

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1762 – Amendment to HER-2 MBS item to allow for trastuzumab deruxtecan for the treatment of patients with metastatic gastric or gastroesophageal junction adenocarcinoma

Applicant: AstraZeneca Pty Ltd

Date of MSAC consideration: 3-4 April 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

A streamlined codependent application requested:

- A minor amendment to a Medicare Benefits Schedule (MBS) item for human epidermal growth factor receptor 2 (*HER2*) testing to determine eligibility for access to Pharmaceutical Benefits Schedule (PBS)-subsidised trastuzumab-deruxtecan (T-DXd, Enhertu®) in patients with stage IV/metastatic *HER2* positive gastric/gastroesophageal junction adenocarcinoma (G/GOJ)
- A PBS listing for trastuzumab-deruxtecan (T-DXd, Enhertu®) in patients with stage IV/metastatic *HER2* positive gastric/gastroesophageal junction adenocarcinoma at second line (2L) or later.

The Executive Summary refers to the ‘Streamlined MSAC submission’ where relevant information was sourced from the submission to the Medical Services Advisory Committee (MSAC).

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported amendment of the existing Medicare Benefits Schedule (MBS) item 73342 for human epidermal growth factor receptor 2 (*HER2*) in situ hybridisation (ISH) testing to determine eligibility for access to Pharmaceutical Benefits Scheme (PBS)-subsidised trastuzumab-deruxtecan (T-DXd, Enhertu®) in patients with stage IV/metastatic *HER2* positive gastric/gastroesophageal junction (G/GOJ) adenocarcinoma, if Pharmaceutical Benefits Advisory Committee (PBAC) recommend PBS-listing of T-DXd. MSAC noted that the PBAC is scheduled to consider T-DXd at its May 2025 meeting. MSAC considered this test would identify patients more likely to benefit from treatment with T-DXd. MSAC supported the amendment of the MBS item from “access to trastuzumab under the Pharmaceutical Benefits Scheme” to “eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme” to future-proof the item. MSAC supported retaining the current MBS fee of \$315.40. MSAC advised that the financial implications to the MBS as a result of amending MBS item 73342 were likely low and reasonable.

Table 1 MSAC's supported amendment of MBS item 73342

Category 6 - Pathology Services Group P7- Genetics
MBS item 73342
An in situ hybridisation (ISH) test to determine human epidermal growth factor receptor 2 (<i>HER2</i>) gene amplification status of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction and documented evidence of <i>HER2</i> overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, if the test is: a) requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient, and b) to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme (PBS). (See para PN.1.2 of explanatory notes to this Category)
Fee: \$315.40 Benefit: 75% = \$236.55 85% = \$268.10

Consumer summary
This application from AstraZeneca Pty Ltd requested changes to existing Medicare Benefits Schedule (MBS) listing for testing of human epidermal growth factor receptor 2 (<i>HER2</i>) gene status for people with a certain type of stomach or oesophagus cancer called gastric or gastro-oesophageal adenocarcinoma to be eligible for access to a medicine called trastuzumab-deruxtecan, if listed on the Pharmaceutical Benefits Scheme (PBS). At the time that this application was made, trastuzumab-deruxtecan was not listed on the PBS, so a codependent application that requested public funding of both the test and the medicine was required. Many cancers are <i>HER2</i>-positive, which means that the cancer cells have too many copies of the gene called <i>HER2</i>. Currently, the MBS item 73342 allows <i>HER2</i> testing for people who have gastric or gastro-oesophageal adenocarcinoma. If they are found to be <i>HER2</i>-positive, they are eligible for treatment with a medicine called trastuzumab. AstraZeneca has developed a new medicine, trastuzumab-deruxtecan (sold under the brand name Enhertu®), that contains trastuzumab and another compound. The application requested that the test's description on the MBS be expanded so that people who are <i>HER2</i>-positive and have responded well to trastuzumab can access this new medicine. People in the earlier stages of gastric and gastro-oesophageal adenocarcinoma often have few or no symptoms. This means that by the time they seek medical attention, the cancer is already at an advanced stage (stage IV) and is metastatic (has spread to other parts of their body). About 15%–20% of people with this type of cancer are <i>HER2</i>-positive and tend to have a poor outlook or prognosis because <i>HER2</i>-positive cancers grow and spread faster than <i>HER2</i>-negative ones. However, the <i>HER2</i>-positive cancers can be specifically targeted by certain medicines, meaning these types of cancers can be more responsive to therapy despite being more aggressive. The <i>HER2</i> can be examined using a type of genetic test called in situ hybridisation (ISH) test. The ISH test uses a single strand of DNA or RNA to look for extra copies of the <i>HER2</i> gene in a cell. This test is done on tissue taken from a tumour biopsy. Before this test is done, the biopsied tissue is tested using a simpler and less precise method called immunohistochemistry. If the result of the immunohistochemistry test comes back positive or equivocal(unclear) the tissue is tested using in situ hybridisation. The in situ hybridisation test is well-established in Australian clinical practice and there are no performance concerns of note.

Consumer summary

Currently, patients who receive a positive *HER2* result on the in situ hybridisation test are eligible for the PBS-subsidised drug trastuzumab. The proposed new medicine, trastuzumab-deruxtecan, is a combination of trastuzumab and a chemical that kills cancer cells. The trastuzumab binds to a *HER2* receptor on cancer cell surface and acts like a key, unlocking the cancer cell so that the drug can directly enter and kill it without damaging nearby healthy cells. This combination of antibody and drug is known as an 'antibody-drug conjugate'.

MSAC noted that a person's *HER2* status can sometimes change over time (either from positive to negative with successful treatment or from negative to positive as the cancer grows). Around **redacted**% of people may need a second biopsy to check if their *HER2* status has changed. MSAC queried whether this would mean that more people should be retested. However, this status change was not backed by strong evidence, and given the risks and challenges associated with taking a new biopsy, MSAC considered that retesting is not usually the best choice in clinical practice. In cases where retesting is clinically necessary, MSAC considered that patients should not be left with out-of-pocket costs. Therefore, MSAC supported to replace the term 'trastuzumab under the PBS' with 'a relevant treatment under the PBS' in the MBS item 73342 to allow people to access the new medicine if PBAC recommends it. MSAC considered that given only a small number of people would be retested, and the test is not expensive, the cost to the MBS would be low.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported an amendment to MBS item 73342 that would replace the term 'trastuzumab under the PBS' with 'a relevant treatment under the PBS' if PBAC recommends PBS listing of trastuzumab-deruxtecan. This will allow the test to be used as evidence of eligibility for treatment with trastuzumab-deruxtecan. MSAC considered that testing was effective and safe.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from AstraZeneca Pty Ltd. was a streamlined codependent submission requesting a minor amendment to Medicare Benefits Schedule (MBS) item 73342, an in situ hybridisation (ISH) test for human epidermal growth factor receptor 2 (*HER2*) gene amplification status to determine eligibility for Pharmaceutical Benefits Schedule (PBS)-subsidised trastuzumab-deruxtecan (T-DXd, Enhertu®) in patients with stage IV/metastatic *HER2*-positive gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) will consider the codependent application requesting PBS listing for T-DXd in patients with stage IV/metastatic *HER2* positive gastric/gastroesophageal junction adenocarcinoma at second line (2L) or later at its May 2025 meeting.

MSAC noted that this application, streamlined submission, focused on the financial implications of *HER2* retesting, as the retesting may involve additional costs to the MBS.

MSAC noted that G/GOJ adenocarcinoma tends to present late and has a poor prognosis, with few treatment options available on progression. Approximately 15%–20% of patients with G/GOJ cancers will have tumours that are *HER2*-positive. T-DXd is an antibody-drug conjugate that binds to *HER2* receptors.

MSAC noted that the population is patients who have *HER2*-positive metastatic G/GOJ adenocarcinoma and have received a first-line (1L) regimen containing trastuzumab. In Australia, *HER2* testing is routine clinical practice for patients with metastatic G/GOJ adenocarcinoma to determine their eligibility for PBS-funded trastuzumab as a 1L treatment.

MSAC noted ISH *HER2* testing for access to trastuzumab in metastatic G/GOJ cancer is currently funded on the MBS using item 73342¹. The descriptor for item 73342 specifically states that ISH testing should be done to determine 'access to trastuzumab'. The applicant sought to expand the descriptor for MBS item 73342 such that it applies not just to trastuzumab but to other trastuzumab-containing agents, including T-DXd. The department recommended that the descriptor be broadened by replacing the drug name with 'relevant treatment under the Pharmaceutical Benefits Scheme'. MSAC agreed that the descriptor should be amended as proposed by the department, acknowledging that the change would futureproof the descriptor and align its wording with the standard terminology used for new MBS items for services that allow access to therapy on the PBS.

MSAC noted that *HER2* status is determined using immunohistochemical (IHC) and ISH testing on a FFPE sample. Because gastric cancer is more heterogeneous than other cancers, such as breast cancer, it is recommended that at least 6 biopsy samples be tested to reduce the likelihood of false negatives. However, MSAC noted *HER2* testing is very well established in Australia and there are no significant performance concerns in real world practice.

MSAC supported retaining the current MBS fee of \$315.40.

MSAC noted that because *HER2* status may change from positive to negative following 1L therapy, or from negative to positive with cancer progression, retesting after 1L treatment could be appropriate. The applicant's proposed amendment to item 73342 would enable this retesting of *HER2* status using a second biopsy taken after progression on 1L treatment with trastuzumab. It would also allow an initial biopsy to be used to determine eligibility for 1L treatment with trastuzumab and subsequently use this initial *HER2* test result to support eligibility for 2L+ treatment with T-DXd. MSAC noted this would avert the need for a patient to undergo a second biopsy if it is not clinically necessary.

MSAC noted the existing clinical management algorithm for newly diagnosed patients with metastatic G/GOJ. *HER2* status is first assessed using IHC, which yields a score of 0 to 3+. In Australia, patients who receive a score of 2+ (equivocal) or 3+ (positive) are eligible for MBS-funded ISH testing, and a patient is only considered *HER2*-positive (and eligible for access to trastuzumab) following a positive ISH result. MSAC noted that this definition is more stringent than the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, which consider an IHC score of 3+ to be *HER2*-positive. However, MSAC considered that the vast majority of 3+ IHC results result in positive ISH results, so the difference is likely to be minimal in practice.

MSAC noted the proposed clinical management algorithm, which adds repeat testing on a new biopsy (if appropriate) following 1L treatment. Patients who are still *HER2*-positive would receive T-DXd, while those whose *HER2* status has changed to negative would receive standard 2L treatments for *HER2*-negative patients.

MSAC noted that safety concerns are due to rebiopsy rather than the test itself. MSAC noted that the risk of a false positive result would result in adverse events from T-DXd treatment, but that false positives are unlikely due to the high specificity of the *HER2* test. MSAC also noted that most T-DXd-eligible patients are unlikely to undergo rebiopsy and retesting due to potential harms from rebiopsy and treatment delays. MSAC noted the applicant's pre-MSAC response, which clarified that the **redacted**% estimate for retesting was based on clinical expert opinion.

MSAC noted that the MSAC Executive at its August 2023 meeting had sought further information on the number of patients who would likely experience *HER2* downregulation following 1L therapy with trastuzumab, given that the commentary identified around 30% of patients may lose *HER2* positivity. MSAC noted the applicant's pre-MSAC response, which stated that the

¹ <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73342&qt=item&criteria=73342>

mechanism of *HER2* downregulation was unclear and that the 30% estimate may be uncertain and not realised in clinical practice.

MSAC noted that the clinical evidence presented was derived from 2 pivotal trials showing key efficacy results for T-DXd therapy: Destiny-Gastric 01 (DG-01; Shitara et al., 2020²) and Destiny-Gastric 02 (DG-02; Van Cutsem et al., 2023³). DG-01 (*N* = 125) was a third line (3L) phase II randomized controlled trial (RCT) involving a *HER2* test done on archival tissue in a South-East Asian population. DG-01 demonstrated that T-DXd treatment significantly improved (statistically) overall survival (Hazard ratio: 0.60, 95% CI: 0.42, 0.86, *p* = 0.01) and progression free survival (Hazard ratio: 0.47, 95% CI: 0.31, 0.71, *p* = 0.0003) compared to the chemotherapy standard of care. MSAC noted DG-02 (*N* = 79) was a single-arm second-line (2L) phase II study involving *HER2* retesting on newly biopsied tissue in a predominantly European population. DG-02 reported similar results for overall survival and progression free survival suggesting that T-DXd therapy would also be effective in 2L patients in the Australian setting. MSAC considered that it is biologically plausible that people confirmed *HER2* positivity on a recent biopsy would have better outcomes with T-DXd. However, the naïve comparison of results from DG-01 and DG-02 reported similar outcomes.

MSAC considered that retesting should not be required to determine eligibility for T-DXd therapy because of the lack of evidence for increased effectiveness, coupled with the difficulties, delays and safety concerns associated with rebiopsy. MSAC considered it appropriate to retest patients if it is clinically necessary, but considered that retesting should not be required to gain access to the therapy, to minimise out-of-pocket costs for patients while also not subjecting them to an unnecessary additional biopsy. MSAC also noted emerging evidence of potential benefits of T-DXd even for patients who do not test *HER2*-positive ('*HER2*-low'), suggesting that the therapy may be effective even if *HER2* downregulation has already been achieved. Further MSAC noted out of session, that *HER2* testing at the time of initial diagnosis rather than waiting for metastatic disease stage avoids treatment delays.

Overall MSAC noted retesting in theory would have superior effectiveness (although potentially inferior safety) to no testing.

MSAC noted that no economic evaluation was performed.

MSAC noted that the number of patients with gastric/ oesophageal adenocarcinoma currently being treated with trastuzumab is less than 200 per year, and therefore considered that testing on patients progressing on trastuzumab would be low and hence the overall financial impact on the MBS to be low. MSAC noted the department's adjustments to the estimated financial cost to the MBS, which was approximately \$redacted in Year 1, decreasing slightly to \$redacted in Year 2 and then increasing again to approximately \$redacted in Years 3 to 6. This adjustment included an updated estimate of utilisation in the commentary from redacted to redacted each year, an increase of approximately 6% compared to the original submission, based on an analysis of initial prescriptions. MSAC also noted the updated financial costs provided by the department updated the costs based on the estimated 30% of patients who may lose *HER2* positivity and therefore receive an *HER2*-negative result on the *HER2* IHC test following rebiopsy.

Given the poor prognosis for this cancer and improved outcomes for patients who receive the new therapy compared to standard treatment, MSAC supported amending MBS item number 73342 by replacing the term 'trastuzumab' with 'eligibility for a relevant treatment under the

² Shitara K, et al. DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated *HER2*-Positive Gastric Cancer. *N Engl J Med*. 2020 Jun 18;382(25):2419-2430. doi: 10.1056/NEJMoa2004413. Epub 2020 May 29. PMID: 32469182

³ Van Cutsem 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):744-756

PBS', if PBAC recommends PBS listing of T-DXd. MSAC also supported several other minor changes to improve consistency and readability (Table 1).

4. Background

MSAC has previously considered *HER2 in situ* hybridisation (ISH) testing for determining eligibility for trastuzumab for the treatment of metastatic HER2-positive G/GOJ adenocarcinoma at the first line (MSAC Application 1163.1⁴) as well as similar amendments to ISH testing in breast cancer (MBS item 73332). The application was supported by the MSAC at its July 2015 meeting.

The applicant requested a minor amendment to an existing MBS item. Following an application from AstraZeneca Pty Ltd to the department, MSAC Executive advice was sought on the appropriate pathway for the application. The MSAC Executive at its August 2023 meeting advised that a streamlined codependent pathway was appropriate for this application. The MSAC Executive further considered that the proposed amendment from this application may potentially increase utilisation and costs of HER2 testing (both immunohistochemistry and ISH) and associated biopsy procedures (MBS item 30473) as some patients may need to undergo re-biopsy and re-testing based on clinical discretion. The MSAC Executive further noted that *HER2* downregulation following trastuzumab treatment is possible. Key matters of concern raised by the MSAC Executive and how the minor submission addressed these are presented in Table 2.

Table 2 Summary of key matters of MSAC concern

Component	Matter of concern	How the current assessment report addressed it
Utilisation of <i>HER2</i> re-testing	The MSAC noted that the majority of T-DXd eligible patients are not likely to undergo retesting due to potential harms and delay of treatment. However further information was requested with regard to the proportion of patients who would undergo retesting.	The commentary considered that the submission had not adequately addressed it. The submission estimated approximately 10% of T-DXd eligible patients would be re-tested, based on clinical opinion. However, the commentary noted that the submission did not describe which patients are more likely to be re-tested.
Prevalence of <i>HER2</i> downregulation	The MSAC Executive considered that <i>HER2</i> downregulation following trastuzumab treatment is possible. Therefore, absence of re-testing in patients whose <i>HER2</i> status changed from positive to negative following trastuzumab treatment may lead to over-use of T-DXd.	The commentary considered that the submission had not addressed it. The commentary identified that approximately 30% of patients are likely to lose <i>HER2</i> positivity. However, the commentary considered that the selection of patients by <i>HER2</i> re-testing did not appear to confer benefit in terms of PFS and OS.

HER2 = human epidermal growth factor receptor 2; MSAC = Medical Services Advisory Committee; OS = overall survival; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan

⁴ <https://www.msac.gov.au/applications/1163-1>

5. Prerequisites to implementation of any funding advice

At the time of the submission lodgement, T-DXd was undergoing review by the Therapeutic Goods Administration (TGA) for HER2 G/GOJ cancer. Since then, T-DXd has received provisional approval by the TGA (TGA Delegate's overview, September 2024).

6. Proposal for public funding

There are two existing MBS items to establish *HER2* status in metastatic G/GOJ cancer patients: item 72848 for immunohistochemical (IHC) testing, and 73342 for ISH. Both items require biopsy in order to obtain the tumour tissue.

There was no proposed change to the current MBS item for IHC testing (MBS item code 72848) because the description does not relate to a specific drug.

The application proposed a minor amendment to MBS item 73342 (Table 3). The application proposed that the MBS item number 73342 be amended to replace the term “trastuzumab” with “trastuzumab-containing agent” so that the same MBS item may be used for trastuzumab alone, or an antibody-drug conjugate containing trastuzumab, such as trastuzumab deruxtecan (T-DXd). The department proposed broadening these terms further by replacing 'access to trastuzumab' with “eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme”. Additional edits have been proposed by the department to improve readability and are reflective of recent MSAC and legislative drafting preferences.

Table 3 Proposed amendments to MBS item 73342

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS Item 73342 An in situ hybridisation (ISH) test to determine human epidermal growth factor receptor 2 (HER2) gene amplification status of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction and, with documented evidence of human epidermal growth factor receptor 2 (HER2) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, if the test is: a) requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient, and b) to determine if the requirements relating to HER2 gene amplification for access to eligibility for a trastuzumab-containing agent relevant treatment under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. (See para <u>PN.1.2</u> of explanatory notes to this Category)	
Fee: \$315.40 Benefit: 75% = \$236.55 85% = \$268.10	

Source: Table 5 of the Streamlined MSAC submission Nov 2024

Abbreviations: HER2= human epidermal growth factor receptor 2; ISH= in situ hybridization; IHC= immunohistochemical

Red font indicates applicant proposed changes, strikethrough indicates deletion, and underline indicates additions proposed by department

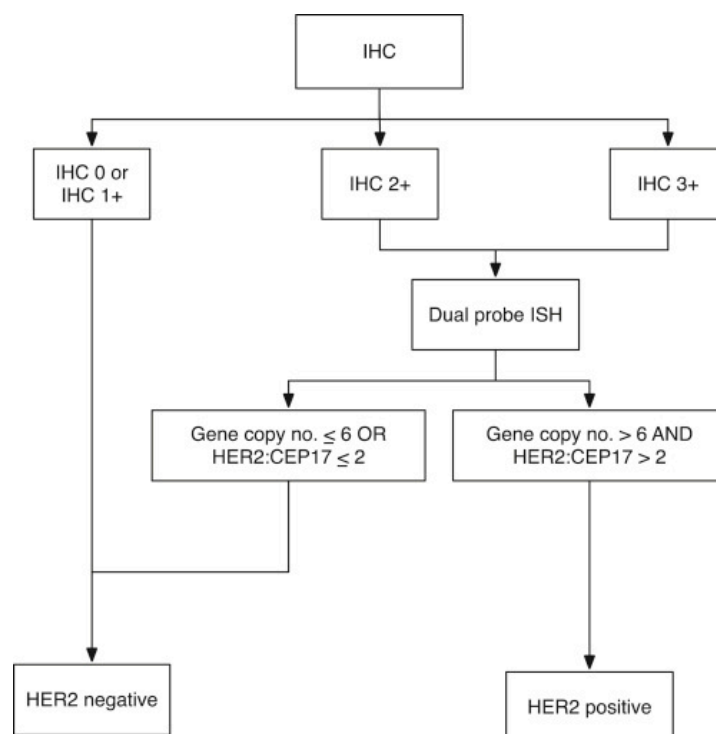
HER2 testing (IHC and ISH) is well-established in laboratories across Australia. The ISH test does not require a specific trademark component.

7. Population

The population intended for ISH *HER2* testing are patients who had *HER2* positive metastatic G/GOJ adenocarcinoma who received a first-line (1L) regimen containing trastuzumab. The current testing algorithm for *HER2* status of G/GOJ adenocarcinoma is described in Figure 1.

HER2 status is first assessed using IHC which results in a score of 0 to +3. Patients who receive a score of +2 (equivocal) or +3 (positive) undergo further ISH testing. A sample is determined ISH-positive if the *HER2* copy number is 6 or more, and if the *HER2* to chromosome 17 centromere ratio is greater than 2.

Figure 1 *HER2* testing in Australia



Source: Figure 1 of the Streamlined MSAC submission Nov 2024

Abbreviations: CEP17 = Chromosome 17; *HER2* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = *in situ* hybridisation

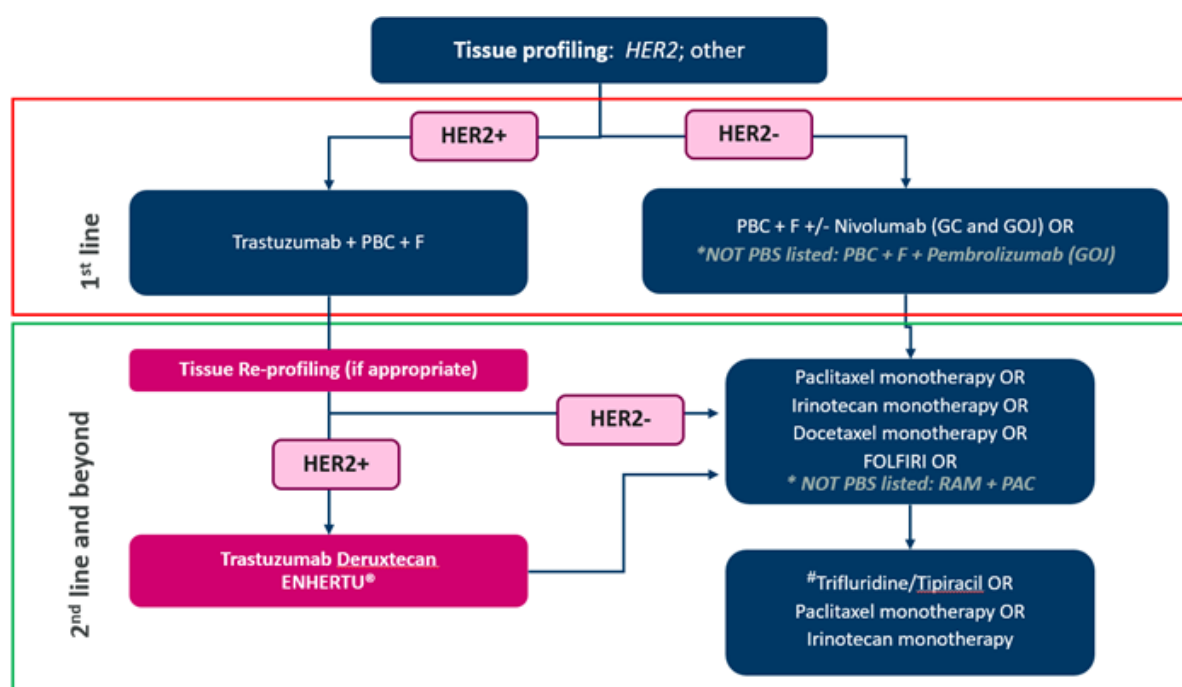
The submission presented according to expert opinion, roughly **redacted**% of the eligible population is expected to be re-tested for *HER2* status by rebiopsy. The commentary noted submission did not detail how clinicians will determine a patient's suitability for re-testing and whether the patients chosen for retesting are more likely to have lost *HER2* positive status than those not chosen. The commentary noted three studies of G/GOJ patients (Seo et al. 2019⁵,

⁵ Seo S, 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):527-535. doi: 10.1007/s10120-018-0891-1. Epub 2018 Nov 1. PMID: 30386954.

Pietrantonio et al. 2016⁶ and Janjigian et al. 2015⁷) who had progressed whilst on trastuzumab reported that 29–35% of patients lost HER2 positivity.

The current clinical management algorithm is presented in Figure 2. The requested PBS listing for T-DXd are patients with stage IV/metastatic HER2 positive gastric/gastroesophageal junction cancer at 2L or later who had progressed whilst receiving trastuzumab. The commentary noted the proposed PBS listing did not require re-testing of *HER2* status in order for the patient to be eligible for T-DXd treatment at the 2L. The listing would only require evidence of *HER2* gene amplification, which would have been established prior to 1L trastuzumab treatment. The commentary noted that the MSAC Executive noted that regulators in the European Union and United States do not specify the need for testing using a post-progression biopsy.

Figure 2 Proposed treatment algorithm describing treatment options for newly diagnosed patients with metastatic G/GOJ



Source: Figure 1-5, p. 23 of the PBAC submission

Abbreviations: GC/GOJ = gastric carcinoma and gastro-oesophageal junction; FOLFIRI = folinic acid, fluorouracil, irinotecan; HER2 = human epidermal growth factor receptor 2; PBC, platinum-based chemotherapy.

*Pembrolizumab was recommended for use in “gastro-oesophageal cancer according to the Australian Product Information” at the May 2022 PBAC meeting but has not progressed to a PBS listing.

*RAM+PAC was recommended by the PBAC at the March 2018 meeting on the condition that a price reduction was met. Following a resubmission considered at the July 2019 PBAC meeting, the PBAC did not recommend a change to the basis of its March 2018 recommendation restating its position that a substantial price reduction would be required in order to achieve a listing.

#Patient must have previously received at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum and either a taxane or irinotecan to access trifluridine/tipiracil on the PBS

⁶ Pietrantonio F, et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. *Int J Cancer*. 2016 Dec 15;139(12):2859-2864. doi: 10.1002/ijc.30408. Epub 2016 Sep 16. PMID: 27578417.

⁷ Yelena Yuri Janjigian et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in HER2-overexpressing esophagogastric (EG) tumors treated with trastuzumab. *J Clin Oncol* 33, 63-63(2015). DOI:10.1200/jco.2015.33.3_suppl.63

8. Comparator

The nominated comparator is no *HER2* re-testing, plus standard of care and chemotherapy.

9. Summary of public consultation input

No public consultation input was received for this application.

10. Characteristics of the evidence base

The clinical evidence presented in the submission was based on two trials: Destiny-Gastric 01 (DG-01) which provided pivotal evidence, and Destiny-Gastric 02 (DG-02) which provided supportive evidence in the Western-European population.

DG-01 (Shitara et al. 2020) is a phase II randomised controlled trial which compared T-DXd to the treating physician's choice of chemotherapy (irinotecan or paclitaxel) in South East (SE)-Asian patients with *HER2*-positive advanced gastric or GOJ adenocarcinoma who had received at least two prior regimens (including a fluoropyrimidine, a platinum agent, and trastuzumab therapy).

DG-02 (Van Cutsem et al. 2023) is a phase II single arm study which reported the efficacy and safety of T-DXd in US and European patients with *HER2*-positive unresectable or metastatic gastric or GOJ adenocarcinoma who had received 1L trastuzumab.

The key features of the study populations are presented in Table 4. Overall, study participants differed in terms of determination of *HER2* status, heritage, line of therapy, and cancer type.

Table 4 Key features of the included studies

Trial ID	Trial design	Trial population	Key population baseline characteristics	Intervention	Comparator
DG-01	Phase II, MC, OL, randomised N=188 T-DXd: 126 Physician's choice: 62	<i>HER2</i> -positive 3L+ advanced gastric or GOJ cancer <i>HER2 testing based on archived tissue</i>	Mean age: 66.0 years Male: 75.9% Asian: 100% (Japan: 79.7%; South Korea: 20.3%) Cancer type: Gastric 87.2%; GOJ 12.8% ECOG PS 0, 1: 49.2%, 50.8% Line of therapy: 3L+ Prior IO therapy: 32.6%	T-DXd 6.4mg/kg Q3W	Irinotecan 150mg/m ² every 2 weeks or paclitaxel 80mg/m ² every week of 28-day cycle
DG-02	Phase II, MC, single-arm N=79	<i>HER2</i> positive 2L advanced gastric or GOJ cancer <i>HER2 testing based on fresh tissue after progression on or after a prior trastuzumab-containing regimen</i>	Mean age: 60.7 years Male: 72.2% Asian: 5.0%; Caucasian: 87.3%; Other: 7.6% Cancer type: Gastric 34.2%; GOJ 65.8% ECOG PS 0, 1: 36.7%, 63.3% Line of therapy: 2L Prior IO therapy: 8.9%	T-DXd 6.4mg/kg Q3W	None

Source: Table 1 of the Streamlined MSAC submission Nov 2024

Abbreviations: DG-01 = Destiny-Gastric 01; DG-02 = Destiny-Gastric 02; GOJ = gastro-oesophageal junction; IO = immunotherapy; MC = multi-centre, OL = open-label, Q3W = every three weeks; *HER2* = human epidermal growth factor receptor 2; ECOG = Eastern Cooperative Oncology Group; T-DXd = trastuzumab deruxtecan

In DG-01, patients were assigned to sub-cohorts based on *HER2* status. However, *HER2* status was determined based on retesting of archival tissue. Therefore, it is unclear how many *HER2* positive patients comprised the study cohort at the point of T-DXd administration. In comparison, participants in DG-02 were required to undergo *HER2* retesting prior to receiving T-DXd (i.e. post-progression on trastuzumab), which consisted of a biopsy of the primary or metastatic tumour, and IHC and/or ISH. Eighty-nine patients were recruited to the study, but only 79 were enrolled. The commentary noted no reasons were provided in the submission for the 10 participants who failed screening, in particular whether they tested *HER2* negative (i.e. lost *HER2* positivity).

DG-01 patients were recruited from SE-Asian populations whereas patients in DG-02 were recruited from predominantly western European populations (87%), the latter being more representative of the Australian clinical context.

Both trial populations had *HER2*-positive GC/GOJ, however patients in DG-01 were being treated at the 3rd line whereas DG-02 were treated from the 2nd line. T-DXd is proposed to be listed for use in 2nd line or later.

In both trials, *HER2* positive status was determined by guidelines from the American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP), which are less-stringent than those used in Australia. The ASCO-CAP guidelines⁸ recommend:

- only patients who test as 2+ (equivocal) on IHC will undergo further ISH
- A sample tests ISH-positive if the *HER2*/ chromosome 17 centromere (*CEP17*) ratio is ≥ 2 OR has an average of ≥ 6 *HER2* gene copies per cell.

Whereas in Australia:

- all IHC 2+/3+ samples undergo ISH
- A sample tests ISH-positive if the *HER2*/*CEP17* ratio is ≥ 2 AND has average of ≥ 6 *HER2* gene copies per cell.

The commentary considered it was unclear how many of the patients in DG-02 (i.e. tested positive by CAP guidelines) would have tested negative by the Australian ISH-testing guidelines and therefore would not be eligible for T-DXd.

11. Comparative safety

No data were presented in the submission to support the comparative safety of ISH testing. Feedback by Australian clinicians featured in the submission stated that adverse events associated with biopsy included bleeding, infection, or damage to the surrounding organs.

Indirect harms are related to inaccurate test performance. That is, T-DXd side effects in patients who were false positive for *HER2*; and disease progression in patients who were not correctly identified as having *HER2* positive G/GOJ cancer. The most-commonly reported serious adverse events (Grade ≥ 3) included anaemia, decreased appetite, fatigue, nausea. An adverse event of special interest associated with T-DXd is interstitial lung disease (ILD). In DG-01, 12.8% of patients experienced ILD versus none in the comparator arm. In DG-02, ILD was the most

⁸ <https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/her2-testing-and-clinical-decision-making-in-gastroesophageal-adenocarcinoma>

common drug-related adverse event associated with discontinuation. However, most instances of ILD were not considered serious (Grade 1 or 2) and were successfully managed.

12. Comparative effectiveness

Clinical claim

No claims were made for *HER2* ISH testing. The goal of testing should be to target T-DXd to those patients most likely to benefit from treatment. The commentary considered if retesting had clinical utility, those retested and remained *HER2* positive should respond to T-DXd better on average than those not retested (as it may be assumed that a sample of patients not retested would include some patients with loss of *HER2* positivity). Further the commentary considered retesting should in theory have superior effectiveness (although potentially inferior safety) to no testing.

Comparative analytical performance

No data were presented in the submission to support the comparative analytical performance of ISH *HER2* testing for T-DXd treatment.

Drug

Overall survival (OS) and progression-free survival (PFS) results for DG-01 and DG-02 are presented in Table 5.

In DG-01, results showed a statistically significant improvement in terms of OS (Hazard ratio: 0.60, 95% CI: 0.42, 0.86, $p = 0.01$) and PFS (Hazard ratio: 0.47, 95% CI: 0.31, 0.71, $p = 0.0003$), favouring T-DXd over physician's choice.

In DG-02, median PFS was 5.6 months (95% CI: 4.2, 8.3) and OS was 12.1 months (95% CI: 9.4, 15.4). The commentary noted, issues with the trial populations notwithstanding, there appeared no appreciable difference in PFS and OS across the T-DXd arms of DG-01 (no retesting) and DG-02 (retested), which suggested limited benefit in retesting of *HER2*.

Table 5 Summary of key efficacy results for DG-01 and DG-02

	DG-01 (no retesting)				DG-02 (retesting)
	T-DXd N = 125	Overall Chemotherapy N = 62	Irinotecan N = 55	Paclitaxel N = 7	T-DXd N = 79
OS					
Median OS, months (95% CI)	12.5 (10.3, 15.2)	8.9 (6.4, 10.4)	8.6 (6.4, 10.4)	14.3 (2.9, NE)	12.1 (9.4, 15.4)
HR (95% CI); p-value	0.60 (0.42, 0.86) p = 0.0051		NC	NC	NE
PFS					
Median PFS, months (95% CI)	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)	2.8 (2.0, 4.3)	4.9 (2.0, NE)	5.6 (4.2, 8.3)
HR (95% CI); p-value	0.47 (0.31, 0.71) p = 0.0003		NC	NC	NE

Source: Table 2 of the Streamlined MSAC submission Nov 2024; Table 1 of the PBAC submission

Abbreviations: DG-01 = Destiny-Gastric 01; DG-02 = Destiny-Gastric 02; OS = overall survival, PFS = progression-free survival, NC = not calculated, N= number of patients HR = hazard ratio, CI = confidence interval, NE = not-estimable; T-DXd = trastuzumab deruxtecan

13. Economic evaluation

No economic evaluation was undertaken in the Streamlined MSAC submission.

14. Financial/budgetary impacts

The submission used an epidemiological approach to determine the patients eligible for treatment with T-DXd. This approach relied on the assumption that the current script volume for patients initiating on 1L trastuzumab has a one-to-one relationship to treated patients. The commentary considered as no repeat scripts are allowed under these items, 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 one initiating script. This results in the under-estimation of the size of the incident and prevalent patient populations. The submission contains incident, prevalent and grandfathered patients.

The incident patients were derived from the trastuzumab scripts dispensed to patients initiating 1L trastuzumab treatment for Stage IV HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction (PBS items 10581X and 10589H) from 2019 to August 2024 (the latest data available at the time of the submission). The submission assumed, based on the restriction, that a script was analogous to a patient. These figures were then linearly extrapolated to provide patient numbers from 2026 to 2030. The commentary noted the patients in 2024 were forecast from data for the first eight months of data, converted to a monthly average and multiplied by 12. The additional months of data have since become available, and the actual number of scripts dispensed in 2024 was 282.

The commentary noted that the forecast effectively commenced in 2026, with the value for 2025 being the mid-point between 2024 and 2026. This removed the “dip” that would otherwise occur as the patient numbers moved from actual to forecast.

In the submission, the prevalent patients were derived from the 2024 incident patients. These were patients who were on or after progression to 2L at the time of T-DXd listing. The submission considered these patients will only occur in the first year of listing, as the incident patients will be treated directly, once T-DXd was listed. The commentary identified a series of issues with the derivation of this population. If the underlying incident population increased when the actual treated population was used rather than the script proxy, then this would increase the prevalent population. The proportion of patients who progressed while on 1L treatment and were alive, as an assumption may have been an overestimate. The commentary considered the proportion of patients treated in 2L was an assumption at the higher end of the range of values provided by the five reported studies may have been an overestimate. The application of the life expectancy reduction (0.88 life years) did not appropriately adjust the number of patients who were available for treatment as it was a measure of how long patients would remain alive on 1L treatment (on average). This had been used in combination with the 26.5% reduction to account for patients who sought treatment. The commentary noted this further calculation applied a proportion of patients to a figure which represented patient-years of treatment which was inappropriate.

The submission included a provision for **redacted** grandfathered patients. These patients were assumed to participate in the sponsor's Co-pay Access Program that will commence in Q1 of 2025. The commentary considered this was appropriate, noting that this number was an assumption and based on a program that, at the time of submission, had not yet commenced.

The estimated number of patients who would be retested if T-DXd was PBS listed is presented in Table 6.

Table 6 Estimation of the number of patients re-tested for *HER2* status if T-DXd is PBS listed

	Description	2025	2026	2027	2028	2029	2030	Source / Calculation
A	Number of patients initiating 1L trastuzumab	285	296	318	340	362	384	PBS data
B	Proportion of 1L trastuzumab patients who receive 2L therapy ^a	redacted%						Clinical opinion, literature: redacted% [alive] x redacted% [ECOG 0-1]
C	Incident patients eligible for T-DXd	redacted	redacted	redacted	redacted	redacted	redacted	A*B
D	Prevalent cases eligible for treatment	redacted						Calculated from 2024 PBS trastuzumab scripts
E	Total eligible T-DXd patients	redacted ^b	redacted	redacted	redacted	redacted	redacted	C+D
F	Number of patients re-tested	redacted	redacted	redacted	redacted	redacted	redacted	Clinical opinion – redacted % of E
G	<i>Revised number of patients re-tested (will receive biopsy and IHC tests)</i>	redacted	redacted	redacted	redacted	redacted	redacted	HTA group revised calculations
H	<i>No. of patients receiving ISH test (MBS item 73342)</i>	redacted	redacted	redacted	redacted	redacted	redacted	<i>Commentary - 30% of relapsed patients with G/GOJ lose HER2 positivity / 70% x G</i>

Source: Table 6 of the MSAC Streamlined submission

^a Adjustment to account for proportion of patients still alive and with an ECOG status 0-1 since PBS criteria for trastuzumab is ECOG 0-2

^b Difference in sum due to rounding in model

Abbreviations: 1L = first-line; 2L = second-line; ECOG = Eastern Cooperative Oncology Group; G/GOJ= gastric/gastroesophageal junction adenocarcinoma; *HER2* = human epidermal growth factor receptor 2; IHC= immunohistochemistry; ISH= *in situ* hybridisation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; T-DXd = trastuzumab deruxtecan

Italics indicate changes made during evaluation

Green font indicates changes by department

The financial implications to the MBS resulting from the proposed listing of *HER2* are summarised in Table 7. The revised cost is derived from corrected population but applying the same fees.

Table 7 Incremental cost to the MBS for additional *HER2* testing

MBS Item Number	MBS Service	Full Fee ^a	2025	2026	2027	2028	2029	2030
72848	IHC	\$74.50	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
73342	ISH	\$315.40	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
30688	Biopsy	\$415.75	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Total cost to MBS (\$)			redacted	redacted	redacted	redacted	redacted	redacted
<i>Revised cost to MBS at 80% of the Fee^b (\$)</i>			<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>
<i>Revised cost to MBS at 85% of the Fee^c (\$)</i>			<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>	<i>redacted</i>
Revised cost to MBS at 85% of the Fee IHC item 72848 (\$63.35) (\$)			redacted	redacted	redacted	redacted	redacted	redacted
Revised cost to MBS at 85% of the Fee for ISH item 73342 (\$268.10) (\$)			redacted	redacted	redacted	redacted	redacted	redacted
Revised cost to MBS at 75% of the Fee for Biopsy item 30688 (\$311.85) inpatient service (\$)			redacted	redacted	redacted	redacted	redacted	redacted
Revised cost to MBS (\$)			redacted	redacted	redacted	redacted	redacted	redacted

Source: Table 7 of the MSAC Streamlined submission

^a Full fee: 80% of MBS Fee applied in the calculations

^b Revised during evaluation

^c Revised during evaluation cost at 85% of MBS Fees

Abbreviations: IHC = Immunohistochemistry; ISH = *in situ* hybridisation; MBS = Medicare Benefits Schedule

Italics indicate changes made during evaluation

Green font indicates changes by department

15. Other relevant information

Nil

16. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)