

FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Enhertu®

QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution contains 20 mg/mL of trastuzumab deruxtecan (see section 11). Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) that contains a humanised anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, produced by mammalian (Chinese Hamster Ovary) cells, covalently linked to DXd, an exatecan derivative and a topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 8 molecules of deruxtecan are attached to each antibody molecule. For the full list of excipients, see section 11.

PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
For the full list of excipients, see section 11.

Patient safety information Card

The marketing of Enhertu is subject to a risk management plan (RMP) including a "patient safety information card". The patient safety information card, emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. 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 *Dosage and Administration* (3), *Warnings and Precautions* (6.1)].**
- **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 *Warnings and Precautions* (6.4), *Use in Specific Populations* (8.1, 8.3)].**

2. Therapeutic indications

2.1 Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:

- in the metastatic setting, or
- in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

2.2 Locally Advanced or Metastatic Gastric Cancer

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

3. DOSAGE AND ADMINISTRATION

3.1 Patient Selection for Locally Advanced or Metastatic Gastric Cancer

Select patients with locally advanced or metastatic gastric cancer based on HER2 protein overexpression or HER2 gene amplification. Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

3.2 Recommended Dosage and Schedules

Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine.

First infusion: Administer infusion over 90 minutes.

Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.

Permanently discontinue ENHERTU in case of severe infusion reactions.

Premedication

ENHERTU is moderately emetogenic [see Adverse Reactions (7.1)] which includes delayed nausea and/or vomiting.

Administer prophylactic antiemetics medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.

Recommended Dosage for Metastatic Breast Cancer

The recommended dosage 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.

Recommended Dosage for Locally Advanced or Metastatic Gastric Cancer

The recommended dosage 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.

3.3 Dose Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in Tables 1 and 2.

Do not re-escalate the ENHERTU dose after a dose reduction is made.

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.

Table 1: Dose Reduction Schedule

Dose Reduction Schedule	Breast Cancer	Gastric 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		Treatment Modification
Interstitial Lung Disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)		Interrupt ENHERTU until resolved to Grade 0, then: <ul style="list-style-type: none"> • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (6.1)].
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		<ul style="list-style-type: none"> • Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (6.1)].
Neutropenia	Grade 3 (less than 1.0 to 0.5 x 10 ⁹ /L)		<ul style="list-style-type: none"> • Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 x 10 ⁹ /L)		<ul style="list-style-type: none"> • 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 1.0 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		<ul style="list-style-type: none"> • 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)		<ul style="list-style-type: none"> • Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
	Grade 4 (platelets less than 25 x 10 ⁹ /L)		<ul style="list-style-type: none"> • Interrupt ENHERTU until resolved to Grade 1 or less. • Reduce dose by one level (see Table 1).
Left Ventricular Dysfunction	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		<ul style="list-style-type: none"> • Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	<ul style="list-style-type: none"> • Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	<ul style="list-style-type: none"> • Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. • If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.

Adverse Reaction	Severity	Treatment Modification
	LVEF less than 40% or absolute decrease from baseline is greater than 20%	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Permanently discontinue ENHERTU.

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

3.4 Preparation for Administration

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU (trastuzumab deruxtecan) and not trastuzumab or ado-trastuzumab emtansine.

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.

ENHERTU (trastuzumab deruxtecan) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed [see *Dosage and Administration (3.2)*].
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- 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.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of 5% Dextrose Injection, USP. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- 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.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2°C to 8°C), allow the solution to reach room temperature prior to administration. Cover the infusion bag to protect from light.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene
- Administer ENHERTU with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.

4 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of trastuzumab deruxtecan as a white to yellowish white lyophilized powder in a single-dose vial for reconstitution and further dilution

5 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

6 WARNINGS AND PRECAUTIONS

6.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU [see *Adverse Reactions (7.1)*].

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥ 0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery [see *Dosage and Administration (3.3)*]. In cases of symptomatic ILD (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. Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD [see *Dosage and Administration (3.3)*].

Metastatic Breast Cancer

In clinical studies, of the 491 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 13% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.4% of patients treated with ENHERTU. Median time to first onset was 5.5 months (range: 1.1 to 20.8).

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

6.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

Monitor complete blood counts 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 *Dosage and Administration (3.3)*].

Metastatic Breast Cancer

In clinical studies, of the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 68% of patients. Eighteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 6 to 664). Febrile neutropenia was reported in 1.2% of patients.

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with 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 72% of patients. Fifty-

one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

6.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see *Dosage and Administration* (3.3)].

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.

Metastatic Breast Cancer

In the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, 13 cases (2.6%) of asymptomatic LVEF decrease were reported.

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

6.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see *Use in Specific Populations* (8.1), *Clinical Pharmacology* (12.1), *Nonclinical Toxicology* (13.1)]. Advise patients of the potential risks to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.1, 8.3)].

7 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease / Pneumonitis [see *Warnings and Precautions* (6.1)]
- Neutropenia [see *Warnings and Precautions* (6.2)]
- Left Ventricular Dysfunction [see *Warnings and Precautions* (6.3)]

7.1 Clinical Trials Experience

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

Metastatic Breast Cancer

The pooled safety population for patients with metastatic breast cancer described in the WARNINGS AND PRECAUTIONS reflects exposure to ENHERTU at 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) in 491 patients in DESTINY-Breast03, DESTINY-Breast01, and Study DS8201-A-J101. Among 491 patients who received ENHERTU, the median duration of treatment was 13 months (range: 0.7 to 37). In this pooled safety population, the most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea (78%), decreased white blood cell count (74%), decreased hemoglobin (68%), decreased neutrophil count (68%), increased aspartate aminotransferase (58%), fatigue (57%), decreased lymphocyte count (56%), vomiting (50%), decreased platelet count (49%), increased alanine aminotransferase (48%), increased blood alkaline phosphatase (45%), alopecia (41%), constipation (35%), hypokalemia (33%), decreased appetite (32%), diarrhea (31%), musculoskeletal pain (28%), increased transaminases (27%), respiratory infection (24%), headache (21%), and abdominal pain (21%).

DESTINY-Breast03

The safety of ENHERTU was evaluated 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 [see *Clinical Studies (14.1)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU and 7 months (range: 0.7 to 25) for patients who received ado-trastuzumab emtansine.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, white blood cell count decreased, neutrophil count decreased, aspartate aminotransferase increased, hemoglobin decreased, lymphocyte count decreased, alanine aminotransferase increased, platelet count decreased, fatigue, vomiting, blood alkaline phosphatase increased, alopecia, hypokalemia, constipation, anemia, musculoskeletal pain, diarrhea, decreased appetite, headache, abdominal pain, blood bilirubin increased, and stomatitis.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast03.

Table 3: Common Adverse Reactions ($\geq 10\%$ All Grades or $\geq 2\%$ Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast03

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	7	30	0.4
Vomiting	49	1.6	10	0.8
Constipation	34	0	20	0
Diarrhea	29	1.2	7	0.4
Abdominal pain ^a	21	0.8	8	0.4
Stomatitis ^b	20	0.8	5	0
Dyspepsia	11	0	6	0

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
General Disorders and Administration Site Conditions				
Fatigue ^c	49	6	35	0.8
Blood and Lymphatic System Disorders				
Anemia ^d	33	7	17	6
Skin and Subcutaneous Tissue Disorders				
Alopecia ^e	37	0.4	3.1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	31	1.2	25	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.6	17	0.4
Investigations				
Weight decreased	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Respiratory infection ^g	22	0.8	12	11
Epistaxis	11	0	16	0.4
Cough	11	0.4	10	0
Interstitial lung disease ^h	11	0.8	1.9	0
Nervous System Disorders				
Headache ⁱ	22	0.4	16	0
Peripheral neuropathy ^j	13	0.4	14	0.4
Dizziness	13	0.4	8	0

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

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

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

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

d Grouped term of anemia includes PTs of anemia, decreased hemoglobin, and decreased red blood cell count.

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

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

g Grouped term of respiratory infection 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.

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

i Grouped term of headache includes PTs of headache and migraine.

j Grouped term of peripheral neuropathy includes PTs of peripheral neuropathy, peripheral sensory neuropathy, and paresthesia.

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

- *Respiratory, Thoracic and Mediastinal Disorders*: dyspnea (8%)
- *Skin and Subcutaneous Tissue Disorders*: pruritus (8%) and skin hyperpigmentation (6%) [grouped term includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Nervous System Disorders*: dysgeusia (6%)
- *Metabolism and Nutrition Disorders*: dehydration (4.3%)

- *Eye Disorders*: blurred vision (3.5%)
- *Cardiac Disorders*: asymptomatic left ventricular ejection fraction decrease (2.7%) [see *Warnings and Precautions* (6.3)]
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (2.3%) [grouped term includes PTs of hypersensitivity and infusion-related reactions]
- *Blood and Lymphatic System Disorders*: febrile neutropenia (0.8%)

Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	74	8	24	0.8
Decreased neutrophil count	70	18	30	2.3
Decreased hemoglobin	64	7	38	6
Decreased lymphocyte count	55	14	23	3.9
Decreased platelet count	52	7	79	24
Chemistry				
Increased aspartate aminotransferase	67	0.8	83	5
Increased alanine aminotransferase	53	1.6	67	6
Increased blood alkaline phosphatase	49	0.8	46	0.8
Hypokalemia	35	4.7	39	1.5
Increased blood bilirubin	20	0	14	0
Increased blood creatinine	16	0.8	8	0.4

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

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-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 in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900). [see *Clinical Studies* (14.1) ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were <65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease

(2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (>20%) adverse reactions (including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, fatigue, vomiting, alopecia, increased aspartate aminotransferase, increased alanine aminotransferase, decreased platelet count, constipation, decreased appetite, diarrhea, hypokalemia, , and cough.

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

Table 5: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	79	7
Vomiting	47	3.8
Constipation	35	0.9
Diarrhea	29	1.7
Abdominal pain ^a	19	1.3
Stomatitis ^b	14	0.9
Dyspepsia	12	0
General Disorders and Administration Site Conditions		
Fatigue ^c	59	6
Skin and Subcutaneous Tissue Disorders		
Alopecia	46	0.4 ^d
Rash ^e	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	32	1.3
Blood and Lymphatic System Disorders		
Anemia ^f	31	7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	20	0
Dyspnea	13	1.3

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Epistaxis	13	0
Interstitial lung disease ^g	9	2.6 ^h
Nervous System Disorders		
Headache ⁱ	19	0
Dizziness	10	0
Infections and Infestations		
Upper respiratory tract infection ^l	15	0
Eye Disorders		
Dry eye	11	0.4 ^k

Events were graded using NCI-CTCAE version 4.03. N=number of patients exposed; PT = preferred term.

- a Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain.
- b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).
- c Grouped term of fatigue includes PTs of fatigue and asthenia.
- d This Grade 3 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for alopecia is Grade 2.
- e Grouped term of rash includes PTs of rash, pustular rash, and maculo-papular rash.
- f Grouped term of anemia includes PTs of anemia, decreased hemoglobin, decreased hematocrit, and decreased red blood cell count.
- g 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.
- h All events had fatal outcomes (n=6).
- i Grouped term of headache includes PTs of headache, sinus headache, and migraine.
- j Grouped term of upper respiratory tract infection includes PTs influenza, influenza like illness and, upper respiratory tract infection.
- k This Grade 4 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for dry eye is Grade 3.

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

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

Table 6: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU in DESTINY-Breast01 and Study DS8201-A-J101

Laboratory Parameter	ENHERTU 5.4 mg/kg N = 234	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	70	7
Decreased hemoglobin	70	7
Decreased neutrophil count	62	16
Decreased platelet count	37	3.4
Chemistry		
Increased aspartate aminotransferase	41	0.9
Increased alanine aminotransferase	38	0.4

Laboratory Parameter	ENHERTU 5.4 mg/kg N = 234	
	All Grades %	Grades 3 or 4 %
Hypokalemia	26	3.0

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

Frequencies were based on NCI-CTCAE v.4.03 grade-derived laboratory abnormalities.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see *Clinical Studies (14.2)*]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, hypokalemia, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia.

Tables 7 and 8 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 7: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

Adverse Reactions	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	63	4.8	47	1.6
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0

Adverse Reactions	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Abdominal pain ^a	14	0.8	15	3.2
Stomatitis ^b	11	1.6	4.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia ^c	58	38	31	23
Febrile neutropenia	4.8	4.8	3.2	3.2
General Disorders and Administration Site Conditions				
Fatigue ^d	55	9	44	4.8
Pyrexia	24	0	16	0
Peripheral edema	10	0	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	22	0	15	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^e	10	2.4	0	0
Hepatobiliary Disorders				
Abnormal hepatic function	8	3.2	1.6	1.6

Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term.

^a Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain.

^b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

^c Grouped term of anemia includes PTs of anemia, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit.

^d Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.

^e 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.

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

- *Cardiac Disorders*: asymptomatic left ventricular ejection fraction decrease (8%) [see *Warnings and Precautions (6.3)*]
- *Infections and Infestations*: pneumonia (6%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (1.6%)

Table 8: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased hemoglobin	75	38	55	23
Decreased white blood cell count	74	29	53	13
Decreased neutrophil count	72	51	45	23
Decreased lymphocyte count	70	28	53	12
Decreased platelet count	68	12	12	5
Chemistry				
Increased aspartate aminotransferase	58	9	32	8
Increased blood alkaline phosphatase	54	8	34	10
Increased alanine aminotransferase	47	9	17	1.7
Hypokalemia	30	4.8	18	8
Increased Blood bilirubin	24	7	5	3.4

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.4.03 grade-derived laboratory abnormalities.

7.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to ENHERTU in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Treatment-emergent anti-trastuzumab deruxtecan antibodies (ADA) developed in 2.1% (27/1311) patients who received ENHERTU across all doses. The incidence of neutralizing antibodies against trastuzumab deruxtecan was 0.1% (1/1311). Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities,

and neonatal death [see Data]. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU [see Clinical Considerations].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan.

8.2 Lactation

Risk Summary

There is no data regarding the presence of trastuzumab deruxtecan in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception

Females

ENHERTU can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose [see Nonclinical Toxicology (13.1)].

Infertility

Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

ENHERTU is not indicated for children and adolescents under 18 years old. Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 491 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 4% were 75 years or older. No overall differences in efficacy within clinical studies were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (60%) as compared to younger patients (49%).

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

8.6 Renal Impairment

No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance (CLcr) ≥ 60 and < 90 mL/min) or moderate (CLcr ≥ 30 and < 60 mL/min) renal impairment [see *Clinical Pharmacology* (12.3)]. No data are available in patients with severe renal impairment. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate or severe renal impairment [see *Warnings and Precautions* (6.1)].

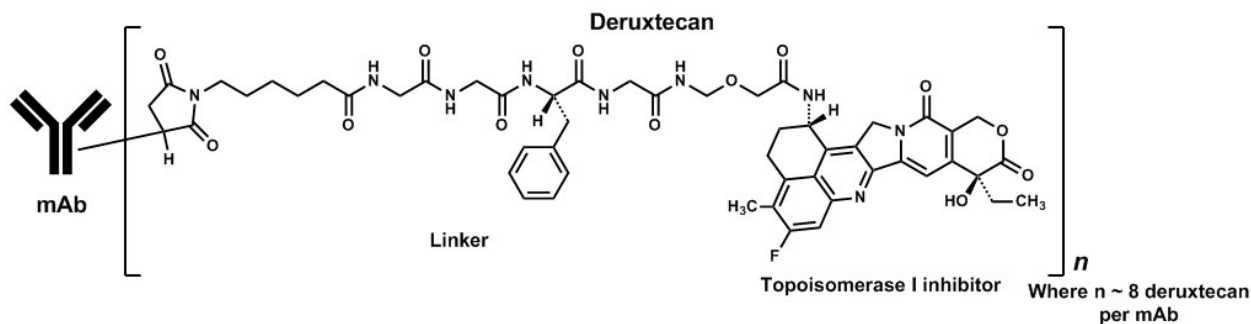
8.7 Hepatic Impairment

No dose adjustment of ENHERTU is required in patients with mild (total bilirubin \leq ULN and any AST $>$ ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see *Dosage and Administration* (3.3)]. No data are available in patients with severe (total bilirubin > 3 to 10 times ULN and any AST) hepatic impairment [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Trastuzumab deruxtecan is a HER2-directed antibody and topoisomerase inhibitor conjugate. Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase inhibitor, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of a protease-cleavable maleimide tetrapeptide linker and the topoisomerase inhibitor, DXd, which is an exatecan derivative.

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. Trastuzumab deruxtecan has the following structure:



ENHERTU (trastuzumab deruxtecan) is a sterile, white to yellowish white, preservative-free lyophilized powder in single-dose vials. Each vial delivers 100 mg of trastuzumab deruxtecan, L-histidine (4.45 mg), L-histidine hydrochloride monohydrate (20.2 mg), polysorbate 80 (1.5 mg), and sucrose (450 mg). Following reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration of trastuzumab deruxtecan is 20 mg/mL with a pH of 5.5. The resulting solution is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Trastuzumab deruxtecan is a HER2-directed antibody-drug conjugate. The antibody is a humanized anti-HER2 IgG1. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker. Following binding to HER2 on tumor cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The administration of multiple doses of ENHERTU (6.4 mg/kg every 3 weeks) did not show large mean effect (i.e. >20 ms) on the QTc interval in an open label, single-arm study in 51 patients with metastatic HER2-positive cancer.

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. Following a single dose, exposures (C_{max} 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).

Metastatic Breast Cancer

At the recommended dosage of ENHERTU for patients with HER2-positive breast cancer, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 131 $\mu\text{g/mL}$ (20%) and 4.4 ng/mL (41%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 769 $\mu\text{g}\cdot\text{day/mL}$ (28%) and 27 ng $\cdot\text{day/mL}$ (40%), respectively, based on population pharmacokinetic analysis. Accumulation of trastuzumab deruxtecan was approximately 35% at steady state (Cycle 3).

Locally Advanced or Metastatic Gastric Cancer

At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean $C_{max,ss}$ of trastuzumab deruxtecan and DXd were 126 $\mu\text{g/mL}$ (18%) and 5.2 ng/mL (42%), respectively, and the AUC $_{ss}$ of trastuzumab deruxtecan and DXd were 743 $\mu\text{g}\cdot\text{day/mL}$ (26%) and 33 ng $\cdot\text{day/mL}$ (43%), respectively, based on population pharmacokinetic analysis. Accumulation of trastuzumab deruxtecan was approximately 39% at steady-state (Cycle 3).

Distribution

Based on population pharmacokinetic analysis, the estimated volume of distribution of the central compartment (V_c) of trastuzumab deruxtecan was 2.71 L.

For humans, DXd plasma protein binding is approximately 97% and the blood-to-plasma ratio is approximately 0.6, in vitro.

Elimination

The median elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer and gastric cancer was approximately 5.7-5.8 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of trastuzumab deruxtecan was 0.42 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd in patients with HER2-positive metastatic breast cancer and gastric cancer was approximately 5.5-5.8 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 19.4 L/h.

Metabolism

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, DXd is primarily metabolized by CYP3A4.

Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (20-96 years), race (Asian [n=759], White [n=449], Black or African American [n=30] and Other [n=69]), sex, body weight (27.3-125.4 kg), mild (total bilirubin \leq ULN and any AST $>$ ULN or total bilirubin $>$ 1 to 1.5 times ULN and any AST, n=385) hepatic impairment, mild (creatinine clearance [CLcr] \geq 60 and $<$ 90 mL/min, n=529) or moderate (CLcr \geq 30 and $<$ 60 mL/min; n=210) renal impairment based on population pharmacokinetic analysis.

The pharmacokinetics of trastuzumab deruxtecan or DXd in patients with moderate to severe hepatic impairment (total bilirubin $>$ 1.5 ULN with any AST) or severe renal impairment (CLcr $<$ 30 mL/min) is unknown.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A Inhibitors on DXd: Coadministration of itraconazole, a strong CYP3A inhibitor, with multiple doses of ENHERTU increased steady state $AUC_{0-17 \text{ days}}$ of trastuzumab deruxtecan by 11% and DXd by 18%. The impact of these changes is not clinically meaningful.

Effect of OATP Inhibitors on DXd: Coadministration of ritonavir, a dual inhibitor of OATP1B/CYP3A, with multiple doses of ENHERTU increased steady state $AUC_{0-17 \text{ days}}$ of trastuzumab deruxtecan by 19% and DXd by 22%. The impact of these changes is not clinically meaningful.

In Vitro Studies

Effects of DXd on CYP Enzymes: DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A nor induce CYP1A2, CYP2B6, or CYP3A.

Effects of DXd on Transporters: At clinically relevant concentrations (steady-state C_{max} of \sim 0.2 $\mu\text{mol/L}$), DXd has a low potential to inhibit OAT1 (IC_{50} value of 12.7 $\mu\text{mol/L}$), OAT3, OCT1, OCT2, OATP1B1 (IC_{50} value of 14.4 $\mu\text{mol/L}$), OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

Effects of Other Drugs on DXd: DXd is a substrate of OATP1B1, OATP1B3, MATE2-K, P-gp, MRP1 and BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

The topoisomerase inhibitor component of trastuzumab deruxtecan, DXd, 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.

Fertility studies have not been conducted with trastuzumab deruxtecan. In a six-week repeat-dose toxicity study in rats, intravenous administration of trastuzumab deruxtecan resulted in spermatid retention at 20 mg/kg and 60 mg/kg (approximately 4 and 9 times the human recommended dose of 5.4 mg/kg based on AUC, respectively). Decreased testes and epididymides weights, tubular atrophy/degeneration in testes, and reduced sperm count in epididymides were observed at a dose of 197 mg/kg (19 times the human recommended dose of 5.4 mg/kg based on AUC). In a three-month repeat-dose toxicity study in monkeys, intravenous administration of trastuzumab deruxtecan resulted in decreased numbers of round spermatids in the testes at seminiferous tubule stages V to VI at ≥ 30 mg/kg (≥ 7 times the human recommended dose of 5.4 mg/kg based on AUC). Evidence of reversibility was observed in monkeys by the end of a three-month recovery period.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

DESTINY-Breast03

The efficacy of ENHERTU was evaluated in study DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ILD/pneumonitis at screening, or clinically significant cardiac disease. Patients were also excluded for untreated and symptomatic brain metastases, ECOG performance status >1 , or 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 ado-trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for all patients at baseline. The major efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and overall survival (OS). Confirmed objective response rate (ORR) was an additional outcome measure.

The median age was 54 years (range: 20-83); 80% were <65 years and 99.6% were female. The majority of patients were Asian (60%), White (27%) and Black (3.6%). Eleven percent (11%) of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (63%) or 1 (37%) at baseline. Seventy-three percent had visceral disease, 16% had brain metastases at baseline, 52% were hormone receptor positive and 48% of patients had 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 10%.

Efficacy results are summarized in Table 9 and Figure 1. At the time of the PFS analysis, 16% of patients had died and overall survival (OS) was immature.

Table 9: Efficacy Results in DESTINY-Breast03

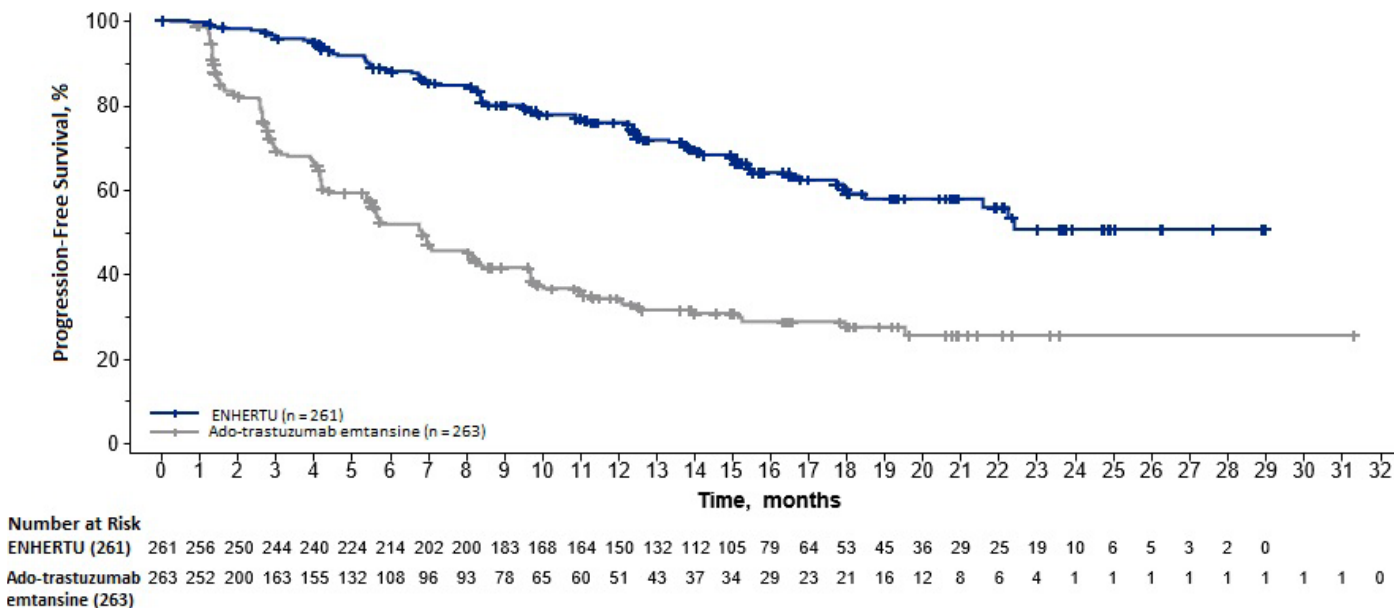
Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
Progression-Free Survival (PFS) per BICR		
N	261	263

Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
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*	
Confirmed Objective Response Rate (ORR) per BICR*		
N	248	241
n (%)	205 (82.7)	87 (36.1)
95% CI	(77.4, 87.2)	(30.0, 42.5)
Complete Response n (%)	39 (15.7)	20 (8.3)
Partial Response n (%)	166 (66.9)	67 (27.8)

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

*Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.

**Figure 1: Kaplan-Meier Plot of Progression-Free Survival per BICR
(Intent-to-Treat Analysis Set)**



DESTINY-Breast01

The efficacy of ENHERTU was evaluated in study DESTINY-Breast01 (NCT03248492), a multicenter, single-arm, trial that enrolled 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status >1. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with brain metastases at baseline. The major efficacy outcomes were confirmed objective response rate (ORR) assessed by independent central review (ICR) using RECIST v1.1 and duration of response (DOR).

The median age was 55 years (range: 28-96); 76% of patients were < 65 years. All 184 patients were female, and the majority were White (55%) or Asian (38%). Patients had an ECOG performance status of 0 (55%) or 1 (44%) at baseline. Ninety-two percent had visceral disease, 29% had bone metastases, and 13% had brain metastases. Fifty-three percent were hormone receptor positive. Sum of diameters of target lesions were < 5 cm in 42%, and ≥ 5 cm in 50% (not evaluable by central review in 8% of patients).

The median number of prior cancer regimens in the locally advanced/metastatic setting was 5 (range: 2-17). All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab.

Efficacy results are summarized in Table 10.

Table 10: Efficacy Results by Independent Central Review in DESTINY-Breast01

Efficacy Parameter	DESTINY-Breast01 N=184
Confirmed Objective Response Rate (95% CI)	60.3% (52.9, 67.4)
Complete Response	4.3%
Partial Response	56.0%
Duration of Response* Median, months (95% CI)†	14.8 (13.8, 16.9)

ORR 95% CI calculated using Clopper-Pearson method

*DOR is based on median duration of follow-up of 11.1 months.

†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

14.2 Locally Advanced or Metastatic Gastric Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Gastric01 (NCT03329690), a multicenter, open-label, randomized trial conducted in Japan and South Korea that enrolled 188 adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH positive), locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. HER2 expression was determined by a central lab on tissue obtained either before or after prior trastuzumab treatment. Patients were excluded for a history of treated or current ILD, a history of clinically significant cardiac disease, active brain metastases, or ECOG performance status >1.

Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician's choice of chemotherapy: irinotecan monotherapy (N=55) 150 mg/m² intravenously every 2 weeks or paclitaxel monotherapy (N=7) 80 mg/m² intravenously weekly. Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH+), ECOG performance status (0 or 1), and region (Japan or South Korea). Tumor imaging assessments were performed at screening and every 6 weeks from the first treatment dose. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and OS in the intent-to-treat population. Additional efficacy outcomes were PFS and DOR.

The median age was 66 years (range 28 to 82); 76% were male; and 100% were Asian. All patients received a trastuzumab product. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 45%

had three or more prior regimens in the locally advanced or metastatic setting. A total of 30% of patients were identified as HER2-positive using tissue obtained following prior treatment with a trastuzumab product.

Efficacy results are summarized in Table 11, and the Kaplan-Meier curve for OS is shown in Figure 2.

Table 11: Efficacy Results in DESTINY-Gastric01

Efficacy Parameter	ENHERTU N=126	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)	
p-value*	0.0097	
Progression-Free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Confirmed Objective Response Rate (ORR)§		
n (%)	51 (40.5)	7 (11.3)
95% CI¶	(31.8, 49.6)	(4.7, 21.9)
p-value#	<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Duration of Response (DOR)§		
Median, months (95% CI)†	11.3 (5.6, NR)	3.9 (3.0, 4.9)

CI = confidence interval; NR = not reached

*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

‡Based on the stratified Cox proportional hazards regression model (stratified by region)

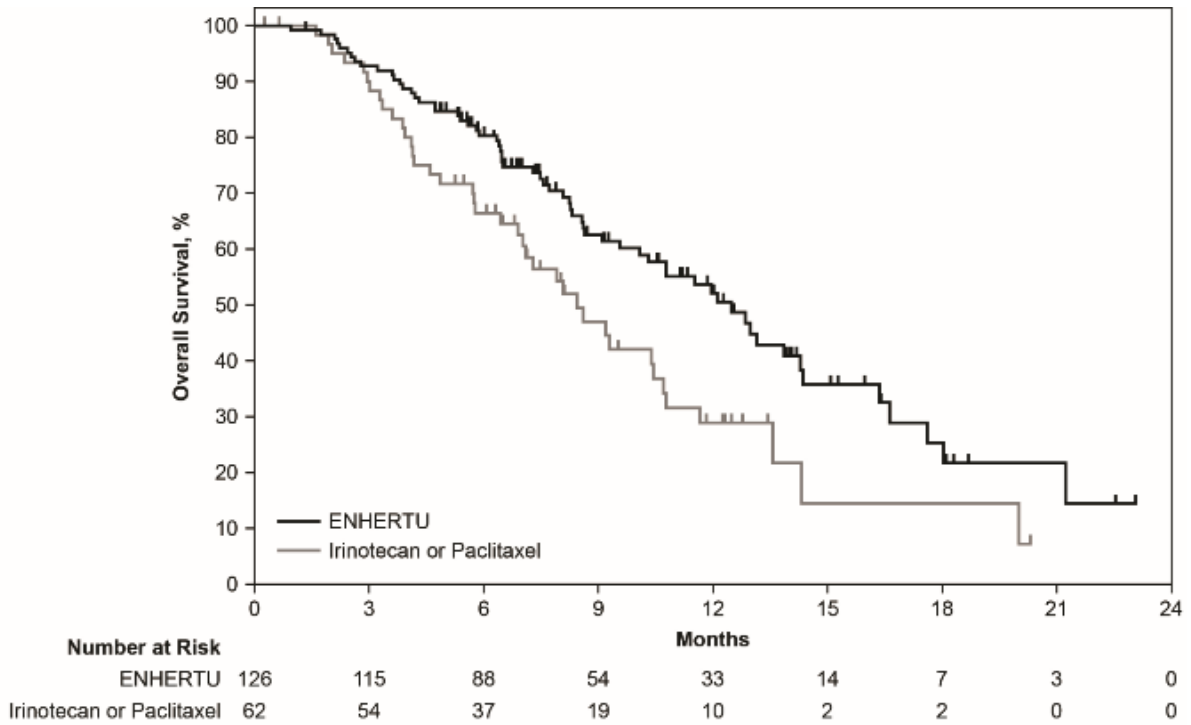
*Based on the stratified log-rank test (stratified by region)

§Assessed by independent central review

¶95% exact binomial confidence interval

#Based on the stratified Cochran-Mantel-Haenszel test (stratified by region)

Figure 2: Kaplan-Meier Plot of Overall Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

ENHERTU (trastuzumab deruxtecan) for injection is a white to yellowish white lyophilized powder supplied as:

Carton Contents
One 100 mg single-dose vial

Store vials in a refrigerator at 2°C to 8°C in the original carton to protect from light until time of reconstitution. Do not freeze. Do not shake the reconstituted or diluted solution [see Dosage and Administration (3.4)].

16.2 Special Handling

ENHERTU (trastuzumab deruxtecan) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Manufactured by:

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1, 85276 Pfaffenhofen, Germany

License holder:

AstraZeneca (Israel) Ltd.,
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Registration number: 167-74-36545-00

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