Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Enhertu

Active ingredient: Trastuzumab deruxtecan

Sponsor: AstraZeneca Pty Ltd

September 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AESI	Adverse event of special interest
ASCO	American Society of Clinical Oncology
BC	Breast cancer
BICR	Blinded independent central review
CAP	College of American Pathologists
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events, Version 5.0
DCO	Data cut off
DOR	Duration of response
Dxd	Deruxtecan
ECOG	Eastern Cooperative Oncology Group
ER	Exposure response
ERBB2	Erb-b2 receptor tyrosine kinase 2
ESMO	European Society for Medical Oncology
FAS	Full analysis set
HEOR	Health economics and outcomes research
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IA	Interim analysis
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
ISH	in situ hybridization
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities, (Version 23.0)
KM	Kaplan-Meier
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
PopPK	Population pharmacokinetics

Abbreviation	Meaning
PR	Partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
RDI	relative dose intensity (% intended dose received)
RECIST	Response Evaluation Criteria in Solid Tumour
SD	Stable disease
SMQ	Standardized MedDRA query
SOC	Standard of care
T-DM1	trastuzumab emtansine (KADCYLA)
T-DXd	trastuzumab deruxtecan (Enhertu)
TEAE	Treatment-emergent adverse event
TPC	The Physician's choice
TTR	Time to response

Enhertu (trastuzumab deruxtecan) submission

Type of submission:	Extension of indications
Product name:	Enhertu
Active ingredient:	Trastuzumab deruxtecan
Decision:	Approved
Date of decision:	24 January 2023
Date of entry onto ARTG:	30 January 2023
ARTG number:	343262
, *Black Triangle Scheme*	No
Sponsor's name and address:	AstraZeneca Pty Ltd, 66 Talavera Road, MACQUARIE PARK NSW 2113
Dose form:	Powder for injection
Strength:	One vial of lyophilized powder for concentrate for solution for infusion delivers 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of trastuzumab deruxtecan
Container:	Enhertu is provided in 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip-off crimp cap.
Pack size:	Each carton contains 1 glass vial.
Approved therapeutic use for the current submission:	**Metastatic Breast Cancer** **HER2-Low** Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (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. Patients with hormone receptor positive (HR+) breast cancer should additionally have received and no longer be considered eligible for endocrine therapy.
Route of administration:	Intravenous infusion
Dosage:	The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The initial dose should be administered as a 90-minute intravenous infusion. If the initial infusion is well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category:

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Trastuzumab deruxtecan can cause fetal harm when administered to a pregnant woman. There are no available data on the effects of trastuzumab deruxtecan in pregnant women. However, in post-marketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of trastuzumab deruxtecan can also cause embryo-fetal harm when administered to a pregnant woman.

Administration of Enhertu to pregnant women is not recommended, and patients should be informed of the potential risks to the fetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a woman becomes pregnant during treatment with Enhertu or within 7 months following the last dose of Enhertu, close monitoring is recommended.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Enhertu (trastuzumab deruxtecan)

Trastuzumab deruxtecan is an antibody–drug conjugate consisting of a monoclonal antibody (trastuzumab) targeting HER2 on cancer cells, chemically linked to a cytotoxic drug (Dxd). Once released, Dxd can kill both targeted cells and surrounding cells, including those with less HER2 expression.

This AusPAR describes the submission by AstraZeneca Pty Ltd (the sponsor) to register Enhertu (trastuzumab deruxtecan) for the following proposed extension of indication:[1]

> *Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy.*

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

HER2-low breast cancer

In 2022, it is estimated that 20,640 Australians will be diagnosed with breast cancer (12% of all new cancer cases diagnosed), with an estimated 3,214 deaths from breast cancer (accounting for an estimated 6.4% of all deaths from cancer)[2]. Approximately 80% of patients with breast cancer will have tumours that are HER2 negative (including hormone receptor (HR) positive/HER2 negative, and HR negative/HER2 negative). Approximately 60% of these tumours may have HER2 expression IHC scores of 2+ or 1+ and negative results on in situ hybridization (i.e. HER2-low)[3]. These HER2-low tumours constitute a heterogeneous population including both HR positive and HR negative breast cancers that vary in prognosis and sensitivity to systemic treatments. Unresectable or metastatic HER2-low breast cancer is a serious and life-threatening condition that is incurable.

Current treatment options for HER2-low breast cancer

There are no specific therapies currently approved in Australia for advanced HER2-low breast cancer. Treatment is guided by HR status, and patients with HER2-low breast cancer are treated as per those with HER2 negative disease.

For patients with metastatic HR+/HER2- breast cancer, the upfront standard of care includes endocrine based therapy (e.g. combination of endocrine therapy with a CDK4/6 inhibitor). On progression, treatment options include additional endocrine therapy or chemotherapy (e.g. anthracyclines, capecitabine, vinorelbine, eribulin, gemcitabine and paclitaxel) if endocrine resistant. For PIK3CA-mutated tumours, another option includes fulvestrant plus targeted therapy with alpelisib. Patients with deleterious or suspected deleterious germline BRCA mutations can be treated with poly ADP-ribose polymerase (PARP) inhibitors.

Patients with metastatic triple negative disease may receive pembrolizumab in combination with chemotherapy (if PD-L1 positive) or chemotherapy options including those agents listed above. For patients with BRCA1/2 mutations, two PARP inhibitors (olaparib or talazoparib) are registered in Australia for the treatment of metastatic TNBC. Sacituzumab govitecan may be used following at least 1 treatment regimen in the metastatic setting. Responses to single agent chemotherapy are often not durable, and additional therapies are needed in these patient populations.

Regulatory status of Enhertu (trastuzumab deruxtecan)

Australian regulatory status

On 5 October 2021 Enhertu was provisionally approved for the following indication:

> *"Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens."*

This was converted to a full approval with a revised indication on 18 July 2022.

Enhertu is currently registered in Australia as follows:

[2] www.canceraustralia.gov.au/cancer-types/breast-cancer/statistics

[3] Modi S, Jacot W, Yamashita J, et al. Trastuzumab Deruxtecan in Previously Treated Advanced Breast Cancer. N Engl J Med 2022;387:9-20.

"Enhertu as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who previously received:

- *trastuzumab and a taxane for metastatic disease, or*
- *one prior anti-HER2-based regimen and developed disease recurrence during or within six months of completing neo-adjuvant or adjuvant therapy."*

This is a Category 1 Type C application (extension of indication) and Category 1 Type J (minor changes within the Product Information). The Sponsor proposes to register a new therapeutic entity for the following indication:

"Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC1+ or IHC 2+/ISH-negative) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy."

The proposed dosing regimen is 5.4mg/kg as an intravenous infusion once every 3 weeks.

The Priority Review Determination was granted on 18 May 2022 for the proposed indication.

International regulatory status

This evaluation was facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 1 summarises these submissions and provides the indications where approved.

Table 1. International submission status: Enhertu for HER2-low breast cancer

Country/Region	Submission date	Approval date	Comment
European Union	31 May 2022	N/A	Centralised procedure
United States of America	26 May 2022 (Project Orbis)	N/A	Breakthrough Therapy Designation granted 22 April 2022
Japan[a]	27 June 2022	N/A	
Canada[b]	17 June 2022 (Project Orbis)	N/A	Priority review granted – 15 June 2022
Switzerland[a]	17 June 2022 (Project Orbis)	N/A	

Country/Region	Submission date	Approval date	Comment
Singapore[b]	Planned Q1 2023 (Project Orbis)	N/A	
United Kingdom[a]	Planned Q3 2023	N/A	Submission using Reliance Route following EU CHMP opinion

a. Sponsor is Daiichi Sankyo Company Limited
b. Sponsor is Astrazeneca

Registration timeline

This submission was evaluated under the priority registration process.

Table 1: Timeline for Submission PM-2022-02867-1-4

Priority review pathway

Description	Date
Priority determination	18 May 2022
Submission dossier accepted and first round evaluation commenced	31 August 2022
Evaluation completed	30 November 2022
Delegate's[4] Overall benefit-risk assessment	3 January 2023
Registration decision (Outcome)	24 January 2023
Registration in the ARTG	30 January 2023
Number of working days from submission dossier acceptance to registration decision*	105

*Target timeframe for priority submissions is 150 working days from acceptance for evaluation to the decision.

[4] The 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who made the final decision to either include the new medicine/indication on the ARTG or reject the submission, under section 25 of the Therapeutic Goods Act.

Submission overview and risk/benefit assessment

Clinical evaluation summary

Summary of clinical studies

The dossier included two pharmacometrics studies, 1 phase 1 study, 1 pivotal phase 3 study, assorted efficacy, safety and immunogenicity analyses in Module 5.3.5.3, and a table of post marketing safety findings.

This application is primarily based on evidence of efficacy and safety of T-DXd from the pivotal phase 3 study U303 (DESTINY-Breast04):

- Study U303 data cut-off (DCO) was 11 January 2022 and analysed 557 subjects, randomised in a 2:1 ratio to T-DXd: 373 subjects and TPC: 184 subjects.

The supportive phase 1 study J101 (two-part, multicentre, nonrandomised, open-label, multiple-dose first-in-human study of T-DXd in subjects with advanced solid malignant tumours) was also included.

- Data from the 54 subjects with HER2-low BC treated with T-DXd 5.4 mg/kg (n = 21) or 6.4 mg/kg (n = 33) in Phase 1 Study J101 from the DCO of 01 Aug 2019 were included in the analysis.

The previous PopPK analysis based on T-DXd and DXd PK data from 9 clinical studies was updated to include data from Study U303 (N = 1675 subjects).

Pharmacology

Trastuzumab deruxtecan (T-DXd; Enhertu; DS-8201a) is a HER2-targeted antibody and topoisomerase I inhibitor conjugate. The antibody-drug conjugate (ADC) consists of 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase I inhibitor, via 3) a tetrapeptide-based cleavable linker.

Summary of key findings from clinical pharmacology assessment

Pharmacokinetics

At the recommended dosage of Enhertu for patients with metastatic breast cancer, the geometric mean (coefficient of variation [CV]%) Cmax of trastuzumab deruxtecan and

DXd were 133 µg/mL (19%) and 4.7 ng/mL (43%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 780 µg·day/mL (27%) and 29 ng·day/mL (42%), respectively, based on population pharmacokinetic analysis. Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan was estimated to be 2.68 L. *In vitro,* the mean human plasma protein binding of the topoisomerase I inhibitor was approximately 97%. *In vitro*, the blood to plasma concentration ratio of the topoisomerase 1 inhibitor was approximately 0.6.

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the active topoisomerase 1 inhibitor. The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as

endogenous IgG. In vitro metabolism studies in human liver microsomes indicate that the topoisomerase 1 inhibitor is metabolized mainly by CYP3A4 via oxidative pathways.

Based on popPK analysis, following intravenous administration of trastuzumab deruxtecan, the clearance of trastuzumab deruxtecan was estimated to be 0.41 L/day and the clearance of the topoisomerase I inhibitor was 19.6 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released topoisomerase I inhibitor was approximately 5.7 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed. Following intravenous administration of the topoisomerase I inhibitor to rats, the major excretion pathway was faeces via the biliary route. The topoisomerase I inhibitor was the most abundant component in urine, faeces, and bile. Following single intravenous administration of trastuzumab deruxtecan (6.4 mg/kg) to monkeys, unchanged released topoisomerase I inhibitor was the most abundant component in urine and faeces.

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, higher levels of AST and total bilirubin resulted in a lower clearance of topoisomerase I inhibitor. The impact of these changes is not expected to be clinically meaningful.

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (estimated by Cockcroft-Gault), the pharmacokinetics of the released topoisomerase I inhibitor was not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Based on popPK analysis, age (23-96 years), race, ethnicity, sex and body weight did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released topoisomerase I inhibitor.

Population pharmacokinetics

- The previous PopPK analysis based on T-DXd and DXd PK data from 9 clinical studies was updated to include data from Study U303 (Total number of subjects from all studies = 1675).
- No new covariates for either T-DXd or DXd PK data, including HER2-low status, were identified when compared with the previous PopPK analysis

Efficacy

The pivotal data for efficacy come from Study U303 (DESTINY-Breast04).

The delegate notes the following relevant publication: Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. 2022;387(1):9-20. Doi:10.1056/NEJMoa2203690.

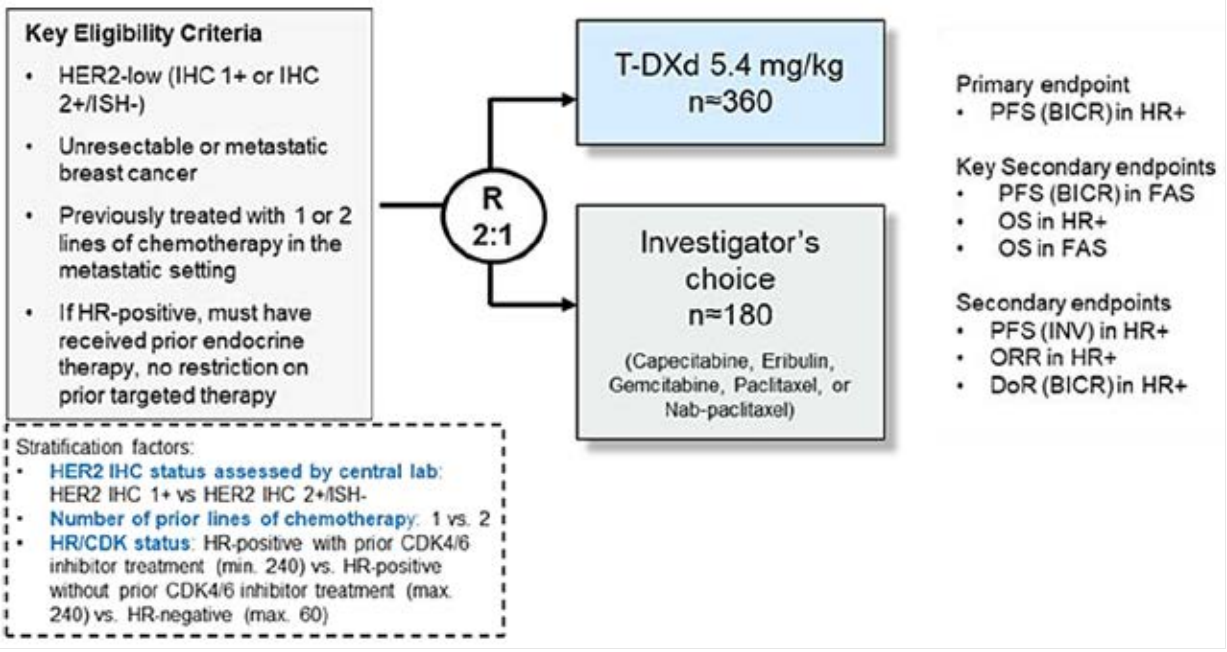
Study U303

Design

Study U303 was a Phase 3, multicentre, randomised, open-label, active-controlled study in subjects with unresectable or metastatic HER2-low BC (defined as IHC 1+ or IHC 2+/ISH-negative) who have received 1 or 2 prior lines of chemotherapy.

Data cut-off (DCO) was 11 January 2022.

Figure 1. Study U303 design.



BICR = blinded independent central review; CDK4/6 = cyclin-dependent kinase 4 and 6; DoR = duration of response; FAS = Full Analysis Set; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemistry; INV = investigator assessment; ISH = in situ hybridization; max = maximum; min. = minimum; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomization; T-DXd = trastuzumab deruxtecan; vs. = versus

The study was conducted at sites in North America (US, Canada), Europe (Austria, Belgium, France, Greece, Hungary, Italy, Portugal, Russia, Spain, Sweden, Switzerland, and the United Kingdom), Israel, and Asia (China, Japan, Republic of Korea, and Taiwan).

There were no study sites in Australia.

Table 2. Study U303: inclusion and exclusion criteria, study treatments, efficacy variables and outcomes.

Patients	Trastuzumab deruxtecan: n=373 Physician's choice chemotherapy: n=184 ***Key inclusion criteria*** • Pathologically documented HER2-low unresectable or metastatic breast cancer, with centrally confirmed low HER2 expression (IHC 1+ or ICH2+/ISH-negative) • Previously received chemotherapy for metastatic disease (at least 1, or at most 2 prior lines) or have had disease recurrence during or within 6 months after completing (neo) adjuvant chemotherapy • Patients with hormone receptor-positive disease must have received at least one line of endocrine therapy, with tumour considered to be refractory to endocrine therapy • ECOG: 0 or 1 • Measurable disease by RECIST v1.1 • Patients with treated, stable brain metastases were eligible

	Key Exclusion criteria • Previous treatment with anti-HER2 therapy • Tumours that previously tested positive for HER2 • History of non-infectious interstitial lung disease that was treated with glucocorticoids or had suspected interstitial lung disease on imaging at screening • Uncontrolled or significant cardiovascular disease, pulmonary compromised, spinal cord compression
Intervention	Trastuzumab deruxtecan 5.4mg/kg, administered intravenously every 3 weeks Treatment was continuous, until disease progression, consent withdrawal or discontinuation due to AEs
Comparator	Physician's choice of chemotherapy (Eribulin 51.5%; Capecitabine 20.1%; Gemcitabine 10.3%; Nab paclitaxel 10.3% or paclitaxel 8.2%), administered in accordance with local label or NCCN guidelines Randomisation was stratified by HER2 IHC status, number of prior lines of chemotherapy in the metastatic setting and HR status/Prior CDK4/6 inhibitor treatment
Endpoints	***Primary endpoint*** • PFS (by blinded independent central review) among patients with hormone receptor-positive disease ***Secondary endpoints*** • PFS (BICR) among all patients • OS in patients with hormone receptor-positive disease • OS among all patients

The choice of comparator(s) is considered to be appropriate and are relevant to Australian clinical practice.

The primary efficacy endpoint and the key secondary efficacy endpoints were tested hierarchically to maintain the overall two-sided Type I error rate to 0.05 or less, in the following order:

a. PFS based on BICR in the hormone receptor-positive cohort;

b. PFS based on BICR in the FAS;

c. OS in the hormone receptor-positive cohort (up to 3 analyses), and

d. OS in the FAS.

The statistical testing for each key secondary endpoint was performed only if the previous analysis in the sequence was statistically significant.

Participant flow

FAS: n=557

Randomised 2:1 ratio: T-DXd n = 373, TPC n=184

- 88.7% had hormone receptor-positive tumours (T-DXd, 331; TPC, 163) and 11.3% had hormone receptor-negative tumours (T-DXd, 42; TPC, 21)

- 543 subjects (T-DXd, 371; TPC, 172) received at least 1 dose of study drug
- In the TPC arm, eribulin was the treatment most frequently chosen by investigators (n=94)

At the DCO of 11 Jan 2022, 11.2% of subjects in the FAS were ongoing on study drug. The proportion of subjects still on treatment was greater in the T-DXd arm than in the TPC arm (15.6% vs. 1.7%, respectively).

Protocol violations/deviations

The clinical evaluator agreed with the Sponsor that they were unlikely to have a material impact on the study results.

Baseline characteristics

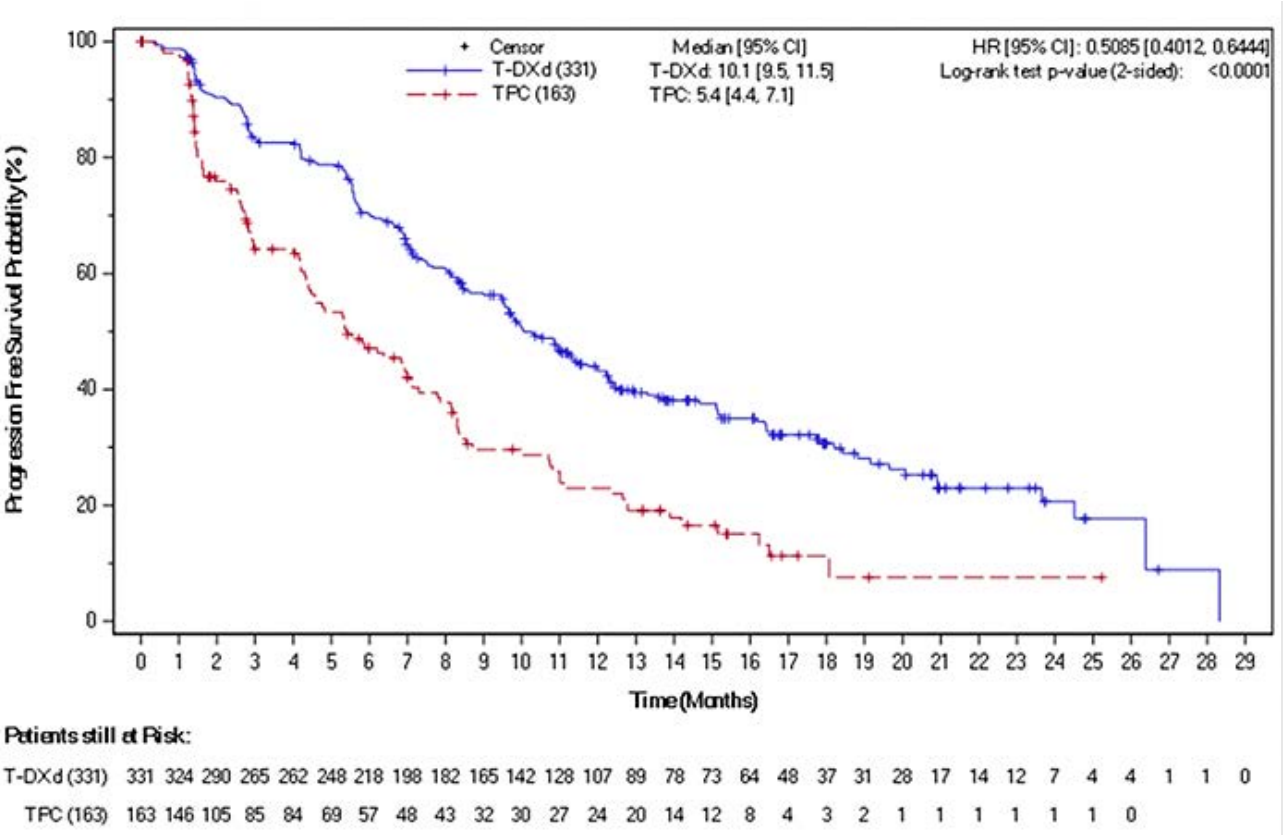
The baseline demographic and clinical characteristics of the patients were similar in the two arms and largely representative of the overall population of patients with HER2-negative breast cancer.

Results

Primary Efficacy Endpoint (PFS by BICR in HR positive cohort)

Treatment with T-DXd resulted in a statistically significant improvement in BICR-assessed PFS compared with TPC. The median PFS based on BICR was 10.1 months (95% CI: 9.5, 11.5) in the T-DXd arm vs. 5.4 months (95% CI: 4.4, 7.1) in the TPC arm. The stratified HR was 0.51 (95% CI: 0.40, 0.64) (2-sided stratified log-rank P <0.0001).

Figure 2. Kaplan-Meier plot of progression-free survival by blinded independent central review in hormone receptor-positive cohort.



The efficacy benefit in PFS provided by T-DXd over TPC was observed consistently across key pre-specified subgroups, including those based on stratification factors. All the sensitivity analyses were consistent with the primary analysis.

Secondary endpoints

PFS (BICR) in FAS

Treatment with T-DXd resulted in a statistically significant improvement in BICR-assessed PFS compared with TPC in the FAS, with the median PFS by BICR in the FAS was 9.9 months (95% CI: 9.0, 11.3) in the T-DXd arm vs. 5.1 months (95% CI: 4.2, 6.8) in the TPC arm, and a stratified HR of 0.50 (95% CI: 0.40, 0.63; 2-sided stratified log-rank test, P <0.0001).

Results in the hormone receptor-negative cohort per IXRS were consistent with those in the FAS, showing a clinically meaningful improvement in PFS in the T-DXd arm compared with the TPC arm (HR: 0.45 [95% CI: 0.23, 0.87]). Median PFS in the hormone receptor-negative cohort was 6.6 months (95% CI: 4.1, 11.7) in the T-DXd arm vs 2.9 months (95% CI: 1.4, 4.0) in the TPC arm.

OS in the HR positive cohort

The first IA for OS was conducted at the DCO date for the primary efficacy analysis of PFS (11 Jan 2022). At DCO, the median duration of OS follow-up was 18.4 months (95% CI: 17.7, 18.9) in the hormone receptor-positive cohort and 18.4 months (95% CI: 17.9, 19.1) in the FAS, respectively). At DCO, 199 subjects in the hormone receptor-positive cohort had died: 126 (38.1%) in the T-DXd arm and 73 (44.8%) in the TPC arm.

Median OS was 23.9 months (95% CI: 20.8, 24.8) in the T-DXd arm vs 17.5 months (95% CI: 15.2, 22.4) in the TPC arm with an HR of 0.64 (95% CI: 0.48, 0.86). The *P*-value of 0.0028 crossed the prespecified IA efficacy stopping boundary of 0.00748.

OS in the FAS

Results were consistent in the FAS, Median OS in the FAS was 23.4 months (95% CI: 20.0, 24.8) in the T-DXd arm vs 16.8 months (95% CI: 14.5, 20.0) in the TPC arm, (HR: 0.64 [95% CI: 0.49, 0.84] which was a statistically significant improvement in OS, stratified *P*-value = 0.0010 that crossed the prespecified IA efficacy stopping boundary of 0.00748.

ORR & DOR

The percentage of patients with a confirmed objective response in the hormone receptor–positive cohort was 52.6% (95% CI, 47.0 to 58.0) in the T-DXd group and 16.3% (95% CI, 11.0 to 22.8) in the physician's choice group. The median duration of response was 10.7 months in the T-DXd group and 6.8 months in the physician's choice group.

The percentage of patients with a confirmed objective response among all patients was 52.3% (95% CI, 47.1 to 57.4) in the T-DXd group and 16.3% (95% CI, 11.3 to 22.5) in the physician's choice group.

Clinical evaluator's summary of efficacy

Study U303

- The trial met its primary efficacy endpoint; treatment with T-DXd resulted in a statistically significant improvement in BICR-assessed PFS compared with TPC, in the hormone receptor-positive cohort. The median PFS based on BICR was 10.1 months (95% CI: 9.5, 11.5) in the T-DXd arm vs. 5.4 months (95% CI: 4.4, 7.1) in the TPC arm. The stratified HR was 0.51 (95% CI: 0.40, 0.64) (2-sided stratified log-rank P <0.0001).

- PFS is an accepted regulatory endpoint.
- The improvement in PFS in study U303 is considered clinically meaningful.
- The efficacy benefit in PFS provided by T-DXd over TPC was observed consistently across key pre-specified subgroups, including those based on stratification factors. All the sensitivity analyses were consistent with the primary analysis.
- Overall survival data are immature, however in the full analysis set, the median overall survival was 23.4 months (95% CI, 20.0 to 24.8) in the T-DXd group and 16.8 months (95% CI, 14.5 to 20.0) in the TPC group (hazard ratio, 0.64; 95% CI, 0.49 to 0.84; P = 0.001).

Study J101

Due to the small number of subjects and two dose levels used, the evaluator did not consider that the data from Study J101 were robust enough to be included in the benefit risk assessment of T-DXd for the proposed extension of indication.

Evaluator's overall summary of efficacy

- Study U303 was a Phase 3, multicentre, randomised, open-label, active-controlled study in subjects with unresectable or metastatic HER2-low BC (defined as IHC 1+ or IHC 2+/ISH-negative) who have received 1 or 2 prior lines of chemotherapy.
- For enrolment, subjects had to have pathologically documented, unresectable or metastatic hormone receptor-positive or hormone receptor-negative BC with centrally-confirmed low HER2 expression (IHC 1+ of IHC 2+/ISH-negative) according to ASCO/CAP 2018 HER2 testing guidelines adapted by Daiichi Sankyo and Ventana Medical Systems.
- Patients were randomised 2:1 to receive either Enhertu 5.4 mg/kg (N=373) by intravenous infusion every three weeks or physician's choice of chemotherapy (N=184, eribulin 51.1%, capecitabine 20.1%, gemcitabine 10.3%, nab paclitaxel 10.3%, or paclitaxel 8.2%).
- The diagnostic step to identify HER2-low tumours is considered a critical step in identifying suitable patients to be targeted by T-DXd therapy. It needs to be demonstrated that the testing utilised in the clinical trial is generalisable to the Australian clinical practice population.
- The choice of comparator(s) is considered appropriate, considering the protocol was finalised in August 2018 and are relevant to Australian clinical practice.
- There were a large number of trial sites meaning that each site managed relative low numbers of patients.
- There may have been some variability in dosing in the comparator arm across sites in different countries as it was 'physician's choice'.
- There were no Australian sites included in the study and the ethnic mix of the trial population may not reflect the Australian community.
- Patients in clinical practice may on average be older, have lower performance status and have more co-morbidities than trial subjects.
- The trial met its primary efficacy endpoint, namely, treatment with T-DXd resulted in a statistically significant improvement in BICR-assessed PFS compared with TPC, in the hormone receptor-positive cohort.).
- PFS is an accepted regulatory endpoint and is considered robust.
- The improvement in PFS in study U303 is considered clinically meaningful.

- A consistent benefit was observed for T-DXd across analysed subgroups.
- Overall survival data are immature, however in the full analysis set, the median overall survival was 23.4 months (95% CI, 20.0 to 24.8) in the T-DXd group and 16.8 months (95% CI, 14.5 to 20.0) in the TPC group (hazard ratio, 0.64; 95% CI, 0.49 to 0.84; P = 0.001).
- For patients with refractory hormone receptor–negative, HER2-negative (triple-negative) disease, sacituzumab govitecan (Trodelvy) was approved by the TGA in September 2021 on the basis of the results of the ASCENT trial, which showed progression-free and overall survival benefits for sacituzumab govitecan over the physician's choice of chemotherapy.
- Data are lacking to compare sacituzumab govitecan with T-DXd in patients with breast cancer.

Safety

Study U303 provides additional safety data for T-DXd (371subjects) to the existing safety database. The focus of the safety analyses for this application is the comparison of safety data from the 543 subjects in the target population of unresectable or metastatic HER2-low BC previously treated with chemotherapy who received at least 1 dose of T-DXd 5.4 mg/kg (371 subjects) or TPC (172 subjects) in Study U303 (Safety Analysis Set).

Patient exposure

In Study U303, the median treatment duration was longer in the T-DXd arm (8.2 months; range: 0.2 to 33.3) than in the TPC arm (3.5 months; range: 0.3 to 17.6).

Adverse events

The observed safety profile in patients in the T-DXd arm of Study U303 was similar to that of the All BC T-DXd 5.4mg/kg pool.

Treatment related AEs

In the T-DXd arm, the commonest drug related AEs of any grade included:

- Nausea 76.0% (vs 30.2% in TPC arm)
- Fatigue 53.6% (vs 48.3% in TPC arm)
- Alopecia 39.6% (vs 33.1% in TPC arm)

In the T-DXd arm, the commonest drug related AEs of grade 3 or higher included:

- Neutropenia 14.0% (vs 41.3% in TPC arm)
- Anaemia 10.2% (vs 5.2% in TPC arm)
- Fatigue 8.6% (vs 4.7% in TPC arm)

Laboratory abnormalities were consistent with the observed TEAs in both treatment arms and generally occurred at a higher incidence than the TEAs. There was a notably higher incidence of all grades of haemoglobin decreased, platelet count decreased, and lymphocyte count decreased in the T-DXd arm than in the TPC arm and a notably higher incidence of Grade 3 or 4 neutrophil count decreased and white blood cell count decreased in the TPC arm.

Deaths

In Study U303, as of DCO of 11 Jan 2022, deaths due to any cause were reported in 39.9% of subjects in the T-DXd arm and 51.2% of subjects in the TPC arm. The commonest cause of death was disease progression in both arms.

Serious Adverse Events

In Study U303, serious TEAEs occurred in similar proportions of subjects in both treatment arms (27.8% in the T-DXd arm vs 25.0% in the TPC arm). Serious TEAEs reported in ≥2% of subjects were adjudicated drug-related Interstitial lung disease (ILD) in the T-DXd arm (4.3%) and overdose (2.9%), febrile neutropenia (2.3%), and neutropenia (grouped term, 2.3%) in the TPC arm.

Discontinuation due to Adverse Effects

In Study U303, the incidence of TEAEs associated with study drug discontinuation was higher in the T-DXd arm (16.2%) than in the TPC arm (8.1%). The most commonly reported TEAEs were adjudicated drug-related ILD (8.4%) in the T-DXd arm and peripheral sensory neuropathy (2.3%) in the TPC arm.

The median time from first dose to the onset of the TEAE associated with study drug discontinuation was 146.0 days (range: 3 to 742) in the T-DXd arm compared with 45.5 days (range: -20 to 494) in the TPC arm.

Dose reduction due to Adverse Events

In Study U303, a lower proportion of subjects had TEAEs associated with dose reduction in the T-DXd arm (22.6%) than in the TPC arm (38.4%).

The most commonly reported TEAEs associated with dose reduction in the T-DXd arm were:

- Nausea 4.6%
- Fatigue 4.6%

The most commonly reported TEAEs associated with dose reduction in the TPC arm were:

- Neutropenia 14.0%
- PPE 5.2%
- Fatigue 4.7%

Dose interruption due to Adverse Events

In Study U303, the incidence of TEAEs associated with study drug interruption was similar in the two treatment arms (38.5% in T-DXd arm vs 41.9% in the TPC arm).

The most frequently reported TEAEs associated with study drug interruption were neutropenia and fatigue in the T-DXd arm (9.2% and 5.1% respectively), and neutropenia and leukopenia in the TPC arm (22.7% and 5.8% respectively).

Interstitial lung disease

In Study U303, all potential events of ILD/pneumonitis reported as of the DCO were reviewed and adjudicated by the ILD adjudication Committee (AC).

- Overall, 15.1% of subjects in the T-DXd arm and 1.2% of subjects in the TPC arm had events of potential ILD/pneumonitis.

- A total of 12.1% of subjects in the T-DXd arm and 0.6% of subjects in the TPC arm had events adjudicated as drug-related ILD
- In the T-DXd arm, most events were Grade 1 or Grade 2, with 1.3% of subjects having Grade 3 events and no subject having a Grade 4 event. Three (0.8%) subjects in the T-DXd arm had Grade 5 adjudicated drug-related ILD.

Cardiovascular safety

In Study U303, LV dysfunction was reported in 4.6% of subjects in the T-DXd arm and no subjects in the TPC arm; the majority of events were Grade 1 (0.3%) or Grade 2 (3.8%) with Grade 3 in 0.5% of subjects and no Grade 4 or 5.

Of the 13 PTs included in the case definition of LV dysfunction, only the PTs of ejection fraction decreased (4.3%) and cardiac failure (0.5%) were reported in this study. The events in the T-DXd arm were associated with study drug interruption in 1.3% of subjects and with study drug discontinuation in 0.8% of subjects; there was no dose reduction associated with LV dysfunction.

14.9% of subjects in the T-DXd arm and 7.7% of subjects in the TPC arm who had a post-baseline LVEF value met the laboratory criteria for a Grade 2 LVEF decrease, and 1.5% of subjects in the T-DXd arm and none in the TPC arm met the criteria for a Grade 3 decrease. Two (0.5%) subjects in the T-DXd arm and none in the TPC arm had a post- baseline resting LVEF of <40%.

The clinical evaluator highlighted the following statement from the sponsor:

> *"Available data are not sufficient to suggest that T-DXd is associated with an increased risk of LV dysfunction. Since LVEF decrease and congestive heart failure have been reported for drugs in a similar class and considering the limited long-term exposure data in the target population, LV dysfunction remains an important potential risk, and should be monitored regularly during treatment and managed as clinically indicated."*

LV dysfunction is an important identified risk in the Australian RMP and there is an associated warning in the PI.

Immunogenicity

In Study U303, the treatment-emergent incidence of ADAs was 2.0% (7/357 subjects).

Post marketing experience

For the period from 20 Dec 2021 through 01 Mar 2022, a total of 840 new AEs meeting PBRER reporting criteria were reported; the majority (670) of those events were non-serious.

Reported events were generally consistent with the established safety profile of T-DXd.

There were no new safety findings during this period.

Clinical evaluator's summary of safety

- The safety profile of T-DXd was assessed in 371 patients with unresectable or metastatic HER2-low breast cancer in the T-DXd arm who received at least 1 dose of T-DXd 5.4 mg/kg as compared to 172 patients treated in the chemotherapy arm (either eribulin, capecitabine, gemcitabine, paclitaxel or nab-paclitaxel) in study U303 (Destiny-Breast04).
- To ensure consistency of the safety profile of T-DXd, the pooled safety analysis provided by the sponsor was also reviewed for all patients with metastatic HER-2 positive BC who had received at least one dose of T=DXd 5.4 mg/kg across multiple studies.
- The overall exposure to T-DXd on study U303 is considered adequate to assess safety.

- Treatment duration was longer in the T-DXd arm than in the TPC arm.
- The median age of patients in the trial is lower than in clinical practice and the performance status is better, meaning some caution is required in generalising the safety results.
- There were 148 patients who died in the T-DXd arm of the trial, including 13 deaths within 30 days of study treatment and 135 deaths post treatment. Of the 13 deaths which occurred on study treatment, 3 were attributed to progression of disease, 8 were due to an adverse event and 2 were 'other' or 'unknown' causes. Of the 135 deaths which occurred post-treatment, 119 were due to progression of disease, 2 were due to an adverse event. Deaths from adverse events were due to pneumonitis, febrile neutropenia, sepsis, ischaemic colitis, DIC and respiratory failure.
- SAEs affected 28% of patients in the T-DXd arm and 25% of patients in the TPC arm.
- The most common SAEs (>1%) were pneumonitis, pneumonia, dyspnoea, musculoskeletal pain, sepsis and hypercalcemia. ILD is captured by the preferred terms pneumonitis, interstitial lung disease and organising pneumonia.
- TEAEs associated with study drug discontinuation were reported in a greater proportion of subjects in the T-DXd arm (16.2%) than in the TPC arm (8.1%). This difference was largely due to the higher incidence of ILD in the T-DXd arm. ILD/pneumonitis is an important identified risk associated with T-DXd and is summarised in the current PI.
- Observed TEAEs associated with dose reduction or study drug interruption were manageable, were generally as expected in this patient population in both treatment arms and were consistent with those previously observed with T-DXd.
- Laboratory abnormalities were consistent with the observed TEAEs in both treatment arms, although the laboratory abnormalities generally occurred at a higher incidence than the TEAEs. There was a notably higher incidence of all grades haemoglobin decreased, platelet count decreased, and lymphocyte count decreased in the T-DXd arm than in the TPC arm and a notably higher incidence of Grade 3 or 4 neutrophil count decreased and white blood cell count decreased in the TPC arm.
- Integrated Assessment of Safety
  - Safety analyses focus primarily on the comparison of safety data from subjects in the target population who received T-DXd 5.4 mg/kg with those from subjects who received TPC in Study U303. To provide additional evidence of the overall safety profile of T-DXd, data are also summarised for 2 pools: the All BC T-DXd 5.4 mg/kg Pool (N = 883) and the All Tumour Types T-DXd ≥5.4 mg/kg Pool (N = 1590). The latter pool included a diverse population of subjects with a variety of tumour types.
  - The median duration of treatment was 9.9 months (range: 0.2 to 37.1 months) in the All BC T-DXd 5.4 mg/kg Pool and 7.8 months (range: 0.2 to 41.0 months) in the All Tumour Types T-DXd ≥5.4 mg/kg Pool.
  - Results in the 2 pools were generally consistent with those from the T-DXd arm of Study U303.
  - The safety profile of T-DXd in Study U303 is generally consistent with the known safety profile of T-DXd. AEs were manageable through dose modifications and routine clinical practice. ILD/pneumonitis is a known serious risk for T-DXd. Most cases were Grade 1 or Grade 2 and were manageable by following dose modification and established treatment guidelines. LV dysfunction remains an important potential risk.
  - T-DXd demonstrated a generally acceptable safety profile given that the target population has metastatic breast cancer.

- In summary, no new safety signal was identified in the U303 T-DXd arm compared to the All breast cancer T-DXd 5.4 mg/kg Pool or compared to the established safety profile represented by the All Tumour Types T-DXd ≥5.4 mg/kg Pool.

Summary of clinical evaluation / benefit-risk assessment

The key findings of the clinical evaluator's benefit-risk assessment are as follows:

- The data from Study U303 demonstrates greater efficacy of T-DXd compared to TPC in the target population of metastatic HER2-low BC, along with a manageable safety profile.
- Therefore, the overall benefit-risk assessment in Study U303 is positive for T-DXd for the treatment of adult patients with unresectable or metastatic HER2-low BC who have received prior systemic chemotherapy.
- Some questions remain about the generalisability of these results to the Australian Clinical population.
- A validated diagnostic test is key to the accurate diagnosis of the HER2-low subset of BC.
- The modest benefits from currently approved systemic therapies might be improved upon with a more targeted therapy if the HER2-low sub-group of BC patients can be satisfactorily identified.
- Expert advice suggests that: "greater training of pathologists in scoring HER2 IHC at the lower end of the spectrum is required along with evidence that training improves scoring concordance." Specifically, "reliable distinction of HER2 IHC 0 from 1+ needs to be established for this assay." If mis-diagnosed, there is a substantial risk that BC patients with a low probability of obtaining benefit (i.e. HER2-0) could be exposed to a treatment (T-DXd) associated with significant adverse events.
- FDA Questions/answers (module 1.11.4) were reviewed and considered that they did not materially alter the benefit risk assessment of Study U303 (see pages 64-66 of clinical evaluation report).
- Swissmedic Questions/answers (module 1.11.4) were reviewed and considered that they did not materially alter the benefit risk assessment of Study U303 (see pages 66-69 of clinical evaluation report).

Having taken the above into consideration, in addition to reviewing the responses from experts regarding conventional HER2 IHC testing (pages 14-19 of clinical evaluation report) and the responses from the Sponsor regarding HER2-low testing (pages 61-64 of clinical evaluation report), the clinical evaluator concluded the following:

- The overall benefit-risk assessment in Study U303 is positive for T-DXd for the treatment of adult patients with unresectable or metastatic HER2-low BC who have received prior systemic chemotherapy. A final decision on approval will be made by the Delegate when all relevant information is available.

The Delegate notes and accepts the additional background information provided by the Sponsor regarding HER2 expression diagnostic testing in the "Response Document, Milestone 5 Evaluation Report Response: 30 November 2022", including the following:

Sponsor's response:

> Acknowledging expert advice as above, AstraZeneca has now commenced the rollout of a HER2-low breast cancer training programme to support the Enhertu launch in Australia. This HER2-low training programme has been designed to upskill Australian pathologists in HER2 slide assessment, including the accurate and reproduceable identification of the

level of HER2 expression, with a particular focus on the differentiation between HER2 IHC 0 and 1+ scoring and reporting. AstraZeneca has engaged key breast pathologists nationally including the principal pathologists/clinical experts who delivered on the successful rollout of HER2 testing training in Australia in 2008. The training programme commenced phase 1 in Q4 2022 with the delivery of the first 'train the trainer' session. This is the first step in a comprehensive programme involving a core group of 15 key breast pathologists who will then lead a series of training sessions for pathology lab staff across Australia. This programme has a target completion date of Q 1 2023.

Regarding the reliability/validity of the diagnostic test in distinguishing HER2 0 from 1+, the sponsor understands from Roche Diagnostics Australia (the sponsor for the VENT ANA HER2 IHC companion diagnostic) that there is an analytical dossier which specifically addresses this question and has been included in the companion diagnostic (CDx) application submitted to the TGA. This dossier includes the same reports submitted in the IVD application to the US FDA, which has been recently approved.

The delegate agrees with the clinical evaluator's overall conclusion on a favourable benefit-risk assessment (see Discussion below). In addition, the delegate acknowledges and highlights the following comments from experts (pathology and clinical) whose opinions were sought by the TGA regarding HER2 IHC testing:

- In Australia, where HER2 IHC is a well-established methodology, from a clinical perspective there are no real concerns regarding the ability to establish HER2 low status using conventional HER2 IHC testing.
- No additional testing would be required to determine HER2-low status.
- Issues relating to sample preparation and heterogeneity are not new and apply to every biopsy test, not specifically HER2-low IHC testing.
- Conventional HER2 IHC to identify HER2-low status of tumours is suitable in so far as HER2 IHC is already in routine use in breast cancer in Australia with the same scoring algorithm as used in the DESTINY-Breast04 study.

Clinical Evaluator's conclusions on the PI

The clinical evaluator's conclusions on the PI are as follows:

The delegate may consider changing the wording in the indication from 'prior systemic therapy' to 'prior chemotherapy', this would align with the eligibility criteria for trial U303 and the FDA-approved indication.

The uploaded Adverse Event Section, providing tables of adverse events from DESTINY:Breast04 (U303) is acceptable.

The description of DESTINY:Breast04 (U303) in the Clinical Trial Section of the PI is acceptable.

The delegate agrees with the clinical evaluator's conclusions on the PI, in particular regarding the wording of the indication, whereby "systemic therapy" be changed to "chemotherapy", i.e.

"Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC1+ or IHC 2+/ISH-negative) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy."

The Sponsor responded to this recommendation as follows:

AstraZeneca acknowledges the revisions to the indication statement proposed by the TGA evaluator, bur respectfully requests to keep 'p1i or systemic therapy· in the label indication.

DESTINY-Breast04 (DB-04) study was designed to include pre-treated patients with HER2- low expressing tumour regardless of HR status. The eligibility criteria were intended to ensure that patients received the most appropriate and approved systemic treatments for metastatic disease before entering a clinical trial with an investigational agent, consequently specific eligibility criteria regarding prior systemic therapy were applied aiming to encompass the differences in treatment paradigm by HR status and future developments in the metastatic BC space (i.e., new antibody drug conjugates [ADCs] might not qualify as chemotherapy).

AstraZeneca considers that 'prior chemotherapy" is included in “prior systemic therapy" and this latter statement represents the subject population included in the DB-04 study who were previously exposed to other SoC therapies such as PARP inhibitors, immunotherapy, CDK4/6 inhibitors, endocrine-based therapy and chemotherapy.

AstraZeneca therefore proposes to maintain the following indication wording which best reflects the population enrolled it1 the DB-04 study:

"Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-1ow (IHC I+ or IHC 2+/ISH-negative} breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Patients with hormone receptor positive (HR+) breast cancer should additional have reached or be ineligible for endocrine therapy."

The Delegate’s view is that the wording of the indication should specify “prior chemotherapy”, based on the following:

- The pivotal study U303 inclusion criterium 3(g) specifically required that each patient must have been treated with at least 1 and no more than 2 prior lines of chemotherapy in the recurrent or metastatic setting.
- In both the Hormone Receptor-positive Cohort and the FAS, 100% of patients in the T-DXd arm had received at least 1 prior chemotherapy (chemotherapy agents shown in Table 3).

Table 3. Most common prior breast cancer systemic therapy administered in the hormone receptor-positive cohort and the full analysis set.

Parameter	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Cyclophosphamide	182 (55.0)	85 (52.1)	207 (55.5)	93 (50.5)
Capecitabine	177 (53.5)	83 (50.9)	191 (51.2)	95 (51.6)
Paclitaxel	161 (48.6)	82 (50.3)	187 (50.1)	93 (50.5)
Docetaxel	109 (32.9)	62 (38.0)	126 (33.8)	68 (37.0)
Epirubicin	68 (20.5)	38 (23.3)	81 (21.7)	42 (22.8)
Chemotherapy	331 (100.0)	162 (99.4)	373 (100.0)	183 (99.5)

- The wording would be in alignment with the study population in Study U303, and with the FDA approved indication / US PI.

Summary and discussion

Background: Condition and current treatment options

Approximately 80% of patients with breast cancer will have tumours that are HER2 negative (including hormone receptor (HR) positive/HER2 negative, and HR negative/HER2 negative), and approximately 60% of these tumours may have HER2 expression IHC scores of 2+ or 1+ and negative results on in situ hybridization (i.e. HER2-low).[5] Unresectable or metastatic HER2-low breast cancer is a serious and life-threatening condition that is incurable.

There are no specific therapies currently approved in Australia for advanced HER2-low breast cancer. Treatment is guided by HR status, and patients with HER2-low breast cancer are treated as per those with HER2 negative disease.

For patients with metastatic HR+/HER2- breast cancer, the upfront standard of care includes endocrine based therapy (e.g. combination of endocrine therapy with a CDK4/6 inhibitor); this is often effective for approximately 2 years before resistance occurs. On progression, treatment options include additional endocrine therapy or chemotherapy (e.g. anthracyclines, capecitabine, vinorelbine, eribulin, gemcitabine and paclitaxel) if endocrine resistant. Patients with metastatic triple negative disease may receive pembrolizumab in combination with chemotherapy (if PD-L1 positive) or chemotherapy options including those agents listed above; Sacituzumab govitecan may be used following at least 1 treatment regimen in the metastatic setting. Responses to single agent chemotherapy are often not durable, and additional therapies are needed in these patient populations.

Proposed indication

The Sponsor proposes to register a new therapeutic entity for the following indication:

[5] Modi S, Jacot W, Yamashita J, et al. Trastuzumab Deruxtecan in Previously Treated Advanced Breast Cancer. N Engl J Med 2022;387:9-20.

- "Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC1+ or IHC 2+/ISH-negative) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy."

Benefits / Uncertainties of benefit

The results of DESTINY-Breast04 study have shown a statistically significant and clinically meaningful improvement in PFS and overall survival with the use of trastuzumab deruxtecan in patients with HER2-low metastatic breast cancer (previously received chemotherapy, and at least one line of endocrine therapy in those with HR positive disease) compared with physician's choice chemotherapy.

DESTINY-Breast 04 is an international, multi-centre, randomised, open-label, active controlled phase 3 study involving adult patients with HER2-low unresectable or metastatic breast cancer; patients must have received chemotherapy for metastatic disease or have had disease recurrence during or within 6 months after completing (neo)adjuvant chemotherapy, and those with HR positive disease must have received at least one line of endocrine therapy or be ineligible for endocrine therapy. IHC scores for HER2 expression were determined through central testing of specimens using conventional IHC assay, with HER2-low tumours defined as those scoring 2+ or 1+ by IHC and no evidence of HER2 gene amplification by ISH. Patients were randomised 2:1 (n=557) to receive trastuzumab deruxtecan 5.4mg/kg IV every 3 weeks or physician's choice of capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel. Of the 373 patients randomised to the trastuzumab deruxtecan group and 184 patients assigned to the physician's choice group (eribulin 51%, capecitabine 20%, nab-paclitaxel 10%, gemcitabine 10% and paclitaxel 8%), 88.7% and 88.6% respectively comprised the hormone receptor positive cohort.

At the date cut-off date for the primary efficacy analysis (January 11, 2022), the median PFS in the HR positive cohort was 10.1 months (95% CI: 9.5, 11.5) in the trastuzumab deruxtecan group and 5.4 months (95% CI: 4.4, 7.1) in the physician's choice group; HR = 0.51 (95% CI: 0.40, 0.64).

Statistically significant and clinically meaningful improvement in the remainder of endpoints was also observed. Among all patients, the median PFS was 9.9 months (95% CI: 9.0, 11.3) in the trastuzumab deruxtecan group and 5.1 months (95% CI: 4.2, 6.8) in the physician's choice group; HR = 0.50 (95% CI: 0.40, 0.63).

The median OS in the HR positive cohort was 23.9 months (95% CI: 20.8, 24.8) in the trastuzumab deruxtecan group and 17.5 months (95% CI: 15.2, 22.4) in the physician's choice group; HR = 0.64 (95% CI: 0.48, 0.86), 2-sided stratified log-rank P value 0.0028 which was statistically significant and crossed the prespecified efficacy stopping boundary of 0.00748.

Among all patients, the median OS, although immature, was 23.4 months (95% CI: 20.0, 24.8) in the trastuzumab deruxtecan group and 16.8 months (95% CI: 14.5, 20.0) in the physician's choice group; HR = 0.64 (95% CI: 0.49, 0.84), which was a statistically significant improvement in OS, stratified P-value = 0.0010 that crossed the prespecified IA efficacy stopping boundary of 0.00748.

The exploratory ORR and DOR results supported the PFS and OS results in both cohorts.

There were 63 patients in the FAS cohort who were HR negative. An exploratory subgroup analysis of PFS and OS was performed; median PFS was 6.6 months (95% CI: 4.1, 11.7) in the trastuzumab deruxtecan group and 2.9 months (95% CI: 1.4, 4.0) in the physician's choice group; HR = 0.45 (95% CI: 0.23, 0.87). The median OS was 16.6 months (95% CI: 11.3, NE) in

the trastuzumab deruxtecan group and 10.3 months (95% CI: 6.1, 15.2) in the physician's choice group; HR = 0.63 (95% CI: 0.32, 1.23). Although this was a small subgroup, the PFS and OS results were consistent with the PFS and OS in the HR positive cohort and did not show any detriment in the HR negative population, i.e. the results in the FAS were not driven by the HR positive cohort, and patients with HR negative disease can be included in the indication.

A consistent benefit was seen for trastuzumab deruxtecan across other subgroups including those with disease progression during or within 6 months of (neo)adjuvant chemotherapy. Exploratory subgroup analysis in the 22 patients in the FAS cohort who progressed on or within 6 months of (neo)adjuvant chemotherapy showed a 6 month PFS improvement favouring T-DXd (HR = 0.38; 95% CI: 0.12, 1.21), with a median PFS of 8.2 months (95% CI: 1.4, NE) in the T-DXd arm compared to 2.2 months (95% CI: 0.6, NE) in the TPC arm, and median OS of 17.2 months (95% CI: 6.0, NE) in the T-DXd arm vs 8.9 months (95% CI: 0.2, 20.6) in the TPC arm.

Uncertainties

Although Sacituzumab govitecan has been shown to improve PFS and OS in patients with heavily treated triple negative disease (ASCENT trial) this agent was not available as a comparator for trastuzumab deruxtecan in DESTINY-Breast04. Consequently, direct comparative data between trastuzumab deruxtecan and Sacituzumab govitecan in patients with TNBC is lacking. Indirectly, in patients with heavily pre-treated triple negative disease, the median PFS and OS compare favourably for trastuzumab deruxtecan (8.5 months and 18.2 months) compared with Sacituzumab govitecan (6 months and 12 months, respectively).

Risks / Uncertainties of risk

The safety profile of trastuzumab deruxtecan in DESTINY-Breast04 was similar to the established safety profile in patients with HER2-positive metastatic breast cancer in DESTINY-Breast03 with similar incidences of AEs. The most common (≥20%) AEs were nausea, decreased white blood cell count, decreased haemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased AST, increased ALT, constipation, increased alkaline phosphatase, decreased appetite, diarrhoea, musculoskeletal pain and hypokalaemia. The commonest AE Grade ≥3 was neutropenia (14%); the incidence of febrile neutropenia was low (1.1%).

Serious AEs occurred in 27.8% of patients who received trastuzumab deruxtecan including ILD/pneumonitis, pneumonia, dyspnoea, musculoskeletal pain, sepsis, anaemia, febrile neutropenia, hypercalcemia, nausea, pyrexia and vomiting.

TEAEs associated with an outcome of deaths occurred in 3.8% of patients in the T-DXd arm including ILD/pneumonitis (n=3), sepsis (n=2), and ischemic colitis, DIC, dyspnoea, febrile neutropenia, general health deterioration, pleural effusion and respiratory failure (1 patient each).

ILD/pneumonitis is an important safety signal related to treatment with T-DXd. Most patients with drug-related ILD or pneumonitis in DESTINY-Breast04 were mild or moderate, with an overall incidence similar to that of previous studies as outlined in the current PI. Of the 371 patients treated with trastuzumab deruxtecan, ILD occurred in 12%; 10% had Grade 1/2 ILD events, 1.3% had Grade 3/4 events and 0.8% had Grade 5 events. Pro-active monitoring of symptoms of ILD/pneumonitis, and active management including prompt dose interruption and early use of glucocorticoid treatment will be required.

No new safety signals for trastuzumab deruxtecan were identified in DESTINY-Breast04.

Benefit/Risk balance

In patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, DESTINY-Breast04 demonstrated statistically significant and clinically meaningful improvements in PFS and OS for those receiving T-DXd compared to treatment of physician's choice. This was observed in both the HR+ cohort as well as the FAS. The safety profile from DESTINY-Breast-04 is consistent with the known tolerable and manageable safety profile of T-DXd and no new safety signals were identified. Overall, the benefit risk assessment for T-DXd in this population is considered to be positive.

Outcome

Based on a favourable benefit risk assessment for T-DXd, the delegate supports approval for the extension of indications of trastuzumab deruxtecan for the following indication:

> *"Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC1+ 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. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy."*

The Delegate recommends that the wording of the indication should specify "prior chemotherapy" (rather than "a prior systemic therapy" as maintained by the Sponsor) based on the inclusion criteria and study population of the pivotal study DESTINY-Breast04.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Enhertu which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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