XOSPATA®
gilteritinib 40mg tablets

Gilteritinib (XOSPATA) is recommended by the National Comprehensive Cancer Network® (NCCN®)[1]

Gilteritinib (XOSPATA) is the **only Category 1 recommendation** for patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with a FLT3 mutation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia[1*†]

FLT3, FMS-like tyrosine kinase 3

*Published 11-12-2020.[1]
†Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[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 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.

Please see additional Important Safety Information on pages 7 and 8 and click here for Full Prescribing Information, including BOXED WARNING.

NCCN suggests testing for FLT3 and other mutations each time a patient has a relapse or progresses[1]

The results of mutation testing help inform a targeted treatment strategy throughout the patient's continuum of care.[1]

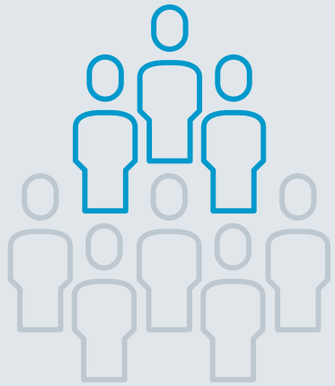
Molecular testing should be repeated at each relapse or progression because FLT3 mutation status can change over the course of a patient's disease.[1-3]

NCCN recommends quick turnaround time for FLT3 testing[1]

Mutation testing results can inform time-sensitive treatment decisions. Thus, NCCN Guidelines® recommend FLT3 testing results be expedited at diagnosis.

ITD, internal tandem duplication; TKD, tyrosine kinase domain

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



37%

Roughly 37% of patients with AML have FLT3 mutations, making them the most common mutations in AML[4]

30%

FLT3-ITD occurs in roughly 30% of patients with AML[4]

In a retrospective, multicenter study of 138 adult patients with relapsed (n=81) or refractory (n=57) AML treated with intensive salvage chemotherapy regimens, *FLT3-ITD* mutations were associated with an adverse impact on overall survival (OS).[5]

7%

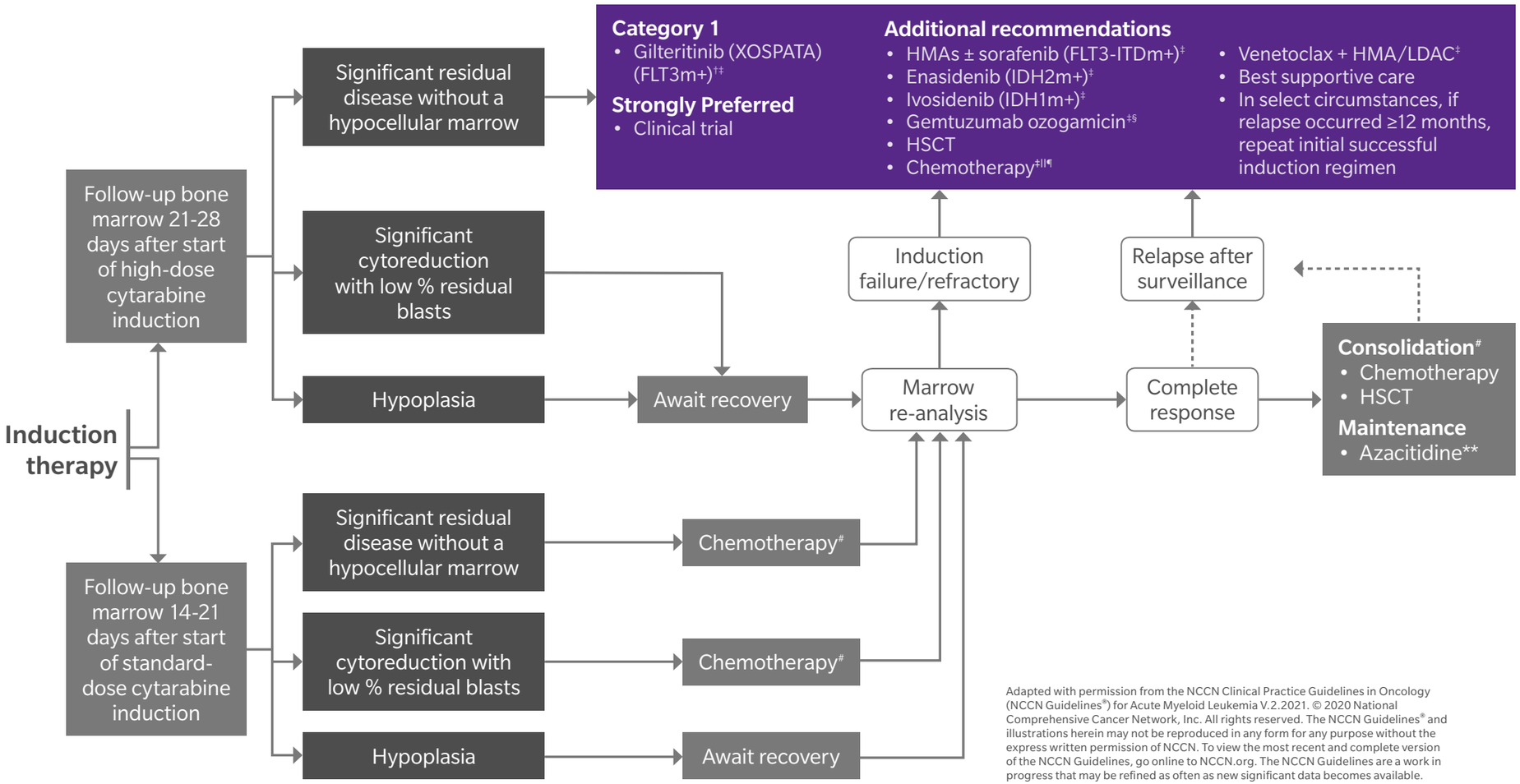
FLT3-TKD occurs in 7% of patients with AML[4]

FLT3-TKD mutations have a less clear impact on prognosis and may be a mechanism of resistance after treatment in patients with *FLT3-ITD* AML.[6,7]

NCCN Guidelines recommend gilteritinib (XOSPATA) as a Category 1 treatment option for patients with R/R AML with a FLT3 mutation[1]

NCCN Guidelines post-induction treatment algorithm for patients with AML in good health or <60 years of age[1]*

Individual patient-related factors, including age, mutation status, comorbidities and performance status, should be considered when determining treatment[1]



CD33, sialic acid binding immunoglobulin-like lectin 3; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IDH, isocitrate dehydrogenase; LDAC, low-dose cytarabine; m+, mutation-positive

*All recommendations are 2A unless otherwise indicated. Not all possible treatment pathways are represented in this diagram. Please refer to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for all possible treatment options. 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.[1]
†For the treatment of relapsed or refractory patients with FLT3m+ AML.[1]
‡Treatment to be followed by HSCT.[1]
§For the treatment of relapsed or refractory patients with CD33m+ AML.[1]
||High- or low-intensity chemotherapy may be used.[1]
¶Low-dose cytarabine recommendation in the relapsed or refractory setting is category 2B.[1]
#Post-induction, consolidation, and post-remission treatment options are not represented in this diagram.[1]
**Recommended in select patients who decline or are not fit or eligible for HSCT. Category 2B for patients with intermediate-risk molecular abnormalities.[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.

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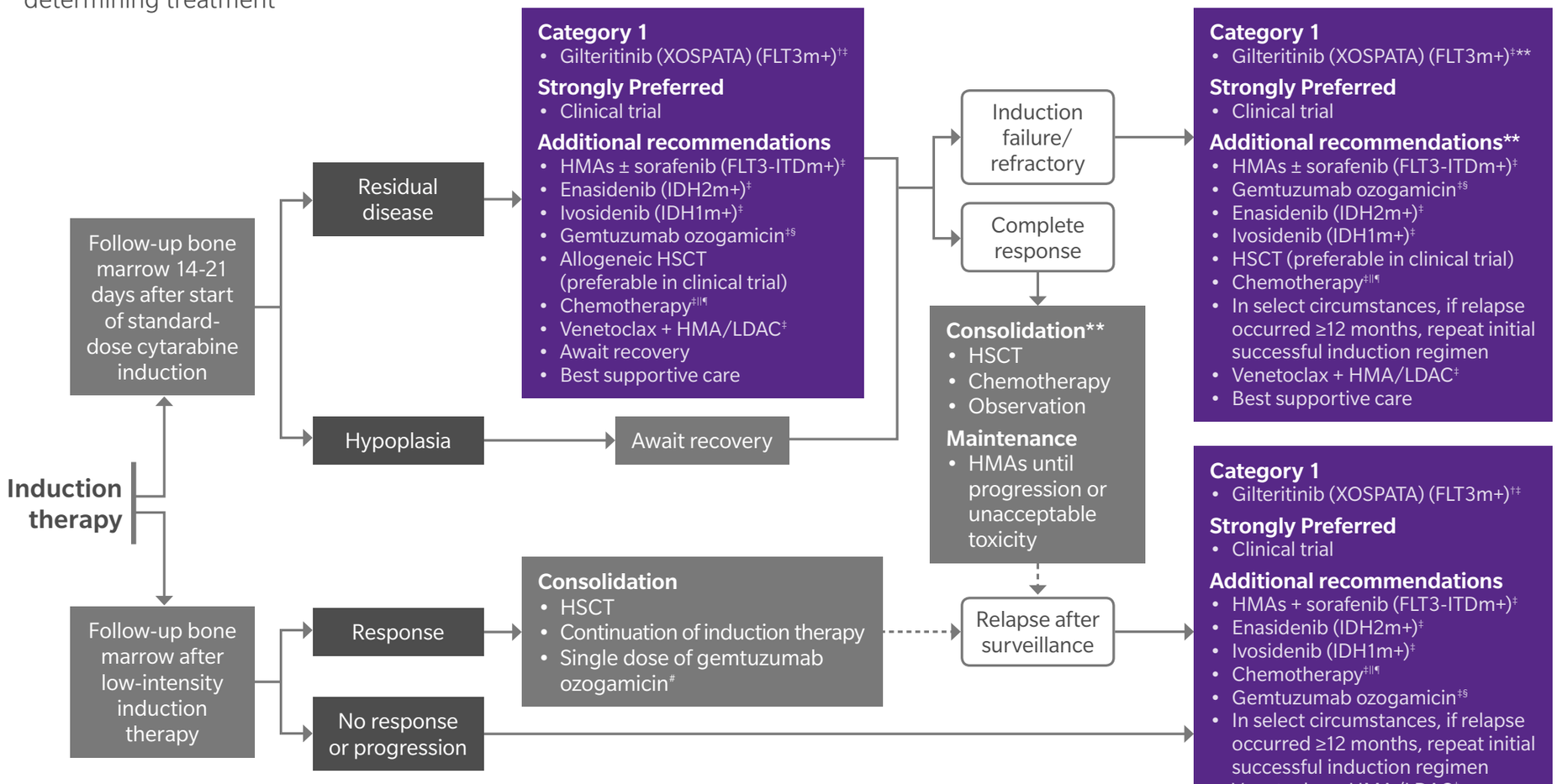
NCCN Guidelines recommend gilteritinib (XOSPATA) as a Category 1 treatment option for patients with R/R AML with a FLT3 mutation (cont'd)[1]

NCCN Guidelines post-induction treatment algorithm for patients with AML in poor health or ≥60 years of age[1]*

Individual patient-related factors, including age, mutation status, comorbidities and performance status, should be considered when determining treatment[1]



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†For the treatment of relapsed or refractory patients with FLT3m+ AML (category 1).[1]
‡Treatment to be followed by HSCT.[1]
§For the treatment of relapsed or refractory patients with CD33m+ AML.[1]
||High- or low-intensity chemotherapy may be used.[1]
¶Low-dose cytarabine recommendation in the relapsed or refractory setting is category 2B.[1]
#Category 2B after no response or progression.[1]
**Post-induction, consolidation, and post-remission treatment options are not represented in this diagram.[1]

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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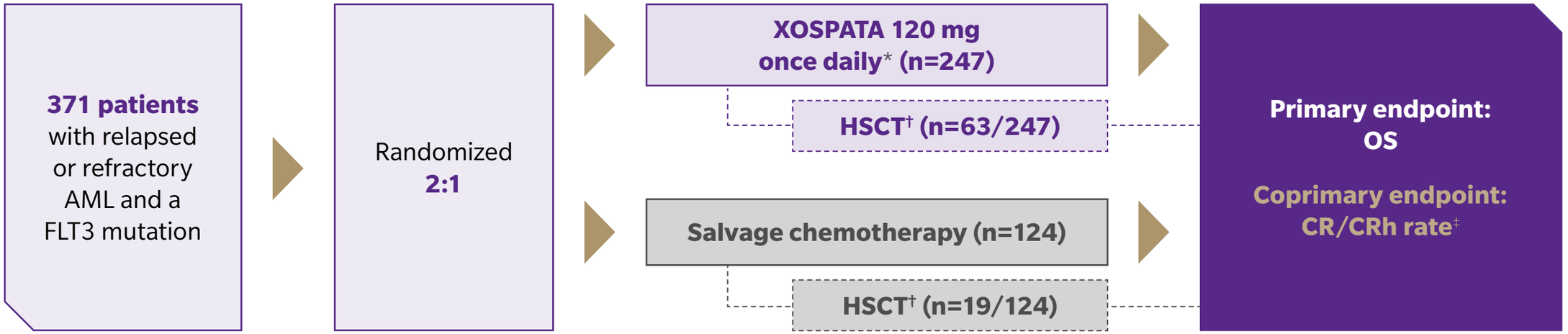
XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial (ADMIRAL)[8,9]

Compared with a prespecified salvage chemotherapy in adult patients with R/R FLT3m+ AML[8,9]

ADMIRAL study design[8,9]



The ADMIRAL trial included patients who were FLT3m+ and eligible for high- or low-intensity chemotherapy. Randomization to XOSPATA or salvage chemotherapy was stratified by patient response to first-line AML treatment and prespecified chemotherapy.§ Prespecified chemotherapy regiments included high- and low-intensity chemotherapy regimens. The efficacy of XOSPATA was based on an interim analysis (n=138) and a final analysis (n=371).[8]

CR, complete remission; CRh, complete remission with partial hematologic recovery

*XOSPATA was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit.[8]
†Patients in the ADMIRAL trial were eligible for HSCT. Patients who went on to receive transplant during the study had achieved a response in either treatment arm that allowed them to undergo HSCT based on each institution's assessment, and had a donor identified. Treatment with XOSPATA was stopped prior to starting the conditioning regimen for HSCT and could be resumed after transplant in patients meeting appropriate study protocol criteria.[9]
‡Only responses prior to HSCT were included in the CR/CRh rate reported in the XOSPATA Prescribing Information.[8]
§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%).[9]

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Living longer with R/R FLT3m+ AML is possible with XOSPATA[8]

Extended OS[8]

9.3
months with XOSPATA
(**n=247**, 95% CI: 7.7, 10.7)

vs **5.6** months with salvage chemotherapy
(95% CI: 4.7, 7.3)

XOSPATA significantly reduced the risk of death by

36%

compared to salvage chemotherapy
(HR=0.64 [95% CI: 0.49, 0.83]; *P*=0.0004).*

Extended DOR[8†]

14.8
months median duration of CR[‡] with XOSPATA
(range: 0.6 to 23.1+ months)

vs **1.8** months with salvage chemotherapy
(range <0.1+ to 1.8 months)

- Rate of CR[‡] was 14.2% with XOSPATA (95% CI: 10.1, 19.2; n=35/247) compared to salvage chemotherapy (CR: 10.5%; 95% CI: 5.7, 17.3; n=13/124)

Transfusion Independence[8¶]

34.5%
of transfusion-dependent patients at baseline became transfusion independent with XOSPATA

during any 56-day post-baseline period
(n=68/197)

- Of the 49 patients in the XOSPATA arm who were transfusion independent at baseline, 59.2% remained transfusion independent during any 56-day post-baseline period (n=29/49)

Select Safety Information

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.

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CI, confidence interval; DOR, duration of remission; HR, hazard ratio

*Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula.[8,9]
†Duration of response was defined as the time from the date of first remission until the date of a documented relapse.[8]
‡CR was defined as normal marrow differential with <5% blasts, absolute neutrophil count (ANC) ≥1.0 × 10^9/L and platelets ≥100 × 10^9/L, no evidence of extramedullary leukemia and must have been red blood cell count (RBC) and platelet-transfusion independent. Only responses prior to HSCT were included in the response rate.[8]
¶Transfusion independence was defined as patients who were dependent on RBC and/or platelet transfusions at baseline and became independent of RBC and platelet transfusions during any 56-day, post-baseline period.[8]

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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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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.

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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.

Specific Populations

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

Click here for Full Prescribing Information including BOXED WARNING for additional safety information.

References: 1. 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. The National Comprehensive Cancer Network 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. **2.** 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. **3.** 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. **4.** 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. **5.** 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. **6.** 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. **7.** 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. **8.** XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **9.** Astellas Pharma US, Inc. XOSPATA. Data on File.

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