



Positive Quality Intervention: Fam-Trastuzumab Deruxtecan-nxki (Enhertu®) Management

Description: The purpose of this PQI is to provide guidance for management of fam-trastuzumab deruxtecan-nxki.

Background: Fam-trastuzumab deruxtecan-nxki is indicated for the treatment of:

- Adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer prior anti-HER2-based regimen either:
 - In the metastatic setting OR
 - In the neoadjuvant/adjuvant setting and have developed recurrence during or ≤ 6 months of completing therapy^{1,2}
- Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy
- Adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen^{1,5}
- Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations

Fam-trastuzumab deruxtecan-nxki is a HER2 directed antibody-drug conjugate (ADC). Fam-trastuzumab deruxtecan-nxki was FDA approved for metastatic breast cancer in December 2019 based on results from the DESTINY-Breast01 trial that established its efficacy and safety in patients previously treated with trastuzumab emtansine. The overall response (complete response and partial response) was 60.9%. Secondary endpoints included a median progression free survival of 16.4 months in all patients and 18.1 months in 24 patients enrolled with asymptomatic brain metastases.² Fam-trastuzumab deruxtecan-nxki was FDA approved in January 2021 for patients with gastric and gastroesophageal junction adenocarcinoma based on the results of the DESTINY-Gastric01 trial. This study evaluated the safety and efficacy versus physician's choice chemotherapy (irinotecan or paclitaxel monotherapy) in patients who had progressed on at least two prior regimens which included trastuzumab, a fluoropyrimidine and a platinum agent. The study demonstrated a statistically significant improvement in the major efficacy outcomes of median overall survival (12.5 vs 8.4 mo) and confirmed objective response rate (43% vs 12%). Additional efficacy outcomes of median progression free survival (5.6 vs 3.5 mo) and median duration of response (11.3 vs 3.9 mo) were also improved.⁵

PQI Process:

- Review the medical record
 - Ensure patient is an appropriate candidate for fam-trastuzumab deruxtecan-nxki
 - Confirm no history of interstitial lung disease (ILD), pneumonitis, or other lung condition
 - These patients were excluded from the clinical trials
 - Although not a contraindication, ILD/pneumonitis is a boxed warning
 - Assess Left Ventricular Ejection Fraction (LVEF) prior to initiation
 - Patients with LVEF $< 50\%$ were not studied^{2,5}
 - Evaluate CBC prior to initiation, as well as prior to each dose, and as clinically indicated
- Review treatment plan
 - Verify premedication orders
 - Antiemetics - Moderately emetogenic³- 5-HT3 antagonist + dexamethasone prior to

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- treatment and consideration for days 2 and 3; PRN antiemetic available for home use
 - Acetaminophen + H1 blocker may be included to prevent infusion related reactions per institutional policy or provider preference
- Slow down or interrupt infusion rate if patient develops infusion-related symptoms
 - Verify dosing of fam-trastuzumab deruxtecan-nxki¹
 - Breast and NSCLC: 5.4 mg/kg IV every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity
 - Gastric, colorectal (HER2 amplified RAS and BRAF wild type disease) (off-label): 6.4 mg/kg IV every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity
 - No dose adjustments required for mild or moderate renal or hepatic impairment
 - Patients with severe renal or hepatic impairment were not studied
- Monitoring¹
 - CBC: Baseline, then before each treatment cycle
 - Grade 3 - Hold for neutrophil count < 1,000 cells/mm³ or a platelet count <50,000/microliter until resolved to ≤ Grade 1
 - Grade 4 – Hold for neutrophil count < 500 cells/mm³ or a platelet count <25,000/microliter until resolved to < Grade 2 and reduce dose by one level
 - Growth factor support may be used to maintain counts when appropriate^{2,4,5}
 - LVEF: Baseline and at regular intervals during treatment as clinically indicated
 - Discontinue treatment if LVEF < 40-45% AND if an absolute LVEF decrease of 10-20% from baseline or symptomatic congestive heart failure
 - If recovery to within 10% resume at same dose
 - ILD and pneumonitis: Monitor, consider imaging, and promptly investigate signs and symptoms including cough, dyspnea, fever, and new or worsening respiratory symptoms
 - Permanently discontinue in all patients with ≥ Grade 2 ILD/pneumonitis, promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisone) and continue upon improvement for at least 14 days followed by gradual taper (e.g., at least 4 weeks)
 - Consider use of [ILD/Pneumonitis Assessment Tool](#)
 - Evaluate the need for dose modifications. Do not re-escalate dose after dose reduction is made
 - Dose modifications for breast cancer and NSCLC
 - First dose reduction: 4.4 mg/kg
 - Second dose reduction: 3.2 mg/kg
 - Further required dose reductions: Discontinue treatment
 - Dose modifications for gastric cancer
 - First dose reduction: 5.4 mg/kg
 - Second dose reduction: 4.4 mg/kg
 - Further required dose reductions: Discontinue treatment
- Preparation¹
 - Reconstitute fam-trastuzumab deruxtecan-nxki 100 mg vials with 5 mL of Sterile Water for Injection, USP for a final concentration of 20 mg/mL
 - Inject dose into a 100 mL bag of 5% Dextrose Injection, USP (do not use sodium chloride)
 - Fam-trastuzumab deruxtecan-nxki is compatible with an infusion bag made of polyvinylchloride, or polyolefin (copolymer of ethylene and polypropylene)
- Administration¹
 - First infusion is administered over 90 minutes with an infusion set made of polyolefin or polybutadiene and a 0.2- or 0.22-micron in-line polyethersulfone or polysulfone filter
 - If patient tolerates the first infusion, subsequent infusions may be given over 30 minutes
 - 5% dextrose is recommended for priming and flushing the administrative line
 - Cover the infusion bag to protect from light

Patient-Centered Activities:^{1,4}

- Provide [Intravenous Cancer Treatment Education \(IVE\)](#) Sheet
- Instruct patient to report any new/worsening shortness of breath, dry cough, wheezing, or fever
- Caution patient regarding increased risk of infection and infection prevention methods
- Review prompt reporting of any chest pain/tightness, rapid weight gain, significant swelling in ankles or trouble breathing due to weakened pumping action of the heart muscle
- Remind patient that this drug may cause significant hair loss
- Instruct patient to report adverse events including fever, diarrhea, nausea/vomiting or fatigue
- Ensure patient has access to supportive medications
 - Anti-nausea: 5-HT3 receptor antagonist, metoclopramide, or prochlorperazine
 - Anti-diarrheal: loperamide
- Patient Assistance: [NCODA Financial Assistance Tool](#)

References:

1. [Enhertu® \(fam-trastuzumab deruxtecan-nxki\) \[prescribing information\]](#).
2. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020;382(7):610-621.
3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Antiemesis.
4. [Fam-trastuzumab Deruxtecan-nxki \(Enhertu®\). JNCCN Spotlights.](#)
5. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med* 2020; 382:2419-2430.