# 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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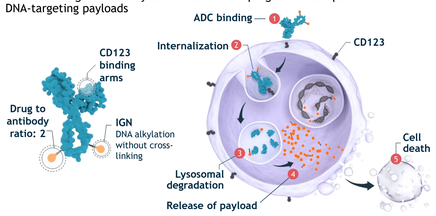
## BACKGROUND

- 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 *TP53*$^{wt}$ 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 survival[4]
- 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 Action[7]

- 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 DNA-targeting payloads

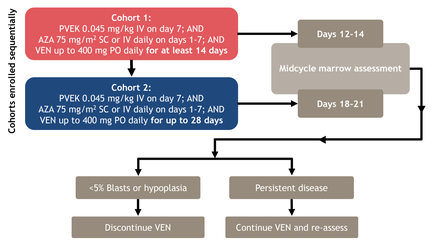



## Objective

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

## Methods: Study Design

**Figure 1. Study Design**




- This is an open-label, multicenter, phase 1b/2 study of PVEK administered in combination regimens in patients with newly diagnosed 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-positive 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 is available for 50 patients (n=25 per cohort) treated with the PVEK+AZA+VEN triplet

## Baseline Characteristics

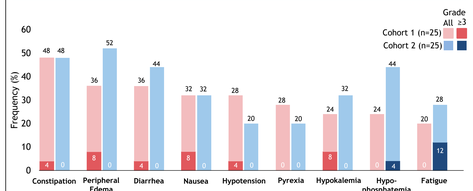
**Table 1. Patient and Disease Characteristics (N=50)**

| | | Cohort 1 PVEK+AZA+VEN ≤14 days (n=25) | Cohort 2 PVEK+AZA+VEN ≤28 days (n=25) | Overall Population (N=50) |
|---|---|---|---|---|
| Age | Median (Range) | 74, (46-83) | 74, (59-83) | 74, (46-83) |
| | ≥75 y | 36% (9) | 48% (12) | 42% (21) |
| Gender, % (n) | Male | 64% (16) | 64% (16) | 64% (32) |
| | Female | 36% (9) | 36% (9) | 36% (18) |
| ECOG PS, % (n) | 0 | 40% (10) | 36% (9) | 38% (19) |
| | 1 | 60% (15) | 64% (16) | 62% (31) |
| AML Classification, % (n) | De novo | 80% (20) | 76% (19) | 78% (39) |
| | Secondary | 20% (5) | 24% (6) | 22% (11) |
| ELN 2017 Risk, % (n) | Favorable | 4% (1) | 4% (1) | 4% (2) |
| | Intermediate | 36% (9) | 16% (4) | 26% (13) |
| | Adverse | 60% (15) | 72% (18) | 66% (33) |
| | Missing/not determined | 0% (0) | 8% (2) | 4% (2) |
| Selected Mutations[a,b], % | *TP53* | 20% (4/20) | 53% (10/19) | 36% (14/39) |
| | *IDH1/2* | 32% (7/22) | 9% (2/22) | 21% (9/44) |
| | *NPM1* | 17% (4/23) | 19% (4/21) | 18% (8/44) |
| | *K/NRAS* | 19% (4/21) | 11% (2/19) | 15% (6/40) |
| | *FLT3*-TKD/ITD | 17% (4/23) | 9% (2/22) | 13% (6/45) |

[a]Characteristics highlighted in red represent notable differences in incidence of mutations between cohorts
[b]There are patients without complete molecular data available

## Results: Safety

**Figure 2. Non-hematological TEAEs (>20% in overall population) by Cohort**




- 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 triplet

**Treatment Discontinuations and Deaths in Overall Population**

- Treatment discontinuation 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 3 |
|---|---|---|
| Edema events[a] | | |
| Peripheral edema | 44% | 4% |
| Generalized edema | 6% | 4% |
| Infusion related reactions (IRRs)[b] | 16% | 0% |
| Hepatotoxicity | | |
| ALT/AST elevation | 8% | 4% |
| Hyperbilirubinemia | 2% | 0% |
| VOD/SOS | 0% | 0% |

[a]Preferred terms (MedDRA v24.0) under edema include: peripheral edema, generalized edema, fluid overload, peripheral swelling, localized edema, fluid retention
[b]To 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 events
  - Median time to onset for an edema event (all grades) was 23 days (range, 1-243)
- 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 reported
  - Concurrent albumin levels < 3 g/dL occurred in only 15% of edema events

## Results: Cycle Delays and Count Recovery Kinetics

**Table 3. Cycle Delays**

| | Blast clearance cycle[b,c] | Post-remission cycles[b] |
|---|---|---|
| Median, days (range)[a] | 11 (1-51) | 13 (-2-63) |

[a]From day 28 of each cycle
[b]In patients achieving CCR
[c]Reported by first cycle achieving blast clearance

- Cycle delays are manageable and consistent with the median post remission cycle delay of 13 days as published in the VEN-AZA arm of the VIALE-A trial[8]

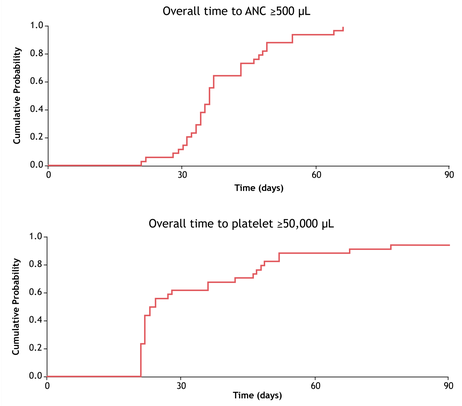
**Table 4. Count Recovery Kinetics[a]**

| | ANC≥500/µL Median, days (range) | PLT≥50k/µL Median, days (range) |
|---|---|---|
| Blast clearance cycle | 34 (20-55) | 22 (20-52) |
| Post-remission cycles | 28 (20-132) | 22 (20-132) |

[a]In 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]**




[a]In efficacy evaluable patients who demonstrated a CR, CRi, CRp, or CRh
[b]In blast clearance cycle

## Dose Modifications

- By cycle 3, 97% of patients on treatment had ≤14 days of VEN per cycle
- 28% of patients had AZA dose modifications

## Results: Antileukemia Activity

**Table 5. Antileukemia Activity[a]**

| | CR rate | CCR rate[b] | $CCR_{mrd-}$[c] |
|---|---|---|---|
| Overall Population (N=50) | 54% (27/50) | 68% (34/50) | 76% (22/29) |
| Meets unfit FDA criteria[d] (n=23) | 61% (14/23) | 78% (18/23) | 79% (11/14) |

[a]Responses determined by ELN 2017 criteria (with addition of CRh)
[b]CCR=CR+CRh+CRp+CRi
[c]MRD rate (assessed centrally [Hematologics, Inc.] by flow cytometry: <0.1% defined as negative)
[d]Unfit 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

- 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 |
|---|---|---|---|
| *TP53* status | Wildtype | CCR | 88% (22/25) |
| | | CR | 84% (21/25) |
| | | MRD- | 80% (16/20) |
| | Mutant | CCR | 50% (7/14) |
| | | CR | 21% (3/14) |
| | | MRD- | 50% (3/6) |
| *FLT3* ITD or TKD | | CCR | 100% (6/6) |
| | | MRD- | 100% (6/6) |
| *IDH1*$^{mut}$ | | CCR | 100% (4/4) |
| | | MRD- | 67% (2/3) |
| *IDH2*$^{mut}$ | | CCR | 100% (6/6) |
| | | MRD- | 83% (5/6) |
| *NPM1*$^{mut}$ | | CCR | 100% (8/8) |
| | | MRD- | 86% (6/7) |
| *K/NRAS*$^{mut}$ | | CCR | 50% (3/6) |
| | | MRD- | 67% (2/3) |

CCR=CR+CRh+CRp+CRi
MRD rate assessed centrally (Hematologics, Inc.) by flow cytometry; <0.1% defined as negative

- Triplet showed broad antileukemia activity across molecular subsets
- There were no substantial differences in responses between cohorts 1 and 2 in the subset analyses
- Study population was enriched for adverse molecular subset of *TP53*$^{mut}$ (36%)

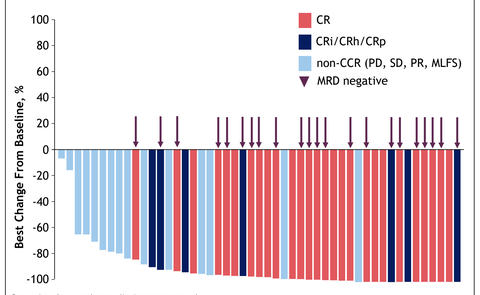
**Table 7. Molecular Stratifications in Subsets of Interest**

| | | PVEK Triplet |
|---|---|---|
| Higher benefit | CCR | 94% (17/18) |
| | CR | 89% (16/18) |
| | MRD- | 73% (11/15) |
| Intermediate benefit | CCR | 71% (5/7) |
| | CR | 71% (5/7) |
| | MRD- | 100% (5/5) |
| Lower benefit | CCR | 50% (7/14) |
| | CR | 21% (3/14) |
| | MRD- | 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 risk[3]
  - 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**

## Results: Best Overall Response

**Figure 4. Best Response in Overall Population (N=50)**

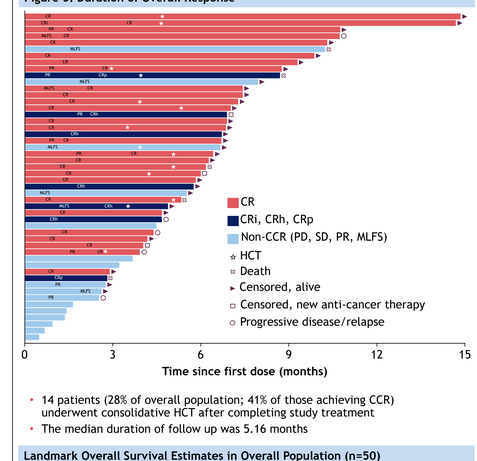



One patient due to early mortality is not represented

- In the overall population the $CCR_{mrd-}$ rate was 76% (22/29)
- Of MRD-negative patients, all except one, had undetectable disease below lower limit of detection (0.02%)

## Results: Response Duration

**Figure 5. Duration of Overall Response**




- 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

**Landmark Overall Survival Estimates in Overall Population (n=50)**

| Landmark, mos | Triplet Estimate (95% CI) |
|---|---|
| 3 | 92% (80-97) |
| 6 | 86% (72-94) |

## CONCLUSIONS

- Non-hematologic safety consistent with known safety profile of PVEK with manageable peripheral edema and mitigated IRR incidence/severity
  - No VOD/SOS was observed
  - Low early mortality and AE-related discontinuations 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
- The triplet regimen demonstrated similar post remission cycle delays (13 days), as what has been published in the VEN-AZA doublet in the VIALE-A trial
- The PVEK triplet demonstrates consistently high rates of CR, CCR, and MRD negativity
  - The CR rates are especially encouraging
  - Broad antileukemia activity 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; CRi, complete remission/response with incomplete recovery; $CR_{mrd-}$, CR without minimal residual disease; CRh, complete remission with partial hematologic recovery; CRp, complete remission/response with incomplete platelet recovery; ECOG PS, Easter Cooperative Oncology Group performance status; ELN, European LeukemiaNet; FDA, US Food and Drug Administration; *FLT3*-ITD, *FMS* related 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 virus; MLFS, morphologic leukemia-free 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, treatment-emergent adverse events; TKD, tyrosine kinase domain; *TP53*, tumor protein 53; VEN, venetoclax; VOD, veno-occlusive disease.

**References:** **1.** DiNardo C, et al. *N Engl J Med*. 2020;383:617-625. **2.** Pollyea D, et al. *Clin Cancer Res*. 2022;28(24):5272-5279. **3.** Dohner H, et al. Presented at: 2022 American Society of Hematology Annual Meeting. December 11, 2022. New Orleans, LA. Abstract 602. **4.** Pratz KW, et al. *J Clin Oncol*. 2022;40(8):855-865. **5.** ClinicalTrials.gov identifier: NCT04086264. Updated October 6, 2023. Accessed November 8, 2023. https://www.clinicaltrials.gov/study/NCT04086264. **6.** Daver N, et al. Presented at: 2022 American Society of Hematology Annual Meeting. December 10-13, 2022; New Orleans, LA. Abstract 62. **7.** Kovtun Y, et al. *Blood Adv*. 2018;2(8):848-858. **8.** Pratz KW, et al. *Am J Hematol*. 2022;97(11):E416-E419.

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