ZIIHERA
TREATMENT GUIDE

ZIIHERA®
(zanidatamab-hrii)
50 mg/ml Injection for IV

Steps for starting and supporting your patients through their treatment journey.

YOUR GUIDE TO:

- DOSING AND ADMINISTRATION
- ADVERSE REACTIONS
- DOSAGE MODIFICATIONS

NCCN RECOMMENDS ZANIDATAMAB-HRII (ZIIHERA)

ZANIDATAMAB-HRII (ZIIHERA) is recommended by the National Comprehensive Cancer Network® (NCCN®) as an NCCN Category 2A option for the subsequent-line systemic treatment of patients with HER2-positive (IHC 3+) unresectable or metastatic BTC upon disease progression[1]

BTC=biliary tract cancer; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry.

INDICATION

ZIIHERA (zanidatamab-hrii) 50 mg/mL for Injection for IV is indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

HELPING PATIENTS START AND STAY ON ZIIHERA

ZIIHERA is a dual HER2-targeted therapy designed for precision. As with targeted therapies, adverse reactions may occur during treatment. **AIM** provides practical strategies to help anticipate and manage these challenges so patients can stay on target and continue therapy when clinically appropriate.[2]

Anticipate:

Recognize that adverse reactions may occur with treatment and prepare proactively

Premedicate all patients with acetaminophen, an antihistamine, and a corticosteroid 30 to 60 minutes prior to each dose[2]

Intervene:

Identify when to take action in response to emerging adverse reactions

Evaluate the severity and progression of adverse reactions to guide treatment modifications

Manage:

Monitor and adjust treatment dosage to mitigate adverse reactions

Modify and resume therapy as appropriate, adjusting dosages or interrupting treatment as recommended

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

ZIIHERA can cause fetal harm when administered to a pregnant woman. 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 during treatment with ZIIHERA and for 4 months following the last dose of ZIIHERA.

Left Ventricular Dysfunction

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

DOSING AND PREPARING ZIIHERA

ZIIHERA® (zanidatamab-hrii) 50 mg/ml Injection for IV

The recommended dosage of ZIIHERA is 20 mg/kg, administered as an IV infusion with a 0.2- or 0.22-micron filter, once every 2 weeks until disease progression or unacceptable toxicity.[2]

Recommended infusion duration: decrease over time to 60 minutes[2]

1st 2nd	120-150 minutes
3rd 4th	90 minutes, if previous infusions were well-tolerated
5th	60 minutes, if previous infusions were well-tolerated

RECONSTITUTION AND DILUTION[2]

Allow vial(s) to reach room temperature. Reconstitute each 300-mg vial with 5.7 mL Sterile Water for Injection to yield a 50 mg/mL solution (6 mL extractable).	Swirl gently until completely dissolved; do not shake.
Inspect the vial; solution should be colorless to light yellow, clear to slightly opalescent, with no visible particles. Use immediately or may be stored: reconstituted solution ≤4 h (18–24°C [64–75°F] or 2–8°C [36–46°F]).	Discard if discoloration or particulate matter is present.
Withdraw required dose; discard unused portion.	Slowly add to infusion bag (0.9% NaCl or 5% Dextrose Injection) for final concentration 0.4–6 mg/mL. Invert gently to mix; do not shake.
Use immediately upon dilution, or may be stored.	If stored: Diluted infusion ≤12 h (18–24°C [64–75°F]) or ≤24 h (2–8°C [36–46°F]).

Administer only as an IV infusion after ZIIHERA is reconstituted and diluted.[2]
See the full Prescribing Information for ZIIHERA to find the complete dosing and administration instructions.

- Do not administer as an IV push or bolus[2]
- Do not co-administer ZIIHERA and other IV drugs through the same IV line[2]

HER2=human epidermal growth factor receptor 2; IV=intravenous; NaCl=sodium chloride.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Left Ventricular Dysfunction (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

THE SAFETY PROFILE WAS ESTABLISHED ACROSS 80 PATIENTS IN HERIZON-BTC-01[2]

ANTICIPATE that adverse reactions may happen with ZIIHERA and proactively prepare[2]

- Remember to premedicate all patients with acetaminophen, an antihistamine, and a corticosteroid 30 to 60 minutes prior to each dose[2]
- Have medications and emergency equipment to treat IRRs available for immediate use[2]

Adverse Reactions (≥15%)	ZIIHERA (N=80)*	
	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders		
Diarrhea†	50	10
Abdominal pain‡	29	1
Nausea	18	1
Vomiting	15	1
Injury, poisoning, and procedural complications		
IRR	35	1
General disorders and administration site conditions		
Fatigue§	24	4
Skin and subcutaneous tissue disorders		
Rash¶	19	0
Metabolism and nutrition disorders		
Decreased appetite	16	0

*Analysis includes 18 patients with HER2 IHC 2+. ARs were graded per CTCAE v5.0.[2]
†Diarrhea includes diarrhea and enteritis.[2]
‡Abdominal pain includes abdominal pain and abdominal pain upper.[2]
§Fatigue includes asthenia and fatigue.[2]
¶Rash includes dermatitis, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, rash, rash maculo-papular, and rash pustular.[2]

Monitor for laboratory abnormalities that worsen from baseline, which may occur with ZIIHERA. Please refer to Table 4 in Section 6.1 of the full Prescribing Information for ZIIHERA to find laboratory abnormalities observed in HERIZON-BTC-01.[2]

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS AND PRECAUTIONS (CONT'D)
Left Ventricular Dysfunction (cont'd)

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is below 50%.

CTCAE DESCRIPTIONS BY AR

Identify when to INTERVENE as adverse reactions emerge or worsen[2,3]

For quick reference, the descriptions below highlight what Grades 3 and 4 can mean for patients across the most common adverse reactions observed with ZIIHERA.

	Grade 3	Grade 4
Diarrhea	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL#	Life-threatening consequences; urgent intervention indicated
Abdominal pain	Severe pain; limiting self-care ADL#	—
Nausea	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	—
Vomiting	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences
IRR	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

A single dash (—) indicates a Grade is not available. Not all Grades are appropriate for all ARs. Therefore, some ARs are listed with fewer than five options for Grade selection.
#Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedbound.[3]
ADL=activities of daily living; AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; IRR=infusion-related reaction; TPN=total parenteral nutrition.

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS AND PRECAUTIONS (CONT'D)
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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

CTCAE DESCRIPTIONS BY AR (CONT'D)[3]

	Grade 3	Grade 4
Fatigue	Fatigue not relieved by rest, limiting self-care ADL*	—
Palmar-plantar erythrodysaesthesia	Severe skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL*	—
Rash maculo-papular	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL*	—
Rash pustular	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	—
Loss of appetite	Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated

A single dash (—) indicates a Grade is not available. Not all Grades are appropriate for all ARs. Therefore, some ARs are listed with fewer than five options for Grade selection.

*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedbound.[3]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Infusion-Related Reactions (cont'd)

Prior to each dose of ZIIHERA, administer premedications to prevent potential IRRs. 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 IRRs.

DOSAGE MODIFICATIONS FOR ARs[2]

ZIIHERA® (zanidatamab-hrii) 50 mg/ml Injection for IV

MANAGE adverse reactions by adjusting dosages and monitoring patients closely[2]

	Severity	Treatment Modification
Left ventricular dysfunction	Absolute decrease of ≥16% points in LVEF from pre-treatment baseline or LVEF ≤50% and absolute decrease of ≥10% points below pre-treatment baseline	• Withhold ZIIHERA for at least 4 weeks • Repeat LVEF assessment within 4 weeks • Resume treatment within 4 to 8 weeks if LVEF returns to normal limits and the absolute decrease is ≤15% points from baseline • Permanently discontinue ZIIHERA if LVEF has not recovered to within 15% points from pre-treatment baseline
	Confirmed symptomatic congestive heart failure	• Permanently discontinue ZIIHERA
Infusion-related reactions	Mild (Grade 1)	• Reduce ZIIHERA infusion rate by 50% • For subsequent ZIIHERA infusions increase infusion rate gradually to the rate prior to the adverse reaction, as tolerated
	Moderate (Grade 2)	• Stop ZIIHERA infusion immediately • Treat with appropriate therapy • Resume ZIIHERA infusion at 50% of previous infusion rate once symptoms resolve • For subsequent ZIIHERA infusions increase infusion rate gradually to the rate prior to the adverse reaction, as tolerated
	Severe (Grade 3)	• Stop ZIIHERA infusion immediately • Promptly treat with appropriate therapy; infusion should not be restarted during the same cycle even if signs and symptoms completely resolve • Subsequent ZIIHERA infusions should be administered at 50% of previous infusion rate • Permanently discontinue ZIIHERA for recurrent Grade 3 reaction
	Life threatening (Grade 4)	• Stop ZIIHERA infusion immediately and permanently discontinue • Promptly treat with appropriate therapy

ADL=activities of daily living; AR=adverse reaction; BSA=body surface area; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; LVEF=left ventricular ejection fraction; TPN=total parenteral nutrition.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Diarrhea

ZIIHERA can cause severe diarrhea.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

DOSAGE MODIFICATIONS FOR ARs (CONT'D)[2]

	Severity	Treatment Modification
Diarrhea	Mild/Moderate (Grades 1/2)	• No dose modification of ZIIHERA is required • Initiate appropriate medical therapy and monitor as clinically indicated
	Severe (Grade 3)	• Withhold ZIIHERA treatment until severity improves to Grade ≤1 • Initiate or intensify appropriate medical therapy and monitor as clinically indicated • Administer subsequent ZIIHERA treatment at the same dose level or consider dose reduction to 15 mg/kg • For recurrent Grade 3 symptoms, withhold ZIIHERA and ensure medical management has been optimized ◦ Resume ZIIHERA treatment at a reduced dose of 15 mg/kg after severity improves to Grade ≤1 ◦ Permanently discontinue ZIIHERA for recurrent Grade 3 symptoms that last >3 days despite optimized medical management
	Life threatening (Grade 4)	• Permanently discontinue ZIIHERA
Pneumonitis	Confirmed Grade ≥2	• Permanently discontinue ZIIHERA
Other adverse reactions (excluding LVD, IRR, diarrhea, and pneumonitis)	Mild/Moderate (Grades 1/2)	• No dosage modification is required for ZIIHERA • Initiate appropriate medical therapy and monitor as clinically indicated
	Severe (Grade 3)	• Withhold ZIIHERA treatment until severity improves to Grade ≤1 • Initiate appropriate medical therapy and monitor as clinically indicated • Administer subsequent ZIIHERA treatment at the same dose; consider dose reduction to 15 mg/kg if Grade 3 symptoms recur
	Life threatening (Grade 4)	• Permanently discontinue ZIIHERA, except as noted below • Initiate appropriate medical therapy and monitor as clinically indicated • ZIIHERA treatment may be resumed at the same dose level for Grade 4 electrolyte imbalances or laboratory abnormalities that are corrected within 3 days of onset; do not resume until symptoms improve to Grade ≤1 • Permanently discontinue ZIIHERA for recurrent Grade 4 electrolyte imbalances or laboratory abnormalities

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Diarrhea (cont'd)

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.

ADVERSE REACTIONS

Serious adverse reactions occurred in 53% of 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA. Serious adverse reactions in >2% of patients included biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%). A fatal adverse reaction of hepatic failure occurred in one patient who received ZIIHERA.

The most common adverse reactions in 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA (≥20%) were diarrhea (50%), infusion-related reaction (35%), abdominal pain (29%), and fatigue (24%).

2.5% of patients who received ZIIHERA permanently discontinued treatment due to an AR. ARs which resulted in permanent discontinuation in ≥1% of patients who received ZIIHERA included decreased ejection fraction and pneumonitis.[2]

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.[2]

AR=adverse reaction; IRR=infusion-related reaction; LVD=left ventricular dysfunction.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS

Pediatric Use

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

Geriatric Use

Of the 80 patients who received ZIIHERA for unresectable or metastatic HER2-positive BTC, 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.

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

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

YOUR GUIDE TO DOSING AND ADMINISTRATION

ZIIHERA®
(zanidatamab-hrii)
50 mg/ml Injection for IV

AIM

Anticipate: Recognize that adverse reactions may occur with treatment and prepare proactively

Intervene: Identify when to take action in response to emerging adverse reactions

Manage: Monitor and adjust treatment dosage to mitigate adverse reactions

Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA to reduce the risk of infusion-related reactions[2]

The recommended dosage of ZIIHERA is 20 mg/kg, administered as an intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity[2]

Refer to the full Prescribing Information for ZIIHERA for complete dosing and administration information.

LEARN MORE ABOUT ZIIHERA ▶

INDICATION

ZIIHERA (zanidatamab-hrii) 50 mg/mL for Injection for IV is indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

References: 1. Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers version 2.2025. © 2025 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed July 2, 2025. To view the most recent and complete version of the guidelines, go online to https://www.nccn.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** ZIIHERA (zanidatamab-hrii) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2025. **3.** U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017. Accessed October 2, 2025. dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf

Jazz Pharmaceuticals