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

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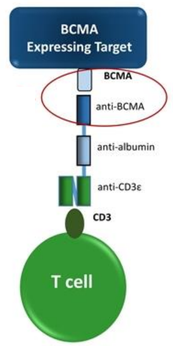
INTRODUCTION

- 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/TNSF13B 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*

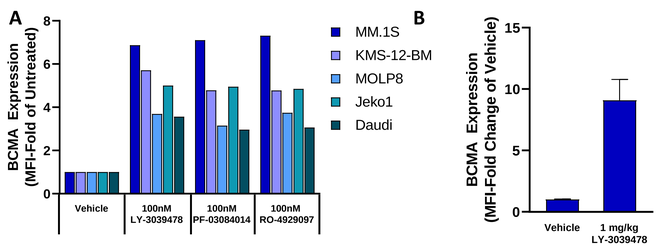
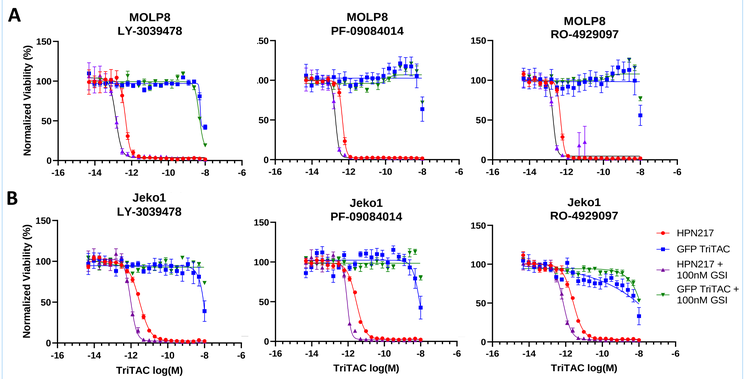
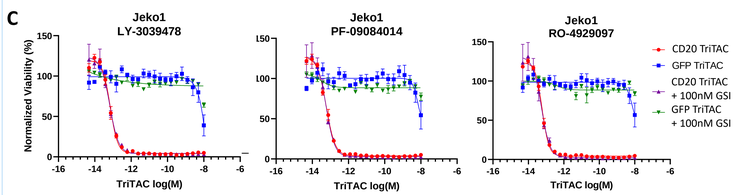


Figure 1: GSI treatment led to increases in membrane bound BCMA. Five BCMA+ cell lines were incubated in media containing 100 nM of one of three GSIs (LY-3039478, PF-0308414, RO-4929097) or DMSO (vehicle) for 20 hours. BCMA expression was then quantitated via flow cytometry **(A)**. A disseminated MOLP8 xenograft was treated with one dose of 1mg/kg LY-3039478 via oral gavage (n=5) 20 hours prior to bone marrow collection. Cells were gated for muCD45⁻ huCD138⁺ to identify MOLP8 cells and BCMA expression was measured by flow cytometry **(B)**.

GSIs increase the potency of HPN217 *in vitro*



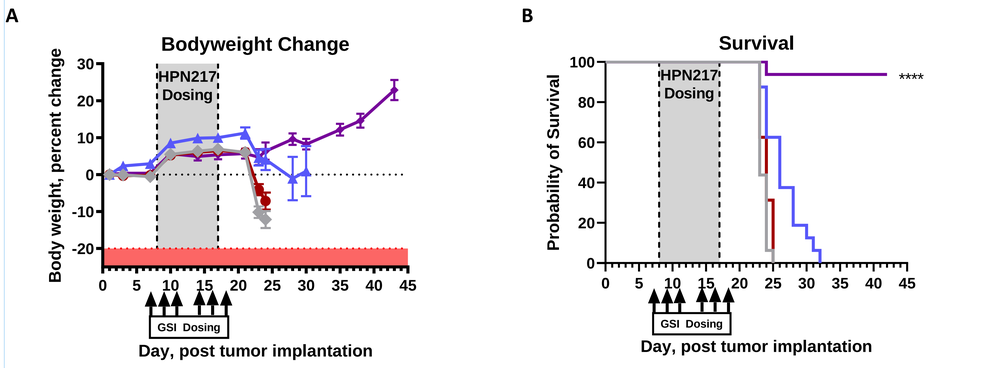
	HPN217 EC_{50} (pM)	HPN217 + GSI EC_{50} (pM)	EC_{50} Shift (Fold)
MOLP8 (LY-303)	0.47	0.14	3.14
MOLP8 (PF-090)	0.45	0.19	2.39
MOLP8 (RO-492)	0.48	0.19	2.56
Jeko1 (LY-303)	2.89	0.96	3.02
Jeko1 (PF-090)	2.79	0.88	3.15
Jeko1 (RO-492)	2.54	0.71	3.56



	CD20 TriTAC EC_{50} (pM)	CD20 TriTAC + GSI EC_{50} (pM)	EC_{50} Shift (Fold)
Jeko1 (LY-303)	0.071	0.067	1.07
Jeko1 (PF-090)	0.059	0.058	1.02
Jeko1 (RO-492)	0.060	0.054	1.11

Figure 2: **GSIs increased the potency of HPN217 in a BCMA-specific manner.** In a T-cell dependent cellular cytotoxicity (TDCC) assay, BCMA+ cell lines were incubated with 100 nM GSI or DMSO for 20 hours prior to co-culturing for 48 hours with human T cells and HPN217, a CD20 TriTAC, or a control TriTAC (GFP). Target cell viability was measured by luciferase activity. The cytotoxic activity (EC_{50}) of the TriTACs in various conditions as well as the fold change in combination treatment vs TriTAC alone were calculated. All three GSIs increased the potency of HPN217 against MOLP8 cells **(A)** and Jeko1 cells **(B)**. GSIs had no effect on the activity of a CD20 TriTAC **(C)** providing evidence that the potency of HPN217 was enhanced by GSIs through modulation of BCMA expression but not from other anti-tumor properties of GSIs.

GSI enhances the efficacy of HPN217 in a disseminated disease mouse model



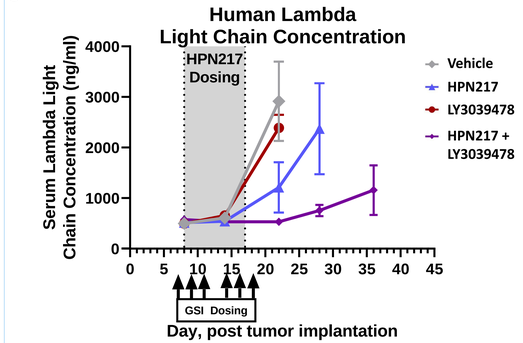


Figure 3: **The combination of GSI and HPN217 led to a significant increase in survival and decrease in tumor burden in the MOLP8 xenograft model.** NSG mice (n=16) were i.v. injected with $2x10^6$ MOLP8 cells (day 0). $2x10^7$ *ex vivo* expanded human T cells were injected i.p. on day 7. The GSI LY-3039478 was dosed at 1 mg/kg p.o. three times weekly for two weeks starting on day 7. HPN217 was dosed at 4 µg/kg daily for 10 days starting on day 8. Tumor progression was monitored by percent bodyweight change **(A)** and survival **(B)**. Tumor burden was measured using the surrogate marker of human lambda light chain concentrations (ng/mL) in serum **(C).**

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

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