

# **Ziihera® (zanidatamab-hrii)**

## **Category:**

Best Product for Orphan/Rare Diseases

## **Company Name:**

Jazz Pharmaceuticals

## **Product/Solution Name:**

Ziihera® (zanidatamab-hrii)

## **Compound/Tech Name:**

zanidatamab-hrii

## **Trade Name:**

Ziihera®

## **Corporate Name:**

N/A

## **Date of Approval:**

2024-11-20

## **Indications:**

Ziihera 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. People with metastatic HER2-positive (IHC 3+) BTC received Ziihera by IV once every 2 weeks.

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## **Therapeutic Areas:**

Biliary Tract Cancer

## **General Information File Document upload:**

N/A

## **Background information and need for drug / device:**

Biliary tract cancers (BTC) are rare, aggressive cancers with limited effective treatment options. Symptoms typically don't present until the cancer has blocked the bile duct, causing various symptoms that eventually point to a life-shattering BTC diagnosis, often at an advanced stage, with median overall survival upon diagnosis of only one year and a five-year survival rate under 5% in the metastatic setting. For patients with HER2-positive BTC-where HER2, a protein, is overexpressed-cancer cells grow faster, resulting in an even poorer prognosis.

BTC accounts for <1% of adult cancers worldwide-with incidence and mortality rates rising. For these individuals, they're not only challenged with a difficult-to-treat disease, they lack the visibility, advocacy and support other cancers receive. In their isolation, they can only hope for science to help extend or save their lives.

"My doctor telling me I had bile duct cancer and that 'this is not good' was devastating," recalls Mark, a patient with advanced BTC. "I wept as I thought, 'you've got to be kidding me.' I had so many thoughts. Why me? Why now? What was I going to do?"

Jazz Pharmaceuticals is a pioneer of new pathways in oncology development and dedicates its oncology resources to cancers with high unmet needs and unique challenges-cancers where people face difficult odds, with few treatment options and limited survival. Rising from that commitment is an important new breakthrough in HER2+ BTC-Ziihera® (zanidatamab-hrii), a dual HER2-targeted bispecific antibody treatment.

In 2024, Ziihera became the first and only dual HER2-targeted bispecific antibody approved for HER2+ BTC in the U.S. Ziihera is a beacon of hope, providing a chemotherapy-free option that mobilizes the patient's immune system to fight the cancer. This innovative therapy marks a paradigm shift in the treatment landscape for patients with HER2+ BTC.

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## **Background File Document upload:**

N/A

## **History of the development of the solution/product:**

Ziihera's journey to approval is a testament to unwavering commitment to patients with rare cancers. Ziihera's path to approval began with Zymeworks, which first created the molecule, and was then advanced through clinical development via strategic partnerships between Jazz Pharmaceuticals and BeOne Medicines (formerly BeiGene).

Ziihera's unique bispecific mechanism of action means that it simultaneously binds to two distinct extracellular domains of HER2, leading to receptor internalization, reduced surface expression and potent anti-tumor activity. Ziihera induces immune-mediated cytotoxicity-and is the only approved bispecific antibody to induce complement-dependent cytotoxicity-further enhancing its ability to inhibit tumor growth and induce cell death.

The pivotal HERIZON-BTC-01 trial, the largest Phase 2b study to date in this patient population, evaluated zanidatamab as a single agent in previously treated HER2-positive BTC. Results demonstrated an unprecedented 52% objective response rate and a median duration of response of 14.9 months, as determined by independent central review. Ziihera also demonstrated median progression-free survival and overall survival of 5.5 months and 15.5 months, respectively, in patients with HER2+ BTC.

The trial's success across its primary and secondary endpoints provided the foundation for accelerated approval. These results were presented at the 2023 American Society of Clinical Oncology Annual Meeting 2023, published in The Lancet Oncology, and recognized in the 2023 Best of ASCO® program.

Ziihera received accelerated FDA approval in November 2024, becoming the first and only dual HER2-targeted bispecific antibody treatment for patients with BTC. In response, Stacie Lindsey, CEO of the Cholangiocarcinoma Foundation stated, \"Metastatic biliary tract cancer, BTC, places a significant burden on patients, affecting their quality of life and emotional and mental well-being ... The approval of Ziihera ... provides patients and their loved ones the possibility of more time together and an improved quality of life, which is invaluable for the entire BTC community.\"

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## **Development File Document upload:**

N/A

## **Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:**

Ziihera represents a paradigm shift in HER2-targeted therapy, demonstrating its potential to become the new HER2 backbone-offering patients the promise of

enhancing HER2 targeting with a single agent while potentially improving upon trastuzumab-based combination approaches to address more aggressive GI cancers.

\\"What excites me about the development of new therapies for patients with HER2+ cancers is the opportunity to redefine the level of care,\" says Stefan Faderl, MD, Vice President, Oncology Development, Jazz Pharmaceuticals. \\"We're dealing with targeted therapy that's very much tailored to the specifics of the cancer cells.\"

HER2 plays an important role in cell growth and survival, and many cancers, including BTC, can overexpress this protein. Around 25% of BTC tumors express HER2, with variation by BTC subtype. Ziihera is a humanized, biparatopic, IgG1-like bispecific antibody that targets two distinct HER2 epitopes and promotes receptor crosslinking that leads to potent complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. Ziihera's mechanism of action differs from those of many current HER2-targeted therapies in that it can bind to two adjacent HER2 proteins simultaneously. Owing to this, neighboring HER2 proteins on the cancer cell are cross-linked, which may help decrease cancer growth signaling, while mediating the direct killing of tumor cells.

Jazz Pharmaceuticals is committed to exploring Ziihera's potential in other HER2-expressing solid tumors and is evaluating its potential in gastroesophageal adenocarcinomas and metastatic breast cancer. Additionally, the Phase 2 DiscovHER-Pan-206 pan-tumor trial is exploring Ziihera monotherapy in rarer HER2+ solid tumors, excluding breast cancer, gastroesophageal adenocarcinomas and BTC, in HER2-treatment-naïve patients.

Ziihera is a shining example of a novel medicine that can transform care, offering a potential foundation for HER-2 targeted therapy. Ziihera is not just a drug; it's a testament to the power of innovation to improve the human condition.

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### **Innovation File Document upload:**

N/A

### **Please provide appropriate references (PubMed, Abstract, Website):**

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