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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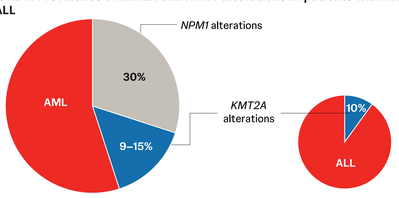
KEY TAKEAWAY

Bleximenib monotherapy at the RP2D of 100 mg BID demonstrated a manageable safety profile and encouraging clinical activity, with a 33% CR/CRh rate in patients with R/R AML harboring *KMT2Ar* or *NPM1* mutations. Higher dosing (150 mg BID) led to increased toxicity without added efficacy, supporting 100 mg BID as the optimal dose

INTRODUCTION

- Relapsed/refractory (R/R) acute leukemias have poor outcomes, and there is a high unmet need for novel therapies
- Bleximenib (JNJ-75276617) is a potent, selective inhibitor of the menin-*KMT2A* complex
- Bleximenib activity has been observed in *KMT2A* rearranged (*KMT2Ar*) or *NPM1* mutated (*NPM1m*) acute myeloid leukemia (AML) when given either as monotherapy (R/R) or in combination with other agents (R/R and newly diagnosed [ND])[1–3]

FIGURE 1: Prevalence of *KMT2A* and *NPM1* alterations in patients with AML or ALL



ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

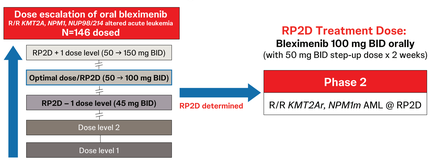
OBJECTIVE

- To evaluate the safety and efficacy of bleximenib monotherapy and to determine the recommended phase 2 dose (RP2D) in participants with R/R acute leukemia with *KMT2A* or *NPM1* alterations

METHODS

Study design

FIGURE 2: cAMeLot-1 study design



NCT04811560

AML, acute myeloid leukemia; BID, twice daily; *KMT2Ar*, *KMT2A* rearranged; *NPM1m*, *NPM1* mutated; *NUP*, nucleoporin; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

- cAMeLot-1 (NCT04811560) assessed the safety and tolerability of bleximenib monotherapy in a dose escalation adaptive design (**FIGURE 2**)
- Participants with R/R acute leukemia with *KMT2A*, *NPM1*, or *NUP* alterations received bleximenib monotherapy in 28-day cycles, escalating to a maximum of 150 mg twice daily (BID)
- RP2D was determined from 3 dosing subgroups (45 mg, 100 mg, and 150 mg BID)
- Safety was evaluated in all dosed participants
- The efficacy was evaluated in the intent-to-treat (ITT) population, including participants with R/R AML and *KMT2Ar*/*NPM1m* who received bleximenib at dose levels of ≥45 mg BID

RESULTS

- As of October 2024, 146 participants had received at least 1 dose of bleximenib; most participants had AML (90.4%), and the *KMT2A* genetic alteration was present in 56.8% of patients (**TABLE 1**)

TABLE 1: Baseline demographic 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)

Data cut-off: October 2024.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; LOT, lines of therapy; R/R, relapsed/refractory.

TABLE 2: Genetic alterations prevalence among 3 dosing subgroups in the RP2D phase

Bleximenib 45 mg BID (n=15)	Bleximenib 90/100 mg BID[a] (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*

[a]Data from participants receiving bleximenib 90/100 mg BID (RP2D) were combined, given the similar doses and overlapping exposures.
BID, twice daily; RP2D, recommended phase 2 dose.

- Overall, bleximenib was associated with a tolerable safety profile
- The most common all-grade treatment-emergent adverse events (TEAEs) included cytopenias and gastrointestinal disturbances (**TABLES 3** and **4**)
- The most common grade ≥3 TEAEs were cytopenias
- No corrected QC interval prolongation signal has been observed to date
- Differentiation syndrome (DS) was observed in 14% of participants across all dose levels

TABLE 3: Safety profile of bleximenib: TEAEs regardless of relatedness

TEAE,[a] n (%)	All grade N=146 patients	Grade ≥3 N=146 patients
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)

Data cut-off: October 2024.
[a]TEAEs occurring in >15% of participants.
AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received ≥1 dose of bleximenib.
AE, adverse event; ALT, alanine transaminase; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; TEAE, treatment-emergent adverse event.

TABLE 4: Safety profile of bleximenib-related TEAEs

TEAE,[a] n (%)	150 mg BID n=33 patients		90/100 mg BID n=31 patients	
	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
AST/ALT increase	4 (12.1)	0	1 (3.2)	0

Data cut-off: October 2024.
[a]Occurring in ≥10% of patients in 150-mg BID dose-level group (all grades).
AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received at least 1 dose of bleximenib.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DS, differentiation syndrome; TEAE, treatment-emergent adverse event.

- Safety profile in participants receiving bleximenib at 90/100 mg BID dose level was favorable over the 150 mg BID dose level
  - Bleximenib discontinuation rate due to related TEAEs at 90/100 mg BID was 6.5%
- Dose modifications and discontinuations due to AEs occurred more frequently in the 150 mg BID group
- Grade ≥3 neutropenias were more commonly reported with bleximenib at 150 mg BID

TABLE 5: DS in R/R acute leukemia

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)

Data cut-off: October 2024.
AEs are graded using the CTCAE v5.0. The safety dataset comprises participants who have received at least 1 dose of bleximenib.
AE, adverse event; BID, twice daily; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DS, differentiation syndrome.

- DS is emerging as a class effect for menin inhibitors and was seen at all dose levels and across both genetic alteration subtypes
- Most cases were low grade; however, 10 participants experienced grade ≥3 DS events, which included 2 deaths (**TABLE 5**)
- The median time to onset of DS was 8 days, and most cases presented during cycle 1
- Along with high levels of vigilance for DS, mitigation measures were introduced, which included step-up dosing, hydroxyurea, and steroids
- The most common signs/symptoms (n≥3) of DS included:
  - Leukocytosis
  - Elevated ferritin
  - Dyspnea
  - Hypotension
  - Increased body weight
  - Bone pain

TABLE 6: Efficacy in the ITT population 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, n (%)	1 (9.1)	3 (14.3)	2 (10.0)
Best overall response by mutation	**Bleximenib 90/100 mg BID**		
	KMT2Ar **(n=9)**	***NPM1m*** **(n=12)**	
cCR, n (%)	4 (44.4)	4 (33.3)	
CR/CRh, n (%)	3 (33.3)	4 (33.3)	

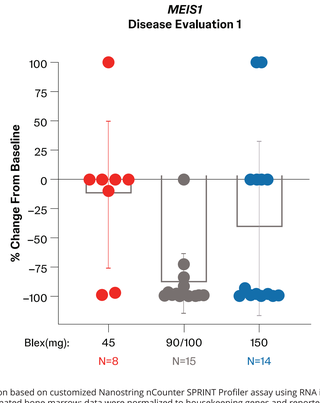
AML, acute myeloid leukemia; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, complete response with partial hematological recovery; CRi, complete response with incomplete count recovery; HCT, hematopoietic cell transplantation; ITT, intent-to-treat; *KMT2Ar*, *KMT2A* rearranged; *NPM1m*, *NPM1* mutated; ORR, overall response rate; PR, partial response; pts, participants; R/R, relapsed/refractory.

- Among all dosed participants (N=146), the median follow-up was 6.5 months and the median duration of complete response (CR)/CR with partial hematological recovery (CRh) was 6 months (95% CI: 1.9–not estimable)

Key pharmacodynamic observations for bleximenib

- Dose-dependent reduction of menin-*KMT2A* target gene expression (ie, *MEIS1*) was observed, which was consistent with bleximenib mechanism of action
- At the dose level of bleximenib 90/100 mg BID:
  - The inhibition of *MEIS1* after first treatment cycle was significantly greater compared with the 45 mg BID dose level
  - The extent of inhibition of *MEIS1* was similar at the 150 mg BID dose level
- These data indicate that the optimal target engagement was achieved at 90/100 mg BID dose level

FIGURE 3: Gene expression of *MEIS1* at different bleximenib dose levels



Gene expression based on customized Nanostring nCounter SPRINT Profiler assay using RNA isolated from unfractionated bone marrow; data were normalized to housekeeping genes and reported as percent change from baseline at disease evaluation 1. Box plot indicates mean ± standard deviation.

CONCLUSIONS

The data from this phase 1 study of bleximenib monotherapy for R/R AML with *KMT2Ar* or *NPM1m* showed that the RP2D was 100 mg BID (with a 50 mg BID step-up dose for 14 days)

- A higher dose level of bleximenib (at 150 mg BID) was associated with more dose modifications/discontinuations due to AEs and increased prevalence of grade ≥3 neutropenia, without signs of improved clinical efficacy or pharmacodynamic activity

At the dose level of bleximenib 100 mg BID, the CR/CRh rate in participants with R/R *KMT2Ar* or *NPM1m* AML was 33%

Bleximenib monotherapy was well tolerated with a manageable safety profile

- No cardiac safety signals were identified
- Mostly low-grade differentiation syndrome was observed and was effectively managed by implementing standard mitigation strategies

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