▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ENHERTU®
(trastuzumab deruxtecan) powder for injection

1 NAME OF THE MEDICINE

Trastuzumab deruxtecan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 (see Section 4.2 Dose and method of administration).

For the full list of excipients, see Section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Powder for injection.

White to yellowish-white lyophilized powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Metastatic Breast Cancer

HER2-Positive

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.

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do not substitute ENHERTU for or with trastuzumab or trastuzumab emtansine. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is ENHERTU (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Patient selection for HER2-low metastatic breast cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH-negative tumor status by using a TGA approved or notified assay performed by a NATA accredited laboratory.

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.

The infusion rate of ENHERTU should be slowed or interrupted if the patient develops infusion-related symptoms. ENHERTU should be permanently discontinued in case of severe infusion reactions.

Premedication

ENHERTU is emetogenic [see Section 4.8 Adverse effects (undesirable effects)], which includes delayed nausea and/or vomiting. Prior to each dose of ENHERTU, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Dose Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as per guidelines provided in Table 1 and Table 2.

ENHERTU dose should not be re-escalated after a dose reduction is made.

Table 1: Dose Reduction Schedule

Dose Reduction Schedule (Starting dose is 5.4 mg/kg.)	Dose to Be Administered
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity		Treatment Modification
Interstitial Lung Disease (ILD)/Pneumonitis	Asymptomatic ILD/Pneumonitis (Grade 1)		Interrupt ENHERTU until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).
	Symptomatic ILD/Pneumonitis (Grade 2 or greater)		• Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile Neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.		• Interrupt ENHERTU until resolved. • Reduce dose by one level (see Table 1).
Left Ventricular Ejection Fraction (LVEF) Decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.

Adverse Reaction	Severity		Treatment Modification
		is less than 10%	
		And absolute decrease from baseline is 10% to 20%	• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. • If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue ENHERTU.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v.5.0).

Delayed or Missed Dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion should be administered at the dose and rate the patient tolerated in the most recent infusion.

Special patient populations

Use in the elderly

No dose adjustment of ENHERTU is required in patients aged 65 years or older.

Paediatric use

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of metastatic breast cancer.

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment. Limited data are available in patients with severe renal impairment. A higher incidence of Grade 1 and 2 ILD/pneumonitis leading to an increase in discontinuation of therapy has been observed in patients

with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*). The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr<30 mL/min).

Hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are insufficient data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

Method of administration

ENHERTU is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. ENHERTU must not be administered as an intravenous push or bolus.

In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is ENHERTU (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the following reconstitution and dilution procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed.
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

Calculation to determine the volume of reconstituted ENHERTU (mL) to be further diluted:

$$\textbf{Reconstituted ENHERTU (mL)} = \frac{\text{ENHERTU dose (mg/kg) x Patient's Body Weight (kg)}}{\text{20 mg/mL}}$$

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Inspect the reconstituted solution for particulates and discoloration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.
- Dilute the calculated volume of reconstituted ENHERTU in an infusion bag containing 100 mL of 5% dextrose solution. Do not use sodium chloride solution (see Section 6.2

Incompatibilities). An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2ºC to 8ºC), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration protected from light.
- Administer ENHERTU as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.
- Cover the infusion bag to project from light.
- Do not mix ENHERTU with other medicinal products or administer other medicinal products through the same intravenous line.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial Lung Disease/Pneumonitis

Cases of interstitial lung disease (ILD) and/or pneumonitis, have been reported with ENHERTU [see Section 4.8 Adverse effects (undesirable effects)]. Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). ENHERTU should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section 4.2). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. ENHERTU should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section 4.2 Dose and method of administration). Patients with a history of ILD/pneumonitis or with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see section 4.2 Dose and method of administration).

In clinical studies, of the 1287 patients with unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 12.8% of patients as determined by independent review. Most ILD cases were Grade 1 (3.3%), Grade 2 (7.6%), or Grade 3 (0.9%). Fatal outcomes occurred in 6.1% of patients treated with ENHERTU. Median time to first onset was 5.8 months (range: 0.9 to 31.5).

Neutropenia

Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of ENHERTU. Complete blood counts should be monitored prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction (see Section 4.2 Dose and method of administration).

Of the 1287 patients with unresectable or metastatic breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 35.7% of patients and 17.5% had Grade 3 or 4 events. Median time to first onset of decreased neutrophil count was 50 days (range: 1 to 972). Febrile neutropenia was reported in 0.9% of patients.

Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. ENHERTU should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. ENHERTU should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see Section 4.2 Dose and method of administration).

In the 1287 patients with unresectable or metastatic breast cancer who received ENHERTU 5.4 mg/kg, 53 cases (4.1%) of LVEF decrease were reported. No decreases of LVEF to less than 20% were observed. Treatment with ENHERTU has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Embryo Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. 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 ENHERTU can also cause embryo-fetal harm when administered to a pregnant woman (see Section 4.6 Fertility, pregnancy and lactation).

The pregnancy status of females of reproductive potential should be verified prior to the initiation of ENHERTU. The patient should be informed of the potential risks to the fetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU (see Section 4.6 Fertility, pregnancy and lactation).

Use in the elderly

Please see Section 4.2 Dose and method of administration/ *Use in the elderly*

Paediatric use

Please see Section 4.2 Dose and method of administration/ *Paediatric use*

Effects on laboratory tests

Please see Section 4.8 Adverse effects (Undesirable effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of Other Medicinal Products on the Pharmacokinetics of ENHERTU

In vitro studies indicate that the released topoisomerase I inhibitor is a substrate of the following transporters: P-glycoprotein (P-gp), OATP1B1, OATP1B3, MATE2K, MRP1, and BCRP. Inhibitors of these transporters could increase plasma concentrations of the released topoisomerase I inhibitor.

Coadministration of ritonavir (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a dual inhibitor of OATP1B/CYP3A, increased exposure (AUC) of trastuzumab deruxtecan by 19% and the released topoisomerase I inhibitor by 22%.

Coadministration of itraconazole (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a strong CYP3A inhibitor, increased exposure (AUC) of trastuzumab deruxtecan by 11% and the released topoisomerase I inhibitor by 18%.

Coadministration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of trastuzumab deruxtecan or the released topoisomerase I inhibitor. No dose adjustment is required during coadministration of trastuzumab deruxtecan with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P-gp, MATE2-K, MRP1, or BCRP transporters.

Effects of ENHERTU on the Pharmacokinetics of Other Medicinal Products

In vitro studies indicate that the topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. *In vitro* studies indicate that the topoisomerase I inhibitor does not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters, but has an inhibitory effect on OAT1 and OATP1B1 with IC_{50} values of 12.7 and 14.4 µmol/L, respectively, which are significantly higher than steady-state C_{max} (0.01 µmol/L) of topoisomerase I inhibitor at 5.4 mg/kg dose administered every 3 weeks. No clinically meaningful drug-drug interaction is expected with drugs that are substrates of OAT1 or OATP1B1 transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of Childbearing Potential

Pregnancy status of women of childbearing potential should be verified prior to initiation of ENHERTU.

Effects on fertility

No dedicated fertility studies have been conducted with trastuzumab deruxtecan. Repeat-dose toxicity studies with trastuzumab deruxtecan (intravenous dosing once every 3 weeks) revealed adverse changes to the male reproductive organs in rats and monkeys. In rats, treatment resulted in decreased testes and epididymides weights and spermatid retention at ≥20 mg/kg (3.3× the clinical AUC at the maximum recommended clinical dose for trastuzumab deruxtecan and 0.14× for the topoisomerase inhibitor) and tubular degeneration in testes and aspermia at 197 mg/kg (22× the clinical AUC for trastuzumab deruxtecan and 1.3× for the topoisomerase inhibitor). In monkeys,

decreased spermatids in seminiferous tubules in the testes were noted at 30 mg/kg (6.5× the clinical AUC for trastuzumab deruxtecan 0.44× for the topoisomerase inhibitor). These changes in the testes of monkeys showed reversibility. Based on results from animal toxicity studies, ENHERTU may impair male reproductive function and fertility.

It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of ENHERTU.

Contraception in Males and Females

Women of childbearing potential should use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Men with female partners of childbearing potential should use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose.

Use in pregnancy – Category D

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.

There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and the topoisomerase I inhibitor component were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

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.

Use in lactation

It is not known if trastuzumab deruxtecan is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with ENHERTU. Women may begin breastfeeding 7 months after concluding treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENHERTU is not expected to affect patients' ability to drive or use machines. Due to potential adverse reactions such as fatigue, headache and dizziness [see Section 4.8 Adverse effects (undesirable effects)], patients should be advised to use caution when driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Breast Cancer

Summary of adverse drug reactions during clinical trials

The safety of ENHERTU 5.4 mg/kg was evaluated in a pooled analysis of 1287 patients with unresectable or metastatic breast cancer in Study DS8201-A-J101 (Breast Cancer cohort, n=71), DESTINY-Breast01 (n=184), DESTINY-Breast02 (n=404), DESTINY-Breast03 (n=257), and DESTINY-Breast04 (n=371). The median duration of treatment was 10 months (range 0.2 to 45.1).

The pooled study population characteristics were as follows: the median age was 55.5 years (range 22 to 96); 99.5% were female; 49.2% were White, 40.8% were Asian, 2.6% were Black or African American; and 56.6% had an Eastern Cooperative Oncology Group (ECOG) performance status 0 and 43.3% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

In the pooled studies, the most common adverse reactions (frequency ≥20%) were nausea (75.8%), fatigue (58.3%), vomiting (43.7%), alopecia (39.9%), neutropenia (35.7%), constipation (35.3%), anaemia (34.7%), decreased appetite (32%), diarrhoea (29.2%), transaminases increased (27.5%), musculoskeletal pain (27.2%), thrombocytopenia (24.7%), leukopenia (23.9%), and abdominal pain (20.6%). In the pooled studies, the most common serious adverse reactions (frequency >1%) were interstitial lung disease (3.7%), vomiting (1.5%), anaemia (1.1%), and nausea (1.1%). There were 14 (1.1%) patients with adverse reactions leading to death, 13 attributed to ILD (1.0%), and 1 attributed to febrile neutropenia (0.1%).

Dose interruptions due to adverse reactions occurred in 32.7% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14%), fatigue (5.1%), anaemia (4.8%), leukopenia (4.1%), thrombocytopenia (3.2%), upper respiratory tract infection (2.8%), and interstitial lung disease (2.5%). Dose reductions occurred in 20.9% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea (5.2%), fatigue (5.1%), neutropenia (3.6%), and thrombocytopenia (2.2%). Discontinuation of therapy due to an adverse reaction occurred in 12.4% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was interstitial lung disease (9.5%).

Tabulated List of Adverse Reactions

The adverse reactions in patients with unresectable or metastatic breast cancer who received at least one dose of ENHERTU 5.4 mg/kg are presented in Table 3. The adverse reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and

not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic Breast Cancer Treated with Trastuzumab Deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Metastatic Breast Cancer Pooled N=1287		
	Any Grade (%)		Grade 3-4 (%)
Blood and Lymphatic System Disorders			
Neutropenia[a]	Very Common	35.7	17.5
Anaemia[b]	Very Common	34.7	9.3
Thrombocytopenia[c]	Very Common	24.7	5.0
Leukopenia[d]	Very Common	23.9	6.8
Lymphopenia[e]	Very Common	11.3	5.1
Febrile Neutropenia	Uncommon	0.9	0.9
Eye Disorders			
Dry eye	Common	5.8	0.2
Vision Blurred[f]	Common	4.5	0
Gastrointestinal Disorders			
Nausea	Very Common	75.8	6.1
Vomiting	Very Common	43.7	2.7
Constipation	Very Common	35.3	0.4
Diarrhoea	Very Common	29.2	2.0
Abdominal pain[g]	Very Common	20.6	1.0
Stomatitis[h]	Very Common	15.2	0.8
Dyspepsia	Very Common	11.8	0
Abdominal distension	Common	4.0	0
Gastritis	Common	2.3	0.2
Flatulence	Common	1.9	0
General Disorders and Administration Site Conditions			
Fatigue[i]	Very Common	58.3	8.6
Pyrexia	Very Common	13.1	0.4
Hepatobiliary disorders			
Transaminases increased[j]	Very Common	27.5	3.8

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Metastatic Breast Cancer Pooled N=1287		
	Any Grade (%)		Grade 3-4 (%)
Infections and Infestations			
Upper respiratory tract infection[k]	Very Common	19.9	0.2
Injury, poisoning and procedural complications			
Infusion related reaction[l]	Common	1.3	0
Investigations			
Weight decreased	Very Common	16.6	0.6
Blood alkaline phosphatase increased	Common	9.0	0.4
Blood bilirubin increased[m]	Common	8.6	0.9
Blood creatinine increased	Common	3.0	0.2
Metabolism and Nutrition Disorders			
Hypokalaemia[n]	Very Common	11.5	3.3
Decreased appetite	Very Common	32.0	1.8
Dehydration	Common	3.0	0.5
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[o]	Very Common	27.2	0.9
Nervous System Disorders			
Headache[p]	Very Common	19.4	0.2
Dizziness	Very Common	10.3	0.3
Dysgeusia	Common	8.2	0
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial lung disease[q]	Very Common	12.8	0.9
Cough	Very Common	14.8	0.1
Epistaxis	Very Common	11.1	0
Dyspnea	Very Common	10.7	0.9
Skin and Subcutaneous Tissue Disorders			
Alopecia	Very Common	39.9	0.2
Rash[r]	Very Common	10.3	0.1
Pruritus	Common	5.4	0.1
Skin hyperpigmentation[s]	Common	5.0	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term

[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

[b] Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased.

[c] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.

[d] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.

[e] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.

[f] Grouped term of vision blurred includes PTs of vision blurred and visual impairment.

[g] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, abdominal pain upper.

[h] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.

[i] Grouped term of fatigue includes PTs of fatigue, asthenia, malaise and lethargy.

[j] Grouped term of transaminases increased includes PTs of transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test abnormal, liver function test increased, and hypertransaminasemia.

[k] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis, and laryngitis.

[l] Grouped term of infusion related reactions includes PTs of hypersensitivity (n=2), and infusion related reaction (n=15).

[m] Grouped term of blood bilirubin increased includes PTs of blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.

[n] Grouped term of hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.

[o] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.

[p] Grouped term of headache includes PTs of headache, migraine, and sinus headache.

[q] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, idiopathic interstitial pneumonia, lung disorder, pulmonary toxicity, acute respiratory failure, alveolitis, hypersensitivity pneumonitis, lung infiltration, lung opacity, lymphangitis, organizing pneumonia, pneumonia, pneumonia fungal, pulmonary fibrosis, radiation pneumonitis, respiratory failure, and pulmonary mass. Grade 5 adjudicated drug-related ILD events were respiratory failure, acute respiratory failure, pulmonary fibrosis, lymphangitis, ILD, and pneumonitis.

[r] Grouped term of rash includes PTs of rash, rash pustular, rash maculo-papular, rash papular, rash macular, and rash pruritic.

[s] Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder.

Adverse events in individual clinical trials

DESTINY-Breast03

The safety of ENHERTU was evaluated in DESTINY-Breast03 in 257 patients with unresectable or metastatic HER2-positive breast cancer (see Section 5.1 Pharmacodynamic properties/ *Clinical trials*). The median duration of treatment was 14.3 months (range: 0.7 to 29.8) in the ENHERTU group and 6.9 months (range: 0.7 to 25.1) in the trastuzumab emtansine group.

In DESTINY-Breast03 (N=257), the most common adverse reactions (frequency ≥20%) were nausea (75.9%), fatigue (49.4%), vomiting (49.0%), neutropenia (42.8%), alopecia (37.0%), constipation (34.2%), anaemia (32.7%), transaminases increased (31.5%), musculoskeletal pain (31.1%), leukopenia (30.4%), decreased appetite (29.2%), diarrhoea (29.2%), thrombocytopenia (25.7%), headache (21.8%), and abdominal pain (21.0 %). The most common serious adverse reactions (frequency >1%) were interstitial lung disease (2.3%) and vomiting (1.9%).

In DESTINY-Breast03, dose interruptions due to adverse reactions occurred in 34.2% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (16.7%), leukopenia (5.1%), thrombocytopenia (4.3%), fatigue (4.3%), anaemia (3.5%), nausea (3.1%), and interstitial lung disease (2.7%). Dose reductions occurred in 19.8% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea (6.2%), neutropenia (3.5%), and fatigue (3.1%). Discontinuation of therapy due to an adverse reaction occurred in 10.5% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (8.2%).

Table 4: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients in DESTINY-Breast03

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	7	30	0.4
Vomiting	49	1.6	10	0.8
Constipation	34	0	20	0
Diarrhoea	29	1.2	7	0.4
Abdominal pain[a]	21	0.8	8	0.4
Stomatitis[b]	20	0.8	5	0
Dyspepsia	11	0	6	0
General Disorders and Administration Site Conditions				
Fatigue[c]	49	6	35	0.8
Blood and Lymphatic System Disorders				
Anaemia[a]	33	7	17	6
Skin and Subcutaneous Tissue Disorders				
Alopecia[e]	37	0.4	3.1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	31	1.2	25	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.6	17	0.4
Investigations				
Weight decreased	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	11	0	16	0.4
Cough	11	0.4	10	0
Interstitial lung disease[g]	11	0.8[h]	1.9	0
Nervous System Disorders				
Headache[i]	22	0.4	16	0

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Dizziness	13	0.4	8	0

Events were graded using NCI CTCAE version 5.0. N = number of patients exposed; PT = preferred term.
Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

[a] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.

[b] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.

[c] Grouped term of fatigue includes PTs of fatigue, asthenia, malaise, and lethargy.

[d] Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, and red blood cell count decreased.

[e] This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.

[f] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.

[g] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.

[h] No Grade 4 or Grade 5 ILD events were adjudicated as drug-related in either arm.

[i] Grouped term of headache includes PTs of headache, migraine.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- Respiratory, Thoracic and Mediastinal Disorders: dyspnoea (8%)
- Skin and Subcutaneous Tissue Disorders: pruritus (8%) and skin hyperpigmentation (6%) [grouped term includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder].
- Nervous System Disorders: dysgeusia (6%)
- Metabolism and Nutrition Disorders: dehydration (4.3%)
- Eye Disorders: vision blurred (3.5%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.3%) [grouped term includes PTs of hypersensitivity, infusion-related reactions]
- Blood and Lymphatic System Disorders: febrile neutropenia (0.8%)

Table 5: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Haematology				
White blood cell count decreased	74	8	24	0.8
Neutrophil count decreased	70	18	30	2.3
Haemoglobin decreased	64	7	38	6
Lymphocyte count decreased	55	14	23	3.9
Platelet count decreased	52	7	79	24

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Aspartate aminotransferase increased	67	0.8	83	5
Alanine aminotransferase increased	53	1.6	67	6
Blood alkaline phosphatase increased	49	0.8	46	0.8
Hypokalaemia	35	4.7	39	1.5
Blood bilirubin increased	20	0	14	0
Blood creatinine increased	16	0.8	8	0.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast02

The safety of ENHERTU was evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02 *(*see Section 5.1 Pharmacodynamic properties/ *Clinical trials*). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 11 months (range: 0.7 to 45) for patients who received ENHERTU.

Serious adverse reactions occurred in 26% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were COVID-19, ILD, pneumonia, vomiting, fatigue, and nausea. Fatalities due to adverse reactions occurred in 2.5% of patients including pneumonitis (2 patients), acute myeloid leukaemia, brain oedema, COVID-19, haemorrhage, hepatitis B, malignant pleural effusion, pneumonia, and vasogenic cerebral oedema (one patient each).

ENHERTU was permanently discontinued in 20% of patients, of which ILD accounted for 9%. Dose interruptions due to adverse reactions occurred in 45% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, COVID-19, anaemia, fatigue, leukopenia, upper respiratory tract infection, and thrombocytopenia. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, neutropenia, and vomiting.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased haemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased alanine aminotransferase, vomiting, increased aspartate aminotransferase, alopecia, increased blood alkaline phosphatase, constipation, decreased appetite, hypokalaemia, diarrhoea, musculoskeletal pain, increased blood bilirubin, abdominal pain, and headache.

Table 6 and Table 7 summarise common adverse reactions and laboratory abnormalities observed in DESTINY-Breast02.

Table 6: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast02

Adverse Reactions	ENHERTU 5.4 mg/kg N=404		Treatment of Physician's Choice (trastuzumab plus capecitabine or lapatinib plus capecitabine) N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	73	7	37	2.6
Vomiting	38	3.7	13	1
Constipation	35	0.3	11	0.5
Diarrhea	27	2.7	54	7
Abdominal pain[a]	22	1	20	2.1
Dyspepsia	12	0	9	0
Stomatitis[b]	12	1	21	1
General Disorders and Administration Site Conditions				
Fatigue[c]	62	9	37	1
Skin and Subcutaneous Tissue Disorders				
Alopecia	37	0.3	4.1	0
Metabolism and Nutrition Disorders				
Decreased appetite	31	1.7	18	0.5
Blood and Lymphatic System Disorders				
Anemia[d]	29	8	14	3.1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[e]	25	0.7	18	0.5
Nervous System Disorders				
Headache[f]	20	0.3	6	0
Investigations				
Decreased weight	18	0.3	3.6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	10	0
Interstitial lung disease[g]	10	0.7	0.5	0.5

Events were graded using NCI CTCAE version 5.0.

[a] Including abdominal discomfort, abdominal pain, upper abdominal pain, lower abdominal pain, and gastrointestinal pain

[b] Including aphthous ulcer, mouth ulceration, and stomatitis

[c] Including asthenia, fatigue, lethargy, and malaise

[d] Including anemia, decreased hemoglobin, and decreased red blood cell count

[e] Including back pain, bone pain, limb discomfort, musculoskeletal chest pain, musculoskeletal pain, muscle spasms, myalgia, neck pain, and pain in extremity

[f] Including headache and migraine

[g] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, idiopathic interstitial pneumonia, lung disorder, pulmonary toxicity, and pneumonia.

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:

- Respiratory, Thoracic and Mediastinal Disorders: dyspnea (8%) and epistaxis (8%)
- Skin and Subcutaneous Tissue Disorders: rash (8%) [including rash, pustular rash, maculo-papular rash, and pruritic rash], pruritis (5%), skin hyperpigmentation (5%) [including skin hyperpigmentation and pigmentation disorder]
- Nervous System Disorders: dizziness (8%) and dysgeusia (8%)
- Cardiac Disorders: asymptomatic left ventricular ejection fraction decrease (4.2%) [see Warnings and Precautions (5.3)]
- Eye Disorders: dry eye (6%) and blurred vision [including blurred vision and visual impairment] (3%)
- Metabolism and Nutrition Disorders: dehydration (2.7%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (1.2%)
- Blood and Lymphatic System Disorders: febrile neutropenia (0.3%)

Table 7: Selected Laboratory Abnormalities in Patients in DESTINY-Breast02

Laboratory Parameter	**ENHERTU 5.4 mg/kg N=404**		**Treatment of Physician's Choice** (trastuzumab plus capecitabine or lapatinib plus capecitabine) **N=195**	
	All Grades %	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Hematology				
Decreased white blood cell count	70	12	42	3.2
Decreased haemoglobin	67	9	54	3.2
Decreased neutrophil count	64	16	34	4.7
Decreased lymphocyte count	58	17	38	4.7
Decreased platelet count	48	2.7	31	1.6
Chemistry				
Increased alanine aminotransferase	43	1	32	1.6
Increased aspartate aminotransferase	37	0.7	29	2.1
Increased blood alkaline phosphatase	37	0	17	0
Hypokalemia	30	3.7	29	8
Increased blood bilirubin	23	0.3	44	2.1
Increased blood creatinine	7	0.3	13	0

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast01 and Study DS8201-A-J101

The safety of ENHERTU has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2 positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY Breast01 and Study DS8201-A-J101. Table 8 lists adverse drug reactions, with incidences regardless of investigators assessment of causality, reported in this patient population. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 9.8 months (range: 0.7 to 37.1).

In ENHERTU treated patients (n=234), the median age was 56 years (range 28 to 96); 99.6% were female; 50.9% were White, 41.5% were Asian, 3.0% were Black or African American; and 57.7% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 41.9% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting alopecia, constipation, decreased appetite, anaemia, neutropenia, diarrhoea, thrombocytopaenia, cough, leukopenia, and headache (see Table 8). The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03) Grade ≥3 adverse reactions (frequency >1%) were neutropenia, anaemia, nausea, fatigue, leukopenia, lymphopenia, vomiting, thrombocytopaenia, hypokalaemia, ILD, diarrhoea, febrile neutropenia, dyspnoea, abdominal pain, decreased appetite, and alanine aminotransferase increased (see Table 8). In six patients (2.6%) ILD led to death.

Dose interruptions due to adverse reactions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14.5%), anaemia (3.4%), upper respiratory tract infection (3.0%), leukopenia (3.0%), ILD (2.6%), thrombocytopaenia (2.6%), and fatigue (2.1%). Dose reductions occurred in 15% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (3.8%), nausea (3.4%), and neutropenia (3.4%). Discontinuation of therapy due to an adverse reaction occurred in 11% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (9.4%).

Table 8: Adverse Drug Reactions Reported in DESTINY-Breast01 and DS8201-A-J101 Trials (occurred in ≥ 10% of subjects for All Grades or ≥ 2% for Grades 3 or 4)

System Organ Class[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Gastrointestinal Disorders		
Nausea	187 (79.9)	16 (6.8)
Vomiting	114 (48.7)	10 (4.3)
Constipation	84 (35.9)	2 (0.9)
Diarrhoea	72 (30.8)	6 (2.6)

System Organ Class[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Abdominal Pain[b]	46 (19.7)	3 (1.3)
Stomatitis[c]	35 (15.0)	2 (0.9)
Dyspepsia	33 (14.1)	0
General Disorders and Administration Site Conditions		
Fatigue[d]	141 (60.3)	15 (6.4)
Skin and Subcutaneous Tissue Disorders		
Alopecia	108 (46.2)	1 (0.4)
Rash[e]	30 (12.8)	1 (0.4)
Metabolism and Nutrition Disorders		
Decreased appetite	81 (34.6)	3 (1.3)
Hypokalaemia	30 (12.8)	8 (3.4)
Blood and Lymphatic System Disorders		
Anaemia[f]	79 (33.8)	21 (9.0)
Neutropenia[g]	76 (32.5)	44 (18.8)
Thrombocytopaenia[h]	54 (23.1)	10 (4.3)
Leukopenia[i]	48 (20.5)	13 (5.6)
Lymphopenia[j]	26 (11.1)	12 (5.1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	50 (21.4)	0
Dyspnoea	34 (14.5)	4 (1.7)
Epistaxis	33 (14.1)	0
Interstitial lung disease[k]	32 (13.7)	1 (0.4)
Nervous System Disorders		
Headache[l]	47 (20.1)	0
Dizziness	25 (10.7)	0
Infections and infestations		
Upper respiratory tract infection[m]	43 (18.4)	15 (6.4)

System Organ Class[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Investigations		
Aspartate aminotransferase increased	35 (15.0)	2 (0.9)
Alanine aminotransferase increased	25 (10.7)	3 (1.3)
Eye disorders		
Dry eye	27 (11.5)	1 (0.4)

N=number of patients exposed; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

[a] Based on MedDRA version 20.1

[b] Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

[c] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

[d] Grouped term of fatigue includes PTs of fatigue and asthenia.

[e] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

[f] Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased.

[g] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

[h] Grouped term of thrombocytopaenia includes PTs of thrombocytopaenia and platelet count decreased.

[i] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.

[j] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.

[k] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

[l] Grouped term of headache includes PTs of headache, sinus headache, and migraine.

[m] . Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

Table 9: Selected Laboratory Abnormalities in Patients in DESTINY-Breast01 and DS8201-A-J101 Trials

Laboratory Abnormalities[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Haematology		
White blood cell count decreased	168 (72.4)	20 (8.6)
Anaemia	166 (71.6)	19 (8.2)
Neutrophil count decreased	150 (64.9)	41 (17.7)

Laboratory Abnormalities[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Platelet count decreased	99 (42.9)	9 (3.9)
Chemistry		
Aspartate aminotransferase increased	103 (44.4)	2 (0.9)
Alanine aminotransferase increased	95 (40.9)	1 (0.4)
Hypokalaemia	64 (27.8)	9 (3.9)

[a] Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 based on laboratory measurements.

DESTINY-Breast04

The safety of ENHERTU was evaluated in DESTINY-Breast04 in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer (see Section 5.1 Pharmacodynamic properties/ *Clinical trials*). The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

In patients treated with ENHERTU in DESTINY-Breast04 (N=371), the most common adverse reactions (frequency ≥20%) were nausea (76.0%), fatigue (53.6%), vomiting (40.4%), alopecia (39.6%), anaemia (38.5%), constipation (34.0%), neutropenia (34.0%), transaminases increased (32.3%), decreased appetite (31.8%), diarrhoea (27.0%), musculoskeletal pain (26.7%), thrombocytopenia (25.6%), and leukopenia (24.0%). Please see Table 5. The most common serious adverse reactions (frequency >1%) were ILD/pneumonitis (4.3%), dyspnoea (1.3%), musculoskeletal pain (1.3%), anaemia (1.1%), febrile neutropenia (1.1%), nausea (1.1%), pyrexia (1.1%), and vomiting (1.1%). There were 5 (1.3%) patients with adverse reactions leading to death, 3 attributed to ILD (0.8%) and 1 (0.3%) each for dyspnoea and febrile neutropenia.

Dose interruptions due to adverse reactions occurred in 25.9% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (9.2%), fatigue (5.1%), anaemia (4.6%), leukopenia (3.5%), ILD/pneumonitis (3.0%), transaminases increased (3.0%), and blood bilirubin increased (2.2%). Dose reductions occurred in 19.9% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (4.6%), nausea (4.6%), thrombocytopenia (3.5%), and neutropenia (3.0%). Discontinuation of therapy due to an adverse reaction occurred in 11.1% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (8.4%).

Table 10: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhoea	27	1.3	22	1.7
Abdominal pain[a]	18	0.5	13	0
Stomatitis[b]	13	0.3	11	0.6
General Disorders and Administration Site Conditions				
Fatigue[c]	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0
Rash[d]	11	0	9	0.6
Blood and Lymphatic System Disorders				
Anaemia[e]	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	27	1.3	26	0
Investigations				
Decreased weight	16	0.3	8	0
Nervous System Disorders				
Headache[g]	15	0.3	6	0
Infections and Infestations				
Upper respiratory tract infection[h]	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Interstitial lung disease[i]	12	1.3	0.6	0
Epistaxis	11	0	1.2	0
Dyspnoea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0. N = number of patients exposed; PT = preferred term.

[a] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain.

[b] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, and mouth ulceration.

[c] Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.

[d] Grouped term of rash includes PTs of rash, pustular rash, maculo-papular rash, papular rash, macular rash, and pruritic rash.

[e] Grouped term of anaemia includes PTs of anaemia, decreased haemoglobin, and decreased red blood cell count.

[f] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, and musculoskeletal chest pain.

[g] Grouped term of headache includes PTs of headache, and migraine.

[h] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.

[i] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU:

- *Nervous System Disorders:* dysgeusia (10%)
- *Respiratory, Thoracic and Mediastinal Disorders:* cough (10%)
- *Gastrointestinal Disorders: abdominal distension* (5%), gastritis (2.7%), flatulence (2.4%)
- *Eye Disorders:* blurred vision (4.9%) [Grouped term includes PTs of blurred vision and visual impairment.]
- *Skin and Subcutaneous Tissue Disorders:* pruritus (3.2%) and skin hyperpigmentation (2.7%) [Grouped term includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder.]
- *Metabolism and Nutrition Disorders:* dehydration (1.9%)
- *Blood and Lymphatic System Disorders:* febrile neutropenia (1.1%)
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (0.5%) [Grouped term includes PTs of injection site reaction and chills.]

Table 11: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Haematology				
Decreased white blood cell count	70	9	78	25
Decreased haemoglobin	64	8	53	6

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Hypokalaemia	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 2.1% (47/2213) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with ENHERTU. The incidence of treatment-emergent neutralizing antibodies against trastuzumab deruxtecan was 0.1% (2/2213). There was no association between development of antibodies and allergic-type reactions.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose with trastuzumab deruxtecan. In the event of overdose, patients should be monitored, and appropriate supportive care should be given.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor bound by a

tetrapeptide-based cleavable linker. The ADC is stable in plasma under in vitro conditions. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death. The topoisomerase I inhibitor, an exatecan derivative, is approximately 10 times more potent than SN38, the active metabolite of irinotecan.

Pharmacodynamic Effects

The administration of multiple doses of trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) did not show any clinically meaningful effect on the QTc interval in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical trials

Metastatic Breast Cancer

DESTINY-Breast03

The efficacy and safety of ENHERTU were demonstrated in a Phase 3, randomised, multicentre, open-label, active-controlled study: DESTINY-Breast03.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with symptomatic brain metastases, patients with a history of clinically significant cardiac disease, and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomised 1:1 to receive either ENHERTU 5.4 mg/kg (N=261) or trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every three weeks. Randomisation was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure. Confirmed objective response rate (ORR) was a secondary endpoint.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 524 patients randomised, the median age was 54 years (range 20 to 83); female (99.6%); Asian (59.9%), White (27.3%), Black or African American (3.6%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); presence of brain metastases at baseline (15.6 %), and 48.3% of patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 9.5%.

At the prespecified interim analysis for PFS (data cut-off 21 May 2021) based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomised to ENHERTU compared to trastuzumab emtansine. The median PFS per BICR was not reached in the ENHERTU arm and was 6.8 months in the trastuzumab emtansine comparator arm (HR=0.28; 95% CI: 0.22, 0.37). Overall survival (OS) was immature at the time of analysis and median OS was not reached. The median duration of

follow-up was 16.2 months (range: 0.0 to 32.7) in the ENHERTU arm and 15.3 months (range: 0.0 to 31.3) in the trastuzumab emtansine arm.

At the overall survival analysis (data cutoff 25 July 2022) the study also demonstrated statistically significant improvement in OS and median OS was not reached. An updated PFS per BICR was provided at the time of this OS analysis. The median duration of follow-up was 28.4 months (range: 0.0 to 46.9) in the ENHERTU arm and 26.5 months (range: 0.0 to 45.0) in the trastuzumab emtansine arm.

Efficacy results are summarised in Table 12 and Figure 1 and Figure 2.

Table 12: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	**ENHERTU 5.4 mg/kg N=261**	**trastuzumab emtansine 3.6 mg/kg N=263**
PFS per BICR (updated)[a]		
Number of events (%)	117 (44.8)	171 (65.0)
Median, months (95% CI)	28.8 (22.4, 37.9)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.33 (0.26, 0.43)	
Overall Survival (OS)[a]		
Number of events (%)	72 (27.6)	97 (36.9)
Hazard ratio (95% CI)	0.64 (0.47, 0.87)	
p-value[b]	p=0.0037	
Confirmed Objective Response Rate (ORR) per BICR[a]		
n (%)	205 (78.5)	92 (35.0)
95% CI	(73.1, 83.4)	(29.2, 41.1)
Complete Response n (%)	55 (21.1)	25 (9.5)
Partial Response n (%)	150 (57.5)	67 (25.5)

CI = confidence interval; NR= not reached, NE=not estimable

[a] Data cutoff 25 July 2022 for a pre-planned OS interim analysis

[b] The p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.013

Figure 1: Kaplan-Meier Plot of Progression-free Survival per BICR Data cutoff 25 July 2022

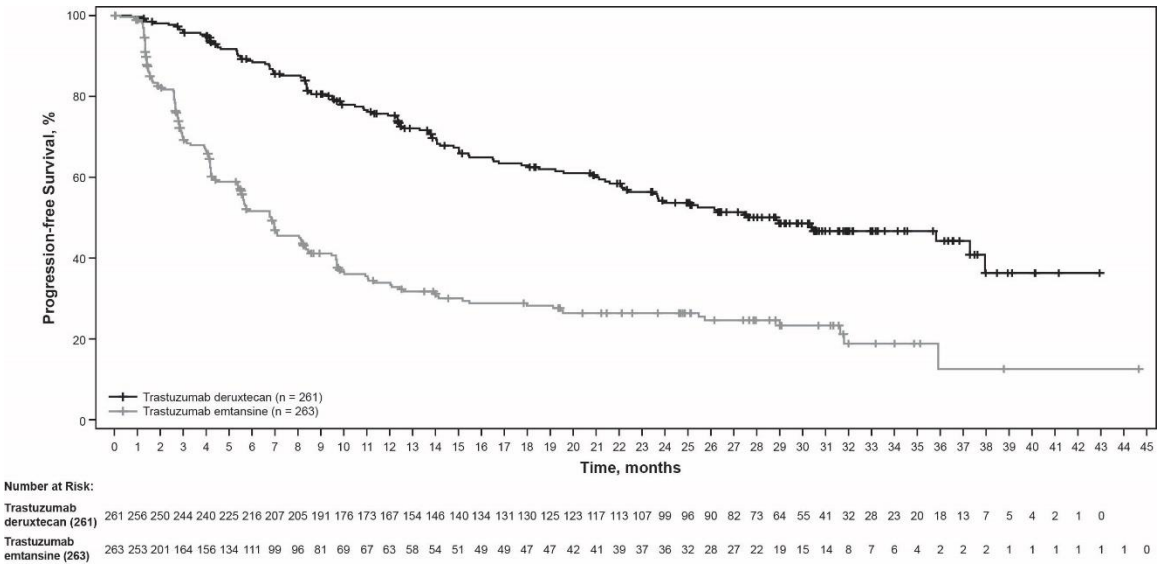
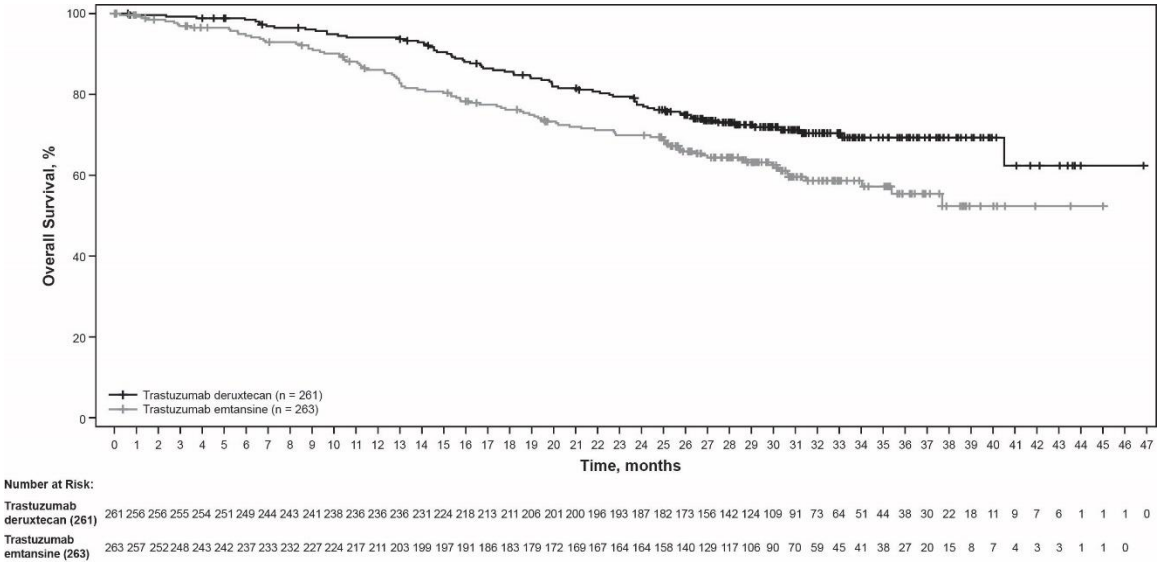


Figure 2: Kaplan-Meier Plot of Overall Survival Data cutoff 25 July 2022



Similar PFS results were observed across prespecified subgroups including prior pertuzumab therapy, hormone receptor status, presence of brain metastases, and presence of visceral disease.

DESTINY-Breast02

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast02, a Phase 3, randomised, multicentre, open-label, active-controlled study that enrolled patients with unresectable or metastatic HER2-positive breast cancer.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who were resistant or refractory to prior trastuzumab emtansine and had documented radiologic progression during or after their most recent treatment or within 6 months after completing adjuvant therapy. Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring

treatment with steroids or ILD/pneumonitis at screening, patients with untreated and symptomatic brain metastases and patients with a history of clinically significant cardiac disease. Patients were randomised 2:1 to receive either ENHERTU 5.4 mg/kg (N=406) by intravenous infusion every three weeks or treatment of physician's choice (N=202, trastuzumab plus capecitabine or lapatinib plus capecitabine). Randomisation was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure. Confirmed objective response rate (ORR) was a secondary objective.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 608 patients randomised, the median age was 54 years (range 22 to 88); female (99.2%); White (63.2%), Asian (29.3%), Black or African American (2.8%); ECOG performance status 0 (57.4%) or 1 (42.4%); hormone receptor status (positive: 58.6%); presence of visceral disease (78.3%); presence of brain metastases at baseline (18.1%), and 4.9% of patients received one line of prior systemic therapy in the metastatic setting.

The study demonstrated a statistically significant improvement in PFS per BICR and OS in patients randomised to ENHERTU compared to treatment of physician's choice. The median duration of follow-up was 21.5 months (range: 0.1 to 45.6) in the ENHERTU arm and 18.6 months (range: 0.0 to 45.7) in the TPC arm.

Efficacy results are summarized in Table 13 and Figure 3 and Figure 4.

Table 13: Efficacy Results in DESTINY-Breast02

Efficacy Parameter	ENHERTU N=406	Treatment of Physician's Choice N=202
PFS per BICR		
Number of events (%)	200 (49.3)	125 (61.9)
Median, months (95% CI)	17.8 (14.3, 20.8)	6.9 (5.5, 8.4)
Hazard ratio (95% CI)	0.36 (0.28, 0.45)	
p-value	p<0.000001[†]	
Overall Survival (OS)		
Number of events (%)	143 (35.2)	86 (42.6)
Median, months (95% CI)	39.2 (32.7, NE)	26.5 (21.0, NE)
Hazard ratio (95% CI)	0.66 (0.50, 0.86)	
p-value[a]	p=0.0021	
Confirmed Objective Response Rate (ORR) per BICR		
n (%)	283 (69.7)	59 (29.2)
95% CI	(65.0, 74.1)	(23.0, 36.0)
Complete Response n (%)	57 (14.0)	10 (5.0)
Partial Response n (%)	226 (55.7)	49 (24.3)

CI = confidence interval; NE=not estimable
†presented as 6 decimal places
[a] The p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.004

Figure 3: Kaplan-Meier Plot of Progression-free Survival Per BICR

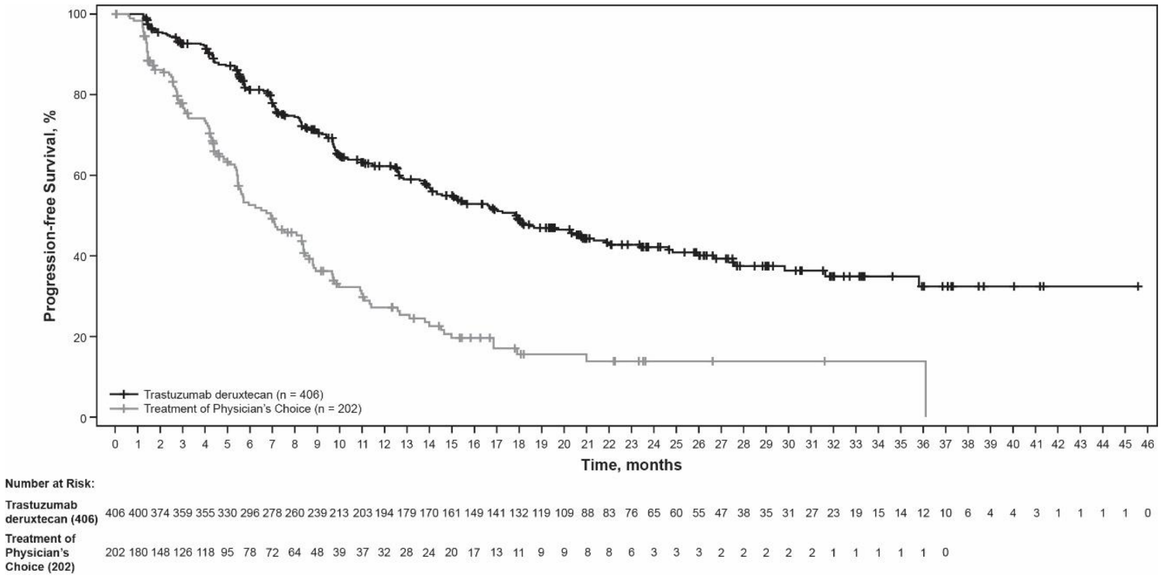
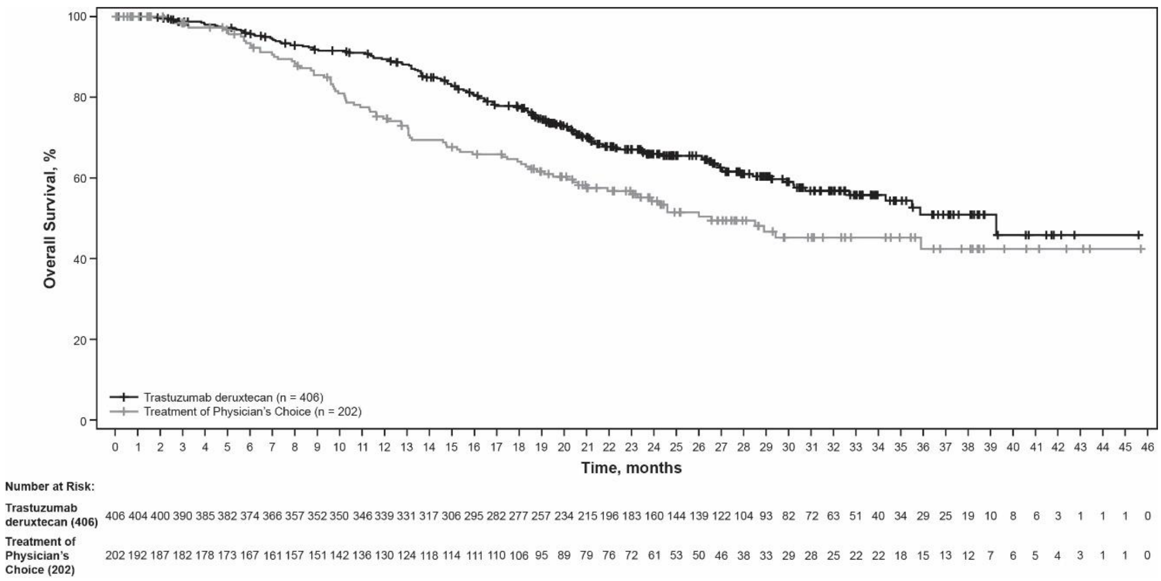


Figure 4: Kaplan-Meier Plot of Overall Survival



Similar PFS results were observed across prespecified subgroups including prior pertuzumab therapy, hormone receptor status, presence of visceral disease, and presence of brain metastases.

DESTINY-Breast01

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, single-agent, open-label, multicentre study: DESTINY-Breast01.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a

history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease. ENHERTU was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Duration of response (DOR) and progression-free survival (PFS) were additional outcome measures.

DESTINY-Breast01 (N = 184) baseline demographic and disease characteristics were: median age 55 years (range 28 to 96); female (100%); White (54.9%), Asian (38.0%), Black or African American (2.2%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease (91.8%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); prior pertuzumab therapy (65.8%); sum of diameters of target lesions (<5 cm: 42.4%, ≥ 5 cm: 50.0%).

Efficacy results based on a data cut-off of 26 Mar 2021 with a median duration of follow-up of 26.5 months and median duration of treatment of 10.1 months are summarised in Table 14.

Table 14: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 N=184
Confirmed objective response rate (ORR) (95% CI)[#§]	62% (54.5, 69.0)
Complete response (CR)	7.1%
Partial response (PR)	54.9%
Duration of Response (DoR)*	
Median, months (95% CI)	18.2 (15.0, NR)
% with duration of response ≥6 months (95% CI)[†]	81.8% (72.5, 88.1)

ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
[#]Confirmed responses (by blinded independent central review) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed.
[§]Of the 184 patients, 35.3% had stable disease, 1.6% had progressive disease and 1.1% were not evaluable.
*Includes 69 patients with censored data
†Based on Kaplan-Meier estimates
Efficacy data based on DCO 21 March 2021, median duration of follow-up of 26.5 months

Consistent antitumor activity was observed with ENHERTU regardless of prior pertuzumab therapy and hormone receptor status. In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 66% (95% CI: 57, 75), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 57% (95% CI: 43, 69). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 60% (95% CI: 49, 70), and those who were hormone receptor negative at baseline had a confirmed ORR of 68% (95% CI: 56, 77).

DESTINY-Breast04

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast04, a Phase 3, randomised, multicentre, open label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor positive (HR+) patients and 63 hormone receptor negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-negative, as determined by the PATHWAY/VENTANA anti-HER-2/neu (4B5) evaluated at a central laboratory. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. 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%). Randomisation was stratified by HER2 IHC status of tumour samples (IHC 1+ or IHC 2+/ISH-negative), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for untreated or symptomatic brain metastases or ECOG performance status >1.

The primary efficacy outcome measure was PFS in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Key secondary efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomised HR+ and HR- patients), OS in HR+ patients, and OS in the overall population. ORR, DOR, and PROs were secondary endpoints.

Demographics and baseline tumour characteristics were similar between treatment arms. Of the 557 patients randomised, the median age was 56.5 years (range: 28.4 to 80.5); 23.5% were age 65 or older; 99.6% were female and 0.4% were male; 47.9% were White, 40.0% were Asian, and 1.8% were Black or African American. Patients had an ECOG performance status of 0 (54.8%) or 1 (45.2%) at baseline; 57.6% were IHC 1+, 42.4% were IHC 2+/ISH-negative; 69.8% had liver metastases, 32.9% had lung metastases, and 5.7% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients randomised to ENHERTU compared to chemotherapy in both the HR+ cohort and the overall population.

Efficacy results are summarised in Table 15 and Figure 5 and Figure 6.

Table 15: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR*				
n (%)	175 (52.6)	27 (16.3)	195 (52.3)	30 (16.3)
95% CI	47.0, 58.0	11.0, 22.8	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)
Duration of Response per BICR*				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5, 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

* Based on data from electronic case report form for the HR+ cohort: N=333 for ENHERTU arm and N=166 for chemotherapy arm.

Consistent OS and PFS benefit was observed across prespecified subgroups, including HR status, prior CDK4/6i treatment, number of prior chemotherapies, and IHC 1+ and IHC 2+/ISH-negative status. In the HR- subgroup, median OS was 18.2 months (95% CI: 13.6, not estimable) in patients

randomised to ENHERTU compared to 8.3 months (95% CI: 5.6, 20.6) in patients randomised to chemotherapy with a hazard ratio of 0.48 (95% CI: 0.24, 0.95). Median PFS was 8.5 months (95% CI: 4.3, 11.7) in patients randomised to ENHERTU and 2.9 months (95% CI: 1.4, 5.1) in patients randomised to chemotherapy with a hazard ratio of 0.46 (95% CI: 0.24, 0.89).

Figure 5: Kaplan-Meier Plot of Overall Survival (Overall Population)

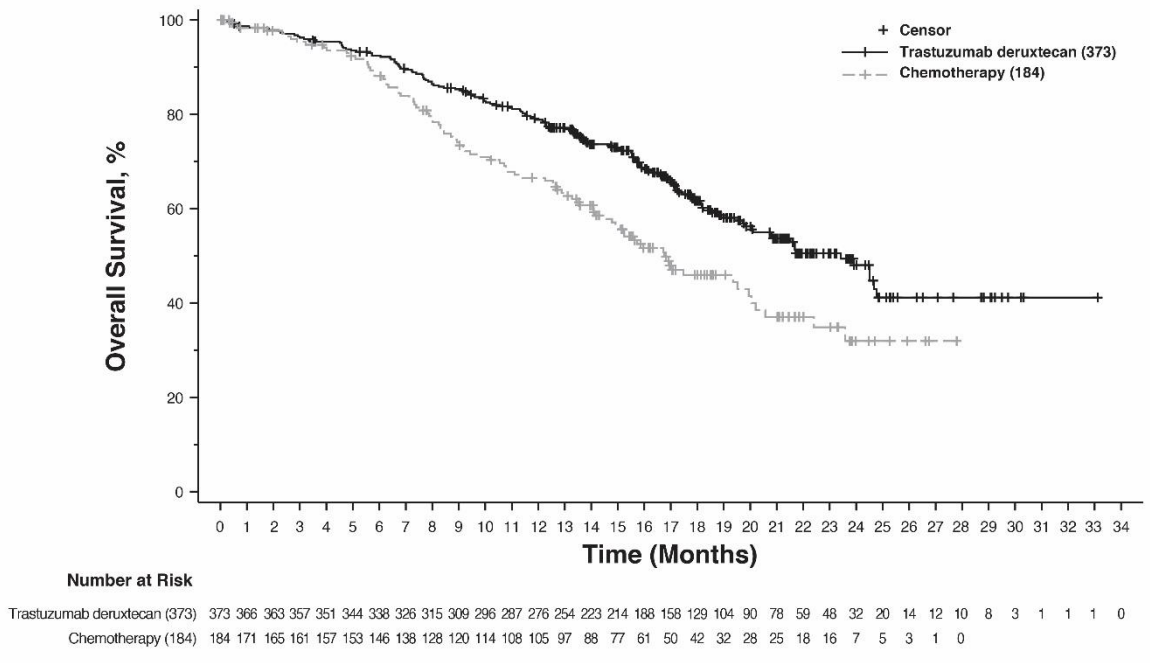
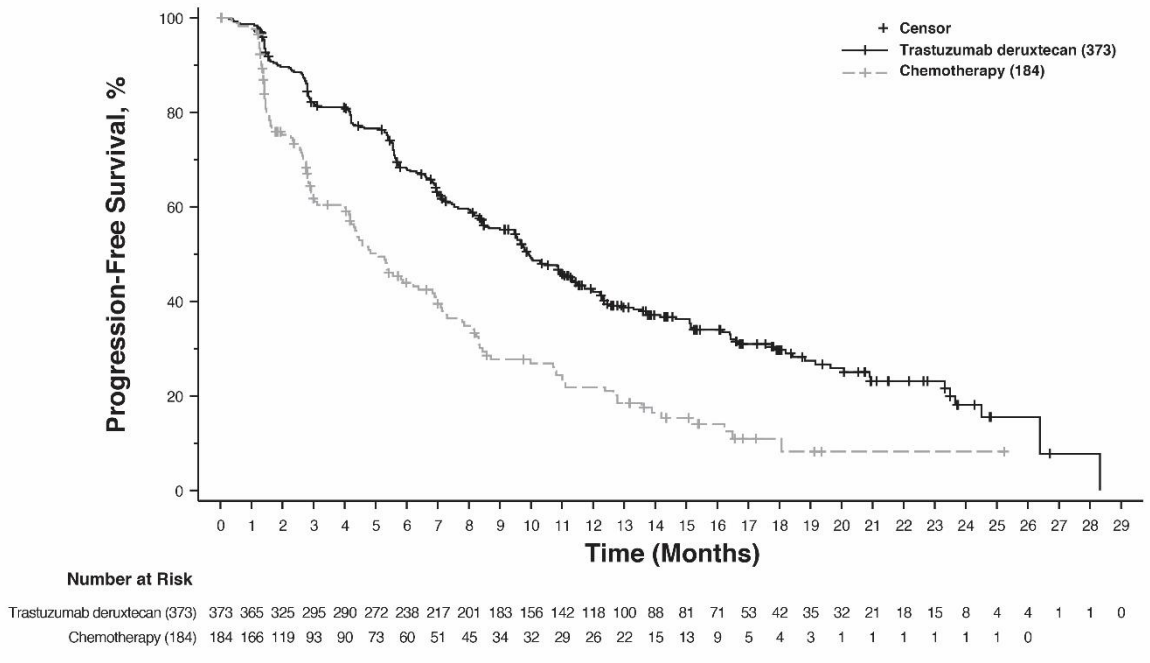


Figure 6: Kaplan-Meier Plot of Progression-free Survival per BICR (Overall Population)



For HR+ patients receiving ENHERTU, health-related quality-of-life was maintained throughout treatment, with the EORTC-QLQ-C30 Global Health status/QoL (primary PRO scale of interest) mean score remaining stable over time up to and including cycle 33.

In addition, the time to definitive deterioration (TTDD) in HR+ patients was longer in the ENHERTU arm compared to the chemotherapy arm for all prespecified scales of the EORTC-QLQ-C30 (global health status, pain symptoms, physical functioning, emotional functioning, and social functioning), suggesting that ENHERTU maintains quality of life longer than chemotherapy in patients with unresectable or metastatic HER2-low breast cancer. Of note, in the QLQ-C30 global health status scale, the median TTDD by at least 10 points in global health status/global QoL scale score was 7.6 months (95% CI: 5.8, 9.2) in the ENHERTU arm versus 5.1 months (95% CI: 3.1, 6.9) in the chemotherapy arm (stratified hazard ratio: 0.71 [95% CI: 0.56, 0.92]). In the QLQ C30 pain symptom subscale, the median TTDD by at least 10 points in pain symptoms was 9.7 months (95% CI: 8.5, 11.1) in the ENHERTU arm versus 4.4 months (95% CI: 2.8, 6.2) in the chemotherapy arm (stratified hazard ratio: 0.51 [95% CI: 0.39, 0.65]). These results are consistent with the primary result and confirm the QoL benefit of ENHERTU versus chemotherapy for patients with metastatic HER2-low breast cancer.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. At the recommended dosage of ENHERTU, 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.

Distribution

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 I inhibitor was approximately 0.6.

Metabolism

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the active topoisomerase I 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 I inhibitor is metabolized mainly by CYP3A4 via oxidative pathways.

Excretion

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan, the clearance of trastuzumab deruxtecan was estimated to be 0.4 L/day and the clearance of the topoisomerase I inhibitor was 18.4 L/h. The apparent elimination half-life (t1/2) 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.

Linearity/Nonlinearity

The exposure of trastuzumab deruxtecan and released topoisomerase I inhibitor when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate interindividual variability.

Specific populations

Age, race, ethnicity, sex and body weight

Based on population pharmacokinetic analysis, age (20-96 years), race, ethnicity, sex and body weight did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released topoisomerase I inhibitor.

Renal impairment

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).

Hepatic impairment

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The topoisomerase I inhibitor component of trastuzumab deruxtecan was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

6.3 SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted Solution

It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light.

Diluted Solution

It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature for up to 4 hours or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. These storage times start from the time of dilution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials in a refrigerator (2ºC to 8ºC) until time of reconstitution.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF 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.

Each carton contains 1 glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanised anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology and the topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

General structure

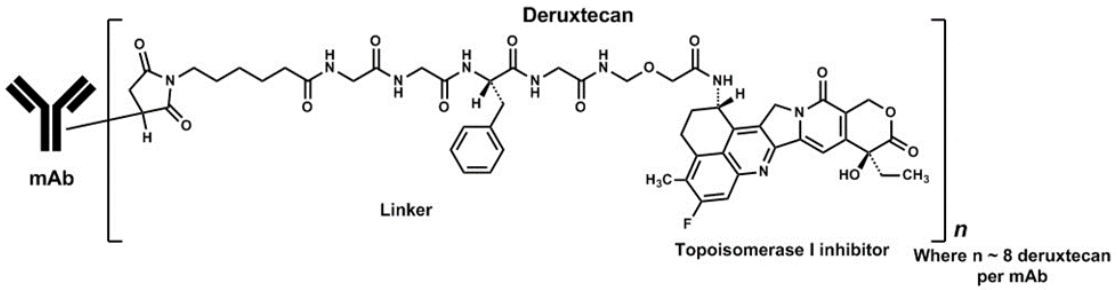


Figure 7 General structure of trastuzumab deruxtecan

CAS number

1826843-81-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

08 October 2021

10 DATE OF REVISION

24 May 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Updates to Interstitial Lung Disease/Pneumonitis, Neutropenia and LVEF Decrease sub-sections to include DESTINY-Breast02
4.8	New metastatic breast cancer pool Addition of DESTINY-Breast02 data Updates to immunogenicity text
5.1	Updates to efficacy data in DESTINY-Breast03 Addition of DESTINY-Breast02 data
5.2	Updates to excretion text
6.3	Editorial Updates

VV-RIM-01450090 v7.0