RP2D Determination of Bleximenib in Combination with VEN + AZA: Phase 1b Study in R/R & ND AML with *KMT2A/NPM1* Alterations

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Bleximenib in Combination with VEN + AZA in R/R or ND AML

Background

- Bleximenib is a potent, selective oral menin inhibitor with demonstrated preclinical and clinical activity in *KMT2Ar* or *NPM1m* AML, both as a monotherapy and in combination with AML therapies, including VEN + AZA[1–5]
- VEN + AZA is approved for treatment of patients with ND AML who are older or unfit for intensive chemotherapy, and is also used in patients with R/R AML[6]
- Promising safety and efficacy of bleximenib in combination with VEN + AZA has been observed in patients with R/R AML harboring *KMT2Ar* or *NPM1m*[2]
- The primary objective of the ongoing ALE1002 study (NCT05453903) is to evaluate safety and preliminary efficacy of bleximenib in combination with AML-directed therapies in participants with R/R or ND AML harboring *KMT2A* or *NPM1* alterations[7]

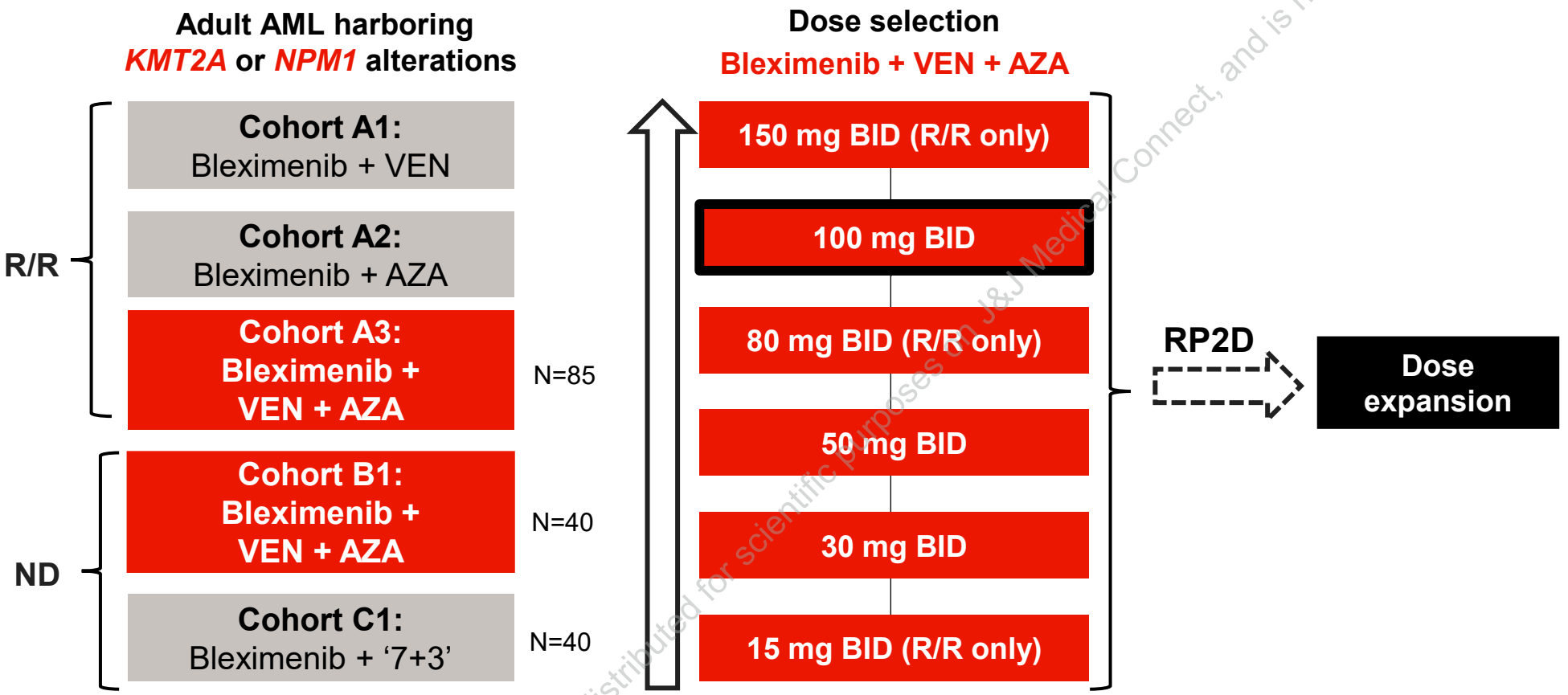
Focus of this presentation: Determination of the RP2D of bleximenib in combination with VEN + AZA in participants with R/R or ND *KMT2Ar* or *NPM1m* AML

AML, acute myeloid leukemia; AZA, azacitidine; *KMT2A*, Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A*-rearranged; ND, newly diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

1. Kwon MC, et al. *Blood* 2024;144:1206–1220; 2. Wei AH, et al. EHA 2024, Abstract S133 (oral presentation); 3. Searle E, et al. ASH 2024, Abstract 212 (oral presentation); 4. Recher C, et al. ASH 2024. Abstract 215 (oral presentation); 5. Jabbour E, at al. ASH 2023, Abstract 57 (oral presentation); 6. Garciaz S, et al. *Cancers (Basel)* 2022;14:2025; 7. clinicaltrials.gov. NCT05453903.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Study Design



Primary objective

- Safety/RP2D

Secondary objectives

- Preliminary clinical activity
- PK
- PD

NCT05453903

7+3, cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; *KMT2A*, histone-lysine N-methyltransferase 2A; ND, newly diagnosed; *NPM1,* nucleophosmin 1; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

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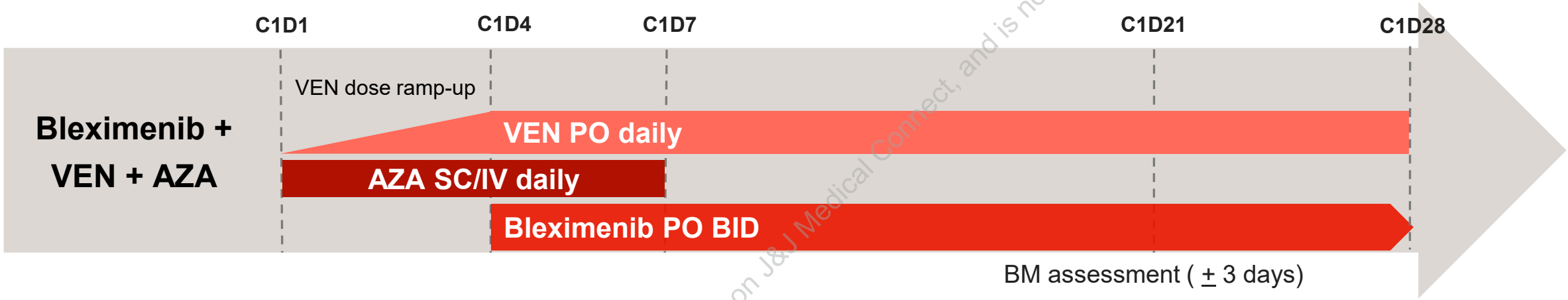
Bleximenib in Combination with VEN + AZA in R/R or ND AML

Dosing Schedule and Exposures



Dosing schedules

- 28-day treatment cycles
- VEN and AZA administration guided by the approved label
  - VEN plateau dose 400 mg daily
  - No significant dose modifications to SOC VEN or AZA required in combination with bleximenib
- Bleximenib BID commenced on C1D4 (+3-day window)
  - 100% relative dose intensity seen in the first 3 cycles
- Hydroxyurea and steroids for DS prophylaxis and treatment permitted
- Isavuconazole primary antifungal of choice, when indicated, with no requirement for bleximenib dose modification

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; BM, bone marrow; C, cycle; D, day; DS, differentiation syndrome; IV, intravenous; n, number; ND, newly-diagnosed; PO, by mouth; R/R, relapsed/refractory; SC, subcutaneous; SOC, standard of care; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Demographics and Baseline Characteristics – All Treated

Characteristics	R/R AML (n=85)	ND AML (n=40)	Combined population (N=125)
Median age, years (range)	60 (19–85)	**75** (43–88)	67 (19–88)
Female, n (%)	51 (60)	21 (52.5)	72 (57.6)
ECOG PS, n (%)			
0	26 (30.6)	9 (22.5)	35 (28)
1	50 (58.8)	24 (60)	74 (59.2)
2	9 (10.6)	7 (17.5)	16 (12.8)
EMD at baseline, n (%)	9 (10.6)	3 (7.5)	12 (9.6)
Genetic alterations, n (%)			
KMT2A	44 (**51.8**)	8 (20)	52 (41.6)
NPM1	41 (48.2)	32 (**80**)	73 (58.4)
Relevant co-mutations occurring in ≥10% of pts, n (%)			
DNMT3A	24 (28.2)	9 (22.5)	33 (26.4)
FLT3	20 (23.5)	10 (25)	30 (24)
TET2	12 (14.1)	8 (20)	20 (16)
IDH2	9 (10.6)	5 (12.5)	14 (11.2)

Characteristics	R/R AML (n=85)
Lines of prior therapy, n (%)	
1	31 (36.5)
2	36 (**42.4**)
3	10 (11.8)
Prior VEN exposure, n (%)	
Yes	40 (**47.1**)
No	45 (52.9)
Prior HMA exposure, n (%)	
Azacitidine	32 (**37.6**)
Decitabine	6 (7.1)
Cedazuridine/decitabine	1 (1.2)
Prior allo-HCT, n (%)	
Yes	26 (**30.6**)
No	59 (69.4)

Data cut-off date: May 7, 2025

Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; HMA, hypomethylating agents; *KMT2A*, Histone-lysine N-methyltransferase 2A; ND, newly-diagnosed; pt, participant; R/R, relapsed/refractory; VEN, venetoclax.

Presented by AH Wei at EHA 2025; June 12 2025; Milan, Italy

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Safety Profile – TEAEs Regardless of Relatedness

TEAEs	Any Grade			Grade ≥3		
	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)
Pts with ≥1 TEAEs, n (%)	45 (100)	49 (100)	125 (100)	43 (96)	47 (96)	121 (97)
Hematological TEAEs occurring in ≥20% of pts						
Thrombocytopenia	26 (58)	30 (61)	72 (58)	25 (56)	29 (59)	69 (55)
Anemia	26 (58)	24 (49)	69 (55)	25 (56)	24 (49)	67 (54)
Neutropenia	23 (51)	29 (59)	62 (50)	23 (51)	29 (59)	62 (50)
Febrile neutropenia	20 (44)	18 (37)	49 (39)	20 (44)	18 (37)	49 (39)
Leukopenia	15 (33)	5 (10)	31 (25)	14 (31)	5 (10)	29 (23)
Non-hematological TEAEs occurring in ≥20% of pts						
Nausea	24 (53)	32 (65)	77 (62)	1 (2)	1 (2)	4 (3)
Vomiting	18 (40)	20 (41)	51 (41)	0	1 (2)	1 (1)
Constipation	20 (44)	17 (35)	44 (35)	2 (4)	1 (2)	3 (2)
Diarrhoea	10 (22)	17 (35)	41 (33)	0	1 (2)	1 (1)
Pyrexia	10 (22)	17 (35)	39 (31)	1 (2)	1 (2)	3 (2)
Fatigue	10 (22)	11 (22)	30 (24)	3 (7)	3 (6)	7 (6)
Asthenia	11 (24)	8 (16)	27 (22)	3 (7)	1 (2)	6 (5)

Key observations

- Safety profile was similar across 50 mg BID and 100 mg BID dose levels
- Safety was consistent with the VEN + AZA backbone
- **No DLTs (n=0/49) at 100 mg BID**
- In pts who achieved CR/CRh at 100 mg BID (R/R, n=9; ND, n=13):
  - Median days (range) to platelet recovery ≥50x10^9/L from C1D1
    - 38 d (21–50) in R/R
    - **29 d (18–57) in ND**
  - Median days (range) to neutrophil recovery ≥0.5x10^9/L from C1D1
    - 32 d (21–67) in R/R
    - **31 d (22–66) in ND**
- Median (range) duration of follow-up at 100 mg BID was 6.9 months (0.2–16.2)

Data cut-off date: May 7, 2025

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete response; CRh, CR with partial haematological recovery; d, day; DLT, dose-limiting toxicity; ND, newly diagnosed; pt, participant; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Adverse Events of Clinical Interest with Menin Inhibition

AE, regardless of relatedness	Any Grade			Grade ≥3		
	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)
Differentiation syndrome, n (%)	5 (11)	2 (4)	7 (6)	3 (7)	2 (4)	5 (4)
QTc prolongation, n (%)	2 (4)	3 (6)	5 (4)	0	0	0

Key observations

- With implementation of safety mitigation measures*, low rates of DS were observed; one Grade 5 event in R/R 50 mg BID combination cohort
- No QTc prolongation signal identified
  - All reported QTc prolongation events were Grade 1; no bleximenib dose interruptions or reductions required

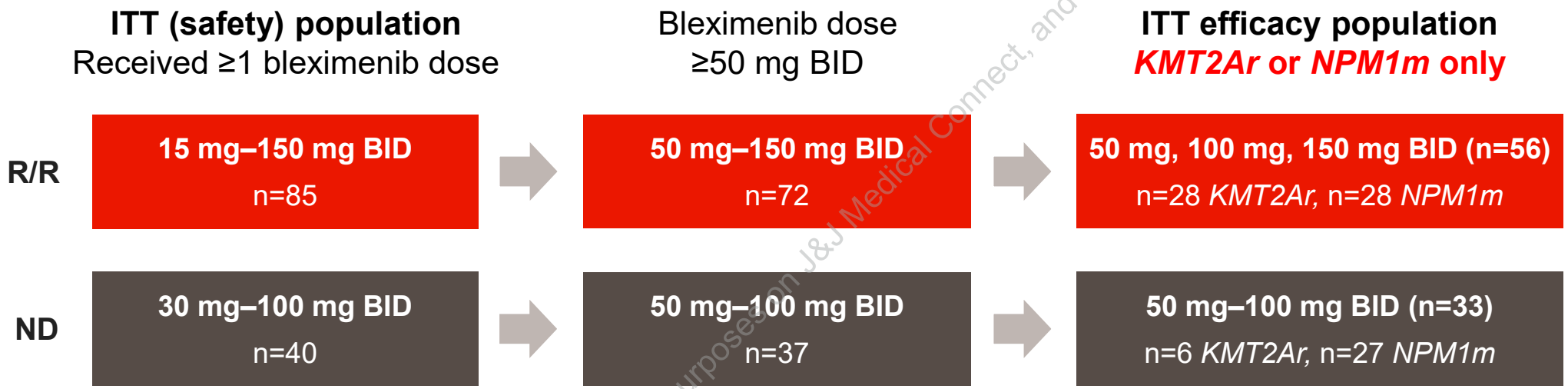
Data cut-off date: May 7, 2025

*Protocol-specified guidance, including study drug interruption, use of prophylactic steroids and hydroxyurea in select participants considered at high-risk for the development of severe DS, and staggered initiation of bleximenib dosing on C1D4 have been implemented as safety measures to mitigate and manage the risk of DS.

AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; C, cycle; D, day; DS, differentiation syndrome; ND, newly-diagnosed; QTc, corrected QT interval; R/R, relapsed/refractory; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Safety and Efficacy Populations



Efficacy population includes all participants who:

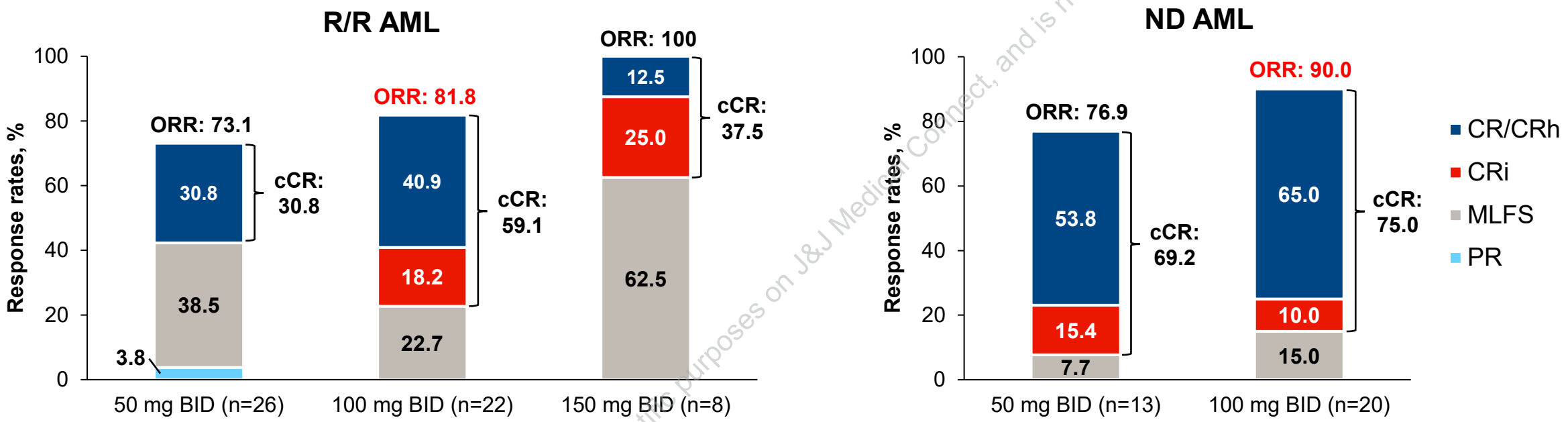
- Received bleximenib at doses of 50 mg, 100 mg, or 150 mg BID
- Participants with *KMT2Ar* or *NPM1m* only
- Participants who discontinued, even if before first disease evaluation, are included

Data cut-off: May 7, 2025

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; ITT, intent to treat; *KMT2A,* Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A-*rearranged; ND, newly-diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; R/R, relapsed/refractory; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Efficacy



cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

Key observations

- Evaluation of the data shows optimized responses with bleximenib 100 mg BID in combination with VEN/AZA
- Response data maturing, with 6 ND pts active on treatment with the potential to deepen response
- In pts receiving 100 mg BID, the median (range) time to first response was 23 days (18–50) in R/R and 22 days (18–57) in ND

Responses of participants with an underlying diagnosis of AML are based upon modified ELN 2017 recommendations (Dohner 2017, Bloomfield 2018) or modified ELN 2022 recommendations (Dohner 2022).

Data cut-off date: May 7, 2025

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, CR with partial haematological recovery; CRi, complete remission with incomplete recovery; ELN, European LeukemiaNet; MLFS, morphologic leukemia-free state; ND, newly diagnosed; ORR, overall response rate; PR, partial response; pt, participant; R/R, relapsed/refractory; VEN, venetoclax.

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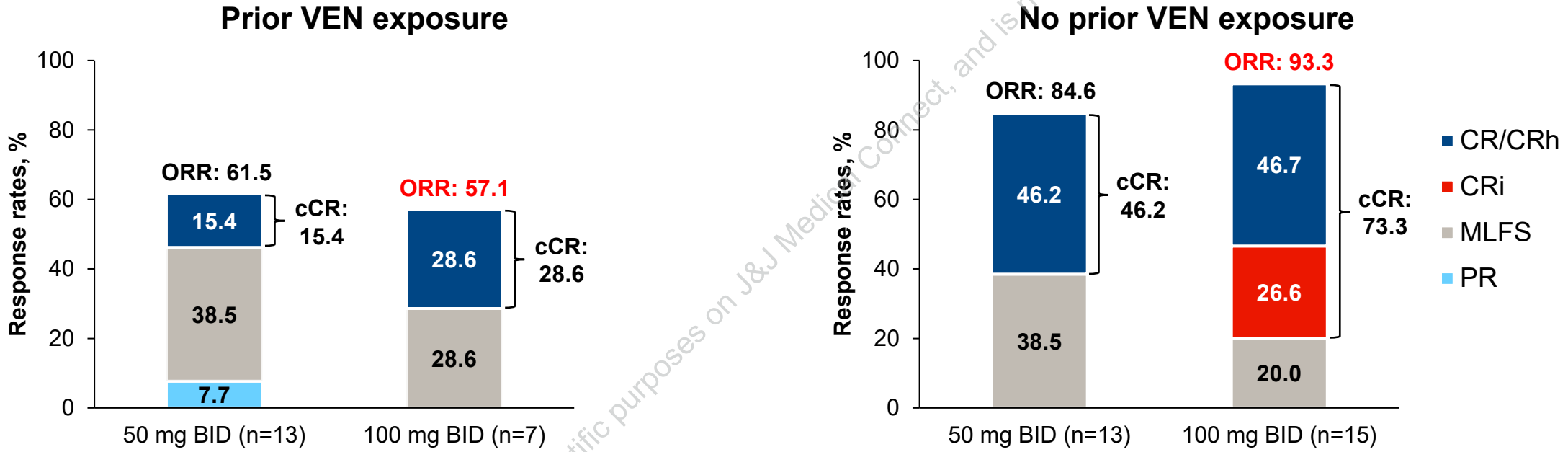
Bleximenib in Combination with VEN + AZA in R/R AML

Efficacy in R/R Participants with/without Prior VEN Exposure



cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

Key observation

- Participants with prior VEN exposure demonstrated response to bleximenib combination therapy

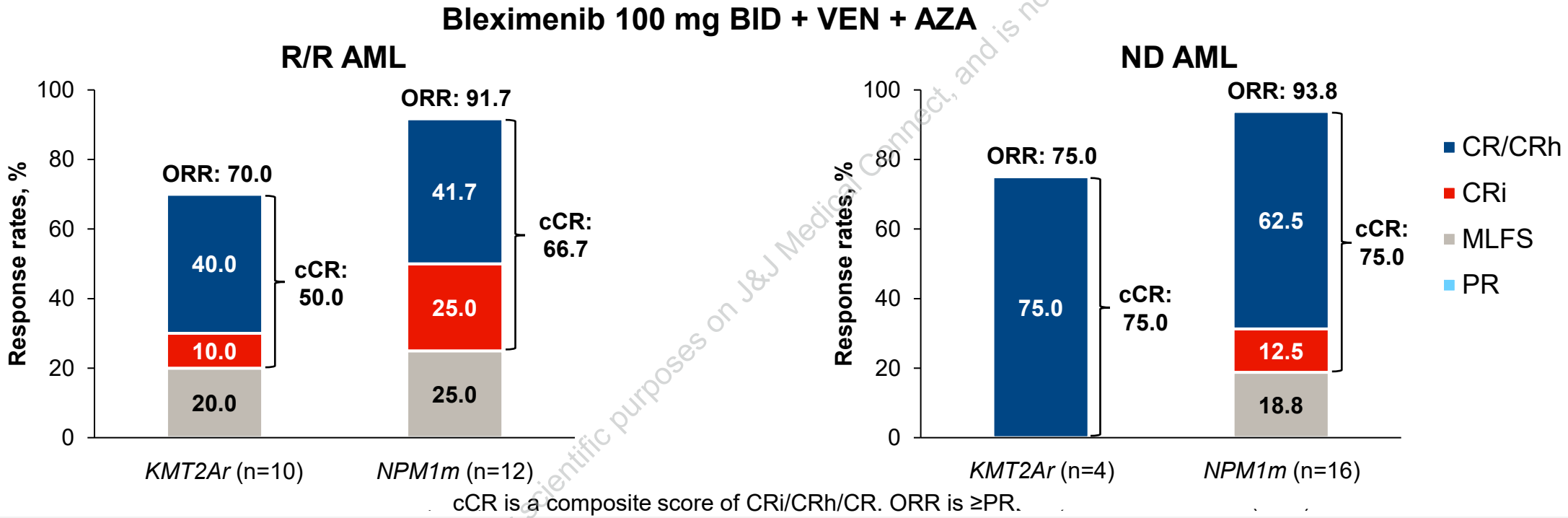
Responses of participants with an underlying diagnosis of AML are based upon modified ELN 2017 recommendations (Dohner 2017, Bloomfield 2018) or modified ELN 2022 recommendations (Dohner 2022).

Data cut-off date: May 7, 2025

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, CR with partial haematological recovery; CRi, complete remission with incomplete recovery; ELN, European LeukemiaNet; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Efficacy in *KMT2Ar* and *NPM1m*



cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

Key observations

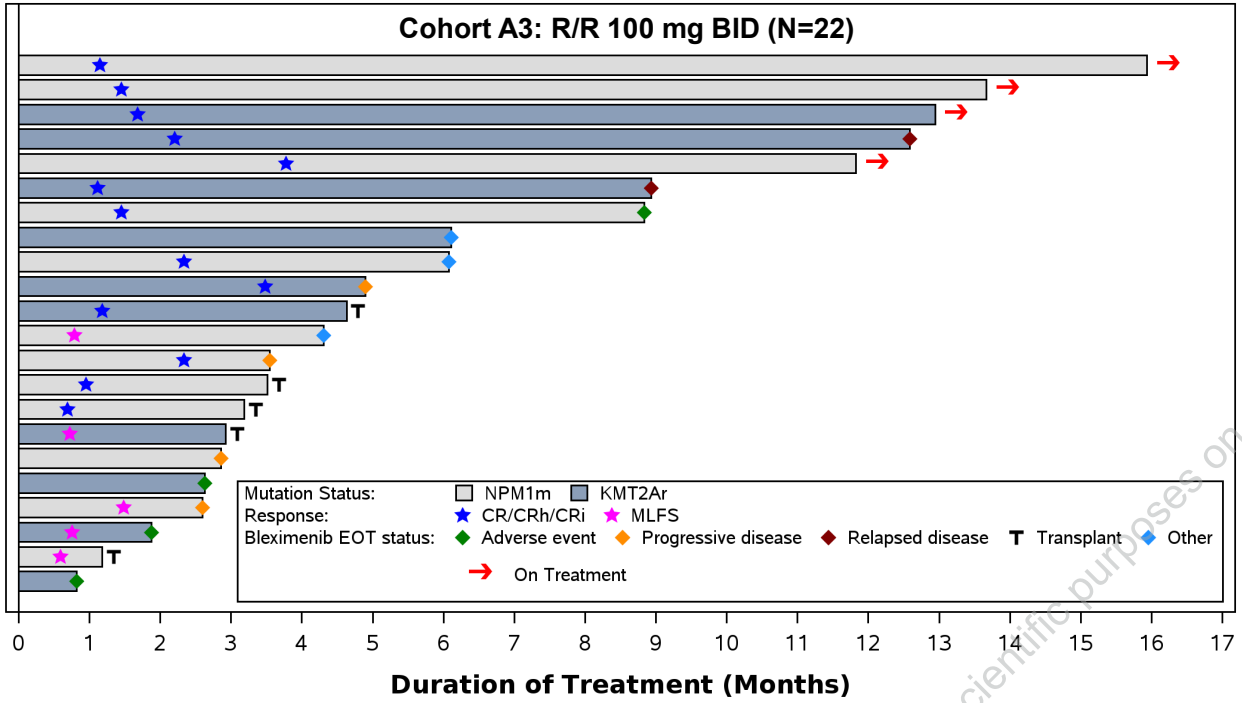
- High rates of response observed in both *KMT2Ar* and *NPM1m* participants
- **No acquired *MEN1* resistance mutations** were identified in 19 pts (R/R cohort) with available on treatment samples (mean 275 days on treatment), including four pts at the time of relapse and two refractory to study treatment

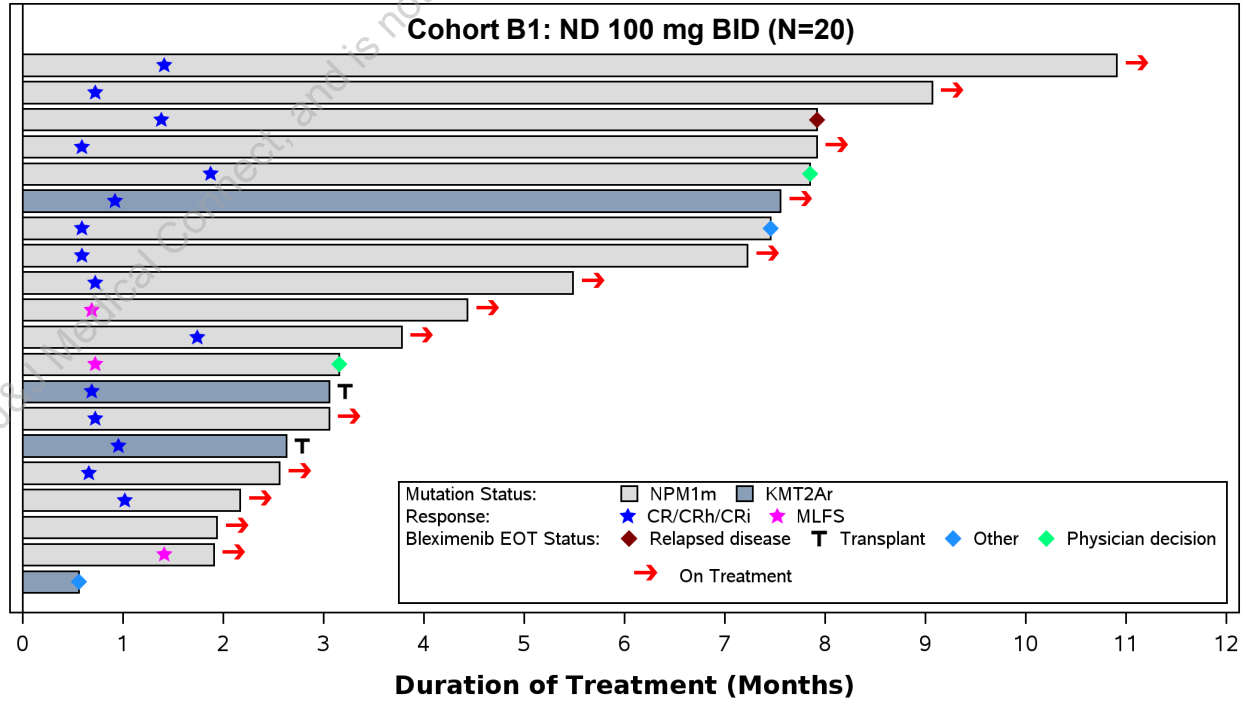
Responses of participants with an underlying diagnosis of AML are based upon modified ELN 2017 recommendations (Dohner 2017, Bloomfield 2018) or modified ELN 2022 recommendations (Dohner 2022).

Data cut-off date: May 7, 2025. AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete response; CRh, CR with partial haematological recovery; CRi , complete remission with incomplete recovery; ELN, European LeukemiaNet; *KMT2A,* Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A* rearranged; MLFS, morphologic leukemia-free state; ND, newly diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; ORR, overall response rate; PR, partial response; pt, participant; R/R, relapsed/refractory; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Duration of Treatment with Bleximenib 100 mg BID





Key observations

- Four R/R (18.2%) and 13 ND (65%) pts were ongoing treatment at data cut-off
- Median (range) number of cycles at 100 mg BID was 3 (1–13) in R/R and 3 (1–6) in ND
- Five R/R (22.7%) and two ND (10%) pts at 100 mg BID proceeded to transplant

Data cut-off: May 7, 2025. AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete response; CRh, CR with partial haematological recovery; CRi , complete remission with incomplete recovery; EOT, end of treatment; *KMT2A,* Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A*-rearranged; MLFS, morphologic leukemia-free state; ND, newly diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; pt, participant; R/R, relapsed/refractory; VEN, venetoclax.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Conclusions

- **The totality of clinical data informed bleximenib 100 mg BID** as the RP2D when used in combination with VEN + AZA for both R/R and ND *KMT2Ar* or *NPM1m* AML
  - High rates of response observed in both *KMT2Ar* and *NPM1m* participants
    - Responses were also observed in participants with prior VEN exposure
    - Five R/R (22.7%) participants proceeded to transplant
  - Safety profile was consistent with the VEN + AZA backbone
  - Low rates of DS observed (4%); no QTc prolongation signal identified
  - No emergent *MEN1* resistance mutations identified to date
- The placebo-controlled **Phase 3 cAMeLot-2** trial investigating VEN + AZA +/- bleximenib in participants with ND AML who are ineligible for intensive chemotherapy is now open and enrolling (NCT06852222)

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; DS, differentiation syndrome; *KMT2A*, Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A*-rearranged; ND, newly diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; QTc, corrected QT interval; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

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Bleximenib in Combination with VEN + AZA in R/R or ND AML

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- This study was funded by Johnson & Johnson Research & Development, LLC
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Bleximenib in Combination with VEN + AZA in AML*

Phase 3 Study Design (cAMeLot-2)

A **Phase 3** double-blind, randomized, **placebo-controlled** study of **bleximenib (menin inhibitor)**, **venetoclax** and **azacitidine** for treatment of participants with **newly diagnosed AML**

N=~600

Key eligibility criteria*

- ND AML with *KMT2Ar or NPM1m*
- Ineligible for intensive chemotherapy
- Adults 18+
- ECOG PS 0–2

Bleximenib PO + **venetoclax** PO + **azacitidine** IV/SC

Placebo PO + **venetoclax** PO + **azacitidine** IV/SC

Primary outcomes:

- CR
- OS

Secondary outcomes:

- EFS
- CR MRD rate
- Duration of CR
- Time to CR
- % transfusion independence
- % allo-HSCT
- AEs

Scan the QR code above to access the Phase 3 cAMeLot-2 study on clinicaltrials.gov

https://clinicaltrials.gov/study/NCT06852222

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*Not a complete list of inclusion and exclusion criteria.

AE, adverse event; Allo-HSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; IV, intravenous; KMT2A, histone-lysine N-methyltransferase 2A; KMT2Ar, KMT2A rearrangement; MRD, minimal residual disease; ND, newly diagnosed; NPM1, nucleophosmin 1; NPM1m, NPM1 mutation; OS, overall survival; PO, orally; PS, performance status; SC, subcutaneous.

Clinicaltrials.gov. Accessed May 2025. https://clinicaltrials.gov/study/NCT06852222

https://www.congresshub.com/EHA2025/Oncology#product-bleximenib

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