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ORAL ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Venetoclax Plus High-Dose Cytarabine and Mitoxantrone (HAM-Ven) As Salvage Treatment for Relapsed/Refractory AML: Updated Results of the Phase-I/II SAL Relax Trial

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Background
Primary refractory disease and relapse remain the main obstacles for cure in AML. In fit patients, several salvage cytostatic options based on higher doses of cytarabine have been published, with complete remission (CR) rates ranging from 40-55%. The BCL2 inhibitor venetoclax has demonstrated impressive antileukemic activity when combined with hypomethylating agents or low-dose cytarabine in newly diagnosed unfit AML patients. In the phase-I part of the RELAX trial of the Study Alliance Leukemia (SAL), we demonstrated the feasibility of combining venetoclax with higher-dose cytarabine plus mitoxantrone (HAM) in relapsed AML, resulting in a CR/CRi rate of 92%. Here, we report the updated results from the phase-I and additional patients from the phase-II dose expansion in relapsed or refractory (r/r) AML patients.

Methods
Patients with r/r AML fit for intensive salvage treatment were eligible. Based on the safety results from the phase-I part, patients were treated with the recommended phase-II dose combination of 400 mg venetoclax PO QD (d1-14) including a 2-day ramp-up, followed by cytarabine 1000 mg/m ^{2} IV BID (d3-5) in combination with mitoxantrone 10 mg/m ^{2} IV QD (d5-7). Concomitant CYP3A inhibitors were allowed with the appropriate dose adjustments, patients did not receive G-CSF. Patients

achieving a CR could enter a maintenance phase with 400 mg venetoclax PO QD over twelve 28-day cycles. This research was supported by a grant from AbbVie Inc. The trial is registered under NCT04330820.

Results

Between April 2020 and June 2023, 12 patients were enrolled in the dose-escalation part and 40 patients in the expansion part, of whom 38 were evaluable for response by the time of writing. Median follow-up was 6.7 months. Among the 12 patients in the dose-escalation part, 3 received 200 mg/m ^{2} cytarabine QD over seven days, 3 received 500 mg/m ^{2} BID over three days and 3 received 1000 mg/m ^{2} BID over three days, each with identical doses of venetoclax (400 mg PO QD d1-14) and mitoxantrone (10 mg/m ^{2} IV QD d5-7). Of all 38 evaluable patients, 17 (44.7%) had adverse genetic risk according to ELN2022, and 1 (2.6%) had progressed from antecedent MDS. Median age was 56 years (range, 26-74 years). All patients experienced CTCAE grade $\geq$3 cytopenias. A median number of two non-hematologic grade 3 and 4 adverse events (AEs) in 32 patients with sufficient data were recorded. Grade 3 and 4 AEs occurring in $\geq$ 10% of patients included febrile neutropenia, pneumonia, sepsis and gastrointestinal disorders. The 30- and 60-day mortality was 2.6% and 5.2%. Remission assessment showed CR/CRi in 31/38 patients (81.6%). Among the seven patients with no CR/CRi, six showed refractory disease and one died in aplasia before response assessment. CR/CRi rate was 100% (8/8), 81,8% (9/11) and 70.6% (12/17) in patients with favorable, intermediate, and adverse risk, respectively. Utilizing LAIP-based DFN MRD approach, 7/32 (21.9%) evaluable patients were classified as MRD negative (CR/CRi $_{MRD-}$). In 7/25 (28%) CR/CRi $_{MRD+}$ patients, the MRD burden was below 0.1% CD45 $^+$ events. Of all 31 CR/CRi patients, 26 are in ongoing CR/CRi, 16 received allogeneic HCT as postremission treatment. Three patients died in CR from infectious complications after allogeneic HCT or post-remission treatment and two relapsed and succumbed to progressive disease. Six patients commenced maintenance treatment, of whom four are in ongoing remission.

Discussion

The combination of venetoclax with higher doses of cytarabine and mitoxantrone (HAM-Ven) is a well-tolerated and very efficacious treatment option leading to complete remissions in 81.6% of patients with r/r AML studied in the RELAX trial. Safety and efficacy compare favorably with published results from the FLAG-Ida-Ven regimen, thereby providing a less dose-intense, fludarabin-free approach for the treatment of fit r/r AML patients. Enrollment into the RELAX trial is currently ongoing. Updated results will be presented at the meeting.

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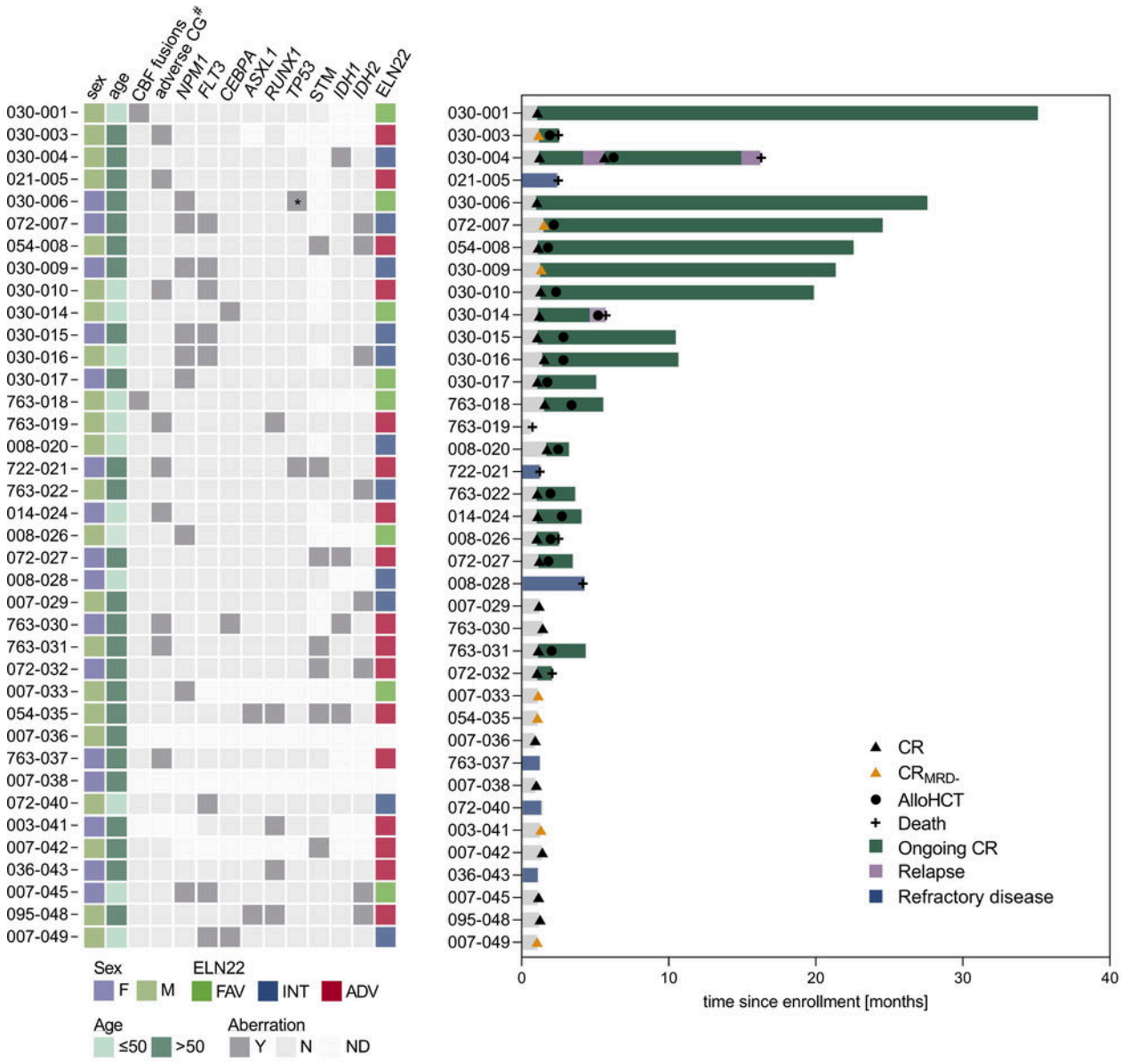

Figure 1. Clinical and molecular features and outcome in patients treated within the SAL RELAX trial.
Left panel, mutational landscape. Each row represents a patient, each column represents a gene/alteration; in addition, clinical features (left) and ELN22 risk classification (right) are shown. Right panel, swimmer plot displaying individual patient outcomes. ADV, ELN22 adverse risk; CBF, core binding factor; CR, complete remission; ELN22, European LeukemiaNet 2022 risk stratification; FAV, ELN22 favorable risk; INT, ELN22 intermediate risk; N, no/not detected; ND, no data/not assessed; STM, secondary-type mutations, i.e. mutations in *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*; Y, yes/present; # includes -7, t(3;3) and complex karyotype; * *TP53* VAF < 10%.

Figure 1

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