4:05–4:45 PM

Fellows Session

MODERATOR

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THE 2nd ANNUAL HemOnc Pulse LIVE AUSTIN 2025

Phase I/II Combination Study of Azacitidine and Venetoclax Post Hypomethylating Agent Failure in High-Risk MDS and CMML

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Presenter

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Background

- Approximately half of MDS patients present with high-risk disease with a median overall survival (OS) of less than a year with best supportive care.
- Only Azacitidine has been shown to result in a survival advantage when compared to conventional care regimens in HR-MDS (24.5 months vs. 15 months). (1)
- Prognosis post HMA failure is extremely poor, with a median survival of 5.6 months post Azacitidine failure.(2)

1- Fenaux et al. Lancet Oncol. (2009)
2- Prebet et al J Clin Oncol. (2011)

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Background

- Therapies beyond hypomethylating agents (HMA) are needed in high-risk myelodysplastic syndromes (HR-MDS) (IPSS ≥1.5).
- Venetoclax is an orally bioavailable B-cell leukemia/lymphoma 2 protein (BCL-2) inhibitor that induces cellular apoptosis.
- It has been shown to possess synergistic activity with HMA in unfit patients with acute myeloid leukemia (AML) and HMA-naive patients with HR-MDS.[1,2]

1. Bazinet et al. *Lancet Haematol*. 2022;9(10):e756-e765.
2. Zeidan et al. *Ann Hematol*. 2023;102(4):749-754.

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Aim

- We aimed to evaluate the safety, tolerability, and activity of azacitidine combined with venetoclax for HMA-pretreated and relapsed or refractory HR-MDS and chronic myelomonocytic leukemia (CMML).

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Methods

- September 2020 to January 2024
- Single-center, phase I/II trial at MD Anderson Cancer Center
- 33 patients (≥18 years) post HMA failure (≥ four cycles of HMA therapy with failure to attain response or progression/relapse at any time after HMA therapy) with >5% bone marrow blasts with HR-MDS (n=32) or CMML (n=1)
- No prior BCL-2 inhibitor therapy exposure

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- **Treatment:** Azacitidine (IV/subcutaneous) (75 mg/m^2) for 5 days + venetoclax (dose range,100-400 mg) for 14 days of each 28-day cycle

- Primary outcome:

1- Safety and tolerability (phase I)

2- Overall response rate (ORR) (phase II)

- Descriptive statistics were used for demographic variables.
- Kaplan-Meier curve with log-rank test was used for overall survival (OS), calculated from the time of presentation.

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Baseline Patient Characteristics

N (%)/Median (range)		Full Cohort (n=33)
Age		77 [55-84]
Male		20 (60)
Ethnic Origin:		
-	**White**	26 (79)
-	**Black**	3 (9)
-	**Asian**	3 (9)
-	**Hispanic**	1 (3)
Hemoglobin (g/dl)		7.8 [6.4-11.6]
Absolute Neutrophil Count (× 109 cells per L)		1.2 [0.09-10.7]
Platelet Count (× 10^9 cells per L)		29 [3-576]
Peripheral Blood Blast %		1 [0-18]
Transfusion Dependent		30 (91)
WHO 2016 Classification:		
-	**MDS with excess blasts 1**	16 (48)
-	**MDS with excess blasts 2**	14 (42)
IPSS		
-	**Very Good – Good**	9 (28)
-	**Intermediate**	12 (36)
-	**Poor – Very Poor**	12 (36)
Complex Cytogenetics		8 (24)
Therapy Related MDS/CMML		6 (18)
***Tp53* mutated**		10 (30)
Prior lines of treatment		2 (1-3)

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Results: Phase I: Safety , Tolerability, and Dose Finding

Phase 1 (n=12)	Venetoclax Dose	Grade 3-4 Adverse Events (AE)
Dose 0 (n=3)	100 mg	Anemia (14%), Thrombocytopenia (17%), Neutropenia (26%)
Dose 1 (n=3)	200 mg	Neutropenia (40%)
Dose 2 (n=6)	400 mg	Thrombocytopenia (23%), Neutropenia (18%)

- No Dose-Limiting Toxicity (DLT)
- Maximum Tolerated Dose: 400 mg
- R2PD: 400 mg

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Response Assessment

	Full Cohort (n=33)
Overall Response Rate (ORR) Entire Cohort	49% (95% CI, 31.4%-65.5%)
ORR phase I (n=12)	58% (95% CI, 30.6%-86%)
ORR phase II (n=21)	43% (95% CI, 21.7%-64%)
Complete Remission (CR)	3% (95% CI, 0%-9%)
Marrow CR (IWG 2006) - **Marrow CR + Hematologic Improvement** - **Marrow CR Alone**	 24% (95% CI, 9.7%-38.8%) 21% (95% CI, 7.3%-35.2%)
Cycles to First Response	1 (1-4)
4 - Weeks Early Mortality	9% (95% CI, 0%-18.7%)
8 - Weeks Mortality	9% (95% CI, 0%-18.7%)

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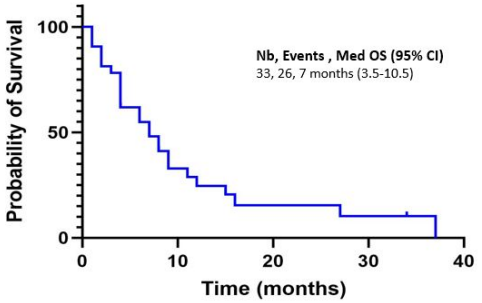
Results: Phase II: Dose Expansion

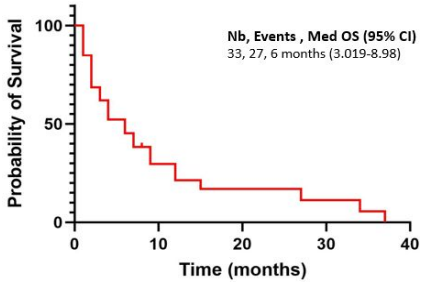
Treatment-Emergent Adverse Events (AEs) (n=21):

	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Any treatment-emergent side effect	410 (68)	123 (20)	63 (10)	4 (2)
Anemia	1	3 (3)	4 (6)	0
Thrombocytopenia	6 (1)	5 (4)	12 (19)	0
Neutropenia	9 (2)	16 (13)	19 (30)	0
N and V	23 (16)	2 (2)	0	0
Disturbed LFTs	18 (4)	6 (5)	0	0
Fatigue	5 (1)	4 (3)	0	0
Pneumonia	0	5 (4)	0	3 (75)
Cellulitis	0	0	0	0
Diverticulitis	0	0	1 (2)	0
Febrile Neutropenia	0	6 (5)	0	0
Pulmonary Edema	1	1(1)	0	0
Respiratory Failure	0	1(1)	3 (5)	1 (25)

Overall Survival HR-MDS and CMML



Progression Free survival (PFS) HR-MDS and CMML



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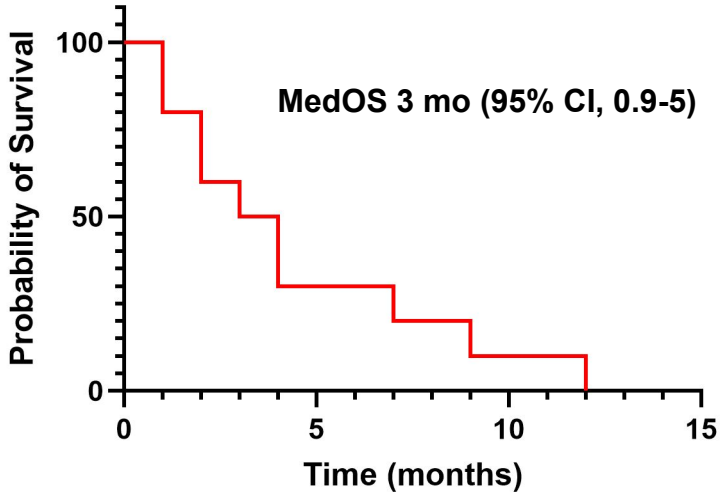
Tp53 Mutation Predicts Worse Outcomes

- 10 of 33 patients had a *Tp53* mutation (30%)
- 50% had a biallelic mutation
- Median variant allele frequency (VAF): 5% (range, 2-10)
- 70% had complex cancer germline (CG)



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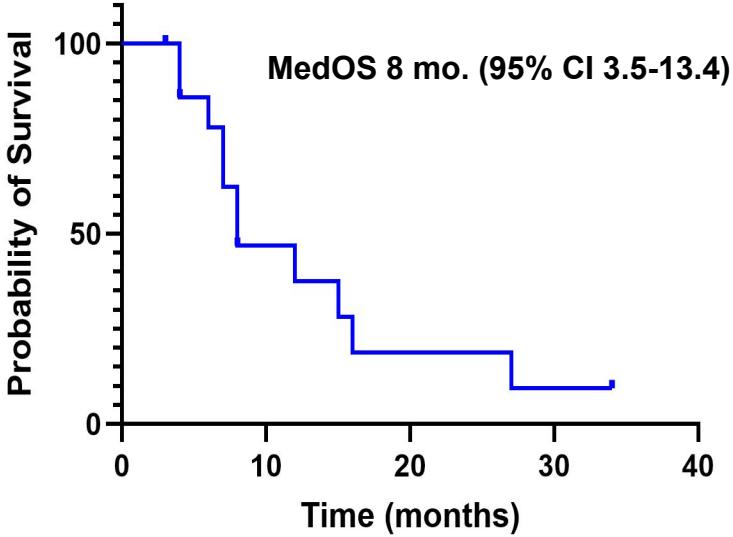
ASXL1 Mutation Outcomes Are Comparable to the Entire Population

-Given the association between *ASXL1* mutations and increased sensitivity to venetoclax.[3]

- 15 patients (45%) in our population had an *ASXL1* mutation.



3. Gangat et al. *Haematologica*. 2022;107(10):2501-2505.

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Conclusions

- Although adding venetoclax to azacitidine appears to be a feasible approach for patients with HR-MDS and CMML for whom prior therapy with an HMA has failed, this combination does not seem to improve patient outcomes.

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THANK YOU

PANEL DISCUSSION

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Q & A

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