

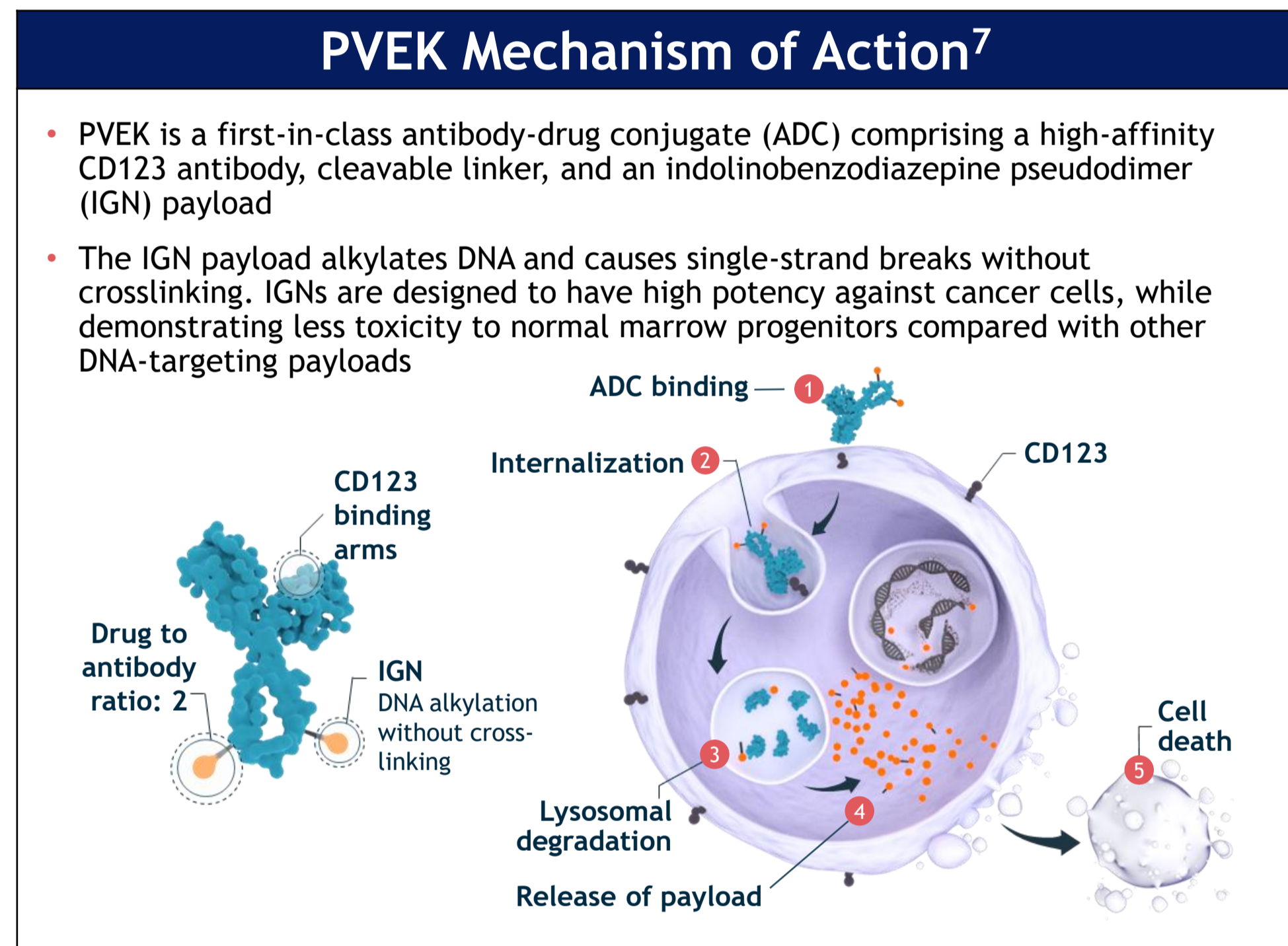
Pivekimab Sunirine (PVEK, IMGN632), a CD123-Targeting Antibody-Drug Conjugate, in Combination with Azacitidine and Venetoclax in Patients with Newly Diagnosed Acute Myeloid Leukemia

Naval Daver,¹ Pau Montesinos,² Jessica K. Altman,³ Eunice S. Wang,⁴ Giovanni Martinelli,⁵ Gail J. Roboz,⁶ Kebede Begna,⁷ Paresh Vyas,⁸ Monia Lunghi,⁹ Uwe Platzbecker,¹⁰ Patrick W. Burke,¹¹ Roland B. Walter,¹² Anjali Advani,¹³ Sylvain Garciaz,¹⁴ Lauris Gastaud,¹⁵ David A. Sallman,¹⁶ Naveen Pemmaraju,¹ Laura Torres,² Yasmin Abaza,³ Onyee Chan,¹⁶ Hagop Kantarjian,¹ Benjamin Oshrine,¹⁷ Yining Du,¹⁷ Kara Malcolm,¹⁷ Kendra Sweet¹⁶

¹The University of Texas, MD Anderson Cancer Center, Houston, Texas, USA; ²Hospital Universitari i Politècnic La Fe, València, Spain; ³Northwestern University, Chicago, Illinois, USA; ⁴Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA; ⁵IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" IRST S.r.l., Meldola, Italy; ⁶Weill Cornell Medicine and The New York Presbyterian Hospital, New York, USA; ⁷Mayo Clinic, Rochester, Minnesota, USA; ⁸University of Oxford, Oxford, United Kingdom; ⁹University of Eastern Piedmont, Novara, Italy; ¹⁰University Hospital of Leipzig, Leipzig, Germany; ¹¹University of Michigan, Ann Arbor, Michigan, USA; ¹²Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; ¹³Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio, USA; ¹⁴Aix-Marseille Univ, Inserm, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France; ¹⁵Antoine Lacassagne Hospital, Tourrettes-sur-Loup, France; ¹⁶H. Lee Moffitt Cancer Center, Tampa, Florida, USA; ¹⁷ImmunoGen, Inc., Waltham, Massachusetts, USA

BACKGROUND

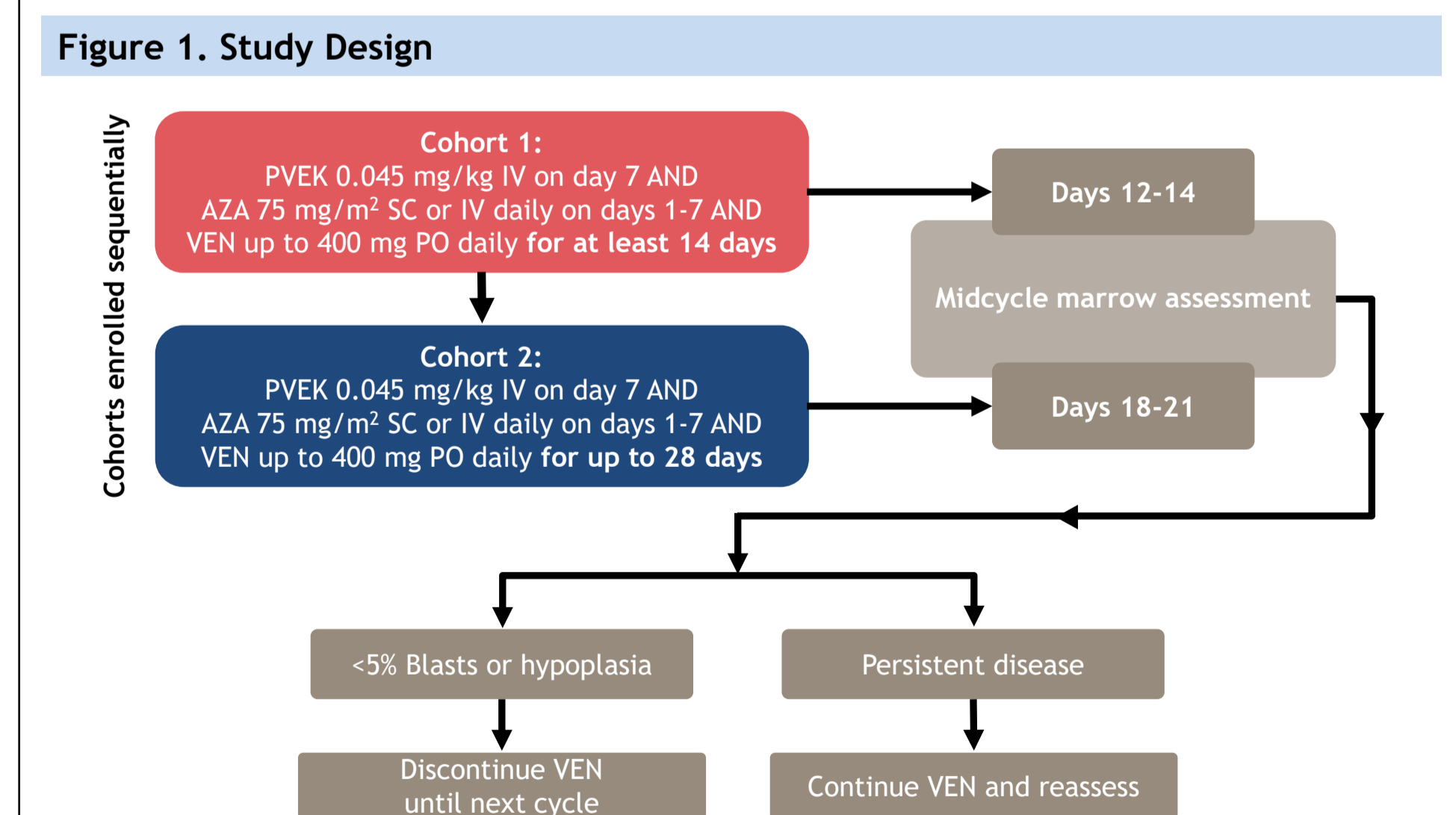
- In unfit patients with newly diagnosed (ND) AML, long-term survival remains short (mOS 14.7 months) despite improved responses (CR 37% and CR/CRi 66%) with azacitidine (AZA) and venetoclax (VEN)¹
- Several prognostic molecular features have been identified that are associated with intermediate (FLT3-ITD, 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^{mut} patients (CR/CRi 70%) compared with TP53^{wt} 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}



Objective

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

Methods: Study Design

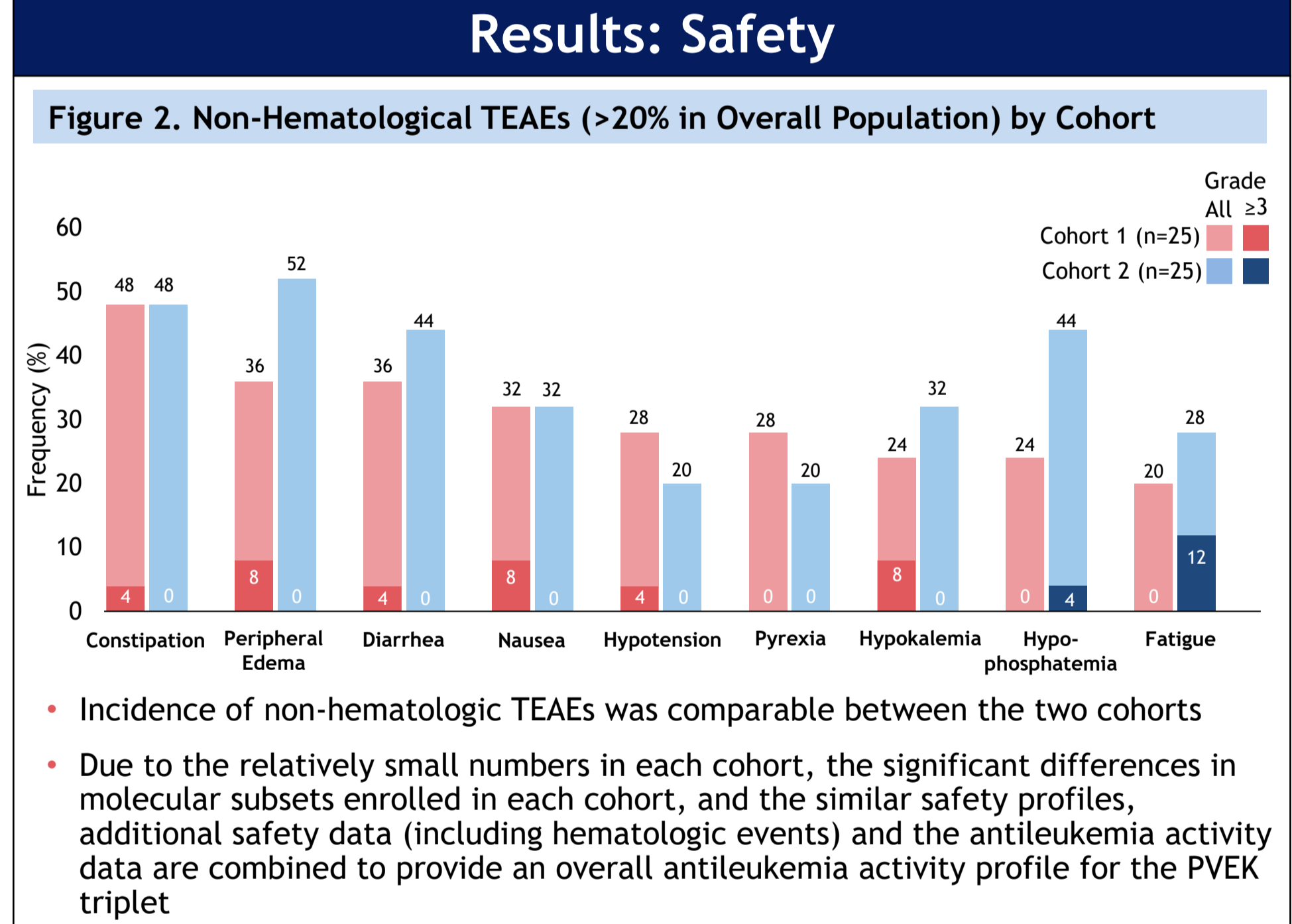


- This is an open-label, multicenter, phase 1b/2 study of PVEK administered in combination regimens in patients with frontline CD123+ AML (NCT04086264)
- Patients will receive the established recommended phase 2 dose (RP2D) of PVEK 0.045 mg/kg IV, as a <30-minute outpatient infusion
- Patients must have 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

Baseline Characteristics

	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) ≥75 y, % (n)	74 (46-83) 36% (9)	74 (46-83) 42% (21)
Sex, % (n)	Male Female	64% (16) 36% (9)	64% (32) 36% (18)
ECOG PS, % (n)	0 1	40% (10) 60% (15)	38% (19) 62% (31)
AML classification, % (n)	De novo Secondary	80% (20) 20% (5)	76% (19) 24% (6)
ELN 2017 risk, % (n)	Favorable Intermediate Adverse Missing/not determined	4% (1) 36% (9) 60% (15) 0% (0)	4% (1) 16% (4) 72% (18) 8% (2)
Selected mutations, % (n/N)^{a,b}	TP53 IDH1/2 NPM1 K/NRAS FLT3-TKD/ITD	20% (4/20) 32% (7/22) 17% (4/23) 19% (4/21) 17% (4/23)	53% (10/19) 9% (2/22) 19% (4/21) 11% (2/19) 9% (2/22)

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



Treatment 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)

Edema events ^a	All Grades	Grade 3
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%

^aPreferred terms (MedDRA v24.0) under edema include peripheral edema, generalized edema, fluid overload, peripheral swelling, localized edema, fluid retention
^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 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, 1-37)
- 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

Results: Cycle Delays and Count Recovery Kinetics

	Blast Clearance Cycle ^{a,b,c}	Post-Remission Cycles ^b
Median, days (range) ^a	11 (1-51)	13 (-2-63)

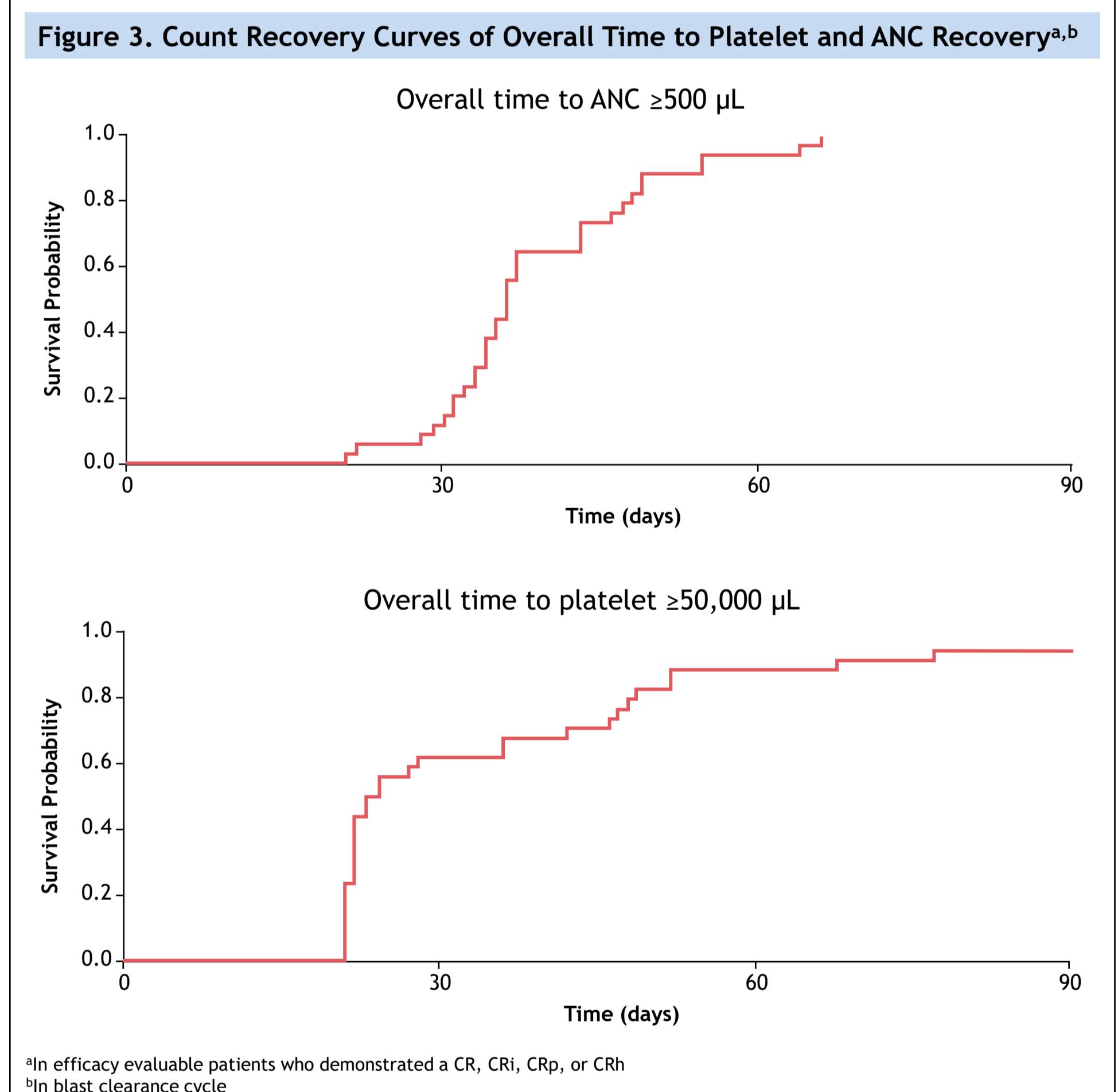
^aFrom day 28 of each cycle
^bIn patients achieving CCR
^cReported by first cycle achieving blast clearance

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 trial⁶

Table 4. Count Recovery Kinetics^a

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

^aIn patients achieving CCR
^b26% of patients had concomitant G-CSF use



Results: 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

	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)

^aResponses determined by ELN 2017 criteria (with addition of CRh)
^bCCR=CR+CRh+CRp+CRi
^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

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: Best Overall Response

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

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: Antileukemia Activity in Subsets of Interest

		PVEK Triplet
TP53 status	Wild type	88% (22/25) 84% (21/25)
	MRD-	80% (16/20)
	Mutant	50% (7/14) 21% (3/14)
FLT3 ITD or TKD	CCR	100% (6/6)
	MRD-	100% (6/6)
	MRD-	67% (2/3)
IDH1 ^{mut}	CCR	100% (4/4)
	MRD-	67% (2/3)
	MRD-	100% (6/6)
IDH2 ^{mut}	CCR	100% (8/8)
	MRD-	83% (5/6)
	MRD-	100% (8/8)
NPM1 ^{mut}	CCR	50% (3/6)
	MRD-	86% (6/7)
	MRD-	50% (3/6)

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 (N=50)

	PVEK Triplet
Higher benefit	94% (17/18) 89% (16/18) 73% (11/15)
Intermediate benefit	71% (5/7) 71% (5/7) 100% (5/5)
Lower benefit	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

Results: Response Duration

Figure 6. 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, 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 were observed
- The addition of PVEK did not notably prolong count recovery, with ANC ≥500/ μ L and platelet ≥50k/ μ L 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 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)