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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Cladribine with Low Dose Cytarabine and Venetoclax Alternated with Azacytidine and Venetoclax for Acute Myeloid Leukemia: Prognostic Analysis of a Phase 2 Clinical Trial

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Introduction: Hypomethylating agents (HMA) with Venetoclax (Ven) is the standard of care for patients (pts) with acute myeloid leukemia (AML) ≥ 75 yrs of age or not candidates to intensive treatment. Döhner, et al. (ASH 2022) demonstrated that the European LeukemiaNet (ELN) risk classifications do not accurately predict prognosis in HMA-Ven treated pts. A prognostic risk signature classification (PRSc) was proposed, stratifying pts by *RAS*, *FLT3* and *TP53* mutations alone. This classification has not been validated in low intensity treatments combining Ven with cladribine (CLAD) and cytarabine. Moreover, *RAS* mutations are common mechanisms of resistance to HMA-Ven, whilst it has been proposed that cytarabine and recently cladribine-based regimens could be effective in AML with this mutation. We report an update of pts treated with CLAD, low dose cytarabine (LDAC) and Ven, focusing on outcomes and risk group stratification.

Methods: This analysis included pts with newly diagnosed AML enrolled in a phase 2 clinical trial with CLAD-LDAC-Ven induction therapy followed by a consolidation phase that alternates courses of azacytidine and Ven with courses of CLAD-LDAC-Ven (NCT03586609). The PRSc allocated pts with [*K/N*]- *RAS* or *FLT3*-ITD mutations in the intermediate benefit group, pts with *TP53* in the lower benefit group, whereas pts with AML lacking these mutations were allocated in the higher benefit group. Cumulative incidence (CI) was calculated for pts achieving remission with death and relapse as competing events.

Results: From 11/2018 to 04/2023, 123 pts were treated on the CLAD-LDAC-Ven clinical trial. Median age was 68 yrs (range, 47-84) and 57% were male. 54% of pts had diploid cytogenetics and 16% had complex karyotype. Most frequent mutations were *DNMT3A* (32%), *NPM1* (24%), *TET2* (22%), *SRSF2* (20%) and *ASXL1* (19%). According to the ELN 2022 classification, 31 (25%), 22 (18%) and 69 (57%) were allocated in the favorable, intermediate and adverse risk categories, respectively. According to the PRSc, 81 (66%), 26 (21%) and 16 (13%) pts were allocated in the higher, intermediate and lower benefit group, respectively (Figure 1).

The overall response rate (ORR) was 85% (105/123), including 92 pts (75%) with complete remission (CR) rate and 13 (10%) having CR with incomplete hematologic recovery (CRi). Among pts achieving response, 78% (82/105) achieved MRD negativity by flow cytometry. According to ELN 2022 classification, ORR was 97%, 82% and 81% for favorable, intermediate, and adverse risk pts, respectively. According to the PRSc, the ORR was 89%, 85% and 69% for pts allocated in the higher, intermediate and lower benefit group. The median number of treatment courses received was 2 (1-18) and 94% of pts achieved best response after first cycle. After achieving remission, 48 (39%) pts underwent allogeneic stem cell transplantation (alloSCT).

The median OS and EFS were 50 months, and the 2-year cumulative incidence of relapse and death without relapse were 22% and 16%, respectively. The 1- and 2-year OS was 76% and 65%, respectively. According to the ELN 2022 classification, median OS was not reached, 39, and 25 months for favorable, intermediate and adverse risk groups (p=0.004, C-index=0.61). According to the PRSc, the median OS was 50, 25 and 15 months for the higher, intermediate and lower benefit group, respectively (p=0.36, C-index=0.56). Median EFS was 53, 15 and 19 months for ELN 2022 favorable, intermediate and adverse risk, respectively. According to the PRSc, the median EFS was 52, 25 and 17 months for months for the higher, intermediate and lower benefit group, respectively (Figure 2).

The 2-yr CI of relapse was 13%, 18% and 28% for pts of allocated in the ELN favorable, intermediate and adverse group, respectively. When using the PRSc classification, the 2-yr CI of relapse was 18%, 17% and 51% for the higher, intermediate and lower benefit group, respectively.

Conclusion: CLAD-LDAC-Ven combination offers an encouraging ORR with long term OS and EFS. In these pts, the ELN 2022 showed a better risk group discrimination regarding OS, compared to the PRSc. Pts of the intermediate-benefit of the PRSc (enriched in *RAS/FLT3* mutations) could benefit the most of CLAD-LDAC-Ven, in which an HMA-Ven approach is associated with a mOS of 12 months.

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Figure 1

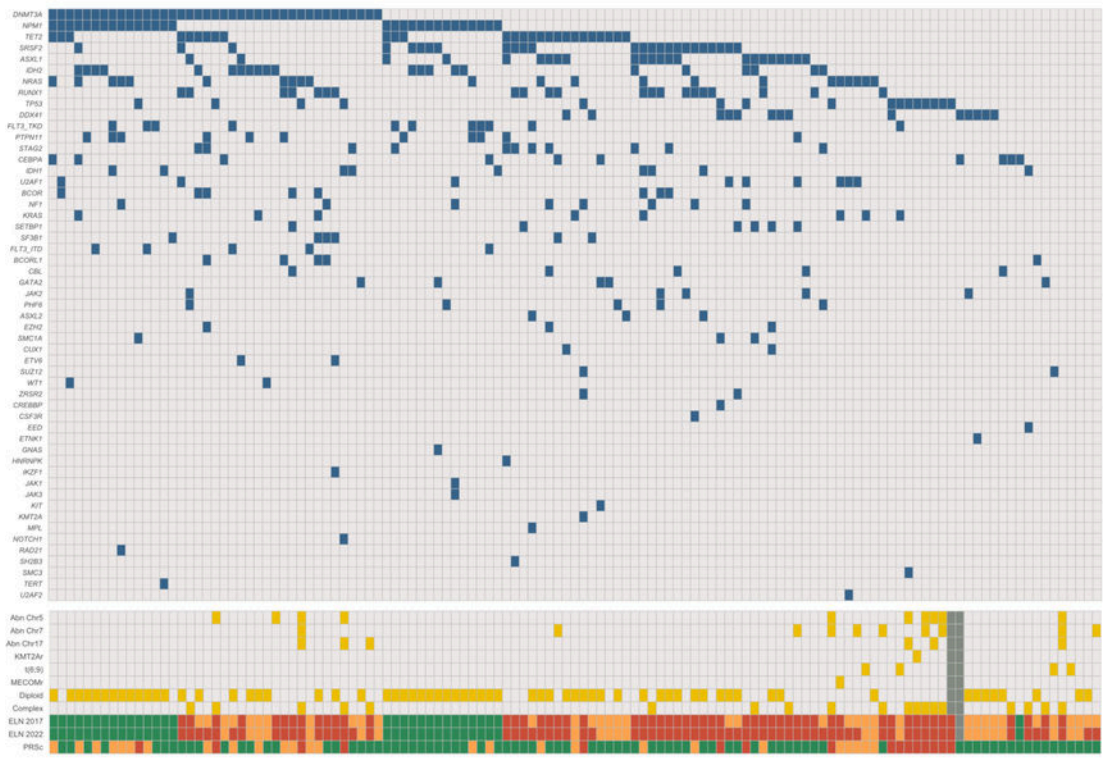

Figure 2

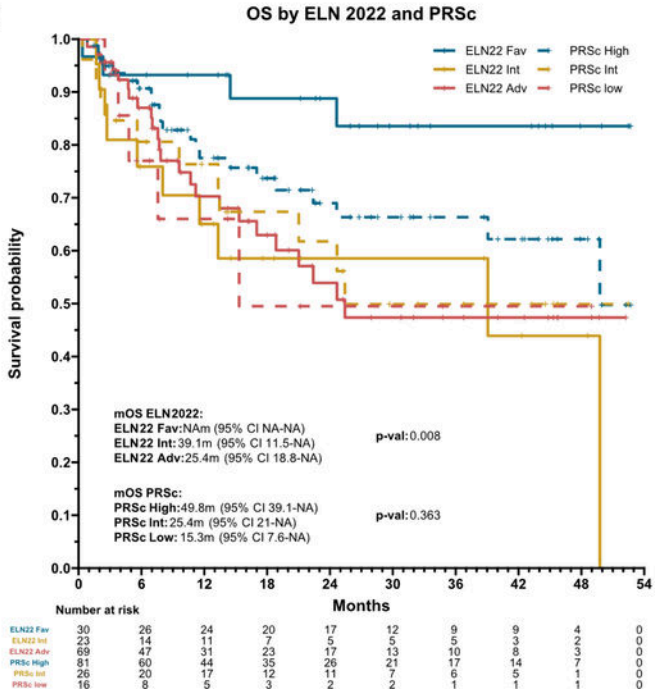

Figure 1

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