PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrENHERTU®

Trastuzumab deruxtecan for injection

Powder for concentrate for solution for infusion, 100 mg, Intravenous infusion

Professed

Antineoplastic Agent (L01FD04)

Enhertu (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Enhertu, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

Enhertu (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable or metastatic human epidermal growth factor 2 (HER2)-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1),
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy, and
- the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy,

have been issued market authorization without conditions.

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

1 Indications	12/2024
3 Serious Warnings and Precautions Box	01/2023
4 Dosage and Administration, 4.1 Dosing Considerations	12/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	12/2024
7 Warnings and Precautions, Cardiovascular	12/2024
7 Warnings and Precautions, Hematologic	12/2024
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7 Warnings and Precautions, 7.1.4 Geriatrics	12/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HER2-Positive Breast Cancer

ENHERTU (trastuzumab deruxtecan for injection) as monotherapy is indicated for:

- the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received at least one prior anti-HER2-based regimen either
  - in the metastatic setting, or
  - in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy.

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1).

HER2-Low Breast Cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received at least one prior line of 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 have received at least one and be no longer considered eligible for endocrine therapy.

HER2-Positive Gastric and Gastroesophageal Junction Cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

1.1 Pediatrics dosage

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No clinically relevant differences in efficacy were observed between patients ≥65 years and those younger than 65 years. Evidence from clinical studies suggests the use in the geriatric population is associated with differences in safety. See 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

Enhertu (trastuzumab deruxtecan) is contraindicated in patients who are hypersensitive to this

drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with Enhertu (trastuzumab deruxtecan). ILD was more frequently reported in patients with moderate renal impairment in clinical trials. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue Enhertu in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms (see 4.2 Recommended Dose and Dosage Adjustment and 7 WARNINGS AND PRECAUTIONS).
- Embryo-Fetal Toxicity: Exposure to Enhertu during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, 7.1 Special Populations).
- There is a risk of medication errors between Enhertu (trastuzumab deruxtecan) and trastuzumab or trastuzumab emtansine. See 4.1 Dosing Considerations.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

There is a risk of medication errors between Enhertu (trastuzumab deruxtecan) and trastuzumab or trastuzumab emtansine. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

HER2-Positive Breast Cancer

Enhertu should only be used in patients with documented HER2-positive tumour status (see 14 CLINICAL TRIALS).

HER2-Low Breast Cancer

Enhertu should only be used in patients with documented HER2-low tumour status (immunohistochemistry [IHC] 1+ or IHC 2+ / in-situ hybridization [ISH] negative tumour status) based on validated assays (see 14 CLINICAL TRIALS).

HER2-Positive Gastric and Gastroesophageal Junction Cancer

Enhertu should only be used in patients with documented HER2-positive tumour status (see 14 CLINICAL TRIALS).

Premedication

Enhertu is emetogenic, which includes delayed nausea and/or vomiting (see 8 ADVERSE REACTIONS). 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 per institutional guidelines.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Metastatic Breast Cancer

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Unresectable Locally Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer

The recommended dose of Enhertu is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Dosage Adjustment

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

Table 2.

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

Table 1 Dose Reduction Schedule

Dose Reduction Schedule	Breast Cancer	Gastric/GEJ Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
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 2 Dose Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Treatment Modification
Interstitial Lung Disease (ILD)/ pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt Enhertu until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose.

Adverse Reaction	Severity[a]		Treatment Modification
			• if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see 7 WARNINGS AND PRECAUTIONS).
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		• Permanently discontinue Enhertu. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see 7 WARNINGS AND PRECAUTIONS).
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)		• Interrupt Enhertu until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 x 10^9/L)		• Interrupt Enhertu until resolved to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile Neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.		• Interrupt Enhertu until resolved. • Reduce dose by one level (see Table 1).
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)		• Interrupt Enhertu until resolved to Grade 1 or less, then maintain dose
	Grade 4 (platelets less than 25 x 10^9/L)		• Interrupt Enhertu until resolved to Grade 1 or less. • Reduce dose by one level (see Table 1)
Left Ventricular Ejection Fraction (LVEF) Decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with Enhertu.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease from	• Interrupt Enhertu.

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

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

Special Populations

Pediatrics (<18 years of age): 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 pediatric population.

Geriatrics (≥65 years of age): No dose adjustment of Enhertu is required in patients aged 65 years or older.

Renal Impairment: No dose adjustment is required in patients with mild (creatinine clearance [CrCL] ≥60 and <90 mL/min) or moderate (CrCL ≥30 and <60 mL/min) renal impairment at baseline. A higher incidence of adverse events leading to dosage discontinuation (including ILD) has been observed in patients with moderate renal impairment. Patients with moderate renal impairment should be monitored carefully for adverse reactions including ILD/pneumonitis (see 7 WARNINGS AND PRECAUTIONS, Respiratory). Limited data are available in patients with severe renal impairment.

Hepatic Impairment: No dose adjustment is required in patients with mild (total bilirubin ≤ upper limit of normal [ULN] and any aspartate aminotransferase [AST] >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment at baseline. There are insufficient data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment, as there was a limited number of patients enrolled in the Enhertu clinical trials. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and

any AST) hepatic impairment.

4.3 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 2°C to 8°C for up to 24 hours from the time of reconstitution, protected from light. Do not freeze (see 11 STORAGE, STABILITY AND DISPOSAL).
- The product does not contain a preservative. Discard unused Enhertu after 24 hours refrigerated.

Table 3 Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
100 mg	5 mL	5 mL	20 mg/mL

Instructions for Dilution

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

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

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Inspect the reconstituted solution for particulates and discolouration. 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**. 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 2°C to 8°C for up to 24 hours, protected from light. Do not freeze (see 11 STORAGE, STABILITY AND DISPOSAL).
- Discard any unused portion left in the vial.

4.4 Administration

Do not replace Enhertu with trastuzumab or trastuzumab emtansine.

The initial dose should be administered as a 90 minute-intravenous infusion. If the prior infusion was 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-related reactions.

Enhertu is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in line polyethersulfone (PES) or polysulfone (PS) filter. Enhertu must NOT be administered as an intravenous push or bolus.

If the prepared infusion solution was stored refrigerated (2°C to 8°C), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration protected from light.

Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

See 12 SPECIAL HANDLING INSTRUCTIONS for additional recommendations.

4.5 Missed Dose

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

5 OVERDOSAGE

There is limited information on overdose with trastuzumab deruxtecan. In clinical studies, the highest dose administered was 8.0 mg/kg. Incidence of severe adverse events appeared higher in patients administered doses higher than the recommended dose. In the event of overdose, patients should be monitored, and appropriate supportive care should be given. There is no antidote for trastuzumab deruxtecan.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Powder for concentrate for solution for	L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose

	infusion/100 mg/vial	

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cardiovascular

Left Ventricular Ejection Fraction Decrease
Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies.

Treatment with Enhertu has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

In the 1287 patients with unresectable or metastatic breast cancer who received Enhertu 5.4 mg/kg, 53 patients (4.1%) of LVEF decrease were reported as adverse events, of which 38 (3.0%) were Grade 2 and 6 (0.5%) were Grade 3 (see 8.3 Less Common Clinical Trial Adverse Reactions). Grade 2 LVEF decrease as abnormal laboratory findings was also observed (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). No decreases of LVEF to less than 20% were observed.

Of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with Enhertu 6.4 mg/kg, LVEF decrease was reported in 15 patients (6.5%), of which 14 (6.1%) were Grade 2 and 1 (0.4%) was Grade 3 (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

LVEF should be assessed prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see 4 DOSAGE AND ADMINISTRATION, Table 2).

Driving and Operating Machinery

Enhertu may impair the ability to drive and use machines as adverse reactions including fatigue, headache and dizziness have been reported. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Anemia/Thrombocytopenia

In patients with gastric cancer treated with Enhertu 6.4 mg/kg (n = 229), 25.3% (58/229) received a transfusion within 28 days after onset of anemia or thrombocytopenia. Transfusions were primarily for anemia.

Neutropenia
Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of Enhertu.

Of the 1287 patients with unresectable or metastatic breast cancer who received Enhertu

5.4 mg/kg, a decrease in neutrophil count was reported in 460 (35.7%) patients and 225 (17.5%) patients had Grade 3 or 4 events. Febrile neutropenia was reported in 0.9% of patients (see 8 ADVERSE REACTIONS).

Of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with Enhertu 6.4 mg/kg a decrease in neutrophil count was reported in 103 (45.0%) patients. Grade 3 or 4 events were reported in 77 (33.6%) patients. Febrile neutropenia was reported in 3.9% of patients (see 8 ADVERSE REACTIONS).

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 4 DOSAGE AND ADMINISTRATION, Table 2).

Immune

Infusion-Related Reactions
Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity were reported in clinical studies of Enhertu (see 8.3 Less Common Clinical Trial Adverse Reactions). Enhertu has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Patients should be monitored for IRRs. Enhertu may require dose interruption or discontinuation, based on the severity of the IRR (see 4 DOSAGE AND ADMINISTRATION).

Race

In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different ethnic groups. Asian patients (154 (67.2%) subjects in pool) with gastric cancer receiving Enhertu 6.4 mg/kg had a higher incidence (≥10% difference) of neutropenia (62.3% vs. 23.0%), anaemia (57.1% vs. 33.8%), leukopenia (40.3% vs. 6.8%), thrombocytopenia (41.6% vs. 20.3%) and lymphopenia (21.4% vs. 5.4%) compared to non-Asian patients (74 (32.3%) subjects in pool). In Asian patients, 4.5% experienced a bleeding event within 14 days after onset of thrombocytopenia compared to 1.4% of non-Asian patients. A total of 49 (31.8%) of Asian patients received a transfusion within 28 days after onset of anemia or thrombocytopenia compared to 9 (12.2%) of non-Asian patients.

Reproductive Health: Female and Male Potential

Fertility
No fertility studies in women and men have been conducted with Enhertu. Based on results from animal toxicity studies, Enhertu may impair male reproductive function and fertility (see 16 NON-CLINICAL TOXICOLOGY).

Teratogenic Risk
Enhertu can cause fetal harm when administered to a pregnant woman. Exposure to Enhertu to a pregnant woman should be avoided (see 7.1.1 Pregnant Women).

Pregnancy status of females of reproductive potential should be verified prior to initiation of Enhertu (see 7.1 Special Populations).

Female patients of reproductive potential should be informed of the potential risks to the fetus. Female patients of reproductive potential should be advised to use effective contraception during treatment with Enhertu and for at least 7 months following the last dose (see 7.1 Special Populations).

Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Enhertu and for at least 4 months following the last dose.

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

Respiratory

Interstitial Lung Disease/ Pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see 8 ADVERSE REACTIONS). Fatal outcomes have been observed.

ILD was more frequently reported in patients with moderate renal impairment (CrCL ≥30 and <60 mL/min) at baseline (see 8.2 Clinical Trial Adverse Reactions, Interstitial Lung Disease/ Pneumonitis).

In clinical studies, of the 1287 patients with unresectable or metastatic breast cancer treated with Enhertu 5.4 mg/kg, adjudicated drug-related ILD occurred in 165 (12.8%) patients as determined by independent review. Most ILD cases were Grade 1 (3.3%) or Grade 2 (7.6%). Grade 3 events occurred in 0.9% of patients. Grade 5 events occurred in 1.0% of patients. Median time to first onset was 5.8 months (range: 0.9 to 31.5).

In clinical studies, of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with Enhertu 6.4 mg/kg, ILD occurred in 25 (10.9%) of patients as determined by independent review; 7.3% of patients were aged <65 years (8/109) and 14.2% of patients were aged ≥65 years (17/120). Most ILD cases were Grade 1 (2.6%) and Grade 2 (6.6%). Grade 3 cases occurred in 0.9% and Grade 4 in 0.4% of patients. One (0.4%) Grade 5 event occurred. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Patients should be advised to immediately report cough, dyspnea, 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 should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. >0.5 mg/kg/day prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see 4 DOSAGE AND ADMINISTRATION). 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 4 DOSAGE AND ADMINISTRATION). Patients with a history of ILD/pneumonitis or patients with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see 4 DOSAGE AND

ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

Enhertu can cause fetal harm when administered to a pregnant woman. There are no available data on the use of Enhertu in pregnant women. However, in post marketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu can also cause embryo fetal harm when administered to a pregnant woman (see 16 NON-CLINICAL TOXICOLOGY).

Enhertu should not be administered to pregnant women and patients should be informed of the potential risks to the fetus before they become pregnant. If a patient becomes pregnant during treatment with Enhertu or within 7 months following the last dose of Enhertu, the patient must immediately contact her doctor and should be apprised of the possibility of harm to the fetus. See 7 WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction for recommendations on pregnancy test and contraception.

7.1.2 Breast-feeding

There are no data regarding the presence of Enhertu in human milk. As human IgG is excreted in human milk, Enhertu, a humanized IgG1 conjugated to deruxtecan (see 13 PHARMACEUTICAL INFORMATION), may be excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with Enhertu. Women may begin breastfeeding 7 months after concluding treatment.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 1287 patients with unresectable or metastatic breast cancer treated with Enhertu 5.4 mg/kg, 282 (21.9%) patients were 65 years or older and 49 (3.8%) patients were 75 years or older. No overall difference in efficacy within clinical trials was observed based on age. The incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (50.4%) and younger patients (43.9%) was similar.

Of the 229 patients with gastric cancer, treated with Enhertu 6.4 mg/kg, 52.4% were 65 years or older and 10.5% were 75 years or older. The incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older was 57.5% and in younger patients was 56.9%. The incidence of serious adverse reactions leading to drug interruptions in patients 65 years or older was 7.5% compared to 2.8% in younger patients. See 7 WARNINGS AND PRECAUTIONS, Respiratory.

Population pharmacokinetic analysis indicates that age does not have an effect on the parameters of population pharmacokinetics of trastuzumab deruxtecan.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

HER2-Positive Breast Cancer

DESTINY-Breast03
The safety of Enhertu (trastuzumab deruxtecan) was evaluated in DESTINY-Breast03 in 257 patients with unresectable or metastatic HER2-positive breast cancer. The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, neutropenia, alopecia, constipation, anemia, transaminases increased, musculoskeletal pain, leukopenia, decreased appetite, diarrhea, thrombocytopenia, headache, and abdominal pain. The most common serious adverse reactions (frequency >1%) were interstitial lung disease and vomiting. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

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

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. The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, constipation, neutropenia, decreased appetite, anemia, diarrhea, musculoskeletal pain, transaminases increased, abdominal pain, thrombocytopenia, headache. Serious adverse reactions in >1% of patients who received Enhertu were interstitial lung disease, vomiting, fatigue and nausea. Fatalities due to adverse events occurred in 2.5% of patients including 2 (0.5%) patients with fatal adverse reactions of ILD.

Dose interruptions due to adverse reactions occurred in 30.7% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (15.4%), anemia (6.2%), fatigue (5.0%), leukopenia (4.0%) and thrombocytopenia (2.5%). Dose reductions occurred in 21.8% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (7.4%), nausea (5.7%), neutropenia (3.7%) and vomiting (2.5%). Discontinuation of therapy due to an adverse reaction occurred in 10.9% of patients treated with Enhertu. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (8.7%).

DESTINY-Breast01 and Study DS8201-A-J101
The safety of Enhertu was 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. The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutrophil count decreased, diarrhea, cough, leukopenia, headache and platelet count decreased (Table 7). Serious adverse reactions occurred in 20% of patients receiving Enhertu. Serious adverse reactions in >1% of patients who received Enhertu were interstitial lung disease, vomiting, nausea, and hypokalemia. Fatalities due to adverse events occurred in 5.1% of patients including interstitial lung disease (2.6%).

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

HER2-Low Breast Cancer

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-) breast cancer. The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, anemia, constipation, neutropenia, transaminases increased, decreased appetite, diarrhea, musculoskeletal pain, thrombocytopenia, and leukopenia. The most common serious adverse reactions (frequency >1%) were ILD/pneumonitis, dyspnea, musculoskeletal pain, anemia, febrile neutropenia, nausea, pyrexia, and vomiting. There were 5 (1.3%) patients with adverse reactions leading to death, 3 attributed to ILD (0.8%) and 1 (0.3%) each for dyspnea and febrile neutropenia.

Dose interruptions due to adverse reactions occurred in 26% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (9.2%), fatigue (5.1%), anemia (4.6%), leukopenia (3.5%), ILD/pneumonitis (3.0%), transaminases increased (3.0%), and blood bilirubin increased (2.2%). Dose reductions occurred in 20% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (4.6%), nausea (4.6%), thrombocytopenia (3.5%), and neutropenia (3.0%). Discontinuation of therapy due to an adverse reaction occurred in 11% of patients treated with Enhertu. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (8.4%).

HER2-Positive Gastric and Gastroesophageal Junction Cancer

The safety of Enhertu 6.4 mg/kg was evaluated in a pooled analysis of 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 (N=125), DESTINY-Gastric02 (N=79) and DS8201-A-J101 (Gastric Cancer cohort, N=25).

In the pooled studies, the most common adverse reactions in patients treated with Enhertu 6.4 mg/kg (frequency ≥20%) were nausea (65.5%), decreased appetite (54.1%), fatigue (52.8%), neutropenia (49.3%), anemia (49.3%), thrombocytopenia (34.5%), vomiting (32.3%),

diarrhea (32.3%), leukopenia (29.3%), constipation (25.8%), alopecia (22.3%), and pyrexia (20.5%). The most common serious adverse reactions (frequency >1%) were decreased appetite (7.0%), ILD (3.9%), pneumonia (3.9%), nausea (2.2%), vomiting (1.7%), dehydration (1.7%), anemia (1.7%), diarrhea (1.3%), abdominal pain (1.3%), and pyrexia (1.3%). There were 2 (0.9%) patients with adverse reactions leading to death, one each attributed to ILD and pneumonia.

Dose interruptions due to adverse reactions occurred in 39.3% of patients treated with 6.4 mg/kg of Enhertu. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (17.9%), anemia (8.3%), decreased appetite (7.0%), leukopenia (5.2%), fatigue (4.4%), ILD (3.5%), pneumonia (3.5%), thrombocytopenia (2.6%), and upper respiratory tract infection (2.2%). Dose reductions occurred in 27.5% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (9.2%), decreased appetite (8.3%), nausea (6.6%), fatigue (5.7%), and febrile neutropenia (2.2%). Discontinuation of therapy due to an adverse reaction occurred in 11.4% of patients treated with Enhertu. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (6.6%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse reactions in real-world use.

HER2-Positive Breast Cancer

DESTINY-Breast03
The safety of Enhertu was evaluated in DESTINY-Breast03 in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of Enhertu 5.4 mg/kg in DESTINY-Breast03. 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. Table 5 lists adverse reactions reported in the study.

Table 5 Common Adverse Reactions (≥1% All Grades) reported in Patients Treated with Enhertu in DESTINY-Breast03

System Organ Class	Enhertu 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	Any Grade n (%)	Grade 3-4 n (%)**	Any Grade n (%)	Grade 3-4 n (%)**
Blood and Lymphatic System Disorders				
Neutropenia[a]	110 (43)	49 (19)	31 (12)	8 (3)
Anemia[b]	84 (33)	19 (7)	45 (17)	15 (6)

System Organ Class	Enhertu 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	Any Grade n (%)	Grade 3-4 n (%)**	Any Grade n (%)	Grade 3-4 n (%)**
Leukopenia[c]	78 (30)	17 (7)	22 (8)	1 (0.4)
Thrombocytopenia[d]	66 (26)	19 (7)	139 (53)	67 (26)
Lymphopenia[e]	29 (11)	10 (4)	9 (3)	3 (1)
Cardiac Disorders				
Ejection fraction decrease	6 (2)	0	1 (0.4)	0
Eye Disorders				
Vision blurred	9 (4)	0	3 (1)	0
Gastrointestinal Disorders				
Nausea	195 (76)	17 (7)	79 (30)	1 (0.4)
Vomiting	126 (49)	4 (2)	26 (10*)	2 (0.8)
Constipation	88 (34)	0	51 (20)	0
Diarrhea	75 (29)	3 (1)	18 (7)	1 (0.4)
Abdominal pain[f]	54 (21)	2 (0.8)	20 (8)	1 (0.4)
Stomatitis[g]	51 (20)	2 (0.8)	14 (5)	0
Dyspepsia	29 (11)	0	16 (6)	0
General Disorders and Administration Site Conditions				
Fatigue[h]	127 (49)	15 (6)	91 (35)	2 (0.8)
Hepatobiliary Disorders				
Transaminases increased[i]	81 (32)	6 (2)	121 (46)	20 (8)
Infections and Infestations				
Respiratory Infections[j]	56 (22)	2 (0.8)	32 (12)	3 (1)
Injury, Poisoning and Procedural Complications				
Infusion-related reactions[k]	6 (2)	0	7 (3.0)	0
Investigations				
Weight decreased	43 (17)	3 (1)	16 (6)	1 (0.4)
Blood alkaline phosphatase increased	35 (14)	1 (0.4)	30 (11)	0
Metabolism and Nutrition Disorders				

System Organ Class	Enhertu 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	Any Grade n (%)	Grade 3-4 n (%)**	Any Grade n (%)	Grade 3-4 n (%)**
Decreased appetite	75 (29)	4 (2)	44 (17)	1 (0.4)
Hypokalemia[l]	33 (13)	9 (4)	26 (10*)	2 (0.8)
Dehydration	11 (4)	1 (0.4)	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[m]	80 (31)	3 (1)	66 (25)	1 (0.4)
Nervous System Disorders				
Headache[m]	56 (22)	1 (0.4)	42 (16)	0
Peripheral neuropathy[o]	33 (13)	1 (0.4)	37 (14)	1 (0.4)
Dizziness	32 (12)	1 (0.4)	22 (8)	0
Dysgeusia	15 (6)	0	8 (3)	0
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	29 (11)	0	42 (16)	1 (0.4)
Cough	27 (11)	1 (0.4)	26 (10*)	0
Interstitial lung disease[p]	27 (11)	2 (0.8)	5 (2)	0
Dyspnea	21 (8)	1 (0.4)	13 (5)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	95 (37)	1 (0.4)	8 (3)	0
Pruritus	21 (8)	0	18 (7)	1 (0.4)
Rash[q]	20 (8)	0	27 (10)	0
Skin hyperpigmentation[r]	15 (6)	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
*Actual number prior to rounding = 9.96
**No Grade 5 adverse reactions were reported in either arm
[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of anemia includes PTs of anemia, hemoglobin 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 abdominal pain includes PTs of abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.
[g] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.
[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, and hepatic function abnormal.
[j] Grouped term includes PTs of respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection.
[k] Grouped term includes PTs of hypersensitivity, infusion-related reactions.
[l] Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.
[m] 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.
[n] Grouped term of headache includes headache and migraine.
[o] Grouped term includes PTs of neuropathy peripheral, peripheral sensory neuropathy, and paresthesia.
[p] Interstitial lung disease includes events that were adjudicated as ILD for Enhertu: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism. Grade 1, Grade 2 and Grade 3 events were reported in 2.7%,7.0% and 0.8% of patients in the Enhertu arm, respectively. No Grade 4 or Grade 5 adjudicated drug-related ILD events were reported in either arm.
[q] Grouped term of rash includes PTs of rash, rash pustular and rash maculo-papular.
[r] Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discolouration, and pigmentation disorder.

DESTINY-Breast02

The safety of Enhertu was evaluated in DESTINY-Breast02 in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of Enhertu 5.4 mg/kg. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the Enhertu group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group. Table 6 lists adverse reactions reported in the study.

Table 6 Common Adverse Reactions (≥1% All Grades) reported in Patients Treated with Enhertu in DESTINY-Breast02

System Organ Class	Enhertu 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Neutropenia[a]	137 (34)	71 (18)	23 (12)	8 (4)
Anemia[b]	118 (29)	33 (8)	27 (14)	6 (3)
Thrombocytopenia[c]	87 (22)	8 (2)	23 (12)	4 (2)
Leukopenia[d]	79 (20)	27 (7)	12 (6)	0
Lymphopenia[e]	50 (12)	19 (5)	6 (3)	2 (1)
Cardiac Disorders				
Ejection fraction decrease	17 (4)	2 (0.5)	1 (0.5)	0
Eye Disorders				

System Organ Class	Enhertu 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Dry eye	23 (6)	1 (0.3)	9 (5)	0
Vision blurred[f]	12 (3)	0	2 (1)	0
Gastrointestinal Disorders				
Nausea	293 (73)	27 (7)	73 (37)	5 (3)
Vomiting	152 (38)	15 (4)	25 (13)	2 (1)
Constipation	142 (35)	1 (0.3)	21 (11)	1 (0.5)
Diarrhea	109 (27)	11 (3)	105 (54)	14 (7)
Abdominal pain[g]	88 (22)	4 (1)	39 (20)	4 (2)
Dyspepsia	48 (12)	0	18 (9)	0
Stomatitis[h]	47 (12)	4 (1)	40 (21)	2 (1)
General Disorders and Administration Site Conditions				
Fatigue[i]	249 (62)	38 (9)	72 (37)	2 (1)
Hepatobiliary Disorders				
Transaminases increased[j]	93 (23)	10 (2)	29 (15)	3 (2)
Injury, poisoning and procedural complications				
Infusion related reaction[k]	5 (1)	0	3 (2)	0
Investigations				
Weight decreased	71 (18)	1 (0.3)	7 (4)	0
Blood bilirubin increased[l]	31 (8)	2 (0.5)	25 (13)	3 (2)
Blood alkaline phosphatase increased	24 (6)	1 (0.3)	8 (4)	0
Blood creatinine increased	8 (2)	0	1 (0.5)	0
Metabolism and Nutrition Disorders				
Decreased appetite	125 (31)	7 (2)	35 (18)	1 (0.5)
Hypokalemia[m]	33 (8)	12 (3)	13 (7)	5 (3)
Dehydration	11 (3)	3 (0.7)	3 (2)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[n]	101 (25)	3 (1)	35 (18)	1 (0.5)

System Organ Class	Enhertu 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Nervous System Disorders				
Headache[o]	82 (20)	1 (0.3)	12 (6)	0
Dizziness	33 (8)	1 (0.3)	13 (7)	0
Dysgeusia	33 (8)	0	12 (6)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	53 (13)	0	20 (10)	0
Interstitial lung disease[p]	42 (10)	3 (0.7)	1 (0.5)	1 (0.5)
Dyspnea	34 (8)	1 (0.3)	32 (16)	0
Epistaxis	33 (8)	0	8 (4)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	150 (37)	1 (0.3)	8 (4)	0
Rash[q]	34 (8)	0	32 (16)	0
Pruritus	22 (6)	0	8 (4)	0
Skin hyperpigmentation[r]	21 (5)	0	8 (4)	0

CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; MedDRA = Medical Dictionary for Regulatory Activities, version 25.0; PT = preferred term

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

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

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

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

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

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

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

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

[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 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 blood bilirubin increased includes PTs of Blood bilirubin increased, Hyperbilirubinemia, Bilirubin conjugated increased, and Blood bilirubin unconjugated increased.

[m] Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.

[n] 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

[o] Grouped term of headache includes PTs of headache and migraine.

[p] Grouped term of interstitial lung disease includes events that were adjudicated as drug-related ILD: interstitial lung disease, pneumonitis, lung disorder, pneumonia, idiopathic interstitial pneumonia, pulmonary toxicity, acute interstitial pneumonia and organizing pneumonia.
[q] Group term of rash includes PTs of Rash, Rash pustular, Rash maculo-papular, Rash papular, Rash macular, and Rash pruritic.
[r] Group term of skin hyperpigmentation includes PTs of Skin hyperpigmentation, Skin discolouration, and Pigmentation disorder.

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 (see 14 CLINICAL TRIALS). The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Table 7 lists adverse reactions, with incidences regardless of investigators assessment of causality, reported in this patient population.

Table 7 Common Adverse Reactions (≥ 10% All Grades or ≥ 2% Grades 3 or 4) Reported in DESTINY-Breast01 and DS8201-A-J101

System Organ Class[a]	Enhertu 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Blood and Lymphatic System Disorders		
Anemia[b]	79 (34)	21 (9)
Neutropenia[c]	76 (32)	44 (19)
Thrombocytopenia[d]	54 (23)	10 (4)
Leukopenia[e]	48 (21)	13 (6)
Lymphopenia[f]	26 (11)	12 (5)
Eye disorders		
Dry eye	27 (12)	1 (0.4)
Gastrointestinal Disorders		
Nausea	187 (80)	16 (7)
Vomiting	114 (49)	10 (4)
Constipation	84 (36)	2 (0.9)
Diarrhea	72 (31)	6 (3)
Abdominal Pain[g]	46 (20)	3 (1)
Stomatitis[h]	35 (15)	2 (0.9)
Dyspepsia	33 (14)	0

System Organ Class[a]	Enhertu 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
General Disorders and Administration Site Conditions		
Fatigue[i]	141 (60)	15 (6)
Infections and infestations		
Upper respiratory tract infections[j]	43 (18)	15 (6)
Investigations		
Aspartate aminotransferase increased	35 (15)	2 (0.9)
Alanine aminotransferase increased	25 (11)	3 (1)
Nervous System Disorders		
Headache[k]	47 (20)	0
Dizziness	25 (11)	0
Metabolism and Nutrition Disorders		
Decreased appetite	81 (35)	3 (1)
Hypokalemia	30 (13)	8 (3)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	50 (21)	0
Dyspnea	34 (15)	4 (2)
Epistaxis	33 (14)	0
Interstitial lung disease[l]	32 (14)	1 (0.4)
Skin and Subcutaneous Tissue Disorders		
Alopecia	108 (46)	1 (0.4)
Rash[m]	30 (13)	1 (0.4)

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

[a] Based on MedDRA version 20.1; events were graded using NCI-CTCAE version 4.03.

[b] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit 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 discomfort, gastrointestinal pain, abdominal 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 blistering.
[i] Grouped term of fatigue includes PTs of fatigue and asthenia.
[j] Upper respiratory tract infection (grouped term) includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.
[k] Grouped term of headache includes PTs of headache, sinus headache, and migraine.
[l.] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis; includes 6 (2.6%) fatal events.
[m] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

HER2-Low Breast Cancer

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-) breast cancer who received at least one dose of Enhertu 5.4 mg/kg in DESTINY-Breast04. 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. Table 8 lists adverse reactions reported in the study.

Table 8 Common Adverse Reactions (≥1% All Grades) Reported in Patients Treated with Enhertu in DESTINY-Breast04

System Organ Class[a]	Enhertu 5.4 mg/kg N=371		Chemotherapy N=172	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Anemia[b]	143 (39)	38 (10)	47 (27)	9 (5)
Neutropenia[c]	126 (34)	52 (14)	90 (52)	71 (41)
Thrombocytopenia[d]	95 (26)	22 (6)	16 (9)	1 (0.6)
Leukopenia[e]	89 (24)	25 (7)	56 (33)	33 (19)
Lymphopenia[f]	32 (9)	20 (5)	13 (8)	6 (3)
Febrile neutropenia	4 (1)	3 (0.8)	6 (3)	6 (3)
Cardiac Disorders				
Ejection fraction decreased	16 (4)	1 (0.3)	0	0
Eye Disorders				
Vision blurred[g]	18 (5)	0	5 (3)	0

System Organ Class[a]	Enhertu 5.4 mg/kg N=371		Chemotherapy N=172	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Gastrointestinal Disorders				
Nausea	282 (76)	17 (5)	52 (30)	0
Vomiting	150 (40)	6 (2)	23 (13)	0
Constipation	126 (34)	3 (0.8)	38 (22)	0
Diarrhea	100 (27)	5 (1)	38 (22)	3 (2)
Abdominal pain[h]	65 (18)	2 (0.5)	23 (13)	0
Stomatitis[i]	49 (13)	1 (0.3)	19 (11)	1 (0.6)
Abdominal distension	20 (5)	0	5 (3)	1 (0.6)
Gastritis	10 (3)	1 (0.3)	1 (0.6)	0
Flatulence	9 (2)	0	0	0
General Disorders and Administration Site Conditions				
Fatigue[j]	199 (54)	32 (9)	83 (48)	8 (5)
Pyrexia	46 (12)	1 (0.3)	22 (13)	0
Hepatobiliary Disorders				
Transaminases increased[k]	120 (32)	21 (6)	54 (31)	17 (10)
Infections and Infestations				
Upper respiratory tract infection[l]	51 (14)	1 (0.3)	9 (5)	0
Investigations				
Weight decreased	60 (16)	1 (0.3)	14 (8)	0
Blood alkaline phosphatase increased	36 (10)	1 (0.3)	5 (3)	0
Metabolism and Nutrition Disorders				
Decreased appetite	118 (32)	9 (2)	33 (19)	2 (1)
Hypokalemia[m]	41 (11)	10 (3)	13 (8)	2 (1)
Dehydration	7 (2)	1 (0.3)	2 (1)	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[n]	99 (27)	5 (1)	45 (26)	0
Nervous System Disorders				

System Organ Class[a]	Enhertu 5.4 mg/kg N=371		Chemotherapy N=172	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Headache[o]	55 (15)	1 (0.3)	11 (6)	0
Peripheral Neuropathy[p]	50 (13)	0	50 (29)	9 (5)
Dizziness[q]	39 (11)	2 (0.5)	11 (6)	0
Dysgeusia	37 (10)	0	16 (9)	1 (0.6)
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[r]	45 (12)	5 (1)	1 (0.6)	0
Epistaxis	39 (11)	0	2 (1)	0
Dyspnea	38 (10)	5 (1)	16 (9)	2 (1)
Cough	36 (10)	0	14 (8)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	147 (40)	0	57 (33)	0
Rash[s]	40 (11)	0	15 (9)	1 (0.6)
Pruritus	12 (3)	1 (0.3)	7 (4)	0
Skin hyperpigmentation[t]	10 (3)	0	1 (0.6)	0

MedDRA = Medical Dictionary for Regulatory Activities, version 24.0; PT = preferred term

[a] National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0 (NCI CTCAE v.5.0)

[b] Grouped term of anemia includes anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.

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

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

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

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

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

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

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

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

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

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

[m] Grouped term of hypokalemia includes hypokalemia and blood potassium decreased.

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

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

[p] Group term of peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia.

[q] Grouped term of dizziness includes dizziness, dizziness postural and vertigo.
[r] Interstitial lung disease includes events that were adjudicated as ILD for Enhertu: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and radiation pneumonitis. Grade 1, Grade 2 and Grade 3 events were reported in 3.5%, 6.5% and 1.3% of patients in the Enhertu arm, respectively. No Grade 4 events were reported in the Enhertu arm. Grade 5 adjudicated drug-related ILD events were in 0.8% of patients in the Enhertu arm.
[s] Grouped term of rash includes rash, rash pustular, rash maculo-papular, rash papular, rash macular, and rash pruritic.
[t] Grouped term includes skin hyperpigmentation, skin discoloration, and pigmentation disorder.

Further Information on Selected Adverse Reactions

Interstitial Lung Disease/Pneumonitis

Of the 1287 patients with unresectable or metastatic breast cancer treated with Enhertu 5.4 mg/kg, 136 (13.5%) had moderate renal impairment at baseline, and adjudicated drug-related ILD was reported in 34 (25.0%) patients in this subgroup (Grade 1 events: 4.4%; Grade 2: 16.9%; Grade 3: 0.7%; Grade 5: 2.9%), compared to 77 (11.1%) and 52 (11.6%) patients with normal renal function (n=696) and mild renal impairment (n=448), respectively. Patients with severe renal impairment (CrCL < 30 mL/min) were excluded from the clinical studies.

HER2-Positive Unresectable Locally Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer

The safety of Enhertu was evaluated in DESTINY-Gastric01 and DESTINY-Gastric02 in 204 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who received at least one dose of Enhertu 6.4 mg/kg. The median duration of treatment in DESTINY-Gastric01 was 4.6 months (range: 0.7 to 29.7) in the Enhertu group of the primary cohort. The median duration of treatment in DESTINY-Gastric02 was 4.3 months (range: 0.7 to 15.9) in the Enhertu single arm study. Table 9 lists adverse reactions in both studies.

Table 9 Common Adverse Reactions (≥1% All Grades) in Patients Treated with Enhertu in DESTINY-Gastric01 and DESTINY-Gastric02

MedDRA System Organ Class/Preferred Term or Grouped Term	DESTINY-Gastric01				DESTINY-Gastric02	
	Enhertu N=125		Physician's Choice of Chemotherapy N=62		Enhertu N=79	
	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)
Blood and Lymphatic System Disorders						
Neutropenia[b]	81 (65)	64 (51)	22 (35)	15 (24)	20 (25)	10 (13)
Anemia[c]	72 (58)	48 (38)	19 (31)	14 (23)	27 (34)	11 (14)
Leukopenia[d]	48 (38)	26 (21)	22 (35)	7 (11)	8 (10)	4 (5)
Lymphopenia[e]	29 (23)	15 (12)	2 (3)	1 (2)	4 (5)	3 (4)
Thrombocytopenia[f]	50 (40)	14 (11)	4 (6.5)	2 (3)	17 (22)	3 (4)

MedDRA System Organ Class/Preferred Term or Grouped Term	DESTINY-Gastric01				DESTINY-Gastric02	
	Enhertu N=125		Physician's Choice of Chemotherapy N=62		Enhertu N=79	
	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)
Febrile neutropenia	6 (5)	6 (5)	2 (3)	2 (3)	2 (3)	2 (3)
Gastrointestinal Disorders						
Nausea	79 (63)	7 (6)	29 (47)	1 (2)	52 (66)	6 (8)
Vomiting	33 (26)	0	5 (8)	0	33 (42)	2 (3)
Diarrhea	41 (33)	3 (2)	20 (32)	1 (2)	28 (35)	1 (1)
Abdominal pain[g]	19 (15)	1 (0.8)	9 (15)	2 (3)	16 (20)	2 (3)
Constipation	31 (25)	0	15 (24)	0	21 (27)	0
Stomatitis[h]	14 (11)	2 (2)	3 (5)	0	1 (1)	0
General Disorders and Administration Site Conditions						
Fatigue[i]	69 (55)	11 (9)	27 (44)	3 (5)	44 (56)	4 (5)
Pyrexia	31 (25)	0	10 (16)	0	8 (10)	0
Edema peripheral	14 (11)	0	0	0	4 (5)	0
Hepatobiliary Disorders						
Hepatic function abnormal	11 (9)	4 (3)	1 (2)	1 (2)	0	0
Infections and Infestations						
Upper respiratory tract infection[j]	21 (17)	1 (0.8)	8 (13)	0	1 (1)	0
Pneumonia	13 (10)	3 (2)	1 (2)	0	2 (3)	2 (3)
Injury, Poisoning and Procedural Complications						
Infusion-related reaction[k]	2 (2)	0	0	0	0	0
Investigations						
Aspartate aminotransferase increased	12 (10)	3 (2)	3 (5)	0	10 (13)	1 (1)
Alanine aminotransferase increased	9 (7)	2 (2)	3 (5)	0	6 (8)	1 (1)
Blood bilirubin increased	10 (8)	1 (0.8)	0	0	4 (5)	1 (1)
Blood alkaline phosphatase increased	11 (9)	4 (3)	2 (3)	0	6 (8)	1 (1)

MedDRA System Organ Class/Preferred Term or Grouped Term	DESTINY-Gastric01				DESTINY-Gastric02	
	Enhertu N=125		Physician's Choice of Chemotherapy N=62		Enhertu N=79	
	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)
Metabolism and Nutrition Disorders						
Hypokalemia	10 (8)	5 (4)	4 (6)	4 (6)	12 (15)	1 (1)
Decreased appetite	76 (61)	21 (17)	28 (45)	8 (13)	26 (33)	4 (5)
Dehydration	8 (6)	3 (2)	2 (3)	1 (2)	2 (3)	0
Respiratory, Thoracic and Mediastinal Disorders						
Interstitial lung disease[l]	16 (13)	3 (2)	0	0	6 (8)	0
Dyspnea	1 (0.8)	0	1 (2)	0	7 (9)	1 (1)
Cough	6 (5)	0	2 (3)	0	8 (10)	1 (1)
Epistaxis	4 (3)	0	0	0	6 (8)	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	28 (22)	0	9 (15)	0	19 (24)	0
Pruritus	10 (8)	0	2 (3)	0	2 (3)	0
Rash[m]	7 (6)	0	3 (5)	0	1 (1)	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
***** Date of data cut-off: 03 June 2020 (DESTINY-Gastric01), 09 April 2021 (DESTINY-Gastric02)
[a] DESTINY-Gastric01 was graded as per National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03 (NCI CTCAE v.4.03). DESTINY-Gastric02 was graded as per NCI CTCAE v.5.0.
[b] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[c] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
[d] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[e] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[f] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet 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 stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
[i] Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.
[j] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.
[k] Cases include PT of infusion-related reaction.
[l] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, and pneumonia.
[m] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

Further Information on Selected Adverse Reactions

Interstitial Lung Disease/Pneumonitis

Of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with Enhertu 6.4 mg/kg, 56 (24.5%) had moderate renal impairment at baseline, and adjudicated drug-related ILD was reported in 8 (14.3%) patients in this subgroup (Grade 1 events: 3.6%; Grade 2: 7.1%; Grade 3: 1.8%; Grade 4: 1.8%), compared to 8 (11.8%) and 9 (9.9%) patients with normal renal function (n=68) and mild renal impairment (n=91), respectively. Patients with severe renal impairment (CrCL < 30 mL/min) were excluded from the clinical studies.

8.3 Less Common Clinical Trial Adverse Reactions

HER2-Positive Breast Cancer

Less Common Clinical Trial Adverse Reactions (<1%) in the DESTINY-Breast03 Trial
Other clinically relevant adverse reaction reported in less than 1% of patients in the Enhertu-treated arm was:

Blood and Lymphatic System Disorders: febrile neutropenia (0.8%)

Less Common Clinical Trial Adverse Reactions (<1%) in DESTINY-Breast02
Other clinically relevant adverse reactions reported in less than 1% of patients in the Enhertu-treated arm was:

Blood and Lymphatic System Disorders: febrile neutropenia (0.3%)

Less Common Clinical Trial Adverse Reactions (<10%) in DESTINY-Breast01 and DS8201-A-J101 Trials
Other clinically relevant adverse reactions reported in less than 10% of patients in the Enhertu-treated arm were:

Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)
Cardiac Disorders: ejection fraction decrease (1.3%)
Infections and Infestations: sepsis (0.9%)
Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)

HER2-Low Breast Cancer

Less Common Clinical Trial Adverse Reactions (<1%) in the DESTINY-Breast04 Trial
Other clinically relevant adverse reactions reported in less than 1% of patients in the Enhertu-treated arm was:

Injury, Poisoning and Procedural Complications: infusion-related reactions[a] (0.5%)
[a] Grouped term includes injection site reaction and chills.

HER2-Positive Gastric and Gastroesophageal Cancer

Less Common Clinical Trial Adverse Reactions (<1%) in DS8201-A-J101, Destiny-Gastric01 and Destiny-Gastric02 Trials
Other clinically relevant adverse reactions reported in less than 1% of patients in the Enhertu-treated arm were:

Infections and Infestations: sepsis (0.9%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

HER2-Positive Breast Cancer

Table 10 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 n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Hematology				
White blood cell count decreased	190 (73.9)	21 (8.2)	62 (23.9)	2 (0.8)
Neutrophil count decreased	179 (69.6)	45 (17.5)	77 (29.7)	6 (2.3)
Hemoglobin decreased	164 (63.8)	17 (6.6)	99 (38.2)	16 (6.2)
Lymphocyte count decreased	142 (55.3)	37 (14.4)	59 (22.8)	10 (3.9)
Platelet count decreased	134 (52.1)	19 (7.4)	204 (78.8)	62 (23.9)
Chemistry				
Aspartate aminotransferase increased	173 (67.3)	2 (0.8)	215 (83.0)	14 (5.4)
Alanine aminotransferase increased	136 (52.9)	4 (1.6)	174 (67.2)	15 (5.8)
Blood alkaline phosphatase increased	126 (49.0)	2 (0.8)	118 (45.6)	2 (0.8)
Blood potassium decreased	90 (35.0)	12 (4.7)	102 (39.4)	4 (1.5)
Blood bilirubin increased	52 (20.2)	0	36 (13.9)	0

Laboratory Parameter	Enhertu 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Blood creatinine increased	40 (15.6)	2 (0.8)	21 (8.1)	1 (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.

Table 11 Selected Laboratory Abnormalities in Patients in DESTINY-Breast02

Laboratory Parameter	Enhertu 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
White blood cell count decreased	282 (69.8)	48 (11.9)	79 (41.6)	6 (3.2)
Hemoglobin decreased	269 (66.6)	35 (8.7)	102 (53.7)	6 (3.2)
Neutrophil count decreased	259 (64.1)	65 (16.1)	64 (33.7)	9 (4.7)
Lymphocyte count decreased	235 (58.2)	68 (16.8)	73 (38.4)	9 (4.7)
Platelet count decreased	192 (47.5)	11 (2.7)	58 (30.5)	3 (1.6)
Chemistry				
Alanine aminotransferase increased	173 (42.8)	4 (1.0)	60 (31.6)	3 (1.6)
Aspartate aminotransferase increased	151 (37.5)	3 (0.7)	56 (29.5)	4 (2.1)
Blood alkaline phosphatase increased	148 (36.7)	0	32/189 (16.9)	0
Blood potassium decreased	120 (29.8)	15 (3.7)	56 (29.5)	15 (7.9)
Blood bilirubin increased	92 (22.8)	1 (0.3)	84 (44.2)	4 (2.1)

Laboratory Parameter	Enhertu 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Blood creatinine increased	30 (7.4)	1 (0.3)	24 (12.6)	0

Percentages were calculated using the number of subjects with both baseline and post-treatment measurements as the denominator, based on CTCAE grade-derived laboratory abnormalities of subjects whose post-baseline grades worse than baseline grades.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities

Table 12 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 n (%)	Grades 3 or 4 n (%)
Hematology		
White blood cell count decreased	168 (72.4)	20 (8.6)
Anemia	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)
Blood potassium decreased	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.

Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) laboratory measurements (ECHO/MUGA) were conducted at baseline and every 2 cycles in Study DS8201-A-J101 and every 4 cycles in Study DESTINY-Breast01. A total of 37/219 (16.9%) patients in the HER2-positive 5.4 mg/kg Pool met the criteria for a Grade 2 LVEF decrease (NCI-CTCAE version 4.03). Twenty-three of these 37 patients subsequently recovered to within 90% of baseline value.

HER2-Low Breast Cancer

Table 13 Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	Enhertu 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Hematology				
White blood cell count decreased	255 (69.7)	33 (9.0)	132 (78.1)	42 (24.9)
Hemoglobin decreased	234 (63.9)	28 (7.7)	90 (53.3)	10 (5.9)
Neutrophil count decreased	233 (64.0)	52 (14.3)	123 (72.8)	64 (37.9)
Lymphocyte count decreased	202 (55.5)	65 (17.9)	67 (39.6)	19 (11.2)
Platelet count decreased	162 (44.3)	21 (5.7)	36 (21.3)	1 (0.6)
Chemistry				
Aspartate aminotransferase increased	140 (38.4)	8 (2.2)	64 (37.9)	7 (4.1)
Alanine aminotransferase increased	132 (36.2)	3 (0.8)	65 (38.5)	7 (4.1)
Blood alkaline phosphatase increased	123 (33.7)	1 (0.3)	41 (24.3)	0
Blood potassium decreased	92 (25.2)	12 (3.3)	28 (16.7)	2 (1.2)
Blood bilirubin increased	59 (16.2)	10 (2.7)	25 (14.8)	1 (0.6)
Blood creatinine increased	53 (14.5)	4 (1.1)	16 (9.5)	1 (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.

HER2-Positive Unresectable Locally Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer

Table 14 Selected Laboratory Abnormalities in Patients in DESTINY-Gastric01 and DESTINY-Gastric02

Laboratory Abnormality	DESTINY-Gastric01				DESTINY-Gastric02	
	Enhertu N=125		Physician's Choice of Chemotherapy N=62		Enhertu N=125	
	Any Grade n (%)	Grades 3-4 n (%)	Any Grade n (%)	Grades 3-4 n (%)	Any Grade n (%)	Grades 3-4 n (%)
Hematology						
Hemoglobin decreased	96 (76.8)	50 (40.0)	33 (55.0)	14 (23.3)	39 (49.4)	7 (8.9)
White blood cell count decreased	94 (75.2)	36 (28.8)	32 (53.3)	8 (13.3)	48 (60.8)	7 (8.9)
Neutrophil count decreased	91 (72.8)	64 (51.2)	27 (45.0)	14 (23.3)	42 (53.2)	8 (10.1)
Lymphocyte count decreased	92 (73.6)	37 (29.6)	32 (54.2)	7 (11.9)	42 (53.2)	12 (15.2)
Platelet count decreased	88 (70.4)	15 (12.0)	7 (11.7)	3 (5.0)	35 (44.3)	1 (1.3)
Chemistry						
Aspartate aminotransferase increased	72 (57.6)	11 (8.8)	20 (33.3)	6 (10.0)	25 (31.6)	2 (2.5)
Blood alkaline phosphatase increased	73 (58.4)	11 (8.8)	21 (35.6)	6 (10.2)	15 (19.2)	1 (1.3)
Alanine aminotransferase increased	62 (49.6)	11 (8.8)	11 (18.3)	2 (3.3)	18 (22.8)	1 (1.3)
Blood potassium decreased	44 (35.2)	6 (4.8)	12 (20.0)	5 (8.3)	22 (27.8)	4 (5.1)
Blood bilirubin increased	32 (25.6)	10 (8.0)	4 (6.8)	2 (3.4)	11 (14.1)	0

Percentages were calculated using the number of subjects with both baseline and post-treatment measurements as the denominator, based on NCI CTCAE v 4.03 (DESTINY-Gastric01) and NCI CTCAE v 5.0 (DESTINY-Gastric02) grade-derived laboratory abnormalities of subjects whose post-baseline grades worse than baseline grades.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) laboratory measurements (ECHO/MUGA) were conducted at baseline and every 2 cycles in Study DS8201-A-J101 and every 4 cycles in Studies DESTINY-Gastric01 and DESTINY-Gastric02. A total of 15/229 (6.6%) patients in the unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma 6.4 mg/kg pool met the criteria for a ≥Grade 2 LVEF decrease (NCI-CTCAE version 4.03 or 5.0). Three of these 15 patients subsequently recovered to within 90% of baseline value.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Effects of Other Medicinal Products on the Pharmacokinetics of Enhertu

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 Enhertu (trastuzumab deruxtecan) or the released topoisomerase I inhibitor. No dose adjustment is required during coadministration of Enhertu with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P glycoprotein (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 component of Enhertu does not inhibit or induce major CYP450 enzymes.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

that < 5% of the intact ADC dissociates into the released DXd form within 21 days.

Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death.

10.2 Pharmacodynamics

Cardiac Electrophysiology
In a phase 1, open-label, single-arm study of Enhertu administered to patients with unresectable and/or metastatic HER2-expressing breast cancer, no large mean increase from baseline in QTc interval (i.e. >20 ms) was detected following treatment with Enhertu at 6.4 mg/kg every 3 weeks (1.2 fold higher than recommended dose) on Cycle 1 or Cycle 3, 7 hours post-dose (N=49).

10.3 Pharmacokinetics

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. Following a single dose, exposures (Cmax and AUC) of trastuzumab deruxtecan and released topoisomerase inhibitor (DXd) increased proportionally over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.6 to 1.5 times the recommended dose). Trastuzumab deruxtecan and DXd pharmacokinetics were similar between patients with HER2-positive and HER2-low breast cancer.

Table 15 PK parameters following administration of 5.4 mg/kg dose of trastuzumab deruxtecan based on a noncompartmental analysis in HER2-positive breast cancer patients

	Cmax (ug/mL[a] or ng/mL[b])	Ctrough (ug/mL[a] or ng/mL[b])	AUCinf (ug/mL*day [a] or ng/mL*day[b])	AUC(tau) (ug/mL*day[a] or ng/mL*day[b])	CL (mL/day /kg) [c]	Vss (L) [c]	half-lives (days)	Tmax[c] (hours)	Accumulation Ratio [d]
Trastuzumab deruxtecan	124 (32.6) [N=232]	5.5 (5.1) [N=215]	609 (203) [N=50]	573 (167) [N=190]	10.4 (3.5) [N=212]	3.66 (0.93) [N=212]	5.6 (1.2) [N=50]	2.2 (0.02 - 167) [N=232]	1.35 (0.15) [N=51]
DXd	8.2 (5.7) [N=232]	0.26 (0.25) [N=226]	36.4 (12.8) [N=45]	33.3 (16.6) [N=109]	ND	ND	5.6 (1.3) [N=45]	6.8 (0.24 - 167) [N=232]	1.09 (0.194) [N=51]

Table shows arithmetic mean (standard deviation) values of PK parameters in Cycle 1;
AUCinf = area under the concentration-time curve from time 0 to infinity; AUC(tau) = area under the serum concentration-time curve during the dosing interval; CL = clearance; Cmax = maximum observed serum concentration; Ctrough = trough serum concentration; DXd = released topoisomerase inhibitor; ND = Not determined (since DXd could not be estimated as an administered dose, Vss and CL for DXd were not estimated) Tmax = time of maximum observed serum concentration; Vss = volume of distribution at steady state.

[a] For trastuzumab deruxtecan
[b] For DXd
[c] Values reported are median (range)
[d] The accumulation ratio of trastuzumab deruxtecan and DXd for AUC(tau) at Cycle 3 vs Cycle 1 were determined following administration of 6.4 mg/kg dose

Distribution: Based on noncompartmental analysis, the volume of distribution at steady state (Vss) is 3.66L.

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 humanized HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

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

Elimination: Based on noncompartmental analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance parameter of trastuzumab deruxtecan was estimated to be 10.4 mL/day/kg. The apparent elimination half life (t1/2) of trastuzumab deruxtecan and released topoisomerase I inhibitor was approximately 5.6 days. *In vitro*, topoisomerase I inhibitor was a substrate of P gp, OATP1B1, OATP1B3, MATE2 K, MRP1, and BCRP. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Following intravenous administration of the topoisomerase I inhibitor to rats, the major excretion pathway was feces via the biliary route. The topoisomerase I inhibitor was the most abundant component in urine, feces, 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 feces.

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.

Special Populations and Conditions

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

Hepatic Insufficiency: The pharmacokinetics of trastuzumab deruxtecan or DXd in patients with moderate to severe hepatic impairment is unknown.

Renal Insufficiency: The pharmacokinetics of trastuzumab deruxtecan or DXd in patients with severe renal impairment is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Storage of Vials
Store Enhertu (trastuzumab deruxtecan) vials in a refrigerator (2°C to 8°C) in the original carton to protect from light until time of reconstitution.

Do not freeze.

Shelf-life of 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 2°C to 8°C for up to 24 hours from the time of reconstitution, protected from light.

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

Disposal
See 12 SPECIAL HANDLING INSTRUCTIONS.

12 SPECIAL HANDLING INSTRUCTIONS

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.

Enhertu is a cytotoxic drug. Appropriate procedures for the storage, preparation, administration and disposal of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the reconstitution and dilution procedures.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

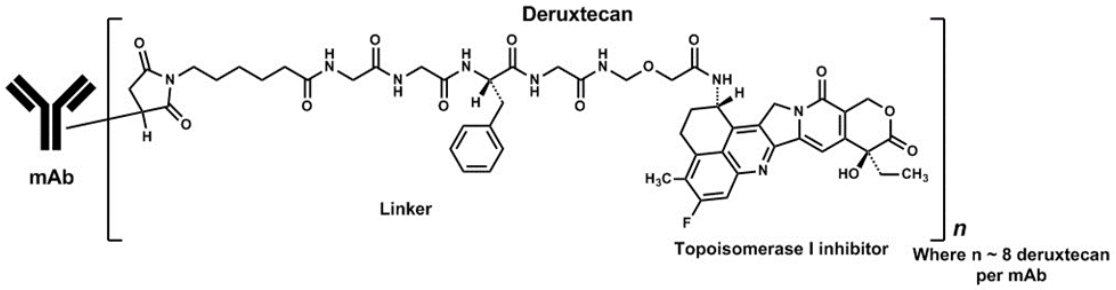
Proper name: trastuzumab deruxtecan

Chemical name: Immunoglobulin G1-kappa, anti-[Homo sapiens ERBB2 (epidermal growth factor receptor 2, receptor tyrosine-protein kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], humanized monoclonal antibody conjugated to deruxtecan, comprising a linker and a camptothecin derivative; gamma1 heavy chain (1-450) [humanized VH (Homosapiens IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*02)[8.8.13] (1-120) -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (217) (121-218), hinge (219-233),CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (Homo sapiens IGKV1-39*01 (86.20%) -IGKJ1*01)[6.3.9] (1'-107') -Homo sapiens IGKC*01, Km3 A45.1, V101 (108'-214')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 8 cysteinyl, to deruxtecan, comprising a linker and a camptothecin derivative

Molecular formula and molecular mass: $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$ +H×8+$C_{52}H_{56}FN_9O_{13}$×8 = $C_{6876}H_{10428}F_8N_{1796}O_{2118}S_{44}$

Mass: 153,701.98 (Deglycosylated, C-term Lys(+))

Structural formula:



Physicochemical properties: Trastuzumab deruxtecan is a white to yellowish white lyophilized powder.

Product Characteristics

Trastuzumab deruxtecan is a HER-2 targeted antibody and topoisomerase inhibitor conjugate. The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology, and the topoisomerase inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

HER2-positive Breast Cancer after at least One Prior Anti-HER2-based Regimen

Table 16 Summary of patient demographics in clinical trial for patients with unresectable or metastatic HER2-positive breast cancer after at least one prior anti-HER2-based regimen

Study #	Trial design	Dosage, route of administration and duration	Study Patients (n)	Mean age (Range)	Sex
DESTINY-Breast03	Phase 3, active-controlled, open-label, multicenter study	Enhertu 5.4 mg/kg IV or Trastuzumab-emtansine (T-DM1) 3.6 mg/kg IV	Enhertu: 261 T-DM1: 263	Enhertu: 54.5 years (27-83) T-DM1: 54.4 years (20-83)	Enhertu: 99.6% female T-DM1: 99.6% female

Trial Design and Study Demographics (DESTINY-Breast03)
The efficacy and safety of ENHERTU (trastuzumab deruxtecan) were demonstrated in a Phase 3, randomized, multicenter, 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 neoadjuvant or adjuvant therapy involving trastuzumab and taxane. 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, patients with a history of clinically significant pulmonary or cardiac disease and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomized 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. Randomization 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 a blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumours (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 generally similar between treatment arms. Of the 524 patients randomized, the median age was 54 years (range 20.2 to 83.1); 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 stable brain

metastases at baseline (15.6%), and 253 (48.3%) 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%, and 6.7% of patients had received exactly one prior anti-HER2 therapy that was intended for the neoadjuvant or adjuvant therapy and experienced disease progression during or within 6 months of completing treatment (12 months for pertuzumab). The most common prior anti-HER2 cancer therapies received by patients included trastuzumab (99.6%), pertuzumab (61.1%), and an anti-HER2 tyrosine kinase inhibitor (14.9%). Forty-two percent of patients had received prior hormone therapy.

Study Results (DESTINY-Breast03)
At the prespecified interim analysis for PFS based on 245 events (73% of total events planned for final analysis), the study demonstrated a clinically meaningful and statistically significant improvement in PFS in patients randomized to Enhertu compared to trastuzumab emtansine. A statistically significant improvement in OS was demonstrated at the prespecified second interim analysis of OS.

Efficacy results are summarized in Table 17 and Figure 1.

Table 17 Efficacy Results in DESTINY-Breast03

Efficacy Parameter	**Enhertu (5.4 mg/kg) N=261**	**trastuzumab emtansine (3.6 mg/kg) N=263**
Progression-Free Survival per BICR		
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio* (95% CI)	0.28 (0.22, 0.37)	
p-value†	p< 0.000001‡	
Overall Survival[b]		
Number of events (%)	72 (27.6)	97 (36.9)
Median, months (95% CI)	NR (40.5, NE)	NR (34.0, NE)
Hazard ratio (95% CI)	0.64 (0.47, 0.87)	
p-value[ɸ]	p=0.0037	
Objective Response Rate per BICR[a]		
n (%)	208 (79.7)	90 (34.2)
95% CI	(74.3, 84.4)	(28.5, 40.3)
Complete Response n (%)	42 (16.1)	23 (8.7)
Partial Response n (%)	166 (63.6)	67 (25.5)

CI = confidence interval; NR= not reached, NE=not estimable
PFS 95% CIs calculated using Brookmeyer and Crowley method
[a] Data cutoff: 21 May 2021. The median duration of follow-up for patients was 15.9 months (range 0.0-32.7) in the ENHERTU arm and 15.3 months (range 0.0-31.3) in the trastuzumab emtansine arm.

[b] Data cutoff: 25 July 2022 for a pre-planned OS interim analysis. The median duration of follow-up for patients was 28.4 months (range 0.0-46.9) in the ENHERTU arm and 26.5 months (range 0.0-45.0) in the trastuzumab emtansine arm.
[c] Confirmed ORR
* Based on stratified Cox proportional hazard model
† Based on stratified log-rank test; compared to the efficacy stopping boundary of 2.04×10^{-4}
‡ Presented as 6 decimal places
ϕ Based on stratified log-rank test; compared to the efficacy stopping boundary of 1.3×10^{-2} (with 68% of total events planned for final analysis)

Figure 1 Kaplan-Meier Plot of Progression-Free Survival per BICR

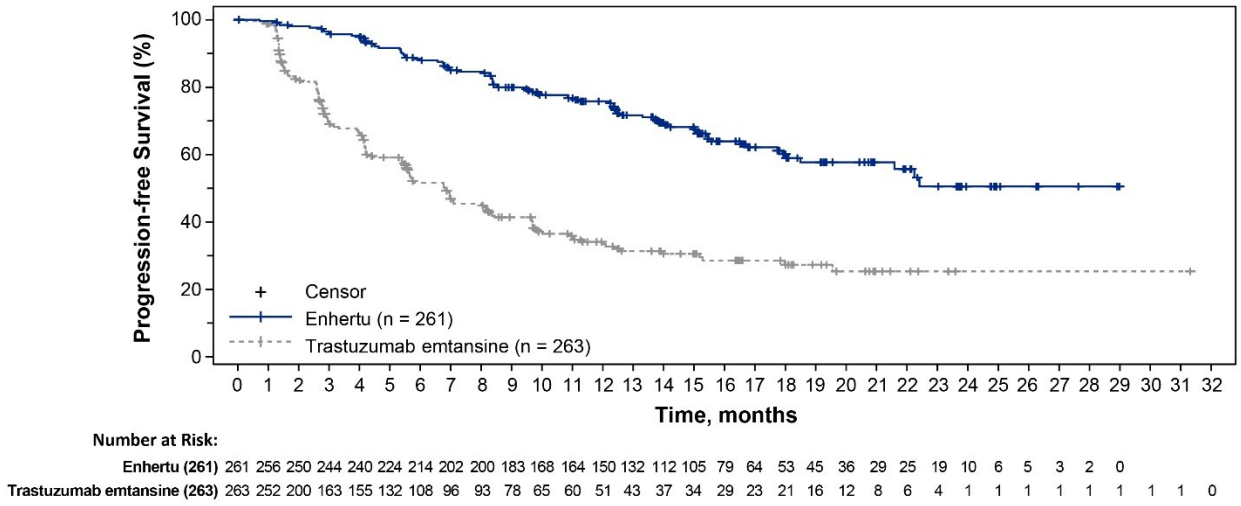
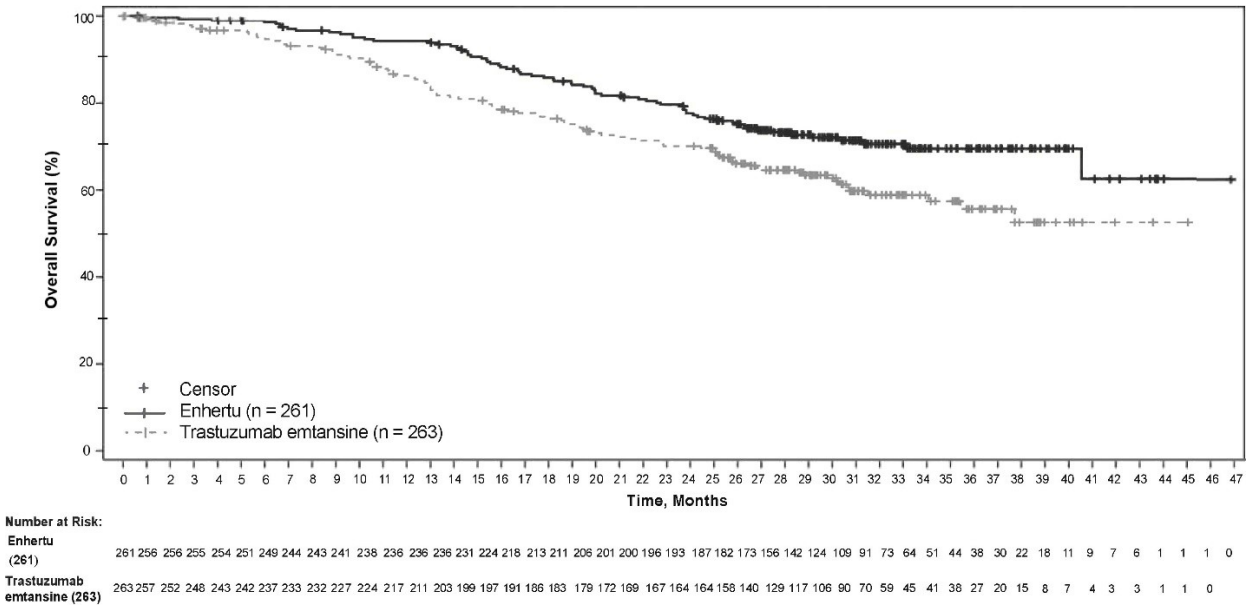


Figure 2 Kaplan-Meier Plot of Overall Survival



The following PFS results per BICR (Enhertu arm vs. trastuzumab emtansine arm) were observed at the prespecified interim PFS analysis across prespecified subgroups based on stratification factors and disease characteristics: the hazard ratios (HRs) were 0.32 (95% CI:

0.22, 0.46) and 0.30 (95% CI: 0.20, 0.44) in patients with positive (n=272) and negative (n=248) hormone receptor status, respectively; the HRs were 0.31 (95% CI: 0.22, 0.43) and 0.30 (95% CI: 0.19, 0.47) in patients with (n=320) or without (n=204) prior pertuzumab treatment, respectively; and the HRs were 0.28 (95% CI: 0.21, 0.38) and 0.32 (95% CI: 0.17, 0.58) in patients with (n=384) or without (n=140) a history of visceral disease, respectively.

HER2-positive Breast Cancer after trastuzumab emtansine

Table 18 Summary of patient demographics in clinical trial for patients with unresectable or metastatic HER2-positive breast cancer after trastuzumab emtansine

Study #	Trial design	Dosage, route of administration and duration	Study Patients (n)	Mean age (Range)	Sex
DESTINY-Breast02	Phase 3, active-controlled, open-label, multicenter study	Enhertu 5.4 mg/kg IV or TPC (trastuzumab plus capecitabine[1] or lapatinib plus capecitabine[2])	Enhertu: 406 TPC: 202 (trastuzumab plus capecitabine: 91; lapatinib plus capecitabine: 111)	Enhertu: 54.6 years (22-89) TPC: 55.1 years (25-87)	Enhertu: 99.3% female TPC: 99.0% female
DESTINY-Breast01	Phase 2, single-agent, open-label, multicenter study	Enhertu 5.4 mg/kg IV	184	56 years (range 28 to 96)	100% female

TPC: Treatment of Physician's Choice

[1] Trastuzumab: 8 mg/kg IV on Day 1 followed by 6 mg/kg every 21 days (cycled every 21 days); Capecitabine: 1250 mg/m^2 orally twice daily on Days 1-14 (cycled every 21 days)

[2] Lapatinib: 1250 mg orally daily on Days 1 to 21 (cycled every 21 days); Capecitabine: 1250 mg/m2 orally twice daily on Days 1-14 (cycled every 21 days)

Study: DESTINY-Breast02

Trial Design and Study Demographics (DESTINY-Breast02)

The efficacy and safety of Enhertu were evaluated in study DESTINY Breast02, a Phase 3, randomized, multicenter, open-label, active-controlled study that enrolled patients with unresectable or metastatic HER2-positive breast cancer who were previously treated with trastuzumab emtansine.

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 randomized 2:1 to receive either Enhertu 5.4 mg/kg (N=406) by intravenous infusion every three weeks or treatment of physician's choice (TPC; N=202, trastuzumab plus capecitabine or lapatinib plus capecitabine). Randomization 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 PFS as assessed by BICR based on RECIST v1.1. OS was a key secondary efficacy outcome measure. Confirmed ORR and duration of response (DOR), were secondary endpoints.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 608 patients randomized, 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%); one line of prior systemic therapy in the metastatic setting (4.9%); and prior pertuzumab therapy (78.0%).

Study Results (DESTINY-Breast02)
The median duration of follow-up for patients was 21.5 months (range 0.1-45.6) in the Enhertu arm and 18.6 months (range 0.0-45.7) in the TPC arm. The study demonstrated a statistically significant improvement in PFS per BICR and OS in patients randomized to Enhertu compared to TPC.

Efficacy results are summarized in Table 19, Figure 3 and Figure 4.

Table 19 Efficacy Results in DESTINY-Breast02

Efficacy Parameter	**Enhertu (N=406)**	**Treatment of Physician's Choice (N=202)**
Progression-Free Survival 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[a] (95% CI)	0.36 (0.28, 0.45)	
p-value[†]	p<0.000001[‡]	
Overall Survival		
Number of events (%)	143 (35.2)	86 (42.6)
Median, months (95% CI)	39.2 (32.7, NE)	26.5 (21.0, NE)
Hazard ratio[a] (95% CI)	0.66 (0.50, 0.86)	
p-value[ϕ]	p=0.0021	
Objective Response Rate per BICR[b]		
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)

Efficacy Parameter	Enhertu (N=406)	Treatment of Physician's Choice (N=202)
Duration of Response per BICR		
Median, months (95% CI)	19.6 (15.9, NE)	8.3 (5.8, 9.5)

CI = confidence interval; NE=not estimable
PFS 95% CIs calculated using Brookmeyer and Crowley method
[a] Based on stratified Cox proportional hazard model
[b] Confirmed Objective Response Rate per BICR
[†] Based on stratified log-rank test
[‡] Presented as 6 decimal places
[ɸ] Based on stratified log-rank test; crossed the efficacy boundary of 0.004

Figure 3 Kaplan-Meier Plot of Progression-Free Survival per BICR

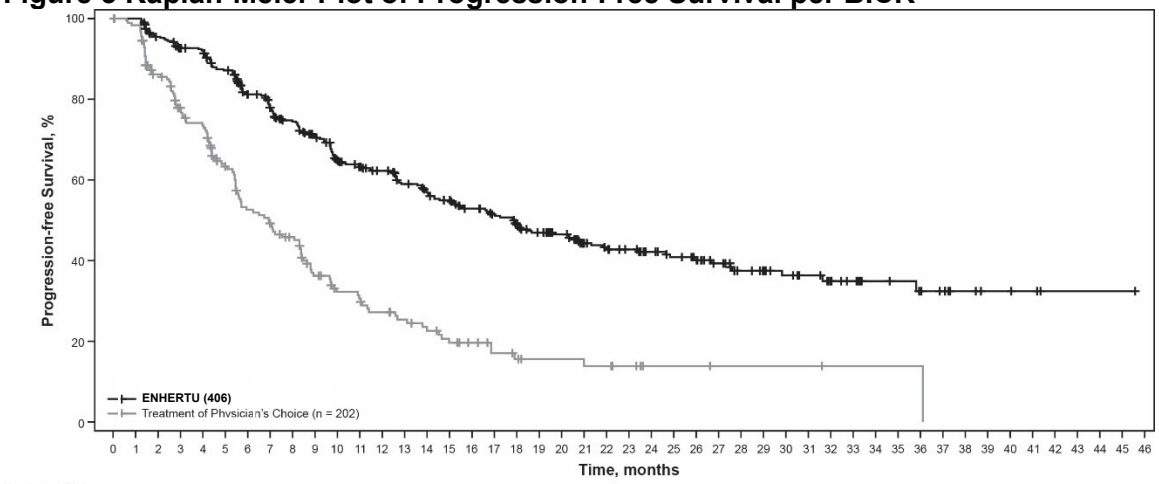
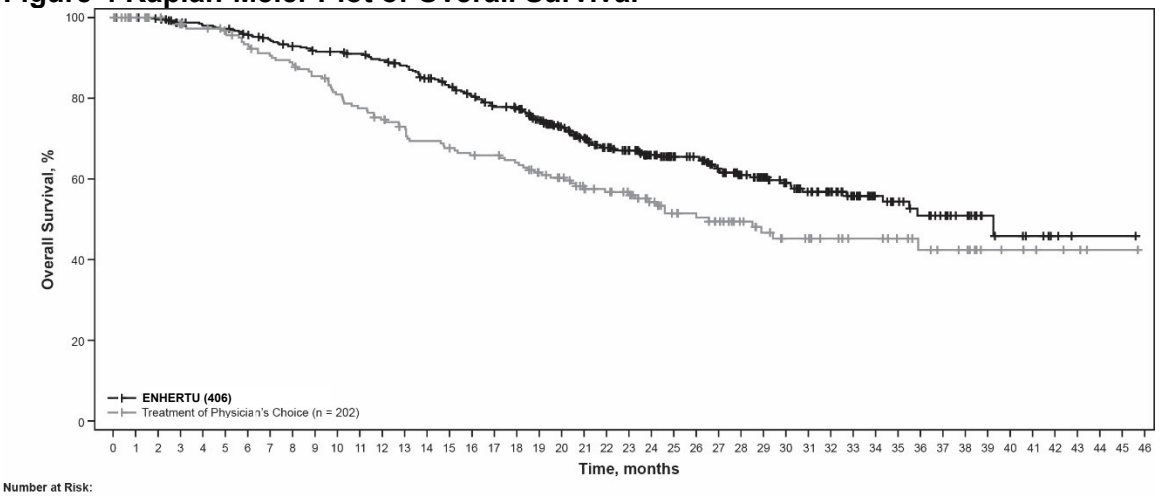


Figure 4 Kaplan-Meier Plot of Overall Survival



Similar PFS results were observed across patient subgroups based on the following stratification factors: hormone receptor status (positive vs. negative), prior treatment with and without pertuzumab, and history of visceral disease.

Study: DESTINY-Breast01

Trial Design and Study Demographics (DESTINY-Breast01)
The efficacy and safety of Enhertu (trastuzumab deruxtecan) were demonstrated in a Phase 2, single-agent, open-label, multicenter study: DESTINY-Breast01.

The study enrolled adult patients with unresectable or metastatic HER2-positive breast cancer who had received prior treatment with trastuzumab emtansine. Patients 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, patients with untreated, symptomatic brain metastases 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) was a secondary efficacy measure.

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%); ECOG performance status 0 (55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease (91.8%); stable brain metastases (13%); 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%).

Study Results (DESTINY-Breast01)
The median duration of follow-up for patients was 11.1 months (range 0.7-19.9). The confirmed ORR was 60.9% (95% CI: 53.4, 68.0) and median DoR with confirmed response was 14.8 months (95% CI: 13.8, 16.9).

Efficacy results are summarized in Table 20.

Table 20 Efficacy Results by Independent Central Review in DESTINY-Breast01

Efficacy Parameter	**DESTINY-Breast01 N=184 n (%)**
Confirmed Objective Response Rate (95% CI)	112 (60.9) (53.4, 68.0)
Complete Response	11 (6.0)
Partial Response	101 (54.9)

Efficacy Parameter	DESTINY-Breast01 N=184 n (%)
Duration of Response Median†, months (95% CI)*	14.8 (13.8, 16.9)

ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
*DOR is based on a median duration of follow-up of 11.1 months.
†Based on Kaplan-Meier estimates

In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 65% (95% CI: 55, 73), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 54% (95% CI: 41, 67). The subgroup of patients who were hormone receptor (HR+) at baseline had a confirmed ORR of 58% (95% CI: 47, 68), and those who were hormone receptor negative (HR-) at baseline had a confirmed ORR of 66% (95% CI: 55, 76). The results should be interpreted with caution given the inherent risks with subgroup analyses in general.

HER2-Low Breast Cancer

Table 21 Summary of patient demographics in clinical trial for patients with unresectable or metastatic HER2-low breast cancer

Study #	Trial design	Dosage, route of administration and duration	Study Patients (n)	Mean age (Range)	Sex
DESTINY-Breast04	Phase 3, open-label, multicenter study	Enhertu 5.4 mg/kg IV or Chemotherapy (eribulin[1], capecitabine[2], gemcitabine[3], nab-paclitaxel[4], or paclitaxel[5])	Enhertu: 373 Chemotherapy: 184 (eribulin[1]: 94; capecitabine[2]: 37; gemcitabine[3]: 19; nab-paclitaxel[4]: 19; paclitaxel[5]: 15)	Enhertu: 56.5 years (46-67) Chemotherapy: 56.5 years (45-68)	Enhertu: 99.5% female Chemotherapy: 100% female

[1] Eribulin 1.4 mg/m^2 IV on Days 1 and 8; cycled every 21 days;
[2] Capecitabine 1000-1250 mg/m^2 orally twice daily on Days 1-14; cycled every 21 days;
[3] Gemcitabine Option 1: 800-1200 mg/m^2 IV on Days 1 and 8 (cycled every 21 days); Option 2: 800-1200 mg/m^2 IV on Days 1, 8 and 15 (cycled every 28 days);
[4] Nab-paclitaxel Option 1: 260 mg/m^2 IV (cycled every 21 days); Option 2: 100 mg/m^2 or 125 mg/m^2 IV Days 1, 8, and 15 (cycled every 28 days);
[5] Paclitaxel Option 1: 175 mg/m^2 IV (cycled every 21 days); Option 2: 80 mg/m^2 IV (weekly)

Trial Design and Study Demographics (DESTINY-Breast04)
The efficacy and safety of Enhertu were evaluated in study DESTINY-Breast04, a Phase 3, randomized, multicenter, 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- according to the College of American Pathologists (CAP) 2018 HER2 Testing in breast cancer guideline evaluated at a central laboratory using Ventana's PATHWAY anti-HER2-/neu (4B5) Rabbit Monoclonal Primary Antibody assay and INFORM HER2 Dual ISH assay. Patients should have received at least one prior line (no more than two prior lines) of chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with HR+ breast cancer should be refractory to prior endocrine therapy (ET), defined as having progressed on at least 1 ET and determined by the investigator that the patient would no longer benefit from further treatment with ET.

Patients were randomized 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, capecitabine, gemcitabine, nab-paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumour samples (IHC 1+ or IHC 2+/ISH-), 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 randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population. ORR and DOR were secondary endpoints.

Demographics and baseline tumour characteristics were generally similar between treatment arms. Of the 557 patients randomized, 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-; 69.8% had liver metastases; 32.9% had lung metastases; 5.7% had stable brain metastases; and 51.9%, 34.5% and 11.5% had normal, mild and moderate renal functions, respectively. 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, median of 2 prior lines of endocrine therapy (range: 0 to 7) with 28.5% having 1 and 30.3% having 2 prior lines, and 3.9% were early progressors (defined as having disease recurrence during or within 6 months of completing neo/adjuvant chemotherapy). In the neo/adjuvant setting, the number of patients that received anthracyclines was 46.3%. In the metastatic setting, patients had received the following cytotoxic agents: taxane (55.1%), capecitabine (49.4%), anthracyclines (19.4%) and eribulin (9.2%). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70.4% had prior CDK4/6i inhibitor treatment.

Study Results (DESTINY-Breast04)
The median duration of follow-up for patients was 16.1 months (range 0.3-33.1) in the Enhertu arm and 13.5 months (range 0.0-27.8) in the chemotherapy arm. The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients

randomized to Enhertu compared to chemotherapy in both the HR+ cohort and the overall population.

Efficacy results are summarized in Table 22, Figure 5, and Figure 6.

Table 22 Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohort)	
	Enhertu (N = 331)	Chemotherapy (N = 163)	Enhertu (N = 373)	Chemotherapy (N = 184)
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	
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		0.0010	

CI = confidence interval; BICR = blinded independent central review
PFS, OS and 95% CIs calculated using Brookmeyer and Crowley method
†Based on stratified Cox proportional hazard model
‡Based on stratified log-rank test; compared to the efficacy stopping boundary of 0.05
*Based on stratified log-rank test; compared to the efficacy stopping boundary of 0.00748

In the HR+ cohort, the ORR was 52.6% (95% CI: 47.0, 58.0) with a median DOR of 10.7 months (95% CI: 8.5, 13.7) in the Enhertu arm, and ORR was 16.3% (95% CI: 11.0, 22.8) with a median DOR of 6.8 months (95% CI: 6.5, 9.9) in the chemotherapy arm. In the overall population, the ORR was 52.3% (95% CI: 47.1, 57.4) with a median DOR of 10.7 months (95% CI: 8.5, 13.2) in the Enhertu arm, and ORR was 16.3% (95% CI: 11.3, 22.5) with a median DOR of 6.8 months (95% CI 6.0, 9.9) in the chemotherapy arm.

Figure 5 Kaplan-Meier Plot of Progression-Free Survival per BICR (Overall Population)

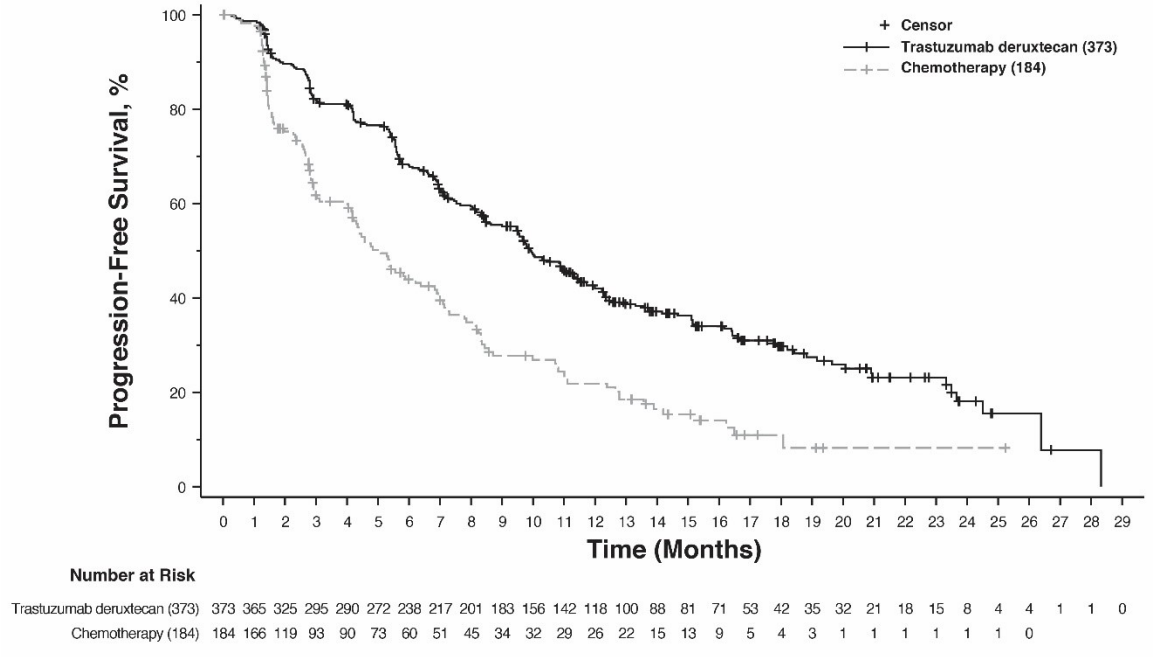
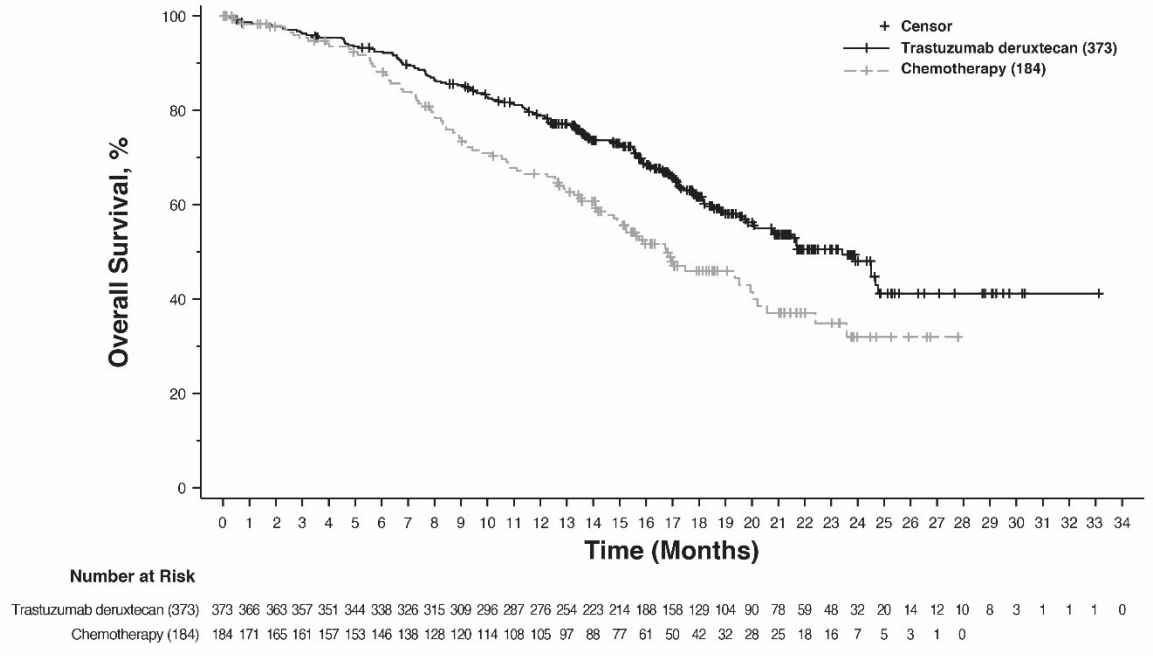


Figure 6 Kaplan-Meier Plot of Overall Survival (Overall Population)



In an exploratory subgroup analysis of sixty-four (11.5%) patients with moderate renal impairment, the hazard ratio for OS was 1.91 (95% CI: 0.84, 4.36). These results should be interpreted with caution given the inherent risks with subgroup analyses.

Unresectable Locally Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer

Table 23 Summary of patient demographics in clinical trial for patients with unresectable locally advanced or metastatic HER2-positive gastric and gastroesophageal junction cancer

Study #	Trial design	Dosage, route of administration and duration	Study Patients (n)	Mean age (Range)	Sex
DESTINY-Gastric01	Phase 2, multicenter, open-label, randomized study	Enhertu 6.4 mg/kg IV every 3 weeks or Chemotherapy (irinotecan[1]; paclitaxel[2])	Enhertu: 126 Chemotherapy: 62 (irinotecan: 55; paclitaxel: 7)	Enhertu: 64 years (34 to 82) Chemotherapy: 65 years (28 to 82)	Enhertu: 76% Male Chemotherapy: 76% Male

[1]Irinotecan monotherapy was administered by intravenous infusion biweekly at 150 mg/m^2
[2]Paclitaxel monotherapy was administered by intravenous infusion weekly at 80 mg/m^2

Trial Design and Study Demographics (DESTINY-Gastric01)
The efficacy and safety of Enhertu were demonstrated in DESTINY-Gastric01, a Phase 2, multicenter, open-label, randomized study conducted at sites in Japan and South Korea. The study included adult patients with unresectable 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 randomized 2:1 to receive either Enhertu (N=126) or physician's choice of chemotherapy: either irinotecan (N=55) or paclitaxel (N=7). Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH-positive), ECOG performance status (0 or 1), and region (Japan or South Korea). Tumour samples were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive as determined according to American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) HER2 test guideline. The study excluded patients with a history of treated or current ILD/pneumonitis, a history of clinically significant cardiac disease, active brain metastases or ECOG performance status >1. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was unconfirmed ORR assessed by ICR (Independent Central Review) based on RECIST v1.1. 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 HER2 IHC 3+ and 23% were IHC 2+/ISH-positive; 65% had inoperable advanced cancer; 35% had postoperative 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 unresectable locally advanced or metastatic setting.

Study Results (DESTINY-Gastric01)
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 the primary analysis are summarized in Table 24 and the Kaplan-Meier curve for the OS is shown in Figure 7. At the primary analysis (08 November 2019) the median duration of survival follow-up was 8.1 months (range 1.0 – 23.1) in the Enhertu arm and 7.0 months (range 0.3 – 20.3) in the chemotherapy arm.

Table 24 Efficacy Results in DESTINY-Gastric01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	**Primary Analysis (08 November 2019)**	
	Enhertu N=126	**Physician's Choice of Chemotherapy (Irinotecan or Paclitaxel) 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	
Objective Response Rate (ORR)§		
n (%)	61 (48.4)	8 (12.9)
95% CI¶	(39.4, 57.5)	(5.7, 23.9)
p-value‡,#	p<0.0001	
Complete Response n (%)	11 (8.7)	0 (0.0)
Partial Response n (%)	50 (39.7)	8 (12.9)
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)

CI = confidence interval.
* 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

At the time of primary analysis, progression-free survival was 5.6 months (95% CI: 4.3, 6.9) in the Enhertu arm and 3.5 months (95% CI: 2.0, 4.3) in the control arm.

The median duration of confirmed response as assessed by independent central review was 11.3 months (95% CI: 5.6, NE) for responders (N =51) in the Enhertu arm and 3.9 months (95% CI: 3.0, 4.9) for responders (N=7) in the control arm.

The efficacy results observed in the updated analysis (03 June 2020) were consistent with those from the primary analysis (08 November 2019).

Figure 7 Kaplan-Meier Plot of Overall Survival (Intent toTreat Analysis Set)

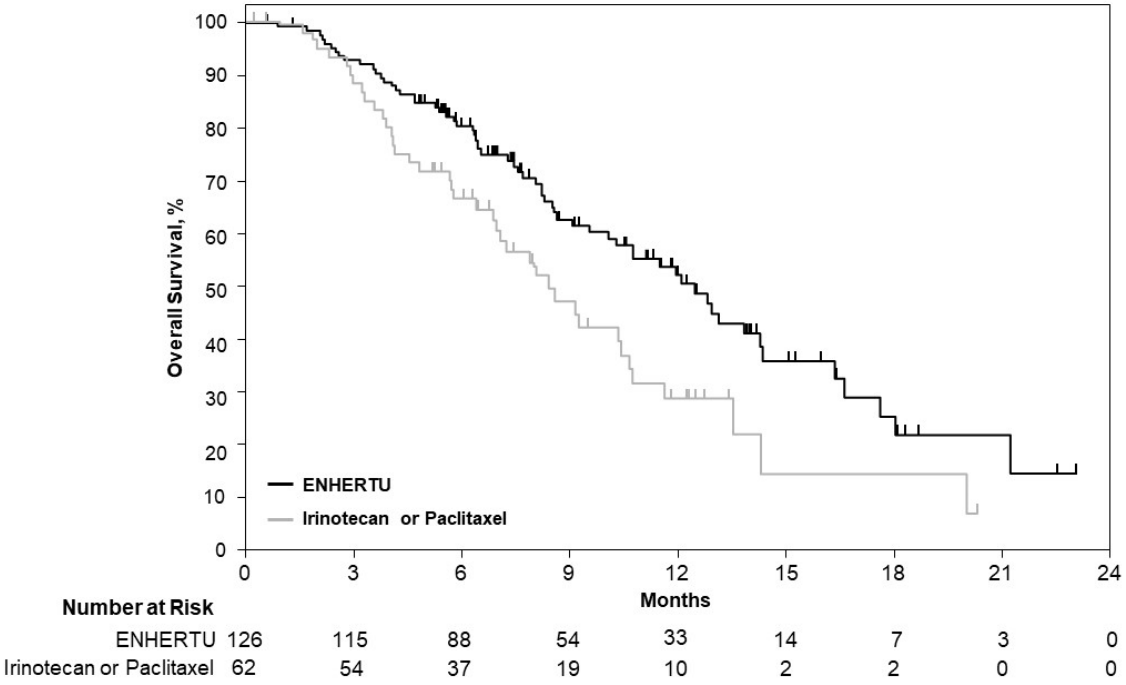


Table 25 Summary of patient demographics in clinical trial for patients with unresectable locally advanced or metastatic HER2-positive gastric and gastroesophageal junction cancer

Study #	Trial design	Dosage, route of administration and duration	Study Patients (n)	Mean age (Range)	Sex
DESTINY-Gastric02	Phase 2, multicenter, open-label, single-arm study	Enhertu 6.4 mg/kg IV every 3 weeks	79	59 years (20 to 78)	72% Male

Trial Design and Study Demographics (DESTINY-Gastric02)
The efficacy and safety of Enhertu were demonstrated in DESTINY-Gastric02, a Phase 2, multicenter, open-label, single-arm study conducted at sites in Europe and the United States.

The study enrolled patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on a prior trastuzumab-based regimen. Patients were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive as determined according to the ASCO-CAP HER2 test guideline. The study excluded patients with a history of treated or current ILD/pneumonitis, a history of clinically significant cardiac disease, with active brain metastases or an ECOG performance status >1. 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.

Of the 79 patients enrolled in DESTINY-Gastric02, demographic and baseline disease characteristics were: median age 61years (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 HER2 IHC 3+ and 13% were IHC 2+/ISH-positive, and 63% had liver metastases. The median number of prior regimens in the unresectable locally advanced or metastatic setting was one.

Study Results (DESTINY-Gastric02)
Efficacy results are summarized in Table 26.

Table 26 Efficacy Results in DESTINYGastric02 (Full Analysis Set[*])[#]

Efficacy Parameter	**DESTINY-Gastric02 N=79**
Confirmed Objective Response Rate (ORR)[†] % (95% CI)[‡]	38.0 (27.3, 49.6)
Complete response n (%)	3 (3.8)
Partial response n (%)	27 (34.2)

*Includes all patients who received at least one dose of Enhertu with a mediation duration of follow up at the primary analysis of 5.9 months
[#]Data cut-off date: 09 April 2021
[†]Assessed by independent central review
[‡]Calculated using Clopper-Pearson method
[§]Based on Kaplan-Meier estimate
[¶]Calculated using the Brookmeyer and Crowley method

The median duration of response at the time of primary analysis was 8.1 months (95% CI: 4.1, NE) for the 30 responders.

The efficacy results observed in the updated analysis (08 November 2021) were consistent with those from the primary analysis (09 April 2021).

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 2.1% (47/2213) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. The incidence of treatment-emergent neutralizing antibodies against trastuzumab deruxtecan was 0.1% (2/2213). Due to the limited

number of patients who tested positive for anti-drug antibody, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Rats
In a six week repeat-dose toxicity study, trastuzumab deruxtecan was administered to rats once every three weeks at doses up to 197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, lymphatic/hematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All changes observed, except for testicular and incisor teeth changes, were reversible following a nine week recovery period.

Cynomolgus Monkeys
In a three month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at doses up to 30 mg/kg (approximately 9 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and histopathologically characterized by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation which showed reversibility after a three month recovery period. Changes observed in other organs, except for those in the skin and kidney, also showed reversibility or a trend toward reversibility by the end of a three month recovery period.

Carcinogenicity and Mutagenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

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.

Reproductive and Developmental Toxicology

Impairment of Fertility
Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.

Developmental Toxicity
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/hematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor was

genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

Juvenile Animal Studies
No juvenile toxicity studies have been conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ℙENHERTU®
Trastuzumab deruxtecan for injection

Read this carefully before you start treatment with **Enhertu** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Enhertu**.

Serious Warnings and Precautions

- Lung problems that may be severe, life-threatening or that may lead to death. Tell your healthcare provider right away if you get any of the following signs and symptoms at any time during treatment:
  - cough
  - trouble breathing or shortness of breath
  - fever
  - other new or worsening breathing symptoms (e.g., chest tightness, wheezing)

  If you develop lung problems your healthcare provider may treat you with corticosteroid medicines.
- Harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with Enhertu.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with Enhertu.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with Enhertu and for at least 7 months after the last dose.
  - Males who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with Enhertu and for at least 4 months after the last dose.
- There is a risk of Enhertu medication errors. Verify with your healthcare provider that you are receiving the authorized Enhertu (trastuzumab deruxtecan) dose and NOT trastuzumab or trastuzumab emtansine.

What is Enhertu used for?

Breast Cancer
Enhertu is used to treat adults who have:

- HER2-positive breast cancer that has spread to other parts of the body (metastatic) or cannot be taken out by surgery **and**
- also received a prior treatment that targeted HER2-positive breast cancer.

Enhertu is used to treat adults who have:

- HER2-low breast cancer that cannot be removed by surgery or that has spread to other parts of the body (metastatic) **and** who have received prior chemotherapy for metastatic disease, **or** the disease has returned during or within 6 months of

completing adjuvant chemotherapy (after surgery). If the breast cancer is also hormone receptor positive (HR+), patients should have received hormonal therapy. A test will be performed to make sure Enhertu is the right treatment.

Stomach (Gastric) Cancer
Enhertu is used to treat adults who have:

- a HER2-positive stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that has spread to areas near the stomach (inoperable locally advanced) or that has spread to other parts of the body (metastatic)
- and who have also received a prior trastuzumab-based treatment.

For the following indication(s) Enhertu has been approved ***without conditions***. This means that it has passed Health Canada's review and can be bought and sold in Canada.

- Enhertu (trastuzumab deruxtecan) is used to treat adults who have HER2-positive breast cancer that has spread to other parts of the body (metastatic) or cannot be taken out by surgery and also received a prior treatment that targeted HER2-positive breast cancer.
- Enhertu (trastuzumab deruxtecan) is used to treat adults who have HER2-positive breast cancer that has spread to other parts of the body (metastatic) or cannot be taken out by surgery and also received prior trastuzumab emtansine (T-DM1).
- Enhertu (trastuzumab deruxtecan) is used to treat adults who have HER2-low breast cancer that cannot be removed by surgery or that has spread to other parts of the body (metastatic) and who have received prior chemotherapy for metastatic disease, or the disease has returned during or within 6 months of completing adjuvant chemotherapy (after surgery). If the breast cancer is also hormone receptor positive (HR+), patients should have received hormonal therapy. A test will be performed to make sure Enhertu is the right treatment.

For the following indication(s) Enhertu has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Enhertu (trastuzumab deruxtecan) is used to treat adults who have a HER2-positive stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that has spread to areas near the stomach (inoperable locally advanced) or that has spread to other parts of the body (metastatic), and who have received a prior trastuzumab-based treatment.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a

serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Enhertu work?
Enhertu contains the active substance trastuzumab deruxtecan, which is made up of a monoclonal antibody connected to a medicine intended to kill cancer cells. The monoclonal antibody delivers the medicine to cancer cells that express HER2 proteins (known as HER2-positive). Once Enhertu enters the cell, the medicine becomes active and kills the cancer cells.

What are the ingredients in Enhertu?
Medicinal ingredients: trastuzumab deruxtecan
Non-medicinal ingredients: L histidine, L histidine hydrochloride monohydrate, polysorbate 80, sucrose.

Enhertu comes in the following dosage forms:
Vial containing 100 mg of trastuzumab deruxtecan.

Do not use Enhertu if:
- You are allergic to trastuzumab deruxtecan or to any ingredients in Enhertu. If you are not sure, talk to your healthcare professional before you are given Enhertu.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Enhertu. Talk about any health conditions or problems you may have, including if you:
- have or have had any lung problems, any kidney problems, any heart problems or any blood problems (low blood count).

Other warnings you should know about:
When you first receive this medicine and anytime during treatment, immediately tell your doctor or nurse if you have:
- cough, shortness of breath, fever, or other new or worsening breathing problems. These may be symptoms of a serious and potentially fatal lung disease (interstitial lung disease [ILD]/ pneumonitis). History of this lung disease or kidney problems may increase the risk of developing ILD. Your doctor may have to monitor your lungs while you are taking this medicine.
- chills, fever, sores in your mouth, stomach pain or pain when urinating. These may be symptoms of an infection caused by low levels of a type of white blood cell called neutrophils (neutropenia).
- new or worsening shortness of breath, cough, feeling tired, swelling of your ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness. These may be symptoms of a problem with your heart's ability to pump blood (decreased left ventricular ejection fraction [LVEF]).
- chills or shaking, shortness of breath or wheezing, itching, rash or hives, flushing, dizziness, fever, feeling like passing out (infusion-related reaction).

Children and adolescents
- Enhertu is not recommended for anyone under the age of 18 years.

Pregnancy
- Enhertu is not recommended if you are pregnant because this medicine may cause harm to the unborn baby.
- Tell your doctor before using Enhertu if you are pregnant, think you may be pregnant or are planning to have a baby.
- Use effective contraception to avoid becoming pregnant while you are being treated with Enhertu. Talk to your doctor about the best contraception for you.
- Females should continue to take contraception for at least 7 months after your last dose of Enhertu. Talk to your doctor before stopping your contraception.
- Male patients with a female partner who could become pregnant should use effective contraception during treatment and for at least 4 months after the last dose of Enhertu.
- If you do become pregnant during treatment with Enhertu, tell your doctor right away.

Breastfeeding
- You should not breastfeed during treatment with Enhertu.
- You should not breastfeed for at least 7 months after your last treatment of Enhertu.
- It is not known whether the ingredients in Enhertu pass into breast milk. Talk to your doctor about this.

Fertility
- Talk to your doctor about sperm storage before treatment with Enhertu because the medicine may reduce your fertility. Do not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

Driving and using machines: Enhertu may reduce your ability to drive or use machines. Be careful if you feel tired, dizzy or have a headache.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Enhertu:
Enhertu will be given to you by a healthcare professional.

Usual dose:
Enhertu will be given to you in a hospital or clinic.
- The recommended dose of Enhertu for the treatment of HER2-positive breast cancer is 5.4 mg for every kilogram of your body weight, every 3 weeks.
- The recommended dose of Enhertu for the treatment of HER2-positive stomach cancer is 6.4 mg for every kilogram of your body weight, every 3 weeks.
- Your doctor or nurse will give you Enhertu through an infusion into your vein (IV).
- Your first infusion will be given to you over 90 minutes. If you have no problems with the first infusion, the infusion on your next visits may be given over 30 minutes.
- Your doctor will decide how many treatments you need.
- Before each Enhertu infusion, your doctor may give you medicines to help prevent nausea and vomiting.
- If you experience infusion-related symptoms, your doctor or nurse may slow, interrupt

or stop your treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much Enhertu, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss an appointment to get Enhertu
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

Do not stop treatment with Enhertu unless you have discussed this with your doctor. If you have any further questions about your treatment, ask your doctor.

What are possible side effects from using Enhertu?

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you experience any side effects, including those not listed in this leaflet.

While you are taking Enhertu
- Your doctor will carry out tests before and during your treatment with Enhertu.
- Depending on the side effects you experience, your doctor may decide to lower your dose, temporarily stop your treatment or permanently stop your treatment.

Tell your doctor right away if you notice any of the following symptoms because some of them may be signs of a serious or possibly fatal condition.
Getting medical treatment right away may help keep these problems from becoming more serious.
- cough, shortness of breath, fever, or other new or worsening breathing problems as these may be symptoms of a lung problem.
- chills, fever, sores in your mouth, stomach pain or pain when urinating as these may be symptoms of an infection.
- new onset or worsening shortness of breath, cough, feeling tired, swelling of your hands, ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness as these may be symptoms of a heart problem.

You may experience the following side effects:

Very common (may affect more than 1 in 10 people)
- Nausea
- Feeling tired (fatigue)
- Vomiting
- Hair loss (alopecia)
- Constipation
- Feeling less hungry
- Diarrhea
- Blood tests showing increased level of liver enzymes such as transaminases

- Pain in muscles and bone
- Decrease in the number of platelets (thrombocytopenia)
- Stomach (abdominal) pain
- Infections of the upper respiratory tract
- Headache
- Weight loss
- Sores in or around your mouth (stomatitis)
- Coughing
- Fever (pyrexia)
- Low potassium in the blood (hypokalemia)
- Indigestion (dyspepsia)
- Severe nosebleeds (epistaxis)
- Difficulty breathing (dyspnea)
- Dizziness
- Rash
- Numbness and tingling in hands and feet

Common (may affect up to 1 in 10 people)
- Abnormal blood test (increase in blood alkaline phosphatase)
- Abnormal blood test (increase in blood bilirubin or blood creatinine)
- Bad taste in mouth (dysgeusia)
- Dry eye
- Itching (pruritus)
- Darkening of the skin (skin hyperpigmentation)
- Blurry vision
- Excessive gas in the stomach or intestine, bloating
- Feeling thirsty, dry mouth (dehydration)
- Inflammation of the stomach (gastritis)
- Reactions related to the infusion of the medicine
- Infection of the lungs (pneumonia)
- Swollen hands, ankles, feet (edema)

These are not all the possible side effects you may feel when taking Enhertu. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Lung problems (interstitial lung disease/pneumonitis): Cough, shortness of breath, fever, or other new or worsening breathing problems as these may be symptoms of a lung problem		✓	
Decrease in the number of white blood cells (leukocytes,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
lymphocytes, or neutrophils): Fever or infection, fatigue, aches and pains, flu-like symptoms			
Decrease in the number of red blood cells (anemia): Fatigue, pale skin, shortness of breath, weakness		✓	
Infections of the upper respiratory tract		✓	
Difficulty breathing (dyspnea)		✓	
COMMON			
Fever along with a decrease in the number of neutrophils (febrile neutropenia)		✓	
Reactions related to the infusion of the medicine. Symptoms within 24 hours of infusion: Chills or shaking, shortness of breath or wheezing, itching, rash or hives, flushing, dizziness, fever, feeling like passing out		✓	
New onset or worsening shortness of breath, cough, fatigue, swelling of your ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness as these may be symptoms of a heart problem (decreased ejection fraction)		✓	
UNCOMMON			
Serious complication of infection (sepsis)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Enhertu will be stored by the healthcare professionals at the hospital or clinic where you receive treatment.

If you want more information about Enhertu:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to date version can be found at www.astrazeneca.ca.

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