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Phase 1b Study of Bleximenib in Combination With Venetoclax in Acute Myeloid Leukemia With *KMT2A* or *NPM1* Alterations

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Key Takeaway

The all-oral combination of the bleximenib + VEN doublet demonstrated a tolerable safety profile, with preliminary clinical activity in R/R *KMT2Ar* or *NPM1m* AML

Data support the phase 3 evaluation of bleximenib in participants with *KMT2Ar* or *NPM1m* AML who are ineligible for IC

Conclusions

In this phase 1b trial, bleximenib + VEN had a tolerable safety profile, with no DS or discontinuations due to TEAEs observed

Bleximenib in combination with VEN demonstrated preliminary clinical activity in participants with R/R AML harboring *KMT2A* or *NPM1* alterations, especially in those naive to VEN treatment

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Acknowledgments

We thank the participants who are taking part in this global study and their caregivers, the physicians and nurses who care for them, the staff at the study sites, and the staff involved in data collection and analysis. This study was funded by Johnson & Johnson. Medical writing support was provided by Agnieszka Looney, PhD, of ApotheCom, and funded by Johnson & Johnson.

Abbreviations

AML, acute myeloid leukemia; ASCT, allogeneic stem cell transplant; AZA, azacitidine; BID, twice daily; BM, bone marrow; C, cycle; cCR, composite complete remission; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; D, day; DLT, dose-limiting toxicity; *DNMT3A*, DNA methyltransferase 3 alpha; DS, differentiation syndrome; EOT, end of treatment; *FLT3*, fms-like tyrosine kinase 3; ITD, internal tandem duplication; ITT, intention to treat; *KMT2A*, lysine methyltransferase 2A gene; *KMT2Ar*, *KMT2A* rearranged; MLFS, morphologic leukemia-free state; *NPM1*, nucleophosmin 1 gene; *NPM1m*, *NPM1* mutated; ORR, overall response rate; PB, peripheral blood; PD, pharmacodynamics; PK, pharmacokinetics; PO, orally; QTc, corrected QT interval; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event; TKD, tyrosine kinase domain; VEN, venetoclax.

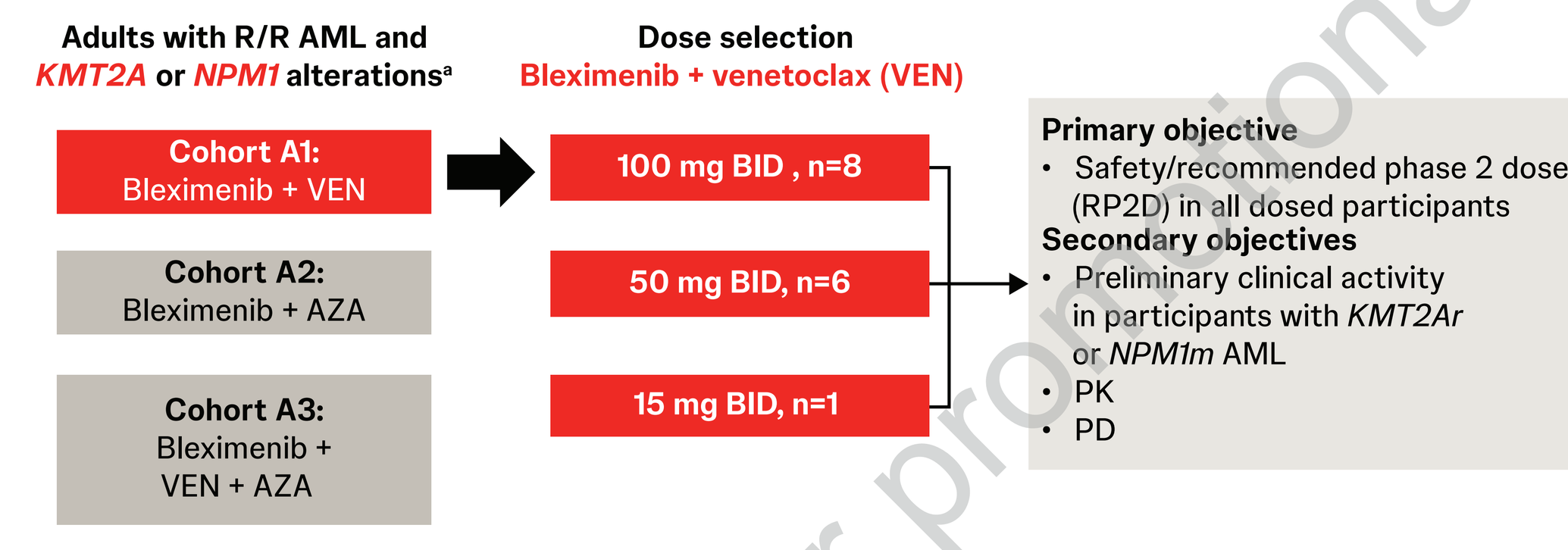
Background

- Despite recent approvals, *KMT2A* rearranged (*KMT2Ar*) and *NPM1* mutated (*NPM1m*) acute myeloid leukemia (AML) remain challenging to treat, requiring more effective, tolerable, and combinable targeted therapies[1,2]
- Bleximenib is the most potent menin inhibitor with respect to binding affinity and cellular potency in *in vitro* studies[3–5]
- In previously reported phase 1 studies, bleximenib as monotherapy and in combination demonstrated clinical benefits with no corrected QT interval (QTc) safety signals in relapsed/refractory (R/R) *KMT2Ar* and *NPM1m* AML[6,7]
- Phase 1 data on bleximenib 100 mg twice daily (BID) (RP2D) in combination with AML-directed therapies in participants with R/R or newly diagnosed AML were previously reported[6]

- **This study reports safety and efficacy from ALE1002 (Cohort A1) for the all-oral combination of the bleximenib + VEN**
- **Median follow-up: 12.98 months (range, 0.95–13.86)**

Methods

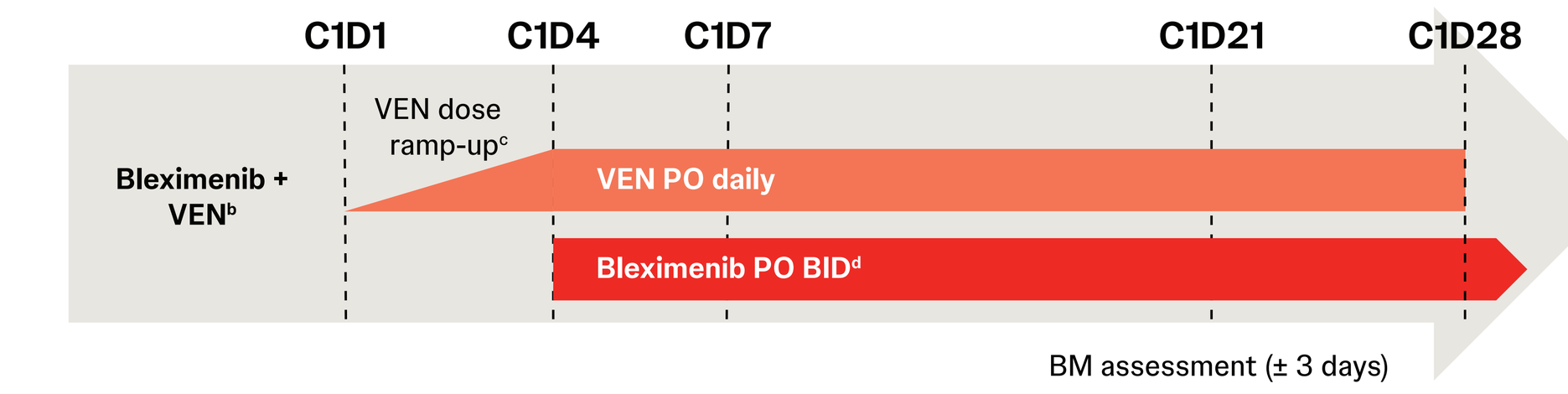
Figure 1: ALE1002 (NCT05453903) study design



[a]Exclusion criteria included use of strong CYP3A4 inhibitors.

Figure 2: Dosing schedule[a]

Participants received increasing doses of bleximenib (15–100 mg BID) in combination with VEN



[a]Isavuconazole was the primary antifungal of choice when indicated, with no requirement for bleximenib dose modification.
[b]VEN dosing was guided by the label, with ramp-up followed by a plateau dose of 400 mg daily in 28-day cycles.
[c]VEN dose was ramped-up from 100 mg on Day 1 to 200 mg on Day 2 and 400 mg on Day 3.
[d]Bleximenib was started on Day 4+ after VEN ramp-up.

Results

Participants

- Key baseline characteristics for 15 participants in Cohort A1 are listed in **Table 1**

Table 1: Baseline demographics and clinical characteristics

Characteristic	Safety population N=15
Age, median (range), years	69.0 (36–81)
Female, n (%)	8 (53.3)
Prior lines of therapy, median (range), n	2.0 (1–4)
Prior VEN, n (%)	6 (40.0)
Prior menin inhibitor, n (%)	1 (6.7)
Prior ASCT, n (%)	3 (20.0)
Genetic alterations, n (%)	
KMT2A	4 (26.7)
NPM1	11 (73.3)
Relevant comutations, n (%)	
DNMT3A	1 (6.7)
FLT3	5 (33.3)
ITD	4 (26.7)
TKD	1 (6.7)

Data cutoff: October 2025.

Safety

- No differentiation syndrome events were observed; 1 treatment-emergent adverse event (TEAE) of unrelated grade 2 QTc prolongation was reported with no bleximenib dose modification required

Table 2: TEAEs occurring in ≥20% of participants, regardless of relatedness

TEAE, n (%)	Safety population N=15	
	Any grade	Grade ≥3
Participants who had ≥1 TEAE	15 (100.0)	15 (100.0)
Hematologic TEAEs		
Thrombocytopenia	7 (46.7)	6 (40.0)
Anemia	7 (46.7)	7 (46.7)
Neutropenia	9 (60.0)	8 (53.3)
Febrile neutropenia	5 (33.3)	5 (33.3)
Nonhematologic TEAEs		
Nausea	6 (40.0)	0
Asthenia	3 (20.0)	0
Vomiting	3 (20.0)	0

Data cutoff: October 2025.

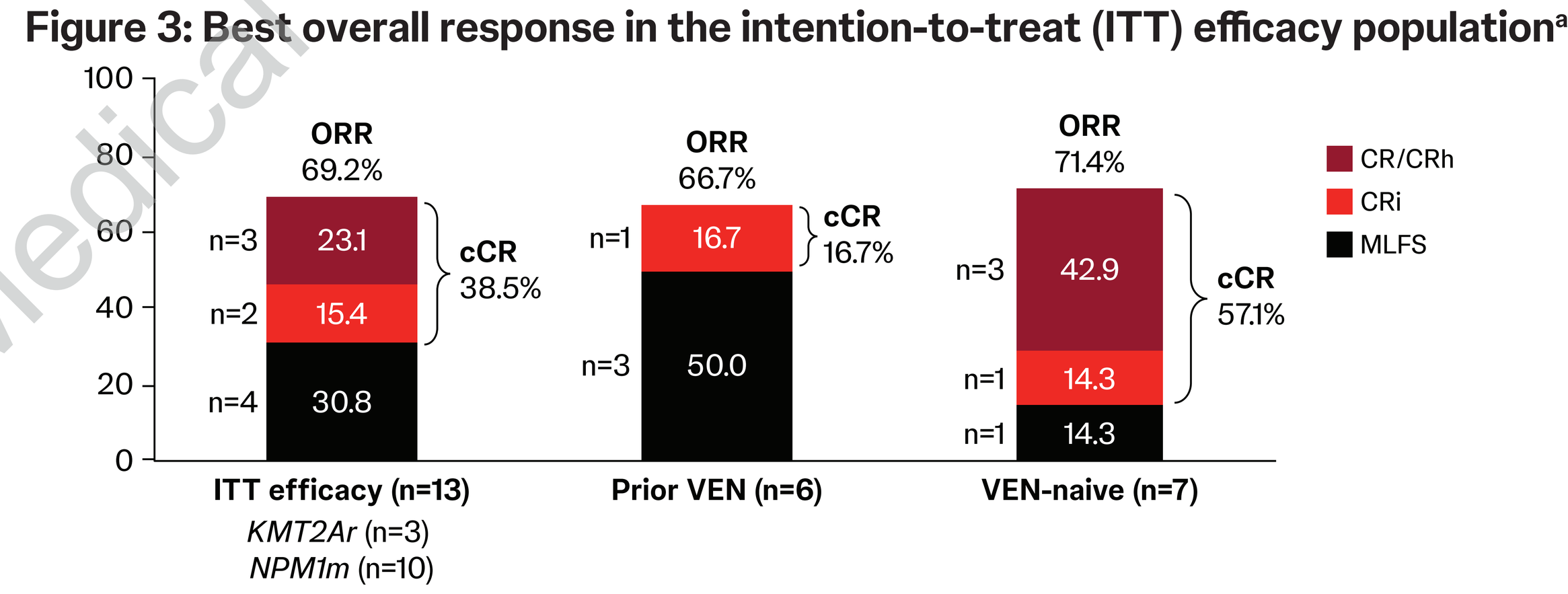
Table 3: Dose-limiting toxicities (DLTs) and grade 5 TEAEs

	Safety population N=15
DLTs,[a] n	1
Grade 5 TEAE (not related),[b] n	2

Data cutoff: October 2025.
[a]One DLT of grade 4 neutropenia and thrombocytopenia was reported; this participant remains on treatment in cycle 14 with a reduction of the bleximenib dose.
[b]Grade 5 TEAEs occurred in 2 participants (COVID-19 lung infection and cardiac arrest in 1 participant each), both unrelated to study treatment.

Efficacy

Figure 3: Best overall response in the intention-to-treat (ITT) efficacy population[a]



	Responders in the ITT population N=9
Time to first response, median (range), days	22 (19–56)

Data cutoff: October 2025.
[a]ITT population comprised participants with *KMT2Ar* or *NPM1m* R/R AML who received bleximenib 50 mg BID or 100 mg BID in combination with VEN, including those who discontinued prior to the first disease evaluation; 2 participants were excluded from efficacy analysis (bleximenib 15 mg BID and prior menin inhibitor in 1 participant each).

- Responses were observed in most participants, including those with prior VEN exposure, although interpretation of these data is limited by the small sample size (**Figure 3**)

Exposure and cycle duration

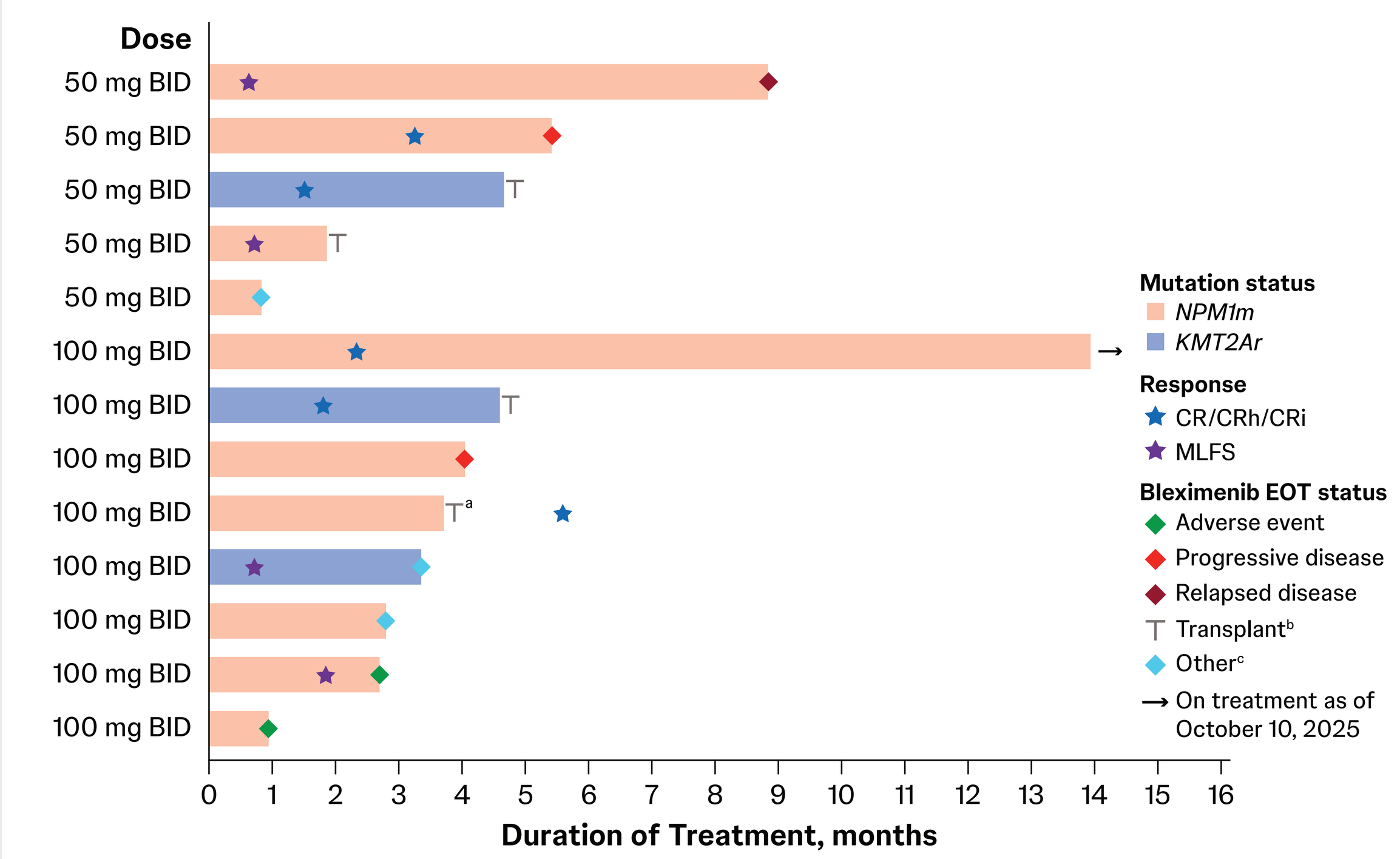
Table 4: Bleximenib and VEN exposures and cycle duration

	Safety population N=15
Relative bleximenib dose intensity, median (range), %	
Cycle 1 (n=15)	100.0 (76.0–100.0)
Cycle 2 (n=12)	100.0 (50.0–100.0)
Cycle 3 (n=9)	78.3 (29.2–100.0)
Duration of VEN treatment, median (range), days	
Cycle 1 (n=15)	28.0 (22.0–28.0)
Cycle 2 (n=12)	23.0 (5.0–28.0)
Cycle duration, median (range), days	
Cycle 1 (n=12)	35.0 (27–71)
Cycle 2 (n=9)	28.0 (28–69)
Cycle 3 (n=5)	28.0 (25–29)

Data cutoff: October 2025.

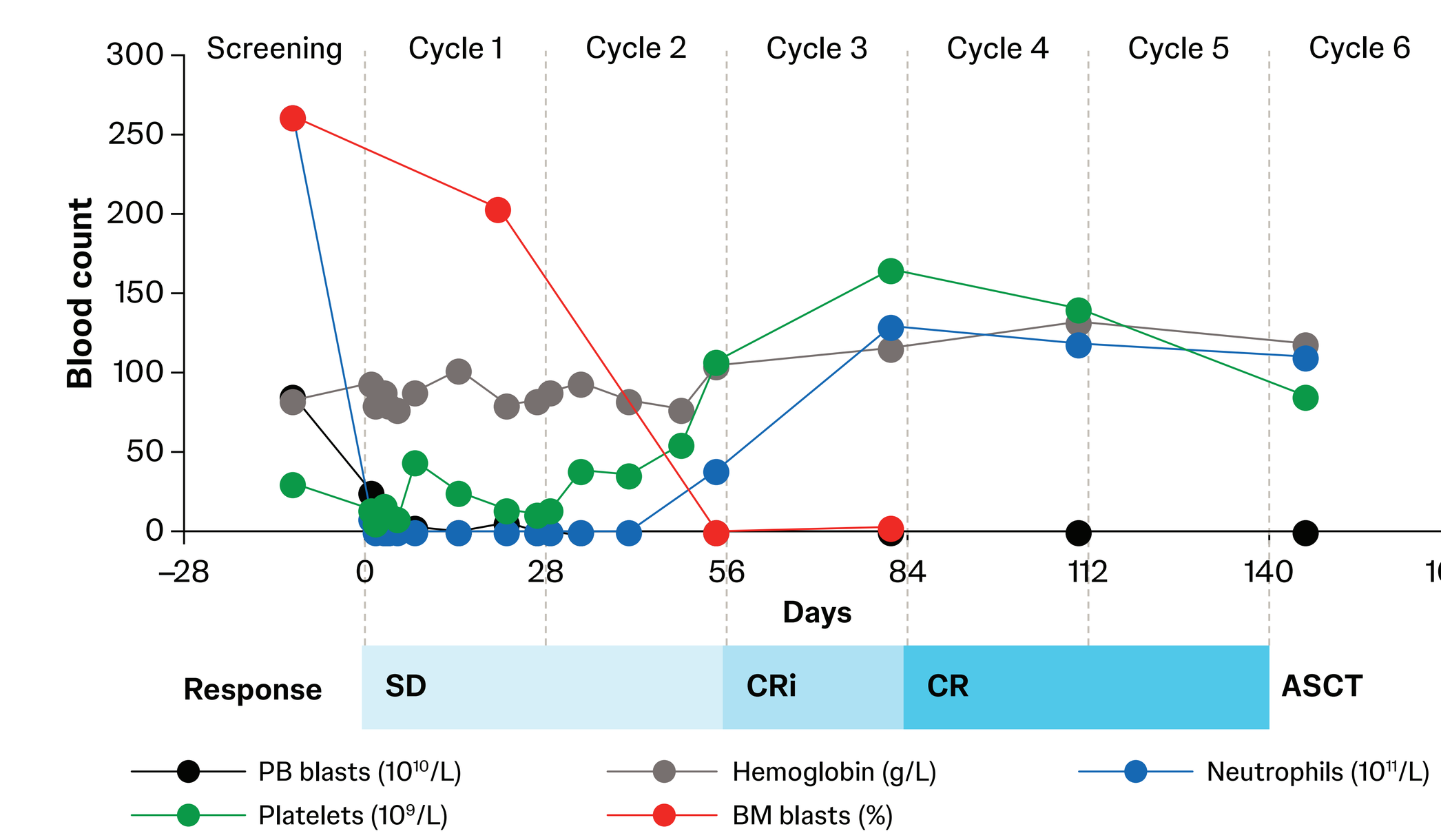
- The median relative dose intensity of bleximenib was 100% in the first 2 cycles, supporting the tolerability and activity of the combination (**Table 4**)

Figure 4: Duration of treatment in the ITT efficacy population



Data cutoff: October 2025.
[a]Participant proceeded to ASCT 3 months after bleximenib discontinuation and achieved a cCR prior to ASCT.
[b]Four of 13 participants (30.8%) proceeded to ASCT.
[c]Other: refractory disease (n=2) and physician decision (n=1).

Figure 5: Case study[a]



[a]This participant was alive as of October 3, 2025

- 36-year-old female
- *KMT2Ar* AML with mutated *FLT3*
- 100 mg BID bleximenib + VEN achieved CRi after cycle 2, improving to CR after cycle 3
- Proceeded to ASCT after cycle 5

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Myeloid Malignancies

Presented by Marc Raaijmakers at the American Society of Hematology (ASH) Annual Meeting; December 6–9, 2025; Orlando, Florida