COVALENT-101

Phase I Study of BMF-219, a Covalent Menin Inhibitor, in Adult Patients With AML, ALL (With KMT2A/ MLL1r, NPM1 Mutations), DLBCL, MM, and CLL/SLL (NCT05153330)

Brian Hill[1], Jacqueline Barrientos[2], Juan Miguel Bergua Burgues[3], John Byrd[4], Jimena Cannata[5], Catherine C. Coombs[6], Herbert Eradat[7], Pau Montesinos[8], Daniel Morillo[9], Lawrence Morris[10], Olalekan Oluwole[11], Ricardo Parrondo[12], Javier Pinilla-Ibarz[13], Joseph Tuscano[14], Alex Cacovean[15], Courtney Follit[15], Mona Vimal[15], Steve Morris[15] , Thomas Butler[15] and William Wierda[16]

[1]Cleveland Clinic, Cleveland, Ohio, United States, [2]Mount Sinai Comprehensive Cancer Center, Miami Beach, Florida, United States, [3]Hospital San Pedro de Alcántara, Spain, [4]University of Cincinnati College of Medicine, Cincinnati, Ohio, United States, [5]Hospital Universitario de la Princesa, Spain, [6]University of California Irvine, Irvine, CA, United States, [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, United States, [8]Hospital Universitari i Politècnic La Fe, Valencia, Spain, [9]Hospital Universitario Fundación Jiménez Díaz, Spain, [10]Blood & Marrow Transplant Group of GA (Northside Hospital), United States, [11]Vanderbilt University Medical Center, United States, [12]Mayo Clinic, Jacksonville, Florida, United States, [13]H Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, United States, [14]University of California Davis, United States, [15]Biomea Fusion, Redwood City, California, United States, [16]University of Texas MD Anderson Cancer Center, Houston, Texas, United States

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 known to play a direct role in oncogenic signaling in multiple cancers.
- Preclinical data of BMF-219 show 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 high potency ex vivo in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, bone marrow mononuclear cells from treatment-naive and R/R MM, and a collection of CLL patient specimens with various cytogenetic backgrounds including TP53 and NOTCH1 mutations, & previous BTK inhibitor therapy.[3]
- BMF-219 is currently supplied as 25, 100 and 200 mg strength capsules for oral administration.

COVALENT-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 daily in patients with R/R ALL, AML, DLBCL, MM & CLL/SLL who have previously received standard therapy.
- As of September 2023, the study is enrolling at 26 sites in the United States, Spain, Italy, Greece and Netherlands. Other US and ex-US sites in startup.

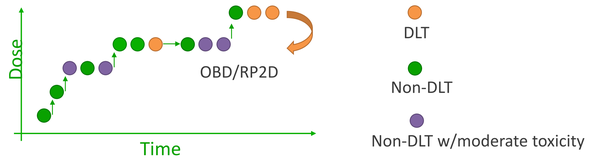
OBJECTIVES & ENDPOINTS

Primary	Determine OBD & RP2D of BMF-219 monotherapy for all Cohorts (1, 2, 3 & 4) and Arm (A & B)	• OBD/RP2D will be determined based on PK/PD/Safety/Efficacy
Secondary	Further evaluate Safety and tolerability of BMF-219	• TEAE / SAE incidence • C_{max}, T_{max}, and $AUC_{0-\infty}$ of BMF-219
	PK/ PD evaluation of BMF-219	• CRR & ORR (all cohorts)
	Additional Evidence of Efficacy of antitumor activity per corresponding response criteria	• DOCR, DOR, PFS, TTR, TTCR & OS (all cohorts) • DCR, TTP (Cohorts 2, 3 & 4)
Exploratory	Characterize the PD effects of BMF-219 for each cohort independently by assessment of changes in gene expression	• Explore predictive and pharmacodynamic markers • Identify predictive biomarkers indicative of sensitivity and/ or resistance to BMF-219 • Determine MRD-negativity rate (Cohorts 1, 3 & 4)

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
Cohort 4	Arm A No CYP3A4	R/R CLL/SLL N = var	R/R CLL/SLL Total N < 20

Accelerated titration design followed by 3+3



- Doses of BMF-219 are 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 (28 days).
- 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 & 4) 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 TBI; ≥ 60 days from stem cell infusion; ≥ 7 days from biologics or steroids; ≥ 21 days from prior immunotherapy; ≥ 14 days from completion of last chemotherapy). Note: prior menin inhibitors are permitted.

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
4	A	R/R CLL/SLL	≥ 2 prior systemic treatment regimens	No

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

Exclusion Criteria

- Known CNS disease involvement
- 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.
3. Preclinical activity of irreversible Menin inhibitor, BMF-219, in chronic lymphocytic leukemia. J Clin Oncol 40, 2022 (suppl 16; abstr 7541).

Biomea Fusion, Inc. / 900 Middlefield Road, 4th Floor / Redwood City, CA 94063

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