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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 is an antibody-drug conjugate that targets HER2 and is linked to a topoisomerase inhibitor with the following indications in adult patients:[1]

- Unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - In the metastatic setting OR
  - In the neoadjuvant/adjuvant setting and have developed recurrence during or within 6 months of completing adjuvant therapy
- Unresectable or metastatic hormone receptor-positive (HR-positive), HER2-low or HER2-ultralow breast cancer that has progressed ≥ 1 endocrine therapies in the metastatic setting
- Unresectable or metastatic HER2-low 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
- Unresectable or metastatic non-small cell lung cancer whose tumors have activating HER2 mutations and who have received a prior systemic therapy
- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen
- Unresectable or metastatic HER2-positive solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

Most common adverse reactions (≥ 20%):

- Decreased: white blood cells and neutrophils, hemoglobin, lymphocytes, platelets, potassium, appetite
- Increased: AST/ALT, bilirubin, alkaline phosphatase
- Other: nausea, vomiting, diarrhea, constipation, fatigue, alopecia, musculoskeletal pain, pyrexia (gastric cancer)

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 emetogenic[3]- 5-HT3 antagonist + dexamethasone prior to

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-nxki[1]
        - 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
- Monitoring[1]
    - CBC: Baseline, then before each treatment cycle
        - Grade 3 - Hold for neutrophil count < 1,000 cells/mm^3 or a platelet count <50,000/microliter until resolved to ≤ Grade 1
        - Grade 4 – Hold for neutrophil count < 500 cells/mm^3 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
- Preparation[1]
    - 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)
- Administration[1]
    - 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 Derutecan-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.