COVALENT-101 (NCT05153330)

Phase 1 first-in-human dose-escalation and dose-expansion study of BMF-219, an oral, covalent, menin inhibitor, in adult patients with acute leukemia (AL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM)

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BACKGROUND

- Menin, a protein involved in transcriptional regulation, impacting cell cycle control, apoptosis, and DNA damage repair, plays a direct role in oncogenic signaling in multiple cancers. Inhibition of menin is a novel approach to cancer treatment.[1]

BMF-219

- BMF-219, is an orally bioavailable, potent and selective covalent inhibitor of menin, an important transcriptional regulator.
- Preclinical data of BMF-219 showed sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo.
- BMF-219 demonstrates a strong anti-proliferative effect on various menin-dependent acute myeloid leukemia (AML) cell lines, DLBCL cell lines representing Double/Triple Hit Lymphoma (DHL/THL), Double Expressor Lymphoma (DEL), and MM cell lines harboring diverse mutational backgrounds.[2]
- BMF-219 also exhibits potent cell killing activity on ex vivo cultured MLL-rearranged and NPM1-mutant AML patient samples, THL and MYC-amplified DLBCL, bone marrow mononuclear cells from treatment-naive and R/R MM[2].
- For current clinical trials, BMF-219 is supplied as 25 and 100 mg strength capsules for once daily oral administration.

COVALENT-101 (BF-MNN-101) STUDY OVERVIEW

- COVALENT-101 is a prospective, open-label, multi-cohort, non-randomized, multicenter, first-in-human Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of oral BMF-219 administered either once or twice daily in patients with R/R ALL, AML, DLBCL & MM who have received standard therapy.
- Approximately 20 clinical sites in the United States.

OBJECTIVES & ENDPOINTS

Primary	Determine OBD & RP2D of BMF-219 for each Cohort (1, 2 & 3) and Arm (A & B)	•OBD/RP2D will be determined based on PK/PD/Safety/Efficacy
Secondary	Further evaluate Safety and tolerability of BMF-219 PK/ PD evaluation of BMF-219 Additional Evidence of Efficacy of antitumor activity	•TEAE / SAE incidence •C_{max}, T_{max}, and $AUC_{0-\infty}$ of BMF-219 •Cohort 1: CRR* •Cohort 2: ORR↗ •Cohort 3: ORR♌ & other efficacy parameters per investigator assessment
Exploratory	To characterize the PD effects of BMF-219 for each cohort independently	•Changes in gene expression •Explore predictive and pharmacodynamic markers

* Based on European LeukemiaNet (ELN) 2017 recommendation for diagnosis and management of AML or the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, ALL (Version 2. 2021)

↗ Revised criteria for response assessment of lymphoma (Cheson, 2014)

♌ International Myeloma Working Group (IMWG) response criteria (Kumar, 2016)

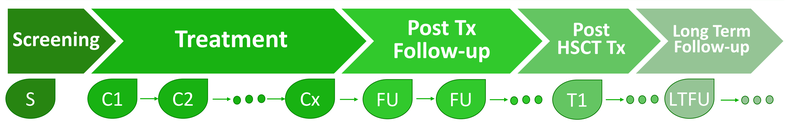
STUDY DESIGN

		Dose Escalation	Dose Expansion
Cohort 1	Arm A No CYP3A4	R/R ALL, AMPL, AML N = var	R/R ALL, AMPL, AML Total N = 30
	Arm B CYP3A4	R/R ALL, AMPL, AML N = var	R/R ALL, AMPL, AML Total N = 30
Cohort 2	Arm A No CYP3A4	R/R DLBCL N = var	R/R DLBCL Total N < 20
Cohort 3	Arm A No CYP3A4	R/R MM N = var	R/R MM Total N < 20

Accelerated titration design followed by 3+3

- Doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either any ≥ Grade 2 related-TEAE which does not meet DLT criteria, or a DLT in the first cycle.
- At that point, the dose level for the specific cohort will follow a classical "3 + 3" dose escalation design.

STUDY FLOWCHART



Screening	• Up to 28 days from consent
Treatment	• Daily treatment with BMF-219 in 28-day cycles
Post Tx Follow-Up	• Regular post-tx efficacy assessment visits
Post HSCT Treatment	• Post adequate response to BMF-219 patient may proceed with HSCT and then resume BMF-219
Long Term Follow-Up	• Survival follow-up calls

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- ≥ 18 years with ECOG performance status of 0-2 and an estimated life expectancy of > 3 months
- Adequate liver function: Bilirubin ≤ 1.5 ULN; ALT/AST ≤ 2.0 ULN
- Adequate renal function: estimated creatinine clearance (eCrCl) ≥ 60 mL/min (Cohort 1) or eCrCl ≥ 30 mL/min (Cohorts 2 & 3) using the Cockcroft-Gault equation
- Prior treatment-related toxicities resolved to ≤ Grade 2 prior to enrollment
- Adequate washout from prior therapies (e.g., ≥ 60 days from RT; ≥ 60 days from stem cell infusion; ≥ 7 days from biologics or steroids; ≥ 21 days from prior immunotherapy; ≥ 14 days from completion of last chemotherapy)

Indication & Prior Regimen Criteria

Cohort	Arm	Indication	Prior treatment regimens	*CYP3A4 inhibitors
1	A	R/R ALL, AMPL, AML agnostic of mutation	No limit, includes prior HSCT	No
1	B	R/R ALL, AMPL, AML agnostic of mutation	No limit, includes prior HSCT	Yes
2	A	R/R DLBCL / DLBCL transformed from previously indolent lymphoma (e.g., follicular lymphoma)	≥ 2 with at least 1 course of anthracycline-based chemotherapy & at least 1 course of anti-CD20 immunotherapy	No
3	A	R/R MM	≥ 3 including proteosome inhibitor & immunomodulatory	No

* Subjects are receiving concomitant medications considered to be strong or moderate inhibitors of CYP3A4

Exclusion Criteria

- Known CNS disease involvement
- Prior menin inhibitor therapy
- WBC count > 50,000/ µL (uncontrollable with cytoreductive therapy)
- Clinically significant cardiovascular disease; LVEF < 45%
- Mean QTcF or QTcB of > 470 millisecond (ms)
- Acute or chronic GVHD except disease limited to skin with adequate control using topical steroids
- Concurrent malignancy in the previous 2 years

REFERENCES

1. Issa, G. C., et al. (2021). Therapeutic implications of menin inhibition in acute leukemias. Leukemia, 35(9), 2482–2495.
2. Anti-tumor activity of irreversible menin inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models. Cancer Res (2022) 82 (12_Supplement): 2654.