Preliminary Safety, Efficacy and Molecular Characterization of Emavusertib (CA-4948) In Relapsed/ Refractory Acute Myeloid Leukemia Patients With *FLT3* Mutation

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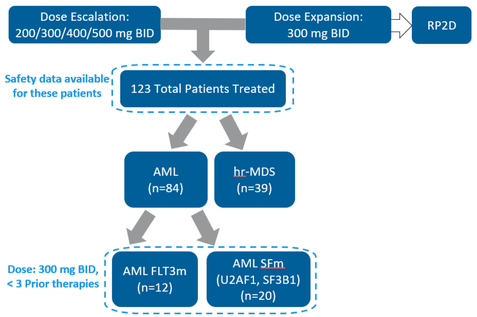
INTRODUCTION

- Acute myeloid leukemia (AML) is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses.
- Internal tandem duplication (ITD) of *FLT3* mutation (*FLT3m*) is considered an acquired late-event mutation and is associated with a poor prognosis in AML.[1] Genetic mutations in splicing factors (*SFm*) *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.[2,3]
- Emavusertib is a potent oral inhibitor of IRAK4, FLT3 (ITD and TKD - Tyrosine kinase domain), and CLK (1, 2, and 4), conferring preclinical efficacy advantages when compared with other IRAK4 or FLT3 inhibitors. In R/R AML patients with *FLT3m*, dual inhibition of IRAK4 and FLT3 by emavusertib can target mechanisms of adaptive resistance through compensatory activation of innate immune stress pathway.[4] 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.[2,3,4,5]
- As of 26 February 2024, the ongoing TakeAim Leukemia trial (NCT04278768) has 123 patients (12 with *FLT3m and* 20 with *SFm*, 300mg BID with < 3 prior lines of therapy) treated with emavusertib monotherapy.

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.
- We present preliminary efficacy of emavusertib in R/R AML patients with *FLT3m* and/or *SFm* (*U2AF1* and *SF3B1*) including molecular disease characterization.
- 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



Note: Two AML patients have both a spliceosome and *FLT3* mutation.

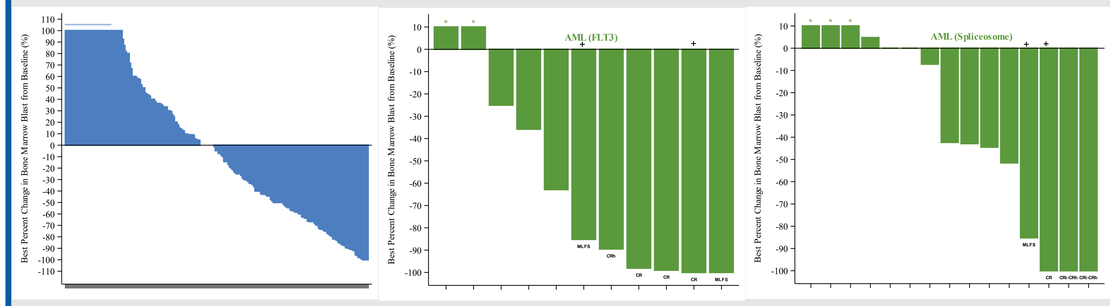
RESULTS

Baseline Characteristics

		AML – *FLT3m* (n = 12)	AML – *SFm* (n = 20)
Male n (%) : Female n (%)		6 (50) : 6 (50)	13 (65) : 7 (35)
Age (yrs): median (range)		74 (44, 83)	74.5 (44, 85)
Race n (%)	Asian	0	0
	Black or African American	0	1 (5)
	White	10 (83.3)	17 (85)
	Others	0	0
	Not reported	2 (16.7)	2 (10)
Median bone marrow blast (%) (range)		33 (18, 98)	27 (5, 56)
Median lines of prior therapy (range)		2 (1, 2)	2 (1, 2)

Single-agent activity in R/R AML

A All patients | **B AML patients with *FLT3m*** | **C AML patients with *SFm***

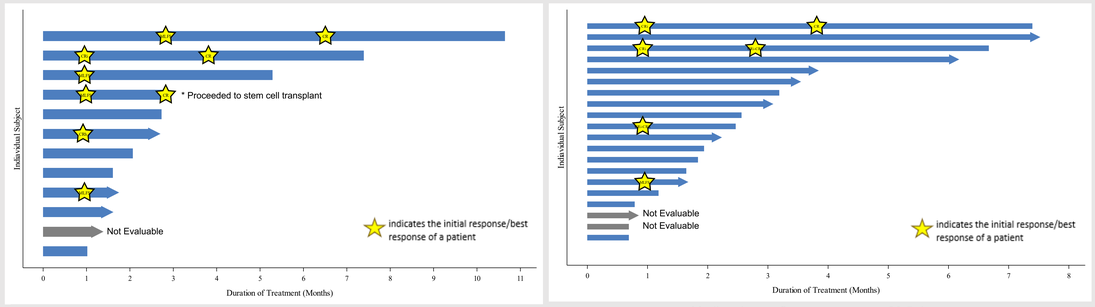


Includes all patients that had baseline and post-treatment bone marrow blast assessments.
* Indicates best percentage change from baseline >100%.

* indicates the best percentage change from baseline >10%
+ 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 B due to not reaching first response assessment yet.
- Among 20 treated AML *SFm* patients, 5 were not included in figure C: Two patients were still undergoing treatment and pending for post-baseline marrow blast data. Three patients discontinued early due to adverse event (1 patient) and disease progression (2 patients) without post-baseline marrow blast assessment.

Duration of treatment in R/R AML patients with targeted mutations

A AML patients with *FLT3m* | **B AML patients with *SFm***



Median time to first response was 29 days

Median time to first response was 28.5 days

Treatment-related adverse events (TRAEs) Grade ≥ 3 in all 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.**

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

Patient #	Age	Sex	ELN risk	# prior therapy	Prior FLT3i	Best response	Co-mutations At Baseline
1	80	M	Intermediate	1	N	CR	*U2AF1, BCOR,WT1*
2	44	M	Adverse	2	Y	CR	*NRAS, WT1*
3	74	M	Adverse	2	N	MLFS	*SF3B1,GATA2, PHF6, RUNX1, CBLC*
4	78	F	Adverse	2	Y	MLFS	Not available
5	79	F	Intermediate	2	N	CR	*DMNT3A, SRSF2*
6	74	M	Intermediate	1	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 prior FLT3i regimens. This is suggestive of the disease-modifying activity of emavusertib.
- Emavusertib has demonstrated anti-leukemic activity in patients with *SFm* and *FLT3m*, including patients who have progressed on 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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