Preclinical Activity of irreversible menin inhibitor, BMF-219, in Chronic Lymphocytic Leukemia

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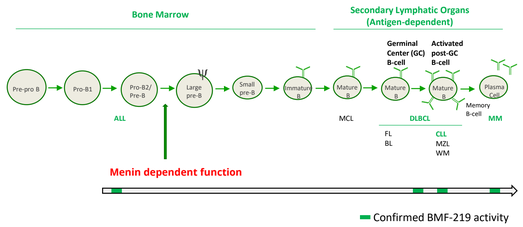
Introduction

- Menin is a scaffold protein that drives oncogenic function through transcriptional modulation directed by its various cofactors.
- A previous report demonstrated that menin regulates a distinct set of gene targets independent of its function with the MLL proteins in hematopoiesis and is essential for B-cell maturation (Li et al.*Blood*.2013;122(12):2039-46.).
- Chronic Lymphocytic Leukemia (CLL) is a disease of malignant B lymphocytes, for which standard-of-care agents are generally well tolerated; however, CLL patients with certain genetic backgrounds demonstrate inferior outcomes to these regimens.



- A major driving feature of CLL is overexpression of the anti-apoptotic marker, BCL2. We previously reported the ability of BMF-219, a selective, covalent menin inhibitor, to downregulate the expression of *BCL2* in acute leukemia cells.
- Additionally, we have reported the synergy of BCL2-targeted agent, venetoclax, with BMF-219 in potent cell killing of diffuse large B-cell lymphoma (DLBCL) preclinical models, prompting our exploration of BMF-219 activity in CLL.
- Here, we provide the first preclinical evidence for menin as a therapeutic target in CLL, by demonstrating high potency of BMF-219 against a diverse collection of CLL patient specimens.

Methods

A comprehensive panel of CLL samples isolated from patients with Rai Stages 1 to 3 disease, including relapsed or refractory disease, were cultured *ex vivo* in the presence of BMF-219 or a clinical reversible menin inhibitor to assess the antileukemic activity of the compounds.

Results

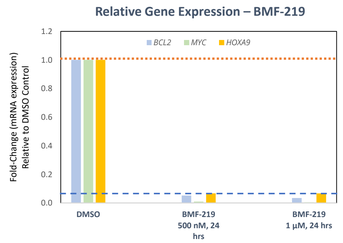


Figure 1. BMF-219 elicits >90% reduction of BCL2 transcript at 24 hours post-treatment in MOLM-13 AML cells. HOXA9 and MYC gene expression was also significantly reduced by >90%. Fold change was calculated relative to vehicle control.

BMF-219 achieves > 98% cell lethality against diverse CLL ex vivo models

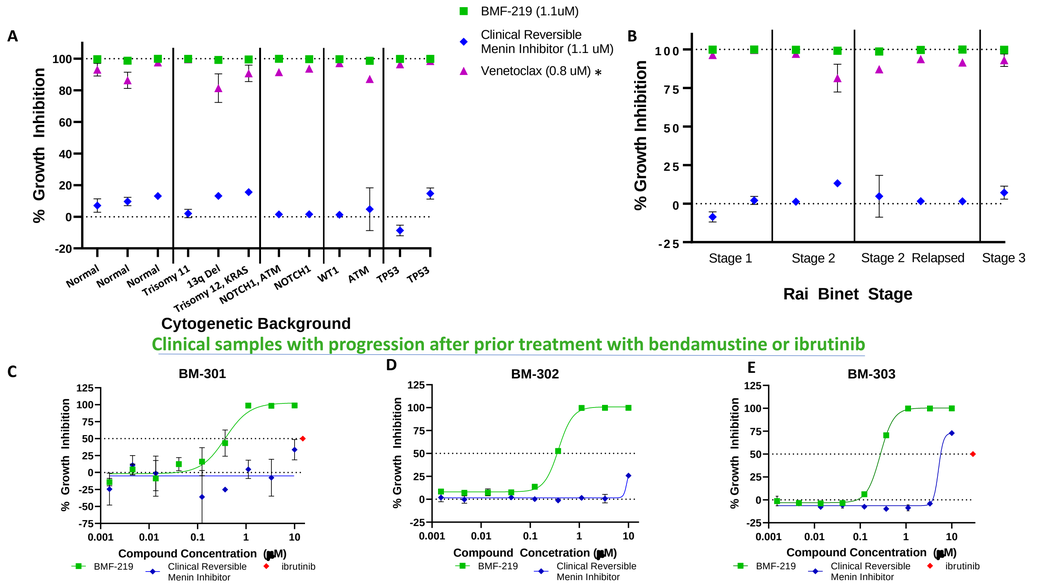


Figure 2. Growth inhibition of CLL patient-derived PDX samples treated with BMF-219 or a clinical reversible menin inhibitor after 6 days of treatment. Percentage growth inhibition at 1.1 µM BMF-219, 0.8 µM venetoclax and 1.1 µM clinical menin inhibitor are plotted for the PDX samples, as grouped by genetic background (A) or Rai-Binet Stage where data is available (B). Representative dose response curves for BMF-219 or clinical reversible menin inhibitor are shown for PDX samples from CLL patients displaying clinical profiles of progression after prior therapy with bendamustine (C) or ibrutinib (D), or ibrutinib pretreated and subsequently progressed on ibrutinib and venetoclax (E). IC_{50} values are summarized in Table 1. Each data point represents average of at least two replicate values. (*Venetoclax concentration set as standard for positive control). Ibrutinib IC_{50} determined as a standalone experiment.

Table 1. Clinical Profiles of CLL Patient Samples and Response to BMF-219

Sample	Mutation	Cytogenetics	Prior Treatment	Rai Binet Stage	BMF 219 IC_{50} (µM)	BMF 219 % Max Inhibition
BM-301	ATM	Normal	Bendamustine (responded, then progressed)	Stage 2 (Relapsed)	0.373	98.7
BM-302	NOTCH1	Normal	Ibrutinib (responded, then progressed)	Stage 2 (Relapsed)	0.332	99.7
BM-303	TP53	N/A	Ibrutinib (responded), (post-collection: ibrutinib and venetoclax- responded, then progressed)	Stage 1	0.285	99.8
BM-304	None or N/A	44, XX, add(3)(q21), -5, add(6)(p12), +11, der(11;13)(q10;q10), -13,t(15;18)(q15;q21), add(16)(p13.3), add(17)(p11.2) [cp15]/46, XX [6]	Ibrutinib (responded)	Stage 1	0.104	99.9
BM-305	WT1	Normal	Rituximab/Ibrutinib (responded)	Stage 2	0.384	100
BM-306	TP53	Normal	Ibrutinib (responded, no progression)	Stage 3	0.380	100
BM-307	KRAS, KMT2A, TET2	47, XY, +12, t(14;19)(q32;q13.3), t(16;20)(p13.3;q13.1) [13]/46, XY [7]	Rituximab/Methylprednisolone (responded), ibrutinib	N/A	0.145	99.5
BM-308	None or N/A	46~47, XY, del(6)(q13q25), dic(7;21)(q31;p13), add(11)(q13), del(13)(q12q14), +2mar, inc [cp4]/46, XY [3]	Rituximab/Ibrutinib (responded, continuing)	Stage 2	0.359	99
BM-309	None or N/A	Normal	Ibrutinib (responded)	Stage 3	0.331	100
BM-310	None or N/A	Normal	Ibrutinib (responded)	N/A	0.357	99
BM-311	NOTCH1, ATM	N/A	N/A	Stage 2 (Relapsed)	0.359	100
BM-312	None or N/A	N/A	N/A	N/A	0.384	100

BMF-219 exhibits higher ex vivo potency compared to Standard-of- Care Agents

Sample	Mutation	BMF 219 IC_{50} (µM)	BMF 219 % Max Inhibition	Ibrutinib IC_{50} (µM)	Bendamustine IC_{50} (µM)	Idelasib IC_{50} (µM)
BM-301	ATM	0.373	98.7	14.8	15.6	8.91
BM-302	NOTCH1	0.332	99.7	N/A	N/A	N/A
BM-303	TP53	0.285	99.8	29.1	31.9	37.2
BM-304	None or N/A	0.104	99.9	N/A	N/A	N/A
BM-305	WT1	0.384	100	34.8	17.1	35.7
BM-306	TP53	0.38	100	24.1	6.65	2.21
BM-307	KRAS, KMT2A, TET2	0.145	99.5	18.3	16.1	0.271
BM-308	None or N/A	0.359	99	26.7	15.7	22.7
BM-309	None or N/A	0.331	100	29.0	25.2	38.1
BM-310	None or N/A	0.357	99	12.4	6.84	1.67
BM-311	NOTCH1, ATM	0.359	100	29.1	32.2	35.7
BM-312	None or N/A	0.384	100	N/A	N/A	N/A

Table 2. BMF-219 potency as determined by IC_{50} values in comparison with standard-of-care agents for CLL. CLL ex vivo patient samples were cultured with BMF-219 for 6 days to determine IC_{50} values. IC_{50} values for Ibrutinib (BTK inhibitor), bendamustine (alkylating agent) and idelasib (PI3K inhibitor) were experimentally determined as standalone experiments in these patient models.

Conclusions

- BMF-219 demonstrated high potency, achieving >98% cell lethality at 1.1 µM exposure in all CLL patient samples tested, with IC_{50} values in the range of 0.1 to 0.38 µM, similar to BMF-219 potency in AML and DLBCL ex vivo models.
- Specimens isolated from patients with clinical profiles containing high-risk genetic backgrounds associated with inferior outcomes to standard therapy, such as mutations in TP53 and NOTCH1, and chromosomal aberrations such as del(13q), trisomy 12 and complex karyotype, exhibited high sensitivity to BMF-219 treatment.
- BMF-219 was also highly effective against patient samples with clinical profiles of resistance to bendamustine or ibrutinib therapy.
- A clinical reversible menin inhibitor demonstrated no significant activity across all patient samples tested, with incalculable IC_{50} values and <15% reduction in cell viability at 1 µM exposure.
- Collectively, our data demonstrate the potent preclinical activity of BMF-219 against CLL patient specimens harboring various mutational and cytogenetic backgrounds, including categories of high unmet need, highlighting the unique potential of covalent menin inhibition as a novel therapeutic option for patients with CLL.

References

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- Somanath, P., Lu, D., Law, B. et al. Novel Irreversible Menin Inhibitor, BMF-219, Shows Potent Single Agent Activity in Clinically Relevant DLBCL Cells. *Blood* 2021; 138 (Supplement 1): 4318.
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We acknowledge Arpeggio Biosciences for generation of RNA-seq data and Champions Oncology for ex vivo data.