TAIHO ONCOLOGY

Taiho Oncology Announces Publication in *The New England Journal of Medicine* of Pivotal Data for Futibatinib in Previously Treated Patients With Metastatic Intrahepatic Cholangiocarcinoma

- *Treatment with futibatinib resulted in durable responses and survival surpassing historical data with chemotherapy in patients with previously treated disease.*
- *Patients in the study reported stable quality of life over nine months of treatment.*
- *Data supported U.S. Food and Drug Administration accelerated approval of LYTGOBI® (futibatinib) tablets in September 2022; continued approval may be contingent upon a confirmatory trial(s).*

PRINCETON, N.J., January 18, 2023 – Taiho Oncology, Inc. today announced the publication of results from the pivotal Phase 2 FOENIX*-CCA2 clinical trial of futibatinib in the January 19, 2023 issue of *The New England Journal of Medicine* (NEJM). The article, "Futibatinib for Intrahepatic Cholangiocarcinoma with FGFR2 Fusions/Rearrangements," reports on data from the FOENIX-CCA2 trial, a global open-label study evaluating patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.

These data supported the U.S. Food and Drug Administration (FDA) accelerated approval of futibatinib tablets – brand name LYTGOBI® – in September 2022 for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic iCCA harboring FGFR2 gene fusions or other rearrangements. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

In the FOENIX-CCA2 trial, futibatinib showed clinically meaningful benefit in previously treated patients with FGFR2 fusion/rearrangement-positive iCCA, including an objective response rate of 42%, as assessed by independent review, and a median response duration of 9.7 months. Treatment with futibatinib resulted in durable responses and survival that surpassed historical data with chemotherapy in patients with previously treated iCCA. According to the investigators, these data suggest that a molecularly-targeted agent like futibatinib can substantially improve outcomes for patients with iCCA harboring FGFR2 fusions/rearrangements.

"The FOENIX-CCA2 trial results demonstrate that futibatinib is an effective treatment for FGFR2 fusion/rearrangement positive cholangiocarcinoma. Its activity and safety profile offer a new treatment in this setting. These data reinforce the importance of molecular profiling in cholangiocarcinoma and represent a step forward for patients facing a difficult disease," said Lipika Goyal, MD, MPhil, the lead investigator for FOENIX-CCA2 and previously a medical oncologist at Mass General Cancer Center and now Associate Professor and Director of Gastrointestinal Cancer at the Stanford School of Medicine.

Cholangiocarcinoma is an aggressive cancer of the bile ducts and is diagnosed in approximately 8,000 individuals each year in the U.S.[2] This includes both intrahepatic (inside the liver) and extrahepatic (outside the liver) forms of the disease. Approximately 10-16% of patients with iCCA have FGFR2 gene rearrangements, including fusions, which promote tumor proliferation.[3,4,5,6,7] Historically, patients with iCCA have a five-year overall survival rate of less than 8% with a median overall survival of approximately one year in advanced stages,[8,9] underscoring the unmet need for additional second-line therapies. Futibatinib is an oral, potent, selective small-molecule inhibitor of FGFR1, 2, 3 and 4.[1] It covalently binds to FGFR and inhibits the signaling pathway,[1] a unique mode of binding compared to the other currently approved FGFR inhibitors, which are reversible ATP-competitive inhibitors.[10,11,12]

Key Findings From the FOENIX-CCA2 Trial

Among the 103 patients enrolled in the study, futibatinib showed a confirmed objective response rate of 42% (95% confidence interval [CI], 32%-52%), according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, as the primary endpoint of the study. Patients responding to futibatinib had a median duration of response, a key secondary endpoint, of 9.7 months (95% CI, 7.6-17.0). The disease control rate was up to 83% (95% CI, 74%-89%).

At data cutoff for the primary analysis on October 1, 2020, median follow-up was 17.1 months (range, 10.1-29.6) and median treatment duration was 9.1 months. Objective responses were observed across all protocol-specified subgroups, including in patients aged at least 65 years and those with one, two or three or more prior treatment lines. Median progression-free survival was 9.0 months (95% CI, 6.9-13.1) and median overall survival was 21.7 months (95% CI, 14.5 to not reached). Similar response and survival data were documented at extended follow-up, 8.0 months after the primary analysis.

Patient-reported outcomes were evaluated as a prespecified secondary objective and results showed stable quality of life over 9.0 months for trial participants. Throughout the observed time period, there were no meaningful changes from baseline across the observed study period in any of the EORTC-QLQ-c30 quality of life (QoL) scales, including physical, role, cognitive, emotional or social domains. In addition, the EQ-5D Visual Analog Scale did not reveal any significant changes in perceived health status across the observed study period.

All patients experienced at least one adverse event of any cause. The most common (≥25%) treatment-related adverse reactions were hyperphosphatemia (85%), alopecia (33%), dry mouth (30%), diarrhea (28%), dry skin (27%) and fatigue (25%). Treatment-related adverse events led to treatment discontinuation in 2% of patients, and no new safety concerns were reported with extended follow-up. No treatment-related deaths occurred.

Genomic Profiling Analysis to Identify FGFR2 Rearrangements

The tumor molecular-profile analysis indicated that responses did not correlate with FGFR2 fusion-partner status or co-occurring alterations in tumor suppressor or

oncogenes. Response rates were 42% and 45% in patients with BICC1- and non-BICC1 fusions, respectively, and ORR ranged from 35% to 49% in patients with or without BAP1, TP53, CDKN2A or CDKN2B co-alterations. Of note, response rates and PFS were similar in patients with and without TP53 co-alterations.

As FGFR2 fusions and other rearrangements are an important actionable alteration in cholangiocarcinoma, utilizing a practical, high-performance method for identifying this therapeutic target will contribute to improved care of patients with this disease. Accurate tumor profiling to identify individuals with FGFR2 gene rearrangements can be challenging if tissue from tumor biopsy is limited. In addition, the failure rate of tissue biopsy profiling in metastatic CCA is as high as 26.8%.[13]

Circulating tumor DNA (ctDNA) profiling offers a non-invasive alternative for patients with no tumor tissue available or failed attempts at tissue profiling. Although the FGFR2 fusion/rearrangement detection rate from blood samples by ctDNA assays has historically been low with some platforms,[14] the fusion partner-agnostic ctDNA platform utilized in the correlative analyses in the FOENIX-CCA2 trial identified FGFR2 fusions or rearrangements in 87% of patients evaluated.[15]

Impact on Treatment Guidelines for Biliary Tract Cancers
In October 2022, futibatinib was included in the latest National Comprehensive Cancer Network® Clinical Practice Guidelines (NCCN Guidelines®) in Oncology for Hepatobiliary Cancers as a subsequent-line therapy for biliary tract cancers if disease progression occurs. Futibatinib is listed as Category 2A, useful in certain circumstances for CCA with FGFR2 fusions or rearrangements. In addition, the latest European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up of biliary tract cancer include that, where available, FGFR inhibitors, including futibatinib, are recommended for the treatment of patients with FGFR2 fusions whose disease has progressed after ≥1 prior line of systemic therapy.

Futibatinib was discovered by Taiho Oncology's parent company, Taiho Pharmaceutical Co., Ltd., which continues to co-develop this product for other potential tumor types.

About LYTGOBI

INDICATION AND USAGE
LYTGOBI is indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.

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).

TAIHO ONCOLOGY

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Ocular Toxicity:** Retinal Pigment Epithelial Detachment (RPED), which may cause symptoms such as blurred vision, occurred in 9% of 318 patients who received LYTGOBI across clinical trials. The median time to first onset of RPED was 40 days. Perform a comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of LYTGOBI. Withhold or reduce the dose of LYTGOBI as recommended. Dry Eye/Corneal Keratitis: Among 318 patients who received LYTGOBI across clinical trials, dry eye occurred in 15% of patients. Treat patients with ocular demulcents as needed.
- **Hyperphosphatemia and Soft Tissue Mineralization:** Hyperphosphatemia, which can cause soft tissue mineralization, calcinosis, nonuremic calciphylaxis, and vascular calcification was reported in 88% of 318 patients treated with LYTGOBI across clinical trials with a median time of onset of 5 days (range 3-117). Phosphate binders were received by 77% of patients who received LYTGOBI. Monitor for hyperphosphatemia throughout treatment. Initiate a low-phosphate diet and phosphate-lowering therapy when serum phosphate level is ≥5.5 mg/dL; initiate or intensify phosphate-lowering therapy when >7 mg/dL; reduce dose, withhold, or permanently discontinue LYTGOBI based on duration and severity of hyperphosphatemia.
- **Embryo-fetal Toxicity:** LYTGOBI can cause fetal harm. Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential, and males with female partners of reproductive potential, to use effective contraception during treatment with LYTGOBI and for 1 week after the last dose.

ADVERSE REACTIONS

- **Serious adverse reactions** occurred in 39% of patients receiving LYTGOBI, and in ≥2% of patients included pyrexia, gastrointestinal hemorrhage, ascites, musculoskeletal pain, and bile duct obstruction.
- **The most common adverse reactions** (≥20%) were nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia syndrome, and vomiting.
- **The most common laboratory abnormalities** (≥20%) were increased phosphate, increased creatinine, decreased hemoglobin, increased glucose, increased calcium, decreased sodium, decreased phosphate, increased alanine aminotransferase, increased alkaline phosphatase, decreased lymphocytes, increased aspartate aminotransferase, decreased platelets, increased activated partial thromboplastin time, decreased leukocytes, decreased albumin, decreased neutrophils, increased creatine kinase, increased bilirubin, decreased

glucose, increased prothrombin international normalized ratio, and decreased potassium.

DRUG INTERACTIONS

- **Dual P-gp and Strong CYP3A Inhibitors:** Avoid concomitant use of drugs that are dual P-gp and strong CYP3A inhibitors.
- **Dual P-gp and Strong CYP3A Inducers:** Avoid concomitant use of drugs that are dual P-gp and strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Because of the potential for serious adverse reactions from LYTGOBI in breastfed children, advise women not to breastfeed during treatment and for 1 week after the last dose.

Please see accompanying full Prescribing Information for complete details.

For more information, visit http://www.LYTGOBI.com

About Taiho Oncology, Inc.
The mission of Taiho Oncology, Inc. is to improve the lives of patients with cancer, their families and their caregivers. The company specializes in the development of orally administered anti-cancer agents and markets these medicines for a range of tumor types in the U.S. Taiho Oncology's growing pipeline of antimetabolic and selectively targeted anti-cancer agents is led by a world-class clinical development organization. Taiho Oncology is a subsidiary of Taiho Pharmaceutical Co., Ltd. which is part of Otsuka Holdings Co., Ltd. Taiho Oncology is headquartered in Princeton, New Jersey and oversees its parent company's European and Canadian operations, which are located in Zug, Switzerland and Oakville, Ontario, Canada.

For more information, visit http://www.taihooncology.com

*FGFR Oral SElective Novel Inhibitor X [across] tumors

###

Taiho Oncology Media Contact:
Judy Kay Moore
Taiho Oncology, Inc.
574-526-2369
jumoore@taihooncology.com
www.taihooncology.com

[1] LYTGOBI [prescribing information]. Princeton, NJ: Taiho Oncology, Inc.; 2022. https://taihocorp-media-release.s3.us-west-2.amazonaws.com/documents/LYTGOBI_Prescribing_Information.pdf. Last accessed: January 2023.
[2] American Cancer Society. Key statistics for bile duct cancer. https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html#:~:text=Bile%20duct%20cancer%20(cholangiocarcinoma)%20is,diagnosed%20with%20it%20each%20year. Last accessed: January 2023.
[3] Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology. Apr 2014;59(4):1427-34.10.1002/hep.26890. https://pubmed.ncbi.nlm.nih.gov/24122810/. Last accessed: January 2023.
[4] Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: Utility of next-generation sequencing for clinical management. Cancer. Dec 15 2016;122(24):3838-3847.10.1002/cncr.30254. https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.30254. Last accessed: January 2023.
[5] Sia D, Losic B, Moeini A, et al. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. *Nat Commun*. Jan 22 2015;6:6087.10.1038/ncomms7087. https://www.nature.com/articles/ncomms7087. Last accessed: January 2023.
[6] Silverman IM, Murugesan K, Lihou CF, et al. Comprehensive genomic profiling in FIGHT-202 reveals the landscape of actionable alterations in advanced cholangiocarcinoma. *Journal of Clinical Oncology*. 2019;37(15_suppl): 4080-4080.10.1200/JCO.2019.37.15_suppl.4080. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4080. Last accessed: January 2023.
[7] Javle MM, Murugesan K, Shroff RT, et al. Profiling of 3,634 cholangiocarcinomas (CCA) to identify genomic alterations (GA), tumor mutational burden (TMB), and genomic loss of heterozygosity (gLOH). *Journal of Clinical Oncology*. 2019;37(15_suppl):4087-4087.10.1200/JCO.2019.37.15_suppl.4087. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4087. Last accessed: January 2023.
[8] Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362(14):1273-81. https://www.nejm.org/doi/full/10.1056/nejmoa0908721. Last accessed: January 2023.
[9] Yu T-H, Chen X, Zhang X-H, Zhang E-C, Sun C-X. Clinicopathological characteristics and prognostic factors for intrahepatic cholangiocarcinoma: a population-based study. *Sci Rep* 2021;11(1):3990. https://www.nature.com/articles/s41598-021-83149-5. Last accessed: January 2023.
[10] Sootome H, et al. Futibatinib is a novel irreversible FGFR 1-4 inhibitor that shows selective antitumor activity against FGFR-deregulated tumors. *Cancer Res* 2020;80(22):4986-97. https://aacrjournals.org/cancerres/article/80/22/4986/645861/Futibatinib-Is-a-Novel-Irreversible-FGFR-1-4. Last accessed: January 2023.
[11] Janssen Pharmaceutical Companies. Balversa (erdafitinib) [prescribing information]. Horsham, PA: Janssen Pharmaceutical Companies; 2020. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/BALVERSA-pi.pdf. Last accessed: January 2023
[12] Incyte Corporation. Pemazyre (pemigatinib) [prescribing information]. Wilmington, DE: Incyte Corporation; 2020. https://www.pemazyre.com/pi/pi. Last accessed: January 2023.
[13] Lamarca A, Kapacee Z, Breeze M, et al. Molecular Profiling in Daily Clinical Practice: Practicalities in Advanced Cholangiocarcinoma and Other Biliary Tract Cancers. *J Clin Med*. 2020 Sep 3;9(9):2854. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7563385/. Last accessed: January 2023.
[14] Berchuck J.E., Facchinetti F, Mody K, Juric D, Goyal L, et al. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer Annals of Oncology. 2022;33(12)1269-83. https://www.annalsofoncology.org/article/S0923-7534(22)04141-2/fulltext Last accessed: January 2023.
[15] Goyal L, Meric-Bernstam F, Hollebecque A, Morizane C, Valle J.W., Karasic T.J., et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. *Journal of Clinical Oncology*. 2022;40(16). https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.4009. Last accessed: January 2023.