ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

Metastatic Solid Tumors

In previously treated HER2+ (IHC 3+) metastatic solid tumors

Your dosing and administration guide for ENHERTU

A comprehensive resource for:

Dosage and Administration | **Management of Select Adverse Reactions** | **ILD/Pneumonitis Symptom Identification**

Please see page 8 for information on ILD/pneumonitis symptom identification.

Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

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.

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 to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Please see Important Safety Information on pages 9-10 and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

ENHERTU dosage and administration

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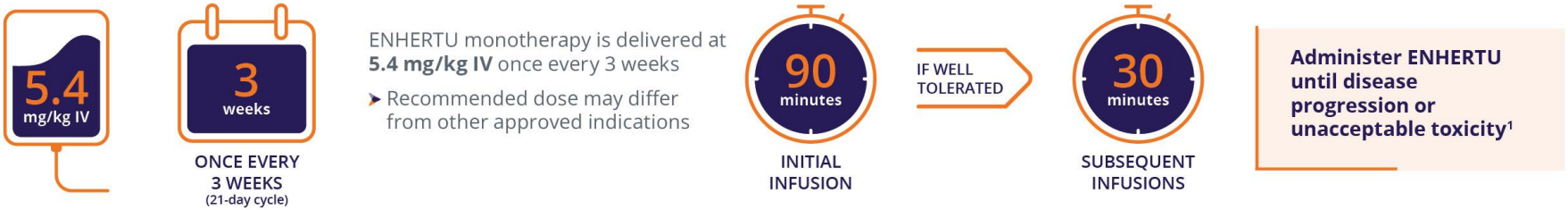
Patient selection considerations for HER2+ (IHC 3+) unresectable or metastatic solid tumors[1]

- Select patients for treatment of unresectable or metastatic solid tumors with ENHERTU based on HER2+ (IHC 3+) tumor specimens. An FDA-approved test for the detection of HER2+ (IHC 3+) solid tumors for treatment with ENHERTU is not currently available
- Information on FDA-approved tests for the detection of HER2 protein expression is available at www.fda.gov/CcompanionDiagnostics

Recommended weight-based dosage and schedule[1]



Dose modifications for ENHERTU for adverse reactions[1]

- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU, per dose modifications provided in the table below and the dose modifications table on page 7
- **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

Dose reduction schedule[1]

Dose reduction schedule	Starting dose of 5.4 mg/kg
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

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NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for prophylactic management of nausea and/or vomiting

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ENHERTU is highly emetogenic, which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.[1]

Premedication is recommended prior to infusion of fam-trastuzumab deruxtecan-nxki (ENHERTU)[2]

- The NCCN Guidelines® for Antiemesis recommends 3-4 prophylactic antiemetic regimens for high emetic risk agents, including fam-trastuzumab deruxtecan-nxki (ENHERTU), to help decrease potential nausea/vomiting[a-c]
- Consider option A, B, or C
- All treatments are Category 1 and should be started before anticancer therapy[d]

Treatment option	Day 1		Days 2, 3, and 4	
A (Preferred)[e]	Use the following:	• Olanzapine[f] • NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following:	• Olanzapine[f] on days 2-4 • Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4
B	Use the following:	• Olanzapine[f] • Palonosetron • Dexamethasone[i,j]	Use the following:	• Olanzapine[f] on days 2-4
C	Use the following:	• NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following:	• Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4

[a]For details regarding recommendations and specific dosing information, please refer to the NCCN Guidelines for Antiemesis.
[b]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[c]Especially for patients with anticipatory, anxiety-related, or breakthrough nausea, may consider adding lorazepam 0.5–1 mg by mouth (PO) or IV or sublingual (SL) every 6 hours as needed on days 1–4. Use the lowest effective dose and dosage interval possible. May be administered with or without H_2 blocker or proton pump inhibitor (PPI) if patient exhibits reflux symptoms.
[d]Category 1 recommendations indicate uniform NCCN consensus that the intervention is appropriate based on high-level evidence.
[e]If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or NK1 RA-containing regimen C). Olanzapine-containing regimens may be useful for patients with severe nausea.
[f]Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for patients who are older or who are oversedated.
[g]If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT3 RA is required.
[h]When used in combination with an NK1 RA, there is no preferred 5-HT3 RA.
[i]Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine).
[j]Use of corticosteroid premedications should be avoided with cellular therapies.

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ENHERTU preparation for administration

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In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU **and not trastuzumab or ado-trastuzumab emtansine.**[1]

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.[1]

ENHERTU is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Before administering ENHERTU[1]

- Monitor complete blood counts prior to initiation and prior to each dose, and as clinically indicated
- Assess left ventricular ejection fraction (LVEF) prior to initiation and at regular intervals during treatment as clinically indicated
- Verify pregnancy status of female patients

Reconstitution[1]

Reconstitute immediately before dilution.

More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed.

Reconstitute each 100 mg vial 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.**

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, protect the vial from light. **Do not freeze.**

The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Reconstitute only with Sterile Water for Injection, USP[1]

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Dilution[1]

Withdraw the calculated amount from the vial(s) using a sterile syringe. 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.

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.

Discard any unused portion left in the vials.

Dilute only with D5W[1]

DO NOT use Sodium Chloride Injection, USP[1]

A cover should be used over the IV infusion bag containing diluted ENHERTU to protect it from light[1]

Administration[1]

If not used immediately, store the diluted ENHERTU in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature between 20°C to 25°C (68°F to 77°F) for up to 4 hours including preparation and infusion time.

Protect from light. **Do not freeze.**

The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours.

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.

ENHERTU administration considerations[1]

- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms
- Permanently discontinue ENHERTU in case of severe infusion reactions

Polyethylene-lined infusion sets and polyvinylchloride tubing are acceptable[1,3]

D5W is recommended for priming and flushing the administration line[4]

Please see Important Safety Information on pages 9-10 and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

How supplied, storage, and handling[1]

ENHERTU for injection is a white to yellowish white lyophilized powder supplied in 100 mg single-dose vials.

Prior to reconstitution
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.**

After reconstitution
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, protect the vial from light. **Do not freeze.** The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

After dilution
If not used immediately, after dilution in IV bag with **D5W**, store the diluted ENHERTU in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature between 20°C to 25°C (68°F to 77°F) for up to 4 hours including preparation and infusion time.

Do not shake the reconstituted or diluted solution.

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PREPARATION & ADMINISTRATION | RECONSTITUTION, DILUTION, & ADMINISTRATION | DOSE MODIFICATIONS | ILD/PNEUMONITIS SYMPTOM IDENTIFICATION | IMPORTANT SAFETY INFORMATION | PI

6

Dose modifications for adverse reactions[1]

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Adverse reaction	Severity	Treatment modification
Interstitial lung disease (ILD)/ pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	▸ Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected ▸ 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 dose reduction table on page 2)
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	▸ Permanently discontinue ENHERTU ▸ Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected
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 dose reduction table on page 2)
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 1 hour	▸ Interrupt ENHERTU until resolved ▸ Reduce dose by one level (see dose reduction table on page 2)
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)	▸ Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose
	Grade 4 (platelets less than 25 x 10^9/L)	▸ Interrupt ENHERTU until resolved to Grade 1 or less ▸ Reduce dose by one level (see dose reduction table on page 2)
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
	LVEF 40% to 45%: 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 NCI-CTCAE v.5.0.

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Early identification of ILD/pneumonitis is key to appropriate management[1,5-7]

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Follow the five "S" strategies to help detect and manage ILD/pneumonitis in patients receiving ENHERTU

KEY: ENHERTU Prescribing Information recommendation

1 SCREEN

Careful patient selection based on baseline risk and screening that continues during treatment are warranted[5]

Before initiating ENHERTU[6,7]

- Complete history and physical
- Consider baseline pulse oximetry (SpO_2), PFT, and high-resolution CT (see **Scan** below), if clinically indicated
- Educate patient and engage multidisciplinary team (see **Synergy** below)

Throughout treatment[1,6,7]

- Advise patients to immediately report signs and symptoms that may indicate ILD/pneumonitis
  - — Cough
  - — Fever
  - — Dyspnea
  - — New or worsening respiratory symptoms
- Continue to monitor vitals (SpO_2 and PFT, if clinically indicated)
- Investigate potential evidence:
  - — Infectious disease evaluation
  - — Bronchoscopy, BAL, and/or ABGs, if clinically indicated and feasible

2 SCAN

Radiological scans remain the fundamental diagnostic tool for ILD[5]

- Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist[1]

CT scans[6]

- Consider CT scans of the chest for baseline prior to treatment, including high resolution CT scans, if feasible
- Repeat at least every 12 weeks (or every 6-9 weeks if baseline respiratory symptoms are present), if feasible
- Consult your institution's guidelines for best practices

3 SYNERGY

Work together with the patient, multidisciplinary care team, and staff[5]

Patient[1]

- Inform patients of the risks of severe or fatal ILD
- Advise patients to contact their HCP immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms

Multidisciplinary team[6]

- Consider consulting pulmonologist/radiologist, including for patients with significant lung comorbidities
- Comprehensive education of staff, nurses, patient navigators, and advanced practice providers/clinicians is an important part of ILD monitoring and management

HCP staff[6]

- Help facilitate open communication with the patient
- Help assess signs/symptoms

If ILD/pneumonitis is suspected when[6,a]:

- Radiographic changes potentially consistent with ILD/pneumonitis are seen
- Patient experiences acute onset of new or worsening pulmonary signs/symptoms, such as dyspnea, cough, or fever

	Asymptomatic (Grade 1) ILD/pneumonitis[1]	Symptomatic (Grade ≥2) ILD/pneumonitis[1]
4 SUSPEND TREATMENT Promptly investigate evidence and **interrupt ENHERTU treatment as soon as ILD is suspected, regardless of which grade is confirmed[1,5]**	Interrupt ENHERTU until resolved to Grade 0, then: • If resolved in ≤28 days from date of onset, maintain dose • If resolved in >28 days from date of onset, reduce one dose level (See dose reductions at right)	**Permanently discontinue ENHERTU**
5 STEROIDS Corticosteroids can be initiated as soon as ILD is suspected, before a pulmonologist consultation[5,6]	• Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected	• Promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected • Continue for ≥14 days followed by a gradual taper for ≥4 weeks

Dose Reduction Schedule[1]

	Breast Cancer, NSCLC and IHC 3+ Solid Tumors
Recommended starting dose	5.4 mg/kg
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue

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

- **ILD can be severe, life-threatening, or fatal. Follow all ILD/pneumonitis events:** Regardless of severity or seriousness, all ILD/pneumonitis events should be followed until resolution, including after drug discontinuation[1,6,7]
- **Monitor patients with moderate renal impairment more frequently:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in these patients[1]
- **In patients with unresectable or mNSCLC:** The approved recommended dose of ENHERTU is 5.4 mg/kg Q3W due to increased toxicity, including ILD/pneumonitis, observed with a higher dose[1]
- Higher systemic exposure to fam-trastuzumab deruxtecan-nxki was associated with a higher incidence rate of any grade ILD[1]

[a]Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist.[1]

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Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

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.

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 to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. 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 ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (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.

Solid Tumors (IHC3+) and Other Solid Tumors (5.4 mg/kg)
In patients with solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU.

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. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

Solid Tumors (IHC3+) and Other Solid Tumors (5.4 mg/kg)
In patients with solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 63% of patients. Seventeen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1% of patients.

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. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and 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. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Solid Tumors (IHC3+) and Other Solid Tumors (5.4 mg/kg)
In patients with solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.8% of patients, of which 0.6% were Grade 3.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. 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.

Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

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Important Safety Information

Adverse Reactions

Solid Tumors (IHC3+) and Other Solid Tumors (5.4 mg/kg)
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 1799 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 65% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (73%), decreased white blood cell count (70%), decreased hemoglobin (66%), decreased neutrophil count (63%), decreased lymphocyte count (58%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (43%), vomiting (40%), increased blood alkaline phosphatase (38%), alopecia (34%), constipation (33%), decreased appetite (32%), decreased blood potassium (31%), diarrhea (29%), musculoskeletal pain (24%), and abdominal pain (20%).

HER2-Positive (IHC3+) Unresectable or Metastatic Solid Tumors
The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. The median duration of treatment was 8.3 months (range 0.7 to 30.2).

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. 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.
- **Lactation:** There are no data regarding the presence of ENHERTU 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.
- **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. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: 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. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01, or DESTINY-CRC02, 39% were 65 years or older and 9% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

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

ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Abbreviations

5-HT3, 5-hydroxytryptamine 3
ABG, arterial blood gas
BAL, bronchoalveolar lavage
CBC, complete blood count
CHF, congestive heart failure
CT, computerized tomography
D5W, dextrose 5% in water
FDA, Food and Drug Administration
H_2, histamine type 2
HCP, healthcare provider
HER2, human epidermal growth factor receptor 2
IHC, immunohistochemistry
ILD, interstitial lung disease
ISH, in situ hybridization
IV, intravenous
LVEF, left ventricular ejection fraction
mNSCLC, metastatic non-small cell lung cancer
NCCN, National Comprehensive Cancer Network® (NCCN®)
NK1, neurokinin-1
NSCLC, non-small cell lung cancer
PFT, pulmonary function test
Q3W, every 3 weeks
RA, receptor antagonist
SpO_2, saturation of peripheral oxygen

References: 1. ENHERTU. Prescribing information. Daiichi Sankyo, Inc.; 2024. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed December 13, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Zhang N, Ding M, Yuan Y. Current advances in biodegradation of polyolefins. *Microorganisms*. 2022;10(8):1537. doi:10.3390/microorganisms10081537 **4.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **5.** Tarantino P, Tolaney SM. Detecting and managing T-DXd-related interstitial lung disease: the five "S" rules. *JCO Oncol Pract*. 2023;19(8):526-527. **6.** Rugo HS, Crossno CL, Gesthalter YB, et al. Real-world perspectives and practices for pneumonitis/interstitial lung disease associated with trastuzumab deruxtecan use in human epidermal growth factor receptor 2–expressing metastatic breast cancer. *JCO Oncol Pract*. 2023;19(8):539-546. **7.** Swain SM, Nishino M, Lancaster LH, et al. Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)-related interstitial lung disease/pneumonitis—focus on proactive monitoring, diagnosis, and management. *Cancer Treat Rev*. 2022;106:102378.

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Please see Important Safety Information throughout as well as on pages 9-10, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.