ENHERTU®
(trastuzumab deruxtecan)

1. NAME OF THE MEDICINAL PRODUCT

ENHERTU powder for concentrate for solution for infusion 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

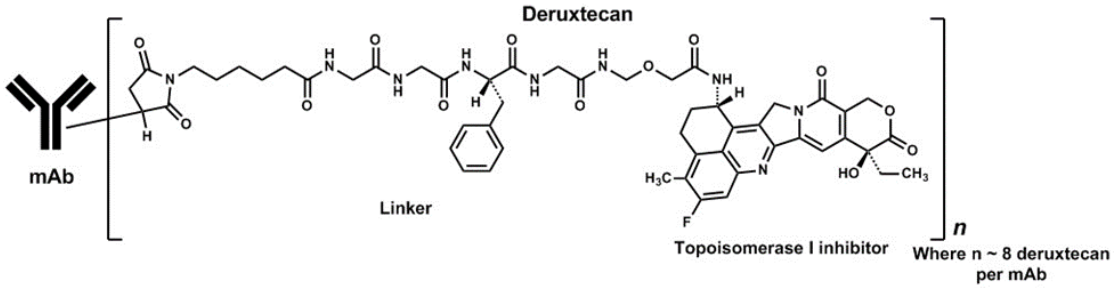
ENHERTU Powder for Concentrate for Solution for Infusion 100 mg

One vial of lyophilized powder for concentrate for solution for infusion delivers 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of trastuzumab deruxtecan (see section 6.6).

Trastuzumab deruxtecan is an 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, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

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

For excipients, see section 6.1.



3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to yellowish-white lyophilized powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Breast Cancer

HER2-Positive

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.

HER2-Low

ENHERTU as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) 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.

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 two or more prior regimens, including a trastuzumab-based regimen.

4.2 Posology and method of administration

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.

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

Patient Selection for HER2-low Metastatic Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH- tumor status.

Premedication

ENHERTU is emetogenic (see section 4.7), which includes delayed nausea and/or vomiting. Prior to each dose of ENHERTU, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Posology

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 reactions.

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.

Locally Advanced or Metastatic Gastric 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.

Dose Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per guidelines provided in Tables 1 and 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 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: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section 4.4).
	Symptomatic ILD/Pneumonitis (Grade 2 or greater)	• Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section 4.4).
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).

Adverse Reaction	Severity		Treatment Modification
Febrile Neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour		• Interrupt ENHERTU until resolved. • Reduce dose by one level (see Table 1).
Left Ventricular Ejection Fraction (LVEF) Decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. • If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue ENHERTU.

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

Delayed or Missed Dose

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

Special Populations

Geriatrics

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

Of the 1590 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 30.3% were 65 years or older and 5.3% were 75 years or older. No overall difference in efficacy was observed based on age. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (55.1%) as compared to younger patients (48.9%).

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 difference in efficacy was observed based on age. There was a higher incidence of ≥Grade 3 adverse reactions observed in younger patients (87%) as compared to patients aged 65 years or older (76%).

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab deruxtecan.

Pediatrics

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.

Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment. Limited data are available in patients with severe renal impairment. A higher incidence of Grade 1 and 2 ILD/pneumonitis leading to an increase in discontinuation of therapy has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see section 4.4).

Hepatic Impairment

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

Method of Administration

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

For instructions on reconstitution and dilution of ENHERTU before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Interstitial Lung Disease/Pneumonitis

Cases of interstitial lung disease (ILD) and/or pneumonitis have been reported with ENHERTU (see section 4.7). Fatal outcomes have been observed.

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/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). ENHERTU should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section 4.2). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. ENHERTU should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section 4.2). Patients with a history of ILD/pneumonitis or with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see section 4.2).

In clinical studies (n=1590) across multiple tumor types, ILD occurred in 14.3% of patients treated with ENHERTU 5.4 mg/kg and above as determined by independent review. Most ILD cases were Grade 1 (3.7%) and Grade 2 (7.7%). Grade 3 cases occurred in 1.2% and Grade 4 cases occurred in 0.1% of patients. Grade 5 events occurred in 1.6% of patients. One patient had pre-existing ILD that worsened post treatment leading to Grade 5 ILD. Median time to first onset was 5.4 months (range: -0.5 to 23.3).

Neutropenia

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

Complete blood counts should be monitored prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction (see section 4.2).

In clinical studies (n=1590) across multiple tumor types, neutropenia was reported in 37.9% of patients treated with ENHERTU 5.4 mg/kg and above and 21.1% had Grade 3 or 4 events. Median time to first onset was 22 days (range: 1 day to 24.8 months). Febrile neutropenia was reported in 2.0% of patients.

Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment

interruption. ENHERTU should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. ENHERTU should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see section 4.2).

In clinical studies (n=1590) across multiple tumor types in patients treated with ENHERTU 5.4 mg/kg and above, LVEF decrease was reported in 3.0% of patients, of which 0.4% were Grade 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.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of ENHERTU can also cause embryo-fetal harm when administered to a pregnant woman (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

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 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.

4.6 Pregnancy and lactation

Contraception in Males and Females

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

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

Pregnancy

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 postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of ENHERTU can also cause embryo-fetal harm when administered to a pregnant woman (see section 5.3).

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

Breastfeeding

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

Women of Childbearing Potential

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

Fertility

No dedicated fertility studies have been conducted with ENHERTU. Based on results from animal toxicity studies, ENHERTU may impair male reproductive function and fertility.

It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek 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.

4.7 Undesirable effects

Summary of the Safety Profile

The pooled safety population has been evaluated for patients who received at least one dose of ENHERTU 5.4 mg/kg and above (n=1590), across multiple tumor types in clinical studies. The median duration of treatment in this pool was 7.8 months (range: 0.2 to 41.0).

Metastatic Breast Cancer

DESTINY-Breast03

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

In DESTINY-Breast03 (N=257), the most common adverse reactions (frequency ≥20%) were nausea (75.9%), fatigue (49.4%), vomiting (49.0%), neutropenia (42.8%), alopecia (37.0%),

constipation (34.2%), anemia (32.7%), transaminases increased (31.5%), musculoskeletal pain (31.1%), leukopenia (30.4%), decreased appetite (29.2%), diarrhea (29.2%), thrombocytopenia (25.7%), headache (21.8%), and abdominal pain (21.0 %). The most common serious adverse reactions (frequency >1%) were interstitial lung disease (2.3%) and vomiting (1.9%).

In DESTINY-Breast03, dose interruptions due to adverse reactions occurred in 34.2% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (16.7%), leukopenia (5.1%), thrombocytopenia (4.3%), fatigue (4.3%), 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%).

Tabulated List of Adverse Reactions

The adverse reactions in patients with unresectable or metastatic HER2-positive breast cancer in DESTINY-Breast03 are presented in Table 3. The adverse reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness in the ENHERTU arm.

Table 3 Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic HER2-positive Breast Cancer in DESTINY-Breast03

MedDRA System Organ Class/Preferred Term or Grouped Term	**ENHERTU (5.4 mg/kg) N=257**			**Trastuzumab emtansine (3.6 mg/kg) N=261**		
	Any Grade (%)		**Grade 3-4 (%)[a]**	**Any Grade (%)**		**Grade 3-4 (%)[a]**
Blood and Lymphatic System Disorders						
Neutropenia[b]	Very common	42.8	19.1	Very common	11.9	3.1
Anemia[c]	Very common	32.7	7.4	Very common	17.2	5.7
Leukopenia[d]	Very common	30.4	6.6	Common	8.4	0.4
Thrombocytopenia[e]	Very common	25.7	7.4	Very common	53.3	25.7
Lymphopenia[f]	Very common	11.3	3.9	Common	3.4	1.1
Febrile neutropenia	Uncommon	0.8	0.8	N/A	0	0
Eye Disorders						
Vision blurred	Common	3.5	0	Common	1.1	0
Gastrointestinal Disorders						
Nausea	Very common	75.9	6.6	Very common	30.3	0.4

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU (5.4 mg/kg) N=257			Trastuzumab emtansine (3.6 mg/kg) N=261		
	Any Grade (%)		Grade 3-4 (%)[a]	Any Grade (%)		Grade 3-4 (%)[a]
Vomiting	Very common	49.0	1.6	Common	10.0[g]	0.8
Constipation	Very common	34.2	0	Very common	19.5	0
Diarrhea	Very common	29.2	1.2	Common	6.9	0.4
Abdominal pain[h]	Very common	21.0	0.8	Common	7.7	0.4
Stomatitis[i]	Very common	19.8	0.8	Common	5.4	0
Dyspepsia	Very common	11.3	0	Common	6.1	0
General Disorders and Administration Site Conditions						
Fatigue[j]	Very common	49.4	5.8	Very common	34.9	0.8
Hepatobiliary Disorders						
Transaminases increased[k]	Very common	31.5	2.3	Very common	46.4	7.7
Injury, Poisoning and Procedural Complications						
Infusion-related reaction[l]	Common	2.3	0	Common	2.7	0
Investigations						
Weight decreased	Very common	16.7	1.2	Common	6.1	0.4
Blood alkaline phosphatase increased	Very common	13.6	0.4	Very common	11.5	0
Blood bilirubin increased[m]	Common	8.6	0.4	Common	6.1	0.4
Blood creatinine increased	Common	4.3	0	Common	1.1	0
Metabolism and Nutrition Disorders						
Decreased appetite	Very common	29.2	1.6	Very common	16.9	0.4
Hypokalemia[n]	Very common	12.8	3.5	Common	10.0[g]	0.8
Dehydration	Common	4.3	0.4	N/A	0	0
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal pain[o]	Very common	31.1	1.2	Very common	25.3	0.4
Nervous System Disorders						

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU (5.4 mg/kg) N=257			Trastuzumab emtansine (3.6 mg/kg) N=261		
	Any Grade (%)		Grade 3-4 (%)[a]	Any Grade (%)		Grade 3-4 (%)[a]
Headache[p]	Very common	21.8	0.4	Very common	16.1	0
Dizziness	Very common	12.5	0.4	Common	8.4	0
Dysgeusia	Common	5.8	0	Common	3.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	Very common	11.3	0	Very common	16.1	0.4
Cough	Very common	10.5	0.4	Common	10.0[g]	0
Interstitial lung disease[q]	Very common	10.5	0.8	Common	1.9	0
Dyspnea	Common	8.2	0.4	Common	5.0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	Very common	37.0	0.4	Common	3.1	0
Pruritus	Common	8.2	0	Common	6.9	0.4
Skin hyperpigmentation[r]	Common	5.8	0	N/A	0	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
[a] No Grade 5 adverse reactions were reported in either arm.
[b] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[c] Grouped term of anemia includes PTs of anemia, hemoglobin 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 thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[f] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[g] Actual number prior to rounding = 9.96.
[h] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.
[i] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.
[j] Grouped term of fatigue includes PTs of fatigue, asthenia, malaise, and lethargy.
[k] 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.
[l] Grouped term of infusion-related reaction includes PTs for ENHERTU (infusion-related reaction n=5, hypersensitivity n=1) and trastuzumab emtansine (infusion-related reaction n=6, infusion-related hypersensitivity reaction n=1).
[m] Grouped term of blood bilirubin increased includes PTs of blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
[n] Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.
[o] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.
[p] Grouped term of headache includes headache and migraine.
[q] 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. No Grade 4 or Grade 5 adjudicated drug-related ILD events were reported in either arm.

[r] Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discoloration, 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. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 9.8 months (range: 0.7 to 37.1).

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

The most common adverse reactions (frequency ≥20%) were nausea (79.9%), fatigue (60.3%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), anemia (33.8%), neutropenia (32.5%), diarrhea (30.8%), thrombocytopenia (23.1%), cough (21.4%), leukopenia (20.5%), and headache (20.1%). The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.5.0) Grade ≥3 adverse reactions (frequency >1%) were neutropenia (18.8%), anemia (9.0%), nausea (6.8%), fatigue (6.4%), leukopenia (5.6%), lymphopenia (5.1%), vomiting (4.3%), thrombocytopenia (4.3%), hypokalemia (3.4%), ILD (3.0%), diarrhea (2.6%), febrile neutropenia (1.7%), dyspnea (1.7%), abdominal pain (1.3%), decreased appetite (1.3%), and alanine aminotransferase increased (1.3%). In six patients (2.6%) ILD led to death.

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

Tabulated List of Adverse Reactions

The adverse reactions in 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg are presented in Table 4. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4 Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with Trastuzumab Deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Blood and Lymphatic System Disorders	
Neutropenia[a]	Very common
Anemia[b]	Very common
Leukopenia[c]	Very common
Lymphopenia[d]	Very common
Thrombocytopenia[e]	Very common
Febrile neutropenia	Common
Eye Disorders	
Dry eye	Very common
Gastrointestinal Disorders	
Nausea	Very common
Vomiting	Very common
Diarrhea	Very common
Abdominal pain[f]	Very common
Constipation	Very common
Stomatitis[g]	Very common
Dyspepsia	Very common
General Disorders and Administration Site Conditions	
Fatigue[h]	Very common
Infections and Infestations	
Upper respiratory tract infection[i]	Very common
Injury, Poisoning and Procedural Complications	
Infusion-related reactions[j]	Common
Investigations	
Alanine aminotransferase increased	Very common
Aspartate aminotransferase increased	Very common
Metabolism and Nutrition Disorders	
Hypokalemia	Very common
Decreased appetite	Very common

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Nervous System Disorders	
Headache[k]	Very common
Dizziness	Very common
Respiratory, Thoracic and Mediastinal Disorders	
Interstitial lung disease[l]	Very common
Dyspnea	Very common
Cough	Very common
Epistaxis	Very common
Skin and Subcutaneous Tissue Disorders	
Alopecia	Very common
Rash[m]	Very common

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.
[c] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[d] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[e] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[f] Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, 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 blistering.
[h] Grouped term of fatigue includes PTs of fatigue and asthenia.
[i] Grouped term of upper respiratory tract infection includes PTs of influenza, influenza-like illness, and upper respiratory tract infection.
[j] Cases of infusion-related reactions include infusion-related reaction (N=4), hypersensitivity (N=1), and flushing (N=1).
[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.
[m] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

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 (see section 5.1). The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

In patients treated with ENHERTU in DESTINY-Breast04 (N=371), the most common adverse reactions (frequency ≥20%) were nausea (76.0%), fatigue (53.6%), vomiting (40.4%), alopecia (39.6%), anemia (38.5%), constipation (34.0%), neutropenia (34.0%), transaminases increased (32.3%), decreased appetite (31.8%), diarrhea (27.0%), musculoskeletal pain (26.7%), thrombocytopenia (25.6%), and leukopenia (24.0%). The most common serious

adverse reactions (frequency >1%) were ILD/pneumonitis (4.3%), dyspnea (1.3%), musculoskeletal pain (1.3%), anemia (1.1%), febrile neutropenia (1.1%), nausea (1.1%), pyrexia (1.1%), and vomiting (1.1%). There were 5 (1.3%) patients with adverse reactions leading to death, 3 attributed to ILD (0.8%) and 1 (0.3%) each for dyspnea and febrile neutropenia.

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

Tabulated List of Adverse Reactions

The adverse reactions in patients with unresectable or metastatic HER2-low breast cancer in DESTINY-Breast04 are presented in Table 5. The adverse reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness in the ENHERTU arm.

Table 5 Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic HER2-low Breast Cancer in DESTINY-Breast-04

MedDRA System Organ Class/Preferred Term or Grouped Term	**ENHERTU 5.4 mg/kg N=371**			**Chemotherapy N=172**		
	Any Grade (%)		**Grade 3 or 4 (%)**	**Any Grade (%)**		**Grade 3 or 4 (%)**
Blood and Lymphatic System Disorders						
Anemia[a]	Very common	38.5	10.2	Very common	27.3	5.2
Neutropenia[b]	Very common	34.0	14.0	Very common	52.3	41.3
Thrombocytopenia[c]	Very common	25.6	5.9	Common	9.3	0.6
Leukopenia[d]	Very common	24.0	6.7	Very common	32.6	19.2
Lymphopenia[e]	Common	8.6	5.4	Common	7.6	3.5
Febrile neutropenia	Common	1.1	0.8	Common	3.5	3.5
Eye Disorders						
Vision blurred[f]	Common	4.9	0	Common	2.9	0
Gastrointestinal Disorders						
Nausea	Very common	76.0	4.6	Very common	30.2	0
Vomiting	Very common	40.4	1.6	Very common	13.4	0
Constipation	Very common	34.0	0.8	Very common	22.1	0
Diarrhea	Very common	27.0	1.3	Very common	22.1	1.7
Abdominal pain[g]	Very common	17.5	0.5	Very common	13.4	0
Stomatitis[h]	Very common	13.2	0.3	Very common	11.0	0.6

Abdominal distension	Common	5.4	0	Common	2.9	0.6
Gastritis	Common	2.7	0.3	Uncommon	0.6	0
Flatulence	Common	2.4	0	N/A	0	0
General Disorders and Administration Site Conditions						
Fatigue[i]	Very common	53.6	8.6	Very common	48.3	4.7
Pyrexia	Very common	12.4	0.3	Very common	12.8	0
Hepatobiliary Disorders						
Transaminases increased[j]	Very common	32.3	5.7	Very common	31.4	9.9
Infections and Infestations						
Upper respiratory tract infection[k]	Very common	13.7	0.3	Common	5.2	0
Injury, Poisoning and Procedural Complications						
Infusion-related reaction[l]	Uncommon	0.5	0	Common	1.2	0.6
Investigations						
Weight decreased	Very Common	16.2	0.3	Common	8.1	0
Blood alkaline phosphatase increased	Common	9.7	0.3	Common	2.9	0
Blood bilirubin increased[m]	Common	8.6	2.2	Common	5.2	0.6
Blood creatinine increased	Common	3.8	0.5	Common	4.1	0
Metabolism and Nutrition Disorders						
Decreased appetite	Very common	31.8	2.4	Very common	19.2	1.2
Hypokalemia[n]	Very common	11.1	2.7	Common	7.6	1.2
Dehydration	Common	1.9	0.3	Common	1.2	0
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal pain[o]	Very common	26.7	1.3	Very common	26.2	0
Nervous System Disorders						
Headache[p]	Very common	14.8	0.3	Common	6.4	0
Dysgeusia	Common	10.0	0	Common	9.3	0.6
Respiratory, Thoracic and Mediastinal Disorders						
Interstitial lung disease[q]	Very common	12.1	1.3	Uncommon	0.6	0
Epistaxis	Very common	10.5	0	Common	1.2	0
Dyspnea	Very common	10.2	1.3	Common	9.3	1.2
Cough	Common	9.7	0	Common	8.1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	Very common	39.6	0	Very Common	33.1	0
Rash[r]	Very common	10.8	0	Common	8.7	0.6
Pruritus	Common	3.2	0.3	Common	4.1	0
Skin hyperpigmentation[s]	Common	2.7	0	Uncommon	0.6	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
[a] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
[b] Grouped term of neutropenia includes PTs of neutropenia and neutrophil 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, and malaise.
[j] Grouped term of transaminases increased includes PTs of aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.
[k] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.
[l] Grouped term of infusion-related reaction includes PTs for ENHERTU (injection site reaction n=1, chills n=1) and chemotherapy (rash pustular n=1, hypersensitivity n=1).
[m] Grouped term of blood bilirubin increased includes PTs of blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
[n] Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.
[o] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, and musculoskeletal chest pain.
[p] Grouped term of headache includes PTs of headache and migraine.
[q] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and radiation pneumonitis. For chemotherapy: sarcoidosis.
[r] Grouped term of rash includes PTs of rash, rash pustular, rash maculo-papular, rash papular, rash macular, and rash pruritic.
[s] Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder.

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. patients received intravenously at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or physician's choice of chemotherapy: either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in ENHERTU-treated patients and 2.8 months (range: 0.5 to 13.1) in physician's choice-treated patients: 2.8 months (range: 0.5 to 7.4) in the irinotecan group and 4.6 months (range: 0.9 to 13.1) in the paclitaxel group.

The study population characteristics in the ENHERTU group and the physician's choice group were similar. The median age was 66 years (range 28 to 82), 76% were male, 100% were Asian, and 49% had an ECOG performance status 0 and 51% had an ECOG performance status of 1. The study excluded patients with a history of treated ILD and/or ILD at screening, and patients with a history of clinically significant cardiac disease.

The most common adverse reactions in patients treated with ENHERTU 6.4 mg/kg (frequency ≥20%) were neutropenia (63.2%), nausea (63.2%), decreased appetite (60.0%), anemia (57.6%), fatigue (55.2%), thrombocytopenia (39.2%), leukopenia (37.6%), diarrhea (32.0%), vomiting (26.4%), constipation (24.0%), pyrexia (24.0%), alopecia (22.4%), and lymphopenia (21.6%). The most common NCI CTCAE v.5.0 Grade ≥3 adverse reactions (frequency >2%) were neutropenia (51.2%), anemia (37.6%), leukopenia (20.8%), decreased appetite (16.8%),

thrombocytopenia (11.2%), lymphopenia (11.2%), fatigue (8.8%), febrile neutropenia (4.8%), nausea (4.8%), hypokalemia (4.0%), hepatic function abnormal (3.2%), blood alkaline phosphatase increased (3.2%), diarrhea (2.4%), dehydration (2.4%), aspartate aminotransferase increased (2.4%), and ILD (2.4%).

Dose interruptions due to adverse reactions occurred in 55.2% of patients treated with 6.4 mg/kg of ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (28.0%), anemia (11.2%), decreased appetite (8.8%), leukopenia (8.0%), fatigue (7.2%), thrombocytopenia (4.0%), ILD (3.2%), lymphopenia (3.2%), pneumonia (3.2%), upper respiratory tract infection (3.2%), diarrhea (2.4%), and hypokalemia (2.4%). Dose reductions occurred in 30.4% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (12.8%), decreased appetite (9.6%), fatigue (8.0%), nausea (4.8%), and febrile neutropenia (2.4%). Discontinuation of therapy due to an adverse reaction occurred in 11.2% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (5.6%).

Tabulated List of Adverse Reactions

The adverse reactions in 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who received at least one dose of ENHERTU 6.4 mg/kg are presented in Table 6. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 6 Tabulated List of Adverse Reactions in Patients with Locally Advanced or Metastatic HER2-positive Gastric or GEJ Adenocarcinoma Treated with Trastuzumab Deruxtecan 6.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	**Frequency**
Blood and Lymphatic System Disorders	
Neutropenia[a]	Very common
Anemia[b]	Very common
Leukopenia[c]	Very common
Thrombocytopenia[d]	Very common
Lymphopenia[e]	Very common
Febrile neutropenia	Common
Gastrointestinal Disorders	
Nausea	Very common
Diarrhea	Very common
Stomatitis[f]	Very common
Abdominal pain[g]	Very common

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Vomiting	Very common
Constipation	Very common
General Disorders and Administration Site Conditions	
Fatigue[h]	Very common
Pyrexia	Very common
Edema peripheral	Very common
Hepatobiliary Disorders	
Hepatic function abnormal	Common
Infections and Infestations	
Pneumonia	Common
Upper respiratory tract infection[i]	Common
Injury, Poisoning and Procedural Complications	
Infusion-related reactions[j]	Common
Investigations	
Blood alkaline phosphatase increased	Common
Aspartate aminotransferase increased	Common
Alanine aminotransferase increased	Common
Blood bilirubin increased	Common
Metabolism and Nutrition Disorders	
Decreased appetite	Very common
Hypokalemia	Common
Dehydration	Common
Respiratory, Thoracic and Mediastinal Disorders	
Interstitial lung disease[k]	Common
Cough	Common
Epistaxis	Common
Dyspnea	Uncommon
Skin and Subcutaneous Tissue Disorders	
Alopecia	Very common
Pruritis	Common
Rash[l]	Common

MedDRA = Medical Dictionary for Regulatory Activities

PT = preferred term
[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit 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 stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
[g] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.
[h] Grouped term of fatigue includes PTs of fatigue, malaise, and asthenia.
[i] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.
[j] Cases include PT of infusion-related reaction.
[k] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
[l] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 2.0% (34/1668) 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% (1/1668). There was no association between development of antibodies and allergic-type reactions.

4.8 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors
ATC code: L01FD04

Mechanism of Action

ENHERTU, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanized anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma. Following binding to HER2 on tumor 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. The topoisomerase I inhibitor, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

Pharmacodynamic Effects

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

Clinical Efficacy

Metastatic Breast Cancer

DESTINY-Breast03

The efficacy and safety of ENHERTU 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 adjuvant therapy. Archival breast tumor 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 or symptomatic brain metastases, patients with a history of clinically significant cardiac disease, and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were 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 blinded independent central review (BICR) based on RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure. PFS based on investigator assessment, confirmed objective response rate (ORR), duration of response (DOR), Patient-Reported Outcomes (PRO), and time to hospitalization were secondary endpoints.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 524 patients randomized, the median age was 54 years (range 20 to 83); female (99.6%); Asian (59.9%), White (27.3%), Black or African American (3.6%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); previously treated and stable brain metastases (21.8%), and 48.3% of patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 9.5%. 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%).

At the prespecified interim analysis for PFS based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomized to ENHERTU compared to trastuzumab emtansine. Overall survival (OS) was immature at the time of analysis.

Efficacy results are summarized in Table 7 and Figures 1 and 2.

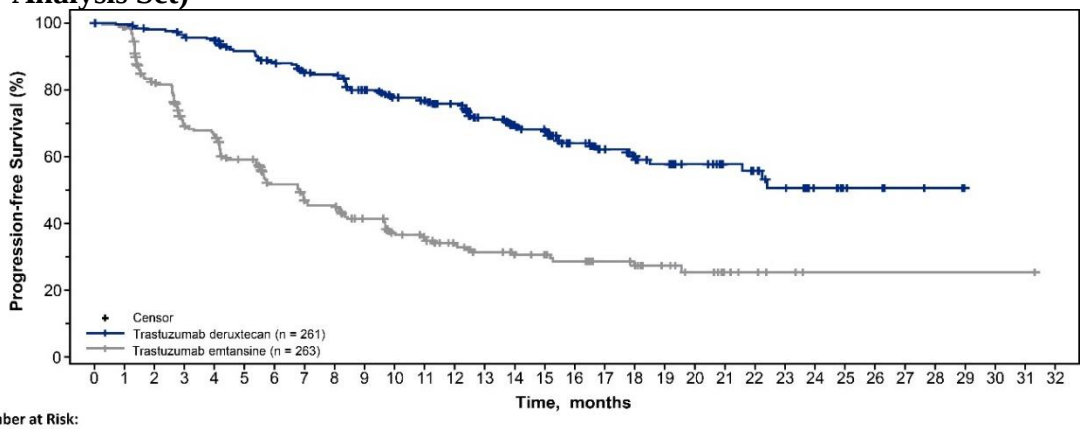
Table 7 Efficacy Results in DESTINY-Breast03 (Intent-to-Treat (ITT) Analysis Set)

Efficacy Parameter	**ENHERTU (5.4 mg/kg) N=261**	**Trastuzumab emtansine (3.6 mg/kg) N=263**
PFS per BICR		

Efficacy Parameter	ENHERTU (5.4 mg/kg) N=261	Trastuzumab emtansine (3.6 mg/kg) N=263
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 (OS)		
Number of events (%)	33 (12.6)	53 (20.2)
Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)
Survival at 12 months (95% CI)	94.1% (90.3, 96.4)	85.9% (80.9, 89.7)
Hazard ratio (95% CI)	0.55 (0.36, 0.86)	
PFS per Investigator Assessment		
Number of events (%)	78 (29.9)	168 (63.9)
Median, months (95% CI)	25.1 (22.1, NE)	7.2 (6.8, 8.3)
Hazard ratio (95% CI)	0.26 (0.20, 0.35)	
Confirmed Objective Response Rate (ORR) per BICR		
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)
Duration of Response per BICR		
Median, months (95% CI)	NR (20.3, NE)	NR (12.6, NE)

CI = confidence interval; NR= not reached, NE=not estimable, HR=hazard ratio
†presented as 6 decimal places

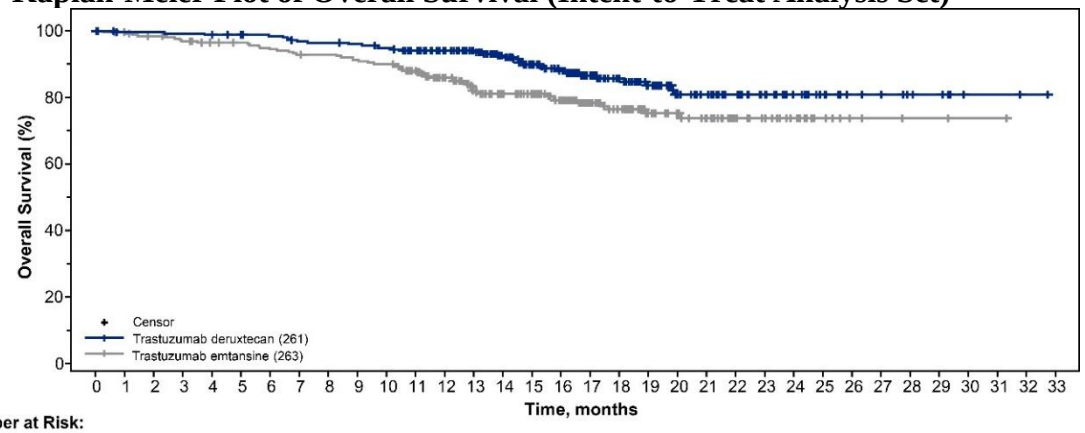
Figure 1 Kaplan-Meier Plot of Progression-free Survival Per BICR (Intent-to-Treat Analysis Set)



Number at Risk:

Trastuzumab deruxtecan (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
Trastuzumab emtansine (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

Figure 2 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Analysis Set)



Number at Risk:

Trastuzumab deruxtecan (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
Trastuzumab emtansine (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

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

As secondary outcome measures, the PRO variables showed that the Quality of Life (QoL) of patients in the ENHERTU arm was either maintained or numerically improved on treatment compared with patients in the trastuzumab emtansine arm. The mean changes from baseline in European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 global health status (the primary PRO variable) demonstrated that overall health and QoL were maintained while patients were on treatment with ENHERTU. The PRO results should be interpreted in the context of an open-label study design and therefore taken cautiously.

For all prespecified subscales, the hazard ratio (HR) for time to definitive deterioration numerically favored the ENHERTU arm over the trastuzumab emtansine arm (HR ranging from 0.69 to 0.90). Median time to definitive deterioration for the global health status from the EORTC QLQ-C30 was 9.7 months (95% CI: 7.3, 12.5) for the ENHERTU arm and 8.3 months (95% CI: 7.0, 10.3) for the trastuzumab emtansine arm (HR: 0.88 [95% CI: 0.70, 1.11]). The unadjusted p-values for the time to definitive deterioration HRs were less than 0.05 for EORTC

QLQ-C30 emotional functioning (HR 0.69 [95% CI 0.53, 0.89]; p-value = 0.0049) and pain symptoms (HR 0.75 [95% CI: 0.59, 0.95]; p-value = 0.0146) subscales, as well as for the visual analogue scale of the EuroQoL-5 dimensions-5 levels of severity (EQ-5D-5L) (HR 0.77 [95% CI: 0.61, 0.98]; p-value = 0.0354) and the arm symptoms subscale of the EORTC QLQ-BR45 (HR 0.70 [95% CI: 0.55, 0.89]; p-value = 0.0033).

Among the 18 (6.9%) patients in the ENHERTU arm and the 19 (7.2%) patients in the trastuzumab emtansine arm who were hospitalized, time to first hospitalization was longer in the ENHERTU arm (median of 219.5 days and 60.0 days, respectively).

DESTINY-Breast01

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

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumor samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease. ENHERTU was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review (ICR). Duration of response (DOR) and progression-free survival (PFS) were additional outcome measures.

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

Efficacy results are summarized in Table 8.

Table 8 Efficacy Results by Independent Central Review in DESTINY-Breast01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	**DESTINY-Breast01 N=184**
Confirmed Objective Response Rate (95% CI)	61.4% (54.0, 68.5)
Complete Response	6.5%
Partial Response	54.9%
Stable Disease	35.9%

Efficacy Parameter	DESTINY-Breast01 N=184
Progressive Disease	1.6%
Not Evaluable	1.1%
Duration of Response Median, months (95% CI)	20.8 (15.0, NR)
% with duration of response ≥6 months (95% CI)†	81.5% (72.2, 88.0)
Progression-free Survival Median, months (95% CI)†	19.4 (14.1, NR)

ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
†Based on Kaplan-Meier estimates
NR = not reached

Consistent antitumor activity was observed with ENHERTU regardless of prior pertuzumab therapy and hormone receptor status. In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 66% (95% CI: 57, 76), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 55% (95% CI: 42, 68). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 59% (95% CI: 48, 69), and those who were HR- at baseline had a confirmed ORR of 68% (95% CI: 56, 77).

DESTINY-Breast04

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast04, a Phase 3, 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-, as determined by the PATHWAY/VENTANA anti-HER-2/neu (4B5) evaluated at a central laboratory. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were 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 51.1%, capecitabine 20.1%, gemcitabine 10.3%, nab paclitaxel 10.3%, or paclitaxel 8.2%). Randomization was stratified by HER2 IHC status of tumor 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, DOR, and PROs were secondary endpoints.

Demographics and baseline tumor characteristics were 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, and 5.7% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

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

Efficacy results are summarized in Table 9 and Figures 3 and 4.

Table 9 Efficacy Results in DESTINY-Breast04

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

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)
Duration of Response per BICR*				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5, 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

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

Figure 3 Kaplan-Meier Plot of Overall Survival (Overall Population)

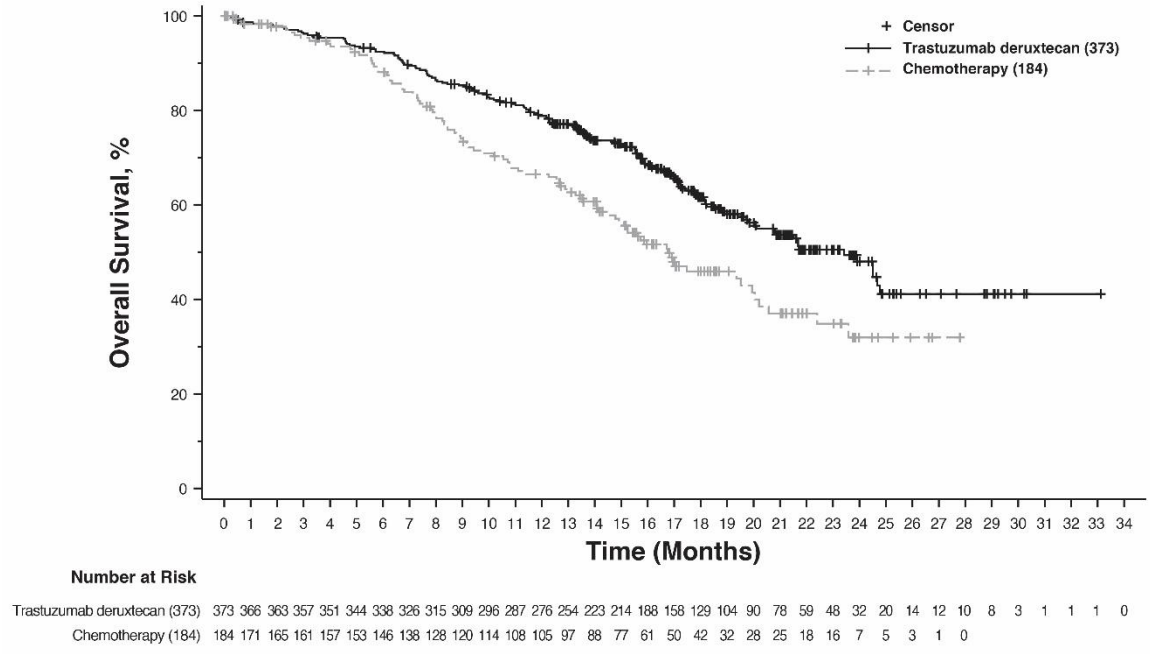
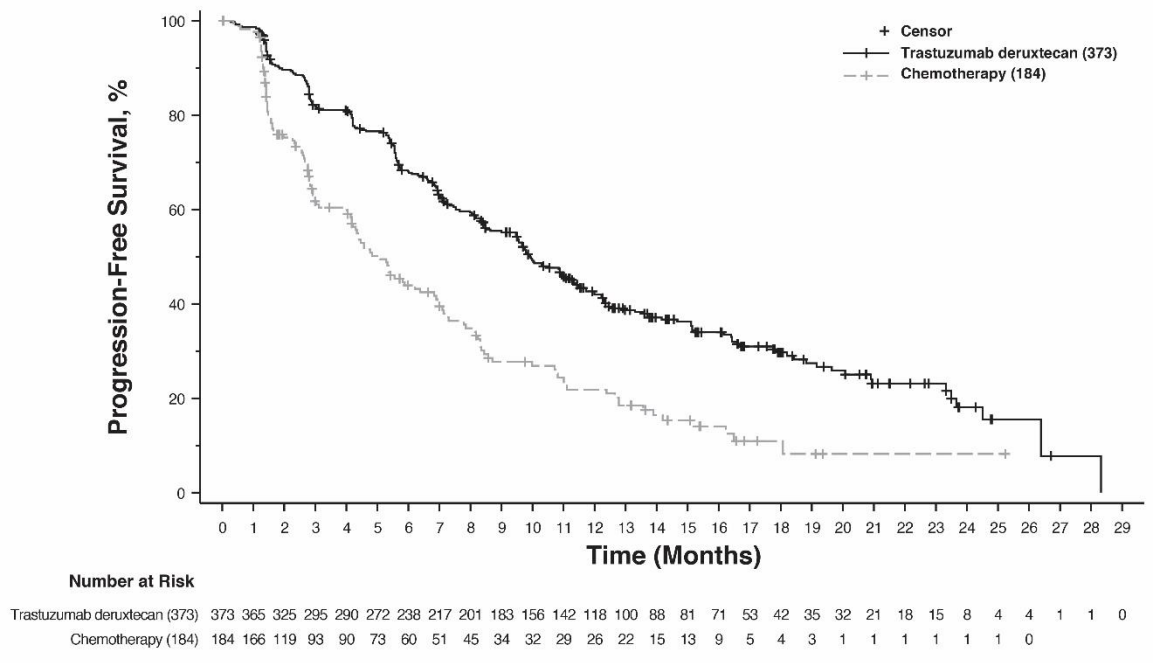


Figure 4 Kaplan-Meier Plot of Progression-free Survival per BICR (Overall Population)



Locally Advanced or Metastatic Gastric Cancer

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, multicenter, open-label, randomized study: DESTINY-Gastric01. The study included adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine agent, and a platinum agent. Patients were 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). ENHERTU was administered by intravenous infusion at 6.4 mg/kg every three weeks. Irinotecan monotherapy was administered by intravenous infusion biweekly at 150 mg/m^2. Paclitaxel monotherapy was administered by intravenous infusion weekly at 80 mg/m^2. Tumor samples were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive. The study excluded patients with a history of treated ILD and/ or ILD at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was ORR assessed by ICR based on RECIST v1.1. Overall survival (OS) was a key secondary endpoint. PFS, DOR, and confirmed ORR were additional secondary outcome measures.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 188 patients, the median age was 66 years (range 28 to 82); 76% were male; 100% were Asian. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH-positive; 65% had inoperable advanced cancer; 35% had 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 locally advanced or metastatic setting.

The study 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 are summarized in Table 10 and the Kaplan-Meier curve for OS is shown in Figure 5.

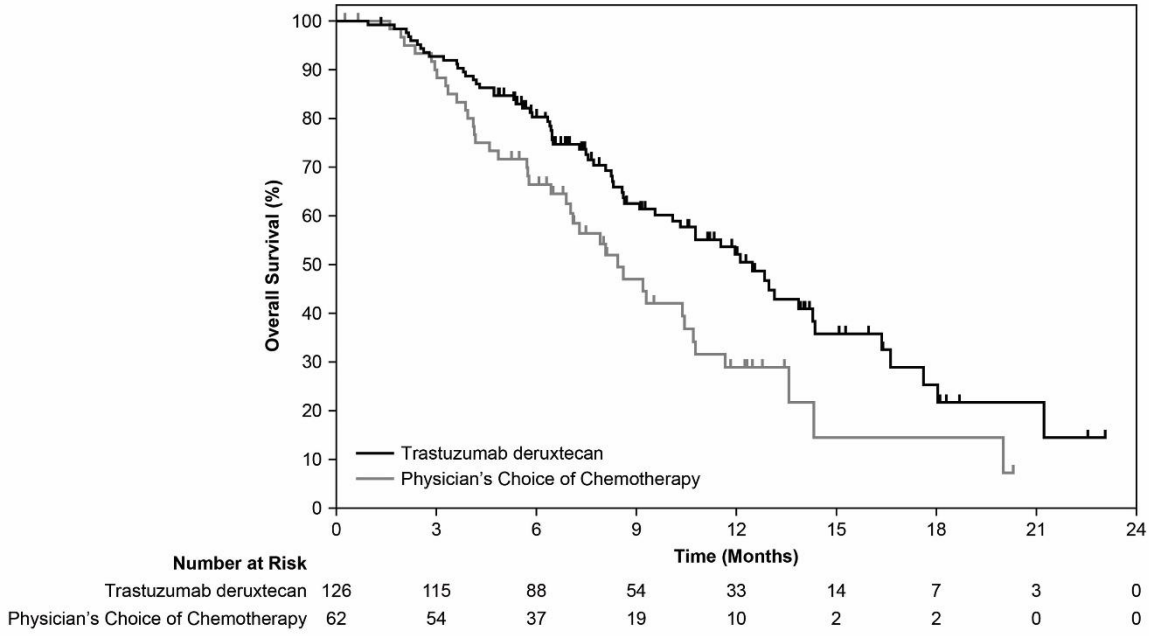
Table 10 Efficacy Results in DESTINY-Gastric01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	**ENHERTU N=126**	**Physician's Choice of Chemotherapy N=62**
Overall Survival (OS)[*]		
Median, months (95% CI)[†]	12.5 (9.6, 14.3)	8.4 (6.9,10.7)
Hazard ratio (95% CI)[‡]	0.59 (0.39, 0.88)	
Stratified Log-rank p-value[‡]	p=0.0097	
Progression-free Survival (PFS)[§]		
Median, months (95% CI)[†]	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)[‡]	0.47 (0.31, 0.71)	
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)
Stable Disease n (%)	46 (36.5)	30 (48.4)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	4 (3.2)	6 (9.7)
Confirmed Objective Response Rate (ORR)[§]		
n (%)	51 (40.5)	7 (11.3)
95% CI[¶]	(31.8, 49.6)	(4.7, 21.9)
p-value[‡,#]	p<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Stable Disease n (%)	55 (43.7)	31 (50.0)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	5 (4.0)	6 (9.7)
Duration of Confirmed Response (DOR)[§]		
Median, months (95% CI)[†]	11.3 (5.6, 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
‡Stratified by region
§Assessed by independent central review
¶95% exact binomial confidence interval
#Based on the Cochran-Mantel-Haenszel test

Figure 5 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Analysis Set)



In the exploratory subgroup analysis of patients who were HER2 IHC 3+, confirmed ORR was 46.9% for Enhertu (N=96; 95% CI: 36.6, 57.3), and 8.5% for chemotherapy (N=47; 95% CI: 2.4, 20.4). In the subgroup of patients who were IHC 2+/ISH-positive, confirmed ORR was 20.7% for Enhertu (N=29; 95% CI: 8.0, 39.7), and 20.0% for chemotherapy (N=15; 95% CI: 4.3, 48.1). In the subgroup of patients who were IHC 3+, median OS was 12.8 months for Enhertu (N=96; 95% CI: 10.3, 18.0) and 8.6 months for chemotherapy (N=47; 95% CI: 6.4, 10.7). In the subgroup of patients who were IHC 2+/ISH-positive, median OS was 10.1 months for Enhertu (N=29; 95% CI: 5.4, 13.1) and 8.4 months for chemotherapy (N=15; 95% CI 3.9, 20.0). The number of IHC 2+/ISH-positive patients was small which limits drawing any meaningful conclusions.

5.2 Pharmacokinetic properties

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan was estimated to be 2.68 L.

In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor was approximately 97%.

In vitro, the blood-to-plasma concentration ratio of the topoisomerase I inhibitor was approximately 0.6.

Biotransformation

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 population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive or HER2-low breast cancer and locally advanced or metastatic gastric or GEJ adenocarcinoma, the clearance of trastuzumab deruxtecan was estimated to be 0.41 L/day and the clearance of the topoisomerase I inhibitor was 19.6 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was 5.7-5.8 days and of released topoisomerase I inhibitor was approximately 5.5-5.8 days. In vitro, topoisomerase I inhibitor was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP. Moderate accumulation of trastuzumab deruxtecan was observed at the 5.4 mg/kg and 6.4 mg/kg doses (approximately 35%-39% in cycle 3 compared to cycle 1).

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.

Pharmacokinetics in Special Populations

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

Renal

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

Hepatic

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, higher levels of AST and total bilirubin resulted in a lower clearance of topoisomerase I inhibitor. The impact of these changes in patients with mild hepatic impairment is not expected to be clinically meaningful. The pharmacokinetics of trastuzumab deruxtecan or the topoisomerase I inhibitor in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) is unknown.

Drug Interaction Studies

Effects of Other Medicinal Products on the Pharmacokinetics of Trastuzumab Deruxtecan

In vitro studies indicate that the topoisomerase I inhibitor is metabolized mainly by CYP3A4 and is a substrate of the following transporters: P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.

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

Coadministration of itraconazole (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a strong CYP3A inhibitor, increased exposure (AUC) of trastuzumab deruxtecan by 11% and the released topoisomerase I inhibitor by 18%. The impact of these changes is not expected to be clinically meaningful.

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

Effects of Trastuzumab Deruxtecan on the Pharmacokinetics of Other Medicinal Products

In vitro studies indicate that the topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. In vitro studies indicate that the topoisomerase I inhibitor does not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters, but has an inhibitory effect on OAT1 and OATP1B1 with IC_{50} values of 12.7 and 14.4 µmol/L, respectively, which are significantly higher than steady-state C_{max} (0.02 µmol/L) of topoisomerase I inhibitor at 5.4 mg/kg dose administered every 3 weeks. No clinically meaningful drug-drug interaction is expected with drugs that are substrates of OAT1 or OATP1B1 transporters.

5.3 Nonclinical safety data

Animal Toxicology and/or Pharmacology

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.

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.

Mutagenesis/Carcinogenesis

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

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

Impairment of Fertility and Teratogenicity

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80

6.2 Incompatibilities

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

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

6.3 Shelf life

Unopened Vial

Please refer to expiry date on the outer carton.

Reconstituted Solution

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

Diluted Solution

It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature (below 30°C) for up to 4 hours or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

6.4 Special precautions for storage

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

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 amber glass vial with an rubber stopper and a flip-off crimp cap contains 100 mg trastuzumab deruxtecan. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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

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

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed (see section 4.2).
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

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

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

Dilution

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

- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

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

Disposal

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion left in the vial.

Product Owner

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United Kingdom

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