Pivekimab Sunirine (PVEK, IMGN632), a CD123-Targeting Antibody-Drug Conjugate, in Combination with Azacitidine and Venetoclax in Patients with Newly Diagnosed Acute Myeloid Leukemia

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Results: Cycle Delays and Count Recovery Kinetics

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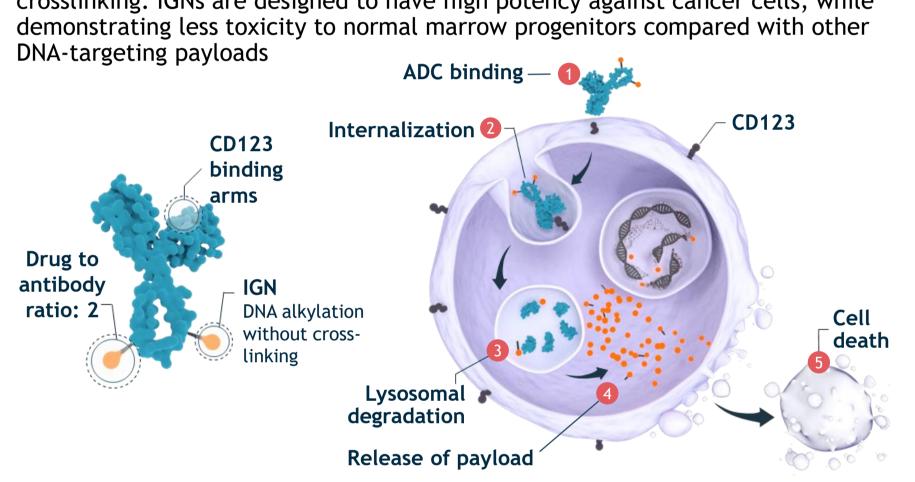
BACKGROUND

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- In unfit patients with newly diagnosed (ND) AML, long-term survival remains short (mOS 14.7 months) despite improved responses (CR 37% and CR/CRi 66%) with azacitidine (AZA) and venetoclax (VEN)¹
- Several prognostic molecular features have been identified that are associated with intermediate (FLT3-ITD, KRAS, and NRAS) and lower (TP53^{mut}) derived treatment benefit in patients receiving AZA+VEN^{2,3}
- In a pooled analysis of AZA+VEN in ND AML patients with poor risk cytogenetics, the response rates were higher in TP53wt patients (CR/CRi 70%) compared with TP53^{mut} patients (CR/CRi 41%)²
- The measurable residual disease-negative rate was 41% among responders to AZA+VEN in the phase 3 VIALE-A trial (NCT02993523) with measurable residual disease negativity associated with improved survival⁴
- Early clinical data reported at ASH 2022 in 10 newly diagnosed patients with AML treated with PVEK+AZA+VEN, demonstrated preliminary antileukemia activity with high rates of early MRD-negative CRs (75%; n=4/5) which led to the continued clinical exploration of the PVEK triplet in patients with newly diagnosed AML^{5,6}

PVEK Mechanism of Action⁷

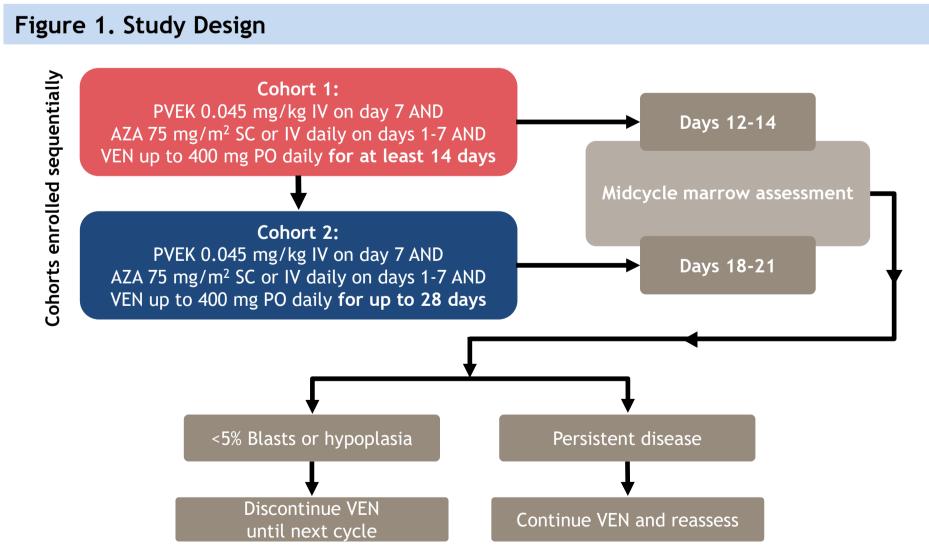
- PVEK is a first-in-class antibody-drug conjugate (ADC) comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload
- The IGN payload alkylates DNA and causes single-strand breaks without crosslinking. IGNs are designed to have high potency against cancer cells, while demonstrating less toxicity to normal marrow progenitors compared with other



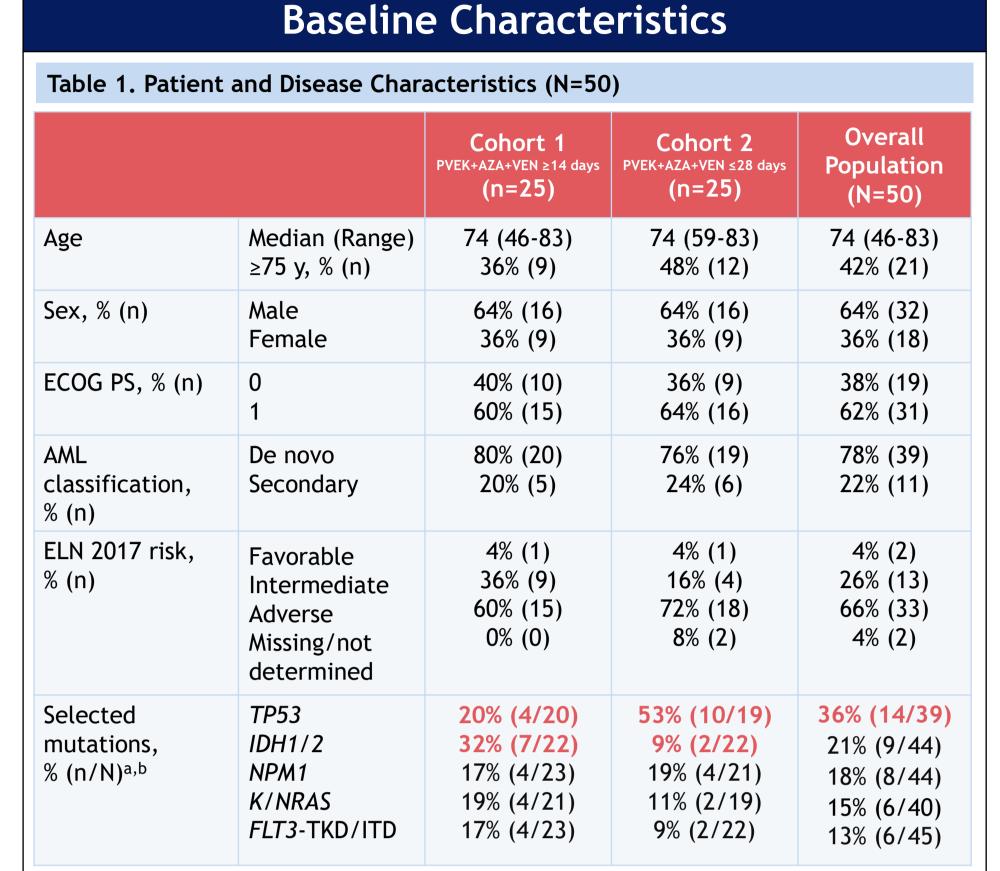
Objective

To evaluate the safety and antileukemia activity in patients with newly diagnosed AML receiving the PVEK+AZA+VEN triplet regimen

Methods: Study Design



- This is an open-label, multicenter, phase 1b/2 study of PVEK administered in combination regimens in patients with frontline CD123+ AML (NCT04086264)
- Patients will receive the established recommended phase 2 dose (RP2D) of PVEK 0.045 mg/kg IV, as a <30-minute outpatient infusion
- Patients must have CD123+ AML (any level), confirmed by local flow cytometry or IHC
- The primary endpoints are composite CR rate (CCR [CR+CRh+CRp+CRi]), MRD rate (assessed centrally [HematoLogics, Inc.] by flow cytometry; <0.1% defined as negative), and duration of remission
- Responses were determined using ELN 2017 criteria (with the addition of CRh) and a 14-day post-marrow count recovery window
- Key secondary endpoints are safety, pharmacokinetics, and immunogenicity
- As of September 29, 2023, data are available for 50 patients (n=25 per cohort) treated with PVEK+AZA+VEN



^aCharacteristics highlighted in red represent notable differences in incidence of mutations between cohorts There are patients without complete molecular data available

Results: Safety Figure 2. Non-Hematological TEAEs (>20% in Overall Population) by Cohort Cohort 1 (n=25) Cohort 2 (n=25) € 40 Nausea Hypotension Pyrexia Hypokalemia

Incidence of non-hematologic TEAEs was comparable between the two cohorts

Due to the relatively small numbers in each cohort, the significant differences in molecular subsets enrolled in each cohort, and the similar safety profiles, additional safety data (including hematologic events) and the antileukemia activity data are combined to provide an overall antileukemia activity profile for the PVEK

reatment Discontinuations and Deaths in Overall Population

- Treatment discontinuations due to AE: 2 patients (4%; generalized edema and prolonged myelosuppression/marrow hypoplasia)
- 30-day mortality: 0%
- 60-day mortality: 2 patients (4%; pneumonia and early disease progression)

Table 2. Selected TEAEs in the Overall Population (N=50)		
	All Grades	Grade
Edema events ^a Peripheral edema Generalized edema	44% 6%	4% 4%
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Edema events ^a Peripheral edema Generalized edema	44 % 6 %	4% 4%
Infusion-related reactions (IRRs)b	16%	0%
Hepatotoxicity ALT/AST elevation Hyperbilirubinemia VOD/SOS	8% 2% 0%	4% 0% 0%

^aPreferred terms (MedDRA v24.0) under edema include peripheral edema, generalized edema, fluid overload, peripheral ^bTo mitigate IRRs, the prophylaxis regimen includes additional steroid doses on the day before the PVEK infusion

Additional Details on Edema Adverse Events

- 48% of patients had ≥1 edema AEs which were mostly grade 1-2, with no grade 4
- Median time to onset for an edema event (all grades) was 23 days
- 74% of all edema events resolved Median time to resolution for all-grade edema events was 10 days (range, 1-87)
- 37% of edema events were treated with diuretic(s) for a median of 7.5 days (range, 1-478)
- 17% of events used ≥2 diuretics No CLS events were reported
- Concurrent albumin levels <3 g/dL occurred in only 15% of edema events

Table 3. Cycle Delays Blast Clearance Cycleb, Post-Remission Cyclesb 11 (1-51) 13 (-2-63) Median, days (range)a ^aFrom day 28 of each cycle bln patients achieving CCR Reported by first cycle achieving blast clearance Cycle delays are manageable and consistent with the median post-remission cycle delay of 13 days as in the AZA+VEN arm as published in the VIALE-A trial8 Table 4. Count Recovery Kinetics^a PLT ≥50k/µL ANC ≥500/µL Median, days (range) Median, days (range) 22 (20-52) 34 (20-55) Blast clearance cycle 28 (20-132) Post-remission cycles 22 (20-132) aln patients achieving CCR 26% of patients had concomitant G-CSF use Figure 3. Count Recovery Curves of Overall Time to Platelet and ANC Recovery^{a,b} Overall time to ANC ≥500 µL Time (days) Overall time to platelet ≥50,000 µL

Results: Dose Modifications By cycle 3, 97% of patients on treatment had ≤14 days of VEN per cycle

Results: Antileukemia Activity Table 5. Antileukemia Activity^a CCR_{MRD-}c CR rate CCR rateb Overall population 54% (27/50) 76% (22/29) 68% (34/50)

Responses determined by ELN 2017 criteria (with addition of CRh)

61% (14/23)

^aIn efficacy evaluable patients who demonstrated a CR, CRi, CRp, or CRh

28% of patients had AZA dose modifications

^bIn blast clearance cycle

Meets unfit FDA

criteriad (n=23)

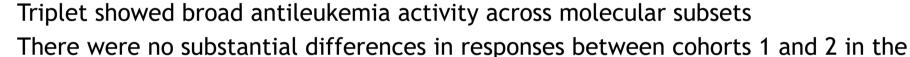
cMRD rate (assessed centrally [HematoLogics, Inc.] by flow cytometry; <0.1% defined as negative) dUnfit by FDA criteria includes patients ≥75 years old, or younger patients with defined organ dysfunction; the 27 patients who were not included in unfit population by FDA criteria were <75 years old without defined comorbidities

78% (18/23)

79% (11/14)

- The median time to MRD clearance was 1.87 months (range, 0.79-5.16)
- Response rates and MRD negativity were comparable between cohorts 1 and 2
- In patients with a duration of VEN ≤14 days (n=21) in cycle 1, 76% of patients had a best overall response of CCR
- In patients with a duration of VEN ≥22 days (n=20) in cycle 1, 75% of patients had a best overall response of CCR
- Similar CCR rates were observed, despite the difference in VEN duration

Results: Antileukemia Activity in Subsets of Interest Table 6. Antileukemia Activity in Subsets of Interest (N=50) **PVEK Triplet** 88% (22/25) 84% (21/25) 80% (16/20) TP53 status 50% (7/14) 21% (3/14) 50% (3/6) 100% (6/6) FLT3 ITD or TKD 100% (6/6) CCR 100% (4/4) 67% (2/3) CCR 100% (6/6) MRD-83% (5/6) CCR 100% (8/8) NPM1^{mut} MRD-86% (6/7) CCR 50% (3/6) K/NRAS^{mut} MRD-67% (2/3) CCR=CR+CRh+CRp+CRi MRD rate assessed centrally (HematoLogics, Inc.) by flow cytometry; <0.1% defined as negative



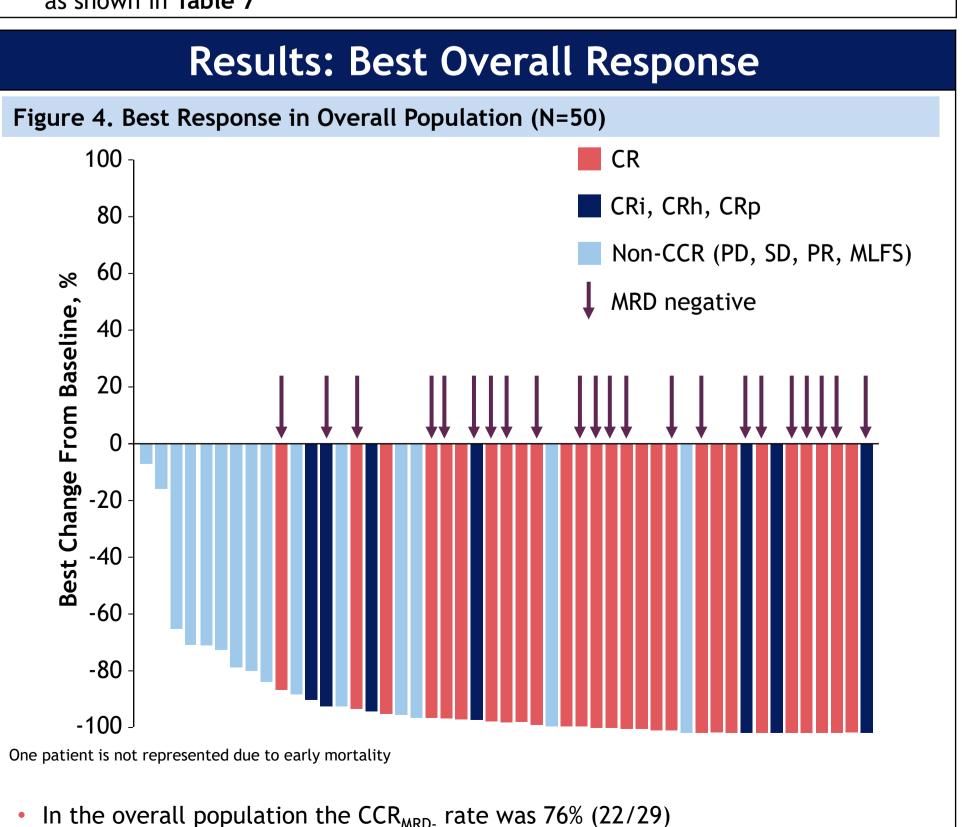
- subset analyses
- Study population was enriched for adverse molecular subset of *TP53*^{mut} (36%)

Table 7. Molecular Stratifications in Subsets of Interest (N=50)			
		PVEK Triplet	
Higher benefit	CCR CR MRD-	94% (17/18) 89% (16/18) 73% (11/15)	
Intermediate benefit	CCR CR MRD-	71% (5/7) 71% (5/7) 100% (5/5)	
Lower benefit	CCR CR MRD-	50% (7/14) 21% (3/14) 50% (3/6)	

A pooled analysis of the phase 3 VIALE-A trial and a phase 1b trial demonstrated that risk stratification based on molecular features predicted response better than ELN/cytogenetic risk³

 Higher benefit group: TP53^{wt}, no FLT3-ITD, K/NRAS^{wt} Intermediate benefit group: TP53^{wt} and FLT3-ITD or K/NRAS^{mut} Lower benefit group: TP53^{mut}

These molecular risk categories have been applied to the PVEK triplet population as shown in **Table 7**



Of MRD-negative patients, all except one had undetectable disease below lower

limit of detection (0.02%)

Results: Response Duration Figure 6. Duration of Overall Response CRi, CRh, CRp Non-CCR (PD, SD, PR, MLFS) □ Death ► Censored, alive Censored, new anti-cancer therapy Progressive disease/relapse Time since first dose (months) 14 patients (28% of overall population; 41% of those achieving CCR) underwent consolidative HCT after completing study treatment The median duration of follow up was 5.16 months

CONCLUSIONS

Landmark Overall Survival Estimates in Overall Population (N=50)

- Non-hematologic safety consistent with known safety profile of PVEK with manageable peripheral edema and mitigated IRR incidence/severity
- No VOD/SOS was observed

Landmark, mos

 Low early mortality and AE-related discontinuations were observed The addition of PVEK did not notably prolong count recovery, with ANC ≥500/µL and platelet ≥50k/µL recovery times of 34 and 22 days, respectively

Triplet Estimate (95% CI)

92% (80-97)

86% (72-94)

- The triplet regimen demonstrated similar post-remission cycle delays (13 days), as what has been published in the VEN-AZA doublet of the VIALE-A trial
- The PVEK triplet demonstrates consistently high rates of CR, CCR, and MRD negativity
- The CR and MRD negativity rates are especially encouraging Broad antileukemia activity was observed across molecular subsets
- Time to achieving MRD clearance suggests rapid and deep disease control These results support continued development of the PVEK triplet in newly
- diagnosed AML The study is continuing to enroll newly diagnosed unfit AML patients (NCT04086264)

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; AST, aspartate aminotransferase; AZA, azacitidine; CCR, composite CR rate; CD, cluster of differentiation; CI, confidence interval; CLS, capillary leak syndrome; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission/response with incomplete recovery; CR_{MRD-}, CR without minimal residual disease; CRp, complete remission/response with incomplete platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; FDA, US Food and Drug Administration; FLT3-ITD, FMS related receptor tyrosine kinase 3; G-CSF, granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant; IDH, isocitrate dehydrogenase; IGN, indolinobenzodiazepine pseudodimer; IHC, immunohistochemistry; IRRs, infusion-related reactions; ITD, internal tandem duplication; IV, intravenously; KRAS, Kirsten rat sarcoma viral oncogene homolog; MLFS, morphologic leukemiafree state; mOS, median overall survival; MRD, minimal residual disease; MRD-, without minimal residual disease; mut, mutation; ND, newly diagnosed; NPM, nucleophosmin; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; PD, progressive disease; PLT, platelet; PO, given by mouth; PR, partial remission; PVEK, pivekimab sunirine; RP2D, recommended phase 2 dose; SC, subcutaneously; SD, stable disease; SOS, sinusoidal obstruction syndrome; TEAEs, treatmentemergent adverse events; TKD, tyrosine kinase domain; TP53, tumor protein 53; VEN, venetoclax; VOD, veno-occlusive disease.

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