IDENTIFYING PATIENTS WHO MAY BENEFIT FROM HER2-TARGETED TREATMENT IN BTC

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

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

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.

IMPROVED OUTCOMES START WITH TESTING AT DIAGNOSIS[1,2]

Up to 30% of patients with BTC have HER2 overexpression, a key driver of tumor growth[3,4]

BTC is categorized into different subtypes. Prevalence of HER2 overexpression and/or amplification among BTC subtypes include 15-30% for GBC and 5-20% for CCAs.[3] The National Comprehensive Cancer Network® (NCCN®) recommends patients diagnosed with unresectable or metastatic BTC be tested for HER2.[3]

HOW TO TEST FOR HER2 IN BTC[5,6]

	HER2 Overexpression	HER2 Amplification	Required Sample (Tissue/Blood)
IHC	X		Tissue
ISH/FISH		X	Tissue
NGS		X	Tissue/Blood

IHC

Confirms and quantifies HER2 protein overexpression in tissue samples[1,3]

- IHC results are reported using the following scale: 3+ (positive), 2+ (equivocal), or 0/1+ (negative)[1]
- Further testing using ISH/FISH is recommended for 2+ but is not required for 3+[7]

ISH and FISH

Quantify the number of HER2 gene copies and can be used to determine HER2 gene amplification in tissue sample[1,3]

NGS

Detects HER2 amplification. If tissue is not available, cfDNA from a blood sample may be analyzed to determine HER2 amplification[3,6,8]

HER2 testing is your road map for therapy—be sure test results are appropriately documented so they follow patients throughout their treatment journey

BTC=biliary tract cancer; CCA=cholangiocarcinoma; cfDNA=cell-free DNA; FISH=fluorescence *in situ* hybridization; GBC=gallbladder cancer; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; NGS=next-generation sequencing.

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.

IMPORTANCE OF TESTING FOR HER2 IN BTC AT INITIAL DIAGNOSIS

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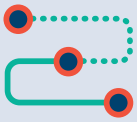
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for HER2 (*ERBB2*) overexpression and/or amplification in patients with unresectable or metastatic BTC to determine if they could benefit from targeted treatment.[3]

WHY TEST FOR HER2 AS PART OF YOUR INITIAL BTC WORKUP[2,8]

Identifies biomarker status early in treatment journey



Informs treatment sequencing for targeted approaches

Minimizes treatment delay

If your patients' test results are HER2-positive, it is time for a targeted approach

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IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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.

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.

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

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. 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.

Diarrhea

ZIIHERA can cause severe diarrhea.

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.

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IDENTIFYING HER2 POSITIVITY AT DIAGNOSIS IS CRUCIAL FOR PATIENTS WITH BTC[1–3]

Test for HER2 to identify patients who may benefit from a dual HER2-targeted bispecific antibody.

Scan to explore ZIIHERA

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

IMPORTANT SAFETY INFORMATION (CONT'D)

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%).

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.

References: 1. Rüschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol.* 2012;25(5):637-650. doi:10.1038/modpathol.2011.198 **2.** Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. *J Clin Oncol.* 2017;35(13):1453-1486. doi:10.1200/JCO.2016.71.9807 **3.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers Version 4.2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 12, 2024. To view the most recent and complete version of the guidelines, go online to https://www.nccn.org **4.** Yu S, Liu Q, Han X, et al. Development and clinical application of anti-HER2 monoclonal and bispecific antibodies for cancer treatment. *Exp Hematol Oncol.* 2017;6:31. doi:10.1186/s40164-017-0091-4 **5.** Furrer D, Sanschagrin F, Jacob S, Diorio C. Advantages and disadvantages of technologies for HER2 testing in breast cancer specimens. *Am J Clin Pathol.* 2015;144(5):686-703. doi:10.1309/AJCPT41TCBUEVDQC **6.** Stenzinger A, Vogel A, Lehmann U, et al. Molecular profiling in cholangiocarcinoma: a practical guide to next-generation sequencing. *Cancer Treat Rev.* 2024;122:102649. doi:10.1016/j.ctrv.2023.102649 **7.** Bartley AN, Washington MK, Ventura CB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med.* 2016;140(12):1345-1363. doi:10.5858/arpa.2016-0331-CP **8.** Fox AH, Nishino M, Osarogiagbon RU, et al. Acquiring tissue for advanced lung cancer diagnosis and comprehensive biomarker testing: a National Lung Cancer roundtable best-practice guide. *CA Cancer J Clin.* 2023;73(4):358-375. doi:10.3322/caac.21774

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