▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indication. 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 lyophilised 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 lyophilised powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Early breast cancer

Post-neoadjuvant treatment

ENHERTU is indicated for the treatment of adult patients with HER2-positive breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment.

Advanced 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 as monotherapy 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.

HER2-low and HER2-ultralow

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

Gastric cancer

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen.

Non-small cell lung cancer (NSCLC)

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic NSCLC whose tumours have activating HER2 (ERBB2) mutations and who have received prior platinum-based chemotherapy with or without immunotherapy. This indication was approved via the **provisional approval** pathway based on objective response rate. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.

Other unresectable or metastatic solid tumours

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior systemic treatment and who have no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway based on objective response rate. Full registration of this indication depends on submission of further clinical data to confirm the clinical benefit of the medicine.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do not substitute ENHERTU (trastuzumab deruxtecan) for, or with, trastuzumab or trastuzumab emtansine**. Check the vial label** prior to administration.

Patient selection

Patient selection for HER2-low or HER2-ultralow advanced breast cancer

Prior to the use of ENHERTU to treat HER2-low or HER2-ultralow unresectable or metastatic breast cancer, the HER2 status of the tumour must be established. Testing used in clinical practice should be comparable to the testing used in the relevant pivotal study (see Section 5.1 Pharmacodynamic properties / *Clinical trials*). In ENHERTU pivotal studies, HER2-low was defined as IHC 1+ or IHC 2+/ISH-negative, and HER2-ultralow was defined as IHC 0 with membrane staining (IHC >0<1+) tumour status. A list of IVD companion diagnostic (CDx) tests that have been assessed is available on the TGA website.

Patient selection for unresectable or metastatic NSCLC with activating HER2 (ERBB2) mutations

Prior to the use of ENHERTU to treat unresectable or metastatic NSCLC, the presence of activating HER2 (ERBB2) mutations must be established. Testing used in clinical practice should be comparable to the testing used in the relevant pivotal study. (see Section 5.1 Pharmacodynamic properties/ *Clinical trials)*. A list of IVD companion diagnostic (CDx) tests that have been assessed is available on the TGA website.

Patient selection for HER2-positive cancers

Prior to the use of ENHERTU to treat HER2-positive cancers, HER2-positive tumour status must be established (see 5.1 Pharmacodynamic properties/ Clinical Trials). Standard testing performed by an accredited local laboratory can be used.

Dosage

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.

Table 1 Recommended dosage

Indication	**Recommended ENHERTU Dosage**	**Duration of Therapy**
Early breast cancer – post-neoadjuvant treatment	5.4 mg/kg given every 3 weeks (21-day cycle) as an intravenous infusion	14 cycles unless disease recurrence or unacceptable toxicity
Advanced cancers other than gastric	5.4 mg/kg given every 3 weeks (21-day cycle) as an intravenous infusion	Until disease progression or unacceptable toxicity
Locally advanced or metastatic gastric cancer	6.4 mg/kg given every 3 weeks (21-day cycle) as an intravenous infusion	Until disease progression or unacceptable toxicity

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 2 and Table 3.

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

Table 2: Dose reduction schedule

Dose reduction schedule	**Breast cancer, NSCLC and other solid tumours**	**Gastric cancer**
Recommended starting dose	5.4 mg/kg	6.4 mg/kg

Dose reduction schedule	Breast cancer, NSCLC and other solid tumours	Gastric cancer
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment	Discontinue treatment

Table 3: Dose modifications for adverse reactions

Adverse reaction	Severity		Treatment modification
Interstitial lung disease (ILD)/Pneumonitis *(for radiotherapy-related pneumonitis see below).*	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 2). • 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 2).
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 2).
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 is less than 10%	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		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.

Adverse reaction	Severity	Treatment modification
	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.
Dose modifications for radiotherapy-related pneumonitis in the post-neoadjuvant early breast cancer setting		
Radiotherapy-related pneumonitis following sequential or concurrent adjuvant radiotherapy (RT) *(Relationship to RT should be confirmed. If drug-related ILD/Pneumonitis is suspected, see Interstitial Lung Disease (ILD)/Pneumonitis section above)*	Grade 1 (asymptomatic)	• Continue treatment with ENHERTU.
	Grade 2 (symptomatic)	• Interrupt ENHERTU until recovered to baseline or Grade ≤1. • Manage per standard of care.
	Grade 3 or 4 (symptomatic, severe or life threatening)	• Permanently discontinue ENHERTU. • Manage per standard of care.

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. Adjust the schedule of administration 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.

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 limited 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 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, 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:

$$\textbf{Reconstituted ENHERTU (mL)} = \frac{\text{ENHERTU dose (mg/kg) x patient's body weight (kg)}}{20\ \text{mg/mL}}$$

- 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 3 (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, patients who received ENHERTU 5.4 mg/kg in clinical studies across multiple tumour types (N=3642), ILD occurred in 11.4% of patients as determined by independent review. Median time to first onset was 4.6 months (range: 0.8 to 40.2). Most ILD cases were Grade 1 (2.6%), Grade 2 (7.4%), or Grade 3 (0.7%). Fatal outcomes occurred in 0.7% of patients who received ENHERTU.

In patients treated with ENHERTU 6.4 mg/kg in clinical studies across multiple tumour types (N=1133), ILD occurred in 15.0% of patients as determined by independent review. Median time to first onset was 4.1 months (range: -0.5 to 21.0). Most ILD cases were Grade 1 (3.9%) and Grade 2 (8.5%). Grade 3 cases occurred in 1.0% and Grade 4 cases occurred in 0.1% of patients. Grade 5 events occurred in 1.6% of patients. One patient had pre-existing ILD that worsened post treatment leading to Grade 5 ILD.

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).

In patients treated with ENHERTU 5.4 mg/kg in clinical studies across multiple tumour types (N=4146), a decrease in neutrophil count was reported in 37.1% of patients and 18.7% had Grade 3 or 4 events. Median time to onset of decreased neutrophil count was 22 days (range:0 day to 51.5 months), and median duration of the first event was 21 days (range: 1 day to 30.8 months). Febrile neutropenia was reported in 0.8% of patients.

In patients treated with ENHERTU 6.4 mg/kg in clinical studies across multiple tumour types (N=1133), neutropenia was reported in 45.9% of patients and 28.4% had Grade 3 or 4 events. Median time of onset was 16 days (range: 1 day to 24.8 months), and median duration of the first event was 9 days (range: 1 day to 17.2 months). Febrile neutropenia was reported in 2.6% of patients.

Left ventricular dysfunction

Left ventricular dysfunction (LVD) has been observed with anti-HER2 therapies. LVD should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. LVD 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 patients treated with ENHERTU 5.4 mg/kg across multiple tumour types in clinical studies (N= 4146), LVD was reported in 210 patients (5.1%).

In patients treated with ENHERTU 6.4 mg/kg across multiple tumour types in clinical studies (N=1133), LVD was reported in 23 patients (2.0%).

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 patient. 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 patient (see Section 4.6 Fertility, pregnancy and lactation).

Patient pregnancy status should be verified prior to the initiation of ENHERTU. Inform patients of the potential risk to a fetus. Patients who could become pregnant should be advised to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Patients whose sperm could cause their partner to become pregnant should 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

Pregnancy status

Pregnancy status 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× the AUC at a clinical dose of 5.4 mg/kg in patients for trastuzumab deruxtecan and ~0.1× for the topoisomerase inhibitor) and tubular degeneration in testes and aspermia at 197 mg/kg (~20× the l AUC at a clinical dose of 5.4 mg/kg in patients for trastuzumab deruxtecan and ~1× for the topoisomerase inhibitor). In monkeys, decreased spermatids in seminiferous tubules in the testes were noted at 30mg/kg (~7× the AUC at a clinical dose of 5.4 mg/kg in patients for trastuzumab deruxtecan and ~0.4× 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, patients should be advised to seek counselling on sperm storage. Patients must not freeze or donate their sperm throughout the treatment period, and for at least 4 months after the final dose of ENHERTU.

Contraception

Patients who could become pregnant should use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Patients whose sperm could cause their partner to become pregnant 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 if a pregnant person is exposed to it. There are no available data on the effects of trastuzumab deruxtecan in human pregnancy. 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.

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 is not recommended during pregnancy. Prior to commencing treatment, inform all patients of the potential risks to a fetus, and of the duration after ceasing ENHERTU that this risk persists. Advise them to contact their doctor immediately if they discover a pregnancy that could be affected, to enable close monitoring.

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, patients should discontinue breastfeeding prior to initiating treatment with ENHERTU. Breastfeeding can be recommenced 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.

Summary of the safety profile

ENHERTU 5.4 mg/kg

The pooled safety population described in Section 4.4 Special warnings and precautions for use has been evaluated for patients who received at least one dose of ENHERTU 5.4 mg/kg (N=4146) in clinical studies across multiple tumour types. The median duration of exposure to ENHERTU was 9.7 months (range 0.1 to76 months).

ENHERTU 6.4 mg/kg

The pooled safety population described in Section 4.4 Special warnings and precautions for use has been evaluated for patients who received at least one dose of ENHERTU 6.4 mg/kg (N=1133) in clinical studies across multiple tumour types. The median duration of exposure to ENHERTU was 5.1 months (range: 0.4 to 41 months).

ENHERTU 5.4 mg/kg followed by THP

The median duration of exposure to any drug for the safety population, described in Special Warnings and Precautions for Use, has been evaluated in patients who received at least one dose of ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11 (N=320) was 5.6 months (range: 0.7 to 9.1 months).

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 3444 patients with breast cancer in Study DS8201-A-J101 (Breast Cancer cohort, n=71), DESTINY-Breast01 (n=184), DESTINY-Breast02 (n=404), DESTINY-Breast03 (n=257), DESTINY-Breast04 (n=371), DESTINY-Breast05 (n=806), DESTINY-Breast06 (n=434), DESTINY-Breast07 (n=110), DESTINY-Breast11 (monotherapy arm, n=283), DESTINY-Breast12 (n=504) and DESTINY-PanTumour01 (n=20). The median duration of treatment was 9.8 months (range 0.1 to 76 months).

The pooled study population characteristics were as follows: the median age was 54 years (range 22 to 96); 99.6% were female; 53% were White, 36.8% were Asian, 2.2% were Black or African American; and 67.2% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 32.5% 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 (72.3%), fatigue (56.8%), neutropenia (37.6%), vomiting (36.7%), constipation (34.6%), alopecia (33.9%), anaemia (31.3%), transaminases increased (28.9%), musculoskeletal pain (28.9%), diarrhoea (28.8%), decreased appetite (25.4%), leukopenia (24.1%), thrombocytopenia (21.5%), and upper respiratory tract infection (20.3%). In the pooled studies, the most common serious adverse reactions (frequency >1%) was interstitial lung disease (2.9%). There were 20 patients with adverse reactions leading to death (0.6%), 19 attributed to ILD (0.6%) and 1 attributed to febrile neutropenia (<0.1%).

Dose interruptions due to adverse reactions occurred in 31.7% of patients who received ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (13.6%), leukopenia (4.0%), fatigue (4.0%), upper respiratory tract infection (3.8%), anaemia (3.7%), thrombocytopenia (3.0%) and interstitial lung disease (2.4%). Dose reductions occurred in 20.6% of patients who received ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (5.9%), nausea (5.2%), neutropenia (3.3%), and thrombocytopenia (2.2%). Discontinuation of therapy due to an adverse reaction occurred in 9.5% of patients who received ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was interstitial lung disease (7.9%).

Tabulated list of adverse reactions

The adverse reactions in patients with breast cancer who received at least one dose of ENHERTU 5.4 mg/kg or ENHERTU 5.4 mg/kg followed by THP are presented in Table 4. 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 4: Tabulated list of adverse reactions in patients with breast cancer who received trastuzumab deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	**ENHERTU Breast cancer Pooled N=3444**		
	Any Grade (%)		**Grade 3-4 (%)**
Blood and Lymphatic System Disorders			
Neutropenia[a]	Very Common	37.6	19.0
Anaemia[b]	Very Common	31.3	6.9
Leukopenia[c]	Very Common	24.1	7.0
Thrombocytopenia[d]	Very Common	21.5	4.7
Lymphopenia[e]	Very Common	11.4	5.4
Febrile Neutropenia	Uncommon	0.7	0.7
Eye Disorders			
Dry eye	Common	5.1	0.1

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Breast cancer Pooled N=3444		
	Any Grade (%)		Grade 3-4 (%)
Vision Blurred[f]	Common	4.1	0
Gastrointestinal Disorders			
Nausea	Very Common	72.3	4.6
Vomiting	Very Common	36.7	1.9
Constipation	Very Common	34.6	0.3
Diarrhoea	Very Common	28.8	1.8
Abdominal pain[g]	Very Common	18.3	0.6
Stomatitis[h]	Very Common	13.6	0.5
Dyspepsia	Very Common	10.7	0
Abdominal distension	Common	3.1	0
Gastritis	Common	2.1	0.1
Flatulence	Common	1.9	0
General Disorders and Administration Site Conditions			
Fatigue[i]	Very Common	56.8	7.2
Pyrexia	Very Common	12.7	0.2
Hepatobiliary disorders			
Transaminases increased[j]	Very Common	28.9	3.4
Infections and Infestations			
Upper respiratory tract infection[k]	Very Common	20.3	0.2
Injury, poisoning and procedural complications			
Infusion related reaction[l]	Common	1.2	0
Investigations			
Weight decreased	Very Common	11.8	0.4
Blood alkaline phosphatase increased	Common	8.0	0.3
Blood bilirubin increased[m]	Common	6.4	0.5
Blood creatinine increased	Common	2.5	0.2
Metabolism and Nutrition Disorders			
Decreased appetite	Very Common	25.4	1.2
Hypokalaemia[n]	Common	9.8	2.7
Dehydration	Common	1.9	0.3

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Breast cancer Pooled N=3444		
	Any Grade (%)		Grade 3-4 (%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[o]	Very Common	28.9	1.0
Nervous System Disorders			
Headache[p]	Very Common	18.7	0.3
Dizziness	Common	9.5	0.2
Dysgeusia	Common	7.4	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	Very Common	15.2	0
Interstitial lung disease[q]	Very Common	11.6	0.7
Epistaxis	Common	8.2	0
Dyspnoea	Common	7.6	0.4
Skin and Subcutaneous Tissue Disorders			
Alopecia	Very Common	33.9	0.2
Rash[r]	Common	8.4	0.2
Pruritus	Common	4.3	0.1
Skin hyperpigmentation[s]	Common	3.1	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 leukopenia includes PTs of leukopenia and white blood cell count decreased.

[d] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet 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, and 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, and infusion related reaction.

[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 arthralgia, 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 drug-related interstitial lung disease for ENHERTU: pneumonitis, interstitial lung disease, radiation pneumonitis, organising pneumonia, pneumonia, lung opacity, pulmonary toxicity, respiratory failure, alveolitis, COVID-19 pneumonia, acute respiratory failure, atypical pneumonia, bronchiectasis, bronchitis, bronchitis chronic, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, lower respiratory tract infection, lung disorder, lung infiltration, lymphangitis, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia fungal, pulmonary fibrosis, pulmonary mass, and radiation fibrosis-lung. Some studies did not have adjudication and were excluded for ILD grouped term. The number of patients in the T-DXd 5.4 mg/kg breast cancer pool for ILD Grouped Term was 2940. Grade 5 adjudicated drug-related ILD events were ILD, pneumonitis, respiratory failure, acute respiratory failure, pulmonary fibrosis, lung opacity and lymphangitis.

[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.

Radiotherapy-related pneumonitis and skin injury in the post-neoadjuvant early breast cancer setting

Among patients receiving sequential or concurrent adjuvant radiotherapy (ART) in DESTINY-Breast-05, radiation pneumonitis occurred in 31.4% of patients receiving ENHERTU 5.4 mg/kg (N=757) and 30.5% of patients receiving trastuzumab emtansine (T-DM1) 3.6 mg/kg (N=750), as reported by the investigator. All cases of patients receiving ENHERTU and ART were either Grade 1 (26.6%) or Grade 2 (4.9%). All cases of patients receiving T-DM1 and adjuvant radiotherapy were either Grade 1 (23.6%) or Grade 2 (6.9%). A higher incidence of radiation pneumonitis was reported for patients who received sequential vs. concurrent ART, irrespective of treatment arm: 34% for ENHERTU vs. 37% for T DM1, respectively, with sequential ART and 29% vs. 27%, respectively, with concurrent ART. For patients treated with ENHERTU, median time to onset of first event of radiation pneumonitis was 4.1 months (range: 1.3 – 11.6 months).

Among patients receiving ART and ENHERTU, radiation skin injury occurred in 20% of all patients, of which 1.6% were Grade 3 and none were Grade 4. Among patients receiving ART and T-DM1, radiation skin injury occurred in 18% of all patients, of which 0.4% were Grade 3 and none were Grade 4.

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 who received 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 who received 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 who received ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (8.2%).

Table 5: 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[d]	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
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 drug-related ILD for ENHERTU: pneumonitis, interstitial lung disease, organising pneumonia, pneumonia, and pulmonary mass. For trastuzumab emtansine: pneumonitis, interstitial lung disease, organising 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 6: 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
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 who received 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 who received 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 7 and Table 8 summarise common adverse reactions and laboratory abnormalities observed in DESTINY-Breast02.

Table 7: Common adverse reactions (≥10% All Grades or ≥2% Grades 3-4) in patients who received 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

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 %
Diarrhoea	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				
Anaemia[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 anaemia, decreased haemoglobin, 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 drug-related 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: dyspnoea (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 8: 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 %**
Haematology				
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
Hypokalaemia	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 9 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, thrombocytopenia, cough, leukopenia, and headache (see Table 9). 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, thrombocytopenia, hypokalaemia, ILD, diarrhoea, febrile neutropenia, dyspnoea, abdominal pain, decreased appetite, and alanine aminotransferase increased (see Table 9). In six patients (2.6%) ILD led to death.

Dose interruptions due to adverse reactions occurred in 25% of patients who received 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%), thrombocytopenia (2.6%), and fatigue (2.1%). Dose reductions occurred in 15% of patients who received 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 who received ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (9.4%).

Table 9: 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)
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)
Thrombocytopenia[h]	54 (23.1)	10 (4.3)

System Organ Class[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
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)
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 thrombocytopenia includes PTs of thrombocytopenia 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 drug-related ILD: pneumonitis, interstitial lung disease, respiratory failure, organising 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 10: 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)
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.

HER2-low and HER2-ultralow metastatic breast cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) or HER2-ultralow (IHC >0<1+) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast06 (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: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease (ILD)/pneumonitis, COVID-19, febrile neutropenia, and hypokalaemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was pneumonitis/ILD. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, decreased neutrophil count, anaemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, decreased neutrophil count, nausea, decreased haemoglobin, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, increased alanine aminotransferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, decreased blood

potassium, diarrhoea, vomiting, constipation, decreased appetite, COVID-19, and musculoskeletal pain.

Table 11 and Table 12 summarise common adverse reactions and laboratory abnormalities observed in DESTINY-Breast06.

Table 11: Common adverse reactions (≥10% All Grades or ≥2% Grades 3 or 4) in patients treated with ENHERTU in DESTINY-Breast06

Adverse Reactions	ENHERTU 5.4 mg/kg N=434		Chemotherapy N=417	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	70	2.1	30	0.5
Diarrhoea	34	2.3	27	2.6
Vomiting	34	1.4	12	0.2
Constipation	32	0.7	15	0.5
Abdominal pain[a]	20	0.5	14	0.2
Stomatitis[b]	15	0	11	0.5
Dyspepsia	12	0	4.8	0
General Disorders and Administration Site Conditions				
Fatigue[c]	53	4.4	40	2.4
Pyrexia	12	0.2	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	48	0	21	0.5
Rash[d]	12	0.2	43	8
Metabolism and Nutrition Disorders				
Decreased appetite	26	1.4	12	0.5
Infections and Infestations				
COVID-19[e]	26	0.9	13	1
Upper respiratory tract infection[f]	19	0	9	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	24	0.5	23	1.9
Nervous System Disorders				
Headache[h]	18	0.5	10	0
Dysgeusia	12	0.2	6	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	16	0	9	0
Interstitial lung disease[i]	11	0.7	0.2	0
Epistaxis	10	0	3.6	0.2

Events were graded using NCI CTCAE version 5.0.

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

[b] Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption

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

[d] Including dermatitis, dermatitis allergic, dermatitis contact, eczema, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular

[e] Including COVID-19, COVID-19 pneumonia

[f] Including influenza, influenza like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis

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

[h] Including migraine, headache, and sinus headache

[i] Including bronchiectasis, interstitial lung disease, lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonitis, and pulmonary toxicity

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

- *Nervous System Disorders:* dizziness (9%)
- *General Disorders and Administration Site Conditions:* peripheral oedema (8%)
- *Investigations:* decreased weight (7%)
- *Eye Disorders:* dry eye (7%) and blurred vision (5%)
- *Respiratory, Thoracic, and Mediastinal Disorders:* dyspnoea (6%)
- *Gastrointestinal Disorders:* abdominal distension (4.8%), flatulence (2.3%), and gastritis (0.7%)
- *Infections and Infestations:* pneumonia (4.6%)
- *Skin and Subcutaneous Tissue Disorders:* pruritus (3.9%) and skin hyperpigmentation (0.9%)
- *Metabolism and Nutrition Disorders:* dehydration (1.6%)
- *Blood and lymphatic system disorders:* febrile neutropenia (1.2%)
- *Injury, Poisoning, and Procedural Complications:* infusion related reaction (1.2%)

Table 12: Selected laboratory abnormalities in patients in DESTINY-Breast06

Laboratory Parameter	**ENHERTU 5.4 mg/kg N=434**		**Chemotherapy N=417**	
	All Grades %	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Haematology				
Decreased white blood cell count	86	13	71	11
Decreased neutrophil count	75	27	53	20
Decreased haemoglobin	69	9	58	5
Decreased lymphocyte count	66	19	46	8
Decreased platelet count	48	6	25	1.0
Chemistry				
Increased alanine aminotransferase	44	3.2	30	0.7
Increased blood alkaline phosphatase	43	0.2	22	0.2
Increased aspartate aminotransferase	41	2.6	27	1.2
Decreased blood potassium	35	8	15	2.9
Increased blood bilirubin	16	1.9	23	1.5
Increased blood creatinine	10	1.9	8	1.0

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-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 who received 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 13. 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 who received 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 who received 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 who received ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (8.4%).

Table 13: Common adverse reactions (≥10% All Grades or ≥2% Grades 3 or 4) in patients who received 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				

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
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				
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 drug-related ILD for ENHERTU: interstitial lung disease, pneumonitis, organising pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients who received 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 14: 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
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.

Locally advanced or metastatic gastric cancer

The safety of ENHERTU 6.4 mg/kg was evaluated in a pooled analysis of 546 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 (N=125), DESTINY-Gastric02 (N=79), DESTINY-Gastric04 (N=244), DESTINY-Gastric06 (N=73), and DS8201-A-J101 (Gastric Cancer cohort, N=25). The median duration of treatment was 4.7 months (range 0.4 to 30.3).

The pooled study population characteristics were as follows: the median age was 63.8 years (range 20 to 84), 75.6% were male, 60.1% were Asian, and 42.7% had an ECOG performance status of 0 and 57.1% had an ECOG performance status of 1. The studies excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, and patients with a history of clinically significant cardiac disease.

In the pooled studies, the most common adverse reactions in patients who received ENHERTU 6.4 mg/kg (frequency ≥20%) were nausea (57.1%), fatigue (54.4%), anaemia (53.7%), neutropenia (51.6%), decreased appetite (46.2%), leukopenia (35.5%), thrombocytopenia (35.5%), diarrhoea (31.5%), vomiting (30.6%), transaminases increased (27.1%), constipation (26.0%) and alopecia (21.1%). The most common serious adverse reactions (frequency >1%) were pneumonia (4.4%), decreased appetite (3.7%), anaemia (3.5%), ILD (2.7%), vomiting (2.6%), thrombocytopenia

(1.8%), abdominal pain (1.6%), febrile neutropenia (1.5%), nausea (1.5%), fatigue (1.5%) and pyrexia (1.3%)). There were 6 (1.1%) patients with adverse reactions leading to death, three attributed to pneumonia (0.5%), two attributed to ILD (0.4%) and one attributed to dyspnoea (0.2%).

Dose interruptions due to adverse reactions occurred in 41.9% of patients who received 6.4 mg/kg of ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14.7%), anaemia (9.9%), fatigue (6.2%), ILD (4.6%), leukopenia (4.6%), decreased appetite (3.8%), pneumonia (3.5%) and thrombocytopenia (3.1%). Dose reductions occurred in 28.2% of patients who received ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (7.7%), nausea (6.0%), fatigue (5.7%), decreased appetite (4.9%), and thrombocytopenia (4.2%).

Discontinuation of therapy due to an adverse reaction occurred in 9.7% of patients who received ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (6.4%).

The adverse reactions in 546 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who received at least one dose of ENHERTU 6.4 mg/kg are presented in Table 15.

Table 15: Adverse reactions in patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who received trastuzumab deruxtecan 6.4 mg/kg (≥10% all Grades or ≥2% Grades 3 or 4)

MedDRA System Organ Class/ Preferred Term or Grouped Term	**ENHERTU HER2-positive Gastric Cancer Pooled[*] N=546**	
	Any Grade [a] %	**Grade 3 or 4[a] %**
Blood and Lymphatic System Disorders		
Anaemia[b]	53.7	26.6
Neutropenia[c]	51.6	31.9
Thrombocytopenia[d]	35.5	11.5
Leukopenia[e]	35.5	12.6
Lymphopenia[f]	14.5	5.9
Febrile neutropenia	3.1	3.1
Gastrointestinal Disorders		
Nausea	57.1	6.0
Diarrhoea	31.5	1.6
Vomiting	30.6	2.6
Constipation	26.0	0
Abdominal pain[g]	18.3	2.2
General Disorders and Administration Site Conditions		
Fatigue[h]	54.4	8.8
Pyrexia	16.7	0
Hepatobiliary Disorders		
Transaminase increased[i]	27.1	3.5

MedDRA System Organ Class/ Preferred Term or Grouped Term	ENHERTU HER2-positive Gastric Cancer Pooled* N=546	
	Any Grade [a] %	Grade 3 or 4[a] %
Infections and Infestations		
Pneumonia	9.3	3.5
Investigations		
Blood alkaline phosphatase increased	10.1	1.1
Metabolism and Nutrition Disorders		
Decreased appetite	46.2	6.6
Hypokalaemia[j]	15.8	6.2
Respiratory, Thoracic and Mediastinal Disorders		
Interstitial lung disease[k]	11.7	0.7
Skin and Subcutaneous Tissue Disorders		
Alopecia	21.1	0

MedDRA = Medical Dictionary for Regulatory Activities

PT = preferred term

* Date of data cut-off: 01 August 2019 (J101), 03 June 2020 (DESTINY-Gastric01), 08 November 2021 (DESTINY-Gastric02), 24 October 2024 (DESTINY-Gastric04), 28 February 2024 (DESTINY-Gastric06).

[a] National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0

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

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

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

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

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

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

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

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

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

[k] Interstitial lung disease includes events that were adjudicated as drug-related ILD: alveolitis, pneumonitis, interstitial lung disease, pneumonia and pulmonary toxicity.

Other clinically relevant adverse reactions reported in less than 10% of patients who received ENHERTU:

- *Gastrointestinal Disorders:* Stomatitis (7.1%) [Grouped term includes PTs of stomatitis, aphthous ulcer and mouth ulceration.
- *General Disorders and Administration Site Conditions:* oedema peripheral (8.8%).
- *Infections and infestations:* Upper respiratory tract infection (9.7%) [Grouped term includes PTs of upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.]
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (0.4%).
- *Investigations*: blood bilirubin increased (8.6%) [Grouped term includes PTs of blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased].
- *Metabolism and Nutrition Disorders:* Dehydration (2.6%).

- *Respiratory, Thoracic and Mediastinal Disorders*: cough (9.0%), dyspnoea (4.9%), epistaxis (3.7%).
- *Skin and Subcutaneous Tissue Disorders*: pruritus (4.6%), rash (4.2%) [Grouped term includes PTs of rash, rash maculo-papular, rash papular and rash pruritic].

Other unresectable or metastatic solid tumours

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who received ENHERTU 5.4 mg/kg in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8.3 months (range 0.7 to 30.2).

The median age was 60 years (range 23 to 96); 74% were female; 51% were White, 42% were Asian, 2.9% were Black or African American, and 51% had an ECOG performance status 0 and 48% had an ECOG performance status of 1.

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, COVID-19, fatigue, anaemia, cellulitis, and dyspnoea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%) and cardiac arrest (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, COVID-19, COVID-19 pneumonia, cerebrovascular accident, general physical health deterioration, neutropenic sepsis, pneumonia, sepsis and haemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, neutropenia, anaemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhoea.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, nausea, decreased haemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhoea, decreased blood potassium, constipation, and upper respiratory tract infection.

Table 16 and Table 17 summarise the common adverse reactions and laboratory abnormalities in DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-Breast01, and DESTINY-CRC02.

Table 16: Common adverse reactions (≥10% All Grades or ≥2% Grades 3 or 4) in HER2-positive (IHC 3+) patients treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Adverse Reactions	ENHERTU 5.4 mg/kg N= 347	
	All Grades %	Grade 3 or 4 %
Gastrointestinal Disorders		
Nausea	69	7
Vomiting	35	3.5
Diarrhoea	31	4.3
Constipation	28	0.6
Stomatitis[a]	15	0.9
Abdominal pain[b]	18	2.0
Dyspepsia	12	0.3
General Disorders and Administration Site Conditions		
Fatigue[c]	59	10
Pyrexia	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	34	2.6
Skin and Subcutaneous Tissue Disorders		
Alopecia	34	0.3
Rash[d]	10	0.6
Infections and Infestations		
Upper respiratory tract infection[e]	20	0
Pneumonia	6	2.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	19	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	16	0
Interstitial lung disease[g]	16	0.6
Dyspnoea	12	1.7
Nervous System Disorders		
Headache[h]	15	0
Investigations		
Decreased weight	10	0.3

[a] Including stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption.

[b] Including abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, gastrointestinal pain.

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

[d] Including rash, pustular rash, maculo-papular rash, popular rash, macular rash, pruritic rash.

[e] Including influenza, influenza-like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis.

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

[g] Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organising pneumonia, respiratory failure, acute respiratory failure, alveolitis, lung opacity, lymphangitis, pneumonia, bacterial pneumonia, pulmonary fibrosis, and radiation pneumonitis. Grade 5 adjudicated drug-induced ILD events were pneumonitis, respiratory failure, acute respiratory failure, lymphangitis, pulmonary fibrosis.

[h] Including migraine, headache, sinus headache.

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

- *Respiratory, thoracic and mediastinal disorders:* epistaxis (9%)
- *Nervous System Disorders:* dizziness (8%) and dysgeusia (6%)
- *General disorders and administration site conditions:* Oedema peripheral (8.4%)
- *Skin and Subcutaneous Disorders:* pruritus (5%) and skin hyperpigmentation (4.3%) [including skin hyperpigmentation, skin discoloration, pigmentation disorder]
- *Eye Disorders*; blurred vision (4.0%) [including blurred vision, visual impairment]
- *Metabolism and Nutrition Disorders*: dehydration (3.2%)
- *Gastrointestinal Disorders:* abdominal distension (2.6%), flatulence (1.7%) and gastritis (0.9%)
- *Blood and Lymphatic System Disorders:* febrile neutropenia (1.7%)
- *Injury, Poisoning, and Procedural Complications*: infusion-related reactions (1.4%) [including administration related reaction, anaphylactic reaction, hypersensitivity, infusion-related reaction and infusion-related hypersensitivity reaction]

Table 17: Selected laboratory abnormalities in HER2-positive (IHC 3+) patients treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Laboratory Parameter	**ENHERTU 5.4 mg/kg N= 347[a]**	
	All Grades %	**Grades 3 or 4 %**
Haematology		
Decreased white blood cell count	75	11
Decreased haemoglobin	67	10
Decreased neutrophil count	66	21
Decreased lymphocyte count	58	21
Decreased platelet count	51	7
Chemistry		
Increased aspartate aminotransferase	45	1.5
Increased alanine aminotransferase	44	1.5
Increased blood alkaline phosphatase	36	1.2
Decreased blood potassium	29	6
Increased blood bilirubin	15	0.6
Increased blood creatinine	14	0.6

[a] Percentages were calculated using the number of patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Unresectable or metastatic NSCLC

HER2-mutant at 5.4 mg/kg

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic lung cancer who received ENHERTU 5.4 mg/kg in DESTINY-Lung02 (see section 5.1). The median duration of treatment was 7.7 months (range: 0.7 to 20.8).

In ENHERTU-treated patients (N=101), the median age was 59 years (range 30 to 83); 64.4% were female; 63.4% were Asian, 22.8% were White; and 29.7% had an ECOG performance status 0 and 70.3% 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.

The most common adverse reactions (frequency ≥20%) were nausea (67.3%), fatigue (44.6%), neutropenia (42.6%), decreased appetite (39.6%), anaemia (36.6%), constipation (36.6%), vomiting (31.7%), leukopenia (28.7%), thrombocytopenia (27.7%), diarrhoea (22.8%), transaminases increased (21.8%), and alopecia (21.8%). The most common serious adverse reactions (frequency >1%) were ILD/pneumonitis (4.0%), thrombocytopenia (3.0%), nausea (2.0%), vomiting (2.0%) and dyspnoea (2.0%). Fatalities due to adverse reactions occurred in 2 patients (2.0%) including ILD/pneumonitis and cerebrovascular accident (one patient each).

Dose interruptions due to adverse reactions occurred in 28.7% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (11.9%) ILD/pneumonitis (5.0%), fatigue (5.0%), and anaemia (4.0%). Dose reductions occurred in 13.9% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (4.0%), fatigue (3.0%) and decreased appetite (3.0%). Discontinuation of therapy due to an adverse reaction occurred in 10.9% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (9.9%).

The adverse reactions in patients with unresectable or metastatic HER2-mutant NSCLC who received at least one dose of ENHERTU 5.4 mg/kg are presented in Table 18.

Table 18: Common adverse reactions (≥10% all Grades or ≥2% Grade 3 or 4) in patients with unresectable or metastatic NSCLC in DESTINY-Lung02 treated with trastuzumab deruxtecan 5.4 mg/kg

MedDRA System Organ Class and PT or Grouped Term	**ENHERTU 5.4 mg/kg N = 101**	
	All Grades %	**Grade 3 or 4 %**
Gastrointestinal disorders		
Nausea	67.3	4.0
Constipation	36.6	1.0
Vomiting	31.7	3.0
Diarrhoea	22.8	1.0
Stomatitis[a]	15.8	0

MedDRA System Organ Class and PT or Grouped Term	ENHERTU 5.4 mg/kg N = 101	
	All Grades %	Grade 3 or 4 %
Blood and lymphatic system disorders		
Neutropenia[b]	42.6	18.8
Anaemia	36.6	10.9
Leukopenia[c]	28.7	5.0
Thrombocytopenia[d]	27.7	5.9
Lymphopenia[e]	6.9	3.0
Metabolism and nutrition disorders		
Decreased appetite	39.6	2.0
Hypokalaemia	12.9	6.9
General disorders and administration site conditions		
Fatigue[f]	44.6	7.9
Skin and subcutaneous tissue disorders		
Alopecia	21.8	0
Investigations		
Transaminases increased[g]	21.8	3.0
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease[h]	12.9	1.0

Events were graded using NCI CTCAE version 5.0.

[a] Grouped term of stomatitis includes PTs of stomatitis and mouth ulceration.

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

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

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

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

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

[g] Grouped term of transaminases increased includes PTs of alanine aminotransferase increased and aspartate aminotransferase increased.

[h] ILD includes events that were adjudicated as drug-related ILD: Interstitial lung disease, Pneumonitis, Pulmonary toxicity, Respiratory failure.

Data are included as of data cut-off of 23 Dec 2022 for Study U206.

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

- *Gastrointestinal Disorders:* abdominal pain (9.9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- *Infections and Infestations:* upper respiratory tract infection (8.9%) [including upper respiratory tract infection, rhinitis, nasopharyngitis, influenza, influenza-like illness, pharyngitis, and laryngitis].
- *Nervous System Disorders:* headache (5.9%) [including headache and migraine]
- *Respiratory, Thoracic and Mediastinal Disorders:* dyspnoea (5%), and epistaxis (4%)
- *Skin and Subcutaneous Disorders:* rash (5%) [including rash and maculo-papular rash]

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 internalisation 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.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across 5.4 mg/kg and 6.4 mg/kg doses evaluated in clinical studies, 2.2% (70/3124) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with ENHERTU. The incidence of treatment-emergent neutralising antibodies against trastuzumab deruxtecan was 0.1% (3/3124). There was no apparent effect of development of antibodies and on the pharmacokinetics, safety and/or effectiveness of ENHERTU.

Clinical trials

Early breast cancer

DESTINY-Breast05

The efficacy and safety of ENHERTU were evaluated in DESTINY-Breast05, a Phase 3, randomised, multicentre, open-label study that enrolled 1635 adult patients with HER2-positive breast cancer with residual invasive disease following neoadjuvant therapy. HER2-positivity (IHC3+ or ISH+) was determined by the PATHWAY/VENTANA anti-HER2/neu (4B5) and the VENTANA HER2 Dual ISH DNA Probe Cocktail at a central laboratory.

Patients were eligible if they had HER2-positive breast cancer with residual invasive disease following neoadjuvant therapy and at least one high risk criteria: inoperable at disease presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) with residual invasive disease in the breast or axillary lymph nodes or operable at disease presentation (clinical stages T1-3, N0-1, M0) with positive pathological node status (ypN1-3) after neoadjuvant therapy.

The study excluded patients who have had history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, or ECOG performance status >1.

Patients received concurrent or sequential adjuvant radiotherapy as per investigator discretion and hormonal therapy as per local guidelines. In addition to all patients receiving computed tomography (CT) scans of the chest at screening, patients receiving radiotherapy also received regular CT scans of the chest during treatment period and after end of treatment.

Patients were randomised 1:1 to receive 14 cycles of either ENHERTU 5.4 mg/kg (N=818) by intravenous infusion every three weeks or trastuzumab emtansine (T-DM1) (N=817) 3.6 mg/kg by intravenous infusion every three weeks. Patients were stratified by operative status at disease presentation (operable, inoperable), post-neoadjuvant pathological nodal status (positive, negative), tumour hormone receptor status (positive, negative), and HER2-targeted neoadjuvant therapy (single, dual). Treatment with ENHERTU was administered for a maximum of 14 cycles or until disease recurrence, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was invasive disease-free survival (IDFS), defined as the time from randomisation to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Key secondary efficacy outcome measure was disease-free survival (DFS). Overall survival (OS) was an additional secondary endpoint.

Of the 1635 patients randomised, the median age was 50.5 years (range: 21 to 83), 10.0% age 65 or older; 99.6% female; 38.8% White, 48.0% Asian, and 2.1% Black or African American. Tumour characteristics were: 71.2% had HR+ status and 28.8% had HR- status; 52.3% had inoperable tumours at disease presentation (T4, N0-3, M0 or T1-3, N2-3, M0); 80.6% had post-neoadjuvant pathological nodal status (ypN1-3). Neoadjuvant treatment characteristics were: 21.2% of patients received single HER2-targeted neoadjuvant therapy; 78.8% received dual HER2-targeted neoadjuvant therapy; 50.3% of patients received anthracyclines and 100% received taxanes as part of neoadjuvant regimen. Characteristics of adjuvant radiotherapy were: 37.0% of patients received sequential adjuvant radiotherapy, 56.1% of patients received concurrent adjuvant RT.

The study demonstrated a statistically significant increase in duration of IDFS amongst patients randomised to ENHERTU compared to T-DM1.

Efficacy results are summarised in Table 19 and Figure 1. At the time of the IDFS analysis, a total of 47 (2.9%) patients had died across both study arms.

Table 19: Efficacy Results in DESTINY-Breast05

Efficacy Parameter	**ENHERTU 5.4 mg/kg N=818**	**Trastuzumab emtansine 3.6 mg/kg N=817**
Invasive Disease-Free Survival (IDFS)		
Number of events (%)	51 (6.2)	102 (12.5)
3-year event free rate, % (95% CI)	92.4 (89.7, 94.4)	83.7 (80.2, 86.7)
Hazard ratio (95% CI)	0.47 (0.34, 0.66)	

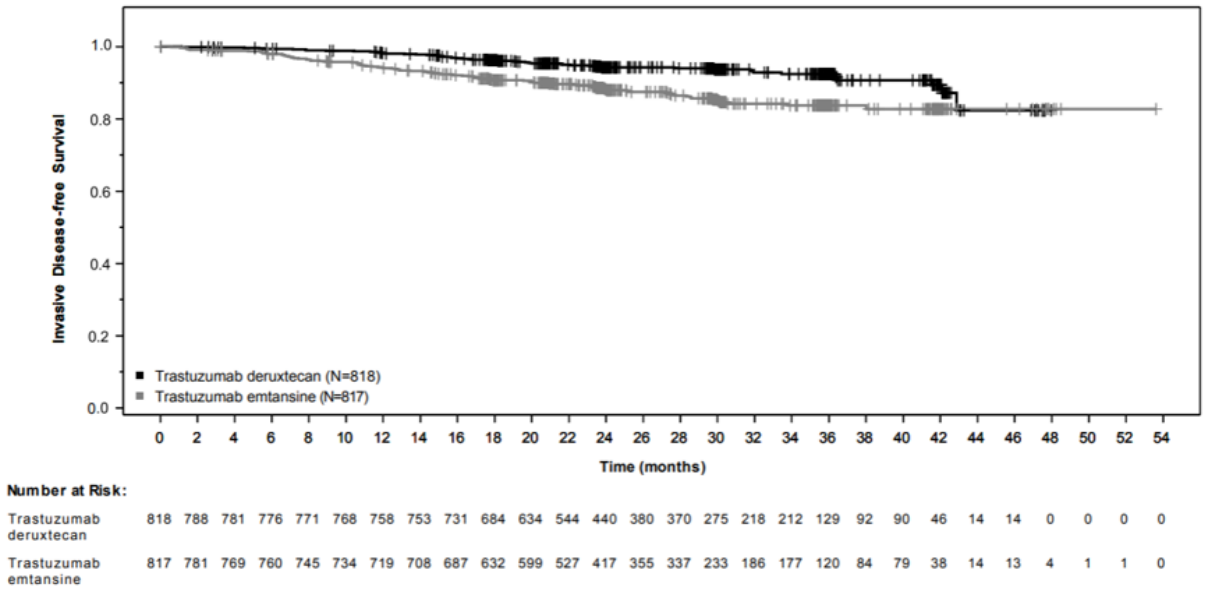
Efficacy Parameter	ENHERTU 5.4 mg/kg N=818	Trastuzumab emtansine 3.6 mg/kg N=817
p-value[a]	p<0.0001	
Disease-Free Survival (DFS)		
Number of events (%)	52 (6.4)	103 (12.6)
3-year event free rate, % (95% CI)	92.3 (89.5, 94.3)	83.5 (79.9, 86.4)
Hazard ratio (95% CI)	0.47 (0.34, 0.66)	
p-value[b]	p<0.0001	

CI = confidence interval

[a] Two-sided p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.0183.

[b] Two-sided p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.0144.

Figure 1 Kaplan-Meier Plot of Invasive Disease-free Survival (IDFS)



IDFS findings did not appear inconsistent across prespecified subgroups based on timing of radiation therapy (sequential vs concurrent) age, race, region, disease operable status (operable vs inoperable disease), HR status, post-neoadjuvant pathological nodal status, and prior use of single or dual HER2-targeted therapy in the neoadjuvant setting.

Metastatic breast cancer

DESTINY-Breast03

The efficacy and safety of ENHERTU were evaluated 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 cut-off 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 20 and Figure 2 and Figure 3.

Table 20: 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)

Efficacy Parameter	ENHERTU 5.4 mg/kg N=261	trastuzumab emtansine 3.6 mg/kg N=263
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 cut-off 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 2: Kaplan-Meier plot of progression-free survival per BICR, data cut-off 25 July 2022

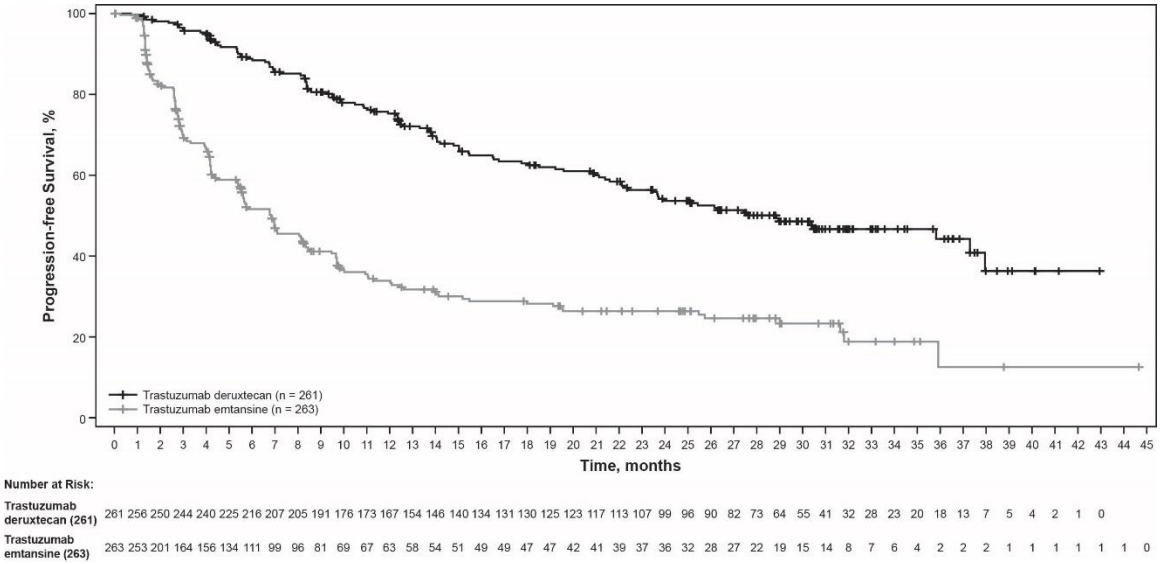
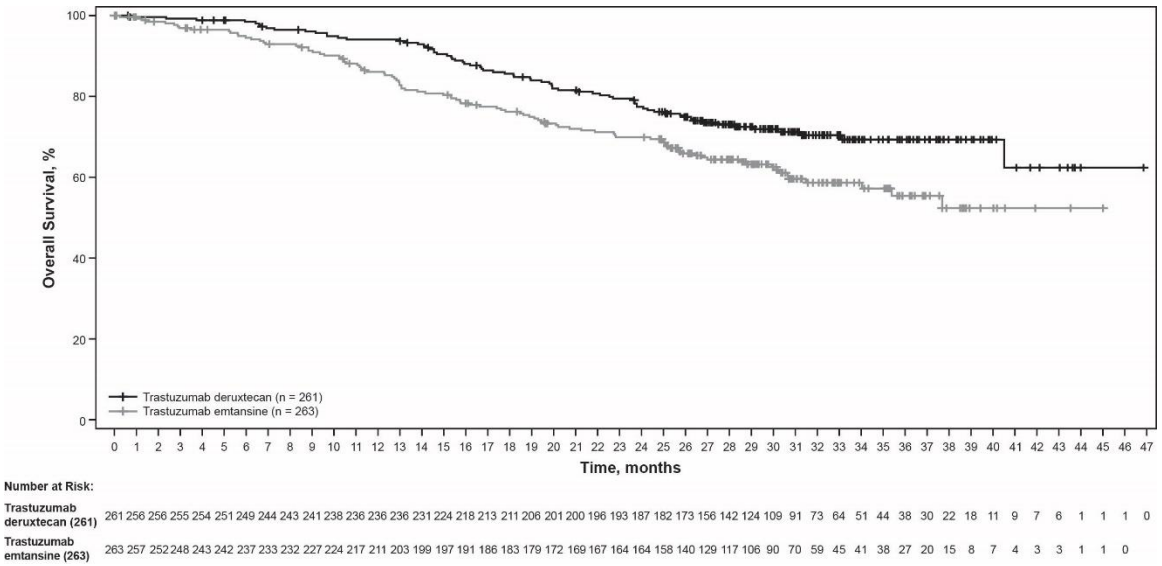


Figure 3: Kaplan-Meier plot of overall survival, data cut-off 25 July 2022



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 summarised in Table 21 and Figure 4 and Figure 5.

Table 21: 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)

Efficacy Parameter	ENHERTU N=406	Treatment of Physician's Choice N=202
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 4: Kaplan-Meier plot of progression-free survival per BICR

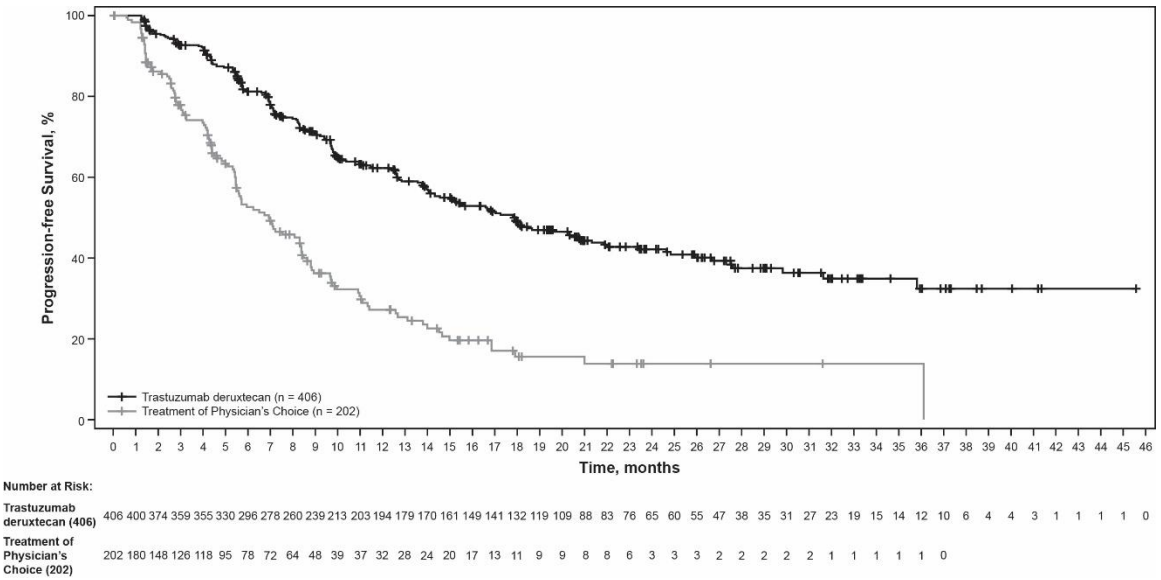
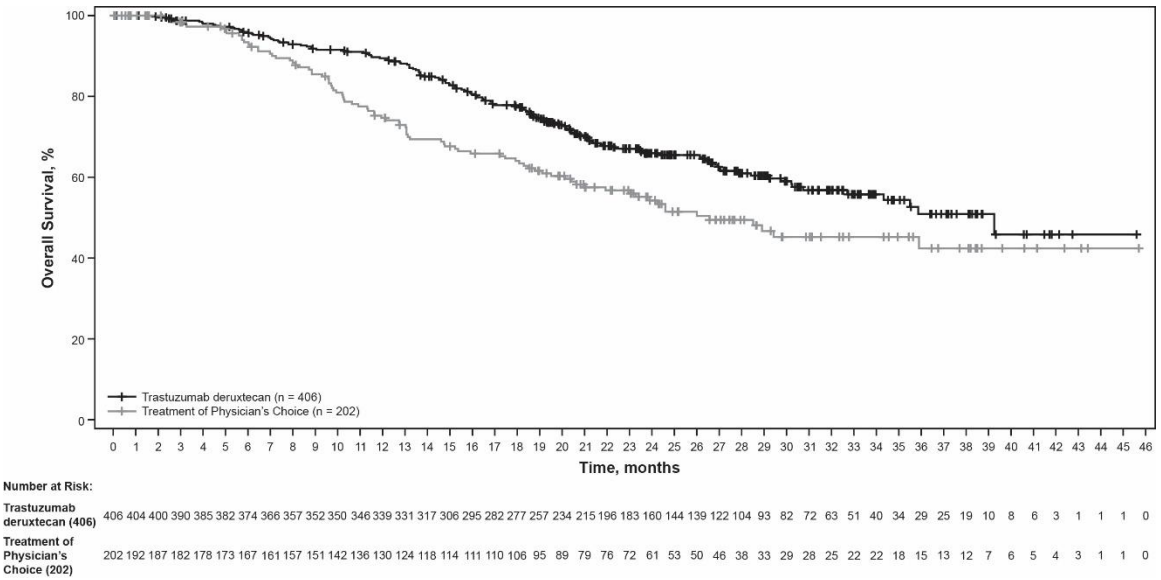


Figure 5: Kaplan-Meier plot of overall survival



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 evaluated 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 22.

Table 22: 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 antitumour 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-Breast06

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast06, a randomised, multicentre, open-label, Phase 3 study that randomised 866 adult patients with advanced or metastatic HR+ breast cancer with HER2-low (IHC 1+ or IHC 2+/ISH-negative) or HER2-ultralow (IHC 0 with membrane staining) expression as determined by the PATHWAY/VENTANA anti-HER2/neu (4B5) evaluated at a central laboratory. HER2-ultralow is defined as membrane HER2 staining that is seen in more than 0% but less than 10% of tumour cells (and may also be notated as IHC >0<1+). Patients were eligible if they had disease progression on (a) at least 2 lines of endocrine therapy in the metastatic setting or (b) one line of endocrine therapy in the metastatic setting and demonstrated progression within 24 months from the start of adjuvant endocrine therapy, or within 6 months of starting first line endocrine therapy in combination with a CDK 4/6 inhibitor in the metastatic setting. Patients with prior chemotherapy in the neo-adjuvant or adjuvant setting were eligible as long as they had a disease-free interval greater than 12 months. The study excluded patients with prior chemotherapy for advanced or metastatic disease, patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, uncontrolled or significant cardiovascular disease, untreated and symptomatic brain metastases, or ECOG performance status >1.

Patients were randomised 1:1 to receive either ENHERTU 5.4 mg/kg (N=436) by intravenous infusion every three weeks or physician's choice of single agent chemotherapy (N=430, capecitabine 60%, nab-paclitaxel 24%, or paclitaxel 16%). Randomisation was stratified by prior CDK4/6 inhibitor use (yes or no), prior taxane use in the non-metastatic setting (yes or no), and HER2 IHC status of tumour samples (IHC 2+/ISH-negative vs. IHC 1+ vs. IHC 0 with membrane staining). Treatment with ENHERTU was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was PFS in patients with HER2-low 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 (HER2-low and HER2-ultralow), OS in HER2-low patients, and OS in the overall population. ORR, DOR, and patient-reported outcomes (PROs) were secondary endpoints.

In the overall population, demographics and baseline tumour characteristics were similar between treatment arms. Of the 866 patients randomised, the median age was 57 years (range: 28 to 87); 31% were age 65 or older; 99.9% were female; 53% were White, 35% were Asian, and 1% were Black or African American. Patients had an ECOG performance status of 0 (59%) or 1 (39%) at baseline; 27% were IHC 2+/ISH-, 55% were IHC 1+, and 18% were IHC 0 with membrane staining; 67% had liver metastases, 32% had lung metastases, 8% had brain metastases, and 3% had bone-only metastases. Patients had a median of 2 prior lines of endocrine therapy in the metastatic setting (range: 1 to 5) with 17% having 1 and 68% having 2. Eighty-nine percent of patients had prior endocrine therapy in combination with CDK4/6i treatment in the metastatic setting, 41% had prior taxane use in the non-metastatic setting.

The study demonstrated a statistically significant increase in PFS in the patients randomised to ENHERTU compared to chemotherapy in both the HER2-low cohort and the overall population. Overall survival (OS) data was immature (39%) at the time of analysis. Efficacy results are summarised in Table 23 and Figure 6.

Table 23: Efficacy results in DESTINY-Breast06

Efficacy parameter	HER2-low		Overall population (HER2-low and HER2-ultralow)	
	ENHERTU (N=359)	Chemotherapy (N=354)	ENHERTU (N=436)	Chemotherapy (N=430)
Progression free survival per BICR				
Number of events (%)	225 (62.7)	232 (65.5)	269 (61.7)	271 (63.0)
Median, months (95% CI)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)
Hazard ratio (95% CI)	0.62 (0.52, 0.75)[a]		0.64 (0.54, 0.76)[b]	
p-value	<0.0001[a]		<0.0001[b]	
Confirmed objective response rate per BICR [c]				
N with measurable disease at baseline per BICR	326	324	393	389
n (%)	202 (62.0)	114 (35.2)	246 (62.6)	134 (34.4)
95% CI	56.5, 67.3	30.0, 40.7	57.6, 67.4	29.7, 39.4
Complete response n (%)	9 (2.8)	0	10 (2.5)	0
Partial response n (%)	193 (59.2)	114 (35.2)	236 (60.1)	134 (34.4)
Duration of response per BICR				
Median, months (95% CI)	14.1 (11.9, 15.9)	8.6 (6.7, 11.3)	14.3 (12.5, 15.9)	8.6 (6.9, 11.5)

BICR = blinded independent central review; CI = confidence interval

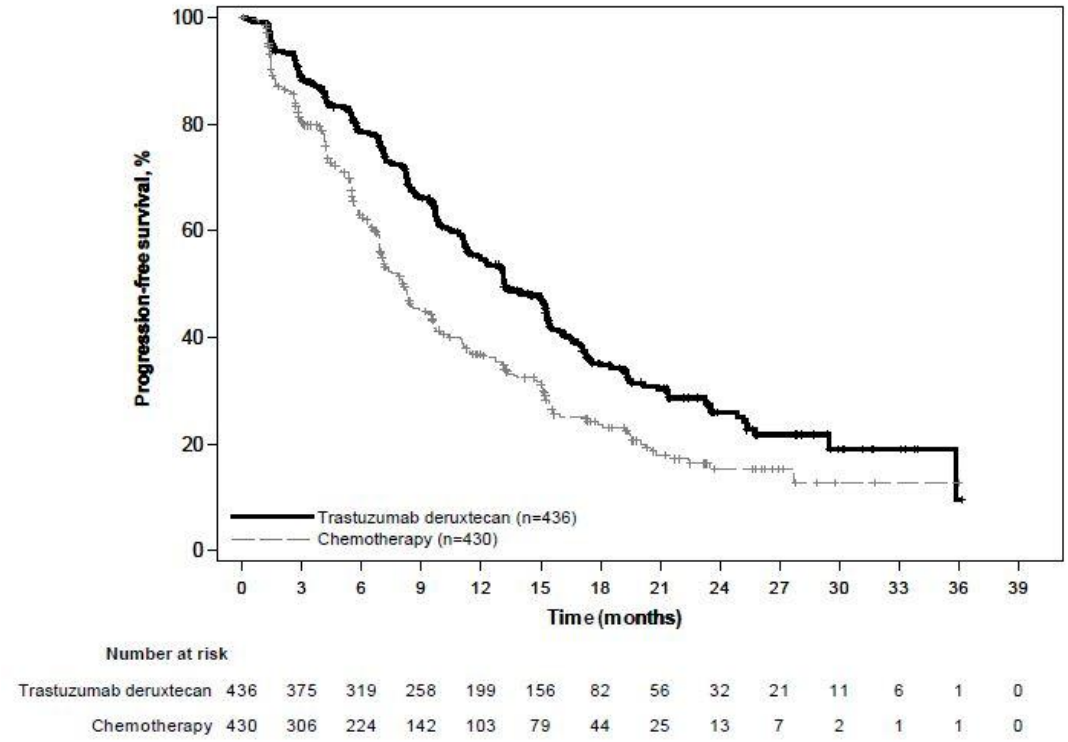
[a] Analysis stratified by prior CDK4/6i use and HER2 IHC

[b] Unstratified analysis

[c] Analysed amongst patients with measurable disease at baseline per BICR

In an exploratory analysis of the HER2-ultralow subgroup (n=153), median PFS was 15.1 months (95% CI: 10.0, 17.3) in patients randomised to ENHERTU and 8.3 months (95% CI: 5.8, 15.2) in patients randomised to chemotherapy with a hazard ratio of 0.76 (95% CI: 0.49, 1.17). Confirmed objective response rate (ORR) per BICR was 65.7% (95% CI: 53.1, 76.8) and 30.8% (95% CI: 19.9, 43.4) in patients randomised to ENHERTU and chemotherapy and with measurable disease at baseline, respectively. Median duration of response was 14.3 months (95% CI: 11.8, not estimable) and 14.1 months (95% CI: 5.9, not estimable) in patients randomised to ENHERTU and chemotherapy, respectively.

Figure 6: Kaplan-Meier plot of progression free survival (PFS) in the overall population of DESTINY-Breast06



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 24 and Figure 7 and Figure 8.

Table 24: 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)

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
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 7: Kaplan-Meier plot of overall survival (Overall Population)

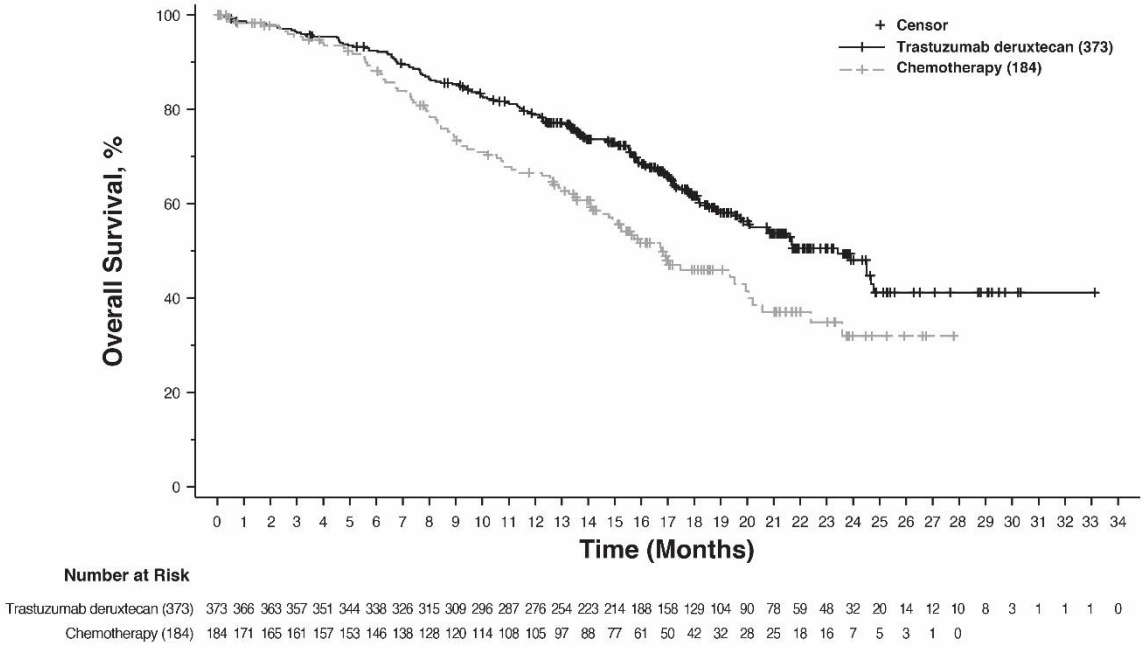
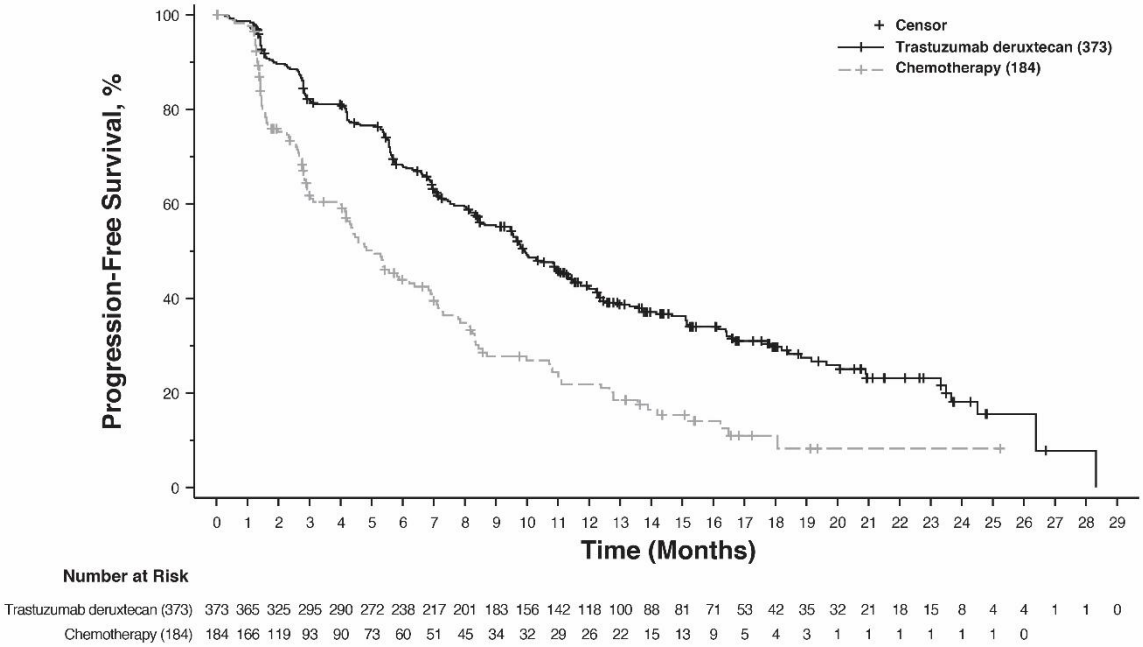


Figure 8: Kaplan-Meier plot of progression-free survival per BICR (Overall Population)



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.

Locally advanced or metastatic gastric cancer

DESTINY-Gastric04

The efficacy and safety of ENHERTU were evaluated in DESTINY-Gastric04, a Phase 3, randomised, multicentre, open-label, active-controlled study. The study included adult patients with HER2-positive locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma who had progressed on or after a trastuzumab-containing regimen. Patients were randomised 1:1 to receive either ENHERTU (N=246) or ramucirumab plus paclitaxel (N=248). Randomisation was stratified by HER2 status (IHC 3+ or IHC 2+/ISH-positive), geographical region (Asia [excluding mainland China] versus Western Europe versus mainland China/rest of the world), and time to progression on first-line therapy (<6 months or ≥6 months). ENHERTU was administered by intravenous infusion at 6.4 mg/kg every three weeks. Ramucirumab was administered by

intravenous infusion on days 1 and 15 of a 28-day cycle at 8 mg/kg. Paclitaxel was administered by intravenous infusion days 1, 8, and 15 of a 28-day cycle at 80 mg/m^2. Tumour samples were required to have locally or centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. Treatment was administered until disease progression, death, or unacceptable toxicity. The primary efficacy outcome measure was overall survival (OS). PFS, confirmed ORR, and DOR were secondary outcome measures.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 494 patients enrolled in DESTINY-Gastric04, the median age was 63.7 years (range 21.1 to 87.0); 79.4% were male; 49.8% were White, 40.1% were Asian, and 0.4% were Black or African American. Patients had an ECOG performance status of either 0 (37.4%) or 1 (61.9%); 61.1% had gastric adenocarcinoma and 38.9% had GEJ adenocarcinoma; 84% were IHC 3+ and 16% were IHC 2+/ISH-positive; 70% of patients had two or more metastatic sites, 61.7% had liver metastases, 6.9% had brain metastases; 15.6% of patients previously received immunotherapy.

The study demonstrated a statistically significant and clinically meaningful improvement in OS in patients randomised to ENHERTU compared with ramucirumab plus paclitaxel. Efficacy results are summarised in Table 25 and Figure 9 and Figure 10.

Table 25: Efficacy Results in DESTINY-Gastric04

Efficacy Parameter	**ENHERTU N=246**	**Ramucirumab plus paclitaxel N=248**
Overall Survival (OS)		
Number of events (%)	124 (50.4)	142 (57.3)
Median, months (95% CI)	14.7 (12.1, 16.6)	11.4 (9.9, 15.5)
Hazard ratio (95% CI)[*]	0.70 (0.55, 0.90)	
p-value[†]	p=0.0044	
Progression-free Survival (PFS) per Investigator Assessment		
Number of events (%)	166 (67.5)	156 (62.9)
Median, months (95% CI)	6.7 (5.6, 7.1)	5.6 (4.9, 5.8)
Hazard ratio (95% CI)[*]	0.74 (0.59, 0.92)	
p-value[†]	p=0.0074	
Confirmed Objective Response Rate (ORR) per Investigator Assessment[††]		
n (%)	104 (44.3)	69 (29.1)
95% CI	(37.8, 50.9)	(23.4, 35.3)
p-value[§]	p=0.0006	
Best Overall Response (BOR) per Investigator Assessment[††]		
Complete Response n (%)	7 (3.0)	3 (1.3)
Partial Response n (%)	97 (41.3)	66 (27.8)
Stable Disease n (%)	112 (47.7)	111 (46.8)
Progressive Disease n (%)	13 (5.5)	22 (9.3)
Not Evaluable n (%)	6 (2.6)	35 (14.8)
Duration of Response (DOR) per Investigator Assessment		
Median, months (95% CI)	7.4 (5.7, 10.1)	5.3 (4.1, 5.7)

CI=confidence interval

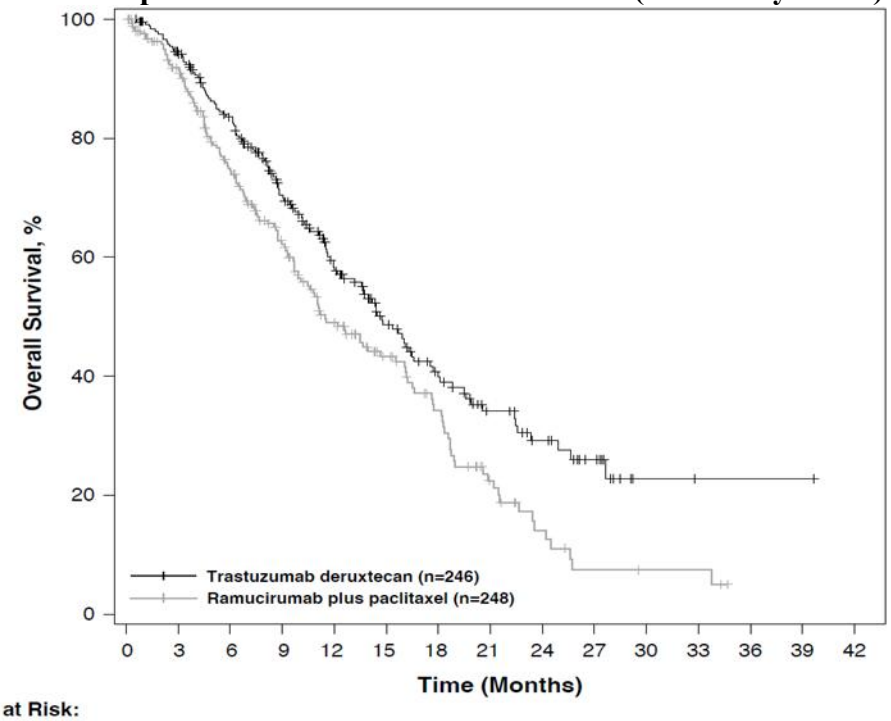
[*] Two-sided p-value from stratified log-rank test and stratified Cox proportional hazards model adjusted for IRT stratification factors: HER2 status (IHC 3+ or IHC 2+/ISH+).

[†] Based on log rank test stratified by HER2 status (IHC 3+ or IHC 2+/ISH+)

†† ORR-eligible subjects are those who were randomised at least 77 days (ie, 2 × 6 weeks - 1 week) before DCO date of interim analysis. Confirmed ORR and BOR are calculated using the eligible subjects as the denominator: ENHERTU = 235, ramucirumab plus paclitaxel = 237

§ p-value is based on the Cochran-Mantel-Haenszel test adjusted for HER2 status (IHC 3+ or IHC 2+/ISH+).

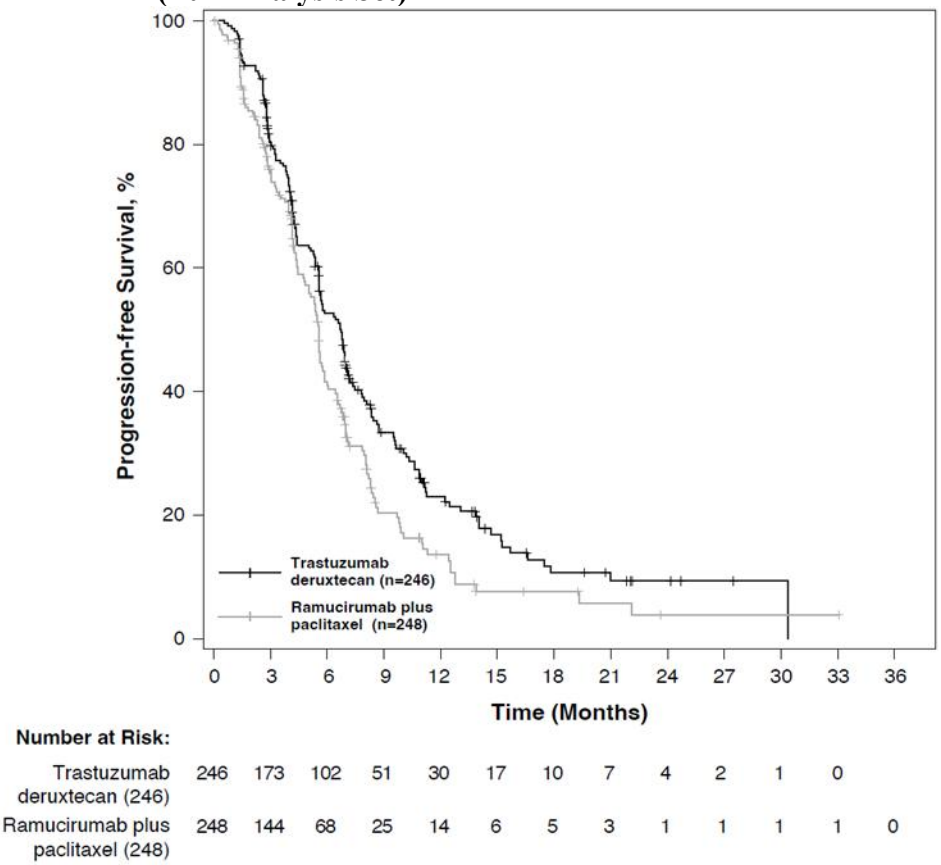
Figure 9: Kaplan-Meier Plot of Overall Survival (Full Analysis Set)



Number at Risk:

Trastuzumab deruxtecan (246)	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
Ramucirumab plus paclitaxel (248)	248	204	150	109	76	52	36	18	9	4	3	3	0		

Figure 10: Kaplan-Meier Plot of Progression-free Survival per Investigator Assessment (Full Analysis Set)



The OS benefit provided by ENHERTU over ramucirumab plus paclitaxel was mostly consistent across key prespecified subgroups including HER2 status (IHC 3+ vs. IHC 2+/ISH+), geographical region (Asia vs. Western Europe vs. mainland China/rest of the world), and time to progression on first-line therapy (<6 months vs. ≥6 months).

DESTINY-Gastric01

The efficacy and safety of ENHERTU were evaluated in DESTINY-Gastric01, a Phase 2, multicentre, open-label, randomised study conducted at sites in Japan and South Korea. The study included adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine agent, and a platinum agent. Patients were randomised 2:1 to receive either ENHERTU (N=126) or physician's choice of chemotherapy: either irinotecan (N=55) or paclitaxel (N=7). Randomisation was stratified by HER2 status (IHC 3+ or IHC 2+/ISH-positive, ECOG performance status (0 or 1), and region (Japan or South Korea). ENHERTU was administered by intravenous infusion at 6.4 mg/kg every three weeks. Irinotecan monotherapy was administered by intravenous infusion biweekly at 150 mg/m^2. Paclitaxel monotherapy was administered by intravenous infusion weekly at 80 mg/m^2. Tumour samples were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was ORR assessed by ICR based on RECIST v1.1. Overall survival (OS) was a key secondary endpoint. PFS, DOR, and confirmed ORR were additional secondary outcome measures.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 188 patients, the median age was 66 years (range 28 to 82); 76% were male; 100% were Asian. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH-positive; 65% had inoperable advanced cancer; 35% had post-operative recurrent cancer; 54% had liver metastases; 29% had lung metastases; the sum of diameters of target lesions was <5 cm in 47%, ≥5 to <10 cm in 30%, and ≥10 cm in 17%; 55 % had two and 45% had three or more prior regimens in the locally advanced or metastatic setting.

The primary analysis demonstrated a statistically significant and clinically meaningful improvement in ORR and OS in the ENHERTU-treated group compared to the chemotherapy-treated group. Efficacy results from Destiny-Gastric-01 are summarised in Table 26 and Figure 11.

Table 26: Efficacy results in DESTINY-Gastric01 (Intent-to-Treat analysis set)

Efficacy Parameter	**Primary analysis (08 November 2019 cut-off)**	
	ENHERTU N=126	**Physician's choice of chemotherapy N=62**
Overall survival (OS)[*]		
Median, months (95% CI)[†]	12.5 (9.6, 14.3)	8.4 (6.9,10.7)
Hazard ratio (95% CI)[‡]	0.59 (0.39, 0.88)	
Stratified Log-rank p-value[‡]	p=0.0097	
Progression-free survival (PFS)[§]		
Median, months (95% CI)[†]	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)[‡]	0.47 (0.31, 0.71)	
Confirmed objective response rate (ORR)[§]		
n (%)	51 (40.5)	7 (11.3)
95% CI[¶]	(31.8, 49.6)	(4.7, 21.9)
p-value[‡,#]	p<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Stable Disease n (%)	55 (43.7)	31 (50.0)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	5 (4.0)	6 (9.7)
Duration of confirmed response (DOR)[§]		
Median, months (95% CI)[†]	11.3 (5.6, NE)	3.9 (3.0, 4.9)

CI = confidence interval; NE = not estimable

[*]OS was evaluated following a statistically significant outcome of ORR.

[†]Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method

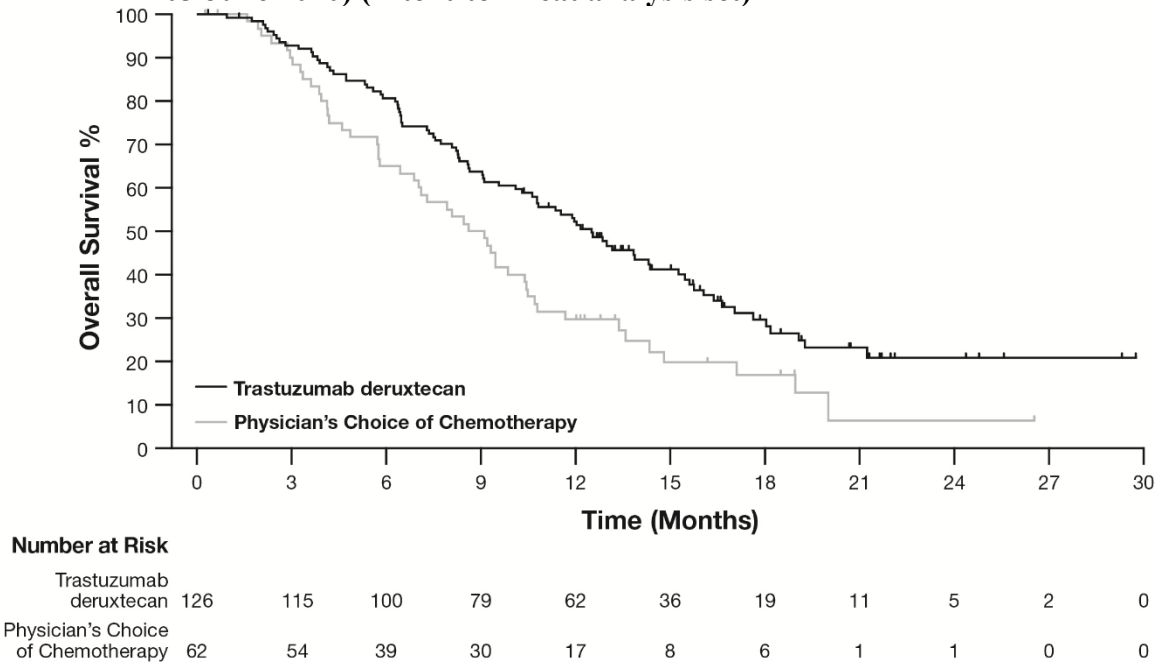
[‡]Stratified by region

[§]Assessed by independent central review

[¶]95% exact binomial confidence interval

[#]Based on the Cochran-Mantel-Haenszel test

Figure 11: Kaplan-Meier plot of overall survival at a subsequent analysis (data cut-off 03 June 2020) (Intent-to-Treat analysis set)



Number at Risk											
Trastuzumab deruxtecan	126	115	100	79	62	36	19	11	5	2	0
Physician's Choice of Chemotherapy	62	54	39	30	17	8	6	1	1	0	0

DESTINY-Gastric02

The efficacy and safety of ENHERTU were also described in DESTINY-Gastric02, a Phase 2, multicentre, open-label, single-arm study conducted at sites in Europe and the United States. The study enrolled patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on a prior anti-HER2-based regimen. Patients were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. ENHERTU was administered by intravenous infusion at 6.4 mg/kg every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed ORR assessed by ICR based on RECIST v1.1. DOR, PFS, and OS were secondary endpoints.

Of the 79 patients enrolled in DESTINY-Gastric02, demographic and baseline disease characteristics were: median age 61 years (range 20 to 78); 72% were male; 87% were White, 5.0% were Asian, and 1.0% were Black or African American. Patients had an ECOG performance status of either 0 (37%) or 1 (63%); 34% had gastric adenocarcinoma and 66% had GEJ adenocarcinoma; 86% were IHC 3+ and 13% were IHC 2+/ISH-positive, and 63% had liver metastases. The median number of prior regimens in the locally advanced or metastatic setting was one.

Efficacy results for ORR and DOR are summarised in Table 27.

Noting the limitations of external comparisons, PFS (median 5.6 months [95% CI: 4.2, 8.3]) and OS (median 12.1 months [95% CI: 9.4, 15.4]) in this DESTINY-Gastric02 population, who were enrolled from Europe and the United States, appeared similar to those reported amongst patients in the ENHERTU arm of the DESTINY-Gastric01 study population, who were enrolled from Japan and South Korea.

Table 27: Efficacy results in DESTINY-Gastric02 (Full Analysis Set*)[#]

Efficacy parameter	DESTINY-Gastric02 N=79
Confirmed objective response rate (ORR)[†] % (95% CI)[‡]	41.8 (30.8, 53.4)
Complete response n (%)	4 (5.1)
Partial response n (%)	29 (36.7)
Stable disease n (%)	31 (39.2)
Progressive disease n (%)	13 (16.5)
Not evaluable n (%)	2 (2.5)
Duration of response (DOR) Median§, months (95% CI)[¶]	8.1 (5.9, NE)

*Includes all patients who received at least one dose of ENHERTU

#Data cut-off date: 08 November 2021

†Assessed by independent central review

‡Calculated using Clopper-Pearson method

§Based on Kaplan-Meier estimate

¶Calculated using the Brookmeyer and Crowley method

Other unresectable or metastatic solid tumours

The efficacy and safety of ENHERTU were evaluated in adult patients with previously treated unresectable or metastatic HER2-positive solid tumours who were enrolled in one of three Phase 2, multicentre, studies: DESTINY-PanTumour02, DESTINY-Lung01, and DESTINY-CRC02.

DESTINY-PanTumour02

DESTINY-PanTumour02 was a Phase 2, multicentre, open-label study that enrolled 267 adult patients with locally advanced, unresectable, or metastatic HER2-expressing (IHC3+, IHC2+) solid tumours who have progressed following at least one prior systemic regimen or who have no satisfactory alternative treatment option.

Patients received ENHERTU 5.4 mg/kg by intravenous infusion every three weeks. 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 and symptomatic brain metastases or ECOG performance status >1.

Efficacy was assessed in the subgroup of patients (N=111) with HER2-positive (IHC 3+ by either local or central assessment) solid tumours. The primary efficacy outcome measure was confirmed objective response rate (ORR) and secondary efficacy outcome measures were duration of response (DOR), progression-free survival (PFS) and overall survival (OS). All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

Of the 111 patients in the HER2-positive (IHC3+) subgroup enrolled in DESTINY-PanTumour02, demographic and baseline disease characteristics were: median age 64 years (range 23 to 85); 60 % were female; 58 % were White, 34 % were Asian, and 4 % were Black or African American. Patients had an ECOG performance status of either 0 (49%) or 1 (51 %) at baseline. The median number of prior regimens was 2.

Efficacy results for HER2-positive (IHC3+) solid tumours are summarised in Table 28 and Table 29.

DESTINY-Lung01

DESTINY-Lung01 was a Phase 2, multicentre, open-label, 2-cohort study that enrolled 181 patients with previously treated, unresectable or metastatic, HER2-expressing (IHC3+ or IHC2+) or HER2-mutant non-small cell lung cancer (NSCLC). Patients received ENHERTU 5.4 mg/kg by intravenous infusion every three weeks. 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 and symptomatic brain metastases or ECOG performance status >1.

Efficacy was assessed in the subgroup of patients (N=17) with HER2-positive (IHC3+) non-small cell lung cancer. The primary efficacy outcome measure was confirmed objective response rate (ORR) and a key secondary efficacy outcome measure was duration of response (DOR). Progression-free survival (PFS) and overall survival (OS) were additional secondary endpoints. All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

Of the 17 patients in the HER2-positive (IHC3+) subgroup, demographic and baseline disease characteristics were: median age 59 years (range 31 to 74); 58.8 % were male; 64.7 % were White, 17.6 % were Asian, and 11.8 % were Black or African American. Patients had an ECOG performance status of either 0 (11.8 %) or 1 (88.2 %) at baseline. The median number of prior regimens was 3.

Efficacy results are summarised in Table 28 and Table 29.

DESTINY-CRC02

DESTINY-CRC02 was a Phase 2, multicentre, randomised, 2-arm study that enrolled 122 patients with previously treated, unresectable or metastatic HER2-expressing (IHC3+ or IHC2+/ISH+) colorectal cancer (CRC). Patients received ENHERTU 5.4 mg/kg by intravenous infusion every three weeks. 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 and symptomatic brain metastases or ECOG performance status >1.

Efficacy was assessed in the subgroup of patients (N=64) with HER2-positive (IHC3+) CRC. The primary efficacy outcome measure was confirmed objective response rate (ORR) and a key secondary efficacy outcome measure was duration of response (DOR). Progression-free survival (PFS) and overall survival (OS) were additional secondary endpoints. All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

Of the 64 patients in the HER2-positive (IHC3+) subgroup, demographic and baseline disease characteristics were: median age 58 years (range 25 to 78); 53.1% were male; 54.7 % were Asian, and 40.6% were White. Patients had an ECOG performance status of either 0 (57.8%) or 1 (42.2%) at baseline. The median number of prior regimens was 4.

Efficacy results are summarised in Table 28 and Table 29.

Table 28: Efficacy results in HER2-positive (IHC3+) Patients in DESTINY-PanTumour02, DESTINY-Lung01, and DESTINY-CRC02

Efficacy Parameter	DESTINY-PanTumour02 N=111	DESTINY-Lung01 N=17	DESTINY-CRC02 N=64
Confirmed Objective Response Rate[†]			
n (%)	57 (51.4)	9 (52.9)	30 (46.9)
95% CI[‡]	(41.7, 61.0)	(27.8, 77.0)	(34.3, 59.8)
Complete Response, n (%)	3 (2.7)	1 (5.9)	0 (0)
Partial Response, n (%)	54 (48.6)	8 (47.1)	30 (46.9)
Duration of Response			
Median[§], months (95% CI)	19.4 (10.0, NE)	6.9 (4.0, 9.8)	5.5 (4.2, 8.1)
Progression-free Survival			
Number of events (%)	65 (58.6)	13 (76.5)	39 (60.9)
Median§, months (95% CI)[*]	10.1 (7.0, 14.2)	7.5 (3.1, 11.0)	7.0 (5.7, 8.2)
Overall Survival			
Number of events (%)	66 (59.5)	10 (58.8)	16 (25.0)
Median§, months (95% CI)[*]	17.7 (12.8, 21.8)	12.5 (9.3, NE)	15.1 (12.6, NE)
Survival at 12 months (95% CI)[*]	63.3 (53.5, 71.6)	50.2% (24.7, 71.2)	80.3% (66.4, 88.9)

CI = Confidence interval, NE = Not estimable

[†]Assessed by independent central review

[‡]CI is derived based on the Clopper-Pearson method

[*] CI is derived based on the Brookmeyer-Crowley method

[§]Calculated using the Kaplan-Meier technique

Table 29: Efficacy results in HER2-positive (IHC3+) patients by tumour type in DESTINY-PanTumour02, DESTINY-Lung01, and DESTINY-CRC02

Tumour Type	Patients N	Confirmed ORR[†] % (95% CI) [‡]	DOR Median[§], months (95% CI) [‡]
Colorectal cancer	64	46.9 (34.3, 59.8)	5.5 (4.2, 8.1)
Bladder Cancer	27	37.0 (19.4, 57.6)	5.7 (4.1, 10.0)
Biliary Tract Cancer	22	45.5 (24.4, 67.8)	10.9 (2.1, NE)
NSCLC	17	52.9 (27.8, 77.0)	6.9 (4.0, 9.8)
Endometrial Cancer	16	56.3 (29.9, 80.2)	NR (5.8, NE)
Ovarian Cancer	15	66.7 (38.4, 88.2)	NR (5.1, NE)
Cervical Cancer	10	70.0 (34.8, 93.3)	NR (9.3, NE)
Salivary Gland Cancer	9	66.7 (29.9, 92.5)	20.1 (5.6, NE)
Pancreatic Cancer	5	0 (0, 52.2)	NA
Oropharyngeal Neoplasm	1	100 (2.5, 100)	NE
Vulvar Cancer	1	100 (2.5, 100)	2.6*
Extramammary Paget's Disease	1	100 (2.5, 100)	19.4*

Tumour Type	Patients N	Confirmed ORR† % (95% CI) ‡	DOR Median§, months (95% CI) ‡
Lacrimal Gland Cancer	1	100 (2.5, 100)	NE
Lip and/or Oral Cavity Cancer	1	0 (0, 97.5)	NE
Esophageal Adenocarcinoma	1	100 (2.5, 100)	2.8*
Esophageal Squamous Cell Carcinoma	1	0 (0, 97.5)	NE

CI = Confidence interval, NE = Not estimable, NR = Not reached, NA = not applicable

†Assessed by independent central review

‡CI is derived based on the Clopper-Pearson method

§Calculated using the Kaplan-Meier technique

*Observed value for individual patient

Unresectable or metastatic NSCLC

ENHERTU was evaluated in DESTINY-Lung01 and at two dose levels in DESTINY-Lung02. The recommended dose of 5.4 mg/kg intravenously every 3 weeks in DESTINY-Lung02 is described below.

The efficacy and safety of ENHERTU were evaluated in DESTINY-Lung02, a Phase 2, randomised, 2-arm, multicentre study. The study included adult patients with HER2-mutated unresectable or metastatic NSCLC who had received at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy drug. Patients were selected for treatment with ENHERTU based on local laboratory testing which documented the presence of activating HER2 (ERBB2) mutations in a tumour tissue specimen. Patients were randomised 2:1 to receive ENHERTU 5.4 mg/kg or 6.4 mg/kg every 3 weeks, respectively. Randomisation was stratified by prior anti-programmed cell death receptor-1 (PD-1) and/or anti-programmed cell death ligand 1 (PD-L1) treatment versus those who received neither. 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 and symptomatic brain metastases or ECOG performance status >1.

The major efficacy outcome was confirmed ORR as assessed by BICR using RECIST v1.1. DOR, PFS, and OS were secondary outcome measures.

Demographic and baseline disease characteristics were: median age 59.4 years (range 31 to 84); female (63.7%); Asian (63.7%), White (22.5%), or Other (13.7%); ECOG performance status 0 (28.4%) or 1 (71.6%); 97.1% had a mutation in the ERBB2 kinase domain, 2.9% in the extracellular domain; 34.3% had stable brain metastases; 46.1% were former smokers, none were current smokers; 21.6% had a prior lung resection. In the metastatic setting, 32.4% had greater than 2 prior systemic therapies, 100% had received platinum-based therapy, 73.5% had received anti-PD-1/PD-L1 therapy, and 50.0% had prior treatment with platinum therapy and anti-PD-1/PD-L1 therapy in combination.

Efficacy results are summarised in Table 30. The median time to initial response was 1.8 months (range 1.2 to 7.0 months).

Table 30: Efficacy results in DESTINY-Lung02

Efficacy Parameter	DESTINY-Lung02 5.4 mg/kg N=102
Confirmed Objective Response Rate	
n (%)	50 (49.0)
(95% CI)*	39.0, 59.1
Complete Response n (%)	1 (1.0)
Partial Response	49 (48.0)
Duration of Response Median, months (95% CI)†	16.8 (6.4, NE)

*ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval, NE = not estimable

†95% CI calculated using Brookmeyer-Crowley method

5.2 PHARMACOKINETIC PROPERTIES

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 metabolised mainly by CYP3A4 via oxidative pathways and does not undergo significant metabolism by UGT or other CYP enzymes.

Excretion

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients across multiple tumour types, 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 median elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was 5.4 - 5.7 days and apparent median $t_{1/2}$ of released topoisomerase I inhibitor was approximately 5.4 - 6.1 days. Moderate accumulation of trastuzumab deruxtecan was observed at the 5.4 mg/kg and 6.4 mg/kg doses (approximately 35% - 39% in cycle 3 compared to cycle 1). In patients with locally advanced or metastatic gastric or GEJ adenocarcinoma, trastuzumab deruxtecan clearance was approximately 20% higher than in patients with metastatic HER2-positive breast cancer.

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 weigh

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, protected from light.

Diluted Solution

It is recommended that the diluted solution be used immediately. If not used immediately, the reconstituted solution diluted in infusion bags containing 5% dextrose solution may be stored 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.

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

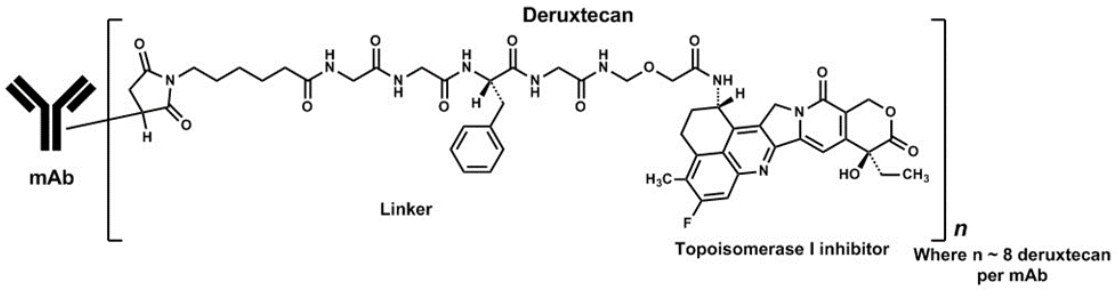


Figure 12 General structure of trastuzumab deruxtecan

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

23 September 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	Addition of indication for patients with HER2-positive breast cancer who have residual invasive disease after neoadjuvant HER2-targeted treatment
4.2	Editorial changes with additional dosage reduction recommendations Updates to patient selection for HER2-positive cancers
4.4	Updates to Interstitial Lung Disease/Pneumonitis
4.8	Update to breast cancer pool based on additional study results
5.1	Updates to efficacy data to include DESTINY-Breast05

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