TAIHO ONCOLOGY

Taiho Oncology Announces Publication of Final Results of the Phase 3 ASCERTAIN Clinical Trial of Oral Decitabine and Cedazuridine Fixed Dose Combination (INQOVI®) in Patients With MDS and CMML

PRINCETON, N.J., Jan. 23, 2024 – Taiho Oncology, Inc. announces publication of the final results from the pivotal ASCERTAIN clinical trial of fixed-dose oral decitabine and cedazuridine (INQOVI®) compared to intravenous decitabine in adults with intermediate and high-risk myelodysplastic syndromes (MDS) including chronic myelomonocytic leukemia (CMML).[1]

The ASCERTAIN trial was the first Phase 3 trial to demonstrate pharmacologic equivalence between an oral and an intravenous (IV) formulation of a hypomethylating agent for use in the treatment of patients with MDS or CMML. As reported in the January 2 issue of *The Lancet Haematology*, median overall survival (mOS) in the trial population was approximately 32 months.[1] In addition, the overall response rate was 62% in the intent to treat patient population. The percentage of patients in this trial who moved to transplantation reached 20%, exceeding expected transplantation rates in patients receiving hypomethylating agents for MDS and CMML.[1]

Safety findings from the study were comparable with those previously observed with IV decitabine. The most common treatment-emergent adverse events of thrombocytopenia, neutropenia and anemia were consistent with expected adverse events with parenteral hypomethylating agent treatment.

The data from the study supported the simultaneous approval of INQOVI® by the U.S. Food and Drug Administration and Health Canada in July 2020 for the treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.[2]

“Until recently, azacitidine and decitabine, both widely used hypomethylating agents, were available only in parenteral form, requiring patients with MDS and CMML to travel to treatment centers daily for 5 or 7 consecutive days of each 28-day treatment cycle,” said Guillermo Garcia-Manero, MD, Professor, Department of Leukemia, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center, Houston, and the lead author on the publication. “The ASCERTAIN study has demonstrated that the orally delivered fixed dose combination of decitabine and cedazuridine is an alternative option to parenteral administration of decitabine for patients with these diseases. The observed median overall survival of greater than 30 months in the ASCERTAIN study compared with historical controls is encouraging.”

Added Tehseen Salimi, MD, MHA, Senior Vice President and Head of Medical Affairs, Taiho Oncology, Inc., “Patients living with MDS and CMML can benefit from the convenience of an at-home hypomethylating agent treatment that may potentially reduce the number of office visits and the travel that comes with it.”

About the ASCERTAIN Trial

The Phase 3 ASCERTAIN clinical trial was a multicenter, randomized, open-label, crossover pharmacokinetics (PK) study comparing oral decitabine (35mg) and cedazuridine (100mg) fixed-dose combination tablet given once daily for 5 days on a 28-day cycle to IV decitabine (20mg/m^2) administered as a daily 1-hour IV infusion for 5 days on a 28-day cycle, in the first 2 cycles in patients with MDS and CMML. Patients continued to receive oral decitabine and cedazuridine from Cycle 3 onwards. The primary endpoint of the study was total 5-day area-under-the-curve (AUC) equivalence of oral decitabine and cedazuridine and IV decitabine.

For more information about ASCERTAIN, please visit:
https://www.clinicaltrials.gov/ct2/show/NCT03306264?term=cedazuridine&draw=3&rank=19.

INDICATIONS
Decitabine and cedazuridine, marketed under the brand name INQOVI®, is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.[2]

INQOVI is the first and only oral hypomethylating agent approved by the FDA and by Health Canada for the treatment of adults with intermediate and high-risk MDS including CMML.

Commercialization of INQOVI in the U.S. and Canada is conducted by Taiho Oncology, Inc. and Taiho Pharma Canada, Inc., respectively.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Myelosuppression
Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended.

Embryo-Fetal Toxicity
INQOVI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise patients to use effective contraception during treatment and for 6 months (females) or 3 months (males) after last dose.

ADVERSE REACTIONS
Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

The most common adverse reactions (≥ 20%) were fatigue (55%), constipation (44%), hemorrhage (43%), myalgia (42%), mucositis (41%), arthralgia (40%), nausea (40%), dyspnea (38%), diarrhea (37%), rash (33%), dizziness (33%), febrile neutropenia (33%), edema (30%), headache (30%), cough (28%), decreased appetite (24%), upper respiratory tract infection (23%), pneumonia (21%), and transaminase increased (21%). The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased (81%), platelet count decreased (76%), neutrophil count decreased (71%), and hemoglobin decreased (55%).

USE IN SPECIFIC POPULATIONS

Lactation
Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for 2 weeks after the last dose.

Renal Impairment
No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr <15 mL/min).

Please see the accompanying Full Prescribing Information.

About Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)
Myelodysplastic syndromes are a heterogeneous group of hematopoietic stem cell disorders characterized by dysplastic changes in myeloid, erythroid, and megakaryocytic progenitor cells, and associated with cytopenias affecting one or more of the three lineages. U.S. incidence of MDS is estimated to be 10,000 cases per year, although the condition is thought to be under-diagnosed.[3,4] The prevalence has been estimated to be from 60,000 to 170,000 in the U.S.[5] MDS may evolve into acute myeloid leukemia (AML) in one-third of patients.[6] The prognosis for MDS patients is poor; patients die from complications associated with cytopenias (infections and bleeding) or from transformation to AML.

CMML is a clonal hematopoietic malignancy characterized by accumulation of abnormal monocytes in the bone marrow and in blood. The incidence of CMML in the U.S. is approximately 1,100 new cases per year,[7] and CMML may transform into AML in 15% to 30% of patients.[8]

About Decitabine and Cedazuridine Fixed-Dose Combination
This product is an orally administered, fixed dose combination of the approved anti-cancer DNA hypomethylating agent, decitabine, together with cedazuridine,[3] an inhibitor of cytidine deaminase.[4] By inhibiting cytidine deaminase in the gut and the liver, the fixed dose combination is designed to allow for oral delivery of decitabine over five days in a given cycle to achieve comparable systemic exposure to IV decitabine administered over five days.

The oral decitabine and cedazuridine fixed-dose combination has been evaluated in a Phase 1/2 pharmacokinetics-guided dose escalation and dose confirmation study, and a Phase 3 exposure equivalence study in patients with MDS and CMML – the ASCERTAIN study.

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 and commercialization of orally administered anti-cancer agents for various tumor types. Taiho Oncology has a robust pipeline of small molecule clinical candidates targeting solid tumor and hematological malignancies, with additional clinical candidates in pre-clinical development. 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 www.taihooncology.com.

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[1] Garcia-Manero G, McCloskey J, Griffiths EA, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study. *Lancet Haematol*. 2024;11(1):e15-e26. doi:10.1016/S2352-3026(23)00338-1
[2] Oral decitabine and cedazuridine (ASTX727) is approved in the U.S. and Canada for the treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. See U.S. full Prescribing Information: https://www.inqovi.com/pi. See Product Monograph: https://www.taihopharma.ca/documents/31/INQOVI_Product_Monograph.pdf
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[4] Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: Incidence and survival in the United States. *Cancer*. 2007; 109(8): 1536–1542.
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[6] Shukron O, Vainstein V, Kündgen A, Germing U, Agur Z. Analyzing transformation of myelodysplastic syndrome to secondary acute myeloid leukemia using a large patient database. *Am J Hematol*. 2012; 87: 853–860.
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[8] About chronic myelomonocytic leukemia (CMML). Cancer Research UK Web site. https://www.cancerresearchuk.org/about-cancer/other-conditions/chronic-myelomonocytic-leukaemia-cmml/what-is-cmml. Accessed November 22, 2023.

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