**INTRODUCTION**

Menin is a scaffold protein that drives oncogenic function through its regulation of genes such as HOXD9, with distinct effects on transcription that are directed by various cofactors. A recent study reported that knockdown of HOXD9 resulted in marked growth inhibition of multiple myeloma (MM) cells (Chapman et al., 2017).

Double/Triple Hit Lymphoma (DHL/THL) and Double Expressor Lymphoma (DEL) are high-grade B-cell lymphomas (HGBLs) that exhibit low responses to standard therapeutic regimens resulting in poor prognosis.

DHI, 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.

We previously reported the ability of irreversible menin inhibitor, BMF-219, to modulate MYC expression and inhibit high potency against DHL, Diffuse Large B-Cell lymphoma (DLBCL) preclinical models (Somanath et al., 2021).

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

**METHODS**

- MM and DLBCL cell lines were cultured in the presence of BMF-219 or bortezomib (PS-341) for 4 days and cell proliferation was measured by CellTiter Glo.
- Patient-derived MM patient derived BMCMs and DLBCL PDX models were cultured ex vivo in the presence of BMF-219 or PS-341 for 4 days and cell proliferation was measured using CellTiter Glo.
- MM 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.

**RESULTS**

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

**CONCLUSIONS**

- BMF-219 achieved >99% cell lethality in MM cell lines with RAS mutations with IC₅₀ values between 0.3 μM and 0.5 μM.
- BMF-219 demonstrated single-agent efficacy (IC₅₀ 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-skewed clinical profile.
- BMF-219 exhibited high potency as a single agent against DHL, THL, and DEL DLBCL cell lines, with IC₅₀ values of 0.3 μM and 0.4 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 induces reduction of menin protein levels across MM and DLBCL cell lines. This reduction however appears to be transient. An incubation time of 14 hours may not be a good predictor of cellular growth inhibition.

**REFERENCES**


