XOSPATA® gilteritinib 40mg tablets

ADMIRAL

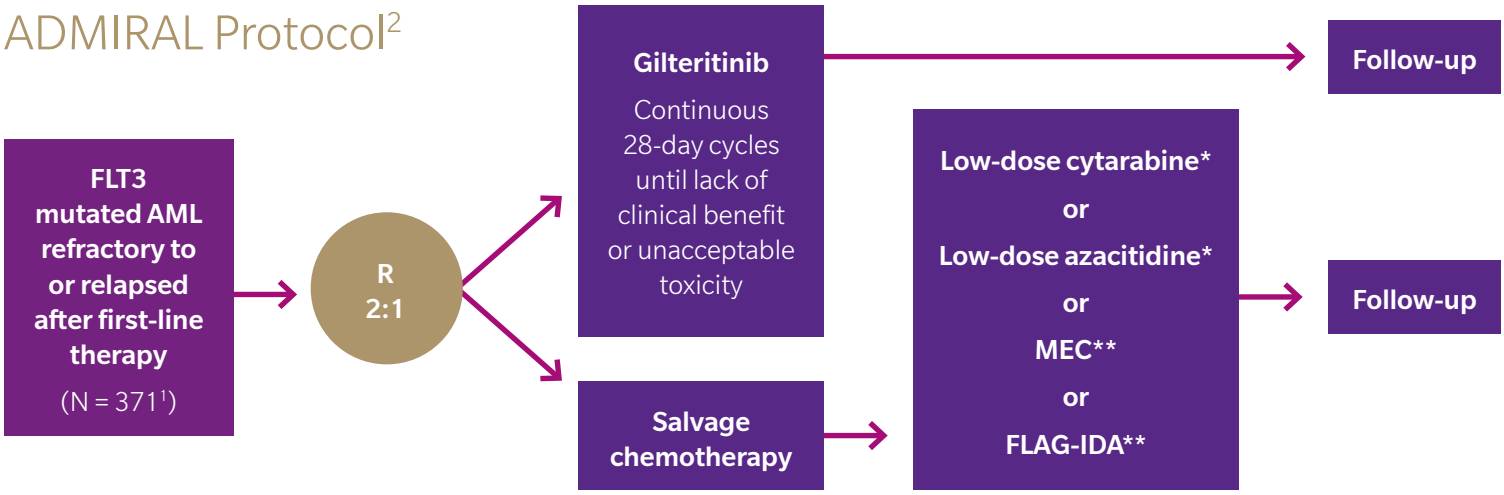
The ADMIRAL Study[1]

The Phase 3 ADMIRAL clinical trial is designed to evaluate the use of XOSPATA® (gilteritinib) versus salvage chemotherapy in adult patients with FLT3 mutations who are refractory to or have relapsed after first-line AML therapy.[1] The open-label, multicenter, randomized study enrolled 371 patients with FLT3 mutations present in bone marrow or whole blood, as determined by central lab.[1] Subjects were randomized in a 2:1 ratio to receive gilteritinib (120 mg) or salvage chemotherapy.[2]

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.[3]

ADMIRAL Protocol[2]



AML = Acute Myeloid Leukemia

FLT3 = FMS-like tyrosine kinase 3

FLAG-IDA = fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin

MEC = mitoxantrone, etoposide and intermediate-dose cytarabine

NR = no response

PD = progressive disease

R = randomized

**Continuous 28-day cycles until lack of clinical benefit or unacceptable toxicity.*
***For a maximum of 2 cycles or until NR or PD.*

Eligibility Criteria Include***:

- Refractory to, or relapsed after, first-line AML therapy[1]
- Positive for FLT3-activating mutation (FLT3 ITD, FLT3 TKD-D835, FLT3 TKD 1836 mutation)[1]
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2[1]

Preplanned Interim Analysis[1]

- Complete Remission and Complete Remission with Partial Hematological Recovery (CR/CRh) rate
- Duration of Remission (DOR)
- Rate of Conversion from Dependence to Transfusion Independence

Trial Endpoints[1]

Primary outcome measures

- Overall Survival (OS data were not mature at the time of the interim analysis)
- Complete Remission and Complete Remission with Partial Hematological Recovery (CR/CRh) rate

Secondary outcome measures

- Event-free Survival
- Complete Remission Rate
- Leukemia-free Survival
- Duration of Remission
- Composite Complete Remission Rate[a]
- Transplantation Rate[b]
- Brief Fatigue Inventory[c]
- Complete Remission with Partial Hematological Recovery (CRh) Rate
- Transfusion Conversion Rate
- Transfusion Maintenance Rate

****Not a complete list of selection criteria.*

[a]Complete remission (CR) + Complete remission with incomplete hematologic recovery (Cri) + Complete remission with incomplete platelet recovery (CRp)

[b]Transplantation rate is defined as the percentage of subjects undergoing Hematopoietic stem cell transplant (HSCT) during the study period.

[c]The Brief Fatigue Inventory (BFI) is used to assess the severity of fatigue and the impact of fatigue on daily functioning in patients with fatigue due to cancer and cancer treatment. The BFI short form has 9 items and a 24-hour recall. A global fatigue score is computed by averaging the 9 items.

Please see Important Safety Information on reverse and click here for Full Prescribing Information for additional safety information.

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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.

Important 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.

WARNINGS AND PRECAUTIONS

Posterior Reversible Encephalopathy Syndrome (PRES) There have been rare reports of PRES with symptoms including seizure and altered mental status with XOSPATA. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 292 patients treated with XOSPATA in the clinical trial, 1.4% 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 There have been rare reports of pancreatitis in patients receiving XOSPATA in clinical studies. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity Based on findings in animals and its mechanism of action, 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

The most frequent non-hematological serious adverse reactions (≥5%) reported in patients were pneumonia (19%), sepsis (13%), fever (13%), dyspnea (7%) and renal impairment (5%).

Overall, 22 of 292 patients (8%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common adverse reactions (>1%) leading to discontinuation were pneumonia (2%), sepsis (2%) and dyspnea (1%). The most common adverse reactions (≥20%) were myalgia/arthralgia (42%), transaminase increased (41%), fatigue/malaise (40%), fever (35%), non-infectious diarrhea (34%), dyspnea (34%), edema (34%), rash (30%), pneumonia (30%), nausea (27%), stomatitis (26%), cough (25%), headache (21%), hypotension (21%), dizziness (20%) and vomiting (20%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (7%), cardiac failure (grouped terms) (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities: The most common lab abnormalities (>20%) that were Grade ≥3 that occurred ≥10% were: hypophosphatemia (12%), alanine aminotransferase increased (12%), hyponatremia (12%), aspartate aminotransferase increased (10%).

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 for additional safety information.

[1]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 (04-25-2018). https://clinicaltrials.gov/ct2/show/NCT02421939?cond=02421939&rank=1. Accessed 04-26-2018.

[2]Gorcea CM, Burthem J, Tholouli E. ASP2215 in the treatment of relapsed/refractory acute myeloid leukemia with FLT3 mutation: background and design of the ADMIRAL trial. Future Oncol (epub). 03-02-2018.

[3]XOSPATA [package insert]. Northbrook, IL: Astellas Inc.

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