Astex Pharmaceuticals, Taiho Oncology, and Otsuka Pharmaceutical announce FDA and Health Canada approval of INQOVI® (decitabine and cedazuridine) tablets, oral hypomethylating agent (HMA) therapy for intermediate and high-risk MDS and CMML

- **INQOVI is the first orally administered hypomethylating agent approved by the FDA and Health Canada**
- **INQOVI is a fixed-dose combination of the hypomethylating agent decitabine and the cytidine deaminase inhibitor cedazuridine, which prevents degradation of decitabine in the gastrointestinal tract and liver and enables its absorption via oral dosing**
- **Approval is based on the ASCERTAIN phase 3 and other supporting studies that compared systemic exposure to decitabine from oral INQOVI with exposure from IV decitabine and assessed safety and efficacy of INQOVI**
- **INQOVI delivers an option for intermediate and high-risk MDS and CMML patients to potentially reduce the number of office visits and to take their medication from the convenience and comfort of their homes**

Pleasanton, CA, Princeton, NJ, and Tokyo, Japan, July 7, 2020. Astex Pharmaceuticals, Inc.; Taiho Oncology, Inc.; and Otsuka Pharmaceutical Co., Ltd. today announce that the U.S. Food and Drug Administration (FDA) and Health Canada have approved INQOVI® (decitabine and cedazuridine) tablets. The three companies are all part of the Otsuka group of companies.

INQOVI is the first and only orally administered hypomethylating agent for the treatment for adults with intermediate and high-risk myelodysplastic syndromes (MDS) including chronic myelomonocytic leukemia (CMML),[1] two blood malignancies.

Approval was based on data from the ASCERTAIN phase 3 study and supporting phase 1 and 2 clinical studies. The ASCERTAIN phase 3 study evaluated the five-day, decitabine exposure equivalence between oral INQOVI and intravenous decitabine. The safety and efficacy of INQOVI was also assessed in the clinical studies.

The review and approval of INQOVI was conducted under the ORBIS initiative from the FDA Oncology Center of Excellence (OCE) with simultaneous submission and regulatory review in the U.S., Canada, and Australia**.** The FDA also reviewed the NDA under Priority Review status. INQOVI is not currently approved in Australia. INQOVI was formerly named ASTX727, its experimental compound code.

“Intravenous or subcutaneous administered hypomethylating agents have been the cornerstone for the treatment of patients with MDS and CMML since the mid-2000s,” said Guillermo Garcia-Manero, MD, Professor and Chief of Section of Myelodysplastic Syndromes, Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston, Texas, and Principal Investigator of the ASCERTAIN clinical study. “The FDA’s approval of INQOVI builds on the proven therapeutic utility of

hypomethylating agents in these diseases and offers a new orally administered option that offers patients an alternative to five consecutive days of IV infusions every month during a treatment period that can extend to several months."

"Until now, patients with intermediate and high-risk MDS and CMML have not had an approved, orally administered hypomethylating agent option for treatment of their disease," said Mohammad Azab, MD, president and chief medical officer of Astex Pharmaceuticals, Inc. "The INQOVI clinical program was designed to deliver an oral alternative to IV decitabine based on comparative decitabine exposure data in the clinical trials, and to assess INQOVI's safety and efficacy profile. As part of the ORBIS project initiative of FDA and Health Canada we were able to share and address information requests simultaneously with both agencies resulting in a more efficient review and completion of assessment in a timely manner. The outcome is expedited availability of this important oral alternative to patients in both countries" added Dr. Azab. "We greatly appreciate the FDA's priority review and Health Canada's review of the INQOVI NDA / NDS under Project ORBIS and the approval of a new therapeutic option for patients with these diseases."

INQOVI is an orally administered, fixed-dose combination of the approved anti-cancer DNA hypomethylating agent, decitabine, together with cedazuridine,[2] an inhibitor of cytidine deaminase.[3] By inhibiting cytidine deaminase in the gut and the liver, INQOVI is designed to allow for oral delivery of decitabine over five days in a given cycle to achieve comparable systemic exposure to IV decitabine (geometric mean ratio of the 5-day cumulative decitabine area-under-the-curve following 5 consecutive once daily doses of INQOVI compared to that of intravenous decitabine was 99% (90% CI: 93, 106).[1] The phase 1 and phase 2 clinical study results have been published in *Lancet Haematology*[4] and *Blood,*[5] respectively. The phase 3 ASCERTAIN study data was presented at the American Society of Hematology (ASH) Meeting in Orlando, Florida, in December 2019 by Dr. Garcia-Manero.[6]

Astex's parent company, Otsuka Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd. previously announced that, subject to regulatory approvals, commercialization of oral INQOVI in the U.S. and Canada will be conducted by Taiho Oncology, Inc. and Taiho Pharma Canada, Inc. respectively.

"Our partnership with Astex is a demonstration of the commitment that Taiho Oncology has to bringing new therapeutic options to patients with cancer," said Tim Whitten, president and chief executive officer of Taiho Oncology, Inc. "The approval of INQOVI makes the possibility of at-home hypomethylating agent treatment of intermediate and high-risk MDS and CMML a reality, enabling patients to take their medication from the convenience and comfort of their home. This is especially significant during the COVID-19 pandemic, allowing patients to potentially reduce the number of office visits needed for current IV treatment administration. We look forward to working with all healthcare professionals to help deliver the first new oral HMA treatment alternative for patients with intermediate and high-risk MDS and CMML in nearly fifteen years."

About INQOVI (See https://www.inqovi.com)

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.[1]

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%.

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 with INQOVI 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, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

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 at least 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.

https://www.inqovi.com/pi

To view the FDA Press Release, please see the following link.

https://www.fda.gov/news-events/press-announcements/fda-approves-new-therapy-myelodysplastic-syndromes-mds-can-be-taken-home

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.[7,8] The prevalence has been estimated to be from 60,000 to 170,000 in the U.S.[9] MDS may evolve into acute myeloid leukemia (AML) in one-third of patients.[10] 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,[11] and CMML may transform into AML in 15% to 30% of patients.[12] The hypomethylating agents decitabine and azacitidine are effective treatment modalities and are FDA-approved for the treatment of intermediate and high-risk MDS and CMML. These agents are administered by IV infusion, or by large-volume subcutaneous injections.

About Astex, Taiho, and Otsuka

Astex is a leader in innovative drug discovery and development, committed to the fight against cancer. Astex is developing a proprietary pipeline of novel therapies and has multiple partnered products in development under collaborations with leading pharmaceutical companies. Astex is a wholly owned subsidiary of Otsuka Pharmaceutical Co. Ltd., based in Tokyo, Japan.

Taiho Oncology, Inc., is a subsidiary of Taiho Pharmaceutical Co., Ltd. and an indirect subsidiary of Otsuka Holdings Co., Ltd. Taiho has established a world-class clinical development organization that works urgently to develop innovative cancer treatments and has built a commercial business in the U.S. Taiho has an oral oncology pipeline consisting of both novel antimetabolic agents and selectively targeted agents.

Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: “Otsuka–people creating new products for better health worldwide.” Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

For more information about Astex Pharmaceuticals, Inc. please visit: https://www.astx.com

For more information about Otsuka Pharmaceutical, please visit: https://www.otsuka.co.jp/en/

For more information about Taiho Pharmaceutical, please visit: https://www.taihooncology.com/

Contact Details:

Craig Heit
GCI Health
On behalf of Astex Pharmaceuticals, Inc. and Taiho Oncology, Inc.
Email: TaihoOncology@gcihealth.com
Tel: +1-212-798-9919

References

1. INQOVI Prescribing Information. www.inqovi.com/pi
2. Oganesian A, Redkar S, Taverna P, Choy G, Joshi-Hangal R, Azab M. Preclinical data in cynomolgus (cyn) monkeys of ASTX727, a novel oral hypomethylating agent (HMA) composed of low-dose oral decitabine combined with a novel cytidine deaminase inhibitor (CDAi) E7727 [ASH Abstract]. *Blood* 2013;**122**(21): Abstract 2526.
3. Ferraris D, Duvall B, Delahanty G, Mistry B, Alt, J, Rojas C, et al. Design, synthesis, and pharmacological evaluation of fluorinated tetrahydrouridine derivatives as inhibitors of cytidine deaminase. *J Med Chem* 2014; **57**:2582-2588.
4. Savona MR, Odenike O, Amrein PC, Steensma DP, DeZern AE, Michaelis LC, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematol* [Internet]. 2019;**6**(4):e194-e203.
5. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML [published online ahead of print, 2020 Apr 13]. *Blood*. 2020;blood.2019004143. doi:10.1182/blood.2019004143
6. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over Phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine. *Blood* 2019; 134 (Supplement_1).
7. Garcia-Manero G. Myelodysplastic syndromes: 2015 update on diagnosis, risk-stratification and management. *Am J Hematol* 2015; **90**(9) 831-841.
8. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: Incidence and survival in the United States. *Cancer* 2007;**109**(8):1536–1542.
9. Cogle C. Incidence and burden of the myelodysplastic syndromes. *Curr Hematol Malig Rep* 2015; **10**(3): 272-281.
10. 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.
11. What are the key statistics about chronic myelomonocytic leukemia? American Cancer Society Web site. https://www.cancer.org/cancer/chronic-myelomonocytic-leukemia/about/key-statistics.html. Accessed 15 June 2020.

12. About chronic myelomonocytic leukemia (CMML). Cancer Research UK Web site. https://www.cancerresearchuk.org/about-cancer/other-conditions/chronic-myelomonocytic-leukaemia-cmml/about. Accessed 15 June 2020.