A Phase 1b Study of the Menin-KMT2A Inhibitor Bleximenib (JNJ-75276617) in Combination with Venetoclax and Azacitidine in Relapsed/Refractory Acute Myeloid Leukemia with Alterations in *KMT2A* or *NPM1*

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Disclosures

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Bleximenib (JNJ-75276617) Menin Inhibitor Phase 1b Combination Trial: Mechanism of Action

- R/R acute leukemias with *KMT2A* or *NPM1* alterations have poor outcomes, with a median OS of approximately 6 months[1–3]
- Bleximenib (JNJ-75276617) is a potent and selective inhibitor of the menin-KMT2A interaction[4]
- Single agent activity of bleximenib was reported in a Phase 1 study (NCT04811560) in participants with R/R acute leukemia harboring *KMT2A* or *NPM1* alterations[5]
- Synergistic antiproliferative activity for bleximenib in combination with VEN + AZA has been demonstrated in preclinical studies of *KMT2A*- and *NPM1*-altered AML[6]

AML, acute myeloid leukemia; AZA, azacitidine; *KMT2A*, histone-lysine N-methyltransferase 2A; *NPM1*, nucleophosmin 1; OS, overall survival; R/R, relapsed/refractory; VEN, venetoclax.

1. Britten O, et al. *Cells.* 2019;8:1341; 2. Issa GC, et al. *Blood Cancer J.* 2021;11:162; 3. Issa GC, et al. *Blood Adv.* 2023;7:933–42; 4. Kwon M, et al. Presented at ASH; December 10–13, 2022; New Orleans, LA, USA. Poster 2637; 5. Jabbour E at al. Presented at ASH; December 10–13, 2022; New Orleans, LA, USA, oral; 6. Kwon M, et al. Presented at ASH; December 10–13, 2022; New Orleans, LA, USA. Poster 4167.

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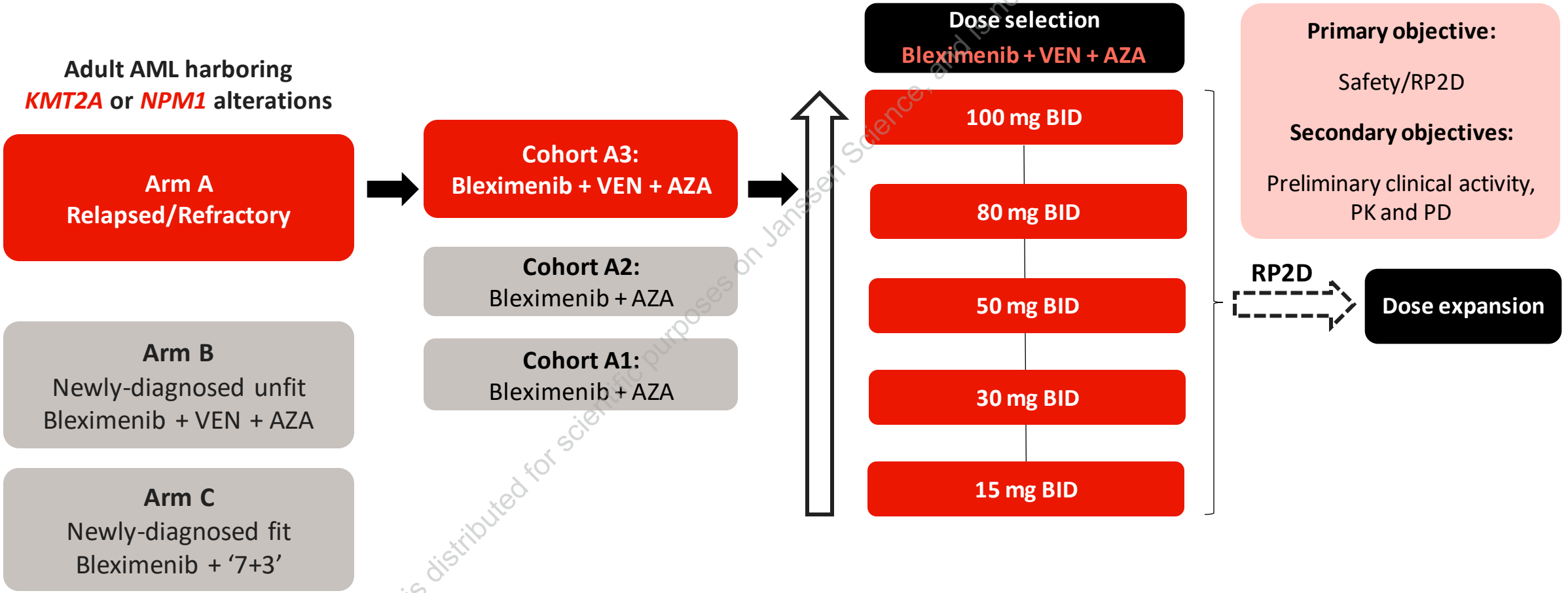
Bleximenib (JNJ-75276617) Phase 1b Combination Trial in AML: Study Design



NCT05453903

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

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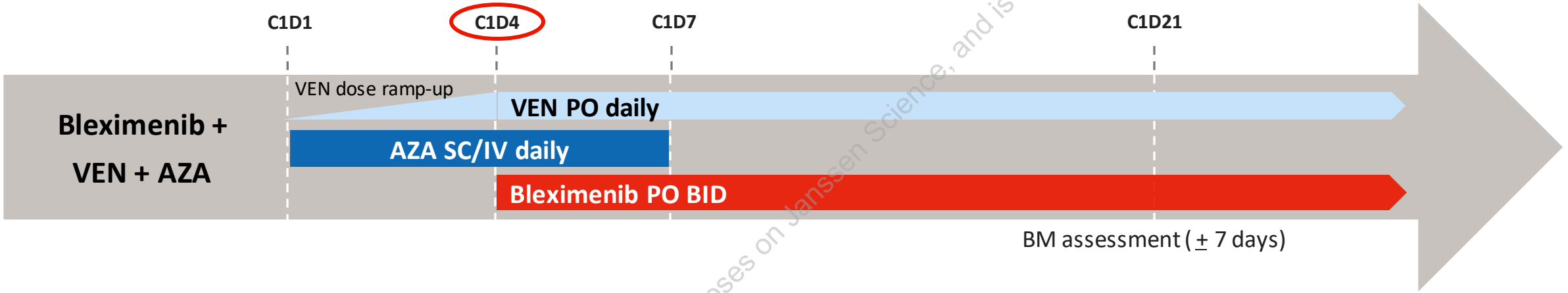
Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Dosing Schedule



Key Considerations for Dosing

- 28-day treatment cycles
- VEN and AZA administration guided by the approved label
  - Bleximenib does not impact VEN exposures
  - Bleximenib exposure in combination similar to monotherapy
- Bleximenib given BID continuously from C1D4
- Isavuconazole primary antifungal of choice, when indicated
- Hydroxyurea and steroids for DS prophylaxis and treatment permitted

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; C, Cycle; D, Day; DS, differentiation syndrome; IV, intravenous; PO, by mouth; R/R, relapsed/refractory; SC, subcutaneous; VEN, venetoclax.

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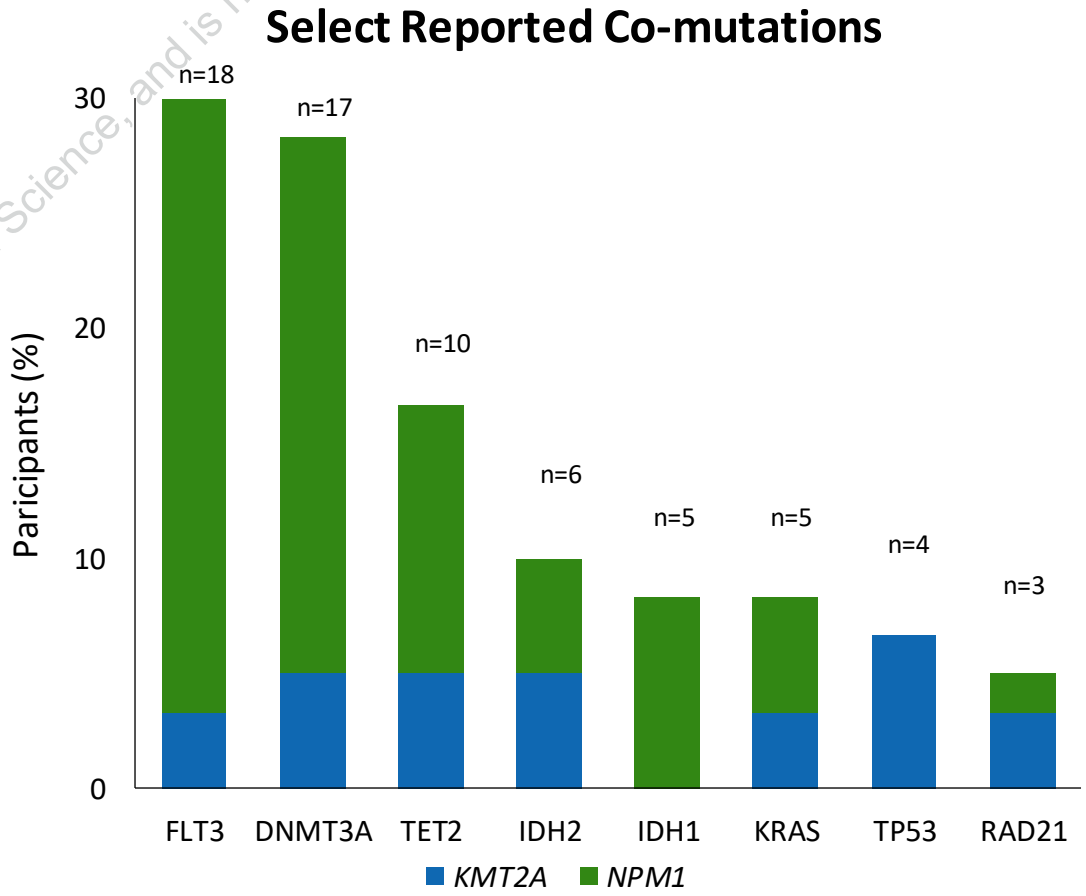
Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Baseline Demographics and Characteristics

	All Treated (N=60)	*KMT2A* (n=30)	*NPM1* (n=30)
Age, median (range), years	60 (20–82)	54 (20–82)	64 (20–81)
Female, n (%)	33 (55)	14 (47)	19 (63)
Male, n (%)	27 (45)	16 (53)	11 (37)
ECOG PS, n (%)			
0	18 (30)	9 (30)	9 (30)
1	34 (57)	16 (53)	18 (60)
2	8 (13)	5 (17)	3 (10)
Prior therapy			
Lines of prior therapy, median (range)	2 (1–5)	2 (1–5)	2 (1–5)
Prior HSCT, n (%)	19 (32)	15 (50)	4 (13)
Prior venetoclax therapy, n (%)	29 (48)	13 (43)	16 (53)

Data cut-off: May 7, 2024.
AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; *KMT2A*, histone-lysine N-methyltransferase 2A; *NPM1*, nucleophosmin 1; R/R, relapsed/refractory.

Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Molecular Characteristics and Associated Co-Mutations

	All Treated (N=60)
***KMT2A* alteration, n (%)**	
Translocation	21 (40)
Other (PTD, amp)/unknown	9 (15)
***NPM1* alteration, n (%)**	
Insertion/frameshift	23 (38)
Translocation	2 (3)
Other/unknown	5 (8)



Data cut-off: May 7, 2024.

AML, acute myeloid leukemia; amp, amplification; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; FLT3, fms related receptor tyrosine kinase 3; IDH1, isocitrate dehydrogenase (NADP(+)) 21; IDH2, isocitrate dehydrogenase (NADP(+)) 2; *KMT2A*, histone-lysine N-methyltransferase 2A; KRAS, KRAS proto-oncogene, GTPase; *NPM1*, nucleophosmin 1; PTD, partial tandem duplication; R/R, relapsed/refractory; TET2, tet methylcytosine dioxygenase 2; TP53, tumor protein p53.

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Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Safety Profile (TEAEs and TRAEs Related to Bleximenib Only)

ITT Safety Population N=60	TEAEs (Regardless of Relationship)	
	All Grades ≥10%	Grade ≥3
Total, n (%)	60 (100)	58 (97)
Nausea	33 (55)	0
Vomiting	25 (42)	1 (2)
Febrile neutropenia	23 (38)	22 (37)
Thrombocytopenia	23 (38)	21 (35)
Anemia	21 (35)	19 (32)
Neutropenia	18 (30)	18 (30)
Diarrhea	15 (25)	0
Pyrexia	15 (25)	0
Leukopenia	13 (22)	13 (22)
Fatigue	13 (22)	2 (3)
Constipation	13 (22)	1 (2)
Abdominal pain	7 (12)	1 (2)
Hypotension	7 (12)	1 (2)
Pneumonia	8 (13)	8 (13)
Headache	8 (13)	1 (2)
Hypokalemia	8 (13)	1 (2)
Asthenia	6 (10)	1 (2)
ALT increased	6 (10)	0

Bleximenib Related AE's of Interest

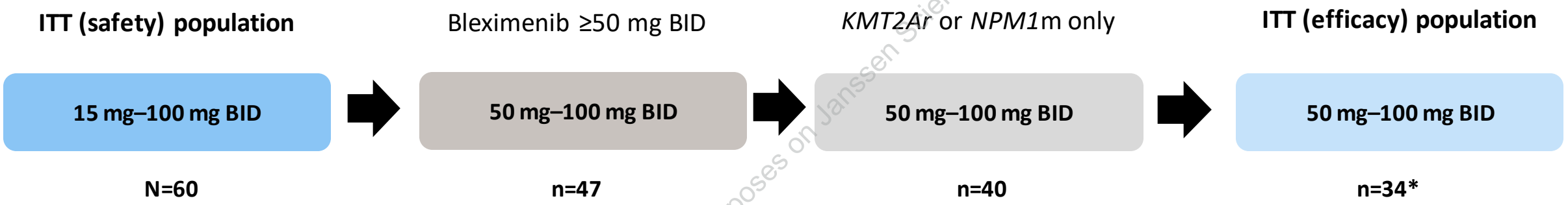
ITT (safety) population N=60	DLT	DS	QTc prolongation	TLS
100 mg BID n=21	0	1 (G3)	0	0
80 mg BID n=7	0	0	0	0
50 mg BID n=19	1 (G5 DS)	1 (G5)	0	0
30 mg BID n=11	0	0	0	0
15 mg BID n=2	0	0	0	0

- Two participants reported DS (Grade 3 at 100 mg BID, Grade 5 at 50 mg BID)
  - G3 case atypical with only fever and later presented in septic shock
  - G5 case with rapid leukocytosis and multiorgan failure
- Bleximenib-related cytopenias do not appear to be dose limiting
- No QTc prolongation or TLS TRAEs were observed
- **RP2D not yet determined**

Data cut-off: May 7, 2024. adverse events were graded according to CTCAE v5.0.

AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; DS, differentiation syndrome; G, Grade; ITT, intent-to-treat; QTc, corrected QT interval; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; TLS, tumor lysis syndrome; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; VEN, venetoclax.

Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Safety and Efficacy Populations



- Efficacy population includes all participants who:
  - Received bleximenib ≥50 mg BID
  - *KMT2Ar* and *NPM1*m only

* Excludes 6 active participants in Cycle 1 without disease evaluation at data cut

Data cut-off: May 7, 2024.

AML, acute myeloid leukemia; BID, twice daily; ITT, intent-to-treat; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; *NPM1*m, nucleophosmin 1 mutations; R/R, relapsed/refractory.

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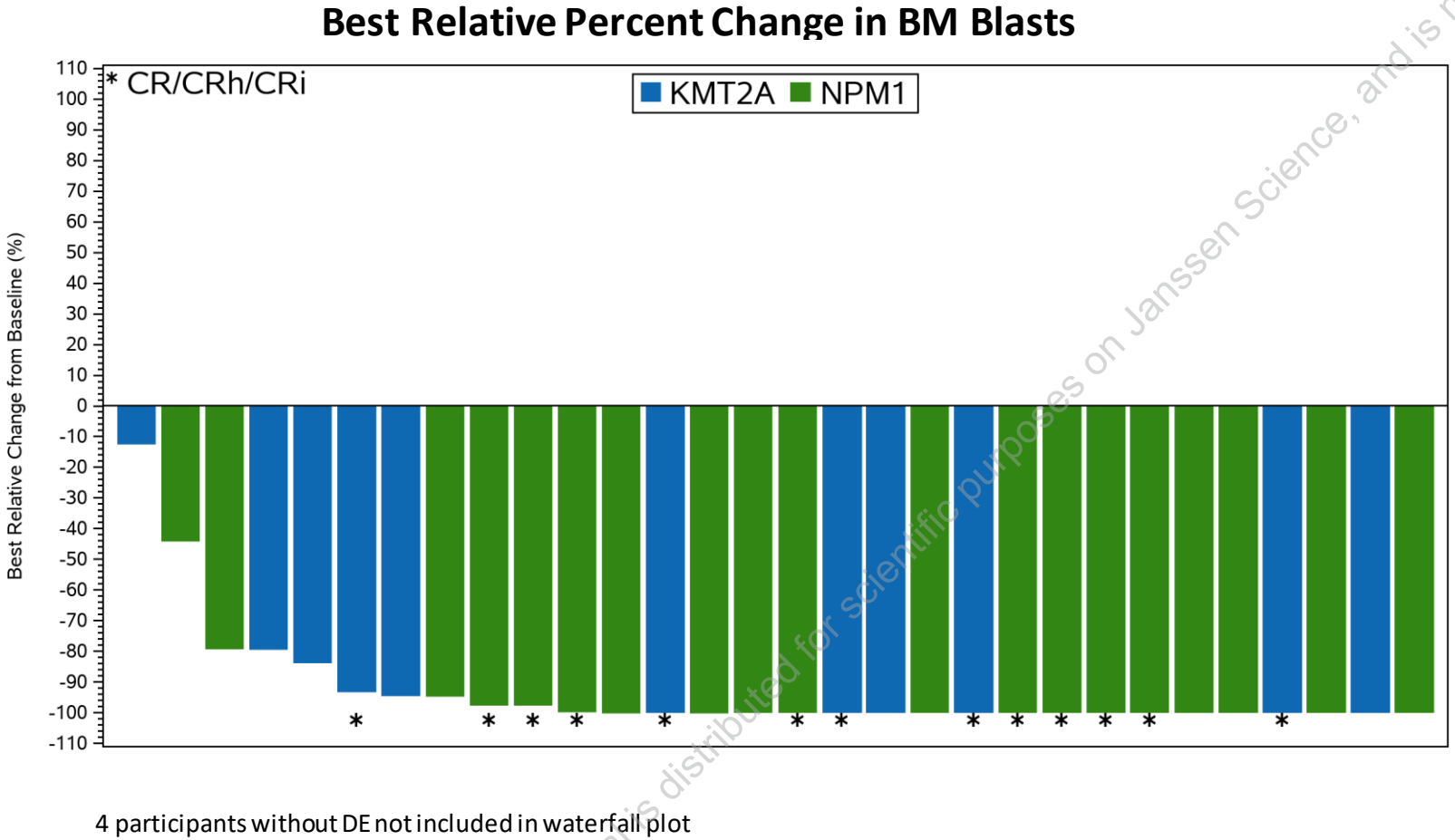
Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Change in Leukemic Burden (N=34)



4 participants without DE not included in waterfall plot

- **34 participants in efficacy population**
  - 13 *KMT2Ar*
  - 21 *NPM1*m
- **All participants with observed reduction in leukemic burden**
- **93% of participants with ≥50% reduction in BM blasts**
- **Reductions observed in both *KMT2Ar* or *NPM1*m**

Data cut-off: May 7, 2024.

Bars are only presented for participants where measurable change from baseline was available; each bar represents a unique participant.

AE, adverse event; AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DE, disease evaluation; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; *NPM1*m, nucleophosmin 1 mutations; PD, progressive disease; R/R, relapsed/refractory.

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Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Preliminary Clinical Activity (N=34)

	Total (N=34)	*KMT2Ar* (n=13)	*NPM1*m (n=21)
ORR (≥PR), n (%)	**27 (79%)**	**8 (62%)**	**19 (90%)**
Best response, n (%)			
CR/CRh/CRi	14 (41%)	5 (39%)	9(43%)
CR/CRh	**8 (24%)**	**4 (31%)**	**4 (19%)**
CR	4 (12%)	1 (8%)	3 (14%)
MLFS	13 (38%)	3(23%)	10 (48%)
SD	1 (3%)	1 (8%)	0 (0%)
PD	2 (6%)	1 (8%)	1 (5%)
NE	4 (12%)	3 (23%)	1 (5%)
Median time to first response, months (range)	0.8 (0.5-1.9)	0.7 (0.5-0.8)	0.8 (0.5-1.9)

Data cut-off: May 7, 2024. Responses were investigator-assessed per modified ELN 2017 recommendations.
AML, acute myeloid leukemia; BID, twice daily; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; NE, not evaluable; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; MLFS, morphologic leukemia-free state; NE, non-evaluable; *NPM1*m, nucleophosmin 1 mutations; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VEN, venetoclax.

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Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Prior VEN Exposure vs No Prior VEN Exposure (N=34)

≥50 mg BID Cohorts

Best timepoint response, n (%)	Prior VEN (n=17)	No Prior VEN (n=17)
ORR (≥PR)	**11 (65%)**	**16 (94%)**
CR/CRh/CRi	5 (29%)	9 (53%)
CR/CRh	3 (18%)	5 (29%)
CR	1 (6%)	3 (18%)
MLFS	6 (35%)	7 (41%)

Participants with prior VEN exposure demonstrated response to bleximenib combination therapy

Data cut-off: May 7, 2024
Responses were investigator-assessed per modified ELN 2017 recommendations (AML).
AML, acute myeloid leukemia; BID, twice daily; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; VEN, venetoclax.

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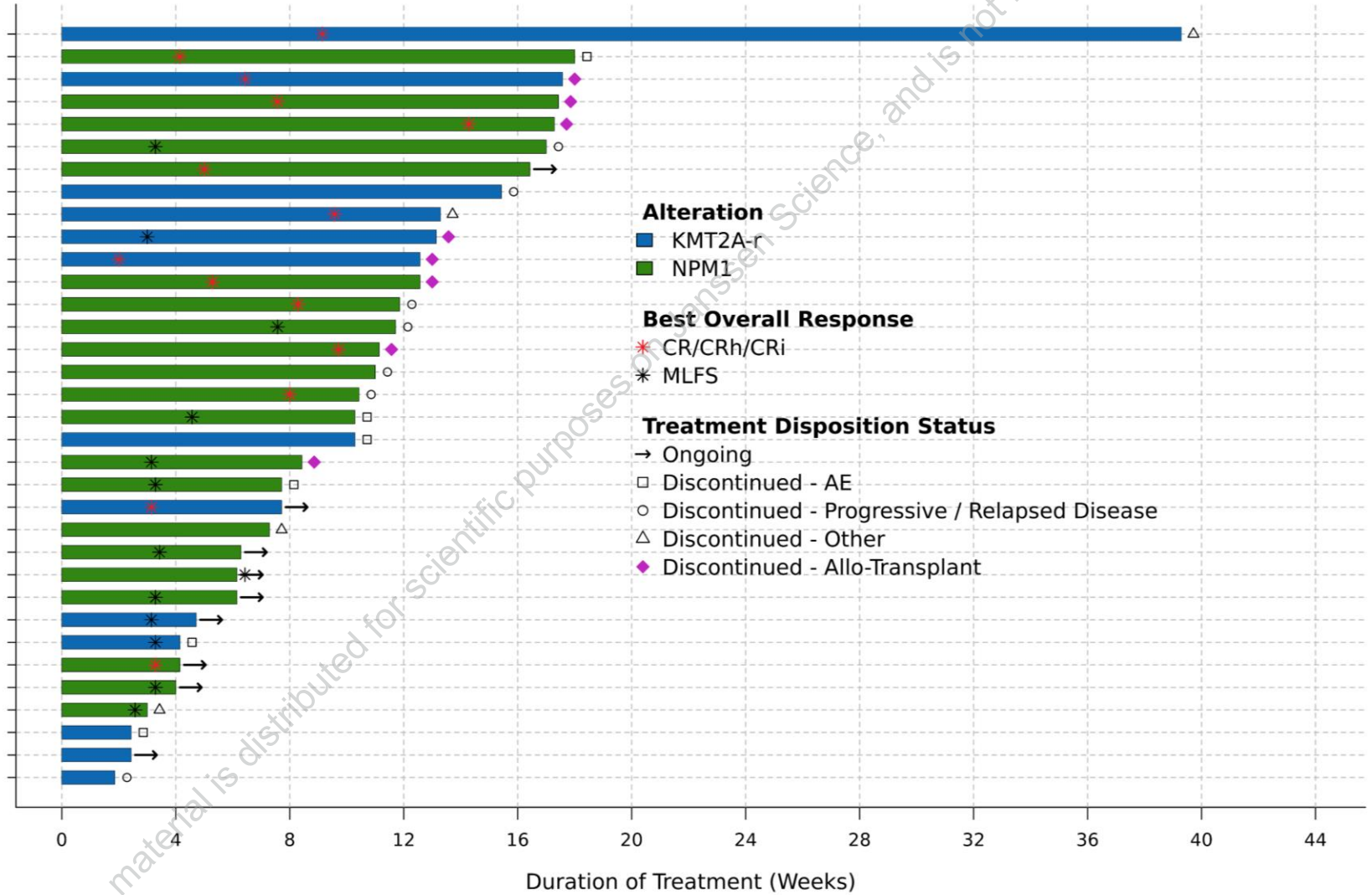
Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Duration of Treatment (N=34)



9 participants bridged to allotransplant*

*1 additional participant went to allotransplant, pending data entry.

Data cut-off: May 7 2024.

AE, adverse event; BID, twice daily; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; MLFS, morphologic leukemia-free state; *NPM1*, nucleophosmin 1.

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Summary and Conclusions

- **Phase 1b study demonstrates the combinability of bleximenib with standard doses of VEN and AZA in R/R AML with *KMT2A* or *NPM1* alterations**
- **Bleximenib combination therapy well tolerated (n=60)**
  - DS observed in 3% (2 participants; G3 & G5/DLT)
  - No bleximenib related events of QT prolongation or TLS
- **Preliminary clinical activity observed in *KMT2Ar* and *NPM1*m R/R AML**
  - Efficacy population (n=34; ≥50 mg BID): ORR 79%; CR/CRh/CRi 41%
  - In participants with prior VEN exposure (n=17): ORR 65%; CR/CRh/CRi 29%
- **Phase 1 dose escalation ongoing to identify RP2D**
  - Exploration of bleximenib in combination with AML directed therapies ongoing in this study (**NCT05453903**):
    - *Newly diagnosed fit AML: bleximenib + '7+3'; newly diagnosed unfit AML (bleximenib + VEN + AZA) participants*
    - *Doublet combinations (bleximenib + VEN or AZA) in relapsed/refractory cohorts*

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete remission; CRh, complete remission with partial hematologic recovery; DLT, dose-limiting toxicity; DS, differentiation syndrome; G, Grade; *KMT2A*, histone-lysine N-methyltransferase 2A; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; *NPM1*, nucleophosmin 1; *NPM1*m, nucleophosmin 1 mutations; ORR, overall response rate; R/R, relapsed/refractory; RP2D, recommended Phase 2 dose; TLS, tumor lysis syndrome; TRAE, treatment-related adverse event; VEN, venetoclax.

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