Jazz Pharmaceuticals Presents Overall Survival and Longer Follow-Up Data from HERIZON-BTC-01 Trial Evaluating Zanidatamab in Previously Treated HER2-Positive Biliary Tract Cancer at ASCO 2024

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Zanidatamab demonstrated a median overall survival (OS) of 15.5 months in patients with centrally confirmed immunohistochemistry (IHC) 2+ or 3+ and a median OS of 18.1 months in patients with IHC 3+ tumors

With approximately two years of median follow-up, as of July 28, 2023, median duration of response (DOR) increased by two months from initial analysis to 14.9 months

DUBLIN, June 1, 2024 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced long-term follow-up results, including the first-ever overall survival (OS) findings, from the Phase 2b HERIZON-BTC-01 clinical trial of zanidatamab in previously treated, unresectable, locally advanced, or metastatic HER2-positive biliary tract cancer (BTC). These data will be featured at the American Society of Clinical Oncology (ASCO) Annual Meeting in a poster presentation during the Gastrointestinal Cancer – Gastroesophageal, Pancreatic, and Hepatobiliary session on June 1, 2024, at 1:30-4:30 p.m. CDT. Zanidatamab is a human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody being studied in multiple solid tumors.

For the trial's primary endpoint, results demonstrated that a confirmed objective response rate (cORR) by independent central review (ICR) was maintained at 41.3% (95% confidence interval (CI): 30.4, 52.8) and one additional patient achieved a complete response (n=2; 2.5%) since initial findings were presented at the ASCO Annual Meeting in 2023. The median duration of response (DoR), one of the trial's key secondary endpoints, increased by approximately 2 months to 14.9 months (95% CI: 7.4, not reached), compared to the previously reported findings. In this data cut, zanidatamab demonstrated a median estimated OS, another secondary endpoint, of 15.5 months (95% CI: 10.4, 18.5) in all patients with HER2+ BTC, 18.1 months (95% CI:12.2, 23.2) in patients with IHC 3+ tumors, and 5.2 months (95% CI: 3.1, 10.2) in patients with IHC 2+ tumors. Results highlight the clinically meaningful benefits of sustained and durable responses with continued treatment with zanidatamab.

"Patients with BTC are typically diagnosed when their disease is at an advanced stage, which is associated with a poor prognosis," said Shubham Pant, M.D., M.B.B.S. professor in the Department of Gastrointestinal Medical Oncology and Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. "Historically, overall survival with standard-of-care chemotherapy in second-line patients with advanced BTC is reported to be between 6-9 months[1] so there is a significant unmet need for targeted therapies that can potentially improve survival. The deep and durable responses seen in this study signal the potential to fill a critical unmet patient need with zanidatamab, a chemotherapy-free option, among patients with HER2-expressing cancers."

"We are encouraged by the updated results from the pivotal HERIZON-BTC-01 trial demonstrating sustained clinical activity in previously treated patients with advanced HER2-positive BTC. Results from HERIZON-BTC-01 were included in the Biologics License Application (BLA) for zanidatamab, which was granted Priority Review by the FDA earlier this week, as well as in the Marketing Authorization Application for zanidatamab which was recently submitted to the European Medicines Agency," said Rob Iannone, M.D., M.S.C.E., executive vice president, global head of research and development of Jazz Pharmaceuticals. "Clinical development of zanidatamab for the treatment of advanced HER2-positive BTC continues with HERIZON-BTC-302 (NCT06282575), the ongoing, global, randomized Phase 3 trial of zanidatamab in combination with standard-of-care therapy in the first-line setting for patients with HER2-positive BTC. We also look forward to investigating zanidatamab's potential in other HER2-expressing solid tumors, including in cases resistant to prior HER2-targeted therapies."

Trial Results

Results from this long-term analysis of the Phase 2b HERIZON-BTC-01 trial (NCT04466891) indicate that zanidatamab monotherapy demonstrated sustained and durable antitumor responses in previously treated patients with HER2-positive unresectable, locally advanced, or metastatic BTC and support the clinically meaningful benefit of continued treatment with zanidatamab. The safety profile in all enrolled patients remained manageable with favorable tolerability compared with the initial analysis. Two (2.3%) patients discontinued treatment due to treatment-related adverse events (TRAEs).

The trial evaluated zanidatamab (20 mg/kg IV once every 2 weeks) in patients with HER2-positive, locally advanced unresectable, or metastatic BTC who had received prior gemcitabine-containing therapy. Patients with prior HER2-targeted therapy use were excluded from the trial. All patients were required to have centrally confirmed HER2-amplified tumors (assessed by *in situ* hybridization). Patients (n=87) were assigned into two cohorts based on tumor IHC status: Cohort 1 (n=80) included patients who were IHC 2+/3+ (HER2-positive) and Cohort 2 (n=7) included patients who were IHC 0/1+. The median duration of follow-up was 21.9 (16-34) months. Tumors were assessed every 8 weeks per RECIST v1.1. Updated efficacy analyses include only Cohort 1, while safety analyses include Cohorts 1 and 2.

As of July 28, 2023, data from HER2-positive BTC patients enrolled in Cohort 1 (n=80) demonstrated:

- With longer follow-up, the cORR was maintained from the initial analysis (n=33; 41.3%) (95% CI: 30.4, 52.8), with one additional complete response (n=2; 2.5%).
    - Although the trial was not designed to detect treatment effects by HER2 status, as previously reported, in a pre-planned subgroup analysis of cORR by HER2 expression, responses were observed in patients with IHC 3+ tumors (cORR: 51.6% [95% CI: 38.6%-64.5%]) and IHC 2+ tumors (cORR: 5.6% [95% CI: 0.1-27.3%])[2].
- A two-month increase in the median DoR to 14.9 months (95% CI: 7.4, not reached).
    - In patients with IHC3+ tumors, the median DoR was 14.9 months (95% CI: 7.4, not reached).
    - The DOR in the 1 responder with IHC 2+ tumors was 7.5 months.

- A median OS (95% CI) of 15.5 months (95% CI: 10.4, 18.5).
    - The median OS in patients with IHC 3+ was 18.1 months (95% CI: 12.2, 23.2).
    - The median OS in patients with IHC 2+ was 5.2 months (95% CI: 3.1, 10.2).
- Median progression-free survival (PFS) was maintained (5.5 months [95% CI: 3.6, 7.3]) compared with the initial analysis, which had a data cutoff of October 10, 2022.
    - In patients with IHC 3+ tumors, the median PFS was 7.2 months (95% CI: 5.4, 9.4) months.
    - In patients with IHC 2+ tumors, the median PFS was 1.7 months (95% CI: 1.0, 3.3) months.

As previously reported for Cohorts 1 and 2, zanidatamab demonstrated a manageable and tolerable safety profile, with no new safety signals identified and no deaths that were treatment related. TRAEs leading to dose reductions remained infrequent. Serious TRAEs occurred in eight (9.2%) patients. One patient experienced serious TRAEs since the initial analysis (alanine aminotransferase increased and aspartate aminotransferase increased).Treatment discontinuation rate was 2.3% and no additional patients discontinued treatment due to TRAEs since the initial analysis.

About BTC
BTC, including gallbladder cancer and intrahepatic and extrahepatic cholangiocarcinoma, account for <1% of all adult cancers globally and are often associated with a poor prognosis.[3,4] The human epidermal growth factor receptor 2 (HER2) is a well-validated target for antitumor therapy in other cancers. Across the U.S., Europe, and Japan, approximately 12,000 people are diagnosed with HER2+ BTC annually.[5,6,7,8]

About Zanidatamab
Zanidatamab is an investigational HER2-targeted bispecific antibody that can simultaneously bind two non-overlapping epitopes of the HER2 receptor, known as biparatopic binding. This unique design and increased binding results in multiple mechanisms of action, including dual HER2 signal blockade, removal of HER2 protein from the cell surface, and immune-mediated cytotoxicity leading to encouraging antitumor activity in patients. 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 U.S. Food and Drug Administration (FDA) has accepted and granted Priority Review of the Biologics License Application (BLA) for zanidatamab with a Prescription Drug User Fee Act (PDUFA) action date of November 29, 2024. Zanidatamab was also granted Breakthrough Therapy designation in patients with previously treated HER2 gene-amplified biliary tract cancers (BTC) and given two Fast Track designations: 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. Zanidatamab was also granted Breakthrough Therapy designation from the Center for Drug Evaluation (CDE) in China.

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 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 to fill a persistent and much-needed treatment gap, growing our portfolio of innovative oncology products and investigational therapies, advancing our broader clinical development program for zanidatamab 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 pharmaceutical product development, 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, 2023, as supplemented by our Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, 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.

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[3] Valle JW, et al. Lancet 2021; 397:428-44

[4] Siegel RL, et al. CA Cancer J Clin 2022; 72;7-33

[5] BTC overall diagnosed patients as per SEER 22;

[6] Assumes anatomic subsites intrahepatic CCA, extrahepatic CCA, gallbladder cancer, and BTC unspecified;

[7] Assumes HER2 positivity rates per anatomical subsite from: Galdy, S., Lamarca, A., McNamara, M.G. et al. Cancer Metastasis Rev 36, 141–157 (2017), Nobuyoshi Hiraoka, et al. Human Pathology, Volume 105, 2020, Pages 9-19

[8] Major markets: U.K, France, Germany, Spain, Italy. Note: HER2+ BTC patients in Jazz-controlled commercial territories, which includes Japan, and excludes other certain Asia Pacific countries licensed to BeiGene, Ltd

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