**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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# Abbreviations

# Decision problem, description of the technology and clinical care pathway

## 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxx.

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   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 | N/A |
| 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.

## 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 xxxxxxxxxx.  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 xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| 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 mA=g/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: xxxxxxxxx † * Cost per course: xxxxxxxxxx ‡   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: xxxxxxx per 100 mg vial   * Cost per cycle: xxxxxxxxx † * Cost per course: xxxxxxxxxx ‡   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 [xxxx months = xxxxx 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.

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| Figure 1: Trastuzumab deruxtecan mechanism of action20 |
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| Abbreviations: HER2, human epidermal growth factor receptor 2; T‑DXd, trastuzumab deruxtecan.  Source: Modi et al., 202120 |

## Health condition and position of the technology in the treatment pathway

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| **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 levels6 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, 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.

### Disease overview

#### 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 disease34 that responds poorly to conventional chemotherapy.60 Anti-HER2 treatments have markedly improved survival outcomes vs. non-targeted chemotherapy37,41 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=7.8×10−22]).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.

#### 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.

#### 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

#### 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

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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

#### 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

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| **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 regimens6 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

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| **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. 202056

### Burden of breast cancer

#### 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

#### 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](#_ENREF_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**).

##### 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[[1]](#footnote-2) and FACT-G[[2]](#footnote-3), and EQ-5D-5L[[3]](#footnote-4) 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[[4]](#footnote-5) 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

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| 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[[5]](#footnote-6)) 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[[6]](#footnote-7) 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

##### Impact of u/mBC on social functioning and mental health

The QoL impact of mBC in women varies by patient demographic, with younger patients[[7]](#footnote-8) 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

#### 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) 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

#### 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

#### 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

#### 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.

##### 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-DXd5 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=7.8×10−22]).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.

##### 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 III46 | Study 301 | 2 | Eribulin | 4.2 | 16.1 |
| 4.0 | 13.5 |
| Pivot et al., 2016  (NR) Phase III43 | Study 301 and Study 305 | ≥2 | Eribulin | 3.7 | 15.1 |
| Twelves et al., 2016  (NCT00337103) Phase III45 | Study 301 | ≥2 | Eribulin | 4.1 | 15.9 |
| Capecitabine | 3.9 | 13.5 |
| Yardley et al., 2016 (298)  (NCT01427933) Phase II47 | - | 2-4 | Eribulin | 4.1 | 11.5 |
| Cortes et al., 2011  (NCT00388726) Phase III44 | EMBRACE | 2–5 | Eribulin | 3.6 | 13.2 |
| HER2-negative/HR-negative (i.e., TNBC) | | | | | |
| Pivot et al., 2016  (NR) Phase III43 | Study 301 and Study 305 | ≥2 | Eribulin | 2.8 | 12.4 |
| Vahdat et al., 2021\*  (NCT0199733) Phase II50 | METRIC | ≤2 | Capecitabine | 2.8 | 8.7 |
| Bardia et al., 2021\*  (NCT02574455) Phase III48 | ASCENT | ≥2 | SG\*\* | 5.6 | 12.1 |
| TPC (eribulin, vinorelbine, capecitabine, gemcitabine) | 1.7 | 6.7 |
| Winer et al., 2021\*  (NCT02555657) Phase III49 | KEYNOTE-119 | 2-3 | TPC (eribulin, vinorelbine, capecitabine, gemcitabine) | 2.3 | 10.8 |
| HER2-negative (any HR-status) | | | | | |
| Claessens et al., 2019  (NR) Phase III52 | Stop&Go | 2 | Capecitabine (intermittent) | 3.7 | 10.9 |
| Capecitabine (continuous) | 5.0 | 12.4 |
| Brufsky et al., 2011\*  (NCT00281697) Phase III53 | RIBBON-2 | 2 | TPC (capecitabine, docetaxel, nab-paclitaxel, paclitaxel, gemcitabine, vinorelbine) | 5.1 | 16.4 |
| Decker et al., 2019\*  (NCT01520103) Phase II51 | VicTORia | 2 | Vinorelbine | 4.1 | 13.8 |
| Decker et al., 2017\*  (NCT01320111) Phase II54 | PASO | 2-3 | Paclitaxel | 6.6 | 20.7 |
| Yardley et al., 2016  (NCT01427933) Phase II47 | - | 2-4 | Eribulin | 4.1 | 11.5 |
| Yardley et al., 2015\*  (NCT01156753) Phase II55 | 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.

### 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.

#### US clinical guidelines

Both the US NCCN 2022 (Version 4.2022)72 and the ASCO Guideline 2022 Rapid Recommendation Update71 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

#### 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.

#### 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.

##### 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

##### 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

##### 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 CG8135 broadly align with ESMO 2021 guidelines42 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 sequence35
  + 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

##### 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 CG8135 and NICE TAs in HER2-negative advanced BC (TA423131 and TA819132).

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 202142 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 202142 guidelines state that there is no optimal treatment sequence.
* UK clinical experts and published data118 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 CG8135 and NICE TAs in HER2-negative advanced BC (TA423131 and TA819132).

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 202142 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 202142 guidelines state that there is no optimal treatment sequence.
* UK clinical experts and published data118 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 TA801134

##### UK real-world data on treatment patterns

Insights from 2022 UK patient data from a cross-sectional patient chart review136 highlight that current practice is nuanced and may differ to NICE CG8135 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: xX% vs. xx%; third-line: Xx% vs xx%).136

##### Clinical expert insights on the treatment pathway

Advice from UK clinical experts at an advisory board in December 2022121 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.

### 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.

### Proposed place of T-DXd in the HER2-low u/mBC treatment pathway

T-DXd is the first and only EMA-3and Food and Drug Administration (FDA)-approved138,139 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 xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

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\*

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\*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 202142 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 202142 guidelines state that there is no optimal treatment sequence.
* UK clinical experts and published data118 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 TA801134

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

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\*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 202142 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 202142 guidelines state that there is no optimal treatment sequence.
* UK clinical experts and published data118 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

### 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**).

#### 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 practice121,136 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 scope1 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 analysis56 and UK clinical experts121 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.

#### 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

#### 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 scope1 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**.

##### 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 setting23 but are not listed in NICE CG8135 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 scope1 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 analysis56 and UK clinical experts121 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.

##### 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=xx; xxx; 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.[[8]](#footnote-9) 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. xxxx [95% CI: xxxx, xxxx], 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. xxxx; 95% CI: [xxxx, xxxx], 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.

#### 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

#### 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 scope1 (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

## Equality considerations

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

# Clinical effectiveness

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| **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 15.3 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 * xxxxxxxxxxxxxxxxxxxxxxxxx by PFS by IA (HR: xxxx for T-DXd vs. TPC; 95% CI: xxxxxxxxxx) 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 xxxxxx (xxxxx), xxxxxxx (xxxxx) and xxxxxxxx (xxxxx). 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx).152 * In the FAS, median TTDD was xxxxxxxxxxxxxxxxxxxxxxxx for EQ-5D-5L VAS (xxx months [95% CI: xxxxxxxxx] vs. xx5 months [95% CI: xxxxxx]; HR: xxxx; 95% CI: xxxx, xxxx; p=xxxxxx), for EORTC QLQ-30 global health status (xxxx months [95% CI: xxxxxxxxx] vs. xxx months [95% CI: xxxxxxxx]; HR: xxxx; 95% CI: xxxx, xxxx; p=xxxxxx), and for the arm symptom scale of the EORTC QLQ-BR45 (xxxx months [95% CI: xxxxxxxxxx] vs. xxx months [95% CI: xxxxxxx]; HR: xxxx; 95% CI: xxxx, xxxx; p=xxxxxx).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.

## 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.

## 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 comparators1 |
| 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. 20226 |
| 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, 20227

## Summary of methodology of the relevant clinical effectiveness evidence

### 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 xxxx months in the FAS (xxxx months in the T-DXd arm and xxxx 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., 20226 |

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:** xxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx x x xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx. The primary endpoint was based on BICR. Xxxxxxxx xx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxx7,153xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxx[.153](#_ENREF_112) |
| Duration of study | Planned: approximately xx months  Median duration of follow-up at DCO (11 Jan 2022; FAS):   * T-DXd: xxxx months (range xxxxxxxxx). * TPC: xxxx months (range: xxxxxxxxx). * Overall: xxxx months (range xxxxxxxxx). |
| 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**   * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xx xxxxxxxxxxxxxxxxxxxxxxxxxx * Pathologically documented BC that:   + was unresectable or metastatic.   + had a history of, or central laboratory assessed, low HER2 expression (defined as IHC1+ or IHC2+/ISH-negative).   + 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.   + 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. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * xxxxxxxxxxxxxxxxxxxxxxxxxxx. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. |
| **Key exclusion criteria**   * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * History of (non-infectious) ILD/pneumonitis requiring steroids, current diagnosed or suspected ILD/pneumonitis, or xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.‡ * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.§ * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxx. * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. |
| 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 xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx). Dosage was xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxx 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 xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. * Eribulin (N=94) was administered at a dose of xxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx. * Gemcitabine (N=19) was administered at a dose of xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx. * Paclitaxel (N=15) was either administered at a dose of xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx. * Nab-paclitaxel (N=19) was either administered at a dose of xxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. |
| 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: xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxx, but for which xxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx), AEs requiring discontinuation (**Appendix M**), or death.†† |
| Concomitant medication | **Permitted concomitant medication:** Prophylactic treatment of xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx was per xxxxxxxxxxxxxxxxx xxxxxxxx and xxxxxxxxxxxx xxxxx xxxxxxx. xxxxxxxxxxxxxxxxxxxxxxxxxxxxx could be used for xxxxxxxxxxxxxxxxxxxxx based on xxxxxxxxxxxxxxxxxxxx (except within xxxxxxxx xxxxxxxxxxxxxxxxx)  Based on currently available clinical safety data, xxxxxxxxxxxxxxxxxxxxxxxx were recommended xxxxxxxxxxxxxxxxxxxxx to T‑DXd infusions  Concomitant use of dietary supplements, medications xxxxxxxxxxxxxxxxxxxxxxxxxxx, and xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx were discouraged but not prohibited  **Prohibited concomitant medication:** Other anti-cancer therapy, xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, xxxxxxxxxxxxx, xxxxxxxx, xxxxxxx, or xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx (concurrent use of xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxx); xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx; xxx xxxxxxxxxor xxxxxxxxxxxxxxxxxx; xxxxxxxxxxxxxxxxxxxxxxxor any xxx xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx; xxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx or xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx,‡‡ 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 * xxxxxxxxx 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 * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx 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 * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.  
§xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx.  
\*\*xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx .   
††Additional reasons not listed above are: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.   
‡‡xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.  
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, xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx were required.7

During the screening period, from xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7

From xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.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 xxxxxxxxxxxxxxxxxxx xxxxx xx xxxxxxxxxxxxxxx xxxxxxxxxxx xxxxxxx xxxx xxxxxxxxxxxxxxxxxxxxxxxx disease progression per BICR xxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxor xxxx xxxxxxxxxxxxxxxxxx | * No baseline evaluable tumour assessment: xxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx * No post-baseline tumour assessment: xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxx * Early death (within 14 weeks of randomisation) for no baseline or no post-baseline tumour assessment: xxxxxxxxxxxxxxxxxxxxxx * Radiographic disease progression/death without missing ≥2 consecutive tumour assessments immediately preceding event: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx * Disease progression or death after missing ≥2 consecutive scheduled tumour assessments: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxx * At least one post-baseline response assessment and no death or objective documentation of radiographic disease progression: xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxxxxxx * Started anti-cancer therapy prior to disease progression, death, or analysis cut-off date: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx xxxxxxxx xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| Key secondary endpoint | | |
| OS in the FAS | Defined as the time from the xxxxxxx xxxxx xxx xxxxxx 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 xxxxxxxxxxxxxxxxxxx xxxxx x xxxxxx xxxxxx xx xxxxxxxxxxxxxxxx xxxxxxxxxxx | The xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx xxxx xxxxxxxxx xxxxxxxxxxxxxx xxxxxx xxxx xxxxxxxxxxxxxxxxxxxx xxxx xx xxxxxxx xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxx xxxxx xxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxx xxxx xxxxx xxx xxxxxxxxx xxxxxxxxxxxxxxxxx xxxxxxx xxxxxx xxxxxxx xxxxxxxxxxxxx xx x xx xxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxx xxxx xxxxxxxxxxxxxxxxxxxxxx xxxx xxxx xxxxxxxxxxxxxxx xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxx xxxxxx xxxxxx xxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxx   * xx xx xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxx xxx x * x x xx xxxx xxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxx xxxxxx xxxx xxxxxx xxxx xxx xxxxx x xxxx xxxxx xxxxxxxxxxxxxxxxxxx * xxxxxxxxxx xxxxxxxxx xxxxxxxxxxxxxxx xxxxxx xxxxxxxxxxxxxxxxxxxx xxxxxxxx xxxxxxxxxxxx |
| 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 progression-free at the time of the analyses were to be censored at the date of the last evaluable tumour assessment | Censoring rules were the same as described above for PFS by BICR |
| PFS by investigator assessment in the FAS | Defined as the time xxxxxxxx xxxxxxxxx xxx x x xxxxxxxxxxxxxxxxxxxx xxxxxxx xx xxx xx x xx xxxxxxxx xx xxxxxxxxxxxxx xx xx xx xxxx xxxxx xxxxxxx disease progression per investigator assessment xxxxxxxxx xxxx xxx xxxxxxxxx xxxxxxx or xxx xxx xxx xxx xxx | 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): xxxxxxxxxxxxxxxxxxxxxx * No death: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx   If baseline and at least one post-baseline QoL assessment:   * Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxxxx xxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxx xxxxxxxxxxxx xxxxx xxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxx xxxxxxxxx xxxxxxxxx xxxxxxxx xxxxxxxx xxxxxxxxx xxxxxxx xxxxx xxxxxxxxx xxxxxxxxx xxxxxxxxx xxxxxxxxx xxx xxxxx xxxxx xxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxx xxxx x xxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxx xxxxxxxxxxx xxxxxxxxx xxxx xxxxxxxxxxxxxxxxxxxDeath by first survival follow-up (3 months from 40-day visit): xxxxxxxxxxxxxxxxxxxxxx * Others: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| 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 | | |
| 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”:   * xxxxxxxxxxxxxxxxxxxxxxxxxxxx, and * xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| 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: xxxxxxxxxxxxxxxxxxxxxx * No death: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx   If patients received new systemic anti-cancer therapy:   * Disease progression during next line therapy before/on the analysis cut-off date: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx * Death during next line therapy and before/on the analysis cut-off date: xxxxxxxxx xxxxxxxxxxxxx * No disease progression/death during next line therapy and received a second new systemic anti-cancer therapy before/on the analysis cut‑off date: xxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxx * 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: xxxxxxxxx xxxxxxxxxxxxxxxxxxxx |
| 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. |
| 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), xxxxxxxxxxxxxxxxxxxx, xxxxxxxxxxxxxx, and xxxxxxxxxxxxxxxxxxxxxxx were to be completed/assessed xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7 The HRQoL questionnaires were completed before any other assessments or procedures were done on the day.

End of treatment assessments were to occur xxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7 Follow-up assessments took place at xxxxxxxxxxxxxxxxx after administration of the last study treatment or before starting new anti-cancer treatment, xxxxxxxxxxxxxxxxxxxx. In long-term follow-up, assessments took place every xxxxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxx xxxxxxxxxxxxxxxxxxxx xxxxxx xxxxxxx, until xxxxx, xxxxxxxxxxxxxxxxxxxxx, xxxxxxxxxxx xxxxxx, or xxxxxxxxxxxxx.7,153

Vital signs and pharmacokinetic blood samples (T-DXd arm only) were assessed xxxxxxxx xxxx xx xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx xxxx xxxxxxxx.7

Tumour assessment (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx were to take place xxxxxxxxxxxxxxx and at xxxxxxxxxxxxxxxxxxxx.153 AEs, concomitant medications, and hospitalisation-related records were recorded xxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx xx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7,153

Questionnaires for HRQoL outcomes were to be completed at xxxxxxxxxxxxxxxxxxx xxxxx xxxxx xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, which was the last data collection timepoint for all questionnaires.7 Survival follow-up was assessed at xxxxx xxxxxx xxxxxxxxxxxxxxxxfollow-up timepoints.7

T-DXd was to be administered every xxxxxxxxxxxxxxx unless study drug interruption/ modification or discontinuation was required. For the TPC arm, if a patient received a regimen other than a xxxxxxxxxxxx, the investigator was to ensure that the subject followed the xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. Tumour assessments and CT/MRI of the brain had to be performed every xxxxxxxxxxxxxxx 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

## Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

### 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx xxxx xx xxxxxxxxx.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 xxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx | 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 xxxxxxx of study treatment (either T‑DXd or TPC). Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxx | 371 (99.5) | 172 (93.5) | 543 (97.5) |
| Per-protocol analysis set (PPS) | Included xxxxxxxxxx xxxxxxxx xxxxxx xxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxx xxx x x xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xx | 361 (96.6) | 164 (89.1) | 525 (94.3) |
| Pharmacokinetic (PK) analysis set | Included xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx | 370 (99.2) | 0 | 370 (66.4) |

\*Major protocol violations included: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx xx xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.  
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

### 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:

**PFS by BICR analysis in HR-positive cohort | conducted at xxxx 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.

**PFS by BICR analysis in the FAS | conducted at xxxx 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

**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 xxx OS events (xx% 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 xxx OS events (xx% 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 xxx OS (xxx% information fraction) events in the HR-positive cohort have been documented.

**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 | Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxx xxxx xxxx xx xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxx xx x xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxx xxxx xxxx xxxxx xxxxx xxx xxxxx xxxxxxxxxxx xxxxxxxxxxx xxxxx xxxxxxxxx xxxxxxxx xxxxxxxx xxxxxxxxxxxxxxxxxx |
| 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 xxx 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 xxx (IA1) and xxx OS events (IA2) and final analyses will take place once xxx 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, xxxxxxxxxxxxxxxxxx xx xx xxxxx xxxxxxxxx xxx xxxxxxxxxxxxxxxxxxxxxxxxxxx * Duration of response (based separately on BICR and IA) was summarised by median duration and its two-sided 95% CI calculated using the xxxxxxxxxxxxxx xx xxxxxxxxx   **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 xxxxxx xxxxxxx x xxxxx xxxxxx. PFS2 HRs and their two-sided 95% CIs were calculated with a xxxxxxxx xxxxxx xxxxxxxxxx xx xxxxx xx xxxxxxx xxxxx xxxx xxx.  **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 xxxxxxxxx xxxxxxxxxxxxxx xxxxxxxxxx xxxxx xxxxxx xxxxxxxx xxxxxxxx xxxxxxxx xxxxxxxxxxxxxxxx xxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx * Changes from baseline in EORTC QLQ‑C30 were assessed using a xx xxxxx xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx, 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, so cial functioning, and pain symptom subscales was assessed using the xxxxx xxxxxx xxxx xxxx xxxxxxx xxx xxxxxxxxxxxxxxxxxxxxxxxx. The survival distributions of time to definition deterioration were estimated by the xxx xxxxxxxx xxxxx xxxxxx xxx x xx xxxx xxxxx xxxx xx x xxxxxxxxxxx xxxx xxxxxx xxxxxxx xxx * Changes from baseline in EORTC QLQ‑BR45 were assessed using a xxxxxxxxxxx xxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, 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 xxxxxxxxxxxxxxxx xxx xxxxxxxxx xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. The survival distributions of time to definition deterioration were estimated by the xxxxxxxxxxxxx xxxx xxxxxxxxxxxxx xxxxxxxxxxxxxxxxxx xxxxxx xxxx xxx xx xxxxxxxxx xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx   **Subgroup analysis of PFS by BICR** was carried out on all pre-specified patient subgroups (detailed in Section B.2.7) that had xxx PFS events in both treatment arms. Xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxx xxxx xx xxxxxxx xxx xxxxxxxxxxxx xxxxxxxxxx xxxxxxxxxxxx xxxxxxxx xxxxx xxxx xxxx xxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx xxxx. |
| Sample size, power calculation | The study was planned with a group sequential design, with a three-look Lan-DeMets alpha spending function and an xxxxxxxxxxxxxxxxx xxxxxxxx xxxx xx xxxxxxx. 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 xxx months in the TPC arm to xxx months in the T-DXd arm under the xxxxxxxxxxxxxxxxxxxxxxxxxxxx.  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 xxx PFS events were documented. With xxx PFS events in approximately 480 patients, the study had approximately xx% 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 xxxxxxx xxxxxx xxxxxxxx xxxxxx xxxxxxxxxx xxxxxxxxxx xxxxxxxxxx xxxx xx xxxxx. The sample size computation was performed using the EAST v6.4.43  Conditional on PFS being significant, a total of xxx OS events would be needed to ensure xx% 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 xx xxxxxxxxxx xxxxxxxxx xxxxxxx x xxxxxxxxxxxxxxx xxxxxxxx xxxxxxxx xxxxxxx xxxx xxxxx xxxxx assuming a HR of 0.72. If the true HR is 0.72, it was estimated that approximately xxx (xx%) and xxx (xx%) 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 xxxx months from the date the first subject was randomised, when xxx 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, xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxx xxxx xxxx xxxxxxx xxxx xx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxx xxx xxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx xxxxxxxx xxxxxxx xxxxxxx xxxxx xxx xxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxx x xxxxxxx xxx xxxxxx 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 xxx BICR-assessed PFS events were observed in the HR-positive cohort. With xxx PFS events, the study will have approximately xx% 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 xxx 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

### 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, xxx (T-DXd, xxx; TPC, xxx) received at least one dose of study drug and xx (T-DXd, x; TPC; xx) 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 xxxx and xxxx months, respectively (**Table 13**). At the DCO in the FAS, xx (xxxxx) patients in the T-DXd arm and x (xxxx) patients in the TPC arm were ongoing treatment; xxx (xxxxx) T-DXd and xxx (xxxxx) TPC patients discontinued due to progressive disease; xx (xxxx) T-DXd and x (xxxx) TPC patients discontinued due to clinical progression; xx (xxxxx) T-DXd and xx (xxxx) TPC patients discontinued due to AEs; and for x (xxxx) T-DXd and x (xxxx) 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 | xxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxxx |
| **Study duration (months)a** | | | | | | |
| Mean (SD) | xxxxxxxxxx | Xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| Min, max | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| **Treatment status(based on SAS)b** | | | | | | |
| N in safety analysis set | xxx | xxx | xxx | 371 | 172 | xxx |
| Ongoing | xxxxxxxxx | xxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxx | xxxxxxxxx |
| Discontinued | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| **Primary reason for study drug discontinuation (based on SAS)b** | | | | | | |
| N in safety analysis set | xxx | xxx | xxx | xxx | xxx | xxx |
| Progressive disease per RECIST v1.1 | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Adverse event | xxxxxxxxx | xxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxx | xxxxxxxxx |
| Withdrawal by subject | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx |
| Clinical progression per investigator | xxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxx | xxxxxxxx |
| Death | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx |
| Physician decision | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx |
| Other | xxxxxxx | x | xxxxxxx | xxxxxxx | x | xxxxxxx |
| Lost to follow-up | x | xxxxxxx | xxxxxxx | x | xxxxxxx | xxxxxxx |

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

### 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 (xxxx vs. xxxx; 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 (xxxxx vs. xxxxx; 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 x 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 x and x, 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 x and x, 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[[9]](#footnote-10) (xxxxx vs. xxxxx in the T-DXd and TPC arms, respectively),7 which aligns to the scope of this appraisal1 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 (xxxxx vs xxxxx; FAS), and slightly lower for two prior lines of chemotherapy in the metastatic setting (xxxxx vs. xxxxx; 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) | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx |
| 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) | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx |
| Median  (range) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| BMI, kg/m2 | | | | |
| Mean (standard deviation) | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Median (range) | xxxxxxxxxxxxxx | xxxxxxxxxxxxxx | xxxxxxxxxxxxxx | xxxxxxxxxxxxxx |
| Smoking status, n (%) | | | | |
| Never | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Former | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| Current | xxxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxx |
| Missing | xxxxxxx | x | xxxxxxx | x |
| 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 | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| HR-positive without prior CDK4/6 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| HR-negative | x | x | xxxxxxxxx | xxxxxxxxx |
| Stable brain metastases, n (%) | xxxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxx |
| Stable brain metastases defined as a reported history of CNS metastases, n (%) | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx |
| Presence of baseline lung metastases, n (%) | xxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| Presence of baseline liver metastases, n (%) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Baseline visceral disease, n (%) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Prior lines of systemic therapy in any setting, n (%) | | | | |
| 1 | xxxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx |
| 2 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| ≥3 | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | x | x | x | x |
| Prior lines of systemic therapy in the metastatic setting, n (%) | | | | |
| 0 | xxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| 1 | xxxxxxxx | xxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| 2 | xxxxxxxxx | xxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| ≥3 | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | x | x | x | x |
| 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 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| Lines of prior endocrine therapy, n (%) | | | | |
| 0 | xxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxxxx |
| 1 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| 2 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| ≥3 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | xxx | xxx | xxx | xxx |
| Lines of prior endocrine therapy in metastatic setting, n (%) | | | | |
| 0 | xxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| 1 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| 2 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| ≥3 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | xxx | xxx | xxx | xxx |
| Lines of prior chemotherapy, n (%) | | | | |
| 0 | x | xxxxxxx\*\* | x | xxxxxxx\*\* |
| 1 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx |
| 2 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| ≥3 | xxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | xxx | xxx | xxx | xxx |
| Stratification factor: Lines of prior chemotherapy in metastatic setting per IXRS†, n (%) | | | | |
| 0\*\* | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx |
| 1 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| 2 | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx |
| ≥3\*\* | xxxxxxx | x | xxxxxxx | x |
| Mean (SD) | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Median | x | x | x | x |

\*xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.\*\*Represents a protocol deviation.  
†If recurrence occurred ≤6 months of (neo)adjuvant chemotherapy, (neo)adjuvant chemotherapy was counted as one line of chemotherapy. Xxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxx xxxxxxxxxxx xxx .   
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

## 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). |
| 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.

### 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

## Clinical effectiveness results of the relevant trials

### DESTINY-Breast04

Data presented in this submission are from the primary analysis for PFS (DCO, 11 Jan 2022) with a median follow-up of xxxx months (range: xxxxxxxx) in the T‑DXd arm (N=373), xxxx months (range: xxxxxxxx) in the TPC arm (N=184), and xxxx months (range: xxxxxxxx) 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 xxxxxxxxxxxxxxxxxxxxxxxxxx.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.

#### Primary efficacy | PFS by BICR in HR-positive cohort

In the HR-positive cohort at DCO, the median duration of PFS follow-up was xxxx months and events of disease progression or death were reported in xxx patients (xxxxx) in the T‑DXd arm and xxx patients (xxxxx) in the TPC arm (**Table 17; Figure 11**).7 Of these, xxx patients (xxxxx) in the T‑DXd arm and xxx patients (xxxxx) in the TPC arm had disease progression.7 Death was the recorded PFS event in xx patients (xxxx) in the T‑DXd arm and xxxx patients (xxxx) in the TPC arm.7

At DCO, xxx patients (xxxxx) in the T-DXd arm and xx patients (xxxxx) in the TPC arm were censored.7 Of these, xx patients (xxxxx) in the T-DXd arm and xxxxx patients (xxxx) in the TPC arm were ongoing without an event.7 The remaining xx patients (xxxxx) in the T‑DXd arm and xx patients (xxxxx) 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, xxxxx (95% CI: xxxxxxxxxx) and xxxxx (95% CI: xxxxxxxxxx) 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 (%) | xxxxxxxxxxx | xxxxxxxxxxx |
| Progressive disease | xxxxxxxxxxx | xxxxxxxxxxx |
| Death | xxxxxxxxx | xxxxxxxx |
| Subjects without events (censored), n (%) | xxxxxxxxxxx | xxxxxxxxxx |
| Ongoing without event | xxxxxxxxxx | xxxxxxxx |
| Other reason\* | xxxxxxxxx | xxxxxxxxx |
| 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) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 6 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 9 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 12 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 18 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 24 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxx |

\*Censoring reasons included: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.   
†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., 20226; Daiichi Sankyo Inc., 2022 (CSR; Data on File).7

#### Key secondary efficacy

##### Key secondary efficacy | PFS by BICR in FAS

In the FAS at DCO, the median duration of follow-up was xxxx months and events of disease progression or death were reported in xxx patients (xxxxx) in the T-DXd arm and xxx patients (xxxxx) in the TPC arm (**Figure 12, Table 18**).7 Of these, xxx (xxxxx) in the T-DXd arm and xxx (xxxxx) in the TPC arm had disease progression.7 Death was the recorded PFS event in xx patients (xxxx) in the T‑DXd arm and xx patients (xxxx) in the TPC arm.7

At DCO, xxx (xxxxx) patients in the T-DXd arm and xx (xxxxx) of patients in the TPC arm were censored.7 Of these, xx patients (xxxxx) in the T‑DXd arm and xxxxx patients (xxxx) in the TPC arm were recorded as ongoing without an event.7 The remaining xx patients (xxxxx) in the T‑DXd arm and xx patients (xxxxx) 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, xxxxx (95% CI: xxxxxxxxxx) and xxxxx (95% CI: xxxxxxxxxx) 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 |
| Graphical user interface, chart, line chart  Description automatically generated |
| 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 (%) | xxxxxxxxxxx | xxxxxxxxxxx |
| Progressive disease | xxxxxxxxxxx | xxxxxxxxxxx |
| Death | xxxxxxxxx | xxxxxxxxx |
| Subjects without events (censored), n (%) | xxxxxxxxxxx | xxxxxxxxxx |
| Ongoing without event | xxxxxxxxxx | xxxxxxxx |
| Other reason\* | xxxxxxxxx | xxxxxxxxx |
| 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) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 6 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 9 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 12 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxx |
| 18 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 24 months (95% CI) | xxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxx |

\*Censoring reasons included: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.   
†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., 20226; 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 months6 and events of death were reported in xxx patients (xxxxx) in the T‑DXd arm and xx patients (xxxxx) in the TPC arm (**Figure 13; Table 19**).7

At DCO, xxx patients (xxxxx) in the T-DXd arm and xx patients (xxxxx) in the TPC arm were censored.7 Of these, xxx patients (xxxxx) in the T‑DXd arm and xx patients (xxxxx) in the TPC arm were alive.7 The remaining xx patients (xxxx) in the T-DXd arm and xx patients (xxxxx) 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, xxxxx (95% CI: xxxxxxxxxx) and xxxxx (95% CI: xxxxxxxxxx) 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 (%) | xxxxxxxxxx | xxxxxxxxx |
| Subjects without events (censored), n (%) | xxxxxxxxxx | xxxxxxxxx |
| Alive | xxxxxxxxxx | xxxxxxxxx |
| Lost to follow-up | xxxxxxx | xxxxxxx |
| Withdrawal by subject | xxxxxxxxx | xxxxxxxxx |
| Other | xxxxxxx | x |
| 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) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 6 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 9 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 12 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 18 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 24 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |

\*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., 20226; 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 months6 and events of death were reported in xxx patients (xxxxx) in the T‑DXd arm and xx patients (xxxxx) in the TPC arm (**Table 20**; **Figure 14**).7

At DCO, xxx patients (xxxxx) in the T-DXd arm and xx patients (xxxxx) in the TPC arm were censored.7 Of these, xxx patients (xxxx%) in the T‑DXd arm and xx patients (xxxxx) in the TPC arm were alive.7 The remaining xx patients (xxxx) in the T-DXd arm and xx patients (xxxxx) 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, xxxxx (95% CI: xxxxxxxxxx) and xxxxx (95% CI: xxxxxxxxxx) 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 (%) | xxxxxxxxxx | xxxxxxxxx |
| Subjects without events (censored), n (%) | xxxxxxxxxx | xxxxxxxxx |
| Alive | xxxxxxxxxx | xxxxxxxxx |
| Lost to follow-up | xxxxxxx | xxxxxxx |
| Withdrawal by subject | xxxxxxxx | xxxxxxxxx |
| Other | xxxxxxx | x |
| 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) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 6 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 9 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 12 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 18 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |
| 24 months (95% CI) | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxx |

\*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

#### 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 xxxxxxxxxxxxxxxxxxxxxx. In the HR-positive cohort, median PFS by IA was xxx months (95% CI: xxxxxxxxx) with T‑DXd compared with xxx months (95% CI: xxxxxxxx) with TPC (HR: xxxx; 95% CI: xxxxxxxxxx).7

xxxxxxxxxxxxxxx were observed for the FAS, where the statistically significant result for PFS by BICR was also xxxxxxxxxxxxxxxxxxxxxx. In the FAS, median PFS by IA in the HR-positive cohort was xxx months (95% CI: xxxxxxxx) with T‑DXd compared with xxx months (95% CI: xxxxxxxx) with TPC (HR: xxxx; 95% CI: xxxxxxxxxx).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[[10]](#footnote-11) 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 xxxxxxxxxxxxxxxxxx the assessment of response by BICR, showing a xxxxxxxxxxxxxxxxxxxxx benefit of T-DXd compared with TPC (**Table 21**).7 xxxxxx xxxxxxxxx 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 : 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 | |
| Confirmed ORR by IA, n (%) | xxxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxx |
| 95% CI | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| p-value | xxxxxxx | | xxxxxxx | |
| 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 | xxxxxxxx | xx | xxxxxxxx | xx |
| PR | xxxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxx |
| SD | xxxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxx |
| PD | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx |
| Not evaluable | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx |

\*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 : 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

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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

#### 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxx xx x xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.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 xxxxx at baseline and xxxxx at the end of treatment for the QLQ-C30 questionnaire, xxxxx at baseline and xxxxx at end of treatment for the QLQ-B45 (QLQ-BR23) questionnaire, and xxxxx at baseline and xxxxx at end of treatment for the EQ-5D-5L.7 In the TPC arm, the compliance rate in the HR-positive cohort was xxxxx at baseline and xxxxx at the end of treatment for the QLQ-C30 questionnaire, xxxxx at baseline and xxxx% at end of treatment for the QLQ-B45 (QLQ-BR23) questionnaire, and xxxx% at baseline and xxxxx at end of treatment for the EQ-5D-5L questionnaire.152 From Cycle 3 onwards, the minimum compliance rate was at least xxxxx 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 xxxxxxxxxxxxxxxxxxxx xxxxxxxxx. For the EQ-5D-5L index score, mean change from baseline to end of treatment was xxxxx in the T-DXd arm and xxxxx in the TPC arm; for the EQ-5D-5L VAS, mean change from baseline to end of treatment was xxxxx in the T-DXd arm and xxxxx in the TPC arm.152

At baseline in the FAS, the median EQ-5D-5L VAS score was xxxx in both the T-DXd arm and the TPC arm.152 At end of treatment, xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx (median change from baseline: xxxxx in both treatment arms).152 xxxxxxxxxxxxxxxxxxxxxxxxxx xxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, 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 xxxxxx in the T-DXd arm than the TPC arm (xxxx (95% CI: xxxxxxxxx) vs. xxx months (95% CI: xxxxxxxxx); HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx).152

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

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| Figure 16: DESTINY-Breast04 | Kaplan-Meier plot of time to definitive deterioration of EQ-5D-5L VAS | FAS |
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| 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 xxxxx in both the T‑DXd arm and the TPC arm (a high score for GHS represents a low QoL).152 At end of treatment, xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx(median change from baseline: xxxx).152 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, the median change from baseline to end of treatment was xxxx in both arms. The exception was for xxxxxxxxxxxxxxxxxxxx for TPC, where QoL decreased as shown by a median increase from baseline of xxxx.152 Mean change from baseline for overall GHS remained stable (within ±10 points) over the course of treatment with T-DXd up to xxxxxxxxx and with TPC up to xxxxxxxxx, after which the number of subjects became too small to allow for meaningful interpretation.152

In the FAS, median TTDD by at least 10 points for the EORTC QLQ-30 GHS was xxxxxx for the T-DXd arm than the TPC arm (xxxx [95% CI: xxxxxxxxx] vs. xxx months [95% CI: xxxxxxxx]; HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx).152 The HR was xxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxx of T‑DXd vs. TPC for nearly xxxxxxxxxxxxxxxxxxxxxxxxxxx, including xxxxxxxxxxxxxxxxxxxxx (xxxx and xxxx months; HR: xxxx; 95% CI: xxxxxxxxxx), xxxxxxxxxxxxxxxxxxxxx (xxxx and xxx months; HR: xxxx; 95% CI: xxxxxxxxxx), xxxxx xxx xxx xxxxxxx (xxxx and xxx months; HR: xxxx; 95% CI: xxxxxxxxxx), xxxxxxxxxxxxxxx (xxxx and xxx months; HR: xxxx; 95% CI: xxxxxxxxxx), xxxxxxxxxxxxx (xxxx and xxx months; HR: xxxx; 95% CI: XXXXX), and xxxxxxx (xxxx and xxx months; HR: xxxx; 95% CI: xxxxxx).152 The exception was for xxxxxxxxxxxxxxxxxxx, where the HR was x xxxxxxxxxxxxxxx of TPC vs. T-DXd (xxx and xxx months; HR: xxxx; 95% CI: xxxxxxxxxx).152

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

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

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

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| Graphical user interface, chart  Description automatically generated with medium confidence |

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

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| Table  Description automatically generated |

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

T-DXd was associated with xxxxxxxxxxx in arm symptoms compared with TPC (xxxx months (95% CI: xxxxxxxxxx) vs. xxx months (95% CI: xxxxxxx); HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx; **Figure 20**).152

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

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

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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), xxx patients (xxxxx) in the T-DXd arm and xx patients (xxxxx) 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 (xxxxx vs. xxxx days).7

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

### 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 data56 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 xxxxxxxxxxxxxxxxxxxxxxxxxxx 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx with T-DXd.152 Additionally, in the FAS, median TTDD was xxxxxx with T-DXd than TPC for EQ-5D-5L-VAS (xxxx [95% CI: xxx xxx] vs. xxx months [95% CI: xxxxxxx]; HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx), EORTC QLQ-C30 GHS (xxxx [95% CI: xxxxxx] vs. xxx months [95% CI: xxxxxxxx]; HR: xxxx; 95% CI: xxxxxxxxx; p=xxxxxx), 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx and a xxxxxx TTDD compared with non-targeted chemotherapy.7,151

## 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)

### 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, as indicated by the subgroup HR estimates lying xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx for the FAS (**Figure 21**).7 The subgroup HR estimates that xxxxxxxxxxxxxxxxxxxxxxxxxx of the FAS were: xxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7 For all of these exceptions, the xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.7

Subgroup analysis show that T-DXd is associated with a xxxxxxxxxxxxxxxxxxxxxx in PFS vs. TPC, including in key subgroups (e.g., xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx), as indicated by the xxxxxxxxxxxxxxxxxx.7 xxxxx xx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx (HR: xxxx; 95% CI: xxxx, xxxx vs. xxxx; 95% CI: xxxx, xxxx) indicating consistency across lines of therapy.7 Treatment effect was also similar across HR-positive and HR-negative subgroups (HR: xxxx CI: xxxx, xxxx vs. xxxx CI: xxxx, xxxx) 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 xxxxxxxxxxxxxxxxx subgroups.

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| Figure 21: DESTINY-Breast04 | Forest plot of PFS by BICR | FAS | Analysis in all subgroupsa |
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| 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 |

### 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: xxxxx vs xxxxx; p=xxxxxx)7 compared with TPC. This confirms the consistent treatment effect of T-DXd vs. TPC across key subgroups. For more information, see **Appendix N**.

## 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.

## 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 scope1 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 2022132 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 (xx and xx years for the T-DXd and TPC arms in the HR-negative cohort in DESTINY-Breast047 vs. 55 and 54 years for the SG and TPC arms in the HER2-low cohort in ASCENT154), 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.

## 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.

### DESTINY-Breast04

The data presented from the DESTINY-Breast04 study are from the January 2022 DCO, with a median follow-up of xxxx months in the T‑DXd arm and xxxx 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

#### 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 xxx mg/kg/3 weeks[[11]](#footnote-12) in the TDXd‑ arm. The mean relative dose intensity (RDI) was xxxx% in the TDXd‑ arm[[12]](#footnote-13) and ranged from xxxx–xxxx% for the agents in the TPC arm[[13]](#footnote-14) (**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) | xxxxxxxxxxxxxx | xxxxxxxxxxxxxx | xxxxxxxxxxxxxx | xxxxxxxxxxxxx | xxxxxxxxxxxxx |
| Patient-years of exposure† | xxxxxx | xxxxx | xxxxx | xxxx | xxxx | xxxx |
| Mean dose intensity, mg/kg/ 3w (std. dev.)‡ | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxx | xxxxxxxxxxxxxxx | xxxxxxxxxxxxx |
| Mean RDI, %  (std. dev.)¶ | xxxxxxxxxxx§ | xxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxx |
| Duration of treatment as of data cut-off date, n (%) | | | | | | |
| ≤3 months | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxx |
| >3 to ≤6 months | xxxxxxxxx | xxxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx |
| >6 to ≤9 months | xxxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxx | xxxxxxxx |
| >9 to ≤12 months | xxxxxxxxx | xxxxxxx | xxxxxxx | x | x | x |
| >12 to ≤18 months | xxxxxxxxx | xxxxxxx | xxxxxxxx | xxxxxxx | x | x |
| >18 to ≤24 months | xxxxxxxx | x | x | x | x | x |
| >24 months | xxxxxxxx | x | x | x | x | x |

\*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

#### Treatment-emergent adverse events

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

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 xxx patients (xxxxx) and xxx patients (xxxxx) 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 xxx patients (xxxxx) and xx patients (xxxxx), 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 xxxx and xxxx events per patient-year of exposure in patients treated with T‑DXd and TPC, respectively.7 Serious drug-related TEAEs were reported by xx patients (xxxxx) in the T‑DXd and xx patients (xxxx%) 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 xxxxxxx, and generally xxxxxxxx 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 xxxxxxxx through to x. 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 | xxxxxxxxxxx | xxxxxxxxxxx |
| **TEAE Grade ≥3** | 195 (52.6) | 116 (67.4) |
| EAIR per patient-year of exposure | 0.69 | 1.82 |
| Drug-related TEAE Grade ≥3 | xxxxxxxxxxx | xxxxxxxxxx |
| **Serious TEAE** | 103 (27.8) | 43 (25.0) |
| EAIR per patient-year of exposure | 0.36 | 0.68 |
| Serious drug-related TEAE | xxxxxxxxxx | xxxxxxxxxx |
| **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.  
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 | xxx | xxx | xxxx | xxx | xxx | xxxx |
| Cycle 2 | xxx | xxx | xxxx | xx | xxx | xxxx |
| Cycle 3 | xxx | xxx | xxxx | xx | xxx | xxxx |
| Cycle 4 | xxx | xxx | xxxx | xx | xxx | xxxx |
| Cycle 5 | xxx | xxx | xxxx | xx | xx | xxxx |
| Cycle 6 | xxx | xxx | xxxx | xx | xx | xxxx |
| Cycle 7 | xxx | xxx | xxxx | xx | xx | xxxx |
| Cycle ≥8\* | xxx | xxx | xxxx | xx | xx | xxxx |
| Cycle ≥18\* | xx | xxx | xxxx | x | x | xxxx |

\*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 (xxx patient; xxxxx), investigations (xxx patients; xxxxx), general disorders and administration site conditions (xxx patients; xxxxx), skin and subcutaneous tissue disorders (xxx patients; xxxxx) and metabolism and nutrition disorders (xxx patients; xxxxx).7 In patients treated with TPC, the most common TEAEs were in the system organ classes of gastrointestinal disorders (xxx patients; xxxxx), investigations (xxx patients; xxxxx), general disorders and administrative site conditions (xxx patients; xxxxx), and skin and subcutaneous tissue disorders (xx patients; xxxxx).7

In the T-DXd arm, the most common TEAEs of any grade were nausea (xxx patients; xxxxx), fatigue (xxx patients; xxxxx) and vomiting (xxx patients; xxxxx).7 In the TPC arm, neutropenia (xx patients; xxxxx), fatigue (xx patients; xxxxx) and alopecia (xx patients; xxxxx) 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 (xx patients; xxxxx), anaemia (xx patients; xxxxx), fatigue (xx patients; xxxx), leukopenia (xx patients; xxxx) and thrombocytopaenia (xx patients; xxxx).7 In patients in the TPC arm, the five most common TEAEs of Grade ≥3 were neutropoenia (xx patients; xxxxx), leukopenia (xx patients; xxxxx) increased transaminases (xx patients; xxx%), anaemia (x patients; xxxx) and fatigue (x patients; xxxx).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† | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxx |
| Neutropoenia\* | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Thrombocytopaenia§ | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxx | xxxxxxxx |
| Leucopoenia‡ | xxxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | xxxxxxxxxx |
| Lymphopenia | xxxxxxxx | xxxxxxxx | xxxxxxxx | xxxxxxxx |
| Febrile neutropenia | xxxxxxx | xxxxxxx | xxxxxxx | xxxxxxx |
| **Gastrointestinal disorders** | | | | |
| Nausea | xxxxxxxxx | xxxxxxxxx | xxxxxxxxxx | x |
| Vomiting | xxxxxxxxx | xxxxxxxx | xxxxxxxxxx | x |
| Constipation | xxxxxxxxx | xxxxxxx | xxxxxxxxxx | x |
| Diarrhoea | xxxxxxxxx | xxxxxxxx | xxxxxxxxxx | xxxxxxx |
| **General disorders** | | | | |
| Fatigue\*\* | xxxxxxxxx | xxxxxxxx | xxxxxxxxxx | xxxxxxx |
| Musculoskeletal pain | xxxxxxxxxx | xxxxxxxx | xxxxxxxxxx | x |
| Abdominal pain | xxxxxxxxxx | xx | xxxxxxxxxx | x |
| **Investigations** | | | | |
| AST Increased | xxxxxxxxxx | xxxxxxxx | xxxxxxxxxx | xxxxxxxx |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | xxxxxxxxxx | xxxxxxxx | xxxxxxxxx | xxxxxxx |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | xxxxxxxxxx | xx | xxxxxxxxxx | x |
| Palmar-plantar erythrodysaesthesia syndrome | xxxxxxx | x | xxxxxxxxx | xxxxxxx |

\*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 xx of the patients treated with T‑DXd were neutropoenia (xx patients; xxxxx), anaemia (xx patients; xxxx), fatigue (xx patients; xxxx), leukopenia (xx patients; xxxx) and thrombocytopaenia (xx patients; xxxx).7 In the TPC arm, these were neutropoenia (xx patients; xxxxx), leukopenia (xx patients; xxxxx) and increased transaminases (xx patients; xxxx).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 | xxxxxxxxxx | xxxxxxx | xxxxxxx | x |
| Musculoskeletal pain | xxxxxxxxx | x | xxxxxxxxx | x |
| **Investigations** | | | | |
| AST increased | xxxxxxxxx | xxxxxxxx | xxxxxxxxx | xxxxxxxx |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 106 (28.6) | 9 (2.4) | 28 (16.3) | 2 (1.2) |
| Weight decreased | xxxxxxxxxx | xxxxxxxx | xxxxxxx | x |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 140 (37.7) | 0 | 56 (32.6) | 0 |
| Interstitial lung disease | xxxxxxxxx | xxxxxxx | xxxxxxx | x |
| Stomatitis | xxxxxxxxxx | xxxxxxx | xxxxxxxxxx | xxxxxxx |
| Palmar-plantar erythrodysaesthesia syndrome | xxxxxxx | x | xxxxxxxxx | xxxxxxx |

\*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 xx patients (xxxx) and ILD in xx patients (xxxx).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[[14]](#footnote-15) (**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[[15]](#footnote-16) 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 | xxxxxxxxx | x |
| Interstitial lung disease | xxxxxxxxxx | xx |
| Peripheral sensory neuropathy | xx | xxxxxxxx |
| **TEAEs associated with study drug dose reduction** | **84 (22.6)** | **66 (38.4)** |
| Fatigue | xxxxxxxxx | xxxxxxxx |
| Nausea | xxxxxxxxx | xxxxxxxx |
| Thrombocytopenia | xxxxxxxxx | xx |
| Neutropenia | xxxxxxxxx | xxxxxxxxxx |
| Leucopoenia | xxxxxxxx | xxxxxxxx |
| Transaminases increased | xxxxxxxx | xxxxxxxx |
| **TEAEs associated with study drug interruption** | **143 (38.5)** | **72 (41.9)** |
| Neutropenia | xxxxxxxxx | xxxxxxxxxx |
| Fatigue | xxxxxxxxx | xxxxxxxx |
| Anaemia | xxxxxxxxx | xxxxxxxx |
| Leukopenia | xxxxxxxxx | xxxxxxxxx |
| COVID-19 | xxxxxxxxx | xxxxxxxx |
| Interstitial lung disease | xxxxxxxxx | xx |
| Transaminases increased | xxxxxxxxx | xxxxxxxx |
| Blood bilirubin increased | xxxxxxxx | xx |
| Nausea | xxxxxxxx | xxxxxxxx |
| Palmar-plantar erythrodysaesthesia syndrome | xx | xxxxxxxx |
| Peripheral sensory neuropathy | xx | xxxxxxxx |

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%). 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-DXd6, 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 xxxxx days (range: xxxxxxxxxx) 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 xx patients (xxxxx), recovered/resolved with sequelae in xxx patients (xxxx) and recovering/resolving in xxxx patients (xxxx).7 xxx patients (xxxxx) in the T-DXd arm had adjudicated ILD events that were not recovered/resolved. In addition, there were xxx (xxxx) adjudicated drug-related ILD events associated with death in the T-DXd arm.7 The event was not recovered/resolved in the xxxxxxxxxxx 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 xx (xxxx), xxx (xxxx) and xx patients (xxxx), respectively of patients treated with T‑DXd.7 In patients treated with TPC, xx 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

### 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 associatedwith 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 xxxxxxx, and xxxxxxxxxxxxxxxxxx over subsequent cycles.7

Of note, Grade ≥3 TEAEs werereported 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 (xxxxx vs. xxxxx), the incidence of drug-related Grade ≥3 TEAEs was higher in the TPC arm (xxxx% vs. xxxxx).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

## 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.

## Interpretation of clinical effectiveness and safety evidence

### 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 data56 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.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 xxxxxxxxxxxxxxxxxxxxxxxxxxx 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 xxxxxx in the T-DXd arm than the TPC arm (xxxx (95% CI: xxxxxxxxx) vs. xxx months (95% CI: xxxxxxxxx); HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx; FAS).152 Similarly, for EORTC QLQ-C30 GHS, the median TTDD was xxxxxx with T-DXd than TPC (xxxx (95% CI: xxxxxxxxx) vs. xxx months (95% CI: xxxxxxxx); HR: xxxx; 95% CI: xxxxxxxxxx; p=xxxxxx; 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 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.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 months6 vs 1.7–6.6 months; 43–55 including similar TPC arms in RIBBON-253 and EMERGE55). 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 months6 vs. 3.6–4.2 months), and median OS was also slightly higher (17.5 months6 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 months6 vs. 1.7–2.8 months), as was median OS (8.3 months6 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 months6 vs. TPC 17.5 months6 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 months6 vs. previous chemotherapy studies 1.7–2.8 months43, 48–50,157) and median OS (T-DXd 18.2 months vs. TPC 8.3 months6 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 xxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxx. 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 : 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 III6 | 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 III43 | Study 301 and Study 305 | ≥2 | Eribulin | 3.7 | 15.1 |
| Pivot et al., 2017  (NCT00337103) Phase III46 | Study 301 | 2 | Eribulin | 4.2 | 16.1 |
| 4.0 | 13.5 |
| Twelves et al., 2016  (NCT00337103) Phase III45 | Study 301 | ≥2 | Eribulin | 4.1 | 15.9 |
| Capecitabine | 3.9 | 13.5 |
| Yardley et al., 2016 (298)  (NCT01427933) Phase II47 | - | 2-4 | Eribulin | 4.1 | 11.5 |
| Cortes et al., 2011  (NCT00388726) Phase III44 | 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 III6 | 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 III43 | Study 301 and Study 305 | ≥2 | Eribulin | 2.8 | 12.4 |
| Vahdat et al., 2021\*  (NCT0199733) Phase II50 | METRIC | ≤2 | Capecitabine | 2.8 | 8.7 |
| Bardia et al., 2021\*  (NCT02574455) Phase III48 | ASCENT | ≥2 | SG \*\* | 5.6 | 12.1 |
| TPC (eribulin, vinorelbine, capecitabine, gemcitabine) | 1.7 | 6.7 |
| Winer et al., 2021\*  (NCT02555657) Phase III49 | 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 III6 | 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 III52 | Stop&Go | 2 | Capecitabine (intermittent) | 3.7 | 10.9 |
| Capecitabine (continuous) | 5.0 | 12.4 |
| Brufsky et al., 2011\*  (NCT00281697) Phase III53 | 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 II54 | PASO | 2-3 | Paclitaxel | 6.6 | 20.7 |
| Yardley et al., 2016  (NCT01427933) Phase II47 | - | 2-4 | Eribulin | 4.1 | 11.5 |
| Yardley et al., 2015\*  (NCT01156753) Phase II125 | 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

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### 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 scope1 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 xxxxxxxxxxxxx xxxxxxxxxx xxx xxxxx.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 xxxxxxxxxxxxxxxxxxxxxxx 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 xxxxxx 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 xxxxxxx, and xxxxxxxxxxxxxxxxxx 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 data56 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

### 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, xxxxxxxxxxxxxxxxxxxxxx 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 EMA3 and the US FDA.138,139 UK Medicines and Healthcare Products Regulatory Agency (MHRA) approval xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx).

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.

# Cost-effectiveness

## 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 TA819132 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. 2016162 | 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. 2015163 | 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 : 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 TA819132 | 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 TA423131 | 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  Subgroup 2: Patients with LABC/mBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine | 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 |
| NICE TA116122 | 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

## 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 TA819132) and NICE-recommended TAs for T-DXd in HER2-positive u/mBC (i.e., TA7044, TA8625).

### 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

### 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

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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

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| Graphical user interface  Description automatically generated |

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 Wales166 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

#### 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.

#### 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

#### 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 trial7 and the anticipated licensed indication164 |
| 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 |
| Source of utilities | Values from Narewska et al 2005167 | 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.

### 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 guidelines35, ESMO 2021 guidelines42, 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.

## 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**)

### 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-Breast047 | Used to inform the estimation of background mortality and measurement of disease severity modifier. |
| Proportion female, % | 99.60 |
| Mean weight, kg | 63.40 (13.57) | Used to inform the calculation of drug dosing and subsequently, drug costs (those dosed according to weight). |
| Mean body surface area, m2 | 1.67 (0.19) |

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.

### 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-Breast047
  + 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**).

#### 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 xxxxx of patients in the T-DXd arm and xxxxx 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 : OS KM from DESTINY-Breast04 in the FAS population (T-DXd and TPC)

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| **Graphical user interface, chart, line chart  Description automatically generated** |

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 14171 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

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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 14171 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

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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

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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

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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

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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 | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Weibull | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Gompertz | xxxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Log-logistic | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Log-normal | xxxxx | xxxxxx | xxxxxx | xxxxxx | xxxxx |
| Generalised gamma | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| **T-DXd** | | | | | |
| Exponential | xxxxx | xxxxxx | xxxxxx | xxxxxx | xxxxx |
| Weibull | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Gompertz | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Log-logistic | xxxxx | xxxxxx | xxxxxx | xxxxxx | xxxxx |
| Log-normal | xxxxx | xxxxxx | xxxxxx | xxxxxx | xxxxx |
| Generalised gamma | xxxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |

\*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 xxxx, xxxx, and xxxxx, 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 xxxx, xxxx and xxxx, 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 curves121 with 5-year OS estimates of xxxxx and xxxxx 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 xxxx, xxxx and xxxx, 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 xxxx months and xxxx 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)

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

#### Progression-free survival

*Assessment of data from DESTINY-Breast04*

Median follow-up in the FAS population of DESTINY-Breast04 was xxxx months,6 during which xxxxx of patients in the T-DXd arm and xxxxx 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 : PFS KM from DESTINY-Breast04 in the FAS population (T-DXd and TPC)

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| Graphical user interface, chart, line chart  Description automatically generated |

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 14171, 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

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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 14171 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

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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

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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 | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Weibull | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Gompertz | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Log-logistic | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Log-normal | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Generalised gamma | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| **T-DXd** | | | | | |
| Exponential | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Weibull | xxxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Gompertz | xxxxx | xxxxxx | xxxxx | xxxxx | xxxxx |
| Log-logistic | xxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Log-normal | xxxx | xxxxxx | xxxxxx | xxxxx | xxxxx |
| Generalised gamma | xxxx | xxxxxx | xxxxx | xxxxx | xxxxx |

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

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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

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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 xxxx months and xxxx 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)

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

#### Time to treatment discontinuation

*Assessment of data from DESTINY-Breast04*

The median follow-up in the FAS population of DESTINY-Breast04 was xxxx months during which xxxxx and xxxxx 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 xxx months and xxx 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)

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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 (xxxxx and xxxxx 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

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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 14171 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 : Observed versus predicted TTD (TPC) in the FAS population over 4 years

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

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

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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 : 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 | xxxx | xxxxx | xxxxx | xxxxx |
| Weibull | xxxx | xxxxx | xxxxx | xxxxx |
| Gompertz | xxxx | xxxxx | xxxxx | xxxxx |
| Log-logistic | xxxx | xxxxx | xxxxx | xxxxx |
| Log-normal | xxxx | xxxxx | xxxxx | xxxxx |
| Generalised gamma | xxxx | xxxxx | xxxxx | xxxxx |
| **T-DXd** | | | | |
| Exponential | xxxx | xxxxxx | xxxxxx | xxxxx |
| Weibull | xxxx | xxxxxx | xxxxx | xxxxx |
| Gompertz | xxxx | xxxxxx | xxxxx | xxxxx |
| Log-logistic | xxxx | xxxxxx | xxxxxx | xxxxx |
| Log-normal | xxxx | xxxxxx | xxxxxx | xxxxx |
| Generalised gamma | xxxx | xxxxxx | xxxxx | xxxxx |

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 guidance171, 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)

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

### 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\* | xxxxxx | xxxxx |
| Anaemia | xxxxxx | xxxxx |
| Neutrophil count decreased | xxxxx | xxxxxx |
| White blood cell count decreased | xxxxx | xxxxxx |
| Platelet count decreased | xxxxx | xxxxx |
| Fatigue | xxxxx | xxxxx |
| Increased ALT | xxxxx | xxxxx |

\*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

### 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

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

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| --- |
|  |

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

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\*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.

## Measurement and valuation of health effects

### Health-related quality-of-life data from clinical trials

In DESTINY-Breast04, EQ-5D-5L, EORTC QlQ-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.

### 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, xxxxx observations were recorded while progression-free with the remaining xxx 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 | xxxxx | xxxxxxxxxxxxx |
| Post-progression | xxx | xxxxxxxxxxxxx |

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 | xxxxxx | xxxxxxxxxxxxxx | x |
| Treatment (T-DXd vs. TPC) | xxxxxx | xxxxxxxxxxxxxx | xxxxxx |
| ECOG performance status (1 vs. 0) | xxxxx | xxxxxxxxxxxx | xxxxxx |
| Progression status (progressed vs. progression free) | xxxxx | xxxxxxxxxxxx | xxxxxx |
| Treatment status (off-treatment vs. on-treatment) | xxxxx | xxxxxxxxxxxx | xxxxxx |

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 xxxxx 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 | xxxxx | xxxxxxxxxxxxxxxxxxxxx | xxx | xxxxxxxxxxxxxxxxxxxx |
| Progressed | xxx | xxxxxxxxxxxxxxxxxxxx | xxx | xxxxxxxxxxxxxxxxxxxx |

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

### 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, 2006169 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:

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 : DESTINY-Breast04 patient characteristics (ages) and objective response rate6,7

|  |  |  |
| --- | --- | --- |
|  | 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.

#### 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 | xxxxx | 0.618 |
| T-DM1 | xxxxx | 0.574 |
| Pooled | xxxxx | 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.

### 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 | TA7044 and TA8625 |
| Anaemia | -0.010 | 42.90 |
| Neutropenia | -0.007 | 40.10 |
| Thrombocytopenia | -0.066 | 42.20 | TA78670 | TA8625 |
| Fatigue | -0.029 | 58.30 | Hudgens (2014)175 | TA7044 and TA8625 |
| ALT increased | -0.050 | 14.66 | TA654176 | |
| Interstitial lung disease (any grade) | -0.170 | 51.10 | Doyle et al. (2011)177 | TA7044 and TA8625 |

Abbreviations: ALT, alanine transaminase.

### 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=xxxxx) using the NICE preferred EQ-5D values.2

For the ‘*post-progression’* health state, limited post-progression observations from DESTINY-Breast04 were available (n=xxx). 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 (xxxxx) compared to patients treated with TPC (xxxxx) (**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 | Xxxx xxxx xxxx xxxx xxx xxxxxx | xxxxxxxxxxxxxxxxxxxxxxxxxxxx | 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 | xxxxxxxxxxxxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxxxxxxxxxxxx | B.3.4.2,  Page 144 | Explore using alternative progressed-disease utilities derived from DESTINY-Breast04 |
| Progressed disease  T-DXd  TPC | xxxxxxxxxxxxxxxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxxxxxxxxxxxx |

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

## 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**.

### Intervention and comparators’ costs and resource use

#### 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 XXXXX per 100mg vial (equivalent to a discount of XXXXX to 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  xxxxxxxxx | 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 SmPC18, 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 : 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/m2 PO twice daily on Days 1-14; cycled every 21 days |
| Eribulin | 1.23 mg/m2 IV on Days 1 and 8; cycled every 21 days |
| Gemcitabine a | 1250 mg/m2 IV on Days 1 and 8; cycled every 21 days |
| Paclitaxel | 175 mg/m2 IV on Day 1; cycled every 21 days |
| Nab-paclitaxel | 260 mg/m2 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; xxxxx for T-DXd and xxxxxxxxxxx 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](#_ENREF_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 | xxxxx%b | 75% | xxxxxxxxxa | DESTINY-Breast047 |
| Weighted TPC | - | - | - | - | £987.24d | - |
| Components of TPC | | | | | | |
| Capecitabine | 1250 mg/kg | 28 | xxxx%c | N/A | £38.12 | DESTINY-Breast047 |
| Eribulin | 1.23 mg/m2 | 2 | xxxx%c | 75% | £1,786.55 | DESTINY-Breast047 |
| Gemcitabine | 1250 mg/m2 | 2 | xxxxx%c | 75% | £93.58 | DESTINY-Breast047 |
| Paclitaxel | 175 mg/m2 | 1 | xxxxx%c | 75% | £30.56 | DESTINY-Breast047 |
| Nab-paclitaxel | 260 mg/m2 | 1 | xxxxx%c | 75% | £529.18 | DESTINY-Breast047 |

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).

#### 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 20/21185 – SB11Z – deliver exclusively oral chemotherapy |
| Parenteral Simple | £381.97 | £281.11 | T-DXd, Eribulin, Gemcitabine, Paclitaxel and Nab-paclitaxel | NHS Cost Collection 20/21185 – SB12Z – deliver simple parenteral chemotherapy |

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

### Health-state unit costs and resource use

Health state resource use costs are based on frequencies reported in TA8625 and TA819132 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 2020/21185 and the PSSRU 2021186 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 | TA8625  TA819132 | PSSRU 2021186 - GP Per patient contact lasting 9.22 minutes with qualifications |
| Medical oncologist | 0.69 | 0.69 | £225.00 | TA8625  TA819132 | NHS Cost Collection 20/21185 – 370 – medical oncologist – consultant led |
| Clinical nurse specialist | 0.69 | 0.69 | £85.00 | TA8625  TA819132 | NHS Cost Collection 20/21185 - N09AF - Specialist Nursing, Breast Care Nursing/Liaison, Adult, Face to face |
| CT scan | 0.23 | 0.23 | £105.66 | TA8625 | NHS Cost Collection 20/21185 - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over - Outpatient |
| ECHO scan | 0.23 | 0.23 | £145.53 | TA8625 | NHS Cost Collection 20/21185 - 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.

### 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 themodel 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 | xxxxxxx |
| TPC | xxxxxxx |

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

### Miscellaneous unit costs and resource use

#### 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 xxxx months is calculated using the number of patients in each treatment arm.7 The duration of subsequent treatment is presented in **Table 59**.

Table : 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 | xxx | xxxx | xxx | xxxx |
| TPC | 184 | xxx | xxxx | xxx |

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, xxxxx and xxxxx 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 (xxxxx) 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 | xxxxxxxxxxxxxx) | xxxxxxxxxx) |  |  |  |  |
| Chemotherapy | | | | | | |
| Paclitaxel | xxxxxxxxxxxxx) | xxxxxxxxxxxx) | | 175.0 mg/m2 | xxxxxx | xxxxxxx |
| Capecitabine | xxxxxxxxxxxxx) | xxxxxxxxxxxx) | | 1250.0 mg/m2 | xxxxxx | xxxxxxx |
| Gemcitabine | xxxxxxxxxxxxx) | xxxxxxxxxxxx) | | 1250.0 mg/m2 | xxxxxxx | xxxxxxx |
| Eribulin | xxxxxxxxxxxxx) | xxxxxxxxxxxx) | | 1.2 mg/m2 | xxxxxxxxx | xxxxxxx |
| Vinorelbine | xxxxxxxxxxxx) | xxxxxxxxxxxx) | | 60.0 mg/m2 | xxxxxx | xxxxxxx |
| Epirubicin | xxxxxxxxxxx) | xxxxxxxxxxx) | | 100.0 mg/m2 | xxxxxx | xxxxxxx |
| Carboplatin | xxxxxxxxxxxx) | xxxxxxxxxxxx) | | 400.0 mg/m2 | xxxxxx | xxxxxxx |
| Endocrine therapy | | | | | | |
| Tamoxifen | xxxxxxxxxxx) | xxxxxxxxxxx) | | 20.0 mg | xxxxx | xxxxxxxxx |
| Fulvestrant | xxxxxxxxxxxx) | xxxxxxxxxxxx) | | 500.0 mg | xxxxxx | xxxxxxx |

\*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 | xxxxxxx | xxxxxxx |
| Total weighted subsequent therapy administration cost per cycle | xxxxxxxxx | xxxxxxxxx |
| Total subsequent therapy cost per progressed patient\* | £xxxxxxxxx | £xxxxxxxxx |
| Proportion receiving subsequent treatment | xxxxx | xxxxx |
| Total subsequent therapy cost per progressed patient applied in the model\* | £xxxxxxxxx | xxxxxxxxxx |

\*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.

#### 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](#_ENREF_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

## Severity

### 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.

### 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.

### 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 guidance191 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 al190 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 xxxxx and the proportional shortfall (PS) is estimated to be xxxxxx (**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 | xxxx | Absolute: xxxxx  Proportional: xxxxx% | 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.

### 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.**

## 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 | ü | ü |  |
| Efficacy | OS |  |  |  |
| PFS |  |  |  |
| TTD |  |  |  |
| Safety | AE rates |  |  |  |
| Utilities | Progression-free |  |  |  |
| Progressed |  |  | ü |
| AE disutilities |  |  |  |
| Costs | Drug costs |  | ü |  |
| Administration costs |  |  |  |
| Resource use costs |  |  |  |
| AE costs |  |  |  |
| Subsequent treatment costs |  |  | ü |
| Terminal care costs | ü | ü |  |

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.

## 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

## Summary of base-case analysis inputs and assumptions

### 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 (m2) | 1.67 | Normal |
| Weight (kg) | 63.40 |
| ***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 | xxxxx | SE: xxxxxx (Beta) | Section B.3.4.5  Table 51 |
| DB04 TPC PF utility | xxxxx | SE: xxxxxx (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 xxxxxxxxx | 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 |
| Paclitaxel - 150 mg | £14.23 |
| Paclitaxel - 300 mg | £39.81 |
| Nab-paclitaxel - 100 mg | £118.36 |
| T-DXd - RDI | xxxxx | Variation: 0.025 (Beta) | Section B.3.5.1.1 Table 54 |
| Capecitabine - RDI | xxxxx |
| Eribulin - RDI | xxxxx |
| Gemcitabine - RDI | xxxxxx |
| Paclitaxel - RDI | xxxxxx |
| Nab-paclitaxel – RDI | xxxxxx |
| 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 | xxxxxx |
| T-DXd - White blood cell count decreased | xxxxx |
| T-DXd - Platelet count decreased | xxxxx |
| T-DXd - Fatigue | xxxxx |
| T-DXd - Increased ALT | xxxxx |
| T-DXd - Interstitial lung disease (any grade) | xxxxxx |
| TPC - Neutrophil count decreased | xxxxxx |
| TPC - Anaemia | xxxxx |
| TPC - White blood cell count decreased | xxxxxx |
| TPC - Platelet count decreased | xxxxx |
| TPC - Fatigue | xxxxx |
| TPC - Increased ALT | xxxxx |
| TPC - Interstitial lung disease (any grade) | xxxxx |
| 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 |
| 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 | xxxxxx | Variation: 0.025 (Beta) | Section B.3.5.4 Table 60 |
| TPC - Proportion receiving subsequent treatment | xxxxxx |
| Sub trt – T-DXd - Capecitabine | xxxxxx |
| Sub trt – T-DXd - Eribulin | xxxxxx |
| Sub trt – T-DXd - Gemcitabine | xxxxxx |
| Sub trt – T-DXd - Paclitaxel | xxxxxx |
| Sub trt – T-DXd - Vinorelbine | xxxxx |
| Sub trt – T-DXd – Fulvestrant | xxxxxx |
| Sub trt – T-DXd – Epirubicin | xxxxx |
| Sub trt – T-DXd – Carboplatin | xxxxx |
| Sub trt – T-DXd – Tamoxifen | xxxxx |
| Sub trt – TPC - Capecitabine | xxxxxx |
| Sub trt – TPC - Eribulin | xxxxxx |
| Sub trt – TPC - Gemcitabine | xxxxxx |
| Sub trt – TPC - Paclitaxel | xxxxxx |
| Sub trt – TPC - Vinorelbine | xxxxxx |
| Sub trt – TPC – Fulvestrant | xxxxxx |
| Sub trt – TPC – Epirubicin | xxxxx |
| Sub trt – TPC – Carboplatin | xxxxxx |
| Sub trt – TPC – Tamoxifen | xxxxx |

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.

### 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 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. | NA |
| Identification of the most appropriate survival curves describing OS, PFS and TTD | Extensive analyses have been undertaken to identify appropriate survival curves describing the long-term efficacy of each treatment, with reference to the guidance from the NICE DSU.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 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 | xxxxx and xxxxx 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 xxx patients (xxxxx) and xxx patients (xxxxx) 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 (xxxxx) 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.

## 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**.

### 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 xxxx and xxxx, respectively. This suggests a substantial improvement in survival and QoL in the u/mBC setting. This benefit is associated with incremental costs of xxxxxx per patient over a lifetime resulting in an ICER of xxxxxxx. 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 xxxxxxxxxxxxxx.

With the 1.2x severity modifier applied, T-DXd (at the PAS price) is associated with LY and adjusted QALY gains of xxxx and xxxx, respectively, resulting in an ICER of xxxxxxx (**Appendix P**). With the 1.7x severity modifier applied, T-DXd (at the PAS price) is associated with LY and adjusted QALY gains of xxxx and xxxx, respectively, resulting in an ICER of xxxxxxx (**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 | xxxxxxx | xxxx | xxxx | - | - | - | - |
| T-DXd | xxxxxxx | xxxx | xxxx | xxxxxxx | xxxx | xxxx | xxxxxxx |

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 | xxxxxxx | xxxx | - | - | - |
| T-DXd | xxxxxxx | xxxx | xxxxxxx | xxxx | xxxxx |

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.

## Exploring uncertainty

### 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 xxxx at an incremental cost of xxxxxxx, resulting in a probabilistic ICER of xxxxxxx. 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 | xxxxxxx | xxxx | xxxx | - | - | - | - |
| T-DXd | xxxxxxx | xxxx | xxxx | xxxxxxx | xxxx | xxxx | xxxxxxx |

\*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 XXXX and at a WTP threshold of £50,000/QALY gained the probability that T-DXd is a cost-effective treatment option is xxxxXx.

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.

### 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) | xxxxxxx | xxxxxxx |
| Relative dose intensity -Trastuzumab deruxtecan - 100 | xxxxxxx | xxxxxxx |
| Utilities - Progressed - Physician's choice | xxxxxxx | xxxxxxx |
| Utilities - Progressed - Trastuzumab deruxtecan | xxxxxxx | xxxxxxx |
| Utilities - Progression-free - Trastuzumab deruxtecan | xxxxxxx | xxxxxxx |
| Utilities - Progression-free - Physician's choice | xxxxxxx | xxxxxxx |
| Average body surface (m2) | xxxxxxx | xxxxxxx |
| Drug cost - Eribulin - 0.88 | xxxxxxx | xxxxxxx |
| Administration costs - Trastuzumab deruxtecan | xxxxxxx | xxxxxxx |
| Health state cost - Progression-free - Total | xxxxxxx | xxxxxxx |

\*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.

### 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** | | | | xxxxxxx | xxxx | xxxxxxx |
| Discount rate | 1 | Discount rates - Costs: 3.5%, outcomes: 3.5% | Discount rates - costs: 0%, outcomes: 0% | xxxxxxx | xxxx | xxxxxxx |
| 2 | Discount rates - costs: 1.5%, outcomes: 1.5% | xxxxxxx | xxxx | xxxxxxx |
| 3 | Discount rates - costs: 6%, outcomes: 6% | xxxxxxx | xxxx | xxxxxxx |
| Time horizon | 4 | 30 years | 20 years | xxxxxxx | xxxx | xxxxxxx |
| Half cycle correction | 5 | Applied | Not applied | xxxxxxx | xxxx | xxxxxxx |
| Subsequent treatment | 6 | Trial treatment-specific proportions on subsequent treatment | Trial pooled, weighted proportions on subsequent treatment | xxxxxxx | xxxx | xxxxxxx |
| AE disutilities | 7 | AE disutilities excluded | AE disutilities included | xxxxxxx | xxxx | xxxxxxx |
| Vial sharing | 8 | Vial sharing 75% | Vial sharing 50% | xxxxxxx | xxxx | xxxxxxx |
| 9 | Vial sharing 100% | xxxxxxx | xxxx | xxxxxxx |
| Utilities | 10 | Progressed disease utilities sourced from Lloyd et al. 2006 | Progressed disease utilities sourced from DESTINY-Breast04 trial. | xxxxxxx | xxxx | xxxxxxx |
| OS extrapolations  (applied to T-DXd and TPC) | 11 | Log-logistic | Exponential | xxxxxxx | xxxx | xxxxxxx |
| 12 | Log-normal | xxxxxxx | xxxx | xxxxxxx |
| PFS extrapolations  (applied to T-DXd and TPC) | 13 | Log-logistic | Exponential | xxxxxxx | xxxx | xxxxxxx |
| 14 | Weibull | xxxxxxx | xxxx | xxxxxxx |
| 15 | Gompertz | xxxxxxx | xxxx | xxxxxxx |
| 16 | Log-normal | xxxxxxx | xxxx | xxxxxxx |
| 17 | Generalised gamma | xxxxxxx | xxxx | xxxxxxx |
| OS and PFS extrapolations  (applied to T-DXd and TPC) | 18 | OS: log-logistic  PFS: log-logistic | OS: Exponential  PFS: Exponential | xxxxxxx | xxxx | xxxxxxx |
| 19 | OS: Log-normal  PFS: Log-normal | xxxxxxx | xxxx | xxxxxxx |

\*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.

## 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.

## 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 xxxxxxxxxxxxxxxxxxxxx, 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**).

## Validation

### 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.

### 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.

### 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).

### 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 scope1 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 : 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 | xxxx | xxxxx | 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 | xxxx | xxxx | 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.

## 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.6,7UK clinical and HEOR experts confirmed the trial is well designed, robust and provides evidence that is generalisable to the UK.121 Published UK biomarker data56 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 scope1 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 XXX at an incremental cost of XXXXX, resulting in an ICER of XXXXX vs TPC in the FAS population. With the 1.2x and 1.7x severity modifier applied, the ICER is xxxxx and xxxxxxx, 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 xxxx and ICER of xxxxxxx, 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 XXX and xxxxxx 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 AAA 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 AAA 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/mBC3 (UK regulatory approval expected xxxxxxxxxxx), 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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1. Functional Assessment of Cancer Therapy – Breast [↑](#footnote-ref-2)
2. Functional Assessment of Cancer Therapy – General [↑](#footnote-ref-3)
3. EuroQol-5 Dimensions-5 Level [↑](#footnote-ref-4)
4. Work Productivity and Activity Impairment [↑](#footnote-ref-5)
5. Defined as fractures, the need for radiation to the bone to control pain or tumour burden, spinal cord compression, or bone surgery [↑](#footnote-ref-6)
6. 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). [↑](#footnote-ref-7)
7. 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). [↑](#footnote-ref-8)
8. 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. [↑](#footnote-ref-9)
9. 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. [↑](#footnote-ref-10)
10. 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 [↑](#footnote-ref-11)
11. 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. [↑](#footnote-ref-12)
12. 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. [↑](#footnote-ref-13)
13. 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. [↑](#footnote-ref-14)
14. 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. [↑](#footnote-ref-15)
15. 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. [↑](#footnote-ref-16)