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# Anti-tumor Activity of Irreversible Menin Inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models

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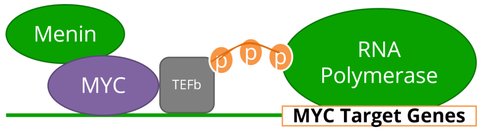
## INTRODUCTION

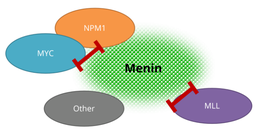
- Double/Triple Hit Lymphoma (DHL/THL) and Double Expresser Lymphoma (DEL) are high-grade B-cell lymphomas (HGBL) that exhibit low responses to standard therapeutic regimens resulting in poor prognosis.
- DHL harbor translocations in MYC and BCL2 or BCL6, THL contain translocations in MYC/BCL2/BCL6, and DEL are characterized by high expression of MYC and BCL2.
- Menin is a scaffold protein that drives oncogenic function through its regulation of genes such as *HOXA9*, with distinct effects on transcription that are directed by various cofactors. A recent study reported that knockdown of *HOXA9* resulted in marked growth inhibition of multiple myeloma (MM) cells (Chapman et al., 2017).
- We previously reported the ability of irreversible menin inhibitor, BMF-219, to modulate MYC expression and exhibit high potency against DHL Diffuse Large B-Cell Lymphoma (DLBCL) preclinical models (Somanath et al., 2021).




*Source: Wu, G. et al. Menin enhances c-Myc-mediated transcription to promote cancer progression. Nat. Commun. 8, 15278 (2017).*

- Here, we demonstrate the anti-tumor activity of BMF-219 in HGBL and MM preclinical models harboring various mutational backgrounds.

Mechanism of Action



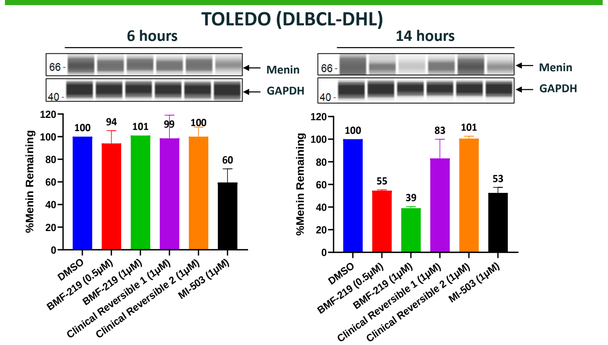

Target Patient Population

- MLL — MLL-r Acute Leukemia
- NPM1 — NPM1 mutant Acute Leukemia
- MYC — DHT / DEL DLBCL
- MYC — Multiple Myeloma
- MYC — KRAS mutant (CRC, Lung, Pancreatic)
- Other — Liquid and Solid Tumors

## METHODS

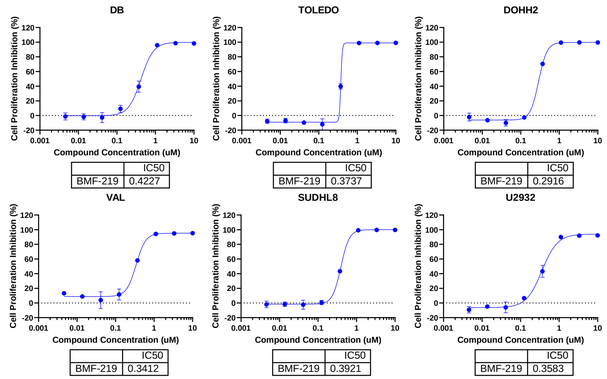
- AML and DLBCL cell lines were cultured in the presence of BMF-219 or clinical reversible menin inhibitors for 14 hours. Menin protein expression was measured by the Wes system and analyzed using the Compass software (automated western blotting, Protein Simple). Signal was normalized to GAPDH and referenced to DMSO control.
- DLBCL and MM cell lines were cultured in the presence of BMF-219 or bortezomib (PS-341) for 4 days and cell proliferation was measured by Cell Titer Glo.
- Patient-derived DLBCL PDX models and MM patient derived BMMCs were cultured *ex vivo* in the presence of BMF-219 or PS-341 for 6 days and cell proliferation was measured by Cell Titer Glo.

## RESULTS




**BMF-219 reduces menin protein in DLBCL cells.** Quantitation of menin protein expression in TOLEDO (DLBCL, DHL) cell line treated with BMF-219, clinical reversible menin inhibitors or preclinical reversible menin inhibitor, MI-503, for 14 hours.

## BMF-219 exerts potent cell lethality in DLBCL cell lines



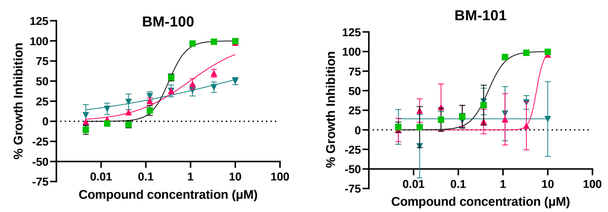

| DLBCL Cell Line | Category | Translocation | Average % Max Inhibition by BMF-219 | Average $IC_{50}$ ± Standard Deviation (μM) |
|---|---|---|---|---|
| DB | DHL | MYC/BCL2 | 98.5 | 0.407 ± 0.067 |
| Toledo | DHL | MYC/BCL2 | 98.8 | 0.311 ± 0.065 |
| DOHH2 | DHL | MYC/BCL2 | 99.7 | 0.323 ± 0.031 |
| VAL | THL | MYC/BCL2/BCL6 | 97.1 | 0.271 ± 0.070 |
| U2932 | DEL-ABC | MYC/BCL2 Overexpression | 92.4 | 0.370 ± 0.012 |
| SUDHL8 | GCB | - | 99.6 | 0.601 ± 0.209 |
| Pfeiffer | GCB | - | 99.6 | 0.167 ± 0.040 |
| OCI-LY7 | GCB | - | 99.6 | 0.650 ± 0.260 |

**Potent killing activity of BMF-219 at clinically relevant concentrations in representative DLBCL cell lines.** Cell lines from DHL (DB, Toledo, DOHH2), THL (VAL), DEL (U2932), and GCB (SUDHL8) subtypes were cultured in the presence of BMF-219 at 8 dose concentrations ranging from 0.005 μM to 10 μM for 4 days and cell killing measured by Cell Titer Glo. Representative dose response curves are shown on the top. Average $IC_{50}$ values of at least two experiments, maximal percentage cell killing and cytogenetic background of DLBCL cell lines are summarized in the table.

## BMF-219 exerts pronounced lethality in DLBCL PDX models *ex vivo*

**THL- Responded, then progressed on R-EPOCH**

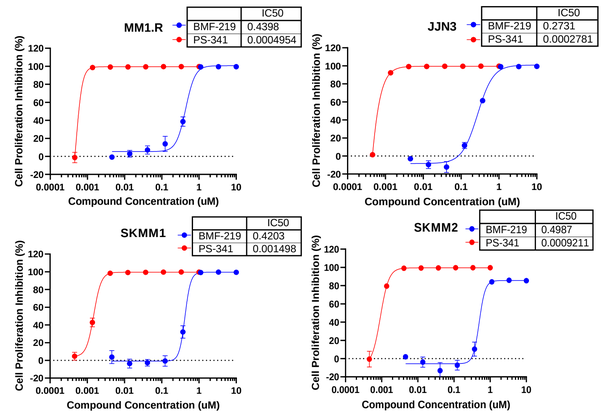
**MYC Amplified- Responded, then progressed on R-CHOP**




| Treatment | Growth Inhibition $IC_{50}$ (μM) | |
|---|---|---|
| | BM100 | BM101 |
| BMF-219 | 0.250 | 0.151 |
| Clinical Reversible-1 | 0.969 | 5.63 |
| Clinical Reversible-2 | 6.31 | Max killing <30% |

**Growth inhibition of patient-derived DLBCL Triple Hit Lymphoma (THL) and MYC-amplified PDX samples treated with BMF-219 or clinical reversible menin inhibitors after 6 days of treatment.**

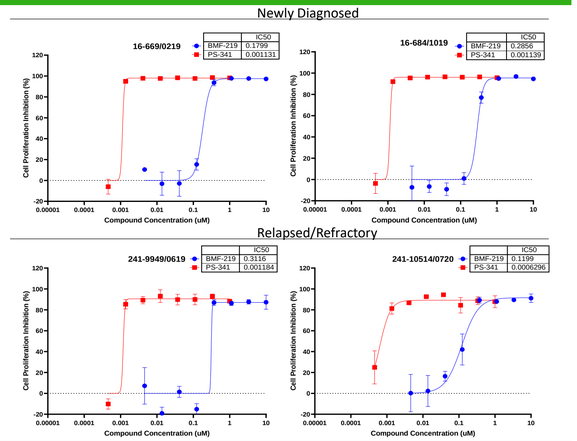
## BMF-219 exerts >99% lethality against MM cell lines




| MM Cell Line | Translocation | Mutation | Average % Max Inhibition by BMF-219 | Average $IC_{50}$ ± Standard Deviation (μM) |
|---|---|---|---|---|
| MM1.S | t(14;16) | KRAS G12A | 99.5 | 0.467 ± 0.17 |
| MM1.R | t(14;16) | KRAS G12A | 99.6 | 0.462 ± 0.17 |
| SKMM1 | t(14;20) | NRAS G12A | 99.2 | 0.467 ± 0.05 |
| SKMM2 | t(11;14) | TP53 | 80.2 | 0.654 ± 0.15 |
| JJN3 | t(14;16) | NRAS Q61K | 99.2 | 0.289 ± 0.02 |

**Potent killing activity of BMF-219 at clinically relevant concentrations in representative MM cell lines.** MM1.R, JJN3, SKMM1 and SKMM2 cell lines were cultured in the presence of BMF-219 (blue) or PS-341 (red) at 8 dose concentrations ranging from 0.005 μM to 10 μM for four days and cell killing measured by Cell Titer Glo. Representative dose response curves are shown on the top. Average $IC_{50}$ values of at least two experiments, maximal percentage cell killing, and cytogenetic background of MM cell lines are summarized in the table.

## BMF-219 dramatically reduces growth of both newly diagnosed and R/R MM patient specimens




| Multiple Myeloma Specimen ID | Stage at Diagnosis | Treatment Status | Prior Therapy and Response | Translocation |
|---|---|---|---|---|
| 16-669/0219 | IIIA | Newly Diagnosed | None | No data |
| 16-684/1019 | IIIA | Newly Diagnosed | None | No data |
| 241-9949/06-19 | IIIA | Refractory | VCD N4 (resistant) | p53 deletion |
| 241-10514/0720 | IIIA | Refractory | VCD N 4 (responded) | p53 deletion-negative |
| | | | High dose CPH (SC-mobilization) (responded) | |
| | | | Consolidation (AutoSCT, double transplant) | |
| | | | Bortezomib- maintenance (resistant) | |
| | | | RVD #4 (resistant) | |
| | | | PRD #4 (resistant) | |

**Growth inhibition of newly diagnosed (A-B) and R/R (C-D) MM patient-derived bone marrow mononuclear cells (BMMCs) after 6 days of treatment with BMF-219 (blue) or PS-341 (red).** Clinical profiles of MM patient-derived BMMC specimens are summarized in the table.

## CONCLUSIONS

- BMF-219 exhibited high potency as a single agent against DHL, THL and DEL DLBCL cell lines, with $IC_{50}$ values of 0.27 μM and 0.37 μM, respectively.
- In *ex vivo* studies, BMF-219 was highly effective against R-CHOP and R-EPOCH refractory patient samples with THL and MYC-amplified genetic backgrounds.
- BMF-219 was multi-fold more potent and exerted dramatically greater growth inhibition compared to clinical reversible menin inhibitors in DLBCL patient-derived *ex vivo* samples.
- BMF-219 achieved >99% cell lethality in MM cell lines with RAS mutations.
- BMF-219 demonstrated single-agent efficacy ($IC_{50}$ values between 0.1 μM and 0.3 μM) against a panel of newly diagnosed and R/R *ex vivo* MM samples, including a p53-deleted clinical profile.

### 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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- Borkin, D. et al. Pharmacologic inhibition of the Menin-MLL interaction blocks progression of MLL leukemia in vivo. *Cancer Cell.* 2015 Apr 13;27(4):589-602.




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