6.13 TRASUTUZUMAB DERUXTECAN, Powder for I.V. infusion, 100 mg, Enhertu®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required listing for trastuzumab deruxtecan (T-DXd) for the treatment of adult patients with hormone receptor positive (HR-positive) human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow unresectable and/or metastatic breast cancer who have received at least one prior line of endocrine therapy (ET) in the metastatic setting and are no longer suitable for further ET.

1.2 Listing was requested on the basis of cost-utility and cost-effectiveness analyses versus investigator's choice of chemotherapy (ICC) (as a proxy of single-agent chemotherapy), consisting of capecitabine, paclitaxel and nab-paclitaxel. The key components of the clinical issues addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with HER2-low (IHC 1+ or IHC 2+/ISH-negative) or HER2-ultralow (IHC 0 with membrane staining) unresectable and/or metastatic HR+ BC who have received at least one prior line of ET in the metastatic setting and are no longer considered suitable for ET
Intervention	Trastuzumab deruxtecan (T-DXd, Enhertu®)
Comparator	Investigators choice of chemotherapy (ICC), consisting of capecitabine, paclitaxel and nab-paclitaxel
Outcomes	Primary: - PFS by BICR in the HR+ HER2-low population Secondary: - OS in the HR+ HER2-low population - PFS by BICR in the ITT population - OS in the ITT population - PFS by INV in the HR+ HER2-low population - ORR and DoR by BICR and by INV in the HR+ HER2-low population - ORR and DoR by BICR and by INV in the ITT population - PFS2 in the HR+ HER2-low population and the ITT population - TFST in the HR+ HER2-low population and the ITT population - TSST in the HR+ HER2-low population and the ITT population - Safety - HRQoL measured by change in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores; time to deterioration in EORTC QLQ-C30 scale scores
Clinical claim	In patients with HR+ HER2-low and HR+ HER2-ultralow unresectable and/or metastatic BC, T-DXd has superior efficacy, and an inferior safety profile compared to PC

Source: Table 1.2, p14 of the submission.
BC = breast cancer, BICR = blinded independent central review, DoR = duration of response, EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ET = endocrine therapy, HR = hormone receptor, HRQoL = health-related quality of life, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemical, ISH = in situ hybridisation, ITT = intent-to-treat, INV = Investigator, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PFS2 = time from randomisation to second progression or death, TFST = time to first subsequent therapy, TSST = time to second subsequent therapy

1 Background

Registration status

1.1 At the time of PBAC consideration T-DXd was approved by the TGA as monotherapy for adult patients with metastatic breast cancer with the following indications:

- Unresectable or metastatic HER2-positive breast cancer (BC) who previously received trastuzumab and a taxane for metastatic disease, or one prior anti-HER2-based regimen and developed disease recurrence during or within 6 months of completing neo-adjuvant or adjuvant therapy.
- Unresectable or metastatic HER2-low (immunochemistry [IHC] 1+ or IHC 2+/in situ hybridisation [ISH]-negative) BC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of

completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received and no longer be considered eligible for endocrine therapy.

- Unresectable or metastatic HR+ and either HER2-low (IHC 1+ or IHC 2+/ISH-negative) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

1.2 The use of T-DXd in the proposed indication requires identification of patients through companion diagnostic testing of tumour for HER2 at the newly defined HER2-low (IHC 1+ and IHC 2+/ISH-) and HER2-ultralow (IHC > 0 < 1+) cutoffs. In the TGA Delegate's overview, it was stated that, while HER2 testing is well established for BC in determining 'positive' from 'negative' and has been standardised and in wide use for decades in Australia (same for ISH testing in Australia), the 'low' and 'ultralow' sub-definitions within HER2-negative, which depend on the IHC component of the HER2 testing, remain more novel than standard.

1.3 The recently updated (June 2025) HER2 Testing for Breast Cancer Guidelines published by the Royal College of Pathologists of Australasia (RCPA) provides a succinct summary of the current state of HER2 testing in BC in Australia, including the concepts of HER2-low and HER2-ultralow. The guidelines note that HER2-ultralow was not relevant to any TGA approval at the time, and that pathologists will require support, peer training and practice to score consistently BC HER2 IHC patterns at the low end of the protein expression (Delegate's overview ENHERTU trastuzumab deruxtecan AstraZeneca PM-2024-04768-1-4).

For more detail on PBAC's view, see section 7 PBAC outcome.

2 Requested listing

2.1 The proposed listing with Secretariat suggested additions in italics and deletions in strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	Dispensed price for maximum amount (DPMA)	№.of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private)	675 mg	Public hospital: Published: $17,542.65 Effective: $[redacted] with SPA Private hospital: Published: $17,832.62 Effective: $[redacted] with SPA	8
Available brands				
Enhertu (trastuzumab deruxtecan 100 mg injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new]				
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: ☒Medical Practitioners			
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)			
Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*				
Administrative Advice: *No increase in the maximum number of repeats may be authorised*				
Administrative Advice: Special pricing arrangements apply				
Severity: Unresectable and/or metastatic				
Condition: HR-positive HER-2 low or HER2-ultralow breast cancer				
Indication: Unresectable and/or metastatic HR-positive HER-2 low or HER2-ultralow breast cancer				
Clinical criteria:				
Patient must have evidence of human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow disease either in the primary tumour or a metastatic lesion				
AND				
~~**Clinical criteria:**~~				
~~Patient must have received at least one prior endocrine therapy in the metastatic setting~~				
AND				
Clinical criteria:				
~~Patients must be unsuitable for further endocrine therapy~~				
Patient must have received at least one prior endocrine therapy or be ineligible for endocrine therapy in the metastatic setting,				
AND				
Clinical criteria:				
Patient must not have received chemotherapy in the advanced/metastatic setting				
AND				
Clinical criteria:				
Patient must not have received chemotherapy in the neoadjuvant or adjuvant setting where they had a disease-free interval of less than 6 months from completion of chemotherapy				
Clinical criteria:				
Patient must have, *at the time of initiating treatment with this drug*, a World Health Organisation (WHO) *performance status* ~~Eastern Cooperative Oncology Group (ECOG)~~ no higher than 1 ~~at treatment initiation~~				
AND				
Clinical criteria:				
The treatment must be the sole PBS-subsidised *systemic anti-cancer* therapy for this PBS indication.				

AND
Clinical criteria
The treatment must not be prescribed where any of the following is present: (i) left ventricular ejection fraction of less than 45%, (ii) symptomatic heart failure; confirm cardiac function testing for the first PBS prescription only
Treatment criteria:
Patient must be undergoing initial treatment with this drug - the following are true: (i) this is the first prescription for this drug, (ii) this prescription seeks no more than 3 repeat prescriptions; or
Patient must be undergoing continuing treatment with drug - the following are true: (i) there has been an absence of further disease progression whilst on active treatment with this drug, (ii) this prescription does not seek to re-treat after disease progression, (iii) this prescription seeks no more than 8 repeat prescriptions; or
Patient must be each of: (i) currently receiving non-PBS-subsidised supply for this drug for this PBS indication, (ii) free of disease progression since commencing on non-PBS-subsidised supply
~~**Population criteria:**~~
~~The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.~~
Prescribing Instructions: HER2-low is defined as an immunohistochemical [IHC] score of 1+ or an IHC score of 2+ and a negative result on in situ hybridisation [ISH]).
Prescribing Instructions: HER2-ultralow is defined as an immunohistochemical [IHC] score of 0 with membrane staining
Prescribing Instructions: Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription: 1) Evidence of HER2-low OR HER2-ultralow status 2) Details of prior drug regimens prescribed for the patient 3) Cardiac function test results
Prescribing Instructions: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg

2.2 The submission requested a special pricing arrangement (SPA). The proposed effective ex-manufacturer price per 100 mg vial of T-DXd was $[redacted], compared with the approved effective price of $[redacted] per 100 mg vial (intended $[redacted] through the Risk Sharing Arrangement) for use of T-DXd for HER2-low BC following chemotherapy (in a later-line treatment setting).

2.3 The proposed PBS restrictions for T-DXd did not align with the eligibility criteria of the pivotal DB-06 trial:

- In DB-06, patients had to have disease progression within 6 months after starting ET + cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) as the first-line treatment for metastatic disease[i] or have disease progression on at least two previous lines of ET[ii] with or without a targeted therapy in the metastatic setting to be eligible. The proposed PBS restriction only requires that patients are no longer eligible for ET following at least one prior line of ET. Patients in DB-06 may have more advanced disease compared with those eligible according to the proposed restriction. The Pre-Sub-Committee-Response (PSCR) stated that the proposed restriction aligned with Australian clinical practice and international

[i] In DB-06, 89.3% of the intent-to-treat (ITT) population had had at least one prior line of CDK4/6i + ET in the metastatic setting.

[ii] In DB-06, 67.6% of the ITT population had had 2 prior lines of ET, and 15.4% had had ≥ 3 prior lines of ET in the metastatic setting.

guidelines. The PSCR argued that requiring additional lines of ET was not consistent with clinical practice and could create treatment delays. The Sub-Committees advised that the sponsor's proposed criteria (one prior ET in the metastatic setting and unsuitable for further were ET) were reasonable and would capture the appropriate population for treatment as per clinical guidelines.

- DB-06 only enrolled chemotherapy naïve patients, however the proposed restriction did not require no prior chemotherapy in the metastatic setting. The PSCR stated that the sponsor is amenable to the addition of "no prior chemotherapy for metastatic disease' to the proposed restriction. The Sub-Committees considered that this addition was reasonable.

2.4 T-DXd is currently listed on the PBS for patients with unresectable and/or metastatic HR-positive HER2-low BC who have received ET or are ineligible for ET in the metastatic setting and have either (1) disease progression during or within 6 months of completing adjuvant chemotherapy, or (2) disease progression on a prior chemotherapy in the metastatic setting. A flow-on change to the current listing of T-DXd may be needed to avoid re-treatment, if T-DXd is listed for the proposed population (i.e., HR-positive HER2-low or HER2-ultralow unresectable and/or metastatic BC).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Population and disease

3.1 BC is the second most commonly diagnosed cancer in Australia (following prostate cancer) and is the most commonly diagnosed cancer in Australian women. In 2025, an estimated 20,336 new cases of BC were diagnosed (207 males and 20,129 females) and 3,353 died from the cancer (40 males and 3,313 females)[iii]. The median age of diagnosis among non-Aboriginal and Torres Strait Islander women was 61 years, with an overall 5-year survival rate of 93% in 2017 to 2021 (improved from 75% in 1987 to 1991). Despite this overall high survival rate, the 5-year survival rate for patients diagnosed with metastatic breast cancer (mBC) was reported to be an average of 32%[iv]. Aboriginal and Torres Strait Islander women were diagnosed with BC at a

[iii] Cancer Australia. Breast cancer in Australia statistics. URL: https://www.canceraustralia.gov.au/cancer-types/breast-cancer/breast-cancer-australia-statistics

[iv] Australian Institute of Health and Welfare. Cancer data in Australia. URL: https://www.aihw.gov.au/getmedia/ea870f59-a9e4-4772-8fa8-e1206b56a552/cancer-data-in-australia.pdf?v=20250120122647&inline=true

younger median age (56 years), and the age-adjusted mortality was 1.3 times the rate of non-Indigenous women[v,vi].

3.2 BC is a heterogenous disease, and the prognosis largely relies on the pathological and molecular characterisation of the disease[vii,viii]. HR (including estrogen receptor [ER] and progesterone receptor [PR]) and HER2 are important prognostic and therapeutic predictive factors for invasive BC. The majority of BC are HR-positive, accounting for approximately 80% of the cases[ix]. HR-positive BCs can be treated with ET, including aromatase inhibitors (AIs). HER2 expression has been traditionally categorised dichotomously as HER2-positive (defined as IHC 3+ staining of HER2 protein on cancer cells or IHC 2+ staining confirmed by a positive ISH testing for the HER2 gene amplification) or HER2-negative (defined as IHC 0 or IHC 1+, or IHC 2+ with a negative ISH testing for the HER2 gene amplification)[x]. HER2 is overexpressed in approximately 20% to 30% of all BCs and is associated with aggressive tumour behaviour, higher recurrence rates, shorter disease-free survival and overall survival without treatment[xi,xii].

3.3 The historical "HER2-negative" expression status has recently been identified as including HER2-low status, defined as IHC 1+ or IHC 2+ staining and a negative result of ISH[xiii,xiv], and HER2-ultralow status, defined as IHC > 0 but < 1+ (i.e., tumours with incomplete or faint/barely perceptible staining in ≤ 10% of BC cells)[xv]. The proportion

[v] Bergin ART, Marvelde, LT, *et al*. Aboriginal and Torres Strait Islander females and survival from breast cancer. *Cancer Epidemiol Biomarkers Prev* 2025; 34(7):1167-1176.

[vi] Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2025: Mortality from breast cancer for Aboriginal and Torres Strait Islander women. URL: https://www.aihw.gov.au/reports/cancer-screening/breastscreen-australia-monitoring-report-2025/contents/outcomes-aboriginal-torres-strait-islander-women/mortality-from-breast-cancer

[vii] Pourzand et al. Hormone receptor status in breast cancer and its relation to age and other prognostic factors. *Breast Cancer (Auckl)* 2011;5:87-92.

[viii] Wen et al. Effect of clinical and treatment factors on survival outcomes of triple negative breast cancer patients. *Breast Cancer (Dove Med Press)* 2020;12:27-35.

[ix] Praise et al. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999-2004. *Breast J* 2009;15(6):593-602.

[x] Wolff et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol* 2018;36(20):2105-2122.

[xi] Orrantia-Borunda et al. Subtypes of breast cancer. *Breast Cancer.* Brisbane (AU) 2022. ISBN 978-0-6453320-3-2.

[xii] Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER2/neu oncogene. *Science* 1987;235(4785):177-182.

[xiii] Schettini et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer* 2021;7(1). DOI 10.1038/s41523-020-00208-2

[xiv] Tarantino et al. HER2-low breast cancer: Pathological and clinical landscape. *J Clin Oncol* 2020;38(17):1951-1962.

[xv] Nakada et al. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull* 2019;67:173-185.

of HER2-low BC was found to be 65.4% in HR-positive cases and 36.6% in triple negative breast cancers (TNBCs)[10]. HER2-ultralow BC was found in 29% of the HER2-negative BCs in a Chinese study and 35-40% in a US study[xvi,xvii].

3.4 The DB-04 trial reported a significantly prolonged survival in patients with HR-positive HER2-low mBC treated with T-DXd following chemotherapy[xviii]. The DB-06 trial (presented as key evidence in the submission) further investigated the survival benefit of T-DXd in chemotherapy naïve patients with HR-positive HER2-low or HER2-ultralow unresectable and/or mBC.

3.5 T-DXd is an antibody drug conjugate (ADC) that is HER2-directed and acts through dual mechanisms: firstly, the monoclonal antibody of the ADC binds to the HER2 receptors, which leads to the inhibition of the protein kinase B (PKB, also known as Akt) phosphorylation by interrupting the phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway. Secondly, the topoisomerase 1 inhibitor's payload permeates the cell nucleus and acts to stop the re-ligation of deoxyribonucleic acid (DNA), leading to strand breaks and cell death, resulting in apoptosis of the target tumour cell. The topoisomerase 1 inhibitor payload also acts on neighbouring tumour cells via membrane permeability.

3.6 The submission proposed T-DXd use in the second line setting (i.e., prior to chemotherapy) for patients with HR-positive HER2-low or HR-positive HER2-ultralow unresectable and/or mBC who have received at least one prior line of ET in the metastatic setting and are no longer considered suitable for further ET.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Comparator

4.1 The submission nominated ICC (as a proxy of single-agent chemotherapy) as the main comparator. The selection of the main comparator was appropriate.

4.2 Single-agent chemotherapies used in the key trial DB-06 and in the economic model included oral capecitabine and intravenous (IV) paclitaxel and nab-paclitaxel. However, in the financial analysis, it was assumed that T-DXd will replace IV chemotherapy options but not oral capecitabine. Based on the data from the PBS sample, it was estimated that approximately 70% of mBC patients receive oral capecitabine, but only 30% of patients choose to receive IV chemotherapy as the post-

[xvi] Chen et al. Is HER2 ultra-low breast cancer different from HER2 null or HER2 low breast cancer? A study of 1363 patients. *Breast Cancer Res Treat* 2023;202(2):313-323.
[xvii] Mehta et al. Prevalence of "HER2 ultra-low" among patients with advanced breast cancer with historical IHC0 status. *J Clin Oncol* 2024;42(16_suppl): e13156.
[xviii] Modi et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022;387(1): 9-20.

ET chemotherapy in the second line treatment setting; whilst in the third line setting 53.8% of patients choose oral capecitabine and 46.2% choose IV chemotherapy. The submission argued that, according to medical oncologists, patients with disease that is not aggressive and patients who are feeling otherwise well or are still in paid employment may prefer oral capecitabine because of the convenience, perceived efficacy, and the lower impact on quality of life associated with oral chemotherapy. For other patients, especially those who have received oral therapies (e.g. AI plus CDK4/6i) in the prior line, alopecia associated with IV chemotherapy may be a key concern. However, a patient's preference between IV chemotherapy and oral chemotherapy may not be applicable to IV T-DXd versus oral chemotherapy. Patients with metastatic disease who have failed prior ET may opt for IV T-DXd rather than oral capecitabine if T-DXd shows benefits in terms of progression-free survival (PFS) and overall survival (OS) (as per the superior efficacy claim in the submission). The Sub-Committees also considered that for some patients there may be a preference to receive the more toxic drug (T-DXd) earlier, as they may be better able to tolerate treatment in the earlier line, reserving oral capecitabine for a later line of therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Consideration of the evidence

Sponsor Hearing

5.1 The sponsor provided a written hearing statement for this item. The clinician outlined the significance of improved PFS for patients treated with T-DXd and stated that T-DXd would be a useful addition to the suite of new agents which are emerging for patients with mBC. The hearing largely focused on the preference for patient and clinician choice to determining the order of treatments for mBC. The clinician noted that earlier use of a more intense regimen such as T-DXd may be preferred in patients with good hepatic and bone marrow function as patients may not be well enough to tolerate it after IV chemotherapy, whereas other patients may prefer an oral therapy to enable travel and work with fewer side effects. The clinician noted that there was an increased risk of interstitial lung disease (ILD) with T-DXd, but stated that clinicians are now familiar with the need for monitoring and early intervention if this occurs.

Consumer input

5.2 The PBAC noted and welcomed the input from a health care professional (1) and organisations (2) via the Office of Health Technology Assessment Consultation Hub. The input from the health professional highlighted the importance of ensuring PBS-subsided options to ensure choice based on clinical considerations and the need for shared decision making to tailor treatment to patient needs. The health professional noted that T-DXd offers rapid and meaningful tumour shrinkage, setting it apart from the other 2L options, and that by extending the duration of disease control in 2L, more

options are likely to become available in 3L with further gradual improvements in OS. The input noted that high response rates and improved PFS is important for patients with visceral disease who require fast treatment response. The input also noted that nausea and vomiting were relevant considerations for patients and that they could be hard to control for some patients.

5.3 The PBAC noted the advice received from Metastatic Breast Cancer Action Australia (MBCAA), which described the burden of mBC on many aspects of life. The input noted that patients would like to have choice regarding the order of treatments and the preference to avoid or delay chemotherapy for as long as possible. Comments noted that chemotherapy is perceived as less effective and with a higher side-effect burden than T-DXd. However MBCAA also noted the disadvantages of T-DXd being the safety profile and side effects, the potential for misclassification of HER2-low and HER2-ultralow pathology, and the need for IV administration (particularly affecting regional patients). The PBAC also noted the advice received from Rare Cancers Australia (RCA), which highlighted the significant challenges experienced by patients with mBC, including the burden of treatment. RCA noted that patients treated with T-DXd reported side effects were usually temporary and manageable. although some side effects of T-DXd may stop some patients from continuing treatment, though many patients still consider these risks acceptable as compared to chemotherapy.

Clinical trials

5.4 The submission was based on one head-to-head open-label Phase 3 randomised trial (DB-06, N=866) comparing T-DXd with ICC in HER2-low (IHC1+ and IHC2+/ISH-; N=713) and HER2-ultralow (IHC> 0 <1+ expression; N=152), HR-positive BC patients whose disease had progressed on ET in the metastatic setting. The ICC comparator arm was single-agent chemotherapy (either capecitabine, nab-paclitaxel, or paclitaxel). Anthracyclines were not considered an appropriate choice for the comparator arm in DB-06 due to the cumulative risk of cardiotoxicity associated with these agents.

5.5 Details of the DB-06 trial and associated reports presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Study report dates/Publication citation
DB-06	Clinical study report: A Phase 3, Randomised, Multi-centre, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice of Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06). Data cutoffs 18 March 2024 (Interim Analysis 1 [IA1]) and 24 March 2025 (Interim Analysis 2 [IA2])	IA1: November 2024 IA2: July 2025
	Bardia, A., et al. Trastuzumab deruxtecan (T-DXd; DS-8201) vs investigator's choice of chemotherapy in patients with hormone receptor positive (HR-positive), HER2 low metastatic breast cancer whose disease has progressed on endocrine therapy in the metastatic setting: A randomised, global phase 3 trial (DESTINY-Breast06).	*Cancer Research* 2021; 81(4 SUPPL):
	Bardia, A., et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer.	*New England Journal of Medicine* 2024; 391(22): 2110-2122.
	Barrios, C. H. E., et al. 299MO DESTINY-Breast06 (DB-06) post-hoc analysis by physician's choice of chemotherapy (TPC) - Efficacy and safety of trastuzumab deruxtecan (T-DXd) vs TPC in hormone receptor positive (HR-positive), HER2-low or -ultralow metastatic breast cancer (mBC).	*ESMO Open* May 2025;10(Suppl.4).
	Hu, X., et al. Patient-reported outcomes with trastuzumab deruxtecan in hormone receptor positive, HER2-low or HER2-ultralow metastatic breast cancer: results from the randomised DESTINY-Breast06 trial.	*ESMO Open* May 2025;10(5):105082
	Hu, X., et al. LBA22 Effects of trastuzumab deruxtecan (T-DXd) vs choice of chemotherapy (TPC) on patient-reported outcomes (PROs) in hormone receptor positive, HER2-low or HER2-ultralow metastatic breast cancer (mBC): Results from DESTINY-Breast06.	*Annals of Oncology* 2025; 35(S2): S1214-S1215.
	Salgado, R. F., et al. LBA21 Human epidermal growth factor receptor 2 (HER2)-low and HER2-ultralow status determination in tumors of patients (pts) with hormone receptor positive (HR-positive) metastatic breast cancer (mBC) in DESTINY-Breast06 (DB-06).	*Annals of Oncology* 2024; 35: (S2) S1213-S1214
	Curigliano, G, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast06 (DB-06).	*Journal of Clinical Oncology* 2024;42(17): ASCO Annual Meeting 2024 LBA1000

Source: Table 2.3, pp50-51 of the submission

5.6 The key features of the DB-06 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/Median duration of follow up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Trastuzumab deruxtecan (T-DXd) vs. investigator's choice of chemotherapy (ICC)						
DB-06	ITT 866	R, OL[a], MC Treatment until disease progression/unacceptable toxicity. IA1: T-DXd 18.6 months ICC 17.8 months IA2: T-DXd 27.6 months ICC 25.0 months	Low for OS High for PFS High for QoL High for safety	HR+/HER2- mBC with prior ET and/or CDK4/6i therapy and not suitable for further ET	Primary endpoint: PFS by BICR Secondary endpoints: OS, ORR, DOR, PRO Safety	PFS, OS, safety

Source: Sections 2.3 -2.4 of the submission and interim analyses reports accompanying the submission.
BICR = Blinded Independent Central Review; CDK = cyclin-dependent kinase; DB = double blind; DCO = data cutoff; DOR = duration of response; ET = endocrine therapy; IA = Interim Analysis; ITT = intention to treat; mBC = metastatic breast cancer; MC = multi-centre; OL = open-label; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; QoL = quality of life; R = randomised.
[a] Sponsor was 'blinded' to allocation.
IA1: DCO March 2024
IA2: DCO March 2025

5.7 DB-06 was an open-label trial for personnel at study sites, but the study was described as 'sponsor blind'[xix]. The risk of bias remains high for investigator assessed PFS, quality of life (QoL) outcomes, and safety.

5.8 Results for two data cutoffs (DCOs) were available in the clinical study reports (CSRs) accompanying the main submission. Interim analysis 1 (IA1) based on the March 2024 DCO and Interim analysis 2 (IA2) based on the March 2025 DCO.

5.9 Although DB-06 enrolled both HER2-low and HER2-ultralow BC patients (one of the stratification factors), the primary analysis per the DB-06 protocol was based on PFS as assessed by blinded independent central review (BICR) in the HER2-low subgroup (~82% of the intention to treat [ITT] population). As the proposed target population consists of both HER2-low and HER2-ultralow BC patients, and the relevant outcome is OS, OS in the ITT population for the more recent DCO is the most informative analysis.

5.10 Inclusion criteria of the clinical trial included disease progression on ET + CDK4/6i within 6 months of starting first-line treatment for metastatic disease and considered appropriate for chemotherapy as the next treatment by the investigator (i.e., primary ET resistance) or disease progression on at least 2 previous lines of ET (with or without a targeted therapy) in the metastatic setting. Disease recurrence while on the first 24 months of starting adjuvant ET was considered a line of therapy and these patients only required 1 line of ET in the metastatic setting.

[xix] The DB-06 clinical study report noted that sponsor personnel involved in the study did not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint.

5.11 An applicability issue is that only 34% of patients in the ICC comparator arm who received subsequent anti-cancer therapies went on to receive T-DXd. Given the current PBS listing of T-DXd for later line use in HER2-low patients, use of T-DXd following progression in the ICC arm of the trial may be low compared with clinical practice. The submission attempted to address this issue in the economic evaluation.

Comparative effectiveness

5.12 Table 4 summarises the pre-specified primary analysis of PFS by BICR in the HER2-low subgroup (82.3% of the ITT population). The corresponding Kaplan-Meier (KM) curves are presented in Figure 1.

Table 4: PFS by BICR in the HER2-low population (IA1 - pre-specified primary analysis in the DB-06 trial)

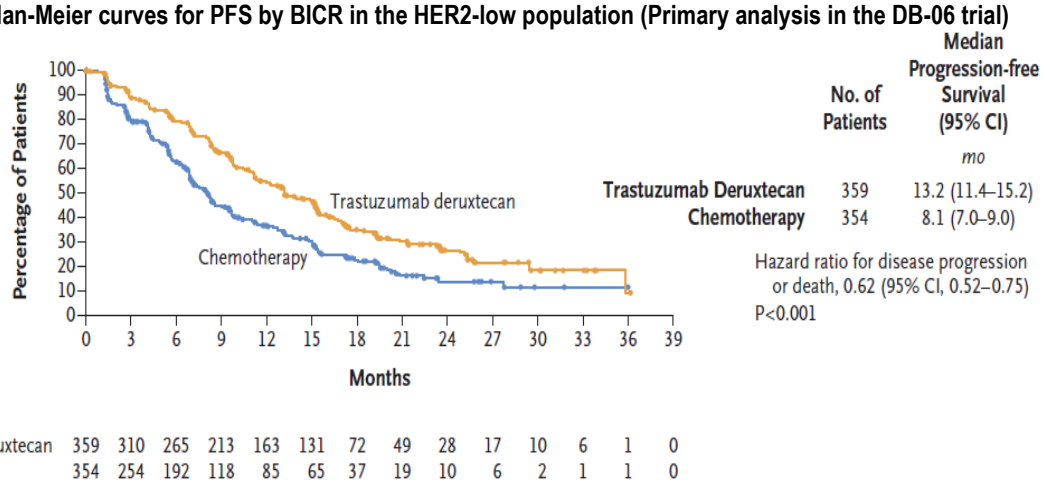
	T-DXd (N=359)	ICC (N=354)
Total PFS events n (%) RECIST progression Death in the absence of progression	225 (62.7) 212 (59.1) 13 (3.6)	232 (65.5) 219 (61.9) 13 (3.7)
Censored patients n (%)	134 (37.3)	122 (34.5)
• Censored death	24 (6.7)	25 (7.1)
• Censored progression free	98 (27.3)	71 (20.1)
• Other including withdrawn consent	12 (3.4)	26 (7.3)
Median PFS, months (95% CI)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)
Hazard ratio (95% CI)	0.62 (0.52, 0.75); p=<0.0001	

Source: Table 2-13, p76 of the submission

BICR = Blinded Independent Central Review, CI = confidence interval, HER2 = human epidermal growth factor receptor 2, IA = Interim analysis; ICC = investigator's choice of chemotherapy; PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan

IA1: DCO March 2024. Median follow up durations of 19.0 months and 18.3 months in the T-DXd and ICC arms, respectively

Figure 1: Kaplan-Meier curves for PFS by BICR in the HER2-low population (Primary analysis in the DB-06 trial)



Source: Figure 2-4, p74 of the submission

BICR = blinded independent central review; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; PFS = progression-free survival

Interim analysis 1, DCO March 2024

5.13 The T-DXd arm showed a statistically significant improvement in PFS at the March 2024 DCO for the primary analysis with median follow up durations of 19.0 months and 18.3 months in the T-DXd and ICC arms, respectively. The median PFS duration (95% confidence interval [CI]) was 13.2 (11.4, 15.2) months in the T-DXd arm and 8.1 (7.0, 9.0) months in the ICC arm. This corresponded to a 38% reduction in the hazard of progression or death associated with T-DXd (hazard ratio: 0.62; 95% CI: 0.52, 0.75; p <0.0001).

5.14 The benefit was apparent by one month and the KM curves were separated during the treatment period. Although a third of the patients were censored at the primary analysis, updated PFS data for IA2 (March 2025 DCO) were similar.

5.15 The subgroup analysis of PFS (BICR) in the HER2-ultralow subgroup is also relevant to the proposed target population. The analysis showed a median PFS duration of 13.2 months in the T-DXd arm (N=76) versus 8.3 months in the ICC arm (N=76). This difference corresponded to a 22% reduction in the hazard of progression or death which was not statistically significant (hazard ratio: 0.78; 95%CI: 0.50, 1.21). Despite the lack of statistical significance, the observed median PFS durations and the difference between the arms were similar to the primary analysis in the complement HER2-low subgroup. There was also substantial overlap in the 95% CIs for the hazard ratios between the HER2-low and HER2-ultralow subgroups.

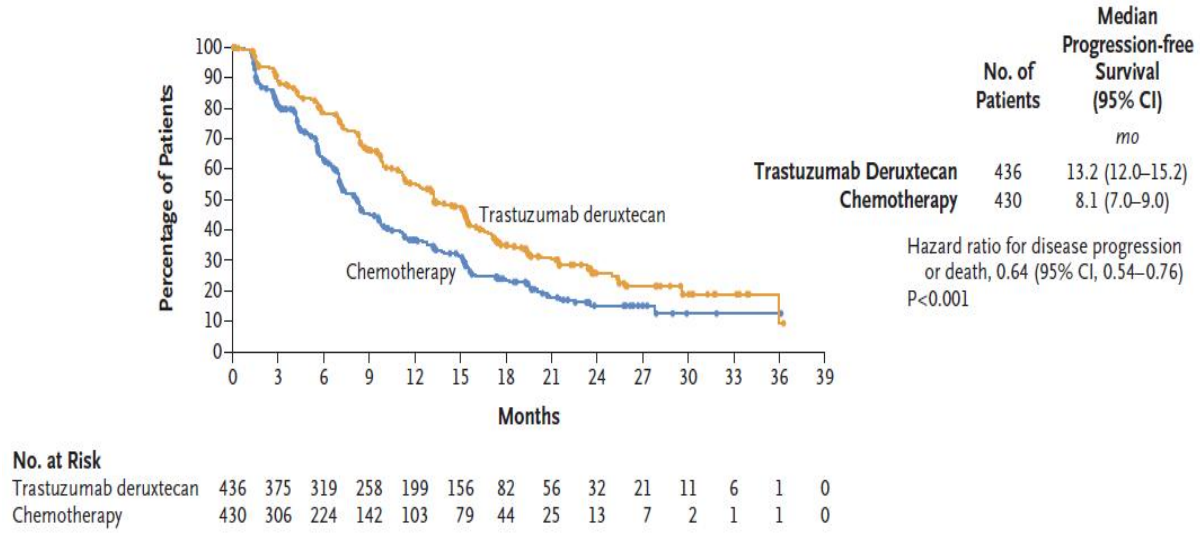
5.16 Results for the ITT analysis of PFS (BICR) are presented in Table 5, with corresponding KM curves presented in Figure 2.

Table 5: IA1 - PFS by BICR in the ITT population (FAS) (key secondary endpoint in DB-06)

	T-DXd (N=436)	ICC (N=430)
Total PFS events n (%) RECIST progression Death in the absence of progression	269 (61.7) 254 (58.3) 15 (3.4)	271 (63.0) 257 (59.8) 14 (3.3)
Censored patients n (%)	167 (38.3)	159 (37.0)
Median PFS, months (95% CI)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)
Hazard ratio (95% CI)	0.64 (0.54, 0.76); p<0.0001	

Source: Table 2-13, p76 of the submission.
BICR = blinded independent central review; CI = confidence interval, FAS = full analysis set, ICC = investigator's choice of chemotherapy; IA = interim analysis; ITT = intention-to-treat; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
Data cutoff March 2024. Median follow up durations of 18.6 months and 17.8 months in the T-DXd and chemotherapy arms, respectively

Figure 2: IA1 - Kaplan-Meier analysis of PFS by BICR (ITT population of the DB-06 trial)



Source: Figure 2-6, p76 of the submission
BICR = blinded independent central review; CI = confidence interval; ITT = intention to treat, PFS = progression-free survival

5.17 Results of the ITT analysis were similar to that of the HER2-low subgroup. This is expected as HER2-low patients made up more than 80% of the ITT population. T-DXd was associated with a statistically significant PFS benefit (by BICR) compared to ICC. The point estimates of the median PFS durations across the arms were identical to those for HER2-low patients (T-DXd: 13.2 months [95% CI: 12.0, 15.2]; ICC: 8.1 months [95% CI: 7.0, 9.0]). This corresponded to a 36% reduction in the hazard of progression or death associated with T-DXd (hazard ratio: 0.64; 95% CI: 0.54, 0.76; p <0.0001).

5.18 Compared to PFS by BICR, results for PFS (investigator assessment) in the ITT population showed a larger reduction (49%) in the hazard of progression or death associated with T-DXd compared with ICC (hazard ratio: 0.51; 95% CI: 0.44, 0.60). This may be due to the open-label design of the trial.

5.19 OS data for the ITT population were available for two DCOs in the DB-06 CSRs provided with the submission:

- DCO 18 March 2024 (IA1): median follow up durations of 18.6 months and 17.8 months in the T-DXd and ICC arms, respectively. OS data were 38.7% mature (335 events/866 patients).
- DCO 24 March 2025 (IA2): median follow up durations of 27.6 months and 25.0 months in the T-DXd and chemotherapy arms, respectively. OS data were 56.0% mature (485 events/866 patients).

The Sub-Committees noted that the OS data were immature at the time of the submission.

5.20 The final OS analysis will be performed when approximately 521 OS events have been observed in the HER2-low population (74% maturity), which is expected to occur approximately 63 months after the first patient is randomised. At this time, it is

estimated that 632 OS events will have been observed in the ITT population (Clinical Study Protocol – 5.0). These data will be informative in the assessment of any long-term OS benefit. The PSCR noted that the final OS analysis is expected in the second half of 2026, though it is event-driven.

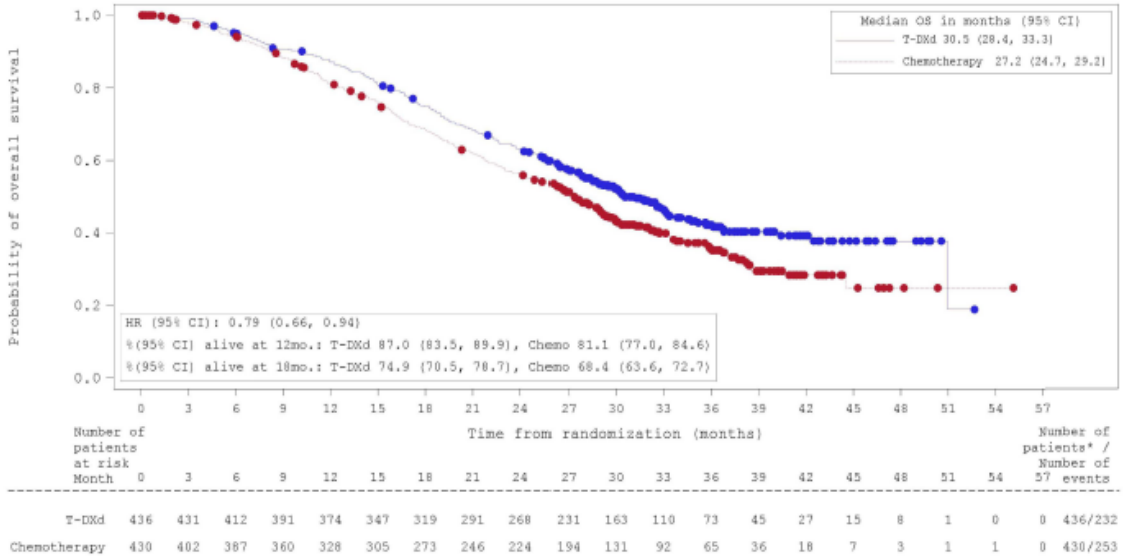
5.21 Results for OS in the ITT population (IA1 and IA2) are summarised in Table 6. The KM curves for IA2 are presented in Figure 3.

Table 6: OS in the ITT population DB-06 Trial

	T-DXd (N=436)	ICC (N=430)
IA1. DCO March 2024. Median follow up	18.6 months	17.8 months
Deaths n (%)	161 (36.9)	174 (40.5)
Censored patients n (%)	275 (63.1)	256 (59.5)
Median OS months (95% CI)	28.9 (26.4, 32.7)	27.4 (23.9, 29.9)
Hazard ratio (95% CI)	0.81 (0.66, 1.01)	
IA2. DCO March 2025. Median follow up	27.6 months	25.0 months
Deaths n (%)	232 (53.2)	253 (58.8)
Censored patients n (%)	204 (46.8)	177 (41.2)
Median OS months (95% CI)	30.5 (28.4, 33.3)	27.2 (24.7, 29.2)
Hazard ratio (95% CI)	0.79 (0.66, 0.94)	
12-month landmark survival, % (95% CI)	87.0 (83.5, 89.9)	81.1 (77.0, 84.6)
18-month landmark survival, % (95% CI)	74.9 (70.5, 78.7)	68.4 (63.6, 72.7)

Source: Table 2-18, p82 and Table 2-21, p85 of the submission
CI = confidence interval, DCO = data cutoff; IA = interim analysis; ICC = investigator's choice of chemotherapy; ITT = intention to treat; OS = overall survival, T-DXd = trastuzumab deruxtecan

Figure 3: IA2 - Kaplan-Meier analysis of OS (ITT population) DB-06



Source: Figure 2-14, p86 of the submission.
CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival; T-DXd = trastuzumab deruxtecan.
Median follow up durations of 27.6 months and 25.0 months in the T-DXd and chemotherapy arms, respectively
Dot (blue in the T-DXd arm and red in the chemotherapy arm) indicates a censored observation.

5.22 The OS results were similar between IA1 and IA2.

5.23 At IA1, the median OS was 28.9 months in the T-DXd arm versus 27.4 months in the ICC arm which corresponded to a 19% reduction in the hazard of death associated with T-DXd which was not statistically significant (hazard ratio: 0.83; 95%CI: 0.66, 1.05). The KM curves for OS indicated there was only a slight separation during follow-up although there was no sign of a detrimental effect.

5.24 At IA2, the median OS was 30.5 months in the T-DXd arm versus 27.2 months in the ICC arm. This difference corresponded to a 21% reduction in the hazard of death associated with T-DXd (hazard ratio: 0.79; 95%CI: 0.66, 0.94). Per the multiple testing procedure (MTP), OS hypothesis in the ITT population was not formally tested for statistical significance. Landmark analysis at 18 months indicated that 74.9% of patients were alive in the T-DXd arm versus 68.4% of patients in the ICC arm. Separation between the OS KM curves during the follow-up period appeared modest.

5.25 OS results by HER2-low and HER2-ultralow subgroups for the IA2 DCO are summarised in Table 7.

Table 7: IA2 (DCO March 2025) – OS results by HER2-low and HER2-ultralow subgroups

Subgroup	Treatment arms	N	Median OS , months (95% CI)	18-month landmark analysis, %, (95% CI)	Hazard ratio (95% CI) [a]
HER2-low population	T-DXd	359	30.4 (26.4, 34.2)	74.0 (69.1, 78.3)	0.81 (0.67, 0.99)
	ICC	354	27.1 (24.4, 29.3)	69.0 (63.7, 73.6)	
HER2-ultralow population	T-DXd	76	30.2 (28.4, NE)	78.7 (67.6, 86.4)	0.70 (0.45, 1.09)
	ICC	76	27.2 (19.9, 35.9)	65.8 (53.4, 75.6)	

Source: p26, Table 3, p27, and Table 2-21, p85 of the submission

CI = confidence interval, DCO = data cutoff; IA = interim analysis; ICC = investigator's choice of chemotherapy; HER2 = human epidermal growth factor receptor 2; ITT = intention to treat; NE = not estimable; OS = overall survival; T-DXd = trastuzumab deruxtecan

[a] Calculated using the Kaplan-Meier technique. CI for median was derived based on Brookmeyer-Crowley method.

5.26 Median duration of follow-up: 27.6 months in the T-DXd arm and 25.2 months in the ICC arm The OS results were similar between the HER2-low and HER2-ultralow. The HER2-ultralow subgroup analysis was imprecise and the 95% CIs of the reduction in hazard of death between the HER2-low (19% reduction) and HER2-ultralow (30% reduction) overlapped. The Sub-Committees noted that the results for the IA2 analysis remained non-robust, given the limited sample size of the ultralow patients.

5.27 Other secondary endpoints included PFS2[xx], objective response rate (ORR), and patient reported outcomes (PROs).

5.28 In the absence of fully mature OS data, PFS2 data for the ITT population may be clinically relevant. For the IA2 analysis, there were 327 PFS2 events in the T-DXd arm compared with 351 events in the ICC arm (DB-06 IA2 CSR). The median PFS2 in the T-DXd arm was 20.0 months versus 14.7 months in the ICC arm (HR 0.66; 95% CI: 0.57, 0.77; nominal p-value <0.0001). These results can cautiously be interpreted as reassuring in that patients treated with T-DXd appeared to have a longer time to second progression on further-line therapy, and, therefore, it would be expected that there would not be a significant detriment to OS. However, these conclusions are

[xx] Time from randomisation to second progression or death.

based on a descriptive analysis and more mature OS data are required to assess any relative treatment effect on OS.

5.29 Confirmed[xxi] ORR by BICR in the ITT population (DCO March 2024) was 57.3% in the T-DXd arm and 31.2% in the ICC arm (DB-06 IA1 CSR). These results were consistent with those observed in the HER2-low and HER2-ultralow subgroups.

5.30 The median duration of response (DoR) by BICR in the ITT population (DCO March 2024) was 13.7 months in the T-DXd arm versus 7.3 months in the ICC arm (DB-06 IA1 CSR). These results were consistent with those observed in the HER2-low and HER2-ultralow subgroups.

5.31 PROs relating to QoL were measured using the change from baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the breast cancer specific module EORTC QLQ-BR45. Overall, there was no clear improvement in QoL between the T-DXd and ICC arms despite the open-label nature of the DB-06 study design. The Guideline on the Clinical Evaluation of Anticancer Medicinal Products (EMA/CHMP/205/95 Rev.6) advises that where PFS is used as the primary outcome measure, and there is no significant difference in OS, that there should be some additional benefit to quality of life (Submission PM-2024-04768-1-4 Clinical Evaluation Report for ENHERTU).

5.32 The mean change from baseline over time using a Mixed Model for Repeated Measures (MMRM) showed no differences between treatment arms in the EORTC QLQ-C30 Global Health Status (GHS)/QoL and functional scales and EORTC QLQ-BR45 functional scales. There were higher scores for nausea and constipation in the T-DXd arm compared to the ICC arm, which for nausea and vomiting was considered clinically meaningful (TGA Submission PM-2024-04768-1-4 Clinical Evaluation Report for ENHERTU, Round 2). However, arm, breast, and endocrine symptoms decreased with T-DXd arm relative to ICC. The Sub-Committees also noted consumer input indicated that nausea and vomiting were relevant considerations for patients and that they could be hard to control for some patients.

5.33 For time to deterioration in EORTC QLQ-C30, except for GHS/QoL which were comparable between the two treatment arms (10.3 months for T-DXd compared to 9.9 months for ICC), median times to deterioration for physical functioning, role functioning and pain were longer in the T-DXd arm than in the ICC arm (18.0 compared to 9.9 months, 9.8 compared to 4.3 months, and 21.4 compared to 6.1 months, for physical functioning, role functioning and pain, respectively).

5.34 Interpretation of these outcomes is limited primarily by the open-label nature of the trial and compliance rates. Overall, there was no clear improvement in QoL with T-DXd over ICC.

[xxi] The percentage of patients who achieve a complete response (CR) or partial response (PR) on their initial scan and maintain that response on a subsequent scan, typically 4 or more weeks later.

Comparative harms

5.35 Adverse events (AEs) by category in the safety analysis population (SAF) at the DCO for IA2 (March 2025) are presented in Table 8.

Table 8: AEs by category in the SAF population DB-06 Trial (DCO March 2025)

AE category	T-DXd (N=434) n (%)	ICC (N=417) n (%)
any AE	429 (98.8)	397 (95.2)
any AE possibly related to treatment	417 (96.1)	373 (89.4)
any CTCAE Grade ≥ 3	239 (55.1)	186 (44.6)
any CTCAE Grade ≥ 3 possibly related to treatment	182 (41.9)	132 (31.7)
any AE with outcome = death	11 (2.5)	6 (1.4)
any AE with outcome = death, possibly related to treatment	5 (1.2)	0 (0.0)
any SAE (includes AE with outcome = death)	90 (20.7)	67 (16.1)
any SAE (includes AE with outcome = death), possibly related to treatment	47 (10.8)	24 (5.8)
AE leading to discontinuation of study treatment, possibly related to treatment	64 (14.7)	35 (8.4)

Source: Table 10, p53 of the DB-06 IA2 Clinical Study Report (DCO March 2025)
AE = adverse event, CTCAE = Common Terminology Criteria Adverse Event, ICC = investigator's choice of chemotherapy; SAE = serious adverse event; SAF = safety analysis set; T-DXd = trastuzumab deruxtecan

5.36 The frequency of AEs was generally higher at the more recent DCO of March 2025 compared with the DCO of March 2024 (Table 2-26, p98 of the submission). Most patients in the T-DXd and ICC arms experienced at least one AE (98.8% vs. 95.2%). Approximately half of the patients had Grade 1 or 2 AEs. In the T-DXd arm, 55.1% of patients experienced a Common Terminology Criteria Adverse Event (CTCAE) of Grade ≥3 AEs, compared with 44.6% in the ICC arm. The frequency of any serious adverse events (SAEs) including death that was possibly related to treatment was almost two-fold in the T-DXd arm compared with the ICC arm (10.8% vs. 5.8%). The percentage of patients with an AE leading to discontinuation of study treatment, which were possibly related to treatment, was also higher in the T-DXd arm compared to the ICC arm (14.7% vs. 8.4%).

5.37 Table 9 summarises treatment-related AEs reported in at least 10% of patients in either treatment arm (non-exhaustive), by preferred term, in the DB-06 SAF population at DCO March 2024.

Table 9: Summary of treatment-related AEs reported in at least 10% of patients in either treatment arm (non-exhaustive), by preferred term, in the SAF population of the DB-06 trial (DCO March 2024)

AE Preferred Term	T-DXd (N=434) n (%)	ICC (N=417) n (%)
Nausea	286 (65.9)	98 (23.5)
Alopecia	197 (45.4)	81 (19.4)
Anaemia	118 (27.2)	78 (18.7)
Vomiting	118 (27.2)	39 (9.4)
Fatigue	108 (24.9)	73 (17.5)
Decreased appetite	102 (23.5)	39 (9.4)
Neutrophil count decreased	97 (22.4)	63 (15.1)
AST increased	96 (22.1)	35 (8.4)
WBC count decreased	75 (17.3)	48 (11.5)
ALT increased	73 (16.8)	38 (9.1)
Constipation	71 (16.4)	25 (6.0)
Platelet count decreased	56 (12.9)	11 (2.6)
Peripheral sensory neuropathy	9 (2.1)	46 (11.0)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.5)	135 (32.4)

Source: Table 2-18, p102 of the submission

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ICC = investigator's choice of chemotherapy; T-DXd = trastuzumab deruxtecan; WBC = white blood cell

5.38 For the March 2024 DCO, treatment-related gastrointestinal AEs were more common in the T-DXd arm versus the ICC arm (65.9% vs. 23.5% for nausea; 27.2% vs. 9.4% for vomiting; 23.5% vs. 9.4% for decreased appetite; and 16.4% vs. 6.0% for constipation). A higher frequency was also observed in the T-DXd arm for alopecia (45.4% vs. 19.4%), decreased platelet count (12.9% vs. 2.6%), and anaemia (27.2% vs. 18.7%). There was a higher frequency in the ICC arm for peripheral sensory neuropathy (11.0% vs. 2.1% in T-DXd) and palmar-plantar erythrodysaesthesia syndrome (32.4% vs. 0.5% in T-DXd). A similar trend was observed for AEs in general (including AEs related or not related to treatment).

5.39 Safety data regarding the frequency of ILD/pneumonitis were sourced from the IA2 (DCO March 2025) CSR. A total of 82 patients (18.9%) in the T-DXd arm and 5 patients (1.2%) in the ICC arm had events of potential ILD/pneumonitis. Events adjudicated as ILD occurred in 59 patients (13.6%) in the T-DXd arm and one patient (0.2%) in the ICC arm. Among these events, a total of 56 patients (12.9%) in the T-DXd arm and one patient (0.2%) in the ICC arm were considered as drug-related.

5.40 At IA2, the percentage of patients who had one or more AE of CTCAE Grade ≥ 3, considered possibly related to treatment by the investigator, was higher in the T-DXd arm (41.9%) than in the ICC arm (31.7%). AEs with the outcome of death were reported in 11 (2.5%) patients in the T-DXd arm and six (1.6%) patients in the ICC arm. Infections and infestations leading to death occurred in six (1.4%) patients in the T-DXd arm and one (0.2%) patient in the ICC arm. Interstitial lung disease, related to treatment, resulted in death in two (0.5%) patients in the T-DXd arm (Table 19, p69 of the IA2 CSR).

5.41 At IA2, SAEs were reported in 90 (20.7%) patients in the T-DXd arm and in 67 (16.1%) patients in the ICC arm. The two most frequently reported SAEs in the T-DXd arm were ILD (8 patients; 1.8%) and pneumonitis (8 patients; 1.8%) (Table 21, p71 of the IA2 CSR).

Benefits/harms

5.42 A summary of the comparative benefits and harms for T-DXd versus chemotherapy is presented in Table 10.

Table 10: Summary of comparative benefits (ITT population) and harms (safety population) for T-DXd versus ICC in DB-06

Benefits				
	T-DXd	**ICC**	**Absolute Difference**	**Hazard ratio (95% CI)**
Progression free survival[a] (Primary analysis IA1; DCO March 2024)				
Median duration of follow-up	18.6 months	17.8 months		
PFS events, n (%)	269/436 (61.7%)	271/430 (63.0%)	-	**0.64 (0.54, 0.76) p< 0.0001**
Median PFS, months (95% CI)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)	5.1	
PFS at 12 months (95% CI)	54.7 (49.6, 59.4)	36.9 (31.7, 42.0)	17.8%	
PFS at 18 months (95% CI)	35.1 (30.1, 40.3)	23.6 (18.8, 28.7)	11.5%	
PFS at 24 months (95% CI)	26.0 (20.7, 31.5)	15.3 (10.6, 20.8)	10.7%	
Overall survival (IA2; DCO March 2025)				
Median duration of follow-up	27.6 months	25.0 months	-	0.79 (0.66, 0.94) No formal statistical analysis
Deaths, n/N (%)	232/436 (53.2%)	253/430 (58.8%)		
Median OS, months (95% CI)	30.5 (28.4, 33.3)	27.2 (24.7, 29.2)	3.3	
Alive at 12 months (95% CI)	87.0 (83.5, 89.9)	81.1 (77.0, 84.6)	5.9%	
Alive at 18 months (95% CI)	74.9 (70.5, 78.7)	68.4 (63.6, 72.7)	6.5%	

Harms					
	T-DXd n/N	**ICC n/N**	**Event rate/100 patients**		**Absolute difference (T-DXd *vs.* ICC)**
Median duration of follow-up (IA2)	27.6 months	25.2 months	**T-DXd**	**ICC**	
CTCAE Grade ≥ 3 possibly related to drug	182/434	132/417	42	32	10
Any SAE, possibly related to treatment	47/434	24/417	11	6	5
Events adjudicated as ILD related to study drug	56/434	1/417	13	1	12

Source: Section 12.2.2 and Table 10, p53 of the DB-06 IA2 Clinical Study Report (DCO March 2025), Table 2-18, p102 and Table 2-26, p99 of the submission.

CI = confidence interval; CTCAE = Common Terminology Criteria Adverse Event; DCO = data cutoff; IA = Interim analysis; ICC = investigator's choice of chemotherapy; ILD = interstitial lung disease; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan.

[a] Landmark analyses for PFS by BICR were provided in the PSCR

5.43 Based on direct evidence presented by the submission, for every 100 patients with HR-positive HER2-low or HER2-ultralow metastatic BC, who had progressed on standard of care and were not suitable for further ET therapy, treated with T-DXd instead of single-agent chemotherapy:

- Approximately 18 additional patients will remain progression free at 12 months, and 11 additional patients at 24 months (median follow-up of 18-19 months).
- Approximately 7 additional patients will remain alive at 18 months (median follow-up of 25-28 months). OS results were not formally tested for statistical significance.

5.44 Based on direct evidence presented by the submission in patients with HR-positive HER2-low or HER2-ultralow metastatic BC, who had progressed on standard of care and not suitable for further ET therapy (median follow-up of 25-28 months), treated with T-DXd instead of single-agent chemotherapy:

- Approximately 10 additional patients would experience a Grade ≥ 3 AE possibly related to T-DXd.
- Approximately 5 additional patients would experience a SAE (includes fatal AE) possibly related to T-DXd.
- Approximately 12 additional patients would experience a lung event which causes inflammation or scarring in the lung.

Clinical claim

5.45 The submission described T-DXd as superior in terms of effectiveness compared with chemotherapy and inferior but with a manageable safety profile compared with chemotherapy. The Sub-Committees noted that T-DXd demonstrated a modest increase in effectiveness in terms of PFS, unclear OS benefit, no clear QoL benefit, and a clear increase in associated harms, including life-threatening adverse events.

5.46 The Sub-Committees agreed with the evaluation that the therapeutic conclusion presented in the submission was partially supported by the evidence from the key DB-06 trial.

5.47 The DB-06 trial data showed that there was a PFS benefit associated with T-DXd relative to ICC. However, no significant benefit in OS was demonstrated as the OS hypothesis in the ITT population was not formally tested for statistical significance. Separation between the OS KM curves appeared modest, despite a lower-than-expected percentage of patients (approximately 34%) in the DB-06 ICC comparator arm who received subsequent therapy with T-DXd. The Sub-Committees considered that this resulted in a high degree of uncertainty determining the benefit of the proposed use of T-DXd. Patients who progress on chemotherapy are likely to gain some OS benefit from later-line T-DXd treatment in clinical practice.

5.48 The risk of AEs in general, including ILD and gastrointestinal AEs was much higher in the T-DXd arm. This AE risk should be considered in the context of a demonstrated PFS benefit associated with T-DXd, but unclear benefit in OS. There was no clear benefit in QoL from the DB-06 trial data. The PSCR stated that due to the availability of T-DXd on the PBS for other indications, clinicians were familiar with the early diagnosis and

treatment of ILD. The Sub-Committees considered that although clinicians are familiar with the use of T-DXd, AEs remain potentially life-threatening and are a relevant consideration in the context of the modest PFS and uncertain OS benefit T-DXd provides. The TGA Delegate's Overview stated that "the toxicities are significant, however, in the setting of this life-threatening and endocrine resistant disease, this treatment provides a therapeutic option that increases the duration of time before progression or death at a population level, at the cost of potentially manageable toxicity". The Sub-Committees noted consumer inputs indicated that patients may accept the risk of side effects where there is a potential efficacy benefit. The pre-PBAC response argued that clinicians are familiar with the early recognition and management of adverse events associated with T-DXd, as noted in the clinician hearing. The pre-PBAC response also cited real-world evidence[xxii] suggesting that AE rates observed in practice are lower than those reported in trials, including rates of ILD.

5.49 Other issues noted during the evaluation include:

- The open-label design of the DB-06 trial which may have impacted QoL and safety assessments in favour of T-DXd.
- The small sample size of the HER2-ultralow population (152 patients). The PSCR stated that while the HER2-ultralow subset is not powered for formal hypothesis testing, the internal consistency of benefit across the HER2-low and ITT populations supports the expectation of clinical benefit for all Australian patients eligible for treatment under the proposed listing.
- The challenges in Australian practice that pathologists may face which include a requirement for support, peer training, and practice to score consistently BC HER2 IHC patterns at the low end of the protein expression (Delegate's overview ENHERTU trastuzumab deruxtecan PM-2024-04768-1-4).

5.50 The PBAC considered that the claim of superior comparative effectiveness in the HER2 low population was reasonable for PFS, with a modest benefit shown, and uncertain for OS based on the data presented. The PBAC considered that the claim of superior comparative effectiveness in the HER2 ultra-low population was considerably less certain as the claim was based on data from a small subset of patient in the DB-06 trial.

5.51 The PBAC considered that the claim of inferior comparative safety in both populations was reasonable.

[xxii] Fountzilas et al. 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC12836521/

Economic analysis

5.52 The submission presented a modelled economic evaluation based on the key DB-06 trial, which compared T-DXd with ICC for the treatment of patients with HR-positive, HER2-low or HER2-ultralow mBC who have received at least one prior line of ET in the metastatic setting and are no longer considered suitable for ET.

5.53 The key components of the economic evaluation are summarised Table 11.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	T-DXd vs. ICC
Time horizon	15 years in the model base case vs. 27.6 months in the T-DXd arm and 25.0 months in the chemotherapy arm in the DB-06 trial
Outcomes	LYs gained, QALYs gained
Methods used to generate results	Partitioned survival model
Health states	PF, PD, death
Cycle length	3-weekly cycles
Allocation to health states	Health state allocation over time in the T-DXd and ICC arms was determined by the PFS and OS data from the DB-06 trial up to the truncation time point (18.0 months and 10.4 months for PFS in the T-DXd and ICC arms, respectively; 24.9 months for OS in both treatment arms). An upward adjustment was applied to the OS curve of the ICC arm to reflect the increased survival likely observed from increased subsequent T-DXd use in clinical practice, compared with that in the clinical trial.
Extrapolation method	PFS and OS were extrapolated using independent parametric functions fitted to the DB-06 trial data. The selection of extrapolation functions was based on goodness of fit to trial data based on AIC/BIC, visual inspection, and shape of hazard function over time. PFS was extrapolated using a log-logistic function for T-DXd and a log-normal function for ICC. A log-logistic distribution was chosen to extrapolate OS in both arms. Australian lifetables were applied after end of trial follow-up to capture all-cause mortality observed after the trial. LYs gained (undiscounted) in the extrapolation period: 54.8% for T-DXd and 50.2% for ICC, with 88.7% of the incremental LYs gained associated with T-DXd relative to ICC accrued during the extrapolation period.
Health related quality of life	PF: 0.8018 for T-DXd and 0.7666 for ICC, based on QoL data from DB-06 with utility scores generated from the Viney 2011 value set. PD: 0.5298 in both arms, by applying the utility decrement associated with disease progression of mBC reported in Lloyd et al 2006 (-0.272) to the PF utility score in the T-DXd arm Disutilities associated with AEs were not included in the base case analysis.

Source: Table 3.1, p120 of the submission.

AIC = Akaike information criterion; BIC = Bayesian information criterion; ICC = investigator's choice of chemotherapy; LYs = life years; mBC = metastatic breast cancer; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; QALYs = quality-adjusted life years; T-DXd = trastuzumab deruxtecan.

5.54 The economic model used a time horizon of 15 years in the base case analysis, considering the mean baseline age of the model patients (58.2 years), PFS and OS benefits associated with T-DXd as reported in the DB-06 trial, and the previous

capivasertib model (for treatment of PKT[xxiii]-pathway altered, HR-positive, HER2-negative, mBC following ET-based therapy). Other mBC economic models previously accepted by the PBAC had a shorter time horizon (5 – 10 years). When the capivasertib submission was reviewed, the ESC acknowledged that 15 years of survival may be clinically plausible for some patients, but considered that a shorter time horizon may be more appropriate given the short duration of follow-up for CAPItello-291 trial (14-15 months) and the high level of uncertainty with regard to longer term outcomes, particularly OS (para 6.59, capivasertib Public Summary Document (PSD), November 2024 PBAC meeting with Addendum March 2025 PBAC meeting). The PBAC advised that that the capivasertib submission's incremental cost-effectiveness ratio (ICER) was likely to be underestimated, primarily due to the optimistic assumptions in the model of OS benefit over a 15-year time horizon, along with other economic issues, and considered that capivasertib would be acceptably cost-effective at the substantially reduced proposed price, which it considered adequately addressed uncertainty in the cost-effectiveness (para 11.7, capivasertib PSD, November 2024 PBAC meeting with Addendum March 2025 PBAC meeting). The evaluation considered the final positive recommendation of listing capivasertib is unlikely to indicate that the 15-year time horizon was considered appropriate by the PBAC. With regard to the current T-DXd model, there were issues regarding the selection of parametric survival functions to extrapolate PFS and OS (paragraph 5.57) and the submission's method of adjustment for higher subsequent T-DXd use in the comparator arm (Paragraph 5.62). It is likely that adopting a shorter time horizon would reduce the uncertainty around extrapolations. The PSCR maintained that a 15 year time horizon is appropriate, as treatment is being used in earlier line settings with better prognoses and stronger evidence than in previous metastatic submissions. Consistent with its advice regarding the capivasertib submission, the Sub-Committees maintained that a 15 year time horizon was optimistic and a 5-10 year time horizon would be appropriate for this patient population (who have progressed on ET and CDK4/6i and would be expected to have a relatively poor prognosis) and in the context of uncertain OS benefit. The pre-PBAC response maintained that a 15-year horizon was justified, given the mean baseline age and based on studies indicating a substantial number of patients surviving post 10 and 15 years after diagnosis of mBC. The sponsor considered that the time horizon for DB-06 should be no shorter than 10 years based on DB-04.

5.55 The submission adopted a partitioned survival analysis model (PSM), in which the proportions of patients in individual health states per cycle were determined by PFS and OS estimates, estimated based on the KM data on PFS by investigator assessment and OS from the DB-06 trial at IA2 DCO. Based on the IA1 results, compared with PFS by BICR, PFS by investigator assessment reported a larger reduction in the hazard of progression or death associated with T-DXd (hazard ratio [95% CI]: 0.51 [0.44, 0.60] vs. 0.64 [0.54, 0.76]). This may be due to the open-label design of the trial. Therefore,

[xxiii] PI3K/AKT/mTOR

the use of investigator assessed-PFS, instead of PFS by BICR, in the economic model was likely to favour T-DXd. The Sub-Committees noted that this could not be tested in sensitivity analyses.

5.56 The submission stated that the extrapolation time point (18.0 months for T-DXd PFS, 10.4 months for ICC PFS, and 24.9 months for OS in both arms) was selected as the point at which approximately 15% of patients remained at risk for a PFS or OS event. The trial KM data used in the economic model were based on the DCO for IA2 (March 2025), whereas the number of patients at risk was apparently derived from the survival curves at an earlier DCO (March 2024). As a result, KM data remained reliable beyond the submission's nominated truncation time point and should be included in the economic model, noting PBAC's preference for observed rather than modelled data, as per PBAC Guidelines (v5.0). Alternative truncation time points based on Gebski (2018) Criterion 2[xxiv] were calculated during the evaluation and used in the sensitivity analysis. The Sub-Committees considered the truncation points used in sensitivity analyses were appropriate and the additional KM data should be used. The Sub-Committees noted that this results in a decrease in the ICER.

5.57 The parametric functions for extrapolation of PFS and OS used in the base case (log-logistic for T-DXd PFS, log-normal for ICC PFS, and log-logistic for OS in both treatment arms) were selected based on goodness of fit to the trial KM data and to the shape of hazard function.

5.58 The log-logistic function selected to extrapolate PFS in the T-DXd arm was not the statistically best fitting parametric function, nor a better visual fit to the trial data. The log-logistic model provided more favourable PFS estimates than any other parametric models (Figure 4), but the clinical plausibility of long-term predictions in the unobserved period was not justified in the submission. The log-normal function for ICC PFS was the best fitting parametric function both statistically and visually, and the model was not sensitive to this variable. The Sub-Committees advised that the gamma distribution provided the best statistical and visual fit for PFS extrapolations in the T-DXd arm, which increased the submission base case ICER by [redacted]%. The pre-PBAC response stated that use of the Gamma function for the T-DXd arm resulted in a PFS curve that dropped well below the tail of the KM data, and that the gamma distribution cannot capture the rise-then-fall pattern associated with the observed hazard shape in the T-DXd arm, where the hazard increases initially and then decreases.

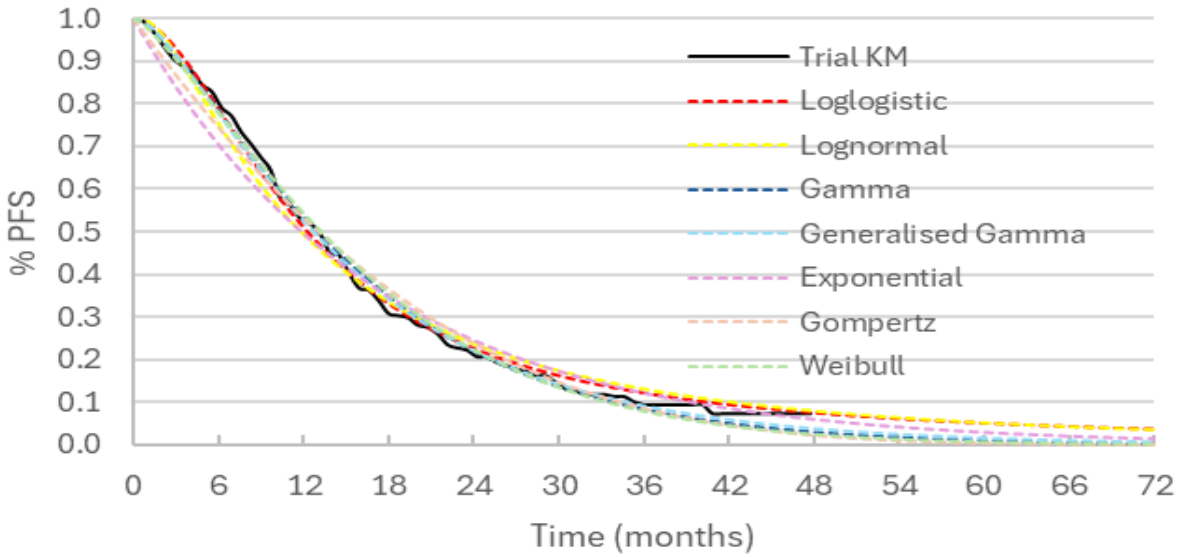
5.59 For OS modelling, the four parametric functions with better goodness of fit statistics (log-logistic, gamma, Weibull, and generalised gamma) fit to the OS KM reasonably well until approximately Month 36, and thereafter the extrapolation curves diverged rapidly. Except for the poorest fitting functions, the log-logistic functions (used in the base case) provided the most optimal survival in both treatment arms, e.g. a 5-year

[xxiv] Gebski V, Garès V, *et al.* Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol*. 2018;47(3):850-9.

survival rate of 24% in the T-DXd arm and 18% in the ICC arm (Figure 5 and Figure 6). The long-term extrapolation of OS following T-DXd or ICC in the proposed target population was not well validated in the submission and remained an area of uncertainty. The Sub-Committees noted that the Weibull and gamma distributions also provided a good fit for the OS extrapolations in the T-DXd arm, where the Weibull curve increases the ICER by [redacted]%, and the gamma curve slightly decreases the ICER.

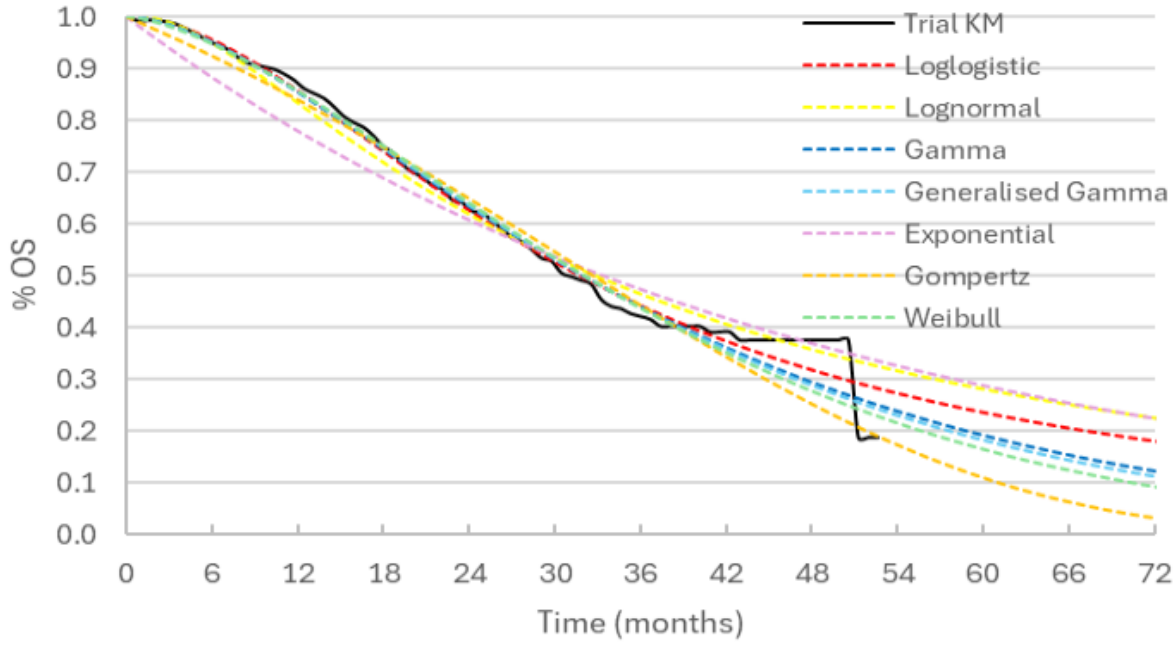
5.60 The Sub-Committees considered that the variation in ICERs based on chosen extrapolation functions demonstrated the uncertainty associated with extrapolation of the trial data over the 15 year time horizon.

Figure 4: Fit of parametric functions to the KM data for T-DXd PFS



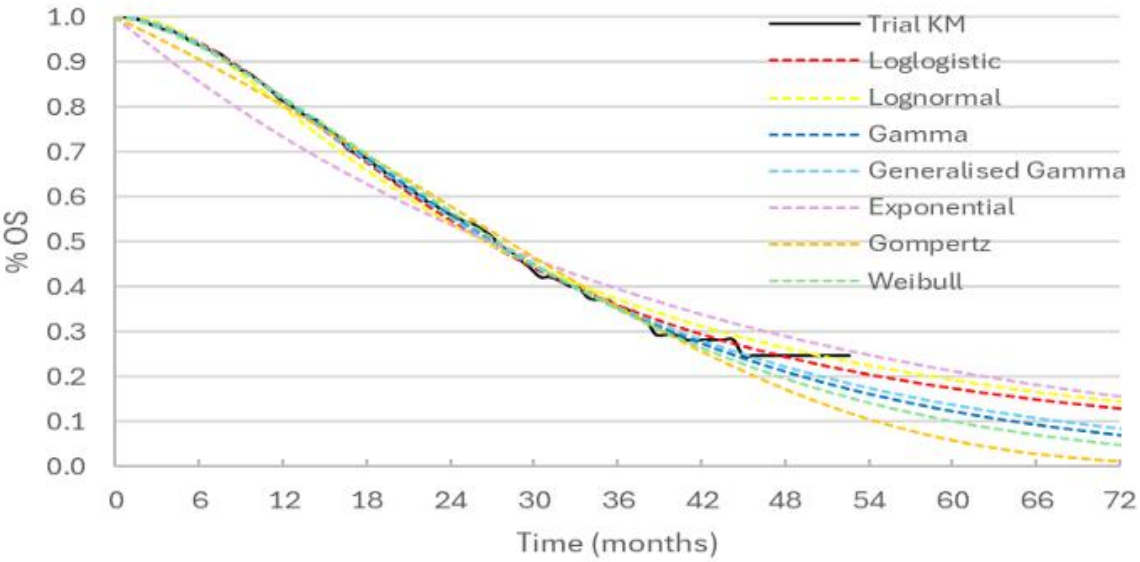
Source: Adapted from Figure 3.3, p134 of the submission, using 'T-DXd extrap' spreadsheet in the "Economic Evaluation" Excel workbook
KM = Kaplan-Meier; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan

Figure 5: Fit of parametric functions to the KM data for T-DXd OS



Source: Adapted from Figure 3.11, p140 of the submission, using 'T-DXd extrap' spreadsheet in the "Economic Evaluation" Excel workbook
KM = Kaplan-Meier; OS = overall survival; T-DXd = trastuzumab deruxtecan

Figure 6: Fit of parametric functions to the KM data for ICC OS



Source: Adapted from Figure 3.11, p140 of the submission, using 'T-DXd extrap' spreadsheet in the "Economic Evaluation" Excel workbook
ICC = investigator's choice of chemotherapy; KM = Kaplan-Meier; OS = overall survival

5.61 The distribution of subsequent therapies after T-DXd or ICC was sourced from the DB-06 trial. At DCO1 of the DB-06 trial, 23.5% of ICC patients who received subsequent anti-cancer therapies were treated with T-DXd. This was substantially lower than

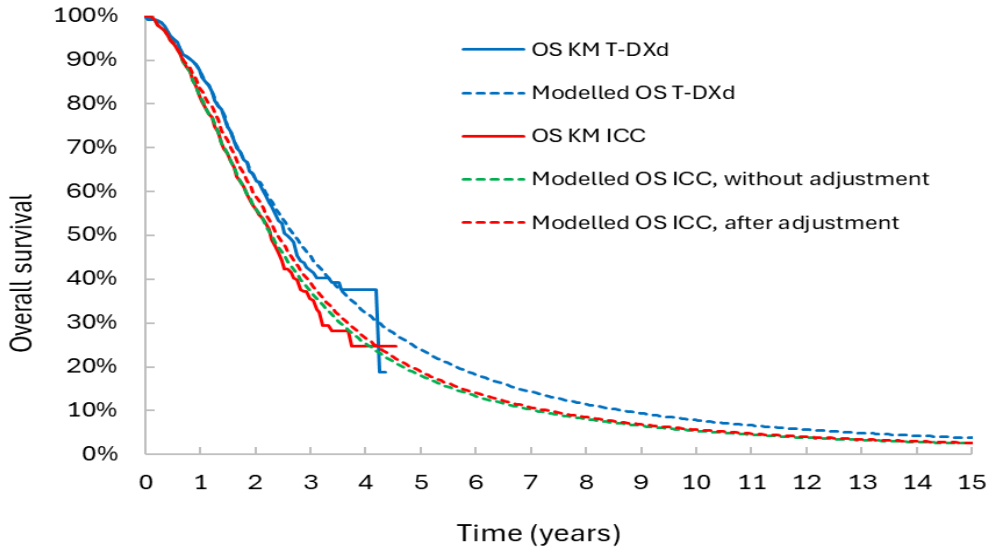
would be expected in Australian clinical practice as T-DXd is PBS listed for HER2-low patients after prior chemotherapy. Based on the distribution of HER2-low versus HER2-ultralow (not eligible for later-line T-DXd) as observed in the DB-06 trial at baseline, the submission assumed that 82.2% of progressed patients in the ICC arm (i.e. 100% of HER2-low patients) would receive subsequent T-DXd in clinical practice. Of the 82.2%, the health outcomes associated with 23.5% use of subsequent T-DXd had already been captured by the trial survival data (adjustment factor of 1), and, thus, OS adjustment would be required to account for the extra 58.7% use in clinical practice. The PSCR noted that the proportion of subsequent T-DXd in the ICC arm increased from 23.5% to 33.6% in the IA2 DCO (which was the DCO applied in the model) and therefore the adjustment factor should only be applied to 48.6% of patients rather than 58.7%.

5.62 The adjustment factor applied to the OS curve was estimated based on the hazard ratio for OS associated with later-line T-DXd versus chemotherapy (0.69) as reported in the external study DB-04 (Table 4, T-DXd PSD, March 2024 PBAC meeting). The weighted adjustment factor was calculated to be 0.779[xxv]. This adjustment factor was applied to the per cycle death derived from the OS function from Month 8 (the median PFS in the ICC arm of DB-06), linearly increasing to 1 at Month 23 (the assumed median time to second disease progression after first subsequent therapy or death). The submission's method of adjustment for OS modelling in the ICC arm only resulted in a slight increase in OS estimates (red dash line vs. green dash line, Figure 7).

5.63 Table 12 compares costs and quality-adjusted life years (QALYs) in the ICC arm of the model when 23.5% (no adjustment for OS required) and 82.2% (using the submission's adjustment assumption) of patients receiving subsequent T-DXd. Results showed that an extra 58.7% patients receiving subsequent T-DXd in the ICC arm provided a QALY gain of 0.052 at a cost of $15,000 to < $25,000. The resulting ICER associated with subsequent T-DXd use exceeded $355,000 to < $455,000/QALY, substantially higher than what the PBAC had previously considered cost-effective (less than $50,000/QALY) (para 5.14, T-DXd PSD, March 2024 PBAC meeting). The inclusion of a non-cost-effective subsequent therapy in the comparator ICC arm favoured T-DXd. To address this issue, an alternative adjustment method was used to estimate the likely ICER for T-DXd versus ICC in Australian clinical practice (see the "Revised economic analysis" section below). The Sub-Committees considered that the submission's approach to adjusting for the higher subsequent use of T-DXd in clinical practice lacked face validity.

[xxv] = 0.69 x 58.7%/82.2% + 1 x 23.5%/82.2%,

Figure 7: Modelled OS curves before and after adjustment to ICC arm



Source: Figure constructed during the evaluation, using the "Economic Evaluation" Excel workbook.
ICC = investigator's choice of chemotherapy, KM = Kaplan-Meier; OS = overall survival; T-DXd = trastuzumab deruxtecan

Table 12: A comparison of costs and QALYs in the ICC arm when 23.5% and 82.2% of patients receiving subsequent T-DXd

Subsequent T-DXd use	Costs[a]	QALYs[b]	ICER
23.5% (trial-based, no adjustment for OS required)	$[redacted]	1.738	–
82.2% (as in the submission's base case)	$[redacted]	1.791	–
Difference	$[redacted]	0.052	$[redacted][1]/QALY

Source: Table compiled during the evaluation
ICC = investigator's choice of chemotherapy; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressive disease; QALYs = quality-adjusted life years; T-DXd = trastuzumab deruxtecan
[a] The differences in costs between the two scenarios include costs associated with subsequent anti-cancer treatment ($[redacted] vs. $[redacted]), disease monitoring in the PD health state ($[redacted] vs. $[redacted]) and terminal care ($[redacted] vs. $[redacted]).
[b] The difference in health outcomes between the two scenarios was the QALYs accrued during the PD health state (1.097 vs. 1.149).
The redacted value corresponds to the following range:
[1] *$355,000 to < $455,000*

5.64 The health state utilities applied to the economic model were derived from the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) data collected in DB-06, converted to EQ-5D-3L utilities using the cross-walk methodology described by van Hout et al (2012)[xxvi] and then applying the Australian value set by Viney et al (2011)[xxvii]. The other Australian algorithm to transform EQ-5D-5L scores into health state utilities (Norman et al 2023[xxviii]) was not used as it generated progression-free (PF) utilities that were overly optimistic for patients with mBC, even higher than the mean utility

[xxvi] van Hout B, Janssen MF, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708-15.
[xxvii] Viney R, Norman R, *et al*. Time trade-off derived EQ-5D weights for Australia. *Value Health*. 2011;14(6):928-36.
[xxviii] Norman R, Mulhern B, *et al*. The Use of a discrete choice experiment including both duration and dead for the development of an EQ-5D-5L value set for Australia. *Pharmacoeconomics*. 2023;41(4):427-38

for the general Australian population (0.8905-0.9135 vs. 0.88 for females aged 55-64 years).

5.65 The model used treatment-specific utilities for patients in the PF health state (0.8018 for T-DXd vs. 0.7666 for ICC), as the regression analyses indicated a statistically significant difference between the two treatment arms. Information regarding compliance rates for EQ-5D by disease progression status across treatment arms was not available. Due to the open-label design of DB-06, PROs were subject to performance/assessment bias. The higher PF utility value in patients receiving T-DXd was not consistent with the inferior safety claim, compared with ICC. The PSCR noted that the overall incidence of grade 3+ AEs was 11% higher in the T-DXd arm, but the incidence of certain AEs (palmar-planter syndrome and diarrhoea) impacting QoL were higher in the ICC arm. The PSCR defended the treatment-specific utilities based on statistically significant difference in trial data (based on regression analysis), longer duration of treatment exposure in the T-DXd arm, and precedent in previous submissions where treatment specific utilities were used in treatments with inferior safety profiles. The Sub-Committees noted that no clear improvement in QoL with T-DXd over ICC was demonstrated in the DB-06 QoL data and there were higher scores for nausea and constipation in the T-DXd arm compared to the ICC arm, with nausea and vomiting having meaningful impacts on QoL. The Sub-Committees also recalled that the ESC had previously recommended use of pooled PF utility values in the model for T-DXd for HER2-low metastatic breast cancer (November 2023) and the model accepted by the PBAC used pooled PF utility values (Table 1, T-DXd PSD, March 2024 PBAC meeting). The Sub-Committees considered that given the potential for bias in the open-label trial and the significantly worse safety profile of T-DXd, a pooled utility for the PF health state was more appropriate. The pre-PBAC response maintained that treatment-specific PF health state utilities were appropriate given DB-06 trial-based EQ-5D data demonstrated statistically significant higher QoL in the T-DXd arm. The use of pooled utility for the PF health state (0.7851) increased the ICER from $55,000 to < $75,000/QALY gained to $55,000 to < $75,000/QALY gained. In a sensitivity analysis conducted for the pre-PBAC response, treatment-specific pre-progression utilities were used until Cycle 38 (equating to 26.5 months follow-up), and the pooled utility thereafter, increasing the ICER from $55,000 to < $75,000 to $55,000 to < $75,000.

5.66 The submission argued that trial-based progressive disease (PD) utility values could not reflect the entire period from first disease progression to death, as, in the trial, EQ-5D data were collected post-progression only when patients were receiving active second-line treatments. The utility score for the PD health state as used in the base case analysis was derived by applying the utility decrement associated with disease progression of mBC reported in Lloyd et al 2006[xxix] (-0.272) to the PF utility score in the T-DXd arm (0.8018), resulting in a PD utility score of 0.5298. This estimate was

[xxix] Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.

within the range of PD health state utility values used in other economic models for later-line treatment of non-TNBC.

5.67 A summary of the key drivers of the model is shown below.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Adjustment to OS curve in ICC arm to account for additional use of T-DXd as a subsequent therapy vs that in DB-06	Adjustment factor increasing from 0.779 at Month 8 to 1 at Month 23.	High, favours T-DXd. Using the Evaluation's alternative method of adjustment[a] increased the ICER to $[redacted][2]/QALY gained. If the use of subsequent T-DXd in clinical practice is the same as that in the trial (23.5%, no adjustment for OS required), the ICER increased to $[redacted][3]/QALY. When using the revised value of 33.6% from IA2 DCO the ICER increased to $[redacted][4]/QALY.
Parametric function to extrapolate PFS and OS in the T-DXd arm	Log-logistic function in the base case.	High, favours T-DXd. Use of gamma distribution to model PFS for T-DXd increased the ICER to $[redacted][4]/QALY gained. Use of Weibull function to model OS for T-DXd increased ICER to $[redacted][1]/QALY gained.
Time horizon	15 years.	Moderate, favours T-DXd. Using a 7-year time horizon increased the ICER to $[redacted][1]/QALY gained.
Health state utility for PF	PF: 0.8018 for T-DXd and 0.7666 for ICC.	Moderate, favours T-DXd Applying a pooled PF health state utility (0.7851) increased the ICER to $[redacted][1]/QALY gained.

Source: Table compiled during the evaluation.
ICC = investigator's choice of chemotherapy; ICER = incremental cost-effectiveness ratio; mBC = metastatic breast cancer; PF = progression-free; PFS = progression-free survival; OS = overall survival; QALY = quality-adjusted life year; T-DXd = trastuzumab deruxtecan
[a] Applying fixed incremental costs ($[redacted]) and QALYs (0.532) to the extra 58.7% of patients receiving subsequent T-DXd in clinical practice
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$155,000 to < $255,000*
[3] *$95,000 to < $115,000*
[4] *$75.000 to < $95,000*

5.68 The results of the economic analysis are presented in Table 14 below. Step 2 as presented in the submission included a number of translational procedures and this step was disaggregated during the evaluation to identify the effect of certain model parameters on the result.

Table 14: Results of the economic evaluation

Step and component	T-DXd	ICC	Increment
Step 1: Trial-based economic evaluation. A duration of 46 months[a]. Costs included were T-DXd and ICC drug costs, administration costs, and costs for management of AEs. The outcome measured was progression-free years gained.			
Costs	$[redacted]	$[redacted]	$[redacted]
Progression-free years gained	1.310	0.795	0.514
Incremental cost/extra progression-free year gained			$[redacted][1]
Step 2a: Incorporating additional costs of health care resource use. Costs for disease monitoring, post-progression treatment (assuming 23.5% use of subsequent T-DXd in the ICC arm as in the clinical trial) and terminal care costs were included. The health outcome measured was LY gained.[b,c]			
Costs	$[redacted]	$[redacted]	$[redacted]
LY gained	2.537	2.306	0.231
Incremental cost/extra LY gained			$[redacted][2]
Step 2b: Extrapolating outcomes and costs to 15 years.[b,d]			
Costs	$[redacted]	$[redacted]	$[redacted]
LY gained	3.862	3.279	0.582
Incremental cost/extra LY gained			$[redacted][3]
Step 2c: Including discount rate of 5% per annum for both costs and health outcomes.[b]			
Costs	$[redacted]	$[redacted]5	$[redacted]
LY gained	3.365	2.907	0.458
Incremental cost/extra LY gained			$[redacted][4]
Step 2d: Increasing use of subsequent T-DXd therapy from 23.5% to 82.2% and incorporating OS upward adjustment.[b]			
Costs	$[redacted]	$[redacted]	$[redacted]
LY gained	3.365	3.006	0.359
Incremental cost/extra LY gained			$[redacted][5]
Step 3: Applying utility weights.			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	2.189	1.791	0.398
Incremental cost/extra QALY gained (base case)			**$[redacted][5]**

Source: Table 3.33, p165 of the submission.

AEs = adverse events; DCO2 = data cutoff 2; ICC = investigator's choice of chemotherapy; ICER = incremental cost-effectiveness ratio; LY = life year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation

[a] Time point where PFS data from DCO2 available for both treatment arms

[b] Steps disaggregated during the evaluation in order to outline the effects of certain model parameters on the ICER.

[c] To generate the trial-based LYs over the time horizon of 46 months, the trial-based PFS, OS, and TTD curves were used up until Cycle 66, the last observation time point where all trial data were available.

[d] Using the extrapolation time points selected in the submission's base case.

The redacted values correspond to the following ranges:

[1] *$115,000 to <$135,000*

[2] *$155,000 to <$255,000*

[3] *$75,000 to < $95,000*

[4] *$95,000 to < $115,000*

[5] *$55,000 to < $75,000*

5.69 Results indicated that the step which affected the result the most was the extrapolation of the model time horizon (Step 2b). Extending the time horizon from 46 months to 15 years resulted in a decrease of ICER from $155,000 to < $255,000/life year (LY) gained to $75,000 to < $95,000/LY gain. Another step that had a big impact on the ICER was 2d – assuming a higher proportion of patients receiving T-DXd following ICC in clinical practice than the trial setting (82.2% vs. 23.5%) reduced the

ICER from $95,000 to < $115,000/LY gained to $55,000 to < $75,000/LY gained. This was due to the inclusion of extra use of subsequent T-DXd therapy in the comparator arm which was modelled as a less cost-effective therapy using the submission's approach to adjustment for health outcomes (see also paragraph 5.76-5.82).

5.70 The disaggregated results of the economic evaluation in terms of costs and health outcomes are summarised in Table 15 and Table 16, respectively.

Table 15: Disaggregated summary of cost impacts (discounted)

	T-DXd	ICC	Incremental	% increment
T-DXd and ICC drug acquisition	$[redacted]	$5,811	$[redacted]	[redacted]%
T-DXd and ICC administration costs	$2,522	$1,543	$979	[redacted]%
Management of AEs	$913	$863	$50	[redacted]%
Subsequent anti-cancer treatment	$2,646	$[redacted]	-$[redacted]	-[redacted]%
Post-progression radiotherapy	$298	$308	-$10	-[redacted]%
Disease monitoring	$61,604	$67,012	-$5,407	-[redacted]%
Terminal care	$17,752	$18,246	-$494	-[redacted]%
Total	**$[redacted]**	**$[redacted]**	**$[redacted]**	**100%**

Source: Table 3.31, p164 of the submission.
AEs = adverse events, ICC = investigator's choice of chemotherapy, T-DXd = trastuzumab deruxtecan

5.71 As expected, the incremental costs were mainly driven by the drug acquisition cost for T-DXd; whereas the cost offsets were mainly due to the use of subsequent T-DXd therapy following ICC in the comparator arm and more hospital admissions during the extended PD health state in the ICC arm, compared with the T-DXd arm.

Table 16: Disaggregated summary of health outcomes (discounted)

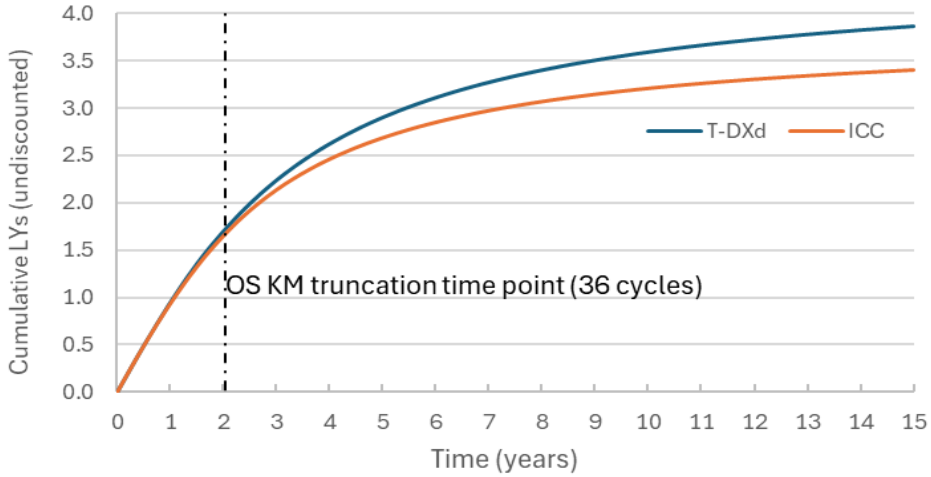
	T-DXd	ICC	Incremental	% increment
LYs				
PF	1.494	0.837	0.657	182.8%
PD	1.871	2.169	-0.298	-82.8%
Total LYs	**3.365**	**3.006**	**0.359**	**100.0%**
QALYs				
PF	1.198	0.642	0.556	139.6%
PD	0.991	1.149	-0.158	-39.6%
AE-related disutilities	0.000	0.000	0.000	0%
Total QALYs	**2.189**	**1.791**	**0.398**	**100%**

Source: Table compiled during the evaluation, based on the 'Trace-T-DXd' and 'Trace-ICC' spreadsheets in the "Economic Evaluation" Excel workbook.
AE = adverse event, ICC = investigator's choice of chemotherapy, PD = progressive disease; PF = progression-free; T-DXd = trastuzumab deruxtecan

5.72 Consistent with the clinical claim, the economic model showed that T-DXd improved PFS, but with some of the incremental LYs accumulated in the PF health state offset by a reduction in time in the PD health state for patients in the T-DXd as they were no longer eligible for T-DXd therapy in the later-line setting whilst patients in the comparator arm would gain survival benefits from use of subsequent T-DXd following ICC.

5.73 The accumulation of undiscounted LYs gained over the model time horizon is depicted in Figure 8.

Figure 8: Cumulative LYs gained over the time horizon of the model (undiscounted)



Source: Figure constructed during the evaluation, based on the 'Trace-T-DXd' and 'Trace-ICC' spreadsheets in the "Economic Evaluation" Excel workbook.
ICC = investigator's choice of chemotherapy, KM = Kaplan-Meier; LYs = life years; OS = overall survival; T-DXd = trastuzumab deruxtecan

5.74 The vast majority (88.7%) of the incremental LYs gained (undiscounted) associated with T-DXd relative to ICC were accrued beyond the extrapolation time point for OS (36 cycles or 25 months) up to the end of the time horizon. As discussed previously, the modelled survival benefit associated with T-DXd was an area of main economic uncertainty, due to the selection of the parametric functions which extrapolated OS for T-DXd optimistically and the likely underestimation of the OS gain from extra T-DXd use following ICC in the comparator arm, both of these approaches favoured T-DXd.

5.75 Results from sensitivity analyses based on the submission's base case showed that the model parameter which had the greatest impact on the result was adjustment for costs and health outcomes due to extra proportion of patients receiving subsequent T-DXd in the ICC arm (Table 13). The economic model was also sensitive to change in PFS and OS parametric functions, especially those in the T-DXd arm. Health state utilities and time horizon moderately affect the result. The use of an extended time horizon and assuming a higher PF health state utility in patients receiving T-DXd than those treated with ICC were not adequately justified in the submission and both favoured T-DXd.

Revised economic analysis

5.76 Assuming the extent of use of later-line T-DXd as in the DB-06 trial, i.e. 23.5%, the ICER was estimated to be $95,000 to < $115,000/QALY gained ($75,000 to < $95,000/QALY when applying the proportion of later-line T-DXd from IA2 (33.6%), see Table 13). In this scenario, no adjustment for ICC OS curve was required, as the impact of use of subsequent T-DXd in the ICC arm on health outcomes had already been captured in the DB-06 OS data. Assuming an extra 58.7% of patients receiving subsequent T-DXd in clinical practice (total 82.2% use) and using the submission's method of adjustment, the ICER decreased to $55,000 to < $75,000/QALY gained (the submission's base case). The Evaluator considered this appeared counter-intuitive. Later-line T-DXd has been recommended by the PBAC as a cost-effective treatment following chemotherapy. The incorporation of a cost-effective later-line therapy in the comparator arm may be expected to increase, or have a negligible effect on, the ICER.

5.77 To address this issue, fixed payoffs that represent the expected incremental costs and incremental health outcomes associated with subsequent use of T-DXd, instead of chemotherapy, were applied by the Evaluator to the extra proportion of patients transitioning into the PD health state. The fixed payoffs were derived from the economic model previously considered by the PBAC for use of T-DXd for the treatment of mBC following chemotherapy. At the March 2024 PBAC meeting, the Committee considered it was reasonable to accept the revised economic model which resulted in an ICER of $55,000 to < $75,000 per QALY gained (incremental costs: $25,000 to < $35,000; incremental QALYs: 0.532), but noted that some outstanding uncertainties remained (Paragraph 5.8 and Table 6, T-DXd PSD, March 2024 PBAC meeting). The PBAC considered that, as previously advised, T-DXd would be cost-effective with an ICER of $45,000 to $50,000 per QALY gained (Paragraph 5.8, T-DXd PSD, March 2024 PBAC meeting). The incremental costs associated with later-line T-DXd was back-calculated using an ICER of $45,000 to < $55,000/QALY and incremental QALYs of 0.532, i.e., $[redacted]. During the evaluation, the base case ICER was re-calculated by applying fixed payoffs of $[redacted] and 0.532 QALYs to 58.7% of patients transitioning into the PD health state in the ICC arm.

5.78 The Evaluator acknowledged the transitivity issues of the previous T-DXd model for later-line T-DXd use to the current T-DXd model (participants enrolled in DB-04 were younger at baseline, had less severe disease and were less heavily pre-treated when they started the T-DXd therapy). The PSCR and pre-PBAC response argued that these transitivity issues result in the revised analysis being biased against T-DXd.

5.79 The PSCR and pre-PBAC response raised additional substantial concerns regarding the methodology of the revised analysis, arguing that these factors biased the results in favour of the ICC arm including:

- Substantial overestimation of the QALYs being accrued in the ICC arm due to (1) the difference in PF and PD utility scores applied in the two models and (2) double counting of QALYs in the PD state due to an error in the calculations.

The sponsor considered the modelled OS in the ICC arm was implausible, as back calculating the modelled OS from half cycle corrected incremental undiscounted life years from the DB-04 model, resulted in the probability of survival in the ICC arm to be over 100% in the early part of the Evaluator's model.

- The drug acquisition costs, and costs for MRU and AEs have decreased since the construction of the DB-04 model and the incremental cost taken from the DB-04 model being applied into the ICC arm of the DB-06 model is therefore underestimated.

5.80 Overall, the Sub-Committees considered that the submission's methodology for adjustment for subsequent treatments was flawed and lacked face validity given the high implied ICER for later line T-DXd. The Sub-Committees noted the limitations of the evaluation's revised analysis but considered that it was conceptually sound and provided a more reasonable adjustment for subsequent treatment, giving a more reliable basis for decision-making than that applied in the submission. The pre-PBAC response argued that the revised evaluation model was not sufficiently reliable to inform decision-making, noting that the issues were more significant than the Sub-Committees estimated, and noting that concerns regarding errors in the evaluation's revised model had not been sufficiently addressed.

5.81 The pre-PBAC response referred to a revised analysis proposed in the PSCR in which a constant rather than waning HR from DB-04 was applied from median PFS until the end of the 15-year time horizon and used IA2 data to inform the percentage use of subsequent T-DXd in the ICC arm (33.6%). At the submission price, the ICER remained below $55,000 to < $75,000/QALY. The PBAC considered that this analysis did not adequately address the concerns identified in the evaluation regarding incorporation of cost-effective later line T-DXd use.

5.82 Results of the revised analysis of T-DXd versus ICC are presented in Table 17. The ICER from the revised economic evaluation was estimated to be $155,000 to < $255,000/QALY gained (around [redacted]% higher than the submission's base case estimate). This was primarily due to the incorporation of the cost-effective later-line T-DXd therapy in the comparator in the revised analysis.

Table 17: Results of the revised economic evaluation[a]

	T-DXd	ICC	Increment
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	2.189	2.044	0.145
Incremental cost/extra QALY gained (revised base case)			**$[redacted][1]**

Source: Table 3.33, p165 of the submission.

ICC = investigator's choice of chemotherapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T-DXd = trastuzumab deruxtecan

[a] By applying fixed incremental costs ($[redacted]) and QALYs (0.532) to extra proportion (58.7%) of patients receiving subsequent T-DXd in clinical practice

The redacted values correspond to the following ranges:

[1] $155,000 to < $255,000

5.83 The Sub-Committees advised a respecified base case could be considered, with corrected proportion of subsequent treatment from IA2 (#1), a 10-year time horizon (#2), pooled PFS utility values (#3), and Gebski criterion for KM truncation point (#4). This resulted in an ICER of $155,000 to < $255,000/QALY.

Drug cost/patient/course

Table 18: Drug cost per patient for proposed and comparator drugs

	T-DXd			ICC		
	DB-06	Economic model	Financial estimates	DB-06	Economic model	Financial estimates
Mean dose per administration[a]	327 mg[b]	327 mg[b]	352 mg[c]	C: 1845.4 mg[d] P: 111.6 mg[d] N: 156.3 mg[d]	C: 2118.8 mg[c] P: 135.6 mg[c] N: 169.5 mg[c]	P: 135.6 mg[c] N: 169.5 mg[c]
Mean duration, months	13.03	13.62	HER2-low: 13.58 HER2-ultralow: 14.27	8.15	8.35	P: 6.3 N: 9.1
Cost/patient/month	$[redacted][e]	$[redacted][e]	$[redacted][e]	Weighted: $700.72[e,f]	Weighted: $[redacted][e,f]	P: $686.24 N: $2,282.16
Cost/patient/ course	$[redacted]	$[redacted]	HER2-low: $[redacted] HER2-ultralow: $[redacted]	$5,711	$[redacted]	P: $1,228.71 N: $16,918.87

Source: Table 9, p50 of CSR Addendum 1 IA2; Table 30, p142 of CSR IA1

C = capecitabine; BSA = body surface area; EFC = Efficient Funding of Chemotherapy; HER2 = human epidermal growth factor receptor 2; IA = interim analysis; ICC = investigator's choice of chemotherapy; N = nab-paclitaxel; P = paclitaxel; RDI = relative dose intensity; T-DXd = trastuzumab deruxtecan

[a] Dosing frequency of:

- Once every 3 weeks for T-DXd,
- Twice daily for 2 weeks, followed by a 1-week rest period for capecitabine,
- Once every week for paclitaxel, and
- Once every week for 3 weeks, followed by a 1-week rest period for nab-paclitaxel.

[b] 5.4 mg/kg x 65.1 kg (mean weight of DB-06 patients) x 92.9% (RDI observed in the trial)

[c] Calculated as trial-based dosing, but assuming 100% RDI

[d] Dosing per administration was estimated based on a BSA of 1.695 m^2 (mean BSA in the trial), applying RDIs as observed in the trial (87.1% for capecitabine, 82.3% for paclitaxel, and 92.2% for nab-paclitaxel)

[e] Assuming no vial sharing for EFC medicine, *i.e.* T-DXd, paclitaxel, and nab-paclitaxel

[f] In the ICC arm, 59.7% receiving capecitabine, 16.1% receiving paclitaxel, and 24.2% receiving nab-paclitaxel

5.84 The economic model and financial estimates assumed that all patients would receive 4 vials (rounded up from the mean dose per administration of 327 mg from the trial). The submission noted that this was in keeping with the approach previously accepted by the PBAC for T-DXd submissions. In practice it would be expected that a proportion of patients would only require 3 vials and therefore the number of vials in the economic model and financial estimates is likely to be overestimated.

Estimated PBS usage & financial implications

5.85 The submission utilised an epidemiological approach to estimate the extent of use and financial impact of listing T-DXd for the treatment of HR-positive, HER2-low or HER2-ultralow, unresectable mBC in patients who have received at least one prior line of ET in the metastatic setting and are no longer considered suitable for ET. A summary of the data sources and parameter values used to estimate the utilisation and financial impact of listing T-DXd is presented in Table 19.

Table 19: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients with HR-Positive, HER2-negative cancer	Yr 1: 2,155 Yr 2: 2,198 Yr 3: 2,242 Yr 4: 2,287 Yr 5: 2,333 Yr 6: 2,379	DUSC estimates of patients that progressed on treatment with CDK 4/6 inhibitors	The use of this population to estimate the eligible population was in line with previous DUSC advice (paragraph 4.24, T-DXd PSD, March 2024 PBAC Meeting). The PSCR clarified that the values represent incident patients treated with CDK4/6is for mBC. The Sub-Committees noted that DUSC provided updated PBS data for CDK4/6i in mBC and eBC and considered that the updated data for mBC should be used. PBS data: Year | | Restriction | Prevalent patients 2025 | ANY_CDK46 | EARLY | 1336 2025 | ANY_CDK46 | METASTATIC | 2315
Prevalent patients	Yr 1: 1,643 Yr 2: 1,676	Based on a survival rate of 79.3% for patients with locally advanced or metastatic disease treated with CDK 4/6 inhibitors, applied to incident patients in years 2024 and 2025.	The Sub-Committees agreed with the evaluation that this was reasonable, noting that a proportion of these patients may have been treated with T-DXd in the 3L setting.
Population 1a: HR-positive, HER2-low patients			
Proportion of HR positive/HER2 negative BC with HER2 low	65.4% of incident and prevalent patients	Based on DUSC advice (paragraph 4.27, T-DXd PSD, March 2024 PBAC Meeting).	This was consistent with published literature on the incidence of HER2-low BC.
Population 1b: HR-positive, HER2-ultralow patients			
Proportion of IHC 0 BC patients	34.6% of incident and prevalent patients	Calculated as 100% minus the proportion of patients with HER2-low cancer (65.4%).	The Sub-Committees agreed with the evaluation that this was reasonable.
Proportion of IHC 0 BC with HER2 ultralow	60%	Based on Mehta et. al [15]	The Sub-Committees agreed with the evaluation that this was reasonable.
Treated population			
Proportion of patients for whom T-DXd is clinically appropriate	90% of HER2-low and HER2-ultralow patients (incident and prevalent)	Assumption	The PBAC has previously noted that 80% of patients would be considered suitable for T-DXd in the 3L setting. The Sub-Committees considered that 90% was reasonable, noting that there will always be a nontrivial proportion of patients unsuitable for T-DXd due to pulmonary, performance status, or other clinical factors.

Data	Value	Source	Comment
Proportion of patients treated with T-DXd	28.9%	Based on the assumption that T-DXd will only replace 2L IV chemotherapy (paclitaxel and nab-paclitaxel) and not 2L oral chemotherapy (capecitabine).	The evaluation considered this was not reasonable as substitution of oral capecitabine with T-DXd would occur in clinical practice if T-DXd improves PFS and OS compared with chemotherapy including capecitabine, as claimed in the submission. The Sub-Committees agreed with the evaluation that the assumption that only IV chemotherapy would be displaced was not supported by the trial or clinical experience (see paragraph 5.87).
Patients progressing within 6 months of 1L ET+CDK 4/6i therapy	8.49%	Additional patients, proportion derived from the DB-06 trial.	The Sub-Committees noted that the population estimates were based on CDK4/6is in the mBC setting only, and as such it may be reasonable to capture additional patients who progressed after being treated with a CDK4/6i in the eBC setting.
Patients with disease recurrence within 24 months of adjuvant ET	6.42%	Additional patients, proportion derived from the DB-06 trial.	
Uptake rate	Yr 1: [redacted]% Yr 2-3: [redacted]% Yr 4-6: [redacted]%	Assumption	The Sub-Committees noted that the uptake rate of [redacted]% in year 6 was potentially overestimated, noting that the previous DUSC accepted value for uptake of T-DXd for mBC was 90-95%. The Sub-Committees and PBAC considered that uptake would also be limited by safety concerns for T-DXd.
Treatment duration	59 and 62 weeks for HER2-low and HER2-ultralow BC, respectively.	DB-06 trial + parametric extrapolation	This was reasonable.
Costs			
2L T-DXd	$[redacted] per vial	Requested ex-manufacturer price	Appropriate
3L T-DXd	$[redacted] per vial	AEMP	
Paclitaxel	Public: $164.79 Private: $211.48	PBS items: 7245T, 4567J	
Nab-paclitaxel	Public: $1,814.01 Private: $1,883.8	PBS items: 7270P, 4531L	

Source: tabulated during the evaluation, from Table 4.1, pp 172-173 of the submission and the "ATT41_~1" excel workbook provided in the submission.

1L = first-line; 2L = second-line; 3L = third-line; BC = breast cancer; CDK = cyclin-dependent kinase; DUSC = Drug Utilisation Sub Committee; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = human receptor; IHC = immunohistochemistry; IV = intravenous; mBC = metastatic breast cancer; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation.

5.86 The submission estimated the total number of patients eligible for treatment with T-DXd based on the inputs presented in Table 19. The patient population was established based on DUSC estimates of incident patients that progressed on first-line treatment with CDK 4/6 inhibitors and ET in the metastatic setting. A 2% yearly increase was applied to project the number of incident patients over the first 6 years of listing as accepted by the PBAC previously (paragraph 4.24, T-DXd PSD, March 2024 PBAC Meeting). CDK 4/6 inhibitors are currently listed on the PBS for the treatment of HR-positive, HER2-negative early BC and mBC. The PSCR clarified that the incident patient population utilised in the submission includes only patients treated with CDK 4/6 inhibitors for metastatic breast cancer. The Sub-Committees noted that updated utilisation data from 2025 was provided and considered that this should be used, which resulted in a slight increase in the number of patients.

5.87 The submission assumed that 90% of patients would be eligible for 2L treatment, of which 28.9% are treated with IV chemotherapy. The submission stated that T-DXd was most likely to replace 2L IV chemotherapy (paclitaxel and nab-paclitaxel) only due to the convenience associated with oral medications (capecitabine). The evaluation considered that T-DXd will replace oral capecitabine in clinical practice in line with the clinical claim of increased PFS and OS compared to chemotherapy (including capecitabine). The PSCR stated "the assumption that T-DXd will mainly replace IV chemotherapy rather than capecitabine reflects clinician advice that treatment choice often prioritises patient convenience. Capecitabine helps patients maintain independence and avoid the burden of transitioning to IV therapy, which is seen as a major escalation. Clinicians are familiar with capecitabine, can adjust dosing for tolerability, and have observed durable responses in some patients. For these reasons, broad substitution away from capecitabine is unlikely despite T-DXd's superior efficacy". The Sub-Committees noted that, although the convenience of oral administration is a factor for some patients, patients treated with capecitabine will still require frequent monitoring. The Sub-Committees acknowledged that for some patients the preferred treatment would be oral capecitabine due to its oral administration and more tolerable safety profile compared with T-DXd. However, the Sub-Committees agreed with the evaluation that the assumption that only IV chemotherapy would be displaced was not reasonable for the following reasons:

- In DB-06 the ICC arm included capecitabine for ~60% of patients, suggesting that replacement with T-DXd would be considered clinically appropriate for these patients.
- The Sub-Committees considered it is likely that some clinicians would want to use T-DXd in place of capecitabine where it is expected to have improved

survival benefit. Recent real world evidence trial emulation confirms the benefit of T-DXd compared with capecitabine and IV chemotherapy[xxx].

- Based on data from the 10% PBS sample, capecitabine accounted for about 71% of all 2L chemotherapy regimens, suggesting that even if a small proportion of patients substitute capecitabine it would have a substantial impact on patient numbers.
- Although the convenience of oral administration is a factor for some patients, patients treated with capecitabine will still require frequent monitoring.
- For some patients there may be a preference to receive the more toxic drug (T-DXd) earlier, as they may be better able to tolerate treatment in the earlier line, reserving oral capecitabine for a later line of therapy. This was consistent with consumer inputs regarding the submission.

5.88 The Sub-Committees noted that it is uncertain what proportion of patients currently treated with capecitabine would receive 2L T-DXd instead, but considered it may be reasonable to assume up to around 50% of patients.

5.89 < 500 grandfathered patients, who will access T-DXd through the sponsor's patient access program were also included in year 1. The submission also included patients who relapsed within 6 months of 1L CDK 4/6i + ET therapy, i.e., 8.49% of incident patients, in addition to the prevalent and incident patients. Additionally, patients with disease recurrence within 24 months of adjuvant ET were also included. This was estimated to be 6.42% of the incident patients in each year, based on the DB-06 trial. The Sub-Committees noted that including additional rapid relapsers who received CDK4/6 inhibitors in the eBC setting would not result in double counting, as the starting values for CDK4/6 inhibitor use include only mBC.

5.90 Uptake rates of [redacted]% in year 1, increasing to [redacted]% in year 6, were applied to the total number of eligible patients (incident + prevalent + grandfathered + relapsers) to determine the total number of patients treated with T-DXd. The Sub-Committees considered that the assumption of [redacted]% uptake in Year 6 may be overestimated, noting that previously accepted DUSC values for mBC were from [redacted]-[redacted]%. The PBAC agreed with the Sub-Committees and considered that uptake would not be expected to increase above [redacted]%.

5.91 The costs associated with T-DXd were based on a proposed ex-manufacturer price of $[redacted] per vial and it was assumed that vial sharing was not allowed. Thus, it was estimated that 4 vials of T-DXd would be required for the average dose of 352 mg equating to $[redacted] for the average dose (see also paragraph 5.84).

[xxx] Jourdain H, Di Meglio A, Mansouri I, Desplas D, Zureik M, Haddy N. Real-world efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine and tucatinib as second-line and third-line treatments for HER2-positive metastatic breast cancer: two target trial emulation studies. Lancet Reg Health Eur. 2025 Sep 5;58:101455. doi: 10.1016/j.lanepe.2025.101455. PMID: 40989560; PMCID: PMC12451362.

5.92 The estimates assumed that T-DXd would replace 2L IV chemotherapy and offset 3L T-DXd in the HER2-low population.

5.93 The submission estimated that the listing of T-DXd would result in additional costs to the MBS due to additional IV administration costs for the HR-positive, HER2-ultralow population. Costs for ECG monitoring were included assuming one ECG every month. Patients treated with T-DXd are at a higher risk for ILD. Costs associated with the monitoring of potential ILD events via radiographic imaging were not included in the submission.

5.94 The net financial implication of listing T-DXd on the PBS is presented in Table 20.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of 2L T-DXd						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][2]	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of T-DXd						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimated financial implications for 2L IV chemotherapy and 3L T-DXd						
Reduction in prescriptions [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Reduction in cost to PBS/RPBS less copayments	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][7]	$[redacted][8]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to MBS	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Net cost to PBS/RPBS/MBS	**$**[redacted][7]	**$**[redacted][8]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]	**$**[redacted][6]

Source: tabulated during the evaluation, from the "ATT41_~1" excel workbook provided in the submission.
2L = second-line; 3L = third-line; IV = intravenous; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; T-DXd = trastuzumab deruxtecan.
[a] 17.33 scripts per patient year-on treatment as estimated by the submission.
[b] 17.33 scripts per patient year-on treatment for paclitaxel and T-DXd and 13 scripts per patient year-on treatment for nab-paclitaxel.
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *10,000 to < 20,000*
[3] *$60 million to < $70 million*
[4] *$70 million to < $80 million*
[5] *$50 million to < $60 million*
[6] *$20 million to < $30 million*
[7] *$30 million to < $40 million*
[8] *$40 million to < $50 million*
[9] *$0 to < $10 million*

5.95 The submission estimated a cost of $30 million to < $40 million in the first year of listing, reducing to $20 million to < $30 million in the sixth year of listing (due to the addition of a prevalent pool in the first 2 years of listing), and a cumulative cost of $100 million to < $200 million across the first 6 years of listing, to the PBS/RPBS.

5.96 The results indicate a substantial increase in the cost to the PBS associated with the listing of T-DXd which does not appear plausible. Offsets from reduced T-DXd in the 3L setting for HER2-low patients were estimated to be $10 million to < $20 million in year 1 in the financial analysis. Moving T-DXd to the 2L increased the cost to

$60 million to < $70 million in year 1. The evaluation noted that this large increase in the cost for moving the line of therapy for T-DXd is not accounted for by the increase in eligibility (90% in 2L T-DXd compared to 80% for 3L T-DXd), nor the treatment durations (13.5 months and 14.3 months for HER2-low and HER2-ultralow, respectively, compared to 10.95 months), nor the inclusion of the HER2-ultralow population (about 24% of all eligible patients), nor the increased proposed price for 2L T-DXd ($[redacted] per 100 mg vial) compared to 3L T-DXd ($[redacted] per 100 mg vial). The Sub-Committees noted that the estimates used the agreed patient numbers from the 3L setting (DB-04) and appear to have assumed that 3L T-DXd would only be offset for patients treated with 2L IV chemotherapy (29%). The Sub-Committees considered that the offsets for 3L T-DXd appear underestimated and inconsistent with the assumption in the economic model that 82.2% of progressed patients (100% of HER2-low patients) in the comparator arm would receive 3L T-DXd.

5.97 The Sub-Committees advised the utilisation estimates are uncertain and appear underestimated due to the high likelihood of T-DXd replacing a proportion of both IV and oral 2L chemotherapy regimens, such as capecitabine. The Sub-Committees noted that the sponsor provided a sensitivity analysis in the submission assuming displacement of 10% of patients who would otherwise receive capecitabine which demonstrated an increase of [redacted]% to the net financial impact. However, these analyses were not able to be verified, and clarification on the sponsor's numbers and approach were not provided in the pre-PBAC response. The Sub-Committees considered that a 50% replacement sensitivity analysis would better reflect the potential replacement level of T-DXd to capecitabine. Revised analyses provided for the ESC/DUSC advice reflecting 10% and 50% replacement of capecitabine are provided in

5.98 Table 21. The revised analyses have not corrected the 3L T-DXd offsets as discussed in paragraph 5.96 and therefore are likely to overestimate the net cost to the PBS/RPBS.

Table 21: Sub-committees' sensitivity analysis assuming replacement of capecitabine

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Scenario analysis: assuming 10% capecitabine use replaced						
Increase in cost to PBS/RPBS (2L T-DXd)	$[redacted][1]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
NET COST TO PBS/RPBS	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Scenario analysis: assuming 50% capecitabine use replaced						
Increase in cost to PBS/RPBS (2L T-DXd)	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
NET COST TO PBS/RPBS	$[redacted][8]	$[redacted][7]	$[redacted][1]	$[redacted][3]	$[redacted][1]	$[redacted][1]

Source: constructed for ESC/DUSC
The analysis assumes 28.9% of mBC patients treated with IV chemotherapy, 71.1% treated with capecitabine.
The redacted values correspond to the following ranges:
[1] *$70 million to < $80 million*
[2] *$90 million to < $100 million*
[3] *$60 million to < $70 million*
[4] *$40 million to < $50 million*
[5] *$50 million to < $60 million*
[6] *$30 million to < $40 million*
[7] *$100 million to < $200 million*
[8] *$80 million to < $90 million*

Quality Use of Medicines

5.99 The Sponsor noted that following the registration of T-DXd in the United States and Europe, testing guidelines were updated to improve accurate reporting and understanding of HER2 expression which is used for determining eligibility for treatment with T-DXd. To aid pathologists with the new testing recommendations, training modules were developed that provided information of clinical context and background requirements for testing and also included guided case reviews. No additional QUM issues were identified.

5.100 The Sub-Committees noted that clinicians are familiar with the use of T-DXd and management of ILD and other potential toxicities.

Financial Management – Risk Sharing Arrangements

5.101 The sponsor noted that there is an RSA in place for the current HER2-low listing of T-DXd and expects the additional listing for T-DXd to join the RSA with no adjustment to the caps for the HER2-low population and an increase in the caps to allow for the provision of T-DXd in the HR-positive, HER2-ultralow population.

Table 22: Existing and proposed subsidisation caps for T-DXd

	Year 1	Year 2	Year 3	Year 4	Year 5
Existing subsidisation caps [a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated impact of HER2-ultralow population [b]	-	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proposed subsidisation caps	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 4.28, p197 of the submission.
HER2 = human epidermal growth factor receptor 2; T-DXd = trastuzumab deruxtecan.
[a] AEMP for T-DXd was $[redacted] per vial
[b] AEMP for T-DXd is $[redacted] per vial

5.102 The current HER2-low RSA caps were expected to be exceeded to achieve a cost-effective price.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC did not recommend trastuzumab deruxtecan (T-DXd) for the treatment of adult patients with hormone receptor positive (HR-positive) human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow unresectable and/or metastatic breast cancer (mBC) who have received at least one prior line of endocrine therapy (ET) in the metastatic setting and are no longer suitable for further ET. The PBAC noted the modest progression free survival benefit and increased toxicity demonstrated in the key trial, compared to the investigator's choice of chemotherapy (ICC). The PBAC also noted that evidence in the HER2-ultralow population was limited and the magnitude of benefit highly uncertain. The PBAC considered that the incremental cost-effectiveness ratio presented in the submission was uncertain and likely underestimated. The PBAC considered that the financial estimates were highly uncertain due to the potential for uptake in patients otherwise treated with oral capecitabine and because offsets from later-line T-DXd did not appear plausible.

6.2 The PBAC considered that the primary reason for this outcome was the economic evaluation.

6.3 The PBAC acknowledged the consumer comments from health professionals and professional organisations which were supportive of the submission and highlighted the burden that mBC and its treatments put on patients and the important clinical need for choice to enable earlier and broader access to T-DXd in select patients, accepting the risk of significant toxicity.

6.4 The PBAC considered the clinical need for earlier and broader access to T-DXd was low, as many treatment options are currently available for HR-positive mBC (e.g. hormone therapy, CKD4/6i, chemotherapy, T-DXd as 3L for HER2 low). The PBAC noted that T-DXd would not decrease the treatment burden compared with chemotherapy due to the requirement for IV administration every three weeks. The PBAC noted that guidelines such as NCCN, ESMO, and UpToDate variably recommend T-DXd as 2L treatment in certain circumstances such as rapidly progressive or

symptomatic disease or classify it under 'other recommended' treatments. The PBAC considered that there may be some benefit in allowing earlier treatment with T-DXd for some patients, and in increasing clinician and patient choice. However, the PBAC considered there is a lack of robust evidence supporting the proposed clinical place, particularly in the HER2 ultralow population, and the additional cost associated with this change was not sufficiently justified in the submission.

6.5 The PBAC considered that the proposed comparator of single-agent chemotherapy was appropriate as T-DXd is likely to replace IV chemotherapy (paclitaxel, nab-paclitaxel) and, for some patients, oral capecitabine. The PBAC noted that this was consistent with the clinical evidence presented and with the economic model, but the financial estimates assumed that only IV chemotherapy would be replaced by T-DXd.

6.6 The PBAC noted that the submission was based on the results of the DB-06 trial, which was an open-label trial that compared T-DXd to ICC monotherapy (either capecitabine, nab-paclitaxel, or paclitaxel) with results available for two interim analyses (IA1 and IA2). The PBAC considered that there was a high risk of bias for PFS, QoL and safety due to the open-label design. The PBAC noted that the trial included patients with both HER2 low and HER2 ultralow mBC, but considered that the HER2 ultralow population appeared under-represented in the trial as less than 20% of patients in DB-06 were classified as HER2 ultralow, compared with ~29-40% of HER2 negative breast cancer (see paragraph 3.3). The PBAC also noted that only 34% of patients in the ICC comparator arm who received subsequent anti-cancer therapies went on to receive T-DXd, whereas it would be expected that in Australian clinical practice most HER2 low patients would receive 3L T-DXd.

6.7 The PBAC noted T-DXd demonstrated a modest but statistically significant increase in PFS over ICC in the ITT population (IA1 [primary PFS analysis]: 13.2 months vs 8.1 months; HR = 0.64; 95% CI: 0.54 , 0.76). The PBAC noted that in the HER2 ultralow subgroup (N=76) the median PFS duration was similar, but the difference was not statistically significant (HR: 0.78; 95% CI: 0.50, 1.21). At IA2 OS data were also available, with median follow up of 27.6 months for the T-DXd arm and 25.0 months for the ICC arm, however OS data were immature and the OS hypothesis in the ITT population was not formally tested for statistical significance as per the multiple testing procedure. The PBAC noted that separation between the OS KM curves appeared modest, despite a lower-than-expected percentage of patients in the ICC arm receiving subsequent therapy with T-DXd. Estimates of OS for the HER2 ultralow subgroup were also imprecise given the small number of patients in the analysis. The PBAC also noted that, overall, there was no clear improvement in QoL with T-DXd over ICC.

6.8 The PBAC considered that the claim of superior comparative effectiveness of T-DXd over ICC in the HER2 low population was supported by the PFS data from the DB-06 trial. The PBAC stated that there was a high degree of uncertainty regarding the magnitude of benefit, due to the high risk of bias for investigator assessed PFS used in

the model. Furthermore, the PBAC considered that the OS benefit may be overestimated, as fewer patients received subsequent T-DXd than would be expected in Australian clinical practice.

6.9 The PBAC considered that the claim of superior comparative effectiveness of T-DXd over ICC in the HER2 ultralow population was uncertain due to the limited data available for this population. In addition, the PBAC considered that limitations in HER2 testing in scoring IHC patterns at the low end of the protein expression make it problematic to consistently identify the HER2 ultralow population. The PBAC considered that this reduces the likelihood that the benefit demonstrated in the trial would be realised in the PBS population.

6.10 The PBAC noted that in DB-06 the risk of AEs was higher in the T-DXd arm. Patients treated with T-DXd experienced higher rates of ILD than the ICC arm (19% vs 1%) and GI events (66% vs 24%). The frequency of any serious adverse events (SAEs) including death that was possibly related to treatment was higher in the T-DXd arm compared with the ICC arm (11% vs. 6%) as was the frequency of deaths possibly related to treatment (2.5% vs 1.6%). The PBAC considered that the claim of inferior comparative safety for T-DXd compared with ICC was reasonable for the overall population (HER2 low and HER2 ultralow). The PBAC acknowledged the real-world studies presented in the pre-PBAC response which outlined lower rates of ILD than observed in DB-06 (3% vs 12%), but maintained that there was a clear increase in harms for T-DXd compared with ICC, including life-threatening AEs.

6.11 The submission presented a modelled economic evaluation based on the DB-06 trial, with adjustment to outcomes and costs to account for the expected proportion of HER2-low patients treated with 3L T-DXd in the comparator arm. The PBAC noted that the adjustment substantially favoured T-DXd due to assumptions which resulted in the benefits of 3L T-DXd being underestimated and/or its costs being overestimated, and considered that the base case model lacked face value. The PBAC noted that the evaluation provided a revised approach to address this issue and the resulting ICER was $115,000 to <$135,000 per QALY, but acknowledged that there were limitations and possible flaws in the revised approach. The PBAC considered that the minor changes to the model proposed in the PSCR analysis (see paragraph 5.81) did not address the issues with the adjustment for subsequent T-DXd. The PBAC noted that other key drivers of the model were the time horizon, extrapolation functions, and the treatment-specific utility values for the PF health state. The PBAC noted that more conservative assumptions for these inputs resulted in an ICER of $155,000 to < $255,000 per QALY using the evaluator's revised model, which the PBAC considered was high and associated with substantial uncertainty.

6.12 The PBAC considered the financial estimates to be uncertain and the cost of 2L T-DXd to be underestimated. The PBAC considered that T-DXd would likely replace a proportion of both oral and IV chemotherapy. The PBAC noted that assuming some replacement of oral chemotherapy resulted in very substantial increases in the

financial estimates. The PBAC considered it would be reasonable for calculation of eligible patients to assume T-DXd would replace chemotherapy for patients who would otherwise receive IV chemotherapy (29% of the total patients) and in 50% of patients who would otherwise be treated with oral chemotherapy (50% of the remaining 71% of patients). The PBAC advised that T-DXd uptake rates should be no higher than [redacted]%, given the additional adverse events associated with T-DXd compared with chemotherapy. The PBAC also noted that the offsets for reduced use of 3L T-DXd, which were based on a proportion of the agreed patient numbers from the 3L setting (DB-04), were substantially underestimated, and inconsistent with the assumption in the economic model that 82.2% of progressed patients (100% of HER2-low patients) in the comparator arm would receive 3L T-DXd. The PBAC considered that offsets should be revised to be consistent with the 2L T-DXd estimates.

6.13 The PBAC noted that the submission proposed an increase in the existing 3L HER2-low T-DXd RSA financial caps for the addition of HER2-ultralow patients, with no increase proposed to account for additional 2L HER2-low patients. The PBAC further noted that expenditure for T-DXd as a 3L treatment has been substantially less than predicted and the current RSA caps were likely inflated even if additional 2L HER2-low patients were included within the existing thresholds. The PBAC considered that an RSA proposal should account for the revised estimates per paragraph 6.12, and adjust the current 3L caps to reflect actual PBS utilisation and intended reduction in cost per patient to be achieved through the caps.

6.14 The PBAC considered any resubmission should provide additional follow-up data from DB-06 if available, and if proposing a listing in the HER2-ultralow population, clinical data beyond the subgroup of patients in DB-06 should be provided. The PBAC considered the issues outlined in this PSD regarding the economic evaluation and financial estimates should also be addressed. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

6.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.