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Covalent Menin Inhibitor BMF-219 in participants with Relapsed or Refractory (R/R) Acute Leukemia (AL): Preliminary Phase 1 Data from the COVALENT-101 Study

[1]Jeffrey Lancet, MD[1]; Farhad Ravandi, MBBS, MD[2]; Pau Montesinos, MD, PhD[3]; Jacqueline Barrientos, MD[4]; Talha Badar MBBS, MD[5]; Adrian Alegre, MD, MPH[6]; Asad Bashey, MD, PhD[7]; Juan Miguel Bergua Burgues, MD[8]; Lorenzo Brunetti, MD, PhD[9]; Emily Curran, MD[10]; David C. Christian de Leeuw, MD, PhD [11]; Enrico Derenzini, MD, PhD[12]; Geert A. Huls, Prof.[13]; Jeroen J. W. M. Janssen, MD, PhD[14]; Deepa Jeyakumar, MD[15]; Mojca Jongen-Lavrencic, MD, PhD[16]; Ashwin Kishtagari, MBBS, MD[17]; Maria Victoria Mateos, MD, PhD[18]; Daniel Morillo, MD[19]; Alessandro Rambaldi, MD[20]; Aaron S. Rosenberg, MD, MS[21]; Gary J. Schiller, MD[22]; Uzma Ahmed, MD, MS[23]; Alexandru Cacovean, MD[23]; Stephan W. Morris, MD[23]; Courtney Follit, PhD[23]; Brian Munneke, PhD[23]; Ganesh Waghmare, MD, MPH[23]; Clarissa Mandap, BSN[23]; Mona Vimal, MS[23]; Thomas Butler, MS, MBA[23] and Hetty E. Carraway, MD, MBA[24]

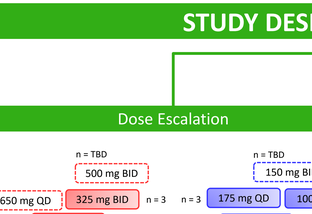
[1]Moffitt Cancer Center, Tampa, FL, USA, [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Hospital Universitari i Politecnic La Fe, Valencia, Spain, [4]Mount Sinai Medical Center, Miami Beach, FL, USA, [5]Mayo Clinic, Jacksonville, FL, USA, [6]Hospital Universitario de La Princesa, Madrid, Spain, [7]Blood & Marrow Transplant Group of GA (Northside Hospital), Atlanta, GA, USA, [8]Hospital San Pedro de Alcantara, Cáceres, Spain , [9]AOU Ospedali Riuniti Ancona, Marche, Italy, [10]University of Cincinnati Medical Center, Cincinnati, OH, USA, [11]Amsterdam UMC, Location VUMC, Amsterdam, Netherlands, [12]European Institute of Oncology (IEO) IRCCS, Milan, Italy, [13]University Medical Center Groningen, Groningen, Netherlands, [14]Radboud University Medical Center, Nijmegen, Netherlands, [15]University of California, Irvine, Irvine, CA, USA, [16]Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands, [17]Vanderbilt University Medical Center, Nashville, TN, USA, [18]Hospital Universitario de Salamanca, Salamanca, Spain, [19]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [20]Department of Oncology and Hematology, University of Milan and Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy, [21]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA, [22]UCLA Department of Medicine, Los Angeles, CA, USA, [23]Biomea Fusion, Redwood City, CA, USA, [24]Cleveland Clinic, Cleveland, OH, USA

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 OVERVIEW

- BMF-219 is the first and only covalent menin inhibitor in clinical development and is being evaluated in multiple hematologic malignancies, solid tumors, and diabetes mellitus



Protein Binding Data
BMF-219 K_d (nM) <1.0 x 10^{-12}

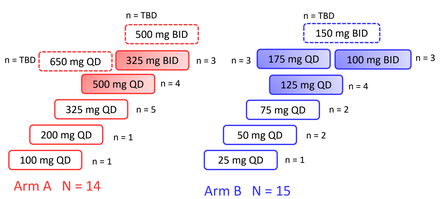
Targetable Cysteine	Binding Selectivity
CYS1	100%
CYS2	0%
CYS3	0%
CYS4	0%
CYS5	0%
CYS6	0%

- BMF-219 is a synthetic small molecule designed to disrupt interactions of menin with various protein partners such as MLL1 and JunD that regulate multiple signaling pathways, including transcriptional and cell-cycle regulation
- BMF-219 exhibits high potency ex vivo in participant samples from *MLL1*-rearranged and *NPM1*-mutant AML, DHL/THL and *MYC*-amplified DLBCL, bone marrow mononuclear cells from treatment-naive and R/R MM, and CLL cells with various cytogenetic backgrounds, including *TP53* and *NOTCH1* mutations, and previous BTK inhibitor therapy[2, 3]
- BMF-219 is supplied as 25 mg, 100 mg and 200 mg strength capsules for oral administration

COVALENT-101 STUDY OVERVIEW

- COVALENT-101 (NCT05153330) is a Phase I, prospective, open-label, first-in-human study evaluating the safety, tolerability, and clinical activity of escalating doses of oral BMF-219 administered daily in participants with R/R ALL, MPAL, AML (Cohort 1), DLBCL (Cohort 2), MM (Cohort 3) & CLL/SLL (Cohort 4)
- As of November 2023, the study is open for enrollment at 28 sites in Greece, Italy, Netherlands, Spain, and the United States; additional sites expected to open soon
- Key eligibility criteria for Cohort 1 (R/R AL) include:
  - Adults (≥18 years of age)
  - ECOG 0-2 and life expectancy > 3 months
  - R/R ALL, AMPL/MPAL, or AML agnostic of mutational profile[#]
  - Failed or ineligible for standard treatment
  - Prior exposure to non-covalent menin inhibitor therapy is permitted
  - Absence of known CNS involvement
- participants receive BMF-219 daily for continuous 28-day cycles until progression/ intolerability
- Expansion cohorts will enroll participants to obtain further safety and efficacy data at the OBD/RP2D
- The study is ongoing and accruing in the dose escalation phase

STUDY DESIGN



- Enrollment occurs in parallel dose-escalation arms:
  - participants not taking moderate or strong CYP3A4 inhibitor (Arm A) or
  - participants taking moderate or strong CYP3A4 inhibitor(Arm B)
- Dose Escalation uses an accelerated titration design followed by classical 3+3*
- Dose Escalation to be followed by a Dose Optimization/ Expansion to determine OBD/ RP2D

**Additional participants may be enrolled as backfill or to replace non-DLT evaluable participants*

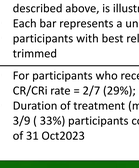
RESULTS

BASELINE DEMOGRAPHICS

Baseline Characteristics	Arm A (N=14)	Arm B (N=15)	Total (N=29)
Median age, years (range)	42 (22, 81)	63 (34, 84)	57 (22, 84)
ECOG Performance Status			
0	5 (35.7%)	4 (26.7%)	9 (31.0%)
1	8 (57.1%)	9 (60.0%)	17 (58.6%)
2	1 (7.1%)	2 (13.3%)	3 (10.3%)
Gender			
Female, n (%)	7 (50.0%)	5 (33.3%)	12 (41.4%)
Male, n (%)	7 (50.0%)	10 (66.7%)	17 (58.6%)
Leukemia type, n (%)			
AML	13 (92.9%)	14 (93.3%)	27 (93.1%)
ALL	1 (7.1%)	1 (6.7%)	2 (6.9%)
Prior Therapies			
Median # prior therapies (range)	4 (1,6)	3 (1,6)	3 (1,6)
Prior Hematopoietic Stem Cell Transplant (HSCT)	9 (64.3%)	4 (26.7%)	13 (44.8%)
Venetoclax, n (%)	10 (71.4%)	10 (66.7%)	20 (69.0%)

- Overall balanced participant population between the two Arms based on key characteristics
- Nearly half (~45%) of the participants received prior HSCT
- Median prior lines of therapy: 3 (range 1,6)

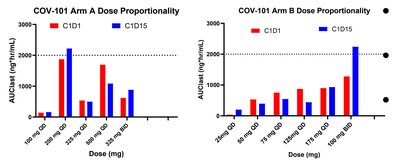
Distribution of genetic AL subsets:



Mutation	Description
MLL1r	*MLL1-r* (mixed lineage leukemia gene, a.k.a. lysine methyltransferase 2A (*KMT2A*) gene
NPM1	*NPM1* (Nucleophosmin 1)
Other[#]	*MLL1-PTD* (*MLL1/KMT2A* partial tandem duplication)
	PICALM-AF10 (Phosphatidylinositol Binding Clathrin Assembly Protein-AF10, a.k.a *CALM-AF10*)
	MN1 (Meningioma-1)
	NUP98 (Nucleoporin 98)
	NUP214 (Nucleoporin 214)
	CEBP/A (CCAAT Enhancer Binding Protein Alpha)
	SETBP1 (SET Binding protein 1)
None	None of the above

[#]Initially participants were enrolled agnostic to mutational status. A subsequent amendment introduced minimum quotas for *KMT2Ar (MLL1r), NPM1,* and other mutations that may be menin-inhibitor sensitive: *CEBP/A, MLL1-PTD, MN1, NUP98, NUP214, PICALM-AF10,* and *SETBP1*

BMF-219 SHOWS DOSE DEPENDENT EXPOSURE

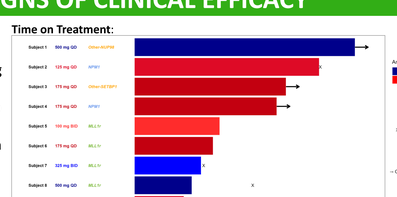


- BMF-219 showed increasing plasma PK exposure with increasing dose
- Dose proportionality was not established due to high PK variability
- Several participants at higher dose levels in Arm A and Arm B showed plasma AUC above the target AUC of 2,000 ng*hr/mL

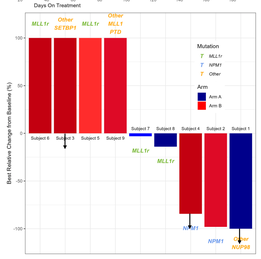
EARLY SIGNS OF CLINICAL EFFICACY

- Efficacy evaluable population is defined as DLT-evaluable participants with AML bearing mutation(s) believed to be menin-inhibitor sensitive who received treatment with BMF-219 at ≥500 mg QD (Arm A) or ≥125 mg QD (Arm B)
- Data cutoff included all participants who initiated treatment on or before 06 Sep 2023; responses assessed as per PI using ELN2017 criteria

Time on Treatment:



Marrow blast response:



- BM blast response for efficacy-evaluable participants (n=9), as described above, is illustrated
- Each bar represents a unique study participant
- participants with best relative change from baseline >100% are trimmed

- For participants who received at least 2 cycles of therapy: CR/CRi rate = 2/7 (29%); mean time to response = 1.8 months
- Duration of treatment (months): mean 2.84 (range: 1.2 - 5.5) ; 3/9 (33%) participants continued treatment as of cutoff date of 31 Oct2023

BMF-219 IS WELL TOLERATED

TRAEs with Preferred Term (Incidence ≥ 10%)	Arm A (N=14)	Arm B (N=15)	Total (N=29)
Subjects with at least one TRAE	5 (35.7%)	1 (6.7%)	6 (20.7%)
Differentiation Syndrome	3 (21.4%)	1 (6.7%)	4 (13.8%)
Vomiting	3 (21.4%)	1 (6.7%)	4 (13.8%)

TEAEs with Preferred Term (Incidence ≥ 15%)	Arm A (N=14)	Arm B (N=15)	Total (N=29)
Subjects with at least one TEAE	14 (100.0%)	15 (100.0%)	29 (100.0%)
Nausea	3 (21.4%)	6 (40.0%)	9 (31.0%)
Febrile neutropenia	1 (7.1%)	6 (40.0%)	7 (24.1%)
Pneumonia	2 (14.3%)	5 (33.3%)	7 (24.1%)
Dyspnoea	1 (7.1%)	5 (33.3%)	6 (20.7%)
Fatigue	2 (14.3%)	4 (26.7%)	6 (20.7%)
Pyrexia	3 (21.4%)	3 (20.0%)	6 (20.7%)
Vomiting	4 (28.6%)	2 (13.3%)	6 (20.7%)
Alanine aminotransferase increased	3 (21.4%)	2 (13.3%)	5 (17.2%)
Cough	3 (21.4%)	2 (13.3%)	5 (17.2%)

- BMF-219 demonstrated a well-tolerated safety profile across all dose levels
- The most common TEAEs across both arms were nausea, febrile neutropenia and pneumonia, none of which were deemed related to the study drug but rather to the disease under study
- Four participants experienced Differentiation Syndrome (DS) ≤ Grade 3, with onset 1-3 weeks after initiation of therapy and an average duration of 10 days, managed by cytoreductive therapy (hydroxyurea and steroids); two participants recovered without dose modification or interruption, and none of the participants discontinued due to DS

Subject Disposition	Arm A (N=14)	Arm B (N=15)	Total (N=29)
Treatment on-going n (%)	2 (14.3%)	2 (13.3%)	4 (13.8%)
Discontinued treatment n (%)	12 (85.7%)	13 (86.7%)	25 (86.2%)
Withdrawal of Consent	3 (21.4%)	1 (6.7%)	4 (13.8%)
Adverse Event (Not related to BMF-219)*	2 (14.3%)	0	2 (6.9%)
Protocol Defined Disease Progression	2 (14.3%)	4 (26.7%)	6 (20.7%)
Lack of Efficacy	0	2 (13.3%)	2 (6.9%)
Physician Decision	1 (7.1%)	5 (33.3%)	6 (20.7%)
Other[&]	4 (28.6%)	1 (6.7%)	5 (17.2%)

* TEAEs leading to treatment discontinuation were deemed not related to BMF-219 and were attributed to underlying disease
[&] Other: death (not related to study treatment)

CASE STUDY: *NUP98-NSD1* AML

- 39-year-old Caucasian male with relapsed AML containing *NUP98-NSD1* as well as *CEBP/A*, *NRAS*, and *WT1* mutations at the time of diagnosis
- High-dose Ara-C therapy was initiated, and 7 doses were administered. Subsequently, conditioning therapy with busulfan and cyclophosphamide was administered followed by a matched unrelated donor allogeneic stem cell transplant
- ~5 months post-transplant, marrow analysis revealed hypocellularity (20%) due to pan-hypoplasia and 10-15% blasts as well as atypical megakaryocytes suggestive of persistent/recurrent AML; repeat aspiration performed 4 weeks later revealed 13% blasts in a hypocellular (10%) marrow
- participant was enrolled in COVALENT-101 Arm A 500 mg QD in continuous 28-day cycles

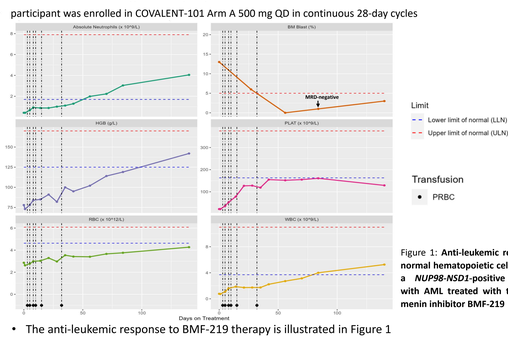


Figure 1: **Anti-leukemic response and normal hematopoietic cell recovery in a *NUP98-NSD1*-positive participant with AML treated with the covalent menin inhibitor BMF-219**

- The anti-leukemic response to BMF-219 therapy is illustrated in Figure 1
  - C2D1: PR with decreased marrow blast percentage from the pre-treatment baseline of 13% to 6%
  - C3D1: CR with 0% blasts, no circulating blasts, and recovering normal hematopoiesis; MRD-positive per local multiparameter flow cytometry (sensitivity >10^{-5})
  - C4D1: continued CR with 1% marrow blasts and MRD-negative
  - C5D1: continued CR with 3% marrow blasts and MRD-positive
- Peripheral hematologic parameters responded favorably immediately after BMF-219 initiation, and progressively improved thereafter towards normalization as depicted
- At study entry the participant was transfusion-dependent receiving blood-product support 3-4 times per week. The frequency decreased rapidly with the last transfusion administered shortly after completion of Cycle 1
- Treatment is ongoing and participant continues in remission at the time of this report

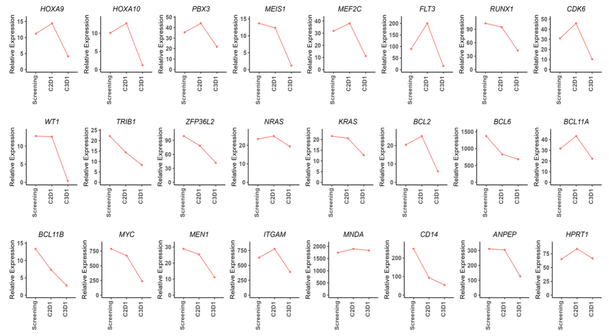


Figure 2: **Gene expression profiling in a participant with AML containing the *NUP98-NSD1* fusion under treatment with covalent menin inhibitor BMF-219.** RNA-seq analysis of bone marrow aspirates reveals differentially expressed genes before and after treatment. Gene expression levels are presented as transcripts per million (TPM).

- C3D1: coincident with attainment of CR, the proleukemogenic gene expression program in the marrow was downregulated > 2-fold compared to pre-treatment
- Gene expression changes included the suppression of:
  - Key hematopoietic transcription factors (*HOXA9, HOXA10, MEIS1, MEF2C*)
  - Other relevant transcription factors (*WT1, TRIB1, BCL6, BCL11B, MYC, PBX3, BCL11A*)
  - Kinases (*FLT3, CDK6*)
  - RNA-binding protein *ZFP36L2*
  - *MEN1* (which encodes menin)
  - *KRAS*
- There was no noticeable upregulation of markers of differentiation (as observed with non-covalent menin inhibitors); instead:
  - BMF-219 led to *CD14, ANPEP*, and *ITGAM* downregulation or maintenance (*MNDA*) of gene expression level
- Housekeeping gene *HPRT1* maintained essentially constant expression across time points

CONCLUSIONS

- BMF-219 is well tolerated with no DLTs observed and without treatment discontinuations due to toxicity
- BMF-219 demonstrates early signs of clinical activity and ability to achieve sustained CR with MRD-negativity
- BMF-219 showed increasing plasma PK exposure with escalating dose levels, and the ability to achieve systemic exposures predicted to be efficacious based on preclinical acute leukemia models
- Pharmacodynamic data show suppression of key leukemogenic genes (e.g. *HOXA9, MEIS1*) as well *MEN1* downregulation, without noticeable increases in differentiation markers (e.g. *CD14, ANPEP, ITGAM*) in contrast to non-covalent menin inhibitors
- COVALENT-101 is ongoing in the dose escalation portion and includes enrollment of participants diagnosed with R/R AL, DLBCL, MM and CLL
- Preliminary safety and clinical activity data support further development of BMF-219 monotherapy and in combinations.

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