The Acute Myeloid Leukemia Treatment Landscape 2018

Approved Agents

Gilteritinib (Xospata)

Indication: Treatment of adult patients with *FLT3* mutation-positive relapsed or refractory acute myeloid leukemia AML) as detected by a Food and Drug Administration-approved test.

Mechanism of Action:A type I tyrosine kinase inhibitor that is highly selective for both Fms-like tyrosine kinase 3 FLT3 and AXL, and demonstrates potent inhibitory activity against the internal tandem duplication (FLT3-ITD) and FLT3-D835Y point mutations.

Key Clinical Trials:

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*. 2018 Mar 2. doi: 10.2217/fon-2017-0582. [Epub ahead of print]

Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. *Lancet Oncol.* 2017;18:1061-1075.

Venetoclax (Venclexta)

Indication: In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction.

Mechanism of Action: Venetoclax is a highly selective, orally bioavailable BCL-2 inhibitor that has shown activity in BCL-2–dependent leukemia and lymphoma cell lines.

Key Clinical Trials:

Konopleva M, Letai A. BCL-2 inhibition in AML - an unexpected bonus?

Blood. 2018 Jul 23. pii: blood-2018-03-828269. doi: 10.1182/blood-2018-03-828269. [Epub ahead of print].

DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018;19(2):216-228.

Glasdegib (Daurismo)

Indication: In combination with low-dose cytarabine in newly-diagnosed AML in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy.

Mechanism of Action: An oral, potent, selective, small-molecule that inhibits the smoothened receptor, thereby disrupting the Hedgehog pathway.

Key Clinical Trials:

Cortes JE, Smith BD, Wang ES, et al. Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: Phase 2 study results. Am J Hematol. 2018 Aug 3. doi: 10.1002/ajh.25238. [Epub ahead of print].

Cortes JE, et al. A phase II randomized study of low dose Ara-C with or without glasdegib (PF-04449913) in untreated patients with AML or High-Risk MDS. Presented at: 58th ASH Annual Meeting and Exposition; December 3-6, 2016; San Diego, CA. Abstract 99.

Midostaurin (Rydapt)

Indication: In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are Fms-like tyrosine kinase 3 (FLT3) mutation–positive, as detected by a US Food and Drug Administration (FDA)-approved test.

Mechanism of Action: Inhibits FLT3 receptor and KIT signaling and cell proliferation and has shown inhibitory activity against several other receptor tyrosine kinases, such as PDGFRα/β, VEGFR2, and members of the serine/threonine kinase PKC family

Key Clinical Trials:

Stone RM, Manley PW, Larson RA, Capdeville R. Midostaurin: its odyssey from discovery to approval for treating acute myeloid leukemia and advanced systemic mastocytosis. *Blood Adv*. 2018;2(4):444-453.

Garcia JS, Percival ME. Midostaurin for the treatment of adult patients with newly diagnosed acute myeloid leukemia that is FLT3 mutation-positive. *Drugs Today (Barc)*. 2017;53(10):531-543.

Enasidenib (Idhifa)

Indication: Adult patients with relapsed or refractory (R/R) AML with an isocitrate dehydrogenese-2 (IDH-2) mutation as detected by an FDA-approved test.

Mechanism of Action: Inhibits mutant IDH2 variants to decrease 2-hydroxyglutarate levels and increases percentages of mature myeloid cells.

Key Clinical Trials:

Krämer A, Bochtler T. Enasidenib. *Recent Results Cancer Res*. 2018;212:187-197.

Abou Dalle I, DiNardo CD. The role of enasidenib in the treatment of mutant IDH2 acute myeloid leukemia. *Ther Adv Hematol.* 2018;9(7):163-173.

CPX-351 (Vyexos)

Indication: Adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Mechanism of Action: Daunorubicin has antimitotic and cytotoxic activity, which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity, inhibiting DNA polymerase

activity, affecting regulation of gene expression, and producing DNA-damaging free radicals. Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Cytarabine acts primarily through inhibition of DNA polymerase.

Key Clinical Trials:

Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia [published online July 19, 2018]. *J Clin Oncol.* doi:10.1200/JCO.2017.77.6112.

Gemtuzumab ozogamicin (Mylotarg)

Indication: Newly diagnosed CD33-positive AML in adults and relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.

Mechanism of Action: Binding of the anti-CD33 antibody portion of gemtuzumab ozogamicin with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove, resulting in DNA double-strand breaks and cell death.

Key Clinical Trials:

Lambert J, Pautas C, Terré C, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase 3 ALFA-0701 trial [published online August 3, 2018]. *Haematologica*. doi:10.3324/haematol.2018.188888.

Baron J, Wang ES. Gemtuzumab ozogamicin for the treatment of acute myeloid leukemia. *Expert Rev Clin Pharmacol.* 2018;11(6):549-559.

Ivosidenib (Tibsovo)

Indication: Adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test.

Mechanism of Action: Ivosidenib is a small-molecule inhibitor that targets the mutant isocitrate dehydrogenase-1 (IDH-1) enzyme. Susceptible IDH1 mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells. The most common such mutations are R132H and R132C substitutions.

Key Clinical Trials:

DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.

Sidaway P. Ivosidenib effective in IDH1-mutant AML. *Nat Rev Clin Oncol*. 2018;15(8):472.

Resources

Acute Myeloid Leukemia – Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

https://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

Initial Diagnostic Workup of Acute Leukemia: A Pocket Guide for Clinicians – American Society of Hematology/College of American Pathologists

file:///C:/Users/Nick%20Zittell/Downloads/AcuteLeukemiaPocketGuideWEB2017%20(7).pdf