

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENHERTU safely and effectively. See full prescribing information for ENHERTU.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- 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 to immediately report symptoms. (2.3, 5.1)
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)

RECENT MAJOR CHANGES

Indications and Usage (1.1)	05/2022
Indications and Usage (1.2)	11/2022
Indications and Usage (1.3)	08/2022
Dosage and Administration (2.1)	08/2022
Dosage and Administration (2.2)	05/2022
Dosage and Administration (2.2)	08/2022
Dosage and Administration (2.3)	08/2022
Warnings and Precautions (5.1, 5.2, 5.3)	08/2022

INDICATIONS AND USAGE

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate 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. (1.1)
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. (1.2)
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. (1.3)

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1.3, 14.3)

- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. (1.4)

DOSAGE AND ADMINISTRATION

- Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine. (2.2, 2.4)
- For intravenous infusion only. Do not administer as an intravenous push or bolus. DO NOT use Sodium Chloride Injection, USP. (2.4)

- Premedicate for prevention of chemotherapy-induced nausea and vomiting. (2.2)
- The recommended dosage of ENHERTU for breast cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for lung cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for gastric cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU. (2.3)

DOSAGE FORMS AND STRENGTHS

For injection: 100 mg lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Neutropenia: Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Manage through treatment interruption or dose reduction. (2.3, 5.2)
- Left Ventricular Dysfunction: Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF). (2.3, 5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥20%), including laboratory abnormalities, in patients with:

- metastatic breast cancer and HER2-mutant NSCLC were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, increased aspartate aminotransferase, vomiting, increased alanine aminotransferase, alopecia, increased blood alkaline phosphatase, constipation, musculoskeletal pain, decreased appetite, hypokalemia, diarrhea, and respiratory infection. (6.1)
- gastric cancer 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of ENHERTU. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

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FULL PRESCRIBING INFORMATION

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 (2.3), Warnings and Precautions (5.1)*].**
- **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 (5.4), Use in Specific Populations (8.1, 8.3)*].**

1 INDICATIONS AND USAGE

1.1 HER2-Positive 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.

1.2 HER2-Low Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [see *Dosage and Administration (2.1)*].

1.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate and duration of response [see *Clinical Studies (14.3)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Unresectable or Metastatic HER2-Low Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+/ISH-) [see *Clinical Studies (14.2)*].

Unresectable or Metastatic HER2-Mutant NSCLC

Select patients for the treatment of unresectable or metastatic HER2-mutant NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens [see *Clinical Studies (14.3)*]. If no mutation is detected in a plasma specimen, test tumor tissue.

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.

Additional Patient Selection Information

Information on FDA-approved tests for the detection of HER2 protein expression, HER2 gene amplification, and activating HER2 mutations is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage and Schedules

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

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 (6.1)*], which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic 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 Unresectable or Metastatic HER2-Mutant NSCLC

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.

2.3 Dosage 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: Dosage Reduction Schedule

Dose Reduction Schedule	Breast Cancer and NSCLC	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: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Interstitial Lung Disease (ILD)/Pneumonitis [see Warnings and Precautions (5.1)]	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.
	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.
Neutropenia [see Warnings and Precautions (5.2)]	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 [see Warnings and Precautions (5.2)]	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 [see Adverse Reactions (6.1)]	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.

Adverse Reaction	Severity		Treatment Modification
	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 [see Warnings and Precautions (5.3)]	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.
	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).

2.4 Preparation and Administration

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

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

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

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 (2.2)*].
- 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 (36°F to 46°F) 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 (36°F to 46°F) 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 [36°F to 46°F]), 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.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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* (6.1)]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

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* (2.3)]. 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 symptomatic (Grade 2 or greater) ILD [see *Dosage and Administration* (2.3)].

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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).

5.2 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 (2.3)*].

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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.

5.3 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 (2.3)*].

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 and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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.

5.4 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 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Neutropenia [see *Warnings and Precautions* (5.2)]
- Left Ventricular Dysfunction [see *Warnings and Precautions* (5.3)]

6.1 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 and HER2-Mutant NSCLC (5.4 mg/kg)

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, 65% were exposed for greater than 6 months and 39% were exposed for greater than one year. In this pooled safety population, the most common ($\geq 20\%$) adverse reactions (including laboratory abnormalities) were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01.

HER2-Positive Metastatic Breast Cancer

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, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocyte count, increased alanine aminotransferase, decreased platelet count, fatigue, vomiting, increased blood

alkaline phosphatase, alopecia, hypokalemia, constipation, musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection, abdominal pain, increased blood bilirubin, and stomatitis.

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

Table 3: Common Adverse Reactions (≥10% All Grades or ≥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
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				
Decreased weight	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Respiratory infection ^g	22	0.8	12	1.1
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.

- a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain
- b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption
- c Including fatigue, asthenia, malaise, and lethargy
- d Including 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 Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort
- g Including 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 Including headache and migraine
- j Including 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%) [including 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 (5.3)]
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (2.3%) [including 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 in DESTINY-Breast01 and Study DS8201-A-J101.

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

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
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
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 ^j	15	0
Eye Disorders		
Dry eye	11	0.4 ^k

Events were graded using NCI CTCAE version 4.03.

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

b Including 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 Including 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 Including rash, pustular rash, and maculo-papular rash

f Including 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 Including headache, sinus headache, and migraine

j Including 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
Hypokalemia	26	3

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.

HER2-Low Metastatic Breast Cancer

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 [see *Clinical Studies (14.2)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

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

Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast04.

Table 7: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhea	27	1.3	22	1.7
Abdominal pain ^a	18	0.5	13	0
Stomatitis ^b	13	0.3	12	0.6
General Disorders and Administration Site Conditions				
Fatigue ^c	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0
Rash ^d	13	0	23	4.7
Blood and Lymphatic System Disorders				
Anemia ^e	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	32	1.3	31	0.6
Investigations				
Decreased weight	16	0.3	8	0
Vascular Disorders				
Hemorrhage ^g	16	0	3.5	0
Nervous System Disorders				
Headache ^h	15	0.3	6	0
Peripheral neuropathy ⁱ	13	0	29	5
Dizziness ^j	11	0.5	6	0
Infections and Infestations				
Upper respiratory tract infection ^k	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^l	12	1.3	0.6	0
Dyspnea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0.

- a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain
- b Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation
- c Including fatigue, asthenia, and malaise
- d Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous
- e Including anemia, decreased hemoglobin, and decreased red blood cell count
- f Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain
- g Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage
- h Including headache and migraine
- i Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia
- j Including dizziness, postural dizziness, and vertigo
- k Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis
- l Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

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

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

Table 8: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased white blood cell count	70	9	78	25
Decreased hemoglobin	64	8	53	6
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Hypokalemia	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

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

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

Unresectable or Metastatic HER2-Mutant NSCLC

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

The safety of ENHERTU was evaluated in 101 patients in DESTINY-Lung02 [see *Clinical Studies (14.3)*]. Patients received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity. Nineteen percent of patients were exposed for greater than 6 months. The median age was 59 years (range 30 to 83); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued due to an adverse reaction in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, hypokalemia, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

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

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table 9: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	61	3.0
Constipation	31	1.0
Vomiting ^a	26	2.0
Diarrhea	19	1.0
Stomatitis ^b	12	0
Blood and Lymphatic System Disorders		
Anemia	34	10
General Disorders and Administration Site Conditions		
Fatigue ^c	32	4.0
Metabolism and Nutrition Disorders		
Decreased appetite	30	1.0
Skin and Subcutaneous Tissue Disorders		

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Alopecia	21	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^d	15	1.0

Events were graded using NCI CTCAE version 5.0.

a Including vomiting and retching

b including mucosal inflammation and stomatitis

c Including asthenia, fatigue, and malaise

d Including back pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity

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

- *Respiratory, Thoracic and Mediastinal Disorders*: interstitial lung disease (6%) [including interstitial lung disease that was adjudicated as ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure], dyspnea (5%), and epistaxis (3%)
- *Gastrointestinal Disorders*: abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- *Skin and Subcutaneous Disorders*: rash (3%) [including rash and maculo-papular rash]
- *Infections and Infestations*: upper respiratory tract infection (4%) [including upper respiratory tract infection, pharyngitis, and laryngitis]
- *Nervous System Disorders*: headache (4%) [including headache and migraine]

Table 10: Select Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=101 ^a	
	All Grades ^b %	Grades 3 or 4 ^b %
Hematology^c		
Decreased white blood cell count	60	4.0
Decreased hemoglobin	58	10
Decreased neutrophil count	52	12
Decreased lymphocyte count	43	16
Decreased platelet count	40	4.0
Chemistry		
Decreased albumin	39	0
Increased aspartate aminotransferase	35	1.0
Increased alanine aminotransferase	34	2.0
Increased alkaline phosphatase	22	0
Hypokalemia	17	2.0

a 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.

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

c The denominator used to calculate the rate varied from 98 to 99 based on the number of patients with a baseline value and at least one post-treatment value.

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 (14.4)*]. 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 11 and 12 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 11: 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
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

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 %
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.

^a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain

^b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering

^c Including anemia, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit

^d Including 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 (5.3)*]
- *Infections and Infestations*: pneumonia (6%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (1.6%)

Table 12: 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

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 %
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.

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 after 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 to 4% and 15 to 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 fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki 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 7 months after 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 4 months after 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

Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.6% 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 (48%).

Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

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)*]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment [see *Warnings and Precautions (5.1)*]. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLCr < 30 mL/min) [see *Clinical Pharmacology (12.3)*].

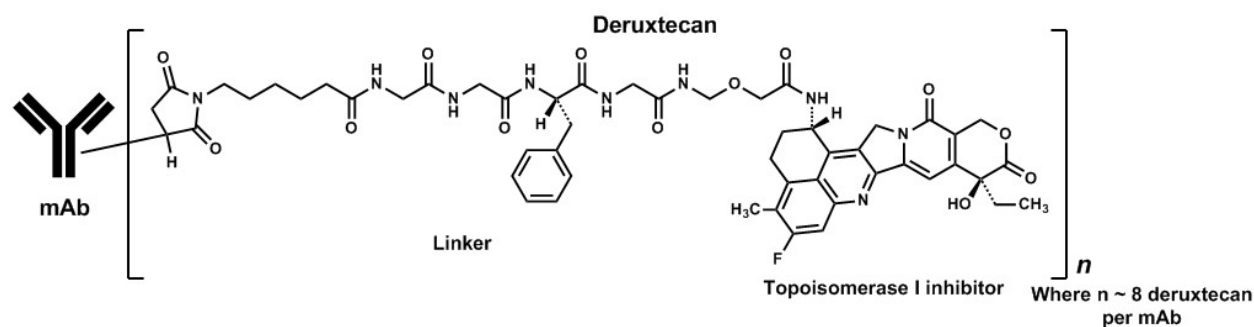
8.7 Hepatic Impairment

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 (2.3)*]. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody and topoisomerase inhibitor conjugate. Fam-trastuzumab deruxtecan-nxki 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. Fam-trastuzumab deruxtecan-nxki has the following structure:



ENHERTU (fam-trastuzumab deruxtecan-nxki) is a sterile, white to yellowish white, preservative-free lyophilized powder in single-dose vials. Each vial delivers 100 mg of fam-trastuzumab deruxtecan-nxki, 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 fam-trastuzumab deruxtecan-nxki 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

Fam-trastuzumab deruxtecan-nxki 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, fam-trastuzumab deruxtecan-nxki 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 a 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 fam-trastuzumab deruxtecan-nxki was evaluated in patients with cancer. Following a single dose, exposures (C_{max} and AUC) of fam-trastuzumab deruxtecan-nxki 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 in breast cancer and NSCLC and 0.5 to 1.25 times the recommended dose in gastric cancer).

Metastatic Breast Cancer

At the recommended dosage of ENHERTU for patients with metastatic breast cancer, the geometric mean (coefficient of variation [CV]%) C_{max} of fam-trastuzumab deruxtecan-nxki and DXd were 133 $\mu\text{g/mL}$ (19%) and 4.7 ng/mL (43%), respectively, and the AUC of fam-trastuzumab deruxtecan-nxki and DXd were 780 $\mu\text{g}\cdot\text{day/mL}$ (27%) and 29 ng $\cdot\text{day/mL}$ (42%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 35% at steady-state (Cycle 3).

Unresectable or Metastatic HER2-Mutant NSCLC

At the recommended dosage of ENHERTU for patients with HER2-mutant NSCLC, the geometric mean (CV%) $C_{max,ss}$ of fam-trastuzumab deruxtecan-nxki and DXd were 141 $\mu\text{g/mL}$ (21%) and 7.2 ng/mL (44%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki and DXd were 775 $\mu\text{g}\cdot\text{day/mL}$ (33%) and 40.9 ng $\cdot\text{day/mL}$ (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 31% at steady-state based on population pharmacokinetic analysis.

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 fam-trastuzumab deruxtecan-nxki and DXd were 126 $\mu\text{g/mL}$ (18%) and 5.2 ng/mL (42%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki 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 fam-trastuzumab deruxtecan-nxki 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 fam-trastuzumab deruxtecan-nxki was 2.68 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 fam-trastuzumab deruxtecan-nxki in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-5.7 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of fam-trastuzumab deruxtecan-nxki was 0.41 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-6.1 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 18.3 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 fam-trastuzumab deruxtecan-nxki or DXd were observed for age (20-96 years); race (Asian [n=906] vs Non-Asian [n=763]), including White [n=619], Black or African American [n=36],

and Other [n=108]; 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=575) hepatic impairment; mild (creatinine clearance [CLcr] ≥ 60 and <90 mL/min, n=646) or moderate (CLcr ≥ 30 and <60 mL/min, n=251) renal impairment based on population pharmacokinetic analysis.

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki 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 days} of fam-trastuzumab deruxtecan-nxki 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 days} of fam-trastuzumab deruxtecan-nxki 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 ~ 0.2 μ mol/L), DXd has a low potential to inhibit OAT1 (IC₅₀ value of 12.7 μ mol/L), OAT3, OCT1, OCT2, OATP1B1 (IC₅₀ value of 14.4 μ 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.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ENHERTU or of other anti-HER2 products.

During the median 14-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast03 with a median ADA sampling period of 13 months, treatment-emergent ADA (or anti-fam-trastuzumab deruxtecan-nxki antibodies) developed in 1.6% (4/256) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.4% (1/256).

During the median 7-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast01 with a median ADA sampling period of 9 months, treatment-emergent ADA developed in 1.2% (3/249) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

During the median 8-month treatment period in HER2-low breast cancer patients in DESTINY-Breast04 with a median ADA sampling period of 8 months, treatment-emergent ADA developed in 2.0% (7/357) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/357).

During the median 3.5-month treatment period in HER2-mutant NSCLC patients in DESTINY-Lung02 with median ADA sampling period of 2.2 months, treatment-emergent ADA developed in 0.7% (1/143) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

During the median 4.6-month treatment period in HER2-positive gastric or GEJ adenocarcinoma patients in DESTINY-Gastric01 with a median ADA sampling period of 4.6 months, treatment-emergent ADA developed in 7.3% (9/123) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/123).

Due to the limited number of patients who tested positive for ADA, the effect of treatment-emergent ADAs and treatment-emergent neutralizing antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of fam-trastuzumab deruxtecan-nxki is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fam-trastuzumab deruxtecan-nxki.

The topoisomerase inhibitor component of fam-trastuzumab deruxtecan-nxki, 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 fam-trastuzumab deruxtecan-nxki. In a six-week repeat-dose toxicity study in rats, intravenous administration of fam-trastuzumab deruxtecan-nxki 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 fam-trastuzumab deruxtecan-nxki 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 HER2-Positive 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 (HR+) 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 13 and Figure 1. At the time of the PFS analysis, 16% of patients had died and overall survival (OS) was immature.

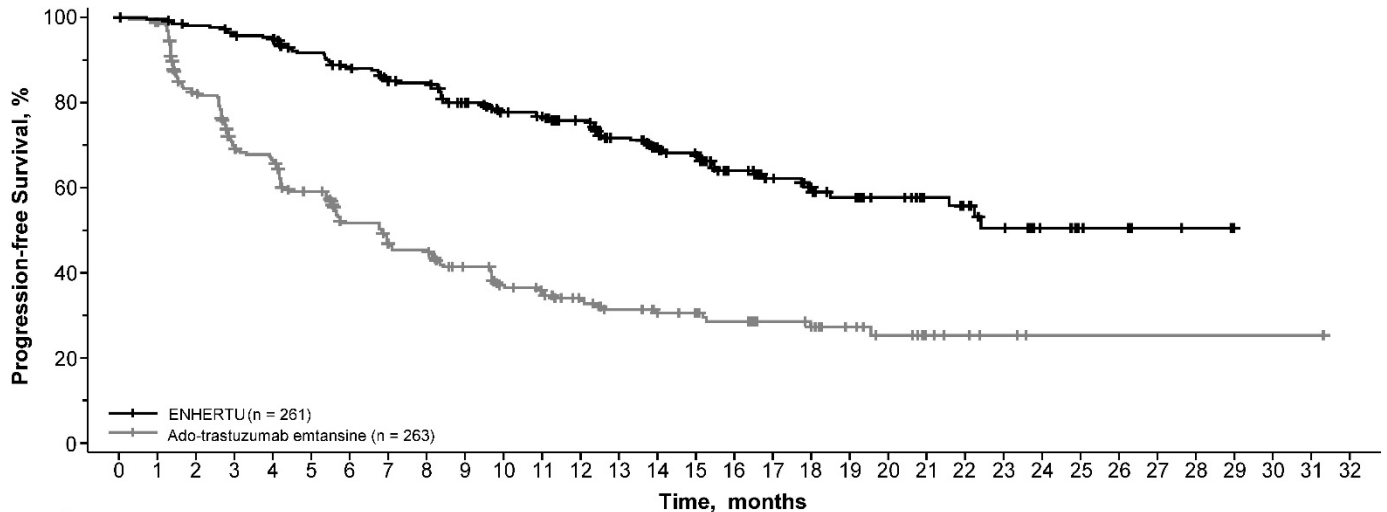
Table 13: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
Progression-Free Survival (PFS) per BICR		
N	261	263
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< 0.0001	
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)



Number at Risk:

ENHERTU (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

Ado-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 0

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 HR+. 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 14.

Table 14: 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 HER2-Low Metastatic Breast Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a 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 at a central laboratory using Ventana's PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay. 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 3 weeks or physician's choice of chemotherapy (N=184, eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel). 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 major efficacy outcome measure was PFS in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Additional 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.

The median age was 57 years (range: 28 to 81); 24% were age 65 or older; 99.6% were female; 48% were White, 40% were Asian, and 2% were Black or African American; 3.8% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (55%) or 1 (45%) at baseline; 58% were IHC 1+, 42% were IHC 2+/ISH-; 70% had liver metastases, 33% had lung metastases, and 6% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 58% having 1 and 41% 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.

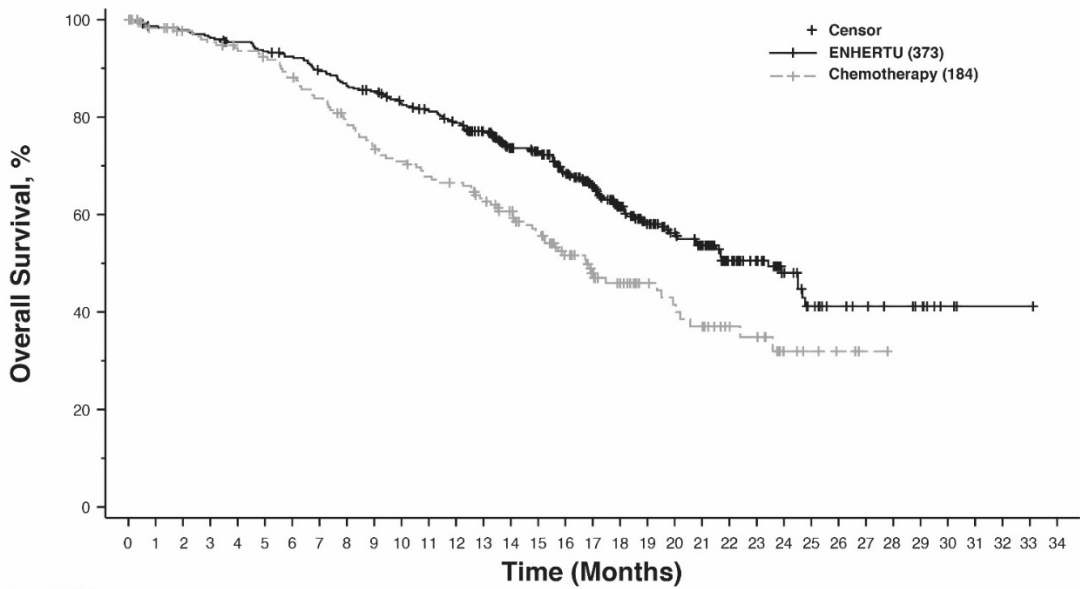
Efficacy results are summarized in Table 15 and Figures 2 and 3.

Table 15: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-Free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR				
n (%)	175 (52.9)	27 (16.6)	195 (52.3)	30 (16.3)
95% CI	47.3, 58.4	11.2, 23.2	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.5)	26 (16.0)	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

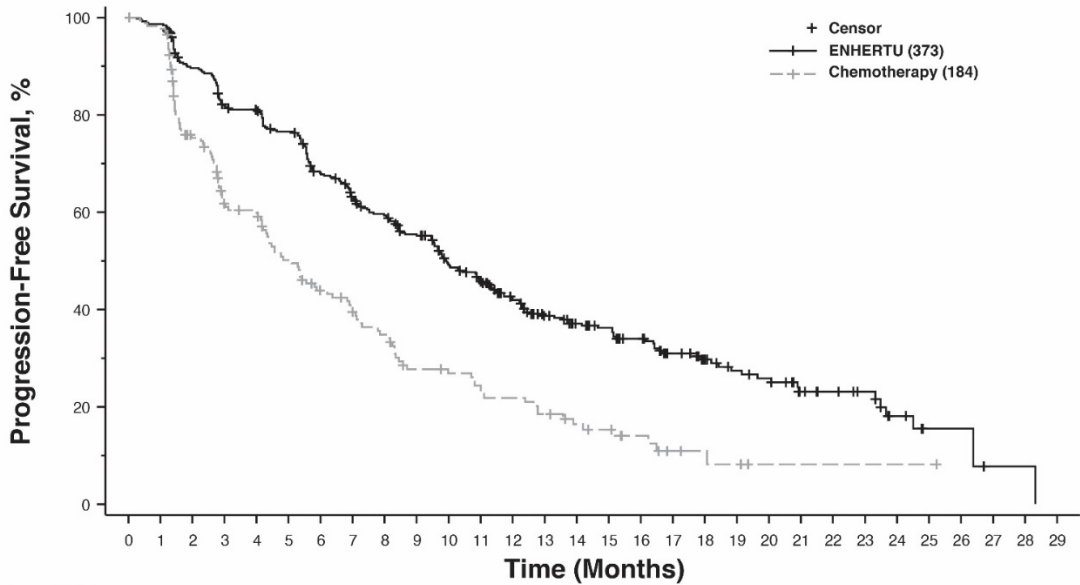
Figure 2: Kaplan-Meier Plot of Overall Survival (Overall Population)



Number at Risk

ENHERTU (373)	373	366	363	357	351	344	338	326	315	309	296	287	276	254	223	214	188	158	129	104	90	78	59	48	32	20	14	12	10	8	3	1	1	1	0			
Chemotherapy (184)	184	171	165	161	157	153	146	138	128	120	114	108	105	97	88	77	61	50	42	32	28	25	18	16	7	5	3	1	0									

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



Number at Risk

ENHERTU (373)	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	1	0						
Chemotherapy (184)	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	1	0									

14.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU was evaluated in DESTINY-Lung01 (NCT03505710) and at two dose levels in DESTINY-Lung02 (NCT04644237). Patients were prospectively selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations by local testing using tissue. Samples from DESTINY-Lung01 were retrospectively tested using OncoPrint™ Dx Target Test (Life Technologies Corporation, Tissue-test) and Guardant360® CDx test (Guardant Health Inc., Plasma test). Demographic and baseline disease characteristics were similar for patients in DESTINY-Lung01 and DESTINY-Lung02, except for race (34% Asian vs 79% Asian, respectively). Response rates were consistent across dose levels. Increased rates of ILD/pneumonitis were observed at the higher dose. The approved recommended dose of 5.4 mg/kg intravenously every 3 weeks in the DESTINY-Lung02 study is described below [see *Adverse Reactions (6.1)*].

The efficacy of ENHERTU was evaluated in DESTINY-Lung02, a multicenter, multi-cohort, randomized, blinded, dose-optimization trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependentILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with stable brain metastases at baseline.

Results from an interim efficacy analysis in a pre-specified patient cohort are described below. The major efficacy outcomes were confirmed ORR as assessed by BICR using RECIST v1.1 and DOR.

The median age was 58 years (range 30 to 78); 69% were female; 79% were Asian, 12% were White, and 10% were other races; 29% had an ECOG performance status of 0 and 71% had 1; 33% had stable brain metastases; 94% had a mutation in the ERBB2 kinase domain and 6% had a mutation in the extracellular domain. The median number of prior regimens was 2 (range: 1 to 12); 100% of patients received prior platinum therapy, 71% received prior immunotherapy, and 44% received both in combination. Fifty percent of patients were never-smokers and 50% were former smokers; 96% of patients had adenocarcinoma histology.

Efficacy results are provided in Table 16.

Table 16: Efficacy Results for DESTINY-Lung02*

Efficacy Parameter	DESTINY-Lung02 N=52
Confirmed Objective Response Rate (95% CI)	57.7% (43.2, 71.3)
Complete Response	1.9%
Partial Response	55.8%
Duration of Response Median, months (95% CI)†	8.7 (7.1, NE)

ORR 95% CI calculated using Clopper-Pearson method

NE=not estimable

*Data cut-off: 22 June 2022

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

14.4 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 currentILD, 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 17, and the Kaplan-Meier curve for OS is shown in Figure 4.

Table 17: 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)

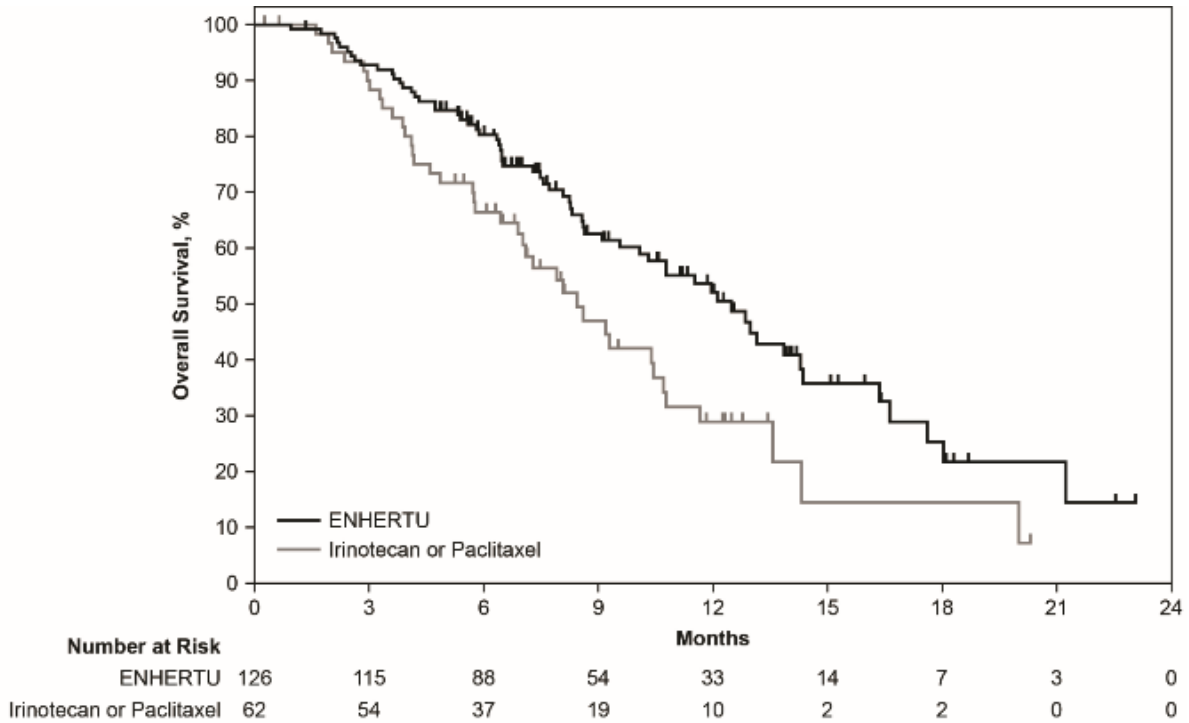
¥Based on the stratified log-rank test (stratified by region)

§Assessed by independent central review

¶95% exact binomial confidence interval

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

Figure 4: Kaplan-Meier Plot of Overall Survival



15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

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

Carton Contents	NDC
One 100 mg single-dose vial	NDC 65597-406-01

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) 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 (2.4)].

16.2 Special Handling

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Interstitial Lung Disease

- Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see *Warnings and Precautions (5.1)*].

Neutropenia

- Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see *Warnings and Precautions (5.2)*].

Left Ventricular Dysfunction

- Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see *Warnings and Precautions (5.3)*].

Embryo-Fetal Toxicity

- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose [see *Use in Specific Populations (8.3)*].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose [see *Use in Specific Populations (8.3)*].

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see *Use in Specific Populations (8.2)*].

Infertility

- Advise males of reproductive potential that ENHERTU may impair fertility [see *Use in Specific Populations (8.3)*].

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