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 (1.2)	01/2021
Dosage and Administration (2.1, 2.2, 2.3)	01/2021
Warnings and Precautions (5.1, 5.2, 5.3)	01/2021

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 two or more prior anti-HER2-based regimens in the metastatic setting. (1.1)

  This indication is approved under accelerated approval based on tumor 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. (1.1, 14.1)
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. (1.2)

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)
- 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 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%) in patients with:

- breast cancer were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough. (6.1)
- gastric cancer were hemoglobin decreased, white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, nausea, decreased appetite, anemia, aspartate aminotransferase increased, fatigue, blood alkaline phosphatase increased, alanine aminotransferase increased, diarrhea, hypokalemia, vomiting, constipation, blood bilirubin increased, 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: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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 Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Locally Advanced or Metastatic Gastric Cancer

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Locally Advanced or Metastatic Gastric Cancer

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

Information on FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification in gastric cancer 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.

First infusion: Administer infusion over 90 minutes.

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

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

Permanently discontinue ENHERTU in case of severe infusion reactions.

Recommended Dosage for Metastatic Breast Cancer

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

Recommended Dosage for Locally Advanced or Metastatic Gastric Cancer

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

2.3 Dose Modifications

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

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

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

Table 1: Dose Reduction Schedule

Dose Reduction Schedule	Breast Cancer	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity		Treatment Modification
Interstitial Lung Disease (ILD)/ Pneumonitis	Asymptomatic ILD/ pneumonitis (Grade 1)		Interrupt ENHERTU until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected *[see Warnings and Precautions (5.1)]*.
	Symptomatic ILD/ pneumonitis (Grade 2 or greater)		• Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected *[see Warnings and Precautions (5.1)]*.
Neutropenia	Grade 3 (less than 1.0 to 0.5 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile Neutropenia	Absolute neutrophil count of less than 1.0 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		• Interrupt ENHERTU until resolved. • Reduce dose by one level (see Table 1).
Thrombo-cytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
	Grade 4 (platelets less than 25 x 10^9/L)		• Interrupt ENHERTU until resolved to Grade 1 or less. • Reduce dose by one level (see Table 1).
Left Ventricular Dysfunction	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. • If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue ENHERTU.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v.4.03).

2.4 Preparation for Administration

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU (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 cytotoxic 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.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene and a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.

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)]*. 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

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Locally Advanced or Metastatic Gastric Cancer

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

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

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 62% of patients. Sixteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

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. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

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.

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)]*.

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

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

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 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, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

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

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	79	7
Vomiting	47	3.8
Constipation	35	0.9
Diarrhea	29	1.7
Abdominal pain[a]	19	1.3
Stomatitis[b]	14	0.9
Dyspepsia	12	0
General Disorders and Administration Site Conditions		
Fatigue[c]	59	6
Skin and Subcutaneous Tissue Disorders		
Alopecia	46	0.4[d]
Rash[e]	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	32	1.3
Blood and Lymphatic System Disorders		
Anemia[f]	31	7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	20	0
Dyspnea	13	1.3
Epistaxis	13	0
Interstitial lung disease[g]	9	2.6[h]
Nervous System Disorders		
Headache[i]	19	0
Dizziness	10	0
Infections and Infestation		
Upper respiratory tract infection[j]	15	0
Eye Disorders		
Dry eye	11	0.4[k]

Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term. Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

a Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.
b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).
c Grouped term of fatigue includes PTs of fatigue and asthenia.
d This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 2.
e Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.
f Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
g Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
h All events had fatal outcomes (n=6).
i Grouped term of headache includes PTs of headache, sinus headache, and migraine.
j Grouped term of upper respiratory tract infection includes PTs of 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 4: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU

Laboratory Parameter	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Hematology		
White blood cell count decreased	70	7
Hemoglobin decreased	70	7
Neutrophil count decreased	62	16
Platelet count decreased	37	3.4
Chemistry		
Aspartate aminotransferase increased	41	0.9
Alanine aminotransferase increased	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.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 *[see Clinical Studies (14.2)]*. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in 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 hemoglobin decreased, white blood cell decreased, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, nausea, decreased appetite, anemia, aspartate aminotransferase increased, fatigue, blood alkaline phosphatase increased, alanine aminotransferase increased, diarrhea, hypokalemia, vomiting, constipation, blood bilirubin increased, pyrexia, and alopecia.

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 5: 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

(continued)

Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Adverse Reactions	**All Grades %**	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia[c]	58	38	31	23
Febrile neutropenia	4.8	4.8	3.2	3.2
General Disorders and Administration Site Conditions				
Fatigue[d]	55	9	44	4.8
Pyrexia	24	0	16	0
Edema peripheral	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				
Hepatic function abnormal	8	3.2	1.6	1.6

Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term. Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

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

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

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

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

[e] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

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

- *Cardiac Disorders:* asymptomatic left ventricular ejection fraction decrease (8%) *[see Warnings and Precautions (5.3)]*
- *Infections and Infestations:* pneumonia (6%)
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (1.6%)

Table 6: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Laboratory Parameter	**All Grades %**	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Hematology				
Hemoglobin decreased	75	38	55	23
White blood cell count decreased	74	29	53	13
Neutrophil count decreased	72	51	45	23
Lymphocyte count decreased	70	28	53	12
Platelet count decreased	68	12	12	5
Chemistry				
Aspartate aminotransferase increased	58	9	32	8
Blood alkaline phosphatase increased	54	8	34	10
Alanine aminotransferase increased	47	9	17	1.7
Hypokalemia	30	4.8	18	8
Blood bilirubin increased	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.

6.2 Immunogenicity

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

Treatment-induced anti-fam-trastuzumab deruxtecan-nxki antibodies (ADA) developed in 1.7% (14/807) patients who received ENHERTU across all doses. Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety. In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (*see Data*). Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells *[see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)]*. Advise patients of the potential risks to a fetus.

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

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

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with 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 at least 7 months following the last dose.

Males

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

Infertility

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

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

8.5 Geriatric Use
Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy 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 (53%) as compared to younger patients (42%).

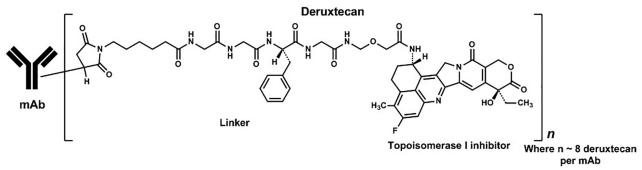
Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of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

8.6 Renal Impairment
No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment *[see Clinical Pharmacology (12.3)]*. No data are available in patients with severe renal impairment.

8.7 Hepatic Impairment
No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) 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)]*. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION
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).

Metastatic Breast Cancer
At the recommended dosage of ENHERTU for patients with HER2-positive breast cancer, the geometric mean (coefficient of variation [CV]%) C_{max} of fam-trastuzumab deruxtecan-nxki and DXd were 122 µg/mL (20%) and 4.4 ng/mL (40%), respectively, and the AUC of fam-trastuzumab deruxtecan-nxki and DXd were 735 µg·day/mL (31%) and 28 ng·day/mL (38%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 35% at steady-state (Cycle 3).

Locally Advanced or Metastatic Gastric Cancer
At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean $C_{max,ss}$ of fam-trastuzumab deruxtecan-nxki and DXd were 126 µg/mL (18%) and 5.2 ng/mL (42%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki and DXd were 743 µg·day/mL (26%) and 33 ng·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 2.78 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 and gastric cancer was approximately 5.7-5.8 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of fam-trastuzumab deruxtecan-nxki was 0.42 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd in patients with HER2-positive metastatic breast cancer and gastric cancer was approximately 5.5-5.8 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 19.6 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 (23-96 years), race (Asian [n=563] and non-Asian [n=245]), sex, body weight (27.3-125.4 kg), mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST, n=312) hepatic impairment, mild (creatinine clearance [CLcr] ≥60 and <90 mL/min, n=292) or moderate (CLcr ≥30 and <60 mL/min, n=54) 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 $AUC_{0\text{-}17\ days}$ 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 $AUC_{0\text{-}17\ days}$ 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 µmol/L), DXd has a low potential to inhibit OAT1 (IC_{50} value of 12.7 µmol/L), OAT3, OCT1, OCT2, OATP1B1 (IC_{50} value of 14.4 µmol/L), OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

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

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with 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 Metastatic Breast Cancer

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

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

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

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

Efficacy results are summarized in Table 7.

Table 7: Efficacy Results by Independent Central Review in DESTINY-Breast01

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

ORR 95% CI calculated using Clopper-Pearson method
*DOR is based on median duration of follow-up of 11.1 months.
†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

14.2 Locally Advanced or Metastatic Gastric Cancer

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

Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician's choice of chemotherapy: irinotecan monotherapy (N=55) 150 mg/m^2 intravenously every 2 weeks or paclitaxel monotherapy (N=7) 80 mg/m^2 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 overall survival (OS) in the intent-to-treat population. Additional efficacy outcomes were progression-free survival (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.

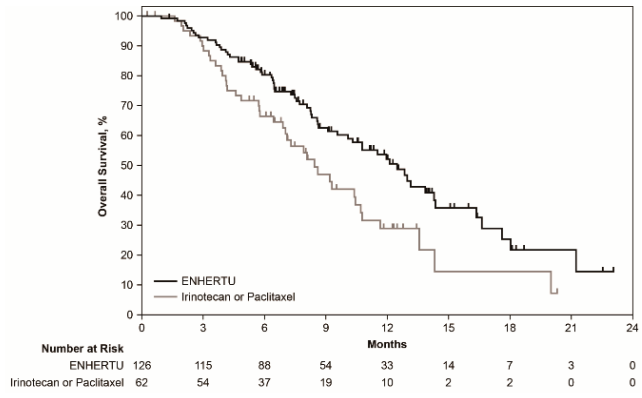
Efficacy results are summarized in Table 8, and the Kaplan-Meier curve for OS is shown in Figure 1.

Table 8: 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 1: 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 cytotoxic 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 at least 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 at least 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)]*.

Manufactured by:
Daiichi Sankyo, Inc., Basking Ridge, NJ 07920

U.S. License No. 2128

Marketed by:
Daiichi Sankyo, Inc., Basking Ridge, NJ 07920 and AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

USPI-ENH-C4-0121-r002

Medication Guide

ENHERTU® (en-HER-too)
(fam-trastuzumab deruxtecan-nxki) for injection

What is the most important information I should know about ENHERTU?

ENHERTU can cause serious side effects, including:

Lung problems that may be severe, life-threatening or that may lead to death. If you develop lung problems your healthcare provider may treat you with corticosteroid medicines. Tell your healthcare provider right away if you get any of the following signs and symptoms:

- cough
- trouble breathing or shortness of breath
- fever
- other new or worsening breathing symptoms (e.g., chest tightness, wheezing)

Low white blood cell count (neutropenia). Low white blood cell counts are common with ENHERTU and can sometimes be severe. Your healthcare provider will check your white blood cell counts before starting ENHERTU and before starting each dose. Tell your healthcare provider right away if you develop any signs or symptoms of an infection or have fever or chills during treatment with ENHERTU.

Heart problems that may affect your heart's ability to pump blood. Your healthcare provider will check your heart function before starting treatment with ENHERTU. Tell your healthcare provider right away if you get any of the following signs and symptoms:

- new or worsening shortness of breath
- coughing
- feeling tired
- swelling of your ankles or legs
- irregular heartbeat
- sudden weight gain
- dizziness or feeling light-headed
- loss of consciousness

Your healthcare provider will check you for these side effects during your treatment with ENHERTU. Your healthcare provider may reduce your dose, delay treatment or completely stop treatment with ENHERTU if you have severe side effects.

Harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ENHERTU.

- If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with ENHERTU.
- **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for at least 7 months after the last dose.
- **Males** who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for at least 4 months after the last dose.

See **"What are the possible side effects of ENHERTU?"** for more information about side effects.

What is ENHERTU?

ENHERTU is a prescription medicine used in adults to treat human epidermal growth factor receptor 2 (HER2)-positive

- breast cancer that cannot be removed by surgery or that has spread to other parts of your body (metastatic), and who have received two or more prior anti-HER2 breast cancer treatments.
- stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that has spread to areas near your stomach (locally advanced) or that has spread to other parts of your body (metastatic), and who have received a prior trastuzumab-based regimen.

It is not known if ENHERTU is safe and effective in children.

Before you receive ENHERTU, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems.
- have signs or symptoms of an infection.
- have or have had any heart problems.
- are breastfeeding or plan to breastfeed. It is not known if ENHERTU passes into your breast milk. Do not breastfeed during treatment with ENHERTU and for 7 months after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ENHERTU?

- You will receive ENHERTU into your vein through an intravenous (IV) line by your healthcare provider.
- ENHERTU is given 1 time every three weeks (21-day treatment cycle).
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider may slow down or temporarily stop your infusion of ENHERTU if you have an infusion-related reaction, or permanently stop ENHERTU if you have severe infusion reactions.
- If you miss a planned dose of ENHERTU, call your healthcare provider right away to schedule an appointment. Do not wait until the next planned treatment cycle.

What are the possible side effects of ENHERTU?

ENHERTU can cause serious side effects. See "What is the most important information I should know about ENHERTU?"

The most common side effects of ENHERTU, when used in people with breast cancer, include:

- nausea
- low white blood cell counts
- low red blood cell counts
- feeling tired
- vomiting
- hair loss
- increased liver function tests
- low platelet counts
- constipation
- decreased appetite
- diarrhea
- low levels of potassium
- cough

The most common side effects of ENHERTU, when used in people with stomach cancer, include:

- low red blood cell counts
- low white blood cell counts
- low platelet counts
- nausea
- decreased appetite
- increased liver function tests
- feeling tired
- diarrhea
- low levels of blood potassium
- vomiting
- constipation
- fever
- hair loss

ENHERTU may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ENHERTU. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ENHERTU.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ENHERTU that is written for healthcare professionals.

What are the ingredients in ENHERTU?

Active Ingredient: fam-trastuzumab deruxtecan-nxki.
Inactive Ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

Manufactured by: Daiichi Sankyo, Inc., Basking Ridge, NJ 07920 U.S. License No. 2128
Marketed by: Daiichi Sankyo, Inc., Basking Ridge, NJ 07920 and AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
 USMG-ENH-C4-0121-r002
For more information, call 1-877-437-7763 or go to https://www.ENHERTU.com

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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