Tagraxofusp in Patients with Chronic Myelomonocytic Leukemia (CMML): Updated Results of an Ongoing Phase 1/2 Trial

Mrinal M. Patnaik, MBBS[1], Haris Ali, MD[2], Eunice S. Wang, MD[3], Abdulraheem Yacoub, MD[4], Vikas Gupta, MD, FRCP, FRCPath[5], Sangmin Lee, MD[6], Gary Schiller, MD[7], James M. Foran, MD[8], Ayalew Tefferi, MD[1], Christopher Brooks, PhD[9], Guillermo Garcia-Manero, MD[10], Terra L. Lasho, PhD[1], Tariq I. Mughal, MD, FRCP, FRCPath[9,11], and Naveen Pemmaraju, MD[10]

[1]Mayo Clinic, Rochester, MN, USA; [2]City of Hope, Duarte, CA, USA; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [4]Kansas University Cancer Center, Westwood, KS, USA; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Weill Cornell Medical Center, New York, NY, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]Mayo Clinic Cancer Center, Jacksonville, FL, USA; [9]Stemline Therapeutics, Inc, New York, NY, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [11]Tufts University Medical School, Boston, MA, USA

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CMML

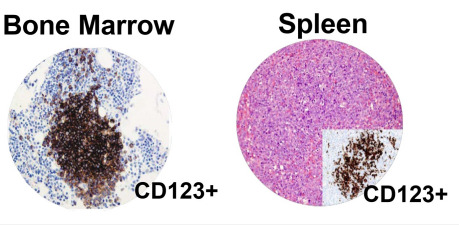
- CMML is an aggressive clonal hematopoietic stem cell disorder of older adults, with a median survival of <36 months
- Poor clinical outcomes in CMML result from bone marrow failure, high risk of transforming to AML, and competing comorbidities in older adults
- Clinical management of patients with CMML is challenging, with the only approved therapies being HMAs, which have no significant effect on the natural history of the disease
- Allogeneic stem cell transplantation can potentially offer cure, but only about 10% of patients are eligible

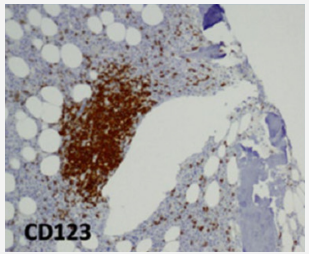
Patnaik MM, Tefferi A. *Am J Hematol*. 2020;95:97-115.

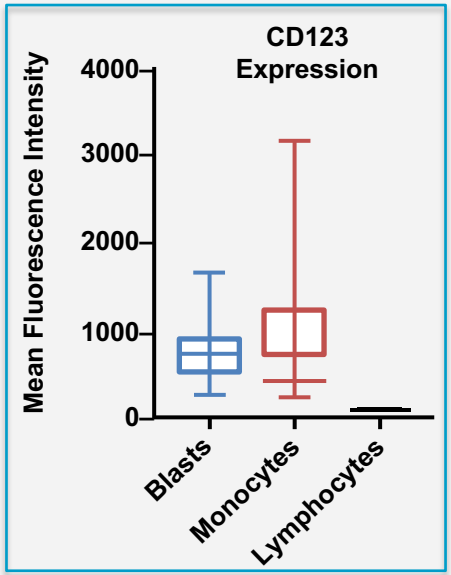
CD123 in CMML

CD123+ Cell Populations in CMML

- Expressed in key disease compartments[1,2]
- Present on both CMML blasts and monocytes[3]
- Clonal pDCs in BM and tumor microenvironment[4]

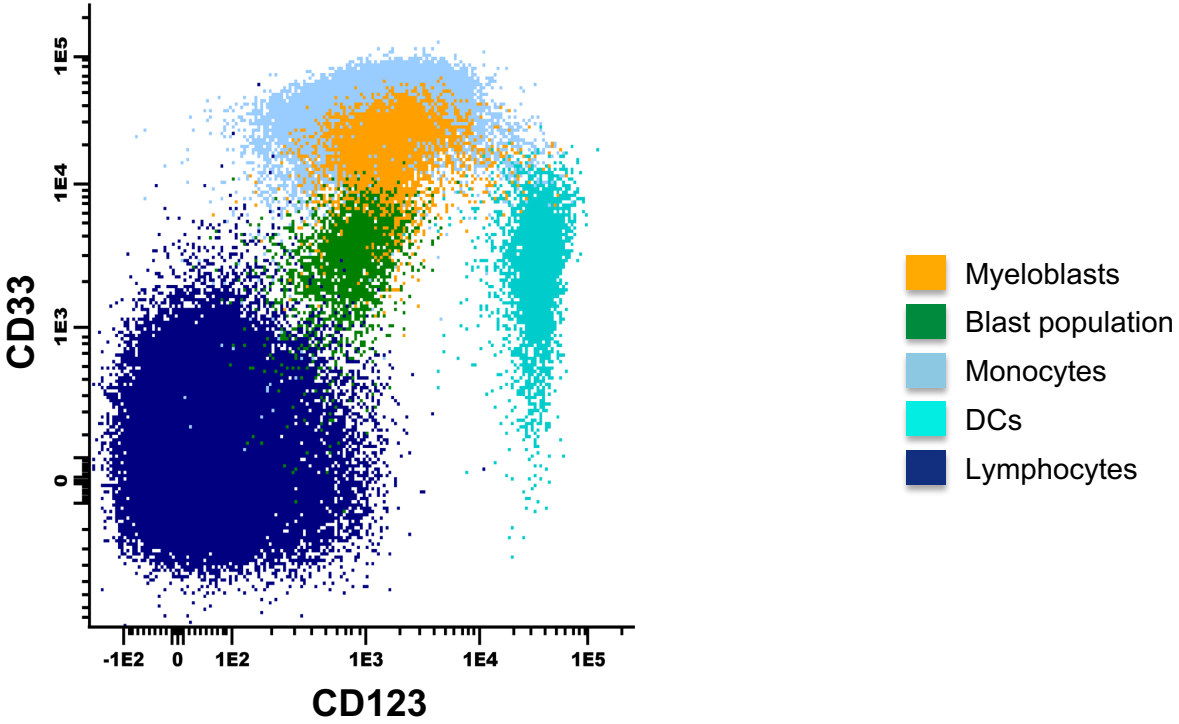






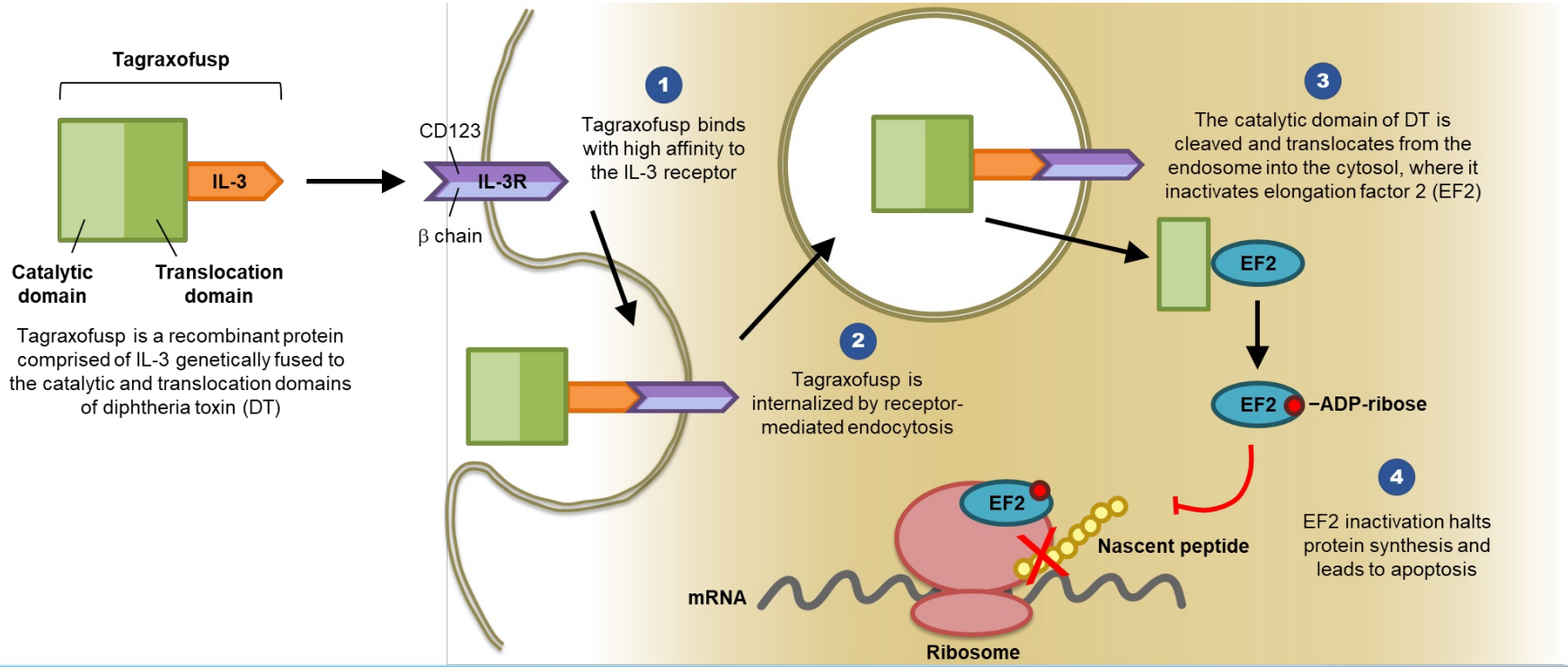
1. Orazi A, Germing U. *Leukemia*. 2008;22:1308-1319. 2. Pophali P, et al. *Am J Hematol.* 2018;93:1347-1357. 3. Krishnan A, et al. *Blood.* 2018;132 (supp 1): abstract 1809. 4. Ji P, et al. *Blood*. 2014;123:3220.

CD123 Expression on Blasts and Monocytes



Targeting CD123

- Tagraxofusp structure and mechanism of action



O'Brien J, et al. *Drugs Future.* 2018;43:873-880.

Study (NCT02268253) Objectives and Design

Multicenter, multistage, phase 1/2 trial of TAG monotherapy in adult patients with CMML

Stage 1: Lead-in (completed) | **Stage 2: Expansion (completed)** | **Stage 3A: 2-arm, non-randomized, open-label multicenter (enrolling)**

- TAG at 7-, 9-, or 12- (Stage 1) and 12-mcg/kg (Stages 2 and 3A) dose infused IV on days 1–3 of 21-day cycles (C 1–4, all stages), 28-day cycles (C 5–7, Stages 1, 2; C ≥5, Stage 3A), 42-day cycles (C ≥8, Stages 1, 2), until clinically significant PD or intolerable toxicity
- Key objectives: safety and efficacy; in Stage 3A, genomic landscape and single-cell mass cytometry are also assessed

Response Criteria

- MDS IWG 2006; MDS/MPN 2015 (with 2021 stable disease amendment)

Key Eligibility Criteria

- Age ≥18; ECOG PS 0–2
- High-risk first L; R/R
- Adequate baseline organ function
- Not eligible for allogeneic stem cell transplant

https://clinicaltrials.gov/ct2/show/NCT02268253

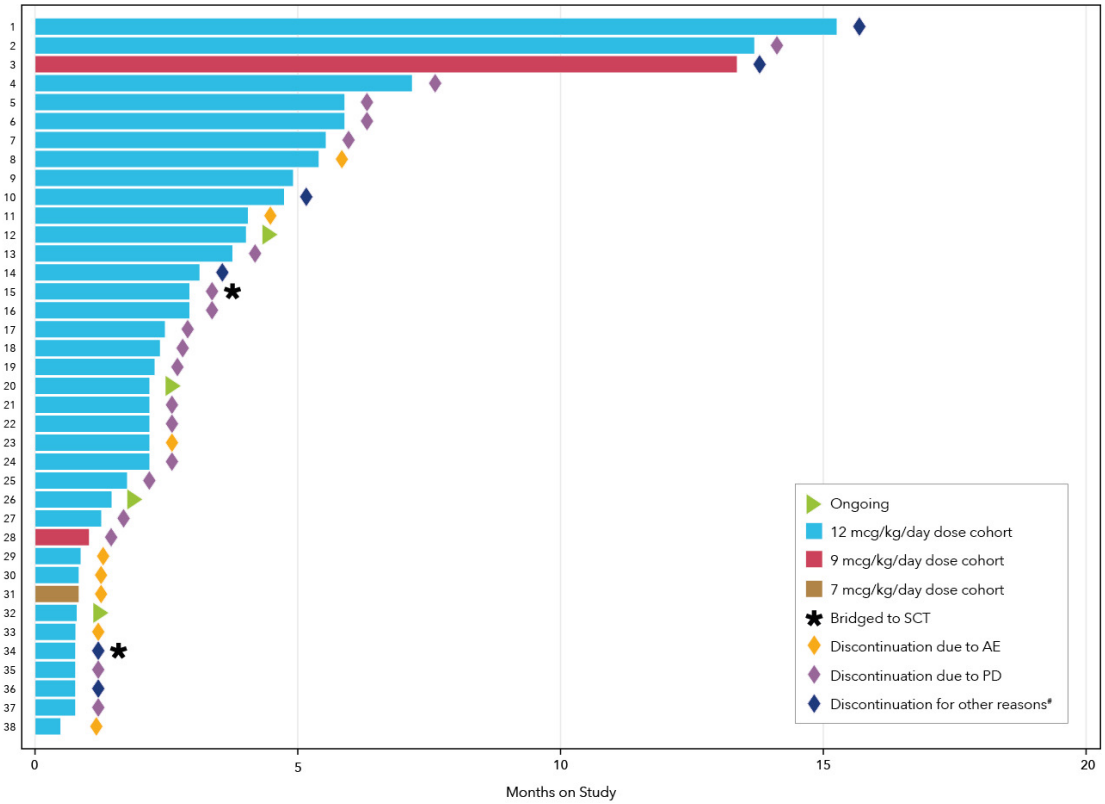
Demographics and Baseline Characteristics

Characteristic	*N=38*
Median age, years (range)	70 (42–87)
Male, n (%)	28 (73.7)
CMML type, n (%)	
CMML-1	20 (52.6)
CMML-2	17 (44.7)
Median ECOG PS (range)	1 (0–2)
Prior lines of therapy	
No/Yes, n (%)	17 (44.7)/21 (55.3)
Median (range)	1 (0–7)

Characteristic	
Cytogenetic risk category, n (%)	
High	12 (31.6)
Intermediate	11 (28.9)
Low	11 (28.9)
Other	2 (5.3)
CPSS-Mol risk, n (%)	
High	9 (23.7)
Intermediate-1	3 (7.9)
Intermediate-2	3 (7.9)
Low	6 (15.8)

This table based on available data

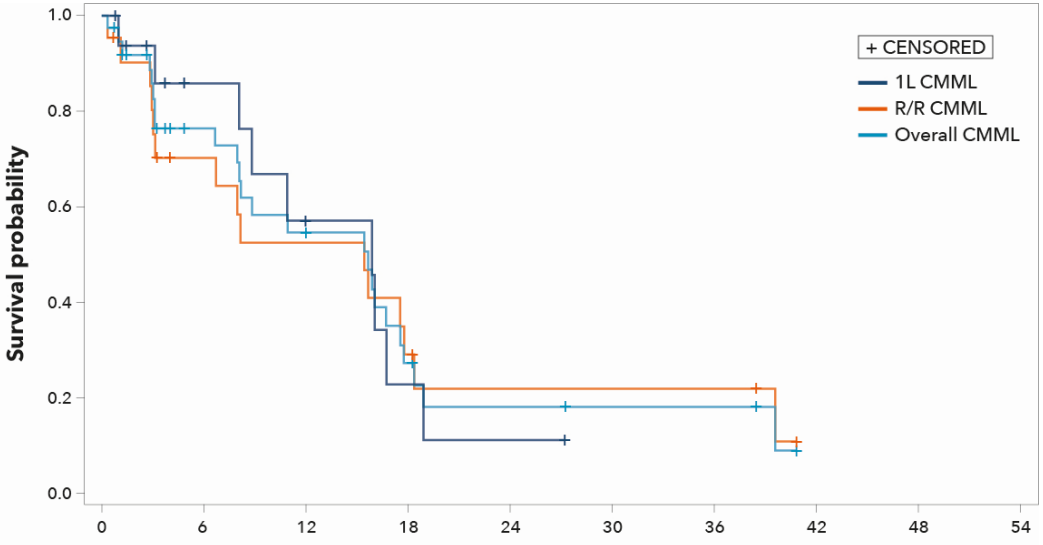
Best Response and Treatment Duration (N=38)



- Median of 4 (range, 1–15) TAG cycles

#Other reasons: disease relapse, physician decision, withdrawal by patient, and other.

Overall Survival (N=38)



No of patients at risk								
1L CMML	17	9	5	2	1	0		
R/R CMML	21	12	9	5	3	3	3	0
Overall CMML	38	21	14	7	4	3	3	0

- Data cutoff date: October 1, 2021
- Overall median OS: 15.6 months (95% CI, 8.1–17.5; range, 0.36–40.77)

Clinical Parameters of Patients with BMCR – Stages 1 and 2 (n=4 of 29)

Pt	*Demographics*		*Disease characteristics*				*TAG*		*BM (% of blasts)*	*PB (% of blasts)*	*Hem improvement/ erythroid response*	*Spleen size (cm)*		
#	Age (yr)	Sex	CMML type	Risk stratification	Line/ Prior therapy	WBC (10^9/L)	Cycles at best response	Total cycles				Baseline	Best response	Reduction
1	68	M	1	Low	R/R Hydroxyurea	17.2	4	15	9→3	1→0	Y	14	nonpalpable	100%
3	69	M	1	Intermediate	R/R Azacitidine	44.7	4	13	6→1	1→0	Y	5	nonpalpable	100%
5	71	M	2	Other	1L None	9.3	4	8	10→1	0→0	Y	4	nonpalpable	100%
34	62	M	2	High	R/R Idarubicin/ Cytarabine	9.1	1	1	15→2 Bridged to alloSCT	0→0	NA	10	2	80%

Clinical Overview: Stage 3A

- Eleven patients have been treated; presenting data on 8

Pt	*Age (yr)*	*Disease characteristics*					*Best response*
#		CMML type	Phenotype	Prior lines of therapy	Cytogenetic risk stratification	Molecular mutations	
9	79	2	Proliferative	1	High	*ASXL1*, *U2AF1*	PR
10	62	1	Dysplastic	1	Low	Not analyzed	SD
12	81	2	Proliferative	2	Low	*NRAS*, *SRSF2*, *TET2* (2 mutations)	BMPR
14	51	2	Proliferative	1	Intermediate	*ASXL1*, *KRAS*, *TET2* (2 mutations)	SD
16	59	2	Proliferative	1	High	*ASXL1, NF1*	SD
17	72	2	Proliferative	2	Low	*ASXL1*, *NRAS*, *SETBP1*, *SRSF2*	Clinical benefit – spleen response
20	62	2	Proliferative	1	Intermediate	*SRSF2*, *ASXL1*, *RUNX1*, *ETV6, SETDB1, STAT5B*	PR
32	82	2	Proliferative	1	High	*CBL, KRAS, NRAS, TET2*	PD

BM and PB Responses Stage 3A (n=8 of 11)

Pt	Age (yr)	WBC	Monocytes	Percentage of blasts
#		Baseline (10^9/L)		BM
9	79	3.5	14→0.5 (10^9/L)	5→NL
10	62	10.1	1.8→1.1 (10^9/L)	2→1
12	81	67.3	15.9→3.2 (%)	5→NL
14	51	27.5	9.6→9.2 (10^9/L)	19→16
16	59	18.6	5.5→5.4 (10^9/L)	16→6
17	72	98.2	44.3→Missing data (%)	NL→NL
20	62	3.3	0.2→Missing data (10^9/L)	0→NL
32	82	22.8	5.1→Missing data (10^9/L)	10→Missing data

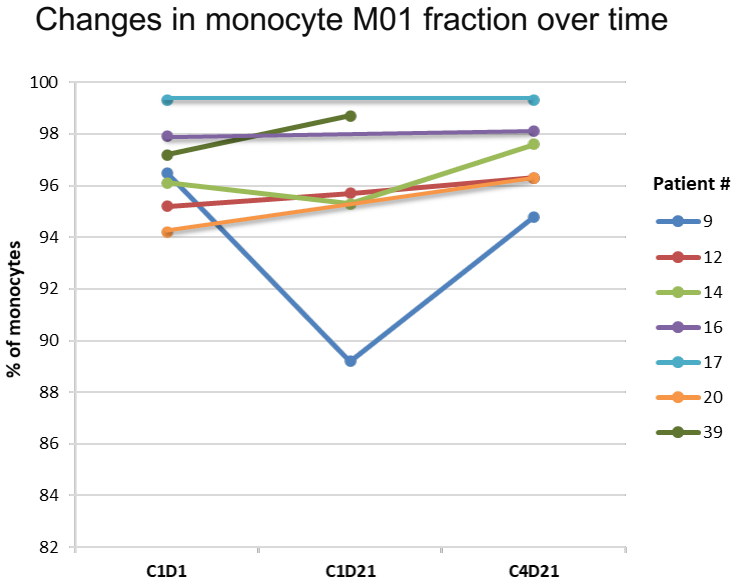
- Responses in patients #9 and 12 were associated with a substantial decrease in monocyte count

NL=normal

Clonal Dynamics on Therapy

Pt #	Gene	Nucleotide	Amino acid	VAF		
				C1D1	C1D21	C4D21
9	*U2AF1*	c.101C>T	S34F	24%	21%	44%
	ASXL1	c.1934dup	G646Wfs*12	21%	16%	38%
12	*NRAS*	c.34G>A	G12S	36%	36%	37%
	SRSF2	c.284C>T	P95L	46%	46%	44%
	TET2	c.3921delG	K1308Sfs*55	69%	67%	64%
	TET2	c.5741T>A	L1914*	42%	41%	42%
14	*ASXL1*	c.3261C>A	Y1087*	41%	44%	43%
	KRAS	c.34G>A	G12S	33%	36%	37%
	TET2	c.1648C>T	R550*	44%	44%	45%
	TET2	c.1960delC	Q654Kfs*46	64%	67%	74%
16	*ASXL1*	c.1773C>A	Y591*	39%	NT	41%
	NF1	c.1989dup	N664Efs*6	65%	NT	77%
20	*ASXL1*	c.1934dup	G646Wfs*12	24%	NT	28%
	ETV6	c.536dupT	L179Ffs*17	30%	NT	31%
	RUNX1	c.1244_1247dup	F416Lfs*185	24%	NT	26%
	SETDB1	c.3685A>C	N1229H	4%	NT	8%
	SRSF2	c.284C>G	P95R	31%	NT	35%
	STAT5B	c.2135T>A	V712G	32%	NT	36%

NT=sample not available



Safety and Tolerability (N=38)

Most common AEs (≥15% of patients)	*TRAEs, n (%)*					*TEAEs, n (%)*
Preferred term	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Nausea	10 (26)	8 (21)	1 (3)	1 (3)	0	14 (37)
Anemia	9 (24)	0	4 (11)	5 (13)	0	15 (40)
Hypoalbuminemia	9 (24)	5 (13)	4 (11)	0	0	14 (37)
Thrombocytopenia	9 (24)	0	1 (3)	3 (8)	5 (13)	9 (24)
CLS	8 (21)	0	4 (11)	4 (11)	0	8 (21)
Vomiting	7 (18)	6 (16)	1 (3)	0	0	11 (29)
ALT increase	6 (16)	5 (13)	1 (3)	0	0	11 (29)
Peripheral edema	6 (16)	5 (13)	1 (3)	0	0	13 (34)
Weight increase	6 (16)	5 (13)	1 (3)	0	0	11 (29)

- TRAEs were reported in 28 (74%) patients
- Most common G≥3 were anemia, CLS, thrombocytopenia, and nausea
- Thrombocytopenia did not occur beyond C1
- Of the 8 pts with CLS, all were in C1, with no recurrences
- Median time to all-grade CLS was 5.5 days (range, 2–26)
- One patient had a TRAE leading to study discontinuation; 13 (34%) patients had a TRAE leading to dose interruption
- No treatment-related deaths occurred

Conclusions

- TAG monotherapy in 38 patients with high-risk CMML (treatment naive and R/R) has shown reasonable clinical activity
- Evolving results suggest clinical benefits in a cohort of poor-risk patients, with 10% BM CRs and associated hematologic improvement and marked reduction in splenomegaly
- TAG monotherapy was well-tolerated in CMML, with a manageable and predictable safety profile
- Stage 3A of the trial is ongoing and, apart from efficacy/safety analysis, includes a translational biomarker discovery component
- Based on the Proof of Concept demonstrated, combination studies are planned

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