Broad Activity for the Pivekimab Sunirine (PVEK, IMGN632), Azacitidine, and Venetoclax Triplet in High-Risk Patients with Relapsed/Refractory and Frontline Acute Myeloid Leukemia (AML)

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BACKGROUND

- Azacitidine (AZA) and venetoclax (VEN) improved outcomes in frontline unfit AML (CR 37% and CR/CRi 66%), but long-term survival remains poor[1]
- Median overall survival for patients with relapsed/refractory (R/R) unfit AML is ~3-7 months[2,3]
- CD123 is expressed on the majority of AML blasts and leukemic stem cells, while minimally expressed on normal hematopoietic stem cells[4]
- Pivekimab sunirine (PVEK) is a novel CD123-targeted antibody drug conjugate (ADC) with single-agent activity in BPDCN and single-agent CR/CRi rates of 22-40% in R/R AML[5]
- Preclinical data demonstrated synergy between PVEK and AZA and/or VEN, including overcoming AZA/VEN resistance in murine AML models[6]
- PVEK is a first-in-class ADC comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload
- The IGN payload alkylates DNA and causes single strand breaks without crosslinking. IGNs are designed to have high potency against tumor cells, while demonstrating less toxicity to normal marrow progenitors than other DNA-targeting payloads[7]

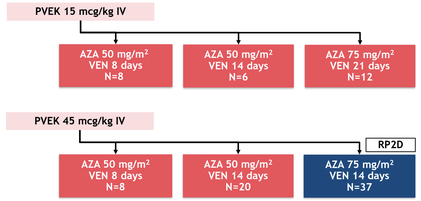
Objectives

- Here we report safety and anti-leukemic activity of PVEK+AZA+VEN from the dose-escalation and expansion cohort in patients with R/R AML and the ongoing expansion cohort in frontline AML
- Primary objective
  - Determine the safety and efficacy of PVEK when administered in combination with AZA and VEN in R/R and frontline patients with AML
  - Responses are determined using European LeukemiaNet (ELN) 2017 criteria (with the addition of CRh and CRp) and a 14-day count recovery window

Study Design and Dosing Cohorts

Open-label, multicenter, Phase 1b/2 study of PVEK in combination with AZA and VEN in patients with R/R and frontline CD123-positive AML

TRIPLET regimen
(3 variable escalation)
-PVEK 15 or 45 mcg/kg on day 7
-AZA 50 or 75 mg/m² IV/SQ on days 1-7
-VEN 400 mg PO for 8 or 14 or 21 days in a 28-day cycle



R/R AML Patient Demographics and Characteristics

Table 1. R/R AML Cohort Demographics and Characteristics (N=91)

Demographics		
Age	Median (range), years	67 (25-83)
	≥ 65 years	57% (52)
Gender	Male : Female	1.8 : 1
AML Disease Characteristics		
History/Type of AML	*De novo*	74% (67)
	Secondary	26% (24)
ELN 2017 risk	Intermediate	24% (22)
	Adverse	53% (48)
	Not Determined/Missing	22% (20)
Key Molecular Features		
	FLT3 Mutant	14% (13)
	TP53 Mutant	18% (16)
	RUNX1 Mutant	20% (18)
Prior Therapies		
Prior Lines of Treatment	2 +	53% (48)
Previous Treatment	First Relapse	35% (32)
	Primary Refractory	35% (32)
	Prior SCT	25% (23)
	Prior VEN	48% (44)

All values are % (n), unless noted otherwise

R/R AML Results: Safety Overview

Table 2. Treatment-Emergent Adverse Events (TEAE) (N=91)

	All Grades ≥ 20%	≥ Grade 3
Febrile Neutropenia	33%	29%
Thrombocytopenia	23%	20%
Dyspnea	22%	6%
Infusion Related Reaction	22%	2%
Hypokalemia	21%	2%
Fatigue	20%	2%

- Rates of cytopenias similar to those observed with HMA+VEN in R/R AML[8]
- Peripheral edema grade 1-2: 19%; no ≥ grade 3; generalized edema grade 3: 2%
- **No tumor lysis syndrome (TLS), no veno-occlusive disease (VOD), no capillary leak syndrome, no cytokine release syndrome**
- Discontinuations due to PVEK-related AEs: 5%
- 30-day mortality 6%; no treatment-related deaths

R/R AML Results: Anti-Leukemic Activity

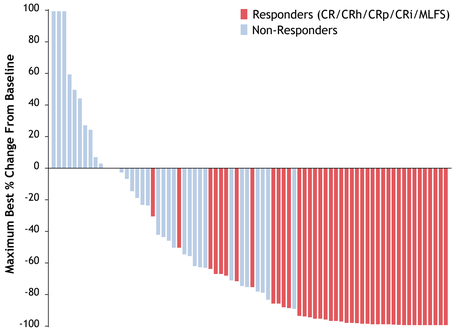
Table 3. Responses in R/R AML Patients

	N	ORR	CCR	CR	CRh	CRp or CRi	MLFS
ITT population#	91	45%	25%	13%	9%	3%	20%
RP2D cohort*	37	38%	22%	14%	5%	3%	16%

ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)
#All doses and schedules
*RP2D = PVEK 45 mcg/kg + AZA 75 mg/m² + VEN 14 days

- Median duration on study (ITT): 2.3 months (range 0.9-16 months)
- Ten patients remain on study at time of data cutoff
- Common reasons for treatment discontinuation (n=81): PD (30%); death (13%); AEs (12%); transplant (11%); and withdrawal/declined further therapy (10%)

Figure 1. Best Decrease in BM Blast (%) in R/R AML ITT Population (N=91)



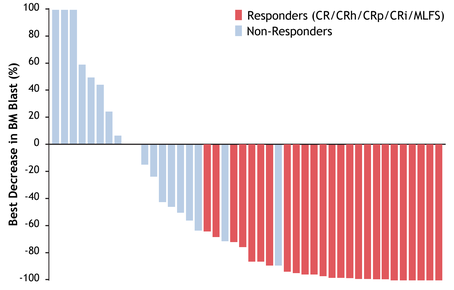
Note: 15 patients are not represented on the plot due to missing bone marrow data: 10 had clinical disease progression; 3 died without an assessment; 2 were otherwise unevaluable

- Median time to CCR was **1.1 months** (range 0.5-6.5 months)
- Median duration of CCR was **7.7 months** (range 0.3-15.6 months)
- Of MRD-evaluable responders, 8 (32%) achieved MRD-negativity*
- 24% of responders (10/41) proceeded to SCT

*MRD assessed centrally by multiparameter flow cytometry with threshold of <0.1% by Hematologics, Inc.

R/R AML Results: Responses in Subsets of Interest

Figure 2. Best Decrease in BM Blast (%) in VEN-Naïve Patients (n=47)



Note: 3 patients are not represented on the plot due to missing bone marrow data: 2 had clinical progression and 1 died without an assessment

- Median time to CCR was **1.4 months** (range 0.5-3.7 months)
- Median duration of CCR was **7.7 months** (range 0.3-12.5 months)

Table 4. Responses in R/R AML Subsets of Interest

ITT Population (all doses and schedules), N=91					
Previous Treatments	**n**	**ORR**	**CCR**	**CR**	**CR/CRh**
VEN-Naïve	47	53%	38%	26%	34%
Prior VEN	44	36%	11%	0%	9%
First Relapse	32	56%	44%	22%	41%
First Relapse & VEN-Naïve	17	65%	59%	41%	53%
Prior Stem Cell Transplant	23	43%	26%	13%	22%
Cytogenetics/Molecular	**n**	**ORR**	**CCR**	**CR**	**CR/CRh**
ELN Adverse Risk	48	42%	21%	10%	16%
IDH2 Mutant	12	67%	50%	33%	50%
FLT3-ITD	11	82%	64%	18%	54%

Frontline AML Patient Demographics and Characteristics

Table 5. Frontline AML Cohort Demographics and Disease Characteristics (N=10)

Demographics		
Age	Median (range), years	74 (62-83)
Gender	Male:Female	4:1
AML Disease Characteristics		
ECOG PS	0	40% (4)
	1	50% (5)
	2	10% (1)
AML Classification	*De novo*	80% (8)
	Secondary	20% (2)
ELN 2017 Risk*	Adverse	40% (4)
	Intermediate	30% (3)
	Favorable	10% (1)
Molecular Features		
	TP53 mutant	20% (2)
	FLT3-TKD	10% (1)
	IDH2 mutant	10% (1)
	NPM1 mutant	10% (1)

All values are % (n), unless noted otherwise
*ELN risk not assessable in 2 (20%) due to missing molecular/cytogenetic data

- All patients treated with PVEK 45 mcg/kg + AZA 75 mg/m² + VEN 14 days
  - Patients with persistent blasts were allowed to continue VEN beyond 14 days at the investigator's discretion

Table 6. Number of VEN Treatment Days Received

9-10 days of VEN	14-15 days of VEN	21-22 days of VEN
2 patients; due to AEs not related to study treatment	6 patients	2 patients; due to persistent blasts

Frontline AML Results: Anti-Leukemic Activity

- CR rate: 5/10 (50%) + 1 IWG PR
  - 1 of 2 patients with *TP53* mutation achieved CR
  - 1 of 1 patient with *FLT3*-TKD mutation achieved CR
- MRD-negative CR: 3/4 (75%)
  - All 3 achieved MRD- at end of first cycle
  - One responder was MRD-unevaluable
  - MRD assessed centrally* by multiparameter flow cytometry with threshold of <0.1%
- At time of data cut with short median follow-up:
  - 5 patients remain on treatment
    - 2 responding patients on study for <3 months
  - 1 patient bridged to allogeneic HCT
  - 1 death within 60 days (1/10)

*Hematologics, Inc. central laboratory assessing MRD

CONCLUSIONS

- PVEK+VEN+AZA demonstrated broad anti-leukemic activity in R/R and frontline AML
- Compelling CR/CRh rates were observed in several R/R AML subgroups, including specifically VEN-naïve, first relapse, and those with *IDH2* and *FLT3* mutations
- The RP2D (using 14+ days of VEN) was not associated with excessive myelosuppression and was well tolerated
- Preliminary anti-leukemic activity, with a high rate of early MRD-negative CRs, and safety in the ongoing expansion cohort of frontline patients are encouraging (NCT04086264)
- Evaluation of optimal VEN duration (14-28 days) in separate cohorts is ongoing

Abbreviations: ADC, antibody-drug conjugate; AEs, adverse events; AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CCR, composite complete remission; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission/response with incomplete recovery; CRp, complete remission/response with incomplete platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; *FLT3*, fms like tyrosine kinase 3; HMA, hypomethylating agent; *IDH2*, isocitrate dehydrogenase 2; IGN, indolinobenzodiazepine pseudodimer; ITD, internal tandem duplication; ITT, intention-to-treat; IV/SQ, intravenous/subcutaneous; IWG, International Working Group; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; *NPM1*, nucleophosmin 1; ORR, overall response rate; PO, *per os*; PR, partial response; PVEK, pivekimab sunirine; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; *RUNX1*, runt-related transcription factor 1; SCT, stem cell transplant; TEAE, treatment-emergent adverse event; TKD, tyrosine kinase domain; TLS, tumor lysis syndrome; TP53, tumor protein P53; VEN, venetoclax; VOD, veno-occlusive disease.

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