In patients with relapsed/refractory AML

Timely identification of a FLT3 mutation can help impact treatment decisions[1-4]

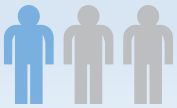
CONSIDER EXPEDITING AML FLT3 TESTING AT RELAPSE OR PROGRESSION[4]

AML= acute myeloid leukemia; FLT3= FMS-like tyrosine kinase 3.

FLT3 mutations are the most common mutations in AML and can now be targeted in R/R AML[4,5]

MANY PATIENTS WITH AML WILL TEST POSITIVE FOR A FLT3 MUTATION[5]

In newly diagnosed patients tested for FLT3 mutations,

1 in 3  **were positive for a FLT3 mutation**

- In one study, 37% of newly diagnosed patients tested positive for a FLT3 mutation* (30% had *FLT3-ITD* and 7% had *FLT3-TKD*)

*Representative of the combined percentage of AML patients with mutations other than FLT3. Individually, each mutation included in the combined representation occurs less frequently than FLT3.

IN R/R AML PATIENTS, *FLT3-ITD* MUTATIONS NEGATIVELY IMPACT SURVIVAL[6]

- *FLT3-ITD* mutations were associated with an adverse impact on OS in a retrospective, multicenter study of 138 adult patients with relapsed (n=81) or refractory (n=57) AML treated with gemtuzumab ozogamicin and intensive chemotherapy as salvage regimen[6]

2-YEAR OVERALL SURVIVAL RATE

40% survival with ***FLT3-ITD* negative** (±5%, n=96*)

VS

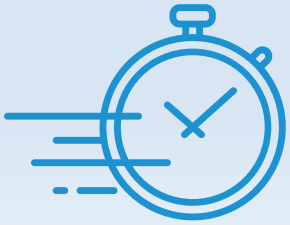
23% survival with ***FLT3-ITD*** (±7%, n=37*)

P=0.03

*5 patients had unknown FLT3 mutation status

Pathologists can make a difference in the patient journey

CONFIRMING FLT3 MUTATION STATUS AT RELAPSE OR PROGRESSION MAY HELP INFORM A TREATMENT STRATEGY[1-4]



Consider expediting AML FLT3 testing at relapse or progression[4]

Targeted therapies are available and designed to address the FLT3 mutation in relapsed/refractory AML[4,7]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing all patients with **AML for FLT3 mutations at each relapse or disease progression[4]**

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.

SELECT 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.

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.

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.

Gilteritinib (XOSPATA) is the **ONLY Category 1** recommendation in the NCCN Guidelines for patients with relapsed or refractory FLT3m+ AML[4]

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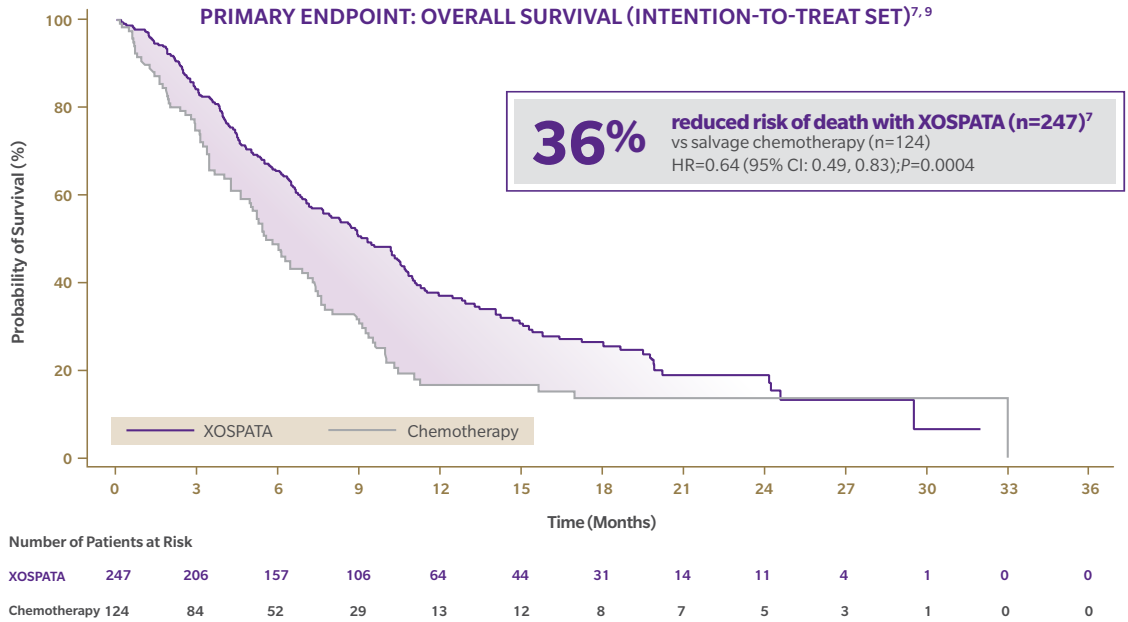
For adult patients with relapsed/refractory AML who have tested positive for FLT3 mutation,

XOSPATA is the only FDA-approved targeted monotherapy to deliver superior overall survival vs salvage chemotherapy[7,8*]

XOSPATA—an oral monotherapy *FLT3-ITD* and *-TKD* inhibitor — was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in 371 adult patients with relapsed or refractory FLT3m+ AML.[†] Prespecified salvage chemotherapy regimens included high-intensity combinations MEC and FLAG-IDA and low-intensity regimens LDAC and AZA.[7,9‡]

[†]FLT3 mutation status: FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD



- The Kaplan-Meier method in combination with the Greenwood formula was used to determine overall survival and corresponding 95% confidence intervals (CIs)[9]

*The OS endpoint was measured from the date of randomization until death by any cause in the final analysis, which included 371 patients randomized 2:1 to receive XOSPATA or a prespecified salvage chemotherapy regimen. Prior AML chemotherapy regimens included standard-dose cytarabine + idarubicin (39%); high-dose cytarabine (27%); standard-dose cytarabine + daunorubicin (26%); azacitidine (7%); decitabine (5%); high-dose cytarabine + daunorubicin (4%); low-dose cytarabine (4%); high-dose cytarabine + idarubicin (3%); standard-dose cytarabine + mitoxantrone (3%); and standard-dose cytarabine + daunorubicin + cladribine (1%); as well as other regimens (44%).[7,10]

‡MEC: mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, and cytarabine 1000 mg/m^2 once daily by IV infusion for 5 days. FLAG-IDA: granulocyte colony-stimulating factor 300 mcg/m^2 once daily by SC injection Days 1 to 5, fludarabine 30 mg/m^2 once daily by IV infusion Days 2 through 6, cytarabine 2000 mg/m^2 once daily by IV infusion Days 2 through 6, idarubicin 10 mg/m^2 once daily by IV infusion Days 2 through 4. LDAC: cytarabine 20 mg twice daily by SC injection or IV infusion for 10 days. AZA: azacitidine 75 mg/m^2 once daily by SC injection or IV infusion for 7 days.[7]

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; HR=hazard ratio; ITD=internal tandem duplication; IV=intravenous; LDAC=low-dose cytarabine; m+=mutation positive; OS=overall survival; SC=subcutaneous; TKD=tyrosine kinase domain.

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INDICATION AND IMPORTANT SAFETY INFORMATION

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IMPORTANT SAFETY INFORMATION

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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 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.

INDICATION AND IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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References: 1. 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. **2.** Warren M, Luthra R, Yin CC, et al. Clinical impact of change of FLT3 mutation status in acute myeloid leukemia patients. Mod Pathol 2012;25(10):1405-12. **3.** 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. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed 12-03-2021. To view the most recent and complete version of the guideline, 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. **5.** Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366(12):1079-89. **6.** 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. **7.** XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **8.** 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 (Epub) 09-25-2020. **9.** Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019;381 (18):1728-40. **10.** Astellas Pharma US, Inc. XOSPATA. Data on File.

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Pathologists can make a difference in the patient journey

FLT3-ITD mutations at relapse or refractory disease **are associated with lower survival.**[6]

Test results for FLT3 mutations at relapse or progression may help **inform a targeted treatment strategy**[1-4]

Consider expediting AML FLT3 testing at relapse or progression[4]

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In AML at relapse or progression, consider expediting FLT3 testing[4]

Learn more at **XOSPATAhcp.com**

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