

Guide to ENHERTU dosing and administration¹

Recommended weight-based dosage and schedule

- ENHERTU is always given as a monotherapy IV infusion once every 3 weeks



In patients with unresectable or metastatic NSCLC, the approved recommended dose of ENHERTU is 5.4 mg/kg Q3W due to increased toxicity, including ILD/pneumonitis, observed with a higher dose

Patient selection considerations

- For unresectable or metastatic HER2-low mBC:** Select patients for treatment with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+/ISH-)
- For unresectable or metastatic HER2-mutant NSCLC:** Select patients for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue
- For locally advanced or metastatic gastric cancer:** Select patients 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 expression, HER2 gene amplification, and activating HER2 mutations is available at: <http://www.fda.gov/CompanionDiagnostics>

Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
 - In the metastatic setting, or
 - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy
This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen

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 throughout as well as on pages 9-12, and [click here for full Prescribing Information](#), including Boxed WARNINGS, and [click here for Medication Guide](#).

ENHERTU preparation for administration¹

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 (IV) infusion. Use appropriate aseptic technique. ENHERTU is a hazardous drug. Follow applicable special handling and disposal procedures.

Before administering ENHERTU

- 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 as clinically indicated
- Verify pregnancy status of females

Premedication

- 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



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.

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, protected 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

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ENHERTU preparation for administration¹ (cont'd)



Dilution¹

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 (D5W)**. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin, which includes polyethylene and polypropylene bags.

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.



Administration¹

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.



⚠ Dilute only with D5W¹

- **DO NOT use Sodium Chloride Injection, USP¹**

Polyethylene and polypropylene are types of polyolefin



A cover should be used over the IV infusion bag containing diluted ENHERTU to protect it from light¹



Polyethylene-lined infusion sets and polyvinylchloride tubing are acceptable^{1,2}



D5W is recommended for priming and flushing the administration line³

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ENHERTU preparation for administration¹ (cont'd)



Additional Information

How supplied, storage, and handling¹

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

Prior to reconstitution

Store vials prior to reconstitution in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. **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, protected from light. **Do not freeze.** The product does not contain a preservative. Discard unused portion left in the vial after 24 hours refrigerated.

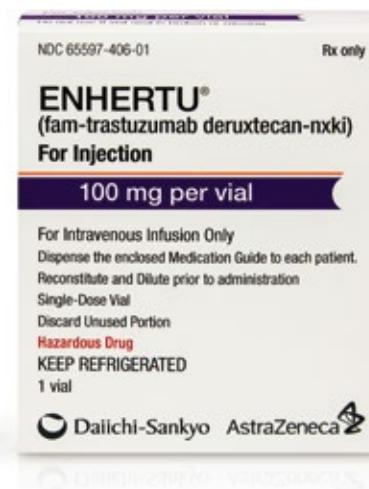
After dilution

If not used immediately, after dilution in IV bag with **D5W**, 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.

Do not shake the reconstituted or diluted solution.



Up to 24-hour storage in a refrigerator at 2°C to 8°C (36°F to 46°F), including preparation and infusion time, is permissible if not used immediately after dilution¹



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PREPARATION & ADMINISTRATION

RECONSTITUTION, DILUTION, & ADMINISTRATION

DOSE MODIFICATIONS

ILD/PNEUMONITIS SYMPTOM IDENTIFICATION

IMPORTANT SAFETY INFORMATION

PRESCRIBING INFORMATION

Recommended dose modifications for adverse reactions¹

Interstitial Lung Disease (ILD)/pneumonitis

Severity	Treatment modification
Asymptomatic ILD/pneumonitis (Grade 1)	<ul style="list-style-type: none"> Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent) Interrupt ENHERTU until resolved to Grade 0, then: <ul style="list-style-type: none"> If resolved in ≤ 28 days from date of onset, resume treatment with ENHERTU at the same dose If resolved in > 28 days from date of onset, reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 7)
Symptomatic ILD/pneumonitis (Grade ≥ 2)	<ul style="list-style-type: none"> Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (eg, ≥ 1 mg/kg/day prednisolone or equivalent) <ul style="list-style-type: none"> Continue for ≥ 14 days followed by gradual taper for ≥ 4 weeks Permanently discontinue ENHERTU

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.

Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (Grade ≥ 2) ILD/pneumonitis

Neutropenia

Severity	Treatment modification
Grade 3 (ANC < 1.0 to $0.5 \times 10^9/L$)	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade ≤ 2, then maintain dose
Grade 4 (ANC $< 0.5 \times 10^9/L$)	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade ≤ 2 Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 7)

Febrile neutropenia

Severity	Treatment modification
ANC $< 1.0 \times 10^9/L$ and temperature $> 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than 1 hour	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 7)

Toxicity grades are in accordance with NCI-CTCAE v5.0.

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Recommended dose modifications for adverse reactions¹ (cont'd)



Thrombocytopenia

Severity	Treatment modification
Grade 3 (platelets <50 to $25 \times 10^9/L$)	<ul style="list-style-type: none">Interrupt ENHERTU until resolved to Grade ≤ 1, then maintain dose
Grade 4 (platelets < $25 \times 10^9/L$)	<ul style="list-style-type: none">Interrupt ENHERTU until resolved to Grade ≤ 1Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 7)

Left ventricular dysfunction

Severity	Treatment modification
LVEF $>45\%$ and absolute decrease from baseline is 10% to 20%	<ul style="list-style-type: none">Continue treatment with ENHERTU
LVEF 40% to 45%	<ul style="list-style-type: none">Continue treatment with ENHERTURepeat LVEF assessment within 3 weeks
	<ul style="list-style-type: none">Interrupt ENHERTURepeat LVEF assessment within 3 weeks<ul style="list-style-type: none">If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTUIf LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose
LVEF $<40\%$ or absolute decrease from baseline is $>20\%$	<ul style="list-style-type: none">Interrupt ENHERTURepeat LVEF assessment within 3 weeks<ul style="list-style-type: none">If LVEF of $<40\%$ or absolute decrease from baseline of $>20\%$ is confirmed, permanently discontinue ENHERTU
Symptomatic congestive heart failure (CHF)	<ul style="list-style-type: none">Permanently discontinue ENHERTU

Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF)

Toxicity grades are in accordance with NCI-CTCAE v5.0.

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Recommended dose modifications for adverse reactions¹ (cont'd)

Dose modifications

- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per dose modifications
- 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 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	mBC and mNSCLC 5.4 mg/kg starting dose	aGC 6.4 mg/kg starting dose
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

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Early identification of ILD/pneumonitis is key to appropriate management^{1,4-6}

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 warranted⁴

Before initiating ENHERTU^{5,6}

- 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^{1,5,6}

- 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 ILD⁴

CT scans⁵

- 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 staff⁴

Patient¹

- 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 team⁵

- 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 staff⁵

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

If ILD/pneumonitis is suspected when^{5,a}:

4 SUSPEND TREATMENT

Promptly investigate evidence and **interrupt ENHERTU treatment as soon as ILD is suspected, regardless of which grade is confirmed^{1,4}**

Asymptomatic (Grade 1) ILD/pneumonitis¹

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)

Symptomatic (Grade ≥ 2) ILD/pneumonitis¹

Permanently discontinue ENHERTU

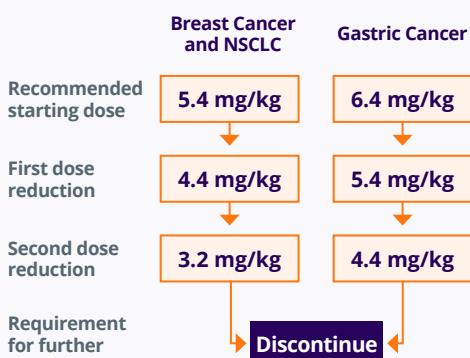
5 STEROIDS

Corticosteroids can be initiated as soon as ILD is suspected, before a pulmonologist consultation^{4,5}

- 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 Schedule¹



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^{1,5,6}
- **Monitor patients with moderate renal impairment more frequently:** a higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in these patients¹
- **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 dose¹

^aEvaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist.¹

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Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
 - In the metastatic setting, or
 - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

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

- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen

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 \leq 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., \geq 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., \geq 1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

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

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU.

Median time to first onset was 6 months (range: 0.9 to 32).

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

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

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

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

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 0.9% of patients.

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

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

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.

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Important Safety Information (cont'd)

Left Ventricular Dysfunction (cont'd)

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.

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

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.9% of patients, of which 0.4% were Grade 3.

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

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

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

Adverse Reactions

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

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 1388 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast02, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, 68% were exposed for >6 months and 42% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (75%), decreased white blood cell count (71%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (57%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (43%), vomiting (42%), increased blood alkaline phosphatase (39%), alopecia (39%), constipation (35%), decreased appetite (32%), hypokalemia (30%), diarrhea (28%), and musculoskeletal pain (26%).

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg intravenously every three weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30).

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

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

thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), hypokalemia (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most

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Important Safety Information (cont'd)

frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and hypokalemia (25%).

Unresectable or Metastatic HER2-Mutant NSCLC (5.4 mg/kg)

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

The safety of ENHERTU was evaluated in 101 patients with unresectable or metastatic HER2-mutant NSCLC who received ENHERTU 5.4 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

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

ENHERTU was permanently discontinued in 8% of patients. Adverse reactions which resulted in

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (21%).

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

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

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

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent

adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), hypokalemia (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

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.

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Important Safety Information (cont'd)

- **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 1287 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥ 65 years and 3.8% were ≥ 75 years. No overall differences in efficacy within clinical studies were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥ 65 years (59%) as compared to younger patients (49%). Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥ 65 years and 8% were ≥ 75 years. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients. Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥ 65 years and 14% were ≥ 75 years. 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.

Abbreviations: 2L, second line; ABG, arterial blood gas; aGC, advanced gastric cancer; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CT, computed tomography; D5W, dextrose 5% in water; ERBB2, erb-b2 receptor tyrosine kinase 2; FDA, Food and Drug Administration; 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; mBC, metastatic breast cancer; mNSCLC, metastatic non-small cell lung cancer; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PFT, pulmonary function test; Q3W, every 3 weeks; SpO₂, saturation of peripheral oxygen.

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