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# Zanidatamab-hrii (Ziihera) for the Management of Biliary Tract Cancer

**Description:**

- The purpose of this document is to discuss the clinical considerations and general management of patients treated with zanidatamab-hrii for unresectable or metastatic biliary tract cancer.

**Background:**

- Zanidatamab-hrii is a 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 treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer.
    - Most common adverse reactions (≥ 20%): diarrhea, infusion-related reactions, abdominal pain, fatigue

**PQI Process:**

- Ensure patient meets indication criteria for zanidatamab-hrii:
    - Verify patient has unresectable or metastatic biliary tract cancer that has progressed on at least one line of systemic treatment
    - Verify HER2-positive (IHC 3+) tumor status
- Review cardiac history and evaluate left ventricular ejection fraction (LVEF) prior to starting zanidatamab-hrii and at regular intervals during treatment
    - Example interval for LVEF monitoring would be every 3 to 6 months depending on patient history
    - The safety of zanidatamab-hrii has not been studied in patients with a baseline ejection fraction of <50%
- Confirm negative pregnancy and breastfeeding status for females of reproductive potential 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.
- Premedicate all patients from potential infusion-related reactions by administering the following 30-60 minutes prior to each dose:
    - Acetaminophen
    - Antihistamine
    - Corticosteroid
- Dosing/Administration: 20mg/kg every 2 weeks until disease progression or unacceptable toxicity; zanidatamab-hrii administration does not require inpatient admission
    - 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; do not wait until next planned dose and maintain a 2-week dosing interval

- Recommended infusion durations:

| Dose Number(s) | Infusion Duration |
|---|---|
| Doses 1 and 2 | Infuse over 120-150 minutes* |
| Doses 3 and 4 | Infuse over 90 minutes (if previous doses were well tolerated) |
| Dose 5 and beyond | Infuse over 60 minutes (if previous doses were well tolerated) |

*Consider an initial infusion time of 150 minutes with dose 1, then if well tolerated, 120 minutes with dose 2 and so on per table above to decrease incidence of infusion-related reactions

- Dose modifications:
  - For Grade 3 adverse reactions, including Grade 3 diarrhea, the recommended dose reduction for zanidatamab-hrii is to 15 mg/kg. If patient cannot tolerate this dose, zanidatamab-hrii should be permanently discontinued.
  - There is no recommended dose reduction for left ventricular dysfunction, infusion-related reactions, or pneumonitis (permanently discontinue for Grade ≥2 pneumonitis)

| Adverse Reaction | Severity | Treatment Modification |
|---|---|---|
| Left Ventricular Dysfunction (LVD) | Absolute decrease of ≥ 16% points in LVEF from baseline<br>or<br>LVEF ≤50% and absolute decrease of ≥10% point below baseline | • Withhold for at least 4 weeks<br>• Repeat LVEF assessment within 4 weeks<br>• Resume treatment within 4-8 weeks if LVEF returns to normal limits and absolute decrease is ≤15% point from baseline |
| Infusion-Related Reactions | Mild (Grade 1) | • Reduce infusion rate by 50%<br>• For subsequent infusions, increase rate gradually to the rate prior to the adverse reaction, as tolerated |
| | Moderate (Grade 2) | • Stop infusion immediately and treat with appropriate therapy<br>• Resume infusion at 50% of previous rate once symptoms resolve<br>• For subsequent infusions, increase rate gradually to the rate prior to the adverse reaction, as tolerated |

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| | Severe (Grade 3) | • Stop infusion immediately and treat with appropriate therapy; infusion should not be restarted during the same cycle even if signs and symptoms completely resolve<br>• Administer subsequent infusions at 50% of previous infusion rate<br>• Permanently discontinue for recurrent Grade 3 reaction |
| | Life Threatening (Grade 4) | • Stop infusion immediately and permanently discontinue<br>• Promptly treat with appropriate therapy |
| Diarrhea | Severe (Grade 3) | • Hold treatment until severity improves to ≤ Grade 1<br>• Initiate or intensify appropriate medical therapy and monitor as clinically indicated<br>• Administer subsequent treatment at the same dose level or consider dose reduction<br>• For recurrent Grade 3 symptoms, hold treatment and optimize medical management. Resume at reduced dose after severity improves to ≤ Grade 1<br>• Permanently discontinue for recurrent Grade 3 symptoms that last > 3 days despite optimized medical management |

**Patient-Centered Activities:**

- Provide patient with a patient information sheet or educational material that explains HER2 positivity, zanidatamab's purpose, dosing, side effects, and important safety information
- 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.
- Inform the patient of regular cardiac monitoring due to risk of cardiac dysfunction. Instruct the patient to promptly report any chest pain/tightness, irregular heartbeat, rapid weight gain, significant swelling in ankles, or trouble breathing.
- Instruct patient to report any new/worsening shortness of breath, dry cough, wheezing, or fever
- Ensure patient has access to anti-diarrheal medication and review how to manage diarrhea with diet, lifestyle, hydration, and medications. Provide patient with diarrhea management education sheet.
- Review other common side effects such as stomach pain and feeling tired.

- Instruct females with reproductive potential to use effective contraception during treatment and for 4 months following the last dose. Instruct patient to promptly report if they become pregnant during treatment.

**References:**


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