

# We Aim to Cure™ 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

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

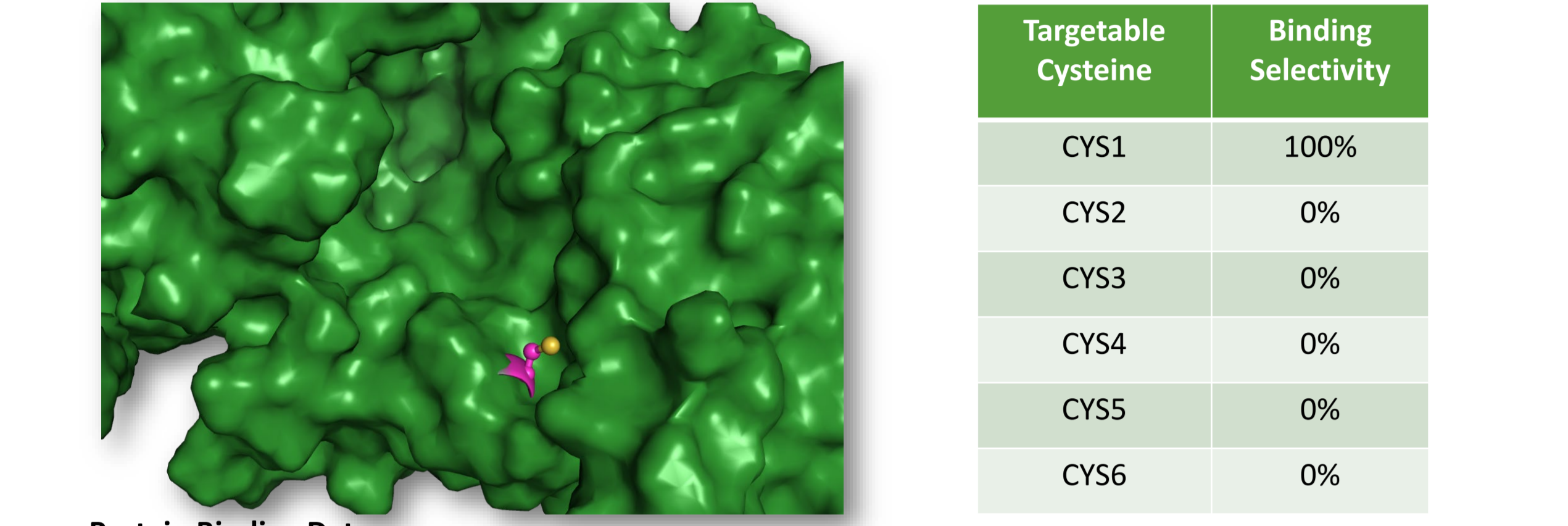
<sup>1</sup>Moffitt Cancer Center, Tampa, FL, USA, <sup>2</sup>University of Texas MD Anderson Cancer Center, Houston, TX, USA, <sup>3</sup>Hospital Universitario i Politecnic La Fe, Valencia, Spain, <sup>4</sup>Mount Sinai Medical Center, Miami Beach, FL, USA, <sup>5</sup>Mayo Clinic, Jacksonville,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

## 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



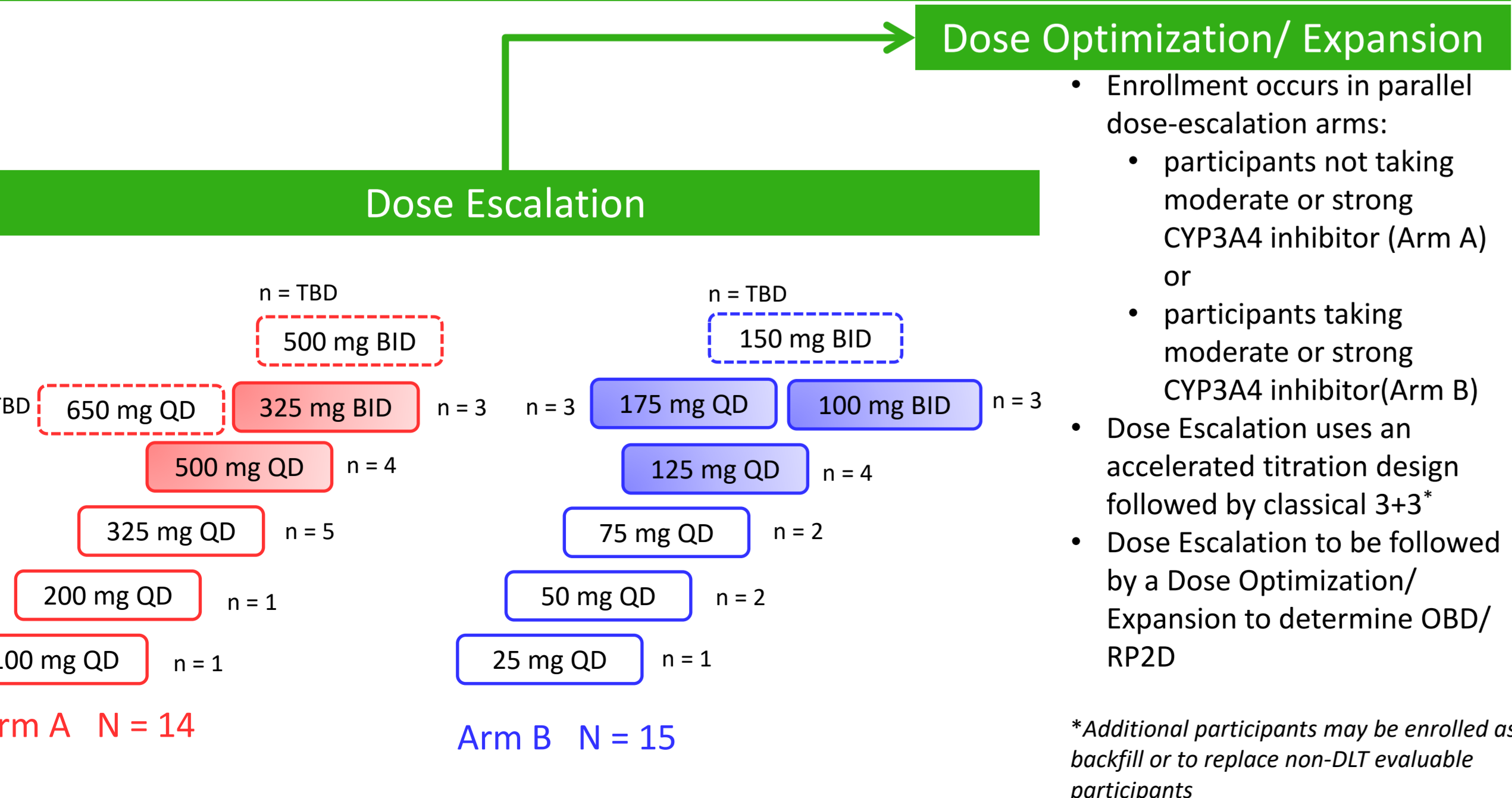
Protein Binding Data  
BMF-219 K<sub>d</sub> (nM) <1.0 x 10<sup>-12</sup>

- 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-naïve and R/R MM, and CLL cells with various cytogenetic backgrounds, including TP53 and NOTCH1 mutations, and previous BTK inhibitor therapy<sup>2,3</sup>
- BMF-219 is supplied as 25 mg, 100 mg and 200 mg strength capsules for oral administration

## COVALENT-101 STUDY OVERVIEW

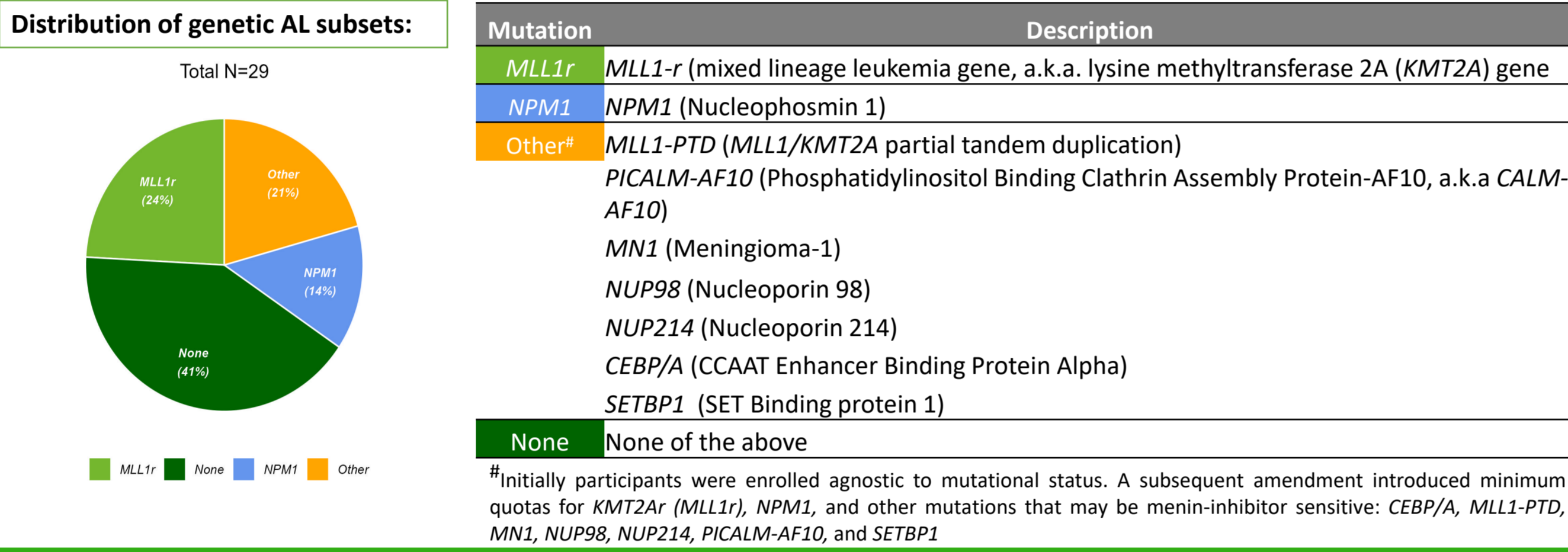
- COVALENT-101 (NCT05153330) is a Phase I, prospective, open-label, first-in-human study evaluating the safety, tolerability, and clinical activity of escalating doses of oral BMF-219 administered daily in participants with R/R ALL, MPAL, AML (Cohort 1), DLBCL (Cohort 2), MM (Cohort 3) & CLL/SLL (Cohort 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<sup>4</sup>
  - 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/ intolerance
- Expansion cohorts will enroll participants to obtain further safety and efficacy data at the OBD/PP2D
- The study is ongoing and accruing in the dose escalation phase

## STUDY DESIGN

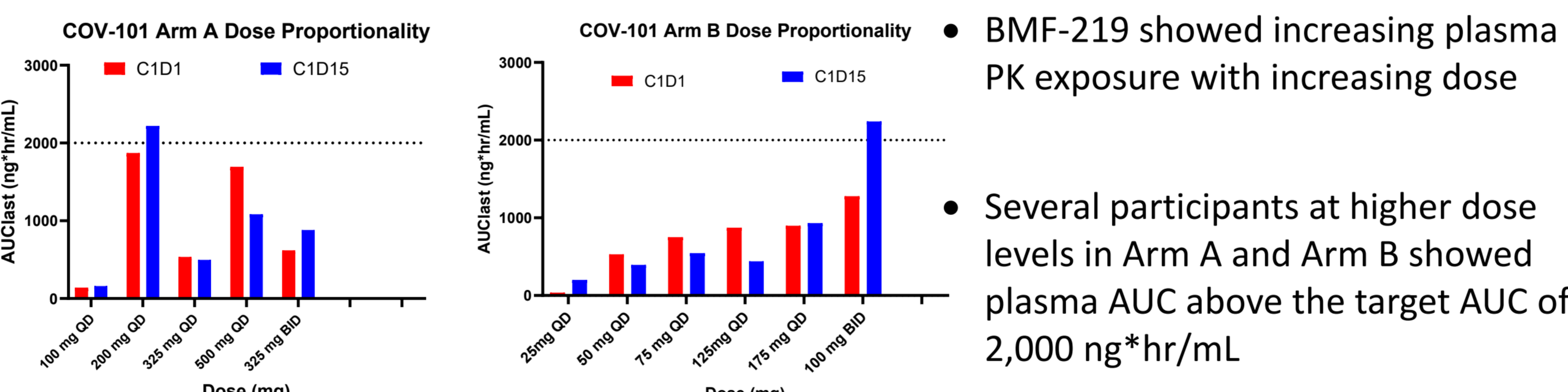


## BASELINE DEMOGRAPHICS

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%)



## BMF-219 SHOWS DOSE DEPENDENT EXPOSURE



## 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
- 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 Oct 2023

## RESULTS

### 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%)

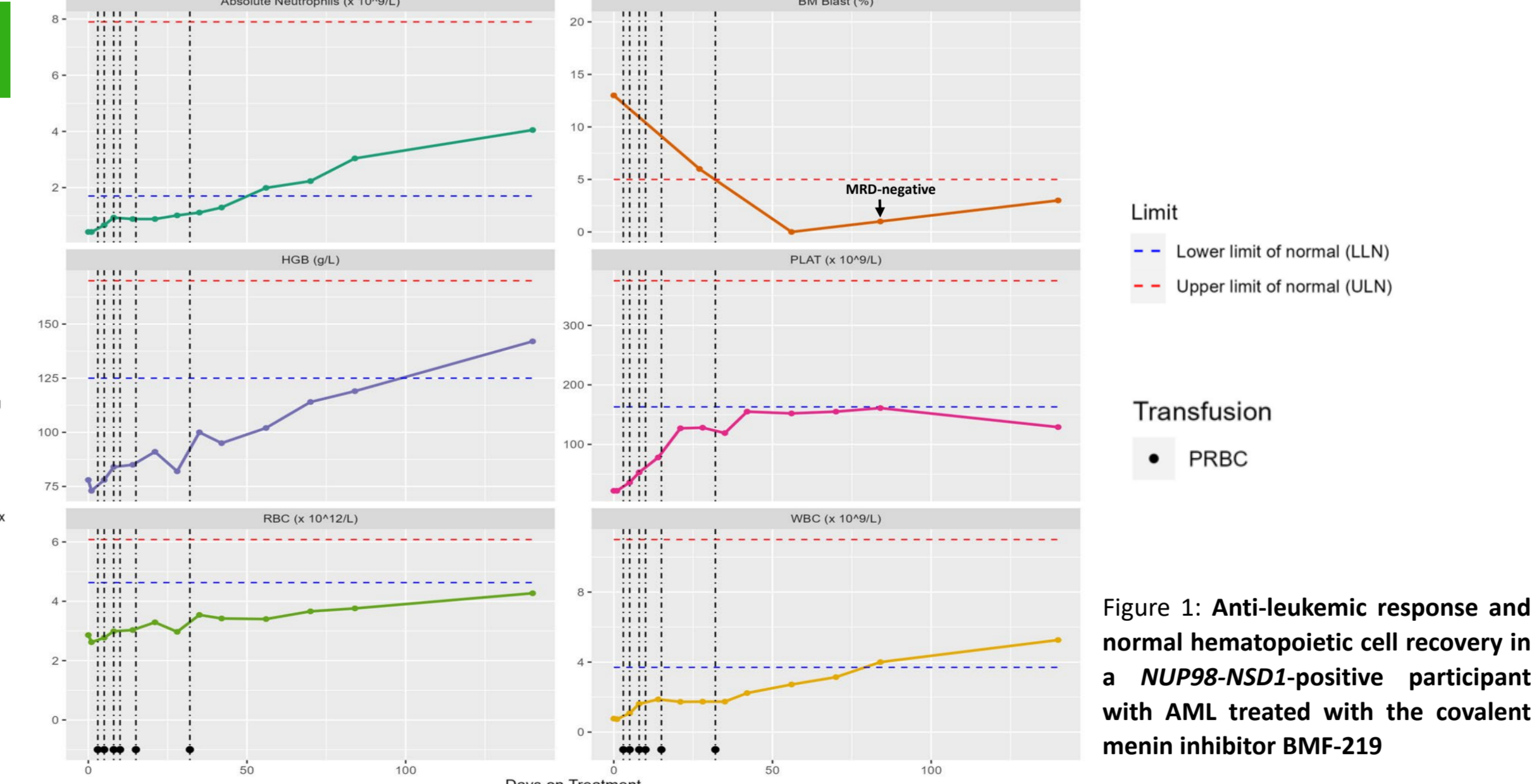
- BMF-219 demonstrated a well-tolerated safety profile across all dose levels
- The most common TEAEs across both arms were nausea, febrile neutropenia and pneumonia, none of which were deemed related to the study drug but rather to the disease under study
- Four participants experienced Differentiation 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 <sup>‡</sup>	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



- 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<sup>-5</sup>)
- 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

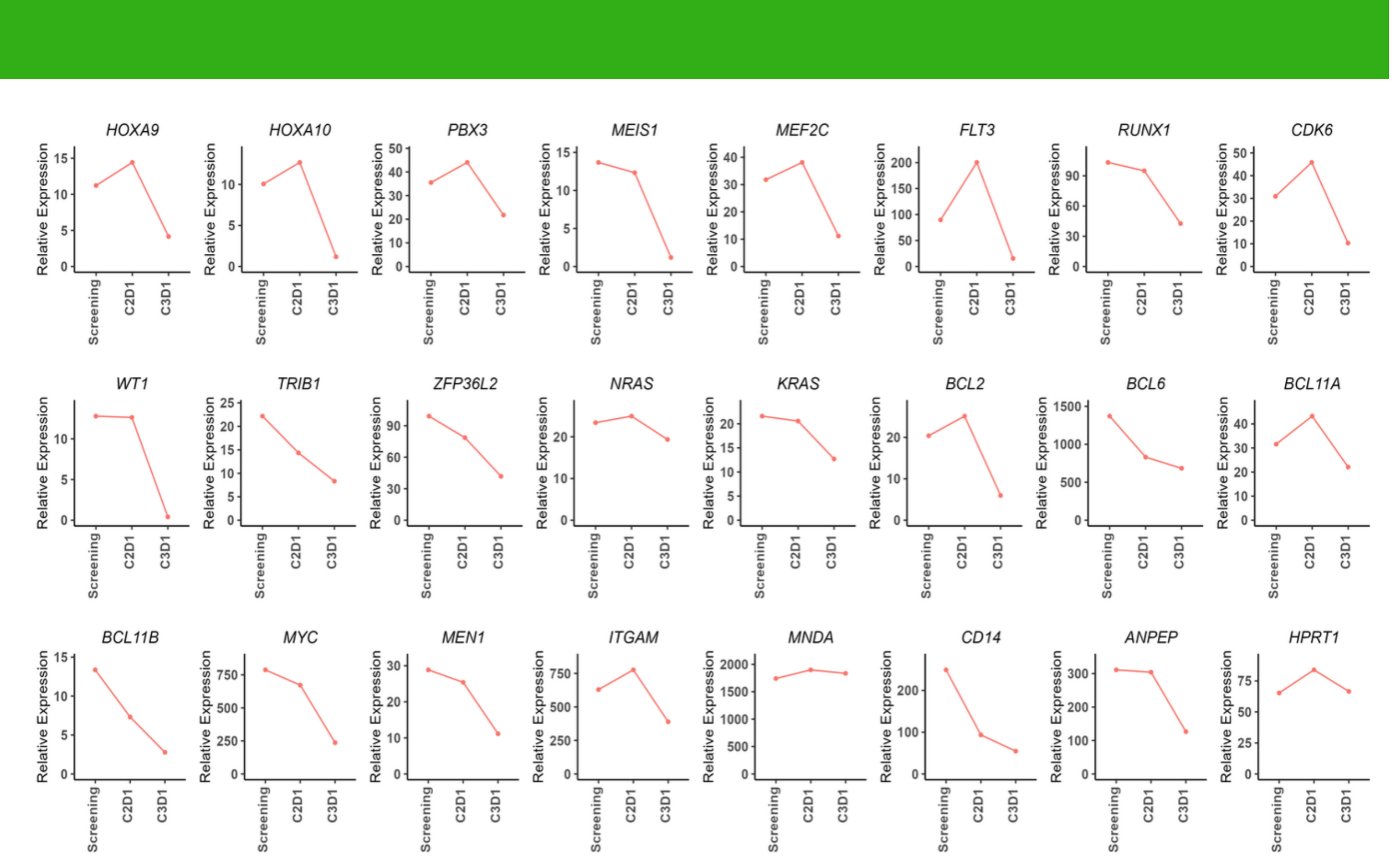


Figure 2: Gene expression profiling in a participant with AML containing the NUP98-NSD1 fusion under treatment with covalent menin inhibitor BMF-219. RNA-seq analysis of bone marrow aspirates reveals differentially expressed genes before and after treatment. Gene expression levels are presented as transcripts 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, BCL11A, 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 (MND A) 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.

## ACKNOWLEDGEMENTS

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