A REVIEW ON ESSENTIAL DOSING AND PRESCRIBING DOSE FOR ZIHERA

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Abstract—**ZIIHERA (zanidatamab-hrii) is a bispecific human epidermal growth factor receptor 2 (HER2)-directed antibody indicated for the treatment of adult patients with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer. The therapeutic administration involves intravenous (IV) infusion, commonly given on a biweekly schedule until disease progression or unacceptable toxicity occurs. To mitigate the risk of infusion-related reactions (IRRs), mandatory premedication with an antipyretic, an antihistamine, and a corticosteroid must be administered 30 to 60 minutes prior to every infusion.The initial two infusions are administered over a specific duration. If well-tolerated, the duration can be reduced for subsequent administrations. Safety profiles require monitoring for left ventricular dysfunction (LVD) and severe diarrhea. Dosage modifications for adverse events may be required, or permanent treatment discontinuation for unmanaged toxicities.**

Index Terms—**ZIHERA HER-2(receptor 2), biliary tract cancer, embryo fetal toxicity, Left ventricular dysfunction**

I. INDICATION AND USAGE

Zanidatamab-hrii (Ziihera) has received accelerated approval for adult patients with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), confirmed via validated companion diagnostics.

II. DOSAGE AND ADMINISTRATION

1. **Patient Selection**: Select patients for treatment of unrespectable or metastatic biliary tract cancer based on HER2positive (IHC 3+) tumor specimens, as detected by an FDA-approved test [see Clinical Studies
2. **Premedication**: Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA to reduce the risk of infusion-related reactions. X Administer acetaminophen, an antihistamine (such as diphenhydramine) and a corticosteroid (such as hydrocortisone).
3. **Recommended Dosage and Administration**: The recommended dosage of ZIIHERA is 20 mg/kg, administered as an intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity. If a planned dose of ZIIHERA is delayed or missed, administer the dose as soon as possible; do not wait until the next planned dose. Adjust the administration schedule to maintain a 2-week interval between doses.
4. **Dosage Modifications for Adverse Reactions**: Dosage Modifications for Adverse Reactions;
    - The recommended dosage reduction of ZIIHERA for adverse reactions is 15 mg/kg as described in Table 1.
    - Permanently discontinue ZIIHERA in patients who cannot tolerate 15 mg/kg.

Table 1 Dosage modifications for Adverse Reactions

Adrverse Reaction	Severity	Clinical Criteria Recommended Protocol Adjustment
Left Ventricular dysfunction (LVD)	16% from baseline OR LVEF 50% with an absolute decline 10% from baseline	[1] Withhold therapy for 4 weeks. [2] Reassess LVEF within 4 weeks. [3] Resume within 4–8 weeks if LVEF normalises and absolute decline is 15% from baseline. [4] Permanently discontinue ZIHERA if confirmed CHF
Infusion related reactions	Mild (Grade 1) Moderate (Grade 2)	[1] Reduce ZIHERA infusion rate by 50%. [2] Stop ZIHERA infusion immediately [3] Resume ZIHERA infusion at 50%of previous infusion rate once symptoms resolve. [4] For subsequent ZIHERA infusions increase gradually to the rate prior to the adverse reaction as tolerated

	Severe (Grade 3) Life threatening (Grad 4)	[5] Stop ZIHERA infusion immediately. [6] Infusion should not restarted during the same cycle even if signs and symptoms completely resolve [7] Premanantly discontinue ZIHERA for recurrent Grade 3 reaction. [8] Stop ZIHERA infusion immediately and permanently discontinue.
Pneumonitis	Confirmed Grade ≥2	[9] Permanently discontinue ZIHERA.
Other Adverse Reactions (excluding LVD, IRR, Diarrhoea,and pneumonitis)	Mild/Moderate (Grade1/2) Severe (Grade 3) Life threatening (Grade 4)	[10] No dosage modification required for ZIHERA [11] With hold ZIHERA treatment until severity improves to grade ≥ 1 [12] Administer ZIHERA at the same dose

		[13] Permanently discontinue ZIHERA, except as noted below. [14] ZIHERA treatment may be resumed at the same dose level for Grade 4 electrolyte imbalance [15] Permanently discontinue ZIHERA for recurrent Grade 4 electrolyte imbalances or laboratory abnormalities.

5. Preparation and Administration Instructions

Reconstitution

- Calculate the recommended dose based on the patient's weight to determine the number of vials needed.
- Remove the vial(s) from the refrigerator and allow the vial(s) to reach room temperature.
- Reconstitute each 300 mg vial of ZIIHERA with 5.7 mL of Sterile Water for Injection by slowly directing the stream toward the inside of the wall of the vial, to obtain a final concentration of 50 mg/mL in an extractable volume of 6 mL.
- Swirl the vial gently until completely dissolved. Do not shake or vigorously swirl. X Allow the reconstituted vial to settle to allow bubbles to dissipate.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted product should be a colorless to light yellow, clear to slightly opalescent solution with no visible particles. Discard the reconstituted vial if any discoloration or particulate matter is observed.
- The product does not contain a preservative. Use the reconstituted ZIIHERA solution immediately or store the reconstituted ZIIHERA solution for up to 4 hours, either at room temperature (18°C to 24°C [64°F to 75°F]) or in a refrigerator (2°C to 8ºC [36°F to 46ºF]).

Dilution

- Withdraw the necessary volume for the calculated dose from each vial [see Dosage and Administration (2.3)].

- Slowly add the necessary dose volume to an infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection to prepare an infusion solution with a final concentration of the diluted solution between 0.4 mg/mL and 6 mg/mL.
- Gently invert the infusion bag to mix. Do not shake.
- The infusion solution must be a clear, colorless solution with no visible particles. Do not use if visible particles are observed or if the solution is discolored.
- Discard any unused portion left in the vial(s).
- Use the infusion solution immediately upon dilution or store the infusion solution at room temperature (18°C to 24°C [64°F to 75°F]) for up to 12 hours or in the refrigerator (2ºC to 8ºC [36ºF to 46ºF]) for up to 24 hours.
    - These time limits include the beginning of reconstitution through the duration of infusion.
    - If these specified times are exceeded, discontinue the current infusion bag and prepare a new bag which contains the remaining dosage of ZIIHERA to be infused.
- Compatibility with intravenous administration materials and the infusion solution has been demonstrated in the following materials:
    - Intravenous (IV) Bag: Polyvinyl chloride (PVC), polyolefin (PO), ethyl vinyl acetate (EVA), polypropylene (PP) and ethylene-propylene copolymer.
    - Infusion sets: Polyvinyl chloride/ bis (2-ethylhexyl) phthalate (PVC/DEHP). Polyurethane (PUR), polyethylene-lined (PE-lined) acrylonitrile-butadiene-styrene (ABS).
    - Inline filters: Polyethersulfone solution filter (PES), polyvinylidene fluoride air filter (PVDF).
    - Closed System Transfer devices: acrylonitrile-butadiene-styrene (ABS), acrylic cpolymer, polycarbonate (PC), polyisoprene (PI), polyester, polypropylene (PP) polytetrafluoroethylene (PTFE), silicone and stainless steel (SS).

Administration

- Administer ZIIHERA as an intravenous infusion with a 0.2 or 0.22 micron filter.
- Do not administer as an intravenous push or bolus.
- Do not co-administer ZIIHERA and other intravenous drugs through the same intravenous line.

Table 2 : Recommended ZIHERA infusion Durations

Dose	Infusion Duration
First and Second	120-150 min
Third and Fourth	90 min
Subsequent	60 min

III. DOSAGE FORMS AND STRENGTHS

For injection: 300mg while lyophilized powder in a single-dose vial.

IV. CONTRA INDICATIONS

NONE

V. WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on the mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman. There are no human or animal data on the use of ZIIHERA in pregnancy. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ZIIHERA. Advise pregnant women and females of reproductive potential that exposure to ZIIHERA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception while receiving ZIIHERA and for 4 months following the last dose of ZIIHERA.

5.2 Left Ventricular Dysfunction

ZIIHERA can cause decreases in left ventricular ejection fraction (LVEF). LVEF declined by greater than 10% and decreased to less than 50% in 4.3% of 233 patients. LVD leading to permanent discontinuation of ZIIHERA was reported in 0.9% of patients. The median time to first occurrence of left ventricular dysfunction was 5.6 months (range: 1.6 to 18.7 months). Left ventricular dysfunction resolved in 70% of patients.

Assess LVEF prior to initiation of ZIIHERA and at regular intervals during treatment. Withhold dose or permanently discontinue ZIIHERA based on severity of adverse reactions [see Dosage and Administration (2.4)].

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is below 50% [see Dosage and Administration (2.4)].

5.3 Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs). An IRR was reported in 31% of 233 patients treated with ZIIHERA as a single agent in clinical studies, including Grade 3 (0.4%), and Grade 2 (25%). IRRs leading to permanent discontinuation of ZIIHERA were reported in 0.4% of patients. IRRs occurred on the first day of dosing in 28% of patients; 97% of IRRs resolved within one day.

Prior to each dose of ZIIHERA, administer premedications to prevent potential IRRs [see Dosage and Administration (2.2)]. Monitor patients for signs and symptoms of IRR during ZIIHERA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use.

If an IRR occurs, slow, or stop the infusion, and administer appropriate medical management. Monitor patients until complete resolution of signs and symptoms before resuming. Permanently discontinue ZIIHERA in patients with recurrent severe or life-threatening infusion-related reactions [see Dosage and Administration (2.4)].

5.4 Diarrhea

ZIIHERA can cause severe diarrhea (nausea vomiting, abdomen pain)

Diarrhea was reported in 48% of 233 patients treated in clinical studies, including Grade 3 (6%) and Grade 2 (17%). If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Withhold or permanently discontinue ZIIHERA based on severity [see Dosage and Administration (2.4)].

VI. ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of the labeling:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Left Ventricular dysfunction [see Warnings and Precautions (5.2)] x Infusion-Related Reactions [see Warnings and Precautions (5.3)]
- Diarrhea [see Warnings and Precautions (5.4)]

VII. USE IN SPECIFIC POPULATION

7**.1 Teratogenic Risk Summary**: Based on its mechanism of action as a HER2-directed antibody, zanidatamab-hrii (Ziihera) can cause severe fetal harm when administered during pregnancy. While direct clinical data in pregnant individuals are unavailable, the class-wide literature for HER2-targeted agents documents significant risks of oligohydramnios and oligohydramnios sequence. This can manifest as lethal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Consequently, treatment is not recommended during pregnancy or in individuals of childbearing potential who are not utilizing highly effective contraception.

7.2 Excretion and Risk Summary: There are no clinical data evaluating the presence of Zanidatamab-hrii in human milk, its effects on milk production, or its impact on the breastfed infant. While endogenous maternal immunoglobulin G (IgG) is known to excrete into breast milk, literature indicates it does not enter the neonatal circulation in clinically significant quantities.

7.3 Females and Males of Reproductive Potential

ZIIHERA can cause fetal harm when administered to a pregnant woman [see Warnings and Precautions (5.1), Use in Specific Populations (8.1)].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of ZIIHERA [see Use in Specific Populations (8.1)].

Contraception

Females

ZIIHERA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with ZIIHERA and for 4 months following the last dose of ZIIHERA.

7.4 Pediatric Use

Safety and efficacy of ZIIHERA have not been established in pediatric patients.

7.5 Geriatric Use

Of the 80 patients who received ZIIHERA for unresectable or metastatic biliary tract cancer in HERIZON-BTC-01, there were 39 (49%) patients 65 years of age and older. Thirty-seven (46%) were aged 65-74 years old and 2 (3%) were aged 75 years or older [see Clinical Studies (14)].

No overall differences in safety or effectiveness were observed between these patients and younger adult patients.

VIII. DESCRIPTION

Zanidatamab-hrii is a humanized, IgG-like, bispecific HER2-directed antibody. Zanidatamab-hrii is produced in Chinese hamster ovary cells via recombinant DNA technology and has a molecular weight of 124.8 kDa.

ZIIHERA (zanidatamab-hrii) for injection is supplied as a sterile, preservative free, white lyophilized powder that requires reconstitution and dilution for intravenous use. Each single-dose vial of reconstituted product contains 300 mg of zanidatamab-hrii and the inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg), succinic acid (4.3 mg), and sucrose (567 mg). Following reconstitution with 5.7 mL Sterile Water for Injection, a solution containing 50 mg/mL zanidatamab-hrii is produced with a deliverable volume of 6 mL, with pH of 4.6. The resulting solution is diluted and administered by intravenous infusion.

IX. CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Zanidatamab-hrii is a directed antibody binds to two extracellular sites on HER2. Results in internalization leading to reduction of the receptor on the tumor cell surface. Zanitadamab-hrii induces complement dependent cytotoxicity, antibody dependent cellular cytotoxicity and antibody dependent cellular phagocytosis. These mechanisms result in tumor growth inhibition and cell death.

9.2 Pharmacodynamics

Zanidatamab-hrii exposure response relationships and the time course response are unknown.

9.3 Pharmacokinetics

Zanidatamab-hrii maximum conc.is 600mg/ml, the lowest measured conc. Is 178mg/ml. The Cmax of zanidatamab-hrii is dose proportional and the total systemic exposure of zihera is greater than dose proportional with increasing doses.The volume of distribution is 7.5 l. The halflife of zanidatamab is 22days.Exretion through kidneys.

9.4 Immunogenecity

There is insufficient information to characterize the anti-drug antibody response to zanidatamab-hrii and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of zanidatamab-hrii.

X. NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been conducted to evaluate the carcinogenic or mutagenic potential of zanidatamab-hrii.

Fertility studies with zanidatamab-hrii have not been conducted.

XI. HOW SUPPLID/STORAGE AND HANDLING

ZIHERA is supplied as a sterile, preservative free, white lyophilized powder in a single dose vial. Each single dose vial contains 300 mg. each carton of ZIHERA contains two single dose vials.

XII. PATIENT COUNSELLING INFORMATION

Embryo-Fetal Toxicity

Fetal Risks: Inform female patients that this medication can harm an unborn baby.

Pregnancy Reporting: Tell patients to contact their doctor immediately if they become pregnant or suspect they are pregnant.

Birth Control: Advise females who can get pregnant to use reliable contraception during treatment and for 4 months after their final dose.

❤️‍🩹 Left Ventricular Dysfunction

Heart Function: Warn patients that ZIIHERA may cause serious heart problems.

Urgent Reporting: Instruct patients to alert a healthcare provider right away if they experience any symptoms of heart distress.

💉 Infusion-Related Reactions

Infusion Risks: Explain to patients that reactions can occur during or after the injection.

Immediate Alerts: Tell patients to notify medical staff immediately if they feel unwell during the infusion.

🤢 Diarrhea

Severe Diarrhea: Warning patients that this drug can cause severe diarrhea.

Management & Help: Teach patients how to treat diarrhea at home and tell them to call their doctor if it does not improve.

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XIII. CONCLUSION

Indication: An IV-infused bispecific antibody for adults with previously treated, advanced HER2-positive (IHC 3+) biliary tract cancer.

Schedule: Administered on a biweekly (14-day) cycle until disease progression or toxicity occurs.

Premedication: Mandatory antipyretic, antihistamine, and corticosteroid 30–60 minutes before every infusion to prevent infusion-related reactions (IRRs).

Infusion Rate: First two doses are infused slowly over 120–150 minutes; subsequent doses can be shortened to 90 or 60 minutes if well tolerated.

Monitoring & Safety: Requires routine assessment for severe diarrhea and decreases in left ventricular ejection fraction (LVEF/LVD).

Dose Modifications: Delays or permanent discontinuation are required if severe toxicities or unmanaged adverse events occur.

XIV. CLINICAL PHARMACOLOGY

The preferred spelling of the word “acknowledgment” in America is without an “e” after the “g”. Avoid the stilted expression, “One of us (R. B. G.) thanks . . .” Instead, try “R. B. G. thanks”. Put applicable sponsor acknowledgments here; DO NOT place them on the first page of your paper or as a footnote.

References

1.FDA Full Prescribing Information (Package Insert): This is the most critical and legally binding reference for initial and adjusted dosing. You can access the official document directly via the FDA Drugs@FDA Database or through the National Library of Medicine DailyMed Service. It provides comprehensive details on reconstitution, multi-step infusion timelines (ranging from 60 to 150 minutes), and adjusted dosing protocols for adverse reactions.

2.The AHFS Drug Information (American Hospital Formulary Service): Published by the American Society of Health-System Pharmacists (ASHP), this book provides deeply vetted, expert-reviewed drug monographs. It features an official AHFS Zanidatamab-hrii Monograph outlining strict therapeutic use, safety profiles, and institutional administration updates.

3.The EMA European Public Assessment Report (EPAR): For practitioners operating within or referencing European guidelines, the European Medicines Agency Ziihera Portal offers full product monographs, official maintenance assessment records, and specific regional handling protocols.

4.The National Comprehensive Cancer Network (NCCN) Guidelines: Though structured as clinical pathways rather than a textbook, the NCCN Guidelines for Hepatobiliary Cancers are considered the gold standard clinical reference book for oncologists. They outline exactly where Zihera fits into systemic therapy lines and include specific notes on managing targeted therapy toxicities.

5.DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology: As a premier reference textbook in oncology, its newer editions or accompanying digital updates detail the pharmacological mechanisms and clinical trial dosing benchmarks for newly approved bispecific antibodies like zanidatamab.