Written By: Jennifer L. Zadlo, Pharm.D., BCOP
Institution: The University of Texas MD Anderson Cancer Center

Zanidatamab-hrii (Ziihera®) for the Management of Gastroesophageal Adenocarcinoma

Description: The purpose of this document is to discuss the clinical considerations and general management of patients treated with zanidatamab-hrii for unresectable/locally advanced or metastatic, HER2-positive gastroesophageal adenocarcinoma.

Background:[1]

- Zanidatamab-hrii is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Binding of zanidatamab-hrii with HER2 results in receptor internalization and antibody/complement mediated cell death. Zanidatamab-hrii is not a T-cell engager.
- Zanidatamab-hrii is indicated for the first-line treatment of adults with unresectable locally advanced or metastatic, HER2-positive gastric, gastroesophageal junction, or esophageal adenocarcinoma:
  - **HER2-positive (IHC 3+ or IHC 2+/ISH+):** In combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab-jsgr.
  - **HER2-positive (IHC 3+):** In combination with fluoropyrimidine- and platinum-containing chemotherapy.
- Most common adverse reactions (≥ 20%) with zanidatamab-hrii in combination with fluoropyrimidine-and platinum-containing chemotherapy, with or without tislelizumab-jsgr: diarrhea, nausea, vomiting, decreased appetite, fatigue, hypokalemia, peripheral neuropathy, infusion-related reactions (IRR), and rash.

  Note: Zanidatamab-hrii is also indicated for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC); however, BTC management is outside the scope of this PQI.

PQI Process:

- Ensure patient meets indication criteria for zanidatamab-hrii:
  - Verify patient has unresectable/locally advanced or metastatic adenocarcinoma of the esophagus, gastroesophageal junction (GEJ) or stomach.
  - Verify HER2-positive (IHC 3+ or IHC 2+/ISH+) tumor status based on the planned treatment regimen:
    - With tislelizumab-jsgr: IHC 3+ or IHC 2+/ISH+
      - Note: PD-L1 expression status is not a required criterion for this treatment regimen.
    - Without tislelizumab-jsgr: IHC 3+
  - Clinical considerations: tumors with a HER2 (ERBB2)/CEP17 ratio ≥2 or an average HER2 (ERBB2) copy number ≥6.0 signals/cell are considered positive for HER2 amplification by ISH/FISH.[2,3]
  - Ensure patient has received no prior systemic therapy in the unresectable/metastatic setting.
- Review cardiac history and evaluate left ventricular ejection fraction (LVEF) prior to starting zanidatamab-hrii and at regular intervals during treatment.

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    - Practical considerations: Consider LVEF monitoring every 6 months, with more frequent monitoring as clinically indicated.
        - *This frequency is practice-based and is not specified in the prescribing information.*
    - The safety of zanidatamab-hrii has not been studied in patients with a baseline ejection fraction of <50%.[1]
- Confirm negative pregnancy status and absence of breastfeeding prior to starting zanidatamab-hrii.
- Consider screening for HBV with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) zanidatamab-hrii; do not delay treatment for screening/results.[4]
- Assess Performance Status (PS); PS of 0-1 was required for enrollment in HERIZON-GEA-01.[5]
- Concomitant therapy considerations
    - Tislelizumab
        - Ensure tislelizumab included on institution formulary
        - Flexible dosing and frequency options
            - 150 mg every 2 weeks
            - 200 mg every 3 weeks
            - 300 mg every 4 weeks
            - 400 mg every 6 weeks
    - Fluoropyrimidine plus platinum
        - Continuous infusion 5-FU (preferred[2,3]) or capecitabine
        - Do not administer fluorouracil as an intravenous bolus due to the potential increase in diarrhea.[1]
            - Oxaliplatin or cisplatin (oxaliplatin preferred[2,3])
- Dosing
    - Flat dosing, weight based

	Actual Body Weight LESS THAN 70 kg		Actual Body Weight GREATER THAN or EQUAL to 70 kg	
Every 2 weeks	1200 mg	Dose modification	1600 mg	Dose modification
		900 mg		1200 mg
Every 3 weeks	1800 mg	Dose modification	2400 mg	Dose modification
		1400 mg		1800 mg

Note: If weight changes (increase or decrease) by 10% AND crosses the 70 kg threshold, recommend zanidatamab dose modification to correlate with appropriate dosing category

- Premedication and Prophylaxis
    - Infusion-related reaction (IRR) premedication: Administer the following 30–60 minutes prior to every dose of zanidatamab-hrii:[1]
        - Acetaminophen
        - Antihistamine
        - Corticosteroid

    - Diarrhea prophylaxis: When zanidatamab-hrii is administered with fluoropyrimidine- and platinum-containing chemotherapy:[1]
        - Administer loperamide 4 mg orally twice daily beginning on Day 1 and continuing for at least 7 days during the first cycle.
        - If diarrhea occurs during the first cycle, continue loperamide 4 mg orally twice daily for at least the first 7 days of each subsequent cycle.
- Administration
    - Administer as an IV infusion with a 0.2 or 0.22 micron filter
    - Do not administer as IV push or bolus
    - Do not co-administer other IV drugs through the same line
    - If a patient misses a dose, administer as soon as possible if 7 days or fewer have passed since the scheduled dose. If more than 7 days have passed, withhold zanidatamab-hrii and resume on Day 1 of the next cycle.
    - Infusion duration
        - Dose 1: infuse over 120 minutes
        - Dose 2: infuse over 90 minutes (if tolerant to previous infusion)
        - Dose 3 and beyond: infuse over 60 minutes (if tolerant to previous infusion)
- Supportive care considerations for patients with dysphagia and/or odynophagia with or without enteral feeding tube[6]
    - *The recommendations in this table represent practice-based guidance and are not specified in the prescribing information. Clinical decision-making regarding medication administration via enteral feeding tubes should consider medication pharmacodynamics, available formulations, cost, and characteristics of the enteral access device, including type, size, and length.*

Medication	**No enteral tube; PO administration**	**G-tube administration**	**J-tube administration**	**NPO or TPN Other route of administration**
Acetaminophen	*Chewable *†Oral suspension	Crush tablet * Using chewable tablet, dissolve in water *†Oral solution/ suspension	*Using chewable tablet, dissolve in water *†Oral solution/ suspension	*Suppository Intravenous solution
Loperamide	Chewable tablet †Oral suspension	Chewable tablet †Oral suspension	Using chewable tablet, dissolve in water †Oral suspension	X
*commonly available in pediatric dose strengths and units; may require higher dose-unit burden				
†liquid formulations may contain nonabsorbable sugars (eg, sorbitol, mannitol, xylitol) that can contribute to diarrhea[6]				

- Adverse events:
    - Black Box Warnings: Severe diarrhea and embryo-fetal toxicity
        - Severe diarrhea, Grade 3+ (in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr)
            - Potential to be life-threatening and/or fatal
            - Monitor for diarrhea and sequelae; treat with supportive measures
                - Dehydration
                - Electrolyte abnormalities: hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia
        - When administered in combination with fluorouracil-containing regimens, administer fluorouracil as an intravenous infusion

- Do NOT administer fluorouracil as a bolus due to the potential increase in diarrhea
    - Median onset for cycle 1 diarrhea = 6 days
    - Median time to resolution = 18 days
    - Dose reductions, interruptions, or discontinuation may be necessary, as follows:

Grade 1	Grade 2	Grade 3	Grade 4
Continue zanidatamab; no dose modification	Continue zanidatamab; no dose modification	Hold zanidatamab Hospitalization indicated[7]	Permanently discontinue Hospitalization indicated[7]
Continue loperamide prophylaxis with subsequent cycles	Continue loperamide prophylaxis with subsequent cycles	Resume when ≤ grade 1	Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea
Loperamide 4 mg followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhea	Increased clinical monitoring (ex: consider nurse phone call to patient[7]; intermittent IV fluid hydration support[7]	Administer subsequent treatment at the same dose level or consider a dose reduction	Add diphenoxylate/atropine, alternating with loperamide[7]
Consider diphenoxylate/atropine[7]	Consider dose modification of conventional chemotherapy agents	Permanently discontinue for recurrent Grade 3 symptoms that last > 3 days despite optimized medical management	Octreotide 100–150 mcg subcutaneous Q8H in severe/refractory cases[7]; consider continuous IV infusion[7]
	Loperamide 4 mg followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhea	Loperamide 4 mg followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhea	
	Add diphenoxylate/atropine[7]	Add diphenoxylate/atropine[7]	
	Consider short course subcutaneous octreotide or opium tincture for refractory cases[7]	Octreotide 100–150 mcg subcutaneous Q8H in severe/refractory cases[7]; consider continuous IV infusion[7]	
		Consider GI consult Consider nutritional support[7]	

- Infusion reactions: Monitor patients during administration and manage reactions according to severity and prescribing information.[1]

Patient-Centered Activities:

- Distribute the zanidatamab-hrii (Ziihera) patient education sheet to the patient.
- Provide patients with extensive education for:
    - Loperamide anti-diarrheal prophylaxis
        - During the first cycle when zanidatamab-hrii is administered in conjunction with fluoropyrimidine- and platinum-containing chemotherapy
        - Take loperamide 4 mg twice daily beginning on Day 1 and continue for at least 7 days during the first cycle of treatment
            - If patients experience diarrhea during the first cycle, continue prophylaxis with loperamide 4 mg twice daily for at least the first 7 days of each subsequent cycle
    - Discontinue all laxatives

- Inform patient on signs and symptoms of dehydration such as dizziness or lightheadedness, dry or cracked lips or mouth, increased thirst, or dark urine; monitor body weight
    - Instruct patients to contact their healthcare team for new or worsening diarrhea, persistent dirarhea despite antidiarrheal therapy, or signs and symptoms of dehydration.
- Inform patient of useful dietary modifications:
    - Eat small meals of mild, low-fiber foods (such as bananas, applesauce, potatoes, chicken, rice, and toast).
    - Avoid high-fiber foods (such as raw vegetables, fruits, and whole grains), gas-producing foods (such as broccoli and beans), dairy (such as milk and yogurt), and spicy, fried, or greasy foods.
    - Drink 8 to 10 glasses of water or other clear fluids daily
- Inform patient on signs and symptoms of electrolyte abnormalities such as new or worsening muscle weakness or cramps, muscle stiffness or spasms, irregular, fast, or pounding heartbeat, or chest pain, extreme tiredness, and/or new or worsening confusion, drowsiness, severe headache, or trouble thinking
- Useful documents: Understanding Diarrhea During Cancer Treatment

- Inform the patient that pre-medications will be given prior to the infusion to help prevent infusion-related reactions. Instruct the patient to promptly report to their nurse if they experience any flushing, chills, rash, itching, chest pain, difficulty breathing, nausea/vomiting, or dizziness during or after their infusion.
- Encourage use of a symptom journal or electronic tracking tool to help follow and identify trends in bowel habits, diet, and medication use
- Instruct females with reproductive potential to use effective contraception during treatment and for 4 months following the last dose. Instruct patients to promptly report if they become pregnant during treatment.
- Other common side effects such as decreased appetite, feeling tired, stomach pains, and nausea/vomiting

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