Prognostic Impact and Clinical Outcomes of *IDH1/IDH2* Mutations in Newly Diagnosed Acute Myeloid Leukemia Treated with Hypomethylating Agents and Venetoclax

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Introduction

- *IDH1* and *IDH2* (*IDH1/2*) mutations are identified in ~20% of patients diagnosed with acute myeloid leukemia (AML)[1,2].
- Studies show *IDH1* mutations are linked to poorer outcomes, while *IDH2* mutations are associated with better responses to both intensive chemotherapy and hypomethylating agent-venetoclax combinations (HMA-Ven)[3,4,5].
- *IDH1/2* mutations are often grouped together but their individual prognostic impact is controversial.

Objective

- Describe the clinical characteristics and outcomes of patients with newly diagnosed AML with *IDH1/2* mutations treated with HMA-Ven.

Methods

- **Design**: retrospective chart review
- **Population**: 173 patients age ≥ 18 years old with newly diagnosed AML who received HMA-Ven from 10/2017 to 2/2025 at The University of Kansas Cancer Center and Vanderbilt University Medical Center.
- **Primary outcome**: composite complete remission (CRc)
- **Secondary outcomes**: overall survival (OS), event-free survival (EFS)
- **Statistical analysis**: CRc rate was assessed using Fisher's exact test. Survival was assessed using Kaplan Meier method with Prism GraphPad v10.

Results

Table 1. Patient Baseline Clinical Characteristics

Characteristics (N=173)	*IDH1* (n=18)	*IDH2* (n=22)
Male, n (%)	14 (77.8)	19 (86.4)
Median age, years	70.9	71.1
Cytogenetics, n		
• "-5"	5	0
• "-7"	2	3
• "-17"	3	0
• KMT2A-rearranged	0	1
• Complex karyotype	4	2
• Monosomal karyotype	1	0
Co-mutations, n		
• *NPM1*	2	8
• *FLT3-ITD*	3	4
• *FLT3-TKD*	2	5
• *RAS*	2	3
• *TP53*	5	0
• Myelodysplasia-related	32	36

Figure 1. Baseline Hemoglobin

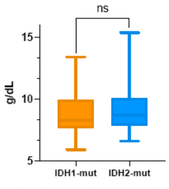


Figure 2. Baseline Platelets

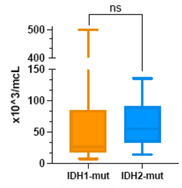


Figure 3. Baseline WBC

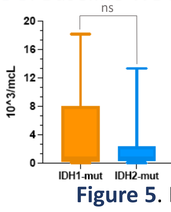


Figure 4. Baseline ANC

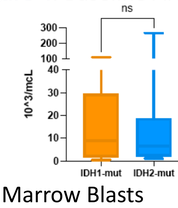
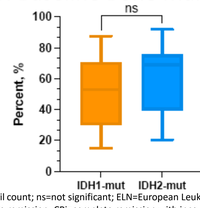


Figure 5. Baseline Bone Marrow Blasts



WBC=white blood cell count; ANC=absolute neutrophil count; ns=not significant; ELN=European LeukemiaNet; mPRS=modified patient risk score; IDH1-mut=*IDH1* mutated; IDH2-mut=*IDH2* mutated; CR=complete remission; CRi=complete remission with incomplete count recovery; CRh=complete remission with partial hematological recovery; PR=partial response; CR1=first complete remission; ASCT=allogeneic stem cell transplant.

Results

Figure 6. ELN'22 Risk Stratification

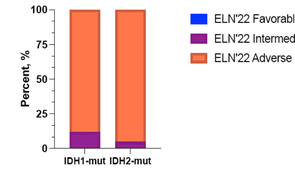


Figure 7. mPRS Risk Stratification

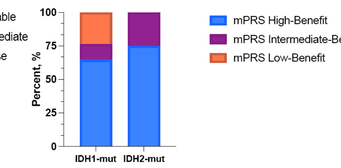


Figure 8. CRc Rate Achieved

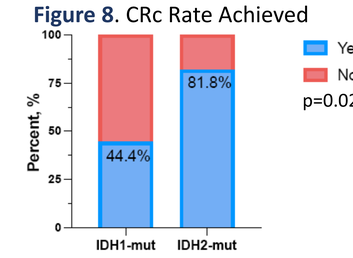


Table 2. Disease Response

Response (N=173)	*IDH1* (n=18)	*IDH2* (n=22)
• **CR, n (%)**	3 (16.7)	10 (45.5)
• **CRi, n (%)**	5 (27.8)	7 (31.8)
• **CRh, n (%)**	0	1 (4.5)
No response, n (%)	4 (22.2)	0
Non-evaluable, n (%)	6 (33.3)	4 (18.1)
Time to CRc, days	26	46.8
Time to progression, months	7.5	8
ASCT in CR1, n (%)	1 (5.6)	6 (27.3)

Figure 9. EFS

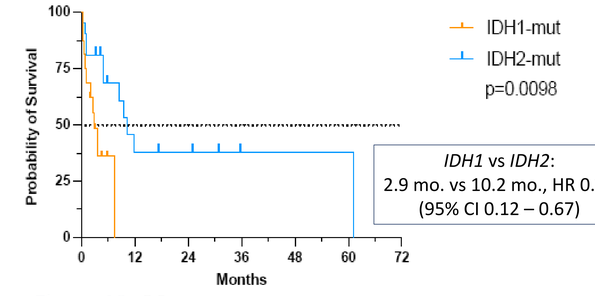
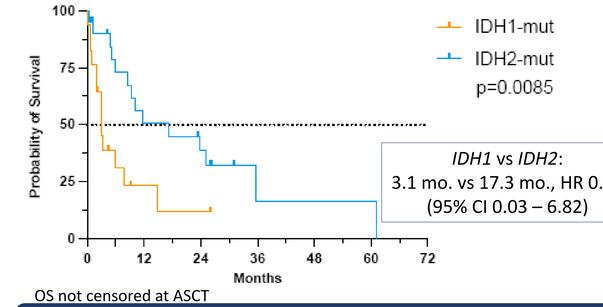


Figure 10. OS



OS not censored at ASCT

Discussion

- Patients with *IDH2* mutations experienced higher rates of CRc and longer EFS and OS compared to patients with *IDH1* mutations.
- Patients with *IDH1/2* mutations presented with numerically different baseline blood counts. While not statistically significant, this result in addition to disease response and survival adds to the evidence that *IDH1* and *IDH2* mutations are clinically distinct.
- Limitations of this study include the retrospective nature, small patient size, and unequal group sizes.
- Our findings support individual characterization of *IDH1/2* mutations due to their significantly different prognostic and clinical implications.
- Future studies for emerging therapies should emphasize the differences in treatment response and survival outcomes between *IDH1* and *IDH2* mutations.

References

1. Issa GC, DiNardo CD. Blood Cancer J. 2021 Jun 3;11(6):107. 2. Byun JM, et al. Blood Res. 2022 Mar 31;57(1):13-19. 3. Pratz KW, et al. Am J Hematol. 2024 Apr;99(4):615-624. 4. Chou W. C., et al. Leukemia. 25, 246–253 (2011). 5. Boissel N., et al. J. Clin. Oncol. 28, 3717–3723 (2010).