Jazz Pharmaceuticals Reports Clinically Meaningful Long-Term Median Overall Survival Data for Ziihera® (zanidatamab-hrii) in First-Line HER2-Positive Metastatic Gastroesophageal Adenocarcinoma at ASCO 2025

June 02, 2025

Phase 2 trial results continue to show clinically meaningful efficacy and durable responses, including 36.5-month median overall survival after four years of follow-up, with a manageable safety profile

Findings presented today at ASCO 2025 and concurrently published in The Lancet Oncology

For U.S. media and investors only

DUBLIN, June 2, 2025 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced long-term data, including the first report of median overall survival (OS) from the Phase 2 trial evaluating Ziihera® (zanidatamab-hrii), a dual HER2-targeted bispecific antibody, in combination with chemotherapy for the investigational use in first-line HER2-positive (IHC 3+ or IHC 2+/FISH+) locally advanced nonresectable gastroesophageal adenocarcinoma (mGEA). The data were featured as a rapid oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, and the results were concurrently published in The Lancet Oncology.

Among 41 patients with centrally confirmed HER2-positive tumors, treatment with *Ziihera* in combination with physician's choice of chemotherapy resulted in a median progression-free survival (PFS) of 15.2 months [95% CI: 9.5, 33.4], and a median overall survival (OS) of 36.5 months [95% CI: 23.6, not estimable (NE)]. Median PFS remained stable with the additional four-year follow-up, consistent with previously reported results.

Among all 46 patients in the study with HER2-expressing mGEA, median PFS was 12.5 months [95% CI: 8.2, 21.8], and median OS also reached 36.5 months [95% CI: 23.6, NE], with the longest observed survival at 57.9 months (censored at data cutoff). Long-term follow-up also demonstrated low discontinuation rates, with no new safety signals observed.

"Gastroesophageal adenocarcinoma remains a highly aggressive cancer with a poor prognosis, even with currently available treatment options," said Dr. Elena Elimova, lead trial investigator and a medical oncologist at Princess Margaret Cancer Centre, Toronto, Canada. "The long-term survival outcomes presented today at ASCO demonstrate the sustained antitumor activity achieved with zanidatamab plus chemotherapy over four years of follow-up. These results are especially encouraging given the high unmet need for better first-line treatment options for this patient population."

"These long-term survival data from our Phase 2 trial build on previously reported results and further strengthen our belief in *Ziihera* as a transformative treatment option for patients with HER2-positive disease," said Rob Iannone, M.D., M.S.C.E., executive vice president, global head of research and development, and chief medical officer of Jazz Pharmaceuticals. "An estimated median overall survival of 36.5 months in this patient cohort is very encouraging given recent observations with standard of care regimens in similar populations, where median survival has typically ranged from 15 to 20 months. The sustained 15.2-month progression-free survival in the centrally confirmed HER2-positive subgroup after four years is a meaningful indicator of durable clinical benefit. We look forward to the top line results of the pivotal Phase 3 HERIZON-GEA-01 trial later this year and remain committed to advancing *Ziihera* across multiple tumor types."

Phase 2 mGEA Trial Results

The data include four-year follow-up and the first report of median OS from an ongoing, open-label Phase 2 trial (NCT03929666) evaluating *Ziihera* in combination with chemotherapy as a first-line treatment for patients with HER2-expressing mGEA, which includes gastric, esophageal and gastroesophageal junction (GEJ) adenocarcinomas. Patients had not received prior HER2-targeted agents nor systemic treatment for mGEA. A total of 46 patients with HER2-expressing mGEA (41 patients with centrally confirmed HER2-positive mGEA) were enrolled from 14 sites across the United States, Canada and South Korea. Patients received *Ziihera* with physician's choice of chemotherapy, including fluoropyrimidine maintenance regimens. Chemotherapy-based regimens remain the current standard first-line treatment for mGEA.

The longer-term data (median duration of follow-up of 48 months [range, 29-59]) demonstrate the promising antitumor activity of *Ziihera* combined with chemotherapy as a first-line treatment for HER2-positive mGEA. In a post-hoc subgroup analysis of the 41 treated patients with centrally confirmed HER2-positive tumors, median PFS was 15.2 months [95% CI: 9.5, 33.4], and median OS was 36.5 months [95% CI: 23.6, NE]. These survival outcomes were consistent with prior analyses, with PFS durability maintained at the four-year follow-up. The confirmed objective response rate (cORR), the study's primary endpoint, was 83.8% [95% CI: 68.0, 93.8], and median duration of response (DOR) was 20.4 months [95% CI: 8.3, 44.1]. These results further support the observed clinical benefit in this centrally confirmed population.

Among all 46 patients in the study, median PFS was 12.5 months [95% CI: 8.2, 21.8], and the estimated 24-month PFS rate was 31% [95% CI: 17%, 46%]. Median OS was also 36.5 months [95% CI: 23.6, NE], with an estimated 24-month OS rate of 65% [95% CI: 49%, 77%]. The cORR was 76.2% [95% CI: 60.5, 87.9], and median DOR was 18.7 months [95% CI: 10.4, 44.1].

With additional follow-up, the safety and tolerability profile of *Ziihera* plus chemotherapy showed low discontinuation rates, with no new safety signals identified. Diarrhea (39%) and hypokalemia (22%) were the most common Grade 3-4 treatment-related adverse events (TRAEs); the incidence of Grade 3 diarrhea was reduced from 52% to 24% for patients enrolled after the implementation of mandated antidiarrheal prophylaxis. There were no treatment-related deaths. Five patients discontinued *Ziihera* due to TRAEs.

Ongoing Phase 3 Trial

The Phase 3 randomized clinical trial, HERIZON-GEA-01 (NCT05152147), evaluating *Ziihera* in combination with standard of care chemotherapy with and without the addition of a PD-1 agent as a first-line treatment for HER2-expressing mGEA is currently underway. This is an events-based trial, and

top-line results are expected to read out in the second half of 2025.

About Gastroesophageal Adenocarcinoma
Gastroesophageal adenocarcinoma (GEA) is the fifth most common cancer worldwide, and approximately 20% of patients have HER2-positive disease.[i,ii,iii] HER2-positive GEA has high morbidity and mortality, and patients are urgently in need of new treatment options. The overall prognosis for patients with GEA remains poor, with a global five-year survival rate of less than 30 percent for gastric cancer and about 19 percent for GEA.[iv]

About Ziihera® (zanidatamab-hrii)
Ziihera (zanidatamab-hrii) is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Binding of zanidatamab-hrii with HER2 results in internalization leading to a reduction in HER2 expression of the receptor on the tumor cell surface. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo.[v] In the United States, *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.[v] The U.S. Food and Drug Administration (FDA) granted accelerated approval for this indication 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). [v]

Zanidatamab is being developed in multiple clinical trials as a targeted treatment option for patients with solid tumors that express HER2. Zanidatamab is being developed by Jazz and BeiGene, Ltd. (BeiGene) under license agreements from Zymeworks, which first developed the molecule.

The FDA granted Breakthrough Therapy designation for zanidatamab development in patients with previously treated HER2 gene-amplified BTC, and two Fast Track designations for zanidatamab: one as a single agent for refractory BTC and one in combination with standard-of-care chemotherapy for 1L gastroesophageal adenocarcinoma (GEA). Additionally, zanidatamab has received Orphan Drug designations from FDA for the treatment of BTC and GEA, as well as Orphan Drug designation from the European Medicines Agency for the treatment of BTC and gastric cancer.

Important Safety Information for ZIIHERA

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

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.

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.

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.

The full U.S. Prescribing Information for ZIIHERA, including BOXED Warning, is available at: https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf

About Jazz Pharmaceuticals
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharma company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing potentially life-changing medicines for people with serious diseases — often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience. Jazz is headquartered in Dublin, Ireland with research and development laboratories, manufacturing facilities and employees in multiple countries committed to serving patients worldwide. Please visit www.jazzpharmaceuticals.com for more information.

Jazz Pharmaceuticals plc Caution Concerning Forward-Looking Statements
This press release contains forward-looking statements, including, but not limited to, statements related to zanidatamab's potential as a transformative treatment option for patients with HER2-positive disease, expected timing of top-line results of the pivotal Phase 3 HERIZON-GEA-01 and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with the successful completion of regulatory activities and uncertain regulatory approval, risks related to failure or delays in successfully initiating or completing clinical trials and assessing patients and other risks and uncertainties affecting Jazz Pharmaceuticals and its development programs, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals plc's Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Annual Report on Form 10-K for the year ended December 31, 2024, as supplement by Jazz Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

Contacts:

Media Contact:
Kristin Bhavnani
Head of Global Corporate Communications
Jazz Pharmaceuticals plc
CorporateAffairsMediaInfo@jazzpharma.com
Ireland +353 1 637 2141
U.S. +1 215 867 4948

Investors:

Jeff Macdonald
Executive Director, Investor Relations
Jazz Pharmaceuticals plc
investorinfo@jazzpharma.com
Ireland +353 1 634 3211
U.S. +1 650 496 2717

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