ENHERTU®

fam-trastuzumab deruxtecan-nxki

20 mg/mL INJECTION FOR INTRAVENOUS USE

This resource provides guidance in multiple tumor types, including:

- **Dosage & Administration of ENHERTU**
- **Management of Select Adverse Reactions**
- **Please see page 10 for information on ILD/pneumonitis symptom identification**

GUIDE TO ENHERTU DOSING AND ADMINISTRATION

HER2+ mBC (IHC 3+ or ISH+)[1]	• 1L therapy in combination with pertuzumab • 2L monotherapy
HER2-low and HER2-ultralow mBC[1]	• HR+, HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) mBC • Eligible previously treated HER2-low (IHC 1+ or IHC 2+/ISH–) mBC
2L *HER2*-mutant mNSCLC[1]	
2L HER2+ aGC (IHC 3+ or IHC 2+/ISH+)[1]	
HER2+ (IHC 3+) **metastatic solid tumors**[1]	

Indications and Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated:

- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic 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.
- HER2-Positive Locally Advanced or Metastatic Gastric Cancer
  - As monotherapy for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen
- HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) 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.

Important Safety 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 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 12-17, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

Administration and management of ENHERTU[1]

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INITIATE PROPHYLAXIS: ENHERTU is highly emetogenic, which can cause delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting

- Please see page 11 for more information on the management of nausea and/or vomiting

ADMINISTER: ENHERTU is administered as an IV infusion once every 3 weeks (21-day cycle) and continues until disease progression or unacceptable toxicity

Recommended weight-based dosage and schedule

	Initial ENHERTU Infusion	If well tolerated, Subsequent Infusions
• **1L HER2+ mBC**	**ENHERTU** 5.4 mg/kg over 90 minutes → Wait ~30 minutes → **Pertuzumab** 840 mg	**ENHERTU** 5.4 mg/kg over 30 minutes → Wait ~30 minutes → **Pertuzumab** 420 mg
• **2L HER2+ mBC** • **HER2-low or HER2-ultralow mBC** • ***HER2*-mutant mNSCLC**[a] • **HER2+ (IHC 3+) metastatic solid tumors**	**ENHERTU 5.4 mg/kg** over 90 minutes	**ENHERTU 5.4 mg/kg** over 30 minutes
• **HER2+ aGC**	**ENHERTU 6.4 mg/kg** over 90 minutes	**ENHERTU 6.4 mg/kg** over 30 minutes

- Refer to the Prescribing Information for pertuzumab for recommended dosing information, including infusion durations
- **Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine**
- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms
- Permanently discontinue ENHERTU in case of severe infusion reactions

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

MANAGE: Treatment with ENHERTU may require dose modifications to manage ARs

- Refer to the guidance in the ENHERTU Prescribing Information for temporary interruption, dose reduction, or treatment discontinuation to manage potential ARs. Refer to the Prescribing Information for pertuzumab for dose modification recommendations. Pertuzumab is not to be administered as a single agent
- **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
- Please see page 9 for the ENHERTU dose reduction schedule

Patient selection considerations

- **For HER2+ unresectable or metastatic breast cancer:** Select patients for treatment with ENHERTU + pertuzumab based on confirmed HER2+ status or *HER2* gene amplification (IHC 3+ or ISH+)
- **For HER2-low or HER2-ultralow unresectable or metastatic breast cancer:** Select patients for treatment with ENHERTU based on HER2 expression that is either HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining)
- **For *HER2*-mutant unresectable or metastatic 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 HER2+ locally advanced or metastatic gastric cancer:** Select patients based on HER2 protein overexpression or *HER2* gene amplification (IHC 3+ or IHC 2+/ISH+). Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU
- **For HER2+ (IHC 3+) unresectable or metastatic solid tumors:** Select patients for treatment with ENHERTU based on HER2+ (IHC 3+) 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, *HER2* gene amplification, and activating *HER2* mutations is available at: http://www.fda.gov/CompanionDiagnostics

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ENHERTU preparation for administration[1]

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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**. Reconstitute and further dilute ENHERTU prior to intravenous 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 LVEF prior to initiation and at regular intervals during treatment 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.

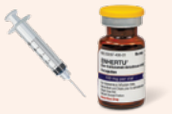
More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed.

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, 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

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PREPARATION & ADMINISTRATION | DOSE MODIFICATIONS | MANAGEMENT OF ARs (ILD, NAUSEA, VOMITING) | IMPORTANT SAFETY INFORMATION | PRESCRIBING INFORMATION | ABBREVIATIONS & REFERENCES

3

ENHERTU preparation for administration[1] (cont'd)

Dilution

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 (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

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

Polyethylene and polypropylene are types of polyolefin

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

Please see Important Safety Information throughout as well as on pages 12-17, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

ENHERTU preparation for administration[1] (cont'd)

Administration[1]

If not used immediately, store the diluted ENHERTU in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for up to 24 hours or at room temperature between 20ºC to 25ºC (68ºF to 77ºF) 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]

- **Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine**
- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms
- Permanently discontinue ENHERTU in case of severe infusion reactions

Polyethylene-lined infusion sets and polyvinylchloride tubing are acceptable[1,2]

D5W is recommended for priming and flushing the administration line[3]

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ENHERTU preparation for administration[1] (cont'd)

Additional Information

How supplied, storage, and handling

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 until time of reconstitution. **Do not freeze. Do not shake the reconstituted or diluted solution.**

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 **100 mL of 5% Dextrose Injection, USP (D5W)**, store 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.** Discard any unused portion left in the vials.

Do not shake the reconstituted or diluted solution.

Special handling
ENHERTU is a hazardous drug. Follow applicable special handling and disposal procedures.

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 dilution

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PREPARATION & ADMINISTRATION | DOSE MODIFICATIONS | MANAGEMENT OF ARs (ILD, NAUSEA, VOMITING) | IMPORTANT SAFETY INFORMATION | PRESCRIBING INFORMATION | ABBREVIATIONS & REFERENCES

Recommended dose modifications for adverse reactions[1]

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Interstitial Lung Disease (ILD)/pneumonitis

Severity	Treatment modification
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 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 9)
Symptomatic ILD/pneumonitis (Grade ≥2)	• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected • 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 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade ≤2, then maintain dose
Grade 4 (ANC <0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade ≤2 • Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 9)

Febrile neutropenia

Severity	Treatment modification
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 • Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 9)

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

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Recommended dose modifications for adverse reactions[1] (cont'd)

Thrombocytopenia

Severity	Treatment modification
Grade 3 (platelets <50 to 25 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade ≤1, then maintain dose
Grade 4 (platelets <25 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade ≤1 • Reduce ENHERTU dose by one level (see dose reductions for adverse reactions on page 9)

Left ventricular dysfunction

Severity		Treatment modification
LVEF >45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with ENHERTU
LVEF 40% to 45%	**And absolute decrease from baseline is <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 <40% or absolute decrease from baseline is >20%		• Interrupt ENHERTU • Repeat LVEF assessment within 3 weeks – If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU
Symptomatic congestive heart failure (CHF)		• Permanently discontinue ENHERTU

Permanently discontinue ENHERTU in patients with symptomatic CHF

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

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Recommended dose modifications for adverse reactions[1] (cont'd)

Dose modifications

- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in the table below. Refer to the Prescribing Information for pertuzumab for dose modification recommendations. Pertuzumab is not to be administered as a single agent
- **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	Breast cancer, NSCLC, and IHC 3+ solid tumors	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	

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

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KEY: ENHERTU Prescribing Information recommendation

1 SCREEN

Careful patient selection based on baseline risk and screening that continues during treatment are warranted[4]

Before initiating ENHERTU[5,6]

- Complete history and physical
- Consider baseline pulse oximetry (SpO_2), PFT, and high-resolution CT scans (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
  - Dyspnea
  - Fever
  - 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[4]

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

CT scans[5]

- 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[4]

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[5]

- 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[5]

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

If ILD/pneumonitis is suspected when[5,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

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/pneumonitis[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 1 dose level (see dose reductions at right)

Symptomatic (Grade ≥2) ILD/pneumonitis[1]

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 Schedule[1]

	Breast cancer, NSCLC, and IHC 3+ solid tumors	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	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[1,5,6]
- **Monitor patients with moderate renal impairment more frequently:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in these 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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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis recommends 3-4–drug prophylactic antiemetic regimens for high emetic risk agents to prevent both acute and delayed emesis during every cycle[7,a-c]

- Consider option A, B, or C
- All treatments are Category 1 and should be started **before** anticancer therapy[d]

	Day 1	Day 2	Day 3	Day 4
Option A Preferred[e,f]	Olanzapine[g]	Olanzapine[g]	Olanzapine[g]	Olanzapine[g]
	NK1 RA	Oral aprepitant (if oral aprepitant used on Day 1)	Oral aprepitant (if oral aprepitant used on Day 1)	
	5-HT3 RA[h,i]			
	Dexamethasone[j,k]	±Dexamethasone[j,k]	±Dexamethasone[j,k]	±Dexamethasone[j,k]
Option B[e]	Olanzapine[g]	Olanzapine[g]	Olanzapine[g]	Olanzapine[g]
	Palonosetron			
	Dexamethasone[j,k]			
Option C[e]	NK1 RA	Oral aprepitant (if oral aprepitant used on Day 1)	Oral aprepitant (if oral aprepitant used on Day 1)	
	5-HT3 RA[h,i]			
	Dexamethasone[j,k]	Dexamethasone[j,k]	Dexamethasone[j,k]	Dexamethasone[j,k]

The high emetic risk protocol includes management for **4 total days**

[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 or anxiety-related 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 (≥85% support of the Panel) that the intervention is appropriate based on high-level evidence (≥1 randomized Phase 3 trials or high-quality, robust meta-analyses). [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]For select patients with additional patient-related risk factors or for whom previous treatment with a 3-drug prophylactic regimen was ineffective, or who are receiving moderately emetogenic chemotherapy (MEC) known to be higher risk, a 4-drug regimen (see option A above) may be considered. [g]Once daily or bedtime on Day 1; bedtime on Days 2-4. Data suggest that a 2.5-mg dose of olanzapine may be efficacious, especially when used as part of a 4-drug regimen. Olanzapine doses of 2.5-5 mg may be less effective than 10 mg when used as part of a 3-drug regimen. Consider lower doses, especially for patients who are older or who are over sedated. [h]If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT3 RA is required. [i]When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. [j]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 day 1 or subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on day 1 or subsequent days, consider the use of an antiemetic combination containing 5-HT3 RA, NK1 RA, and olanzapine on day 1, and olanzapine for delayed chemotherapy-induced nausea and vomiting. [k]Use of corticosteroid premedications should be avoided with cellular therapies. Clinicians may wish to consider a dexamethasone-sparing approach with immune checkpoint inhibitor therapy as well.

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Indications and Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated:

- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic 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.
- HER2-Positive Locally Advanced or Metastatic Gastric Cancer
  - As monotherapy for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen
- HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) 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.

Important Safety 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 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 monotherapy or ENHERTU in combination with pertuzumab. 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 1 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.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients 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 0.9% of patients treated with ENHERTU.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

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Important Safety Information (cont'd)

HER2-Positive 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 monotherapy or ENHERTU in combination with pertuzumab. 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 1 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 1 level.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy
In patients treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen 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 1.2% of patients.

ENHERTU in Combination with Pertuzumab
In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994). Twenty-nine percent had Grade 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% of patients.

HER2-Positive 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. 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.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy
In patients treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

ENHERTU in Combination with Pertuzumab
In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), LVEF decrease was reported in 11% of patients, of which 2.1% were Grade 3 or 4.

HER2-Positive 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.

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Important Safety Information (cont'd)

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 1 level.

Adverse Reactions

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% 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 decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

ENHERTU in Combination with Pertuzumab

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg in combination with pertuzumab intravenously every 3 weeks in 431 patients in DESTINY-Breast07 (n=50), and DESTINY-Breast09 (n=381). Among these patients, 86% were exposed for >6 months and 73% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased hemoglobin (80%), decreased neutrophil count (79%), nausea (74%), increased alanine aminotransferase (65%), diarrhea (64%), increased aspartate aminotransferase (63%), decreased lymphocyte count (61%), decreased platelet count (55%), increased blood alkaline phosphatase (54%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (32%), constipation (31%), decreased appetite (31%), decreased weight (28%), musculoskeletal pain (23%), abdominal pain (22%), and increased blood bilirubin (23%).

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

The safety of ENHERTU 5.4 mg/kg in combination with pertuzumab was evaluated in DESTINY-Breast09, a randomized, three-arm, multicenter study including 763 patients with HER2-positive (IHC 3+ or ISH+) unresectable or metastatic breast cancer. Three hundred eighty-one patients received ENHERTU in combination with pertuzumab and 382 patients received THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab). Among patients who received ENHERTU in combination with pertuzumab, the median duration of treatment was 22 months (range: 0.3 months to 44.5 months).

Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to adverse reactions occurred in 3.4% of patients including pneumonia (n=3), ILD (n=2), sepsis (n=2), pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (one patient each).

ENHERTU was discontinued for adverse reactions in 21% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (6.6%). Dose interruptions due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased. Dose reductions occurred in 46% of patients treated with ENHERTU in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), nausea (75%), increased alanine aminotransferase (66%), diarrhea (64%), increased aspartate aminotransferase (62%), decreased lymphocyte count (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (33%), constipation (33%), decreased appetite (32%), decreased weight (30%), COVID-19 (28%), musculoskeletal pain (24%), increased blood bilirubin (23%), and abdominal pain (23%).

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU.

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

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Important Safety Information (cont'd)

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%), decreased blood potassium (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 and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast06. The median duration of treatment was 11 months (range: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, COVID-19, febrile neutropenia, and hypokalemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%).

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 once 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 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 decreased blood potassium (25%).

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

DESTINY-Lung02 evaluated 2 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 HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

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Important Safety Information (cont'd)

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, decreased blood potassium, 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%).

HER2-Positive 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 1 dose of either ENHERTU (N=125) 6.4 mg/kg every 3 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) 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 1 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 decreased blood potassium. 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%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC 3+) 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 1 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%).

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Important Safety Information (cont'd)

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:** *ENHERTU as Monotherapy*: Of the 2355 patients with HER2-positive, HER2-low, or HER2-ultralow breast cancer treated with ENHERTU 5.4 mg/kg, 23% were ≥65 years and 5% 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 (55%) as compared to younger patients (50%). Of the 101 patients with HER2-mutant unresectable or metastatic 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 HER2-positive locally advanced or metastatic 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. 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 and 9% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. *ENHERTU in Combination with Pertuzumab*: In patients with HER2-positive unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), 17% were ≥65 years and 3% 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.

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

Abbreviations & References

Abbreviations: 1L, first line; 2L, second line; 5-HT3, 5-hydroxytryptamine 3; ABG, arterial blood gas; aGC, advanced gastric cancer; ANC, absolute neutrophil count; AR, adverse reaction; BAL, bronchoalveolar lavage; CHF, congestive heart failure; CT, computed tomography; D5W, dextrose 5% in water; *ERBB2*, erb-b2 receptor tyrosine kinase 2; H_2, histamine type 2; HCP, healthcare provider; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; 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; NCCN, National Comprehensive Cancer Network® (NCCN®); NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; 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.

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