Preliminary Efficacy and Molecular Characterization of Relapsed/ Refractory Acute Myeloid Leukemia Patients With *FLT3* Mutation with single agent Emavusertib (CA-4948)

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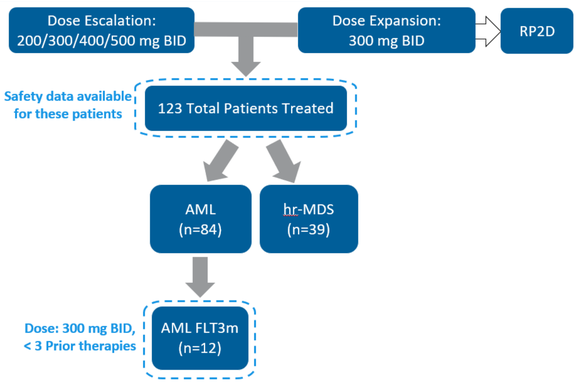
INTRODUCTION

- Acute myeloid leukemia (AML) is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses.
- Patients with relapsed/refractory (R/R) AML who have failed standard therapies, including venetoclax (VEN), hypomethylating agents (HMA), and/or FLT3 inhibitors (FLT3i) have limited therapeutic options. These patients often acquire molecular mutations leading to therapy resistance and dismal overall survival.[1,2]
- In R/R AML patients with FLT3 mutations (FLT3m), these changes can also include mechanisms of adaptive resistance through compensatory activation of innate immune stress pathways via IRAK4.[3]
- Emavusertib is a potent oral inhibitor of IRAK4, FLT3 (ITD and TKD), and CLK (1, 2, and 4), conferring preclinical efficacy advantages when compared with other IRAK4 or FLT3 inhibitors. Treatment with emavusertib inhibits the NF-kB and MAPK pathways, thus offering a potential mechanism to address known pathways of resistance to BCL2 and FLT3 inhibitors.[4,5]
- As of 26 February 2024, the ongoing TakeAim Leukemia trial (NCT04278768) has 123 patients (12 with *FLT3m,* 300mg BID with < 3 prior lines of therapy) treated with emavusertib monotherapy.
- We present preliminary efficacy and molecular characterization of emavusertib in R/R AML patients with *FLT3m*.

METHOD

- The safety, clinical activity, and potential biomarkers of emavusertib in relapsed/refractory (R/R) AML and higher-risk myelodysplastic syndrome (hr-MDS, IPSS-R score> 3.5) are being investigated.
- Mutational profiles of patients were documented based on local testing results. Bone marrow and peripheral blood of enrolled patients were collected at the baseline and on treatment.

STUDY POPULATION



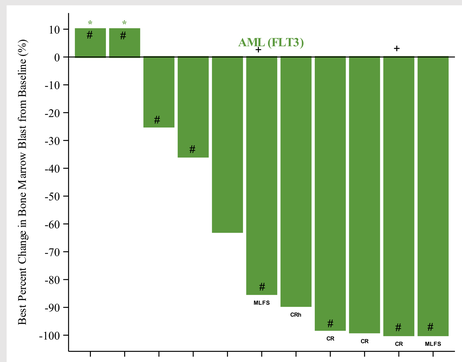
RESULTS

Baseline Characteristics

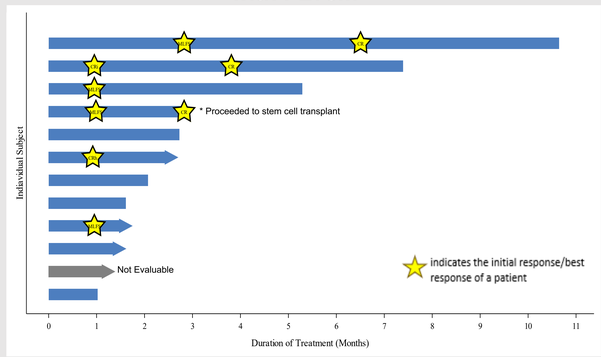
		AML – *FLT3m* (n = 12)
Male n (%) : Female n (%)		6 (50) : 6 (50)
Age (yrs): median (range)		74 (44, 83)
Race n (%)	Asian	0
	Black or African American	0
	White	10 (83.3)
	Others	0
	Not reported	2 (16.7)
Median bone marrow blast (%) (range)		33 (18, 98)

Single-agent activity in R/R AML

A AML patients with *FLT3m*



B Duration of treatment in R/R AML patients with *FLT3m*



* indicates the best percentage change from baseline >10%
\# prior venetoclax exposure
\+ indicates 2 AML patients having both a spliceosome and *FLT3* mutation.
- Among 12 treated AML *FLT3m* patients, one was on-going with treatment and not included in the figure A due to not reaching first response assessment yet.

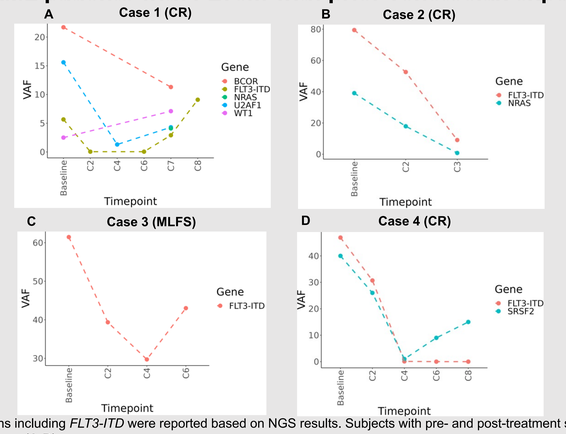
Median time to first response was 29 days

Treatment-related adverse events (TRAEs) Grade ≥ 3 in all TakeAim Leukemia trial patients

Grade 3+ Treatment-Related Adverse Event reported in > 1 patients, n (%)	200 mg BID (N = 27)	300 mg BID (N = 78)	400 mg BID (N = 15)	500 mg BID (N = 3)	Total (N=123)
# of patients having grade 3+ TRAEs	4 (14.8)	21 (26.9)	7 (46.7)	2 (66.7)	34 (27.6)
# of patients having non-hematological grade 3+ TRAEs	3 (11.1)	17 (21.8)	6 (40)	2 (66.7)	28 (22.8)
Blood creatine phosphokinase increased	0	6 (7.7)	0	0	6 (4.9)
Platelet count decreased	1 (3.7)	3 (3.8)	2 (13.3)	0	6 (4.9)
Rhabdomyolysis*	0	2 (2.6)	1 (6.7)	1 (33.3)	4 (3.3)
Anemia	0	3 (3.8)	0	0	3 (2.4)
Aspartate aminotransferase increased	1 (3.7)	2 (2.6)	0	0	3 (2.4)
Alanine aminotransferase increased	2 (7.4)	0	0	0	2 (1.6)
Dizziness	1 (3.7)	1 (1.3)	0	0	2 (1.6)
Febrile neutropenia	0	2 (2.6)	0	0	2 (1.6)
Lipase increased	0	2 (2.6)	0	0	2 (1.6)
Neutropenia	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Neutrophil count decreased	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Syncope	0	1 (1.3)	0	1 (33.3)	2 (1.6)

Note: After discussion with regulatory authorities of investigator-reported AEs, objective laboratory criteria for the determination of rhabdomyolysis were adopted from existing approved drug labels (CPK >10 x ULN and SCr ≥ 1.5 x ULN). Previously, reported events of rhabdomyolysis were determined by subjective criteria. **Using the objective criteria, rhabdomyolysis was reported in 1/123 patients.**

Emavusertib monotherapy exhibits disease modifying activity in R/R AML patients with *FLT3m* with prior venetoclax exposure



Genetic mutations including *FLT3-ITD* were reported based on NGS results. Subjects with pre- and post-treatment sequencing results were shown. **(A-D)**

Clinical activity in responders with R/R AML - *FLT3m*

#	Age	Sex	ELN risk per 2017	FLT3 mutation	# prior therapy	Prior BCL2i	Prior HMA	Prior FLT3i	Best response	Co-mutations At Baseline
1	80	M	Intermediate	ITD	1	Y	Y	N	CR	*U2AF1, BCOR,WT1*
2	44	M	Adverse	ITD	2	Y	N	Y	CR	*NRAS, WT1*
3	74	M	Adverse	Not available	2	Y	Y	N	MLFS	*SF3B1,GATA2, PHF6, RUNX1, CBLC*
4	78	F	Adverse	ITD	2	Y	Y	Y	MLFS	Not available
5	79	F	Intermediate	ITD	2	N	Y	N	CR	*DMNT3A, SRSF2*
6	74	M	Intermediate	ITD	1	N	Y	Y	CRh	Not available

CONCLUSIONS

- Emavusertib has an acceptable and manageable safety profile in R/R AML and hr-MDS patients.
- The mutation profiles of responders indicate that emavusertib may be able to target diverse underlying genetic mechanisms of resistance to VEN, HMA, or FLT3i regimens. This is suggestive of emavusertib's disease-modifying activity.
- Emavusertib monotherapy has demonstrated anti-leukemic activity in patients with *FLT3m*, including patients who have progressed on VEN, HMA and/or FLT3i regimens.
- Enrollment in this trial is continuing at the RP2D dose of 300 mg BID (phase 2 expansion cohort) in patients (*SFm* and *FLT3m*) with < 3 prior lines of therapy.

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