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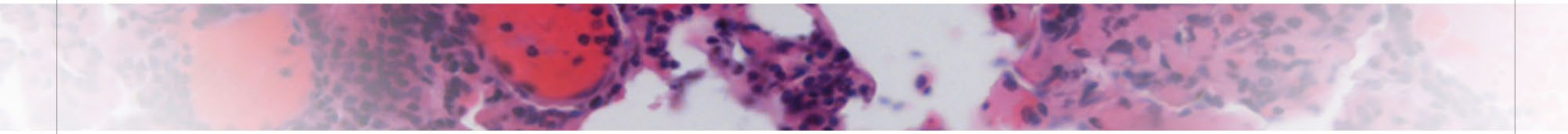

Broad activity for the pivekimab sunirine (PVEK, IMGN632), azacitidine, and venetoclax triplet in high-risk patients with relapsed/refractory and frontline acute myeloid leukemia (AML)

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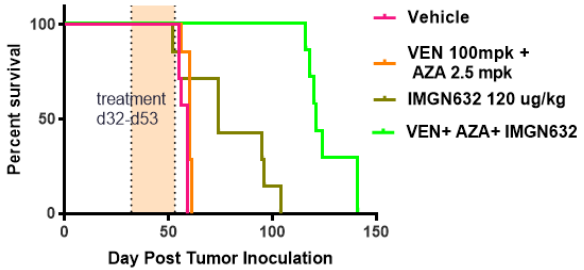
Background

- 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 with single agent activity in BPDCN[4] 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]
- 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
  - Ongoing expansion cohort in frontline AML



[6]Kuruvilla et al. *Blood* (2020); 136 (S1): 32–33.

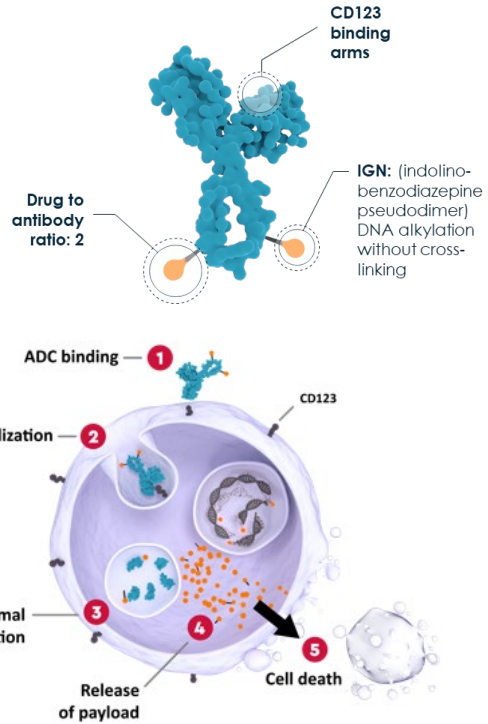
1. DiNardo CD et al. *NEJM.* 2020; 383 (7):617-629. 2.Bewersdorf JP et al. *Haematologica.* 2020; 105(11):2659-2663. 3. Ganzel C et al. *Am J Hematol.* 2018; 93(8):1074-1081.
4. Gill S, et al. *Blood.* 2014; 123(15):2343-2354. 4. Daver N et al. *Blood.* 2019;134 (supp 1):2601. 5. Daver N et al. *Blood.* 2019; 134 (supp 1):734. 6. Kuruvilla VM et al. *Blood.* 2020; 136 (supp 1):32-33.

AML, acute myeloid leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete remission; CRi, complete remission/response with incomplete recovery.

PVEK Background

- PVEK is a first-in-class antibody-drug conjugate (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[1]



1. Kovtun Y,et al. *Blood Adv.* 2018; 2(8):848-858.

Study Design and Objectives

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

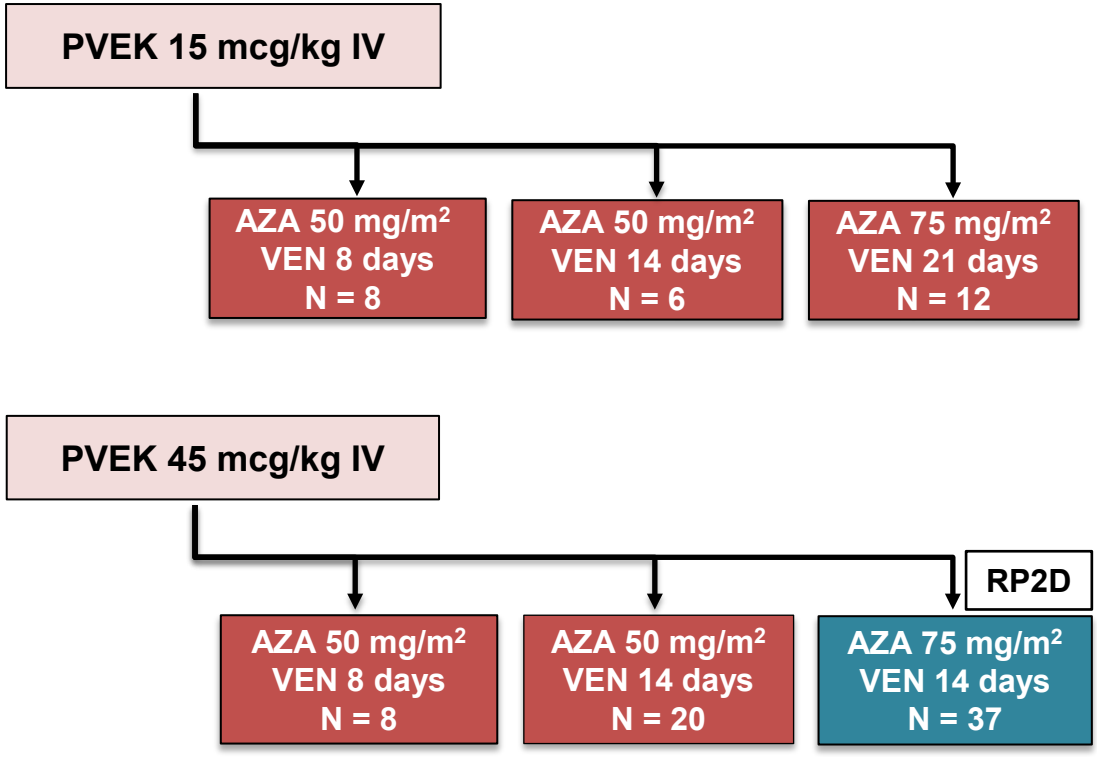
- Primary Objective:
  - Determine the safety and efficacy of PVEK when administered in combination with AZA and VEN in R/R and frontline patients with AML
  - Responses are determined using European LeukemiaNet (ELN) 2017 criteria (with the addition of CRh and CRp) and a 14-day count recovery window

AML, acute myeloid leukemia; AZA, azacitidine; CRh, complete remission with partial hematologic recovery; CRp, complete remission/response with incomplete platelet recovery; PVEK, pivekimab sunirine; R/R, relapsed/refractory; VEN, venetoclax.

Study Schema and Dosing Cohorts in R/R AML Patients

TRIPLET regimen
(3 variable escalation)

-PVEK 15 OR 45 mcg/kg on day 7
-AZA 50 OR 75 mg/m^2 IV/SQ on days 1-7
-VEN 400 mg PO for 8 OR 14 OR 21 days in a 28-day cycle



AZA, azacitidine; PVEK, pivekimab sunirine; RP2D, recommended phase 2 dose; VEN, venetoclax.

R/R AML Patient Characteristics (N=91)

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

All values are % (N), unless noted otherwise

AML, acute myeloid leukemia; ELN, European LeukemiaNet; R/R, relapsed/refractory; SCT, stem cell transplant; VEN, venetoclax.

R/R AML Safety Overview (N=91)

Treatment Emergent Adverse Effects (TEAE)	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[1]
- 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

1. Schuler E et al. *Annals of Hematology.* 2021; 100(4):959-968.

AEs, adverse events; AML, acute myeloid leukemia; HMA, hypomethylating agent; R/R, relapsed/refractory, VEN, venetoclax.

Anti-Leukemic Activity 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%**

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

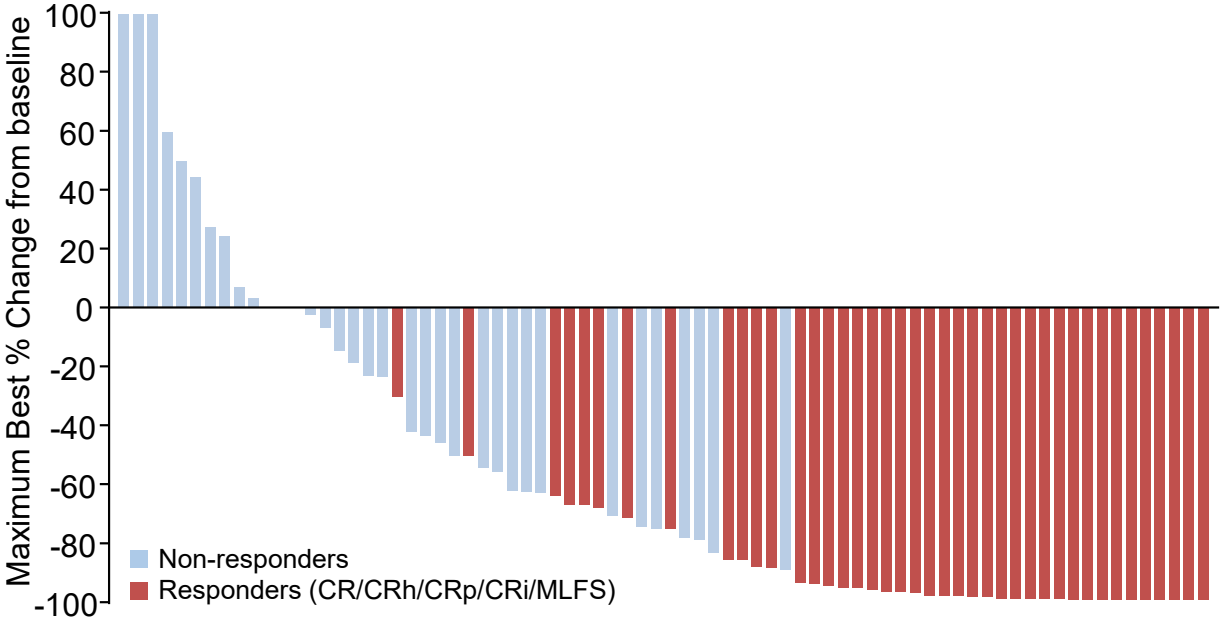
ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)

All doses and schedules

*RP2D =PVEK 45 mcg/kg + AZA 75 mg/m^2 + VEN 14 days

AEs, adverse events; 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; ITT, intention-to-treat; MLFS, morphologic leukemia-free state; ORR, overall response rate; PD, progressive disease; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Anti-Leukemic Activity in R/R AML
ITT Population



- Median time to CCR was 1.1 months (range 0.5-6.5)
- 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

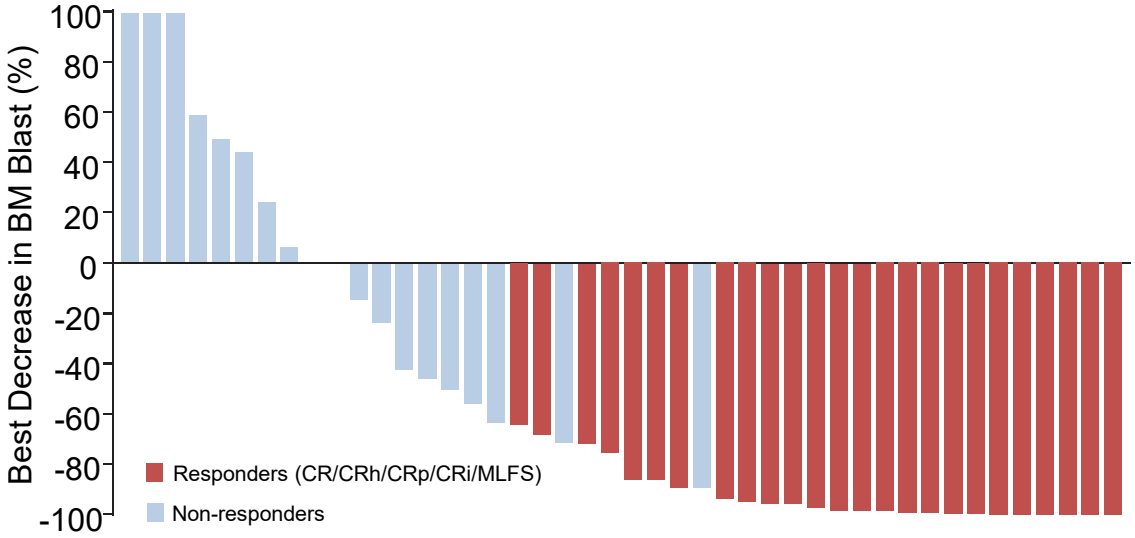
Note: 15 patients are not represented on the plot due to missing bone marrow data: 10 had clinical disease progression; 3 died without an assessment; 2 were otherwise unevaluable

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

BM, bone marrow; CCR, composite complete remission; CR, complete remission; ITT, intention-to-treat; MRD, minimal residual disease; R/R, relapsed/refractory; SCT, stem cell transplant.

Anti-Leukemic Activity in R/R AML VEN Naïve Subset

	N	ORR	CCR	CR	CR/CRh
VEN naïve patients	**47**	**53%**	**38%**	**26%**	**34%**



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

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

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

CR, complete remission; CRh, complete remission with partial hematologic recovery; ORR, overall response rate; R/R, relapsed/refractory.

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	**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%

CCR, composite complete remission; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission/response with incomplete recovery; ELN, European LeukemiaNet; ITD, internal tandem duplication; ITT, intention-to-treat; ORR, overall response rate; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

Frontline AML Patient Baseline Characteristics

Patient and Disease Characteristics (N=10)		
Age	**Median (Range)** **≥ 75y**	**74y (62-83y)** **40% (4)**
Gender	**Male:Female**	**4:1**
ECOG PS	**0** **1** **2**	**4** **5** **1**
AML Classification	**Secondary** **De novo**	**20% (2)** **80% (8)**
ELN 2017 Risk*	**Favorable** **Intermediate** **Adverse**	**10% (1)** **30% (3)** **40% (4)**
Molecular Features	**TP53 mutant** **FLT3-TKD** **IDH2 mutant** **NPM1 mutant**	**20% (2)** **10% (1)** **10% (1)** **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/m^2 + VEN 14 days
  - Patients with persistent blasts were allowed to continue VEN at the investigator's discretion

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

AEs, adverse events; AML, acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; PVEK, pivekimab sunirine; R/R, relapsed/refractory; TKD, tyrosine kinase domain; VEN, venetoclax.

Outcomes in Frontline AML Patients

- 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 toxic death within 60 days (1/10)

*Hematologics, Inc. central laboratory assessing MRD

AML, acute myeloid leukemia; CR, complete remission; CRmrd, complete remission without minimal residual disease; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; PR, partial response; TKD, tyrosine kinase domain.

Conclusions

- PVEK+VEN+AZA has 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
- Preliminary anti-leukemic activity, with a high rate of early MRD-negative CR, and safety in the ongoing expansion cohort of frontline patients are encouraging (NCT04086264)
- The RP2D (using 14+ days of VEN) was not associated with excessive myelosuppression and was well tolerated
- Evaluation of optimal VEN duration (14-28 days) in separate cohorts is ongoing

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRh, complete remission with partial hematologic recovery; PVEK, pivekimab sunirine; PR2D, recommended phase 2 dose; MRD, minimal residual disease; R/R, relapsed/refractory; VEN, venetoclax.

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