ENHERTU PREPARATION AND ADMINISTRATION CONSIDERATIONS

for healthcare professionals

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) specifies fam-trastuzumab deruxtecan-nxki (ENHERTU) is preferred in patients with visceral metastases if progression on second-line ado-trastuzumab emtansine (T-DM1)[1,a]

[a]The guidelines note fam-trastuzumab deruxtecan (ENHERTU) may be used as a third- or fourth-line treatment option and optimal sequence for third-line therapy and beyond is not known.[1]

Recommended weight-based dosage and schedule[2]

ENHERTU is always given as a monotherapy

Continue until disease progression or unacceptable toxicity

Important Safety Information

Indication

HER2+ Metastatic Breast Cancer

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

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

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Please see Important Safety Information on pages 6 to 7, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

ENHERTU PREPARATION FOR ADMINISTRATION[2,3]

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

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

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

Before administering ENHERTU[2]

- 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

How supplied, storage, and handling[2]

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**. ENHERTU does not contain a preservative.

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 and protected from light. **Do not freeze**. Discard unused portion after 24 hours refrigerated.

After dilution
If not used immediately, after dilution in IV bag with 5% Dextrose Injection, USP (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.

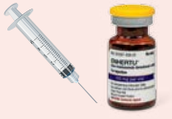
24-hour storage after dilution is permissible in addition to 24-hour storage following reconstitution[2]

Reconstitution[2]

Reconstitute immediately before dilution.

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.



Reconstitute only with Sterile Water for Injection, USP[2]

Swirl the vial gently until completely dissolved.
Do not shake.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.

Dilution[2]

Dilution may occur immediately after or within 24 hours of reconstitution.

Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of D5W. **Do not use Sodium Chloride Solution, USP**. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin, which includes polyethylene and polypropylene bags.

- **In clinical trials, dilution in 250 mL infusion bags of 5% dextrose with a drug concentration of 1 mg/mL to 6.7 mg/mL was permitted[4]**

⚠ **Dilute only with D5W[2]**

- **Do not use Sodium Chloride Solution, USP[2]**

Polyethylene and polypropylene are types of polyolefin[5]

Gently invert the infusion bag to thoroughly mix the solution. **Do not shake.**

Cover the infusion bag to protect from light.

A light protection cover should be used over the IV infusion bag containing diluted ENHERTU[2]

Discard any unused portion left in the vial.

Administration[2]

If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration.

Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene and a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.

Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.

Polyethylene-lined infusion sets and polyvinylchloride tubing are acceptable[2,4,5]

Prior to initiating, and following administration, flush in-line filtered tubing with D5W[2,4]

Additional information

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis lists fam-trastuzumab deruxtecan-nxki (ENHERTU) as moderate emetic risk and recommends several prophylactic antiemetic regimens to decrease potential vomiting.[6]

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation.[2,a]

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.[2]

Do not re-escalate the ENHERTU dose after a dose reduction is made.[2]

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

[a]See Table 2 in the ENHERTU Prescribing Information for information on dose modifications for adverse reactions.

Important Safety Information

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

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Neutropenia

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

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. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3ºC or a sustained temperature of ≥38ºC for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. 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.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. 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.

Important Safety Information (continued)

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 at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

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. Reduce dose by one level.

Adverse Reactions

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (79%), white blood cell count decreased (70%), hemoglobin decreased (70%), neutrophil count decreased (62%), fatigue (59%), vomiting (47%), alopecia (46%), aspartate aminotransferase increased (41%), alanine aminotransferase increased (38%), platelet count decreased (37%), constipation (35%), decreased appetite (32%), anemia (31%), diarrhea (29%), hypokalemia (26%), and cough (20%).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following 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 at least 7 months following the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. 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 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

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.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed March 31, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** ENHERTU [prescribing information]. Daiichi Sankyo Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2021. **3.** OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html. **4.** Data on file. Daiichi Sankyo Inc., Basking Ridge, NJ. **5.** Chemical Retrieval on the Web. Polymer database website. https://polymerdatabase.com/polymer%20classes/Polyolefin%20type.html. Accessed January 15, 2021. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis. V.1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 15, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **7.** Kubo K, Azuma A, Kanazawa M, et al; Japanese Respiratory Society Committee. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig*. 2013;51(4):260-277. **8.** Ripley BA, Kelil T, Gill RR. Deciphering drug-induced interstitial lung disease: A mechanistic approach. *Appl Radiol*. 2016;45(4):9-18.

ILD/PNEUMONITIS SYMPTOM IDENTIFICATION[2,a]

Identification of the signs and symptoms of potentially fatal ILD/pneumonitis is an important aspect of patient management.

Use this guide to help identify symptoms in your patients.

Patients with ILD/pneumonitis may present with symptoms such as[2]:

- Cough
- Trouble breathing or shortness of breath
- Fever
- Other new or worsening breathing symptoms (eg, chest tightness, wheezing)

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms.

Potential questions to ask your patients to help identify ILD/pneumonitis[7,8]

- ☐ Have you been coughing recently?
- ☐ Is it a dry cough?
- ☐ Have you had any shortness of breath, especially during or after physical activity?
- ☐ Have you experienced any new breathing or respiratory problems?
- ☐ If you already have respiratory problems, have they gotten worse?
- ☐ Have you had a fever?
- ☐ Have you been feeling tired?
- ☐ Have you lost weight?

Promptly investigate evidence of ILD/pneumonitis[2]

- Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist
- Initiate management at first sign of ILD/pneumonitis

ILD, interstitial lung disease.

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

Indication

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

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Selected Information Regarding Warnings and Precautions

ENHERTU is associated with a number of serious, potentially fatal, Warnings and Precautions, including Interstitial Lung Disease/Pneumonitis, Neutropenia, Left Ventricular Dysfunction, Embryo-Fetal Toxicity. Please see Important Safety Information.

Please see Important Safety Information on pages 6 to 7, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.