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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Survival and Prognosis Among 301 Patients with Newly-Diagnosed Acute Myeloid Leukemia Following Venetoclax Plus Hypomethylating Agent Therapy

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Background:
Venetoclax (Ven) in combination with hypomethylating agent (HMA) is the preferred treatment for elderly/unfit patients with newly-diagnosed acute myeloid leukemia (AML). Current prognostication for AML is based on European LeukemiaNet (ELN) genetic risk stratification which has limited applicability in patients treated with Ven-HMA (*Blood, 2022*). Accordingly, our primary objective was to determine predictors of treatment response and survival outcomes in treatment-naïve AML patients receiving Ven-HMA.

Methods:
Our study population was recruited from Mayo Clinic (MN, FL, AZ), after institutional review board approval and based on documentation of newly-diagnosed AML treated with Ven-HMA outside of clinical trials between November 2018 and April 2023. Cytogenetic and molecular studies were performed by conventional karyotype, and next-generation sequencing, respectively. Response was assessed according to the 2022 ELN criteria

Results:
Patient characteristics
A total of 301 newly-diagnosed AML patients (median age 73 years, 66% male, 62% *de novo*) received a median of 3 cycles (range 1-48) of azacitidine 75 mg/m2 days 1-7 (*n*=100) or decitabine 20 mg/m2 days 1-5 (*n*=201) with Ven. ELN 2022 cytogenetic risk included favorable (1%, *n*=4), intermediate (61%, *n*=184) or adverse (38%, *n*=113). Mutations involved *TP53* in 77/301 (25%), *ASXL1* in 54/279 (19%), *RUNX1* in 54/296 (18%), *NPM1* in 44/299 (15%), *DNMT3A* in 40/296 (13%), *K/NRAS* in 41/296 (14%), *IDH1* in 20/301 (6%), *IDH2* in 30/301 (10%), *FLT3-ITD* in 25/301 (8%) and *DDX41* in 9/247 (4%) of informative cases.
Predictors of response
Complete remission, with (CR) or without (CRi), count recovery, was documented in 182 (60%) patients, including CR in 36% and measurable residual disease (MRD) negative by flow cytometry in 77% of 105 informative cases that achieved CR/CRi. Median time to CR/CRi was 1.4 months. In univariate analysis, CR/CRi was more likely to occur in the presence of *NPM1* mutation, (86% vs. 56%; $p < .01$), *IDH2* mutation, (80% vs. 58%; $p = .02$), *DNMT3A* mutation, (78% vs. 57%; $p = .01$), or *DDX41*

mutation, (100% vs. 58%; p <.01), and in the absence of adverse karyotype, (71% vs. 42%; p < .01), *TP53* mutation, (67% vs. 40%; p <.01), *FLT3-ITD* mutation, (63% vs. 36%; p = .01), or *RUNX1* mutation, (64% vs. 44%; p = .01); in multivariable analysis, adverse karyotype, (p < .01), *FLT3-ITD* (p < .01), *RUNX1* (p < .01), *NPM1* (p = .03), *IDH2* (p = .04), and *DDX41*, (p = .01) mutations remained significant.

Predictors of survival

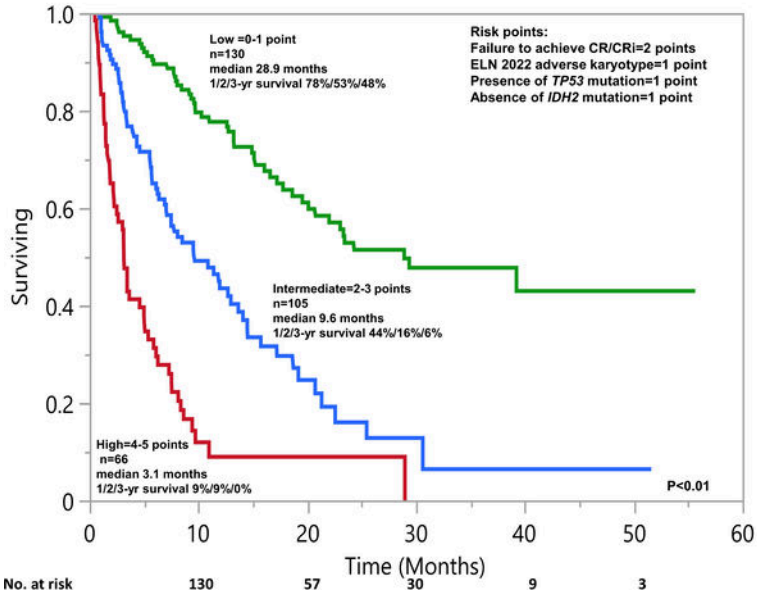
After a median follow-up of 8.5 months (range 0.5-56), 13.2 months for living patients, 174 (58%) deaths, 73 relapses (40% of those achieving CR/CRi), and 41 (14%; including 35 in CR/CRi) allogeneic hematopoietic stem cell tranplants (AHSCT) were documented. In univariate analysis of pre-treatment variables, thrombocytopenia < 100 x 10^9/l, (HR 1.5, 95% CI 1.03-2.2; p = .03), adverse karyotype, (HR 2.8, 95% CI 2.1-3.8; p < .01) *TP53* mutation, (HR 2.5, 95% CI 1.8-3.5; p < .01), or absence of *IDH2* mutation, (HR 3.5, 95% CI 1.7-7.6; p < .01) predicted inferior survival. Failure to achieve CR/CRi (HR 4.5, 95% CI 3.3-6.1; p < .01) was also associated with inferior survival and in multivariable analysis, failure to achieve CR/CRi, (HR 3.4, 95% CI 2.5-4.8; p< .01), presence of adverse karyotype, (HR 1.6, 95% CI 1.1-2.6; p = .02), *TP53* mutation, (HR 1.6, 95% CI 1.002-2.4; p = .04), and absence of *IDH2* mutation (HR 2.2, 95% CI 1.004-4.7; p = .04) were identified as risk factors for survival. Subsequent HR-weighted scoring resulted in three-tiered risk stratification: low (0-1 point; n= 130), intermediate (2-3 points; n= 105), and high (4-5 points; n= 66), with respective median survival (3-year rate) of 28.9 (48%), 9.6 (6%), and 3.1 (0%) months (p < .01) (Figure). AHSCT had an independent favorable impact on survival (HR 0.3, 95% CI 0.1-0.6; p < .01), most apparent in low (p =0.04), and intermediate (p <.01), as opposed to high (p = .06) risk.

Conclusions:

In the current single institutional series of Ven-HMA treated newly-diagnosed AML, response to Ven-HMA was the foremost predictor of survival. Additional risk factors for survival included adverse karyotype, presence of *TP53* and absence of *IDH2* mutations. These observations allowed for a three-tiered genetics-enhanced survival model with CR/CRi as a backbone, and also confirmed survival advantage from AHSCT, regardless of risk category.

Disclosures Alkhateeb: *Mayo Clinic:* Current Employment. **Begna:** *MEI Pharma:* Research Funding; *Immunogen:* Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Shah:** *Astellas:* Research Funding; *AbbVie:* Research Funding; *MRKR Therapeutics:* Research Funding; *Celgene:* Research Funding. **Patnaik:** *Epigenetix:* Research Funding; *Kura:* Research Funding; *CTI BioPharma:* Membership on an entity's Board of Directors or advisory committees; *StemLine:* Research Funding. **Murthy:** *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Senti Biosciences:* Membership on an entity's Board of Directors or advisory committees; *CRISPR Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Bavarian Nordic:* Membership on an entity's Board of Directors or advisory committees. **Foran:** *NCI:* Membership on an entity's Board of Directors or advisory committees; *Actinium:* Research Funding; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *CTI:* Membership on an entity's Board of Directors or advisory committees; *Kura:* Research Funding; *Sellas:* Research Funding; *Roivant:* Research Funding; *Novartis:* Research Funding; *Celgene:* Research Funding; *Astellas:* Research Funding; *BMS:* Membership on an entity's Board of Directors or advisory committees. **Palmer:** *Jubliant:* Consultancy; *morphosys:* Consultancy, Other: Money went to institution; *Sierra Oncology:* Consultancy, Other: Money went to Institution; *CTI BioPharma Corp.:* Consultancy, Honoraria, Other: Money went to institution; *Incyte:* Consultancy, Other: Money went to the institution. **Khera:** *Incyte:* Honoraria.

Figure 1. Survival of 301 AML patients receiving frontline Ven-HMA, stratified by HR-weighted scoring system, HR (95% CI), failure to achieve CR/CRi, 3.4 (2.5-4.8), presence of adverse karyotype, 1.6 (1.06-2.5), presence of *TP53* mutation, 1.54 (1.002-2.4), absence of *IDH2* mutation, 2.2 (1.004-4.7), allocating 2 adverse points for not achieving CR/CRi, one adverse point each for adverse karyotype, *TP53* mutation and absence of *IDH2* mutation. OS stratified by low risk (0-1 points), intermediate risk (2-3 points) and high risk (4-5 points) is shown.



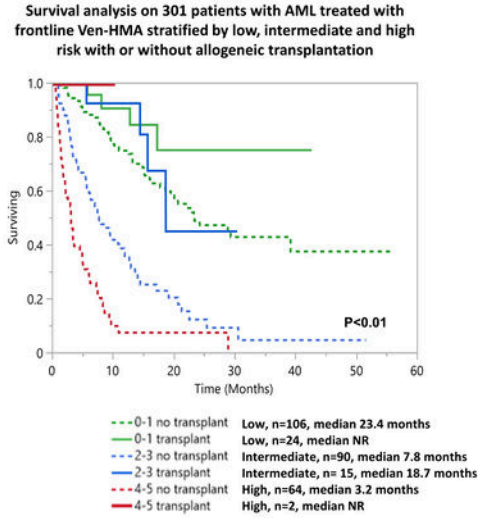


Figure 1

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