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Bleximenib in Combination With Intensive Chemotherapy: A Phase 1b Study in Newly Diagnosed Acute Myeloid Leukemia With *KMT2A* or *NPM1* Alterations

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Key Takeaway

Bleximenib combined safely with '7+3' IC in participants with ND AML and data informed bleximenib 100 mg BID as the RP2D

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

Conclusions

In participants with ND AML who are eligible for IC, the safety profile of bleximenib plus '7+3' IC was consistent with '7+3' IC; no DS events and no QTc prolongation signals were observed

Early efficacy results showed high response rates with bleximenib plus '7+3' IC that were comparable across *KMT2Ar* or *NPM1m* mutational subtypes

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Abbreviations

'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); ALT, alanine aminotransferase; AML, acute myeloid leukemia; Anthr, anthracycline; ASCT, allogeneic stem cell transplant; AST, aspartate aminotransferase; AZA, azacitidine; BID, twice daily; 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; IC, intensive chemotherapy; ITT, intention to treat; *KMT2A*, lysine methyltransferase 2A gene; *KMT2Ar*, *KMT2A* rearranged; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; ND, newly diagnosed; *NPM1*, nucleophosmin 1 gene; *NPM1m*, *NPM1* mutated; NR, not reached; ORR, overall response rate; PCR, polymerase chain reaction; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; QTc, corrected QT interval; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; VEN, venetoclax.

Background

- *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 resulted in clinical benefits with no corrected QT interval (QTc) safety signals in participants with relapsed/refractory (R/R) *KMT2Ar* and *NPM1m* AML[6,7]
- Currently, no menin inhibitors are approved for newly diagnosed (ND) *KMT2Ar* or *NPM1m* AML in patients eligible for intensive chemotherapy (IC)
- Based on previous results from the phase 1b, dose-finding study ALE1002, bleximenib in combination with '7+3' IC (Cohort C1) resulted in high response rates and acceptable safety in IC-eligible participants with ND *KMT2Ar* or *NPM1m* AML[8]

- **This analysis reports updated safety and efficacy from ALE 1002 (Cohort C1) at the RP2D of bleximenib 100 mg BID**
- **Median follow-up: 9.1 months (range, 1.3–24.8)**

Methods

Figure 1: ALE1002 (NCT05453903) study design

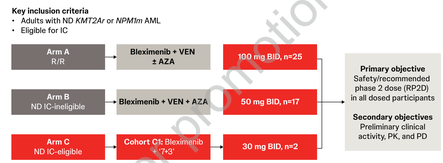
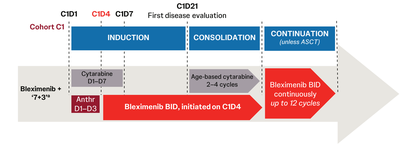


Figure 2: Dosing schedule

Cohort C1 received increasing doses of bleximenib (30, 50 or 100 mg BID) in combination with '7+3' induction and cytarabine consolidation, followed by optional bleximenib monotherapy in continuation phase[a]



[a]Isavuconazole was the primary antifungal of choice when indicated, with no requirement for bleximenib dose modification.

Results

Participants

- Key baseline characteristics for 44 participants (19 with *KMT2A* alterations, 25 with *NPM1m*) across all dose levels were similar (**Supplementary Table 1**)

Safety

- Safety profiles were similar across all 3 dose levels, including the dose level of 100 mg BID (RP2D), and were consistent with an IC backbone (**Table 1**)
- Across all dose levels, no differentiation syndrome (DS) events were observed; 3 events of QTc prolongation were reported, all of which were grade 1 or 2 and resolved without bleximenib interruption
- Hematologic events were the most commonly reported events across all dose levels, occurring less frequently during the bleximenib continuation phase than during the induction and consolidation phases (**Supplementary Table 2**)

Table 1: TEAEs occurring in ≥30% of participants at 100 mg BID (RP2D), regardless of relatedness to study treatment

TEAE, n (%)	Bleximenib 100 mg BID[a] N=25	
	Any grade	Grade ≥3
Participants with ≥1 TEAE	25 (100.0)	25 (100.0)
Hematologic TEAEs		
Thrombocytopenia	22 (88.0)	22 (88.0)
Neutropenia	19 (76.0)	19 (76.0)
Anemia	18 (72.0)	18 (72.0)
Febrile neutropenia	17 (68.0)	17 (68.0)
Leukopenia	11 (44.0)	11 (44.0)
Nonhematologic TEAEs		
Diarrhea	18 (72.0)	2 (8.0)
Nausea	17 (68.0)	1 (4.0)
Pyrexia	16 (64.0)	1 (4.0)
Stomatitis	14 (56.0)	5 (20.0)
ALT increased	13 (52.0)	2 (8.0)
Peripheral edema	10 (40.0)	0
AST increased	9 (36.0)	2 (8.0)
Headache	8 (32.0)	0
Hypokalemia	8 (32.0)	1 (4.0)
Hypotension	8 (32.0)	2 (8.0)
Constipation	8 (32.0)	0
Vomiting	8 (32.0)	1 (4.0)

Data cutoff: October 2025.
[a]The list of TEAEs for the entire safety population is provided in the **Supplementary Table 3**.

Table 2: Mortality rates in the safety population

Mortality rate, n (%)	N=44[a]
30-day	0
60-day[b]	1 (2.3)[c]

Data cutoff: October 2025.
[a]Safety population comprised all dosed participants who received bleximenib at 30 mg BID (n=2), 50 mg BID (n=17), or 100 mg BID (n=25).
[b]Two of 25 participants in the 100 mg BID group ended the study before the 60-day follow-up.
[c]Due to progressive disease.

Table 3: Exposure and dose modifications[a]

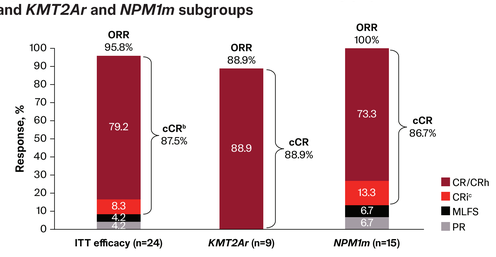
Median (range)	N=44
Relative dose intensity of bleximenib during induction, %	100 (16–100)[b]
Duration of treatment with bleximenib, days	166.5 (12–627)

Data cutoff: October 2025.
[a]Information on dose modifications and dose intensity during consolidation are provided in the **Supplementary Material**.
[b]With no required dose reduction of coagents.

Efficacy in participants treated at the RP2D

- Among 24 participants in the intention-to-treat (ITT) efficacy population who received bleximenib 100 mg BID, responses were similar across mutational subtypes (**Figure 3**)

Figure 3: Best overall response in the ITT efficacy population[a] and *KMT2Ar* and *NPM1m* subgroups



Median (range), days	Responders in the ITT population N=23
Time to first response	28 (15–78)
Time to CR	28 (22–92)
Duration of response	NR

Data cutoff: October 2025.
[a]ITT population comprised participants with *KMT2Ar* or *NPM1m* ND AML who were eligible for IC, and who received bleximenib 100 mg BID in combination with '7+3' IC, including those who discontinued prior to the first disease evaluation; 1 participant with *KMT2A* amplification was excluded from the analysis.
[b]No CRh events occurred.
[c]As of October 10, 2025, 1 participant who achieved CRi remains active on treatment with a potential to deepen the response.

Table 4: Efficacy outcomes

Outcome	
MRD negativity[a]	80% (12 of 15 participants with evaluable samples)
Median event-free survival[b]	NR[c]

Data cutoff: October 2025.
[a]Central assessment of MRD negativity was performed using molecular-based methods (next-generation sequencing or PCR) in 15 of 19 participants with *KMT2Ar* or *NPM1m* who achieved CR.
[b]Time from first dose of study treatment until treatment failure or death, whichever occurs first. Assessed in the ITT efficacy population.
[c]Kaplan-Meier plot of event-free survival is shown in **Supplementary Figure 1**.

Count recovery

- No clinically significant myelosuppression was observed in the induction phase beyond that expected with an IC backbone, including no significant difference in hemoglobin, neutrophil, or platelet values

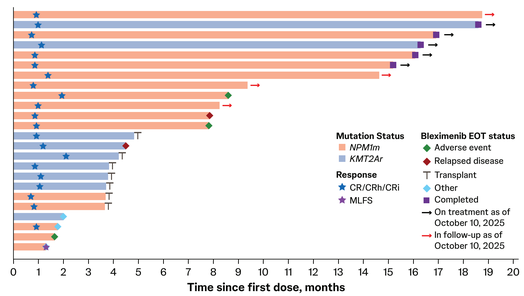
Table 5: Median times for count recovery

Time, median (range), days	N=22[b]
From day 1 of induction to platelet count recovery (≥50 × 10^9/L)[a]	31.5 (22.0–71.0)
From day 1 of induction to neutrophil count recovery (≥0.5 × 10^9/L)[a]	30.0 (25.0–69.0)

Data cutoff: October 2025.
[a]Hematologic parameters over time are shown in **Supplementary Figure 2**.
[b]Participants who received bleximenib 100 mg BID and achieved cCR (comprising CR, CRh, and CRi)

Treatment disposition

Figure 4: Response and duration of treatment in the ITT efficacy population[a]



Data cutoff: October 2025
[a]Among 24 participants in the ITT efficacy population who received bleximenib 100 mg BID, 15 participants (62.5%) discontinued (7 participants [29.2%] proceeded to receive ASCT, other reasons for discontinuation are listed in **Supplementary Material**) 4 participants (16.7%) remained active, and 5 participants (20.8%) completed therapy.

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Myeloid Malignancies

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