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HYBRID JUNE 9-17 VIENNA

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TAKEAIM LEUKEMIA- A PHASE 1/2A STUDY OF THE IRAK4 INHIBITOR EMAVUSERTIB (CA-4948) AS MONOTHERAPY OR IN COMBINATION WITH AZACITIDINE OR VENETOCLAX IN RELAPSED/REFRACTORY AML OR MDS

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Date: June 11, 2022
Session Title: Novel insights into AML treatment
Abstract: S129

Disclosures

Research support from:

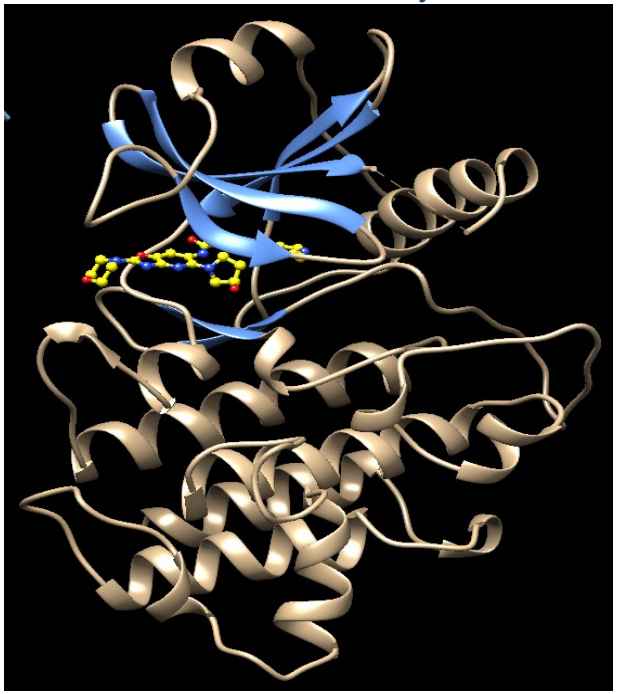
Curis, Astex, Abbvie, BMS, Jazz, Novartis, Aprea, ALX, Gilead, Seattle Genetics

Emavusertib, An Oral IRAK4 Inhibitor

Emavusertib:

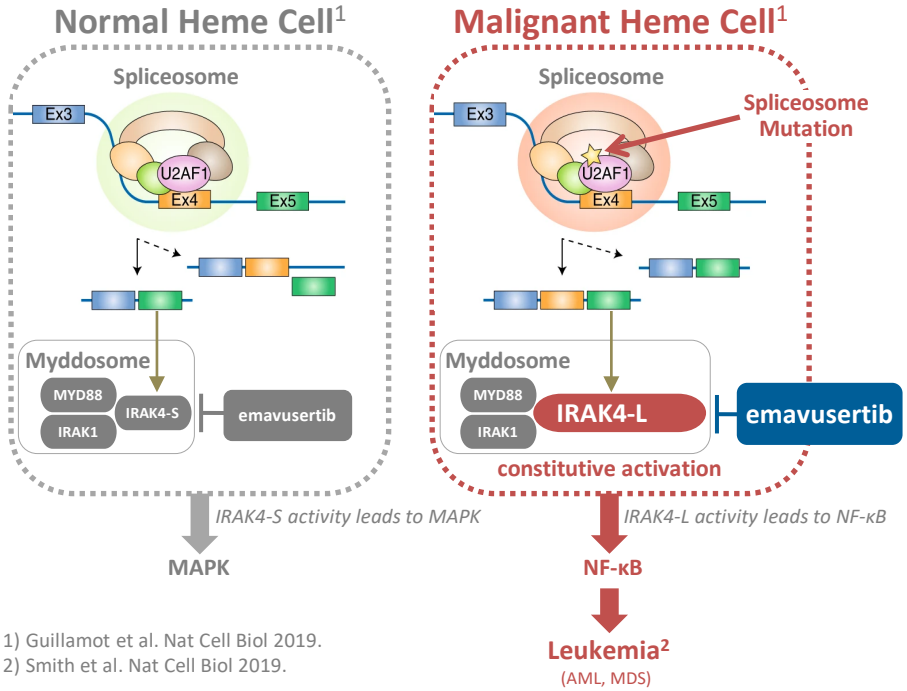
- Selective, small molecule inhibitor of IRAK4
- ATP-competitive, type 1 inhibitor, reversible
- Excellent drug-like properties:
  - Orally bioavailable (>100% dog/mouse)
  - Moderate plasma binding (77% human)
  - Stable in plasma, liver microsomes, hepatocytes
  - No inhibition of 7 major CYP450s
  - No significant metabolism *in vitro*
  - Humans: rapid absorption/clearance, $T_{1/2}$ 6 hr, no accumulation with QD dosing

IRAK4/Emavusertib Co-crystal Structure



2.4Å resolution

Emavusertib: Introduction

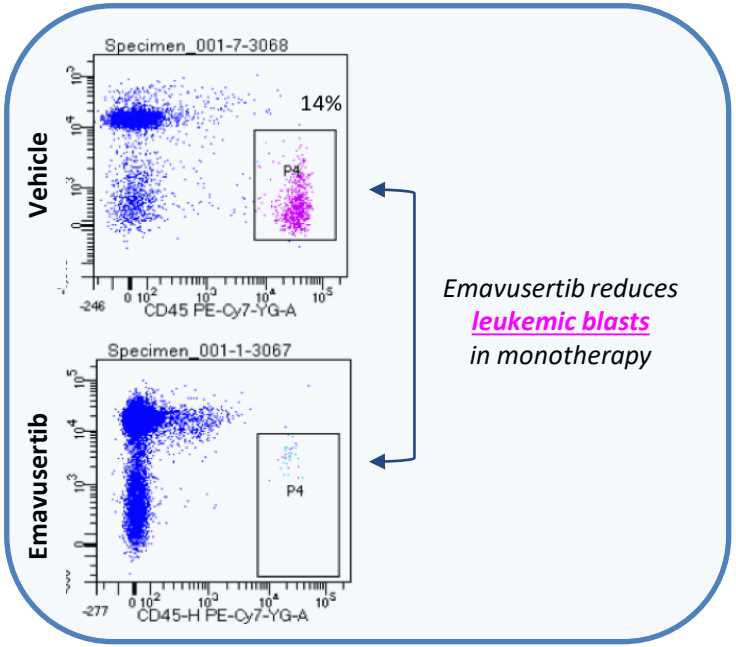


- Emavusertib (CA-4948), a novel oral IRAK4 inhibitor has potential anti-leukemia activity
- Specific genetic mutations (*SF3B1*, *U2AF1*) in the spliceosome drive overexpression of IRAK4 long isoform (IRAK4-L)
- IRAK4-L then causes constitutive activation of the myddosome, leading to overactivity of NF-κB
- Therefore, this drug can target patients with splicing mutations
- Emavusertib also targets FLT3 and has shown potential synergetic activity with other drugs

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

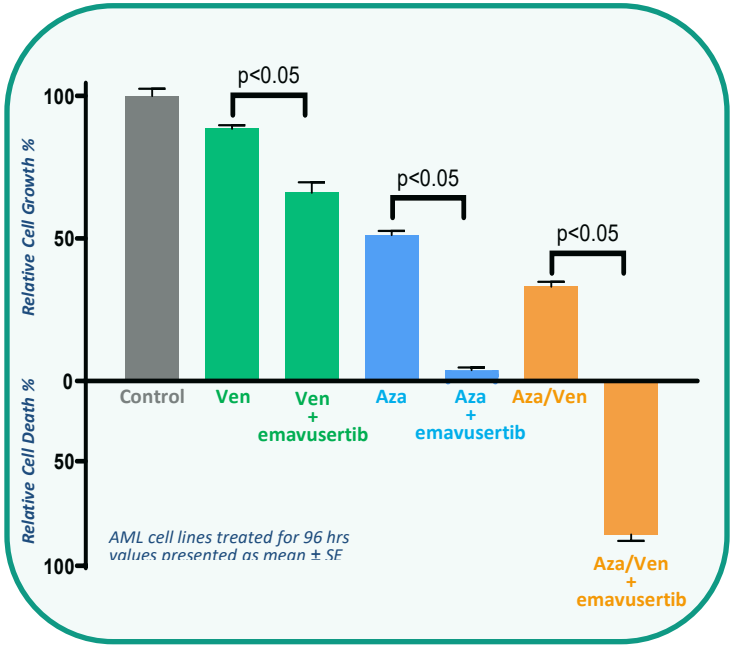
Emavusertib: Preclinical Activity in AML and MDS

Monotherapy



Emavusertib demonstrates monotherapy activity in patient-derived xenografts[1]

Combination Therapy

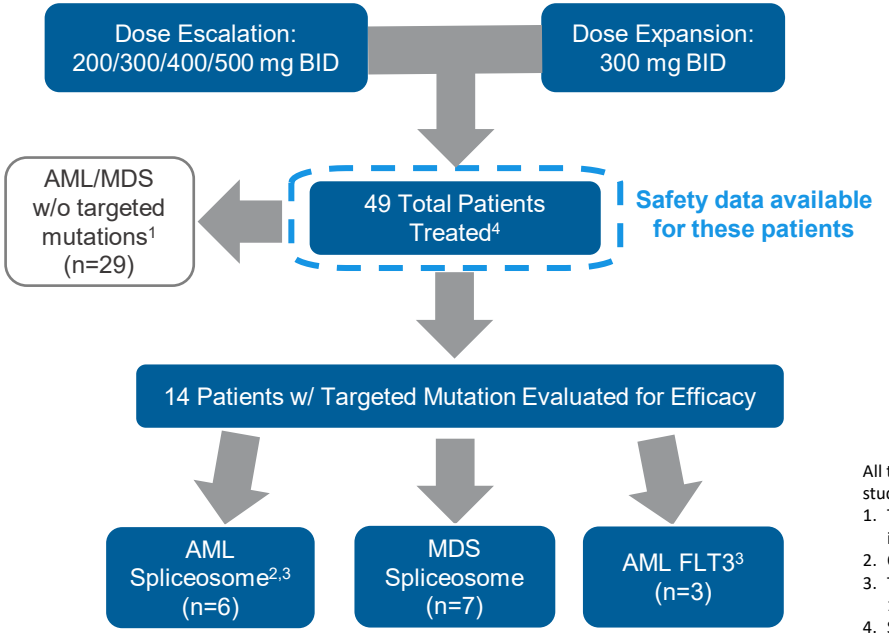


Emavusertib demonstrates synergy with both azacitidine and venetoclax in THP-1 model[2]

1. Choudhary et al. AACR 2017; 2. Curis AML MDS poster, EHA 2021

Emavusertib: Study Design

TakeAim Leukemia (NCT #04278768): Open-label, single arm, Phase 1/2 dose escalation and expansion 3+3 study design in R/R AML or high-risk MDS (HR-MDS)



Study Objectives

1°: Determine maximum tolerated dose
Determine recommended Phase 2 dose

2°: Pharmacokinetic (PK) profile
Preliminary anti-cancer activity

Study Population

- Relapsed/Refractory AML or high-risk MDS
- ECOG performance Status of ≤ 2
- Age ≥ 18 years

Dosing

- Oral, BID Dosing
- 28-day cycles

All the data 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

Emavusertib: 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 bone marrow blasts (%) (range)		-	33 (20, 95)	8 (3, 12)	60 (39, 95)
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

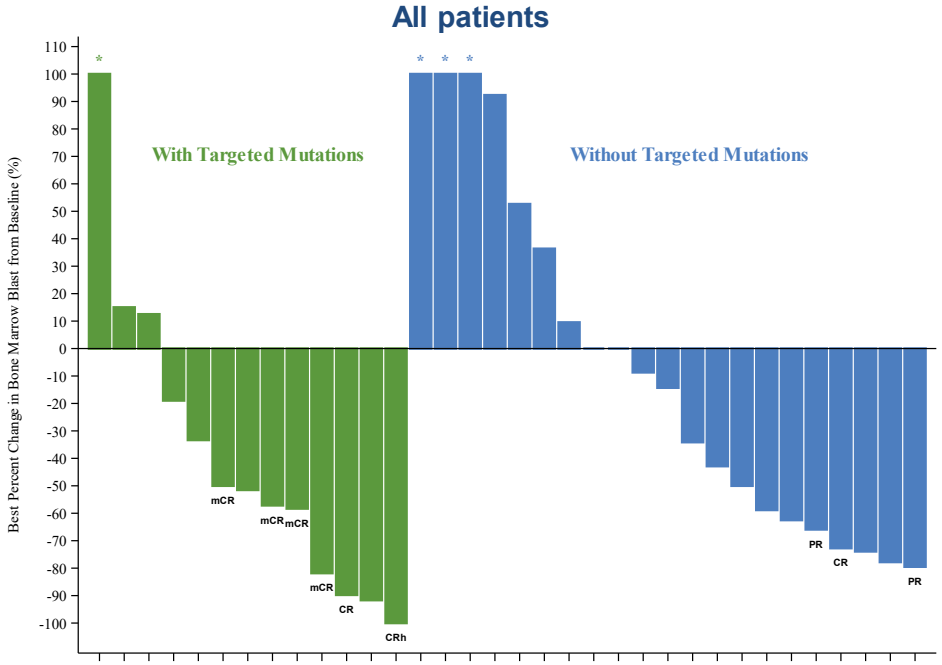
Emavusertib: Toxicities Profile

- During the initial dose escalation phase, no DLT was observed in 200-400 mg BID dose levels. Additional patients were enrolled at 300 mg and 400 mg BID to further explore the safety profile.

Grade 3+ Treatment-Related Adverse Event	200 mg BID (N = 3)	300 mg BID (N = 26)[1]	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.

Emavusertib: Single-agent Activity in AML and HR-MDS



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

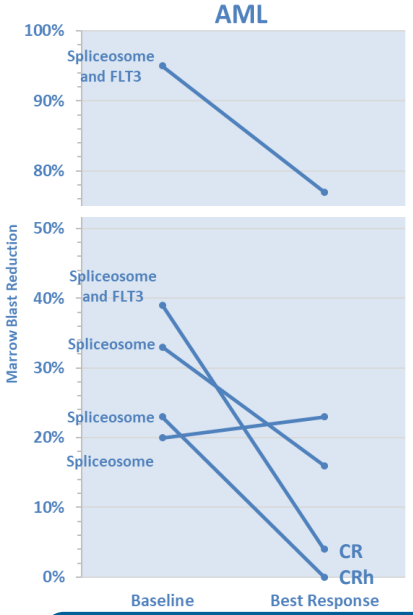
* Indicates the best percentage change from baseline >100%

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

Emavusertib: Single-agent Activity in R/R AML with Spliceosome Mutation



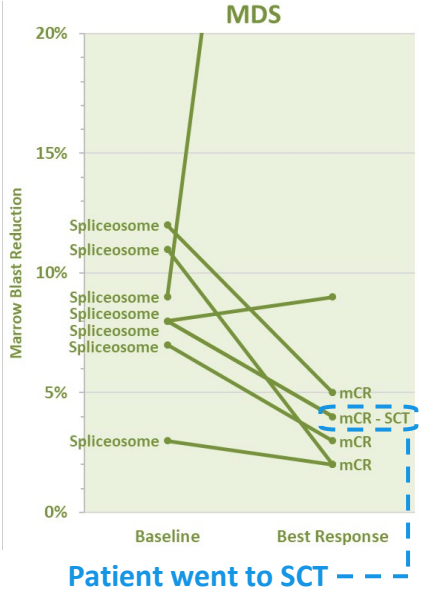
Dose (BID)	Risk (ELN)	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response[1]	% Change
300 mg	Intermediate	SF3B1, RUNX1, WT1,	1	7	23	0	-100% (CRh)
300 mg	Intermediate	U2AF1, FLT3, BCOR, WT1	1	6+	39	4	-90% (CR)
300 mg	Intermediate	U2AF1, 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%

Data extraction date: Dec 16, 2021; "+" 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).

Emavusertib achieved 40% CR/CRh rate,
despite transformed AML being historically highly resistant to treatment

AML Spliceosome Mutation

Emavusertib: Single-Agent Activity in R/R HR-MDS with Spliceosome Mutation



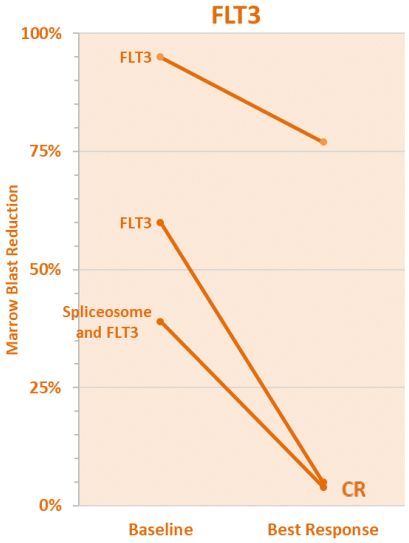
Dose (BID)	IPSS-R	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response	% Change
200 mg	Very High Risk	U2AF1 ,ASXL1, NF1, PHF6, GFI1, KDM6A, TET2	1	5.7	11	2	-82% (mCR)
300 mg	Very High Risk	U2AF1, DNMT3A, BCOR, STAG2, BCORL1, ETV6, SETBP1	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	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%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.

Emavusertib achieved 57% ORR,
including one patient who was able to proceed to transplant

MDS
Spliceosome
Mutation

Emavusertib: Single-agent 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[1]	% 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%

Data extraction date: Dec 16, 2021; "+" 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).

Emavusertib achieved 33% CR rate,
and FLT3 mutation eradicated in 2 out of 3 patients

AML
FLT3
Mutation

Summary

TakeAim

- Emavusertib has a manageable safety profile
- Demonstrates oral, single-agent, anti-cancer activity in heavily pretreated AML and HR-MDS patients with targeted mutations (*U2AF1*, *SF3B1*, or *FLT3*)
- Potential candidate for use in combination therapy for all AML/HR-MDS patients, including patients without a targeted mutation

Next Steps:

- Correlative analysis ongoing
- Trials in lymphoma and solid tumors are being explored

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

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