An addendum to this Public Summary Document has been included at the end of the document.

6.07 TRASTUZUMAB 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 Program) Authority Required (Telephone/Online) listing for trastuzumab deruxtecan (T-DXd) for the treatment of metastatic human epidermal growth factor receptor 2-positive (HER2+) gastric or gastroesophageal junction (G/GOJ) cancer following trastuzumab therapy.

1.2 The Sponsor submitted a streamlined co-dependent submission to the Medical Services Advisory Committee (MSAC), to support this Pharmaceutical Benefits Advisory Committee (PBAC) submission, requesting a minor change to the current in situ hybridisation (ISH) MBS item 73342 descriptor from "trastuzumab" to "a trastuzumab-containing agent[1] to allow re-testing prior to treatment with T-DXd.

1.3 Listing of T-DXd was requested on the basis of a cost utility analysis versus standard of care (SoC) which is chemotherapy in the Australian setting. The key components of the clinical issues addressed by the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with metastatic HER2-positive G/GOJ adenocarcinoma who have progressed following treatment with a trastuzumab-containing regimen.
Intervention	Trastuzumab deruxtecan (T-DXd, Enhertu) given as a 6.4 mg/kg infusion every three weeks (Q3W) (21-day cycle) until disease progression or unacceptable toxicity.
Comparator	SoC chemotherapy consisting of either monotherapy (with paclitaxel, irinotecan, or docetaxel) or FOLFIRI
Outcomes	Objective response rate (ORR), overall survival (OS), progression-free survival (PFS), duration of response (DoR), confirmed disease control, confirmed objective response, quality of life (QoL), safety
Clinical claim	T-DXd has superior efficacy and an inferior but manageable safety profile compared to chemotherapy in patients with metastatic HER2-positive G/GOJ adenocarcinoma who have received a prior trastuzumab-based regimen.

Source: Table 1-1, p5 of the submission.
HER2 = human epidermal growth factor receptor 2; FOLFIRI = folinic acid, fluorouracil, and irinotecan combination regimen; G/GOJ = gastric or gastro-oesophageal junction, SoC = standard of care; T-DXd = trastuzumab deruxtecan.

[1] MSAC Application 1762 – Amendment to HER-2 MBS item to allow for trastuzumab deruxtecan for the treatment of patients with metastatic gastric or gastroesophageal junction adenocarcinoma, https://www.msac.gov.au/applications/1762.

2 Background

Registration status

2.1 **The TGA status at the time of PBAC consideration:** Trastuzumab deruxtecan was provisionally included on the Australian Register of Therapeutic Goods (ARTG) on 25 March 2025 for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen[2].

2.2 The TGA clinical evaluator's report and the Delegate's Overview were provided with the PBAC submission. On 10 September 2024, the Delegate recommended approval via the provisional approval pathway based on objective response rate. Continued approval of this indication depends on verification and description of benefit in a clinical trial.

2.3 T-DXd is also registered in unresectable and metastatic breast cancer for use as:

- treatment of unresectable or metastatic HER2 positive breast cancer in patients who have previously received trastuzumab and a taxane for metastatic disease or one prior anti-HER2 based regimen and developed recurrence during or within six months of completing neo-adjuvant or adjuvant therapy.
- treatment of adult patients with unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/ISH-negative) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Previous PBAC considerations

2.4 This is the first submission requesting Pharmaceutical Benefits Scheme (PBS) listing for T-DXd in G/GOJ adenocarcinoma. T-DXd is currently PBS listed for unresectable and metastatic breast cancer.

2.5 PBAC considered 1L trastuzumab for patients with metastatic (Stage IV) HER2-positive G/GOJ adenocarcinoma at its July 2015 meeting (trastuzumab Public Summary Document [PSD], July 2015 PBAC meeting). PBAC submissions for 1L pembrolizumab (pembrolizumab PSD, November 2021 PBAC Meeting with March 2022 Addendum), 1L nivolumab (nivolumab PSD, November 2021 PBAC Meeting with March 2022 Addendum), and 2L ramucirumab (ramucirumab PSD, March 2018 PBAC meeting) included patients with G/GOJ adenocarcinoma but without any restriction regarding HER2 status as these are not HER2-targeted therapies.

2.6 At the November 2019 PBAC meeting, the PBAC recommended listing of trifluridine with tipiracil, in fixed dose combinations for third (or subsequent) line treatment of patients with metastatic G/GOJ previously treated with at least two prior lines of

[2] https://www.tga.gov.au/resources/artg/343262

chemotherapy that included a fluoropyrimidine, a platinum, and either a taxane- or irinotecan.

2.7 PBS listing of 1L tislelizumab for the treatment of advanced or metastatic gastro-oesophageal cancer was recommended by the PBAC in November 2024.[3] At that time the PBAC considered it was appropriate for tislelizumab to be included in the risk sharing arrangement currently in place for gastro-oesophageal cancers. The recommended population for tislelizumab overlaps with the proposed population for T-DXd in the current submission, as it does not exclude patients based on HER2 status (tislelizumab PSD, November 2024 PBAC meeting). The PBS listing for tislelizumab was implemented on 1 April 2025.

2.8 A submission for zolbetuximab for the 1L treatment of locally advanced unresectable or metastatic HER2 negative G/GOJ adenocarcinoma was considered at the March 2025 PBAC meeting[4].

3 Requested listing

3.1 The sponsor's proposed restrictions are shown below, with suggestions and additions proposed by the Secretariat and PBAC added in italics and suggested deletions in strikethrough.

[3] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2024-11/files/tislelizumab-psd-nov-2024.pdf

[4] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/2025/March-2025-PBAC-Meeting.pdf

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private)	~~700~~ *800* mg	8
Available brands			
Enhertu trastuzumab deruxtecan 100 mg injection, 1 vial			
Restriction Summary [new] / Treatment of Concept: [new]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)			
Severity: *Locally advanced unresectable or* Metastatic (Stage IV)			
Condition: *Adenocarcinoma of the stomach* ~~Gastric~~ or gastro-oesophageal junction ~~adenocarcinoma~~			
Indication: *Locally advanced unresectable or* metastatic (Stage IV) HER2 positive *adenocarcinoma of the stomach* ~~gastric~~ or gastro-oesophageal junction ~~adenocarcinoma~~			
~~**Treatment Phase:** Initial and continuing~~			
Clinical Criteria:			
Patient must have evidence of human epidermal growth factor 2 (HER2) gene amplification			
AND			
Clinical Criteria:			
The condition must have progressed following treatment with *at least one prior* ~~a~~ trastuzumab-containing regimen for metastatic *adenocarcinoma of the stomach* ~~gastric~~ or gastro-oesophageal junction ~~adenocarcinoma~~			
AND			
Clinical Criteria:			
Patient must have, at the time of initiating treatment with this drug, a WHO performance status no higher than 1			
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 50% (ii) symptomatic heart failure; confirm cardiac function testing for the first prescription only			
Treatment criteria:			
Patient must be undergoing initial treatment with this drug – the following is true: (i) this is the first prescription for this drug, (ii) this prescription seeks no more than 3 repeats prescriptions; or			
Patients must be undergoing continuing treatment with this drug – the following are true (i) there has been an absence of 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			
Prescribing Instructions: Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription: 1) *Confirmation* ~~Evidence~~ of HER2 gene amplification (evidence obtained in relation to past PBS treatment is acceptable). 2) Details of prior HER2 directed drug regimens prescribed for the patient. 3) Cardiac function test results (evidence obtained in relation to past PBS treatment is acceptable).			
Prescribing Instructions: Increased maximum amounts may only be authorised where a patient's weight is greater than 125 kg			

3.2 The recommended T-DXd dose in G/GOJ adenocarcinoma is 6.4 mg/kg IV administered every 3 weeks (Q3W), until disease progression or unacceptable toxicity. The proposed max amount of 700 mg would allow for treatment of patients up to 110 kg, however an additional vial would be required for patients weighing more than 110 kg.

The PBAC considered it would be appropriate for the maximum amount to be increased to 800 mg to allow for patients weighing up to 125 kg, with increases to the maximum amount allowable where a patient's weight is >125 kg.

3.3 The submission proposed a special pricing arrangement (SPA). The effective ex-manufacturer price proposed in the submission for G/GOJ adenocarcinoma is $ per 100 mg vial.

3.4 The requested listing allows grandfathered patients using the Sponsor's Co-pay Access Program to continue on PBS-funded T-DXd. The submission assumed there would be < 500 grandfathered patients.

3.5 The requested indication for T-DXd (Metastatic (Stage IV) HER2 positive gastric or gastro-oesophageal junction adenocarcinoma) is consistent with the current restriction for 1L trastuzumab (Metastatic (Stage IV) HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction). The Secretariat has proposed wording that matches the indication for 1L trastuzumab, for consistency. However, the proposed indication is narrower than the TGA indication and the populations enrolled in the two supporting studies, Destiny Gastric 1 (DG-01) and Destiny Gastric 2 (DG-02) in that use for locally advanced G/GOJ adenocarcinoma was not requested. The PBAC considered the PBS listing should include patients with locally advanced/unresectable G/GOJ adenocarcinoma consistent with the TGA indication and clinical evidence.

3.6 The requested restrictions require prior use of a trastuzumab-containing regimen (consistent with studies DG-01 and DG-02, whereas the TGA indication is for patients who have received a prior anti-HER2-based regimen. The requested restrictions did not exclude patients with a history of interstitial lung disease (ILD) or pneumonitis requiring corticosteroids; these patients were excluded from studies DG-01 and DG-02. However, prior history of ILD or pneumonitis is not contraindicated in the PI for T-DXd, although it is included under "Precautions for Use".

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

4 Population and disease

4.1 Metastatic G/GOJ adenocarcinomas comprise 90% of gastric cancers. They are aggressive and difficult to treat, with a significant impact on patients' quality of life. Most patients with metastatic G/GOJ adenocarcinomas progress rapidly after 1L treatment with limited options available for second and subsequent lines of therapy. The 5-year survival rate for metastatic disease is currently ~5%.[5]

[5] Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *The Lancet Oncology*. 2019 2019/11/01/;20(11):1493-505.

4.2 HER2 is a biomarker in G/GOJ cancer which is over-expressed in approximately 18% of patients.[6] The prevalence of HER2 positivity in advanced G/GOJ adenocarcinoma ranges from 10% – 20%, depending on the definition of HER2 positivity applied, which varies in different global jurisdictions.[7]

4.3 HER2 status is tested to determine eligibility to 1L PBS-funded trastuzumab using IHC (MBS Item 72848) and ISH testing (MBS Item 73342). However, patients receiving 1L trastuzumab may develop HER2 resistance leading to loss of treatment response. Potential mechanisms for resistance to trastuzumab treatment have been identified in exploratory studies, including reduction or loss of HER2 overexpression or gene amplification. This observation could potentially impact on response to subsequent HER2-targeted therapy, such as T-DXd. The DG-01 study protocol highlighted that a reduction in HER2 expression from HER2-positive to HER2-negative has been reported in approximately 29% of patients with gastric cancer after receiving trastuzumab treatment. However, estimates in the literature for loss of HER2 positive status post trastuzumab identified during the evaluation varied from 29% to 47% (Seo et al (2019)[8], Saeki et al (2018)[9].

4.4 The proposed treatment algorithm included in the submission provided an option for tumour tissue re-profiling by obtaining a new tumour sample/biopsy and retesting for HER2 status. The submission stated that HER2 re-testing prior to treatment with T-DXd would be limited to approximately % of patients and clinicians considered it was unlikely to be carried out prior to initiation of T-DXd treatment due to patient-related and logistical challenges with obtaining new biopsies in the proposed population.

4.5 There are no standard Australian guidelines for treating G/GOJ adenocarcinoma patients. Patients who test positive for HER2 were likely be treated with trastuzumab which is PBS funded as a first-line therapy. There are no anti-HER2 therapies currently TGA approved for 2L treatment of patients with disease progression on 1L trastuzumab therapy. The submission stated that, in Australia, current treatment options in the 2L or later setting are chemotherapies with 29% of patients receiving paclitaxel, 28% receiving irinotecan, 7% receiving docetaxel and 36% receiving folinic acid, fluorouracil, and irinotecan combination regimen (FOLFIRI). Treatments not previously received are used in the 3L or later setting. Trifluridine/tipiracil

[6] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010 Aug 28;376(9742):687-97.

[7] Boku N. HER2-positive gastric cancer. Gastric Cancer. 2014;17(1):1-12, Kumarasinghe MP, et al. Pathology. 2017;49(6):575-81., Lee S, et al. Histopathology. 2011;59(5):832-40.

[8] Seo S, Ryu MH, Park YS, et al. Loss of HER2 positivity after anti-HER2 chemotherapy in HER2-positive gastric cancer patients: results of the GASTric cancer HER2 reassessment study 3 (GASTHER3). Gastric Cancer. 2019 May;22(3):527-35.

[9] Saeki H, Oki E, Kashiwada T, et al. Re-evaluation of HER2 status in patients with HER2-positive advanced or recurrent gastric cancer refractory to trastuzumab (KSCC1604). *Eur J Cancer*. 2018 Dec;105:41-9.

combination therapy is PBS reimbursed for use in the 3L setting but PBS data indicates that use is minimal due to an unfavourable efficacy and toxicity profile.

4.6 T-DXd is a novel antibody-drug conjugate (ADC) comprising trastuzumab linked covalently to a topoisomerase I inhibitor deruxtecan (DXd) via a tetrapeptide based cleavable linker. The ADC delivers cytotoxic DXd directly to HER2-expressing tumour cells. DXd released from lysed tumour cells is subsequently absorbed by and may be cytotoxic to adjacent tumour cells regardless of their HER2 status; this is known as a bystander effect.

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

5 Comparator

5.1 The submission nominated standard of care (SoC) chemotherapy, consisting of paclitaxel, irinotecan, docetaxel or FOLFIRI, as the comparator. The nominated comparator is appropriate however only two of the nominated SoC chemotherapies were included in the pivotal DG-01 study. The submission stated that current 2L chemotherapy utilisation in Australia is 36% FOLFIRI, 29% paclitaxel, 28% irinotecan, and 7% docetaxel based on advice from a clinician Advisory Board. Of 187 treated patients in DG-01, 125 received trastuzumab deruxtecan and 62 received physician's choice of chemotherapy (55 received irinotecan 150 mg/m^2 Q2W and 7 received paclitaxel 80 mg/m^2 QW for 3 weeks followed by a 2-week rest period). The chemotherapy selected for each participant was dependent upon prior treatment received.

5.2 The submission stated that the PBAC and international guidelines have previously accepted these chemotherapies have similar efficacy but different toxicity profiles and therefore, irinotecan and paclitaxel were considered appropriate proxies for SoC chemotherapies. The PBAC's advice regarding the equivalent efficacy for these chemotherapies for treatment of G/GOJ adenocarcinoma could not be located during the evaluation. The European Society for Medical Oncology (ESMO) clinical guidelines for gastric cancer state that paclitaxel, docetaxel and irinotecan have equivalent efficacy but different toxicity profiles, based on clinical evidence from a meta-analysis and a comparative clinical trial. However, there were limited data to show the comparative efficacy and safety of FOLFIRI relative to other chemotherapies[10].

5.3 The Pre-Sub-Committee Response (PSCR) maintained that there was sufficient clinical evidence to support equivalent efficacy of the nominated comparators, and that the two DG-01 comparators, irinotecan and paclitaxel, could be considered as proxies for the efficacy of FOLFIRI. The PSCR provided additional evidence from two small studies: a Phase 2 study and a retrospective review (Sym SJ et al., 2013; Ürün, M. et al., 2023) for FOLFIRI vs irinotecan monotherapy and FOLFIRI vs paclitaxel to demonstrate that

[10] Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022 Oct;33(10):1005-20.

FOLFIRI has equivalent efficacy to the other three nominated comparators in the submission. The ESC considered that similar efficacy was seen with the available 2L chemotherapy options, and that the nominated comparator was appropriate.

5.4 Although RAM + PAC was recommended by PBAC at the March 2018 PBAC meeting for the treatment of G/GOJ adenocarcinoma, the PBS listing of ramucirumab did not proceed. The PBAC had advised that a price reduction would be required for ramucirumab to be cost-effective when compared with paclitaxel in the proposed PBS population. In March 2018, the PBAC considered paclitaxel monotherapy was the appropriate main comparator and advised that taxanes or irinotecan were the most common second-line treatment used in the Australian clinical practice (paragraph 7.5 and 7.6, ramucirumab PSD, March 2018 PBAC meeting). The submission reasonably proposed that ramucirumab was not an appropriate comparator for T-DXd in the Australian setting.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from Rare Cancers Australia and the Pancare foundation highlighted the poor prognosis for HER2+ G/GOJ adenocarcinoma and the benefits of increased choice of treatment for the population. The Pancare foundation noted improved response rates and overall survival for T-DXd compared to chemotherapy, as well as the potential for hope and reduced financial burden and equitable access if it is PBS listed. Consumer input also noted the potential for significant side effects from T-DXd, and the health professional described the importance of educating clinicians regarding monitoring and early intervention for pneumonitis.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the T-DXd submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for T-DXd, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[11], based on the single arm DG-02 study. The PBAC noted that the ESMO-MCBS score is 4 out of 5 based on the DG-01 study.

[11] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

Clinical studies

6.4 The submission included two studies. Pivotal evidence was from an open-label, 2:1 randomised controlled trial (RCT) that evaluated the safety and efficacy of T-DXd (N=126) compared to SoC (N=62), either irinotecan (N=55) or paclitaxel (N=7), in HER2-positive East-Asian patients with advanced G/GOJ adenocarcinoma, who had progressed on at least two prior regimens (Destiny Gastric 01; DG-01), including one trastuzumab-based regimen. Randomisation was stratified by region (Japan or Korea), Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and HER2 status (HER2 IHC 3+ or IHC 2+/ISH+). The primary endpoint was objective response rate (ORR) assessed by independent central review (ICR) based on Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. Secondary efficacy outcomes included OS, PFS and health-related quality of life (HRQoL).[12]

6.5 Supporting evidence was provided by a single arm study evaluating the safety and efficacy of T-DXd (N=79) in patients with HER2-positive advanced or metastatic G/GOJ adenocarcinoma who had progressed on a prior trastuzumab-containing regimen (Destiny Gastric 02; DG-02); the study population was recruited from Europe and North America.[13]

6.6 In study DG-01, patients were required to meet inclusion criteria for HER2 positivity (centrally confirmed HER2 IHC 3+ or IHC 2+/ISH+) using archival tumour samples obtained prior to trastuzumab treatment, or fresh samples where archival tissue was not available. In study DG-02, criteria for HER2 positive status were the same but based on fresh tumour tissue obtained after progression on or after a prior trastuzumab-containing regimen. The time that tumour samples or biopsies were obtained in DG-01 (before prior treatment with trastuzumab) means that it was not possible to accurately determine the HER2 positive status of patients at the point of T-DXd treatment initiation due to the potential development of HER2 resistance following prior trastuzumab treatment, as discussed in para. 4.3. However, testing prior to 1L trastuzumab is consistent with how testing would occur in clinical practice as no requirement for re-biopsy/re-testing is proposed.

6.7 The studies presented in the submission, and their associated reports are provided in Table 2.

6.8 The key features of studies DG-01 and DG-02 are summarised in Table 3.

[12] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med*. 2020 Jun 18;382(25):2419-30.

[13] Van Cutsem E, di Bartolomeo M, Smyth E, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. *Lancet Oncol*. 2023 Jul;24(7):744-56.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Destiny Gastric 01 (DG-01) NCT03329690	DG-01 CSR DCO1 (8 November 2019) DG-01 CSR DCO2 (3 June 2020) DG-01 Protocol v6.0 Shitara, K., Bang, Y. J., Iwasa, S., et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GOJ) adenocarcinoma: A randomized, phase II, multicenter, open-label study (DESTINY-Gastric01). Shitara, K., Bang, Y. J., Iwasa, S., et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. Shitara, K., Bang, Y. J., Chung, H. C., et al. A phase II, multicenter, open-label study of [fam-] trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing gastric cancer. Shitara, K., Bang, Y. J., Sakai, D., et al. A randomized, phase II, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing gastric cancer. Yamaguchi, K., Bang, Y. J., Iwasa, S., et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GOJ) adenocarcinoma: Final overall survival (OS) results from a Randomized, multicenter, open-label, phase 2 study (DESTINYGastric01). Yamaguchi, K., Bang, Y., Iwasa, S., et al. O-11 Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma: a randomized, phase 2, multicenter, open-label study (DESTINY-Gastric01). Yamaguchi, K., Bang, Y. J., Sakai, D., et al. 2018. A randomized phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing gastric cancer.	NA NA NA J Clin Oncol, 2020; Conference, 38 NEJM, 2020; 382(25), 2419-2430 J Clin Oncol, 2019; Conference, 37 Ann Oncol, 2018; 29 J Clin Oncol, 2022; Conference, 40 Ann Oncol, 2020; 31, 235 J Clin Oncol, 2018; 36
Destiny Gastric 02 (DG-02) NCT04014075	DG-02 CSR DCO1 (9 April 2021) DG-02 CSR DCO2 (8 November 2021) DG-02 Protocol v1.0 (23 April 2019) Ku, G.Y., et al. 1205MO Updated analysis of DESTINY-Gastric02: A phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in Western patients (Pts) with HER2-positive unresectable/metastatic gastric/gastroesophageal junction (GOJ) cancer who progressed on or after trastuzumab-containing regimen. Van Cutsem, E., Di Bartolomeo, M., Smyth, E., et al. LBA55 Primary analysis of a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in Western patients (Pts) with HER2-positive (HER2+) unresectable or metastatic gastric or gastroesophageal junction (GOJ) cancer who progressed on or after a trastuzumab-containing regimen. Van Cutsem, E., Di Bartolomeo, M., Smyth, E., et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study.	NA NA NA Ann. Oncol., 2022; 33: p. S1100 Ann Oncol, 2021; 32(Supp. 5), S1332 Lancet Oncol, 2023; 24(7): 744-756

Source: Table 2-4, pp 40-41 of the submission.
CSR = Clinical Study Reports; DCO1 = data cut-off 01; DCO2 = data cut-off 02; DG-01 = DESTINY-Gastric 01; DG-02 = DESTINY-Gastric 02; NCT = National Clinical Trial.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
T-DXd vs. SoC (irinotecan or paclitaxel)						
DG-01 NCT03329690 Shitara 2020	188	Phase II, OL, MC, RCT Conducted in Korea and Japan All comers (ITT): DCO1 (8 November 2019): Primary ORR and first interim OS analysis DCO2 (3 June 2020): Final OS analysis	Low	HER2-positive 3L+ locally advanced and metastatic G/GOJ adenocarcinoma after failure on prior trastuzumab HER2 testing based on archived tissue or fresh tissue if not available.	ORR OS PFS DoR HRQoL Safety	Used
T-DXd (no comparator)						
DG-02 NCT04014075 Van Cutsem, 2023	79	Phase II, OL, MC, SA Conducted in Europe and US Full analysis set (ITT): DCO1 (9 April 2021): Primary ORR analysis DCO2 (8 Nov 2021): Updated analysis*	High	HER2 positive 2L advanced G/GOJ cancer after failure on prior trastuzumab HER2 testing based on fresh tissue after progression on or after a prior trastuzumab-containing regimen	ORR OS PFS DCR HRQoL Safety	Used

Source: Table 2-5, p 43 of the submission; Table 6, p vii of the executive summary
2L = second-line; 3L+ = third-line or later; DCO = data cut-off; DCR = disease control rate; DoR = duration of response; G/GOJ = gastric and gastro-oesophageal; HRQoL = health-related quality of life; IO = immunotherapy; MC = multicentre; OL = open-label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every three weeks; SoC = standard of care chemotherapy; T-DXd = trastuzumab deruxtecan;
*Not pre-specified. Requested as part of a health authority review.

6.9 The risk of bias was considered low in study DG-01 except for subjective outcomes such as patient reported outcomes (PROs) and patient reported adverse events (AEs) as there was no allocation concealment. Assessment by blinded ICR was used to overcome bias associated with lack of allocation concealment for clinical outcomes for treatment response in DG-01.

6.10 The population in study DG-01 was East-Asian patients recruited from Japan and Korea. The most frequently administered prior anticancer agents in the whole study population were trastuzumab (98.9%), ramucirumab (72.2%), capecitabine (71.7%), paclitaxel (70.6%), nivolumab (25.7%), irinotecan (7.0%) and pembrolizumab (6.4%). Reported outcomes from DG-01 may have limited applicability to efficacy and safety of T-DXd in the proposed Australian setting due to the following issues: differences in population characteristics, differences in incidence of gastric vs GOJ adenocarcinoma, differences in the incidence of the intestinal vs diffuse histological subtype, diagnosis at an earlier disease stage via nationwide screening programs, differences in disease

management, more extensively pretreated as 3L or later use of T-DXd, different definition of HER2 positive status, use of treatments not reimbursed in Australia (e.g. ramucirumab, nivolumab) prior to T-DXd treatment, use of nivolumab treatment which is not reimbursed in Australia after failure on T-DXd, increased susceptibility to ILD that is an AE of special interest for T-DXd treatment, and exclusion of patients with prior ILD requiring corticosteroids.

6.11 The population in study DG-02 was predominantly Caucasian (87.3%) recruited from Europe and North America. The population demographics, disease characteristics, proposed 2L use of T-DXd, and absence of ramucirumab treatment prior to T-DXd were more aligned with the Australian setting than study DG-01. Only the characteristics of the patients recruited from Europe were used in the economic model as these were considered more representative of the Australian population than those of the North American participants, who had a higher median body weight than the European population in DG-02.

6.12 The PSCR acknowledged the applicability issues discussed above in relation to DG-01 and noted that DG-02 was included as supportive evidence. The PSCR maintained that the combined evidence from studies DG-01 and DG-02 supports the clinical benefit of T-DXd for the proposed PBS population. In addition, the PSCR provided OS data from DG-04, a Phase 3 study of T-DXd vs ramucirumab + paclitaxel to support the applicability of the data presented in the submission to the Australian setting. The PSCR reported a median OS of 14.7 months in DG-04, which is longer than the OS of reported in DG-01 and DG-02 (approximately 12 months, Table 4). The ESC noted that a statistically significant improvement in median OS was observed for T-DXd vs RAM+PAC study DG-04, and considered this was supportive evidence although this study does not directly inform the relative efficacy of T-DXd vs SoC chemotherapy, the main comparator for the current submission.

Comparative effectiveness

6.13 For study DG-01 (DCO2; 3 June 2020), the median duration of follow-up for the T-DXd and SoC arms was 11.9 months and 8.5 months, respectively. Similar median follow-up was reported for the T-DXd population of DG-02 (10.2 months). Relative dose intensity and duration of treatment was numerically higher for T-DXd versus SoC and was higher for paclitaxel versus irinotecan; more patients in the SoC arm received irinotecan (n=55) versus paclitaxel (n=7) which had an impact on the efficacy and safety results reported for the SoC arm in DG-01.

6.14 The primary endpoint for both DG-01 and DG-02 was ORR assessed by ICR. DG-01 met its primary endpoint demonstrating a superior confirmed ORR by ICR for T-DXd versus SoC (ORR, 40.5%, 95% CI: 31.8, 49.6 vs 11.3%, 95% CI: 4.7, 21.9; absolute difference, 28.4%, 95% CI: 14.2, 39.6, p<0.0001). Results for T-DXd in DG-02 were similar to DG-01 with a confirmed ORR by ICR of 41.8% (95% CI: 30.8, 53.4).

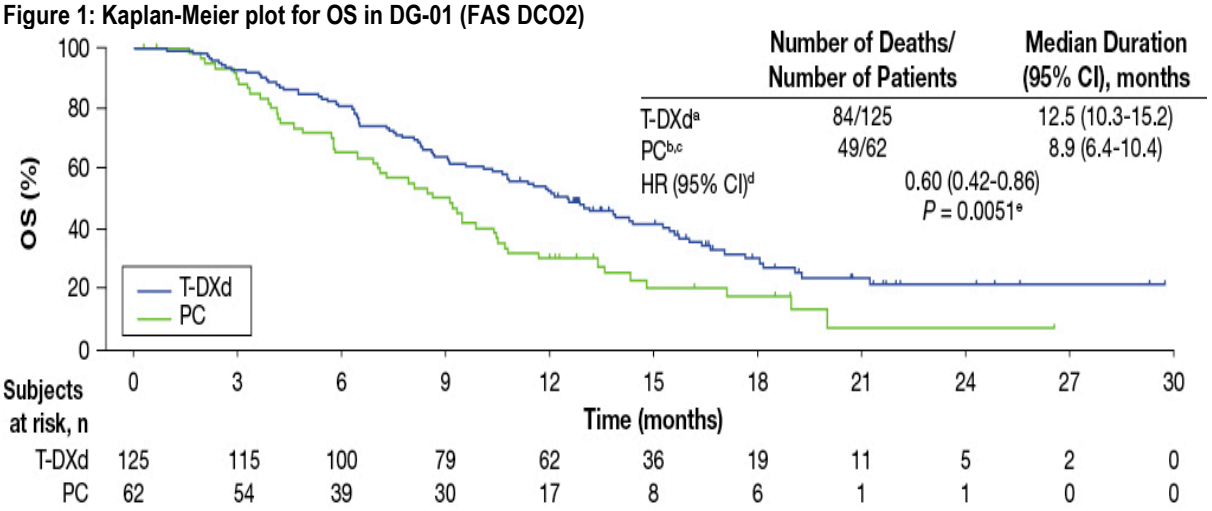
6.15 OS and PFS outcomes for studies DG-01 and DG-02 are summarised in Table 4. The Kaplan-Meier (KM) OS plot and PFS plot for DG-01 is presented in Figure 1 and Figure 2, respectively.

Table 4: Summary of survival outcomes in studies DG-01 and DG-02 (FAS)

	DG-01				DG-02
	T-DXd N=125	**SoC N=62**	**Absolute difference**	**HR (95% CI)**	**T-DXd N=79**
Progression-free survival					
Events, n (%)	82/125 (65.6)	36/62 (58.0)			
Median PFS, months (95% CI)	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)	2.1	**0.47 (0.31, 0.71)**	5.6 (4.2, 8.3)
% not progressed at 3 months (95% CI)	71.9 (63.0, 79.1)	50.3 (35.5, 63.5)	21.6		70.5 (58.7, 79.5)
% not progressed at 6 months (95% CI)	43.0 (33.6, 52)	20.6 (8.9, 35.6)	22.4		48.9 (36.6, 60.2)
% not progressed at 9 months (95% CI)	33.3 (24.4, 42.4)	NE	NE		36.3 (24.5, 48.1)
% not progressed at 12 months (95% CI)	30.4 (21.5, 39.7)	NE	NE		20.0 (9.4, 33.3)
Overall survival					
Deaths, n/N (%)	84/125 (67.2)	49/62 (79.0)			46/79 (58.2)
Median months OS (95% CI)	12.5 (10.3, 15.2)	8.9 (6.4, 10.4)	3.6	**0.60 (0.42, 0.86)**	12.1 (9.4, 15.4)
% alive at 3 months (95% CI)	92.7 (86.5, 96.2)	90.0 (79.1, 95.4)	2.7		—
% alive at 6 months (95% CI)	80.7 (72.5, 86.6)	65.0 (51.5, 75.6)	15.7		77.8 (66.8, 85.6)
% alive at 9 months (95% CI)	63.7 (54.6., 71.5)	50.0 (36.8, 61.8)	13.7		—
% alive at 12 months (95% CI)	52.2 (43.1, 60.6)	29.7 (18.7, 41.5)	22.5		50.6 (38.4, 61.5)

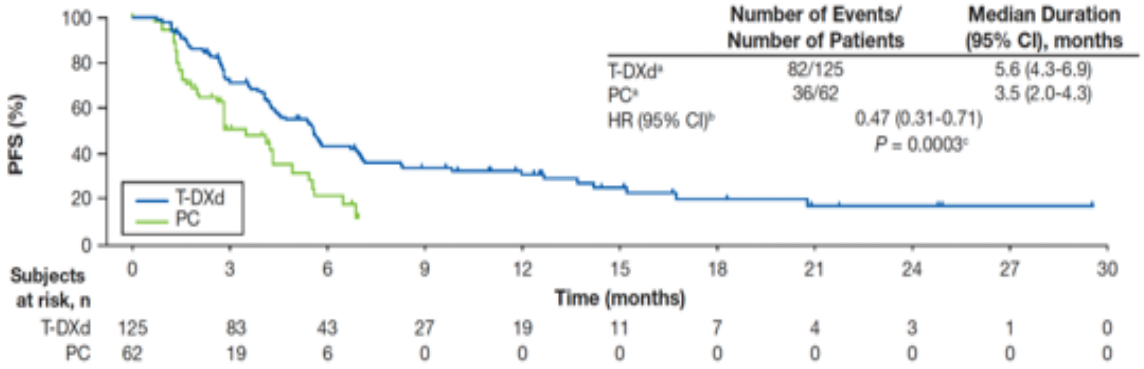
Source: Table 2-22, p71 and Table 2-23, p74 of the submission.
CI = confidence interval; FAS = full analysis set defined as all patients that received at least one dose of study drug; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not evaluable; OS = overall survival; PFS = progression-free survival; SoC = standard of care; T-DXd = trastuzumab deruxtecan.
Bold indicates statistically significant results.

Figure 1: Kaplan-Meier plot for OS in DG-01 (FAS DCO2)



Source: Figure 2-4, p73 of the submission, Yamaguchi K et al. 2021 (slide 16)
CI = confidence interval; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; OS = overall survival; PC = physician's choice (standard of care) chemotherapy (irinotecan or paclitaxel); T-DXd = trastuzumab deruxtecan.
[a] In the T-DXd arm, 41 patients (32.8%) were censored.
[b] In the PC arm, 13 patients (21.0%) were censored.
[c] One patient in the PC arm received crossover treatment of T-DXd
[d] HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.

Figure 2: Kaplan-Meier plot of PFS in DG-01 (FAS DCO2)



Source: Figure 2-6, p75 of the submission, Yamaguchi K et al. 2021 (slide 16)
CI = confidence interval; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; OS = overall survival; PC = physician's choice (standard of care) chemotherapy (irinotecan or paclitaxel); T-DXd = trastuzumab deruxtecan.
[a] In the T-DXd arm, 71 patients (56.8%) had PD and 11 (8.8%) had death as the first event. In the PC arm, 34 patients (54.8%) had PD and two (3.2%) had death as the first event. 43 (34.4%) and 26 (41.9%) were censored in the T-DXd and PC arms , respectively, for no baseline (T-DXd [n=0]; PN [n=2]) or postbaseline tumour assessment (n=1; n=3), receiving new anti-cancer therapy (n=14; n=14) and missing two consequative tumour assessments (n=5; n=1); the remaining patients were censored without an event.
[b] HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region
[c] Comparison between T-DXd and PC overall using a stratified log-rank test with region as a stratification factor.

6.16 In study DG-01 (DCO2, 3 June 2020), the OS data were 70.7% mature (133 events). There was a statistically significant improvement in OS in the T-DXd arm versus the SoC arm (HR, 0.60, 95% CI: 0.42, 0.86, p = 0.005) with an estimated 3.6-month improvement in median OS with T-DXd treatment versus SoC (12.5, 95% CI: 10.3, 15.2 months vs 8.9, 95% CI: 6.4, 10.4 months). There was an early separation of the curves between the T-DXd and SoC arms in the KM plot for OS that was sustained during follow-up (Figure 1). In study DG-02 (final DCO), the OS data were 58% mature

with a median OS of 12.1 (95% CI: 9.4, 15.4) months; this was consistent with the median OS reported in DG-01 (Table 4).

6.17 In study DG-01, the median PFS and HR was the same at the interim (DCO1) and final analysis (DCO2). There was a statistically significant improvement in PFS in the T-DXd arm versus the SoC arm with a 53% reduction in risk of disease progression or death (HR, 0.47, 95% CI: 0.31, 0.71, p = 0.0003). The KM plot for PFS by ICR displayed a clear separation of the curves from around 1 month following treatment initiation (Figure 2). The median PFS in study DG-02 was 5.6 (95% CI: 4.2, 8.3) months which was comparable to PFS in the T-DXd arm of DG-01 (Table 4).

6.18 The submission did not present the prespecified subgroup analyses for OS from DG-01. These data were obtained from the DG-01 Clinical Study Report (CSR) (DCO2, 03 Jun 2020). Subgroup analyses for OS based on HER2 status indicate that T-DXd may be more effective than SoC in patients with the higher HER2 IHC 3+ status (N=143; HR: 0.47 [95% CI, 0.31, 0.71]) than in patients with a HER2 IHC 2+/ISH+ status (N=44; HR: 1.48 [95% CI, 0.70, 3.16]) although confidence in the HR estimate was lower in the HER2 IHC 2+/ISH+ subgroup due to the small sample size. This observation regarding efficacy was also made for the prespecified subgroup analyses based on HER2 status for ORR and PFS. Data from the DG-02 subgroup analyses support observations from DG-01 for HER2 status.

6.19 Prior treatment with ramucirumab was not associated with an increased HR for OS for T-DXd versus SoC. However, an increase in PFS and OS HRs for T-DXd treatment relative to the primary population were observed for participants receiving the following: prior gastrectomy, prior adjuvant/neoadjuvant therapy, prior treatment with checkpoint inhibitor or other immune-oncology therapy, and prior treatment with nivolumab.

6.20 In the prespecified subgroup analyses of DG-02, survival outcomes (PFS, OS) were lower in the North American subgroup (n=34) than in the European subgroup (n=45) although differences observed were not tested for significance.

6.21 Health-related quality of life (HRQoL) of participants in DG-01 at DCO1 and in DG-02 was measured using the European Organization for Research and Treatment of Cancer (EORTC) EuroQol 5 dimension 5-level (of severity) assessment (EQ-5D-5L). At the end of treatment, completion rates were lower in the T-DXd arm (66.4%) than in the SoC arm (85.5%) and lower in both arms than at baseline. The mean EQ-5D-5L scores at the end of treatment were similar in the T-DXd arm (0.7009; mean reduction of 0.1269) vs the SoC arm (0.7251; mean reduction of 0.1329). The submission concluded that treatment with T-DXd did not deteriorate HRQoL compared to SoC. No explanation was provided for the higher non-completion rate in the T-DXd arm. This is a significant source of bias in the HRQoL data. The impact of treatment with T-DXd on HRQoL in DG-01 was uncertain based on the data provided. Similar observations applied to the data available from DG-02.

Comparative harms

6.22 The submission made a claim of inferior but manageable safety for T-DXd compared to SoC based on the safety data presented in the submission.

6.23 A summary of the safety results from DG-01 and DG-02 are presented in Table 5. Analyses of safety were carried out for all patients who received study treatment (safety analysis set; SAS). The safety data for DG-01 and DG-02 presented in the submission were based on DG-01 DCO2 (3 June 2020) and DG-02 DCO2 (8 Nov 2021). Median (range) duration of follow-up was 5.8 (0.8, 29.1) months in the T-DXd arm and 3.2 (1.9, 4.5) months in the SoC arm.

Table 5: Summary of key adverse events in studies DG-01 and DG-02 (SAS)

TEAE category, n (%)	DG-01				DG-02
	T-DXd N = 125 n (%)	Irinotecan N=55 n (%)	Paclitaxel N=7 n (%)	SoC N = 62 n (%)	T-DXd N=79 n (%)
Any TEAE	125 (100.0)	54 (98.2)	7 (100.0)	61 (98.4)	79 (100)
Drug-related TEAEs [a]	122 (97.6)	51 (92.7)	5 (71.4)	56 (90.3)	75 (95)
Grade ≥3 TEAEs [b]	107 (85.6)	33 (60.0)	2 (28.6)	35 (56.5)	44 (56)
Drug-related Grade ≥3+ TEAEs b	94 (75.2)	25 (45.5)	2 (28.6)	27 (43.5)	24 (30.4)
Serious TEAEs	56 (44.8)	15 (27.3)	1 (14.3)	16 (25.8)	33 (42)
Drug-related serious TEAEs	30 (24.0)	5 (9.1)	0 (0.0)	5 (8.1)	10 (12.7)
TEAEs associated with discontinuation of study treatment	22 (17.6)	4 (7.3)	0 (0.0)	4 (6.5)	15 (19)
Drug-related TEAEs associated with discontinuation of study treatment	14 (11.2)	3 (5.5	0 (0.0)	3 (4.8)	10 (12.7)
TEAEs associated with dose reduced	40 (32.0)	21 (38.2)	0 (0.0)	21 (33.9)	17 (21.5)
Drug-related TEAEs associated with dose reduced	38 (30.4)	21 (38.2)	0 (0.0)	21 (33.9)	14 (17.7)
TEAEs associated with drug interrupted	79 (63.2)	20 (36.4)	3 (42.9)	23 (37.1)	23 (29.1)
Drug-related TEAEs associated with drug interrupted	65 (52.0)	17 (30.9)	2 (28.6)	19 (30.6)	8 (10.1)
TEAEs associated with outcome of death	8 (6.4)	1 (1.8)	1 (14.3)	2 (3.2)	11 (13.9)
Drug-related TEAEs associated with outcome of death	1 (0.8)	0 (0.0)	0 (0.0)	0	2 (2.5)

Source: Table 2-25, p78 of the submission

CTCAE = common terminology criteria for adverse events; N = number; SAS = Safety Analysis Set; SoC = standard of care (physician's choice chemotherapy); TEAE = treatment-emergent adverse events; T-DXd = trastuzumab deruxtecan

[a] If relationship was missing, the TEAE was considered to be related to the drug

[b] A subject was counted once at the maximum severity if they reported at least 1 TEAE. If a subject had both missing and non-missing CTCAE grades for a TEAE, the worst CTCAE grade was based on non-missing grade.

6.24 The most common drug-related treatment-emergent AEs (TEAEs) in the T-DXd group were gastrointestinal or haematologic AEs. These are known AEs associated with topoisomerase 1 inhibitors. The drug-related TEAEs with a ≥10% higher incidence in the T-DXd arm versus the SoC arm were neutropenia (64.0% vs 35.5%), nausea (57.6% vs 40.3%), decreased appetite (52.8% vs 40.3%), anaemia (40.8% vs 21.0%), thrombocytopenia (39.2% vs 6.5 %), malaise (34.4% vs 14.5%), lymphopenia (23.2% vs 1.6%), and vomiting (20.8% vs 6.5%).

6.25 In DG-01, 99 (79.2%) patients treated with T-DXd experienced a Grade 3 or 4 TEAE, with the majority Grade 3 (60.8%). Fewer patients (n=33; 53.2%) in DG-01 treated with SoC (irinotecan or paclitaxel) experienced a Grade 3 or 4 TEAE with most events (41.9%) being Grade 3 in severity.

Table 6: Grade 3+ TEAEs (≥5% of patients in either treatment arm) by MedDRA preferred term for DG-01 and DG-02 (SAS)

MedDRA preferred term	T-DXd N = 125		SoC N = 62	
CTCAE Grade	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
All TEAEs	76 (60.8)	23 (18.4)	26 (41.9)	7 (11.3)
Anaemia	48 (38.4)	0 (0.0)	13 (21.0)	1 (1.6)
Decreased appetite	21 (16.8)	0 (0.0)	8 (12.9)	0 (0.0)
Hypokalaemia	5 (4.0)	0 (0.0)	4 (6.5)	0 (0.0)
Nausea	7 (5.6)	0 (0.0)	1 (1.6)	0 (0.0)
Fatigue	9 (7.2)	0 (0.0)	2 (3.2)	0 (0.0)

Source: Table 2-26, p78 of the submission
CTCAE = common terminology criteria for adverse events; N = number; SAS = Safety Analysis Set; SoC = standard of care (physician's choice chemotherapy); TEAE = treatment-emergent adverse events; T-DXd = trastuzumab deruxtecan

6.26 The most frequently reported Grade 3 or 4 TEAEs in the T-DXd arm were anaemia (38.4%), decreased appetite (16.8%), fatigue (8.0%) and nausea (5.6%). The most frequently reported Grade 3 or 4 TEAEs in the SoC arm were anaemia (22.6%), decreased appetite (12.9%) and hypokalaemia (6.5%). In DG-02, the most frequently reported ≥Grade 3 TEAEs with T-DXd were similar to those reported in DG-01 but observed at a lower frequency.

6.27 Patients treated with T-DXd also experienced (by grouped term) neutropenia (51.2%), leukopenia (21.6%), thrombocytopenia (11.2%) and lymphocyte count (12.0%). Patients treated with SoC also experienced neutropenia (24.2%) and leukopenia (11.3%). The majority of these in both arms were Grade 3 and based on SoC of investigations and. Rates observed were lower in the SoC arm than in the T-DXd arm.

6.28 Adverse events of special interest reported in the PI for T-DXd are ILD and decrease in LVEF.

6.29 In the T-DXd arm of DG-01, 16 (12.8%) patients had events adjudicated as drug-related ILD. The majority of drug-related ILD events were <Grade 2 (10.4%) in severity and managed by dose modification and adherence to the clinical practice guidelines for ILD. Study treatment was discontinued in 8 (6.4%) and interrupted in 6 (4.8%) of participants in the T-DXd arm due to drug-related ILD. ILD was the TEAE that caused

the most treatment discontinuation. No participants in the SoC arm had reports of potential ILD events. Of the 16 participants in the T-DXd arm of DG-01 with adjudicated drug-related ILD events, 10 (62.5%) were reported as recovered or recovering and 6 (37.5%) were reported as not recovered. Similarly, 10.1% of patients in DG-02 experienced an ILD event of which 7.6% were Grade 1 or 2 and two (2.5%) participants died.

6.30 Decrease in LVEF is an AE of special interest associated with trastuzumab (part of the ADC T-DXd). Patients included in studies DG-01 and DG-02 trials were required to have a minimum LVEF ≥50%. This is also included in the proposed PBS restriction criteria for T-DXd and the draft T-DXd PI. No LVEF decrease or cardiac failure AEs were reported in DG-01 although 11 (9.4%) patients in the T-DXd arm had a post-baseline LVEF value in DG-01 that met the criteria for a Grade 2 LVEF decrease based on laboratory measurements. There was one Grade 2 LVEF decrease reported in DG-02; no Grade 3 or 4 events were reported.

Benefits/harms

6.31 A summary of the comparative benefits and harms for T-DXd versus SoC is presented in Table 7.

Table 7: Summary of comparative benefits and harms for T-DXd vs SoC from DG-01

Event	T-DXd	SoC	Absolute difference	HR (95% CI)
Progression free survival*				
Events, n/N (%)	82/125 (65.6)	36/62 (58.0)		**0.47 (0.31, 0.71)**
Median PFS, months (95% CI)	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)	2.1	
3-month PFS rates, % (95% CI)	71.9 (63.0, 79.1)	50.3 (35.5, 63.5)	21.6	
6-month PFS rates, % (95% CI)	43.0 (33.6, 52)	20.6 (8.9, 35.6)	22.4	
9-month PFS rates, % (95% CI)	33.3 (24.4, 42.4)	NE	NE	
12-month PFS rates, % (95% CI)	30.4 (21.5, 39.7)	NE	NE	
Overall survival*				
Deaths, n/N (%)	84/125 (67.2)	49/62 (79.0)		**0.60 (0.42, 0.86)**
Median months OS (95% CI)	12.5 (10.3, 15.2)	8.9 (6.4, 10.4)	3.6	
3-month OS rates, % (95% CI)	92.7 (86.5, 96.2)	90.0 (79.1, 95.4)	2.7	
6-month OS rates, % (95% CI)	80.7 (72.5, 86.6)	65.0 (51.5, 75.6)	15.7	
9-month OS rates, % (95% CI)	63.7 (54.6., 71.5)	50.0 (36.8, 61.8)	13.7	
12-month OS rates, % (95% CI)	52.2 (43.1, 60.6)	29.7 (18.7, 41.5)	22.5	

Harms						
	T-DXd n/N	**SoC n/N**	**RR (95% CI)**	**Event rate/100 patients***		**Absolute difference**
				T-DXd	**SoC**	
Grade 3+ TEAEs	99/125	33/62	1.49 (1.16, 1.91)	79.2	53.2	26.0
ILD	16/125	0/62	NE	12.8	0	12.8

Source: Table 2-22, p71, Table 2-23, p74, Table 2-26, p78, Table 2-27, p79, Table 2-30, p83 of the submission.
CI = confidence interval; HR = hazard ratio; ILD = interstitial lung disease; NE = not estimable; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = risk ratio; SoC = standard of care; T-DXd = trastuzumab deruxtecan.
Bold = statistically significant.
Italics = calculated during the evaluation.

6.32 On the basis of the direct comparative evidence presented by the submission, for every 100 patients treated with T-DXd in comparison with SoC over a median duration of follow-up 11.9 months for T-DXd and 8.5 months for SoC:

- Approximately 23 more patients would have survived at 12 months.
- Approximately 22 additional patients would have remained free of disease progression at 6 months.
- Approximately 26 additional patients would experience an AE of Grade 3 or greater.
- 13 additional patients would develop ILD, a potentially-life threatening condition requiring prompt diagnosis and treatment with corticosteroids.

Clinical claim

6.33 The clinical claim proposed in the submission was that T-DXd has superior efficacy and an inferior but manageable safety profile compared to chemotherapy in patients with metastatic HER2-positive G/GOJ adenocarcinoma who have received a prior trastuzumab-based regimen. The ESC considered that a claim of superior efficacy was reasonable on the basis of ORR and OS in the DG-01 study. The applicability issues in relation to DG-01 were partially addressed by single arm DG-02 study.

6.34 The superior efficacy claim was adequately supported by evidence included in the submission but the magnitude of the improvement in PFS and OS in the proposed Australian population is considered to be uncertain. Key issues were:

- Differences in demographic and disease characteristics in the East-Asian population in the pivotal trial versus the Australian population;
- Differences in diagnosis and disease management and the trial and in Australian clinical practice;
- The treatments in the comparator arm of the DG-01 trial do not fully reflect clinical practice;
- Differences in the definition of HER2 positive status between the pivotal trial and the PBS criteria for eligibility for 1L trastuzumab; and
- Uncertainty about the impact of resistance to HER2-targeted treatment developed during 1L trastuzumab treatment on the efficacy of 2L treatment with T-DXd. Subgroup analyses suggest that T-DXd may be less effective in patients with a lower HER2-postive score based on IHC and ISH testing. This observation suggests that the benefit/risk profile for T-DXd in a subgroup of the proposed PBS population is different from the overall population.
- Concerns around the applicability of the trial population to the Australian setting were also identified for the DG-02 study.

6.35 The inferior safety claim was supported by clinical evidence presented in the submission, although there is some uncertainty about the degree of risk in the Australian population due to applicability of the evidence to the Australian setting. People from Japan (as in DG-01) have increased susceptibility to ILD so the rates of ILD in the Australian population may be overestimated from the trial data. However, patients with prior ILD or pneumonitis were excluded from the trial; this, however, may not be representative of Australian clinical practice. No cardiac events due to deceased LVEF were observed in the pivotal trial, but this is a known safety concern for T-DXd treatment. In addition, only two of the SoC chemotherapies, i.e. irinotecan and paclitaxel, were included in the key trial. As the treatments in the comparator arm of the trial do not reflect the relative use of SoC chemotherapies in Australian clinical practice, the comparative safety of T-DXd versus irinotecan and paclitaxel as reported in the trial may not be applicable to the Australian setting. The ESC considered that a claim of inferior safety was supported by clinical evidence presented.

6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.37 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.38 The submission presented a cost-utility analysis based on the Phase 2 randomised controlled trial DG-01 comparing T-DXd to SoC, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained. The submission noted that only irinotecan and paclitaxel, were used as comparators in DG-01, however considered that results from the comparator arm in the trial were appropriate to apply as a proxy for SoC (irinotecan, paclitaxel, FOLFIRI or docetaxel) in the model. The submission assumed that these chemotherapies have “equivalent efficacy but different toxicity profiles”. The key components of the cost utility analysis are presented in Table 8.

Table 8: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Life years and quality-adjusted life years gained
Time horizon	7.5 years in the model base case (vs. a median duration of follow-up of 11.9 months for T-DXd and 8.5 months for Physician's choice chemotherapy in the DG-01 trial). The PBAC and ESC have previously noted that a shorter time horizon of 2 years may be more appropriate in the setting of later-line treatment of G/GOJ adenocarcinoma (paragraph 6.49, ramucirumab PSD, March 2018 PBAC meeting).
Methods used to generate results	Three-state partitioned survival (area under the curve) analysis
Health states	Progression-free, post-progression and dead
Cycle length	1 week, with half-cycle correction
Allocation to health states	Derived from PFS and OS KM curves from the DG-01 study.
Extrapolation method	KM data from DG-01 for PFS and OS were applied until 16.5 and 11 months for OS and 9 and 3 months for PFS for T-DXd and SoC treatment arms respectively. The truncation time points nominated were not well justified. The submission incorrectly applied the Gebski criteria[1] (Criterion 2) previously recommended by ESC (sacituzumab govitecan PSD, July 2023, para 6.36). The ICER was sensitive to the change in truncation point for OS. Independent parametric models were fitted to OS and PFS KM data for both treatment arms. Log-logistic (T-DXd) and log-normal (SoC) distributions were chosen to model OS and log-normal distribution was chosen to model PFS in both treatment arms based on AIC/BIC and visual fit. Whilst PFS data were mature and not sensitive to changes in parametric functions, there was substantial variation between modelled OS curves. The three best fitting curves (log-logistic, lognormal and Weibull) each had similar AIC/BIC values; however the Weibull distribution had a better visual fit and clinical plausibility. The ICER was sensitive to this change. ToT curves were not extrapolated. KM data from DG-01 was used to model the entire treatment period. The ICER increased by 11% when the ToT curves were extrapolated. ToT curves were extrapolated in the respecified base case analysis.
Discount rate	3.5% per annum for the costs and benefits in the base case. This is not consistent with the current PBAC Guidelines. While the HTA Review outcomes considered applying a discount rate of 3.5%, these have not yet been implemented in practice. Respecified base case analyses are presented using a 5% per annum discount rate.
Health related quality of life	Health state utility for progression free health state (0.746) was derived from EQ-5D-5L data from the DG-02 trial. A utility decrement (0.15) was estimated from the utility values for PF (0.737) and PD (0.587) used in the NICE TA378 (evidence from RAINBOW trial for gastric cancer) and applied to the PF utility value to estimate the PD utility value.
Costs	Direct treatment costs, costs for disease management (PF and PD), costs for subsequent treatments, costs for treatment of AEs and terminal care costs were applied. While the costs included in the economic model were appropriate, the approach to estimate drug costs was incorrect. Relative dose intensity was applied to the weighted cost of dispensed drug which included EFC dispensing fee, instead of applying it to the planned dose to account for dose reductions. Corrected cost estimates were used in the respecified base case analysis.

Source: Table 3-1, p105 of the submission.

AIC = Akaike information criterion; BIC = Bayesian information criterion; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; ESC = Economics Sub Committee; GOJ = Gastro-oesophageal junction; HTA = Health technology assessment; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; NICE = National Institute for Health and Care Excellence; OS = Overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = Progressed disease; PF = Progression-free; PFS = Progression-Free Survival; PSD = Public summary document; SoC = Standard of care; T-DXd = trastuzumab deruxtecan; ToT = Time on treatment

[1] Gebski, V., et al. 2018, Data maturity and follow-up in time-to-event analyses. International Journal of Epidemiology. 47(3): p. 850-859.

6.39 The submission employed a partitioned survival model and modelled three health states: progression-free (PF), post progression (PP) and death. Allocation to the three

health states was based on the OS and PFS curves for the T-DXd and SoC (Physician's choice chemotherapy) arms of the DG-01 trial. The structure of the economic model was reasonable.

6.40 The submission nominated a time horizon of 7.5 years in the model base case (vs. a median duration of follow-up of 11.9 months for T-DXd and 8.5 months for SoC in the DG-01 trial). The PBAC and ESC have previously noted that a shorter time horizon of 2 years may be more appropriate in the setting of later-line G/GOJ adenocarcinoma (paragraph 6.49, ramucirumab PSD, March 2018 PBAC meeting). The time horizon nominated in the submission was optimistic given that only approximately 20% of patients remained alive at 2 years. The ICER was sensitive to changing the time horizon from 7.5 to 2 years. The ESC considered a time horizon of 4 years would be appropriate to capture a more clinically plausible survival duration for this population. The Pre-PBAC response argued a 5 year time horizon would be reasonable for a revised base case, arguing that this is consistent with previous PBAC decisions in 1L metastatic setting such as nivolumab and pembrolizumab for gastroesophageal cancer (PSDs November 2021), where time horizons on 7.5 years were accepted. However, in both cases the PBAC considered that a 5 year time horizon was more appropriate (paragraph 7.10, pembrolizumab PSD and paragraph 7.10, nivolumab PSD, November 2021 PBAC meeting).

6.41 Health state membership was determined based on the PFS and OS curves from the DG-01 trial data. KM data were used until 16.5 and 11 months for OS and 9 and 3 months for PFS for T-DXd and SoC treatment arms, respectively. The truncation time points nominated were not well justified. The submission incorrectly applied the Gebski criteria[14] (Criterion 2) previously recommended by ESC (para 6.36, sacituzumab govitecan PSD, July 2023 PBAC Meeting). The ICER was moderately sensitive to the choice of truncation time points for OS. The pre-PBAC response acknowledged that amendments to the truncation time points applied in the evaluation were appropriate.

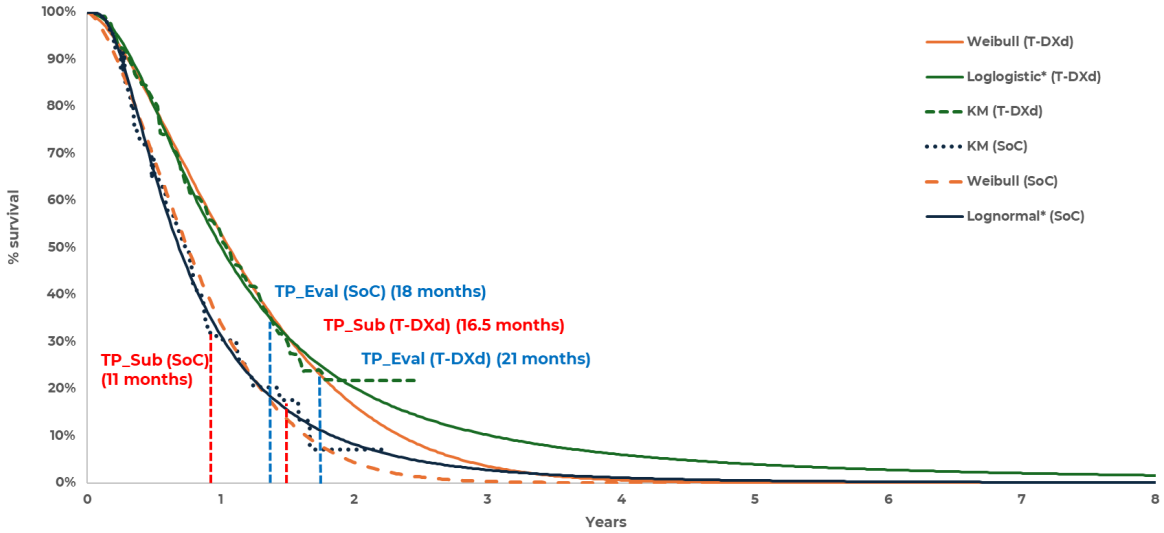
6.42 Independent parametric models were fitted to OS and PFS KM data for both treatment arms. Log-logistic (T-DXd) and log-normal (SoC) distributions were chosen to model OS and log-normal distributions was chosen to model PFS in both treatment arms based on AIC/BIC and visual fit. Whilst PFS data were mature and not sensitive to changes in parametric functions, there was substantial variation between modelled OS curves as discussed below.

6.43 The submission selected a log-logistic function to extrapolate T-DXd OS which produced OS rates that were substantially favourable to the T-DXd arm and resulted in a very long tail during the extrapolated period. The log-normal function selected for extrapolation of SoC OS was among the functions that predicted the lowest survival.

[14] Val Gebski, Valérie Garès, Emma Gibbs, Karen Byth, Data maturity and follow-up in time-to-event analyses, *International Journal of Epidemiology*, Volume 47, Issue 3, June 2018, Pages 850–859, https://doi.org/10.1093/ije/dyy013

Extrapolation using the Weibull model, which had similar AIC and BIC to the log-logistic (AIC: 634 vs 631; BIC: 640 vs 636), may result in more plausible survival estimates (all patients dead by 4 years). Additionally, the independent Weibull curves estimate convergence of the OS curves at approximately 4 years (see Figure 3), which, in the absence of any explicit treatment waning effect being incorporated into the model, appears more plausible. When the more clinically plausible Weibull function was used for extrapolating OS curves for both T-DXd and SoC, the base case ICER ($95,000 to < $115,000 per QALY) increased by % ($135,000 to < $155,000/QALY). The ESC agreed with the evaluation that the use Weibull extrapolations for OS produced more clinically plausible outcomes. The pre-PBAC response maintained the parametric functions used to extrapolate OS were appropriate as they were the best statistically fitting curves and had good visual fit and clinical plausibility. The pre-PBAC response disagreed with use of Weibull extrapolations for OS on the basis that is it the 3rd or 4th best fit statistically, based on AIC and BIC values. The pre-PBAC response also argued it is highly plausible that survival would be higher in practice than observed in the trial as patients were more heavily pre-treated than expected in Australian clinical practice. In addition, the pre-PBAC response argued that the choice of OS extrapolations was supported by the DG-04 OS data, which shows a greater magnitude of benefit than DG-01 in a larger population that is more applicable to the Australian setting.

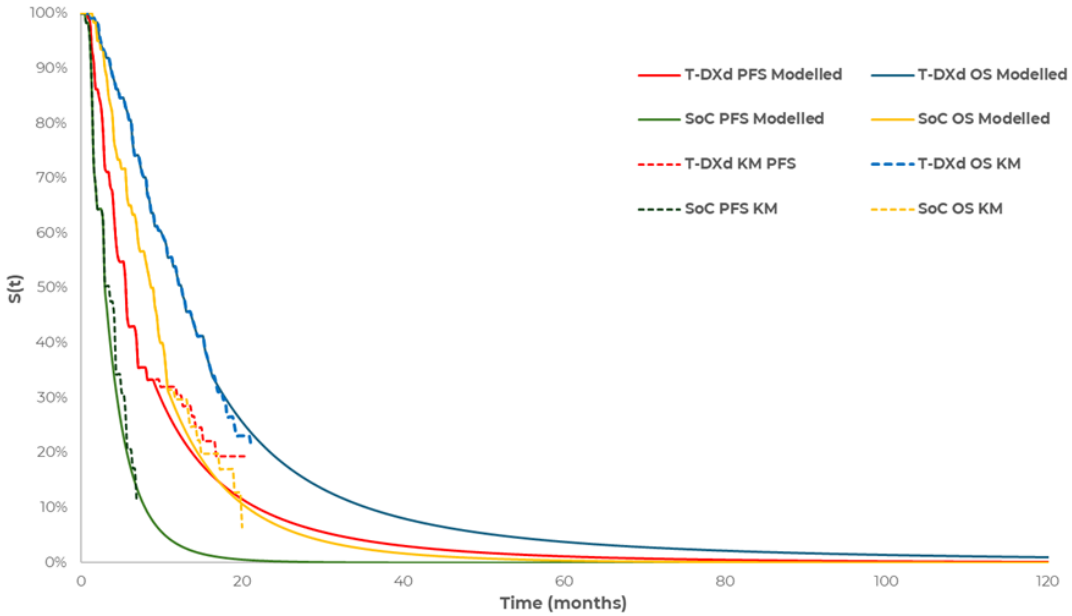
Figure 3: Parametric functions and truncation points used for extrapolating overall survival



Source: Figure constructed during the evaluation using data from the Attachment 14 – T-DXd cost-effectiveness model workbook included with the submission, and OS KM curves digitised using graph presented in Figure 2-6, p75 of the submission due to incomplete KM data provided in Excel workbook.
Note: * represents the submission's choice of parametric function for extrapolation
KM = Kaplan-Meier; SoC= Standard of care (physician's choice chemotherapy); T-DXd = trastuzumab deruxtecan; TP = truncation point for observed KM data; TP_Eval = truncation point estimated during evaluation; TP_Sub = truncation point presented in the submission

6.44 Comparisons of the observed KM PFS and OS data to the modelled curves for both arms are presented in Figure 4.

Figure 4: Kaplan-Meier and modelled curves for PFS and OS



Source: Constructed during the evaluation, based on the ""Attachment 14 – T-DXd cost-effectiveness model" Excel workbook included with the submission.
KM = Kaplan Meier; OS = overall survival; PFS = progression free survival; SoC = standard of care chemotherapies; T-DXd = trastuzumab deruxtecan

6.45 The submission applied utility weights of 0.746 to patients in the PF health state and 0.596 in the PD state. The utility weight for the PF health state was derived from the Health-related quality of life (HRQoL) assessments of the DG-02 study using the EQ-5D-5L data and mapped using the algorithm by Hernandez-Alava et al (2017)[15]. A utility decrement (0.15) estimated from the utility values reported for PF (0.737) and PD (0.587) in the NICE TA 378 (evidence from the RAINBOW trial for gastric cancer)[16] was applied to the PF utility from DG-02 to estimate the utility in PD health state. The ICER was not found to be sensitive to the alternate utility estimates for PF and PP when tested in a sensitivity analysis.

6.46 QALY decrements for each serious TEAE of Grade 1-4 and with an incidence of ≥2% was estimated by applying a disutility to the incidence and duration of AEs observed in DG-01. The overall weighted AE-associated disutility was applied as a one-off event in the first cycle of the model. The submission made a claim of inferior but manageable safety for T-DXd compared to SoC which was reflected in the reported incidence of TEAEs. The evaluation considered this was reasonable.

6.47 T-DXd acquisition costs in the model were derived through a weighted dispensed price per infusion that would account for PBS dispensing fees multiplied by relative dose intensity (RDI) of 92.5%. The submission's application of RDI (representing the

[15] Hernández-Alava, M., Wailoo, A., & Pudney, S. E. (2017). Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal. Report by the NICE Decision Support Unit, University of Sheffield.
[16] NICE 2015, *TA 378 -Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy*, NHS, UK.

reduction or interruptions in dose) to estimate the cost per week of T-DXd and SoC was incorrect. The submission applied the RDI to the weighted cost inclusive of the dispensing fee in the model rather than to the planned dose per treatment cycle. By applying RDI to the cost per dispensed drug the submission assumed that EFC dispensing fees are proportional to the cost of the medicine (whereas these are fixed and so apply regardless of amount dispensed). The costs per drug were revised in the respecified base case analysis by correctly applying the RDI to the planned dose and then estimated the weighted cost. This resulted in an increase in ICER by %.

6.48 An administration cost of $123.05 (Scheduled fee for MBS item 13950 parenteral administration) per cycle was applied for all IV infusions. The submission applied the cost per infusion administration for FOLFIRI regimen (irinotecan, folinic acid and fluorouracil) twice arguing that the fluorouracil is administered as infusion pump over 46 hours. This was inappropriate as the MBS item 13950 specifies that the administration starts with the establishment of the parenteral route and ends with the disconnection of the infusion, regardless of the time elapsed. Importantly, medical practitioners can only bill item 13950 once per treatment session, even if multiple antineoplastic agents are administered. The impact of this on ICER is likely very low.

6.49 Time on treatment (ToT) curves were not extrapolated. KM data from DG-01 was used to model the entire treatment period. The submission stated that the time on treatment data were mature (8% of patients remained on treatment at the time of DC02) and did not require extrapolation. The evaluation considered this was not reasonable and underestimates the costs associated with T-DXd in the model. Sensitivity analyses were performed to extrapolate ToT curves. A sensitivity analysis using extrapolation of the ToT curves from 16.9 months for T-DXd and 11 months for SoC led to an % increase in the ICER (from $95,000 to < $115,000/QALY to $115,000 to < $135,000/QALY). ToT curves were extrapolated in the respecified base case analysis in the Commentary. The PSCR disagreed with the extrapolation of treatment curves used in the Commentary respecified base case. The PSCR argued that the data were mature, however in the intervention arm 8% of patients remained on T-DXd (at the end of 17 months). The proposed listing for T-DXd allows for treatment until disease progression. Therefore, the ESC considered if survival is extrapolated, treatment duration should be extrapolated accordingly to avoid bias in cost-effectiveness results. The Pre-PBAC response maintained it was not appropriate to extrapolate treatment duration as the trial data are highly mature.

6.50 The submission assumed that approximately 27% of patients would receive a subsequent therapy, which is not expected to differ by treatment arm, and was based on the subsequent therapy use in the DG-01 trial (nivolumab in 27% of patients) and study by Ullao-Gomez[17]. Nivolumab is not available in Australia for G/GOJ patients

[17] Gómez-Ulloa, D., et al., Real-world treatment patterns, healthcare resource use and clinical outcomes of patients receiving second line therapy for advanced or metastatic gastric cancer. BMC Gastroenterol, 2020. 20(1): p. 133.

with HER2-positive disease. The distribution of utilisation of each subsequent treatment was as used for SoC based on the advice from Advisory Board. There is currently no clear proven benefit for third line treatment in this setting and a variety of agents (including those considered as a part of SoC) may be offered. Therefore, the submission's choice of subsequent treatment (SoC in 27% of patients post discontinuation) may be reasonable.

6.51 Key model drivers are presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained (respecified base case).
OS Extrapolation	Independent parametric models were fitted to OS and PFS KM data, with log-logistic (T-DXd) and log-normal (SoC) distributions chosen to model OS and log-normal distributions (T-DXd and SoC) chosen to model PFS based on AIC/BIC and visual fit. The independent Weibull curve had similar visual and statistical fit than the submission's base case and estimated convergence of the OS curves at approximately 4 years, indicating a diminishing treatment effect.	High, favours T-DXd. Use of independent Weibull OS curves in both arms increased the ICER to $[redacted][2]/QALY gained
Truncation time point	Truncation time points re-estimated by correctly applying Gebski Criteria 2 (T-DXd OS 21 months, SoC OS 18 months)	Moderate, favours T-DXd. Use of correct application of Gebski Criteria increased the ICER to $[redacted][3]/QALY gained
Time horizon	Time horizon of 7.5 years in the model base case (vs. a median duration of follow-up of 11.9 months for T-DXd and 8.5 months for SoC in the DG-01 trial).	High, favours T-DXd. Use of time horizon of 2 years increased the ICER to $[redacted][2]/QALY gained.

Source: Constructed during the evaluation.

AIC = Akaike information criterion; BIC = Bayesian information criterion; ESC = Economics Sub Committee; GOJ = Gastro-oesophageal junction; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = Overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = Progression-Free Survival; PSD = Public summary document; QALY = Quality-adjusted life-years; SoC = Standard of care; T-DXd = trastuzumab deruxtecan

The redacted values correspond to the following ranges:

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

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

[3] *$135,000 to < $155,000*

6.52 The following issues or errors were identified during the evaluation and were revised in a respecified base case analysis presented in the evaluation: a 5% per annum discount rate (compared to 3.5% used in the base case analysis); extrapolation of the ToT curves; and application of RDI to dose rather than cost of T-DXd and SoC treatments. The results of the stepped analysis, using the respecified base case, are presented in Table 10. Although the submission regarded Step 1 as a trial-based analysis, it incorporated several modelled assumptions, such as the employment of parametric models to extrapolate PFS and OS, and the specifics of the treatments and distributions as part of the SoC chemotherapy. Additionally, the time horizon of 24 months extended beyond reliable KM data, surpassing the median follow-up durations of 11.9 months in the T-DXd arm and 8.5 months in the SoC treatment arm.

Table 10: Results of the stepped economic evaluation (respecified base case analysis)

Step and component	T-DXd	SoC	Increment
Step 1: trial-based costs and outcomes (24 months): based on the PFS and OS KM data from the DG-01 trial extrapolated with parametric functions. Costs included were T-DXd treatment costs; SoC treatment costs; AEs costs, terminal care costs, costs for disease management and subsequent treatments.			
Costs	$	$52,864	$
LYG	1.071	0.794	0.277
Incremental cost/extra LYG gained			$ [1]
Step 2: time horizon extended to 7.5 years: As in Step 1, extrapolated over the modelled time horizon			
Costs	$	$56,072	$
LYG	1.341	0.853	0.488
Incremental cost/extra LYG gained			$ [2]
Step 3: transformation into QALYs: As in step 2 with utility weights applied based on the progression status			
Costs	$	$56,072	$
QALYs	0.913	0.558	0.355
Incremental cost/extra QALY gained (respecified base case)			$ [3]

Source: Table 3-29, p 138 of the submission. All results costs and outcomes are based on the respecified base case analysis. The submission reported a base case ICER of $95,000 to < $115,000/QALY (see paragraph 6.52 regarding corrections made in respecified base case).

KM = Kaplan-Meier; LYG = Life-years gained; OS = Overall survival; PFS = Progression-Free Survival; QALY = Quality-adjusted life-years; SoC = Standard of care; T-DXd = trastuzumab deruxtecan

The redacted values correspond to the following ranges:

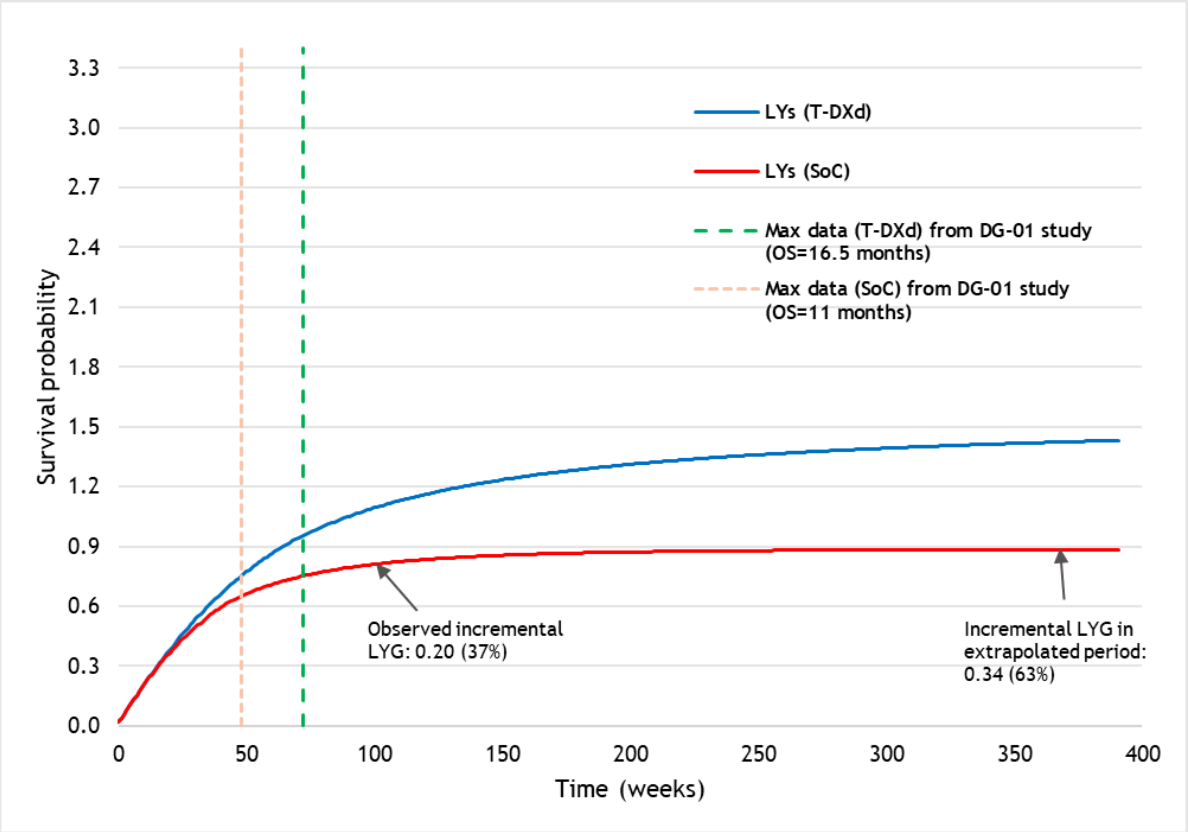
[1] *$135,000 to < $155,000*

[2] *$75,000 to < $95,000*

[3] *$115,000 to < $135,000*

6.53 Figure 5 depicts life years gained over the time horizon. The evaluation noted that 63% of the incremental life years in the base case occurred after the maximum trial observation period, which may be overly optimistic due to the approach used to extrapolate OS.

Figure 5: Incremental LYs (undiscounted) gained over the modelled time horizon by treatment arm.



Source: constructed during the evaluation using Attachment 14 – T-DXd cost-effectiveness model, included with the submission.
LYG = Life-years gained; LYs = Life-years; Max = maximum; OS = Overall survival; SoC = standard of care chemotherapies; T-DXd = trastuzumab deruxtecan

6.54 The disaggregated summary for costs and health outcomes is presented in Table 11. The largest contributor to the incremental costs for T-DXd versus SoC were the treatment costs, with cost-offsets driven by a reduction in terminal care costs. Patients in the T-DXd arm accrued more life years and QALYs in both the PF and PP health states. While the incremental outcome gain in the PP health state was small, due to the time horizon and parametric models used for OS extrapolation, the absolute life years gained are likely to be overestimated.

Table 11: Disaggregated summary of cost impacts and health outcomes (discounted)

Resource item	T-DXd	SoC	Increment	% of total increment
Costs				
HER2 test costs	$94.23	$0.00	$94.23	[redacted]%
Drug costs	$[redacted]	$1,582.61	$[redacted]	[redacted]%
Administration of infusion	$1,271.99	$1,266.20	$5.79	[redacted]%
Subsequent treatment with administration cost	$754.52	$760.99	-$6.47	[redacted]%
Disease management	$3,924.29	$1,960.31	$1,963.99	[redacted]%
Management of AEs	$1,035.99	$414.53	$621.46	[redacted]%
Terminal care	$48,247.03	$50,087.35	-$1,840.31	[redacted]%
Total cost	**$[redacted]**	**$56,071.99**	**$[redacted]**	
Outcomes				
Progression-free LYs	0.769	0.332	0.437	89.6%
Progressed LYs	0.572	0.521	0.051	10.4%
Total LYs	**1.341**	**0.853**	**0.488**	
Progression-free QALYs	0.574	0.248	0.326	91.9%
Progressed QALYs	0.341	0.311	0.030	8.5%
Disutility due to AEs	0.002	0.000	0.002	–0.4%
Total QALYs	**0.913**	**0.558**	**0.355**	

Source: Table 3-30 and 3-31, p139 of the submission regenerated with respecified base case results
HER2 = human epidermal growth factor receptor 2; SoC = Standard of care; T-DXd = trastuzumab deruxtecan

6.55 Key sensitivity analyses conducted during the evaluation using respecified base case are presented in Table 11. The model was most sensitive to the time horizon and the nominated OS parametric model extrapolation.

6.56 The PSCR proposed a new respecified base case with corrections to the discounting rate and application of RDI as in the commentary revised base case, and the following additional changes:

- Using the mean RDI (89.95%) instead of the median value (92.5%).
- Re-estimating the truncation points for OS and PFS by using criteria of 20% of patients remaining at risk for OS and PFS, respectively.
- Changing the mean patient weight to 64.8 kg (72.5 kg used in the submission) based on the mean patient weight in the RAINBOW trial.

6.57 The ESC considered the change to the mean patient weight proposed in the sponsor's PSCR was not appropriate. The expected average weight of Australian patients is likely to be higher than the RAINBOW baseline patient population in which around one-third of all patients were Asian. According to the National Health Survey 2017–18, an average Australian male weighs around 87 kg and female weighs 72 kg[18]. Based on measured data from the ABS 2022 National Health Survey (NHS)[19], 65.8% of Australians aged 18 years and over were living with overweight or obesity. The pre-PBAC response noted that, accounting for wastage, 5 vials of T-DXd are required for patients weighing 72.4 kg, whereas only 4 vials are required for patients weighing

[18] https://www1.racgp.org.au/newsgp/clinical/health-snapshot-of-the-%E2%80%98typical-australian%E2%80%99
[19] https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity/contents/summary

64.8 kg (accounting for RDI). The pre-PBAC response argued that, given that both mean patient weights are plausible and result in a mean dose close to 400 mg, the assumption of 4 dispensed vials per infusion is reasonable. The pre-PBAC response also proposed that uncertainty with regard to the number of vials required per patient may be addressed via risk-sharing arrangements.

6.58 The ESC noted that the method of truncation in the PSCR proposed respecified base case was based on 20% of patients at risk for OS and PFS. This appeared consistent with ESC's preferred approach for estimating the truncation points based on Gebski Criteria 2 (20% patients at risk) as discussed in the evaluation.

6.59 The ESC advised that an appropriate re-specified base case would apply the following: 1) Time horizon of 4 years; 2) Gebski criterion to inform truncation points; and 3) Weibull extrapolations for OS. The corresponding MVSA has been added to Table 12 below. The pre-PBAC response argued that this reflected highly conservative assumptions [redacted]

6.60 The Pre-PBAC proposed a modified respecified base case with assumptions the sponsor considered reasonable and plausible. The pre-PBAC respecified base case included: 1) Time horizon of 5 years; 2) Gebski criterion to inform truncation points; 3) Mean patient weight 64.8 kg; 4) Maintaining OS extrapolations as per base case. The sponsor considered these inputs were justifiable in the context of conservative modelling of outcomes based on DG-01, which had a shorter median OS compared with DG-04 (12.5 months vs 14.7 months) as it was in a more heavily pre-treated population. The pre-PBAC response stated that these changes resulted in an ICER of $95,000 to < $115,000 per QALY.

Table 12: Results of univariate and multivariate sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change from baseline
Revised base case	**$**	**0.35**	**$** 1	**-**
Time horizon (base case: 7.5 years)				
2 years **#1**	$	0.214	$ 2	%
3 years	$	0.273	$ 2	%
4 years	$	0.306	$ 3	%
5 years	$	0.327	$ 3	%
Utilities (base case: PF = 0.746; PD = 0.596)				
PF = 0.746; PD = 0.644	$	0.357	$ 1	- %
PF = 0.700; PD = 0.640	$	0.337	$ 3	%
Truncation time point (base case: T-DXD – PFS = 9 months, OS = 16.5 months; SoC – PFS = 3 months, OS = 11 months; ToT as for OS)				
ToT: 15 months(T-DXd)	$	0.355	$ 3	%
PFS: 15 months (T-DXd) (#A)	$	0.369	$ 1	- %
PFS: 18 months (T-DXd) (#B)	$	0.370	$ 1	- %
OS T-DXd: 21 months, SoC: 18 months (#C)	$	0.318	$ 3	%
OS T-DXd: 18 months, SoC: 15 months (#D)	$	0.343	$ 1	%
TP as estimated from Gebski (#B and #C) **#4**	$	0.332	$ 3	%
TP as assessed from visual fit (#A and #D) **#5**	$	0.357	$ 1	%
Extrapolation of OS (base case: log-logistic for T-DXd OS and lognormal for SoC OS)				
Weibull for both T-DXd: and SoC **#2**	$	0.274	$ 2	%
Lognormal for T-DXd and loglogistic for SoC **#3**	$	0.327	$ 3	%
Multivariate sensitivity analyses				
#1 and #2	$	0.221	$ 2	%
#1 and #2 and #4	$	0.205	$ 2	%
#1 and #2 and #5	$	0.218	$ 2	%
#1 and #3 and #4	$	0.200	$ 2	%
#1 and #3 and #5	$	0.213	$ 2	%
PSCR				
PSCR base case: 5% discount rate, truncation point 20% at risk, apply RDI to average dose, patient weight 64.8 kg	$	0.342	$ 4	- %
ESC Respecified base case				
Step 1 - 4 Year TH	$	0.306	$ 3	%
Step 2 - 4 Year TH and TP as estimated from Gebski	$	0.285	$ 2	%
Step 3 - 4 Year TH and Weibull for both T-DXd: and SoC	$	0.273	$ 2	%
ESC MVSA - 4 Year TH and TP as estimated from Gebski and Weibull for both T-DXd: and SoC (includes corrections to discount rate, application of RDI and extrapolation of ToT as per commentary revised base case)	$	0.260	$ 2	%
Pre-PBAC response respecified				
Time horizon of 5 years; Gebski criterion to inform truncation points; mean patient weight 64.8 kg; maintaining OS extrapolations as per base case and no extrapolation of ToT. (includes corrections to discount rate, application of RDI, but not extrapolation of ToT as per commentary revised base case)	$ a	0.305	$ b4	- %

Source: Table constructed during the evaluation using data from the Attachment 14 – T-DXd cost-effectiveness model workbook included with the submission; *PSCR Table 3.*

ICER = incremental cost-effectiveness ratio; MVSA = multivariate sensitivity analysis; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PFS = Progression-Free Survival; QALY = Quality-adjusted life-years; SoC = Standard of care; T-DXd = trastuzumab deruxtecan; ToT = Time on treatment.

a Reported as $ in the pre-PBAC response

b Reported as $95,000 to < $115,000 in the pre-PBAC response

The redacted values correspond to the following ranges:
[1] $115,000 to < $135,000
[2] $155,000 to < $255,000
[3] $135,000 to < $155,000
[4] $95,000 to < $115,000

Drug cost/patient/course

6.61 Table 13 presents the cost per patient per course for the T-DXd and SoC. Note, as 8% of patients remained on treatment at the latest data cut (Table 7.2, DCO2 CSR), treatment duration based on ToT extrapolation would have been more appropriate for the financial estimates.

Table 13: Drug cost per patient for T-DXd and SoC (assuming no vial sharing)

	T-DXd			SoC		
	DG-01	**Economic Model**	**Financial Estimates**	**DG-01**	**Economic Model**	**Financial Estimates**
Mean dose per administration (mg)	428.61[a] (5 vials)	428.61[a] (5 vials)	428.61 (5 vials)	I: 232.96[b] P: 124.25[b]	I (MT): 232.96 I (CT): 279.56 P: 124.25 D: 116.48 FA: 50 FU: 4,348.64	I (MT): 279 I (CT): 335 P: 148.8 D: 139.5 FA: 50 FU: 5,208
Mean duration (months)	6.71	7.35	29.10 weeks (6.70 months)	3.18[c]	3.23	14.48 weeks (3.3 months)
Cost/patient/month	$	$	$	$348	$495	$969
Cost/patient/course	$	$	$	$1,106	$1,599	$3,877

Source: Constructed during the evaluation, based on the "Attachment 14 – T-DXd cost-effectiveness model" Excel workbook included with the submission.
CT = combination therapy; D = docetaxel; I = irinotecan; FA = folinic acid; FU = Fluorouracil; mg = milligram; MT = monotherapy; P = Paclitaxel; SoC = Standard of care; T-DXd = trastuzumab deruxtecan
[a] 6.4 mg/kg × 72.5 kg (median weight of European patients in DG-02) × 92.5% RDI reported in CSR, assuming no vial sharing.
[b] RDI for irinotecan and paclitaxel weighted by use in DG-01 (83.7%) × Recommended dose × 1.86 m^2 (median BSA of European patients in DG-02) for SoC drugs, assuming no vial sharing
[c] Mean duration estimated by weighting the mean duration of treatment observed for irinotecan and paclitaxel (2.97 months and 4.83 months respectively) by their use in DG-01 study.

Estimated PBS usage & financial implications

6.62 This submission was not considered by DUSC. The submission used an "epidemiological" approach to determine the patients eligible for treatment with T-DXd, starting with the number of patients receiving initiating scripts for 1L trastuzumab. This approach relied on the assumption that the current script volume has a direct relationship to treated patients, where the number of 1L trastuzumab patients per year is identifiable from the initial trastuzumab (loading dose) PBS codes. The logic of this approach is sound, however an analysis of script data held by the Department indicates that some patients are receiving more than a single initial script. This increases the size of the patient population from which the incident and prevalent patients are estimated.

Table 14: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
No. Stage IV G/GOJ patients treated with 1L trastuzumab	Increasing from 285 in Yr 1, to 384 in Yr 6	Linear projection of the number of initiating scripts for 1L trastuzumab (PBS items 10581X and 10589H) in 2019–August 2024, to 2030	The assumption that one script equals one patient is reasonable, however an analysis of PBS data suggested that some patients received more than one script
No. patients eligible for 2L treatment	76%	Advice from the Clinical Advisory Board, assuming 95% progress following 1L treatment, and 80% able to receive 2L	This may be an overestimate as the 80% of patients with an appropriate ECOG status as at the upper end of the five reported studies.
No. prevalent patients (assumed in Year 1 only)	183	Projection of the number of initiating scripts for 1L trastuzumab (PBS items 10581X and 10589H) in 2019–August 2024, to 2024 (273), assuming 76% receive 2L treatment, assuming a life expectancy of 0.88 years.	The submission has underestimated the size of this population through the application of life expectancy and an uptake rate that effectively apply the same reduction twice.
No. prevalent patients eligible for 3L treatment	26.5%	Gomez-Ulloa et al., 2020 and Clinical Advisory Board	The study was based on data from 2013-2015 with Australian patients making up 12.2% of the population. The small proportion may obscure differences between Australian patients and patients from the remaining countries.
Treatment utilisation			
Uptake rate	[redacted]%	Advice from the Clinical Advisory Board, based on uptake of [redacted]% in patients who undergo HER2 retesting and [redacted]% uptake in the remaining patients who do not undergo HER2 retesting	The application of different uptake rates for tested and untested patients is appropriate[a].
No. grandfathered patients	[redacted] [1]	Sponsor assumption	The Patient Access program will not commence until Q1 2025. Grandfathered patients were subtracted from the prevalent patients to ensure no double counting.
T-DXd duration of treatment	Initiating patients: 29.1 weeks (9.7 scripts) Grandfathered: 14.6 weeks (4.9 scripts)	Section 3, DG-01 ToT curve (without extrapolation)	As 8% of patients remained on treatment at the latest data cut (Table 7.2, DCO2 CSR), treatment duration based on ToT extrapolation is more appropriate.
T-DXd RDI	92.5%	DG-01	This rate has been applied as a compliance rate which is incorrect and reduces the costs of the proposed medicine.
Costs			
Proposed medicine	$[redacted] public $[redacted] private	Requested price - published	The DPMA values have been correctly calculated from the AEMP values.

Data	Value	Source	Comment
Proposed medicine	$[redacted] public $[redacted] private	Requested price - effective	The DPMA values have been correctly calculated from the AEMP values.
Comparator	$160.13 $205.80 $163.69 $209.38 $156.83 $202.44 $160.13 $205.80 $112.97 $157.96 $38.90	4451G - irinotecan 7249M - irinotecan 7254T - paclitaxel 4567J - paclitaxel 10148D - docetaxel 10158P - docetaxel 4451G - irinotecan (FOLFIRI) 7249M - irinotecan (FOLFIRI) 4394G - fluorouracil (FOLFIRI) 7234R - fluorouracil (FOLFIRI) 1899Y - folinic acid (FOLFIRI)	Treatment comparators based on advice from the Clinical Advisory Board. The comparator costs are at the maximum amount without adjusting for the actual dose provided. This overstates the cost of the comparators.
Patient copayment	$19.26 PBS $7.54 RPBS	Weighted copayment for trastuzumab 1L (PBS items: 10581X, 10588G, 10589H, 10597R) in 2023.	The two copayment groups have been correctly calculated based on the current market.
MBS costs	$123.05 $74.50 $315.40 $415.75 $17.70 $16.95 $615.40 $87.30	13950 - IV chemotherapy administration 72848 - Immunohistochemistry (IHC) 73342 - In situ hybridisation (ISH) 30688 - Biopsy 66512 - Hepatic and renal function test 65070 - Full blood count 56807 - CT scan 116 - Consultation visit	Most of the MBS items associated with the affected medicines had the incorrect service costs applied. This has been corrected in Table 15 below. These corrections more than double the expected MBS impact.

Source: Financial estimates model of the submission.

AEMP = Approved Ex-manufacturer Price; CSR = Clinical study report; DPMA = Dispensed Price for Maximum Amount; ECOG = Eastern cooperative oncology group; FOLFIRI = folinic acid, fluorouracil, and irinotecan combination regimen; GOJ = Gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemical; ISH = In situ hybridisation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; T-DXd = trastuzumab deruxtecan; ToT = Time on treatment; Yr = year

The redacted values correspond to the following ranges:

[1] *< 500*

Table 15: Estimated use and financial implications (using proposed effective price of T-DXd)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Revised patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Revised scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of T-DXd						
PBS/RPBS impact less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]
Revised PBS/RPBS impact less copayments	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implications for affected medicines						
PBS/RPBS impact less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Revised PBS/RPBS impact less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][3]	$[redacted][3]
Revised PBS/RPBS	$[redacted][4]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Revised MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][3]	$[redacted][3]
Revised PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]

Source: Submission workbook, worksheet 5, with revisions prepared during evaluation (see paragraph 6.62)
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; T-DXd = trastuzumab deruxtecan
[a] Assuming 9.7 per year for initiating patients and 4.9 per year for grandfathered patients and 92.5% compliance as estimated by the submission.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5000*
[3] *$0 to < $10 million*
[4] *$10 million to < $20 million*

6.63 The total cost to the PBS/RPBS of listing T-DXd was estimated to be $10 million to < $20 million in Year 6, and a total of $60 million to < $70 million in the first 6 years of listing (after correction by evaluators).

6.64 The estimates are impacted by a range of issues, some of which increase the overall cost and some of which decrease the overall cost of listing T-DXd. When taken in aggregate, the evaluation considered the likely impact is to increase the cost of listing for the PBS/RPBS and MBS.

6.65 Regarding the number of initiating scrips for 1L trastuzumab, using the full year of data for 2024 rather than extrapolating from the first eight months increases the number of incident patients (as shown in Table 15). The submission also assumed that there is a one-to-one relationship between trastuzumab scripts and patients, however review of the script level data indicated that this is not a valid assumption and adjusting for this will decrease the patient population. The derivation of the prevalent patients was calculated based on from the 2024 incident patient population and is therefore affected by the increase in incident patients. The approach to calculation of the

number of prevalent patients was also uncertain and is likely to be underestimated due to the application of both uptake and life expectancy.

6.66 The submission presented the duration of therapy for T-DXd as 29.1 weeks (6.69 months). The evaluation of the economic model identified that the duration of treatment for patients receiving T-DXd should have been 32.45 weeks (7.5 months) with extrapolation of ToT applied. This underestimates the impact of listing T-DXd.

6.67 The submission has applied the median relative dose intensity (RDI) from the clinical trial as a compliance rate to both the proposed and affected medicines. This is inappropriate as the RDI changes neither the duration of therapy nor the number of scripts dispensed. This underestimates the number of scripts required for both T-DXd and the affected medicines.

6.68 The submission presented irinotecan, paclitaxel, docetaxel and FOLFIRI as the affected medicines. An arithmetical error was introduced into the derivation of the scripts required for the FOLFIRI component that resulted in a significant underestimate of the number of scripts. This underestimates the impact of the offset medicines.

6.69 The submission considered the affected medicines were dispensed at the maximum amount, rather than applying the adjusted doses that were seen in the clinical trial. This overestimates the impact of the offset medicines.

6.70 The PSCR noted the commentary correctly identified some errors in costs relating to treatment cost offsets and MBS items but did not provide a corrected financial model. The PSCR argued the impact of these discrepancies is relatively small. The PSCR did not address the concerns raised by the evaluation regarding the estimated number of T-DXd scripts. The pre-PBAC response proposed reducing the number of vials to 4 and revising the treatment duration to reflect the trial duration (without extrapolation), consistent with the pre-PBSC proposed economic model.

6.71 The submission includes a provision for < 500 grandfathered patients. These patients are assumed to participate in the sponsor's Co-pay Access Program that will commence in Q1 of 2025. This number was an assumption and based on a program that had not commenced (at the time of submission).

6.72 Consistent with the proposed respecified base case for the CUA in this pre-PBAC response, two further changes have been made to the evaluator's financial estimates:

- Average of 4 vials per infusion (instead of 5 vials)
- ToT reverted back to reflect the trial period only (not extrapolated).

Financial Management – Risk Sharing Arrangements

6.73 The Pre-PBAC response indicated that the sponsor was open to consider a Risk-Sharing Arrangement (RSA) to mitigate any remaining uncertainties in the estimate of the average number of vials per patient.

Quality Use of Medicines

6.74 The submission proposed clinician education/training meeting in the use of T-DXd in the gastric setting. Monitoring will also ensure that adverse event information will be shared with the sponsor's pharmacovigilance team.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for trastuzumab deruxtecan (T-DXd for treatment of metastatic human epidermal growth factor receptor 2-positive (HER2+) gastric or gastroesophageal junction (G/GOJ) cancer following trastuzumab therapy to allow for further consultation with the sponsor regarding a pathway forward. The PBAC accepted standard of care (SoC) chemotherapy, consisting of paclitaxel, irinotecan, docetaxel or FOLFIRI, as the main comparator as proposed by the submission. The PBAC also accepted the submission's clinical claim, that T-DXd has superior efficacy and an inferior safety profile compared to SoC in patients with metastatic HER2-positive G/GOJ adenocarcinoma who have received a prior trastuzumab-based regimen. While the PBAC considered the superior efficacy claim was supported by evidence included in the submission, it considered the magnitude of the improvements in PFS and OS in the proposed Australian population to be uncertain, which had implications for the extent of benefit assumed in the economic model. The PBAC agreed with amendments to the economic model as advised by the ESC, and considered that the ICER associated with the revised model was unacceptably high and uncertain at the proposed price.

7.2 The PBAC advised that it would be willing to recommend PBS listing of T-DXd in this indication with a price reduction that would reduce the ICER to an acceptable level. The PBAC considered that based on the data available in the submission, a significant price reduction would be required to reduce the ICER to an acceptable level. Alternatively, if the sponsor is not willing to progress the PBS listing on this basis, the PBAC was of a mind to not recommend T-DXd in this indication and the sponsor will need to make a resubmission incorporating updated clinical data from DG-04, in addition to revised inputs to the economic model and a reduced price.

7.3 The PBAC considered there is a high clinical need for more effective treatments, given the poor prognosis of HER2+ G/GOJ adenocarcinoma after progression on 1L treatment. The PBAC noted the input from health care professionals and organisations received for this submission was supportive of the submission given the superior efficacy albeit at a risk of significant side effects, and also highlighted the clinical need for effective treatments after progression on 1L trastuzumab and the financial burden of unfunded treatments.

7.4 The PBAC considered a streamlined authority level would be appropriate for the listing of T-DXd, consistent with the 1L trastuzumab listing for HER2+ G/GOJ

adenocarcinoma. The requested indication for T-DXd (Metastatic (Stage IV) HER2 positive gastric or gastro-oesophageal junction adenocarcinoma) was consistent with the current restriction for 1L trastuzumab. However, the proposed indication is narrower than the TGA indication and the populations enrolled in the two supporting studies, Destiny Gastric 1 (DG-01) and Destiny Gastric 2 (DG-02) in that use for locally advanced G/GOJ adenocarcinoma was not requested. The PBAC considered the PBS listing should include patients with locally advanced/unresectable G/GOJ adenocarcinoma consistent with the TGA indication and clinical evidence, noting that this would result in a small number of additional patients.

7.5 The PBAC considered the comparator of SoC chemotherapy, consisting of paclitaxel, irinotecan, docetaxel or FOLFIRI, was reasonable. The PBAC noted that only irinotecan and paclitaxel, were used as comparators in the pivotal evidence (DG-01), however considered that results from the comparator arm in the trial were reasonable to apply as a proxy for SoC in Australian clinical practice (irinotecan, paclitaxel, FOLFIRI or docetaxel).

7.6 The PBAC noted that the pivotal evidence was from an open-label RCT (DG-01) comparing the safety and efficacy of T-DXd compared to SoC (physician's choice of either irinotecan or paclitaxel), in HER2-positive patients with advanced G/GOJ adenocarcinoma, who had progressed on at least two prior regimens, including one trastuzumab-based regimen. The PBAC noted that the applicability of this trial to the proposed PBS population was limited for several reasons, the most significant issues being the line of treatment (DG-01 was in 3L or later) and the trial setting/ethnicity of patients (DG-01 being conducted in Korea and Japan only). Supporting evidence was provided by a single arm study evaluating the safety and efficacy of T-DXd in patients with HER2-positive advanced or metastatic G/GOJ adenocarcinoma who had progressed on a prior trastuzumab-containing regimen, in a study population recruited from Europe and North America (DG-02). The PBAC also noted that the PSCR also provided OS data from DG-04, a Phase 3 study of T-DXd vs ramucirumab + paclitaxel, which is to be the basis for converting the provisional TGA registration to a full registration.

7.7 The PBAC noted that DG-01 met its primary endpoint, demonstrating a statistically significant superior ORR for T-DXd. There were also statistically significant improvements in OS and PFS. The PBAC considered that DG-02 helped to address the applicability issues for DG-01, as ORR, OS and PFS were similar for patients treated with T-DXd in each of the trials. The PBAC also considered that that early outcomes from DG-04 were supportive of a treatment effect for T-DXd, despite including a comparator that would be expected to be somewhat more effective than SoC in Australian clinical practice.

7.8 The PBAC noted that the most common drug-related treatment-emergent AEs in the T-DXd group were gastrointestinal or haematologic AEs, which are known AEs associated with topoisomerase 1 inhibitors. Decrease in LVEF is also an AE of special interest associated with trastuzumab. The PBAC considered that ILD is a significant

safety concern for T-DXd. The PBAC noted that safety outcomes from DG-01 were limited by applicability issues and considered that DG-04 is likely to provide more informative comparative safety.

7.9 Overall the PBAC considered that T-DXd has a modest but clinically relevant survival benefit in comparison to SoC chemotherapy but is associated with additional toxicity, particularly significantly increased risk of ILD.

7.10 The PBAC noted that, at its April meeting, MSAC had supported amendment of the existing Medicare Benefits Schedule (MBS) item 73342 for HER2 ISH testing to determine eligibility for access to PBS-subsidised T-DXd in patients with metastatic HER2 positive G/GOJ adenocarcinoma. This change would allow re-testing of HER2 status, for access to T-DXd under the PBS. The PBAC considered that the majority of patients would not have a re-biopsy but would rely on HER2 testing conducted prior to treatment with 1L trastuzumab and therefore the increase in testing costs from re-testing would be minimal. The PBAC considered that although there is some risk of a change in HER2 status following treatment with trastuzumab, re-biopsy was not practical or justified, and the trial outcomes for DG-01 also reflected testing of archived tissue where available.

7.11 The PBAC noted the submission presented a cost-utility analysis based on the DG-01 trial. The PBAC considered that the corrections to the discount rate and application of the RDI applied in the Commentary were appropriate. The PBAC also considered that it was reasonable to apply extrapolation to the time on treatment, consistent with the extrapolation of other OS and PFS. Although ToT data from the trial were relatively mature, 8% of patients remained on treatment at DC02 and it would be expected that some patients remain on treatment for an extended time, consistent with the extrapolated PFS curves. The PBAC also agreed with the ESC that a time horizon of 4 years was reasonable and clinically plausible and would be expected to adequately capture costs and benefits for patients included in the DG-01 trial.

7.12 The PBAC considered that changes to the truncation point for KM data in the revised analyses presented in the PSCR, ESC advice, and pre-PBAC response were appropriate in applying the observed time to event data up to the point at which the observed data become unreliable. The PBAC noted PFS data were relatively mature and therefore the choice of extrapolation had a small impact on the ICER. However, the submission selected functions to extrapolate OS (log-logistic for TDX-d and lognormal for SoC) which produced OS benefit that was substantially favourable to the T-DXd arm and resulted in a very long tail for TDX-d during the extrapolated period. The PBAC considered that the use of Weibull extrapolations, as proposed in the Commentary and ESC advice, for OS produced more clinically plausible outcomes. The pre-PBAC response maintained the parametric functions used to extrapolate OS were appropriate as they were the best statistically fitting curves and had good visual fit and clinical plausibility. The PBAC noted that the pre-PBAC response also argued it is plausible that survival would be higher in practice than observed in the trial as patients were more heavily pre-treated than expected in Australian clinical practice. However,

this would also impact on OS in the SoC arm, which may also have more favourable OS compared to the SoC arm in DG-01. The pre-PBAC response argued that the choice of OS extrapolations was supported by the DG-04 OS data, which shows a greater magnitude of benefit than DG-01 in a larger population that is more applicable to the Australian setting. The PBAC noted that data from DG-04 were not available at the time of PBAC's consideration, but considered that it would be informative in consideration of extrapolation of OS for both arms.

7.13 The PBAC considered that the re-specified base case as proposed by the ESC was appropriate. This respecified base case corrected the discounting rate, RDI application and extrapolation of ToT and revised the following inputs: 1) time horizon from 7.5 to 4 years; 2) applied Gebski criterion to inform truncation points; and 3) applied Weibull extrapolations for OS for both arms. The PBAC noted that the pre-PBAC response argued that this reflected highly conservative assumptions and would likely necessitate a very low price for T-DXd, making it unviable for the sponsor to proceed with a listing in this indication. The PBAC noted that the pre-PBAC response proposed a modified respecified base case with assumptions the sponsor considered reasonable and plausible, which used a reduced patient weight, used the mean RDI of 89.95% instead of the median (92.5%) and maintained the favourable OS extrapolations. The PBAC considered that in the absence of any additional data to support different extrapolation of OS or patient weight, the ESC respecified base case remained the most appropriate analysis for decision-making. The PBAC noted that at the proposed price for TDX-d, this would result in an ICER of $155,000 to < $255,000, which the PBAC considered was unacceptably high and remained uncertain due to the limited applicability and uncertain extrapolation of the comparative trial data from DG-01. The PBAC considered that TDX-d would be considered acceptably cost-effective at a reduced price that would result in an ICER of no more than $55,000 to < $75,000 per QALY.

7.14 The PBAC considered that the approach to estimating patient numbers was reasonable, however a number of errors in the financial estimates were identified during the evaluation. The PBAC considered that these issues should be amended, including: changes to the number of incident and prevalent patients based on trastuzumab scripts (paragraph 6.65), adjustment to the duration of therapy consistent with the revised economic model (paragraph 6.66), correction of the application of RDI (paragraph 6.67) and corrections to calculation of costs offsets for SoC (paragraphs 6.68 and 6.69).

7.15 The Pre-PBAC response indicated that the sponsor would consider an RSA to mitigate any remaining uncertainties in the estimate of the average number of vials per patient, which was reduced in the sponsor's respecified economic model. The PBAC advised that based on inputs in the ESC respecified base case (as per paragraph 7.13, i.e. without reduction in the patient weight) an RSA is not required as the assumed number of vials required was unlikely to be underestimated and there is a low risk of leakage or use of T-DXd beyond progression.

7.16 Should the sponsor advise it is not willing to progress the PBS listing on the basis of the PBAC's recommendations in paragraph 7.13, the PBAC was of a mind to not recommend T-DXd in this indication. In this case the sponsor will need to make a resubmission incorporating updated clinical data to support changes to the economic model. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the May 2025 PBAC Public Summary Document:

10 PBAC Outcome

10.1 Following PBAC's deferral in May 2025, the sponsor provided a proposal for T-DXd for the treatment of adults with HER2-positive unresectable or metastatic gastric or gastroesophageal junction (GC/GOJ) adenocarcinoma after prior trastuzumab. The PBAC noted that the economic model presented in the proposal did not incorporate its previous advice and the ICER remained unacceptably high. On this basis the PBAC did not recommend T-DXd in this indication.

10.2 The proposal provided by the sponsor included:

- Revision of the requested ex-manufacturer price (EMP) for T-DXd from $[redacted] to $[redacted] per 100 mg vial (reduced by [redacted]%).
- Additional evidence from trial DG-04 (not directly used in the revised model).
- Revised inputs to the model from the previous submission: (1) the price for T-DXd, (2) assuming 4 vials per infusion, and (3) incorporating updated fees and mark-ups, resulting in an ICER of $75,000 to < $95,000/QALY.
- Updated financial estimates including the revised price for T-DXd, assuming 4 vials per infusion, and incorporating revised mark-ups and 1L trastuzumab PBS services data.
- Revised restriction wording amending “post HER2 directed therapy” (from “post trastuzumab containing therapy”).

10.3 The PBAC noted that the revised model inputs in the proposal did not apply the changes as outlined in paragraph 7.13 and retained inputs previously not accepted by the PBAC, including:

- Use of DG-01 trial data with log-log and log-normal extrapolations (PBAC recommended the more conservative Weibull function).
- Use of a 5 year time horizon (PBAC recommended 4 years).
- Revised (reduced) patient weight and vials based on Rainbow and DG-04 trials (PBAC did not recommend changes to weight and vial number).
- No extrapolation of ToT curve (PBAC recommended extrapolation of ToT consistent with extrapolated PFS/OS).

The PBAC noted that, despite applying more optimistic assumptions than those accepted by the Committee, the revised model resulted in an ICER of $75,000 to < $95,000 per QALY gained, whereas the PBAC had advised that T-DXd would be considered acceptably cost-effective at a reduced price that would result in an ICER of no more than $55,000 to < $75,000 per QALY gained (paragraph 7.13).

10.4 Noting that the proposed model and ICER for T-DXd deviated substantially from its previous advice as outlined in paragraph 7.13, the PBAC considered that T-DXd was not cost-effective at the proposed price.

10.5 The PBAC reiterated that the sponsor may make a resubmission incorporating updated clinical data to support changes to the economic model as per paragraph 7.16. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

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

Outcome:
Not recommended

11 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.

12 Sponsor's Comment

The sponsor had no comment.