Anti-tumor Activity of HPN217, a BCMA-targeting, Trispecific T cell Engager, is Enhanced by γ-Secretase Inhibitors in Preclinical Models

Payton C. Laurie, Mary Ellen Molloy, Patrick P. Ng, Banmeet S. Anand
Harpoon Therapeutics, South San Francisco, CA

INTRODUCTION

- B-cell maturation antigen (BCMA/tnfrsf17/CD269) is expressed on B lineage cells. Plasma cell malignancies such as multiple myeloma (MM) show increased BCMA expression.
- APRIL/TNFSF13 and BAFF/TNFSF13B are ligands for BCMA and activate the MAP kinase and BCL-2/XL pathways that promote proliferation and survival.
- HPN217 is a Trispecific T Cell-Activating Construct (TriTAC) engineered to target BCMA. It is currently being evaluated in a phase 1 clinical trial for relapsed or refractory multiple myeloma (NCT04184050).
- The extracellular domain of BCMA can be cleaved by γ-secretase, decreasing membrane bound BCMA and potentially affecting anti-tumor efficacy of BCMA-targeting therapies.
- γ-Secretase inhibitors (GSIs) have been shown to increase membrane bound BCMA on MM cells, providing a rational for combining GSIs and HPN217.

GSIs increase membrane bound BCMA in vitro and in vivo

The combination of GSI and HPN217 led to a significant increase in survival and decrease in tumor burden in the MOLP8 xenograft model. NSG mice (n=16) were i.v. injected with 2x10^6 MOLP8 cells (day 0). 2x10^6 expanded human T cells were injected i.p. on day 7. The GSI LY-3039478 was dosed at 1 mg/kg p.o. three times weekly for two weeks starting on day 7. HPN217 was dosed at 4 mg/kg daily for 10 days starting on day 8. Tumor progression was monitored by percent bodyweight change (μg/kg daily for 10 days starting on day 8). Tumor progression was monitored by percent bodyweight change (μg/kg daily for 10 days starting on day 8).

SUMMARY

- γ-Secretase inhibitors increased membrane bound BCMA expression in vitro and in vivo
- γ-Secretase inhibitors increased the potency of HPN217 in a BCMA-specific manner in multiple cell lines
- Combination therapy using the GSI LY-3039478 and a sub-therapeutic dose of HPN217 led to decreased tumor burden and increased survival when compared to either treatment alone in a disseminated disease mouse model of multiple myeloma