RESA OS. Other key assumptions were the distribution used to model TTD for T-DXd, the source of comparator efficacy data and the HR used vs. TH3RESA.

Only six of the 40 scenarios considered comparing T-DXd vs. capecitabine resulted in an ICER higher than £50,000 per QALY; only one of

these scenarios resulted in an ICER higher than £60,000 per QALY. In the base-case, a comparison against each comparator in a strictly HER2-positive patient population could not be made. However, a scenario is presented comparing T-DXd vs. eribulin using data from Barni et al., which presents data on a 100% HER2-positive population, resulting in an ICER of £41,414.

Probabilistic analysis indicated that there is a [redacted] likelihood of T-DXd being cost-effective at a willingness to pay threshold of £50,000 per QALY.

3.2.8. Base-case results, list price (addendum to Document B, Section B.3.7)

3.2.8.1. Base-case incremental cost-effectiveness analysis results, list price (addendum to Document B, Section B.3.7.1)

A confidential PAS has been agreed for T-DXd, and therefore the results presented in this section are indicative and do not represent the true cost-effectiveness results for T-DXd.

3.2.8.1.1 Primary analysis

In the primary analysis (in which OS data are censored at 20.5 months), eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the primary analysis, fully incremental results is presented in Table 113.

Table 113: Primary analysis results (censoring T-DXd OS at 20.5 months), T-DXdlist price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

3.2.8.1.2 Secondary analysis

Secondary analyses are considered in which the full OS Kaplan-Meier data for T-DXd are used, assuming each of the exponential and generalised gamma distributions. Due to the high level of censoring from 20.5 months, the Kaplan Meier data from this point onwards is not considered to be informative. Therefore, this analysis is expected to be a conservative estimate of the cost-effectiveness of T-DXd and it is proposed that the primary analysis is used for decision making purposes.

In the secondary analysis (in which all available OS data are used), assuming a generalised gamma distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented in Table 114. Due to the high level of censoring from 20.5 months OS, the Kaplan Meier data is not informative. Therefore, this analysis is expected to be a conservative estimate of cost-effectiveness.

Table 114: Secondary analysis results (full use of K-M data), T-DXd OS distribution: generalised gamma (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the secondary analysis, assuming an exponential distribution for T-DXd OS, eribulin is found to be dominated and vinorelbine is extendedly dominated. T-DXd is associated with incremental costs of [redacted] and [redacted] incremental QALYs compared with capecitabine, resulting in an ICER of [redacted] per QALY gained. A summary of the fully incremental results is presented in Table 115.

Table 115: Secondary analysis results (full use of K-M data), T-DXd OS distribution: exponential (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

3.2.9. Sensitivity analyses (addendum to Document B, Section B.3.8)

3.2.9.1. Probabilistic sensitivity analysis, list price (addendum to Document B, Section B.3.8.1)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

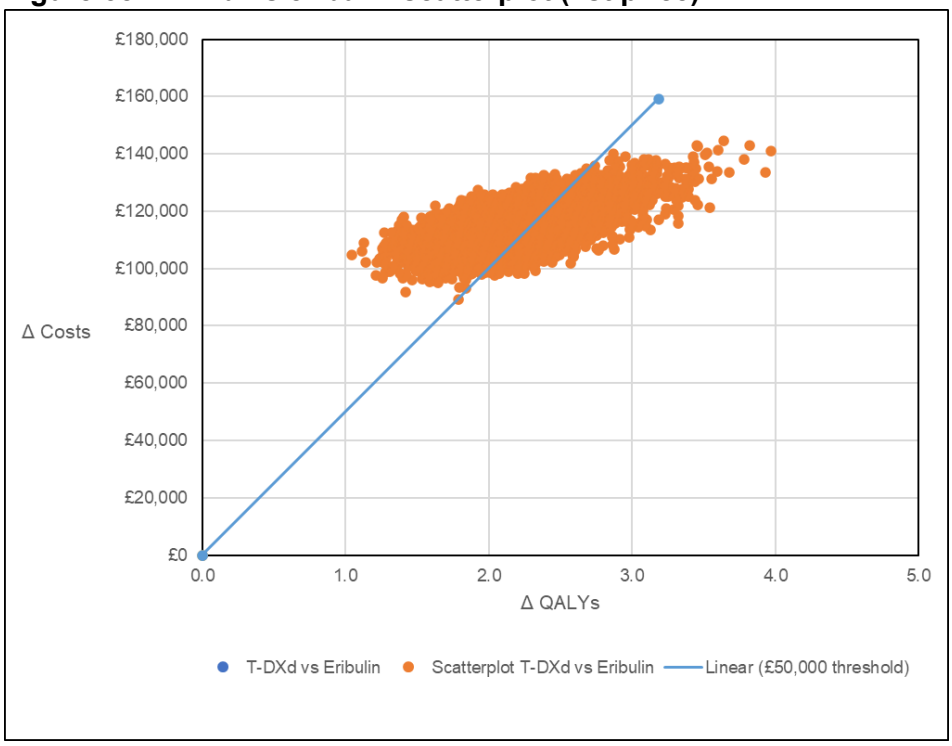
The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted] compared with capecitabine, giving a probabilistic ICER of [redacted] This is highly congruent with deterministic changes in costs of [redacted] and QALYs of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of [redacted] per QALY was [redacted]. A summary of the probabilistic, fully incremental results is presented in Table 116. The cost-effectiveness plane vs. each comparator and CEAC are presented in Figure 58, Figure 59, Figure 60 and Figure 61.

Table 116: PSA results (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

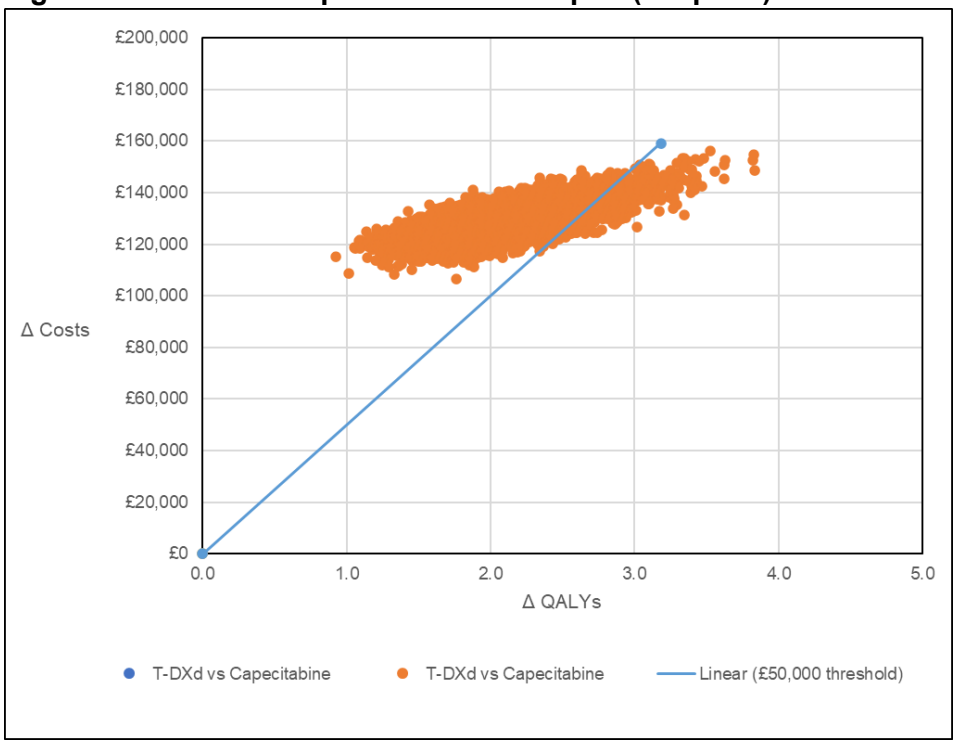
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 58: T-DXd vs eribulin scatterplot (list price)



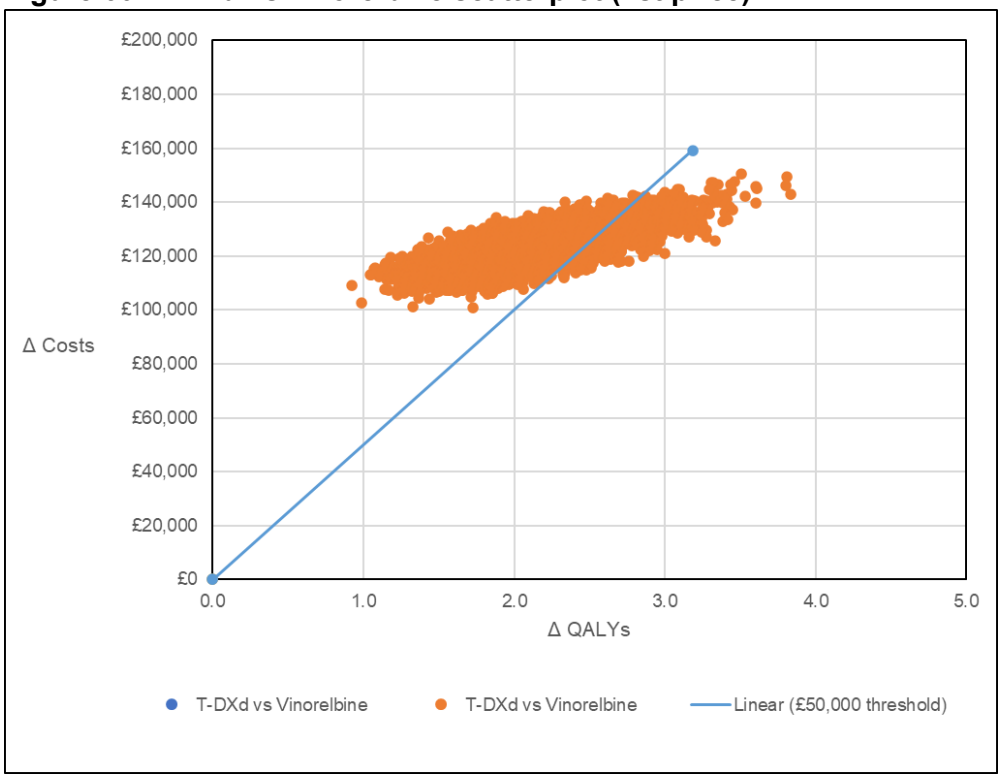
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 59: T-DXd vs capecitabine scatterplot (list price)



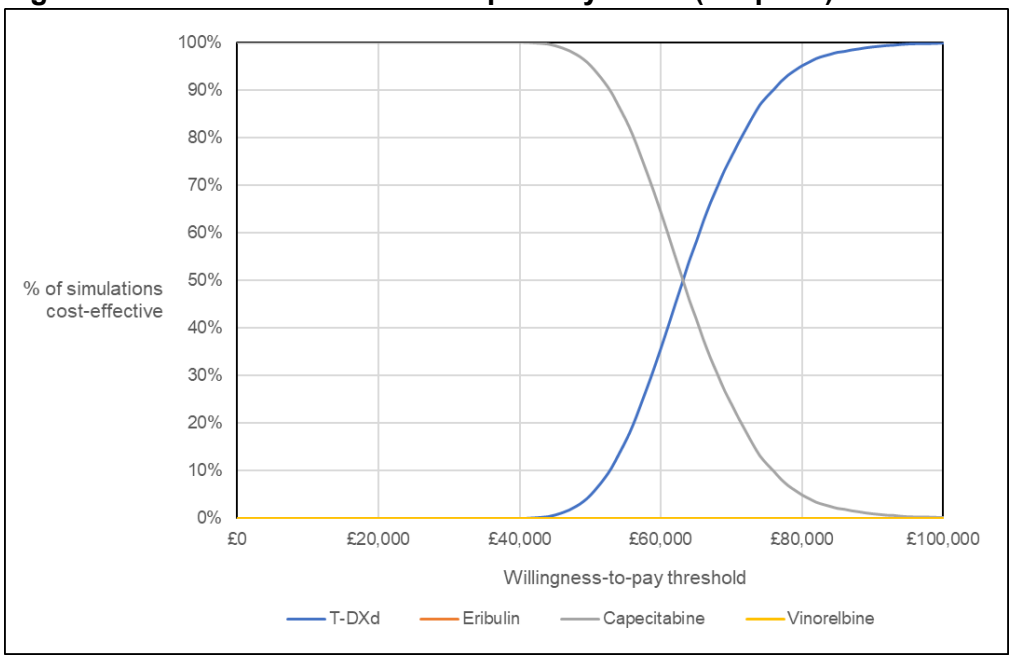
Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 60: T-DXd vs vinorelbine scatterplot (list price)



Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 61: Cost-effectiveness acceptability curve (list price)



Abbreviations: T-DXd, trastuzumab deruxtecan.

3.2.9.2. Deterministic sensitivity analysis, list price (addendum to Document B, Section B.3.8.2)

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±10% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram. All deterministic sensitivity analyses were conducted from the primary analysis.

Results for the 10 most influential parameters are reported for each pairwise comparison. For each comparator, the most influential parameter was the HR applied to TH3RESA curve to model T-DXd OS. As the survival gains in the T-DXd arm of the model are the primary driver of results in the model, it is to be expected that the OS HR that informs T-DXd survival would have the largest impact on results. Other influential parameters include the HER2-positive efficacy adjustment HR and health state utility values, although the effect of varying these parameters on results is small.

3.2.9.2.1 T-DXd vs eribulin, list price (addendum to Document B, Section B.3.8.2.1)

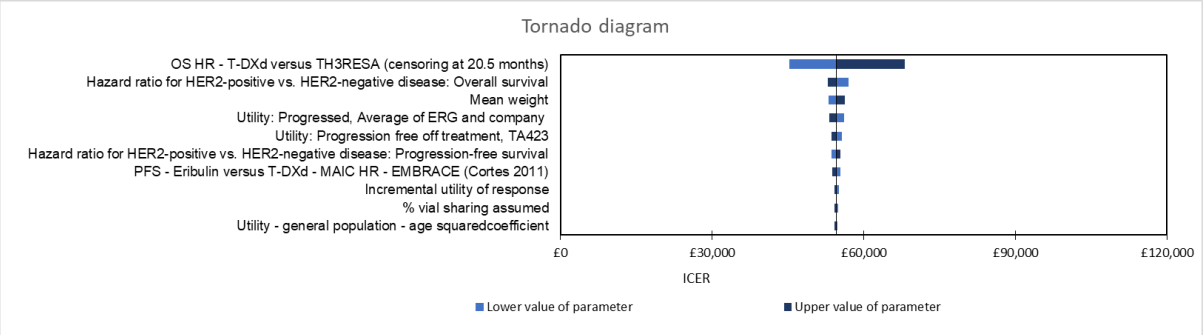
The OWSA results for the comparison of T-DXd vs. eribulin are presented in Table 117; the tornado diagram is presented in Figure 62.

Table 117: OWSA results - T-DXd vs eribulin (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: OS	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: PFS	[redacted]	[redacted]
PFS - Eribulin versus T-DXd - MAIC HR - EMBRACE (Cortes 2011)	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
% vial sharing assumed	[redacted]	[redacted]
Utility - general population - age squared coefficient	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival, OWSA; one-way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan, IV; intravenous

Figure 62: T-DXd vs eribulin - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS; overall survival, OWSA, one-way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan, IV; intravenous

3.2.9.2.2 T-DXd vs capecitabine, list price (addendum to Document B, Section B.3.8.2.2)

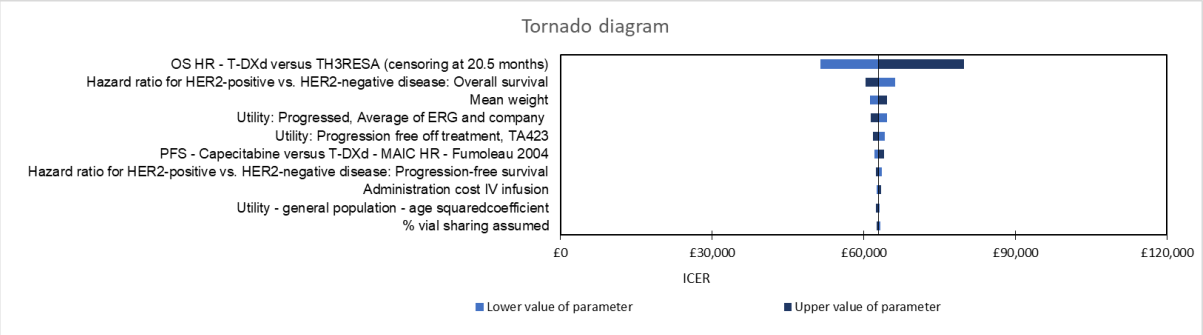
The OWSA results for the comparison of T-DXd vs. capecitabine are presented in Table 118; the tornado diagram is presented in Figure 63.

Table 118: OWSA results - T-DXd vs capecitabine (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: OS	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
PFS - Capecitabine versus T-DXd - MAIC HR - Fumoleau 2004	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: PFS	[redacted]	[redacted]
Administration cost IV infusion	[redacted]	[redacted]
Utility - general population - age squared coefficient	[redacted]	[redacted]
% vial sharing assumed	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan

Figure 63: T-DXd vs capecitabine - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; PFS; progression-free survival, RDI; relative dose intensity,T-DXd, trastuzumab deruxtecan

3.2.9.2.3 T-DXd vs vinorelbine, list price (addendum to Document B, Section B.3.8.2.3)

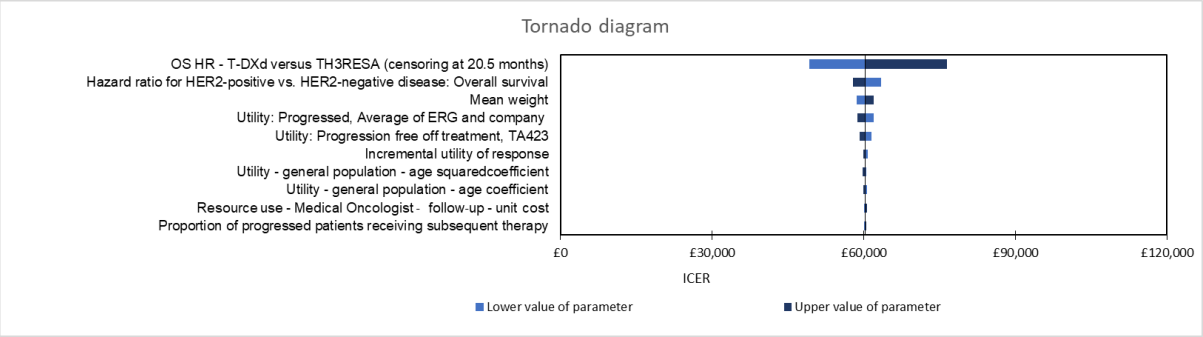
The OWSA results for the comparison of T-DXd vs. vinorelbine are presented in Table 119, and the tornado diagram is presented in Figure 64.

Table 119: OWSA results - T-DXd vs vinorelbine (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	[redacted]	[redacted]
Hazard ratio for HER2-positive vs. HER2-negative disease: OS	[redacted]	[redacted]
Mean weight	[redacted]	[redacted]
Utility: Progressed, Average of ERG and company	[redacted]	[redacted]
Utility: Progression free off treatment, TA423	[redacted]	[redacted]
Incremental utility of response	[redacted]	[redacted]
Utility - general population - age squared coefficient	[redacted]	[redacted]
Utility - general population - age coefficient	[redacted]	[redacted]
Resource use - Medical Oncologist - follow-up - unit cost	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy	[redacted]	[redacted]

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan

Figure 64: T-DXd vs vinorelbine - OWSA tornado diagram (list price)



Abbreviations: ERG; evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one-way sensitivity analysis; RDI; relative dose intensity, T-DXd, trastuzumab deruxtecan

3.2.9.3. Scenario analysis, list price (addendum to Document B, Section B.3.8.3)

Scenario analyses were performed in which key structural assumptions were varied. All scenario analyses were conducted from the primary analysis. For all comparators, modelling T-DXd by anchoring to eribulin had a significant effect and increased the ICER by over 30%. Modelling T-DXd OS based on a HR vs. T-DM1 generated using no censoring increased the ICER by over 20% vs. all comparators when the generalised gamma distribution was selected. Also, the selection of different distributions for the TH3RESA OS extrapolation, choosing the log-normal or log-logistic distributions decreased the ICER by over 20% in each analysis, and choosing the Gompertz distribution increased the ICER by over 20%. The distribution chosen for TTD also had a large impact on the ICER. Choosing the Weibull and Gompertz distribution decreased the ICER by over 10% and choosing the log-logistic and generalised gamma distributions increased the ICER. Other influential scenarios included choosing different baseline survival curve sources for each comparator.

3.2.9.3.1 T-DXd vs Eribulin, list price (addendum to Document B, Section B.3.8.3.1)

Scenario analyses for the analysis vs. eribulin are presented in Table 120.

Table 120: T-DXd vs eribulin - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Eribulin: Using EMBRACE - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using EMBRACE - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using EMBRACE - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using EMBRACE - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using EMBRACE - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Barni - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Cortes 2010 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Gamucci 2014 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Gamucci 2014 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Gamucci 2014 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Eribulin: Using Gamucci 2014 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Gamucci 2014 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin: Using Gamucci 2014 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

3.2.9.3.2 T-DXd vs capecitabine, list price (addendum to Document B, Section B.3.8.2.3)

Scenario analyses for the analysis vs. capecitabine are presented in Table 121.

Table 121: T-DXd vs capecitabine - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Cap: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

†Note that in the PSA, the incremental costs are rounded to two decimal places, and therefore the base case ICER can differ slightly from that of the base case results in the model.

T-DXd vs vinorelbine, list price (addendum to Document B, Section B.3.8.3.3)

Scenario analyses for the analysis vs. vinorelbine are presented in Table 122.

Table 122: T-DXd vs vinorelbine - scenario analysis (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
No discounting	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	[redacted]	[redacted]
OS: Anchoring to eribulin	[redacted]	[redacted]	[redacted]	[redacted]
No HER2 adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progression free - equal to Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 company value	[redacted]	[redacted]	[redacted]	[redacted]
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - Le et al	[redacted]	[redacted]	[redacted]	[redacted]
Utility - progressed - TA423 ERG	[redacted]	[redacted]	[redacted]	[redacted]
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	[redacted]	[redacted]
No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	[redacted]	[redacted]
No age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Cap: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Cap: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using gompertz distribution	[redacted]	[redacted]	[redacted]	[redacted]
TH3RESA: Using weibull distribution	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - exponential	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - weibull	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; cap, capecitabine; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

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5. Addenda to Appendices

5.1. Addendum to Appendix D: Identification, selection and synthesis of clinical evidence

Appendix D has been updated to reflect OS, PFS and response data from the June 2020 data cut for DESTINY-Breast01.

Model diagnostics for the 7 MAIC analyses

Model diagnostics for all MAIC analyses are presented in Figure 65 to Figure 101. For each included study, the following diagnostics are presented:

- Histogram of rescaled weights
- Bootstrapped hazard ratios for OS
- Schoenfeld residuals for proportional hazards assumption for OS
- Bootstrapped hazard ratios for PFS
- Schoenfeld residuals for proportional hazards assumption for PFS

Figure 65: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Eribulin (Barni 2019)

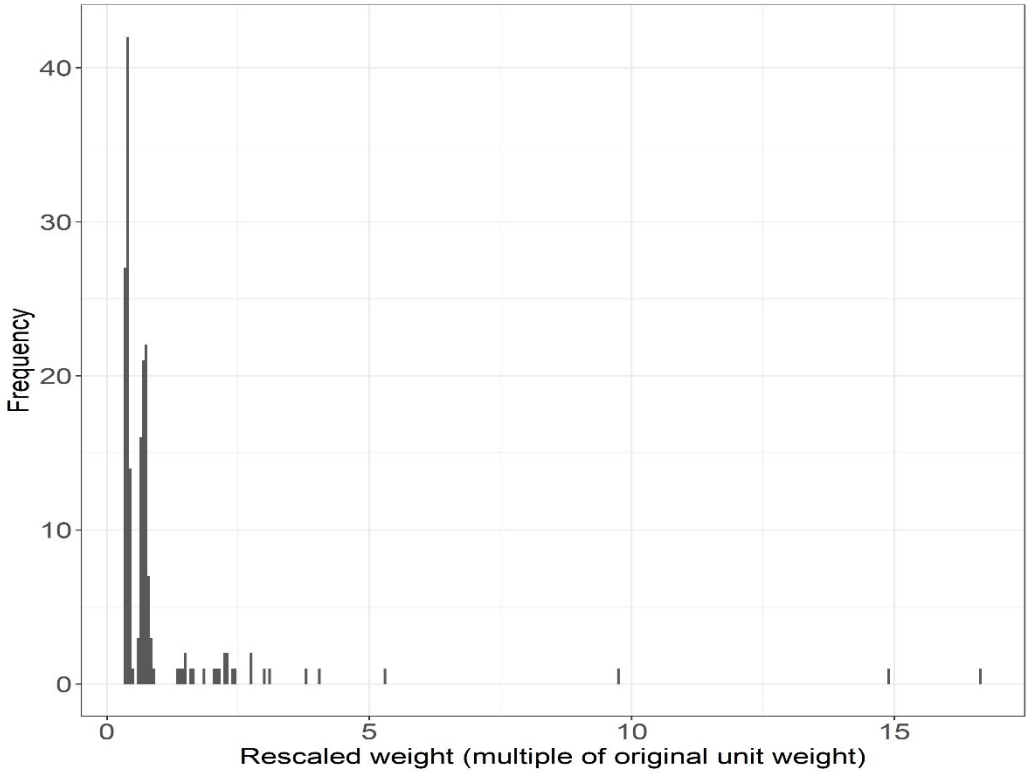


Figure 66: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Barni 2019)

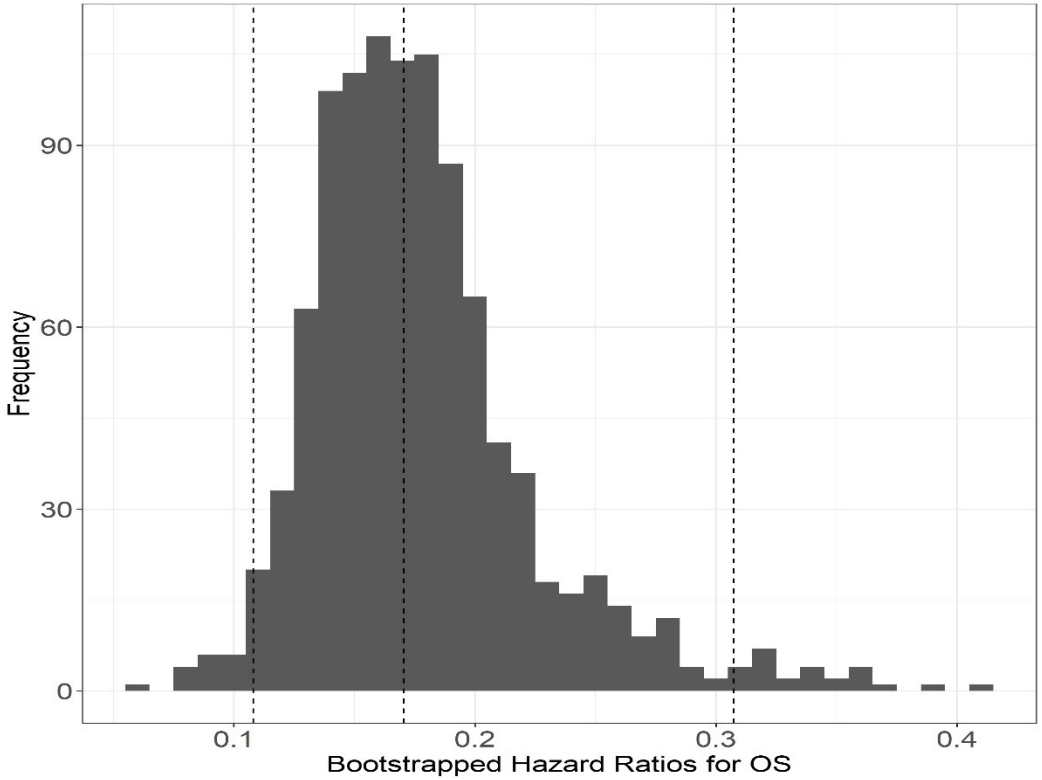


Figure 67: Schoenfeld residuals for PH assumption for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Barni 2019)

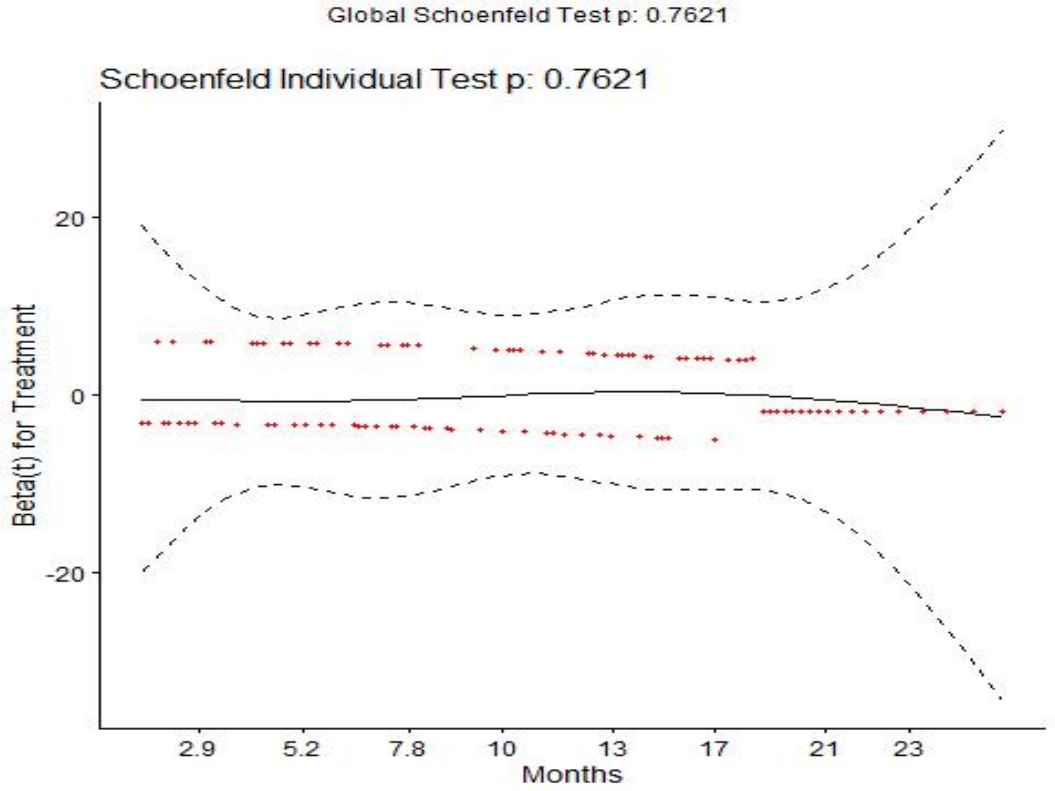


Figure 68: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Barni 2019)

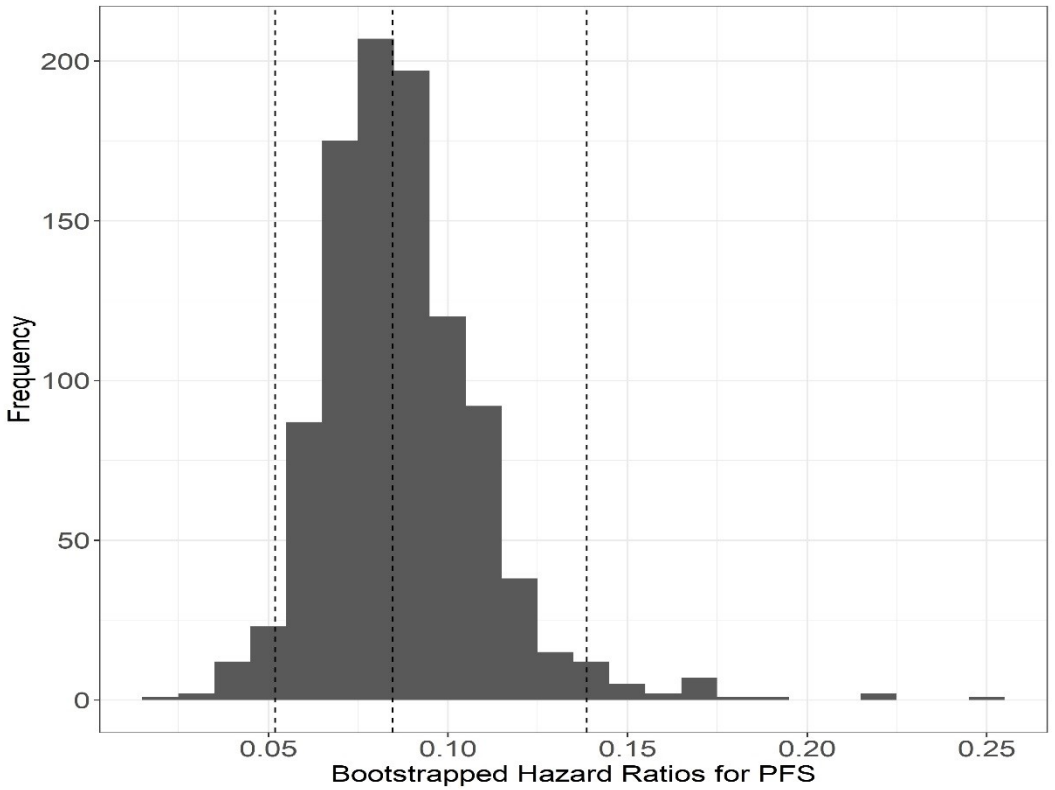


Figure 69: Schoenfeld residuals for PH assumption for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Barni 2019)

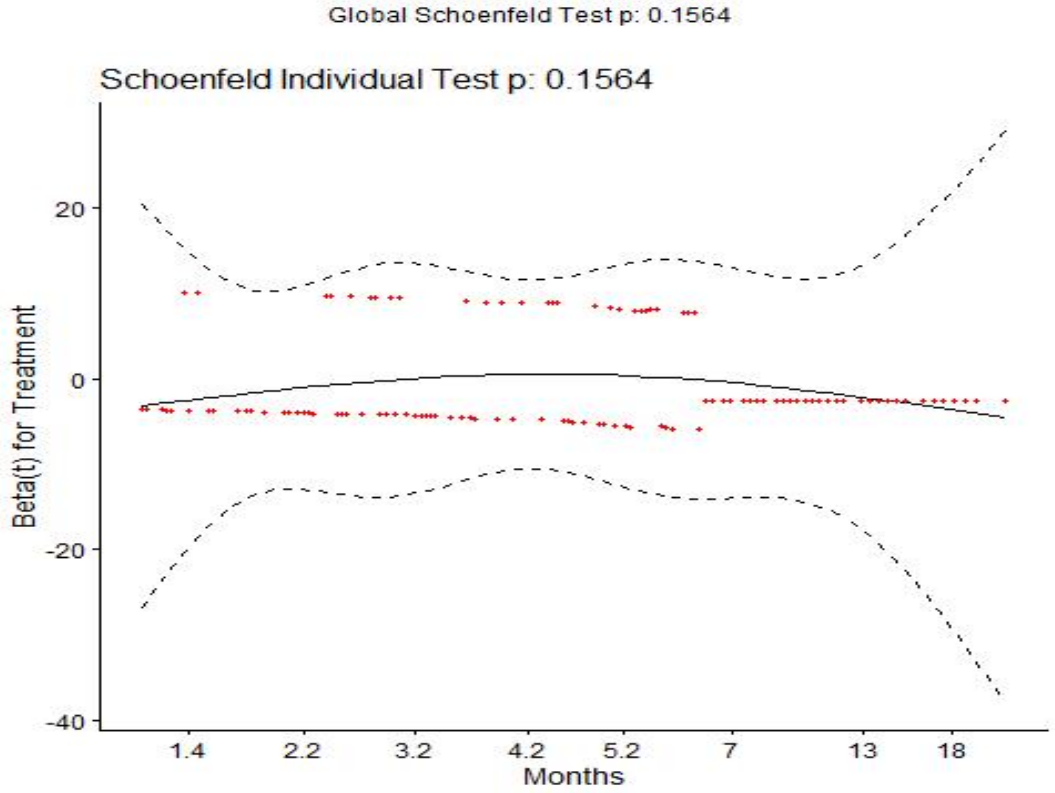


Figure 70: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2010)

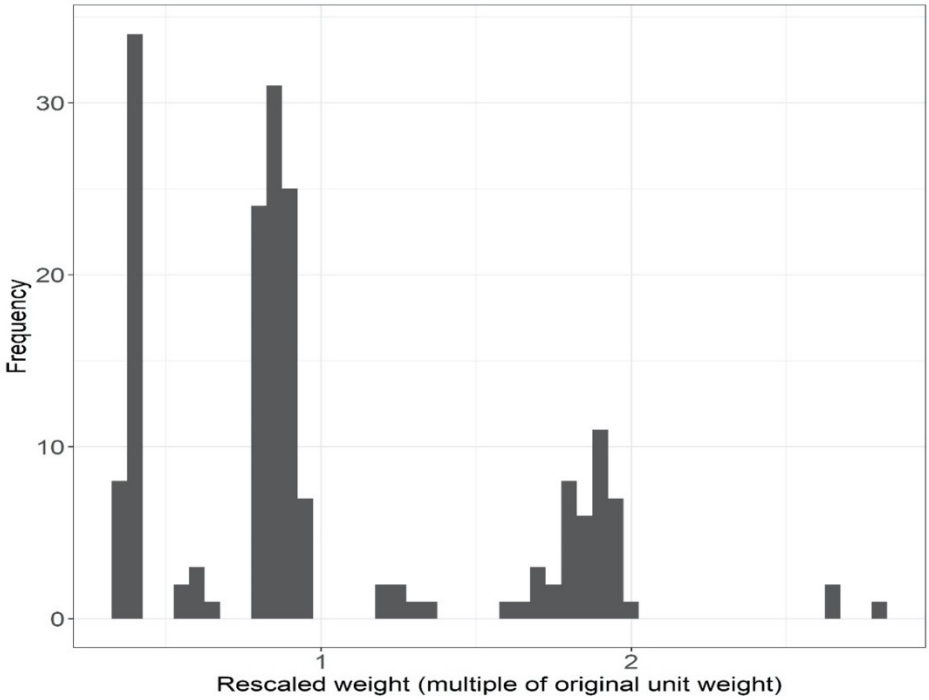


Figure 71: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2010)

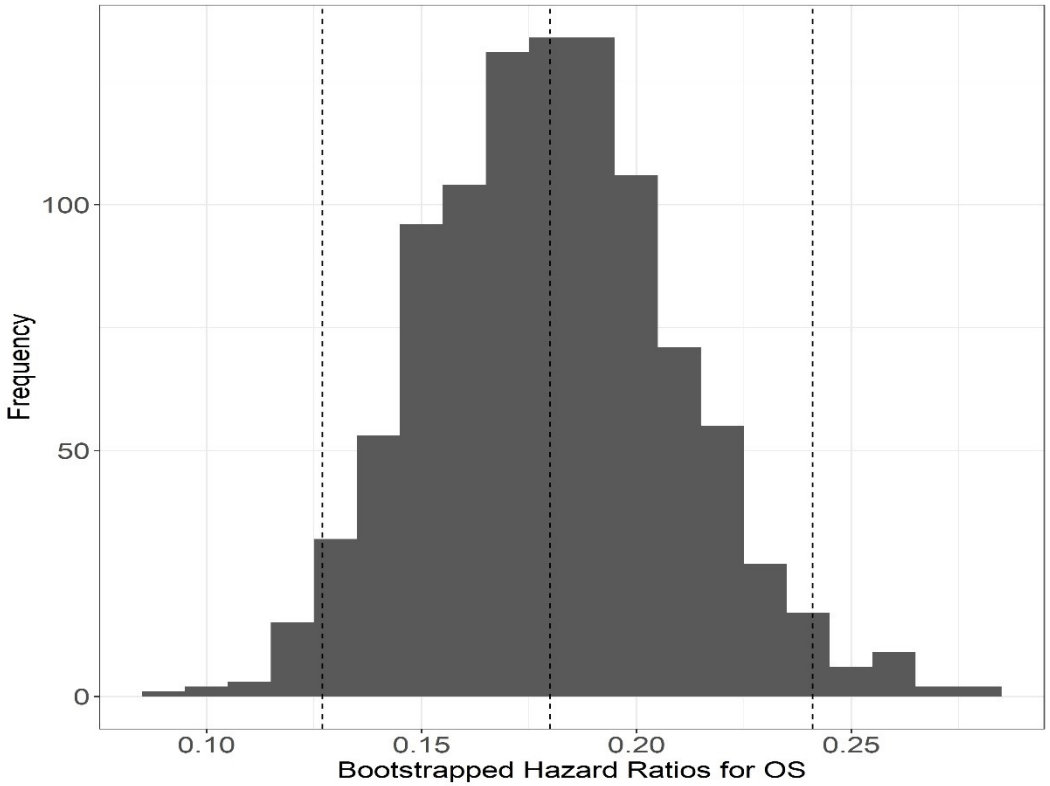


Figure 72: Schoenfeld residuals for PH assumption for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2010)

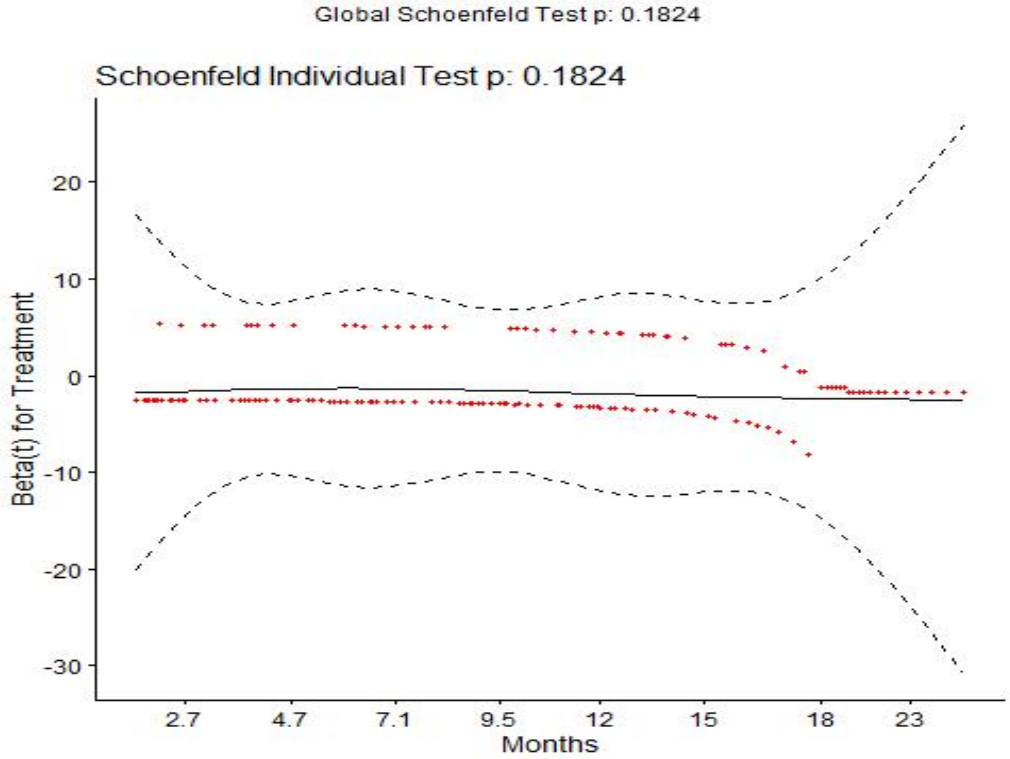


Figure 73: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2010)

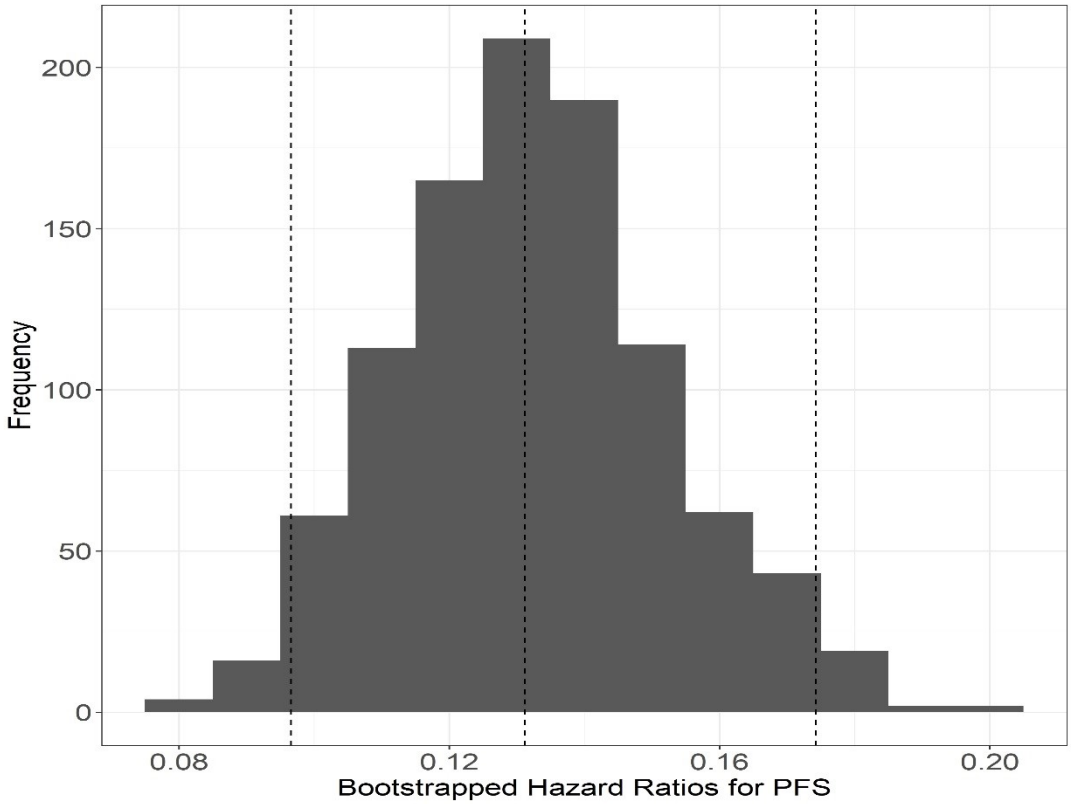


Figure 74: Schoenfeld residuals for PH assumption for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2010)

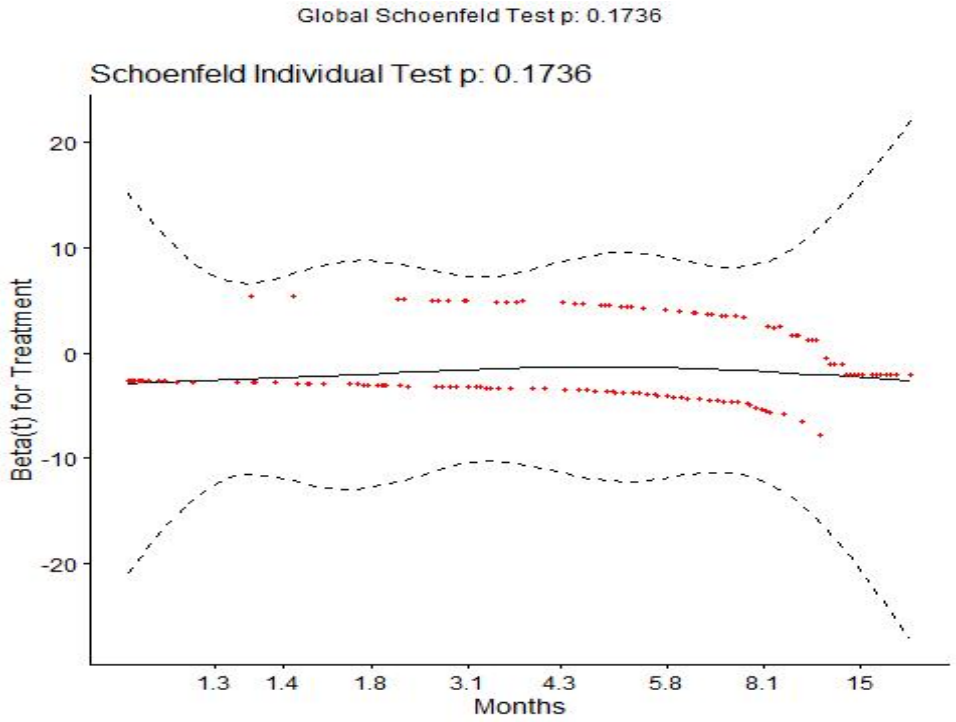


Figure 75: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Capecitabine (Fumoleau 2004)

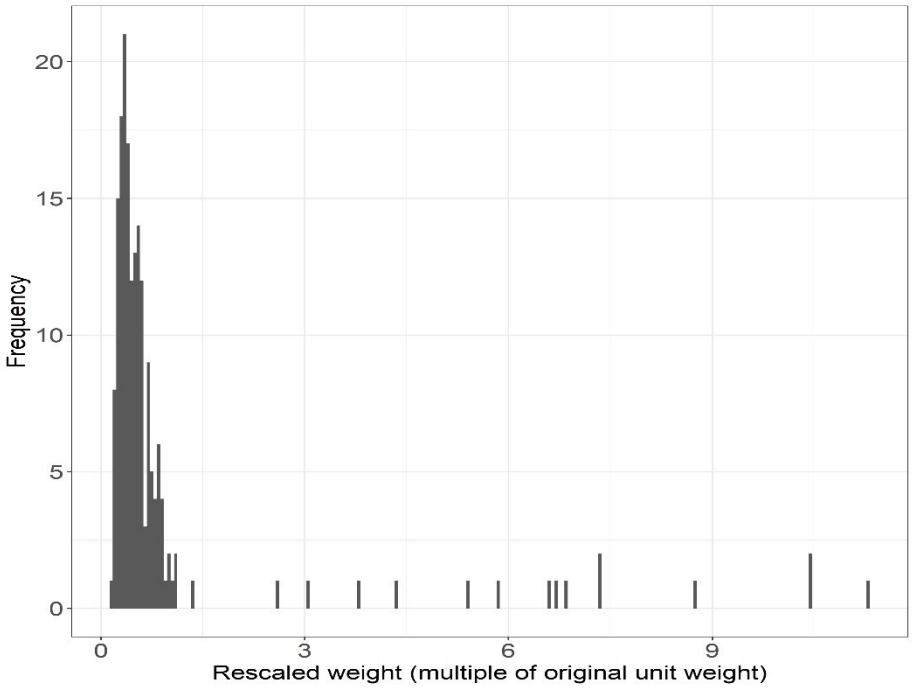
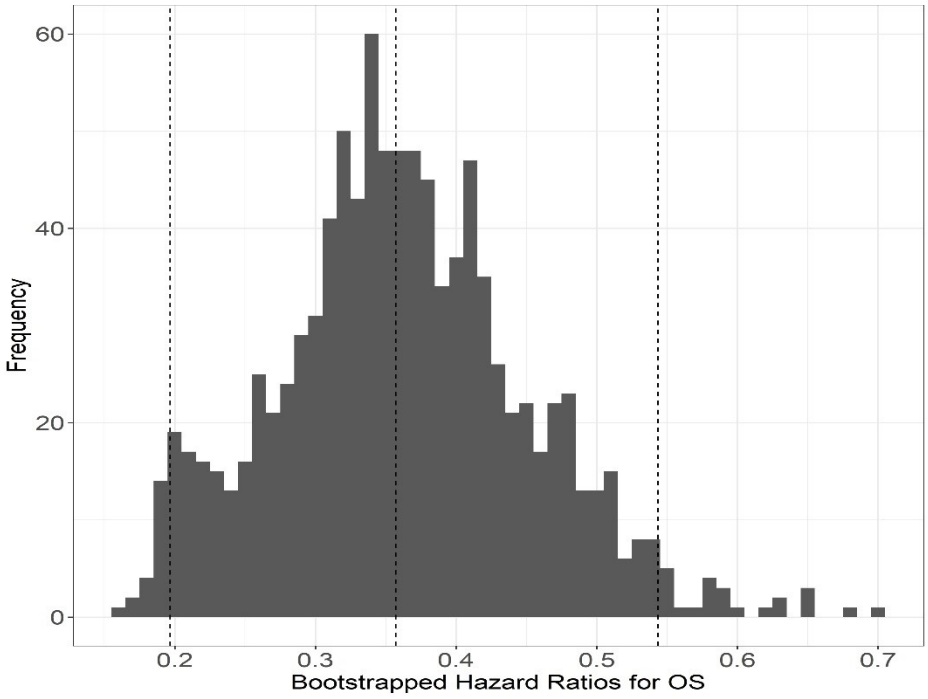


Figure 76: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Capecitabine (Fumoleau 2004)†



†For the MAIC comparison between DESTINY-Breast01 and data from Fumoleau 2004, it was only possible to match on three of the confounding characteristics (age; ECOG-PS; prior lines ≥3), yet the ESS was small at ~40 due to the differences between the trials, in particular the proportion of patients receiving ≥3 prior lines was <50% in Fumoleau compared with 91.8% in DESTINY-Breast01. For this comparison there may be other confounding factors that could not be adjusted for based on the lack of published data for the Fumoleau study, and thus the assumption on which the unanchored comparison is formed, that all prognostic variables and effect modifiers are accounted for, may be implausible in this analysis.

Figure 77: Schoenfeld residuals for PH assumption for OS - T-DXd (DESTINY-Breast01) vs Capecitabine (Fumoleau 2004)

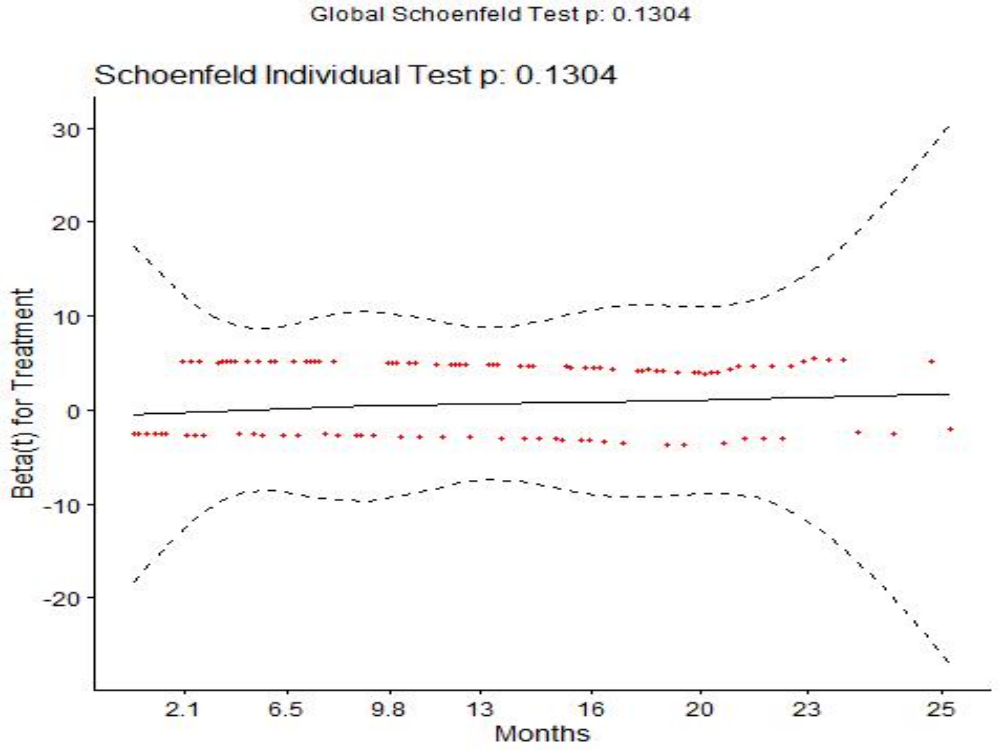


Figure 78: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Capecitabine (Fumoleau 2004)

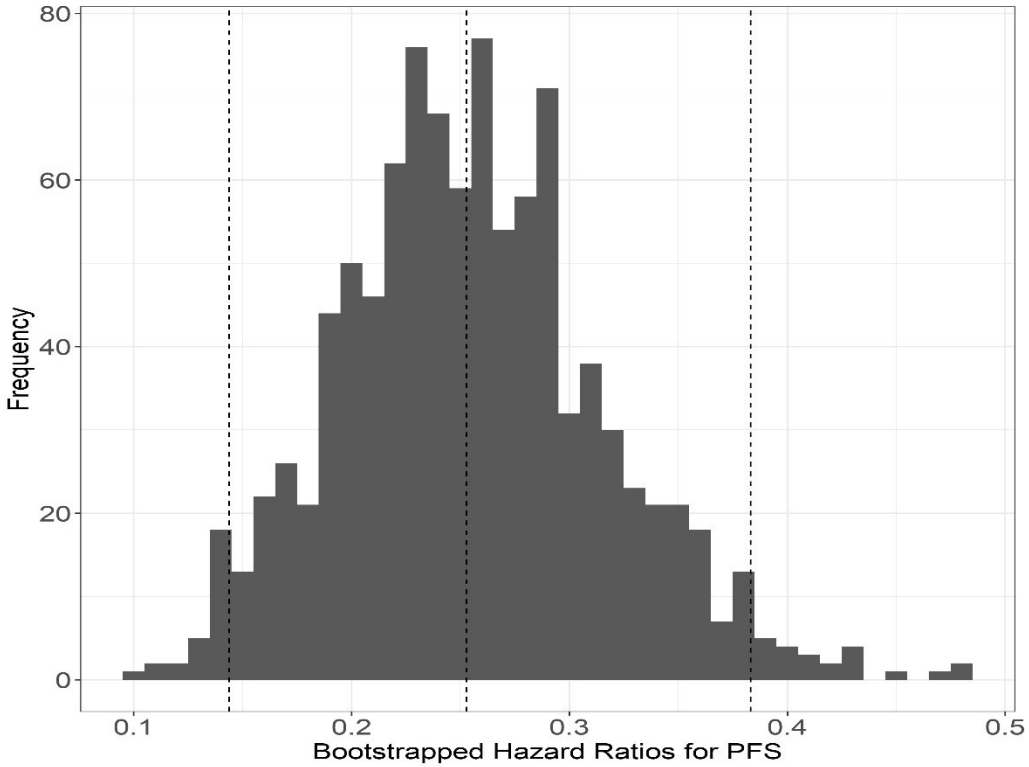


Figure 79: Schoenfeld residuals for PH assumption for PFS - T-DXd (Destiny Breast 01) vs Capecitabine (Fumoleau 2004)

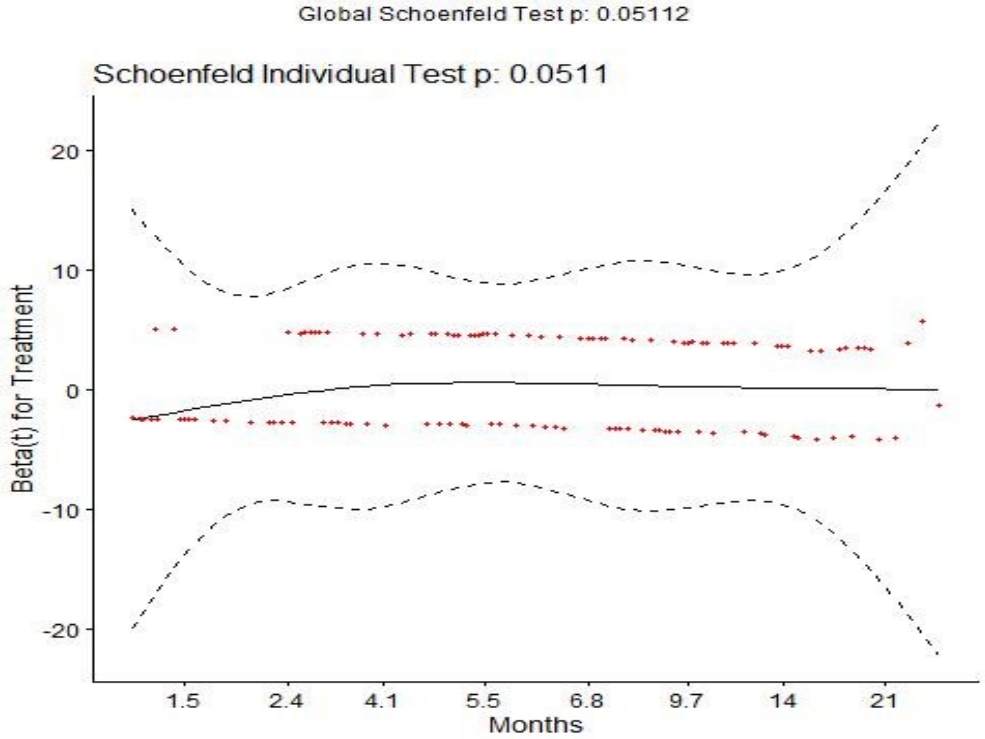


Figure 80: Histogram rescaled weights - T-Dxd (DESTINY-Breast01) vs Vinorelbine (Sim 2019)

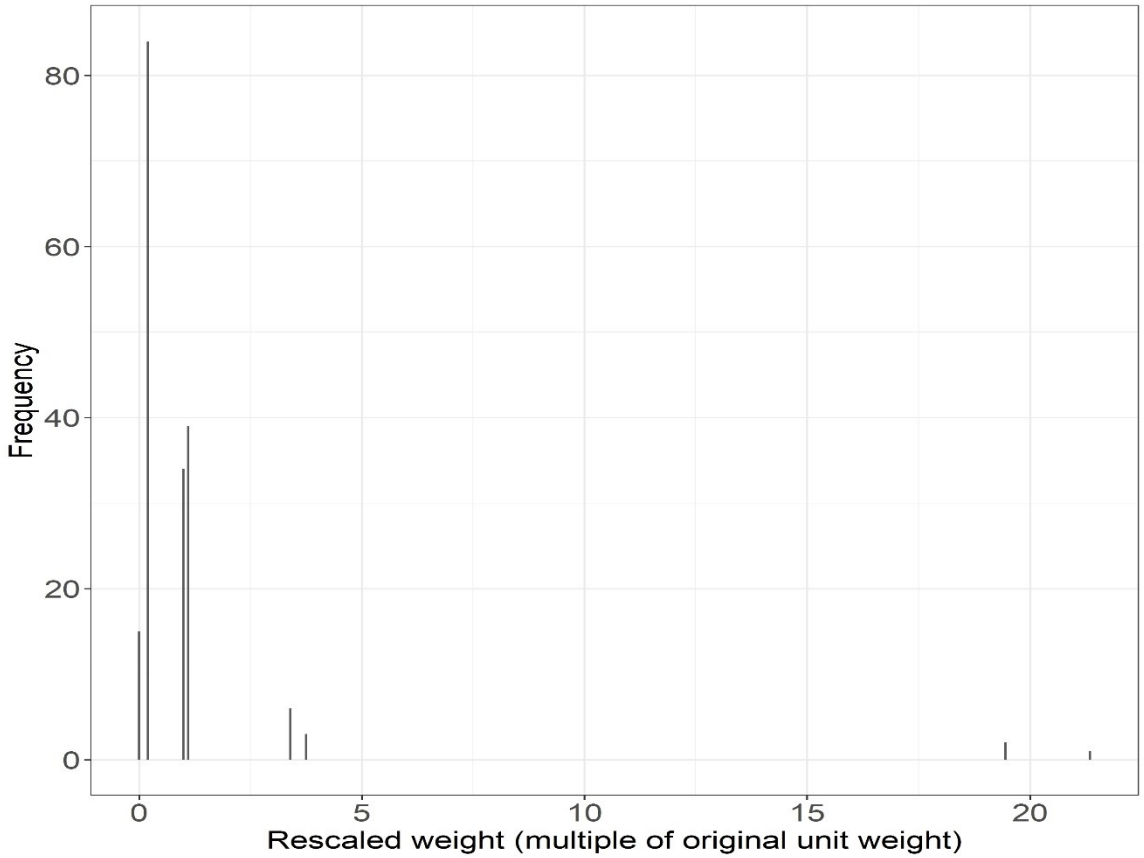
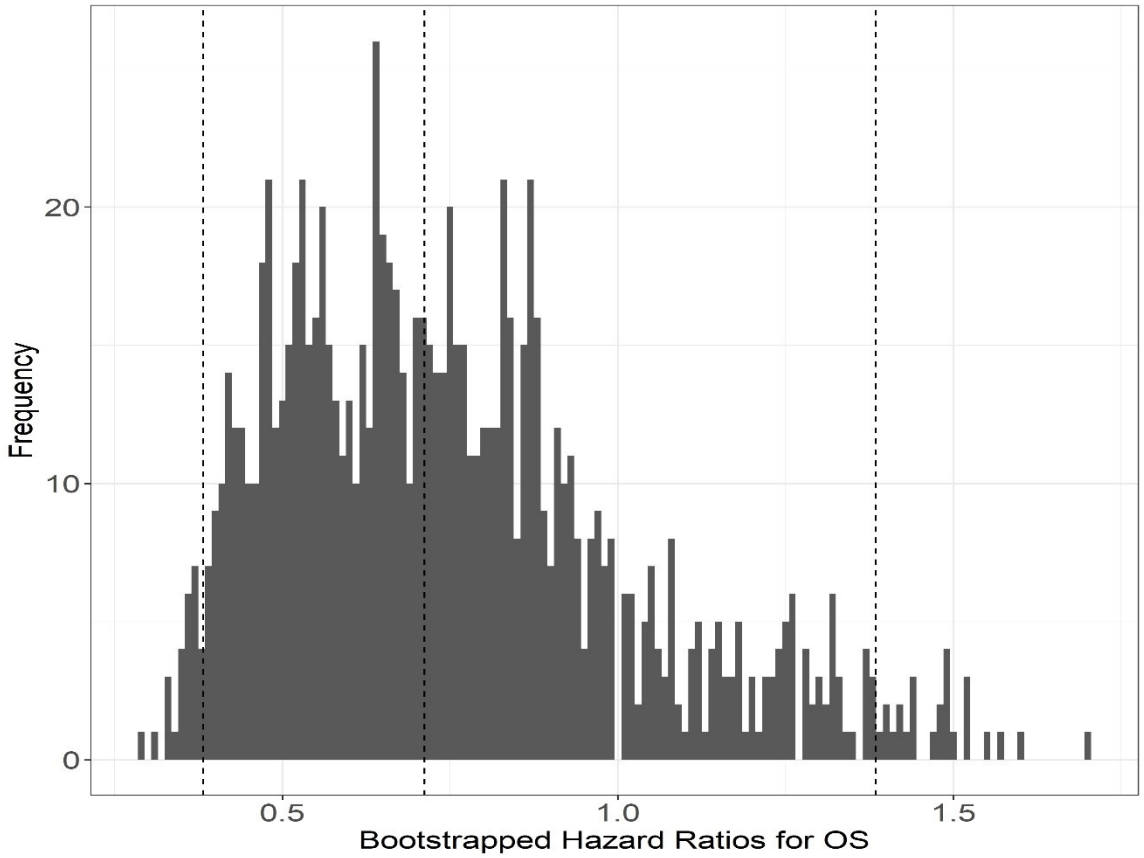


Figure 81: Bootstrapped Hazard Ratios for OS - T-Dxd (DESTINY-Breast01) vs Vinorelbine (Sim 2019)†



†The bootstrapped HRs suggest that the potentially plausible values for the HR estimate vary quite widely, ranging from 0.13 at the lower 95% CI to a value of ten times that at the upper 95% CI (1.30). This suggests a lot of uncertainty around the point estimate, although it can be seen in the graph that the majority of the bootstrap estimates are <1.0. Given the immaturity of the OS data from the DESTINY-Breast01 and the small ESS, resulting in a wide 95% CI, the results estimated in the MAIC may not be substantiated should additional data become available and this leads to concerns over whether the statement that there is no significant difference between the two treatments is robust.

Figure 82: Schoenfeld residuals for PH assumption for OS - T-Dxd (DESTINY-Breast01) vs Vinorelbine (Sim 2019)

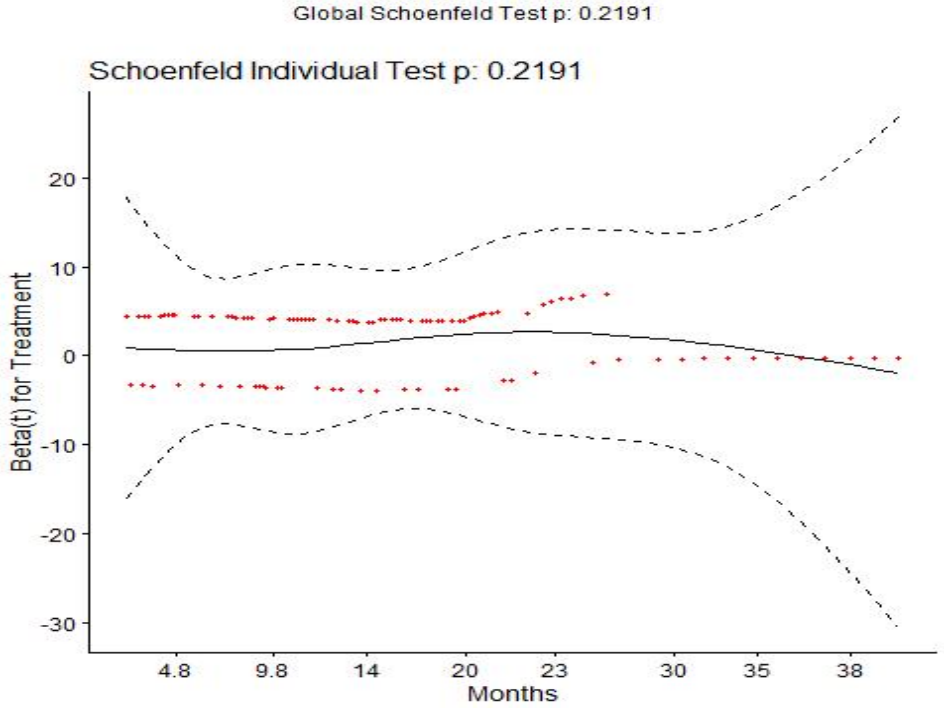


Figure 83: **Bootstrapped Hazard Ratios for PFS - T-Dxd (DESTINY-Breast01) vs Vinorelbine (Sim 2019)**

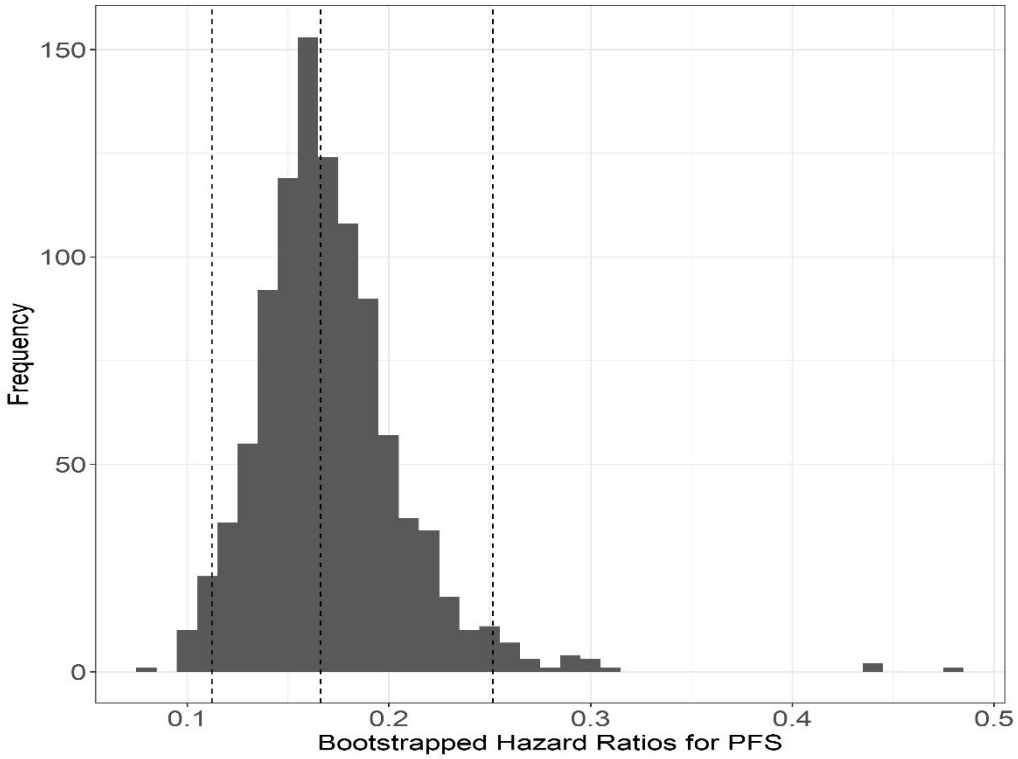


Figure 84: Schoenfeld residuals for PH assumption for PFS - T-Dxd (DESTINY-Breast01) vs Vinorelbine (Sim 2019)

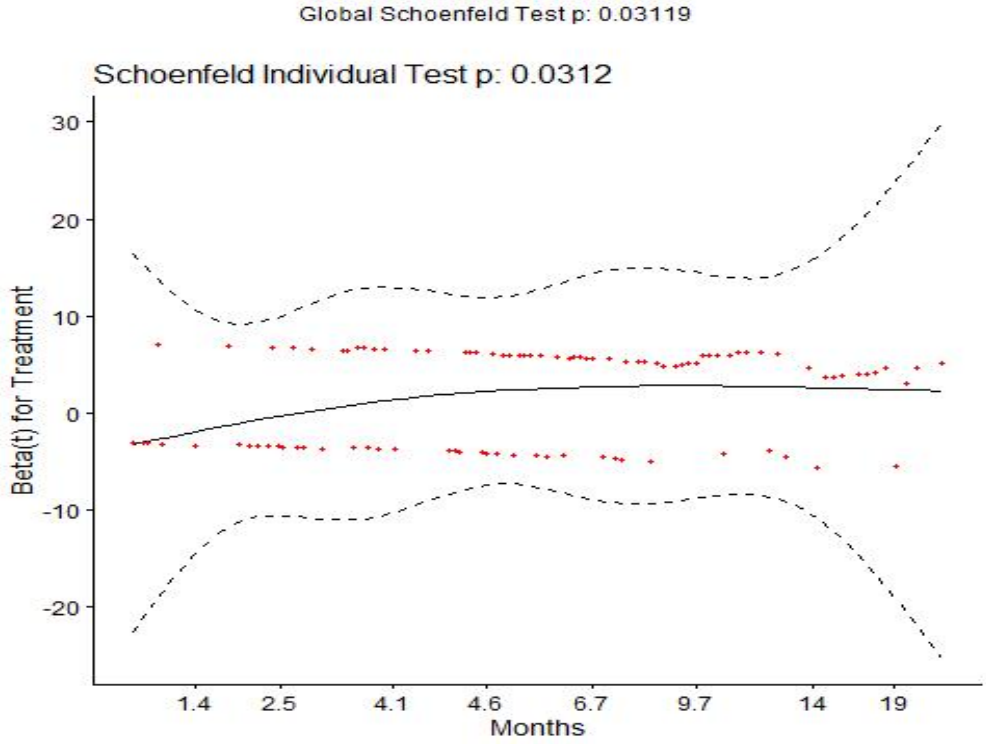


Figure 85: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2011)

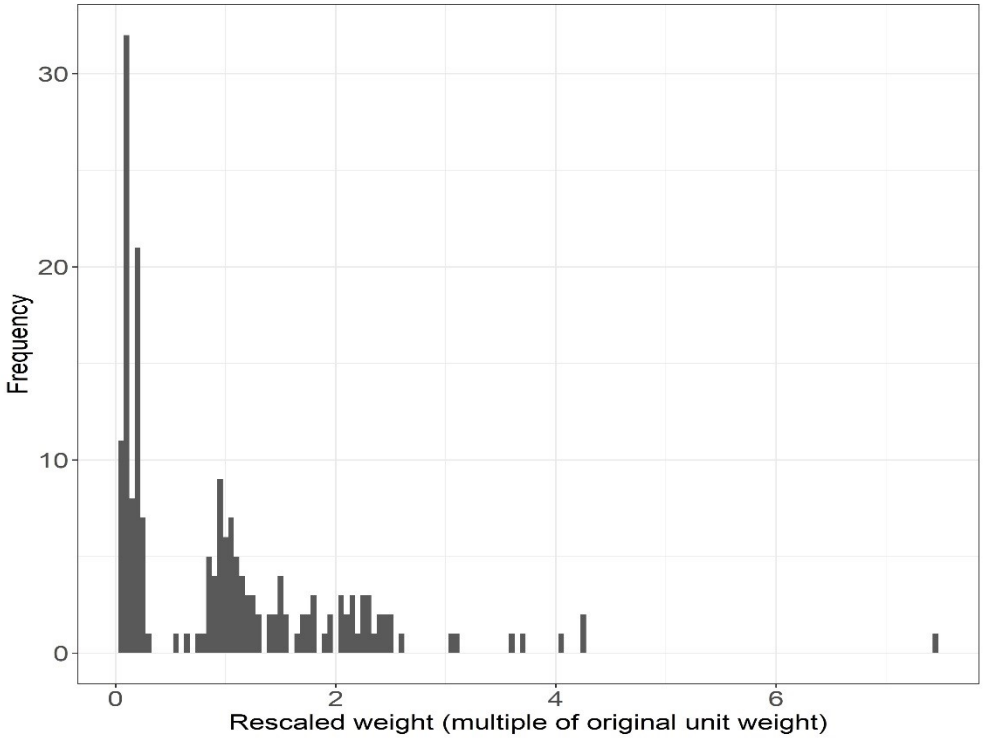


Figure 86: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2011)

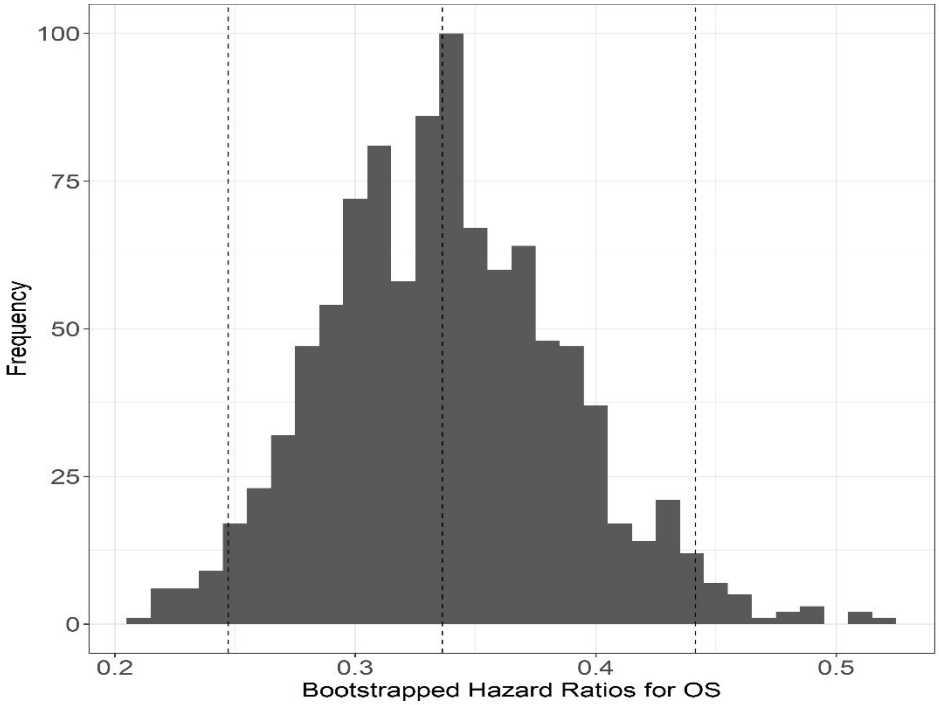


Figure 87: Schoenfeld residuals for PH assumption for OS - T-DXd (Destiny Breast 01) vs Eribulin (Cortes 2011)

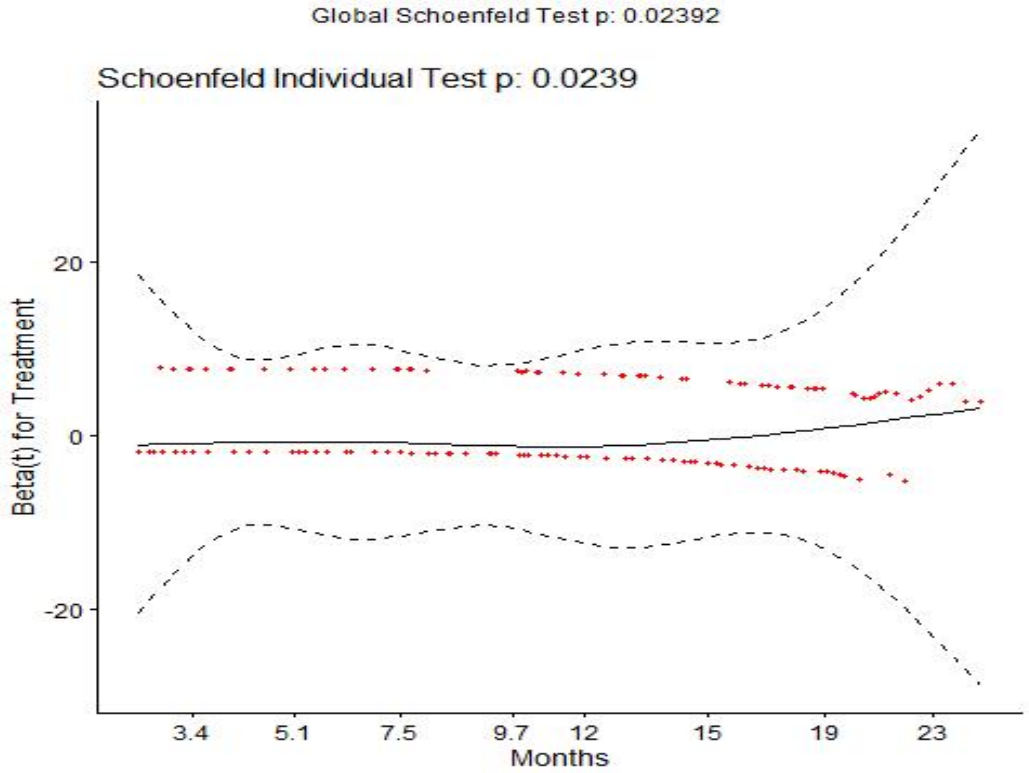


Figure 88: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Cortes 2011)

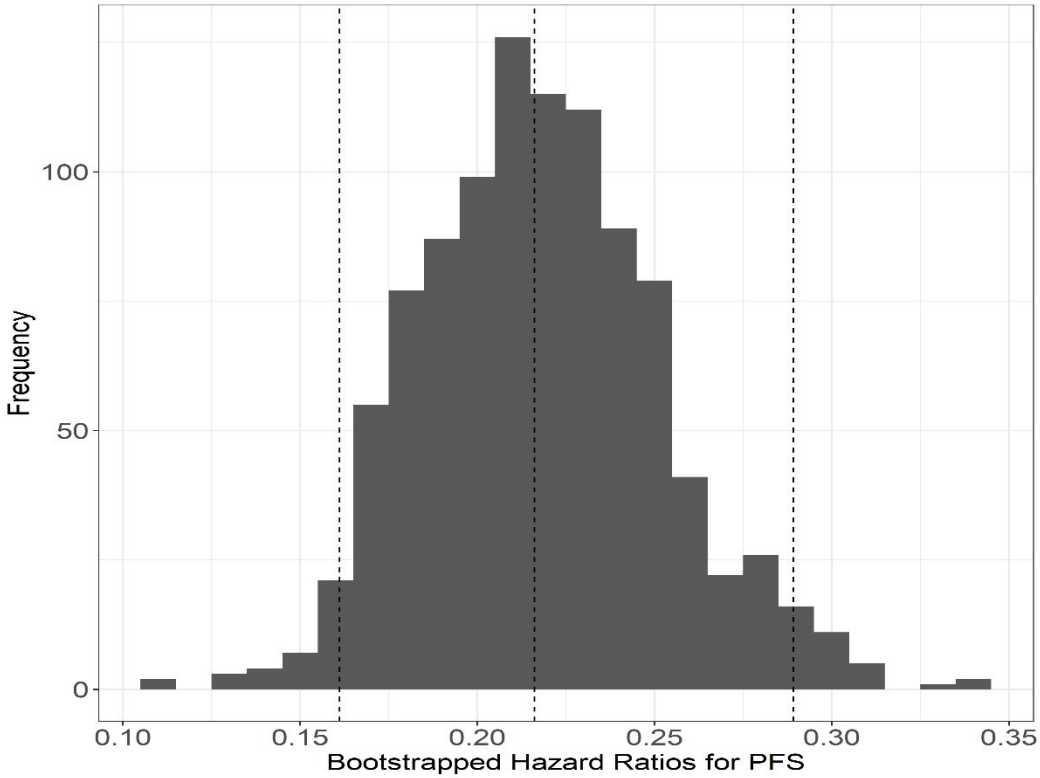


Figure 89: Schoenfeld residuals for PH assumption for PFS - T-DXd (Destiny Breast 01) vs Eribulin (Cortes 2011)

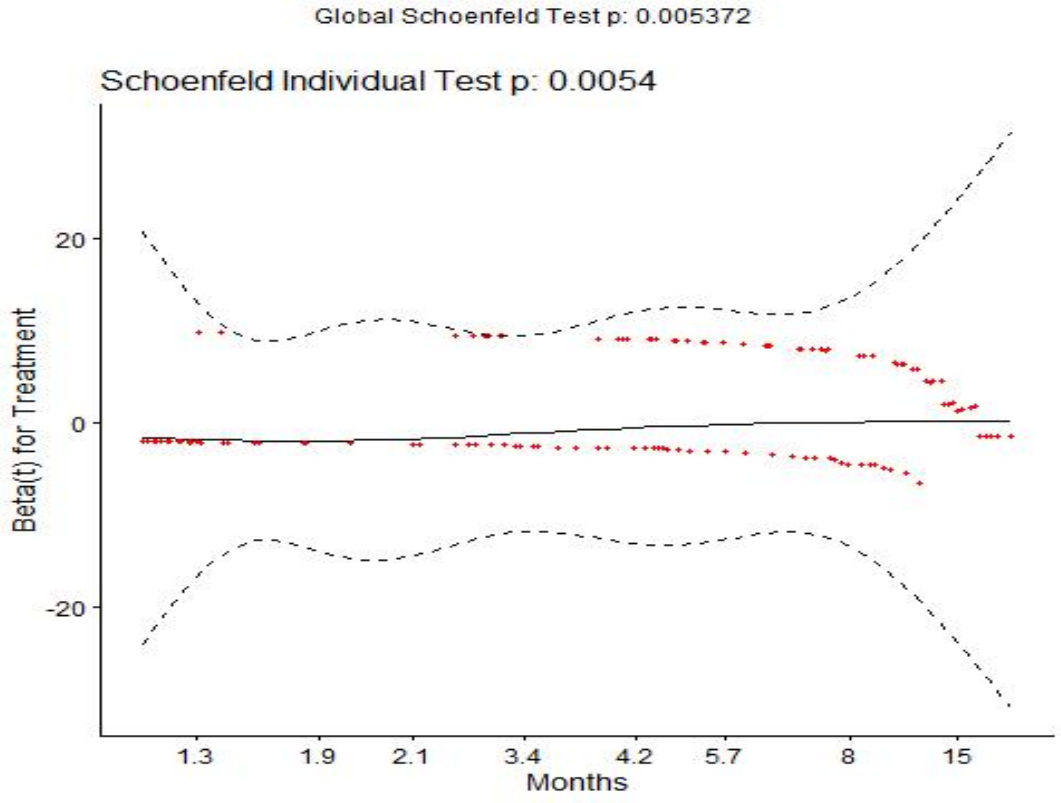


Figure 90: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

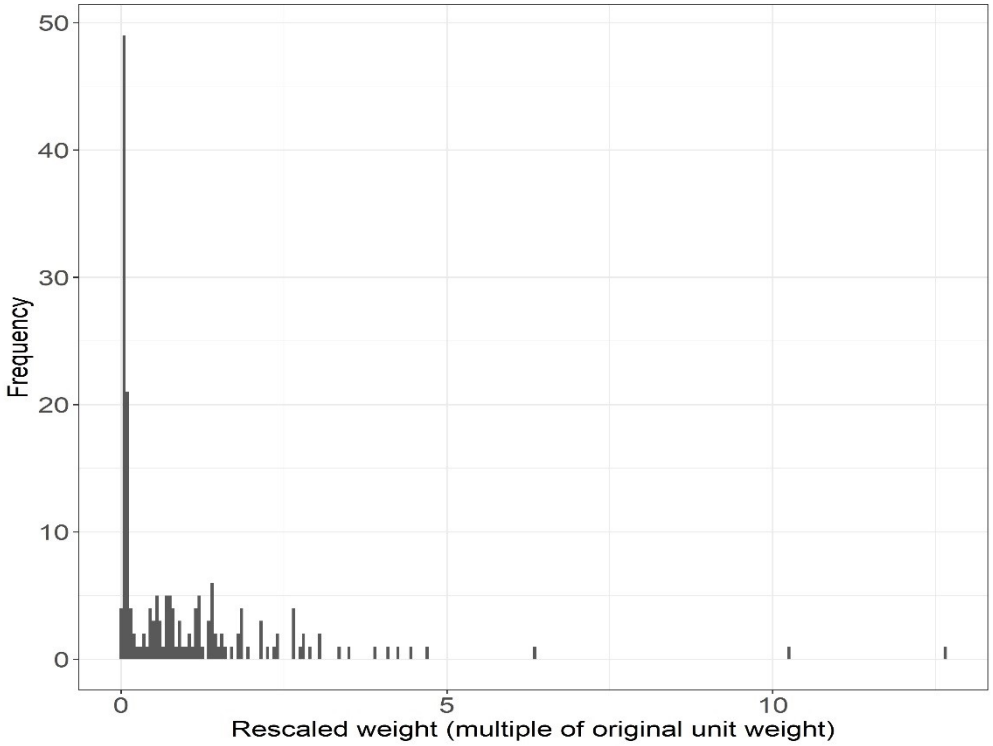


Figure 91: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

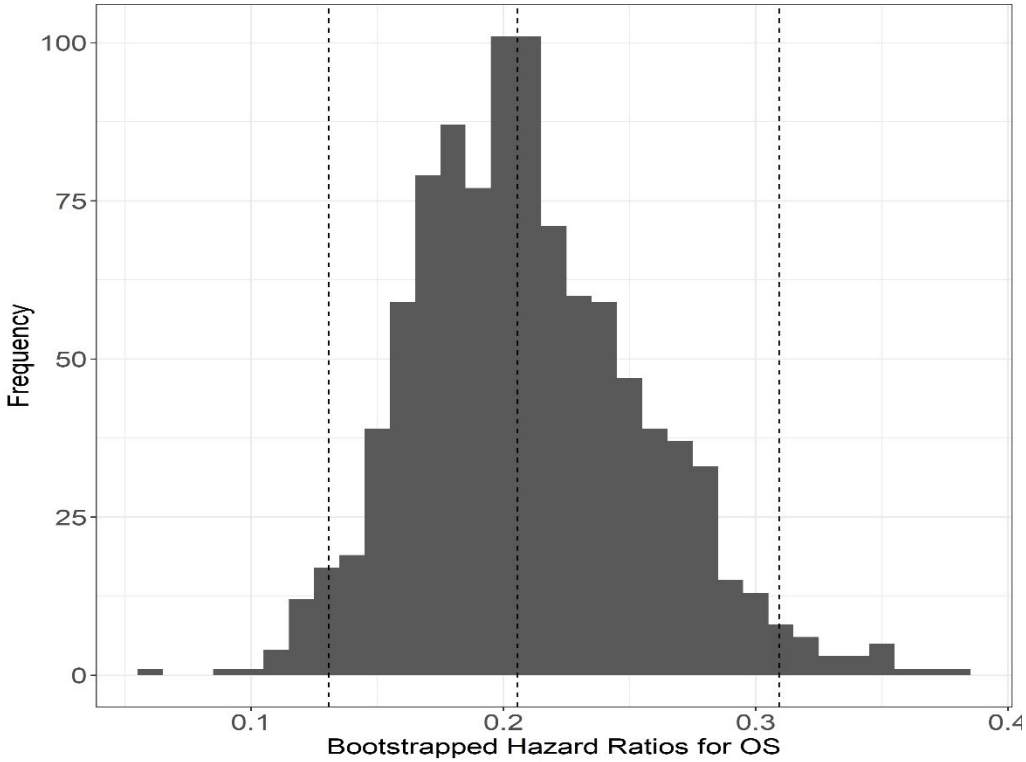


Figure 92: Schoenfeld residuals for PH assumption for OS - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

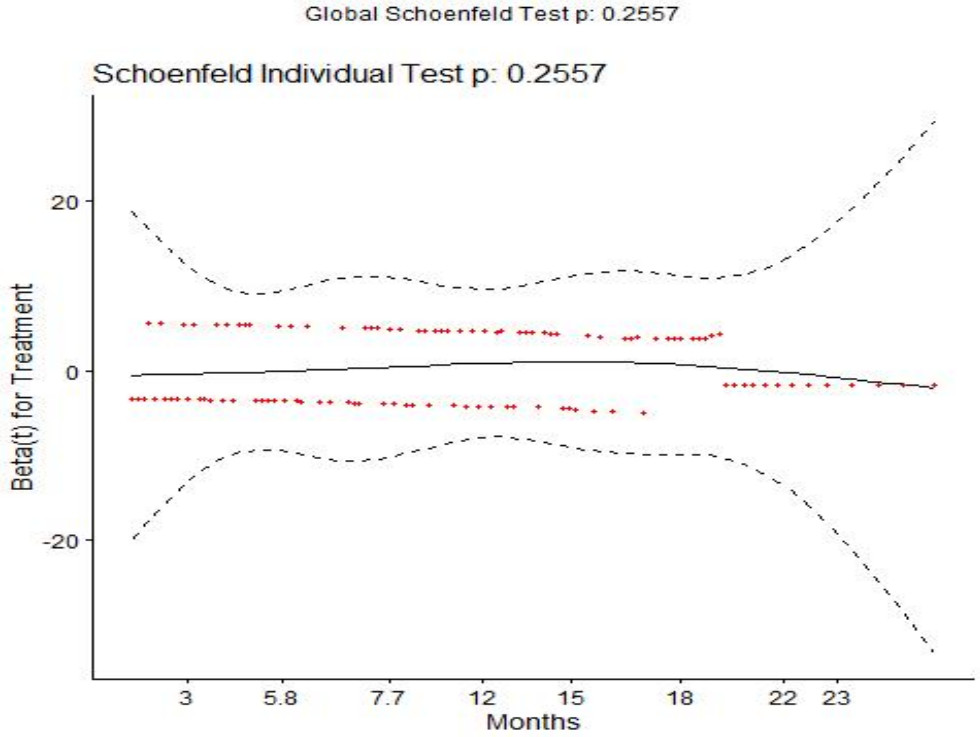


Figure 93: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

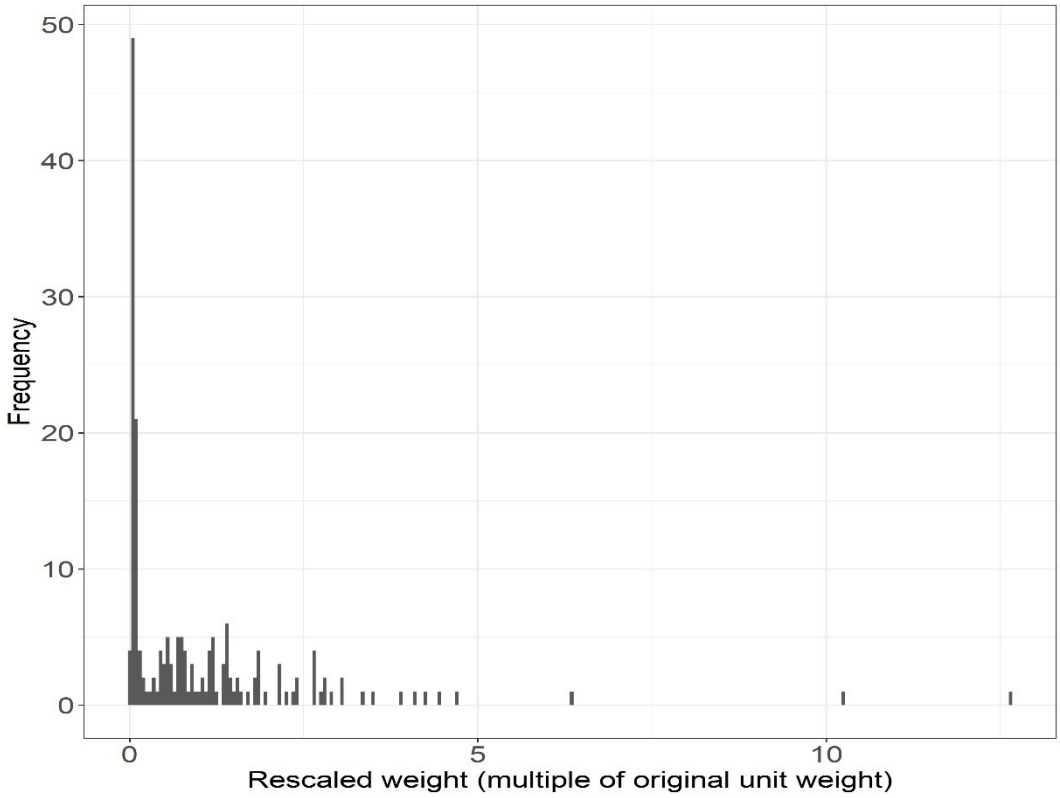


Figure 94: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

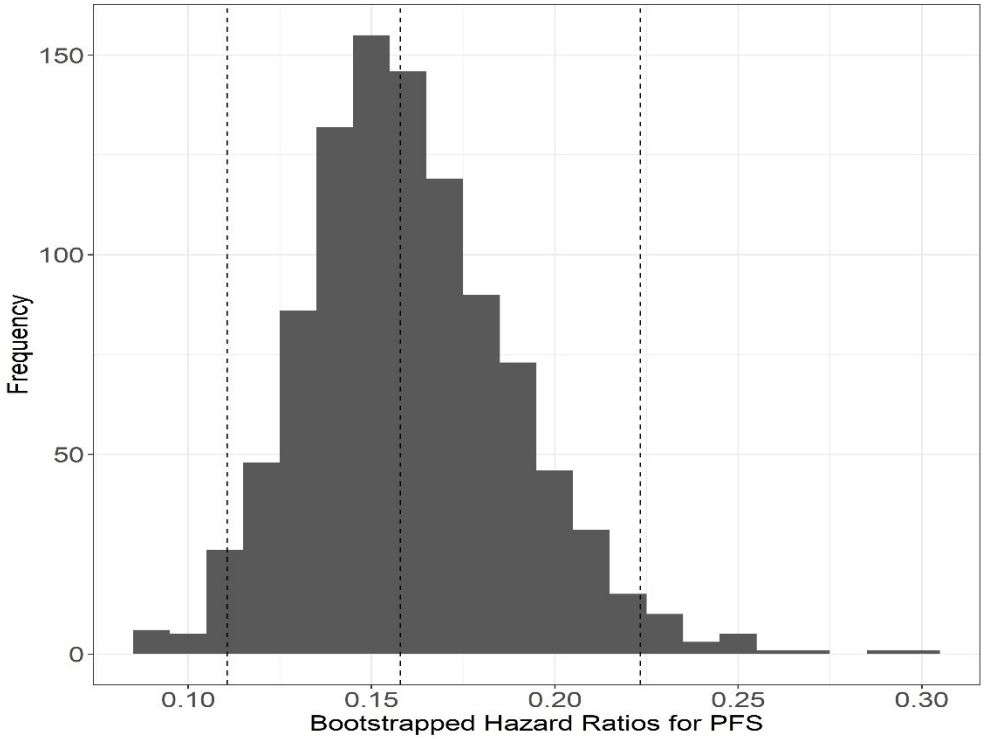


Figure 95: Schoenfeld residuals for PH assumption for PFS - T-DXd (DESTINY-Breast01) vs Capecitabine (Blum 2001)

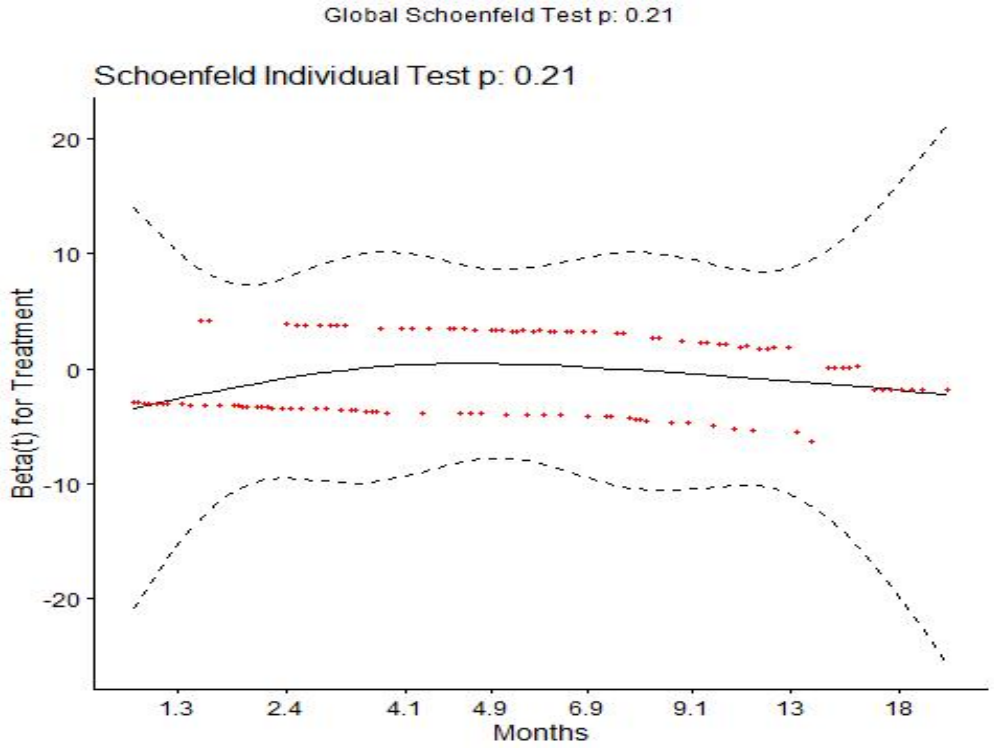


Figure 96: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)

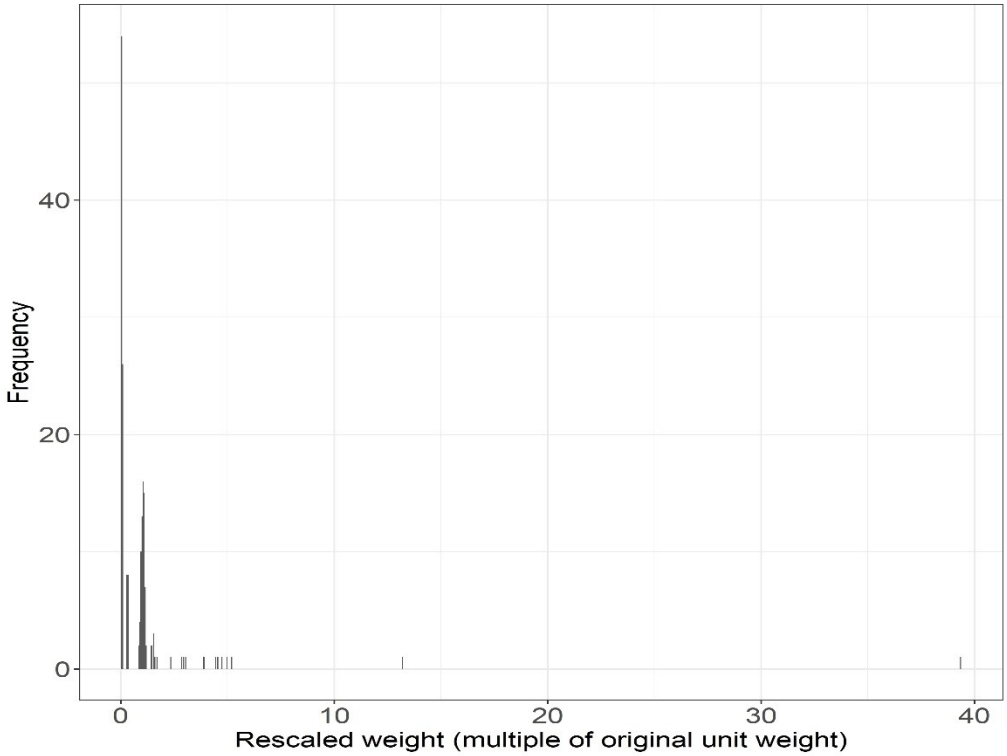


Figure 97: Bootstrapped Hazard Ratios for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)

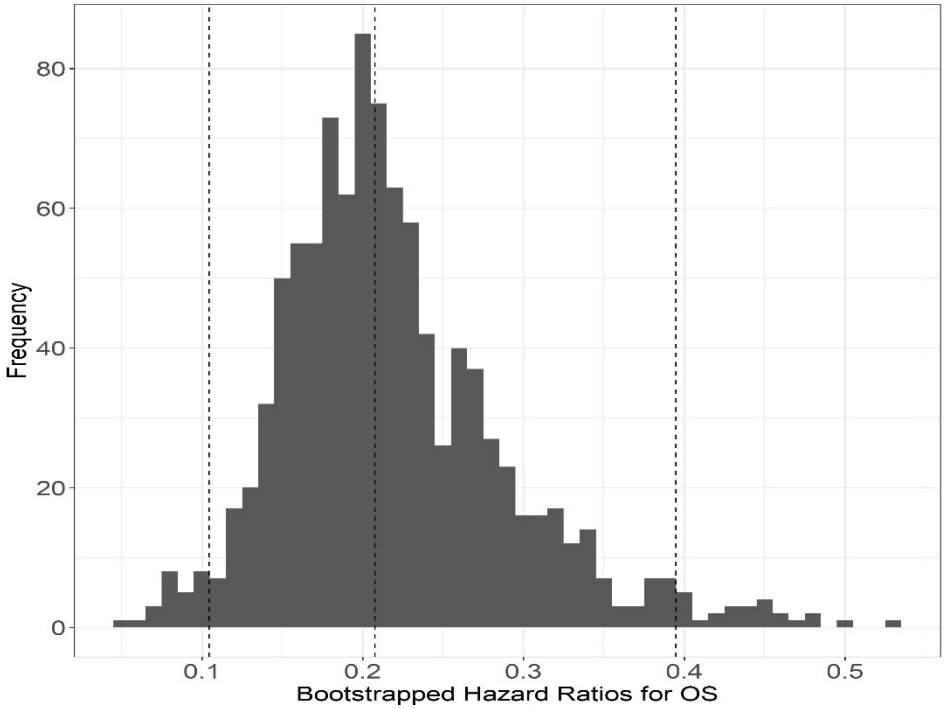


Figure 98: Schoenfeld residuals for PH assumption for OS - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)

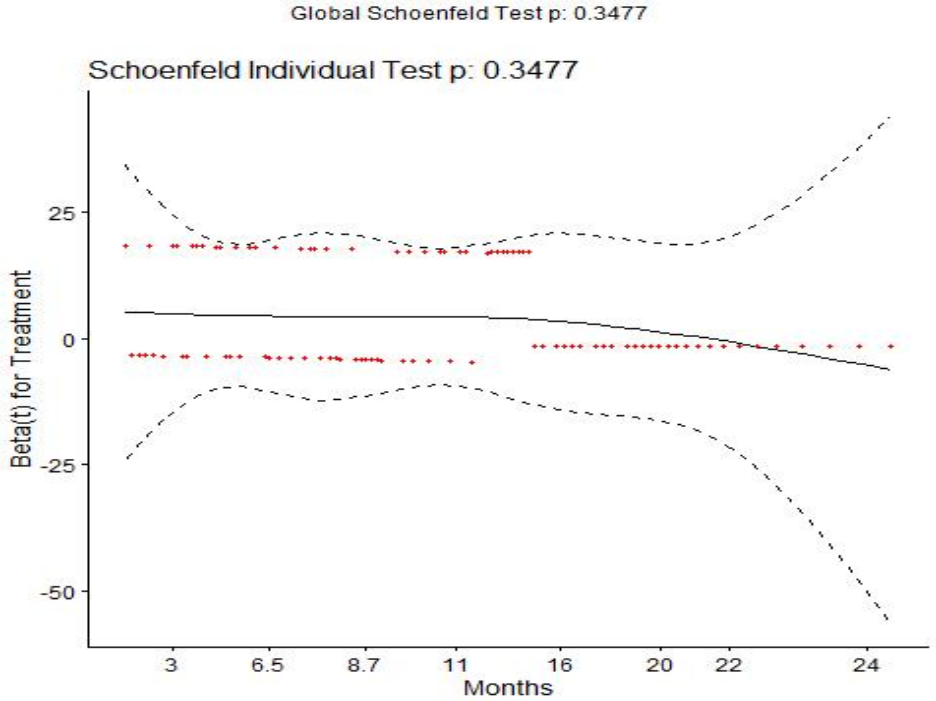


Figure 99: Histogram rescaled weights - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)

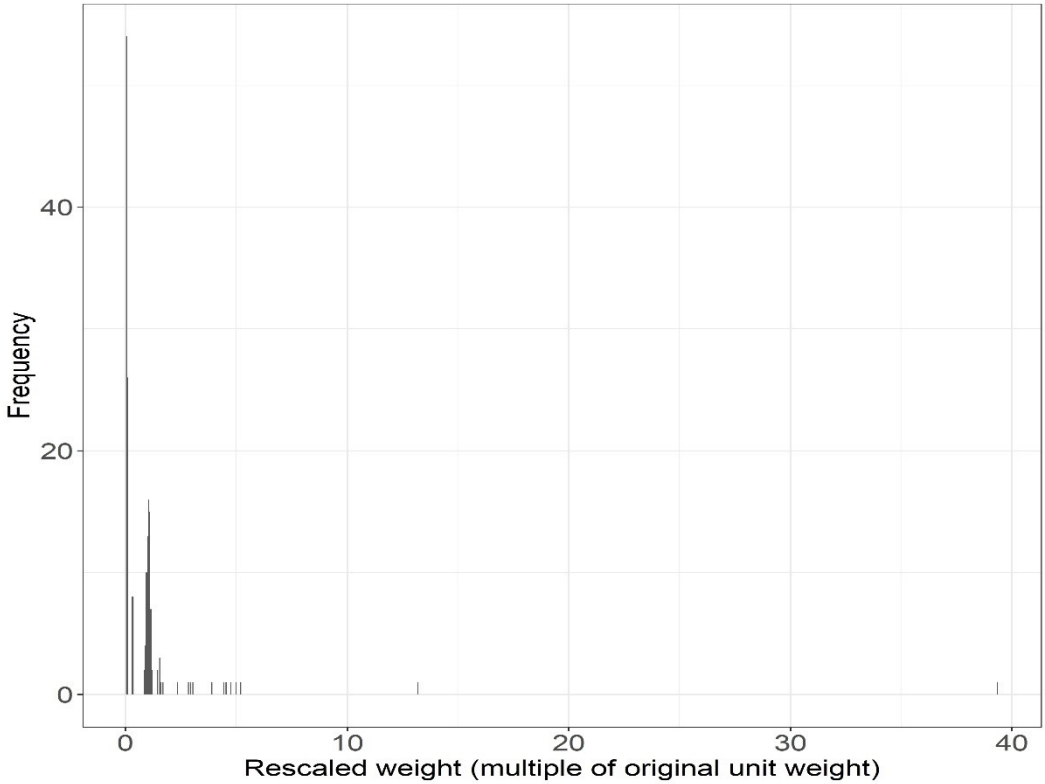


Figure 100: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)

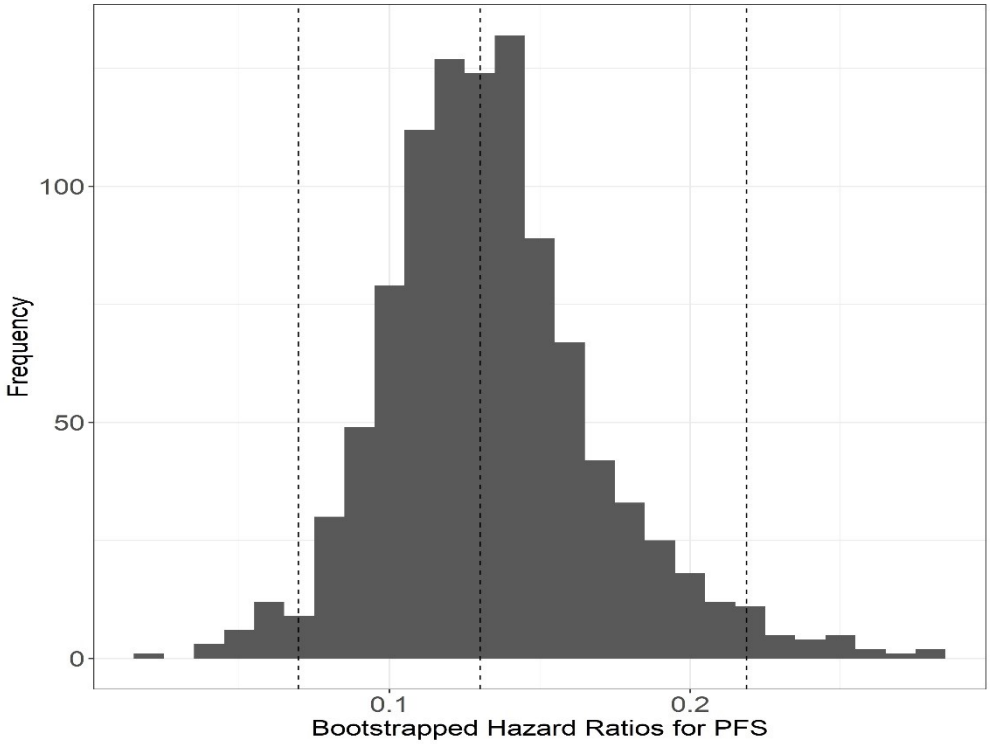
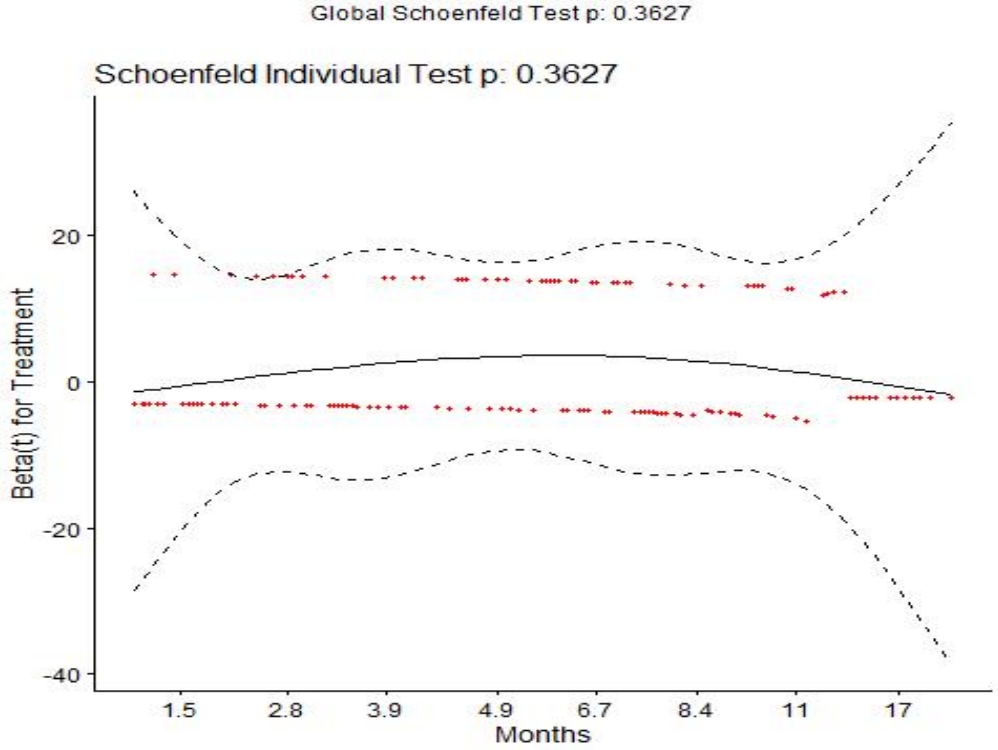


Figure 101: Schoenfeld residuals for PH assumption for PFS - T-DXd (DESTINY-Breast01) vs Eribulin (Gamucci 2014)



5.2. Addendum to Appendix J: Clinical outcomes and disaggregated results from the model

Appendix J has been updated to reflect OS, PFS, TTD, response, adverse event and relative dose intensity data from the June 2020 data cut for DESTINY-Breast01.

5.2.1. Clinical outcomes from the model (addendum to J1.1)

A comparison between the modelled and original study results is presented in Table 123. However, it is noted that progression-free survival (PFS) results for capecitabine, vinorelbine and eribulin are expected to differ between the original studies and the economic model, given that unanchored MAICs were performed to adjust for differences between the comparator studies and DESTINY-Breast01. Overall survival (OS) results for vinorelbine are also expected to differ substantially between the economic model and the original study; clinical experts at the August advisory board considered the results of the Sim 2019 study (the only available source of data for vinorelbine) to be clinically implausible. OS for vinorelbine was therefore assumed to be equivalent to that for capecitabine. Further details are provided in Section B.3.3.1.2.

Table 123: Comparison between study and model outcomes

Technology	Outcome	Original study result	Model result
Capecitabine	Median PFS (months)	Fumoleau 2004: 4.9	[redacted]
	Median OS (months)	Fumoleau 2004: 15.2	[redacted]
Vinorelbine	Median PFS (months)	2.8	[redacted]
	Median OS (months)	18.9	[redacted]
Eribulin	Median PFS (months)	Cortes 2011 (EMBRACE): 3.7	[redacted]
	Median OS (months)	Cortes 2011 (EMBRACE): 13.1	[redacted]
T-DXd	Median PFS (months)	16.4	[redacted]
	Median OS (months)	NA	[redacted]

Abbreviations: OS, overall survival; PFS, progression-free survival.

5.2.2. Disaggregated results of the base-case incremental cost-effectiveness analysis, PAS price (addendum to J1.2)

A summary of the disaggregated outcomes in the analysis vs. eribulin, capecitabine and vinorelbine are presented in Table 124, Table 125 and Table 126.

Table 124: QALY gain by health state – T-DXd vs eribulin

Health state	QALYs (T-DXd)	QALYs (Eribulin)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year.

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

Table 125: QALY gain by health state – T-DXd vs capecitabine

Health state	QALYs (T-DXd)	QALYs (Capecitabine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year.

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

Table 126: QALY gain by health state - TDXd vs vinorelbine

Health state	QALYs (T-DXd)	QALYs (Vinorelbine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year.

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

A summary of costs by health state assuming the PAS price of T-DXd in the analyses vs. eribulin, capecitabine and vinorelbine is presented in Table 127, Table 128 and Table 129.

Table 127: Summary of costs by health state - T-DXd vs eribulin, PAS price

Health state	Cost (T-DXd)	Cost (Eribulin)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 128: Summary of costs by health state - T-DXd vs capecitabine, PAS price

Health state	Cost (T-DXd)	Cost (Capecitabine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 129: Summary of costs by health state - T-DXd vs vinorelbine, PAS price

Health state	Cost (T-DXd)	Cost (Vinorelbine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

A summary of the disaggregated costs assuming the PAS price of T-DXd in the analyses vs. eribulin, capecitabine and vinorelbine is presented in Table 130, Table 131 and Table 132.

Table 130: Summary of costs - T-DXd vs eribulin, PAS price

Item	Cost intervention (T-DXd)	Cost comparator (Eribulin)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life; T-DXd, trastuzumab deruxtecan					

Table 131: Summary of costs - T-DXd vs capecitabine, PAS price

Item	Cost intervention (T-DXd)	Cost comparator (Capecitabine)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life; T-DXd, trastuzumab deruxtecan					

Table 132: Summary of costs - T-DXd vs vinorelbine, PAS price

Item	Cost intervention (T-DXd)	Cost comparator (Vinorelbine)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life; T-DXd, trastuzumab deruxtecan					

5.2.3. Disaggregated results of the base-case incremental cost-effectiveness analysis, list price (addendum to J1.2)

Table 133: Summary of costs by health state - T-DXd vs eribulin, list price

Health state	Cost (T-DXd)	Cost (Eribulin)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 134: Summary of costs by health state - T-DXd vs capecitabine, list price

Health state	Cost (T-DXd)	Cost (Capecitabine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 135: Summary of costs by health state - T-DXd vs vinorelbine, list price

Health state	Cost (T-DXd)	Cost (Vinorelbine)	Increment	Absolute increment	% absolute increment
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 136: Summary of predicted resource use by category of cost - T-DXd vs eribulin, list price

Item	Cost intervention (T-DXd)	Cost comparator (Eribulin)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life;					

Table 137: Summary of predicted resource use by category of cost - T-DXd vs capecitabine, list price

Item	Cost intervention (T-DXd)	Cost comparator (Capecitabine)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life;					

Table 138: Summary of predicted resource use by category of cost - T-DXd vs vinorelbine, list price

Item	Cost intervention (T-DXd)	Cost comparator (Vinorelbine)	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; EoL, End of life.					

5.3. Addendum to Appendix N: Cost-effectiveness results using PAS price

At the time of the original submission, a proposed PAS for T-DXd had been submitted but not approved, and therefore all results based on the PAS price were presented in an Appendix. Following the approval of the PAS scheme for T-DXd, results based on the PAS price are presented in section 2.7, 3.2.5, and 5.2.

5.4. Addendum to Appendix O: Extrapolation of OS, PFS and TTD

Appendix O has been updated to reflect OS, PFS and TTD data from the June 2020 data cut for DESTINY-Breast01.

5.4.1. Base-case statistical models

The base case statistical models are presented in Table 139, Table 140, Table 141, Table 142 and Table 143.

5.4.1.1. OS

Table 139: Model parameters: T-DM1 – OS (TH3RESA), gen. gamma

Parameter	Coefficient	SE	95% CI	
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]
Kappa	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; gen. gamma, generalised gamma; OS, overall survival; se, standard error

Table 140: Model parameters: Eribulin – OS (Cortes, 2011), gen. gamma

Parameter	Coefficient	SE	95% CI	
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]
Kappa	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; gen. gamma, generalised gamma; OS, overall survival; se, standard error

Table 141: Model parameters: Capecitabine – OS (Fumoleau), Gompertz

Parameter	Coefficient	SE	95% CI	
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; OS, overall survival; se, standard error

5.4.1.2. PFS

Table 142: Model parameters: T-DXd – PFS (DESTINY-Breast01), log-normal

Parameter	Coefficient	SE	95% CI	
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; PFS, progression-free survival; se, standard error; T-DXd, trastuzumab deruxtecan

5.4.1.3. TTD

Table 143: Model parameters: T-DXd – TTD (DESTINY-Breast01), exponential

Parameter	Coefficient	SE	95% CI	
Constant	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; se, standard error; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

5.4.2. T-DXd OS: Scenario applying HR to eribulin

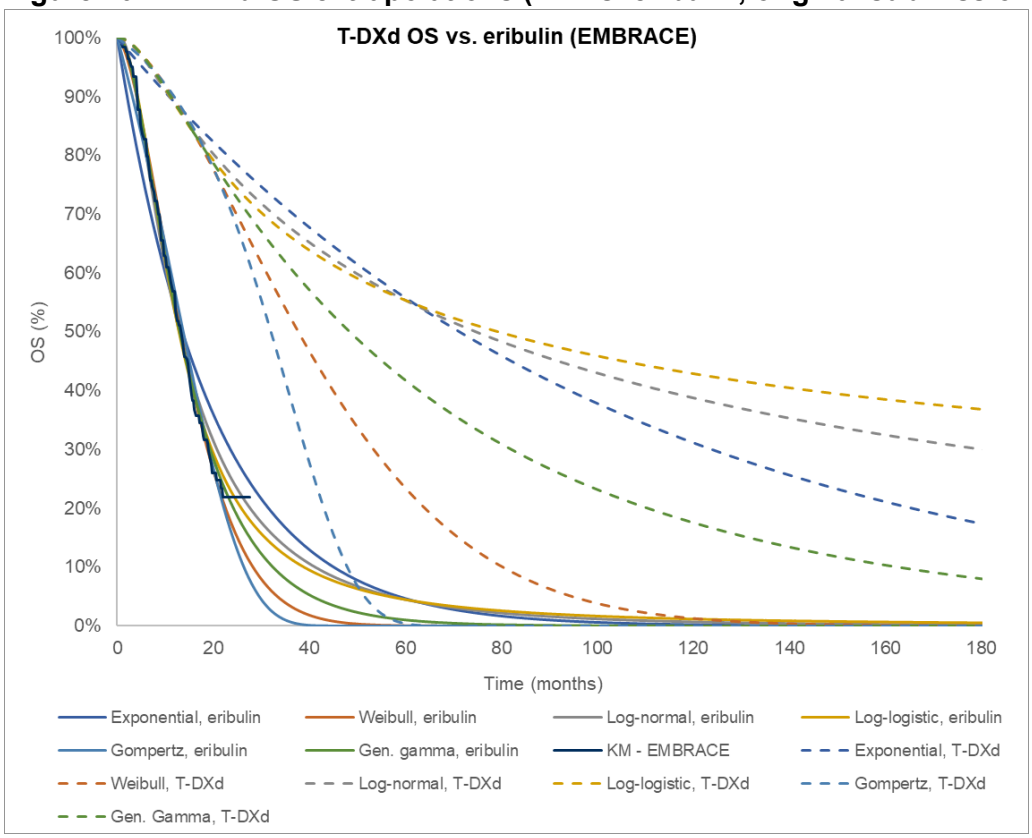
For completeness, a scenario is considered in which T-DXd OS is modelled by applying the HR from the MAIC vs. Cortes 2011 to the eribulin survival curve (Section B.3.3.1.2 of Document B); however, this scenario is considered to be less clinically relevant, given that eribulin is not a targeted treatment. Comparisons using HRs vs. capecitabine and vinorelbine were not considered on the basis that:

- Eribulin is the only NICE assessed comparator, with a pivotal Phase 3 trial evidence base available that was used to support licensing
- Vinorelbine OS data were not considered clinically plausible by clinical experts at the August advisory board (see also Section B.3.3.1.2 in Document B)
- In both available capecitabine studies, the proportion of patients who are HER2+ is unknown.

Section B.3.3.1.2 of Document B (main submission) presents the alternative extrapolations of OS for eribulin. In a scenario analysis, OS for T-DXd is generated by applying the OS HR for T-DXd vs. eribulin [redacted]; see Section B.2.9 of Document B for further details of the MAICs.

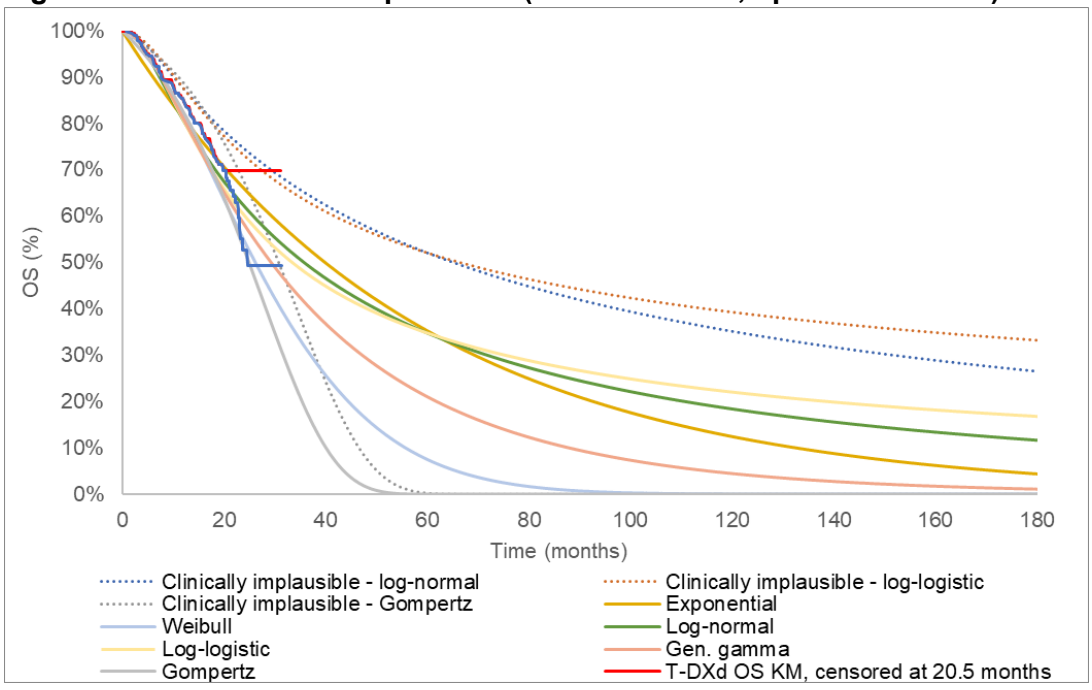
Extrapolations of T-DXd OS in Figure 102 (based on the August 2019 data cut) were presented to UK clinical experts at the August advisory board. The log-logistic, log-normal and Gompertz distributions were considered to be clinically implausible. Figure 103 shows the extrapolations based on the updated HR ([redacted]) compared to the three distributions that clinicians considered to be clinically implausible; the extrapolations based on the Gompertz and Weibull distributions fell below a curve considered implausibly low at the advisory board, and were therefore removed from consideration. Of the remaining distributions, the generalised gamma had the lowest AIC and was therefore chosen for the scenario analysis.

Figure 102: T-DXd OS extrapolations (HR vs. eribulin, original submission)



Abbreviations: gen. gamma, generalised gamma; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival, T-DXd, trastuzumab deruxtecan

Figure 103: T-DXd OS extrapolations (HR vs. eribulin, updated data-cut)



Abbreviations: gen. gamma, generalised gamma; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival, T-DXd, trastuzumab deruxtecan

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Response to clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID2697 Trastuzumab deruxtecan_Response to ERG clarification letter update [AIC]	V1.0	Yes	15th October 2020

Section A: Clarification on effectiveness data

Identification and selection of relevant studies

A1. Identification and selection of relevant studies

The company states (Company submission [CS], Appendix D1.1) that two independent reviewers performed screening and quality assessment of included publications. Please confirm if two reviewers also independently extracted data from the included studies.

All extracted data was verified against the original source publication by a second independent researcher.

A2. Search strategy

The company has provided details of their search strategy in the CS (Appendix D1). Please clarify the following:

i. Were any date limits set for the original searches run in April 2019 (Appendix D1, Text and Tables 2-4) of the electronic databases, or were all of the databases searched from inception?

Original searches for April 2019 were run from the date of database inception.

ii. Were any date limits applied to the first or second update of the PubMed database searches (Appendix D1, Tables 3, 5 and 9)?

Neither the original nor subsequent updates for MEDLINE-In Process searches were limited by any dates or time-frame.

iii. Did the first update search of the Embase database (Appendix D1, Table 7) include Embase and Medline, as in the original and second update searches (Appendix D1, Tables 2 and 8)?

Both the original and subsequent updates of Embase.com searches included MEDLINE and EMBASE databases.

A3. DESTINY-Breast01, secondary efficacy endpoints

Summary results of some secondary efficacy outcomes from the DESTINY-Breast01 study are provided in the CS (Table 14). In this table, the number of censored patients is reported to be 83 (74.1%). Please clarify which population/outcomes this censoring relates to.

The number of censored patients refers to the duration of response (DoR) analysis in 112 patients who had a response. Please see the adjusted CS Table 14.

CS Table 14: DESTINY-Breast01: Summary of other secondary efficacy endpoints as assessed by ICR (EAS)

Secondary endpoints	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
DCR, n (% [95% CI])	179 (97.3 [93.8, 99.1])
CBR, n (% [95% CI])	140 (76.1 [69.3, 82.1])
Median DoR, months (95% CI)	14.8 (13.8, 16.9)
Events, n/N patients with response, (%)	29/112 (25.9)
Censored, n/N patients with response (%)	83/112 (74.1)
Median TTR, months (95% CI)	1.6 (1.4, 2.6)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; DoR, duration of response; EAS, enrolled analysis set; ICR, independent central review; TTR, time to response; T-DXd, trastuzumab deruxtecan.
Data-cut: August 1, 2019
DoR and TTR is shown for the 112 patients who had a complete or partial response among the 184 patients treated with the recommended dose of 5.4 mg/kg T-DXd
Source: Modi 2020[1]

A4. DESTINY-Breast01, treatment-emergent adverse events (TEAEs), TEAE-associated deaths and interstitial lung disease (ILD)

It is stated in the CS that:

(a) "There were 9 (4.9%) TEAE-associated deaths (respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock haemorrhagic; 1 patient had two TEAEs associated with death: acute kidney injury and acute hepatic failure." (p100)

(b) "Overall, 9 (4.9%) patients had TEAEs associated with a fatal outcome on-study (defined as occurring on or after first dose until 47 days after last dose), with 2 (1.1%) patients having at least one study drug-related TEAE associated with a fatal outcome on-study based on investigator assessment." (p91)

(c) "Overall, a total of 25 deaths (any death) were reported in patients treated with 5.4 mg/kg T-DXd, including 7 that occurred during treatment as a result of either disease progression (in 3 patients) or TEAEs (haemorrhagic shock, general physical health deterioration, pneumonia, and acute organ failure in 1 patient each)." (p91)

(d) "During survival follow-up (which was defined as 47 days after the end of treatment), 18 of the 25 deaths occurred, 2 of which were caused by events associated with ILD that started during treatment and are among those described below (TEAEs of special interest: Section B.2.10.1.4); the remaining 16 deaths were considered by investigators to be unrelated to T-DXd." (p91)

(e) "Overall, 25 patients (13.6%) had ILD related to the receipt of T-DXd, as determined by an independent adjudication committee.[62] These events were primarily CTCAE Grade 1 or 2 (10.9%); 1 patient (0.5%) had a Grade 3 event, and no patients had a Grade 4 event. Four deaths (2.2% of the patients) were attributed to ILD by independent adjudication and were initially reported as respiratory failure, acute respiratory failure, lymphangitis, and pneumonitis in one patient each by the treating investigators; the primary cause of death was reported as disease progression (in 2 patients) and adverse events during survival follow-up (in 2 patients)." (p95)

Please clarify the following:

i. Which two of the nine TEAEs referred to in (a) were considered to be drug-related TEAEs in (b)?

The two events considered to be drug-related TEAEs based on investigator assessment were: respiratory failure and pneumonitis. Both of these events occurred more than 47 days after the last dose of study medication.

ii. In (c), is it correct to assume that “acute organ failure” is the same as “acute kidney injury” and/or “acute hepatic failure”, as referred to in (a)?

This is correct, one subject had two events (acute hepatic failure and acute kidney injury). The primary cause of death in this subject was “Other (acute organ failure)”.

iii. Why was “disease progression” listed as a TEAE death for one patient in (b)?

Disease progression (PD) was reported as a serious adverse event (SAE) if the subject died from PD with no other immediate causes according to the clinical study protocol for DESTINY-Breast01.[2]

iv. Is it correct to conclude from the above, (c) and (d), that there were three deaths from disease progression and four deaths from TEAEs during treatment and 13 deaths from disease progression and five deaths from TEAEs during survival follow-up (i.e., at least 47 days after the end of treatment)?

This is correct. On-study death refers to death, based on the investigator assessment of the primary cause of death, that occurred during study treatment or within 47 days after the last dose in DESTINY-Breast01.

Of the 7 on-treatment deaths, the primary cause of death was as follows:

- Disease progression (3 subjects). Of these 3 deaths, the TEAEs associated with death were disease progression, acute respiratory failure and lymphangitis. The events of acute respiratory failure and lymphangitis were adjudicated as drug-related interstitial lung disease (ILD).
- Adverse event (3 subjects); the TEAEs were: haemorrhagic shock, general physical health deterioration and pneumonia.
- Other (acute organ failure) (1 subject) who had 2 TEAEs (acute hepatic failure and acute kidney injury).

In the survival follow-up period, an additional 18 subjects died. Of these, 13 patients died due to disease progression; for 2 patients the primary cause of death was adverse events (1 due to pneumonitis and 1 due to respiratory failure). In 2 patients

the cause of death was unknown, and 1 patient died due to alteration of general condition due to cancer.

v. If, as stated in (d), there were 18 deaths during survival follow-up but 16 were not drug-related, does this mean that the two treatment-related deaths from adverse events (AEs) that were previously referred to in (i) were in fact ILD?

In the survival follow-up period, there were 2 treatment-related deaths based on investigator assessment, and the primary cause of death for both events was an adverse event. The adverse events were pneumonitis and respiratory failure. Both deaths occurred in the survival follow-up period. Both deaths were sent for adjudication by the Adjudication Committee (AC) as the onset of both events occurred while the subjects were on study medication. Both deaths were adjudicated as drug-related ILD.

vi. As reported in in (e), four patients died from ILD, and these deaths were initially classified as respiratory failure, acute respiratory failure, lymphangitis, and pneumonitis. However, the primary cause of death was reported as disease progression (in two patients) and AEs during survival follow-up (in two patients). Does this mean that only two deaths from ILD were considered to be drug-related AEs? Are these the same two drug related deaths referred to in (b)?

Disease progression was the primary cause of death for the 2 events (acute respiratory failure and lymphangitis) that were on-study deaths. Two other adverse events (respiratory failure and pneumonitis) which occurred in the survival follow-up period were adverse events that were the primary cause of death. All 4 deaths were adjudicated by the AC as drug-related ILD.

A5. Priority question: Treatment received prior to T-DXd

i. The ERG notes (CS, Appendix M, Table 2) that information about lines of previous treatment in Study DS8201-A-J101 includes hormone therapies for breast cancer and treatments received in the (neo)adjuvant setting. Please clarify if the information about lines of previous treatment for DESTINY-Breast01 study patients refers only to treatment received for metastatic disease (as reported in the published paper by Modi et al (*N Engl J Med* 2020;382:610-21. DOI: 10.1056/NEJMoa1914510). Please also confirm whether information

about lines of previous treatment received by patients in the DESTINY-Breast01 study includes or excludes hormone therapy (see also ii).

The information about previous cancer regimens refers to treatment for locally advanced or metastatic breast cancer. Please see A5(ii) for information on previous treatment including and excluding hormone therapy, and A5(iii) for further information on the definitions for prior therapy.

ii. In the CS (Table 7), it is stated that the median (range) number of previous cancer regimens excludes hormone therapy and is 6 (2-27). However, these data differ to those reported in the CSR. Please clarify why there is a difference.

This was an error, and it should have stated “including hormone therapy”: the median number of previous lines of therapy for locally advanced breast cancer (BC) or metastatic breast cancer (mBC) including hormone therapy was 6 (range, 2 to 27), and excluding hormone therapy was 6 (range, 2 to 24). The data refers to median number of prior anticancer regimens for locally advanced or metastatic BC.

iii. The Evidence Review Group (ERG) notes that the numbers of patients who had received 2, 3, 4, 5 and >5 prior lines of systemic cancer therapy (including hormone therapy) reported in the clinical study report (CSR) (Table 7.5) do not match the numbers of patients reported to have received 2, 3, 4, 5 and >5 prior lines of systemic cancer therapy (including hormone therapy) reported in the subgroup analysis poster (Table 1) presented by Modi et al at the ASCO virtual scientific program. Please explain why the numbers do not match.

The definition of prior lines of systemic cancer therapy according to the statistical analysis plan (SAP; page 35) was:

1. Any regimens intended for Locally Advanced/Metastatic or Palliative setting as entered in eCRF [electronic case report form] pages.

2. Any regimens intended for “Neo-Adjuvant”, “Adjuvant”, or “Maintenance” setting as entered in eCRF pages, but with progression occurring within 6 months from end of the therapy (12 months for pertuzumab).

During its assessment of T-DXd, the US Food and Drug Administration (FDA) requested a revised definition to additionally include the following (FDA: NDA/BLA Multi-disciplinary Review and Evaluation, page 134/135) [3]:

3. Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.

The prior lines of systemic cancer therapy (including hormone therapy) reported in the CSR reported the values using the SAP definition, whereas the Modi et al poster presented at the American Society of Clinical Oncology (ASCO) virtual scientific programme used the definition requested by the FDA. Table 1 presents data on the number of lines of prior cancer systemic therapy according to the different criteria.

Table 1: DESTINY-Breast01: Number of lines of prior cancer systemic therapy for the 5.4 mg/kg dose of T-DXd

Regimens of prior cancer systemic therapy including hormone therapy	Definition according to the SAP	Definition requested by the FDA
Median	6	5
Range	2, 27	2, 17
n (%)		
1	0	0
2	15 (8.2)	30 (16.3)
3	16 (8.7)	24 (13.0)
4	22 (12.0)	26 (14.1)
5	16 (8.7)	28 (15.2)
>5	115 (62.5)	76 (41.3)

Abbreviations: FDA, Food and Drug Administration; SAP, statistical analysis plan
Data-cut: August 1, 2019
Source: FDA briefing document for ENHERTU (fam-trastuzumab deruxtecan-nxki)[3]

iv. The CSR reports the number of patients who received 2, 3, 4, 5 and >5 prior lines of systemic cancer therapy. However, given the range of treatments was stated to be 2-27, patients who had >5 prior lines of systemic cancer therapy include patients with a large range of lines of treatment (6-27). Please provide the numbers of patients who received 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 and 27 lines of treatment (i) including and (ii) excluding hormone therapy.

The number and proportion of patients who received prior lines of treatment (1-27) (i) including and (ii) excluding hormone therapy are shown in Table 2.

Table 2: DESTINY-Breast01: Number of lines of prior cancer systemic therapy for the 5.4 mg/kg dose of T-DXd

Regimens of prior cancer systemic therapy	Including hormone therapy (N=184) n (%)	Excluding hormone therapy (N=184) n (%)
1	[redacted]	[redacted]
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
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27		

A6. Most frequently prescribed prior treatments

Please provide a list of the ten previous treatments that were most frequently prescribed to patients prior to their entry into the DESTINY-Breast01 study (i) including and (ii) excluding hormone therapy. Please also provide details of the number and proportions of patients who received each of these ten treatments (i) including and (ii) excluding hormone therapy.

The number and proportions of patients who received each of these ten treatments (i) including and (ii) excluding hormone therapy are shown in Table 3.

Table 3: DESTINY-Breast01: Most frequently prescribed prior treatments for the 5.4 mg/kg dose of T-DXd

Most frequently prescribed prior treatments including hormone therapy (N=184) n (%)		Most frequently prescribed prior treatments excluding hormone therapy (N=184) n (%)	
Treatment	**n (%)**	**Treatment**	**n (%)**
Trastuzumab	184 (100)	Trastuzumab	184 (100)
Trastuzumab emtansine	184 (100)	Trastuzumab emtansine	184 (100)
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan.

A7. Subsequent treatments

Please provide details of the number of DESTINY-Breast01 study patients who receive at least one treatment following discontinuation of T-DXd. Please list the subsequent treatments and provide details of the numbers and proportions of patients who received each subsequent treatment.

Data on subsequent treatments were not collected in the DESTINY-Breast01 study, as per the clinical study protocol and SAP.[2,4]

A8. Reasons for censoring

At the time of the 1 August 2019 data cut-off of the DESTINY-Breast01 study, 126 patients (CS, Table 13) and 159 patients (CS, p51) had been censored for the analyses of PFS and OS, respectively. Please provide the reasons why patients were censored for these analyses.

The reasons why patients were censored for PFS is shown in Table 4. At the August 1, 2019 data-cut, 118 patients were censored due to “No PD or death”; [redacted] were continuing on treatment (please note there was error in the previous response document that reported that [redacted] were on-going).

Table 4: DESTINY-Breast01: PFS as assessed by ICR (EAS): Data-cut: August 1, 2019

PFS	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Median PFS, months (95% CI)	**16.4 (12.7, NE)**
PFS events, n (%)	58 (31.5)
Progressive disease, n (%)	48 (26.1)
Death, n (%)	10 (5.4)
Censored, n (%)	126 (68.5)
Subjects ongoing at data-cut	[redacted]
Reasons for censoring	
New anticancer therapy	[redacted]
No post-baseline assessment	[redacted]
No PD or death	[redacted]

Abbreviations: CI, confidence interval; EAS, Enrolled Analysis Set; ICR, independent central review; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Source: Modi 2020[1] and Daiichi-Sankyo, Inc., 2020 (data on file)

The reasons why patients were censored for overall survival (OS) are shown in Table 5. At the August 1, 2019 data-cut, 159 subjects were censored, of whom [redacted] were censored due to being alive at data cut-off.

Table 5: DESTINY-Breast01: OS as assessed by ICR (EAS): Data-cut: August 1, 2019

OS	T-DXd 5.4 mg/kg (Part 1+2a+2b) (N=184)
Median OS, months (95% CI) (ICR assessed)	**NE (NE, NE)**
Events	25 (13.6%)
Censored, n (%)	159 (86.4%)
Reasons for censoring	
Alive	[redacted]
Lost to follow-up	[redacted]
Withdrawal by subject	[redacted]

Abbreviations: CI, confidence interval; EAS, Enrolled Analysis Set; ICR, independent central review; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan
Data-cut: August 1, 2019
Source: Modi 2020[1] and Daiichi-Sankyo, Inc., 2020 (data on file)

A9. Time to response

For the analysis of time to response, using data from the 1 August 2019 data cut-off of the DESTINY-Breast01 study, please clarify how many events had occurred and how many patients had been censored.

Time to response is defined as the time interval between the date of randomisation (the date of registration for not randomised subjects) and the date of first documentation of objective response (complete response [CR] or partial response [PR]). Time to response was measured for responding subjects (best overall response of PR or CR) only i.e. in 112 patients at the 1 August 2019 data-cut-off. Patients were not censored in this analysis.

A10. MAIC methods

Please provide details of the matching adjusted indirect comparison (MAIC) methods used to calculate effect estimates and confidence intervals (CIs) for response outcomes (objective response rate [ORR], disease control rate [DCR] and clinical benefit rate [CBR]).

The MAIC methods implemented for response outcomes were those proposed in the NICE DSU TSD 18 Appendix D example code. The patient characteristic matching calculation in each analysis was identical to that for the survival outcomes. A binomial general linear model was implemented to estimate the indirect comparison between T-DXd and comparator on the log odds ratio (OR) scale. A sandwich estimator was used to calculate the variance of the log OR, from which the standard error and confidence intervals could be calculated.

A11. Median OS and PFS from studies included in the MAICs

The ERG has noted discrepancies between some of the CIs around the median OS and PFS results reported in the CS for the studies included in the MAIC (Tables 19, 21, 25, 27, 31, 33, 37, 39, 43, 45, 49, 51, 55, 57) and the results (from the same studies) presented in the CS (Appendix D, Table 12). Please explain why the CIs differ.

The data reported in Table 12, Appendix D, are the data from the original aggregate study publications, for example, in Cortes 2011[5] (EMBRACE) the median PFS is reported as 3.7 months (95% CI 3.3, 3.9). The data reported in the individual MAIC

tables are the estimated median PFS and 95% CI calculated from the reconstructed individual patient-level data extracted from the Kaplan-Meier (K-M) curves, for example, for Cortes 2011 (EMBRACE) this was estimated as 3.66 months (95% CI 3.26, 3.81) (Document B, Table 21).

A12. MAIC results

Please clarify whether the following (i-iv) MAIC results (CS, p27) are correct (they are inconsistent with those reported in the MAIC results section [Tables 23, 29, 35, 56, 58]):

i. Comparator: vinorelbine; study: Sim 2019; outcomes: OS (HR [redacted]) and PFS (HR [redacted])

   For OS, the hazard ratio (HR) value of [redacted] in the summary table is a reporting error; this should be [redacted] (95% CI [redacted], [redacted]) as per Table 56. Similarly, for PFS, the HR should be [redacted] (95% CI [redacted], [redacted]) as per Table 58.

ii. Comparator: eribulin study: Barni 2019; outcomes: ORR (OR [redacted]), DCR (OR [redacted]) and CBR (OR [redacted]).

   The first three rows in the table on page 27 were misaligned. The response ORs should be as presented in Table 6.

Table 6: Corrected results from response MAICs

Comparator	Study	Odds ratio for T-DXd vs comparator		
		ORR	DCR	CBR
Eribulin	Barni 2019	[redacted]	[redacted]	-
	Cortes 2010	[redacted]	[redacted]	[redacted]
	Cortes 2011	[redacted]	[redacted]	[redacted]
	Gamucci 2014	[redacted]	[redacted]	[redacted]
Capecitabine	Fumoleau 2004	[redacted]	[redacted]	-
	Blum 2001	[redacted]	[redacted]	-
Vinorelbine	Sim 2019	[redacted]	-	[redacted]

iii. Comparator: eribulin study: Cortes 2010; outcomes: ORR (OR [redacted]), DCR (OR [redacted]) and CBR ([redacted]).

   As above (see Table 6).

iv. Comparator: eribulin study: Cortes 2011; outcomes: ORR (OR [redacted]), DCR (OR [redacted]) and CBR (OR [redacted]).

As above (see Table 6).

A13. Number of participants contributing data to the Barni 2019 MAIC

Please clarify why, in Table 24, Figure 12 and Table 27 of the CS, the number of participants in the eribulin arm of the Barni 2019 study is reported to be 95, while in Figure 11 and Table 25 of the CS, the number of participants in the eribulin arm of the Barni 2019 study is reported to be 100, and in Table 11 of Appendix D to the CS, the number of HER2+ patients in this study is reported to be 103.

Different numbers of HER2+ patients had available data for each of the survival analyses. Figure 3 of Barni 2019[6] indicates 95 HER2+ patients had PFS data; Figure 4 of Barni 2019 indicates 100 HER2+ patients had OS data and there were 103 HER2+ patients in total included in the study.

A14. Effective sample size of the Sim 2019 MAIC

Please clarify why, in Table 54 of the CS, the effective sample size (ESS) for the weighted T-DXd arm of the DESTINY-Breast01 study is reported to be [redacted], while in the text on p84, Table 55 and Table 57 of the CS, the ESS is reported to be [redacted].

The effective sample size (ESS) should be [redacted]; the value stated in Table 54 represents a reporting error.

A15. Bias in MAIC estimates

It is stated in Technical Support Document (TSD) 18 (pp4-5) that:

> "An unanchored MAIC or STC effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate."

It is also recommended in TSD 18 (p56) that:

> "…if unanchored forms of population adjustment are to be presented, it is essential that submissions include information on the likely bias attached to the estimates, due to unobserved prognostic factors and effect modifiers distributed differently in the studies."

Please provide information on the likely range of bias attached to the unanchored MAIC estimates.

In Document B, the process by which prognostic factors and effect modifiers were identified is described. In summary, there were two methods used to identify potential confounding factors:

- Through published literature
- Via personal communication with an external clinical expert.

Of the relevant factors identified from these two sources, imbalance in unobserved factors may occur in all MAIC analyses due to the lack of published aggregate data with respect to:

- Brain metastases
- Comorbidities (e.g. prior respiratory or cardiac disease)
- Number of metastatic sites (not available from DESTINY-Breast01).

Number of lines of treatment prior to T-DM1 was also very poorly reported, mostly due to the fact that comparator studies were not designed to specifically enrol only HER2+ patients. It is unclear what the impact of not including these variables in the model would have on the adjusted outcome. However, several analyses resulted in small ESS and thus, in these analyses, it may not have been practical to include additional variables.

Of the confounding factors that were available for some or most studies (Table 7), we conducted sensitivity analyses to explore the potential impact on PFS of not matching the pre-specified variable, for example in the case where data were not reported. All studies reported age and proportion of patients having undergone ≥3 prior lines of treatment. Note that although the analysis with age matching excluded was selected

for Sim 2019[7] in the base-case (due to the slightly increased ESS), the exploratory analyses reported here match for all possible variables included, except the one under investigation.

In Table 7, cells shaded in orange are the highest/lowest values for each variable. For the sensitivity analyses, the respective matching variable was removed from the relevant study. In each case, there was no change in the unadjusted HR estimate; these are provided purely for comparison with the weighted results.

In conclusion, our exploratory analyses suggest that matching the proportion of patients with ≥3 prior lines of therapy may be the variable with the greatest influence on the relative treatment effects in the form of HR values and therefore, if this data were missing for any particular study, this could bias the analysis results. However, all studies reported data for this variable and so it was possible to match this characteristic for all base-case analyses.

Table 7: Variables used for matching in the MAIC

Study	Age	ECOG-PS = 0	Prior hormone therapy = yes	Prior lines ≥3	Visceral disease = yes	Hormone receptor = positive†
DESTINY-Breast01[1]	56.0	55.4%	48.9%	91.8%	91.8%	52.7%
Barni 2019[6]	59.5	40.9%		64.6%	59.4%	
Blum 2001[8]	52.5		70.2%	66.2%	79.7%	
Cortes 2010[9]	56.0	37.2%		89.6%	71.0%	
Cortes 2011 (EMBRACE)[5]	55.0	42.7%	85.0%	87.0%		64.4%
Fumoleau 2004[10]	54.0	43.7%		45.2%		
Gamucci 2014[11]	62.0		69.2%	50.4%	80.5%	84.0%
Sim 2019[7]	52.0	25.7%		100.0%	50.0%	45.9%
# of studies not reporting variable	**0**	**2**	**4**	**0**	**2**	**4**
Label for sensitivity analysis (SA)	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**	**SA6**

† Oestrogen receptor positive and/or progesterone receptor positive.

SA1: MAIC without matching for age

Although all studies reported average age at baseline, an analysis was conducted to consider the impact of not matching for age, given the potential for both younger and older patients to fare worse than patients aged in the middle of the range, regardless of treatment. Gamucci 2014[11] had the highest average age and Sim 2019[7] had the lowest average age of all the comparator studies. These two studies were chosen for SA1 to show the potential impact of not matching for age.

For the comparison with Gamucci 2014, excluding age had no observable impact on the median PFS (95% CI) compared with matching all variables for the matched DESTINY-Breast01 patients (Table 8), and a very limited impact on the weighted HR (

Table **9**).

Table 8: Comparison of baseline characteristics - T-DXd (DESTINY-Breast 01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Mean/ median age	Prior hormone therapy (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	48.9	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) not matching age	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)[11]	133.0	62.0	69.2	50.4	84.0	80.5	115	4.45 (3.74 to 5.24)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan
*Calculated using Brookmeyer and Crowley method

Table 9: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA1: not matching age*
Unadjusted	T-DXd vs eribulin	[redacted]	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

In contrast, for the comparison with Sim 2019, there was a greater impact of removing age from the matching variables, however, the median PFS for T-DXd improved compared with matching all variables and there was a small decrease in the weighted HR estimate in favour of T-DXd (Table 11). The matching without age also increased the ESS by ~50%, although this was still a small sample size ([redacted] vs [redacted], respectively). Note that the analysis without age was chosen as the base case for Sim 2019 due to the larger ESS.

Table 10: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not matching age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)[7]	74.0	52.0	25.7	100.0	45.9	50.0	65	2.73 (2.51 to 4.22)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 11: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA1: not matching age*
Unadjusted	T-DXd vs vinorelbine	[redacted]	[redacted]

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA1: not matching age*
Weighted standard CI	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

SA2: MAIC without matching for proportion with ECOG of 0

Two studies did not report the percentage with ECOG=0 (Blum 2001[8], Gamucci 2014[11]). All other comparator studies reported lower percentage with ECOG=0 compared with DESTINY-Breast01. For SA2 we chose the study with the lowest percentage which was Sim 2019 to show the potential impact of not matching for percentage with ECOG=0 on the results of the MAIC versus Blum 2001 and Gamucci 2014. There was no observable impact on the K-M estimates of the weighted data compared with matching all factors (Table 12) and minimal impact on the point estimate for the HR with a narrower 95% CI (Table 13), likely due to the slightly larger ESS when matching without including ECOG (ESS [redacted] vs [redacted], respectively). Matching based on proportion of patients with ECOG=0 may not have as great an influence on the MAIC analyses, compared with other variables that we considered.

Table 12: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Mean/ median age	ECOG = 0 (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) not matching % ECOG=0	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)[7]	74.0	52.0	25.7	100.0	45.9	50.0	65	2.73 (2.51 to 4.22)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 13: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA2: not matching % ECOG=0*
Unadjusted	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

SA3: MAIC without matching for proportion with prior hormone therapy

Four studies did not report the percentage with prior hormone therapy (Barni 2019[6], Cortes 2010[9], Fumoleau 2004[10] and Sim 2019[7]). The remaining three comparator studies reported higher percentages with prior hormone therapy compared to DESTINY-Breast01. For SA3 we picked the study with the highest percentage which was Cortes 2011[5] (EMBRACE) to show the potential impact of not matching for percentage with prior hormone therapy on the results of the MAIC versus Barni 2019, Cortes 2010, Fumoleau 2004 and Sim 2019. The ESS was almost doubled when excluding matching for prior hormone therapy, but there was only a limited impact on the median PFS and 95% CI compared with the weighted analysis based on all available covariates (Table 14). The HR slightly decreased and remained significantly in favour of T-DXd.

Table 14: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior hormone therapy (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	48.9	91.8	52.7	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior hormone therapy (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Events	Median (95% CI*)
matching prior hormone				[redacted]				
Eribulin (Cortes 2011)[5]	508.0	55.0	42.7	85.0	87.0	64.4	357	3.66 (3.26 to 3.81)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method

Table 15: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Cortes 2011)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA3: not matching % prior hormone therapy*
Unadjusted	T-DXd vs eribulin	[redacted]	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

SA4: MAIC without matching for proportion with three or more prior treatment lines

All studies reported the proportion with three or more prior lines of treatment at baseline. Fumoleau 2004[10] had the lowest proportion of all the comparator studies and Sim 2019[7] had the highest proportion of all the comparator studies. These two studies were chosen for SA4 to show the potential impact of not matching for the proportion of patients receiving ≥3 prior treatment lines. Removing this variable appears to have a greater impact on the analysis results when there is a large imbalance (45.2% vs 91.8%, in the Fumoleau 2004 and DESTINY-Breast01, respectively) compared with the other variables we were able to include, therefore it is advantageous that we were able to match this variable in all comparisons.

For the Fumoleau (capecitabine) comparison, the ESS increased four-fold in the sensitivity analysis ([redacted] vs [redacted], respectively) (Table 16). Compared with matching on all available variables, the value of the HR was slightly larger, but still significantly favouring T-DXd over capecitabine.

Table 16: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Treatment (study)	N/ ESS	Mean/ Median age	ECOG= 0 (%)	Prior line ≥3 (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not matching % ≥3 prior lines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Fumoleau 2004)[10]	126.0	54.0	43.7	45.2	110	4.90 (3.96 to 6.48)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 17: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs capecitabine (Fumoleau 2004)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA4: not matching % ≥3 prior lines*
Unadjusted	T-DXd vs capecitabine	[redacted]	[redacted]
Weighted standard CI	T-DXd vs capecitabine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs capecitabine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

There was a smaller impact on the MAIC analysis which included Sim 2019[7] when prior line ≥3 was excluded, because in this case the proportion of patients before matching was already more similar (100% vs 91.8%, respectively). The median PFS increased for T-DXd compared with matching for all variables and consequently, the HR decreased, in favour of T-DXd.

Table 18: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not matching % ≥3 prior lines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)[7]	74.0	52.0	25.7	100.0	45.9	50.0	65	2.73 (2.51 to 4.22)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 19: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA4: not matching % ≥3 prior lines*
Unadjusted	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

SA5: MAIC without matching for proportion with visceral disease

Two studies did not report the proportion with visceral disease (Cortes 2011[5], Fumoleau 2004[10]). For all other comparator studies, a lower proportion with visceral disease was reported compared to DESTINY-Breast01. For SA5 we picked the study with the lowest proportion which was Sim 2019[7] to show the potential impact of not matching for proportion with visceral disease on the results of the MAIC versus Cortes 2011 and Fumoleau 2004.

When the proportion of patients with visceral disease is not similar between studies (91.8% vs 50.0% in DESTINY-Breast01 and Sim 2019, respectively) this clearly has a big impact on the ESS. When excluding a match for visceral disease, the ESS increased dramatically from [redacted] to [redacted] (Table 20). However, the increase in ESS does not translate to a large change in the HR values which increase somewhat but are still significantly in favour of T-DXd (Table 21).

Table 20: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not matching % visceral disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Vinorelbine (Sim 2019)[7]	74.0	52.0	25.7	100.0	45.9	50.0	65	2.73 (2.51 to 4.22)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 21: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA5: not matching % visceral disease*
Unadjusted	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

SA6: MAIC without matching for proportion with hormone receptor positive disease

Four studies did not report the proportion with hormone receptor positive disease at baseline (Barni 2019[6], Blum 2001[8], Cortes 2010[9] and Fumoleau 2004[10]). Gamucci 2014[11] had the average highest proportion of the comparator studies and Sim 2019 had lowest. These two studies were chosen for SA6 to show the potential impact of not matching for hormone receptor positive status on the MAIC results versus Barni 2019, Blum 2001, Cortes 2010 and Fumoleau 2004.

Excluding hormone receptor positive disease had no observable impact on median PFS and 95% CI in Gamucci 2014 (Table 22) and similarly, little impact on the HR values (Table 23). For Sim 2019, the median PFS and 95% CI varied from the analysis where all possible weightings were included (Table 24) but as with Gamucci, there was little impact on the HR (Table 25).

Table 22: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Treatment (study)	N/ ESS	Mean/ median age	Prior hormone therapy (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	48.9	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) not matching for % hormone receptor positive disease	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Eribulin (Gamucci 2014)[11]	133.0	62.0	69.2	50.4	84.0	80.5	115	4.45 (3.74 to 5.24)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 23: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs eribulin (Gamucci 2014)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA6: not matching for % HR positive disease*
Unadjusted	T-DXd vs eribulin	[redacted]	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hormone receptor; T-DXd, trastuzumab deruxtecan.

Table 24: Comparison of baseline characteristics - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Treatment (study)	N/ ESS	Mean/ median age	ECOG= 0 (%)	Prior line ≥3 (%)	Hormone receptor positive (%)	Visceral disease (%)	Events	Median (95% CI*)
T-DXd unadjusted (DESTINY-Breast01)[1]	184.0	55.96	55.4	91.8	52.7	91.8	58	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd weighted (DESTINY-Breast01) - not matching for % hormone receptor positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine (Sim 2019)[7]	74.0	52.0	25.7	100.0	45.9	50.0	65	2.73 (2.51 to 4.22)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; T-DXd, trastuzumab deruxtecan.
*Calculated using Brookmeyer and Crowley method.

Table 25: Hazard ratios for PFS - T-DXd (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Method	Comparison	Hazard ratio (95% CI)	*Hazard ratio (95% CI) SA6: not matching for % HR positive disease*
Unadjusted	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted standard CI	T-DXd vs vinorelbine	[redacted]	[redacted]
Weighted bootstrapped CI	T-DXd vs vinorelbine	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

Section B: Clarification on cost effectiveness data

B1. Priority question: Comparative analysis

Please provide a comparative analysis of the baseline characteristics of patients participating in the DESTINY-Breast01 study and in the TH3RESA trial to demonstrate that there are no important differences between these two populations.

A comparison of the baseline characteristics of patients in DESTINY-Breast01 and TH3RESA is presented in Table 26; the baseline characteristics of the two studies are considered to be broadly aligned.

Table 26: Comparison of baseline characteristics in DESTINY-Breast01 and TH3RESA

Characteristic	DESTINY-Breast01 (Modi 2020[1]) (n = 184)	TH3RESA (Krop 2014[12]) (n=404)
Age (years) – median (range)	55 (28–96)	53 (27–89)
≥65 years – n (%)	44 (24%)	59 (14%)
World region – n (%)		
North America	53 (29%)	99 (25%)
Europe	68 (37%)	-
Western Europe	-	171 (42%)
Asia	63 (34%)	-
Other	-	134 (33%)
Race – n (%)		
White	101 (55%)	325 (80%)
Asian	70 (38%)	57 (14%)
Other	9 (5%)	22 (5%)
Missing data	4 (2%)	-
ECOG performance-status – n (%)		
0	102 (55%)	180 (45%)
1	81 (44%)	200 (50%)
2	1 (1%)	22 (5%)
Hormone-receptor status – n (%)		
Positive	97 (53%)	208 (51%)
Negative	83 (45%)	185 (46%)
Unknown	4 (2%)	11 (3%)
HER2 expression – n (%)		
IHC 3+	154 (84%)	-
IHC 1+ or 2+, ISH-positive	28 (15%)	-
Missing data	2 (1%)	-
Median sum of diameters of target lesions – cm (range)	5.5 (1.2–24.5)	-
Visceral disease involvement – n (%)	-	302 (75%)
Disease extent – n (%)		
Metastatic	-	391 (97%)
Unresectable locally advanced or recurrent	-	13 (3%)
Measurable disease	-	345 (85%)
No. of previous cancer regimens for advanced breast cancer†		
Median (range)	6 (2–27)	4 (1–14)
≤3 – n (%)	31 (17%)	131 (33%)

4–5 – n (%)	38 (21%)	149 (37%)
>5 – n (%)	115 (62%)	122 (30%)
Previous systemic cancer therapy – n (%)		
Trastuzumab	184 (100%)	404 (100%)
Duration (months)	-	24.3 (1.4–140.5)
Lapatinib	-	404 (100%)
Duration (months)	-	7.98 (0.1–71.2)
Trastuzumab emtansine	184 (100%)	-
Pertuzumab	121 (66%)	-
Other anti-HER2 therapy	100 (54%)	-
Hormone therapy	90 (49%)	-
Other systemic therapy	183 (99.5%)	-
Previously treated asymptomatic brain metastasis – no. (%)	24 (13%)	40 (10%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.
† Note that the number of previous cancer regimens for advanced breast cancer is more similar between DESTINY-Breast01 and TH3RESA when considering the updated definition of prior therapies for DESTINY-Breast01 (see Question A5.iii); under this updated definition, the median number of prior therapies is 5 (range: 2 to 17).

B2. Priority question: Proportional hazards

Please undertake and provide results from testing of the OS proportional hazards assumption using data from the DESTINY-Breast01 study and the TH3RESA trial.

The proportional hazards assumption was assessed on the basis of Schoenfeld residuals (Figure 1) and visual inspection of the log-log plot (Figure 2). The assumption of proportional hazards is considered to be valid on the basis that:

- The locally weighted scatterplot smoothing (LOWESS) curve lies close to the y=0 line
- The assumption of proportional hazards between T-DXd and T-DM1 could not be rejected based on the results of the Schoenfeld residual test (p=0.593)
- The log-log plots for each patient group were broadly parallel over time.

Figure 1: Schoenfeld residuals (overall survival), DESTINY-Breast01 vs TH3RESA

[redacted]

Figure 2: Log-log plot (overall survival), DESTINY-Breast01 vs TH3RESA

[redacted]

B3. Priority question: Alternative approach to modelling OS

IF (i) there are important differences between the baseline patient characteristics of patients participating in the DESTINY-Breast01 study and the TH3RESA trial **OR, IF (ii)** the OS data from the DESTINY-Breast01 study and the TH3RESA trial are not proportional (the proportional hazards assumption does not hold), then please undertake an alternative approach to that described in the CS (and company model) to estimating OS for patients treated with T-DXd. Please also provide an updated company model and cost effectiveness results generated using this alternative approach to modelling OS.

No alternative approaches to modelling OS for patients treated with T-DXd were undertaken in response to this question, on the basis that:

- No important differences were observed between the baseline characteristics of patients participating in the DESTINY-Breast01 and TH3RESA studies (see B1)
- The proportional hazards assumption is shown to hold (see B2).

Section C: Additional clarification question

C1. Confidence intervals

The ERG has noted that the CI for median PFS in the DESTINY-Breast trial reported in Table 13 of the CS differs to the CI for median PFS in the DESTINY-Breast trial reported in the MAIC results tables (Table 21, Table 27, Table 33, Table 39, Table 45, Table 51, Table 57). Please explain why the CIs differ.

The CI data presented in Table 13 of the CS match those in the key publication for DESTINY-Breast01 (Modi 2020[1]), which were calculated using Brookmeyer and Crowley methods. In the MAICs we have used a linear confidence interval method. Implementing the log-log method instead, the 95% CIs match Modi 2020 for DESTINY-Breast01 and there is a small impact on the 95% CI estimates for the comparator study (Table 27). However, as would be expected, the HR remains unchanged (Table 28).

Table 27: Example KM summary of PFS - T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019) – linear method vs log-log method for confidence interval calculations

Treatment (study)	N/ ESS	Events	Median (95% CI linear method)	Median (95% CI log-log method)
T-DXd unadjusted (DESTINY-Breast 01)[1]	184.0	58	16.36 (15.21 to 18.07)	16.36 (12.68 to NA)
T-DXd weighted (DESTINY-Breast 01)	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin (Barni 2019)[6]	95.0	79	3.28 (2.72 to 3.94)	3.28 (2.66 to 3.94)

Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; NA, not applicable; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Table 28: HRs for PFS using log-log method – T-DXd (DESTINY-Breast01) vs eribulin (Barni 2019)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs eribulin	[redacted]
Weighted standard CI	T-DXd vs eribulin	[redacted]
Weighted bootstrapped CI	T-DXd vs eribulin	[redacted]

Abbreviations: CI, confidence interval; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

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	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care.
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.] If so, please state the name of manufacturer, amount, and purpose of funding.	Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. In 2019/20 Breast Cancer Now has either received or been pledged the following funding from pharmaceutical companies which are listed in the matrix for this appraisal: - Roche, £20,000, Helpline grant - Roche, £30,000, as part of the UK Interdisciplinary Breast Cancer Symposium (hosted by Breast Cancer Now, in partnership with a number of professional bodies) - Roche £44,121, Living with Secondary Breast Cancer Service - Daiichi Sankyo, £30,000, as part of the UK Interdisciplinary Breast Cancer Symposium (hosted by Breast Cancer Now, in partnership with a number of professional bodies) - Daiichi Sankyo, £22.5k, Helpline grant - Eisai, £2,850, as part of the UK Interdisciplinary Breast Cancer Symposium (hosted by Breast Cancer Now, in partnership with a number of professional bodies)

	Further details about our income are set out in our annual report, which is available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts.
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 those affected by breast cancer to gather information about patient experience. It has been difficult to find patients with direct experience of this treatment for this indication given the small UK population involved in the phase II trial.
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?	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. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed with secondary breast cancer right from the start, or they can develop the condition months or years after treatment for their primary breast cancer has ended. Some breast cancer cells have a higher than normal level of a protein called HER2 on their surface, which stimulates them to grow. This is known as HER2 positive breast cancer. Around one in five invasive breast cancers are HER2 positive. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary

	breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". 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 hospital appointments. People living with secondary breast cancer have shared the following: "It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all". "My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand". 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 continuous pain and tightness in the chest. Also 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. 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 when considering their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Although in recent years there has been the welcome introduction of new HER2 targeted therapies in the first and second line setting for patients with HER2 positive secondary breast cancer, there are currently no targeted treatments recommended for use after 2 or more prior lines of treatment. This can be incredibly agonising for those who have already progressed beyond these treatment options. The exact treatment for patients who have already received 2 or more anti-HER2 therapies may differ. Eribulin is an option which may be considered as it is recommended for treating patients with secondary breast cancer after 2 or more chemotherapy regimens. Other chemotherapies may also be considered, including capecitabine or vinorelbine. One patient with HER2 positive secondary breast cancer who has been on Kadcyla for over three years told us: "Every time I meet my clinician we horizon-scan because I'm well aware I'm on Kadcyla after Perjeta didn't work for me at all so we always have that conversation. It's always a pretty depressing conversation. There isn't anything else out there beyond Kadcyla apart from broad spectrum chemotherapies. I'm always looking for something which is effective and has similar or more tolerable side effects. I've been on Kadcyla for 3.5 years. It's relentless. The cycle of every three weeks and every quarter a PET scan. The first week is just hideous for me. My life is divided into those period of times. I can't see any other future option out there at the moment. Please don't give up on new drugs that a) could be potential options to prolong people's lives and b) drugs that could give me as a secondary breast cancer patient a good quality of life."

8. Is there an unmet need for patients with this condition?	Yes, there is an urgent need for new and clinically-effective treatments for pre-treated patients who progress on current treatments. There have been welcome treatment developments for HER2 positive secondary breast cancer including pertuzumab in combination with trastuzumab and docetaxel as a first line treatment and trastuzumab emtansine in the second line setting. However, there is a currently a lack of targeted treatment options for third and later lines when these initial treatments stop working. A patient with HER2 positive secondary breast cancer told us: “The more this goes on, the more I live with it, the more I go through the relentless cycle, the more the idea going for a broad-spectrum chemotherapy after Kadcyla is completely scary. Why would I do that? I need drugs that are tolerable from a quality of life point of view and can build upon for a considerable point of time. If and when Kadcyla stops working, I’ve already spoken to my oncologist about what could be next and the chemotherapy. I know what this feels like, to put my body through so much. I don’t think that would be an option for me. At the moment, Kadcyla is the only thing keeping me going. I’d be highly likely to choose no treatment when and if Kadcyla fails.”
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, we do not have any additional data beyond what is already in the public domain at the time of submission via the published phase II trial. The trial demonstrated that with this treatment there is an objective response rate of 60.9% with a median duration of progression free survival of 16.4 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Delaying progression can also have a positive impact on patients’ emotional wellbeing and mental health, as it may mean that the individual can continue doing 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 which in turn could help to reduce any stress the patient is experiencing worrying about the impact on those closest to them.

	Importantly, the introduction of this treatment would provide another treatment option which could be considered and delay the use of chemotherapy alone which is traditionally associated with more severe side effects and potentially a poorer quality of life for patients. People can also often be particularly anxious and worried about starting chemotherapy treatment.
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. At the time of this patient submission there is no published data on side effects of this drug when compared to other another treatment option. In the phase II trial, the majority of patients had at least one adverse event during treatment and of these patients 57.1% had an adverse event of a grade 3 or higher. During the study, the most common adverse events of grade 3 or higher were a decreased neutrophil account (in 20.7% of patients), anaemia (in 8.7%) and nausea (in 7.6%). The drug was also associated with interstitial lung disease in 13.6% of patients, with some higher-grade cases. If patients experience some of these side effects, it could have a negative impact on their quality of life. It will be important for healthcare professionals to carefully monitor these side effects and take the appropriate measures as required and that the correct risk management is in place. 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 receive treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option

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.	
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?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of incurable 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 a significant unmet need for later line treatments for secondary breast cancer. This treatment could add to the drug options available for patients with this type of breast cancer which is incurable. Any new treatments that can delay the need to start on chemotherapy which is generally associated with more severe side effects and a poorer quality of life is welcomed by patients.
- The trial demonstrated that with this treatment there is an objective response rate of 60.9% with a median duration of progression free survival of 16.4 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends.
- There are side effects associated with this treatment which could negatively impact on an individual's quality of life. The benefits and risks of this treatment would need to be clearly discussed with the patient so they can make a decision that is right for them.

Thank you for your time.

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after two or more anti-HER2 therapies

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after two or more anti-HER2 therapies [ID2697]

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LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
AE	Adverse event
CI	Confidence interval
CSR	Clinical study report
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
FDA	Food and Drug Administration
HER2+	Human epidermal growth factor 2 overexpression (positive)
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IPD	Individual patient data
ISH	In situ hybridisation
LABC	Locally advanced breast cancer
MAIC	Matching-adjusted indirect comparison
MBC	Metastatic breast cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
PSS	Personal social services
QALY	Quality adjusted life year
RCT	Randomised controlled trial
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TTD	Time to treatment discontinuation
TTR	Time to response
UBC	Unresectable breast cancer

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of company's key model outcomes and the modelling assumptions that have the greatest effect on the ICER per quality adjusted life year (QALY). Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID2697	Summary of issue	Report sections
1	Immature DESTINY-Breast01 study data	Section 1.3, Section 2.4.1, Section 3.3.3, Section 3.5.4, Section 3.5.5, Section 3.6, Section 4.2.6, Section 6.1
2	Lack of direct effectiveness evidence for the comparison of T-DXd versus relevant comparators	Section 1.3,Section 2.4.1, Section 3.2.1, Section 3.3, Section 3.6, Section 6
3	Relevance of DESTINY-Breast01 study results to NHS clinical practice	Section 1.4, Section 2.3.1, Section 3.2.1, Section 3.6
4	Company eribulin and capecitabine MAIC results are not suitable for decision-making	Section 1.4, Section 2.4.4, Section 3.5, Section 3.6
5	Company vinorelbine OS MAIC results are inconclusive	Section 1.4, Section 3.5, Section 3.6
6	Company OS modelling of T-DXd is not robust	Section 1.5, Section 6.2
7	Company OS modelling of comparator treatments is not robust	Section 1.5, Section 6.3
8	NICE End of Life criteria may not be met	Section 7

MAIC= matching-adjusted indirect comparison; OS=overall survival; T-DXd=trastuzumab deruxtecan

The relative effectiveness of trastuzumab deruxtecan (T-DXd) versus the comparators cannot be determined with any degree of certainty. This means that the company cost effectiveness results are unreliable and should not be used as the basis for decision making. The ERG has therefore not generated any alternative cost effectiveness results.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (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 increasing survival
- as patients in the progression-free survival health state who receive T-DXd have a higher ulitity than patients who receive comparator drugs.

Overall, the technology is modelled by the company to affect costs by:

- longer time on treatment combined with higher drug cost
- longer time alive with associated health care costs.

The company modelling assumptions that have the greatest effect on the ICER per QALY gained are:

- overall survival projections
- relative dose intensity estimates
- utility value for progressed disease.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Immature DESTINY-Breast01 study data

Report section	Section 2.4.1, Section 3.3.3, Section 3.5.4, Section 3.5.5, Section 3.6, Section 4.2.6, Section 6
Description of issue and why the ERG has identified it as important	The DESTINY-Breast01 study is immature (median duration of follow-up 11.1 months; range, 0.7 months to 19.9 months). Median OS has not been reached (13.6% patients had died) and median PFS and DoR are uncertain (the occurrence of an additional event in the "at risk" population could have a significant impact on the size of these results)
What alternative approach has the ERG suggested?	The ERG acknowledges that there are no datasets that provide long- term results demonstrating the efficacy of T-DXd
What is the expected effect on the cost effectiveness estimates?	The absence of mature survival data means that the company cost effectiveness results are not robust
What additional evidence or analyses might help to resolve this key issue?	The ERG has been informed that updated DESTINY-Breast01 study results will be made available during the technical engagement process. However, without robust evidence to allow a comparison of the efficacy of T-DXd versus the comparators of interest, more mature T-DXd evidence from any single-arm source is of limited value

DoR=duration of response; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; T-DXd=trastuzumab deruxtecan

Issue 2 Lack of direct evidence for the comparison of the effectiveness of T-DXd versus relevant comparators

Report section	Section 2.4.1, Section 3.2.1, Section 3.3, Section 3.6, Section 6
Description of issue and why the ERG has identified it as important	The DESTINY-Breast01study is a single-arm phase II study. This means that there is no direct effectiveness evidence for the comparison of T-DXd versus eribulin, capecitabine or vinorelbine
What alternative approach has the ERG suggested?	The ERG acknowledges that there are no alternative datasets that provide relevant data to allow a direct comparison of T-DXd versus eribulin, capecitabine or vinorelbine
What is the expected effect on the cost effectiveness estimates?	Uncertainty around the validity of comparative effectiveness results leads to uncertainty around the validity of the company cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	Direct evidence for the comparison of T-DXd versus any of the relevant comparators would be useful. The ERG highlights that the phase III DESTINY-Breast02 trial of T-DXd versus investigator's choice is scheduled to complete in [redacted]. However, neither of the comparator treatments (trastuzumab+capecitabine or lapatinib+capecitabine) in this trial are currently recommended by NICE

ERG=Evidence Review Group; T-DXd=trastuzumab deruxtecan

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 3 Relevance of DESTINY-Breast01 study results to NHS clinical practice

Report section	Section 2.3.1, Section 3.2.1, Section 3.6
Description of issue and why the ERG has identified it as important	The focus of this appraisal is on T-DXd as a ≥third-line treatment option for patients with UBC and mBc. The company anticipates that T-DXd will be used in the third-line setting. Although all patients had received at least two prior anti-HER2-treatments, [redacted] of patients in the trial received exactly two prior anti-HER2 treatments (excluding hormone therapy); the remaining patients received ≥3 prior therapies Patients enrolled in the DESTINY-Breast01 study had received a median of six (range 2 to 24) prior lines of treatment for LABC or MBC (excluding hormone therapy). The ERG considers that most patients treated in the NHS are unlikely to receive six lines of treatment In addition to at least two lines of anti-HER2 therapy that are recommended by NICE, over half of the patients in the DESTINY-Breast01 study had received additional anti-HER2 therapies that are not currently recommended by NICE
What alternative approach has the ERG suggested?	The ERG acknowledges that there are no data available from a population that more closely matches patients treated in NHS clinical practice
What is the expected effect on the cost effectiveness estimates?	The effect of these issues on efficacy results for OS and PFS, and therefore on cost effectiveness results, is not known
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; HER2(+)=human epidermal growth factor 2 (positive); LABC=locally advanced breast cancer; MBC=metastatic breast cancer; NHS=National Health Service; UBC=unresectable breast cancer; RCT=randomised controlled trial; T-DXd=trastuzumab deruxtecan

Issue 4 Company eribulin and capecitabine MAICs results are not suitable for decision-making

Report section	Section 2.4.4, Section 3.5, Section 3.6
Description of issue and why the ERG has identified it as important	None of the comparator trials included in the MAICs for T-DXd versus eribulin and T-DXd versus capecitabine were wholly conducted in the patient population relevant to this appraisal, namely patients with HER2+ disease who had received two or more prior lines of anti-HER2 therapy. The company was unable to adjust for HER2 status or prior anti-HER2 therapy in these MAICs (as all patients in the DESTINY-Breast01 study had HER2+ disease and had received two or more lines of anti-HER2 therapy). This renders these results unsuitable for decision-making
What alternative approach has the ERG suggested?	The ERG considers that there is no alternative approach
What is the expected effect on the cost effectiveness estimates?	Limited impact - the company only used results from the eribulin and capecitabine MAICs to model PFS (and TTD) for comparator treatments
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; HER2(+)=human epidermal growth factor 2 (positive); MAIC=matching-adjusted indirect comparison; OS=overall survival; RCT=randomised controlled trial; T-DXd=trastuzumab deruxtecan; TTD=time to treatment discontinuation

Issue 5 Company vinorelbine OS MAIC results are inconclusive

Report section	Section 3.5, Section 3.6
Description of issue and why the ERG has identified it as important	As PH was violated for both OS and PFS in this MAIC, median survival times rather than HRs were used to compare survival outcomes. As DESTINY-Breast01 study OS data are immature, and the median has not been reached, there is no way to meaningfully compare OS MAIC T-DXd versus vinorelbine results
What alternative approach has the ERG suggested?	The ERG considers that there is no alternative approach
What is the expected effect on the cost effectiveness estimates?	None - the company does not use results from the vinorelbine MAIC in their economic analysis
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; MAIC=matching-adjusted indirect comparison; OS-overall survival; PFS=progression-free survival; PH=proportional hazards; RCT=randomised controlled trial; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan

1.5 The cost effectiveness evidence: summary of the ERG's key issues

Issue 6 Company OS modelling of T-DXd is not robust

Report section	Section 6.2
Description of issue and why the ERG has identified it as important	The DESTINY-Breast01 study OS data are very uncertain (median follow-up=11.1 months, 13.6% deaths). The company used a simple between trial analysis of data from the single-arm, phase II DESTINY-Breast01 study and data from the T-DM1 arm of the phase III TH3RESA trial (T-DM1 versus physician's choice) to model OS for patients receiving T-DXd. The ERG considers that this approach was not robust and that company projections of OS for patients receiving T-DXd are of limited use for decision making
What alternative approach has the ERG suggested?	The only alternative approach to modelling OS for patients receiving T-DXd would be to use results from the company MAICs. The ERG considers that the weaknesses of the evidence base mean that there are no reliable approaches to modelling OS for patients receiving T-DXd
What is the expected effect on the cost-effectiveness estimates?	There is a high degree of uncertainty around the validity of the company cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; MAIC=matching-adjusted indirect comparison; OS=overall survival; RCT=randomised controlled trial; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan

Issue 7 Company OS modelling of comparator treatments is not robust

Report section	Section 6.3
Description of issue and why the ERG has identified it as important	The company used unadjusted (except for HER2 status) K-M data from the comparator trials as the basis for modelling OS. The ERG considers that this approach is not robust as other treatment effect modifiers are also important
What alternative approach has the ERG suggested?	The only alternative approach to modelling OS for patients receiving T-DXd would be to use results from the company MAICs. The ERG considers that the weaknesses of the evidence base mean that there are no reliable approaches to modelling OS for patients receiving T-DXd
What is the expected effect on the cost-effectiveness estimates?	There is a high degree of uncertainty around the validity of the company cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; OS=overall survival; MAIC=matching-adjusted indirect comparison; RCT=randomised controlled trial; T-DXd=trastuzumab deruxtecan

1.6 Other key issues: summary of the ERG's view

Issue 8 NICE End of Life criteria may not be met

Report section	Section 7
Description of issue and why the ERG has identified it as important	All of the evidence presented in the studies of the comparators suggests that life expectancy is less than 24 months. However, whether the life expectancy of HER2+ patients who progress after receipt of TDM-1 as a second-line treatment and are fit enough for a third-line treatment is less than 24 months is unclear Whilst results from the company model suggest that the OS gain for patients receiving T-DXd could exceed 3 months, without more robust comparative OS data this gain is highly uncertain
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator

ERG=Evidence Review Group; OS=overall survival; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan

1.7 Summary of ERG's preferred assumptions and resulting ICER

The ERG considers that the relative effectiveness of T-DXd versus the comparators cannot be determined with any degree of certainty and has, therefore, not generated any preferred cost effectiveness results. The list price for T-DXd has yet to be finalised. The ERG highlights that eribulin is available to the NHS at a confidential discounted Patient Access Scheme (PAS) price and the company has made a T-DXd PAS application to the Patient Access Scheme Liaison Unit.

Company base case cost effectiveness results (list prices)

Technologies	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years gained; T-DXd=trastuzumab deruxtecan

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of trastuzumab deruxtecan (T-DXd; Enhertu®) to treat human epidermal growth factor receptor 2 positive (HER2+) unresectable breast cancer (UBC) or metastatic breast cancer (MBC) after two or more anti-HER2 therapies. In this Evidence Review Group (ERG) report, references to the company submission (CS) are to the company's document B, which is the company's full evidence submission.

2.2 Disease, intervention and comparators

2.2.1 HER2+ unresectable or metastatic breast cancer

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases.[1,2] The majority of cases are diagnosed in the early stages of the disease; however, a small proportion of patients are not diagnosed until the tumour is in the advanced stage and has spread within the breast (locally advanced [LABC]) or to other organs (metastatic).[3] Some patients with LABC have unresectable breast cancer (UBC) and all patients with MBC have unresectable disease. A proportion of patients diagnosed with early stage breast cancer will go on to develop a local recurrence or metastases.[4,5] The most advanced forms of breast cancer can be treated but are considered incurable.[6] Symptoms, which can be severe and debilitating, include cancer-related fatigue, pain and complications associated with affected organs (Table 1).[7-9] Health-related quality of life (HRQoL) in patients with advanced breast cancer (ABC) is particularly poor due to the incurable nature of the disease and the burdensome symptom profile.[10,11]

Table 1 Symptoms associated with advanced breast cancer

Site	Associated symptoms
General	Fatigue, difficulty sleeping, depression
Bone	Pain, hypercalcemia, pathologic fracture, loss of mobility
Brain	Headache, confusion, weakness, pain, seizure, altered mentation, cranial nerve palsies, speech impairment
Lymph nodes	Brachial plexopathies, pain
Liver	Discomfort or pain, nausea, swollen abdomen, loss of appetite, jaundice
Lungs	Pain, dyspnoea, haemoptysis, cough

Source: CS, Table 3 (Irvin 2011;[8] Cancer Research UK 2017[7])

Approximately 13% to 20% of breast cancer tumours are classified as HER2+ type.[12] In HER2+ breast cancer there is an over-expression of the HER2 protein present on the surface of the tumour cells.[12] A study of patients with HER2+ MBC found that the most frequently reported symptoms were tiredness, decreased sexual interest, lack of energy, sore muscles,

worrying, difficulty sleeping and joint pain.[13] In addition, brain metastases appeared more common compared to other subtypes of breast cancer, with studies reporting that up to 50% of women with HER2+ disease had developed brain metastases.[14] Brain metastases are associated with other debilitating symptoms, including seizures, stroke and personality changes,[15] which lead to reductions in HRQoL.[16]

The National Institute for Health and Care Excellence (NICE) and the UK National Coordinating Committee for Breast Pathology[12,17] recommend that HER2 status in patients with breast cancer should be routinely assessed in all cases of primary invasive breast carcinomas and in recurrent or metastatic tumours where biopsy tissue is available. Testing for HER2 status is carried out using immunohistochemistry (IHC) or in situ hybridisation (ISH) techniques.[12] IHC methods detect expression of the HER2 gene and score the extensivity of membrane staining of the tumour as positive (3+), negative (0/1+) or equivocal and warranting further assessment (2+).[12] A HER2+ result is defined as a >10% staining of the membrane in tumour cells.[12] ISH methods, which are used either upfront or for IHC borderline cases, are used to detect HER2 gene amplification.[12]

Historically, survival for patients with HER2+ MBC has been poor relative to other types of breast cancer;[18,19] however, since 2010, and the introduction of targeted treatments for this group of patients, survival gains have increased.[20] However, the life expectancy for patients with HER2+ UBC or MBC is <2 years;[21] even with the use of targeted HER2+ treatments, nearly all patients progress due to de novo or acquired resistance.[20] There is currently no approved HER2-targeted therapy for patients with HER2+ UBC or MBC who have received two or more prior anti-HER2 therapies.[22]

2.2.2 Trastuzumab deruxtecan

The focus of this appraisal is on the use of T-DXd. The company has provided details about the mechanism of action and marketing authorisation for T-DXd in the CS (Table 2) and in the draft Summary of Product Characteristics (CS, Appendix C). The mechanism of action of T-DXd is summarised in Box 1, and marketing authorisation details are provided in Box 2.

Box 1 Mechanism of action for T-DXd

- T-DXd is a HER2 targeted ADC. It is composed of a monoclonal antibody which specifically targets HER2 and which has with the same amino acid sequence as trastuzumab. This antibody is synthetically bonded to a topoisomerase I inhibitor
- T-DXd binds to the HER2 on the surface of the tumour cell and is internalised by the cell. The synthetic bond is broken, and the topoisomerase inhibitor is released into the cell nucleus causing damage to the cell's DNA. The inhibitor is also membrane permeable allowing it to penetrate and destroy neighbouring tumour cells regardless of HER2 status
- T-DXd is administered intravenously in a 5.4 mg/kg dose once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

ADC=antibody drug conjugate; DNA=deoxyribonucleic acid; HER2=human epidermal growth factor 2; T-DXd=trastuzumab deruxtecan
Source: CS, Table 2 and CS, Appendix C (draft SmPC)

Box 2 Marketing authorisation for T-DXd for use in Europe

- On [redacted], an application for marketing authorisation was submitted to the EMA under the [redacted]. Opinion from the CHMP is anticipated on [redacted], with a final decision expected before [redacted]
- [redacted] It is anticipated that the licence wording will be in the public domain by [redacted]

CHMP=Committee for Medicinal Products for Human Use; EMA=European Medicines Agency; HER2=human epidermal growth factor 2; HER2+=human epidermal growth factor 2 overexpression (positive); T-DXd=trastuzumab deruxtecan
Source: CS, Table 2

2.2.3 Comparators

As listed in the final scope[23] issued by NICE, comparator treatments to T-DXd are eribulin, capecitabine and vinorelbine:

- Eribulin is an intravenous chemotherapy drug licensed in the European Union (EU) for the treatment of adult patients with LABC or MBC who have progressed after at least one chemotherapeutic regimen for ABC.[24] Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments. Eribulin is also licensed for the treatment of liposarcoma.[24]

- Capecitabine is an oral chemotherapy drug licensed in the EU in combination with docetaxel for the treatment of patients with LABC or MBC after failure of cytotoxic chemotherapy.[25] Prior therapy should have included an anthracycline.[25] Capecitabine is also indicated as a monotherapy for the treatment of patients with LABC or MBC after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.[25] Capecitabine is also licensed for the treatment of other cancers, namely colon, colorectal and gastric cancers.[25]

- Vinorelbine is an intravenous[26] or oral[27] chemotherapy drug licensed in the EU as a monotherapy, or in combination, for the treatment of Stage III or Stage IV ABC

relapsing after or refractory to an anthracycline containing regimen.[26,27] Vinorelbine is also licensed for the treatment of non-small cell lung cancer.[26,27]

Eribulin is the only treatment recommended by NICE (TA423)[21] as an option for treating LABC or MBC in adults whose disease has progressed after at least two chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine). In the NICE clinical guideline[28] for the diagnosis and treatment of ABC (CG81), capecitabine or vinorelbine are second- or third-line treatment options for patients with ABC. As highlighted by the company (CS, p22), NICE recommendations for the use of eribulin, capecitabine and vinorelbine are not specific to patients with HER2+ ABC and there is a paucity of evidence for the use of these agents for this specific type of ABC.

2.3 Company's overview of current service provision

2.3.1 Treatment pathway

A slightly modified version of the company's representation of the current treatment pathway and the proposed positioning of T-DXd for patients with HER2+ UBC or MBC who have received two or more anti-HER2 therapies is provided in Figure 1. Clinical advice to the ERG is that this pathway is representative of the treatments available to most patients seen in UK clinical practice who have HER2+ UBC or MBC and who have received two or more prior anti-HER2 therapies.

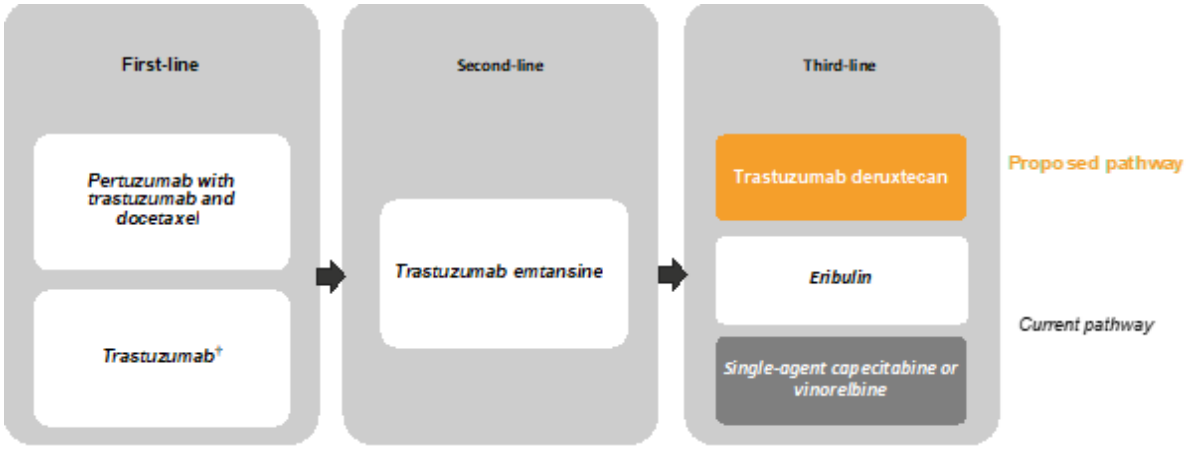

Figure 1 Current treatment pathway and the proposed position of T-DXd

† Trastuzumab in combination with paclitaxel [TA34]
Source: CS, adapted from Figure 3

2.3.2 First- and second-line treatments

A summary of first- and second-line treatments recommended by NICE for people with HER2+ ABC is provided in Table 2.

Table 2 Summary of first- and second-line treatments for HER2+ ABC recommended by NICE

	Treatment	Patient population for whom treatment is recommended
First-line	Pertuzumab with trastuzumab and docetaxel [TA509][29]	• HER2+ locally recurrent or MBC • No prior anti-HER2 therapy or chemotherapy
	Trastuzumab with paclitaxel [TA34][30]	• HER2: IHC 3+ score • No prior chemotherapy for MBC • Anthracycline treatment is inappropriate
Second-line	T-DM1 [TA458][31]	• HER2+ in UBC, LABC or MBC • Prior treatment with trastuzumab and taxane (separately or in combination) • Patients should have received either: ○ prior therapy for locally advanced metastatic disease or ○ developed disease recurrence during or within 6 months of completing adjuvant therapy

ABC=advanced breast cancer; HER2=human epidermal growth factor 2; HER2+=human epidermal growth factor 2 overexpression (positive); IHC=immunohistochemistry; IHC 3+=immunohistochemistry score (positive); LABC=locally advanced breast cancer; MBC=metastatic breast cancer; T-DM1=trastuzumab emtansine; UBC=unresectable breast cancer
Source: CS, extracted from Section B.1.3.5

2.3.3 First-line treatment

NICE recommends pertuzumab+trastuzumab+docetaxel as a treatment option for adults with HER2+ locally recurrent breast cancer or MBC who have not received prior treatment with chemotherapy or targeted HER2 therapy.[29] NICE also recommends treatment with trastuzumab+paclitaxel as an option for patients with HER2+ tumours scored at IHC level 3+ for patients who have not received chemotherapy for MBC and in whom anthracycline treatment is inappropriate.[30]

Guidelines from the European School of Oncology/European Society of Medical Oncology (ESO/ESMO) state that standard first-line treatment for people with advanced HER2+ breast cancer with no prior anti-HER2 therapy is trastuzumab+pertuzumab+chemotherapy, as it is superior to trastuzumab+chemotherapy in terms of overall survival (OS) for these patients.[6]

Clinical advice to the ERG is that, in UK clinical practice, approximately 75-80% of patients are treated in the first-line setting with pertuzumab+trastuzumab+docetaxel. Clinical advice to the ERG is that, in UK clinical practice, most patients who are treated in the first-line setting are generally fit (Eastern Cooperative Oncology Group Performance Score [ECOG PS] of 0 or 1) and receive pertuzumab+trastuzumab+docetaxel. Patients not able to tolerate docetaxel are likely to be treated with trastuzumab+paclitaxel and the small proportion of patients unable to tolerate this combination therapy may receive trastuzumab either as monotherapy or if they

have hormone receptor positive (ER+) disease, with hormone therapy, i.e., an aromatase inhibitor.

2.3.4 Second-line treatment

Trastuzumab emtansine (T-DM1) is recommended by NICE as a treatment option for adults with HER2+ UBC or MBC who have received prior treatment with trastuzumab and a taxane (separately or combined) and, have either had prior treatment for LABC or MBC, or have had disease recurrence during, or within, 6 months of completing adjuvant therapy.[31] It is stated in the ESO/ESMO guidelines[6,32] for ABC that T-DM1 provides superior efficacy relative to other HER2 treatments in the second-line (such as lapatinib+capecitabine). It is further stated that due to OS benefit, patients who have progressed following at least one line of trastuzumab-based therapy should be treated with T-DM1. The ERG notes that second-line treatment with lapatinib+capecitabine is not recommended by NICE; however, clinical opinion provided at an Advisory Board[33] Meeting held by the company in March 2020 was that second-line treatment [redacted] The ERG notes that second-line treatment with lapatinib+capecitabine is not recommended by NICE; however, at the Company's Advisory Board[33] Meeting [redacted].

2.3.5 Third-line (or later) treatments

A summary of treatments recommended by NICE in the third-line setting for patients with ABC is provided in Table 3. At a Market Access and Medical Advisory Board Meeting held in August 2020,[34] the frequency of use of treatments in the third-line setting was reported as 45% for capecitabine, 45% for vinorelbine, and ~10% for eribulin. Clinical advice to the ERG is that the low use of eribulin could be due to:

- the NICE recommendation that eribulin should only follow treatment with at least two chemotherapy regimens, which may include an anthracycline or a taxane, and which must include capecitabine,[21] thus making eribulin more commonly used in the ≥fourth-line setting for patients with ABC
- eribulin not being available as an oral treatment
- eribulin having a higher toxicity than capecitabine or vinorelbine.

Table 3 Summary of ≥third-line treatments for ABC recommended by NICE

Setting	Treatment	Patient population
Third-line (or later)	Eribulin [TA423][21]	• LABC or MBC • Where progression after ≥2 chemotherapy regimens (may include anthracycline or a taxane, and capecitabine)
	Singe-agent capecitabine or vinorelbine [CG81][28]	• ABC

ABC=advanced breast cancer; MBC=metastatic breast cancer; LABC=locally advanced breast cancer
Source: CS, Section B.1.3.5

The ERG notes that in NHS clinical practice, although not recommended by NICE, some oncologists currently prescribe trastuzumab in combination with chemotherapy after initial treatment with trastuzumab and T-DM1 (i.e., in the third-line setting). A recent online survey, advertised among UK breast cancer groups, between November 2019 and January 2020, found that, from 52 responding centres in England, trastuzumab was being prescribed as a third-line treatment in 50% of these centres.[35] Clinical advice to the ERG is that trastuzumab+chemotherapy is increasingly being considered by clinicians as standard of care.

In clinical trials recruiting patients treated with ≥two prior anti-HER2 therapies, trastuzumab+chemotherapy is being used as a comparator treatment, for example:

- Phase III DESTINY-Breast02 trial (ongoing; NCT03523585):[36] T-DXd versus trastuzumab+capecitabine or lapatinib+capecitabine
- Phase III HER2CLIMB trial:[37] tucatinib+trastuzumab+capecitabine versus placebo+trastuzumab+capecitabine
- Phase II TULIP trial (ongoing; NCT03262935)[38] (phase II): vic-trastuzumab duocarmazine versus trastuzumab+capecitabine, vinorelbine or eribulin.

It is stated in the ESO/ESMO guidelines[6] that:

- In case of progression on trastuzumab-based therapy, the combination trastuzumab+lapatinib is a reasonable treatment option for some patients. There are, however, no data on the use of this combination after progression on pertuzumab or T-DM1.
- T-DXd has shown important activity in the phase II DESTINY-Breast01 study in heavily pretreated patients with HER2-positive ABC (median lines of therapy: 6), and is a treatment option in this setting, where approved.

- Dual blockade with tucatinib+trastuzumab+capecitabine has shown a small benefit in median PFS (2 months) and median OS (4 months) over trastuzumab+capecitabine in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with brain metastases, at the expense of higher toxicity (i.e. diarrhoea). If approved, it can be considered a treatment option in this setting.

- The combination of neratinib+capecitabine and margetuximab+chemotherapy are not recommended for routine clinical practice.

Proposed position of T-DXd

The company's proposed positioning of T-DXd is as a treatment option in the third-line setting for patients with HER2+ UBC or MBC and who have received two or more anti-HER2 therapies (Figure 1). Clinical advice to the ERG is that T-DXd would be best placed as a third-line treatment option, rather than used later in the treatment pathway.

2.4 Critique of the company's definition of the decision problem

A summary of the decision problem outlined in the final scope[23] issued by NICE and addressed by the company is presented in Table 4. Each parameter is discussed in more detail in the text following Table 4 (Section 2.4.1 to Section 2.4.8).

Table 4 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Intervention	Trastuzumab deruxtecan	As per scope	As per scope
Population	People with HER2+, unresectable or metastatic breast cancer who have received two or more prior anti-HER2 therapies	As per scope	Evidence for T-DXd is provided from a population that is in line with the final scope[23] issued by NICE. The only trial that provides evidence for any of the comparators in a population comprising only patients with HER2+ disease (and who have received ≥2 anti-HER2 therapies) is the KCSG BR11-16 trial[39]
Comparator(s)	Eribulin (for people who have had 2 or more chemotherapy regimens) Capecitabine Vinorelbine	As per scope	In line with the scope, the company has presented clinical effectiveness evidence for the comparison of T-DXd versus eribulin, capecitabine and vinorelbine. As the primary source of clinical effectiveness evidence for T-DXd is a phase II, single-arm study (DESTINY-Breast01), the company performed a series of unanchored MAICs to compare T-DXd to each of the comparators. MAICs were conducted using data from the DESTINY-Breast01 study and from the studies providing comparator evidence (four studies for eribulin,[40-43] two studies for capecitabine,[44,45] and one study for vinorelbine[39])

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • HRQoL	The outcome measures from DESTINY-Breast01 (the pivotal clinical study) that are presented and included in the economic model are: • Progression-free survival • Overall survival • Objective response rate according to ICR (primary endpoint) (to inform progression-free, on treatment utility values) • Adverse effects of treatment In addition, data from the following key secondary endpoints from the DESTINY-Breast01 study are also presented: **Key secondary endpoints:** • ORR as confirmed by the investigator • Disease control rate and clinical benefit rate as confirmed by ICR • Duration of response as confirmed by ICR • Best percent change in the sum of the diameter of measurable tumours • Time to response HRQoL data were not collected in DESTINY-Breast01; however, alternative sources of HRQoL data have been used to inform the economic model	In the clinical section of the CS, the company has presented data for all outcomes except HRQoL (these data were not collected in the DESTINY-Breast01 study) Clinical advice to the ERG is that the outcomes specified by NICE are the most relevant outcomes for patients with HER2+ UBC or MBC

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY 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	A cost utility analysis will be performed, with the key outcome being the incremental cost per QALY gained 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	As per scope

CS=company submission; HER2=human epidermal growth factor 2; HRQoL=health-related quality of life; ICR=Independent Central Review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year; T-DXd=trastuzumab deruxtecan
Source: Final scope[23] issued by NICE; CS, Table 1

2.4.1 Source of direct clinical effectiveness data

The primary source of clinical effectiveness evidence presented by the company is the DESTINY-Breast01 study.[46] This study is a phase II, two-part, open-label, multicentre, single group dose-finding study, evaluating T-DXd in adults with pathologically documented HER2+ UBC or MBC who had received prior treatment with T-DM1.[46] The ERG agrees with the company that evidence from the phase II DESTINY-Breast01 study is the more relevant to this appraisal than the phase I study of T-DXd (DS8201-A-J101[47]); the results from the phase I study can be found in Appendices 1 to 3 (Section 9.1 to 9.1.3 of this report).

The ERG highlights that OS data from the DESTINY-Breast01 study are immature as median OS has not been reached (median follow-up: 11.1 months). The company has provided OS estimates at 6 months and 12 months. Progression-free survival (PFS) and duration of response (DoR) data are heavily censored; heavy censoring makes median PFS and DoR values uncertain as the occurrence of an additional event in the "at risk" population could have a significant impact on the size of the median values. The ERG has been informed that updated DESTINY-Breast01 study results will be made available during the technical engagement process.

The key characteristics of the DESTINY-Breast01 study are presented in the CS (Table 5). Analyses and results of this study are presented in Sections 3.3 and 3.5.

2.4.2 Intervention

In line with the final scope[23] issued by NICE, the company has presented clinical effectiveness evidence for T-DXd.

[redacted] The recommended dosage is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) (CS, Table 2). The initial dose is administered as a 90-minute intravenous infusion and, if well-tolerated, subsequent doses can be administered as 30-minute infusions (CS, Table 5).

2.4.3 Population

The company has presented direct clinical effectiveness evidence for patients with HER2+ UBC or MBC who have received ≥2 prior anti-HER2 therapies from the single-arm DESTINY-Breast01 study, in line with the final scope[23] issued by NICE [redacted].

The ERG highlights that in the DESTINY-Breast01 study:

- patients had received a median of six prior lines of treatment for LABC or MBC, including hormone therapy. Clinical advice to the ERG is that most patients treated in the NHS would not receive this number of prior treatments

- although all patients had received at least two prior anti-HER2-treatments, [redacted] of patients in the trial received exactly two prior anti-HER2 treatments (excluding hormone therapy); the remaining patients received ≥3 prior therapies. The company anticipates that T-DXd will be used as a third-line treatment (CS, Figure 1)

- over half of the patients had received anti-HER2 therapy (likely to include lapatinib) in addition to trastuzumab, pertuzumab or T-DM1. NICE does not recommend lapatinib for this population.

It is not clear how these points affect the generalisability of the DESTINY-Breast01 study results to NHS clinical practice.

The ERG highlights that the only trial identified by the company that provides evidence for any of the comparators in a population comprising only patients with HER2+ disease (and who have received ≥2 anti-HER2 therapies) is the KCSG BR11-16 trial[39] which considered patients treated with vinorelbine. The ERG notes that although patients received ≥2 lines of anti-HER2 therapy in KCSG BR11-16 trial,[39] pertuzumab and T-DM1 were not routinely used in clinical practice when this trial was conducted.

2.4.4 Comparators

The comparator treatments listed in the final scope[23] issued by NICE are eribulin, capecitabine and vinorelbine. As noted in Section 2.3.1, all are used in NHS clinical practice to treat patients with UBC or MBC in the ≥third-line setting. Clinical advice to the ERG is that eribulin tends to be used less frequently than capecitabine or vinorelbine.[21]

The company performed a series of unanchored matching-adjusted indirect comparisons (MAICs) to assess the comparative effectiveness of T-DXd versus eribulin, capecitabine and vinorelbine. MAICs were conducted using data (OS, PFS and response outcomes) from the following studies:

- Eribulin (3 studies and 1 trial): Barni (2019),[40] Cortes (2010),[41] Gamucci (2014)[43] and EMBRACE trial (2011)[42]
- Capecitabine (2 studies): Fumoleau (2004),[45] Blum (2001)[44]
- Vinorelbine (1 trial): KCSG BR11-16 (2019).[39]

The only trial identified by the company that provides evidence for any of the comparators in a population comprising only patients with HER2+ disease (and who have received ≥2 anti-HER2 therapies) is the KCSG BR11-16 trial[39] which included patients treated with vinorelbine.

2.4.5 Outcomes

The outcomes listed in the final scope[23] issued by NICE are PFS, OS, response rate (objective response rate [ORR]), DoR, adverse events (AEs) of treatment and HRQoL. Clinical advice to the ERG is that these are the most relevant outcomes for patients with HER2+ UBC or MBC.

The company has presented data relating to all of these outcomes from the DESTINY-Breast01 study, with the exception of HRQoL as HRQoL data were not collected as part of the DESTINY-Breast01 study. The ERG notes that HRQoL outcomes are being collected in the ongoing, DESTINY-Breast02 study (NCT03523585),[36] a phase III randomised controlled trial (RCT) of T-DXd versus investigator's choice (trastuzumab+capecitabine or lapatinib+capecitabine) that is anticipated to complete in [redacted].[36]

2.4.6 Economic analysis

As specified in the final scope[23] issued by NICE, cost effectiveness results were expressed in terms of incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a lifetime time horizon of 40 years. Costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.4.7 Subgroups

No subgroup analyses were specified in the final scope[23] issued by NICE. The company reports findings from pre-specified DESTINY-Breast01 study subgroups for the following outcomes: ORR, DoR and PFS (CS, Appendix E). The pre-specified subgroups were patients who had received prior pertuzumab therapy, hormone receptor status, receipt of T-DXd immediately after initial T-DM1 therapy, number of prior regimens, and patients with central nervous system metastasis at baseline.

2.4.8 Other considerations

No equality issues were identified by the company. However, feedback to the company from the Advisory Board[33] Meeting held in March 2020 was that patients in some regions of England may currently be able to access treatment which is not currently recommended by NICE, either via clinical trials or through early access programmes, [redacted].

The ERG highlights that the list price for T-DXd has yet to be finalised. The company has made a Patient Access Scheme (PAS) application to the PAS Liaison Unit. If accepted, T-DXd will be available to the NHS at a discounted price. Eribulin is available to the NHS at a confidential discounted PAS price. Oral vinorelbine is also available at a confidential discounted price agreed with the NHS England Commercial Medicines Unit.

The company considers that the NICE End of Life criteria[48] apply to the current appraisal. The ERG considers that the evidence to assess whether the criteria are met is uncertain.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence of the effectiveness of T-DXd versus other comparators for patients with HER2+ UBC or MBC who have received ≥2 prior anti-HER2 therapies are presented in the CS (Appendix D). An assessment of the extent to which the review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 5. Overall, the ERG considers the methods used by the company were of a good standard.

Table 5 ERG appraisal of the company's systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D1.1, Table 1
Were appropriate sources searched?	Yes	See CS, Appendix D1.1
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D1.1 and clarification response to question A2
Were appropriate search terms used?	Yes	See CS, Appendix D1.1
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D1.1
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D1.1
Was data extracted by two or more reviewers independently?	Yes	See clarification response to question A1
Were appropriate criteria used to assess the risk of bias and/or quality of the included studies?	Yes	See CS, Section B.2.5 and CS, Appendix D1.1, Tables 13 and 14
Was the quality assessment conducted by two or more reviewers independently?	Yes	See CS, Appendix D1.1, Table 13
Were attempts to synthesise evidence appropriate?	Yes	See Section 3.3 and Section 3.5 for an in-depth discussion of the company's methods and the ERG's critique of the syntheses of direct and indirect evidence

ERG=Evidence Review Group, RCT=randomised controlled trial
Source: LR*i*G in-house checklist

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The company identified two studies of T-DXd, the phase II DESTINY-Breast01 study and the phase I DS8201-A-J101[47] study; both studies evaluated the efficacy and safety of T-DXd in patients with HER2+ UBC or MBC who had received prior treatment with T-DM1. The company has presented the phase II DESTINY-Breast01 study as the primary source of clinical effectiveness evidence for T-DXd, and details from the phase I DS8201-A-J101[47] study as supporting evidence. The ERG agrees with the company that the evidence from the phase II DESTINY-Breast01 study is the most relevant to this appraisal and therefore the primary focus of this ERG report is on efficacy and safety results from the phase II DESTINY-Breast01 study. Details of the DS8201-A-J101[47] study, including study and patient characteristics, quality assessment and efficacy and safety results are provided in Appendix 1 (Sections 9.1).

The company identified seven studies that provided clinical effectiveness evidence for the three comparators listed in the final scope[23] issued by NICE:

- Eribulin (3 studies and 1 trial): Barni (2019),[40] Cortes (2010),[41] Gamucci (2014)[43] and EMBRACE trial (2011)[42]
- Capecitabine (2 studies): Fumoleau (2004),[45] Blum (2001)[44]
- Vinorelbine (1 trial): KCSG BR11-16 (2019).[39]

3.2.1 The DESTINY-Breast01 study

DESTINY-Breast01 study: study characteristics

The company provided details of the characteristics of the DESTINY-Breast01 study in the CS (Table 5). The DESTINY-Breast01 study is a two-part, open-label, single-group, multicentre, phase II study, evaluating T-DXd in adults with pathologically documented HER2+ UBC or MBC who had received prior treatment with trastuzumab and TDM-1. The study was conducted at 72 sites in eight countries: Canada, Japan, South Korea, Belgium, France, Italy, Spain, and the United Kingdom (UK).

The dosing aspect of the DESTINY-Breast01 study comprised two parts (CS, Figure 4). Part 1 consisted of a pharmacokinetics stage where subjects were randomised 1:1:1 to receive one of three doses of T-DXd (5.4 mg/kg, 6.4 mg/kg or 7.4 mg/kg) administered by intravenous infusion once every 3 weeks. This informed the dose finding stage where subjects were randomised 1:1 to receive one of two doses (5.4 mg/kg or 6.4 mg/kg) once every 3 weeks. Part 2 was not randomised and comprised two cohorts of patients: patients whose disease

had progressed during or after prior treatment with T-DM1 (part 2a), and patients who had discontinued T-DM1 for reasons other than disease progression (part 2b). All subjects in part 2 received a dose of 5.4 mg/kg once every 3 weeks. The DESTINY-Breast01 study evidence presented in the CS relates to 184 patients (part 1: n=50; part 2a: n=130, and part 2b: n=4) who received 5.4 mg/kg of T-DXd.

Evidence is presented in the CS from the 1 August 2019 data-cut (10 months of follow-up after the last patient enrolled into the study). The median length of follow up was 11.1 months (range: 0.7 months to 19.9 months) (CS, Section B.2.4.3).

DESTINY-Breast01 study: population characteristics

A summary of the baseline characteristics of patients included in the DESTINY-Breast01 study is presented in Appendix 1 (Section 9.1.2) of this ERG report. All patients were female. The median age of the population was 55 years (range 28 to 96), and approximately three-quarters (76.1%) were aged <65 years. Over 90% of patients were either white (54.9%) or Asian (38.0%), and the remainder whose ethnicity was recorded (4.9%) were described as 'other ethnicity'.

Clinical advice to the ERG is that the age of patients included in the DESTINY-Breast01 study is similar to the age of patients treated in UK clinical practice. However, it was highlighted that the study includes a higher number of Asian patients than typically seen in the NHS. Clinical advice also emphasised that differences have been identified between Asian and Caucasian populations in terms of side-effects and toxicities.[49,50]

Patients in the DESTINY-Breast01 study had received a median of six (range 2 to 24) prior lines of therapy for LABC or MBC, excluding hormone therapy. Only [redacted] patients had received two prior lines of systemic therapy excluding hormone therapy and were therefore receiving T-DXd as a third-line treatment. [redacted] patients had received ≥3 prior lines of systemic therapy, excluding hormone therapy,[51] i.e., were receiving T-DXd as >3 line of treatment. All patients had received T-DM1. All patients had also received trastuzumab, and most had received pertuzumab (65.8%) or other additional anti-HER2 therapies (54.3%).

Clinical advice to the ERG is that patients enrolled in the DESTINY-Breast01 study had received more lines of prior therapy (median: 6; range 2 to 27 including hormone therapy and range 2 to 24 excluding hormone therapy) than is current practice in the NHS. Furthermore, over half of the patients had received anti-HER2 therapy in addition to trastuzumab, pertuzumab or T-DM1. The ERG notes that this additional therapy is likely to be lapatinib (as was the case for most patients in the DS8201-A-J1010[47] supporting study) and highlights that

the only anti-HER2 therapies recommended by NICE are trastuzumab, pertuzumab and T-DM1. It is not clear how these differences affect the generalisability of the DESTINY-Breast01 study results to NHS clinical practice.

DESTINY-Breast01 study: quality assessment

The company conducted a quality assessment of the DESTINY-Breast01 study using the Downs and Black checklist.[52] The company's assessment of this study, with ERG comments, is presented in Appendix 2 (Section 9.2.1). The ERG considers that the DESTINY-Breast01 study is of a good standard; however, highlights that it is a single-arm study.

3.2.2 Statistical approach adopted for the analysis of DESTINY-Breast01 study data

Information about the statistical approach taken by the company to analyse DESTINY-Breast01 study data has been extracted from the Clinical Study Report (CSR),[51] the statistical analysis plan (SAP),[53] the study protocol,[54] and the CS. A summary of the ERG checks of the pre-planned statistical approach used by the company is provided in Appendix 2 (Section 9.2.2). Overall, the ERG considers that the statistical approach taken was appropriate.

3.3 Efficacy results from the DESTINY-Breast01 study

The company has presented results from the most recent analysis of DESTINY-Breast01 study data (data cut-off date: 1 August 2019) based on a median duration of follow-up of 11.1 months (range: 0.7 months to 19.9 months). Efficacy results are presented for the enrolled analysis set (EAS; all patients who signed an informed consent form and were randomised in part 1 or registered in part 2).

3.3.1 Objective response rate

The primary endpoint of the DESTINY-Breast01 study was ORR by independent central review (ICR); ORR by investigator assessment was a secondary endpoint. A summary of ORR results from the DESTINY-Breast01 study is provided in Table 6.

Table 6 Summary of DESTINY-Breast01 study ORR results (EAS)

Response	T-DXd 5.4 mg/kg (N=184)	
	ICR	Investigator assessment
ORR, n (% [95% CI])	112 (60.9 [53.4 to 68.0])	123 (66.8 [59.5 to 73.6])
Complete response, n (%)	11 (6.0)	8 (4.3)
Partial response, n (%)	101 (54.9)	115 (62.5)
Stable disease, n (%)	67 (36.4)	56 (30.4)
Progressive disease, n (%)	3 (1.6)	4 (2.2)
Not evaluable, n (%)	2 (1.1)	1 (0.5)

CI=confidence interval; EAS=enrolled analysis set; ICR=independent central review; ORR=overall response rate; T-DXd=trastuzumab deruxtecan
Source: CS, Table 12

The confirmed ORR by ICR was similar to the confirmed ORR by investigator assessment for the 184 patients in the DESTINY-Breast01 study who received T-DXd at a dose of 5.4 mg/kg.

The results of a post-hoc subgroup analysis for ORR by number of prior lines of systemic therapy were provided in the CS (Appendix E, Table 1). The company highlighted that patients achieved a confirmed ORR >50% regardless of the number of prior lines of systemic therapy they had received, and that the highest ORR was observed in those who had received only two prior lines (CS, p48), i.e. as a third-line treatment. The ERG notes that this subgroup analysis was performed according to the Food and Drug Administration (FDA)-requested definition of number of prior lines of systemic therapy (company response to the ERG clarification letter, question A5). This definition differs to the definition of number of prior lines of systemic therapy pre-specified in the study SAP,[53] which is used in the summary of baseline characteristics of the DESTINY-Breast01 study (Section 3.2.1), and as a matching factor in the company's MAICs (Section 3.5). Results of a pre-specified subgroup analysis using the SAP definition are available (CS, Appendix E, Figure 1) for patients receiving third-line treatment versus patients who had received three or more prior lines of therapy. The ORR

was higher in the subgroup of patients receiving third-line treatment (76%; 95% confidence interval [CI]: 50% to 93%) than in the subgroup of patients who had received ≥3 prior lines of treatment (59%; 95% CI: 51% to 67%). For both the FDA- and SAP-defined subgroup analyses, results were based on data from small numbers of patients (patients receiving third-line treatment being n=30 and n=17, respectively), and the ERG therefore considers that it is difficult to draw firm conclusions about how the effect of treatment with T-DXd varies by number of prior lines of systemic therapy.

The company provided a waterfall plot of change from baseline in tumour size for 168 patients who received the 5.4 mg/kg dose of T-DXd and who had had both baseline and post-baseline target legion assessments by ICR (CS, Figure 5). The majority (n=161, 95.8%) of these patients had a reduction in tumour size at the time of data cut-off, and most had a partial or complete response.

3.3.2 Progression-free survival

A summary of DESTINY-Breast01 study PFS results by ICR is provided in Table 7.

Table 7 Summary of DESTINY-Breast01 study PFS results by ICR results (EAS)

Progression-free survival outcomes	T-DXd 5.4 mg/kg (N=184)
Median PFS, months (95% CI)	16.4 (12.7 to NE)
PFS events, n (%)	58 (31.5)
Progressive disease, n (%)	48 (26.1)
Death, n (%)	10 (5.4)
Censored, n (%)	126 (68.5)

CI=confidence interval; EAS=enrolled analysis set; ICR=independent central review; NE=not evaluable; PFS=progression-free survival; T-DXd=trastuzumab deruxtecan
Source: CS, Table 13

At the time of the August 2019 data cut-off, only 58 PFS events had occurred. The ERG notes that PFS data from the DESTINY-Breast01 study are heavily censored, and median PFS (16.4 months; 95% CI: 12.7 months to not evaluable [NE]) was reached at a time when only a small number of patients were being followed up for PFS (nine patients remained at risk at 16 months; CS, Figure 6). The ERG considers that the median PFS value is uncertain as the occurrence of just one additional event among the “at risk” population could have a considerable impact on the value of median PFS.[55]

3.3.3 Overall survival

The OS data from the DESTINY-Breast01 study are immature; only 25 of 184 (13.6%) patients had died at the time of the August 2019 data cut-off. Consequently, median OS has not been reached. The company has provided estimated OS rates at 6 months (93.9%; 95% CI: 89.3%

to 96.6%) and at 12 months (86.2%; 95% CI: 79.8% to 90.7%), and a Kaplan-Meier (K-M) curve (CS, Figure 7).

3.3.4 Other efficacy outcomes

A summary of the results for disease control rate (DCR), clinical benefit rate (CBR), DoR and time to response (TTR) from the DESTINY-Breast01 study are presented in Table 8.

Table 8 Summary of DCR, CBR, DoR and TTR results from the DESTINY-Breast01 study (EAS, all outcomes assessed by ICR)

Outcome	T-DXd 5.4 mg/kg (N=184)
DCR, n (% [95% CI])	179 (97.3 [93.8 to 99.1])
CBR, n (% [95% CI])	140 (76.1 [69.3 to 82.1])
Median DoR, months (95% CI)[a] Events, n/N patients with response (%) Censored, n/N patients with response (%)	14.8 (13.8 to 16.9) 29/112 (25.9) 83/112 (74.1)
Median TTR, months (95% CI)[a]	1.6 (1.4 to 2.6)

CBR=clinical benefit rate; CI=confidence interval; DCR=disease control rate; DoR=duration of response; ICR=independent central review; TTR=time to response; T-DXd=trastuzumab deruxtecan
[a] DoR and TTR were assessed in 112 patients who had a complete or partial response among the 184 patients treated with the dose of 5.4 mg/kg T-DXd
Source: CS, Table 14; company response to the ERG clarification letter, question A3

At the time of the August 2019 data cut off, 112 patients had experienced a complete or partial response but only 29 (25.9%) of these patients had experienced an event (disease progression or death); data for the DoR outcome are therefore heavily censored. Median DoR (14.8 months; 95% CI: 13.8 months to 16.9 months) was reached when only a small number of patients were being followed up for DoR (four patients remained at risk at 14 months; CS, Figure 8). The ERG therefore considers that the median DoR value is uncertain, and that the occurrence of just one additional event among the “at risk” population could have a considerable impact on median DoR.

3.4 Safety and tolerability

DESTINY-Breast01 study safety and tolerability data were presented in the CS (Section B.2.10) from the 1 August 2019 data-cut. DESTINY-Breast01 study safety and tolerability data were presented in the CS (Section B.2.10). The following categories of AE data from patients who received the 5.4 mg/kg dose of T-DXd have been provided: exposure (CS, Section B.2.10.1), a summary of all AEs (CS, Table 61), the incidence of AEs experienced by ≥10% of patients (CS, Table 63), and select AEs by treatment cycle (CS, Table 63). The company also reported AEs of special interest (AEOSIs) (CS, Table 64), [redacted] (CSR, p154). Adverse events from the DS8201-A-J101 study were reported in Section B.2.10.2 of the CS. The company did not present any information on AEs for the comparator treatments relevant to this appraisal.

3.4.1 Exposure to T-DXd in the DESTINY-Breast01 study

In the overall 5.4 mg/kg dose cohort, 42.9% of patients were still on treatment with T-DXd at the time of the 1 August 2019 data-cut. The median treatment duration was 10 months (range, 0.7 to 20.5) and the median number of cycles initiated was 14 (range, 1 to 29).

3.4.2 Summary of adverse events in the DESTINY-Breast01 study

Nearly all patients in the DESTINY-Breast01 study experienced an AE (99.5%) or a drug-related AE (99.5%). Approximately half also experienced a Grade ≥3 AE (57.1%) or drug-related Grade ≥3 AE (48.4%). Serious AEs were reported by 22.8% of patients (12.5% drug-related) and 15.2% patients experienced an AE leading to drug discontinuation; the majority were drug-related (14.7% of study population). AEs leading to dose reduction were experienced by 23.4% (21.7% of study population drug-related) and AEs leading to dose interruptions by 35.3% (28.8% of study population drug-related). AEs leading to death occurred in nine patients (4.9%) of which two were drug-related (1.1% of study population).

3.4.3 Types of adverse events reported in the DESTINY-Breast01 study

A summary of the AEs reported in patients in DESTINY-Breast01 study is provided in Appendix 3 (Section 9.3.1). The most common AEs were gastrointestinal and haematologic in nature. Decreased neutrophil count was the only Grade ≥3 AE that was reported in ≥10% of patients in the DESTINY-Breast01 study.

3.4.4 Timing of adverse event occurrence in the DESTINY-Breast01 study

The company reported some AEs by treatment cycle for cycles 1 to 7, cycles ≥8 and cycles ≥18 (CS, Table 63). Of these select AEs, in the first cycle, nausea was the most commonly occurring AE (65.2%), followed by fatigue (29.3%), vomiting (27.2%), decreased appetite (17.9%), constipation (15.8%) and diarrhoea (11.4%). The proportion of patients experiencing each AE decreased in frequency with each cycle of treatment until cycle 7; nausea remained the most frequently occurring AE, followed by vomiting or fatigue, and diarrhoea was the least common in the majority of cycles. In patients receiving ≥8 treatment cycles, nausea was again the most common AE (16.3%), followed by fatigue and vomiting (12.5% each), constipation was the least frequent AE (8.2%). AE frequency experienced by patients receiving ≥18 cycles were: nausea, vomiting and fatigue (1.6% each) and diarrhoea (1.1%).

3.4.5 Adverse events of special interest in the DESTINY-Breast01 study

The frequencies of adverse events of special interest (AEOSI) in the DESTINY-Breast01 study are shown in Table 9. The company highlighted that "significant cardiotoxicity was not observed" (CS, p96). However, T-DXd was associated with a risk of interstitial lung disease (ILD) (13.6%) and, in accordance with the study protocol,[54] this was managed with dose reductions, discontinuations, administration of glucocorticoids and supportive care. Nonetheless, although reported to be mostly <Grade 3 in severity, there were four deaths from ILD, and these deaths accounted for 16.0% of all patients who experienced this AEOSI. Characteristics of the four patients who died from ILD are reported in the CSR (p144-145). The company clarified that these four deaths were initially reported by treating investigators as being due to different reasons for each patient (namely, respiratory failure, acute respiratory failure, lymphangitis, and pneumonitis) but were later attributed to ILD by independent adjudication (Clarification response A4). The company has, therefore, recommended education and close monitoring of signs and symptoms of ILD, which include fever, cough and dyspnoea.

Table 9 AEOSIs in the DESTINY-Breast01 study (5.4 mg/kg dose, August 2019 data cut)

Adverse event, n (%)	Any Grade	Grade 3	Grade 4
Interstitial lung disease†	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased LVEF‡	3 (1.6)	1 (0.5)¶	0

AEOSI=adverse events of special interest; LVEF=left ventricular ejection fraction; T-DXd=trastuzumab deruxtecan
†The presence of interstitial lung disease was determined by an independent adjudication committee. Four patients who died were included in the category of any grade
‡ The LVEF was measured on echocardiography or multigated acquisition scans every four treatment cycles
¶ In this patient, the LVEF was ≥55% during treatment
Source: CS, Table 64 and Modi (2020)[46]

3.4.6 Adverse events in the DS8201-A-J101 study

All patients in the DS8201-A-J101 study had had one or more AE of any grade; the majority (98/115 [98%]) of these events were drug-related. Compared to the DESTINY-Breast01 study, lower frequencies of AEs were reported among patients in the DS8201-A-J101 study for AEs of Grade ≥3, serious AEs, and AEs leading to drug discontinuation, dose reduction or interruption. It is unclear why there were differences in frequencies between the studies. However, in part, this may be as a result of small numbers of patients in both studies, particularly the 5.4 mg/kg treatment arm of the DS8201-A-J101 study. Additional AE data related to the DS8201-A-J101 study is summarised in Appendix 3 (Section 9.3.1).

3.4.7 Adverse events associated with comparator treatments

The ERG has extracted data from the studies that were considered for inclusion in the company's MAICs and summarised the data in Appendix 3 (Section 9.3.2). The ERG highlights that the purpose of this data extraction is only to provide a context as to the safety profiles of the comparator treatments, not to provide data for comparison. These results only show frequencies of AEs reported in previous studies, all of which included patients with mixed or unknown HER2 disease with data on prior anti-HER therapy not reported. The data do not suggest that patients treated with T-DXd are at any greater risk of experiencing treatment emergent or drug-related any Grade AEs, Grade ≥3 AEs, serious AEs, AEs leading to drug discontinuation, AEs leading to dose modification, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to dose delay or AEs leading to death.

3.4.8 Interpretation of adverse event data

Clinical advice to the ERG is that T-DXd appears to have a manageable toxicity profile, however also highlighted that four deaths from ILD may indicate that ILD is an AE of concern.

3.5 ERG critique of the indirect evidence

The DESTINY-Breast01 study is a single-arm study and there is no evidence to allow a direct comparison of T-DXd versus any of the comparators listed in the final scope[23] issued by NICE, namely eribulin, capecitabine and vinorelbine. The company's systematic review (described in Section 3.1 of this ERG report) was used to identify relevant studies for inclusion in indirect comparisons.

As the evidence network is disconnected it was not possible for the company to perform network meta-analyses (NMAs) or Bucher indirect comparisons. The company has, therefore, generated indirect evidence using unanchored MAICs to compare T-DXd versus relevant comparators for the following outcomes: OS, PFS and response outcomes.

The company was not able to perform MAICs for time to treatment discontinuation (TTD), as none of the comparator studies provided K-M data for this outcome. The company did not present indirect evidence for HRQoL as data for HRQoL outcomes were not collected in the DESTINY-Breast01 study. The company did not present MAICs for safety outcomes. No rationale was provided for this by the company but the ERG does not consider this to be a major limitation of the evidence base for T-DXd as the safety profiles of the comparator drugs are well known.

3.5.1 Critique of trials identified and included in the MAICs

The company's literature search identified 105 relevant studies that included the comparators listed in the final scope[23] issued by NICE. After the exclusion of 96 studies according to the company's eligibility criteria (CS, Appendix D), nine studies remained. A further two studies were further excluded for the following reasons:

- Venturini (2007),[56] a study of capecitabine, was excluded on the basis that only one of the identified matching factors (age) was reported and, as other studies reported more than one matching factor the company considered them to be more useful

- Oruc (2019)[57] was excluded as this was a small study (N=80) specific to a Turkish population, and was therefore considered by the company to provide less robust data for a comparison versus eribulin than other identified studies.

The ERG considers that the exclusion criteria applied by the company were reasonable, and that no important studies were inappropriately excluded from the consideration process. Following the two exclusions, seven relevant comparator studies were included in the MAICs. The seven included studies comprised three phase II single-arm studies,[41,44,45] one phase II RCT,[39] one phase III RCT[42] and two single-arm retrospective studies.[40,43] The company

therefore conducted seven MAICs (one MAIC for each comparator study identified). For each MAIC, the company estimated effectiveness in terms of OS, PFS and, where possible, response rates (ORR, DCR, and CBR). The ERG highlights that when including results from phase II and phase III studies in a MAIC, it is important to note that the treatment effects demonstrated in phase II trials are often greater than those observed in phase III trials.[58]

Characteristics of the comparator studies included by the company are provided in Table 10.

Table 10 Summary of studies included in the MAICs

Comparator	Study	Study design	Location	Aim of study
Eribulin	Barni (2019)[40]	Multicentre, retrospective cohort	39 centres in Italy	Efficacy of eribulin in patients with MBC in a real-world setting, with HER2+ subgroup data for OS and PFS
	Cortes (2010)[41]	Phase II, single-arm, open-label	78 sites in the US and Western Europe	Safety and efficacy of eribulin mesylate in patients with LABC or MBC who received prior treatment with anthracycline, a taxane and capecitabine
	EMBRACE trial 2011[42]	Phase III, randomised controlled, open-label	135 centres in 19 countries	To compare eribulin and treatment of physician's choice amongst patients with locally recurrent or MBC who had received prior treatment with chemotherapy
	Gamucci 2014[43]	Multi-centre, retrospective observational study	11 centres in Italy	Safety and efficacy of eribulin in real-world patients with advanced breast cancer who have received prior treatment with ≥2 lines of chemotherapy
Capecitabine	Blum 2001[44]	Multicentre, phase II single-arm	4 North American centres and 1 French centre	Efficacy and safety of capecitabine in patients with MBC who failed taxane therapy
	Fumoleau (2004)[45]	Multicentre, phase II single-arm	17 French centres	To evaluate the capecitabine monotherapy in MBC patients who had received prior treatment with anthracycline and taxane
Vinorelbine	KCSG BR11-16 trial 2019[39]	Phase II, randomised controlled, open-label	South Korea (multicentre)	To compare lapatinib+vinorelbine vs vinorelbine alone in patients with HER2 + MBC who progressed on both trastuzumab and lapatinib

LABC=locally advanced breast cancer; MAIC=matching-adjusted indirect comparison; MBC=metastatic breast cancer; HER2+=human epidermal growth factor 2 over expression (positive); OS=overall survival; PFS=progression-free survival
Source: CS, Table 15

Importantly, only two studies[39,40] reported outcome data (OS, PFS and response rates) for HER2+ patients. Only one of these two studies (the KCSG BR11-16 trial[39]) included a population of HER2+ patients who had received at least two prior lines of anti-HER2 therapy (including trastuzumab), making this the only comparator trial population relevant to this appraisal. The ERG also notes that while patients had received two prior lines of anti-HER2

therapy in this trial, in most instances these treatments did not include T-DM1 or pertuzumab (which are recommended by NICE[29,30]) but did include lapatinib (which has not been recommended by NICE[59,60]).

3.5.2 Quality assessment of the studies included in the MAICs

The company included seven studies in the MAIC analysis:

Two[39,42] of the comparator studies included in the MAICs were randomised trials. The company assessed the quality of these trials using the NICE quality assessment tool,[48] which is based on the University of York Centre for Reviews and Dissemination guidance.[61] The company's and ERG assessment of the quality of these trials is presented in

- Table 38. The ERG considers that the RCTs were well-conducted and are of good quality.

- Five[40,41,43-45] of the comparator studies included in the MAICs were single-arm studies. The company performed a quality assessment of these studies using the Downs and Black checklist.[52] The company's and ERG's assessment of the quality of these studies is presented in Table 39. The ERG considers that these studies are of good quality; however, highlights that they are single-arm studies.

3.5.3 Methodological approach to the MAICs

Unanchored MAICs

Unanchored MAICs can be used to obtain indirect estimates of effect for a specific comparison in scenarios when the two interventions of interest share no common comparator, i.e., when the network of evidence is disconnected. In this scenario, it is essential to adjust for between-study differences in baseline characteristics so that the effects of the two interventions can appropriately be compared.

An unanchored MAIC requires the strong assumption that every prognostic variable and treatment effect modifier that is imbalanced between the two studies is accounted for in the analysis. To achieve this, the patient population of the intervention study is re-weighted to match the patient population of the comparator study in terms of these prognostic factors and effect modifiers, or "matching variables". The company's MAICs included individual patient data (IPD) from the DESTINY-Breast01 study and used published aggregate data from the seven comparator studies[39-45] to estimate relative effects for T-DXd versus eribulin, capecitabine and vinorelbine.

OS and PFS data extraction

The company used IPD data from the DESTINY-Breast01 study, including information on baseline characteristics and outcome data. For the comparator studies,[39-45] pseudo-IPD for OS and PFS were constructed from published K-M curves, using the algorithm proposed by Guyot (2012).[62] The company extracted aggregate data on response outcomes (i.e., total number of patients in the relevant treatment arm and number or percentage of patients with an event) from the study publications.[39-45]

Identification of prognostic factors and treatment effect modifiers

A summary of the variables identified by the company as potential prognostic factors or effect modifiers that the company considered should be accounted for in the MAICs, and the sources of each of these variables are presented in Table 11. The ERG has also indicated in Table 11 which variables were included in the final list of matching variables included in the company MAICs.

Table 11 Important prognostic factors and effect modifiers identified by the company

Prognostic factors and effect modifiers	Source	Included in final matching variables
Age	Daiichi Sankyo medical team	Yes
ECOG PS (0/1+)	Daiichi Sankyo medical team	Yes
HER2 status	UK clinical expert	No - 100% of patients in the DESTINY-Breast01 study had HER2+ disease
Hormone receptor status (positive/negative)	Published evidence in UBC and MBC population[63-66]	Yes
Number of lines of prior therapy (<3, ≥3)	Published evidence in UBC and MBC population[67,68]	Yes[b]
Prior hormone therapy (yes/no)	UK clinical expert	Yes
Prior pertuzumab treatment	Published evidence in UBC and MBC population[32,69-71]	No – not reported in any of the comparator studies[a]
Prior trastuzumab treatment	UK clinical expert	No - 100% of patients in the DESTINY-Breast01 study had received prior treatment with trastuzumab
Number of metastatic sites	UK clinical expert	No - not collected in the DESTINY-Breast01 study
Presence of visceral disease (yes/no)	Daiichi Sankyo medical team	Yes
Brain metastases	Daiichi Sankyo medical team	No - this was either not reported in the comparator study, or reported as the number of patients who **only** had brain metastases (Barni (2019)[40])[c]
Comorbidities (including prior respiratory disease)	UK clinical expert	No - not reported for any of the comparator studies

ECOG PS=Eastern Cooperative Oncology Group performance status; HER2=human epidermal growth factor 2; MBC=metastatic breast cancer; UBC=unresectable breast cancer
[a] Pertuzumab was not used routinely when any of the comparator studies were conducted (it was recommended by NICE in March 2018)[29]
[b] The company confirmed (CS, p58) that when no other data were available, number of prior lines of chemotherapy was used as a proxy for the total number of prior lines
[c] This variable is not comparable with the brain metastases variable measured in the DESTINY-Breast01 study, which indicates whether a patient had any brain metastases at all
Source: CS, adapted from Table 16

Some comparator studies did not report data for all matching variables, so the set of matching variables differed between each MAIC. The set of matching variables included in each MAIC is provided in Section 3.5.4 and Appendix 4 (Section 9.4.2) of this ERG report.

The ERG considers that the most important variables to adjust for were HER2+ disease and prior anti-HER2 therapy. It was not possible to adjust for HER2+ status or prior trastuzumab or any prior anti-HER2 therapy in any of the MAICs since all patients in the DESTINY-Breast01 study had HER2+ disease and had received prior anti-HER2 therapy, including trastuzumab. The ERG therefore considers that the only valid MAIC is the comparison of T-DXd with

vinorelbine, using data from the KCSG BR11-16 trial,[39] as all patients in this trial were HER2+ and had received at least two prior lines of anti-HER2 therapy.

Baseline characteristics of the studies included in the company's MAICs

A summary of the unadjusted baseline characteristics of studies included in the MAICs is provided in Table 12.

Table 12 Summary of baseline characteristics of studies included in the MAICs

	T-DXd	Eribulin				Capecitabine		Vinorelbine
	DESTINY-Breast01	Barni 2019[40]	Cortes (2010)[41]	EMBRACE trial 2011[42]	Gamucci 2014[43]	Blum 2001[44]	Fumoleau (2004)[45]	KCSG BR11-16 trial 2019[39]
N	184	574	269	508	133	74	126	74
Mean/ median age	56.0	59.5	56	55	62	52.5	54	52
ECOG-PS = 0 (%)	55.4	40.9[a]	37.2	42.7[a]	-	-	43.7[a]	25.7
Visceral disease = yes (%)	91.8	59.4	-	-	80.5	79.7	-	50.0
Brain metastases = yes (%)	13.0	1.2[b]	-	-	-	-	-	-
HR+ (%)[c]	52.7[a]	Not known[d]	71.3	64.4[a]	84.2	-	-	45.9
HER2+ (%)	100	19.6	10.8	16.3[a]	21.1	-	-	100
HER2-, ER+ and/or PgR+ (%)	0	67.1	-	-	-	-	-	0
HER2-, ER- and PgR- (%)	0	13.3	20.1	18.3	10.5	-	-	0
Prior pertuzumab (%)	65.8	-	-	-	-	-	-	-
Prior hormone therapy (%)	48.9	-	-	85.0	69.2	70.2	-	-
Prior treatment lines								
Mean prior lines	6.6	-	-	-	-	-	-	-
Prior lines ≥3 (%)	91.8	-	-	-	-	-	-	100
Treatment lines prior to T-DM1 <2 (%)	18.5	-	-	-	-	-	-	-
Prior chemo lines ≥3 (%)	[redacted]	64.6	89.6	87.0	50.4	66.2	45.2	41.9
Prior chemo lines ≥5 (%)	[redacted]	23.7	20.4	19.3	19.5	Not known[d]	Not known[d]	Not known[d]
Prior HER2+ therapy (%)	100	-	-	-	-	-	-	100[e]
Other comments	100% prior T-DM1							100% prior trastuzumab

ECOG=Eastern Cooperative Oncology Group; ER(+/-)=oestrogen receptor (positive/negative); HER2(+/-)-=human epidermal growth factor 2-(positive/negative); HR(+)=hormone receptor (positive); MAIC=matching-adjusted indirect comparison; PgR(+/-)=progesterone receptor (positive/negative); PS=performance status; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan

[a] Missing data counted as 'no' or negative in calculation of %

[b] 1.2% had brain metastases only, which does not match the variable from DESTINY which includes any brain metastases

[c] ER+ and/or PgR+ (does not include HER2+/OR-/PgR- patients)

[d] Not known means cannot be calculated from data which are presented

[e] 100% of patients had 2 previous lines of anti-HER2 therapy

Source: CS, Table 17; CS, Appendix D, Table 11; CSR, Table 7.5 and published papers: Tamura 2019,[47] Cortes 2011,[42] Barni (2019),[40] Cortes (2010),[41] Gamucci (2019),[43] Fumoleau (2004),[45] Blum (2001),[44] Sim (2019)[39]

The ERG notes that there are some imbalances in baseline characteristics between the DESTINY-Breast01 study and the comparator studies; however, where baseline characteristics were reported, and the company had identified these characteristics to be potential prognostic factors or effect modifiers, the company was mostly able to adjust for these differences in the MAICs. The exception to this is HER2+ status, which was reported for five of the comparator studies,[39-43] but could not be adjusted for as all patients in the DESTINY-Breast01 study had HER2+ disease. The proportion of patients with HER2+ disease in the comparator studies was low in four studies[40-43] (ranging from 10.8%[41] to 21.1%[43]); however, 100% of patients in the KCSG BR11-16 trial[39] had HER2+ disease.

MAICs require the assumption that all prognostic factors and treatment effect modifiers that are imbalanced between the two studies are accounted for in the analysis. It is, therefore, imbalances in prognostic factors and effect modifiers that have not been measured and/or reported in both studies, and consequently were not adjusted for in the MAICs, that are of particular concern to the ERG. This issue is discussed further in Section 3.5.4.

Matching baseline characteristics between the DESTINY-Breast01 study and the comparator studies

To balance the distribution of the matching variables between the DESTINY-Breast01 study and each comparator study, individual patients in the DESTINY-Breast01 study were assigned weights; each individual patient's weight was equal to the estimated odds of being enrolled in the comparator study versus the DESTINY-Breast01 study for that particular patient. Weights were obtained from a logistic regression model, with matching variables included as predictors in the model. The company used a method of moments to allow the logistic regression model to be estimated without IPD for the comparative study. Following the re-weighting of the DESTINY-Breast01 patient population, outcomes could be compared between T-DXd and each comparator of interest. For each outcome, the effect estimate for T-DXd versus the relevant comparator was then estimated in the population of the comparator study, rather than in the DESTINY-Breast01 study.

The company considered the robustness of each MAIC by calculating an effective sample size (ESS). The ESS is the number of independent non-weighted individuals who would be required for an estimate with the same precision as the weighted sample estimate to be obtained.[72] A small ESS is an indication that the weights are highly variable due to a lack of population overlap and that the estimate may be unstable.

To account for the fact that weights were estimated and subject to sampling uncertainty, 95% CIs for the MAIC hazard ratios (HRs) were calculated using a bootstrap estimator as follows:

- T-DXd treated patients were sampled with replacement (a bootstrap dataset)
- For each bootstrap dataset, a set of weights was derived using a logistic regression model
- For each bootstrap dataset and corresponding set of weights, the relative treatment effect was estimated using a Cox proportional hazards (PH) model to estimate an adjusted HR for T-DXd relative to comparator treatments.

The company stated that this procedure was repeated a "sufficiently large" number of times to obtain a distribution of effect estimates for each outcome from each MAIC. The 2.5th and 97.5th percentiles were used to generate the limits of a 95% CI for the relative treatment effect.

For response outcomes, the company implemented a binomial general linear model to estimate the log odds ratio (OR) for T-DXd versus each comparator. A sandwich estimator was used to calculate the variance of the log OR; this variance was then used to calculate the standard error and CIs of the log OR.

3.5.4 MAIC results and critique

Results: T-DXd vs eribulin and vs capecitabine

The ERG considers that the results of the six MAICs are not suitable for decision-making as the populations enrolled in the comparator trials do not wholly match the population described in the final scope[23] issued by NICE and so the ERG has only presented the MAIC results in Appendix 4 (Section 9.4.1).

Results: T-DXd versus vinorelbine

The ERG considers that the only relevant MAIC considers the comparison of T-DXd versus vinorelbine, using data from the KCSG BR11-16 trial;[39] both trials included patients with HER2+ disease who had received two or more prior lines of anti-HER2 therapy and matches the population described in the final scope[23] issued by NICE.

A summary of the results for T-DXd versus vinorelbine from the MAIC with the KCSG BR11-16 trial[39] is provided in Table 13. The table also includes details showing which variables were matched in this MAIC.

Table 13 Summary of MAIC results for T-DXd versus vinorelbine

	T-DXd unadjusted (DESTINY-Breast01, N=184)	MAIC with KCSG BR11-16 trial[39]	
		T-DXd weighted (DESTINY-Breast01, ESS=[redacted]	Vinorelbine (KCSG BR11-16, n=74)
Mean/median age	**56.0**	-	
ECOG-PS = 0 (%)	**55.4**	[redacted]	25.7
Prior hormone therapy (%)	**48.9**	-	-
Prior line ≥3 (%)	**91.8**	[redacted]	100.0
HR+ (%)	**52.7**	[redacted]	45.9
Visceral disease (%)	**91.8**	[redacted]	50.0
Overall survival			
No. of events	**25**	[redacted]	53
Median, months (95% CI)	**NA (NA to NA)**	[redacted]	18.9 (13.3 to 29.1)
Adjusted HR (95% CI)	**-**	Proportional hazards violated	
Progression-free survival			
No. of events	**58**	[redacted]	65
Median, months (95% CI)	**16.4 (15.2 to 18.1)[a]**	[redacted]	2.7 (2.5 to 4.2)
Adjusted HR (95% CI)	**-**	Proportional hazards violated	
Response rates[b]: adjusted ORs (95% CI)			
ORR	**-**	[redacted]	
CBR	**-**	[redacted]	

CBR=clinical benefit rate; CI=confidence interval; DCR=disease control rate; ECOG-PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; HR=hazard ratio; HR+=hormone receptor positive; MAIC=matching-adjusted indirect comparison; NA=not applicable; OR=odds ratio; ORR=objective response rate; T-DXd=trastuzumab deruxtecan
[a] The 95% CI for median PFS differs to that reported in Table 7 as the company calculated 95% CIs for median survival using a linear method in the MAICs (as opposed to the log-log method used in the original analyses of DESTINY-Breast01 study data)
[b] DCR was not reported for the KCSG BR11-16 trial[39] so could not be included as an outcome in this MAIC
Source: CS, Tables 54 to 59

[redacted] The ERG has not presented the adjusted HRs for OS and PFS due to PH violations.

As DESTINY-Breast01 study OS data are immature, and the median has not been reached, there is no way to meaningfully compare OS MAIC T-DXd versus vinorelbine results. However, for PFS, there appears to be a directional effect of T-DXd versus vinorelbine ([redacted]). The ERG highlights that T-DXd median OS and PFS results from the T-DXd versus vinorelbine MAIC are [redacted] DESTINY-Breast01 results.

ERG critique: all MAICs

For OS and PFS, the company uses HRs to represent the treatment effect of T-DXd versus each comparator over time. This approach requires the assumption of PH; that is, the event hazards associated with the intervention and comparator data are proportional over time. The company generated Schoenfeld residuals plots and performed accompanying statistical tests to explore the validity of the PH assumption (CS, Appendix D). For analyses where the

Schoenfeld residual plot and accompanying statistical test suggested that the PH assumption was not valid, the ERG considers that the generated HRs are unreliable and not suitable for decision-making.

The company presents unadjusted HRs alongside adjusted HRs from the MAICs; the ERG has not presented the unadjusted HRs in this report, as these HRs are from analyses that do not account for any differences in baseline characteristics between the DESTINY-Breast01 study and the relevant comparator study. The ERG considers that these unadjusted HRs are therefore not suitable for decision-making, and that the adjusted HRs are more valid.

The company presents adjusted HRs with 95% CIs calculated using both a standard and a bootstrap estimator. The company also presents adjusted ORs (for CBR, DoR, ORR) with 95% CIs calculated using both a sandwich estimator and a GLM model. In this report, the ERG presents adjusted HRs with 95% CIs calculated using a bootstrap estimator, and adjusted ORs with 95% CIs calculated using a sandwich estimator as these methods account for uncertainty in the estimated weights applied to the DESTINY-Breast01 study IPD.

ERG critique: T-DXd vs eribulin and capecitabine

None of the comparator trials included in the MAICs for T-DXd versus eribulin and T-DXd versus capecitabine were only conducted in the patient population relevant to this appraisal, namely patients with HER2+ disease who had received two or more prior lines of anti-HER2 therapy. The company was unable to adjust for HER2 status or prior anti-HER2 therapy in these MAICs (as all patients in the DESTINY-Breast01 study had HER2+ disease and had received two or more lines of anti-HER2 therapy). This renders these results unsuitable for decision-making.

ERG critique: T-DXd vs vinorelbine

The ERG notes that based on advice received during an Advisory Board Meeting held in August 2020,[34] the company considered the OS findings reported in the KCSG BR11-16 trial[39] to lack “face validity” (CS, p121) and to be “clinically implausible” (CS, p89). The company suggests (CS, 120) that the OS results from KCSG BR11-16 trial[39] are inconsistent with OS results from other studies and this may be as a result of subsequent treatment(s) following disease progression. However, clinical advice to the ERG is that while subsequent therapy on disease progression may have driven the high OS rate in the KCSG BR11-16 trial,[39] the results may also be attributable to prior anti-HER2 therapy received. The ERG considers that the results from the KCSG BR11-16 trial[39] are informative.

For OS, the company visually inspected K-M curves for T-DXd and vinorelbine (from the DESTINY-Breast01 study and the KCSG BR11-16 trial,[39] respectively) and concluded that the PH assumption was violated (CS, p85). The ERG agrees with this assessment. For PFS, the company did not comment on the validity of the PH assumption; however, the ERG notes that the Schoenfeld residuals plot and accompanying statistical test presented in Appendix D (Figure 21) suggest that the PH assumption is violated. The ERG therefore considers these generated PFS and OS HRs are unreliable and are not suitable for decision-making.

Although age was reported in both the DESTINY-Breast01 study and the KCSG BR11-16 trial,[39] the company did not include age as a matching variable in the MAIC for T-DXd versus vinorelbine. The company explained (CS, p59) that at an Advisory Board Meeting held in August 2020,[34] it was highlighted that age may not be a reliable matching factor as both extremes of young and old age are associated with worse prognosis in MBC. The company investigated the effect of removing age from the matching variables for the MAIC with the KCSG BR11-16 trial,[39] and found that the ESS for the weighted DESTINY-Breast01 data included in this MAIC increased when age was removed as a matching variable. For this reason, age was then excluded as a matching variable in the MAIC that used data from the KCSG BR11-16 trial.[39] Although clinical advice to the ERG is that extremes of young and old age may be associated with worse prognosis in MBC, the ERG does not consider this to be a valid reason to exclude age as a prognostic factor from the company's MAICs.

Furthermore, the company was not able to adjust for the following potential prognostic factors and effect modifiers: comorbidities, number of metastatic sites, prior hormone therapy, type of prior anti-HER2 therapy and presence of brain metastases. The ERG therefore considers that the assumption that all effect modifiers and prognostic factors have been accounted for is highly uncertain.

It is recommended in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18[72] that when unanchored MAICs are performed, evidence should be provided to demonstrate that the degree of bias due to imbalance in unaccounted for covariates is acceptable. In response to the ERG clarification letter (question A15), the company provided results of sensitivity analyses performed to investigate the likely range of bias attached to the unanchored MAIC estimates. As none of the company's MAICs adjusted for all six of the final matching variables, the company explored how PFS outcomes were impacted when each of these variables in turn was excluded from the MAICs (for MAICs where adjustments for this variable were possible). The results of these analyses suggested that, for the outcome of PFS, the impact of excluding each matching variable in turn (from MAICs where adjustments for this variable were possible) was generally minimal. However, the ERG considers these

analyses to be limited as only PFS was considered. Further, the company did not provide any estimates of residual bias attached to the MAIC estimates due to effect modifiers and prognostic factors that it was not possible to account for in any of the MAICs.

Finally, the ERG considers that there are sources of uncertainty in the MAIC with the KCSG BR11-16 trial,[39] due to the fact that an insufficient number of bootstrap samples may have been generated for the analysis of OS, and also that the ESS for the weighted DESTINY-Breast01 study data for T-DXd was very small (ESS=[redacted]). Results for OS and PFS were consequently based on very small numbers of events among patients receiving T-DXd (n=[redacted] for OS and n=[redacted] for PFS).

3.5.5 ERG conclusions: all MAICs

The ERG considers that there is evidence from the MAIC that used data from the KCSG BR11-16 trial[39] to suggest that treatment with T-DXd delivers [redacted] compared with vinorelbine. As PH was violated for both OS and PFS in this MAIC, median survival times rather than HRs were used to compare survival outcomes. As DESTINY-Breast01 study OS data are immature, and the median has not been reached, there is no way to meaningfully compare OS MAIC T-DXd versus vinorelbine results. However, for PFS, there appears to be a directional effect of T-DXd versus vinorelbine ([redacted]). The ERG highlights that T-DXd median OS and PFS results from the T-DXd versus vinorelbine MAIC are [redacted] DESTINY-Breast01 results.

Results from the eribulin and capecitabine MAICs relate to populations that are not wholly relevant to the decision problem and, therefore, should not be used for decision making.

3.6 Summary and conclusions of the clinical effectiveness section

3.6.1 Summary

Positioning of T-DXd in the treatment pathway

The anticipated wording of the T-DXd licence for use in the European Union is [redacted]. Clinical advice to the ERG is that, if recommended by NICE, it is likely that T-DXd would be used as a third-line treatment.

Efficacy evidence

Efficacy evidence was provided in the clinical sections of the CS for all outcomes specified in the final scope[23] issued by NICE, with the exception of HRQoL. HRQoL data were not collected in the DESTINY-Breast01 study which is the primary source of direct clinical effectiveness evidence presented by the company.

The DESTINY-Breast01 study[46] is a phase II, two-part, open-label, multicentre, single-arm study evaluating T-DXd in adults HER2+ UBC or MBC who had received prior treatment with anti-HER2 therapy, including trastuzumab and T-DM1. The majority of patients had received ≥two prior lines of systemic therapy (median six lines). The available efficacy data from this study are immature; after 11.1 months follow-up, only 13.6% of patients had died and median OS had not been reached. Furthermore, median PFS and DoR are also uncertain as the occurrence of an additional event in the "at risk" population could have a significant impact on the size of these results.

To compare the effectiveness of T-DXd versus the relevant comparators, the company identified seven studies[39-45] they considered were relevant for the conduct OS, PFS and ORR MAICs. While the company attempted to match for six clinically important variables, the ERG considers that the most important variables to adjust for were HER2+ status and prior anti-HER2 therapy. It was impossible to match for these variables since all patients in the DESTINY-Breast01 study had HER2+ disease and received two or more anti-HER2 therapies. Therefore, the ERG considers that only MAICs in which all patients in the comparator study had HER2+ disease and received two or more anti-HER2 therapies could generate valid results. Of the comparator studies, only the KCSG BR11-16 trial[39] of vinorelbine included only patients with HER2+ disease. It was also the only study in which all patients had received prior anti-HER2 therapy. However, the ERG considers that results from the MAIC that used data from the KCSG BR11-16 trial[39] data are uncertain as adjustments could not be made for all matching variables identified by the company and the PH assumption was violated for OS and

PFS. The ERG considers, therefore, that there is only evidence to suggest [redacted] and a directional effect of T-DXd versus vinorelbine for the outcome of PFS ([redacted]).

Safety data

The AE data from the DESTINY-Breast01 study appear to show that the safety profile from treatment with T-DXd is manageable. However, clinical advice to the ERG is that the relatively high number of deaths (n=4) from ILD may be a concern. The company has, therefore, highlighted that, for early detection of ILD, clinician education and close monitoring of patients for signs and symptoms of ILD are required.

3.6.2 ERG conclusions

DESTINY-Breast01 study is a phase II single-arm study of T-DXd and follow up data are only available for a median of 11.1 months (13.6% deaths).

The ERG considers that the company has been unable to provide evidence that allows a robust comparison of T-DXd versus eribulin and capecitabine because results from these MAICs relate to populations that are not wholly relevant to the decision problem.

The ERG considers that there is evidence from the vinorelbine MAIC to suggest that treatment with T-DXd delivers [redacted]. For PFS, there appears to be a directional effect [redacted] (using median estimates). As median OS has not been reached in the DESTINY-Breast01 study, a meaningful comparison of T-DXd versus vinorelbine for this outcome cannot be undertaken.

4 COST EFFECTIVENESS EVIDENCE

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 ERG critique of the company systematic review methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant economic evidence (e.g., modelling studies, utility studies and cost and resource use studies) of treatments for patients with HER2+ MBC in the ≥third-line setting are presented in the CS (Section B.3.1 and Appendix G). Three studies[73-75] from five publications[73-77] were summarised (CS, Table 67), quality assessed (CS, Appendix G) and discussed by the company (CS, Appendix G). None of the three studies[73-75] included treatment with T-DXd.

An assessment of the extent to which the company's review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 14. The ERG considers the methods used to conduct the company's systematic review of cost effectiveness evidence to be of a good standard.

Table 14 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	n/s
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	n/s
Were attempts to synthesise evidence appropriate?	Yes

ERG=Evidence Review Group; n/s=not stated
Source: LRiG in-house checklist

4.2 ERG conclusions regarding company systematic review methods of review(s)

Searches carried out by the ERG did not identify any relevant studies. Overall, the ERG is satisfied that there are no relevant economic studies of T-DXd.

4.2 ERG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 15 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on the company's economic evaluation
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
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	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. Values from previous STAs were used
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No. Values from previous STAs were used
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
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

ERG=Evidence Review Group; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[48] and ERG comment

Table 16 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	No	Evidence for T-DXd is drawn from an immature, single-arm phase II study (DESTINY-Breast01 study)
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG=Evidence Review Group; T-DXd=trastuzumab deruxtecan
Source: Drummond and Jefferson 1996[78] and ERG comment

4.2.2 Model structure

The company has produced a cost utility model. It is a partitioned survival model with four health states: progression free, on treatment; progression-free, off treatment; progressed and death. The structure of the company model is shown in Figure 2.

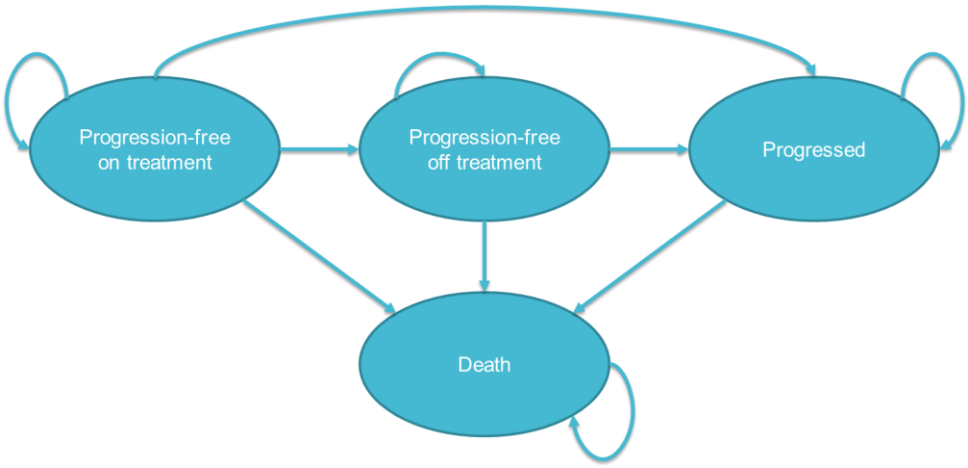

Figure 2 Structure of the company model

Source: CS, Section B.3.2.2, Figure 23

4.2.3 Population

The population simulated in the company model is adults with HER2+ UBC or MBC, who have received two or more prior anti-HER2 therapies. This is in line with the population considered in the DESTINY-Breast01 study, [redacted] and the final scope[23] issued by NICE. The starting age of patients in the model is 56 years.

4.2.4 Interventions and comparators

The intervention and comparators of interest are listed in Table 17, along with information about the drug dosages used in the company model.

Table 17 Intervention and comparator dosages

Drug	Category	Dose	Dosage
T-DXd	Intervention	5.4 mg/kg	Once per 21 days
Eribulin	Comparator	1.23 mg/kg	Days 1 and 8 of a 21-day cycle
Capecitabine	Comparator	1250 mg/m^2	Twice daily for 14 days of every 21-day cycle
Vinorelbine	Comparator	60 mg/m^2	Days 1 and 8 of a 21-day cycle

T-DXd=trastuzumab deruxtecan
Source: CS, Section B.3.2.4

4.2.5 Perspective, time horizon and discounting

The company states that they have used an NHS and PSS perspective, in line with the NICE Reference Case.[48] The cycle length in the company model is 1 week, the time horizon is 40 years and costs and outcomes are discounted at 3.5% per annum.

4.2.6 Treatment effectiveness and extrapolation

Patient level-data from the DESTINY-Breast01 study were used to inform the modelling of survival outcomes (OS, PFS), TTD and AEs (durations and frequencies) for patients receiving T-DXd.

The PFS results of unanchored MAICs were used to inform the comparison of T-DXd versus eribulin, capecitabine and vinorelbine.

Overall survival

The company (CS, Section B.3.3.1) considers that the OS data from the DESTINY-Breast01 study are very immature (approximately 80% of patients were alive at the August 2019 data cut-off). The company chose to use OS data from the T-DM1 arm of the TH3RESA trial[79] as the basis for modelling OS for patients treated with T-DXd.

To model OS for patients receiving T-DXd, the company first calculated a HR (DESTINY-Breast01 study (T-DXd) data versus TH3RESA trial[79] trastuzumab emtansine [T-DM1] OS

data). The TH3RESA trial[79] was a randomised, parallel assigned open-label phase III trial of T-DM1 versus physician choice. Eligible patients were adults with centrally confirmed HER2-positive advanced breast cancer previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and with progression on two or more HER2-directed regimens in the advanced setting. Long term T-DXd OS was modelled beyond the study period by using the generalised gamma function. The extrapolation of T-DM1 OS data assuming the generalised gamma distribution and other considered distributions are presented in Figure 3. All distributions were considered in scenario analyses.

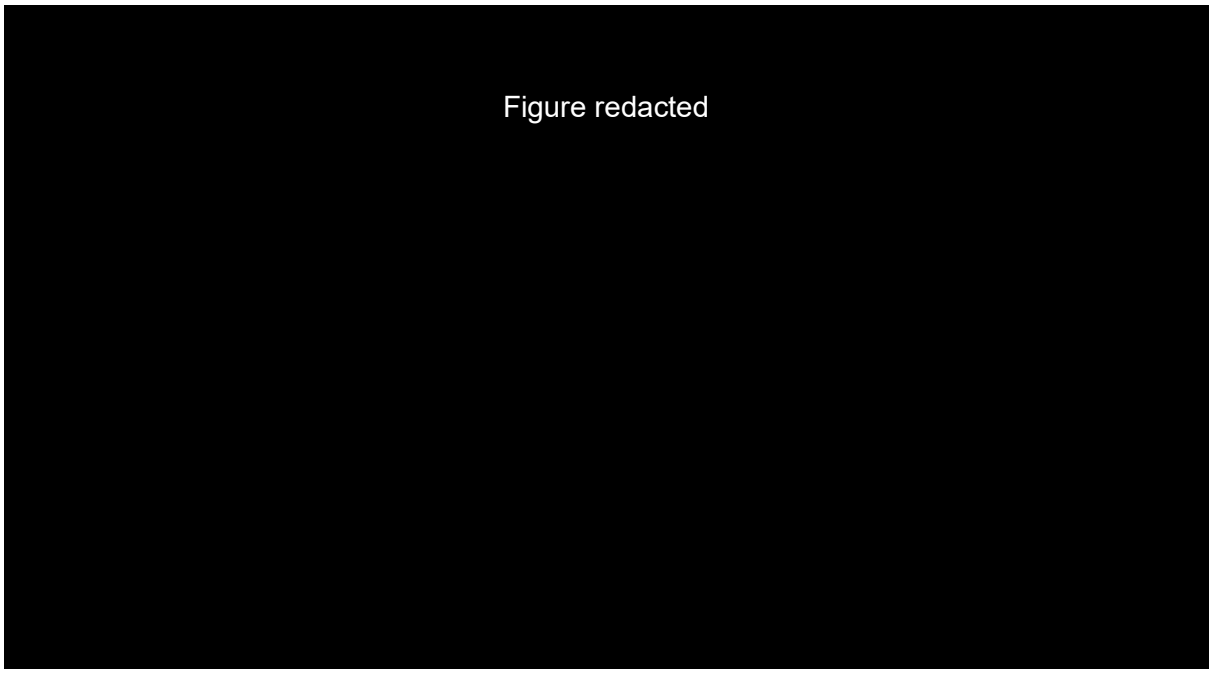

Figure 3 T-DXd OS extrapolations (hazard ratio applied to T-DM1 data from the TH3RESA trial)

KM=Kaplan-Meier; OS=overall survival; T-DM1=trastuzumab emtansine
Source: CS, Figure 26

OS for patients treated with eribulin and capecitabine was estimated by fitting parametric survival curves to digitised K-M data from the EMBRACE trial[42] and Fumoleau (2004) study[45] respectively. Clinical advice to the company was that available data for vinorelbine were not plausible or reflective of survival outcomes for UK patients. So, as PFS estimates for patients treated with vinorelbine were similar to those for patients treated with capecitabine, OS for patients treated with vinorelbine was the same as that for patients treated with capecitabine. In the CS, all of the OS extrapolations considered for eribulin (Figure 30) and for capecitabine (Figure 31) are presented. The generalised gamma and Gompertz functions were selected by the company to represent the experience of patients treated with eribulin and capecitabine, respectively. All distributions were considered in scenario analyses.

Age- and gender-specific probabilities of death were taken from published national life tables[80] for England and Wales, using data for 2019. Life tables were used to ensure the weekly probability of mortality never fell below that of the general population.

Progression-free survival

The median PFS of patients participating in the DESTINY-Breast01 study was 16.34 months. The company assessed alternative survival extrapolations (see Figure 4) and, in the base case, chose to use the log-normal distribution to represent the experience of patients treated with T-DXd as it was associated with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC).

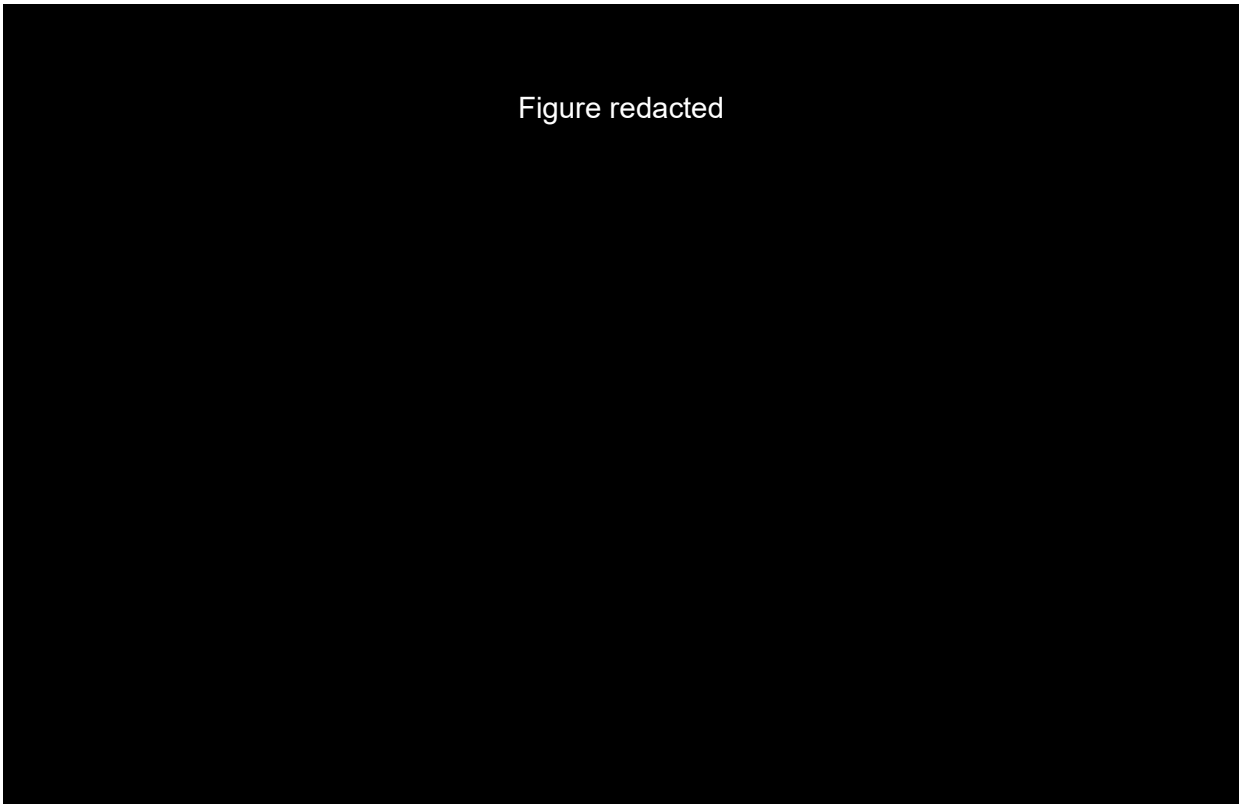

Figure 4 Potential progression-free survival models for patients treated with T-DXd

KM=Kaplan-Meier; PFS=progression-free survival; T-DXd=trastuzumab deruxtecan
Source: CS, Figure 32

Unanchored MAICs were conducted (CS, Section B.2.9) for all relevant comparators and HRs from the MAICs were applied to the extrapolated T-DXd PFS curve. Figure 5 presents the extrapolated survival curves for each comparator in the model, given the base case HRs (from the MAICs using data from the EMBRACE trial[42] and Fumoleau (2014) study.[45]

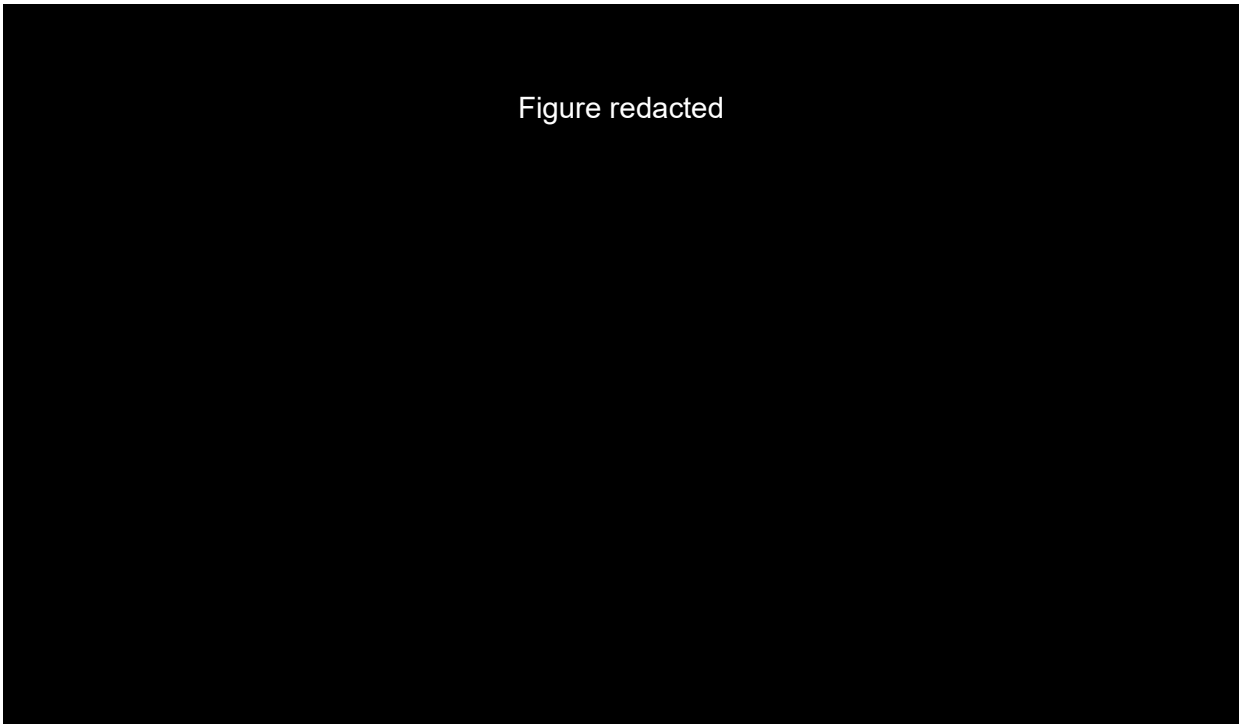

Figure 5 Potential progression-free survival models for comparator treatments

PFS=progression-free survival; T-DXd=trastuzumab deruxtecan
Source: CS, Figure 33

Time to treatment discontinuation

Data from the DESTINY-Breast01 study showed that the median TTD for patients treated with T-DXd was 10.59 months. The company assessed which of six different parametric distributions best represented TTD for patients treated with T-DXd (Figure 6). The company considered that the curves could be divided into two groups. One group (log-normal, log-logistic, generalised gamma, and exponential) implied that a proportion of patients would remain on treatment beyond 5 years, and the other group (Gompertz and Weibull) implied that patients would discontinue treatment by 5 years.

The company, after consultation with clinical experts, concluded that the exponential function should be selected for use in the model base case as it was the least optimistic of the first group of curves and could be considered as the midpoint between the two groups.

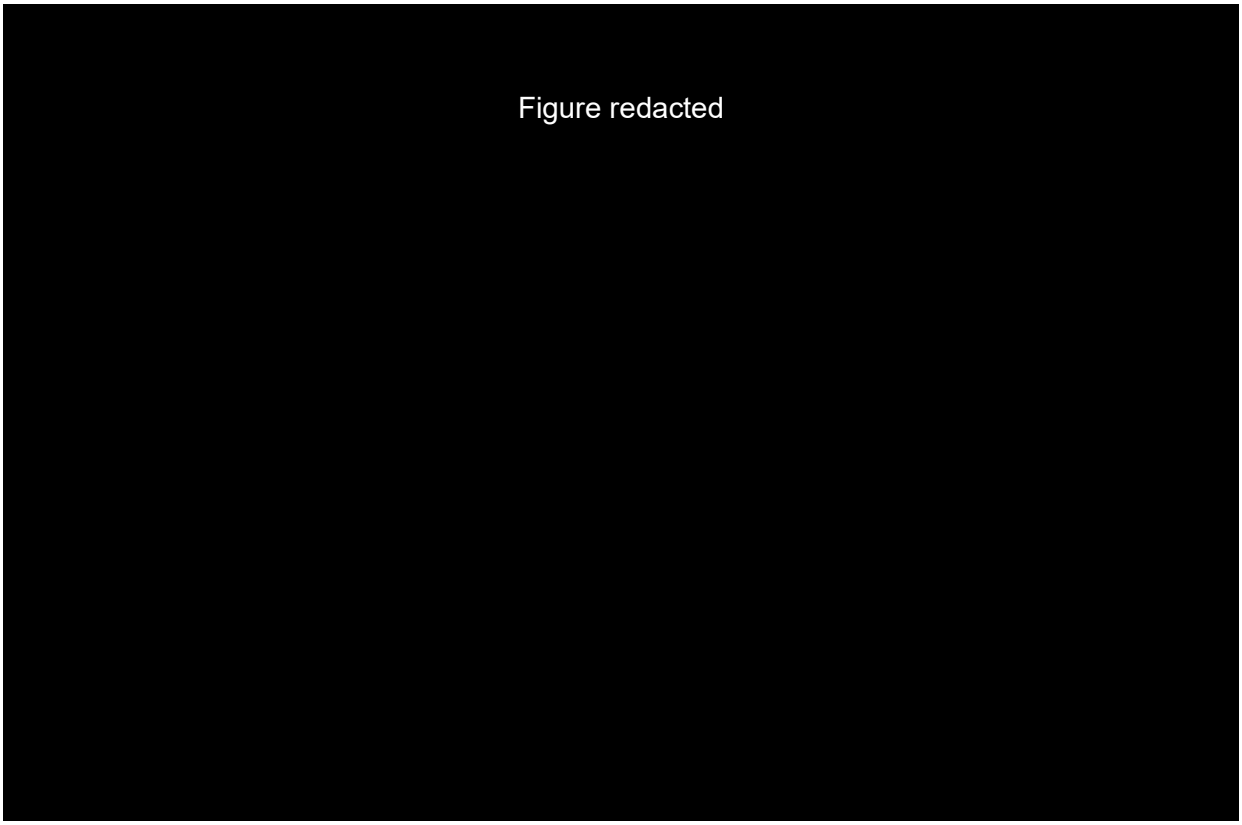

Figure 6 TTD, T-DXd

Gen.=generalised; KM=Kaplan-Meier; TTD=time to treatment discontinuation
Source: CS, Figure 24

TTD K-M data were not available for eribulin, capecitabine or vinorelbine. In the model base case, treatment to progression was assumed for these comparators. A scenario is considered in which a hazard ratio is applied to the T-DXd curve such that each curve passes through the observed median TTD in each study, with the exception of the KCSG BR11-16 trial,[39] which did not present median TTD. The TTD distributions used in the company model are shown in Figure 7.

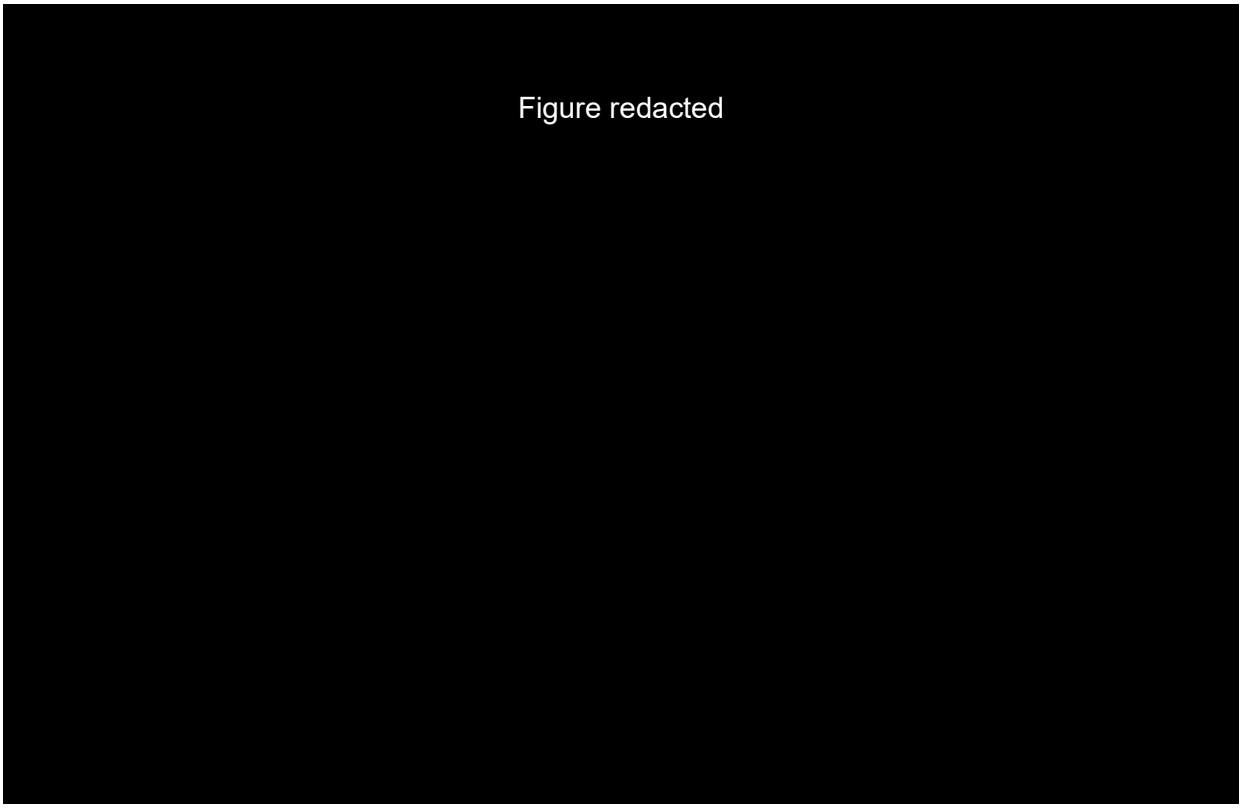

Figure 7 TTD, all comparators

T-DXd=trastuzumab deruxtecan; TTD=time to treatment discontinuation
Source: CS, Figure 35

HER2+ efficacy adjustment

All patients in the DESTINY-Breast01 study had HER2+ disease, while several of the comparator studies included a mix of patients with HER2+ and HER2- disease. Clinical advice to the company was that HER2+ disease is a more aggressive phenotype then HER2- disease and has always been associated with poorer outcomes. The company therefore used the HR reported by Lv (2018)[81] to adjust OS and PFS estimates in studies which included HER2- patients; the results of the company adjustment are shown in Table 18. In the absence of other evidence, the HR from the Lv (2018) study[81] was assumed for both OS and PFS; a scenario is considered in which no adjustment is made for HER2 status.

Table 18 HER2+ efficacy adjustment hazard ratios

Comparator	HER2+ adjustment HR, OS	HER2+ adjustment HR, PFS
Eribulin	1.69	1.69
Capecitabine	1.67	1.67
Vinorelbine	N/A	1

HER2=human epidermal growth factor receptor 2; HR=hazard ratio; OS=overall survival; PFS=progression-free survival
Source: CS, Table 79

Adverse events

The AE inputs used in the T-DXd arm of the company model are described in the CS (Table 80). Only Grade ≥3 AEs that occurred in at least 5% of patients were included for each comparator. In addition, any AEOSIs in the DESTINY-Breast01 study report or AEs of clinical importance mentioned by clinicians were also included. Incidence of AEs were recorded during the safety period of the DESTINY-Breast01 study (Day 1 through to the end of treatment visit or 30-days after the last study treatment, whichever was later). AEs have not been extrapolated beyond the safety period and all costs and QALY losses associated with AEs are assumed to occur in the first cycle of the model.

4.2.7 Health-related quality of life

HRQoL data were not collected in the DESTINY-Breast01 study, therefore, the company carried out a systematic review of HRQoL (utilities) studies. Full details of the studies identified by the company are presented in the CS, Appendix H. In the company model, disutilities associated with AEs are modelled separately from health state utility values.

Impact of adverse events on health-related quality of life

The impact of AEs on HRQoL is captured as a one-off QALY loss in the first cycle of the model; frequencies, durations and disutilities for each treatment were sourced from published studies.[21,82-87] Where available, AE disutilities were taken directly from HRQoL studies of patients with LABC or MBC treated with eribulin or capecitabine. The AE disutilities and durations used in the model are shown in Table 19.

.

Table 19 AE disutilities and durations

Adverse event	Disutility	Source	AE duration (days)	QALY decrement
Neutrophil count decreased	0.0070	Hudgens (2014)[83]	40.10	0.0008
Anaemia	0.0100		42.90	0.0012
Neutropenia	0.0070		40.10	0.0008
Nausea	0.0210		36.20	0.0021
Fatigue	0.0290		58.30	0.0046
White blood cell count decreased	0.0030		42.20	0.0003
Dyspnoea	0.0270		9.6	0.0009
Febrile neutropenia	0.0120		7	0.0002
Electrocardiogram QT prolonged	0.0000	Lachaine (2015)[84]	31.40	0.0000
Interstitial lung disease	0.1700	Doyle (2011)[82]	51.10	0.0238
Ejection fraction decreased	0.0590	Sandhu (2016)[86]	31.00	0.0050
Pneumonitis†	0.1700	Doyle (2011)[82]	51.10	0.0238
Vomiting	0.1030	Lloyd (2006)[85]	13.70	0.0039
Diarrhoea	0.0060	TA423[21]	17.00	0.0003
PPE	0.1160	Shlomai (2018)[87]	14.00	0.0044
Dehydration‡	0.0060	TA423[21]	17.00	0.0003
Stomatitis	0.1510	TA250[88]	10.00	0.0041
Abdominal pain‡	0.0060	TA423[21]	17.00	0.0003
Peripheral neuropathy	0.0140	TA423[21]	40.10	0.0015

† Another term for interstitial lung disease
‡ Assumed equal to diarrhoea
AE=adverse event; QALY=quality adjusted life year; PPE=palmar-plantar erythrodysesthesia syndrome; TA=technology appraisal
Source: CS, Table 84

The company estimated the total QALY loss due to AEs for each of the treatment arms in the model as follows: T-DXd (0.0013); eribulin (0.0003), capecitabine (0.0006) and vinorelbine (0.0006).

Modelling health state utility values in the company model

As per the approach undertaken by the company in TA423,[21] 'progression-free, on treatment' utility values were calculated as a function of ORR and AE rates. For all treatments, as shown in Table 20, baseline utility, tumour response utility and incremental utility of response values were taken directly from TA423.[21] 'Progression-free, on treatment' utility values were calculated using individual treatment ORR values; the ORR for T-DXd was taken from the DESTINY-Breast01 study and the ORRs for comparators were taken from the results of the company unanchored MAICs.

Table 20 Progression-free, on-treatment utility values

	Eribulin	Capecitabine	Vinorelbine	T-DXd
Baseline	0.704	0.704	0.704	0.704
Tumour response	0.780	0.780	0.780	0.780
Incremental utility of response	0.076	0.076	0.076	0.076
ORR	EMBRACE (2011):[42] 14.0% Barni (2019):[40] 17.2% Cortes (2010):[41] 10.0% Gamucci (2014):[43] 26.0%	Fumoleau (2004):[45] 19.0% Blum (2001):[44] 22.5%	KCSG BR11-16 (2019):[39] 31.6%	60.9%
Progression-free, on treatment utility value†	EMBRACE (2011):[42] 0.715 Barni (2019):[40] 0.717 Cortes (2010):[41] 0.712 Gamucci (2014):[43] 0.724	Fumoleau (2004):[45] 0.718 Blum (2001):[44] 0.721	KCSG BR11-16 (2019):[39] 0.728	0.750

† Progression-free, on treatment utility=baseline + (ORR*incremental utility of response)
T-DXd=trastuzumab deruxtecan; ORR=objective response rate
Source: CS, Table 86

In the base case analysis, the health state 'progression-free, off treatment' utility value (0.704) is the same as the baseline utility value shown in Table 20 and, in line with the Appraisal Committee's recommendation during TA423,[21] the progressed disease health state value (0.598) is the average of the TA423[21] ERG value (0.496) and the company's value (0.679). The utility values used in the model are shown in Table 21.

Scenarios are presented in the CS using the original TA423[21] ERG progressed disease heath state utility value (0.496), the company progressed disease health state utility value (0.697) and the progression-free (0.700) and progressed disease (0.500) health state utility values described in a publication by Le (2016).[75]

Table 21 Summary of utility values for cost effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
Progression-free, T-DXd	0.750	0.68 to 0.83	Derived from the 3L MBC submission TA423[21]
Progression-free, eribulin	0.713	0.64 to 0.78	
Progression-free, capecitabine	0.725	0.65 to 0.80	
Progression-free, vinorelbine	0.717	0.64 to 0.79	
Progression-free, blended SoC	0.713	0.64 to 0.78	
Progression-free, off treatment	0.704	0.63 to 0.77	
Progressed	0.588	0.53 to 0.65	

MBC=metastatic breast cancer; 3L=third-line; SoC=standard of care; T-DXd=trastuzumab deruxtecan
Source: CS, Table 88

In the model, after the first year, age-specific multipliers,[89] based on the ratio between the general population utility values for current age and starting age (56 years), were applied.

4.2.8 Resources and costs

The following categories of costs were included in the company model (CS, Section B.3.5.1):

- Acquisition costs
- Administration costs
- Subsequent therapy costs
- Health state costs
- AEs costs
- Miscellaneous costs (palliative care and end-of-life costs)

Costs taken from related technology appraisals[21,88] were inflated to 2018/2019 prices using the inflation indices provided in the PSSRU Unit Costs of Health and Social Care.[90]

Acquisition costs

The drug acquisition costs used in the company model are provided in

Table 22. The proposed list price of T-DXd is currently confidential, as is the proposed PAS price.

Table 22 Acquisition costs

Drug	Dose	mg/pack	Pack price	Pack size	Source
T-DXd (list price)†	5.4 mg/kg	100 mg	[redacted]	1	All costs were sourced from eMIT where available or the BNF
T-DXd (PAS price)†	5.4 mg/kg	100 mg	[redacted]		
Eribulin	1.23 mg/m^2	2 ml	£361.00	1	
		3 ml	£541.50		
Capecitabine	1250 mg/m^2	150mg	£4.17	60	
		300mg	£7.26		
Vinorelbine	60 mg/m^2	1 ml	£36.71	10	
		5 ml	£133.28		

† A list price application has been made to the Department of Health and an application has been made to the Patient Access Scheme Liaison Unit (PASLU)
BNF=British National Formulary; eMIT=electronic market information tool; PAS=Patient Access Scheme; T-DXd= trastuzumab deruxtecan
Source: CS, Table 89

Administration costs

The administration costs used in the company model are provided in Table 23.

Table 23 Administration costs

Method	Cost per single treatment dose	Source/service code	Drug and number of doses
Oral – one off cost	£92.00	PSSRU 2019 - 13 Hospital-based nurse cost per hour of patient contact (band 5)[91]	Capecitabine
IV infusion	£254.14	NHS reference costs 2018/2019/SB12Z – day case[92]	T-DXd (one dose) Capecitabine and vinorelbine (two doses)

IV=intravenous; NHS=National Health Service; PSSRU= Personal and Social Services Research Unit; T-DXd=trastuzumab deruxtecan
Source: CS, Table 92

Wastage and relative dose intensity

The company assumed that, in the absence of data, 50% wastage occurred and considered 0% and 100% wastage options in scenario analyses. The cost per dose without wastage and cost per dose with wastage were combined and weighted by the assumed proportion of vial sharing. The adjusted cost per dose for each treatment is presented in the CS (Table 90).

The relative dose intensity (RDI) for T-DXd (93.19%) is taken from the DESTINY-Breast01 study, the RDI for eribulin was assumed equal to the RDI for eribulin presented in TA423[21] (84.00%). The RDI for capecitabine and vinorelbine was assumed to equal the RDI for eribulin. An RDI of 100% was assumed for subsequent therapies.

Subsequent therapies

In the company base case, 60% of patients incurred a lifetime cost of subsequent therapies when they transitioned into the 'progressed' health state. The average weekly cost of a treatment was calculated as an average of the weekly cost over 3 weekly cycles (as this was the maximum treatment cycle length for some of the treatments listed in Table 24) to account for differing treatment cycle lengths.

Table 24 Subsequent therapy costs

Drug	Dose	Administration method	Cost per dose	Frequency	Treatment distribution
Vinorelbine IV	60 mg/kg	IV	£15.02	Weekly	18.4%
Vinorelbine oral	60 mg/m^2	Oral	£219.90	Weekly	18.4%
Gemcitabine	1250 mg/m^2	IV	£35.55	Day 1 & 8 of 21-day cycle	27.7%
Docetaxel	100 mg/m^2	IV	£37.50	Every 3 weeks	6.0%
Paclitaxel	175 mg/kg	IV	£37.76	Every 3 weeks	15.7%
Doxorubicin	68 mg/m^2	IV	£17.21	Every 3 weeks	13.9%

IV=intravenous
Source: CS, Table 93

Health state costs

Medical resource use costs and frequencies were informed by the resource use presented in TA423[21] for pre- and post-progression health states. The monthly and weekly costs of the pre-progression and post-progression health states were estimated at £253.70 and £58.34 respectively using 2019/20 prices.

Adverse event costs

The costs of AEs were applied to the proportion of each event that was estimated to result in hospitalisation. For the AEs that were reported for T-DXd and comparators, the proportion of events that resulted in hospitalisation was based on the proportion of hospitalisations reported for each T-DXd event. For events that occurred in the comparator studies that did not occur with T-DXd in the DESTINY-Breast01 study, it was assumed that 0% would lead to hospitalisation; this assumption was tested in a sensitivity analysis. The unit cost of each AE and cost source are reported in the CS (Table 96). The company estimated AE costs using results costs published in previous NICE Technology Appraisals,[21,88] 2018/19 NHS Reference Costs[92] and 2019 PSSRU costs.[90] The total AE costs by treatment are presented in Table 25.

Table 25 Total adverse event costs by treatment

Treatment	Adverse event cost
T-DXd	£40.73
Eribulin	£43.48
Capecitabine	£9.23
Vinorelbine	£25.81

T-DXd=trastuzumab deruxtecan
Source: CS, Table 97

Palliative care and end-of-life costs

In line with the approach adopted in TA423,[21] the cost of palliative care (£358.43 per month) was assigned to each patient in the progressed state for 5.5 months before patients transitioned into the 'Dead' health state. The frequency of resource use for patients who were receiving palliative care was sourced from estimates presented in TA423.[21] The costs resources associated with palliative care were estimated using 2018/2019 costs (see CS, Table 98 for details).

Similarly, end-of-life costs were applied to each patient who transitioned to the 'Dead' health state for 2 weeks before death. The cost of end-of-life treatment at a hospital or medical institution, hospice or at home, and the proportion of patients who died in each setting was taken from the estimates presented in TA423.[21] The end-of-life treatment cost used in the model was £4,262.64 (see CS, Table 100 for details).

The company sums the palliative care cost and the end-of-life treatment cost to generate a total terminal care cost of £6,234.

5 COST EFFECTIVENESS RESULTS

5.1 Base case incremental cost effectiveness analysis results

The company provided fully incremental cost effectiveness analysis results (CS, Table 104). For the comparison of T-DXd versus capecitabine, the incremental cost-effectiveness ratio (ICER) per QALY gained is [redacted]; T-DXd is more expensive [redacted] and more effective [redacted] than capecitabine.

Table 26 Base case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Inc. LYG	Incr. QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inc.=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life years gained; T-DXd=trastuzumab deruxtecan
Source: CS, Table 104

5.2 Probability sensitivity analysis

For the comparison of T-DXd versus capecitabine, the average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], generating a probabilistic ICER per QALY gained of [redacted]. The proportion of simulations considered cost effective at a threshold of [redacted] per QALY gained was [redacted].

Table 27 PSA results (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]			[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years; T-DXd=trastuzumab deruxtecan
Source: CS, Table 105

The scatterplots for the comparison of T-DXd versus eribulin, capecitabine and vinorelbine are presented in the CS (Figure 36, Figure 37 and Figure 38 respectively). The cost effectiveness acceptability curve for the comparison of T-DXd versus the comparator drugs (eribulin, capecitabine and vinorelbine) is shown in Figure 8. The proportion of simulations for the

comparison of T-DXd versus capecitabine considered cost effective at a threshold of [redacted] per QALY was [redacted].

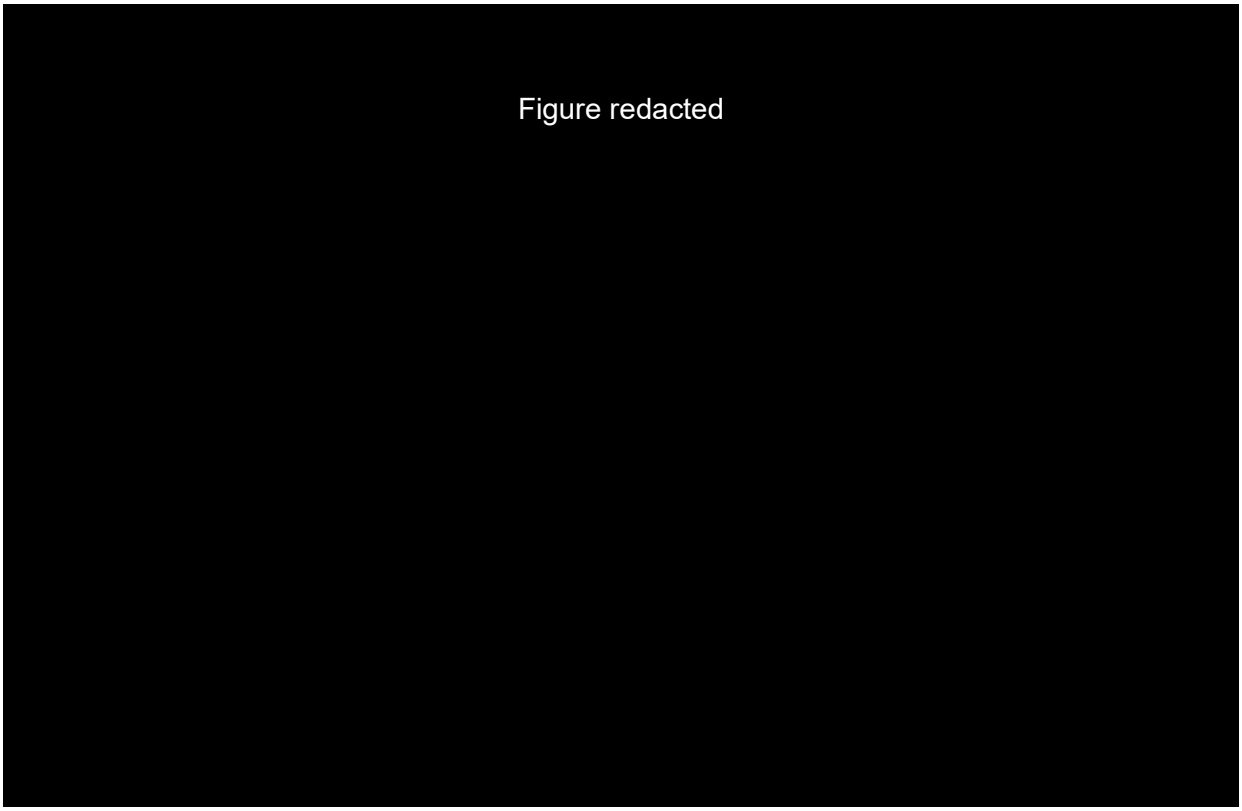

Figure 8 Cost effectiveness acceptability curve (list prices)

Source: CS, Figure 39

5.3 Deterministic sensitivity analysis

For all three comparisons (T-DXd versus eribulin, capecitabine and vinorelbine), parameter uncertainty was tested using univariate sensitivity analysis; all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±10% where no estimates of precision were available (CS, Table 106, 107 and 108). For each comparison, the ICER per QALY gained was recorded at the upper and lower values to produce a tornado diagram (CS, Figure 40, 41 and 42). For each comparator, the most influential parameter was the HR applied to the TH3RESA trial[79] data to model T-DXd OS.

For all three comparisons (T-DXd versus eribulin, capecitabine and vinorelbine), scenario analyses were also carried out in which key structural assumptions were varied (CS, Table 109, 110 and 111). For all comparisons, the selection of different distributions for the TH3RESA trial[79] OS extrapolation had the biggest impact on the size of the ICERs per QALY gained.

5.4 Model validation and face validity

The model validation exercise comprised a review of (i) formulae, (ii) consistency with the model decision problem, (iii) visual basic for applications implementation, (iv) model inputs and (v) model functionality, and this was carried out by internal model developers and an external health economist. In addition, all model inputs and assumptions were discussed at an Advisory Board Meeting of four UK clinical experts in breast cancer and four independent health economists.

6 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The ERG is satisfied that the algorithms in the company model are accurate and that the parameter values used in the model match those in the CS. Further, the ERG considers that the modelled patient pathway and the use of a Markov model structure were appropriate.

The ERG acknowledges the efforts made by the company to generate comparative cost effectiveness results. However, the currently available clinical evidence on the absolute effectiveness of T-DXd are generated by an immature (11.1 months follow-up) single-arm phase II study. The weaknesses of the T-DXd OS and PFS data mean that it is not possible to generate robust comparative results, and this means that it is not possible to generate robust cost effectiveness results.

The most important comparative clinical effectiveness outcome, from the perspective of generating cost effectiveness results, is OS (in the company model, approximately 95% of the QALY gain associated with treatment with T-DXd is driven by gains in OS). The magnitude of uncertainty around OS means that the impact of other areas of uncertainty on cost effectiveness results cannot be determined accurately, although in some cases the likely direction of the uncertainty on the cost effectiveness results can be determined.

Summary details of the ERG's critique of the company model are provided in Table 28.

Table 28 Summary of ERG company model critique

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Patient pathway	• The patient pathway is appropriate	6.1
Modelling OS and PFS	• The OS data are so uncertain (single-arm, phase II study; median follow-up=11.1 months) that any modelling of OS is of limited use for decision making • PFS modelled using results from the company MAICs which are unreliable (Section 3.5.4) • The progression and mortality hazards for patients receiving T-DXd are always lower than those for patients receiving comparator drugs for the 40-year model time horizon. The ERG does not consider that this is plausible	6.2
TTD	• PFS data were used to model TTD for comparator drugs. The validity of this approach is not known	NA
Utility values	• The methods used by the company to elicit health state values are not in line with the NICE Reference Case[48] • The company assumed that patients receiving T-DXd have a higher utility in the PFS state than patients receiving comparator drugs. No direct evidence was available to support this assumption	6.3
Drug costs	• The ERG is broadly satisfied with the approach used by the company to estimate drug costs, however: o more information on vial sharing/wastage would be required to generate a more accurate ICER per QALY gained o the dose of vinorelbine used by the company (60 mg/m^2) is higher than that reported in the SmPC[26] (25-30 mg/m^2)	6.3
Resource use	• Long-term health state costs may have been overestimated	6.3
AEs	• AEs have a minimal impact on cost and QALYs and are not a driver of cost effectiveness	NA

AE=adverse event; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; QALY=quality adjusted life year; SmPC=summary of product characteristics; T-DXd=trastuzumab deruxtecan
Source: LR*i*G in-house checklist

6.2 Modelling overall survival for patients treated with T-DXd

The company used a simple between study analysis of data from the DESTINY-Breast01 study and data from the T-DM1 arm of the TH3RESA trial[79] to model OS for patients receiving T-DXd. The TH3RESA trial[79] was a phase III randomised, multicentre, two-arm, open-label comparison of T-DM1 versus physician's choice. The population comprised adults with centrally confirmed HER2+ ABC; all patients had been previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and had progressed on ≥2 HER2-targeted regimens in the advanced setting. The ERG considers that results from a simple data comparison are not reliable as this approach means that no adjustments were

made for differences between the characteristics of the patients enrolled in the DESTINY-Breast01 study and the TH3RESA trial.[79]

In response to clarification question B1, the company provided a table that highlighted the differences between DESTINY-Breast01 and TH3RESA trial[79] populations. Notable differences were:

- median number of prior therapies (DESTINY-Breast01 study: 6; TH3RESA trial:[79] 4)
- proportion of population Asian (DESTINY-Breast01 study: 38%; TH3RESA trial:[79] 14%)
- ECOG PS 0 (DESTINY-Breast01 study: 55%; TH3RESA trial:[79] 45%).

Failure to account for these differences means that the results of comparisons between the DESTINY-Breast01 study and the TH3RESA trial[79] are unreliable.

Further, all patients enrolled in the DESTINY-Breast01 study had received prior treatment with T-DM1. At baseline, just over two-fifths (42.9%) of patients in the DESTINY-Breast01 study had had a best response to T-DM1 that was at least stable disease (54.5% of patients where response was evaluated), with 21.7% having a complete or partial response (27.6% of patients response where evaluated). Therefore, potentially, over half of patients in the DESTINY-Breast01 study had responded well to T-DM1. Any patients who died or had significant disease progression that resulted in a decrease in PS whilst taking TDM-1 either did not, or could not, enter the DESTINY-Breast01 study. In contrast, the TH3RESA trial[79] included patients who had not previously been treated with TDM-1 and, therefore, their response to TDM-1 was unknown at the time of entry.

DESTINY-Breast01 is a phase II single-arm study and the TH3RESA trial[79] is a phase III RCT. It is important to note that treatment effects in phase II studies are often greater than those observed in phase III trials.[58]

Comparison of the limited DESTINY-Breast01 study OS K-M data and the digitised OS K-M data from the TH3RESA trial[79] suggest that mortality hazards are similar for patients in the DESTINY-Breast01 study and patients in the T-DM1 arm of the TH3RESA trial[79] for approximately the first 6 to 8 months, and then they diverge. This pattern suggests that the PH assumption does not hold, which means that using a non-time variant mortality hazard ratio in the model is inappropriate (Figure 9). In clarification question B2, the ERG asked the company to test the OS PH assumption between the DESTINY-Breast01 study and the TH3RESA trial.[79] In response, the company provided a Schoenfeld residual chart (**Figure 10**),

a residual test (PH could not be rejected) and a log-log plot (**Figure 11**) and concluded that these results suggested that PH held. The ERG disagrees with the company's interpretation of results from their tests of PH and considers that the charts provide evidence that hazards are not proportional and that the result from the residual test is an artefact of a small number of data points and, therefore, is not robust. Whilst assessment of the PH assumption is subjective, even if the evidence pointed conclusively to the assumption holding, the evidence would only show that, for the 8 month to 10 month period that reasonably robust data from the DESTINY-Breast01 study are available (around 2% of the remaining 40 year model time horizon), mortality hazards are proportional.

In conclusion, the ERG considers that the company's OS projections for T-DXd are unreliable.

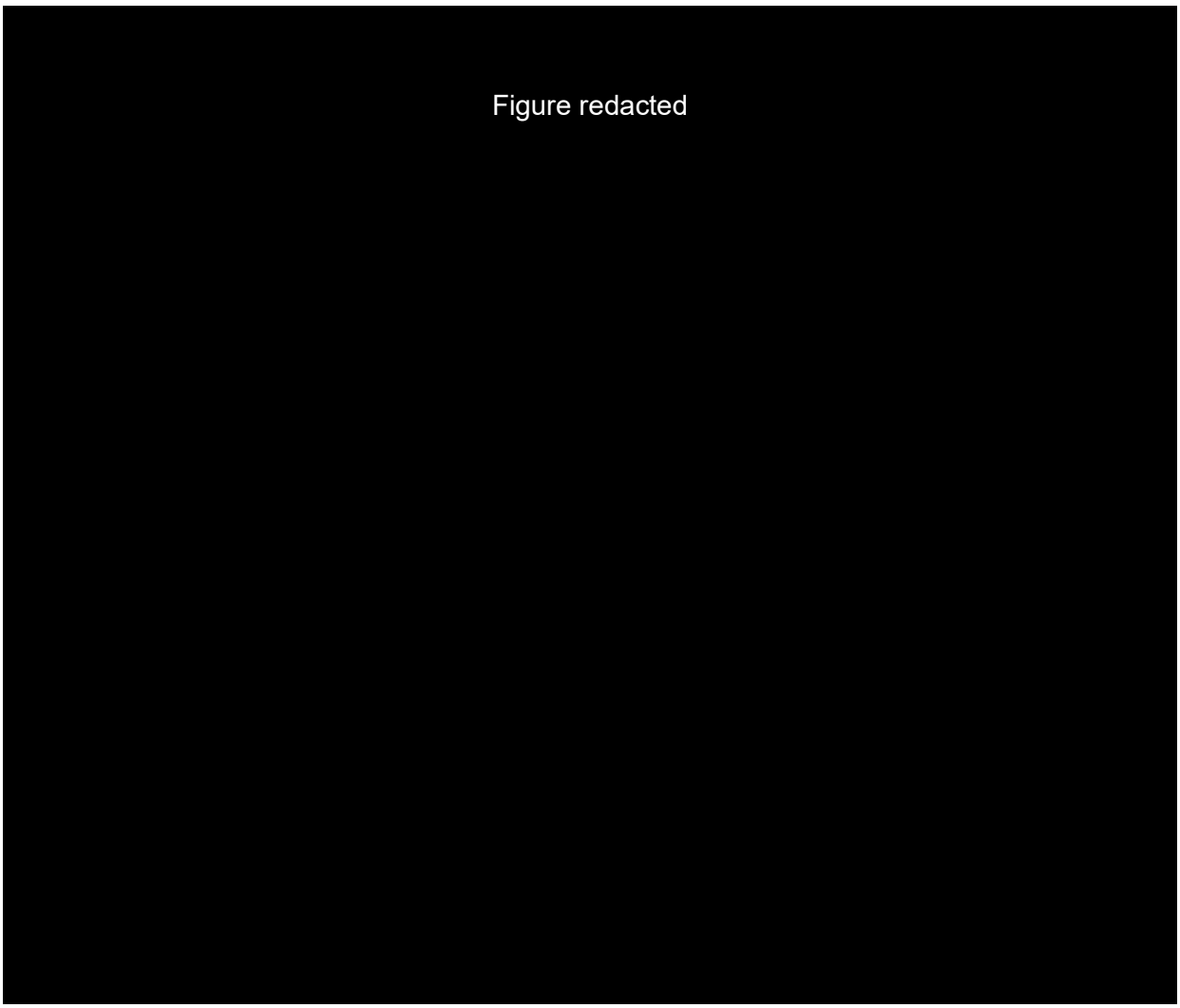

Figure 9 Overall survival Kaplan-Meier data: DESTINY-Breast01 study and TH3RESA trial (T-DM1)

KM=Kaplan-Meier; T-DM1=trastuzumab emtansine
Source: Company economic model

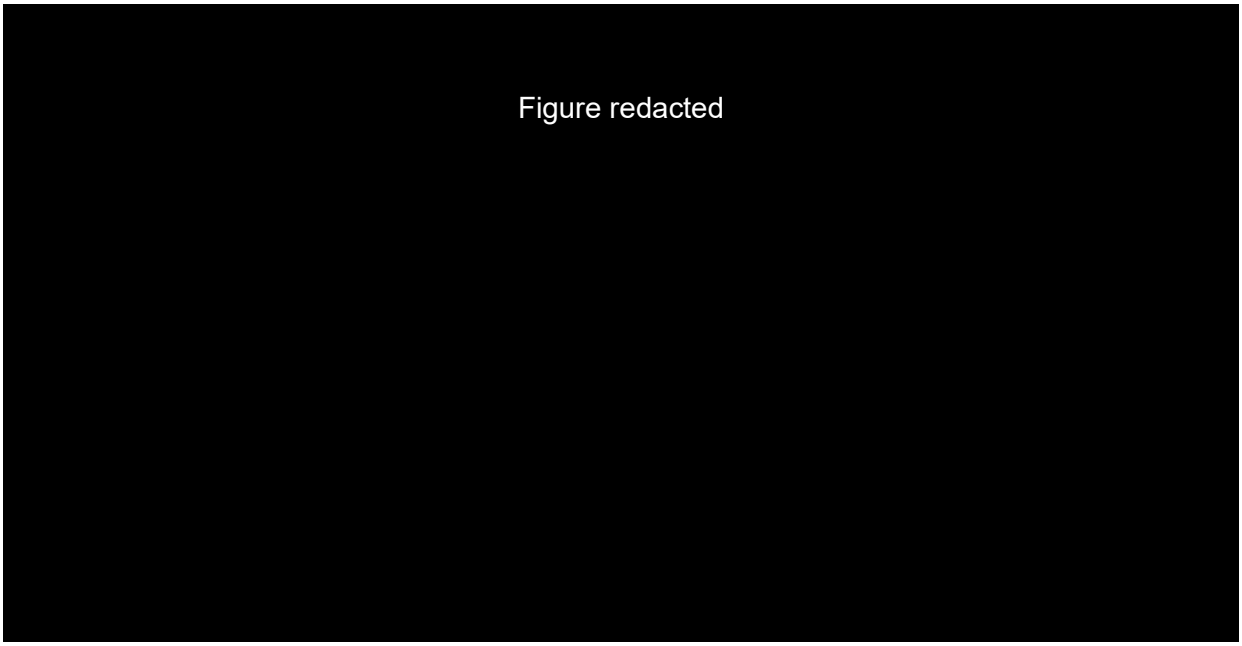

Figure 10 Schoenfeld residuals (overall survival): DESTINY-Breast01 study versus TH3RESA trial (T-DM1)

KM=Kaplan-Meier; T-DM1=trastuzumab emtansine
Source: Clarification question B2

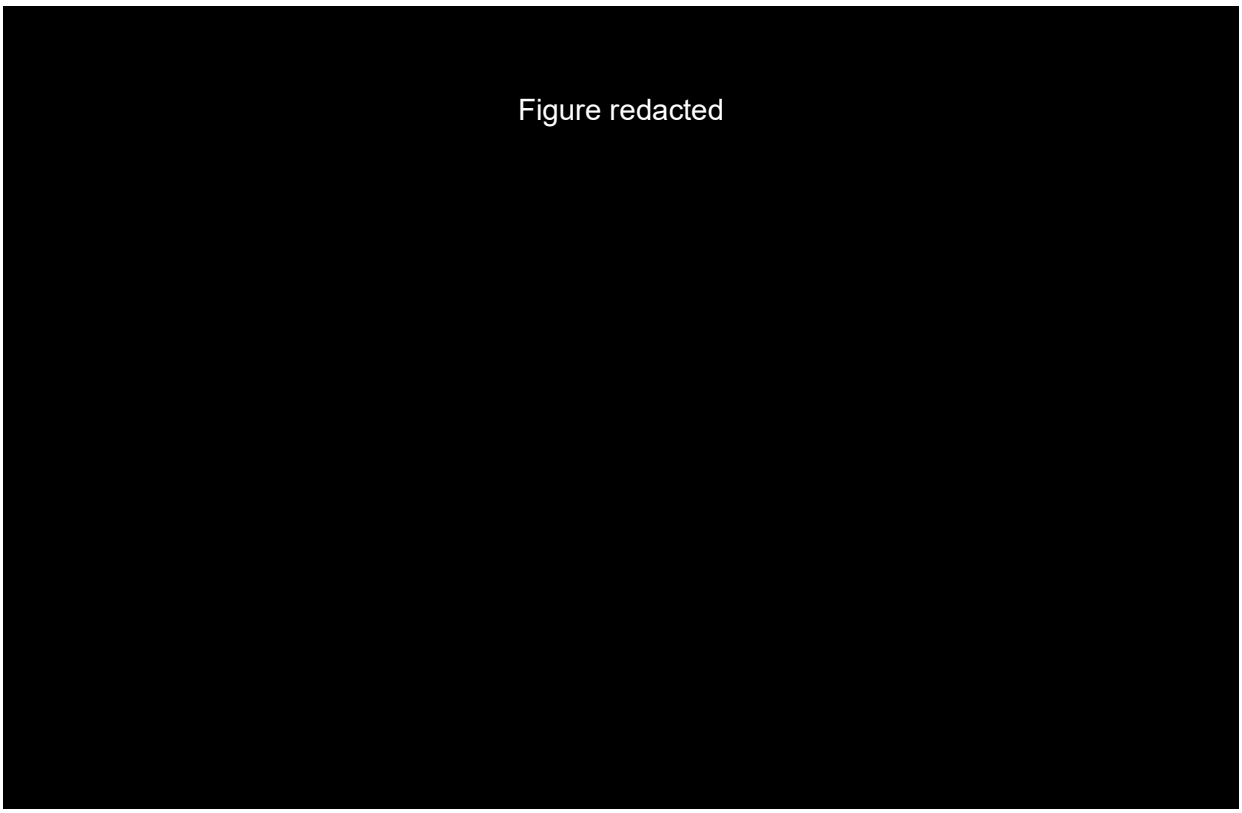

Figure 11 Log-log plot (overall survival): DESTINY-Breast01 study versus TH3RESA trial (T-DM1)

KM=Kaplan-Meier; T-DM1=trastuzumab emtansine
Source: Clarification question B2

The only alternative approach to modelling OS for patients receiving T-DXd would be to use results from the company MAICs. However, the ERG considers that the company's MAIC results cannot be used to inform the economic model (see Section 3.5.4 for details). The ERG considers that the weaknesses of the evidence base mean that there are no reliable approaches to modelling OS for patients receiving T-DXd.

6.3 Further areas of uncertainty

Comparator overall survival and progression-free survival estimates

The company was unable to produce robust OS and PFS estimates for patients treated with any of the comparators.

The company has used unadjusted (except for HER2 status) K-M data from the comparator studies[40-45] as the basis for modelling OS. As this, essentially, is a simple between study analysis unadjusted for patient characteristics without robust ITC techniques, the validity of the comparator OS estimates is uncertain.

The company applied eribulin and capecitabine MAIC HR results to DESTINY-Breast01 study PFS data to generate PFS estimates for the comparator treatments. The ERG considers that, as the results from these MAICs do not wholly relate to the population of interest (Section 3.5.4), the PFS estimates in the model generated from the MAICs are unreliable.

Adjustment of comparator OS and PFS data for HER2 status

The company has adjusted the comparator OS and PFS curves to take into account the proportion of patients with HER2+ disease in the studies that provide comparator effectiveness data. The company has assumed that patients with HER2+ disease have a worse prognosis than those who have HER2- or unknown disease status. The consequence of the adjustments made by the company is to decrease the effectiveness (OS and PFS) of the comparator treatments.

Historically, treatment options for patients with HER2+ disease were limited and, as a consequence, the prognosis for these patients was worse than that of patients with HER2- disease. However, with the advent of HER2-targeted therapies, it is unclear whether this is still true. The company cited one study[40] that found no difference in outcomes between patients with HER2+ and HER2- MBC who had been treated with eribulin in Italy, and also reported results from another study[81] that found that outcomes for patients with HER2+ disease not treated with trastuzumab were inferior to the outcomes for patients with HER2- disease.

If, OS and PFS do not differ by HER2 status, the HER2 adjustments to OS and PFS applied by the company will have underestimated the ICERs per QALY gained for T-DXd versus each comparator.

Utilities

The company used utility values that had been used to inform the previous NICE technology appraisal[21] of eribulin for treating LABC or MBC after two or more chemotherapy regimens, coupled with assumptions around the impact of response on PFS utility. This resulted in patients receiving treatment with T-DXd having a higher utility in the PFS state than patients receiving any comparator. If there was no utility gain for patients treated with T-DXd in the PFS state, then this would increase the size of the company's base case ICERs per QALY gained for all comparisons.

Health state costs

The company has assumed that there is a monthly background health care cost of £212.92 regardless of progression state. The magnitude of this cost is largely driven by a monthly oncologist appointment. The ERG considers that it is unlikely that patients who respond to treatment and are still alive at 5 years will continue to have monthly oncologist appointments, rather, there would be longer periods between appointments. This would reduce the overall background health state costs for patients who respond well to treatments and enjoy significant long-term survival. If treatment with T-DXd were to extend life more than the comparator treatments (as claimed by the company), and if more appropriate long-term health state costs were used, then this would decrease the size of the company's base case ICERs per QALY gained for all comparisons.

Lifetime duration of treatment effect

At all timepoints in the model, the progression and mortality risks are lower for patients in the T-DXd arm than for patients in any of the comparator treatment arms. The ERG considers that this is a very strong assumption. Whilst it is uncertain how long the T-DXd treatment effect would last after treatment is discontinued, if the treatment effect did not last a patient's lifetime, i.e., mortality and progression hazards became equal for all treatments at a future point in time, this would increase the size of the ICER per QALY gained for the comparison of T-DXd versus all of the comparators.

Vial sharing

The company has presented no evidence relating to vial sharing for any treatment administered intravenously. In the company base case it has been assumed that, for all intravenous treatments, 50% of an unused vial would be wasted. As the proportion of wastage decreases, the cost effectiveness of T-DXd versus other IV treatments increases; this is due to T-DXd being more expensive per cycle than all other IV treatments. It is unclear whether this assumption is optimistic or pessimistic.

6.4 Conclusions of the cost effectiveness section

The relative effectiveness of T-DXd versus the comparators cannot be determined with any degree of certainty. This means that the company cost effectiveness results are unreliable and should not be used as the basis for decision making.

7 NICE END OF LIFE CRITERIA

The company considers that the NICE End of Life criteria[48] apply to the current appraisal of T-DXd (Table 29). The company's and the ERG's assessments are provided in Table 29.

Table 29 Company and ERG assessment of whether NICE End of Life criteria apply to the current appraisal of T-DXd

Criterion	Company evidence	ERG comment
The treatment is indicated for patients with a short life expectancy, normally <24 months	Company model mean OS estimates: • eribulin: [redacted] • capecitabine: [redacted] • vinorelbine: [redacted]	All of the evidence presented in the studies of the comparators[39-45] suggests that life expectancy is less than 24 months. However, whether the life expectancy of HER2+ patients who progress after receipt of TDM-1 as a second-line treatment and are fit enough for a third-line treatment is less than 24 months is unclear
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Company model mean OS for patients receiving T-DXd is [redacted], resulting in the following estimates of extension to life versus: • eribulin: [redacted] • capecitabine: [redacted] • vinorelbine: [redacted]	Whilst results from the company model suggest that the OS gain for patients receiving T-DXd could exceed 3 months, without more robust comparative OS data this gain is highly uncertain

OS=overall survival; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan
Source: CS Document A, Table 13

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9 APPENDICES

9.1 Appendix 1 The DS8201-A-J101 study

9.1.1 DS8201-A-J101 study: study characteristics

The company has provided details of the characteristics of the DS8201-A-J101 study in the CS (Appendix M). The DS8201-A-J101 study is a two-part (dose escalation and dose expansion), non-randomised, open-label, phase I study, evaluating T-DXd in patients with HER2+ breast cancer who had received prior treatment with T-DM1. The study was conducted at 14 hospitals and clinics (USA: n=8; Japan: n=6). Eligible patients received one of two doses of T-DXd: 5.4 mg/kg or 6.4 mg/kg administered intravenously once every three weeks.

9.1.2 DS8201-A-J101 study: population characteristics

The baseline characteristics of patients included in the DS8201-A-J101 study are summarised in Table 30. The ERG notes that as in the DESTINY-Breast01 study all patients in the DS8201-A-J101 study had received treatment with T-DM1, with the majority also having had prior treatment with trastuzumab (99%). A higher proportion of patients in the DS8201-A-J101 study had prior treatment with pertuzumab compared to DESTINY-Breast01 patients (86% versus 65.8% respectively). Comparable numbers of patients in the DS8201-A-J101 study and DESTINY-Breast01 study had prior treatment with other anti-HER2 treatment (59% versus 54.3% respectively).

Clinical advice to the ERG is that the ages of patients in the DS8201-A-J101 study (median: 55; range: 47 to 66 years) and those seen in NHS clinical practice are similar. Clinical advice further highlighted that the study population included a greater proportion of Asian patients (54%) than would normally be seen in the NHS, indicating that there were known differences in terms of safety compared to Caucasian populations.[49,50] Patients in the DS8201-A-J101 study had received prior treatments (median: 7; range: 5 to 11); clinical advice to the ERG is that currently, patients seen in the NHS, would have received fewer prior therapies.

Table 30 Baseline characteristics of patients in the DESINY-Breast01 study and DS8201-A-J101 study

Characteristic	DESTINY-Breast01 T-DXd 5.4 mg/kg (N=184)	DS8201-A-J101 T-DXd 5.4 mg/kg or T-DXd 6.4 mg/kg (N=115)
Age		
Age, median (range), years	55.0 (28.0–96.0)	55.0 (47.0–66.0)
<65 years	140 (76.1)	-
≥65 years	44 (23.9)	-
Female, n (%)	184 (100)	114 (99)
Race, n (%)		
Asian	70 (38.0)	-
White	101 (54.9)	-
Other	9 (4.9)	-
Missing data	4 (2.2)	-
Region, n (%)		
Europe	68 (37.0)	-
Asia	63 (34.2)	62 (54) [all Japan]
North America	53 (28.8)	53 (46) [all USA]
ECOG performance-status score, n (%)		
0	102 (55.4)	72 (63)
1	81 (44.0)	43 (37)
2	1 (0.5)	0
Hormone-receptor status, n (%)		
Positive	97 (52.7)	81 (70)
Negative	83 (45.1)	33 (29)
Unknown	4 (2.2)	1 (1)
HER2 expression (immunohistochemistry)		
3+	154 (83.7)	79 (69)
IHC 1+ or 2+, ISH-positive	28 (15.2)	32 (28)
Missing or not examined	2 (1.1)	4 (3)
Time from initial diagnosis (months), median (range)	-	69.7 (48.0–117.2)
Tumour size (cm)		
Sum of diameters, median (range)	5.5 (1.2–24.5)	6.0 (3.6–10.0)
Subjects with following metastases[†], n (%)		
Yes	172 (93.5)	-
Brain	24 (13.0)	-
Bone	53 (28.8)	-
Lung	105 (57.1)	-
Liver	56 (30.4)	-
Visceral	169 (91.8)	-

Characteristic	DESTINY-Breast01 T-DXd 5.4 mg/kg (N=184)	DS8201-A-J101 T-DXd 5.4 mg/kg or T-DXd 6.4 mg/kg (N=115)
Prior cancer surgery, n (%)	-	88 (77)
Prior radiotherapy, n (%)	-	94 (82)
Median no. of prior cancer regimens (range)	6 (2–27)	7.0 (5-11)
≥3 prior anticancer regimens, n (%)	169 (91.8) [redacted]	-
≥5 prior anticancer regimens, n (%)	[redacted]	94 (82)
Prior systemic cancer therapy, n (%)		
Pertuzumab	121 (65.8)	99 (86)
Trastuzumab	184 (100)	114 (99)
T-DM1	184 (100)	115 (100)
Other anti-HER2 therapy	100 (54.3)	67 (59) §
Hormone therapy	90 (48.9)	-
Other systemic therapy	183 (99.5)	-
Best response to T-DM1 therapy, n (%)		
CR/PR	40 (21.7)	-
SD	39 (21.2)	-
CR/PR/SD	79 (42.9)	-
PD	66 (35.9)	-
Could not be evaluated	39 (21.2)	-

CR=complete response; ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridisation; PD=progressive disease; PR=partial response; SD=stable disease; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.
§ lapatinib 62 (54%) in study DS8201-A-J101[47]
Source: CS, adapted from Table 7, Table 17 and Appendix M; CSR, adapted from Table 7.5

9.1.3 Quality assessment of the DS8201-A-J101 study

The company assess the quality of the DS8201-A-J101 using the Downs and Black criteria.[52] A summary of the company's assessment, with ERG comments, is provided in Table 31. The ERG considers that the DS8201-A-J101 study is of a good standard for a single-arm study.

Table 31 Quality assessment for the DS8201-A-J101 study

Downs and Black checklist criteria	Company's score	ERG score
Q1. Is the hypothesis/aim/objective of the study clearly described?	Y	Y
Q2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y	Y
Q3. Are the characteristics of the patients included in the study clearly described?	Y	Y
Q4. Are the interventions of interest clearly described?	Y	Y
Q5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y	P¶
Q6. Are the main findings of the study clearly described?	Y	Y
Q7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y
Q8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y
Q9. Have the characteristics of patients lost to follow-up been described?	N	N
Q10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N	N
Q11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y
Q12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	Y
Q13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	UTD	UTD
Q14. Was an attempt made to blind study subjects to the intervention they have received?	N	N
Q15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N
Q16. If any of the results of the study were based on 'data dredging', was this made clear?	Y	Y
Q17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Y	Y
Q18. Were the statistical tests used to assess the main outcomes appropriate?	Y	Y

Downs and Black checklist criteria	Company's score	ERG score
Q19. Was compliance with the intervention(s) reliable?	Y	Y
Q20. Were the main outcome measures used accurate (valid and reliable)?	Y	Y
Q21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA
Q22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	NA
Q23. Were study subjects randomised to intervention groups?	NA	NA
Q24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA
Q25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N	N
Q26. Were losses of patients to follow-up taken into account?	Y	Y
Q27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Y	Y

ERG=Evidence Review Group; NA=not applicable; N=No; P=partial; UTD=unable to determine; Y=Yes
¶Confounders not explicitly defined. Patient characteristics are clearly presented
Source: CS, adapted from Table 11 and Downs and Black[52]

9.1.4 Efficacy results in the DS8201-A-J101 study

Table 32 Results from the supportive DS8201-A-J101 study

Population and outcome		5.4 mg/kg or 6.4 mg/kg dose	5.4 mg/kg dose
Modified ITT population[a]		N=115	N=49
Treatment duration (months), median (range)		8.3 (4.4 to 12.0)	7.7 (NR)[b]
Follow-up (months), median (range)		9.9 (6.9 to 14.3)	8.9 (NR)[c]
Confirmed objective response, n (% [95% CI])		66 (57.4 [47.8 to 66.6])	26 (53.1 [38.3 to 67.5])
Confirmed disease control[d], n (% [95% CI])		105 (91.3 [84.6 to 95.8])	43 (87.8 [75.2 to 95.4])
Efficacy evaluable population[e]		N=114	N=48
PFS (months), median (range [95% CI])		22.1 (0.8** to 27.9** [NE])	22.1 (0.8** to 22.4** [NE])
Evaluable for confirmed response population[f]		N=111	N=46
Confirmed best overall response, n (%)	CR	3 (3)	1 (2)
	PR	63 (57)	25 (54)
	SD	38 (34)	16 (35)
	PD	6 (5)	3 (7)
	Non-evaluable	1 (1)	1 (2)
Confirmed objective response, n (% [95% CI])		66 (59.5 [49.7 to 68.7])	26 (56.5 [41.1 to 71.1])
Confirmed disease control[d], n (% [95% CI])		104 (93.7 [87.4 to 97.4)	42 (91.3 [79.2 to 97.6])
N evaluable for TTR and DoR		N=73[g]	N=30[h]
TTR (months), median (range [95% CI])		1.6 (1.2 to 9.0 [1.4 to 2.8])	1.5 (1.2 to 9.0 [1.4 to 2.8])
DoR (months), median (range [95% CI])		20.7 (0** to 21.8** [NE])	20.7 (0.0** to 20.7 [7.2 to 20.7])

CI=confidence interval; CR=complete response; DoR=duration of response; ITT=intention to treat; NE=not estimable; NR=not reported; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease; T-DXd= trastuzumab deruxtecan; TTR=time to response
** indicates censored observation
[a] All patients who received at least one dose of T-DXd
[b] IQR: 4.1 to 12.0 months
[c] IQR: 5.8 to 16.7 months
[d] Disease control was calculated as the proportion of patients demonstrating CR, PR, or SD for a minimum of 5 weeks from the first dosing date
[e] All patients who received at least one dose of T-DXd, for whom both baseline and posttreatment activity data were available
[f] Evaluable patients for confirmed response had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan
[g] n=73; includes seven cases of unconfirmed response.
[h] n=30; it is not reported why an additional four patients to the 26 who achieved confirmed response are included in this analysis
Source: CS, adapted from Appendix M (Table 3) and Tamura (2019)[47]

Generally, results from the overall population of the DS8201-A-J101 study (who received either the 5.4 mg/kg dose or the 6.4 mg/kg dose) were very similar to those from the subgroup of patients who received the 5.4 mg/kg dose. However, baseline characteristics are not available for the subgroup of patients who received the 5.4 mg/kg dose, so it is difficult to draw conclusions about the impact of dose on treatment efficacy within the DS8201-A-J101 study. For the same reason, it is also difficult to draw conclusions about the comparability of results from patients who received the 5.4 mg/kg dose in the DS8201-A-J101 study and those who received the 5.4 mg/kg dose in the DESTINY-Breast01 study.

The ERG notes that ORR by investigator assessment was lower in the DS8201-A-J101 study (57.4% in patients who received either the 5.4mg/kg or the 6.4 mg/kg dose, and 53.1% in patients who received the 5.4 mg/kg dose) than in the DESTINY-Breast01 study (66.8%). Here the ERG has compared results from the enrolled analysis set of the DESTINY-Breast01 study with results from the modified intention to treat population (rather than the evaluable for confirmed response population) of the DS8201-A-J101 study as these are more comparable populations. Clinical advice to the ERG is that as more patients in the DS8201-A-J101 study had hormone receptor positive (HR+) disease (70.4%) than in the DESTINY-Breast01 study (52.7%), it is not surprising that fewer patients achieved an objective response as HR+ status is associated with worse prognosis for UBC and MBC patients. Clinical advice to the ERG is that the proportion of patients with HR+ seen in clinical practice is likely to be more similar to the proportion observed in the DESTINY-Breast01 study than in the DS8201-A-J101 study.

The ERG also notes that PFS and DoR were even more impressive in the DS8201-A-J101 study than in the DESTINY-Breast01 study. Median PFS was 5.7 months longer in the DS8201-A-J101 study (22.1 months in patients who received either the 5.4 mg/kg or the 6.4 mg/kg dose, and the subgroup of patients who received the 5.4 mg/kg dose) than in the DESTINY-Breast01 study. Median DoR was 5.9 months longer in the DS8201-A-J101 study (20.7 months in both patients who received either the 5.4 mg/kg or the 6.4 mg/kg dose, and the subgroup of patients who received the 5.4 mg/kg dose) than in the DESTINY-Breast01 study.

9.2 Appendix 2 Additional information about the DESTINY-Breast01 study

9.2.1 Quality assessment of the DESTINY-Breast01 study

The company assessed the quality of the DESTINY-Breast01 study using the Downs and Black[52] criteria. The company's assessments and ERG comments are presented in Table 33.

Table 33 Quality assessment of the DESTINY-Breast01 study

Downs and Black checklist criteria	Company's score	ERG score	ERG comment (where the ERG and company scores differ)
Q1. Is the hypothesis/aim/objective of the study clearly described?	Y	Y	
Q2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y	Y	
Q3. Are the characteristics of the patients included in the study clearly described?	Y	Y	
Q4. Are the interventions of interest clearly described?	Y	Y	
Q5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y	P	Patient characteristics are well described, but confounders are not explicitly defined
Q6. Are the main findings of the study clearly described?	Y	Y	
Q7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y	
Q8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y	
Q9. Have the characteristics of patients lost to follow-up been described?	Y	Y	
Q10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Y	NA	P values are not reported in the study publication[46]
Q11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y	
Q12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	Y	
Q13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Y	Y	

Downs and Black checklist criteria	Company's score	ERG score	ERG comment (where the ERG and company scores differ)
Q14. Was an attempt made to blind study subjects to the intervention they have received?	N	N	
Q15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N	
Q16. If any of the results of the study were based on 'data dredging', was this made clear?	N	N	
Q17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	NA	NA	
Q18. Were the statistical tests used to assess the main outcomes appropriate?	Y	Y	
Q19. Was compliance with the intervention(s) reliable?	Y	Y	
Q20. Were the main outcome measures used accurate (valid and reliable)?	Y	Y	
Q21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Y	Y	
Q22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Y	Y	
Q23. Were study subjects randomised to intervention groups?	Y	Y	
Q24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Y	N	Not clear if treatment allocation was concealed until the end of recruitment. Patients in part 2 of the study were not randomised
Q25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Y	NA	Given that the DESTINY-Breast01 study is a single-arm study, there is no need to adjust for confounders and there is no evidence that this was done
Q26. Were losses of patients to follow-up taken into account?	Y	Y	

Downs and Black checklist criteria	Company's score	ERG score	ERG comment (where the ERG and company scores differ)
Q27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?	N	N	

ERG=Evidence Review Group; NA=not applicable; N=No; P=partial; UTD=unable to determine; Y=Yes
Source: CS, adapted from Table 11 and Downs and Black checklist[52]

9.2.2 ERG assessment of statistical approaches used in the DESTINY-Breast01 study

Table 34 ERG assessment of statistical approaches used in the DESTINY-Breast01 study

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The definitions of all study populations analysed in the DESTINY-Breast01 study are provided in the CS (Table 8). The ERG is satisfied that these populations were pre-specified in the SAP (p30)
Was an appropriate sample size calculation pre-specified?	Yes	The DESTINY-Breast01 study sample size calculation was pre-specified in the SAP (p29); the ERG is satisfied that this sample size calculation was appropriate
Were all protocol amendments made prior to analysis?	Yes	Protocol amendments are listed in the CSR (pp64-68). The first DESTINY-Breast01 study data cut-off date was 21 March 2019. All amendments were made prior to the date of the first data cut. These amendments were, therefore, not driven by results from the analyses
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	In the CS, results are presented for the primary efficacy outcome (ORR by ICR) and for the following secondary efficacy outcomes: ORR by investigator assessment, change from baseline in tumour size, PFS, OS, CBR, DCR, and DoR. Results for TRR, the exploratory efficacy outcome, are also presented. Definitions and analysis approaches for these outcomes were pre-specified in the SAP (pp19-23, 34, 37). The ERG is satisfied that the company appropriately defined and analysed all efficacy outcomes presented in the CS
Was the analysis approach for PROs appropriate and pre-specified?	N/A	Data on PROs were not collected in the DESTINY-Breast01 study
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data relating to exposure and treatment-emergent AEs (including treatment-emergent AEs occurring in ≥10% of patients and treatment-emergent AESIs) are presented in the CS (p89-95). Safety analyses were descriptive only, and were pre-specified in the SAP (p37-42)
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the SAP for efficacy outcomes (pp19-23). No specific approach is outlined for safety outcomes; however, the protocol confirms that missing or dropout data would not be imputed for the purpose of data analysis, unless otherwise specified (p82). The ERG is satisfied that the approaches described were appropriate

Item	ERG assessment	Statistical approach with ERG comments
Were all subgroup and sensitivity analyses pre-specified?	Partial	Results from subgroup analyses for ORR, PFS and DoR for several demographic and baseline characteristics are presented in Appendix E to the CS. For ORR and DoR, most demographic and baseline characteristics explored in the subgroup analyses were pre-specified in the SAP (pp35-37). For PFS, no subgroup analyses were pre-specified and so the presented analyses should only be considered exploratory The company referred to a subgroup analysis for ORR by number of lines of prior therapy, in which patients were grouped as follows: 2, 3, 4, 5, 6+ lines of prior therapy. The ERG notes that this subgroup analysis was not pre-specified, and so should only be considered exploratory No sensitivity analyses were pre-specified In the SAP or presented in the CS

AE=adverse event; AESI=adverse event of special interest; CBR=clinical benefit rate; CS=company submission; CSR=clinical study report; DCR=disease control rate; DoR=duration of response; ERG=Evidence Review Group; ICR=independent central review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; SAP=statistical analysis plan; TTR=time to response
Source: CS, CSR, study protocol and SAP

9.3 Appendix 3 Adverse events

9.3.1 Adverse events in the DESTINY-Breast01 and DS8201-A-J101 studies

A summary of the AEs experienced by patients in the DESTINY-Breast01 and DS8201-A-J101 studies are reported in Table 36.

Table 35 Summary of adverse events in the DESTINY-Breast01 study and the DS8201-A-J101 study

	DESTINY-Breast01[46]	DS8201-A-J101[47¶]	DS8201-A-J101[47¶]
Type of AE, n (%)	T-DXd 5.4 mg/kg	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg
	(N=184)	(N=49)	(N=66)
AEs	99.5%	100%	100%
Drug-related AEs	99.5%	98.0%	98.5%
AEs Grade ≥3	57.1%	38.7%	57.6%
Drug-related AEs Grade ≥3	48.4%	-	-
Serious AEs	22.8%	16.3%	21.2%
Drug-related serious AEs	12.5%	8.2%	13.6%
Grade ≥3 serious AEs	-	12.2%	18.2%
AEs leading to drug discontinuation	15.2%	4.1%	16.7%
Drug-related AEs leading to drug discontinuation	14.7%	4.1%	16.7%
AEs leading to dose modification	-	-	-
Drug-related AEs leading to dose modification	-	-	-
AEs leading to dose reduction	23.4%	8.2%	25.8%
Drug-related AEs leading to dose reduction	21.7%	6.1%	22.7%
AEs leading to dose interruption	35.3%	28.6%	30.3%
Drug-related AEs leading to dose interruption	28.8%	18.3%	24.2%
AEs leading to dose delay	-	-	-
Drug-related AEs leading to dose delay	-	-	-
AEs leading to death	4.9%	3/115 (2.6%) deaths due to AEs: progressive disease: 1 drug-related pneumonitis: 2	

Source: CS Tables 61 and 65

The types of AEs experienced by patients in the DESTINY-Breast01 and DS8201-A-J101 studies are summarised in Table 36.

Decreased neutrophil count was the only common Grade ≥3 AE that was reported in ≥10% of patients in both the DESTINY-Breast01 study and the patients in the DS8201-A-J101 study who received the 5.4mg/kg dose at 19.6% and 11% of patients respectively. Anaemia of Grade

≥3 severity was also reported for ≥10% of patients for the DS8201-A-J101 study (16%), but not the DESTINY-Breast01 study (8.2%).

Table 36 Types of adverse events experienced by ≥10% of patients in the DESTINY-Breast01 study and the DS8201-A-J101 study

Adverse event type, n (%)	DESTINY-Breast01[46] study T-DXd 5.4 mg/kg			DS8201-A-J101[47] study T-DXd 5.4 mg/kg and 6.4 mg/kg			
	Any grade N=183 (99.5)	Grade 3 N=89 (48.4)	Grade 4 N=7 (3.8)	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Haematological							
Neutrophil count decreased	64 (34.8)	36 (19.6)	2 (1.1)	16 (14)	13 (11)	3 (3)	0
Anaemia	55 (29.9)	15 (8.2)	1 (0.5)	26 (23)	18 (16)	1 (1)	0
Platelet count decreased	39 (21.2)	7 (3.8)	1 (0.5)	23 (20)	7 (6)	2 (2)	0
White blood cell count decreased	39 (21.2)	11 (6.0)	1 (0.5)	15 (13)	8 (7)	2 (2)	0
Lymphocyte count decreased	26 (14.1)	11 (6.0)	1 (0.5)	-	-	-	-
Gastrointestinal							
Nausea	143 (77.7)	14 (7.6)	0	87 (76)	4 (3)	0	0
Vomiting	84 (45.7)	8 (4.3)	0	55 (48)	5 (4)	0	0
Constipation	66 (35.9)	1 (0.5)	0	41 (36)	1 (1)	0	0
Diarrhoea	54 (29.3)	5 (2.7)	0	41 (36)	2 (2)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0	13 (11)	0	0	0
Stomatitis	27 (14.7)	2 (1.1)	0	24 (21)	0	0	0
Dyspepsia	26 (14.1)	0	0	14 (12)	0	0	0
Other							
Fatigue	91 (49.5)	11 (6.0)	0	46 (40)	5 (4)	0	0
Alopecia	89 (48.4)	1 (0.5)	0	54 (47)	0	0	0
Decreased appetite	57 (31.0)	3 (1.6)	0	62 (54)	2 (2)	0	0
Headache	36 (19.6)	0	0	12 (10)	1 (1)	0	0
Cough	35 (19.0)	0	0	22 (19)	0	0	0
Dyspnoea	27 (14.7)	3 (1.6)	0	-	-	-	-
Aspartate aminotransferase increased	26 (14.1)	2 (1.1)	0	-	-	-	-
Asthenia	26 (14.1)	2 (1.1)	0	-	-	-	-
Interstitial lung disease	25 (13.6)	1 (0.5)	0	-	-	-	-
Epistaxis	24 (13.0)	0	0	12 (10)	0	0	0

Adverse event type, n (%)	DESTINY-Breast01[46] study T-DXd 5.4 mg/kg			DS8201-A-J101[47] study T-DXd 5.4 mg/kg and 6.4 mg/kg			
	Any grade N=183 (99.5)	Grade 3 N=89 (48.4)	Grade 4 N=7 (3.8)	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Hypokalaemia	21 (11.4)	6 (3.3)	0	16 (14)	3 (3)	0	0
Dry eye	21 (11.4)	0	1 (0.5)	-	-	-	-
Upper respiratory tract infection	20 (10.9)	0	0	12 (10)	0	0	0
Pyrexia	-	-	-	24 (21)	2 (2)	0	0
Malaise	-	-	-	24 (21)	0	0	0
Dysgeusia	-	-	-	17 (15)	0	0	0
Rash	-	-	-	15 (13)	0	0	0
Oedema peripheral	-	-	-	14 (12)	0	0	0
Hypoalbuminaemia	-	-	-	12 (10)	1 (1)	0	0
Weight decreased	-	-	-	12 (10)	1 (1)	0	0
Nasopharyngitis	-	-	-	12 (10)	0	0	0
Hyponatraemia	-	-	-	7 (6)	3 (3)	0	0

'-'=not reported; T-DXd=trastuzumab deruxtecan
Source: CS, adapted from Table 62 and Appendix F
Note: Data for DS8201-A-J101[47] not presented for each dose

9.3.2 Adverse events reported in studies of comparator treatments

A descriptive summary of AEs reported in the studies considered for inclusion in its MAICs is presented in Table 37. There have been no notable differences in terms of treatment emergent or drug-related any Grade AEs, Grade ≥3 AEs, serious AEs, AEs leading to drug discontinuation, AEs leading to dose modification, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to dose delay or AEs leading to death.

In terms of specific types of AEs, Grade ≥3 AEs which have been found to be reported as the "most common"[40] and/or occurring in >5% patients in studies of comparator treatments[39,41-45] were:

- eribulin:
    - neutropenia 12.2%,[40] 14.3%,[43] 45.1%[42] and 54.0%[41]
    - febrile neutropenia 5.5%[41]
    - leukopenia 13.9%[42] and 14.0%[41]
    - fatigue/asthenia 7.4%,[40] 8.7%[42] and 10.0%[41]
    - neuropathy/peripheral neuropathy 6.9%[41]/8.2%[42]
- capecitabine:
    - hand-foot syndrome 7.6%,[56] 20.6%[45] and 21.6%[44]
    - neutropenia 14.3%[45]
    - diarrhoea 9.0%,[56] 10.0%[45] and 18.9%[44]
    - stomatitis 12.2%[44]
    - nausea 9.5%[44]
    - fatigue 8.1%[44]
    - dehydration 6.8[44]
- vinorelbine:
    - neutropenia 65.2%[39]
    - febrile neutropenia 5.4%[39]
    - abdominal pain 12.2%%[39]

Table 37 Descriptive summary of the AEs reported in the studies considered for inclusion in the company's MAIC analysis

	Eribulin		Capecitabine		Vinorelbine
Adverse event	**EMBRACE trial (N=503)[42]****	**Barni (2019) (N=574)[40] Cortes (2010) (N=291)[41] Gamucci (2019) (N+133)[43]**	**EMBRACE trial (N=44)[42]****	**Fumoleau (2004) (N=126)[45] Blum 2001 (N=74)[44] Venturini (2007) (N=631)[56]**	**EMBRACE trial (N=61)[42]****
AEs, any Grade	98.8%	-	93.2%	83.7%[56]	93.4%
Drug-related AEs, , any Grade	94.2%	-	79.5%	74.2%-89.2%[44,56]	80.3%
AEs Grade ≥3	90.7%	-	34.1%	-	85.2%
Drug-related AEs Grade ≥3	-	-	-	~25% ***	-
Serious AEs	25.0%	-	29.5%	-	26.2%
Drug-related serious AEs	11.7%	-	9.1%	-	8.2%
Grade ≥3 serious AEs	-	-	-	-	-
AEs leading to drug discontinuation	13.3%	4.5%-8.2%[41,43]	11.4%	-	11.5%
Drug-related AEs leading to drug discontinuation	-	-	-	21.2%[56]	-
AEs leading to dose modification	-	-	-	-	-
Drug-related AEs leading to dose modification	-	-	-	27.3%[56]	-
AEs leading to dose reduction	16.9%	19.3%[40]	18.2%	-	19.7%
Drug-related AEs leading to dose reduction	-	-	-	-	-
AEs leading to dose interruption	5.0%	-	22.7%	-	11.5%
Drug-related AEs leading to dose interruption	-	-	-	-	-
AEs leading to dose delay	35.2%	-	22.7%	-	44.3%
Drug-related AEs leading to dose delay	-	-	-	-	-
AEs leading to death	4.0%	-	9.1%	-	4.9%
Drug-related AEs leading to death	-	0[41]*	-	0-13.0%[44,45,56]	-

AE=adverse event
Source: Cortes (2011),[42] Barni (2019),[40] Cortes (2010),[41] Gamucci (2019),[43] Fumoleau (2004),[45] Blum (2001),[44] Venturini (2007)[56]
*No deaths during study treatment were considered probably related to study treatment, and only one death (cause unknown) was considered possibly related to study treatment
** Data taken from company submission for ID964 [TA423] (Table 33)[21]
*** approximately 25% of all treatment-related adverse events classified as Grade 3 (23%) or Grade 4 (2%).

9.4 Appendix 4 Additional MAIC information and results

9.4.1 Quality assessment of the included studies in the MAIC analysis: RCTs

Two[39,42] of the comparator studies included in the MAIC analysis were randomised trials. The company assessed the quality of these trials using the NICE quality assessment tool,[48] which is based on the University of York Centre for Reviews and Dissemination guidance.[61] The company's and ERG assessment of the quality of these trials is presented in Table 38.

Table 38 Quality assessment of RCTs included in the MAIC analysis

Questions	EMBRACE trial[42]		KCSG BR11-16 trial[39]	
	Company	ERG	Company	ERG
Was randomisation carried out appropriately?	Yes, randomisation was carried out using an interactive voice recognition system and was stratified geographical region, prior capecitabine treatment, and human epidermal growth factor receptor 2	Agreed	Yes. The patients were randomised to either arm receiving a combination of lapatinib plus vinorelbine (LV) or vinorelbine alone (V) by computer-generated allocation. Randomisation was stratified according to previous response to lapatinib (CR + PR vs SD) and the presence of visceral metastasis	Agreed
Was the concealment of treatment allocation adequate?	Yes, randomisation was carried out using an interactive voice recognition system	Agreed	No, method of concealment was not reported	Agreed
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, Baseline demographic characteristics were well balanced across treatment groups	Agreed	Yes, the baseline characteristics were well balanced between the groups	Agreed
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, the study is open label. Patients and investigators were not masked to treatment allocation	Agreed	No. This was open level trial	Agreed
Were there any unexpected imbalances in drop-outs between groups?	No, there was no unexpected imbalances in drop-outs between groups were reported.	Agreed	No, there was no unexpected imbalances in drop-outs between groups were reported	Agreed

Questions	EMBRACE trial[42]		KCSG BR11-16 trial[39]	
	Company	ERG	Company	ERG
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, there is no evidence to suggest that the authors measured more outcomes than they reported	Agreed	No, there is no evidence to suggest that the authors measured more outcomes than they reported	Agreed
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, primary outcome was ITT for efficacy but rest of the outcomes and safety outcomes were for mITT. No method was used for handling of missing data.	Agreed	Yes, the analysis include an intention-to-treat analysis. To account for missing appropriate methods used	Agreed, but no mention of methods for handling missing data

CR=complete response; ERG=Evidence Review Group; ITT=intention to treat; mITT=modified intention to treat; PR=partial response; SD=stable disease
Source: CS, adapted from Appendix D, Table 13

Quality assessment of the included studies in the MAIC analysis: Single-arm studies

Five[40,41,43-45] of the comparator studies included in the MAIC analysis were single-arm studies. The company performed a quality assessment of these studies using the Downs and Black checklist.[52] The company's assessment of the quality of these studies along with ERG comments is presented in Table 39.

Table 39 Quality assessment of comparator studies

Questions	Cortes (2010)[41]		Fumoleau (2004)[45]		Blum 2001[44]		Gamucci 2014[43]		Barni (2019)[40]	
	Company	ERG	Company	ERG	Company	ERG	Company	ERG	Company	ERG
Q1. Is the hypothesis/aim/objective of the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q3. Are the characteristics of the patients included in the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q4. Are the interventions of interest clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y	N	Y	N	Y	N	N	N	Y	N
Q6. Are the main findings of the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y, IQRs and CI's reported
Q8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q9. Have the characteristics of patients lost to follow-up been described?	Y	Y	N	N	Y	N, not clear if patients lost to follow up	N	N	Y	Y

Questions	Cortes (2010)[41]		Fumoleau (2004)[45]		Blum 2001[44]		Gamucci 2014[43]		Barni (2019)[40]	
	Company	ERG	Company	ERG	Company	ERG	Company	ERG	Company	ERG
Q10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N	N	N	Y, actual value reported	Y	Y	Y	Y	Y	Y
Q11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q14. Was an attempt made to blind study subjects to the intervention they have received?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q15. Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q16. If any of the results of the study were based on 'data dredging', was this made clear?	N	N	N	N	N	N	Y	Y	N	N

Questions	Cortes (2010)[41]		Fumoleau (2004)[45]		Blum 2001[44]		Gamucci 2014[43]		Barni (2019)[40]	
	Company	ERG	Company	ERG	Company	ERG	Company	ERG	Company	ERG
Q17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	N	NA	Y	NA	Y	NA	Y	NA	Y	NA
Q18. Were the statistical tests used to assess the main outcomes appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q19. Was compliance with the intervention(s) reliable?	N	N	N	UTD	N	UTD	Y	Y	Y	Y
Q20. Were the main outcome measures used accurate (valid and reliable)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA
Q22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q23. Were study subjects randomised to intervention groups?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Questions	Cortes (2010)[41]		Fumoleau (2004)[45]		Blum 2001[44]		Gamucci 2014[43]		Barni (2019)[40]	
	Company	ERG	Company	ERG	Company	ERG	Company	ERG	Company	ERG
Q24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N	N	N	N	N	N	N	N	Y	N
Q26. Were losses of patients to follow-up taken into account?	Y	NA, no patients lost to follow up	N	N	Y	N, not clear if patients lost to follow up	UTD	UTD	Y	Y
Q27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Y	Y	N	Y,power calculation performed	Y	N, no power calculation	N	N	N	N

NA=not applicable; N=No; UTD=unable to determine; Y=Yes
Source: adapted from CS (Appendix D, Table 14)

9.4.2 Results from the MAICs for T-DXd versus eribulin and T-DXd versus capecitabine

T-DXd versus eribulin

A summary of the results for T-DXd versus eribulin from four MAICs (one for each comparator study) is provided in Table 40. The table also includes details showing which variables were matched in each MAIC.

Table 40 Summary of MAIC results for T-DXd versus eribulin

	T-DXd unadjusted (DESTINY-Breast01, N=184)	MAIC with Barni (2019)[40]		MAIC with Cortes (2010)[41]		MAIC with EMBRACE[42]		MAIC with Gamucci 2014[43]	
		T-DXd weighted (DESTINY-Breast01, ESS=[redacted])	Eribulin (Barni (2019), N=103[a])	T-DXd weighted (DESTINY-Breast01, ESS=[redacted])	Eribulin (Cortes (2010), N=269)	T-DXd weighted (DESTINY-Breast01, ESS=[redacted])	Eribulin (EMBRACE, N=508)	T-DXd weighted (DESTINY-Breast01, ESS=[redacted])	Eribulin (Gamucci 2014, N=133)
Mean/median age	**56.0**	[redacted]	59.5	[redacted]	56.0	[redacted]	55.0	[redacted]	62.0
ECOG-PS = 0 (%)	**55.4**	[redacted]	40.9	[redacted]	37.2	[redacted]	42.7	-	-
Prior hormone therapy (%)	**48.9**	-	-	-	-	[redacted]	85.0	[redacted]	69.2
Prior line ≥3 (%)	**91.8**	[redacted]	64.6	[redacted]	89.6	[redacted]	87.0	[redacted]	50.4
HR+ (%)	**52.7**	-	-	[redacted]	71.0	[redacted]	64.4	[redacted]	84.0
Visceral disease (%)	**91.8**	[redacted]	59.4	-	-	-	-	[redacted]	80.5
Overall survival									
No. of events	**25**	[redacted]	65	[redacted]	191	[redacted]	274	[redacted]	46
Median, months (95% CI)	**NA (NA to NA)**	[redacted]	10.8 (8.9 to 12.0)	[redacted]	10.4 (9.3 to 11.5)	[redacted]	13.1 (12.1 to 14.6)	[redacted]	NA (11.7 to NA)
Adjusted HR (95% CI)	**-**	[redacted]		[redacted]		[redacted]		[redacted]	
Progression-free survival									
No. of events	**58**	[redacted]	79	[redacted]	224	[redacted]	357	[redacted]	115
Median, months (95% CI)	**16.4 (15.2 to 18.1)[b]**	[redacted]	3.3 (2.7 to 4.0)	[redacted]	2.7 (2.3 to 3.2)	[redacted]	3.7 (3.3 to 3.8)	[redacted]	4.5 (3.8 to 5.2)
Adjusted HR (95% CI)	**-**	[redacted]		[redacted]		Proportional hazards violated		[redacted]	
Response rates: Weighted ORs (95% CI)									
ORR	**-**	[redacted]		[redacted]		[redacted]		[redacted]	
DCR	**-**	[redacted]		[redacted]		[redacted]		[redacted]	
CBR	**-**	-		[redacted]		[redacted]		[redacted]	

CBR=clinical benefit rate; CI=confidence interval; DCR=disease control rate; ECOG-PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; HR=hazard ratio; HR+=hormone receptor positive; MAIC=matching-adjusted indirect comparison; NA=not applicable; OR=odds ratio; ORR=objective response rate; T-DXd=trastuzumab deruxtecan;
[a] 103 patients with HER2+ disease were included in this study: 95 patients with HER2+ disease had PFS data, 100 patients with HER2+ disease had OS data
[b] The 95% CI for median PFS differs to that reported in Table 7 as the company calculated 95% CIs for median survival using a linear method in the MAICs (as opposed to the log-log method used in the original analyses of DESTINY-Breast01 study data)
Source: CS, Tables 18 to 41

[redacted] The ERG has not presented the adjusted PFS HR from the EMBRACE trial[42] MAIC. On examination of the Schoenfeld test and residual plot (CS, Appendix D, Figure 26), the company concluded that the PH assumption was violated for this analysis (CS, pp64-65); the ERG agrees with this assessment.

It was not possible for the company to adjust for all six matching factors for any of the eribulin MAICs; it is therefore possible that important differences in patient characteristics between studies have not been adjusted for in all the MAICs. The ERG highlights that the ESSs for the DESTINY-Breast01 T-DXd data are particularly small for the Barni (2019)[40] and Gamucci (2014)[43] MAICs (ESS=[redacted] and ESS=[redacted], respectively). These analyses are therefore based on small numbers of events (particularly for OS), introducing further uncertainty to the results from these MAICs

T-DXd versus capecitabine

A summary of the results for T-DXd versus capecitabine from two MAICs (one for each comparator study[44,45]) is provided in Table 41. The table also includes details showing which variables were matched in each MAIC.

Table 41 Summary of MAIC results for T-DXd versus capecitabine

	T-DXd unadjusted (DESTINY-Breast01, N=184)	MAIC with Blum 2001[44]		MAIC with Fumoleau (2004)[45]	
		T-DXd weighted (DESTINY-Breast01, ESS=[redacted]	Capecitabine (Blum (2001), N=74)	T-DXd weighted (DESTINY-Breast01, ESS=[redacted]	Capecitabine (Fumoleau (2004), N=126)
Mean/median age	**56.0**	[redacted]	52.5	[redacted]	54.0
ECOG-PS = 0 (%)	**55.4**	-	-	[redacted]	43.7
Prior hormone therapy (%)	**48.9**	[redacted]	70.2	-	-
Prior line ≥3 (%)	**91.8**	[redacted]	66.2	[redacted]	45.2
HR+ (%)	**52.7**	-	-	-	-
Visceral disease (%)	**91.8**	[redacted]	79.7	-	-
Overall survival					
No. of events	**25**	[redacted]	48	[redacted]	81
Median, months (95% CI)	**NA (NA to NA)**	[redacted]	12.2 (7.7 to 15.2)	[redacted]	15.8 (13.4 to 19.6)
Adjusted HR (95% CI)	**-**	[redacted]		[redacted]	
Progression-free survival					
No. of events	**58**	[redacted]	70	[redacted]	110
Median, months (95% CI)	**16.4 (15.2 to 18.1)[a]**	[redacted]	3.2 (2.4 to 4.3)	[redacted]	4.9 (4.0 to 6.5)
Adjusted HR (95% CI)	**-**	[redacted]		[redacted]	
Response rates: Adjusted ORs (95% CI)[b]					
ORR	**-**	[redacted]		[redacted]	
DCR	**-**	[redacted]		[redacted]	

CBR=clinical benefit rate; CI=confidence interval; DCR=disease control rate; ECOG-PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; HR=hazard ratio; HR+=hormone receptor positive; MAIC=matching-adjusted indirect comparison; NA=not applicable; OR=odds ratio; ORR=objective response rate; T-DXd=trastuzumab deruxtecan;
[a] The 95% CI for median PFS differs to that reported in Table 7 as the company calculated 95% CIs for median survival using a linear method in the MAICs (as opposed to the log-log method used in the original analyses of DESTINY-Breast01 study data)
[b] CBR was not reported for the Fumoleau (2004) study[45] or the Blum 2001 study[44] so was not included as an outcome in either MAIC
Source: CS, Tables 42 to 53

[redacted]

The company were only able to adjust for four of the six matching factors for the MAIC with Blum (2001)[44] and for three of the six matching factors for the MAIC with Fumoleau (2004);[45] it is therefore possible that, in both MAICs, adjustments have not been made for important differences in patient characteristics between studies. The ERG also highlights that the ESSs for the T-DXd data from the DESTINY-Breast01 study are small for both MAICs; in particular, analyses for the outcome of OS are based on very few events (eight events for the MAIC with Blum [(2001][44] and 11 events for the MAIC with Fumoleau [2004][45]) introducing further uncertainty to the results from these MAICs.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 **5pm on Thursday 12 November 2020** 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Abbreviations

ABC	Advanced breast cancer
AE	Adverse event
BC	Breast cancer
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CM&D IG	Commercial Medicines and Devices Investment Group
CMU	Commercial Medicines Unit
CS	Company submission
CSR	Clinical study report
DoR	Duration of response
DS	Daiichi Sankyo
DSU	Decision Support unit
EoL	End of life
ERG	Evidence review group
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
EU	European Union
FDA	Food and Drug Administration
HER2	Human epidermal growth factor 2 overexpression
HR	Hazard ratio
HR	Hormone receptor
HR-	Hormone receptor negative
HR+	Hormone receptor positive
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratios
LABC	Locally advanced breast cancer
MAIC	Matching-adjusted indirect comparison
MBC	Metastatic breast cancer
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PFS	Progression free survival
PH	Proportional hazards
RCT	Randomised controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SoC	Standard of care
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment emergent adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UBC	Unresectable breast cancer

Issue 1 Maturity of DESTINY-Breast01 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the absence of mature survival data means that the company cost-effectiveness results are not robust. Locations: • Page 10 • Page 26 paragraph 2 • Page 35, lines 28-30 • Page 49, lines 13-14 • Page 52 line 15 • Page 53, line 18 • Page 57, table 16, third point • Page 74, lines 7-8	Please clarify that further longer-term survival data will be available from the [redacted] data cut for DESTINY-Breast01 at the start of technical engagement for this appraisal. Additionally, the Phase III DESTINY-Breast02 trial (ongoing; NCT03523585; T-DXd versus trastuzumab+capecitabine or lapatinib+capecitabine) is expected to report in [redacted]. This multinational RCT enrols patients with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1.	Further longer-term survival data will be available from the [redacted] data cut for DESTINY-Breast01 (at the start of technical engagement as agreed with NICE) and the DESTINY-Breast02 study (reporting in [redacted]). Uncertainty due to immaturity of survival data is likely to be reduced following availability of this data. Furthermore, as stated in the evidence submission, DS consider T-DXd to be a candidate for the CDF. It is anticipated that evidence from the Phase III DESTINY-Breast02 RCT could further address the clinical uncertainty (i.e. data maturity and comparative efficacy), and that the CDF could provide interim, timely, managed patient access to an innovative and promising treatment in this disease area of very high unmet need.	This is not a factual inaccuracy. The ERG has acknowledged in its original (and updated) report that "The ERG has been informed that updated DESTINY-Breast01 study results will be made available during the technical engagement process" (page 10, Issue 1). The ERG has repeated this statement on page 27 of the updated ERG report. The ERG highlights data from the Phase III DESTINY-Breast02 trial are expected in [redacted] on pages 10 (Issue 2) and page 28 of the original and page 29 of the updated ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that median PFS and DoR are uncertain. • Page 10 • Page 26 paragraph 2 • Page 35, lines 24-26 • Page 53, lines 19-21	Please clarify that additional longer-term [redacted] data will be available from the [redacted] data cut, reducing uncertainty in these outcomes.	Additional [redacted] data will be available from the [redacted] data cut.	This is not a factual inaccuracy. The ERG has acknowledged in its original (and updated) report that "The ERG has been informed that updated DESTINY-Breast01 study results will be made available during the technical engagement process" (page 10, Issue 1). The ERG has repeated this statement on page 27 of the updated ERG report.

Issue 2 Direct effectiveness evidence for the comparison of T-DXd versus relevant comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that: • Page 10: "direct evidence for the comparison of T-DXd versus any of the relevant comparators would be useful". • Page 13: "Long-term OS data for the relevant population are required, preferably from a phase III RCT that includes the intervention and at least one relevant comparator"	Please clarify that trastuzumab+capecitabine (a comparator in the Phase III DESTINY-Breast02 RCT) is used in clinical practice and that there would be the potential to conduct a network meta-analysis to estimate the comparative effectiveness of T-DXd versus capecitabine on the basis of data from DESTINY-Breast02, and other RCTs including a trastuzumab+capecitabine and capecitabine arm, the German Breast Group 26/Breast International Group 03-05 Study[1].	The ERG notes on page 22 that "trastuzumab+chemotherapy is increasingly being considered by clinicians as standard of care". Comparative data between trastuzumab+capecitabine and capecitabine are expected to be available from analysis of the German Breast Group 26/Breast International Group 03-05 Study[1]. T-DXd is being studied within a Global clinical trials programme, and as such collected comparative data will be reflective of Global standard of care. Direct comparative data versus the NICE Final Scope comparators for this appraisal, which are not reflective of those specified in international treatment guidelines[2], will therefore not be available.	This is not a factual inaccuracy. No changes made to the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that “without robust evidence to allow a comparison of the efficacy of T-DXd versus the comparators of interest, more mature T-DXd evidence from any single-arm source is of limited value”. Location: • Page 10	Please clarify that: • Seven matching-adjusted indirect comparisons (MAICs) were conducted versus capecitabine, eribulin and vinorelbine, providing alternative comparisons where possible and making best use of all available data. • MAICs are a standard method as described in NICE DSU TSD 18[3] • Single-arm trial (SAT) data with indirect treatment comparison methods (including unanchored MAICs) are commonly used to support decision-making in NICE HTAs	The current wording implies that a robust comparison of the efficacy of T-DXd versus the comparators cannot be made on the basis of SAT data. Increasingly, recommendations are being given by NICE based on SAT data, particularly for late-stage oncology treatments. Previous examples of oncology TAs that received a positive recommendation based on SAT data include: • TA522 [4] • TA554 [5] • TA571 [6]	This is not a factual inaccuracy. No changes made to the updated report.

Issue 3 Relevance of DESTINY-Breast01 study results to NHS clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG wording for the number of prior therapies may be misleading. Locations: • Page 11 • Page 27	Please change from: "Only [redacted] of patients in the trial had received two prior anti-HER2 treatments" To: "Although all patients had received at least two prior anti-HER2-treatments, [redacted] of patients had received exactly two prior systemic cancer therapies (excluding hormone therapy); the remaining patients received ≥3 prior therapies"	The current wording suggests that [redacted] of patients had received fewer than two lines of prior therapy. The current wording also mislabels 'systemic cancer therapies (excluding hormone therapy)' as 'anti-HER2 treatments'.	This is not a factual inaccuracy. However, the ERG agrees that the wording in its original report could have been clearer and has amended the text in the updated ERG report so that it is similar to the wording suggested by the company.
The ERG wording for the number of prior therapies may be misleading. Location: • Page 27	Please change from: "Patients enrolled in the DESTINY-Breast01 study had received a median of six (range 2 to 27) prior lines of treatment for LABC or MBC, including hormone therapy" To: "Patients enrolled in the DESTINY-Breast01 study had received a median of five (range 2 to 24) prior lines of treatment for LABC or MBC, excluding hormone therapy"	The current phrasing implies that the numbers quoted in this bullet point are directly comparable with the subsequent bullet point (see row above in current table); however, one set of values includes hormone therapy, and the other does not.	The ERG has amended the text in the updated ERG report on pages 11 and 33 (the ERG could not find this statement on page 27 of the original ERG report) so that it is similar to the wording suggested by the company. Please note that the median number of prior lines of treatment for LABC or MBC, excluding hormone therapy, was reported to be six (and not five) in the [redacted] company's response to clarification question A5ii.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that “over half of the patients in the DESTINY-Breast01 study had received treatments that are not currently recommended by NICE”. Location: • Page 11	Please change from: “Over half of the patients in the DESTINY-Breast01 study had received treatments that are not currently recommended by NICE” To: All patients in DESTINY-Breast01 received standard NICE-approved therapies at first and second line.	All patients in DESTINY-Breast01 received standard NICE-approved therapies at first and second line.	This is not a factual inaccuracy. The ERG agrees that the wording in its original report could have been clearer and has amended the text to: “In addition to at least two lines of anti-HER2 therapy that are recommended by NICE, over half of the patients in the DESTINY-Breast01 study had received additional anti-HER2 therapies that are not currently recommended by NICE”
The ERG states that the effect of including a mixture of patients with >2 lines of prior therapy on efficacy, and therefore on cost effectiveness, is not known Location: • Page 11	Please change from: The effect of these issues on efficacy, and therefore on cost effectiveness, is not known. To: The effect of these issues on efficacy, and therefore on cost effectiveness, is not known, however efficacy in the full DESTINY-Breast01 population is likely to be an underestimate of efficacy in individuals with exactly two prior lines of therapy.	Previous publications have demonstrated that prognosis at later lines of cancer therapy is poorer than for earlier lines[7,8]. As noted in the ERG report (Page 35) evidence available from DESTINY-Breast01 demonstrates improved objective response rate in patients with exactly two prior lines of therapy, compared with those with >2 prior lines of therapy.	This is not a factual inaccuracy. The ERG agrees that the wording in its original report could have been clearer and has amended the text to: The effect of these issues on efficacy results for OS and PFS, and therefore on cost effectiveness results, is not known.

Issue 4 Company eribulin and capecitabine MAICs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG considers that the results of the six MAICs versus eribulin and capecitabine are not suitable for decision-making as the populations enrolled in the comparator trials do not wholly match the population described in the final scope. Locations: • Page 11 • Page 48 • Page 50 • Page 52, last sentence • Page 54, penultimate paragraph • Page 75, table 28: "PFS modelled using results from the company MAICs which are unreliable" • Page 79, lines 14-17	Please clarify that: • The inability to adjust for HER2 status for some comparisons likely results in conservative estimates of comparative effectiveness • The comparison against eribulin, the only NICE assessed and recommended treatment in 3L mBC, from the Barni 2019 study is based on a HER2-positive subgroup • Additional data in HER2-positive patients for eribulin and capecitabine is unlikely to become available given that these are not HER2-targeted therapies; the strict requirement to make comparisons within this subgroup would therefore limit the potential for HER2-targeted therapies to become available at third-line, where there remains a very high unmet need.	HER2-positive status is associated with worse prognosis in individuals receiving the same non-targeted therapy[9]. This was confirmed by clinical experts attending the August 2020 advisory board. Comparing outcomes in HER2-positive patients in DESTINY-Breast01 against populations with mixed HER2 status will therefore underestimate the comparative effectiveness of T-DXd. The comparison against the Barni 2019 study (considered in a scenario analysis) was based on a subgroup of 103 HER2-positive patients. Eribulin and capecitabine are not HER2-targeted therapies, and therefore additional data are unlikely to become available in the HER2-positive subgroup. In particular, future trials for HER2-targeted therapies would not include eribulin or capecitabine as comparators given that these	This is not a factual inaccuracy. As stated in the ERG report (page 79 of original report, page 80 of updated report): "Historically, treatment options for patients with HER2+ disease were limited and, as a consequence, the prognosis for these patients was worse than that of patients with HER2- disease. However, with the advent of HER2-targeted therapies, it is unclear whether this is still true." Patients included in the Barni reference cited by the company had HER2+ disease but had not received at least two prior lines of anti-HER2 therapy (i.e. they did not fully match the population of interest to this appraisal) and the only MAIC that included relevant patients in a comparator trial was the MAIC comparing T-DXd with vinorelbine.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		therapies are not optimised for a HER2-positive population. A strict requirement for eribulin and capecitabine data in the HER2-positive population would limit the possibility for HER2-targeted therapies to ever be reimbursed in third-line advanced breast cancer. It should be noted that eribulin was recommended by NICE in the patient population specific to this appraisal based on data not specific to HER2 positive disease from the EMBRACE trial.	

Issue 5 Company vinorelbine MAICs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the only valid MAIC is the comparison of T-DXd with vinorelbine, and that OS in the KCSG BR11-16 trial may be attributable to prior anti-HER2 therapy received. Locations: • Page 44 • Page 50	Please clarify that the use of prior anti-HER2 therapies could explain longer OS observed in KCSG BR11-16 but is not able to explain the substantial difference between median PFS and median OS (12 weeks and 18.9 months, respectively).	The use of prior anti-HER2 therapies could impact outcomes; however, this would be expected to impact both PFS and OS. The views of clinicians attending the August 2020 advisory board are therefore expected to hold; i.e. 12 weeks of PFS leading to 18.9 months of OS is not clinically plausible in the absence of effective post-progression therapies. In addition, within the KCSG BR11-16 trial , the combination treatment arm of lapatinib + vinorelbine was associated with longer PFS but shorter OS than the vinorelbine alone arm, which may also be considered clinically implausible in the absence of differing post-progression therapy use.	This is not a factual inaccuracy. In the original report (page 50) and updated ERG report (page 51) it is stated that clinical advice to the ERG was that subsequent therapy on disease progression may also have driven the high OS rate in the KCSG BR11-16 trial.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that it is not possible to compare median OS between T-DXd and vinorelbine. Locations: • Page 12 • Page 49, line 14 • Page 52 • Page 54 last paragraph	Please clarify that additional longer-term OS data for T-DXd will be available from the [redacted] data cut for DESTINY-Breast01.	Additional longer-term OS data for T-DXd will be available from the [redacted] data cut for DESTINY-Breast01 (to be provided in an addendum at the start of technical engagement).	This is not a factual inaccuracy. Please see response to Issue 1.
The ERG state that there is a 'directional' effect of T-DXd versus vinorelbine for PFS. Location: • Page 49 • Page 54, lines 2-3 • Page 54 last paragraph	Please amend the wording to state that T-DXd was associated with a statistically significant benefit ([redacted]) compared with vinorelbine in the PFS MAIC which was consistent with NICE DSU TSD 18 methodology on unanchored MAICs[3].	T-DXd was associated with a statistically significant benefit ([redacted]) compared with vinorelbine in the PFS MAIC.	This is not a factual inaccuracy. As stated in the ERG report (pages 49, 51, 52 and 54 of the original report and pages 50, 52, 53 and 55 of the updated report), the proportional hazards assumption is violated for PFS and so no conclusions can be drawn about statistical significance based on hazard ratio results.

Issue 6 Company OS modelling of T-DXd

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that the use of a between-trial analysis between T-DXd and T-DM1 is not robust. Locations: • Page 13 • Pages 75-76	Please clarify that no claims of comparative effectiveness are made versus T-DM1, and that the T-DM1 curve is only used to generate a survival curve that passes through the observed data for T-DXd and follows the same 'shape' as for T-DM1.	The hazard ratio for T-DXd versus T-DM1 is used to generate a survival curve that passes through the observed overall survival data for T-DXd, and reflects the shape of the T-DM1 overall survival curve. This hazard ratio is not used to imply improved efficacy for T-DXd compared with T-DM1. Clinical experts at the August 2020 advisory board confirmed that the shape of the T-DXd OS curve is expected to more closely reflect the shape of the T-DM1 curve than that of the model comparators, and that a 'tail' may be expected as observed for T-DM1. The TH3RESA data for T-DM1 was considered the most relevant due to similarities in mechanism of action (as T-DM1 is also a HER2 targeting therapy) and line of therapy.	This is not a factual inaccuracy. No changes made to the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that the proportional hazards assumption does not hold for the comparison between T-DXd and T-DM1. Location: • Pages 76-78	Please clarify that: • Assessment of proportional hazards cannot be made on the basis of visual inspection of Kaplan-Meier curves, as implied by the current text in the ERG report. • According to NICE DSU guidelines, proportional hazards would be considered to hold in this circumstance, on the basis that the log-cumulative hazard plot produces an approximately straight line[10].	The Schoenfeld residuals (Figure 10 in the ERG report) lie relatively close to the y=0 line, implying the slope of scaled residuals on (scaled) time is zero and therefore that there is no violation of the proportional hazards assumption. The log cumulative hazard plot of OS shows two lines that are approximately straight and parallel (Figure 11 in the ERG report).	This is not a factual inaccuracy but a matter of opinion. No changes made to the updated report.
The ERG state that evidence of proportional hazards is only available for a small proportion of the modelling time horizon. Location: • Page 77	Please change from: “even if the evidence pointed conclusively to the assumption holding, the evidence would show that, for the 8 month to 10 month period that reasonably robust data from the DESTINY-Breast01 study are available (around 2% of the remaining 40 year model time horizon), mortality hazards are proportional” To: “even if the evidence pointed conclusively to the assumption holding, the evidence would show that, for the 8 month to 10 month period that reasonably robust data from the DESTINY-Breast01 study are available (around 14-18% of the remaining 4.7 year mean survival time), mortality hazards are proportional”	Although a 40-year time horizon is used, ~90% of patients are modelled to have died in the T-DXd arm by Year 10. Comparing the duration of trial follow-up with the full model time horizon may be misleading, as it implies that the modelled extrapolation beyond 10 years has substantial impact on the ICER.	This is not a factual inaccuracy. No changes made to the updated report.

Issue 7 Company OS modelling of comparator treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that company OS modelling of comparator treatments is not robust. Locations: • Page 8 • Page 13 • Page 78, section "Comparator overall survival and progression-free survival estimates"	Please clarify that although the modelling of OS for comparator treatments represents a naïve comparison, this is expected to result in a conservative estimate of T-DXd comparative effectiveness.	Although it is true that the modelling of comparator OS currently represents a naive comparison, data from the OS MAICs versus the studies used in the model base-case (Cortes 2001 and Fumoleau 2004) suggests that this is a conservative estimate of comparative efficacy. Comparison of the unadjusted HRs for T-DXd vs. comparators and the weighted HRs suggest that the naive comparison is a conservative estimate of T-DXd comparative efficacy (i.e. the relevant hazard ratios improve when adjusting for key prognostic factors): **Eribulin – Cortes 2011 (EMBRACE)** • Unadjusted HR: [redacted] • Weighted HR: [redacted] **Capecitabine – Fumoleau 2004** • Unadjusted HR: [redacted] • Weighted HR: [redacted] Although it was not possible to adjust for HER2 status in the MAICs, separate adjustment is	This is not a factual inaccuracy. No changes made to the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		made for HER2 status in the economic model.	

Issue 8 NICE End of Life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that NICE End of Life criteria may not be met. Locations: • Page 8 • Page 14 • Page 29 • Page 82	Please revise wording to clarify that available evidence supports that comparator life expectancy is expected be less than 24 months, and life extension with T-DXd is expected to be greater than 3 months, although some uncertainty remains. NICE End of Life criteria are therefore expected to be met.	**Comparator life expectancy is expected to be below 24 months** The ERG state that there is uncertainty around the assumption that the comparator life expectancy is less than 24 months as no comparator evidence was identified in patients who have both: • HER2-positive breast cancer • Progressed on second line T-DM1 and are fit enough to receive a third line therapy. The data presented in the comparator studies are based on mixed HER2-status patient groups, with the exception of the Barni 2019 study, which reported median OS of 10.2 months in the HER2-positive subgroup. It is well established in the literature that HER2-positive BC is a more aggressive form of BC. When patients receive non-HER2-targeted therapies, HER2-positive patients have poorer outcomes than HER2-negative patients[9]. For each comparator in the company model, life expectancy is [redacted];	This is not a factual inaccuracy but a matter of opinion. No changes made to the updated report.

		restricting this to HER2-positive patients only would likely reduce the modelled life expectancy further. At the August 2020 advisory board, the company was advised by clinical experts that the OS results in the Sim study (vinorelbine median OS: 18.9 months) were clinically implausible and not reflective of what is seen in NHS practice[11]. Even if results from this paper were used, median OS is still below the 24-month threshold. Furthermore, in the report the ERG writes that "the life expectancy for patients with HER2+ UBC or MBC is <2 years; even with the use of targeted HER2+ treatments ", acknowledging the poor outcomes in this patient population.[12] There are currently no published data to suggest that life expectancy in 3L HER2+ UBC or MBC patients is greater than 24 months. Furthermore, in addition to the Barni 2019 study, more recent studies have provided evidence that life expectancy of HER2+ patients who progress after receipt of TDM-1 as a second-line treatment and are fit enough for a third-line treatment is less than 24 months; please see Table 1.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		Life extension with T-DXd is expected to be greater than 3 months Although DESTINY-Breast01 OS data is relatively immature, the OS Kaplan-Meier estimator at 12 months was approximately 80%. Assuming [redacted] months median OS in the comparators, there would need to be a considerable number of events in the subsequent 4 months in order for the EoL criteria not to be satisfied. Furthermore, in the company model, the median OS in T-DXd patients is [redacted] months, meaning the model would need to be substantially overestimating survival for the EoL criteria not to be satisfied. In all model scenarios presented in the company submission, the EoL criteria is satisfied. It should also be noted that median PFS in DESTINY-Breast01 was 16.4 months – this is longer than modelled OS for all comparators listed in the NICE final scope for this appraisal. Following availability of longer-term OS data from the [redacted] data cut,	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		estimates of life extension will be more certain.	

Issue 9 ERG's preferred assumptions and the resulting ICERs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state that the report "includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs)." Location: • Page 8	Revision of wording to state that no preferred assumptions and the resultant ICERs have been presented in the report.	The ERG has not presented any preferred assumptions and the resultant ICERs. Daiichi Sankyo consider it would be informative if the ERG could provide their preferred assumptions and resultant ICERs based on the available data in order to make the most efficient use of the technical engagement step.	The ERG is not able to provide any preferred assumptions and resultant ICERs and has deleted the following sentence from the updated report on page 8: "It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs)."

Issue 10 DESTINY-Breast01 study: population characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Lack of clarity on differences in adverse events between Asian and Caucasian populations Location: • Page 32, DESTINY-Breast01 study: population characteristics, second paragraph, final sentence	Please add to the following: "However, it was highlighted that the study includes a higher number of Asian patients than typically seen in the NHS. Clinical advice also emphasised that differences have been identified between Asian and Caucasian populations in terms of side-effects and toxicities".[13,14] The additional text: "[redacted]"	In the context of the sentence, DS believe that the ERG should acknowledge that safety data for Asian vs White subjects are available in the [redacted]	This is not a factual inaccuracy. The ERG recognises that the data reported here by the company supports its argument. However, no changes have been made to the updated report.
Lack of clarity on differences in adverse events between Asian and Caucasian populations	Please change from: "However, it was highlighted that the study includes a higher number of Asian patients than typically seen in the	In the context of the sentence, DS believe that the ERG should clarify that in the references that they cited,[13,14] the side-effects were	This is not a factual inaccuracy. No changes made to the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Location: • Page 32, DESTINY-Breast01 study: population characteristics, second paragraph, final sentence	NHS. Clinical advice also emphasised that differences have been identified between Asian and Caucasian populations in terms of side-effects and toxicities.[13,14]" To: "Clinical advice also emphasised that differences have been identified between Asian and Caucasian populations in terms of side-effects and toxicities, although Asian patients generally experienced more toxicities.[13,14]"	typically higher in the Asian population. In particular, Swain et al[13] conclude that: In our study, patients with HER2-positive metastatic breast cancer from Asia experienced more toxicities from treatment with pertuzumab, trastuzumab, and docetaxel than patients from other regions. In addition, in Toi et al[14] they state that the number of patients requiring dose reductions/interruptions was larger in the Asian subset than in the non-Asian subset, in both the everolimus and placebo arms (88.3% vs 84.4% in the everolimus arm and 79.8% vs 68.7% in the placebo arm). The most common cause of dose reduction/interruption was adverse events and this was similar in the everolimus arms of Asian and the non-Asian subset (95.4% vs 95.3%) Adverse events leading to discontinuation in the Asian and non-Asian subsets (Supplemental Table S4) all occurred more frequently in the Asian patients than	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		the non-Asian subsets, except for pneumonitis. Serious adverse events were rare, and were similar across subsets (Supplemental Table S4).	

Issue 11 Objective response rate: ORR by number of prior lines of systemic therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Lack of clarity on published precedent for how efficacy changes with line of therapy Location: • Page 35, Section 3.3.1 Objective response rate, last but one paragraph, final sentence	Please change from: "For both the FDA- and SAP-defined subgroup analyses, results were based on data from small numbers of patients (patients receiving third-line treatment being n=30 and n=17, respectively), and the ERG therefore considers that it is difficult to draw firm conclusions about how the effect of treatment with T-DXd varies by number of prior lines of systemic therapy." To: "… the ERG therefore considers that it is difficult to draw firm conclusions about how the effect of treatment with T-DXd varies by number of prior lines of systemic therapy, however evidence from the literature suggests that there is usually increasing benefit of treatments in patients with fewer lines of prior therapy. Overall, the data conservatively shows that response rates are at the very least consistent across the number of prior treatment lines."	As described by the ERG, patients achieved a confirmed ORR >50% regardless of the number of prior lines of systemic therapy they had received, and that the highest ORR was observed in those who had received only two prior lines. In addition, results of a pre-specified subgroup analysis using the SAP definition are available (CS, Appendix E, Figure 1) for patients receiving third-line treatment versus patients who had received three or more prior lines of therapy. The ORR was higher in the subgroup of patients receiving third-line treatment (76%; 95% CI: 50% to 93%) than in the subgroup of patients who had received ≥3	This is not a factual inaccuracy. No changes made to the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		prior lines of treatment (59%; 95% CI: 51% to 67%). These data are in line with the wealth of evidence showing poorer outcomes through successive lines of therapy in both breast cancers and other cancers[16-22], leading to the general view that the more prior lines a patient has had, the harder they are to effectively treat. Despite that, DS believe that the ERG should acknowledge that the data conservatively shows that outcomes are at the very least consistent across the treatment lines (please also see CS Appendix E showing that DoR and PFS are consistent across subgroups including prior therapies), and therefore it should not be a concern if patients treated in the NHS are unlikely to have received six lines of treatment i.e. they have had fewer prior lines of therapy compared with patients in the DESTINY-Breast01 trial.	

Issue 12 Hormone receptor status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Lack of clarity on outcomes across hormone receptor status Location: • Page 94, Section 9.1.4 Efficacy results in the DS8201-A-J101 study, second paragraph regarding hormone receptor (HR) status	Please add the following to the end of the paragraph: "The ERG notes that ORR by investigator assessment was lower in the DS8201-A-J101 study (57.4% in patients who received either the 5.4mg/kg or the 6.4 mg/kg dose, and 53.1% in patients who received the 5.4 mg/kg dose) than in the DESTINY-Breast01 study (66.8%). Here the ERG has compared results from the enrolled analysis set of the DESTINY-Breast01 study with results from the modified intention to treat population (rather than the evaluable for confirmed response population) of the DS8201-A-J101 study as these are more comparable populations. Clinical advice to the ERG is that as more patients in the DS8201-A-J101 study had hormone receptor positive (HR+) disease (70.4%) than in the DESTINY-Breast01 study (52.7%), it is not surprising that fewer patients achieved an objective response as HR+ status is associated with worse prognosis for UBC and MBC patients. Clinical advice to the ERG is that the proportion of patients with HR+ seen in clinical practice is likely to be more similar to the proportion observed in the DESTINY-Breast01 study than in the DS8201-A-J101 study. However, please note that subgroup data from DESTINY-Breast01 and DS8201-A-J101 have shown consistent outcomes in patients with HR+ and HR- status."	In the context of this paragraph, DS feel it is important to acknowledge that subgroup analysis from the DESTINY-Breast01 study demonstrated consistent outcomes (ORR, PFS and DoR) in HR+ and HR- patients with no significant differences between subgroups: HR+: Response 56 of 97 patients (58%); DoR: 13.8 (9.7-15.0); PFS 15.2 (10.6-NE) HR-: Response 55 of 83 patients (66%); DoR: 14.8 (14.8-NE); PFS 17.6 (12.7-NE) Subgroup analysis in DS8201-A-J101 also demonstrated consistent responses in HR+ and HR- patients, although as noted there were more patients with HR+ disease.	This is not a factual inaccuracy. No changes made to the updated report.

Issue 13 Standard of care

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report does not clarify that there is currently no standard of care for HER2-targeted therapy in people with metastatic HER2-positive breast cancer whose disease has progressed on or after T-DM1. Location: • Page 19, Section 2.2.3 Comparators, final sentence	Please change from: "As highlighted by the company (CS, p22), NICE recommendations for the use of eribulin, capecitabine and vinorelbine are not specific to patients with HER2+ ABC and there is a paucity of evidence for the use of these agents for this specific type of ABC." To: "As highlighted by the company (CS, p22), NICE recommendations for the use of eribulin, capecitabine and vinorelbine are not specific to patients with HER2+ ABC and there is a paucity of evidence for the use of these agents for this specific type of ABC. In addition, the final NICE scope also acknowledges that there is currently no standard of care for HER2-targeted therapy in people with metastatic HER2-positive breast cancer whose disease has progressed on or after trastuzumab emtansine."	For completeness and clarity regarding comparators, DS suggest that the ERG adds that NICE, in the final scope, also acknowledges that there is currently no standard of care for HER2-targeted therapy in people with metastatic HER2-positive breast cancer whose disease has progressed on or after trastuzumab emtansine.	This is not a factual inaccuracy. No changes made to the updated report.

Issue 14 First-line treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The current ESO/ESMO reference does not reflect the latest publication. Location: • Page 20, Section 2.3.3 First-line treatment, second paragraph	Please update the reference cited for the following statement: "Guidelines from the European School of Oncology/European Society of Medical Oncology (ESO/ESMO) state that standard first-line treatment for people with advanced HER2+ breast cancer with no prior anti-HER2 therapy is trastuzumab+pertuzumab+chemotherapy, as it is superior to trastuzumab+chemotherapy in terms of overall survival (OS) for these patients". No changes to the wording are required, as the recommendation is still the same.	Best practice is to use the latest guidelines (ESMO/ESO (ABC5) statements that were published in September 2020[2]).	Thank you for highlighting this. Updated reference included in updated ERG report.

Issue 15 Second-line treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Omittance of key guidelines reference. Location: • Page 21, Section 2.3.4, Second-line treatment, second sentence	In addition to Verma et al (cited reference 32), please also add the reference to the new ESMO/ESO guidelines: It is stated in the ESO/ESMO guidelines[32,2] for ABC that T-DM1 provides superior efficacy relative to other HER2 treatments in the second-line (such as lapatinib+capecitabine). No changes to the wording are required, as the recommendation is still the same.	ESMO/ESO guidelines (ESMO/ESO (ABC5) that were published in September 2020[2]) are key for clinical practice in England.	Thank you for highlighting this. Updated reference included in updated ERG report.
The wording used by the ERG does not fully reflect what was in the advisory board meeting minutes. Location: • Page 21, Section 2.3.4 Second-line treatment, last but one sentence	Change from: The ERG notes that second-line treatment with lapatinib+capecitabine is not recommended by NICE; however, clinical opinion provided at an Advisory Board[23] Meeting held by the company in March 2020 was that [redacted]. To: Clinical opinion provided at an Advisory Board[23] Meeting held by the company in March 2020 was that second-line [redacted]	The proposed wording fully reflects the advisory board meeting minutes.	The ERG agrees that the company's suggested wording is a more accurate summary and has amended the text to include the wording suggested by the company in the updated ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	[redacted] The ERG notes that second-line treatment with lapatinib+capecitabine is not recommended by NICE; however, at the Company's Advisory Board[23] Meeting [redacted];		

Issue 16 Third-line treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ESO/ESMO guidelines for third-line treatment are not reflected. Location: • Page 21, Section 2.3.5 Third-line (or later) treatments	Please add the following: The ESO/ESMO guidelines state that: • In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. There are, however, no data on the use of this combination after progression on pertuzumab or T-DM1. • Trastuzumab deruxtecan (DS-8201) showed important activity in a phase II study in heavily pretreated patients with HER2-positive ABC (median lines of therapy: 6), and is a treatment option in this setting, where approved. • Dual blockade with tucatinib + trastuzumab + capecitabine showed a small benefit in median PFS (2 months) and median OS (4 months) over trastuzumab + capecitabine in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with brain metastases, at the expense of higher toxicity (i.e. diarrhoea). If approved, it can be considered a treatment option in this setting. • The combination of neratinib + capecitabine and margetuximab + chemotherapy are not recommended for routine clinical practice.	For completeness and consistency with the first-line and second-line sections, DS suggest that the ERG add ESO/ESMO guidelines for third-line treatment, using the most recent guidelines[2]	Thank you for highlighting the recommendations in the updated guidelines. The ERG has included these in the updated ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Location: • Page 22, Section 2.3.5 Third-line (or later) treatments, first paragraph after Table 3	Change from: A recent online survey, advertised among UK breast cancer groups, between November 2019 and January 2020, found that, from 52 responding centres in England, trastuzumab was being prescribed as a third-line treatment in 50% of these centres.[24] Clinical advice to the ERG is that trastuzumab+chemotherapy is increasingly being considered by clinicians as standard of care. To: A recent online survey, advertised among UK breast cancer groups, between November 2019 and January 2020, found that, from 52 responding centres in England, trastuzumab was being prescribed as a third-line treatment in 50% of these centres.[24] Clinical advice to the ERG is that trastuzumab+chemotherapy may be increasingly being considered by clinicians as standard of care in some areas in England. However, the survey highlights the lack of a standard of care for third-line treatments across the NHS in England, together with a lack of robust clinical evidence for using trastuzumab beyond progression.	DS believes that the wording used by the ERG does not fully convey the conclusions of the survey. In particular, the survey highlights a wide variation in NHS practice in England in the third-line setting: 50% of the centres do not use trastuzumab beyond progression, but rather prescribe single agent chemotherapy (56.6% of centres), prescribe single agent chemotherapy or refer for a trial (24.5%), refer straight for a trial (5.7%), offer either chemotherapy or endocrine therapy (if patients were oestrogen receptor positive [one centre; 1.9%]), or prescribe lapatinib (one centre; 1.9%). In addition, the authors stated that the evidence for trastuzumab as part of third or subsequent lines of therapy is limited. Overall, this survey highlights the lack of a standard of care and robust clinical evidence for third-line treatments on the NHS in England.	This is not a factual inaccuracy. No changes made to the updated report.

Issue 17 Baseline characteristics of studies included in MAICs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Baseline characteristics reported in the ERG report for the Barni 2019 study reflect a mixture of the full population and the HER2-positive subgroup Location: • Page 46, Table 12	Please amend reporting to reflect either the full population or the HER2-positive subgroup.	The current reporting may be misleading.	Thank you for highlighting this error. The number of patients with HER2+ disease was erroneously reported as the total number of patients in this study. Text in Table 12 amended in the updated report.
Prior chemotherapy lines in DESTINY-Breast01 reported in the ERG report are a mixture of number of lines including or excluding hormone therapy • Page 46, Table 12	Please either amend the proportion of patients with ≥3 prior chemotherapy lines to be [redacted] (i.e. excluding hormone therapy) or amend the proportion of patients with ≥5 prior chemotherapy lines to be [redacted] (i.e. including hormone therapy)	The current reporting may be misleading	Thank you for highlighting this error. Text amended in the updated report.

Issue 18 Regulatory status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Location: • Page 15	Please add: "T-DXd is already approved in the US and in Japan."	For completeness, please add the regulatory status in T-DXd in the US and Japan.	This is not a factual inaccuracy. Box 2 heading amended for clarity.

Issue 19 List and PAS prices for T-DXd

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect statement on T-DXd list price Location: • Page 15	Please change from: "The list price for T-DXd has yet to be finalised" To: "Provisional acceptance of the T-DXd list price was provided by the Department of Health on 25th September 2020, contingent on the marketing authorisation for T-DXd"	The T-DXd list price has been provisionally accepted, contingent on the label.	Thank you for providing this additional information. However, this is not a factual inaccuracy. No changes made to the updated report.
Incorrect statement on T-DXd PAS price Location: • Page 15	Please change from: "The company has made a T-DXd PAS application to the Patient Access Scheme Liaison Unit" To: "The proposed PAS for T-DXd has been approved by NHS England via the Commercial Medicines and Devices Investment Group (CM&D IG)"	The T-DXd PAS has been approved by NHS England via the Commercial Medicines and Devices Investment Group (CM&D IG).	Thank you for providing this additional information. However, this is not a factual inaccuracy. No changes made to the updated report.
Cost-effectiveness results do not reflect the most relevant price for decision-making for T-DXd Location: • Pages 71-72	Please present cost-effectiveness results using the PAS price for T-DXd.	The T-DXd PAS has been approved by NHS England via the Commercial Medicines and Devices Investment Group (CM&D IG).	The cost effectiveness results using all relevant PAS prices have been presented in a confidential appendix.

Issue 20 Time to discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The approach to modelling time to discontinuation is incorrectly reported Location: • Page 62	Please change from: “A scenario is considered in which a hazard ratio is applied to the T-DXd curve such that each curve passes through the observed median TTD in each study” To: “A scenario is considered in which a hazard ratio is applied to the T-DXd curve such that each curve passes through the observed median TTD in each study, with the exception of the Sim 2019 study, which did not present median TTD”	Median TTD data were not available from the Sim 2019 study.	Thank you for highlighting this error. Text amended in the updated report.

Issue 21 Numerical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Numerical error Location: • Page 37, Section 3.4.2	Please change from: "Serious AEs were reported by 22.5% of patients" To: "Serious AEs were reported by 22.8% of patients"	To correct the value for the percentage of patients with SAEs.	Thank you for highlighting this error. Text amended in the updated report.
Numerical error Location: • Page 104, Table 37, Descriptive summary of the AEs reported in the studies considered for inclusion in the company's MAIC analysis, final column (Vinorelbine; EMBRACE trial); row for Serious AEs	Please change from: 23.0% To: 26.2%	DS believe that, according to the reference cited by the ERG, the value should be 26.2%	Thank you for highlighting this error. Text amended in the updated report.

Issue 22 Typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographic error Location: • Page 12: Issue 5 Company vinorelbine OS MAIC results are inconclusive, second row	Please change from: "As PH was violated for both OS and PFS in this MAIC, median survival times rather than HRs were used to compared survival outcomes." To: "As PH was violated for both OS and PFS in this MAIC, median survival times rather than HRs were used to compare survival outcomes."	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.
Typographic error Location: • Page 16: first sentence	Please change from: "Ehurtu" To: "Enhertu"	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.
Typographic error Location: • Page 18: Box 1 Mechanism of action for T-DXd, 3rd bullet point	Please change from: "T-DXd is administered intravenously in a 5.4 mg/kg dose once every 3 weeks (21-day cycle until disease progression or unacceptable toxicity" To: "T-DXd is administered intravenously in a 5.4 mg/kg dose once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity"	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographic error Location: • Page 18: Section 2.2.3 Comparators, first bullet point	Please change from: "Eribulin is an intravenous chemotherapy drug licensed in the European Union (EU) for the for the treatment of adult patients with LABC or MBC who have progressed after at least one chemotherapeutic regimen for ABC" To: "Eribulin is an intravenous chemotherapy drug licensed in the European Union (EU) for the treatment of adult patients with LABC or MBC who have progressed after at least one chemotherapeutic regimen for ABC"	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.
Typographic error Location: • Page 26: Section 2.4.3 Population, first paragraph	Please change from: "issued by NICE [redacted]." To: "issued by NICE [redacted]."	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.
Typographic error Location: • Page 37: Section 3.4.3	Please change from: "The most common AEs were gastrointestinal and hematologic in nature." To: "The most common AEs were gastrointestinal and haematologic in nature."	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographic error Location: • Page 104: Table 37, Descriptive summary of the AEs reported in the studies considered for inclusion in the company's MAIC analysis, table footnotes	Please change from: "** Data taken from company submission for ID964 [TA423] (Table 28)" To: "** Data taken from company submission for ID964 [TA423] (Table 33)"	DS believe that the source of the data is from Table 33 in the CS for ID964 [TA423]	Thank you for highlighting this error. Text amended in the updated report.
Typographic error Location: • Page 38, Section 3.4.4 Timing of adverse event occurrence in the DESTINY-Breast01 study, second sentence	Please change from: "In the first cycle, nausea was the most commonly occurring AE (65.2%), followed by fatigue (29.3%), vomiting (27.2%), decreased appetite (17.9%), constipation (15.8%) and diarrhoea (11.4%)." To: "Of these select TEAEs, in the first cycle, nausea was the most commonly occurring AE (65.2%), followed by fatigue (29.3%), vomiting (27.2%), decreased appetite (17.9%), constipation (15.8%) and diarrhoea (11.4%)."	DS suggest to make this change to resolve any potential ambiguity in the sentence.	This is not a factual inaccuracy. The ERG agrees that the wording in its original report could have been clearer and has amended the text in the updated ERG report so that it reflects the wording suggested by the company.
Typographic error Location: • Page 61, penultimate paragraph	Please change from:" and the other group (Gomertz and Weibull) implied that patients would discontinue treatment by 5 years" To: "and the other group (Gompertz and Weibull) implied that patients would discontinue treatment by 5 years"	Correction of the typographic error will improve the clarity of the report.	Thank you for highlighting this error. Text amended in the updated report.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
None identified	None identified	None identified	No changes required

Table 1: Summary of studies evaluating overall survival in HER2+ patients in the third-line setting in the post-T-DM1 era

Study	Study design	Population	Intervention	Prior therapies	Median OS (95% CI) (months)
Laakmann 2020[25]	PRAEGNANT mBC registry (NCT02338167) in Germany	Patients with HER2+ mBC who have completed a treatment with T-DM1 (N=85)	Treatment following T-DM1 included: Lapatibib /Chemo: 21 (24.7%) Trastuzumab/Chemo: 17 (20.0%) Chemo: 10 (11.8%) Pertuzumab / Trastuzumab /Chemo: 10 (11.8%) Lapatibib / Trastuzumab: 6 (7.1%) Trastuzumab:4 (4.7%)	40% of the patients (n = 34) treated with T-DM1 in the second line and 27.1% (n = 23) treated in the third line. 87.1% patients had been treated with any HER2 treatment before T-DM1	18.4 months (15.5–21.3)
Watanuki 2020[26]	Retrospective observational study in Japan	Patients with HER2+ MBC who had discontinued T-DM1 and received a therapy following T-DM1 (N=30)	First therapy following T-DM1: Eribulin: 10 (33.3%) Trastuzumab + capecitabine: 6 (20%) Doxorubicin + cyclophosphamide: 6 (20%) Lapatinib + capecitabine: 2 (6.7%) Trastuzumab + pertuzumab + taxane: 1 (3.3%) Trastuzumab + vinorelbine: 1 (3.3%) Trastuzumab alone: Trastuzumab + taxane: 1 (3.3%) Trastuzumab + endocrine therapy: 1 (3.3%) Gemcitabine: 1 (3.3%)	All patients had received T-DM1; median number of prior therapies 2 (range 1-7); Prior therapies for MBC before T-DM1 included: Trastuzumab + pertuzumab + taxane: 13 (43.3%) Trastuzumab + taxane: 10 (33.3%) Trastuzumab + capecitabine: 8 (26.7%) Trastuzumab + vinorelbine: 7 (23.3%)	20.6 (13.5 – NR)
Kazmi 2020[27]	A retrospective, observational study using de-identified patient electronic health records January 1, 2012 through October 13, 2018	Patients with MBC with lung or liver metastasis treated with eribulin, gemcitabine, or capecitabine as third-line therapy; N=61 HER2+ patients (9% of total population)	Eribulin as third-line in HER2+ patients (N=21)	Not reported; however T-DM1 was approved in the US in early 2013 and would therefore be expected to be received by the majority of patients as a prior therapy	10.3 (6.0–NR)
			Capecitabine as third-line in HER2+ patients (N=19)		15.4 (7.6–NR)
			Gemcitabine as third-line in HER2+ patients (N=21)		12.8 (7.0–NR)
Murthy 2020[28]	HER2CLIMB Phase III RCT	Patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1 (N=612)	Tucatinib combined with trastuzumab + capecitabine (N=410)	Median prior lines for MBC: 3 (1–14)	21.9 (18.3–31.0)
			Placebo combined with trastuzumab + capecitabine (N=202)	Median prior lines for MBC: 3 (1–13)	17.4 (13.6–19.9)

Abbreviations: Chemo, chemotherapy; CI, confidence interval; CTCA, Cancer Treatment Centers of America; MBC, metastatic breast cancer; NR not reached: OS, overall survival; T-DM1, trastuzumab emtansine

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Technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Thursday 7 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**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

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Please note that on 10th December 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Enhertu® (trastuzumab deruxtecan) for the treatment of metastatic HER2-positive breast cancer (1). The European Commission decision is expected in February 2021.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Immature DESTINY-Breast01 study data	**NO**	The ERG report states that: • The DESTINY-Breast01 study is immature, with median duration of follow-up of 11.1 months • Median overall survival has not been reached • Median progression-free survival and duration of response are uncertain. Company response: • The company submission to NICE was based on the August 2019 data cut from DESTINY-Breast01. • Following submission, data from the June 2020 data cut for DESTINY-Breast01 became available. • These new data have been submitted as an addendum at the start of Technical Engagement following agreement with NICE. • In the June 2020 data cut, preliminary median overall survival (with 35% death events occurring) is reported for the first time and

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<td>more mature estimates of median progression-free survival and duration of response are available (Table 1).

Table 1: Data from August 2019 and June 2020 data cuts
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Median, months (95% confidence interval)</th></tr>
<tr><th>August 2019 data cut</th><th>June 2020 data cut</th></tr>
<tr><td>Duration of follow-up</td><td>11.1
(0.7, 19.9)</td><td>20.5
(0.7, 31.4)</td></tr>
<tr><td>Overall survival</td><td>Median not reached</td><td>24.6
(23.1, not evaluable)</td></tr>
<tr><td>Progression-free survival</td><td>16.4
(12.7, not evaluable)</td><td>19.4
(14.1, not evaluable)</td></tr>
<tr><td>Duration of response</td><td>14.8
(13.8, 16.9)</td><td>20.8
(15.0, not evaluable)</td></tr>
</table>

Daiichi Sankyo consider trastuzumab deruxtecan to be a candidate for use within the Cancer Drugs Fund. If trastuzumab deruxtecan were recommended for use within the Cancer Drugs Fund, reappraisal would be possible using confirmatory, randomised data from DESTINY-Breast02 (the Phase III randomised controlled trial used to support the full marketing authorisation application in this indication; see Appendix A).
Of the last 10 drugs to be recommended for use within the Cancer Drugs Fund (August 2019 to present), 9 out of 10 recommendations were based on trial data in which median overall survival was not reached at the time of the original appraisal (2-10).

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<tr>
<td>Key issue 2: Lack of direct effectiveness evidence for the comparison of T-DXd versus relevant comparators</td>
<td>NO</td>
<td>The ERG report states that:

There is no direct effectiveness evidence for the comparison of T-DXd versus eribulin, capecitabine or vinorelbine.

</td>
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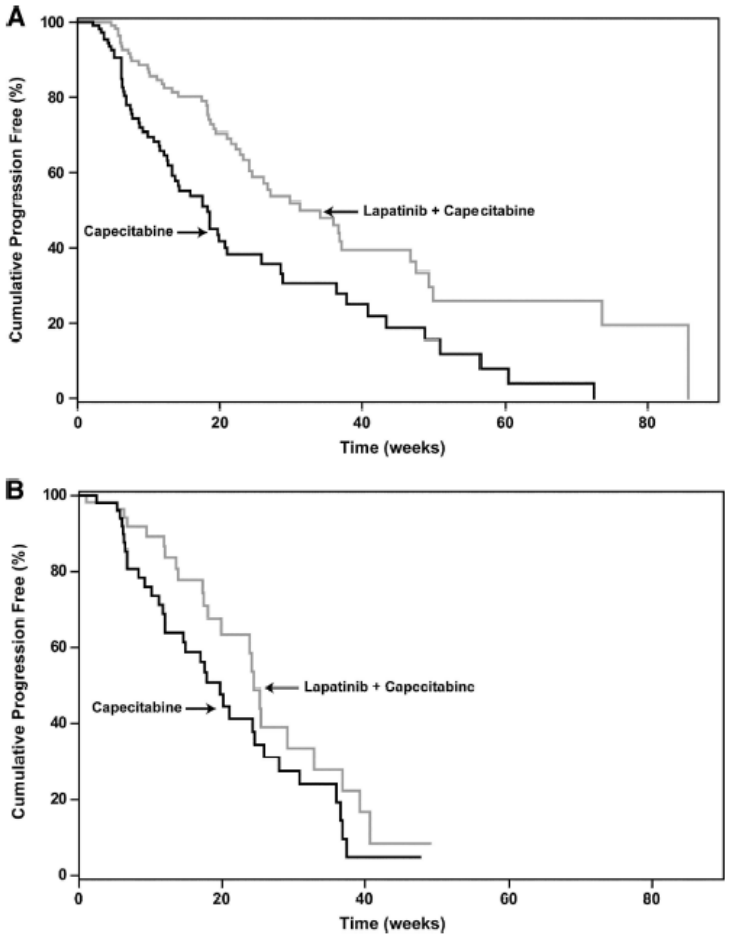
</table>

		Company response:
		• Single-arm trial data are available from the Phase II trial DESTINY-Breast01.
		  ○ The Committee for Medicinal Products for Human Use has adopted a positive opinion on the basis of these data.
		  ○ Trastuzumab deruxtecan has been approved in the US and in Japan, where it was assessed under the US Food and Drug Administration's Breakthrough Therapy and Priority Review programme and Japan's conditional early approval system.
		• A confirmatory, randomised Phase III trial (DESTINY-Breast02) is ongoing and is due to report in 1H 2022.
		• NICE decision-making on the basis of indirect comparison is common (11, 12), and the appropriate methods for this are well-documented by the NICE Decision Support Unit (13).
		  ○ All analyses presented in the company submission were performed in line with NICE Decision Support Unit guidance.
		• Eribulin, capecitabine and vinorelbine are not HER2-targeted therapies, and are therefore not included as monotherapies in the comparator arms of any current global trials for HER2-targeted therapies in third-line metastatic breast cancer such as trastuzumab deruxtecan; there are no NICE -recommended HER2-targeted therapies for third-line metastatic breast cancer.
		  ○ A strict requirement to provide direct effectiveness evidence versus eribulin, capecitabine and vinorelbine would therefore prevent any HER2-targeted therapy from being recommended in this patient population, where there remains a very high unmet need.
		• Of the last 10 drugs to be recommended for use within the Cancer Drugs Fund, 3 were based on Phase I or II single-arm trials (4, 5, 10).
		  ○ One of these used methods suggested by the NICE Decision Support Unit on population-adjusted indirect

		comparisons, with the remainder using naïve comparisons for comparator data. • Daiichi Sankyo consider trastuzumab deruxtecan to be a candidate for use within the Cancer Drugs Fund; in this case, direct effectiveness evidence would be available versus trastuzumab + capecitabine and lapatinib + capecitabine from the DESTINY-Breast02 trial to inform the subsequent reappraisal. ○ The ERG report acknowledges on page 22 that the trastuzumab + capecitabine combination is commonly used in clinical practice in the UK (although not NICE-recommended or funded). ○ Trial data from DESTINY-Breast02 can be used to inform an indirect treatment comparison versus at least one comparator included in the NICE final scope for this appraisal.
Key issue 3: Relevance of DESTINY-Breast01 study results to NHS clinical practice	**YES**	The ERG report states that: • Trastuzumab deruxtecan is expected to be used at third line, but only 9.2% of patients in DESTINY-Breast01 received exactly two prior anti-HER2 treatments and patients in DESTINY-Breast01 received a median of six prior lines of treatment • Over half of the patients in DESTINY-Breast01 had received additional anti-HER2 therapies that are not currently recommended by NICE. Company response: • It is acknowledged that the primary population of interest for the decision problem is those who have received two prior NICE-recommended anti-HER2 therapies. ○ Overall response rate was higher in this subgroup of DESTINY-Breast01 (76%; 95% confidence interval: 50% to 93%) compared with those with greater than two prior therapies (59%; 95% confidence interval: 51% to 67%). ○ Estimates of efficacy for trastuzumab deruxtecan in this population are therefore expected to be conservative.

		○ This is consistent with results presented by Cameron et al (14), in which time to progression at earlier lines of HER2-targeted therapy appears to be longer than at later lines of therapy in a HER2-positive metastatic breast cancer population treated with capecitabine or lapatinib + capecitabine (Figure 1); see Key Issue 4 for further details on the study reported by Cameron et al. • Although trastuzumab deruxtecan is expected to be used primarily at third line, the licensed indication includes third and later lines, and so is expected to be used in a proportion of patients who have received more than three prior therapies. ○ This may be particularly pronounced in the short-term, as trastuzumab deruxtecan will become available to some patients after they have already progressed beyond third line. • There is a substantial unmet need at third line of therapy, and so it is anticipated that trastuzumab deruxtecan will be predominantly used at this line. ○ As noted by Breast Cancer Now: "There are currently no targeted treatments recommended for use after 2 or more prior lines of treatment. This can be incredibly agonising for those who have already progressed beyond these treatment options". **Figure 1: Reproduced from Cameron et al, 2010. Kaplan-Meier estimates of time to progression in patients receiving: one prior**

		metastatic trastuzumab-based regimen (A) or more than one prior metastatic trastuzumab-based regimen (B) 

Key issue 4: Company eribulin and capecitabine MAIC results are not suitable for decision-making	**YES**	The ERG report states that:
		• None of the comparator trials included in the matching-adjusted indirect comparisons for trastuzumab deruxtecan versus eribulin or capecitabine were wholly conducted in the patient population relevant to the appraisal (i.e., patients with HER2-positive disease who had received two or more prior lines of anti-HER2 therapy).
		
		Company response:
		• Please note that neither eribulin nor capecitabine are HER2-targeted therapies; however, eribulin is recommended in the NICE pathway for HER2-positive metastatic breast cancer following appraisal.
		• Following both the original company submission and the subsequent addendum, an additional data source for capecitabine was identified which is relevant to the decision problem.
		  ○ This study was captured in the original systematic literature review, but was listed as a source of data for lapatinib + capecitabine only (i.e. a categorisation error).
		  ○ The remainder of the studies identified in the systematic literature review have been thoroughly reassessed to ensure that no further data sources have been missed.
		• Study EGF100151 is a Phase III, randomised, open-label, multi-centre study comparing lapatinib + capecitabine against capecitabine alone in women with HER2-positive locally advanced or metastatic breast cancer after treatments that included but were not limited to an anthracycline, a taxane, and trastuzumab.
		  ○ The majority of patients had received at least two prior therapies, of which at least one was HER2-targeted (trastuzumab) (see Key Issue 8 and Appendix B for further details).
		  ○ This study is reported by Geyer et al 2006 (15), Cameron et al 2008 (16) and Cameron et al 2010 (14).
		• A matching-adjusted indirect comparison was performed comparing trastuzumab deruxtecan with capecitabine based on data from Study EGF100151.

- There is evidence that the proportional hazards assumption may be violated for overall survival; additional analyses were therefore performed in which accelerated failure time parametric survival models were fitted to the weighted data (see Appendix B for further details).
- Trastuzumab deruxtecan is shown to be associated with significant improvement in overall survival, progression-free survival and response vs capecitabine (Table 2).

- Further details on this matching-adjusted indirect comparison are provided in Appendix B, and the impact of this change on the base-case results is presented in 'Summary of changes to the company's cost-effectiveness estimate(s)'.

Table 2: Results of matching-adjusted indirect comparison for trastuzumab deruxtecan versus capecitabine using Study EGF100151

Outcome	Measure	Result (95% confidence interval)
Overall survival	Hazard ratio	[redacted]
Overall survival	Time ratio	[redacted]
Progression-free survival	Hazard ratio	[redacted]
Overall response rate	Odds ratio	[redacted]
Disease control rate	Odds ratio	[redacted]
Clinical benefit rate	Odds ratio	[redacted]

- A matching-adjusted indirect comparison was presented in the company submission in which trastuzumab deruxtecan is compared against eribulin using data from the HER2-positive subgroup of Barni et al, 2019 (a real-world evidence study) (17).
  - This comparison results in the most favourable hazard ratios for trastuzumab deruxtecan vs eribulin (Table 3).

Table 3: Results of matching-adjusted indirect comparisons versus eribulin

Study	Hazard ratio (95% confidence interval) for trastuzumab deruxtecan versus eribulin	
	Overall survival	Progression-free survival
Cortes 2011	[redacted]	[redacted]
Barni 2019	[redacted]	[redacted]
Cortes 2010	[redacted]	[redacted]
Gamucci 2014	[redacted]	[redacted]

† See Table 3 of the addendum submitted to NICE on Thursday 26th November.

- When receiving the same (non-HER2-targeted) therapy, outcomes in HER2-positive patients have been shown to be worse than those for HER2-negative patients (18, 19).
    - This was confirmed by clinicians attending the August 2020 advisory board.
    - The inability to control for HER2 status in some comparisons is therefore expected to result in conservative efficacy estimates for trastuzumab deruxtecan vs eribulin.
- An adjustment for HER2 status is made to survival data for eribulin in the model using the hazard ratio reported by Lv et al (18).
- Eribulin and capecitabine are not HER2-targeted therapies, therefore future trials for HER2-targeted therapies would not include eribulin or capecitabine monotherapy arms as comparators, given that these therapies are not optimised for a HER2-positive population; additional data are therefore unlikely to become available in the HER2-positive subgroup.
- Given no prior randomised controlled trials have been identified which investigate eribulin in a HER2+ population, a strict requirement for eribulin RCT data in the HER2-positive population

		would limit the possibility for HER2-targeted therapies to ever be reimbursed in third-line metastatic breast cancer.
Key issue 5: Company vinorelbine OS MAIC results are inconclusive	**NO**	The ERG report states that: • The proportional hazards assumption was violated for both overall survival and progression-free survival in this matching-adjusted indirect comparison • Median overall survival has not been reached in DESTINY-Breast01, and so there is no way to meaningfully compare overall survival between trastuzumab deruxtecan and vinorelbine. Company response: • In the addendum submitted to NICE on Thursday 26th November, matching-adjusted indirect comparisons were presented based on the updated data cut; in the analyses vs vinorelbine using Sim 2019, there was evidence that the proportional hazards assumption may be violated for progression-free survival, but not for overall survival. • To explore the impact of the proportional hazards assumption on the progression-free survival comparison vs vinorelbine, additional analyses were performed in which accelerated failure time parametric survival models were fitted to the weighted data. • For all parametric distributions, trastuzumab deruxtecan was shown to be associated with statistically significantly longer progression-free survival compared with vinorelbine; see Appendix C for further details.
Key issue 6: Company OS modelling of T-DXd is not robust	**YES**	The ERG report states that: • The company used a simple between-trial analysis of data from DESTINY-Breast01 and the trastuzumab emtansine arm of the Phase III TH3RESA trial • The ERG does not consider this approach to be robust.

		Company response:
		• The current approach aims to generate a survival curve that passes through the trastuzumab deruxtecan data and is informed by longer-term survival from another antibody drug conjugate, as opposed to a non-HER2 targeted therapy.
		  ○ Clinical experts at the August 2020 advisory board confirmed that the shape of the trastuzumab deruxtecan overall survival curve is expected to more closely reflect the shape of the trastuzumab emtansine curve than that of the model comparators, and that a 'tail' may be expected as observed for trastuzumab emtansine.
		• It should be noted that there is no requirement to make a clinical comparison between trastuzumab deruxtecan and trastuzumab emtansine.
		  ○ Any population differences between the DESTINY-Breast01 and TH3RESA trials would therefore only impact on the validity of the approach if these factors were to substantially impact on the *shape* of the overall survival curve, but not the absolute level.
		• However, in response to this issue, an exploratory scenario analysis has been performed in which overall survival data from the June 2020 data cut of DESTINY-Breast01 are directly extrapolated.
		  ○ Note that, as in the addendum submitted to NICE on Thursday 26th November, only overall survival data up to 20.5 months are used.
		  ○ Overall survival data beyond 20.5 months were not considered to be informative given the substantial censoring observed beyond this time point: 79 patients (86% of those remaining) are censored and only 13 (14%) OS events occur after 20.5 months.
		  ○ [redacted]% of all censored patients in DESTINY-Breast01 were censored due to still being alive at the time of the June 2020 data cut.

		• The directly extrapolated survival curves are presented in Figure 2 and compared against the addendum base-case curve and overall survival curves considered by clinicians at the August 2020 advisory board.
		  ○ The Weibull curve is similar to a curve considered implausibly low by clinical experts, and the exponential curve is similar to a curve considered implausibly high by clinical experts; there are no extrapolated curves between these two distributions.
		  ○ On this basis, an average of the Weibull and exponential curves was assumed to represent the best estimate of long-term survival for trastuzumab deruxtecan. This can be seen in **Error! Reference source not found.** alongside the addendum base-case curve.
		
		Figure 2: Direct extrapolation of trastuzumab deruxtecan overall survival data
		 

		Note: The addendum base case (dated 26/11/20) is the cost-effectiveness model base case that was submitted to NICE as an addendum, using the new June 2020 data cut from DESTINY-Breast01 and modelling overall survival for trastuzumab deruxtecan assuming a hazard ratio vs trastuzumab emtansine. **Figure 3: Direct extrapolation of trastuzumab deruxtecan overall survival data using the average of the Weibull and exponential curves**  • Cost-effectiveness results based on the averaged survival curve are presented in Table 4 and are associated with a small change (+8%) from the updated base-case ICER (see 'Summary of changes to the company's cost-effectiveness estimates').

<table>
<tr>
<td></td>
<td></td>
<td>Table 4: Cost-effectiveness results using direct extrapolation of overall survival for trastuzumab deruxtecan using the average of the Weibull and exponential curves
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Capecitabine</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Vinorelbine</td><td>[redacted]</td><td>[redacted]</td><td>Extendedly dominated</td></tr>
<tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
<tr><td>Trastuzumab deruxtecan</td><td>[redacted]</td><td>[redacted]</td><td>£49,028</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year</td>
</tr>
<tr>
<td>Key issue 7: Company OS modelling of comparator treatments is not robust</td>
<td>NO</td>
<td>The ERG report states that:
The company used unadjusted (except for HER2 status) Kaplan-Meier data from the comparator trials.
The ERG does not consider this approach to be robust.
Company response:
The current approach represents a naïve comparison between trastuzumab deruxtecan and the modelled comparators.
The only alternative approach to this would be to use the results of the matching-adjusted indirect comparisons.
However, clinical experts stated that the shape of the overall survival curve would be different between trastuzumab deruxtecan and non-targeted comparators, and that a ‘tail’ may be expected at the end of the survival curve for trastuzumab deruxtecan as observed for other antibody-drug conjugates.
In the matching-adjusted indirect comparisons, adjustment for baseline characteristics in the comparisons versus the base-case eribulin and capecitabine studies resulted in improved hazard ratios for trastuzumab deruxtecan.</td>
</tr>
</table>

		○ This suggests that the inability to adjust for differences in baseline characteristics results in a conservative estimate of relative efficacy and therefore cost-effectiveness for trastuzumab deruxtecan vs eribulin and capecitabine.
Key issue 8: NICE End of Life criteria may not be met	**NO**	The ERG report states that: • It is unclear whether the life expectancy of HER2-positive patients who progress after receipt of trastuzumab emtansine as a second-line treatment is less than 24 months • The OS gain for patients receiving trastuzumab deruxtecan could exceed 3 months, but this is highly uncertain without more robust comparative OS data. Company response: <u>Comparator survival is less than 24 months</u> • In NICE TA458, the committee agreed that trastuzumab emtansine met the end of life criteria (20) in second-line metastatic breast cancer; in particular, survival with lapatinib + capecitabine was expected to be less than 24 months. ○ Given that eribulin, capecitabine and vinorelbine are used at a later line of therapy, are not HER2-targeted, and are monotherapies, survival is expected to be lower. • In NICE TA423 (21), the committee agreed that end-of-life criteria were met for eribulin in third-line metastatic breast cancer, on the basis of mean modelled overall survival of 13.53 months for treatment of physician's choice and 16.92 months for eribulin. • All available published literature for eribulin, vinorelbine and capecitabine (including in HER2-positive populations following availability of trastuzumab emtansine at second-line; see Appendix D) shows survival of less than 24 months. ○ No evidence has been identified of survival longer than 24 months with eribulin, capecitabine or vinorelbine. • In particular, median overall survival for vinorelbine patients in Sim et al 2019 was 18.9 months (22).

		○ The study by Sim et al includes only HER2-positive patients who have received ≥2 prior anti-HER2 therapies ○ Clinical experts consulted at the August 2020 advisory board stated that overall survival data from Sim et al lacked face validity, with survival in a UK patient population expected to be significantly lower with available therapies; it was suggested that the observed survival may be due to the use of post-progression therapies not available in the UK. ○ 18.9 months may therefore be considered an upper bound for median overall survival in the population of interest. • In HER2CLIMB, patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab and trastuzumab emtansine had median survival of 21.9 and 17.4 months with tucatinib + trastuzumab + capecitabine and trastuzumab + capecitabine treatment, respectively (23). ○ Patients treated with non-HER2-targeted monotherapies, such as capecitabine, in the same indication are expected to experience shorter survival (Figure 1). • In a population with HER2-positive locally advanced or metastatic breast cancer who have progressed after treatments that included but were not limited to an anthracycline, a taxane, and trastuzumab, Cameron et al report median overall survival of 75.0 weeks (17.3 months) and 56.4 weeks (13.0 months) in lapatinib + capecitabine and capecitabine patients, respectively (14). ○ 85% of patients had received ≥3 prior chemotherapy regimens, and it is anticipated that the majority of the remainder would have received at least two prior chemotherapy regimens, given the proportions receiving each prior therapy (○ ○ Table **5**). ○ Almost all patients had received trastuzumab (i.e. a HER2-targeted therapy) previously.

Table 5: Previous therapies received in Cameron et al, 2010 (14)

Previous therapy	Number (%)	
	Lapatinib + capecitabine (N=163)	Capecitabine (N=161)
Anthracyclines	158 (97%)	156 (97%)
Taxanes	159 (98%)	156 (97%)
Fluorouracil	83 (51%)	92 (57%)
Vinorelbine	71 (44%)	70 (43%)
Trastuzumab	157 (96%)	156 (97%)

<u>Life extension with trastuzumab deruxtecan is greater than 3 months</u>

- Preliminary median overall survival reported for trastuzumab deruxtecan from the June 2020 data cut for DESTINY-Breast01 was 24.6 months.
    - Assuming an upper bound for comparator survival of 18.9 months (as described above), the increase in median survival associated with trastuzumab deruxtecan is expected to be greater than 5.7 months.
    - Based on the lower bound of the trastuzumab deruxtecan median overall survival, the increase in overall survival associated with trastuzumab deruxtecan would still be expected to be greater than 3 months compared to the upper bound for comparator survival.
    - Given the 'tail' expected for trastuzumab deruxtecan (see response to Key Issue 7), gains in mean survival are expected to be substantially greater than gains in median survival.
    - The modelled increase in mean survival for trastuzumab deruxtecan is [redacted], [redacted] and [redacted] months compared with eribulin, capecitabine and vinorelbine, respectively.
    - These modelled estimates suggest that trastuzumab deruxtecan increases life expectancy substantially more

		than 3 months versus current standard of care in this setting. • This is supported by median progression-free survival for trastuzumab deruxtecan (19.4 months), which is longer than median overall survival for any of the comparator studies included in the cost-effectiveness model.

Additional technical team issues

Please use the table below to respond to questions raised by the NICE technical team related key issues presented in the ERG report. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>1. Please provide updated analyses with the latest data cut from DESTINY-Breast01</td><td>YES</td><td>Updated analyses using the June 2020 data cut were presented in an addendum submitted to NICE on Thursday 26th November. Updates to clinical data are presented in the response to Key Issue 1. The base-case fully incremental cost-effectiveness ratio based on the updated data cut was £45,216 per quality-adjusted life-year in the submitted addendum; these results are now superseded following the updates described in ‘Summary of changes to the company’s cost-effectiveness estimate(s)’ below. Current base-case results using the latest data cut and incorporating these updates are presented in Table 6. Please note that these results are based on the approach to overall survival taken in the addendum (i.e. applying a hazard ratio to trastuzumab emtansine), and not the direct extrapolation approach discussed in Key Issue 6.

Table 6: Base-case results
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
</table>
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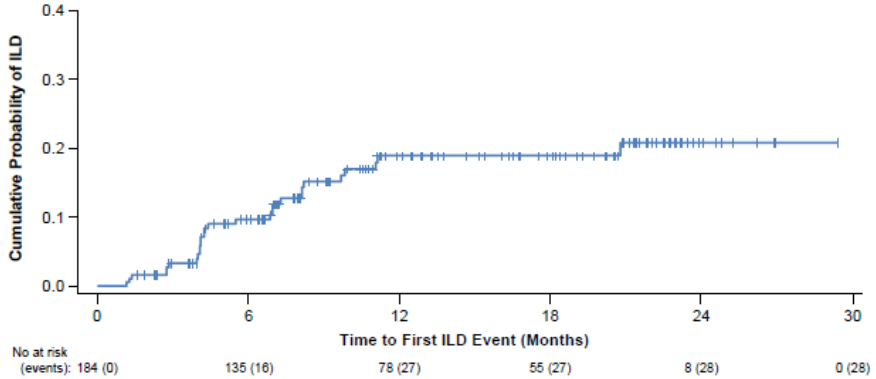
		<table><tr><td>Capecitabine</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Vinorelbine</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Ext. Dominated</td></tr><tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr><tr><td>Trastuzumab deruxtecan</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£47,230</td></tr></table> Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
2. Please explain how these data can lift some of the uncertainties raised by the ERG	**NO**	In the June 2020 data cut, preliminary median overall survival (with 35% death events occurring) is reached and estimates of median progression-free survival and duration of response are more certain (see 'Key issue 1'). Modelled estimates of overall survival and progression-free survival are therefore associated with less uncertainty than those in the original submission. Daiichi Sankyo consider the new June 2020 data cut from DESTINY Breast01 and additional relevant analyses presented within this Technical Engagement response provides further useful information for the ERG to develop a preferred base case ICER ahead of the Appraisal Committee meeting.
3. Would additional data collection in the Cancer Drugs Fund, alongside the ongoing RCT Destiny-Breast 02 reduce the uncertainty?	**NO**	The primary source of additional data will be the confirmatory, randomised Phase III trial, DESTINY-Breast02. Data collected from the Systemic Anti-Cancer Therapy data set during managed access is expected to be supportive only.

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: interstitial lung disease	Section 3.4.8, page 40	YES	The ERG report states that: • "clinical advice to the ERG is that T-DXd appears to have a manageable toxicity profile, however also highlighted that four deaths from ILD may indicate that ILD is an AE of concern". Company response: • Since the August 2019 data cut, 3 new cases of trastuzumab deruxtecan–related interstitial lung disease as determined by an independent adjudication committee were reported (24); however, trastuzumab deruxtecan showed a generally tolerable safety profile, consistent with previous results. • In the June 2020 data cut, the rate of discontinuation or interstitial lung disease did not notably increase compared with the August 2019 data cut. • Most first interstitial lung disease events occurred during the first 12 months of treatment; among the patients who did not have an interstitial lung disease event for ≥12 months, only 1 subsequently developed interstitial lung disease; 2 cases were pending adjudication at data cutoff. • The risk of adjudicated drug-related interstitial lung disease appears lower after approximately 12 months on treatment, suggesting that the risk of developing interstitial lung disease is not related to a cumulative dose of trastuzumab deruxtecan; continued attention to pulmonary symptoms and careful monitoring is warranted.

Figure 4: Cumulative probability of adjudicated drug-related any-grade interstitial lung disease



- Dose modifications relating to interstitial lung disease (25) are presented in Table 7.

Table 7: Dose modifications for interstitial lung disease

Severity	Treatment modification
Asymptomatic (Grade 1)	Interrupt trastuzumab deruxtecan until resolved to Grade 0, then: • If resolved in 28 days or less from date of onset, maintain dose. • If resolved in greater than 28 days from date of onset, reduce dose one level. • Consider corticosteroid treatment as soon as interstitial lung disease is suspected.

			Symptomatic (Grade 2 or greater)	• Permanently discontinue trastuzumab deruxtecan. • Promptly initiate corticosteroid treatment as soon as interstitial lung disease is suspected.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

The base-case fully incremental ICER in the addendum submitted to NICE on Thursday 26th November was £45,216 per quality-adjusted life-year. Following submission of the addendum, it was identified that discontinuation analyses for trastuzumab deruxtecan assumed (in error) that death is a censoring event rather than a discontinuation event; this error has now been corrected, and the resulting ICER is [redacted]. This result is referred to as the 'corrected base-case'.

Please note that the updated base-case models overall survival for trastuzumab deruxtecan by applying a hazard ratio to trastuzumab emtansine (as in the original submission and addendum); however, the results in which overall survival data for trastuzumab deruxtecan are extrapolated directly are shown to be highly consistent with the current approach (see Key Issue 6).

Key issue(s) in the ERG report 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 ICER
Key Issue 4: Company eribulin and capecitabine MAIC	In the original company submission and subsequent addendum, the capecitabine arm of the cost-effectiveness model	An additional study has subsequently been identified (Study EGF100151; see Key Issue 4) including data for	Fully incremental ICER: £47,230

results are not suitable for decision-making	used data from Fumoleau et al, 2004 (26). This study included both HER2-positive and HER2-negative patients.	capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer who have received an anthracycline, a taxane, and trastuzumab. The population of this study is expected to be closer to the population of DESTINY-Breast01 than previously identified capecitabine studies. The following updates have been made to the model: • The hazard ratio for progression-free survival and the odds ratio for overall response rate have been updated to reflect the matching-adjusted indirect comparison versus Study EGF100151. • Parametric survival curves have been fitted to the digitized Kaplan-Meier curve for overall survival from Study EGF100151. • The Weibull curve has been selected for overall survival for capecitabine based on Akaike information criterion and Bayesian information criterion. • The proportion of patients with HER2-positive disease set to 100%.	Change vs. corrected base-case: +9%
Company's preferred base case following technical engagement	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Fully incremental ICER: £47,230

	Please note that eribulin is dominated and vinorelbine is extendedly dominated in the fully incremental analysis.	Please note that eribulin is dominated and vinorelbine is extendedly dominated in the fully incremental analysis.	Change vs. corrected base-case: +9% Full model results are provided in Appendix E.

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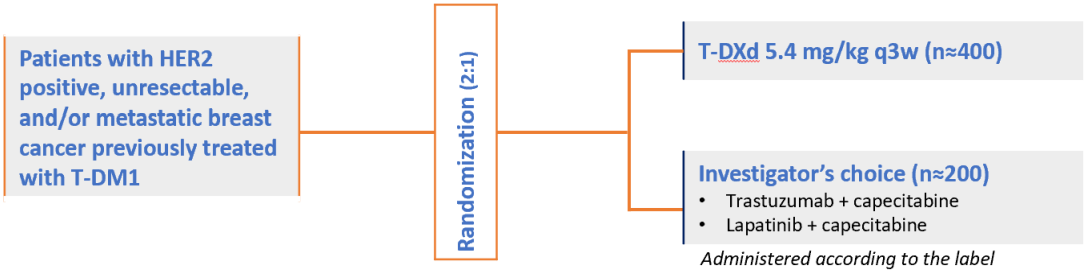
Appendix A: DESTINY-Breast02 study design

The trial design for DESTINY-Breast02 is presented in Figure 5.

Figure 5: DESTINY-Breast02 trial design



Abbreviations: HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; q3w, every 3 weeks
Source: DESTINY-Breast 02 study protocol.(27)

Appendix B: Matching-adjusted indirect comparison versus Study EGF100151

To compare trastuzumab deruxtecan with capecitabine, weights were estimated relative to the Study EGF100151 population baseline characteristics. Table 8 presents the DESTINY-Breast01 (unadjusted and weighted) and Study EGF100151 baseline characteristics for the five matching variables. Matching was based on mean age, Eastern Cooperative Oncology Group performance status, prior treatment lines (<3/≥3), percentage hormone receptor positive, and percent visceral disease. The effective sample size after matching was [redacted]. This is a moderate effective sample size compared with the original sample size of 184. Patients from the DESTINY-Breast01 trial had higher mean age, slightly lower proportion of Eastern Cooperative Oncology Group performance status of zero, a higher number of prior lines, higher percentage with hormone receptor positive status, and higher percent with visceral disease, compared with Study EGF100151. The histogram of rescaled weights is presented in

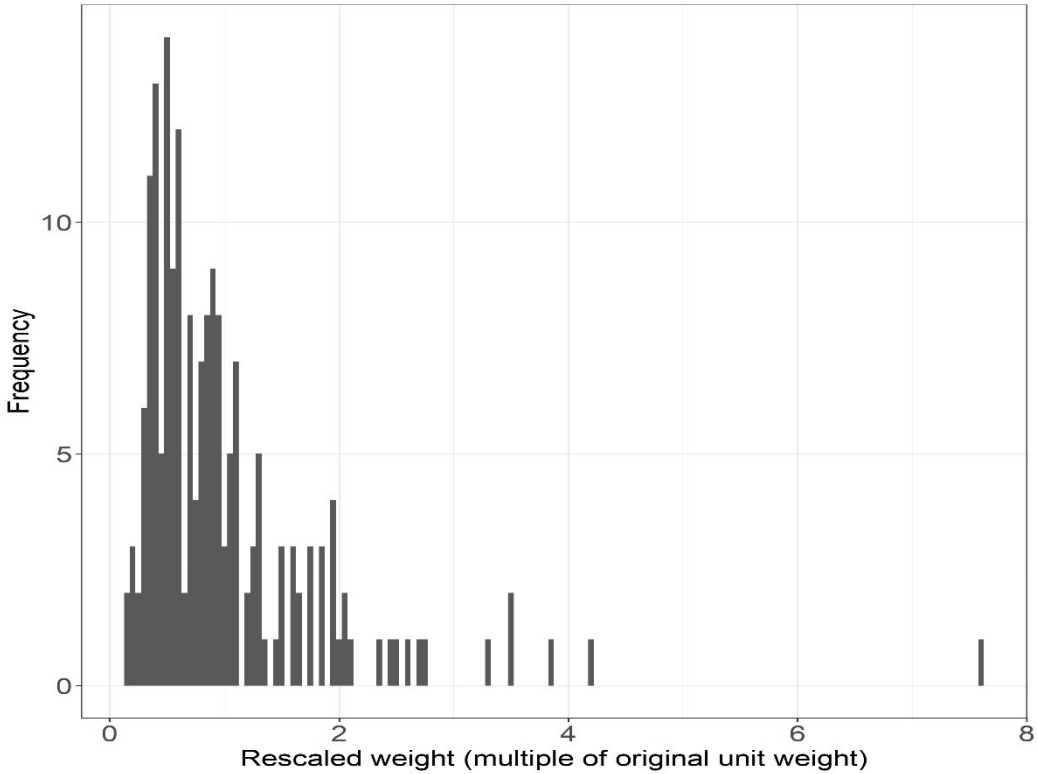
Figure **6**.

Table 8: Comparison of baseline characteristics – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Treatment (study)	N/ESS	Average age	Percent ECOG= 0	Percent prior line >3	Percent hormone receptor positive	Percent visceral disease
T-DXd unadjusted (DESTINY-Breast01)	184.0	56	55.4	91.8	52.7	91.8
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine (Study EGF100151)	165.0	51	58.2	81.6	46.3	78.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; N, sample size.

Figure 6: Histogram rescaled weights – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



Unadjusted and weighted Kaplan-Meier plots of overall survival are shown in Figure . The Kaplan-Meier plots show that weighting has resulted in only a very small improvement in overall survival outcomes for the trastuzumab deruxtecan arm. Table 10 presents the weighted hazard ratio results, alongside unadjusted naïve hazard ratios for comparison. The weighted patients receiving trastuzumab deruxtecan demonstrated significantly greater improvements in OS compared with patients receiving capecitabine (weighted HR: [redacted]). The bootstrapped hazard ratios are presented in

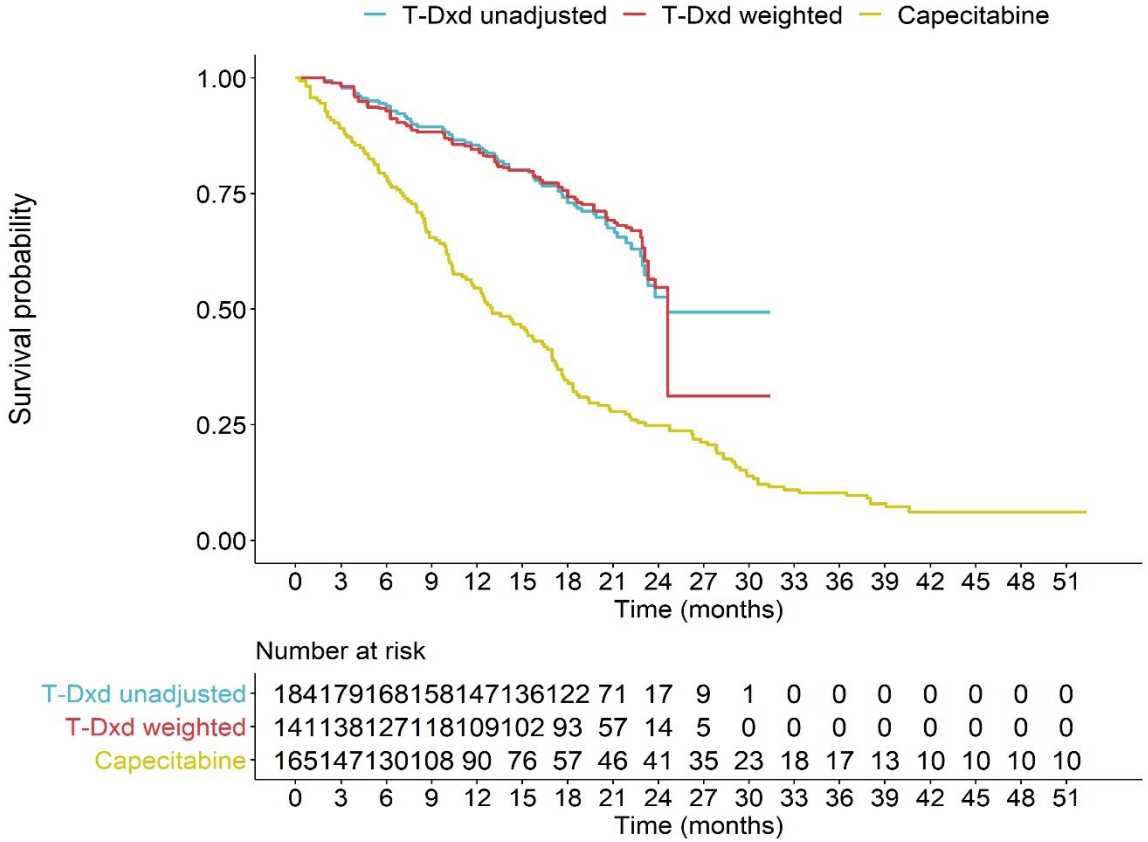
Figure **8**.

However, there is evidence to suggest that the proportional hazards assumption may be violated for the matching overall survival curves (see

Figure **9** and

Figure **10**); please note that this may be driven by the high amount of censoring in the overall survival data after 20.5 months.

Figure 7: Kaplan-Meier plot of overall survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



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

Table 9: Kaplan-Meier summary of overall survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Treatment (study)	N/ESS	Events	Median (95% CI)
T-DXd unadjusted (DESTINY-Breast01)	184.0	65	24.61 (23.10 to NA)
T-DXd weighted (DESTINY-Breast01)	[redacted]	[redacted]	[redacted]
Capecitabine (Study EGF100151)	165.0	155	13.02 (10.42 to 16.33)

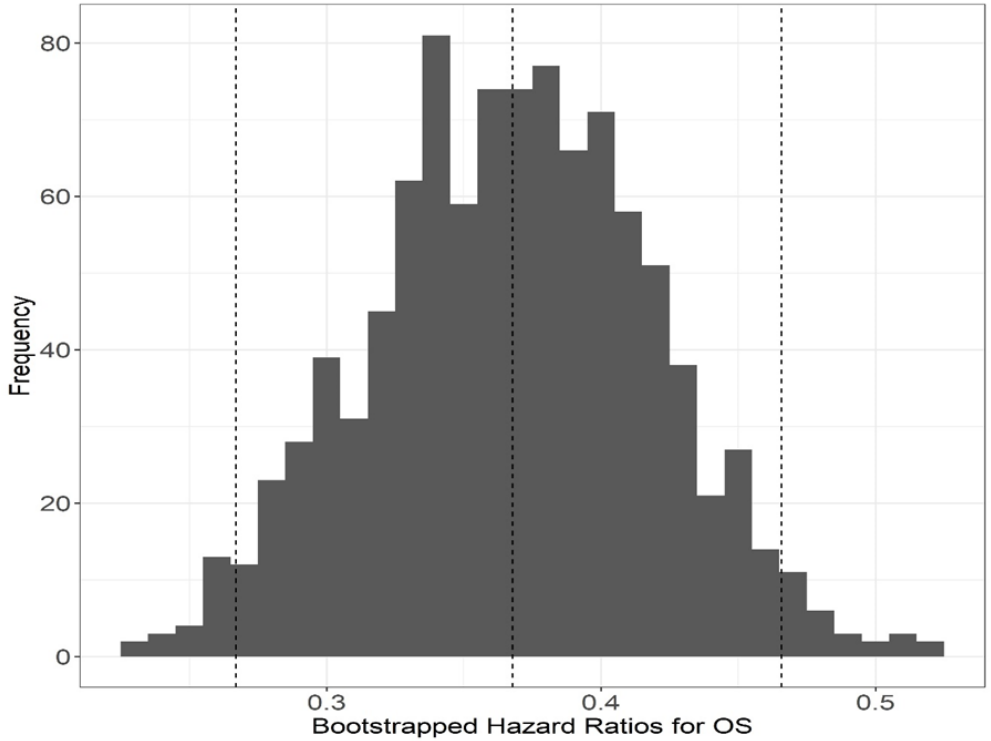
Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; NA, not applicable; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Table 10: Hazard ratios for overall survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs Capecitabine	[redacted]
Weighted standard CI	T-DXd vs Capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs Capecitabine	[redacted]

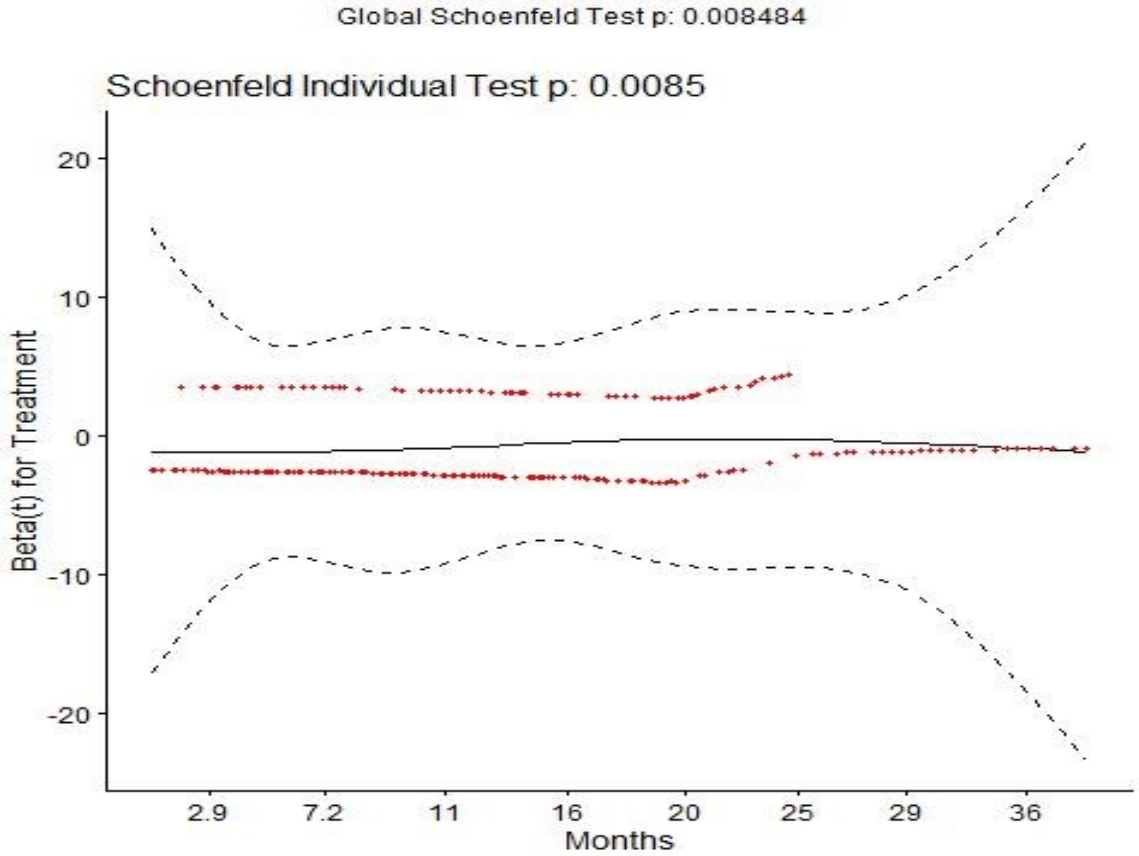
Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

Figure 8: Bootstrapped hazard ratios for overall survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



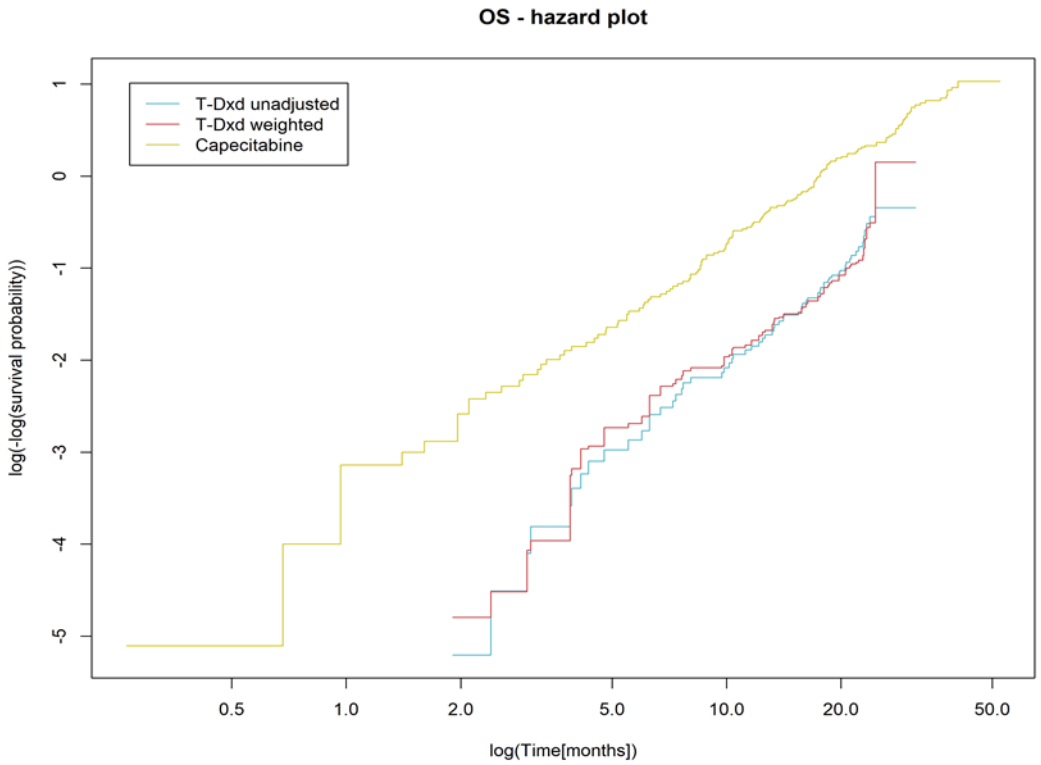
Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan.

Figure 9: Schoenfeld residuals for proportional hazards assumption for overall survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



Abbreviations: OS, overall survival; PH, proportional hazards.

Figure 10: Cumulative hazard plot of overall survival - trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan.

Given that there was some evidence that the proportional hazards assumption may be violated (

Figure **9** and

Figure **10**), additional analyses were performed in which accelerated failure time parametric survival models were fitted to the weighted data. The statistical fit of the weighted parametric survival models is presented in Table 11, and the ratio of the expected survival times is presented in Table 12. For all parametric distributions, trastuzumab deruxtecan was shown to be associated with statistically significantly longer survival compared with capecitabine.

Table 11: Statistical fit of weighted parametric survival models (overall survival) - trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Survival model	AIC	AIC Rank	BIC	BIC Rank
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (AFT form)	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 12: Ratio of the expected survival times for weighted parametric models (overall survival) – trastuzumab deruxtecan (DESTINY-Breast01) vs. capecitabine (Study EGF100151)

Survival model	Survival time ratio (95% CI)
Generalised gamma	[redacted]
Loglogistic	[redacted]
Lognormal	[redacted]
Weibull (AFT form)	[redacted]

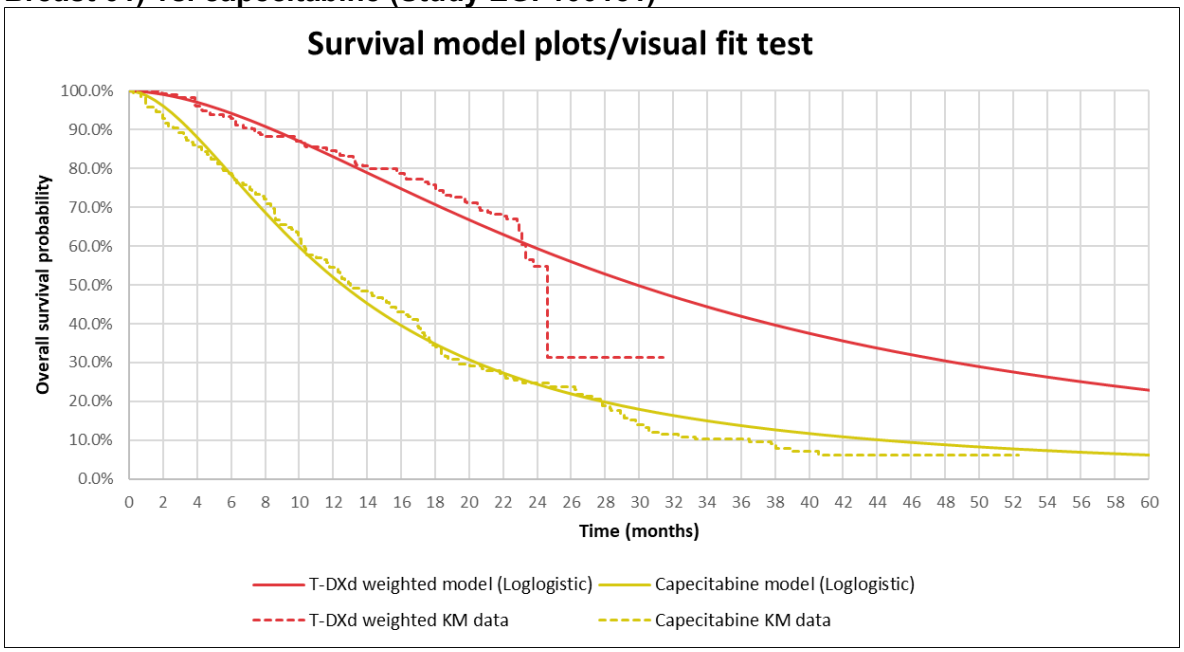
Abbreviations: AFT, accelerated failure time; CI, confidence interval.

The Kaplan-Meier curve for overall survival is overlaid on each of the six survival model plots to demonstrate the visual fit of each parametric model (

Figure **11** to

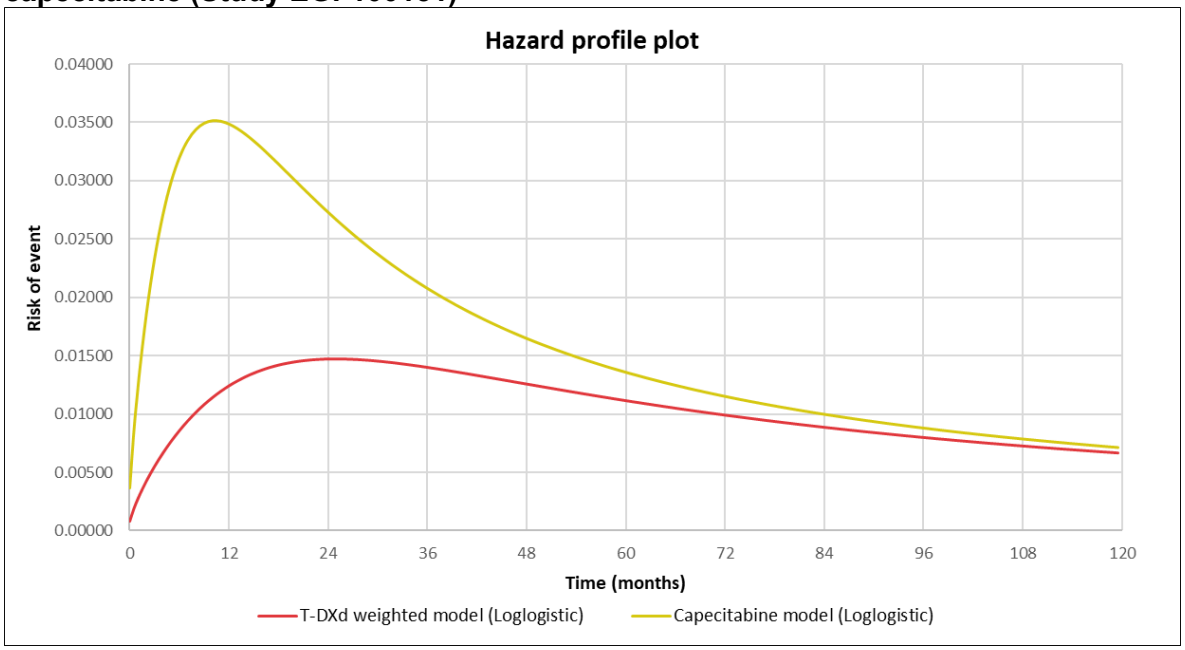
Figure **18**). The generalised gamma and loglogistic models have very similar statistical fit, however, the loglogistic appears to have a slightly better fit on the tail for the capecitabine group. In the loglogistic model, the expected overall survival is [redacted] longer for those who received trastuzumab deruxtecan as compared with capecitabine.

Figure 11: Parametric loglogistic model for overall survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



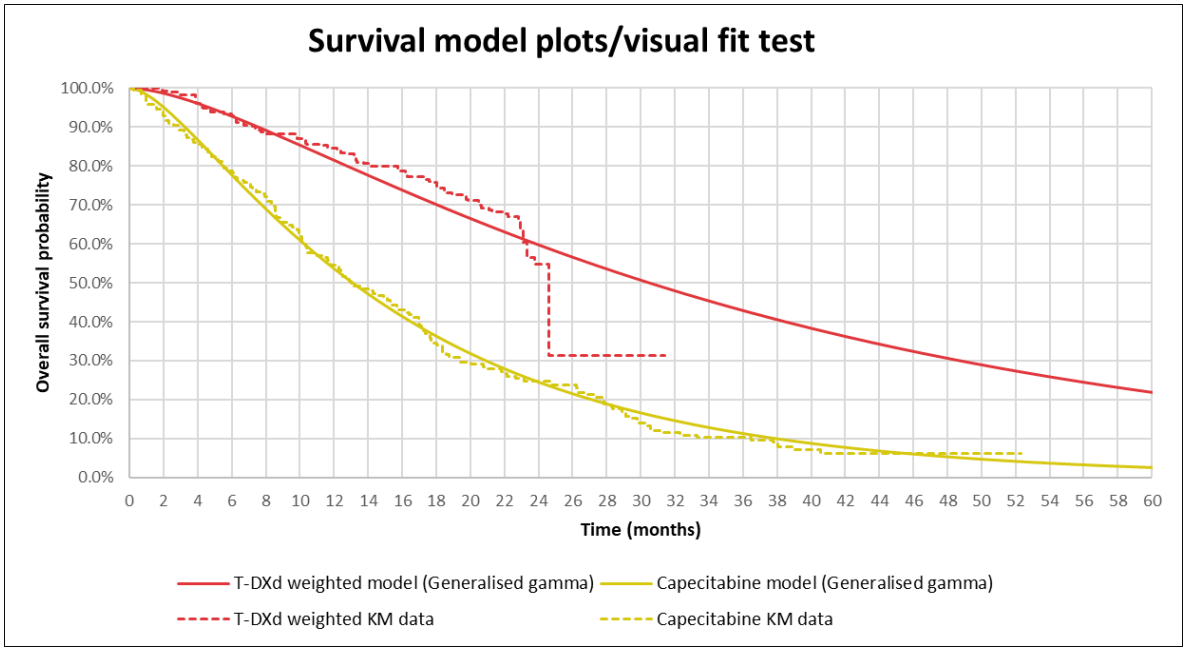
Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Figure 12: Cumulative hazard plot of overall survival – loglogistic model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



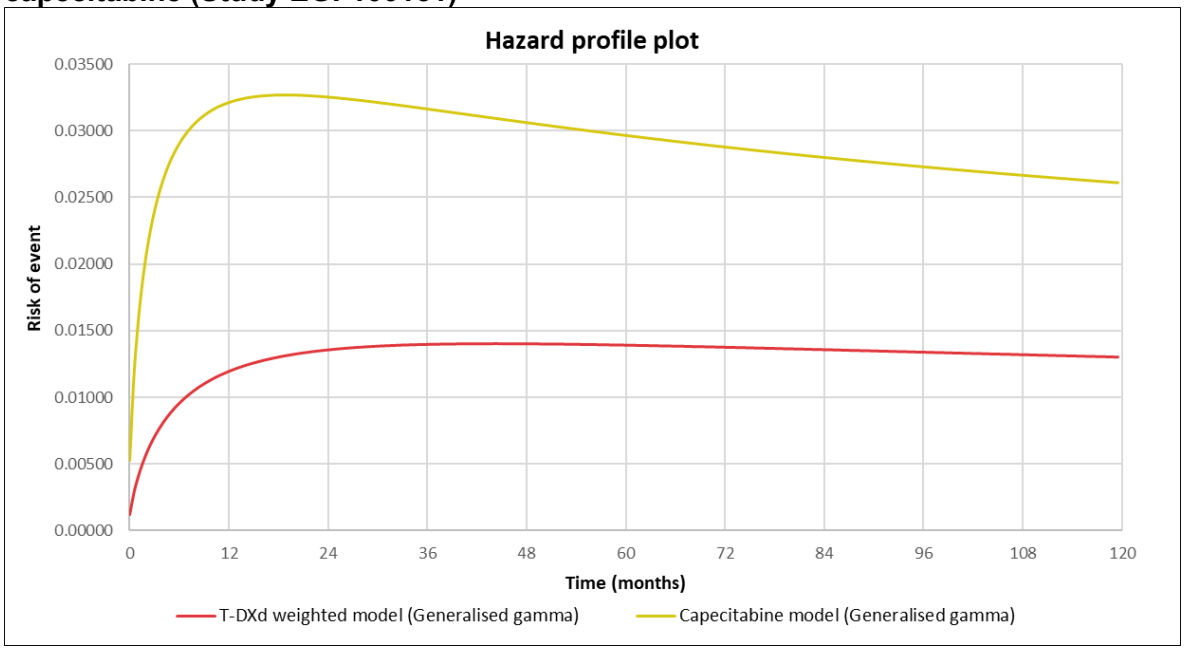
Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 13: Parametric generalised gamma model for overall survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



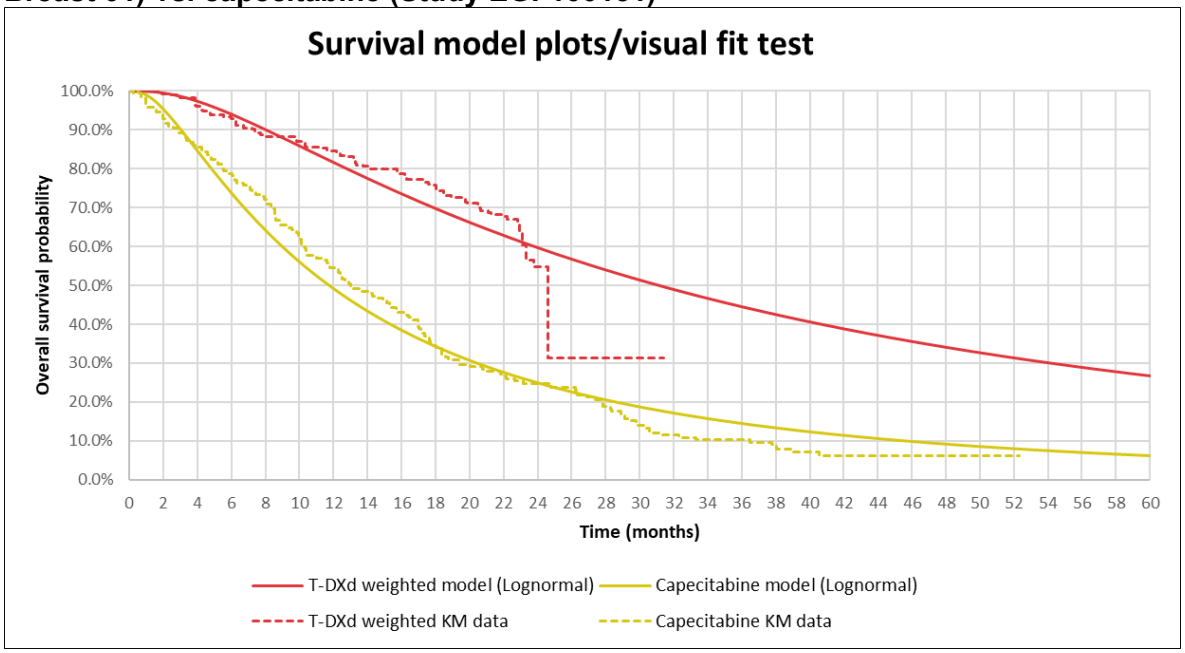
Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Figure 14: Cumulative hazard plot of overall survival – generalised gamma model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



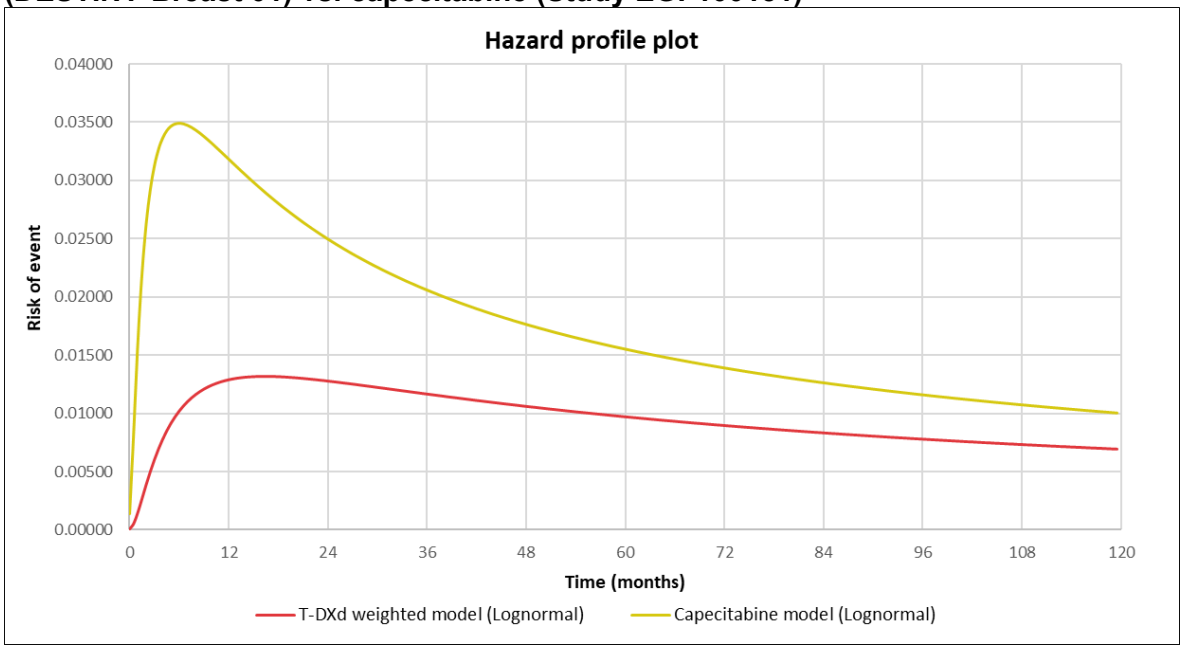
Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 15: Parametric lognormal model for overall survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



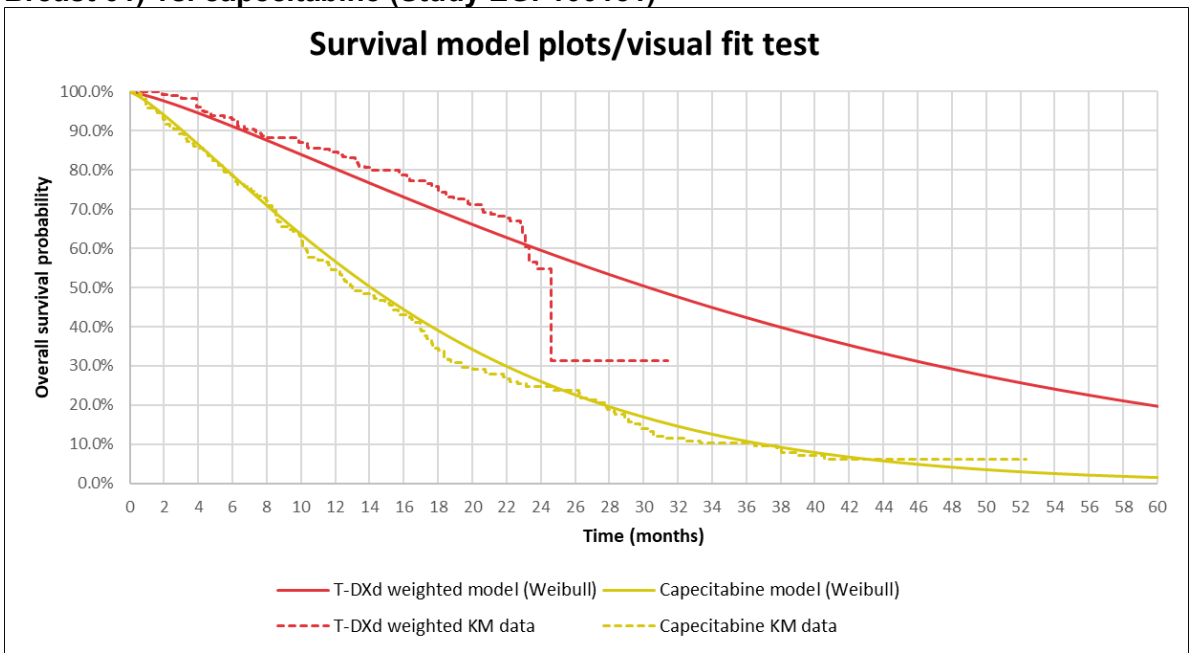
Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 16: Cumulative hazard plot of overall survival, with treatment as a covariate – lognormal model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 17: Parametric Weibull AFT model for overall survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)



Abbreviations: AFT, accelerated failure time; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan

Figure 18: Cumulative hazard plot of overall survival – Weibull AFT model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. capecitabine (Study EGF100151)

Abbreviations: AFT, accelerated failure time; OS, overall survival; T-DXd, trastuzumab deruxtecan

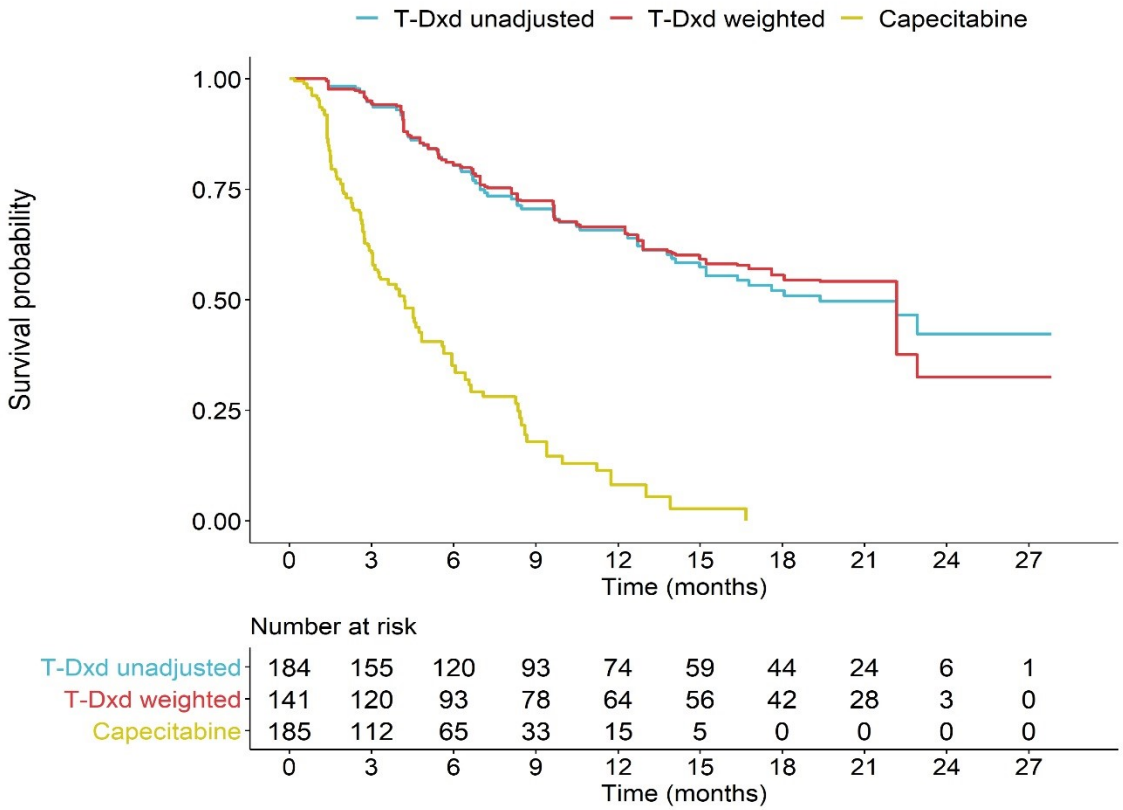
Unadjusted and weighted Kaplan-Meier plots of progression-free survival are shown in Figure 19. The Kaplan-Meier plots show that weighting has resulted in some improvement in progression-free survival outcomes for the trastuzumab deruxtecan arm; the median survival time changed slightly before and after weighting (

Table **13**). Table 14 presents the weighted hazard ratio results, alongside unadjusted naïve hazard ratios for comparison. The bootstrapped hazard ratios are presented in

Figure **20**. The proportional hazards assumption was not violated (Figure 21).

The weighted patients receiving trastuzumab deruxtecan demonstrated significantly greater improvements in PFS compared with patients receiving eribulin (weighted HR: [redacted]).

Figure 19: Kaplan-Meier plot of progression-free survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)



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

Table 13: Kaplan-Meier summary of progression-free survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Treatment (study)	N/ ESS	Events	Median (95% CI)
T-DXd unadjusted (Destiny Breast 01)	184.0	70	19.38 (14.09 to NA)
T-DXd weighted (Destiny Breast 01)	[redacted]	[redacted]	[redacted]
Capecitabine (Study EGF100151)	185.0	185	4.19 (3.12 to 4.73)

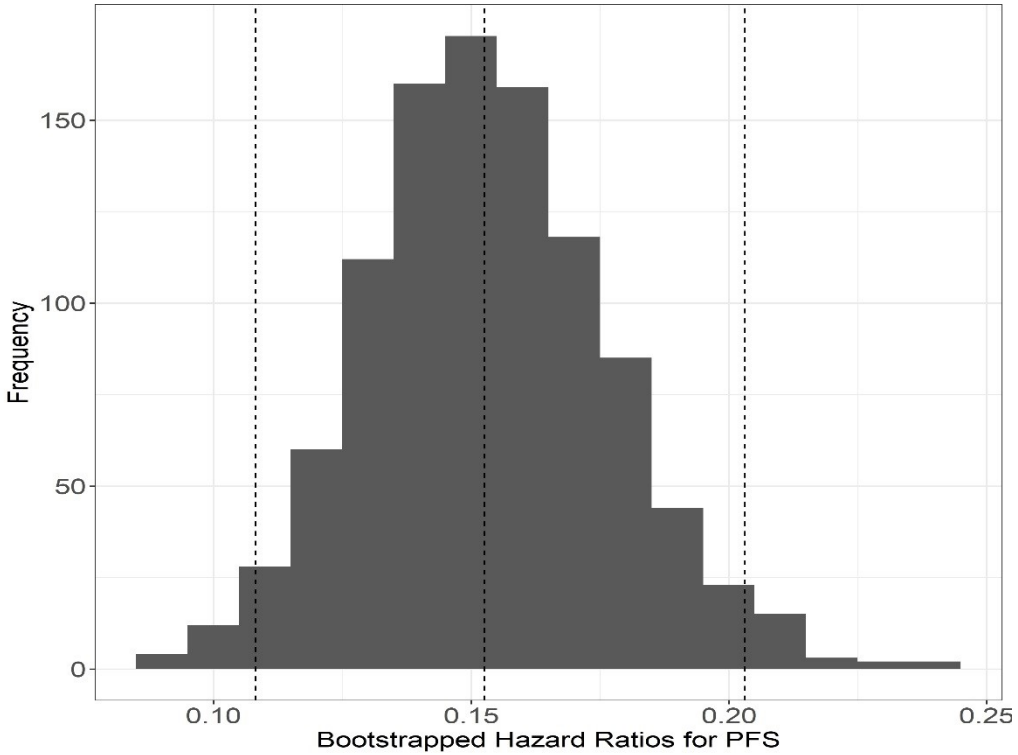
Abbreviations: CI, confidence interval; ESS, effective sample size; N, sample size; NA, not applicable; T-DXd, trastuzumab deruxtecan.

Table 14: Hazard ratios for progression-free survival – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	T-DXd vs Capecitabine	[redacted]
Weighted standard CI	T-DXd vs Capecitabine	[redacted]
Weighted bootstrapped CI	T-DXd vs Capecitabine	[redacted]

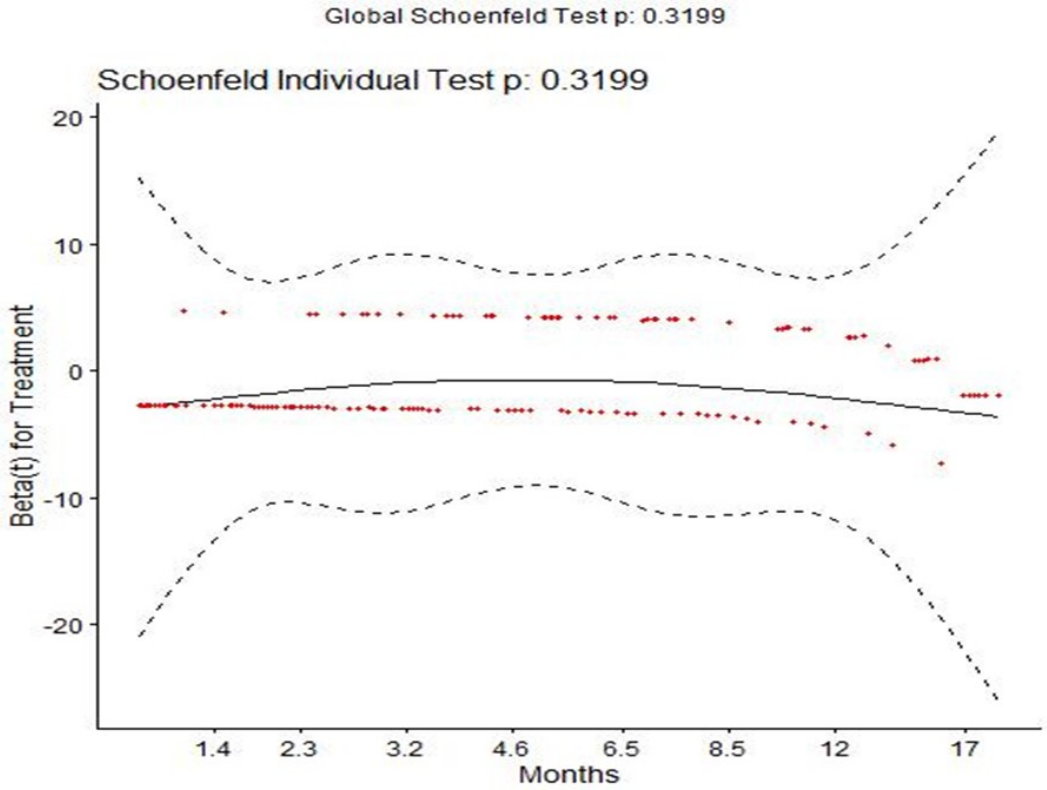
Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan.

Figure 20: Bootstrapped Hazard Ratios for PFS - T-DXd (DESTINY-Breast01) vs Capecitabine (Study EGF100151)



Abbreviations: PFS, progression free survival; T-DXd, trastuzumab deruxtecan.

Figure 21: Schoenfeld residuals for PH assumption for PFS - T-DXd (DESTINY-Breast01) vs Capecitabine (Study EGF100151)



Abbreviations: PFS, progression free survival; PH, proportional hazards.

Table **15** presents the unadjusted and weighted results for the response outcomes. The effective sample size is the same as that outlined in Table 8. Trastuzumab deruxtecan demonstrates significantly improved outcomes for response compared with capecitabine.

Table 15: Odds ratio for ORR, DCR and CBR – trastuzumab deruxtecan (DESTINY-Breast01) vs capecitabine (Study EGF100151)

Outcome	Method	Comparison	Odds ratio (95% CI)
ORR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
DCR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]
CBR	Unadjusted	T-DXd vs capecitabine	[redacted]
	Weighted GLM model	T-DXd vs capecitabine	[redacted]
	Weighted sandwich estimator	T-DXd vs capecitabine	[redacted]

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; GLM, generalised linear model; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

Appendix C: Matching-adjusted indirect comparison versus Sim 2019

Given that there was some evidence that the proportional hazards assumption may be violated for the progression-free survival comparison against Sim 2019, additional analyses were performed in which accelerated failure time parametric survival models were fitted to the weighted data. The statistical fit of the weighted parametric survival models is presented in Table 16, and the ratio of the expected survival times is presented in Table 19. For all parametric distributions, trastuzumab deruxtecan was shown to be associated with statistically significantly longer progression-free survival compared with vinorelbine.

Table 16: Statistical fit of weighted parametric survival models (progression-free survival) - trastuzumab deruxtecan (DESTINY-Breast01) vs vinorelbine (Sim 2019)

Survival model	AIC	AIC Rank	BIC	BIC Rank
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (AFT form)	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 17: Ratio of the expected survival times for weighted parametric models – PFS T-DXd (Destiny Breast 01) vs. Vinorelbine (Sim 2019)

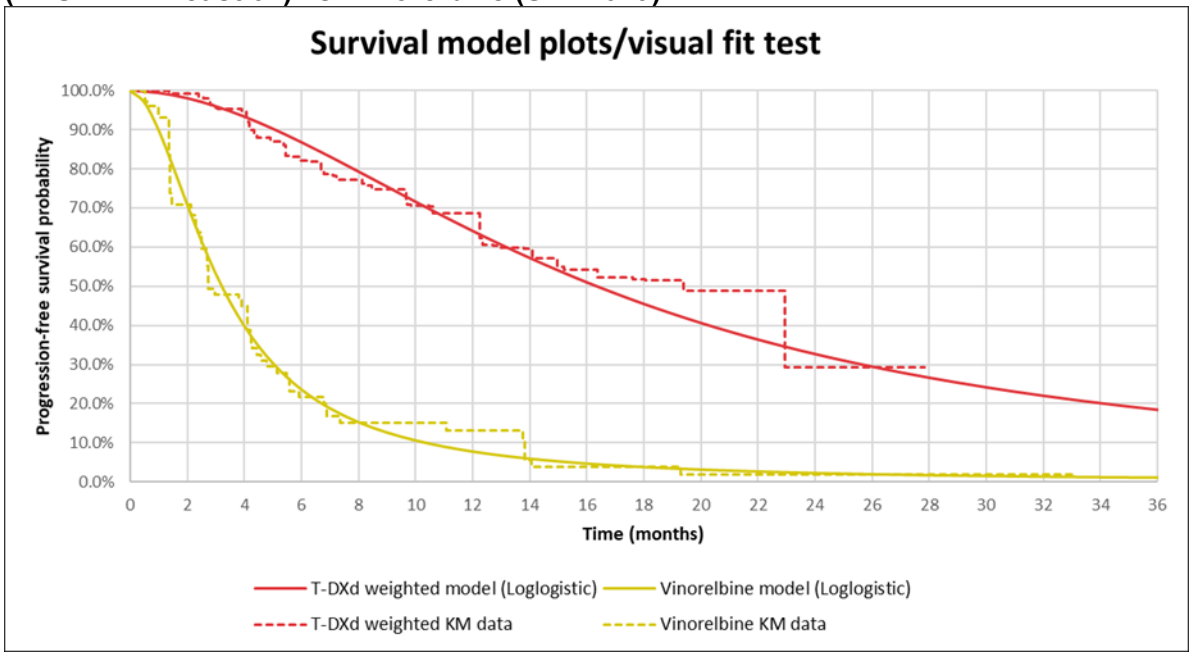
Survival model	Survival time ratio (95% CI)
Generalised gamma	[redacted]
Loglogistic	[redacted]
Lognormal	[redacted]
Weibull (AFT form)	[redacted]

Abbreviations: AFT, accelerated failure time; CI, confidence interval.

The Kaplan-Meier curve for progression-free survival is overlaid on each of the six survival model plots to demonstrate the visual fit of each parametric model (Figure 22 to

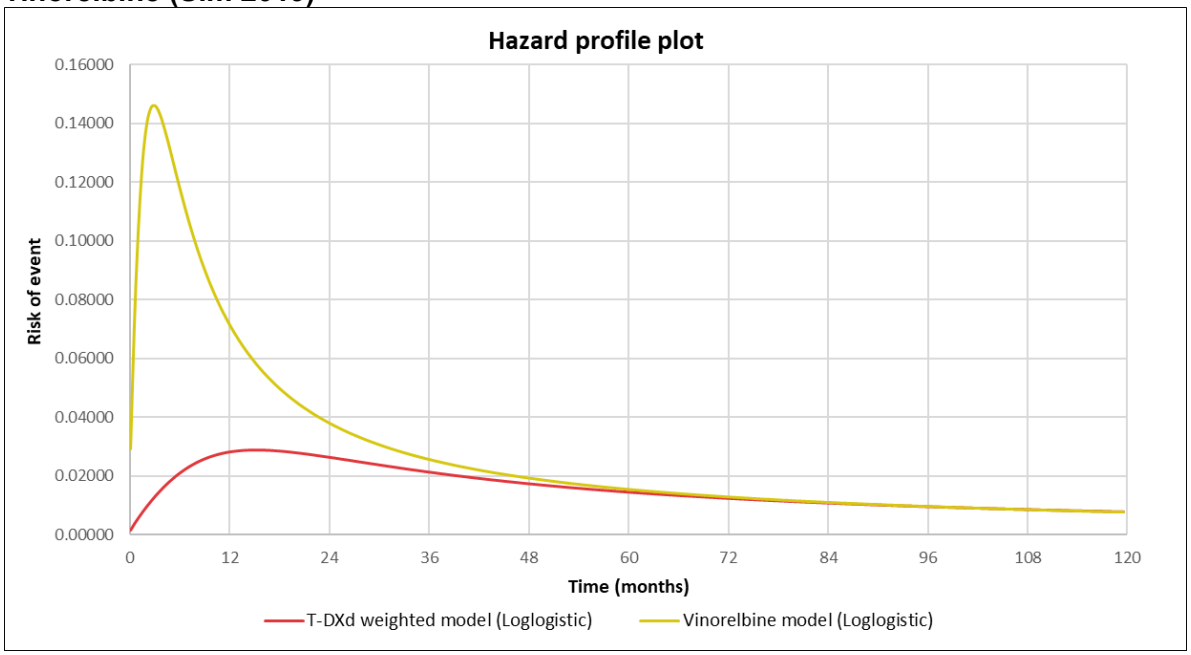
Figure **29**). The lognormal model is the best statistical fit and has the best visual fit for trastuzumab deruxtecan. In the lognormal model, the expected progression-free survival is [redacted] longer for those who received trastuzumab deruxtecan as compared with vinorelbine.

Figure 22: Parametric loglogistic model for progression-free survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



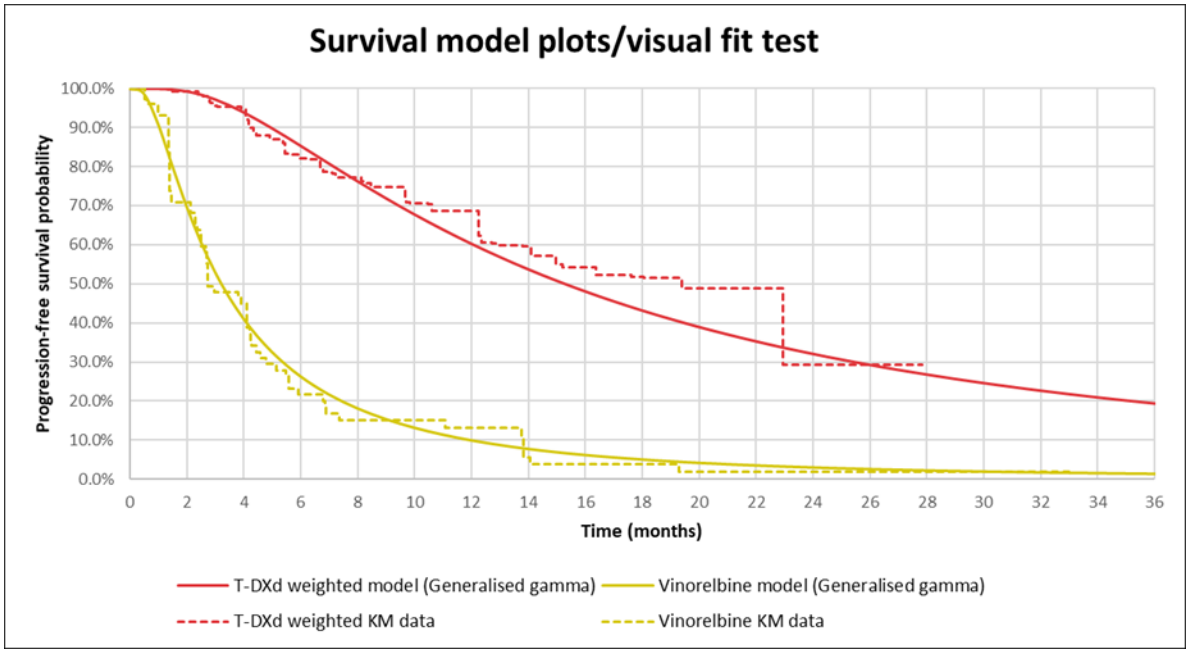
Abbreviations: KM, Kaplan-Meier; OS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Figure 23: Cumulative hazard plot of progression-free survival – loglogistic model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



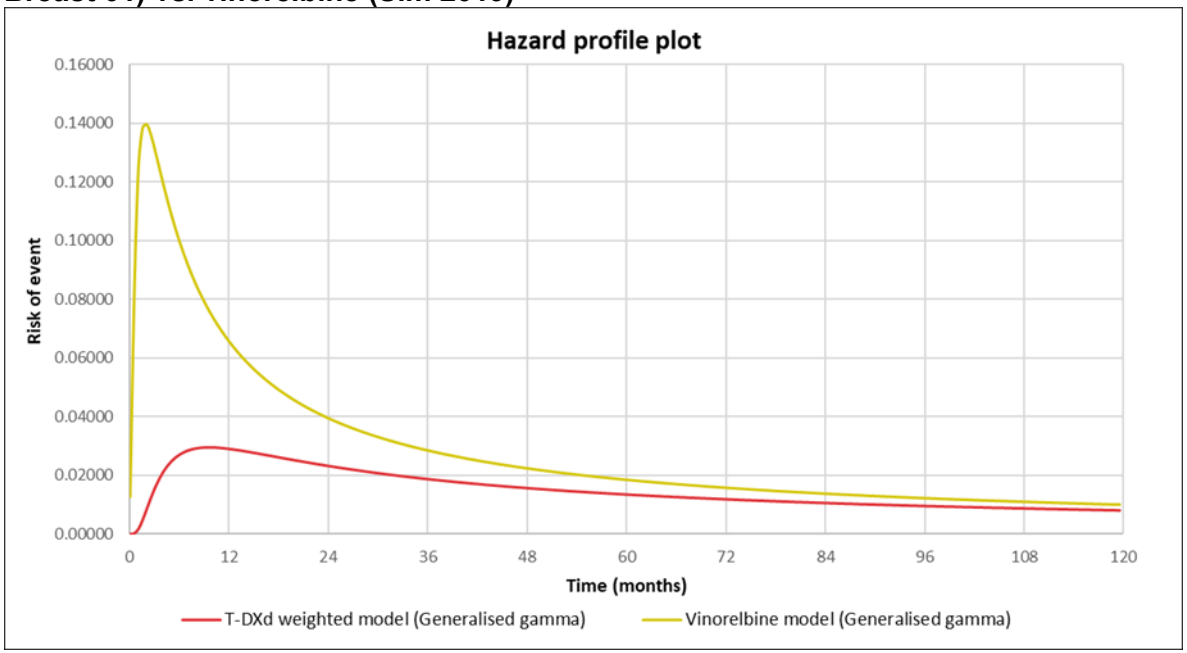
Abbreviations: OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 24: Parametric generalised gamma model for progression-free survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



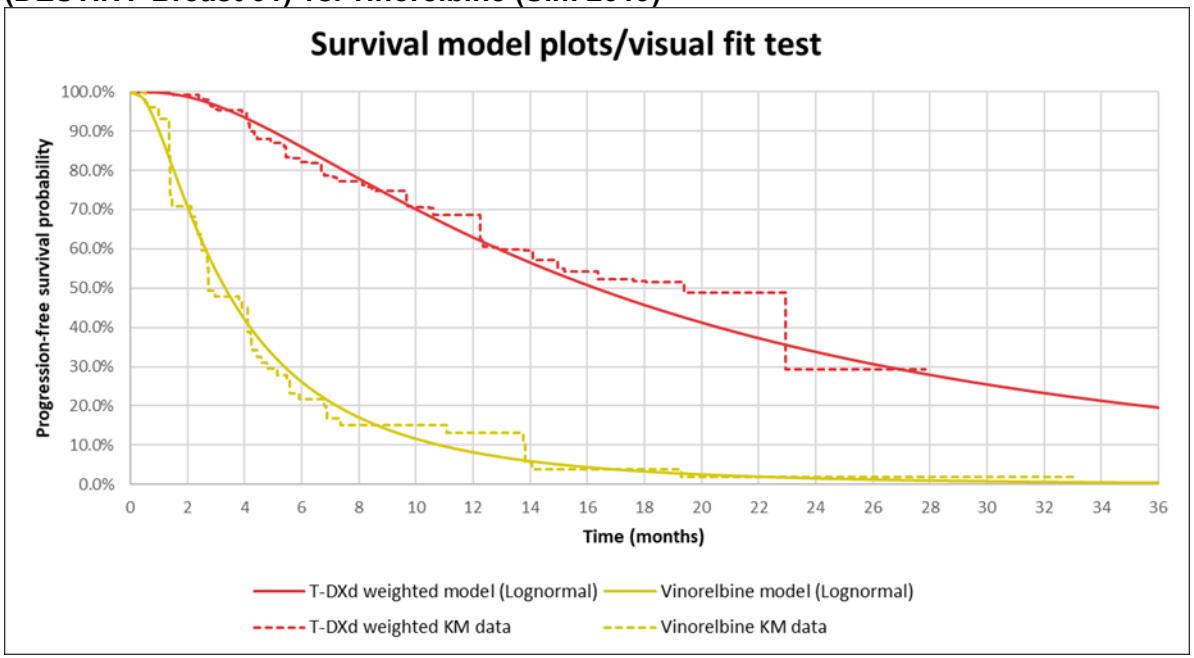
Abbreviations: KM, Kaplan-Meier; OS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Figure 25: Cumulative hazard plot of progression-free survival – generalised gamma model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



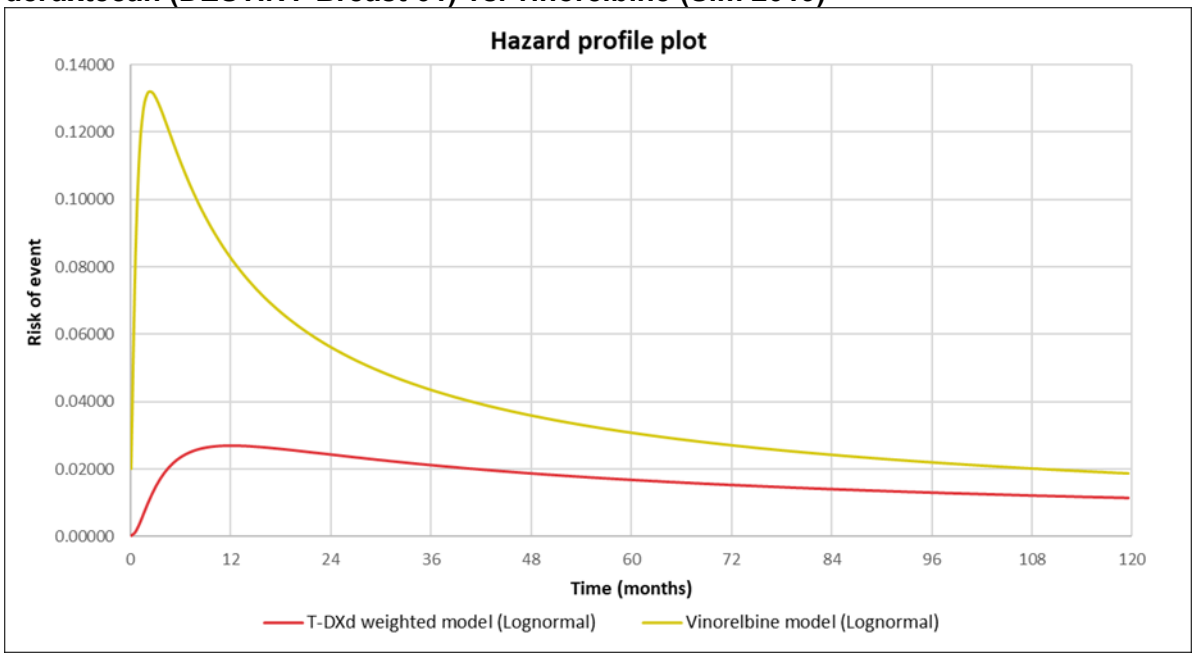
Abbreviations: OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 26: Parametric lognormal model for progression-free survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



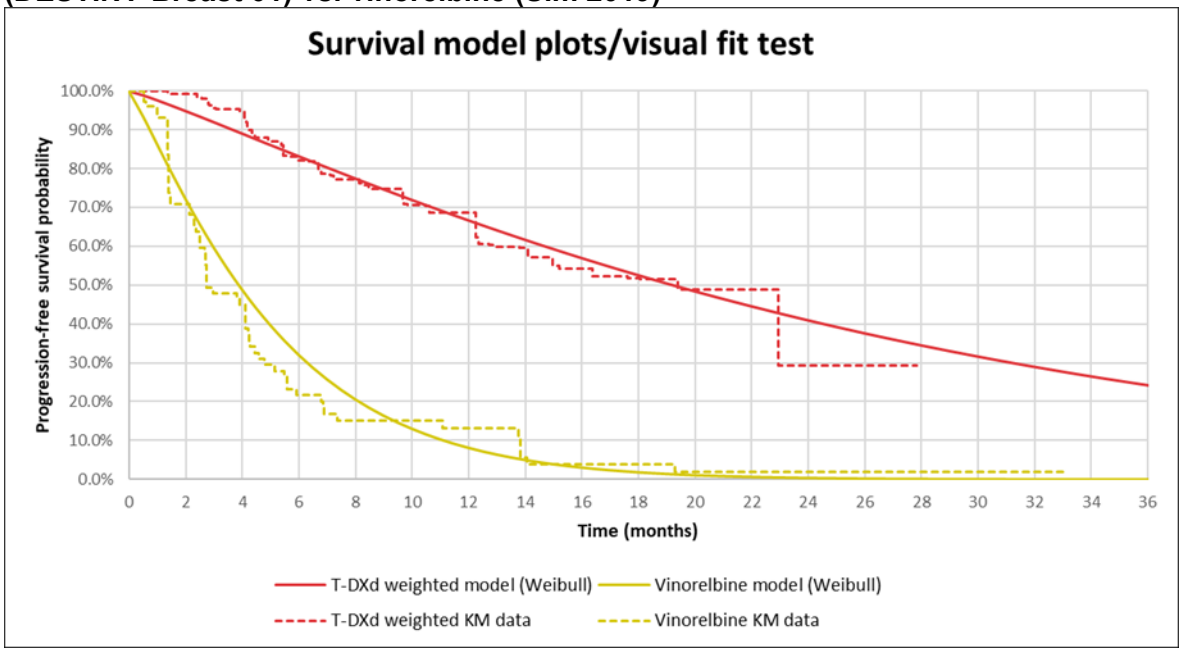
Abbreviations: KM, Kaplan-Meier; OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 27: Cumulative hazard plot of progression-free survival, with treatment as a covariate – lognormal model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



Abbreviations: OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 28: Parametric Weibull AFT model for progression-free survival, with visual fit to Kaplan-Meier – trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)



Abbreviations: AFT, accelerated failure time; KM, Kaplan-Meier; OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Figure 29: Cumulative hazard plot of progression-free survival – Weibull AFT model - trastuzumab deruxtecan (DESTINY-Breast 01) vs. vinorelbine (Sim 2019)

Abbreviations: AFT, accelerated failure time; OS, progression-free survival; T-DXd, trastuzumab deruxtecan

Appendix D: Overall survival in third-line HER2-positive patients in the post-trastuzumab emtansine era

Table 18: Summary of studies evaluating overall survival in HER2-positive patients in the third-line setting in the post T-DM1 era

Study	Study design	Population	Intervention	Prior therapies	Median OS (95% CI) (months)
Barni 2019 (17)	Multicentre retrospective cohort study in Italy	Patients with locally advanced or metastatic breast cancer; HER2+ subgroup data available	Eribulin	93.8% of patients received at least two prior chemotherapy regimens.	HER2+ subgroup: 10.2 (8.8-12.0)
Laakmann 2020 (28)	PRAEGNANT mBC registry (NCT02338167) in Germany	Patients with HER2+ mBC who have completed a treatment with T-DM1 (N=85)	Treatment following T-DM1 included: Lapatinib/Chemo: 21 (24.7%) Trastuzumab/Chemo: 17 (20.0%) Chemo: 10 (11.8%) Pertuzumab/Trastuzumab/Chemo: 10 (11.8%) Lapatibib/Trastuzumab: 6 (7.1%) Trastuzumab:4 (4.7%)	40% of the patients (n = 34) treated with T-DM1 in the second line and 27.1% (n = 23) treated in the third line. 87.1% patients had been treated with any HER2 treatment before T-DM1.	18.4 months (15.5–21.3)
Watanuki 2020 (29)	Retrospective observational study in Japan	Patients with HER2+ mBC who had discontinued T-DM1 and received a therapy following T-DM1 (N=30)	First therapy following T-DM1: Eribulin: 10 (33.3%) Trastuzumab + capecitabine: 6 (20%) Doxorubicin + cyclophosphamide: 6 (20%) Lapatinib + capecitabine: 2 (6.7%) Trastuzumab + pertuzumab + taxane: 1 (3.3%) Trastuzumab + vinorelbine: 1 (3.3%) Trastuzumab alone: Trastuzumab + taxane: 1 (3.3%) Trastuzumab + endocrine therapy: 1 (3.3%) Gemcitabine: 1 (3.3%)	All patients had received T-DM1; median number of prior therapies 2 (range 1-7); Prior therapies for MBC before T-DM1 included: Trastuzumab + pertuzumab + taxane: 13 (43.3%) Trastuzumab + taxane: 10 (33.3%) Trastuzumab + capecitabine: 8 (26.7%) Trastuzumab + vinorelbine: 7 (23.3%)	20.6 (13.5 – NR)
Kazmi 2020 (30)	A retrospective, observational study using de-identified	Patients with mBC with lung or liver metastasis treated with eribulin,	Eribulin as third-line in HER2+ patients (N=21)	Not reported; however, T-DM1 was approved in the US in early 2013 and would therefore be expected to be received by the	10.3 (6.0–NR)
			Capecitabine as third-line in HER2+ patients (N=19)		15.4 (7.6–NR)

	patient electronic health records January 1, 2012 through October 13, 2018	gemcitabine, or capecitabine as third-line therapy; N=61 HER2+ patients (9% of total population)	Gemcitabine as third-line in HER2+ patients (N=21)	majority of patients as a prior therapy	12.8 (7.0–NR)
Murthy 2020 (23)	HER2CLIMB Phase III RCT	Patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1 (N=612)	Tucatinib combined with trastuzumab + capecitabine (N=410)	Median prior lines for MBC: 3 (1–14)	21.9 (18.3–31.0)
			Placebo combined with trastuzumab + capecitabine (N=202)	Median prior lines for MBC: 3 (1–13)	17.4 (13.6–19.9)

Abbreviations: Chemo, chemotherapy; CI, confidence interval; CTCA, Cancer Treatment Centers of America; MBC, metastatic breast cancer; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine.

Appendix E: Results

Base-case results, patient access scheme price (superseding Addendum, Section 3.2.5)

Base-case incremental cost-effectiveness analysis results, patient access scheme price (superseding Addendum, Section 3.2.5.1)

A simple patient access scheme for trastuzumab deruxtecan in the National Health Service has been approved in the form of a fixed price of [redacted] per 100mg vial.

Primary analysis, patient access scheme price

In the primary analysis, censoring trastuzumab deruxtecan overall survival at 20.5 months, eribulin is found to be dominated and vinorelbine is extendedly dominated. Trastuzumab deruxtecan is associated with incremental costs of [redacted] and [redacted] incremental quality-adjusted life-years compared with capecitabine, resulting in an incremental cost-effectiveness ratio of £47,230 per quality-adjusted life-year gained. A summary of the fully incremental results using the patient access scheme price for trastuzumab deruxtecan are presented in Table 19.

Table 19: Primary analysis results (censoring T-DXd OS at 20.5 months)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£450,239	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,230	£47,230
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan								

Secondary analysis, patient access scheme price

Secondary analyses are considered in which the full overall survival Kaplan-Meier data for trastuzumab deruxtecan are used, assuming each of the exponential and generalised gamma distributions. Due to the high level of censoring from 20.5 months, the Kaplan Meier data from this point onwards is not considered to be informative. Therefore, this analysis is expected to be a conservative estimate of the cost-effectiveness of trastuzumab deruxtecan and it is proposed that the primary analysis is used for decision making purposes.

In the secondary analysis assuming an exponential distribution for trastuzumab deruxtecan overall survival, eribulin is found to be dominated and vinorelbine is extendedly dominated. Trastuzumab deruxtecan is associated with incremental costs of [redacted] and [redacted] incremental quality-adjusted life-years compared with capecitabine, resulting in an incremental cost-effectiveness ratio of £51,148 per quality-adjusted life-year gained. A summary of the fully incremental results is presented in Table 20.

Table 20: Secondary analysis results, T-DXd OS distribution: exponential

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£450,239	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,148	£51,148
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the secondary analysis assuming a generalised gamma distribution for trastuzumab deruxtecan overall survival, eribulin is found to be dominated and vinorelbine is extendedly dominated. Trastuzumab deruxtecan is associated with incremental costs of [redacted] and [redacted]

incremental quality-adjusted life-years compared with capecitabine, resulting in an incremental cost-effectiveness ratio of £57,844 per quality-adjusted life-year gained. A summary of the fully incremental results is presented in Table 21**Error! Reference source not found.**.

Table 21: Secondary analysis results, T-DXd OS distribution: generalised gamma

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£450,239	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,844	£57,844
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses, patient access scheme price (superseding Addendum, Section 3.2.6)

Probabilistic sensitivity analysis, patient access scheme price (superseding Addendum, Section 3.2.6.1)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis, in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane and a cost-effectiveness acceptability curve was generated.

The average incremental costs over the simulated results were [redacted] and the average incremental quality-adjusted life-year were [redacted] compared with capecitabine, giving a probabilistic incremental cost-effectiveness ratio of £46,314. This is highly congruent with deterministic changes in costs of [redacted] and quality-adjusted life-years of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of £50,000 per quality-adjusted life-year was [redacted]%. A summary of the probabilistic, fully incremental results using the patient access scheme price for trastuzumab deruxtecan are presented in Table 22. The cost-effectiveness plane vs. each comparator and cost-effectiveness acceptability curve are presented in Figure 30, Figure 31, Figure 32 and Figure 33.

Table 22: PSA results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	£449,846	Ext. Dominated
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	£46,314	£46,314

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan

Figure 30: T-DXd versus eribulin scatterplot

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

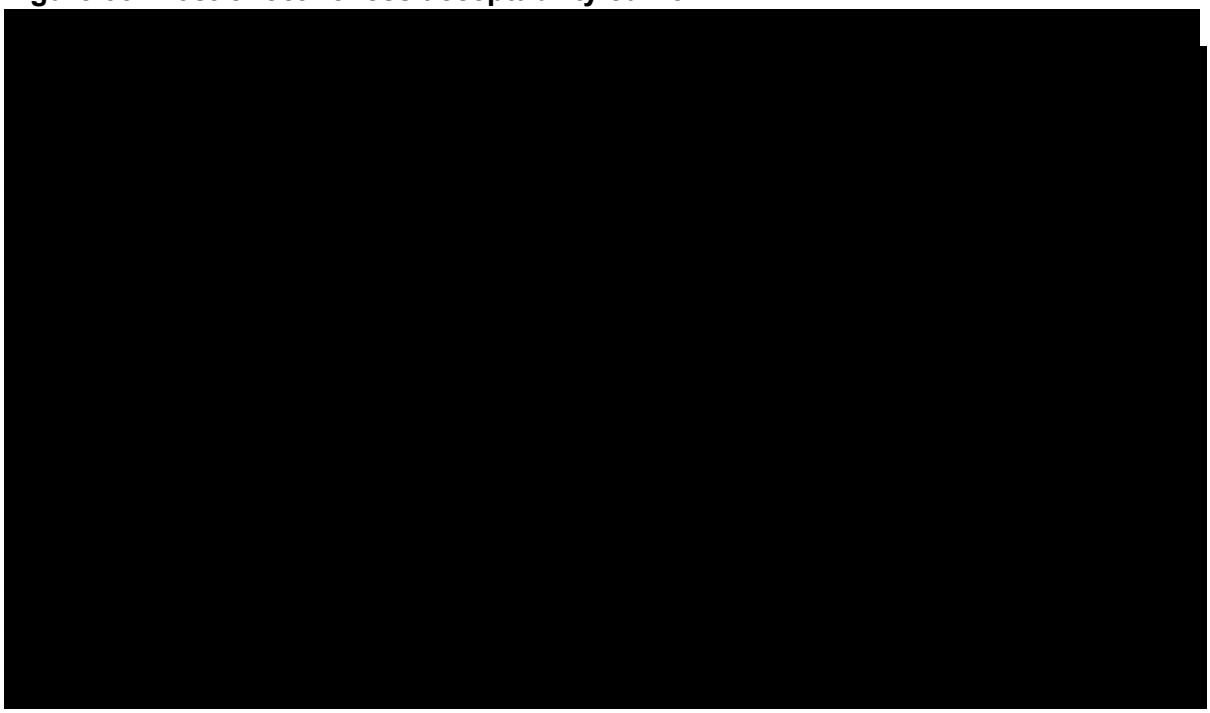
Figure 31: T-DXd vs capecitabine scatterplot

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 32: T-DXd vs vinorelbine scatterplot

Abbreviations: QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan.

Figure 33: Cost-effectiveness acceptability curve



Abbreviations: T-DXd, trastuzumab deruxtecan.

Deterministic sensitivity analysis (superseding Addendum, Section 3.2.6.2)

Parameter uncertainty was tested using one-way sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or ±10% where no estimates of precision were available. The incremental cost-effectiveness ratio was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are reported for each pairwise comparison. For each comparator, the most influential parameter was the hazard ratio applied to TH3RESA curve to model trastuzumab deruxtecan overall survival. As the survival gains in the trastuzumab deruxtecan arm of the model are the primary driver of results in the model, it is to be expected that the overall survival hazard ratio that informs trastuzumab deruxtecan survival would have the largest impact on results. Other influential parameters include the HER2-positive efficacy adjustment hazard ratio and health state utility values, although the effect of varying these parameters on results is small.

Trastuzumab deruxtecan vs eribulin

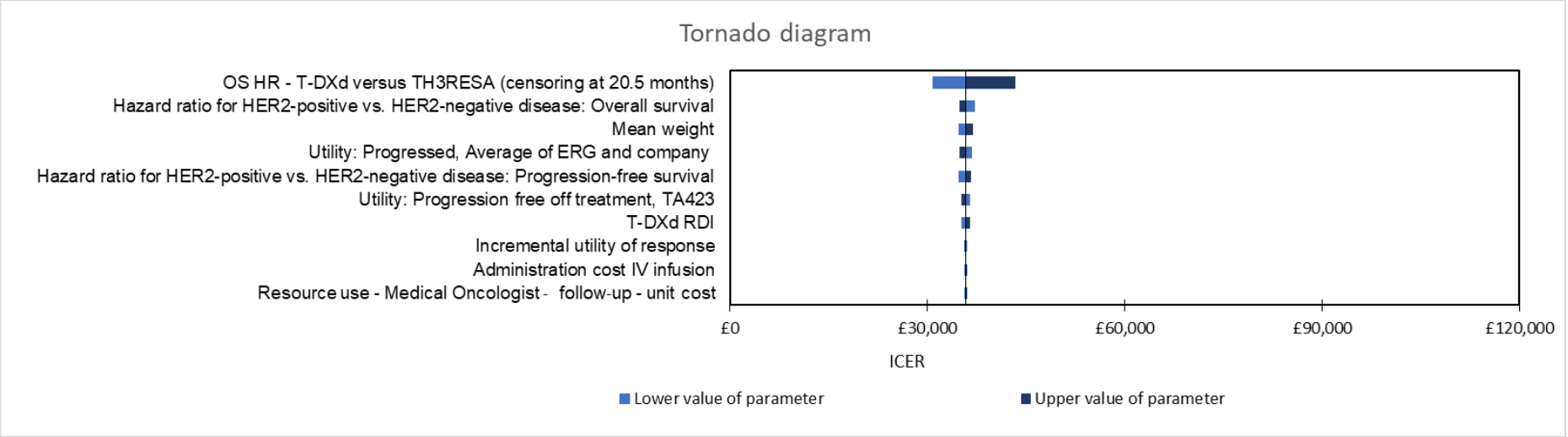
The one-way sensitivity analysis results for the comparison of trastuzumab deruxtecan vs. eribulin are presented in Table 23; the tornado diagram is presented in Figure 34.

Table 23: OWSA results - T-DXd vs eribulin

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	£30,751	£43,327
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	£37,164	£34,855
Mean weight	£34,805	£36,860
Utility: Progressed, Average of ERG and company	£36,823	£34,895
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	£34,784	£36,647
Utility: Progression free off treatment, TA423	£36,530	£35,162
T-DXd RDI	£35,223	£36,443
Incremental utility of response	£36,124	£35,545
Administration cost IV infusion	£35,558	£36,108
Resource use - Medical Oncologist - follow-up - unit cost	£35,566	£36,099

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; T-DXd, trastuzumab deruxtecan

Figure 34: T-DXd vs Eribulin - OWSA tornado diagram



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one-way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan

Trastuzumab deruxtecan vs capecitabine

The one-way sensitivity analysis results for the comparison of trastuzumab deruxtecan vs. capecitabine are presented in Table 24; the tornado diagram is presented in Figure 35.

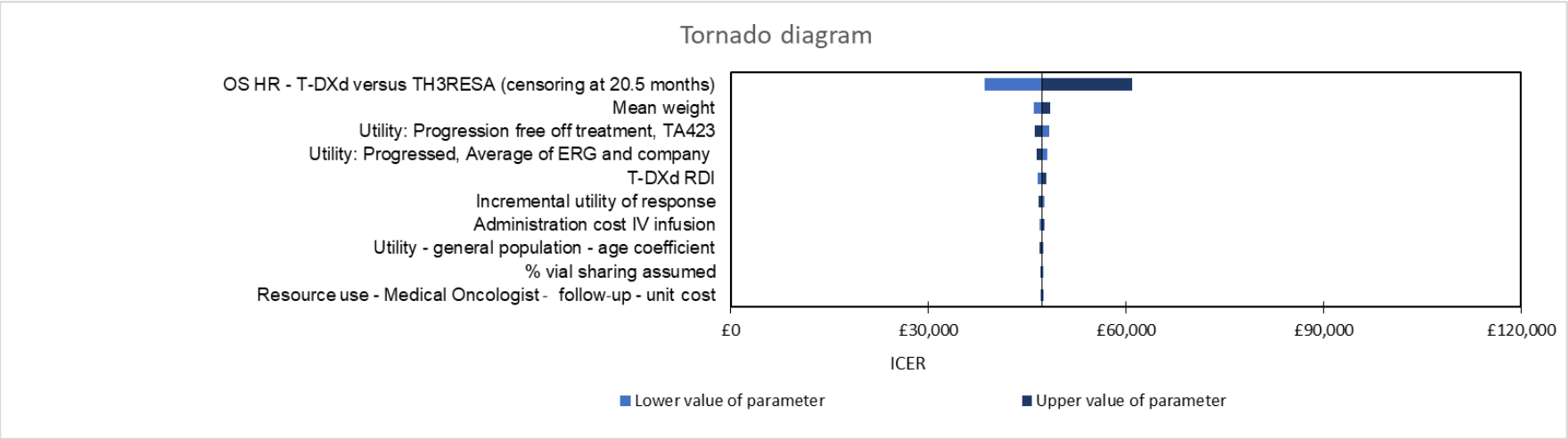
Table 24: OWSA results - T-DXd vs capecitabine

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	£38,607	£60,915

Mean weight	£46,034	£48,426
Utility: Progression free off treatment, TA423	£48,282	£46,223
Utility: Progressed, Average of ERG and company	£48,013	£46,472
T-DXd RDI	£46,520	£47,940
Incremental utility of response	£47,682	£46,785
Administration cost IV infusion	£46,814	£47,646
Utility - general population - age coefficient	£47,532	£46,953
% vial sharing assumed	£47,501	£46,959
Resource use - Medical Oncologist - follow-up - unit cost	£46,970	£47,490

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival OWSA, one way sensitivity analysis; T-DXd, trastuzumab deruxtecan

Figure 35: T-DXd vs Capecitabine - OWSA tornado diagram



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan

Trastuzumab deruxtecan vs vinorelbine

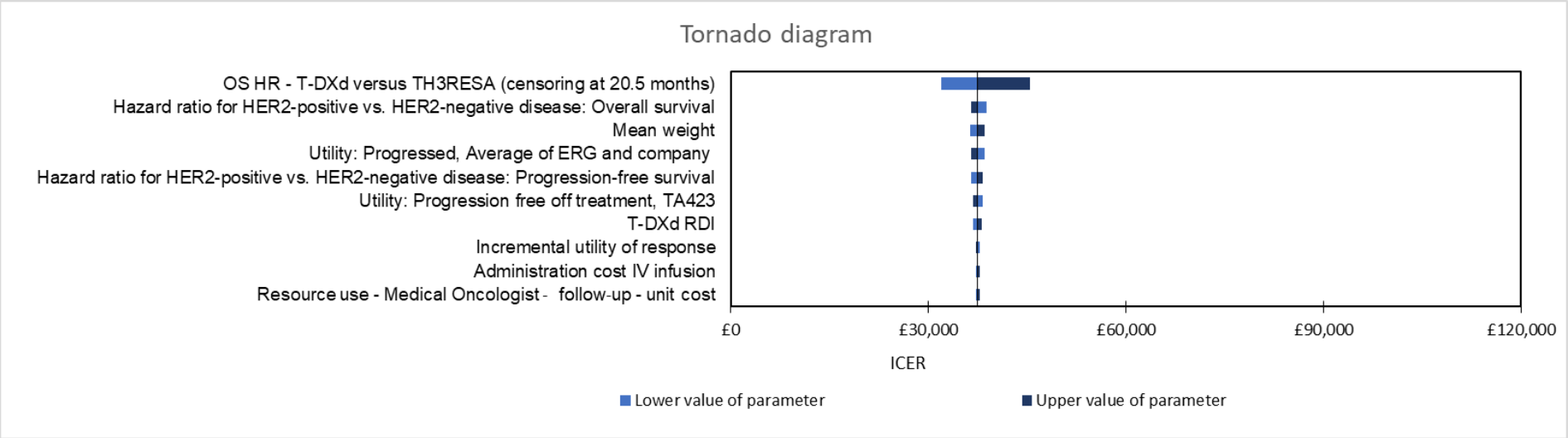
The one-way sensitivity analysis results for the comparison of trastuzumab deruxtecan vs. vinorelbine are presented in Table 25, and the tornado diagram is presented in Figure 36.

Table 25: OWSA results - T-DXd vs vinorelbine

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS HR - T-DXd versus TH3RESA (censoring at 20.5 months)	£32,021	£45,477
Hazard ratio for HER2-positive vs. HER2-negative disease: Overall survival	£38,897	£36,424
Mean weight	£36,398	£38,545
Utility: Progressed, Average of ERG and company	£38,505	£36,492
Hazard ratio for HER2-positive vs. HER2-negative disease: Progression-free survival	£36,432	£38,278
Utility: Progression free off treatment, TA423	£38,199	£36,771
T-DXd RDI	£36,834	£38,109
Incremental utility of response	£37,792	£37,155
Administration cost IV infusion	£37,185	£37,758
Resource use - Medical Oncologist - follow-up - unit cost	£37,205	£37,737

Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan

Figure 36:T-DXd vs vinorelbine - OWSA tornado diagram



Abbreviations: ERG; evidence review group; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival OWSA, one way sensitivity analysis; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan

Scenario analysis (superseding Addendum, Section 3.2.6.3)

Scenario analyses were performed in which key structural assumptions were varied. For all comparators, the scenarios with the biggest impact on the incremental cost-effectiveness ratio were modelling trastuzumab deruxtecan overall survival by anchoring to eribulin, or the selection of different distributions for the TH3RESA overall survival extrapolation. Choosing the log-normal or log-logistic overall survival distributions decreased the incremental cost-effectiveness ratio by over 20% in each analysis and choosing the Gompertz distribution increased the incremental cost-effectiveness ratio by over 20%. Modelling trastuzumab deruxtecan overall survival by using a hazard ratio vs. TH3RESA with no additional censoring applied to the trastuzumab deruxtecan data also increased the incremental cost-effectiveness ratio by over 10% when the generalised gamma distribution was selected. The distribution chosen for time-to-discontinuation also had a large impact on the incremental cost-effectiveness ratio. Choosing the Weibull and Gompertz distribution decreased the incremental cost-effectiveness ratio by over 10% and choosing the log-logistic and generalised gamma distributions increased the incremental cost-effectiveness ratio. Other influential scenarios included choosing different baseline survival curve sources for each comparator.

Trastuzumab deruxtecan vs eribulin

Scenario analyses for the analysis vs. eribulin are presented in Table 26. Comparing against eribulin data in the HER2-positive population from the Barni 2019 study still resulted in an incremental cost-effectiveness ratio below £50,000 per quality-adjusted life-year.

Table 26: T-DXd vs eribulin - scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	£35,833	-
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	£41,700	16.4%
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	£38,037	6.2%
No discounting	[redacted]	[redacted]	£33,148	-7.5%
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	£32,780	-8.5%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
OS: Anchoring to eribulin (Cortes 2011, no censoring)	[redacted]	[redacted]	£44,494	24.2%
No HER2 adjustment	[redacted]	[redacted]	£36,269	1.2%
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	£36,581	2.1%
Utility - progression free - equal to Le et al	[redacted]	[redacted]	£36,797	2.7%
Utility - progressed - TA423 company value	[redacted]	[redacted]	£34,393	-4.0%
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	£35,921	0.2%
Utility - progressed - Le et al	[redacted]	[redacted]	£37,327	4.2%
Utility - progressed - TA423 ERG	[redacted]	[redacted]	£37,399	4.4%
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	£33,012	-7.9%
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	£33,429	-6.7%
No vial sharing	[redacted]	[redacted]	£37,911	5.8%
100% vial sharing	[redacted]	[redacted]	£33,755	-5.8%
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	£35,828	0.0%
No age adjusted utilities	[redacted]	[redacted]	£34,945	-2.5%
Eribulin OS: Using EMBRACE - weibull distribution	[redacted]	[redacted]	£35,720	-0.3%
Eribulin OS: Using EMBRACE - Exponential distribution	[redacted]	[redacted]	£36,092	0.7%
Eribulin OS: Using EMBRACE - log-normal distribution	[redacted]	[redacted]	£36,140	0.9%
Eribulin OS: Using EMBRACE - log-logistic distribution	[redacted]	[redacted]	£36,077	0.7%
Eribulin OS: Using EMBRACE - gompertz distribution	[redacted]	[redacted]	£35,603	-0.6%
Eribulin OS: Using Barni - weibull distribution	[redacted]	[redacted]	£38,174	6.5%
Eribulin OS: Using Barni - Exponential distribution	[redacted]	[redacted]	£39,461	10.1%
Eribulin OS: Using Barni - log-normal distribution	[redacted]	[redacted]	£39,615	10.6%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Eribulin OS: Using Barni - log-logistic distribution	[redacted]	[redacted]	£40,134	12.0%
Eribulin OS: Using Barni - gompertz distribution	[redacted]	[redacted]	£37,949	5.9%
Eribulin OS: Using Barni - gen. gamma distribution	[redacted]	[redacted]	£40,001	11.6%
Eribulin OS: Using Cortes 2010 - weibull distribution	[redacted]	[redacted]	£35,708	-0.3%
Eribulin OS: Using Cortes 2010 - Exponential distribution	[redacted]	[redacted]	£35,505	-0.9%
Eribulin OS: Using Cortes 2010 - log-normal distribution	[redacted]	[redacted]	£35,776	-0.2%
Eribulin OS: Using Cortes 2010 - log-logistic distribution	[redacted]	[redacted]	£35,892	0.2%
Eribulin OS: Using Cortes 2010 - gompertz distribution	[redacted]	[redacted]	£35,677	-0.4%
Eribulin OS: Using Cortes 2010 - gen. gamma distribution	[redacted]	[redacted]	£35,787	-0.1%
Eribulin OS: Using Gamucci 2014 - weibull distribution	[redacted]	[redacted]	£38,845	8.4%
Eribulin OS: Using Gamucci 2014 - Exponential distribution	[redacted]	[redacted]	£40,723	13.6%
Eribulin OS: Using Gamucci 2014 - log-normal distribution	[redacted]	[redacted]	£40,442	12.9%
Eribulin OS: Using Gamucci 2014 - log-logistic distribution	[redacted]	[redacted]	£40,028	11.7%
Eribulin OS: Using Gamucci 2014 - gompertz distribution	[redacted]	[redacted]	£38,766	8.2%
Eribulin OS: Using Gamucci 2014 - gen. gamma distribution	[redacted]	[redacted]	£50,562	41.1%
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	£32,921	-8.1%
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	£28,236	-21.2%
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	£28,923	-19.3%
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	£44,366	23.8%
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	£39,424	10.0%
T-DXd PFS distribution - exponential	[redacted]	[redacted]	£38,088	6.3%
T-DXd PFS distribution - weibull	[redacted]	[redacted]	£39,028	8.9%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	£36,055	0.6%
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	£38,736	8.1%
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	£32,890	-8.2%
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	£36,279	1.2%
T-DXd TTD distribution - weibull	[redacted]	[redacted]	£33,794	-5.7%
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	£41,264	15.2%
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	£38,733	8.1%
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	£33,189	-7.4%
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	£37,408	4.4%

Abbreviations: AE, adverse event; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS, progression free survival; QALYs, quality adjusted life year; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Trastuzumab deruxtecan vs capecitabine

Scenario analyses for the analysis vs. capecitabine are presented in Table 27.

Table 27: T-DXd vs capecitabine - scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	£47,230	-
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	£57,844	22.5%
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	£51,148	8.3%
No discounting	[redacted]	[redacted]	£42,577	-9.9%
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	£42,890	-9.2%
OS: Anchoring to eribulin	[redacted]	[redacted]	£63,225	33.9%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
No HER2 adjustment	[redacted]	[redacted]	£47,230	0.0%
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	£48,382	2.4%
Utility - progression free - equal to Le et al	[redacted]	[redacted]	£48,722	3.2%
Utility - progressed - TA423 company value	[redacted]	[redacted]	£46,060	-2.5%
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	£47,366	0.3%
Utility - progressed - Le et al	[redacted]	[redacted]	£48,406	2.5%
Utility - progressed - TA423 ERG	[redacted]	[redacted]	£48,462	2.6%
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	£45,393	-3.9%
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	£45,745	-3.1%
No vial sharing	[redacted]	[redacted]	£49,939	5.7%
100% vial sharing	[redacted]	[redacted]	£44,522	-5.7%
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	£47,093	-0.3%
No age adjusted utilities	[redacted]	[redacted]	£45,968	-2.7%
OS - Cap: Using Fumoleau 2004 - Weibull distribution	[redacted]	[redacted]	£43,714	-7.4%
OS - Cap: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	£43,772	-7.3%
OS - Cap: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	£45,625	-3.4%
OS - Cap: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	£45,396	-3.9%
OS - Cap: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	£43,355	-8.2%
OS - Cap: Using Fumoleau 2004 - gompertz distribution	[redacted]	[redacted]	£43,527	-7.8%
OS - Cap: Using Blum 2001 - weibull distribution	[redacted]	[redacted]	£41,330	-12.5%
OS - Cap: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	£41,352	-12.4%
OS - Cap: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	£42,358	-10.3%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
OS - Cap: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	£42,007	-11.1%
OS - Cap: Using Blum 2001 - gompertz distribution	[redacted]	[redacted]	£41,207	-12.8%
OS - Cap: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	£41,368	-12.4%
OS - Cap: Using Cameron 2010 - Exponential distribution	[redacted]	[redacted]	£47,325	0.2%
OS - Cap: Using Cameron 2010 - log-normal distribution	[redacted]	[redacted]	£49,210	4.2%
OS - Cap: Using Cameron 2010 - log-logistic distribution	[redacted]	[redacted]	£50,333	6.6%
OS - Cap: Using Cameron 2010 - gompertz distribution	[redacted]	[redacted]	£47,162	-0.1%
OS - Cap: Using Cameron 2010 - gen. gamma distribution	[redacted]	[redacted]	£47,371	0.3%
OS - TH3RESA: Using exponential distribution	[redacted]	[redacted]	£42,213	-10.6%
OS - TH3RESA: Using log-normal distribution	[redacted]	[redacted]	£34,453	-27.1%
OS - TH3RESA: Using log-logistic distribution	[redacted]	[redacted]	£35,536	-24.8%
OS - TH3RESA: Using gompertz distribution	[redacted]	[redacted]	£62,305	31.9%
OS - TH3RESA: Using weibull distribution	[redacted]	[redacted]	£53,485	13.2%
PFS - T-DXd distribution - exponential	[redacted]	[redacted]	£48,692	3.1%
PFS - T-DXd distribution - weibull	[redacted]	[redacted]	£51,279	8.6%
PFS - T-DXd distribution - log-logistic	[redacted]	[redacted]	£47,230	0.0%
PFS - T-DXd distribution - gompertz	[redacted]	[redacted]	£49,685	5.2%
PFS - T-DXd distribution - gen. gamma	[redacted]	[redacted]	£43,168	-8.6%
HR vs. T-DXd applied through median for Eribulin	[redacted]	[redacted]	£47,230	0.0%
TTD - T-DXd distribution - weibull	[redacted]	[redacted]	£44,877	-5.0%
TTD - T-DXd distribution - log-logistic	[redacted]	[redacted]	£53,495	13.3%
TTD - T-DXd distribution - log-normal	[redacted]	[redacted]	£50,576	7.1%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
TTD - T-DXd distribution - gompertz	[redacted]	[redacted]	£44,178	-6.5%
TTD - T-DXd distribution - gen.gamma	[redacted]	[redacted]	£49,047	3.8%

Abbreviations: AE, adverse event; cap, capecitabine ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis; PFS, progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Trastuzumab deruxtecan vs vinorelbine

Scenario analyses for the analysis vs. vinorelbine are presented in Table 28.

Table 28: T-DXd vs vinorelbine - scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	£44,170	-
OS: HR T-DXd versus TH3RESA (no censoring), gamma distribution	[redacted]	[redacted]	£53,944	22.1%
OS: HR T-DXd versus TH3RESA (no censoring), exponential distribution	[redacted]	[redacted]	£47,767	8.1%
No discounting	[redacted]	[redacted]	£39,950	-9.6%
Discount rate of 1.5% for outcomes	[redacted]	[redacted]	£40,086	-9.2%
OS: Anchoring to eribulin	[redacted]	[redacted]	£58,916	33.4%
No HER2 adjustment	[redacted]	[redacted]	£44,170	0.0%
Utility - progression free - T-DXd equal to Eribulin	[redacted]	[redacted]	£45,255	2.5%
Utility - progression free - equal to Le et al	[redacted]	[redacted]	£45,387	2.8%
Utility - progressed - TA423 company value	[redacted]	[redacted]	£42,981	-2.7%
Utility value - progression free - off treatment - Le et al	[redacted]	[redacted]	£44,298	0.3%
Utility - progressed - Le et al	[redacted]	[redacted]	£45,370	2.7%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Utility - progressed - TA423 ERG	[redacted]	[redacted]	£45,427	2.8%
Duration of subsequent treatment costs = 6 months	[redacted]	[redacted]	£42,239	-4.4%
Source of subsequent treatment cost = TA423	[redacted]	[redacted]	£42,559	-3.6%
No vial sharing	[redacted]	[redacted]	£46,878	6.1%
100% vial sharing	[redacted]	[redacted]	£41,463	-6.1%
100% hospitalisation for non-TDXd AE's	[redacted]	[redacted]	£44,141	-0.1%
No age adjusted utilities	[redacted]	[redacted]	£42,983	-2.7%
OS - Cap: Using Fumoleau 2004 - Weibull distribution	[redacted]	[redacted]	£40,937	-7.3%
OS - Cap: Using Fumoleau 2004 - exponential distribution	[redacted]	[redacted]	£41,007	-7.2%
OS - Cap: Using Fumoleau 2004 - log-normal distribution	[redacted]	[redacted]	£42,679	-3.4%
OS - Cap: Using Fumoleau 2004 - log-logistic distribution	[redacted]	[redacted]	£42,470	-3.8%
OS - Cap: Using Fumoleau 2004 - gen. gamma distribution	[redacted]	[redacted]	£40,618	-8.0%
OS - Cap: Using Fumoleau 2004 - Gompertz distribution	[redacted]	[redacted]	£40,770	-7.7%
OS - Cap: Using Blum 2001 - Weibull distribution	[redacted]	[redacted]	£39,215	-11.2%
OS - Cap: Using Blum 2001 - Exponential distribution	[redacted]	[redacted]	£39,255	-11.1%
OS - Cap: Using Blum 2001 - log-normal distribution	[redacted]	[redacted]	£40,170	-9.1%
OS - Cap: Using Blum 2001 - log-logistic distribution	[redacted]	[redacted]	£39,842	-9.8%
OS - Cap: Using Blum 2001 - Gompertz distribution	[redacted]	[redacted]	£39,111	-11.5%
OS - Cap: Using Blum 2001 - gen. gamma distribution	[redacted]	[redacted]	£39,248	-11.1%
OS - Cap: Using Cameron 2010 - Exponential distribution	[redacted]	[redacted]	£44,266	0.2%
OS - Cap: Using Cameron 2010 - log-normal distribution	[redacted]	[redacted]	£45,980	4.1%
OS - Cap: Using Cameron 2010 - log-logistic distribution	[redacted]	[redacted]	£47,008	6.4%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
OS - Cap: Using Cameron 2010 - Gompertz distribution	[redacted]	[redacted]	£44,114	-0.1%
OS - Cap: Using Cameron 2010 - gen. gamma distribution	[redacted]	[redacted]	£44,296	0.3%
TH3RESA OS: Using exponential distribution	[redacted]	[redacted]	£39,580	-10.4%
TH3RESA OS: Using log-normal distribution	[redacted]	[redacted]	£32,525	-26.4%
TH3RESA OS: Using log-logistic distribution	[redacted]	[redacted]	£33,512	-24.1%
TH3RESA OS: Using gompertz distribution	[redacted]	[redacted]	£58,163	31.7%
TH3RESA OS: Using weibull distribution	[redacted]	[redacted]	£49,947	13.1%
T-DXd PFS distribution - exponential	[redacted]	[redacted]	£46,065	4.3%
T-DXd PFS distribution - weibull	[redacted]	[redacted]	£48,156	9.0%
T-DXd PFS distribution - log-logistic	[redacted]	[redacted]	£44,259	0.2%
T-DXd PFS distribution - gompertz	[redacted]	[redacted]	£46,990	6.4%
T-DXd PFS distribution - gen. gamma	[redacted]	[redacted]	£40,289	-8.8%
HR vs. T-DXd applied through median, for Eribulin and Capecitabine	[redacted]	[redacted]	£44,170	0.0%
T-DXd TTD distribution - weibull	[redacted]	[redacted]	£41,794	-5.4%
T-DXd TTD distribution - log-logistic	[redacted]	[redacted]	£50,497	14.3%
T-DXd TTD distribution - log-normal	[redacted]	[redacted]	£47,550	7.7%
T-DXd TTD distribution - gompertz	[redacted]	[redacted]	£41,087	-7.0%
T-DXd TTD distribution - gen.gamma	[redacted]	[redacted]	£46,005	4.2%

Abbreviations: AE, adverse event; cap, capecitabine; ERG; evidence review group; ICER, incremental cost-effectiveness ratio; gen. gamma, generalised gamma; MAIC, matched adjusted indirect comparison; OS, overall survival OWSA, one way sensitivity analysis;; PFS progression free survival; QALYs, quality adjusted life year;T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation

Summary of base-case results and sensitivity analysis (superseding Addendum, Section 3.2.7)

When the proposed patient access scheme for trastuzumab deruxtecan is applied, trastuzumab deruxtecan is associated with a base-case incremental cost-effectiveness ratio of £47,230. Given that end-of-life criteria are expected to apply, trastuzumab deruxtecan may be considered a cost-effective use of national health service resources. The approach taken to model trastuzumab deruxtecan in the base-case was informed by clinical expert opinion and aims to more accurately model overall survival in a HER2-targeted therapy.

The results of sensitivity analyses demonstrate that in all cases trastuzumab deruxtecan is expected to provide a significant increase in quality-adjusted life-years vs. each comparator.

Deterministic analyses showed that the most influential parameter was the hazard ratio for trastuzumab deruxtecan vs. TH3RESA that defined the survival extrapolations in overall survival; this is to be expected as the cost-effectiveness results are primarily driven by survival gains. Beyond this parameter, the impact of varying other parameters in the model was small.

Scenario analyses showed that the parameter with the most influence on the incremental cost-effectiveness ratio was the distribution chosen to model TH3RESA overall survival. Other key assumptions were the distribution used to model time-to-discontinuation for trastuzumab deruxtecan, the source of comparator efficacy data and the hazard ratio used vs. TH3RESA. Only nine of the 40 scenarios considered comparing trastuzumab deruxtecan vs. capecitabine resulted in an incremental cost-effectiveness ratio higher than £50,000 per quality-adjusted life-year; only two of these scenarios resulted in an incremental cost-effectiveness ratio higher than £60,000 per quality-adjusted life-year.

Probabilistic analysis indicated that there is a [redacted]% likelihood of trastuzumab deruxtecan being cost-effective at a willingness to pay threshold of £50,000 per quality-adjusted life-year.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- 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.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **7 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1. Your name	**Professor Peter Schmid**
2. Name of organisation	**Barts Health NHS Trust**
3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
The aim of treatment for HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment for HER2-positive metastatic breast cancer (MBC) after 2 or more anti-HER2 therapies is the same as the overall aim of treatment for advanced breast cancer, which is to improve and extend the lives of women and men living with MBC. Whilst the impact of treatments on extending lives is clearly demonstrated through overall survival (OS) benefits, improving the lives of patients can be captured by a number of parameters, including maintenance or improvement of quality of life (QoL), delay in disease progression, induction of an objective tumour response (which is linked with improvement of tumour-associated symptoms), induction of disease control (which is often defined as a reduction in the size of the disease or disease stabilisation for a certain period of time) or the duration of response or clinical benefit. In addition, treatment-related adverse effects have to be taken into consideration.
9. What do you consider a clinically significant treatment response? (For example, a	Whilst the criteria for assessing a treatment response are generally well defined for all the endpoints listed above, a clinically significant treatment response is largely dependent on the treatment indication. In patients with HER2-positive MBC who have received 2 or more prior lines of anti-HER2 therapies, treatment options are currently limited. The median progression-free survival (PFS) with standard therapy is around 3.3-5.6

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	months at best with response rates between 9% and 26.7%. These results can serve as a benchmark in this indication.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Patients with HER2-positive MBC who have received 2 or more prior lines of anti-HER2 therapies have built up treatment resistance and treatment options are currently limited. Given the limited efficacy of chemotherapy as outlined above, there remains a high unmet need for effective treatments in these patients.
What is the expected place of trastuzumab deruxtecan in current practice?	
11. How is the condition currently treated in the NHS?	in the NHS, the current standard first-line therapy for patients previously untreated with anti-HER2 therapy is the combination of Taxane-based chemotherapy with trastuzumab and pertuzumab based on the established OS survival benefit compared to chemotherapy + trastuzumab in this population. After first-line trastuzumab-based therapy, T-DM1 is generally used as 2nd line therapy based on the OS benefit in randomised trials. As currently only 2 lines of HER2-targeted therapy are funded in the NHS, patients with HER2-positive MBC after 2 or more anti-HER2 therapies generally receive single agent chemotherapy, e.g. capecitabine, vinorelbine or eribulin. In some regions in England, some patients are able to access further HER2-targeted treatments through clinical trials or expanded access programmes.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The international advanced breast cancer (ABC) guidelines state that “Patients progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway. The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered and the relapse-free interval. The optimal sequence of all available anti-HER2 therapies is currently unknown. The optimal duration of anti-HER2 therapy for ABC (i.e. when to stop these agents) is currently unknown”.

	Whilst the benefit for 2nd line HER2-targeted therapy is clearly established based on the OS benefit in randomised trials, the benefits of subsequent HER2-targeted therapy are less well characterised which is reflected in the guideline statement on "optimal duration". The ABC guidelines state that "For later lines of therapy, trastuzumab can be administered with several chemotherapy agents, including but not limited to, vinorelbine (if not given in first line), taxanes (if not given in first line), capecitabine, eribulin, liposomal anthracyclines, platinums, gemcitabine or metronomic CM. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability." The most recent ABC5 guidelines also state that "Trastuzumab deruxtecan (T-DXd; DS-8201) showed important activity in heavily pre-treated patients with HER2-positive ABC (median lines of therapy: 6) and is a treatment option in this setting, where approved." Furthermore, the ABC5 guidelines stated that "Dual blockade with tucatinib + trastuzumab + capecitabine showed a small benefit in median PFS (2 months) and median OS (4 months) over trastuzumab + capecitabine in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with brain metastases, at the expense of higher toxicity (i.e. diarrhoea)" and recommended that "If approved, it can be considered a treatment option in this setting".
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Whilst oncologists would generally consider giving more than 2 lines of HER2-targeted treatment in MBC, the current NHS pathway does not reimburse HER2-targeted treatment in patients who have already received 2 lines of HER2-targeted treatment in MBC, limiting treatment options to chemotherapy alone. However, in some regions in England, some patients are able to access further HER2-targeted treatments through clinical trials or expanded access programmes.
• What impact would the technology have on the current pathway of care?	Given the high activity of T-DXd and the unmet need, it is expected that T-DXd would have a significant impact on the management of patients with HER2-positive MBC after at least 2 anti-HER2 therapies, establishing a new standard of care in this setting with markedly improved treatment outcomes.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	T-DXd is currently not available in the NHS. Patients with HER2-positive MBC after 2 or more anti-HER2 therapies currently have access to chemotherapy, but not to further HER2-targeted treatment. The efficacy of chemotherapy alone is limited in this setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	T-DXd should be given in cancer centres specialised in the management of patients with metastatic breast cancer
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Beyond the costs associated with the application of T-DXd, there is no obvious need for further investment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The benefits of chemotherapy without HER2-targeted therapy are well established but generally limited in patients with HER2-positive MBC and 2 or more prior anti-HER2 therapies. In recent phase 3 trials in patients with HER2-positive MBC and at least 2 prior anti-HER2 therapies (THERESA, SOPHIA, NALA, HER2CLIMB), the median PFS in the control arms (chemotherapy + HER2-targeted therapy) was 3.3-5.6 months with response rates between 9% and 26.7% and a median OS of 15.8-19.8 months. The current experience with T-DXd suggests substantially increased and clinically meaningful benefits. With a median PFS of 16.4 months (95% CI: 12.7, not evaluable [NE]) and an objective response rate of 60.9% (95% CI: 53.4, 68.0), the outcomes with T-DXd are substantially better compared to any other trial in this setting. The fact that

	the best response to prior T-DM1 in the DESTINY-Breast01 trial was only 21.7% makes it highly unlikely that the high activity of T-DXd was a result of patient selection and instead suggest superior efficacy.
• Do you expect the technology to increase length of life more than current care?	The DESTINY-Breast01 study provides mature results for the primary endpoint objective response rates (ORR) and for the key secondary endpoints PFS, clinical benefit rate (CBR), disease control rate (DCR) and duration of response (DOR), but OS data are still immature. ORR, PFS, CBR, DCR and DOR clearly demonstrate substantially higher activity compared to other treatments in the same setting. The OS data are immature and the median OS has not been reached but the estimated OS rates of 86.2% (95% CI, 79.8 to 90.7) at 12 months compare very favourably with the median OS of 15-19 months in other phase 3 trials in this setting, many of them with a less heavily pre-treated population.
• Do you expect the technology to increase health-related quality of life more than current care?	As Health-related quality of life data are currently not available for T-DXd in this indication, the impact of T-DXd on QoL can only be assessed indirectly. In MBC, there is a clear link between objective responses (which can be associated with improvement of cancer-related symptoms), progression-free survival (which is associated with a delay or prevention of the deterioration of symptoms and/or QoL) and treatment-emergent adverse events. The substantial benefits of T-DXd seen in terms of objective response rates and PFS together with the well characterised safety profile make it highly likely that T-DXd will substantially increase health-related quality of life more than current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	T-DXd is generally indicated in all patients with HER2-positive MBC after 2 or more anti-HER2 therapies, provided there are no contraindications to the use of T-DXd. Administration of T-DXd to pregnant women is not recommended, and patients should be informed of the potential risks to the foetus before they become pregnant. The DESTINY-Breast01 study demonstrated that T-DXd has consistent efficacy across all clinically relevant subgroups, including previous receipt of pertuzumab, hormone receptor status, receipt of T-DXd immediately after initial T-DM1 therapy, number of prior regimens (≥3 and <3 prior regimens, excluding hormone therapy) and in patients with CNS (brain) metastases at baseline.
The use of the trastuzumab deruxtecan	

15. 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.)	As for all Her2-targeted treatment, it is advisable that T-DXd is administered at cancer centres that have experience with treating patients with HER2-positive MBC. With the exception of ILD/pneumonitis, the safety profile and administration of T-DXd does not seem to be substantially different from other HER2-targeted treatments, and consequently, there are no specific additional requirements. Cardiac monitoring is standard at all centres using HER2-targeted agents. The main implication of the introduction of T-DXd are early recognition and optimal management of ILD/pneumonitis. This will initially require some training although ILD/pneumonitis is a well-established side effect with many anti-cancer therapies, including commonly used breast cancer drugs such as everolimus or atezolizumab, but also occasionally trastuzumab. Resources for monitoring patients should be available at sites with limited capacity impact.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard oncology rules will be applied to start and stop treatment with T-DXd. As for all treatments in MBC, treatment should be continued as long as patients benefit, which generally means there is no evidence of disease progression and the treatment is well tolerated. This should not require additional testing over and above the current standards of care
17. 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 QALY calculation for T-DXd at this stage is not without challenges given the non-randomised clinical trial data, the immature OS data and the lack of QoL data. Nevertheless, the substantial clinical activity demonstrated in the response rates, the duration of response and the progression-free survival, together with the established safety profile suggest substantial health-related benefits

the quality-adjusted life year (QALY) calculation?	
18. 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 improve the way that current need is met?	T-DXd is a highly innovative, targeted anticancer drug that is expected to have a significant and clinically meaningful impact on the management and outcome of patients with HER2-postiive MBC and more than 2 prior lines of HER2-targeted therapy.
• Is the technology a 'step-change' in the management of the condition?	As outlined above, the current experience with T-DXd suggests a substantial and clinically meaningful impact on health-related benefits. With a median PFS of 16.4 months (95% CI: 12.7, NE) and an objective response rate of 60.9% (95% CI: 53.4, 68.0), the outcomes with T-DXd are substantially better compared to any other trial in this setting, suggesting this constitutes a step-change in the management of patients with HER2-positive MBC and 2 or more prior anti-HER2 therapies.
• Does the use of the technology address any particular unmet need of the patient population?	The current experience with T-DXd clearly indicates that the efficacy of T-DXd substantially exceeds those of currently available treatments in this difficult to treat population with increasing drug resistance and a high unmet clinical need. Given that patients on this treatment indication are often symptomatic and experience rapid disease progression, the high response rates with T-DXd together with the long PFS are of particular relevance in this patient population. Importantly, efficacy in patients with brain metastases seemed to be similar to the overall population, which is particularly encouraging given the limited treatment options and high unmet need of this subgroup of patients (ORR: 58.3% (95% CI: 36.6, 77.9); median PFS: 18.1 months (95% CI: 6.7, 18.1).
19. How do any side effects or adverse effects of the technology	The treatment-emergent adverse events associated with T-DXd are largely consistent with safety profiles of chemotherapy regimens alone or in combination with HER2-targted therapy. Gastrointestinal and haematological

affect the management of the condition and the patient's quality of life?	adverse events were the most common side effects but were generally mild to moderate. They were generally manageable without a need for treatment discontinuation. Although other HER2-targeted therapies, have been associated with a risk of cardiomyopathy, clinically significant cardiotoxicity was not observed in DESTINY-Breast01 or in the DS8201-A-J101 study. Nevertheless, cardiac monitoring as with other HER2-targeted agents seems advisable. T-DXd was associated with a risk of ILD/pneumonitis in 13.6% of patients, which led to death in some patients. Guidelines for early recognition and management have been developed, minimising the risks and possible impact on patient's QoL.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials with T-DXd were, in part, conducted in the UK. The patient population in the trial is reflective of the UK practice in terms of disease characteristics and pre-treatment, although patients in the trial might have received more prior HER2-targeted treatments than currently reimbursed in the NHS. The efficacy of T-DXd might be even higher than described in the DESTINY-Breast01, if patients have received fewer lines of HER2-targeted therapy, suggesting that patients in the UK might possible derive an even greater benefit
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	As outlined above, the current experience with T-DXd demonstrates substantial and clinically meaningful activity. Response rates seems to be at least twice as high compared to other trials in this setting and responses are very durable. The median time to response of 1.6 months also suggests a rapid response and therefore benefit to the treatment. Importantly, efficacy in patients with brain metastases seemed to be similar to the overall population, which is particularly encouraging given the limited treatment options and high unmet need of this subgroup of patients. Key outcome measures in the DESTINY-Breast01trial are: • a median PFS of 16.4 months (95% CI: 12.7, NE) • an objective response rate of 60.9% (95% CI: 53.4, 68.0) based on independent central review (ICR) • a median duration of response (DoR) of 14.8 months (95% CI: 13.8, 16.9) • a disease control rate (DCR) of 97.3% (95% CI: 93.8, 99.1) • a clinical benefit rate (CBR) of 76.1% (95% CI: 69.3, 82.1)

	The results in the Study DS8201-A-J101 trial are very similar, providing further support for the technology. Overall, the outcomes with T-DXd are substantially better compared to any other trial in this setting, suggesting this a step-change in the management of patients with HER2-positive MBC and 2 or more prior anti-HER2 therapies.
• 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?	N/A
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA423?	N/A

23. How do data on real-world experience compare with the trial data?	Real-world data are currently not available with T-DXd.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equity or equality issues are anticipated for the appraisal of T-DXd within the NHS. Equality issues might be arising if access to T-DXd is possible outside the NHS.
24b. Consider whether these issues are different from issues with current care and why.	N/A

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has 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 ERG report, these will also be considered by the committee.	
Key issue 1: Immature DESTINY-Breast01 study data	The DESTINY-Breast01 study provides mature results for the primary endpoint objective response rates (ORR) and for the secondary endpoint PFS, clinical benefit rate (CBR), disease control rate (DCR) and duration of response (DOR), but the OS data are still immature. ORR, PFS, CBR, DCR and DOR clearly demonstrate substantially higher activity compared to other treatments in the same setting. The OS data are immature and the median OS has not been reached but the estimated OS rates of 86.2% (95% CI, 79.8 to 90.7) at 12 months make compare very favourably with the median OS of 15-19 months in other phase 3 trials in this setting, many of them with less heavily pre-treated patients.
Key issue 2: Lack of direct effectiveness evidence for the comparison of T-DXd versus relevant comparators	Whilst the current evidence for T-DXd is limited to a non-randomised phase 2 trial, there a several randomised phase 3 trials of other agents/combinations in patients with HER2-positive MBC with at least 2 prior lines of anti-HER2 therapies (THERESA, SOPHIA, NALA, HER2CLIMB); the control arms of these trials used combinations of chemotherapy and HER2-targeted therapies and provide an excellent benchmark for the efficacy of cancer treatments in this setting. The median PFS in the control arms was 3.3-5.6 months with response rates between 9% and 26.7% and a median overall survival of 15.8-19.8 months.

	Considering that the efficacy of the combination of chemotherapy and HER2-targeted therapy in the control arms should be at least as high (and likely higher) than what is commonly achieved with chemotherapy alone, these trials provide an excellent comparator for the DESTINY-Breast01 trial With a median PFS of 16.4 months (95% CI: 12.7, not evaluable [NE]) and an objective response rate of 60.9% (95% CI: 53.4, 68.0) based on independent central review (ICR) the results with T-DXd are substantially higher compared to any other trial in this setting. This has to be considered despite the lack of a direct comparator. The fact that the best response to prior T-DM1 in the DESTINY-Breast01 was only 21.7% makes it highly unlikely that the high activity of T-DXd is a result of patient selection.
Key issue 3: Relevance of DESTINY-Breast01 study results to NHS clinical practice	The DESTINY-Breast01 study results are highly relevant to the current NHS practice. The patient population treated in the trial is representative of the current UK population of patients with HER2-positive MBC and at least 2 prior anti-HER2 therapies. All patients in the DESTINY-Breast01 trial had received prior T-DM1 and the majority of patients had also received prior trastuzumab plus pertuzumab, which are the standard 1st and 2nd line treatments in the UK. As more than half of patients in the trial had received additional anti-HER2 therapy, the population is possibly slightly more pre-treated with HER2-targeted agents; considering that additional lines of HER2-targeted pre-treatment could result in a lower probability of response, UK could possibly experience an even higher benefit from T-DXd than observed in DESTINY-Breast01.
Key issue 4: Company eribulin and capecitabine MAIC results are not suitable for decision-making	In accordance with the NICE methodology, Eribulin and capecitabine have been selected as comparators for the matching-adjusted indirect analysis. This is based on the fact that Eribulin and Capecitabine are currently the main treatments available in the NHS for these patients. These recommendations are not specific to HER2+ patients and the trials results with Eribulin and Capecitabine include patients with all breast cancer subtypes. Whilst there are clearly limitations with the available datasets, the selection of these comparators is ultimately based on the currently available treatments in the NHS. On the other hand, it is also important to look beyond the standard NICE criteria for indirect and mixed treatment comparisons. Several randomised phase 3 trials have recently been evaluating novel agents/combinations in patients with HER2-positive MBC after 2 or more anti-HER2 therapies; the control arms of these trials provide an excellent benchmark for the efficacy of cancer treatments in this setting (although might be slightly more effective than the current NHS standard). Most of these phase 3 trials use combinations of chemotherapy and HER2-targeted therapy for the control arm. Although the use of HER2-targeted treatment is currently not reimbursed in the NHS in patients with HER2-

	positive MBC and 2 or more anti-HER2 therapies, as the added benefit to chemotherapy has not definitively been established, the control arms of these trials are likely to provide better and more relevant comparators than chemotherapy alone in unselected patients (including patients with ER-positive or triple-negative breast cancer. Consequently, the efficacy of the combination of chemotherapy and HER2-targeted therapy in the control arms should be at least as high (and likely higher) than what is commonly achieved with chemotherapy alone, thus possibly over-estimating the benefit of the currently available standard treatments in the NHS if used as a benchmark for treatment comparisons. In recent phase 3 trials in patients with HER2-positive MBC and 2 or more prior anti-HER2 therapies (THERESA, SOPHIA, NALA, HER2CLIMB), the median PFS in the control arms (chemotherapy + HER2-targeted therapy) was 3.3-5.6 months with response rates between 9% and 26.7% and a median overall survival of 15.8-19.8 months. With a median PFS of 16.4 months (95% CI: 12.7, not evaluable [NE]) and an objective response rate of 60.9% (95% CI: 53.4, 68.0) based on independent central review (ICR), the results with T-DXd are substantially higher compared to any other trial in this setting which has to be taken into consideration, despite the lack of a direct comparator. The fact that the best response to prior T-DM1 in the DESTINY-Breast01 was only 21.7% makes it highly unlikely that the high activity of T-DXd is a result of patient selection.
Key issue 5: Company vinorelbine OS MAIC results are inconclusive	As outlined above, there are limitations in selection for comparators for the matching-adjusted indirect analysis as per NICE methodology.
Key issue 6: Company OS modelling of T-DXd is not robust	The OS data are immature and the median OS has not been reached; nevertheless, the estimated OS rates of 86.2% (95% CI, 79.8 to 90.7) at 12 months compare very favourably with the median OS of 15-19 months in other phase 3 trials in this setting, many of them with less heavily pre-treated patients.

Key issue 7: Company OS modelling of comparator treatments is not robust	Whilst there are limitations with modelling of the comparator treatments, the results compare well with data from the control arms of other recent phase 3 trials in patients with HER2-positive MBC with at least 2 prior lines of anti-HER2 therapies (THERESA, SOPHIA, NALA, HER2CLIMB)
Key issue 8: NICE End of Life criteria may not be met	The median OS of patients with HER2-positive MBC with at least 2 prior lines of anti-HER2 therapies and no access to further HER2-targeted therapy is <2 years. In the Theresa trial, which provided access to further HER2-targeted therapy in the control group (and therefore might have slightly better outcomes compared to standard UK practice), median OS was 15.8 months. In the absence of a comparative trial and mature OS data, a definitive answer on the potential OS benefit cannot be provided. However, considering that the median PFS with T-DXd in the DESTINY-Breast01 seems almost 10-12 months longer than what is commonly achieved in this setting with chemotherapy, it is expected that T-DXd will meet the NICE EoL criteria for OS benefit.
Are there any important issues that have been missed in the ERG report?	Whilst the ERG report follows the established criteria, it should be pointed out that some of the limitations could be addressed by considering the outcomes from the control arms of recent phase 3 trials in the same indication (even if they might slightly overestimate the efficacy of currently available therapies), as they are more reflective of the outcomes in HER2-positive disease, than data from trials across all breast cancer subtypes.
Additional technical team questions	
The DESTINY-Breast01 trial included patients with at least 2 previous therapies. Only [redacted]% had exactly received 2 previous therapies and other patients in the trial received ≥3 prior	The majority of patients in the DESTINY-Breast01 trial was heavily pre-treated. Only [redacted]% received T-DXd as 3rd line therapy. In addition, patients in the DESTINY-Breast01 trial might have received more prior HER2-targeted treatments than what is currently reimbursed in the NHS. Subgroup analyses demonstrate that patients achieved a confirmed ORR >50% regardless of the number of prior lines of systemic therapy they received; however, the highest ORR was observed in those who had received only two prior lines.

therapies. Is this representative of UK clinical practice? How would this impact overall survival (OS) and progression-free survival (PFS)?	Considering that patients in the UK are likely to have received fewer HER2-targeted therapies, it is plausible that the efficacy of T-DXd might be even higher in the UK clinical practice. The impact on lines of therapy on PFS and OS is well established. In the 1st line setting eg, the median PFS with HER2-targeted combination therapy is around 18 months, compared to a median PFS of around 9 months in the 2nd line setting and 3-6 months in 3rd and subsequent line setting. Similar trends are observed for OS. It is therefore conceivable, that the UK population might derive an even higher benefit if patients are less heavily pre-treated compared to the DESTINY-Breast01 trial.
Do you consider that patients with HER2-positive disease have worse prognosis than HER2-negative disease?	Before the introduction of HER2-targeted therapy, patients with HER2-positive breast cancer had a worse prognosis and outcome compared to patients with other subtypes. Effective HER2-taregted therapy has changed this to some degree and it is anticipated that the introduction of even more effective therapies such as T-DXd will continue to change this.
Do you expect patients who previously received trastuzumab emtansine (T-DM1) to survive longer compared to those who received other treatments in the previous lines?	Randomised trials have demonstrated an OS benefit with T-DM1 of 5-7 months; most of this benefit is considered to be a direct result of the treatment with T-DM1 and is therefore observed whilst patients are on treatment. It is unlikely that remaining OS from the time of progression on T-DM1 differs substantially from patients who have received alternative treatments up to a comparable timepoint.
The company's indirect treatment comparison compares DESTINY-Breast01 (100% HER2-positive patients and received T-DM1) to	The selection of the comparators is defined by the NICE submission criteria. As HER2-targeted therapy is currently not reimbursed in the NHS beyond 2 lines of treatment, patients receive a treatment that is not fully compatible with the standard in other countries, where HER2-targeted therapy would be continued for more than 2 lines. Modern trials are reflective of this and routinely used combinations of HER2-targeted therapy and chemotherapy in this setting. Consequently, data on chemotherapy alone can only be derived from relatively old trials, many of which will not provide subgroup-specific results.

<table>
<tr><td>other trials (mixed populations in terms of HER2 status). Do you consider that the MAIC (indirect treatment comparison) results are conservative?</td><td>It is therefore worthwhile looking at the control arms from several randomised phase 3 trials of other agents/combinations in patients with HER2-positive MBC with at least 2 prior lines of anti-HER2 therapies (THERESA, SOPHIA, NALA, HER2CLIMB); the control arms of these trials used combinations of chemotherapy and HER2-targeted therapies and provide an excellent benchmark for the efficacy of cancer treatments in this setting. The median PFS in the control arms was 3.3-5.6 months with response rates between 9% and 26.7% and a median overall survival of 15.8-19.8 months.

These data support the data provided in the MAIC</td></tr>
<tr><td>Are the company’s estimates of overall survival (OS) in the model plausible?

<table><tr><td colspan="3">OS with T-Dxd in the model</td></tr><tr><td>1 year</td><td>5 years</td><td>10 years</td></tr><tr><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr></table></td><td>It is difficult to comment on the OS estimates; the 1-year OS data seem robust but there is less certainty around longer-term estimates. [redacted]% at 5 years would seem optimistic with current treatments but is unclear whether this might be achievable with T-DXd</td></tr>
<tr><td>Do you consider that the TH3RESA trial (trastuzumab emtansine) is an appropriate source to derive overall survival for trastuzumab deruxtecan, in</td><td>The control arm of the Theresa trial would be an appropriate source as would be the control arms for other trials such as SOPHIA, NALA, or HER2CLIMB.</td></tr>
</table>

absence of mature data from DESTINY-Breast01 trial?	
What is the life expectancy of HER2+ patients who progress after receipt of T-DM1 as a second-line treatment and are fit enough for a third-line treatment?	The estimated median OS of patients in this situation without access to further HER2-taregeted therapy would be around 12-15 months

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- The current treatment options for patients with HER2-positive MBC and at least 2 prior lines of anti-HER2 therapies are limited and there remains a high unmet need for new effective treatments.
- Trastuzumab deruxtecan (T-DXd) is an innovative, HER2-targeted anticancer drug that has shown substantial activity in HER2-positive MBC with at least 2 prior lines of anti-HER2 therapies.
- With a median progression-free survival of 16.4 months and an objective response rate of 60.9%, the treatment outcomes with T-DXd are substantially better compared to other treatments currently available in this setting.
- The safety profile of T-DXd is well established
- The use of T-DXd is recommended as per international guidelines

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- 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.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **7 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want 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 15 pages.

PART 1 – Living with or caring for a patient with HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies and current treatment options	
About you	
1.Your name	**Mrs Claire Myerson**
2. Are you (please tick all that apply):	☒ a patient with HER2-positive unresectable or metastatic breast cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with HER2-positive unresectable or metastatic breast cancer? ☐ 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 below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it. I have also made some additional comments about my own experience – see below Part 1 Q6 & Q7 and Part 3 Key Messages ☐ 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/experience (e.g. 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
Living with the condition	
6. What is your experience of living with HER2-positive unresectable or metastatic breast cancer? If you are a carer (for someone with HER2-positive unresectable or metastatic breast cancer) please share your experience of caring for them.	I was diagnosed with HER2+ primary breast cancer in 2013 and then, in 2015, with metastatic breast cancer that has spread to the bones. Since diagnosis I have had the full range of available treatments: chemotherapy, radiotherapy, mastectomy & reconstructive surgery, as well as further chemotherapy & targeted therapy (Perjeta) for metastatic disease. After 3 cycles of Perjeta it was clear that this wasn't working & the tumour in my pelvis had continued to grow at 1cm per month. For the past 4 years I have been having IV treatments of the targeted therapy Kadcyla every 3 weeks (I am currently on cycle 74) which I will continue to take for as long as it works to keep the cancer at bay. 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. The drug makes me very nauseous, upsets my stomach, causes horrible nail, skin & sore mouth problems, makes my eyes & nose stream and gives me neuropathic pain in my feet like being stung by a thousand bees. But I'm still here. It's tolerable & it's keeping me alive.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I meet with my oncologist every 3 months. She has always been honest with me about my prognosis and that the life expectancy for patients with HER2+ MBC is <2 years. I know that nearly all patients in my position will eventually have progression and that there is currently no approved targeted therapy for MBC patients like me beyond Kadcyla. At every meeting we talk about what new treatments, if any, are on the horizon. I'm always looking for something which is effective and has similar or more tolerable side effects to Kadcyla from a quality of life point of view. It's always a pretty depressing conversation. There isn't anything else out there beyond Kadcyla, apart from broad spectrum chemotherapies. 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. As time goes on I also become more and more certain of my end of life choices & my wish to accept the end gracefully & avoid the kind of aggressive broad spectrum chemotherapy treatment that I experienced before I moved onto targeted therapy. It is very important to me to make clear that I don't want to be "napalmed" in the final weeks / months of my life: dying on chemotherapy in a hospital ward, after all that I have been through over these last years, would for me be such a failure & will not be a choice that I am likely to make. At the moment, Kadcyla is the only thing keeping me going, and so if there are no further targeted therapy treatments available to me then I will have run out of options.
8. If there are disadvantages for patients of **current NHS treatments** for HER2-positive unresectable or	

metastatic breast cancer after 2 or more anti-HER2 therapies (for example how trastuzumab deruxtecan is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of trastuzumab deruxtecan over current treatments on the NHS please describe these. For example, the impact 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/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	

Disadvantages of this treatment	
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 affects you have heard about, please describe them and explain why.	
Patient population	
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	

Equality	
12. Are there any potential equality issues that should be taken into account when considering HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-	

read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
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
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has 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 ERG report, these will also be considered by the committee.
ERG report key issues

Key issue 1: Immature DESTINY-Breast01 study data	
Key issue 2: Lack of direct effectiveness evidence for the comparison of T-DXd versus relevant comparators	
Key issue 3: Relevance of DESTINY-Breast01 study results to NHS clinical practice	
Key issue 4: Company eribulin and capecitabine MAIC results are not suitable for decision-making	
Key issue 5: Company vinorelbine OS MAIC results are inconclusive	

Key issue 6: Company OS modelling of T-DXd is not robust	
Key issue 7: Company OS modelling of comparator treatments is not robust	
Key issue 8: NICE End of Life criteria may not be met	
Are there any important issues that have been missed in ERG report?	
Additional technical team questions	
The DESTINY-Breast01 trial included patients with at least 2 previous therapies. Only [redacted]% had exactly received 2 previous therapies and other patients in the trial received ≥3	

prior therapies. Is this representative of UK clinical practice? How would this impact overall survival (OS) and progression-free survival (PFS)?	
Do you consider that patients with HER2-positive disease have worse prognosis than HER2-negative disease?	
Do you expect patients who previously received trastuzumab emtansine (T-DM1) to survive longer compared to those who did not receive it previously?	
The company's indirect treatment comparison compares DESTINY-Breast01	

<table>
<tr><td>(100% HER2-positive patients and received T-DM1) to other trials (mixed populations in terms of HER2 status). Do you consider that the MAIC (the indirect treatment comparison) results are conservative?</td><td></td></tr>
<tr><td>Are the company’s estimates of overall survival (OS) in the model plausible?

<table><tr><td colspan="3">OS with T-Dxd in the model</td></tr><tr><td>1 year</td><td>5 years</td><td>10 years</td></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td></td></tr>
<tr><td>Do you consider that the TH3RESA trial (trastuzumab emtansine) is an appropriate source to derive overall survival for trastuzumab</td><td></td></tr>
</table>

deruxtecan, in absence of mature data from DESTINY-Breast01 trial?	
What is the life expectancy of HER2+ patients who progress after receipt of T-DM1 as a second-line treatment and are fit enough for a third-line treatment?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- My experience as a metastatic breast cancer patient has shown me 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 experience has also made me certain of my end of life choices & my wish to accept the end gracefully and avoid the kind of aggressive broad spectrum chemotherapy treatment that I experienced before I moved onto targeted therapy
- T-DM1 (Kadcyla) is the last targeted therapy available on the NHS right now that I can try - I have seen the Kadcyla survival data and I know from the many friends who have sadly died from MBC that it is likely that it will eventually stop working and my cancer will progress again
- 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

- T-DXd is precisely that – a targeted therapy that, if approved, could give me a realistic option to prolong my life, with an acceptable quality of life, & most importantly live to see my children grow into young adults. Without it, I am out of options.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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TECHNICAL ENGAGEMENT RESPONSE FORM

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]

ERG response to company response to technical engagement

Note

The evidence provided by the company to support this appraisal comprises the company submission (CS) and additional evidence presented in an addendum to the CS that was submitted to NICE in November 2020. When responding to the technical engagement issues, the company has not identified the November 2020 addendum as new evidence; however, this is the first opportunity that the ERG has had to provide comment on the evidence presented in the addendum.

1. Key issue 1

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Immature DESTINY-Breast01 study data	**NO**	The ERG report states that: • The DESTINY-Breast01 study is immature, with median duration of follow-up of 11.1 months • Median overall survival has not been reached • Median progression-free survival and duration of response are uncertain. Company response: • The company submission to NICE was based on the August 2019 data cut from DESTINY-Breast01. • Following submission, data from the June 2020 data cut for DESTINY-Breast01 became available. • These new data have been submitted as an addendum at the start of Technical Engagement following agreement with NICE. • In the June 2020 data cut, preliminary median overall survival (with 35% death events occurring) is reported for the first time and more mature estimates of median progression-free survival and duration of response are available (Table 1).

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 1: Data from August 2019 and June 2020 data cuts
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Median, months (95% confidence interval)</th></tr>
<tr><th>August 2019 data cut</th><th>June 2020 data cut</th></tr>
<tr><td>Duration of follow-up</td><td>11.1
(0.7, 19.9)</td><td>20.5
(0.7, 31.4)</td></tr>
<tr><td>Overall survival</td><td>Median not reached</td><td>24.6
(23.1, not evaluable)</td></tr>
<tr><td>Progression-free survival</td><td>16.4
(12.7, not evaluable)</td><td>19.4
(14.1, not evaluable)</td></tr>
<tr><td>Duration of response</td><td>14.8
(13.8, 16.9)</td><td>20.8
(15.0, not evaluable)</td></tr>
</table>

Daiichi Sankyo consider trastuzumab deruxtecan to be a candidate for use within the Cancer Drugs Fund. If trastuzumab deruxtecan were recommended for use within the Cancer Drugs Fund, reappraisal would be possible using confirmatory, randomised data from DESTINY-Breast02 (the Phase III randomised controlled trial used to support the full marketing authorisation application in this indication; see Appendix A).
Of the last 10 drugs to be recommended for use within the Cancer Drugs Fund (August 2019 to present), 9 out of 10 recommendations were based on trial data in which median overall survival was not reached at the time of the original appraisal (2-10).

</td></tr>
<tr><td>ERG response to Key issue 1</td><td></td><td>Thank you for providing data from the June 2020 data cut. The ERG considers that the available OS data are still immature as at this time point, only 35.3% of patients had died. The updated PFS and DoR data are also still immature: 38.0% of patients had experienced a PFS event and 34.8% of patients had experienced a DoR event. However, the additional follow-up time means that, compared with data from the August</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		2019 data cut, data from fewer patients have been censored and therefore the median PFS and median DoR results are more robust than those presented in the CS.

2. Key issue 2

Key issue	Does this response contain new evidence, data or analyses?	Response

Key issue 2: Lack of direct effectiveness evidence for the comparison of T-DXd versus relevant comparators	**NO**	The ERG report states that:
		• There is no direct effectiveness evidence for the comparison of T-DXd versus eribulin, capecitabine or vinorelbine.
		
		Company response:
		• Single-arm trial data are available from the Phase II trial DESTINY-Breast01.
		  ○ The Committee for Medicinal Products for Human Use has adopted a positive opinion on the basis of these data.
		  ○ Trastuzumab deruxtecan has been approved in the US and in Japan, where it was assessed under the US Food and Drug Administration's Breakthrough Therapy and Priority Review programme and Japan's conditional early approval system.
		• A confirmatory, randomised Phase III trial (DESTINY-Breast02) is ongoing and is due to report in 1H 2022.
		• NICE decision-making on the basis of indirect comparison is common (11, 12), and the appropriate methods for this are well-documented by the NICE Decision Support Unit (13).
		  ○ All analyses presented in the company submission were performed in line with NICE Decision Support Unit guidance.
		• Eribulin, capecitabine and vinorelbine are not HER2-targeted therapies, and are therefore not included as monotherapies in the comparator arms of any current global trials for HER2-targeted therapies in third-line metastatic breast cancer such as trastuzumab deruxtecan; there are no NICE -recommended HER2-targeted therapies for third-line metastatic breast cancer.

Key issue	Does this response contain new evidence, data or analyses?	Response
		○ A strict requirement to provide direct effectiveness evidence versus eribulin, capecitabine and vinorelbine would therefore prevent any HER2-targeted therapy from being recommended in this patient population, where there remains a very high unmet need. • Of the last 10 drugs to be recommended for use within the Cancer Drugs Fund, 3 were based on Phase I or II single-arm trials (4, 5, 10). ○ One of these used methods suggested by the NICE Decision Support Unit on population-adjusted indirect comparisons, with the remainder using naïve comparisons for comparator data. • Daiichi Sankyo consider trastuzumab deruxtecan to be a candidate for use within the Cancer Drugs Fund; in this case, direct effectiveness evidence would be available versus trastuzumab + capecitabine and lapatinib + capecitabine from the DESTINY-Breast02 trial to inform the subsequent reappraisal. ○ The ERG report acknowledges on page 22 that the trastuzumab + capecitabine combination is commonly used in clinical practice in the UK (although not NICE-recommended or funded). ○ Trial data from DESTINY-Breast02 can be used to inform an indirect treatment comparison versus at least one comparator included in the NICE final scope for this appraisal.
ERG response to Key issue 2		No additional comment.

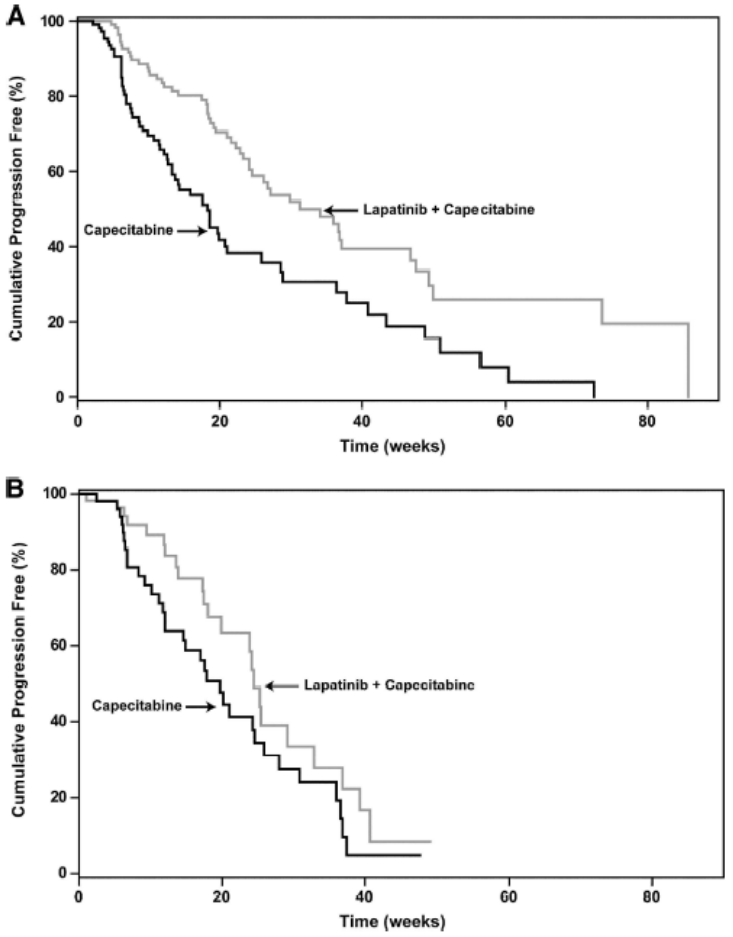
3. Key issue 3

Key issue	Does this response contain new evidence, data or analyses?	Response

Key issue 3: Relevance of DESTINY-Breast01 study results to NHS clinical practice	**YES**	The ERG report states that:
		• Trastuzumab deruxtecan is expected to be used at third line, but only 9.2% of patients in DESTINY-Breast01 received exactly two prior anti-HER2 treatments and patients in DESTINY-Breast01 received a median of six prior lines of treatment
		• Over half of the patients in DESTINY-Breast01 had received additional anti-HER2 therapies that are not currently recommended by NICE.
		
		Company response:
		• It is acknowledged that the primary population of interest for the decision problem is those who have received two prior NICE-recommended anti-HER2 therapies.
		  ○ Overall response rate was higher in this subgroup of DESTINY-Breast01 (76%; 95% confidence interval: 50% to 93%) compared with those with greater than two prior therapies (59%; 95% confidence interval: 51% to 67%).
		  ○ Estimates of efficacy for trastuzumab deruxtecan in this population are therefore expected to be conservative.
		  ○ This is consistent with results presented by Cameron et al (14), in which time to progression at earlier lines of HER2-targeted therapy appears to be longer than at later lines of therapy in a HER2-positive metastatic breast cancer population treated with capecitabine or lapatinib + capecitabine (Figure 1); see Key issue 4 for further details on the study reported by Cameron et al.
		• Although trastuzumab deruxtecan is expected to be used primarily at third line, the licensed indication includes third and later lines,

Key issue	Does this response contain new evidence, data or analyses?	Response
		and so is expected to be used in a proportion of patients who have received more than three prior therapies. ○ This may be particularly pronounced in the short-term, as trastuzumab deruxtecan will become available to some patients after they have already progressed beyond third line. • There is a substantial unmet need at third line of therapy, and so it is anticipated that trastuzumab deruxtecan will be predominantly used at this line. ○ As noted by Breast Cancer Now: “There are currently no targeted treatments recommended for use after 2 or more prior lines of treatment. This can be incredibly agonising for those who have already progressed beyond these treatment options”.

Figure 1: Reproduced from Cameron et al, 2010. Kaplan-Meier estimates of time to progression in patients receiving: one prior metastatic trastuzumab-based regimen (A) or more than one prior metastatic trastuzumab-based regimen (B)



Key issue	Does this response contain new evidence, data or analyses?	Response
ERG response to Key issue 3		The ERG has previously highlighted (ERG report, p27) that the generalisability of the DESTINY-Breast01 study results to NHS clinical practice is not clear as, in the DESTINY-Breast01 study: • patients had received a median of six prior lines of treatment for LABC or MBC, including hormone therapy. Clinical advice to the ERG is that most patients treated in the NHS would not receive this number of prior treatments • only [redacted] of patients received T-DXd as a third-line treatment. The company anticipates that T-DXd will be used as a third-line treatment (CS, Figure 1) • over half of the patients had received anti-HER2 therapy (likely to include lapatinib) in addition to trastuzumab, pertuzumab or T-DM1. NICE does not recommend lapatinib for this population. The ERG acknowledges that results of subgroup analyses suggest that, compared with the results of the subgroup of patients who had received >3 lines of treatment prior to receiving T-DXd, ORR is better for the subgroup of patients who received T-DXd as a third-line treatment. The ERG highlights that this finding is in line with the PFS results presented by Cameron 2010 for patients treated with lapatinib+capecitabine or capecitabine monotherapy, which show that patients who had received only one prior anti-HER2 therapy had better results than patients who had received two prior lines. This reinforces the importance of including trials of patients who had received ≥2 prior anti-HER therapies in the MAICs (see ERG response to key issue 4).

4. Key issue 4

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 4: Company eribulin and capecitabine MAIC results are not suitable for decision-making	**YES**	The ERG report states that: • None of the comparator trials included in the matching-adjusted indirect comparisons for trastuzumab deruxtecan versus eribulin or capecitabine were wholly conducted in the patient population relevant to the appraisal (i.e., patients with HER2-positive disease who had received two or more prior lines of anti-HER2 therapy). Company response: • Please note that neither eribulin nor capecitabine are HER2-targeted therapies; however, eribulin is recommended in the NICE pathway for HER2-positive metastatic breast cancer following appraisal. • Following both the original company submission and the subsequent addendum, an additional data source for capecitabine was identified which is relevant to the decision problem. o This study was captured in the original systematic literature review, but was listed as a source of data for lapatinib + capecitabine only (i.e. a categorisation error). o The remainder of the studies identified in the systematic literature review have been thoroughly reassessed to ensure that no further data sources have been missed. • Study EGF100151 is a Phase III, randomised, open-label, multi-centre study comparing lapatinib + capecitabine against capecitabine alone in women with HER2-positive locally advanced or metastatic breast cancer after treatments that included but were not limited to an anthracycline, a taxane, and trastuzumab. o The majority of patients had received at least two prior therapies, of which at least one was HER2-targeted

Key issue	Does this response contain new evidence, data or analyses?	Response
		(trastuzumab) (see Key issue 8 and Appendix B for further details). ○ This study is reported by Geyer et al 2006 (15), Cameron et al 2008 (16) and Cameron et al 2010 (14). • A matching-adjusted indirect comparison was performed comparing trastuzumab deruxtecan with capecitabine based on data from Study EGF100151. ○ There is evidence that the proportional hazards assumption may be violated for overall survival; additional analyses were therefore performed in which accelerated failure time parametric survival models were fitted to the weighted data (see Appendix B for further details). ○ Trastuzumab deruxtecan is shown to be associated with significant improvement in overall survival, progression-free survival and response vs capecitabine (Table 2). • Further details on this matching-adjusted indirect comparison are provided in Appendix B, and the impact of this change on the base-case results is presented in 'Summary of changes to the company's cost-effectiveness estimate(s)'.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 2: Results of matching-adjusted indirect comparison for trastuzumab deruxtecan versus capecitabine using Study EGF100151
<table>
<tr><th>Outcome</th><th>Measure</th><th>Result (95% confidence interval)</th></tr>
<tr><td>Overall survival</td><td>Hazard ratio</td><td>[redacted]</td></tr>
<tr><td>Overall survival</td><td>Time ratio</td><td>[redacted]</td></tr>
<tr><td>Progression-free survival</td><td>Hazard ratio</td><td>[redacted]</td></tr>
<tr><td>Overall response rate</td><td>Odds ratio</td><td>[redacted]</td></tr>
<tr><td>Disease control rate</td><td>Odds ratio</td><td>[redacted]</td></tr>
<tr><td>Clinical benefit rate</td><td>Odds ratio</td><td>[redacted]</td></tr>
</table>

A matching-adjusted indirect comparison was presented in the company submission in which trastuzumab deruxtecan is compared against eribulin using data from the HER2-positive subgroup of Barni et al, 2019 (a real-world evidence study) (17).

This comparison results in the most favourable hazard ratios for trastuzumab deruxtecan vs eribulin (Table 3).

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

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 3: Results of matching-adjusted indirect comparisons versus eribulin
<table>
<tr><th rowspan="2">Study</th><th colspan="2">Hazard ratio (95% confidence interval) for trastuzumab deruxtecan versus eribulin</th></tr>
<tr><th>Overall survival</th><th>Progression-free survival</th></tr>
<tr><td>Cortes 2011</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Barni 2019</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Cortes 2010</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gamucci 2014</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
† See Table 3 of the addendum submitted to NICE on Thursday 26th November.

When receiving the same (non-HER2-targeted) therapy, outcomes in HER2-positive patients have been shown to be worse than those for HER2-negative patients (18, 19).

This was confirmed by clinicians attending the August 2020 advisory board.
The inability to control for HER2 status in some comparisons is therefore expected to result in conservative efficacy estimates for trastuzumab deruxtecan vs eribulin.

An adjustment for HER2 status is made to survival data for eribulin in the model using the hazard ratio reported by Lv et al (18).
Eribulin and capecitabine are not HER2-targeted therapies, therefore future trials for HER2-targeted therapies would not include eribulin or capecitabine monotherapy arms as comparators, given that these therapies are not optimised for a HER2-positive population; additional data are therefore unlikely to become available in the HER2-positive subgroup.

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

Key issue	Does this response contain new evidence, data or analyses?	Response
		• Given no prior randomised controlled trials have been identified which investigate eribulin in a HER2+ population, a strict requirement for eribulin RCT data in the HER2-positive population would limit the possibility for HER2-targeted therapies to ever be reimbursed in third-line metastatic breast cancer.
ERG response to Key issue 4		New MAIC for T-DXd versus capecitabine 1. The capecitabine study (Study EGF100151) was conducted in a population of patients who had received at least one prior anti-HER2 therapy. No information is available in the trial publication about how many patients had received two prior anti-HER2 therapies. The ERG considers that Study EGF100151 is more relevant to the current appraisal than the studies of capecitabine included in the MAICs presented in the CS (none of which specified that patients had received prior anti-HER2 therapy). However, ideally, only results from those patients who had received ≥2 lines of anti-HER2 treatment should have been included in the analysis. 2. Although not explicitly stated in the information provided by the company, it appears that the source of OS data from Study EGF100151 is 165 patients in the capecitabine arm who did not crossover to the combination therapy arm at the point when crossover was permitted. The exclusion of 36 patients who did crossover to the combination therapy arm is an approach that is highly likely to be prone to selection bias. Results from a MAIC that only includes data for the 165 patients from the capecitabine arm who did not crossover to the combination therapy arm may be unreliable. 3. It is not clear why only 185 patients from the monotherapy arm of Study EGF100151 were included in the PFS analysis, when 201 patients were randomised to this treatment arm.

Key issue	Does this response contain new evidence, data or analyses?	Response
		4. There is insufficient information in the company's Appendix B to carry out any checks of the data inputs used for the MAICs that generated ORR, DCR and CBR outcomes. Overall, the ERG considers that Study EGF100151 is more relevant to the appraisal than the studies originally included in the MAICs for T-DXd versus capecitabine. However, the issues highlighted above raise uncertainty around the reliability of results from the new MAIC. <u>New MAIC for T-DXd versus eribulin (using data from the June 2020 data cut)</u> 1. The ERG's concerns, highlighted in the ERG report (p50), about the relevance of the trials included in the MAICs for T-DXd versus eribulin to the current appraisal remain. In particular, the ERG is concerned that patients in the Barni 2019 study had not received prior anti-HER2 therapy. 2. Although the company used data for the subgroup of HER2+ patients from the Barni 2019 study in this MAIC, baseline characteristics were only available for the whole study population. The DESTINY-Breast 01 study patients were therefore matched to the whole Barni 2019 study population rather than to the characteristics of the subgroup of HER2 patients.

5. Key issue 5

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 5: Company vinorelbine OS MAIC results are inconclusive	**NO**	The ERG report states that: • The proportional hazards assumption was violated for both overall survival and progression-free survival in this matching-adjusted indirect comparison • Median overall survival has not been reached in DESTINY-Breast01, and so there is no way to meaningfully compare overall survival between trastuzumab deruxtecan and vinorelbine. Company response: • In the addendum submitted to NICE on Thursday 26th November, matching-adjusted indirect comparisons were presented based on the updated data cut; in the analyses vs vinorelbine using Sim 2019, there was evidence that the proportional hazards assumption may be violated for progression-free survival, but not for overall survival. • To explore the impact of the proportional hazards assumption on the progression-free survival comparison vs vinorelbine, additional analyses were performed in which accelerated failure time parametric survival models were fitted to the weighted data. • For all parametric distributions, trastuzumab deruxtecan was shown to be associated with statistically significantly longer progression-free survival compared with vinorelbine; see Appendix C for further details.
ERG response to Key issue 5		Company analyses of DESTINY-Breast01 study OS data from the June 2020 data cut suggest that it may be reasonable to assume proportional hazards. The ERG therefore does not have concerns about the use of a

Key issue	Does this response contain new evidence, data or analyses?	Response
		hazard ratio to summarise the relative OS for T-DXd versus vinorelbine from this updated MAIC. The ERG also notes that the new analyses presented by the company for PFS overcome the issue of non-proportional hazards for the PFS data, as accelerated failure time models are used rather than proportional hazards models. However, the ERG's concerns regarding covariates that have not been adjusted for and the small effective sample size for the weighted DESTINY-Breast01 study data (ERG report, pp50-52), remain valid for both OS and PFS outcomes. Therefore, although the new MAICs overcome the issues of non-proportional hazards, the other concerns outlined in the ERG report about the MAIC for T-DXd versus vinorelbine still remain. The company has suggested (CS, p120) that the OS results from the KCSG BR11-16 trial are inconsistent with the OS results from other studies and this may be the result of subsequent treatment(s) following disease progression. The ERG recognises that OS results may be affected by treatments received on disease progression in this trial. Data on subsequent treatment received are not presented in the published paper for the KCSG BR11-16 trial.

6. Key issue 6

Key issue	Does this response contain new evidence, data or analyses?	Response

Key issue 6: Company OS modelling of T-DXd is not robust	**YES**	The ERG report states that:
		• The company used a simple between-trial analysis of data from DESTINY-Breast01 and the trastuzumab emtansine arm of the Phase III TH3RESA trial
		• The ERG does not consider this approach to be robust.
		
		Company response:
		• The current approach aims to generate a survival curve that passes through the trastuzumab deruxtecan data and is informed by longer-term survival from another antibody drug conjugate, as opposed to a non-HER2 targeted therapy.
		  ○ Clinical experts at the August 2020 advisory board confirmed that the shape of the trastuzumab deruxtecan overall survival curve is expected to more closely reflect the shape of the trastuzumab emtansine curve than that of the model comparators, and that a 'tail' may be expected as observed for trastuzumab emtansine.
		• It should be noted that there is no requirement to make a clinical comparison between trastuzumab deruxtecan and trastuzumab emtansine.
		  ○ Any population differences between the DESTINY-Breast01 and TH3RESA trials would therefore only impact on the validity of the approach if these factors were to substantially impact on the *shape* of the overall survival curve, but not the absolute level.
		• However, in response to this issue, an exploratory scenario analysis has been performed in which overall survival data from

Key issue	Does this response contain new evidence, data or analyses?	Response
		the June 2020 data cut of DESTINY-Breast01 are directly extrapolated. ○ Note that, as in the addendum submitted to NICE on Thursday 26th November, only overall survival data up to 20.5 months are used. ○ Overall survival data beyond 20.5 months were not considered to be informative given the substantial censoring observed beyond this time point: 79 patients (86% of those remaining) are censored and only 13 (14%) OS events occur after 20.5 months. ○ [redacted]% of all censored patients in DESTINY-Breast01 were censored due to still being alive at the time of the June 2020 data cut. • The directly extrapolated survival curves are presented in Figure 2 and compared against the addendum base-case curve and overall survival curves considered by clinicians at the August 2020 advisory board. ○ The Weibull curve is similar to a curve considered implausibly low by clinical experts, and the exponential curve is similar to a curve considered implausibly high by clinical experts; there are no extrapolated curves between these two distributions. ○ On this basis, an average of the Weibull and exponential curves was assumed to represent the best estimate of long-term survival for trastuzumab deruxtecan. This can be seen in **Error! Reference source not found.** alongside the addendum base-case curve.

		Figure 2: Direct extrapolation of trastuzumab deruxtecan overall survival data  Note: The addendum base case (dated 26/11/20) is the cost-effectiveness model base case that was submitted to NICE as an addendum, using the new June 2020 data cut from DESTINY-Breast01 and modelling overall survival for trastuzumab deruxtecan assuming a hazard ratio vs trastuzumab emtansine.

Figure 3: Direct extrapolation of trastuzumab deruxtecan overall survival data using the average of the Weibull and exponential curves

- Cost-effectiveness results based on the averaged survival curve are presented in Table 4 and are associated with a small change (+8%) from the updated base-case ICER (see 'Summary of changes to the company's cost-effectiveness estimates').

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 4: Cost-effectiveness results using direct extrapolation of overall survival for trastuzumab deruxtecan using the average of the Weibull and exponential curves
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Capecitabine</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Vinorelbine</td><td>[redacted]</td><td>[redacted]</td><td>Extendedly dominated</td></tr>
<tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
<tr><td>Trastuzumab deruxtecan</td><td>[redacted]</td><td>[redacted]</td><td>£49,028</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year
</td></tr>
<tr><td>ERG response to Key issue 6</td><td></td><td>The ERG highlights that Figure 2 appears to display parametric OS curves generated by applying a hazard ratio to the TH3RESA trial OS data and does not display direct extrapolations from DESTINY-Breast01 study data, as stated by the company.

The company considers that the data from the June 2020 data cut are still too immature to be used directly to estimate OS for the 40-year model time horizon. The ERG considers that if this is the case, then it follows that the available data are also too immature to estimate hazard ratios between T-DXd and comparator treatments.</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		The ERG highlights that the company technical engagement base case OS estimates that anchor T-DXd OS to TH3RESA trial data appear optimistic compared to the DESTINY-Breast01 trial K-M data at 20 months (company base case OS estimate: [redacted]*; DESTINY-Breast01 trial OS K-M data: 70%). Further, acknowledging that censoring increases after 20 months, the ERG highlights that by 24 months, the DESTINY-Breast01 trial OS K-M data suggest that 53% of patients receiving T-DXd are alive, whilst the company technical engagement base case OS estimates suggest that [redacted] are alive. The DESTINY-Breast01 trial OS K-M data and the company base case extrapolations are shown below. [redacted] *Source: Company addendum model

Key issue	Does this response contain new evidence, data or analyses?	Response
		The ERG remains concerned that the approach used by the company to generate long-term T-DXd OS estimates is not robust and leads to optimistic estimates which, in turn, lead to optimistic ICERs per QALY gained for comparisons of T-DXd versus comparator drugs. However, the ERG agrees with the company that DESTINY-Breast01 OS study data are still too immature to robustly estimate long-term OS for patients receiving T-DXd with any reasonable degree of certainty. The ERG considers that whilst the currently available cost effectiveness results presented by the company are not implausible but are highly uncertain.

7. Key issue 7

Key issue	Does this response contain new evidence, data or analyses?	Response

Key issue 7: Company OS modelling of comparator treatments is not robust	**NO**	The ERG report states that:
		• The company used unadjusted (except for HER2 status) Kaplan-Meier data from the comparator trials.
		• The ERG does not consider this approach to be robust.
		
		Company response:
		• The current approach represents a naïve comparison between trastuzumab deruxtecan and the modelled comparators.
		• The only alternative approach to this would be to use the results of the matching-adjusted indirect comparisons.
		  ○ However, clinical experts stated that the shape of the overall survival curve would be different between trastuzumab deruxtecan and non-targeted comparators, and that a 'tail' may be expected at the end of the survival curve for trastuzumab deruxtecan as observed for other antibody-drug conjugates.
		• In the matching-adjusted indirect comparisons, adjustment for baseline characteristics in the comparisons versus the base-case eribulin and capecitabine studies resulted in improved hazard ratios for trastuzumab deruxtecan.
		  ○ This suggests that the inability to adjust for differences in baseline characteristics results in a conservative estimate of relative efficacy and therefore cost-effectiveness for trastuzumab deruxtecan vs eribulin and capecitabine.

ERG response to Key issue 7		The ERG agrees with the company that the current approach to modelling OS for comparators is naïve. As the results of the MAICs are uncertain, it

Key issue	Does this response contain new evidence, data or analyses?	Response
		is not possible to determine whether the naïve approach generates optimistic or pessimistic OS projections for the comparators.

8. Key issue 8

Key issue	Does this response contain new evidence, data or analyses?	Response

Key issue 8: NICE End of Life criteria may not be met	**NO**	The ERG report states that:
		• It is unclear whether the life expectancy of HER2-positive patients who progress after receipt of trastuzumab emtansine as a second-line treatment is less than 24 months
		• The OS gain for patients receiving trastuzumab deruxtecan could exceed 3 months, but this is highly uncertain without more robust comparative OS data.
		
		Company response:
		
		<u>Comparator survival is less than 24 months</u>
		• In NICE TA458, the committee agreed that trastuzumab emtansine met the end of life criteria (20) in second-line metastatic breast cancer; in particular, survival with lapatinib + capecitabine was expected to be less than 24 months.
		  ○ Given that eribulin, capecitabine and vinorelbine are used at a later line of therapy, are not HER2-targeted, and are monotherapies, survival is expected to be lower.
		• In NICE TA423 (21), the committee agreed that end-of-life criteria were met for eribulin in third-line metastatic breast cancer, on the basis of mean modelled overall survival of 13.53 months for treatment of physician's choice and 16.92 months for eribulin.
		• All available published literature for eribulin, vinorelbine and capecitabine (including in HER2-positive populations following availability of trastuzumab emtansine at second-line; see Appendix D) shows survival of less than 24 months.
		  ○ No evidence has been identified of survival longer than 24 months with eribulin, capecitabine or vinorelbine.

Key issue	Does this response contain new evidence, data or analyses?	Response

		• In particular, median overall survival for vinorelbine patients in Sim et al 2019 was 18.9 months (22).
		  ○ The study by Sim et al includes only HER2-positive patients who have received ≥2 prior anti-HER2 therapies
		  ○ Clinical experts consulted at the August 2020 advisory board stated that overall survival data from Sim et al lacked face validity, with survival in a UK patient population expected to be significantly lower with available therapies; it was suggested that the observed survival may be due to the use of post-progression therapies not available in the UK.
		  ○ 18.9 months may therefore be considered an upper bound for median overall survival in the population of interest.
		• In HER2CLIMB, patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab and trastuzumab emtansine had median survival of 21.9 and 17.4 months with tucatinib + trastuzumab + capecitabine and trastuzumab + capecitabine treatment, respectively (23).
		  ○ Patients treated with non-HER2-targeted monotherapies, such as capecitabine, in the same indication are expected to experience shorter survival (Figure 1).
		• In a population with HER2-positive locally advanced or metastatic breast cancer who have progressed after treatments that included but were not limited to an anthracycline, a taxane, and trastuzumab, Cameron et al report median overall survival of 75.0 weeks (17.3 months) and 56.4 weeks (13.0 months) in lapatinib + capecitabine and capecitabine patients, respectively (14).
		  ○ 85% of patients had received ≥3 prior chemotherapy regimens, and it is anticipated that the majority of the remainder would have received at least two prior

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
chemotherapy regimens, given the proportions receiving each prior therapy (
○
○ Table 5).
○ Almost all patients had received trastuzumab (i.e. a HER2-targeted therapy) previously.

Table 5: Previous therapies received in Cameron et al, 2010 (14)
<table>
<tr><td rowspan="2">Previous therapy</td><td colspan="2">Number (%)</td></tr>
<tr><td>Lapatinib + capecitabine (N=163)</td><td>Capecitabine (N=161)</td></tr>
<tr><td>Anthracyclines</td><td>158 (97%)</td><td>156 (97%)</td></tr>
<tr><td>Taxanes</td><td>159 (98%)</td><td>156 (97%)</td></tr>
<tr><td>Fluorouracil</td><td>83 (51%)</td><td>92 (57%)</td></tr>
<tr><td>Vinorelbine</td><td>71 (44%)</td><td>70 (43%)</td></tr>
<tr><td>Trastuzumab</td><td>157 (96%)</td><td>156 (97%)</td></tr>
</table>

<u>Life extension with trastuzumab deruxtecan is greater than 3 months</u>
• Preliminary median overall survival reported for trastuzumab deruxtecan from the June 2020 data cut for DESTINY-Breast01 was 24.6 months.
○ Assuming an upper bound for comparator survival of 18.9 months (as described above), the increase in median survival associated with trastuzumab deruxtecan is expected to be greater than 5.7 months.
○ Based on the lower bound of the trastuzumab deruxtecan median overall survival, the increase in overall survival associated with trastuzumab deruxtecan would still be
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		expected to be greater than 3 months compared to the upper bound for comparator survival. ○ Given the 'tail' expected for trastuzumab deruxtecan (see response to Key issue 7), gains in mean survival are expected to be substantially greater than gains in median survival. ○ The modelled increase in mean survival for trastuzumab deruxtecan is [redacted], [redacted] and [redacted] months compared with eribulin, capecitabine and vinorelbine, respectively. ○ These modelled estimates suggest that trastuzumab deruxtecan increases life expectancy substantially more than 3 months versus current standard of care in this setting. • This is supported by median progression-free survival for trastuzumab deruxtecan (19.4 months), which is longer than median overall survival for any of the comparator studies included in the cost-effectiveness model.
ERG response to Key issue 8		No additional comment.

9. Additional technical team issues

Please use the table below to respond to questions raised by the NICE technical team related key issues presented in the ERG report. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>1. Please provide updated analyses with the latest data cut from DESTINY-Breast01</td><td>YES</td><td>Updated analyses using the June 2020 data cut were presented in an addendum submitted to NICE on Thursday 26th November. Updates to clinical data are presented in the response to Key issue 1. The base-case fully incremental cost-effectiveness ratio based on the updated data cut was £45,216 per quality-adjusted life-year in the submitted addendum; these results are now superseded following the updates described in ‘Summary of changes to the company’s cost-effectiveness estimate(s)’ below. Current base-case results using the latest data cut and incorporating these updates are presented in Table 6. Please note that these results are based on the approach to overall survival taken in the addendum (i.e. applying a hazard ratio to trastuzumab emtansine), and not the direct extrapolation approach discussed in Key issue 6.

Table 6: Base-case results
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Capecitabine</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Vinorelbine</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Ext. Dominated</td></tr>
<tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
<tr><td>Trastuzumab deruxtecan</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£47,230</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.</td></tr>
</table>

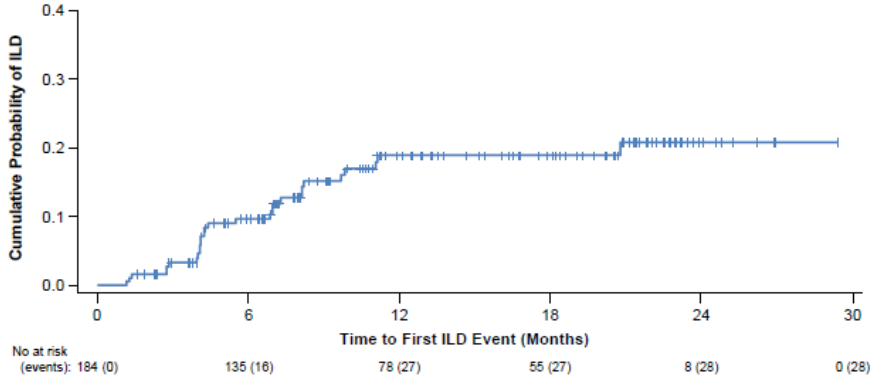
Key issue	Does this response contain new evidence, data or analyses?	Response
ERG response		The ERG can confirm that the results presented in Table 6 can be reproduced by the model provided as part of the company response to technical engagement. The ERG can also confirm that the company model provided at technical engagement has correctly implemented the changes described in Section 11 of this report.
2. Please explain how these data can lift some of the uncertainties raised by the ERG	**NO**	In the June 2020 data cut, preliminary median overall survival (with 35% death events occurring) is reached and estimates of median progression-free survival and duration of response are more certain (see 'Key issue 1'). Modelled estimates of overall survival and progression-free survival are therefore associated with less uncertainty than those in the original submission. Daiichi Sankyo consider the new June 2020 data cut from DESTINY Breast01 and additional relevant analyses presented within this Technical Engagement response provides further useful information for the ERG to develop a preferred base case ICER ahead of the Appraisal Committee meeting.
ERG response		The ERG considers that the ICERs per QALY gained generated by the company are uncertain. However, using the data currently available, the ERG is not able to generate more plausible cost effectiveness results. The ERG considers that, in particular, the uncertainty around long-term OS for patients receiving T-DXd is likely to mean the ICERs per QALY gained generated by the company are optimistic.
3. Would additional data collection in the Cancer Drugs Fund, alongside the ongoing RCT Destiny-	**NO**	The primary source of additional data will be the confirmatory, randomised Phase III trial, DESTINY-Breast02. Data collected from the Systemic Anti-Cancer Therapy data set during managed access is expected to be supportive only.

Key issue	Does this response contain new evidence, data or analyses?	Response
Breast 02 reduce the uncertainty?		
ERG response		No additional comment.

10. Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: interstitial lung disease	Section 3.4.8, page 40	YES	The ERG report states that: • "clinical advice to the ERG is that T-DXd appears to have a manageable toxicity profile, however also highlighted that four deaths from ILD may indicate that ILD is an AE of concern". Company response: • Since the August 2019 data cut, 3 new cases of trastuzumab deruxtecan–related interstitial lung disease as determined by an independent adjudication committee were reported (24); however, trastuzumab deruxtecan showed a generally tolerable safety profile, consistent with previous results. • In the June 2020 data cut, the rate of discontinuation or interstitial lung disease did not notably increase compared with the August 2019 data cut. • Most first interstitial lung disease events occurred during the first 12 months of treatment; among the patients who did not have an interstitial lung disease event for ≥12 months, only 1 subsequently developed interstitial lung disease; 2 cases were pending adjudication at data cutoff. • The risk of adjudicated drug-related interstitial lung disease appears lower after approximately 12 months on treatment, suggesting that the risk of developing interstitial lung disease is not related to a cumulative dose of trastuzumab deruxtecan; continued attention to pulmonary symptoms and careful monitoring is warranted.

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			Figure 4: Cumulative probability of adjudicated drug-related any-grade interstitial lung disease  • Dose modifications relating to interstitial lung disease (25) are presented in Table 7.

<table>
<tr><th>Issue from the ERG report</th><th>Relevant section(s) and/or page(s)</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td>Table 7: Dose modifications for interstitial lung disease
<table>
<tr><th>Severity</th><th>Treatment modification</th></tr>
<tr><td>Asymptomatic (Grade 1)</td><td>Interrupt trastuzumab deruxtecan until resolved to Grade 0, then:
If resolved in 28 days or less from date of onset, maintain dose.
If resolved in greater than 28 days from date of onset, reduce dose one level.
Consider corticosteroid treatment as soon as interstitial lung disease is suspected.</td></tr>
<tr><td>Symptomatic (Grade 2 or greater)</td><td>Permanently discontinue trastuzumab deruxtecan.
Promptly initiate corticosteroid treatment as soon as interstitial lung disease is suspected.</td></tr>
</table></td></tr>
<tr><td>ERG response</td><td></td><td></td><td>No additional comment.</td></tr>
</table>

11. Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

The base-case fully incremental ICER in the addendum submitted to NICE on Thursday 26th November was £45,216 per quality-adjusted life-year. Following submission of the addendum, it was identified that discontinuation analyses for trastuzumab deruxtecan assumed (in error) that death is a censoring event rather than a discontinuation event; this error has now been corrected, and the resulting ICER is [redacted]. This result is referred to as the 'corrected base-case'.

Please note that the updated base-case models overall survival for trastuzumab deruxtecan by applying a hazard ratio to trastuzumab emtansine (as in the original submission and addendum); however, the results in which overall survival data for trastuzumab deruxtecan are extrapolated directly are shown to be highly consistent with the current approach (see Key issue 6).

Key issue(s) in the ERG report 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 ICER
Key issue 4: Company eribulin and capecitabine MAIC results are not suitable for decision-making	In the original company submission and subsequent addendum, the capecitabine arm of the cost-effectiveness model used data from Fumoleau et al, 2004 (26). This study included both HER2-positive and HER2-negative patients.	An additional study has subsequently been identified (Study EGF100151; see Key issue 4) including data for capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer who have received an anthracycline, a taxane, and trastuzumab. The population of this study is expected to be closer to the population of DESTINY-Breast01 than previously identified capecitabine studies. The following updates have been made to the model: • The hazard ratio for progression-free survival and the odds ratio for overall response rate have	Fully incremental ICER: £47,230 Change vs. corrected base-case: +9%

Key issue(s) in the ERG report 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 ICER
		been updated to reflect the matching-adjusted indirect comparison versus Study EGF100151. • Parametric survival curves have been fitted to the digitized Kaplan-Meier curve for overall survival from Study EGF100151. • The Weibull curve has been selected for overall survival for capecitabine based on Akaike information criterion and Bayesian information criterion. • The proportion of patients with HER2-positive disease set to 100%.	
Company's preferred base case following technical engagement	Incremental QALYs: [redacted] Please note that eribulin is dominated and vinorelbine is extendedly dominated in the fully incremental analysis.	Incremental costs: [redacted] Please note that eribulin is dominated and vinorelbine is extendedly dominated in the fully incremental analysis.	Fully incremental ICER: £47,230 Change vs. corrected base-case: +9% Full model results are provided in Appendix E.

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