Bleximenib Dose Optimization and Determination of Recommended Phase 2 Dose From a Phase 1 Study in Relapsed/Refractory Acute Leukemia with *KMT2A* or *NPM1* Alterations

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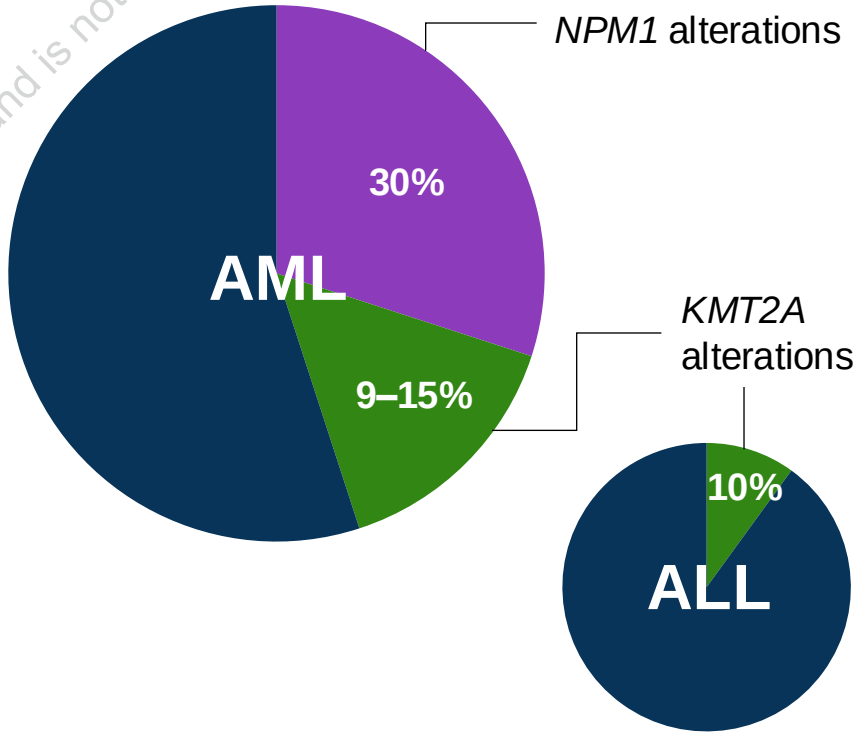
Presented by E Searle at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Background

- R/R altered acute leukemias have **poor outcomes**, with high unmet need for novel therapies
- Bleximenib (JNJ-75276617) is a **potent, selective inhibitor** of the menin-*KMT2A* complex
- **Activity** has been observed in *KMT2Ar* or *NPM1m* AML when given either as **monotherapy (R/R) or in combination (R/R and ND)[1–3]**



Focus: Review data that informed the bleximenib RP2D from the ongoing Phase 1 multicenter dose-finding study of bleximenib monotherapy for *KMT2A*- or *NPM1*-altered R/R acute leukemia

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *KMT2A*(*r*), lysine methyltransferase 2A (rearranged); ND, newly-diagnosed; *NPM1*(*m*), nucleophosmin 1 (mutated); RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

1. Kwon M, et al. Presented at ASH; December 10–13, 2022; New Orleans, LA, USA. Poster presentation 2637. 2. Jabbour E at al. Presented at ASH; December 10–13, 2022; New Orleans, LA, USA. Oral presentation 57. 3. Wei AH, et al. Presented at EHA; June 13–16, 2024; Madrid, Spain. Oral presentation.

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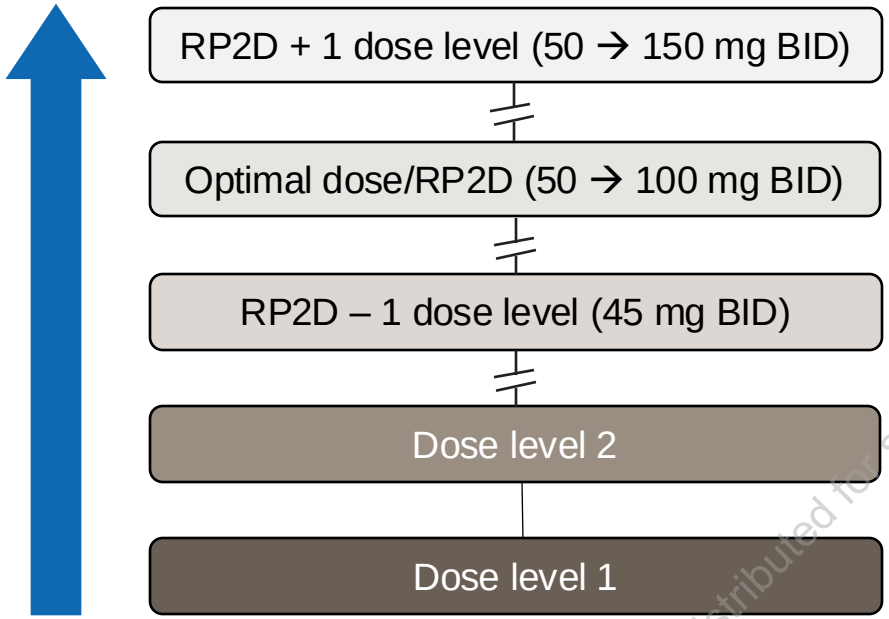
Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Study Design

Dose escalation of oral bleximenib
R/R *KMT2A, NPM1 , NUP98/214* altered acute leukemia
N=146 dosed



RP2D determined

RP2D Treatment Dose:
Bleximenib 100 mg BID orally
(with 50 mg BID step-up dose x 2 weeks)

Phase 2
R/R *KMT2Ar, NPM1m* AML @ RP2D

NCT04811560
AML, acute myeloid leukemia; BID, twice daily; *KMT2A(r)*, lysine methyltransferase 2A (rearranged); *NPM1*(*m*), nucleophosmin 1 (mutated); *NUP*, nucleoporin; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

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Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Baseline Demographics and Characteristics

Characteristic	Overall population (N=146)
R/R acute leukemia type, n (%)	
AML	132 (90.4)
ALL	7 (4.8)
Other acute leukemias	7 (4.8)
Age, median (range), years	60 (17–85)
Female, n (%)	80 (54.8)
Genetic alterations, n (%)	
KMT2A	83 (56.8)
NPM1	58 (39.7)
NUP98 or NUP214	5 (3.5)
Number of prior LOT, median (range)	2 (1–7)
≥1 prior HSCT, n (%)	36 (24.7)
ECOG PS, n (%)	
0	55 (37.7)
1	76 (52.1)
2	14 (9.6)

- To determine the RP2D, data were evaluated across three composite **focused dosing subgroups**:

Bleximenib 45 mg BID (n=15)	Bleximenib 90/100 mg BID* (n=31)	Bleximenib 150 mg BID (n=33)
6 (40%) *KMT2A*	15 (48.4%) *KMT2A*	18 (54.5%) *KMT2A*
9 (60%) *NPM1*	14 (45.2%) *NPM1*	14 (42.4%) *NPM1*
	2 (6.5%) *NUP*	1 (3.0%) *NUP*

Data cut-off: October 2024. *Data from participants receiving bleximenib 90/100 mg BID (RP2D) were combined, given the similar doses and overlapping exposures. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; *KMT2A*, lysine methyltransferase 2A; LOT, lines of therapy; *NPM1*, nucleophosmin 1; *NUP*, nucleoporin; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

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Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Safety Profile of Bleximenib – TEAEs Regardless of Relatedness

Most Common TEAEs Occurring in >15% Pts

(All-dosed; N=146)

TEAE, n (%)	All grade	Grade ≥3
Thrombocytopenia	53 (36.3)	46 (31.5)
Anemia	47 (32.2)	39 (26.7)
Nausea	44 (30.1)	1 (0.7)
Neutropenia	41 (28.1)	37 (25.3)
Constipation	32 (21.9)	1 (0.7)
Febrile neutropenia	28 (19.2)	27 (18.5)
Vomiting	28 (19.2)	2 (1.4)
Peripheral edema	26 (17.8)	0 (0)
ALT increased	25 (17.1)	4 (2.7)
Diarrhea	25 (17.1)	0 (0)

Key Observations

- Bleximenib associated with a tolerable safety profile
- Most common all grade TEAEs included: cytopenias and GI disturbances
- ≥Grade 3 most common TEAEs were cytopenias
- No QTc prolongation signal observed to date
- Differentiation syndrome (DS) observed in 14% of participants across dose levels

Data cut-off: October 2024.

AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received at least one dose of bleximenib.

AE, adverse event; ALT, alanine transaminase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; pt, participant; QTc, corrected QC interval; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

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Safety Profile of Bleximenib – Related TEAEs

Most Common Related TEAEs at 90/100 mg BID vs 150 mg BID Dose

Occurring in ≥10% pts relative to 150 mg BID dose level (all grades)

TEAE, n (%)	150 mg BID (n=33)		90/100 mg BID (n=31)	
	All grade	Grade ≥3	All grade	Grade ≥3
Total	**28** (84.8)	**12** (36.4)	**17** (54.8)	**7** (22.6)
DS	**6** (18.2)	**3** (9.1)	**6** (19.4)	**2** (6.5)
Neutropenia	**6** (18.2)	**5** (15.2)	**1** (3.2)	**1** (3.2)
Thrombocytopenia	**4** (12.1)	**3** (9.1)	**3** (9.7)	**3** (9.7)
Nausea	**6** (18.2)	**0**	**4** (12.9)	**0**
Vomiting	**5** (15.2)	**1** (3.0)	**0** (0)	**0**
AST or ALT increase	**4** (12.1)	**0**	**1** (3.2)	**0**

Key Observations

- Safety profile **optimized** with bleximenib **90/100 mg BID** dose level
  - Bleximenib discontinuation due to related TEAEs at 90/100 mg BID: 6.5%
- **Dose modifications and discontinuations** occurred more frequently at bleximenib 150 mg BID due to AEs
- **≥Grade 3 related neutropenia** more commonly reported with bleximenib **150 mg BID**

Data cut-off: October 2024.

AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received at least one dose of bleximenib.

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DS, differentiation syndrome; pt, participant; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

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Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Differentiation Syndrome Observed in R/R Acute Leukemia

DS emerging as class effect for menin inhibitors

AE, n (%)	All-dosed population (n=146)		90/100 mg BID (n=31)	
	All grade	Grade ≥3	All grade	Grade ≥3
DS	**21** (14.4)	**10** (6.8)	**6** (19.4)	**2** (6.5)

- Median time to onset: 8 days; some pts experienced recurrent DS
- Most initial cases of DS occurred in Cycle 1
- Most common signs/symptoms (n≥3) of DS include:
  - Leukocytosis
  - Elevated ferritin
  - Dyspnea
  - Hypotension
  - Increased body weight
  - Bone pain

Key Observations

- Majority of DS events observed were **low grade**
- DS observed similarly **across *KMT2A* and *NPM1*** altered leukemias
- **2 fatal cases** of DS observed (all-dosed)

DS mitigation measures

- Temporary **interruption** of bleximenib with initiation of **hemodynamic monitoring**
- Systemic **corticosteroids** +/- hydroxyurea
- Supportive care as indicated
- Consider **resuming bleximenib** when signs/symptoms resolve to Grade 1 or baseline

Data cut-off: October 2024.

AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received at least one dose of bleximenib.

AE, adverse event; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DS, differentiation syndrome; *KMT2A*, lysine methyltransferase 2A; *NPM1*, nucleophosmin 1; pt, participant; R/R, relapsed/refractory.

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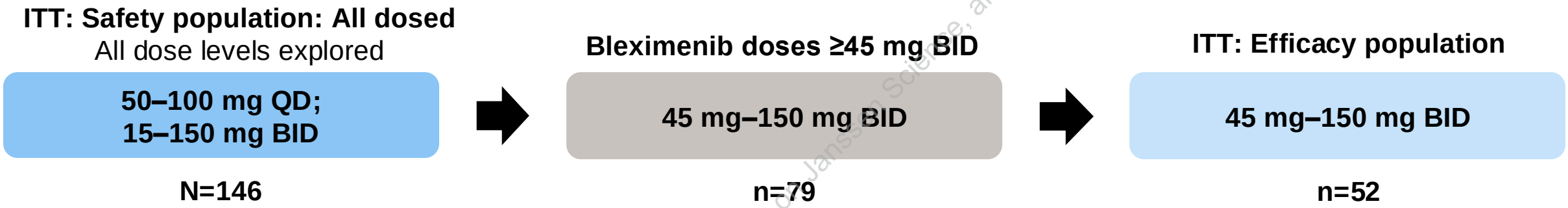
Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Safety and Efficacy ITT Populations



ITT efficacy population defined as:

- R/R AML (≥5% bone marrow blasts) with *KMT2Ar* or *NPM1m*
- Received bleximenib dose levels ≥45 mg BID
- Pts who discontinued - even if before first disease evaluation

Data cut-off: October 2024.

AML, acute myeloid leukemia; BID, twice daily; ITT, intent-to-treat; *KMT2Ar*, lysine methyltransferase 2A rearranged; *NPM1m*, nucleophosmin 1 mutated; pt, participant; QD, daily; R/R, relapsed/refractory

Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

ITT Efficacy in Dosing Subgroups – R/R *KMT2Ar* or *NPM1m* AML

Efficacy Parameter	Bleximenib 45 mg BID (n=11)	Bleximenib 90/100 mg BID (n=21)	Bleximenib 150 mg BID (n=20)
ORR (≥PR), n (%)	**4** (36.4)	**10 (47.6)**	**11** (55.0)
Best response			
Composite CR (CR/CRh/CRi), n (%)	**2** (18.2)	**8 (38.1)**	**8** (40.0)
CR/CRh, n (%)	**2** (18.2)	**7 (33.3)**	**8** (40.0)
Median time to first response, months (range)	**1.5** (1.0–1.9)	**1.4 (0.9–4.7)**	**1.0** (0.9–2.1)
Pts proceeded to allogeneic HCT (%)	**1** (9%)	**3 (14.3%)**	**2** (10%)

Responses were investigator-assessed per modified ELN 2017

- Median follow-up 6.5 months (N=146; 0.07–25.9)
- Median duration of CR/CRh = 6 mos (95% CI: 1.9–NE)
- 12 pts proceeded to allogeneic HCT

Best overall response by mutation, n (%)	Bleximenib 90/100 mg BID cohort	
	KMT2Ar (n=9)	*NPM1m* (n=12)
cCR, n (%)	**4** (44.4)	**4** (33.3)
CR/CRh , n (%)	**3** (33.3)	**4** (33.3)

AML, acute myeloid leukemia; BID, twice daily; cCR, composite complete response; CI, confidence interval; CR, complete response; CRh, CR with partial haematological recovery; CRi, complete remission with incomplete count recovery; DOR, duration of response; ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation; *KMT2Ar*, lysine methyltransferase 2A rearranged; NE, not estimable; *NPM1m*, nucleophosmin 1 mutated; ORR, overall response rate; PR, partial response; pt, participant; R/R, relapsed/refractory.

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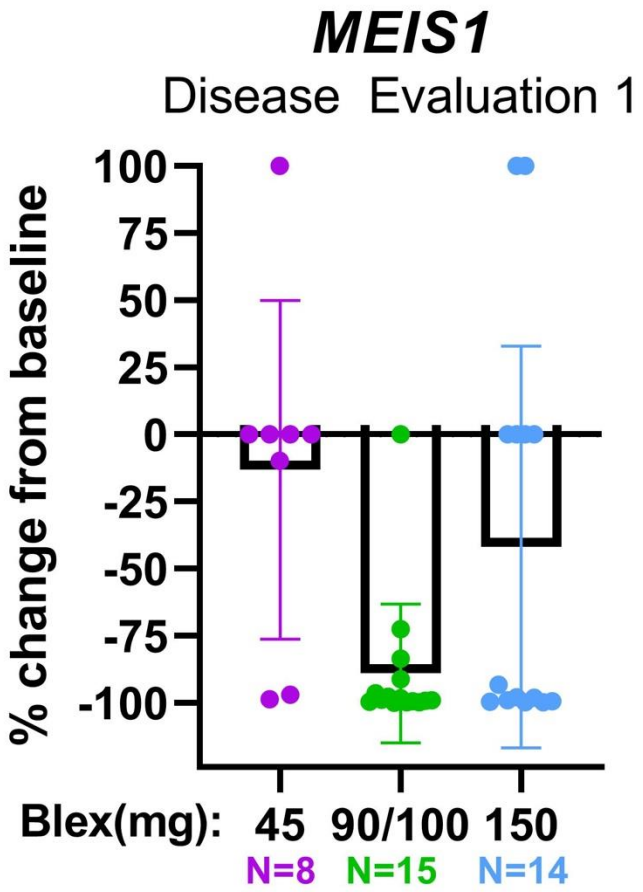
Key Pharmacodynamic Observations for Bleximenib

- **Dose-dependent reduction of menin-*KMT2A* target gene expression (eg, *MEIS1*) was observed, consistent with MOA**
- **At bleximenib 90/100 mg BID dose level:**
  - **Significantly greater inhibition of *MEIS1*** after first treatment cycle compared to 45 mg BID dose level
  - Similar inhibition observed at 150 mg BID
- **Data indicate optimal target engagement rapidly achieved at 90/100 mg BID**



Gene expression based on customized Nanostring nCounter SPRINT Profiler assay using RNA isolated from unfractionated BM; data were normalized to house-keeping genes and reported as percent change from baseline at disease evaluation 1. Box plot indicates mean ± SD.
BID, twice daily; BM, bone marrow; *KMT2A*, lysine methyltransferase 2A; *MEIS1*, Meis homeobox 1; MOA, mechanism of action; R/R, relapsed/refractory; SD, standard deviation.

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Bleximenib Menin Inhibitor Monotherapy (**cAMeLot-1**) in R/R Acute Leukemia

Conclusions

- The Phase 1 data informed a **bleximenib RP2D of 100 mg BID** (with a 50 mg BID step-up dose for 14 days) as monotherapy in R/R AML harboring *KMT2Ar* or *NPM1m*
  - Bleximenib 150 mg BID dose associated with more AE-induced dose modifications/discontinuations and increased Grade ≥3 neutropenia, without clear improvement in clinical efficacy or PD activity

- Efficacy optimized at **100 mg BID**, with **33% CR/CRh rate** for bleximenib monotherapy in R/R AML

- Bleximenib monotherapy was well tolerated with a **manageable safety profile**
  - No cardiac safety signal identified
  - DS emerging as class effect; strategies to mitigate DS appear effective

The Phase 2 portion of **cAMeLot-1** study to further evaluate bleximenib monotherapy at the RP2D in R/R AML with *KMT2Ar* or *NPM1m* is ongoing

NCT04811560

AE, adverse event; AML, acute myeloid leukemia; BID, twice daily; CR, complete response; CRh, CR with partial hematological recovery; DS, differentiation syndrome; *KMT2Ar*, lysine methyltransferase 2A rearranged; *NPM1m*, nucleophosmin 1 mutated; PD, pharmacodynamic; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

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Acknowledgements

- We thank the participants who are taking part in this 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 analyses
- This study was funded by Janssen Research & Development, LLC
- Medical writing support was provided by Ashfield MedComms and funded by Janssen Global Services, LLC

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