Preliminary Safety And Efficacy Of Emavusertib (CA-4948) In Acute Myeloid Leukemia Patients With *FLT3* Mutation

Eric S. Winer, MD[1], Amit Verma M.B.B.S[2], Stefanie Groepper, MD[3], Katharina S. Götze, MD[4], Yasmin Abaza, MD[5], Christoph Schliemann, MD[6], Gaurav S. Choudhary, PhD[7], Wanying Zhao, PhD[7], Cole Gallagher, BSc[7], Reinhard von Roemeling, MD[7], Daniel J. DeAngelo, MD[1]

1. Dana-Farber Cancer Institute, Boston, MA; 2. Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; 3. Marien Hospital / Univ. of Düsseldorf, Düsseldorf, Germany; 4. Technical University of Munich School of Medicine, Munich, Germany; 5. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; 6. University Hospital Münster, Department of Medicine A, Germany; 7. Curis Inc., Lexington, MA

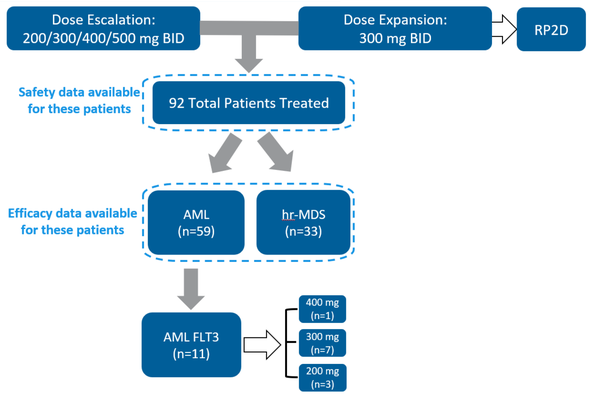
INTRODUCTION

- Acute myeloid leukemia (AML) is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses.
- Internal tandem duplication (ITD) of *FLT3* is considered an acquired late-event mutation and is associated with a poor prognosis in AML.
- Emavusertib dual targeting of IRAK4 and *FLT3* (ITD and TKD) confers potential efficacy advantages compared to other IRAK4 and *FLT3* inhibitors.
- IRAK4 is upregulated during anti-*FLT3* or other cytotoxic therapies, which could drive a resistance pathway of early relapse and progression.[1,2,3]
- As of June 12, 2023, the ongoing TakeAim Leukemia trial (NCT04278768) has 92 patients (11 with *FLT3* mutation) 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) are being investigated. The dosing was escalated in 3+3 fashion and followed by dose expansion.
- Here we present preliminary safety and efficacy data in the subset of enrolled AML patients who carried *FLT3* mutation (*FLT3m*) at enrollment and were treated with emavusertib monotherapy.
- 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.
- Mutations were also documented based on patients' molecular pathology reports provided by trial sites.

STUDY POPULATION



RESULTS

Baseline Characteristics

		All patients (AML and hr-MDS) (n=92)	AML – *FLT3* (n=11)
Female n (%) : Male n (%)		30 (32.6) : 62 (67.4)	5 (45.5) : 6 (54.5)
Age (yrs): median (range)		74 (32, 88)	78 (61, 87)
Race n (%)	Asian	2 (2.2)	0
	Black or African American	2 (2.2)	0
	White	80 (87)	11 (100)
	Others	3 (3.3)	0
	Not reported	5 (5.4)	0
Median platelets (10^3/mm^3) (range)		25.5 (1, 275)	21 (1, 38)
Median bone marrow blast (%) (range)		33.5 (4, 98) (AML) 10.0 (2, 19) (hr-MDS)	50 (4, 98)
Median lines of prior therapy (range)		2 (1, 7)	2 (1, 6)

Single-agent activity in R/R AML and hr-MDS

A All patients

68 Response evaluable patients with baseline and post-treatment bone marrow blast counts are included.
* Indicates the best percentage change from baseline >100%

B Subset of AML patients with *FLT3* mutation

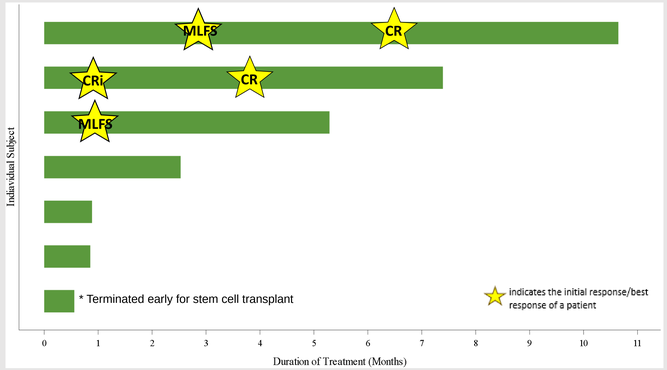
- Four AML patients have both a spliceosome and *FLT3* mutation *indicates the best percentage change from baseline >10%
- Among 11 treated AML *FLT3* patients, one was not response evaluable because of treatment discontinuation for stem cell transplant prior to first response assessment.

Treatment-related adverse events (TRAEs) Grade ≥ 3 in all treated patients

Grade 3+ Treatment-Related Adverse Event reported in > 1 patients	200 mg BID (N = 24)	300 mg BID (N = 50)	400 mg BID (N = 15)	500 mg BID (N = 3)	Total (N=92)
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients having grade 3+ TRAEs	4 (16.7)	14 (28.0)	7 (46.7)	2 (66.7)	27 (29.3)
Platelet count decreased	1 (4.2)	2 (4.0)	2 (13.3)	0	5 (5.4)
Blood creatine phosphokinase increased	0	3 (6.0)	0	0	3 (3.3)
Neutrophil count decreased	0	2 (4.0)	1 (6.7)	0	3 (3.3)
Alanine aminotransferase increased	2 (8.3)	0	0	0	2 (2.2)
Anemia	0	2 (4.0)	0	0	2 (2.2)
Lipase increase	0	2 (4.0)	0	0	2 (2.2)
Neutropenia	0	1 (2.0)	1 (6.7)	0	2 (2.2)
Syncope	0	1 (2.0)	0	1 (33.3)	2 (2.2)

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 1/92 patients.

Duration of treatment in R/R AML patients with *FLT3* mutations at 300 mg BID



Clinical activity in R/R AML with *FLT3* Mutation at 300mg BID

	# prior therapy	Prev. FLT3i	FLT3 mutation	Co-mutations At Baseline	Best response	Best FLT3 response
Patient 1	1	N	ITD	SRSF2, DNMT3A	CR	Negative by PCR
Patient 2	1	N	ITD	~~BCOR~~, ~~U2AF1~~, ~~WT1~~ (These mutations disappeared under Tx)	CR	Negative by PCR
Patient 3	2	Y	ITD	None Reported	MLFS	Positive by PCR
Patient 4	4	Y	TKD	NRAS, PTPN11, RAD21, RUNX1, SF3B1, TET2, GATA2, STAT3	SD	N/A
Patient 5	4	N	ITD	BCOR, ETV6, KRAS, NRAS, RUNX1, U2AF1	PD	N/A
Patient 6	3	Y	ITD	NPM1, TET2 x 2	SD	N/A
Patient 7	4	Y	ITD	DNMT3A, KRAS, NRAS, SBDS	NE	N/A

CONCLUSIONS

- Emavusertib has an acceptable and manageable safety profile in R/R AML and hr-MDS patients.
- No dose-limiting myelosuppression was reported.
- Changes in mutational profiles are suggestive of disease-modifying activity of emavusertib.
- Emavusertib has demonstrated strong anti-cancer activity in patients with *FLT3m*, including patients who have progressed on a prior *FLT3* inhibitor.
- Enrollment in this trial is continuing at the RP2D dose of 300 mg BID (phase 2 expansion cohort) in patients with ≤ 2 prior therapies.

REFERENCES

1. Metzeler *et al.* Blood. 2016 Aug;128(5):686-698.
2. Smith *et al.* Nat Cell Biol. 2019 May;21(5):640-650.
3. Choudhary *et al.* Elife. 2022 Aug;11:e78136.

ACKNOWLEDGEMENTS

We would like to thank the patients, their families and caregivers for their invaluable contribution and participation in this study.

CONTACT INFORMATION

Reinhard von Roemeling, MD
SVP, Clinical Development
Curis
rvonroemeling@curis.com