A First-in-Human Phase 1/2 Study of the Menin-KMT2A (MLL1) Inhibitor BN104 in Adult Patients with Relapsed or Refractory Acute Leukemia

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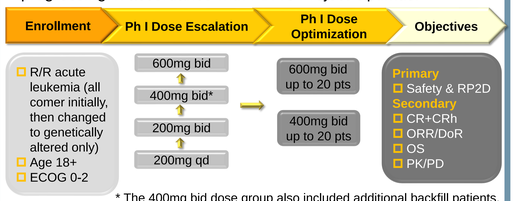
INTRODUCTION

- NPM1 mutation (NPM1m) is the most common genetic alteration in adult acute myeloid leukemia (AML), constituting of 30% cases. KMT2A rearrangement (KMT2Ar), presents in up to 10% of cases, is an aggressive AML subtype characterized with high relapse rates and unfavorable survival. Menin, a critical cofactor, plays a significant role in leukemogenesis in both KMT2Ar and NPM1m AML[1,2,3] .
- Menin inhibitors, through disrupting the menin-KMT2A protein-protein interaction, have demonstrated promising clinical activities in AML patients harboring KMT2Ar or NPM1m with efficacy (CR/CRh) percentage in mid-twenties, albeit from dose-limiting toxicities such as Grade 3 QTc prolongation and/or severe differentiation syndrome [4,5].
- BN104 is a novel, highly potent and selective menin inhibitor designed to avoid the risk of QTc prolongation that results in improved safety margin, thus may have the potential to show superior treatment outcomes than other menin inhibitors[6].
- Herein, we present the initial clinical trial data from the Phase 1 part of an ongoing phase 1/2 study of BN104 in patients with relapsed/refractory (R/R) acute leukemia.

OBJECTIVES AND STUDY DESIGN

- BN104-101 trial (NCT06052813) is a phase 1/2 open-label study to evaluate the safety, tolerability and efficacy of BN104 administered orally, either once or twice daily, in every 28-day treatment cycles in patients with R/R acute leukemia.
- The primary objective of phase 1 part is to determine the safety and recommended phase 2 dose (RP2D) of single agent BN104, whereas the phase 2 part is a single-arm pivotal study powered to evaluate BN104 efficacy in R/R AML patients with target genetic alterations.
- The dose escalation portion of the phase 1 trial has been completed, and enrollment for the dose optimization portion is progressing in accordance with FDA's Project Optimus.



* The 400mg bid dose group also included additional backfill patients.

- Key eligibility criteria: 1) R/R acute leukemia patients diagnosed according to the 2022 WHO criteria; 2) KMT2Ar or NPM1m. Patients were excluded if they had definite active central nervous system leukemia or uncontrolled active infection.
- Adverse events (AEs) are graded by CTCAE v5.0. Efficacy assessment are conducted by study investigators according to ELN2022 criteria and are scheduled periodically at screening, C2D1, C3D1, Day 1 of every 2 subsequent treatment cycles up to C13D1, and then Day 1 of every 6 cycles thereafter as well as at the end of treatment visit.

RESULTS

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- As of October 18, 2024, 40 R/R acute leukemia patients had been enrolled in the phase 1 study (Table 1)

Table 1. Patient Baseline Demographics and Disease Characteristics

Parameter	All Enrolled Patients (N=40)
Median age, y (range)	46(19-82)
Sex, n(%)	
Male	16(40.0)
Female	24(60.0)
Ethnicity, n(%)	
Chinese	40(100)
Race	
Asian	40(100)
Median % of bone marrow blasts (range)	32.3(5-95)
Acute Leukemia type, n(%)	
AML	39(97.5)
ALL	1(2.5)
Genetic Alterations, n(%)	
KMT2Ar	25(62.5)
NPM1m	6(15.0)
Others	9(22.5)
Number of prior lines of therapy, median(range)	2(1-8)
≥4 prior lines of therapy, n(%)	10(25.0)
Prior venetoclax, n(%)	35(87.5)
Prior HSCT, n(%)	10(25.0)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; NPM1m, mutated nucleophosmin 1.

SAFETY

- No DLT, no new safety finding
- In all enrolled population (N=40), 62.5% and 70% of patients had SAE and ≥Grade 3 TRAE, respectively
- ECG QTc prolongation reported in 6 patients (15.0%)
  - All are transient grade 1 and asymptomatic, and are also recovered
- Differentiation syndrome (DS) reported in 7 patients (17.5%)
  - All are grade 1 or 2 and recovered
  - No mortality or permanent discontinuations due to DS
  - No DS prophylaxis with BN104

Table 2. ≥ Grade 3 Treatment related AEs

Preferred Term	200mg qd (n=1)	200mg bid (n=3)	400mg bid (n=24)	600mg bid (n=12)	All Enrolled Patients (N=40)
Patients with ≥Gr 3 treatment-related AE, n(%)	1(100)	1(33.3)	17(70.8)	9(75.0)	28(70.0)
Platelet count decreased	1(100)	0	4(16.7)	5(41.7)	10(25.0)
White blood cell count decreased	0	0	5(20.8)	5(41.7)	10(25.0)
Neutrophil count decreased	0	0	5(20.8)	5(41.7)	10(25.0)
Lymphocyte count decreased	0	0	3(12.5)	3(25.0)	6(15.0)
Anaemia	0	0	2(8.3)	2(16.7)	4(10.0)
Pneumonia	1(100)	0	3(12.5)	0	4(10.0)
Myelosuppression	0	0	3(12.5)	0	3(7.5)
Febrile neutropenia	0	0	2(8.3)	1(8.3)	3(7.5)
Vomiting	0	0	2(8.3)	1(8.3)	3(7.5)
Nausea	0	0	1(4.2)	1(8.3)	2(5.0)
Gamma-glutamyltransferase increased	0	0	1(4.2)	1(8.3)	2(5.0)
Sepsis	0	0	2(8.3)	0	2(5.0)
Hypokalaemia	0	1(33.3)	1(4.2)	0	2(5.0)
Hyponatraemia	1(100)	0	0	0	1(2.5)
Tuberculosis	1(100)	0	0	0	1(2.5)
Urinary tract infection	0	1(33.3)	0	0	1(2.5)
Bacterial infection	0	0	0	1(8.3)	1(2.5)
Lower respiratory tract infection fungal	0	0	0	1(8.3)	1(2.5)
Asthenia	0	0	0	1(8.3)	1(2.5)
Soft tissue infection/Herpes zoster/Pain/Acute kidney injury/Hypertriglyceridaemia	0	0	1(4.2)	0	1(2.5)

EFFICACY

- Of the 40 patients, 28 patients are included in the efficacy analysis (efficacy evaluable population is defined as those treated with at least one dose BN104 and would have at least one post-baseline response evaluation with central laboratory confirmed KMT2Ar or NPM1m), which exclude:
  - 9 patients without target genetic mutations (KMT2Ar or NPM1m)
  - 3 patients withdrew from the study early before the first efficacy assessment
- Overall response rate (ORR) was 89.3% in the efficacy population with CR/CRh of 57.1%
- Among patients with KMT2Ar, the CR/CRh was 60.9% and ORR was 91.3%. Among patients with NPM1m, the CR/CRh was 40.0% and ORR was 80.0% (Table 3)
- Significant activity (CR/CRh) was observed at doses as low as 200mg qd and there is a trend of increasing activities with increasing doses

Table 3. Response by Dose and Target Genetic Subtype (n=28)

	KMT2Ar (n=23)				NPM1m (n=5)			
Response	200mg bid (n=2)	400mg bid (n=14)	600mg bid (n=7)	Total (n=23)	200mg qd (n=1)	400mg bid (n=3)	600mg bid (n=1)	Total (n=5)
ORR, n(%)	2(100)	12(85.7)	7(100)	21(91.3)	1(100)	3(100)	0	4(80.0)
Best response, n(%)								
CR	1(50)	4(28.6)	4(57.1)	9(39.1)	1(100)	0	0	1(20.0)
CRh	1(50)	2(14.3)	2(28.6)	5(21.7)	0	1(33.3)	0	1(20.0)
CRi	0	2(14.3)	0	2(8.7)	0	0	0	0
MLFS	0	4(28.6)	1(14.3)	5(21.7)	0	2(66.7)	0	2(40.0)
No response	0	2(14.3)	0	2(8.7)	0	0	1(100)	1(20.0)
CR+CRh rate, n(%)	2(100)	6(42.9)	6(85.7)	14(60.9)	1(100)	1(33.3)	0	2(40.0)
CRc, n(%)	2(100)	8(57.1)	6(85.7)	16(69.6)	1(100)	1(33.3)	0	2(40.0)

CR,complete remission; CRc, composite CR(CR+CRh+CRi); CRh,CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; MLFS, morphological leukemia-free state; NPM1m, mutated nucleophosmin 1; ORR, overall response rate(CRc+MLFS).

- 28(100%) patients with ≥50% reduction in leukemic burden (Figure 1)
- Responses tend to get deeper with longer treatment duration. Eighteen patients (18, 64%) achieved remission after 1 cycle of treatment, and the vast majority of patients achieved disease remission after 2 cycles of treatment (Figure 2)

Figure 1. Maximum Change from Baselined BM Blasts in Efficacy Evaluable Patients with Target Genetic Alterations (n=28)

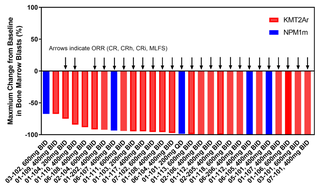
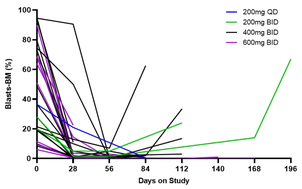
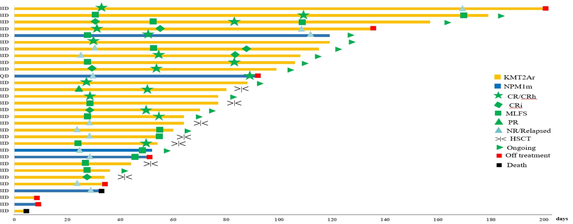


Figure 2. Change from Baseline BM Blasts Over Time in Efficacy Evaluable Patients with Target Genetic Alterations (n=28)



- To date, the longest duration of treatment reached 6.7 months. Of the 25 responders, 6 (24%) patients opted to receive HSCT (Figure 3)

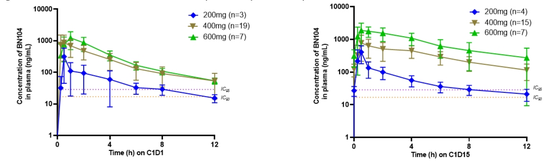
Figure 3. Duration of Treatment - All Enrolled Patients with Target Genetic Alterations (n=31)



PHARMACOKINETICS PROFILE

- BN104 is absorbed rapidly and peaked at 0.5-1 hour. $T_{1/2}$ is approximately 3.7-7.9 hours
- Drug exposure increased with dose. Doses above 400mg bid provided 12-hour coverage above IC_{90} level

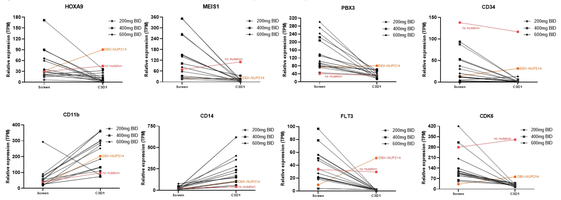
Figure 4. PK Profiles of BN104 (PK Population)



PHARMADYNAMIC PROFILE

- Preliminary PD data indicate the biological impact of BN104 even at a low dose (200mg bid), confirming its mechanism of action
- BN104 demonstrated a reduction in the expression of menin-related oncogenic genes (HOXA9, MEIS1 and PBX3), downstream transcription factor (FLT3, CDK6) and blast cells (CD34+) and an increase in the expression of differentiation-associated genes (CD11b and CD14) in patients with target alterations

Figure 5. PD Profiles of BN104 (PD Population)



Fresh bone marrow samples were collected at baseline and after dosing (C3D1) to measure gene expression levels via RNA sequencing in the central laboratory

CONCLUSIONS

- BN104 up to 600mg bid is well tolerated with a mild safety profile that is expected in R/R AML patients. No DLT or greater than G1 QTc prolongation or greater than G2 DS
- Promising dose-response association has been observed at doses as low as 200mg qd, with complete responses peaked at 600mg bid; all dose groups combined CR/CRh of 60.9% in KMT2Ar patients and 40.0% in NPM1m patients
- Dose optimization is ongoing with 400mg bid and 600mg bid cohorts, and is expected to be completed in Q4 2024
- Pivotal Phase 2 trial is expected to start by year end 2024

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