FDA approves gilteritinib for relapsed or refractory acute myeloid leukemia

Background[1-3]	• FLT3 mutations are present in up to 30% of patients with acute myeloid leukemia (AML)[1] • Gilteritinib (Xospata®) is an inhibitor of FLT3[2] • In cells that exogenously express FLT3 ITD and TKD, gilteritinib inhibits receptor signaling and proliferation and induces apoptosis in leukemic cells expressing FLT3-ITD[2]
Dosage[3]	• Dosed 120 mg orally once-daily with or without meals • Available as 40 mg tablets • Recommended to continue for a minimum of 6 months to allow time for clinical response

Efficacy[2,3]	ADMIRAL trial (NCT02421939)
	• 138 patients with relapsed or refractory AML Relapsed or refractory AML
	  ○ Median age: 60 years
	  ○ Relapsed AML 59%, refractory AML 41%
	  ○ FLT3 ITD 88%, FLT3 TKD 9%, FTL3 ITD and TKD 4%
	• Median follow up: 4.6 months
	  ○ CR or CRi: 29 (21%, CI 14.5-28.8%)
	  ○ Transfusion independence within 56 days: 33 (31.1%)
	  ▪ 17 (53.1%) maintained transfusion independence

Warnings, Precautions, & Drug interactions[3]	• Posterior reversible encephalopathy syndrome (PRES):
	  ○ Discontinue gilteritinib
	• QT prolongation:
	  ○ QTc >500 msec – interrupt and resume at 80 mg when interval within 30 msec of base or ≤480 msec
	  ○ QTc increase >30 msec on cycle 1, day 8 EKG – confirm with EKG on day 9. If confirmed, reduce to 80 mg once daily
	  ○ Avoid other QT prolonging medications
	  ○ Monitor K^+ and Mg^{2+}
	• Pancreatitis:
	  ○ Interrupt and resume at 80 mg once daily after pancreatitis resolves
	• Embryo-Fetal Toxicity
	  ○ Avoid use in patients who may be pregnant
	  ○ Males with female partners that are able to become pregnant should use effective birth control during treatment with gilteritinib and for at least 4 months after the last dose
	• Strong 3A4 inhibitors
	  ○ Avoid when able. If use is essential, closely monitor for gilteritinib adverse effects
	  ○ Itraconazole increases AUC ~120% while fluconazole increases AUC ~40%

Side effects[3]	• Common grade ≥3 ADE: febrile neutropenia (39%), anemia (25%), sepsis (14%), thrombocytopenia (13%), and pneumonia (12%) • Common ADE (≥20%): myalgia/arthralgia, transaminase increase, fatigue/malaise, noninfectious diarrhea, dyspnea, edema, rash, nausea, stomatitis, cough, headache, hypotension, dizziness and vomiting
Bottom Line	Gilteritinib monotherapy is well-tolerated and represents a new option for patients with relapsed/refractory FLT3 positive AML. Gilteritinib allowed patients to obtain and maintain transfusion independence and produced complete responses in an arduous disease state.

References:

1. Stone RM, Mandrekar SJ, Sanford BL, et. al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017. 377(5):454-464. DOI: 10.1056/NEJMoa1614359.
2. Perl A, Altman J, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukemia: a multicenter, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017;18:1061-75. doi 10.1016/S1470-2045(17)30416-3
3. Xospata® (gilteritinib) package insert. Astellas Pharma US, Inc. Northbrook, IL; 2018.
4. FDA approves gilteritinib for relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. U.S. Food and Drug Administration, 2018.