When Treating R/R FLT3m+ AML in Your Practice, Remember:

For patients with AML, relapsing or becoming refractory with a FLT3 mutation can be devastating, but there is a targeted treatment option[1-4]

Please see Important Safety Information on pages 5-6 and **click here** for Full Prescribing Information including BOXED WARNING.

RELAPSED/REFRACTORY

Suspect AML Relapse or Progression? It's Time to Act

***FLT3-ITD* mutations drive AML progression and may lead to lower survival rates.**[1-3]

2-YEAR OS RATE IN PATIENTS WITH R/R AML (N=138)[1]

40% (±5%) **survival with no *FLT3-ITD* mutation** (n=96)

VS

***P*=0.03**

23% (±7%) **survival with *FLT3-ITD* mutation** (n=37)

Data are from a retrospective, multicenter study including 138 adult patients with relapsed (n=81) or refractory (n=57) AML treated with a combination of gemtuzumab ozogamicin and intensive salvage chemotherapy (96 patients had no *FLT3-ITD* mutation, 37 had *FLT3-ITD* mutation, and 5 had an unknown FLT3 mutation status).[1]

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.

Indication

XOSPATA (gilteritinib) 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.

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RETEST

Identify Mutation Status–FLT3 is an Actionable Target[5]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend repeat testing for all patients with AML at each relapse or disease progression.[5]

Consider using a quick FLT3 test[6]*:
PCR RESULTS
Up to 3 business days

FLT3 MUTATION STATUS MAY CHANGE AT RELAPSE, HIGHLIGHTING THE IMPORTANCE OF RETESTING[7]

AT DIAGNOSIS

17% of patients had a *FLT3-ITD* mutation (n=56/324)

AT RELAPSE

21% of relapsed patients had a *FLT3-ITD* mutation (n=21/102)

At relapse: 13 patients (52%, n=13/25) **retained and 8 patients** (10%, n=8/77) **acquired a *FLT3-ITD* mutation**

Retrospective analysis of 324 patients with AML treated with front-line Phase 2 induction chemotherapy protocols. *FLT3-ITD* mutation testing performed at diagnosis, post-induction, and at relapse.[8]

In another retrospective analysis that included 54 patients with *FLT3-ITD* AML from the RATIFY, AMLSG 16-1014, AMLSG 07-04, and AMLSG 11-08 trials, who were refractory to or relapsed after intensive chemotherapy in combination with a multikinase inhibitor, *FLT3-ITD* clones were shown to be present at diagnosis and relapse. It was observed that FLT3 mutations can change, remain, or be lost in patients treated with a multikinase inhibitor as part of an induction regimen.[9]

Contraindications

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

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*FLT3 mutation statuses that can be obtained: *FLT3-ITD*, *FLT3-TKD*, and *FLT3-ITD/TKD*.[6]

A Targeted Treatment Option Is Available[4]

XOSPATA (gilteritinib) is the only FDA-approved targeted monotherapy indicated for the treatment of adult patients with R/R FLT3m+ AML.[4,10]*

XOSPATA DELIVERED SUPERIOR OS COMPARED TO SALVAGE CHEMOTHERAPY FOR PATIENTS WITH R/R FLT3m+ AML[4‡]

36% reduced risk of death with XOSPATA (n=247)
vs salvage chemotherapy (n=124)
HR=0.64 (95% CI: 0.49, 0.83); *P*=0.0004

9.3 months median OS[§] with XOSPATA (95% CI: 7.7, 10.7)
vs 5.6 months with salvage chemotherapy (95% CI: 4.7, 7.3)

14.2% CR[‖] with XOSPATA (95% CI: 10.1, 19.2; n=35/247)
vs 10.5% CR with salvage chemotherapy (95% CI: 5.7, 17.3; n=13/124)

XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in 371 adult patients with R/R FLT3m+ AML.[4,11]

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[‡]Only responses prior to HSCT were included in the response rate and were based on the Kaplan-Meier method and Greenwood formula.[4,12]
[§]Median OS was based on Kaplan-Meier method and the Greenwood formula.[12]
[‖]CR was defined as normal marrow differential with <5% blasts, ANC ≥1.0 x 10^9/L and platelets ≥100 x 10^9/L, no evidence of extramedullary leukemia, and must have been RBC and platelet transfusion independent, and were based on the Kaplan-Meier method and Greenwood formula.[4,12]

AML=acute myeloid leukemia; AMLSG=acute myeloid leukemia study group; ANC=absolute neutrophil count; CI=confidence interval; CR=complete remission; FLT3=FMS-like tyrosine kinase 3; HR=hazard ratio; HSCT=hematopoietic stem cell transplant; ITD=internal tandem duplication; m+=mutation-positive; NCCN=National Comprehensive Cancer Network; OS=overall survival; PCR=polymerase chain reaction; RBC=red blood cell; R/R=relapsed or refractory; TKD=tyrosine kinase domain.

References: 1. Chevallier P, Labopin M, Turlure P, et al. A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. Leukemia 2011;25(6):939-44. **2.** Smith CC, Wang Q, Chin CS, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. Nature 2012;485(7397):260-3. **3.** Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. J Clin Oncol 2012;30(7):735-41. **4.** XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed 05-21-2024. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **6.** Invivoscribe. LeukoStrat® CDx FLT3 mutation assay. https://invivoscribe.com/uploads/collateral/LabPMM-Flyer_Leukostrat-CDx_FLT3_8.5x11_20170419_v2.pdf. Accessed 01-22-2024. **7.** McCormick SR, McCormick MJ, Grutkoski PS, et al. FLT3 mutations at diagnosis and relapse in acute myeloid leukemia: cytogenetic and pathologic correlations, including cuplike blast morphology. Arch Pathol Lab Med 2010;134(8):1143-51. **8.** Nazha A, Cortes J, Faderl S, et al. Activating internal tandem duplication mutations of the fms-like tyrosine kinase-3 (FLT3-ITD) at complete response and relapse in patients with acute myeloid leukemia. Haematologica 2012;97(8):1242-5. **9.** Schmalbrock LK, Dolnik A, Cocciardi S, et al. Clonal evolution of acute myeloid leukemia with FLT3-ITD mutation under treatment with midostaurin. Blood 2021;137(22):3093-104.**10.** Ballesta-López O, Solana-Altabella A, Megías-Vericat JE, Martínez-Cuadrón D, Montesinos P. Gilteritinib use in the treatment of relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Future Oncol 2021;17(2):215-27. **11.** ClinicalTrials.gov. A study of ASP2215 versus salvage chemotherapy in patients with relapsed or refractory acute myeloid leukemia (AML) with FMS-like tyrosine kinase (FLT3) mutation (11-25-2024). https://clinicaltrials.gov/ct2/show/NCT02421939. Accessed 11-25-2024.**12.** Astellas. XOSPATA. Data on File.

Indication and Important Safety Information

Indication

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Important Safety Information

Contraindications

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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 and other clinical findings 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 1 day and up to 82 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.

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Important Safety Information (continued)

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 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 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 (≥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 (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in ≤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.

P-gp, BCRP, and OCT1 Substrates Based on *in vitro* data, gilteritinib is a P-gp, breast cancer resistant protein (BCRP), and organic cation transporter 1 (OCT1) inhibitor. Coadministration of gilteritinib may increase the exposure of P-gp, BCRP, and OCT1 substrates, which may increase the incidence and severity of adverse reactions of these substrates. For P-gp, BCRP, or OCT1 substrates where small concentration changes may lead to serious adverse reactions, decrease the dose or modify the dosing frequency of such substrate and monitor for adverse reactions as recommended in the respective prescribing information.

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.
For important state pricing disclosure information, click here.

XOSPATA® gilteritinib 40mg tablets

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