#7016: Phase 1/2a Study of the IRAK4 Inhibitor, Emavusertib (CA-4948), as Monotherapy or in Combination with Azacitidine or Venetoclax in Patients with Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

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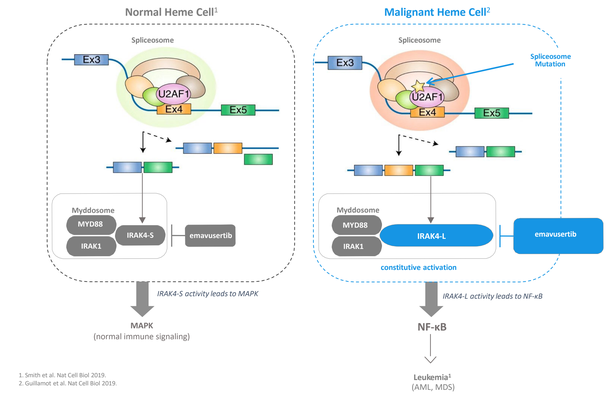
Background

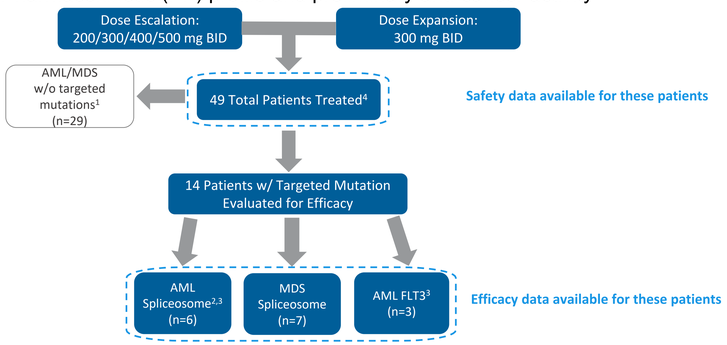


1. Smith et al. Nat Cell Biol 2019.
2. Guillamot et al. Nat Cell Biol 2019.

- Specific genetic mutations in the spliceosome (*SF3B1*, *U2AF1*) drive overexpression of IRAK4 long isoform (IRAK4-L), which then causes constitutive activation of the myddosome, leading to overactivity of NF-κB
- Emavusertib, a novel oral IRAK4 inhibitor, with dual targeting of IRAK4 and FLT3 confers a potential efficacy advantage and expands potential to additional genetic population

Study Design and Results

- TakeAim-Leukemia (NCT #04278768): Open-label, single arm, Phase 1/2 dose escalation and expansion study in R/R AML or high-risk MDS (HR-MDS)
- Study objectives:
  - 1o: Determine maximum tolerated dose and recommended Phase 2 dose
  - 2o: Pharmacokinetic (PK) profile and preliminary anti-cancer activity



All the data in the poster was extracted on Dec 16, 2021. Patients began enrollment into the combination therapy portion of the study in November 2021. 1. These are non-targeted patients, due to lack of spliceosome or *FLT3* mutation, this population will be addressed in the combination therapy study; 2. One patient was not response evaluable because of discontinuation due to patient decision; 3. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation). 4. Six patients did not start treatment by September 30th, 2021, which did not allow 2 on-study disease assessments.

Baseline Characteristics

		All patients (n=49)	AML/MDS Subsets		
			AML Spliceosome[1] (n=6)	MDS Spliceosome (n=7)	AML FLT3[1] (n=3)
Female n (%) : Male n (%)		16 (33) : 33 (67)	0 (0) : 6 (100)	5 (71) : 2 (29)	0 (0) : 3 (100)
Age (yrs): median (range)		74 (32, 87)	76 (60, 84)	74 (61, 80)	80 (78, 87)
ECOG: n 0/1/2		11/30/8	0/4/2	2/5/0	0/1/2
Median platelets (10^3/mm^3) (range)		30 (4, 275)	28 (21, 80)	16 (7, 146)	21 (9, 23)
Median ANC (10^3/mm^3) (range)		0.64 (0, 14.75)	0.23 (0, 3.3)	1.85 (0.15, 11.0)	0.05 (0, 0.11)
Median lines of prior therapy (range)		2 (1, 5)	2.5 (1, 4)	2 (1, 4)	2 (1, 4)
Prior therapy, n (%)	HMA[2]	-	6 (100)	7 (100)	3 (100)
	Chemotherapy[3]	-	3 (50)	0 (0)	1 (33)
	Venetoclax	-	4 (67)	1 (14)	3 (100)

1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or FLT3 mutation); 2. HMA includes azacitidine, decitabine, and guadecitabine; 3. Chemotherapy includes cytarabine.

Tolerable AE Profile with No Cumulative Toxicities

Grade 3+ Treatment-Related Adverse Event	200 mg BID (N = 3)	300 mg BID (N = 26)	400 mg BID (N = 17)	500 mg BID (N = 3)
	n (%)	n (%)	n (%)	n (%)
Number of patients having grade 3+ TRAEs	1 (33.3)	6 (23.1)	6 (35.3)	2 (66.7)
Alanine aminotransferase increased	1 (33.3)			
Blood creatine phosphokinase increased		1 (3.8)		
Dizziness	1 (33.3)			
Dyspnoea			1 (5.9)	
Enterobacter infection			1 (5.9)	
Fatigue			1 (5.9)	
Gastrointestinal haemorrhage		1 (3.8)		
Hypophosphataemia		1 (3.8)		
Hypotension		1 (3.8)		
Lipase increased		2 (7.7)		
Platelet count decreased		1 (3.8)		
Presyncope			1 (5.9)	
Rhabdomyolysis		1 (3.8)	2 (11.8)	1 (33.3)
Syncope				1 (33.3)

1. Data for the two patients that have escalated from 300 mg BID to 400 mg BID were included in the 400 mg BID dose group. One death occurred after the data extraction date, currently under review.

Summary

- ***Emavusertib has a tolerable safety profile and may provide advantage to the existing standard of care therapies***
- ***Demonstrates single-agent anti-cancer activity in heavily pretreated AML and HR-MDS patients with U2AF1 / SF3B1 or FLT3 mutations***
- ***A potential candidate for addition to combination therapy regimens in AML/HR-MDS patients w/o targeted mutations***

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

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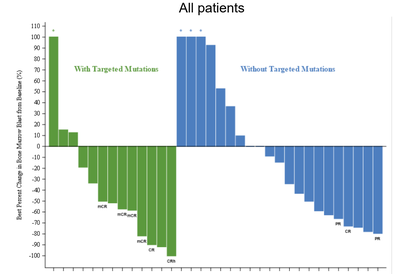
TakeAim

Single-agent Activity in AML/HR-MDS

All patients



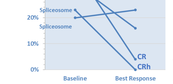
Only evaluable patients with baseline and post-treatment bone marrow blast counts are included in the waterfall plot; among the patients w/o targeted mutations (*SF3B1 / U2AF1 / FLT3* mutation), 1 reached CR and 2 PR.
* Indicates the best percentage change from baseline >100%

Subset of patients with targeted mutations (*SF3B1 / U2AF1 / FLT3* mutation)

Best Response	Efficacy
Population #1: AML Spliceosome Patients[1, 2]	
CR/CRh Rate	2/5 (40%)
CR	*1/5 (20%)*
CRh	*1/5 (20%)*
Population #2: MDS Spliceosome Patients	
Objective Response Rate (ORR)	4/7 (57%)
CR	*0/7 (0%)*
mCR	*4/7 (57%)*
Population #3: AML FLT3 Patients[1]	
CR/CRh Rate	1/3 (33%)
CR	*1/3 (33%)*
CRh	*0/3 (0%)*

1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation)
2. One patient was not response evaluable because of discontinuation due to patient decision

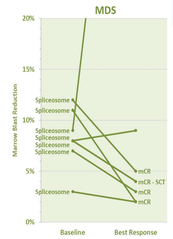
Clinical Activity in R/R AML with *SF3B1 / U2AF1* Mutation



Dose (BID)	Risk (ELN)	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response	% Change
300 mg	Intermediate	SF3B1, RUNX1, WT1	1	7	23	0	-100% (CRh)
300 mg	Intermediate	U2AF1, FLT3, BCOR, WT1	1	6+	39	4	-90% (CR)
300 mg	Intermediate	U2AF1, NRAS	4	2.5	33	16	-52%
300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	2.6	95	77	-19%
400 mg	Adverse	SF3B1, DNMT3A, P53	1	2	20	23	15%

"+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation).

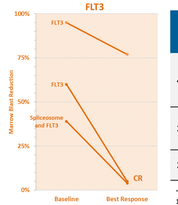
Clinical Activity in R/R MDS with *SF3B1 / U2AF1* Mutation



Dose (BID)	IPSS-R	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response	% Change
200 mg	Very High Risk	U2AF1 ,ASXL1, NF1, PHF6, GFI1, KDM6A, TET2	1	5.7	11	2	-82% (mCR)
300 mg	Very High Risk	U2AF1, DNMT3A, BCOR, STAG2, BCORL1, ETV6, SETBP1	1	3.3+	12	5	-58% (mCR)
400 mg	Very High Risk	SF3B1, RUNX1, NFE2	2	4.3	7	3	-57% (mCR)
300 mg	High Risk	SF3B1, DNMT3A, ASXL1, TET2, EZH2	2	0.9 (went to SCT)	8	4	-50% (mCR)
300 mg	High Risk	U2AF1, ASXL1	4	5.3+	3	2	-33%
300 mg	Very High Risk	SF3B1, ASXL1, NF1, SH2B3, RUNX1, PHF6, CBL, GFI1, EZH2	3	1.6	8	9	13%
400 mg	Very High Risk	U2AF1, ASXL1, BCOR, DNMTA, GATA2, SETBP1	1	1.2	9	62	>100%

"+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.

Clinical Activity in R/R AML with *FLT3* Mutation



Dose (BID)	Risk (ELN)	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response	% Change
400 mg	Adverse	FLT3 *(eradicated at C3D1)*, ASXL1, BCOR, CEBPA *(eradicated at C3D1)*, CSF3R, EZH2, NRAS, RUNX1 (X3), STAG2, TET2(X2,1) *(eradicated at C3D1)*	2	5.1	60	5	-92%
300 mg	Intermediate	FLT3 *(eradicated at C4D1)*, BCOR *(eradicated at C4D1)*, U2AF1 *(decreased to 1.3 VAF at C4D1)*, WT1 *(eradicated at C4D1)*	1	6.2+	39	4	-90% (CR)
300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	2.6	95	77	-19%

"+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation).