Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Daiichi-Sankyo UK
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2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
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4. **External Assessment Report** prepared by ScHARR
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-low unresectable or metastatic breast cancer after chemotherapy [ID3935]

Document B

Company evidence submission

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ID3935_T-DXd_HER2-low mBC_Document B_31Aug2023_[FullyRedacted]	2.0	Yes	31/08/2023

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Abbreviations

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

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

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

B.1.1 Decision problem

This submission focuses on trastuzumab deruxtecan (T-DXd) as a treatment for unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer (BC) after chemotherapy.

The submission covers the technology's full marketing authorisation for this indication and is consistent with the final scope issued by the National Institute of Health and Care Excellence (NICE) and the NICE reference case.[1,2]

The European Medicines Agency (EMA) marketing authorisation for T-DXd (Enhertu®) in this indication is: *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2).*[3]

The UK marketing authorisation wording for this indication is expected to be the consistent with the EMA label.

T-DXd is currently recommended by NICE – via the Cancer Drugs Fund (CDF) – for treating HER2-positive unresectable or metastatic BC after 2 or more anti-HER2 therapies (Technology Appraisal 704 [TA704]),[4] and for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments [TA862].[5]

The decision problem for this appraisal is presented in **Table 1**.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with HER2-low, unresectable or metastatic BC previously treated with chemotherapy	As per the final scope issued by NICE	N/A
Intervention	Trastuzumab deruxtecan (Enhertu®)	As per the final scope issued by NICE	N/A
Comparator(s)	The comparators stated in the final scope are: • established clinical management without T-DXd, including: anthracyclines, capecitabine, platinum therapies, taxanes, and vinorelbine; • for people who have had 2 or more lines of chemotherapy for metastatic disease: eribulin; • for people whose disease is HR-negative: SG.[1]	The key comparator in the company submission is the TPC arm from the pivotal Phase III DESTINY-Breast04 study, which is comprised of a basket of non-targeted chemotherapy agents.[6,7] The TPC arm comprises the following single-agent chemotherapies: eribulin, capecitabine, paclitaxel, gemcitabine, and nab-paclitaxel.	The TPC arm is an appropriate comparator for this appraisal for the reasons summarised below (for more information on the relevance of TPC to UK clinical practice and the decision problem, see **Section B.1.3.6**): • The DESTINY-Breast04 TPC arm broadly aligns with UK clinical practice (**Section B.1.3.6.1**). • Using the DESTINY-Breast04 TPC arm means directly leveraging data from prespecified analyses from the key evidence source for the appraisal (**Section B.1.3.6.2**) • Differences between the final scope comparators and TPC arm therapies are unlikely to impact decision-making (**Section B.1.3.6.3**). • A similar TPC arm was accepted as the comparator by NICE in a recent HER2-negative u/mBC appraisal (**Section B.1.3.6.4**).
Outcomes	The outcome measures to be considered include: • PFS • OS • Response rate • Duration of response • Adverse effects of treatment • HRQoL	The outcome measures from DESTINY-Breast04 that are presented and included in the economic model are: • PFS by BICR (primary endpoint) • OS • HRQoL measured via the EQ-5D-5L • Adverse effects of treatment • Response rates by BICR	N/A

		In addition, data from the following endpoints from the DESTINY-Breast04 trial are also presented in this evidence submission: • PFS by IA • Response rates by BICR and IA • Clinical benefit rate by BICR • Duration of response by BICR • Time to response • HRQoL measured by the EORTC QLQ-C30 and EORTC QLQ-BR45 • Hospitalisation-related endpoints	
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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	As per final scope issued by NICE • A cost-utility analysis will be performed, with the key outcome being the ICER. • A lifetime time horizon will be used. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	N/A

Abbreviations: BICR, blinded independent central review; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire; EQ-5D-5L, EuroQol five-dimension, five level instrument; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality-of-life; IA, investigator assessment; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health

and Care Excellence; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, Treatment of physician's choice.

B.1.2 Description of the technology being appraised

A description of T-DXd is presented in **Table 2**. The current summary of product characteristics (SmPC) is provided in **Appendix C**. The European Public Assessment Report (EPAR) is provided in **Appendix C** and the reference pack.[8]

Table 2: Technology being appraised

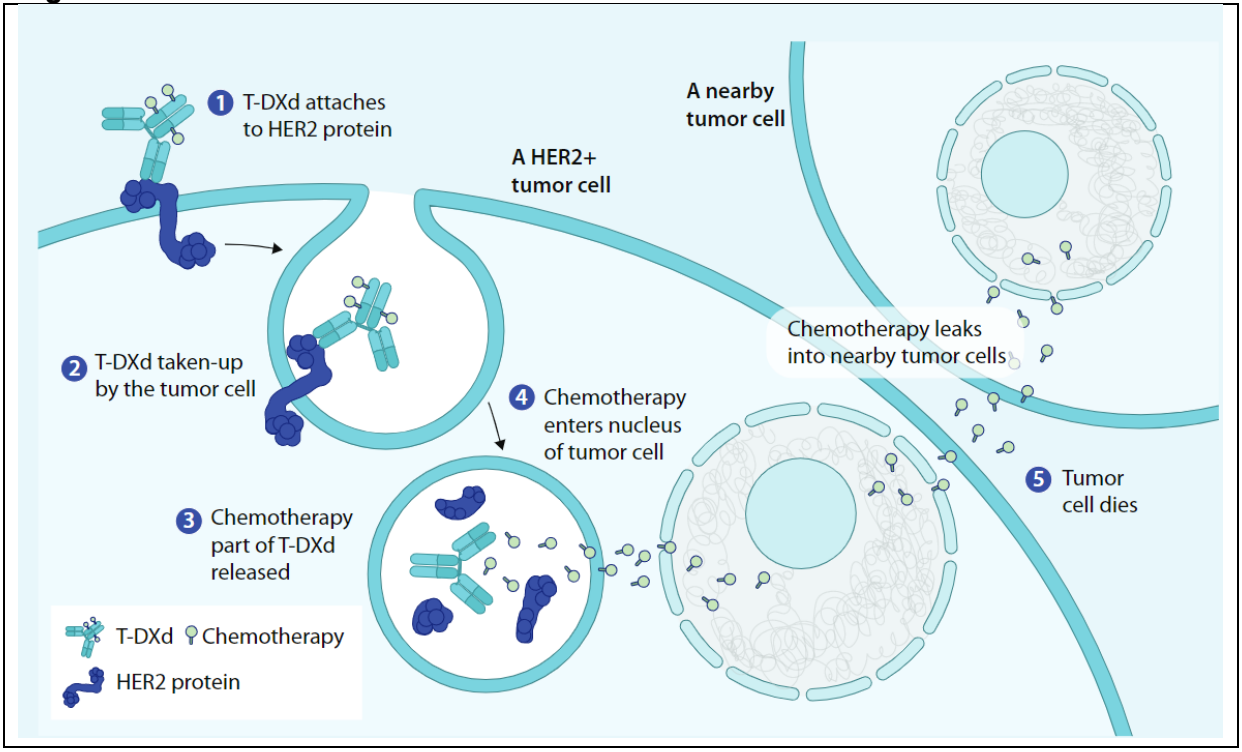
UK approved name and brand name	Trastuzumab deruxtecan (T-DXd; ENHERTU®)
Mechanism of action (See Figure 1)	Using optimised technology, DXd ADCs are composed of a mAb covalently linked to a potent membrane-permeable topoisomerase I inhibitor payload (an exatecan derivative, DXd) via a stable tetrapeptide-based linker selectively cleaved within tumour cells. Evidence supports the portability of DXd ADC technology to multiple tumour targets.[9] DXd ADCs are specifically designed to enhance selective tumour cell death and reduce systemic exposure to the topoisomerase I inhibitor payload. Intact DXd ADCs display long-term stability in plasma. The tetrapeptide-based cleavable linker and payload are stable in plasma.[10–13] The stable linker ensures minimal release of payload in circulation, reducing the risk of off-target toxicity. The linker is selectively cleaved by lysosomal enzymes typically upregulated in tumour cells.[10,11] The payload is cell membrane-permeable, which enables a bystander antitumour effect resulting in elimination of both target and surrounding tumour cells.[11–14] The payload has a short half-life in systemic circulation.[10,11] T-DXd is composed of a humanised anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab covalently linked to the membrane-permeable topoisomerase I inhibitor payload DXd via a stable tetrapeptide-based linker selectively cleaved within tumour cells.[10,11] The drug-to-antibody ratio of T-DXd is optimised and homogeneous and is approximately 8*. The HER2-directed mAb selectively binds to its target, HER2, which is expressed on the tumour cell surface.[10] The ADC is internalised by the tumour cell, where intracellular lysosomal enzymes typically upregulated in tumour cells selectively cleave the tetrapeptide-based linker.[15–17] The payload is released into the cytoplasm of the cell.[10] The released payload enters the cell nucleus and damages the tumour cell's DNA, which results in tumour cell death.[6,18]
Marketing authorisation/CE mark status	T-DXd received European Commission approval in HER2-low u/mBC in January 2023. T-DXd is being assessed for the indication in this submission by the MHRA through the European Commission Decision Reliance Procedure. MHRA approval is expected in March 2023. T-DXd was awarded the Innovation Passport designation by the ILAP steering group in May 2022 (ILAP reference number ILAP/IP/22/08265/01)
Indications and any restriction(s) as described in the SmPC	The current licensed indications for T-DXd are: • *T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.* • *T-DXd as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or*

	gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. The EMA marketing authorisation in this indication is: • *T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2).*[3] The wording of the UK marketing authorisation is expected to be the consistent with the EMA label.
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	HER2 status is routinely assessed in NHS clinical practice through IHC and ISH. According to a 2022 update to UK HER2 testing recommendations, the introduction of HER2-low does not require a change in practice in terms of testing procedures.[19] Therefore, no additional tests are required to determine eligibility for T-DXd in HER2-low BC.
List price and average cost of a course of treatment	List price: £1,455.00 per 100 mg vial • Cost per cycle: [redacted] † • Cost per course: [redacted] ‡ All costs exclude VAT
Patient access scheme (if applicable)	A simple discount PAS for T-DXd in the form of a fixed price is currently operational in the NHS. PAS price: [redacted] per 100 mg vial • Cost per cycle: [redacted] † • Cost per course: [redacted] ‡ All costs exclude VAT

*ADCs are a mixture of molecules in which the drug-to-antibody ratio is variable. Homogeneity of drug-to-antibody ratio refers to a mixture in which there is low variability of drug-to-antibody ratio; the payload number per antibody falls into a narrow range.
† Cost calculation is based on assumptions in the company CE model base case in B3.
‡ Cost per course calculated as median time on treatment [[redacted] months = [redacted] cycles] multiplied by cost per cycle, calculated in the cost-effectiveness analysis.
Abbreviations: ADC, antibody-drug conjugate; BC, breast cancer; CHMP, Committee for Medicinal Products for Human Use; DNA, deoxyribonucleic acid; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; mAb, monoclonal antibody; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan; VAT, value added tax.

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

Figure 1: Trastuzumab deruxtecan mechanism of action[20]



Abbreviations: HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.
Source: Modi et al., 2021[20]

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

There is an unmet need for effective targeted therapies in HER2-low u/mBC given that current treatment after prior chemotherapy is limited to non-targeted chemotherapies which are associated with limited efficacy.

- BC is the most common cancer in the UK with 45,291 cases recorded in England in 2020.[21] Most cases (>70%) of BC are diagnosed at Stage I–II.[22]
- Since therapy with curative potential is available for Stage I–III BC,[23] prognosis is good, with age-standardised 1-year survival ranging from 95.7−100.0%, and 5-year survival ranging from 73.8–98.7%.[24]
- For patients diagnosed with – or who develop – unresectable (inoperable Stage III) or metastatic (Stage IV) disease, no curative therapy is available. Survival outcomes for patients diagnosed with mBC are poor, with 1- and 5-year age-standardised survival of 66.2% and 26.6%, respectively.[24]
- The burden of mBC is high, predominantly due to symptoms caused by secondary tumours, which contribute substantial physical and mental burden, impair QoL, and increase hospital and treatment costs compared with early-stage disease.[25–31]
- The goal of treatment for u/mBC is to delay disease progression and prolong survival while maintaining QoL through disease control and a manageable safety profile.[32,33]

- HER2 is a key biomarker in BC associated with aggressive disease.[34–37] Patients are classified as either HER2-positive or HER2-negative and treated accordingly.[38]
- HER2-targeted therapies such as trastuzumab, T-DM1 and T-DXd,[4,39,40] have transformed the treatment pathway in HER2-positive u/mBC by delivering significant improvements in PFS and OS across lines of therapy compared with conventional chemotherapy.[37,41]
- For patients with HER2-negative mBC, the only options available for the majority of patients after exhausting targeted therapies (e.g., CDK4/6i, ET and PARP inhibitors) are sequential lines of non-targeted, single-agent chemotherapy.[35,42]
- Survival outcomes are poor with non-targeted chemotherapy in the metastatic setting in HER2-negative u/mBC. In HER2-negative/HR-positive u/mBC, median PFS is 3.6–4.2 months and median OS of 11.5–16.1 months.[43–47] Outcomes are even poorer in HER2-negative/HR-negative (TNBC) u/mBC, where median PFS is 1.7–2.8 months and median OS is 6.7–12.4 months.[43,48–50] Across all studies of patients with HER2-negative u/mBC (i.e., any HR-status: HR-negative, HR-positive, or HR-status unspecified), non-targeted chemotherapy is associated with a median PFS of 1.7–6.6 months and median OS of 6.7–20.7 months.[43–55]
- A significant proportion of patients currently classified as HER2-negative (~59%) have tumours expressing lower levels of the HER2 receptor (HER2-low BC).[56]
- The efficacy of existing anti-HER2 therapies has only been demonstrated with HER2-positive disease,[57,58] meaning that patients with HER2-low BC are treated according to HER2-negative treatment pathways.
- There is a need, therefore, for effective, novel treatment approaches in HER2-negative u/mBC, including those expressing lower levels of HER2.
- T-DXd is an ADC that selectively binds to HER2 expressed on tumour cells and releases the highly potent cytotoxic DXd payload within the cell, causing cell death.[10,11,14]
- While existing anti-HER2 therapies have only demonstrated efficacy in HER2-positive BC, T-DXd has shown evidence of antitumour activity across a range of HER2 expression levels[6] and is the first HER2-targeted treatment to show efficacy in HER2-low u/mBC.
- Based on DESTINY-Breast04, T-DXd is the first and only EMA- and MHRA-approved therapy for HER2-low u/mBC.
- In the UK clinical pathway, T-DXd is expected to replace non-targeted chemotherapies in the treatment of patients with HER2-low u/mBC who have received prior chemotherapy in the metastatic setting or developed disease recurrence within 6 months of completing adjuvant chemotherapy. The UK indication wording is expected to be consistent with the EMA label, which is: *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2).*[3]

Abbreviations: ADC, antibody-drug conjugate; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CG81, Clinical Guideline 81; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NICE, National Institute for Health and Care Excellence; OS, overall survival; PARP, poly ADP-ribose polymerase; PFS, progression-free survival; T-DM1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan; u/mBC, unresectable or metastatic breast cancer; QoL, quality-of-life; TNBC, triple-negative breast cancer.

B.1.3.1 Disease overview

B.1.3.1.1 Breast cancer overview

Breast cancer is the most common cancer in the UK with 45,291 cases recorded in England in 2020.[21] BC predominantly affects women, who comprise 99% of cases,[59,60] and prevalence increases with age.[60] Staging of BC categorises the disease according to extent of spread: early BC (Stage I–II) is still localised in the breast tissue, Stage III (locally advanced) disease has typically spread beyond the breast tissue to the lymph nodes, and Stage IV (advanced or metastatic) disease occurs when the tumour has metastasised to other organs.[61,62]

Over 70% of patients are diagnosed at Stage I–II BC,[22] and for these patients, and many with Stage III disease, tumour resection is the mainstay of therapy because it has curative potential and provides good survival outcomes.[23] Historically, outcomes in BC have improved over time,[24] largely due to improved screening and early identification.[63] Early diagnosis allows treatment at an earlier disease stage, typically when the tumour remains localised to the breast tissue and surgical resection remains a treatment option.[63] Consequently, age-standardised 1-year survival for Stage I–III BC ranges from 95.7−100.0%, and 5-year survival from 73.8–98.7%.[24]

Despite the general improvement in BC outcomes over time, an unmet need remains for those patients with unresectable (inoperable) Stage III or metastatic (Stage IV) BC (**Section B.1.3.4**). Survival outcomes in these patients are poor: 1-year and 5-year age-standardised survival for patients diagnosed with Stage IV BC is 66.2% and 26.6%, respectively.[24] Patients with mBC also face a greater disease burden than patients with early BC,[28] as metastases impose symptoms such as seizures, jaundice, and pleural effusion. [25,26] Treatment resistance is frequent in advanced disease,[41] which effectively reduces available treatment options.

Prognosis and treatment of BC is based on various factors, including disease severity and the presence of specific biomarkers. The key biomarkers in BC are HER2 and hormone receptor expression (comprising oestrogen and progesterone receptors).[35,36] Under current treatment pathways, patients are classified as either HER2-positive or HER2-negative, and hormone receptor positive (HR-positive) or hormone receptor negative (HR-negative).[38]

HER2-positive BC, which is present in 13–20% of patients with BC,[56,64] results in aggressive disease[34] that responds poorly to conventional chemotherapy.[60] Anti-HER2 treatments have markedly improved survival outcomes vs. non-targeted chemotherapy[37,41] and have become the standard of care in HER2-positive unresectable or metastatic BC (u/mBC). In first line, pertuzumab with trastuzumab and docetaxel is associated with a median progression-free survival (PFS) and median OS of 18.7 months and 56.5 months, respectively.[40,65] In second-line, trastuzumab emtansine (T-DM1), which has been available since 2014 (via the CDF) and was recommended by NICE in 2017, is associated with a median PFS and median OS of 9.4 and 29.9 months, respectively.[66,67] Recently (February 2023), T-DXd received a positive NICE recommendation for use in the CDF for treating HER2-positive u/mBC after one or more anti-HER2 therapies [TA862][5] based on the first interim analysis of DESTINY-Breast03, which demonstrated an unprecedented efficacy benefit for T-DXd compared with T-DM1 in these patients (PFS by BICR; HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[68] A second interim analysis of DESTINY-Breast03 subsequently confirmed the PFS benefit (HR: 0.33; 95% CI: 0.26, 0.43; P<0.0001) and demonstrated statistically significant OS benefit (HR: 0.64; 95% CI: 0.47, 0.67; p=0.0037) compared with T-DM1.[69] After two or more prior

anti-HER2 therapies, HER2-targeted therapies including T-DXd, and tucatinib with trastuzumab and capecitabine, are recommended by NICE for HER2-positive u/mBC.[4,70] These HER2 targeted treatments have transformed treatment of HER2-positive disease across lines of therapy compared with non-targeted chemotherapies.

HER2-negative BC is currently characterised by no or lower levels of HER2 expression on the surface of BC cells and accounts for 80–87% of all cases of BC.[56,64] Once patients with HER2-negative u/mBC have exhausted targeted treatment options such as cyclin-dependent kinase inhibitors (CDK4/6is), endocrine therapy (ET) and poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors,[35,42] treatment options are predominantly limited to non-targeted chemotherapies which are associated with poor outcomes. After at least one line of chemotherapy in the metastatic setting, non-targeted chemotherapy is associated with a median PFS of 3.6–4.2 months and median OS of 11.5–16.1 months in HER2-negative/HR-positive u/mBC.[43–47] In HER2-negative/HR-negative u/mBC, outcomes are even worse, with median PFS and median OS of 1.7–2.8 months and 6.7–12.4 months, respectively.[43,48–50] This highlights the need for more effective therapies for patients with u/mBC currently classified as HER2-negative.

Although the current HER2 classification paradigm is binary, with patients categorised as either HER2-negative or HER2-positive, a proportion of HER2-negative patients have tumours that express lower levels of HER2, classified as HER2-low. While HER2-low u/mBC is clinically recognised as a new category of BC in recent clinical guidelines by the ESMO,[42] the American Society of Clinical Oncology (ASCO),[71] and US National Comprehensive Cancer Network (NCCN),[72] in the UK these patients are currently treated according to HER2-negative treatment pathways. While the first anti-HER2 targeted therapies were not effective in HER2-low u/mBC,[73] the emergence of newer, more effective HER2-targeted therapies means that there may be an opportunity for improved outcomes in patients with HER2-low u/mBC.

B.1.3.1.2 Epidemiology

In total, 45,291 new BC cases were recorded in England in 2020.[21] Late-stage BC accounts for a small proportion of BC diagnoses overall: in 2020, 6.5% of new cases were diagnosed as Stage IV.[74] Although no data are published on the specific proportion of patients with Stage III unresectable disease, the majority of Stage III cases are expected to be suitable for surgery. Patients with unresectable BC for whom potentially curative therapy is not an option are therefore expected to be predominantly diagnosed with, or have progressed to, Stage IV metastatic disease. The annual probability of progression from early to mBC is estimated to be 3.7% based on a published meta-analysis that reported a five-year distant recurrence rate of 17.2% in patients with node-positive, early-stage HR-positive/HER2-negative BC receiving adjuvant ET.[75] When accounting for patients with initial Stage IV diagnoses (6.5% in England) and patients who have progressed from earlier stages (3.7%), the total number of patients who are diagnosed with or progress to u/mBC each year is 4,511.

According to an analysis of biomarkers from over 199,000 BCs in the UK, 49% of all BC cases are HER2-low (i.e. IHC1+, IHC2+/ISH-).[56] Of the 4,511 total annual population of u/mBC in England, 2,210 are estimated to have HER2-low u/mBC specifically (based on a reported 49% of all BC cases being HER2-low).[76] A UK-based real world evidence study that characterised treatment sequence and outcomes for patients with HER2-negative/HR-positive mBC at a major regional NHS cancer centre showed that 98.0% of patients are expected to receive first-line therapy in the metastatic setting, of which 66.8% and 61.0% subsequently receive second- and third-line therapy, respectively.[77] T-DXd is positioned for

use in HER2-low/HR-positive and HER2-low/HR-negative patients as a third- and second-line option, respectively. Based on this, there are an estimated 946 eligible patients relevant to this appraisal.

B.1.3.1.3 Diagnosis

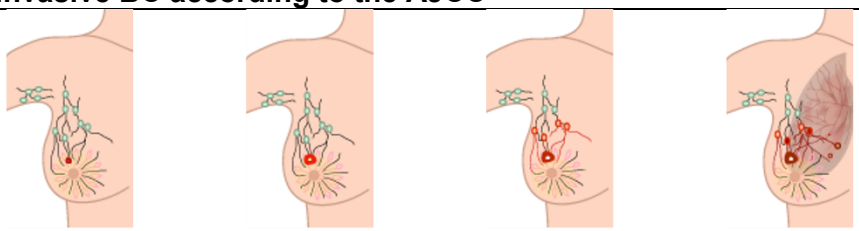
Initial diagnosis of BC is through breast x-ray (mammogram) and ultrasound, with any breast tissue displaying abnormal characteristics under imaging subjected to biopsy or fine needle aspirates for laboratory diagnosis.[78]

For patients with advanced/metastatic BC, diagnostic assessment is conducted to determine the extent of metastatic spread. Visceral metastases are assessed with a combination of plain radiography, ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scans.[35] For bone metastases, CT scan with bone windows or MRI (for axial skeleton), bone scintigraphy (axial skeleton or proximal limbs) or plain radiography (proximal limbs) can be conducted. Patients with undiagnosed mBC, for whom imaging inconclusively suggests metastasis, should have positron emission tomography (PET)-CT.[35]

B.1.3.1.4 Staging and prognostication

Severity and invasiveness of BC is established through TNM (tumour, node, and metastasis) staging according to the American Joint Cancer Committee (AJCC), categorising disease as Stage 0 (non-invasive) or Stage I–IV (invasive; **Figure 2**).[61] Staging is based on tumour size (T), extent of spread to nearby lymph nodes (N), presence of metastases (M), and since 2018 also upon HER2 expression, hormone receptor expression, and the cancer grade.[61,79]

Figure 2: Staging of invasive BC according to the AJCC



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

TNM staging categorises cancer stage by size and characteristics of primary tumour (T) and presence of nodal tumours (N), with increasing severity indicated by increasing numbers (from 0–4). Absence or presence of metastases (M) are indicated by M0 or M1, respectively.
Green bars represent the proportion surviving at each timepoint. Grey dashed bars indicate the proportion dead at that timepoint.
Abbreviations: M, metastasis; N, node, T, tumour.
Sources: adapted from American College of Surgeons, 2021 (diagram);[80] Cancer Research UK, 2020 (staging information);[62] Public Health England, 2020 (survival graphs).[24]

B.1.3.1.5 Current biomarkers in breast cancer and HER2-low

Although BC exhibits broad and diverse genetic characteristics, prognostication and treatment choice for BC is based on expression of HER2 and hormone receptors (oestrogen and progesterone). Both HER2 and hormone receptor status are routinely tested in clinical practice.[36,81]

Under the current paradigm both HER2 and hormone receptor status are binary – BC is either HER2-positive or HER2-negative, and HR-positive or HR-negative. HER2-positive tumours express specific levels of the HER2 receptor: immunohistochemistry level 3+ (IHC3+) or IHC 2+ with gene amplification (as assessed by in situ hybridisation [ISH]; IHC2+/ISH+). HR-positive tumours express either or both the oestrogen and progesterone receptors. The definitions for HER2 and hormone receptor biomarker status are provided in **Table 3.**

Under the current paradigm, BC is therefore classified as either: (i) HER2-positive/HR-positive; (ii) HER2-positive/HR-negative; (iii) HER2-negative/HR-positive; or (iv) triple negative BC (TNBC;HER2-negative/HR-negative).[38]

Table 3: Current biomarker status for breast cancer

Biomarker status	Pathological nomenclature
HER2-positive	IHC 3+ or IHC2+/ISH+
HER2-negative	IHC 0/1+ or IHC2+/ISH-
HR-positive	Express either or both the oestrogen or progesterone receptors
HR-negative	No HR receptor expression (<1% expression*)

TNBC is HER2-negative/HR-negative.
*As per ASCO/CAP guideline.
Abbreviations: ASCO, American Society for Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation.

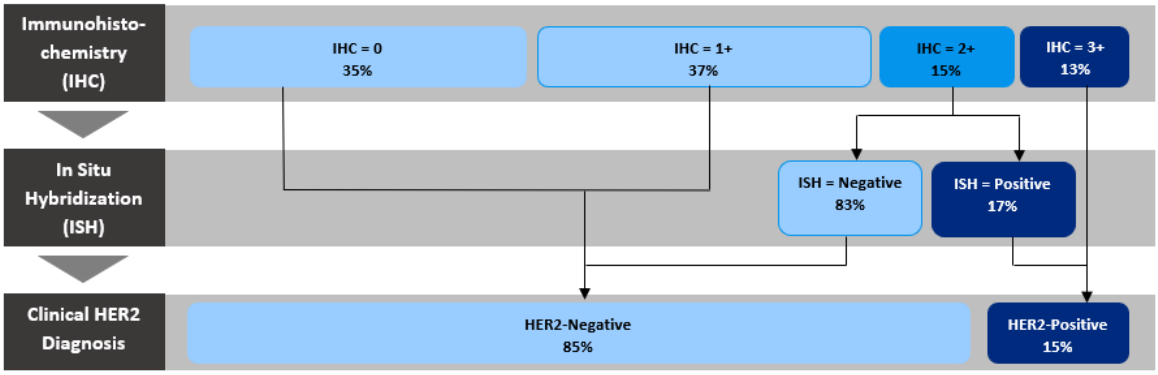
While HER2 status in BC has traditionally been binary, this does not recognise that 58% of patients currently classified as HER2-negative have tumours that express low levels of HER2 (i.e. HER2-low) defined as IHC1+ or IHC2+/ISH-.[56,82] While the first anti-HER2 therapies were not effective in HER2-low,[73] the emergence of newer, more effective HER2-targeted therapies that have improved outcomes in HER2-positive disease compared with earlier HER2-targeted regimens[6] has renewed clinical interest in further refining the HER2 paradigm to include HER2-low. Under this new paradigm, HER2 status is based on a three-tier system: i) HER2-positive, ii) HER2-negative, and iii) HER2-low.

HER2-low is now recognised in recent US (ASCO and NCCN)[71,72] and European (ESMO)[42] clinical guidelines for the management of BC, highlighting its potential importance in further defining the management of patients with mBC. In addition, HER2-low is recognised in a 2022 update to UK HER2 testing recommendations, which states that testing for HER2-low will not require a change in current UK practice in terms of testing procedures.[19]

Figure 3 compares the traditional HER2 testing paradigm (**Figure 3A**) with the new paradigm including HER2-low (**Figure 3B**).

Figure 3: HER2 testing paradigm

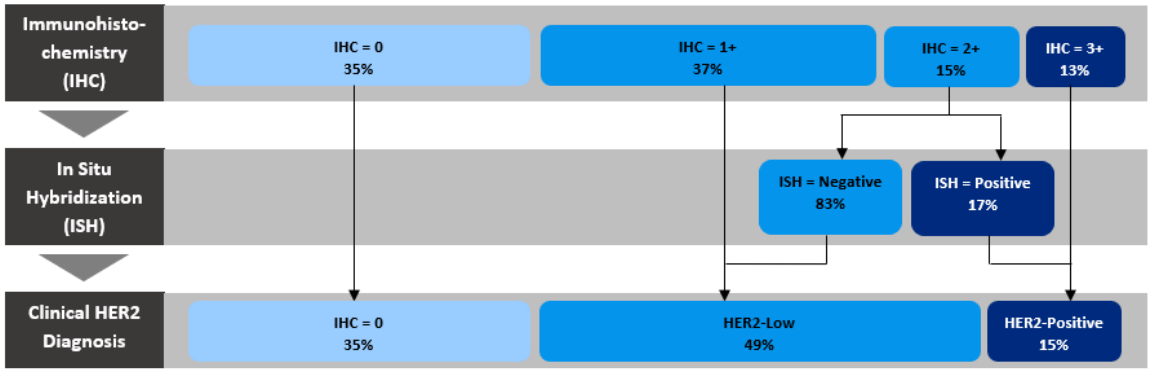
A: Traditional HER2 testing paradigm (no HER2-low)



Under the current testing paradigm, there are two HER2 categories:

- HER2-positive: IHC3+ or IHC2+/ISH+
- HER2-negative: IHC 0/1+ or 2+/ISH-

B: New HER2 testing paradigm (includes HER2-low)



Under the new testing paradigm, there will be three HER2 categories:

- HER2-positive: IHC3+ or IHC2+/ISH+
- HER2-negative: IHC score of 0
- HER2-low: IHC1+ or IHC2+/ISH-

Percentages may not equal 100 due to rounding.
Abbreviations: HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; ISH, in situ hybridisation
Source: Dodson et al. 2020[56]

B.1.3.2 Burden of breast cancer

B.1.3.2.1 Clinical burden of u/mBC

As a progressive, terminal disease, people with u/mBC experience an increasing symptom burden and shorter time to next progression each time their disease progresses.[83]

Symptoms such as pain, breast or lymph node swelling, or changed appearance of the breast are typically experienced during all stages of BC.[84] However, unlike early-stage BC, u/mBC imposes a substantial additional symptom burden, including lethargy and low energy levels, reduced appetite, and unexplained weight loss, alongside symptoms specific to the location of the metastases (**Table 4**).[25,26]

Metastases in BC can involve visceral or non-visceral tissue. Visceral metastases are defined as metastases in the liver, lungs, abdominal cavity (leading to ascites), pleural space (leading to pleural effusion) and the central nervous system (CNS), with related symptoms varying from jaundice (liver metastases) to dyspnoea (lung metastases) and memory

problems (brain metastases; **Table 4**).[25] Non-visceral metastases are defined as bone, skin, and lymph node metastases.[85] Metastasis to the bone is common across all BC subtypes and is the first site of metastasis for more than half of women who develop Stage IV BC.[86] Bone metastases result in symptoms such as pain and impaired mobility, confusion (due to hypercalcaemia induced by the bone tumour), or if spinal metastases arise, symptoms such as poor bladder control (**Table 4**).[25,26,87]

In HER2-low specifically, the liver and brain are the most common visceral metastatic sites, occurring in 14% and 11% of cases, respectively.[88] Complications that arise from liver metastases include sudden hepatic failure, refractory ascites, portal vein thrombosis, and nutritional compromise.[89] These consequences contribute to a poor prognosis – patients with liver metastases at initial BC diagnosis have a median survival of only 9.0 months (TNBC) and 21.0 months (HER2-negative/HR-positive), respectively.[90] Brain metastases are associated with neurological impairment on both cognitive and sensory functions.[91] Breast cancer patients who develop brain metastases have a poor prognosis, with a median survival of 2.0–25.3 months despite treatment.[92]

Symptoms of metastases may incur additional resource use and costs due to requirement for further treatment and monitoring and can havnative QoL impact, due to pain and difficulties for the patient in coping with symptoms.

Table 4: Site-specific symptoms of metastases in BC

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

Source: Irvin 2011;[25] Cancer Research UK 2017.[26]

B.1.3.2.2 Quality-of-life burden

As expected for a terminal disease with a high symptom burden, BC has a substantial and negative impact on patient quality and quantity of life. In a 2019 analysis in the UK, the total disability-adjusted life years (DALYs) lost to BC were 282,537 (95% confidence interval [CI]: 263,582, 301,298) in England and 17,358 (95% CI: 15,831, 19,046) in Wales, indicating substantial burden of disease at a population level.[68] Estimates from the Global Burden of Disease Study (1990–2017) indicate that BC is the leading cause of DALY loss of any cancer type in women.[93]

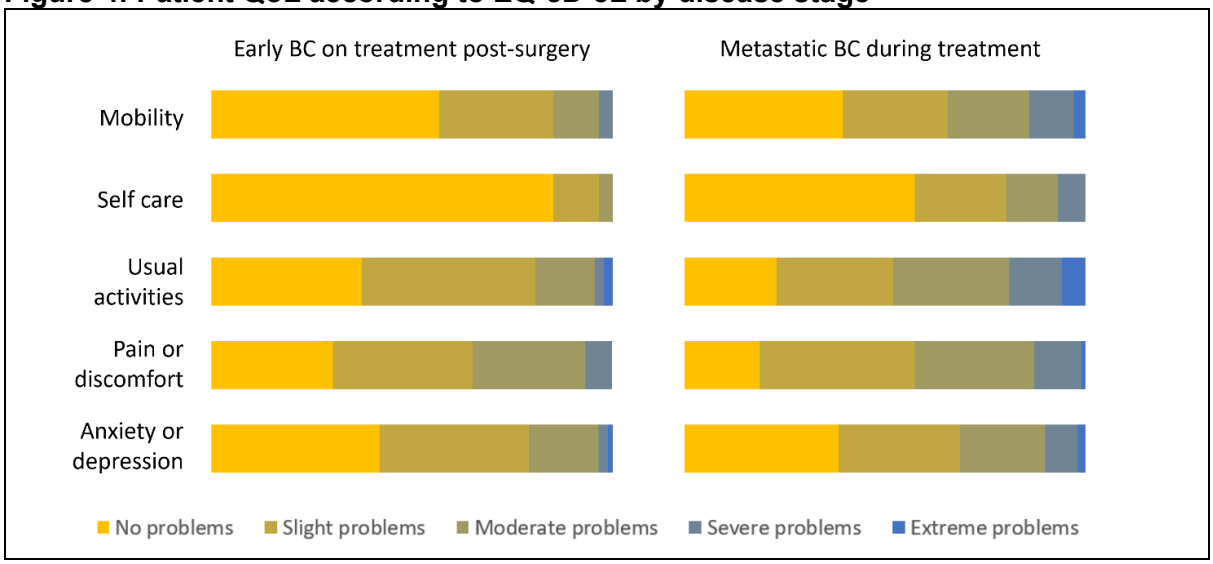
The high DALY loss in BC derives largely from years of life lost, accounting for 93% of the total,[93] and so is likely to be driven by the terminal or incurable stages of disease (unresectable Stage III and Stage IV) rather than the early stages, which have good survival outcomes (**Section B.1.3.2.6**).

B.1.3.2.2.1 Impact of disease stage on QoL

Quality-of-life (QoL) for patients with BC is lower than for the general population in similar age categories,[28,94] and worsens with disease stage.[28] A UK study of HER2-positive BC

found that metastatic BC is associated with significantly lower health-related quality-of-life (HRQoL) measured by FACT-B[a] and FACT-G[b], and EQ-5D-5L[c] than both early BC in remission and early BC undergoing active treatment after surgery (all p<0.001).[28] Overall, patients with mBC reported significantly higher activity impairment – measured using the WPAI[d] activity impairment subscale – compared with patients with early BC on treatment post-surgery or after treatment completion (48.1% vs. 34.0% vs. 27.6%; p<0.001).[28] Moreover, mBC imposes restrictions on patients in terms of self-care and usual activities, with more patients reporting moderate or worse problems across EQ-5D-5L domains than in early BC (**Figure 4**).[28]

Figure 4: Patient QoL according to EQ-5D-5L by disease stage



Abbreviations: BC, breast cancer; QoL, quality-of-life.
Source: adapted from Verrill et al, 2020.[28]

In a US study of patients with HER2-negative BC, a more advanced disease stage was associated with lower QoL, as measured by FACT-B (p<0.05).[95] Another study of HER2-negative mBC found disease progression to be associated with worsening of physical symptoms, treatment-emergent adverse events (AEs), acute distress, and impaired performance scores, all of which are likely to have a negative impact on patient QoL.[96]

Metastatic BC also impacts QoL in ways specific to the metastatic location. For example, in patients with bone metastases, skeletal-related events (SREs[e]) were found to cause substantial decrement in QoL – assessed using the Brief Pain Inventory – in a pooled analysis of 5,543 patients with solid tumours (including BC) from three Phase III trials.[97] In the BC population specifically, there was a significant risk of clinically meaningful worsening[f] from baseline in pain interference overall and with physical activity, in patients with SREs (specifically surgery to bone, radiation to bone, and pathological fractures) compared to patients without SREs (both p<0.05).[97]

[a] Functional Assessment of Cancer Therapy – Breast
[b] Functional Assessment of Cancer Therapy – General
[c] EuroQol-5 Dimensions-5 Level
[d] Work Productivity and Activity Impairment
[e] Defined as fractures, the need for radiation to the bone to control pain or tumour burden, spinal cord compression, or bone surgery
[f] A clinically meaningful worsening in pain was a ≥2-point increase from baseline in pain scores according to the Brief Pain Inventory Short Form (BPI-SF).

B.1.3.2.2.2 Impact of u/mBC on social functioning and mental health

The QoL impact of mBC in women varies by patient demographic, with younger patients[g] more likely to experience impaired social wellbeing than older patients.[98] Patients with children are more likely to have impaired functional wellbeing than those without, suggesting the disease impacts on their ability to parent actively and fulfil their social role.[98]

BC symptoms are also associated with a significant mental burden for patients.[27,29] In a US study using the Hospital Anxiety and Depression Scale (HADS; N=125), depressive symptoms were significantly associated with the symptom burden of disease in women with BC, regardless of age ($p<0.01$).[27] In another study, young North American women diagnosed with *de novo* mBC (N=54) reported a significant association between higher physical symptom scores and higher HADS anxiety scores ($p=0.005$).[29]

Advanced BC also has a considerable emotional impact. According to a cross-sectional study of 739 BC patients across the US and Europe, patients with HER2-negative/HR-positive advanced BC reported lower emotional wellbeing scores in the FACT-B questionnaire compared to general population norms (13.1 vs. 19.9; lower score indicates worse emotional wellbeing).[99]

B.1.3.2.3 Treatment burden

Beyond the clinical symptoms and QoL impact for patients with u/mBC, treatment itself may be burdensome. Once patients have exhausted targeted treatment options (e.g., CDK4/6i, ET, PARP inhibitors), treatment options are predominantly limited to non-targeted chemotherapies (**Section B.1.3.3**).

Non-targeted chemotherapy is associated with considerable treatment burden. Patients with BC treated with chemotherapy report high symptom burden immediately before receiving the next dose of chemotherapy, and at one and two weeks after receiving chemotherapy. The five highest occurring symptoms at the three timepoints are lack of energy (86.3%, 90.3% and 86.2, respectively), difficulty sleeping (74.5%, 72.2%, and 66.6%, respectively), hair loss (69.5%, 57.3%, and 54.4%, respectively), pain (60.7%, 69.7%, and, 62.4%, respectively), and feeling drowsy (60.3%, 65.6%, and 51.8%, respectively).[100]

Treatment with non-targeted chemotherapy is also associated with a negative QoL and anxiety impact in patients with BC. In a UK study, treatment with chemotherapy vs. without chemotherapy was associated with a reduction in QoL – measured using the Quality-of-life in Adult Cancer Survivors (QLACS) tool – across generic domains (hazard ratio [HR]: 8.70; 95% CI: 3.80, 13.70) and cancer-specific domains (HR: 10.90; 95% CI: 7.10, 14.70), as well as increased anxiety, measured using the HADS tool (HR: 1.10; 95% CI: 0.20, 2.00).[101] Across treatment types, chemotherapy is associated with significantly greater total toxicity than targeted or hormone therapies ($p=0.03$). Additionally, disease-limited social activity and a negative impact of BC on closest family are reported by 70% and 61%, respectively, of patients treated with chemotherapy, compared with 50% and 51%, respectively, of those treated with targeted therapy.[102]

Among mBC patients with HER2-negative/HR-positive disease, treatment with chemotherapy is significantly associated with lower emotional wellbeing scores than treatment with hormone therapy (FACT-B; $p<0.05$).[103] A 2016 US-based study of 140 patients with mBC (97 of whom had HER2-negative mBC) found that chemotherapy (N=100)

[g] Unlike BC generally, HER2-positive BC is more common in younger women (defined as those aged <56 years) than older women (defined as those aged ≥56 years).

was associated with lower scores (worse HRQoL) on the FACT-B Trial Outcome Index (66.1 vs. 72.5; p<0.01) and a higher rate of depression symptoms (HADS-D score >7; 22% vs. 7.5%; p=0.03) compared with targeted therapy (N=40).[104]

B.1.3.2.4 Economic burden

The high mortality and morbidity associated with mBC presents a significant economic burden. In general, the management of BC requires substantial resource use in England and Wales. In 2010, the total age-standardised cost of BC care in England was £371 million and £134 million for patients aged 18–64 and ≥65 years, respectively.[105]

Generally, the cost of treating and caring for patients with BC rises as the disease progresses: costs of disease-related hospital care and treatment increase as patients progress to locally advanced or metastatic disease.[30,31] Hospital costs over 15 months were significantly associated with disease spread to lymph nodes and with how aggressive the cancer was (i.e., Grade 3 BC) in both univariate and multivariate regression analyses in a UK study (all p<0.001).[30] Treatment costs for distant BC were reported to be 165% higher than for local BC in a global systematic review,[31] and in the first year after diagnosis, Stage III–IV BC is associated with incremental care costs of £2,569 per patient vs. Stage I–II BC in England (the per-patient first-year cost of Stage I–II BC is £10,746).[105]

Cost drivers associated with mBC include treatment type, inpatient care, outpatient care, home care, surgery, continuous care, and laboratory tests.[106,107] Despite lower rates of surgery due to the unresectable nature of many late-stage BC cases, later-stage BC in England is associated with an additional 2.93 inpatient days in the first 12 months, and more day case/regular admissions than early-stage BC.[105] The highest hospital care costs are those in the months prior to death (the 'terminal' phase of disease).[105] Other cost drivers associated with mBC include palliative care and toxicity management, including the treatment of AEs and treatment of metastases in common sites such as bone.[108]

B.1.3.2.5 Caregiver burden

Caregivers of patients with mBC are also impacted by the disease as they may face economic difficulties, psychological problems, marital or familial anxieties, and worries about their loved one's wellbeing, disease status, and ability to maintain usual life activities.[109] The Global Status of Advanced/Metastatic Breast Cancer 2005–2015 Decade Report comprehensively assessed the caregiver burden of BC through surveys and a literature review.[109] As a consequence of the psychological and economic strain associated with caring for someone with the disease, caregivers may overlook their own needs, resulting in decreased wellbeing and an increase in symptoms of stress. Caring for a patient with mBC can also impact a caregiver's work, as they may need to take annual or special leave or quit work all together, leading to financial strain and increased indirect economic costs of mBC.[109] In a Canadian study of mBC, 69% of caregivers surveyed at the start of the palliative period reported that they had missed work due to caregiving (N=58).[110]

Caregivers often report their tasks to be physically and emotionally demanding. In a US study evaluating caregiver burden of patients with mBC, 86% of caregivers reported that their life had been negatively affected as a direct result of providing care, with 77% reporting it to be an emotional burden, and 56% reporting it to be a physical burden.[111]

B.1.3.2.6 Mortality and prognosis in u/mBC

Survival outcomes in patients with mBC in England remain poor compared with patients at earlier stages of BC. According to Public Health England, the 5-year survival between 2014

and 2019 was 98.7% for Stage I BC, 90.2% for Stage II BC, 73.8% for Stage III BC, and only 26.6% for Stage IV (advanced/metastatic) BC (**Figure 2**).[24] The proportion of patients surviving their first year from diagnosis gives particular context to the poor prognosis of late-stage BC: whilst net one-year survival is 95.7% in Stage III BC, for which curative resection is possible in some patients, it is just 66.2% in Stage IV (i.e. unresectable and metastatic) BC.

B.1.3.2.6.1 HER2-positive u/mBC

While HER2-positive u/mBC is associated with aggressive disease,[34] the introduction of HER2-targeted therapies has substantially improved prognosis in the HER2-positive population.[112] The introduction of trastuzumab in the first-line setting increased OS in HER2-positive mBC, resulting in 5-year OS of 29.7% and 17.7% in patients with HR-positive and HR-negative BC, respectively (vs. 14.5% and 8.9%, respectively, in patients who did not receive trastuzumab).[113] Subsequently, the CLEOPATRA trial established combination therapy with pertuzumab plus trastuzumab and docetaxel as a new first-line standard of care demonstrating 4-year OS of 57.6%.[42,65] The pertuzumab combination was associated with median PFS of 18.7 months (vs. 12.4 months for placebo plus trastuzumab and docetaxel), and median OS of 56.5 months (vs. 40.8 months).[42,65] Regimens based around anti-HER2 therapies are now the mainstay of first-line treatment in HER2-positive mBC in England rather than chemotherapy alone.

HER2-targeted therapies are also the standard of care in HER2-positive disease in the second- and later-line HER2-positive u/mBC setting. T-DM1 has been available since 2014 (via the CDF) and then subsequently via a NICE recommendation in 2017 (TA458).[39] The EMILIA trial, conducted between 2009–2012, enrolled patients treated with prior trastuzumab and a taxane.[40,114] In EMILIA, T-DM1 demonstrated median PFS and median OS of 9.6 months and 30.9 months, respectively, compared with 6.4 months and 25.1 months, respectively, with lapatinib plus capecitabine.[66,67]

The introduction of T-DXd[5] has further improved outcomes in second-line HER2-positive u/mBC. In February 2023, T-DXd received a positive NICE recommendation for use in the CDF for treating HER2-positive u/mBC after one or more anti-HER2 therapies [TA862] based on the first interim analysis of DESTINY-Breast03, which demonstrated an unprecedented efficacy benefit for T-DXd compared with T-DM1 (PFS by BICR; HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[68] A second interim analysis of DESTINY-Breast03 subsequently confirmed the PFS benefit (HR: 0.33; 95% CI: 0.26, 0.43; P<0.0001) and demonstrated statistically significant OS benefit (HR: 0.64; 95% CI: 0.47, 0.67; p=0.0037) compared with T-DM1.[69] The results of DESTINY-Breast03 demonstrated the unprecedented survival benefits of T-DXd vs. an already very effective drug and the current standard of care, T-DM1.

In the third-/later-line metastatic setting, HER2-targeted therapies have also delivered PFS and OS benefits in HER2-positive u/mBC. As well as being recently approved in the second-line setting, T-DXd is the current standard of care in heavily pre-treated patients (i.e. third-or-later line in the metastatic setting).[4,42] In the DESTINY-Breast01 Phase II single-arm study, involving patients who were resistant or refractory to T-DM1, T-DXd was associated with median PFS of 16.4 months and median OS of 29.1 months.[115] Results from DESTINY-Breast01 were validated in a confirmatory Phase III study, DESTINY-Breast02, in which T-DXd was associated with median PFS of 17.8 months (vs. 6.9 months for TPC; HR: 0.36; p<0.0001), and median OS of 39.2 months (vs. 26.5 months; HR: 0.66; p=0.0021).[116] Tucanitib with trastuzumab and capecitabine is also available as a targeted treatment option

in the third- or-later line setting. In the HER2CLIMB study involving patients previously treated with trastuzumab, pertuzumab, and T-DM1, tucanitib plus trastuzumab and capecitabine was associated with median PFS of 7.8 months (vs. 5.6 months with placebo plus trastuzumab and capecitabine) and median OS of 21.9 months (vs. 17.4 months in the placebo combination group).[117]

Together, these data highlight that effective HER2-targeted options are available through treatment lines in HER2-positive u/mBC and, since their introduction, have substantially improved prognosis. In particular, the introduction of T-DXd has led to unprecedented benefits in HER2-positive disease.

B.1.3.2.6.2 HER2-negative u/mBC

While the introduction of effective HER2-targeted therapies have transformed outcomes across lines of treatment in HER2-positive u/mBC, HER2-targeted treatments have not been effective in HER2-negative u/mBC. Under current treatment pathways, patients with HER2-negative/HR-positive u/mBC are initially treated with therapies targeting the hormone receptor pathway, for example CDK4/6is, ET and PARP inhibitors. Once these targeted options are exhausted, treatment is limited to non-targeted chemotherapies,[35,42] which are associated with poor outcomes.[43–46,51] For patients with HER2-negative/HR-negative u/mBC (i.e. TNBC), treatment is even more limited. Across the entire HER2-negative/HR-negative u/mBC pathway, only three targeted options are available: atezolizumab and pembrolizumab as first-line targeted therapies (for patients with programmed death ligand 1 (PD-L1)-positive disease only), and sacituzumab govitecan (SG) as second- or later-line targeted therapy.

PFS and OS outcomes by line of therapy in HER2-negative u/mBC (HR-status positive, negative, any) are presented in **Table 5**. In patients currently classified as HER2-negative/HR-positive who have received one or more lines of chemotherapy in the metastatic setting, non-targeted chemotherapy is associated with median PFS of 3.6–4.2 months and median OS of 11.5–16.1 months.[43–47] In patients currently classified as HER2-negative/HR-negative (i.e., TNBC) outcomes are even worse, with median PFS and median OS of 1.7–2.8 months and 6.7–12.4 months, respectively.[43,48–50] In studies of patients with HER2-negative u/mBC (unspecified HR-status), non-targeted chemotherapy is associated with a median PFS of 2.0–6.6 months and median OS of 7.4–20.7 months.[47,51–55] Across all studies of patients with HER2-negative u/mBC (i.e., any HR-status: HR-negative, HR-positive, or HR-status unspecified), non-targeted chemotherapy is associated with a median PFS of 1.7–6.6 months and median OS of 6.7–20.7 months.[43–55] This highlights that outcomes in HER2-negative disease are very poor and underscores the need for innovation in HER2-negative u/mBC.

As demonstrated in **Table 5**, there is unlikely to be a significant difference in efficacy across non-targeted single-agent chemotherapies used in the mBC setting. In line with this, a 2009 systematic review of RCTs on the clinical efficacy of cytotoxic agents used in Europe in anthracycline- and taxane- pre-treated advanced BC found there to be no RCTs that demonstrated a significant OS difference between any of the regimens (capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles).[118]

Given the role of HER2 in driving poor prognosis and the benefits demonstrated by HER2-targeted treatments in HER2-positive disease,[119,120] effective HER2-targeted therapies have the potential to improve outcomes in the subset of HER2-negative u/mBC patients who express lower levels of HER2. UK clinical experts confirmed that there is a need for effective HER2-targeted therapies for patients with HER2-low u/mBC.[121]

Table 5: PFS and OS outcomes by line of therapy in HER2-negative u/mBC

Author and study details	Study name	Line of chemotherapy in the metastatic setting	Treatment	Median PFS, months	Median OS, months
HER2-negative/HR-positive					
Pivot et al., 2017 (NCT00337103) Phase III[46]	Study 301	2	Eribulin	4.2	16.1
				4.0	13.5
Pivot et al., 2016 (NR) Phase III[43]	Study 301 and Study 305	≥2	Eribulin	3.7	15.1
Twelves et al., 2016 (NCT00337103) Phase III[45]	Study 301	≥2	Eribulin	4.1	15.9
			Capecitabine	3.9	13.5
Yardley et al., 2016 (298) (NCT01427933) Phase II[47]	-	2-4	Eribulin	4.1	11.5
Cortes et al., 2011 (NCT00388726) Phase III[44]	EMBRACE	2–5	Eribulin	3.6	13.2
HER2-negative/HR-negative (i.e., TNBC)					
Pivot et al., 2016 (NR) Phase III[43]	Study 301 and Study 305	≥2	Eribulin	2.8	12.4
Vahdat et al., 2021* (NCT0199733) Phase II[50]	METRIC	≤2	Capecitabine	2.8	8.7
Bardia et al., 2021* (NCT02574455) Phase III[48]	ASCENT	≥2	SG**	5.6	12.1
			TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	1.7	6.7
Winer et al., 2021* (NCT02555657) Phase III[49]	KEYNOTE-119	2-3	TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	2.3	10.8
HER2-negative (any HR-status)					
Claessens et al., 2019 (NR) Phase III[52]	Stop&Go	2	Capecitabine (intermittent)	3.7	10.9
			Capecitabine (continuous)	5.0	12.4
Brufsky et al., 2011* (NCT00281697) Phase III[53]	RIBBON-2	2	TPC (capecitabine, docetaxel, nab-paclitaxel, paclitaxel, gemcitabine, vinorelbine)	5.1	16.4
Decker et al., 2019* (NCT01520103) Phase II[51]	VicTORia	2	Vinorelbine	4.1	13.8
Decker et al., 2017* (NCT01320111) Phase II[54]	PASO	2-3	Paclitaxel	6.6	20.7
Yardley et al., 2016 (NCT01427933) Phase II[47]	-	2-4	Eribulin	4.1	11.5
Yardley et al., 2015* (NCT01156753) Phase II[55]	EMERGE	2-7	TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	2.0	7.4

*Publication identified as part of the clinical SLR for this appraisal. **SG is not a non-targeted chemotherapy but is included as it is in the NICE scope
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; NICE, National Institute of Health and Care Excellence; NR, not reported; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

B.1.3.3 Current treatment pathway

The overarching goal of treatment in u/mBC is to delay disease progression and prolong survival while maintaining QoL through disease control and a manageable safety profile.[32,33]

There are currently no UK-specific clinical or reimbursement guidelines for HER2-low and patients are treated according to HER2-negative treatment guidelines. In the absence of UK-specific guidelines, US and European clinical guidelines provide recommendations on the emerging role of HER2-low in the treatment paradigm, while UK clinical expert advice, NICE guidelines, and NICE TAs for HER2-negative u/mBC provide insights into the current treatment landscape for HER2-low u/mBC.

B.1.3.3.1 US clinical guidelines

Both the US NCCN 2022 (Version 4.2022)[72] and the ASCO Guideline 2022 Rapid Recommendation Update[71] include recommendations for HER2-low u/mBC. In NCCN 2022, T-DXd is recommended as the Category 1 preferred regimen and the only option for patients with HER2-low BC who have received at least one prior line of chemotherapy for metastatic disease and, if the tumour is HR-positive, are refractory to ET.[72] Similarly, in the ASCO 2022 Rapid Recommendation Update, T-DXd is recommended for patients with HER2-low who have received at least one prior chemotherapy for metastatic disease, and if HR-positive are refractory to ET.[71]

B.1.3.3.2 European clinical guidelines

The Europe-wide treatment guideline of relevance to this submission is the 2021 ESMO guideline for mBC.[42] The guidelines do not currently include specific treatment recommendations for HER2-low, but do include HER2-low in the diagnostic work-up and staging of mBC.[42] They also acknowledge that outcomes from HER2-low trials may necessitate a change in biomarker assessment when diagnosing mBC.[42]

In the absence of HER2-low recommendations specifically, the ESMO 2021 guidelines for HER2-negative disease are relevant.[42] ESMO 2021 guidelines recommend that chemotherapy should be used at the end of the treatment pathway in HER2-negative u/mBC, following exhaustion of earlier targeted options.[42] Specific statements and recommendations related to chemotherapy in the metastatic setting include:[42]

- Sequential single-agent chemotherapy is generally preferred over combination strategies.
- Available drugs for single-agent chemotherapy include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents.
- The optimal sequence of chemotherapy has not been established. Available options should be discussed with the patient.

At an advisory board in December 2022, UK clinical experts confirmed that these statements from the ESMO 2021 guidelines reflect the treatment of HER2-negative u/mBC in the UK.

B.1.3.3.3 NICE guidance

The scope of this appraisal is for the treatment of HER2-low u/mBC after chemotherapy in the metastatic setting. As there is currently no specific guidance for HER2-low u/mBC NICE Technology Appraisals in HER2-negative u/mBC and NICE Clinical Guideline 81 (CG81; Advanced breast cancer: diagnosis and treatment)[35] provide insight into the potential NICE

treatment pathway for HER2-low u/mBC. In addition, given the nuances of the pathway, UK clinical expert input and UK real-world data provide further relevant insights.

B.1.3.3.3.1 NICE TAs in HER2-negative/HR-positive u/mBC

NICE TAs for HER2-negative/HR-positive advanced or metastatic BC are summarised in **Table 6**. NICE recommend a CDK4/6i agent combined with an ET (comprising of an aromatase inhibitor [AI]) for first-line treatment in patients with HER2-negative/HR-positive u/mBC. In the second-line setting, further targeted therapy combined with ET is recommended, after which patients are treated with non-targeted chemotherapies.

Table 6: Summary of published NICE TAs with a positive recommendation in HER2-negative/HR-positive advanced BC*

TA	Year	Intervention	LoT	Title
First line				
116	2007	Gemcitabine + paclitaxel	≥1	Gemcitabine for the treatment of metastatic breast cancer
495	2017	Palbociclib + an AI	1	Palbociclib with an AI for previously untreated, HR+/HER2-, locally advanced or metastatic BC
496	2017	Ribociclib + an AI	1	Ribociclib with an AI for previously untreated, HR+/HER2- locally advanced or metastatic BC
563	2019	Abemaciclib + an AI	1	Abemaciclib with an AI for previously untreated, HR+/HER2-, locally advanced or metastatic BC
Second line				
421	2016	Everolimus + exemestane	2	Everolimus with exemestane for treating advanced breast cancer after ET
836	2022	Palbociclib + fulvestrant	2	Palbociclib with fulvestrant for treating HR+/HER2- advanced BC after ET
687	2021	Ribociclib + fulvestrant	2	Ribociclib with fulvestrant for treating HR+/HER2- advanced BC after ET
725	2021	Abemaciclib + fulvestrant	2	Abecaciclib with fulvestrant for treating HR+/HER2- advanced BC after ET
816	2022	Alpelisib + fulvestrant	2	Alpelisib with fulvestrant for treating HR+/HER2-, PIK3CA-mutated advanced BC
Third line				
423	2016	Eribulin	≥3	Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens

*The scope of this appraisal is for patients with HER2-low u/mBC after one line of chemotherapy in the metastatic setting. In the Destiny-Breast04 trial, patients with HR-positive disease had to have progressed on ≥1 line of ET and be considered no longer able to benefit from further ET. ETs listed in this table are therefore not relevant to the scope.
Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; LoT, line of therapy; TA, technology appraisal.
Sources: NICE, 2007 (TA116);[122] NICE, 2017 (TA495);[123] NICE, 2017 (TA496);[124] NICE, 2017 (TA563);[125] NICE, 2016 (TA421);[126] NICE, 2020 (TA836);[127] NICE, 2021 (TA687);[128] NICE, 2021 (TA725);[129] NICE, 2022 (TA816);[130] NICE, 2016 (TA423)[131]

B.1.3.3.3.2 NICE TAs in HER2-negative/HR-negative u/mBC

NICE TAs for HER2-negative/HR-negative (i.e., TNBC) advanced or metastatic BC are summarised in **Table 7**. At first line, NICE recommend atezolizumab with chemotherapy or pembrolizumab with chemotherapy for patients whose tumours express PD-L1, after

whichpatients are treated with non-targeted chemotherapies. SG is also an option for patients with HER2-negative/HR-negative u/mBC at second line* and beyond.

Table 7: Summary of published NICE TAs with a positive recommendation in HER2-negative/HR-negative advanced BC (i.e. TNBC)

TA	Year	Intervention	LoT	Title
First line				
116	2007	Gemcitabine + paclitaxel	≥1	Gemcitabine for the treatment of metastatic breast cancer
639	2020	Atezolizumab + nab-paclitaxel	1	Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer
801	2020	Pembrolizumab + chemotherapy	1	Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer
Second line				
819	2022	Sacituzumab govitecan	≥2*	Sacituzumab govitecan for treating unresectable triple-negative advanced BC after 2 or more therapies
Third line				
423	2016	Eribulin	≥3	Eribulin for treating locally advanced or metastatic BC after 2 or more chemotherapy regimens

*In patients who have progressed following adjuvant or (neo)adjuvant chemotherapy, SG can be used at second-line.[132]

Abbreviations: BC, breast cancer; LoT, line of therapy; NA, not applicable; PD-L1, programmed cell death ligand 1; TA, technology appraisal; TNBC, triple-negative breast cancer

Sources: NICE, 2007 (TA116);[122] NICE, 2020 (TA639);[133] NICE, 2020 (TA801); NICE, 2016 (TA423);[131] NICE, 2022 (TA819)[132]

B.1.3.3.3.3 NICE Clinical Guideline 81

Recommendations for the management of advanced BC (including HER2-negative) are included in NICE Clinical Guideline 81 (CG81), which was first published in 2009 and last updated in 2017.[35]

According to NICE CG81, treatment at earlier lines is determined by HR-status, while treatment at later lines is limited to non-targeted chemotherapies.[35] Chemotherapy recommendations in NICE CG81[35] broadly align with ESMO 2021 guidelines[42] and include:

- Offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. [2009][35]
- Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. [2009][35]
- For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence[35]
    - First line: single-agent docetaxel. [2009]
    - Second line: single-agent vinorelbine or capecitabine. [2009]

- Third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment). [2009]

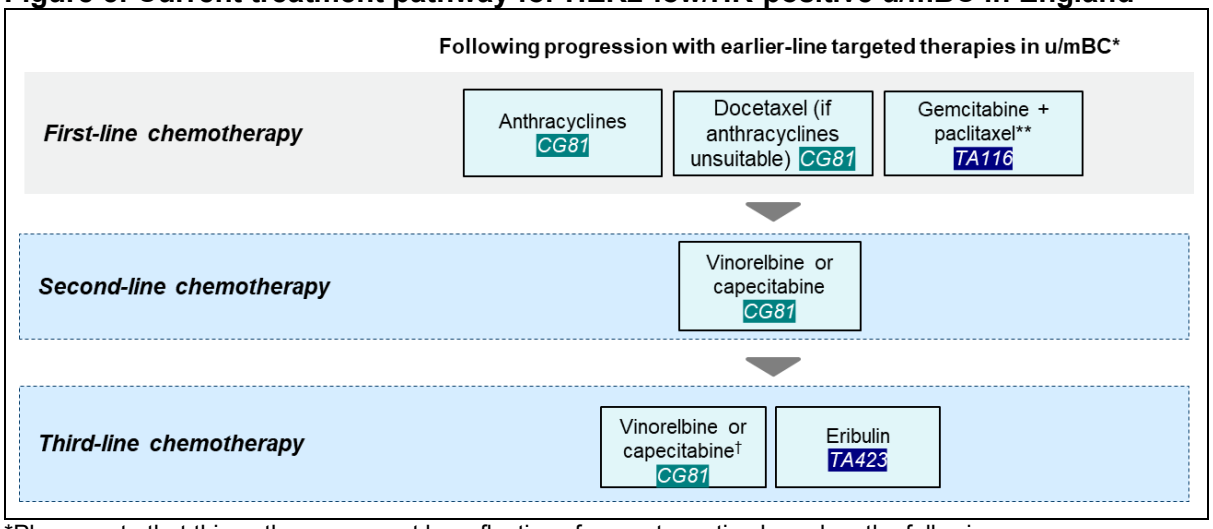
NICE has recognised that these guidelines for advanced breast cancer need updating, with an update expected in 2023.[135] In addition, at an advisory board in December 2022, UK clinical experts stated that NICE CG81 recommendations are not fully reflective of UK practice.[121] For example, UK clinical experts state that gemcitabine in combination with paclitaxel is rarely used in practice, while vinorelbine tends to be used at much later lines (e.g., fourth- and fifth-line chemotherapy in the metastatic setting) than stated in NICE CG81.[121]

B.1.3.3.3.4 Current UK pathway for HER2-low u/mBC

HER2-low/HR-positive u/mBC

The proposed current UK pathway for HER2-low/HR-positive u/mBC following progression after one line of chemotherapy in the metastatic setting is presented in **Figure 5**, based on recommendations from NICE CG81[35] and NICE TAs in HER2-negative advanced BC (TA423[131] and TA819[132]).

Figure 5: Current treatment pathway for HER2-low/HR-positive u/mBC in England



*Please note that this pathway may not be reflective of current practice based on the following:
- NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121]
- UK clinical experts and ESMO 2021[42] guidelines state that treatment decisions are made on an individual patient basis, taking into consideration prior therapies, patient fitness, and patient preference.
- UK clinical experts and ESMO 2021[42] guidelines state that there is no optimal treatment sequence.
- UK clinical experts and published data[118] indicate that all single-agent chemotherapies have similar efficacy.

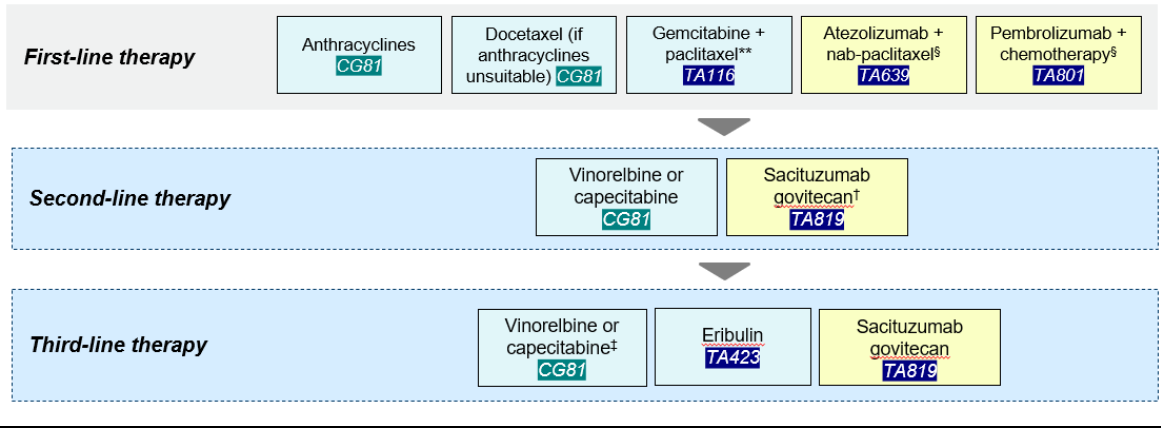
**Recommended as an option only when docetaxel monotherapy or docetaxel plus capecitabine would be considered appropriate.
†Whichever was not used as second-line treatment.
Abbreviations: CG, clinical guideline; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor; HR, hormone receptor; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; u/mBC, unresectable/metastatic breast cancer.
Sources: NICE, 2009 (CG81);[35] NICE, 2007 (TA116);[122] NICE, 2016 (TA423).[131]

HER2-low/HR-negative u/mBC

The proposed current UK pathway for HER2-low/HR-negative u/mBC following progression after one line of chemotherapy in the metastatic setting is presented in **Figure 6**, based on

recommendations from NICE CG81[35] and NICE TAs in HER2-negative advanced BC (TA423[131] and TA819[132]).

Figure 6: Current pathway for HER2-low/HR-negative u/mBC in England*



Key: Blue = Non-targeted chemotherapy; Green = targeted therapy
*Please note that this pathway may not be reflective of current practice based on the following:

- NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121]
- UK clinical experts and ESMO 2021[42] guidelines state that treatment decisions are made on an individual patient basis, taking into consideration prior therapies, patient fitness, and patient preference.
- UK clinical experts and ESMO 2021[42] guidelines state that there is no optimal treatment sequence.
- UK clinical experts and published data[118] indicate that all single-agent chemotherapies have similar efficacy.

**Recommended as an option only when docetaxel monotherapy or docetaxel plus capecitabine would be considered appropriate.
§Recommended in patients with PD-L1 positive disease only.
†Recommended after 2 or more systemic therapies, at least 1 of which was for advanced disease..
‡Whichever was not used as second-line treatment.
Abbreviations: CG, clinical guideline; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor; HR, hormone receptor; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death ligand 1; TA, technology appraisal; u/mBC, unresectable/metastatic breast cancer.
Sources: NICE, 2009 (CG81);[35] NICE, 2007 (TA116);[122] NICE, 2016 (TA423);[131] NICE, 2022 (TA819);[132] NICE TA639;[133] NICE TA801[134]

B.1.3.3.3.5 UK real-world data on treatment patterns

Insights from 2022 UK patient data from a cross-sectional patient chart review[136] highlight that current practice is nuanced and may differ to NICE CG81[35] and relevant TAs. While insights from the cross-sectional patient chart review should be interpreted with caution, they indicate that a wide range of chemotherapy agents are prescribed to patients with HER2-negative u/mBC at each line of therapy, suggesting that there is no clear single chemotherapy of choice at any point in the treatment pathway.[136] In addition, they show that vinorelbine is used comparatively infrequently in real-world practice relative to capecitabine (second-line use of vinorelbine vs. capecitabine: [redacted]% vs. [redacted]%; third-line: [redacted]% vs [redacted]%).[136]

B.1.3.3.3.6 Clinical expert insights on the treatment pathway

Advice from UK clinical experts at an advisory board in December 2022[121] aligned with real-world data and included the following:

- There are no clinically meaningful differences in the efficacy of non-targeted chemotherapy agents in the u/mBC setting.

- There is no optimal treatment sequence for non-targeted chemotherapy agents in the metastatic setting; non-targeted chemotherapy agents may be used interchangeably across lines of therapy.
- Treatment decisions are based on the specific prior treatments received, patient fitness, individual patient needs and preference, and clinical choice.

This further highlights that NICE CG81 may be outdated and that there is no clear standard of care of treatment pathway following one line of chemotherapy in the metastatic setting.

B.1.3.4 Unmet need for effective targeted therapy in HER2-low u/mBC

For patients who present with, or develop, u/mBC curative therapy is not available. Symptom burden is very high, largely due to metastases, and life expectancy and QoL are often poor.

Despite the step-change in outcomes for patients with HER2-positive u/mBC since the introduction of effective HER2-targeted therapies, these treatments are not effective in HER2-negative u/mBC. Following exhaustion of the limited targeted options such as CDK4/6is and ET (HER2-negative/HR-positive) at early lines, the only option for the majority of patients with HER2-negative u/mBC are non-targeted chemotherapies. These non-targeted chemotherapies are associated with poor outcomes; in patients currently classified as HER2-negative/HR-positive u/mBC, non-targeted chemotherapy is associated with median PFS of 3.6–4.2 months and median OS of 11.5–16.1 months.[43–47] In HER2-negative/HR-negative u/mBC, outcomes are even worse, with median PFS and median OS of 1.7–2.8 months and 6.7–12.4 months, respectively.[43,48–50] There is a clear unmet need, therefore, for novel treatments in HER2-negative u/mBC after one or more lines of chemotherapy in the metastatic setting.

A subset of HER2-negative u/mBC patients have tumours expressing low levels of HER2 and may therefore be categorised as HER2-low (IHC1+ or IHC2+/ISH-; as described in **Section B.1.3.1**). Despite tumours expressing low levels of HER2, the first available HER2 targeted therapies (e.g. trastuzumab) have proven ineffective in this population; a Phase III RCT showed no statistically significant difference in OS with the addition of trastuzumab to adjuvant chemotherapy (HR: 1.33; 95% CI 0.90, 1.95; p=0.15),[57] with five-year OS point estimates of 94.8% and 96.3% for the chemotherapy plus trastuzumab and chemotherapy arms, respectively.[57] Given the known role of HER2 in driving BC, and the OS and PFS benefit of HER2-targeted therapies in HER2-positive disease, there remains an opportunity for effective HER2-targeted therapies to improve outcomes in HER2-low u/mBC. In line with this, UK clinical experts agreed at an advisory board in December 2022 that there is a demand for effective HER2-targeted therapies in patients with HER2-low u/mBC.[121]

In addition to an unmet need to improve clinical outcomes in HER2-low u/mBC, novel treatments are needed to help ensure the NHS meets its Long Term Plan. The NHS Long Term Plan, published in 2019, outlined a number of commitments that aim to improve diagnosis, treatment, care and outcomes for BC patients. Among these commitments is a goal of 55,000 more people each year surviving for at least five years following cancer diagnosis by 2028, as well as improved QoL and patient experience outcomes.[137] The NHS could meet these long-term ambitions by making available new, effective, targeted treatments for a patient population whose current options are largely limited to non-targeted single-agent chemotherapies, which have poor efficacy.

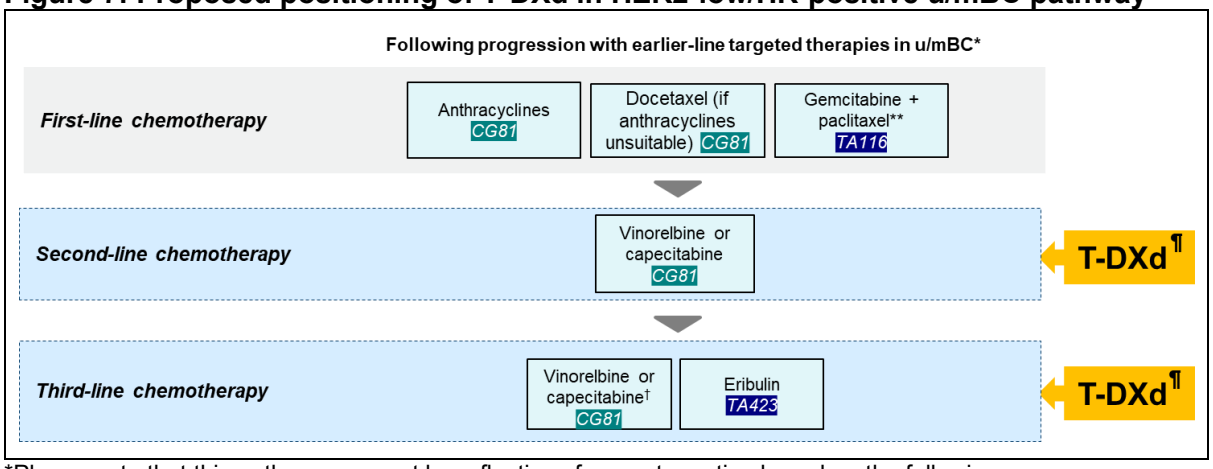
B.1.3.5 Proposed place of T-DXd in the HER2-low u/mBC treatment pathway

T-DXd is the first and only EMA-[3] and Food and Drug Administration (FDA)-approved[138,139] therapy for HER2-low u/mBC specifically. The EMA marketing authorisation in this indication is: *as monotherapy for the treatment of adult patients with unresectable or metastatic HER2 low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2).* The UK marketing authorisation wording is expected to be consistent with the EMA label.

T-DXd is expected to be positioned for patients with HER2-low u/mBC who have exhausted earlier targeted therapies and received at least one prior line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting (**Figure 7** [HR-positive] and **Figure 8** [HR-negative]). This positioning is in line with the marketing authorisation and was considered appropriate by clinical experts at an advisory board in December 2022.[121]

It should be noted that, while the pathway is aligned to NICE CG81 and NICE TAs at the relevant line of therapy, ESMO 2021 guidelines,[42] UK real-world data,[136] and clinical expert insights indicate that there is no optimal sequencing of chemotherapy agents in the metastatic setting (**Section B.1.3.3.3.4**).[118]

Figure 7: Proposed positioning of T-DXd in HER2-low/HR-positive u/mBC pathway*

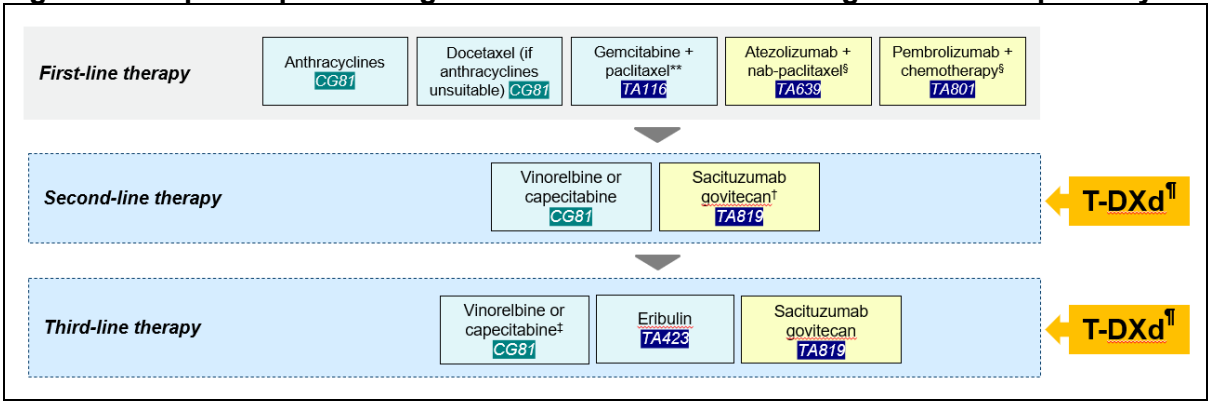


*Please note that this pathway may not be reflective of current practice based on the following:

- NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121] NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121]
- UK clinical experts and ESMO 2021[42] guidelines state that treatment decisions are made on an individual patient basis, taking into consideration prior therapies, patient fitness, and patient preference.
- UK clinical experts and ESMO 2021[42] guidelines state that there is no optimal treatment sequence.
- UK clinical experts and published data[118] indicate that all single-agent chemotherapies have similar efficacy.

**Recommended as an option only when docetaxel monotherapy or docetaxel plus capecitabine would be considered appropriate.
¶For patients with HER2-low (IHC1+ or IHC2+/ISH-) u/mBC after one line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting.
†Whichever was not used as second-line treatment.
Abbreviations: CG, clinical guidelines; ESMO, European Society for Medical Oncology; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridisation; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; u/mBC, unresectable/metastatic breast cancer; T-DXd, trastuzumab deruxtecan.
Sources: NICE, 2009 (CG81);[35] NICE, 2007 (TA116);[122] NICE, 2016 (TA423);[131] NICE, 2022 (TA819);[132] NICE TA639;[133] NICE TA801[134]

Figure 8: Proposed positioning of T-DXd in HER2-low/HR-negative u/mBC pathway*



*Please note that this pathway may not be reflective of current practice based on the following:

- NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121] NICE CG81 guidelines were published in 2009 and last updated in 2017.[35] NICE has recognised the need for these guidelines to be reviewed, with an update expected in 2023.[135] As such, NICE CG81 recommendations may no longer reflect UK clinical practice, as confirmed by UK experts at a December 2022 advisory board.[121]
- UK clinical experts and ESMO 2021[42] guidelines state that treatment decisions are made on an individual patient basis, taking into consideration prior therapies, patient fitness, and patient preference.
- UK clinical experts and ESMO 2021[42] guidelines state that there is no optimal treatment sequence.
- UK clinical experts and published data[118] indicate that all single-agent chemotherapies have similar efficacy.

**Recommended as an option only when docetaxel monotherapy or docetaxel plus capecitabine would be considered appropriate.
§Recommended in patients with PD-L1 positive disease only.
¶For patients with HER2-low (IHC1+ or IHC2+/ISH-) u/mBC after one line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting.
†Recommended after 2 or more systemic therapies, at least 1 of which was for advanced disease.
‡Whichever was not used as second-line treatment.
Abbreviations: CG, clinical guidelines; ESMO, European Society for Medical Oncology; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridisation; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death ligand 1; TA, technology appraisal; u/mBC, unresectable/metastatic breast cancer; T-DXd, trastuzumab deruxtecan.
Sources: NICE, 2009 (CG81);[35] NICE, 2007 (TA116);[122] NICE, 2016 (TA423);[131] NICE, 2022 (TA819).[132]

B.1.3.6 Relevance of the DESTINY-Breast04 TPC arm to UK clinical practice and the comparators in the decision problem

The comparator used throughout this submission is the TPC arm from the Phase III DESTINY-Breast04 study, which is the primary evidence source for this appraisal. The TPC arm in DESTINY-Breast04 comprises eribulin (51.1%), capecitabine (20.1%), paclitaxel (8.2%), nab-paclitaxel (10.3%), and gemcitabine (10.3%).[140]

The TPC arm is an appropriate comparator for this appraisal for the following reasons:

- The DESTINY-Breast04 TPC arm broadly aligns with UK clinical practice (see **Section B.1.3.6.1**).
- Using the DESTINY-Breast04 TPC arm means leveraging direct clinical trial data from prespecified analyses from the key evidence source for the appraisal (see **Section B.1.3.6.2**)
- Differences between the final scope comparators and TPC arm therapies are unlikely to impact decision-making (see **Section B.1.3.6.3**).
- A similar TPC arm was accepted as the comparator by NICE in a recent HER2-negative u/mBC appraisal (see **Section B.1.3.6.4**).

B.1.3.6.1 The DESTINY-Breast04 TPC arm broadly aligns with UK clinical practice

Defining specific comparators at each stage of the HER2-low u/mBC pathway is challenging. There are no UK clinical or reimbursement guidelines related to HER2-low specifically, with HER2-low u/mBC currently treated according to HER2-negative treatment pathways (see **Section B.1.3.3**). In HER2-negative u/mBC, there is no clear standard of care or treatment algorithm for patients who have received at least one line of chemotherapy in the metastatic setting. This is supported by NICE CG81 (see **Section B.1.3.3.3**),[35] ESMO 2021 guidelines (see **Section B.1.3.3.2**),[42] UK real-world data (see **Section B.1.3.3.3.5**),[136] and insights from UK clinical experts (see **Section B.1.3.3.3.6**),[121] which indicate that a broad range of non-targeted single-agent chemotherapies are used in the UK (e.g., capecitabine, eribulin, paclitaxel) and that there is no single standard of care, with treatment decisions driven by prior therapies received, patient fitness, individual patient needs and preference, and clinical choice.[35, 42, 121,141] While NICE CG81 (developed in 2009, last updated in 2017) states that sequential single-agent chemotherapy should be used in advanced BC and lists options to use at first-, second-, and third-line,[35] NICE has recognised that these guidelines require an update to reflect the evolving treatment landscape (update expected in 2023).[135] UK clinical experts also agree that NICE CG81 is not reflective of current practice.[121]

In addition to the lack of an established treatment pathway in HER2-low u/mBC, based on the available evidence, there is unlikely to be any significant difference in efficacy between individual non-targeted chemotherapy agents in the metastatic setting.[142,143] This is supported by evidence from a systematic review on the clinical efficacy of cytotoxic agents in Europe in anthracycline- and taxane- pre-treated advanced BC patients, in which none of the included RCTs demonstrated a significant OS difference between any of the regimens (capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles).[118] UK clinical experts also confirmed this at an advisory board meeting held by Daiichi Sankyo in December 2022, stating that there are no clinically meaningful differences in the efficacy of non-targeted chemotherapy agents in the metastatic setting or across lines of therapy.[121]

The TPC agents in DESTINY-Breast04 (capecitabine, eribulin, paclitaxel, nab-paclitaxel, gemcitabine) were chosen because they are among the most commonly used agents across key markets in the US, Japan, and Europe (including the UK).[7] TPC is a relevant comparator as it comprises single-agent chemotherapies that are broadly used in UK practice[121,136] and because, by definition, it allowed clinicians to choose the most suitable agent for each patient, which is how treatment decisions are made in real-world UK practice. The NICE final scope[1] comparators are well represented in the TPC arm, and UK clinical experts advising Daiichi Sankyo validated that the TPC arm is reflective of and generalisable to UK clinical practice.[121] A published UK real-world biomarker analysis[56] and UK clinical experts[121] also confirmed that the proportion of patients in DESTINY-Breast04 with HR-positive and HR-negative status is aligned to UK clinical practice.

Therefore, the TPC arm from DESTINY-Breast04 is representative of UK clinical practice and an appropriate comparator for this appraisal.

B.1.3.6.2 Using the DESTINY-Breast04 TPC arm means leveraging direct clinical trial data from prespecified analyses from the key evidence source for the appraisal

The TPC arm from DESTINY-Breast04 is the most robust comparator for this appraisal. DESTINY-Breast04 is the only Phase III head-to-head trial comparing T-DXd with a relevant comparator in HER2-low specifically, which means that it is the only study that provides data

on the efficacy and safety of chemotherapy in the specific population of interest for this appraisal (i.e., patients with HER2-low u/mBC after one line of chemotherapy in the metastatic setting). Using the complete TPC comparator arm from the FAS of DESTINY-Breast04 ensures use of a robust, pre-specified analysis that maintains randomisation and is aligned to the licenced population for which reimbursement is sought in this appraisal. Consistent with this, HEOR experts (including ex-NICE committee and EAG representatives) advised that the combined TPC arm is the most appropriate comparator for decision-making in this appraisal, as stratifying by HR-status, individual chemotherapy, or line of therapy would considerably reduce the sample size and add to uncertainty.[121]

B.1.3.6.3 Differences between the final scope comparators and TPC arm therapies are unlikely to impact decision-making

The TPC arm in DESTINY-Breast04 is broadly aligned to the final scope given that agents in the final NICE scope are well-represented in the TPC arm.[1,140] UK clinical experts also confirmed the TPC arm is reflective of UK practice and relevant for decision-making.[1, 121,140]

The comparators in the final scope are stated as: established clinical management without T-DXd, including:[1]

- Anthracyclines, capecitabine, platinum therapies, taxanes, and vinorelbine
- For people who have had 2 or more lines of chemotherapy for metastatic disease: eribulin
- For people whose disease is HR-negative: SG

While using the complete TPC arm in DESTINY-Breast04 is the most robust and appropriate approach for this appraisal, not all therapies in the final scope are included in the trial (i.e., anthracyclines, platinum therapies, vinorelbine, and SG [HR-negative population only]; **Section B.1.3.6.3.1**).[1,7] Additionally, in line with its licensed indication,[144] eribulin was permitted after either one or two prior chemotherapies in the metastatic setting in DESTINY-Breast04. [6] This is different to the final scope[1] as it is recommended by NICE only after two or more prior lines of chemotherapy in the locally advanced or metastatic setting (NICE TA423;[131] **Section B.1.3.6.3.2**). These differences are unlikely to have a material impact on decision-making, as discussed below in **Section B.1.3.6.5**.

B.1.3.6.3.1 Comparators in the NICE scope but not the TPC arm

Although the TPC arm of DESTINY-Breast04 is reflective of UK practice, as agreed by UK clinical experts,[121] it does not include anthracyclines, platinum therapies, vinorelbine, or SG.

Anthracyclines

Anthracyclines were not considered appropriate for the TPC arm of DESTINY-Breast04 because they are not commonly used in the metastatic setting (1% globally, 7% in Europe) according to 2018 real-world prescription data.[145] This aligns with NICE Guideline 101 (NG101) for early and locally advanced BC, which recommends anthracyclines in the (neo)adjuvant setting,[23] and NICE CG81,[35] which suggests that anthracyclines are used as first-line chemotherapy in the metastatic setting. This also aligns with UK clinical experts, who stated that anthracyclines are either used in the (neo)adjuvant setting or, beyond fourth-line chemotherapy in de novo mBC patients due to poor tolerability and cumulative cardiotoxicity.[121] Anthracyclines are therefore not relevant to this appraisal as they are used outside of the setting in which T-DXd is likely to be reimbursed.

Platinum therapies

Similarly, platinum therapies (e.g., cisplatin) are recommended in NICE NG101 in the (neo)adjuvant setting[23] but are not listed in NICE CG81[35] as second- or third-line chemotherapy options in the metastatic setting, nor are they widely used in this setting according to UK real-world data and clinical expert insights.[121,136] UK clinical experts confirmed that platinum therapies are often used in the (neo)adjuvant setting or first-line metastatic setting in HER2-negative/HR-negative patients, and at fourth-line metastatic setting or beyond in patients with other mBC subtypes (e.g., HER2-negative/HR-positive).[121] Platinum therapies are therefore not relevant to this appraisal as they are used outside of the setting in which T-DXd is likely to be reimbursed.

While vinorelbine is in the final scope[1] but not in the TPC arm of DESTINY-Breast04,[6] this will not materially impact decision-making as there is no significant difference in efficacy between vinorelbine and other in-scope single-agent chemotherapies, as shown in a published review of RCTs for chemotherapies used in Europe for advanced BC.[118] This lack of significant difference was confirmed by UK clinical experts at an advisory board, who also stated that vinorelbine is usually used later in the pathway (e.g., fourth- or fifth-line).[121] Given the similar efficacy, other agents in the TPC arm may act as suitable proxies for vinorelbine.

Sacituzumab govitecan

SG was recommended by NICE for patients with triple-negative breast cancer (TNBC) i.e., HER2-negative/HR-negative (TA819) based on the ASCENT trial.[132] While SG is in the final scope [1] it is not included in the company evidence submission as it is only a potentially relevant comparator for a small subset (i.e., HR-negative) of the overall HER2-low population considered in this appraisal. Of patients with HER2-low BC, the proportion who are HR-negative in clinical practice is very small (~10%).[146] Within this small proportion, SG is not currently considered to be standard of care within its licened indication given that it was only recently recommended by NICE [132] and its uptake in UK clinical practice is uncertain. A published UK real-world biomarker analysis[56] and UK clinical experts[121] confirmed that the distribution of HR-positive and HR-negative patients in DESTINY-Breast04 is generalisable to UK practice. Clinical experts also advised that the majority of HER2-low patients would be treated with non-targeted chemotherapy.[121]

Additionally, given the differences in study populations between DESTINY-Breast04 and ASCENT, the small sample size (N=42) of the HR-negative cohort in DESTINY-Breast04,[7] and the small sample size (N=63) and post hoc nature of analyses of HER2-low/HR-negative patients in the ASCENT trial,[48] an ITC between T-DXd and SG would be highly uncertain and not sufficiently robust for decision-making, as concluded in two independent ITC feasibility assessments (see **Section B.2.9**).[147,148] In line with this, HEOR experts advised that any comparison with SG would be highly uncertain given the small sample size and need to adjust for differences in trial populations.[121]

Based on clinical feedback relating to the generalisability of the distribution of HR-status in DESTINY-Breast04, the current treatment of these patients, and the uncertainty associated with any ITC, HEOR experts advised that, for decision making, the FAS is the relevant dataset and TPC the relevant comparator for the population under consideration in this appraisal.

B.1.3.6.3.2 Eribulin use at second- and third-line in DESTINY-Breast04

In addition to the TPC arm not including all in-scope comparators, eribulin could be used after one or two prior lines of chemotherapy in the metastatic setting in DESTINY-Breast04, which, while aligned to its licensed indication,[144] is not aligned to the NICE recommendation in TA423 or the final scope which restricts use to after two prior lines of chemotherapy.[1, 7,131]

While the company acknowledges this difference, eribulin was used frequently after two lines of chemotherapy in the metastatic setting in DESTINY-Breast04 (N=[redacted]; [redacted]; of all eribulin-treated patients),[149] meaning a considerable proportion of patients treated with eribulin were treated in the same setting as they would be in UK clinical practice.

Moreover, the removal of eribulin at second-line chemotherapy in the metastatic setting from the TPC arm has minimal impact on the treatment effect of T-DXd, as shown by results from a post hoc analysis in which patients were excluded if they were assigned to second-line eribulin prior to randomisation.[h] In this analysis, the OS HR of T-DXd vs. TPC was similar when comparing the FAS to the analysis in which second-line eribulin patients were excluded (HR: 0.64 [95% CI: 0.49, 0.87] vs. [redacted] [95% CI: [redacted], [redacted]], respectively). The PFS HR was also similar between the FAS and the analysis in which second-line eribulin patients were removed (HR: 0.50 [95% CI: 0.40, 0.63] vs. [redacted]; 95% CI: [[redacted], [redacted]], respectively).[150] Although the company acknowledges the uncertainty in post hoc analyses, the similarity between HRs indicates that the inclusion of second-line eribulin in the TPC arm of the FAS would not impact the conclusions of this appraisal. Given the increased uncertainty created by stratifying the DESTINY-Breast04 analyses by line of therapy, as confirmed by HEOR experts at an advisory board in December 2022,[121] the company considers it to be appropriate as well as robust to directly use the pre-specified DESTINY-Breast04 FAS analyses including the full TPC arm.

B.1.3.6.4 A similar TPC arm was accepted as the comparator by NICE in a recent HER2-negative u/mBC appraisal

Using a pooled TPC comparator arm in this appraisal is appropriate as a similar TPC comparator arm was recently accepted by NICE in triple-negative u/mBC (TA819; SG in unresectable triple-negative advanced BC after 2 or more therapies; August 2022).[132] The TPC arm in this appraisal consists of a similar mix of agents as TA819, including capecitabine (ASCENT: 12.6%; DESTINY-Breast04: 20.1%), eribulin (ASCENT: 53.1%; DESTINY-Breast04: 51.1%), and gemcitabine (ASCENT: 14.5%; DESTINY-Breast04: 10.3%).[7,132] In TA819, the EAG and NICE Committee accepted TPC as a suitable proxy for usual care in the NHS and a clinically relevant comparator for the population under consideration.[132] Given the similarities between the TPC arms, coupled with the robustness of directly using the pre-specified FAS analyses from a head-to-head trial, the company considers the full TPC dataset of DESTINY-Breast04 to be the most relevant comparator for this appraisal. This was confirmed by HEOR experts at an advisory board, who agreed that the pooled TPC arm is the most relevant and robust comparator for decision-making.[121]

[h] As the TPC agent was declared for each patient prior to randomisation, it was possible to exclude patients that would've been assigned to second-line eribulin from both arms.

B.1.3.6.5 Conclusion

In summary, the TPC arm is the most robust and appropriate comparator for this appraisal for the following reasons:

- There is no clear pathway in HER2-low mBC in the UK and the TPC arm of DESTINY-Breast04 is representative of and generalisable to usual care in the NHS, as confirmed by UK clinical and HEOR experts at an advisory board in December 2022.[121]
- Comparators in the final scope[1] (capecitabine, eribulin, taxanes [paclitaxel]) are well represented in the TPC arm of DESTINY-Breast04, which is generalisable to UK practice.[140]
- Any differences in the agents listed in the TPC arm vs. the final scope are expected to have minimal impact on decision-making due to similar efficacy across non-targeted chemotherapies.[118] In addition, some therapies in the final scope but not in the TPC arm are unlikely to be used in the same position as T-DXd so are unlikely to be relevant for this appraisal.
- Using the FAS of the pooled TPC arm of DESTINY-Breast04 means directly leveraging data from pre-specified analyses with the largest sample size of the key evidence source (i.e., a Phase III, head-to-head comparison with T-DXd), which the company considers to be the most robust and relevant approach and ensures consistency across the appraisal.
- Using the FAS across both treatment arms ensures the outcomes are powered to detect differences across the whole HER2-low population and maintains randomisation: efficacy analyses in the HR-negative subgroup are exploratory only.
- A TPC arm containing a similar basket of agents as the DESTINY-Breast04 TPC arm was recently accepted by NICE as a suitable proxy for usual care in the NHS and a clinically relevant comparator for the population under consideration in NICE TA819.[132]

B.1.4 Equality considerations

No equality issues are anticipated for this appraisal of T-DXd in HER2-low u/mBC.

B.2 Clinical effectiveness

Evidence for this submission comes from the pivotal, Phase III, multicentre, open-label, randomised, active-controlled DESTINY-Breast04 trial assessing the efficacy and safety of T-DXd vs. TPC in patients with HER2-low u/mBC after treatment with one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting[6,7]

- DESTINY-Breast04 is the first ever head-to-head Phase III study in HER2-low u/mBC to show a statistically significant and clinical meaningful benefit of a HER2-targeted treatment versus non-targeted chemotherapy.
- An SLR to identify studies of T-DXd in this setting confirmed there is no additional evidence of relevance for this appraisal.
- DESTINY-Breast04 is ongoing, with evidence presented in this submission from the primary analysis of PFS (DCO 11 January 2022) with median follow-up of [redacted] months in the FAS (16.1 months with the T-DXd arm and 13.5 months with TPC).[7]
- DESTINY-Breast04 met statistical significance for all key efficacy endpoints.[7]

DESTINY-Breast04 provides evidence on treatment with T-DXd that is generalisable and relevant to UK patients

- DESTINY-Breast04 enrolled patients with either HR-positive or HR-negative HER2-low u/mBC who had received one or two lines of chemotherapy in the unresectable or metastatic setting. If recurrence occurred within six months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as one line of chemotherapy. Patients with HR-positive u/mBC had to have progressed after previous treatment with at least one line of ET, and be deemed to no longer benefit from further ET.[7]
- The comparator arm was TPC, consisting of eribulin (51.1%), capecitabine (20.1%), nab-paclitaxel (10.3%), gemcitabine (10.3%), and paclitaxel (8.2%).[6] The generalisability of the TPC arm to UK practice was validated with UK clinical experts;[121] no clear standard of care exists following prior chemotherapy, chemotherapies used in UK practice have similar efficacy and are well represented in the TPC arm.[118,142,143]

DESTINY-Breast04 met the primary endpoint of statistically significant PFS benefit by BICR in the HR-positive cohort[6,7]

- Median PFS by BICR in the HR-positive cohort was 10.1 months (95% CI: 9.5, 11.5) in the T-DXd arm vs. 5.4 months (95% CI: 4.4, 7.1) in the TPC arm.[6]
- T-DXd was associated with a statistically significant 49% lower risk of progression or death compared with TPC (HR: 0.51; 95% CI: 0.40, 0.64; p<0.001) in the HR-positive cohort.[6]
- PFS by BICR was confirmed by PFS by IA (HR: [redacted] for T-DXd vs. TPC; 95% CI: [redacted]) in the HR-positive cohort.[7]

DESTINY-Breast04 also met its key secondary endpoints of PFS by BICR in the FAS, OS in the HR-positive cohort and OS in the FAS[6]

- In the FAS, T-DXd was associated with a statistically significant improvement in PFS by BICR compared with TPC (HR: 0.50; 95% CI: 0.40, 0.63; p<0.001).[6]
- In the HR-positive cohort, T-DXd was associated with a statistically significant improvement in OS compared with TPC (HR: 0.64; 95% CI: 0.48, 0.86; p=0.003).[6]

- In the FAS, T-DXd was associated with a statistically significant improvement in OS compared with TPC (HR: 0.64; 95% CI: 0.49, 0.84; p=0.001).[6]

T-DXd was associated with a statistically significant confirmed ORR and higher CR and PR rates than TPC[6,7]

- In the FAS, T-DXd was associated with a significantly greater confirmed ORR by BICR (52.3%) compared with TPC (16.3%) at DCO (p<0.0001).[6,7]
- In the FAS, a best overall response of CR and PR by BICR was observed in more than twice as many patients in the T-DXd arm as the TPC arm (CR: 3.5% vs. 1.1%; PR: 49.1% vs. 15.2%).[6]

PFS benefit was consistent across stratification factors and pre-specified subgroups

- PFS benefit was consistent across key subgroups, including HER2 status, HR-status, number of prior lines of chemotherapy in the metastatic setting, prior CDK4/6 inhibitor use, and ECOG performance status.[7,140]

T-DXd has a manageable and well-known safety profile in u/mBC, with no new safety concerns identified in DESTINY-Breast04[7]

- Exposure-adjusted AE rates were lower for T-DXd than TPC for TEAEs, Grade ≥3 TEAEs, drug-related TEAEs, and TEAEs related to dose modification.[6]
- In the T-DXd arm, the most common TEAEs of any grade were nausea (76.0%), fatigue (53.6%) and vomiting (40.4%). The majority of TEAEs associated with T-DXd were low grade.[7]
- No new AEs of concern were identified with T-DXd in the DESTINY-Breast04 study vs. previous studies of T-DXd, including DESTINY-Breast01 and DESTINY-Breast03.[20,68]

In DESTINY-Breast04, T-DXd was associated with longer TTDD in QoL than TPC across PRO tools in the FAS and HR-positive cohort[151]

- In the FAS, HRQoL as measured by the EORTC QLQ-30 and EORTC QLQ-BR45 was maintained from baseline to end of treatment in the T-DXd arm (median change from baseline: [redacted] for both scales).[152]
- In the FAS, median TTDD was longer with T-DXd vs. TPC for EQ-5D-5L VAS ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]), for EORTC QLQ-30 global health status ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]), and for the arm symptom scale of the EORTC QLQ-BR45 ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]).[152]

Abbreviations: AE, adverse event; BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CR, complete response; DCO, data cut-off; ECOG, Eastern Cooperate Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol-5 Dimension-5 Level; ET, endocrine therapy; FAS, full analysis set; HER2, human epidermal growth factor receptor-2; HR, hazard ratio; HR-positive, hormone receptor-positive; HRQoL, health-related quality-of-life; IA, investigator assessment; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; QLQ-30, Quality-of-life Questionnaire Core 30; QLQ-BR45, Quality-of-life Questionnaire Breast Cancer; QoL, quality-of-life; SLR, systematic literature review; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice; TTDD, time to definitive deterioration; VAS, Visual Analogue Scale.

B.2.1 Identification and selection of relevant studies

A systemic literature review (SLR) was conducted to identify the existing clinical evidence detailing the efficacy, safety, and QoL associated with currently available and investigational therapies used for patients with HER2-negative or HER2-low u/mBC, who have received prior chemotherapy in the recurrent or metastatic setting. See **Appendix D.1** for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

Comprehensive literature searches for clinical evidence were undertaken in electronic databases (MEDLINE, Embase and The Cochrane Library [including the Cochrane Database of Systematic Reviews {CDSR} and the Cochrane Central Register of Controlled Trials {CENTRAL}]) for studies published prior to 25 February 2022. These were supplemented by further targeted searches that covered recent abstracts, posters, and podium presentations that were yet to be included in the aforementioned databases (2020-2022). Data from eligible studies were extracted and assessed for methodological quality and applicability.

In total, the SLR identified 12,358 unique publications after removing duplicates, of which 11,321 were excluded at title or abstract review. Of the remaining 1,037 publications, 953 were excluded at abstract or full text review, primarily because they did not have an appropriate study design, had unclear baseline characteristics, were the wrong line of treatment, did not include the relevant population, or were non-English. A final total of 97 relevant publications in HER2-negative or HER2-low u/mBC were included for data extraction (including 13 publications identified through bibliographic and grey literature searches). For a summary of the methodology and outcomes of included studies, see **Appendix D**.

Of the studies included for data extraction, only one (ASCENT; SG vs. TPC in metastatic TNBC) reported data for HER2-low patients specifically, and within this study the HER2-low population was a small subgroup of the full TNBC population. This highlights the lack of studies in HER2-low u/mBC specifically.

At the time of the initial SLR (25 February 2022), results from the key trial of T-DXd in HER2-low u/mBC (DESTINY-Breast04) were not published. The company therefore conducted hand searches to identify data published from 25 February 2022 to 13 February 2023 related to T-DXd in HER2-low in this setting, given that T-DXd is the intervention under consideration in this appraisal. In addition, as ASCENT was identified in the original SLR as the only study reporting data for a HER2-low population, hand searches were also conducted for further published data related to ASCENT. These hand searches identified two publications related to DESTINY-Breast04 and six articles related to ASCENT. Data from publications identified in these hand searches were extracted using the same approach as the initial SLR (see **Appendix D** for outputs of the data extractions).

As per NICE's preference for RCTs that directly compare the technology with one or more relevant comparators, the only study evaluating T-DXd with relevant comparators was DESTINY-Breast04, which was reported in no publications in the original SLR (25 February 2022) and in three publications in the hand searches (13 February 2023). This submission therefore focuses on the key evidence from DESTINY-Breast04, as reported in these publications (**Table 8**) as well as the clinical study report (CSR).

DESTINY-Breast04 is a Phase III, head-to-head study comparing the efficacy and safety of T-DXd versus TPC in patients with HER2-low u/mBC following one or two prior lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. If recurrence occurred within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as one line of chemotherapy.

B.2.2 List of relevant clinical effectiveness evidence

Table 8: Clinical effectiveness evidence

Study	**DESTINY-Breast04 (NCT03734029)**
Study design	Phase III, multicentre, open-label, randomised, active-controlled, trial. 2:1 treatment assignment.
Population	Adult patients with HER2-low u/mBC who have received one or two prior lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting
Intervention(s)	T-DXd administered by IV infusion at a dose of 5.4 mg/kg (N=373)
Comparator(s)	Physician's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel, administered in accordance with the local label or the NCCN guidelines (N=184)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	Pivotal trial in relevant patient population versus relevant comparators[1]
Reported outcomes specified in the decision problem	• **PFS** • **OS** • **Response rates** • Duration of response • **AEs** • **HRQoL**
All other reported outcomes	• Time to response • **Time to treatment discontinuation** • Hospitalisation
Key publication	Modi et al. 2022[6]
Secondary sources	Daiichi Sankyo Inc., DESTINY-Breast04 CSR. Data on file, 2022.[7] Modi, S. et al., ASCO, 2022.[140] Ueno, N. et al., EMSO, 2022.[151]

Outcomes incorporated in the model are shown in **bold**.
Abbreviations: AE, adverse event; BC, breast cancer; CSR, clinical study report; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality-of-life; IV, intravenous; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; u/mBC, unresectable or metastatic breast cancer.
Sources : Modi et al., 2022 ;[6] Daiichi Sankyo Inc., DESTINY-Breast04 CSR. Data on file, 2022[7]

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

B.2.3.1 DESTINY-Breast04

Study design

DESTINY-Breast04 is a Phase III, multicentre, randomised, two-arm, open-label, multicentre trial conducted across multiple countries including the UK (study design shown in **Figure 9**).[7,153] The study enrolled adults with HER2-low u/mBC (defined by tissue biopsy as IHC 1+ or IHC 2+/ISH-negative) who had previously been treated with at least one and no more than two lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within six months of (neo)adjuvant chemotherapy, this would count as one line of chemotherapy.[7] Targeted agents (e.g. CDK4/6 inhibitors, PARP inhibitors, PD-L1 inhibitors) and ET did not contribute to the count of prior lines of chemotherapy unless they were used in combination with a chemotherapy agent.[7]

The study enrolled patients with either HR-positive or HR-negative HER2-low u/mBC. Approximately 60 patients with HR-negative BC were to be enrolled, after which enrolment was limited to patients with HR-positive u/mBC. Patients with HR-positive u/mBC had to have been previously treated with at least one line of ET but had progressed and were determined by the investigator to no longer benefit from further ET.[7] The protocol specified enrolment of no more than 240 patients with HR-positive BC who had no prior therapy with a CDK4/6 inhibitor and at least 240 patients with HR-positive BC who had prior therapy with a CDK4/6 inhibitor.[7]

Approximately 540 patients were randomised 2:1 to T-DXd or TPC by an interactive web/voice response system (IXRS). Randomisation was stratified by HER2 IHC status (IHC 1+ vs. IHC2+/ISH-negative), number of prior lines of chemotherapy (1 vs. 2), and HR/CDK status (HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative).[7]

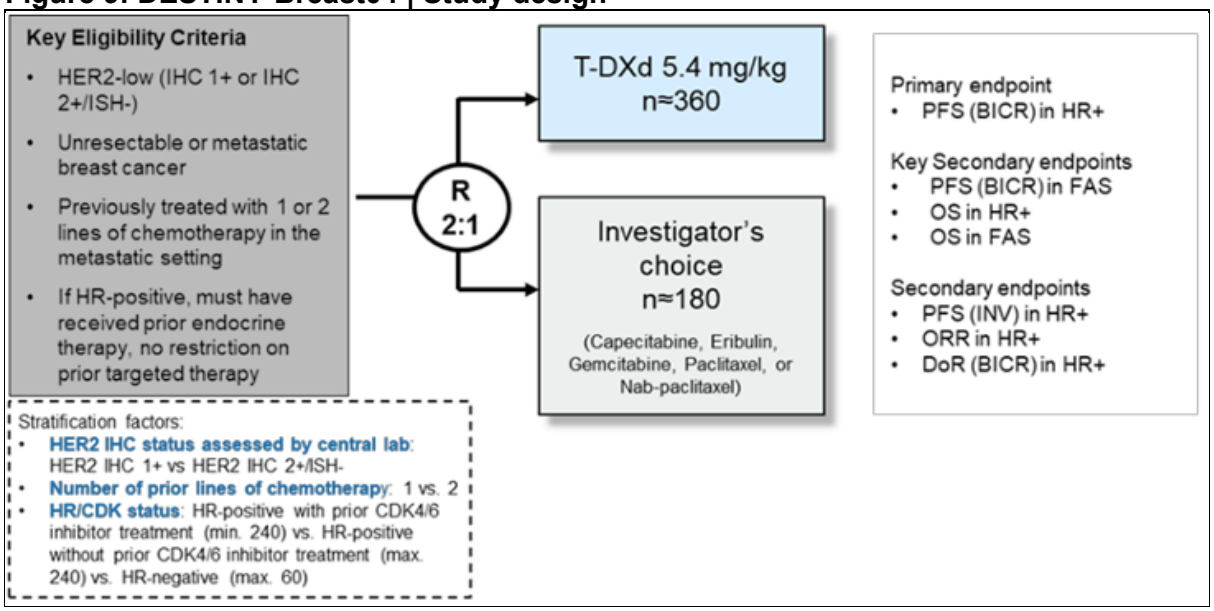
T-DXd was administered intravenously at a dose of 5.4 mg/kg every 3 weeks, based primarily on efficacy and safety data from DESTINY-Breast01, supplemented by pharmacology information from other studies (Study J101, DS8101-A-J102, DS8201-A-A103, DS8201-A-A104).[7] TPC consisted of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel, which were chosen based on the five most commonly used single-agent chemotherapy regimens across the US, France, Germany, Italy, Spain, UK, and Japan.[7] The dose, regimen, mode of administration, and dose modification of TPC agents was aligned to the local label or NCCN guidelines.[7]

The primary endpoint of the study was PFS by blinded independent central review (BICR) in the HR-positive cohort. Key secondary endpoints were PFS by BICR in the FAS, and OS in the HR-positive cohort and OS in the FAS.[7] The data cut-off (DCO) date for all evidence in this submission was 11 January 2022 which was the primary analysis of PFS (no formal interim analysis were planned for PFS). [7]

At the 11 January 2022 DCO date, median duration of follow-up was [redacted] months in the FAS (16.1 months in the T-DXd arm and 13.5 months in the TPC arm).[7] The study met its primary endpoint of PFS by BICR in the HR-positive cohort.[7] Key secondary endpoints in accordance with the hierarchical testing procedure were also met: PFS by BICR in the FAS, OS in the HR-positive cohort, and OS in the FAS.[7]

A summary of the methodology of DESTINY-Breast04 is shown in **Table 9**.

Figure 9: DESTINY-Breast04 | Study design



Abbreviations: BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4 and 6; DoR, duration of response; FAS, Full Analysis Set; HER2, human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; IHC, immunohistochemistry; INV, investigator assessment; ISH, in situ hybridisation; max, maximum; min., minimum; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; T-DXd, trastuzumab deruxtecan; vs., versus.
Sources: Modi et al., 2022[6]

Table 9: Summary of DESTINY-Breast04 methodology

Trial design	A randomised, two-arm, Phase III, open-label, multicentre study to compare the safety and efficacy of T-DXd vs. TPC in subjects with HER2-low, u/mBC.
	Randomisation: 2:1 by Interactive Web/Voice Response System (IXRS) **Stratification factors:** HER2 IHC status (IHC +1 vs. IHC +2/ISH-negative), prior lines of chemotherapy (1 vs. 2), and HR/CDK status (HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative). **Blinding:** Open-label, as it was infeasible to blind treatment allocations due to differences in routes of administration and treatment schedules between T-DXd and TPC. The primary endpoint was based on BICR. The study team did not perform or have access to efficacy analysis/summary during the study.[7,153] An independent biostatistician generated the randomisation schedule per the randomisation specification.[153]
Duration of study	Planned: approximately [redacted] months Median duration of follow-up at DCO (11 Jan 2022; FAS): • T-DXd: 16.1 months (range [redacted]). • TPC: 13.5 months (range: [redacted]). • Overall: [redacted] months (range [redacted]).
Settings and locations where data were collected	161 centres in 19 countries, including Europe (Austria, Belgium, France, Greece, Hungary, Israel, Italy, Portugal, Russia, Spain, Sweden, Switzerland, UK), Asia (China, Japan, South Korea, Taiwan), and North America (Canada, US)
Participant eligibility criteria	**Key inclusion criteria** • Aged ≥18 years (or in line with local regulatory requirements if legal age of consent was >18 years)

	• Pathologically documented BC that: o was unresectable or metastatic. o had a history of, or central laboratory assessed, low HER2 expression (defined as IHC1+ or IHC2+/ISH-negative). o was previously treated with at least one and no more than two prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within six months of (neo)adjuvant chemotherapy it would count as one line of chemotherapy. Targeted agents (e.g. CDK4/6 inhibitors, PD-L1 inhibitors) and ET did not count as a line of chemotherapy unless administered in combination with chemotherapy. o if HR-positive, was previously treated with at least one line of ET before progressing and being deemed to no longer benefit from further ET. • Documented radiologic progression (during or after most recent treatment or within six months after completing adjuvant therapy). • Presence of ≥1 measurable lesion per modified RECIST v1.1. • ECOG performance status 0–1. • Adequate bone marrow function, renal function, hepatic function, and blood clotting function within 14 days before randomisation.
	Key exclusion criteria • Prior treatment with the declared TPC comparators in the metastatic setting, or an ADC consisting of an exatecan derivative. • Uncontrolled or significant cardiovascular disease. • History of (non-infectious) ILD/pneumonitis requiring steroids, current diagnosed or suspected ILD/pneumonitis, or clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses. • Spinal cord compression or clinically active CNS metastases defined as untreated, symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.‡ • History of severe hypersensitivity to drug substances or inactive ingredients in the drug product, or to other mAbs. • Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals, or patients with HIV, or active hepatitis B or C. • Multiple primary malignancies within 3 years.§ • Unresolved non-alopecia toxicities from prior anti-cancer therapy. • Therapeutic radiation therapy or major surgery within 4 weeks before randomisation, or palliative stereotactic radiation therapy within 2 weeks before randomisation. • Systemic anti-cancer therapy within three weeks before randomisation, or antibody-based anti-cancer therapy within four weeks before randomisation. • Pregnancy, breastfeeding, or plan to become pregnant.
Trial drugs	**Intervention:** T-DXd (N=373) was administered at a starting dose of 5.4 mg/kg (based on patient weight at screening), as IV infusion over 90 minutes for the first infusion. Subsequent doses were infused over a minimum of 30 minutes** every 21 days (± 2 days). Dosage was recalculated if a patient's weight changed by ≥10% of their baseline weight value. **Comparator:** TPC (N=184) from 5 options: capecitabine, eribulin, gemcitabine, paclitaxel and nab-paclitaxel. • Capecitabine (N=37) was administered at a dose of 1000-1250 mg/m^2 orally, twice daily on Days 1-14 of a 21-day cycle.

	• Eribulin (N=94) was administered at a dose of 1.4 mg*/m^2 intravenously, on Days 1 and 8 of a 21-day cycle. • Gemcitabine (N=19) was administered at a dose of 800-1200 mg/m^2 intravenously, on either Days 1 and 8 of a 21-day cycle or on Days 1, 8, and 15 of a 28-day cycle. • Paclitaxel (N=15) was either administered at a dose of 175 mg/m^2 intravenously, on Days 1 of a 21-day cycle, or at a doses of 80 mg/m^2 intravenously, on Day 1 of a weekly cycle. • Nab-paclitaxel (N=19) was either administered at a dose of 260 mg/m^2 intravenously, on Day 1 of a 21-day cycle, or at a doses of 100 mg/m^2 or 125 mg/m^2 intravenously, on Days 1, 8 and 15 of a 28-day cycle.
	Dose modifications for T-DXd in the event of toxicity were to be made on the basis of AE type, severity, and relatedness to study drug, outlined in the T-DXd management guideline (**Appendix O**) Dose modifications for TPC were made in accordance with the label approved in the country of drug administration or NCCN guidelines. **Dose interruption:** Both T-DXd and TPC could be delayed/interrupted for up to 28 days from the planned date of administration (49 days from the last infusion date). Patients were to discontinue in the event that their dosing was delayed or interrupted for longer than 28 days (49 days from last infusion date). **Dose reduction:** Two dose reduction levels in the event of toxicity were permitted for T-DXd (4.4 kg/kg and 3.2 mg/kg). Once a reduction was made due to toxicity, all subsequent cycles were at the lower dose level unless further dose reductions were required. Continued toxicity after two dose reductions resulted in discontinuation of T-DXd. For the TPC arm, dose adjustments were made in accordance with the local label or NCCN guidelines. **Study drug discontinuation:** Patients were to discontinue T-DXd or TPC for the following reasons: PD according to RECIST v1.1, clinical progression (definitive clinical signs of PD, but for which recent radiographic assessment did not meet RECIST PD criteria), AEs requiring discontinuation (**Appendix M**), or death.[††]
Concomitant medication	**Permitted concomitant medication:** Prophylactic treatment of study drug-induced nausea and vomiting was per investigator's discretion and institutional guidelines. Haematopoietic growth factors could be used for prophylaxis/treatment based on investigator's judgement (except within 1 week prior to screening) Based on currently available clinical safety data, prophylactic antiemetic agents were recommended before and subsequent to T-DXd infusions Concomitant use of dietary supplements, medications not prescribed by investigator, and alternative/complementary treatments were discouraged but not prohibited **Prohibited concomitant medication:** Other anti-cancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anti-cancer hormonal treatment (concurrent use of noncancer-related conditions was acceptable); other investigational therapeutic agents; chloroquine or hydroxychloroquine; radiotherapy to thorax or any radiotherapy not for palliative therapy for known metastatic sites; chronic systemic corticosteroids (IV or oral) or other immunosuppressive medications except for managing AEs,[‡‡] or (for the TPC arm) any products prohibited by the relevant local label.

Primary outcomes	PFS by BICR in the HR-positive cohort (see **Section B.2.4.2** for further details of outcomes and **Section B.2.4.1** for details of analysis sets)
Other outcomes used in the model/specified in scope	• PFS by BICR in the FAS • OS in the FAS • Safety (AEs) • QoL assessed by EQ-5D • ORR by BICR
Other outcomes of interest	• OS in the HR-positive cohort • PFS by IA in the HR-positive cohort and the FAS • Confirmed ORR by BICR and IA in the HR-positive cohort and FAS • DoR by BICR in the HR-positive cohort and FAS • TTR in by BICR in the HR-positive cohort and FAS • CBR by BICR in the HR-positive cohort • DCR by BICR in the HR-positive cohort • PFS, OS, confirmed ORR and DoR in the HR-negative subgroup • Best percentage change in diameter of tumour in the HR-positive cohort • HRQoL assessed by EORTC QLQ-C30 in HR-positive cohort • HRQoL assessed by EORTC QLQ-BR45 in HR-positive cohort • Hospitalisation-related endpoints in the HR-positive cohort and FAS
Pre-planned subgroups	Subgroup analyses for PFS based on BICR were performed for the HR-positive cohort and the FAS. Subgroup analyses of OS were performed for the HR-positive cohort and FAS using the same subgroups defined for the PFS analysis and using the same methodology, provided PFS and OS analyses are significant for both the HR-positive cohort and FAS. Subgroup analyses were only performed for a category of subgroup if at least 10 events were observed in both treatment arms. Pre-specified subgroups were: hormone receptor status; HER2 status; HR-status; lines of prior chemotherapy; prior CDK4/6 inhibitor; lines of prior ET; best response to last prior anti-cancer systemic therapy; baseline renal function; baseline hepatic function; baseline visceral disease; baseline CNS metastases; history of CNS metastases; age; race; region; ECOG performance status.

* Refers to eribulin mesylate (1.23 mg eribulin base = 1.4 mg eribulin mesylate).
‡Patients with brain metastases that were clinically inactive or no longer symptomatic and not requiring corticosteroids/anticonvulsants were eligible if recovered from acute toxic effects of radiotherapy.
§Exceptions were adequately resected non-melanoma skin cancer, curatively treated *in situ* disease, or contralateral BC.
**Infusion time was reduced to ≥30 minutes only if no infusion-related reactions were observed in the patient.
††Additional reasons not listed above are: pregnancy, withdrawal of patient consent, lost to follow-up, protocol deviation, physician decision, or study terminated by sponsor. Patients could continue to receive treatment if they were receiving benefit from it, despite meeting a criterion for discontinuation, if approved by the investigator, sponsor, and sponsor medical monitor.
‡‡Inhaled steroids or intra articular steroid injections were permitted, and patients who required intermitted use of bronchodilators were not excluded from the study.
Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclic-dependent kinase; CNS, central nervous system; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HR-positive, hormone receptor-positive; HRQoL, health-related quality-of-life; IA, investigator assessment; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTR, time to response; u/mBC, unresectable or metastatic breast cancer.
Sources: Modi et al., 2022;[6] Daiichi Sankyo Inc., 2022 (CSR; Data on File);[7] Daiichi Sankyo Inc., 2022 (SAP; Data on File)[153]

Screening period assessments

During initial tissue screening, a tumour sample for HER2 status (archived tissue appropriate for central laboratory HER2 testing, or fresh biopsy if archived tissue not available) and serious AEs related to tumour biopsy (unless documentation of other AEs were also recorded because of requirement by local law) were required.[7]

During the screening period, from Day -28 to Day -1, a range of assessments were conducted, including left ventricular dysfunction assessments (echocardiogram or multigated acquisition scan), CT/MRI tumour assessments, CT/MRI of the brain, and tests for human immunodeficiency virus, hepatitis B, and hepatitis C.[7]

From Day -14 to Day -1, a range of assessments were conducted, including those for study eligibility, demographics, medical and surgical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, pre-treatment AEs, concomitant medications, 12-lead electrocardiogram (ECG) in triplicate, and haematology/biochemistry of patients.[7]

Trial outcomes

Trial endpoints, their definitions, and censoring rules are shown in **Table 10**.

Table 10: DESTINY-Breast04 | Summary of key endpoints

Endpoint/assessment	Details	Censoring rules
Primary endpoint		
PFS (by BICR) in the HR-positive cohort	Defined as the time from the date of randomisation to the earliest date of the first objective documentation of radiographic disease progression per BICR according to mRECIST version 1.1 or death due to any cause	• No baseline evaluable tumour assessment: censored at date of randomisation • No post-baseline tumour assessment: censored at date of randomisation • Early death (within 14 weeks of randomisation) for no baseline or no post-baseline tumour assessment: event at date of death • Radiographic disease progression/death without missing ≥2 consecutive tumour assessments immediately preceding event: event at date of progressive disease assessment or death • Disease progression or death after missing ≥2 consecutive scheduled tumour assessments: censored at date of last evaluable tumour assessment prior to earliest death/progression date and analysis cut-off date • At least one post-baseline response assessment and no death or objective documentation of radiographic disease progression: censored at date of last evaluable tumour assessment (prior to analysis cut-off date) • Started anti-cancer therapy prior to disease progression, death, or analysis cut-off date: censored at date of last evaluable tumour assessment prior to anti-cancer therapy other than the study drug (for sensitivity analysis only)
Key secondary endpoint		
OS in the FAS	Defined as the time from the date of randomisation to the date of death for any cause. If no death was reported for a patient before the data cut-off for OS analysis, OS was censored at the last contact date at which the patient was known to be alive	The last contact date was defined as the last date the patient was known to be alive at the analysis cut-off date. The date was the latest date among the below. Only dates with actual assessments were used • Last non-missing assessment/onset date captured under the following eCRF pages (or if a date of assessment/onset is not available the “date of visit” for the eCRF page can be used): adverse events, vital signs, physical examination, ECOG PS, ECG, clinical laboratory test, tumour

Endpoint/assessment	Details	Censoring rules
		assessment, and also PK/biomarker/other specimen sample collection date • Last dosing date of study drug, last date of concomitant medications, and last date of non-drug 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
PFS (by BICR) in the FAS	As per PFS (by BICR) in the HR-positive cohort	As per PFS (by BICR) in the HR-positive cohort
OS in the HR-positive population	As per OS in the FAS	As per OS in the FAS
Secondary endpoints		
ORR (by BICR) in the FAS and HR-positive cohort	Defined as the proportion of patients who achieved a best overall response of CR or PR, based on BICR. Confirmation of CR or PR was required. Response definitions: • CR: disappearance of all target lesions • PR: ≥30% decrease in the sum of diameters of target lesions from baseline • PD: ≥20% increase in sum of diameters of target lesions, taking the smallest sum of diameters since study, or appearance of a new lesion • SD: response not fitting the criteria for PR or PD	Not applicable
Duration of response (by BICR) in the FAS and HR-positive cohort	Defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression based on BICR or investigator's assessment or to the date of death due to any cause. Duration of response was to be measured for only patients with a response of CR or PR. Subjects who were	Censoring rules were the same as described above for PFS by BICR

Endpoint/assessment	Details	Censoring rules
	progression-free at the time of the analyses were to be censored at the date of the last evaluable tumour assessment	
PFS by investigator assessment in the FAS	Defined as the time from the date of randomisation to the earliest date of the first objective documentation of radiographic disease progression per investigator assessment according to mRECIST version 1.1 or death due to any cause	As per PFS by BICR in the HR-positive cohort
QoL endpoints (related to TTDD) in the FAS and HR-positive cohort	Endpoints included EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L	If no baseline evaluable QoL and/or no post-baseline QoL assessment: • Death by first survival follow-up (3 months from 40-day visit): event at date of death • No death: censored at date of randomisation If baseline and at least one post-baseline QoL assessment: • Increase of ≥10 points (compared with baseline) at ≥2 consecutive time points on the symptom subscale score in question (confirmed): event at date of first deterioration of the consecutive assessments with an increase of ≥10 points • Increase of ≥10 points (compared with baseline) at last assessment on the symptom subscale score in question: event at date of last assessment if that is the last one • Death by first survival follow-up (3 months from 40-day visit): event at date of death • Others: censoring at date of last assessment
Resource use/ hospitalisation endpoints in the FAS and HR-positive cohort	Hospitalisation-related endpoints, including: • Reasons for hospitalisation • Discharge status • Length of hospital and/or ICU stay • Time to first hospitalisation, defined as the time from the date of randomisation to the date of the first hospitalisation during the study treatment (from date of first dose to 47 days after last dose)	Not applicable
Exploratory endpoints		

Endpoint/assessment	Details	Censoring rules
Time to response (by BICR) in the FAS and HR-positive cohort	Defined as the time from the date of randomisation to the date of the first documentation of objective response (CR or PR), based on BICR. Time to response was measured for only those patients who had a CR or PR	NA
Best percent change in the sum of the diameter of measurable tumours based on BICR in the FAS and HR-positive cohort	The tumour measurement at the Screening Visit was used as the baseline tumour measurement	NA
Clinical benefit rate (by BICR) in the FAS and HR-positive cohort	Defined as the sum of CR rate, PR rate, and more than 6 months SD rate, based on BICR	Both of the following conditions must have been met for “more than 6 months SD”: • Best overall response was SD, and • Duration of SD was 183 days or more
PFS on the next line of therapy (by IA) in the FAS and HR-positive cohort	Defined as the time from date of randomisation to the first documented progression on next-line therapy or death due to any cause, whichever occurs first	If patients did not receive new systemic anti-cancer therapy: • Death: event at date of death • No death: censored at date of last contact date If patients received new systemic anti-cancer therapy: • Disease progression during next line therapy before/on the analysis cut-off date: event at date of progressive disease assessment • Death during next line therapy and before/on the analysis cut-off date: event at date of death • No disease progression/death during next line therapy and received a second new systemic anti-cancer therapy before/on the analysis cut-off date: censored at end date of the first new systemic anti-cancer therapy • No disease progression/death during next line therapy did not receive a second new systemic anti-cancer therapy before/on the analysis cut-off date: censored at last contact date
Disease control rate (by BICR or IA) in the FAS and HR-positive cohort	Defined as the proportion of subjects with BOR of CR, PR, or SD, based on BICR and investigator assessment.	NA
PFS, OS, ORR, and duration of response in the HR-negative cohort	As per their respective definitions in the HR-positive cohort and FAS.	As per their respective definitions in the HR-positive cohort and FAS.

Endpoint/assessment	Details	Censoring rules
Safety endpoints		
Assessment of AEs and SAEs	Safety endpoints included SAEs, TEAEs, AEs of special interest, TEAEs associated with dose reduction and/or study drug interruption, TEAEs associated with discontinuation of study treatment, TEAEs associated with an outcome of death, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings. All AEs were categorised using the MedDRA. AEs and abnormal laboratory test results, if applicable, were graded using NCI CTCAE Version 5.0	NA

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Echo, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report from; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HR-positive, hormone receptor-positive; IA, investigator assessment; ICU, intensive care unit; MedDRA, Medical Dictionary for Regulatory Activities; mRECIST, modified Response Evaluation Criteria in Solid Tumours; MUGA, multigated acquisition scan; NA, not applicable; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QLQ-BR45, Quality-of-life Breast Cancer questionnaire; QLQ-C30, Quality-of-life of Cancer Patients questionnaire; SAP, Statistical Analysis Plan; SD, stable disease; TEAE, treatment-emergent adverse event; TTDD, time to definitive deterioration.
Source: Modi et al., 2022;[6] Daiichi Sankyo, Inc., 2022 (SAP; Data on File)[153]

Assessment timepoints and follow-up

HRQoL questionnaires (EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L), physical examination, patient weight, and ECOG performance status were to be completed/assessed before infusion at the start of each cycle.[7] The HRQoL questionnaires were completed before any other assessments or procedures were done on the day.

End of treatment assessments were to occur within seven days of the date the investigator decided to discontinue study treatment.[7] Follow-up assessments took place at 40 days (+7 days) after administration of the last study treatment or before starting new anti-cancer treatment, whichever came first. In long-term follow-up, assessments took place every three months (±14 days) from the date of the 40-day follow-up assessment, until death, withdrawal of consent, loss to follow-up, or study closure.[7,153]

Vital signs and pharmacokinetic blood samples (T-DXd arm only) were assessed both before and after infusion at every cycle, at end of treatment, and at 40-day follow-up.[7]

Tumour assessment (CT and/or MRI with ≤5 mm cuts of chest, abdomen, pelvis, and any other sites of disease) and CT/MRI of the brain were to take place every six weeks and at the end of treatment.[153] AEs, concomitant medications, and hospitalisation-related records were recorded from Cycle 1 to the end of treatment, and at 40-day follow-up and long-term follow-up.[7,153]

Questionnaires for HRQoL outcomes were to be completed at end of treatment, at 40-day follow-up, and at the first three-month follow-up, which was the last data collection timepoint for all questionnaires.[7] Survival follow-up was assessed at long-term (every 3 months) follow-up timepoints.[7]

T-DXd was to be administered every 21 days ±2 days unless study drug interruption/ modification or discontinuation was required. For the TPC arm, if a patient received a regimen other than a 21-day cycle, the investigator was to ensure that the subject followed the study-defined schedule of events per a 28-day cycle. Tumour assessments and CT/MRI of the brain had to be performed every 6 weeks ±7 days from randomisation date. Laboratory and safety assessment before drug administration were to be appropriately performed according to the TPC label approved in the country of drug administration.[7]

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

B.2.4.1 Analysis sets

Patient data sets analysed in DESTINY-Breast04 are described in **Table 11**. Efficacy analyses were performed on the HR-positive cohort and FAS, and safety analyses on the safety analysis set (SAS).[7,153]

The per-protocol analysis set (PPS) included HR-positive patients who complied sufficiently with the protocol with respect to study drug exposure, tumour assessment, and absence of major protocol violations, and was to be used for sensitivity analysis of the primary endpoint.[7] Pharmacokinetic (PK) endpoints were to be evaluated using the PK analysis set, which included patients who received at least one dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and DXd.[7] Analyses

based on the PPS and PK are not considered to be of relevance to this submission and are not presented here.

Table 11: DESTINY-Breast04 | Analysis sets

Analysis set	Definition	Number of patients, n (%)		
		T-DXd	TPC	Total
Full analysis set (FAS)	Included all patients randomised into the study. Following the intention-to-treat principle, patients were analysed according to the treatments and strata they were assigned to at randomisation	373 (100.0)	184 (100.0)	557 (100.0)
Primary analysis set: HR-positive cohort	Included all patients randomised into the study who were HR-positive. This is the primary analysis set for the efficacy analyses, following the intention-to-treat principle	331 (88.7)	163 (88.6)	494 (88.7)
Safety analysis set (SAS)	Included all randomised patients who received ≥1 dose of study treatment (either T-DXd or TPC). Patients were summarised according to treatment actually received. Treatment received was the randomised treatment unless the alternative treatment was received throughout the study	371 (99.5)	172 (93.5)	543 (97.5)
Per-protocol analysis set (PPS)	Included all patients in the HR-positive population with sufficient compliance to the protocol with respect to exposure to study treatment, availability of tumour assessments, and absence of major protocol deviations likely to impact efficacy outcome. To be eligible for inclusion in the PPS, patients had to meet the following criteria: • Received ≥1 dose of study drug as assigned by randomisation • Had ≥1 evaluable post-baseline tumour assessment by BICR or died within 14 weeks of first dose • Absence of major protocol violations*	361 (96.6)	164 (89.1)	525 (94.3)
Pharmacokinetic (PK) analysis set	Included all patients who received ≥1 dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and/or DXd	370 (99.2)	0	370 (66.4)

*Major protocol violations included: not signing main consent form; violation of major inclusion/exclusion criteria; receipt of study drug regimen not assigned by randomisation.
Abbreviations: BICR, blinded independent central review; CDK, cyclic-dependent kinase; FAS, full analysis set; HER2; human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; PK, pharmacokinetic; PPS, per-protocol analysis set; SAS, safety analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (SAP and CSR; Data on File)[7,153]

B.2.4.2 Statistical analyses

Statistical methods used, or to be used, in DESTINY-Breast04 are summarised below (**Table 12**). The primary efficacy endpoint, and the key secondary efficacy endpoints, will be tested hierarchically to maintain the overall two-sided type-I error rate to 0.05 or less in the following order:

1. **PFS by BICR analysis in HR-positive cohort | conducted at ≥318 PFS events:** the observed two-sided p-value threshold was p=0.001 to conclude superiority of T-DXd over TPC for the primary endpoint.[153]
    - **If PFS not statistically significant:** PFS in FAS and OS analysis not conducted.
    - **If PFS statistically significant:** PFS in FAS and OS analysis conducted.
2. **PFS by BICR analysis in the FAS | conducted at ≥318 PFS events (in the HR-positive cohort) assuming PFS significant in the HR-positive population:** the observed two-sided p-value threshold was p=0.001 to conclude superiority of T-DXd over TPC.[153]
3. **OS in the HR-positive cohort:** Statistical testing will be performed only when superiority in PFS is demonstrated for both the HR-positive cohort and the FAS. Up to three OS analyses are planned, in the order below:
    - First interim analysis at the time of the primary analysis for PFS (provided PFS is significant in both the HR-positive cohort and the FAS), at which point a total of [redacted] OS events ([redacted]% information fraction) in the HR-positive cohort are expected.
    - If the first OS interim analysis is not significant, a second interim analysis for OS is planned when approximately [redacted] OS events ([redacted]% information fraction) in the HR-positive cohort have been documented.
    - If the second OS interim analysis is not significant, a final analysis for OS is planned after approximately [redacted] OS ([redacted]% information fraction) events in the HR-positive cohort have been documented.
4. **OS in the FAS:** As above, up to three OS analyses were planned. As per the hierarchical testing, the statistical testing will be performed only when the analyses in the hierarchy above have demonstrated statistical significance.

Table 12: DESTINY-Breast04 | Summary of statistical analyses

Hypothesis objective	Compared with TPC, T-DXd confers a significant benefit to subjects with HER2-low BC [redacted]
Statistical analysis	The primary efficacy endpoint, and the key secondary endpoints, will be tested hierarchically to maintain the overall two-sided type-I error rate to 0.05 or less, in the order below: 1. PFS based on BICR in the HR-positive cohort 2. PFS based on BICR in the FAS 3. OS in the HR-positive cohort (up to 3 analyses) 4. OS in the FAS (up to 3 analyses) **Primary endpoint (PFS by BICR in the HR-positive)** was analysed through comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test, with strata being the same as the randomisation stratification factors from IXRS, at an overall two-sided significance level of 0.05. The primary efficacy analysis is planned to be performed after approximately 318 BICR PFS events in the HR-positive subjects have been documented in the study (primary analysis for PFS). The treatment effect HR of PFS and its two-sided 95% CI were estimated using a stratified Cox proportional hazards regression model with the

	same stratification factors as the randomisation stratification factors taken from IXRS. Median PFS time and the two-sided 95% CIs using the Brookmeyer-Crowley method were provided for each treatment group, as well as Kaplan-Meier estimates of PFS rates at fixed time points **Key secondary efficacy endpoints:** • PFS by BICR in the FAS was analysed as described above for the primary endpoint (PFS in the HR-positive cohort). Statistical testing will be performed only when PFS in the HR-positive cohort is statistically significant. • OS (for FAS and HR-positive) was analysed through comparison of the two treatment groups using a stratified log-rank test, with strata being the same as the randomisation stratification factors from IXRS, at an overall two-sided significance level of 0.05. The survival distribution will be estimated by the Kaplan-Meier method. Median OS with two-sided 95% CIs was calculated with the Brookmeyer-Crowley method. A HR with two-sided 95% CIs was calculated with a stratified Cox proportional hazards regression model. Interim analyses will take place at approximately 162 (IA1) and 233 OS events (IA2) and final analyses will take place once 333 OS events have occurred. As per the hierarchical testing procedure, OS in the FAS could not be tested until statistical significance was demonstrated in PFS by BICR in the HR-positive and FAS groups, and in OS in the HR-positive group. **Other secondary efficacy endpoints** • PFS by IA survival distribution was estimated by the Kaplan-Meier method. Median PFS by IA with two-sided 95% CIs was calculated with the Brookmeyer-Crowley method. A HR with two-sided 95% CIs was calculated with a stratified Cox proportional hazards regression model • ORR was summarised by treatment group, with two-sided 95% CIs calculated using the Clopper-Pearson method • Duration of response (based separately on BICR and IA) was summarised by median duration and its two-sided 95% CI calculated using the Brookmeyer-Crowley method **Exploratory endpoints** Both CBR and DCR were determined using the same analyses as for ORR by BICR. TTR was summarised using descriptive statistics. The change of sum of diameters from baseline to post-baseline was summarised using a waterfall plot for each patient and each treatment group, with vertical lines representing the sorted values of percent changes. The survival distribution of PFS2 was estimated using the Kaplan-Meier method. Median PFS2 with two-sided 95% CIs were calculated with the Brookmeyer-Crowley method. PFS2 HRs and their two-sided 95% CIs were calculated with a stratified Cox proportional hazards regression model. **Safety endpoints** were assessed with descriptive statistics **QoL and resource use/hospitalisation endpoints** were summarised by time point for each treatment group • EQ-5D-5L was assessed with descriptive statistics and Kaplan-Meier methods. Summary of visit-level scores and change from baseline were assessed for both the VAS and index scores. Time to definitive deterioration on the VAS was assessed using the stratified log-rank test and a two-sided type-I error rate of 5%. A survival distribution of time to definition deterioration was estimated by the [redacted]

	• Changes from baseline in EORTC QLQ-C30 were assessed using a linear mixed effect model for longitudinal data, and the descriptive p-values, differences in least square means, and the corresponding two-sided 95% CI was calculated. Time to definitive deterioration on the global QoL scale and physical functioning, emotional functioning, social functioning, and pain symptom subscales was assessed using the stratified log-rank test and at two-sided type-I error rate of 5%. The survival distributions of time to definition deterioration were estimated by the Kaplan-Meier method, and HRs and their 95% CIs were calculated with a stratified Cox proportional hazards regression model • Changes from baseline in EORTC QLQ-BR45 were assessed using a linear mixed effect model for longitudinal data, and the descriptive p-values, differences in least square means, and the corresponding two-sided 95% CI was calculated. Time to definitive deterioration on the 'breast symptoms' and 'arm symptoms' subscales was assessed using the stratified log-rank test and at two-sided type-I error rate of 5%. The survival distributions of time to definition deterioration were estimated by the Kaplan-Meier method, and HRs and their 95% CIs were calculated with a stratified Cox proportional hazards regression model **Subgroup analysis of PFS by BICR** was carried out on all pre-specified patient subgroups (detailed in Section B.2.7) that had ≥10 PFS events in both treatment arms. Kaplan-Meier estimates of median PFS and two-sided 95% CIs were obtained, with the HR and corresponding 95% CI calculated using the unstratified Cox regression model.
Sample size, power calculation	The study was planned with a group sequential design, with a three-look Lan-DeMets alpha spending function and an O'Brien-Fleming type stopping boundary. In the HR-positive, it was hypothesised that treatment with T-DXd would result in an HR of 0.68, a 32% reduction in the hazard rate of PFS (disease progression or death), which would correspond to a 47% improvement in median PFS from 4.2 months in the TPC arm to 6.2 months in the T-DXd arm under the exponential model assumption. Approximately 480 patients, with HR-positive BC, were planned for randomisation (320 patients to T-DXd and 160 patients to TPC). In addition, 60 patients, with HR-negative BC, were also planned for randomisation (40 to T-DXd and 20 to TPC). The primary PFS analysis in the HR-positive was to occur after approximately 318 PFS events were documented. With 318 PFS events in approximately 480 patients, the study had approximately 90% power to detect an HR of 0.68 in PFS at an overall two-sided significance level of 0.05 to reject the null hypothesis of no difference in PFS distributions (HR=1) using a log-rank test and a two-look group sequential design with O'Brien-Fleming efficacy boundary. The sample size computation was performed using the EAST v6.4.43 Conditional on PFS being significant, a total of 333 OS events would be needed to ensure 80% power of a log-rank test to reject a null hypothesis of no difference in OS distributions at an overall 2-sided significance level of 0.05 under a 3-look group sequential design with O'Brien-Fleming type superiority stopping boundary of Lan-DeMets alpha spending function assuming a HR of 0.72. If the true HR is 0.72, it was estimated that approximately 162 (49%) and 233 (70%) of the targeted OS events would be documented in the HR-positive cohort at the time of the first and second OS IAs, respectively, with the first OS IA performed at the time of the PFS primary analysis. The primary OS analysis was projected to occur approximately 49.3 months from the date the first subject was randomised, when 333 OS events had been documented in the hormone receptor positive cohort. The sample size computation was performed using the EAST v6.4.

Data management, patient withdrawals	In general, missing or dropout data were not to be imputed for the purpose of data analysis, except for incomplete date of AEs, prior and concomitant medications, prior and new anti-cancer therapy, determination of time since diagnosis, incomplete death date, missing severity assessment of AEs, and missing relationship to study drug of AEs. The rules for censored data for each endpoint are defined in Table 10.
Statistical analysis timepoints	The primary efficacy analysis was planned for when approximately 318 BICR-assessed PFS events were observed in the HR-positive cohort. With 318 PFS events, the study will have approximately 90% power of a log-rank test to reject the null hypothesis of no difference in PFS distributions at an overall 2-sided significance level of 0.05, assuming a hazard ratio of 0.68. At the DCO, there were [redacted] PFS events in the HR-positive cohort and statistical significance was demonstrated for primary and key secondary endpoints of PFS and OS, so there is no protocol requirement for further data analyses.

Abbreviations: AE, adverse event; BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HR-positive, hormone receptor-positive; HR-negative, hormone receptor negative; HR, hazard ratio; IA, investigator assessment; IXRS, Interactive Web/Voice Response System; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; QLQ-BR45, Quality-of-life Breast Cancer questionnaire; QLQ-C30, Quality-of-life of Cancer Patients questionnaire; QoL, quality-of-life; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTR, time to response; VAS, visual analogue scale.
Source: Daiichi Sankyo, 2022, (CSR and SAP; Data on File).[7,153]

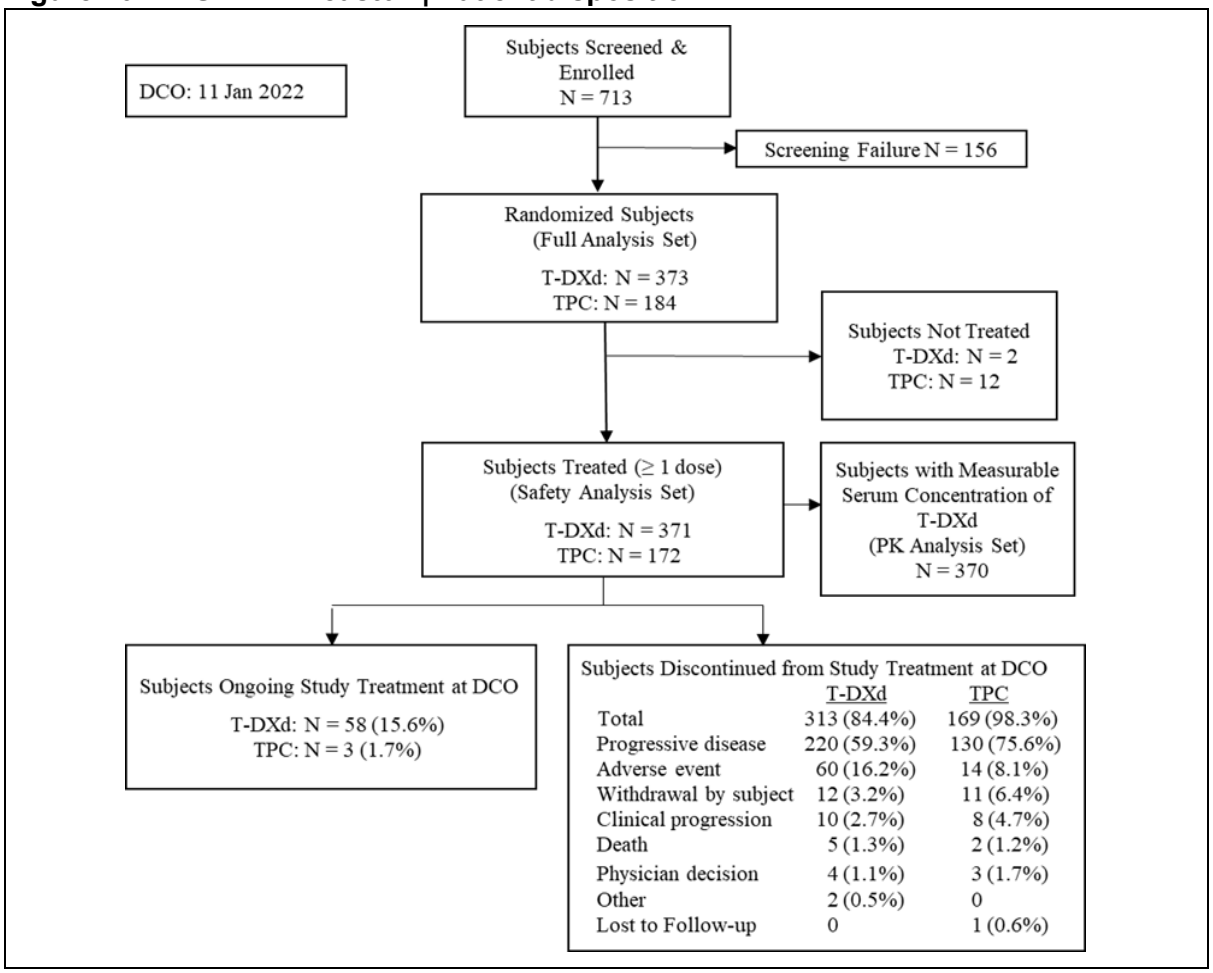
B.2.4.3 Patient flow in DESTINY-Breast04

In the FAS, 557 patients were randomised 2:1 to receive T-DXd and TPC, respectively (**Table 13** and **Figure 10**). Of the 373 and 184 patients randomised to T-DXd and TPC, 331 and 163 patients, respectively, were HR-positive. Of the 557 patients randomised, 543 (T-DXd, 371; TPC, 172) received at least one dose of study drug and 14 (T-DXd, 2; TPC; 12) were randomised but not treated, with a majority withdrawing consent after randomisation.[7]

At the primary analysis for PFS (DCO, 11 January 2022) the median follow-up in the FAS for T-DXd and TPC was 16.1 and 13.5 months, respectively (**Table 13**). At the DCO in the FAS, 58 (15.6%) patients in the T-DXd arm and 3 (1.7%) patients in the TPC arm were ongoing treatment; 220 (59.3%) T-DXd and 130 (75.6%) TPC patients discontinued due to progressive disease; 10 (2.7%) T-DXd and 8 (4.7%) TPC patients discontinued due to clinical progression; 60 (16.2%) T-DXd and 14 (8.1%) TPC patients discontinued due to AEs; and for 5 (1.3%) T-DXd and 2 (1.2%) TPC patients, the reason for discontinuation was death.[7] All percentages are based on the SAS.

Among the single-agent chemotherapies permitted in TPC, eribulin was the most commonly used (94 [51.1%] patients in the FAS), followed by capecitabine (37 [20.1%]), nab-paclitaxel (19 [10.3%]), gemcitabine (19 [10.3%]) and paclitaxel (15 [8.2%]).[140]

Figure 10: DESTINY-Breast04 | Patient disposition



Abbreviations: DCO, data cut-off; PK, pharmacokinetic; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 13: Disposition of all screened patients | HR-positive cohort and FAS

Parameter	Number (%) of patients					
	HR-positive cohort			FAS		
	T-DXd (N=331)	TPC (N=163)	Total (N=494)	T-DXd (N=373)	TPC (N=184)	Total (N=557)
Randomised	331	163	494	373	184	557
Randomised but not treated	[redacted]	[redacted]	[redacted]	2 (0.5)	12 (6.5)	14 (2.5)
Study duration (months)[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status (based on SAS)[b]						
N in safety analysis set	[redacted]	[redacted]	[redacted]	371	172	543
Ongoing	[redacted]	[redacted]	[redacted]	58 (15.6)	3 (1.7)	61 (11.2)
Discontinued	[redacted]	[redacted]	[redacted]	313 (84.4)	169 (98.3)	482 (88.8)
Primary reason for study drug discontinuation (based on SAS)[b]						
N in safety analysis set	[redacted]	[redacted]	[redacted]	371	172	543
Progressive disease per RECIST v1.1	[redacted]	[redacted]	[redacted]	220 (59.3)	130 (75.6)	350 (64.5)
Adverse event	[redacted]	[redacted]	[redacted]	60 (16.2)	14 (8.1)	74 (13.6)

Withdrawal by subject	[redacted]	[redacted]	[redacted]	12 (3.2)	11 (6.4)	23 (4.2)
Clinical progression per investigator	[redacted]	[redacted]	[redacted]	10 (2.7)	8 (4.7)	18 (3.3)
Death	[redacted]	[redacted]	[redacted]	5 (1.3)	2 (1.2)	7 (1.3)
Physician decision	[redacted]	[redacted]	[redacted]	4 (1.1)	3 (1.7)	7 (1.3)
Other	[redacted]	[redacted]	[redacted]	2 (0.5)	0	2 (0.4)
Lost to follow-up	[redacted]	[redacted]	[redacted]	0	1 (0.6)	1 (0.2)

[a] Study duration for a subject (months) was defined as (date of last known alive minus date of randomisation plus 1)/365.25×12.
[b] The percentage was based on the SAS.
Abbreviations: HR-positive, hormone receptor-positive; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Sources: Modi et al., 2022 ;[6] Daiichi Sankyo Inc., 2022 (CSR, Data on File)[7]

Table 14: TPC single-agent chemotherapy use | All screened patients (N=184)

Single-agent chemotherapy	Patients, N (%)
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Abbreviations: TPC, treatment of physician's choice
Source: Modi et al., ASCO 2022;[140] Daiichi Sankyo Inc., 2022 (CSR; Data on File)[7]

B.2.4.4 Patient baseline characteristics

Patient baseline characteristics for DESTINY-Breast04 are presented in **Table 15**. Between December 27, 2018, and December 31, 2021, 557 patients with HER2-low mBC were enrolled at 161 centres in 19 countries.[7]

Demographically, patients were generally well balanced across treatment arms at baseline (**Table 15**). Median age was similar in the T-DXd and TPC treatment arms (57.5 vs. 55.9 years in the FAS),[6] as was the proportion of patients who were female (99.5% vs. 100%, FAS); only two male patients were enrolled (both in the T-DXd arm).[6] The proportion of patients who were white, black, Asian, and of other ethnicity was similar between the T-DXd and TPC arms (in the FAS: white: 47.2% vs. 49.5%; black: 1.9% vs. 1.6%; Asian: 40.5% vs. 39.1%;other: 10.5% vs. 9.2%).[6] Current smoking status was also similar in the T-DXd and TPC arms ([redacted] vs. [redacted]; FAS).[7]

Baseline disease characteristics were also generally similar between the two treatment arms (**Table 15**). The proportion of patients with HER2-low IHC 1+ was the same in each arm (57.6%, FAS), as was the proportion with IHC2+/ISH-negative (42.4%, FAS).[6] The proportion of patients with positive hormone receptor status was also similar for T-DXd vs. TPC (89.3% vs. 90.2%, FAS).[6] The proportion of patients with ECOG performance status 1 was slightly higher in the T-DXd arm (46.4 vs. 42.9%; FAS).[6] Similarly, a slightly higher proportion of T-DXd vs. TPC had baseline liver metastases (71.3% vs. 66.8%, FAS),[6] and visceral disease (89.0% vs. 85.3%; FAS).[7] The proportions with baseline lung metastases (32.2% vs. 34.2% for T-DXd and TPC, respectively [FAS])[6] and stable brain metastases (6.4% vs. 4.3%, FAS)[6] were similar.

In terms of prior BC therapies (including CDK4/6i/ET, targeted therapies and chemotherapies; **Table 15**), the median number of lines of prior systemic therapy in any setting and in the metastatic setting was 4 and 3, respectively, in both treatment arms.[6,7] The

proportion of patients with 1, 2, or ≥3 prior lines of systemic treatment in the metastatic setting was similar between treatment arms.[6]

The median number of prior lines of ET in any setting and in the metastatic setting was 2 and 2, respectively, in both treatment arms.[7] The proportion of patients who received prior ET and who received 0, 1, 2 or ≥3 prior lines of ET in the metastatic setting was similar between treatment arms.[7]

The median number of prior lines of chemotherapy in any setting and in the metastatic setting was 2 and 1, respectively, in both treatment arms.[7] As per the eligibility criteria, nearly all patients in both treatment arms had received one or two prior lines of chemotherapy in the metastatic setting[i] (98.1% vs. 99.4% in the T-DXd and TPC arms, respectively),[7] which aligns to the scope of this appraisal[1] and proposed positioning of T-DXd in HER2-low u/mBC in the UK. The proportion of patients who had received one prior line of chemotherapy in the metastatic setting was slightly higher in the T-DXd vs. TPC arm (59.2% vs 54.3%; FAS), and slightly lower for two prior lines of chemotherapy in the metastatic setting (38.9% vs. 45.1%; FAS).[7]

The proportion of patients who had received prior ET, targeted therapy including CDK4/6 inhibitors and immunotherapy, and chemotherapy was also similar across the two arms.[7]

Table 15: DESTINY-Breast04 | Patient baseline characteristics

Characteristic	HR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Age, years				
Mean (standard deviation)	56.3 (10.57)	56.3 (11.39)	56.5 (10.58)	56.5 (11.51)
Median (range)	56.8 (31.5–80.2)	55.7 (28.4–80.0)	57.5 (31.5– 80.2)	55.9 (28.4–80.5)
Female, %	99.4	100.0	99.5	100.0
Region, n (%)				
Europe	149 (45.0)	73 (44.8)	166 (44.5)	85 (46.2)
Asia	128 (38.7)	60 (36.8)	147 (39.4)	66 (35.9)
North America	54 (16.3)	30 (18.4)	60 (16.1)	33 (17.9)
Race, n (%)				
Asian	131 (39.6)	66 (40.5)	151 (40.5)	72 (39.1)
White	156 (47.1)	78 (47.9)	176 (47.2)	91 (49.5)
Black or African American	7 (2.1)	2 (1.2)	7 (1.9)	3 (1.6)
Other	37 (11.2)	16 (9.8)	39 (10.5)	17 (9.2)
Missing data	0	1 (0.6)	0	1 (0.5)
Weight, kg				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)				
Never	[redacted]	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]	[redacted]
Current	[redacted]	[redacted]	[redacted]	[redacted]

[i] If recurrence occurred within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy was counted as 1 line of chemotherapy in the advanced disease setting. Patients with 0 and 3 prior lines of chemotherapy represent protocol deviations.

Characteristic	HR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Stratification factor: HER2 IHC status per IXRS, n (%)				
1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
2+/ISH-negative	138 (41.7)	68 (42.4)	158 (42.4)	78 (42.4)
ECOG PS, n (%)				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
Hormone receptor status (derived based on factors captured in electronic data capture), n (%)*				
Positive	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Negative	3 (0.9)	1 (0.6)	40 (10.7)	18 (9.8)
Stratification factor: HR/CDK status per IXRS, n (%)				
HR-positive with prior CDK4/6	233 (70.4)	115 (70.6)	233 (62.5)	115 (62.5)
HR-positive without prior CDK4/6	98 (29.6)	48 (29.4)	98 (26.3)	48 (26.1)
HR-negative	0	0	42 (11.3)	21 (11.4)
Stable brain metastases, n (%)	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Stable brain metastases defined as a reported history of CNS metastases, n (%)	30 (9.1)	13 (8.0)	37 (9.9)	15 (8.2)
Presence of baseline lung metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of baseline liver metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline visceral disease, n (%)	298 (90.0)	146 (89.6)	332 (89.0)	157 (85.3)
Prior lines of systemic therapy in any setting, n (%)				
1	2 (0.6)	3 (1.8)	5 (1.3)	4 (2.2)
2	37 (11.2)	24 (14.7)	48 (12.9)	33 (17.9)
≥3	292 (88.2)	136 (83.4)	320 (85.8)	147 (79.9)
Mean (SD)	4.3 (1.70)	4.4 (1.97)	4.2 (1.71)	4.2 (1.95)
Median	4	4	4	4
Prior lines of systemic therapy in the metastatic setting, n (%)				
0	29 (8.8)	18 (11.0)	61 (16.4)	35 (19.0)
1	23 (6.9)	14 (8.6)	39 (10.5)	19 (10.3)
2	85 (25.7)	4 (25.2)	100 (28.6)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	234 (62.7)	112 (60.9)
Mean (SD)	3.3 (1.49)	3.3 (1.45)	3.2 (1.52)	3.1 (1.45)
Median	3	3	3	3
Type of prior systemic cancer therapy, n (%)				
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Chemotherapy	331 (100.0)	162 (99.4)	373 (100.0)	183 (99.5)
Supportive Therapy	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior endocrine therapy, n (%)				
0	1 (0.3)	3 (1.8)	26 (7.0)	19 (10.3)
1	65 (19.6)	34 (20.9)	74 (19.8)	35 (19.0)
2	112 (33.8)	46 (28.2)	117 (31.4)	49 (26.6)
≥3	153 (46.2)	80 (49.1)	156 (41.8)	81 (44.0)
Mean (SD)	2.6 (1.26)	2.6 (1.37)	2.4 (1.37)	2.3 (1.48)
Median	2.0	2.0	2.0	2.0
Lines of prior endocrine therapy in metastatic setting, n (%)				
0	28 (8.5)	17 (10.4)	60 (16.1)	34 (18.5)
1	105 (31.7)	49 (30.1)	108 (29.0)	51 (27.7)

Characteristic	HR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
2	110 (33.2)	53 (32.5)	115 (30.8)	54 (29.3)
≥3	88 (26.6)	44 (27.0)	90 (24.1)	45 (24.5)
Mean (SD)	2.6 (1.26)	2.6 (1.37)	2.4 (1.37)	2.3 (1.48)
Median	2.0	2.0	2.0	2.0
Lines of prior chemotherapy, n (%)				
0	0	1 (0.6)**	0	1 (0.5)**
1	89 (26.9)	49 (30.1)	93 (24.9)	52 (28.3)
2	155 (46.8)	61 (37.4)	176 (47.2)	71 (38.6)
≥3	87 (26.3)	52 (31.9)	104 (27.9)	60 (32.6)
Mean (SD)	2.0 (0.81)	2.1 (0.93)	2.1 (0.81)	2.1 (0.95)
Median	2.0	2.0	2.0	2.0
Stratification factor: Lines of prior chemotherapy in metastatic setting per IXRS†, n (%)				
0**	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3**	3 (0.9)	0	6 (1.6)	0
Mean (SD)	1.4 (0.51)	1.4 (0.51)	1.4 (0.53)	1.4 (0.51)
Median	1	1	1	1

*[redacted].

**Represents a protocol deviation.

†If recurrence occurred ≤6 months of (neo)adjuvant chemotherapy, (neo)adjuvant chemotherapy was counted as one line of chemotherapy. Subjects with 0 or 3 prior lines of chemotherapy represent protocol deviations.

Abbreviations: BMI, body mass index; CDK, cyclic-dependent kinase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; ITT, intent-to-treat; IXRS, interactive web/voice response system; PS, performance status; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Sources: Modi et al., 2022;[6] Daiichi Sankyo Inc., 2022 (CSR and SAP, Data on File)[7,153]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of DESTINY-Breast04 was conducted using the NICE single technology assessment: User guide for company evidence submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination; **Table 16**).

The quality assessment review was initially conducted by an agency consultant used by the company to support submission development, and subsequently independently and separately checked by two representatives from the company. Any disagreements were resolved through discussion between the reviewers. It was not possible to conduct the review in a blinded manner as all reviewers were aware that DESTINY-Breast04 was the only relevant trial identified by the systematic review. The assessment decisions are as described in **Appendix D.2**.

Table 16: DESTINY-Breast04 | Quality assessment results

Questions	DESTINY-Breast04
Was randomisation carried out appropriately?	**Yes:** Patients were randomised 2:1 by an IXRS and stratified by HER2 IHC status (HER2 IHC 1+ vs. HER2 IHC 2+/ISH-negative), number of prior lines of chemotherapy (1 vs. 2) and HR and CDK status (HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative).

Questions	DESTINY-Breast04
Was the concealment of treatment allocation adequate?	**Not applicable:** DESTINY-Breast04 is an open-label study. To minimise any risk of bias, the sponsor was blinded to aggregate data by treatment arm, although the study participant and investigator would be aware of the study drug administered. It was not feasible to blind treatment allocations for individual subjects because of different routes of administration and different treatment schedules between T-DXd and TPC. The study team did not perform or have access to efficacy analysis/summary during the study. An independent biostatistician generated the randomisation schedule per the randomisation specification. Methods of concealment to study arms (i.e., via IXRS) are summarised in the row above.
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No:** Open-label study design. As stated in the CSR, it was not feasible to blind treatment allocations for individual patients because of different routes of administration and different treatment schedules between T-DXd and TPC. Outcome assessors for key endpoints – including the primary endpoint (PFS by BICR in the HR-positive cohort) and a key secondary endpoint (PFS by BICR in the FAS) – were blinded to treatment allocation. The study team did not perform or have access to efficacy analysis/summary during the study. An independent biostatistician generated the randomisation schedule per the randomisation specification.
Were there any unexpected imbalances in drop-outs between groups?	**No:** Dropout rates from randomisation to first dose were lower in the T-DXd arm versus TPC arm (2 [0.5%] vs. 12 [6.5%]; FAS). The majority of drop-outs were due to withdrawal of consent after randomisation.
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.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analyses were performed using the FAS and HR-positive cohort. Following the intention-to-treat principle, subjects were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: In general, missing or dropout data were treated as missing, and were not imputed for the purpose of data analysis, unless otherwise specified in the SAP.

Abbreviations: AE, adverse event; BICR, blinded independent central review; CDK, cyclic-dependent kinase; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR-positive, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; IXRS, interactive voice and web response system; PFS, progression-free survival; RCT, randomised controlled trial; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; SAP, statistical analysis plan.

B.2.5.1 Limitations of the evidence base

The open-label study design presents a limitation to the evidence base, but the impact is considered minimal given that key endpoints, including the primary endpoint (PFS by BICR in the HR-positive cohort) were assessed by BICR.[7]

Another potential limitation was that study recruitment restricted the total number of patients in the HR-negative cohort to ~60.[7] The relative proportion of patients in DESTINY-Breast04

with HR-positive and HR-negative BC was 88.7% and 11.3%, respectively.[7] This is consistent with a published UK biomarker analysis involving over 199,000 patient data sets, which showed that 89.6% of all HER2-low u/mBC patients are HR-positive and 10.4% are HR-negative.[56] This confirms that the DESTINY-Breast04 population is representative of UK clinical practice and consistent with UK Clinical expert feedback received by the company (Dec 2022 advisory board).[121]

Another limitation may be that the number of patients receiving individual TPC agents is too small to allow meaningful subgroup analyses (e.g., by individual chemotherapy agent or by line of therapy). However, this is not expected to have an impact on the interpretation of DESTINY-Breast04 results, as there was consensus from UK clinical experts (December 2022 advisory board) that there is no difference in efficacy across non-targeted chemotherapy agents in the metastatic setting.[121] In addition, as described in **Section B.1.3.6**, the pooled TPC arm is broadly representative of UK practice, as there is no single standard of care in this setting, and is the most robust comparator for this appraisal.

At the time of the primary analysis database lock, targeted source data verification could not be completed for some sites due to site access limitations as a result of the COVID-19 pandemic. The risk to data quality was considered minimal, as alternative methods of risk-based monitoring/central monitoring of data review and data cleaning activities were conducted over the course of the study.[7]

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 DESTINY-Breast04

Data presented in this submission are from the primary analysis for PFS (DCO, 11 Jan 2022) with a median follow-up of 16.1 months (range: [redacted]) in the T-DXd arm (N=373), 13.5 months (range: [redacted]) in the TPC arm (N=184), and [redacted] months (range: [redacted]) in total (N=557), in the FAS.[7] Efficacy analyses were conducted in the HR-positive and FAS, following the intention-to-treat principle (see Section B.2.4.1).[2,3]

DESTINY-Breast04 met its primary endpoint, with a statistically significant improvement in BICR-assessed PFS in HR-positive patients treated with T-DXd compared with TPC (HR: 0.51; p<0.001; HR-positive cohort).[6] The statistically significant result for the primary endpoint of PFS by BICR was confirmed by PFS by IA.[7] T-DXd was also associated with statistically significant improvements over TPC in the secondary efficacy endpoints of PFS by BICR in the FAS (HR: 0.50; p<0.001), OS in the HR-positive cohort (HR: 0.64; p=0.003), and OS in the FAS (HR: 0.64; p=0.001).[6] T-DXd was similarly associated with statistically significant improvements over TPC in other clinically meaningful endpoints including the secondary efficacy endpoint of confirmed objective response rate (ORR) by BICR (p<0.0001; FAS) and key exploratory endpoints, including the clinical benefit rate (CBR) by BICR (p<0.0001; FAS), and the disease control rate (DCR) by BICR (p<0.0001; FAS).[6,7]

The primary efficacy endpoint in DESTINY-Breast04 is PFS by BICR in the HR-positive cohort. This submission focuses on the FAS although key results in the HR-positive cohort are presented for completeness.

B.2.6.1.1 Primary efficacy | PFS by BICR in HR-positive cohort

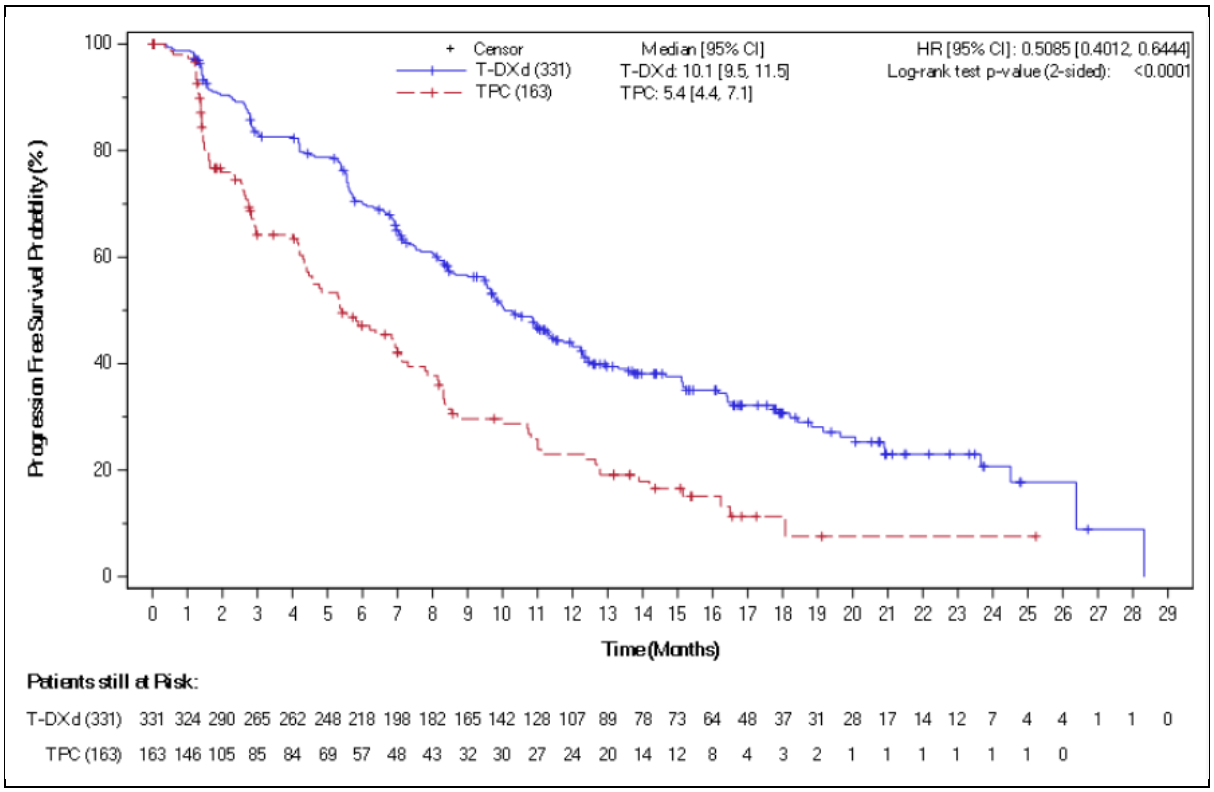
In the HR-positive cohort at DCO, the median duration of PFS follow-up was [redacted] months and events of disease progression or death were reported in 211 patients (63.7%) in the T-DXd arm and 110 patients (67.5%) in the TPC arm (**Table 17; Figure 11**).[7] Of these, 180 patients (54.4%) in the T-DXd arm and 101 patients (62.0%) in the TPC arm had disease progression.[7] Death was the recorded PFS event in 31 patients (9.4%) in the T-DXd arm and nine patients (5.5%) in the TPC arm.[7]

At DCO, 120 patients (36.3%) in the T-DXd arm and 53 patients (32.5%) in the TPC arm were censored.[7] Of these, 67 patients (20.2%) in the T-DXd arm and eight patients (4.9%) in the TPC arm were ongoing without an event.[7] The remaining 53 patients (16.0%) in the T-DXd arm and 45 patients (27.6%) in the TPC arm were censored for other reasons (**Table 17**).[7]

T-DXd was associated with a statistically significant 49% lower risk of progression or death compared with TPC (HR: 0.51; 95% CI: 0.40, 0.64; p<0.001).[6] DESTINY-Breast04 therefore met its primary endpoint of PFS by BICR in the HR-positive cohort.[6]

Median PFS by BICR was 10.1 months (95% CI: 9.5, 11.5) in the T-DXd arm vs. 5.4 months (95% CI: 4.4, 7.1) in the TPC arm.[6] At 12 months, [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) of patients were alive and progression free in the T-DXd and TPC arms, respectively (**Figure 11**).[7] There was an early and sustained separation of the PFS curves in favour of T-DXd that was maintained throughout the study.

Figure 11: DESTINY-Breast04 | Kaplan-Meier of PFS by BICR | HR-positive cohort



Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; HR-positive, hormone receptor-positive; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC; treatment of

physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 17: DESTINY-Breast04 | Analysis of PFS by BICR | HR-positive cohort

	T-DXd (N=331)	TPC (N=163)
Subjects with events, n (%)	211 (63.7)	110 (67.5)
Progressive disease	180 (54.4)	101 (62.0)
Death	31 (9.4)	9 (5.5)
Subjects without events (censored), n (%)	120 (36.3)	53 (32.5)
Ongoing without event	67 (20.2)	8 (4.9)
Other reason*	53 (16.1)	45 (17.6)
Median PFS, months†	10.1	5.4
(95% CI)†	(9.5, 11.5)	(4.4, 7.1)
Stratified Cox hazard ratio‡	0.5085	
(95% CI)§	(0.4012, 0.6444)	
Stratified log-rank p-value	<0.0001	
Proportion alive and progression-free at landmark (%)§		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

*Censoring reasons included: no baseline evaluable tumour assessment, no post-baseline tumour assessment, early death (within 14 weeks of randomisation) without baseline or post-baseline tumour assessment, radiographic disease progression or death without missing two or more consecutive tumour assessments immediately preceding the event, disease progression or death after missing ≥2 consecutive scheduled tumour assessments (i.e., more than 14 weeks), at least one post-baseline response assessment, patient with no death or objective documentation of radiographic disease progression (progression-free), anti-cancer therapy started prior to disease progression, death or analysis cut-off date.
†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by the IXRS.
§Estimate and CI for PFS rate at the specified time point are from the KM analysis.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR-positive, hormone receptor-positive; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Modi et al., 2022[6]; Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

B.2.6.1.2 Key secondary efficacy

Key secondary efficacy | PFS by BICR in FAS

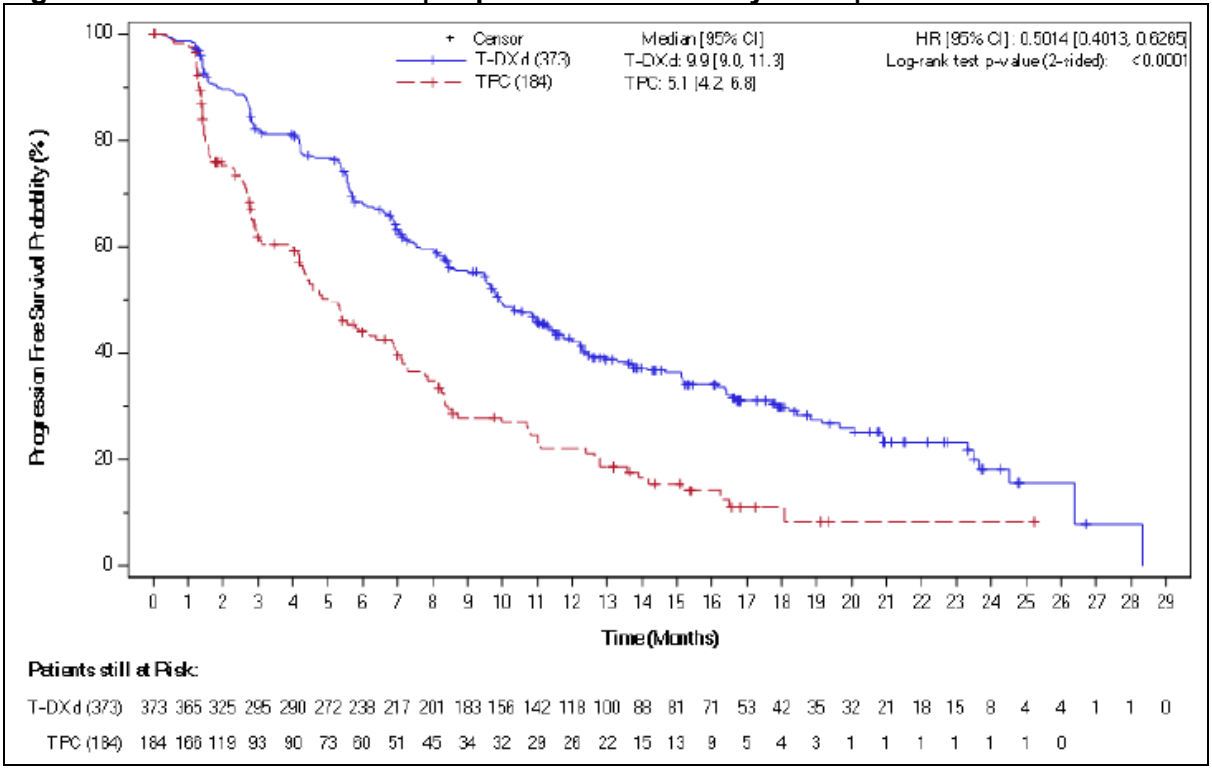
In the FAS at DCO, the median duration of follow-up was [redacted] months and events of disease progression or death were reported in 243 patients (65.1%) in the T-DXd arm and 127 patients (69.0%) in the TPC arm (**Figure 12, Table 18**).[7] Of these, 208 (55.8%) in the T-DXd arm and 117 (63.6%) in the TPC arm had disease progression.[7] Death was the recorded PFS event in 35 patients (9.4%) in the T-DXd arm and 10 patients (5.4%) in the TPC arm.[7]

At DCO, 130 (34.9%) patients in the T-DXd arm and 57 (31.0%) of patients in the TPC arm were censored.[7] Of these, 69 patients (18.5%) in the T-DXd arm and eight patients (4.3%) in the TPC arm were recorded as ongoing without an event.[7] The remaining 61 patients (16.4%) in the T-DXd arm and 49 patients (26.7%) in the TPC arm were censored for other reasons (**Table 18**).[7]

Results in the FAS were consistent with those in the HR-positive cohort. T-DXd was associated with a statistically significant 50% lower risk of progression or death compared with TPC (HR: 0.50; 95% CI: 0.40, 0.63; p<0.001).[6] DESTINY-Breast04 therefore met its secondary endpoint of PFS by BICR in the FAS.

Median PFS by BICR in the FAS was 9.9 months (95% CI: 9.0, 11.3) in the T-DXd arm vs. 5.1 months (95% CI: 4.2, 6.8) in the TPC arm.[6] At 12 months, [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) of patients were alive and progression-free in the T-DXd and TPC arms, respectively (**Figure 12**).[7] There was an early and sustained separation of the PFS curves in favour of T-DXd that was maintained throughout the study.

Figure 12: DESTINY-Breast04 | Kaplan-Meier of PFS by BICR | FAS



Abbreviations: BICR; blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan, TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 18: DESTINY-Breast04 | Analysis of PFS by BICR | FAS

	T-DXd (N=373)	TPC (N=184)
Subjects with events, n (%)	243 (65.1)	127 (69.0)
Progressive disease	208 (55.8)	117 (63.6)

	T-DXd (N=373)	TPC (N=184)
Death	35 (9.4)	10 (5.4)
Subjects without events (censored), n (%)	130 (34.9)	57 (31.0)
Ongoing without event	69 (18.5)	8 (4.3)
Other reason*	61 (16.4)	49 (26.7)
Median PFS, months†	9.9	5.1
(95% CI)†	(9.0, 11.3)	(4.2, 6.8)
Stratified Cox hazard ratio‡	0.5014	
(95% CI)§	(0.4013, 0.6265)	
Stratified log-rank p-value	<0.0001	
Proportion alive and progression-free at landmark (%)§		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

*Censoring reasons included: no baseline evaluable tumour assessment, no post-baseline tumour assessment, early death (within 14 weeks of randomisation) without baseline or post-baseline tumour assessment, radiographic disease progression or death without missing two or more consecutive tumour assessments immediately preceding the event, disease progression or death after missing ≥ 2 consecutive scheduled tumour assessments (i.e., more than 14 weeks), at least one post-baseline response assessment, subject with no death or objective documentation of radiographic disease progression (progression-free), anti-cancer therapy started prior to disease progression, death or analysis cut-off date.
†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by the IXRS.
§Estimate and CI for PFS rate at the specified time point are from the KM analysis.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Modi et al., 2022[6]; Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Key secondary efficacy | OS in HR-positive cohort

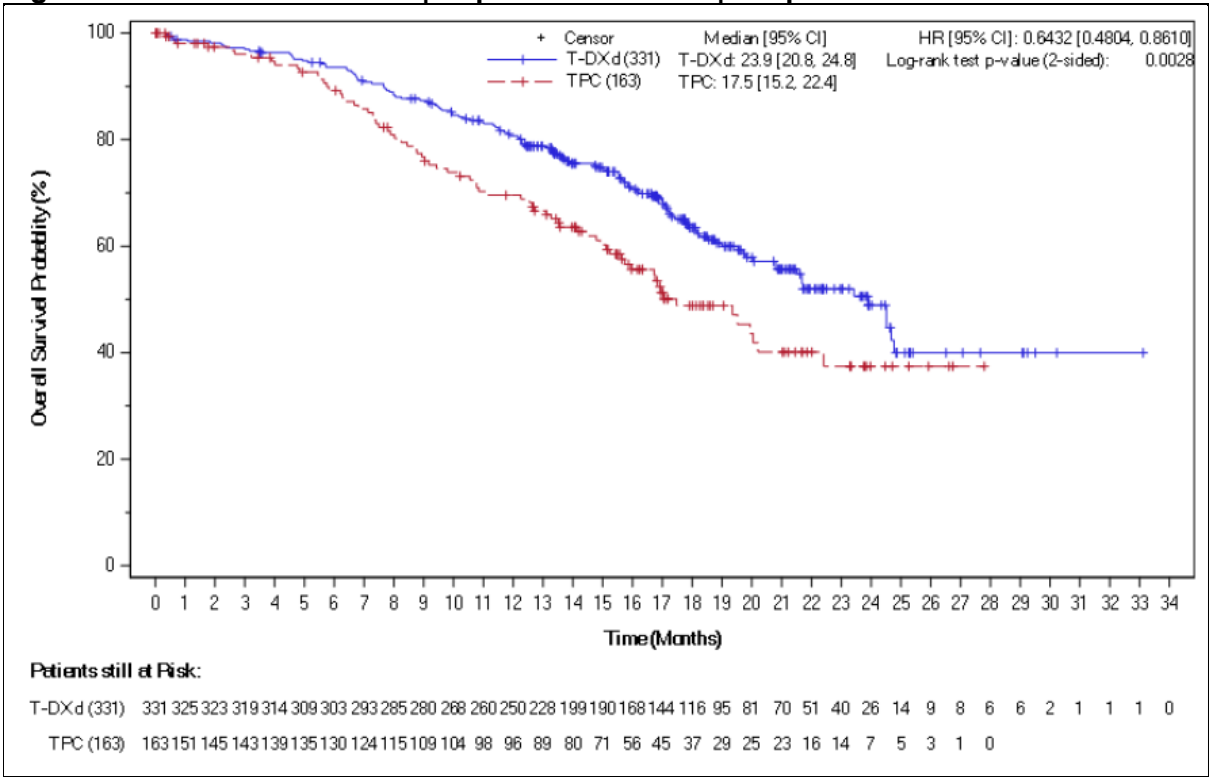
At DCO in the HR-positive cohort, the median duration of survival follow-up was 18.4 months[6] and events of death were reported in 126 patients (38.1%) in the T-DXd arm and 73 patients (44.8%) in the TPC arm (**Figure 13; Table 19**).[7]

At DCO, 205 patients (61.9%) in the T-DXd arm and 90 patients (55.2%) in the TPC arm were censored.[7] Of these, 183 patients (55.3%) in the T-DXd arm and 67 patients (41.1%) in the TPC arm were alive.[7] The remaining 22 patients (5.9%) in the T-DXd arm and 23 patients (12.5%) in the TPC arm were censored for other reasons (**Table 19**).[7]

T-DXd was associated with a statistically significant 36% lower risk of death compared with TPC (HR: 0.64; 95% CI: 0.48, 0.86; p=0.003).[6] The stratified log-rank p-value of 0.003 crossed the pre-specified efficacy stopping boundary of 0.0075, confirming the efficacy of T-DXd vs. TPC for this outcome.[6] DESTINY-Breast04 therefore met its secondary endpoint of OS in the HR-positive cohort.

Median OS was 23.9 months (95% CI: 20.8, 24.8) in the T-DXd arm vs. 17.5 months (95% CI: 15.2, 22.4) in the TPC arm.[6] At 12 months, 80.7% (95% CI: 76.0, 84.6) and 69.6% (95% CI: 61.3, 76.4) of patients were alive in the T-DXd and TPC arms, respectively (**Figure 13**).[7] A sustained separation of the KM OS curve in favour of the T-DXd arm was observed starting at approximately 4 months.

Figure 13: DESTINY-Breast04 | Kaplan-Meier of OS | HR-positive cohort



Abbreviations: CI, confidence interval; HR, hazard ratio; HR-positive, hormone receptor-positive; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 19: DESTINY-Breast04 | Analysis of OS | HR-positive cohort

	HR-positive cohort	
	T-DXd (N=331)	**TPC (N=163)**
Subjects with events (deaths), n (%)	126 (38.1)	73 (44.8)
Subjects without events (censored), n (%)	205 (61.9)	90 (55.2)
Alive	183 (55.3)	67 (41.1)
Lost to follow-up	5 (1.5)	1 (0.6)
Withdrawal by subject	16 (4.8)	22 (13.5)
Other	1 (0.3)	0
Median overall survival, months*	23.9	17.5
(95% CI)*	(20.8, 24.8)	(15.2, 22.4)
Stratified Cox proportional hazards model hazard ratio†	0.6432	
(95% CI)†	(0.4804, 0.8610)	
Stratified log-rank test p-value†	0.0028	
3 months (95% CI)	97.0 (94.4, 98.4)	96.1 (91.5, 98.2)
6 months (95% CI)	93.6 (90.3, 95.8)	89.2 (83.0, 93.3)
9 months (95% CI)	87.4 (83.3, 90.6)	76.7 (68.9, 82.8)
12 months (95% CI)	80.7 (76.0, 84.6)	69.6 (61.3, 76.4)

	HR-positive cohort	
	T-DXd (N=331)	TPC (N=163)
18 months (95% CI)	63.5 (57.4, 69.0)	48.8 (39.5, 57.5)
24 months (95% CI)	48.9 (40.9, 56.5)	37.4 (26.8, 48.0)

*Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
†Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by the IXRS.
‡Estimate and CI for OS rate at the specified timepoint are from KM analysis.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR-positive, hormone receptor-positive; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Sources: Modi et al., 2022[6]; Daiichi Sankyo Inc., 2022 (CSR, Data on File)[7]

Key secondary efficacy | OS in FAS

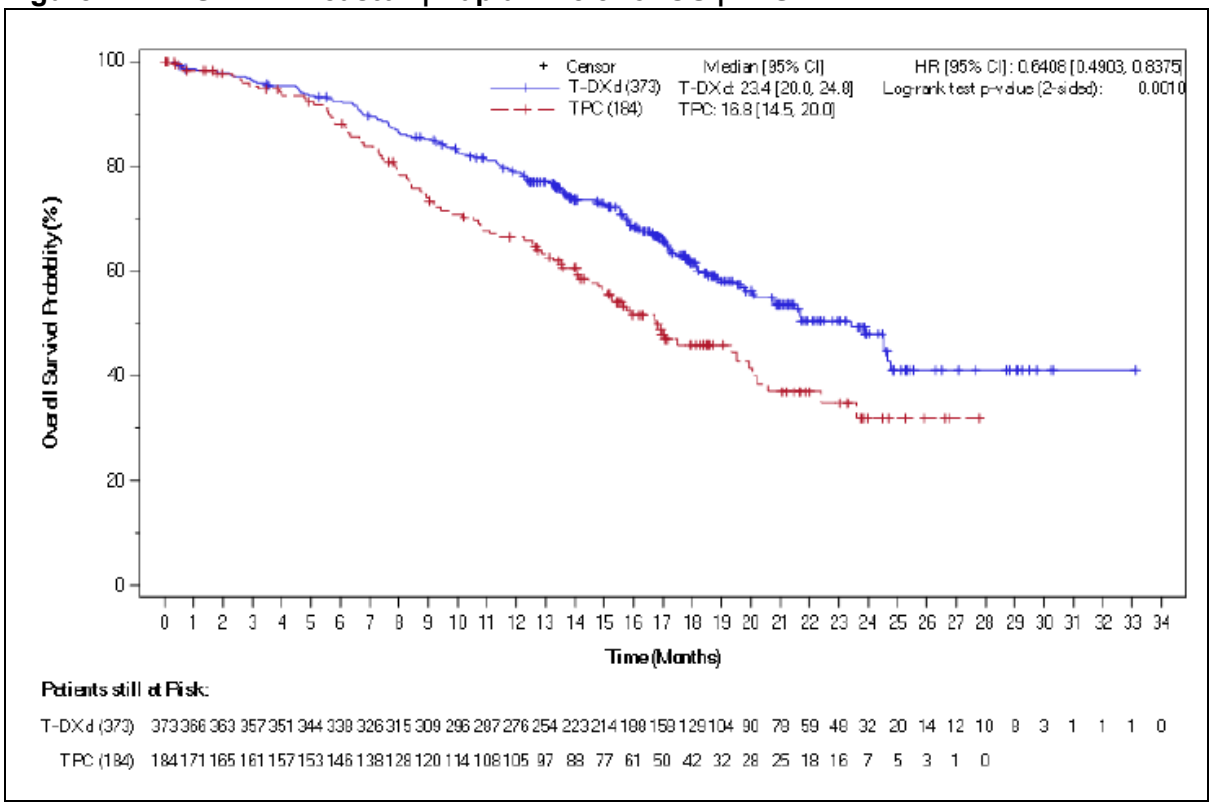
At DCO in the FAS, median duration of survival follow-up was 18.4 months[6] and events of death were reported in 149 patients (39.9%) in the T-DXd arm and 90 patients (48.9%) in the TPC arm (**Table 20**; **Figure 14**).[7]

At DCO, 224 patients (60.1%) in the T-DXd arm and 94 patients (51.1%) in the TPC arm were censored.[7] Of these, 201 patients (53.9%) in the T-DXd arm and 70 patients (38.0%) in the TPC arm were alive.[7] The remaining 23 patients (6.2%) in the T-DXd arm and 24 patients (13.0%) in the TPC arm were censored for other reasons (**Table 20**).[7]

OS results in the FAS were consistent with those from the HR-positive cohort. T-DXd was associated with a statistically significant 36% lower risk of death compared with TPC (HR: 0.64 [95% CI: 0.49, 0.84]; p=0.001).[6] The stratified log-rank p-value of 0.001 crossed the pre-specified efficacy stopping boundary of 0.0075, confirming the efficacy of T-DXd vs. TPC for this outcome.[6] DESTINY-Breast04 therefore met its secondary endpoint of OS in the FAS.

Median OS in the FAS was 23.4 months (95% CI: 20.0, 24.8) in the T-DXd arm vs. 16.8 months (95% CI: 14.5, 20.0) in the TPC arm.[6] At 12 months, 78.8% (95% CI: 74.3, 82.7) and 66.5% (95% CI: 58.8, 73.2) of patients were alive in the T-DXd and TPC arms, respectively (**Figure 14**).[7] A sustained separation of the KM OS curve in favour of the T-DXd arm was observed starting at approximately 4 months.

Figure 14: DESTINY-Breast04 | Kaplan-Meier of OS | FAS



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 20: DESTINY-Breast04 | Analysis of OS | FAS

	FAS	
	T-DXd (N=373)	**TPC (N=184)**
Subjects with events (deaths), n (%)	149 (39.9)	90 (48.9)
Subjects without events (censored), n (%)	224 (60.1)	94 (51.1)
Alive	201 (53.9)	70 (38.0)
Lost to follow-up	6 (1.6)	1 (0.5)
Withdrawal by subject	16 (4.3)	23 (12.5)
Other	1 (0.3)	0
Median overall survival, months*	23.4	16.8
(95% CI)*	(20.0, 24.8)	(14.5, 20.0)
Stratified Cox proportional hazards model hazard ratio†	0.6408	
(95% CI)†	(0.4903, 0.8375)	
Stratified log-rank test p-value†	0.0010	
3 months (95% CI)	96.2 (93.7, 97.8)	95.3 (90.9, 97.6)
6 months (95% CI)	92.4 (89.2, 94.7)	88.1 (82.2, 92.2)
9 months (95% CI)	85.3 (81.3, 88.5)	74.0 (66.6, 80.0)
12 months (95% CI)	78.8 (74.3, 82.7)	66.5 (58.8, 73.2)
18 months (95% CI)	61.7 (55.9, 66.9)	45.9 (37.5, 54.0)
24 months (95% CI)	48.1 (40.8, 54.9)	32.0 (21.9, 42.4)

*Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
†Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by the IXRS.
‡Estimate and CI for OS rate at the specified timepoint are from KM analysis.
Abbreviations: CI, confidence interval; FAS, full analysis set; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of

physician's choice.
Sources: Modi et al., 2022;[6] Daiichi Sankyo Inc., 2022 (CSR, Data on File)[2]

B.2.6.1.3 Other secondary efficacy

Other secondary efficacy | PFS by IA | HR-positive cohort and in the FAS

The statistically significant result for the primary endpoint of PFS by BICR in the HR-positive cohort was confirmed by PFS by IA. In the HR-positive cohort, median PFS by IA was 9.6 months (95% CI: 8.4, 10.0) with T-DXd compared with 4.2 months (95% CI: 3.4, 4.9) with TPC (HR: 0.37; 95% CI: 0.30, 0.47).[7]

Similar results were observed for the FAS, where the statistically significant result for PFS by BICR was also confirmed by PFS by IA. In the FAS, median PFS by IA in the HR-positive cohort was [redacted] months (95% CI: [redacted]) with T-DXd compared with [redacted] months (95% CI: [redacted]) with TPC (HR: [redacted]; 95% CI: [redacted]).[7]

Other secondary efficacy | Response rates | FAS and HR-positive cohort

At DCO in the FAS, the DCR (defined as sum of patients with best overall response of complete response (CR), partial response (PR), or stable disease (SD)) by BICR was statistically significantly greater in the T-DXd arm (87.1%; 325 of 373 patients) compared with the TPC arm (65.8%; 121 of 184 patients; p<0.0001).[6,7] Similarly, the confirmed ORR (CR+PR) by BICR was also statistically significantly greater with T-DXd (52.3%; 195[j] patients) compared with TPC (16.3%; 30 patients; p<0.0001; **Table 21**).[6,7]

A best overall response by BICR of CR was observed in 3.5% (13 of 373 patients) in the T-DXd arm and 1.1% (2 of 184 patients) in the TPC arm.[6] A best response of PR was observed in 49.1% (183 patients) in the T-DXd arm and 15.2% (28 patients) in the TPC arm.[6] A best response of SD was observed in 34.6% (129 patients) in the T-DXd arm and 49.5% (91 patients) in the TPC arm.[6] Progressive disease (PD) was observed in 8.3% (31 patients) in the T-DXd arm compared with 22.3% (41 patients) in the TPC arm.[6]

The CBR by BICR (CBR; a best response of CR, PR, or SD for ≥6 months) was significantly higher with T-DXd than with TPC at DCO: 70.2% (262 patients) compared with 33.7% (62 patients),[6] respectively (p<0.0001).[7]

Response rates by IA in the FAS were consistent with the assessment of response by BICR, showing a statistically significant benefit of T-DXd compared with TPC (**Table 21**).[7] Similar results were also seen in the HR-positive cohort (BICR and IA).[7] Waterfall plots (**Figure 15**) visually display the impact of T-DXd and TPC on percentage change in sum of diameters of target lesions from baseline to best (minimum) post-baseline value based on BICR (FAS).

Table 21: DESTINY-Breast04 | Best overall response and ORR by BICR or IA | FAS and HR-positive cohort

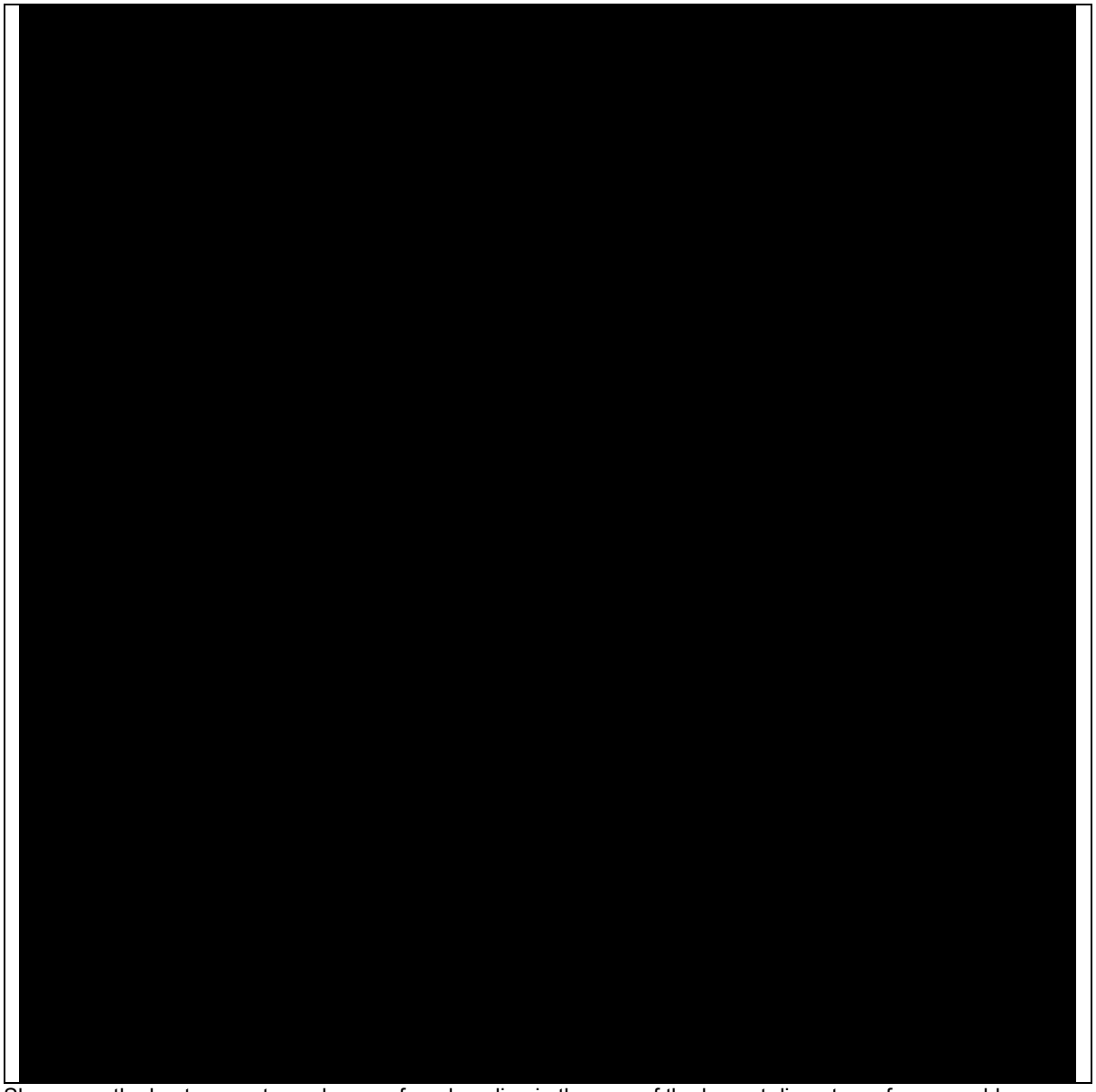
	HR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Confirmed ORR by BICR, n (%)	175 (52.9)[a]	27 (16.6)	195 (52.3)[a]	30 (16.3)
95% CI	(47.3, 58.4)	(11.2, 23.2)	(47.1, 57.4)	(11.3, 22.5)
p-value*	<0.0001		<0.0001	

[j] One subject in the T-DXd arm who had a confirmed best overall response of complete or partial response had a baseline scan done after randomisation but before the first dose and thus was considered a non-responder in the calculation of confirmed ORR

	HR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Confirmed ORR by IA, n (%)	[redacted]			
95% CI				
p-value				
Disease control rate by BICR**, n (%)	291 (87.9)	108 (66.3)	325 (87.1)	121 (65.8)
95% CI	(83.9, 91.2)	(58.4, 73.5)	(83.3, 90.4)	(58.4, 72.6)
p-value*	<0.0001		<0.0001	
Clinical benefit rate by BICR†, n (%)	238 (71.9)	57 (35.0)	262 (70.2)	62 (33.7)
95% CI	(66.7, 76.7)	(27.7, 42.8)	(65.3, 74.8)	(26.9, 41.0)
p-value*	<0.0001		<0.0001	
Best overall response by BICR, n (%)				
CR	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
PR	164 (49.5)	26 (16.0)	183 (49.1)	28 (15.2)
SD	115 (34.7)	81 (49.7)	129 (34.6)	91 (49.5)
PD	26 (7.9)	34 (20.9)	31 (8.3)	41 (22.3)
Not evaluable	14 (4.2)	21 (12.9)	17 (4.6)	22 (12.0)
Best overall response by IA, n (%)				
CR	[redacted]			
PR				
SD				
PD				
Not evaluable				

*Two-sided p-value based on the Cochran-Mantel-Haenszel test adjusted for stratification factors.
**CR + PR + SD.
†CR + PR + SD ≥6 months.
[a] One subject in the T-DXd arm who had a confirmed best overall response of complete or partial response had a baseline scan done after randomisation but before the first dose and thus was considered a non-responder in the calculation of confirmed ORR.
Abbreviations: CI, confidence interval; CR, complete response; FAS, full analysis set; HR-positive, hormone receptor-positive; IA, investigator assessment; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Modi et al., 2022;[6] Daiichi Sankyo Inc. (CSR, Data on file)[7]

Figure 15: DESTINY-Breast04 | Waterfall plot of percentage change in sum of diameters of target lesions from baseline to best post-baseline value based on BICR | FAS



Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumours in patients for whom data from both baseline and post-baseline assessments of target lesions by BICR were available. For each subject, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical line. Only subjects with measurable disease at baseline and at least one post-baseline assessment are included in the waterfall graphs.
Abbreviations: BICR, blinded independent central review; FAS, full analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc. (DESTINY-Breast04 CSR, Data on file)[7]

Other secondary efficacy | Duration of confirmed response | FAS

The median duration of response (DoR) in patients with a confirmed objective response (CR or PR, by BICR or by IA) was numerically higher with T-DXd than with TPC in the FAS (median DoR by BICR: 10.7 vs 6.8 months).[6] Similar results were observed for the HR-positive cohort (median DoR by BICR: 10.7 vs. 6.8 months).[6]

Other secondary efficacy | Time to response | FAS

In the FAS, the median time to response (TTR) based on BICR among responders (patients with CR or PR) was 2.73 months (range: 1.2, 14.0) in the T-DXd arm and 2.22 months (range: 1.2, 8.3) in the TPC arm.[6,7] Similar results were observed for the HR-positive cohort (median TTR: 2.76 vs. 2.73 months).[7]

B.2.6.1.4 Patient-reported outcomes and hospitalisation

Overview

In DESTINY-Breast04, EQ-5D-5L, EORTC QLQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL. Questionnaires were completed by patients prior to infusion on day 1 of Cycle 1, 2 and 3 and then every 2 cycles thereafter until the end of treatment assessments.[7] Patients were then followed up at the Day 40 (+7 days) first follow-up assessment (after last study drug administration) or before initiation of new anti-cancer treatment, whichever came first, and then at the first long-term/survival follow-up assessments three months later, which was the last data collection point for all HRQoL questionnaires.[7] Patients were required to complete questionnaires before any other study assessments or procedures were performed on the day and prior to infusion.[7]

Questionnaire compliance

In the T-DXd arm, the compliance rate in the FAS was [redacted] at baseline and [redacted] at the end of treatment for the QLQ-C30 questionnaire, [redacted] at baseline and [redacted] at end of treatment for the QLQ-B45 (QLQ-BR23) questionnaire, and [redacted] at baseline and [redacted] at end of treatment for the EQ-5D-5L.[7] In the TPC arm, the compliance rate in the HR-positive cohort was [redacted] at baseline and [redacted] at the end of treatment for the QLQ-C30 questionnaire, [redacted] at baseline and [redacted]% at end of treatment for the QLQ-B45 (QLQ-BR23) questionnaire, and [redacted]% at baseline and [redacted] at end of treatment for the EQ-5D-5L questionnaire.[152] From Cycle 3 onwards, the minimum compliance rate was at least [redacted] across the questionnaires in both treatment arms, except for one cycle.[152]

Patient-reported outcome | EQ-5D-5L | FAS

HRQoL as measured by EQ-5D-5L (both index and VAS) was maintained while on treatment. For the EQ-5D-5L index score, mean change from baseline to end of treatment was [redacted] in the T-DXd arm and [redacted] in the TPC arm; for the EQ-5D-5L VAS, mean change from baseline to end of treatment was [redacted] in the T-DXd arm and [redacted] in the TPC arm.[152]

At baseline in the FAS, the median EQ-5D-5L VAS score was [redacted] in both the T-DXd arm and the TPC arm.[152] At end of treatment, HRQoL was maintained in both arms (median change from baseline: [redacted] in both treatment arms).[152] QoL with T-DXd was maintained over the course of treatment [redacted], after which the number of subjects was too low (N<10) to allow for meaningful interpretation, and did not deteriorate compared to the TPC arm.[152]

In the FAS, median time to definitive deterioration (TTDD) by at least 10 points for the EQ-5D-5L VAS was longer in the T-DXd arm than the TPC arm ([redacted] (95% CI: [redacted]) vs. [redacted] months (95% CI: [redacted]); HR: [redacted]; 95% CI: [redacted]; p=[redacted]).[152]

Results in the HR-positive cohort were consistent with those in the FAS.[7,151]

Figure 16: DESTINY-Breast04 | Kaplan-Meier plot of time to definitive deterioration of EQ-5D-5L VAS | FAS

Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue score.
Source: Daiichi Sankyo Inc., 2022 (FAS PRO tables and figures, Data on File)[152]

Patient-reported outcome | EORTC QLQ-C30 | FAS

At baseline in the FAS, the median global health status (GHS) score was [redacted] in both the T-DXd arm and the TPC arm (a high score for GHS represents a low QoL).[152] At end of treatment, GHS was maintained in the T-DXd arm (median change from baseline: [redacted]).[152] [redacted], the median change from baseline to end of treatment was [redacted] in both arms. The exception was for [redacted] for TPC, where QoL decreased as shown by a median increase from baseline of [redacted].[152] Mean change from baseline for overall GHS remained stable (within ±10 points) over the course of treatment with T-DXd up to [redacted] and with TPC up to [redacted], after which the number of subjects became too small to allow for meaningful interpretation.[152] [redacted]

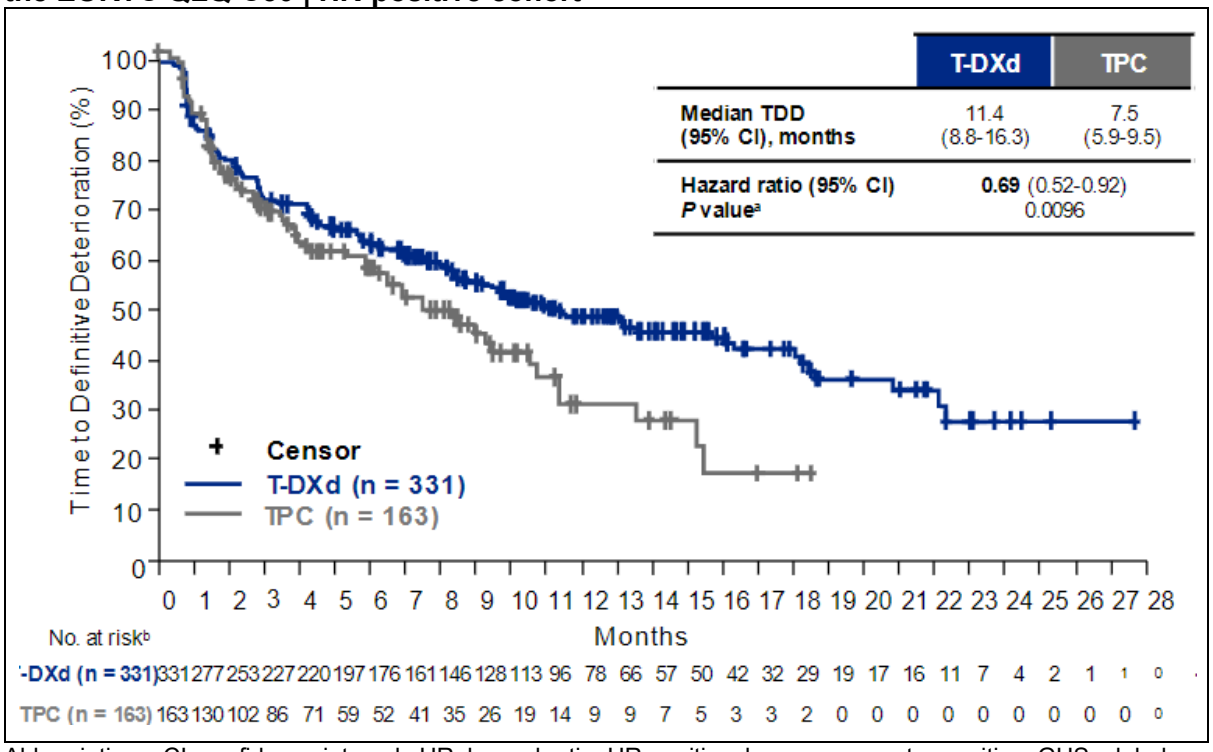
In the FAS, median TTDD by at least 10 points for the EORTC QLQ-30 GHS was longer for the T-DXd arm than the TPC arm ([redacted] [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted]; p=[redacted]).[152] The HR was statistically significantly in favour of T-DXd vs. TPC for nearly all pre-specified subscales, including emotional functioning ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), social functioning ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), physical functioning ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), pain symptoms ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), and fatigue ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]).[152] The exception was for nausea and vomiting, where the HR was statistically significantly in favour of TPC vs. T-DXd ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]).[152]

Results in the HR-positive cohort were consistent with those in the FAS (**Figure 18** and **Figure 19**).[7,151]

Figure 17: DESTINY-Breast04 | Kaplan-Meier plot of time to definitive deterioration of EORTC QLQ-30 GHS | FAS

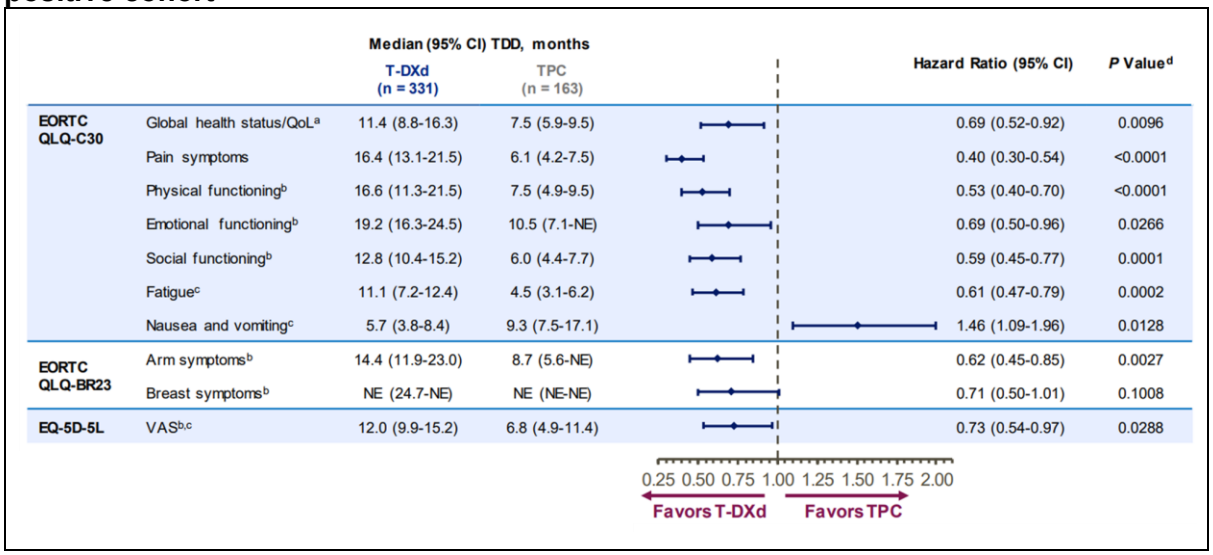
Abbreviations: CI, confidence interval; FAS, full analysis set; GHS, global health status; HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (FAS PRO tables and figures, Data on File)[152]

Figure 18: DESTINY-Breast04 | Kaplan-Meier plot of time to definitive deterioration of the EORTC QLQ-C30 | HR-positive cohort



Abbreviations: CI, confidence intervals;HR, hazard ratio; HR-positive, hormone receptor-positive; GHS, global health status; QoL, quality-of-life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Ueno, N. et al. ASCO, 2022.[151]

Figure 19: DESTINY-Breast04 | Time to definitive deterioration in PRO measures | HR-positive cohort



Abbreviations: CI, confidence intervals; EQ-5D-5L, EuroQol 5-dimensions 5-levels; EORTC, European Organisation for Research and Treatment of Cancer; HR-positive, hormone receptor-positive; NE, not evaluable; PRO, patient-reported outcome; QLQ-BR23, Quality-of-life Breast Cancer 23 questionnaire; QLQ-C30, Quality-of-life Core 30 questionnaire; QoL, quality-of-life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue scale
Source: Ueno, N. et al. ASCO, 2022.[151]

Patient-reported outcome | EORTC QLQ-BR45 (QLQ-BR23) | FAS

For the breast symptoms scale, the median baseline score was [redacted] in both treatment arms.[152] At end of treatment, median baseline breast symptom scores were [redacted] (median change from baseline: [redacted] and [redacted], in the T-DXd arm and TPC arm, respectively).[152] For the arm symptoms scale, the median baseline score was [redacted] in both arms, and at the end of treatment, the median change from baseline was [redacted] in both arms.[152]

T-DXd was associated with longer TTDD in arm symptoms compared with TPC ([redacted] months (95% CI: [redacted]) vs. [redacted] months (95% CI: [redacted]); HR: [redacted]; 95% CI: [redacted]; p=[redacted]; **Figure 20**).[152]

Results in the HR-positive cohort were consistent with those in the FAS (**Figure 19**).[7,151]

Figure 20: DESTINY-Breast04 | Kaplan-Meier plot of time to definitive deterioration of EORTC QLQ-BR45 | FAS

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HR, hazard ratio; QLQ-BR45, Quality-of-life Breast Cancer 45 questionnaire; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue score.
Source: Daiichi Sankyo Inc., 2022 (FAS PRO tables and figures, Data on File)[152]

Patient-reported outcome | Hospitalisation | FAS

Hospitalizations were summarized during study treatment (from on and after date of the first dose of study drug to date of last dose plus 47 days).[7]

In the FAS at DCO (Jan 2022), [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the TPC arm had been hospitalised.[7] The median time to first hospitalisation was longer in the T-DXd arm than the TPC arm ([redacted] vs. [redacted] days).[7]

In the HR-positive population at DCO, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the TPC arm had been hospitalised.[7] At DCO, median time to first hospitalisation [redacted] in the T-DXd arm compared with the TPC arm ([redacted] and [redacted] days, respectively).[7]

B.2.6.2 Efficacy conclusions

DESTINY-Breast04 is a head-to-head trial of T-DXd vs. TPC in patients with HER2-low u/mBC after one or two lines of chemotherapy in the metastatic setting. UK clinical and HEOR experts consulted at an advisory board in December 2022 considered the trial design to be robust and appropriate for decision-making in the UK.[121] Clinical experts confirmed patient characteristics to be generalisable to the UK, with the higher proportion of Asian patients in DESTINY-Breast04 than in UK clinical practice not expected to impact outcomes as there is no biological reason for ethnicity to affect the efficacy of T-DXd.[121] Published UK biomarker data[56] and UK clinical expert insights confirm that the distribution of HR-positive and HR-negative patients in DESTINY-Breast04 is aligned to UK clinical practice.[121] UK experts also confirmed that the TPC arm in DESTINY-Breast04, which included chemotherapy agents commonly used in the UK (including capecitabine, eribulin and paclitaxel), to be generalisable to UK clinical practice.[121]

In DESTINY-Breast04, T-DXd demonstrated statistically significant superiority compared with TPC for the primary endpoint of PFS by BICR in the HR-positive cohort (median PFS: 10.1 vs 5.4 months; HR: 0.51; p<0.001).[6] The findings of the primary endpoint were confirmed by analysis of PFS by IA.[7] T-DXd was also associated with statistically significant superiority over TPC for all secondary efficacy endpoints: PFS by BICR in the FAS (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001), OS in the HR-positive cohort (median OS: 23.9 months vs. 17.5 months; HR: 0.64; p=0.003) and OS in the FAS (median OS: 23.4 months vs.16.8 months; HR: 0.64; p=0.001).[6] Results demonstrate consistency between the FAS and HR-positive cohorts.

In addition, T-DXd showed benefit over TPC across a range of other clinically meaningful endpoints. In the FAS, the DCR (CR+PR+SD) by BICR was statistically significantly greater in the T-DXd arm compared with the TPC arm (87.1% vs. 65.8%; p<0.0001).[6,7] A statistically significantly greater proportion of patients achieved a confirmed ORR (CR + PR) by BICR and by IA with T-DXd compared with TPC (both p<0.0001; FAS).[6,7] A best overall response of CR and PR was observed in more than three times as many patients in the T-DXd arm as the TPC arm (CR: 3.5% vs. 1.1%; PR: 49.1% vs. 15.2%; FAS).[6] The CBR by BICR, demonstrating sustained response (CR+PR+SD) for at least six months, was also statistically significantly greater with T-DXd than TPC (70.2% vs. 33.7%; p<0.0001; FAS).[6,7]

Health-related quality-of-life of patients in the T-DXd arm was maintained on treatment across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-30 and EORTC QLQ-BR45) PRO instruments with longer TTDD across almost all measures and scales compared with TPC. In the FAS, the mean/median changes from baseline to end of treatment in EQ-5D-5L, EORTC QLQ-C30 GHS and EORTC QLQ-BR45, demonstrated that QoL was maintained while patients were on treatment with T-DXd.[152] Additionally, in the FAS, median TTDD was longer with T-DXd than TPC for EQ-5D-5L-VAS ([redacted] [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted]; p=[redacted]), EORTC QLQ-C30 GHS ([redacted] [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted]; p=[redacted]), and for the vast majority of pre-specified subscales of the EORTC QLQ-C30 and EORTC QLQ-BR45.[152] Results were consistent in the HR-positive cohort. [7]

Overall, the efficacy data from DESTINY-Breast04 across a range of clinically meaningful outcomes confirm the substantial efficacy benefit of T-DXd compared with TPC. Multiple PRO endpoints demonstrate maintenance of QoL while on treatment and a longer TTDD compared with non-targeted chemotherapy.[7,151]

B.2.7 Subgroup analysis

Pre-specified subgroups for analysis were:[7]

- HER2 status (IHC+1, IHC 2+/ISH-negative)
- FAS only – hormone receptor status (positive, negative)
- Lines of prior chemotherapy in the metastatic setting (1, ≥2)
- Prior CDK4/6 (yes, no)
- Lines of prior ET received in the metastatic setting (0, 1, 2, ≥3)
- Best response to last prior cancer systemic therapy (complete response/partial response, stable disease, progressive disease, unknown)
- Renal function at baseline (normal function, mild impairment, moderate impairment)

- Hepatic function at baseline (normal function, mild impairment)
- Baseline visceral disease (yes, no)
- Baseline CNS metastases (yes, no)
- Reported history of CNS metastases (yes, no)
- Age (<65, ≥65 years)
- Race (including white, Asian, other)
- Region (Asia, North America, Europe + Israel)
- ECOG performance status (0, 1)

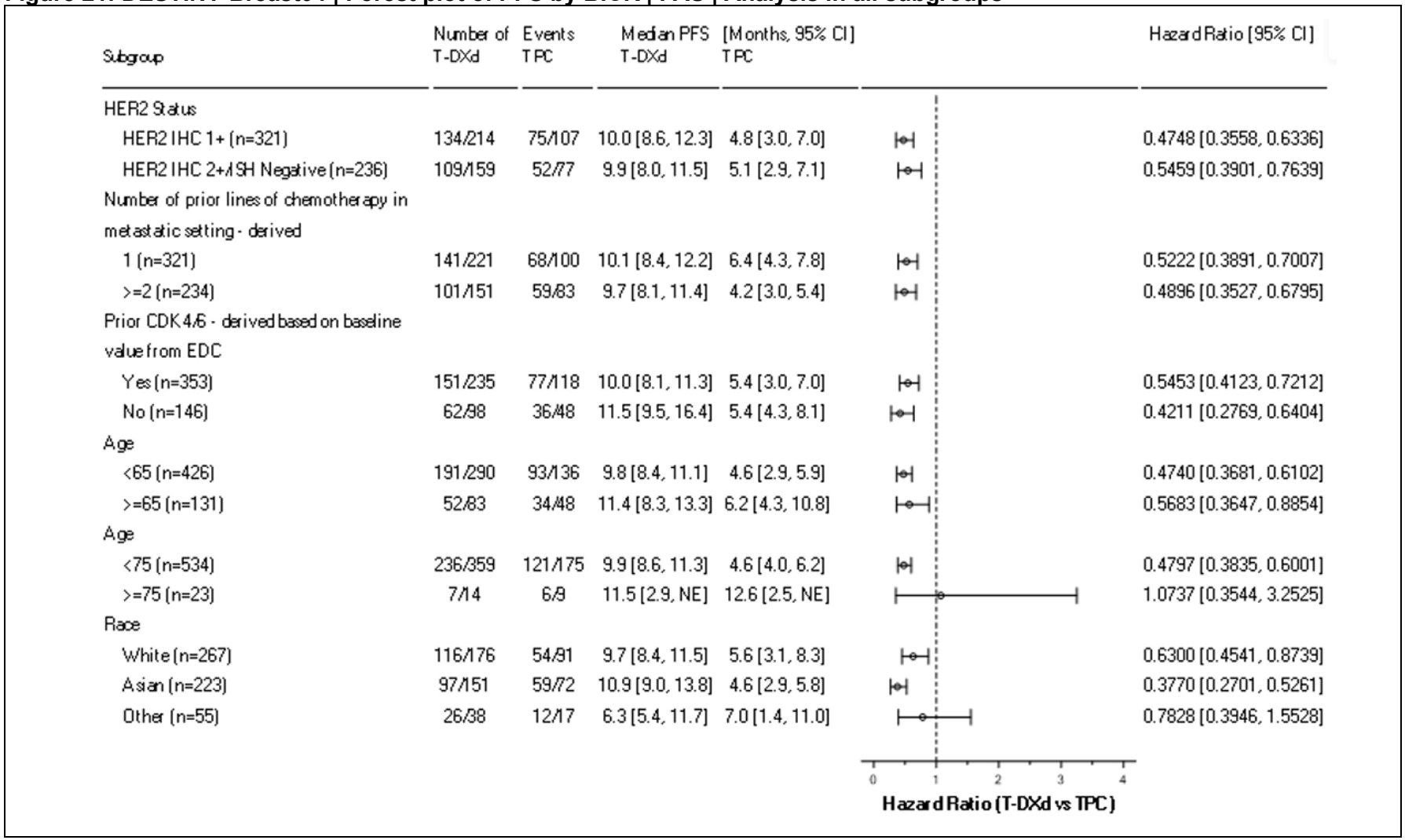
B.2.7.1 PFS by BICR | Pre-specified analysis in key subgroups | FAS

In the FAS, T-DXd demonstrated a statistically significant improvement in PFS by BICR compared to the TPC arm with a HR of 0.50 (95% CI: 0.40, 0.63).[6] The treatment effect was consistent across the majority of pre-specified patient subgroups, as indicated by the subgroup HR estimates lying within the 95% CI bounds of the HR for the FAS (**Figure 21**).[7] The subgroup HR estimates that were not within the 95% CI of the FAS were: age ≥75, Asian race, Other race, Asian region, 0, 1, and 2 prior lines of ET in the metastatic setting, partial response, baseline CNS metastases, and no baseline visceral disease.[7] For all of these exceptions, the 95% CIs overlapped with the FAS 95% CI.[7]

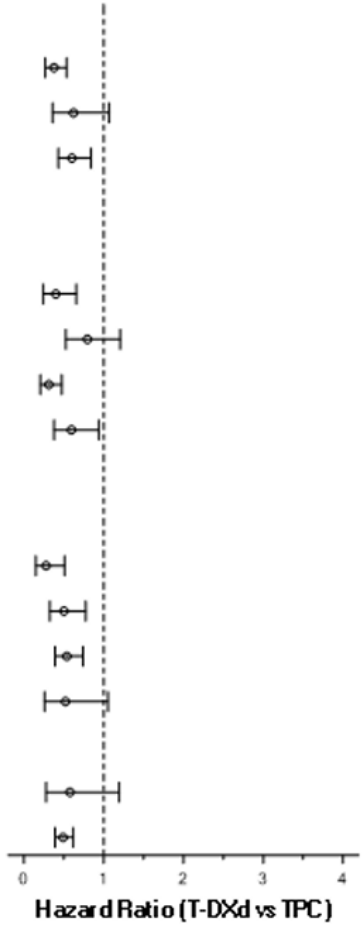
Subgroup analysis show that T-DXd is associated with a consistent improvement in PFS vs. TPC, including in key subgroups (e.g., HR-status, number of lines of prior chemotherapy in the metastatic setting, visceral disease, ECOG performance status), as indicated by the HRs of less than 1.[7] Notably, the treatment effect in the subgroup of patients who had received 1 prior line of chemotherapy in the metastatic setting (N=321) was similar to those who had received ≥2 prior lines of chemotherapy in the metastatic setting (HR: 0.52; 95% CI: 0.39, 0.70 vs. 0.49; 95% CI: 0.35, 0.68) indicating consistency across lines of therapy.[7] Treatment effect was also similar across HR-positive and HR-negative subgroups (HR: 0.51 CI: 0.40, 0.64 vs. 0.46 CI: 0.24, 0.89) demonstrating the benefit of T-DXd in the HR-negative population where outcomes are particularly poor.

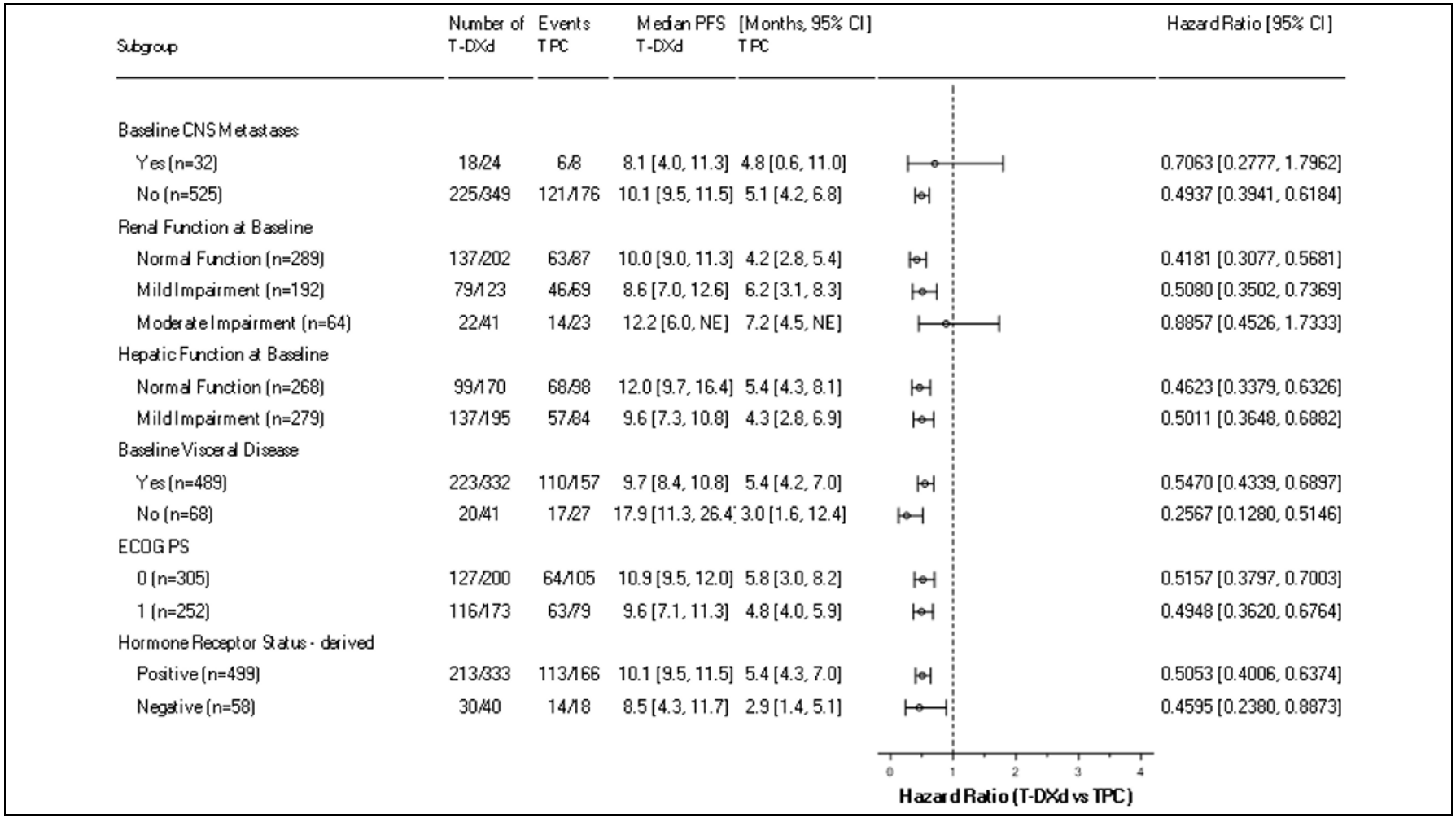
Overall, the subgroup data highlight the superiority of T-DXd over TPC and show that treatment effect is consistent across subgroups.

Figure 21: DESTINY-Breast04 | Forest plot of PFS by BICR | FAS | Analysis in all subgroups[a]



Subgroup	Number of T-DXd	Events TPC	Median PFS T-DXd	[Months, 95% CI] TPC	Hazard Ratio [95% CI]
Region					
Asia (n=213)	94/147	53/66	10.9 [9.0, 13.8]	4.6 [2.8, 6.4]	0.3778 [0.2672, 0.5341]
North America (n=93)	46/60	20/33	8.0 [4.2, 10.0]	4.5 [2.9, 7.2]	0.6207 [0.3599, 1.0704]
Europe + Israel (n=251)	103/166	54/85	10.3 [8.5, 12.3]	6.9 [2.9, 8.4]	0.6027 [0.4321, 0.8407]
Lines of prior endocrine therapy received in the metastatic setting - derived					
0 (n=94)	41/60	27/34	9.5 [5.7, 12.2]	4.0 [1.4, 5.1]	0.3990 [0.2427, 0.6559]
1 (n=159)	77/108	32/51	8.5 [6.9, 9.9]	7.8 [4.2, 10.7]	0.7962 [0.5257, 1.2058]
2 (n=169)	64/115	39/54	12.0 [9.9, 15.1]	4.5 [2.9, 5.9]	0.3125 [0.2056, 0.4750]
>=3 (n=135)	61/90	29/45	10.3 [7.5, 13.3]	5.4 [2.7, 11.0]	0.5964 [0.3795, 0.9371]
Best Response to the Last Prior Cancer Systemic Therapy					
Partial Response (n=70)	33/48	17/22	11.4 [7.1, 13.8]	2.8 [1.4, 4.8]	0.2775 [0.1511, 0.5096]
Stable Disease (n=137)	47/82	40/55	12.0 [8.4, 19.2]	8.1 [4.4, 10.7]	0.5021 [0.3253, 0.7751]
Progressive Disease (n=259)	123/174	57/85	8.6 [7.2, 9.9]	4.6 [2.9, 6.2]	0.5381 [0.3912, 0.7402]
Unknown (n=72)	34/53	11/19	10.0 [7.5, 16.6]	4.5 [2.3, 8.5]	0.5209 [0.2579, 1.0522]
Reported History of CNS Metastases					
Yes (n=52)	30/37	10/15	8.1 [5.4, 10.0]	2.0 [1.2, 11.0]	0.5777 [0.2791, 1.1956]
No (n=505)	213/336	117/169	10.3 [9.5, 11.7]	5.3 [4.2, 6.9]	0.4915 [0.3906, 0.6186]





Notes: [a] subgroup analyses were only conducted if there were at least 10 patients in each arm of the subgroup.
Abbreviations: BICR, blinded independent central review; CDK, cyclic-dependent kinase; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; NE, not estimable; No, number; PFS, progression-free survival; PS, performance status; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR, Data on File).[7]

B.2.7.2 Exploratory efficacy | Efficacy in the HR-negative cohort

Analyses in the HR-negative cohort demonstrate that T-DXd is associated with an improvement in PFS by BICR (8.5 vs. 2.9 months; HR: 0.46; 95% CI: 0.24, 0.89), OS (18.2 vs. 8.3 months; HR: 0.48; 95% CI: 0.24, 0.95),[6] and response rates (confirmed ORR by BICR: 47.6% vs 14.5%; p=[redacted])[7] compared with TPC. This confirms the consistent treatment effect of T-DXd vs. TPC across key subgroups. For more information, see **Appendix N**.

B.2.8 Meta-analysis

Not applicable. A meta-analysis was not performed because DESTINY-Breast04 is a Phase III RCT in the relevant population comparing T-DXd with comparators that are reflective of UK standard of care.

B.2.9 Indirect and mixed treatment comparisons

Not applicable. As above, an indirect or mixed treatment comparison was not performed because DESTINY-Breast04 is a Phase III RCT investigating T-DXd vs. comparators that are reflective of UK standard of care (see **Section B.1.3.6**). The comparators listed in the NICE final scope[1] are well represented in the TPC arm of DESTINY-Breast04.

As stated in **Section B.1.3.6**the company acknowledges that SG is included in the NICE scope as a comparator in the HR-negative cohort but is not included in the TPC arm of DESTINY-Breast04.[1] The company does not consider SG to be a relevant comparator as it is only recommended by NICE for patients with TNBC i.e. HER2-negative/HR-negative (TA819),[132] which represents a small proportion (~10%) of the total HER2-low u/mBC population in UK practice.[146] Within this small proportion, SG cannot currently be considered to be standard of care within its licenced indication given that it was recommended by NICE as recently as August 2022[132] and therefore its uptake in UK clinical practice is currently uncertain.

However, the company has performed a feasibility assessment to determine the possibility and robustness of an indirect comparison between T-DXd and SG using DESTINY-Breast04 and published data from the ASCENT study.[147] The feasibility assessment reported a number of limitations that indicate an ITC would not be robust or suitable for decision-making.[147] The limitations related to conducting an ITC for T-DXd vs. SG are:[147]

- **Data availability:** While the company has access to individual patient data (IPD) for DESTINY-Breast04, any ITC is limited by the availability of published data for ASCENT.[154] Notably, there are limited published data from ASCENT for HER2-low patients specifically, including data on the baseline characteristics that would be required for the purposes of matching. The only baseline characteristics published for the HER2-low subgroup of ASCENT are median age, race, ECOG performance status and number of prior chemotherapy lines. Of these characteristics, the DESTINY-Breast04 and ASCENT HER2-low populations are similar for age and ECOG performance status, but different for race and unknown for the number prior chemotherapy lines. Thus, it may only be possible to match the populations using age and ECOG status.

- **Study design:** ASCENT was a Phase III study investigating the efficacy and safety of SG vs. TPC in the metastatic TNBC population. While this population included

HER2-low patients, the study was not powered to analyse efficacy in HER2-low nor was HER2 status (by IHC and ISH levels) a randomisation stratification factor or a pre-specified subgroup analysis. DESTINY-Breast04 is the only study powered to detect a treatment effect in HER2-low u/mBC specifically.

- **Population size:** DESTINY-Breast04 included only a small number of HER2-low/HR-negative patients treated with T-DXd (N=42), while ASCENT also included a relatively small number of HER2-low patients treated with SG (N=63). This means that after matching, the effective sample size of any ITC would be limited, in turn meaning that any analyses would be uncertain.
- **Differences in populations and trial inclusion/exclusion criteria:** There are a number of differences across populations in ASCENT and DESTINY-Breast04 that may impact treatment effect and may be covariates that cannot be adjusted for:
    - Prior chemotherapy: Data on prior lines of chemotherapy is reported differently in DESTINY-Breast04 and ASCENT (number of lines in a metastatic setting [1 vs. 2] vs. number of previous lines in any setting [2–3 vs. >3]), making it challenging to explore the impact of this variable on relative treatment effect. Eligibility criteria for prior chemotherapy and randomisation stratification factors based on this were also different between the trials (1 or 2 for metastatic disease in DESTINY-Breast04 vs. ≥2 for advanced disease in ASCENT).
    - Race: The DESTINY-Breast04 and ASCENT populations are very different in terms of proportion of White (48% vs. 84%) and Asian (48% vs. 5%) patients.
    - Region: Region was used as a randomisation factor in ASCENT (North America vs. rest of the world) without reporting the proportion of patients in each region. It is therefore not possible to adjust the populations based on this variable.
    - Metastases: The presence of metastases is likely to be detrimental for survival but, due to limited published data on the presence of metastases in HER2-low patients in ASCENT (e.g., did not include brain metastases), it is unknown whether the two subpopulations have a similar proportion of patients with brain, liver, or lung metastases.
    - Patient age: There is a small difference in median age between the two populations ([redacted] and [redacted] years for the T-DXd and TPC arms in the HR-negative cohort in DESTINY-Breast04[7] vs. 55 and 54 years for the SG and TPC arms in the HER2-low cohort in ASCENT[154]), but the age distributions of each population are unavailable, meaning that it is not possible to explore the effect of age on relative efficacy. A subgroup analysis from ASCENT suggests that age may have an impact on results. Without seeing the whole age distribution, it is difficult to predict exactly how much overlap there is between the age distributions for DESTINY-Breast04 and ASCENT, and therefore the effect that age difference is likely to have on the HRs.

Due to differences in reporting for the above characteristics, it is not possible to determine whether the populations can be adjusted for these variables.

Further to this, ITC methodologies (e.g. a matching-adjusted indirect comparison [MAIC]) would require adjustment of the DESTINY-Breast04 population to better match the ASCENT population. A MAIC would likely result in an even smaller effective sample size than the original population, leading to wide confidence intervals and high uncertainty.[147]

A second feasibility assessment was also performed independently of the analysis summarised above.[148] This independent feasibility assessment also highlighted that any indirect comparison between T-DXd and SG would be uncertain due to low effective sample sizes and limited reporting of relevant data from ASCENT.[148]

The possibility of conducting indirect analyses was also discussed with UK HEOR experts (including ex-NICE Committee and EAG members), who suggested that an ITC with SG would be highly uncertain due to small sample sizes and differences in study design and populations as well as the limited availability of data from the ASCENT study.[121] Following clinical advice, the experts also advised that stratifying DESTINY-Breast04 data would increase uncertainty and that, for decision-making, in the full in-scope population, the FAS is the relevant dataset and the TPC arm of DESTINY-Breast04 is the relevant comparator.[121]

In conclusion, the company considers an indirect comparison with SG would be highly uncertain, and not informative for decision-making.

B.2.10 Adverse reactions

The safety of T-DXd in patients with HER2-low u/mBC, previously treated with one or two lines of chemotherapy in the recurrent or metastatic setting, was evaluated in the DESTINY-Breast04 study, as presented below.

B.2.10.1 DESTINY-Breast04

The data presented from the DESTINY-Breast04 study are from the January 2022 DCO, with a median follow-up of 16.1 months in the T-DXd arm and 13.5 months in the TPC arm.[7] TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities (MedDRA, Version 24.0), and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Potential episodes of interstitial lung disease (ILD), an AE of special interest, were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE version 5.0. Safety analyses were performed on the SAS.

In general, T-DXd had a safety profile similar to that observed in previous studies of T-DXd, with no new Aes of concern identified in DESTINY-Breast04.[6, 20,68]

B.2.10.1.1 Exposure to T-DXd

At DCO (Jan 2022), the median treatment duration was 8.2 months (range: 0.2–33.3) for TDXd- and 3.5 months (range: 0.3–17.6) for TPC (**Table 22**).[6] The mean study dose intensity was [redacted] mg/kg/3 weeks[k] in the TDXd- arm. The mean relative dose intensity (RDI)

[k] The starting dose was 5.4 mg/kg for T-DXd. Two dose reductions were permitted for each treatment arm in the event of toxicity, with withdrawal from study drug if toxicity continued after two dose reductions. Increases in study drug were not permitted.

was [redacted]% in the TDXd- arm[l] and ranged from [redacted]–[redacted]% for the agents in the TPC arm[m] (**Table 22**).[7]

At DCO, 58 patients (15.6%) in the T-DXd arm and 3 patients (1.7%) in the TPC arm were continuing study treatment.

Table 22: DESTINY-Breast04 | Study drug exposure | SAS

	T-DXd (N=371)	Eribulin (N=89)	Capecitabine (N=36)	Nab-paclitaxel (N=17)	Gemcitabine (N=16)	Paclitaxel (N=14)
Median treatment duration, months (range)*	8.2 (0.2–33.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-years of exposure†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean dose intensity, mg/kg/ 3w (std. dev.)‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean RDI, % (std. dev.)¶	[redacted]§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment as of data cut-off date, n (%)						
≤3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>3 to ≤6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>6 to ≤9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>9 to ≤12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>12 to ≤18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>18 to ≤24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Treatment duration = (last dose date – first dose date + 21) × 12/365.25.
†Patient-years of exposure = total of treatment duration of all patients within each treatment group.
‡Dose intensity (units/cycle length in weeks) = cumulative dose level (units)/(duration of treatment [days]/cycle length [days]). Due to different cycle durations among the individual TPC treatments, dose intensity is not presented for the overall TPC arm.
§RDI for T-DXd was calculated using an amended methodology to that stated in the CSR: RDI (%) = Dose Intensity/Planned Dose Intensity × 100, where Planned Dose Intensity for T-DXd = 5.4 mg/kg / Duration of exposure (day) × cycle length in days × expected number of cycles, where cycle length is 21 days for T-DXd and number of cycles expected is based on the duration of treatment exposure.
¶RDI for TPC was calculated as per the CSR: RDI (%) = dose intensity / planned dose intensity ×100, where planned dose intensity (units/cycle lengths in weeks) = planned cumulative dose (units)/planned duration of exposure (day)/cycle length in day. Due to different cycle durations among the individual TPC treatments, relative dose intensity is not presented for the overall TPC arm
Abbreviations: CSR, clinical study report; RDI, relative dose intensity; SAS, safety analysis set; std. dev., standard deviation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; w, weeks.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

B.2.10.1.2 Treatment-emergent adverse events

A summary of TEAEs reported in patients in the DESTINY-Breast04 study are shown in **(Table 23)**.

[l] RDI for T-DXd was calculated using an amended methodology to that stated in the CSR: RDI (%) = Dose Intensity/Planned Dose Intensity × 100, where Planned Dose Intensity for T-DXd = 5.4 mg/kg / Duration of exposure (day) × cycle length in days × expected number of cycles, where cycle length is 21 days for T-DXd and number of cycles expected is based on the duration of treatment exposure.
[m] RDI for TPC was calculated as per the CSR: RDI (%) = dose intensity / planned dose intensity ×100, where planned dose intensity (units/cycle lengths in weeks) = planned cumulative dose (units)/planned duration of exposure (day)/cycle length in day. Due to different cycle durations among the individual TPC treatments, relative dose intensity is not presented for the overall TPC arm.

TEAEs were reported in 369 of 371 patients (99.5%) who received T-DXd and 169 of 173 patients (98.3%) who received TPC (**Table 23**).[6] When the incidence of TEAEs were adjusted for patient-years of exposure, the event rate per patient year was 1.30 and 2.66 with T-DXd and TPC, respectively.[6] When assessed by the investigator for causality to treatment, TEAEs reported by 357 patients (96.2%) and 162 patients (94.2%) treated with T-DXd and TPC, respectively, were considered drug-related.[7]

In total, CTCAE Grade ≥3 TEAEs were reported by 195 patients (52.6%) treated with T-DXd and 116 patients (67.4%) treated in the TPC arm;[6] in 154 patients (41.5%) and 99 patients (57.6%), respectively, the investigator deemed these drug-related.[7] When adjusted by patient-years of exposure, the rate of Grade ≥3 Aes was 0.69 events per patient year in the T-DXd arm and 1.82 events per patient year in the TPC arm.[6]

Serious TEAEs were reported by 103 patients (27.8%) treated with T-DXd and 43 patients (25.0%) in the TPC arm.[6] Adjusted for drug exposure, serious TEAEs occurred at a rate of [redacted] and [redacted] events per patient-year of exposure in patients treated with T-DXd and TPC, respectively.[7] Serious drug-related TEAEs were reported by 48 patients (12.9%) in the T-DXd and 19 patients (11.0%) in the TPC arm.[7] Seven drug-related TEAEs led to death in the T-DXd arm and none led to death in the TPC arm.[6]

In the T-DXd arm, TEAEs leading to discontinuation or dose reduction occurred in 60 patients (16.2%) and 84 patients (22.6%), respectively, and in the TPC arm, 14 patients (8.1%) and 66 patients (38.4%), respectively, with most considered drug-related (see **Table 23**).[6]

The proportion of TEAEs by cycle was highest in [redacted], and generally [redacted] across subsequent cycles (**Table 24**).[7] Each of the final two rows in **Table 24** contain more than one cycle, hence the proportion of patients with TEAEs appears to increase compared with the data for [redacted] through to [redacted]. Overall, treatment discontinuation rates were relatively low considering that most patients experienced TEAEs (**Table 23**).

Table 23: DESTINY-Breast04 | Summary of TEAEs | SAS

N (%)	T-DXd (N=371)	TPC (N=172)
Any TEAE	369 (99.5)	169 (98.3)
EAIR per patient-year of exposure	1.30	2.66
Any drug-related TEAE	357 (96.2)	162 (94.2)
TEAE Grade ≥3	195 (52.6)	116 (67.4)
EAIR per patient-year of exposure	0.69	1.82
Drug-related TEAE Grade ≥3	154 (41.5)	99 (57.6)
Serious TEAE	103 (27.8)	43 (25.0)
EAIR per patient-year of exposure	0.36	0.68
Serious drug-related TEAE	48 (12.9)	19 (11.0)
TEAE associated with an outcome of death	14 (3.8)	5 (2.9)
EAIR per patient-year of exposure	0.05	0.08
Drug-related TEAE associated with an outcome of death	7 (1.9)	0
TEAE associated with study drug discontinuation	60 (16.2)	14 (8.1)
EAIR per patient-year of exposure	0.21	0.22
Drug-related TEAE associated with discontinuation	56 (15.1)	12 (7.0)
TEAE associated with dose reduction	84 (22.6)	66 (38.4)
EAIR per patient-year of exposure	0.30	1.04
Drug-related TEAE associated with dose reduction	77 (20.8)	64 (37.2)
TEAE associated with study drug interruption	143 (38.5)	72 (41.9)

N (%)	T-DXd (N=371)	TPC (N=172)
EAIR per patient-year of exposure	0.50	1.13
Drug-related TEAE associated with study drug interruption	106 (28.6)	62 (36.0)

Abbreviations: EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; treatment of physician's choice.
Sources: Modi et al, 2022;[6] Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Table 24: DESTINY-Breast04 | TEAEs by cycle | SAS

	T-DXd (N=371)			TPC (N=172)		
	Subjects with any TEAEs, n	Subjects at risk, n	Proportion with TEAEs, %	Subjects with any TEAEs, n	Subjects at risk, n	Proportion with TEAEs, %
Cycle 1	[redacted]					
Cycle 2	[redacted]					
Cycle 3	[redacted]					
Cycle 4	[redacted]					
Cycle 5	[redacted]					
Cycle 6	[redacted]					
Cycle 7	[redacted]					
Cycle ≥8*	[redacted]					
Cycle ≥18*	[redacted]					

*Contains more than one cycle.
Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; treatment of physician's choice.
Source: Daiichi Sanko Inc., 2022 (CSR tables and figures; Data on File).[7]

Most common TEAEs

In patients treated with T-DXd, the most common TEAEs (any grade, reported by ≥50% of patients) were in the system organ classes of gastrointestinal disorders ([redacted] patient; [redacted]), investigations ([redacted] patients; [redacted]), general disorders and administration site conditions ([redacted] patients; [redacted]), skin and subcutaneous tissue disorders ([redacted] patients; [redacted]) and metabolism and nutrition disorders ([redacted] patients; [redacted]).[7] In patients treated with TPC, the most common TEAEs were in the system organ classes of gastrointestinal disorders ([redacted] patients; [redacted]), investigations ([redacted] patients; [redacted]), general disorders and administrative site conditions ([redacted] patients; [redacted]), and skin and subcutaneous tissue disorders ([redacted] patients; [redacted]).[7]

In the T-DXd arm, the most common TEAEs of any grade were nausea (282 patients; 76.0%), fatigue (199 patients; 53.6%) and vomiting (150 patients; 40.4%).[7] In the TPC arm, neutropenia (90 patients; 52.3%), fatigue (83 patients; 48.3%) and alopecia (57 patients; 33.1%) were the most common TEAEs of any grade.[7]

The five most common TEAEs of Grade ≥3 that occurred in patients treated with T-DXd were neutropoenia (52 patients; 14.0%), anaemia (38 patients; 10.2%), fatigue (32 patients; 8.6%), leukopenia (25 patients; 6.7%) and thrombocytopaenia (22 patients; 5.9%).[7] In patients in the TPC arm, the five most common TEAEs of Grade ≥3 were neutropoenia (71 patients; 41.3%), leukopenia (33 patients; 19.2%) increased transaminases (17 patients; 9.9%), anaemia (9 patients; 5.2%) and fatigue (8 patients; 4.7%).[7]

A summary of TEAEs (any grade) experienced by ≥20% of patients treated with T-DXd or TPC in the DESTINY-Breast04 trial in order of decreasing frequency is presented in **Table 25.**

Table 25: DESTINY-Breast04 | TEAEs in ≥20% of patients | SAS

	T-DXd (N=371)		TPC (N=172)	
Patient-years of exposure	283.55		63.59	
System organ class, Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Anaemia†	143 (38.5)	[redacted]	47 (27.3)	[redacted]
Neutropenia*	126 (34.0)	[redacted]	90 (52.3)	[redacted]
Thrombocytopaenia§	95 (25.6)	[redacted]	16 (9.3)	[redacted]
Leucopoenia‡	89 (24.0)	[redacted]	56 (32.6)	[redacted]
Lymphopenia	[redacted]	20 (5.4)	[redacted]	6 (3.5)
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders				
Nausea	282 (76.0)	17 (4.6)	52 (30.2)	0
Vomiting	150 (40.4)	[redacted]	23 (13.4)	[redacted]
Constipation	126 (34.0)	[redacted]	38 (22.1)	[redacted]
Diarrhoea	100 (27.0)	[redacted]	38 (22.1)	[redacted]
General disorders				
Fatigue**	199 (53.6)	[redacted]	83 (48.3)	[redacted]
Musculoskeletal pain	99 (26.7)	[redacted]	45 (26.2)	[redacted]
Abdominal pain	65 (17.5)	[redacted]	23 (13.4)	[redacted]
Investigations				
AST Increased	120 (32.3)	21 (5.7)	54 (31.4)	17 (9.9)
Metabolism and nutrition disorders				
Decreased appetite	118 (31.8)	[redacted]	33 (19.2)	[redacted]
Skin and subcutaneous tissue disorders				
Alopecia	147 (39.6)	[redacted]	57 (33.1)	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	5 (1.3)	0	24 (14.0)	7 (4.1)

*This category includes the preferred terms neutrophil count decreased and neutropoenia.
†This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased.
‡This category includes the preferred terms white blood cell count decreased and leucopoenia.
§This category includes platelet count decreased and thrombocytopaenia.
**This category includes the preferred terms fatigue, asthenia, and malaise.
Abbreviations: AST, aspartate aminotransferase; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sanko Inc., 2022 (CSR tables and figures; Data on File). [7]

Most common drug-related TEAEs

The five most common drug-related TEAEs (all grades) in the T-DXd arm were nausea (271 patients; 73.0%), fatigue (177 patients; 47.7%); alopecia (140 patients; 37.7%), vomiting (126 patients; 34.0%) and neutropoenia (123 patients; 33.2%).[2] In the TPC arm, the five most common drug-related TEAEs were neutropenia (88 patients; 51.2%), fatigue (73 patients; 42.4%), alopecia (56 patients; 32.6%), leucopoenia (54 patients; 31.4%) and nausea (41 patients; 23.8%).[2]

Drug-related TEAEs of Grade ≥3 that occurred in more than 5% of the patients treated with T-DXd were neutropoenia (51 patients; 13.7%), anaemia (30 patients; 8.1%), fatigue (28 patients; 7.5%), leukopenia (24 patients; 6.5%) and thrombocytopaenia (19 patients; 5.1%).[7] In the TPC arm, these were neutropoenia (70 patients; 40.7%), leukopenia (33 patients; 19.2%) and increased transaminases ([redacted] patients; [redacted]).[7]

A summary of drug-related TEAEs (any grade) experienced by ≥10% of patients treated with T-DXd or TPC in the DESTINY-Breast04 trial in order of decreasing frequency is presented in **Table 26**.

Table 26: DESTINY-Breast04 | Drug-related TEAEs in ≥10% of patients | SAS

	T-DXd (N=371)		TPC (N=172)	
Patient-years of exposure	283.55		63.59	
System organ class, Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Neutropoenia*	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anaemia†	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Leucopoenia‡	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Thrombocytopaenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhoea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
General disorders				
Fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Abdominal pain	45 (12.1)	[redacted]	4 (2.3)	[redacted]
Musculoskeletal pain	34 (9.2)	[redacted]	20 (11.6)	[redacted]
Investigations				
AST increased	87 (23.5)	[redacted]	39 (22.7)	[redacted]
Metabolism and nutrition disorders				
Decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Weight decreased	46 (12.4)	[redacted]	8 (4.7)	[redacted]
Skin and subcutaneous tissue disorders				
Alopecia	140 (37.7)	0	56 (32.6)	0
Interstitial lung disease	45 (12.1)	[redacted]	1 (0.6)	[redacted]
Stomatitis	42 (11.3)	[redacted]	18 (10.5)	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	4 (1.1)	[redacted]	24 (14.0)	[redacted]

*This category includes the preferred terms neutrophil count decreased and neutropoenia.
†This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased.
‡This category includes the preferred terms white blood cell count decreased and leucopoenia.
§This category includes platelet count decreased and thrombocytopaenia.
**This category includes the preferred terms fatigue, asthenia, and malaise.
Abbreviations: AST, aspartate aminotransferase; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Modi et al., 2022;[6] Daiichi Sanko Inc., 2022 (CSR tables and figures; Data on File).[7]

Treatment-emergent adverse events associated with changes to treatment

The key TEAEs associated with study drug discontinuation, dose reduction, or treatment interruption are summarised in **Table 27**.

In total, 60 patients (16.2%) in the T-DXd arm and 14 patients (8.1%) in the TPC arm had TEAEs associated with study drug discontinuation (**Table 27**).[6] These TEAEs were considered drug-related by the investigator in 56 patients (15.1%) treated with T-DXd and 12 patients (7.0%) treated with TPC. The most common TEAEs associated with study drug discontinuation in the T-DXd arm were pneumonitis in [redacted] patients ([redacted]) and ILD in [redacted] patients ([redacted]).[7]

A total of 84 patients (22.6%) in the T-DXd arm and 66 patients (38.4%) in the TPC arm had TEAEs resulting in dose reduction[n] (**Table 27**).[6] In most cases, the investigator considered the TEAE associated with dose reduction to be drug-related.[6]

Treatment-emergent Aes that led to study drug interruption[o] were reported for 143 patients (38.5%) in the T-DXd arm and 72 patients (41.9%) in the TPC arm (**Table 27**).[6] The TEAE leading to study drug interruption was considered by the investigator to be drug-related in 106 T-DXd patients (28.6%) and 62 TPC patients (36.0%), respectively (**Table 27**).[6]

Table 27: TEAEs associated with changes to treatment occurring in ≥2% of patients in either arm | SAS

Preferred term or grouped term, n (%)	T-DXd (N=371)	TPC (N=172)
TEAEs associated with study drug discontinuation	**60 (16.2)**	**14 (8.1)**
Pneumonitis	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Peripheral sensory neuropathy	0	4 (2.3)
TEAEs associated with study drug dose reduction	**84 (22.6)**	**66 (38.4)**
Fatigue	17 (4.6)	8 (4.7)
Nausea	17 (4.6)	4 (2.3)
Thrombocytopenia	13 (3.5)	0
Neutropenia	11 (3.0)	24 (14.0)
Leucopoenia	3 (0.8)	7 (4.1)
Transaminases increased	3 (0.8)	6 (3.5)
TEAEs associated with study drug interruption	**143 (38.5)**	**72 (41.9)**
Neutropenia	34 (9.2)	39 (22.7)
Fatigue	19 (5.1)	4 (2.3)
Anaemia	17 (4.6)	4 (2.3)
Leukopenia	13 (3.5)	10 (5.8)
COVID-19	11 (3.0)	2 (1.2)
Interstitial lung disease	11 (3.0)	0
Transaminases increased	11 (3.0)	6 (3.5)
Blood bilirubin increased	8 (2.2)	0
Nausea	5 (1.3)	4 (2.3)
Palmar-plantar erythrodysaesthesia syndrome	0	6 (3.5)
Peripheral sensory neuropathy	0	4 (2.3)

Abbreviations: ILD, interstitial lung disease; SAS, safety analysis set; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
Source: Modi et al., 2022;[6] Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Treatment-emergent adverse events of special interest

Adverse events identified as of special interest in DESTINY-Breast04 were ILD and left ventricular (LV) dysfunction, which are summarised in **Table 28** and **Table 29**, respectively. Cases of potential ILD or pneumonitis in either study arm were reviewed by an independent ILD adjudication committee.[7]

A total of 45 patients (12.1%) in the T-DXd arm and one patient (0.6%) in the TPC arm had events adjudicated as being drug-related ILD of any grade (**Table 28**).[140] The majority of cases in the T-DXd arm were Grade 1 (13 patients; 28.9%) or Grade 2 (24 patients; 53.3%).

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

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

Grade 3, 4 and 5 adjudicated drug-related ILD was reported in five (1.3%), zero and three (0.8%) subjects in the T-DXd arm.[140] The overall incidence of ILD was consistent with previous studies of T-DXd[6, 38, 78, 144] and events were manageable by following established ILD management guidelines, which included monitoring signs and symptoms of ILD (e.g., cough, fever, dyspnoea) and proactively managing events with early intervention (including dose modification, treatment, and supportive care).[7]

Median time to onset of the first adjudicated drug-related ILD event was [redacted] days (range: [redacted]) in the T-DXd arm.[7]

In the T-DXd arm, the outcome of the worst adjudicated drug-related ILD event experienced by the patient was recovered/resolved in 25 patients (55.6%), recovered/resolved with sequelae in two patients (4.4%) and recovering/resolving in four patients (8.9%).[7] Ten patients (22.2%) in the T-DXd arm had adjudicated ILD events that were not recovered/resolved. In addition, there were two (4.4%) adjudicated drug-related ILD events associated with death in the T-DXd arm.[7] The event was not recovered/resolved in the one patient with an adjudicated ILD event in the TPC arm.[7]

Events of ILD associated with study drug interruption, dose reduction, or discontinuation were reported in 11 (3.0%), two (0.5%) and 31 patients (8.4%), respectively of patients treated with T-DXd.[7] In patients treated with TPC, no ILD-related drug interruptions, dose reductions, or discontinuations were reported.[7]

Table 28: TEAEs adjudicated as drug-related ILD/pneumonitis* by CTCAE v5.0 Grade

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N=371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (N=172)	1 (0.6)	0	0	0	0	1 (0.6)

*Patients with prior history of ILD/pneumonitis requiring steroids were excluded.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Modi et al., ASCO 2022;[140] Daiichi Sankyo Inc., 2022 (CSR; Data on File) [7]

Left ventricular dysfunction (any Grade) was reported in 17 patients (4.6%) in the T-DXd arm (**Table 29**).[140] Most were Grade 1 or 2 in severity (15 patients; 4.1%).[140]

Table 29: TEAEs of LV dysfunction by CTCAE v5.0 Grade

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N=371)	1 (0.3)	14 (3.8)	2 (0.5)	0	0	17 (4.6)
TPC (N=172)	0	0	0	0	0	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; LV, left ventricular; T-DXd, trastuzumab deruxtecan, TPC, treatment of physician's choice.
Source: Modi et al., ASCO 2022;[140] Daiichi Sankyo Inc., 2022 (CSR; Data on File) [7]

B.2.10.2 Safety conclusions

The safety of T-DXd in the DESTINY-Breast04 study was generally manageable and tolerable. T-DXd had a similar safety profile in DESTINY-Breast04 to that observed in previous studies of T-DXd, including DESTINY-Breast01 and DESTINY-Breast03, with no new AEs of concern identified in this study.[6, 20,68]

The treatment arms were similar in the overall incidence of TEAEs, SAEs, TEAEs associated with study drug interruption, and TEAEs associated with an outcome of death.[6] The majority of TEAEs were Grade 1 or 2 in severity, occurred most frequently in [redacted], and [redacted] over subsequent cycles.[7]

Of note, Grade ≥3 TEAEs were reported at a lower incidence in the T-DXd arm (52.6%) than in the TPC arm (67.4%).[6] Similarly, while drug-related TEAEs were reported in a similar incidence in the T-DXd and TPC arms (96.2% vs. 94.2%), the incidence of drug-related Grade ≥3 TEAEs was higher in the TPC arm (41.5% vs. 57.6%).[7] In most patients, drug-related TEAEs with T-DXd were manageable with dose modifications and routine clinical care.[7]

Drug-related TEAEs with T-DXd did not necessitate study drug discontinuation in most patients.[7] While a higher proportion of patients discontinued the study drug in the T-DXd arm than the TPC arm (16.2% vs. 8.1%), this was primarily driven by protocol-defined dose modification criteria for events of ILD (an AE of special interest for T-DXd).[6,7] Additionally, the proportion of patients requiring dose reductions was lower in the T-DXd arm than the TPC arm (22.6% vs. 38.4%).[6] The proportion of patients requiring dose interruptions was similar with T-DXd vs. TPC (38.5% vs 41.9%).[6]

It should be noted that median treatment duration was considerably longer in the T-DXd arm than in the TPC arm (8.2 vs 3.5 months). Exposure-adjusted incidence rates (EAIR) were lower for T-DXd than TPC for all parameters including overall TEAEs, Grade ≥3 TEAEs, TEAEs associated with study drug interruptions, and TEAEs associated with dose reduction.[6]

Adverse events of special interest (ILD/pneumonitis and LV dysfunction) associated with T-DXd were generally of mild or moderate severity and were well managed through the use of established management guidelines, which included monitoring signs and symptoms of ILD and proactively managing events with early intervention.[7]

B.2.11 Ongoing studies

No additional studies are planned in the population of interest. As statistical significance was demonstrated for primary and key secondary endpoints of PFS and OS in the HR-positive and FAS populations, there is no protocol-defined requirement for further data analyses of DESTINY-Breast04.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence

DESTINY-Breast04 demonstrates that T-DXd offers significant clinical benefit over TPC in patients with HER2-low u/mBC following one or two lines of chemotherapy in the metastatic setting. Published UK biomarker data[56] and UK clinical expert insights confirm that the distribution of HR-positive and HR-negative patients in DESTINY-Breast04 is aligned to UK clinical practice.[121]

In DESTINY-Breast04, T-DXd demonstrated statistically significant superiority compared with TPC for the primary endpoint of PFS by BICR in the HR-positive cohort (median PFS: 10.1 vs 5.4 months; HR: 0.51; p<0.001).[6] The findings of the primary endpoint were confirmed by analysis of PFS by IA.[7] T-DXd was also associated with statistically significant

improvements over TPC for all secondary efficacy endpoints: PFS by BICR in the FAS (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001), OS in the HR-positive cohort (median OS: 23.9 months vs. 17.5 months; HR: 0.64; p=0.003) and OS in the FAS (median OS: 23.4 months vs.16.8 months; HR: 0.64; p=0.001).[6] Likewise, T-DXd was associated with improved PFS and OS outcomes vs. TPC in an exploratory analysis of the HR-negative cohort, with statistically significantly longer PFS (median PFS by BICR: 8.5 vs. 2.9 months; HR: 0.46; p=0.0135) and numerically longer OS (median OS: 18.2 vs. 8.3 months; HR: 0.48; p=0.1732).[6,7] Together, these results demonstrate consistent and clinically relevant efficacy across HR-status subgroups.

The efficacy of T-DXd was confirmed across multiple clinically meaningful endpoints, including all those listed in the final scope, covering the most important outcomes in oncology.[1,7] In the FAS, confirmed ORR by BICR was achieved in more than three times as many patients in the T-DXd arm compared with TPC (52.3% vs. 16.3%, respectively; p<0.0001).[6,7] The CBR associated with T-DXd was more than twice that of TPC (70.2% vs. 33.7%, respectively p<0.0001) demonstrating durability of response for at least six months.[6,7] Consistent with this, median duration of response was longer with T-DXd than TPC (median DoR by BICR: 10.7 vs 6.8 months).[6]

Subgroup analyses of PFS by BICR confirm that T-DXd offers a statistically significant clinical benefit compared with TPC across pre-specified prognostic and demographic subgroups, including hormone receptor status, number of prior lines of chemotherapy in the metastatic setting, prior treatment with CDK4/6 inhibitors, ECOG performance status, baseline visceral disease, and baseline brain metastases.[6,7] The magnitude of benefit was similar across subgroups and compared with the FAS, demonstrating consistency in treatment effect.[7]

Health-related quality-of-life of patients was maintained on treatment with T-DXd across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-C30 and EORTC QLQ-BR45) PRO instruments with longer TTDD across almost all measures and scales compared with TPC.[7,151] For EQ-5D-5L VAS, median TTDD was longer in the T-DXd arm than the TPC arm ((95% CI:) vs. months (95% CI:); HR: ; 95% CI: ; p= ; FAS).[152] Similarly, for EORTC QLQ-C30 GHS, the median TTDD was longer with T-DXd than TPC ((95% CI:) vs. months (95% CI:); HR: ; 95% CI: ; p= ; FAS).[152]

The safety of T-DXd in the DESTINY-Breast04 study was generally manageable and tolerable. A similar proportion of patients experienced TEAEs in both the T-DXd (99.5%) and TPC (98.3%) arms with most of Grade 1 or 2 severity and manageable through routine clinical practice.[7] A lower proportion of patients in the T-DXd arm experienced Grade ≥3 TEAEs (52.6% vs. 67.4%).[6] Treatment-emergent AEs occurred most frequently in the first cycle and generally .[7] It should also be noted that median treatment duration was considerably longer with T-DXd than TPC (8.2 vs 3.5 months). Exposure-adjusted rates were lower for T-DXd than TPC for all parameters including TEAEs (1.30 vs. 2.66), Grade ≥3 TEAEs (0.69 vs. 1.82), treatment-emergent SAEs (0.36 vs. 0.68), and TEAEs related to dose modification (discontinuation: 0.21 vs. 0.22; reduction: 0.30 vs. 1.04; interruption: 0.50 vs. 1.13).[6] For T-DXd, AEs of special interest (ILD/pneumonitis and LV dysfunction) were mostly of mild or moderate severity and manageable through the use of established guidelines which included monitoring signs and symptoms of ILD and proactively managing events with early intervention.[7] Overall, the safety of T-DXd in DESTINY-Breast04 was consistent with previous studies of T-DXd in u/mBC, including

DESTINY-Breast01 and DESTINY-Breast03, with no new AEs of concerned identified in this study.[7, 20,68]

At an advisory board meeting in December 2022, UK clinical and HEOR experts confirmed that the DESTINY-Breast04 trial is well designed, robust, and the population is generalisable to UK clinical practice.[121] In particular, and as described in detail in **Section B.1.3.6**, clinical experts agreed that the comparator arm of the trial (comprising eribulin, capecitabine, nab-paclitaxel, gemcitabine and paclitaxel) is relevant as it includes treatments widely used in the UK after one or two prior lines of non-targeted chemotherapy in the metastatic setting.[121] The range of comparators reflects how u/mBC is treated in the UK, where the choice of non-targeted chemotherapy at later lines is based on clinician preference as well as patient-specific needs and preference.[121] While SG is included as a comparator in the final NICE scope,[1] it is only recommended in a very small proportion (~10%)[56] of the population being considered in this appraisal and a feasibility assessment concluded that an ITC would not be robust for decision making due to the high degree of uncertainty caused by very small sample sizes and differences in trial design.[147] Clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal and that the comparators listed in the NICE final scope are well represented in the TPC arm of DESTINY-Breast04.[1,121] As such, Daiichi Sankyo consider evidence from DESTINY-Breast04 to be highly relevant to the decision problem.

There are currently no UK-specific treatment guidelines for HER2-low u/mBC and patients are treated according to HER2-negative treatment pathways. Standard of care for HER2-negative u/mBC after a prior chemotherapy in the metastatic setting in UK clinical practice is further lines of single-agent non-targeted chemotherapy.[35,42] At an advisory board in December 2022, UK clinical experts unanimously agreed that outcomes with non-targeted chemotherapies are poor in the mBC setting, and that efficacy is similar across individual non-targeted chemotherapy agents.[121] This aligns with a published systematic review of RCTs for single-agent chemotherapies used in Europe, which concluded that none of the included RCTs demonstrated a significant difference in OS between the chemotherapy agents.[118]

Aside from DESTINY-Breast04, there are no prior studies powered to evaluate efficacy in a HER2-low u/mBC population specifically, so the external validity of DESTINY-Breast04 may be assessed by comparing the TPC arm to previous studies in a similar setting in HER2-negative u/mBC (**Table 30**). In the FAS, median PFS by BICR with TPC in DESTINY-Breast04 was within the range of median PFS for non-targeted single-agent chemotherapies across all previous studies of HER2-negative u/mBC of any HR-status (5.1 months[6] vs 1.7–6.6 months; [43–55] including similar TPC arms in RIBBON-2[53] and EMERGE[55]). Median OS (16.8 months)[6] was also within the range reported in prior studies (6.7–20.7 months).[43–55] In the HR-positive cohort of DESTINY-Breast04 specifically, median PFS by BICR with TPC was slightly higher than the range in previous studies of HER2-positive/HR-positive u/mBC (5.4 months[6] vs. 3.6–4.2 months), and median OS was also slightly higher (17.5 months[6] vs. 11.5–16.1 months).[43–47,156] In the HR-negative cohort, median PFS in the TPC arm of DESTINY-Breast04 was similar to previous studies (2.9 months[6] vs. 1.7–2.8 months), as was median OS (8.3 months[6] vs 6.7–12.4 months).[43, 48–50,157] This confirms the external validity of the TPC arm in DESTINY-Breast04.

A comparison with previous studies highlights the unprecedented efficacy benefit of T-DXd in DESTINY-Breast04 compared with non-targeted single-agent chemotherapies (**Table 30**). In the FAS, median PFS by BICR for T-DXd was considerably longer than the DESTINY-

Breast04 TPC arm (9.9 vs. 5.1 months; HR: 0.50; p<0.001)[6] and the chemotherapy arms from previous studies (1.7–6.6 months).[43–55] Median OS for T-DXd was also considerably longer than the TPC arm (23.9 vs. 17.5 months; HR: 0.64; p=0.003; FAS)[6] and chemotherapy arms from all previous studies (6.7–20.7 months).[43–55] In the HR-positive cohort of DESTINY-Breast04 specifically, median PFS by BICR with T-DXd was considerably higher than TPC (median PFS by BICR: 10.1 vs. 5.4 months; HR: 0.51; p<0.0001)[6] and the range in previous studies in HER2-positive/HR-positive u/mBC (3.6–4.2 months). Similar findings were observed for median OS in the HR-positive cohort (T-DXd 23.9 months[6] vs. TPC 17.5 months[6] vs. previous chemotherapy studies 11.5–16.1 months).[43–47,156] Likewise, T-DXd offers profound survival benefit over chemotherapy in the HR-negative cohort in terms of median PFS by BICR (T-DXd 8.5 months vs. TPC 2.9 months[6] vs. previous chemotherapy studies 1.7–2.8 months[43, 48–50,157]) and median OS (T-DXd 18.2 months vs. TPC 8.3 months[6] vs. previous chemotherapy studies 6.7–12.4 months).[43, 48–50,157]

In conclusion, the DESTINY-Breast04 study clearly demonstrates the unprecedented survival benefit of T-DXd compared with single-agent chemotherapy in HER2-low u/mBC. Naïve comparison of DESTINY-Breast04 with external studies in similar settings provides further confidence in the conclusions from the trial. The unprecedented efficacy demonstrated in DESTINY-Breast04 has led to T-DXd becoming the first HER2-targeted therapy to receive EMA regulatory approval in HER2-low u/mBC,[3] with UK regulatory approval expected imminently. T-DXd therefore represents a step-change in the treatment paradigm and highlights a need for UK clinical pathways to be updated to further categorise HER2 status. UK clinical experts confirmed that there is an unmet need for better outcomes and that DESTINY-Breast04 has demonstrated the efficacy of T-DXd in this setting.[121]

Table 30: External validity comparison of PFS and OS in DESTINY-Breast04 with previous studies in HER2-negative u/mBC

Author and study details	Study name	Line of chemotherapy in the metastatic setting	Treatment	Median PFS, months	Median OS, months
HER2-negative/HR-positive (HER2-low/HR-positive cohort for DESTINY-Breast04)					
Modi et al., 2022 (NCT03734029) Phase III[6]	DESTINY-Breast04	2-3	T-DXd	10.1	23.9
			TPC (eribulin, capecitabine, nab-paclitaxel, gemcitabine, paclitaxel)	5.4	17.5
Pivot et al., 2016 (NR) Phase III[43]	Study 301 and Study 305	≥2	Eribulin	3.7	15.1
Pivot et al., 2017 (NCT00337103) Phase III[46]	Study 301	2	Eribulin	4.2	16.1
				4.0	13.5
Twelves et al., 2016 (NCT00337103) Phase III[45]	Study 301	≥2	Eribulin	4.1	15.9
			Capecitabine	3.9	13.5
Yardley et al., 2016 (298) (NCT01427933) Phase II[47]	-	2-4	Eribulin	4.1	11.5
Cortes et al., 2011 (NCT00388726) Phase III[44]	EMBRACE	2–5	Eribulin	3.6	13.2
HER2-negative/HR-negative (HER2-low/HR-negative cohort for DESTINY-Breast04)					
Modi et al., 2022 (NCT03734029) Phase III[6]	DESTINY-Breast04	2-3	T-DXd	8.5	18.2
			TPC (eribulin, capecitabine, nab-paclitaxel, gemcitabine, paclitaxel)	2.9	8.3
Pivot et al., 2016 (NR) Phase III[43]	Study 301 and Study 305	≥2	Eribulin	2.8	12.4
Vahdat et al., 2021* (NCT0199733) Phase II[50]	METRIC	≤2	Capecitabine	2.8	8.7
Bardia et al., 2021* (NCT02574455) Phase III[48]	ASCENT	≥2	SG **	5.6	12.1
			TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	1.7	6.7
Winer et al., 2021* (NCT02555657) Phase III[49]	KEYNOTE-119	2-3	TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	2.3	10.8
HER2-negative [any HR status] (HER2-low FAS for DESTINY-Breast04)					
Modi et al., 2022 (NCT03734029) Phase III[6]	DESTINY-Breast04	2-3	T-DXd	9.9	23.4
			TPC (eribulin, capecitabine, nab-paclitaxel, gemcitabine, paclitaxel)	5.1	16.8
Claessens et al., 2019 (NR) Phase III[52]	Stop&Go	2	Capecitabine (intermittent)	3.7	10.9
			Capecitabine (continuous)	5.0	12.4

Brufsky et al., 2011* (NCT00281697) Phase III[53]	RIBBON-2	2	TPC (capecitabine, docetaxel, nab-paclitaxel, paclitaxel, gemcitabine, vinorelbine)	5.1	16.4
Decker et al., 2019* (NCT01520103) Phase II	VicTORia	2	Vinorelbine	4.1	13.8
Decker et al., 2017* (NCT01320111) Phase II[54]	PASO	2-3	Paclitaxel	6.6	20.7
Yardley et al., 2016 (NCT01427933) Phase II[47]	-	2-4	Eribulin	4.1	11.5
Yardley et al., 2015* (NCT01156753) Phase II[125]	EMERGE	2-7	TPC (eribulin, vinorelbine, capecitabine, gemcitabine)	2.0	7.4

*Publication identified as part of the clinical SLR for this appraisal. **SG is not a non-targeted chemotherapy but is included as it is in the NICE scope.
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; NICE, National Institute of Health and Care Excellence; NR, not reported; OS, overall; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

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

Strengths of the evidence base

The key strength of the evidence base is the DESTINY-Breast04 study, a Phase III, multicentre, open-label, randomised trial of T-DXd versus TPC, which is representative of the current standard of care in the UK after prior chemotherapy in the metastatic setting.[7, 121,151] DESTINY-Breast04 is the first ever head-to-head Phase III study to show a statistically significant efficacy benefit for a HER2-targeted treatment versus non-targeted chemotherapy in HER2-low u/mBC. The trial provides data on a range of clinically meaningful efficacy endpoints as well as safety and QoL via generic and cancer-specific PRO instruments.

The number of patients randomised in DESTINY-Breast04 was large (N=554) and the treatment arms were well-balanced in terms of baseline demographics and disease characteristics.[7] UK clinical and HEOR experts confirmed that DESTINY-Breast04 is well designed and robust, and the patient population is generalisable to UK clinical practice.[121] The trial population is reflective of the UK patient population in terms prior ET in the metastatic setting (83%).[7] Published UK biomarker data and UK clinical experts confirm that the proportion of patients in each HR-status group (HR-positive: 88.7%; HR-negative: 11.3%) was reflective of UK clinical practice, therefore confirming the use of the FAS in the trial.[121]

Clinical experts agreed that the comparator arm of DESTINY-Breast04 (comprising eribulin, capecitabine, nab-paclitaxel, gemcitabine and paclitaxel) is relevant as it includes treatments widely used in the UK after one or two prior lines of non-targeted chemotherapy in the metastatic setting.[121] The range of comparators reflects how u/mBC is treated in the UK where the choice of non-targeted chemotherapy at later lines is based on clinician preference as well as patient-specific needs.[7,121] Given that there is no single standard of care in the UK and a wide range of chemotherapies are used,[1] the relevance of TPC as the comparator arm in DESTINY-Breast04 is a strength of the evidence base.[121] The comparators listed in the NICE final scope[1] are well represented in the TPC arm of DESTINY-Breast04. Clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal.[121]

Another strength of the evidence base is in the efficacy of T-DXd which was confirmed across multiple clinically meaningful endpoints, including all those listed in the final scope, covering the most important outcomes in oncology.[1,7] In DESTINY-Breast04, T-DXd demonstrated statistically significant superiority compared with TPC for the primary endpoint of PFS by BICR in the HR-positive cohort (median PFS: 10.1 vs 5.4 months; HR: 0.51; p<0.001).[6] The findings of the primary endpoint were confirmed by analysis of PFS by IA.[7] T-DXd was also associated with statistically significant superiority over TPC for all secondary efficacy endpoints: PFS by BICR in the FAS (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001), OS in the HR-positive cohort (median OS: 23.9 months vs. 17.5 months; HR: 0.64; p=0.003) and OS in the FAS (median OS: 23.4 months vs.16.8 months; HR: 0.64; p=0.001).[6] Likewise, T-DXd was associated with improved PFS and OS outcomes vs. TPC in an exploratory analysis of the HR-negative cohort, with longer PFS (median PFS by BICR: 8.5 vs. 2.9 months; HR: 0.46; p=0.0135) and longer OS (median OS: 18.2 vs. 8.3 months; HR: 0.48; p=0.1732).[6,7]

The magnitude of survival benefit with T-DXd over TPC was consistent across all key subgroups, including number of prior lines of chemotherapy in the metastatic setting, prior treatment with CDK4/6 inhibitors, ECOG performance status, baseline visceral disease, and

baseline brain metastases.[7] The consistency of these results demonstrates the reliability of the evidence base. The reliability and external validity of the evidence base is reinforced by a naïve comparison of survival outcomes in DESTINY-Breast04 vs. previous studies of single-agent non-targeted chemotherapies in HER2-negative u/mBC (**Table 30**). The naïve comparison confirms the external validity of DESTINY-Breast04 given the similarity in survival in the TPC arm with previous studies. It also provides confidence that T-DXd offers unprecedented survival benefit over non-targeted single-agent chemotherapies.

Quality-of-life of patients was maintained on treatment with T-DXd across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-C30 and EORTC QLQ-C30) PRO instruments, and T-DXd was associated with longer TTDD across almost all QoL measures and subscales compared with TPC.[7,152]

The safety profile of T-DXd in DESTINY-Breast04 was generally manageable and tolerable. Toxicities in DESTINY-Breast04 were consistent with previous studies of T-DXd.[20,68] The majority of TEAEs were Grade 1 or 2 in severity, occurred most frequently in [redacted], and [redacted] over subsequent cycles.[7] Grade ≥3 TEAEs and Grade≥3 drug-related TEAEs were reported at lower rates with T-DXd than TPC.[7] In addition, EAIRs were lower for T-DXd than TPC for all parameters including overall TEAEs, Grade ≥3 TEAEs, drug-related TEAEs, and TEAEs related to dose modification.[6] AEs of special interest (ILD/pneumonitis and LV dysfunction) associated with T-DXd were generally of mild or moderate severity and well managed through the use of established management guidelines, which included monitoring signs and symptoms of ILD and proactively managing events with early intervention.[7] In general, T-DXd had a similar safety profile in DESTINY-Breast04 to that observed in previous studies of T-DXd, including DESTINY-Breast01 and DESTINY-Breast03, with no new AEs of concern.[20,68]

Potential limitations

A potential limitation of DESTINY-Breast04 is the open-label nature of the trial. Although this is unlikely to have substantially affected interpretation of the primary endpoint (PFS for the primary endpoint was analysed by a blinded assessor) it should be considered when interpreting efficacy and safety findings from the trial.[7,158]

As confirmed by published UK biomarker data[56] while the proportion of patients with HR-positive vs. HR-negative disease (88.7% vs 11.3%) in the trial is representative of real-world proportions,[56] HR-negative results should be interpreted with caution as this was an exploratory analysis with a limited sample size.[7]

Finally, while the number of patients receiving individual TPC agents is too small to allow meaningful subgroup analyses, this is not expected to have an impact on the interpretation of the results, as published data and clinical expert feedback suggest that single-agent non-targeted chemotherapies have comparable efficacy in this setting.[118,121] The consistency in efficacy between non-targeted chemotherapy agents in prior studies of HER2-negative u/mBC in settings broadly aligned to the scope of this appraisal and the TPC arm of DESTINY-Breast04 support the external validity of trial results (**Table 30**). Notably clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal and that the comparators listed in the NICE final scope are well represented in the TPC arm of DESTINY-Breast04 (see **Section B.1.3.6** for more information).[1,121]

B.2.12.3 Summary

For patients with HER2-positive u/mBC, the introduction of HER2-targeted therapies, starting with trastuzumab in 1998, has transformed the pathway of care and altered the natural history of disease.[113] Since then, NICE has recommended a number of HER2-targeted therapies, as monotherapy or combination therapy, for HER2-positive u/mBC. T-DXd received a positive recommendation from NICE for reimbursement via the CDF for treating HER2-positive u/mBC after two or more anti-HER2 therapies (TA704) based on DESTINY-Breast01,[4] and after one or more anti-HER2 therapies (TA862)[5] based on the Phase III DESTINY-Breast03 trial following unprecedented survival benefits over the current UK standard of care, T-DM1 (HR for progression or death: 0.28; 95% CI: 0.22, 0.37; p<0.001).[68]

For patients with HER2-negative u/mBC, options are generally limited to non-targeted, single-agent chemotherapy once earlier targeted therapies (e.g., ET and CDK4/6i for HR-positive/HER2-negative u/mBC) have been exhausted. Non-targeted, single-agent chemotherapies are associated with poor outcomes; in HER2-negative/HR-positive u/mBC, median PFS is 3.6–4.2 months and median OS of 11.5–16.1 months.[43–47] Outcomes are even poorer in HER2-negative/HR-negative (TNBC) u/mBC, where median PFS is 1.7–2.8 months and median OS is 6.7–12.4 months.[47,51–55] At a December 2022 advisory board, UK clinical experts unanimously agreed that single-agent chemotherapies are associated with similarly poor efficacy and that novel treatments are needed.[121]

Current HER2 classification is binary, either positive or negative, yet a considerable proportion (58%) of patients traditionally classified as HER2-negative u/mBC have tumours expressing low levels of HER2 (ICH1+ or ICH2+/ISH-).[56] Despite expressing low levels of HER2, the benefits of HER2-targeted therapies in HER2-positive BC have not yet translated to HER2-low. For example, despite demonstrating survival benefits in HER2-positive high-risk invasive BC, trastuzumab plus adjuvant chemotherapy did not improve survival outcomes compared with adjuvant chemotherapy alone in women with HER2-low high-risk invasive BC.[57] Similarly, the efficacy of T-DM1 was considerably worse in patients with lower levels of HER2 expression than those with HER2-positive u/mBC.[159] There remains an opportunity, therefore, for effective HER2-targeted therapies to improve outcomes in patients with HER2-low u/mBC.

Following unprecedented survival benefits compared with other HER2-targeted agents in patients with HER2-positive disease,[68,160] DESTINY-Breast04 evaluated T-DXd in patients with HER2-low u/mBC following one or two lines of chemotherapy in the metastatic setting.[6] DESTINY-Breast04 met its key primary endpoint of PFS by BICR in the HR-positive cohort, demonstrating statistically significant superiority of T-DXd compared with TPC.[6] T-DXd was also associated with statistically significant superiority over TPC for all key secondary efficacy endpoints – PFS by BICR in the FAS, OS in the HR-positive cohort, and OS in the FAS – as well as other clinically meaningful secondary endpoints including response rates.[6] The magnitude of benefit across pre-specified subgroups, including hormone receptor status, number of prior lines of chemotherapy in the metastatic setting, prior treatment with CDK4/6 inhibitors, ECOG performance status, baseline visceral disease, and baseline brain metastases, demonstrate the consistency of treatment effect and strength of the data.[6,7]

Quality-of-life of patients was maintained on treatment with T-DXd across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-C30 and EORTC QLQ-C30) PRO instruments with longer TTDD across almost all measures and scales compared with TPC.[7,151] The safety profile of T-DXd in DESTINY-Breast04 was consistent with previous studies of T-DXd in u/mBC,[6] and the majority of TEAEs were mild or moderate in severity,

[redacted] through cycles.[7] Despite similar rates of overall TEAEs and drug-related TEAEs, T-DXd was associated with lower rates of and Grade ≥3 TEAEs and drug-related Grade ≥3 TEAEs than TPC. Exposure-adjusted rates for all parameters were lower for T-DXd vs. TPC, including Grade ≥3 TEAEs, drug-related Grade ≥3 TEAEs, and all TEAEs associated with study drug interruption, dose reduction and discontinuation.[6] Adverse events of special interest (ILD/pneumonitis and LV dysfunction) associated with T-DXd were generally of mild or moderate severity and well managed through the use of established management guidelines.[7]

Overall, DESTINY-Breast04 clearly demonstrates the efficacy and safety of T-DXd compared with standard of care in a population of patients aligned to the final scope for this appraisal.[1] UK clinical and HEOR experts confirmed that DESTINY-Breast04 is well designed, robust and generalisable to UK clinical practice, including a comparator arm that is reflective of the range of single-agent chemotherapy options used in the metastatic setting, where the choice of non-targeted chemotherapy at later lines is based on clinician preference as well as patient-specific needs and preference.[121] Clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal and that the comparators listed in the NICE final scope are well represented in the TPC arm of DESTINY-Breast04 (see **Section B.1.3.6** for more information).[121] As such, Daiichi Sankyo consider the results from DESTINY-Breast04 to be highly relevant to the decision problem.

DESTINY-Breast04 is the first ever head-to-head Phase III trial to show a significant benefit of HER2-targeted treatment in HER2-low u/mBC after one or two lines of chemotherapy in the recurrent or metastatic setting compared with non-targeted chemotherapy.[6] The unprecedented efficacy demonstrated in DESTINY-Breast04 has led to T-DXd becoming the first and only HER2-targeted therapy to receive EMA regulatory approval in HER2-low u/mBC,[3] representing a step-change in the treatment paradigm and supporting a need for UK clinical pathways to further categorise HER2 status. In light of the suboptimal survival outcomes in HER2-negative u/mBC (**Table 30**), T-DXd offers hope of extended life and QoL for patients, carers, and families. UK clinical experts confirmed that there is an unmet need for better outcomes in this setting.[121]

In recognition of its innovation, T-DXd was awarded an Innovation Passport designation by the Innovative Licensing and Access Pathway (ILAP) steering group in May 2022 (ILAP reference number: ILAP/IP/22/08265/01). T-DXd is now approved in HER2-low u/mBC by the EMA[3] and the US FDA.[138,139] UK Medicines and Healthcare Products Regulatory Agency (MHRA) approval is expected imminently (March 2023).

Based on the DESTINY-Breast04 study, US NCCN 2022 guidelines recommend T-DXd as a Category 1 preferred regimen for patients with HER2-low BC who have received at least one prior line of chemotherapy for metastatic disease and, if the tumour is HR-positive, are refractory to ET.[43] Similarly, in the ASCO 2022 Rapid Recommendation Update, T-DXd is recommended for patients with HER2-low who have received at least one prior chemotherapy for metastatic disease, and if HR-positive are refractory to ET.[71] Furthermore, ESMO guidelines recognise HER2-low as a clinically relevant subgroup of patients with u/mBC.[42] This confirms that T-DXd is expected to transform the pathway of care in patients with HER2-low u/mBC.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted on 25 February 2022 to identify relevant economic evaluations of treatments for patients with HER2-negative or HER2-low u/mBC previously treated with chemotherapy. As HER2-low is currently not yet established as classification, the use of a non-standardised definition of 'HER2-low' in the SLR could affect the results of a literature search because this term is not yet widely used in clinical trials or medical guidelines. The populations identified as relevant for the SLR for the anticipated licensed indication were "adult patients with HER2-negative/HR-positive, unresectable and/or metastatic breast cancer" and "adult patients with triple-negative, unresectable and/or metastatic breast cancer". A detailed description of the review methods and results are reported in **Appendix G**.

The original SLR (searches conducted on 25 February 2022) found no economic publications evaluating T-DXd in the relevant population, but identified two published economic evaluations of treatments for HER2-negative u/mBC (summarised in **Table 31**).[161] A quality assessment of the identified studies is presented in **Appendix G**. Both models identified in the SLR used a partitioned survival approach.[161]

NICE TA819[132] was identified as part of the initial SLR (25 February 2022), but data for this appraisal were not yet published. The company therefore conducted hand searches on 13 February 2023 to identify data related to NICE TA819, as well as other potentially relevant NICE TAs. The following three NICE TAs were identified as being applicable to this appraisal as they relate to technologies used at a relevant line of therapy in the current treatment pathway for HER2-negative/HR-positive, or HER2-negative/HR-negative u/mBC: NICE TA819,[132] NICE TA423,[131] and NICE TA116.[122] The additional TAs identified are summarised in **Table 32**. Data from these TAs were extracted using the same approach as the original SLR (see **Appendix G** for further details on extracted data from the hand searches).

Table 31: Summary list of published cost-effectiveness studies (original SLR; 25 February 2022)

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
G. Tremblay et al. 2016[162]	2014/2015 (₩)	PartSA model Cycle length: 1 month Time horizon: lifetime	South Korean patients with HER2-negative mBC who have progressed after at least one chemotherapeutic regimen for advanced disease (second-line therapy)	Eribulin vs. capecitabine and vinorelbine: 0.24	Costs per cycle: Eribulin: ₩1,103,807 Capecitabine: ₩267,628 Vinorelbine: ₩494,254	Eribulin vs. capecitabine and vinorelbine: ₩16,898,483M (approx. $14,800)
U. Majethia et al. 2015[163]	NR (€)	PartSA model Cycle length: NR Time horizon: 5 years	Spanish patients with HER2-negative mBC who have progressed following one prior chemotherapeutic regimen (second-line therapy)	Eribulin vs. capecitabine: 0.23	Eribulin: €320 per vial	Eribulin vs. capecitabine: €36,951

Abbreviations: ICER, incremental cost-effectiveness ratio; mBC, metastatic breast cancer; NR, not reported; PartSA, partitioned survival analysis; QALY, quality-adjusted life-years; ₩, South-Korean Won.
Source: Daiichi Sankyo Inc., 2022 (Economic SLR report; Data on File)[161]

Table 32: Summary list of published cost-effectiveness evaluations from relevant NICE TAs (hand search update; 13 February 2023)

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
NICE TA819[132]	2022 (£)	PartSA model Cycle length: 1 week Time horizon: 10 years	Patients aged ≥18 years with unresectable locally advanced or mTNBC who have received ≥2 prior systemic therapies, including ≥1 prior therapy for locally advanced or metastatic disease	NR (information is redacted)	NR (information is redacted)	Base case ICER (including confidential PAS discount for SG and the list price for comparators and subsequent treatments): SG vs. TPC: £47,170
NICE TA423[131]	2016 (£)	PartSA model Cycle length: 1 month Time horizon: 5 years	Subgroup 1: HER2-negative patients with LABC/mBC, whose disease has progressed after one prior chemotherapy regimen	Eribulin vs. capecitabine: Subgroup 1: 0.25 Subgroup 2: 0.16	NR (information is redacted)	Eribulin vs. capecitabine: Subgroup 1: £36,244 Subgroup 2: £35,624

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
			Subgroup 2: Patients with LABC/mBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine			
NICE TA116[122]	2007 (£)	Markov model Cycle length: 3 weeks	Patients who have relapsed and developed mBC following anthracycline-based (neo)adjuvant chemotherapy or non-anthracycline-based chemotherapy where anthracyclines are contraindicated Patients who are younger and fitter than the general population of patients with mBC, suitable for taxane-based therapy, and require higher efficacy than what could be achieved from monotherapy, without the toxicity usually associated with a combination regimen	Gemcitabine plus paclitaxel vs. docetaxel monotherapy: 0.23	Gemcitabine plus paclitaxel vs. docetaxel monotherapy: £4,013	Gemcitabine plus paclitaxel vs. docetaxel monotherapy: £17,200

Abbreviations: HER2, human epidermal growth factor receptor 2, ICER, incremental cost-effectiveness ratio; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; NICE, National Institute for Health and Care Excellence; NR, not reported; PartSA, partitioned survival analysis; QALY, quality-adjusted life-years; SG, sacituzumab govitecan; TA, technical appraisal; TPC, treatment of physician's choice
Source: Daiichi Sankyo Inc., 2022 (Economic SLR report; Data on File)[161]

B.3.2 Economic analysis

No published economic evaluations of T-DXd were identified in the cost-effectiveness SLR in the HER2-negative or HER2-low mBC setting (see **Section B.3.1** and **Appendix G**). Therefore, a *de novo* economic model was developed to assess the cost-effectiveness of T-DXd vs. TPC, which the company considers to be standard of care in this setting, for patients with HER2-low u/mBC previously treated with chemotherapy in the (neo)adjuvant (if recurrence occurred within 6 months) or metastatic setting (see **Section B.1.1** for further information on the comparator arm in this appraisal).

In addition to the publications identified within the economic SLR,[162,163] relevant NICE TAs were used to inform the *de novo* model structure, assumptions and data sources. These TAs included treatments recommended by NICE at a potentially relevant line of therapy in the HER2-negative/HR-positive and HER2-negative/HR-negative pathways (i.e., TA116,[122] TA423,[131] TA819[132]) and NICE-recommended TAs for T-DXd in HER2-positive u/mBC (i.e., TA704[4], TA862[5]).

B.3.2.1 Patient population

The cost-effectiveness analysis (CEA) considers adult patients with HER2-low u/mBC after prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. This is in line with the FAS population in the pivotal DESTINY-Breast04 clinical trial,[7] the final scope issued by NICE,[1] the European licensed indication for T-DXd in HER2-low,[3] and the anticipated UK licensed indication for T-DXd.[164]

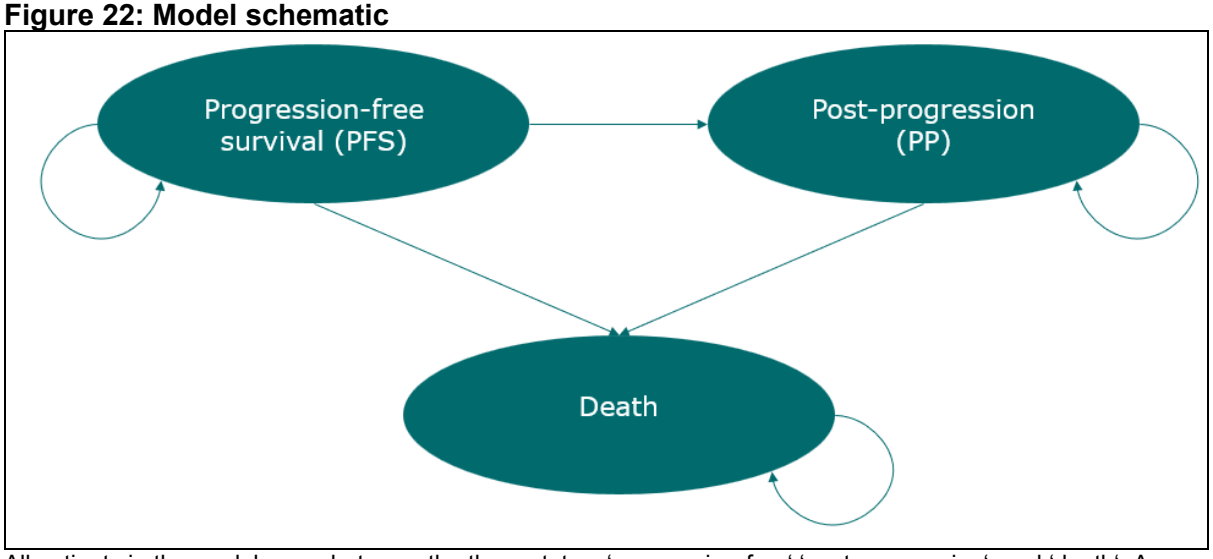
B.3.2.2 Model structure

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

- This structure is in line with the primary outcome (PFS) and key secondary outcome (OS) in the DESTINY-Breast04 trial.[7]
- Progression-based models are commonly used within oncology cost-effectiveness analyses because they provide an intuitive application of the outcomes seen in cancer-based trials and accurately reflect the progressive nature of BC. NICE Decision Support Unit (DSU) confirms their appropriateness based on their intuitive nature and ability to easily communicate outcomes.[165]
- The PartSA structure is consistent with that used in previous NICE appraisals in u/mBC, which have been accepted as appropriate for decision making by the respective committees.[5,131,132]

The model structure and permitted flow of patients is shown in **Figure 22**. All patients enter the model in the *'progression-free'* health state and receive treatment with either T-DXd or TPC, and within this health state patients are at risk of disease progression or death. Patients in the *'post-progression*' health state cannot return to the *'progression-free'* state and are at risk of transitioning to *'death'*, which is an absorbing state.

Figure 22: Model schematic

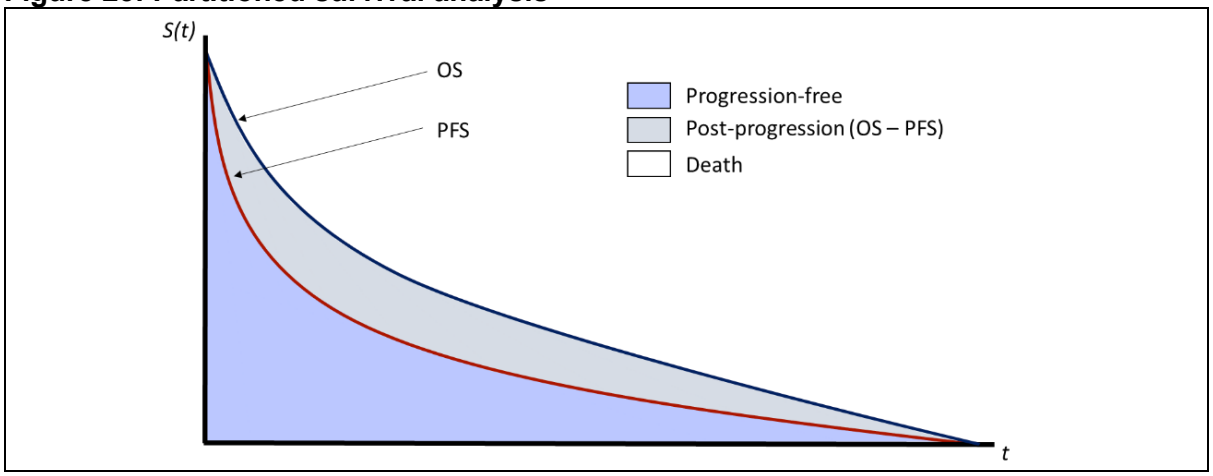


All patients in the model move between the three states: 'progression-free' 'post-progression', and 'death'. Arrows indicate the transition possibilities between the health states.

The occupancy of the '*progression-free'* state is calculated as the area underneath the PFS curve (informed by patient-level data from DESTINY-Breast04), while the *'post-progression*' state is calculated as the area between the OS curve (informed by patient-level data from DESTINY-Breast04) and the PFS curve (**Figure 23**). The proportion of patients in each health state at any time point (per cycle) is therefore calculated as follows:

- Progression-free = PFS
- Post-progression = OS – PFS
- Death = 1 – OS

Figure 23: Partitioned survival analysis



Abbreviations: OS, overall survival; PFS, progression-free survival; *S*, survival; *t*, time.

A time to treatment discontinuation (TTD) curve is used (informed by individual PLD from DESTINY-Breast04) to calculate the proportion of patients within the '*progression-free'* health state who are on treatment and is used for drug cost calculations. Details of how the TTD, PFS and OS curves are derived is provided in **Section B.3.3.2**.

Extrapolated OS curves are adjusted for background general population mortality informed by the 2018-2020 National Life Tables for England and Wales[166] to ensure that the probability of death per cycle never falls below that of the general population; general population mortality estimates are adjusted using weighted averages of male and female mortality risks to reflect the sex distribution of participants in the DESTINY-Breast04 trial.[7]

B.3.2.2.1 Time horizon and cycle length

The base case CEA adopts a 'lifetime' horizon of 30 years, which is considered long enough to adequately capture the lifetime of patients in this setting (the mean starting age in the cost-effectiveness analysis is 56.5 years, which is aligned with the baseline characteristics in DESTINY-Breast04).[7] By this time point, using the base-case curve selection outlined in **Section B.3.3.2.1**, less than 1% of patients in the T-DXd arm or TPC arm remain alive in the model. A 30-year time horizon is consistent with the time horizon used in the economic model as part of the NICE appraisal of T-DXd in HER2+ u/mBC (TA862).[5]

A cycle length of 3 weeks is selected to align with the dosing schedule of T-DXd and is considered short enough to adequately capture and reflect relevant changes in patient health status, costs and QoL. The model base case applies a half-cycle correction to account for uncertainty in the exact timing of transitions within the cycle period.

B.3.2.2.2 Discount rate and perspective

As per the NICE reference case, the analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) for costs and health outcomes. All health outcomes are measured in QALYs, and a 3.5% discount rate per annum is used for QALYs and costs.[2]

B.3.2.2.3 Features of the economic analysis

Table 33 presents the key features of the economic analysis in comparison to previous NICE appraisals of either T-DXd or of other technologies appraised for the treatment of mBC after one or two lines of chemotherapy in the metastatic setting. These include:

- TA862:[5] T-DXd in HER2-positive u/mBC after trastuzumab and a taxane.
- TA704:[4] T-DXd in HER2-positive u/mBC after two or more anti-HER2 therapies.
- TA116:[122] gemcitabine for treating locally advanced or metastatic BC.
- TA423:[131] eribulin for treating locally advanced or metastatic BC after two or more lines of chemotherapy.
- TA819:[132] SG for treating unresectable triple-negative advanced BC after two or more lines of chemotherapy.

Table 33: Features of the economic analysis

Factor	Previous appraisals						Current appraisal (ID3935)
	TA116 (2007)[122]	TA423 (2016)[131]	TA704 (2021)[4]	TA819 (2022)[132]	TA862 (2023)[5]	Chosen values	Justification
Model type	Markov model	PartSA	PartSA	PartSA	PartSA	PartSA	This approach is generally consistent with previous models in mBC and other oncology indications.
Patient population	Adults with locally advanced or metastatic BC previously treated with anthracycline-based therapies	Adults with locally advanced or metastatic BC after ≥2 lines of chemotherapy	Adults with HER2-positive u/mBC after ≥2 prior anti-HER2 therapies	Adults with locally advanced or metastatic triple-negative BC after ≥2 lines of chemotherapy	Adults with HER2-positive u/mBC after 1 or more anti-HER2 treatments	Adults with HER2-low u/mBC previously treated with chemotherapy	Reflects the FAS population of the pivotal DESTINY-Breast04 clinical trial[7] and the anticipated licensed indication[164]
Intervention and comparator	• Gemcitabine with paclitaxel • Licensed taxane-based regimens	• Eribulin • TPC	• T-DXd • Eribulin • Capecitabine • Vinorelbine	• SG • TPC	• T-DXd • T-DM1	• T-DXd • TPC	TPC as a comparator is aligned with TA423 and TA819 and is representative of SoC in the treatment setting.
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	As per NICE reference case.[2]
Time horizon	3 years	5 years	40 years	10 years	30 years	30 years	As per NICE reference case: lifetime horizon for the patient population.[2]
Cycle length	3 weeks	1 month	1 week	1 week	1 week	3 weeks	Considered appropriate to accurately capture the dosing schedules and changes in health.
Discount rate	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs	As per the NICE reference case.[2]
Outcome measure	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	As per the NICE reference case.[2]

Factor	Previous appraisals						Current appraisal (ID3935)
	TA116 (2007)[122]	TA423 (2016)[131]	TA704 (2021)[4]	TA819 (2022)[132]	TA862 (2023)[5]	Chosen values	Justification
Source of utilities	Values from Narewska et al 2005[167]	Values from Study 301 adjusted for response rates (PFS, PD)	Values from TA423 adjusted for response rates (PFS, PD)	EORTC-QLQ C30 values from ASCENT trial mapped to EQ-5D-3L	DESTINY-Breast03 (PFS)[168] Lloyd et al 2006 (PD)[169]	DESTINY-Breast04 (PFS)[7] Lloyd et al 2006 (PD)[169]	EQ-5D utilities collected from the relevant population within the trial, as per the NICE reference case.[2] Literature values used for *'post-progression'* and scenarios.
Source of costs	MIMS NHS Cost Collection NHS TFR returns National blood bank	eMIT MIMS PSSRU NHS Cost Collection	eMIT BNF PSSRU NHS Cost Collection NICE - Marie Curie report	eMIT BNF MIMS PSSRU NHS Cost Collection	eMIT BNF PSSRU NHS Cost Collection	eMIT BNF PSSRU NHS Cost Collection	As per the NICE reference case.[2]

Abbreviations: BC, breast cancer; BNF, British National Formulary; eMIT, electronic market information tool; EQ-5D, EuroQol-5 Dimension; mBC, metastatic breast cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PartSA, partitioned survival analysis; PD, progressed disease; PFS, progression-free survival; PSS – Personal Social Service; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted adjusted life-years; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TFR, Trust Financial Returns; TPC, treatment of physician's choice; u/mBC, unresectable or metastatic breast cancer.

B.3.2.3 Intervention technology and comparators

The intervention modelled in the analysis is T-DXd, administered as an intravenous infusion at the recommended dose of 5.4 mg/kg once per 21-day cycle. Treatment is administered until disease progression or unacceptable toxicity, as per the SmPC and dose received in DESTINY-Breast04 (as outlined in **Section B.2.3.1**).[7,170] The CEA includes dose adjustments and modifications as per the DESTINY-Breast04 trial, which allowed dose adjustments in line with the SmPC (see **Section B.3.5.1**).[7,170]

The comparator in the model is the TPC arm from DESTINY-Breast04, which comprises of a basket of single-agent chemotherapies:

- eribulin (51%)
- capecitabine (21%)
- nab-paclitaxel (10%)
- gemcitabine (9%)
- paclitaxel (8%)

According to NICE CG81 guidelines[35], ESMO 2021 guidelines[42], and feedback from UK clinical experts,[121] a broad range of non-targeted single-agent chemotherapy agents (e.g., capecitabine, eribulin, paclitaxel) are used in the UK for patients with HER2-negative u/mBC following prior chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting (see **Section B.1.1.1**). In addition, in a published systematic review of RCTs of single-agent chemotherapies in anthracycline- and taxane-pretreated advanced BC, none of the included RCTs demonstrated a significant OS difference between any of the regimens (capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles), indicating similar efficacy across single-agent chemotherapies.[118] In line with this, UK clinical experts confirmed that non-targeted single-agent chemotherapies have similar efficacy in this setting and that the TPC arm of DESTINY-Breast04 is reflective of the range of options used in the UK, where choice of chemotherapy agent is based on clinician preference as well as patient-specific needs and preference.[121] Therefore, UK clinical and HEOR experts (including ex-NICE Committee and EAG members) agreed that, for decision-making, TPC is the relevant comparator in this appraisal and that the comparators listed in the final NICE scope are well represented in the TPC arm of DESTINY-Breast04.[121] Please refer to **Section B.1.1** for further information.

B.3.3 Clinical parameters and variables

The principal source of data used to inform the CEA is the pivotal DESTINY-Breast04 trial. These data comprise the key evidence base concerning the use of T-DXd as a treatment for patients with HER2-low u/mBC previously treated with chemotherapy. HEOR and clinical experts considered the trial to be well-deigned and robust, and outcomes generalisable to UK practice.[121] Clinical data for the following inputs/endpoints/events are used to inform the estimation of costs and outcomes within the model:

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

- Safety (**Section B.3.3.2.3**)

B.3.3.1 Baseline patient characteristics

The baseline patient characteristics used to inform the CEA are presented in **Table 34**. A more detailed summary of baseline patient demographics is provided in **Section B.2.4.4**. The baseline characteristics were considered generalisable to the UK population by UK clinical experts.[121]

Table 34: Baseline patients characteristics informing the economic model | FAS

Characteristic	Value **(SD)**	Source	Use in model
Mean age, years	56.50 (10.89)	DESTINY-Breast04[7]	Used to inform the estimation of background mortality and measurement of disease severity modifier.
Proportion female, %	99.60		
Mean weight, kg	[redacted]		Used to inform the calculation of drug dosing and subsequently, drug costs (those dosed according to weight).
Mean body surface area, m^2	[redacted]		

Abbreviations: FAS, full analysis set; HRQoL, health-related quality-of-life; kg, kilograms; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.3.2 Efficacy

Due to the specification of a lifetime horizon over which modelled costs and QALYs are required to be estimated (in line with the NICE reference case),[2] survival modelling was required to extrapolate outcomes beyond those observed in the DESTINY-Breast04 trial. The following section outlines the approach taken to extrapolate the OS, PFS and TTD data, which are in line with the best practice guidance set out in the NICE DSU Technical Support Document (TSD) 14.[171]

- Data and statistical tests from DESTINY-Breast04[7]
    - Inspection of the Kaplan-Meier (KM) curves
    - Inspection of the log-cumulative hazard plots (LCHP) to determine potentially suitable approaches to fitting parametric models
- Inspection of statistical goodness-of-fit scores for fitted models (i.e., the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC])
- Visual inspection of suitable fitting models compared to the KM curves
- Assessment of the plausibility of fitted models after the end of the follow-up period for DESTINY-Breast04 via clinical expert validation and external data sources (see **Section B.3.14**).

B.3.3.2.1 Overall survival

DESTINY-Breast04 provides evidence for T-DXd compared with the relevant comparator (TPC) from a well-conducted RCT,[7] and UK clinicians considered the trial outcomes to be generalisable to UK practice.[121]

Median survival follow-up in the FAS population of DESTINY-Breast04 was 18.4 months,[6] during which 39.9% of patients in the T-DXd arm and 48.9% in the TPC arm had an OS event.[7] T-DXd was associated with a statistically significant improvement in OS compared with TPC (HR: 0.64; 95% CI: 0.49, 0.84 [p=0.0010] using a stratified Cox-proportional

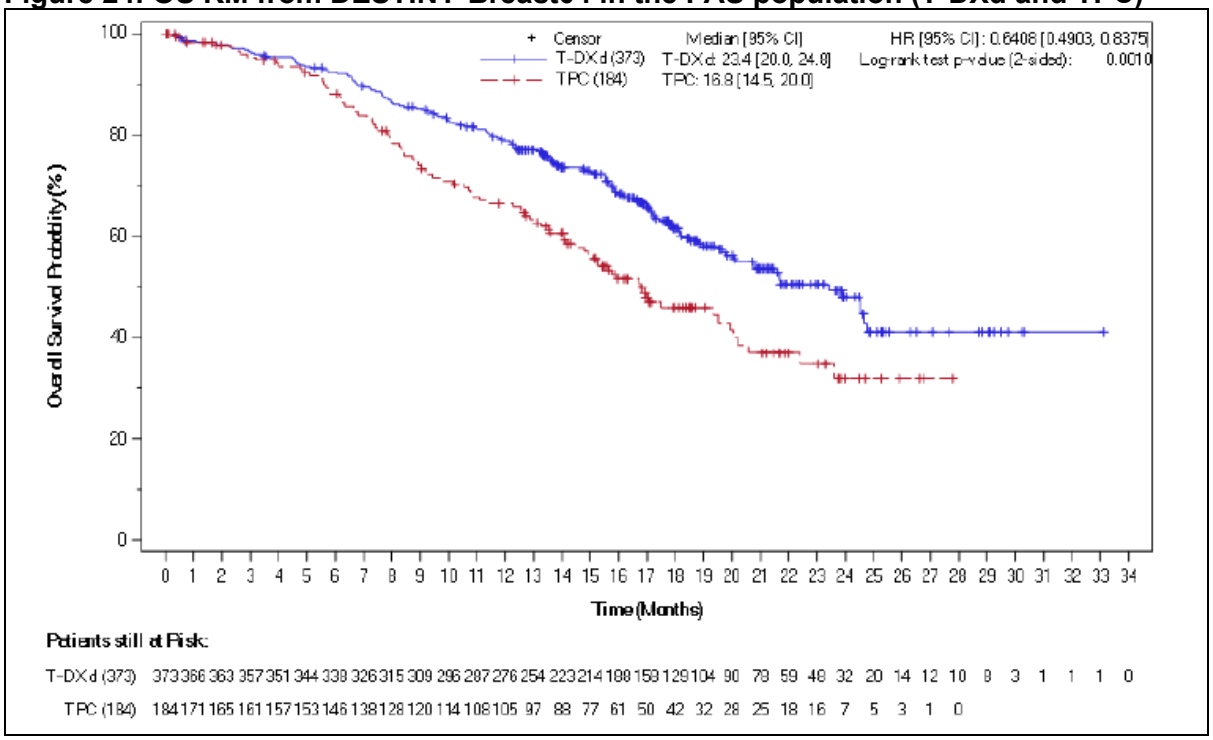
hazard model; FAS) with median OS reached in both arms (23.4 months vs. 16.8 months, respectively).[6] Given that OS data from DESTINY-Breast04 are considered mature, data were directly extrapolated from observed patient-level data using parametric survival modelling.

To ensure that the model projections do not lead to an estimated hazard of death below that of the age- and sex-adjusted general population, an adjustment is made to the OS projections in both arms of the economic model. National life tables from the Office of National Statistics (ONS) were used to populate this adjustment and this ensures that the hazard of death is, at a minimum, that of the general population.[166]

Assessment of data from DESTINY-Breast04

A summary of the OS data from DESTINY-Breast04 is provided in **Section B.2.6.1** and **Figure 24** below. OS data are mature with medians reached in both arms.[7] Extrapolation of outcomes was performed to inform cost-effectiveness estimates over a lifetime horizon.

Figure 24: OS KM from DESTINY-Breast04 in the FAS population (T-DXd and TPC)



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Prior to the fitting of parametric models, a LCHP was produced to assess whether the proportional hazards (PH) assumption may hold. **Figure 25** presents the LCHP based on OS data from DESTINY-Breast04. As can be seen from the LCHP, the curves are not parallel over time: converging at the start and diverging after approximately 5 months. This indicates that the ratio of the hazards between the two treatment arms is not constant and there is no clear evidence that the PH assumption holds.

Given the assessment that PH for the OS data is inconclusive and cannot be clearly justified, the approach was taken to use independent models. This is in line with recommendations in NICE DSU TSD 14[171] which state that "generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption" and that "PH modelling

should only be used if the proportional hazards assumption can be clearly justified using log-cumulative hazard plots, external information and clinical expert opinion". Mature patient level data for T-DXd and TPC from DESTINY-Breast04 provide robust evidence to inform long-term extrapolations using independent parametric curves for each treatment arm. Use of independent parametric curves, fitted to mature patient level data, is likely to result in better fitting curves for each treatment arm, compared to the use of dependently fitted models. Given the strong assumptions required to use dependent curves, which have not been met for OS, UK clinical and HEOR experts advised at an advisory board meeting in December 2022 that the use of independent curves is deemed the most appropriate for informing the cost-effectiveness analysis.[121]

Figure 25: Log-cumulative hazard plot of OS from DESTINY-Breast04 in the FAS population

Abbreviations: FAS, full analysis set; LCHP, log-cumulative hazard plot; OS, overall survival.

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

Independent parametric survival models (PSMs) were fitted in R® using the '*flexsurv*' package. Six standard parametric forms discussed in NICE DSU TSD 14[171] were fitted to patient-level survival data from DESTINY-Breast04 to provide long-term extrapolations for the economic model:

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

AIC and BIC scores provide informative statistical tests to determine the relative fit of alternative parametric models to the observed data. AIC and BIC scores for the extrapolated OS for DESTINY-Breast04 data are presented in **Table 35**. Lower AIC and BIC scores indicate a better statistical fit to the observed data.

For the TPC arm, the log-logistic parametric curve provides the overall best fit based on the goodness-of-fit statistics. The Weibull provides the second-best statistical fit for AIC and BIC. The exponential, Gompertz, log normal and generalised gamma curves were more than 5 AIC or BIC points from best fitting curve and considered to have a poor statistical fit to the KM data.

For the T-DXd arm, the Gompertz parametric curve provides the best statistical fit. The Weibull, log-logistic and generalised gamma curves were within 5 AIC or BIC points of the best fitting curve and could be considered to be a good fit, while the exponential and log-normal curves were more than 5 AIC or BIC points from the best-fitting curve and considered to have a poor statistical fit to the KM data.

Overall, the log-logistic and Weibull curves provided a good statistical fit for both T-DXd and TPC.

Table 35: Statistical goodness-of-fit scores (OS, independent models) in the FAS population

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	765.60	768.81	1389.90	1393.83
Weibull	751.16	757.59	1366.90	1374.74
Gompertz	756.20	762.63	**1366.87**	**1374.71**
Log-logistic	**751.10**	**757.53**	1371.38	1379.22
Log-normal	759.16	765.59	1390.55	1398.39
Generalised gamma	753.01	762.65	1367.59	1379.35

Bold indicates best statistical fit.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Fitting of parametric models and visual fit against KM data

Visual assessment of observed KM data versus predicted OS curves (**Figure 26** and **Figure 27**), in addition to clinical validation of long-term modelled survival (**Figure 28** and **Figure 29**) and landmark time points (**Table 36**) were used to determine the suitability of the different PSMs.

Figure 26: Observed versus predicted OS for TPC over a 3-year time horizon in the FAS population

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 27: Observed versus predicted OS for T-DXd over a 3-year time horizon in the FAS population

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

Following visual assessment of the KM data and parametric curves for TPC and T-DXd arms, the exponential curves were not considered to be a good visual fit as they fall below the KM data for over a year of the observed period in both arms. Similarly, while the log-normal curves for TPC and T-DXd curves provide a reasonable visual fit to the KM data until approximately 18 months, they lie above the KM after this point for both T-DXd and TPC.

The log-logistic, Weibull, generalised gamma and gompertz curves were all considered to provided an acceptable visual fit to the KM data for both T-DXd and TPC.

Long-term clinical plausibility

Figure 30 and **Figure 29** present the model predictions for T-DXd and TPC, respectively, over a 25-year time horizon.

Figure 28: Observed versus predicted OS for TPC in the FAS population over a 25-year time horizon in the FAS population

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 29: Observed versus predicted OS for T-DXd in the FAS population over a 25-year time horizon in the FAS population

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Table 36: OS in the FAS population: Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)*	1-Year OS	3-Year OS	5-Year OS	10-Year OS
TPC					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Median time in months is estimated after OS has been capped by the general population mortality.
Abbreviations: FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Following feedback from UK clinicians based on modelled survival at landmark time points, the log-logistic, exponential and log-normal curves were considered the most clinically plausible to inform the TPC arm. The log-logistic, exponential, and log-normal curves estimate 5-year OS of [redacted], [redacted], and [redacted], respectively, in the TPC arm. The remaining Weibull, generalised gamma and Gompertz curves were not considered to be clinically plausible due to long-term survival estimates being too pessimistic, with 5-year OS estimates of [redacted], [redacted] and [redacted], respectively. UK clinical experts determined that these curves were not appropriate as more than 2% of patients are expected to remain alive at 5 years in the TPC arm.

For the T-DXd arm, the log-logistic and exponential were considered the most clinically plausible curves[121] with 5-year OS estimates of [redacted] and [redacted] respectively. Additionally, clinicians indicated that some patients would be expected to remain alive at 10-years in the T-DXd arm and therefore considered the Weibull, generalised gamma and Gompertz parametric curves to be too pessimistic with respect to the T-DXd arm, with 10-year OS estimates of [redacted], [redacted] and [redacted], respectively.

Conclusion

Based on the assessments above, the log-logistic distribution was considered the most appropriate curve to inform the TPC base case extrapolations of OS, reflecting the best statistical and visual fit to the KM and clinical validity of long-term modelled survival at landmark time points. The log-logistic curve was also considered the most appropriate curve for T-DXd based on the same criteria (visual fit to the KM, statistical goodness of fit and clinical plausibility of long-term modelled survival at landmark time points). Additionally, the median OS predicted in the model using a log-logistic curve of [redacted] months and [redacted] months, for TPC and T-DXd respectively, is similar to the observed median OS in DESTINY-Breast04, of 16.8 months and 23.4 months the TPC arm and the T-DXd arm, respectively.

Clinical and HEOR experts concluded that the log-logistic curve was the most appropriate curve to inform the base case. This conclusion was reached based on the same criteria: statictical fit, visual fit and long-term clinical plausibility. Experts agreed that it was preferable to use the same distribution for both treatment arms for consistency unless there is a clear clinical rationale to use alternative distributions. Alternative extrapolations which provided plausible long term estimates of survival (log-normal and exponential) were explored in scenario analyses (see Section B.3.11.3).

Summary of base-case model

Figure 30 provides a summary of the base-case extrapolation for OS applied within the model (using the log-logistic distribution). Internal and external validation is presented in Section B.3.14.

Figure 30: Base-case extrapolations for OS in the FAS population (log-logistic, T-DXd and TPC)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

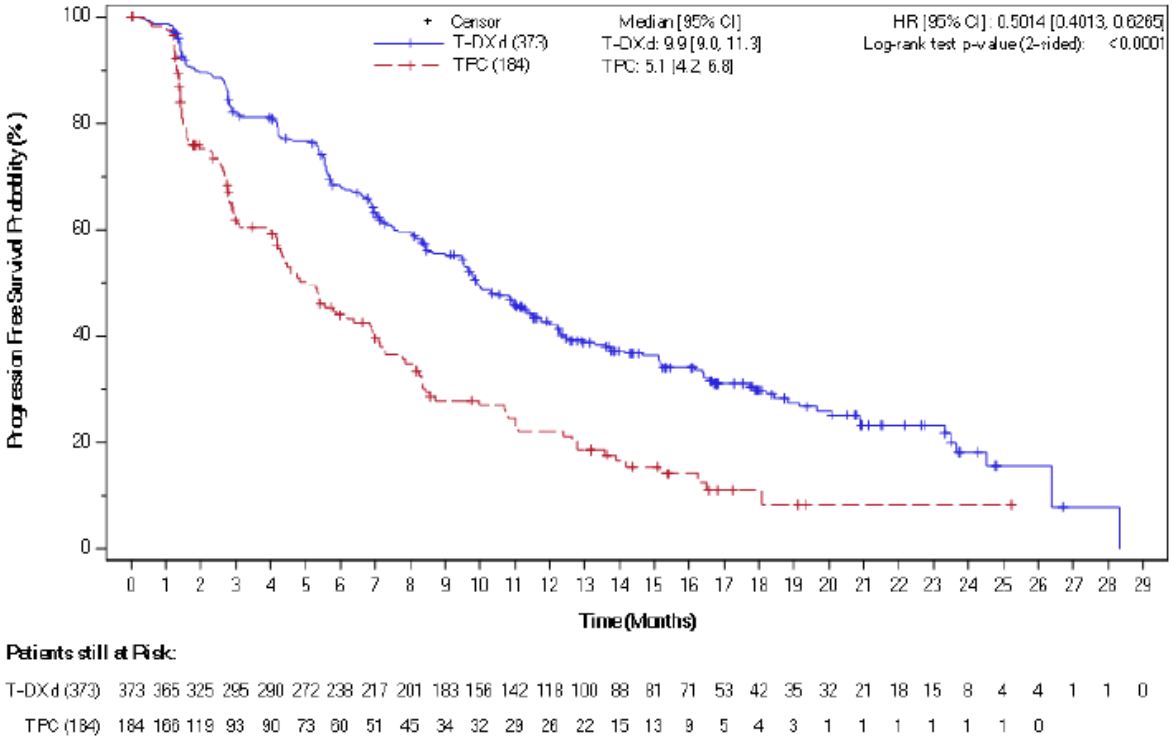
B.3.3.2.2 Progression-free survival

Assessment of data from DESTINY-Breast04

Median follow-up in the FAS population of DESTINY-Breast04 was [redacted] months,[6] during which 65.1% of patients in the T-DXd arm and 69.0% in the TPC arm had a PFS event.[7] T-DXd was associated with a statistically significant improvement in PFS compared with TPC in the FAS population (HR: 0.50; 95% CI: 0.40, 0.63 [p<0.0001] using a stratified Cox proportional hazard model) with medians reached in both arms (9.9 months vs. 5.1 months in the T-DXd and the TPC arms, respectively).[7] A summary of the PFS data from DESTINY-Breast04 is provided in **Section B.2.6.1** and **Figure 31** below. Given that PFS data from DESTINY-Breast04 are considered mature, data were directly extrapolated from observed patient level data, using parametric survival modelling.

For all analyses within the cost-effectiveness model, the BICR definition of PFS has been used, which was used for the primary and key secondary analyses in DESTINY-Breast04 (Section B.2.6.1).

Figure 31: PFS KM from DESTINY-Breast04 in the FAS population (T-DXd and TPC)



Abbreviations: BICR; blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

As with OS data, a LCHP was produced for PFS (**Figure 32**). The LCHP shows that the curves are not consistently parallel over time, crossing at the start and beginning to converge towards the end. This suggests that there is no clear evidence of a constant hazard of progression and the PH assumption does not hold for the duration of the data.

Given the assessment that PH for the PFS data is inconclusive and cannot be clearly justified, the approach was taken to use independent models. This is in line with recommendations in NICE DSU TSD 14[171], as stated in **Section B.3.3.2.1**. Mature patient level data for T-DXd and TPC PFS from DESTINY-Breast04 provides robust evidence to inform long-term extrapolations using independent parametric curves for each treatment arm. Use of independent parametric curves, fitted to mature patient level data, is likely to result in better fitting curves for each treatment arm, compared to the use of dependently fitted models. Given the strong assumption required to justify the use of dependent curves, which have not been met for PFS, UK clinical and HEOR experts confirmed that the use of independent curves is deemed the most appropriate for informing the cost-effectiveness analysis at an advisory board meeting in December 2022.[121]

Figure 32: DESTINY-Breast04 – Log-cumulative hazard plot – PFS, FAS population

Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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

PSMs were fitted in R® using the '*flexsurv*' package. As per the OS estimates, six standard parametric forms discussed in NICE DSU TSD 14[171] were fitted for completeness. AIC and BIC scores for the extrapolated PFS for DESTINY-Breast04 data are presented in **Table 37**.

For the TPC arm, the generalised gamma and log-normal curves provide the best statistical fit as they have the lowest AIC and BIC values, respectively. The log-logistic curve also provides a good statistical fit with the third lowest AIC and BIC. The exponential, Weibull and Gompertz curves were considered to have a poor statistical fit to the KM data with more than 15 AIC and BIC points from the best fitting generalised gamma and log-normal curves.

For the T-DXd arm, as with TPC, the generalised gamma and log-normal curves provide the best statistical fit as they have the lowest AIC and BIC values, respectively. The log-logistic curve also provides a good statistical fit with the third lowest AIC and second lowest BIC, and the Weibull also provides a good fit for the T-DXd arm. The exponential and Gompertz curves were considered to have a poor statistical fit to the KM data as they were more than 5 AIC and BIC points from the best fitting generalised gamma and log-normal curves.

Overall, the generalised gamma, log-normal and log-logistic curves all provided a good statistical fit for both T-DXd and TPC arms.

Table 37: Statistical goodness-of-fit scores (PFS, independent models) in the FAS population

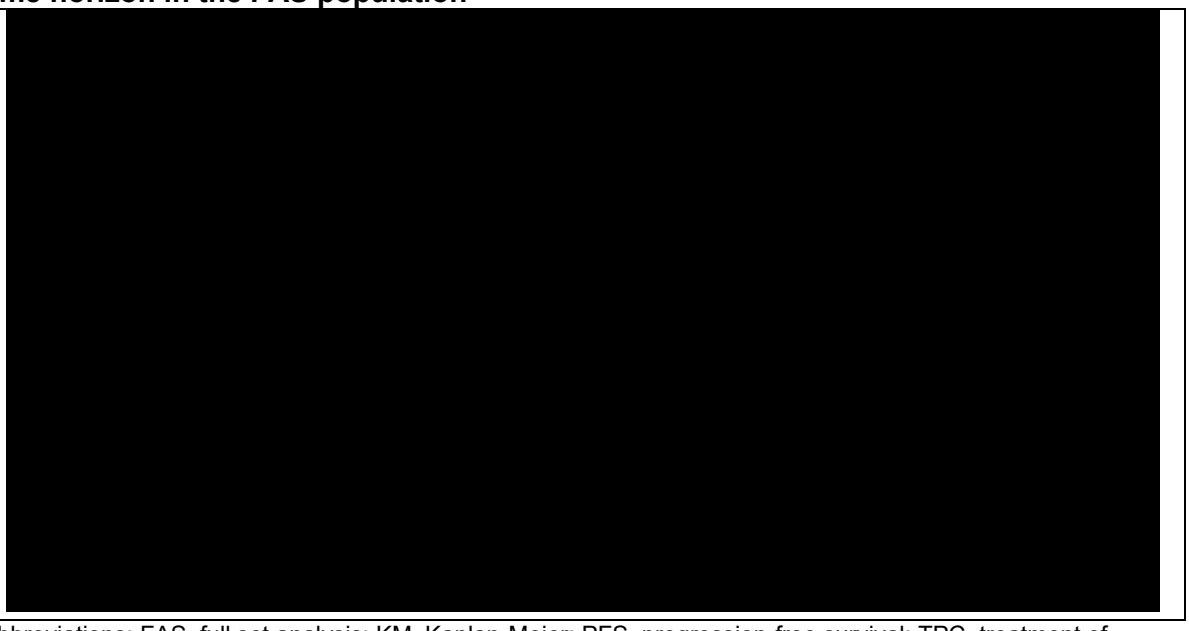
Model	TPC		T-DXd	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	774.26	777.47	1793.22	1797.14
Weibull	773.77	780.20	1784.94	1792.78
Gompertz	776.20	782.63	1791.19	1799.03
Log-logistic	761.91	768.34	1783.60	1791.44
Log-normal	755.24	**761.67**	1782.50	**1790.35**
Generalised gamma	**754.84**	764.48	**1781.29**	1793.06

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Fitting of parametric models and visual fit against KM data

Visual assessment of observed KM data versus predicted PFS curves (**Figure 33** and **Figure 34**), in addition to clinical validation of long-term modelled survival (**Figure 35** and **Figure 36**) and landmark time points (**Table 38)** were used to determine the suitability of the different PSMs

Figure 33: Observed versus predicted PFS (TPC) in the FAS population over a 3-year time horizon in the FAS population



Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

Figure 34: Observed versus predicted PFS (T-DXd) in the FAS population over a 3-year time horizon in the FAS population

Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

For the TPC arm, the Weibull, Gompertz and exponential curves overestimate PFS for TPC in the first year and as such were not considered a good visual fit to the TPC KM data, while the log-logistic, generalised gamma and log-normal provide a good visual fit to the KM data in the TPC arm.

For the T-DXd arm, all curves appeared to provide a reasonable visual fit, however the log-logistic and generalised gamma curves in particular appeared to provide the closest visual fit.

Long-term clinical plausibility

Figure 35 and **Figure 36** present the model predictions for T-DXd and TPC, respectively, over a 10-year time horizon. Given the maturity of the PFS data, the long-term estimates presented in **Table 38** were relatively similar across curves at all time points, however feedback from UK clinicians based on modelled survival at landmark time points, was that the log-logistic and generalised gamma curves were considered the most clinically plausible to inform the TPC arm.

Table 38: PFS in the FAS population: Predictions by independently fitted distributions in T-DXd and TPC

Distribution	Median (months)*	1-Year PFS	3-Year PFS	5-Year PFS	10-Year PFS
TPC					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *Median time in months is estimated after PFS has been capped by OS.
Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 35: Observed versus predicted PFS (TPC) in the FAS population over a 10-year time horizon in the FAS population

Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

Figure 36: Observed versus predicted PFS (T-DXd) in the FAS population over a 10-year time horizon in the FAS population

Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Conclusion

Based on the assessments above, the log-logistic distribution was considered the most appropriate curve to inform the base case extrapolations of PFS for TPC and T-DXd providing a good statistical and visual fit to the KM, as well as clinical validity of long-term modelled survival at landmark time points. In addition, the use of log-logistic PFS distribution is consistent with the log-logistic OS base case distribution (Section B.3.3.2.1). Furthermore, the median PFS predicted in the model using a log-logistic curve of [redacted] months and [redacted] months, for TPC and T-DXd respectively, is very similar to the observed median PFS in DESTINY-Breast04, 5.1 months and 9.9 months for the TPC and T-DXd arms, respectively, which further supports the selection of the log-logistic parametric curve for PFS in the base case.

Clinical and HEOR experts concluded that the log-logistic curve was the most appropriate curve to use in the base case for PFS.[121] This conclusion was reached based on similar criteria as above such as fit to the observed DESTINY-Breast04 data (statistical and visual), clinical validity of long-term predictions and curve shape. Clinical and HEOR experts also agreed that it would be preferable to fit the same distribution to the observed PFS and OS data from DESTINY-Breast04.[121] All other distributions were explored in sensitivity analysis given they all provided similar long term estimates for PFS (see Section B.3.11.3).

Summary of base-case models

Figure 37 provides a summary of the base-case extrapolation for PFS applied within the model (using a log-logistic distribution). Internal and external validation of the base case curves are presented in Section B.3.14.

Figure 37: Base-case extrapolations for PFS in the FAS population (log-logistic, T-DXd and TPC)

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.

B.3.3.2.3 Time to treatment discontinuation

Assessment of data from DESTINY-Breast04

The median follow-up in the FAS population of DESTINY-Breast04 was [redacted] months during which 98.3% and 84.4% of treatment discontinuation events having occurred in TPC arms and T-DXd, respectively. Given that TTD data from DESTINY-Breast04 are considered mature, data were directly extrapolated from observed patient level data, using parametric survival modelling.

Median TTD observed in DESTINY-Breast04 was [redacted] months and [redacted] months, in the TPC and T-DXd arms, respectively. As with PFS and OS, PSMs were also required to inform the estimation of the long-term treatment duration within the economic analysis. Patient-level TTD data are used within the model to determine the drug and administration costs associated with T-DXd and TPC. A summary of the TTD KM data from the DESTINY-Breast04 is provided below in **Figure 38**.

Figure 38: TTD KM from DESTINY-Breast04 in the FAS population (T-DXd and TPC)

Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR; Data on File).[7]

Similar to PFS and OS, a LCHP was produced for TTD (**Figure 39**). The LCHP shows that the curves are not parallel over time, indicating no clear evidence that the PH assumption holds. Therefore, independent curves were fitted to the DESTINY-Breast04 data to inform TTD for T-DXd and TPC. Given the maturity of the data (84.4% and 98.3% events for T-DXd and TPC, respectively) and likely independence of treatment discontinuation across both treatment arms (i.e., due to different adverse event profiles, or disease progression), independent curves were deemed the most appropriate to inform TTD. The use of independent curves to model TTD also aligns with the clinical and HEOR expert advice received.[121]

Figure 39: Log-cumulative hazard plot of TTD from DESTINY-Breast04

Abbreviations: DB04, DESTINY-Breast04; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

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

As with PFS and OS, the six standard parametric forms discussed in the NICE DSU TSD 14[171] were fitted to TTD data from the DESTINY-Breast04 trial for completeness. AIC and BIC scores for the extrapolated TTD curves are presented in **Table 39**. Based on the goodness-of-fit statistics, the log-logistic and generalised gamma provide the best statistical fit to the DESTINY-Breast04 data as they have the lowest AIC and BIC values when assessing the T-DXd and TPC arms. The log-normal TPC parametric curve has a good statistical fit to the observed KM data; however, the log-normal T-DXd parametric curve has a poorer statistical fit to the observed T-DXd KM data.

Table 39: Statistical goodness-of-fit scores (TTD, independent models) in the FAS population

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	900.68	903.89	2137.87	2141.79
Weibull	893.62	900.05	2115.29	2123.14
Gompertz	902.68	909.10	2132.04	2139.88
Log-logistic	**870.59**	**877.02**	2108.93	**2116.77**
Log-normal	875.69	882.12	2116.24	2124.08
Generalised gamma	876.46	886.11	**2108.90**	2120.67

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Fitting of parametric models and visual fit against KM data

Visual assessment of the extrapolated TTD data (**Figure 40** and **Figure 41**) and the long-term estimates of the proportion of patients on treatment (**Table 40**) were used to determine the suitability of the different PSMs.

Figure 40: Observed versus predicted TTD (TPC) in the FAS population over 4 years

Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation.

Figure 41: Observed versus predicted TTD (T-DXd) in the FAS population over 4 years

Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation.

The log-logistic and generalised gamma provide a good visual fit to the KM data over the duration of the observed period in the T-DXd and TPC arms and were therefore considered the most plausible parametric curves for the base case selection.

The exponential distribution underestimates TTD over the first approximately 9 months in the T-DXd arm. The Gompertz and Weibull curves also underestimate TTD in the initial period (approximately 6 months) in the T-DXd arm. The Weibull and Gompertz curves, conversely, overestimated TTD in the TPC arm when visual fit to the KM is assessed.

Table 40: TTD in the FAS population: Predictions by independently fitted distributions in TPC and T-DXd

Distribution	Median (months)	1-Year TTD	2-Year TTD	5-Year TTD
TPC				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

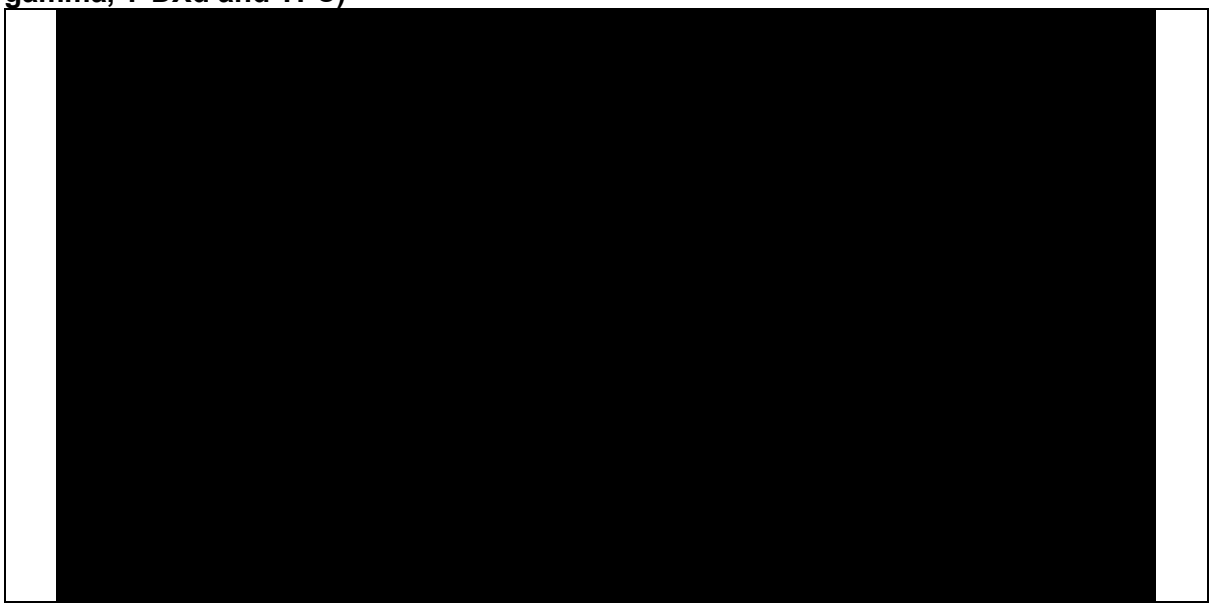
Abbreviations: KM, Kaplan-Meier; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

In line with the SmPC, patients are treated until progression or unacceptable toxicity; the majority of patients will discontinue treatment due to progression (as observed in both treatment arms of DESTINY-Breast04); however, some may discontinue treatment due to other reasons such as unacceptable toxicity prior to progression.[7,164] As such, the TTD curve should not exceed the PFS curve at any time, and TTD is capped by PFS in the model. The generalised gamma curve was selected to inform the model base case as it provides a good statistical fit and good visual fit to the KM data. In line with NICE DSU guidance[171], the same parametric curves were considered for both treatment arms.

Summary of base case models

Figure 42 provides a summary of the base-case extrapolation for TTD applied within the model (generalised gamma curves considered for both T-DXd and TPC).

Figure 42: Base-case extrapolations for TTD in the FAS population (generalised gamma, T-DXd and TPC)



Abbreviations: KM, Kaplan-Meier; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

B.3.3.3 Safety

TEAEs that occurred in the DESTINY-Breast04 study are reported in Section B.2.10. Grade ≥3 AEs with an incidence of ≥5% in either treatment arm of the DESTINY-Breast04 trial were included in the economic model. TEAEs that occurred in <5% of the population are not included as they are not expected to materially impact the cost-effectiveness results. Two AEs of special interest were identified in the DESTINY trial programme: ILD and LV dysfunction. The economic model accounts for ILD, which occurred at any grade, as the incidence was ≥5% in either treatment arm in DESTINY-Breast04. All grades of ILD were included in the model regardless of severity. LV dysfunction was not included within the model as the incidence of LV dysfunction, which occurred at any grade, was <5% and therefore did not meet the threshold for inclusion in the economic evaluation; 4.6% (n=17) of patients in T-DXd arm and 0% patients in the TPC arm experienced LV dysfunction at any grade, 0.5% (n=2) of patients in T-DXd arm and 0% patients in the TPC arm experienced LV dysfunction at Grade ≥3.

Table 41 presents the AEs from DESTINY-Breast04 included within the economic model.

Table 41: Adverse event incidence included in the economic model

Adverse event, n (%)	T-DXd (n=371)	TPC (n=172)
Interstitial lung disease*	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Increased ALT	[redacted]	[redacted]

*Interstitial lung disease was included, regardless of severity. Interstitial lung disease includes events that were adjudicated as interstitial lung disease and assessed to be related to the use of T-DXd or TPC.
Abbreviations: ALT, alanine transaminase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (CSR, Data on File)[7]

B.3.3.4 Efficacy summary

A summary of the main clinical parameters and variables applied in the economic model is provided in **Table 42**. The base case survival models (OS, PFS and TTD) used to inform the cost-effectiveness model are provided in **Figure 43** and **Figure 44** for T-DXd and TPC, respectively.

Table 42: Summary of clinical model parameters and variables used in economic model base case

Parameter	Value	Rationale	Section
Baseline characteristics	As presented in Table 34 informed by DB04	Aligned to the observed efficacy in DB04 and considered generalisable to UK practice	B.3.3.1
OS models	Independent log-logistic models	Provides the best statistical and visual fit to the KM data out of the curves considered to have clinically plausible long-term survival estimates across both T-DXd and TPC arms	B.3.3.2
PFS models	Independent log-logistic models	Provides a good visual and statistical fit to the KM data, considered to have clinically plausible long-term survival estimates across both T-DXd and TPC arms	B.3.3.2
TTD models	Independent generalised gamma models	Provides a good visual and statistical fit to the mature KM data.	B.3.3.2
Adverse events	Grade ≥3 AEs occurring in ≥5% of patients in either treatment arm, in addition to ILD (an AE of special interest) for which all grades of AE were included	Considered to reflect the main AEs experienced by patients and those that could impact the economic analysis	B.3.3.2.3

Abbreviations: AE, adverse event; DB04, DESTINY-Breast04; ILD, interstitial lung disease; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC – treatment of physician's choice; TTD, time-to-treatment discontinuation.

Figure 43: Summary of base case* efficacy (OS, PFS and TTD) for T-DXd in the FAS population

*The following distributions are presented for the base case: log-logistic for OS, log-logistic for PFS, and generalised gamma for TTD.
Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Figure 44: Summary of base case efficacy* (OS, PFS and TTD) for TPC in the FAS population

*The following distributions are presented for the base case: log-logistic for OS, log-logistic for PFS, and generalised gamma for TTD.
Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation; TPC, treatment of physician's choice.

Figure 45: Summary of base case efficacy* (OS, PFS and TTD) for TPC and T-DXd in the FAS population

*The following distributions are presented for the base case: log-logistic for OS, log-logistic for PFS, and generalised gamma for TTD.
Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.4 Measurement and valuation of health effects

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

In DESTINY-Breast04, EQ-5D-5L, EORTC QIQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL.[7] Questionnaires were completed by patients prior to infusion on Day 1 of Cycle 1, 2 and 3 and then every 2 cycles thereafter until the end of treatment assessments, when there was a further questionnaire.[7] Patients were then followed up at the Day 40 (±7 days) first follow-up assessment (after the last study drug administration) or before initiation of new anti-cancer treatment, whichever occurred first, and then at the first long-term/survival follow-up assessments three months later.[7] Patients were required to complete questionnaires before any other study assessments or procedures were performed on the day.

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

In line with NICE methods guidance, the EQ-5D-5L responses directly collected in DESTINY-Breast04 were mapped to EQ-5D-3L values using the mapping algorithm developed by the NICE DSU which utilises the EEPRU dataset.[2,173]

In total, 4,161 EQ-5D-5L observations were available. Of these, [redacted] observations were recorded while progression-free with the remaining [redacted] recorded post-progression. A tabulated summary of the EQ-5D-5L mapped to EQ-5D-3L utility values by progression status is provided in **Table 43**.

Table 43: Summary of utility values by progression status in the FAS population

Health state	Number of observations	Mean (SD)
Progression-free	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

Abbreviation: FAS, full analysis set; SD, standard deviation.
Source: Daiichi Sankyo Inc., 2022 (CSR, Data on File).[7]

A linear transformation of 1- the utility scores was conducted to model utility decrements using a log-normal distribution. This was done as utility values are not typically left-skewed with a higher concentration of values close to 1. By taking a linear transformation, common distributions for right-skewed data could be applied. Utility scores were calculated from DESTINY-Breast04 using a data driven generalized linear mixed model approach. The mixed models were estimated using restricted maximum likelihood. EQ-5D-5L scores from all available time points, including baseline, were included in a mixed model as dependent variables. The mean utility values and associated 95% confidence intervals for the progression-free and post-progression health states for each treatment group from the best fitting models were derived from the model using least squares means (LSM) and regression coefficients.

An overview of the regression coefficients for the final model in the FAS population is provided in **Table 44**. As a linear transformation was conducted to model utility decrements, negative regression coefficients denote an improvement in QoL.

Table 44: Regression coefficients

Coefficient	Value	95% CI	p-value
Final regression model			
Intercept	[redacted]	[redacted]	[redacted]
Treatment (T-DXd vs. TPC)	[redacted]	[redacted]	[redacted]
ECOG performance status (1 vs. 0)	[redacted]	[redacted]	[redacted]
Progression status (progressed vs. progression free)	[redacted]	[redacted]	[redacted]
Treatment status (off-treatment vs. on-treatment)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (Model technical report, Data on File)[174]

A backwards selection approach was used to determine the final model, using a p-value threshold of <0.05 to remove covariates which were not statistically significantly associated with utility. Progression, being off-treatment, and having a baseline ECOG performance status of 1 are associated with a statistically significant reduction in utility, whereas T-DXd is associated with a significant increase in utility. **Table 45** presents the resulting cross-walked EQ-5D-3L utility values from the DESTINY-Breast04 study by progression status and treatment arm included in the model, based on the LSM. The LSM is estimated at the mean time point, equal to [redacted] days, and assumes that the distribution between the other variables (ECOG and treatment status) are the values from the DESTINY-Breast04 trial at the mean time point.

Table 45: Mapped UK EQ-5D-3L utility values from DESTINY-Breast04 by progression status and treatment arm

Health state	T-DXd		TPC	
	n*	LSM (95% CI)	n*	LSM (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]

Note: *Number of visits/timepoints with the condition.
Abbreviations: CI, confidence interval; LSM, least square mean; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Source: Daiichi Sankyo Inc., 2022 (Model technical report, Data on File)[174]

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

An SLR to identify relevant HRQoL studies was conducted. **Appendix H** provides full details of the methods, overview of studies and results of the identified studies, together with the quality assessments. The SLR identified five utility studies, however, none of the identified studies fully qualified for the preferred NICE reference case as the HRQoL of patients was not measured using the EQ-5D instrument recommended by NICE.[2]

Nevertheless, the majority of studies referred to Lloyd et al, 2006[169] from which the values used in these studies were based on. This was also the case for the majority of prior NICE appraisals identified as being relevant to this appraisal (see Section B.3.4.3.1 below). As such, this study has been included within the model as an option to derive utility estimates.

Lloyd et al, 2006 is a preference-based study estimating utilities at distinct stages of mBC in the general population.[169] The health state valuations were analysed using a mixed model analysis with random effects which revealed that all disease states and toxicities were independently significant predictors of utility. Using the coefficients of the mixed model the utility values were calculated specifically for the patient population within this submission using the following equation:

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

The coefficients used to calculate the treatment-specific and combined utilities for T-DXd and TPC were age, response rates and progression status based on data from DESTINY-Breast04 (**Table 46**). Values used to estimate treatment-specific utilities for T-DXd and TPC, and combined (pooled for T-DXD and TPC) utilities, are presented in **Table 47**. First, the responder and non-responder utilities were calculated using the coefficients and the equation above. Then the responder and non-responder utilities were weighted by response rates from DESTINY-Breast04. The resulting utilities estimated are presented in **Table 48**. This approach is consistent with the preferred approach outlined by the Evidence Assessment Group (EAG) in TA423, TA704, and TA862.[4,5,131]

Table 46: DESTINY-Breast04 patient characteristics (ages) and objective response rate[6,7]

	T-DXd	TPC
Median age (years)	57.5	55.9
Treatment response (ORR)	52.3%	16.3%

Abbreviations: ORR – objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 47: Inputs to derive utilities from Lloyd et al. [169]

Parameter	Coefficient value	T-DXd multiplier	TPC multiplier	Pooled weighted multiplier
Intercept	0.009	0.009	0.009	0.009
Median age (years)	0.024	1.374	1.336	1.362
Treatment response (ORR)	0.406	0.213	0.066	0.164
Progression	-1.148	-1.148	-1.148	-1.148

Abbreviations: ORR – objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 48: Utilities derived from Lloyd et al. [169]

	Utility*			
Parameter	**Response specific utilities**	**T-DXd**	**TPC**	**Pooled**
PF	Responder: 0.855 Non responder: 0.797	**0.831**	**0.804**	**0.823**
PD	Responder: 0.652 Non responder: 0.555	**0.610**	**0.566**	**0.596**

Note: *Resulting utilities after applying the coefficients to the equation
Abbreviations: PD, progressed disease; PF, progression-free; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.4.3.1 Utilities used in previous appraisals

As well as consideration of the utilities reported within the literature, utilities reported within prior NICE appraisals that include patients with mBC were also assessed for appropriateness of inclusion within the economic model.

TA862 (T-DXd – second line HER2-positive mBC),[5] TA423 (eribulin – third line mBC),[131] TA509 (pertuzumab – first line HER2-positive mBC)[40] and TA458 (T-DM1 – second line HER2-positive mBC)[39] implemented utility values based on the Lloyd et al. (2006) regression.[169]

In TA423 (eribulin – third line mBC),[131] EQ-5D utilities were derived from QLQ-C30 HRQoL data collected in Study 301 using the Crott and Briggs mapping algorithm. For the *'progression-free'* health state, the baseline utility (0.704), tumour response utility (0.780) and the incremental utility of response (0.076) were used to calculate the overall utility values for eribulin and TPC (0.706 and 0.701, respectively). For the *'progressed disease',* utility was also calculated from Study 301 mapped values and assumed to be equal for both treatment arms based on pooled data (0.679). The EAG stated that the value used by the company for *'progressed disease'* from Study 301 was unrealistic as it did not represent a large enough reduction in utility after patients experienced disease progression, and instead

used a value of 0.496 derived from Lloyd et al. (2006). The committee stated that the most plausible utility value for the *'progressed disease'* health state was likely to be somewhere between the company and EAG estimated values, as clinicians stated that the reduction in utility was likely smaller than suggested by the EAG.

In TA704 (T-DXd – third line HER2-positive mBC),[4] the baseline utility value (0.704), tumour response utility (0.780) and the incremental utility of response (0.076) were taken from TA423. *'Progression-free, off-treatment'* used the baseline utility value. For *'progression-free, on treatment'*, to calculate treatment-specific utilities, the baseline value, and tumour response utility were used to derive the utilities on treatment incorporating the ORR for each treatment from the DESTINY-Breast01 trial and the literature. For *'progressed disease'*, TA704 used the average value from TA423 recommended by the committee (0.588).

In TA819 (SG – third line triple-negative mBC),[132] the utility scores from the ASCENT trial were analysed using multivariate utility models, which included treatment arm and progression status as predictors. The resulting treatment-specific utility values were used in the company's base case. The mean predicted utility in the *'progression-free'* health state was 0.710 (95% CI: 0.690, 0.730) and 0.626 (95% CI: 0.601, 0.651) in the SG and TPC arms, respectively. For the *'progressed disease'* health state, the mean predicted utilities were 0.653 (95% CI: 0.631, 0.676) in the SG arm and 0.569 (95% CI: 0.543, 0.596) in the TPC arm.

In TA862 (T-DXd – second line HER2-positive mBC),[5] the most recent mBC NICE appraisal, the company assigned treatment-specific utilities in the *'pre-progression'* health state derived directly from the DESTINY-Breast03 trial. Treatment-specific utilities in the '*progressed*' health state were derived based on the algorithm from Lloyd et al. (2006).[169] A summary of the utility values used in previous submissions that were applied in the economic analysis are presented in **Table 49**.

Table 49: Summary of utility values applied in previous submissions

Submission (treatment line)	Treatment	Progression-free	Post-progression
TA423 (3L)[131]	Eribulin	0.706	Company: 0.679 EAG: 0.496
	TPC	0.701	
TA704 (3L)[4]	T-DXd	0.750	0.588
	SoC	0.713	
TA819 (3L)[9]	SG	0.710	0.653
	TPC	0.626	0.569
	Pooled	0.676	0.619
TA862 (2L)[5]	T-DXd	[redacted]	0.618
	T-DM1	[redacted]	0.574
	Pooled	[redacted]	0.596

Abbreviations: 2L, second line; 3L, third line; EAG, Evidence Assessment Group; SG, sacituzumab govitecan; SoC, standard of care; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.4.4 Adverse reactions

In the base case, disutilities associated with AEs are not applied as it is assumed that the utilities derived from DESTINY-Breast04 (see Section B.3.4.5) capture the QoL impact of AEs. The impact of AEs on patient HRQoL is explored in the cost-effectiveness model as a scenario (see Section B.3.11.3).

The utility decrements per AE and duration of each AE were sourced from published literature and are presented in **Table 50**. The incidence of AEs in both arms were obtained from DESTINY-Breast04 as outlined in Section B.3.3.2.3.

Table 50: Disutilities for adverse events

Adverse event	Utility decrement	Duration (days)	Source (disutility)	Source (duration)
Leukopenia	-0.003	42.20	Hudgens (2014)[175]	TA704[4] and TA862[5]
Anaemia	-0.010	42.90		
Neutropenia	-0.007	40.10		
Thrombocytopenia	-0.066	42.20	TA786[70]	TA862[5]
Fatigue	-0.029	58.30	Hudgens (2014)[175]	TA704[4] and TA862[5]
ALT increased	-0.050	14.66	TA654[176]	
Interstitial lung disease (any grade)	-0.170	51.10	Doyle et al. (2011)[177]	TA704[4] and TA862[5]

Abbreviations: ALT, alanine transaminase.

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

For the model base case, utilities derived from DESTINY-Breast04 have been used directly to inform treatment-specific values for the *'progression-free'* health state (see Section B.3.4.1). The values derived from DESTINY-Breast04 are based directly on the relevant population and treatments received, and measure the health states using EQ-5D-5L mapped to EQ-5D-3L, which is in line with the NICE reference case.[173]

The clinical experts consulted during an advisory board meeting in December 2022 noted that a difference in pre-progression QoL between patients treated with T-DXd and patients treated with TPC is expected, due to the different adverse event profiles of T-DXd and chemotherapies.[121] In DESTINY-Breast04, patients treated with T-DXd also had a better response to treatment compared to patients treated with TPC, as observed in the ORR (52.3% and 16.2% for T-DXd and TPC, respectively), which is associated with improved QoL and higher pre-progression utility. Trial-based utilities estimated using DESTINY-Breast04 data were considered the most appropriate source of evidence by both clinical and economic experts for the *'progression-free'* health state in this submission as they are derived directly from a relevant patient population with a large observation sample size (n=[redacted]) using the NICE preferred EQ-5D values.[2]

For the '*post-progression'* health state, limited post-progression observations from DESTINY-Breast04 were available (n=[redacted]). Experts considered that the post-progression utility values derived from DESTINY-Breast04 were high in comparison to previously accepted '*progressed disease'* utility values within mBC populations (**Table 49**).[121] Clinical experts also expected a greater reduction in QoL as patients progress than observed in the

trial.[121] In DESTINY-Breast04, HRQoL questionnaires were completed at the Day 40 first follow-up assessment (after last study drug administration) or before initiation of further treatment (whichever came first), and then at the first long-term/survival follow-up assessment three months later, which was the last data collection point. This means that limited long-term HRQoL data for progressed patients were collected, which may contribute to the implausibly high post-progression trial-based utility values.

Therefore, values derived from Lloyd et al, 2006 are used to inform the model base case for the *'post-progression'* health state. Treatment-specific post-progression utility values are used to inform the base case as there is an expectation that patients who progress on T-DXd have a better QoL than those who progress on TPC due to the improved and longer response rates and better disease control (Section B.2.6.1). This is demonstrated in DESTINY-Breast04; higher utility values were observed in the T-DXd arm in patients who experienced disease progression ([redacted]) compared to patients treated with TPC ([redacted]) (**Table 45**). Patients who experience disease progression following treatment with T-DXd will be starting with a 'higher' utility upon progression than those patients who experience disease progression following treatment with TPC; this is due to lower tumour burden in patients treated with T-DXd (see **Table 45**). The use of treatment-specific *'post-progression'* utility values was considered to be plausible in previous NICE appraisals in u/mBC.[5, 70,132]

A scenario analysis considering post-progression utility data derived directly from DESTINY-Breast04 is explored, in line with the NICE preferred EQ-5D values.[2]

Table 51 summarises the utility values included within the cost-effectiveness analysis base case and scenarios.

Table 51: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
Progression-free T-DXd TPC	[redacted]	[redacted]	B.3.4.2, Page 144	Derived from DESTINY-Breast04
Progressed disease T-DXd TPC	0.6101 0.5655		B.3.4.3, Page 145	Previously accepted algorithm from Lloyd et al using DESTINY-Breast04 response data
Scenario 1 – progressed-disease utilities derived from DESTINY-Breast04				
Progression-free T-DXd TPC	[redacted]	[redacted]	B.3.4.2, Page 144	Explore using alternative progressed-disease utilities derived from DESTINY-Breast04
Progressed disease T-DXd TPC	[redacted]	[redacted]		

Abbreviations: SE, standard error; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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-negative or HER2-low u/mBC breast cancer previously treated with chemotherapy. Full details of the SLR methods, identified studies and results are presented in **Appendix I**.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

The drug unit costs for each treatment included in the model were sourced from the electronic Market Information Tool (eMIT)[178], where available, or the British National Formulary (BNF)[179], in line with the NICE methods manual,[2] and are presented in **Table 52**. A confidential simple discount Patient Access Scheme (PAS) for T-DXd is currently operational in the NHS, resulting in a fixed net price of [redacted] per 100mg vial (equivalent to a discount of [redacted] the list price). A PAS is in in place for eribulin, however as this is commercially confidential it is not applied within the analysis.

Table 52: Unit drug costs

Drug	Formulation	Unit size	Pack size	List price (with PAS)	Source
T-DXd	Vial	100mg	1	£1,455.00 [redacted]	BNF 2022
Capecitabine	Tablet	150 mg	60	£6.49	eMIT 2022
		300 mg	60	£31.17	
		500 mg	120	£39.23	
Eribulin	Vial	0.88 mg	1	£361.00	BNF 2022
Gemcitabine	Vial	1000 mg	1	£32.99	eMIT 2022
		1600 mg	1	£35.99	
		1800 mg	1	£38.99	
		2000 mg	1	£42.73	
		2200 mg	1	£49.50	
Paclitaxel	Vial	100 mg	1	£12.47	eMIT 2022
		150 mg	1	£14.23	
		300 mg	1	£39.81	
Nab-paclitaxel	Vial	100 mg	1	£118.36	eMIT 2022

Abbreviations: BNF – British National Formulary; eMIT – electronic Market Information Tool; PAS, patient access scheme; T-DXd, trastuzumab deruxtecan.

The dosing schedule for T-DXd was taken from the proposed posology for T-DXd in this indication and aligned with the dosing schedule used in DESTINY-Breast04. T-DXd is administered at a dose of 5.4 mg/kg once per 21-day cycle.[7] The dosing schedules of individual agents in the TPC arm in DESTINY-Breast04 protocol were aligned with local licenses for each country. For the purposes of the cost-effectiveness modelling, doses of individual TPC agents were taken from the SmPC[18, 144,180–182] to accurately reflect the dose patients are expected to receive in the UK, which is consistent with DESTINY-Breast04 for all drugs except gemcitabine.[7] As gemcitabine as a monotherapy is not licensed in the UK, the dose and frequency of administration for gemcitabine is aligned with the SmPC for

gemcitabine in combination with paclitaxel.[183] **Table 53** provides details of all treatment dosing regimens modelled in the CEM.

Table 53: Dose regimens for T-DXd and TPC

Treatment	Dosing Regimen used in the model
T-DXd	5.4 mg/kg once per 21-day cycle
Capecitabine	1250 mg/m^2 PO twice daily on Days 1-14; cycled every 21 days
Eribulin	1.23 mg/m^2 IV on Days 1 and 8; cycled every 21 days
Gemcitabine [a]	1250 mg/m^2 IV on Days 1 and 8; cycled every 21 days
Paclitaxel	175 mg/m^2 IV on Day 1; cycled every 21 days
Nab-paclitaxel	260 mg/m^2 IV; cycled every 21 days

[a] Gemcitabine is only recommended for use in combination with paclitaxel. Therefore, dosing is inconsistent with the UK label, where gemcitabine is used in combination with paclitaxel (175 mg/m2) IV on Day 1, followed by gemcitabine (1250 mg/m2) IV on Days 1 and 8, cycled every 21 days.
Abbreviations: IV, intravenous, T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Sources: Daiichi Sankyo Inc. 2022. (CSR; Data on file)[7]

In DESTINY-Breast04, no dose modifications for T-DXd were permitted for Grade 1 and 2 AEs unless specified in the protocol.[158] For Grade ≥3 toxicities, two dose reductions were permitted for T-DXd, which is in line with the SmPC.[158] The dose could be reduced to 4.4 mg/kg (Level-1) then further to 3.2 mg/kg if required (Level-2) and finally, withdrawal. Once the dose of study treatment had been reduced because of toxicity, all subsequent cycles were to be administered at that lower dose level unless further dose reduction was required. If toxicity continued after two dose reductions, then the subject was withdrawn from study treatment. Study treatment dose increases for T-DXd were not allowed in DESTINY-Breast04.[158] For TPC, dose adjustments were made in accordance with the label approved in the country of drug administration or the NCCN guidelines.[7,158]

Therefore, to account for dose reductions, missed doses and treatment interruptions, the RDI from DESTINY-Breast04 is included in the base case; [redacted] for T-DXd and [redacted] for TPC agents. This ensures that the dose intensity and subsequent drug costs in the model are consistent with the efficacy data used in the model from DESTINY-Breast04.

Drug costs for treatments administered parenterally were estimated using the average patient body weight from DESTINY-Breast04 for T-DXd, and average body surface area for eribulin, gemcitabine, paclitaxel and nab-paclitaxel. Drug costs per cycle were calculated through the method of moments approach to calculate the average number of vials that would be required per one administration of treatment.[155] The method of moments first derives a normal distribution for the average patient weight or body surface area using the mean and standard deviation measured at baseline in DESTINY-Breast04. This is then used to predict the proportion of patients within each body weight or surface area range and the number of vials required to administer the required dose. This method assumes that patients only receive whole vials (i.e., no vial sharing), and thus accounts for drug wastage.

Vial sharing is available in some UK centres and applied in the base case. In the recent approval of T-DXd for treating HER2-positive u/mBC after 1 or more anti-HER2 treatments (TA862), 50% vial sharing was accepted as plausible and the NHS England Cancer Drugs Fund clinical lead confirmed that vial sharing is expected to occur regularly with T-DXd, in at least 50% of cases, due to dose banding.[5] Recommendation of T-DXd for use in additional

indications, such as HER2-low, would be expected to lead to larger patient numbers being treated with T-DXd in NHS practice and subsequently the number of centres that are able to vial share could increase. Therefore, in the base case, 75% vial sharing was applied for both treatment arms. The use of increased vial sharing also supports the NHS Long Term Plan, which aims to accelerate the production of 'off the shelf' licensed pharmaceuticals and the use of compounders to minimise drug wastage.[184] Scenario analysis considering 50% and 100% vial sharing are presented (Section B.3.11.3).

The drug cost per cycle for capecitabine, which is administered orally, was calculated by applying the minimum number of tablets required to administer the required dose based on the average patient body weight in DESTINY-Breast04.

Table 54 presents the dosing schedules, dose intensity and final cost per treatment cycle used in the model base case. The cost per dose is then applied within the model to patients on treatment every 3 weeks as per the administration frequency.

Table 54: Dosing schedules and cost per 21-day treatment cycle

Treatment	Dose	Doses per cycle	Relative dose intensity (RDI)	% vial sharing	Cost per cycle	Source (RDI)
T-DXd	5.4 mg/kg	1	[redacted]%[b]	75%	[redacted][a]	DESTINY-Breast04[7]
Weighted TPC	-	-	-	-	£987.24[d]	-
Components of TPC						
Capecitabine	1250 mg/kg	28	[redacted]%[c]	N/A	£38.12	DESTINY-Breast04[7]
Eribulin	1.23 mg/m^2	2	[redacted]%[c]	75%	£1,786.55	DESTINY-Breast04[7]
Gemcitabine	1250 mg/m^2	2	[redacted]%[c]	75%	£93.58	DESTINY-Breast04[7]
Paclitaxel	175 mg/m^2	1	[redacted]%[c]	75%	£30.56	DESTINY-Breast04[7]
Nab-paclitaxel	260 mg/m^2	1	[redacted]%[c]	75%	£529.18	DESTINY-Breast04[7]

Abbreviations: RDI, Relative dose intensity; T-DXd, trastuzumab deruxtecan; TPC, the physician's choice.
Note: [a] Cost per cycle includes the PAS on the list price of T-DXd.
[b] For T-DXd: relative dose intensity (%) = dose intensity/planned dose intensity × 100, where planned dose intensity for T-DXd = 5.4 mg/kg / Duration of exposure (day) * cycle length in days * expected number of cycles. Cycle length is 21 days and number of cycles expected is based on the duration of treatment exposure.
[c] For TPC: relative dose intensity (%) = dose intensity / planned dose intensity × 100, where planned dose intensity (units/cycle lengths in weeks) = planned cumulative dose (units)/planned duration of exposure (day)/cycle length in days. Due to different cycle durations among the individual TPC treatments, relative dose intensity is not presented for the overall TPC arm.
[d] TPC cost per cycle is weighted by the distribution of treatments in the TPC arm, presented in Table 14: TPC single-agent chemotherapy use | All screened patients (N=184).

B.3.5.1.2 Administration costs

T-DXd and all TPC treatments except capecitabine, which is administered as an oral tablet, are administered via intravenous infusion. The initial dose of T-DXd should be administered as a 90-minute infusion. If the prior infusion is well tolerated, subsequent doses may be administered over 30 minutes. For intravenous treatments in the TPC arm, the SmPC for

each agent was checked for administration guidance and all agents are recommended to be administered over 30 minutes or less.

The cost per administration for all therapies used in the model were sourced from the National Schedule of NHS Costs 2020/21.[185] Healthcare Resource Group (HRG) code SB12Z: deliver simple parenteral chemotherapy was used for T-DXd and TPC agents delivered intravenously. This includes an overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.[185] For capecitabine, HRG code SB11Z: deliver exclusively oral chemotherapy was used. Within each HRG code the day-case cost was also applied for the first cycle patients received and the outpatient cost for all subsequent cycles, to reflect potentially greater resource use at the first administration.

The cost per administration is provided in **Table 55** and is applied in the model as a single cost per treatment dose to all treatments.

Table 55: Administration costs

Method	Cost per administration (first cycle)	Cost per administration (Subsequent cycles)	Model treatment	Source
Oral	£304.62	£215.80	Capecitabine	NHS Cost Collection 20/21[185] – SB11Z – deliver exclusively oral chemotherapy
Parenteral Simple	£381.97	£281.11	T-DXd, Eribulin, Gemcitabine, Paclitaxel and Nab-paclitaxel	NHS Cost Collection 20/21[185] – SB12Z – deliver simple parenteral chemotherapy

Abbreviations: National Health Service; T-DXd, trastuzumab deruxtecan.

B.3.5.2 Health-state unit costs and resource use

Health state resource use costs are based on frequencies reported in TA862[5] and TA819[132] which are the two most recent appraisals in mBC.[5,132] Health state resource use is split by health state ('*progression-free'* and '*post-progression'*) and assumes the same resource use across health states and treatment arms, as advised by clinical experts.[121]

Table 56 presents resource use for monitoring and disease management in the *'progression-free'* and *'post-progression'* health states. Unit costs were sourced from the NHS Cost Collection costs 2020/21[185] and the PSSRU 2021[186] based on the setting of care.[5]

Table 56: Monitoring costs and frequencies

Resource	Frequency (per cycle)		Unit cost	Frequency source	Cost source
	PF	PD			
GP contact	0.69	0.69	£39.00	TA862[5] TA819[132]	PSSRU 2021[186] - GP Per patient contact lasting 9.22 minutes with qualifications
Medical oncologist	0.69	0.69	£225.00	TA862[5] TA819[132]	NHS Cost Collection 20/21[185] – 370 – medical oncologist – consultant led
Clinical nurse specialist	0.69	0.69	£85.00	TA862[5] TA819[132]	NHS Cost Collection 20/21[185] - N09AF - Specialist Nursing, Breast Care Nursing/Liaison, Adult, Face to face
CT scan	0.23	0.23	£105.66	TA862[5]	NHS Cost Collection 20/21[185] - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over - Outpatient
ECHO scan	0.23	0.23	£145.53	TA862[5]	NHS Cost Collection 20/21[185] - RN22Z - Multi-Gated Acquisition (MUGA) Scan
Total cost	**£298.56**	**£298.56**	N/A		

Abbreviations: ECHO, echocardiogram; CT, Computerised Tomography; GP, general practitioner; NHS, National Health Service; PD, progressed disease; PF, progression-free; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse event unit costs and resource use

The unit costs associated with the management of AEs were sourced from the NHS Cost Collection 2020/21 and PSSRU 2021.[185,186] **Table 57** summarises the costs associated with each adverse event. The unit cost of each adverse event is applied to the incidence rate of each AE within each treatment arm (as outlined in Section B.3.3.2.3 and **Table 41**). The total weighted cost per treatment arm was calculated and applied as a one-off cost within the first cycle of the economic model as the greatest proportion of TEAEs in DESTINY-Breast04 occurred in the first cycle and subsequently declined through cycles (see Section B.2.10.1). Only AEs of common terminology criteria for AEs (CTCAE) grade ≥3 with an incidence of ≥5% are included in the model, except for the AE of special interest, ILD, which was included with an incidence rate of ≥5%, regardless of CTCAE grade. It is assumed that all AEs included in the model lead to hospitalisation as the grade requirement restricts AEs to serious AEs. The total costs associated with the AEs are shown in **Table 58**.

Table 57: Adverse event costs included in the model

Adverse event	Cost per adverse event	Source
Leukopenia	£761.01	NHS Cost Collection 20/21 – NES – SA35A-E – Agranulocytosis*
Anaemia	£735.80	NHS Cost Collection 20/21 – NES – SA04G-L – Iron Deficiency Anaemia*
Neutropenia	£761.01	NHS Cost Collection 20/21 – NES – SA35A-E – Agranulocytosis*
Thrombocytopenia	£881.88	NHS Cost Collection 20/21 – NES – SA12G-K – Thrombocytopenia*
Fatigue	£41.00	PSSRU 2020 Section 13&14: 1 hour hospital nurse (band 5) visit (Assumption from Hardy [2010][187])
ALT increased	£745.27	NHS Cost Collection 20/21 – NES – GC17A-K – Non-Malignant, Hepatobiliary or Pancreatic Disorders*
Interstitial lung disease (any grade)	£782.27	NHS Cost Collection 20/21 – NES – DZ11K-V – Lobar, Atypical or Viral Pneumonia*

Note: *weighted average of costs based on the number of finished consultant episodes and the national average unit cost associated with each code.
Abbreviations: ALT, alanine transaminase; NES, non-elective short stay; NHS, National Health Service.

Table 58: Total adverse event costs

Treatment	Total cost
T-DXd	[redacted]
TPC	[redacted]

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatments

Subsequent treatment costs were included in the model as an average cost per patient applied as a one-off cost to patients leaving the '*progression-free'* health state. In the base case, the distribution of subsequent treatments is consistent with the treatments received in DESTINY-Breast04 in each treatment arm to align modelled costs with efficacy. The cost of subsequent treatments is modelled as a weighted distribution of these treatments, aligning with the methods used in TA862.[5] The duration for which patients are treated for, post-progression, is the difference between median PFS2 and median PFS from DESTINY-Breast04 which may be considered a proxy for time on next treatment; a weighted average of [redacted] months is calculated using the number of patients in each treatment arm.[7] The duration of subsequent treatment is presented in **Table 59**.

Table 59: Weighted median duration of subsequent treatment | FAS

Treatment	n	Median PFS (months)	Median PFS2 (months)	PFS2 – PFS (months)	Weighted median duration of subsequent treatment (PFS2-PFS) (months)
T-DXd	371	9.9	15.5	5.6	5.53
TPC	184	5.1	10.5	5.4	

Abbreviations: FAS – full analysis set; PFS – progression-free survival; PFS2 – progression-free survival 2; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice .

Subsequent treatments that were included in the model were based on what patients received following progression in DESTINY-Breast04. The chemotherapy agents included in the model were paclitaxel, capecitabine, gemcitabine, eribulin, vinorelbine, epirubicin and carboplatin. The included endocrine therapies were tamoxifen and fulvestrant.

In the DESTINY-Breast04 study, [redacted] and [redacted] of patients in the T-DXd arm and TPC arms, respectively, received subsequent treatment following disease progression. Therefore, in the model it is assumed these proportions respectively receive subsequent treatment in the base case.

A scenario analysis was conducted to explore the uncertainty associated with subsequent treatment costs. A scenario considered the average proportion of patients ([redacted]) who received subsequent treatment in the FAS population of DESTINY-Breast04.[2]

Table 60 presents the subsequent treatment distributions and cost per each treatment applied within the economic model base case. Unit costs for the subsequent therapies are provided in **Appendix K**. **Table 61** presents the total subsequent therapy cost applied in each treatment arm.

Table 60: Subsequent therapy costs

Treatment	Distribution over trial period (%)*		Dose	Cost per cycle (3 weeks)	Admin cost per cycle (3 weeks)
	T-DXd (n=373)	TPC (n=184)			
Subsequent treatments	[redacted])	[redacted])			
Chemotherapy					
Paclitaxel	[redacted])	[redacted])	175.0 mg/m^2	[redacted]	[redacted]
Capecitabine	[redacted])	[redacted])	1250.0 mg/m^2	[redacted]	[redacted]
Gemcitabine	[redacted])	[redacted])	1250.0 mg/m^2	[redacted]	[redacted]
Eribulin	[redacted])	[redacted])	1.2 mg/m^2	[redacted]	[redacted]
Vinorelbine	[redacted])	[redacted])	60.0 mg/m^2	[redacted]	[redacted]
Epirubicin	[redacted])	[redacted])	100.0 mg/m^2	[redacted]	[redacted]
Carboplatin	[redacted])	[redacted])	400.0 mg/m^2	[redacted]	[redacted]
Endocrine therapy					
Tamoxifen	[redacted])	[redacted])	20.0 mg	[redacted]	[redacted]
Fulvestrant	[redacted])	[redacted])	500.0 mg	[redacted]	[redacted]

*The proportion of patients on who received individual subsequent treatments exceeds 100% as patients were able to receive multiple lines of therapy or treatments in combination.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 61: Total subsequent therapy costs applied in the model

	T-DXd	TPC
Total weighted subsequent therapy acquisition cost per cycle	[redacted]	[redacted]
Total weighted subsequent therapy administration cost per cycle	[redacted]	[redacted]
Total subsequent therapy cost per progressed patient*	[redacted]	[redacted]
Proportion receiving subsequent treatment	[redacted]	[redacted]
Total subsequent therapy cost per progressed patient applied in the model*	[redacted]	[redacted]

*Total subsequent therapy cost assumes that patients are treated for 6 months following progression.
Distribution of subsequent treatments is presented in Table 60.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.5.4.2 Terminal care costs

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

The end-of-life (EOL) cost was based on Round et al (2015).[161] Round et al was a modelling study estimating the cost of caring for cancer patients at the end of their life. The study reports a mean cost among four cancer types (breast, colorectal, lung and prostate). The total end of life health care cost associated with BC care was reported as £4,346 which was then uplifted to 2021 prices using the NHS cost inflation indices (£4,856).[186]

B.3.6 Severity

B.3.6.1 Overview

Patients with HER2-low u/mBC are currently treated according to HER2-negative treatment pathways in the UK, which, after prior chemotherapy in the adjuvant or metastatic setting, predominantly comprise of further non-targeted single-agent chemotherapies (see **Section B.1.3.3** for more information). Non-targeted chemotherapy is associated with poor survival outcomes in HER2-negative/HR-positive u/mBC patients with a median PFS of 3.6–4.2 months and a median OS of 11.5–16.1 months. [43–47] Outcomes are even poorer in HER2-negative/HR-negative u/mBC patients, where median PFS is 1.7–2.8 months and median OS is 6.7–12.4 months.[43,48–50] Given the severity of the condition and the very poor life expectancy using current standard of care, there is a clear unmet for effective treatments that improve survival outcomes for patients with HER2-low u/mBC previously treated with chemotherapy in the metastatic setting.[43–47] As the first HER2-targeted therapy to demonstrate significant efficacy in HER2-low u/mBC,[6] T-DXd addresses this unmet need.

Until February 2022, the value of innovation and improved outcomes for severe conditions with poor life expectancy was recognised through the end-of-life (EOL) criteria,[188] and since the NICE methods update in 2022, is recognised through the severity modifier.[2] The applicability and impact of each of these decision modifiers to this appraisal is discussed below.

B.3.6.2 End-of-life criteria

Prior to the 2022 NICE methods update,[2] NICE Committees considered the following decision-modifiers, amongst others, when making judgements on the value of new technologies:[189]

- The innovative nature of the technology.
- Whether the technology meets the EOL criteria.
- Aspects that relate to non-health objectives of the NHS (e.g., better use of resources)

The EOL modifier was introduced to recognise the potential value of technologies that extend life in populations at the end of life, namely:[188]

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months compared to current NHS treatment.

In practical terms, this weighting led to appraisals that met the criteria being assessed against a Willingness to Pay (WTP) threshold of £50,000 per QALY gained.[189]

T-DXd in HER2-low u/mBC meets the previous NICE EOL criteria:

- **T-DXd is for patients with a short life expectancy (<24 months):** As per the TPC arm in DESTINY-Breast04, median OS with standard of care is just 16.8 months in the FAS population relevant to this appraisal.[6] This is consistent with survival reported in prior studies of single-agent chemotherapies in a similar setting in HER2-negative u/mBC (any HR-status: HR-positive, HR-negative, HR-unspecified), where life expectancy is 6.7–20.7 months.[43–55]
- **T-DXd extends life by over 3 months compared with current standard of care:** In the FAS of DESTINY-Breast04, T-DXd statistically significantly extended median OS by 6.6 months versus TPC (median OS: 23.4 vs. 16.8 months; p=0.0010).[6] In the HR-positive and HR-negative cohorts, T-DXd increased median OS by 6.4 months and 9.9 months, respectively.[6]

Therefore, until recently, this appraisal would have been appraised at a £50,000 per QALY gained WTP threshold.

B.3.6.3 Severity modifier

In line with the NICE 2022 methods guide,[2] the absolute and proportional QALY shortfall associated with current standard of care in patients with HER2-low u/mBC who have previously been treated with chemotherapy compared with the general population was calculated. Within the new framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within specified cut-off ranges (**Table 62**).

Table 62: QALY weights referenced within the new NICE manual

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

Abbreviations: QALY, quality-adjusted life-year.

To estimate the shortfall, the Schneider et al. (2021) estimator tool was used,[190] which was cited by NICE as a potential option for calculating applicability of a severity modifier. This tool uses ONS data from England to generate the general population survival with various sources of data to inform utility estimates.[166] Given NICE DSU guidance[191] indicates that directly collected EQ-5D-3L using the Health Survey for England (HSE) 2014 dataset is a preferred method of capturing utility values, the reference case data source in the Schneider et al tool, which uses directly collected EQ-5D-3L from the HSE 2014, was considered to represent the most recent and robust source for the base case QALY shortfall calculations.[190]

The QALY shortfall was calculated assuming a mean cohort age of 57 years and 100% female (as per the DESTINY-Breast04 study; **Table 63**). The expected total QALYs for the general population were calculated using the Schneider et al[190] tool reference case for general population utilities (MVH value set + HSE 2014 ALDVMM [Hernandez Alava, et al.]; **Table 64**).[191] The total expected QALYs for patients with the disease treated with current standard of care was based on the modelled TPC arm of the company base case. The total expected QALYs in patients with the disease on current standard of care were then compared to the general population QALYs to calculate the absolute and proportional shortfall.

Table 63: Summary features of QALY shortfall analysis | FAS population

Factor	Value	Reference to section in submission
Sex distribution	100% female	Section B.3.3.1 (Table 34)
Starting age	57 years	Section B.3.3.1 (Table 34)

Abbreviations: FAS, full analysis set; QALY, quality-adjusted life-year.

Based on the above, the absolute QALY shortfall (AS) is estimated to be [redacted] and the proportional shortfall (PS) is estimated to be [redacted] (**Table 64**). The results show that this appraisal meets the threshold of a QALY weight of 1.2 for both AS and PS under the current NICE cut-off threshold criteria.

Table 64: Results of the QALY shortfall analysis | FAS population

General population QALY source	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight†
Reference case: MVH value set + HSE 2014 ALDVMM [Hernandez Alava M, et al.]	13.85	[redacted]	Absolute: [redacted] Proportional: [redacted]%	1.2x

*Based on the total QALYs in the TPC arm of the company economic model base case for this appraisal.
†All calculations based on the tool developed by Schneider et al., 2021.[190]
Abbreviations: ALDVVM, adjusted limited dependent variable mixture model; HSE, Health Survey for England; MVH, York Measurement and Valuation of Health; QALY, quality-adjusted life-year.

B.3.6.4 Impact of the loss of end-of-life criteria and relevance of an equivalent 1.7x QALY weighting to this appraisal

As outlined, there is a clear unmet need for effective targeted therapies for patients with HER2-low u/mBC after prior chemotherapy in the metastatic setting due to the very poor survival outcomes with currently available treatments. In recognition of the poor life

expectancy of the population, and the innovation and survival benefit of T-DXd demonstrated in DESTINY-Breast04,[6] this appraisal would robustly meet the EOL criteria that NICE previously considered for Technology Appraisals submitted up until as recently as February 2022.

In February 2022,[2] NICE changed the way in which it assessed the value of products for severe conditions. Under the new methodology, additional weight is applied to the QALY gain for technologies used in severe conditions, as determined by QALY shortfall in people with vs. without the condition.[2] According to the new NICE methodology, this appraisal may not qualify for the 1.7 QALY weight. Daiichi Sankyo consider that a severity modifier weight of x1.2 does not appropriately reflect the severity of patients with HER2-low u/mBC after prior chemotherapy, a concern which was independently raised by a key stakeholder during the scoping consultation process for this topic.

Indeed, the current implementation/cut-off thresholds for the NICE severity modifier mean that very few new technologies will qualify for the x1.7 weighting and the discrete categorisation results in a lack of sensitivity in quantifying severity on a scale given the large interval between cut-off thresholds. To highlight this point for this appraisal, based on the starting age and sex distribution from DESTINY-Breast04, if the TPC QALYs were 0.70 a 1.2x weighting would be applicable similar to if the TPC QALYs were 2.06. This large interval in TPC QALYs highlights the limitations in how increasing severity is quantified. The base case total QALYs for TPC in this appraisal (1.36 QALYs) clearly demonstrate that severity is not appropriately captured with a 1.2x weighting.

This appraisal highlights a case where the previous EOL criteria would have been robustly met, but under the new framework a commensurate x1.7 severity modifier may not be applicable. This inequity could have a significant impact on access to innovative cancer treatments for UK patients.

In order to capture the full extent of the severity of HER2-low u/mBC during this initial phase of implementation, monitoring and review of the severity modifier, Daiichi Sankyo considers that additional flexibilities in the form of a QALY weight of 1.7 equivalent to the previous EOL should be applied in decision-making. This would more appropriately reflect the severity of the condition based on the poor survival outcomes in HER2-low u/mBC under current standard of care.

Additionally, Daiichi Sankyo would like to reiterate the substantial innovation of T-DXd in this indication. As highlighted by the Innovation Passport, T-DXd is an innovative therapy and is the first and only HER2-targeted treatment to show a statistically significant efficacy benefit over non-targeted chemotherapy in patients with HER2-low u/mBC providing substantial improvement quality and quantity of life.[6] T-DXd is therefore a step-change that will transform the care of patients with HER2-low u/mBC. This was reflected by comments from UK clinical experts, who informed Daiichi Sankyo that there is a high demand for T-DXd to be made available in HER2-low u/mBC.

Cost-effectiveness results in **Section B.3.10** and **Section B.3.11** have been presented with no severity modifier applied. Base case and scenario results with 1.2x severity modifier and 1.7x severity modifier applied are presented in **Appendix P.**

B.3.7 Uncertainty

In DESTINY-Breast04, T-DXd demonstrated substantial, statistically and clinically significant improvements in PFS and OS compared with TPC in the FAS.[7] T-DXd was associated with significantly longer PFS (9.9 vs. 5.1 months; HR: 0.50; 95% CI: 0.40, 0.63; p<0.001) and OS (23.4 vs. 16.8 months; HR: 0.64, 95% CI: 0.49, 0.84, p=0.001) compared with TPC.[7] Results were consistent across subgroups.[7]

The model base case has been informed by clinical and health economic expert opinion as well as external validation (See Section B.3.14). Extensive sensitivity analyses have been performed to test the structural and parameter uncertainty with a summary of components and approaches tested provided in **Table 65** (see Section B.3.11 for results). Scenario analyses have also been explored to explore the impact of uncertainty (Section B.3.11.3).

Table 65: Summary of variables applied and tested in economic model

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

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

B.3.8 Managed access proposal

Daiichi Sankyo consider the Phase III RCT DESTINY-Breast04 (assessing the safety and efficacy of T-DXd compared with TPC in patients with HER2-low u/mBC previously treated with chemotherapy) to be a suitable basis for a routine commissioning decision. There is no protocol requirement for further analyses,[158] as the trial met the primary and all secondary endpoints (see Section B.2.6.2 for more details).[7]

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

B.3.9.1 Summary of base-case analysis input

In line with the NICE reference case, the analysis was conducted from the NHS and PSS perspective using a lifetime horizon (30 years) and with costs and QALYs discounted at 3.5% (see Section B.3.2). **Table 66** summarises base case variables and ranges used for probabilistic and one-way sensitivity analysis.

Table 66: Summary of base case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Patient characteristics			
Age	56.5 years	Not varied	Section B.3.3.1 Table 34
% female	99.6%		
BSA (m^2)	[redacted]	Normal	
Weight (kg)	[redacted]		
Efficacy			
T-DXd/TPC curves - OS	Log-logistic (indepdent)	Multinormal distribution	Section B.3.3.4 Table 42
T-DXd/TPC curves - PFS	Log-logistic (indepdent)		
T-DXd/TPC curves - TTD	Generalised gamma (independent)		
Utilities			
DB04 T-DXd PF utility	[redacted]	SE: [redacted] (Beta)	Section B.3.4.5 Table 51
DB04 TPC PF utility	[redacted]	SE: [redacted] (Beta)	
Lloyd et al. 2006 T-DXd PD utility	0.610	Variation: 0.025 (Beta)	
Lloyd et al. 2006 TPC PD utility	0.565		
Drug costs			
T-DXd - 100 mg (with PAS)	£1,455.00 [redacted]	Not varied	Section B.3.5.1.1 Table 52
Capecitabine - 150 mg	£6.49		
Capecitabine - 300 mg	£31.17		
Capecitabine - 500 mg	£39.23		
Eribulin - 0.88 mg	£361.00		
Gemcitabine - 1000 mg	£32.99		
Gemcitabine - 1600 mg	£35.99		
Gemcitabine - 1800 mg	£38.99		
Gemcitabine - 2000 mg	£42.73		
Gemcitabine - 2200 mg	£49.50		
Paclitaxel - 100 mg	£12.47		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Paclitaxel - 150 mg	£14.23		
Paclitaxel - 300 mg	£39.81		
Nab-paclitaxel - 100 mg	£118.36		
T-DXd - RDI	[redacted]	Variation: 0.025 (Beta)	Section B.3.5.1.1 Table 54
Capecitabine - RDI	[redacted]		
Eribulin - RDI	[redacted]		
Gemcitabine - RDI	[redacted]		
Paclitaxel - RDI	[redacted]		
Nab-paclitaxel – RDI	[redacted]		
Administration cost – parental infusion – day-case	£381.97	Variation: 0.025 (Gamma)	Section B.3.5.1.2 Table 55
Administration cost – parental infusion – outpatient	£281.11		
Administration cost – exclusively oral – day-case	£304.62		
Administration cost – exclusively oral - outpatient	£215.80		
Adverse events			
T-DXd - Neutrophil count decreased	8.10%	Variation: 0.025 (Beta)	Section B.3.3.3 Table 41
T-DXd - Anaemia	[redacted]		
T-DXd - White blood cell count decreased	[redacted]		
T-DXd - Platelet count decreased	[redacted]		
T-DXd - Fatigue	[redacted]		
T-DXd - Increased ALT	[redacted]		
T-DXd - Interstitial lung disease (any grade)	[redacted]		
TPC - Neutrophil count decreased	[redacted]		
TPC - Anaemia	[redacted]		
TPC - White blood cell count decreased	[redacted]		
TPC - Platelet count decreased	[redacted]		
TPC - Fatigue	[redacted]		
TPC - Increased ALT	[redacted]		
TPC - Interstitial lung disease (any grade)	[redacted]		
Neutrophil count decreased – cost	£761.01	Variation: 0.025 (Gamma)	Section B.3.5.3 Table 57
Anaemia - cost	£735.80		
White blood cell count decreased - cost	£761.01		
Platelet count decreased - cost	£881.88		
Fatigue - cost	£41.00		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Increased ALT - cost	£745.27		
Interstitial lung disease (any grade) - cost	£782.27		
Resource use			
RU - PF - GP visit	0.69	Variation: 0.025 (Gamma)	B.3.5.2 Table 56
RU - PF - Clinical nurse specialist	0.69		
RU - PF - Medical oncologist	0.69		
RU - PF - ECHO scan	0.23		
RU - PF - CT scan	0.23		
RU - PD - GP visit	0.69		
RU - PD - Clinical nurse specialist	0.69		
RU - PD - Medical oncologist	0.69		
RU - PD - ECHO scan	0.23		
RU - PD - CT scan	0.23		
RU - unit cost – GP visit	£39.00	Variation: 0.025 (Gamma)	
RU - unit cost - Clinical nurse specialist	£85.00		
RU - unit cost - Medial oncologist	£225.00		
RU - unit cost - ECHO scan	£145.53		
RU - unit cost - CT scan	£105.66		
End of life costs			
Terminal care cost	£4,856.38	Variation: 0.025 (Gamma)	B.3.5.4.2
Subsequent treatment			
Sub trt – T-DXd - Capecitabine	£6.49	Variation: 0.025 (Gamma)	Section B.3.5.1.1 Table 52
Sub trt – T-DXd - Eribulin	£361.00		
Sub trt – T-DXd - Gemcitabine	£32.99		
Sub trt – T-DXd - Paclitaxel	£12.47		
Sub trt – T-DXd - Vinorelbine	£166.13		
Sub trt – T-DXd – Fulvestrant	£80.03		
Sub trt – T-DXd – Epirubicin	£11.03		
Sub trt – T-DXd – Carboplatin	£6.58		
Sub trt – T-DXd – Tamoxifen	£3.42		
T-DXd - Proportion receiving subsequent treatment	[redacted]	Variation: 0.025 (Beta)	Section B.3.5.4 Table 60
TPC - Proportion receiving subsequent treatment	[redacted]		
Sub trt – T-DXd - Capecitabine	[redacted]		
Sub trt – T-DXd - Eribulin	[redacted]		
Sub trt – T-DXd - Gemcitabine	[redacted]		
Sub trt – T-DXd - Paclitaxel	[redacted]		
Sub trt – T-DXd - Vinorelbine	[redacted]		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Sub trt – T-DXd – Fulvestrant	[redacted]		
Sub trt – T-DXd – Epirubicin	[redacted]		
Sub trt – T-DXd – Carboplatin	[redacted]		
Sub trt – T-DXd – Tamoxifen	[redacted]		
Sub trt – TPC - Capecitabine	[redacted]		
Sub trt – TPC - Eribulin	[redacted]		
Sub trt – TPC - Gemcitabine	[redacted]		
Sub trt – TPC - Paclitaxel	[redacted]		
Sub trt – TPC - Vinorelbine	[redacted]		
Sub trt – TPC – Fulvestrant	[redacted]		
Sub trt – TPC – Epirubicin	[redacted]		
Sub trt – TPC – Carboplatin	[redacted]		
Sub trt – TPC – Tamoxifen	[redacted]		

Abbreviations: BSA, body surface area; CT, computerised tomography; GP, general practitioner; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; Sub trt, subsequent treatment; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time to treatment discontinuation; RDI, relative dose intensity; RU, resource use.

B.3.9.2 Assumptions

Assumptions underlying the base case analysis are summarised in **Table 67**. The table also outlines a summary of how each assumption was tested in sensitivity or scenario analyses.

Table 67: Summary of key model assumptions

Topic	Assumption	Justification/reason	Sensitivity
Cycle length	Model cycle length of 3 weeks	A 3-week cycle length is assumed to be sufficiently short to represent the frequency of clinical events and interventions. Furthermore, 3-weeks is aligned to the dosing schedule of T-DXd, chemotherapy agents within the TPC arm and the multiple subsequent treatments included in the model.	Not tested
Time horizon	A lifetime horizon of 30 years	Reflects the lifetime of patients based on a starting age of 57. Less than 1% of patients in both arms are alive after this time.	**Scenario analysis** The impact of alternative time horizons on the results was tested
Efficacy	Independent models are appropriate for OS, PFS and TTD	Log-cumulative hazard plots were inconclusive for the proportional hazards assumption and could not be clearly justified. Therefore, in line with recommendations in NICE DSU TSD 14 which state that a strong assumption is required to use dependent curves,[171] independent curves were selected for the model. UK HEOR and clinical experts confirmed	NA

Topic	Assumption	Justification/reason	Sensitivity
		that the use of independent curves is deemed the most appropriate approach.[121] In addition, given the availability of patient-level data for each treatment and maturity of the data, the reliance on the proportional hazard assumption was considered unnecessary and therefore, independent models were considered more appropriate.	
	Identification of the most appropriate survival curves describing OS, PFS and TTD	Extensive analyses have been undertaken to identify appropriate survival curves describing the long-term efficacy of each treatment, with reference to the guidance from the NICE DSU.[171] The approach and identified survival extrapolations have been validated by UK HEOR and clinical experts.	**Scenario Analysis** Evaluation of clinically plausible alternative extrapolations **PSA** Variation of base case distribution parameters via variance co-variance matrix
Utilities	Utility values were assumed to differ by treatment arm and health state.	Direct EQ-5D data collected within DESTINY-Breast04 show a difference between treatment arms in utilities in both *'progression-free'* and *'post-progression'* health states. This may be due to the improved and longer response rates with T-DXd leading to better disease control and lower tumour burden. Based on the response rates with T-DXd and TPC, utility values are expected to be greater for T-DXd which is demonstrated by the observed direct evidence from DESTINY-Breast04. Patients on T-DXd are expected to have greater utility when progressing due to lower tumour burden which follows into the progression health state. Similar assumptions have been made in prior appraisals. The different safety profiles across the trial arms also support differences in utilities.	**Scenario Analysis** Use of alternative progressed-disease utility values, sourced from DESTINY-Breast04 **OWSA, PSA** Variation of utility value through the SE and confidence intervals
	Post-progression utilities were derived from Lloyd et al, 2006.	Limited long-term QoL data were collected post-progression in DESTINY-Breast04. The utility values derived from the trial were higher than would be expected in clinical practice as suggested by UK clinical experts and based on previously accepted utilities within mBC populations.[121] Prior breast cancer appraisals including TA862 (T-DXd second line in HER2-positive u/mBC)[5] and TA423 (eribulin third line HER2-positive mBC)[131] also implemented PD utility	

Topic	Assumption	Justification/reason	Sensitivity
		values based on the Lloyd et al. (2006) regression.	
Vial sharing	75% of centres vial share and therefore have no wastage	In TA862 (a recent approval of T-DXd in HER2-positive u/mBC), 50% vial sharing was accepted by the committee.[5] The approval of T-DXd in additional indications would lead to a larger patient population and an increased number of centres that would be able to vial share. This would also support the NHS Long Term Plan, which aims to accelerate the production of 'off the shelf' licensed pharmaceuticals and the use of compounders to minimise drug wastage.[184] Therefore, in the base case, 75% vial sharing was applied for both treatment arms for treatments administered intravenously.	**Scenario analysis** 50% and 100% vial sharing tested in scenario analysis. **OWSA, PSA** OWSA and assuming a beta distribution.
Subsequent treatments	[redacted] and [redacted] of patients in the T-DXd and TPC arms, respectively, who progress will receive subsequent treatments	The proportion of patients who receive subsequent treatment are derived from observed data from DESTINY-Breast04. PFS data in DESTINY-Breast04 are mature, as 243 patients (65.1%) and 127 patients (69.0%) had a progression event as assessed by BICR in the FAS population at data cut-off in the T-DXd and TPC cohorts, respectively.[7]	**Scenario analysis** Alternative proportion of patients received subsequent treatment ([redacted]) which is equalised across the T-DXd and TPC arms based on pooled data from DESTINY-Breast04 **OWSA and PSA** Varied across confidence interval and assuming a beta distribution
	Cost of subsequent treatment based on distribution of specific subsequent treatments from DESTINY-Breast04	The distribution of subsequent treatments in the model is based on DESTINY-Breast04 data as the trial was considered generalisable to UK practice. This aligns efficacy and costs.	**OWSA and PSA** The proportion of patients on specific subsequent treatments is varied across confidence intervals assuming a Dirichlet distribution

Abbreviations: AE, adverse event; DSU, Decision Support Unit; NHS, National Health Service; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; QoL, quality-of-life; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time to treatment discontinuation.

B.3.10 Base-case results

As discussed in **Section B.3.6**, according to NICE's threshold criteria, this appraisal meets the 1.2x severity modifier. Daiichi considers that additional flexibility in the form of a QALY weight of 1.7 equivalent to the previous EOL should be applied in decision making to reflect the severity of the condition in the context that this appraisal would have qualified for the EOL criteria prior to the NICE methods update in February 2022. All results presented in **Section B.3.10** are presented with no modifier applied. Results with the 1.2x and 1.7x modifier are presented in **Appendix P**.

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

The base case deterministic cost-effectiveness results for T-DXd (at the PAS price) vs. TPC in the FAS are presented in **Table 68**. The results demonstrate that, compared with TPC, T-DXd is associated with LY and unadjusted QALY gains of [redacted] and [redacted], respectively. This suggests a substantial improvement in survival and QoL in the u/mBC setting. This benefit is associated with incremental costs of [redacted] per patient over a lifetime resulting in an ICER of [redacted]. The base case results for disaggregated costs by treatment arm are presented in **Tables 56–58** in **Appendix J. Table 69** presents the net-health benefit (NHB) at the £30,000/QALY WTP threshold. Results demonstrate that at a WTP threshold of £30,000/QALY when no severity modifier is applied, the NHB is [redacted].

With the 1.2x severity modifier applied, T-DXd (at the PAS price) is associated with LY and adjusted QALY gains of [redacted] and [redacted], respectively, resulting in an ICER of [redacted] (**Appendix P**). With the 1.7x severity modifier applied, T-DXd (at the PAS price) is associated with LY and adjusted QALY gains of [redacted] and [redacted], respectively, resulting in an ICER of [redacted] (**Appendix P**).

Table 68: Base case deterministic results in the FAS population (T-DXd PAS price; no severity modifier)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 69: Net health benefit (at the PAS price, no severity modifier)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000 WTP threshold
TPC	[redacted]	[redacted]	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; WTP, willingness-to-pay.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) where all parameters are assigned probability distributions and varied jointly (see **Table 66**). PSA was run for 5,000 iterations, by which point, results had stabilised and therefore considered reliable to explore the uncertainty.

The mean results from the probabilistic analysis are presented in **Table 70** and the incremental cost-effectiveness plane (CE-plane) in **Figure 46**. The probabilistic results show consistency with the deterministic analysis providing a mean QALY gain of [redacted] at an incremental cost of [redacted], resulting in a probabilistic ICER of [redacted]. All iterations in the CE-plane were within the North-East quadrant demonstrating a positive QALY gain and confirming the clinical benefit of T-DXd vs. TPC when parameter uncertainty is evaluated.

Table 70: Mean PSA results (at the PAS price, no severity modifier applied)*

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

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 46: Cost-effectiveness plane – T-DXd (at the PAS price) vs. TPC (no severity modifier applied)*

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 47 presents the cost-effectiveness acceptability curve for T-DXd vs. TPC. At a WTP threshold of £30,000/QALY the probability that T-DXd is a cost-effective treatment option is [redacted] and at a WTP threshold of £50,000/QALY gained the probability that T-DXd is a cost-effective treatment option is [redacted].

Figure 47: Cost-effective acceptability curve – T-DXd (at the PAS price) vs. TPC (no severity modifier)*

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PAS, patient-access scheme; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B.3.11.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameters when their values are set to the lower and upper limits of the confidence intervals (presented in **Table 66**) while all other parameters are maintained at the base case setting. **Table 71** and **Figure 48** present the ICERs and the tornado plot showing the 10 parameters which had the largest impact on the ICER.

Variation of the average weight of patients had the largest impact on the ICER followed by the RDI of T-DXd. Other parameters had a lower impact on the ICER when varied between their upper and lower bounds.

Table 71: OWSA results (T-DXd [at the PAS price] vs. TPC, no severity modifier applied)*

Parameter	ICER at lower bound	ICER at upper bound
Average weight (kg)	[redacted]	[redacted]
Relative dose intensity -Trastuzumab deruxtecan - 100	[redacted]	[redacted]
Utilities - Progressed - Physician's choice	[redacted]	[redacted]
Utilities - Progressed - Trastuzumab deruxtecan	[redacted]	[redacted]
Utilities - Progression-free - Trastuzumab deruxtecan	[redacted]	[redacted]
Utilities - Progression-free - Physician's choice	[redacted]	[redacted]
Average body surface (m^2)	[redacted]	[redacted]
Drug cost - Eribulin - 0.88	[redacted]	[redacted]
Administration costs - Trastuzumab deruxtecan	[redacted]	[redacted]
Health state cost - Progression-free - Total	[redacted]	[redacted]

*10% variation applied in the OWSA, in the absence of SE or CIs.
Abbreviations: ICER, incremental cost-effectiveness ratio; kg – kilograms; OWSA, one-way sensitivity analysis; PAS, patient-access scheme; TPC, treatment of physician's choice.

Figure 48: Tornado plot showing OWSA results on the ICER (T-DXd [at the PAS price] vs. TPC , no severity modifier applied)*

*10% variation applied in the OWSA, in the absence of SE or CIs.
Abbreviations: ICER, incremental cost-effectiveness ratio; kg – kilograms; OWSA, one-way sensitivity analysis; PAS, patient-access scheme; TPC, treatment of physician's choice.

B.3.11.3 Scenario analysis

Scenario analyses were performed in order to test key structural and inputs assumptions. A PSA was run for all scenarios where all parameters are assigned probability distributions and varied jointly under a given scenario. The results of probabilistic scenario analyses are presented in **Table 72**, together within the cost-effectiveness plane (**Figure 49**). PSAs for all scenarios were run for 1,000 iterations. The largest deviations from the base case ICER came from using log-normal distribution to extrapolate overall survival over the lifetime horizon of the economic model.

Table 72: Scenario analysis (probabilistic results – T-DXd [at the PAS price] vs. TPC, no severity modifier applied)

Parameter	Scenario number	Base case	Scenario	Incremental costs	Incremental QALYs	ICER
Base case probabilistic results				[redacted]	[redacted]	[redacted]
Discount rate	1	Discount rates - Costs: 3.5%, outcomes: 3.5%	Discount rates - costs: 0%, outcomes: 0%	[redacted]	[redacted]	[redacted]
	2		Discount rates - costs: 1.5%, outcomes: 1.5%	[redacted]	[redacted]	[redacted]
	3		Discount rates - costs: 6%, outcomes: 6%	[redacted]	[redacted]	[redacted]
Time horizon	4	30 years	20 years	[redacted]	[redacted]	[redacted]
Half cycle correction	5	Applied	Not applied	[redacted]	[redacted]	[redacted]
Subsequent treatment	6	Trial treatment-specific proportions on subsequent treatment	Trial pooled, weighted proportions on subsequent treatment	[redacted]	[redacted]	[redacted]
AE disutilities	7	AE disutilities excluded	AE disutilities included	[redacted]	[redacted]	[redacted]
Vial sharing	8	Vial sharing 75%	Vial sharing 50%	[redacted]	[redacted]	[redacted]
	9		Vial sharing 100%	[redacted]	[redacted]	[redacted]
Utilities	10	Progressed disease utilities sourced from Lloyd et al. 2006	Progressed disease utilities sourced from DESTINY-Breast04 trial.	[redacted]	[redacted]	[redacted]
OS extrapolations (applied to T-DXd and TPC)	11	Log-logistic	Exponential	[redacted]	[redacted]	[redacted]
	12		Log-normal	[redacted]	[redacted]	[redacted]
PFS extrapolations (applied to T-DXd and TPC)	13	Log-logistic	Exponential	[redacted]	[redacted]	[redacted]
	14		Weibull	[redacted]	[redacted]	[redacted]
	15		Gompertz	[redacted]	[redacted]	[redacted]
	16		Log-normal	[redacted]	[redacted]	[redacted]
	17		Generalised gamma	[redacted]	[redacted]	[redacted]
OS and PFS extrapolations (applied to T-DXd and TPC)	18	OS: log-logistic PFS: log-logistic	OS: Exponential PFS: Exponential	[redacted]	[redacted]	[redacted]
	19		OS: Log-normal PFS: Log-normal	[redacted]	[redacted]	[redacted]

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality adjusted life-years

Figure 49: Cost-effectiveness plane for the scenario analysis (probabilistic results, based on results with PAS, no severity modifier applied)

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: CEP, cost-effectiveness plane; ICER, incremental cost-effectiveness ratio; PAS, patient-access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; WTP, willingness-to-pay.

B.3.12 Subgroup analysis

A consistent treatment effect was observed across all pre-specified subgroups in DESTINY-Breast04.[7] Therefore, subgroup analyses were not considered relevant for the economic analysis. Daiichi Sankyo consider this appraisal should be based on the DESTINY-Breast04 FAS which includes the full anticipated licensed population.

B.3.13 Benefits not captured in the QALY calculation

Unresectable or metastatic BC has a considerable impact on patients' QoL and their ability to conduct usual activities (Section B.1.3.2.2). The majority of patients diagnosed with u/mBC are of working age with the impact of disease and effects of treatment having substantial consequences on productivity and ability to work. A recent UK study investigating the relationship between disease and treatment stage found that metastatic patients had lower employment rates in comparison to early BC after surgery or adjuvant therapy (27.5% vs 50.6% or 50.9%, respectively).[28] The study also found that metastatic patients most often reported not being able to attend work and that poor HRQoL was significantly associated with high work impairment ($p<0.001$). The results of this study support the premise that being able to delay or prevent the metastatic recurrence of BC, for example by extending the time patients are in remission, has wider benefits in terms of patient productivity. Although the EQ-5D has a 'Usual activities' domain which refers to elements such as work, family activities or leisure activities, the questionnaire is unable to detect the more subtle

differences in HRQoL which may impact a patients' ability to attend work and productivity when at work. These productivity changes and wider societal impacts of BC are not captured in the current EQ-5D-5L framework.

Caregivers of patients with u/mBC are also impacted by the disease which is not captured within the QALY calculation. As a consequence of the psychological and economic strain associated with caring for someone with the disease, caregivers may overlook their own needs, resulting in decreased wellbeing and an increase in symptoms of stress (see Section B.1.3.2.5).[109] Caring for a patient with mBC can also impact a caregiver's work, leading to financial strain and increased indirect economic costs.[109] A treatment that allows patients to lead a near normal life for longer by improving response rates and reducing progression rates will therefore substantially improve caregiver and patient QoL and productivity.

Whilst there has been a significant improvement in outcomes for patients with HER2-positive u/mBC since the introduction of effective HER2-targeted therapies, there remains a large unmet need for effective, novel treatment options for patients with HER2-negative u/mBC, including those expressing lower levels of HER2. Following exhaustion of targeted options such as ET/CDK4/6is (HER2-negative/HR-positive) at earlier lines, the only option for the majority of patients with HER2-negative u/mBC are sequential lines of non-targeted, single-agent chemotherapies.[35,42] These non-targeted chemotherapies are associated with poor outcomes (Section B.1.3.4).[43–47] Treatments shown to increase OS and PFS are highly valued by patients with incurable breast cancer, but where possible, should provide efficacy without the high levels of toxicity imposed by chemotherapy.[192,193] A subset of HER2-negative u/mBC patients may be categorised as HER2-low, for which previous HER2 targeted therapies have been ineffective.[57] T-DXd offers the first HER2-targeted treatment to demonstrate efficacy in a HER2-low population, representing a shift in the classification and treatment paradigm of BC.

DESTINY-Breast04 demonstrates that T-DXd significantly improves response rates, PFS and OS in patients with HER2-low u/mBC, whilst maintaining their QoL, which may allow more patients to perform their usual activities for longer including the ability to work.[7,140] As such, T-DXd not only greatly improves patients overall QALYs (see Section B.3.10) but can also have a substantial benefit in terms of societal gains and economic production.

T-DXd is an innovative treatment based on its potential to make a significant and substantial impact on health-related benefits, representing a step-change in the treatment paradigm for patients with HER2-low u/mBC. In recognition of its innovation, T-DXd was awarded an Innovation Passport designation by the UK Medicines and Healthcare Regulatory Agency in May 2022. The clinical development of T-DXd represents an important innovation in the treatment of HER2-low u/mBC, which is uncaptured by the severity modifier (**Section B.3.6**).

B.3.14 Validation

B.3.14.1 Independent technical cost-effectiveness model QC

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

B.3.14.2 Expert validation of cost-effectiveness analysis

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

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

The following key aspects were discussed and validated:

- DESTINY-Breast04 trial generalisability to UK clinical practice
- DESTINY-Breast04 efficacy and safety
- UK treatment pathway and positioning of T-DXd
- Generalisability of the comparator treatment arm (TPC) in DESTINY-Breast04 to UK clinical practice
- The model structure and appropriateness to the decision problem
- Survival methods and extrapolation of OS and PFS beyond the observed period
- Validity of model inputs including utilities, costs and resource use
- Subsequent treatment

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

B.3.14.3 Internal validation

PFS, OS and TTD Kaplan-Meier data from DESTINY-Breast04 trial were compared with the PFS, OS and TTD outputs from the model (see **Appendix J**).

For both T-DXd and TPC, the model survival projections are consistent with the observed trial data for all outcomes (OS, PFS and TTD).

B.3.14.4 External validation

The economic analysis conducted as part of this appraisal is, to the company's knowledge, the first cost effectiveness analysis in HER2-low u/mBC specifically. This means that it is not possible to compare the parameters and outputs of this model with other economic analyses relevant to this appraisal.

The validity of the chosen comparator (TPC) for this appraisal was confirmed by UK clinical experts external to the company, who confirmed that the TPC arm is reflective of, and generalisable to, UK clinical practice in the target population (see **Section B.1.3.6.1**).[121] The similar efficacy across individual non-targeted chemotherapy agents included within TPC was confirmed by UK clinical experts as well as in a published systematic review of RCTs for single-agent chemotherapies used in Europe.[118] The comparators listed in the NICE final

scope[1] are well represented in the TPC arm of DESTINY-Breast04, and clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal.[121]

The validity of the modelled outcomes may be inferred by comparing the observed DESTINY-Breast04 data against previous studies and thereafter comparing results with the modelled outcomes. Aside from DESTINY-Breast04, there are no prior studies powered to evaluate efficacy in a HER2-low u/mBC population specifically, so the external validity of DESTINY-Breast04 may be assessed by comparing the TPC arm to previous studies in a similar setting. Median PFS and OS results in the TPC arm of DESTINY-Breast04 are comparable with outcomes of studies in HER2-negative u/mBC including single-agent chemotherapies (**Section B.2.12.1** and **Table 30**), demonstrating that DESTINY-Breast04 is consistent with these studies.

Given that mature OS and PFS data from DESTINY-Breast04 were used in the economic analyses, and the modelled outcomes are very similar to the observed data (**Table 73**), it can be inferred that the modelled outcomes for TPC are likely to be robust and valid. While it is not possible to compare T-DXd outcomes to previous trials as there have been no previous trials for T-DXd in HER2-low u/mBC, data are mature and the modelled survival outcomes align well with the observed DESTINY-Breast04 survival outcomes (**Table 73**).

Table 73: Internal and external validation for modelled OS and PFS | TPC

Study	Treatment	Median PFS (months)	Median OS (months)	Source
Economic model (based on DESTINY-Breast04 FAS)	TPC	[redacted]	[redacted]	Section B.3.3.2
DESTINY-Breast04 FAS (observed)	TPC	5.1	16.8	Modi 2022
Economic model (based on DESTINY-Breast04 FAS)	T-DXd	[redacted]	[redacted]	Section B.3.3.2
DESTINY-Breast04 FAS (observed)	T-DXd	9.9	23.4	Modi 2022

Abbreviations: FAS, full analysis set; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice

The external validity of the economic analysis was further confirmed by UK clinical and HEOR experts at an advisory board in December 2022.[121] Clinical and HEOR experts (including ex-NICE committee and EAG members) agreed that the model structure is robust and appropriate for decision making. In addition, clinical experts generally considered the modelled clinical inputs and outputs to be clinically plausible.[121] This provides confidence that the economic model is robust and appropriate for decision-making.

B.3.15 Interpretation and conclusions of economic evidence

Evidence for this submission comes from the pivotal, Phase III, multicentre, open-label, randomised, active-controlled DESTINY-Breast04 trial assessing the efficacy and safety of T-DXd vs. TPC in patients with HER2-low u/mBC after treatment with one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting.[6,7] UK clinical and HEOR experts confirmed the trial is well designed, robust and provides evidence that is generalisable to the UK.[121] Published UK biomarker data[56] and UK clinical expert insights confirm that the distribution of HR-positive and HR-negative patients in DESTINY-Breast04 is aligned to UK clinical practice supporting the appropriateness of the FAS.[120] Clinical and HEOR experts agreed that, for decision-making, TPC is the relevant comparator in this appraisal as it reflects how patients are currently treated in this setting and that the comparators listed in the NICE final scope[1] are well represented in the TPC arm of DESTINY-Breast04.[121] As such, Daiichi Sankyo consider evidence from DESTINY-Breast04 in the FAS population to be highly relevant to the decision problem.

DESTINY-Breast04 is the first ever head-to-head Phase III trial to show a significant benefit of HER2-targeted treatment in HER2-low u/mBC after one or two lines of chemotherapy in the recurrent or metastatic setting compared with non-targeted chemotherapy.[6] In DESTINY-Breast04, T-DXd demonstrated statistically significant superiority compared with TPC for the primary endpoint of PFS by BICR in the HR-positive cohort (median PFS: 10.1 vs 5.4 months; HR: 0.51; p<0.001).[6] T-DXd was also associated with statistically significant improvements over TPC for all secondary efficacy endpoints: PFS by BICR in the FAS (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001), OS in the HR-positive cohort (median OS: 23.9 months vs. 17.5 months; HR: 0.64; p=0.003), and OS in the FAS (median OS: 23.4 months vs.16.8 months; HR: 0.64; p=0.001).[6] The efficacy of T-DXd was confirmed through multiple clinically meaningful endpoints, including all those listed in the final scope,[1] covering the most important outcomes in oncology.[6]

The economic analysis has been conducted in the FAS population to reflect the anticipated licensed population. The analysis is performed within a *de novo* economic model with a structure designed to reflect the natural history of HER2-low u/mBC. The model structure is consistent with prior breast cancer appraisals and brings together the most relevant clinical efficacy and safety data.

In line with the NICE manual,[2] the severity of the condition was assessed by calculating the absolute and proportional QALY shortfall associated with standard of care in HER2-low u/mBC compared with the general population. Daiichi Sankyo acknowledge that using the current NICE criteria, based on the QALY shortfall calculations outlined in **Section B.3.6**, a QALY weighting of 1.2x is met. That said, it should be highlighted that T-DXd would have robustly met the previous NICE EOL criteria in this indication and would therefore have been appraised at a £50,000 per QALY gained ICER threshold and thus the current QALY shortfall methodology and cut-off threhsolds fails to adequately capture the extent of disease severity in this condition to a similar level.

HER2-low u/mBC is a severe, terminal condition, associated with rapid disease progression and substantial physical and mental burden.[27, 29,83] There are currently no effective, targeted treatment options for patients with HER2-low/HR-positive u/mBC after prior chemotherapy and effective treatment options in HER2-low/HR-negative u/mBC are limited.[73] Non-targeted chemotherapies are associated with poor outcomes; in patients currently classified as HER2-negative/HR-positive u/mBC, non-targeted chemotherapy is associated with median PFS of 3.6–4.2 months and median OS of 11.5–16.1 months.[43–47] Outcomes are even poorer in HER2-negative/HR-negative u/mBC patients, where median PFS is 1.7–2.8 months and median OS is 6.7–12.4 months.[43,48–50] Accordingly, Daiichi Sankyo consider that greater flexibility in the form of a x1.7 severity modifier, commensurate with the previous EOL weighting, should be applied for decision-making in this appraisal.

Additionally, Daiichi Sankyo would like to reiterate the substantial innovation of T-DXd in this indication. As highlighted by the Innovation Passport, T-DXd is an innovative therapy and is the first and only HER2-targeted treatment to show a statistically significant efficacy benefit over non-targeted chemotherapy in patients with HER2-low u/mBC providing substantial improvement quality and quantity of life.[6] T-DXd is therefore a step-change that will transform the care of patients with HER2-low u/mBC. This was reflected by comments from UK clinical experts, who informed Daiichi Sankyo that there is a high demand for T-DXd to be made available in HER2-low u/mBC.

Cost-effectiveness results in this document are presented with no modifier applied. Results with the 1.2x and 1.7x modifier are presented in **Appendix P**. Base case results

demonstrate that T-DXd (at the PAS price) is associated with a QALY gain of [redacted] at an incremental cost of [redacted], resulting in an ICER of [redacted] vs TPC in the FAS population. With the 1.2x and 1.7x severity modifier applied, the ICER is [redacted] and [redacted], respectively (**Appendix P**). This demonstrates that T-DXd (at the PAS price) is a cost-effective use of NHS resources, at a WTP threshold of £50,000 per QALY gained, given the unmet need in the population of interest, the severity of the condition, and the innovation of T-DXd as the first and only EMA-approved HER2-targeted treatment to show efficacy in HER2-low u/mBC.

In line with the guidance from the NICE methods manual,[2] both structural and parameter uncertainty has been extensively explored. The robustness of base case results was assessed via comprehensive probabilistic, deterministic, and scenario analyses with results demonstrating the stability of base case with a high level of certainty:

- PSA was performed to explore joint parameter uncertainty. The probabilistic results are consistent with the deterministic results with a probabilistic QALY gain of [redacted] and ICER of [redacted], with no severity modifier applied. Results demonstrate the robustness of the base case when evaluating joint parameter uncertainty. T-DXd (at the PAS price) has a [redacted] and [redacted] probability of being a cost-effective use of NHS resources at a WTP threshold of £30,000/QALY and £50,000/QALY gained, respectively.
- Parameter uncertainty was evaluated through OWSA. The analysis shows that the cost-effectiveness results were mostly sensitive to the patients' weight and the RDI of T-DXd. Other parameters had a lower impact on the ICER when varied between their upper and lower bounds, with all results consistently showing that T-DXd (at the PAS price) is a cost-effective use of NHS resources at a WTP threshold of £50,000 per QALY gained.
- A range of probabilistic scenario analyses were performed to evaluate key model assumptions and alternative choices of inputs to test the robustness of the base case results. The model was most sensitive to the choice of survival distribution.

A strength of the analysis is that key inputs for the economic model are taken from DESTINY-Breast04 which provides a head-to-head comparison between the relevant intervention and comparator in the appropriate population for this appraisal.

The key limitation of the economic analysis is that although HER2-low is clinically recognised as a new category of BC in recent ESMO,[42] ASCO,[71] and NCCN clinical guidelines,[72] these patients are currently treated according to HER2-negative treatment pathways. Therefore, there is limited published data available to compare and validate the model inputs and outputs for the specific population of interest. However, extensive clinical and HEOR validation was sought to alleviate areas of uncertainty. For example, a range of plausible survival extrapolations have been explored and outcomes quantified.

DESTINY-Breast04 established T-DXd as the first HER2 targeted therapy to demonstrate a statistically significant efficacy benefit in HER2-low u/mBC after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting compared with non-targeted chemotherapy via a head-to-head Phase III trial.[6] The unprecedented efficacy demonstrated in DESTINY-Breast04 has led to T-DXd becoming the first HER2-targeted therapy to receive regulatory approval in Europe in HER2-low u/mBC[3] (UK regulatory approval expected in March 2023), representing a step-change in the treatment paradigm and supporting a need for clinical pathways to further categorise HER2 status. In light of the suboptimal survival outcomes in HER2-negative u/mBC, T-DXd offers

hope of extended life and QoL for patients, carers, and families in a setting where there is a substantial unmet need. UK clinical experts confirmed that there is an unmet need for better patient outcomes in this setting.[121] T-DXd clearly addresses this unmet need by demonstrating significant improvements across clinically meaningful endpoints while providing a manageable safety profile and maintaining quality-of life compared with current standard of care. When a severity modifier equivalent to the previous EOL weighting is applied, T-DXd is a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Summary of Information for Patients (SIP)

March 2023

File name	Version	Contains confidential information	Date
ID3935_T-DXd_HER2-low mBC_SIP form_10Mar2023_[ACIC]	1.0	No	10 March 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

- Trastuzumab deruxtecan (T-DXd; Enhertu®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

- The European Medicines Agency (EMA) marketing authorisation for T-DXd in this indication is: *as monotherapy for the treatment of adult patients with unresectable or metastatic human epidermal growth factor (HER2)-low breast cancer (HER2-low u/mBC) who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see **Section 4.2**).*[1]
- The population that is being appraised by NICE is aligned to the full indication.[2]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

In January 2023, T-DXd received approval from the European Commission for the indication described in **Section 1b** above. UK regulatory approval from the Medicines and Healthcare Regulatory Agency (MHRA) is expected imminently. Please see Section B.1.2 of Document B of the company submission for more information.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Daiichi Sankyo has no existing collaborations with the relevant patient groups. However, in 2022, Daiichi Sankyo provided grant money to Breast Cancer Now for a *Living With Secondary Breast Cancer* peer support service.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is HER2-low unresectable or metastatic breast cancer?

Unresectable (inoperable) and metastatic breast cancers (u/mBC) are the most advanced forms of BC. As part of BC diagnosis, samples of the tumour are taken from the breast tissue and are tested for levels of various biomarkers (i.e., naturally occurring molecules that may predict disease prognosis, including the HER2 protein and hormone receptor (HR) protein).[3,4] HER2 protein is a biomarker in BC as it signals cells to grow, meaning tumours with high HER2 expression are fast-growing and aggressive.[5] Classifying BC by HER2 expression is important as it informs prognosis and treatment decisions. Until recently, there were two categories of HER2 expression:[6] HER2-positive (i.e., high levels of HER2 protein; 13–20% of all BC cases[7,8]) and HER2-negative (i.e., no/low levels of HER2 protein; 80–87% of all BC cases[7,8]). HER2-positive BC is typically treated with therapies that specifically target the HER2 protein (e.g., Herceptin® [trastuzumab]). HER2-targeted therapies have proven to be very effective in HER2-positive disease, but not HER2-negative disease.[9,10]

A subgroup of patients with HER2-negative u/mBC have tumours that express HER2 at low levels (i.e., HER2-low; see **Figure 1** for HER2 testing information).[7,11] Of all BC cases, 49% are reported to be HER2-low.[12] Despite the tumours expressing low levels of HER2, most HER2-targeted therapies have proven ineffective in patients with HER2-low u/mBC.[13,14] There is an opportunity, therefore, for effective HER2-targeted therapies to improve outcomes in patients with HER2-low u/mBC.

How common is HER2-low u/mBC?

In total, 45,291 patients were diagnosed with BC in England in 2020.[15] Of these BC patients, an estimated 6.5% are diagnosed with u/mBC specifically.[16] Annually, approximately 3.7% of early BC patients progress to metastatic disease.[17] This means that 4,511 patients are diagnosed with u/mBC every year, of which 2,210 have HER2-low u/mBC specifically.

The population eligible to receive T-DXd in HER2-low u/mBC are patients who have received a prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. Of patients with u/mBC, an estimated 98.0% will receive first-line systemic therapy (this could be a targeted therapy such as endocrine therapy, or non-targeted chemotherapy), 66.8% of these a second-line systemic therapy, and 61.0% of these a third-line systemic therapy.[18] Based on the above, the total estimated number of patients with HER2-low u/mBC who may be eligible to receive T-DXd within its licensed indication each year and who are therefore relevant to this appraisal is 946.[18]

Clinical impact

HER2-low u/mBC presents a high clinical burden. Patients with u/mBC experience a range of debilitating symptoms, including pain, breast swelling, low energy levels, reduced appetite and weight loss.[19–21] This is in addition to symptoms associated with metastases (i.e., the process by which cancer cells spread to other parts of the body).[19,20] The liver and brain are the most common metastatic sites in HER2-low u/mBC,[22] and can lead to serious complications such as poor nutritional status and impairment in nervous system function.[23,24]

As HER2-low is a new disease classification in BC, patients with HER2-low u/mBC are currently treated as per HER2-negative u/mBC pathways.[25,26] At the line of therapy relevant to this appraisal (i.e., after prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting), treatments are broadly limited to non-targeted chemotherapies.[2,25,26] Non-targeted chemotherapies are associated with poor survival outcomes; in patients with HER2-negative/HR-positive u/mBC, the average survival time from the start of treatment is just 11.5–16.1 months.[27–31] In HER2-negative/HR-negative (i.e.,

triple negative breast cancer [TNBC]) u/mBC, the average survival time from the start of treatment is even worse, ranging from 6.7–12.4 months.[27,32–34] This highlights an unmet need for additional effective, targeted treatments.

Patient impact

HER2-low u/mBC has a substantial negative impact on patient quality of life (QoL). The negative QoL impact of BC is driven by disease progression,[35] physical BC symptoms,[36,37] and metastatic symptoms.[38] Patients with mBC also suffer from impaired social[39] and emotional wellbeing[40] and experience symptoms of depression.[36] The QoL impact is particularly profound in younger women and women with children.[39]

Side effects of treatment may also impact patient QoL. Patients treated with non-targeted chemotherapy may experience a lack of energy, difficulty sleeping, hair loss, pain, and drowsiness.[41] Chemotherapy is also associated with higher rates of depression than treatment with targeted therapy,[42] and patients treated with chemotherapy report worse total side effects than those treated with hormonal therapy.[24] In addition, a higher proportion of patients treated with chemotherapy than targeted therapy report that their disease limits social activity (70% vs. 50% of patients) and has a negative impact on close family (61% vs. 51% of patients).[24]

Burden to families and caregivers

In addition to the impact on patients themselves, caregivers of patients with mBC may be impacted physically, emotionally, and financially. Caregivers often report their caregiving tasks to be physically and emotionally demanding, leading to an increase in stress levels and decreased wellbeing as they often overlook their own needs.[43] Caring for a patient with mBC may also lead to financial strain, as the impact of caregiving may force them to take annual leave or quit work altogether.[44] Family members are also impacted by the disease as they worry about their loved one's wellbeing, disease status, and ability to maintain usual life activities.[44]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Initial diagnosis of BC is through breast X-ray and ultrasound, combined with laboratory analysis of breast tissue samples.[45] For patients with suspected advanced/metastatic BC, further scans may be performed to determine the extent of the metastases (e.g., radiography, ultrasound, magnetic resonance imaging [MRI], and computed tomography [CT]).[25] As with other cancers, BC staging is typically established based on the tumour size, extent of spread to lymph nodes, and presence of metastases.[46]

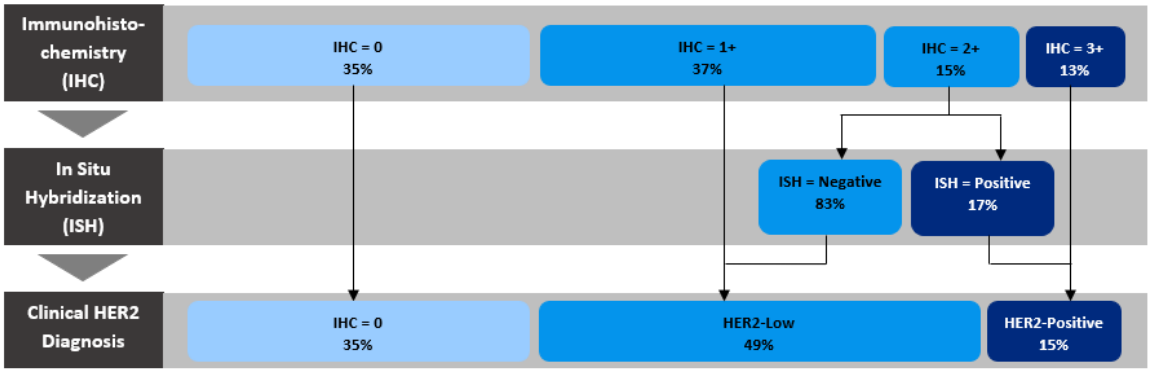
To inform prognosis and treatment decisions, tests are conducted on the breast tissue to determine the presence and extent of expression of HER2 and hormone receptor (i.e., oestrogen and progesterone receptors) proteins, which are key biomarkers in BC. HER2 status is currently determined through the following tests, which are routinely performed in the National Health Service (NHS) for patients with BC:

- Immunohistochemistry (IHC): this test uses antibodies to check for certain antigens in a small sample of tissue taken from the patient, providing a score from 0–3.[47]
- In situ hybridisation (ISH): this test uses fluorescent probes to visualise specific deoxyribose nucleic acid (DNA) sequences within a small sample of tissue taken from the patient, providing a positive or negative result for gene amplification.[48]

Based on the above tests, a BC is classified as HER2-positive if the tested breast tissue has an IHC score of 3+ or an IHC score of 2+ and a positive ISH test (**Figure 1**). Diagnosis of HER2-low u/mBC requires an IHC score of 1+ or an IHC score of 2+ and a negative ISH test (**Figure 1**).[11]

BC may be further classified by HR status. A BC is HR-positive if it expresses either the oestrogen receptor or the progesterone receptor, and HR-negative if it expresses neither the oestrogen nor the progesterone receptor. In accordance with the EMA marketing authorisation,[1] patients with HER2-low u/mBC who have previously received at least one prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting, irrespective of HR-status, would be eligible to receive T-DXd.

Figure 1: Determining HER2 status in breast cancer



Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation.
Source: Dodson et al. 2020[7]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

HER2-low is a new disease classification in BC, so there are currently no specific treatment guidelines in the UK or Europe. Patients with HER2-low u/mBC are therefore currently treated according to HER2-negative treatment pathways. There are currently two treatment pathways in HER2-negative u/mBC: (i) HER2-negative/HR-positive, and (ii) HER2-negative/HR-negative (i.e., TNBC).

(i) HER2-negative/HR-positive treatment pathway

In the first-line setting, HER2-negative/HR-positive u/mBC is treated with cyclin-dependent kinase inhibitors (targeted agents that inhibit the function of cyclin-dependent kinases) combined with endocrine therapy (treatment that adds, blocks, or removes hormones).[26] The endocrine therapy used is usually an aromatase inhibitor (drug that blocks the activity of an aromatase enzyme to lower the level of oestrogen produced). The targeted therapies recommended by the UK National Institute for Health and Care Excellence (NICE) are listed below.

First-line targeted therapies currently used in the UK:

- Palbociclib plus an aromatase inhibitor (AI)[49]
- Ribociclib plus an AI[50]
- Abemaciclib plus an AI[51]

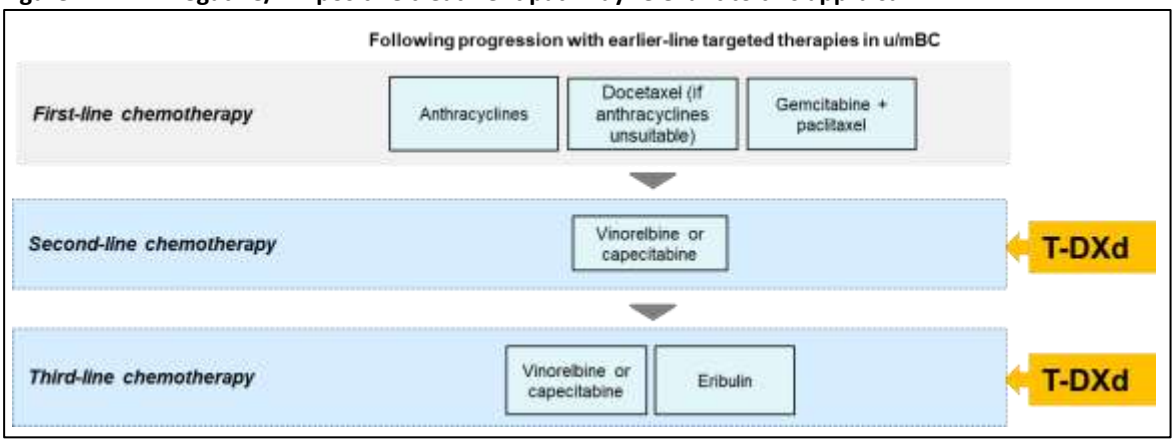
Second-line targeted therapies currently used in the UK:

- Everolimus plus exemestane[52]
- Palbociclib plus fulvestrant[53]
- Ribociclib plus fulvestrant[54]
- Abemacicblib plus fulvestrant[55]
- Alpelisib plus fulvestrant[56]

Once a patient has exhausted all targeted options, they are typically treated with lines of non-targeted, single-agent chemotherapies.[25,26] The agents recommended in NICE guidelines at each line of chemotherapy in the u/mBC setting are provided in **Figure 2**. T-DXd is expected to be made available as a treatment option alongside second- and later-line chemotherapy.

It should be noted that, while the pathway in **Figure 2** is aligned to UK guidance,[25,57,58] UK clinical experts[59] and real-world data[60] indicate that there is no standard of care at second- and later-line chemotherapy in the unresectable or metastatic setting, and that a range of non-targeted chemotherapies are used. In addition, a published review of clinical trials highlights that non-targeted chemotherapies have similar efficacy in patients previously treated with an anthracycline and taxane.[61]

Figure 2: HER2-negative/HR-positive treatment pathway relevant to this appraisal[25]



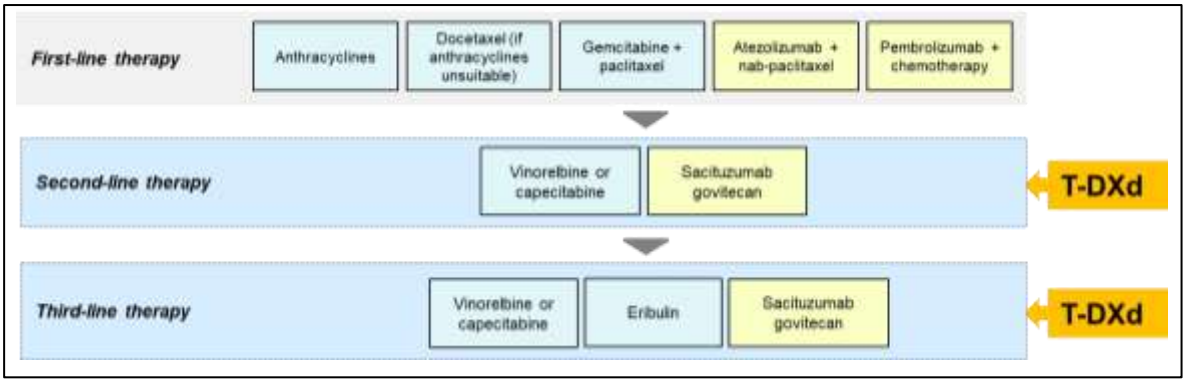
Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; T-DXd, trastuzumab deruxtecan; u/mBC, unresectable/metastatic breast cancer.

(ii) HER2-negative/HR-negative (i.e., TNBC) treatment pathway

In the first-line setting, patients with HER2-negative/HR-negative u/mBC whose tumours overexpress programmed cell death ligand 1 (PD-L1; a protein responsible for preventing T cells from attacking cancer cells) may be treated with PD-L1-targeting immunotherapy (a type of treatment that helps the immune system fight cancer) combined with non-targeted chemotherapy. The only first-line option for patients whose tumours do not overexpress PD-L1 is non-targeted chemotherapy. In the second-line setting and beyond, treatment options are limited to non-targeted chemotherapy or the targeted therapy sacituzumab govitecan, which has recently been recommended. T-DXd is expected to be made available as a treatment option at the second- and later-line setting (**Figure 3**).

As with the HER2-positive/HR-negative pathway, UK clinical experts[59] and real-world data[60] indicate that a range of non-targeted chemotherapies may be used at second- and later-line therapy.

Figure 3: HER2-negative/HR-negative treatment pathway relevant to this appraisal



Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; T-DXd, Trastuzumab deruxtecan.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Impact of living with u/mBC on patient QoL

As expected for an incurable disease with a high symptom burden, BC has a substantial negative impact on patient QoL, which worsens with disease stage.[35] A study of HER2-negative mBC found disease progression to be associated with worsening of physical symptoms, side effects from treatment, acute distress, and impaired performance scores, all of which are likely to have a negative impact on patient QoL.[62]

Physical BC symptoms are also associated with a significant mental burden for patients. According to a study of BC patients across the US and Europe, patients with HER2-negative/HR-positive advanced BC reported lower emotional wellbeing scores (indicating worse emotional wellbeing) compared to the general population.[40] Another US study found symptoms of BC to be significantly associated with depressive symptoms in women with BC.[36] Additionally, the QoL impact of living with u/mBC varies between patients, with younger patients more likely to experience impaired social wellbeing than older patients.[39] Patients with children are also more likely to experience impaired functional wellbeing than those without, as the disease impacts their ability to carry out normal parental activities and fulfil their social role.[39]

Beyond the physical symptoms and QoL impact for patients with HER2-low u/mBC, side effects from treatment may also impact QoL. Treatment with non-targeted chemotherapy is associated with a number of side effects that may reduce QoL, including a lack of energy, difficulty sleeping, hair loss, pain and drowsiness.[41] Furthermore, chemotherapy is associated with higher rates of depression than treatment with targeted therapy,[42] and patients treated with chemotherapy report worse total side effects than those treated with hormonal therapy.[24] A higher proportion of patients treated with chemotherapy than targeted therapy report that their disease limits social activity (70% vs. 50% of patients) and has a negative impact on close family (61% vs. 51% of patients).[24]

Impact on caregiver QoL

Caregivers of patients with mBC are also impacted by the disease as they may face financial difficulties, psychological problems, familial anxieties, and worries about their loved one's wellbeing, disease status, and ability to maintain usual life activities.[44] The Global Status of Advanced/Metastatic Breast Cancer 2005–2015 Decade Report found that caregivers experience a decrease in wellbeing and increase in stress levels because caregiving causes them to overlook their own needs.[44]

Caregivers also report caregiving tasks to be physically and emotionally challenging. In a US study evaluating caregiver burden of patients with mBC, 86% of caregivers reported that their life had been negatively affected as a direct result of providing care, with 77% reporting it to be an emotional burden, and 56% reporting it to be a physical burden.[43] Caregivers may also need to take annual leave or quit work altogether as a result of their caregiving tasks,[44] with 69% of caregivers reporting that they had missed work due to caregiving during the patient's palliative period (i.e., the months before death).[63]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Overview of T-DXd

- The summary of product characteristics (SmPC) for T-DXd can be found here: https://www.medicines.org.uk/emc/product/12135/smpc
- A patient information leaflet for T-DXd is available here: https://www.medicines.org.uk/emc/product/12135/pil

T-DXd targets the HER2 protein on the surface of breast cancer tumour cells

Enhertu® (T-DXd) is a cancer medicine made up of an antibody (trastuzumab) with a chemotherapy (DXd) attached (**Figure 4**). Trastuzumab is a HER2-targeted antibody that attaches specifically to tumour cells that have the HER2 protein on their surface.[64] Once T-DXd has attached to HER2 on the surface of HER2-expressing tumour cells, it enters the cells.[65–67] Inside the cells, cellular enzymes cut apart the antibody and chemotherapy components of T-DXd. This releases the DXd chemotherapy,[64] enabling it to kill the cells.[68,69] Once released inside the cell of a HER2-expressing cell, DXd can travel to and kill surrounding tumour cells, including the tumour cells that do not express the HER2 protein.[70–73]

The use of trastuzumab to target the DXd chemotherapy to HER2-expressing cells is novel and helps to prevent DXd from killing healthy cells, while the release of DXd to neighbouring cells helps to ensure that it kills cancer cells in tumours that contain a mixture of cells, including those that do and those that do not express the HER2 protein.

T-DXd addresses the unmet need for effective targeted treatments in HER2-low u/mBC

Currently available HER2-targeted therapies (e.g., Herceptin® and Kadcyla®) have so far proven ineffective in HER2-low u/mBC.[13,14] With its novel mechanism of action, T-DXd is the first HER2-targeted treatment to show efficacy in patients with HER2-low u/mBC (see **Section 3e** and **3h** for more information). In recognition of its therapeutic potential, T-DXd has been awarded an Innovation Passport designation by the UK Innovative Licensing and Access Pathway (ILAP) steering group (ILAP reference number: ILAP/IP/22/08265/01).

Figure 4: Mechanism of action of T-DXd

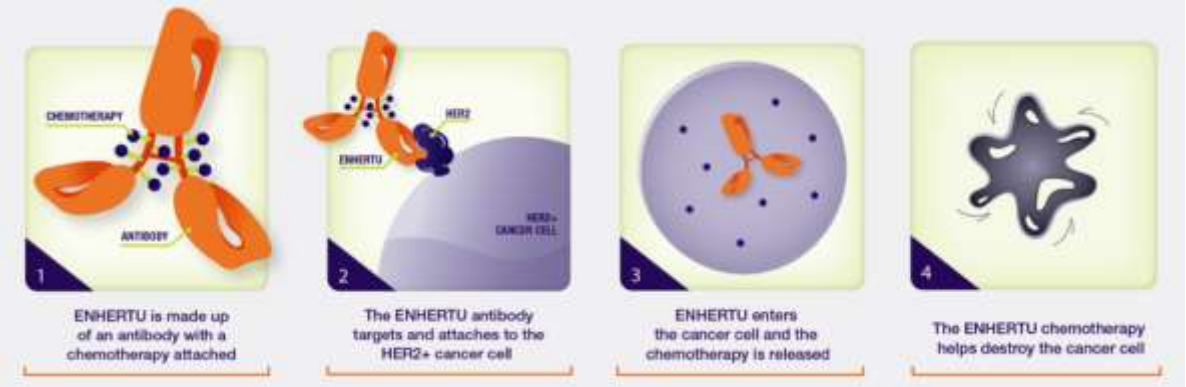


Figure represents the mechanism of action in HER2-positive disease, which is the same for HER2-low.
Abbreviations: HER2, human epidermal growth factor receptor 2..

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No, T-DXd is not intended to be used in combination with any other medicines in this indication.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
T-DXd is given under the supervision of a healthcare professional who has experience in the administration of cancer medicines. It is given intravenously, usually as an infusion into the hand or arm. The first infusion takes about 90 minutes so the clinician can see if there are any side effects or problems.[74] Future infusions should only take about 30 minutes, if the first infusion was well tolerated.[74] It is given to the patient in an outpatient clinic every three weeks, for as long as the patient is benefiting from the drug and does not experience any problems.[74]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

T-DXd has been extensively studied in Phase II and Phase III clinical trials in HER2-positive u/mBC through DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03. The key studies relevant to the HER2-low u/mBC population are DESTINY-Breast04 and DESTINY-Breast06.

DESTINY-Breast04 is a Phase III, multicentre, open-label, randomised, active-controlled clinical trial of T-DXd vs. treatment of physician's choice (TPC) in patients with HER2-low u/mBC who have received one or two lines of prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting.[68] It is the key and only study providing clinical evidence for this NICE appraisal. The study reached its primary completion date in January 2022.

In addition to DESTINY-Breast04, the DESTINY-Breast06 study is an ongoing Phase III, multicentre, open-label, randomised, active-controlled clinical trial of T-DXd vs. investigator's choice chemotherapy (capecitabine, paclitaxel, nab-paclitaxel) in patients with HER2-low/HR-positive u/mBC whose disease has progressed on endocrine therapy in the metastatic setting.[75] This study is currently ongoing and results from the study are not yet available. It is therefore not a key study for this appraisal.

A summary of both trials is provided in **Table 1**.

Table 1: Summary of T-DXd randomised controlled trials in HER2-low u/mBC

Title	Location	Population	Patient group size	Key inclusion and exclusion criteria	Completion dates	References

DESTINY-Breast04
(NCT03734029)
	United States, Austria, Belgium, Canada, China, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Portugal, Russia, Spain, Sweden, Switzerland, Taiwan, United Kingdom	Adults with HER2-low u/mBC, defined as IHC 1+ or IHC 2+/ISH-negative, previously treated with one or two lines of prior chemotherapy in the metastatic setting	In the FAS:
			• T-DXd: 373
			• TPC: 184
				Inclusion criteria:
				• Is the age of the majority in their country
				• Has pathologically documented breast cancer that:
				  ○ Has low HER2 expression defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested)
				  ○ Is HR-positive or HR-negative
				  ○ Has progressed on, and would no longer benefit from, endocrine therapy
				  ○ Has been treated with 1 or 2 prior lines of chemotherapy/ adjuvant in the metastatic setting
				  ○ Was never previously HER2-positive (IHC 3+ or ISH+) on prior pathology testing (per ASCO/CAP guidelines)
				• Has documented radiologic progression (during or after most recent treatment)
				• Has adequate archival tumour samples available or is willing to provide fresh biopsies prior to randomisation for:
				  ○ Assessment of HER2 status
				  ○ Assessment of post-treatment status
				• Has at least one protocol-defined measurable lesion
				• Has protocol-defined adequate cardiac, bone marrow, renal, hepatic and blood clothing functions
					Primary completion date: January 11, 2022
					Estimated study completion date: March 2023
						ClinicalTrials.gov[76]
						Modi et al. 2022[68]

				• Male and female participants of reproductive/childbearing potential, agrees to follow instructions for method(s) of contraception and agrees to avoid preserving ova or sperm for at least 4.5 months after treatment (or longer, per locally approved labels) Exclusion criteria: • Is ineligible for all options in the physician's choice arm • Has breast cancer ever assessed with high-HER2 expression • Has previously been treated with any anti-HER2 therapy, including an antibody drug conjugate • Has uncontrolled or significant cardiovascular disease • Has spinal cord compression or clinically active central nervous system metastases • Has history of (non-infectious) ILD /pneumonitis that required steroids, has current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening • Has any medical history or condition that per protocol or in the opinion of the investigator is inappropriate for the study		

DESTINY-Breast06 (NCT04494425)	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Mexico, Netherlands, Poland, Portugal, Russia, Saudi Arabia, Singapore, Spain, Sweden,	Adults with HER2-low/HR-positive BC whose disease has progressed on ET in the metastatic setting	Estimated enrolment: 850	Inclusion criteria:
				• Patients must be ≥18 years of age
				• Pathologically documented breast cancer that:
				  ○ Is advanced or metastatic
				  ○ Has a history of HER2-low or negative expression by local test, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested) or HER2 IHC 0 (ISH- or untested)
				  ○ Has HER2-low or HER2 IHC >0 <1+ expression as determined by the central laboratory result established on a tissue sample taken in the metastatic setting
				  ○ Was never previously HER2-positive
				  ○ Is documented HR-positive disease in the metastatic setting
				• No prior chemotherapy for advanced or metastatic breast cancer
				• Must have either:
				  ○ Disease progression within 6 months of starting first line metastatic treatment with an endocrine therapy combined with a CDK4/6 inhibitor or
				  ○ Disease progression on at least 2 previous lines of ET with or without a targeted therapy in the metastatic setting. Of note with regards to the ≥2 lines of previous
					Estimated primary completion date: July 31, 2023
					Estimated study completion date: June 19, 2026
						ClinicalTrials.gov[75]

	Taiwan, United Kingdom,			ET requirement: disease recurrence while on the first 24 months of starting adjuvant ET, will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting • Has protocol-defined adequate organ and bone marrow function Exclusion criteria: • Ineligible for all options in the investigator's choice chemotherapy arm • Lung-specific intercurrent clinically significant illnesses • Uncontrolled or significant cardiovascular disease or infection • Prior documented ILD/ pneumonitis that required steroids, current ILD/ pneumonitis, or suspected ILD/ pneumonitis that cannot be ruled out by imaging at screening • Patients with spinal cord compression or clinically active central nervous system metastases • Prior randomisation or treatment in a previous trastuzumab deruxtecan study regardless of treatment arm assignment • Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study during the follow up period of a prior interventional study (pre-screening for this study while a patient is on treatment in another clinical study is acceptable)		

Abbreviations: ASCO/CAP, American Society of Clinical Oncology/ College of American Pathologists; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridisation; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DXd, Trastuzumab deruxtecan; TPC, treatment of physician's choice.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

DESTINY-Breast04

The efficacy of T-DXd in HER2-low u/mBC was established in DESTINY-Breast04, a Phase III, multicentre, open-label, randomised, active-controlled clinical trial of T-DXd vs. TPC in patients with HER2-low u/mBC after one or two lines of prior chemotherapy in the (neo)adjuvant (if recurrence occurred within 6 months) or metastatic setting.

The study objective was to assess the safety and efficacy of T-DXd (100 mg, administered intravenously (IV) at a dose of 5.4 mg/kg every 3 weeks) compared to chemotherapy TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) in patients with HER2-low breast cancer.[68]

The full analysis set (FAS) included all subjects randomised into the study and is the population of relevance to this appraisal as it applies to the full indication of T-DXd in HER2-low (i.e., all patients with HER2-low, irrespective of HR status). Results of the HR-positive cohort of the FAS are also presented below, as the primary efficacy analyses of DESTINY-Breast04 was in this cohort.[68]

DESTINY-Breast04 demonstrated that T-DXd is associated with unprecedented benefits vs. TPC in patients with HER2-low u/mBC:

- The primary endpoint of progression-free survival (PFS) based on blinded independent central review (BICR) in the HR-positive cohort was met. T-DXd patients in the HR-positive cohort were 49% less likely to experience progression or death compared with patients receiving TPC (hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.40, 0.64; p<0.001).[68] Median PFS by BICR in the HR-positive cohort was 10.1 months in the T-DXd arm vs. 5.4 months in the TPC arm.[68]
- Results in the FAS were consistent with those in the HR-positive cohort, with T-DXd demonstrating a 50% lower risk of progression or death compared with TPC (HR: 0.50, 95% CI: 0.40, 0.63; p=0.003).[68] Median PFS by BICR in the FAS was 9.9 months in the T-DXd arm vs. 5.1 months in the TPC arm.[68]
- T-DXd was also associated with improvements over TPC for the key secondary efficacy endpoints of overall survival (OS) in the HR-positive cohort and OS in the FAS.[68]
    - T-DXd patients in the HR-positive cohort were 36% less likely to experience death compared to patients receiving TPC (HR: 0.64; 95% CI: 0.48, 0.86; p=0.003).[68] Median OS in the HR-positive cohort was 23.9 months in the T-DXd arm vs. 17.5 in the TPC arm.[68]
    - T-DXd patients in the FAS were 36% less likely to experience death compared to patients receiving TPC (HR: 0.64; 95% CI: 0.49, 0.84; p=0.001).[68] Median OS in the FAS was 23.4 months in the T-DXd arm vs. 16.8 months in the FAS.[68]
- Exploratory analysis in the HR-negative cohort demonstrated that T-DXd was also associated with an improvement in PFS by BICR and OS compared with TPC.[68]

In addition, a higher proportion of patients treated with T-DXd than TPC (3.5% vs. 1.1% in the FAS) achieved a 'complete response', meaning their tumour could not be seen on imaging.[68] Almost half of patients treated with T-DXd (49.1%) achieved a 'partial response,' meaning their tumour shrank by at least 30%, compared with 15.2% in patients treated with TPC.[68] A higher proportion of patients treated with T-DXd than TPC (87.1% vs. 65.8% in the FAS) also achieved a sustained response (i.e., disease control), meaning treatment with T-DXd led to a complete response, partial response, or stable disease (stable disease means the cancer that is neither decreasing nor increasing in extent or severity).[68] The benefit of T-DXd vs. TPC in terms of response rates was consistent in the HR-positive cohort and HR-negative cohorts.[68]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In DESTINY-Breast04, health-related quality of life (HRQoL) was measured using the EuroQol 5-Dimension 5-level (EQ-5D-5L) questionnaire, the European Organization for Research and Treatment-QoL questionnaire (EORTC QLQ-C30) and the breast cancer specific module (EORTC QLQ-BR45).[77] The EQ-5D-5L is a generic instrument measuring HRQoL across five domains (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). The EORTC QLQ-C30 and QLQ-BR45 are cancer and breast cancer specific questionnaires measuring cancer patients' physical, psychological, and social functions.

Health-related quality-of-life was maintained on treatment with T-DXd across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-30 and EORTC QLQ-BR45) QoL surveys.[77] T-DXd was also associated with a longer time to definitive deterioration in QoL scores (TTDD; 'definitive deterioration' defined as a worsening of 10 points from baseline in the QoL score) vs. TPC across all QoL surveys in the FAS and HR-positive cohorts.[77] For example, in the HR-positive cohort, median TTDD was longer with T-DXd than TPC for the EORTC QLQ-30 global health score (11.4 vs. 7.5 months; HR: 0.69; 95% CI: 0.52, 0.92; p=0.0096).[77]

Disease progression in patients with mBC has a considerable negative impact on the QoL of patients; therefore, delaying disease progression and extending life expectancy are reported to be priorities for patients with mBC and their carers.[78–80] The delayed progression and increased life expectancy with T-DXd vs. TPC is therefore likely to translate into patient and carer QoL benefits that are hard-to-quantify in clinical trials (due to limitations in the measurement of QoL in clinical trials).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, T-DXd can cause side effects, although not everybody experiences them. The safety profile of T-DXd is well-known and well-characterised as it has been studied across a range of BC subtypes and is already used in UK clinical practice in HER2-positive u/mBC.[68,81,82]

In DESTINY-Breast04, most side effects were low grade (mild),[68] and no new side effects of concern were identified in this trial compared to previous studies of T-DXd.[68,81,82] Additionally, the proportion of patients experiencing Grade ≥3[a] side effects during study treatment was lower for T-DXd than TPC (52.6% vs. 67.4%), and the proportion of patients requiring dose reductions due to side effects was also lower for T-DXd than TPC (38.5% vs. 41.9%).[68] Notably, the rate of Grade ≥3 treatment-related side effects was over two times lower with T-DXd than TPC when adjusting for patient years of exposure (0.69 vs 1.82 events per patient year).[68]

Some serious or life-threatening side effects may affect the lungs, heart, or white blood cell count, affecting the patient's ability to fight infection. Serious side effects associated with T-DXd in DESTINY-Breast04 were

[a]**Grade 3 side effect**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living. **Grade 4:** Life-threatening consequences; urgent intervention indicated. **Grade 5:** Death related to side effect

generally of mild or moderate severity and were well managed through the use of established management guidelines.[68] The clinician will check for these problems and may reduce the dose, delay treatment, or completely stop treatment with T-DXd if the side effects are severe.

The most common side effects of T-DXd in DESTINY-Breast04 include[68]:

- Nausea
- Fatigue
- Vomiting
- Hair loss
- Blood tests showing decreased white blood cells
- Constipation
- Blood tests showing increased levels of the liver enzymes such as transaminases
- Decreased appetite
- Pain in muscles and bones
- Blood tests showing decreased platelets

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Life expectancy and QoL in patients with u/mBC are poor, as no curative therapies are available and symptom burden is very high.[36,37] Despite the improvement in outcomes for patients with HER2-positive u/mBC following the introduction of effective HER2-targeted therapies,[9,10] HER2-targeted therapies have so far proven ineffective in HER2-negative u/mBC.

A subset of patients with HER2-negative BC have tumours that express low levels of HER2 (i.e., HER2-low); despite this, currently available HER2-targeted therapies have proven ineffective in this population.[13,14] Given the known survival benefit of HER2-targeted therapies in HER2-positive disease, there remains an opportunity for effective HER2-targeted therapies to improve outcomes in HER2-low u/mBC.

DESTINY-Breast04 is the first ever head-to-head Phase III trial to show a significant benefit of HER2-targeted treatment in HER2-low u/mBC compared with non-targeted chemotherapy.[68] The efficacy results presented in **Section 3e** clearly and robustly demonstrate that T-DXd can delay disease progression and prolong life expectancy considerably compared with current standard of care in the UK.[68] T-DXd also increases the proportion of patients who see their tumours shrink in size, stop growing, or grow more slowly, compared with TPC.[68] Furthermore, the safety of T-DXd in DESTINY-Breast04 was generally manageable and tolerable, and QoL was maintained on treatment with T-DXd.[68,77]

Given that the delayed progression and prolonged survival are valued by patients and caregivers,[78–80] the clear survival benefit of T-DXd vs. TPC may alleviate the substantial burden and impact on families and caregivers of patients with HER2-low u/mBC (although it should be noted that this was not measured in DESTINY-Breast04).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

T-DXd is administered to the patient as an infusion through the vein every three weeks, under the supervision of a healthcare professional in an outpatient clinic.[74] The first infusion can take about 90

minutes to administer, while future infusions take about 30 minutes.[74] While this mode of administration is similar to other treatments for u/mBC, some patients may experience some discomfort and may find it inconvenient to travel to the outpatient clinical every three weeks for infusion.

T-DXd has an acceptable safety profile,[68] but like all medicines it can cause side effects.[74] In DESTINY-Breast04, the frequency of Grade ≥3 side effects was lower with T-DXd than with TPC, but the exact side effects may differ and varies from patient-to-patient. [68] Therefore, as with most cancer therapies, monitoring for certain side effects is required during treatment with T-DXd and may involve visits to the doctor.[74]

Some patients treated with T-DXd may be at risk of:[74]

- A lung disease called interstitial lung disease with symptoms that can include cough, shortness of breath, fever, or other new or worsening breathing problems
- An infection called neutropenia, caused by reduced number of neutrophils (a type of white blood cell). Symptoms can include chills, fever, sores in your mouth, stomach pain or pain when urinating
- A heart problem called decreased left ventricular ejection fraction with symptoms that can include new or worsening shortness of breath, cough, tiredness, swelling of ankles or legs, irregular heartbeat, sudden weight gain, dizziness or unconsciousness

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

For a treatment to be reimbursed by the NHS, the manufacturer must provide an economic model (also called a cost-effectiveness model) to demonstrate that the treatment will provide value for money and is therefore a good use of NHS resources. An overview of the economic model for T-DXd vs. TPC in patients with HER2-low u/mBC is provided below.

How the model reflects the condition

The economic model for this submission uses data from DESTINY-Breast04 and published literature and compares survival, QoL and costs for patients with HER2-low u/mBC receiving T-DXd compared with TPC across a lifetime period. The TPC arm is reflective of standard of care in the NHS as it comprises of single-agent chemotherapies, such as capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel that are used in UK clinical practice.[25,26,59]

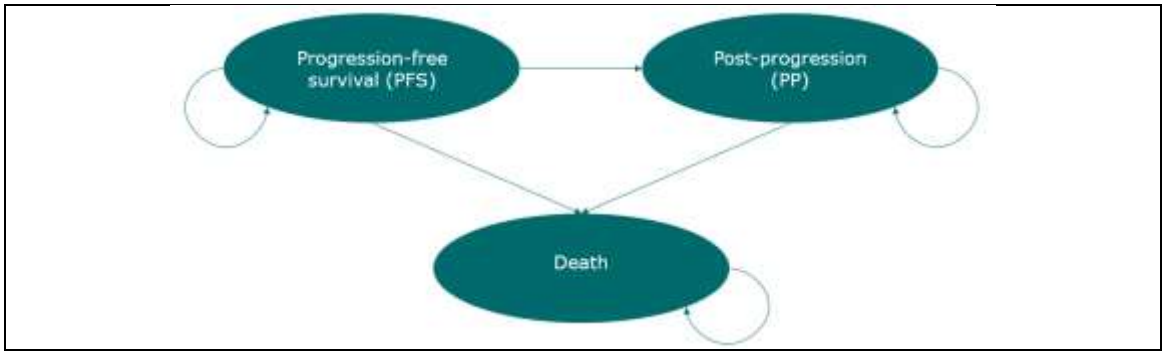
The model consists of three health states to reflect the typical disease course of patients with HER2-low u/mBC:

- Progression-free
- Post-progression
- Death

All patients enter the model in the 'progression-free' health state, which reflects that patients are defined as being progression-free when they first start treatment in clinical practice). Over time, the cancer may worsen (e.g., the number or size of tumours increases). At this point, the patient is no longer considered 'progression-free', and they will move to the 'post-progression' health state in the model. If a patient dies, they are removed from the model and enter the 'death' state (Figure 5). This model structure is very commonly used for modelling cancer, including u/mBC.

Each health state is associated with specific healthcare resource use and costs, survival and QoL (referred to as "utility"). Patients in the 'progression-free' health state feel better, i.e., have higher utility than those in the 'post-progression' health state.

Figure 5: Cost-effectiveness model structure and patient flow



Modelling how much a treatment extends life

T-DXd is expected to delay disease progression and extend the life of patients with HER2-low u/mBC.[68] As discussed in **Section 3e**, the efficacy of T-DXd was demonstrated in DESTINY-Breast04, where T-DXd was associated with a 50% lower risk of progression or death compared with TPC (HR: 0.50, 95% CI: 0.40, 0.63; p=0.003; FAS).[68] In addition, T-DXd was associated with a statistically significant improvements in OS vs. TPC, with a median OS of 23.4 months vs. 16.8 months (HR: 0.64; 95% CI: 0.49, 0.84; p=0.0010; FAS).[68]

Survival is modelled in the economic analysis based on the OS and PFS data observed in DESTINY-Breast04. The median duration of follow-up in the trial was 18.4 months (95% CI: 17.7, 18.9).[68] Beyond the trial follow-up period, the trial data are extrapolated in the economic model using well-established statistical models validated by UK clinical and economic experts.[59]

Modelling how much a treatment improves QoL

As expected for a terminal disease with a high symptom burden, u/mBC has a substantial negative impact on patients' QoL (see **Section 2d** for more details). By delaying disease progression and prolonging survival, T-DXd is expected to significantly improve patient QoL compared with TPC.[68]

The QoL benefit expected with T-DXd is captured in the economic model, where patient QoL varies based on progression status and treatment received. QoL data used for the 'progression-free' health state in the model are calculated directly from data reported in DESTINY-Breast04. HRQoL in the trial was measured using the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-BR45 questionnaires for the patients (see **Section 3f**).[77] The long-term HRQoL data are limited for progressed patients in the trial, so QoL data for the 'progressed' health state in the model are derived from the published literature.[83] The methods used to determine QoL of patients in the model were supported by UK clinical expert opinion.[59] The economic model shows that T-DXd is associated with a modelled QoL benefit compared with TPC.

Modelling how the costs of treatment differ with the new treatment

Costs considered in the model for both treatment arms include treatment costs, monitoring and resource use costs, adverse event (AE) costs, subsequent treatment costs, and terminal care costs. The total costs associated with T-DXd are higher than the total costs with TPC. AE-related costs, subsequent treatment costs, and mortality costs are lower with T-DXd than with TPC, as T-DXd delays progression and prolongs survival of patients, ensuring they remain healthier for longer.[68]

Uncertainty

HER2-low u/mBC has only recently been recognised as a new category of BC in recent European Society for Medical Oncology,[26] American Society of Clinical Oncology,[84] and National Comprehensive Cancer Network [85] clinical guidelines. Therefore, there is a lack of an established treatment pathway in HER2-low u/mBC and there are limited published data on outcomes with standard of care treatments in HER2-low u/mBC specifically.

Every effort has been made to reduce the impact of uncertainties in the economic model, including discussion and validation of the methods and assumptions used with leading UK breast cancer medical oncologists and economic experts.[59] Furthermore, the uncertainty in model assumptions and data sources has been explored through extensive scenario and sensitivity analyses.

Key uncertainties in the model include:

- The long-term OS and PFS outcomes of patients were modelled beyond the trial follow-up period using statistical models validated by UK clinical and economic experts.[59]
- DESTINY-Breast04 had limited long-term HRQoL data for progressed patients, so values used to measure the QoL of 'progressed' patients were derived from published literature.[83]

Cost-effectiveness results

Cost-effectiveness results for T-DXd compared with TPC are presented from **Section B.3.10 in the Company Submission** as a metric known as the incremental cost-effectiveness ratio (ICER), which measures the cost per additional quality-adjusted life year (QALY) with a product vs. a comparator. The QALY is a generic measure of disease burden, with one QALY equivalent to one year of life in perfect health.[86]

The results of the cost-effectiveness analysis indicate that T-DXd prolongs survival and substantially improves the patient's QoL, resulting in greater QALYs compared with TPC. Treatment with T-DXd also leads to additional costs, reflective of its status as a novel and innovative medicine compared with TPC, which comprises non-targeted chemotherapy agents (some of which have been available in the UK for decades).

For more information on the cost-effectiveness results for T-DXd vs TPC, please refer to **Section B.3.10 in the Company Submission**.

Additional factors – End of Life criteria, severity modifier, and innovation

In February 2022, NICE changed the way in which it assesses the value of innovation and improved outcomes for severe conditions with poor life expectancy. Prior to February 2022, it was recognised through the end-of-life (EOL) criteria,[187] and since February 2022, is recognised through the "severity modifier".[2]

T-DXd in HER2-low u/mBC meets the previous NICE EOL criteria:

- **T-DXd is for patients with a short life expectancy (<24 months):** As per the TPC arm in DESTINY-Breast04, median OS with standard of care is just 16.8 months in the FAS (i.e. the population relevant to this appraisal).[68] This is consistent with survival reported in prior studies of single-agent chemotherapies in a similar setting in HER2-negative u/mBC (any HR-status: HR-positive, HR-negative, HR-unspecified), where life expectancy is 6.7–20.7 months.[27–34,87–91]
- **T-DXd extends life by over 3 months compared with current standard of care:** In the FAS of DESTINY-Breast04, T-DXd statistically significantly extended median OS by 6.6 months vs. TPC (median OS: 23.4 vs. 16.8 months; p=0.0010).[68]

Treatments that extend life at the end of life would have been appraised with a willingness-to-pay threshold of £50,000/QALY under the previous EOL criteria.

As part of its Methods and Process update in 2022, NICE replaced the EOL criteria with the severity modifier.[92] The severity modifier recognises the value that society places on the most severe and/or life-limiting diseases by determining the number and/or proportion of QALYs remaining in patients treated with current standard of care, compared to age- and sex-matched members of the general UK population.

Appraisals may meet the criteria for one of two severity modifiers: the 1.2x severity modifier or the 1.7x severity modifier. The 1.7x severity modifier suggests a more severe condition than the 1.2x severity modifier. Application of the 1.2x or 1.7x severity modifier means that the incremental QALY gain with T-DXd is multiplied by a factor of 1.2 or 1.7, respectively. Whilst it is acknowledged that the severity modifier is to

be applied as a QALY weight, in practical terms, the impact of the 1.2x severity modifier can also be thought of as increasing NICE's willingness-to-pay threshold from the conventional £30,000/QALY to £36,000/QALY. The 1.7x severity modifier effectively means a willingness-to-pay threshold of £51,000/QALY (similar to the £50,000/QALY threshold that would have applied under the previous EOL criteria).

This appraisal is not likely to qualify for the 1.7x severity modifier according to NICE's new criteria. Therefore, despite T-DXd meeting the previous EOL criteria, it is expected to be appraised at a significantly lower Willingness To Pay threshold under the new NICE methods and processes. The replacement of the previous EOL criteria with the severity modifier will therefore have a direct impact on this appraisal.

As stated in **Section 2c**, patients with HER2-low u/mBC are currently treated via HER2-negative pathways, largely comprising non-targeted chemotherapies with poor efficacy. In order to capture the full extent of the severity of HER2-low u/mBC, Daiichi Sankyo considers that additional flexibilities in the form of a QALY weight of 1.7x, equivalent to the previous EOL, should be applied in decision-making. This would appropriately reflect the severity of the condition based on the poor survival outcomes in HER2-low u/mBC with current standard of care.

Additionally, Daiichi Sankyo would like to reiterate the substantial innovation of T-DXd in this indication. As highlighted by the Innovation Passport, T-DXd is an innovative therapy and is the first and only HER2-targeted treatment to show a statistically significant efficacy benefit over non-targeted chemotherapy in patients with HER2-low u/mBC providing substantial improvement quality and quantity of life.[68] T-DXd is therefore a step-change that will transform the care of patients with HER2-low u/mBC. This was reflected by comments from UK clinical experts, who informed Daiichi Sankyo that there is a high demand for T-DXd to be made available in HER2-low u/mBC.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

T-DXd is an innovative treatment that is the first effective HER2-targeted treatment for patients with HER2-low u/mBC

Prior to T-DXd, HER2-targeted therapies have failed to demonstrate superiority over chemotherapy in patients with HER2-low u/mBC. [13,14] Despite the improvement in outcomes for patients with HER2-positive u/mBC following the introduction of HER2-targeted therapies,[9,10] there remains an unmet need for an effective HER2-targeted treatment that can reduce the risk of disease progression or death and improve response rates in patients with HER2-low u/mBC who have previously been treated with chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting.

As detailed in **Section 3e**, clinical evidence from DESTINY-Breast04 demonstrates the unprecedented survival benefits that T-DXd provides compared with non-targeted chemotherapy in the HER2-low population.[68] As the first and only treatment approved for HER2-low u/mBC specifically, T-DXd represents a step-change and will transform the pathway of care for HER2-low u/mBC. The innovative nature was recognised by the MHRA, who awarded T-DXd an Innovation Passport in May 2022.

QALY benefits not captured in the economic model that also need to be considered:

The EQ-5D-5L QoL survey may not be sensitive to capture important but hard-to-quantify benefits of treatment, such as patient optimism and hope from receiving an effective, targeted treatment. Additionally, it may not detect the subtle QoL benefits, such as impact of treatment on lifestyle and daily activities.

Most patients with u/mBC are of working age, yet the cost per QALY measure does not capture the benefits of a treatment to wider society in terms of employment and work productivity. By delaying progression vs. non-targeted chemotherapy, T-DXd may delay the need for an employed patient to retire, reduce the number of sick days, and/or increase patient productivity while at work.

Caregivers of patients with u/mBC are also impacted by the disease (**Section 2d**), which is not captured in the QALY calculation. A treatment that allows patients to live healthier lives for longer than current standard of care is likely to improve caregiver QoL and may reduce caregiving demands, in turn potentially improving work productivity. These benefits are not captured in the economic model.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues are anticipated for T-DXd in this indication. T-DXd should be made available to all eligible patients in the UK.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• What is HER2-low? Available here: https://www.bcrf.org/blog/her2-low-breast-cancer-explained/ • About HER2 status. Available here: https://www.breastcancer.org/pathology-report/her2-status • AstraZeneca press release 2022. Available here: https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html • DESTINY-Breast04 clinical trial. Available here: https://www.nejm.org/doi/full/10.1056/NEJMoa2203690 • Information for patients. Available here: https://www.enhertu.com/ • NICE severity modifier information. Available here: https://vitaccess.com/blogs/nice-severity-modifier-not-all-qalys-are-created-equal/#:~:text=NICE%20is%20now%20introducing%20a,multiplier%20of%201.2%20or%201.7. Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **EuroQol-5 Dimensions 5-Levels (EQ-5D-5L):** EQ-5D-5L is a tool to measure the QoL of a person, based on their response to questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D is NICE's preferred QoL measure and is scored from a scale of 0–1, with 1 denoting perfect health.
- **Human epidermal growth factor receptor 2 (HER2):** HER2 proteins are receptors present on breast cells. HER2 receptors help control how a healthy breast cell grows, divides, and repairs. When the HER2 gene makes too many copies of itself, the breast cells grow and divide in an uncontrolled way.
- **Incremental cost-effectiveness ratio (ICER):** The incremental cost-effectiveness ratio is calculated by dividing the difference in total costs by the difference in health outcomes for an intervention (e.g. T-DXd) vs. a comparator (e.g. non-targeted chemotherapy). It provides a value of the extra cost per unit of the health effect.
- **Metastatic:** Spread of cancer from the primary site to other parts of the body.
- **Open-label study**: A type of study in which both the health providers and the patients are aware of the drug or treatment being given. In the DESTINY-Breast04 study, it was not possible to "blind" patients or study investigators to the treatment being given due to different modes of administration. Other measures were taken (e.g., blinded review of the scans to determine disease progression) to minimise any potential bias of an open-label design.
- **Overall response rate (ORR):** ORR is the percentage of patients whose cancer shrinks (known as a "partial response") or completely disappears (known as a "complete response") after treatment.
- **Overall survival (OS):** OS is the length of time that patients diagnosed with a disease remain alive from the date of diagnosis or the start of treatment. In DESTINY-Breast04, OS was measured from date of randomisation to date of death (any cause).
- **Prognosis:** A probable course or outcome of a disease.
- **Progression-free survival (PFS):** PFS is the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse. PFS is technically defined in the DESTINY-Breast04 study as the time from the date of randomisation to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause.
- **Quality-adjusted life year (QALY):** The QALY is a standardised unit of measure of the state of health of a person or group in which remaining years of life are adjusted to reflect the QoL during those remaining years of life. One QALY is equal to 1 year of life in perfect health.
- **Randomised controlled trial (RCT)**: An RCT is a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention.
- **Real-world data (RWD):** RWD are data collected in patients treated with a drug outside the context of a clinical trial.
- **Severity modifier:** The severity modifier is a multiplication factor (1.2x or 1.7x) applied in NICE appraisals to the QALY gain for therapies for particularly severe diseases. It was introduced as part of the NICE 2022 methods update[92] to capture the added value that society places on products that provide QoL and/or survival benefits for particularly severe and/or life-limiting diseases. The severity modifier is quantified by comparing the QALY shortfall in people with vs. without a given condition.
- **Time to definitive deterioration (TTDD):** TTDD in DESTINY-Breast04 was the time from randomisation to the date when a definitive QoL score deterioration event was first recorded. For example, for the EQ-5D Visual Analog Scale, a definitive deterioration was defined as a reduction in score by ≥10 points (out of a total score of 100 points).
- **Utility:** The measure of the preference or value that an individual or society gives a particular health state. Utility is usually scored from 0–1, with 1 reflecting perfect health.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Clarification questions

April 2023

File name	Version	Contains confidential information	Date
ID3935 T-DXd HER2-low EAG CQs_FINAL_ 31Aug2023_[FullyRedacted]	2.0	Yes	31 August 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature searching and systematic literature review

A1. Company submission (CS) Sections B.2.1 and B.3.1. The EAG notes that the searches for both systematic literature reviews (SLRs) were conducted in February 2022 and that only "hand searches" have been conducted to identify more recent evidence. Please provide additional details on how these searches were run (including full details of sources; terms used; any other relevant information that would be required for them to be replicated).

At the time of the initial submission, a full update of the systematic literature review (SLR) was ongoing. The original SLR (25 February 2022) did not identify any publications in the main databases (Pubmed, Embase, Cochrane) related to studies in human epidermal receptor 2 (HER2)-low unresectable or metastatic breast cancer (u/mBC) population. The SLR grey literature searches did, however, identify a published conference abstract reporting results for sacitizumab govitecan (SG) vs. treatment of physician's choice (TPC) in triple-negative breast cancer (TNBC; i.e., HER2-negative/hormone receptor negative [HR-negative] u/mBC), including a post hoc analysis in HER2-low patients.

In addition to the ASCENT study, the company published results from the DESTINY-Breast04 study between February 2022 and February 2023, which was after the date of the original SLR. Given the relevance of the DESTINY-Breast04 study and the potential relevance of the ASCENT study, the company conducted hand searches as an interim solution to pragmatically identify publications relevant to these studies so that the most up-to-date evidence could be considered in the company submission.

The company can now confirm that a full SLR update has been completed.[1] The SLR searches were re-run to identify articles published between 25 February 2022 (date of the original SLR) and 30 January 2023 (date of the SLR update). The SLR update was conducted using the same methodology as the original SLR.

For more information on the SLR update (30 January 2023), please refer to the clinical and economic SLR update reports provided in the PDF reference pack associated with these responses.[1,2] Please also see the company response to A3, where we detail if any additional potential relevant studies beyond DESTINY-Breast04 and ASCENT were identified in the hand search update.

A2. PRIORITY. CS Section B.2.1. Please clarify why the SLR search was not simply re-run to update the SLR for the missing year (25th Feb 2022 to 13th Feb 2023).

Please see the company response to A1. A full SLR update (30 January 2023) has now been completed and the associated clinical and economic SLR update reports are provided in the PDF reference pack associated with these responses.[1,2]

A3. PRIORITY. CS Section B.2.1. It appears that the hand searches – unlike the SLR search conducted to 25th February 2022 – only looked for publications related to ASCENT and for studies of trastuzumab deruxtecan (T-DXd) in the relevant population, and not all studies of the relevant population, as per the SLR eligibility criteria (Appendix D Table 4 and Appendix G Table 36). Please clarify if this is correct and, if so, whether it means that additional studies published since February 2022, and potentially relevant for an indirect

treatment comparison/matching-adjusted indirect comparison (ITC/MAIC), like ASCENT, might have been missed.

As per the company response to question A1, the company can confirm that the hand searches only looked for publications related to ASCENT (for SG in HER2-negative/HR-negative u/mBC) and DESTINY-Breast04 (for T-DXd in HER2-low u/mBC) and did not look for all studies in the relevant population as per the SLR eligibility criteria.

A full SLR update (30 January 2023) has now been completed,[1] which searched for all studies in the relevant population, and the updated SLR reports are provided in the PDF reference pack associated with these responses. The SLR update identified the following studies relevant to in-scope comparators for this appraisal: DESTINY-Breast04 (T-DXd vs TPC) and ASCENT (SG vs TPC). The SLR update did not identify any new publications related to these studies that were not captured in the additional hand searches conducted by the company in the initial submission.

In addition to ASCENT and DESTINY-Breast04, the SLR update identified the TROPiCS-02 study, a Phase III study of SG versus TPC in patients with HER2-negative/HR-positive mBC who have received 2–4 prior lines of chemotherapy.[3] TROPiCS-02 was conducted in a HR-positive population, meaning that the SG arm is not relevant to the decision problem for this appraisal as SG is currently reimbursed by NICE in HR-negative patients only (TA819), and listed by NICE in the final scope of this appraisal as a comparator in the HR-negative subgroup only.[4]

However, the TPC comparator arm of TROPiCS-02 includes non-targeted chemotherapy agents (e.g., capecitabine) that are used or reimbursed in HER2-negative/HR-positive (i.e., in-scope) patients in the UK.[3] The comparator arm of TROPiCS-02 therefore provides useful supportive information related to the generalisability of the outcomes for the TPC arm in the HR-positive cohort of DESTINY-Breast04. In the HR-positive cohort, the DESTINY-Breast04 TPC arm performs slightly better than the TROPiCS-02 TPC arm for both median progression free survival (PFS; 5.4 months vs. 4.0 months, respectively) and median overall survival (OS; 17.5 months vs. 12.3 months, respectively).[3,5]

These differences in survival outcomes are likely due to differences in the trial eligibility criteria and patient baseline characteristics. Most notably, the TROPiCS-02 study included more heavily pretreated patients than DESTINY-Breast04; TROPiCS-02 enrolled patients who had received 2–4 prior lines of chemotherapy in the metastatic setting,[3] DESTINY-Breast04 enrolled patients who had received 1–2 prior lines of chemotherapy in the metastatic setting.[5] The median number of prior lines of chemotherapy in the metastatic setting was therefore lower in DESTINY-Breast04 versus TROPiCS-02 (1 vs 3), and over 55% of the TROPiCS-02 trial population had received ≥3 prior lines of chemotherapy compared with 1% in DESTINY-Breast04.[3,6] It should be noted that this 1% of patients in DESTINY-Breast04 Breast04 represents a protocol deviation, as the eligibility criteria in DESTINY-Breast04 limited patients to no more than two prior lines of chemotherapy in the recurrent or metastatic setting.[6]

A4. CS Appendices D.1.1.1 and G.1.1.1. Please explain the rationale for limiting all searches to evidence published since 1 January 2011.

The search was limited to 2011 to capture all published evidence from the last 10 years (11 years when including the SLR update conducted on 30 January 2023). This time horizon was adopted to capture the most recent relevant studies. Additionally, because HER2-low u/mBC is a new indication, it was not anticipated that searching before this date would yield any additional relevant comparative evidence.

A5. CS Appendices D and G. The PRISMA-S guidance on reporting of searches for systematic reviews recommends that search strategies include the number of results retrieved by each line. These details are missing from the strategies reported - please provide a full version including these details for maximum transparency.

Full versions of the search strategies for the initial clinical SLR and economic SLR (25 February 2022) and the SLR updates (30 January 2023), including the number of results retrieved by each line of the search string, are provided in the following files in the PDF reference pack.

- T-DXd in HER2-low_Clinical SLR search strategy_initial SLR and SLR update[7]

- T-DXd in HER2-low_Economic SLR search strategy_initial SLR and SLR update[8]

A6. CS Appendices D and G. Please provide details of the source for the search filters used to identify eligible studies for each SLR - including a citation to any published studies validating their accuracy when used for this purpose.

While the search filters used are not derived from a published study that validates their accuracy, the entire search string is broadly based on the validated sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in PubMed. The search strategies were thoroughly reviewed by a librarian from the University Medical Center Groningen and were deemed to be accurate and highly inclusive. The strategy employed for the search is also broader than the Cochrane strategy.

Therefore, the company is confident that the search strings have captured all evidence relevant to the decision problem. Similar search filters were applied for the SLRs in TA862 (T-DXd for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments).[9]

A7. CS Section 2.1. Please clarify which of the following statements are correct? 'These hand searches identified two publications related to DESTINY-Breast04 ..', and, 'DESTINY-Breast04, which was reported in no publications in the original SLR (25 February 2022) and in three publications in the hand searches (13 February 2023).'.

The company acknowledges the typographical error and inconsistency in reporting of the number of DESTINY-Breast04 publications from the hand searches. The hand searches identified four publications related to DESTINY-Breast04:

- Modi S et al. 2022. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. NEJM 2022;387(1):9-20. doi: 10.1056/NEJMoa2203690.
- Modi S et al. 2022. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a

randomized, phase 3 study. J Clin Oncol 40, 2022 (suppl 17; abstr LBA3). DOI: 10.1200/JCO.2022.40.17_suppl.LBA3

- Harbeck N et al. 2022. Trastuzumab deruxtecan vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Subgroup analyses from DESTINYBreast04. Abstract #P1-11-01. Presented at the San Antonio Breast Cancer Symposium, 6 December 2022.

- Ueno N et al. Patient-reported outcomes (PROs) from DESTINY-Breast04, a randomized phase 3 study of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low metastatic breast cancer (MBC). Ann Oncol. 2022;33(suppl 7):217O. doi:10.1016/annonc/annonc1040

The SLR update (30 January 2023) has now been completed and identified no new publications related to DESTINY-Breast04 other than those identified in the hand searches. The SLR update report is available in the reference pack.

A8. CS Appendix D.1.2. Please provide more details on what the 'grey literature' search consisted of (sources, dates etc.).

The grey literature search encompassed systematic screening of published abstracts from the following relevant conferences:

- American Society of Clinical Oncology (ASCO) Breast Cancer Symposium
- European Society for Medical Oncology (ESMO)
- ESMO breast cancer
- European Breast Cancer Conference (EBCC)
- San Antonio Breast Cancer Symposium (SABCS)
- Japan Society of Clinical Oncology Annual meetings (JSCO)

This search covered all held conferences from the list above between 1 July 2020 and 30 December 2022. The company anticipated that any high-quality publications from conferences before 2020 would have been published as a peer-reviewed

journal article in the intervening period and hence would have been captured in the main database search. This is a typical approach for identifying relevant clinical evidence for health technology assessment (HTA) from conferences.

Searches were conducted in two phases. In the first phase, abstract books were screened by title and included based on the criteria “HER2”, "Triple-negative” and “breast cancer”. In the second phase, the abstracts were screened with the same PICOS criteria that were used for the main database search.

Additionally, searches were conducted in the clinicaltrials.gov and the World Health Organisation (WHO) international clinical trials registry platforms. The clinicaltrials.gov website was searched by using the search terms “HER2 negative”, “HER2 low”, “metastatic”, and “breast cancer”, and searches were conducted on 23 August 2022 (Initial SLR) and 20 February 2023 (SLR update). The WHO register was searched using the same search terms on 19 August 2022 (Initial SLR) and 24 February 2023 (SLR update).

The databases of the following HTA bodies were also searched using the search terms “HER2”, “Triple negative”, and “metastatic breast cancer”:

- NICE (UK)
- Canadian Agency for Drugs and Technologies in Health (CADTH; Canada)
- Medical Services Advisory Committee (MSAC; Australia)

Searches in these databases were conducted on 25 August 2022 (Initial SLR) and 28 February 2023 (SLR update).

Finally, the bibliographies of SLR and meta-analyses publications that were retrieved from the main database searches were searched to identify potentially relevant individual studies.

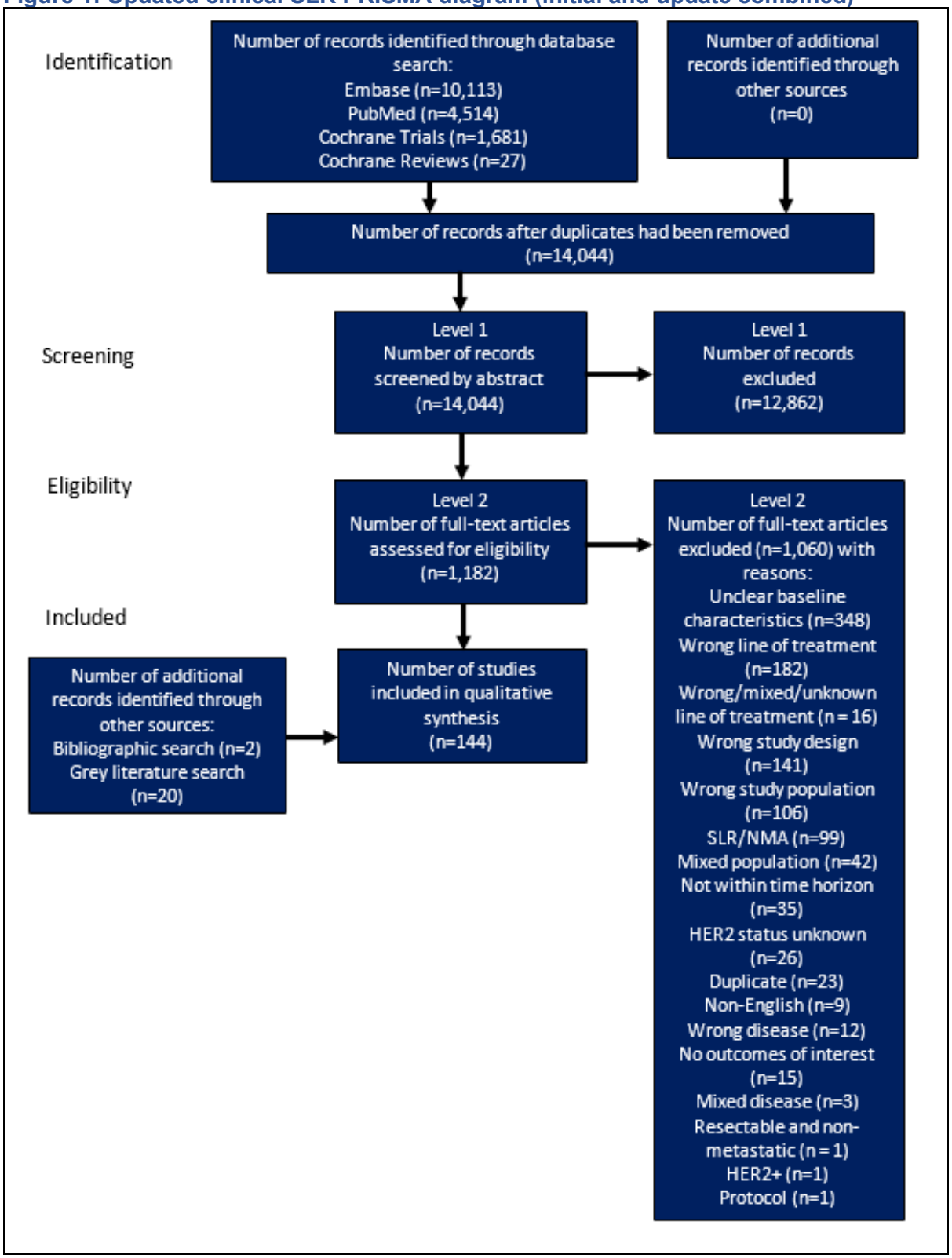
All grey literature articles were reviewed by two independent reviewers and assessed with the same PICOS criteria used for the main database searches. The Initial SLR and SLR update used the same methodologies.

A9. CS Appendix D Figure 1. Please clarify why the details and results from the updated hand searches are not recorded in the PRISMA flowchart.

As stated in response to A1, the hand search updates were conducted as a pragmatic interim solution while the full SLR update was ongoing. The full SLR update (30 January 2023) has now been completed and the updated SLR reports are provided in the PDF reference pack associated with these clarification responses.[1,2]

Figure 1 displays the updated PRISMA diagram of evidence identified in the initial clinical SLR (25 February 2022) combined with the updated (30 January 2023) clinical SLR.

Figure 1: Updated clinical SLR PRISMA diagram (initial and update combined)



Abbreviations: HER2, human epidermal growth factor receptor 2; NMA, network meta-analysis; SLR, systematic literature review.

A10. CS Appendix D Table 5. Please clarify why the table lists only the RCTs (n=23) identified by the original SLR search (to 25th Feb 2022), rather than the full list of included studies satisfying the eligibility criteria (n=97).

The company acknowledges that Appendix D Table 5 should have included the full list of included studies satisfying the eligibility criteria (N=97) rather than just the included RCTs (N=23). This was an error in the original submission.

Please see **Table 1, Table 3** and **Table 5** for study details of the 23 RCTs, 63 non-RCTs and 11 grey literature studies included from the Initial SLR search.

As the full SLR update (30 January 2023) has now been completed, study details of included articles published between 25 February 2022 and 30 January 2023 are provided in **Table 2**, **Table 4** and **Table 6**.

Table 1: Initial clinical SLR (25 February 2022) | Included RCTs (N=23)

Author	Study ID	Trial name; Phase	Journal	Title
Diéras et al. 2011	NCT01045305	NR; Phase II	Cancer Research	P3-16-08: A Phase 2, Randomized Open-Label Study of Iniparib, Administered Either Weekly or Twice-Weekly in Combination with Gemcitabine Plus Carboplatin in Patients with mTNBC
O'Shaughnessy et al. 2015	NCT00938652	NR; Phase II	Journal of Clinical Oncology	Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer
Baselga et al. 2017	NCT01234337	RESILIENCE; Phase III	Clinical Breast Cancer	RESILIENCE: Phase III Randomized, Double-Blind Trial Comparing Sorafenib With Capecitabine Versus Placebo With Capecitabine in Locally Advanced or Metastatic HER2-Negative Breast Cancer
Malorni et al. 2018	NCT02549430	TREnd; Phase II	Annals of Oncology	Palbociclib as single agent or in combination with the endocrine therapy received before disease progression for estrogen receptor-positive, HER2-negative metastatic breast cancer: TREnd trial
Brufsky et al. 2011	NR	RIBBON-2; Phase III	Journal of Clinical Oncology	RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy for Second-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer
Vahdat et al. 2019	NCT01997333	METRIC; Phase IIb	Cancer Research	Abstract P6-20-01: METRIC: A randomized international phase 2b study of the antibody-drug conjugate (ADC) glembatumumab vedotin (GV) in gpNMB-overexpressing, metastatic, triple-negative breast cancer (mTNBC)
Turner et al. 2021	NCT01905592	BRAVO; Phase III	Clinical Cancer research	Niraparib for advanced breast cancer with germline BRCA1 and BRCA2 mutations: the EORTC 1307-BCG/BIG5-13/TESARO PR-30-50-10-C BRAVO study
Bardia et al. 2021	NCT02574455	ASCENT; Phase III	Annals of Oncology	Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer
Bardia et al. 2021	NCT02574455	ASCENT; Phase III	Lancet Oncology	Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer
Winer et al. 2021	NCT02555657	KEYNOTE-119; Phase III	Lancet Oncology	Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial
Huang et al. 2019	NCT01516307	NR; Phase II	Journal for Immunotherapy of Cancer	Globo H-KLH vaccine adagloxad simolenin (OBI-822)/OBI-821 in patients with metastatic breast cancer: phase II randomized, placebo-controlled study
Claessens et al. 2020	EU Clinical Trials Register=2010-021519-18	Stop&Go; Phase III	ACTA Oncologica	Secondary analyses of the randomized phase III Stop&Go study: efficacy of second-line intermittent versus continuous chemotherapy in HER2-negative advanced breast cancer

Author	Study ID	Trial name; Phase	Journal	Title
Im et al. 2020	NCT02000622	OlympiAD; Phase III	Scientific Reports	Olaparib monotherapy for Asian patients with a germline BRCA mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis
Decker et al. 2020	EudraCT no.: 2013–005329-22.	IMPROVE; Phase IV	BMC cancer	Final results from IMPROVE: a randomized, controlled, open-label, two-arm, cross-over phase IV study to determine patients' preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab in advanced HR-positive, HER2-negative breast cancer
Decker et al. 2019	NCT01520103	VicTORia; Phase II	Breast Cancer Res Treat	VicTORia: a randomised phase II study to compare vinorelbine in combination with the mTOR inhibitor everolimus versus vinorelbine monotherapy for second-line chemotherapy in advanced HER2-negative breast cancer
Vahdat et al. 2021	NCT01997333	METRIC; Phase IIb	Nature Partner Journals Breast Cancer	Glembatumumab vedotin for patients with metastatic, gpNMB overexpressing, triple-negative breast cancer ("METRIC"): a randomized multicenter study
Park et al. 2019	NCT01501669	PROCEED; Phase III	Cancer Research Treatment	Randomized Open Label Phase III Trial of Irinotecan Plus Capecitabine versus Capecitabine Monotherapy in Patients with Metastatic Breast Cancer Previously Treated with Anthracycline and Taxane: PROCEED Trial (KCSG BR 11-01)
Yardley et al. 2015	NCT01156753	EMERGE Phase II	Journal of Clinical Oncology	EMERGE: A Randomized Phase II Study of the Antibody Drug Conjugate Glembatumumab Vedotin in Advanced Glycoprotein NMB–Expressing Breast Cancer
O'Shaughnessy et al. 2014	NCT00938652	NR; Phase III	Journal of Clinical Oncology	Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer
Schwartzberg et al. 2013	NCT00493636	AC01B07; Phase IIb	Clin Cancer Res	Sorafenib or Placebo with Either Gemcitabine or Capecitabine in Patients with HER-2–Negative Advanced Breast Cancer That Progressed during or after Bevacizumab
Brufsky et al. 2012	NR	RIBBON-2 trial; Phase III	Breast Cancer Research and Treatment	Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial
Baselga et al. 2012	EudraCT ID: 2007-000290-32	SOLTI-0701; Phase II	Journal of Clinical Oncology	Sorafenib in combination with capecitabine: an oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer
Decker et al. 2017	NCT01320111	PASO; Phase II	BMC cancer	A randomized phase II study of paclitaxel alone versus paclitaxel plus sorafenib in second- and third-line treatment of patients with HER2-negative metastatic breast cancer (PASO)

Table 2: Clinical SLR update (30 January 2023) | Included RCTs (N=20)

Author	Study ID	Trial name; Phase	Journal	Title
Bailleux et al. 2023	NCT02585388	CHEOPS; Phase II	Breast Cancer	CHEOPS trial: a GINECO group randomized phase II assessing addition of a non-steroidal aromatase inhibitor to oral vinorelbine in pre-treated metastatic breast cancer patients
Li et al. 2022	NCT03254654	NAN; Phase II	Breast Cancer	Apatinib plus vinorelbine versus vinorelbine for metastatic triple-negative breast cancer who failed first/second-line treatment: the NAN trial
Weide et al. 2022	NCT02574455	ASCENT; Phase III	Oncology Research and Treatment	Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study
Rugo et al. 2022	NCT03901339	TROPiCS-02; Phase III	Journal of Clinical Oncology	Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer
Schmid et al. 2022	NCT03901339	TROPiCS-02; Phase III	Annals of Oncology	Sacituzumab govitecan (SG) efficacy in hormone receptor positive/human epidermal growth factor receptor 2-negative (HR+/HER2e) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study
Rugo et al. 2022	NCT03901339	TROPiCS-02; Phase III	Annals of Oncology	Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HRD/HER2- metastatic breast cancer (mBC)
Modi et al. 2022	NCT03734029	DESTINY-Breast04; Phase III	Journal of Clinical Oncology	Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study.
Sideras et al. 2022	NCT01086605	NR; Phase II	The Oncologist	Randomized Phase II Study of Two Doses of Pixantrone in Patients with Metastatic Breast Cancer (NCCTG N1031, Alliance)
Tan et al. 2022	NCT03018080	PePPy; NR	Cancer Research	A pilot study of paclitaxel plus pembrolizumab in patients with metastatic HER2-negative breast cancer (PePPy)
Lee et al. 2022	NR	KCSG-BR15-17; Phase II	Cancer Research	Abstract P1-16-01: Pemetrexed plus vinorelbine versusvinorelbine monotherapy in patients with metastaticbreast cancer: A randomized, open-label, multicenter,phase II trial (KCSG-BR15-17)
Cortés et al. 2022	NCT02574455	ASCENT; Phase III	Cancer Research	Abstract P5-16-15: Post-progression therapy outcomes in patients (pts) from the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC)
Kaufman et al. 2022	NR	FORTRESS; Phase III	Cancer Research	Abstract PD13-01: Balixafortide (a CXCR4antagonist)+eribulin versus eribulin alone in patients withHER2 negative, locally recurrent or metastatic breastcancer: An international, randomized, phase 3 trial(FORTRESS)
Loibl et al. 2022	NCT02574455	ASCENT; Phase III	American Association for	Assessment of health-related quality oflife by clinical response from the phase 3 ASCENT study inmetastatic triple-negative breast cancer (mTNBC)

			Cancer Research	
Carey et al. 2022	NCT02574455	ASCENT; Phase III	American Association for Cancer Research	Assessment of sacituzumab govitecan(SG) in Black patients (pts) from the phase 3 ASCENT study inmetastatic triple-negative breast cancer (mTNBC)
Modi et al. 2022	NCT03734029	DESTINY-Breast04; Phase III	The New England Journal of Medicine	Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer
Carey et al. 2022	NCT02574455	ASCENT; Phase III	Npj Breast Cancer	Sacituzumab govitecan as second-line treatment for metastatic triple-negative breast cancer—phase 3 ASCENT study subanalysis
O'Shaughnessy et al. 2022	NCT02574455	ASCENT; Phase III	Breast Cancer Research and Treatment	Analysis of patients without and with an initial triple-negative breast cancer diagnosis in the phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer
Hamilton et al. 2022	NCT02747004	nextMonarch; Phase II	Breast Cancer Research and Treatment	nextMONARCH Phase 2 randomized clinical trial: overall survival analysis of abemaciclib monotherapy or in combination with tamoxifen in patients with endocrine-refractory HR +, HER2– metastatic breast cancer
Loibl et al. 2022	NCT02574455	ASCENT; Phase III	European Journal of Cancer	Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer
Rugo et al. 2022	NCT02574455	ASCENT; Phase III	NPJ Breast Cancer	Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer

Table 3: Initial clinical SLR (25 February 2022) | Included non-RCTs (N=63)

Author	Study ID	Trial name; Phase	Journal	Title
Zhang et al. 2021	NCT02684266	NR; Phase I	Biomarker Research	A phase 1 study of dalpiciclib, a cyclin dependent kinase 4/6 inhibitor in Chinese patients with advanced breast cancer
Yuan et al. 2020	NCT02971761	NR; Phase II	The Oncologist	A Phase II Clinical Trial of Pembrolizumab and Enobosarm in Patients with Androgen Receptor-Positive Metastatic Triple-Negative Breast Cancer
Francisco-Anderson et al. 2021	NCT03775850	NR; Phase I/II	Cancer Res	A phase I/II clinical trial of EDP1503 with pembrolizumab for triple-negative breast cancer
Gatti-Mays et al. 2020	NCT02203513	NR; Phase II	The Oncologist	A Phase II Single Arm Pilot Study of the CHK1 Inhibitor Prexasertib (LY2606368) in BRCA Wild-Type, Advanced Triple-Negative Breast Cancer

Xu et al. 2020	NCT01441947	NR; Phase II	The Oncologist	A Phase II Trial of Cabozantinib in Hormone Receptor-Positive Breast Cancer with Bone Metastases
Bedard et al. 2020	NCT03568422	NR; Phase Ib	Annals of Oncology	A phase Ib trial of CFI-402257 in combination with weekly paclitaxel in patients with advanced HER2-negative (HER2-) breast cancer (aBC)
Diamond et al. 2018	NCT01639248	NR; Phase II	Breast Cancer Res	A phase II clinical trial of the Aurora and angiogenic kinase inhibitor ENMD-2076 for previously treated, advanced, or metastatic triple-negative breast cancer
Blum et al. 2015	NCT00580112	NR; Phase II	Breast Cancer Res Treat	A phase II trial of trabectedin in triple-negative and HER2-overexpressing metastatic breast cancer
Li et al. 2015	NCT01658033	NR; Phase II	Plos One	Bevacizumab in Combination with Modified FOLFOX6 in Heavily Pretreated Patients with HER2/Neu-Negative Metastatic Breast Cancer: A Phase II Clinical Trial
Gartner et al. 2012		NR; Phase II	Breast Cancer Res Treat	A phase II study of 17-allylamino-17-demethoxygeldanamycin in metastatic or locally advanced, unresectable breast cancer
Liu et al. 2013	NCT01116648	NR; Phase I	European journal of cancer	A Phase 1 trial of the PARP inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer
Smith et al. 2020	NCT02481050	NR; Phase II	Clinical Breast Cancer	Phase II Study of Eribulin Mesylate Administered Biweekly in Patients With Human Epidermal Growth Factor Receptor-2-negative Metastatic Breast Cancer
Pernas et al. 2018	NCT01837095	NR; Phase I	The Lancet Oncology	Balixafortide plus eribulin in HER2-negative metastatic breast cancer: a phase 1, single-arm, dose-escalation trial
Awada et al. 2016	NR	NR; Phase II	Clinical Breast Cancer	Phase II Study of Trabectedin in Patients with Hormone Receptor Positive, HER2 Negative, Advanced Breast Carcinoma, According to The Expression of The Xeroderma Pigmentosum G Gene
Leone et al. 2019	NCT02260531	NR; Phase II	Breast Cancer Res Treat	A phase II study of cabozantinib alone or in combination with trastuzumab in breast cancer patients with brain metastases`
Sachdev et al. 2020	NCT01770353	NR; Phase I	Breast Cancer Res Treat	Phase I study of liposomal irinotecan in patients with metastatic breast cancer: fndings from the expansion phase
Morimoto et al. 2020	The University Hospital Medical Information Network Center (ID 000006383)	NR; Phase I	Clinical Breast Cancer	Phase 1 Dose-Escalation Study of Triweekly Nab-Paclitaxel Combined With S-1 for HER2-Negative Metastatic Breast Cancer
Turner et al. 2019	NCT02034916	ABRAZO; Phase II	American Association for Cancer Research	A phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patientys with advanced breast cancer and germline BRCA1/2 mutations (ABRAZO)
Adams et al. 2019	NCT02447003	KEYNOTE; Phase II	Annals of Oncology	Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study

Keenan et al. 2020	NR	NR; Phase II	Clinical Cancer Research	Clinical efficacy and molecular response correlates of the WEE1 inhibitor adavosertib combined with cisplatin in patients with metastatic triple-negative breast cancer (mTNBC)
Anampa et al. 2017	NCT01351909	NR; Phase I	Clinical Breast Cancer	Phase I trial of veliparib, a poly ADP ribose polymerase inhibitor, plus metronomic cyclophosphamide in metastatic HER2 negative breast cancer
Ho et al. 2019	NCT02730130	NR; Phase II	Cancer	A Phase 2 Clinical Trial Assessing the Efficacy and Safety of Pembrolizumab and Radiotherapy in Patients With Metastatic Triple-Negative Breast Cancer
Emens et al. 2019	NCT01375842	PCD4989g; Phase I	JAMA Oncology	Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer A Phase 1 Study
Morris et al. 2018	NR	NR; Phase II	Clinical Breast Cancer	Phase II Study of Paclitaxel and Dasatinib in Metastatic Breast Cancer
Zhang et al. 2021	NCT04488107	NR; Phase Ia	Investigational New Drugs	Phase 1a study of the CDK4/6 inhibitor, FCN-437c, in Chinese patients with HR + /HER2- advanced breast cancer
de la Cruz-Merino et al. 2021	NCT03025880	PANGEA-Breast; Phase II	Cancers	Pembrolizumab Plus Gemcitabine in the Subset of Triple-Negative Advanced Breast Cancer Patients in the GEICAM/2015-04 (PANGEA-Breast) Study
Tolaney et al. 2021	NCT02513472	ENHANCE 1; Phase Ib/II	Clinical Cancer research	Eribulin Plus Pembrolizumab in Patients with Metastatic Triple-Negative Breast Cancer (ENHANCE 1): A Phase Ib/II Study
Boni et al. 2022	NCT03149549	CTMX-M-2009-001; Phase I/II	Clinical Cancer research	Praluzatamab Ravtansine, a CD166-Targeting Antibody–Drug Conjugate,in Patients with Advanced Solid Tumors: An Open-Label Phase I/II Trial
Anders et al. 2022	NCT02768701	NR; Phase II	Journal for Immunotherapy Cancer	Evaluating the efficacy of a priming dose of cyclophosphamide prior to pembrolizumab to treat metastatic triple negative breast cancer
Hu et al. 2021	NCT04002284	NR; Phase II	Cancer Biology & Medicine	Anlotinib has good efficacy and low toxicity: a phase II study of anlotinib in pre-treated HER-2 negative metastatic breast cancer
Zhu et al. 2021	NCT02768415	NR; Phase II	Cancer Biology & Medicine	Phase II study of apatinib in combination with oral vinorelbine in heavily pretreated HER2-negative metastatic breast cancer and clinical implications of monitoring ctDNA
Pérez-García et al. 2021	NCT02778685	KELLY; Phase II	European Journal of Cancer	Pembrolizumab plus eribulin in hormone-receptor-positive, HER2-negative, locally recurrent or metastatic breast cancer (KELLY): An open-label, multicentre, single-arm, phase II trial
De Angelis et al. 2021	NCT02175446	GIM11-BERGI; Phase II	ESMO Open	Eribulin in combination with bevacizumab as second-line treatment for HER2-negative metastatic breast cancer progressing after first-line therapy with paclitaxel and bevacizumab: a multicenter, phase II, single arm trial (GIM11-BERGI)
Krop et al. 2021	NCT02980341	NR; Phase II	Cancer Research	Safety and efficacy results from the phase 1/2 study of U3-1402, a human epidermal growth factor receptor 3 (HER3)-directed antibody drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC)

Gariddo-Castro et al. 2020	NCT01790932 + NCT01629615.	NR; Phase II	Breast Cancer Research	Phase 2 study of buparlisib (BKM120), a pan-class I PI3K inhibitor, in patients with metastatic triple-negative breast cancer
Quintela-Fandino et al. 2020	NCT02802098	NR; Phase Ib	Breast Cancer Research	Immuno-priming durvalumab with bevacizumab in HER2-negative advanced breast cancer: a pilot clinical trial
Kalinsky et al. 2020	NCT01631552	IMMU-132-01; Phase I/II	Annals of Oncology	Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial
Lim et al. 2019		NR; Phase II	Cancer Science Wiley	The impact of food on tolerability of abemaciclib in patients with previously treated hormone receptor-positive, HER2-negative, metastatic breast cancer: An open-label, randomized phase 2 study
Tamura et al. 2020	NCT03207672	NR; Phase I	Annals of Oncology	Phase I study of the liposomal formulation of eribulin (E7389-LF): Results from the HER2-negative breast cancer expansion
Koutras et al. 2020	NCT01693549	HeCOG; Phase II	British Journal of Cancer	Phase 2 study of cabazitaxel as second-line treatment in patients with HER2-negative metastatic breast cancer previously treated with taxanes—a Hellenic Cooperative Oncology Group (HeCOG) Trial
Toh et al. 2020	UMIN000014616	NR; Phase II	Cancer Science Wiley	Early phase II study of mixed 19-peptide vaccine monotherapy for refractory triple-negative breast cancer
Shah et al. 2020	NCT03044730	NR; Phase II	Journal for ImmunoTherapy of Cancer	Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2−negative endocrine-refractory metastatic breast cancer
Fenn et al. 2020	NCT01650506	NR; Phase I	Clinical Breast Cancer	Phase I study of erlotinib and metformin in metastatic triple negative breast cancer
Bian et al. 2019	NCT02838823	NR; Phase I	Ann Transl Med	JS001, an anti-PD-1 mAb for advanced triple negative breast cancer patients after multi-line systemic therapy in a phase I trial
Tolaney et al. 2018	NR	NR; Phase Ib/II	Cancer Research	Abstract PD6-13: Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer
Hui et al. 2018	NCT02053636	FINESSE; Phase II	Annals of Oncology	Lucitanib for the treatment of HR1 HER2- metastatic breast cancer (MBC) patients (pts): Results from the multicohort phase II FINESSE trial
Smith et al. 2018	NR	NR; Phase II	Cancer Research	Abstract P6-14-05: Phase 2 study evaluating the efficacy and safety of eribulin mesylate administered biweekly for patients with human epidermal growth factor receptor 2-negative metastatic breast cancer
Diamond et al. 2018	NR	NR; Phase II	Cancer Research	Abstract PD3-16: Clinical safety and efficacy of the aurora and angiogenic kinase inhibitor ENMD-2076 in previously treated, locally advanced or metastatic triple-negative breast cancer
Dickler et al. 2017	NCT02102490	MONARCH 1; Phase II	Biology of Human Tumors	MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer

Yamamura et al. 2017	UMIN000004839	NR; Phase II	Chemotherapy	Gemcitabine and Vinorelbine Combination Chemotherapy in Taxane-Pretreated Patients with Metastatic Breast Cancer: A Phase II Study of the Kinki Multidisciplinary Breast Oncology Group (KMBOG) 1015
Bardia et al. 2017	NCT01631552	NR; Phase II	Journal of Clinical Oncology	Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer
Rugo et al. 2017	NCT02102490	MONARCH 1: Phase II	Cancer Research	MONARCH 1: Final overall survival analysis of a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2-breast cancer, after chemotherapy for advanced disease
Adams et al. 2017	NCT02447003	KEYNOTE-086; Phase II	Journal of Clinical Oncology	Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A.
Maeda et al. 2017	ID: UMIN000007121	NR; Phase II	The Breast	Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes
Han et al. 2017	NR	NR; Phase II	Cancer Research	Phase II trial of selinexor for metastatic triple negative breast cancer
Tolaney et al. 2017	NCT01738438	NR; Phase II	The Oncologist	Phase II and Biomarker Study of Cabozantinib in Metastatic Triple-Negative Breast Cancer Patients
Adams et al. 2016	NCT01633970	NR; Phase Ib	Journal of Clinical Oncology	Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC)
Tolaney et al. 2015	NCT01575522	NR; Phase II	Invest New Drugs	Phase II study of tivantinib (ARQ 197) in patients with metastatic triple-negative breast cancer
Cao et al. 2014	NCT01653574	NR; Phase II	Cancer Chemother Pharmacol	Hypothyroidism as a potential biomarker of efficacy of famitinib,a novel VEGFR-2 inhibitor in metastatic breast cancer
Hayashi et al. 2013	KMBOG0610B	NR; Phase II	Breast Cancer	Phase II study of bi-weekly irinotecan for patients with previously treated HER2-negative metastatic breast cancer: KMBOG0610B
Lee et al. 2013	NCT00532714	NR; Phase II	Invest New Drugs	Phase II study of irinotecan plus capecitabine in anthracycline- and taxane-pretreated patients with metastatic breast cancer
Villanueva et al. 2011	NR	TEGATAX; Phase II	Breast	Phase II trial of paclitaxel and uraciletegafur in metastatic breast cancer. TEGATAX trial
Nanda et al. 2016	NCT01848834	KEYNOTE-012; Phase Ib	Journal of Clinical Oncology	Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study

Table 4: Clinical SLR update (30 January 2023) | Included non-RCTs (N=18)

Author	Study ID	Trial name; Phase	Journal	Title
Xu et al. 2022	NCT04454437	EVER-132-001; Phase IIb	International Journal of Cancer	A Phase IIb, single arm, multicenter trial of sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer who received at least two prior treatments
Lee et al. 2022	NCT00527930	KCSG-BR07-03; Phase II	CANCER RESEARCH AND TREATMENT (CRT)	A Phase II Trial of S-1 and Oxaliplatin in Patients with Metastatic Breast Cancer Previously Treated with Anthracycline and Taxane (KCSG-BR07-03)
Xu et al. 2022	NCT04454437	EVER-132-001; Phase IIb	Annals of Oncology	Efficacy and safety of sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer (mTNBC) by baseline HER2 expression level: Subgroup analysis from a phase IIb trial
Yin et al. 2022	NCT04624711	NR; Phase II	Annals of Oncology	Eribulin combined with anlotinib for patients with HER2-negative metastatic breast cancer: A single-arm, multicenter, phase II study
Aftimos et al. 2022	NCT03901469	NR; Phase Ib/II	Journal of Clinical Oncology	A phase 1b/2 study of the BET inhibitorZEN-3694 in combination with talazoparibfor treatment of patients with TNBCwithout gBRCA1/2 mutations.
Ho et al. 2022	NCT03989089	NR; Phase II	Journal of Clinical Oncology	A phase II, single-arm, open label, Simon two-stage study of pembrolizumab in patients with metastatic HER2-negative breast cancer: Evaluation of impact of germline variants in APOBEC3B (AUROR).
Anders et al. 2022	NCT02768701	NR; Phase II	Journal for Immunotherapy of Cancer	Evaluating the efficacy of a priming dose of cyclophosphamide prior to pembrolizumab to treat metastatic triple negative breast cancer
Isakoff et al. 2022	NCT04634747	NR; Phase Ib	Cancer Research	A phase 1b study of PVX-410 vaccine in combination with pembrolizumab in metastatic triple negative breast cancer (mTNBC)
Batalani et al. 2022	NCT01623349	NR; Phase Ib	Clinical Cancer Research	Phase 1b Clinical Trial with Alpelisib plus Olaparib for Patients with Advanced Triple-Negative Breast Cancer
Liu et al. 2022	NCT04303741	NR; Phase II	Nature Communications	Multicenter phase II trial of Camrelizumab combined with Apatinib and Eribulin in heavily pretreated patients with advanced triple-negative breast cancer
Savas et al. 2022	NCT02506556	NR; Phase II	Cancer Discovery	Alpelisib Monotherapy for PI3K-Altered, Pretreated Advanced Breast Cancer: A Phase II Study
Rugo et al. 2022	NCT02779751	NR; Phase Ib	NPJ Breast cancer	Abemaciclib in combination with pembrolizumab for HR+, HER2− metastatic breast cancer: Phase 1b study
Telli et al. 2022	NCT02157792	NR; Phase I	NPJ Breast cancer	Phase 1b study of berzosertib and cisplatin in patients with advanced triple-negative breast cancer

Cruz-Merino et al. 2022	NCT03025880	PANGEA-Breast; Phase II	BMC Cancer	Pembrolizumab in combination with gemcitabine for patients with HER2-negative advanced breast cancer: GEICAM/2015–04 (PANGEA-Breast) study
Radovich et al. 2022	NCT03243331	NR; Phase I	Clinical Cancer Research	Initial phase I safety study of gedatolisib plus cofetuzumab pelidotin for patients with metastatic triple-negative breast cancer
Tsuji et al. 2022	NCT02448771	NR; Phase Ib/II	Clinical Cancer Research	Clinical Efficacy and Whole-Exome Sequencing of Liquid Biopsies in a Phase IB/II Study of Bazedoxifene and Palbociclib in Advanced Hormone Receptor–Positive Breast Cancer
Awada et al. 2022	NCT02210364	NR; Phase I	ESMO open science for optimal cancer care	Antitumor activity of lurbinectedin in combination with oral capecitabine in patients with metastatic breast cancer
Shimomura et al. 2023	NCT03366428	DS8201-A-J102; Phase I	CLINICAL PHARMACOLOGY & THERAPEUTICS	Effect of Trastuzumab Deruxtecan on QT/QTc Interval and Pharmacokinetics in HER2-Positive or HER2-Low Metastatic/Unresectable Breast Cancer

Table 5: Initial clinical SLR (25 February 2022) | Included grey literature studies (N=11)

Author	Study ID	Trial name; Phase	Journal	Title
Sohn et al. 2022	NCT03752723	KEYNOTE-899; Phase Ib/II	American Society Of Clinical Oncology	Phase 1b/2 study of GX-I7 plus pembrolizumab in patients with refractory or recurrent (R/R) metastatic triple-negative breast cancer (mTNBC): The KEYNOTE-899 Study.
Rugo et al. 2022	NCT03901339	NR; Phase III	American Society Of Clinical Oncology	Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer.
NR; 2022	NCT03703466	NR; Phase II	WHO	An Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability When Receiving Abemaciclib for Patients With Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer
NR; 2019	NCT01997333	NR; Phase II	WHO	A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE)in Patients With Metastatic, gpNMB Over-Expressing, Triple Negative Breast Cancer (The METRIC Study)
NR; 2019	NCT01964924	NR; Phase II	WHO	A Single Arm, Phase II Study of Single Agent Trametinib Followed by Trametinib in Combination With GSK2141795 in Patients With Advanced Triple Negative Breast Cancer
NR; 2022	NCT01498458	NR; Phase I	WHO	Phase I Study to Assess the Optimal Dose for Pazopanib in Combination With Capecitabine in Patients With HER2-negative, Metastatic Breast Cancer (PazoX)

NR; 2011	NR	NR; Phase II	WHO	Phase II, multicenter, open-label, clinical trial of Trabectedin (Yondelis®) in Metastatic Breast Cancer Patients with triple negative profile (ER-, PR-, HER2-), HER2 overexpressing tumors and BRCA1 or BRCA2 mutation carriers
NR; 2015	NCT00929240	NR; Phase III	Clinicaltrials.gov	A Randomized Study of the Effect of Maintenance Therapy With Bevacizumab + Capecitabine Versus Bevacizumab Alone on Progression-free Survival in Patients With HER2-negative Metastatic Breast Cancer That Has Not Progressed During First-line Docetaxel Plus Bevacizumab Therapy
NR; 2020	NCT02624700	NR; Phase II	Clinicaltrials.gov	Phase 2 Study of Pemetrexed and Sorafenib for Treatment of Recurrent or Metastatic Triple Negative Breast Cancer
NR; 2021	NCT02878057	NR; Phase II	Clinicaltrials.gov	Multicenter Phase II Study of Apatinib in Patients With HER-2 Negative Advanced Breast Cancer With Chest Wall Metastasis
Hurvitz et al. 2022	NCT02574455	ASCENT; Phase III	ESMO Breast Cancer	Sacituzumab Govitecan Efficacy in Patients with Metastatic Triple-Negative Breast Cancer by HER2 Immunohistochemistry Status: Findings from the Phase 3 ASCENT Study

Table 6: Clinical SLR update (30 January 2023) | Included grey literature studies (NS=9)

Author	Study ID	Trial name; Phase	Journal	Title
Rugo et al. 2022	NCT03901339	TROPiCS-02; Phase III	Grey lit: JSCO 2022	Primary data from TROPiCS-02: Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2–) advanced breast cancer
Harbeck et al. 2022	NCT03734029	DESTINY-Breast04; Phase III	Grey lit: SABCS 2022	Trastuzumab deruxtecan vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Subgroup analyses from DESTINYBreast04
Metic-Bernstam et al. 2022	NCT03401385	TROPION-PanTumor01; Phase I	Grey lit: SABCS 2022	TROPION-PanTumor01; TROPION-Breast01 - Phase 1 TROPION-PanTumor01 Study evaluating Datopotamab Deruxtecan (Dato-DXd) in unresectable or metastatic hormone receptor–positive/HER2–negative breast cancer (BC)
Bardia et al. 2022	NCT03401385	TROPION-PanTumor01; Phase I	Grey lit: SABCS 2022	Datopotamab deruxtecan in advanced/metastatic HER2-breast cancer: Results from the phase 1 TROPION-PanTumor01 study
Rugo et al. 2022	NCT03901339	TROPiCS-02; Phase III	Grey lit: SABCS 2022	Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2– Metastatic Breast Cancer (mBC)
Tolaney et al. 2022	NCT03901339	TROPiCS-02; Phase III	Grey lit: SABCS 2022	Exposure-adjusted incidence rates (EAIRs) of adverse events (AEs) from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in HR+/HER2- metastatic breast cancer (MBC)

Marmé et al. 2022	NCT03901339	TROPiCS-02; Phase III	Grey lit: SABCS 2022	Effect of sacituzumab govitecan vs chemotherapy in HR+/HER2- metastatic breast cancer: patient-reported outcomes from the TROPiCS-02 trial
Ueno et al. 2022	NCT03734029	DESTINY-Breast04; Phase III	Grey lit: ESMO2022	217O Patient-reported outcomes (PROs) from DESTINY-Breast04, a randomized phase III study of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low metastatic breast cancer (MBC)
Xu et al. 2022	NCT04454437	EVER-132-001; Phase IIb	Greylit: ESMO2022	248P Sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer who received at least two prior treatments

A11. CS Appendix D Table 21 and Section B.2.1. Please clarify the number of publications relating to the ASCENT trial. B.2.1, p.45 states, 'These hand searches identified two publications related to DESTINY-Breast04 and six articles related to ASCENT'. Appendix D.2.2.1 Table 21 – recording the results of the hand search – reports eight ASCENT publications.

The company acknowledges the typographical error and inconsistency in reporting of the number of ASCENT publications from the hand searches. The hand searches identified nine publications related to ASCENT:

- Weide R et al. 2022. Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study. Oncol Res Treat. 45(suppl 1):7–284.
- Cortés J et al. 2022. Abstract P5-16-15: Post-progression therapy outcomes in patients (pts) from the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). Cancer Res. 82 (4_Supplement): P5-16-15. DOI: 10.1158/1538-7445.SABCS21-P5-16-15.
- Loibl S et al. 2022. Abstract P5-16-01: Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). Cancer Res (2022) 82 (4_Supplement): P5-16-01. DOI: 10.1158/1538-7445.SABCS21-P5-16-01.
- Loibl S et al. 2022. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. Eur J Cancer. 178:23–33. DOI: 10.1016/j.ejca.2022.10.003.
- Carey L et al. 2022. Abstract P5-16-07: Assessment of sacituzumab govitecan(SG) in Black patients (pts) from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). Cancer Res. 82 (4_Supplement): P5-16-07. DOI: 10.1158/1538-7445.SABCS21-P5-16-07.

- Carey L et al. 2022. Sacituzumab govitecan as second-line treatment for metastatic triple-negative breast cancer-phase 3 ASCENT study subanalysis. NPJ breast cancer. 8(1):72. DOI: 10.1038/s41523-022-00439-5.
- O'Shaughnessy J et al. 2022. Analysis of patients without and with an initial triple-negative breast cancer diagnosis in the phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer. Breast Cancer Res Treat. 195(2):127–139. DOI: 10.1007/s10549-022-06602-7.
- Rugo H et al. 2022. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. NPJ Breast Cancer. 8(1):98. DOI: 10.1038/s41523-022-00467-1.
- Hurvitz S et al. 2022. Poster 168P: Sacituzumab govitecan efficacy in patients with metastatic triple-negative breast cancer by HER2 immunohistochemistry status: findings from the phase 3 ASCENT study. Presented at the European Society for Medical Oncology.

The SLR update (30 January 2023) has now been completed and identified no new publications related to ASCENT in addition to those identified in the hand searches. The SLR update report is available in the reference pack.

Clinical effectiveness evidence and statistical analysis

A12. DESTINY-Breast04 participants are inconsistently referred to as having 'recurrent' (e.g., B.2.1, B.2.3.1 p.47, B.2.10, etc.) or 'unresectable' breast cancer (BC; Title, B.1.1, B.1.2 Table 2, B.2.3.1 Table 9, etc.) as well as mBC. The decision problem requires: 'Adults with HER2-low, unresectable or metastatic BC previously treated with chemotherapy' (Table 1 p.11). Please clarify if the population being considered in the submission is 'unresectable or metastatic' or 'recurrent or metastatic'.

The company confirms that the population being considered in the appraisal is adults with HER2-low "unresectable or metastatic" BC who have received prior

chemotherapy in the recurrent (if recurrence occurred within six months of (neo)adjuvant chemotherapy) or metastatic setting.

This aligns with:

- The full UK marketing authorisation for T-DXd in HER2-low u/mBC: *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see Section 4.2).*[10]

- The DESTINY-Breast04 inclusion criteria,[11] which specifies that:

    - *Patients must have pathologically documented breast cancer that was unresectable or metastatic*.

    - *Patients must have been previously treated with at least one and no more than two prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within six months of (neo)adjuvant chemotherapy it would count as one line of chemotherapy. Targeted agents (e.g. cyclin-dependent kinase 4/6 [CDK4/6] inhibitors, programmed death ligand 1 [PD-L1] inhibitors) and endocrine therapy (ET) did not count as a line of chemotherapy unless administered in combination with chemotherapy*.

A13. PRIORITY. CS Section B.2.5.1 states that DESTINY-Breast04 participants reflect the UK population in terms of proportions of HR-positive and HR-negative patients. Please clarify why the primary analysis was only conducted on HR-positive patients rather than the whole sample (CS Table 11).

DESTINY-Breast04 was initially designed to include HER2-low/HR-positive patients given that most HER2-low BC patients are HR-positive and preliminary studies on the efficacy of T-DXd in the HER2-low population (DS8201-A-J101) primarily included patients with HR-positive mBC.[12–14] However, the mechanism of action of

T-DXd is theoretically not dependent on HR status, so a similar treatment effect was expected in HR-positive and HR-negative patients.[15–17] Therefore, [redacted].[18]

Given that the HR-negative cohort was added as an exploratory analysis [redacted], the primary analysis remained in the HR-positive cohort, as planned in the original protocol.

Although the primary endpoint in DESTINY-Breast04 was PFS by blinded independent central review (BICR) in the HR-positive population, the full set analysis (FAS) population was a pre-specified analysis for the key secondary endpoints of PFS by BICR and OS.[19] The FAS was included in regulatory submissions to inform the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) licence extension for T-DXd in the HER2-low indication and is the population relevant to this appraisal as it covers the full marketing authorisation for T-DXd in HER2-low u/mBC.[20,21]

A14. CS Section B.2.4.3. Please provide details of the post-randomisation withdrawals, which produced a noted disparity in untreated participants between the treatment of physician's choice (TPC) arm (n=[redacted]) and the T-DXd arm (n=[redacted]).

Table 7 below provides details of patients who withdrew following randomisation. Of patients who did not receive at least one dose of a study drug:

- The majority withdrew from the study within one month of being randomised (N=[redacted] of the patients who withdrew from the TPC arm and N=[redacted] patients who withdrew from the T-DXd arm).
- [redacted] patients in the TPC arm remained in the trial for [redacted] to [redacted] months without receiving any study drug.

- [redacted] patients ([redacted] in the T-DXd arm and [redacted] in the TPC arm) [redacted] months of their randomisation date.

Further details on the reason for post-randomisation withdrawals were not collected in the study aside from the information in **Table 7** below.

It should be noted that patient withdrawal post-randomisation is a common limitation in open-label studies as patients are aware of their treatment allocation. DESTINY-Breast04 was an open-label study because it was not feasible to blind patients to their treatment allocation due to different routes of administration, different treatment schedules, and different adverse event (AE) profiles between T-DXd and the TPC agents.

The open-label nature of the study is unlikely to impact the study outcomes as key clinical endpoints (including the primary endpoint of PFS in the HR-positive cohort) were evaluated by BICR. Similarly, the open-label study design would not impact the evaluation of OS as survival data in the trial were collected for all patients, including those who withdrew from the trial, as specified in Protocol Section 5.7.2: *"Subjects will be followed for survival status by collecting public records (e.g., death certificates) unless prohibited by local laws."* Based on this, differences in withdrawals following randomisation between the TPC and T-DXd arms are unlikely to impact efficacy outcomes.

Table 7: Details of patients who were randomised but did not receive study treatment – Full Analysis Set

Subject ID/Group/Age/Sex/ Hormone Receptor Status	Randomization date	Study duration (months)	Follow-up outcome	Date of withdrawal from study	Last date known alive	First started new cancer treatment date
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

A15. PRIORITY. CS Section B.2.4.4 Table 15. Please clarify why Eastern Cooperative Oncology Group performance status (ECOG PS) 2 patients are excluded.

As stated in Table 9 of the company submission, an inclusion criteria of DESTINY-Breast04 was Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with an ECOG PS of 2 or more were therefore excluded from the study.[19] This is consistent with other oncology trials, which commonly exclude patients with ECOG PS ≥2 – according to a 2020 FDA exploratory analysis of ECOG PS, of all adult oncology protocols assessed (N=297), 284 (96%) specified a patient PS requirement for inclusion or exclusion, and over half of these protocols (178 [60%]) specified an ECOG PS of 0 or 1 or equivalent Karnofsky PS of ≥70% for inclusion.[22]

Regarding BC specifically, recent u/mBC studies have also only included patients with ECOG PS of 0 or 1, including:

- ASCENT (2021): SG vs. TPC in TNBC.[23]
- TROPiCS-02 (2020): SG vs TPC in HER2-negative/HR-positive BC.[3]
- KEYNOTE-119 (2021): Pembrolizumab vs. chemotherapy in TNBC.[24]
- DESTINY-Breast01 (2020): T-DXd in previously treated HER2-positive BC.[11]
- DESTINY-Breast03 (2022): T-DXd vs. trastuzumab emtansine (T-DM1) in HER2-positive u/mBC.[25]
- EMILIA (2012): T-DM1 vs. capecitabine plus lapatinib in HER2-positive locally advanced or mBC.[26]
- CLEOPATRA (2015): Pertuzumab, trastuzumab, and docetaxel vs. placebo, trastuzumab, and docetaxel in HER2-positive mBC.[27]
- HER2CLIMB (2020): Tucatinib in combination with trastuzumab and capecitabine vs. placebo with trastuzumab with capecitabine in HER2-positive u/mBC.[28]

The DESTINY-Breast04 eligibility criteria related to ECOG PS are therefore consistent with the majority of oncology trials, including recent trials in u/mBC that formed the basis of company submissions for technologies recommended for reimbursement by NICE (e.g., SG in TA819; T-DXd in TA862).[9,29]

A16. CS Section B.2.6.1.1 Table 17. Please provide details of the reasons for the death events observed before progression as reported in the T-DXd arm and TPC arm (n=[redacted], [redacted] vs n=[redacted], [redacted]).

The primary cause of death was reported in the patient case report form for all deaths that occurred during the study period in DESTINY-Breast04. The number of death events observed as part of PFS and/or death events before progression in the HR-positive cohort is provided in Table 17 of CS.

As summarised in **Table 8** (HR-positive patients), among patients with death events observed before progression, [redacted] was the primary cause of death in both the T-DXd ([redacted] of [redacted] deaths) and TPC arms ([redacted] of [redacted] deaths). Most of the remaining deaths in the T-DXd arm were due to [redacted] ([redacted] of [redacted] deaths).

Table 8: Cause of death: Patients with death events before progression: HR-positive cohort

Cause of death, N (%)	T-DXd (N=[redacted])	TPC (N=[redacted])	Total (N=[redacted])
Disease progression	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Cachexia due to cancer	[redacted]	[redacted]	[redacted]
Clinical progression	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Disease progression (liver dysfunction)	[redacted]	[redacted]	[redacted]

N: Number of subjects with death event before disease progression without missing two or more consecutive tumour assessments immediately preceding the event.
Abbreviations: FAS, full analysis set; HR-positive; hormone receptor positive; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

A17. CS Section B.2.7. Please clarify why the HR-status is not in the list of pre-specified subgroups considering it is listed in CS Table 9 and Figure 21.

As stated in response A13, DESTINY-Breast04 was initially designed to include HER2-low/HR-positive patients given that most HER2-low BC patients are HR-positive and preliminary studies on the efficacy of T-DXd in the HER2-low population (DS8201-A-J101) primarily included patients with HR-positive mBC.[12–14]

While an exploratory HER2-low/HR-negative cohort was added [redacted], the primary analysis

remained in the HR-positive cohort, as planned in the original protocol. As per the trial protocol,[18] the subgroup analyses were therefore specified to be performed in the HR-positive cohort, and HR-status was not a pre-specified subgroup.

The Statistical Analysis Plan for DESTINY-Breast04 (Section 7.2.2.3 and Section 7.2.4.6)[30] reflected the addition of the exploratory HER2-low/HR-negative cohort and subsequently listed HR-status as a subgroup for analysis in the FAS population only. Thus, HR-status is included in the case study report (CSR) as a subgroup analysis in the FAS population.[6]

Given the above, HR-status was listed as a subgroup analysis in the company submission in the summary of trial methodology (Table 9) and forest plot (Figure 21), in line with the CSR for the FAS.

A18. CS Section B.2.4.2. Please clarify why a stratified Cox model was used for analysing progression free survival (PFS) and overall survival (OS) instead of a standard Cox model. Please provide the test for the proportional hazards assumption in the stratified Cox model.

To analyse PFS and OS, stratified Cox models were used and included the stratification factors from randomisation: HER2 immunohistochemistry [IHC] status (IHC +1 vs. IHC +2/in situ hybridisation [ISH]-negative), number of prior lines of chemotherapy for metastatic disease (1 vs. 2), and HR/cyclin-dependent kinase (CDK) status (HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative). This approach is in accordance with the EMA guidelines, which state that randomisation stratification factors should be included as covariates or stratification factors in the primary analysis.[31,32]

Stratified Cox models allow the baseline hazard to be different within each of the strata considered and assume proportional hazards across the strata. The following tests were conducted to assess the proportional hazards assumption and are reported below for each stratum for PFS by BICR and OS in the FAS:

- Schoenfeld residuals plot based on a Cox model including treatment arm as the only covariate, with p-value of the Grambsch-Therneau test[33]

- Log-cumulative hazards plots by treatment group: $log\left(-log\left(S(t)\right)\right) vs. log(t)$

PFS by BICR in the FAS

Figure 2 displays the diagnostic plots to assess the proportional hazards assumption by HER2 IHC status of tissue samples assessed by a central laboratory for PFS by BICR in the FAS. The Schoenfeld residuals do not show a distinct trend, and the Grambsch and Therneau test of non-proportionality fails to reject the null hypothesis that proportional hazards holds (p=[redacted]), indicating that the proportional hazards assumption may be valid. The proportionality of the hazards is further demonstrated in the log-cumulative hazards plot, which has relatively straight and parallel lines, especially after one month.

The proportional hazards assumption also appears to hold for the other two stratification factors for PFS by BICR in the FAS (number of prior lines of chemotherapy [**Figure 3**] and HR/CDK status [**Figure 4**]). The Schoenfeld residuals do not show a distinct trend, and the Grambsch and Therneau tests of non-proportionality fail to reject the null hypothesis (p=[redacted] and p=[redacted], respectively). In addition, the log-cumulative hazards plots are relatively straight and parallel for both strata.

Figure 2. Diagnostic plots of stratification factor – HER2 IHC status of tissue samples assessed by a central laboratory – PFS based on BICR – FAS

Abbreviations: BICR, blinded independent central review; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; PFS, progression-free survival.

Figure 3. Diagnostic plots of stratification factor – Number of prior lines of chemotherapy – PFS based on BICR – FAS

Abbreviations: BICR, blinded independent central review; FAS, full analysis set; PFS, progression-free survival.

Figure 4. Diagnostic plots of stratification factor – HR/CDK status – PFS based on BICR – FAS

Abbreviations: BICR, blinded independent central review; CDK, cyclin-dependent kinase; FAS, full analysis set; HR, hormone receptor; PFS, progression-free survival.

OS in the FAS

As with PFS by BICR in the FAS, the proportional hazards tests for OS in the FAS support that the proportional hazards assumption may hold across stratification factors.

For HER2 IHC status (**Figure 5**), the Schoenfeld residuals do not show a distinct trend, and the Grambsch and Therneau test of non-proportionality fails to reject the null hypothesis (p=[redacted]) indicating that the proportional hazards assumption may be valid. The proportionality of the hazards is further demonstrated by the log-cumulative hazards plot, where the lines are relatively straight and parallel. Similar

findings are observed by investigation of proportional hazards for OS in the FAS for prior lines of chemotherapy (**Figure 6**) and HR/CDK status (**Figure 7**). The Schoenfeld residuals do not show a distinct trend, and the Grambsch and Therneau tests of non-proportionality fail to reject the null hypothesis (p=[redacted] and p=[redacted], respectively). In addition, the log-cumulative hazards plots are relatively straight and parallel for both strata.

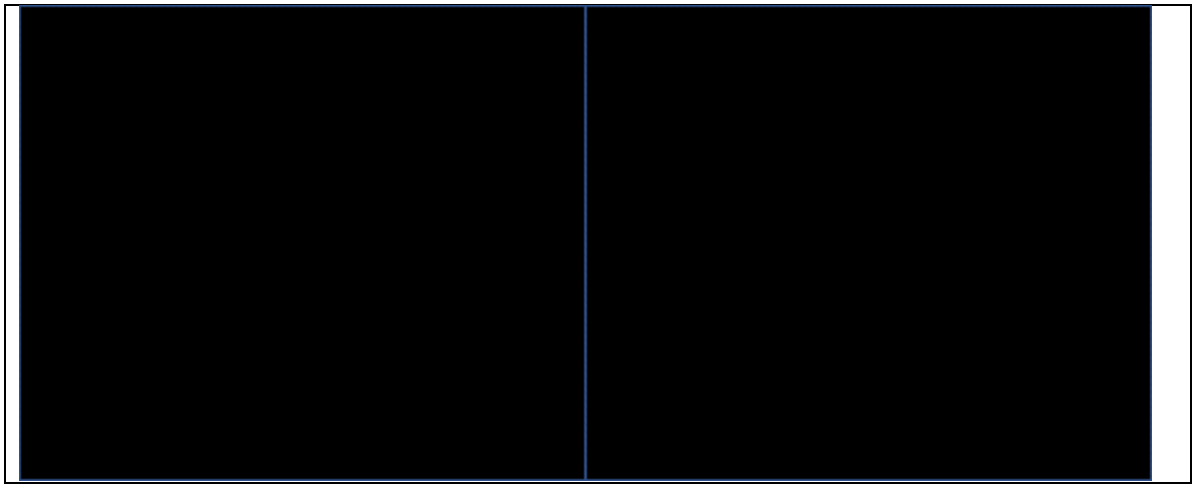
Figure 5. Diagnostic plots of stratification factor – HER2 IHC status of tissue samples assessed by a central laboratory – Overall survival – FAS

Abbreviations: FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation.

Figure 6. Diagnostic plots of stratification factor – Number of prior lines of chemotherapy – Overall survival – FAS

Abbreviations: FAS, full analysis set.

Figure 7. Diagnostic plots of stratification factor – HR/CDK status – Overall survival – FAS



Abbreviations: CDK, cyclin-dependent kinase; FAS, full analysis set; HR, hormone receptor.

A19. CS Section B.2.4.2. Please clarify how the sample size of 60 was calculated for the HR-negative BC patient cohort.

As stated in response A13, DESTINY-Breast04 was initially designed to include HER2-low/HR-positive patients, but,

[redacted].

Approximately 480 HR-positive patients were planned to be randomised in DESTINY-Breast04.[6,18,30] This sample size for the HR-positive cohort was calculated to ensure that the study was adequately powered to detect a clinically meaningful difference between T-DXd and TPC for the primary endpoint, PFS by BICR. In addition to the 480 HR-positive patients, approximately 60 HR-negative patients were planned to be enrolled for the exploratory cohort [redacted].[6,18,30]

Planned enrolment of patients with HR-negative disease in DESTINY-Breast04 was therefore 11.1% of the overall FAS population.[6,18,30] This proportion was chosen as it was representative of the real-world prevalence of HR-negative disease within the overall HER2-low population:

- In a Spanish study of clinicopathological data from 3,689 patients with HER2-negative disease, 11.8% of the HER2-low population had HR-negative disease.[13]

- In a UK biomarker analysis involving over 199,000 patient data sets, 10.4% of the HER2-low population had HR-negative disease.[34]

Planned enrolment of patients with HR-negative disease in DESTINY-Breast04 was therefore ~60 of 540 (11.1%) patients.

Indirect treatment comparisons

A20. CS page 40 states that "*While SG is in the final scope it is not included in the company evidence submission as it is only a potentially relevant comparator for a small subset (i.e., HR-negative) of the overall HER2-low population considered in this appraisal.*" CS page 91 states that "*The company does not consider SG to be a relevant comparator as it is only recommended by NICE for patients with TNBC i.e. HER2-negative/HR-negative (TA819), which represents a small proportion (~10%) of the total HER2-low u/mBC population in UK practice.*" The two statements seem to contradict each other. Please clarify if the company considers sacituzumab govitecan (SG) as a potential relevant comparator for a small subset (HR-negative and HER2-low population) in this appraisal.

SG is recommended by NICE for treating unresectable TNBC after two or more therapies (TA819).[29] The population covered by TA819 (i.e. TNBC) includes patients who are HER2-low/HR-negative,[29] which means that it includes a subset of patients that are in the scope of this appraisal (i.e., HER2-low/HR-positive and HER2-low/HR-negative).[4] The company therefore acknowledges that SG may be considered a potential comparator in the small subset of patients with HER2-low/HR-negative u/mBC.

Within this small subset (representing ~10% of the overall HER2-low population),[34] SG was only recently recommended in August 2022,[29] and its use in UK practice is not yet known, meaning that it cannot yet be considered routine National Health Service (NHS) practice. For these reasons, the company does not consider SG to be a relevant or important comparator for decision-making in the full licensed indication for T-DXd in HER2-low.

The company considers that the comparison of T-DXd vs. TPC in the FAS from DESTINY-Breast04 (a head-to-head phase III randomised clinical trial in HER2-low

u/mBC) provides the most robust evidence for decision-making in the full licensed indication for T-DXd in HER2-low. Clinical and Health Economics and Outcomes Research (HEOR) experts consulted during an Advisory Board meeting agreed that, for decision-making, the FAS is the relevant dataset and the TPC arm of DESTINY-Breast04 is the most relevant comparator. They also agreed that the comparators listed in the NICE final scope are well represented in the TPC arm of DESTINY-Breast04.[35]

A21. PRIORITY. Clinical advice received by the EAG would support SG being a highly relevant comparator for the HR-negative subgroup of patients (i.e. HER2-low/HR-negative). The CS does not currently provide any estimates of relative efficacy for T-DXd versus SG and the EAG expects this to be a key area of uncertainty for the committee unless the company can provide some evidence. To address this uncertainty and assist the committee in making evidence-based recommendations for the HR-negative subgroup we would request that the company provides the following:

- the results of PFS and OS outcomes from the ASCENT trial for HER2-low population.
- the comparisons of the potential treatment effect modifiers between ASCENT full population, ASCENT HER2-low population, and DESTINY-Breast04 HR-negative population. Please also comment on the population differences in terms of the potential treatment effect modifiers between the ASCENT HER2-low population and DESTINY-Breast04 HR-negative population.
- an indirect treatment comparison (ITC) analysis of T-DXd and SG for PFS and OS adjusting for population differences.

As detailed in response to A20, SG is a treatment option for HER2-low/HR-negative u/mBC, which reflects a small subset (~10%)[34] of the overall HER2-low population. The company therefore does not consider SG to be a relevant or important comparator for decision-making in the full HER2-low population relevant to this appraisal. In the full HER2-low indication, the most robust evidence for decision-making is a comparison of T-DXd vs. TPC in the FAS population of DESTINY-Breast04.

The company commissioned two independent indirect treatment comparison (ITC) feasibility assessments[36,37] to identify if an ITC between T-DXd and SG could be conducted in the HER2-low/HR-negative u/mBC population based on the DESTINY-Breast04 and ASCENT studies. The ITC feasibility assessments concluded that a comparison between T-DXd and SG in the HER2-low/HR-negative cohort would be highly uncertain and not appropriate for decision-making for the following reasons:

- **Study design:** ASCENT was a Phase III study investigating the efficacy and safety of SG vs. TPC in the metastatic TNBC population (i.e., includes HER2-negative/HR-negative). While this population included HER2-low patients, the study was not powered to analyse efficacy in HER2-low nor was HER2 status (by IHC and ISH levels) a randomisation stratification factor or a pre-specified subgroup. Any results from ASCENT in the HER2-low/HR-negative population should therefore be interpreted with caution. In addition, a benefit/risk assessment for SG in the HER2-low population specifically has not been performed for marketing authorisation purposes, unlike for DESTINY-Breast04.
- **Patient numbers:** There are limited patient numbers for the relevant comparison in HER2-low/HR-negative u/mBC for DESTINY-Breast04 (T-DXd N=40, TPC N=18)[6] and ASCENT (SG N=63, TPC N=60).[38] Given the differences in baseline characteristics, matching the populations would result in even smaller effective sample sizes and, in turn, any ITC would be highly uncertain for decision-making.
- **Data availability:** While the company has access to individual patient data from DESTINY-Breast04, any ITC is limited by the availability of published data from ASCENT. Published data from ASCENT for HER2-low/HR-negative patients specifically is only available from a conference poster,[38] which has limited reporting of data, including on potential prognostic factors and treatment effect modifiers. This means that it is not possible to assess the impact of all potential prognostic factors and treatment effect modifiers.
- **Population characteristics:** There are potentially important differences in the eligibility criteria for DESTINY-Breast04 and ASCENT (e.g., number of prior lines of chemotherapy), meaning that some treatment effect modifiers cannot

be adjusted for. In addition, there are differences in the limited baseline characteristics for which data are available in the HER2-low/HR-negative population from both DESTINY-Breast04 and ASCENT (e.g., ECOG PS). These differences would be difficult to adjust for and/or would reduce the effective sample size of a matched analysis, in turn increasing decision-making uncertainty.

Despite these limitations, the company has responded to the EAG's clarification questions below in order to support decision-making.

- the results of PFS and OS outcomes from the ASCENT trial for HER2-low population.

As highlighted above, it should be noted that the ASCENT study was not designed to assess the efficacy of SG in the HER2-low/HR-negative patient population specifically and results in the HER2-low population were derived from a post hoc analysis. In addition, of 529 patients enrolled in ASCENT, HER2 IHC data were missing for 113 patients (21.3%) and only 63 patients in the SG arm and 60 patients in the TPC arm could be classified as HER2-low.[38]

PFS and OS outcomes for the HER2-low/HR-negative populations in DESTINY-Breast04 and ASCENT are presented in **Table 9**. Numerically, T-DXd offers longer median PFS (8.5 vs. 6.2 months) and median OS (18.2 vs. 14.0 months) compared with SG.

Both DESTINY-Breast04 and ASCENT used a TPC comparator arm comprising a similar mix of non-targeted chemotherapy agents. These included capecitabine (ASCENT: 12.6%; DESTINY-Breast04: 20.1%), eribulin (ASCENT: 53.1%; DESTINY-Breast04: 51.1%), and gemcitabine (ASCENT: 14.5%; DESTINY-Breast04: 10.3%).[6,29] A naïve, unadjusted, comparison of the treatment effect of T-DXd vs. TPC and SG vs. TPC shows that the hazard ratios (HRs) for both PFS and OS are similar in DESTINY-Breast04 and ASCENT.

These results, along with the overlap in confidence intervals across trials, indicate that there is no evidence to demonstrate that one treatment is more effective than the other in the HER2-low/HR-negative population.

Table 9: DESTINY-Breast04 and ASCENT PFS and OS outcomes

Study (population)	Comparison	Outcome	Median, months	Difference in median, months	HR (95% CI)
ASCENT (HER2-low/HR-negative)[38]	SG vs. TPC	PFS	SG: 6.2 TPC: 2.9	3.3	0.44 (0.27, 0.72)
		OS	SG: 14.0 TPC: 8.7	5.3	0.43 (0.28, 0.67)
DESTINY-Breast04 (HER2-low/HR-negative)[19]	T-DXd vs. TPC	PFS	T-DXd: 8.5 TPC: 2.9	5.6	0.46 (0.24, 0.89)
		OS	T-DXd: 18.2 TPC: 8.3	9.9	0.48 (0.24, 0.95)

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR-negative, hormone receptor negative; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

- the comparisons of the potential treatment effect modifiers between ASCENT full population, ASCENT HER2-low population, and DESTINY-Breast04 HR-negative population. Please also comment on the population differences in terms of the potential treatment effect modifiers between the ASCENT HER2-low population and DESTINY-Breast04 HR-negative population.

The company conducted two independent ITC feasibility assessments ("*ITC feasibility assessment A*"[37] and "*ITC feasibility assessment B*"[36]) to determine whether a comparison between T-DXd and SG in the HER2-low/HR-negative population would be possible based on available data from the DESTINY-Breast04 and ASCENT studies.

ITC feasibility assessment A[37] identified relevant treatment effect modifiers by assessing the frequency that they were reported in a literature search of HTAs for advanced cancer treatments. Searches were conducted in the NICE and CADTH databases, supplemented by a grey literature search of ITCs and RCTs in HER2-negative u/mBC. Treatment effect modifiers were also evaluated by reviewing subgroup analyses conducted in the FAS of DESTINY-Breast04.

Based on the literature review, the most frequently reported treatment effect modifiers were: age, number of prior lines of therapy, ECOG performance status/Karnofsky score, sex/gender, tumour location, race/geographic region, HR-status, and brain metastases. Other potential treatment effect modifiers identified included smoking status, site of metastasis, stage at diagnosis, weight, time since diagnosis, duration and response to prior therapy, and disease-free interval.[37]

While data were available for all of the identified treatment effect modifiers in the HER2-low/HR-negative cohort of DESTINY-Breast04, for the HER2-low/HR-negative population in ASCENT, data were only reported for age, race, ECOG PS score, and number of prior chemotherapies. This relative paucity of published data from the ASCENT study means that it is not possible to assess the full range of identified treatment effect modifiers for a comparison between SG and T-DXd in the relevant population.

ITC feasibility assessment A[37] concluded the following regarding those treatment effect modifiers for which data were available for the HER2-low/HR-negative populations of both DESTINY-Breast04 and ASCENT:

- **Age:** Patient median age is slightly higher for the HER2-low/HR-negative population in DESTINY-Breast04 vs. ASCENT. Therefore, any matching based on age may reduce the effective sample size.
- **Number of lines of prior chemotherapy:** The ASCENT study enrolled patients treated with two or more prior lines of chemotherapy in the metastatic setting, whereas DESTINY-Breast04 enrolled patients with 1–2 prior lines of chemotherapy, meaning that there are differences in the inclusion criteria for this characteristic. In addition, there are differences in the reporting of data (DESTINY-Breast04 provided data on the proportion of patients receiving 1, 2, and ≥3 prior lines of chemotherapy in the metastatic setting, whereas ASCENT reported data on proportion receiving 2–3 or >3 prior lines of therapy), limiting the ability to provide a direct comparison. Based on this, there is limited ability to adjust for differences and any matching based on prior lines of chemotherapy would result in a reduced effective sample size due to limited overlap between the two trials.
- **ECOG PS**: *ITC feasibility assessment A*[37] reported differences in ECOG PS, with ASCENT having a higher proportion of patients with a ECOG score of 0 (indicating a healthier population) than in DESTINY-Breast04. These differences would need to be adjusted for in a matching-adjusted analysis, which would reduce the effective sample size.
- **Site of metastases**: Data on the proportion of patients with lung, liver, and brain metastases are not available in the HER2-low/HR-negative population of

ASCENT. However, based on data from the full population of ASCENT, the proportions are similar to those in DESTINY-Breast04. Given the lack of data in the HER2-low/HR-negative population of ASCENT, it is not possible to conclude with certainty on the comparability of the populations in terms of metastatic sites.

- **Race**: There was a large difference in the proportion of white and Asian patients in the HER2-low/HR-negative populations of DESTINY-Breast04 and ASCENT. This difference would need to be accounted for in an ITC and would reduce the effective sample size in a matched analysis.

ITC feasibility assessment A[37] concluded that there is limited availability of data for most treatment effect modifiers identified by the literature search, and for those modifiers with data available, there are clear differences in the populations between ASCENT and DESTINY-Breast04. This means that any unadjusted ITC would likely be highly uncertain and biased. In addition, a matching-adjusted indirect comparison (MAIC) would be limited by the treatment effect modifiers on which matching can be conducted and the reduced effective sample size would increase uncertainty. Based on this, *ITC feasibility assessment A* concluded that an ITC or MAIC is likely to be unreliable for decision-making.

In *ITC feasibility assessment B,*[36] treatment effect modifiers were conservatively assumed to be any reported randomisation stratification factors, any baseline characteristics, or any variables explored in subgroup analyses across DESTINY-Breast04 and ASCENT. *ITC feasibility assessment B*[36,36] concluded that a robust ITC would not be possible given the limited data availability for the treatment effect modifiers in the HER2-low/HR-negative population in ASCENT:

- **Stratification factors:** There were some differences in the stratification factors for DESTINY-Breast04 (HER2 IHC status, lines of prior chemotherapy in the metastatic setting, HR/CDK status) and ASCENT (lines of prior chemotherapy for advanced disease, brain metastases at baseline, geographic region), indicating differences in the study design.
- **Subgroup analyses:** There were similarities in the subgroup analyses considered for the full populations of DESTINY-Breast04 and ASCENT, but limited reporting of data for these variables in the ASCENT HER2-low/HR-

negative population specifically. This means that it is not possible to explore the impact of any differences in the ASCENT and DESTINY-Breast04 populations for these subgroups.

- **Baseline characteristics:** As noted in the *ITC feasibility assessment A*[37] and in the company submission Section B.2.9, there is limited data reporting for baseline characteristics in the HER2-low/HR-negative population of ASCENT specifically (data are only available for age, ECOG PS, and number of prior lines of chemotherapy). The impact of unreported treatment effect modifiers cannot be appropriately adjusted for in an ITC between T-DXd and SG. For the characteristics with available data:
    - **Age:** Median age was slightly higher in DESTINY-Breast04 than ASCENT in the HER2-low/HR-negative population, and the overlap between the age distributions is not known.
    - **Region:** There is limited reporting of data on region in the ASCENT HER2-low/HR-negative population specifically, meaning any differences cannot be adjusted for.
    - **Race:** There are large differences in race between the studies, with a much higher proportion of Asian patients in the DESTINY-Breast04 study vs. the ASCENT study. This means that any matching based on race is likely to result in a small effective sample size.
    - **Site of metastases:** While data exist for the DESTINY-Breast04 population, there are no published data on the presence of metastases in the HER2-low population of ASCENT specifically. For the full ASCENT population, the presence of liver and lung metastases is only reported for patients without brain metastases. These limitations in the reporting data in ASCENT means that matching the DESTINY-Breast04 and ASCENT populations based on metastatic sites would be challenging.
    - **Prior chemotherapy:** There are differences in the inclusion and exclusion criteria of ASCENT and DESTINY-Breast04 in terms of prior chemotherapy. There are also differences in the way in which the data

are reported, meaning the comparability of the populations cannot be proven.

- **ECOG PS:** The proportions of patients with ECOG PS 0 and 1 were considered similar between the two studies.[36]

As with *ITC feasibility assessment A,*[37] *ITC feasibility assessment B*[36] concluded that any ITC would be highly limited due to the small sample sizes in the HER2-low/HR-negative populations in the two studies and a lack of reported data for baseline characteristics in the ASCENT HER2-low population, which would prevent a robust assessment of potential treatment effect modifiers between the two studies. *ITC feasibility assessment B*[36] also confirmed that any matching-adjusted analyses would result in small effective sample sizes and wide confidence intervals for any point estimates, meaning results of any ITC would be highly uncertain. This reinforces the conclusion that an ITC would not be robust for HTA decision-making.

- an indirect treatment comparison (ITC) analysis of T-DXd and SG for PFS and OS adjusting for population differences.

As stated above, and in company submission Section B.2.8 and B.2.9, an ITC between T-DXd and SG in the HER2-low/HR-negative population would be of limited relevance and not robust for decision-making for the following reasons:

- The FAS in DESTINY-Breast04 is the relevant population for the scope of this appraisal as this reflects the full licensed indication for T-DXd in HER2-low u/mBC. The TPC arm of DESTINY-Breast04 is the relevant comparator in this appraisal and provides robust data for decision-making.
- SG is a treatment option for the HR-negative population only, which reflects a small subset (~10%)[34] of the full population relevant to this appraisal. SG is therefore not a relevant comparator for the full population under consideration in this appraisal.
- Given the available data, two independent ITC feasibility assessments[36,37] concluded that an ITC between T-DXd and SG, based on the HER2-low/HR-negative populations from DESTINY-Breast04 and ASCENT, would be highly uncertain and not robust for decision-making. The key reasons are the limited patient numbers, differences in trial eligibility criteria, limited reporting of

baseline characteristics (both of which limit the ability to adjust for the impact of potential treatment effect modifiers), and differences in the populations for the treatment effect modifiers for which data are available (which impacts the effective sample size once these differences are appropriately adjusted for).

The possibility of conducting indirect comparisons was also discussed with UK clinical and HEOR experts (including ex-NICE Committee and EAG members) at an Advisory Board in December 2022.[35] HEOR experts suggested that an ITC versus SG would be highly uncertain due to small sample sizes, differences in study design and heterogeneity between populations as well as the limited availability of data from the ASCENT study.[35] They concluded that an ITC would not be robust for HTA decision-making.[35]

In addition, clinical experts stated that the relative proportion of HR-positive and HR-negative patients in DESTINY-Breast04 was reflective of those seen in UK practice,[35] highlighting that the FAS data are generalisable to UK practice. Based on this, the uncertainty of any ITC, and clinical expert feedback relating to the current treatment of HER2-low patients in the UK, HEOR experts advised that stratifying DESTINY-Breast04 data based on HR-status would increase uncertainty.[35] The experts therefore concluded that, for decision-making in the full in-scope population under consideration in this appraisal, the FAS is the relevant dataset and the TPC arm of DESTINY-Breast04 is the relevant comparator.[35]

In conclusion, the company considers that the results of an ITC between T-DXd and SG in the HER2-low/HR-negative population would be highly uncertain and not informative for decision-making. In the full HER2-low indication relevant to this appraisal, a comparison of T-DXd vs. TPC from DESTINY-Breast04 in the FAS population provides the most robust evidence for decision-making.

Section B: Clarification on cost-effectiveness data

New company base case

Questions B35 and B37, as well as an additional question from NICE, resulted in corrections being made to the cost-effectiveness model. The ICER and associated change from the CS ICER for each correction are presented in **Table 10**. The updates result in a new base case ICER of £[redacted]. This is referred to as the “new

base case ICER". The original CS ICER of £[redacted] is referred to as the "CS base case ICER."

Table 10: A summary of the corrections and updates made to the base case CEA*

Question that the change relates to	Change	ICER*	Change from company submission base case ICER*
CS base case		[redacted]	–
B35	Corrected the formula for calculating administration cost for oral subsequent treatments. Updated the frequency of oral administration costs for capecitabine.	[redacted]	[redacted]
B37	Corrected the weightings of drugs in TPC.	[redacted]	[redacted]
Additional question on eMIT pricing of gemcitabine from NICE	Corrected the unit options that were available for gemcitabine	[redacted]	[redacted]
New base case ICER		[redacted]	[redacted]

*Changes have compounding effect on the ICER and therefore values do not add to the total.
Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; EAG, Economic Assessment Group; eMIT, electronic market information tool; ICER, incremental cost-effectiveness ratio; TPC, treatment of physician's choice.

The new company deterministic base case results (T-DXd patient access scheme [PAS] price; no severity modifier) are presented in **Table 11**. For reference, the CS deterministic base case results (T-DXd PAS price; no severity modifier) are presented in **Table 12**.

Table 11: New base case deterministic results in the FAS population (T-DXd PAS price; no severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 12: Company submission base case deterministic results in the FAS population (T-DXd PAS price; no severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Clinical effectiveness and survival analyses

B1. PRIORITY. Please provide a cost-effectiveness analysis of T-Dxd vs SG in the HER2-low/HR-negative subgroup informed by the ITC requested in question A21. This will assist the committee in making evidence-based recommendations for the HR-negative subgroup and the EAG anticipates that this will be key area of uncertainty for the committee if this comparison is not provided.

As per the response to A20, the company does not consider SG to be a relevant comparator for the full appraisal population, and as per A21, it is not possible to conduct a robust ITC for the HER2-low/HR-negative subgroup to inform decision-making. Company response to Question A21 summarises findings from the two independent feasibility assessments, which determined that a robust ITC between T-DXd and TPC in the HER2-low/HR-negative population would not be possible given the limited data availability for treatment effect modifiers in ASCENT and the differences in populations between ASCENT and DESTINY-Breast04. The company therefore considers that a cost-effectiveness analysis of T-DXd vs SG would not be informative for decision-making and as such an analysis is not presented.

While a robust ITC is not possible, the naïve comparison in the company response to A21 shows that T-DXd and SG have similar relative treatment effect for PFS and OS vs. TPC in the HER2-low/HR-negative population. This supports a conclusion of similar efficacy between T-DXd and SG in the HER2-low/HR-negative population. To assist the Committee in their decision-making for this subset of patients, the company has therefore presented an exploratory cost-minimisation analysis (CMA) comparing T-DXd and SG in the HER2-low/HR-negative population.

Efficacy

The company have assumed equal efficacy between T-DXd and SG in the HER2-low/HR-negative population throughout the time horizon of the model. This includes:

- Equal PFS, OS, and time to treatment discontinuation (TTD) distributions for T-DXd and SG.

- An equal proportion of patients receive subsequent treatment following T-DXd and SG, and equal distributions of the subsequent treatments received.

Treatment acquisition costs

The cost of SG was sourced from the British National Formulary (BNF) and is presented in **Table 13**. The dosing regimen of SG was sourced for the Summary of Product Characteristics (SmPC) and is presented in **Table 14**.

Table 13: Unit drug cost for SG

Drug	Formulation	Unit size	Pack size	List price	Source
Sacituzumab govitecan	Vial	180mg	1	£793	BNF 2022

Table 14: Dose regimens for Sacituzumab govitecan

Treatment	Dosing Regimen used in the model
Sacituzumab govitecan	10 mg/kg twice on Days 1 and 8; cycled every 21 days

Adverse events

The company have assumed equal AE rates between T-DXd and SG in the HR-negative population. As safety data were not presented for the HR-negative subgroup within the CSR for DESTINY-Breast04, AE rates in the safety analysis set (SAS) for T-DXd were used. Specific AE rates sourced from the ASCENT trial are applied in a scenario analysis in **Table 16**.

Results

The deterministic CMA results for T-DXd vs SG are presented in **Table 15**. They demonstrate a total cost of £[redacted] for T-DXd and a total cost of £[redacted] for SG, resulting in an incremental saving of £[redacted] over a lifetime horizon. Whilst the company recognise that the CMA scenario has been run with a list price for SG, the cost-savings associated with T-DXd are considerable compared to SG.

Table 15: Deterministic CMA results in the HR-negative population

Technology	Total costs (£)	Incremental costs (£)
T-DXd	[redacted]	-
SG	[redacted]	[redacted]

Abbreviations: CMA, cost-minimisation analysis; FAS, full analysis set; T-DXd, trastuzumab deruxtecan; SG, sacituzumab govitecan.

Scenario analysis

As an additional scenario, the company have applied AE rates, as sourced from the ASCENT trial, to the SG treatment arm.[23] Febrile neutropenia was included as an additional Grade ≥3 AE as it occurred in 5.81% of SG patients, as sourced from the ASCENT trial (SAS). The same AE occurred in only 0.3% of T-DXd patients (SAS).[6,23] The cost for febrile neutropenia was sourced from TA423, aligned with TA819, and inflated to 2021 using PSSRU 2021.[29,39,40]

The deterministic CMA results for T-DXd vs SG for this scenario are presented in **Table 16**. They demonstrate a total cost of £[redacted] for T-DXd and a total cost of £[redacted] for SG, resulting in an incremental saving of £[redacted] over a lifetime horizon.

Table 16: Deterministic CMA results in the HR-negative population with AE rates sourced from ASCENT and applied to the SG treatment arm

Technology	Total costs (£)	Incremental costs (£)
T-DXd	[redacted]	-
SG	[redacted]	[redacted]

Abbreviations: CMA, cost-minimisation analysis; FAS, full analysis set; T-DXd, trastuzumab deruxtecan; SG, sacituzumab govitecan.

B2. PRIORITY. CS Section B3.3. Please provide plots showing the empirical/unsmoothed and smoothed hazard functions for the data used in the analysis for PFS, OS and time to treatment discontinuation (TTD). Please also plot the modelled hazards of each of the parametric survival models for PFS, OS and TTD on top of the empirical and smoothed hazard.

The empirical/unsmoothed and smoothed hazard functions for PFS, OS, and TTD are provided in **Figure 8**, **Figure 9**, and **Figure 10**, respectively. The smoothed hazards were estimated using the muhaz function in R, which is subject to some limitations. In particular, kernel smoothing is subject to unreliable estimates in the boundary region, as the support of the kernel exceeds the observed data.[41]

[redacted] For OS, the smoothed hazard rates follow a similar trend between the two arms, [redacted]

[redacted]

The modelled hazards for each of the parametric survival models can be found in the reference pack along with the smoothed and unsmoothed hazard rates. For PFS, similar modelled hazards were obtained for the log-normal, log-logistic, and generalised gamma distributions, with hazards [redacted]. For OS, similar modelled hazards were obtained for the log-normal and log-logistic distributions, with hazards [redacted]. For TTD, similar shapes for the modelled hazards were obtained for the log-normal, log-logistic, and generalised gamma distributions. However, the hazards [redacted] for the generalised gamma distribution throughout the time horizon than for log-logistic and log-normal, which may be more indicative of the true proportion of patients still on treatment throughout the extrapolation phase of TTD.

Figure 8: Smoothed and unsmoothed hazard rates - Progression-free survival based on BICR - FAS

Abbreviations: BICR, blinded independent central review; FAS, full analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 9: Smoothed and unsmoothed hazard rates - Overall survival - FAS

Abbreviations: FAS, full analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 10: Smoothed and unsmoothed hazard rates - Time to treatment discontinuation - FAS

Abbreviations: FAS, full analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B3. CS Section B.3.3.2.1. Please provide the reference that parametric fits whose AIC/BIC scores are within 5 points could be considered alternatively good fits.

A study supports that parametric fits whose Aikake Information Criterion (AIC)/Bayesian Information Criterion (BIC) scores are within 5 points could be considered alternatively good fits:

- Burnham & Anderson (2011) provides a rule of thumb when assessing the differences between AIC scores. On page 29 they state that "*Models where Δ is in the 2–7 range have some support and should rarely be dismissed*". See also Figure 2 on page 25 of Burnham & Anderson (2011).[42]

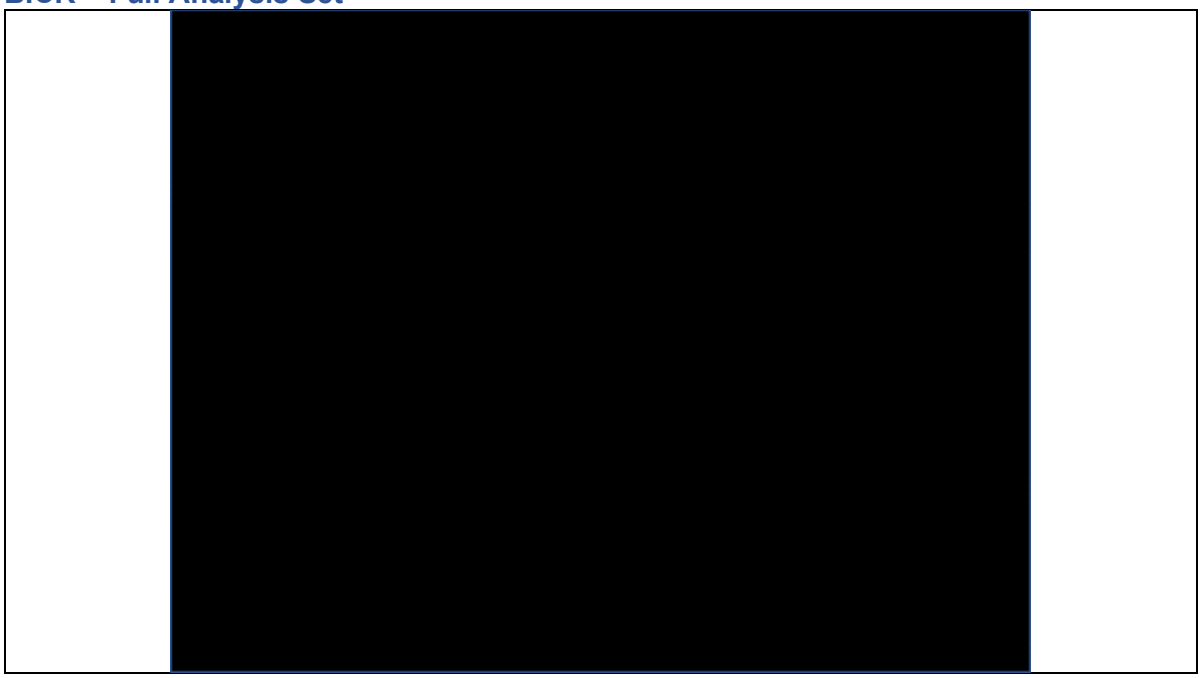
Reference:

- Burnham, K.P., Anderson, D.R. & Huyvaert, K.P. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. Behav Ecol Sociobiol 65, 23–35 (2011). https://doi.org/10.1007/s00265-010-1029-6

B4. CS Section B.3.3.2. Please provide the plots (log (S(t)/(1-S(t))) vs log(t)) to check the suitability of log-logistic distributions for PFS, OS and TTD.

The plots of (log (S(t)/(1-S(t))) vs log(t)) for PFS, OS, and TTD can be found in **Figure 11**, **Figure 12**, and **Figure 13**, respectively. For all three endpoints, [redacted] As such, based on the visual assessment of the diagnostic plot, the log-logistic model would be a suitable choice for PFS, OS, and TTD. This is also supported by the AIC and BIC statistics.

Figure 11: Plot of (log (S(t)/(1-S(t))) vs log(t)) – Progression-free survival based on BICR – Full Analysis Set



Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 12: Plot of (log (S(t)/(1-S(t))) vs log(t)) – Overall survival – Full Analysis Set

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 13: Plot of (log (S(t)/(1-S(t))) vs log(t)) – Time to treatment discontinuation – Full Analysis Set

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B5. CS Section B.3.3.2. Please provide the plots (Inverse.normal(1-S(t)) vs log(t)) to check the suitability of log-normal distributions for PFS, OS and TTD.

The plots of (Inverse.normal(1-S(t)) vs log(t)) for PFS, OS, and TTD can be found in **Figure 14**, **Figure 15**, and **Figure 16**, respectively. For PFS,

[redacted] As such, based solely on the visual assessment of the diagnostic plot, a log-normal distribution may fit the data well. For OS,

[redacted] indicating that the log-normal distribution may not fit the data well. Finally, for TTD,

[redacted] indicating that it may be an appropriate model choice.

Figure 14: (Inverse.normal(1-S(t)) vs log(t)) – Progression-free survival based on BICR – Full Analysis Set

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 15: (Inverse.normal(1-S(t)) vs log(t)) – Overall survival – Full Analysis Set

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 16: (Inverse.normal(1-S(t)) vs log(t)) – Time to treatment discontinuation – Full Analysis Set

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B6. CS Section B.3.3.2.3. Please clarify why the generalised gamma curve was selected to inform the base case analysis for TTD for both arms given that both the log-logistic and generalised gamma provide a good visual fit.

Across the T-DXd and TPC arms, the generalised gamma and log-logistic distributions, respectively, provide the best visual and statistical fit to the Kaplan-Meier (KM) TTD data from DESTINY-Breast04. In addition, both distributions provide a good fit to both trial arms. Therefore, for consistency, the same distribution was selected for both arms as advised for PFS and OS by HEOR and clinical experts. This is also recommended by NICE Technical Support Document (TSD) 14 that says "similar types of models should be used for the different treatment arms unless there is strong evidence to suggest an alternative is more plausible".[43] The generalised gamma was selected for the base case given the log-logistic predicted long-term estimates of time on treatment which were considered an outlier compared with all other distributions (CS Table 40).[44] This was considered important given the maturity of the data and the closeness of fit of all distributions to the KM data;

- The log-logistic distribution for TPC predicts that [redacted] of patients would remain on treatment at 5 years, compared with all other modelled distributions which predict [redacted] (**Table 17**).
- The log-logistic distribution for T-DXd predicts that [redacted] of patients would remain on treatment at 5 years, compared with all other modelled distributions which predict [redacted] (**Table 17**).

The long-term TTD survival predictions with the generalised gamma distributions lie in the centre of the range of all distributions ([redacted] and [redacted] at 5 years, for TPC and T-DXd, respectively) and this was considered a plausible long-term estimate of time on treatment in both arms. Therefore, the generalised gamma was selected for the model base case for TTD.

Table 17: 5-year TTD in the FAS population: Predictions by independently fitted distributions for TPC and T-DXd (CS Table 40)

Distribution	TPC	T-DXd
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time to treatment discontinuation.

B7. CS Section B.3.3.2.1. Please clarify if the survival estimates for OS provided in Table 36 are after adjustment for all-cause mortality. Please also confirm if the EAG is correct in understanding that all-cause mortality hazards for each cycle have been added to the hazard of death for each cycle predicted by the parametric survival modelling without any adjustment for the fact that breast cancer contributes to all-cause mortality.

The company can confirm that in order to ensure the modelled survival estimates for OS do not lead to an estimated hazard of death below that of the age- and sex-adjusted general population, all-cause mortality hazards are added to the hazard of death for each cycle in the model; this is the internal additive hazards approach and is consistent with NICE guidance.[45,46] Age-specific background mortality rates were derived from the 2018–2020 National Life Tables for England & Wales,[47] and weighted averages of male and female mortality risks were added to extrapolations, reflecting the sex distribution of patients in the DESTINY-Breast04 trial.

The approach taken used all-cause mortality data that had not been adjusted for HER2-low breast cancer-related mortality in the general population. The population of HER2-low u/mBC patients eligible for treatment with T-DXd is estimated to be 946 from a population of 45,291 breast cancer patients.[34] Therefore, due to the small proportion of HER2-low BC patients, adjustment is unlikely to have a significant impact on general population mortality.

Finally, survival estimates in Table 36 of the CS do include adjustment for general population mortality. The footnote under Table 36 applies to all columns, and should be corrected to "*Median time in months **and predicted OS** are estimated after OS has **been adjusted to include general population mortality**". The footnote under

CS Table 38 also applies to all columns, and should be amended to "*Median time in months **and predicted PFS** are estimated after PFS has been capped by OS". A footnote should be added to CS Table 40, applying to all columns, stating "Median time in months and **predicted TTD** are estimated after TTD has been capped by PFS".

B8. CS Sections B.3.3.2.2. and B.3.3.4. Please clarify why the Kaplan-Meier (KM) curve of PFS for T-DXd in Figure 37 (where it drops to zero) is different from the KM curve of PFS for T-DXd in Figure 43.

Thank you for bringing this to our attention. The T-DXd PFS KM data presented in Figure 31, Figure 34, Figure 36 and Figure 37 of the CS are correctly showing PFS KM curves ending with a drop to zero; these figures are consistent with the T-DXd PFS KM presented in the CSR. The graphs in Figure 43 and Figure 45 of the CS, that did not drop to zero, did not include the last data point on the T-DXd PFS KM curve from the economic model. An updated version of CS Figure 43 (**Figure 17**) and CS Figure 45 (**Figure 18**) are provided below. No changes were required in the submitted economic model, as all KM data and associated plots were correct.

Figure 17: Summary of base case* efficacy (OS, PFS and TTD) for T-DXd in the FAS population (correction to Figure 43 in CS)

*The following distributions are presented for the base case: log-logistic for OS, log-logistic for PFS, and generalised gamma for TTD.
Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Figure 18: Summary of base case efficacy* (OS, PFS and TTD) for TPC and T-DXd in the FAS population (correction to Figure 45 in CS)

*The following distributions are presented for the base case: log-logistic for OS, log-logistic for PFS, and generalised gamma for TTD.
Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Quality of life

B9. CS Section B.3.4. Please provide the following density plots for the following:

- progression-free utility for patients on T-DXd
- post-progression utility for patients on T-DXd
- progression-free utility for patients on TPC
- post-progression utility for patients on TPC

The histograms and density plots for the progression-free and post-progression utilities for patients in the T-DXd and TPC arms can be found in **Figure 19** to **Figure 22**. The density plots include both the normal probability density function and the kernel density estimation. The distribution of progression-free utilities for T-DXd patients (**Figure 19**) is [redacted] with a greater concentration of utility values close to [redacted]. In addition, there is a peak in which over [redacted]% of observations have a utility value of [redacted]. The distribution of post-progression utilities for T-DXd (**Figure 20**) shows a similar [redacted] distribution, with a high concentration of utility values near [redacted]. Similar results were obtained for TPC (**Figure 21** and **Figure 22**), though

the distribution of utilities in both the progression-free and progressed health states are slightly lower than what was observed for T-DXd.

Figure 19: Histogram and density plot of progression-free utilities for T-DXd patients – FAS

Abbreviations: FAS, full analysis set; T-DXd, trastuzumab deruxtecan.

Figure 20: Histogram and density plot of post-progression utilities for T-DXd patients – FAS

Abbreviations: FAS, full analysis set; T-DXd, trastuzumab deruxtecan.

Figure 21: Histogram and density plot of progression-free utilities for TPC patients – FAS

Abbreviations: FAS, full analysis set; TPC, treatment of physician's choice.

Figure 22: Histogram and density plot of post-progression utilities for TPC patients – FAS

Abbreviations: FAS, full analysis set; TPC, treatment of physician's choice.

B10. PRIORITY. CS Section B.3.4.2. Please add the following subgroups to the summary utility results presented in CS Table 43:

- T-DXd; TPC

- On-treatment; off-treatment
- T-DXd & progression-free; T-DXd & post-progression; TPC & progression-free; TPC & post-progression
- T-DXd & progression-free & on-treatment; T-DXd & progression-free & off-treatment; TPC & progression-free & on-treatment; TPC & progression-free & off-treatment

The economic model uses a three-state structure; utilities are stratified by progression status and by treatment arm. As such a fourth health state (off-treatment) is not included in the model. A three-state structure is consistent with previously accepted models in TA509, TA458, TA862, TA423, and TA786.[9,39,48–50]

The summary of utility values by treatment (T-DXd and TPC) and overall can be found in **Table 18**. The mean utility values, across health states, were [redacted] and [redacted] for T-DXd and TPC, respectively.

Table 19 reports the utility values by treatment status (on-treatment and off-treatment). In the FAS, the mean utility value on-treatment was [redacted], which is the same as the mean utility value observed for the progression-free health state in CS Table 43. Off-treatment, the mean utility value dropped to [redacted], which is slightly lower than the mean utility observed post-progression ([redacted]).

Utility values by progression status (progression-free and progressed) can be found in **Table 20.** The mean utility values are higher in the progression-free health state than the progressed health state, with higher values obtained for T-DXd than TPC. In the progression-free health state, the mean observed utility values were [redacted] for T-DXd and [redacted] for TPC. Post-progression, the mean values dropped to [redacted] and [redacted] for T-DXd and TPC, respectively.

Finally, **Table 21** presents the progression-free utility values by treatment status. As expected, higher average utility values are obtained in the progression-free health state when still on treatment than after discontinuing treatment. While on treatment, mean progression-free utility values were [redacted] for T-DXd and [redacted] for TPC. Off-treatment, the mean utility values dropped to [redacted] for T-DXd and [redacted] for TPC.

Table 18: Summary of utility values by treatment group – Full Analysis Set

Utility scores	T-DXd (N=373)	TPC (N=184)	Total (N=557)
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

*N is the number of visits/timepoints.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 19: Summary of utility values by treatment status – Full Analysis Set

Utility scores	T-DXd (N=373)	TPC (N=184)	Total (N=557)
On-treatment			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Off-treatment			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

*N is the number of visits/timepoints.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 20: Summary of utility values by progression status – Full Analysis Set

Utility scores	T-DXd (N=373)	TPC (N=184)	Total (N=557)
Progression-free			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Progressed			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Utility scores	T-DXd (N=373)	TPC (N=184)	Total (N=557)
Min, Max	[redacted]	[redacted]	[redacted]

*N is the number of visits/timepoints.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 21: Summary of progression-free utility values by treatment status – Full Analysis Set

Utility scores	T-DXd (N=373)	TPC (N=184)	Total (N=557)
Progression-free & on-treatment			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Progression-free & off-treatment			
N*	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

*N is the number of visits/timepoints.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B11. CS Section B.3.4.2. Please specify the model equation used for the final model in the generalised linear mixed approach. Please also clarify how the error terms were modelled across time (e.g., independent or correlated). If a correlation structure was assumed, please specify the model for error terms across time.

The final generalised linear mixed model can be written as follows:

$$\ln(y_{ij}) = \beta_0 + \alpha_{0i} + \beta_1 trt_i + \beta_2 ECOG_i + \beta_3 prog_{ij} + \beta_4 trt\_stat_{ij} + \alpha_{1i} t_{ij} + e_{ij}$$

Where y_{ij} equals $1 - utility_{ij}$ for patient i at visit j, trt_i is the planned treatment for patient i (T-DXd or TPC), $ECOG_i$ is the ECOG performance status at baseline for patient i, $prog_{ij}$ is the progression status (progression-free or progressed) for patient i at visit j, and trt_stat_{ij} is the treatment status (on or off-treatment) for patient i at visit j. Therefore, β corresponds to the coefficients of the fixed effects, and the final model contained both a random intercept, α_{0i}, and a random slope, $\alpha_{1i} t_{ij}$, where t_{ij} is the jth visit time in days for patient i.

The model assumes that the residuals for each subject are independent, $e_{ij} \sim \mathcal{N}(0, \sigma_e^2)$. In addition, an unstructured covariance matrix was used to model the within-subject correlation of the random effects, α_{0i} and α_{1i}. The optimal covariance matrix was selected based on the lowest AIC and BIC among the following: unstructured, autoregressive, and compound symmetry. The resulting unstructured covariance matrix resulted in three covariance parameter estimates, the variance of the random patient-specific time effects, the variance of the random patient-specific intercepts, and the covariance between the two patient-specific random effects.

B12. CS Section B.3.4.2. Please specify the initial model used in the utility analysis. Please also clarify why no interaction terms (such as an interaction between progression status and treatment status) were included in the model.

The model selection was based on a backward elimination approach, where the initial full model included treatment, age, number of metastatic sites, ECOG performance status, hormone receptor status, progression status (progression versus progression-free) at the corresponding visit, treatment status (on-treatment versus off-treatment) at the corresponding visit, and interaction terms between each health state of interest and treatment (i.e., progression status*treatment, treatment status*treatment). Interaction terms between other variables were not included in the initial model because the primary interest was to report health state utilities overall and by treatment arm; including other interaction terms would have made reporting utilities by progression status and treatment status more complex. In addition, certain combinations of an interaction term between progression status and treatment status would not contain enough data points, such as progressed patients on-treatment, as disease progression would constitute treatment discontinuation in accordance with the protocol.

Using the initial full model, the optimal random effects (subject, timing of questionnaire, or both) were identified based on the lowest AIC and BIC. The full model with the optimal random effects was then be used to identify the most appropriate covariance matrix structure based on the lowest AIC and BIC among the following: unstructured, autoregressive, and compound symmetry.

Starting from the full model using the optimal random structure, the fixed effects to include were then selected. The variable with the highest p-value based on the t-

statistic was eliminated in a stepwise fashion, until all variables included in the model were significant at a 5% significance level.

The fit of the final model was then assessed by plotting the conditional studentized residuals against the predicted values. The normality of the residuals was evaluated graphically through histograms of the residuals. If the residuals showed heterogeneity or non-normality, then a log-normal distribution of modelling utility decrements (1-utility) was considered.[51]

B13. CS Section B.3.4.2. The final model includes ECOG performance status. Please clarify if only ECOG at baseline was included as a covariate in the model.

Only ECOG at baseline was included as a covariate in the model. This is because ECOG scores post-randomisation could be affected by the treatment received. As such, only health states (progression status and treatment status) were included as covariates at each visit; all other covariates were included at baseline only.

B14. CS Section B.3.4.2. Please clarify how to interpret the regression coefficients presented in CS Table 44.

The regression coefficients provided in Table 44 of the CS correspond to the regression coefficients of $\ln(1 - utility)$, where $\ln(1 - utility) \sim \mathcal{N}(\mu, \sigma^2)$. As such, without conducting a back transformation to their natural scale, it is possible to conclude that negative regression coefficients denote an improvement in quality of life, but the numerical values should not be interpreted. In Table 45 of the CS, the following back transformation was applied to obtain the utility values per health state on their natural scale:[52]

$$\omega = \exp(\sigma^2)$$
$$\hat{u} = 1 - \exp(\mu)\sqrt{\omega}$$
$$Var(\hat{u}) = \exp(2\mu)\,\omega(\omega - 1)$$

Where $\hat{u}$ is the estimated utility value on its natural scale after applying the back transformation.

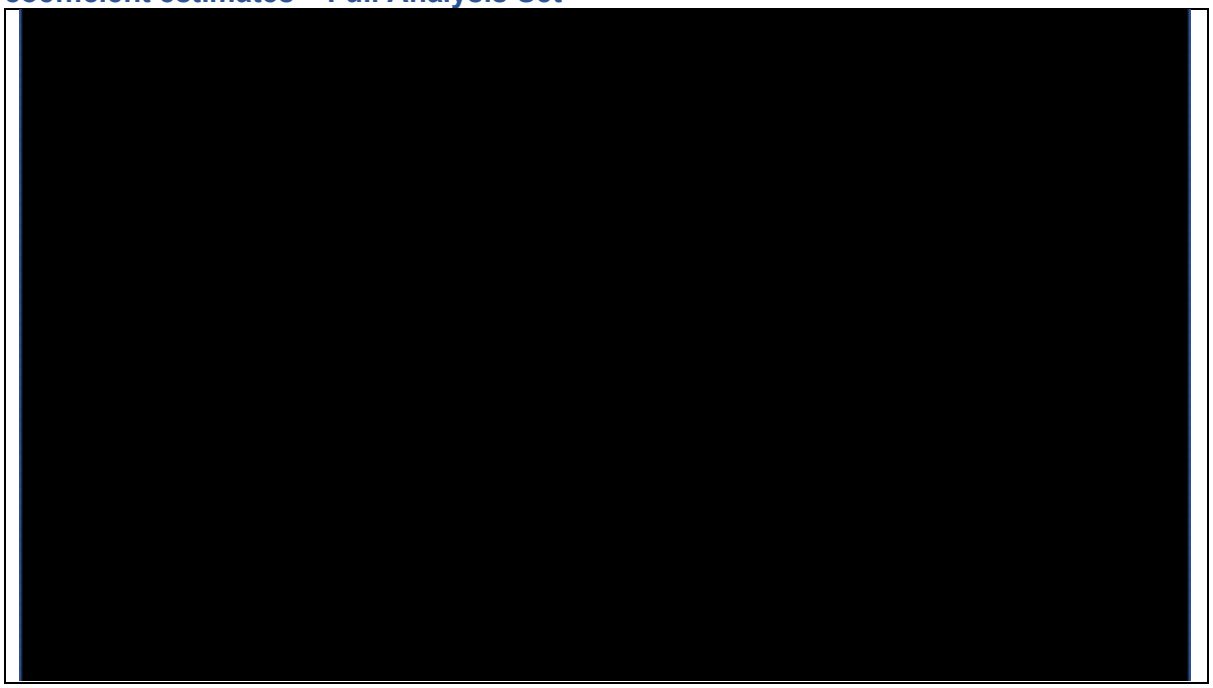
B15. PRIORITY. CS Section B.3.4.2 Table 45: Please provide the detailed calculation on how the utility values were derived. Please justify the choice of

using the mean time point (equal to [redacted] days) to derive the utility values in Table 45 and please comment on the impact if a different time point was used.

The utility values were estimated using the final generalised linear mixed model as described in B11. The utility values per health state were then derived from this model using least-square means, which estimate the population averages over a balanced population. As such, least-square means automatically calculate the response variable (utilities) at the mean timepoint of all included observations. For the other covariates included in the final model (ECOG at baseline and treatment status), the coefficients were changed to be proportional to those found in the input dataset of DESTINY-Breast04 for the model rather than balanced (assuming a 50/50 split). However, it is not possible to use a different time point for calculating the least-square means as time was not included as a fixed effect model but only as a random effect. As it was not included as a covariate, the choice of timepoint should not have a significant impact on the utility value estimates as it would only impact the covariance of the random effects.

An additional analysis was conducted that calculated the utility values for each pairwise combination of covariates based on the back-transformed regression coefficients (**Figure 23**). The mean utility values based on the regression coefficients do not make an assumption on the timepoint at which the utilities were derived. The population averages obtained from the least-square means per health state (progression-free and progressed) are similar to the back-transformed utility values for each pairwise combination of covariates based on the regression coefficients. The lowest utility values were obtained for observations off-treatment with a baseline ECOG score of 1, but as this combination does not represent a large proportion of observations in the dataset, the least-square means more closely resembles the other pairwise combinations.

Figure 23: Forest plot of mapped UK EQ-5D-3L utility values from DESTINY-Breast04 based on generalised linear mixed model – least square means versus regression coefficient estimates – Full Analysis Set



Abbreviations: GLMM: generalised linear mixed model; LSM: least-square means; CI: confidence interval.

B16. CS Section B.3.4.2. Please explain why the utility values by progression status and treatment arm presented in CS Table 45 are significantly different to the summary utility values presented in CS Table 43.

Differences in the utility values by progression status and treatment arm in the generalised linear mixed model (GLMM) compared to the descriptive statistics can be attributed to several reasons:

1. Utility values are [redacted], with a greater proportion of values closer to [redacted]. The raw means may therefore bias the results by being more heavily influenced by the outlying values closer to zero.

2. The effect of progression status on utilities is prone to confounding bias when only evaluating the values descriptively, since other variables, such as ECOG performance status and treatment status, have both an impact on quality of life and are risk factors for progression.

The GLMM approach mitigates these limitations by taking a linear transformation to model utility decrements and choosing a log-normal distribution, as recommended in the ISPOR Good Research Practices Task Force Report,[51] and using a backward elimination approach to select all significant variables in the model.

B17. CS Section B.3.4.2. Please clarify what software was used to perform the generalised linear mixed model and provide the code.

SAS version 9.4 was used to perform the generalised linear mixed model using the GLIMMIX Procedure. The derivation details can be found below:

[redacted]

[redacted]

[redacted]

B18. CS Section B.3.4.3 Table 46. Why were different ages used for each treatment arm when calculating the utility values for progressed disease using the Lloyd algorithm? Please recalculate using the mean age for the whole trial cohort.

The company considers that it is appropriate to apply a treatment-specific age in the *'post-progression'* health state utility calculations within the company base case, consistent with the utility estimates in the *'progression-free'* health state.

'*Progression-free*' utility values were derived from EQ-5D-5L data, directly collected in DESTINY-Breast04. EQ-5D-5L data were mapped to EQ-5D-3L to estimate treatment-specific utility values using the function developed by Hernandez Alava et al.,[53] in line with the reference case in the NICE methods guide;[54] age is included in the mapping function. Mapped EQ-5D-3L utility values were subsequently used within the GLMM to estimate '*progression-free*' health state utility values, and therefore age within each treatment arm is incorporated into the '*progression-free*' utilities for T-DXd and TPC.

The Lloyd et al. algorithm[55] was used to calculate treatment-specific utilities for post-progression and therefore different ages were used for each treatment arm. The Lloyd et al. algorithm implemented treatment-specific coefficients into the regression model, which included age and treatment response, to reflect the estimated utilities more accurately in each arm and to take into account the potential differences in age. Therefore, the use of treatment-specific age within the *'post-progression'* utility estimates is consistent with the use of treatment-specific age in the *'progression-free'* health state utility estimates.

As requested, the company have recalculated the utility values for '*post-progression*' using the Lloyd et al. algorithm and the mean age of 56.5 years for the whole trial cohort (CS Table 15).[44,55] The progressed utility values are very similar using the mean age for the entire trial ([redacted] and [redacted] for T-DXd and TPC, respectively) rather than median age for each treatment arm (0.6101 and 0.5655 for T-DXd and TPC, respectively [CS Table 51]) since age was well balanced between the two treatment arms given the randomised design of the trial. The utility values calculated for the '*post-progression*' health state using the mean age for the whole trial cohort are presented in **Table 22**.

Table 22: Summary of utility values for cost-effectiveness analysis using the mean age of the trial cohort to calculate the PP utility values with the Lloyd algorithm

Technology	Progressed disease utility value: mean
T-DXd	[redacted]
TPC	[redacted]

Abbreviations: PP, post-progression; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

A scenario analysis using the utility values presented in **Table 22** has been performed within the corrected model. The deterministic cost-effectiveness results are presented in **Table 23** and demonstrate a minimal increase from the new base case ICER of £[redacted] to £[redacted].

Table 23: Scenario deterministic results in the FAS population (T-DXd PAS price; no severity modifier, utility values for 'post-progression' calculated using mean age for whole trial cohort)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B19. CS Section B.3.4.4. Please justify why no disutilities were applied for adverse events (AEs) likely to have symptoms that would expected to impact health-related quality of life (HRQoL), particularly anaemia, fatigue and interstitial lung disease (ILD).

The company considers that it is not appropriate to include disutilities associated with AEs in the base case analysis. As detailed in Section B.2.10.2 of the CS[44], the majority of TEAEs were Grade 1 or 2 in severity, occurred most frequently in [redacted], and [redacted] over subsequent cycles and hence the impact would most likely be accounted for within the '*progression-free*' health state. To align with this, in Section B.3.4.5 of the CS, the company specify that in the '*progression-free'* health state, the base case applies treatment-specific EQ-5D-3L utilities derived from directly collected EQ-5D-5L data from DESTINY-Breast04[6]. Therefore, it is expected that the impact of AEs on HRQoL is already captured within the treatment-specific, trial-based utilities. The implementation of additional disutilities due to AEs would therefore lead to double counting of utility decrement.

The use of treatment-specific utility values based on EQ-5D data collected from clinical trials and the exclusion of AE disutilities being implemented in a cost-effectiveness analysis (CEA) base case has been accepted as a reasonable assumption in previous NICE Technology Appraisals (TAs), including TA862 (T-DXd for treating HER2-positive u/mBC after 1 or more anti-HER2 treatments),[9] TA819 (sacituzumab govitecan for treating unresectable triple-negative advanced BC after 2 or more therapies)[29] and TA786 (tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced BC after 2 or more anti-HER2 therapies).[50]

However, the company does explore the impact of applying AE disutilities as a scenario within the CS (scenario 7 probabilistic results presented in Table 72 of the CS).[44] Deterministic results of this scenario, updated after the correction of errors identified by the EAG within the base case and within Question B36, are presented in **Table 24**. Results show a minimal impact on cost-effectiveness from the new base case, increasing the ICER from £[redacted] to £[redacted] (**Table 10**).

Table 24: Scenario deterministic results in the FAS population (T-DXd PAS price; no severity modifier, AE disutilities included)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B20. CS Section B.3.4.5. Please justify and provide evidence on why the post-progression utility benefit of T-DXd compared with TPC would continue for the duration of the person's life. Additionally, please provide a scenario analysis where the benefit is only applied for a limited period of time post-progression.

The company considers that a post-progression utility benefit for patients treated with T-DXd is an appropriate assumption to be included in the base case. As detailed in Section B.3.4 of the CS[44], post-progression utility benefit of T-DXd compared with TPC was assumed to continue for the duration of a person's life due to lower tumour burden and higher utility at progression in patients treated with T-DXd; this is supported by evidence demonstrated within DESTINY-Breast04 and as detailed in Section B.2.6.1.3 of the CS.[6,44]

Complete response (CR) and partial response (PR) are considered important and valuable measures of the efficacy of T-DXd and were measured as part of the secondary objectives of DESTINY-Breast04.[6] The disease control rate (defined as the sum of patients with best overall response of CR, PR or stable disease [SD]) by BICR was statistically significantly greater in the T-DXd arm (87.1%; 325 of 373 patients) compared with the TPC arm (65.8%; 121 of 184 patients; p<0.0001).[6] Similarly, the confirmed objective response rate (ORR) (CR+PR) by BICR was more than three times higher and also statistically significantly greater with T-DXd (52.3%; 195[a] patients) compared with TPC (16.3%; 30 patients; p<0.0001; Table 21 of the CS). The clinical benefit rate (CBR) (CR+PR+SD) by BICR, demonstrating sustained response for at least six months, was also statistically significantly greater with T-

[a] One subject in the T-DXd arm who had a confirmed best overall response of complete or partial response had a baseline scan done after randomisation but before the first dose and thus was considered a non-responder in the calculation of confirmed ORR

DXd than TPC (70.2% vs. 33.7%; p<0.0001; FAS). The clinical evidence demonstrates significantly better disease control during progression-free disease.

Along with this, within DESTINY-Breast-04, Grade ≥3 TEAEs, which are expected to have a greater impact on patients' HRQoL due to the increased severity, were reported at a lower incidence in the T-DXd arm (52.6%) than in the TPC arm (67.4%) thereby reducing the burden on patients' HRQoL. Similarly, while drug-related TEAEs were reported in a similar incidence in the T-DXd and TPC arms (96.2% vs. 94.2%), the incidence of drug-related Grade ≥3 TEAEs was lower in the T-DXd arm (41.5% vs. 57.6%) which again is reflected in higher HRQoL in patients treated with T-DXd compared with TPC.[6]

The greater response rates and lower incidence of Grade ≥3 TEAEs highlighted above, provides clinical rationale for the higher HRQoL for patients receiving T-DXd. Whilst this is evidently supported and demonstrated in DESTINY-Breast04 through the higher '*progression-free'* utility values for patients treated with T-DXd ([redacted]) compared to patients treated with TPC ([redacted]), it is also clearly supported through '*post-progression'* utility values derived from DESTINY-Breast04 for patients treated with T-DXd ([redacted]) compared to patients treated with TPC ([redacted]) (Table 45 of the CS). This result means that patients who experience disease progression following treatment with T-DXd have a higher utility upon progression than those patients who experience disease progression following treatment with TPC. Both a lower tumour burden at progression and maintenance of HRQoL, as demonstrated in DESTINY-Breast04 across a range of generic (EQ-5D-5L) and cancer-specific (EORTC QLQ-C30 and EORTC QLQ-BR45) patient-reported outcomes (PRO) instruments, support a higher utility at progression in patients treated with T-DXd compared to patients treated with TPC.

Given the clinical and HRQoL outcomes observed in DESTINY-Breast04, it would not be appropriate to assume an equal '*post-progression'* utility for both treatment arms as it is not clinically plausible that patients treated with T-DXd would experience such a large and immediate decline in HRQoL as soon as they progress. Post-progression HRQoL data collected in DESTINY-Breast04 do not support an immediate equalisation of utilities at progression.

Furthermore, in TA819 (sacituzumab govetican for third-line triple-negative advanced BC), the company used different utility values for pre-and post-progression between treatment arms based on the values calculated from the ASCENT trial.[29] Clinical experts stated that this was plausible due to the greater objective response rate for sacituzumab govitecan compared with physician's choice. In addition, "*they considered it plausible that this would carry over upon disease progression, because people on sacituzumab govitecan enter the progressed health state with a reduced tumour burden compared with those who had treatment of physician's choice*". The Committee agreed that it is plausible that quality of life (QoL) is better for the sacituzumab arm but that the effect could deteriorate as people progress.

In TA786 (tucatinib for third-line HER2+ mBC), the company used different post-progression utility values for the different treatments and clinical experts stated that patients brain metastases may impact QoL, and that *"people with disease that is better controlled would have better quality of life before and after progression than those with disease that is less well controlled. This is because the decline in quality of life related to progression will start from a higher level than in people with disease that is less well controlled and with lower quality of life before progression."* Based on this, the Committee considered differences in HRQoL between treatment arms could be plausible.[50]

Therefore, the company consider the assumption that T-DXd treated patients would continue to experience a HRQoL benefit after progression and throughout their lifetime to be appropriate within the base case.

The company provide a conservative scenario where instead of assuming a utility benefit for T-DXd in the *'post-progression'* health state across patients' lifetime, an incremental utility benefit is applied to patients treated with T-DXd for an initial period of 12 months (17 model cycles) before assuming a pooled utility value for both T-DXd and TPC arms for the remainder of the model time horizon.

Utility values for the '*post-progression*' health state are derived using the algorithm from Lloyd et al. 2006.[55] Treatment-specific and non-treatment-specific health state utility values derived from Lloyd et al. 2006 are presented in **Table 25**.

Table 25: Post-progression health state utility values derived from Lloyd et al. 2006

	Lloyd et al. 2006 – treatment-specific	Lloyd et al. 2006 – non-treatment-specific
Progressed: T-DXd	0.610	0.596
Progressed: TPC	0.565	

Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

In this scenario, patients in both treatment arms enter the post-progression (PP) health state with a non-treatment-specific utility value, as calculated using Lloyd et al., and the model then applies a one-off utility increment to patients in the T-DXd arm assuming a utility benefit of 17 cycles.

The utility increment uses the following inputs and assumptions:

- The utility benefit for T-DXd over TPC
    - This is calculated as the difference between the annual PP utility values for each treatment arm as calculated using the Lloyd et al. algorithm – (0.610 [T-DXd] – 0.565 [TPC] = 0.0447)
    - The utility benefit per cycle is calculated as:
        - [annual utility benefit] / 365.25 * [Cycle_length_weeks] * 7 = 0.0026
- Time point assumed for treatment-specific benefit
    - As outlined above and demonstrated within DESTINY-Breast04[6], patients treated with T-DXd experience better disease control and have lower tumour burden at progression which is expected to translate into an improvement in HRQoL. Therefore, the company believe a time point of 12 months (17 cycles) is appropriate for the utility benefit to be applied.
- Proportion of patients who leave the PF health state due to disease progression versus death

    - This is calculated using the DESTINY-Breast04 trial where [redacted] out of the [redacted] ([redacted]%) PFS events were progression events over death events in the T-DXd arm.[6]

- The utility increment is then calculated as:
    - (Utility benefit per cycle x time [cycles] x % progressed)
    - This resulted in a utility increment of [redacted] for 17 cycles (12 months)
- When this scenario is applied, the PP utility value for both arms is set to the pooled utility value calculated using Lloyd et al. (non-treatment-specific) (**Table 25**) with the utility increment applied as a one-off benefit to the number of patient who have left the PF health state and entered the PP health state for T-DXd.

The deterministic scenario results are presented in **Table 26**, with an ICER of £[redacted]. This increase, compared to the new base case ICER, is driven by the decrease in incremental QALYs from [redacted] in the base case to [redacted] in this scenario (**Table 26**).

Table 26: Scenario deterministic results in the FAS population (T-DXd PAS price; no severity modifier, utility benefit T-DXd for PP health state for an initial 17 cycles)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Resource use

B21. CS Section B.3.3.3 Table 41. Why is interstitial lung disease included in the economic evaluation, but pneumonitis is not included when both occur in >5% of treated patients when including any grade of AE ([redacted] for ILD and [redacted] for pneumonitis, according to Table 27 of the CS). Please provide a scenario analysis including pneumonitis or explain why this would not be appropriate.

Interstitial lung disease (ILD) was identified as an AE of special interest in DESTINY-Breast04. For AEs of special interest, the inclusion criteria for the economic model were an incidence of at least 5%, regardless of severity. In the model, the incidence of adjudicated ILD which was adjudicated as drug-related was used, as some events may only be suspected. This includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD. The Preferred Terms adjudicated were: ILD, pneumonia and pneumonitis. Table 10.23 in the CS reports the incidence of events adjudicated as drug-related ILD, regardless of grade, as 12.10% (45 cases) for the T-DXd arm, using any Preferred Term[6]. As such, ILD met the criteria for inclusion in the economic model. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD, including pneumonitis. Of these 45 adjudicated drug-related ILD cases, 22 were interstitial lung disease, 21 were pneumonitis and 2 were pneumonia (CS Table 14.3.1.8.1).[6] Therefore, the use of adjudicated ILD captures the incidence of both ILD and pneumonitis.

Additionally, the base case applies treatment-specific EQ-5D-3L utilities derived from directly collected EQ-5D-5L data from DESTINY-Breast04[6]. Therefore, it is expected that the impact all of AEs on HRQoL is captured within the treatment-specific utilities. The implementation of additional disutilities due to AEs would therefore lead to double counting of utility decrement. This approach is consistent with what has been accepted previously in BC TAs (TA423, TA819 and TA862).[9,29,39]

B22. CS Section B.3.3.3. Left ventricular (LV) dysfunction was excluded from the economic analysis because it was observed at <5% in the study. However, rare side effects should be included in the model if they have the potential to have significant cost or HRQoL implications as they may have a bigger impact on cost-effectiveness

than slightly more frequent but less clinically significant side-effects. Please provide a scenario analysis including LV dysfunction as an adverse event or justify why this would not be appropriate.

Left ventricular (LV) dysfunction is an AE of special interest and was reported in 17 patients (4.6%) in the T-DXd arm, and no patients in the TPC arm. The majority of events (88.2%) were Grade 1 (one patient) or Grade 2 (14 patients). Grade 3 events occurred in two patients and there were no Grade 4 or 5 events.[6] LV dysfunction did not meet the criteria for inclusion in the economic model as the incidence was not ≥5% (any grade).

Given that LV dysfunction was experienced in a small proportion of patients in DESTINY-Breast04 and was typically low grade, the company considers that the existing AE criteria are appropriate to capture significant costs and HRQoL. As a result, the company considers that the inclusion of this AE would not meaningfully impact cost-effectiveness. Consequently, the inclusion LV dysfunction has not been provided as a scenario analysis. As discussed in our response to B19, it is expected that the impact of LV dysfunction (and all AEs) on HRQoL is already captured within the treatment-specific EQ-5D-3L utilities, derived from directly collected EQ-5D-5L data from DESTINY-Breast04.[6]

LV dysfunction as listed in the CS may be graded as left ventricular ejection fraction (LVEF) in Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[6,56] A summary of the definitions of LVEF by grade according to CTCAE v5.0, and its management is provided in **Table 27**.

Table 27: LVEF grading, definition, and management

CTCAE v5.0 Grade	Definition	Management
Grade 1	No description	• No description according to CTCAE v5.0 therefore it is assumed that minimal management is required
Grade 2	Resting LVEF of 40 to 50% or 10 to 19% decrease from baseline[56]	• European Society of cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure states that "*patients with an LVEF in the range of 40–49% represent a 'grey area', which we now define as heart failure with mid-range ejection fraction.*"[57] • King's Health Partners "Heart Failure Pathways for use in General Practice" guidance states that "*There are currently no evidence based*

		therapies for this group termed heart failure with LVEF from 41-49% as heart failure with mid-range ejection fraction, these patients can therefore be treated as heart failure with preserved ejection fraction pending clinical trials," with recommended management as "*Prescribe diuretics to relieve symptoms & signs of congestion and manage comorbidities*" with GPs requested to identify and treat co-morbidities in primary care.[58]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GP; general practitioner; LVEF; left ventricular ejection fraction.

As Grade 2 LVEF is typically managed in primary care and treated with relatively inexpensive medications, such as diuretics, beta blockers and angiotensin-converting enzyme inhibitors, the company do not expect the resource use associated with Grade 2 LV dysfunction to have a material impact on total costs or cost-effectiveness of T-DXd.

Grade 3 LVEF is defined as a resting LVEF of 20% to 39% or a ≥20% decrease from baseline.[56] Two patients treated with T-DXd (0.8%) experienced Grade 3 LV dysfunction; given the low incidence of Grade 3 LV dysfunction, there is unlikely to be any significant impact on total costs, and therefore the company considers that the exclusion of LV dysfunction from the economic analysis is justified.

B23. CS Section B.3.3.3. Please clarify whether low white cell count and low neutrophil count are two separate adverse events. If not, please clarify why they were included in the economic model separately.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), consistent with DESTINY-Breast01 (TA704) and DESTINY-Breast03 (TA862).[9,59] The company would like to clarify that leukopenia (low white blood cell count) and neutropenia (low neutrophil count) are listed as two separate (ungrouped) MedDRA terms,[6] and therefore, including them in the economic model separately is appropriate.

B24. CS Section B.3.5.3. Please clarify why all grade 3+ adverse events except fatigue are assumed to result in a non-elective short stay? What treatments would be given in each case and why would these require an admission? In particular, please clarify why neutropenia requires admission in cases where it is not associated with a

fever or other symptoms of sepsis and consider including febrile neutropenia in the model instead of low white cell count and low neutrophil count. Also, please clarify what the purpose of admission would be for the management of elevated alanine aminotransferase (ALT).

The methodology used to cost AEs in the model is consistent with that employed in recent TAs in mBC including TA819, TA704, and TA862.[9,29,59] The most relevant Healthcare Resource Group (HRG) codes were sourced from NHS Cost Collection rather than a micro-costing approach as this reflects the payment structure in the NHS.

As stated in the CS Section B.3.5.3, except for ILD, only Grade 3 or greater AEs were included in the economic model. The CTCAE v5.0[56] defines Grade 3+ events as:

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL (Activities of Daily Living).
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

Given this, all Grade 3+ AEs included in the economic model (including neutropenia, leukopenia and elevated ALT as highlighted in the question) were assumed to be severe and lead to hospital admission. In line with the costs accepted in recent NICE TAs, Grade 3+ AEs were assumed to result in a non-elective short stay, except for fatigue, which was costed for an hour of band 5 nurse time (**Table 28**).[9,29,59–61]

Table 28: Modelled adverse events and their associated codes that have been used in previous appraisals

Adverse event	Code from NHS Cost Collection 20/21	Submission(s)
Leukopenia (Grade 3+)	NES – SA35A-E – Agranulocytosis	TA862[9]
Anaemia (Grade 3+)	NES – SA04G-L – Iron Deficiency Anaemia	TA704[59]; TA862[9]
Neutropenia (Grade 3+)	NES – SA35A-E – Agranulocytosis	TA819[29]; TA862[9]; TA760[61]; TA850[60]
Thrombocytopenia (Grade 3+)	NES – SA12G-K – Thrombocytopenia	TA862[9]
ALT increased (Grade 3+)	NES – GC17A-K – Non-Malignant, Hepatobiliary or Pancreatic Disorders	TA760[61]*
Interstitial lung disease (any grade)	NES – DZ11K-V – Lobar, Atypical or Viral Pneumonia	TA704[59]; TA862[9]

Note: *To our knowledge, there are no NICE TAs for breast cancer that included increased ALT as an adverse event in the economic model. Therefore, for reference, we referred to a recent oncology NICE TA, which included increased ALT of Grades 3-4 in their submission.
Abbreviations: ALT, alanine transaminase; NES, non-elective short stay; NHS, National Health Service.

Grade 3+ leukopenia (low white blood cell count) and neutropenia (low neutrophil count) occurred in >5% of patients in both treatment arms, meeting the criteria for inclusion in the economic model, while febrile neutropenia occurred in [redacted]% and [redacted]% of patients in the T-DXd and TPC arms, respectively.[6] Therefore, febrile neutropenia did not meet the criteria for inclusion in the economic model and as such, it was not considered appropriate to include. Given the frequencies of this AE in each arm, inclusion of febrile neutropenia is likely to have a minimal impact on cost-effectiveness and would favour T-DXd. As mentioned in response B18, the impact of all AEs on the HRQoL is expected to be already captured within the treatment-specific EQ-5D-3L utilities in the model as these utilities were derived from directly collected EQ-5D-5L data from DESTINY-Breast04.[6] Management of Grade 3+ neutropenia is costed as 'agranulocytosis', using code SA35A:K in the NHS Cost Collection; the same HRG code was accepted for the management of neutropenia in multiple recent BC and other oncology TAs: TA819; TA862, TA760, and TA850.[9,29,60,61]

Increased ALT was included as a Grade 3+ AE, which is assumed to result in a non-elective short stay in line with a previous NICE TA (see CS Table 11): the justification accepted by the Committee as part of TA654 was "*increased ALT levels are linked to potential liver damage; hepatobiliary includes the liver plus gallbladder or bile ducts*".[62]

As outlined, the company considers the application of AE management costs in the economic model to be appropriate and consistent with other TAs.

B25. CS Section B.3.5.2. Please clarify how the resource use estimates in Table 56 were obtained and why it is assumed that no additional resources are required for progressed disease relative to pre-progression. Please comment if this is consistent with the resource use assumed in other relevant technology appraisals.

The resource use estimates in Table 56 of the CS were informed by what has been recently accepted in previous NICE TAs (TA704, TA819, TA862).[9,29,59] The specific resource use estimates are consistent with TA862.[9] These submissions typically

assumed that resource use did not vary by treatment or health state. The resource use estimates were considered appropriate by UK clinical experts, who were consulted as part of an Advisory Board meeting in December 2022, and subsequent follow-up.[35] Clinical experts advised that resource use was unlikely to differ by health state or treatment, as patients who progress are expected to require the same level of monitoring as patients who are progression-free since approximately 70% of patients go on to receive subsequent treatments following disease progression.[6] Therefore it was assumed that the clinical management and resource use is the same across health states.

B26. CS Section B.3.5.2. Please clarify why there are no additional CT scans required to monitor for ILD for patients receiving T-DXd. The EAG's clinical expert stated they would do the same number of staging scans for both T-DXd and TPC but additional high resolution chest scans are required every 2 cycles for T-DXd that are not required on TPC.

The T-DXd SmPC does not mandate the use of regular imaging of all patients to identify ILD.[10] Section 4.4 of the SmPC[10] states that "*Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms*. *Patients should be monitored for signs and symptoms of ILD/pneumonitis"* and only patients with suspected ILD should be evaluated, "*Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging, preferably a computed tomography (CT) scan*."[10]

As per the DESTINY-Breast04 Clinical Study Protocol, CT scans are used as part of general BC care and are not used specifically to detect ILD.[18] This forms routine NHS practice as confirmed by clinical insight received by the company. If changes in the lung are detected, further high-resolution CT scans would be performed to identify ILD and ILD management guidelines would be followed if required.[6] Regulatory bodies including the MHRA, EMA and FDA do not mandate regular CT scanning or high-resolution CT scans.[10,63] The company would only expect a high-resolution CT scan to be reserved for when ILD is suspected.[10,64–66]

The company therefore considers that additional CT scans are not used as part of a routine monitoring of T-DXd patients, every two cycles, to screen for ILD.

In previous BC appraisals, CT scans have been included and accepted in economic models as part of general BC care, and equal resource use has been accepted by NICE across intervention and comparators in TA862, TA819, and TA423.[9,29,39]

B27. CS Section B.3.5.2. Please clarify why echocardiograms are required at the same frequency for TPC and T-DXd in the model. Our clinical expert stated that they would use these every 6 months for T-DXd due to the increased risk of LV dysfunction but these are not required for TPC. They also stated that a proportion of these would be multigated acquisition (MUGA) scans rather than echocardiograms. Please provide a scenario assuming that a proportion of these scans would be MUGA scans.

Cardiac monitoring is captured as part of routine BC monitoring, therefore no additional resource use is required for T-DXd patients vs. TPC.[10] This approach is aligned with previous T-DXd appraisals including TA704, which assumed equal resource use for disease monitoring, including LV dysfunction monitoring, between T-DXd and non-targeted chemotherapies.[59] This was accepted by the Committee as a reasonable approach.

The company recognise that there may be some differences in monitoring between different chemotherapies and some individual BC patients may require additional monitoring based on their medical history and risk profile, however on balance the average patient would have equal monitoring.

For example, patients treated with capecitabine undergo electrocardiogram scans prior to treatment initiation[67] and cardiotoxicity is listed as a main toxicity/adverse reaction. The Thames Valley Cancer Alliance protocol states that cardiac function should be monitored *"to minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue"*.[68]

Additionally, as per the following from Section 4.4 of the T-DXd SmPC, "*Standard cardiac function testing (echocardiogram or MUGA [multigated acquisition] scanning) should be performed to assess LVEF*", MUGA scans are not mandated.[21] Further, the DESTINY-Breast04 protocol allowed the use of either echocardiograms or MUGA, allowing sites to choose and continue that same scan to be used throughout

the patient journey.[18] The company believe echocardiograms would be more widely used based on cost, ease of access in the NHS, and it providing the satisfactory images needed to assess the cardiac function for the majority of patients.[69]

B28. CS Section B.3.5.4 Table 60. Please clarify why the subsequent therapies included in the model are a subset of those reported in Table 14.1.3.5.2: Post Anti-Cancer Treatment - Full Analysis Set in the document named "Daiichi Sankyo Inc. DB04 CSR additional tables CONFIDENTIAL.pdf". How was the subset selected? Why were other frequently used treatments excluded? (e.g. vinorelbine tartrate, paclitaxel albumin, gemcitabine hydrochloride, eribulin mesilate, cyclophosphamide, cisplatin, exemestane, letrozole, everolimus).

The subsequent treatments included in the model were based on what patients received following progression in DESTINY-Breast04. The chemotherapy agents included in the model were paclitaxel, capecitabine, gemcitabine, eribulin, vinorelbine, epirubicin and carboplatin, and included endocrine therapies were tamoxifen and fulvestrant. Some of the treatments in Table 14.1.3.5.2 of the CS are listed with their respective salts expressed separately, and they refer to the same therapeutic agent included in the model. These treatments were therefore not excluded in the model but combined into a single input and included together under the relevant therapeutic agent. This is the case for eribulin (eribulin mesylate), gemcitabine (gemcitabine hydrochloride), vinorelbine (vinorelbine tartrate), epirubicin (epirubicin hydrochloride), and tamoxifen (tamoxifen citrate).

Clinical experts, who were consulted as part of an Advisory Board meeting in December 2022 and during subsequent follow-up, confirmed that the subsequent therapies used in the economic model align with the UK clinical practice. Furthermore, based on a UK cross-sectional patient chart review in 2022,[70] the subsequent treatments included in the model are representative of the most commonly used third-line chemotherapies and hormone therapies for patients with mBC in the UK. Therefore, the company considers that the subsequent treatments included in the economic model are appropriate.

B29. Please clarify if the 5 single-agent therapies (in the TPC arm) in the trial were offered until progression or whether some were offered for a maximum number of cycles (e.g. paclitaxel limited to 6 months).

All patients receiving individual TPC agents were dosed until progression or unacceptable toxicity, in line with the trial protocol.[18] This is consistent with the licensed use of the five single-agent therapies, where treatment is continued until either disease progression, unacceptable toxicity or the occurrence of pre-specified AEs, as detailed in the SmPC of each therapy.[21,71–75] The number of cycles for the five single-agent therapies in the TPC arm of the DESTINY-Breast04 clinical trial were not restricted to a fixed duration or maximum number of cycles.
The economic model aligns with the above and does not incorporate a maximum number of cycles for the five single-agent therapies in the TPC arm. Within the model, the costs for time on treatment for TPC are modelled using a single TTD curve.

B30. Please provide a scenario using a time horizon of 45 years, taking the age at the end of the model up to 100 years (or the maximum time horizon possible within the current model structure).

The company considers that a 30-year time horizon is appropriate for the base case analysis. As detailed in Section B.3.2.2.1 of the CS, the company adopted a 30-year 'lifetime' horizon as it was considered long enough to appropriately capture the lifetime of patients in this setting (the mean starting age used in the CEA is 56.5 years aligned with DESTINY-Breast04). At 30 years, using the base case curve selection outlined in B.3.3.2.1 of the CS, less than 1% of patients in the T-DXd and TPC arms remain alive in the model. Therefore, given the very small proportion of patients alive at 30 years, extending the time horizon beyond this time point would not significantly impact costs or QALYs; as a result, the extended time horizon would have minimal impact on the ICER.

To demonstrate this, a scenario analysis was conducted using a time horizon of 45 years and deterministic cost-effectiveness results are presented in **Table 29**. The deterministic scenario results demonstrate a small increase in incremental costs and QALYs; incremental costs of £[redacted] and incremental QALYs of [redacted]. This results in

an ICER of £[redacted], a small reduction of £[redacted] versus the company's new base case (**Table 10**).

Table 29: Scenario deterministic results in the FAS population (T-DXd PAS price; no severity modifier, 45-year time horizon)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modelling assumptions and calculations

B31. Please provide a cost-effectiveness analysis where the treatment costs for the TPC arm are calculated using the specific proportion of patients and mean time on treatment per each single therapy.

As requested and clarified by the EAG at the clarification call held on Tuesday 12th April, the company have provided a scenario using the specific proportion of patients and mean time on treatment per each single therapy in the TPC arm and for T-DXd.

The specific proportion of patients are presented in Table 14 of the CS and **Table 30** below. The mean time on treatment for each single therapy are presented in **Table 31** using the SAS, as per the CSR for DESTINY-Breast04.[6]

Table 30: TPC single-agent chemotherapy use | Safety Analysis Set (N=172)

Single-agent chemotherapy	Patients, N (%)
Eribulin	89 (51.7)
Capecitabine	36 (20.9)
Nab-paclitaxel	17 (9.9)
Gemcitabine	16 (9.3)
Paclitaxel	14 (8.1)

Abbreviations: TPC, treatment of physician's choice.
Source: Modi et al., ASCO 2022;[5] Daiichi Sankyo Inc., 2022 (CSR; Data on File)[6]

Table 31: Treatment duration (months) (Safety Analysis Set)

Parameter	T-DXd (N=371)	Treatment of Physician's Choice				
		Eribulin (N=89)	Capecitabine (N=36)	Nab-paclitaxel (N=17)	Gemcitabine (N=16)	Paclitaxel (N=14)

n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration on treatment (Std Dev)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Std Dev, standard deviation; T-DXd, trastuzumab deruxtecan.

Using the patient proportions (**Table 30**) and mean treatment durations (**Table 31**), total treatment acquisition and administration costs were calculated for each therapy based on the number of cycles required to achieve the mean duration of treatment as presented in **Table 32**. Costs were applied as a one-off cost in the first cycle of the economic model. This replaces the cost per cycle applied to the proportion of patients on treatment derived from the TTD curve for each treatment arm. Applying treatment costs derived from mean treatment duration in this scenario results in a total weighted treatment acquisition cost of £[redacted] and total weighted treatment administration cost of £[redacted] for the T-DXd treatment arm and a total weighted treatment acquisition cost of £[redacted] and total weighted treatment administration cost of £[redacted] for the TPC treatment arm. This compares to a total weighted treatment acquisition cost of £[redacted] and total weighted treatment administration cost of £[redacted] for the T-DXd treatment arm and a total weighted treatment acquisition cost of £[redacted] and total weighted treatment administration cost of £[redacted] for the TPC treatment arm using TTD curves and aligning to the new company base case.

Table 32: Total treatment acquisition and administration costs for each single therapy using the mean treatment duration as derived from the CSR of DESTINY-Breast04

Single-agent chemotherapy	One-off drug acquisition cost for mean treatment duration	One-off drug administration cost for mean treatment duration
Trastuzumab deruxtecan	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Total weighted cost	[redacted]	[redacted]

The deterministic cost-effectiveness results for T-DXd vs. TPC incorporating mean treatment duration per single therapy are presented in **Table 33**. The results demonstrate that, in this scenario, T-DXd is associated with incremental costs of £[redacted] compared with incremental costs of £[redacted] in the company's corrected

base case. The ICER of £[redacted] represents a £[redacted] reduction from the company's new base case of £[redacted].

Table 33: Scenario deterministic results in the FAS population (T-DXd PAS price; no severity modifier, mean T-DXd and mean TPC time on treatment)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B32. Please provide a cost-effectiveness analysis where data from the KM curves are used directly to model PFS and TTD and then parametric fits are used to extrapolate beyond the KM curves.

The company have not implemented this scenario in the economic model due to time limitations and consideration of the likely impact on the ICER. Given the good visual fit and similar trajectories of the KM and parametric curves for each treatment arm over the observed follow-up period, the company consider that a scenario using a piecewise curve, where data from the KM curves are used directly to model PFS and TTD and then parametric fits are used to extrapolate beyond the KM curves, will have a minimal impact on the ICER.

As presented in Figure 33, Figure 34, Figure 40 and Figure 41 of the CS, the KM curves for PFS and TTD are a good fit to the parametric curves extrapolated over the observed follow-up period. Furthermore, given that the PFS and TTD data from DESTINY-Breast04 are considered mature, the close fit between the KM and parametric curves is considered an accurate representation of PFS and TTD.

B33. CS Section B.3.11.3 Table 72. Please explain why the incremental costs have changed from the base case when a different source for utility values was used at scenario 10.

The results for scenarios included in the CS were calculated probabilistically rather than deterministically, in line with the new NICE methods manual.[54] As a result, in each scenario, incremental costs (and QALYs) are expected to vary slightly from the deterministic base case even if the scenario does not affect costs (or QALYs) directly. This explains the difference in incremental costs for scenario 10 and

scenario 7, which explored different sources for utility values and inclusion of AE disutilities, respectively.[44] When calculated deterministically, there is no change in incremental costs compared with the base case when using the alternative utility sources (scenario 10); incremental costs remain at £[redacted] resulting in a deterministic ICER of £[redacted] for the scenario, compared with the company submission base case of £[redacted].

B34. CS Section B.3.2.2.1. Please clarify why a cycle length of 3 weeks was preferred over a cycle length over 1 week used with recent NICE TAs (TA704, TA819, TA862).

The three-week cycle length is appropriate for the model. As discussed in the CS Section B.3.2.2.1, a three-week cycle length was selected as the most appropriate since it reflects the administration cycles for T-DXd and TPC agents. The time period is also considered sufficient to capture relevant changes in the disease and the impact of mBC events which may affect patient health status, costs, and QoL. For example, three weeks was considered more appropriate than one week to capture the QoL impact and resolution of AEs. The model base case also applies a half-cycle correction to account for uncertainty in the exact timing of transitions within the cycle period.

B35. PRIORITY CS Section B.3.5.1.2: Cost of administering capecitabine as part of TPC is calculated as £215*28/60=£100.71 whereas cost of administering capecitabine as subsequent therapy is simply £215*28=. £6042.48. Given this inconsistency, we assume the latter is an error. Please correct in a revised model to resolve this inconsistency or explain why the current calculation is correct in both cases. Does a similar error occur for Tamoxifen?

Thank you for bringing this to the company's attention. In the company submission base case, administration costs associated with capecitabine as part of TPC were applied per pack. This was incorrect; administration costs associated with capecitabine should have been applied once per treatment cycle. This has been corrected and the cost of administration per cycle for capecitabine for the first and subsequent cycles are £304.62 and £215.80, respectively. A treatment administration cost applied once per cycle is consistent with the monitoring required each cycle before treatment is dispensed and administered, such as patient weight,

full blood count (FBC), urea and electrolytes (U&E) and liver function tests (LFTs). This is consistent with capecitabine Systemic Anti-Cancer Therapy SACT protocols in NHS clinical practice.[67,68]

For tamoxifen, the administration costs are applied per pack; no additional monitoring is required per cycle before treatment is dispensed and administered.

The corrected administration cost for capecitabine as a comparator has increased from £142.15 in the first cycle to £304.62 and from £100.71 to £215.80 in subsequent cycles. The corrected cost of administration per cycle for subsequent treatment with capecitabine and tamoxifen is £215.80 and £151.06, respectively (**Table 34**).[44] Together, these lead to a £[redacted] increase in the CS base case ICER from £[redacted] to £[redacted]. The new base case, reflecting the corrected administration costs and corrections proposed by the EAG, is £[redacted] (**Table 10**).

B36. CS, Section B.3.4.4. Adverse events in Table 50 do not match those in Cells B105 to D111 of the 'Data Inputs' sheet in all cases (e.g. thrombocytopenia) and these values do not accurately follow through into Cells D30 to D36 of the 'Set_Utilities' sheet. Please account for these discrepancies and present updated results for the scenario analysis incorporating these data if necessary.

Thank you for bringing this to the company's attention. As AE utility decrements were not included in the base case, this correction does not alter the CS or new base case ICER.

The formulae had not been copied down correctly from cells D30 and E30 through to D36 and E36 in the 'Set_Utilities' sheet. This meant the utility decrements, and their durations, were incorrect for all AEs other than neutrophil count decreased.

The error has been corrected and impacts scenario 7 which explores the impact of AE utility decrement. Compared with the new company base case, the ICER in this scenario increases minimally from £[redacted] to £[redacted].

B37. CS, Section B.3.2.3. Please clarify how the mix of therapies included in TPC stated on CS page 119 has been calculated. Table 10.1 of the CSR would suggest the proportions are as follows: eribulin (89/172 =51.7%); capecitabine (36/172=20.9%); nab-paclitaxel (17/172 = 9.9%); gemcitabine (16/172=9.3%); and

paclitaxel (14/172 = 8.1%). Please account for the discrepancy and correct if necessary.

Thank you for bringing this to the company's attention. In the CS, the mix of therapies in the TPC arm were calculated using the data from FAS population. The company considers the SAS dataset, as proposed by the EAG in question B37, to be a more appropriate data source to derive the proportion of patients treated with each single agent in the TPC arm and is consistent with the safety data in the economic model. Correcting the proportions of patients receiving each treatment in TPC used in the model (FAS population), to the values above (SAS population), leads to a decrease in the original CS deterministic base case ICER of £[redacted] from £[redacted] to £[redacted]. The new company base case, incorporating this update and other corrections proposed by the EAG, is £[redacted] (**Table 10**).

B38. Please clarify why the relative dose intensity (RDI) data in the model do not match those in [redacted] of the CSR.

The relative dose intensity (RDI; %) values presented in the CSR are calculated as dose intensity/planned dose intensity ×100, where planned dose intensity (units/cycle lengths in weeks) = planned cumulative dose (units)/planned duration of exposure (day)/cycle length in day.

An amended RDI method was used for T-DXd, where the planned dose intensity (PDI) was based on the planned starting dose of 5.4mg/kg instead of the planned cumulative dose per protocol, which is based on the amount of dose planned to be taken at each dosing record in the case report form. As the planned dose per protocol could include dose reductions for AE management, it risks inflating the RDI. As such, by setting the planned dose to 5.4mg/kg, a more accurate depiction of the RDI is obtained.

Due to different dosing regimens among the individual TPC treatments, RDI is not presented for the overall TPC arm. This approach could not be applied to the TPC arm, as there were several possible dosing regimens for the different TPC agents and granularity on the planned starting dose amongst the different options was not available in the data (e.g., capecitabine dosing regimen was 1000-1250 mg/m^2 PO twice daily Days 1-14; cycled every 21 day). As such, the PDI for the TPC arm was based on the dose planned to be taken per protocol. The median values were

chosen because they are less affected by outliers than the mean, and, because TPC has fewer patients on each chemotherapy treatment, the mean will be more sensitive to these outliers.

B39. Gemcitabine is costed in the model as 2 doses per cycle, but two options were included in the TPC arm of the trial, one of which was 2 doses per 21 days and the other was [redacted] (based on Table 6.1 of the CSR). Please clarify why only one of these options was costed in the model. Paclitaxel and nab-paclitaxel also had alternative dosing regimens. Please clarify why only one option was included in the model for these drugs. Please conduct a scenario analysis to assess the impact on the ICER of assuming the alternative dosing regimen in each case where there was an alternative.

The trial protocol had multiple dosing options as there were different licensed regimens across the different regions included in the enrolled trial population. Therefore, in the model, the dosing regimen for gemcitabine was aligned with its dosing regimen in the UK,[76] where it is licensed as a combination therapy; a similar approach was taken with paclitaxel and nab-paclitaxel.[77,78] The dosing regimen for each drug in the model is aligned with the referenced SmPC dosing. Where more than one SmPC dosing was available, a conservative approach was taken, and the lowest cost regimen was selected. The alternative scenarios are not presented as these doses would not be compatible with the SmPC for each treatment.

B40. CS, Section B.3.5.4.1. Gemcitabine and eribulin both appear to have an admin cost of £562.22 per cycle in the model but only [redacted] per cycle in Table 60. Please explain these discrepancies and correct where necessary.

Thank you for bringing this to the company's attention. The model contains the correct administration cost per cycle of £562.22 and therefore there is no change in the ICER. Patients treated with gemcitabine and eribulin are required to have two doses per cycle on different days, hence the administration cost is £281.11 multiplied by two.[71,76] An updated version of CS Table 60 has been provided below with the corrected administration cost for gemcitabine and eribulin, and also accounts for the correction highlighted in question B35 for tamoxifen and capecitabine (**Table 34**).

Table 34: Subsequent therapy costs

Treatment	Distribution over trial period (%)*		Dose	Cost per cycle (3 weeks)	Admin cost per cycle (3 weeks)
	T-DXd (n=373)	TPC (n=184)			
Subsequent treatments	[redacted])	[redacted])	-	-	-
Chemotherapy					
Paclitaxel	[redacted])	[redacted])	175.0 mg/m^2	[redacted]	[redacted]
Capecitabine	[redacted])	[redacted])	1250.0 mg/m^2	[redacted]	[redacted]
Gemcitabine	[redacted])	[redacted])	1250.0 mg/m^2	[redacted]	[redacted]
Eribulin	[redacted])	[redacted])	1.2 mg/m^2	[redacted]	[redacted]
Vinorelbine	[redacted])	[redacted])	60.0 mg/m^2	[redacted]	[redacted]
Epirubicin	[redacted])	[redacted])	100.0 mg/m^2	[redacted]	[redacted]
Carboplatin	[redacted])	[redacted])	400.0 mg/m^2	[redacted]	[redacted]
Endocrine therapy					
Tamoxifen	[redacted])	[redacted])	20.0 mg	[redacted]	[redacted]
Fulvestrant	[redacted])	[redacted])	500.0 mg	[redacted]	[redacted]

*The proportion of patients on who received individual subsequent treatments exceeds 100% as patients were able to receive multiple lines of therapy or treatments in combination.
Abbreviations: T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

B41. 'KM data' sheet rows BD to BZ. Please explain what the 'Amended KM - FAS population' data relate to and whether it is used in any of the scenarios presented by the company.

The data labelled 'Amended KM – FAS population' is referring to the adjustment made to account for 90-degree angle steps for the KM data and is the same data presented in the 'KM data' sheet rows B to X and in the 'Set_Distributions' sheet. The 'Amended KM – FAS population' data is used to plot the KM curves on graphs in the economic model, which were subsequently included in the CS. That is, the KM data in the economic model is the same as the PFS, OS and TTD data derived from DESTINY-Breast04.[6]

Severity modifier calculation

B42. PRIORITY. CS Section B.3.6.3.The starting age for the calculation of the severity modifier is based on the DESINTY-Breast04 trial. Trial populations are in general younger than populations treated in clinical practice. Please provide an estimate of the average age for patients having 2nd or 3rd line treatment for u/mBC that is HER-low or HER-negative from a real world source. Please

explore whether the severity modifier is higher or lower when using this estimate of starting age.

The company considers it is appropriate to use a mean starting age of 57 years as it is derived directly from DESTINY-Breast04, which aligns with the rest of the clinical data included in this CEA. Clinical experts confirmed at an Advisory Board that the population included in DESTINY-Breast04 was generalisable to UK practice.[35] Furthermore, a mean starting age as derived directly from clinical trials has been accepted in multiple previous TAs, including TA862 (T-DXd for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments)[9], TA704 (T-DXd for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies)[59] and TA423 (eribulin for treating locally advanced or metastatic BC after 2 or more chemotherapy regimens)[39].

As presented in Section B.3.6 of the CS, using the Schneider et al. (2021) estimator[79] and a mean age of 57 years and an 100% female proportion to reflect DESTINY-Breast04,[6] this appraisal robustly meets the threshold for a QALY weight of 1.2 according to NICE's criteria for both absolute QALY shortfall (AS) estimated to be [redacted] and the proportional shortfall (PS) estimated to be [redacted]% (Table 64 of the CS).

In response to this question, the company has explored real-world evidence (RWE) sources for alternative mean ages for patients having second- or third-line treatment for HER2-low or HER2-negative u/mBC. Of relevant RWE that the company are aware of, median ages range from 54 years for triple-negative advanced BC patients identified in the ASCENT trial for SG (N=529) to 65 years for HER2-negative advanced BC patients undergoing treatment after ET (from the SACT dataset presented within the Committee papers for the NICE appraisal of abemaciclib (TA725)).[29,80] In addition, UK real-world patient data available to the company reports a mean age of [redacted] years in patients receiving chemotherapy at third-line.[70]

The company explored the QALY shortfall calculations in a scenario using the lowest age (54 years) and highest age (65 years) from the above sources and a 100% female proportion (**Table 35**). Using the same method as outlined above and within Section B.3.6.3 of the CS, an AS of [redacted] and a PS of [redacted]% is estimated when an age of 65 years is used. The results show that using an age of 65 years in the QALY

shortfall calculations still results in this appraisal meeting the threshold for a QALY weight of 1.2 according to NICE's criteria. For completeness, the age from the clinical trials of relevant previous NICE Technology Appraisals have also been included to calculate the severity modifier in **Table 36**.

As detailed in the CS, in order to capture the full extent of the severity of HER2-low u/mBC during this initial phase of implementation, monitoring and review of the severity modifier, Daiichi Sankyo considers that additional flexibilities in the form of a QALY weight equivalent to the previous EOL (i.e. 1.7x) should be applied in decision-making. This would more appropriately reflect the severity of the condition based on the poor survival outcomes in HER2-low u/mBC with current standard of care.

Table 35: Results of the QALY shortfall analysis using ages identified in RWE and clinical trials from previous NICE TAs

General population QALY source	Age	Data source	Number of previous lines of chemotherapy	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight†
Reference case: MVH value set + HSE 2014 ALDVMM [Hernandez Alava M, et al.]	54 years	ASCENT study consisting of 529 triple-negative advanced BC patients (identified in TA819)[29]	At least 2	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	55 years	EMBRACE (study 305) consisting of 762 HER2+/HER2- patients (as identified in TA423)[39]	At least 2	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	[redacted] years	AstraZeneca/Daiichi-Sankyo led study (N=31) - HER2-low/HR-negative patients ([redacted])	At least 1	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]%	1.2x
	[redacted] years	AstraZeneca/Daiichi-Sankyo led study (N=31) - HER2-low/HR-positive patients	At least 1	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]%	1.2x
	65 years	SACT dataset of HER2-negative advanced BC patients (identified in TA725)[80]	After endocrine therapy	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]%	1.2x

*Based on the total QALYs in the TPC arm of the company economic model base case for this appraisal.
†All calculations based on the tool developed by Schneider et al., 2021.[79]
Abbreviations: ALDVVM, adjusted limited dependent variable mixture model; BC, breast cancer; CEA, cost-effectiveness analysis; HER, human epidermal growth factor receptor; HR, hormone receptor; HSE, Health Survey for England; MVH, York Measurement and Valuation of Health; QALY, quality-adjusted life-year; SACT, Systemic Anti-cancer Therapy; TA, technology appraisal.

B43. PRIORITY. CS Section B.3.6.3. Please clarify if the utilities in the model are age-adjusted or if a constant utility is assumed over time according to treatment and whether the patient has progressed. Please consider estimating utility multipliers relative to an age-adjusted absolute utility value and applying a constant utility multiplier over time to age-adjusted general population utilities instead. This would allow a better comparison to the estimate of QALYs in the general population, which presumably are age-adjusted, for the purposes of the severity modifier calculation.

The company can clarify that the utilities in the model are not age-adjusted over time for each treatment arm and a constant utility is assumed according to treatment and disease progression status.

As detailed in the company's response to Question B42 and as demonstrated in Section B.3.6.3 of the CS,[44] this appraisal robustly meets the QALY weighting of 1.2 under the current NICE severity modifier threshold criteria. The company expect that using age-adjusted utilities in the economic model would decrease the QALYs in the TPC arm and increase the AS and PS estimates within the severity modifier calculations. Based on the current estimated absolute and proportional QALY shortfalls in relation to the cut-off thresholds defined by NICE, the company does not consider that the severity modifier weight would be impacted by estimating utility multipliers relative to an age-adjusted absolute utility value and applying a constant utility multiplier over time to age-adjusted general population utilities. The company have therefore not provided the results of this scenario.

Section C: Textual clarification and additional points

C1. CS references 121, 147, and 148. Please provide the following references:

- Daiichi Sankyo Inc. T-DXd in HER2-low u/mBC. UK Advisory Board meeting report. Data on File. 2022.
- Daiichi Sankyo Inc. Estima: Feasibility of performing an indirect treatment comparison between ENHERTU® and TRODELVY® in a hormone-receptor negative and HER2-low population. Data on file. 2023.

- Daiichi Sankyo Inc. ASc Academics: A feasibility assessment of indirect treatment comparisons with T-DXd in HER2-low unresectable and/or metastatic breast cancer. 2022.

The above reports will be provided separately to this response document as communicated to NICE.

C2. CS Section B.2.3.1 Table 9 page 51 states, 'Pre-specified subgroups were: hormone receptor status; HER2 status; HR-status …'. Please clarify whether HR and hormone receptor are the same or different.

The company acknowledges the typographical error in CS Table 9 on page 51. The company can confirm that "hormone receptor status" and "HR-status" are the same.

C3. CS Section B.3.4.2 page 143 states, 'EQ-5D-5L scores from all available time points, including baseline, were included in a mixed model as dependent variables.' Please clarify whether "EQ-5D-5L" is a typo and should be EQ-5D-3L instead.

The company acknowledges the typographical error in Section B.3.4.2 page 143 and confirms that "EQ-5D-3L" is the correct terminology. The EQ-5D-5L data directly collected in DESTINY-Breast04 were mapped to EQ-5D-3L values using the mapping algorithm by Hernández-Alava.[81] These EQ-5D-3L values were then included in a mixed model to obtain the health state utility values using least-square means and regression coefficients.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK charity that's steered by world-class research and powered by life-changing care. We provide support for today and hope for the future.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Breast Cancer Now has received funding from a number of drug companies towards our support services, however, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. Over the last 12 months (February 2022-February 2023) we have not received any funding from the relevant companies listed in the stakeholder list for this appraisal. In December 2021 we received £45,000 from Daiichi Sankyo towards our living with secondary breast cancer support service.
4c. Do you have any direct or indirect links	None.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of people affected by breast cancer to gather information about patient experience, including our online Breast Cancer Now Forum, as well as our online and face to face services. We have also spoken to patients whose breast cancer has been categorised as HER2-low.

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, so treatment aims to control and slow down the spread of the cancer, relieve symptoms and give patients the best quality of life for as long as possible. A patient can be diagnosed with secondary cancer from the start (de novo metastatic), or they can develop the condition months or years after treatment for their primary breast cancer has ended. For decades, breast tumours have been classified on expression of HER2 levels – as HER2 positive or HER2 negative. However, if we look more closely at breast cancers that are currently classified as HER2 negative, some could be called HER2 low. Research suggests around 50% of all breast cancers show low levels of HER2. Around 80% of secondary breast cancers are HER2 negative, with 55-60% of those having low levels of HER2. The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or pain when breathing. In addition, all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health. As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day-to-day activities, which may include working, household and parental responsibilities as well as travelling to and from regular hospital appointments. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as

	length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	To date, breast cancer has been categorised according to whether the tumour is HER2 positive or HER2 negative and this is significant in informing treatment decisions. If there are low levels of HER2, patients would currently be treated according to the HER2 negative pathway. For those patients who are hormone receptor positive, they would have access to a CDK 4/6 inhibitor alongside hormone therapy and once they have progressed on approved targeted treatments and hormone treatment, they would move onto chemotherapy. This could include a range of chemotherapies, such as capecitabine. Eribulin is also available for treating locally advanced or secondary breast cancer after 2 or more chemotherapy regimens. There may be individual preferences and reasons for choosing one treatment over another, including side effect profile or practicalities in delivery. Whilst there has been the introduction of CDK 4/6 inhibitors which has been hugely welcomed by patients, there remains a need for new effective treatments following progression on a CDK 4/6 inhibitor. A patient with secondary breast cancer whose tumour has been classified as HER2 low explains: “My cancer mutating to HER2 Low was a very lonely and scary place to be knowing that there were no drugs to treat me.” For patients whose breast cancer is currently classified as triple negative breast cancer but for whom some could potentially fall within the HER2 low category, after prior chemotherapy (i.e. the same as the indication being assessed), sacituzumab govitecan (Trodelvy) is approved for use which was a big step forward in the treatment options available for this group of patients. However, a need for new effective treatments to delay progression and increase how long people live are still desperately needed.
8. Is there an unmet need for patients with this condition?	Currently, patients with unresectable or secondary breast cancer with lower levels of HER2 expression are not treated with a HER2-targeted treatment. This treatment would provide an important new option instead of chemotherapies. This treatment would open the door to some patients previously categorised as HER2-negative being able to access a new targeted treatment option which could potentially delay progression and improve survival. There remains an unmet need for treatments which can control progression for longer periods of time, extend how long people live and have an acceptable tolerability profile to enable people to live well for a long as possible.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In the clinical trial (DESTINY-Breast04), there was a statistically significant improvement in both progression free survival and overall survival compared to the chemotherapy comparators. These are two key outcomes for this group of patients. - Among all patients in the trial, trastuzumab deruxtecan provided on average an additional 4.8 months delay in disease progression compared to chemotherapy - Among all patients, the median overall survival was 23.4 months compared to 16.8 months. The trial showed that the risk of disease progression or death was approximately 50% lower and the risk of death was 36% lower with trasuzumab deruxtecan compared to chemotherapy. This was regardless of hormone receptor status. These benefits are key. It can mean more quality time to spend with relatives and friends, as well enabling people who are able to and wish to continue to work and contribute to society. Maintaining a good quality of life for as long as possible is currently the best outcome for this patient group. Improvement of progression free survival can help with symptom control. It can mean that patients may be able to continue to do the activities that matter most to them and can have a positive impact on their emotional wellbeing and mental health. Patients can be fearful of moving onto broad spectrum chemotherapies and worry about how effective they may be in controlling their disease. Whereas accessing a targeted treatment like trastuzumab deruxtecan may provide reassurance to patients that they are receiving the optimum treatment for their type of breast cancer. The hope this treatment may bring patients is also likely to bring some comfort to their relatives and friends. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about the impact on their friends and family.

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 that can be associated with it. In the clinical trial, the most common side effects of any grade included nausea (which occurred in 73% of patients), fatigue (47.7%) and alopecia (37.7%). The most common adverse event of higher grade (grade 3 or above) was neutropenia. Interstitial lung disease or pneumonitis remains an important side effect to consider that can be associated with this drug. There are important steps in place for the surveillance and monitoring of this to help identify cases. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to have treatment will understandably vary. Trastuzumab deruxtecan is already available to patients via the Cancer Drugs Fund in 2 other indications, therefore, clinical teams are already familiar with the associated side effects and toxicity management. This treatment is also administered intravenously every 3 weeks which will involve time spent in hospital receiving the drug. For many patients, the benefits this treatment may bring will outweigh the potential risk of side effects. A patient with experience of trastuzumab deruxtecan explains: "there are side effects. I found these to be manageable. There are some rare side effects which necessitate monitoring, but again, not unlike other treatments."

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.	We understand that although the study was not designed to look primarily at people with triple negative breast cancer, some patients with triple negative breast cancer could be considered HER2-low and were in the trial. This could be an important option for those patients who continue to have limited effective treatment options. This treatment may not be appropriate for patients who are at increased risk of experiencing lung disease or pneumonia.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	The introduction of this treatment reframes the way that breast cancer has been classified for years. As highlighted earlier, for decades breast cancer has been classified on the levels of HER2 expression, and those tumours with low levels have been classified as HER2 negative.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of secondary breast cancer can cause considerable anxiety and fear for people and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people. There is no cure for secondary breast cancer, so the aim of treatment is to delay disease progression and extend length of life for as long as possible, whilst providing a good quality of life. • This treatment could open the door to a HER2 targeted therapy benefiting a new population – those who will be classified as HER2-low. It could result in patients living longer, with their disease being under control for a longer period of time, compared to chemotherapy. • Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. If trastuzumab deruxtecan is approved, it would be important for clinicians to clearly discuss its specific potential side effects with patients, so that they can make informed decisions, regarding treatment options, with the support of their clinician. • Trastuzumab deruxtecan showed significant benefits over chemotherapy options in certain patients classified with HER2-low breast cancer. This highlights the importance of redefining groups of breast cancers so that eligible patients whose tumours are HER2 low can benefit from a targeted anti-HER2 treatment.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab Deruxtecan (Enhertu) for treating HER2-low Metastatic Breast Cancer

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	METUPUK
3. Job title or position	Patient advocate
4a. Brief description of the organisation (including who funds it). How many members does it have?	METUPUK is a volunteer led patient advocacy organisation working for the unmet needs of patients with metastatic breast cancer (MBC). Our three main objectives are: raising MBC awareness and education; campaigning for equitable treatment, including access to drugs; and improvements in patient care. Our services aim to inform patients with primary breast cancer, their family and friends and clinicians of the red flag signs and symptoms of metastatic breast cancer. For patients with metastatic breast cancer, we campaign for improved access to drugs and treatments. This may include addressing disparities in accessing treatment and clinical trials in the four nations of the UK, or between different commissioning groups within a given nation. We also campaign for access to new therapeutics and radiotherapy treatments so NHS and private patients have the same access to treatment. We call on Trusts to collect accurate and timely data on their patients with MBC. Through our social media channels, we provide signposting for peer support and to other charitable organizations that also offer support. We became a registered charity in 2021, but the organisation began as a small group of patients frustrated by the poor prognosis for MBC in 2016, and has grown since then. We are not a membership organisation, but we do reach out to the metastatic patient community with over 9000

	followers on social media platforms. Our funding is entirely from public donations. All our trustees and volunteers are unpaid.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have used our social media channels of Facebook, Instagram and Twitter to gather experiences of patients on trastuzumab deruxtecan. We also reached out to those who had been on the HER2-low arms of the DESTINY-Breast Trial using Enhertu. Currently trastuzumab deruxtecan has been approved for use in patients with HER2-low metastatic breast cancer in the US and the EU, and MBC patients are anxiously awaiting timely approval in the UK.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with MBC is to live with uncertainty. We live from scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Even with the best available drug therapy, for most patients, decades of life will be lost. It is a severe life-limiting disease. We mourn this loss of life - milestones, precious memories with families and friends, ambitions for future careers, income and contributions to our communities and society. Some of us grieve the loss of being parents and others agonise over leaving children parentless. Patient advocate Ann describes living with MBC: Living with MBC brings a level of sadness which is always there and cannot be shifted. You are constantly aware that your life is time limited and planning of any kind is exceptionally difficult. You feel helpless and despair that you have no control over your illness and are wholly dependent on the availability of drugs to keep you alive. The psychological benefits of knowing that medical advancements continue to be pursued and will be made available cannot be emphasised enough- it reduces the mental stress of MBC and brings real hope. MBC is also incredibly difficult for carers. Partners find their role in a family changes quite suddenly from lover to carer for the patient, often balancing this with the financial need to work and sometimes manage childcare. Many patients have children under 18 living with them who face the considerable difficulties of being a young carer while balancing their studies and losing out on their youth. Patients' parents face the awful prospect of their children dying before them, with very little support. Joe's wife has metastatic breast cancer and he describes how "our lives are turned upside-down, organised around treatments and care. We make plans we hope will come to pass but do not presume. We value the life of those we love like we have never done before, and knowing it will not last, we cherish what we have" Nick writes, "There are so many compromises to be made that you don't even think about. I love my wife and spending time with her, so it's largely positive although being on call when she's sick is challenging. The mental side is very hard. I don't like seeing her so sick. It makes me sad."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with HER2-low metastatic breast cancer do not have access to any lines of anti-HER2 therapy because they are currently classified as HER2-negative. Many patients are aware of trastuzumab deruxtecan because it has been covered extensively in the scientific and mainstream press and have asked their oncologist if they have HER2-low breast cancer. Patients find it frustrating that a treatment which is available in countries with comparable healthcare systems is not available to them. Patient opinion about current treatments differs as some patients who have HER2-low metastatic breast cancer have a hormone positive cancer, and others a triple negative cancer, and there are distinct differences in the range of drug treatment options available to each sub-type. Regardless of these differences, patients much prefer targeted treatments to untargeted cytotoxic chemotherapy. This is because targeted treatments give better outcomes to conventional chemotherapy, and also have less adverse side effects, therefore giving patients a longer and better quality of life. Tassia writes about her experience as a patient: Care can be awful, and inconsistent between healthboards. I personally do not have a keyworker or secondary breast care nurse. If you are HER2-low there is not enough treatment out there to live a longer and better quality of life. There needs to be better ways to treat leptomeningeal mets in breast cancer. Michael's wife has HER2-low metastatic breast cancer and has gone through three different lines of treatment in the last year. He has become her carer which has taken a toll on him emotionally. He would welcome trastuzumab deruxtecan as an option for her in the future. He says that his wife and other patients should not be denied these treatments because of previous lines of drugs. Michael feels when drugs are denied by NICE, it truly feels like the system does not care about patients and their families.

8. Is there an unmet need for patients with this condition?	Yes there is an unmet need for patients with HER2-low metastatic breast cancer. Given that 60% of patients diagnosed with HER2 negative metastatic breast cancer have low levels of HER2, this represents a sizeable unmet need. HER2-low metastatic breast cancer is a severe, incurable and life-limiting disease. Even with best available care, disease progression occurs and patients require new treatments to extend their lives. According to the Office of National Statistics, in England in 2020, metastatic breast cancer was the leading cause of deaths in females in the 35 – 64 age group. Patients with HER2-low metastatic breast cancer have a life expectancy of less than two years on NHS standard of care. Any disease which slashes years and often decades off lives, is by any reasonable assessment a severe disease. At the time of submission, patients with HER2-low metastatic breast cancer do not have access to any lines of targeted anti-HER2 therapies. Trastuzumab deruxtecan has been shown in clinical trials to increase both progression free survival and overall survival for patients with HER2-low MBC. We believe it is in the public interest to approve trastuzumab deruxtecan because it is the only drug available to treat HER2-low metastatic breast cancer and its results significantly outperform current standard of care. This drug offers life and hope to patients with this severe end of life disease. For patients, it is important that oncologists can choose at which line to use trastuzumab deruxtecan. Every patient has different needs, and these are best assessed by their medical team.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Trastuzumab deruxtecan is a targeted treatment. Clinical trial results indicate that this treatment increases the length of time before cancer progresses and how long patients live. This is decisively the biggest advantage for patients and their families. Living with a lower burden of disease for longer allows patients to spend more time in better health. Also targeted therapy translates to fewer side effects and a better quality of life compared to conventional chemotherapy. Patient Gemma says she is so glad she was prescribed the drug because she understands how the drug works and was excited to have a targeted therapy for her HER2 low status. It has bought her several months of stability. She felt for a while because of her HER2 status, a targeted treatment would make a difference, and this was supported by her oncologist

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients are concerned about the side effects of the drug, including interstitial lung disease and problems with heart function, which may require treatment to be stopped. There are also concerns about nausea and fatigue, and problems with low blood counts. However these concerns are not specific to trastuzumab deruxtecan, and trials have shown that these side effects are less severe than standard chemotherapy. So relatively speaking, trastuzumab deruxtecan is a much better option for patients. Patients are concerned that they will be denied access to trastuzumab deruxtecan for their HER2-low status because of prior lines of treatment they may have taken. They are also concerned that future lines of treatment may be denied if they do get access to trastuzumab deruxtecan. For example, patients with hormone positive HER2-low metastatic breast cancer do not want to lose access to endocrine treatments. Patients with hormone negative HER2-low metastatic breast cancer do not want to lose access to the drugs on the triple negative pathway, specifically immunotherapy if applicable and Trodelvy.

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.	HER2 low metastatic breast cancer patients

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are concerned that the absolute shortfall in the severity modifier calculation discriminates against the protected characteristic of age, and that the proportional shortfall does not adequately reduce the impact of this.

Other issues

13. Are there any other issues that you would like the committee to consider?	With the NHS focus on patient-centred care, regulatory systems should function to benefit patients needs, and should be flexible enough to adapt to patients' prior lines of treatment. Patients value the clinical acumen of their oncologist and would like them to have a large toolkit of drugs. Only then can the NHS provide personalised care for patients. We believe it is in the public interest to approve trastuzumab deruxtecan because its results significantly outperform current standard of care. This drug offers life and hope to patients with this severe end of life disease.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an unmet need for a targeted treatment for HER2-low metastatic breast cancer, which is a severe end of life disease • Trastuzumab deruxtecan increases the length of time before HER2-low MBC progresses and overall survival compared with standard chemotherapy • Patients value targeted treatments because they are associated with fewer side effects and a better quality of life compared to standard chemotherapy • Oncologists should be given the flexibility to decide at which treatment line to use trastuzumab deruxtecan for their patients • Patients with HER2-low MBC do not want to lose access to endocrine drugs specific to hormone positive MBC or to drugs specific to the triple negative pathway

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Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-Low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	RCP registrar
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? A specialist in the clinical evidence base for this condition or technology? Other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. 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.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Delay progression of metastatic disease and to maintain or improve quality of life
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of tumour volume by 30% (stable disease also clinically meaningful)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes - no established treatments for HER2 low metastatic breast cancer patients (would be treated as HER2 negative)

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

9. How is the condition currently treated in the NHS?	This would be following chemotherapy for HER2low metastatic breast cancer - the most likely comparator would be 2nd line chemotherapy
9a. Are any clinical guidelines used in the	Advanced breast cancer: diagnosis and treatment (2009; updated 2017). NICE guideline 81. No specific guidelines on this subtype of breast cancer.

treatment of the condition, and if so, which?	
9b. 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.)	Not well defined as a newly defined subtype of metastatic breast cancer (treatment would usually be guided by ER status in these patients and they would previously have been treated as HER2 negative)
9c. What impact would the technology have on the current pathway of care?	New line and type of treatment for a distinct group of patients which was not available previously
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes (currently used for metastatic breast cancer patients who are HER2 positive)
10a. How does healthcare resource use differ between the technology and current care?	Cost of new therapy likely to be much more expensive as compared to standard chemotherapy treatments. Other resource implications similar.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Breast oncology clinics (secondary or tertiary care)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Technology for testing already in place

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Will be applicable to ~50% of patients with metastatic breast cancer.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Extra monitoring and assessment for pneumonitis would likely be required (Likely more CT scans)

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CT chest would likely be indicated to assess for pneumonitis if symptomatic (12% of patients)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is a completely new and additional form of treatment for a significant proportion of metastatic breast cancer patients
16a. Is the technology a 'step-change' in the management of the condition?	Yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Metastatic breast cancer still has a poor overall prognosis and so anything that can improve survival in these patients is an advantage for them
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No specific data yet available on quality of life though the risks of lung toxicity (pneumonitis) are more significant and there was a 0.8% death rate from pneumonitis itself, but an overall benefit in terms of survival.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, overall survival, adverse event rates, quality of life - quality of life measures were not included
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogates not used
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	It's a relatively new drug and only used currently in clinical trials so real-world experience not yet available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Important new treatment option for a new category of metastatic breast cancer patients • Clinical trial data has shown both progression free and overall survival benefit for these patients • Pneumonitis rates are a specific toxicity from this drug and will need to be assessed in a real world setting • Quality of life measures not currently available • Real world data not yet available

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Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	23/05/2023

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

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

This report should be referenced as follows:

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Contributions of authors

Mark Clowes critiqued the company's search strategy. Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren and Sarah Ren critiqued the statistical aspects of the submission. Sarah Davis and Andrew Metry critiqued the health economic analysis submitted by the company. Nicolò Battisti provided clinical advice. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

AEs	Adverse events
AIC	Akaike Information Criterion
ALT	Alanine Transaminase
AST	Aspartate Transferase
BC	Breast cancer
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CG	Clinical guideline
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DCO	Data cut-off
DoR	Duration of response
EAG	Evidence assessment group
ECOG	Eastern Cooperative Oncology Group
ECOG	Eastern Cooperative Oncology Group performance score
EQ-5D-3L	EuroQol 5 Dimension 3 Level
FAS	Full analysis set
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HorR	Hormone receptor
HRQoL	Health-related quality of life
IA	Investigator assessment
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
ISH	In situ hybridisation
ILD	Interstitial Lung Disease
IPD	Individual patient data
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier

LV	Left ventricular
LYs	Life years
mBC	Metastatic breast cancer
MUGA	Multigated acquisition scan
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazard
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Response rate
SAS	Safety analysis set
SG	Sacituzumab govitecan
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
T-DXd	Trastuzumab deruxtecan
TEAEs	Treatment emergent adverse events
TPC	Treatment of physician's choice
TTD	Time-to-treatment discontinuation
uBC	Unresectable breast cancer
u/mBC	Unresectable or metastatic breast cancer

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessemnt Group (EAG) as being potentially important for decision making in their review of the company submission for the appraisal of trastuzumab deruxtecan (T-DXd) as monotherapy for treating adult patients with unresectable or metastatic breast cancer (u/mBC) with low levels of human epidermal growth factor receptor 2 (HER2), and who have had at least one prior chemotherapy.

It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of cost per quality-adjusted life year (QALY).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest impact on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are contained in the main report.

All issues identified represent the view of the EAG, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and QALYs are summarised in Table 1. A fuller description of each issue, together with potential alternative approaches, the expected impact on the ICER of such approaches and additional evidence that would resolve the issue are contained in Sections 1.3 to 1.5.

Table 1: Overview of the EAG's key issues

ID 3935	Summary of issues (More detail is provided in Section 3.3, 5.2.2, and 5.3.3)
Issue 1	The deviation of the comparator arm from the NICE scope
Issue 2	Exploratory comparison against sacituzumab govitecan (SG) for hormone receptor-negative (HorR-negative) subgroup assumes clinical equivalence
Issue 3	Generalisability of the trial population of DESTINY-Breast04 to the patient population seen in England
Issue 4	Extrapolation of overall survival (OS)
Issue 5	Estimation of patients entering the post-progression and death health states
Issue 6	Extrapolation of progression-free survival (PFS)
Issue 7	Extrapolation of time to treatment discontinuation (TTD)
Issue 8	Health utility values for progression-free and post-progression states
Issue 9	Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter
Issue 10	Implementation of relative dose intensity (RDI) when calculating the drug acquisition costs
Issue 11	Vial sharing for intravenous therapies

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers different parametric fits for extrapolating OS data
- As the TPC arm from the key clinical trial deviates from the NICE scope, the EAG adjusted the mix of treatments within the TPC arm to bring it closer to what is expected in clinical practice
- The EAG preferred to use a different set of utility values that had better face validity, and also limited the benefit post-progression to six months in line with previous appraisals
- The EAG prefers different parametric fits for extrapolating PFS data

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology improves length (overall survival (OS)) and quality of life, using QALYs. In the company's model, T-DXd treatment increases QALYs compared with the comparators by increasing expected OS. This includes additional life-years gained both pre- and post-progression compared with comparator treatments. In addition, the company's base case assumes that patients treated with T-DXd experience better quality of life (higher utility values) than those treated with comparators both pre- and post-progression. Overall, the costs associated with T-DXd treatment compared with comparators are greater, primarily due to the acquisition cost of T-DXd.

The assumptions within the company's base case modelling that the EAG believes are either incorrect, or uncertain, and that impact most on the ICER, are provided in Table 1.

The ICER estimates discussed in Sections 1.3 to 1.5 are based on the deterministic model, when applying a QALY weight of 1.2X in line with the company's assessment of the severity modifier, as discussed at Section 6. ICERs with and without QALY weighting are summarised in Section 1.6, Table 2. The ICERs presented in this report include a patient access scheme (PAS) price for T-DXd, but do not include any confidential discounts for comparator treatments. ICERs when implementing confidential discounts for comparator treatments are included in a confidential appendix.

1.3 The decision problem: summary of the EAG's key issues

The EAG has one key issue with the decision problem addressed by the company and this relates to the discrepancy between the comparators listed in the NICE scope and those used in the comparator arm of the key trial (DESTINY-Breast04) used in the company's submission (CS). These concerns are further discussed in Issue 1 and 2, in Section 1.4, as they have implications for the assessment of clinical effectiveness and cost effectiveness for T-DXd versus standard care without T-DXd.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The key clinical evidence presented in the CS and that informs the economic analysis for T-DXd is from the DESTINY-Breast04 clinical trial. This compared T-DXd with single-agents chemotherapies (capecitabine, eribulin, gemcitabine, paclitaxel, & nab-paclitaxel) as one basket of therapies called collectively 'Treatment of physician's choice' (TPC).

The EAG's first key issue regarding the clinical effectiveness evidence is uncertainty over whether the components of TPC are reflective of those used in clinical practice in England and whether similar efficay can be assumed among the different comparators included in TPC (Issue 1). In addition there was uncertainty regarding the assumption of equivalent efficay between T-DXd and sacituzumab govitecan (SG) which was recently recommended in the second-line setting for hormone receptor-negative patients (HorR-negative) (Issue 2). Issue 3 was the comparability of the trial population to the population likely to be treated in clinical practice in England, in terms of the exclusion of patients from the trial with an ECOG PS score of 2 and the proportion of people of Asian ethnicity, which was higher in the trial than would be expected in many treatment centres in England. These were considered to be potentially important differences as both of these factors were considered by the company to be potential treatment effect modifiers. It could be also argued that the trial population was younger; all of which the EAG believe to be a currently unresolvable issue that is a cause of uncertainty regarding the expected relative treatment effect of T-DXd versus TPC within the population likely to be treated in England. Issue 4 was the immaturity of the OS data meaning that different extrapolations result in significantly different ICER estimates. This is further discussed in Section 1.5 (Issue 4) as the long-term extrapolation of OS has implications for the assessment of cost-effectiveness.

Issue 1. The deviation of the comparator arm from the NICE scope

Report section	Sections 3.3, 5.3.3.11, 5.4.2.12, and 5.4.2.13
Description of issue and why the EAG has identified it as important	The TPC arm included eribulin as a second-line therapy when it is only recommended by NICE after two previous lines of chemotherapy (i.e. third-line). The TPC arm also included gemcitabine which was not included in the NICE scope. Gemcitabine is not currently prescribed as a single-agent chemotherapy and is instead generally offered in combination with carboplatin. Also, nab-paclitaxel is rarely presecribed in England as it is only used when patients show hypersensitivity reaction to taxanes. In contrast, there were other comparators listed in the NICE scope, but not used in the TPC arm. These included anthracyclines, carboplatin, and vinorelbine.
What alternative approach has the EAG suggested?	Assuming similar efficacy among these treatments, the EAG removed eribulin and gemcitabine it its base case and redistributed the proportions receiving gemcitabine and eribulin across the remaining treatments according to the distribution of the remaining treatments in DESTINY-Breast04. In two scenario analyses, the EAG explored 100% of the patients receiving the highest cost component of TPC (eribulin) and 100% of patients receive the lowest cost component of TPC (capecitabine). The intention was to explore the sensitivity of the cost-effectiveness to uncertainty in the treatment mix and not to reflect plausible scenarios in clinical practice
What is the expected effect on the cost-effectiveness estimates?	Removal of eribulin and gemcitabine increased the ICER for the company's corrected base case from [redacted] to [redacted]. Assuming the highest cost component (eribulin) to represent 100% of TPC decreased the EAG's base case ICER estimate from [redacted] to [redacted], whereas assuming 100% receiving capecitabine increased it slightly to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Real world evidence (RWE) comparing TPC components used in England to T-DXd in the intended population of patients with metastatic breast cancer with low expression of HER2, or real world evidence on the efficacy of TPC and performing an appropriate indirect treatment comparison to the T-DXd arm from DESTINY-Breast04 trial. RWE is also needed for informing proportions receiving each different treatment.

Issue 2. Exploratory comparison against SG for HorR-negative subgroup assumes clinical equivalence

Report section	Sections 5.3.3.2 and 5.4.2.20
Description of issue and why the EAG has identified it as important	The NICE scope states SG, which was recently recommended in TA819, as a relevant comparator for people whose disease is HorR-negative. The CS lacked any comparative data between T-DXd and SG. In response to clarification questions, the company judged that it was infeasible to conduct an indirect treatment comparison (ITC) between the two drugs due to different trial populations and presented a cost-minimisation analysis assuming equivalent clinical outcomes, including PFS, OS, adverse events (AEs) and TTD. No incremental analysis was presented to assess whether T-DXd, SG or TPC would be the most cost-effective treatment in the HorR-negative subgroup of the HER2-low population, which is potentially important when considering that clinical outcomes are generally worse in this subgroup. In addition the average patient weight for the whole population of the DESTINY-Breast04 trial was used instead of the average weight for HorR-negative patients, and RDI for SG was assumed to be 100%.
What alternative approach has the EAG suggested?	The EAG highlights that the cost-effectiveness of SG compared to standard care in the HER2-low population is unknown and therefore it is not sufficient to demonstrate that T-DXd is cost-saving relative to SG in the HorR-negative subgroup in order to demonstrate that T-DXd is cost-effective in the HorR-negative subgroup. Hence, the company has not properly assessed the cost-effectiveness of T-DXd against SG in the HoR-negative subgroup. For illustration purposes only, the EAG changed some of the assumptions in the cost-minimisation analysis to assess sensitivity of the cost-saving claims including; using average patient weight for the HorR-negative patients, and using the RDI and treatment duration estimates for SG from TA819 (6 months and 94% respectively).
What is the expected effect on the cost-effectiveness estimates?	Using the list price for SG, the overall cost saving reduced from £[redacted] in the company's base case to £[redacted] for T-DXd compared to SG over the patient's life-time.
What additional evidence or analyses might help to resolve this key issue?	A RWE study comparing T-DXd to SG in the HER2-low population would help clinicians select the most effective treatment in patients eligible for either T-DXd or SG.

Issue 3. Generalisability of the trial population of DESTINY-Breast04 to the patient population seen in England

Report section	Sections 3.1 and 4.2.4
Description of issue and why the EAG has identified it as important	The DESTINY-Breast04 trial excluded patients with ECOG performance scores (ECOG PS) of 2 or more although this group is eligible for treatment. In addition, around 40% of the trial population were Asians, and the average age for the whole population was 56.5 years. Clinical advice to the EAG stated that the population seen in practice had lower proportion of Asians and are older.
What alternative approach has the EAG suggested?	The EAG would highlight that ECOG PS scores and ethnicity distribution are considered treatment effect modifiers. In absence of alternative data, the EAG was not able to adopt another approach.
What is the expected effect on the cost-effectiveness estimates?	-
What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see subgroup analysis of a population that is similar to the one seen in clinical practice in terms of OS, PFS, TTD, and treatment allocation data. However, the EAG acknowledges that this may be associated with lower sample size and higher uncertainty.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

This section expands on the remaining issues listed in Table 1 and focuses on the key issues that the EAG considers are likely to affect decision making. A complete list of all issues identified by the EAG, can be found in Section 5.3.3. Some of these were also explored in the EAG's exploratory analyses, as described in Section 5.4, and therefore feature in Table 2, Section 1.6, but are not discussed in detail in Section 1.5 as they had minimal impact on the ICER.

Issue 4. Extrapolation of OS

Report section	Sections 5.3.3.4 and 5.4.2.3
Description of issue and why the EAG has identified it as important	The EAG disagrees with the company's choice of using the log-logistic distribution to extrapolate OS as the base case for the following reasons. Firstly, the EAG judges that the log-logistic model overestimates the survival probability after approximately 18 months until 27 months for the T-DXd arm which results in a much longer tail compared to most of the other distributions and the company rejected the log-normal distribution for similar reasons. Secondly, the log-logistic predictions are inconsistent with clinical expert advice that ≤1% of patients are expected to remain alive at 10 years. Thirdly, the smoothed hazard functions do not seem to capture the shape of the unsmoothed hazard functions well due to censoring at the end of the trial. The unsmoothed hazard functions for both arms indicate an increasing trend in the hazard over time, whereas the smoothed hazard functions are unimodal functions with hazard increasing then decreasing.
What alternative approach has the EAG suggested?	The EAG prefers a gamma distribution, which seems to provide a reasonable long-term prediction in between the log-logistic and the Weibull distribution which may underestimate the 5-year survival probability. However, the company's model did not provide the estimates for the gamma distribution so the Weibull fit was selected by the EAG as more plausible than the log-logistic distribution.
What is the expected effect on the cost-effectiveness estimates?	The choice of parametric extrapolation for OS had a significant impact on the ICER. The ICER for the company's corrected base case increased from [redacted] to [redacted], when replacing the log-logistic distribution with the Weibull distribution. The ICER for the EAG's preferred base case scenario, which included the Weibull distribution for OS, decreased from [redacted] to [redacted] when the Weibull distribution was replaced by the log-logistic distribution.
What additional evidence or analyses might help to resolve this key issue?	Additional data from the next expected data cut off point could provide considerably more data on OS and may resolve some of the uncertainty in the ICER. The data in the CS are based on a data cut-off point of 11th January 2022. In addition, the company have provided plots for a gamma function fitted to OS which suggest that this curve may be more appropriate than either the log-logistic or the Weibull, but they have not provided the parameters for the gamma function. If would be helpful if this curve could be included in the economic model for sensitivity analysis.

Issue 5. Estimation of patients entering the post-progression and death health states

Report section	Sections 5.3.3.3 and 5.4.2.2
Description of issue and why the EAG has identified it as important	The company's model structure assumes that the risk of death from the post-progression state is zero for the purposes of estimating the proportion of newly progressed patients each cycle.
What alternative approach has the EAG suggested?	The EAG corrected the formulae used to estimate the proportion of newly progressed patients each cycle so that it properly reflects the proportion of deaths occurring from the pre-progression state and the post-progression state.
What is the expected effect on the cost-effectiveness estimates?	This had minimal impact on the ICER increasing it by [redacted] when applied in isolation to the company's corrected base case, but the EAG considers that the correction increases the validity of the model.
What additional evidence or analyses might help to resolve this key issue?	-

Issue 6. Extrapolation of PFS

Report section	Sections 5.3.3.4 and 5.4.2.3
Description of issue and why the EAG has identified it as important	The company regarded the log-logistic and generalised gamma models to provide the most plausible fits for PFS, and selected the log-logisistc model to provide a consistent functional form with the base case distribution for OS. The EAG acknowledges that OS and PFS data are correlated, but this relationship does not warrant that the hazard function of OS and PFS would follow the same trend and hazard functions estimated using the trial data do not suggest that the same functional form should be selected. Given the fact that the PFS data are considered almost mature, the EAG considers that the log-logistic model may be less plausible compared to the generalised gamma distribution as the log-logistic model gives a longer tail which is less consistent with the Kaplan-Meier (KM) data observed for T-DXd.
What alternative approach has the EAG suggested?	The EAG adopts the generalised gamma distribution in its base case for PFS.
What is the expected effect on the cost-effectiveness estimates?	This increased the ICER for the company's corrected base case from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The company could use the mature KM data to estimate PFS directly in the model and limit parametric extrapolations to the time period beyond where KM data is available.

Issue 7. Extrapolation of TTD

Report section	Sections 5.3.3.6 and 5.4.2.5
Description of issue and why the EAG has identified it as important	The EAG agrees with the company that the log-logistic and generalised gamma model were the most plausible models for the base case extrapolation for TTD. The company used the latter in their base case despite its AIC/BIC statistics being 5 points higher for the TPC arm.
What alternative approach has the EAG suggested?	The EAG explored two scenarios where the restricted mean treatment duration approach was used as the lower limit for treatment duration, and the log-logistic TTD extrapolation was used as the upper limit.
What is the expected effect on the cost-effectiveness estimates?	The first scenario reduced the EAG's base case ICER from [redacted] to [redacted], whereas the second scenario increased the ICER to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The company could use the mature KM data to estimate treatment discontinuations directly in the model and limit parametric extrapolations to the time period beyond where KM data is available.

Issue 8. Health utility values for progression-free and post-progression states

Report section	Sections 5.3.3.7 and 5.4.2.6
Description of issue and why the EAG has identified it as important	The EAG notes that the estimates of pre-progression utility based on the company's generalised linear mixed model are high and lack face validity (for e.g. patients on T-DXd treatment have higher utility than members of general population of the same age). In addition, the EAG notes that the post-progression utility values estimated from the Lloyd algorithm are not consistent with the NICE reference case because they do not represent utilities obtained directly from patients with breast cancer.
What alternative approach has the EAG suggested?	The EAG decided to use the PFS utility estimates from the summary values by trial arm provided by the company as these were more plausible and in line with previous appraisals. The EAG considers that it would be more appropriate to use the utility decrement for progression estimated from the Lloyd algorithm and apply it to the trial-based estimates of pre-progression utility values, to calculate post-progression utility values that are treatment specific.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred utility set increased the ICER for the company's corrected base case from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	A study collecting HRQoL post-progression data for patients who were treated by either T-DXd or TPC.

Issue 9. Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter

Report section	Sections 5.3.3.7 and 5.4.2.7
Description of issue and why the EAG has identified it as important	The company's base case assumed that post-progression, patients who had been on T-DXd would have higher utilities compared to those on TPC and these differences would persist for the remainder of the patient's lifetime.
What alternative approach has the EAG suggested?	In line with TA819, the EAG preferred to assume that any difference in the utilities between treatment arms only persisted for 6 months following progression after which all patients would adopt the TPC utility.
What is the expected effect on the cost-effectiveness estimates?	Limiting the post-progression benefit to 6 months assuming the company's preferred utilities increased the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	A study collecting HRQoL post-progression data for patients who were treated by either T-DXd or TPC.

Issue 10. Implementation of RDI when calculating the drug acquisition costs

Report section	Sections 5.3.3.8 and 5.4.2.8
Description of issue and why the EAG has identified it as important	The company's approach to implementing the RDI is inconsistent between the T-DXd (calculated relative to the planned dose intensity) and the TPC arms (where the planned dose was not always the same as the dose costed in the model).
What alternative approach has the EAG suggested?	The EAG base case used the RDIs estimated from the clinical study report (CSR) relative to the drug dose assumed in the model.
What is the expected effect on the cost-effectiveness estimates?	This increased the company's corrected ICER increasing from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	-

Issue 11. Vial sharing for intravenous therapies

Report section	Sections 5.3.3.11 and 5.4.2.11
Description of issue and why the EAG has identified it as important	The company assumed that vial sharing will result in zero wastage in 75% of administrations for T-DXd and all intravenous therapies included in TPC. This was higher than the figure used in TA862 (50%), and the company argues that the increase is based on broadening of usage for T-DXd to include the HER-low population.
What alternative approach has the EAG suggested?	Due to paucity of data, the EAG used 50% in its base case in line with TA862.
What is the expected effect on the cost-effectiveness estimates?	This increased the company's corrected base case ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Real national figures of current levels of vial sharing for T-DXd and comparators would be useful.

1.6 Summary of EAG's preferred exploratory analyses

Table 2 provides the results from the EAG's exploratory analyses including both the crude ICERs and those accounting for the disease severity modifier as discussed at Section 6. When considering all the possible amendments, the EAG's preferred deterministic ICER was [redacted] considering a QALY weight of 1.2X (probabilistic ICER = [redacted]). The EAG's scenario analysis demonstrates that uncertainty regarding the long-term expectations for OS is associated with substantial uncertainty in the ICER, with use of the company's preferred log-logistic extrapolation reducing the ICER (when maintaining the EAG's other preferences) to [redacted]. In addition, the exploratoy analysis suggests that the ICER is sensitive to the choice of post-progression utility values and the mix of treatments received under current standard care without T-DXd. The EAG would have liked to generate illustrative ICERs for T-DXd versus TPC and SG in the HorR-negative subgroup of the HER2-low population; however, an ITC was difficult to generate as there were concerns regarding the comparability of the populations in the key studies for T-DXd (DESTINY-Breast04) and SG (ASCENT).

Table 2 Results of the EAG's exploratory analyses

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company base case - post-clarification (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case: correcting programming and implementation errors in the company's economic model						

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: EAG approach to estimating the proportion of patients entering the post-progression and death states						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Assuming a Weibull curve for OS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming a Generalised gamma curve for PFS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Applying the EAG's preferred utility values (maintaining a difference in post-progression utility values life-long)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying the HRQoL difference between treatment arms in the PD state for six months only and applying the post-progression utility value of TPC onwards to both arms (using company's preferred utility post-progression utility values)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Assuming RDIs relative to the modelled doses						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Applying administration costs for tamoxifen every three months						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Decreasing vial sharing from 75% to 50%						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 10: Adjusting the mix of subsequent therapies to include drugs recorded by their equivalent salts						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
EAG exploratory analysis 11: Assuming the same dose costs for the subsequent treatments used in TPC						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 12: Including arm-specific time on subsequent treatment						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 13: Applying age-related decrements to utility values						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Probabilistic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Assuming a log-logistic curve for OS extrapolations)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Assuming a Generalised gamma curve for PFS extrapolations with a cap for TPC)*						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Treatment costs are calculated using restricted mean treatment duration)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Treatment costs are calculated using log-logistic curve for TTD)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming administration costs for capecitabine every other cycle)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Assuming TPC costs equivalent to 100% receiving eribulin)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Assuming TPC costs equivalent to 100% receiving capecitabine)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Increasing CT scans to proactively detect ILD in patients receiving T-DXd)						

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 9 (Increasing frequency of cardiac monitoring for patients on T-DXd relative to TPC)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 10 (Changing paclitaxel schedule to 80 mg/m^2 IV every week)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG - evidence assessment group, HRQoL - health-related quality of life, ILD - interstitial lung disease, OS - overall survival, PD - progressed disease, PFS - progression-free survival, T-DXd - trastuzumab deruxtecan, TPC - treatment of physician's choice, TTD - time to treatment discontinuation

**This scenario is giving the same results as the base case because these curves are not crossing in the EAG's base case*

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

This single technology appraisal (STA) focuses on the use of trastuzumab deruxtecan (T-DXd) as monotherapy for treating adult patients with unresectable or metastatic breast cancer (u/mBC) with low levels of human epidermal growth factor receptor 2 (HER2), and who have had at least one prior chemotherapy.

Section B.1.3.1 of the company submission (CS) contains an accurate overview of the health condition, epidemiology, diagnosis and staging, and current biomarker usage for identifying HER2-low patients.[1]

Breast cancer is one of the most common cancers in the UK with over 45,000 people being diagnosed in England in 2020.[2] Breast cancer that spreads further from the breast to distant organs such as the bones, lungs, or other parts of the body is known as metastatic breast cancer (mBC) whereas that which cannot be removed by surgery is called unresectable breast cancer (uBC). Breast cancer cells are tested for the presence or absence of molecular markers of hormone receptors (HorR) for oestrogen and progesterone, and HER2, as these inform both prognosis and treatment planning. Epidermal growth factors occur naturally in the body and attach themselves to HER2, but when they attach to the HER2 receptors on cancerous cells, it stimulates them to divide and grow.

HER2 status is defined according to the immunohistochemistry (IHC) and in situ hybridisation (ISH) criteria. HER2-positive breast cancer is defined as tumours with an IHC score of 3+ for HER2 staining or IHC score of 2+ with HER2 gene amplification by ISH assay. Currently, it is a binary categorisation where samples not achieving the aforementioned biomarker criteria are classified as HER2-negative.

However, the introduction of HER2-low has redefined the classification of HER2-negative into: HER2-low which refers to tumours with an IHC score of 1+, or 2+ without HER2 gene amplification; and HER2-negative which refers to tumours with an IHC score of 0.[3] Therefore, HER2-low is a subgroup of the group previously denoted as HER2-negative, which can be identified using the tests already carried out routinely to identify HER-positive patients. An Austrian study of 1729 mBC patients found that around 35% were HER2-low.[4] About 6% of people with breast cancer in England in 2020 had stage IV (metastatic) breast cancer when they were diagnosed.[5]

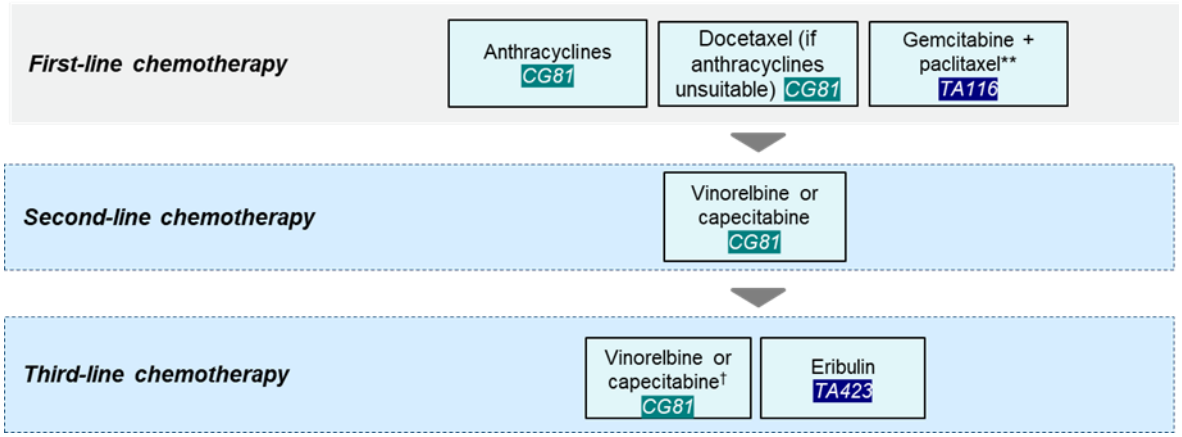
Currently, there are no recommended treatments specifically for HER2-low u/mBC. NICE Clinical Guideline 81[6] (CG81; 2017), which is for the management of advanced BC in general, recommends sequential chemotherapy treatments based on the HorR status as detailed in Section 2.2.

2.2 Critique of company's overview of current treatment pathway

The company could not identify any NICE or European guidance specific to the management of HER2-low u/mBC. Instead, the CS details the treatment pathways for managing HER2-negative u/mBC patients whose HorR status is either positive or negative (CS Section B.1.3.3.3.4). These were based on NICE CG 81[6] for the management of advanced BC in addition to previous NICE STAs with positive recommendations (TA116[7], TA423[8], TA639[9], TA801[10], TA819[11]).

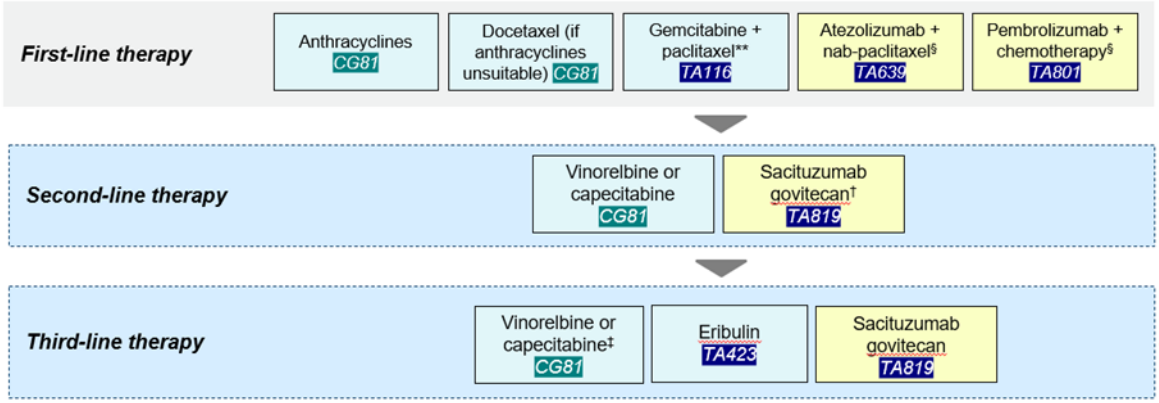
According to the current treatment pathway presented in the CS, patients with HorR-positive disease should be offered systemic chemotherapy in the sequence detailed in Figure 1, whereas those with HorR-negative disease should be offered the treatment sequence shown in Figure 2.

Figure 1 Treatment pathway for HER2-low HorR-positive u/mBC (reproduced from CS, Figure 5)



CG – clinical guideline; HER2 – human epidermal growth factor receptor 2; HorR – hormone receptor; TA – technology appraisal; u/mBC - unresectable/metastatic breast cancer
***Gemcitabine in combination with paclitaxel, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.*
†Whichever was not used as second-line treatment.

Figure 2 Treatment pathway for HER2-low HorR-negative u/mBC (reproduced from CS, Figure 6)



Key: Blue = Non-targeted chemotherapy; Green = targeted therapy
CG – clinical guideline; HER2 – human epidermal growth factor receptor 2; HorR – hormone receptor; TA – technology appraisal; u/mBC - unresectable/metastatic breast cancer
***Gemcitabine in combination with paclitaxel, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.*
§Recommended in patients with PD-L1 positive disease only.
†Recommended after 2 or more systemic therapies, at least 1 of which was for advanced disease.
‡Whichever was not used as second-line treatment.

The company states that both pathways may not reflect the current practice for several reasons: NICE CG81 was published in 2009, updated in 2017 with another update expected soon; treatment decisions are tailored per case and there are no optimal sequences; and all single-agent chemotherapies are of similar efficacy.

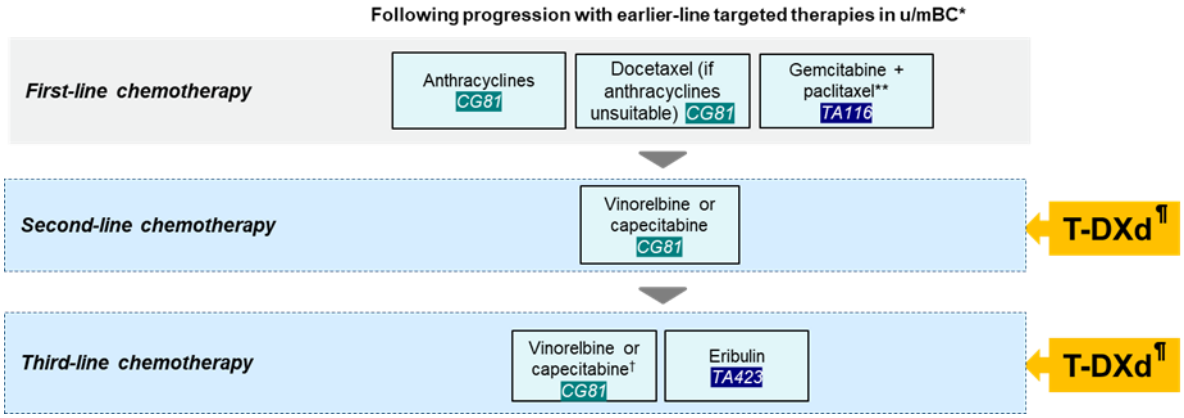
Clinical advice received by the EAG was that single-agent chemotherapies are likely to be prescribed sequentially rather than in combination and that such sequences vary among patients depending mainly on previous lines of therapy, tolerability, patient preferences, and comorbidities. In addition, other chemotherapies such as carboplatin could be used as second-line or beyond if a patient has not had them previously. The EAG's clinical experts highlighted that the main difference between the HorR-positive and HorR-negative pathways, in terms of second-line therapies and beyond, is the availability of sacituzumab govitecan (SG) for the latter. They also highlighted that eribulin is restricted only as a third-line option or beyond for both pathways. However, they noted that they rarely used gemcitabine in combination with paclitaxel as a first-line therapy as recommended in TA116, and it was generally used in combination with carboplatin further down the treatment sequence.

2.3 Critique of company's proposed positioning of trastuzumab deruxtecan in the treatment pathway

The company's proposed positioning of trastuzumab deruxtecan is "*as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of*

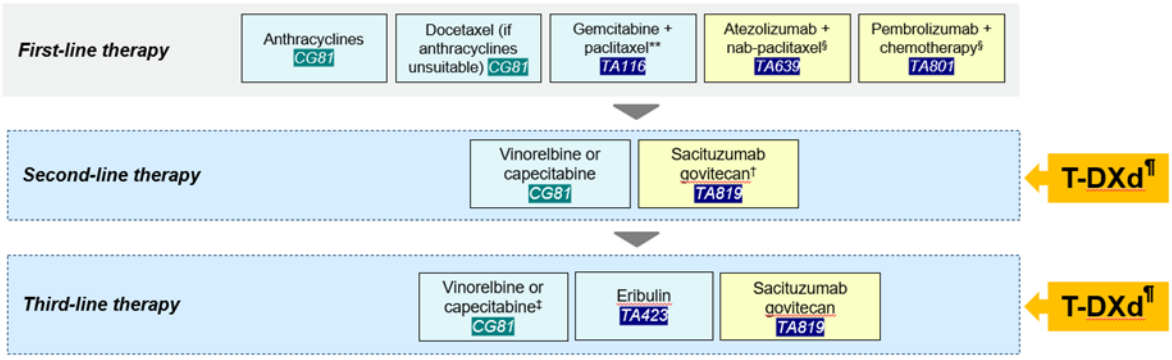
completing adjuvant chemotherapy".[1] This means that eligible patients should have received at least one prior line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting, which positions T-DXd as a second-line or beyond option, following initiation of chemotherapy. Clinical advice received by the EAG suggests that this positioning is aligned with how clinicians would want to use T-DXd in clinical practice. Figure 3 and Figure 4 show the expected positioning for T-DXd in the HorR-positive and HorR-negative pathways respectively, as stated in the CS.

Figure 3 Proposed positioning of T-DXd in HER2-low HorR-positive u/mBC (reproduced from CS, Figure 7)



¶*For patients with HER2-low (IHC1+ or IHC2+/ISH-) u/mBC after one line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting.*

Figure 4 Proposed positioning of T-DXd in HER2-low HorR-negative u/mBC (reproduced from CS, Figure 8)



¶*For patients with HER2-low (IHC1+ or IHC2+/ISH-) u/mBC after one line of chemotherapy in the adjuvant (if recurrence occurs within 6 months) or metastatic setting.*

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

Table 3 summarises the decision problem as presented by the company and the EAG critique. These are discussed below.

3.1 Population

The population defined in the NICE scope is: "*Adults with unresectable or metastatic HER2-low breast cancer previously treated with chemotherapy*".[12] This is in line with the new indication for T-DXd in HER2-low breast cancer (summary of product characteristics [SmPC] dated 22nd March 2023[13]) and the clinical trial for T-DXd, the DESTINY-Breast04 trial.[14] However, the DESTINY-Breast04 trial only included patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1. The EAG's clinical experts stated that the DESTINY-Breast04 trial did not include patients with ECOG PS2, many of whom would be offered second-line chemotherapy in current clinical practice. Additionally, the proportion of the trial population who were Asians (~40%) was higher than the proportion expected in the majority of UK centres and the average age was younger than expected in clinical practice.

The EAG is concerned that ECOG PS scores and the ethnicity distribution are not representative of the patient population seen in England, and would highlight that both factors are considered treatment effect modifiers as stated in the company's response to clarification question A21.[15]

3.2 Intervention

The intervention defined in the NICE scope is T-DXd.[12] The intervention outlined within the CS is in line with this: T-DXd administered as an intravenous (IV) infusion at 5.4 mg/kg of body weight every 21 days, with patients being treated with T-DXd until disease progression or toxicity, as per the SmPC.{, #619}

3.3 Comparators

The comparators listed in the NICE scope were anthracyclines, capecitabine, platinum therapies, taxanes, vinorelbine, eribulin for patients who have had more than 2 line of chemotherapy for metastatic disease, and SG for HorR-negative patients.[12] However, the comparator arm in DESTINY-Breast04 included only a subset of the comparators listed in the scope: capecitabine; taxanes in the form of paclitaxel and nab-paclitaxel; and eribulin (not restricted to third-line or beyond). This was in addition to gemcitabine as a single-agent chemotherapy, which was not listed in the NICE scope. Therefore, anthracyclines, platinum therapies, vinorelbine, and SG were excluded from the comparator arm of the DESTINY-Breast04 trial, whilst being included in the NICE scope. It is worth noting that the company

decided to use all of the comparator single-agents chemotherapies (capecitabine, eribulin, gemcitabine, paclitaxel, & nab-paclitaxel) as one basket of therapies called collectively 'Treatment of physician's choice' (TPC) instead of comparing T-DXd to each treatment individually.

The company stated that the lack of an established clear pathway and the lack of evidence of difference in efficacy between the different chemotherapy agents makes the trial evidence relevant to the decision problem. It also mentions that anthracyclines and platinum therapies are used early in the first-line or neoadjuvant settings. In addition, it argues that the exclusion of vinorelbine *"will not materially impact decision-making as there is no significant difference in efficacy between vinorelbine and other in-scope single-agent chemotherapies"*, and that SG is only relevant for a small subset (i.e., HorR-negative; ~10%)[15] of the overall HER2-low population. For eribulin, the company conducted a *post hoc* analysis comparing the full population of the DESTINY-Breast04 trial to a subset where patients were excluded if they were assigned to second-line eribulin, and found similar results in terms of the hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) for T-DXd versus the comparator arm.[16]

Clinical advice to the EAG confirmed that whilst capecitabine, paclitaxel and eribulin account for the majority of treatments offered second-line and beyond in this patient population, anthracyclines, carboplatin, and vinorelbine could be used as second-line options or beyond. They stated that anthracyclines and carboplatin may be used if the patient has not previously had them and vinorelbine is often used later in the treatment pathway, and the omission from the trial comparator arm of these comparators may not be trivial. Even in the absence of evidence on differential efficacy, these agents have different safety profiles. For example, some patients who wish to avoid alopecia may prefer vinorelbine over other agents. In addition to these omitted comparators, the EAG's clinical experts stated that eribulin is only available as a third-line option and beyond and gemcitabine is rarely used as a single agent in the UK clinical practice. The EAG finds it hard to evaluate the impact of such deviations and omissions and would highlight that the relative efficacy of T-DXd versus some of the comparators listed in the NICE scope is unknown from the evidence submitted in the CS.

Although the EAG acknowledges that the recommendation for SG was recent, the EAG's clinical experts stated that SG is a relevant comparator for HorR-negative patients and its omission from the CS for this subgroup is significant. They welcomed the potential opportunity to have multiple effective therapies to choose from in this subgroup, if T-DXd is recommended by NICE, but stated that guidance from NICE to help clinicians select the most appropriate treatment, which is based on the best available evidence, would be welcome. The EAG acknowledges that in response to a clarification request, the company has provided an exploratory cost-minimisation comparison between T-DXd and SG.[15] However, the EAG does not consider that this adequately addresses the question of whether T-DXd is

clinically effective or cost-effective in comparison to SG because it assumes clinical equivalence between the two treatments. This is further discussed in Section 4.3.3.2.

3.4 Outcomes

The NICE final scope[12] lists the following outcome measures:

- PFS
- OS
- Response rate (RR)
- Duration of response (DoR)
- Adverse effect of treatment
- Health-related quality of life (HRQoL)

These were all assessed in the DESTINY-Breast04 trial (CS, Table 1).[1] In addition, the company also assessed time to response and hospitalisation.

The economic analysis estimates the incremental costs and incremental quality-adjusted life-years (QALYs) over a 30-year time horizon (discounted at 3.5% per annum) to provide an incremental cost-effectiveness ratio (ICER) expressed in terms of cost per QALY for T-DXd versus the TPC comparator, which was comprised of 5 single-agent chemotherapies. Costs are assessed from an NHS and Personal Social Services (PSS) perspective in the base case whereas QALYs are those accrued by patients based on treatment received and progression status.

3.5 Other relevant factors

In line with the current NICE methods guide,[17] the company calculated the absolute and proportional QALY shortfall associated with current available care in patients with HER2-low u/mBC who have previously been treated with chemotherapy compared with the general population. These were found to be [redacted] discounted QALYs and [redacted] respectively which qualifies the QALYs for this STA to be weighed at 1.2x (full details can be found in the CS, Section B.3.6.3). The company's estimate of the severity modifier is further discussed in Section 5.

The CS also notes that T-DXd meets the superseded end-of-life criteria as patients with u/mBC after one prior chemotherapy have a life expectancy of less than 24 months and T-DXd extends this expectancy by more than 3 months. However, the end-of-life criteria no longer form part of the NICE process and methods since the introduction of the new NICE process and methods guide, which applies to topics such as this one which started after 1st February 2022.[17] As such, the end-of-life criteria, is not discussed further in the document.

Table 3 The decision problem (reproduced from CS, Table 1 with minor amendments and comments from the EAG)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
Population	People with HER2-low unresectable or metastatic breast cancer previously treated with chemotherapy	As per scope	-
Intervention	Trastuzumab deruxtecan	As per scope	-
Comparators	Established clinical management without trastuzumab deruxtecan, including: • anthracyclines • capecitabine • platinum therapies • taxanes • vinorelbine For people who have had 2 or more lines of chemotherapy for metastatic disease: • eribulin For people whose disease is hormone receptor negative: • sacituzumab govitecan	A basket of single non-targeted chemotherapy agents (TPC) comprising: eribulin, capecitabine, paclitaxel, gemcitabine, and nab-paclitaxel. The company states that NICE CG81 is outdated awaiting an imminent update, and that the choice of treatment is heavily dependent on a number of individualised factors, such as prior therapies received, the patient's fitness level with regard to what they can tolerate, and an individual patient's preferences. In particular, anthracyclines and platinum therapies are used in the neoadjuvant setting, meaning they are not available for metastatic disease. The company states that the exclusion of vinorelbine would not bias the outcomes of the DESTINY-Breast04 trial as all non-targeted chemotherapies are of similar efficacy, whereas a *post hoc* analysis showed eribulin to have no significant impact on the relative treatment effect of T-DXd. Finally, sacituzumab govitecan (SG) is only relevant to a small subset of the population	TPC included gemcitabine which, according to the EAG's clinical advisors, is not used as a single agent in the UK because of poor efficacy Clinicians agreed that there is no standard sequence followed for prescribing such chemotherapies, however anthracyclines and carboplatin could be used in clinical practice when not used previously. Eribulin is prescribed only as a third-line option and beyond whereas it was allowed as a second-line treatment in DESTINY-Breast04. The EAG is unsure of the significance of these omissions and deviations from the NICE final scope, given that clinical advice was that capecitabine, paclitaxel and eribulin (third-line only) make up the majority of treatments offered second-line and beyond.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
		relevant to the decision problem (i.e., HorR-negative)	However, the omission of SG as a comparator from the CS for HorR-negative patients is considered significant. The EAG considers that the question of whether T-DXd is clinically effective or cost-effective compared to SG in the HorR-negative subgroup is not adequately addressed by the exploratory cost-minimisation analysis provided by the company because it assumes clinical equivalence between T-DXd and SG.
Outcomes	• overall survival • progression free survival • response rate • duration of response • adverse effects of treatment • health-related quality of life.	As per scope	The outcomes match the NICE scope and the trial evidence included additional secondary outcomes: clinical benefit rate and time to response
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	As per scope	The economic analysis is in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
	differences in costs or outcomes between the technologies being compared. Costs will be considered from NHS and PSS perspective.		
Subgroups to be considered	None		HoR-negative subgroup is considered in the exploratory cost-minimisation analysis, but no subgroups are considered in the main cost-effectiveness analysis.
Special considerations including issues related to equity or equality	None		

Abbreviations: EAG - evidence assessment group; HER2 - Human epidermal growth factor receptor 2; HorR - hormone receptor; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; PSS - personal social services; TPC - treatment of physician's choice; UK - United Kingdom

4 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR) of clinical evidence for T-DXd for treating HER2-low or HER2-negative u/mBC after one or two lines of chemotherapy;
- Summary and results for the DESTINY-Breast04 trial

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details are presented in the Section B.2 of the CS and CS Appendix D.[1]

4.1 Critique of the methods of review(s)

The primary clinical evidence detailed in the CS comes from the DESTINY-Breast04 trial - an international phase III, multi-centre, open-label, randomised controlled trial (RCT) comparing T-DXd with TPC in adult patients with HER2-low u/mBC after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting (NCT03734029). Four published papers[14, 18-20] and conferences abstracts relating to this trial were identified by the SLR update 'hand search' (CS, Appendix D.1.1.2, Table 2).[1] The principal data reported in the CS were extracted from the main trial publications[14, 18] and the Clinical Study Reports (CSRs). DESTINY-Breast04 compared T-DXd with TPC, principally single-agent chemotherapies (see Section 3.3).

4.1.1 Searches

Appendix D of the CS reports an SLR of the efficacy and safety of T-DXd and relevant comparators for treating patients with HER2-low u/mBC. For the purposes of the literature searches the population was broadened out to HER2-negative u/mBC.

Searches were conducted in February 2022 and cover all the core databases required by NICE. The strategies appear to be well designed and logically structured, using free text and indexing terms (where available), though the EAG was unable to reproduce them exactly due to the platforms used (Embase.com and EBSCOhost). International trial registers and relevant conference proceedings were also searched for terms relating to the population of interest (clarification question A8).

The results of these February 2022 searches were updated with hand searches for more recent evidence specifically relating to the ASCENT and DESTINY-Breast04 studies (the latter of which was published after the original SLR). The EAG queried the focus on these two specific studies rather than the broader decision problem (clarification letter A3).

In its clarification response (A3), the company stated that they had subsequently completed a comprehensive SLR update of studies in the relevant population evidence up to 30th January 2023, for

which they provided further detail in the accompanying reference packs. In addition to DESTINY-Breast04 and ASCENT, this SLR update additionally identified the TROPiCS-02 study (in a non-relevant population).

Searches were limited to studies published since 2011. The EAG queried the reason for this and the company argued that this was due to HER2-low u/mBC being a new indication (clarification A4). The methodological filters used to identify eligible study types had been modified but were based on a reputable Cochrane source and checked by a librarian (clarification A6).

The original CS did not contain numbers of results retrieved by each line of the searches, meaning the reporting fell short of Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S) standards of transparency; this was corrected in the reports accompanying their clarification response. There were also some inconsistencies in the reporting of the number of publications identified by the hand searches, which the company resolved to the EAG's satisfaction in clarification responses A7 and A9. While the EAG recognises that STA timelines are sometimes beyond the company's control and that hand searches were a pragmatic interim solution, it would have been preferable to have received the full updated SLR at the time of the original CS.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the SLR are reported in Table 4 (modified from CS, Appendix, D.1.2, Table 4). However, HER2-low BC patients are a subset of the HER2-negative population, and so the literature searches were more sensitive, including terms to capture potential comparator data on the broader HER2-negative population. These criteria were consistent with the NICE scope (CS, Section B.1.1 Table 1)[1] with the exception of the potential comparators, which could have included anthracyclines, platinum-based therapies, vinorelbine and SG (CS, Section B.1.1 Table 1).[1] These therapies were absent from the TPC arm of the pivotal DESTINY-Breast04 trial.

The SLR criteria included the key effectiveness outcomes from the final NICE scope. These included: PFS, OS, response rate, duration of response, adverse effects of treatment and health-related quality of life (for patients and carers) (CS, Section B.1.1 Table 1).[1]

Table 4 Inclusion and exclusion criteria for the SLR (adapted from CS Appendix D.1.2, Table 4)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	**Primary:** Adult (age ≥18 years) patients with HER2-negative/ HorR-positive u/mBC **Secondary:** Adult (age ≥18 years) patients with triple-negative and/or metastatic BC, who have previously been treated in the metastatic setting or after disease recurrence within 6 months of (neo)adjuvant chemotherapy Studies assessing a mixed population shall be included if >80% of the study population is the target population, as described above	• Healthy volunteers • Patients with HER2-positive BC • Patients who are eligible for endocrine therapy (i.e., patients not previously treated with endocrine therapy) • Non-invasive or Stage 0, 1, and 2 BC • Patients with an ECOG PS score >1
Intervention and comparators	Any, except endocrine therapies	Endocrine therapies
Outcomes	• Progression Free Survival (PFS) • Overall survival (OS) • Duration of response (DoR) • Overall response rate (ORR) • Adverse events (AEs) of treatment • Health-related Quality of Life (HRQoL) • Complete response (CR) • Partial response (PR) • Disease control rate (DCR) • Time to response (TTR) • Time to progression (TTP) • Time on treatment (TOT)	Studies that do not report at least one of the outcomes of interest
Study design and publication type	• RCTs: both parallel-group and crossover (double-blind, single-blind, open-label) • Single-arm trials	• In vitro studies • Preclinical studies • Reviews, comments, letters, and editorials • Case reports, case series • Systematic reviews and meta-analyses of RCTs (flagged but excluded) • Real-world evidence studies • Retrospective/prospective cohort studies
Limits	English language, 2011 onwards	Non-English articles

Abbreviations: AE, adverse events; BC, breast cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; HorR-positive, hormone-receptor positive; RCTs, randomised controlled trials; SLR, systematic literature review; u/m, unresectable/metastatic.

4.1.3 Critique of study selection, data extraction and quality assessment

CS Appendix D.1.2 reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers, and any discrepancies were reconciled by discussion and consensus between the two reviewers.[1] The EAG considers independent study selection by two or more reviewers, as conducted here, to be best practice in systematic reviewing.

The results of the study selection process were detailed, as required, by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (CS Appendix D.1.2, Figure 1).[1] However, the PRISMA flowchart, as reported in the CS, did not include the results of the update 'hand search'. This was corrected by the company in response to a clarification request from the EAG, including data from the updated SLR up to the 30th January 2023 (Clarification response, A9).

Data extracted from the included clinical studies are presented in Sections B.2.3-2.7 and 2.10 of the CS.[1] Details of the data extraction process for the clinical effectiveness SLR were not provided in the CS; the EAG assumes the same process was conducted for the clinical effectiveness SLR as for the cost-effectiveness SLR (CS, Appendix G.1.4).[1] This process was undertaken by two reviewers, with a second reviewer checking the data extracted by the first reviewer. The EAG considers independent data extraction by two or more reviewers to be best practice in systematic reviewing.

CS section B.2.5[1] reports that the quality assessment process was undertaken independently by two reviewers, and any discrepancies were reconciled by discussion and consensus between these reviewers. The EAG considers independent risk of bias/quality assessment by two or more reviewers, with referral to a third, if necessary, to be best practice in systematic reviewing.

4.1.4 Results of the company's SLR

The clinical SLR presented in the CS identified one phase III trial of T-DXd that was relevant to the decision problem: DESTINY-Breast04 (clinicaltrials.gov: NCT03734029) – an international phase III, multi-centre, open-label, RCT comparing T-DXd with TPC in adult patients with HER2-low u/mBC after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. This study forms the key evidence within the CS for clinical effectiveness and safety of T-DXd within this indication. The CS reported inconsistent numbers of publications relating to the DESTINY-Breast04 trial; the company therefore responded to a clarification request from the EAG and confirmed that only four published items,[14, 18-20] plus the Clinical Study Report (CSR)[21], related to the trial (Clarification response, A7). Four items related to this trial were identified by the hand search update to the SLR (CS, Appendix D.2.2.1 and D.2.2.2) and no further publications were identified in the updated SLR to 30 January 2023: one principal publication[18] and three published conference abstracts,[14, 19, 20] one of which covered a range of specific subgroups[20] and one quality of life outcomes.[19] Additional relevant items are one protocol (clinicaltrials.gov: NCT03734029) and the CSR.[21] The principal data reported in the CS were extracted from the main trial publications and the CSR.

The EAG believes that no additional relevant published phase III trials of T-DXd in relevant patient groups have been omitted from the CS that could have provided data on safety and efficacy. However, the SLR also identified two publications and reports for the ASCENT trial (CS, Appendix D.1.2.1,

Table 5), which included a subgroup of HER2-low/HorR-negative patients (i.e., TNBC) (n=63), who receive SG as second or third-line therapy. The CS reported inconsistent numbers of publications relating to the ASCENT trial when combining results of the original search and the update 'hand search'; the company therefore responded to a clarification request from the EAG and confirmed that eleven published items related to the trial were identified (Clarification response, A11). Two items were identified by the original search[22, 23] and nine additional items related to this trial were identified by the hand search update to the SLR (CS, Appendix D.2.2.1 and D.2.2.2). No additional items relating to ASCENT were identified in the full SLR update to 30 January 2023 (Clarification response, A11).

The CS argued for omitting the ASCENT trial and evidence from the appraisal for two reasons: the number of potentially relevant patients in practice is likely to be small (approximately 10%); SG, while within the NICE decision problem scope, is not currently considered to be standard of care within its licensed indication and its uptake in UK clinical practice is uncertain (CS, section B.1.3.6 and 2.9).[1] Clinical advice to the EAG, however, suggested that SG would be used in clinical practice and so an indirect comparison of evidence for T-DXd and SG in the HER2-low/HorR-negative patient group would be helpful. The company presented a feasibility assessment to determine the value of such an analysis and concluded that the findings of any such analysis would be uncertain, principally due to population, inclusion criteria and study design differences between the ASCENT and DESTINY-Breast04 trials and the small number of potentially matched patients from the two trials (n=42 from DESTINY-Breast04 and n=63 from ASCENT) (CS section B.2.9).[1] Therefore, the EAG considers that the relative treatment efficacy of T-DXd versus SG in TNBC patients is uncertain.

As a result of the updated SLR search, the company also identified another RCT satisfying the inclusion criteria: TROPiCS-02, comparing SG with TPC.[24] The cited trial reference was published in 2020, so it is unclear how it was missed by the original searches, and identified by the update search (covering 25 February 2022 - 30 January 2023); however, this trial only evaluated SG in HER2-negative/HorR-positive u/mBC patients, not TNBC patients (the indication recommended by NICE), and so was correctly considered not to be relevant (Clarification response, A3).

4.2 Critique of the DESTINY-Breast04 trial of T-DXd

4.2.1 Study design: DESTINY-Breast04 trial

DESTINY-Breast04 is a phase III, randomised, international, multi-centre, open-label, RCT initiated in December 2018 and conducted in 161 centres across 19 countries, including seven centres in the UK (NCT03734029). DESTINY-Breast04 is a two-arm efficacy and safety trial of T-DXd compared with TPC in adult patients with unresectable or metastatic HER2-low breast cancer (u/mBC) after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. Details of study design, duration, settings and locations, inclusion and exclusion criteria, treatments,

permitted and prohibited concomitant medications and relevant outcomes are reported in Table 5. The primary completion date was January 2022, but the final completion date is listed as March 2023 (NCT03734029). Overall, 713 adult patients were enrolled and screened, and 557 patients who satisfied all eligibility criteria were randomised 2:1 (T-DXd: TPC). Randomisation was stratified by HER2 IHC status (IHC 1+ vs. IHC2+/ ISH-negative), number of prior lines of chemotherapy (1 vs. 2), and HorR/CDK status (HorR-positive with prior cyclin-dependent kinases [CDK] 4/6 inhibitor treatment vs. HorR-positive without prior CDK4/6 inhibitor treatment vs. HorR-negative).

Table 5 Summary of the trial design of DESTINY-Breast04 (adapted from CS, Section B.2.3.1, Table 9)

Trial design	A randomised, two-arm, phase III, open-label, multicentre study to compare the safety and efficacy of T-DXd vs. TPC in subjects with HER2-low, u/mBC.
	Randomisation: 2:1 by Interactive Web/Voice Response System (IXRS) **Stratification factors:** HER2 IHC status (IHC +1 vs. IHC +2/ISH-negative), prior lines of chemotherapy (1 vs. 2), and HorR/CDK status (HorR-positive with prior CDK4/6 inhibitor treatment vs. HorR-positive without prior CDK4/6 inhibitor treatment vs. HorR-negative). **Blinding:** [redacted]. The primary endpoint was based on BICR. [redacted].
Duration of study	Planned: approximately [redacted] months Median duration of follow-up at DCO (11 Jan 2022; FAS): • T-DXd: [redacted] months (range [redacted]). • TPC: [redacted] months (range: [redacted]). • Overall: [redacted] months (range [redacted]).
Settings and locations where data were collected	161 centres in 19 countries, including Europe (Austria, Belgium, France, Greece, Hungary, Israel, Italy, Portugal, Russia, Spain, Sweden, Switzerland, UK), Asia (China, Japan, South Korea, Taiwan), and North America (Canada, US)
Participant eligibility criteria	**Key inclusion criteria** • [redacted] • Pathologically documented BC that: o was unresectable or metastatic. o had a history of, or central laboratory assessed, low HER2 expression (defined as IHC1+ or IHC2+/ISH-negative). o was previously treated with at least one and no more than two prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within six months of (neo)adjuvant chemotherapy it would count as one line of chemotherapy. Targeted agents (e.g. CDK4/6 inhibitors, PD-L1 inhibitors) and ET did not count as a line of chemotherapy unless administered in combination with chemotherapy.

	o if HorR-positive, was previously treated with at least one line of ET before progressing and being deemed to no longer benefit from further ET. • [redacted] • [redacted]. • [redacted]. • [redacted].
	Key exclusion criteria • [redacted] • [redacted]. • History of (non-infectious) ILD/pneumonitis requiring steroids, current diagnosed or suspected ILD/pneumonitis, or [redacted]. • [redacted].‡ • [redacted]. • [redacted]. • [redacted].§ • [redacted]. • [redacted]. • [redacted]. • [redacted].
Trial drugs	**Intervention:** T-DXd (N=373) was administered at a starting dose of 5.4 mg/kg (based on patient weight at screening), as [redacted]. Dosage was weight value. **Comparator:** TPC (N=184) from 5 options: capecitabine, eribulin, gemcitabine, paclitaxel and nab-paclitaxel. • Capecitabine (N=37) was administered at a dose of [redacted]. • Eribulin (N=94) was administered at a dose of [redacted]. • Gemcitabine (N=19) was administered at a dose of [redacted].

	• Paclitaxel (N=15) was either administered at a dose of [redacted]. • Nab-paclitaxel (N=19) was either administered at a dose of [redacted].
	Dose modifications for T-DXd in the event of toxicity were to be made on the basis of AE type, severity, and relatedness to study drug, outlined in the T-DXd management guideline (**Appendix O[1]**) Dose modifications for TPC were made in accordance with the label approved in the country of drug administration or NCCN guidelines. **Dose interruption:** Both T-DXd and TPC could be delayed/interrupted for up to 28 days from the planned date of administration (49 days from the last infusion date). Patients were to discontinue in the event that their dosing was delayed or interrupted for longer than 28 days (49 days from last infusion date). **Dose reduction:** Two dose reduction levels in the event of toxicity were permitted for T-DXd (4.4 mg/kg and 3.2 mg/kg). Once a reduction was made due to toxicity, all subsequent cycles were at the lower dose level unless further dose reductions were required. Continued toxicity after two dose reductions resulted in discontinuation of T-DXd. For the TPC arm, dose adjustments were made in accordance with the local label or NCCN guidelines. **Study drug discontinuation:** Patients were to discontinue T-DXd or TPC for the following reasons: [redacted], but for which [redacted]), AEs requiring discontinuation (**Appendix M[1]**), or death.[††]
Concomitant medication	**Permitted concomitant medication:** Prophylactic treatment of [redacted] was per [redacted] and [redacted]. [redacted] could be used for [redacted] based on [redacted] (except within [redacted]) Based on currently available clinical safety data, [redacted] were recommended [redacted] to T-DXd infusions Concomitant use of dietary supplements, [redacted], and [redacted] were discouraged but not prohibited **Prohibited concomitant medication:** Other anti-cancer therapy, [redacted] (concurrent use of [redacted] or any [redacted] or [redacted],[‡‡] or (for the TPC arm) any products prohibited by the relevant local label.
[redacted]	[redacted]

Other outcomes used in the model/specified in scope	• PFS by BICR in the FAS • OS in the FAS • Safety (AEs) • QoL assessed by EQ-5D • ORR by BICR
Other outcomes of interest	• OS in the HorR-positive cohort • [redacted] in the HorR-positive cohort and the FAS • Confirmed ORR by BICR and IA in the HorR-positive cohort and FAS • DoR by BICR in the HorR-positive cohort and FAS • TTR in by BICR in the HorR-positive cohort and FAS • CBR by BICR in the HorR-positive cohort • DCR by BICR in the HorR-positive cohort • PFS, OS, confirmed ORR and DoR in the HorR-negative subgroup • [redacted] in the HorR-positive cohort • HRQoL assessed by EORTC QLQ-C30 in HorR-positive cohort • HRQoL assessed by EORTC QLQ-BR45 in HorR-positive cohort • [redacted] in the HorR-positive cohort and FAS
Pre-planned subgroups	Subgroup analyses for PFS based on BICR were performed for the HorR-positive cohort and the FAS. Subgroup analyses of OS were performed for the HorR-positive cohort and FAS using the same subgroups defined for the PFS analysis and using the same methodology, provided PFS and OS analyses are significant for both the HorR-positive cohort and FAS. Subgroup analyses were only performed for a category of subgroup if at least 10 events were observed in both treatment arms. Pre-specified subgroups were: HER2 status; HorR-status; lines of prior chemotherapy; prior CDK4/6 inhibitor; lines of prior ET; best response to last prior anti-cancer systemic therapy; baseline renal function; baseline hepatic function; baseline visceral disease; baseline CNS metastases; history of CNS metastases; age; race; region; ECOG performance status.

** Refers to eribulin mesylate (1.23 mg eribulin base = 1.4 mg eribulin mesylate).*

‡Patients with brain metastases that were [redacted].

§[redacted].

****[redacted].

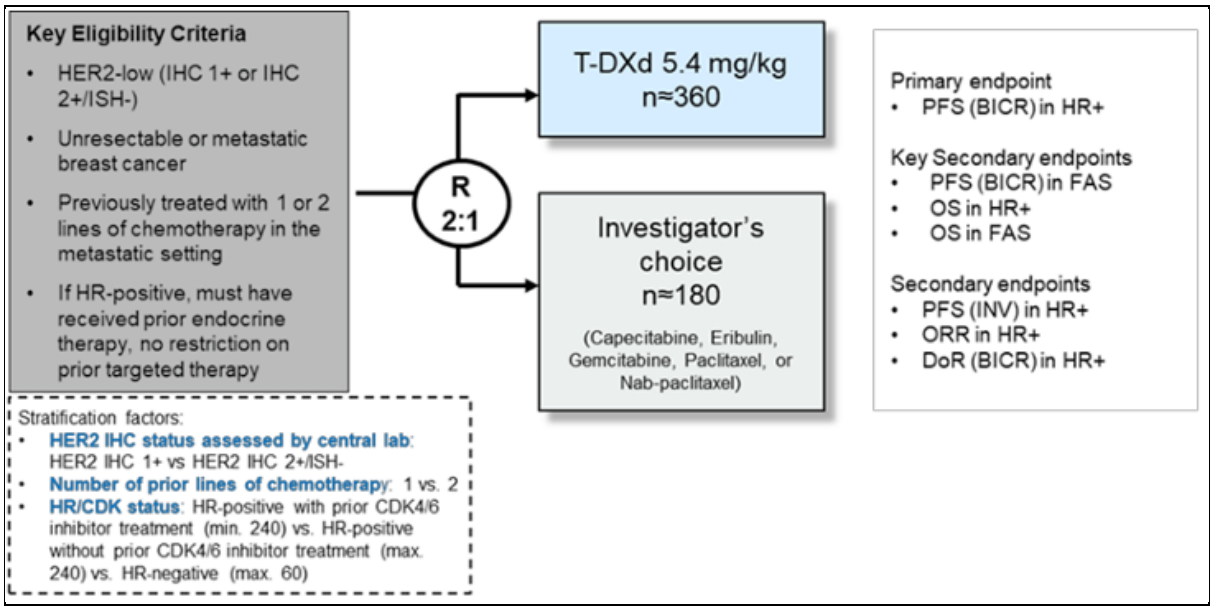
††Additional reasons not listed above are: [redacted].

‡‡[redacted].

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclic-dependent kinase; CNS, central nervous system; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HorR-positive, hormone receptor-positive; HRQoL, health-related quality-of-life; IA, investigator assessment; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTR, time to response; u/mBC, unresectable or metastatic breast cancer.

The patient cohorts assessed in the clinical effectiveness review are presented in Figure 5 **Error! Reference source not found.**and a full summary of the DESTINY-Breast04 trial methodology is provided in Table 5.

Figure 5 Overview of the DESTINY-Breast04 trial design (reproduced from CS, Section B.2.3.1, Figure 9[1])



Abbreviations: BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4 and 6; DoR, duration of response; FAS, Full Analysis Set; HER2, human epidermal growth factor receptor 2; HorR-positive, hormone receptor-positive; IHC, immunohistochemistry; INV, investigator assessment; ISH, in situ hybridisation; max, maximum; min., minimum; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; T-DXd, trastuzumab deruxtecan; vs., versus.

T-DXd was administered intravenously (IV) every 3 weeks at a dose of 5.4 mg/kg of body weight. All TPC agents were administered in accordance with the local label or the National Comprehensive Cancer Network guidelines. The TPC arm consisted of treatment with capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel. The CS reports that these therapies were chosen based on the five most commonly used single-agent chemotherapy regimens across the US, France, Germany, Italy, Spain, UK, and Japan (CS, section B.2.3.1). The EAG noted that the following therapies listed in the NICE scope were absent from the control arm treatments: anthracyclines, platinum-based therapies, vinorelbine, and SG for TNBC patients (CS, Section B.1.1 Table 1).[1] The EAG notes that TNBC patients constitute 11.3% (63/557) of the population in the DESTINY-Breast04 trial (CS, section B.2.4.4, Table 15).[1] The CS reports that this proportion of TNBC patients is consistent with published figures for eligible HER2-low UK patients (10.4%) (CS, section B.2.5.1).

The CS reported that the following proportions of patients received each of the comparator chemotherapies: eribulin (94/184, 51.1%, patients in the Full Analysis Set [FAS]); capecitabine (37/184, 20.1%), nab-paclitaxel (19/184, 10.3%), gemcitabine (19/184, 10.3%) and paclitaxel (15/184, 8.2%) (CS, section B.2.4.3, Table 14).[1] The EAG notes that eribulin – the most commonly used comparator treatment in the control arm

– is only used as third line therapy in England and Wales[8], while the indication under consideration is second and third lines. Clinical advice received by the EAG suggested that nab-paclitaxel is generally not used for this indication in England and Wales as it's restricted by funding requirements to a minority experiencing hypersensitivity reactions to other taxanes, and that gemcitabine is given principally in combination with carboplatin.

4.2.2 Quality assessment of DESTINY-Breast04 trial

The CS performed a quality assessment of DESTINY-Breast04 using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations in the NICE user guide). The findings were reported in the CS (section B.2.5, Table 16)[1], but are reproduced in Table 6 together with EAG judgements.

The EAG agrees with the company's responses to the majority of the checklist's criteria: randomisation was conducted appropriately; treatment allocation concealment was not possible due to the open-label design of the trial; blinding of care providers, participants and outcome assessors was largely absent; the two groups were similar at baseline for prognostic factors; there is no evidence of selective outcome reporting; and an appropriate intention-to-treat analysis was used. The EAG assessed as 'unclear' the question of imbalances in drop-outs between groups, in contrast to the company's assessment that there was no such imbalance. The CS reports that the drop-out rate in the TPC control arm was 6.5% compared with 0.5% in the T-DXd arm due to withdrawal of consent. This does represent an imbalance, but the EAG accepts that this disparity is unlikely to affect outcomes.

Table 6 Quality assessment of the DESTINY-Breast04 RCT (adapted from CS section B.2.5, Table 16)

Questions	CS and EAG assessments
Was randomisation carried out appropriately?	**CS:** Yes: Patients were randomised 2:1 by an IXRS and stratified by HER2 IHC status (HER2 IHC 1+ vs. HER2 IHC 2+/ISH-negative), number of prior lines of chemotherapy (1 vs. 2) and HorR and CDK status (HorR-positive with prior CDK4/6 inhibitor treatment vs. HorR-positive without prior CDK4/6 inhibitor treatment vs. HorR-negative). **EAG**: Agree
Was the concealment of treatment allocation adequate?	**CS:** Not applicable: DESTINY-Breast04 is an open-label study. To minimise any risk of bias, the sponsor was blinded to aggregate data by treatment arm, although the study participant and investigator would be aware of the study drug administered. It was not feasible to blind treatment allocations for individual subjects because of different routes of administration and different treatment schedules between T-DXd and TPC. The study team did not perform or have access to efficacy analysis/summary during the study. An independent biostatistician generated the randomisation schedule per the randomisation specification. Methods of concealment to study arms (i.e., via IXRS) are summarised in the row above. **EAG**: Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms. **EAG**: Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No:** Open-label study design. As stated in the CSR, it was not feasible to blind treatment allocations for individual patients because of different routes of administration and different treatment schedules between T-DXd and TPC. Outcome assessors for key endpoints – including the primary endpoint (PFS by BICR in the HorR-positive cohort) and a key secondary endpoint (PFS by BICR in the FAS) – were blinded to treatment allocation. The study team did not perform or have access to efficacy analysis/summary during the study. An independent biostatistician generated the randomisation schedule per the randomisation specification. **EAG**: Agree – blinding of PFS outcome assessment only.
Were there any unexpected imbalances in drop-outs between groups?	**No:** Dropout rates from randomisation to first dose were lower in the T-DXd arm versus TPC arm (2 [0.5%] vs. 12 [6.5%]; FAS). The majority of drop-outs were due to withdrawal of consent after randomisation. **EAG**: Unclear. Other than the statement of 'withdrawal of consent', the reasons for the withdrawals are not reported, and details of those patients, relative to the remaining trial population, are also not reported. These withdrawals do also represent an imbalance. However, the overall numbers are small and unlikely to affect outcomes.
Is there any evidence to suggest that the authors measured	**No:** There is no evidence to suggest that the authors measured more outcomes than they reported.

Questions	CS and EAG assessments
more outcomes than they reported?	**EAG**: Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analyses were performed using the FAS and HorR-positive cohort. Following the intention-to-treat principle, subjects were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: In general, missing or dropout data were treated as missing, and were not imputed for the purpose of data analysis, unless otherwise specified in the SAP. **EAG**: Agree

Abbreviations: AE, adverse event; BICR, blinded independent central review; CDK, cyclic-dependent kinase; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HorR-positive, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; IXRS, interactive voice and web response system; PFS, progression-free survival; RCT, randomised controlled trial; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; SAP, statistical analysis plan.

The EAG also conducted a quality assessment using the Cochrane Risk of Bias tool (version 2)[25], which is the international standard for quality assessment of RCTs. This assessment is presented in Table 7. The risk of bias arising from the randomisation process, deviations from the interventions, or due to missing data or selective reporting, was judged to be 'Low'. The risk of outcome assessment bias was judged to be 'Having some concerns' due to the unblinded assessment of some outcomes. Overall, on account of the judgement of some concerns only in the domain of outcome assessment, and only for some outcomes, the EAG judges the level of risk of bias affecting the DESTINY-Breast04 trial to be 'Low'. The CS did not offer an overall judgement on the risk of bias in the DESTINY-Breast04 trial (CS, section B.2.5 and Appendix D.1.3, as shown in Table 7 in this report).[1]

Table 7 Cochrane Risk of bias v.2.0: DESTINY-Breast04

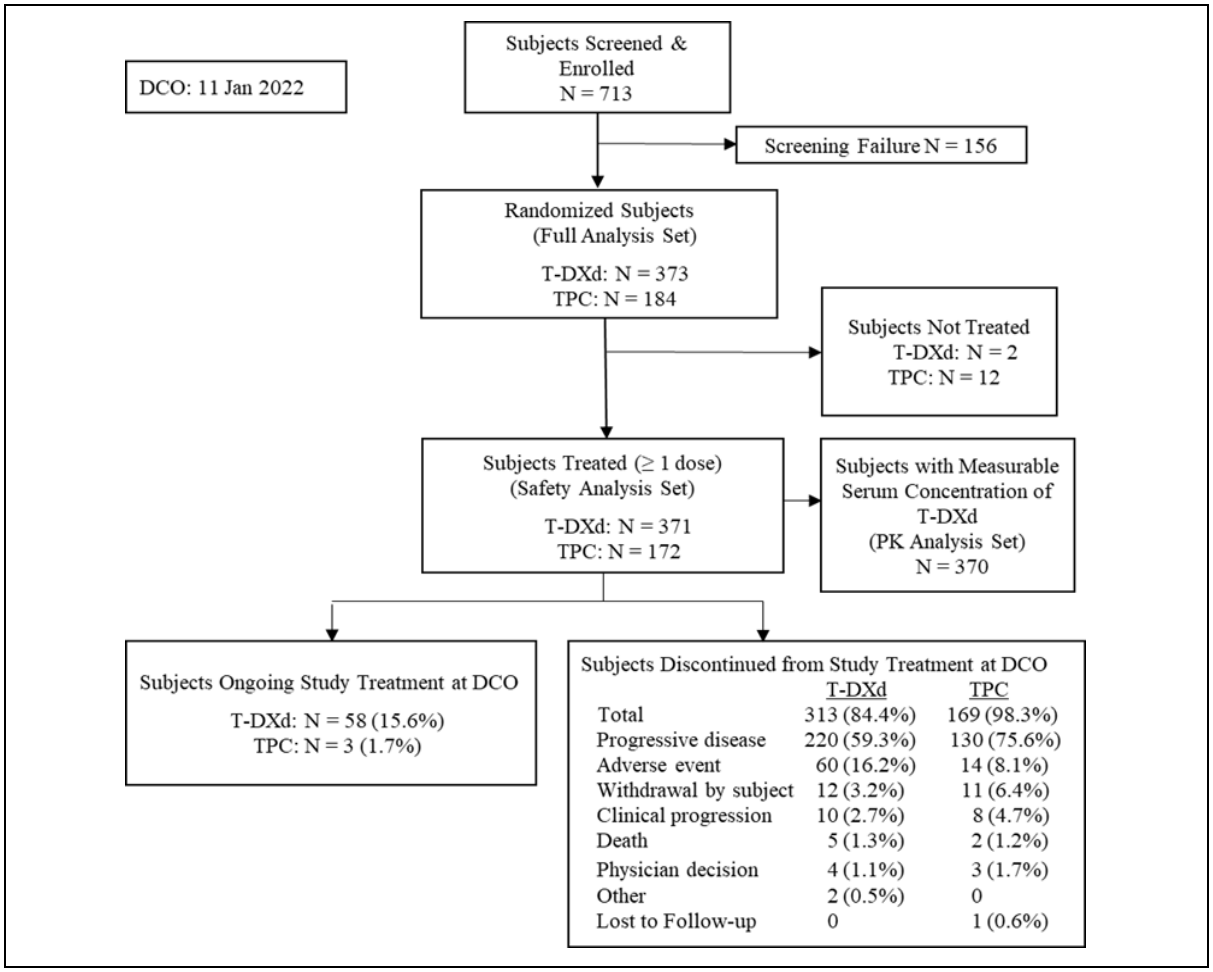
	Bias arising from the randomisation process: sequence generation, allocation concealment, balance between groups)	Bias due to deviations from intended intervention (deviations with likely effect on outcomes)	Bias due to missing data (attrition)	Bias due to measurement of outcome (blinding of assessors, potential for differences between groups)	Bias in selection of reported results (prespecified outcomes, potentially different measures)	Overall risk of bias
Assessment	**Low**	**Low**	**Low**	**Some concerns**	**Low**	**Low**
Details	*'Randomization will be managed through an Interactive Web/Voice Response System (IXRS) for subjects meeting all eligibility criteria… It is not feasible to blind treatment allocations for individual subjects because of different routes of administration, different treatment schedules, and different AE profiles between DS-8201a and physician's choice therapy…An independent biostatistician, not otherwise part of the sponsor study team, will generate the randomization schedule'* (protocol supplement[18]) An open-label trial, but randomisation was adequate and arms were balanced at baseline for most known prognostic factors, although some known factors, such as tumour grade and circulating tumour cell (CTC) count were not reported.[26]	Pre-randomisation: [redacted] (T-DXd, [redacted]; TPC; [redacted]) were randomised but not treated, with a majority withdrawing consent There were no deviations from the intended interventions	Number of post-randomisation withdrawals was relatively small (T-DXd 3.2% vs TPC 6.4%), and ITT analyses were conducted	*'Progression-free survival and response to treatment were assessed by means of blinded independent central review. The primary end point was progression-free survival among patients with hormone receptor–positive disease. Key secondary end points were progression-free survival among all patients and overall survival in the hormone receptor–positive cohort and among all patients. Secondary and other end points included investigator-assessed progression-free survival, confirmed objective response, duration of response, and efficacy in the hormone receptor–negative cohort'*[18] Almost all outcomes except PFS were assessed unblinded. This included some possible patient-reported outcomes for safety, e.g., pain, nausea, fatigue as well as HRQoL	The protocol published as a supplement with the principal manuscript reported all pre-specified outcomes. It should be noted that the clinicaltrials.gov published protocol only reported the primary outcome PFS by BICR, and the secondary outcomes of PFS by Investigator assessment, OS, ORR, and DoR	As a result of the assessment of 'Some concerns' in only one domain, and low risk of bias in the other domains

BICR – Blinded independent central review; CSR – Clinical Study Report; ITT – intention-to-treat; PFS – progression free survival; ORR - Overall Response rate; OS - Overall survival

4.2.3 Participant flow and analysis populations

In total, 557 patients were randomised 2:1 to receive T-DXd and TPC, respectively. Of the patients randomised, [redacted] (T-DXd, [redacted]; TPC, [redacted]) received at least one dose of study drug; [redacted] (T-DXd, [redacted]; TPC; [redacted]) were randomised but not treated, withdrawing consent after randomisation. The company responded to an EAG request for clarification of the reasons for these withdrawals, given the resulting imbalance between arms; the company responded that these details were not available and stated that such withdrawals were not uncommon in open-label trials (Clarification response, A14). The data cut-off (DCO) for the primary analyses was 11 January 2022. A full CONSORT diagram of participant flow in the DESTINY-Breast04 trial is presented in Figure 6.

Figure 6 Participant flow in the DESTINY-Breast04 trial (reproduced from CS, section B.2.4.3, Figure 10[1])



Abbreviations: DCO, data cut-off; PK, pharmacokinetic; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The patient data sets analysed in DESTINY-Breast04 are described in Table 8**.** The FAS consisted of all randomised patients (including untreated patients); the primary analysis set consisted of all randomised patients (including untreated patients) who were diagnosed as HER2-low/HorR-positive;

and the safety analysis set (SAS) consisted of all patients who received at least one dose of a study treatment. The EAG noted that the primary analysis set excluded HER2-low/HorR-negative patients, although secondary efficacy analyses were conducted on the FAS population and exploratory analyses in the HER2-low/HorR-negative subgroup (CS, Appendix N). The CS did not explain why HER2-low/HorR-negative patients were excluded from the primary outcome analysis, and only stated that this group represented approximately 10% of eligible patients (CS, sections B.1.3.6.3.1 and B.2.9), despite these proportions being consistent with the likely make-up of HER2-low patients in UK practice, as reported in the CS (CS, section B.2.5.1).[1] The company responded to an EAG request for clarification of this rationale by stating that [redacted] (Clarification response, A13).

Details of a pharmacokinetic analysis set and a per-protocol analysis set, which included HorR-positive patients who complied sufficiently with the protocol with respect to study drug exposure, tumour assessment, and absence of major protocol violations, were not considered to be relevant to this submission and are not presented here (CS, section B.2.4.1).[1]

Table 8 Analysis sets for the DESTINY-Breast04 trial (reproduced from CS, section B.2.4.1, Table 11[1]).

Analysis set	Definition	Number of patients, n (%)		
		T-DXd	TPC	Total
Full analysis set (FAS)	Included all patients randomised into the study. Following the intention-to-treat principle, patients were analysed [redacted]	373 (100.0)	184 (100.0)	557 (100.0)
Primary analysis set: HorR-positive cohort	Included all patients randomised into the study who were HorR-positive. This is the primary analysis set for the efficacy analyses, following the intention-to-treat principle	331 (88.7)	163 (88.6)	494 (88.7)
Safety analysis set (SAS)	Included all randomised patients who received [redacted] of study treatment (either T-DXd or TPC). [redacted]	371 (99.5)	172 (93.5)	543 (97.5)

Abbreviations: BICR, blinded independent central review; CDK, cyclic-dependent kinase; FAS, full analysis set; HER2; human epidermal growth factor receptor 2; HorR-positive, hormone receptor-positive; PK, pharmacokinetic; PPS, per-protocol analysis set; SAS, safety analysis set; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The CS reported that, for the primary efficacy analysis for PFS (DCO, 11 January 2022) the median follow-up in the FAS for T-DXd and TPC was [redacted] and [redacted] months, respectively (CS, section B.2.4.3). At the DCO in the FAS, [redacted] ([redacted]) patients in the T-DXd arm and [redacted] ([redacted]) patients in the TPC arm were ongoing treatment; [redacted] ([redacted]) T-DXd and [redacted] ([redacted]) TPC patients discontinued due to progressive disease; [redacted] ([redacted]) T-DXd and [redacted] ([redacted]) TPC patients discontinued due to clinical progression; [redacted] ([redacted]) T-DXd and [redacted] ([redacted]) TPC patients discontinued due to AEs; and for [redacted] ([redacted]) T-DXd and [redacted] ([redacted]) TPC patients, the reason for discontinuation was death. All percentages reported here are based on the SAS (Figure 2).

4.2.4 Baseline characteristics in DESTINY-Breast04

Participant baseline characteristics in DESTINY-Breast04 are presented in Table 9 (and CS, section B.2.4.4).[1] The mean age in the FAS was 56.5 years in both trial arms. Clinical advice to the EAG stated that the trial population was slightly younger than the patients seen in practice. This difference from clinical practice generally was also reported in the principal trial publication.[18] The mean number of prior systemic therapies in the metastatic setting was [redacted] in the T-DXd arm and [redacted] in the TPC arm of the FAS population. The stratification factors were: HER2 IHC status; HorR/CDK status; and lines of prior chemotherapy in the metastatic setting. The reported characteristics of patients were well balanced between groups, including for stratification factors and other known prognostic factors such as the number and sites of metastases, number of prior lines of systemic therapy in the metastatic setting, and

ECOG PS, although some prognostic factors, such as tumour grade and circulating tumour cell count were not reported.[26] The EAG noted that the DESTINY-Breast04 trial excluded patients with ECOG PS 2. Clinical advice to the EAG stated that a proportion of patients in UK practice would be ECOG PS 2, and therefore this group would lack efficacy and safety data for T-DXd for this indication. Recent real-word evidence studies in cohorts of adult patients with HER2-negative/HorR-positive mBC reported 10-12% of patients with ECOG PS 2.[27, 28] The EAG requested clarification of the reasons for excluding patients with ECOG PS 2; the company responded that it was common for trials in HER2 BC and similar populations to exclude ECOG PS 2 patients, including recent trials in u/mBC for therapies that were recommended by NICE (Clarification response, A15). In summary, the T-DXd and TPC groups were well balanced at baseline and were generally likely to reflect the patients for this indication in clinical practice in the UK, with the exception of patients being older in practice and a proportion being ECOG PS 2.

Table 9 Characteristics of participants in DESTINY-Breast04 at baseline (reproduced from CS, B.2.4.4, Table 15[1])

Characteristic	HorR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Age, years				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	56.8 (31.5–80.2)	55.7 (28.4–80.0)	57.5 (31.5– 80.2)	55.9 (28.4–80.5)
Female, %	99.4	100.0	99.5	100.0
Region, n (%)				
Europe	149 (45.0)	73 (44.8)	166 (44.5)	85 (46.2)
Asia	128 (38.7)	60 (36.8)	147 (39.4)	66 (35.9)
North America	54 (16.3)	30 (18.4)	60 (16.1)	33 (17.9)
Race, n (%)				
Asian	131 (39.6)	66 (40.5)	151 (40.5)	72 (39.1)
White	156 (47.1)	78 (47.9)	176 (47.2)	91 (49.5)
Black or African American	7 (2.1)	2 (1.2)	7 (1.9)	3 (1.6)
Other	37 (11.2)	16 (9.8)	39 (10.5)	17 (9.2)
Missing data	0	1 (0.6)	0	1 (0.5)
Weight, kg				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)				
Never	[redacted]	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]	[redacted]
Current	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Stratification factor: HER2 IHC status per IXRS, n (%)				
1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)

Characteristic	HorR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
2+/ISH-negative	138 (41.7)	68 (42.4)	158 (42.4)	78 (42.4)
ECOG PS, n (%)				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
Hormone receptor status (derived based on factors captured in electronic data capture), n (%)*				
Positive	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Negative	3 (0.9)	1 (0.6)	40 (10.7)	18 (9.8)
Stratification factor: HorR/CDK status per IXRS, n (%)				
HorR-positive with prior CDK4/6	[redacted]	[redacted]	[redacted]	[redacted]
HorR-positive without prior CDK4/6	[redacted]	[redacted]	[redacted]	[redacted]
HorR-negative	[redacted]	[redacted]	[redacted]	[redacted]
Stable brain metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Stable brain metastases defined as a reported history of CNS metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of baseline lung metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of baseline liver metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline visceral disease, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of systemic therapy in any setting, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of systemic therapy in the metastatic setting, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Type of prior systemic cancer therapy, n (%)				
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Chemotherapy	331 (100.0)	162 (99.4)	373 (100.0)	183 (99.5)
Supportive Therapy	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior endocrine therapy, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior endocrine therapy in metastatic setting, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	HorR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior chemotherapy, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Stratification factor: Lines of prior chemotherapy in metastatic setting per IXRS†, n (%)				
0**	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3**	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

*[redacted]

***Represents a protocol deviation; [redacted]*

†If recurrence occurred ≤6 months of (neo)adjuvant chemotherapy, (neo)adjuvant chemotherapy was counted as one line of chemotherapy.

Abbreviations: BMI, body mass index; CDK, cyclic-dependent kinase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HorR-positive, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; ITT, intent-to-treat; IXRS, interactive web/voice response system; PS, performance status; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

4.2.5 Study endpoints in DESTINY-Breast04

T-DXd was to be administered every [redacted] unless study drug interruption/modification or discontinuation was required. For the TPC arm, if a patient received a regimen other than a [redacted], the investigator was to ensure that the subject followed the [redacted]. The study endpoints with definitions are presented in Table 10. These were principally: PFS by blinded and investigator assessment in the HorR-positive cohort and the FAS; and OS and response in the HorR-positive cohort and the FAS. Timing of the assessments were described in the CS (section B.2.3.1)[1] and the CSR.[21] Tumour assessments ([redacted] had to be performed every [redacted] from randomisation date, and [redacted]. Survival follow-up was assessed at [redacted] follow-up timepoints. AEs were recorded [redacted]. Follow-up assessments took place at [redacted] after administration of the last study treatment or before starting new anti-cancer treatment, [redacted]. In long-term follow-up, assessments took place every [redacted]

[redacted], until [redacted]. HRQoL questionnaires, [redacted], were to be completed/assessed [redacted] before any other assessments or procedures. Questionnaires for HRQoL outcomes were to be completed at [redacted], which was the last data collection timepoint for all questionnaires.

In addition to the endpoints listed in Table 10, the CS also reported on exploratory endpoints in the FAS and HorR-positive cohort: Time to response; best percentage change in diameters of measurable tumours; clinical benefit rate; PFS on the next line of therapy; and disease control rate. PFS, OS, ORR and DoR were also reported for the HorR-negative cohort (CS, Appendix N).[1]

Table 10 Study endpoints in DESTINY-Breast04 (adapted from CS, B.2.3.1, Table 10[1])

Endpoint/assessment	Details	Censoring rules
Primary endpoint		
PFS (by BICR) in the HorR-positive cohort	Defined as the time from the date of [redacted] disease progression per BICR [redacted]	• No baseline evaluable tumour assessment: [redacted] • No post-baseline tumour assessment: [redacted] • Early death (within 14 weeks of randomisation) for no baseline or no post-baseline tumour assessment: [redacted] • Radiographic disease progression/death without missing ≥2 consecutive tumour assessments immediately preceding event: [redacted] • Disease progression or death after missing ≥2 consecutive scheduled tumour assessments: [redacted] • At least one post-baseline response assessment and no death or objective documentation of radiographic disease progression: [redacted] • Started anti-cancer therapy prior to disease progression, death, or analysis cut-off date: [redacted]
Key secondary endpoint		
OS in the FAS	Defined as the time from the [redacted] to the date of death for any cause. If no death was reported for a patient before the data cut-off for OS analysis, OS was [redacted]	[redacted]

Endpoint/assessment	Details	Censoring rules
		[redacted]
PFS (by BICR) in the FAS	As per PFS (by BICR) in the HorR-positive cohort	As per PFS (by BICR) in the HorR-positive cohort
OS in the HorR-positive population	As per OS in the FAS	As per OS in the FAS
Secondary endpoints		
ORR (by BICR) in the FAS and HorR-positive cohort	Defined as the proportion of patients who achieved a best overall response of CR or PR, based on BICR. Confirmation of CR or PR was required. Response definitions: • CR: disappearance of all target lesions • PR: ≥30% decrease in the sum of diameters of target lesions from baseline • PD: ≥20% increase in sum of diameters of target lesions, taking the smallest sum of diameters since study, or appearance of a new lesion • SD: response not fitting the criteria for PR or PD	Not applicable
Duration of response (by BICR) in the FAS and HorR-positive cohort	Defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression based on BICR or investigator's assessment or to the date of death due to any cause. Duration of response was to be measured for only patients with a response of CR or PR. Subjects who were progression-free at the time of the analyses	Censoring rules were the same as described above for PFS by BICR

Endpoint/assessment	Details	Censoring rules
	were to be censored at the date of the last evaluable tumour assessment	
PFS by investigator assessment in the FAS	Defined as the time [redacted] disease progression per investigator assessment [redacted]	As per PFS by BICR in the HorR-positive cohort
QoL endpoints (related to TTDD) in the FAS and HorR-positive cohort	Endpoints included EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L	If no baseline evaluable QoL and/or no post-baseline QoL assessment: • Death by first survival follow-up (3 months from 40-day visit): [redacted] • No death: [redacted] If baseline and at least one post-baseline QoL assessment: • [redacted] • [redacted] • Death by first survival follow-up (3 months from 40-day visit): [redacted] • Others: [redacted]
Resource use/ hospitalisation endpoints in the FAS and HorR-positive cohort	Hospitalisation-related endpoints, including: • Reasons for hospitalisation • Discharge status • Length of hospital and/or ICU stay • Time to first hospitalisation, defined as the time from the date of randomisation to the date of the first hospitalisation during the study treatment (from date of first dose to 47 days after last dose)	Not applicable

Endpoint/assessment	Details	Censoring rules
Safety endpoints		
Assessment of AEs and SAEs	Safety endpoints included SAEs, TEAEs, AEs of special interest, TEAEs associated with dose reduction and/or study drug interruption, TEAEs associated with discontinuation of study treatment, TEAEs associated with an outcome of death, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings. All AEs were categorised using the MedDRA. AEs and abnormal laboratory test results, if applicable, were graded using NCI CTCAE Version 5.0	NA

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Echo, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report from; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HorR-positive, hormone receptor-positive; IA, investigator assessment; ICU, intensive care unit; MedDRA, Medical Dictionary for Regulatory Activities; mRECIST, modified Response Evaluation Criteria in Solid Tumours; MUGA, multigated acquisition scan; NA, not applicable; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QLQ-BR45, Quality-of-life Breast Cancer questionnaire; QLQ-C30, Quality-of-life of Cancer Patients questionnaire; SAP, Statistical Analysis Plan; SD, stable disease; TEAE, treatment-emergent adverse event; TTDD, time to definitive deterioration

4.3 Clinical effectiveness of T-DXd (DESTINY-Breast04 study)

Efficacy endpoints were presented and described for DESTINY-Breast-04 (DCO 11 January 2022) in CS section B.2.6.1.[1]

4.3.1 Primary efficacy outcome in DESTINY-Breast04: PFS by BICR

For the primary analysis, the CS presented data with a median follow-up of [redacted] months (range: [redacted]) in the T-DXd arm (n=373), [redacted] months (range: [redacted]) in the TPC arm (n=184). In terms of the primary outcome, PFS by blinded independent central review (BICR) for the HorR-positive cohort only, the median PFS by BICR was 10.1 months (95% Confidence Interval [CI]: 9.5, 11.5) in the T-DXd arm compared with 5.4 months (95% CI: 4.4, 7.1) in the TPC arm (Table 11). T-DXd also significantly reduced the probability of disease progression compared with TPC by 49%: HR 0.51 (95% CI: 0.40-0.64, p<0.001) (Table 11 and Figure 7). Death was the recorded PFS event in [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the TPC arm (Table 11). The specific reasons for some of the PFS recorded deaths ([redacted]) were not reported in the CS or CSR and are therefore unclear. The EAG requested clarification of the reasons for these deaths; the company responded that [redacted] however, the details of these [redacted] were not provided (Clarification response, A16).

Table 11 PFS by BICR in the HorR-positive cohort from DESTINY-Breast04 (adapted from CS, section 2.6.1, Table 17[1])

	T-DXd (N=331)	TPC (N=163)
Subjects with events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects without events (censored), n (%)	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Other reason*	[redacted]	[redacted]
Median PFS, months†	10.1	5.4
(95% CI)†	(9.5, 11.5)	(4.4, 7.1)
Stratified Cox hazard ratio‡	0.5085	
(95% CI)§	(0.4012, 0.6444)	
Stratified log-rank p-value	<0.001[a]	
Proportion alive and progression-free at landmark (%)§		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

**Censoring reasons included:* [redacted]

[a] *It should be noted that CS, section B.2.6.1, Table 17[1] and CSR Table 8.1[21] reports this value as p<0.0001, but the CS text[1] and the publication[18] report the figure p<0.001.*

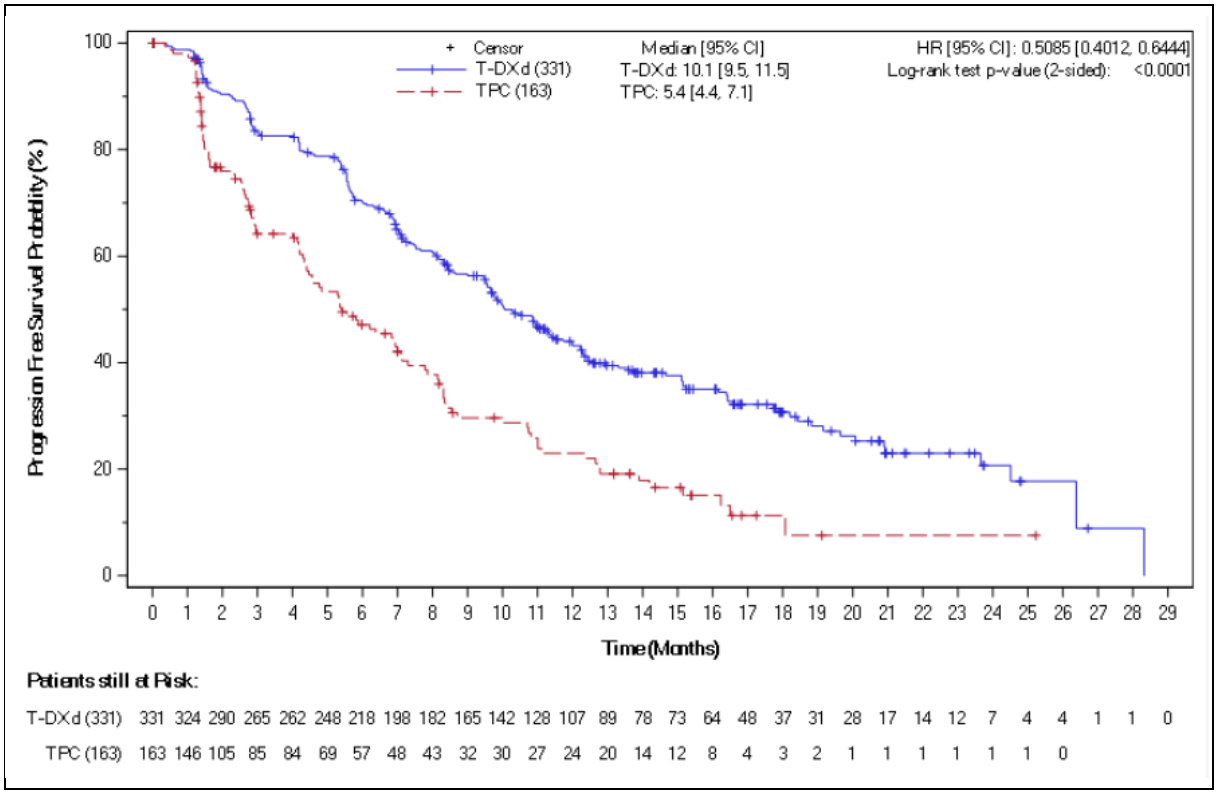
†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method.

‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HorR/CDK status, as defined by the IXRS.

§Estimate and CI for PFS rate at the specified time point are from the KM analysis.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HorR-positive, hormone receptor-positive; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 7 Kaplan-Meier of PFS by BICR in the HorR-positive cohort from DESTINY-Breast04 (reproduced from CS, section 2.6.1, Figure 11)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; HorR-positive, hormone receptor-positive; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC; treatment of physician's choice.

4.3.2 *Key secondary efficacy outcomes*

The key secondary outcomes were PFS by BICR for the FAS and OS, both for the HorR-positive cohort only and for the FAS. The full results for these outcomes were reported in the CS (section B.2.6.1.2).[1] For the secondary analyses, principally in the FAS, the CS presented data with a median follow-up of [redacted] months (range: [redacted]) in total (n=557) (CS, section B.2.6.1).[1]

PFS in the FAS

In terms of the secondary outcome, median PFS by BICR for the FAS was 9.9 months (95% CI: 9.0, 11.3) in the T-DXd arm compared with 5.1 months (95% CI: 4.2, 6.8) in the TPC arm (Table 12). T-DXd also significantly reduced the probability of disease progression compared with TPC by 50%: HR 0.50 (95% CI: 0.40-0.63, p<0.001) (Table 12 and Figure 8). These results were consistent with the findings for the HorR-positive only cohort.

Table 12 PFS by BICR in the FAS from DESTINY-Breast04 (adapted from CS, section 2.6.1, Table 18[1])

	T-DXd (N=373)	TPC (N=184)
Subjects with events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects without events (censored), n (%)	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Other reason*	[redacted]	[redacted]
Median PFS, months†	9.9	5.1
(95% CI)†	(9.0, 11.3)	(4.2, 6.8)
Stratified Cox hazard ratio‡	0.5014	
(95% CI)§	(0.4013, 0.6265)	
Stratified log-rank p-value	<0.001[a]	
Proportion alive and progression-free at landmark (%)§		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

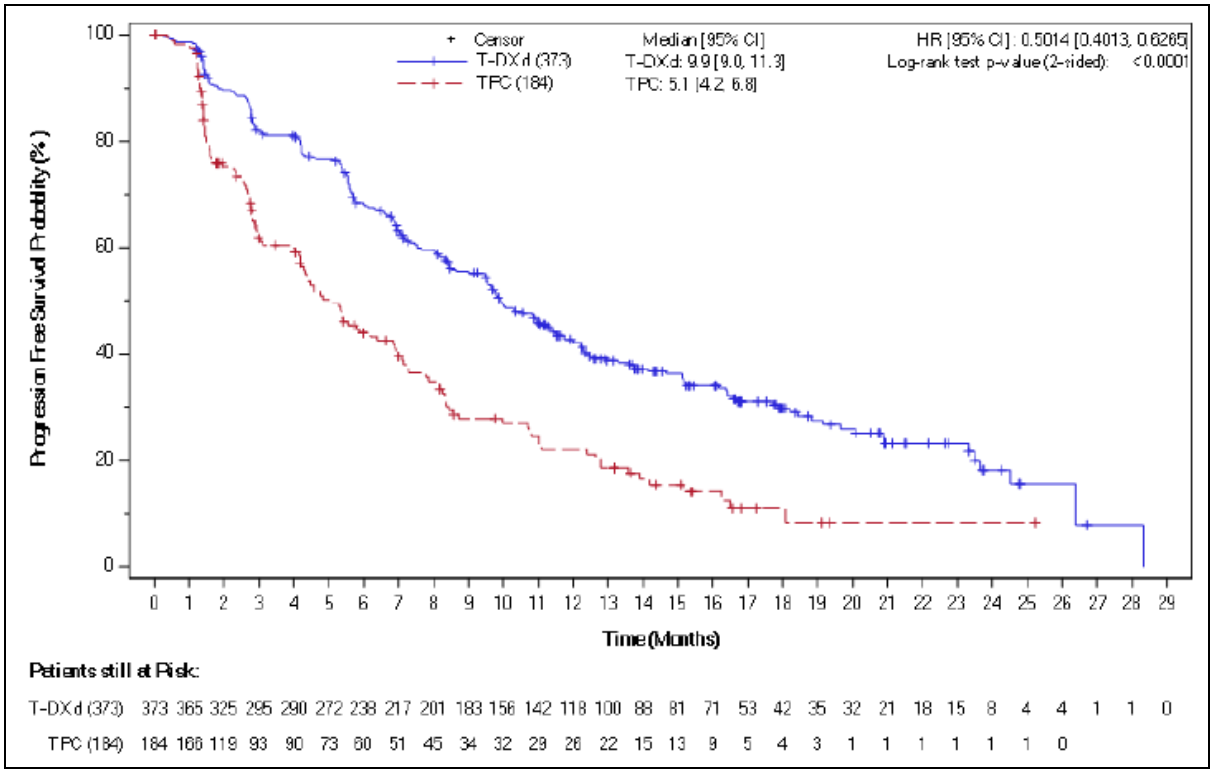
**Censoring reasons included:* [redacted]

[a] It should be noted that CS, section B.2.6.1, Table 17[1] and CSR, Table 8.4[21] reports this value as p<0.0001, but the CS text[1] and the publication[18] report the figure p<0.001.

†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method. ‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HorR/CDK status, as defined by the IXRS. §Estimate and CI for PFS rate at the specified time point are from the KM analysis.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HorR-positive, hormone receptor-positive; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 8 Kaplan-Meier of PFS by BICR in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.6.1, Figure 12)



Abbreviations: BICR; blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan, TPC, treatment of physician's choice.

OS in the HorR-positive cohort

For secondary outcome of OS for the HorR-positive cohort only, at DCO the median duration of survival follow-up was 18.4 months.[18] The median OS was 23.9 months (95% CI: 20.8, 24.8) in the T-DXd arm compared with 17.5 months (95% CI: 15.2, 22.4) in the TPC arm (Table 13). T-DXd significantly reduced the probability of death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p=0.0028) (Table 13 and Figure 9).

Table 13 OS in the HorR-positive cohort from DESTINY-Breast04 (adapted from CS, section 2.6.1, Table 19[1])

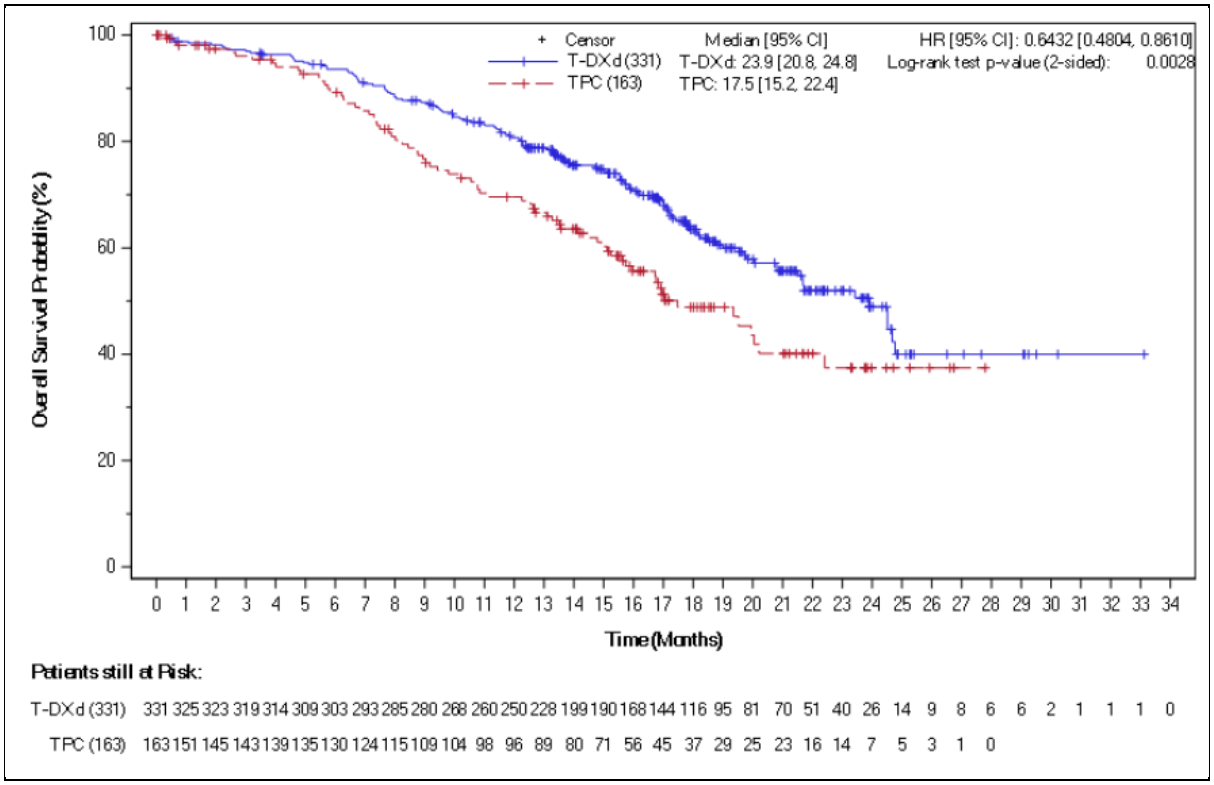
	HorR-positive cohort	
	T-DXd (N=331)	**TPC (N=163)**
Subjects with events (deaths), n (%)	[redacted]	[redacted]
Subjects without events (censored), n (%)	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Other	[redacted]	[redacted]
Median overall survival, months*	23.9	17.5
(95% CI)*	(20.8, 24.8)	(15.2, 22.4)
Stratified Cox proportional hazards model hazard ratio†	0.6432	
(95% CI)†	(0.4804, 0.8610)	
Stratified log-rank test p-value†	0.0028	
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

**Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method. †Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HorR/CDK status, as defined by the IXRS.*

‡Estimate and CI for OS rate at the specified timepoint are from KM analysis.

Abbreviations: CI, confidence interval; FAS, full analysis set; HorR-positive, hormone receptor-positive; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 9 Kaplan-Meier of OS in the HorR-positive from DESTINY-Breast04 (reproduced from CS, section 2.6.1, Figure 13)



Abbreviations: CI, confidence interval; HR, hazard ratio; HorR-positive, hormone receptor-positive; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in the FAS

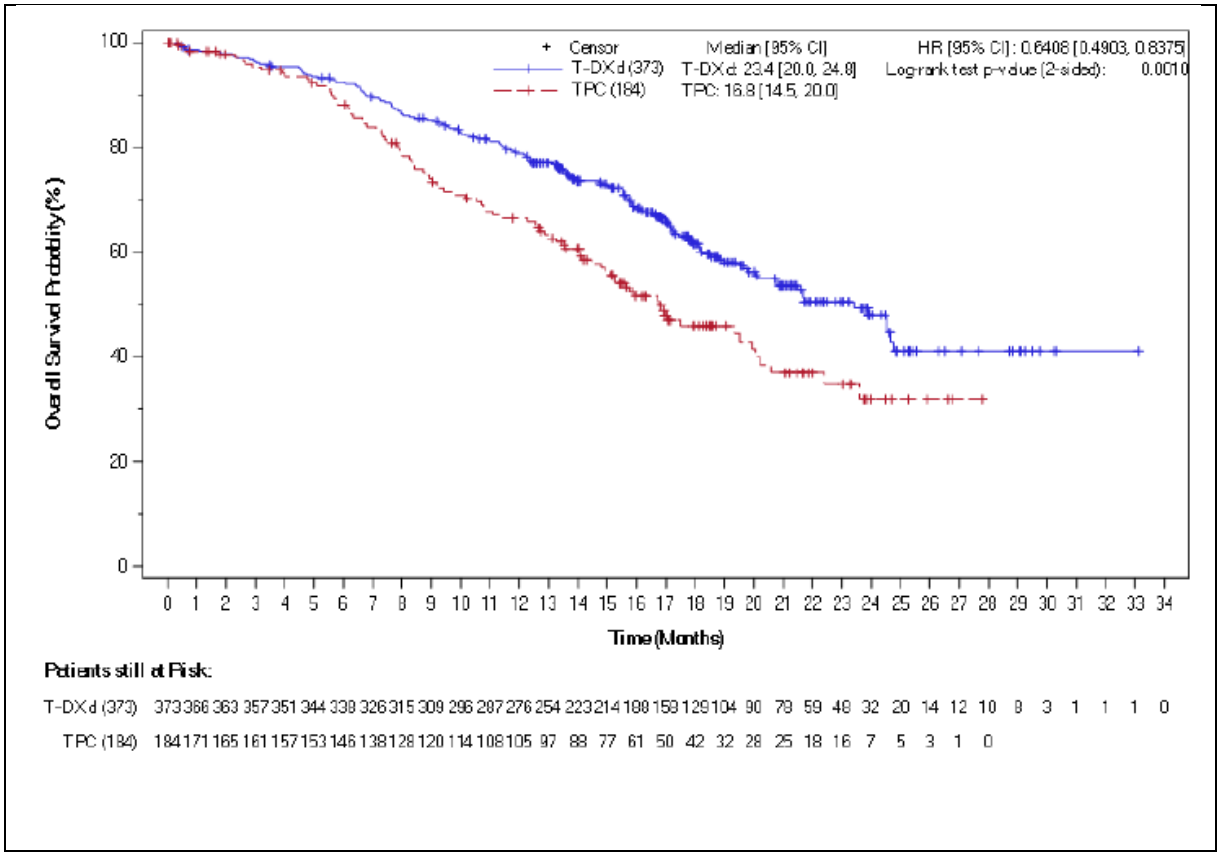
For secondary outcome of OS for the FAS, at DCO the median duration of survival follow-up was 18.4 months.[18] The median OS was 23.4 months (95% CI: 20.0, 24.8) in the T-DXd arm compared with 16.8 months (95% CI: 14.5, 20.0) in the TPC arm (Table 14). T-DXd significantly reduced the probability of death by 36% compared with TPC: HR 0.64 (95% CI: 0.49-0.84, p<0.001) (Table 14 and Figure 10). These results were consistent with the findings for the HorR-positive only cohort. As stated in the CS (Section B.2.6.1.2), "*the stratified log-rank p-value of 0.001 crossed the pre-specified efficacy stopping boundary of 0.0075, confirming the efficacy of T-DXd vs. TPC for this outcome. DESTINY-Breast04 therefore met its secondary endpoint of OS in the FAS*."

Table 14 OS in the FAS from DESTINY-Breast04 (adapted from CS, section 2.6.1, Table 20[1])

	FAS	
	T-DXd (N=373)	TPC (N=184)
Subjects with events (deaths), n (%)	[redacted]	[redacted]
Subjects without events (censored), n (%)	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Other	[redacted]	[redacted]
Median overall survival, months*	23.4	16.8
(95% CI)*	(20.0, 24.8)	(14.5, 20.0)
Stratified Cox proportional hazards model hazard ratio†	0.6408	
(95% CI)†	(0.4903, 0.8375)	
Stratified log-rank test p-value†	0.0010	
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

**Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method.*
†Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HorR/CDK status, as defined by the IXRS.
‡Estimate and CI for OS rate at the specified timepoint are from KM analysis.
Abbreviations: CI, confidence interval; FAS, full analysis set; HorR-positive, hormone receptor-positive; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 10 Kaplan-Meier of OS in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.6.1, Figure 14)



Abbreviations: CI, confidence interval; HR, hazard ratio; HorR-positive, hormone receptor-positive; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

4.3.3 Other secondary efficacy outcomes

The other secondary efficacy outcomes reported in the CS include: PFS by investigator assessment (IA), response and HRQoL (CS, section B.2.6.1.3 and B.2.6.1.4).[1]

PFS by Investigator Assessment (IA)

The median PFS by IA for the HorR-positive cohort was [redacted] months (95% CI: [redacted]) for T-DXd compared with [redacted] months (95% CI: [redacted]) for TPC (HR: [redacted]; 95% CI: [redacted]). This suggested superior efficacy compared with the BICR assessment reported above, which reported 10.1 and 5.4 months for T-DXd and TPC respectively, and a HR of 0.51 (a probability of disease progression for T-DXd compared with TPC of 49% by BICR rather than 63% as reported for PFS by IA). In the same way, the median PFS by IA in the FAS was [redacted] months (95% CI: [redacted]) for T-DXd compared with [redacted] months (95% CI: [redacted]) for TPC (HR: [redacted]; 95% CI: [redacted]). As reported, the BICR FAS assessment reported 9.9 and 5.4 months for T-DXd and TPC respectively, and an HR of 0.50 (a probability of disease progression for T-DXd compared with TPC of 50% by BICR rather than 63% as reported for PFS by IA).

Response

At the DCO, the confirmed overall response rates (ORR) by BICR were significantly higher in the T-DXd arm: 52.9% and 52.3% (HorR-positive cohort and the FAS, respectively) compared with the TPC arm: 16.6% and 16.3% ($p<0.0001$) (Table 15). Similar findings were reported for the disease control rate and the clinical benefit rate. Complete response (CR) rates by BICR were higher in the T-DXd arm compared with the TPC arm, but incidence was low: 3.6% and 3.5% (HorR-positive cohort and the FAS, respectively) compared with 0.6% and 1.1% ($p<0.0001$) (Table 15). The principal response benefit for T-DXd compared with TPC was partial response (PR) by BICR: 49.5% and 49.1% (HorR-positive cohort and the FAS, respectively) compared with 16.0% and 15.2% ($p<0.0001$) (Table 15). It should be noted that some of these figures, percentages and confidence intervals differ very slightly from the data as they appear in Table 2 of the principal trial publication.[18]

Table 15 Response rates in the HorR-positive and FAS populations from DESTINY-Breast04 (adapted from CS, section 2.6.1, Table 21)

	HorR-positive cohort		FAS	
	T-DXd (N=331)	TPC (N=163)	T-DXd (N=373)	TPC (N=184)
Confirmed ORR by BICR, n (%)	175 (52.9)[a]	27 (16.6)	195 (52.3)[a]	30 (16.3)
95% CI	(47.3, 58.4)	(11.2, 23.2)	(47.1, 57.4)	(11.3, 22.5)
p-value*	<0.0001		<0.0001	
Confirmed ORR by IA, n (%)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
Disease control rate by BICR**, n (%)	291 (87.9)	108 (66.3)	325 (87.1)	121 (65.8)
95% CI	(83.9, 91.2)	(58.4, 73.5)	(83.3, 90.4)	(58.4, 72.6)
p-value*	<0.0001		<0.0001	
Clinical benefit rate by BICR†, n (%)	238 (71.9)	57 (35.0)	262 (70.2)	62 (33.7)
95% CI	(66.7, 76.7)	(27.7, 42.8)	(65.3, 74.8)	(26.9, 41.0)
p-value*	<0.0001		<0.0001	
Best overall response by BICR, n (%)				
CR	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
PR	164 (49.5)	26 (16.0)	183 (49.1)	28 (15.2)
SD	115 (34.7)	81 (49.7)	129 (34.6)	91 (49.5)
PD	26 (7.9)	34 (20.9)	31 (8.3)	41 (22.3)
Not evaluable	14 (4.2)	21 (12.9)	17 (4.6)	22 (12.0)
Best overall response by IA, n (%)				
CR	[redacted]		[redacted]	
PR	[redacted]		[redacted]	
SD	[redacted]		[redacted]	
PD	[redacted]		[redacted]	
Not evaluable	[redacted]		[redacted]	

**Two-sided p-value based on the Cochran-Mantel-Haenszel test adjusted for stratification factors.*
***CR + PR + SD.*
†CR + PR + SD ≥6 months.
[a] One subject in the T-DXd arm who had a confirmed best overall response of complete or partial response had a baseline scan done after randomisation but before the first dose and thus was considered a non-responder in the calculation of confirmed ORR.
Abbreviations: BICR, Blinded independent central review ; CI, confidence interval; CR, complete response; FAS, full analysis set; HorR-positive, hormone receptor-positive; IA, investigator assessment; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The median DoR in patients with a confirmed objective response (CR or PR, by BICR) was reported to be numerically higher with T-DXd than with TPC both in the HorR-positive cohort (median DoR by BICR: 10.7 vs. 6.8 months) and in the FAS (median DoR by BICR: 10.7 vs 6.8 months); p values were not reported. The median time to response based on BICR among responders (patients with CR or PR) was 2.76 months for T-DXd compared with 2.73 months for TPC in the HorR-positive cohort, and 2.73 months (range: 1.2, 14.0) and 2.22 months (range: 1.2, 8.3), respectively, in the FAS; p values were not reported.

4.3.4 *Health-related Quality of life (HRQoL)*

HRQoL was assessed using the following questionnaires in the DESTINY-Breast04 trial: EQ-5D-5L; EORTC QLQ-C30 and EORTC QLQ-BR45 (CS, section B.2.6.1.4).[1] The CS reported data on compliance rates for completion of the questionnaires at baseline and end of treatment (CS, section B.2.6.1.4). Across the three questionnaires, the CS reported compliance rates in the HorR-positive cohort and FAS of between [redacted] and [redacted] at baseline and [redacted] and [redacted] at end of treatment (CS, section B.2.6.1.4).

EQ-5D-5L

The CS reported that the mean change from baseline to end of treatment in the EQ-5D-5L index score was [redacted] in the T-DXd arm and [redacted] in the TPC arm, and for the EQ-5D-5L VAS, the mean change from baseline to end of treatment was [redacted] in the T-DXd arm and [redacted] in the TPC arm.[29] At baseline in the FAS, the median EQ-5D-5L VAS score was [redacted] in both the T-DXd arm and the TPC arm. At end of treatment, [redacted] (median change from baseline: [redacted] in both treatment arms).[29] The median time to definitive deterioration (TTDD) was also reported for the FAS (Figure 11): the TTDD by at least 10 points for the EQ-5D-5L VAS was [redacted] in the T-DXd arm than the TPC arm: [redacted] (95% CI:[redacted]) vs. [redacted] months (95% CI: [redacted]); HR: [redacted]; 95% CI: [redacted]; p=[redacted]).[29] The CS reported that the results in the HorR-positive cohort[19] were consistent with those in the FAS (CS, section B.2.6.1.4, Figure 19).[1]

Figure 11 Kaplan-Meier of time to definitive deterioration of EQ-5D-5L VAS in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.6.1.4, Figure 16[1])

Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue score.

EORTC-QLQ-C30

The CS reported the mean change from baseline to end of treatment in the FAS for the EORTC-QLQ-C30: a high score represents a low QoL. At baseline, the median global health status score was [redacted] in both the T-DXd arm and the TPC arm.[29] At end of treatment, [redacted] (median change from baseline: [redacted]).[29] [redacted], the median change from baseline to end of treatment was [redacted] in both arms. The exception was [redacted] for TPC, where QoL decreased as shown by a median increase from baseline of [redacted].[29]

The median time to definitive deterioration was also reported for the FAS (Figure 12): the TTDD by at least 10 points for the EORTC QLQ-30 GHS was [redacted] in the T-DXd arm than the TPC arm ([redacted] [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]; HR: [redacted]; 95% CI: [redacted]; p=[redacted]).[29] The HR was [redacted] of T-DXd compared with TPC for nearly [redacted], including [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]), and [redacted] ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]).[29] The exception was [redacted], where the HR was [redacted] of TPC vs. T-DXd ([redacted] and [redacted] months; HR: [redacted]; 95% CI: [redacted]).[29] The CS reported that the results in the HorR-positive cohort[19] were consistent with those in the FAS (CS, section B.2.6.1.4, Figures 18 and 19).[1]

Figure 12 Kaplan-Meier of time to definitive deterioration of EORTC QLQ-30 GHS in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.6.1.4, Figure 17[1])

Abbreviations: CI, confidence interval; FAS, full analysis set; GHS, global health status; HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

EORTC-QLQ-BR45 (BR23)

The CS reported the mean change from baseline to end of treatment in the FAS for the EORTC-QLQ-BR45 (QoL relating to symptoms). At baseline, the breast symptoms scale score was [redacted] in both the T-DXd arm and the TPC arm, and the median baseline arm symptoms scale score was [redacted] in both arms.[29] At end of treatment, the median baseline breast symptom scores were [redacted] (median change from baseline: [redacted] and [redacted], in the T-DXd arm and TPC arm, respectively).[29] The median time to definitive deterioration was also reported for the EORTC QLQ-BR45 for the FAS (Figure 13): T-DXd was associated with [redacted] in arm symptoms compared with TPC ([redacted] months (95% CI: [redacted]) vs. [redacted] months (95% CI: [redacted]); HR: [redacted]; 95% CI: [redacted]; p= [redacted]. The CS reported that the results in the HorR-positive cohort[19] were consistent with those in the FAS (CS, section B.2.6.1.4, Figure 19).[1]

Figure 13 Kaplan-Meier of time to definitive deterioration of EORTC QLQ-BR45 in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.6.1.4, Figure 20[1])

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HR, hazard ratio; QLQ-BR45, Quality-of-life Breast Cancer 45 questionnaire; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue score.

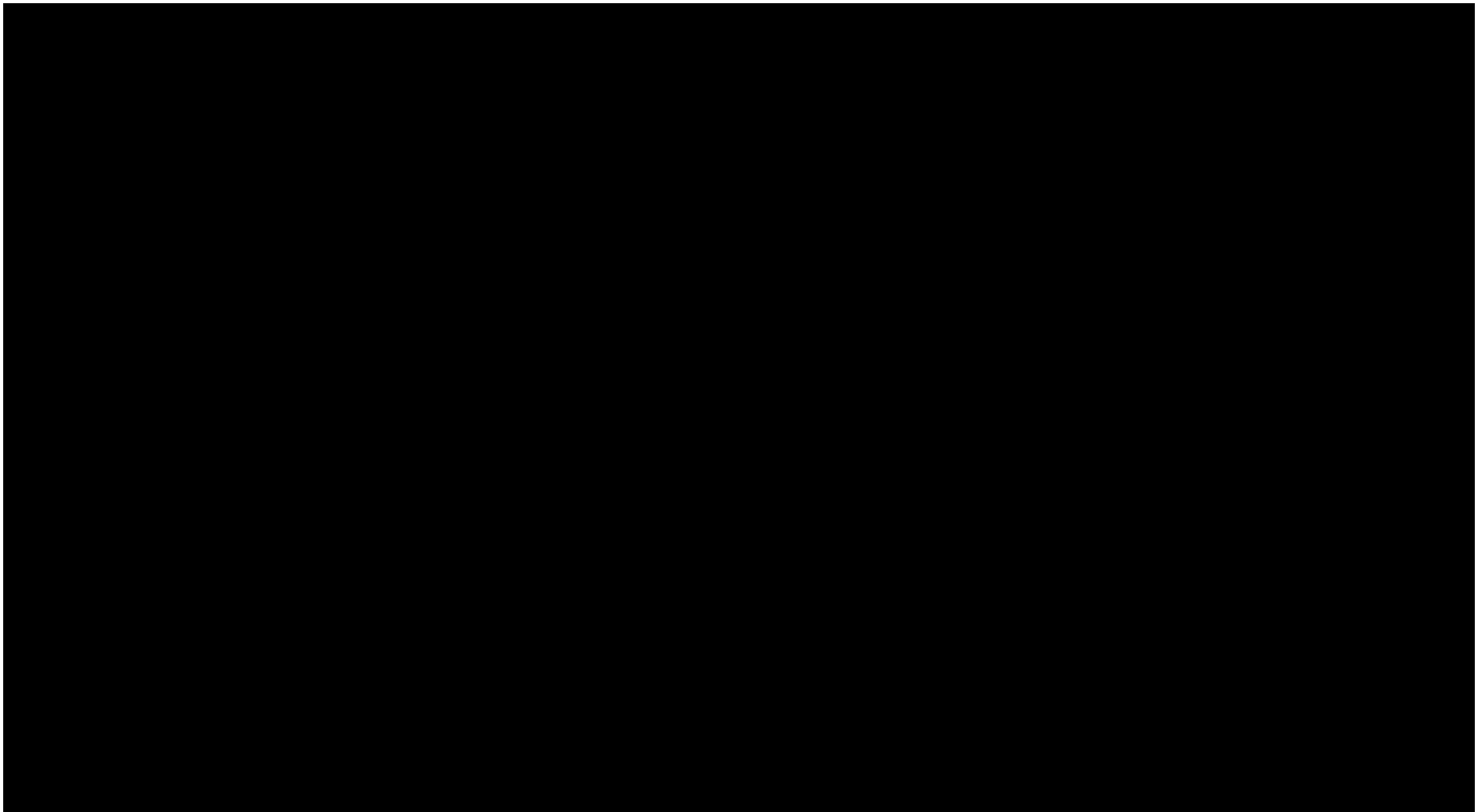
4.3.5 *Subgroup analyses*

Pre-specified subgroup analyses for PFS by BICR for the FAS are reported in the CS section B.2.7.1. PFS by BICR for the FAS was a key secondary outcome of the DESTINY-Breast04 trial: overall, T-DXd demonstrated a statistically significant improvement in PFS by BICR compared to the TPC arm with a HR of 0.50 (95% CI: 0.40, 0.63).[18] The subgroup analyses presented in Figure 14 indicate that the treatment effect of T-DXd was [redacted]. The subgroup HR midpoint estimates that [redacted] of the FAS were: [redacted] (Figure 9).

The CS also reported analyses in the HorR-negative cohort. The EAG noted that the sample size of this cohort and the related results, reported in the CS, Appendix N, and the main publication, {Modi, 2022 #46} differ from those reported in the CSR. The results reported in the CS (section B.2.7.2) concern a sample of 58 patients. In the HorR-negative subgroup of the DESTINY-Breast04 trial, when compared with TPC (n=18), T-DXd (n=40) was associated with an improvement in the following outcomes: PFS by BICR (8.5 vs. 2.9 months; HR: 0.46; 95% CI: 0.24, 0.89); OS (18.2 vs. 8.3 months; HR: 0.48; 95% CI: 0.24, 0.95)[18]; and response rates (confirmed ORR by BICR: 50% vs 16.7%)[18], which were reported in the CS (B.2.7.2) as [redacted] vs [redacted]; p=[redacted]). The results reported in the CSR (section 8.2.4.3) concern the whole HorR-negative sample of 63 patients. In the HorR-negative subgroup of the

DESTINY-Breast04 trial, when compared with TPC (n=21), T-DXd (n=42) was associated with [redacted].

Figure 14 Subgroup analysis Forest plot of PFS by BICR in the FAS from DESTINY-Breast04 (reproduced from CS, section 2.7.1, Figure 21)



Notes: [a] subgroup analyses were only conducted if there were at least 10 patients in each arm of the subgroup.
Abbreviations: BICR, blinded independent central review; CDK, cyclic-dependent kinase; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; NE, not estimable; No, number; PFS, progression-free survival; PS, performance status; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

4.4 Safety

4.4.1 Safety data reported for DESTINY-Breast04 trial

The CS presented data from the DESTINY-Breast04 study in section B.2.10. The data were from the 11 January 2022 DCO, with a median follow-up of [redacted] months in the T-DXd arm and [redacted] months in the TPC arm (CS, section B.2.10.1).

The CS reported that the median treatment duration with T-DXd was 8.2 months (range: 0.2–33.3) and, for TPC, it was 3.5 months (range: 0.3–17.6) (CS, section B.2.10.1.1[1] and Modi *et al*., 2022[18]). In the T-DXd arm the mean study dose intensity was [redacted] mg/kg/3 weeks and the mean relative dose intensity (RDI) was [redacted]% (CS, section B.2.10.1.1, Table 22). In the TPC arm, the mean RDI ranged from [redacted]% for the agents in the TPC arm (CS, section B.2.10.1.1, Table 22). The CS incorrectly states that the mean RDI for the TPC treatments ranged from [redacted]% but this refers to the range of the medians across the 5 agents (CSR Table 10.1). It also should be noted that in the figures presented in CS, Table 22, the company used different definitions to calculate the RDI for T-DXd compared to the agents included TPC, with the mean RDI for T-DXd reported as [redacted]% in the CSR (median [redacted]), when using the same definition applied to the TPC treatments. This inconsistency is further discussed in Section 5.3.3.8. At DCO, 58 patients (15.6%) in the T-DXd arm and 3 patients (1.7%) in the TPC arm were continuing study treatment.

Treatment-emergent AEs were categorised according to the Medical Dictionary for Regulatory Activities (Version 24.0) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Potential episodes of interstitial lung disease (ILD), an AE of special interest, were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE version 5.0. Safety analyses were performed on the SAS (CS, section B.2.10.1).[1]

The overall safety data for the SAS are summarised in Table 16. The frequency of any TEAE was very high for both T-DXd and TPC (99.5% vs 98.3% respectively); drug-related AEs Grade ≥3 AEs were high but lower for T-DXd ([redacted]) than TPC ([redacted]); and numbers of patients with serious drug-related TEAEs were low and similar between arms ([redacted] for T-DXd vs [redacted] for TPC). The only drug-related SAEs of >1% in the T-DXd arm were interstitial lung disease (ILD) [redacted] and nausea [redacted] (CSR, Table 10.19[21]). In the TPC arm, the only drug-related SAEs of >1% were [redacted] and [redacted]. Drug-related TEAEs associated with discontinuation were higher for TDX-d compared with TPC (15.1% vs 7.0%). The principal reasons for these discontinuations in the T-DXd arm were pneumonitis [redacted] and ILD [redacted] (CS, section B.2.10.1.2, Table 27).[1] Drug-related TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively). This was principally due to the frequency of neutropenia in the TPC arm: [redacted] in the T-DXd arm vs [redacted] in the TPC arm leading to dose

reductions; and [redacted] in the T-DXd arm vs [redacted] in the TPC arm leading to dose interruptions (CS, section B.2.10.1.2, Table 27).[1]

Drug-related TEAEs with the outcome of death were also higher in the T-DXd arm compared with the TPC arm (n=7, 1.9% vs 0%). The principal trial publication[18] and the CSR reports that these drug-related TEAEs include pneumonitis, (n=2), sepsis, colitis ischaemic, febrile neutropenia, dyspnoea, and disseminated intravascular coagulation (n=1 each) (CSR, table 14.3.2.9).[21] The CS also reports that, across both the T-DXd and TPC arms, the frequency of TEAEs was high in [redacted] of treatment, but declined thereafter up to [redacted]; combined data were presented for [redacted], but overall duration of cycles was not reported (CS, section B.2.10.1.2, Table 24).[1]

Table 16 Summary of safety outcomes from DESTINY-Breast04 (SAS) (reproduced from CS, section B.2.10.1.2, Table 23[1])

N (%)	T-DXd (N=371)	TPC (N=172)
Any TEAE	369 (99.5)	169 (98.3)
EAIR per patient-year of exposure	1.30	2.66
Any drug-related TEAE	[redacted]	[redacted]
TEAE Grade ≥3	195 (52.6)	116 (67.4)
EAIR per patient-year of exposure	0.69	1.82
Drug-related TEAE Grade ≥3	[redacted]	[redacted]
Serious TEAE	103 (27.8)	43 (25.0)
EAIR per patient-year of exposure	0.36	0.68
Serious drug-related TEAE	[redacted]	[redacted]
TEAE associated with an outcome of death	14 (3.8)	5 (2.9)
EAIR per patient-year of exposure	0.05	0.08
Drug-related TEAE associated with an outcome of death	7 (1.9)	0
TEAE associated with study drug discontinuation	60 (16.2)	14 (8.1)
EAIR per patient-year of exposure	0.21	0.22
Drug-related TEAE associated with discontinuation	56 (15.1)	12 (7.0)
TEAE associated with dose reduction	84 (22.6)	66 (38.4)
EAIR per patient-year of exposure	0.30	1.04
Drug-related TEAE associated with dose reduction	77 (20.8)	64 (37.2)
TEAE associated with study drug interruption	143 (38.5)	72 (41.9)
EAIR per patient-year of exposure	0.50	1.13
Drug-related TEAE associated with study drug interruption	106 (28.6)	62 (36.0)

Abbreviations: EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; treatment of physician's choice.

The most common TEAEs are summarised in Table 17. The following TEAEs were both frequent and more common in the T-DXd arm than in the TPC arm in the DESTINY-Breast04 trial: Nausea ([redacted]% in the T-DXd arm vs [redacted]% in the TPC arm); vomiting ([redacted]% vs [redacted]%); anaemia ([redacted]% vs [redacted]%); constipation ([redacted]% vs [redacted]%); decreased appetite ([redacted]% vs [redacted]%) and thrombocytopenia ([redacted]% vs [redacted]%). The following TEAEs were both frequent and more

common in the TPC arm than in the T-DXd arm in the DESTINY-Breast04 trial: Neutropenia ([redacted] in the TPC arm vs [redacted] in the T-DXd arm), leucopenia ([redacted] vs [redacted]), and palmar-plantar erythrodysaesthesia syndrome ([redacted] vs [redacted]).

The incidence of Grade ≥3 TEAEs was also higher for T-DXd compared with TPC for some of these events: nausea ([redacted]% vs [redacted]%); anaemia ([redacted]% vs [redacted]%); thrombocytopenia ([redacted]% vs [redacted]%), as well as fatigue ([redacted]% vs [redacted]%). However, the incidence of the following Grade ≥3 TEAEs were higher in the TPC arm than the T-DXd arm: neutropenia; leucopenia; elevated AST and Palmar-plantar erythrodysaesthesia syndrome. These findings were consistent with the results for the most common drug-related TEAEs, some of which had a lower incidence in the T-DXd arm than in the TPC arm (Table 18) and are reported in Table 3 of the main trial publication.[18]

Table 17 Summary of DESTINY-Breast04 most common TEAEs with incidence of ≥20% in either arm (SAS) (reproduced from CS, section B.2.10.1.2, Table 25[1])

	T-DXd (N=371)		TPC (N=172)	
Patient-years of exposure	283.55		63.59	
System organ class, Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Anaemia†	[redacted]	[redacted]	[redacted]	[redacted]
Neutropoenia*	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia§	[redacted]	[redacted]	[redacted]	[redacted]
Leucopoenia‡	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders				
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
General disorders				
Fatigue**	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Investigations				
AST Increased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders				
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders				
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]	[redacted]	[redacted]

**This category includes the preferred terms neutrophil count decreased and neutropoenia.*
†This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased.
‡This category includes the preferred terms white blood cell count decreased and leucopoenia.
§This category includes platelet count decreased and thrombocytopaenia.
***This category includes the preferred terms fatigue, asthenia, and malaise.*
Abbreviations: AST, aspartate aminotransferase; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 18 Summary of DESTINY-Breast04 most common drug-related TEAEs with incidence of ≥10% in either arm (SAS) (reproduced from CS, section B.2.10.1.2, Table 26[1])

	T-DXd (N=371)		TPC (N=172)	
Patient-years of exposure	283.55		63.59	
System organ class, Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Neutropoenia*	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anaemia†	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Leucopoenia‡	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Thrombocytopaenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhoea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
General disorders				
Fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Investigations				
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders				
Decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders				
Alopecia	140 (37.7)	0	56 (32.6)	0
Interstitial lung disease	45 (12.1)	[redacted]	1 (0.6)	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]	[redacted]	[redacted]

**This category includes the preferred terms neutrophil count decreased and neutropoenia.*
†This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased.
‡This category includes the preferred terms white blood cell count decreased and leucopoenia.
§This category includes platelet count decreased and thrombocytopaenia.
***This category includes the preferred terms fatigue, asthenia, and malaise.*
Abbreviations: AST, aspartate aminotransferase; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Adverse events of special interest

The principal AEs identified as of special interest in DESTINY-Breast04 were ILD and left ventricular (LV) dysfunction. The CS reported that cases of potential ILD or pneumonitis in either study arm were reviewed by an independent ILD adjudication committee (CS, section B.2.10.1.2). ILD (any Grade) was reported in 45 patients (12.1%) in the T-DXd arm and in only one patient in the TPC arm (0.6%) (Table 19). The majority (37 patients, 10%) were Grade 1 and 2; five patients (1.3%) experienced Grade 3 and three patients (0.8%) Grade 5 ILD. Events of ILD associated with study drug interruption, dose reduction, or discontinuation were reported in [redacted] ([redacted]), [redacted] ([redacted]) and [redacted] patients ([redacted]), respectively, of patients treated with T-DXd.[21] In patients treated with TPC, [redacted] ILD-related drug interruptions, dose reductions, or discontinuations were reported.[21]

Table 19 Summary of special interest TEAE: drug-related ILD/pneumonitis* by CTCAE v5.0 in DESTINY-Breast04 (SAS) (reproduced from CS, section B.2.10.1.2, Table 28[1, 14])

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N=371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (N=172)	1 (0.6)	0	0	0	0	1 (0.6)

**Patients with prior history of ILD/pneumonitis requiring steroids were excluded.*
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

LV dysfunction (any Grade) was reported in 17 patients (4.6%) in the T-DXd arm and in no patients in the TPC arm (Table 20). The majority were Grade 1 or 2 in severity (15 patients, 4.1%); 2 patients (0.5%) experienced Grade 3 LV dysfunction.

Table 20 Summary of special interest TEAE: LV dysfunction by CTCAE v5.0 in DESTINY-Breast04 (SAS) (reproduced from CS, section B.2.10.1.2, Table 29[1])

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N=371)	1 (0.3)	14 (3.8)	2 (0.5)	0	0	17 (4.6)
TPC (N=172)	0	0	0	0	0	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; LV, left ventricular; T-DXd, trastuzumab deruxtecan, TPC, treatment of physician's choice.

4.5 Ongoing studies

The EAG could not identify any relevant ongoing phase III trials or studies of T-DXd in patients with HER2 u/mBC. The only active trial for T-DXd is a phase I/II trial comparing T-DXd + durvalumab with alternative combination therapies as first line therapy in metastatic TNBC patients (NCT03742102). The CS reports that there are no relevant ongoing studies and no plans to conduct ongoing analyses of the DESTINY-Breast04 data, given the significant findings for the primary and secondary outcomes (section B.2.11).[1]

4.6 Meta-analysis

The EAG agrees with the CS (section B.2.8)[1] that a meta-analysis is not appropriate given only a single relevant trial with the correct population, intervention and one or more relevant comparators was identified (DESTINY-Breast04), and no similar, relevant trial has been missed.

4.7 Indirect treatment comparisons

As discussed in Section 3.3, the company does not consider SG to be a relevant or important comparator in the full HER2-low population in this appraisal. The company conducted two independent feasibility assessments[30, 31] for indirect treatment comparison (ITC) between T-DXd and SG and concluded that the ITC between T-DXd and SG in the HER2-low/HorR-negative population based on the DESTINY-Breast04 and ASCENT trials would be highly uncertain and not appropriate for decision-making. A summary of the reasons is listed below.

- Study design: The ASCENT trial was not powered to analyse efficacy in the HER2-low population. The stratification factors used in DESTINY-Breast04 and ASCENT were different.
- Data availability: There is limited reporting of data from a conference poster[32] for the HER2-low/HorR-negative population from ASCENT.
- Population characteristics: Based on the available data, the company reported there are differences in the following treatment effect modifiers between DESTINY-Breast04 and ASCENT: age; prior chemotherapy; ECOG score; site of metastases; race and region.
- Patient numbers: Matching the population between the DESTINY-Breast04 and ASCENT trials would result in small effective sample size given the differences in baseline characteristics between the two trials and the small sample size in the HER2-low/HorR-negative population (T-DXd N=40, TPC N=18 from DESTINY-Breast04) and ASCENT (SG N=63, TPC N=60 from ASCENT).

In response to clarification question A21,[15] the company presented the PFS and OS results in the HER2-low/HorR-negative population in the DESTINY-Breast04 and ASCENT trials (see Table 21). The company concluded that T-DXd and SG have similar efficacy in the HER2-low/HorR-negative population based on a naïve, unadjusted, comparision which shows that the HRs for both PFS and OS are similar in DESTINY-Breast04 and ASCENT and there is overlap in confidence intervals across trials.

Table 21 DESTINY-Breast04 and ASCENT PFS and OS outcomes (reproduced from response to clarification question A21)

Study (population)	Comparison	Outcome	Median, months	Difference in median, months	HR (95% CI)
ASCENT (HER2-low/HorR-negative)	SG vs. TPC	PFS	SG: 6.2 TPC: 2.9	3.3	0.44 (0.27, 0.72)
		OS	SG: 14.0 TPC: 8.7	5.3	0.43 (0.28, 0.67)
DESTINY-Breast04 (HER2-low/HorR-negative)	T-DXd vs. TPC	PFS	T-DXd: 8.5 TPC: 2.9	5.6	0.46 (0.24, 0.89)
		OS	T-DXd: 18.2 TPC: 8.3	9.9	0.48 (0.24, 0.95)

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HorR-negative, hormone receptor negative; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The EAG agrees with the findings from the two feasibility assessments that there are differences in the population characteristics between DESTINY-Breast04 and ASCENT which may result in a biased ITC estimates without adjustments. The EAG also agrees that using a matching-adjusted indirect comparison (MAIC) may lead to small effective sample size.

The EAG notes that the company has assumed equal efficacy between T-DXd and SG in the HER2-low/HorR-negative population and presented an exploratory cost-minimisation analysis in response to clarification question B1.[15] The EAG's clinicians felt this is unsupported by evidence and that the two drugs showed different efficacy and safety profiles within two different trial populations where the average number of prior lines of treatment and HER2 expression statistics were different.

The EAG cautions the interpretation of the results from the naïve, unadjusted, comparison and the company's assumption of equal efficacy as it may be subject to confounding bias. Without formal adjustments, it is difficult to quantify the magnitude of this bias. The EAG notes that the estimate of the HR for both PFS and OS in the HER2-low/HorR-negative population are more in favour of SG than T-DXd when comparing with TPC. The HER2-low/HorR-negative population in the ASCENT trial received third-line treatments, whereas the HER2-low/HorR-negative population in the DESTINY-Breast04 trial received second-line treatments. This could indicate that the population in ASCENT is more difficult to treat which may have an impact on the relative efficacy. This is also supported by the utility values collected during PFS in both trials with the estimated PFS utility being lower from the ASCENT trial than the DESTINY-Breast04 trial.

4.8 Additional work on clinical effectiveness undertaken by the EAG

The EAG did not undertake any additional work relating to the clinical effectiveness of T-DXd in adults with HER2-low u/mBC after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting.

4.9 Conclusions of the clinical effectiveness section

The pivotal trial (DESTINY-Breast04) is a phase III, randomised, international, multi-centre, open-label RCT, which was initiated in December 2018 and conducted in 161 centres across 19 countries, including seven centres in the UK (NCT03734029). DESTINY-Breast04 is a two-arm efficacy and safety trial of T-DXd compared with TPC in adult patients with unresectable or metastatic HER2-low breast cancer (u/mBC) after one or two lines of chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. The primary completion date was January 2022, but the final completion date is listed as March 2023 (NCT03734029). In total, 557 patients were randomised 2:1 to receive T-DXd and TPC, respectively. Randomisation was stratified by HER2 IHC status, number of prior lines of chemotherapy (1 vs. 2), and HorR/CDK status. The T-DXd and TPC groups were well balanced at baseline and were considered likely to reflect the patients for this indication in clinical practice in the UK, with the exception of patients being older in practice and a proportion of patients in practice being ECOG PS 2. The proportions of HorR-positive and HorR-negative patients in the trial were consistent with data on the UK HER2-low population: 88.7% and 11.3% respectively.

Overall, on account of the judgement of 'some concerns' only in the domain of outcome assessment, and only for some outcomes, the EAG judged the level of risk of bias affecting the DESTINY-Breast04 trial to be 'Low'. The DCO for the efficacy and safety analyses was 11 January 2022.

The median follow-up in the FAS for T-DXd and TPC was [redacted] and [redacted] months, respectively. The primary outcome was PFS by BICR for the HorR-positive cohort only: the median PFS by BICR was 10.1 months (95% CI: 9.5, 11.5) in the T-DXd arm compared with 5.4 months (95% CI: 4.4, 7.1) in the TPC arm. T-DXd also significantly reduced the probability of disease progression compared with TPC by 49%: HR 0.51 (95% CI: 0.40-0.64, p<0.001). The CS did not explain why HER2-low/HorR-negative patients were excluded from the primary outcome analysis. However, secondary efficacy analyses were conducted on the FAS (which included HER2-low/HorR-negative patients) and the results were consistent with the findings for the HorR-positive only cohort. Death was the recorded PFS event in [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the TPC arm; the reasons for these PFS deaths were not reported in the CS or CSR and are therefore unclear. Pre-specified subgroup analyses for PFS by BICR for the FAS indicated that the treatment effect of T-DXd was [redacted].

For the secondary outcome of OS for the HorR-positive cohort only (18.4 months follow-up), the median OS was 23.9 months (95% CI: 20.8, 24.8) in the T-DXd arm compared with 17.5 months (95% CI: 15.2, 22.4) in the TPC arm. T-DXd significantly reduced the probability of death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p=0.0028). The FAS results were consistent with the findings for the HorR-positive only cohort. The confirmed overall response rates (ORR) by BICR were significantly higher in the T-DXd arm: 52.9% and 52.3% (HorR-positive cohort and the FAS, respectively) compared with the TPC arm: 16.6% and 16.3% (p<0.001). HRQoL was assessed using the following questionnaires in the DESTINY-Breast04 trial: EQ-5D-5L; EORTC QLQ-C30 and EORTC QLQ-BR45. Generally, all three found that baseline quality of life was maintained up to end of treatment in both the T-DXd and TPC arms, but that T-DXd was associated with a longer median time to definitive deterioration.

In terms of safety, the CS reported that the profile of T-DXd for this indication was consistent with findings for other indications. The frequency of any TEAE was very high for both T-DXd and TPC (99.5% vs 98.3%); drug-related AEs Grade ≥3 AEs were high but lower for T-DXd ([redacted]) than TPC ([redacted]); and numbers of patients with serious TEAEs were low and similar between arms ([redacted] for T-DXd vs [redacted] for TPC). Drug-related TEAEs associated with discontinuation were higher for T-DXd compared with TPC (15.1% vs 7.0%). The principal reasons for these discontinuations in the T-DXd arm were pneumonitis ([redacted]) and ILD ([redacted]). Drug-related TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively), principally due to the frequency of neutropenia in the TPC arm: [redacted] in the T-DXd arm vs [redacted] in the TPC arm leading to dose reductions; and [redacted] in the T-DXd arm vs [redacted] in the TPC arm leading to dose interruptions. Drug-related TEAEs with the outcome of death were also higher in the T-DXd arm compared with the TPC arm (1.9% vs 0%). The CS also reports that, across both the T-DXd and TPC arms, the frequency of TEAEs was high in [redacted] of treatment, but declined thereafter up to [redacted], and increased again from cycle ≥8.

The company did not conduct a meta-analysis due to the absence of any similar, relevant trials. The company also did not conduct an ITC given the availability of only a single additional trial comparing T-DXd with a potentially relevant comparator, SG, in a relevant subgroup (HER2-low/HorR-negative/triple negative breast cancer [TNBC]) (ASCENT). The company argued that there was likely to be only a small sample of patients from the DESTINY-Breast04 and ASCENT trials who would be eligible for such an analysis and the findings from any such analysis would be highly uncertain.

5 COST EFFECTIVENESS

This section describes the company's economic model and the resulting cost-effectiveness estimates for T-DXd versus TPC in adult patients with HER2-low u/mBC after at least one line of prior chemotherapy in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting. This section also presents the EAG's critical appraisal of the updated model post-clarification, and the methods and results of additional exploratory analyses undertaken by the EAG.

5.1 EAG's comment on company's review of cost-effectiveness evidence

5.1.1 Company's search objective and methods

Appendices G, H and I of the CS report the reviews of economic studies, HRQOL and cost and resource use evidence respectively. All three reviews were informed by the same set of literature searches (reported in Section G.1.1 of the CS), conducted initially in February 2022 before being updated in January 2023 (this time as separate searches, reported in the reference pack accompanying the company's clarification response).

The sources searched included all the key databases recommended by NICE as well as relevant conference proceedings and the websites of international HTA agencies.

As with the clinical searches, the searches appear well-designed. Methodological filters used to identify relevant study types were modified from their original published form, however this is unlikely to have compromised their sensitivity, so the EAG is broadly satisfied they would have retrieved most studies eligible for inclusion.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria used by the company are presented in CS Appendix G Table 36 for the cost-effectiveness studies, Appendix H Table 43 for HRQoL studies, and Appendix I Table 49 for cost and healthcare resource studies. The EAG considers the inclusion criteria to be appropriate to capture recent and relevant evidence.

5.1.3 Findings of the cost effectiveness review

The results of the SLR were provided in CS Table 31 for the two identified economic evaluation studies,[33, 34] however these focused on HER2-negative mBC. CS Table 32 reported three NICE STAs related to technologies used in the current treatment pathway for HER2-negative mBC (TA116 for gemcitabine,[7] TA423 for eribulin,[8] and TA819 for sacituzumab govitecan[11]). Therefore, none of the studies were related to the the HER2-low population.

CS Appendix H Table 44 summarises the results from 6 studies identified for utility values, whereas CS Appendix I Table 50 describes the 11 included studies for cost and utilisation data. For both categories, the SLRs were used alongside more targeted searches to inform the model parameters as detailed through this section.

5.1.4 Conclusions of the cost effectiveness review

As no models were identified that fully addressed the decision problem, the company built a *de novo* model which is described and critiqued in Section 5.2.

5.2 Summary of the company's submitted economic analysis

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft® Excel. The company submitted an updated model in response to the clarification request.[15] The EAG report describes the company's updated post-clarification model, but for transparency we have indicated where this differs from the version described in the company's original submission.

The company also submitted an exploratory cost-minimisation analysis comparing T-DXd to SG in the HorR-negative subgroup, but as this was an entirely separate model from the cost-effectiveness analysis, it is described separately in Section 5.2.7.

5.2.1 Population

The population considered in the model is adult patients with HER2-low u/mBC after at least one line of prior chemotherapy in the metastatic setting or where recurrence occurs within 6 months of chemotherapy given in the adjuvant or neoadjuvant setting. The baseline characteristics for patients in the model are based on the FAS of the DESTINY-Breast04 trial and are summarised in Table 22. The model includes both male and female patients with the proportion of female patients being 99.6% and the mean age being 56.50 years.

No subgroup analyses are presented for the cost-effectiveness analysis. The EAG notes that the cost-effectiveness model does not provide the facility to consider outcomes separately for the HorR-positive and HorR-negative subgroups of the target population.

Table 22 Baseline characteristics for the modelled population (reproduced from CS, Table 34)

Characteristic	Value (SD)	Source	Use in model
Mean age, years	56.50 (10.89)	DESTINY-Breast04 FAS[14]	Used to inform the estimation of background mortality and measurement of disease severity modifier.
Proportion female, %	99.60		
Mean weight, kg	[redacted] (13.57)		Used to inform the calculation of drug dosing and subsequently, drug costs (those dosed according to weight or BSA).
Mean body surface area (BSA), m^2	[redacted] (0.19)		

Abbreviations: body surface area (BSA); FAS, full analysis set; SD, standard deviation

5.2.2 Interventions and comparators

The intervention is T-DXd by intravenous infusion given once every 3 weeks (i.e., on day 1 of a 21-day cycle) at a dose of 5.4mg/kg in a secondary care setting. T-DXd is assumed to be given until progression or unacceptable toxicity which is in accordance with the SmPC and the treatment protocol of the DESTINY-Breast04 trial.[13, 21]

The comparator in the model is the TPC arm of the DESTINY-Breast04 trial which allowed patients to have any one of 5 single-agent chemotherapies. The mix of chemotherapies within the TPC 'basket' of therapies as represented in the model is summarised in Table 23. The CS states the dosing regimens assumed in the cost-effectiveness model are aligned with the SmPCs for these drugs to reflect the dose patients are expected to receive in the UK. The CS states that these are consistent with the doses specified in DESTINY-Breast04 for all drugs except gemcitabine. As gemcitabine is not licensed in the UK as a monotherapy, but is instead licensed in combination with paclitaxel, the dosing regimen is assumed to be equivalent to that given when it is used in combination with paclitaxel. The EAG however, noted that for some of the other treatments (e.g. paclitaxel and nab-paclitaxel) more than one possible dosing regimen was specified in the DESTINY-Breast04 trial to allow for different dosing regimens in different countries, but only the regimen consistent with the SmPC in the UK was possible within the model (see clarification response B39).[15] All single-agent chemotherapies within the TPC comparator are assumed to be given until disease progression or unacceptable toxicity with duration of time on treatment estimated from DESTINY-Breast04 (see Section 5.2.5.1.3).

Table 23 Dose regimens for TPC (adapted from CS, Table 53 and clarification response Table 30)

Single-agent chemotherapy	% of TPC [a]	Dosing Regimen used in the model
Eribulin	51.7%	1.23[b] mg/m^2 IV on Days 1 and 8; cycled every 21 days
Capecitabine	20.9%	1250 mg/m^2 PO twice daily on Days 1-14; cycled every 21 days
Nab-paclitaxel	9.9%	260 mg/m^2 IV; cycled every 21 days
Gemcitabine [c]	9.3%	1250 mg/m^2 IV on Days 1 and 8; cycled every 21 days
Paclitaxel	8.1%	175 mg/m^2 IV on Day 1; cycled every 21 days

[a] *The company updated the mix of treatments in the post clarification model using data from the SAS instead of the FAS, see clarification response B37, but the proportions were very similar to those specified previously in CS, Section B.3.2.3*
[b] *1.23 mg of eribulin is equivalent to 1.4mg of eribulin mesylate*
[c] *Gemcitabine is only recommended for use in combination with paclitaxel. Therefore, dosing is inconsistent with the UK label, where gemcitabine is used in combination with paclitaxel (175 mg/m2) IV on Day 1, followed by gemcitabine (1250 mg/m2) IV on Days 1 and 8, cycled every 21 days.*
Abbreviations: IV, intravenous; PO, orally; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

SG was not included as a comparator in the main cost-effectiveness comparison. In response to the clarification request, the company also provided an exploratory cost-minimisation comparing T-DXd to SG in the HorR-negative subgroup.[15] As this was a completely separate analysis from the main cost-effectiveness analysis, this is described separately in Section 5.2.7.

5.2.3 Perspective, time horizon and discounting

The model takes an NHS and PSS perspective for costs and the benefits considered are QALYs gained by patients, with caregiver QALYs not included. Costs and QALYs are estimated over a 30-year time-horizon. Future costs and QALYs are discounted at 3.5% per annum.

5.2.4 Model structure

The company submitted a partitioned survival model (PartSA) which consists of three health states; progression free, post-progression and death (see Figure 15). The occupancies of the progression-free and death states are determined by the cumulative PFS and OS survival curves respectively (see Section 5.2.5.1). All remaining patients reside in the post-progression state. The CS uses the following statements to define the occupancy of the health states:

- Progression-free = PFS
- Post-progression = OS – PFS
- Death = 1 – OS

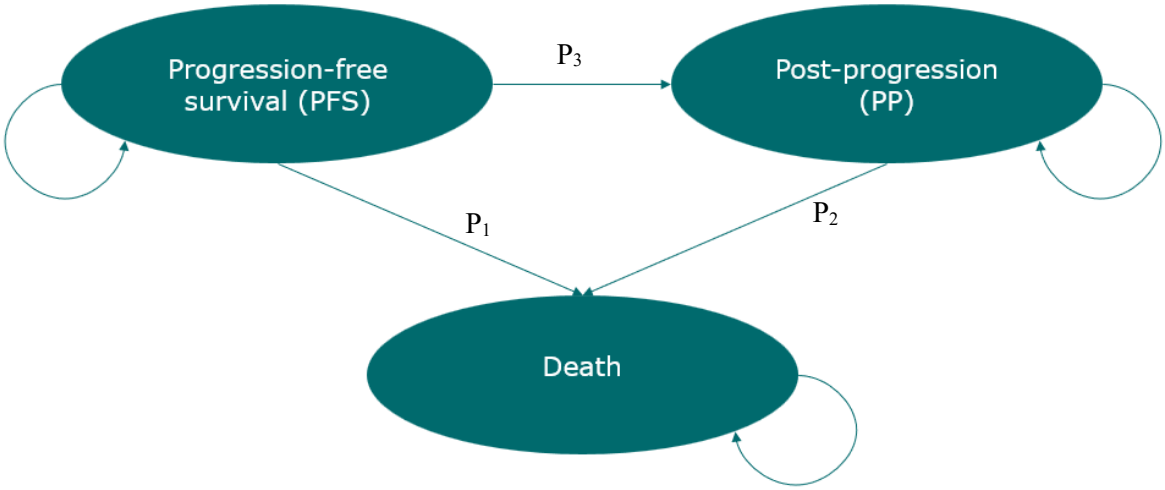
However, the relationship between the occupancies of the various states can also be defined by considering the probabilities of moving between each state during a cycle (i.e., between time t_1 to t_2). If P_1 is the risk of death from the progression-free state, P_2 is the risk of death from the post-progression state and P_3 is the risk of progression each cycle (see Figure 15), then the changes in OS and PFS each cycle can be described as follows;

[1] $OS(t_2) = OS(t_1) - P_1 - P_2$

[2] $PFS(t_2) = PFS(t_1) - P_1 - P_3$

The model tracks the proportion of patients in the progression-free state who remain on treatment which is informed by the time to treatment discontinuation (TTD) curve (see Section 5.2.5.1.3). The model calculates the numbers moving to the death state each cycle (i.e., P_1+P_2) in order to apply costs of terminal care. It also tracks the proportion of the cohort moving to the post-progression state each cycle (P_3) as these are used to estimate subsequent treatment costs. When estimating the number of patients entering the post-progression state, the model assumes that all deaths occur from within the PFS state (i.e. P_2=0). This model assumption is further explained and critiqued in Section 5.3.3.3. The cycle length is 3 weeks to coincide with the treatment cycle for T-DXd. Health-state occupancy is half-cycle corrected, such that the events that move patients between health states are assumed to occur on average half-way through each cycle.

Figure 15 Model schematic (adapted from CS, Figure 22)



The costs included in the model are: drug acquisition and administration costs for T-DXd and the five singe-agent chemotherapies included in TPC; AE costs; costs of subsequent therapies after progression; disease management costs for pre- and post-progression health states; and costs of terminal care.

HRQoL for patients who remain alive is a function of the treatment allocation (T-DXd or TPC) and whether the patient has progressed.

The key structural assumptions employed within the company's model are presented in CS Table 67, with key points presented here:

- The characteristics of patients in the DESTINY-Breast04 trial (e.g., start age, mean weight, height, BSA, proportion female, proportion HorR-negative) are representative of those likely to receive treatment in the NHS
- Overall survival never exceeds that of the general population as the risk of death from any cause in the general population is added to the risk of death predicted by the overall survival curve for each cycle
- Proportion remaining progression-free is capped so it cannot exceed the proportion who are alive
- Proportion remaining on treatment is capped so it cannot exceed the proportion who remain progression-free
- All deaths are assumed to occur from the progression-free state for the purposes of calculating the number of patients entering the post-progression state each cycle
- HRQoL is allowed to differ by treatment received (T-DXd vs TPC) for patients in the same health-state
- HRQoL pre-progression was estimated from the EQ-5D values reported in the DESTINY-Breast04 trial
- Post-progression HRQoL was estimated based on an algorithm using patient characteristics (age and ORR) post-progression in each arm of the DESTINY-Breast04 trial
- Health-utilities are not adjusted to reflect average declines in utility with age reported in the general population
- HRQoL impact of AEs are captured within the treatment specific utility values for the health-states in the base case but additional utility decrements for AEs are explored in scenario analysis
- Vial sharing to reduce waste occurs in 75% of administrations for all intravenous therapies
- Subsequent treatments received differ by treatment arm to capture differences in the DESTINY-Breast04 trial
- Only a subset of subsequent treatments received in DESTINY-Breast04, which the company considered to be reflective of UK clinical practice, are included in the costing of subsequent treatments (see Section 5.2.5.3.4)
- Subsequent treatments are received for a fixed period ([redacted] months) after progression reflecting the weighted average time from first to second progression across both of the DESTINY-Breast04 trial arms.

- Disease management costs within the progression-free state (excluding those related to AEs) are the same across treatment arms (T-DXd and TPC) and are constant over time
- Disease management costs within the post-progression state (excluding subsequent treatments) are the same as in the progression-free state and are constant over time
- All AEs are managed by hospital admission as only grade≥3 AEs are included (with the exception of ILD where any grade is included but again management is assumed to require admission)

5.2.5 Evidence used to inform the company's model parameters

Table 24 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 24 Summary of evidence sources used to inform the model parameters

Parameter type	T-DXd	TPC
Patient characteristics	**Baseline characteristics across both arms of the DESTINY-Breast04 trial**	
PFS	Log-logistic model fitted independently to the PFS KM data of the DESTINY-Breast04 T-DXd arm	Log-logistic model fitted independently to the PFS KM data of the DESTINY-Breast04 TPC arm
OS	Log-logistic model fitted independently to the OS KM data of the DESTINY-Breast04 T-DXd arm	Log-logistic model fitted independently to the OS KM data of the DESTINY-Breast04 TPC arm
	All-cause mortality for the general population, from national life tables for England and Wales,[35] is added to the risk of death predicted by the parametric curve each cycle	
TTD	Generalised gamma model fitted independently to the TTD KM data of the DESTINY-Breast04 T-DXd arm	Generalised gamma model fitted independently to the TTD KM data of the DESTINY-Breast04 TPC arm
AE frequencies	Incidence of AEs in DESTINY-Breast04 T-DXd arm occurring at Grade ≥3 in ≥5% of patients in either arm plus ILD of any grade	Incidence of AEs in DESTINY-Breast04 TPC arm occurring at Grade ≥3 in ≥5% of patients in either arm plus ILD of any grade
AE costs	NHS reference costs[36] for a non-elective short stay hospital admission for all AEs except fatigue for which PSSRU[37] unit cost of 1 hour of hospital nursing time is applied	
AE utilities	Not applied in the base case but scenario analysis applies utility decrements and durations based on literature and previous NICE TAs[38-43]	
Progression-free HRQoL	DESTINY-Breast04 T-DXd arm pre-progression mapped from EQ-5D-5L to EQ-5D-3L and analysed using a generalised linear mixed model	DESTINY-Breast04 TPC arm pre-progression mapped from EQ-5D-5L to EQ-5D-3L and analysed using a generalised linear mixed model
Post-progression HRQoL	Lloyd algorithm[44] using characteristics of the DESTINY-Breast04 T-DXd arm post-progression	Lloyd algorithm[44] using characteristics of the DESTINY-Breast04 TPC arm post-progression

Parameter type	T-DXd	TPC
Patient characteristics	**Baseline characteristics across both arms of the DESTINY-Breast04 trial**	
Drug costs	Unit costs as per existing PAS Duration of treatment as per TTD RDI from DESTINY-Breast04 T-DXd arm Vial sharing of 75% for intravenous therapies (assumption)	Unit costs from eMIT[45] and BNF[46] Duration of treatment as per TTD RDI from DESTINY-Breast04 TPC arm Vial sharing of 75% for intravenous therapies (assumption)
Admin costs	NHS reference costs[36] for day-case (first) and outpatient (subsequent) administrations. Frequency of once per administration for intravenous therapies, once per cycle for capecitabine and once per pack for other oral therapies (tamoxifen).	
Health state costs	Frequency of GP, medical oncologist and clinical nurse specialist contacts and frequency of CT and echocardiogram scans based on TA862 and TA819.[11, 40] Unit costs form NHS reference costs and PSSRU[36, 37]	
Subsequent therapies	DESTINY-Breast04 T-DXd arm for subset of nine therapies used as subsequent therapies	DESTINY-Breast04 TPC arm for subset of nine therapies used as subsequent therapies

RDI, relative dose intensity

5.2.5.1 Treatment effectiveness and extrapolation in the base case

For both OS and PFS, the company used standard parametric survival models (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma), fitted to the Kaplan-Meier (KM) data from the DESTINY-Breast04 trial to reflect expected outcomes in the model both during and beyond the follow-up period available from the trial. Choice of parametric survival model was based on inspection of the KM curves and the log-cumulative hazard plots, measures of statistical goodness-of-fit to the observed data (Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]), visual inspection of the curves in comparison to the KM data and assessment of plausibility beyond the data available using clinical expert validation and external sources. The choice of OS models is described in more detail here than the choice of models for PFS, as the OS data are less mature than the PFS data and therefore the choice of distribution for extrapolation beyond the observed data is more important. However, full details for each are provided in CS Section 3.3.2.

5.2.5.1.1 Overall survival

The company fitted independent models to the OS KM data from the T-DXd and TPC arms of the DESTINY-Breast04 trial because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots. The six parametric models fitted, and the statistical goodness-of-fit scores are summarised in Table 25. The exponential and log-normal models were the least well fitting for T-DXd and TPC, respectively based on AIC and BIC. The company concluded that the log-logistic and Weibull models provided a good statistical fit for both arms despite previously concluding that the Gompertz model provided the best

statistical fit for the T-DXd arm. The company concluded that the log-logistic, Weibull, generalised gamma and Gompertz models were all acceptable based on visual inspection of the curves over a 3-year horizon, as shown in Figure 16 and Figure 17.

The long-term predictions for each parametric survival model are presented in Figure 18 and Figure 19 and summarised in Table 26. The company's UK clinical experts believe that more than 2% of patients are expected to be alive at 5 years and a small proportion (≤1%) of patients are expected to be alive at 10 years in the TPC arm.[47]

Based on the visual fit to the short-term OS KM data, statistical goodness-of-fit and the clinical plausibility of the long-term extrapolations, the company selected the log-logistic model for both treatment arms as the base case. The median survival predicted by the log-logistic distribution is [redacted] and [redacted] months for the T-DXd and TPC arms, respectively (see Table 26). It should be noted that these estimates of median survival have been adjusted to include all-cause mortality after the survival distributions fitted to the KM data. This was achieved by adding the risk of death from any cause, for age and sex matched members of the general population,[35] to the hazard predicted by the survival function each cycle, and then re-estimating the cumulative survival function. The company considered the median survival estimates for the log-logistic distribution to be sufficiently similar to the median OS in DESTINY-Breast04 ([redacted] versus 23.4 for T-DXd and [redacted] versus 16.8 for TPC).

Table 25 Statistical goodness-of-fit scores (OS, independent models) in the FAS population (reproduced from CS, Table 35)[1]

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	765.60	768.81	1389.90	1393.83
Weibull	751.16	757.59	1366.90	1374.74
Gompertz	756.20	762.63	**1366.87**	**1374.71**
Log-logistic	**751.10**	**757.53**	1371.38	1379.22
Log-normal	759.16	765.59	1390.55	1398.39
Generalised gamma	753.01	762.65	1367.59	1379.35

Bold *indicates best statistical fit.*
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 16 Observed versus predicted OS for TPC over a 3-year time horizon in the FAS population (reproduced from CS, Figure 26)

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 17 Observed versus predicted OS for T-DXd over a 3-year time horizon in the FAS population (reproduced from CS, Figure 27)

Figure 18 Observed versus predicted OS for TPC in the FAS population over a 25-year time horizon in the FAS population (reproduced from CS, Figure 28)

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Figure 19 Observed versus predicted OS for T-DXd in the FAS population over a 25-year time horizon in the FAS population (reproduced from CS, Figure 29)

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

Table 26 OS in the FAS population: Predictions by independently fitted distributions in T-DXd and TPC (reproduced from CS, Table 36)

Distribution	Median (months)	1-Year OS*	3-Year OS*	5-Year OS*	10-Year OS*
TPC					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Median time in months and predicted OS are estimated after OS has been adjusted to include general population mortality.*
Abbreviations: FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

5.2.5.1.2 Progression-free survival

For all analyses which informed the economic model, the BICR definition of PFS was used and the dataset analysed was the FAS population. The company fitted independent models to the PFS KM data from the T-DXd and TPC arms of the DESTINY-Breast04 trial because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots. The same set of six parametric models previously considered for OS were also considered for PFS.

After considering the AIC and BIC measures of statistical goodness-of-fit the company concluded that the generalised gamma, log-normal and log-logistic models all provided a good statistical fit for both arms (see Table 27).[1] After visual inspection of the 3-year plots of PFS for similarity with the KM data (see CS, Figure 33 and 34),[1] the company concluded that the log-logistic, generalised gamma and log-normal models provided a good visual fit for the TPC arm, whilst only the log-logistic and generalised gamma models provided a good visual fit for the T-DXd arm.

Table 27 Statistical goodness-of-fit scores (PFS, independent models) in the FAS population (reproduced from CS, Table 37)[1]

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	774.26	777.47	1793.22	1797.14
Weibull	773.77	780.20	1784.94	1792.78
Gompertz	776.20	782.63	1791.19	1799.03
Log-logistic	761.91	768.34	1783.60	1791.44
Log-normal	755.24	**761.67**	1782.50	**1790.35**
Generalised gamma	**754.84**	764.48	**1781.29**	1793.06

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

After considering the long-term extrapolations (CS Figure 35, Figure 36 and Table 38) the company concluded that the log-logistic and generalised gamma models were the most plausible for the TPC arm. Out of these two options, the log-logistic model were selected for both arms because these provided consistency with the parametric distribution selection for OS.[1] The CS reports a median PFS prediction of [redacted] and [redacted] months for the T-DXd and TPC arms, respectively when using the log-logistic distribution. The company considered these predictions to be similar to the observed median PFS in the DESTINY-Breast04 trial of 9.9 months and 5.1 months, respectively. The selected base case models for PFS are summarised in Figure 20.

Figure 20 Base-case extrapolations for PFS in the FAS population (log-logistic, T-DXd and TPC) (reproduced from CS, Figure 37)

Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.

5.2.5.1.3 Time to treatment discontinuation and extrapolation in the base case

The company fitted independent models to the TTD KM data from the T-DXd and TPC arms of the DESTINY-Breast04 trial because they did not consider that it was appropriate to assume proportional hazards between the trial arms based on inspection of the log-cumulative hazards plots, consideration of data maturity and likely independence of treatment discontinuation across arms. The same set of six parametric models previously considered for OS and PFS were also considered for TTD.

After considering the AIC and BIC measures of statistical goodness-of-fit the company concluded that the generalised gamma and log-logistic models provided a good statistical fit for both arms (see Table 28).[1] Whilst the log-normal model provided a good fit for the TPC arm, it was a poor fit for the T-DXd arm and was therefore discounted. After visual inspection of the 3-year plots of TTD for similarity with the KM data (CS, Figures 40 and 41), the company concluded that the log-logistic and generalised gamma models provided a good visual fit for both arms.[1] The company selected the generalised gamma distribution because it provides a good statistical fit and the long-term TTD predictions with the generalised gamma lie in the centre of the range of all distributions (clarification response B6).[15]

The CS reports a median TTD prediction of [redacted] and [redacted] months for the T-DXd and TPC arms, respectively when using the generalised gamma distribution.[1] These predictions are slightly lower than the median TTD in the DESTINY-Breast04 trial reported in the submission as [redacted] months and [redacted] months, respectively.[1] The EAG notes that the mean duration of treatment exposure in the safety

analysis set is reported as being [redacted] months for T-DXd and [redacted] months for TPC (CSR Table 14.1.5.1.1).[21] The selected base case models for TTD are summarised in Figure 21.

Table 28 Statistical goodness-of-fit scores (TTD, independent models) in the FAS population (reproduced from CS, Table 39)[1]

Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Exponential	900.68	903.89	2137.87	2141.79
Weibull	893.62	900.05	2115.29	2123.14
Gompertz	902.68	909.10	2132.04	2139.88
Log-logistic	**870.59**	**877.02**	2108.93	**2116.77**
Log-normal	875.69	882.12	2116.24	2124.08
Generalised gamma	876.46	886.11	**2108.90**	2120.67

Bold indicates best statistical fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan

In response to the clarification request (question B31), the company also provided a scenario analysis in which the mean duration of treatment exposure for each drug was used to estimate a weighted average for drug and administration costs instead of using the TTD curve.[15] This analysis is further described and critiqued in Section 5.3.3.6.

Figure 21 Base-case extrapolations for TTD in the FAS population (generalised gamma, T-DXd and TPC, reproduced from CS, Figure 42)[1]

Abbreviations: KM, Kaplan-Meier; TPC, treatment of physician's choice; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

5.2.5.1.4 Adverse event risks

The company's model includes TEAEs of Grade ≥3 that occurred with an incidence of ≥5% in either treatment arm of the DESTINY-Breast04 trial. In addition, there were two conditions designated as AEs of special interest within the DESTINY trial programme: ILD and LV dysfunction. The incidence of LV dysfunction at any grade was <5% and therefore this AE was excluded from the model. However, ILD of any grade occurred at ≥5% in the TPC arm and therefore ILD was included as an AE in the economic model. The frequencies of AEs included in the model are summarised in Table 29.

Table 29 Adverse event incidence included in the economic model (Grade ≥3 except ILD*) (reproduced from CS, Table 41)

Adverse event, n (%)	T-DXd (n=371)	TPC (n=172)
Interstitial lung disease*	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Increased ALT	[redacted]	[redacted]

**Interstitial lung disease was included, regardless of severity. Interstitial lung disease includes events that were adjudicated as interstitial lung disease and assessed to be related to the use of T-DXd or TPC.*
Abbreviations: ALT, alanine transaminase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

5.2.5.2 Health-related quality of life

5.2.5.2.1 Health-related quality of life associated with model health states

The company's base case applies utility values estimated from the DESTINY-Breast04 trial for the progression-free health state. As EQ-5D-5L was collected in the trial, the company mapped these observations to provide EQ-5D-3L utility scores using the mapping algorithm developed by the NICE DSU which utilises the EEPRU dataset.[48] This is in line with the preferred methods specified in the NICE reference case.[17]

EQ-5D-3L utility scores were analysed using a generalised linear mixed model approach. The final model was determined using a backwards selection approach and it adjusted for treatment indication (T-DXd vs. TPC), ECOG performance status (1 vs. 0), progression status (progressed vs. progression-free) and treatment status (off-treatment vs. on-treatment). The mean treatment-dependent utility value for progression-free and progressed states (see

Table 30) was estimated at the mean timepoint of all included observations ([redacted] days), the mean ECOG value at the baseline and the mean of treatment status.

For the post-progression health state, the company argued that the utility values provided using the generalised linear mixed model fitted to the DESTINY-Breast04 trial were high in comparison to previously accepted utility values for progressed disease in metastatic breast cancer populations. One possible reason given for this was that the number of data points available post-progression was smaller than the number of observations available pre-progression. A second possible reason given was that longitudinal collection of HRQoL was limited to 3 months after either the initiation of a subsequent therapy or the 40 days post treatment follow-up visit, which may not be sufficient time to capture the average decline in HRQoL occurring between the time of progression and death. For these reasons, the company used an algorithm published by Lloyd *et al.* to estimate the expected post-progression utility by trial arm.[44]

The regression coefficients included by the company in their implementation of the Lloyd algorithm were age, treatment response (ORR) and progression (which was set to progressed for both arms). This resulted in a higher utility value for progressed-disease in the T-DXd arm, mainly due to the higher incidence of a treatment response being recorded for T-DXd than TPC (52.3% versus 16.3%). The company argued that this was reasonable because patients who achieved a treatment response would have had a lower tumour burden at the point at which they progressed. The EAG notes that the company also assumed different ages in the T-DXd and TPC arms which also contributed to the difference in post-progression utility between T-DXd and TPC, but to a lesser extent. The difference between the utilities from the T-DXd and TPC arms reduced from 0.0446 to [redacted] when the mean age across both arms was used (see clarification response B18) instead of the median age specific to each trial arm.[15]

The company also explored alternative utility values for the post-progression health states in three scenario analyses. Firstly, the company explored using the data from the treatment specific estimates from the DESTINY-Breast04 trial for the post-progression health state utilities in a scenario analysis. Secondly, in response to the clarification request, the company also provided a scenario analysis in which the post-progression utilities were still estimated using the Lloyd algorithm,[44] but the average age across the whole trial cohort was applied.[15] This still resulted in lower post-progression utilities for TPC (see

Table 30) as the ORR applied was still trial arm specific. Finally in response to a clarification request, the company also explored a scenario analysis in which trial arm specific post-progression utility values are applied only for the first 12 months (17 cycles), and thereafter a pooled utility value is applied for the remainder of the model time horizon.[15] In practice this was implemented by calculating the QALY gain over 12 months for patients progressing on T-DXd compared to those progressing on TPC, which the company estimates to be [redacted] QALYs (see clarification response B20). This is calculated as a utility difference of 0.0447 being applied for 17 cycles (~1 year) to the proportion of the PFS events that were progressions ([redacted]). This is then applied as an adjustment at the time of progression, with the utilities for the progressed-disease state being the same in both arms. The EAG notes that the non-treatment specific utility applied to both arms after the first year is based on the average across both arms rather than the utility for the TPC arm. This means that the effective utility after progression is 0.596 for the TPC arm, and [redacted] ([redacted]) for the T-DXd arm in the first year after progression, returning to 0.596 thereafter. The utility data for the health states applied in the base case and in these three scenario analyses are summarised in

Table 30.

Table 30 Summary of utility values for cost-effectiveness analysis (adapted from CS, Table 51 with additional data from clarification response B20)

State	Utility value: mean (SE)	95% confidence interval	Source
Base case			
Progression-free T-DXd TPC	[redacted]	[redacted]	DESTINY-Breast04 trial outcomes mapped from EQ-5D-5L to EQ-5D-3L; regression prediction using trial arm specific characteristics pre-progression
Progressed disease T-DXd TPC	0.6101 0.5655	NR NR	Lloyd algorithm[44] using trial arm specific characteristics of the DESTINY-Breast04 trial arms post-progression
Scenario 1 – progressed-disease utilities derived from DESTINY-Breast04*			
Progressed disease T-DXd TPC	[redacted]	[redacted]	DESTINY-Breast04 trial outcomes mapped from EQ-5D-5L to EQ-5D-3L; regression prediction using trial arm specific characteristics pre- and post-progression
Scenario 2 – progressed-disease utilities from Lloyd using mean age across the trial cohort*			
Progressed disease T-DXd TPC	[redacted]	NR NR	Lloyd algorithm[44] using trial arm specific estimates of ORR from the DESTINY-Breast04 trial arms post-progression but average age across whole trial cohort
Scenario 3 – progressed-disease utilities are trial arm specific only for the first year*			
Progressed disease T-DXd in year 1 TPC in year 1 Both arms thereafter	[redacted] 0.596 0.596	NR NR NR	Lloyd algorithm[44] using trial arm specific characteristics from the DESTINY-Breast04 trial arms post-progression in the first year after progression but average characteristics whole trial cohort thereafter

**Progression-free utilities remain at their base case values in each of the scenario analyses*
Abbreviations: NR, not reported; SE, standard error; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

5.2.5.2.2 Health related quality of life associated with adverse events

The company's base case assumes that any HRQoL decrement associated with AEs is captured within the treatment specific utilities for the progression-free health state. Additional utility decrements for specific adverse events are explored in a scenario analysis and these can be found in CS, Table 50. These are applied as one-off decrements in the first cycle with durations ranging from 15 days to 58 days.

5.2.5.3 Resources and costs

The resource use and costs included: drug acquisition and administration costs for T-DXd and the five singe-agent chemotherapies included in TPC; AE costs; drug acquisition and administration costs for subsequent therapies after progression; disease management costs for pre- and post-progression health states; and costs of terminal care.

5.2.5.3.1 Treatment costs

The company states that there is a confidential simple discount PAS in operation for T-DXd resulting in a fixed net price of £[redacted] per 100mg vial. This is equivalent to a [redacted]% discount relative to the £1455 list price. Unless otherwise stated, all costs for T-DXd in this report use the PAS price.

The company calculated the cost per cycle, when assuming no wastage, by using the mean weight to calculate the cost per patient and assuming a proportionate reduction in the cost to reflect the RDI reported in DESTINY-Breast04 ([redacted]%), which allowed dose reductions to manage toxicities. This gave a cost of £[redacted] per cycle when assuming no wastage. However, in their base case they also made the assumption that vial sharing to reduce wastage only occurs in 75% of administrations. In the 25% of cases without vial sharing, the company used the mean and standard deviation for weight reported in DESTINY-Breast04 to calculate the average number of vials required (3.92 vials when assuming that weight is normally distributed) resulting in an average cost per cycle of £[redacted] without vial sharing. This gave an average cost of £[redacted] per cycle for the company's base case assumption of 75% vial sharing. The company's assumptions for drugs costs for T-DXd are further discussed in Section 5.3.3.7.

For TPC, the company used a similar approach to estimate drug costs for intravenous therapies as that used for T-DXd, with vial sharing assumed to occur in 75% of administrations, and doses based on the mean patient characteristics (weight or BSA as appropriate) when assuming no wastage and the distribution of patient characteristics when assuming wastage (assuming weight and BSA are normally distributed). For capecitabine, the average BSA was used to estimate the average dose in mg, with the cost based on the cost per mg, thereby assuming no wastage due to pack size or dose per tablet. This approach is critiqued in Section 5.3.3.8. The company again applied the RDI reported in DESTINY-Breast04 to reflect the actual dose received relative to the planned dose for each of the 5 single-agent chemotherapies within the TPC comparator. The company's estimation of the RDI for TPC therapies is further described and critiqued in Section 5.3.3.8. The company's analysis does not include the PAS for eribulin as this is commercially confidential, however, this comparator PAS and the ICERs when incorporating this comparator PAS are provided in a confidential appendix to this report. Unit costs for all other comparators included in the model can be found in CS, Table 52.

Table 31 Dosing schedules and cost per 21-day treatment cycle (adapted from CS, Table 54)

Treatment	Dose	Doses per cycle	Relative dose intensity (RDI)	% vial sharing	Cost per cycle	Source (RDI)
T-DXd	5.4 mg/kg	1	[redacted]%[b]	75%	[redacted][a]	DESTINY-Breast04[7]
Weighted TPC	-	-	-	-	£1034.04[d] / £995.89[e]	-
Components of TPC						
Capecitabine	1250 mg/kg	28	[redacted]%[c]	N/A	£38.12	DESTINY-Breast04[7]
Eribulin	1.23 mg/m^2	2	[redacted]%[c]	75%	£1,786.55	DESTINY-Breast04[7]
Gemcitabine	1250 mg/m^2	2	[redacted]%[c]	75%	£503.49 / £93.33[e]	DESTINY-Breast04[7]
Paclitaxel	175 mg/m^2	1	[redacted]%[c]	75%	£30.56	DESTINY-Breast04[7]
Nab-paclitaxel	260 mg/m^2	1	[redacted]%[c]	75%	£529.18	DESTINY-Breast04[7]

Abbreviations: RDI, Relative dose intensity; T-DXd, trastuzumab deruxtecan; TPC, the physician's choice.
Note: [a] Cost per cycle includes the PAS on the list price of T-DXd.
*[b] For T-DXd: relative dose intensity (%) = dose intensity/planned dose intensity × 100, where planned dose intensity for T-DXd = 5.4 mg/kg / Duration of exposure (day) * cycle length in days * expected number of cycles. Cycle length is 21 days and number of cycles expected is based on the duration of treatment exposure. The figure in the CS, Table 54 is given as [redacted]% but [redacted]% is used in the model and presented in CS, Table 22 so we presume this was a typo and [redacted]% is the correct figure. The figure given in CS Table 10.1 is [redacted]*
[c] For TPC: relative dose intensity (%) = dose intensity / planned dose intensity × 100, where planned dose intensity (units/cycle lengths in weeks) = planned cumulative dose (units)/planned duration of exposure (day)/cycle length in days. Due to different cycle durations among the individual TPC treatments, relative dose intensity is not presented for the overall TPC arm.
[d] TPC cost per cycle is weighted by the distribution of treatments in the TPC arm. This was initially based on all screened patients as presented in CS, Table 14, giving a cost of £987.24, but was updated post clarification to be based on the safety analysis set, as presented in Table 30 of the clarification response, giving the average cost presented here.

[e] This cost was given as £93.58 in the original submission. This was updated in the post clarification model, but was an error was introduced in the updated model leading to a cost of £503.49. When the EAG corrected this error, the cost was £93.33. See Sections 4.3.3.1 and 4.4.2.1. The Weighted TPC cost per cycle is £1034.04 without the EAG correction and £995.89 after the EAG correction.

5.2.5.3.2 Drug administration costs

For T-DXd and intravenous components of TPC, the company assumes day-case administration for delivering a simple parenteral chemotherapy (HRG code SB12Z) for the first cycle (£381.97) and outpatient administration (£281.11) for all subsequent cycles.[36] The administration time is assumed to be 90 minutes for the first administration and 30 minutes or less for subsequent administrations. For capecitabine, which is an oral therapy the company assumed one secondary care appointment for

delivering an exclusively oral chemotherapy (HRG code SB11Z) per cycle.[36] (This was previously once per pack but updated to once per cycle in response to clarification question B35).[15] It is assumed that the first administration would be a day-case admission (£304.62) and subsequent appointments would be outpatient visits (£215.80).[36] RDI is not applied to the administration costs, but only to drug acquisition costs which would be consistent with the company assuming that the RDI reflects reduced (or increased) doses given according to the planned schedule rather than doses being skipped or delayed. The company's assumptions for administration costs for capecitabine are further discussed in Section 5.3.3.9.

5.2.5.3.3 Medical resource use associated with health state

The company's economic model assumes identical resource use for the progression-free and post-progression health states (see CS, Table 56). Briefly, the company assumes contact with a GP, a medical oncologist and a clinical nurse specialist once per month. It assumes four computerised tomography (CT) scans and four echocardiogram scans per year. The EAG's critique of these assumptions can be found in Section 5.3.3.16.

5.2.5.3.4 Subsequent treatment costs for progressed patients

Following disease progression, new patients entering the post-progression state are allocated a cost for subsequent therapies. The proportion of patients receiving subsequent therapies and the mix of subsequent therapies received was based on data from the DESTINY-Breast04 trial with arm specific estimates being used in the company's base case and an average across both arms explored in the company's scenario analysis. The nine subsequent therapies included from DESTINY-Breast04 are summarised in Table 32. The duration of subsequent therapy was based on the difference between median PFS and median PFS2, where PFS2 is defined as time from randomisation to progression or death on next-line therapy. The company provides this by trial arm ([redacted] months for T-DXd and [redacted] months for TPC) but then estimates a weighted average across both arms to give a duration of subsequent treatment of [redacted] months (see CS, Table 59) which is applied to both arms in the model. The resulting average cost of subsequent therapies, which is applied as a one-off cost for patients entering the post-progression state, is similar across arms at £[redacted] for T-DXd and £[redacted] for TPC.

Table 32 Costs of subsequent treatments (adapted from company clarification response, Table 34)

Treatment	Distribution over trial period (%)*		Dose	Cost per cycle (3 weeks)	Admin cost per cycle (3 weeks)
	T-DXd (n=373)	TPC (n=184)			
Subsequent treatments	[redacted]	[redacted]	-	-	-
Chemotherapy					
Paclitaxel	[redacted]	[redacted]	175.0 mg/m^2	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	1250.0 mg/m^2	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	1250.0 mg/m^2	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	1.2 mg/m^2	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	60.0 mg/m^2	[redacted]	[redacted]
Epirubicin	[redacted]	[redacted]	100.0 mg/m^2	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	400.0 mg/m^2	[redacted]	[redacted]
Endocrine therapy					
Tamoxifen	[redacted]	[redacted]	20.0 mg	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]	500.0 mg	[redacted]	[redacted]

[a] *The figure implemented in the model is [redacted] instead of [redacted] which the EAG believe to be a transcription error and has therefore corrected (see Section 5.3.1).*
[b] *The figure implemented in the model is [redacted]% instead of [redacted]% which the EAG assume is a transcription error and this has been corrected (see Section 5.3.1)*

5.2.5.3.5 AE costs

The model assumes that all AEs included in the economic analysis are managed by hospital admission (see CS, Table 57).[1] The rationale for this is that only grade ≥3 AEs are included in the model, although the EAG notes the exception that ILD of any grade was also included. For fatigue, the company assumes 1 hour of hospital nurse time. For all other AEs, the company assumes a non-elective short-stay admission. The EAG's critique of the company's AE costs is provided in Section 5.3.3.16.

5.2.5.3.6 Terminal care costs

The model includes the costs of terminal care to all patients of £4,856 which is specific to breast cancer patients and was based an estimate from Round et al. (2015),[49] which has been uplifted to current prices using NHS cost inflation indices.[37] These are applied to all deaths occurring in the model including those arising from the inclusion of general population mortality risks.

5.2.5.4 Model validation and face validity check

The company describes their validation approach as including discussion with an advisory board comprising three UK clinicians and two health economics experts regarding DESTINY-Breast04 trial generalisability and results, key clinical inputs and model assumptions. The CS reports that model verification was undertaken via internal validation comparing model outputs with the trial results and external validation via the advisory board. No assessment of cross validity was possible due to a lack of published cost-effectiveness analyses addressing the same decision problem to compare against.

5.2.6 Cost effectiveness results

All results presented in this section include the company's agreed PAS for T-DXd and include the company's amendments to the model following the clarification process. The company has presented evidence to support a QALY weight of 1.2, based on their assessment of the severity modifier. The company's evidence to support this severity modifier is further discussed in Section 5. The EAG has presented company results both with and without this QALY weight.

Central estimates of cost-effectiveness

The company's base case cost-effectiveness results are presented in Table 33, which shows the probabilistic estimates of the company's base case estimated using the average costs and QALYs across 1000 probabilistic sensitivity analysis (PSA) samples when the model was rerun by the EAG. Total costs, QALYs and ICERs were judged to have been already converged after running the PSA 1,000 iterations.

The probabilistic version of the model suggests that T-DXd is expected to generate an additional [redacted] QALYs at an additional cost of £[redacted] per patient compared to TPC resulting in an ICER of [redacted] per QALY gained ([redacted] when the QALY weight is 1.2). The deterministic version of the model produces a slightly lower ICER ([redacted] per QALY gained without QALY weight). QALY gains relate to differences in survival ([redacted] additional life years gained on T-DXd), and differences in utility values based on the treatment received as discussed in Section 5.2.5.2.1.

Table 33 The company's base case results

Technology	Life years gained	QALYs accrued	Total costs incurred	Incremental			ICER	ICER with 1.2x QALY weight
				Life years	QALYs	Costs		
Probabilistic model (1000 runs by the EAG)								
TPC	[redacted]	[redacted]	[redacted]	-	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,217	£35,181
Deterministic model								
TPC	[redacted]	[redacted]	[redacted]	-	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,989	£34,991

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

The company presents disaggregated outcomes for the deterministic model in terms of costs accrued by different elements and QALYs accrued in different health states. These results are presented in Table 34. The differences in costs are primarily associated with the acquisition cost of T-DXd whilst the additional QALY gain is mainly a consequence of additional time spent and higher utility values in the progression-free health state on T-DXd compared to TPC.

Table 34 Base case disaggregated outcomes for company's base case (deterministic model)

Description	T-DXd	TPC	Incremental
Disaggregated costs (discounted)			
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Resource use costs related to progression-free	[redacted]	[redacted]	[redacted]
Resource use costs related to post-progression	[redacted]	[redacted]	[redacted]
Adverse event related costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
Progression-free health state	[redacted]	[redacted]	[redacted]
Post-progression health state	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Uncertainty around the central estimates of cost-effectiveness from the probabilistic sensitivity analysis

Figure 22 presents the cost-effectiveness plane for the company's base case PSA, and Figure 23 shows the corresponding cost-effectiveness acceptability curve (CEAC) (both based on the EAG's re-run of

1000 PSA samples). The EAG's re-run of the company's PSA suggests that the probability that T-DXd generates more net monetary benefit than TPC at a WTP threshold of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted] respectively. The same probabilities are [redacted] and [redacted] respectively when a QALY has 1.2x weight.

Figure 22 Company's base case PSA scatterplot (run by the EAG)

Figure 23 Company's base case CEAC (run by the EAG)

5.2.7 Company's deterministic sensitivity analyses

The company's deterministic sensitivity analyses were rerun by the EAG post-clarification and are presented using a tornado plot (Figure 24 and Figure 25 for a QALY weight of 1 and 1.2 respectively). The analyses are performed by using the lower and upper bounds of 95% confidence intervals assuming that the standard error was set as 10% of the mean.

The company's results show that the parameters which had the biggest impact on the ICER were: the average weight for patients; relative dose intensity for T-DXd; health state utility values associated with progressed state for both TPC and T-DXd; and the utility value used for patients on TPC and still in the progression-free state. None of the parameter ranges explored decreased the ICER below £30,000 per QALY gained regardless of the QALY weight used.

Figure 24 Tornado plot showing OWSA results for the company's post-clarification base case at a QALY weight of 1

Figure 25 Tornado plot showing OWSA results for the company's post-clarification base case at a QALY weight of 1.2

5.2.8 Company's scenario analyses

5.2.7.1 Scenario analyses for the cost-effectiveness analysis

The company carried out several scenario analyses in the original CS whose results were not updated post-clarification; this was in addition to other scenario analyses requested by the EAG in the

clarification process. Table 35 presents the results of these scenario analyses rerun by the EAG for the former set of analyses and reproduced for the latter. All the ICERs reported within the text of this Section are without the QALY weight. The scenarios with the largest impact and increased the ICER were the use of alternative PFS fits of exponential, Weibull, Gompertz, or Generalised gamma for both arms (ICERs between [redacted] to [redacted]), using discount rates of 6% (~[redacted]), assuming post-progression benefit of T-DXd continue only for 1 year (~[redacted]), and decreasing the time horizon to 20 years (~[redacted]). The following scenarios had a large impact but decreased the ICER; using a log-normal distribution for extrapolating OS for both arms (ICER of ~[redacted]), assuming no or 1.5% discounting (~[redacted] to [redacted]), and calculating treatment costs using restricted mean treatment duration (~[redacted]).

The following scenarios had less impact on the ICER (less than [redacted]) compared with the above mentioned scenarios: increasing the time horizon to 45 years, removal of half cycle correction, assuming trial pooled weighted proportions for different subsequent treatments to both arms, inclusion of disutility values for adverse events, changing vial sharing assumptions, using the progressed disease utilities from DESTINY-Breast04 trial, using the exponential distribution for OS extrapolations, and using the trial mean age to calculate the utility values for progressed disease from the Lloyd algorithm.

Table 35 Scenario analyses of the company's post-clarification deterministic results – run by the EAG

Base case	Scenario	Incremental			ICER	ICER with 1.2x QALY weight
		Life years	QALYs	Costs		
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate of 3.5% applied to costs and QALYs	No discounting is applied to costs and QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate of 1.5% applied to costs and QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate of 6% applied to costs and QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon of 30 years	20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	45 years[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Half cycle correction applied	Half cycle correction removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial arm-specific proportions on different	Trial pooled weighted proportions on different	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case	Scenario	Incremental			ICER	ICER with 1.2x QALY weight
		Life years	QALYs	Costs		
subsequent treatments	subsequent treatments					
AE disutilities excluded[2]	AE disutilities included					
Vial sharing 75% for all IV treatments	Vial sharing 50%					
	Vial sharing 100%					
Progressed disease utilities sourced from Lloyd et al. 2006	Progressed disease utilities sourced from DESTINY-Breast04 trial					
Log-logistic OS extrapolations applied to both arms	Exponential					
	Log-normal					
Log-logistic PFS extrapolations applied to both arms	Exponential					
	Weibull					
	Gompertz					
	Log-normal					
	Generalised gamma					
Log-logistic OS and PFS extrapolations applied to both arms	Exponential					
	Log-normal					
Using arm-specific age to calculate the utility values for progressed disease[3]	Using the trial mean age to calculate the utility values for progressed disease					
Post-progression benefit of T-DXd continue for lifetime[4]	Post-progression benefit of T-DXd continue for 1 year					
Treatment costs are calculated using TTD extrapolations for both arms[5]	Treatment costs are calculated using restricted mean treatment duration					

[1]This scenario was reported in the clarification response to question B30
[2]This scenario was reported in the clarification response to question B19
[3]This scenario was reported in the clarification response to question B18
[4]This scenario was reported in the clarification response to question B20
[5]This scenario was reported in the clarification response to question B31
AE - adverse event; ICER - incremental cost-effectiveness ratio; OS - overall survival; PFS - progression-free survival; QALYs - quality adjusted life-years; TTD - time to treatment discontinuation

Base case	Scenario	Incremental			ICER	ICER with 1.2x QALY weight
		Life years	QALYs	Costs		

5.2.7.2 Exploratory cost-minimisation analysis

The company has provided an exploratory cost-minimisation analysis in which it has compared T-DXd to SG in the HorR-negative subgroup. The company has used the same model structure as for the cost-effectiveness analysis. However, in this cost-minimisation analysis, the company has assumed identical clinical outcomes (PFS, OS, TTD, AEs) and identical use of subsequent therapies for T-DXd and SG. Therefore, the only differences in economic outcomes between the T-DXd and SG arms of the cost-minimisation analysis relate to differences in drug acquisition and administration costs, and assuming an RDI of 100% and the list price for SG. The per-cycle cost for T-DXd is as per the main cost-effectiveness analysis. For SG, the company assumes a dose of 10 mg/kg on days 1 and 8 of a 21-day cycle. The company assumes that vial sharing occurs in 75% of administrations, consistent with the assumption for T-DXd and TPC. The company assumes 100% RDI for SG, and the average number of vials required takes into account the distribution of weight across the population. The costs per cycle with and without vial sharing are £[redacted] and £[redacted] respectively giving an average cost per cycle of £[redacted]. The administration cost is £763.94 per cycle in the first cycle and £562.22 per cycle thereafter based on the same reference cost being assumed for administration of SG and T-DXd, but accounting for 2 administrations per cycle for SG. The EAG estimates that this would mean a cost-saving of £[redacted] in the first cycle for T-DXd compared to SG and a cost-saving of £[redacted] for each subsequent cycle.

The total cost-saving over the patient's life-time is dependent on the number of cycles of treatment received, which the company assumes is the same for T-DXd and SG. The TTD curve applied in the cost-minimisation analysis is different to that applied in the cost-effectiveness analysis, because the company has incorporated a TTD curve for the HorR-negative subgroup of the DESTINY-Breast04 trial. This results in a mean duration of treatment of [redacted] cycles or [redacted] months. This compares to a mean duration of treatment of [redacted] cycles, or [redacted] months for T-DXd in the main cost-effectiveness model that includes data on both HorR-positive and HorR-negative patients. The company's cost-minimisation analysis concludes that there is an overall cost saving of £[redacted] for T-DXd compared to SG over the patient's life-time. The EAG has not invested time validating the company's TTD estimate as this is irrelevant as to whether T-DXd is cost saving compared to SG, if the company's assumptions of identical TTD and all other clinical outcomes being equal (PFS, OS, AEs) are accepted. Under these assumptions, only the cost-saving per cycle is relevant. If these assumptions are not accepted, then the company's cost-minimisation approach as a whole is invalid and therefore the robustness of the TTD estimate included within it is irrelevant.

5.3 Critique of company's submitted economic evaluation by the EAG

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS using the company's executable model.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification

The EAG believes the company's updated version of the model to be generally well programmed and free from major errors, and that the model structure and parameter values used are appropriate for the decision problem. However, the EAG identified a number of minor errors which are described in Section 5.3.3.1. The impact of correcting these errors is explored in Section 5.4.

5.3.2 Adherence of the company's model to the NICE reference case

The company's economic analysis of T-DXd compared to TPC is generally in line with the NICE Reference Case. The EAG's summary of the adherence of the company's model to the NICE Reference Case is provided in Table 36.

Table 36 Adherence of the company's economic analysis to the NICE reference case

Element	Reference case	EAG comments
Population	The scope developed by NICE	The population considered in the company's cost-effectiveness analysis (see Section 5.2.1) is consistent with the population specified in the NICE scope. However, the EAG notes that no subgroup analyses are provided for the HorR-negative and HorR-positive subgroups in the cost-effectiveness analysis, despite the scope specifying that SG is a comparator only for the HorR-negative subgroup.
Intervention	As listed in the scope developed by NICE	The intervention is T-DXd at a dose of 5.4mg/kg given intravenously every 3 weeks (see Section 5.2.2) which is consistent with the NICE scope and the SmPC.
Comparator(s)	As listed in the scope developed by NICE	The comparator treatments are represented in the model by the TPC arm of the DESTINY-Breast04 trial. The EAG notes several discrepancies between the TPC comparator and the comparators listed in the NICE scope as discussed in Section 3.3. Anthracyclines, platinum therapies, vinorelbine, and SG were excluded from the TPC comparator arm of the DESTINY-Breast04 trial, whilst being included in the NICE scope. Furthermore, gemcitabine was included in the TPC comparator arm as a single-agent chemotherapy but was not listed in the NICE scope. In addition, eribulin was included in the TPC arm as a second-line or third-line therapy whereas it is specified as a third-line therapy in the NICE scope. The company has also provided an exploratory cost-minimisation model of T-DXd versus SG in the HorR-negative subgroup of the population specified in the scope.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company's approach is consistent with the NICE reference case. Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on carers are not included.
Perspective on costs	NHS and PSS	The company's base case analysis adopts an NHS and PSS perspective. This is therefore consistent with the NICE reference case.

Element	Reference case	EAG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company has not provided a fully incremental analysis comparing T-DXd to each of the comparators specified in the NICE scope. The EAG considers that the company's approach of using a 'basket' of single-agent therapies combined in a single TPC comparator is acceptable in principle, as this approach has been previously accepted in TA819, but notes the inconsistencies between the therapies included in the scope and those included in the TPC arm of DESTINY-Breast04. The EAG considers that the question of whether T-DXd is cost-effective compared to SG in the HorR-negative subgroup may not be adequately addressed by the company's exploratory cost-minimisation analysis because it assumes clinical equivalence between T-DXd and SG. In addition, the cost-effectiveness of SG versus standard care was not estimated specifically for the HorR-negative subgroup in TA819.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A 30-year horizon has been adopted. This is considered by the EAG to be consistent with the NICE reference case as the company's analysis exploring a longer time horizon (40 years) did not materially affect the cost-effectiveness results.
Synthesis of evidence on health effects	Based on systematic review	The company conducted a systematic review, but only one study, DESTINY-Breast04, was identified to inform the clinical outcomes in the model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. Utility values obtained from the EQ-5D-5L in the DESTINY-Breast04 study have been incorporated in the company's economic analysis for the PFS health state. The EQ-5D-5L outcomes from DESTINY-Breast04 have been mapped to EQ-5D-3L general population valuations using the method specified in the NICE methods guide.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	

Element	Reference case	EAG comments
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Data were also available from DESTINY-Breast04 for the post-progression health state using the same approach. However, the company has used an external published algorithm by Lloyd *et al.* to estimate utility values for the post-progression health state. The utility values in the Lloyd *et al.* study were based on standard gamble valuations of vignettes by the general population. Therefore, the utility values for the progressed disease health state are not consistent with the reference case as they are not derived from EQ-5D scores measured in patients themselves.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The EAG considers this to be consistent with the NICE reference case. The company has presented evidence to support a severity modifier of 1.2x. The company has presented ICERs both with and without the severity modifier applied.
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	The company's base case cost-effectiveness analysis generally used appropriate estimates of resource use and unit costs that were consistent with the NICE reference case.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum. This is consistent with the NICE reference case. However, discounting is not applied in the first year of the model.

5.3.3 EAG Critique of the modelling performed by the company

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses. These main issues are detailed in full alongside other more minor issues in Sections 5.3.3.1 to 5.3.3.19.

Box 1 Summary of the main issues identified within the company's health economic model (ranked in the same order as the issues discussed in the executive summary)

(1) Inclusion of eribulin and gemcitabine within TPC (Section 5.3.3.11)
(2) A fully incremental analysis of T-DXd versus both SG and TPC is not provided for the HorR-negative subgroup (Section 5.3.3.2)
(3) Methods used to estimate proportion of patients entering the post-progression and deaths states during each cycle (Section 5.3.3.3)
(4) Extrapolation of OS - Weibull versus log-logistic (Section 5.3.3.4)
(5) Extrapolation of PFS - Generalised gamma versus log-logistic (Section 5.3.3.5)
(6) Extrapolation of TTD - Log-logistic or restricted mean versus generalised gamma (Section 5.3.3.6)
(7) High health utility values for progression-free state relative to general population and use of Lloyd to estimate absolute utility values for post-progression states rather than decrement relative to progression-free (Section 5.3.3.7)
(8) Limiting duration of difference in utility between treatment arms for progressed disease to 6 months and using utility of TPC for both arms thereafter (Section 5.3.3.7)
(9) RDI estimated differently for T-DXd and TPC (Section 5.3.3.8)
(10) Proporition of adminstrations for intravenous therapies where vial sharing occurs (Section 5.3.3.10)

5.3.3.1 Presence of programming and implementation errors

The company made several corrections to the model in response to the clarification request (see clarification response Table 10, and responses to clarification questions B35, B36, B37)[15] which the EAG accepted as appropriate and these are not described further here.

The EAG identified one additional error affecting the company's base case in the post-clarification model. This was an error in the estimate of drug costs when assuming wastage for gemcitabine, whereby the wrong column is being referred to when estimating the weighted cost across patients falling into different weight categories. This was corrected by the EAG in its exploratory analysis (see Section 5.4.2.1 for further details).

The EAG identified that the company was estimating drug costs for capecitabine by using a cost per mg and combining this with the dose in mg required for a patient with average BSA ([redacted]mg for a patient with BSA of [redacted]). This provides a cost per dose of £[redacted], but the calculation does not allow for the fact that the tablets are only available in specific strengths (150mg, 300mg and 500mg). The EAG identified that the dose specified for patients with a BSA of [redacted] in the SmPC is four 500mg tablets plus one 150mg tablet. This provides a cost per dose of £[redacted]. However, this approach still assumes a mean BSA. Therefore, the EAG prefers to use the distribution of doses required according to the distribution of BSA. The EAG notes that the company estimated this on the 'Waste_Calcs' sheet but failed to account for pack size resulting in an incorrect cost of £[redacted] per dose. Once pack size is accounted for correctly, the cost per dose when using the company's assumed distribution of BSA is £[redacted]. This gives a cost per cycle of £[redacted] after accounting for the RDI, compared with a cost per cycle of £[redacted] when using the company's base case approach that assumes average BSA and no restriction for tablet strength.

The EAG identified that the proportion receiving gemcitabine as a subsequent therapy in the T-DXd arm appears to have been entered into the model as [redacted]% instead of [redacted]%. Similarly, the proportion in the model receiving fulvestrant as a subsequent therapy is entered as [redacted]% instead of [redacted]. The EAG corrected these errors as part of their exploratory analyses to ensure that the data in the model matched that presented in Table 34 of the clarification response.

The EAG identified an error in the company's implementation of a scenario analysis exploring the use of agent specific treatment duration data. It does not affect the company's base case. The error is described in Section 5.3.3.6, where the approach to estimating treatment duration is critiqued.

The EAG also identified an error in the company's implementation of the scenario analysis in which treatment specific utilities are applied only to the first year, which does not affect the company's base case. This is further described in Section 5.3.3.7 where the approach to estimating HRQoL in the progressed disease state is discussed.

The company's model includes discounting only from the end of the first year. The EAG considers this incorrect as although discounting rates are often stated as a % per annum, it is logical that they would apply continuously rather than as a discrete value that changes once per year. The company has also adopted an approach which allows the discounting rate to increase each cycle from year 2 onwards, so the logically consistent approach would be to apply discounting using the same method within the first year.

5.3.3.2 Exploratory comparison against SG for HorR-negative subgroup assumes clinical equivalence
Whilst the company has provided a cost-minimisation analysis comparing T-DXd to SG in the HorR-negative subgroup, the assumption of equivalent clinical outcomes, including PFS, OS, AEs and TTD, render the cost-minimisation analysis equivalent to a simple comparison of drug and administration costs per cycle. The assumption of equivalent clinical outcomes is not supported by a robust ITC and is based on a naïve, unadjusted, comparison of OS and PFS results using subgroups of the ASCENT and DESTINY-Breast04 trials (see Section 4.7). The company has also not presented an incremental analysis to assess whether T-DXd, SG or TPC would be the most cost-effective treatment in the HorR-negative subgroup of the HER2-low population. In particular, there is no comparison of T-DXd versus TPC in the HorR-negative subgroup available from the main cost-effectiveness model, as this only provides estimates for the HER-low population as a whole which includes both HorR-positive and HorR-negative patients. This is important given that median PFS and OS in the TPC arm of the DESTINY-Breast04 trial were shorter in the HorR-negative cohort compared with the HorR-positive cohort (see Section 4.3.5). Therefore, the balance of costs and benefits for the different treatment options may not be consistent across the HorR-positive and HorR-negative cohorts due to their different prognosis on TPC. Also, whilst SG was recommended in TA819 on the basis that it was considered cost-effective relative to standard care, with the effectiveness of standard care being informed by the TPC arm of the ASCENT trial, this comparison was not made in a HER2-low population. Therefore, the cost-effectiveness of SG compared to standard care in the HER2-low population is unknown. It is therefore not sufficient to demonstrate that T-DXd is cost-saving relative to SG in the HorR-negative subgroup in order to demonstrate that T-DXd is cost-effective in the HorR-negative subgroup. The EAG therefore considers that the company has not properly addressed the decision problem specified in the NICE scope as it has not assessed the incremental cost-effectiveness of T-DXd, SG and TPC in the HorR-negative subgroup of the HER-low population.

The EAG also notes that the cost-minimisation analysis does not use the average patient weight for HorR-negative patients. If this is lower or higher than the average weight in the DESTINY-Breast04 cohort as a whole, then this could affect the average number of vials required for either T-DXd or SG when assuming wastage. This would therefore affect the cost-savings per cycle. The EAG has explored using the average patient weight for HorR-negative patients in their exploratory analysis for the cost-minimisation approach (see Section 54.2.20).

In addition, the company has assumed that the treatment duration for SG is equivalent to that for T-DXd and that the RDI for SG is 100%. However, the mean time on treatment reported in TA819 for SG was 6.12 months and the RDI was 94.2%. The mean time on treatment for SG in the ASCENT study is [redacted] than the mean time on treatment for T-DXd in the DESTINY-Breast04 study ([redacted] months) but it is unclear if this is driven by [redacted] progression or patients stopping treatment [redacted] progression.

If it relates to [redacted] progression, then a similar time on treatment would be expected when assuming a similar PFS curve. However, if the difference relates to patients stopping treatment for reasons other than progression, then it would be reasonable to apply a [redacted] treatment duration for SG in the cost-minimisation analysis. The EAG has explored applying the mean time on treatment and the RDI for SG from the ASCENT trial, combined with mean time on treatment for T-DXd, in the cost-minimisation analysis (see Section 5.4.2.20).

5.3.3.3 Estimation of patients entering the post-progression and death health states

The model estimates the proportion of the cohort moving to the post-progression state each cycle. This is used to estimate the subsequent treatment costs which are applied as a one-off cost for each patient entering the post-progression health state. However, the PartSA model structure is based around the occupancy of the health states at each time point rather than the transitions between the health states. Therefore, the number of new patients entering the post-progression health state must be inferred from the data available on cumulative PFS at OS and this requires an assumption to be made regarding how many of the deaths occur from the progression free survival state and how many from the post-progression state. The company calculates the new patients entering the post-progression state for any given cycle (P_3 in Figure 15) as the difference between the decrease in OS and the decrease in PFS during that cycle as per equation [3].

[3] $(PFS(t_1) - PFS(t_2)) – (OS(t_1) - OS(t_2)) = P_3$

However, the EAG notes that rearranging the equations [1] and [2], as defined previously in Section 5.2.4, would lead to equation [4]. By comparing [4] and [3] we can see that the company has essentially assumed that the risk of death from the post-progression state (P_2) is zero when calculating the new patients entering the post-progression state.

[4] $(PFS(t_1) - PFS(t_2)) – (OS(t_1) - OS(t_2)) = P_3 – P_2$

This assumption does not appear to be realistic as combining data from CS, Tables 18 and 20 shows that [redacted] of the [redacted] deaths occurring in the TPC arm (FAS) before DCO (data cut-off of 11th Jan 2022) were pre-progression deaths. Similarly, [redacted] of the [redacted] deaths occurring in the T-DXd arm (FAS before DCO) were pre-progression. Based on these data the proportion of deaths occurring from the post-progression state varies from [redacted] fall deaths across the two arms. If we define the proportion of deaths occurring from the post-progression states as α, such that,

[5] $P_2 = \alpha (OS(t_1) - OS(t_2))$ and equivalently,

[6] $P_1 = (1- \alpha) (OS(t_1) - OS(t_2))$,

then we can define P_3 as,

[7] $P_3 = (PFS(t_1) - PFS(t_2)) – (1- \alpha) (OS(t_1) - OS(t_2))$.

The company's approach in which α is assumed to be zero, for the purposes of estimating the subsequent treatment costs, underestimates the proportion of patients passing through the progressed-disease state

and therefore the subsequent treatment costs. Whilst the value of α can be estimated over a fixed period of time, it is likely to be time variant and therefore any assumed value of α is unlikely to be accurate over the whole follow-up period. However, the EAG prefers to assume non-zero values for α, based on the cumulative outcomes reported in the CS for the FAS at the DCO.

In addition, the EAG noted that the purpose of estimating P_3 is to estimate the number of patients entering the progression health state and that this estimate already relates to patients entering the progression state during the time period between the start and the end of the cycle. Therefore, this estimate does not need to be half-cycle corrected, however, in the company's base case the number of newly progressed patients was estimated from the half-cycle corrected health state occupancy. Similarly, the estimates of new patients entering the death state (P_1+P_2) during a cycle is also already calculated across a time period of one cycle and therefore does not need to be estimated from the half-cycle corrected model as it relates to events occurring across a time period and not average occupancy of a health state over a time period. The EAG has therefore corrected the company's method in their exploratory analysis. The EAG's exploratory analyses on this is described in Section 5.4.2.2.

5.3.3.4 Extrapolation of OS

The EAG agrees with the use of the independent models for extrapolating the time-to-event outcomes. The EAG notes that the gamma distribution which is another standard parametric model was not included in the extrapolation of any of the time-to-event outcomes.

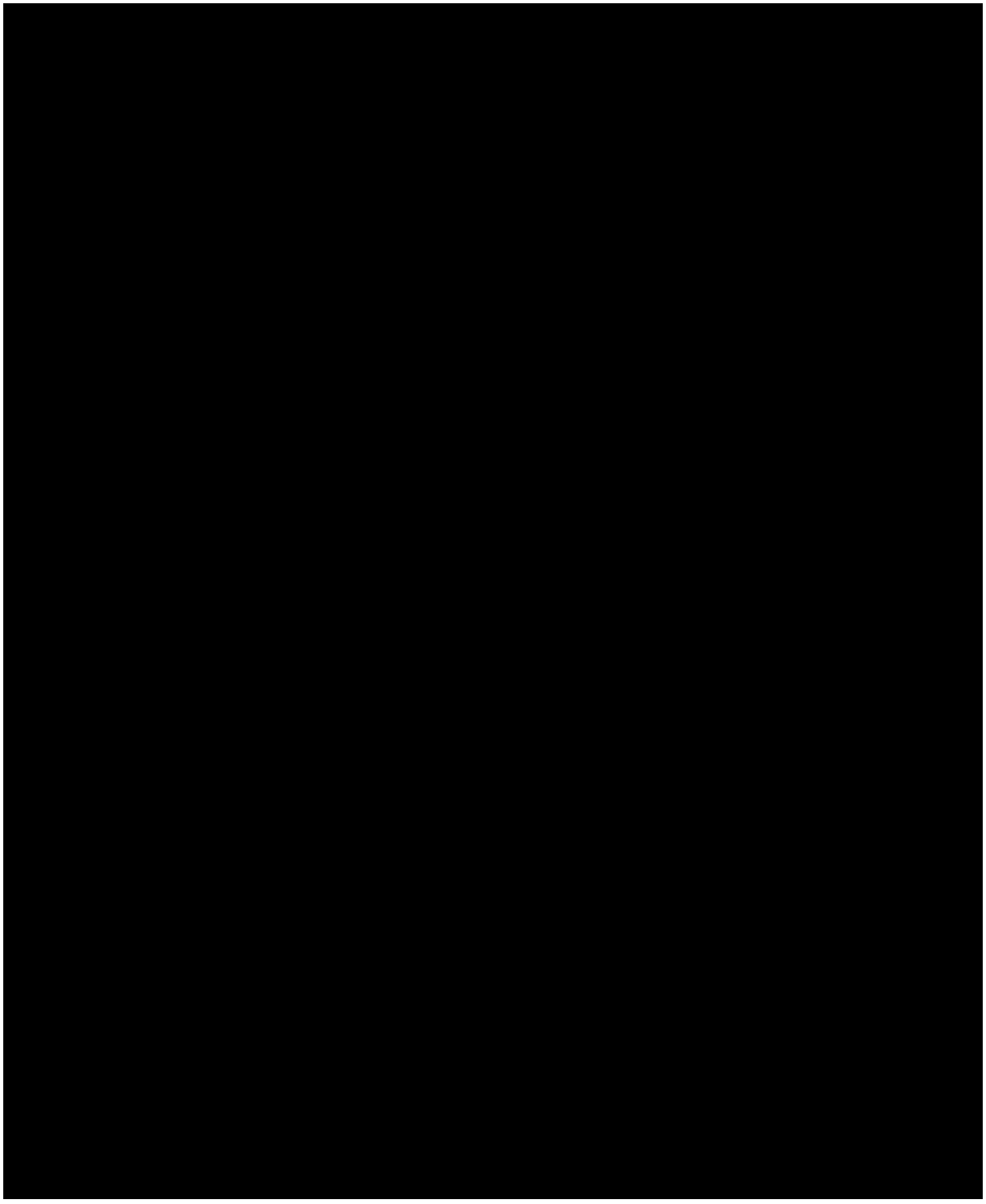
The EAG agrees with the company that the log-logistic and Weibull distributions provide a good statistical fit to both the T-DXd and TPC arm for OS. However, the EAG disagrees with the company's choice of using the log-logistic distribution to extrapolate OS as the base case given the following reasons: (i) similar to the log-normal model which was dismissed by the company due to overestimating the survival probability after approximately 18 months, the EAG judges that the log-logistic model also overestimates the survival probability after approximately 18 months until 27 months for the T-DXd arm which results in a much longer tail compared to most of the other distributions (see Figure 26); (ii) the EAG's clinical advisors judged that ≤1% of patients are expected to remain alive at 10 years; (iii) the smoothed hazard functions do not seem to capture the shape of the unsmoothed hazard functions well due to censoring at the end of the trial. The unsmoothed hazard functions for both arms indicate an increasing trend in the hazard over time, whereas the smoothed hazard functions are unimodal functions with hazard increasing then decreasing.

The EAG notes that one EAG's clinical advisor considered that it is more reasonable that the 5-year survival probability is approximately [redacted] as predicted by the log-logistic model rather than approximately [redacted] as predicted by the Weibull model. The EAG's other clinical advisor considered

an estimate of 5% survival at 5-years was reasonable under current care. Based on the visual fit to the KM data, statistical goodness-of-fit and the clinical plausibility of the long-term extrapolations, the EAG decided to use the Weibull model as the base case (the fitted distribution and the estimated hazard can be found in Figure 26) and the log-logistic model as a scenario analysis.

The EAG acknowledges that the Weibull model may underestimate 5-year survival probability and highlight that the use of Weibull as the base case may provide a pessimistic result for both the T-DXd and TPC arms. The EAG also notes that in response to clarification question B2,[15] the company shows the observed versus predicted OS using a gamma distribution, which seems to provide a reasonable long-term prediction in between the log-logistic and Weibull distribution (see Figure 26). However, because the estimates of the gamma distribution for both arms were not provided by the company in the economic model, the EAG is not able to investigate the impact of using the gamma distribution to extrapolate OS on the ICER.

Figure 26 Observed versus predicted OS for T-DXd using the log-logistic, Weibull and gamma distribution in the FAS population (reproduced from response to clarification question B2, Figure 4.15.38)



5.3.3.5 Extrapolation of PFS

The EAG agrees with the company that the log-logistic and generalised gamma model were the most plausible models for both arms. However, the EAG disagrees with the use of whether the distribution for PFS is consistent with the base case distribution for OS as an additional criterion for choosing the base case for PFS. The EAG acknowledges that OS and PFS data are correlated, but this relationship does not warrant that the hazard function of OS and PFS would follow the same trend. The company's

response to clarification question B2 indicates that the shape of the hazard for OS and PFS are not the same.[15] The log-logistic distribution provides a much longer tail than the PFS KM data compared to the generalised gamma distribution. Given the fact that the PFS data are considered almost mature, the EAG considers that the log-logistic model may be less plausible compared to the generalised gamma distribution. Based on the above considerations, the EAG concludes that the generalised gamma distribution to be the most plausible model for extrapolating PFS.

The EAG notes that when using the generalised gamma distribution to extrapolate, the fitted curve of the TPC arm and the T-DXd arm cross approximately at 5 years (see Figure 27). This reflects the fact that the KM curves between the two arms are about to cross at the end of the trial. To investigate the impact of this crossing, the EAG proposed a scenario analysis imposing a cap on the fitted curves so that from the point of crossing the PFS for the TPC arm is the same as the PFS for the T-DXd arm.

Figure 27 Observed versus predicted PFS for T-DXd using the generalised gamma distribution in the FAS population (reproduced from response to clarification question B2, Figure 4.15.37)

5.3.3.6 Extrapolation of TTD

The EAG agrees with the company that the log-logistic and generalised gamma model were the most plausible models for the base case extrapolation for TTD. The EAG notes that both distributions provide the same median TTD prediction, however the AIC/BIC of the generalised gamma model is 5 points higher than the AIC/BIC of the log-logistic model for the TPC arm indicating that the log-logistic model provides better statistical fit to the KM data.

The company has used the TTD models to estimate duration of treatment in their base case cost-effectiveness analysis. However, they have also provided a scenario analysis in which the duration of treatment is based on the mean treatment exposure reported in the safety analysis set. The EAG notes

that this is akin to a restricted mean and therefore it provides a lower limit for the expected time on treatment. However, the KM curves for TTD suggest that relatively few patients ([redacted] of T-DXd and [redacted] of TPC) remained on treatment at the time of the data cut point (11th Jan 2022), so the bias introduced by not having a treatment end date for every patient is likely to be small.

The EAG also identified an error in the company's implementation, in that they estimated the treatment costs as a one-off cost to be applied in the first cycle of the model, but it then multiplied this by the half-cycled corrected health-state occupancy, such that the one-off cost is not applied to 100% of the patients starting treatment. The EAG corrected this error in its exploratory analysis that incorporated this approach (see Section 5.4.2.1).

Overall, the EAG preferred to explore the mean treatment duration as a scenario analysis representing the lower limit for treatment duration, and a treatment duration based on the log-logistic TTD extrapolation as the upper limit for treatment duration (see Section 5.4.2.5). The EAG has maintained the company's preference for the generalised gamma extrapolation to estimate TTD in its preferred base case.

5.3.3.7 Health utility values

The EAG agrees with the company in the use of the generalised linear mixed model for utility scores. Although the company has not presented the step-by-step selection process for obtaining the final model, based on the code provided (see response to clarification question B17)[15] the EAG is satisfied with the model selection process in principle.

The EAG notes that the estimates of pre-progression utility based on the company's generalised linear mixed model are high ([redacted] for T-DXd and [redacted] for TPC) relative to the utility values for the general population which are incorporated in the company's estimate of the severity modifier (MVH value set + HSE 2014 ALDVMM [Hernandez Alava, et al.][50]). For example, the QALY shortfall calculator includes a utility of 0.840 for women in the general population aged 57 years.[51] The EAG also notes that the estimated mean utility for T-DXd in the progression-free state is [redacted].

The EAG highlights that the utility data used in the generalised linear mixed model include patients in the progressed state but still on-treatment ([redacted] in T-DXd arm and [redacted] in TPC arm, where the numbers were calculated by the EAG using the company's response to clarification question B10),[15] which is contrary to the fact that patients should have discontinued treatment upon progression.

Based on the lack of face validity for high PFS utilities, the EAG therefore decided to use the utility estimates for PFS ([redacted] for T-DXd and [redacted] for TPC) from the summary values by trial arm provided in Table 20 of the company's clarification response (B10)[15] as these were more comparable to the utility values for PFS health-states applied within previous appraisals (see CS, Table 49). These were considered to have greater face validity because [redacted]. Although TA862 was an appraisal of T-DXd as a 2nd line therapy, it was for a HER2-positive population who might be expected to have better HRQoL as they would have benefitted from HER2 targeted therapies in earlier lines of treatment.

The EAG notes that the utility values estimated from the Lloyd algorithm are not consistent with the NICE reference case because they do not represent utilities obtained directly from patients with breast cancer. Instead, a series of vignettes were valued by members of the general population using a standard gamble technique. There were 15 health states specified with the main disease-specific states being stable disease, responding disease and progressed disease. In addition, there were various states which combined stable and responding disease with specific side-effects. A mixed effects model regression analysis was then used to estimate the impact of treatment response, disease progression and the various side effects relative to a base-state of stable disease without side effects. Importantly, progressed-disease health states were not described according to whether the patient had been previously responding to treatment. For this reason, the EAG does not consider it reasonable for the company to apply the pre-progression response rate when calculating the post-progression utility value by trial arm. In addition, given that Lloyd *et al.* present the utility decrement for progressed disease relative to a progression-free health-state (0.272), the EAG considers that it would be more appropriate to apply this decrement to the trial-based estimates of pre-progression utility values, to calculate post-progression utility values that are treatment specific. This would provide estimates of [redacted] and [redacted] for the progressed-disease health states in the T-DXd and TPC arms respectively (estimated by subtracting 0.272 from the progression-free utilities reported in clarification response, Table 20). This approach uses the company's assumption that a difference in utility is maintained between the treatment arms post-progression, due to the higher treatment response reported for T-DXd, which is expected to provide a lower treatment burden at the time of progression.

However, the EAG also notes that in the appraisal of SG (TA819[11]), the committee preferred to assume that any difference in the utilities between treatment arms only persisted for 6 months following progression. This assumption is difficult to implement within a PartSA model. The EAG notes that the company's attempt to restrict the difference in utilities to the first year after progression was incorrectly implemented as the QALY gain was multiplied both by the current occupancy of the health state and by the number of new arrivals. The EAG corrected this error (see Section 5.4.2.1). The EAG prefers to

include this time restriction on the difference between trial arms in the PFS state in its base case (see Section 5.4.2.7), but it also prefers to restrict the difference to the first 6 months after progression, instead of the first 12 months after progression, in line with the assumption accepted by the committee in TA819.

The EAG also prefers to set the baseline utility for the progressed-disease health state to the TPC utility, rather than the average value across both T-DXd and TPC when implementing the scenario with time-limited differences between arms. This is because the QALY gain is being applied to reflect the difference between the arms so this should apply to the TPC utility which should be consistent with the TPC utility when the difference is not time limited.

5.3.3.8 Implementation of RDI when calculating the drug acquisition costs

The company's approach to implementing the RDI is inconsistent between the T-DXd and the TPC arms. In the T-DXd arm, the RDI was calculated relative to the planned dose intensity i.e., 5.4mg/kg, rather than the planned dose in the case report form which allowed for reduced doses in response to AEs. This meant that for T-DXd the RDI was relative to the full dose costed in the model which the EAG believes is correct. However, for the drugs included in the TPC, the RDI applied in the model is the median RDI relative to the planned dose, which was not always the same as the dose costed in the model because the DESTINY-Breast04 trial allowed variation in the doses and dosing schedules. For example, capecitabine could be given as 1000-1250mg/m^2 in the TPC arm of the trial, so if someone had 1000 mg/m^2 as their planned dose, then their individual RDI would be recorded as 100% even though they received only 80% of the 1250mg costed in the model. However, the EAG notes that CSR Table 10.1 provides the mean dose intensity as units per cycle, allowing the RDI to be calculated relative to the dose assumed in the model for each drug. The EAG has explored this as an alternative approach in its base case (see Section 5.4.2.8).

The EAG also notes that the implementation of RDI only applies to drug acquisition costs and not administration costs which would be consistent with an assumption that the RDI reflects reduced doses rather than delayed or missed doses.

5.3.3.9 Drug administration costs for oral therapies

For capecitabine, the company has assumed that patients are seen every cycle and has therefore applied an administration cost once per cycle. The EAG's clinical experts advised that patients receiving oral capecitabine may be seen once per cycle or once every other cycle. The EAG has therefore explored the impact of assuming patients are seen every other cycle in a scenario analysis.

The company's estimate of administration cost for tamoxifen as a subsequent therapy is estimated as one administration visit per pack of tablets, which is roughly once per month (after the company corrected an error in the model in response to clarification question B35).[15] The EAG's clinical advisors stated that patients receiving tamoxifen are usually initiated on treatment in secondary care, with repeat prescriptions managed in primary care, and they are seen every 3 to 6 months in secondary care for staging scans. Therefore, the EAG reduced the frequency of administration appointments for tamoxifen to once every 3 months in its base case.

5.3.3.10 Vial sharing for intravenous therapies

The company has assumed that vial sharing will result in zero wastage in 75% of administrations for T-DXd and intravenous therapies included in TPC. The company's justification is that the NHS England Cancer Drugs Fund clinical lead advised during TA862 that vial sharing is expected to occur in at least 50% of cases for T-DXd, which led to 50% vial sharing being assumed by the committee in TA862. The company further argues that the broadening of usage for T-DXd to the HER-low population is likely to increase the potential for vial sharing and a future increase in the use of vial sharing is part of the NHS Long Term Plan. The EAG believes that it is more appropriate to assume that vial sharing of 50% should be applied given that this was the assumption accepted in TA862.

5.3.3.11 Mix of TPC therapies

Eribulin is only recommended by NICE after two previous lines of chemotherapy, and the clinical advice received by the EAG was that current practice for prescribing eribulin is consistent with the NICE recommendation, with usage restricted to third-line treatment. As the proposed positioning of T-DXd in the CS is for patients who have received prior chemotherapy, it is possible that a proportion of the patients who would be eligible to receive T-DXd, will be those having third-line rather than second-line therapy, especially in the initial period after any positive NICE recommendation. However, in the long-term it is likely that clinicians would want to offer T-DXd at second-line whenever possible and therefore eribulin will not be a relevant comparator for most patients in the long-term. As the company has argued that all of the single-agent chemotherapies included in TPC are of similar efficacy, it seems reasonable to assume that any of the other single-agent chemotherapies could replace eribulin in the TPC comparator without any loss of efficacy on average across the TPC arm. The EAG therefore considers it reasonable to explore scenarios in which eribulin is replaced within TPC by the remaining chemotherapies with the proportion receiving eribulin within DESTINY-Breast04 redistributed across the remaining therapies according to their relative frequency within the DESTINY-Breast04 TPC arm.

The EAG also noted the clinical expert's advice that gemcitabine is not currently prescribed as a single-agent chemotherapy and is instead generally offered in combination with carboplatin. The EAG also noted that in current NICE guidance, gemcitabine is only recommended first-line in combination with

paclitaxel and therefore it would not be considered a relevant comparator for T-DXd which the company proposes for use as a second or later line chemotherapy. This is consistent with gemcitabine not being included in the final NICE scope. The EAG has therefore also explored scenarios in which the proportion receiving gemcitabine is redistributed across the remaining three single-agent chemotherapies having removed eribulin as well. This analysis also makes the assumption that any of the single-agent chemotherapies within TPC can be substituted for another without a significant impact on efficacy which the company states is supported by clinical expert opinion (CS, pages 33, 34, 36 and 176).

The EAG's base case removing both eribulin and gemcitabine is described further in Section 5.4.2.12. Given that the mix of subsequent therapies in UK current practice is not provided in the CS, the EAG has also explored the maximum potential impact of a different mix being offered in practice by assuming 100% of the patients receive either the highest or lowest cost therapies to provide an upper and lower range on the cost of TPC.

5.3.3.12 Dosing regimens for paclitaxel

One of the EAG's clinical advisors noted that it is more common to use a weekly dosing regimen for paclitaxel in which it is given at a dose of 80mg/m^2 on days 1, 8 and 15 of a 28 day cycle, as there is evidence that weekly taxane regimens are more clinically effective.[52] The EAG notes that a weekly dosing regimen of 80 mg/m^2 on day 1 of each week was also permissible in the TPC arm of the DESTINY-Breast04 trial in addition to the regimen of 175mg/m^2 every 3 weeks included in the economic modelling of the TPC arm (see Table 23). The EAG is not aware of any data on the proportion receiving each dosing regimen for paclitaxel within the TPC arm that is available within the CS and the company declined to provide a scenario analysis exploring the impact of assuming that patients receive the alternative dosing regimen (see clarification response to B39). The EAG has explored the potential impact on the ICER of assuming the weekly dosing regimen has been used (see Section 5.4.2.21).

5.3.3.13 Mix of subsequent therapies

The company stated in response to clarification B28 that it had based the mix of subsequent therapies on the therapies patients received following progression in DESTINY-Breast04 which are listed in Table 14.1.3.5.2 of the CSR.[15] They stated that some of the treatments in Table 14.1.3.5.2 are listed separately with their respective salts but these are the same therapeutic agent (e.g., eribulin and eribulin mesylate). They stated that they combined these as a single agent, however, the EAG confirmed that the company had not in fact included drugs listed as their respective salts. For example, [redacted] patients who received eribulin are included in the calculation of the mix of subsequent therapies, but the [redacted] who received eribulin mesylate according to Table 14.1.3.5.2 are not. The EAG has corrected this in

their exploratory analysis by including the respective salts for any subsequent therapies included by the company.

In addition, the company did not provide the requested clarification as to why some treatments received as subsequent therapies in DESTINY-Breast04 were not included in the model. The EAG can understand that including every single treatment received would require considerable effort. However, some of the treatments not included, such as cisplatin (n=[redacted]), exemestane (N=[redacted]), letrozole (N=[redacted]) and cyclophosphamide (N=[redacted]), were excluded despite being received in a higher number of patients than some of the included therapies such as tamoxifen (N=[redacted] patients). The EAG was unable to correct these omissions in their exploratory analyses in the time available as this would have involved introducing additional subsequent therapies into the model.

5.3.3.14 Doses for subsequent treatments

The EAG noted that there were several discrepancies between the dosing regimens for subsequent therapies assumed in the model and either the doses specified in the relevant SmPC or the advice from clinical experts regarding the use of these therapies in clinical practice. For example, fulvestrant is assumed to be given once per 3-week cycle, but the SmPC specifies monthly dosing (with an additional dose at 2 weeks in the first cycle). Carboplatin is assumed to be given once per 3-week cycle, but the SmPC states it should in general be given more frequently than once every 4 weeks. Clinical experts said that 3-weekly usage of carboplatin is consistent with clinical practice but it is often given with gemcitabine rather than as a single agent. The dose for epirubicin is 100mg/m^2 once per 3 week cycle, but a lower dose for epirubicin of 75mg/m^2 was assumed in TA819. The EAG's clinical advisors noted that the dose of 75mg/m^2 is the dose used when epirubicin is given in combination with cyclophosphamide, but epirubicin is often given as a single agent at later disease stages at a lower dose of 20-30 mg/m^2 weekly. The dose of vinorelbine assumed is 60mg/m^2 by intravenous infusion, giving a total dose of 100mg despite the SmPC stating a dose of 25-30mg/m^2 with a maximum dose of 60mg. However, the EAG's clinical advisors stated that intravenous vinorelbine has been largely superseded by a 60mg/m^2 oral dose. Exploring these alternative dosing regimens for subsequent treatments is unlikely to have a significant impact on the ICER as usage of these treatments is similar across arms and subsequent treatment costs are not a significant driver of the ICER. Therefore, the EAG did not attempt to correct or explore alternative dosing regimens for subsequent treatments themselves.

For any treatment where the EAG has corrected the cost in the TPC arm, e.g., for capecitabine, the EAG has also used the corrected cost when the same treatment is used at the same dose as part of subsequent therapies.

The EAG also notes that the company has assumed no wastage when treatments are used as subsequent therapies which is inconsistent with the assumption applied when treatments are used as part of TPC. However, given that this applies equally to both arms, the EAG does not expect that this will have introduced significant bias.

5.3.3.15 Duration of subsequent treatment

The company has assumed the same duration of subsequent treatment for the T-DXd and TPC arms based on the weighted average duration across both arms. However, the EAG believes that it is plausible for the duration of subsequent treatment to differ if T-DXd delays the start of subsequent treatment by delaying progression, or extends the duration of subsequent treatment by delaying death. Therefore, the EAG has explored including an estimate of duration for subsequent treatment that is specific to the trial arm in its preferred base case.

5.3.3.16 Health resource use for progression-free and post-progression states

The advice received from the EAG's clinical experts suggested that there may be some variation in clinical practice with regards to the use of scans specifically to detect ILD. One clinical expert stated that they used high resolution CT scans every other cycle for T-DXd but not for TPC and the other clinical expert stated that they would repeat CT scans every third cycle for most drugs including T-DXd and therefore they would not expect additional scans for T-DXd relative to TPC. The EAG therefore explored alternative assumptions around this in the scenario analysis (see Section 5.4.2.17).

Both of the EAG's clinical experts agreed that T-DXd required additional scans to detect LV dysfunction which were not required for TPC. One expert stated that they used either echocardiogram or multigated acquisition (MUGA) scans every 6 months in patients receiving T-DXd, with the other stating that echocardiograms every 3 months were standard for T-DXd but not for most therapies included in TPC. Although the company stated, in response to clarification question B27, that capecitabine required electrocardiograms before treatment,[15] these are much lower cost than either echocardiograms or MUGA scans. The company also stated that patients receiving anthracyclines undergo cardiac monitoring, but the type of monitoring is not specified and anthracyclines are not one of the treatments included in TPC. To reflect the potential for T-DXd to result in an increased burden for cardiac monitoring relative to TPC, the EAG has explored the impact of assuming no echocardiograms for TPCs combined with 6 monthly MUGA scans for T-DXd (see Section 5.4.2.18).

5.3.3.17 Resource use for AEs

The EAG does not consider it reasonable to assume that all AEs included in the model would be managed by hospital admission. In particular, the EAG's clinical experts stated that neutropenia would only require admission if it was complicated by fever or other signs of sepsis, thrombocytopenia would

require admission for plasma infusion only if symptomatic or grade 4 and most patients with elevated ALT would not require admission. Whilst ILD of any grade was included in the model, the EAG's clinical experts stated that only ILD of grade ≥3 would require admission for IV steroids with lower grade cases being managed with oral steroids. The EAG therefore considered that the costs of AEs were likely to be overestimated in the company's model. The company argued, in response to clarification question B24,[15] that the assumption that adverse events of grade ≥3 require hospitalisation is consistent with the approach taken in previous TAs, and it noted that the definition of grade 3 adverse events included *"hospitalisation or prolonged hospitalisation"*. However, the EAG notes that the definition of grade 3 AEs also included AEs which are disabling or which limit self-care activities of daily living, and these would not necessarily require hospitalisation. However, the EAG notes that the model is not particular sensitive to the assumptions regarding resource use for AEs and therefore these have not been explored in the EAG's exploratory analyses.

5.3.3.18 Drug acquisition cost for subsequent therapies

The company's calculation of drug acquisition cost for subsequent therapies for gemcitabine is inconsistent with their calculation for the drug acquisition cost for gemcitabine within TPC despite the dose assumed being identical. This is because when calculating the cost for gemcitabine as a subsequent therapy, the company assumes the vial size with the highest cost per mg (1000 mg at £0.03 per mg) is used rather than the vial size with the lowest cost per mg (2000 mg at £0.02 per mg). This results in a cost per dose of £[redacted] instead of a cost per dose of £[redacted]. In addition, the company assumes no wastage for subsequent therapies which is equivalent to 100% vial sharing whereas the cost per dose is £[redacted] within TPC where 75% vial sharing is assumed for gemcitabine.

The same inconsistency is present for paclitaxel where the vial size with the lowest cost per mg (150 mg at £0.09 per mg) and 75% vial sharing is assumed within TPC, whereas a vial size with a higher cost per mg (100 mg at £0.12 per mg) and 100% vial sharing is assumed when calculating costs for paclitaxel as a subsequent therapy. The EAG prefers to assume that the cost per dose calculations used for TPC are applied when the same drugs are used as subsequent therapies at the same dose (see Section 5.4.2.15).

5.3.3.19 Health state utility values are not age-adjusted

The EAG notes that the health state utility values are not age-adjusted. This may not lead to a significant bias in the cost-effectiveness of one drug relative to another given that the utility decrement each year is small and the average life-expectancy in this population is low. Therefore, the utility decrements related to aging may be insignificant compared to the changes in utility that are driven by disease progression over the life-time of these patients. However, the company's approach potentially leads to an inconsistency between the QALYs estimated in the cost-effectiveness analysis and those estimated

for the general population for the purposes of the severity modifier calculation. The EAG has explored the impact of correcting this as described in Section 5.4.2.19.

5.4 Exploratory analyses undertaken by the EAG

5.4.1 Overview of EAG's exploratory analyses

The methods for the exploratory analyses performed by the EAG are provided in Section 5.4.2, with results presented in Section 5.4.3.

5.4.2 EAG's exploratory analyses - methods

5.4.2.1 Correcting programming and implementation errors in the company's economic model

The EAG corrected the company's estimate of the cost of gemcitabine when including wastage by correcting the formulae that calculate the number of vials of each size (Cells C98:H98 of Waste_Calcs sheet) so that they refer to the distribution of patient weights (U89:U96 of Waste_Calcs) instead of the column to the left (T89:T96). This reduced the average cost for gemcitabine with wastage from £[redacted] per dose prior to correction to £[redacted] per dose, which is much more consistent with the cost without wastage of £[redacted] per dose. The cost per cycle when assuming 75% vial sharing was £503.49 before the EAG correction, and £93.33 after the EAG correction (as presented in Table 31).

The EAG corrected the company's estimate of the acquisition costs of capecitabine to account for the fact that tablets are only available in specific strengths and pack sizes. This provides a cost per dose of £[redacted] instead of the £[redacted] estimated by the company.

The EAG also corrected the proportion receiving gemcitabine and fulvestrant as subsequent therapies in the T-DXd arm such that the data in the model matched that presented in Table 34 of the company's clarification response.

The EAG corrected the company's scenario analysis including agent specific treatment duration data such that the one-off cost of the whole treatment course was applied to all patients starting treatment rather than the half-cycle corrected occupancy during the first cycle.

The EAG corrected the company's scenario in which the difference between utilities for post-progression patients receiving T-DXd versus TPC is only maintained for 1 year. In the company's implementation, the additional QALYs resulting from the utility difference are applied as one-off QALY gains at the point the patient progresses. However, the company had incorrectly multiplied this QALY gain both by the proportion of patients entering the progressed disease health state and by the proportion of patients residing in the progressed disease health states, incorrectly reducing the proportion receiving this QALY gain. The EAG corrected this to ensure that the QALY gain applies to

100% of the patients entering the progressed disease health state using the figures from the newly progressed column of the state-transition model.

The company's model only incorporates discounting from the end of the first year. The EAG corrected this to apply discounting from the start of the model.

5.4.2.2 Estimating the proportion of patients entering the post-progression and death health states

The EAG calculated the proportion of patients entering the post-progression health state to account for the fact that not all deaths are occurring from the progression-free health state. Thus, the EAG applied equation [7] with a value of [redacted] and [redacted] for α in the T-DXd and TPC arms respectively. This was a change from the company's approach which had been equivalent to assuming that α was zero for both arms. The EAG also preferred to use the estimate of newly progressed patients and new deaths estimated prior to half-cycle correction, as these estimates relate to the events occurring during a time period and not occupancy of a state at a particular point in time. This change was implemented concurrently with the introduction of the α variable.

5.4.2.3 Choice of curve for OS

The EAG has explored implementing the Weibull distribution as it considers this to be the most plausible model for extrapolating OS and assumed the log-logistic fit within a scenario analysis.

5.4.2.4 Choice of curve for PFS

The EAG has explored implementing the generalised gamma distribution as it considers this to be the most plausible model for extrapolating PFS. The distributions were used without restrictions in the EAG's base case whereas a cap was introduced in a scenario where PFS on TPC is restricted by that on T-DXd.

5.4.2.5 Choice of curve for TTD

The EAG maintained the company's preference of the generalised gamma curve for their base case but explored scenarios using the mean time on treatment as the minimum plausible treatment duration and the log-logistic fit as their maximum plausible treatment duration.

5.4.2.6 Health utility values for PFS and PD states

For the progression-free state, the EAG applied the average utilities from the T-DXd and TPC arms of the DESTINY-Breat04 trial for progression-free patients provided in Table 20 of the clarification response ([redacted] for T-DXd and [redacted] for TPC).[15] These differed from the company's base case values

as the company preferred to use the values from the regression, but the EAG considered that these lacked face validity relative to utility values applied in previous appraisals.

For the post-progression health state, the EAG applied the utility decrement of 0.272 from Lloyd to the utility values for the PFS health states. This resulted in utility values for the progressed disease state of of [redacted] and [redacted] for the T-DXd and TPC arms respectively.

5.4.2.7 Duration of HRQoL difference between treatment arms in the PD state and applying the post-progression utility of TPC to both arms afterwards

The EAG preferred to limit the duration of difference in utility values applied to progressed disease between the trial arms to 6 months, as this is consistent with the assumption applied in TA819. The EAG used the company's approach to restricting the duration in which the utility value for the PD state for TPC is applied throughout and the QALY gains for the difference between the T-DXd and TPC PD health states is applied as a one-off at the time of progression. However, the EAG limited this to 9 cycles (6.2 months), rather than the 17 cycles (11.7 months) preferred by the company. In addition, when limiting the difference between the arms, the EAG prefers to use the same post-progression utility for TPC as when not limiting the difference (i.e., [redacted]) rather than the average across the T-DXd and TPC arms [redacted].

5.4.2.8 RDI relative to dose modelled

The EAG used the data in the CSR to estimate the RDI for each drug relative to the drug dose assumed in the model when estimating drug acquisition costs. This resulted in RDIs as shown in Table 37, which are presented alongside the company's preferred RDIs for reference.

Table 37 RDIs when using the company's and the EAG's preferred approaches.

Drug	RDI relative to dose planned within trial* (company approach)	RDI relative to dose assumed when calculating drug cost (EAG preferred approach)
T-DXd	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]

** For T-DXd only, the company modified the RDI such that it was estimated relative to the dose specified in the SmPC rather than the dose planned during each treatment cycle which was sometimes reduced.*

5.4.2.9 Administration costs for capecitabine

The EAG accepted the company's assumption of one administration cost per cycle in their base case but explored a scenario in which patients are only seen in person once every other cycle as a scenario.

5.4.2.10 Administration costs for taxmoifen

The EAG prefers to assume that patients receiving tamoxifen are seen in person once every 3 months rather than once per pack of tablets prescribed (which is approximately once per month).

5.4.2.11 Vial sharing for intravenous therapies

The EAG prefers to assume 50% vial sharing for T-DXd and intravenous treatments included in the TPC arm in its base case as this is consistent with the assumption in TA862.

5.4.2.12 Eribulin and gemcitabine removed from TPC

The EAG has removed both eribulin and gemcitabine from the TPC arm, for the reasons described in Section 5.3.3.11, whilst assuming that these are replaced with one of the remaining therapies included within TPC with no resultant change in clinical effectiveness, as the company asserts that all treatments included in TPC are similarly effective. The EAG has redistributed the proportions receiving gemcitabine and eribulin across the remaining treatments according to the distribution of the remaining treatments in DESTINY-Breast04. This provided a final mix of TPC treatments of 53.7%, 20.9% and 25.4% for capecitabine, paclitaxel and nab-paclitaxel respectively.

5.4.2.13 Uncertainty regarding the mix of treatments offered in the UK

To reflect the uncertainty in the mix of treatment likely to be used second-line in the UK, the EAG has explored scenarios in which 100% of the patients receiving the highest cost component of TPC (eribulin) and 100% of patients receiving the lowest cost component of TPC (capecitabine). These scenarios are intended to explore the sensitivity of the cost-effectiveness to uncertainty in the treatment mix and are not intended to reflect plausible scenarios as eribulin is not recommended as a second-line option in England.

5.4.2.14 Correcting mix of subsequent therapies to include drugs recorded by their equivalent salts

The EAG recalculated the mix of subsequent therapies to include those recorded as receiving either the drug or its equivalent salt (e.g. eribulin and eribulin mesylate). This resulted in the mix of subsequent therapies being updated as per Table 38. The cost per arm for subsequent therapies was [redacted] for T-DXd and [redacted] for TPC when including drugs and their respective salts to estimate the distribution of therapeutic agents. This is an increase from £[redacted] for T-DXd and £[redacted] for TPC, when using the company's approach. The costs for subsequent therapies are therefore more similar across the T-DXd and TPC arms when using the distributions in Table 38.

Table 38 Distribution of subsequent treatments updated by the EAG to include both drugs and their respective salts (CSR Table 14.1.3.5.2)[21]

Treatment	Distribution over trial period (%)*	
	T-DXd (n=373)	TPC (n=184)
Chemotherapy		
Paclitaxel	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Epirubicin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Endocrine therapy		
Tamoxifen	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]

5.4.2.15 Cost of subsequent therapies

The EAG's base case assumed the same cost per dose for gemcitabine, paclitaxel and eribulin when used as either part of TPC or subsequent therapies. These are £[redacted], £[redacted] and £[redacted] respectively (instead of £[redacted], £[redacted] and £[redacted] in the company's base case).

5.4.2.16 Duration of subsequent treatments

The EAG prefers to include an estimate of duration for subsequent treatment that is specific to the trial arm rather than the average across the T-DXd and TPC trial arms. This is because it is plausible for the duration of subsequent treatment to differ if T-DXd delays the start of subsequent treatment by delaying progression, or extends the duration of subsequent treatment by delaying death. The EAG has applied the treatment specific duration of subsequent therapy from CS, Table 59, which was [redacted] months for T-DXd and [redacted] months for TPC in its base case.

5.4.2.17 Increased CT scans to proactively detect ILD in patients receiving T-DXd

The EAG maintained the company's assumption of four CT scans a year for both arms in their base case but explored a scenario analysis in which scans are required every other cycle for T-DXd to proactively detect ILD.

5.4.2.18 Increased use of cardiac monitoring for T-DXd relative to TPC

The EAG has explored in a scenario analysis the impact of assuming no echocardiograms for patients receiving TPC and a 6-monthly MUGA scan for patients receiving T-DXd but has not included this assumption in its base case. The cost for a MUGA scan is £444 (HRG code RN22Z).[36]

5.4.2.19 Age-related utility decrements

The EAG has applied an adjustment to correct for expected age-related utility decrements in the model to make the QALY estimates from the cost-effectiveness model consistent with the estimate of QALY gain in the general population for the purposes of calculating the severity modifier.

5.4.2.20 Duration of treatment, RDI and mean patient weight for SG

The EAG has explored applying the mean time on treatment (6.12 months) and the RDI (94.2%) for SG from the ASCENT trial in the cost-minimisation instead of taking the company's approach of assuming that these are equivalent to the data for T-DXd. For T-DXd the mean treatment duration in DESTINY-Breast04 was applied ([redacted] months). The EAG has also updated the analysis to include the mean patient weight in the HorR-negative population ([redacted]). This analysis was replicated in the confidential appendix using the PAS price for SG.

5.4.2.21Assuming a weekly dosing schedule for paclitaxel

The EAG has explored in a scenario analysis the impact of administering paclitaxel as 80 mg/m^2 IV cycled weekly instead of 175 mg/m^2 IV once cycled every 21 days in the company's base case.

5.4.3 EAG's exploratory analyses – results

The results of the EAG's exploratory analysis are shown in Table 39. The EAG's corrected company base case implements the corrections described in Section 5.4.2.1. This is followed by implementing individual changes using the EAG's corrected company base case as the starting point, which are described as EAG exploratory analyses 1 to 13. These are then combined in an EAG base case, for which a deterministic result is presented followed by a probabilistic estimate of the ICER. Deterministic scenario analyses 1 to 10 are presented using the EAG base case as the starting point. It is worth noting that probabilistic ICER for the EAG base case is slightly higher (2%) than its deterministic counterpart.

It should be noted that all ICERs reported in this section are presented without the QALY weighting for disease severity. The severity modifier is discussed in Section 6, where the results including the QALY weighting are then presented.

5.4.3.1 Impact of individual changes

After correcting errors in the company's deterministic model, the ICER for T-DXd versus TPC is estimated to be [redacted] per QALY gained. The largest change in the ICER was seen when the EAG used the Weibull curve for extrapolating OS for both arms. This increases the ICER to [redacted] per QALY gained. The other two changes increasing the ICER above [redacted] are removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies, and using the EAG's preferred utility set as described at Section 5.3.3.7.

Two changes increased the ICER above [redacted] per QALY; using the generalised gamma curve for extrapolating PFS for both arms and applying the difference in utilities used between treatment arms in the PD state for six months only and applying the post-progression utility value of TPC onwards to both arms. Assuming RDIs relative to the modelled doses, applying age-related decrements to utility values, and decreasing vial sharing to 50% increase the ICER between [redacted] and [redacted] per QALY. The remaining individual changes either reduced the ICER or had marginal impact, with the lowest ICER of [redacted] generated by the EAG's correction to the methods used to calculate the proportion of patients entering the PD and death states each cycle.

When including all the changes preferred by the EAG, the deterministic ICER increased to [redacted] per QALY (probabilistic ICER = [redacted] per QALY). Calculating treatment costs using the log-logistic curve for TTD further increased the ICER by approximately [redacted]. The other scenarios that marginally increased the ICER were; assuming TPC costs equivalent to 100% receiving capecitabine (increase ~[redacted]), increasing frequency of cardiac monitoring for patients on T-DXd (increase ~[redacted]) relative to TPC, increasing CT scans to proactively detect ILD in patients receiving T-DXd (increase ~[redacted]), and assuming administration costs for capecitabine every other cycle (increase ~ [redacted]).

Assuming TPC costs equivalent to 100% receiving eribulin decreased the ICER by approximately [redacted] whereas assuming a log-logistic curve for OS extrapolations and calculating treatment costs using restricted mean treatment duration reduced the ICER by [redacted] and [redacted] respectively. Changing the paclitaxel schedule to 80 mg/m^2 IV every week decreased the ICER by ~[redacted].

Table 39 Results of the EAG's exploratory analyses

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Company base case – post-clarification (Deterministic)					
TPC	[redacted]	[redacted]	-	-	

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case: correcting programming and implementation errors in the company's economic model					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: EAG approach to estimating the proportion of patients entering the post-progression and death states					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Assuming a Weibull curve for OS extrapolations					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming a Generalised gamma curve for PFS extrapolations					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Applying the EAG's preferred utility values (maintaining a difference in post-progression utility values life-long)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying the HRQoL difference between treatment arms in the PD state for six months only and applying the post-progression utility value of TPC onwards to both arms (using company's preferred utility post-progression utility values)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Assuming RDIs relative to the modelled doses					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Applying administration costs for tamoxifen every three months					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Decreasing vial sharing from 75% to 50%					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
EAG exploratory analysis 10: Adjusting the mix of subsequent therapies to include drugs recorded by their equivalent salts					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 11: Assuming the same dose costs for the subsequent treatments used in TPC					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 12: Including arm-specific time on subsequent treatment					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 13: Applying age-related decrements to utility values					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Deterministic)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Probabilistic)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Assuming a log-logistic curve for OS extrapolations)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Assuming a Generalised gamma curve for PFS extrapolations with a cap for TPC)*					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Treatment costs are calculated using restricted mean treatment duration)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Treatment costs are calculated using log-logistic curve for TTD)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming administration costs for capecitabine every other cycle)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Assuming TPC costs equivalent to 100% receiving eribulin)					
TPC	[redacted]	[redacted]	-	-	

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Assuming TPC costs equivalent to 100% receiving capecitabine)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Increasing CT scans to proactively detect ILD in patients receiving T-DXd)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 9 (Increasing frequency of cardiac monitoring for patients on T-DXd relative to TPC)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 10 (Changing paclitaxel schedule to 80 mg/m^2 IV every week)					
TPC	[redacted]	[redacted]	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG – evidence assessment group, HRQoL – health-related quality of life, ILD – interstitial lung disease, OS – overall survival, PD – progressed disease, PFS – progression-free survival, T-DXd – trastuzumab deruxtecan, TPC – treatment of physician's choice, TTD – time to treatment discontinuation
**This scenario is giving the same results as the base case because these curves are not crossing in the EAG's base case*

5.4.3.2 The EAG's estimate of the ICER

The exploratory analyses conducted by the EAG, which are provided in Table 39, indicate that there are plausible changes to parameter values which would considerably increase the company's estimate of the ICER but where the most appropriate value remains uncertain. Such parameters include the parametric fits used for OS extrapolations, and the utility values used in the PF and PD states and how these differ between arms. Uncertainty regarding OS could be reduced by further follow-up from the DESTINY-Breast04 trial. Uncertainty regarding the health utility values could be reduced by observational studies reporting HRQoL data collection from a large sample size on both drugs especially those who are in PD for more than three months. Real world evidence on the mix of treatments currently offered in the absence of T-DXd at both second and third-line would also be useful as this has the potential to have a large impact on the ICER for T-DXd versus current standard care.

5.4.3.3 The EAG's estimate of the cost savings from the cost minimisation analysis of T-DXd versus SG in the HorR-negative subgroup

The EAG applied the changes described at Section 5.4.2.20 to the cost minimisation model submitted by the company in response to the clarification questions. These reduced the overall cost saving from

£[redacted] to £[redacted] for T-DXd compared to SG over the patient's life-time using the list price for SG. The EAG reiterates its concerns regarding significant uncertainty around the assumption of clinical equivalence in efficacy and safety between T-DXd and SG made in this analysis.

5.5 Discussion

The model submitted by the company was implemented to a good standard. However, the EAG believes that the base case ICER is likely to be higher than that estimated by the company and prefers an ICER of between [redacted] and [redacted] given the current data available and not taking into account the severity of the condition discussed in Section 6. The largest component in increasing the ICER is the use of a Weibull distribution to model OS in both arms and the utility values used in PF and PD health states, in addition to the duration the difference in HRQoL is assumed to endure between both arms following progression. Additionally, the EAG is uncertain about how well the TPC arm of the DESTINY-Breast04 trial reflects the cost and efficay of the mix of treatments received in current practice under standard care without T-DXd.

The current cost minimisation analysis submitted by the company is highly dubious in its assumptions of equivalent clinical effectiveness between T-DXd and SG as these two drugs have been trialled within different populations with different eligibility criteria and baseline characteristics, thus extreme caution should be exercised in interpreting any results from it.

6 SEVERITY OF THE CONDITION

The company has presented evidence on the absolute and proportional shortfall in QALYs for patients with HER2-low u/mBC receiving TPC relative to age and sex matched members of the general population. These were estimated using the Schneider et al. tool which combines ONS estimates of mortality in the general population with one of several general population dataset utility.[51] The company selected the option to use a utility dataset that is consistent with NICE's preferences (MVH value set + HSE 2014 ALDVMM [Hernandez Alava, et al.][50]). The company used age and sex inputs (57 years, 100% female) consistent with their baseline characteristics in the economic analysis which were based on the DESTINY-Breast04 FAS population cohort. The tool requires an estimate of discounted lifetime expected QALYs in patients receiving standard care, and for this the company used the QALYs predicted by their economic model for TPC. CS, Section B3.6.3 presents absolute and proportional QALY shortfalls of [redacted] and [redacted] respectively which would equate to a severity modifier (QALY weighting) of 1.2X.

In response to the clarification letter (question B42), the company explored the impact of altering the starting age in the model which updates the QALY estimates for the general population, and to a lesser degree the QALY estimates from the TPC arm of the economic model. The EAG identified an error in the reporting of these (Table 35 of the clarification response), in that the QALYs for the general population were incorrectly reported, but the absolute and proportional QALY shortfalls were correct. The EAG has provided a corrected version of this table in the Appendices Table 42 for reference. Whilst varying the age at the start of treatment from 54 to 65 years somewhat modified the absolute and proportional shortfall estimates, it did not result in any change to the appropriate severity modifier which remained at 1.2X in all the scenarios explored by the company.

The EAG is broadly satisfied with the company's approach to estimating the severity modifier, but considers that the QALY shortfall may have been underestimated due to the company not applying age-related utility decrements when estimating expected QALYs under standard care using the TPC arm of the cost-effectiveness model. The EAG has corrected this within their base case analysis. In addition, the implementation of the EAG's preferred utility values and the EAG's preferred survival curves for OS and PFS will have impacted the QALYs gained in the TPC arm of the model. Table 40 represent the QALY shortfall analysis for the company's and EAG's base case using the Schneider et al. tool and the outputs of the company's economic model for the TPC arm. The company's estimate of the lifetime discounted QALYs for patients receiving TPC is [redacted], but this reduced to [redacted] QALYs when using the EAG's preferred base case. However, this lower lifetime QALY estimate for the TPC arm still results in a severity modifier of 1.2X. None of the EAG's scenario analyses generated lifetime QALY gains that were compatible with a severity modifier of either 1X or 1.7X. The EAG concludes that the

most appropriate severity modifier based on the proportion and absolute QALY shortfall calculations is likely to be 1.2X.

Table 41 reproduces Table 39 with the addition of the ICERs calculated based on a QALY weight of 1.2X.

Table 40 Results of the QALY shortfall analysis

Base case	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight
Company	13.85	[redacted]	Absolute: [redacted] Proportional: [redacted] %	1.2x
EAG	13.85	[redacted]	Absolute: [redacted] Proportional: [redacted] %	1.2x

Based on the total QALYs in the TPC arm of the company economic model deterministic base case for this appraisal.

Table 41 Results of the EAG's exploratory analyses with QALY weighing of 1.2x

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company base case - post-clarification (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case: correcting programming and implementation errors in the company's economic model						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: EAG approach to estimating the proportion of patients entering the post-progression and death states						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Assuming a Weibull curve for OS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming a Generalised gamma curve for PFS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Applying the EAG's preferred utility values (maintaining a difference in post-progression utility values life-long)						
TPC	[redacted]	[redacted]	-	-		

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying the HRQoL difference between treatment arms in the PD state for six months only and applying the post-progression utility value of TPC onwards to both arms (using company's preferred utility post-progression utility values)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Assuming RDIs relative to the modelled doses						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Applying administration costs for tamoxifen every three months						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Decreasing vial sharing from 75% to 50%						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 10: Adjusting the mix of subsequent therapies to include drugs recorded by their equivalent salts						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 11: Assuming the same dose costs for the subsequent treatments used in TPC						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 12: Including arm-specific time on subsequent treatment						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 13: Applying age-related decrements to utility values						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-13 (Probabilistic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
EAG scenario 1 (Assuming a log-logistic curve for OS extrapolations)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Assuming a Generalised gamma curve for PFS extrapolations with a cap for TPC)*						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Treatment costs are calculated using restricted mean treatment duration)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Treatment costs are calculated using log-logistic curve for TTD)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming administration costs for capecitabine every other cycle)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Assuming TPC costs equivalent to 100% receiving eribulin)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Assuming TPC costs equivalent to 100% receiving capecitabine)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Increasing CT scans to proactively detect ILD in patients receiving T-DXd)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 9 (Increasing frequency of cardiac monitoring for patients on T-DXd relative to TPC)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 10 (Changing paclitaxel schedule to 80 mg/m^2 IV every week)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG - evidence assessment group, HRQoL - health-related quality of life, ILD - interstitial lung disease, OS - overall survival, PD - progressed disease, PFS - progression-free survival, T-DXd – trastuzumab deruxtecan, TPC - treatment of physician's choice, TTD - time to treatment discontinuation

**This scenario is giving the same results as the base case because these curves are not crossing in the EAG's base case*

7 OVERALL CONCLUSIONS

The key evidence for clinical effectiveness within the CS comprised one open-label RCT (DESTINY-Breast04) comparing T-DXd versus a combination of five single-agent chemotherapies called TPC. The company assumed the comparator arm is reflective of the current agents used in England. Clinical advice provided to the EAG highlighted that SG is a significant omission from the TPC arm in the HorR-negative population (although the EAG acknowledges the recent nature of its approval). In addition eribulin is not used as second-line treatment in England, and the TPC arm does not include some of the agents which were included in the NICE scope that are sometimes prescribed in clinical practice. The EAG also had doubts regarding the comparability of the trial population to the UK population especially in some characteristics that the company considered to be potential treatment modifiers including ECOG PS (scores of 2 were excluded) and the proportion of the population who reported Asian ethnicity. It could be also argued that the trial population was slightly younger than the population expected to be treated in clincal practice.

The company presented clinical effectiveness data in terms of OS, PFS and TTD and used them to generate ICERs. The company mapped and modelled the EQ-5D data collected to generate utility values for the PF state, however it used an external published algorithm to estimate the values for the PD state.

The EAG noted that the PFS and TDD KM appears to be mature and preferred assumptions reflecting that in its base case. The EAG doubted the face validity of the utility values used in the company's base case and worked out alternative values which align more with those used in previous related STAs.

The model submitted by the company was implemented to a good standard, although the ERG explored alternative assumptions to those used by the company. When considering all the possible amendments the EAG's preferred deterministic ICER was [redacted] (probabilistic ICER = [redacted]), when considering a QALY weight of 1.2X, which the EAG considered likely to be an appropriate severity modifier based on the evidence in the CS. The EAG's exploratory and scenario analyses demonstrate that these ICERs change significantly with different assumptions regarding OS extrapolations and utility values. They are also sensitive to the mix of treatments likely to make up standard care in the absence of T-DXd as these affect the costs of the comparator strategy. The EAG would have liked to generate illustrative ICERs for T-DXd versus SG in the HorR-negative subgroup of the HER-low population; however, an ITC was difficult to generate as there were concerns regarding the comparability of the populations in the key studies for T-DXd (DESTINY-Breast04) and SG (ASCENT).

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9 APPENDICES

Table 42 Results of the QALY shortfall analysis using ages identified in RWE and clinical trials from previous NICE TAs (adapted from Table 35 of the clarification response with corrections from the EAG)

General population QALY source	Age	Data source	Number of previous lines of chemotherapy	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight
Reference case: MVH value set + HSE 2014 ALDVMM [Hernandez Alava M, et al.]	54 years	ASCENT study consisting of 529 triple-negative advanced BC patients (identified in TA819)[29]	At least 2	14.81	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	55 years	EMBRACE (study 305) consisting of 762 HER2+/HER2- patients (as identified in TA423)[39]	At least 2	14.49	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	[redacted] years	AstraZeneca/Daiichi-Sankyo led study (N=31) - HER2-low/HR-negative patients (aligned with the mean age used in the company's base case CEA)	At least 1	13.85	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	[redacted] years	AstraZeneca/Daiichi-Sankyo led study (N=31) - HER2-low/HR-positive patients	At least 1	12.85	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x
	65 years	SACT dataset of HER2-negative advanced BC patients (identified in TA725)[80]	After endocrine therapy	11.11	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.2x

[a]*Estimates extracted by EAG from Schneider et al. tool as the company reported 11.11 for every value in this column*

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low unresectable or metastatic breast cancer after chemotherapy [ID3935]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 2nd June 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccuracies in the clinical sections

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, page 20 The EAG have not accurately reported the treatment requirement for eligible patients. *"This means that eligible patients should have received at least one prior line of chemotherapy, which positions T-DXd as a second-line option or beyond"*	*"This means that eligible patients should have received at least one prior line of chemotherapy* ***in the adjuvant (if recurrence occurs within 6 months) or metastatic setting*** *which positions T-DXd as a second-line or beyond option,* ***following initiation of chemotherapy****."*	Additional wording to accurately describe the eligible population, in accordance with the licensed indication. Additional text is proposed to clarify that positioning of T-DXd as *"a second-line or beyond option"* is with reference to prior chemotherapy and does not include earlier-line endocrine or targeted therapies.	The EAG has amended its text as proposed.
Section 3.5, page 24, table 3	"People with HER2-**low** unresectable or metastatic breast cancer…"	Incorrect indication.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect indication stated as the population of interest forming the decision problem: “People with HER2-positive unresectable or metastatic breast cancer…” which the company believes may a typographical error.			
Section 3.5, page 25, table 3 Duration of response is excluded from the outcomes listed in the final scope issued by NICE (row 4).	• overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life • **Duration of response**	To accurately describe outcomes listed in the NICE final scope and CS.	The EAG has amended its text as proposed.
The EAG have not accurately reported the wording for the trial population in the following sections: **Section 4.1, page 27** **Section 4.1.4 page 30**	*“…adult patients with HER2-low u/mBC after one or two lines of chemotherapy* ***in the (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting.”***	To accurately describe the DESTINY-Breast04 trial population.	The EAG has amended its text as proposed within the mentioned sections.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.1, page 31 **Section 4.8, page 78** **Section 4.9, page 78** **Section 5, page 80** *"…adult patients with HER2-low u/mBC after one or two lines of chemotherapy."*			
Section 4, page 27 "A systematic literature review (SLR) of clinical evidence for T-DXd for treating HER2-low u/mBC after one or two lines of chemotherapy"	"A systematic literature review (SLR) of clinical evidence for T-DXd for treating HER2-low **or HER2-negative** u/mBC after one or two lines of chemotherapy"	To accurately describe the scope of the clinical SLR.	The EAG has amended its text as proposed.
Section 4.1.4, page 31 *"No additional items relating to ASCENT were identified in the full SLR update to 20 January 2023."*	*"No additional items relating to ASCENT were identified in the full SLR update to **30** January 2023."*	Incorrect reporting of the SLR update date.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.4, page 31 *"SG, while within the NICE decision problem scope, is not currently being used in England and Wales and its likely uptake is uncertain (CS, section B.1.3.6 and 2.9)."*	*"SG, while within the NICE decision problem scope, is not currently* ***considered to be standard of care within its licenced indication and its uptake in UK clinical practice is uncertain*** *(CS, section B.1.3.6 and 2.9)."*	The company feels the existing text is not correctly reflecting the current clinical landscape or company position on SG as detailed in the CS.	The EAG has amended its text as proposed.
Section 4.2.4, page 43 The EAG have reported the value for the HR-positive cohort instead of the FAS population. *"The mean number of prior systemic therapies in the metastatic setting was 3.3 in both trial arms."*	*"The mean number of prior systemic therapies in the metastatic setting was* [redacted] ***in the T-DXd arm and*** [redacted] ***in the TPC arm of the FAS population****."*	To correct a factually inaccurate statement; the mean number of systemic therapies in the metastatic setting was 3.3 in both arms in the HorR positive population.	The EAG has amended its text as proposed.
Section 4.2.4, **page 43**	"Participant baseline characteristics in DESTINY-Breast04 are presented in Table 9 (and CS, section **B.2.4.4**)."	Incorrect section reference of CS.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Participant baseline characteristics in DESTINY-Breast04 are presented in Table 9 (and CS, section B.2.4.5)." **page 44** "Table 9 Characteristics of participants in Destiny-Breast04 at baseline (reproduced from CS, B.2.4.5, Table 15)."	"Table 9 Characteristics of participants in Destiny-Breast04 at baseline (reproduced from CS, **B.2.4.4**, Table 15)."		
Section 4.3.2, page 54 *"…in the T-DXd arm compared with 5.4 months (95% CI: 4.2, 6.8)…"*	*"…in the T-DXd arm compared with **5.1** months (95% CI: 4.2, 6.8)…"*	To correct an incorrect value.	The EAG has amended its text as proposed.
Section 4.3.2, page 56 *"…death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p<0.0028)."*	*"…death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p=0.0028)."*	To correct an inaccurate symbol.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.2, page 58, Figure 9 title *"Figure 9 Kaplan-Meier of OS in the HorR-positive from DESTINY-Breast04 (reproduced from CS, section 2.6.1, Figure 14)."*	*"Figure 9 Kaplan-Meier of OS in the HorR-positive from DESTINY-Breast04 (reproduced from CS, section 2.6.1, **Figure 13**)."*	Incorrect figure reference.	The EAG has amended its text as proposed.
Section 4.3.3, page 61 *"The principal response benefit for T-DXd compared with TPC was partial response (PR): 49.2% and 50.1%..."*	*"The principal response benefit for T-DXd compared with TPC was partial response (PR): **49.5**% and **49.1**%..."*	To correct incorrect values.	The EAG has amended its text as proposed.
Section 4.4.1, page 71 The EAG have combined the principal reasons for discontinuations in the T-DXd arm: *"The principal reasons for these discontinuations in the T-DXd arm were [redacted]"*	*"The principal reasons for these discontinuations in the T-DXd arm were pneumonitis ([redacted]) and ILD ([redacted])."*	For accuracy as per Table 27 of the CS.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.1, page 71 The percentages reported are *drug-related* TEAEs, associated with dose reduction and interruption. *"TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively)."*	*"TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (**22.6%** vs **38.4%**, and **38.5%** vs **41.9%**, respectively)."* *OR* *"**Drug-related TEAEs** associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively)."*	To correct a factually inaccurate statement. The figures referred to by the EAG are drug-related TEAEs associated with dose reduction and interruption.	The EAG has amended its text as proposed in the second statement.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.1, page 73 The EAG have inaccurately reported the following: *"However, the incidence of the following TEAEs were higher in the TPC arm than the T-DXd arm, both for any TEAE and Grade >3 TEAEs: [redacted]*	*"However, **the following Grade ≥3 TEAEs were more common in the TPC arm than in the T-DXd arm in the DESTINY-Breast04 trial: neutropenia ([redacted] in the TPC arm vs [redacted] in the T-DXd arm), leucopenia ([redacted] vs [redacted]), elevated AST ([redacted] vs [redacted]), and palmar-plantar erythrodysaesthesia syndrome ([redacted] vs [redacted]).**"*	To correct a factually inaccurate statement that the listed TEAEs are higher in the TPC arm than the T-DXd arm for any TEAE.	The EAG has amended its text to "However, the incidence of the following Grade ≥3 TEAEs were higher in the TPC arm than the T-DXd arm: [redacted]
"These findings were consistent with the results for the most common drug-related TEAEs, the incidence of which are sometimes slightly lower."	*"These findings were consistent with the results for the most common drug-related TEAEs, **some of which had a lower incidence in the T-DXd arm than in the TPC arm**."*	For clarity	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.7, page 76 *"…in the HER2-low/HorR-negative population (T-DXd N=40, TPC N=18 from DESTINY-Breast04)…"*	*"…in the HER2-low/HorR-negative population (T-DXd N=**42**, TPC N=18 from DESTINY-Breast04)…"*	To correct an incorrect value.	The EAG did not correct the value as it was mentioned in response to clarification question A21.
Section 4.9, page 78 [redacted]"	"[redacted]	To correct a factually inaccurate statement.	The EAG has amended its text as proposed.
Section 4.9, page 79 *"…death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p<0.0028)"*	*"…death by 36% compared with TPC: HR 0.64 (95% CI: 0.48-0.86, p=0.0028)"*	To correct an incorrect symbol.	The EAG has amended its text as proposed.
Section 4.9, page 79 *"The principal reasons for these discontinuations in the T-DXd arm were [redacted]."*	*"The principal reasons for these discontinuations in the T-DXd arm were pneumonitis ([redacted]) and ILD ([redacted])"*	To correct a factually inaccurate statement.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.9, page 79 *"TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively)…"*	*"…were lower in the T-DXd arm than the TPC arm (**22.6% vs 38.4%**, and **38.5% vs 41.9%**, respectively)…"* OR *"**Drug-related** TEAEs associated with dose reduction and interruption were lower in the T-DXd arm than the TPC arm (20.8% vs 37.2%, and 28.6 vs 36.0%, respectively)…"*	To correct incorrect values. The figures referred to by the EAG are drug-related TEAEs associated with dose reduction and interruption.	The EAG has amended its text as proposed in the second statement.

Issue 2 Severity Modifier

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5, page 23 The EAG report does not acknowledge that the	No specific amendments are proposed but the company would request that	As stated in Section B.3.6.4 of the CS, "In order to capture the full extent of the severity of HER2-low u/mBC during	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company considers that additional flexibilities in the form of a QALY weight of 1.7, commensurate to the previous EOL criteria that the appraisal would have robustly met, should be applied in decision-making for this appraisal. . *"…which qualifies the QALYs for this STA to be weighted at x1.2…"*	the report is updated to acknowledge the company position.	this initial phase of implementation, monitoring and review of the severity modifier, Daiichi Sankyo considers that additional flexibilities in the form of a QALY weight of 1.7 equivalent to the previous EOL should be applied in decision-making."	The EAG has noted in Section 3.5 that the company has claimed that this topic would have met the superseded end-of-life criteria. We consider this to be sufficient.
Section 6, page 142 – 143 *"The EAG concludes that the most appropriate severity modifier based on the proportion and absolute QALY shortfall calculations is likely to be 1.2X."*	***"**The EAG concludes that the most appropriate severity modifier based on the proportion and absolute QALY shortfall calculations is likely to be 1.2X.* ***In the CS, the company considered that the 1.2X severity modifier did not appropriately reflect the severity of the condition or the level of innovation associated with T-DXd in an area of high unmet need, and the company therefore considered that additional***	In order to accurately reflect the company position and information presented in the CS.	This is not a factual inaccuracy. The EAG's remit is to critique the evidence provided in the company's submission according to the current NICE methods guide. The company's arguments on this point in Section B.3.6.4 relate to the change in methods from using

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	flexibilities in the form of a QALY weight of 1.7 equivalent to the previous EOL should be applied in decision-making for this appraisal."		end-of-life criteria to the severity modifier approach. It is outside of the EAG's role to comment on this in Section 6 of the EAG report as it is not relevant to the quantitative assessment of the severity modifier. The EAG has already noted the company's point that the technology would have met the end-of-life criteria in Section 3.5 for the committee's information.

Issue 3 Inaccuracies in the economic sections

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.5.2.1, page 97 An error in the reported utility value after progression for the T-DXd arm.	"This means that the effective utility after progression is 0.596 for the TPC arm, and [redacted] in the T-DXd arm for the total	As described in the company's response to clarification question B20, the total utility	The EAG believes that the report is factually correct.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"This means that the effective utility after progression is 0.596 for the TPC arm, and [redacted] for the T-DXd arm in the first year after progression, returning to 0.596 thereafter."	duration of the first year after progression, returning to 0.596 thereafter."	benefit gained over 12 months by patients progressing on T-DXd compared to those progressing on TPC is estimated to be [redacted]. The company apply this benefit to the pooled utility value across both arms which is 0.596. Therefore, the effective utility after progression for the T-DXd arm is 0.596 + [redacted] = [redacted].	The 0.0372 value incorporated % progressed whereas the value reported in the EAG (0.641) is basically 0.596 + the utility increment estimated at 0.0447. Text has been amended to add the following (=0.596+0.0447) after the value of 0.641 to make this clear.
Section 5.2.5.2.1, page 98, Table 30, last row: ***Scenario 3 – progressed-disease utilities are trial arm specific only for the first year****	***Scenario 3 – progressed-disease utilities are trial arm specific only for the first year****		Value remains unchanged for the same reason mentioned in the previous issue

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Progressed disease [redacted] T-DXd in year 1 0.596 TPC in year 2 0.596 Both arms thereafter	Progressed disease [redacted] T-DXd in year 1 0.596 TPC in year 2 0.596 Both arms thereafter		
Section 5.2.5, page 103 An error in the reported additional life years gained on T-DXd. "QALY gains relate to differences in survival ([redacted] additional live years gained on T-DXd), and differences…"	"QALY gains relate to differences in survival ([redacted] additional live years gained on T-DXd), and differences…"	As stated within Table 11 of the company's response to the clarification questions, and within the company's updated cost-effectiveness model, the incremental life years gained are [redacted].	The EAG has amended its text as proposed.
Section 5.2.5, page 104, table 34; 4th column, third row An error in the reported incremental drug acquisition cost.	The incremental costs associated with the drug acquisition costs should be amended to £[redacted].	As presented within the company's updated cost-effectiveness model, and within the total drug acquisition costs for T-DXd and TPC listed in the same table 34, the incremental costs	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		associated with drug acquisition are calculated as £[redacted] - £[redacted] = £[redacted].	
Section 5.2.7.1, page 108, Table 35, 3rd column, 4th row. An error in the reported incremental LYs gained for the "No discounting is applied to costs and QALYs" scenario.	The incremental LYs gained for the "No discounting is applied to costs and QALYs" scenario should be [redacted].	As presented in the company's updated cost-effectiveness model.	The EAG has amended its text as proposed.
Section 5.2.7.1, page 108, Table 35, 3rd column, 5th row. An error in the reported incremental LYs gained for the "Discount rate of 1.5% applied to costs and QALYs" scenario.	The incremental LYs gained for the "Discount rate of 1.5% applied to costs and QALYs" scenario should be [redacted].		The EAG has amended its text as proposed.
Section 5.2.7.1, page 108, Table 35, 3rd column, 6th row. An error in the reported incremental LYs gained for the "Discount rate of	The incremental LYs gained for the "Discount rate of 6% applied to costs and QALYs" scenario should be [redacted].		The EAG has amended its text as proposed.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>6% applied to costs and QALYs” scenario.</td><td></td><td></td><td></td></tr>
<tr><td>Section 5.4.2.8, page 133, Table 37, 3rd column, 4th row.

An error in the reported RDI relative to dose assumed when calculating drug cost (EAG preferred approach) for eribulin.

Table 1 RDIs when using the company’s and the EAG’s preferred approaches.
<table><tr><th>Drug</th><th>RDI relative to dose planned within trial* (company approach)</th><th>RDI relative to dose assumed when calculating drug cost (EAG preferred approach)</th></tr><tr><td>T-DXd</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Capecitabine</td><td></td><td></td></tr></table></td><td>The RDI relative to dose assumed when calculating drug cost for eribulin is [redacted].

Table 2 RDIs when using the company’s and the EAG’s preferred approaches.
<table><tr><th>Drug</th><th>RDI relative to dose planned within trial* (company approach)</th><th>RDI relative to dose assumed when calculating drug cost (EAG preferred approach)</th></tr><tr><td>T-DXd</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Capecitabine</td><td></td><td></td></tr><tr><td>Eribulin</td><td></td><td></td></tr><tr><td>Gemcitabine</td><td></td><td></td></tr><tr><td>Paclitaxel</td><td></td><td></td></tr><tr><td>Nab-paclitaxel</td><td></td><td></td></tr></table></td><td>As described in Section 5.3.3.8 of the EAG’s final draft report, the EAG has explored (and included in the EAG’s preferred base case) an alternative scenario where RDI has been recalculated using the mean dose intensity as units per cycle from the CSR relative to the dose assumed for each drug in the model. The EAG recalculates RDI by dividing the mean dose intensity as units per cycle for each drug (as presented in Table 10.1 of the CSR) by the assumed dose of each drug as stated in the</td><td>The EAG has used the data in Table 10.1 of the CSR to estimate RDI. For the outcome of “Dose intensity [c] (units/ 3 weeks)”, the data is [redacted] mg/m^2 per three-week cycle in the Eribulin column as the company states. However, the footnote states, “eribulin = mg*/m2, where * refers to eribulin mesylate. 1.23 mg eribulin base</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<table><tr><td>Eribulin</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Gemcitabine</td><td></td><td></td></tr><tr><td>Paclitaxel</td><td></td><td></td></tr><tr><td>Nab-paclitaxel</td><td></td><td></td></tr></table> ** For T-DXd only, the company modified the RDI such that it was estimated relative to the dose specified in the SmPC rather than the dose planned during each treatment cycle which was sometimes reduced.*	** For T-DXd only, the company modified the RDI such that it was estimated relative to the dose specified in the SmPC rather than the dose planned during each treatment cycle which was sometimes reduced.*	EAG's and company's models. The company notes that for the EAG's calculation of eribulin RDI, the dose of 1.23 mg/m^2 per administration that is assumed in the model has not been used. The dose of 1.23 mg/m^2 per administration, with two administrations per cycle (on days 1 and 8), is also aligned with the SmPC dose for eribulin.[1] The mean dose intensity of eribulin received in DESTINY-Breast04, stated in Table 10.1 of the CSR, is [redacted] mg/m2 per three-week cycle. The dose per cycle used to estimate drug	= 1.4 mg eribulin mesylate". The EAG interpreted this to mean that the reported value refers to mg/m^2 of erubulin mesylate. Therefore, the expected dose of eribulin mesylate per cycle is 2 x 1.4mg/m^2 = 2.8mg/m^2. The RDI is therefore [redacted]/2.8 =[redacted]. Therefore, the EAG believes their estimate is correct. For the company's estimate to be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		acquisition costs in the EAG and company's model is 1.23 mg/m2 twice per three-week cycle, as per the SmPC. Therefore, the recalculated RDI for eribulin, in line with the EAG's methods, is as stated below: [redacted] /(1.23 *2) = [redacted] %	correct the value in Table 10.1 would need to be referring to eribulin not eribulin mesylate as stated in the footnote.

Issue 4 Requests to clarify wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, page 6-13 The EAG have listed ICERs associated with each economic issue along with the resulting ICERs after an EAG scenario/correction has been applied, however, there is no clarification on whether these ICERs are with a QALY weight of 1x or a QALY weight of 1.2x.	Please may the EAG add text to highlight that the ICERs and the corresponding scenario ICERs listed within Issue 1 – Issue 11 are with a QALY weight of 1.2x applied.	As the EAG report looks at model results and ICERs with both a QALY weight of 1x and 1.2x applied within different sections, it is important to clarify what results correspond to each QALY weight.	This is already clarified at Section 1.2 “The ICER estimates discussed in Sections 1.3 to 1.5 are based on the deterministic model, when applying a QALY weight of 1.2X in line with the company’s assessment of the severity modifier, as discussed at Section 6. ICERs with and without QALY weighting are summarised in Section 1.6, Table 2.”
Section 2.1, page 17 The EAG have excluded the word “specifically” from the following sentence:	*“Currently, there are no treatments recommended **specifically** for HER2-low u/mBC.”*	The company would like to request additional wording to make it clear that there are no recommended treatments for HER2-low specifically, but patients may be	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Currently, there are no recommended treatments for HER2-low u/mBC."		treated according to HER2-negative treatment guidelines.	
Section 2.2, page 18 The reference to the CS has not been included in the following sentence: "*According to the current treatment pathway, patients with HorR-positive disease…"*	"*According to the current treatment pathway **presented in the CS**, patients with HorR-positive disease…"*	The company would like to request that the signpost to the CS be included for clarity and ease of reference.	The EAG has amended its text as proposed.
Section 4.1.1, page 27 *"In its clarification response (A3), the company revealed that they had subsequently completed a comprehensive SLR…"*	*"In its clarification response (A3), the company **stated** they had subsequently completed a comprehensive SLR …"*	The company would like to clarify that the SLR was completed close to submission deadline and not provided due to time constraints. The current wording implies that this information was intentionally omitted from the CS.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.2, page 28 *"However, HER2-low BC population are a subset of…"*	*"However, HER2-low BC **patients** are a subset of…"*	To provide clarity.	The EAG has amended its text as proposed.
Section 4.1.3, page 30 *"Data extracted from the included studies are presented in Sections B.2.3-2.7 and 2.10 of the CS."*	*"Data extracted from the included **clinical** studies are presented in Sections B.2.3-2.7 and 2.10 of the CS."*	To provide clarity that the listed sections report only the clinical studies.	The EAG has amended its text as proposed.
Section 4.1.4, page 30 *"However, the SLR also identified two publications and reports for the ASCENT trial (CS, Appendix D.1.2)…"*	*"However, the SLR also identified two publications and reports for the ASCENT trial (CS, Appendix D.1.2.1, **Table 5**)…"*	To provide clarity.	The EAG has amended its text as proposed.
Section 4.1.4, page 31 *"…the company therefore responded to a clarification request from the EAG and confirmed that eleven published*	*"…the company therefore responded to a clarification request from the EAG and confirmed that eleven published items related to the trial (Clarification response, A11) **were identified**."*	To provide clarity.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
items related to the trial (Clarification response, A11).”			
Section 4.2.1, page 36 *“TPC were administered in accordance…”*	*“All TPC **agents** were administered in accordance…”*	To provide clarity.	The EAG has amended its text as proposed.
Section 4.2.2, page 39 *“…bias in the DESTINY-Breast04 trial (CS, section B.2.5 and Appendix D.1.3, Table 7.”*	*“…bias in the DESTINY-Breast04 trial (CS, section B.2.5 and Appendix D.1.3; **as shown in** Table 7 **in this report**.”*	To provide clarity and avoid confusion with Table 7 of the CS.	The EAG has amended its text as proposed.
Section 4.3.5, page 66 *“…Appendix N, and the main publication, differ from those reported in the CSR.”*	*“…Appendix N, and the main publication **(Modi et al., 2022[18])**, differ from those reported in the CSR.”*	To provide clarity on which publication the sentence is referring to.	The reference is added.
Section 5.2.5.2.1, page 97 **“***In practice this was implemented by*	*“In practice this was implemented by calculating the QALY gain over 12 months for patients progressing on T-DXd compared to those progressing on TPC, which the company estimates to be [redacted] QALYs (see clarification response B20),and **translates to an added per***	As it is already stated what the utility benefit is over the full year (12 months/17 cycles), this provides further clarity on	The company’s language is very confusing. You can have a QALY gain per cycle but not a utility gain per cycle.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
calculating the QALY gain over 12 months for patients progressing on T-DXd compared to those progressing on TPC, which the company estimates to be [redacted] *QALYs (see clarification response B20), and applying this as an adjustment at the time of progression, with the utilities for the progressed-disease state being the same in both arms***."**	***cycle utility benefit of*** [redacted]***. This is then applied*** *as an adjustment at the time of progression, with the utilities for the progressed-disease state being the same in both arms."*	what the added utility benefit is *per cycle*.	The proposed amendment could still be unclear if the reader tries dividing the QALY estimate only by number of cycles as the estimate of 0.0372 QALYs takes into account the utility difference, the time it applies for and the **proportion** it applies to. To make this company's approach clearer, the EAG has amended the text as follows "…[redacted] QALYs (see clarification response B20). This is calculated as a utility difference of 0.0447 being applied for 17 cycles (~1 year) to the proportion of the PFS events that were

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			progressions ([redacted]). This is then applied as …"
Section 5.2.7.1, page 107 The EAG have listed ICERs associated with each scenario analysis for the cost-effectiveness analysis, however, there is no clarification on whether these ICERs are with a QALY weight of 1x or a QALY weight of 1.2x.	Please may the EAG add text to highlight that the ICERs for each scenario are with a QALY weight of 1x applied.	As the EAG report looks at modelled results and ICERs with both a QALY weight of 1x and 1.2x applied within different sections, it is important to clarify what results correspond to each QALY weight.	A statement has been added now before reporting ICER results to clarify that.
Section 5.4.3.1, page 137 The EAG have listed ICERs associated with each scenario analysis for the cost-effectiveness analysis, however, there is no clarification on whether these ICERs are	Please may the EAG add text to highlight that the ICERs for each scenario are with a QALY weight of 1x applied.	As the EAG report looks at model results and ICERs with both a QALY weight of 1x and 1.2x applied within different sections, it is important to clarify what results correspond to each QALY weight.	There is already a clarification of that stated at Section 5.4.3. No change is required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
with a QALY weight of 1x or a QALY weight of 1.2x.			

Issue 5 Missing information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, page 17 The EAG have not included some information from the following sentence which may be useful for understanding: *"NICE Clinical Guideline 81 (CG81) recommends…"*	*"NICE Clinical Guideline 81 (CG81;* ***2017), which is for the management of advanced BC generally****, recommends…"*	Additional wording to clarify the date and purpose of NICE Clinical Guideline 81.	The EAG has amended its text as proposed.
Section 2.2 The EAG have missed some detail from this section regarding information presented in the CS. **Page 18:** *"According to the current treatment pathway,*	*"According to the current treatment pathway* ***presented in the CS****, patients with HorR-positive disease…"*	Additional wording to clarify that information being referred to is reported in the CS.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients with HorR-positive disease…" **Page 20:** *"Figure 3 and Figure 4 show the expected positioning for T-DXd in the HorR-positive and HorR-negative pathways respectively."*	*"Figure 3 and Figure 4 show the expected positioning for T-DXd in the HorR-positive and HorR-negative pathways respectively,* ***as stated in the CS.****"*		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1, page 21 The EAG have missed some information from this section which may be useful to include. *"However, the DESINY-Breast04 trial only included patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1."* *"Additionally, the proportion of the trial population who were Asians (~40%) was higher than the proportion expected in the majority of UK centres…"*	*"However, the DESINY-Breast04 trial only included patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1,* ***consistent with the majority of oncology trials, including recent trials in u/mBC used in company submissions for technologies that received a positive recommendation from NICE****.*[2–7]*"* *"Additionally, the proportion of the trial population who were Asians (~40%) was higher than the proportion expected in the majority of UK centres,* ***however subgroup analysis showed little difference in outcomes between patients according to ethnicity (HR: 0.38; 95% CI: 0.27, 0.53)***[8]***."***	The company feels the existing text is missing key information that was described in the CS.	This is not factually incorrect. The intention of the EAG's text was to compare to the real practice, not to other trials or show results of subgroup analysis. Text remains unchanged.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2, page 21 The EAG have missed some detail on the source of information for the following sentence: *"T-DXd administered as an intravenous (IV) infusion at 5.4mg/kg of body weight every 21 days, with patients being treated with T-DXd until disease progression or toxicity."*	*"T-DXd administered as an intravenous (IV) infusion at 5.4mg/kg of body weight every 21 days, with patients being treated with T-DXd until disease progression or toxicity,* ***as per the SmPC.***[9]*"*	Additional wording and reference to clarify source.	The EAG has amended its text as proposed.
Section 4.2.4, page 44 *"…it was common for trials in HER2 BC and similar populations to exclude ECOG PS 2 patients (Clarification response, A15)."*	*"…it was common for trials in HER2 BC and similar populations to exclude ECOG PS 2 patients,* ***including recent trials in u/mBC for therapies that were recommended by NICE*** *(Clarification response, A15)."*	To provide context to the data with respect to other appraisals and the suitability of the data for decision-making.	The EAG has amended its text as proposed.
Section 4.2.5, page 46 ***"****HRQoL questionnaires, and* [redacted]*, were to be*	*"HRQoL questionnaires,* [redacted]*, and* [redacted]*, were to be*	For completeness and to accurately reflect the trial assessments listed in CS Section B.2.3.1.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
completed/assessed [redacted]"	*completed/assessed [redacted]"*		
Section 4.3.2, page 58 The company believes that the section "*OS in the FAS*" is missing key information.	Please add the following sentence to the section: *"As stated in the CS (Section B.2.6.1.2), the stratified log-rank p-value of 0.001 crossed the pre-specified efficacy stopping boundary of 0.0075, confirming the efficacy of T-DXd vs. TPC for this outcome. DESTINY-Breast04 therefore met its secondary endpoint of OS in the FAS."*	The company considers that the conclusion is missing key information.	The EAG has amended its text as proposed.
Section 4.3.3, page 61 *"Complete response (CR) rates were higher in the T-DXd arm…"* *"The principal response benefit for T-DXd compared with TPC was partial response (PR): 49.2% and 50.1%..."*	*"Complete response (CR) rates **by BICR** were higher in the T-DXd arm…"* *"The principal response benefit for T-DXd compared with TPC was partial response (PR) **by BICR**: 49.2% and 50.1%..."*	Additional wording to accurately describe the efficacy outcomes.	The EAG has amended its text as proposed, and corrected the values for PR as previously highlighted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.1, page 71 The EAG have not included the drug-related SAEs of >1% in the TPC arm. *"The only drug-related SAEs of >1% in the T-DXd arm were interstitial lung disease (ILD) (4.3%) and nausea (1.1%)."*	*"The only drug-related SAEs of >1% in the T-DXd arm were interstitial lung disease (ILD) (4.3%) and nausea (1.1%).* ***In the TPC arm, the only drug-related SAEs of >1% were neutropenia (2.3%) and febrile neutropenia (1.7%)."***	For completeness and to accurately reflect the outcomes in CSR Table 10.19.	The EAG has amended its text as proposed.
Section 4.4.1, page 72 The EAG have not included the frequent and more common TEAEs in the TPC arm: *"The following TEAEs were both frequent and more common in the T-DXd arm than in the TPC arm in the DESTINY-Breast04 trial:* [redacted]	*"The following TEAEs were both frequent and more common in the T-DXd arm than in the TPC arm in the DESTINY-Breast04 trial:* [redacted]	For balance and completeness.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[redacted]	[redacted]. ***The following TEAEs were both frequent and more common in the TPC arm than in the T-DXd arm in the DESTINY-Breast04 trial: Neutropenia ([redacted] in the TPC arm vs [redacted] in the T-DXd arm), leucopenia ([redacted] vs [redacted]), and palmar-plantar erythrodysaesthesia syndrome ([redacted] vs [redacted])."***		
Section 6 *"The company used age and sex inputs (57 years, 100% female) consistent with their baseline characteristics in the economic analysis which were based on the DESTINY-Breast04 cohort."*	*''The company used age and sex inputs (57 years, 100% female) consistent with their baseline characteristics in the economic analysis which were based on the DESTINY-Breast04* ***FAS population*** *cohort."*	Additional wording to clarify the specific population being referred to.	The EAG has amended its text as proposed.

Issue 6 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.2, page 4	*"In addition, the company's base case assumes…"*	Incorrect position of apostrophe.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, page 17 *"Therefore, HER2-low is a subgroup of the group previously denoted as HER-negative, which can be identified using the tests already carried out routinely to identify HER-positive patients."*	*"Therefore, HER**2**-low is a subgroup of the group previously denoted as HER**2**-negative, which can be identified using the tests already carried out routinely to identify HER2-positive patients.*	Incorrect spelling of "HER2".	The EAG has amended its text as proposed.
Section 4.1.1, page 27 Repetition of *"patients"* which the company believes is a typographical error. "…and relevant comparators for treating patients with HER2-low u/mBC **patients**."	*"… and relevant comparators for treating patients with HER2-low u/mBC."*	To correct the repetition.	The EAG has amended its text as proposed.
Section 4.2.1, page 36 The cross-reference is for the incorrect table: "…and a full summary of the DESTINY-Breast04 trial methodology is provided in Table 6."	"…and a full summary of the DESTINY-Breast04 trial methodology is provided in **Table 5**."	Incorrect cross-reference.	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3, page 42 "The EAG noted that the primary analysis set excluded HER2-low/HorR-negative patients, although secondary efficacy analyses were conducted on the FAS also, and a series of exploratory analyses were conducted on this group of patients."	Please revise the sentence to be clear what is meant. "The EAG noted that the primary analysis set excluded HER2-low/HorR-negative patients, although secondary efficacy analyses were conducted on the FAS **population and exploratory analyses in the HER2-low/HorR-negative subgroup**."	Revision required for clarity.	The EAG has amended its text as proposed.
Section 4.2.3, page 42 "…represented approximately 10% of eligible patients (CS, sections B.1.3.6.1 and B.2.9), despite these proportions being consistent with the likely make-up of HER2-low patients in UK practice, as reported in the CS (CS, section B.2.5.1)."	"…represented approximately 10% of eligible patients (CS, sections **B.2.5.1**), despite these proportions being consistent with the likely make-up of HER2-low patients in UK practice, as reported in the CS (**CS, sections B.1.3.6.3.1 and B.2.9**)."	Incorrect section references of CS.	The 10% value was not mentioned in Section B.2.5.1 whereas the real-world data was mentioned in Section B.2.5.1. However, the EAG spotted that the 10% value was mentioned in Section B.1.3.6.3.1 not B.1.3.6.1, and

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			therefore amended the text to reflect this.
Section 4.3.1 title, page 52 *"Section 4.3.1 Primary efficacy outcome in DESTINY-Breast04: PFS by BIRC."* **Section 4.3.3, page 60** ***"…**compared with TPC of 50% by BIRC rather than 63% as reported for PFS by IA)."*	*"Section 4.3.1 Primary efficacy outcome in DESTINY-Breast04: PFS by **BICR**."* ***"…**compared with TPC of 50% by **BICR** rather than 63% as reported for PFS by IA)."*	Incorrect spelling of "BICR".	The EAG has amended its text as proposed.
Section 4.4.1, page 71 "…and numbers of patients with serious drug-related TEAEs were low and similar between arms (12.9% for T-DXd vs 11.0% for TPC),."	"…and numbers of patients with serious drug-related TEAEs were low and similar between arms (12.9% for T-DXd vs 11.0% for TPC)**.**"	Revision required to remove comma.	The EAG has amended its text as proposed.
Section 4.7, page 76	*"The ASCENT trial was not powered to analyse efficacy in **the** HER2-low population."*	Correction	The EAG has amended its text as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The ASCENT trial was not powered to analyse efficacy in HER2-low population."			
Section 4.9, page 79 *"…associated with discontinuation were higher for TDX-d compared with TPC (15.1% vs 7.0%)."*	*"…associated with discontinuation were higher for **T-DXd** compared with TPC (15.1% vs 7.0%)."*	Incorrect spelling of "T-DXd"	The EAG has amended its text as proposed.
Section 5.2.5, page 86, page 103 There are two sections labelled 5.2.5. "5.2.5 *Evidence used to inform the company's model parameters"* *"5.2.5 Cost effectiveness results"*	There are two sections labelled 5.2.5. Section referencing should be updated.	To correct repetition.	The EAG has amended the numbering as proposed.
Section 5.2.5.1.3, page 93 "After visual inspection of the 3-year plots of TTD for similarity with the KM data (CS, Figures 40 and 41). The company concluded that the log-logistic and generalised gamma	"After visual inspection of the 3-year plots of TTD for similarity with the KM data (CS, Figures 40 and 41)**, the** company concluded that the log-logistic and generalised gamma models provided a good visual fit for both arms."	Grammatical error.	The EAG has amended its text as proposed.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>models provided a good visual fit for both arms.”</td><td></td><td></td><td></td></tr>
<tr><td>Section 5.2.5.1.3, page 94

“This analysis is further described and critiqued in Section 5.3.3.5.”</td><td>“This analysis is further described and critiqued in Section 5.3.3.”</td><td>The text references this incorrect section for this scenario.</td><td>The EAG has amended its text to “Section 5.3.3.6”.</td></tr>
<tr><td>Section 5.2.5.2.1, page 98, Table 30, last row:

<table><tr><th colspan="2">Scenario 3 – progressed-disease utilities are trial arm specific only for the first year*</th></tr><tr><td>Progressed disease</td><td></td></tr><tr><td>T-DXd in year 1</td><td>[redacted]</td></tr><tr><td>TPC in year 2</td><td>0.596</td></tr><tr><td>Both arms thereafter</td><td>0.596</td></tr></table></td><td><table><tr><th colspan="2">Scenario 3 – progressed-disease utilities are trial arm specific only for the first year*</th></tr><tr><td>Progressed disease</td><td></td></tr><tr><td>T-DXd in year 1</td><td>[redacted]</td></tr><tr><td>TPC in year 1</td><td>0.596</td></tr><tr><td>Both arms thereafter</td><td>0.596</td></tr></table></td><td>As stated in the heading of the table, the scenario is only applied within the first year, therefore this should state the utility value for TPC in year 1.</td><td>The EAG has amended its text as proposed.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.3.3.2, page 117 An unnecessary comma. "This is important given that, median PFS and OS in the TPC arm of the DESTINY-Breast04 trial were…"	"This is important given **that** median PFS and OS in the TPC arm of the DESTINY-Breast04 trial were…"	Grammatical error.	The EAG has amended its text as proposed.

Issue 7 ACIC markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.4, page 6, Issue 1 **Row:** What is the expected effect on the cost-effectiveness estimates?	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	*"Removal of eribulin and gemcitabine increased the ICER for the company's corrected base case from £[redacted] to £[redacted].* *Assuming the highest cost component (eribulin) to represent 100% of TPC decreased the EAG's base case ICER estimate from £[redacted] to £[redacted], whereas assuming 100% receiving capecitabine increased it slightly to £[redacted]."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.5, page 9, Issue 4	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*The choice of parametric extrapolation for OS had a significant impact on the ICER. The ICER for the company's corrected base case increased from £[redacted] to £[redacted], when replacing the log-logistic distribution with the Weibull distribution.* *The ICER for the EAG's preferred base case scenario, which included the Weibull distribution for OS, decreased from £[redacted] to £[redacted] when the Weibull distribution was replaced by the log-logistic distribution."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 1.5, page 10, Issue 5	All ICERs and associated costs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*This had minimal impact on the ICER increasing it by ~£[redacted] when applied in isolation to the company's corrected base case…"*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.5, page 10, Issue 6	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*This increased the ICER for the company's corrected base case from £[redacted] to £[redacted]"*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 1.5, page 11, Issue 7	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*The first scenario reduced the EAG's base case ICER from £[redacted] to £[redacted], whereas the second scenario increased the ICER to £[redacted]."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.5, page 11, Issue 8	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*Applying the EAG's preferred utility set increased the ICER for the company's corrected base case from £[redacted] to £[redacted].*"	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 1.5, page 12, Issue 9	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*Limiting the post-progression benefit to 6 months assuming the company's preferred utilities increased the ICER from £[redacted] to £[redacted].*"	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.5, page 12, Issue 10	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*This increased the company's corrected ICER increasing from £[redacted] to £[redacted].*"	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 1.5, page 13, Issue 11	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	*"This increased the company's corrected base case ICER from £[redacted] to £[redacted]."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.6, page 13	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	*"When considering all the possible amendments, the EAG's preferred deterministic ICER was £[redacted] considering a QALY weight of 1.2X (probabilistic ICER = £[redacted])."* *"…the company's preferred log-logistic extrapolation reducing the ICER (when maintaining the EAG's other preferences) to £[redacted]."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 1.6, Table 2, page 13 - 16	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	Please mark all values in columns 6 and 7, labelled "ICER (QALY weight of 1x)" and "ICER (QALY weight of 1.2x)" as CIC.	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 4.2.3, page 42	The treatment dose for the SAS population should be AIC.	*"…who received [redacted] of a study treatment."*	This is not AIC in the CS, page 63. Text remains unchanged.
Section 4.2.4, page 43	The mean age of the population should be AIC.	*"The mean age in the FAS was [redacted] years in both trial arms."*	The EAG has amended its marking as proposed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	The mean baseline number of prior systematic therapies of patients should be AIC.	*"The mean number of prior systemic therapies in the metastatic setting was* [redacted] ***in the T-DXd arm and*** [redacted] ***in the TPC arm of the FAS population****…"*	The EAG has amended its marking as proposed.
Section 4.2.5, page 46	The timings of screening assessments should be AIC.	*"…from randomisation date, and* [redacted]*"*	The EAG has amended its marking as proposed.
Section 4.3.4, page 63 **Section 4.3.4, page 64**	The underline is missing: *"At baseline in the FAS, the median EQ-5D-5L VAS score was* [redacted] *in both the T-DXd arm and the TPC arm."* *"…* [redacted] *(*[redacted] *and* [redacted] *months; HR:* [redacted]*; 95% CI:* [redacted]*)…"*	*"At baseline in the FAS, the median EQ-5D-5L VAS score was* [redacted] *in both the T-DXd arm and the TPC arm."* *"…* [redacted] *(*[redacted] *and* [redacted] *months; HR:* [redacted]*; 95% CI:* [redacted]*)…"*	The EAG has amended its marking as proposed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.3.5, page 66	"(Figure 9)." does not need to be underlined.	"… **(Figure 9)."**	The EAG has removed its marking as proposed.
Section 4.4.1, page 71	Text regarding drug-related SAEs of >1% does not need to be AIC but the values remain AIC.	*"The only drug-related SAEs of >1% in the T-DXd arm were interstitial lung disease (ILD) ( ) and nausea ( )."*	The EAG has removed its marking as proposed.
Section 4.4.1, page 71	The principal reasons for discontinuations in the T-DXd arm do not need to be AIC. The principle reason for lower TEAEs associated with dose reduction and interruption in the T-DXd arm than the TPC arm does not need to be AIC.	*"The principal reasons for these discontinuations in the T-DXd arm were pneumonitis/ILD ( )."* *"This was principally due to the frequency of neutropenia in the TPC arm: in the T-DXd arm vs in the TPC arm leading to dose reductions."*	The EAG has removed its marking as proposed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.4.1, page 72	Drug-related TEAEs with the outcome of death are not AIC.	*"…and the CSR reports that these drug-related TEAEs include pneumonitis, (n=2), sepsis, colitis ischaemic, febrile neutropenia, dyspnoea, and disseminated intravascular coagulation (n=1 each)."*	The EAG has removed its marking as proposed.
Section 4.4.1, page 72 **Page 73**	The listed TEAEs are not AIC; only the reported incidence data is AIC.	*"Nausea ([redacted]% in the T-DXd arm vs [redacted]% in the TPC arm); vomiting ([redacted]% vs [redacted]%); anaemia ([redacted]% vs [redacted]%); constipation ([redacted]% vs [redacted]%); decreased appetite ([redacted]% vs [redacted]%) and thrombocytopenia ([redacted]% vs [redacted]%)."* *"nausea ([redacted] vs [redacted]); anaemia ([redacted] vs [redacted]); thrombocytopenia ([redacted] vs [redacted]), as well as fatigue ([redacted] vs [redacted])."* *"However, the incidence of the following TEAEs were higher in the TPC arm than the T-DXd arm, both for any TEAE and Grade ≥3 TEAEs: neutropenia; leucopenia; elevated AST and Palmar-plantar erythrodysaesthesia syndrome."*	The EAG has removed its marking as proposed.
Section 4.4.1, page 74	ILD proportions in Table 18 are not AIC.	[redacted]	The EAG has removed its marking as proposed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.9, page 79	The frequency of TEAEs across cycles are AIC.	*"The CS also reports that, across both the T-DXd and TPC arms, the frequency of TEAEs was high in [redacted] of treatment, but declined thereafter up to [redacted]."*	The EAG has amended its marking as proposed.
Section 4.9, page 79	The drug-related TEAEs associated with discontinuation are not AIC.	*"The principal reasons for these discontinuations in the T-DXd arm were pneumonitis/ILD…"* "…*principally due to the frequency of neutropenia in the TPC arm…"*	The EAG has removed its marking as proposed.
Section 5.2.5, page 104, Table 33	All total and incremental costs, QALYs, LYs and ICERs are CiC.	All data in the 2nd, 5th, 8th and 9th columns of Table 33 are CiC along with the rest of the confidential data within Table 33.	All total and incremental costs and QALYs are already marked. LYs are marked now. The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td>Section 5.2.5, page 105</td><td>The probability that T-DXd generates a greater net monetary benefit than TPC is CiC.</td><td>“The EAG’s re-run of the company’s PSA suggests that the probability that T-DXd generates more net monetary benefit than TPC at a WTP threshold of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted] respectively. The same probabilities are [redacted] and respectively when a QALY has 1.2x weight.”</td><td>The EAG has amended its marking as proposed.</td></tr>
<tr><td>Section 5.2.5.2.1, page 97</td><td rowspan="2">The effective utility after progression within the scenario analysis for the T-DXd is AIC.</td><td>“This means that the effective utility after progression is 0.596 for the TPC arm, and [redacted] for the T-DXd arm in the first year after progression, returning to 0.596 thereafter.”</td><td rowspan="2">The EAG did not amend its marking as the value results from the addition of two values that are not AIC (i.e., 0.596+0.045)</td></tr>
<tr><td>Section 5.2.5.2.1, page 98, Table 30, last row:</td><td>
<table>
<tr><th colspan="2">Scenario 3 – progressed-disease utilities are trial arm specific only for the first year*</th></tr>
<tr><td>Progressed disease</td><td></td></tr>
<tr><td>T-DXd in year 1</td><td>[redacted]</td></tr>
<tr><td>TPC in year 2</td><td>0.596</td></tr>
<tr><td>Both arms thereafter</td><td>0.596</td></tr>
</table>
</td></tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.2.5, page 103	All incremental costs, incremental QALYs and ICERs are CiC to avoid back calculation of PAS discount.	*"The probabilistic version of the model suggests that T-DXd is expected to generate an additional [redacted] QALYs at an additional cost of £[redacted] per patient compared to TPC resulting in an ICER of £[redacted] per QALY gained (£[redacted] when the QALY weight is 1.2). The deterministic version of the model produces a slightly lower ICER (£[redacted] per QALY gained without QALY weight). QALY gains relate to differences in survival ([redacted] additional live years gained on T-DXd), and differences in utility values based on the treatment received as discussed in Section 5.2.5.2.1."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 5.2.5, page 104, Table 33	All incremental costs, incremental QALYs, incremental LYs and ICERs are CiC to avoid back calculation of PAS discount.	All data in the 2nd, 5th, 8th and 9th columns of table 33 needed to be marked CiC along with the rest of the confidential data within Table 33.	All total and incremental costs and QALYs are already marked. LYs are marked now. The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.2.7.1, page 107	All incremental costs, incremental QALYs and ICERs are CiC to avoid back calculation of PAS discount.	"*The scenarios with the largest impact and increased the ICER were the use of alternative PFS fits of exponential, Weibull, Gompertz, or Generalised gamma for both arms (ICERs between £[redacted] to £[redacted]), using discount rates of 6% (~£[redacted]), assuming post-progression benefit of T-DXd continue only for 1 year (~£[redacted]), and decreasing the time horizon to 20 years (~£[redacted]). The following scenarios had a large impact but decreased the ICER; using a log-normal distribution for extrapolating OS for both arms (ICER of ~£[redacted]), assuming no or 1.5% discounting (~£[redacted] to £[redacted]), and calculating treatment costs using restricted mean treatment duration (~£[redacted]).*"	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 5.2.7.1, page 107	All ICERs and associated costs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*The following scenarios had less impact on the ICER (less than £[redacted]) compared with the above mentioned scenarios:…"*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.2.7.1, page 108, Table 35	All incremental costs, incremental QALYs and ICERs are CiC to avoid back calculation of PAS discount.	All data in the 3rd, 6th and 7th columns should be marked as CiC along with the rest of the confidential data within Table 35.	All total and incremental costs and QALYs are already marked. LYs are marked now. The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 5.4.3.1, page 136	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	*"After correcting errors in the company's deterministic model, the ICER for T-DXd versus TPC is estimated to be £[redacted] per QALY gained. The largest change in the ICER was seen when the EAG used the Weibull curve for extrapolating OS for both arms. This increases the ICER to £[redacted] per QALY gained. The other two changes increasing the ICER above £[redacted] are removing eribulin and gemcitabine from TPC and…"* *"Two changes increased the ICER above £[redacted] per QALY;…"*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		"Assuming RDIs relative to the modelled doses, applying age-related decrements to utility values, and decreasing vial sharing to 50% increase the ICER between £[redacted] and £[redacted] per QALY. The remaining individual changes either reduced the ICER or had marginal impact, with the lowest ICER of £[redacted] generated by the EAG's correction to the methods used to calculate the proportion of patients entering the PD and death states each cycle." *"When including all the changes preferred by the EAG, the deterministic ICER increased to £[redacted] per QALY (probabilistic ICER = £[redacted] per QALY). Calculating treatment costs using the log-logistic curve for TTD further increased the ICER by approximately £[redacted]. The other scenarios that [redacted] increased the ICER were; assuming TPC costs equivalent to 100% receiving capecitabine (increase ~£[redacted]), increasing frequency of cardiac monitoring for patients on T-DXd (increase ~£[redacted]) relative to TPC, increasing CT scans to proactively detect ILD in patients receiving T-DXd (increase ~£[redacted]), and assuming administration costs for capecitabine every other cycle (increase ~£[redacted]).*	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		Assuming TPC costs equivalent to 100% receiving eribulin decreased the ICER by approximately £[redacted] whereas assuming a log-logistic curve for OS extrapolations and calculating treatment costs using restricted mean treatment duration reduced the ICER by £[redacted] and £[redacted] respectively. Changing the paclitaxel schedule to 80 mg/m2 IV every week decreased the ICER by ~£[redacted]."	
Section 5.4.3, page 137, Table 39	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	All data in the 6th column should be marked CiC along with the rest of the confidential data in Table 39.	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.
Section 5.5, page 141	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	"*However, the EAG believes that the base case ICER is likely to be higher than that estimated by the company and prefers an ICER of between £[redacted] and £[redacted] given the current data available and not taking into account the severity of the condition discussed in Section 6."*	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 6, page 143, Table 41	All ICERs are CiC to avoid back calculation of incremental QALYs, incremental costs and PAS discount.	All data in the 6th and 7th columns should be marked CiC along with the rest of the confidential data in Table 41.	The EAG, in agreement with NICE, don't think that ICERs should be CIC marked as back calculation is not feasible based on the current marking of costs and QALYs.

Issue 8 Inaccuracies in the EAG's cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'Cost&QALY_T-DXd' Sheet, cell V32 **'Cost&QALY_Comps' Sheet, cell V32** The annual discount rate calculation has not been applied to the adverse events (AE) costs for T-DXd and TPC in cycle 1.	The annual discount rate calculation should be applied to the AE costs for T-DXd and TPC in cycle 1 within the EAG's corrections as the discount rate has been applied to every other cost used in cycle 1 to evaluate T-DXd and TPC in the model.	As described in Section 5.4.2.1 of the EAG's final draft report, the EAG reportedly corrected the model to apply discounting from the start of the model. The company are aware this has minimal impact on the ICER, however, it is inconsistent with the way discount rate has been applied to the other costs used to evaluate T-DXd and TPC in the model.	The costs related to AEs are applied as one-off cost in cycle 1, therefore no discounting was applied.
'Set_Drug_Adm_costs', cell O25 The alternative RDI used for eribulin is calculated using the eribulin mesylate dose rather than the eribulin dose used in the CEM or SmPC.	The RDI value used for the EAG preferred based case should be calculated using the eribulin base dosing. Eribulin RDI: [redacted] % = [redacted] / (1.23*2)	As described in Section 5.3.3.8 of the EAG's final draft report, the EAG has explored an alternative scenario where RDI has been recalculated using the mean dose intensity as units per cycle from the CSR and the RDI assumed in the model. Eribulin is administered twice in a 21-day cycle, on days 1 and 8. The company notes that for the EAG's calculation of eribulin RDI, the dose	The EAG has used the data in Table 10.1 of the CSR to estimate RDI. For the outcome of "Dose intensity [c] (units/ 3 weeks)", the data is [redacted] mg/m^2 per three-week cycle in the Eribulin column as the company states. However, the footnote states, "eribulin = mg*/m2, where * refers to eribulin mesylate. 1.23 mg eribulin base = 1.4 mg eribulin

		per administration of eribulin mesylate (1.4 mg/m^2) has been used instead of the eribulin dose (1.23 mg/m^2) assumed in the model. The eribulin dose of 1.23 mg/m^2 is also aligned with the SmPC dose for eribulin.[1]	mesylate". The EAG interpreted this to mean that the reported value refers to mg/m^2 of erubulin mesylate. Therefore, the expected dose of eribulin mesylate per cycle is 2 x 1.4mg/m^2 = 2.8mg/m^2. The RDI is therefore [redacted]/2.8 = [redacted]. Therefore, the EAG believes their estimate is correct. For the company's estimate to be correct the value in Table 10.1 would need to be referring to eribulin not eribulin mesylate as stated in the footnote.

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3. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies | NICE [TA862] [Internet]. NICE; 2023 [cited 2023 Feb 5]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10804/documents

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5. NICE. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane | NICE [TA458} [Internet]. NICE; [cited 2022 Nov 8]. Available from: https://www.nice.org.uk/guidance/ta458

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9. European Medicines Agency (EMA). EMA Enhertu Summary of Product Characteristics (SmPC) [Internet]. 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 12 July 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 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

Introductory note from the company

Daiichi Sankyo would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the key issues raised as part of the appraisal of trastuzumab deruxtecan (T-DXd) for treating human epidermal growth factor receptor (HER2)-low unresectable or metastatic breast cancer (u/mBC) after chemotherapy. With the aim of addressing as many key issues as possible prior to the first appraisal committee meeting, the company has provided evidence-based responses, which may include new data analyses or model scenarios to inform decision-making and reduce uncertainty. The revised company base case is detailed in the '*Summary of changes to the company's cost-effectiveness estimate(s)*' section, including a full set of updated results, consisting of deterministic results, one-way sensitivity analyses, probabilistic sensitivity analyses, and select scenario analyses. All incremental cost-effectiveness ratios (ICERs) in this document are based on the revised company base case, unless stated otherwise.

As outlined in the company submission (CS) and in the External Assessment Group (EAG) report, there is a very high unmet clinical need for novel treatments in patients with HER2-low u/mBC after chemotherapy. Current treatment options are broadly limited to repeated lines of single-agent, non-targeted chemotherapies, which have limited efficacy. As the first treatment licensed for HER2-low specifically, T-DXd is a significant innovation and represents a step change in the treatment of HER2-low u/mBC. UK clinical expert comments received by the company confirms this, with high clinical demand for T-DXd to be made available for patients with HER2-low u/mBC.

As stated in the CS and in the '*Additional issues*' section, this appraisal would have been assessed under the previous end-of-life (EOL) criteria, resulting in a willingness-to-pay threshold of £50,000 per quality adjusted life year (QALY) used for decision-making. Under the new NICE framework, this appraisal exceeds the minimum criteria for the 1.2x QALY modifier, but the company considers that this modifier underestimates the severity of the condition and does not adequately recognise the high unmet need, innovation, clinical value, and clinical and patient demand for T-DXd in HER2-low u/mBC. As the first and only treatment licensed for HER2-low u/mBC specifically, T-DXd is a highly innovative therapy (as recognised by the Medicines and Healthcare product Regulatory Agency (MHRA) innovation passport) and offers clear and substantial clinical benefits over current standard of care. Beyond the benefits captured in the QALY calculations, T-DXd is expected to benefit wider society in terms of work productivity and quality of life (QoL) benefit for carers and families of patients with HER2-low u/mBC.

Given the above, the company believes that additional flexibility should be considered when applying the severity modifier for this appraisal to ensure that the severity of the condition, high unmet need, and value of T-DXd are appropriately quantified and qualitatively valued in committee decision-making. The company considers ICERs presented with a 1.2x modifier to be conservative and has therefore presented ICERs in this document using both the 1.2x QALY modifier and the 1.7x QALY modifier (commensurate to the previous EOL weighting which this appraisal would have confidently met) to provide a range. The company revised base case following changes at technical engagement is [redacted] (with 1.2x modifier) and [redacted] (with 1.7x modifier).

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Comparators. What medicines are used in NHS clinical practice to treat HER2-low metastatic or unresectable breast cancer after chemotherapy?	Yes	The External Assessment Group (EAG) noted that the comparators included in the treatment of physician's choice (TPC) arm in DESTINY-Breast04 may not be reflective of those used in clinical practice in England. As stated in Section B1.3.6 of the Company Submission (CS), the company considers the TPC arm of DESTINY-Breast04 to be an appropriate comparator for this appraisal for the following reasons: • **The TPC arm is broadly aligned to UK practice:** UK clinical experts consulted by the company at an advisory board in December 2022 confirmed that the TPC arm of DESTINY-Breast04 is broadly aligned to UK clinical practice, where treatment options for the majority of patients are limited to non-targeted single-agent chemotherapies, with the choice of agent based on clinician preference as well as patient-specific needs and preference.[1] • **Treatments in the NICE scope are well-represented in the TPC arm of DESTINY-Breast04:** Clinical advice to the EAG confirmed that capecitabine, paclitaxel and eribulin, which are in-scope and represent 79.4% of the TPC arm of DESTINY-Breast04, account for the majority of treatments offered second-line and beyond in the patient population relevant to this appraisal, highlighting the generalisability of the TPC arm of DESTINY-Breast04. This was also confirmed by

Key issue	Does this response contain new evidence, data or analyses?	Response
		UK clinical expert advice to the company sought during the technical engagement. In addition, the EAG's clinical expert(s) noted that vinorelbine (in-scope, but not in the TPC arm) is used at later lines, which aligns with clinical advice to the company during an advisory board meeting[1] and in advice to the company during the technical engagement. Other agents in the NICE scope but not in the TPC arm of DESTINY-Breast04 (i.e., anthracyclines, platinum therapies) are recommended in NICE guidelines for early or locally advanced BC (NG101)[2] or as first-line therapy in the metastatic setting for mBC in NICE guidelines for advanced BC (CG81),[3] meaning they are unlikely to be relevant to this appraisal. This was confirmed by UK clinical experts consulted by the company during an advisory board meeting[1] and also by a UK medical oncologist consulted by the company during the technical engagement, who stated that anthracyclines are used in the earlier setting and platinum therapies are used either early or very late (e.g., fourth- or fifth-line) in the treatment pathway. • **Differences between the TPC arm of DESTINY-Breast04 and UK practice are unlikely to impact decision-making:** In a published systematic literature review of single-agent chemotherapies in advanced or metastatic breast cancer, none of the included randomised clinical trials (RCTs) demonstrated a significant overall survival (OS) difference between any of the regimens (capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and nab-paclitaxel), indicating similar efficacy across single-agent chemotherapies.[4] UK clinical experts agreed that there are no clinically meaningful differences in the efficacy of non-targeted single-agent chemotherapies in the setting relevant to this appraisal.[1] Based on this, any differences between the agents included in the TPC arm vs. UK practice or the final NICE scope are expected to have a minimal impact on decision-making.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• **Robustness of data for decision-making:** Using the DESTINY-Breast04 TPC arm means leveraging direct clinical trial data from pre-specified analyses in the largest sample size from the key evidence source for the appraisal. • **NICE precedence:** A similar TPC arm was accepted for decision -making in a recent u/mBC appraisal.[5] While the company considers the TPC arm of DESTINY-Breast04 to be an appropriate comparator reflective of UK practice and appropriate for decision-making, it is acknowledged that some agents in the TPC arm do not align with their use in National Health Service (NHS) England practice. Firstly, as highlighted by the EAG, eribulin is included at both 2L and 3L in the TPC arm of DESTINY-Breast04, in accordance with its licensed indication, but is recommended by NICE at 3L and beyond (i.e., after 2 or more lines of prior chemotherapy [TA423][6]). Secondly, the EAG suggested that gemcitabine is not currently prescribed or licensed as a single-agent chemotherapy for u/mBC in NHS England clinical practice yet is included in the TPC arm of DESTINY-Breast04. The company considers that these differences would be unlikely to impact cost-effectiveness.[4] To explore this issue further, the EAG assumed equivalent efficacy across TPC agents and explored the impact of removing eribulin and gemcitabine drug acquisition costs and redistributing the eribulin and gemcitabine patient proportions to the remaining TPC agents to calculate the TPC arm drug acquisition costs. The company does not consider the complete removal of eribulin costs from TPC to be appropriate as eribulin is licensed for treating advanced or mBC after 1 or more lines of chemotherapy (i.e., 2L) and recommended by NICE for treating advanced or mBC after 2 or more lines of chemotherapy (TA423),[6] and clinical feedback to the company is that eribulin is a relevant comparator for this decision problem as clinicians prefer to use it as early as possible in

Key issue	Does this response contain new evidence, data or analyses?	Response
		the pathway. Any exploratory scenarios used for decision-making should therefore include 3L eribulin costs in the TPC arm, particularly as this appraisal is for the full licensed indication of T-DXd (i.e., after one *or more* lines of chemotherapy in the advanced or metastatic setting); as such, the use of T-DXd and eribulin in the 3L setting is relevant. The EAG also suggested that UK real-world evidence (RWE) comparing the efficacy of individual TPC agents with each other or comparing TPC agents with T-DXd may help to resolve this issue. Unfortunately, the company is unaware of such RWE. To address the EAG's concern and explore the uncertainty in the TPC arm, the company performed an exploratory post-hoc scenario analysis to evaluate the cost-effectiveness of T-DXd vs. TPC when eribulin 2L and gemcitabine (2L/3L) efficacy and costs are removed from the analysis. In this scenario, 2L patients assigned to eribulin and patients assigned to gemcitabine at any line (2L/3L), prior to randomisation, were removed from DESTINY-Breast04 to ensure that the TPC arm more closely reflects agents included in the final NICE scope. The resulting distributions of the remaining agents in the TPC arm were: eribulin 3L (n=[redacted], [redacted]%), capecitabine (n=[redacted], [redacted]%), nab-paclitaxel (n=[redacted], [redacted]%), and paclitaxel (n=[redacted], [redacted]%). As the choice of TPC agent was declared for each individual subject *before* randomisation (see Protocol v5.0 Section 5.1.1), it was possible to exclude corresponding patients from the T-DXd arm (i.e., it was possible to exclude patients in the T-DXd arm who would have been assigned 2L eribulin or gemcitabine (2L/3L) had they been randomised to receive TPC). This approach preserves randomisation, as the observed and unobserved patient characteristics should still be balanced between the two treatment arms after excluding these patients. In addition, since the number of prior lines of chemotherapy was a randomisation stratification factor in the trial, the 2:1 distribution of T-DXd to TPC is

Key issue	Does this response contain new evidence, data or analyses?	Response
		maintained in this analysis. It should be noted that this an exploratory post-hoc analysis that results in a smaller sample size than the full analysis set (FAS). In this exploratory scenario analysis, T-DXd (N=247) was associated with a [redacted]% lower risk of progression or death compared with TPC (N=118; progression-free survival [PFS] by blinded independent central review [BICR] HR: [redacted]; 95% CI [redacted], [redacted]; p<[redacted]), which is consistent with the outcome for the FAS population (HR: 0.50; 95% CI: 0.40, 0.63; p<0.0001). T-DXd was also associated with a [redacted]% lower risk of death compared with TPC in the exploratory scenario (OS HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]), which was consistent with the outcome for the FAS population (HR: 0.64; 95% CI: 0.49, 0.84; p=0.001).[7] The similarities between outcomes in the FAS and exploratory scenario (2L eribulin and gemcitabine 2L/3L removed) discussed above indicate that TPC agents have broadly similar efficacy and that the FAS is a robust population for decision-making.[7] The efficacy data from the above scenario was applied to the economic model (using all the same settings as the revised company base case), and the TPC costs were adjusted accordingly to evaluate the cost-effectiveness results compared with the FAS. In the revised company base case, in the FAS T-DXd is associated with [redacted] incremental QALYs and £[redacted] incremental costs, resulting in an ICER of £[redacted] with the 1.2x severity modifier applied. In the exploratory scenario analysis, T-DXd is associated with [redacted] incremental QALYs and £[redacted] incremental costs, translating to an ICER of £[redacted] with the 1.2x severity modifier applied. The similarity in these ICERs demonstrates that adjusting the TPC arm costs and efficacy in this exploratory scenario,

<table>
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to more closely reflect NHS England practice, has minimal impact on the cost-effectiveness results.

While the results in the exploratory scenario reduce the ICER vs. the company revised base case, the company maintains the FAS in the base case as this is the most robust population to inform decision-making.

Table 1: Scenario deterministic results in the FAS population | Efficacy and costs of eribulin 2L and gemcitabine (2L/3L) removed (T-DXd PAS price; 1.2x severity modifier)
<table>
<tr><th>Technology</th><th>Total costs (£)</th><th>Total life years gained (LYG)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£)</th></tr>
<tr><td colspan="8">Company base case</td></tr>
<tr><td>TPC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>T-DXd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="8">Exploratory scenario: Efficacy and costs of eribulin 2L and gemcitabine (2L/3L) removed</td></tr>
<tr><td>TPC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>T-DXd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: 2L, second-line; 3L, third-line; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 2: Trastuzumab deruxtecan is assumed to be clinically equivalent to sacituzumab govitecan in the hormone receptor (HorR)-negative subgroup	No	The EAG highlighted that the company's exploratory cost-minimisation analysis (CMA) between T-DXd and sacituzumab govitecan (SG) does not adequately address the question of whether T-DXd is clinically effective or cost-effective in comparison to SG because it assumes clinical equivalence between the two treatments. Importantly, the EAG agreed with the company's findings from two independent indirect treatment comparison (ITC) feasibility assessments that an ITC between T-DXd and SG would be highly uncertain and not sufficiently robust for decision-making due to the differences in study populations between DESTINY-Breast04 and ASCENT, the small sample size (N=42) of the HR-negative cohort in DESTINY-Breast04, and the small sample size (N=63), post hoc nature of analyses of HER2-low/HR-negative patients, and limited data reporting in the ASCENT trial.[8] The EAG also accepted that there are material differences in the population characteristics between DESTINY-Breast04 and ASCENT that may result in biased ITC estimates without adjustments and that using a matching-adjusted indirect comparison (MAIC) may lead to a small effective sample size. This limits any comparisons between T-DXd and SG. The company also recognises that the EAG suggested that RWE comparing T-DXd to SG in the HER2-low population would help clinicians select the most effective treatment in patients eligible for either T-DXd or SG. Unfortunately, such data do not currently exist. Given the limitations in any ITC between T-DXd and SG, and the absence of RWE in HER2-low u/mBC, in response to EAG clarification question A21, the company presented a naïve, unadjusted comparison of outcomes from ASCENT vs. DESTINY-Breast04. This showed that the HRs for both PFS and OS are similar between T-DXd vs. TPC and SG vs. TPC, and the 95% CIs overlap considerably (Table 2). In the absence of more robust

<table>
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<tr><td></td><td></td><td>evidence, the company has used the naïve comparison to assume comparable relative efficacy between T-DXd and SG and consequently conducted a CMA between T-DXd and SG.

Table 2: DESTINY-Breast04 (FAS) and ASCENT PFS and OS outcomes
<table>
<tr><th>Study (pop.)</th><th>Analysis</th><th>Outcome</th><th>Median, months</th><th>Difference in median, months</th><th>HR (95% CI)</th></tr>
<tr><td rowspan="2">ASCENT (HER2-low/HR-negative)[9]</td><td rowspan="2">SG vs. TPC</td><td>PFS</td><td>SG: 6.2
TPC: 2.9</td><td>3.3</td><td>0.44 (0.27, 0.72)</td></tr>
<tr><td>OS</td><td>SG: 14.0
TPC: 8.7</td><td>5.3</td><td>0.43 (0.28, 0.67)</td></tr>
<tr><td rowspan="2">DESTINY-Breast04 (HER2-low/HR-negative)[7]</td><td rowspan="2">T-DXd vs. TPC</td><td>PFS</td><td>T-DXd: 8.5
TPC: 2.9</td><td>5.6</td><td>0.46 (0.24, 0.89)</td></tr>
<tr><td>OS</td><td>T-DXd: 18.2
TPC: 8.3</td><td>9.9</td><td>0.48 (0.24, 0.95)</td></tr>
</table>
Abbreviations: CI, confidence interval; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR-negative, hormone receptor negative; OS, overall survival; PFS, progression-free survival; pop, population; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

While the company acknowledges that SG is a relevant comparator in a small subpopulation of the full appraisal population, given it is not possible to conduct a robust ITC between T-DXd and SG for the HER2-low/HR-negative subgroup, the CMA is a pragmatic solution to explore the relative incremental cost of T-DXd vs. SG. Using the</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		naive analysis presented above to assume equivalent efficacy, the exploratory CMA results presented in response to Clarification Question B1 show that T-DXd (PAS price) is associated with a total cost of £[redacted] and SG a total cost of £[redacted], meaning that T-DXd is associated with a saving of £[redacted] over a lifetime time horizon. The company notes that the EAG preferred to make some adjustments to the company CMA. The company agrees with the EAG's use of average patient weight for HR-negative patients from DESTINY-Breast04 and using the relative dose intensity (RDI) estimates for SG from TA819. The company disagrees with the EAG's use of SG time-on-treatment data from TA819 because the ASCENT and DESTINY-Breast04 populations are different and because time-on-treatment is dependent on, and may impact, a wide range of clinical factors, including toxicity and efficacy. Instead of different time-on-treatment values, the company proposes applying the Grade ≥3 treatment-related treatment-emergent adverse event (TEAE) rate from the SG arm in ASCENT to the SG arm of the model and the corresponding rates for the T-DXd arm of DESTINY-Breast04 to the T-DXd arm in the model. Based on these updates to the CMA, T-DXd is associated with a total cost of £[redacted] and SG a total cost of £[redacted], meaning that T-DXd is associated with a savings of £[redacted] over a lifetime time horizon. While the naïve comparison and exploratory CMA have limitations, they indicate that T-DXd is associated with lower costs and lower use of NHS resources compared with SG. Notwithstanding the limitations of this exploratory analysis, the company considers that the information is useful for the committee for decision-making in a population with a very high unmet need. Notably, exploratory efficacy analyses from DESTINY-Breast04 demonstrate that T-DXd is associated with a 54% improvement in PFS by BICR compared

Key issue	Does this response contain new evidence, data or analyses?	Response
		with TPC in the HER2-low/HR-negative population (HR: 0.46; 95% CI: 0.24, 0.89).[10] Similarly, T-DXD is associated with a 52% improvement in OS compared with TPC (HR: 0.48; 95% CI: 0.24, 0.95).[10] Given the poor outcomes with single-agent chemotherapy and the limited effective treatment options, these efficacy results highlight the need for T-DXd to be made available to patients with HER2-low/HR-negative u/mBC.
Issue 3: Is the population of DESTINY-Breast04 generalisable to people likely to have trastuzumab deruxtecan in the NHS?	Yes	The EAG stated that the baseline characteristics of the population enrolled in DESTINY-Breast04 may not reflect the characteristics of patients seen in UK clinical practice. In particular, the EAG noted that the DESTINY-Breast04 population excluded patients with Eastern Cooperative Oncology Group performance status (Eastern Cooperative Oncology Group [ECOG] progression status [PS]) of ≥2, had a relatively high proportion of Asian patients (40%), and had a younger average age (56.5 years) compared to patients potentially seen in UK clinical practice. ***Generalisability of DESTINY-Breast04*** As is common in global RCTs, variation in geographic locations of study sites can lead to demographic and baseline characteristic differences between intention-to-treat (ITT) populations and real-world populations in individual countries. This is a common challenge with health technology appraisals (HTA) decision-making, where local reimbursement decisions are based on data from global RCTs. While the company acknowledges that there will inevitably be discrepancies between the DESTINY-Breast04 trial population and the population expected to receive T-DXd in UK practice, we strongly consider that the differences would not impact decision-making and that the DESTINY-Breast04 population is generalisable to UK clinical practice. This was confirmed by UK clinical experts at an advisory board in December 2022, who agreed that the DESTINY-Breast04 population is generalisable to UK patients with HER2-low u/mBC, including both demographic and

Key issue	Does this response contain new evidence, data or analyses?	**Response**
		prognostic factors.[1] This was also confirmed by UK clinician advice to the company during technical engagement. ***Identifying prognostic factors and treatment effect modifiers in the ITC*** The company would also like to make a point of clarification. In the EAG report, page 5, the EAG states that the company considers ECOG PS and Asian ethnicity to be potential treatment effect modifiers. This was based on content in the CS and EAG clarification questions related to the potential prognostic factors and treatment effect modifiers explored in the company's ITC feasibility assessments.[11,12] However, in the company ITC feasibility assessments, a broad and comprehensive approach was taken to exploring data on prognostic factors and treatment effect modifiers to leverage as much of the limited published data as possible. In ITC feasibility assessment A,[12] modifiers were identified by assessing the frequency that they were reported in a literature search of HTAs for advanced cancer treatments in NICE and Canadian Agency for Drugs and Technologies in Health databases and also by looking at the subgroups identified for subgroup analyses in DESTINY-Breast04. In ITC feasibility assessment B,[11] modifiers were conservatively assumed to be any reported randomisation stratification factors, any baseline characteristics, or any variables explored in subgroup analyses across DESTINY-Breast04 and ASCENT. This comprehensive approach to identifying potential modifiers does not mean that the company definitively considers the identified factors to be treatment effect modifiers. To address the EAG's concern regarding specific differences related to ECOG PS, race, and age, the company has provided supplemental subgroup analyses below. These analyses should be interpreted with caution as DESTINY-Breast04 was not powered to assess efficacy differences between subgroups.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Efficacy based on ethnicity The EAG highlighted that the DESTINY-Breast04 study had a higher proportion of Asian patients than would be expected in UK practice. This is to be expected for a global RCT – particularly for this study as the sponsor (Daiichi Sankyo Inc.) is a Japanese company – and does not necessarily mean that the results of the study cannot be generalised to the population expected to receive T-DXd in the UK. Firstly, as expected in an RCT setting, the patient characteristics were well-balanced between the two treatment arms in the FAS population of DESTINY-Breast04, with 40.5% vs 39.1% Asian patients in T-DXd and TPC arms, respectively.[13] Thus, any differences in ethnicity apply to both arms of the study, which should minimise the impact on the relative treatment effect of T-DXd vs. TPC. Secondly, ethnicity does not significantly impact the treatment effect of T-DXd vs. TPC, as shown by pre-specified subgroup analyses in the FAS of DESTINY-Breast04. For PFS by BICR, the statistically significant effect of T-DXd vs. TPC was consistent between the FAS, Asian ethnicity subgroup, and White ethnicity subgroup, as shown by overlapping 95% CIs (FAS: HR 0.50, 95% CI 0.40, 0.63; Asian subgroup: HR 0.38, 95% CI 0.27, 0.53; White subgroup: HR 0.63, 95% CI 0.45, 0.87).[13] Similar findings were also observed with OS, where subgroup analysis of the FAS showed a consistent effect of T-DXd vs. TPC in the FAS, Asian ethnicity subgroup, and White ethnicity subgroup, as indicated by similar HRs and overlapping 95% CIs (FAS: HR 0.64; 95% CI: 0.49, 0.84; Asian subgroup: HR [redacted], 95% CI [redacted], [redacted]; White subgroup: HR [redacted], 95% CI [redacted], [redacted]). These subgroup analyses suggest that ethnicity has no meaningful impact on the treatment effect of T-DXd. This was also confirmed by UK clinical experts at a December 2022 advisory board,

Key issue	Does this response contain new evidence, data or analyses?	Response
		who agreed that there is no biological reason for ethnicity to impact outcomes or the relative treatment effect of T-DXd in u/mBC. ***Efficacy based on ECOG PS*** As stated in response to EAG clarification question A15, the majority (60%) of oncology trials exclude patients with ECOG PS ≥2 or equivalent Karnofsky PS of ≥70%.[14] This includes a number of recent u/mBC studies, including studies that formed the basis of NICE recommendations (e.g., DESTINY-Breast01 in TA704; ASCENT study in TA819; DESTINY-Breast03 in TA862).[5,15,16] The DESTINY-Breast04 study eligibility criteria related to ECOG PS is therefore comparable to recent oncology studies, and should be considered appropriate for decision-making for this appraisal. In addition, T-DXd is expected to predominantly be used in patients with ECOG PS 0 or 1 in UK clinical practice. This is in line with the Cancer Drugs Fund (CDF) managed access agreement criteria for T-DXd in HER2-positive mBC after ≥1 anti-HER2 treatment (TA862)[16] and after ≥2 anti-HER2 treatments (TA704),[15] which restrict the use of T-DXd to patients with ECOG 0 or 1. [redacted][17] This highlights that the DESTINY-Breast04 eligibility criteria, which include patients with ECOG PS of 0 or 1, are generalisable to UK clinical practice. The subgroup analyses in the FAS of DESTINY-Breast04 confirm that ECOG PS has no meaningful impact on the relative effect of T-DXd vs. TPC. For PFS by BICR, the treatment effect of T-DXd vs. TPC was consistent in the FAS, the ECOG PS 0 subgroup (N=305), and the ECOG PS 1 subgroup (N=252), as shown by similar HRs and overlapping 95% CIs

Key issue	Does this response contain new evidence, data or analyses?	Response
		(FAS: HR 0.50, 95% CI: 0.40, 0.63; ECOG PS 0: HR 0.52; 95% CI: 0.38, 0.70; ECOG PS 1: HR 0.49; 95% CI: 0.36, 0.68).[13] Similar findings were observed with OS (FAS: HR 0.64, 95% CI: 0.49, 0.84; ECOG PS 0: HR [redacted], 95% CI: [redacted], [redacted]; ECOG PS 1 HR: [redacted], 95% CI: [redacted], [redacted]).[13] These data demonstrate that ECOG PS is not a significant treatment effect modifier for T-DXd in HER2-low u/mBC. UK clinical experts agreed that they expect the treatment effect of T-DXd vs. TPC to be consistent across all subgroups, including ECOG PS.[1] ***Efficacy based on age*** The EAG noted that the population seen in UK clinical practice are older than the population enrolled in DESTINY-Breast04. However, [redacted], which aligns with the median age of the FAS population of DESTINY-Breast04 (56.5 years).[17] UK clinical experts consulted by the company also agreed that baseline characteristics, including age, were generalisable to UK clinical practice and were well-balanced across trial arms. UK clinical experts also commented that it is typical for trials to recruit younger patients. The subgroup analyses of patients aged <65 years and ≥65 years in DESTINY-Breast04 showed consistent results to the FAS for the relative efficacy of T-DXd vs. TPC. The treatment effect of T-DXd vs. TPC in terms of PFS by BICR was consistent across the FAS, the subgroup of patients aged <65 years (n=426), and the subgroup aged ≥65 years (n=131), as shown by similar HRs and overlapping 95% CIs (FAS: HR 0.50, 95% CI 0.40, 0.63; <65 years old: HR 0.47, 95% CI 0.37, 0.61; ≥65 years old subgroup: HR 0.57, 95% CI: 0.36, 0.89).[13] Similar findings were observed with OS (FAS: HR 0.64, 95% CI: 0.49, 0.84; <65 years subgroup: HR [redacted], 95% CI [redacted], [redacted]; ≥65 years subgroup: HR

Key issue	Does this response contain new evidence, data or analyses?	**Response**
		[redacted], 95% CI [redacted], [redacted]).[13] Subgroup analyses therefore indicate that age has no meaningful impact on the relative efficacy of T-DXd. ***Summary*** In conclusion, the company considers the DESTINY-Breast04 study to be generalisable to and consistent with UK practice. Subgroup analyses show that the efficacy of T-DXd is consistent across pre-specified subgroups, including Asian ethnicity, ECOG PS 0 and 1, and patient age. Given that the DESTINY-Breast04 FAS is aligned with the licensed indication and population for T-DXd, the company considers the FAS to be the most robust and appropriate population for decision-making in this appraisal.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 4: Extrapolation of overall survival. Which extrapolated survival curve is more clinically plausible? Log-logistic or gamma or Weibull?	Yes	***Introduction*** The EAG disagreed with the company's base case choice of the log-logistic curve for OS, deeming it to overestimate survival. Instead, the EAG used the Weibull curve to estimate OS in their preferred base case. To help resolve the issue, the EAG suggested that OS data from the next data cut from DESTINY-Breast04 may help. However, DESTINY-Breast04 met its key secondary endpoint of OS in the FAS population; the difference in OS between T-DXd and TPC was statistically significant and

median OS was reached in both treatment arms (Table 3) and no further planned data cuts are required as per the trial protocol (CS, Section B.2.6.2). As such, the company considers that the OS data are robust and mature, which support long-term extrapolations suitable for decision making.

In developing the base case, the company has taken a comprehensive approach to determine the most appropriate methods for the extrapolation of survival data from DESTINY-Breast04, in line with best practice guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[18] (discussed in CS Section B.3.3.2). The full range of recommended parametric curves were evaluated, and the appropriate base case was selected using a series of statistical criteria, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the parametric curve fit to the observed data and assessment of the plausibility of fitted models after the end of the follow-up period. Clinical and health economics and outcomes research (HEOR) validation was sought at each stage, including assessment of the plausibility of long-term estimates of the fitted parametric curves. In addition, the company compared the long-term extrapolations with available RWE for u/mBC to determine the clinical plausibility of the curves.

Based on the criteria above, the company considers the log-logistic curve to be the most appropriate curve to inform the T-DXd and TPC base case extrapolations of OS as it reflects the best statistical and visual fit to the TPC KM and provides clinically plausible, but conservative, long-term survival estimates.

Table 3: DESTINY-Breast04 | Analysis of OS | FAS

	FAS	
	T-DXd (N=373)	**TPC (N=184)**
Median overall survival, months*	23.4	16.8
(95% CI)*	(20.0, 24.8)	(14.5, 20.0)
12 month survival probability, % (95% CI)‡	78.8 (74.3, 82.7)	66.5 (58.8, 73.2)
24 month survival probability, % (95% CI)‡	48.1 (40.8, 54.9)	32.0 (21.9, 42.4)
Stratified Cox proportional hazards model hazard ratio†	0.6408	
(95% CI)†	(0.4903, 0.8375)	

		Stratified log-rank test p-value† | 0.0010 *Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method. †Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by the IXRS. ‡Estimate and CI for OS rate at the specified timepoint are from KM analysis. Abbreviations: CI, confidence interval; FAS, full analysis set; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. Sources: Modi et al., 2022;[7] Daiichi Sankyo Inc., 2022 (CSR, Data on File)[2] The response to this issue is structured as follows: • Assessment of the statistical goodness-of-fit scores for fitted models • Fitting of parametric models and visual fit against KM data • Long-term clinical plausibility o TPC o T-DXd • Validation against real-world evidence • Additional data: gamma curve • Summary Given that the company base case includes the log-logistic curve and the EAG's preferred base case is the Weibull curve, the focus of the responses is on these two curves. However, the log-normal curve is also discussed as it provides clinically plausible long-term extrapolations. ***Assessment of the statistical goodness-of-fit scores for fitted models*** As detailed in the CS (B.3.3.2.1) and in Table 4, the log-logistic curve provides the best overall fit to the clinical data for the TPC arm based on the goodness-of-fit statistics, with the lowest AIC and BIC scores across all fitted curves. For the T-DXd arm, the log-logistic curve remained within 5 AIC and BIC points of the best-fitting curve and was therefore considered to be a good statistical fit.[20]

Table 4: Statistical goodness-of-fit scores (OS, independent models) in the FAS population

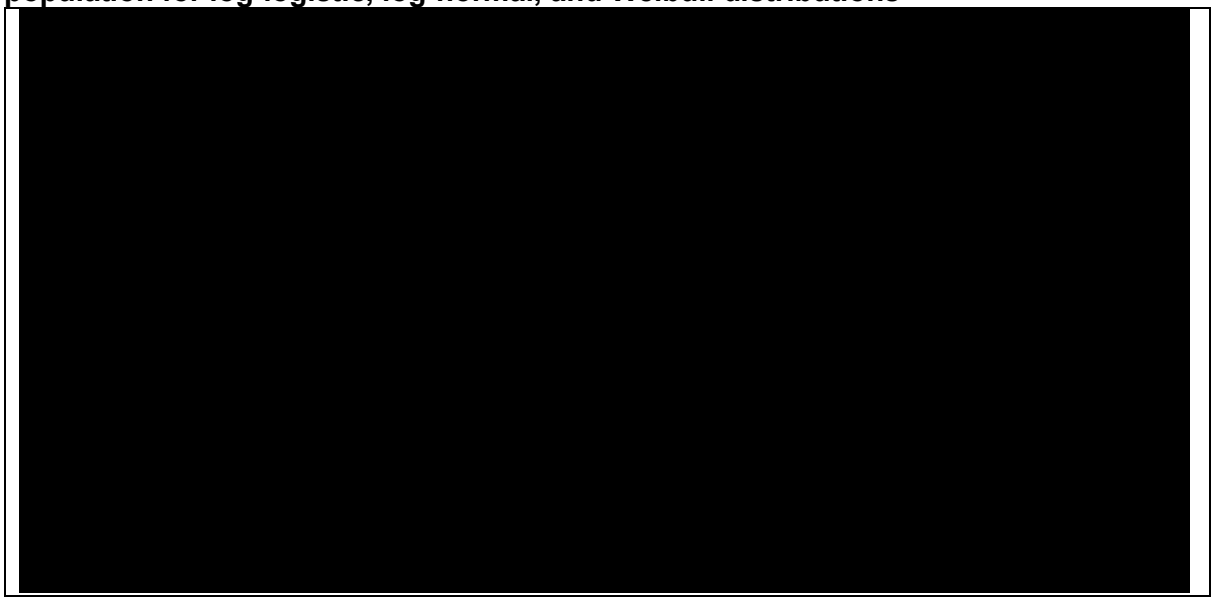
Model	TPC		T-DXd	
	AIC	BIC	AIC	BIC
Log-logistic (Company base case)	**751.10**	**757.53**	1371.38	1379.22
Weibull (EAG base case)	751.16	757.59	1366.90	1374.74
Exponential	765.60	768.81	1389.90	1393.83
Gompertz	756.20	762.63	**1366.87**	**1374.71**
Log-normal	759.16	765.59	1390.55	1398.39
Generalised gamma	753.01	762.65	1367.59	1379.35

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FAS, full analysis set; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Fitting of parametric models and visual fit against KM data

Observed KM data versus predicted log-logistic, log normal and Weibull curves are presented below for TPC and T-DXd (Figure 1 and Figure 2, respectively). While both the log-logistic and Weibull curves provide a good visual fit to the observed KM data in both treatment arms, the company considers the log-logistic curve to provide the best visual fit.

		Figure 1: Observed verses predicted OS for TPC over a 10-year time horizon in the FAS population for log-logistic, lognormal and Weibull distributions  Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

		Figure 2: Observed verses predicted OS for T-DXd over a 10-year time horizon in the FAS population for log-logistic, log-normal, and Weibull distributions  Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; T-DXd, trastuzumab deruxtecan. The EAG considered that the smoothed hazard functions of the log-logistic distribution do not seem to capture the shape of the unsmoothed hazard functions well due to censoring at the end of the trial. The company acknowledge this variation and would like to highlight the small number of patients at risk at later timepoints, particularly in the TPC arm (7 patients at risk at 2 years); therefore, the company considers that the shape of unsmoothed hazard curves after two years should be interpreted with caution. The strength of the visual and statistical fit of the log-logistic curve is further demonstrated when modelled OS estimates are compared against the observed data from DESTINY-Breast04 across both treatment arms; median OS predicted in the model using a log-logistic curve of [redacted] months and [redacted]

		months, for TPC and T-DXd respectively, is similar to the observed median OS in DESTINY-Breast04 of 16.8 months and 23.4 months for the TPC arm and the T-DXd arm, respectively. ***Long-term clinical plausibility*** Following feedback from UK clinical experts consulted by the company as part of an advisory board meeting in December 2022, the log-logistic, log-normal and exponential curves were considered clinically plausible for both TPC and T-DXd arms based on long-term extrapolation and landmark survival estimates. However, the exponential curve was dismissed as it does not provide a good visual fit to the KM data, nor a good statistical fit (Figure 26, Figure 27 and Table 35 of CS). The clinical plausibility of the long-term extrapolations for the TPC and T-DXd arms is described in more detail below. *TPC* For the TPC arm, UK clinical experts consulted by the company during an advisory board (December 2022) independently stated that it is not plausible to assume that less than [redacted]% of patients will be alive at 5 years. Further UK clinical advice was sought during NICE technical engagement (June 2023); UK clinical expert advice was that [redacted]% of patients treated with TPC would be alive at 5 years and a small proportion would be alive at 10 years. Based on this feedback, of the TPC arm OS curves (Table 5), the Weibull, Gompertz, and generalised gamma curves were considered too pessimistic and not clinically plausible to inform the TPC OS extrapolation, whereas the log-logistic, log-normal, and exponential curves were considered plausible. Clinical experts considered the log-logistic curve to be the most clinically plausible to inform the TPC arm, with a 5-year OS estimate of [redacted]% and a 10-year OS estimate of [redacted]% (Table 5). The exponential curve was dismissed due to poor visual fit to the DESTINY-Breast04 Kaplan Meier data. While the log-normal curve was also considered to be clinically plausible based on expert advice, the company selected log-logistic for the base case as it has a better visual fit to the observed TPC KM data and is more conservative. This is further supported by the EAG's clinical advisors, who "*considered that it is more reasonable that the 5-year survival probability is approximately [redacted] as predicted by the log-logistic model rather than approximately [redacted] as predicted by the Weibull model*" and "*an estimate of [redacted] survival at 5-years was reasonable under current care"* (page 119-120 of the final EAG report). The EAG also

acknowledge that the Weibull curve may lack clinical validity: "*the Weibull model may underestimate 5-year survival probability and highlight that the use of Weibull as the base case may provide a pessimistic result for both the T-DXd and TPC arms*" (page 122). Clinical expert advice to the company during NICE technical engagement also noted that the decline in survival from Year 1 to 3 is too extreme for the Weibull curve, resulting in long-term estimates that are too pessimistic.

The company considers that the log-logistic curve therefore provides the most conservative plausible OS estimate for TPC, is within the clinically plausible range across timepoints as defined by UK clinical experts consulted by the company and is best aligned to the EAG's clinical advisors feedback.

Table 5: TPC OS in the FAS population: Predictions by independently fitted distributions

Distribution	Median (months)*	1-Year OS	1.5-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
DB-04 – FAS population (observed data)	16.8	66.5%	45.9%	32.0%	-	-	-
Weibull (EAG base case)	[redacted]						
Log-logistic (company base case)	[redacted]						
Log-normal	[redacted]						
Exponential	[redacted]						
Gompertz	[redacted]						
Generalised gamma	[redacted]						

*Median time in months and predicted OS are estimated after OS has been adjusted to include general population mortality
Abbreviations: DB04 – DESTINY-Breast04; FAS – full analysis set; OS – overall survival; TPC, treatment of physician's choice.

T-DXd

The log-logistic curve was considered by UK clinical experts at an advisory board (December 2022) to be among the most clinically plausible curves to inform the T-DXd arm, as the curve provides the most plausible OS estimates for T-DXd at 5 and 10 years. The company notes that the EAG considers the log-logistic curve to overestimate survival probability from approximately months 18–24. The landmark OS estimates at 1.5 and 2 years using the log-logistic curve are similar to the observed OS from the

DESTINY-Breast04 FAS population at these timepoints. In the longer-term, clinical experts indicated that some patients would still be expected to be alive at 10 years in the T-DXd arm and therefore considered the Weibull curve to be too pessimistic, with a 10-year OS estimate of [redacted]% compared with [redacted] % using the log-logistic curve (Table 6). Clinical experts also considered the log-normal curve to be plausible, but the company considered that log-logistic to be more conservative (Figure 2) and therefore included it in the base case for the T-DXd arm.

While not explicitly stated, the EAG's clinical advisors appear to align with the clinical experts consulted by the company. For the TPC arm, the EAG's clinical advisors "*considered that it is more reasonable that the 5-year survival probability is approximately* [redacted] *as predicted by the log-logistic model rather than approximately* [redacted] *as predicted by the Weibull model*" and "*an estimate of 5% survival at 5-years was reasonable under current care"* (page 119-120 of the final EAG report). Given that T-DXd demonstrated a statistically significant benefit in OS compared with TPC in DESTINY-Breast04, OS estimates for TPC should serve as a minimum estimated OS for T-DXd. If 5% OS is considered clinically plausible for the TPC arm based on the EAG clinical expert comments above, the Weibull estimate of [redacted]% for the T-DXd arm – [redacted] to the 5% TPC value estimated by clinical experts – highlights that the Weibull curve may underestimate the OS benefit of T-DXd as it implies that there is [redacted] OS benefit associated with T-DXd at 5 years; this is inconsistent with feedback from clinical experts consulted by the company who stated that an OS benefit is expected as far as 10 years. The Weibull curve therefore appears to be too pessimistic for the T-DXd arm, whereas the log-logistic curve appears to be conservative but clinically plausible.

Table 6: T-DXd OS in the FAS population: Predictions by independently fitted distributions

Distribution	Median (months)*	1-Year OS	1.5-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
DB04 –FAS population (observed data)	23.4	78.8%	61.7%	48.1%	-	-	-
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Log-normal	[redacted]	
Exponential	[redacted]	
Gompertz	[redacted]	
Generalised gamma	[redacted]	

*Median time in months and predicted OS are estimated after OS has been adjusted to include general population mortality
Abbreviations: DB04 – DESTINY-Breast04; FAS – full analysis set; OS – overall survival; T-DXd – trastuzumab deruxtecan.

Validation against real-world evidence

The appropriateness of the log-logistic OS curve is further supported by long-term OS estimates from RWE studies, most notably findings from an as-yet unpublished 2023 company data on file analysis of data from the Flatiron Health Enhanced Datamart database conducted by the company (hereon termed 'Flatiron study').

Flatiron study

The Flatiron database provides longitudinal patient-level data from electronic health records from cancer care providers across the United States (80% community practices, 20% academic centres). The Flatiron study is a large, retrospective, observational cohort study aimed to examine survival outcomes among a real-world cohort of [redacted] (i.e., to assess real-world outcomes with current standard of care in a patient cohort similar to the DESTINY-Breast04 FAS population).[21] For this analysis, data from a [redacted] data cut were used, including data from [redacted]. The data presented relate to the [redacted] which reflects eligibility criteria broadly aligned to those in DESTINY-Breast04 and [redacted]

Of [redacted] patients with a confirmed mBC diagnosis during the study period, a total of [redacted] patients met the inclusion criteria for the analysis, having a population similar to the DESTINY-Breast04 trial population [redacted]).[21]

		Patients had a mean age of [redacted] years (vs. 55.9 and 56.5 years in the TPC and T-DXd arms, respectively, of the DESTINY-Breast04 FAS).[21] Of patients with known ECOG PS, [redacted]% were ECOG PS 0 ([redacted]%) or 1 ([redacted]%), indicating [redacted] than the DESTINY-Breast04 FAS (ECOG PS 0: 57.1% and 53.6%, ECOG PS 1: 42.9% and 46.4% for TPC and T-DXd, respectively).[21] The [redacted] in the Flatiron study [redacted], which were all part of the TPC arm of DESTINY-Breast04 and are well represented in the NICE final scope. In the Flatiron study, of [redacted] patients, there were [redacted] OS events (Figure 3).[21] Median OS was [redacted] months (95% CI: [redacted], [redacted]) and the one-year survival rate was [redacted]% (95% CI: [redacted]%, [redacted]%).[21] This is [redacted] the median OS in the TPC arm of the DESTINY-Breast04 FAS (median: 16.8 months; 95% CI: 14.5, 20.0) and the 1-year survival rate (66.5%; 95% CI: 58.8%, 73.2%), as indicated by [redacted].[21] Notably, Figure 3 and Figure 4 show that the Flatiron data validate the choice of the log-logistic curve as a clinically plausible curve for OS extrapolation for the TPC arm, as selected in the company base case. In the Flatiron study, the 5-year survival rate was [redacted]% (95% CI [redacted]%, [redacted]%) and the 10-year survival rate was [redacted]% (95% CI: [redacted]%, [redacted]%).[21] By comparison, the log-logistic curve predicted a 5-year survival rate for the TPC arm of [redacted]% and a 10-year survival rate of [redacted]% and the Weibull curve predicted 5- and 10-year survival rates of [redacted]% and [redacted]%, respectively (Table 5). This highlights that the Weibull curve, as preferred in the EAG base case, is too pessimistic, while the log-logistic curve is clinically plausible and may be conservative. Of note, the log-normal curve predicts 5- and 10-year survival rates of [redacted]% and [redacted]%, respectively, which [redacted]. In addition, the shape of the Flatiron OS curve [redacted] (Figure 4), particularly with regards to the tail, whereby the curve begins to plateau at ~[redacted]% survival rate from around [redacted] and a proportion of patients continue to survive in the longer-term (including [redacted] ([redacted]) in the Flatiron study). By contrast, the shape of the Flatiron study OS curve highlights that the modelled Weibull curve is too pessimistic, as [redacted] by [redacted] in the TPC arm with the OS Weibull curve.[21]

		In summary, while the Flatiron study is based on a US population and is an as-yet unpublished data on file analysis, it provides further support for the log-logistic curve as a conservative, clinically plausible choice for the OS extrapolations. The Flatiron study aligns with input from UK clinical experts, who stated that a small proportion of patients are expected to survive in the long-term. The Flatiron curve also indicates that the Weibull curve is pessimistic (consistent with clinical advice to the company and to the EAG) and that the log-normal curve is a clinically plausible curve (Figure 4). While the company maintains the use of the log-logistic curve as a conservative and clinically plausible base case, cost-effectiveness results from a scenario using the log-normal curve (also clinically plausible) are presented in Table 26.

Figure 3: Flatiron study: US real-world survival in patients with HER2-low mBC aligned to the FAS population in DESTINY-Breast04[21]

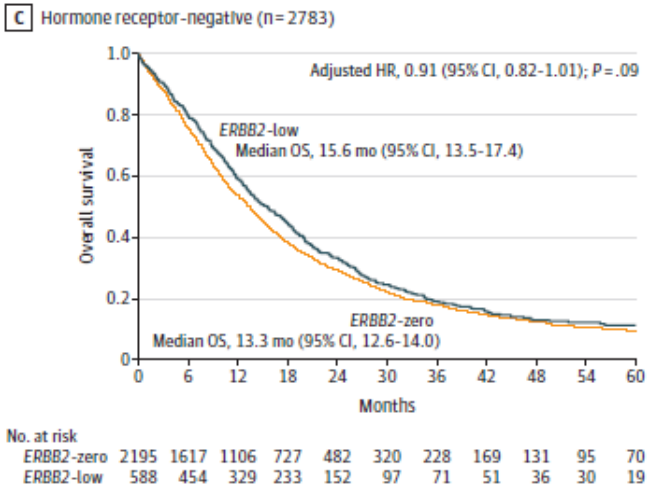
Abbreviations: CI, confidence interval

		Figure 4: Comparison of OS extrapolations from the TPC arm of DESTINY-Breast04 with Flatiron US real-world KM OS data in patients with HER2-low mBC aligned to the FAS population in DESTINY-Breast04[21]  Abbreviations: CI, confidence interval; FAS, full analysis set; OS, overall survival; RWE, real-world evidence; TPC; treatment of physician's choice.

		Other RWE To validate the OS curves and confirm the findings from the Flatiron study, the company identified two further RWE studies from Graff *et al*. (2023)[22] and de Calbiac *et al*. (2022).[23] Graff *et al*. presented a retrospective analysis of OS in 1,348 HER2-low/HR-positive advanced BC patients treated with CDK4/6 inhibitors. In this study, long-term (~7 years) OS is ~15%. By comparison, at 7 years the estimated OS in the TPC arm of DESTINY-Breast04 is [redacted]% using the Weibull distribution and [redacted]% using the log-logistic curve. The DESTINY-Breast04 patient cohort have received at least one additional line of therapy, therefore the OS is expected to be lower compared with the HER2-low cohort presented by Graff *et al* given their more advanced disease; however, OS is not expected to differ to such a large degree of [redacted]%, as proposed by using the Weibull curve. Therefore, while there are differences in the populations between the Graff study vs. the DESTINY-Breast04 study, the Graff study indicates that OS estimated using the log-logistic curve is more clinically plausible than the Weibull curve, which is pessimistic. The Graff study also aligns with the Flatiron study and supports UK clinical expert insights that a small proportion of patients survive in the long-term. The Graff study also presents an analysis of OS in 49 HER2-low/HR-negative advanced BC patients treated with first immune checkpoint inhibitors and showed OS at ~3 years of approximately ~43%.[22] At 3 years in the TPC arm of DESTINY-Breast04, estimated OS using the log-logistic curve is [redacted]% compared with [redacted]% when using the Weibull curve. The notably [redacted] OS estimate generated with the Weibull curve for the TPC arm of DESTINY-Breast04 ([redacted]%) than reported in Graff *et al*., (~43%)[22] further supports the assertion that the Weibull OS estimates are too pessimistic to be considered clinically plausible, and the log-logistic OS estimates are more closely aligned with RWE. The de Calbiac *et al*. (2022)[23] retrospective cohort study included 15,054 patients with mBC from the Epidemiological Strategy and Medical Economics database in France and assessed survival in HER2-low mBC compared with HER2-negative mBC. Of the 4,671 patients with HER2-low mBC (87.4% of which were HR-positive, similar to the DESTINY-Breast04 study), 1,514 (32.4%) patients received

chemotherapy with endocrine therapy and 28.8% of patients received chemotherapy without endocrine therapy as first-line treatment in the metastatic setting. Patients with HER2-low mBC had a 5-year OS of ~32%. This is considerably higher than the [redacted]% using the Weibull curve for the TPC arm of DESTINY-Breast04, and higher than the [redacted]% using the log-logistic curve, though it should be noted that the treatment line in the de Calbiac study was earlier than in DESTINY-Breast04. The de Calbiac[23] study also highlights that a small proportion of patients (~10%) survive in the long-term, as shown by the long tail in the OS KM curve for the HER2-low/HR-negative population (Figure 5). This long tail is consistent with the results from the Flatiron study and UK clinical expert advice to the company, and the shape of the curve is similar to the shape of the log-logistic curve from DESTINY-Breast04 (Figure 1).

Figure 5: Reproduced from de Calbiac *et al*. (2022)[23] | Kaplan-Meier analysis for OS according to ERBB2* status (ERBB2-low [HER2-low] vs ERBB2-Zero [HER2-negative])



*ERBB2 is the gene th*at encodes the HER2 protein*

Abbreviations: CI, confidence interval; ERBB2, Erb-B2 Receptor Tyrosine Kinase 2; HER2, human epidermal growth receptor 2; OS, overall survival.

		Summary of RWE Taken together, RWE indicates that the OS estimates using the Weibull curve are pessimistic, which aligns with clinical expert advice to both the company and the EAG. In particular, the Flatiron study, which is in a population of patients aligned to the DESTINY-Breast04 FAS population, highlights that a proportion of patients survive in the long-term and that the log-logistic OS estimates are clinically plausible, as selected in the company base case. ***Additional data: gamma curve*** While the EAG suggested it may be useful to provide the parameters for the gamma function to assess its impact in sensitivity analysis, the company would like to highlight that the six parametric curves included in the cost-effectiveness analysis (CEA) align with guidance from DSU TSD 14[18]: "*Exponential, Weibull, Gompertz, Log-logistic, log normal and Generalised Gamma models should be considered and if these appear unsuitable due to poor fit or implausible extrapolation, the use of piecewise modelling and other novel survival modelling methods such as those demonstrated by Royston and Parmar and Jackson et al. should be considered"*. As outlined above, the company considers that the log-logistic curve provides a strong statistical and visual fit to the clinical data, and generates long-term extrapolations aligned with RWE and clinical feedback provided to both the company and EAG. Therefore, the company does not believe it is necessary to explore the impact of alternative distributions or survival modelling methods, including the gamma distribution. ***Summary*** Given the maturity of the DESTINY-Breast04 OS data, statistical fit, visual assessment, and long-term clinical plausibility, the company considers that the log-logistic curve remains the most clinically plausible curve to inform the TPC and T-DXd base case extrapolations for OS. Notably, the log-logistic curve aligns with clinical expert input and RWE (particularly the Flatiron study, which reflects a population aligned to this appraisal), estimating that a proportion of patients survive in the long-term. The company therefore retain the log-logistic curve for both treatment arms in the revised company base case.

		By comparison, visual assessment and long-term clinical plausibility of the Weibull curve indicate that it does not provide a clinically plausible long-term extrapolation of OS at 5 and 10 years. Notably, clinical experts consulted by the company and the EAG, as well as the Flatiron study, confirm that a proportion of patients are expected to survive in the long-term. The Weibull curve estimates that [redacted]% of patients are alive at Year 5 and [redacted]% at Year 10. The company therefore considers that the Weibull curve generates highly pessimistic long-term survival estimates and is not appropriate to use in decision-making.

<table>
<tr>
<td>Issue 5: Estimation of patients entering the post-progression and death health states</td>
<td>No</td>
<td>The EAG noted in their report that the formulae used for the purposes of estimating the proportion of newly progressed patients in each cycle of the model essentially assumes that the risk of death from the post-progression (PP) state is zero. The EAG also highlighted that half-cycle correction does not need to be applied given the purpose of this update is to estimate the number of patients entering the progressed disease (PD) health state. The EAG adjusted the formulae used to account for the risk of death from the PP state. The company accepts the EAG amendment to the formulae.

Table 7 presents the scenario results of the revised company base case without this amendment. This scenario leads to an increase in the ICER of £[redacted] to £[redacted] compared with the revised company base case, with the 1.2x severity modifier applied.

Table 7: Scenario deterministic results in the FAS population, uncorrected post-progression calculations (T-DXd PAS price; 1.2x severity modifier)
<table>
<tr><th>Technology</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£)</th></tr>
<tr><td>TPC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td></td></tr>
<tr><td>T-DXd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PF, progression-free; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice.</td>
</tr>
<tr>
<td>Issue 6: Extrapolation of progression free survival.
Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?</td>
<td>No</td>
<td><u>Introduction</u>
The EAG highlighted that the company identified two curves, the log-logistic and generalised gamma, that provided the most plausible fits for PFS. The EAG suggested that generalised gamma may be more plausible than the log-logistic model because the longer tail of the log-logistic curve may be less consistent with the KM data for T-DXd. The company maintains that the log-logistic is the most appropriate model for extrapolation of PFS data based on visual fit, clinical validation, and the implausibility of the T-DXd and TPC generalised gamma curves crossing at approximately five years.</td>
</tr>
</table>

The company would like to highlight that DESTINY-Breast04 met its key secondary endpoint of PFS in the FAS population. A statistically significant difference was observed between T-DXd and TPC (HR: 0.5014, 95% CI: 0.4013 – 0.6265, p<0.001). Median PFS was reached in both arms (9.9 months and 4.2 months for T-DXd and TPC, respectively), and PFS data are therefore considered to be robust and mature to support long-term extrapolations for decision-making (Table 8).

In developing the base case, the company has taken a comprehensive approach to determine the most appropriate methods for the extrapolation of survival data from DESTINY-Breast04, in line with best practice guidance from DSU TSD 14[18] (discussed in CS Section B.3.3.2). The full range of recommended parametric curves was evaluated, and the appropriate base case was selected using a series of statistical criteria, including AIC and BIC statistics, visual inspection of the parametric curve fit to the observed data, and assessment of the plausibility of fitted models after the end of the follow-up period. Clinical and HEOR validation was sought at each stage, including the plausibility of long-term estimates of the fitted parametric curves.

Table 8: DESTINY-Breast04 | Analysis of PFS by BICR | FAS

	T-DXd (N=373)	**TPC (N=184)**
Median PFS, months†	9.9	5.1
(95% CI)†	(9.0, 11.3)	(4.2, 6.8)
Proportion alive and progression-free at specific timepoints (%)§		
12 months (95% CI)	[redacted]	[redacted]
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]
Stratified Cox hazard ratio‡	0.5014	
(95% CI)§	(0.4013, 0.6265)	
Stratified log-rank p-value	<0.0001	

†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, HR/CDK status, as defined by

		the IXRS. §Estimate and CI for PFS rate at the specified time point are from the KM analysis. Abbreviations: BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. Source: Modi et al., 2022[7]; Daiichi Sankyo Inc., 2022 (CSR; Data on File).[13] ***Statistical fit and visual assessment*** The log-logistic, log-normal and generalised gamma curves all provided good statistical fits for both the TPC and T-DXd arms, based on their AIC and BIC statistics. The strong fit of the log-logistic curves is also reflected in alignment between the estimated and observed PFS; the median PFS predicted in the model using a log-logistic curve is [redacted] months and [redacted] months, for TPC and T-DXd respectively, and is very similar to the observed median PFS in DESTINY-Breast04 of 5.1 months and 9.9 months for the TPC and T-DXd arms, respectively. Furthermore, the log-logistic curves had a good visual fit to the KM data, as demonstrated in Figure 6 and Figure 7. Based on the above, the company considers the log-logistic curves provide a strong statistical and visual fit to the KM data.

		Figure 6: Observed versus predicted PFS (TPC) in the FAS population for the log-logistic and generalised gamma curves  Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

		Figure 7: Observed versus predicted PFS (T-DXd) in the FAS population for the log-logistic and generalised gamma curves  Abbreviations: FAS, full set analysis; KM, Kaplan-Meier; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan. ***Long-term clinical plausibility*** The log-logistic curve provides good long-term TPC and T-DXd PFS estimates that are similar to the observed proportions in DESTINY-Breast04 (Table 9). For example, the 2-year estimates of PFS using the log-logistic curve are [redacted]% and [redacted]% for the TPC and T-DXd arms, respectively, which are closely aligned to the 2-year observed PFS from DESTINY-Breast04 of 8.2% and 18.1% for the TPC and T-DXd arms, respectively. The company notes that the landmark estimates from the log-logistic curve are similar to those predicted by the EAG's preferred curve (generalised gamma) across a range of timepoints.

The appropriateness of the log-logistic curve is supported by clinical and HEOR experts, who considered the log-logistic curve to be the most appropriate curve for PFS based on statistical fit, visual fit and clinical plausibility at landmark timepoints. Clinical and HEOR experts agreed that it would be preferable to use the same distribution for both PFS and OS, with clinical experts noting that there is an inherent relationship between PFS and OS. As demonstrated in Issue 4, the company considers the log-logistic curve to be the most appropriate for OS, while the generalised gamma is not relevant (due to poor statistical and visual fit and implausible long-term estimates). This suggests that the log-logistic curve is the most appropriate option for PFS.

Table 9: Observed PFS proportions derived from DESTINY-Breast04 compared to predicted proportions using the log-logistic and generalised gamma curves in the FAS population

Timepoint	TPC arm			T-DXd		
	DB-04 observed	Log-logistic	Generalised gamma	DB-04 observed	Log-logistic	Generalised gamma
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Plausibility of the generalised gamma curve

As highlighted in the EAG report, the EAG considers generalised gamma to be the most appropriate curve to extrapolate PFS. However, the EAG also note that the use of the generalised gamma curve to inform PFS extrapolations for both TPC and T-DXd arms results in a crossing of curves at approximately five years (Figure 8).

The company considers it highly implausible for the PFS curves for the TPC and T-DXd arms to cross. Crossing of the PFS curves for TPC and T-DXd means that, following the crossover, PFS would be lower for T-DXd than TPC. The company does not consider this clinically plausible given that mature trial data from DESTINY-Breast04 demonstrate a statistically significant improvement in PFS by BICR

		in the T-DXd vs. TPC arm (median PFS: 9.9 months vs. 5.1 months; HR: 0.50; p<0.001; FAS).[13] While the EAG note that the PFS KM curves are about to cross at the end of the DESTINY-Breast04 trial, this is likely an artefact due to the low numbers of patients-at-risk at the end of the PFS KM curve in DESTINY-Breast04. Although the EAG explore a scenario where a cap is imposed on the TPC PFS so that it remains the same as the T-DXd at the point of intersection, the company still consider it clinically implausible to assume equal PFS between T-DXd and TPC arms at five years given the treatment effect observed in the trial, where T-DXd demonstrated a statistically significant improvement in PFS vs. TPC. Additionally, given the substantial improvement that treatment with T-DXd has shown on multiple patient outcomes, the assumption of equal PFS at five years is considered clinically implausible. The generalised gamma curve is also inappropriate as the PFS estimates are inconsistent with what has been considered appropriate in previous appraisals. In TA819 (SG for treating unresectable locally advanced or metastatic triple-negative breast cancer [TNBC] after 2 or more therapies[5]), the selected base case PFS curve for the TPC arm (a similar TPC arm to DESTINY-Breast04) estimated that 0.09% of patients were progression-free at 10-years. This is higher than the [redacted]% estimated to be progression-free using the generalised gamma curve fitted to DESTINY-Breast04 data, despite ASCENT being a study of patients with TNBC, who are expected to have a poorer prognosis than the DESTINY-Breast04 FAS (~90% HR-positive) as TNBC outcomes are generally substantially worse than HER2-negative/HR-positive u/mBC. ASCENT was also conducted in a later-line population than DESTINY-Breast04. The EAG in TA819 stated that the company base case PFS curves were acceptable which further supports the case that intersecting PFS curves between treatment arms at such an early timepoint (i.e. 5 years), and therefore the use of the generalised gamma curve is implausible.

		Figure 8: TPC and T-DXd PFS extrapolations in the FAS population using the generalised gamma curve  Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

		Figure 9: TPC and T-DXd PFS extrapolations in the FAS population using the log-logistic curve  Abbreviations: FAS, full analysis set; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. ***Summary*** To conclude, the company maintain that the log-logistic curve is the most appropriate curve to inform the T-DXd and TPC base case extrapolations of PFS. This is based on statistical and visual fit, the similarity between the predicted and observed proportion at different timepoints over the long-term, clinical expert validation, and the implausibility of the TPC and T-DXd PFS curves intersecting when using the generalised gamma curves.

Issue 7: Extrapolation of time to treatment discontinuation. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	The company agrees with the EAG's preference to use the generalised gamma curve for the extrapolation of time-to-treatment discontinuation (TTD), in line with the company base case. TTD data from DESTINY-Breast04 are considered mature, with 98.3% and 84.4% of treatment discontinuation events having occurred in TPC arms and T-DXd, respectively. Across the T-DXd and TPC arms, the generalised gamma and log-logistic distributions, respectively, provide the best statistical fit to the TTD KM data from DESTINY-Breast04. In addition, both distributions provide a good fit to both trial arms. As stated in the CS and in response to EAG clarification question B6, the company used the generalised gamma curve to inform the model base case TTD for both trial arms as it provides a good statistical and visual fit to the KM data. For consistency, the same distribution was selected for both arms as advised for PFS and OS by HEOR and clinical experts. This is also recommended by NICE TSD 14, which says "*similar types of models should be used for the different treatment arms unless there is strong evidence to suggest an alternative is more plausible*".[18] The generalised gamma was preferred over the log-logistic because the log-logistic curve predicted estimates of time-on-treatment that were notably higher in the long-term than all other curves at most time points, which suggests it is an outlier. For example, the log-logistic curve predicted that [redacted]% of TPC patients would remain on treatment at 5 years, compared with [redacted]% for all other modelled distributions. For the T-DXd arm, log-logistic predicted that [redacted]% of patients would remain on treatment at 5 years, compared with [redacted]% for all other distributions (CS, Table 40). By contrast, the long-term time-on-treatment predictions with the generalised gamma distributions lie in the centre of the range of all other distributions. This was considered important given the maturity of the data and the closeness of fit of all distributions to the KM data. The company therefore considers the generalised gamma distribution to be the most plausible for TTD. The company acknowledges that the EAG suggested an alternative approach could be taken to the TTD extrapolations, using mature KM data to estimate treatment discontinuation directly in the model and limiting parametric extrapolations to the time period beyond the KM data. However, as stated in response to clarification question B32 and as demonstrated in Figure 40 of the CS, the company considers that this would provide limited additional value and would have minimal impact on the ICER. This is because all parametric curves used to estimate TTD are a good fit to the KM data due to the maturity of TTD in DESTINY-Breast04 (as shown in Figure 40 and 41 of the CS). Use of parametric curves to model TTD also allows for time-on-treatment to be included in sensitivity analyses, such as a

		probabilistic sensitivity analysis (PSA). Additionally, the EAG's scenario using the restricted mean treatment duration approach (exploratory scenario 3) resulted in a decrease in the ICER.

Issue 8: Health utility values for progression-free and post-progression states. Which utility values are more plausible? Company or EAG?	No	The EAG raised a number of issues related to the values used for the progression-free (PF) and post-progression (PP) utilities, particularly the face validity of the PF utility values and the approach to utilising PP values derived from Lloyd *et al*. While the company acknowledges the EAG's comments regarding the face validity of the PF values, the company maintains that our overall approach is methodologically robust and appropriate. To address the EAG's concerns, the company response is structured as follows:
		• Summary of the EAG's preferred approach and the revised company approach
		• PF utilities: Rationale for using the generalised linear mixed model (GLMM) vs. descriptive statistics
		• PP utilities: Rationale for company approach using the Lloyd *et al.* algorithm
		• Face validity of PF utilities
		• Face validity of PP utilities
		• Exploring uncertainty in the PF utility values
		• Conclusion
		
		For a discussion on the appropriate duration of the PP utility benefit for T-DXd vs TPC, refer to the company response to Issue 9.
		
		Summary of the EAG's preferred approach and the revised company approach
		In the EAG's preferred base case, mean utility values (descriptive statistics), derived from EQ-5D and collected directly from DESTINY-Breast04, are used for PF utilities. PP utilities are calculated by applying the PP decrement from Lloyd *et al.* to the PF values:
		
		• PF utilities: DESTINY-Breast04 mean descriptive statistics
		  ○ T-DXd PF: [redacted]
		  ○ TPC PF: [redacted]

		• PP utilities are calculated by applying a progression decrement (0.272) derived from Lloyd *et al*., to the PF utilities. This leads to higher PP utilities for T-DXd vs. TPC.
		  ○ T-DXd PP: [redacted]
		  ○ TPC PP: [redacted]
		• The EAG agree with the company that T-DXd would be associated with a PP utility benefit over TPC. The EAG apply this by adding the PP utility benefit of T-DXd vs. TPC ([redacted] – [redacted] = 0.026) to the PP utility value for TPC ([redacted]). This utility benefit is assumed to last for 6 months in the EAG base case and is applied as a one-off utility benefit, equivalent to a 6-month duration, upon disease progression.
		• Thereafter, the T-DXd PP utility value reverts to the same utility value as in the TPC arm (i.e., [redacted]).
		
		In the revised company base case, PF utilities for T-DXD and TPC are derived from a GLMM using EQ-5D collected directly from DESTINY-Breast04. PP utilities are estimated for T-DXd and TPC using the Lloyd *et al*. algorithm, applying trial-specific inputs for T-DXd and TPC from DESTINY-Breast04. To enable resolution, the company has adopted two changes to the T-DXd PP utility estimates:
		1. The company has adopted the EAG's proposed approach of applying the TPC PP utility to both trial arms following a period of utility benefit associated with T-DXd.
		2. The company has limited the period of T-DXd PP utility benefit in the revised company base case to 12 months instead of a lifetime (discussed further in response to Issue 9).
		The utility values included in the EAG's preferred base case and the revised company base case are presented in Table 10.

Table 10: Progression-free and post-progression utilities by treatment, as suggested by the EAG and the company

Treatment arm	EAG			Company		
	Progression-free	Post-progression	Progression decrement (Lloyd *et al*.)	Progression-free (GLMM)	Post-progression (Lloyd *et al*.)	Progression decrement
T-DXd	[redacted]	[redacted]	0.272	[redacted]	0.565**	[redacted]
TPC	[redacted]	[redacted]	0.272	[redacted]	0.565	[redacted]

* [redacted] used to estimate T-DXd utility benefit in EAG base case for defined period of 6 months

** [redacted] used to estimate T-DXd utility benefit in company base case for defined period of 12 months

Abbreviations: EAG, economic assessment group; GLMM, generalised linear mixed model; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PF utilities: Rationale for using the GLMM vs. descriptive statistics

The EAG considered the PF utility values in the company base case (derived from EQ-5D responses directly collected in DESTINY-Breast04 and estimated using a GLMM) to be too high and lacking face validity. Instead, the EAG proposed the use of mean utility values from the trial (descriptive statistics). The company believes that the utility values derived from the GLMM are more appropriate for the PF utility values because, unlike using descriptive statistics, they are less biased by extreme outliers and account for the effects of covariates and intra-subject correlation.

The use of descriptive statistics (mean) for estimating utilities is less robust as descriptive statistics are susceptible to being heavily influenced and skewed by outlying values. As is typical with utility data,[24] the utility values in DESTINY-Breast04 are [redacted] with a high concentration of values near [redacted] and capped at [redacted] (Figure 10 and Figure 11). For both T-DXd and TPC PF utilities, over [redacted]% of observations have a utility value in the highest category closest to [redacted], so using the raw means is likely to bias the results as means are more heavily influenced by the outlying values close to zero. For this reason, using mean

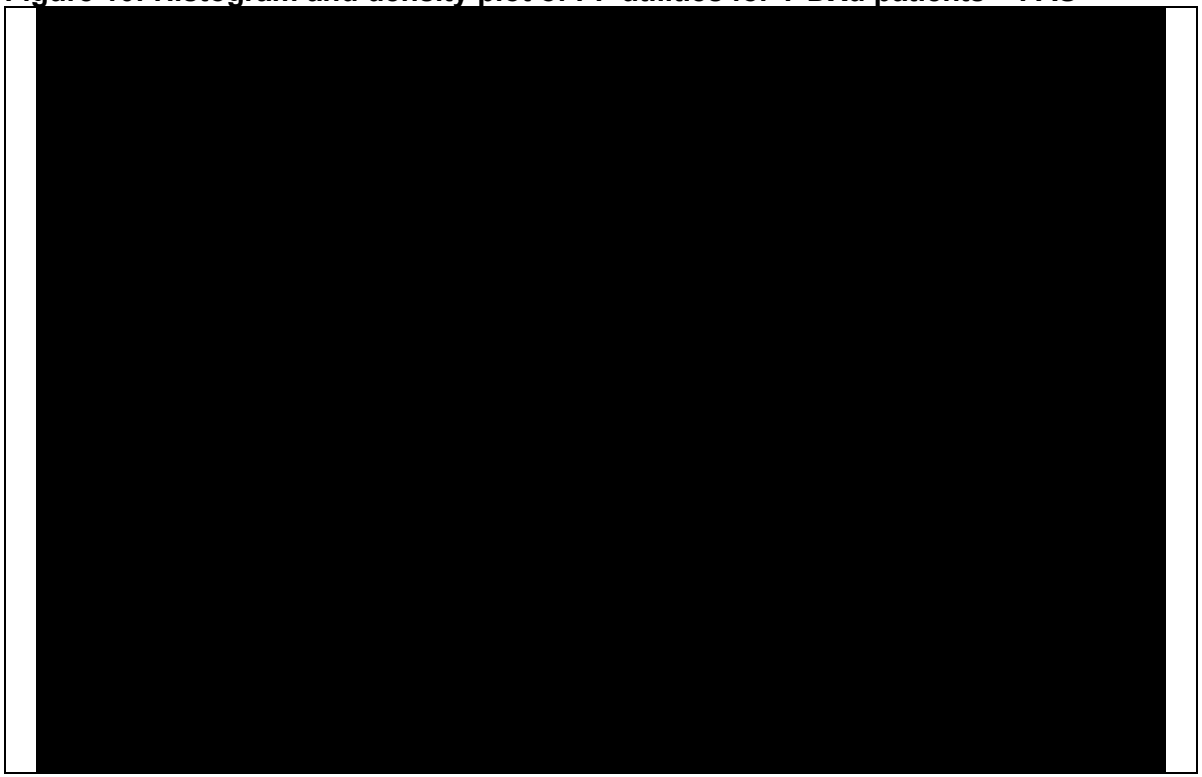
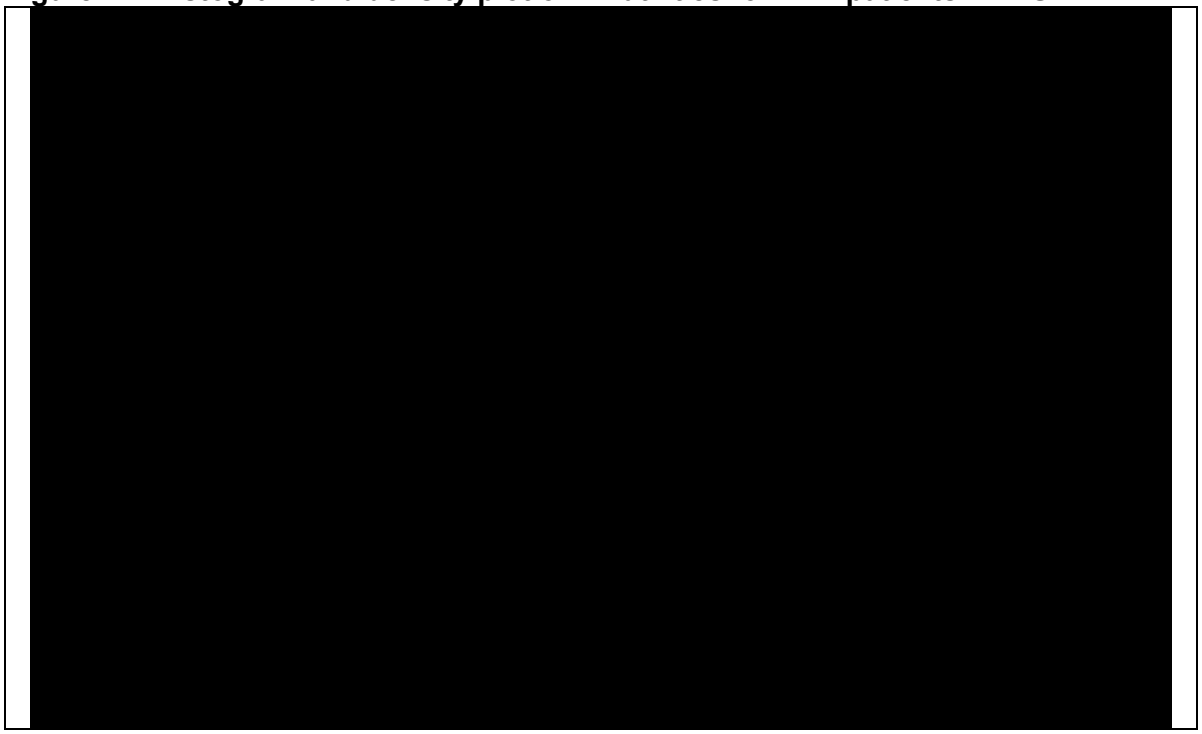
		utilities is not considered the most appropriate, and the company prefers more robust methodologies that take into account the distribution of the data and intra-subject correlation, such as GLMM. **Figure 10: Histogram and density plot of PF utilities for T-DXd patients – FAS**  Abbreviations: FAS, full analysis set; PF, progression-free; T-DXd, trastuzumab deruxtecan

Figure 11: Histogram and density plot of PF utilities for TPC patients – FAS



Abbreviations: FAS, full analysis set; PF, progression-free; TPC, treatment of physician's choice.

As a more robust method than using raw means, the company undertook a GLMM approach, using a linear transformation of patient-level utility data from the DESTINY-Breast04 trial to estimate 1-utilities for patients in the PF health state using a log-normal distribution. The approach to the GLMM followed the recommendations presented in the ISPOR Good Research Practices Task Force Report.[24] This is similar to the approach taken in Lloyd *et al*. (2006), where a log transformation of patient level utility data was used in a simple regression model to estimate health state mBC patient utilities.[25]

		The GLMM approach is robust and more appropriate than descriptive statistics because it overcomes issues with skewed data, takes into account intra-subject correlation due to the longitudinal nature of the EQ-5D-5L questionnaire data, and minimises confounding bias from the effect of progression by including additional covariates using a backward selection approach. In particular, the GLMM includes additional covariates that impact quality of life, including planned treatment (T-DXd vs. TPC), ECOG PS (1 vs. 0), progression status (progressed vs. progression free) and treatment status (off-treatment vs. on-treatment). A backward elimination approach was taken to determine the final factors to be included in the GLMM. Therefore, the company's use of the GLMM for utility scores is an appropriate method. This was confirmed by the EAG, who agreed with the GLMM approach for utility scores including the model selection process (EAG report, Section 5.3.3.7). The EAG highlights that the utility data used in the GLMM includes patients that have progressed but are still on-treatment ([redacted] observations in the T-DXd arm and [redacted] observations in the TPC arm). The company would like to clarify that this is the number of EQ-5D *observations* of patients still on-treatment and in the progressed state, not the number of patients. Further, progression status, included in the utility analysis, is defined by progression based on BICR. The decision to discontinue treatment is led by the investigator, who also provides an investigator assessment of disease progression (PFS defined by investigator assessment [IA]). BICR defined progression may therefore be earlier than investigator assessed progression for some patients and therefore some patients may be defined as progressed in the utility analysis, based upon BICR, but may not yet have discontinued treatment. Additionally, patients are considered on treatment up until the last treatment administration + 21 days for T-DXd, and some patients may have progressed during this window and therefore would still be considered on-treatment despite disease progression. ***PP utilities: Rationale for the company approach with the Lloyd et al. algorithm*** The EAG highlighted that PP utility values estimated from the Lloyd *et al*. algorithm are not consistent with the NICE reference case[26] because they do not represent utilities taken

		directly from BC patients. The company recognises the preferred approach in the NICE reference case is for the utility data to be reported directly from patients in the key clinical study.[26] However, trial data of patients in the PP state in DESTINY-Breast04 were limited, resulting in uncertainty. As stated in the CS, HRQoL questionnaires in DESTINY-Breast04 were completed at the Day 40 first follow-up assessment (after last study drug administration) or before initiation of further treatment (whichever came first), and then at the first long-term/survival follow-up assessment three months later, which was the last data collection point.[13] This meant that there were limited HRQoL data points for PP patients and consequently high uncertainty with the trial-based PP utility values. The company therefore used the Lloyd *et al*. algorithm. The company considers that the use of PP utility values estimated using the Lloyd algorithm is appropriate as Lloyd *et al*. (2006)[25] is a preference-based study aimed at estimating utilities at distinct stages of mBC in patients from the general UK population. Estimates using the algorithm have been accepted and/or preferred in previous mBC TAs, with the following appraisals using Lloyd algorithm based utility estimates: TA862 (T-DXd – second line HER2-positive mBC),[16] TA423 (eribulin – third line mBC),[6] TA509 (pertuzumab – first line HER2-positive mBC),[27] TA704 (T-DXd – third line HER2-positive mBC)[15] and TA458 (T-DM1 – second line HER2-positive mBC)[28]. Notably, in TA423, the EAG expressed a preference for utility values derived using the Lloyd algorithm over the *'progressed disease'* utilities presented by the company.[6] Given the precedent set by the routine use of the Lloyd algorithm in previous submissions, their use in the CS is considered appropriate and justified. The EAG preferred to use the PP utility decrement (0.272) from Lloyd *et al.* and subtract this from the trial-based PP utility values from DESTINY-Breast04.The company considers this approach to be suboptimal.

		Firstly, it applies the Lloyd *et al.* utility decrement to the PF utilities derived from descriptive trial data, which, as outlined above, the company considers less methodologically robust than using the GLMM. Second, the utility values estimated from the Lloyd algorithm were based on a mixed model analysis that included age, treatment response, specific adverse events (AEs) (febrile neutropenia, diarrhoea and vomiting, hand-foot syndrome, stomatitis, fatigue and hair loss) and progression. In the EAG's approach to PP utilities, a disease progression utility decrement (from Lloyd *et al.*) is applied to the PF utility values. The company considers this approach to be less robust than the company's approach in using the algorithm. The company's approach models trial-specific data, including treatment response, from DESTINY-Breast04 and coefficients from the Lloyd model that were statistically significant; this approach is consistent with the intended use of the Lloyd model. Treatment response (similar to progression status) was a significant determinant of HRQoL within the data and the mixed model and should therefore be considered when deriving a PD utility for either arm. The company approach uses PP utility estimates that are derived from the patient population relevant to this appraisal, which is more appropriate, in the company's assessment, than the EAG's approach. ***Face validity of PF utilities*** The EAG noted that the company's PF utility values for T-DXd and TPC lacked face validity as the values for T-DXd [redacted] the general population utility for women aged 57 years old in the UK ([redacted] vs. 0.840[29]). Given the methodological rigour and appropriateness of the GLMM, the utility estimates generated are the best available, as they are taken directly from the population relevant to the decision problem and are therefore representative of the relevant population's utility. Furthermore, the evidence is collected for both T-DXd and TPC under the same conditions as part of an RCT, reinforcing the robustness of the evidence. The utilities presented in the company base case are similar to the values accepted in TA862 for HER2-positive u/mBC after 1 or more anti-HER2 treatments.[16] In TA862, the pre-

progression utility values for T-DXd and the comparator, T-DM1, were 0.835 and 0.801, respectively. These utility values are closer to the values in the company base case and therefore support the utility values used in the company base case compared to the EAG's.

The company's revised base case therefore retains the GLMM estimates for PF utility values ([redacted] and [redacted] for T-DXd and TPC, respectively) (Table 10).

Face validity of PP utilities

Finally, the EAG's PP utilities (T-DXd: [redacted], TPC: [redacted], Table 10) are considerably lower than what has been accepted previously in mBC TAs. PP utilities in previous submissions have ranged from 0.5402 (TA862; TPC 2L HER2+ mBC) to 0.653 (TA819; SG 3L mBC) (Table 11).[5,6,15,16,30] By comparison, the company's PP utility (0.566 for T-DXd and TPC, Table 10) is within the range accepted by NICE committees. This shows that the company PP utility values offer better face validity compared to the EAG's PP utility values.

Table 11: PP utility values from previous similar NICE technology appraisals

NICE Technology Appraisal	Post-progression utility value
Eribulin 3L (TA423)[6]	0.588*
TPC 3L (TA423)[6]	0.588*
T-DXd 2L (TA862)[16]	0.540
T-DM1 2L (TA862)[16]	0.540
SG 3L (TA819)[5]	0.653
TPC 3L (TA819)[5]	0.569
T-DXd 3L (TA704)[15]	0.588
SoC 3L (TA704)[15]	0.588
Tucatinib 3L (TA786)[30]	0.698
Eribulin/capecitabine/vinorelbine 3L (TA786)[30]	0.588

*Derived mid-point value – the committee agreed that a PP utility value between 0.496 and 0.679 was appropriate

Abbreviations: 2L, second-line; 3L, third-line; NICE, National Institute for Health and Care Excellence; PP, post-progression; SG, sacituzumab govitecan; SoC, standard of care; TA, technology appraisal; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

		Exploring uncertainty in the PF utilities While the company considers that the utilities included in the revised company base case are robust and the most appropriate for decision-making, the company has explored two additional exploratory scenarios to test uncertainty and demonstrate the robustness of the company base case PF utility values. *Scenario 1: Using median PFS utility values from DESTINY-Breast04 (descriptive statistics)* In this scenario, the company applied the median utility values (descriptive statistics) from DESTINY-Breast04 for the PF state only. The median values are less prone to bias by outliers than the mean values and are therefore considered more reliable utility values than the EAG's preferred mean utility values (descriptive statistics). The company revised base case values and assumptions are used for all other utility inputs (i.e., Lloyd algorithm for post-progression utilities, treatment-specific PP utility benefit for 12 months [see Issue 9 below] followed by TPC post-progression utilities for both arms). The utility values used in this scenario are provided below: • T-DXd PF (median DESTINY-Breast04): [redacted] • T-DXd PP (Lloyd *et al*): [redacted] • T-DXd utility decrement: [redacted] • TPC PF (median DESTINY-Breast04): [redacted] • TPC PP (Lloyd *et al*): [redacted] • TPC utility decrement: [redacted] Table 12 presents the cost-effectiveness results from this scenario (1.2x severity modifier). This scenario leads to an increase in the ICER of £[redacted] to £[redacted] compared to the revised company base. Given the similarity to the company base case, which is considered methodologically more robust, the company considers this scenario to be supportive in providing confidence that the company base case is appropriate.

Table 12: Scenario deterministic results in the FAS population (T-DXd PAS price; 1.2x severity modifier, PF utilities derived from the median utility values [descriptive statistics] from DESTINY-Breast04)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PF, progression-free; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Scenario 2: using PF utility values derived from a linear mixed model regression

A linear mixed model was constructed to obtain mean utility scores by progression status, as a scenario to the GLMM presented in the company's base case. Utility scores from all available timepoints, including baseline, were included as the dependent variable. The optimal random effects (subject, timing of questionnaire, or both) were identified based on the lowest AIC and BIC. A linear mixed model was constructed, including progression status (PP, PP) at the corresponding visit and planned treatment as independent variables. For these models, an unstructured correlation matrix was used to model the correlation within patients. In the event of the statistical model failing to converge or other presenting issues with the model, the covariance structure was modified to an autoregressive (AR) model, with an AR(1) covariance matrix. Furthermore, in the case where the AR(1) model also failed to converge, a compound symmetry covariance structure was used. The mean utility values, associated 95% CIs, and p-values for the different health states were derived from the model using least square means.

In this scenario, the company applied the utility values derived from the linear mixed model for the PF state only. Aside from this, the company revised base case values and assumptions are used for other utility inputs (i.e., Lloyd algorithm for PP utilities, treatment-specific PP utility benefit for 12 months [see Issue 9 below] followed by TPC PP utilities for both arms). The utility values used in this scenario are provided below:

- T-DXd PF (linear mixed model): [redacted]
- T-DXd PP (Lloyd *et al*): [redacted]
- T-DXd utility decrement: [redacted]
- TPC PF (linear mixed model): [redacted]
- TPC PP (Lloyd *et al*): [redacted]
- TPC utility decrement: [redacted]

This scenario generates PF utility values that are lower than the general population, which may address the concerns raised by the EAG regarding face validity of the company base case values. In addition, the PP utility values are within the range previously accepted in NICE TAs (0.540–0.653).[5,6,15,16,30]

Table 13 presents the cost-effectiveness results from this scenario (1.2x severity modifier). This scenario leads to an increase in the ICER of £[redacted] to £[redacted] compared to the revised company base. Given the similarity to the company base case, which is methodologically robust, the company considers this scenario to be supportive in providing confidence that the company base case is appropriate.

Table 13: Scenario deterministic results in the FAS population (T-DXd PAS price; 1.2x severity modifier, utilities derived from the linear mixed model)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PF, progression-free; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

		Conclusion The company considers that the company base case utility values are robust, clinically plausible and should be used for decision-making. The company PF utilities were derived directly from trial data using a methodologically rigorous approach, and the values obtained are not dissimilar to those accepted in TA862. In addition, the company explored uncertainty in the PF values using a different regression model and confirmed that this has a minimal impact on the ICER. Furthermore, the company's PP utilities from Lloyd *et al* are appropriate as they are clinically plausible, comparable to previously accepted values, and the use of the algorithm has been widely accepted in previous mBC NICE appraisals. Comparatively, the EAG's approach to the PF utilities is prone to bias due to outliers and the [redacted] of the distribution. In addition, the PP utility values proposed by the EAG are lower than any values accepted in prior appraisals. Overall, therefore, the company considers the base case values are appropriate.
Issue 9: Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter. After progression, would utility values be different for people who had trastuzumab deruxtecan rather than comparator treatments? If so, would this difference last for 6 months or a lifetime?	No	The EAG preferred the assumption that patients treated with T-DXd would only maintain a utility benefit PP for 6 months, which differed to the company's assumption (at time of submission) that utility benefit associated with T-DXd would be sustained for a patient's lifetime. After the 6 months of PP utility benefit, the EAG assumed that all surviving patients in the T-DXd arm would revert to the PP utility associated with the TPC arm. The company agrees with the EAG that there would be a PP utility benefit for T-DXd but considers that the utility benefit resulting from treatment with T-DXd would persist over a longer term and that an assumed 6-month PP utility benefit is conservative. Evidence from DESTINY-Breast04, presented in Section B.2.6.1.3 of the CS,[31] supports the assumption that there is a PP utility benefit for patients treated with T-DXd over those treated with TPC.[13,31] In order to support resolution, the company has adopted a pragmatic assumption of a 12-month PP utility benefit associated with T-DXd in the revised base case. The company believes a post progression utility benefit >6 months is plausible based on the reasons detailed below. Following the 12-month PP utility benefit, the company has aligned with the EAG's approach and used the TPC PP utility value for both trial arms.

		Disease control The EAG preferred to apply the disease progression decrement from Lloyd *et al.* (2006) to PF mean descriptive utilities from DESTINY-Breast04 (see Issue 8 response) to estimate PP utilities instead of using the Lloyd algorithm as preferred by the company. The company considers the EAG approach to be less robust as it does not reflect the full range of co-efficients included in the regression or include trial-specific input data to derive utility values, resulting in a non-trial-based progression-related decrement. The Lloyd regression model demonstrates that treatment response affects PP utilities. In the model, utilities were derived from a mixed model analysis that included age, treatment response, specific AEs (febrile neutropenia, diarrhoea and vomiting, hand-foot syndrome, stomatitis, fatigue and hair loss), and progression. Notably, the p-value presented for the response coefficient was statistically significant. Therefore, response (similar to progression status) was a significant determinant of HRQoL within the data and the mixed model and should therefore should be considered when deriving a PD utility for either arm in this appraisal. This supported by UK clinical expert statements in TA786[30] (tucatinib for third-line HER2+ mBC): *"People with disease that is better controlled would have better quality of life before and after progression than those with disease that is less well controlled. This is because the decline in quality of life related to progression will start from a higher level than in people with disease that is less well controlled and with lower quality of life before progression."* DESTINY-Breast04 demonstrates an improvement in disease response with T-DXd vs. TPC, as shown by statistically significantly higher objective response rate (ORR) (complete response + partial response) by blinded independent central review [BICR] (52.3% vs. 16.3%; p<0.0001; FAS).[13] Similarly, the clinical benefit rate (CBR) (complete response + partial response + stable disease) by BICR, which demonstrates sustained response for at least six months, was also statistically significantly greater with T-DXd than TPC (70.2% vs. 33.7%; p<0.0001; FAS).[13] Therefore, clinical evidence demonstrates that T-DXd is associated with significantly better disease control during PF disease than TPC. Given that disease progression is based on the percentage increase in tumour size, it is likely that this better initial disease control with T-DXd vs. TPC would translate into a lower tumour burden

		at progression and slower disease progression on the next-line therapy. This is confirmed by the statistically significantly longer PFS2 in the FAS with T-DXd vs. TPC (median PFS2: 15.4 vs. 10.5 months; HR: 0.55).[13] This, combined with the observed higher utility at the point of progression with T-DXd vs. TPC, and UK clinical expert comments, suggests that the better disease control with T-DXd vs. TPC is expected to translate to better QoL both before and after progression. The company's assumption of a PP utility benefit with T-DXd vs. TPC is therefore both methodologically and clinically valid. This was also accepted by the EAG, who included treatment-specific PP utilities in their base case. Treatment-specific PP utilities were also accepted in a number of other NICE TAs in u/mBC (see response to issue 8). ***12-month post-progression benefit*** While the application of a PP utility benefit with T-DXd vs. TPC is accepted by the EAG, the company acknowledges that the precise duration of the benefit is uncertain. The EAG preferred to limit the utility benefit associated with T-DXd to 6 months. The company affirms that 6 months is too conservative, as not only did DESTINY-Breast04 show significantly improved disease control with T-DXd vs. TPC, but also a statistically significant PP utility benefit for the duration of PP utility data collection. Given that the last timepoint at which the HRQoL data were collected was at the long-term follow-up assessment, which was three months after the first follow-up assessment on Day 40 after the last study drug administration,[13] the substantial post-progression utility benefit persisted for at least four months PP in the trial.[13] It is unlikely that this PP utility benefit would have eroded within 7 weeks, as would be the case under the EAG's assumption of a 6-month PP utility benefit. The company therefore considers the EAG's assumption of a 6-month PP utility benefit with T-DXd to be too conservative. The company believes a longer-term benefit is plausible, but, to reach a resolution, provides a conservative and pragmatic change to the revised base case whereby the T-DXd PP utility benefit is assumed to persist for 12 months. ***EAG's proposed PP utilities*** The EAG propose that following a defined period of utility benefit in the PP health state, T-DXd patients should have the same PP utility as TPC patients. As stated in issue 8, while the company believes that it is more appropriate to use pooled utilities values after this timepoint

		as this reflects the data collected in all patients, the company accepts the EAG's proposed change to equalise T-DXd PP utilities with TPC PP utilities. The company has therefore updated their revised base case. The PP utility for T-DXd, following a 12-month treatment-specific utility benefit in the revised company base case, is 0.565; this is aligned with the TPC PP utility derived from Lloyd *et al*. 2006.
		
		Conclusion
		DESTINY-Breast04 has demonstrated that, compared with TPC, patients receiving T-DXd have significantly higher response rates and a higher PP utility for at least four months following progression. The company therefore considers that it is unlikely that the utility benefit would diminish within 6 months of progression and, accordingly, the EAG base case may underestimate the duration of utility benefit. The company acknowledges the uncertainty in the assumed duration of PP utility benefit associated with T-DXd and have therefore adopted a more conservative approach, applying a PP utility benefit of 12 months in the revised company base case. The company has also accepted the EAG's proposal to use the TPC PP utility value for both treatment arms after the period of utility benefit, instead of a pooled PP utility.
		
		Revised base case
		The following is applied in the revised company base case:
		• Lloyd algorithm base PP utilities
		  ○ T-DXd PP: 0.6014
		  ○ TPC PP: 0.5655
		• Utility benefit associated with T-DXd persists for 12 months PP and then all patients are assigned TPC PP utility.
		  ○ PP utility of patients after 12 months: 0.5655

Scenario assuming T-DXd utility benefit until death

In the revised company base, the company has assumed a utility benefit of 12 months PP, with patients thereafter being assigned a utility value of 0.565 (equal to TPC PP utility). This value is estimated using the Lloyd algorithm, with whole trial average characteristics applied to the algorithm.

A deterministic scenario applying a PP utility benefit associated with T-DXd for the remainder of the model time horizon is presented in Table 14. This results in an ICER of £[redacted] representing a decrease of £[redacted] compared to the revised company base case, which assumes that the T-DXd PP utility benefit lasts for 12 months only. Results are presented using the 1.2x severity modifier.

Table 14: Scenario deterministic results in the FAS population | utility benefit associated with T-DXd for PP health state until death (T-DXd PAS price; 1.2x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

Issue 10: Implementation of RDI when calculating the drug acquisition costs	Yes	The EAG highlighted that different approaches were taken to calculating relative dose intensity (RDI; %) in the T-DXd and TPC arms, which is used to calculate drug acquisition costs and suggest an alternative method using the dose intensity per cycle divided by the planned dosing assumed in the model. To enable a resolution, the company have adopted the RDIs estimated in the EAG's preferred base case for TPC, excluding eribulin. The company have conducted a post-hoc analysis to estimate eribulin RDI using the same methodology as that used to estimate T-DXd RDI, for greater consistency. ***Approach in the company submission*** RDI for T-DXd was calculated as dose intensity/planned dose intensity x100, where planned dose intensity was based on the planned starting dose of 5.4 mg/kg. This approach is aligned with the method used to calculate RDI in TA862.[16] It is preferable to use the planned starting dose where available to avoid overinflating RDI, given planned dose reductions due to AEs. The EAG noted that it agrees with the approach taken for calculating T-DXd RDI. The same method could not be applied for all TPC agents. This is because there were several possible dosing regimens for some of the TPC agents, and planned starting doses for individual patients were unavailable. Therefore, instead of using the planned starting dose to calculate the planned dose intensity, the planned cumulative dose was used as the next best alternative. ***The EAG approach*** The company notes that, whilst the EAG's approach allows the same RDI calculation to be applied to both arms, it is likely to underestimate the RDI for TPC agents. This is because there were several possible dosing regimens for certain individual TPC agents in the clinical trial (e.g., capecitabine). The dosing regimens assumed in the model are reflective of the summary of product characteristics (SmPC) for that agent in the UK, which was usually at the higher end of the range of doses permissible in DESTINY-Breast04. The EAG's approach, which estimates RDI using the dose specified in the model and the dose intensity from trial, may therefore underestimate the RDI given that the SmPC dose was typically at

the higher end of dosing options in trial; this approach could therefore underestimate the cost of comparators.

Revised company base case approach

The company has conducted a post-hoc analysis to estimate the eribulin RDI using the same methodology as that applied to estimate T-DXd RDI in the CS. The RDI for eribulin is relative to the full dose costed in the model; the EAG agreed this approach was correct for T-DXd. The resulting RDI for eribulin is [redacted]% and this has been incorporated into the revised base case. The post-hoc analysis RDI for eribulin is [redacted] than the eribulin RDI in the CS ([redacted]%). The company has adopted the EAG's preferred approach to estimate RDI for remaining TPC agents in the company's revised base case.

Scenario using the EAG's preferred methodology to estimate RDI for T-DXd and TPC

The company has explored an alternative scenario, where the EAG's methodology for estimating RDI is used for T-DXd and all comparators. The ICER increases by £[redacted] from £[redacted] in the revised company base case to £[redacted], with a 1.2x severity modifier applied. The results for this scenario are presented in Table 15.

Table 15: Scenario deterministic results in the FAS population with revised company base case and EAG RDIs (T-DXd PAS price; 1.2x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

		Conclusion The company has conducted a post-hoc analysis to estimate the RDI for eribulin using the same methodology as that applied for T-DXd, using data from DESTINY-Breast04. This ensures that the same approach is used for treatments for which the dose initiated in DESTINY-Breast04 is aligned with the SmPC dose costed in the model. The company considers that the EAG's suggested method may underestimate the RDI of some TPC agents. However, to support a resolution, the revised company base case now adopts the RDI for T-DXd and eribulin derived from DESTINY-Breast04 using the company's approach, and applies the EAG's preferred approach to estimate RDI for the remaining TPC agents.
Issue 11: Vial sharing for intravenous therapies. Is it likely that vials will be shared so there is no wastage? If so, what proportion of intravenous drug administration would be shared? 50% or 75% or another proportion?	No	The EAG report noted that the assumption of 75% vial sharing for intravenous therapies was higher than the figure accepted in TA862[16] (50%) and proposed using an assumption of 50% to align with previous NICE appraisals. In TA862, the CDF clinical lead stated that vial sharing would occur in at least 50% of centres. This was based on a HER2-postive population which is a markedly smaller subset of mBC than HER2-low. The company believes that introducing T-DXd as a treatment option for HER2-low would increase the opportunity for vial sharing due to a larger population of T-DXd-treated patients compared with current practice. The EAG's assumption of 50% vial sharing, to align with TA862[16], may therefore underestimate the proportion of centres that will vial share, and the company therefore considers, that whilst the precise proportion is uncertain, the assumption of 75% vial sharing to be appropriate. The results of the revised base case, but with the assumption that vial sharing occurs in 50% of centres, are summarised in Table 16. The ICER increases from £[redacted] to £[redacted] (+£[redacted]).

Table 16: Scenario deterministic results, where vial sharing is assumed to be 50% (T-DXd PAS price, 1.2x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Severity modifier	Section 6: Severity of the condition	No	As discussed in Section B.3.6 of the CS, the change in NICE methods for assessing the value of technologies for severe conditions – moving from the previous EOL criteria to the severity modifier – has considerable implications for this appraisal. While this appraisal qualifies for the 1.2x severity modifier according to the current NICE framework, the position of the company, supported by clinical and patient group feedback, is that this "medium" severity QALY weighting underestimates the severity of the condition and does not adequately recognise the high unmet need, innovation, and clinical value of T-DXd, as well as the clinical and patient enthusiasm for T-DXd. Further detail is provided below. *Impact on this appraisal of the change from EOL criteria to severity modifier* Prior to the 2022 NICE methods update,[32] NICE Committees considered the following decision modifiers, amongst others, when making judgements on the value of new technologies:[33] • The innovative nature of the technology. • Whether the technology meets the EOL criteria. • Aspects that relate to non-health objectives of the NHS (e.g., better use of resources)

			The EOL modifier was introduced to recognise the potential value of technologies that extend life in populations at the end of life, namely:[34] • The treatment is indicated for patients with a short life expectancy, normally less than 24 months. • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months compared with current NHS treatment. In practical terms, this weighting led to appraisals that met the criteria being assessed against a willingness-to-pay (WTP) threshold of £50,000 per QALY gained.[33] T-DXd in HER2-low u/mBC meets the previous NICE EOL criteria: • **T-DXd is for patients with a short life expectancy (<24 months):** As per the TPC arm in DESTINY-Breast04, median OS with standard of care is 16.8 months in the FAS population relevant to this appraisal.[7] This is consistent with survival reported in prior studies of single-agent chemotherapies in a similar setting in HER2-negative u/mBC (any HR-status: HR-positive, HR-negative, HR-unspecified), where life expectancy is 6.7–20.7 months.[8,35–46] • **T-DXd extends life by over 3 months compared with current standard of care:** In the FAS of DESTINY-Breast04, T-DXd statistically significantly extended median OS by 6.6 months versus TPC (median OS: 23.4 vs. 16.8 months; p=0.0010).[7] In the HR-positive and HR-negative cohorts, T-DXd increased median OS by 6.4 months and 9.9 months, respectively.[7] Therefore, until recently, this appraisal would have been appraised at a £50,000 per QALY gained WTP threshold. Under the updated NICE methods, the EOL criteria were replaced with a severity modifier, which uses absolute and proportional QALY shortfall in patients treated with current standard of care to determine a QALY weighting of 1x, 1.2x or 1.7x. As stated in CS B.3.6.3 and the EAG report, this appraisal robustly meets criteria for the 1.2x severity modifier (practically equivalent to a WTP threshold of £36,000 per QALY gained) but not the 1.7x QALY modifier. Both the company and EAG base cases and all model scenarios resulted in absolute and

			proportional QALY shortfalls exceeding the minimum threshold required to qualify for the 1.2x QALY modifier, regardless of the general population sources in the Schneider *et al*.[29] QALY shortfall calculator tool. As a consequence, if a 1.2x QALY modifier is applied for decision-making, the WTP threshold for this appraisal is considerably lower under the new NICE process (with severity modifier) than under the old NICE process (EOL criteria). *The 1.2x severity modifier underestimates the severity of the condition for this appraisal, meaning that cost-effectiveness results with the 1.2x QALY modifier are conservative* Based on the above information, Daiichi Sankyo considers that the 1.2x QALY modifier underestimates the severity of the condition for this appraisal as it does not appropriately and fully recognise the severity of HER2-low u/mBC after chemotherapy nor the innovation and clinical value of T-DXd in this population. This was echoed by comments from a consultee during this appraisal, who expressed concern with the severity modifier: "*We are concerned that the absolute shortfall in the severity modifier calculation discriminates against the protected characteristic of age, and that the proportional shortfall does not adequately reduce the impact of this*." *The company requests that the committee give additional consideration to the high unmet need, innovation, and clinical value of T-DXd in HER2-low to ensure the totality of evidence is both quantitatively and qualitatively considered in decision-making* In addition to considering flexibilities on the appropriate application of the severity modifier to reflect the severity of the condition, the company requests that the committee gives additional qualitative consideration for the innovation, high unmet need, and clinical value of T-DXd in HER2-low u/mBC. Following exhaustion of targeted options such as ET/CDK4/6is at earlier lines, treatment for patients with HER2-low u/mBC is predominantly limited to sequential lines of non-targeted, single-agent chemotherapies, which are associated with poor outcomes.[35,41–44] Therefore, as discussed in B.3.13 of the CS, there remains a substantial unmet need for effective, novel treatment options for these patients. As highlighted by the MHRA Innovation Passport, T-DXd is an innovative therapy and is the first and only HER2-targeted treatment to show a statistically significant efficacy benefit over non-targeted chemotherapy in patients with HER2-low u/mBC.[7] T-DXd is therefore a step-change that will transform the care of patients

			with HER2-low u/mBC. This was reflected by comments from UK clinical experts, who highlighted to Daiichi Sankyo that there is a high demand for T-DXd to be made available in HER2-low u/mBC given the current lack of effective treatment options. In addition to the innovation, clinical value, and fulfilment of a high unmet need, T-DXd has the potential to offer benefits not captured in the QALY calculation. As stated in B.3.13 of the CS, a considerable proportion of patients with u/mBC are of working age at diagnosis, suggesting that the disease impacts their employment and work productivity as well as their ability to parent actively and fulfil their social role. Treatments that delay progression and maintain QoL, such as T-DXd, may therefore provide wider societal benefits. In addition, given that a diagnosis of u/mBC profoundly impacts caregivers and loved ones, a treatment such as T-DXd, which offers hope and allows patients to lead a normal life for longer than current standard of care, will provide QoL benefits to caregivers, loved ones, and children of patients with HER2-low u/mBC. While difficult to quantify, these potential benefits of T-DXd should not be underestimated and should be qualitatively considered in the decision-making. Given the above, in order to fully reflect the extent of the severity of HER2-low u/mBC and innovation and clinical value of T-DXd, the company has presented ICERs in the CS and in these technical engagement responses using both the 1.2x QALY weighting and the 1.7x QALY weighting (equivalent to the previous EOL weighting, which would have been used for this appraisal before the NICE process change). Daiichi Sankyo are committed to working collaboratively with NICE and other relevant stakeholders to provide the totality of evidence to support decision-making based on both the quantitative calculation and qualitative benefits not captured by the QALY calculation, with the ultimate objective of ensuring patients have timely access to this important new therapy.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: *If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.*

The company have revised the base case to support appropriate and timely decision-making. The changes to the company base case are detailed in Table 19, with the impact on the ICER based on a comparison with the version of the company base case submitted in response to clarification questions. Table 17 presents the company base case ICERs (with T-DXd PAS price) submitted at clarification questions, for reference. The revised company base case results, following technical engagement, are presented in Table 18.

Table 17: Company base case after clarification questions deterministic results in the FAS population (T-DXd PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (no severity modifier)	ICER (1.2x severity modifier)	ICER (1.7x severity modifier)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 18: Revised company base case after technical engagement deterministic results in the FAS population (T-DXd PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (no severity modifier)	ICER (1.2x severity modifier)	ICER (1.7x severity modifier)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 19: Revised company base case cost-effectiveness estimate, with reference to base case at clarification questions

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER submitted at clarification questions (T-DXd PAS price)
Changes in response to key issues			
Issue 5: Estimation of patients entering the post-progression and death health states	The formulae for estimating the number of patients entering the post-progression and death health states assumed that the risk of death from the post-progression is zero for the purposes of estimating the proportion of newly progressed patients each cycle.	The formulae have been corrected by the EAG to estimate the proportion of newly progressed patients each cycle such that it accounts for the proportion of deaths in the pre-progression and post-progression states.	• ICER with 1.2x modifier: £[redacted] ○ Change: -£[redacted] • ICER with 1.7x modifier: £[redacted] ○ Change: -£[redacted]
Issue 9: Duration of difference in utility values between treatment arms for post-progression state	The company assumed that the post-progression utility benefit for patients treated with T-DXd	The company has amended this assumption to be more conservative, by assuming that the post-progression utility benefit persists for 12 months following	• ICER with 1.2x modifier: £[redacted] ○ Change: £[redacted] • ICER with 1.7x modifier: £[redacted]

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and the value to be used for both arms thereafter.	would persist for the remainder of the patient's lifetime.	disease progression. After 12 months post-progression, T-DXd patients adopt a PP utility value equal to PP TPC (derived from the Lloyd algorithm for PP TPC).	○ Change: £[redacted]
Issue 10: Implementation of RDI when calculating the drug acquisition costs	The company implemented two different approaches to calculating RDI for T-DXd and components of TPC, whereby TPC RDIs were calculated using the planned dose intensity in each cycle. This is different than for T-DXd, where it was calculated relative to the planned starting dose.	The company has implemented the approach used for T-DXd in the company submission for eribulin RDI, where it is calculated relative to the planned starting dose. This reduced the RDI from [redacted]% to [redacted]%. The RDIs for other TPC agents were changed to reflect those calculated by the EAG.	• ICER with 1.2x modifier: £[redacted] ○ Change: £[redacted] • ICER with 1.7x modifier: £[redacted] ○ Change: £[redacted]
Corrections			
Correcting wastage calculation formula	In the company submission, a formula used to calculate the drug cost including wastage of gemcitabine referenced the wrong range of cells.	The company implemented the EAG's correction to these formulae that referenced the appropriate range.	• ICER with 1.2x modifier: £[redacted] ○ Change: £[redacted] • ICER with 1.7x modifier: £[redacted] ○ Change: £[redacted]
QALY difference between arms only applied to newly progressed patients	The company submission at clarification questions applied a QALY difference for all progressed patients rather just to newly progressed patients.	The company implemented the EAG's correction to the formulae to ensure that the QALY difference only applied to newly progressed patients.	• ICER with 1.2x modifier: £[redacted] ○ Change: £[redacted] • ICER with 1.7x modifier: £[redacted] ○ Change: £[redacted]
Removing half-cycle correction on one-off treatment costs	In the company submission, a half cycle correction was applied to one-off costs that occurred in cycle one.	The company has corrected this and no longer applies half-cycle corrections to one-off costs that occur in cycle one.	• ICER with 1.2x modifier: £[redacted] ○ Change: £[redacted] • ICER with 1.7x modifier: £[redacted] ○ Change: £[redacted]

Correcting the cost per dose in wastage calculation of capecitabine	In the company submission, the wastage calculations did not correctly divide by the pack size.	The company implemented the EAG's correction to cost per dose including wastage.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: -£[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: -£[redacted]

Incorrect percentages for patients on each subsequent therapy	A transcription error meant that the proportion patients receiving certain subsequent treatments was incorrect.	The model now reflects the correct proportions of patients receiving these subsequent treatments.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: -£[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: -£[redacted]

Discounting of first year costs and QALYs	In the company submission, no discounting had been applied to costs and QALYs in cycles in the first year.	The company implemented the EAG's correction and applied discounting to all costs and QALYs, including those before year 1.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: -£[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: -£[redacted]

Other changes			

Application of administration costs for tamoxifen every 3 months	In the company submission after corrections at clarification questions, the company applied tamoxifen administration costs once per pack of 30 tablets - approximately once per month.	The company implemented the EAG's suggestion of applying administration costs once every three months.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: £[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: £[redacted]

Recalculation of percentages of subsequent treatment distributions based on Table 14.1.3.5.2 in the CSR	The values used for the proportion of patients receiving each subsequent treatment was based on just the drugs and not their equivalent salts.	The company implemented the EAG's suggestion and included both the drug and equivalent salt in the calculation of subsequent treatment proportions.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: -£[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: -£[redacted]

Assuming the same drug costs for subsequent treatments	In the company's submission, subsequent treatments did not account for wastage and this	The company implemented the EAG's suggestion and ensured that the drug costs for subsequent	• ICER with 1.2x modifier: £[redacted] ○ Change: -£[redacted]

as they do in the TPC arm	meant that components of TPC that were also used as subsequent treatments would have different costs if wastage was included for their use in the TPC arm.	treatments used in the TPC arm reflected their cost in the TPC arm. This meant that there was no difference in drug costs for components of TPC depending on whether they were subsequent treatments or comparators.	• ICER with 1.7x modifier: £[redacted] ○ Change: -£[redacted]

Include arm-specific time on treatment for subsequent treatments	In the company's submission it was assumed that time on subsequent treatment was the same across treatment arms in the trial ([redacted] cycles). A simple mean average time on treatment from across the two arms was used for time on treatment.	The company implemented the EAG's suggestion that time on subsequent treatment would be treatment arm specific. Time on subsequent treatment was taken from the DESTINY-Breast04 clinical trial.
		T-DXd: [redacted] cycles
		TPC: [redacted] cycles
			• ICER with 1.2x modifier: £[redacted]
			  ○ Change: £[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: £[redacted]

Adjusting utility according to age	In the company's submission, there were no age-related utility decrements applied to patients' utility, beyond what had been included in the initial Lloyd algorithm.	The company implemented the EAG's suggestion to apply utility decrements, based on Ara and Brazier, to patients in the progression-free and progressed disease state.	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: £[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: £[redacted]

Company's base case following technical engagement (or revised company base case)	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	• ICER with 1.2x modifier: £[redacted]
			  ○ Change: £[redacted]
			• ICER with 1.7x modifier: £[redacted]
			  ○ Change: £[redacted]

Deterministic results for revised base case

The deterministic cost-effectiveness results for the revised company base case with the 1.2x and 1.7x severity modifier applied are given in Table 20 and Table 21, respectively.

Table 20: Revised company base case, with 1.2 severity modifier applied and T-DXd PAS price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Table 21: Revised company base case, with 1.7 severity modifier applied and T-DXd PAS price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Sensitivity analyses for revised base case with 1.2x severity modifier

The mean PSA results for the revised company base case, with 1.2 severity modifier applied and T-DXd PAS price, are presented in Table 22 and the incremental cost-effectiveness plane in Figure 12. Figure 13 presents the cost-effectiveness acceptability curve for T-DXd vs. TPC.

Table 22: Probabilistic analysis results with revised company base case, with 1.2 severity modifier applied and T-DXd PAS price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 12: Cost-effectiveness plane, with revised company base case, with 1.2 severity modifier applied and T-DXd PAS price

Abbreviations: CEP – cost-effectiveness plane; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALYs – quality-adjusted life years; T-DXd – trastuzumab deruxtecan; TPC – treatment of physician's choice.

Figure 13: Cost-effective acceptability curve – T-DXd PAS price vs. TPC (x1.2 severity modifier)*

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PAS, patient-access scheme; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Results of the one-way sensitivity analysis, with revised company base case, with 1.2 severity modifier applied and T-DXd PAS price, are presented in Table 23, with the top 10 parameters which had the largest impact on the ICER. The accompanying tornado diagram is presented in Figure 14.

Table 23: One-way sensitivity analysis results, with revised company base case, with 1.2 severity modifier applied and T-DXd PAS price

Parameter	ICER at lower bound	ICER at upper bound
Average weight (kg)	[redacted]	[redacted]
Relative dose intensity -Trastuzumab deruxtecan - 100	[redacted]	[redacted]
Utilities - Progression-free - Trastuzumab deruxtecan	[redacted]	[redacted]
Utilities - Progression-free - Physician's choice	[redacted]	[redacted]
Average body surface (m^2)	[redacted]	[redacted]
Drug cost - Eribulin - 0.88mg vial	[redacted]	[redacted]
Relative dose intensity -Eribulin - 0.88	[redacted]	[redacted]
Administration costs - Trastuzumab deruxtecan	[redacted]	[redacted]
Health state cost - Progression-free - Total	[redacted]	[redacted]
Proportion of Eribulin as subsequent treatment - T-DXd arm	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; PAS – patient access scheme; T-DXd – trastuzumab deruxtecan.

Figure 14: One-way sensitivity analysis tornado diagram, with revised company base case, with 1.2 severity modifier applied and T-DXd PAS price

Abbreviations: ICER – incremental cost-effectiveness ratio; PAS – patient access scheme; T-DXd – trastuzumab deruxtecan; TPC – treatment of physician's choice.

Sensitivity analyses for revised base case with 1.7x severity modifier

The mean PSA results for the revised company base case, with 1.7 severity modifier applied and T-DXd PAS price, are presented in Table 24 and the incremental cost-effectiveness plane in Figure 15. Figure 16 presents the cost-effectiveness acceptability curve for T-DXd vs. TPC.

Table 24: Probabilistic analysis results with revised company base case, with 1.7 severity modifier applied and T-DXd PAS price

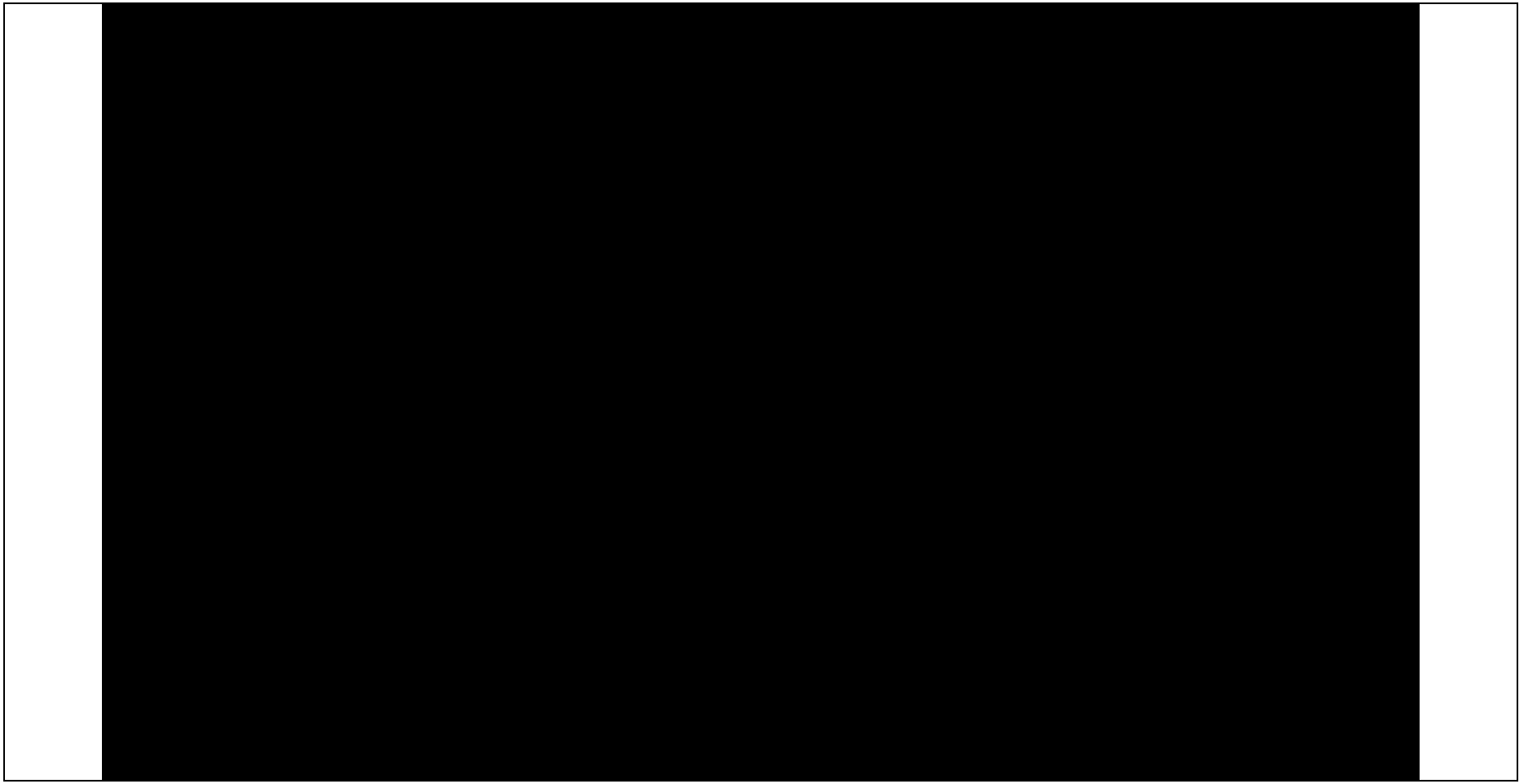
Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Figure 15: Cost-effectiveness plane, with revised company base case, with 1.7 severity modifier applied and T-DXd PAS price

Abbreviations: CEP – cost-effectiveness plane; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALYs – quality-adjusted life years; T-DXd – trastuzumab deruxtecan; TPC – treatment of physician's choice.

Figure 16: Cost-effective acceptability curve – T-DXd PAS price vs. TPC (x1.7 severity modifier)*



*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PAS, patient-access scheme; QALY, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Results of the one-way sensitivity analysis, with revised company base case, with 1.7 severity modifier applied and T-DXd PAS price, are presented in Table 25, with the top 10 parameters which had the largest impact on the ICER. The accompanying tornado diagram is presented in Figure 17.

Table 25: One-way sensitivity analysis results, with revised company base case, with 1.7 severity modifier applied and T-DXd PAS price

Parameter	ICER at lower bound	ICER at upper bound
Average weight (kg)	[redacted]	[redacted]
Relative dose intensity -Trastuzumab deruxtecan - 100	[redacted]	[redacted]
Utilities - Progression-free - Trastuzumab deruxtecan	[redacted]	[redacted]
Utilities - Progression-free - Physician's choice	[redacted]	[redacted]
Average body surface (m2)	[redacted]	[redacted]
Drug cost - Eribulin - 0.88mg vial	[redacted]	[redacted]
Relative dose intensity -Eribulin - 0.88	[redacted]	[redacted]
Administration costs - Trastuzumab deruxtecan	[redacted]	[redacted]
Health state cost - Progression-free - Total	[redacted]	[redacted]
Proportion of Eribulin as subsequent treatment - T-DXd arm	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; PAS – patient access scheme; T-DXd – trastuzumab deruxtecan.

Figure 17: One-way sensitivity analysis tornado diagram, with revised company base case, with 1.7 severity modifier applied and T-DXd PAS price

Abbreviations: ICER – incremental cost-effectiveness ratio; PAS – patient access scheme; T-DXd – trastuzumab deruxtecan; TPC – treatment of physician's choice.

Table 26: Scenario analysis (deterministic results – T-DXd [PAS price] vs. TPC, for 1.2x and 1.7x severity modifier)

Parameter	Scenario number	Base case	Scenario	Incremental costs	Incremental QALYs	ICER (1.2x modifier)	ICER (1.7x modifier)
Base case deterministic results				[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	1	Discount rates - Costs: 3.5%, outcomes: 3.5%	Discount rates - costs: 0%, outcomes: 0%	[redacted]	[redacted]	[redacted]	[redacted]
	2		Discount rates - costs: 1.5%, outcomes: 1.5%	[redacted]	[redacted]	[redacted]	[redacted]
	3		Discount rates - costs: 6%, outcomes: 6%	[redacted]	[redacted]	[redacted]	[redacted]
Vial sharing	4	Vial sharing 75%	Vial sharing 50%	[redacted]	[redacted]	[redacted]	[redacted]
	5		Vial sharing 100%	[redacted]	[redacted]	[redacted]	[redacted]
Utilities	6	Progressed disease utilities sourced from Lloyd *et al.* 2006	Progressed disease utilities sourced from DESTINY-Breast04 trial.	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolations (applied to T-DXd and TPC)	7	Log-logistic	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	8		Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
PFS extrapolations (applied to T-DXd and TPC)	9	Log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	10		Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Scenario number	Base case	Scenario	Incremental costs	Incremental QALYs	ICER (1.2x modifier)	ICER (1.7x modifier)
Base case deterministic results				[redacted]	[redacted]	[redacted]	[redacted]
OS and PFS extrapolations (applied to T-DXd and TPC)	11	OS: log-logistic PFS: log-logistic	OS: Log-normal PFS: Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Scenarios presented in issues							
Comparators included in the model (including respective costs and KM data)	Issue 1	All comparators included	Removal of 2L eribulin use and gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Correction for formula estimating the proportion of patient's progressing	Issue 5	Including the EAG's correction	Excluding the EAG's correction	[redacted]	[redacted]	[redacted]	[redacted]
PF utilities for TPC and T-DXd	Issue 8	T-DXd: GLMM TPC: GLMM	T-DXd: Trial median TPC: Trial median	[redacted]	[redacted]	[redacted]	[redacted]
	Issue 8		T-DXd: Linear mixed model TPC: Linear mixed model	[redacted]	[redacted]	[redacted]	[redacted]
Utility benefit	Issue 9	Sustained for 12 months	Sustained for lifetime	[redacted]	[redacted]	[redacted]	[redacted]
RDIs	Issue 10	T-DXd and eribulin: company method All others: EAG method	All treatments: EAG method	[redacted]	[redacted]	[redacted]	[redacted]
Vial sharing	Issue 11	Vial sharing 75%	Vial sharing 50%	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; OS – overall survival; PAS – patient access scheme; PFS – progression-free survival; QALY – quality-adjusted life years; T-DXd – trastuzumab deruxtecan; TPC – treatment of physician's choice.

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Appendix

Issue 1:
Scenario deterministic results in the FAS population | Efficacy and costs of eribulin 2L and gemcitabine (2L/3L) removed (T-DXd PAS price; 1.7x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Issue 5:
Scenario deterministic results in the FAS population, uncorrected post-progression calculations (T-DXd PAS price; 1.7x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Issue 8:
Scenario deterministic results in the FAS population (T-DXd PAS price; 1.7x severity modifier, PF utilities derived from the median utility values [descriptive statistics] from DESTINY-Breast04)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	

T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Scenario deterministic results in the FAS population (T-DXd PAS price; 1.7x severity modifier, utilities derived from the linear mixed model)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Issue 9:

Scenario deterministic results in the FAS population | utility benefit associated with T-DXd for PP health state until death (T-DXd PAS price; 1.7x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Issue 10:

Scenario deterministic results in the FAS population with revised company base case and EAG RDIs (T-DXd PAS price; 1.7x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	

T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Issue 11:
Scenario deterministic results, where vial sharing is assumed to be 50% (T-DXd PAS price, 1.7x severity modifier)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
TPC	[redacted]	[redacted]	[redacted]	-	-	-	
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PP, post-progression; QALYs, quality-adjusted life years; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on trastuzumab deruxtecan and its possible use in the NHS.

You can provide a unique perspective on trastuzumab deruxtecan in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of trastuzumab deruxtecan is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR sections 1.4 and 1.5. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

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.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **21st July 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-low metastatic or unresectable breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Emma Beddowes
2. Name of organisation	Guys and St Thomas NHS Trust
3. Job title or position	Medical Oncology Consultant
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 HER2-low metastatic or unresectable breast cancer? ☐ A specialist in the clinical evidence base for HER2-low metastatic or unresectable breast cancer or trastuzumab deruxtecan? ☐ 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 did not submit one, I do not 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.	None

8. What is the main aim of treatment for HER2-low metastatic or unresectable breast cancer? (For example, to stop progression, to improve mobility, to cure HER2-low metastatic or unresectable breast cancer, or prevent progression or disability)	To delay progression and to improve or maintain quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	➢ or equal to a 20% reduction in tumour size
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-low metastatic or unresectable breast cancer?	Yes
11. How is HER2-low metastatic or unresectable breast cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of HER2-low metastatic or unresectable breast cancer, and if so, which? • 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.) • What impact would trastuzumab deruxtecan have on the current pathway of care?	Not currently a separate clinical entity so they would be treated as either 1. ER+ve HER2-ve - current pathway would be first line endocrine therapy +/- CDK4/6i then either second line endocrine therapy or chemotherapy depending on nature of progression and if CDK4/6i used first line or not. Chemotherapy is typically monotherapy - paclitaxel / epirubicin / capecitabine. Eribulin is used in the 3rd line setting for chemotherapy. 2. ER-ve HER2-ve. First line abraxane + atezolizumab if PDL-1 positive / usually carboplatin + paclitaxel (or monotherapy) first line if PDL-1 negative. Or capecitabine or epirubicin monotherapy. Then Sacituzumab govitecan 2nd line if have had a taxane and also adjuvant chemotherapy. 3rd line as above in terms of chemotherapy plus eribulin also an option.

	TDxD could be used second line for patients in group 1. As an alternative to cytotoxic chemotherapy or as an option post 1st line chemotherapy. For group 2. It is likely that Trastuzumab deruxtecan would be directly in competition with Sacituzumab govitecan unless patients had de novo metastatic disease. They could be used in sequence as they target different antibodies but it is hard to know how effective this would be and which order would be better. No guidelines currently specific to this group and this would be the first approved treatment for HER2 low patients specifically.
12. Will trastuzumab deruxtecan 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 trastuzumab deruxtecan and current care? • In what clinical setting should trastuzumab deruxtecan be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce trastuzumab deruxtecan? (for example, for facilities, equipment, or training)	It is already used for patients in a secondary care setting for advanced breast cancer patients with HER2 positive breast cancer. No extra training or resources would be needed other than medical training in when and which indication to use the drug.
13. Do you expect trastuzumab deruxtecan to provide clinically meaningful benefits compared with current care? • Do you expect trastuzumab deruxtecan to increase length of life more than current care?	Yes I do as evidenced by the statistically significant increases in progression free survival and overall survival.

• Do you expect trastuzumab deruxtecan to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom trastuzumab deruxtecan would be more or less effective (or appropriate) than the general population?	Patients with a significant pre-existing lung conditions may not be suitable for trastuzumab deruxtecan due to the risks of pneumonitis.
15. Will trastuzumab deruxtecan 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)	I would say it is similar. Monitoring for pneumonitis may lead to an increased use of radiology resources.
16. Will any rules (informal or formal) be used to start or stop treatment with trastuzumab deruxtecan? Do these include any additional testing?	Chest CT for pneumonitis.
17. Do you consider that the use of trastuzumab deruxtecan will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of trastuzumab deruxtecan or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	None that I can think of.
18. Do you consider trastuzumab deruxtecan 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?	Yes I do – it gives a different form of therapy for this group of patients that they have no previously had access to.

• Is trastuzumab deruxtecan a 'step-change' in the management of HER2-low metastatic or unresectable breast cancer? • Does the use of trastuzumab deruxtecan address any particular unmet need of the patient population?	Yes in the type of therapy this is Extra treatment options for this group
19. How do any side effects or adverse effects of trastuzumab deruxtecan affect the management of HER2-low metastatic or unresectable breast cancer and the patient's quality of life?	
20. Do the clinical trials on trastuzumab deruxtecan reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We wouldn't currently use eribulin as a second line therapy (only approved 3rd line) so this is less relevant as a comparator Most important outcomes are overall survival and quality of life – OS improved and HRQOL maintained
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering HER2-low metastatic or unresectable breast cancer and trastuzumab deruxtecan? Please explain if you think any groups of	

people with HER2-low metastatic or unresectable breast cancer 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. Please state if you think this evaluation could • exclude any people for which trastuzumab deruxtecan is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, 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 committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Comparators. What medicines are used in NHS clinical practice to treat HER2-low metastatic or unresectable breast cancer after chemotherapy?	Not currently managed as a separate group and would be treated as HER2 negative. Hormone therapy (or different chemotherapy) can be used for ER+ve HER2-ve subgroup. Sacituzumab govitecan can be used for ER-ve HER2-ve.
Issue 2: Clinical equivalence of trastuzumab deruxtecan and sacituzumab govitecan in the hormone receptor-	I think this is difficult to answer as no head to head trials are available and Sacituzumab govitecan was trialled in a later line of therapy (at least 2 prior therapies). The incremental benefit in PFS is similar for for both drugs (~5months; Ascent trial and Destiny-04) so this is not entirely unreasonable but no direct information is available.

negative subgroup. In this subgroup, the economic model assumes this these two medicines are clinically equivalent. Is this appropriate?	
Issue 3: Is the population of DESTINY-Breast04 generalisable to people likely to have trastuzumab deruxtecan in the NHS?	Yes
Issue 4: Extrapolation of overall survival. Which extrapolated survival curve is more clinically plausible? Log-logistic or gamma or Weibull?	I agree with the reasoning for the University of Sheffield analysis (gamma) though I am not an expert in statistics
Issue 6: Extrapolation of progression free survival. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	Generalised gamma

Issue 7: Extrapolation of time to treatment discontinuation. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	Generalised gamma
Issue 8: Health utility values for progression-free and post-progression states. Which utility values are more plausible? Company or EAG?	EAG
Issue 9: Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter. After progression, would utility values be different for people who had trastuzumab deruxtecan rather than comparator treatments? If so,	I don't think we know the answer to this

would this difference last for 6 months or a lifetime?	
Issue 11: Vial sharing for intravenous therapies. Is it likely that vials will be shared so there is no wastage? If so, what proportion of intravenous drug administration would be shared? 50% or 75% or another proportion?	Not sure
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This drug provides an extra line of likely effective therapy for a newly defined subgroup of advanced breast cancer patients.
The company comparator of eribulin is not a valid TPC in this line of treatment (and gemcitabine not used as monotherapy in general)
I think RWD on sequencing of trastuzumab deruxtecan and comparison with sacitzumab govitecan in the HOR negative subgroup would be valuable information to have and I think direct clinical comparisons between these treatments are difficult to make.
Click or tap here to enter text.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **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.

NICE National Institute for Health and Care Excellence

Patient expert statement

Breast cancer (HER2-Low metastatic, unresectable) – trastuzumab deruxtecan (after chemotherapy) [ID3935]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Kirstin Jane Spencer**

2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	METUP UK
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating	**X** 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.)

organisation's submission)	
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.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition?	Treatment for stage 4 breast cancer can often be difficult and patients are left in a horrible situation coping with many psychological and physical side effects taking effect on their mental and physical state. There is the financial impact of having

What do carers experience when caring for someone with the condition?	to give up work, pay for extra care around the house and struggling to look after their children. Such huge emotional and financial implications can completely devastate patients and their families. There is constant anxiety because patients are scanned every few months for the rest of their lives to assess whether the cancer is reducing, stable or progressing. When treatment lines fail, deterioration can be rapid as the cancer develops greater dexterity and proliferation across the organs. The knowledge of this adds to patients' distress.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Metastatic breast cancer is the biggest killer of women between the ages of 35-49 in England and Wales (Deaths registered in England and Wales, Office for National Statistics 2021). There is no cure but there are multiple systemic therapies potentially available for the disease. The most important treatment goals are to maintain or improve quality of life compared with currently available treatments, delay the progression of cancer and the need for hospitalisation. Patients much prefer targeted treatments to untargeted cytotoxic chemotherapy. This is because targeted treatments give better outcomes to conventional chemotherapy, and also have less adverse side effects which may support the independence of the patient and perhaps give them the opportunity to remain in or gain employment. Therapies, beyond first line setting lack high quality evidence for prolongation of survival but trastuzumab deruxtecan may offer precious extra time for metastatic breast cancer patients that have HER 2 low disease profile. Patients with HER2-low metastatic breast cancer do not have access to any lines of anti-HER2 therapy because they are classified as HER2-negative. Many patients are aware of trastuzumab deruxtecan because it has been covered extensively in the scientific and mainstream press and have asked their oncologist if they have HER2-low breast cancer. Patients find it frustrating that a treatment which is available in countries with comparable healthcare systems is not available to them. **Patient voice:** Michael's wife has HER2-low metastatic breast cancer and has gone through three different lines of treatment in the last year. He has become her carer which has taken a toll on him emotionally. He would welcome trastuzumab deruxtecan as an option for her in the future. He says that his wife and other patients should not be denied these treatments because of previous lines of drugs. Michael feels when drugs are denied by NICE, it truly feels like the system does not care about patients and their families.

	" I was diagnosed with ER/PR positive HER2 negative Lobular breast cancer in January 2018, I had an excellent prognosis but was warned that vigilant follow up would be paramount to successful monitoring of recurrence. I was told I was cured by a new Doctor and symptoms of recurrence were ignored until I became very ill in January 2021 and was diagnosed with local recurrence in my skin and extensive skeletal metastasis." " I was sacked when my employers heard about my diagnosis, being immuno-suppressed as a teacher in a school was not ideal, I got COVID as soon as the students had returned to accompany my metastatic diagnosis. The knock on effect of this on my family, friends and especially my 8 year old daughter is devastating. She begs me to live long enough to look after her through school." **References;** Howlader, N., Altekruse, S., Li, C., Chen, V., Clarke, C., Ries, L. and Cronin, K., 2014. US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status. *JNCI: Journal of the National Cancer Institute*, 106 (**5**). Office of National Statistics, U.K., 2021. *Deaths registered in England and Wales – Office for National Statistics* [online] Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2021> [Accessed 18 July 2023].
10. Is there an unmet need for patients with this condition?	Yes. The majority of breast cancer patients have hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative disease (Female Breast Cancer Subtypes - SEER, 2019; Howlader et al., 2014). For this majority of breast cancer patients, once their disease has advanced and/or metastasised to overcome the current hormone suppressors and cdk 4/6 inhibitors, options are very limited. The Destiny-breast04 trial showed that trastuzumab deruxtecan successfully prolonged both progression free survival and overall survival among patients that were categorised as having low HER 2 (1+and 2+) unresectable metastatic breast cancer compared to physicians choice of standard single agent chemotherapy. This is being further explored in the Destiny-breast06 trial where direct comparisons are being made between paclitaxel/capecitabine/nab-paclitaxel and trastuzumab deruxtecan. **References;** Surveillance, Epidemiology and End Results Program (SEER). 2019. Female Breast Cancer Subtypes - SEER. [online] Available at: <https://seer.cancer.gov/statfacts/html/breast-subtypes.html> [Accessed 18 August 2023].

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Living longer with a better quality of life. If you have triple negative HER2 low breast cancer it can offer another line of treatment. "I tolerated Enhertu well with a good quality of life for 9 months until my disease progressed. It halted my ER-positive HER2-negative disease for most of this time. I was happy to be on it and happy it was made available to me". "Triple negative HER2 low patients urgently need more lines of effective treatment available to them".
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	**Patient voice:** "After six months on this incredibly effective drug which regressed my disease I became very breathless and discovered I had developed interstitial lung disease (ILD). The drug had to be stopped." "Patients must be warned of ILD symptoms as it can be fatal."
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please	The majority of breast cancer patients where hormone receptor is known have hormone receptor (HR) positive and human epidermal growth receptor 2 (HER2) negative advanced breast cancer (Walsh, Smith and Stearns, 2020) . Triple negative patients who are HER2-low and have restricted treatment options may also benefit from this treatment. The DESTINY breast-04 trial found that statistically significant prolongation of progressive free survival when trastuzumab deruxtecan was used in the treatment of patients with HR+, HER2- advanced breast cancer (Modi *et al.,* 2022). **Patient voice:** "I fear the passing of time, any milestone I am scared to celebrate as I feel on a conveyor belt toward my death." **References:**

describe them and explain why.	Modi S., Jacot W., Yamashita T., Sohn J., Vidal M., Tokunaga E., Tsurutani J., Ueno N.T., Prat A., Chae Y.S., Lee K.S., Niikura N., Park Y.H., Xu B., Wang X., Gil-Gil M., Li W., Pierga J.Y., Im S.A., Moore H., Rugo H., Yerushalmi R., Zagouri F., Gombos A., Kim S., Liu Q., Luo T., Saura C., Schmid P., Sun T., Gambhire D., Yung L., Wang Y., Singh J., Vitazka P., Meinhardt G, Harbeck N., Cameron D.; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *New England Journal of Medicine*. 2022 Jul 7;387(**1**):9-20. doi: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782. Walsh E., Smith K., Stearns V. Management of hormone receptor-positive, HER2-negative early breast cancer. *Semin Oncol.* 2020 Aug;47(**4**):187-200. doi: 10.1053/j.seminoncol.2020.05.010. Epub 2020 Jun 3. PMID: 32546323; PMCID: PMC7374796.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There can be inequalities in 'standard of care' for metastatic breast cancer patients between countries within the United Kingdom and even Trusts. Targeted and accessible treatment pathways to support personalised treatment need to be accessible for NHS patients as well as Privately funded ones allowing us to move forward into a humane era of precision oncology. **Patient voice:** "Care can be awful and inconsistent between health boards. I personally do not have a keyworker or secondary breast care nurse. If you are HER2-low there is not enough treatment out there to live a longer and better quality of life." "I worry that in the future, a drug may work for me but won't be accessible due to budget constraints." "I was devastated to be refused treatment at my local NHS hospital only to find out that my friend on the NHS was able to access the treatment via her different trust"
Other issues	
15. Are there any other issues that you would	

like the committee to consider?	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Patients and their families highly value treatments extending quality of life, independence.
- Patients extra time with their families is priceless.
- Current research shows Trastuzumab Deruxtecan is effective in treating patients with HER 2 low unresectable breast cancer
- Concern over interstitial lung disease. Patients need to be aware of signs and symptoms of this disease.
- Targeted treatments with reduced toxicities and their associated drain on limited resources are preferred by patients

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.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 12 July 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 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)	METUPUK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	We received a one off educational grant of £5000 from Daiichi Sankyo to go towards a Metastatic Breast Cancer conference in Manchester in June 2023. Daiichi Sankyo had no input into the agenda, selection of speakers, scientific content or engagement for the event. No representatives from Daiichi Sankyo attended the event.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Comparators. What medicines are used in NHS clinical practice to treat HER2-low metastatic or unresectable breast cancer after chemotherapy?	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 2: Trastuzumab deruxtecan is assumed to be clinically equivalent to sacituzumab govitecan in the hormone receptor (HorR)-negative subgroup	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 3: Is the population of DESTINY-Breast04 generalisable to people likely to have trastuzumab deruxtecan in the NHS?	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 4: Extrapolation of overall survival. Which extrapolated	No	Please provide your response to this key issue, including any new evidence, data or analyses

survival curve is more clinically plausible? Log-logistic or gamma or Weibull?		
Issue 5: Estimation of patients entering the post-progression and death health states	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 6: Extrapolation of progression free survival. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 7: Extrapolation of time to treatment discontinuation. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 8: Health utility values for progression-free and post-progression states. Which utility values are more plausible? Company or EAG?	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 9: Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter. After progression, would utility values be different for people who had trastuzumab deruxtecan rather	No	Please provide your response to this key issue, including any new evidence, data or analyses

than comparator treatments? If so, would this difference last for 6 months or a lifetime?		
Issue 10: Implementation of RDI when calculating the drug acquisition costs	No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 11: Vial sharing for intravenous therapies. Is it likely that vials will be shared so there is no wastage? If so, what proportion of intravenous drug administration would be shared? 50% or 75% or another proportion?	No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Severity Modifier	Please indicate the section(s) of the EAR that discuss this issue B 3.6 Technical papers Section 6 EAR	Yes	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making Metastatic breast cancer is a severe disease, the largest cause of death in women aged 35-65. T-DXd is an innovative drug and is the only option available to target HER2-low metastatic breast cancer. The severity modifier, with the discrete 1.2 and 1.7 categories does not provide the flexibility to capture the impact on this devastating disease. With a median survival of just 16.8 months, T-DXd increased survival by over 6 months, easily meeting the previous end of life funding of £50,000 per QALY gained. As a patient group we are very concerned that if the severity modifier of 1.2 is applied to this drug, there is a risk that the drug company and NICE will not agree on a price that is fair to both the taxpayer and the company. We understand that NICE is closely monitoring the impact of the severity modifier on access to innovative drugs. We hope that in all deliberations both parties are mindful that patients are individuals with high hopes that T-Dxd will give them additional time with their families.

Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 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)	Eisai Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Comparators. What medicines are used in NHS clinical practice to treat HER2-low metastatic or unresectable breast cancer after chemotherapy?	No	Comparators have been captured accurately
Issue 2: Trastuzumab deruxtecan is assumed to be clinically equivalent to sacituzumab govitecan in the hormone receptor (HorR)-negative subgroup	No	Eisai believes that trastuzumab deruxtecan and sacituzumab govitecan are not clinically equivalent. Sacituzumab govitecan is indicated for metastatic triple-negative breast cancer, whilst trastuzumab deruxtecan is indicated for metastatic HER2-positive breast cancer or metastatic HER2-low breast cancer (which is histologically HER2 3+ by immunohistochemistry and/or has a HER2 amplification ratio of at least 2 by in-situ hybridisation). These populations are not equivalent. The two medicines have different safety profiles. *References: NHS England, National Cancer Drugs Fund List. Available at: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/ .* - *Relevant sections on Blueteg form ref: SAC1, criterion 4, Blueteg form ref: TRAD1_v1.1, criterion 3, and Blueteg form ref: TRAD2_v1.0, criterion 3.*

Issue 3: Is the population of DESTINY-Breast04 generalisable to people likely to have trastuzumab deruxtecan in the NHS?	No	Eisai does not believe that the population of DESTINY-Breast04 is generalisable to people likely to have trastuzumab deruxtecan in the NHS. In the Cancer Drug Funds list, criterion 3 for trastuzumab deruxtecan (Blueteq form refs: TRAD1_v1.1 and TRAD2_v1.0) specifies: 'the patient has histologically documented breast cancer which is HER2 3+ by immunohistochemistry and /or has a HER2 amplification ratio of at least 2.0 by in situ hybridisation'. At the moment, patients whose disease is HER2-low are treated as though they were HER2-negative so they would not fulfil criterion 3. *References:* 1. *Modi, S. et al. (2022) 'Trastuzumab Deruxtecan in previously treated HER2-low advanced breast cancer', New England Journal of Medicine, 387(1), pp. 9–20. doi:10.1056/nejmoa2203690.* 2. *NHS England, National Cancer Drugs Fund List. Available at: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/ .*
Issue 4: Extrapolation of overall survival. Which extrapolated survival curve is more clinically plausible? Log-logistic or gamma or Weibull?	No	No comment
Issue 5: Estimation of patients entering the post-progression and death health states	No	No comment
Issue 6: Extrapolation of progression free survival. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	No comment
Issue 7: Extrapolation of time to treatment discontinuation.	No	No comment

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Issue 10: Implementation of RDI when calculating the drug acquisition costs	No	No comment
Issue 11: Vial sharing for intravenous therapies. Is it likely that vials will be shared so there is no wastage? If so, what proportion of intravenous drug administration	No	No comment

would be shared? 50% or 75% or another proportion?		

Additional issues

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Additional issue 1: N/A	Please indicate the section(s) of the EAR that discuss this issue	No	N/A

NICE National Institute for Health and Care Excellence

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No comment			

Sensitivity analyses around revised base case

N/A

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 12 July 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 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)	Gilead Sciences Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/a**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Comparators. What medicines are used in NHS clinical practice to treat HER2-low metastatic or unresectable breast cancer after chemotherapy?	No	The comparator medicines highlighted by the EAG are in line with our understanding of clinical practice
Issue 2: Trastuzumab deruxtecan is assumed to be clinically equivalent to sacituzumab govitecan in the hormone receptor (HorR)-negative subgroup	No	No comment
Issue 3: Is the population of DESTINY-Breast04 generalisable to people likely to have trastuzumab deruxtecan in the NHS?	No	We note that that proportion of the population 40% east Asian, which is higher than the epidemiology in England
Issue 4: Extrapolation of overall survival. Which extrapolated	No	N/a

survival curve is more clinically plausible? Log-logistic or gamma or Weibull?		
Issue 5: Estimation of patients entering the post-progression and death health states	No	No comment
Issue 6: Extrapolation of progression free survival. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	No comment
Issue 7: Extrapolation of time to treatment discontinuation. Which extrapolated curve is more clinically plausible? Log-logistic or generalised gamma?	No	No comment
Issue 8: Health utility values for progression-free and post-progression states. Which utility values are more plausible? Company or EAG?	No	No comment
Issue 9: Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter. After progression, would utility values be different for people who had trastuzumab deruxtecan rather	No	Potentially yes, we assume the utility values will converge at death rather than at defined time period.

than comparator treatments? If so, would this difference last for 6 months or a lifetime?		
Issue 10: Implementation of RDI when calculating the drug acquisition costs	No	N/a
Issue 11: Vial sharing for intravenous therapies. Is it likely that vials will be shared so there is no wastage? If so, what proportion of intravenous drug administration would be shared? 50% or 75% or another proportion?	No	Vial sharing is likely. TA819 estimated 50% vial sharing so 75% is a fair assumption for this larger treatment population

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: N/a	N/a	No	N/a

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy [ID3935]. A Single Technology Appraisal

Addendum: EAG comments of the company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Sarah Davis, Senior Lecturer in Health Economics, ScHARR, University of Sheffield, Sheffield, UK Christopher Carroll, Reader in Systematic review and Evidence Synthesis, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Sarah Ren, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Date completed	27/07/2023

1. Introduction

In July 2023, the company submitted their response to technical engagement (TE) for the appraisal of trastuzumab deruxtecan (T-DXd) as monotherapy for treating adult patients with unresectable or metastatic breast cancer (u/mBC) with low levels of human epidermal growth factor receptor 2 (HER2), and who have had at least one prior chemotherapy.(1) The company's TE response includes a written response form which presents a brief discussion of each of the key issues identified in the External Assessment Group (EAG) report. The TE response also includes a new version of the model which had been used to generate updated cost-effectiveness estimates. No updated model version of the cost minimisation analysis (CMA) comparing T-DXd to sacituzumab govitecan (SG) was submitted.

This addendum provides a brief commentary on the company's TE response and should be read in conjunction with the EAG report. Section 2 provides a summary of the company's response and the EAG's critique of these points; whist Section 3 presents a fuller description of the EAG's critique on the company's response to particular issues and new analyses presented by the company. Section 4 provides a brief description of the changes in the updated model submitted by the company. Section 5 presents the methods for additional exploratory analyses undertaken by the EAG. Section 6 presents the results of additional exploratory analyses undertaken by the EAG.

All results presented in this document include the Patient Access Scheme (PAS) discount which reduces the cost per 100 mg vial from a list price of £[redacted] to £[redacted]. This is unchanged from the discount offered at the time of the original company submission (CS).(2)

2. Summary of company's TE response and EAG comments

The main points discussed in the company's TE response and the EAG's comments are summarised in Table 1. Where further critique was considered necessary, this is provided in Section 3.

Table 1: Summary of company's TE response and EAG comments

<table>
<tr><th>Key issue</th><th>Headline points in company's TE response</th><th>EAG comments</th></tr>
<tr>
<td>Key issue 1:
The deviation of the comparator arm from the NICE scope</td>
<td>

The company reiterated the reasons based on which the TPC (treatment of physician's choice) arm of DESTINY-Breast04 is viewed as an appropriate comparator for this appraisal as detailed in the original CS Section B.1.3.6.(2)
The company performed an exploratory post-hoc analysis of DESTINY-Breast04 where second line (2L) eribulin and gemcitabine when used beyond the first-line setting are removed from efficacy and cost estimates. The distribution of the remaining TPC agents were: eribulin 3L (n=[redacted], [redacted]%), capecitabine (n=[redacted], [redacted]%), nab-paclitaxel (n=[redacted], [redacted]%), and paclitaxel (n=[redacted], [redacted]%).
As the choice of the TPC agent was decided before randomisation, the analysis excluded patients who would have received the removed TPC agents and ended up receiving T-DXd. This left the T-DXd arm with 247 out of the 373 patients included in the full analysis set (FAS).
Results of the exploratory analysis compared to the FAS were as follows:

<table>
<tr><th rowspan="2"></th><th colspan="2">PFS HR</th><th colspan="2">OS HR</th></tr>
<tr><th>FAS</th><th>Exploratory analysis</th><th>FAS</th><th>Exploratory analysis</th></tr>
</table>
</td>
<td>Based on the absence of any new evidence or arguments to show that the TPC arm is representative of the comparator arm in the NICE scope, the EAG stands by its position that the TPC arm of the FAS from DESTINY-Breast04 is not indicative of either the agents prescribed in the UK clinical practice, or their distribution as was discussed in Sections 1.4 and 3.3 of the EAG report.

The EAG thinks the new exploratory analysis conducted by the company removes some uncertainty with the exclusion of these agents that are not used in the UK clinical practice. However, the EAG remains unsure of the real-world distribution of the remaining agents, and uncertainty remains regarding efficacy and cost estimates of other comparators stated in the NICE scope if they had been included in DESTINY-Breast04 (e.g. anthracyclines, carboplatin, and vinorelbine).

In addition, The EAG notes also that there are some discrepancies between patient numbers on the TPC agents included in the exploratory analysis and those mentioned in the CS. CS, Table 9 states that there were 37 patients on capecitabine, 19 on nab-</td>
</tr>
</table>

Key issue	Headline points in company's TE response	EAG comments

Midpoint value	0.50	[redacted]	0.64	[redacted]
95% CI	0.40,0.63	[redacted]	0.49,0.84	[redacted]
p value	<0.0001	[redacted]	0.001	[redacted]

CI - confidence interval; FAS - full analysis set; HR - hazard ratio; PFS - progression-free survival; OS - overall survival

- The company concluded that the outcome endpoints are similar between the FAS and exploratory analysis, and provided cost-effectiveness estimates for the exploratory analysis as a scenario.

paclitaxel, and 15 on paclitaxel. However, the EAG thinks these could have minimal impact on the ICERs estimated for this scenario.

The EAG highlights that implementing the efficacy and cost estimates from this scenario did make a significant difference in the outcomes of the TPC arm where total discounted costs and total discounted QALYs decreased from £[redacted] and [redacted] to £[redacted] and [redacted] respectively, with the latter equivalent to a decrease of more than 10%. This reduces the company's ICER by 7% from its updated post TE base case (£[redacted] versus £[redacted] when applying a QALY weighting of 1.2).

The company's scenario analysis excluding patients who received gemcitabine or second-line eribulin does not use the HRs for the post-hoc subgroup provided in the company's response to TE, but instead uses updated parametric curves fitted to the new restricted population. The company has not presented in its TE response any information to allow the EAG to assess the choice of parametric extrapolation in this new data set.

In addition, the EAG is concerned that the exclusion of patients who were allocated to receive eribulin as a second line treatment is not

Key issue	Headline points in company's TE response	EAG comments
		only a post-hoc analysis that reduces the sample size, but it also biases the trial population towards those who have had more than one line of prior therapy. The EAG considers it likely that clinicians will want to use T-DXd at second line whenever possible (EAG report, page 126), and therefore usage of T-DXd at third-line is likely to be limited once the initial prevalent population has been treated. Therefore, incorporating an analysis which uses OS and PFS curves fitted to a population which is biased towards patients having later lines of therapies reduces the generalisability of the cost-effectiveness estimates to the expected population likely to receive T-DXd in the long-term in NHS practice. The EAG prefers to maintain their original approach in which patients receiving eribulin and gemcitabine are assumed to have the same clinical outcomes, but their costs are based on the distribution of treatments received by other patients randomised to TPC. This approach relied on the assumption that clinical outcomes are expected to be similar across the single-agent chemotherapies included in the TPC arm, and this assumption seems to be supported by the company's TE response (page 6).
Key issue 2: Exploratory	• The company does not provide any new evidence to support the clinical equivalence claim between T-DXd and SG in the	If the company believes that the populations of ASCENT and DESTINY-Breast04 are different, then significant caution should be

Key issue	Headline points in company's TE response	EAG comments
comparison against sacituzumab govitecan (SG) for hormone receptor (HorR)-negative subgroup assumes clinical equivalence	HER2-low HorR-negative subgroup, and reports again the results of the naïve, unadjusted, comparison of OS and PFS results using subgroups of the ASCENT and DESTINY-Breast04 trials. • The company accepted the changes proposed by the EAG in the cost-minimisation model regarding using the average patient weight for HorR-negative patients from DESTINY-Breast04 and using the relative dose intensity (RDI) estimates for SG from TA819. • However, the company disagrees with the EAG's approach to use the time-on-treatment (ToT) for SG sourced from TA819 *"because the ASCENT and DESTINY-Breast04 populations are different and because time-on-treatment is dependent on, and may impact, a wide range of clinical factors, including toxicity and efficacy"*. Instead, the company proposes applying "*the Grade ≥3 treatment-related treatment-emergent adverse event (TEAE) rate from the SG arm in ASCENT to the SG arm of the model and the corresponding rates for the T-DXd arm of DESTINY-Breast04 to the T-DXd arm in the model*".	considered when interpreting the results of the naïve unadjusted comparison. Moreover, the EAG notes that in response to the TE process, Eisai Ltd has submitted a form where they mention that "*Eisai believes that trastuzumab deruxtecan and sacituzumab govitecan are not clinically equivalent,*" because "*These populations [of ASCENT and DESTINY-Breast04] are not equivalent. The two medicines have different safety profiles*." The EAG notes that the company chose not to apply the SG ToT, and instead used the TEAEs specific to SG. The EAG considers this insufficient to estimate costs related to SG, and thus stands its position that the ToT for SG should be applied. The EAG updated its base case to include SG-specific TEAEs, however, it still stands by its position to include SG ToT from ASCENT. In addition, the EAG still considers that the cost-minimisation analysis is associated with significant uncertainty because the relative efficacy and cost-effectiveness of T-DXd and SG in the HER2-low HorR-negative population is unknown (see EAG report, Key Issue 2 and Section 5.3.3.2).
Key issue 3: Generalisability of	• The EAG highlighted in its report that the population of DESTINY-Breast04 may not be representative of the patient	The EAG does not consider the subgroup analysis conducted based on ethnicity to be consistent particularly in terms of PFS outcomes.

<table>
<tr><th>Key issue</th><th>Headline points in company's TE response</th><th>EAG comments</th></tr>
<tr><td>the trial population of DESTINY-Breast04 to the patient population seen in England</td><td>
population seen in practice as the study had younger average age, excluded patients with Eastern Cooperative Oncology Group performance status (Eastern Cooperative Oncology Group [ECOG] progression status [PS]) of ≥2, and had a relatively high proportion of Asian patients. The company addressed each of these characteristics separately.
• The company claims that the subgroup analysis conducted based on ethnicity showed consistency among the subgroups of Asian ethnic (n=223) and white ethnic (n=267) subgroups as shown in the table below:
<table>
<tr><th rowspan="2"></th><th colspan="2">PFS HR</th><th colspan="2">OS HR</th></tr>
<tr><th>White subgroup</th><th>Asian subgroup</th><th>White subgroup</th><th>Asian subgroup</th></tr>
<tr><td>Midpoint value</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>95% CI</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="5">CI - confidence interval; FAS - full analysis set; HR - hazard ratio; PFS - progression-free survival; OS - overall survival</td></tr>
</table>
• For ECOG PS criteria, The company claims that T-DXd is "expected to predominantly be used in patients with ECOG PS 0 or 1 in UK clinical practice … in line with the Cancer
</td><td>
Although there is a limited overlap between both 95% CIs, the HR point estimates are different.

The company did not provide any evidence to support that T-DXd has the same efficacy in patients with ECOG PS 2 versus those with scores 0 or 1. Although the company claims that the use of T-DXd in the CDF is restricted to treating patients with ECOG 0 or 1, the EAG notes that the T-DXd marketing authorisation does not exclude patients with ECOG 2 in whom there are no data on clinical effectiveness.

The EAG acknowledges that the median ages reported from the [redacted] and the FAS population of DESTINY-Breast04 are similar. However, the EAG would like to highlight that the Supplementary Appendix p25 of Modi et al. which is the key publication for DESTINY-Breast04 mentions that "The age of trial participants was slightly lower than the median age of patients diagnosed with HER2-low breast cancer (55.9-57.5 years versus 59 years)."(3) It is also arguable from the subgroup analysis whether the HR point estimates particularly for PFS are similar between the two age-based subgroups.
</td></tr>
</table>

<table>
<tr><th>Key issue</th><th>Headline points in company's TE response</th><th>EAG comments</th></tr>
<tr><td></td><td>
Drugs Fund (CDF) managed access agreement criteria for T-DXd in HER2-positive mBC after ≥1 anti-HER2 treatment (TA862) and after ≥2 anti-HER2 treatments (TA704), which restrict the use of T-DXd to patients with ECOG 0 or 1." The company then reported the findings of the subgroup analysis for ECOG PS 0 versus 1.
• Regarding age, the company presented data from the [redacted] versus [redacted] years in the FAS population. The company also reported findings of the subgroup analysis for patients aged <65 years (n=426) and ≥65 years (n=131) as shown below:
<table>
<tr><th></th><th colspan="2">PFS HR</th><th colspan="2">OS HR</th></tr>
<tr><th></th><th><65-year subgroup</th><th>≥65-year subgroup</th><th><65-year subgroup</th><th>≥65-year subgroup</th></tr>
<tr><td>Midpoint value</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>95% CI</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="5">CI - confidence interval; FAS - full analysis set; HR - hazard ratio; PFS - progression-free survival; OS - overall survival</td></tr>
</table>
</td><td>
The EAG would also like to note that the company reports results of an unpublished RWE US observational study in response to key issue 4, named the Flatiron study where the mean age was [redacted] years, and ~ [redacted]% of the patients with known performance status were ECOG PS 2, 3 or 4 (based on the eligibility criteria).

Therefore, the EAG did not change its view that these characteristics are potentially treatment effect modifiers as the company did not submit any concrete evidence to refute it. Hence, the EAG still skeptical that the trial population is representative of the population seen in clinical practice in England.
</td></tr>
</table>

Key issue	Headline points in company's TE response	EAG comments
Key issue 4: Extrapolation of overall survival (OS)	• The company maintains its preference for the log-logistic curve for the reasons discussed in CS Section B.3.3.2. • The company implies that there are no further planned data cuts for DESTINY-Breast04 as it met its key secondary endpoint of OS. • The company consulted clinical experts during NICE TE who advised that [redacted]% of patients treated with TPC would be alive by 5 years, and a "*small proportion*" by 10 years. The log-logistic curve estimates survival probabilities of [redacted]% and [redacted]% respectively. Table 5 of the company's TE response shows the different predictions by parametric fits at 1, 1.5, 2, 3, 5, and 10 years for TPC. • For T-DXd, the Weibull extrapolation predicts a [redacted]% survival probability at 5 years which the company says is "[redacted]" to the 5% elicited by the EAG's clinical experts for TPC at 5 years; which implies that T-DXd has [redacted] OS benefit at 5 years. Table 6 of the company's TE response shows the different predictions by parametric fits at 1, 1.5, 2, 3, 5, and 10 years for T-DXd. • The company provides real-world evidence (RWE) to support the appropriateness of the log-logistic curve. These were the 'Flatiron study' and two additional studies by Graff *et al.*, and	The EAG does not consider that the company provided enough evidence to support the log-logistic distribution as the most suitable for modelling OS. The EAG maintains its position on preferring the gamma distribution which was not available in the original submitted model (but was shown in the file submitted by the company containing plots of the various fitted distributions in response to clarification questions [Daiichi Sankyo Inc. OS extrapolations FAS CONFIDENTIAL page 9]). However, the company's updated model too does not provide the estimates for it, so the Weibull was selected once again as being more plausible than the log-logistic distribution, and using the latter as a scenario analyses. A more detailed EAG critique of the company's TE response to this issue is presented in Section 3 of this addendum.

Key issue	Headline points in company's TE response	EAG comments
	de Calbiac *et al.* These are discussed in the EAG critique of the company's TE response to this issue in Section 3 of this addendum. • The company refused to fit the gamma distribution preferred by the EAG (a potential midway between the log-logistic and Weibull fits) as it was not included within the candidate six parametric curves from the DSU TSD 14. Based on the "*strong*" fit of the log-logistic distribution and the long-term extrapolations from the log-logistic aligned with RWE and clinical feedback, "*the company does not believe it is necessary to explore the impact of alternative distributions or survival modelling methods, including the gamma distribution.*"	
Key issue 5: Estimation of patients entering the post-progression and death health states	• The company accepts the way the EAG adjusted the formulae to correctly calculate the risk of death from the post-progression state.	The EAG considers this issue is resolved.
Key issue 6:	• The log-logistic, log-normal and generalised gamma curves all provided good statistical fits for both the TPC and T-DXd arms, based on their AIC and BIC statistics.	The EAG notes that the median PFS predicted by the generalised gamma curve are [redacted] months and [redacted] months, for TPC and T-DXd

Key issue	Headline points in company's TE response	EAG comments
Extrapolation of progression free survival (PFS)	• However, the company maintains its preference for the log-logistic curve as it predicts a median PFS of [redacted] months and [redacted] months, for TPC and T-DXd respectively, which is similar to the observed median PFS in DESTINY-Breast04 of 5.1 months and 9.9 months for the TPC and T-DXd arms, respectively. • The log-logistic curve showed good long-term TPC and T-DXd PFS estimates. For example, the 2-year estimates are [redacted]% and [redacted]% for the TPC and T-DXd arms, respectively, which are closely aligned to the 2-year observed PFS from DESTINY-Breast04 of [redacted]% and [redacted]s% for the TPC and T-DXd arms, respectively. • The company reiterates again that "*it would be preferable to use the same distribution for both PFS and OS, with clinical experts noting that there is an inherent relationship between PFS and OS.*" • The company considers the fact that the PFS KM curves for T-DXd and TPC are about to cross at the end of the trial to be a "*likely artefact due to the low numbers of patients-at-risk at the end of the PFS KM curve in DESTINY-Breast04*." • The company considers it is implausible to assume equal PFS between T-DXd and TPC arms at five years (as proposed by	respectively which are identical to the estimates from the log-logistic curve. The EAG notes that the 2-year estimates associated with the generalised gamma curve are [redacted]% and [redacted]%, which are obviously better aligned to the observed PFS from the DESTINY-Breast04 trial compared to the log-logistic curve. The EAG maintains its view that the log-logistic model overestimates the tail area of the T-DXd arm (0% around 28 months from the KM data vs. [redacted]% at 10-years extrapolated by the log-logistic distribution) and considers that the generalised gamma presents a better fit to the KM data. The EAG notes that Figure 6 (observed vs. predicted PFS (TPC)) in the company's TE response should be treated with caution as the KM data plotted are not the observed KM data (CS Figure 12) and have a shorter follow-up (approximately 1.8 years vs. 2.3 years from the trial). The EAG reiterates its position again regarding using the same curve for both PFS and OS that the relationship between PFS and OS "*does not warrant that the hazard function of OS and PFS would follow the same trend".*

Key issue	Headline points in company's TE response	EAG comments
	the cap introduced by the EAG to ensure that PFS estimates for TPC are not higher than that of T-DXd at a given time point) given the treatment effect observed in the trial. • The selection of the generalised gamma curve provides inconsistent PFS estimates with previous appraisals, TA819 in particular.	The company did not provide any evidence to support that the likely crossing at the end of the trial of both KM curves (CS, Figure 12) could be an artefact. Moreover, the EAG highlights that the treatment effect observed in the trial in terms of PFS is not necessarily going to remain till 5 years when the fitted generalised gamma distributions cross for both arms. The company did not provide any evidence contrary to this. Also, as illustrated in the EAG comments to Key Issue 2, the trial population for TA819 is different to that of DESTINY-Breast04 trial. Therefore, the EAG is cautious about the relevance of any comparisons regarding PFS estimates. The EAG is unaware of the reasons why the approach suggested by the EAG using the mature KM data and only using parametric extrapolations beyond the KM data, was ignored by the company. Based on the absence of any new evidence to show that the log-logistic is the most appropriate model to extrapolate PFS, the EAG stands by its position regarding its preference for the generalised gamma curves over the log-logistic curves. The EAG also notes that

Key issue	Headline points in company's TE response	EAG comments
		in response to clarification question B2, the company presented extrapolation using the spline models for PFS which have similar shorter tails as the generalised gamma model but the extrapolated TPC and T-DXd arm do not cross. The EAG considers that the spline models may be more appropriate than either the log-logistic or the generalised gamma model. However, the company did not provide the estimate of the model parameters for the spline models and did not consider the spline models in the updated model.
Key issue 7: Extrapolation of time to treatment discontinuation (TTD)	• The company and the EAG agree on using the generalised gamma fit for the extrapolation of TTD data in their base cases. • However, the EAG recommended using the mature KM data and limit parametric extrapolations to the time period beyond where KM data is available. • The company considers that this would provide "*limited additional value and would have minimal impact on the ICER.*"	The company neither submitted the analysis requested by the EAG nor showed why it would be of minimal impact on the ICER. The EAG notes that the two scenarios explored, where the restricted mean treatment duration approach was used as the lower limit for treatment duration, and the log-logistic TTD extrapolation was used as the upper limit, produced significantly different ICERs (~[redacted] and ~ [redacted] respectively). Therefore, the EAG considers the uncertainty within this key issue to be unresolved.
Key issue 8: Health utility values for progression-free	• The company maintains the view that their approach to estimate PF utilities for T-DXd and TPC derived from a generalised linear mixed model (GLMM) using EQ-5D data	The company did not provide new evidence but provides a revised approach to estimate PP utilities assuming that the period of T-DXd PP utility benefit is 12 months instead of a lifetime.

Key issue	Headline points in company's TE response	EAG comments
and post-progression states	collected from DESTINY-Breast04 is methodologically robust and appropriate. • In the company's revised base case, PF utilities are based on the estimates from a GLMM as in the company's original base case. PP utilities are based on the estimates from the Lloyd *et al.* algorithm as in the company's original base case, but the company has limited the period of T-DXd PP utility benefit to 12 months instead of a lifetime. • The company highlights that the PF "*utilities presented in the company's base case are similar to the values accepted in TA862 for HER2-positive u/mBC after 1 or more anti-HER2 treatments*" and "*therefore support the utility values used in the company base case compared to the EAG's*". • The company also highlights that the EAG's PP utilities are "*considerably lower than what has been accepted previously in mBC TAs*"), and the company PP utilities are "*within the range accepted by NICE committees*". • The company explored two scenario analyses using median PF utilities from DESTINY-Breast04 and using PF utilities derived from a linear mixed model. In these scenario analyses, PP utilities are modelled the same as the company's revised base case.	The EAG agrees with the company that the GLMM approach is a more sophisticated approach than the descriptive statistics approach. However, the EAG notes that using a sophisticated approach does not necessarily guarantee face validity of the results. The EAG maintains its view that the company's PF utilities derived from a GLMM lack face validity, because it provides [redacted] and [redacted] the general population utility for women aged 57 years old in the UK. The EAG notes that the company scenario analyses estimating PF utilities using median values and a linear mixed effect model are all lower than the PF utilities estimated from a GLMM and closer to the EAG's original base case using mean values. The EAG reiterates that the company has not applied the Lloyd *et al.* algorithm appropriately for deriving utilities for the PP state. Based on the above considerations, the EAG's revised base case uses PF utilities from the company's scenario analysis derived from a mixed linear model; PP utilities from Lloyd *et al.* considering age

Key issue	Headline points in company's TE response	EAG comments
		and progression status and assuming that the period of T-DXd PP utility benefit is 6 months. A more detailed EAG critique of the company's TE response to this issue is presented in Section 3 of this addendum.
Key issue 9: Duration of difference in utility values between treatment arms for post-progression state and the value to be used for both arms thereafter	• In line with TA819, the EAG preferred to assume that any difference in the utilities between treatment arms only persisted for 6 months following progression after which all patients would adopt the TPC utility. This was in contrast to the company's approach where the utility benefit was assumed to persist for the patient's lifetime. • In its TE response, the company agrees that TPC utility values should apply after the waning of treatment effect, however it believes this utility benefit should persist for more than 6 months and assumes 12 months for the following two reasons; (i) T-DXd is associated with better initial disease control compared to TPC, which translates into a lower tumour burden at progression and slower disease progression on the next-line therapy as confirmed with the statistically significantly longer PFS2 in the FAS with T-DXd vs. TPC; (ii) DESTINY-Breast04 showed statistically significant PP utility benefit for the duration of PP utility data collection, and	The EAG accepts that better disease control prior to progression may mean that patients have higher utility post-progression, but it also believes that this benefit will be time limited, as per the committee's considerations in TA819. The company's analysis of PFS2 did show a statistically significant reduction in the risk of progression on the next line of therapy. However, an extension in median PFS2 of ~[redacted] months ([redacted] months on TPC to [redacted] months on T-DXd), does not provide strong support for the company's position that post-progression utility should be improved for more than 6 months. The company claims that T-DXd showed, "*a statistically significant PP utility benefit for the duration of PP utility data collection*" relative to TPC. However, the EAG is unclear what evidence is available to support this claim. The company's response to clarification (B10, Table 20) reported post-progression utilities by

Key issue	Headline points in company's TE response	EAG comments
	the last timepoint at which the HRQoL data were collected was at the long-term follow-up assessment, which was three months after the first follow-up assessment on Day 40 after the last study drug administration. The 6-month PP utility benefit means that this benefit "*would have eroded within 7 weeks;*" The company has updated its base case to model utility in the T-DXd arm using its preferred post-progression utility value for the T-DXd arm (0.610) for 12 months, followed by its preferred post-progression utility value for the TPC arm (0.565) for the reminder of the patient's life expectancy. In the TPC arm its preferred value is used life-long.	trial arm but no p-values are provided. Although progression status was a statistically significant regression coefficient in the company's GLMM regression (CS, Table 44), Figure 23 of the clarification response and CS Table 45 shows no statistically significant difference between the predicted post-progression utilities for T-DXd and TPC (overlapping 95% confidence intervals of [redacted] and [redacted]) The EAG is also unclear how the company has assessed whether the difference is persistent over, "*the duration of PP utility data collection*." Observations of utility were at 40 days after the end of treatment and again 3 months later. However, the end of treatment did not always coincide with disease progression. CS, Table 45 reports [redacted] observations informing the utility estimates of progressed patients for the T-DXd arm and [redacted] observations for the TPC arm, but [redacted] and [redacted] of these observations respectively were in patients still classed as being on treatment. This was either because they were not yet deemed to have progressed according to the investigating clinician but had been classified as progressed by blinded independent central review (BICR), or they were within 21 days of stopping T-DXd (see company TE response to Issue 8). Given that there were 208 and 117 patients with progression in the T-DXd and

Key issue	Headline points in company's TE response	EAG comments
		TPC arms respectively (CS, Table 18), the number of post-progression observations falling after the end of treatment is expected to be fairly low ([redacted] for TPC and [redacted] for T-DXd per progressed patient), suggesting that most patients had only one post progression utility measurement at 40 days after ending treatment. Therefore, the EAG does not consider that the post-progression utility data from the trial can be used to support a utility benefit for more than 6 months. The EAG has maintained its preference for a utility gain lasting 6 months in its base case analysis as per the assumption accepted by the committee in TA819.
Key issue 10: Implementation of RDI when calculating the drug acquisition costs	• The company states that the approach used by the EAG to calculate the RDI by comparing the cumulative dose in mg against the dose specified in the SmPC is not appropriate because the dose range permissible in the trial was often lower than the SmPC dose. • However, the company accepts the EAG's approach for all agents included in TPC other than eribulin. • The company has used the dose administered relative to the planned dose in the study for T-DXd and eribulin. • It states that the EAG accepted this approach for T-DXd	The EAG maintains its preference for calculating RDI relative to the dose used for calculating drug acquisition costs in the model. The EAG used the same approach for T-DXd and all elements of TPC, and therefore the EAG does not understand why the company believes it is necessary to use an updated RDI figure for eribulin if it agrees with the EAG's approach for T-DXd. The EAG notes that although the company's updated RDI estimate for eribulin is described as being consistent with the approach preferred for T-DXd by the EAG, the numbers calculated by the company are slightly different for both T-DXd ([redacted]% versus [redacted]%) and eribulin ([redacted]% versus [redacted]%). The EAG is assuming that in both cases this difference is due to errors introduced by the drug dose

Key issue	Headline points in company's TE response	EAG comments
		being reported to 0.1 mg in CSR Table 10.1 which the EAG used to calculate its RDI estimates. Given that this is a plausible explanation for the difference, and the impact on the ICER is small, the EAG accepts the company's updated RDI for eribulin.
Key issue 11: Vial sharing for intravenous therapies	• The company considers the EAG's assumption of 50% vial sharing may underestimate the proportion of centres that will vial share. • The EAG made this assumption in line with TA862. The company claims that in TA862 the CDF clinical lead stated that vial sharing would occur in at least 50% of centres. TA862 was based on an HER2-postive population which is a markedly smaller subset of mBC than HER2-low.	As mentioned in its report (Section 5.3.3.10), the EAG preferred to stick to the 50% vial sharing assumption as it was accepted in TA862. The EAG cannot validate the 75% assumption as it is not supported by any evidence. Therefore, the EAG stands its position on the 50% vial sharing assumption.
Additional issue 1: Considering a 1.7x severity modifier	• The company argues that the 1.2x severity modifier *"underestimates the severity of the condition and does not adequately recognise the high unmet need, innovation, and clinical value of T-DXd, as well as the clinical and patient enthusiasm for T-DXd.*" and presents a new set of results using the 1.7x severity modifier. • The company corroborates that by mentioning that both the company and EAG base cases and all model scenarios resulted in absolute and proportional QALY shortfalls exceeding the	The EAG notes that the company did not provide any new evidence to support the 1.7x severity modifier. The absolute and proportional QALY shortfall may exceed the minimum threshold required for the 1.2x modifier, however they fail to meet the minimum threshold for the 1.7x modifier. Additionally, the EAG highlights that these benefits mentioned by the company and uncaptured in the model in terms of employment and work productivity, are outside the NHS perspective.

Key issue	Headline points in company's TE response	EAG comments
	minimum threshold required to qualify for the 1.2x QALY modifier. • In addition, *"T-DXd has the potential to offer benefits not captured in the QALY calculation."* These benefits include *"employment and work productivity as well as their ability to parent actively and fulfil their social role.*"	Therefore, the EAG presents results as with the original CS and the EAG report using the 1x and 1.2x QALY weights.

Abbreviations: CDF - Cancer Drug Fund; CI - confidence interval; CSR - clinical study report; ECOG PS - Eastern Cooperative Oncology Group progression status; GLMM - generalised linear mixed model; HorR - hormone receptor; HR - hazard ratio; ICER - incremental cost-effectiveness ratio; NHS - National Health Services; OS - overall survival; PFS - progression free survival; PP - post-progression; QALY - quality adjusted life year; RDI - relative dose intensity; SG - sacituzumab govetecan; T-DXd - trastuzumab deruxtecan; TEAE - treatment emergent adverse events; ToT - time on treatment; TPC - treatment of physician's choice; TTD - time to treatment discontinuation

3. EAG's critique on key issues 4 and 8.

The EAG has already made brief comments on issues 1-3, 5-7 and 9-11 in Table 1 and does not consider it necessary to provide further commentary on these issues. However, additional critique is provided below on the company's responses to issues 4 and 8.

Key issue 4: Extrapolation of OS

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

The company argues that "*the log-logistic curve provides the best overall fit to the clinical data for the TPC arm based on the goodness-of-fit statistics, with the lowest AIC and BIC scores across all fitted curves.*" However, the EAG notes that AIC and BIC scores for the Weibull model are nearly identical to those of the log-logistic. AIC scores were 751.10 versus 751.16 whilst BIC scores were 757.53 versus 757.59 for log-logistic and Weibull models, respectively. For T-DXd, "*the log-logistic curve remained within 5 AIC and BIC points of the best-fitting curve*". The EAG notes that the best-fitting curve is the Gompertz (AIC: 1366.87; BIC: 1374.71) and the Weibull model provides almost identical AIC and BIC to the Gompertz (AIC: 1366.87; BIC: 1374.74).

Fitting of parametric models and visual fit against KM data

The company considers that "*the log-logistic curve to provide the best visual fit.*" The company presented figures showing survival probabilities of the Weibull and log-logistic curves versus the KM data. The EAG maintains its view that that the log-logistic model overestimates the survival probability in the tail area, and the Weibull model provides a better fit to the KM data including the tail area.

The company evaluates the strength of the visual and statistical fit for the log-logistic curve "*is further demonstrated when modelled OS estimates are compared against the observed data from DESTINY-Breast04 across both treatment arms; median OS predicted in the model using a log-logistic curve of* [redacted] *months and* [redacted] *months, for TPC and T-DXd respectively, is similar to the observed median OS in DESTINY-Breast04 of 16.8 months and 23.4 months for the TPC arm and the T-DXd arm, respectively."* The EAG notes that the Weibull curve provided similar estimates of [redacted] months and [redacted] months, respectively. The EAG highlights that assessing the visual fit based on the median could be misleading as the fit should be assessed against the whole KM curve rather than the point estimate and reiterates that the log-logistic model overestimates the survival probability in the tail area.

Long-term clinical plausibility

The company mentions that during NICE technical engagement, they sought further clinical advice for the OS long-term predictions which instructed that "[redacted]*% of patients treated with TPC would be alive at 5 years and a small proportion would be alive at 10 years.*" While the company's clinical experts

failed to give figures for what this "*small proportion*" might be, one of the EAG's clinical experts estimates that it's a 0% at 10 years and the other one estimates a 0-1% at 10 years. The 10-year prediction from the Weibull model ([redacted]%) is more aligning with the clinical opinion than the log-logistic model ([redacted]%) (see Table 2). However, the EAG acknowledges that the 5-year predictions associated with the Weibull model seem pessimistic.

For T-DXd, the EAG agrees with the company that "*OS estimates for TPC should serve as a minimum estimated OS for T-DXd*" meaning that the 5-year survival probability predicted by the Weibull of [redacted]% for T-DXd is pessimistic compared to the EAG's clinical advice that 5-year prediction for TPC is 5%. However, the EAG is unsure that this value should be as much high as [redacted]% as predicted by the log-logistic model, and the company did not provide any evidence to support that.

The EAG reiterates that the EAG believes that the Weibull model may have underestimated the benefit at 5 and 10 years and the log-logistic may have overestimated the benefit at 5 and 10 years. The gamma model may be more appropriate than either the log-logistic or the Weibull model. The company provided the fitted gamma model in response to clarification question B2 but did not provide the estimate of the model parameters and did not consider it in the updated model.

Table 2: OS in the FAS population: Predictions by independently fitted distributions (reproduced from Table 5 and Table 6 at the company's TE response form)

Distribution	Median (months)*	1-Year OS	1.5-Year OS	2-Year OS	5-Year OS	10-Year OS
TPC arm						
DB-04 – FAS population (observed data)	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd arm						
DB04 –FAS population (observed data)	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Weibull (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Median time in months and predicted OS are estimated after OS has been adjusted to include general population mortality

Abbreviations: DB04 – DESTINY-Breast04; FAS – full analysis set; OS – overall survival; TPC, treatment of physician's choice.

Validation against real-world evidence

The first piece of RWE evidence provided by the company to support the clinical plausibility of long-term OS probabilities as predicted by the log-logistic model was the Flatiron study. The company presents results from this unpublished study, however the EAG would like to note that they only received the study protocol as data on file and cannot comment either on the baseline characteristics or the results reported by the company in their TE response.

The Flatiron study is a retrospective observational cohort study of US patients with HER2-low mBC; an analysis of the mortality data from Flatiron was conducted *"to support the ongoing NICE appraisal."* The EAG notes that this study design inherently has a risk of selection bias and that TPC components allowed in the analysis included arguably more effective treatments than those observed in DESTINY-Breast04 or real practice such as [redacted] and [redacted]. Therefore, the EAG considers that this comparator arm does not represent the TPC arm of the decision problem at hand.

Graff *et al.* was a US study and had the same retrospective design as the Flatiron study, and was available only as an abstract.(4) The company reports OS results that were not available to the EAG to critique from the abstract. The EAG notes that treatments involved again could be more effective than those observed in DESTINY-Breast04 or real practice such as immunotherapy (atezolizumab, pembrolizumab, and nivolumab) and alpelisib. Therefore, the EAG considers that this comparator arm does not represent the TPC arm of the decision problem at hand.

de Calbiac *et al.* was a French retrospective observational study comparing survival outcomes in HER2-low mBC versus HER2-negative mBC.(5) The study included patients "*who started a first-line anticancer treatment for mBC*". The EAG considers that this study population deviates from the target population of this appraisal where patients should have received at least a previous line of chemotherapy.

Overall, the EAG considers that the company's choice of real-world evidence to validate long-term plausibility of the extrapolation lack of generalisability to the population in this appraisal.

<u>Additional data: gamma curve</u>

Although the company *"does not believe it is necessary to explore the impact of alternative distributions or survival modelling methods, including the gamma distribution,"* the EAG highlights that the fitted gamma curve provided by the company in response to clarification question B2 showed *"a reasonable long-term prediction in between the log-logistic and Weibull distribution"* as mentioned in the EAG report Section 5.3.3.4. The EAG is unaware of the reasons why the estimates for this curve

were not provided in the model and again is unable to investigate the impact of using the gamma distribution to extrapolate OS on the ICER.

Key issue 8: Health utility values for progression-free and post-progression states

PF utilities

The company provides a rationale for using a GLMM approach by stating that "*the utility values derived from the GLMM are more appropriate for the PF utility values because, unlike using descriptive statistics, they are less biased by extreme outliers and account for the effects of covariates and intra-subject correlation*", and the use of the GLMM approach follows the recommendations from the ISPOR Good Research Practices Task Force Report(6) and is similar to the approach taken in Lloyd *et al*.(7)

The company maintains the use of the PF utilities derived from a GLMM and argues that "*the utilities presented in the company base case are similar to the values accepted in TA862 for HER2-positive u/mBC after 1 or more anti-HER2 treatments*".

The company explores uncertainty in the PF utilities by conducting two scenario analyses for estimating PF utilities: (i) using median PFS utility values from DESTINY-Breast04 (descriptive statistics) because the median values are less prone to bias by outliers than the mean values; (ii) using PF utilities derived from a linear mixed effect model with planned treatment and progression status as covariates. Table 3 shows the company's revised base case utilities and utilities for the two scenario analyses (described as Company post-TE - Issue 8 scenario 1 and 2). The EAG notes that the PF utilities based on the company scenario analyses using median and a linear mixed effect model are all lower than the PF utilities estimated from a GLMM and closer to the EAG's original base case using mean.

The EAG agrees with the company that the GLMM approach is a more sophisticated approach than the descriptive statistics approach. However, the EAG notes that using a sophisticated approach does not necessarily guarantee face validity of the results. The company's PF utilities derived from a GLMM are [redacted] and [redacted] the general population utility for women aged 57 years old in the UK. The EAG maintains its view that the company's PF utilities derived from a GLMM are too high and lack face validity.

The EAG acknowledges the limitations of using descriptive statistics. In the EAG's revised base case, the EAG adopts the use of the PF utilities derived from a linear mixed effect model from the company's scenario analysis given that this approach accounts for the effects of covariates and intra-subject correlation and provide estimated PF utilities with face validity.

PP utilities

There are disagreements between the company and the EAG how the Lloyd *et al*. algorithm should be applied (Issue 8) and how long the T-DXd PP utility benefit should be assumed for (Issue 9).

The company argues that the company's way of using the Lloyd *et al*. algorithm to estimate absolute post progression utilities is more robust than using the EAG's approach of applying the utility decrement associated with progression, reported by Lloyd *et al*., to the treatment specific disease progression-free utility values.

The EAG has looked again at the Lloyd *et al*. paper and still considers that the company's implementation of the Lloyd *et al*. algorithm in which they include the proportion of patients who responded to treatment when estimating the post-progression utility values is incorrect. The vignette study valued health states that were categorised as stable disease, responding to treatment (50% reduction in five largest tumours), or progressed disease (25% growth in five largest tumours). The regression then included stable disease as the reference category with coefficients for patients who were responding to treatment or progressed. There is no category for patients who have progressed disease that previously responded to treatment. Therefore, including the proportion of patients who responded when estimating absolute utilities for patients with progressed disease, as the company has done, is an incorrect application of the algorithm.

However, the EAG acknowledges that patients who responded to treatment may have a lower tumour burden prior to progression and this difference may persist for a time-limited period. The EAG has therefore applied the same utility decrement for disease progression to both arms, which results in higher post-progression utilities due to the higher utility for progression-free patients in the T-DXd arm. The EAG acknowledges that the decrement for progression predicted by the algorithm varies according to other characteristics, such as age, because of the non-linear form of the algorithm. In the EAG report, the EAG used the decrement reported by Lloyd *et al*. of 0.272, which was estimated for age 38.2 years. The EAG has recalculated this using the average age from the study cohort, and this provides a utility decrement for progression of [redacted]. Using this increment provides post-progression utilities of [redacted] and [redacted] for T-DXd and TPC respectively when using the linear mixed effects model to estimate PF utilities. These values have been included in the EAG's updated base case.

The post-progression utility gain attributable to having previously received T-DXd instead of TPC is therefore [redacted]. This is higher than the equivalent [redacted] value in the EAG's previous base case because of the EAG's adoption of progression-free utilities from the linear mixed effects model. This is because it reflects the difference in utility between the trial arms for progression-free patients. However, the EAG

only apply the T-DXd specific utility for 6 months with the TPC value applied thereafter (see Issue 9). The EAG notes that in comparison to the company's post TE approach, using the data from Lloyd *et al.*, provides a post-progression utility gain for having previously received T-DXd of [redacted], which incorporates both the difference in ages between the trial arms and the difference in the proportion responding to treatment. The equivalent value when using the same age in both trial arms would be [redacted]. The company's approach therefore assumes a greater difference between treatment arms post-progression that was assumed pre-progression under any company or EAG scenario (see Table 3).

Overall, the EAG considers that the company's approach lacks face validity because it estimates a larger difference between the trial arms post-progression than was observed pre-progression in the trial and this is because it relies on the absolute values from the Lloyd *et al.* algorithm which it has implemented incorrectly to calculate post-progression utilities.

Table 3 Comparison of utility values used in the company and EAG analyses

Scenario	Sources for utility values	Progression-free (PF)		Δ between arms in PFS	Progressed disease (PD) - short-term		Δ between arms in PD short-term	Switch from short- to long-term	PD – long-term	
		T-DXd	TPC		T-DXd	TPC			T-DXd	TPC
Company pre-TE - base case	PF: GLMM regression PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	NA - lifetime	0.6101	0.5655
Company post-TE- base case	PF: GLMM regression PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	12 months	0.5655	0.5655
Company post-TE - Table 26, scenario 6	PF: GLMM regression PD: GLMM regression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12 months	[redacted]	[redacted]
Company post-TE - Issue 8 scenario 1	PF: Median by trial arm PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	12 months	0.5655	0.5655
Company post-TE - Issue 8 scenario 2	PF: Linear mixed model PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	12 months	0.5655	0.5655
Company post-TE - Issue 9 scenario	PF: GLMM regression PD: Lloyd algorithm	[redacted]	[redacted]	[redacted]	0.6101	0.5655	0.0447	NA - lifetime	0.6101	0.5655
EAG pre-TE – base case	PF: Mean by trial arm PD=PFS-0.272; Lloyd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]
EAG post-TE – exploratory analysis 1	PF: Mean by trial arm PD=PFS-0.243; Lloyd - age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]
EAG post-TE – exploratory analysis 2	PF: Linear mixed model PD=PFS-0.272; Lloyd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]
EAG post-TE – base case	PF: Linear mixed model PD=PFS-0.243; Lloyd - age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]

4. Summary on the changes of the updated economic analysis presented by the company

Table 2 summarises the company's original base case model in the CS, the EAG's preferred analysis in the EAG report, and the company's updated base case model as presented in the company's TE response. It also indicates whether there is now agreement between the company's TE model and the EAG's preferences or whether the EAG considers a particular issue to remain unresolved.

In response to key issues 2, 5, 8, 9 and 10, the company has updated its base case analysis. These changes have been briefly described in Table 1, with further information provided in Section 3 on issue 8. In addition to these changes, the company also accepted the EAG's preferences with regards to: correcting wastage calculation formula; correcting the implementation of QALY difference between arms to be applied only to the newly progressed; removing half-cycle correction on one-off treatment costs occurring in the first model cycle; correcting the cost per dose in wastage calculation of capecitabine; correcting the transcription error regarding percentages of patients on each subsequent therapy; applying discounting to costs and QALYs of the first year; application of administration costs for tamoxifen every 3 months; recalculation of percentages of subsequent treatment distributions based on Table 14.1.3.5.2 in the CSR; assuming the same drug costs for subsequent treatments as they do in the TPC arm; include arm-specific time on treatment for subsequent treatments; and adjusting utility according to age. However, the company's updated base case does not implement the EAG's preferred survival extrapolations for OS and PFS (issues 4 and 6 respectively) and maintains the preference for log-logistic curves. The company has provided scenario analyses exploring the impact of removing patients who received or would have received 2L eribulin or gemcitabine (issue 1); excluding the EAG's correction for estimating the proportion of patients progressing from PFS events (issue 5); using the trial median values and the linear mixed model for estimating utilities (issue 8); assuming utility benefit post-progression to be sustained for lifetime (issue 9); using the EAG's approach for calculating RDIs (issue 10); and assuming 50% vial sharing (issue 11).

Table 4 Summary of company's original base case (CS), EAG-preferred analysis (EAG report) and company's updated base case (TE response)

Aspect of model/ issue identified in the EAG report Section 5.3.3	Company's original base case	EAG-preferred analysis	Company's updated base case	Agreement between EAG-preferred and updated company's base case
EAG corrected company base case: correcting programming and implementation errors in the company's economic model	No	Yes	Yes	Yes
EAG approach to estimating the proportion of patients entering the post-progression and death states	No	Yes	Yes	Yes
Assuming a Weibull curve for OS extrapolations	Log-logistic	Weibull	Log-logistic	No
Assuming a Generalised gamma curve for PFS extrapolations	Log-logistic	Generalised gamma	Log-logistic	No
EAG's preferred utility values for pre and post progression	See Table 3	See Table 3	See Table 3	No, See Table 3
Limiting post progression utility difference to 6 months	Life-long	6 months	12 months	No, EAG prefers 6 months
TPC utility for T-DXd for long term when limiting duration of difference	Average of TPC and T-DXd values	TPC value	TPC value	Yes
Assuming RDIs relative to the modelled doses	No	Yes	Yes, but new figure for T-DXd and eribulin	Yes, EAG accepts company's updated approach
Applying administration costs for tamoxifen every three months	No	Yes	Yes	Yes
Vial sharing	75%	50%	75%	No, EAG prefers 50%
Removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies	No	Yes	No, but exploratory analysis provided	No, EAG maintains their pre-TE approach
Adjusting the mix of subsequent therapies to include drugs recorded by their equivalent salts	No	Yes	Yes	Yes
Assuming the same dose costs for the subsequent treatments used in TPC	No	Yes	Yes	Yes
Including arm-specific time on subsequent treatment	No	Yes	Yes	Yes
Adjusting utilities for age	No	Yes	Yes	Yes
Issues related to comparison with SG				
Assume equivalent clinicial efficacy for T-DXd and SG	Yes	Uncertain	Yes	No, EAG still uncertain

Aspect of model/ issue identified in the EAG report Section 5.3.3	Company's original base case	EAG-preferred analysis	Company's updated base case	Agreement between EAG-preferred and updated company's base case
Using the average patient weight for Hormone Receptor-negative patients from DESTINY-Breast04	No	Yes	Yes	Yes
Sourcing the mean time on treatment for SG from ASCENT	No	Yes	No	No
Sourcing the RDI for SG from ASCENT	No	Yes	Yes	Yes
Applying the Grade ≥3 TEAE rates for SG from ASCENT	No	No	Yes	Yes, EAG accepts the company's approach
Additional issues				
The 1.2x QALY modifier is conservative, and disease severity may qualify for the 1.7x modifier	No	No	Yes	No

Abbreviations: OS - overall survival; PFS - progression free survival; RDI - relative dose intensity; SG - sacituzumab govetecan; T-DXd - trastuzumab deruxtecan; TEAE - treatment emergent adverse events; TPC - treatment of physician's choice

5. Methods of the EAG's TE exploratory analyses

Company changes adopted by the EAG

The EAG base case has incorporated the updated approach suggested by the company for calculating the RDI of eribulin. For the CMA of T-DXd versus SG, the EAG included the specific Grade ≥3 TEAEs for SG from ASCENT.

Exploratory analyses 1 to 7

The EAG's TE base case differs from the company's TE base case in six ways explored individually using the company's TE base case as the starting point (see Table 5). These six changes are as follows:

- The EAG has maintained its preference for removing eribulin and gemcitabine and redistributing the proportions receiving gemcitabine and eribulin across the remaining treatments according to the distribution of the remaining treatments in DESTINY-Breast04.
- The EAG has maintained its preference for using the Weibull distribution for extrapolating OS.
- The EAG has maintained its preference for using the generalised gamma distribution for extrapolating PFS.
- The EAG revised its preference and adopts the use of the progression-free utilities as estimated from the linear mixed effect model.
- The EAG has maintained its preference of applying the T-DXd specific utility of post-progression for only 6 months.
- The EAG has maintained its preference of assuming a 50% vial sharing.

For the CMA of T-DXd versus SG, the EAG maintained its preference of sourcing time on treatment for SG from ASCENT.

EAG TE scenario analyses

EAG TE scenario analyses are then provided, in Table 5 using the EAG preferred base case as the starting point. These scenarios explore the impact of using alternative curves for OS, and TTD extrapolations, assuming TPC costs equivalent to either the highest cost component of TPC (eribulin) or the lowest cost component of TPC (capecitabine), calculating costs and QALYs based on the exploratory analysis described under key issue 1 regarding removal of patients on 2L eribulin and gemcitabine, estimating progression-free utilities from mean values, applying the Lloyd algorithm without age adjustment, and applying a utility benefit for T-DXd after progression for 12 months.

The EAG has not explored the impact of scenario analyses 2, 5, and 8 to 10 as presented in Table 39 of the EAG report as the ICER was not sensitive to these scenarios.

6. Results of the EAG's TE exploratory analyses

The results in Table 5 show that the key driver of the difference in the ICER between the EAG's TE base case and the company's TE base case is the curve choice for OS extrapolation, as implementing this alone increases the ICER from £39,118 to £51,777 per QALY (all reported ICERs in-text are using the 1.2x QALY weight as this was considered appropriate in Section 6 of the main EAG report). Both removing eribulin and gemcitabine from the TPC arm and redistributing the patients to the remaining chemotherapies, and using the generalised gamma curve for PFS extrapolation have a smaller, but still important impact, increasing the ICER by ~£7000 and ~£5700 respectively. Applying the EAG's preferred PF utility values from the linear mixed model also has a similar impact increasing the ICER to £43,633.

Conversely, the cost-effectiveness does not seem particularly sensitive to limiting the utility benefit of T-DXd post-progression to 6 months instead of 12 months and assuming a 50% vial sharing. When including all the changes preferred by the EAG, the deterministic ICER increased to £80,997 per QALY (probabilistic ICER = £79,836 per QALY).

The scenario analyses confirmed that different ways for estimating time on treatment and assuming other OS curves significantly impact the ICER. However, estimating progression-free utilities from trial mean values instead of the linear mixed model or not adjusting the Lloyd algorithm for the trial age do not notably change the ICER.

For the CMA, when calculating treatment costs using the treatment-specific mean time on treatment for T-DXd from DESTINY-Breast04 and SG from ASCENT, T-DXd is associated with a total cost of £[redacted] (compared to £[redacted] in the company's TE base case) and SG a total cost of £[redacted] (compared to £[redacted] in the company's TE base case), meaning that T-DXd is associated with a savings of £[redacted] (compared to £[redacted] in the company's TE base case) over a lifetime time horizon. The EAG notes that this analysis uses the list price for SG and the cost differences was re-estimated in the confidential appendix using the PAS price for SG.

Table 5: Results of the EAG's exploratory analyses with QALY weighing of 1x and 1.2x

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company TE base case (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
EAG exploratory analysis 1: Removing eribulin and gemcitabine from TPC and reallocating their proportions to the remaining three single-agent chemotherapies						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Assuming a Weibull curve for OS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming a Generalised gamma curve for PFS extrapolations						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Applying the EAG's preferred PF utility values from the linear mixed model						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying the EAG preferred utility benefit for T-DXd in the PD state for six months only and applying the post-progression utility value of TPC onwards to both arms						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Decreasing vial sharing from 75% to 50%						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-6 (Deterministic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-6 (Probabilistic)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Assuming a log-logistic curve for OS extrapolations)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Treatment costs are calculated using restricted mean treatment duration)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Treatment costs are calculated using log-logistic curve for TTD)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Assuming TPC costs equivalent to 100% receiving eribulin)						
TPC	[redacted]	[redacted]	-	-		

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming TPC costs equivalent to 100% receiving capecitabine)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Using efficacy data from subgroup analysis where 2L eribulin and gemcitabine are removed)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Estimating progression-free utilities from trial mean values)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Applying the Lloyd algorithm without age adjustment)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 9 (Applying the utility benefit for T-DXd after progression for 12 months)						
TPC	[redacted]	[redacted]	-	-		
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG - evidence assessment group, OS - overall survival, PD - progressed disease, PFS - progression-free survival, T-DXd – trastuzumab deruxtecan, TPC - treatment of physician's choice, TTD - time to treatment discontinuation

7. Discussion

The EAG considers that there remains significant uncertainty regarding eight of the 11 key issues mentioned in the executive summary of the EAG main report. The EAG still thinks that the comparator arm of the DESTINY-Breast04 deviates from that mentioned in the NICE scope. Although the company provided a post-hoc exploratory analyses where patients who received (or would have received if were randomised to TPC) 2L eribulin and gemcitabine were removed from efficacy data from both arms of the trial, the EAG is worried that this subgroup is even less representative of the majority of target population in the UK who are likely to receive T-DXd as second line. Also, uncertainty remains regarding the the impact of the treatments used as TPC in clinical practice but not included in the trial.

For key issue 2, the company did not provide any evidence to support clinical equivalence between T-DXd and SG, hence the EAG still interprets the results from the CMA with caution. The same is observed for key issue 3 where the impact of the differences in mean age, ECOG PS, and ethnicity between the trial and what is seen in clinical practice is still unknown.

The company did not provide the EAG with the additional evidence needed to properly model OS, PFS and TTD extrapolations, hence these three issues are still unresolved. For utility values, the company still uses the GLMM to estimate progression-free utilities which the EAG views as lacking face validity, and the EAG still disagrees with the company on how the Lloyd algorithm was used to estimate the post-progression utilities and for how long a utility differential should apply between patients on T-DXd versus those on TPC. For key issue 11, the EAG is still uncertain on the percentage to apply for vial sharing and the company does not provide any evidence to support the 75% assumption.

Other key issues were resolved regarding estimating the proportion of patients entering the post-progression and death states, utility to be used post-progression for long term after the duration of difference is over, and the approach to calculate RDIs.

The probabilistic ICER based on the EAG's preferred data and assumptions following the company's response to TE is £[redacted] with a 1.2x QALY weight. However, as was shown in the scenario analyses the EAG's base case ICER can range between £[redacted] when all patients on TPC are assumed to incur the costs for eribulin, and £[redacted] when a log-logistic curve is assumed for extrapolating TTD.

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