(PF426) MITIGATING MCL-1-DRIVEN CARDIOTOXICITY: PRECLINICAL CHARACTERIZATION OF THE FIRST-IN-CLASS MCL-1 DEGRADER

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

MCL-1 is a key anti-apoptotic regulator, the overexpression of which drives survival and therapeutic resistance across diverse hematological and solid malignancies. Unlike conventional inhibitors that require high concentrations for target saturation, Targeted Protein Degradation (TPD) facilitates protein depletion at sub-stoichiometric dosages. This approach mitigates dose-limiting cardiac toxicities inherent to occupancy-based inhibition, significantly expanding the therapeutic window. Here, we describe the preclinical evaluation of a highly potent, first-in-class MCL-1 degrader engineered for the selective ablation of MCL-1 in hematological malignancies. Our MCL-1 degrader demonstrates rapid and robust apoptosis induction across multiple *in vitro* and *in vivo* models, translating enhanced selectivity and sustained pharmacodynamic responses into a broadened therapeutic window for MCL-1 targeting.

Aims

To evaluate the pharmacological profile of our MCL-1 degrader and establish its therapeutic potential as a cardiosafe monotherapy or venetoclax-combination treatment for R/R AML.

Methods

Ternary complex formation between the degrader, CRBN and MCL-1 was validated through biophysical assays, while degradation efficiency and cytotoxicity were assessed via Western blot and CellTiter-Glo assay across a panel of cancer cell lines, including MV-4-11, OPM2, NCI-H838 and DMS114. Comparative cardiotoxicity was evaluated in human iPSC-derived cardiomyocytes by monitoring MCL-1 levels and viability. *In vivo* efficacy was studied in MV-4-11 AML xenograft model, both as monotherapy and in combination with low-dose venetoclax. Finally, the PK/PD profile and systemic safety were characterized in cynomolgus macaques.

Results

Biophysical assays confirmed degrader-mediated ternary complex formation (CRBN/MCL-1). In MV-4-11, OPM2, and DMS114 cells, our MCL-1 degrader demonstrated potent anti-proliferative activity (IC_{50} = 0.99 ± 0.57 nM for MV-4-11; 10.17 ± 7.1 nM for OPM-2 cells; 31.6 ± 17.3 nM for DMS-114 cells) and robust MCL-1 degradation, with a 1-hour treatment sufficient to trigger irreversible apoptosis. In human iPSC-derived cardiomyocytes, our degrader demonstrated no toxicity, avoiding the persistent MCL-1 accumulation typically observed with small-molecule inhibitors, following washout. In AML xenograft models, our degrader demonstrated potent anti-tumor activity both as a monotherapy and in combination. Notably, the combination with low-dose venetoclax promoted tumor regression in the MV-4-11 model, demonstrating a highly synergistic effect. Studies in non-human primates (NHP) confirmed a favorable PK/PD profile and cardiac safety at exposures significantly exceeding predicted efficacious doses.

Summary/Conclusion

Our first-in-class MCL-1 degrader was designed to overcome the cardiotoxicity typical of traditional inhibitors, which are often constrained by toxic protein accumulation. By achieving irreversible target depletion and demonstrating a superior safety profile in NHP models, our degrader represents a potent therapeutic strategy for relapsed/refractory AML. The compound is currently in IND/CTA-enabling studies, with a First-in-Human Phase 1 trial expected to commence by the end of 2026 to evaluate its efficacy as monotherapy and in combination with venetoclax.