In Relapsed or Refractory AML

Retesting for FLT3 May Impact Treatment Outcomes[1,2]

Gilteritinib (XOSPATA) is the ONLY Category 1 recommendation for patients with relapsed or refractory AML with a FLT3 mutation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[3]

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; NCCN=National Comprehensive Cancer Network.

INDICATION

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.

CONTRAINDICATION

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.

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XOSPATA®
gilteritinib 40mg tablets

In AML, the Prognosis for Patients With Relapsed or Refractory Disease Is Poor[4]

Mutations in FLT3 are the most common mutations in AML[5]

Of patients newly diagnosed with AML and tested for FLT3 mutations:

30%
were positive for *FLT3-ITD*

***FLT3-ITD* mutations are associated with higher risk of relapse and shorter OS compared with wild-type FLT3[6,7]**

7%
were positive for *FLT3-TKD*

***FLT3-TKD* mutations may be a potential mechanism of treatment resistance[8]**

In newly diagnosed patients, *FLT3-ITD* mutations in AML are associated with poor outcomes[7]

- Higher risk of relapse
- Shorter remission
- Reduced survival

***FLT3-ITD* mutations cut survival short in relapsed or refractory AML[4]**

FLT3 Mutation Status Can Change Over the Patient's Disease Course[9]

- In an analysis of pooled data from 15 studies,

22% of patients (n=11/50)
with AML had a FLT3 mutation status that changed from diagnosis to relapse[10]

FLT3-ITD mutations may emerge at relapse in patients with AML[2,9,10]

- In a retrospective analysis of 324 patients with AML, 268 patients did not have *FLT3-ITD* mutations at diagnosis[9]
  - Of the 77 patients without *FLT3-ITD* mutations who relapsed after treatment, **10%** (n=8) tested positive for a *FLT3-ITD* mutation at relapse

Among patients with *FLT3-ITD* mutations at diagnosis, *FLT3-TKD* mutations may be present after treatment[8]

- In a retrospective analysis of patients treated with a FLT3 inhibitor, among patients diagnosed with a single *FLT3-ITD* mutation prior to treatment,

25% of patients (n=15/60)
had both *FLT3-ITD* and *-TKD* mutations at the end of therapy

- The impact of *FLT3-TKD* mutations on prognosis is not clear.[11] Some studies have shown they have no prognostic significance and may depend on other genetic mutations to have an impact on prognosis[11,12]

NCCN Guidelines® recommend testing all AML patients for FLT3 mutations at relapse and progression[3]

ITD=internal tandem duplication; m+=mutation-positive; OS=overall survival; TKD=tyrosine kinase domain.

PCR Tests Can Help Inform a Targeted Treatment Strategy[2,3,13]

Patients with AML who are appropriate for treatment with a targeted therapy can be selected based on the presence of FLT3 mutations in the blood or bone marrow as detected by an FDA-approved test. Information about FDA-approved tests for the detection of FLT3 mutations in AML is available at http://www.fda.gov/companiondiagnostics[14,15]

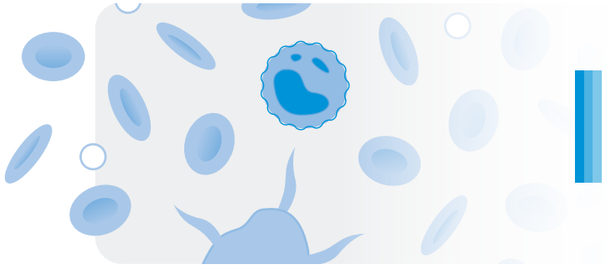
PCR tests create many copies of a specific segment of DNA[13]

- Detect *FLT3-ITD* and *FLT3-TKD*[13]
- Detect emergence of new mutations at relapse[2]

PCR results can be provided in[13,14] **2 to 3 BUSINESS DAYS**

The LeukoStrat® CDx FLT3 Mutation Assay is a PCR test and the only FDA-approved companion diagnostic for detecting FLT3 mutations[14,15]

PCR Tests Are Highly Sensitive[16]



PCR tests are able to detect **1 leukemia cell** in a background of **1 million normal cells**[16]

PCR tests demonstrate specificity and sensitivity across *FLT3-ITD* mutations in AML[16]

In a real-time quantitative assessment, PCR tests detected

0.01% to 0.001%

of *FLT3-ITD*-positive samples

Testing for FLT3 mutations at relapse and progression may help inform a targeted treatment strategy[3]

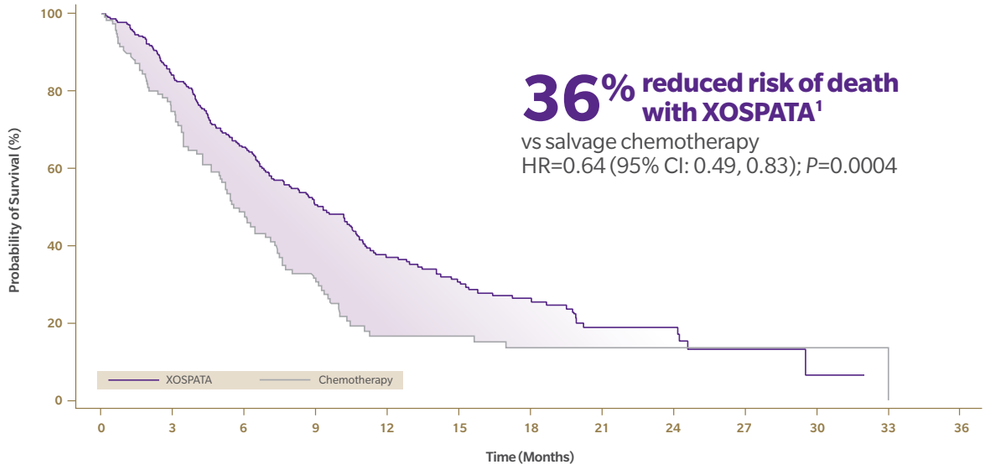
CDx=companion diagnostic; DNA=deoxyribonucleic acid; FDA=Food and Drug Administration; PCR=polymerase chain reaction.

ADMIRAL TRIAL

XOSPATA Delivered Superior Overall Survival vs Salvage Chemotherapy in Relapsed or Refractory FLT3m+ AML[1]*

- XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in adult patients with relapsed or refractory FLT3m+ AML.[1,17] Prespecified chemotherapy regimens included high-intensity combinations MEC† and FLAG-IDA‡ and low-intensity regimens LDAC§ and AZA‖[1]

PRIMARY ENDPOINT: OVERALL SURVIVAL (INTENTION-TO-TREAT SET)[1,17]



36% reduced risk of death with XOSPATA[1]
vs salvage chemotherapy
HR=0.64 (95% CI: 0.49, 0.83); *P*=0.0004

Number of Patients at Risk													
XOSPATA	247	206	157	106	64	44	31	14	11	4	1	0	0
Chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

*FLT3 mutation status: *FLT3-ITD*, *FLT3-TKD*, and *FLT3-ITD-TKD*.[1]
†MEC: mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, and cytarabine 1000 mg/m^2 once daily by IV infusion Days 1 to 5.[1]
‡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.[1]
§LDAC: cytarabine 20 mg twice daily by SC injection or IV infusion for 10 days.[1]
‖AZA: azacitidine 75 mg/m^2 once daily by SC injection or IV infusion for 7 days.[1]

SELECT SAFETY INFORMATION

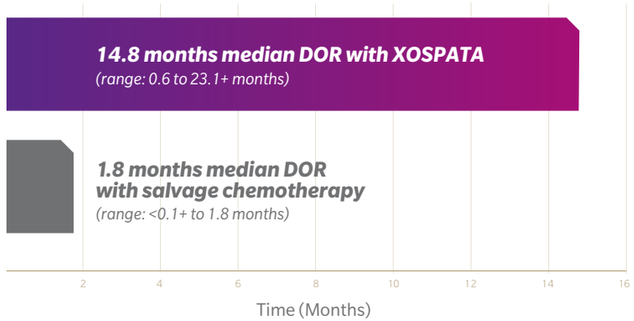
Posterior Reversible Encephalopathy Syndrome (PRES) 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis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

XOSPATA Improved Complete Remission Rate[1]

HIGHER RATE OF CR¶ WITH XOSPATA VS SALVAGE CHEMOTHERAPY[1#]

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)

EXTENDED MEDIAN DURATION OF COMPLETE REMISSION[1#**]



¶CR was defined as ANC ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been RBC and platelet transfusion independent and have had no evidence of extramedullary leukemia.[1]
#Only responses prior to HSCT were included in the response rate.[1]
**DOR was defined as the time from the date of first remission until the date of a documented relapse.[1]

ANC=absolute neutrophil count; CI=confidence interval; CR=complete remission; DOR=duration of remission; HR=hazard ratio; HSCT=hematopoietic stem cell transplant; IV=intravenous; LDAC=low-dose cytarabine; RBC=red blood cell; SC=subcutaneous.

SELECT SAFETY INFORMATION

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.

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Important Safety Information

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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 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.

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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 (≥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.

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. XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **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.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed 11-18-2020. 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. **4.** 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. **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.** 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. **7.** Whitman SP, Maharry K, Radmacher MD, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood 2010;116(18):3622-6. **8.** Alvarado Y, Kantarjian HM, Luthra R, et al. Treatment with FLT3 inhibitor in patients with FLT3-mutated acute myeloid leukemia is associated with development of secondary FLT3-tyrosine kinase domain mutations. Cancer 2014;120(14):2142-9. **9.** 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. **10.** 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. **11.** Bacher U, Haferlach C, Kern W, Haferlach T, Schnittger S. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters—an analysis of 3082 patients. Blood 2008; 111(5):2527-37. **12.** Boddu P, Kantarjian H, Borthakur G, et al. Co-occurrence of FLT3-TKD and NPM1 mutations defines a highly favorable prognostic AML group. Blood Adv 2017; 1(19):1546-50. **13.** Patnaik MM. The importance of FLT3 mutational analysis in acute myeloid leukemia. Leuk Lymphoma 2018;59(10):2273-86. **14.** Invivoscribe. LeukoStrat® CDx FLT3 mutation assay. https://www.invivoscribe.com/clinical-services/leukostrat-cdx-flt3-mutation-assay. Accessed 10-14-2020. **15.** US Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools) (11-09-2020). https://www.fda.gov/media/119249/download. Accessed 11-10-2020. **16.** Stirewalt DL, Willman CL, Radich JP. Quantitative, real-time polymerase chain reactions for FLT3 internal tandem duplications are highly sensitive and specific. Leuk Res 2001;25(12):1085-8. **17.** Astellas. XOSPATA. Data on File.

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