

Press Release

Astellas Presents Updated Results from Phase 1 Study of Gilteritinib Plus Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

TOKYO – December 3, 2018 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D. “Astellas”) today announced updated results from a Phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in patients newly diagnosed with FLT3 mutation-positive (FLT3mut+) Acute Myeloid Leukemia (AML). The data were presented today in an oral presentation ([Abstract 564](#)) at the 60th American Society of Hematology (ASH) Annual Meeting.

“A diagnosis of AML can be devastating for patients. It is a life-threatening disease and treatment usually needs to start as quickly as possible,” said Keith W. Pratz, M.D., of John Hopkins Sidney Kimmel Comprehensive Cancer Center, who presented the data at the ASH Annual Meeting. “Typical treatment for AML consists of induction and consolidation therapy. However, treatment options targeted for specific mutations may be important tools in physicians’ armamentarium of therapies for patients with AML. These results help advance our scientific understanding of how to potentially address these mutations in first-line treatment of AML.”

The purpose of this ongoing, open-label dose escalation/expansion Phase 1 clinical study (NCT02236013) is to assess the safety, tolerability and antitumor effects of gilteritinib when combined with induction and consolidation chemotherapy, and as single-agent maintenance therapy, in adult patients with newly diagnosed AML.¹

The two-part trial first enrolled patients to successive cohorts to determine the Maximum Tolerated Dose. Patients in the dose expansion cohort received gilteritinib at the recommended expansion dose established during dose escalation.

As of October 11, 2018, 68 subjects had been enrolled in the study; 66 are included in the safety analysis set. Of these patients, 36 (54.5%) had FLT3 mutations (FLT3-ITD, n=26). During dose-escalation, two patients in the 40 mg/day cohort who had received gilteritinib on days 1-14 experienced dose-limiting toxicities (DLTs; neutropenia, thrombocytopenia, decreased ejection fraction). After the gilteritinib induction schedule change, no more DLTs occurred at this dose. Two patients in the 200 mg/day cohort experienced DLTs (neutropenia, neutropenic enterocolitis). The maximum tolerated dose and the recommended expansion dose were established at 120 mg/day.

Additional key findings include:

- The end-of-treatment investigator-reported rate of composite complete remission (CRc) for response evaluable FLT3mut+ subjects receiving gilteritinib 120 mg on Schedule 1 (n=17) was 100%.

- The CRc rate in FLT3mut+ subjects receiving Schedule 2 induction with daunorubicin was also 100%.
- The CRc rate in FLT3mut+ subjects receiving Schedule 2 induction with idarubicin was 66.7%.
- Among subjects who received ≥ 80 mg/day gilteritinib (n=52), the CRc rate for FLT3mut+ subjects was 90.3% (n=28/31).
- Median overall survival has not been reached. Median disease-free survival was 430 days (95% CI: 155, 630).
- Grade ≥ 3 adverse events (AEs) in $\geq 10\%$ of subjects were febrile neutropenia (63.6%), thrombocytopenia (19.7%), decreased platelet count (19.7%), decreased white blood cell count (19.7%), neutropenia (19.7%), decreased neutrophil count (16.7%), anemia (13.6%), and sepsis (10.6%).
- Serious drug-related AEs in >1 subject were febrile neutropenia (n=11), sepsis (n=4), small intestinal obstruction, and decreased ejection fraction (both n=2).

Gilteritinib, under the brand name XOSPATA[®], is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.² Gilteritinib is also approved by the Japan Ministry of Health, Labor and Welfare (MHLW) for relapsed or refractory AML with FLT3 mutations.

About Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a cancer that impacts the blood and bone marrow, and its incidence increases with age. The American Cancer Society estimates that in 2018, approximately 19,000 new patients will be diagnosed with AML in the U.S.³

About XOSPATA

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory Acute Myeloid Leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.² XOSPATA is also approved by the Japan Ministry of Health, Labor and Welfare (MHLW) for relapsed or refractory AML with FLT3 mutations.

XOSPATA was discovered through a research collaboration with Kotobuki Pharmaceutical Co., Ltd., and Astellas has exclusive global rights to develop, manufacture and potentially commercialize XOSPATA.

Important Safety Information

Contraindications

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

Warnings and Precautions

Posterior Reversible Encephalopathy Syndrome (PRES) There have been rare reports of PRES with symptoms including seizure and altered mental status with XOSPATA. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 292 patients treated with XOSPATA in the clinical trial, 1.4% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancreatitis There have been rare reports of pancreatitis in patients receiving XOSPATA in clinical studies. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity Based on findings in animals and its mechanism of action, XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

Adverse Reactions

The most frequent non-hematological serious adverse reactions ($\geq 5\%$) reported in patients were pneumonia (19%), sepsis (13%), fever (13%), dyspnea (7%) and renal impairment (5%).

Overall, 22 of 292 patients (8%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common adverse reactions ($>1\%$) leading to discontinuation were pneumonia (2%), sepsis (2%) and dyspnea (1%). The most common adverse reactions ($\geq 20\%$) were myalgia/arthralgia (42%), transaminase increased (41%), fatigue/malaise (40%), fever (35%), non-infectious diarrhea (34%), dyspnea (34%), edema (34%), rash (30%), pneumonia (30%), nausea (27%), stomatitis (26%), cough (25%), headache (21%), hypotension (21%), dizziness (20%) and vomiting (20%).

Other clinically significant adverse reactions occurring in $\leq 10\%$ of patients included: electrocardiogram QT prolonged (7%), cardiac failure (grouped terms) (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities: The most common lab abnormalities ($>20\%$) that were Grade ≥ 3 that occurred $\geq 10\%$ were: hypophosphatemia (12%), alanine aminotransferase increased (12%), hyponatremia (12%), aspartate aminotransferase increased (10%).

Drug Interactions

Combined P-gp and Strong CYP3A Inducers: Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure, which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A inhibitors: Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor: Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

Specific Populations

Lactation: Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

Please see Full Prescribing Information for additional safety information.

About Astellas

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. For more information, please visit our website at <https://www.astellas.com/en>.

Cautionary Notes

In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

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¹ ClinicalTrials.gov. A study of ASP2215 in combination with induction and consolidation chemotherapy in patients with newly diagnosed acute myeloid leukemia (07-23-2018).

<https://clinicaltrials.gov/ct2/show/NCT02236013>. Accessed 09-14-2018.

² XOSPATA [package insert]. Northbrook, IL: Astellas Inc.

³ American Cancer Society. Key statistics for acute myeloid leukemia (01-04-2018).

<https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html>. Accessed 03-12-2018.