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TREATMENT PLAN: Instructions for using ENHERTU® (fam-trastuzumab deruxtecan-nxki) Treatment Plan for locally advanced or metastatic gastric cancer indication: Please note that the dosing for the locally advanced or metastatic gastric cancer indication is different from the dose for metastatic breast cancer. This document is a draft treatment plan for implementation into an electronic medical record (EMR) or paper treatment plans. Modify as needed to meet institutional standards. **Please [click here](#) for the full Prescribing Information, including Boxed WARNINGS, and Medication Guide.**

Reference article title: ENHERTU. Package insert. Daiichi Sankyo, Inc; 2021.

Reference article URL: www.ENHERTUPI.com

Vial size	NDC	J-code
One 100 mg single-dose vial	65597-406-01	J9358

Pieces of the EMR form are left blank and may require specific guidance from a patient’s insurer.

Precycle Checklist (1 day), Planned	
⇒	Day 1, Cycle 1 – Planned for [XX/XX/XXXX]
⇒	Prior Authorization
	Please fill out the following: ATTENDING PROVIDER: *** Medication: ENHERTU® (fam-trastuzumab deruxtecan-nxki) for locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma 6.4 mg/kg is given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Diagnosis: Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma in adult patients who have received a prior trastuzumab-based regimen. Clinical Information: *** Contact information for any additional questions for prior authorization staff: Name: ***; Phone: ***
⇒	Take-home Medications
⇒	Precycle Supportive Care
⇒	Chemotherapy

Cycle 1 – (21 days), Planned	
⇒	Day 1, Cycle 1
⇒	Prior Authorization
⇒	Take-home Medications
⇒	Precycle Supportive Care

⇒	Precycle Chemotherapy										
⇒	Communication Orders										
	Please see the full Prescribing Information for additional information regarding therapeutic interventions before every infusion.										
	Check weight and blood pressure before every infusion on each day of therapy.										
⇒	Treatment Parameters										
	Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described below and in Tables 1 and 2 in the full Prescribing Information.										
	<u>Do not re-escalate the ENHERTU dose after a dose reduction is made.</u>										
	If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.										
	Dose Reduction Schedule: Locally Advanced or Metastatic Gastric Cancer										
	<table border="1"> <thead> <tr> <th>Dose Reduction Schedule</th> <th>Dose to be Administered</th> </tr> </thead> <tbody> <tr> <td>Recommended starting dose</td> <td>6.4 mg/kg</td> </tr> <tr> <td>First dose reduction</td> <td>5.4 mg/kg</td> </tr> <tr> <td>Second dose reduction</td> <td>4.4 mg/kg</td> </tr> <tr> <td>Requirement for further dose reduction</td> <td>Discontinue treatment</td> </tr> </tbody> </table>	Dose Reduction Schedule	Dose to be Administered	Recommended starting dose	6.4 mg/kg	First dose reduction	5.4 mg/kg	Second dose reduction	4.4 mg/kg	Requirement for further dose reduction	Discontinue treatment
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Second dose reduction	4.4 mg/kg										
Requirement for further dose reduction	Discontinue treatment										
	Dose Modifications for Adverse Reactions:										
	For Interstitial Lung Disease (ILD) / Pneumonitis										
	<ul style="list-style-type: none"> • Asymptomatic ILD/pneumonitis (Grade 1) <ul style="list-style-type: none"> ○ Interrupt ENHERTU until resolved to Grade 0, then: <ul style="list-style-type: none"> ▪ if resolved in 28 days or less from date of onset, maintain dose. ▪ if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1 in the full Prescribing Information or dose reduction schedule table above). ○ Management Considerations <ul style="list-style-type: none"> ▪ as soon as ILD/pneumonitis is suspected, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). ▪ withhold ENHERTU until recovery [see Warnings and Precautions]. • Symptomatic ILD/pneumonitis (Grade 2 or greater) <ul style="list-style-type: none"> ○ Management Considerations <ul style="list-style-type: none"> ▪ as soon as ILD/pneumonitis is suspected, promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. ▪ permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD [see Warnings and Precautions]. 										
	For Neutropenia:										
	<ul style="list-style-type: none"> • Grade 3 (less than 1.0 to 0.5 x 10⁹/L) <ul style="list-style-type: none"> ○ Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. • Grade 4 (less than 0.5 x 10⁹/L) 										

- Interrupt ENHERTU until resolved to Grade 2 or less.
- Reduce dose by one level (see Table 1 in the full Prescribing Information).

For Febrile Neutropenia:

- Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature greater than $38.3^\circ C$ or a sustained temperature of $38^\circ C$ or greater for more than one hour
 - Interrupt ENHERTU until resolved.
 - Reduce dose by one level (see Table 1 in the full Prescribing Information).

For Thrombocytopenia

- Grade 3 (platelets less than 50 to $25 \times 10^9/L$)
 - Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
- Grade 4 (platelets less than $25 \times 10^9/L$)
 - Interrupt ENHERTU until resolved to Grade 1 or less.
 - Reduce dose by one level (see Table 1 in the full Prescribing Information).

For Left Ventricular Dysfunction:

- LVEF greater than 45% and absolute decrease from baseline is 10% to 20%
 - Continue treatment with ENHERTU.
- LVEF 40% to 45% and absolute decrease from baseline is less than 10%
 - Continue treatment with ENHERTU.
 - Repeat LVEF assessment within 3 weeks.
- LVEF 40% to 45% and absolute decrease from baseline is 10% to 20%
 - Interrupt ENHERTU.
 - Repeat LVEF assessment within 3 weeks.
 - If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU.
 - If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
- LVEF less than 40% or absolute decrease from baseline is greater than 20%
 - Interrupt ENHERTU.
 - Repeat LVEF assessment within 3 weeks.
 - If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
- Symptomatic congestive heart failure (CHF)
 - Permanently discontinue ENHERTU.

⇒ Labs

Add/modify/delete tests as needed to meet institutional standards.

⇒ Nursing Orders

Dosing:

Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine.

First infusion: Administer infusion over 90 minutes.

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

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

Permanently discontinue ENHERTU in case of severe infusion reactions.

The recommended dosage of ENHERTU for locally advanced or metastatic gastric/GEJ cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Select patients with locally advanced or metastatic gastric cancer based on HER2 protein overexpression or HER2 gene amplification. Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

Preparation for Administration

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

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

ENHERTU® (fam-trastuzumab deruxtecan-nxki) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed [*see Dosage and Administration*].
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of 5% Dextrose Injection, USP. Do not use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.

- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene and a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.

⇒	Prehydration
⇒	Premedications
⇒	Chemotherapy
⇒	Research Medications
⇒	Postmedications
⇒	Posthydration
⇒	PRN Medications
⇒	Other
	Please click here for full Prescribing Information, including Boxed WARNINGS, and Medication Guide for complete dosage and administration instructions.
⇒	Imaging
⇒	Stem Cell Infusion Orders
⇒	Supportive Care
⇒	Survivorship Care
⇒	Emergency Medications
⇒	Physician Ordered

Abbreviation: USP=US Pharmacopeia.

Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction 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. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

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

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. Reduce dose by one level. For febrile neutropenia ($ANC < 1.0 \times 10^9/L$ and temperature $> 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than 1 hour), 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 DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF $< 50\%$ prior to initiation of treatment.

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

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 $25 \times 10^9/L$) 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. Reduce dose by one level.

Adverse Reactions

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 once every three 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) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

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

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

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

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

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