

## Press release

### **Astellas Presents New Data on XOSPATA<sup>®</sup> (gilteritinib) in FLT3 Mutation-Positive Relapsed/Refractory Acute Myeloid Leukemia at the 2019 American Society of Hematology Annual Meeting**

*Emerging mutations in patients with treatment resistance, from Phase 3 ADMIRAL study, will be focus of oral presentation*

**TOKYO, Dec. 3, 2019** – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) today announced the presentation of new data in acute myeloid leukemia (AML) at the 61<sup>st</sup> American Society of Hematology (ASH) Annual Meeting, taking place Dec. 7-10 in Orlando, Fla.

Seven abstracts sponsored by Astellas focus on patients with relapsed (disease that has returned) or refractory (resistant to treatment) AML with a FLT3 mutation (FLT3mut+). The abstracts include new findings from the Phase 3 ADMIRAL trial – an oral presentation on emerging mutations in patients who develop resistance after an initial response to XOSPATA and two poster presentations focused on patient-reported outcomes – as well as data on cost-effectiveness, FLT3 testing and treatment patterns, and venetoclax combination therapy.

“Astellas is committed to elevating care in hard-to-treat cancers, and since the approval of XOSPATA one year ago, we have continued expanding our research program to better understand and address unmet medical needs of patients with FLT3 mutation-positive AML,” said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas.

#### **Oral Presentation:**

**Title:** Emerging Mutations at Relapse in Patients with FLT3-Mutated Relapsed/Refractory Acute Myeloid Leukemia Who Received Gilteritinib Therapy in the Phase 3 ADMIRAL Trial ([Abstract 14](#))

**Presenter:** Catherine C. Smith, M.D., Division of Hematology and Blood and Marrow Transplantation, University of California San Francisco

- Session Date/Time: Saturday, Dec. 7, 7:45 a.m. EST
- Location: Orange County Convention Center, W304 Level 3

**Key Abstracts Presented During Poster Sessions or Available Online:**

**Title:** The Relationship between Hospitalization and Patient-Reported Outcomes (PROs) in Patients with FLT3-Mutated (FLT3mut+) Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML): Results from the Phase 3 ADMIRAL Study ([Abstract 1332](#))

*Lead Author:* Ellen K. Ritchie, M.D., Weill Cornell Medicine, New York

- Session Date/Time: Saturday, Dec. 7, 5:30-7:30 p.m. EST
- Location: Orange County Convention Center, Hall B, Level 2

**Title:** The Relationship between Transplant Status and Patient-Reported Outcomes in Patients with FLT3-Mutated Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML): Results from the Phase 3 ADMIRAL Study ([Abstract 3850](#))

*Lead Author:* David Cella, Ph.D., Northwestern University, Feinberg School of Medicine, Chicago

- Session Date/Time: Monday, Dec. 9, 6-8 p.m. EST
- Location: Orange County Convention Center, Hall B, Level 2

**Title:** Cost-Effectiveness Analysis of Gilteritinib Versus Salvage Chemotherapy (SC) for the Treatment of Relapsed or Refractory (R/R) FLT3-Mutated (FLT3mut+) Acute Myeloid Leukemia (AML) ([Abstract 3859](#))

*Lead Author:* Amer M. Zeidan, MBBS, MHS, Department of Internal Medicine, Section of Hematology, Yale University School of Medicine and Yale Cancer Center, New Haven, Conn.

- Session Date/Time: Monday, Dec. 9, 6-8 p.m. EST
- Location: Orange County Convention Center, Hall B, Level 2

**Title:** Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1b Study ([Abstract 3910](#)) (*Supported by AbbVie, Astellas and Genentech*)

*Lead Author:* Alexander E. Perl, M.D., Abramson Cancer Center of the University of Pennsylvania, Philadelphia

- Session Date/Time: Monday, Dec. 9, 6-8 p.m. EST
- Location: Orange County Convention Center, Hall B, Level 2

**Title:** STREAMLINE - Study of Relapse or Refractory (R/R) FLT3-Mutated Acute Myeloid Leukemia (AML) Using Electronic Medical Records (EMR): First Analysis from a Multicenter, Retrospective Cohort Study ([Abstract 5082](#))

*Lead Author:* Amer M. Zeidan, MBBS, MHS, Department of Internal Medicine, Section of Hematology, Yale University School of Medicine and Yale Cancer Center, New Haven, Conn.

**Title:** Cost-Effectiveness Analysis of Gilteritinib Versus Best Supportive Care (BSC) for the Treatment of Relapsed or Refractory (R/R) FLT3 Mutation-Positive (FLT3mut+) Acute Myeloid Leukemia (AML) ([Abstract 5085](#))

*Lead Author:* Amer M. Zeidan, MBBS, MHS, Department of Internal Medicine, Section of Hematology, Yale University School of Medicine and Yale Cancer Center, New Haven, Conn.

### **Astellas-Supported Satellite Symposia**

Astellas will support the following pre-meeting Friday Satellite Symposia:

**Title:** Data + Perspectives: Exploring the Role of Novel Agents and Emerging Strategies in the Management of Acute Myeloid Leukemia

- Session Date/Time: Friday, Dec. 6, 7-11 a.m. EST
- Location: Hilton Orlando, Orange Ballroom (Lower Level)

**Title:** Treating Acute Myeloid Leukemia: Case Challenges and Emerging Therapies

- Session Date/Time: Friday, Dec. 6, 6-10 p.m. EST
- Location: Hyatt Regency Orlando, Plaza International D-F

### **About the Gilteritinib Clinical Trial Program**

Astellas is investigating gilteritinib in various FLT3 mutation-positive AML patient populations. Key planned or ongoing trials include ADMIRAL ([NCT02421939](#)) for patients with FLT3 mutated AML who are refractory to or have relapsed after first-AML therapy, LACEWING ([NCT02752035](#)) for newly diagnosed patients ineligible for intensive chemotherapy, MORPHO ([NCT02997202](#)) for patients with a FLT3-ITD mutation after allogeneic transplant, GOSSAMER ([NCT02927262](#)) for FLT3-ITD positive patients after consolidation therapy, and COMMODORE ([NCT03182244](#)) for patients who are refractory to or have relapsed after first-line therapy in China and several other countries. Visit <http://www.clinicaltrials.gov> to learn more.

### **About XOSPATA® (gilteritinib)**

Gilteritinib was discovered through a research collaboration with Kotobuki Pharmaceutical Co., Ltd., and Astellas has exclusive global rights to develop, manufacture and commercialize gilteritinib. Gilteritinib was approved in the U.S. and Japan in 2018 and in Europe in 2019 for the treatment of adult patients who have relapsed or refractory FLT3mut+ AML.<sup>1,2,3</sup> As of December 2019 it is available in the US, Japan and several countries in Europe. In August 2019, gilteritinib was indicated as appropriate treatment for FLT3 mutation positive relapsed and refractory AML patients as Category 1 Recommendation from the National Comprehensive Cancer Network®.<sup>4</sup> In October 2019, results from the Phase 3 ADMIRAL trial were published in The New England Journal of Medicine.<sup>5</sup>

### **About XOSPATA® (gilteritinib) in the United States**

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with an FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.<sup>6</sup>

### **Important Safety Information**

#### **WARNING: DIFFERENTIATION SYNDROME**

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

### **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**

**Differentiation Syndrome (See BOXED WARNING)** 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

**Posterior Reversible Encephalopathy Syndrome (PRES)** 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

**Prolonged QT Interval** XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial 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** 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

**Embryo-Fetal Toxicity** 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

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent ( $\geq 5\%$ ) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common ( $>1\%$ ) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent ( $\geq 5\%$ ) grade  $\geq 3$  nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in  $\leq 10\%$  of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

**Lab Abnormalities** Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate

aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

### **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 including **BOXED WARNING** 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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## References

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<sup>1</sup> US Food and Drug Administration. FDA Approves Treatment for Adult Patients who Have Relapsed or Refractory Acute Myeloid Leukemia (AML) with a Certain Genetic Mutation. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm627072.htm>. Last accessed November 2019.

<sup>2</sup> Japan Pharmaceutical and Medical Devices Agency (PMDA). New Drug Approvals, April 2018 - March 2019. Available at: <http://www.pmda.go.jp/files/000229380.pdf#page=5>. Last accessed October 2019.

<sup>3</sup> XOSPATA. Summary of Product Characteristics (SmPC). Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/xospata>. Last accessed November 2019.

<sup>4</sup> National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute Myeloid Leukemia Version 2.2020 (09-03-2019). Available at: <https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=3683>. Last accessed September 2019.

<sup>5</sup> Perl A, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-mutated AML. N Engl J Med 2019; 381:1728-40.

<sup>6</sup> XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc.