MOLECULAR CHARACTERIZATION OF CLINICAL RESPONSE IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA AND HIGH-RISK MYELODYSPLASTIC SYNDROME PATIENTS TREATED WITH SINGLE AGENT EMAVUSERTIB

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INTRODUCTION

- Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are myeloid malignancies that exhibit a dynamic mutational landscape as the disease progresses.
- Genetic mutations in splicing factors *SF3B1* and *U2AF1* drive overexpression of a highly active long isoform of interleukin-1 receptor-associated kinase 4 (IRAK4), which is critical in triggering inflammation, oncogenesis, and survival of cancer cells.[1, 2]
- Emavusertib dual targeting of IRAK4 and FLT3 (ITD and TKD) confers a potential efficacy advantage.
- As of October 12, 2022, the ongoing TakeAim Leukemia trial (NCT04278768) has 71 patients treated with emavusertib monotherapy. The safety profile remains well tolerated without significant cumulative side effects.

AIM

Sub-analysis of the monotherapy cohort (45 AML and 26 high-risk MDS [HR-MDS]) aims to:

- Investigate the mutational landscape at baseline and on-treatment
- Assess the association of targeted biomarkers and gene expression signatures with clinical activity

METHOD

- Bone marrow and peripheral blood of enrolled patients were collected at the baseline and on treatment.
- Targeted next generation sequencing (NGS) and RNA sequencing were performed on bone marrow (BMMC) or peripheral blood mononuclear cells (PBMC).
- Mutations were also documented based on patients' molecular pathology reports provided by trial sites.

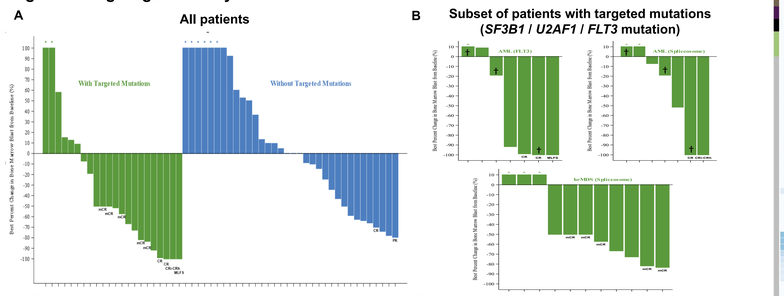
RESULTS

Table 1: Patient demographics

		All patients (n=71)	AML/MDS Subsets[2]		
			AML Spliceosome[1] (n=12)	MDS Spliceosome (n=12)	AML FLT3[1] (n=8)
Female n (%) : Male n (%)		21 (29.6) : 50 (70.4)	1 (8.3) : 11 (91.7)	5 (41.7) : 7 (58.3)	3 (37.5) : 5 (62.5)
Age (yrs): median (range)		74 (32, 87)	71 (60, 84)	75 (61, 80)	78 (61, 87)
Race n (%)	Asian	1 (1.4)	0 (0)	1 (8.3)	0 (0)
	Black or African American	2 (2.8)	0 (0)	0 (0)	0 (0)
	White	61 (85.9)	11 (91.7)	9 (75)	8 (100)
	Others	7 (9.9)	1 (8.3)	2 (16.7)	0 (0)
Median platelets (10^3/mm^3) (range)		26 (1, 275)	22 (1, 80)	11 (1, 146)	22 (1, 38)
Median ANC (10^3/mm^3) (range)		0.56 (0, 14.75)	0.3 (0, 3.3)	1.33 (0.15, 11.02)	0.13 (0, 0.88)
Median lines of prior therapy (range)		2 (1, 6)	2.5 (1, 5)	2 (1, 4)	2.5 (1, 5)

1. Three AML patients have both a spliceosome (*U2AF1* or *SF3B1*) and *FLT3* mutation and are included in both populations.
2. There are 29 total patients with spliceosome or *FLT3* mutation, of which 24 are response evaluable subjects, 27 have received prior HMAs.

Figure 1: Single-agent activity in R/R AML and HR-MDS



Response evaluable patients with baseline and post-treatment bone marrow blast counts are included. Responses assessed by the investigators were shown above.
* indicates the graphic cutoff as 100%

Two additional AML patients with spliceosome mutation had no post-treatment bone marrow blast count but reported progressive disease and were also considered as response evaluable.
* indicates the graphic cutoff as 10%
† indicates three AML patients with both a spliceosome and *FLT3* mutation that are included in both populations

Table 2: Characteristics of sequenced samples

A

Targeted DNA sequencing		
Total patient samples (n)		106
Total patients (n)		33
Female n (%) : Male n (%)		12 (36%) : 21 (64%)
Age (yrs): median (range)		74 (32 - 87)
Diagnosis	AML	19
	HR-MDS	14
Cell type	BMMC	37
	PBMC	69

B

RNA sequencing		
Total patient samples (n)		32
Total patients (n)		20
Female n (%) : Male n (%)		7 (35%) ; 13 (65%)
Age (yrs): median (range)		74.5 (32 – 87)
Diagnosis	AML	13
	HR-MDS	7
Cell type	BMMC	0
	PBMC	32

Figure 2: Mutational landscape before and during emavusertib monotherapy

24 subjects (15 AML and 9 HR-MDS) with pre- and on-treatment samples were included in the bar plot. NGS results from two platforms were used (10 subjects used 68-gene heme panel [3], and 14 subjects used 648-gene panel [4,5]).

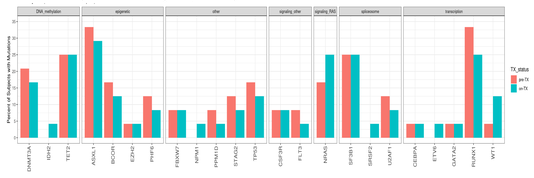


Figure 3: The mutational landscape demonstrated AML and MDS genetically heterogeneous diseases

648-gene NGS panel of 17 subjects with pre- and on-treatment samples were included in the heat map. Genes that are mutated in two or more samples were plotted.

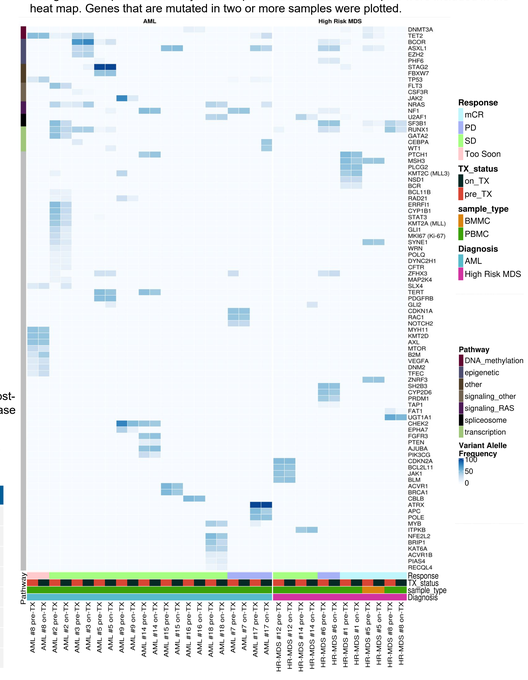


Figure 4: Emavusertib monotherapy may induce molecular responses and exhibit disease modifying activity

Genetic mutations including FLT3-TKD were reported based on NGS results; FLT3-ITD mutation was reported based on qPCR results. Targeted mutations (*i.e., SF3B1*, *U2AF1*, and *FLT3*) are highlighted in red. Subjects with pre- and post-treatment sequencing results were shown. (**A-E**) Responders with targeted mutation(s) (**F**) Responder without targeted mutation. (**G-H**) Non-responders with targeted mutation(s). (**I**) FLT3-ITD mutation at different time points.

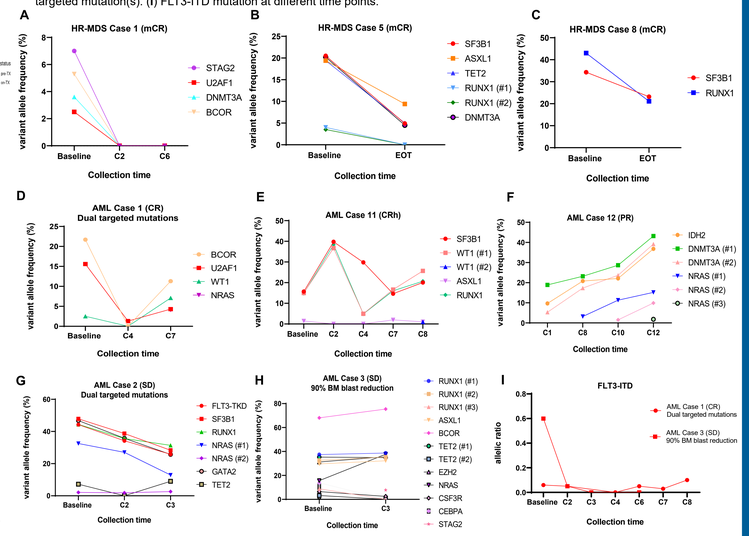
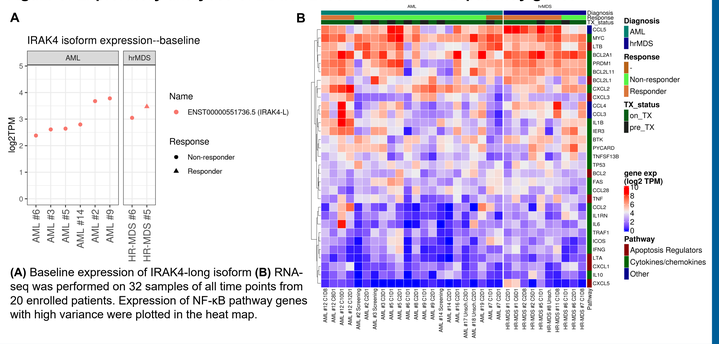


Figure 5: Exploratory analyses of IRAK4-L isoform and NF-κB pathway genes



(A) Baseline expression of IRAK4-long isoform **(B)** RNA-seq was performed on 32 samples of all time points from 20 enrolled patients. Expression of NF-κB pathway genes with high variance were plotted in the heat map.

CONCLUSIONS

- Emavusertib monotherapy demonstrated anti-cancer activity in R/R AML and HR-MDS patients, especially in those with *FLT3*, *U2AF1*, or *SF3B1* mutations.
- The preliminary NGS data is suggestive of molecular responses and disease-modifying activity of emavusertib.
- Patients with targeted mutations responded to emavusertib, even in the presence of co-mutations (e.g., *ASXL1*, *RUNX1*) that are typically associated with poor prognosis.
- We will continue to explore potential genomic biomarkers of emavusertib sensitivity and resistance.

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