FDA Grants Accelerated Approval for Frontline Venetoclax in Elderly Patients with Acute Myelogenous Leukemia (AML)

Background

- Patients ≥65 years with AML who are unfit for intensive chemotherapy have limited options; monotherapy with hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) yield modest responses– CR/CRi rates 10 - 26%.[1]
- B-cell lymphoma 2 (BCL-2) protein is a key regulator of the mitochondrial apoptotic pathway and plays an important role in the survival and persistence of AML blasts.[2]
- Venetoclax is a potent, selective, oral inhibitor of BCL-2
- Relapsed or refractory AML patients treated with venetoclax monotherapy demonstrated activity and a tolerable safety profile in a phase II study.[3]

Dosage[4]

Formulation: Tablets - 10 mg, 50 mg, 100 mg
Administration: Orally once daily with a meal and water
Given in combination with azacitidine or decitabine or low-dose cytarabine

Dosing Schedule for Ramp-up Phase in Patients with AML

Day 1: 100 mg	Day 2: 200 mg	Day 3: 400 mg	Days 4 and beyond: 400 mg with azacitidine or decitabine; 600 mg with low-dose cytarabine

Efficacy

Wei A, et al. Blood 2016 128:102 (Study M14-387, NCT02287233)

- Study: Phase I/II, multicenter, two stage study
- Intervention: Venetoclax five-day dose ramp-up to 600 mg daily with low-dose cytarabine 20 mg/m^2 daily given days 1-10 subcutaneous (SC)
- Patients: (n=82) newly diagnosed, ≥65 years, ineligible for standard induction chemotherapy
- Results: Median age – 76 years, 74% were ≥75 years, 93% had intermediate or poor-risk cytogenetics
    - ORR (CR + CRi + PR): 75% patients
        - CR + CRi: 70%
    - 12-month overall survival: 74.7%
    - Common grade 3/4 AE excluding cytopenias: febrile neutropenia (35%), hypertension (20%), hypophosphatemia (20%)
        - No tumor lysis syndrome (TLS) was observed

Dinardo CD et al. Blood. 2019;133(1):7-17 (Study M14-358, NCT02203773)

- Study: Phase 1b dose-escalation and expansion study
- Intervention: Venetoclax ramp up to 400 mg, 800, or 1200 mg daily in combination with either decitabine 20 mg/m^2 IV on days 1-5,or azacitidine 75 mg/m^2 IV/SC on days 1-7
- Patients: (n=145) newly diagnosed, ≥65 years, ineligible for standard induction chemotherapy, and intermediate or poor-risk cytogenetics
- Results: Median age - 74 years, 49% had poor-risk cytogenetics
    - CR + CRi: 73% patients (venetoclax 400 mg + HMA cohort)
        - Poor-risk cytogenetics CR + CRi: 60%
        - ≥75 years old CR + CRi: 65%
    - Median duration of CR + CRi: 11.3 months
    - Median overall survival: 17.5 months
    - Common AE (>30%): nausea, diarrhea, constipation, febrile neutropenia, fatigue, hypokalemia, decreased appetite, and decreased WBC
        - No TLS was observed

Management of Potential Interactions[4]

Posaconazole	Other strong CYP3A4 inhibitor	Moderate CYP 3A4 inhibitor
• Day 1: 10 mg • Day 2: 20 mg • Day 3: 50 mg • Day 4: 70 mg • After ramp-up phase: 70 mg	• Day 1: 10 mg • Day 2: 20 mg • Day 3: 50 mg • Day 4: 100 mg • After ramp-up phase: 100 mg	• Reduce dose by at least 50% P-gp inhibitor • Reduce dose by at least 50%

Strong or moderate CYP3A inducers: Avoid co-administration	P-gp substrates with narrow therapeutic index: Take at least 6 hours before venetoclax

Warnings

TLS (more concerning in CLL/SLL; consider prophylaxis during ramp-up in AML) and myelosuppression

Bottom Line

- Venetoclax in combination with a HMA or LDAC has proven to be a well-tolerated and efficacious regimen in elderly AML patients ineligible to receive intensive chemotherapy
- Confirmatory phase III studies, VIALE-A (NCT02993523) and VIALE-C (NCT03069352), will evaluate venetoclax in combination with HMAs and LDAC with OS as the primary endpoint

References

1. Wei A, Strickland SA, Roboz GJ et al. Safety and Efficacy of Venetoclax Plus Low-Dose Cytarabine in Treatment-Naive Patients Aged ≥65 Years with Acute Myeloid Leukemia. Blood 2016 128:102.
2. Dinardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7-17.
3. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov. 2016;6(10):1106-1117.
4. Venclexta (venetoclax) [prescribing information]. North Chicago, IL: AbbVie Inc; November 2018.