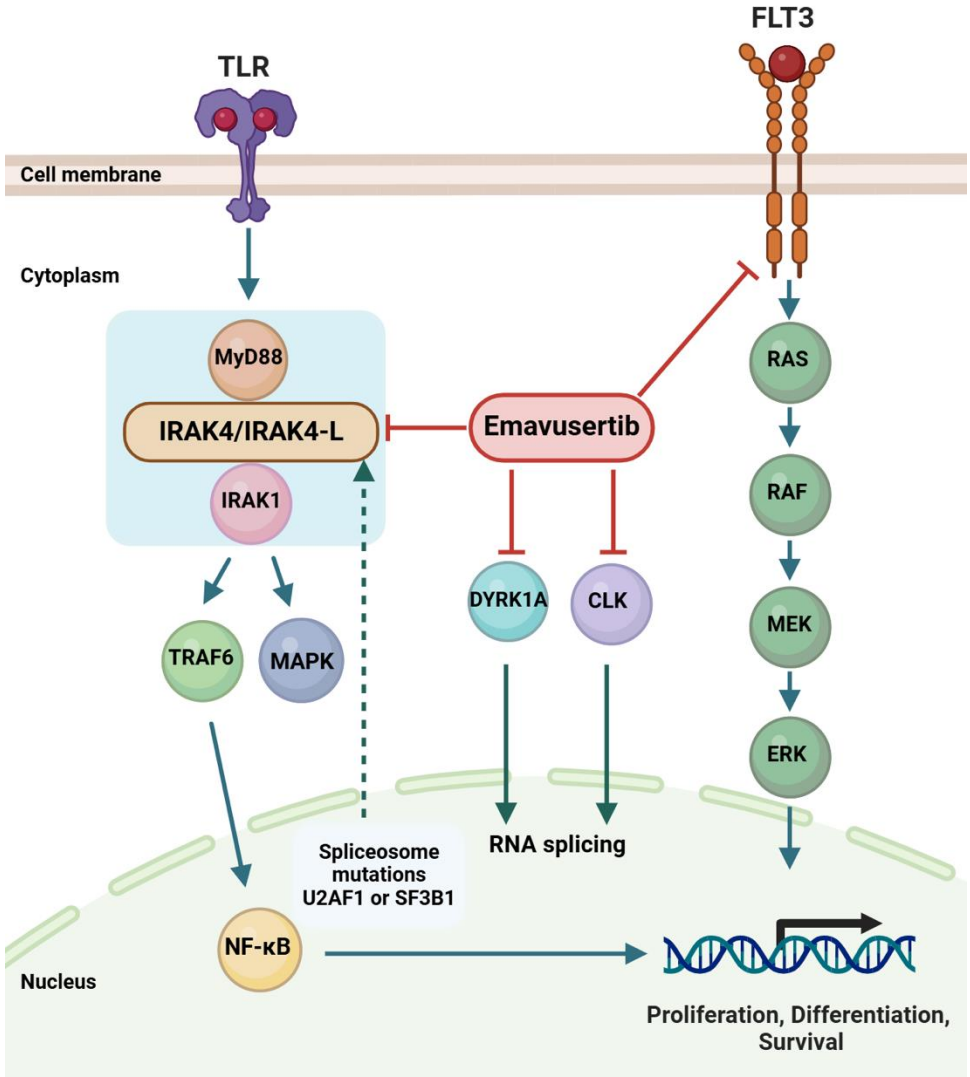
Preliminary Safety, Efficacy and Molecular Characterization of Emavusertib (CA-4948) in Relapsed/Refractory Acute Myeloid Leukemia Patients

E.S. Winer[1], D. Sallman[2], A. de la Fuente[3], A. Verma[4], K. Götze[5], Y. Abaza[6], J. Dugan[7], T. Cluzeau[8], E. Rodriguez Arboli[9], A. Mims[10], S. Groepper[11], I. Zilbershatz[12], J. Liesveld[13], W. Fiedler[14], S. Tarantolo[15], L. Ades[16], N. Papadantonakis[17], C. Schliemann[18], G. Choudhary[19], M. Lane[19], W. Zhao[19], A. Jain[19], C. Gallagher[19], G. Garcia-Manero[20]

1. Dana-Farber Cancer Institute, Boston, MA; 2. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; 3. MD Anderson Cancer Center, Madrid, Spain; 4. Montefiore Medical Center, Bronx, NY; 5. Technical University of Munich School of Medicine, Munich, Germany; 6. Northwestern Medicine, Chicago, IL; 7. Novant Health Cancer Institute, Winston-Salem, NC; 8. CHU of Nice, Nice, France; 9. Avenida Manuel Siurot s/n Sevilla, Spain; 10. The Ohio State University Comprehensive Cancer Center, Columbus, OH; 11. Univ. of Düsseldorf, Düsseldorf, Germany; 12. The Edith Wolfson Health Center, Holon, Israel; 13. University of Rochester Medical Center, Rochester, NY; 14. University Hospital Hamburg Eppendorf, Hamburg, Germany; 15. Nebraska Cancer Specialists, Omaha, NE; 16. Hospital Saint Louis, Paris, France; 17. Emory University, Atlanta, GA; 18. Albert-Schweitzer-Campus 1, Gebäude A1, Münster; 19. Curis Inc., Lexington, MA; 20. University of Texas, MD Anderson Cancer Center, Houston, TX.

Introduction



Acute myeloid leukemia (AML) is a heterogeneous disease which exhibits a dynamic mutational landscape as the disease progresses.

Patients with relapsed/refractory (R/R) AML who have failed standard therapies, including conventional chemotherapy, venetoclax (VEN), hypomethylating agents (HMA), and/or FLT3 inhibitors (FLT3i) have limited therapeutic options.[1,2]

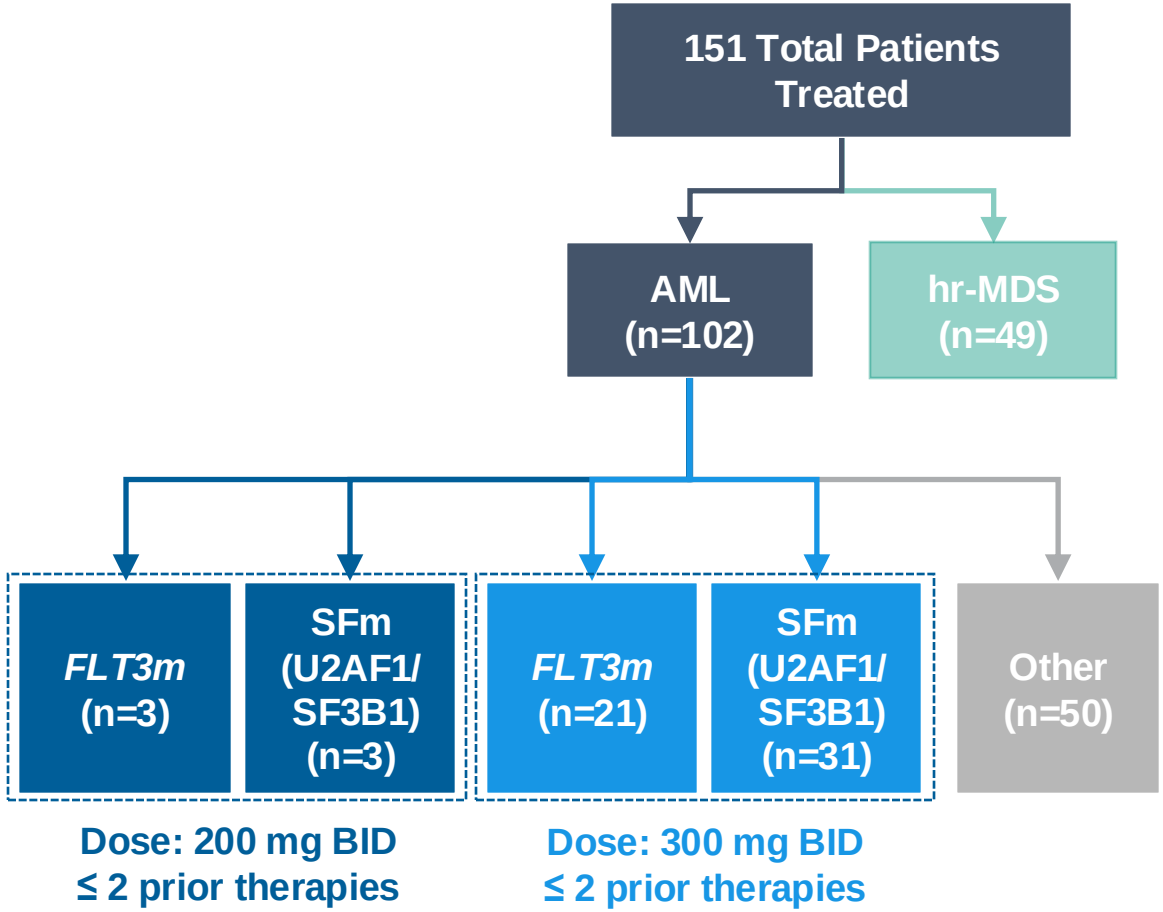
Splicing factor mutations (SFm) SF3B1 and U2AF1 drive the interleukin-1 receptor-associated kinase 4 (IRAK4) mediated inflammatory pathway that is critical in oncogenesis and survival of cancer cells.[3]

Emavusertib is an oral dual IRAK4 and FLT3 (ITD and TKD) inhibitor which also inhibits the NF-kB and MAPK pathways, thus offering a potential mechanism to address known pathways of resistance to BCL2 and FLT3 inhibitors.[3,4,5]

References: 1. Maiti et al. Haematologica 2021;106(3):894-898; 2. DiNardo et al. Blood 2019;133(1):7-17; 3. Smith et al. Nat Cell Biol. 2019;21(5):640-650; 4. Melgar et al. Sci Transl Med 2019;11(508):eaaw8828; 5. Gummadi et al. ACS Med Chem Lett 2020;11(12):2374-2381.

TakeAim Leukemia Trial

- The safety, clinical activity, and potential biomarkers of emavusertib in relapsed/refractory (R/R) AML and higher-risk myelodysplastic syndrome (hr-MDS) were investigated
- Major inclusion criteria: Diagnosis of AML, ≥ 18 years of age, ≤ 2 lines of therapy*, CrCl ≥ 35mL/min, WBC ≤ 25K/µL
- Major exclusion criteria: Active CNS disease, allogeneic transplant within 60 days, active uncontrolled infection, QTcF > 450 msec, clinically significant graft-versus-host disease requiring up-titration of immunosuppression, history of ≥ grade 3 rhabdomyolysis
- Here we present preliminary safety and efficacy data of the **TakeAim Leukemia trial** with emphasis on the subset of enrolled AML patients who carried FLT3 mutations (*FLT3m*) and/or a splicing factor mutation (SFm) (*U2AF1 and/or SF3B1*) with ≤ 2 lines of prior therapy at enrollment and were treated with emavusertib 200-300 mg BID monotherapy
- Mutational profiles were documented based on local testing results. Bone marrow and peripheral blood of enrolled patients were collected at the baseline and on treatment



Note: 6 patients had both *FLT3m* and SFm

* Induction, consolidation, and transplant was considered a single line of therapy.

Data-cut: October 31, 2024

Baseline Characteristics – TakeAim Leukemia Trial

		AML – *FLT3m* patients ≤ 2 lines of prior therapy (n=24)*		AML – SFm patients ≤ 2 lines of prior therapy (n=34)*		All AML Patients (n=102)#
		200 mg BID (n=3)	300 mg BID (n=21)	200 mg BID (n=3)	300 mg BID (n=31)	
Male n (%): Female n (%)		2 (66.7): 1 (33.3)	11 (52.4): 10 (47.6)	3 (100): 0	22 (71.0): 9 (29.0)	68 (66.7): 34 (33.3)
Age (yrs): median (range)		77 (75, 82)	74 (44, 83)	82 (76, 85)	74 (44, 85)	73.5 (32, 87)
Race n (%)	**Asian**	0	0	0	0	0
	Black or African American	0	1 (4.8)	0	4 (12.9)	7 (6.9)
	White	3 (100)	18 (85.7)	3 (100)	24 (77.4)	86 (84.3)
	Others	0	0	0	0	1 (1.0)
	Not reported	0	2 (9.5)	0	3 (9.7)	8 (7.8)
Median platelets (10^3/mm^3) (range)		25 (9, 45)	26 (8, 73)	24 (23, 25)	27 (4, 400)	25 (1, 400)
Median ANC (10^3/mm^3) (range)		1.2 (0, 1.68)	0.5 (0, 7.03)	0.28 (0, 0.84)	0.5 (0, 7.17)	0.48 (0, 7.17)
Lines of prior therapy n (%)	**1**	0	5 (23.8)	2 (66.7)	14 (45.2)	33 (32.4)
	2	3 (100.0)	16 (76.2)	1 (33.3)	17 (54.8)	39 (38.2)
	3	0	0	0	0	12 (11.8)
	4	0	0	0	0	11 (10.8)
	5+	0	0	0	0	7 (6.9)

* Note: 6 patients had both *FLT3m* and SFm and are included in both populations. # Includes 50 additional patients from category “Other” in study design.

Data-cut: October 31, 2024

Grade ≥ 3 Treatment-Related Adverse Events (TRAEs) in All Treated R/R AML Patients

Emavusertib has an acceptable and manageable safety profile in R/R AML patients

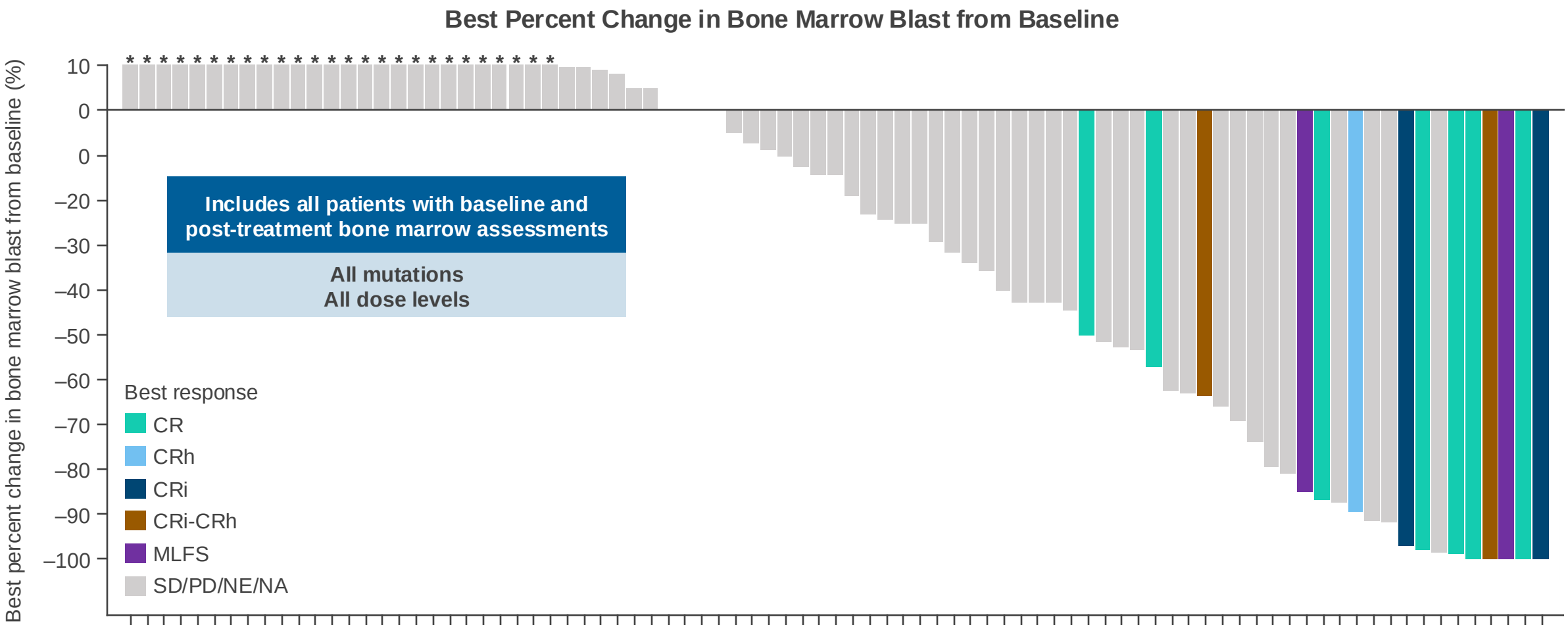
Grade 3+ Treatment-Related Adverse Event Reported in > 1 patients, n (%)	200 mg BID (n = 17)	300 mg BID (n = 75)	400 mg BID (n = 8)	500 mg BID (n = 2)	All AML Patients (n = 102)
# of patients having grade 3+ TRAEs	1 (5.9)	29 (38.7)	3 (37.5)	1 (50.0)	34 (33.3)
Blood creatine phosphokinase increased	0	6 (8.0)	0	0	6 (5.9)
Neutropenia	0	5 (6.7)	1 (12.5)	0	6 (5.9)
Anaemia	0	5 (6.7)	0	0	5 (4.9)
Platelet count decreased	0	3 (4.0)	0	0	3 (2.9)
Rhabdomyolysis*	0	2 (2.7)	1 (12.5)	0	3 (2.9)
Syncope	0	1 (1.3)	1 (12.5)	1 (50.0)	3 (2.9)
Aspartate aminotransferase increased	0	2 (2.7)	0	0	2 (2.0)
Febrile neutropenia	0	1 (1.3)	1 (12.5)	0	2 (2.0)
Leukopenia	0	2 (2.7)	0	0	2 (2.0)
Orthostatic hypotension	0	2 (2.7)	0	0	2 (2.0)
Thrombocytopenia	0	2 (2.7)	0	0	2 (2.0)

* Three events of rhabdomyolysis were investigator-reported, 1/3 met laboratory defined criteria for rhabdomyolysis (CPK >10 x ULN and SCr ≥ 1.5 x ULN).

Data-cut: October 31, 2024.

Single-Agent Activity in R/R AML Patients

All patients treated with emavusertib monotherapy

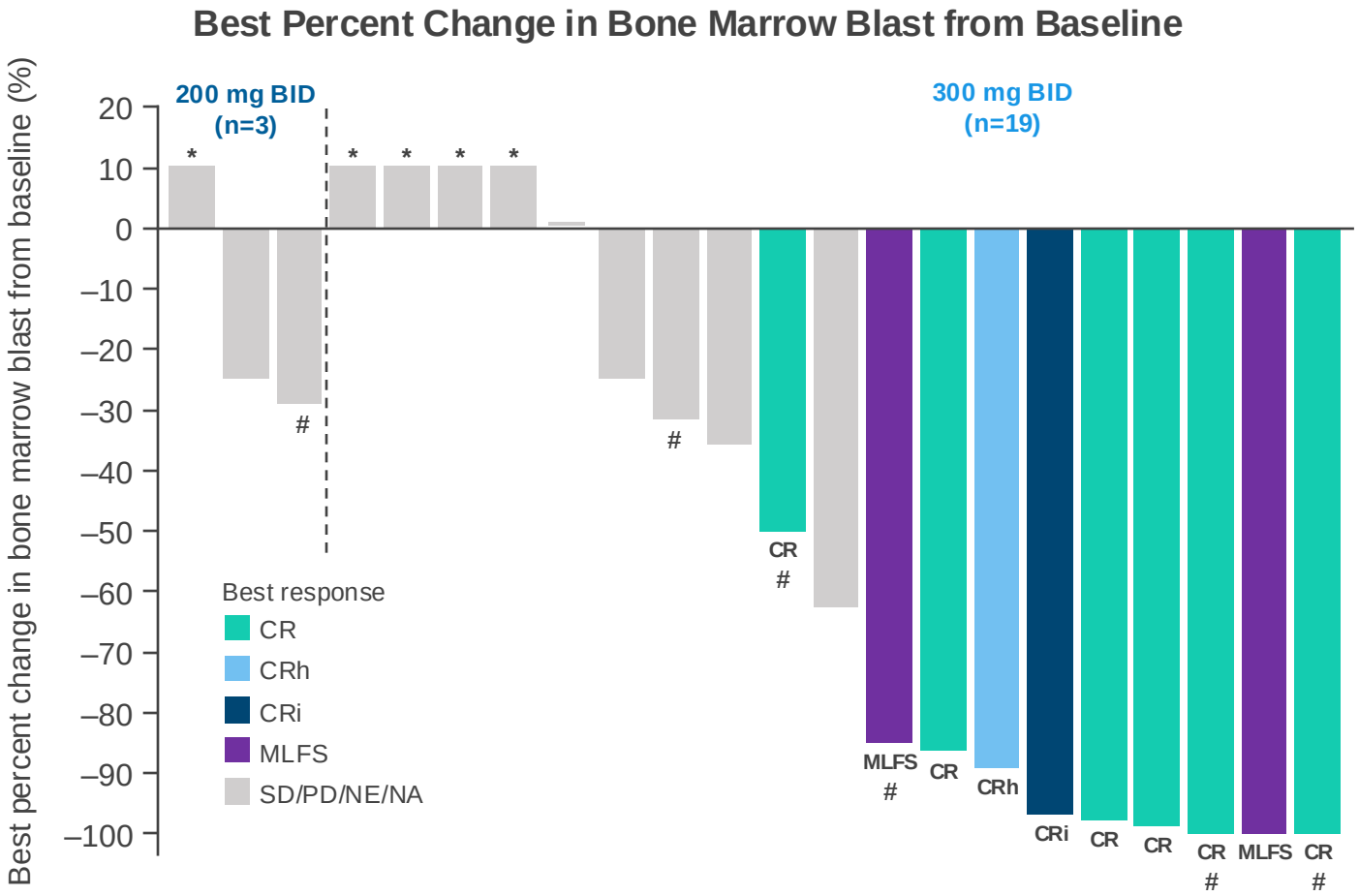


Among 102 treated patients, 17 patients discontinued treatment without post-baseline bone marrow blast assessment (4 due to death; 7 due to PD, 4 due to AE, and 2 withdrew consent).
* Indicates the best percentage change from baseline >10%.

Data-cut: October 31, 2024.

Single-Agent Activity in R/R AML With *FLT3m*

Patients treated with emavusertib at 200-300 mg BID with ≤ 2 lines of prior therapy



Among 21 R/R AML *FLT3m* patients treated at 300 mg BID with ≤ 2 lines of prior therapy:

Composite CR (CR+CRh+CRi): 38.1% (8/21)
ORR (CR+CRh+CRi+MLFS): 47.6% (10/21)

Among 19 patients assessed†:

Composite CR (CR+CRh+CRi): 42.1% (8/19)
ORR (CR+CRh+CRi+MLFS): 52.6% (10/19)

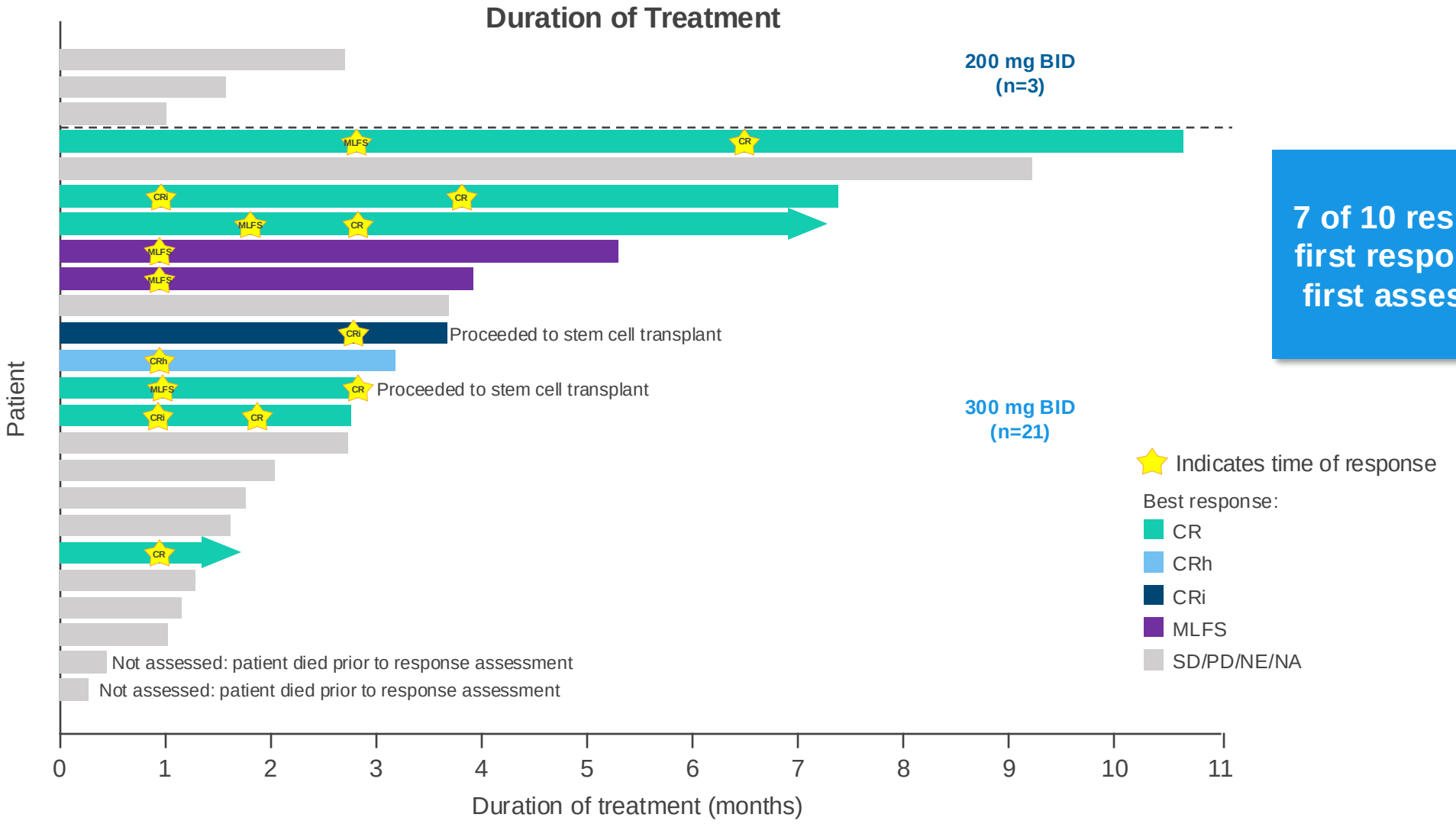
2 of 21 patients were treated, but discontinued treatment prior to first disease response assessment (death occurred at Day 8 and Day 13, respectively)

* Indicates the best percentage change from baseline >10%. # indicates patients having both SFm and *FLT3m*. † Assessed patients are those with a baseline and post-treatment response assessment.

Data-cut: October 31, 2024

Single-Agent Activity in R/R AML With *FLT3m*

Patients treated with emavusertib at 200-300 mg BID with ≤ 2 lines of prior therapy

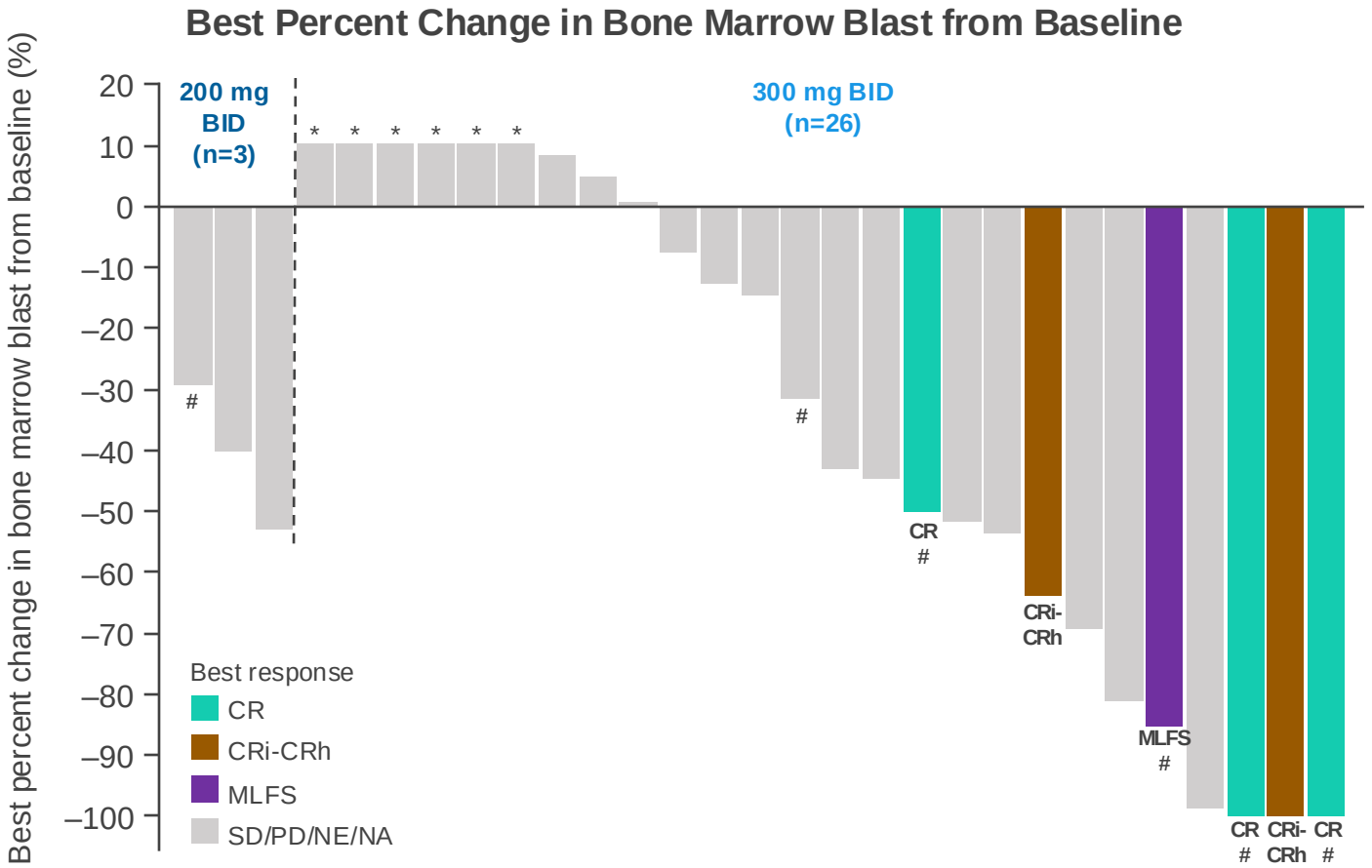


7 of 10 responders achieved their first response (MLFS or better) at first assessment (Cycle 2 Day 1)

Data-cut: October 31, 2024

Single-Agent Activity in R/R AML With SFm (U2AF1 and/or SF3B1)

Patients treated with emavusertib at 200-300 mg BID with ≤ 2 lines of prior therapy



Among 31 R/R AML SFm patients treated at 300 mg BID with ≤ 2 lines of prior therapy:

Composite CR (CR+CRh+CRi): 16.1% (5/31)
ORR (CR+CRh+CRi+MLFS): 19.4% (6/31)

Among 28 patients assessed †:

Composite CR (CR+CRh+CRi): 17.9% (5/28)
ORR (CR+CRh+CRi+MLFS): 21.4% (6/28)

3 of 31 patients were treated, but discontinued treatment prior to first disease response assessment (2 AE, 1 WC)

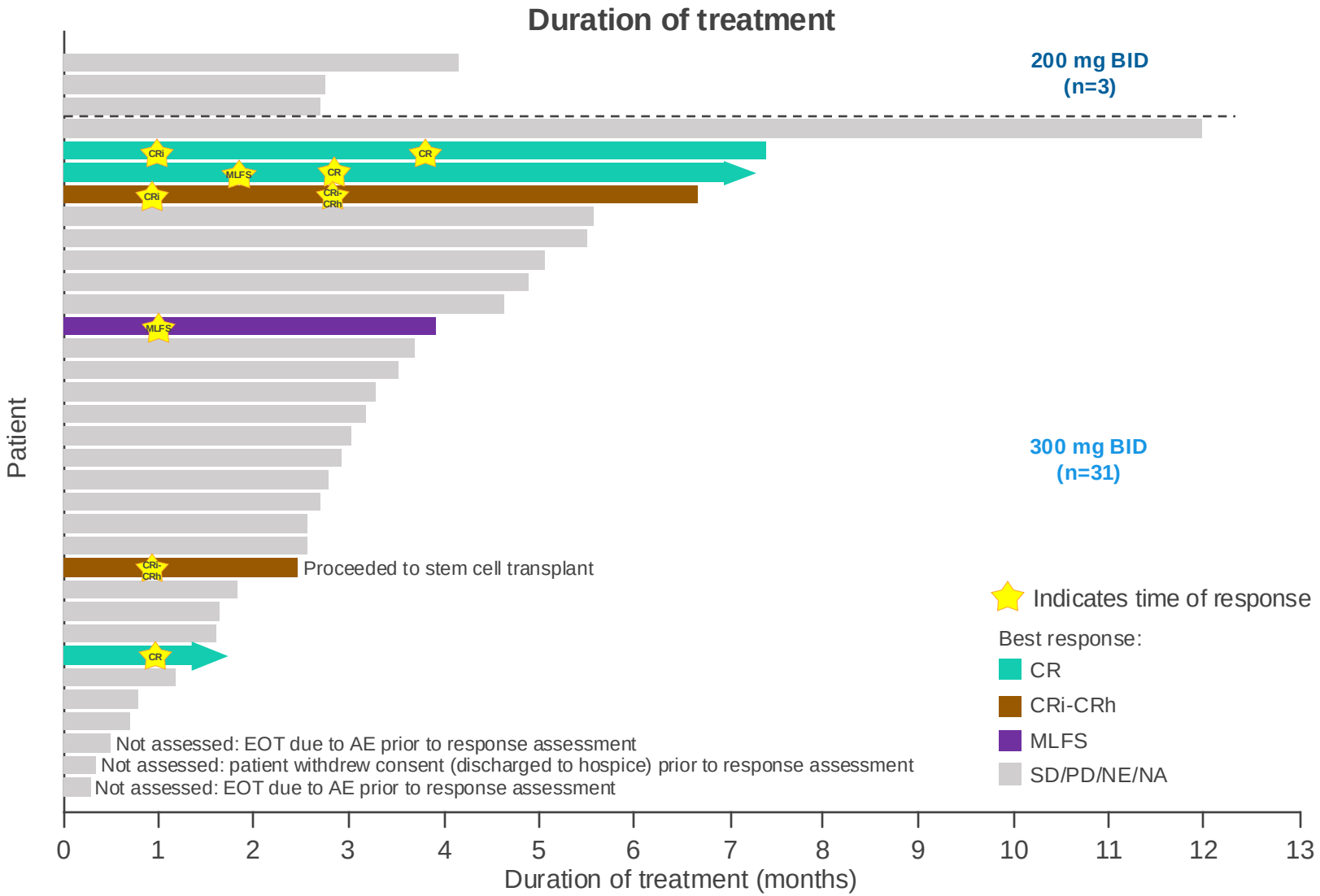
2 additional patients discontinued treatment due to PD, but did not have a post-baseline bone marrow blast assessment (i.e., could not be included in the waterfall chart)

AE: discontinued treatment due to adverse event; WC: discontinued treatment due to withdrawal of consent.
* Indicates the best percentage change from baseline >10%. # indicates patients having both SFm and *FLT3m*. † Assessed patients are those with a baseline and post-treatment response assessment.

Data-cut: October 31, 2024

Single-Agent Activity in R/R AML With SFm (U2AF1 and/or SF3B1)

Patients treated with emavusertib at 200-300 mg BID with ≤ 2 lines of prior therapy



5 of 6 responders achieved their first response (MLFS or better) at first assessment (Cycle 2 Day 1)

Data-cut: October 31, 2024

Results

Clinical activity in R/R AML with FLT3m at 300 mg BID

Patient #	Age	Sex	ELN risk	# prior therapies	*FLT3m*	Prior BCL2i	Prior HMA	Prior FLT3i	Best response	Co-mutations at baseline
1*	80	M	Intermediate	1	ITD	Y	Y	N	CR	**U2AF1**, BCOR, WT1
2	44	M	Adverse	2	ITD	Y	N	Y	CR	NRAS, WT1
3*	74	M	Adverse	2	NA	Y	Y	N	MLFS	**SF3B1**, GATA2, PHF6, RUNX1, CBLC
4	78	F	Adverse	2	ITD	Y	Y	Y	MLFS	Not available
5	79	F	Intermediate	2	ITD	N	Y	N	CR	DMNT3A, **SRSF2**
6	74	M	Intermediate	1	ITD	N	Y	Y	CRh	Not available
7*	77	M	Intermediate	1	ITD	Y	Y	N	CR	**U2AF1**, RUNX1, SH2B3, ASXL1
8	58	F	Intermediate	1	ITD	N	N	Y	CRi	Not available
9	52	F	Adverse	1	TKD	N	N	Y	CR	Not available
10*	69	M	Adverse	2	ITD	N	N	Y	CR	**SF3B1**

50% of responders had prior venetoclax exposure

60% of responders had prior exposure to HMA regimen

60% of responders had prior FLT3 inhibitor exposure

Emavusertib may be able to target diverse underlying genetic mechanisms of resistance to VEN, HMA, or FLT3i regimens

* Indicates patients having both SFm and *FLT3m.*

Data-cut: October 31, 2024

Results

Clinical activity in R/R AML with splicing factor (U2AF1, SF3B1) mutation at 300 mg BID

Patient #	Age	Sex	ELN risk	# prior therapy	Prior BCL2i	Prior HMA	Best response	Co-mutations at baseline
1*	80	M	Intermediate	1	Y	Y	CR	U2AF1, BCOR, WT1
2	65	M	Adverse	1	Y	Y	CRi-CRh	BCOR, STAG2, TP53, U2AF1
3*	74	M	Adverse	2	Y	Y	MLFS	SF3B1, GATA2, PHF6, RUNX1, CBLC
4	84	M	Intermediate	1	N	Y	CRi-CRh	SF3B1, RUNX1, WT1
5*	77	M	Intermediate	1	Y	Y	CR	U2AF1, RUNX1, SH2B3, ASXL1
6*	69	M	Adverse	2	N	N	CR	SF3B1

67% of responders had prior venetoclax exposure

83% of responders had prior exposure to HMA regimen

Emavusertib may be able to target diverse underlying genetic mechanisms of resistance to VEN or HMA regimens

* Indicates patients having both SFm and *FLT3m*.

Data-cut: October 31, 2024

Summary

Emavusertib has an acceptable and manageable safety profile in R/R AML patients

Emavusertib demonstrates responses among diverse groups of mutations in R/R AML patients

Emavusertib monotherapy has demonstrated high rates of anti-leukemic activity in patients with *FLT3m* including patients who have progressed on VEN, HMA and/or FLT3i regimens

Preclinical data (not presented) have shown that emavusertib in combination with azacitidine and venetoclax demonstrated synergistic anti-leukemic effects in AML cell lines

Enrollment is ongoing in a study evaluating the addition of emavusertib to the azacitidine/venetoclax doublet in MRD-positive patients at the time of CR or CRh, to investigate if emavusertib has the potential to achieve MRD negativity without significant additional toxicity (EUCTR#2023-505828-58)

Acknowledgments

Patients, their families, and caregivers

Study Sites:

- Dana-Farber Cancer Center, Boston, MA
- H. Lee Moffitt Cancer Center, Tampa, FL
- MD Anderson Cancer Center, Madrid, Spain
- Montefiore Medical Center, Bronx, NY
- Technical University of Munich School of Medicine, Munich, Germany
- Northwestern Medicine, Chicago, IL
- Novant Health Cancer Institute, Winston-Salem, NC
- CHU of Nice, Nice, France
- University of Seville, Seville, Spain
- The Ohio State University Comprehensive Cancer Center, Columbus, OH
- University of Dusseldorf, Dusseldorf, Germany
- The Edith Wolfson Health Center, Holon, Israel
- Wilmot Cancer Institute, Rochester, NY
- University Hospital of Hamburg Eppendorf, Hamburg, Germany
- Nebraska Cancer Specialists, Omaha, NE
- Hospital St Louis Paris, France
- Winship Cancer Institute of Emory University, Atlanta, GA
- University Hospital Münster, Münster, Germany
- MD Anderson Cancer Center, Houston, TX
- Universitaetsklinikum Leipzig, Germany
- Hospital Universitario La Princesa, Madrid, Spain