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Sonrotoclax plus azacitidine demonstrates broad antileukemic activity across ELN 2024 genetic risk groups in treatment-naive acute myeloid leukemia unfit for intensive chemotherapy

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Introduction: The European LeukemiaNet (ELN) 2024 is a genomic risk stratification framework for treatment-naïve (TN) acute myeloid leukemia (AML) treated with lower-intensity hypomethylating agent (HMA)-based therapies. Sonrotoclax is a next-generation BCL2 inhibitor designed to have high target selectivity, enhanced pharmacologic potency, and an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation. These properties may enable deeper target inhibition while mitigating toxicity. In an ongoing phase 1b/2 trial (BGB-11417-103; NCT04771130), the safety and efficacy of sonrotoclax plus azacitidine were evaluated across ELN 2024 risk groups in TN AML unfit for intensive therapy.

Methods: Patients with TN AML were defined as unfit if aged ≥65 years or had ≥1 protocol-defined comorbidity. Sonrotoclax once daily was evaluated across target doses of 40-320 mg and durations of 10-28 days in combination with azacitidine 75 mg/m^2 for 7 days in 28-day cycles. In cycle 1, a 4-day sonrotoclax ramp-up began at 1/8th the target dose. DLTs were assessed through day 28 for nonhematologic events and through day 42 or cycle 2 initiation for hematologic events. TEAEs were classified per MedDRA v29.0 and graded per CTCAE v5.0. Antileukemic activity was assessed per ELN 2017 criteria. MRD was assessed by flow cytometry, with MRD negativity defined as <10^{-3} leukemic cells. Post-hoc ELN 2024 risk stratification was performed based on centrally available mutation data.

Results: As of May 1, 2026, 95 patients with TN unfit AML (74% de novo; 26% secondary) were treated. Median age was 73 (range, 59-91) years; 98% were aged ≥65 years. Among patients with secondary AML (n=25), 6 had received prior HMA for MDS; 2 had prior SCT. At a median follow-up of 11.5 (range, 0.3-59.0) months, 88% of patients discontinued treatment, and 12% remained on therapy. The most common reasons for discontinuation were leukemia relapse (28%), followed by investigator decision (21%) and AEs (13%). Five (5%) patients proceeded to allogeneic SCT. Across cohorts, 6 DLTs occurred in 5 patients due to grade 4

neutropenia (n=2) and grade 4 thrombocytopenia (n=4). No cohort met the prespecified safety stopping criteria. Ninety-four (99%) patients experienced at least 1 grade ≥3 TEAE. The most common (≥20%) grade ≥3 TEAEs were neutropenia (46%), febrile neutropenia (43%), neutrophil count decreased (42%), anemia (39%), thrombocytopenia (38%), platelet count decreased (34%), and pneumonia (20%). Grade 5 TEAEs occurred in 12% of patients, most frequently due to infections and infestations (6%). Tumor lysis syndrome occurred in 4 patients (2 clinical); all resolved in ≤4 days without sequelae. Fifty-two (55%) patients achieved complete remission (CR), with 87% of these achieving CR by the end of cycle 4. The CR/CR with incomplete hematologic recovery (CRi) rate was 68%. Median times to CR and CR/CRi were 1.9 and 1.3 months. Among 63 patients with mutation data, 33 (52%), 20 (32%), and 10 (16%) had ELN 2024 favorable-, intermediate-, and adverse-risk disease, respectively. Mutations included *IDH1/2* (n=15), *NPM1* (n=12), *FLT3-ITD* (n=7), *DDX41* (n=3), *NRAS* (n=13), *KRAS* (n=6), *TP53* (n=10), and MDS-related gene mutations (n=42). CR and CR/CRi rates were 67% and 82% in the ELN 2024 favorable-risk group, 55% and 70% in the intermediate-risk group, and 40% and 60% in the adverse-risk group. Median follow-up for patients with mutation data was 12.6 (range, 0.3-56.7) months. Among patients achieving CR, median duration of response was 21.2 (95% CI, 7.5-NE), 6.9 (95% CI, 2.4-8.7), and 12.8 (95% CI, 6.3-NE) months in the favorable-, intermediate-, and adverse-risk groups, respectively. By the end of cycle 7, MRD negativity ($<10^{-3}$) among CR patients was 46-50% across risk groups. Follow-up for survival is ongoing. Preliminary exposure-response analyses indicated higher response rates at sonrotoclax doses ≥160 mg. Among patients in the pooled sonrotoclax 160/320-mg, 14-day dosing cohorts, CR and CR/CRi rates were 57% and 93% (8/14; 13/14), 63% and 63% (5/8 for both), and 50% and 50% (2/4 for both) in the ELN 2024 favorable-, intermediate-, and adverse-risk groups, respectively.

Conclusion: Sonrotoclax plus azacitidine was tolerable and demonstrated promising efficacy in TN unfit AML, with favorable CR rates across all ELN 2024 risk groups. These findings further support the broad clinical activity of sonrotoclax across hematologic malignancies.