An Interim Report on a Phase 1/2 Study of HPN217, a Half-Life Extended Tri-Specific T Cell Activating Construct (TriTAC®) Targeting B Cell Maturation Antigen for the Treatment of Relapsed/Refractory Multiple Myeloma

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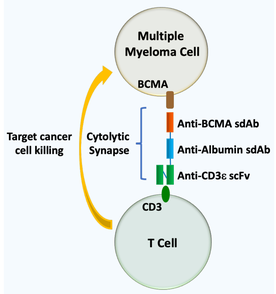
BACKGROUND

- HPN217 is a recombinant polypeptide of ~50 kDa containing three humanized antibody-derived binding domains:
  - BCMA (for multiple myeloma cell binding)
  - Albumin (for half-life extension)
  - CD3 (for T cell engagement)
- HPN217 is a small, globular protein, designed to enable optimal drug exposure in target tumor tissues, half-life extension, and excellent functional stability under physiological conditions
- HPN217 mediates potent target tumor cell killing in a BCMA-specific manner in vitro and in xenograft models in the presence of T cells
- HPN217 binds monovalently to CD3 and BCMA, minimizing non-specific T-cell activation

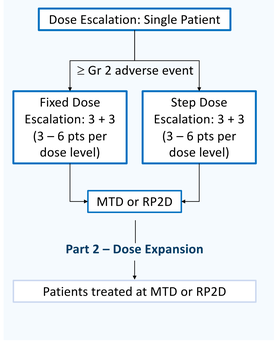
Figure 1. HPN217 Mechanism of Action



TRIAL DESIGN

Dose Escalation / Expansion, Safety & PK Study in Relapsed/Refractory Multiple Myeloma

Figure 2. HPN217-3001 Trial Design



Target Population
- Relapsed/refractory multiple myeloma
- At least 3 prior therapies, including proteasome inhibitor, immuno-modulatory drug (IMiD), and an anti-CD38 antibody

Trial Design
- Objectives: characterization of safety, PK, identification of the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D)
- Tumor assessments based on IMWG* Response Criteria

Dosing, Administration & Exposure
- HPN217 is administered weekly by 1-hour IV infusion
- Premedication to manage cytokine release syndrome (CRS)

*International Myeloma Working Group Uniform Response Criteria For Multiple Myeloma and Minimal Residual Disease Assessment in Multiple Myeloma

Table 1. Dose Escalation Steps

Dose Level (µg/week)	N
5	1
15	1
30	2
90	1
270	2
810	4
1620	6
2150	11
2860	6
1620 (priming)→3240 (target)	3
Total	**37**

- As of November 10, 2021, 37 patients were treated in either fixed dose or step dose cohorts
- Highest target doses evaluated to-date:
  - Fixed Dose: 2860 µg/week
  - Step Dose: 1620 µg/week (Priming) → 3240 µg/week (Target)

BASELINE CHARACTERISTICS

Table 2. Baseline Characteristics and Demographics

Baseline Characteristics	Total N = 37
Age (yr), Median (range)	71 (38 – 78)
Duration of Disease (yr), Median (range)	8 (1 – 20)
Prior Transplantation, N (%)	28 (76%)
Prior Systemic Therapies, Median (range)	7 (2 – 16)
Best Response To Most Recent Regimen	**N (%)**
Complete Response	1 (3%)
Very Good Partial Response	4 (11%)
Partial Response	5 (14%)
Minimal Response	1 (3%)
Stable Disease	10 (27%)
Progressive Disease	12 (32%)
Missing	4 (11%)

Table 3. Prior Systemic Therapies

Therapeutic Class and Agents		Total N = 37, N (%)
Proteasome Inhibitor	Bortezomib	34 (92%)
	Carfilzomib	30 (81%)
	Ixazomib	10 (27%)
Anti-CD38	Daratumumab	33 (89%)
	Isatuximab	3 (8%)
IMiD	Lenalidomide	34 (92%)
	Pomalidomide	31 (84%)
	Thalidomide	11 (30%)
BCMA-Targeted Therapy	Belantamab Mafodotin	6 (16%)
	SEA-BCMA	2 (5%)
	Bispecific TCE	1 (3%)
	CAR T-Cell Therapy	1 (3%)

- Heavily refractory population
- Median of 7 prior systemic therapies
- 27% had a response of PR or better to the regimen received prior to enrolling on this trial

ADVERSE EVENTS

Table 4. Common Treatment-Emergent Adverse Events Per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grading, >15% frequency

Event	Grade 1 or Grade 2	≥ Grade 3	All Grades (N=37)
Hematological Adverse Events*			
Anemia	3 (8%)	14 (38%)	17 (46%)
Non-Hematological Adverse Events*			
Fatigue	11 (30%)	1 (3%)	12 (32%)
Aspartate Aminotransferase Increase	2 (5%)	5 (14%)	7 (19%)
Cough	7 (19%)	0 (0%)	7 (19%)
Alanine Aminotransferase Increase	3 (8%)	3 (8%)	6 (16%)
Epistaxis	6 (16%)	0 (0%)	6 (16%)
Headache	6 (16%)	0 (0%)	6 (16%)
Arthralgia	5 (14%)	1 (3%)	6 (16%)
Nausea	6 (16%)	0 (0%)	6 (16%)
Diarrhea	6 (16%)	0 (0%)	6 (16%)
Dyspnea	5 (14%)	1 (3%)	6 (16%)

*Common TEAEs per CTCAE V5.0 Grading

- One Dose Limiting Toxicity (DLT) reported: Grade 4 AST, resolved
- MTD not reached
- Most common (>20%) adverse events (AEs) include anemia, fatigue, and cytokine release syndrome (CRS)
- 22% of patients had at least 1 event of transaminitis; majority of events were observed at C1D1, all were transient, with no clinical sequalae

Table 5. Cytokine Release Syndrome and Infusion Related Reactions

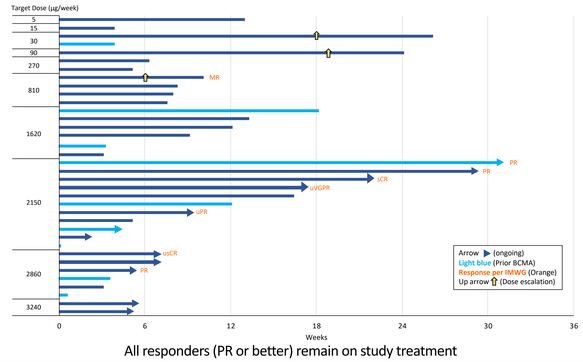
Event	5/15/30/90/270 µg/wk (N=7)	810 µg/wk (N=4)	1620 µg/wk (N=6)	2150 µg/wk (N=11)	2860 µg/wk (N=6)	1620→3240 µg/wk (N=3)	Total (N=37)
CRS (Grade 1 or Grade 2)	0 (0%)	0 (0%)	1 (17%)	6 (55%)	2 (33%)	0 (0%)	9 (24%)
CRS Grade 1*	0 (0%)	0 (0%)	1 (17%)	4 (36%)	1 (17%)	0 (0%)	6 (16%)
CRS Grade 2*	0 (0%)	0 (0%)	0 (0%)	2 (18%)	1 (17%)	0 (0%)	3 (8%)
IRR	0 (0%)	1 (25%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	2 (5%)
Pyrexia	0 (0%)	1 (25%)	1 (17%)	6 (55%)	2 (33%)	0 (0%)	10 (27%)
Hypotension	0 (0%)	0 (0%)	0 (0%)	4 (36%)	1 (17%)	0 (0%)	5 (14%)

*Grading per ASTCT 2019 Criteria

- Grade 1 or 2 CRS events have been observed in 24% of patients; No Grade 3 CRS reported
- One patient in 2860 µg/week cohort received tocilizumab due to Grade 2 CRS on C1D1
- No ASTCT-defined ICANS reported

TIME ON TREATMENT

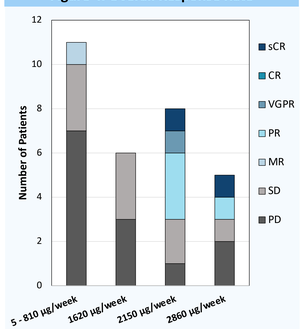
Figure 3. Time on Treatment for All Patients Treated



All responders (PR or better) remain on study treatment

RESPONSE ASSESSMENT

Figure 4. Overall Response Rate



Disease-evaluable patients shown: Responses are measured by International Myeloma Working Group Uniform Response Criteria For Multiple Myeloma and Minimal Residual Disease Assessment in Multiple Myeloma

Table 6. Overall Response and Disease Control Rates

Cohort	ORR* (PR and Better)	DCR** (SD and Better)
5 – 810 µg/week	0/11 (0%)	4/11 (36%)
1620 µg/week	0/6 (0%)	3/6 (50%)
2150 µg/week	5/8 (63%)	7/8 (88%)
2860 µg/week	2/5 (40%)	3/5 (60%)

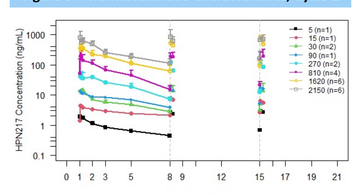
* ORR = overall response rate
** DCR = disease control rate

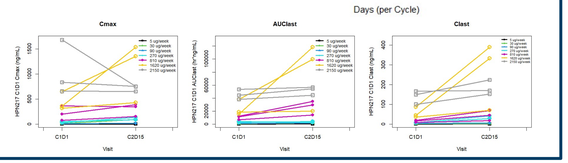
- In 8 disease-evaluable patients enrolled at 2150 µg/wk, one stringent CR, one VGPR, and three PRs observed, including patient with prior BCMA-targeting therapy exposure
- 2 patients with stringent CR are MRD negative as assessed by next generation flow cytometry
- All responders remain on study treatment

PHARMACOKINETICS

- Linear pharmacokinetic (PK) profile: dose-proportional increase in Cmax and AUC, dose-independent clearance and volume of distribution
- Median half-life ($T_{1/2}$) is 74 hours
- Evidence for HPN217 accumulation: C1D1 vs C2D15
  - ~1.5 – 2-fold increase in Cmax and AUC
  - ~2 – 3-fold increase in Clast

Figure 5. Pharmacokinetic Characteristics, Cycle 1

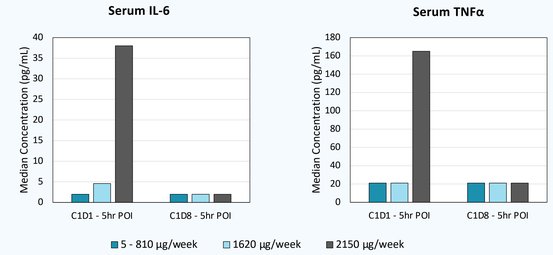




PHARMACODYNAMICS: CYTOKINES

- Serum cytokine concentrations 5 hours after first (C1D1) and second (C1D8) dose of HPN217
- Trend of attenuation for IL-6, TNFα, and INFγ (data not shown) after second dose compared to first dose

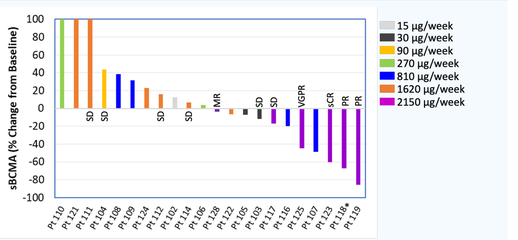
Figure 6. Attenuation of Cytokine Secretion in the Periphery



PHARMACODYNAMICS: BCMA

- On-treatment changes observed in serum BCMA (sBCMA) from Baseline to C1D15 Predose (after 2 doses of HPN217)
- Patients in 2150 µg/week cohort with evaluable baseline and C1D15 measurements all showed reduction in sBCMA

Figure 7. On-Treatment Changes in Serum BCMA



* Prior BCMA, orvacabtagene autoleucel (JCARH125) treatment

SUMMARY

- HPN217 is generally well tolerated; One DLT of Grade 4 AST that resolved; MTD has not been reached
- Transient CRS reported in 9 of 37 patients (24%); all were Grade 1 or 2
  - CRS symptoms generally occur on C1D1
  - Limited CRS symptoms with subsequent doses was associated with attenuated serum cytokine levels of IL-6, TNFα, and IFNγ
  - CRS has not limited re-challenge with HPN217 nor dose escalation
- HPN217 is clinically active at higher dose levels
  - 7 of 8 disease evaluable patients in the 2150 µg/week cohort demonstrated clinical benefit
  - 63% ORR and 88% DCR observed in the 2150 µg/week cohort
  - Responders include 1 patient with prior orvacabtagene autoleucel (JCARH125) treatment
  - Reduction of sBCMA from baseline was observed in patients with PR, VGPR, or sCR
- Dose escalation is ongoing to define the RP2D and/or the MTD, exploring both step dose cohorts and less frequent dosing schedules

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Contact the author at Sumit.Madan@bannerhealth.com for questions or comments