Updated Interim Results from a Phase 1 Study of HPN217, a Half-Life Extended Tri-Specific T Cell Activating Construct (TriTAC) Targeting B Cell Maturation Antigen (BCMA) for Relapsed/Refractory Multiple Myeloma (RRMM)

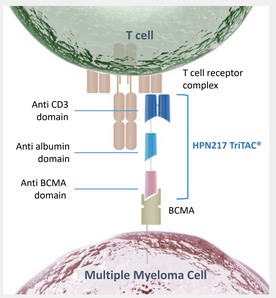
Al-Ola Abdallah, MD[1], Andrew J Cowan[2], MD, Xavier Leleu, MD, PhD[3], Cyrille Touzeau, MD[4], Brea Lipe, MD[5], Eva Medvedova, MD[6], Caitlin Costello, MD[7], Jens Hillengass, MD, PhD[8], P. Leif Bergsagel, MD[9], Raya Mawad, MD[10], Henning Schade, MD[11], Daniel Morillo MD[12], Albert Oriol, MD[13], Yifah Yaron, MD, PhD[14], Patrick P Ng, PhD[14] and Sumit Madan, MD[15]

[1]Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas Medical Center, Westwood, KS; [2]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA; [3]Department of Oncology, Hematology and Cellular Therapy, Poitiers University Hospital, Poitiers, France; [4]Hematology Department, Nantes University Hospital, Nantes, France; [5]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY; [6]Knight Cancer Institute, Oregon Health and Science University, Portland, OR; [7]University of California, San Diego, La Jolla, CA; [8]Roswell Park, Buffalo, NY; [9]Division of Hematology and Medical Oncology, Mayo Clinic, Scottsdale, AZ; [10]Center for Blood Disorders and Stem Cell Transplantation, Swedish Cancer Institute, Seattle, WA; [11]Colorado Blood Cancer Institute, Denver, CO; [12]Department of Hematology, University Hospital Fundación Jiménez Díaz, Madrid, Spain; [13]Institut Josep Carreras and Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [14]Harpoon Therapeutics, South San Francisco, CA; [15]Banner MD Anderson Cancer Center at Banner University Medical Center, Phoenix, AZ

BACKGROUND

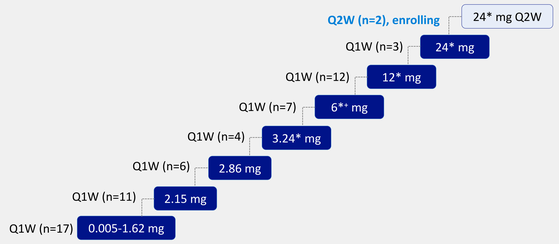
- HPN217 is a BCMA-targeting T-cell engaging bispecific containing three humanized antibody-derived binding domains:
  - BCMA (for multiple myeloma cell binding)
  - Albumin (for half-life extension)
  - CD3 (for T cell engagement)
- HPN217 is a small (~50 kDa) globular protein, designed to increase the therapeutic window by minimizing off-target toxicities and CRS
- Here we present efficacy and safety results from HPN217-3001, which enrolled heavily pre-treated patients with and without prior exposure to BCMA-targeted treatment

HPN217 Mechanism of Action



HPN217-3001 TRIAL DESIGN

Dose Escalation 3+3 Study Design



Fixed dose and step dose escalation cohorts: 3-6 patients per dose level; backfilling permitted; *1 step dose regimen; *+2 step dose regimen; target dose levels indicated for step dose regimens

Key Eligibility Criteria
- Relapsed/refractory multiple myeloma
- At least 3 prior therapies, including a PI, IMiD, and an anti-CD38 antibody
- Prior BCMA-targeted therapies allowed

Key Objectives
- Primary Objectives: characterization of safety, PK, identification of the MTD or the RP2D
- Secondary Objectives: Clinical activity based on IMWG (International Myeloma Working Group) Response Criteria

Dosing and Administration
- HPN217 is administered by 1-hour IV infusion as a flat dose
- Weekly and bi-weekly administration schedules
- Dexamethasone premedication at initial doses for CRS prophylaxis

Patient Disposition

Disposition	All Patients (N=62)
Treatment Ongoing, n (%)	23 (37%)
Median duration of treatment, months (range)	2 (1-18+)
Discontinued Treatment, n (%)	39 (63%)
Disease Progression	32 (52%)
Adverse Events [a]	6 (10%)
Death [b]	1 (2%)

[a] One patient (2.86 mg/week) discontinued due to treatment related Gr 4 ALT/AST increase; all other patients' AEs leading to study discontinuation were not related to study treatment
[b] One patient (2.15 mg/week) died of general physical health deterioration (not treatment related)

BASELINE CHARACTERISTICS

Patient Baseline Characteristics and Demographics

Baseline Characteristics	Total N = 62
Age (yr), Median (range)	70 (38 – 83)
Age ≥ 75 years, n (%)	12 (19%)
Time Since Initial MM Diagnosis (yr), Median (range)	8 (1 – 20)
Baseline sBCMA (ng/mL), Median (range)	240 (27– 2444)
ECOG, n (%)	
0, 1, 2	14 (23%), 46 (74%), 1 (2%)
Revised ISS Stage at Study Entry, n (%)	
I, II,III, Missing	16 (26%), 17 (27%), 26 (42%), 3 (5%)

Prior Systemic Therapies

Prior Cancer Therapy	Total N = 62
Prior Systemic Therapies, Median (range)	6 (2-19)
Prior Transplantation, n (%)	46 (74%)
Exposure Status, n (%)	
Triple-class[a] exposed	58 (94%)
Penta-drug[b] exposed	41 (66%)
BCMA exposed	13 (21%)
Refractory Status, n (%)	
Triple-class[a] refractory[c]	47 (76%)
Penta-drug[b] refractory[c]	26 (42%)
BCMA refractory	11 (18%)

[a] IMiD, PI, and anti CD38; [b] At least 2 PIs, at least 2 IMiDs, and at least 1 anti CD38 antibody; [c] No response to regimen or discontinued regimen due to progression, adapted from Rajkumar et al (Blood 2011)

SAFETY SUMMARY

Treatment-Emergent Adverse Events (Regardless of Relationship) ≥ 15%

AE Preferred Term	All Grades (N=62)[a]	≥ Grade 3 (N=62)[a]
Anemia	27 (44%)	21 (34%)
Fatigue	20 (32%)	2 (3%)
Cytokine release syndrome[b]	17 (27%)	0 (0%)
Headache	15 (24%)	0 (0%)
Hypokalemia	13 (21%)	2 (3%)
Nausea	13 (21%)	0 (0%)
Back Pain	11 (18%)	1 (2%)
Diarrhea	11 (18%)	1 (2%)
Hypophosphatemia	11 (18%)	4 (7%)
AST increased	11 (18%)	5 (8%)
Cough	11 (18%)	0 (%)
Arthralgia	10 (16%)	1 (2%)
Neutrophil count decreased	10 (16%)	8 (13%)
Dyspnea	10 (16%)	2 (3%)
ALT increased	9 (15%)	4 (7%)
Constipation	9 (15%)	0 (%)
Hypercalcemia	9 (15%)	1 (2%)

Dose Limiting Toxicity
- Fixed dose: 2 patients at 2.86 mg/week, reversible transaminitis (Gr 3, n=1; Gr 4, n=1), no clinical sequelae
- Step dose: No DLTs; MTD not reached

Neurologic/Psych Events[c]
- Treatment related events reported in 10 patients
  - All events Grade 1 - 2
  - Most common: Headache (n=6) and Confusion (n=2)
- No ICANS events reported

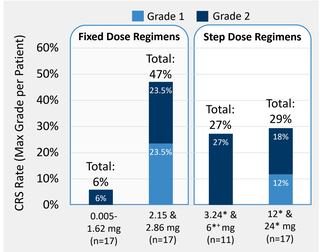
Infections[d]
- Reported in 28 (45%) patients (Gr 3/4, 16%)
- Most common: Pneumonia (n=6), upper respiratory tract infection (n=5) and urinary tract infection (n=5)

No treatment related Grade 5 AEs

[a] Grading per CTCAE v5.0; [b] Grading per ASTCT 2019 Criteria; [c] SOC nervous system disorders and psychiatric disorders; [d] SOC infections and infestations

CYTOKINE RELEASE SYNDROME

Maximum CRS Grade by Dose Group



CRS Summary in all Patients

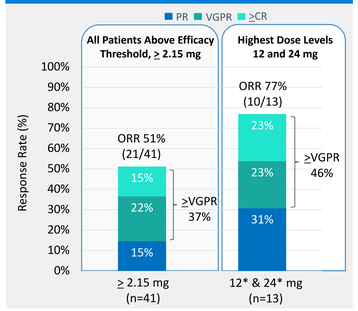
Parameter	All Patients (N=62)
Patients with CRS[a], n (%)	17 (27%)
Grade 1	11 (18%)
Grade 2	6 (10%)
Grade ≥ 3	0 (0%)
Patients with > 1 CRS event	3 (5%)
Received supportive measures for CRS, n (%)	**All Patients (N=62)**
Tocilizumab	4 (6%)
Dexamethasone	1 (2%)

[a] Grading per ASTCT 2019 Criteria

- No ≥ Grade 3 CRS Reported
- 95% of CRS events occurred following the first or second dose; the remaining event was associated with the third dose

RESPONSE ASSESSMENT

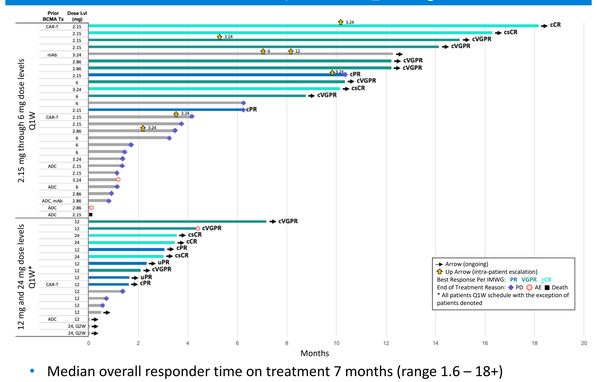
Overall Response Rate[a], Dose Levels ≥ 2.15 mg



- 18/21 responders remain on study treatment with sustained response, with many responses deepening over time
- 3/3 patients evaluated for MRD, are MRD negative ($<10^{-5}$)[b]

[a] Confirmed and unconfirmed responses per investigator assessment, efficacy evaluable population includes all patients who had received ≥1 dose of HPN217 and opportunity for first disease assessment at C1D15; [b] MRD: Minimal Residual Disease, assessment for MRD performed for patients who achieved ≥CR; *1 step dose regimen

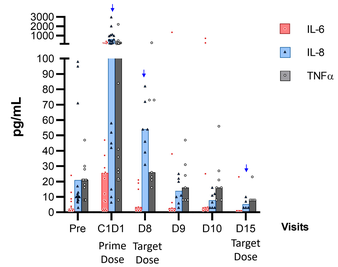
Time on Treatment, Dose Levels ≥ 2.15 mg



- Median overall responder time on treatment 7 months (range 1.6 – 18+)
- 2.15 – 6 mg cohorts: All patients with at least 9 months of follow up; median responder time on treatment 12 months (range 6 – 18+)
- 12 and 24 mg step dose cohorts: Enrollment ongoing; median responder time on treatment 3 months (range 1.6 – 7+)

PHARMACODYNAMICS: CYTOKINES

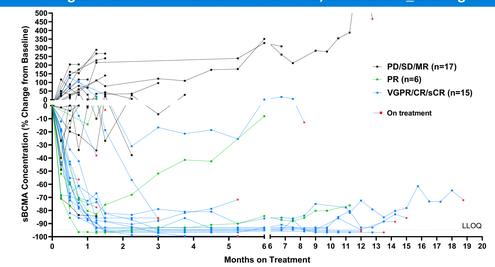
Median Post-Infusion Cytokine Concentrations in the 12 and 24 mg Step Dosing Cohorts



- In step dosing, the cytokine spikes induced by target doses were lower than those induced by the priming dose

PHARMACODYNAMICS: SOLUBLE BCMA

Changes in sBCMA Concentration Over Time, Dose Levels ≥ 2.15mg



- Majority of responders had decreases in sBCMA by week 2 on treatment
- sBCMA remained undetectable at 9 months in many responders who achieved ≥VGPR

SUMMARY

- **HPN217 is well tolerated with a low incidence of CRS**
  - Low-grade CRS in 29% of patients across highest step dose regimens; seen primarily in earliest doses
  - No ≥ Grade 3 CRS events
  - No ICANS
- **Step dosing enabled increases in dose level while maintaining tolerability**
  - No increase of CRS at higher dose levels (12 and 24 mg)
  - Use of priming dose reduced cytokine spikes at target dose
  - No DLTs observed across all step dose cohorts; MTD has not been reached
- **HPN217 is active across a wide dose range (2.15 to 24 mg) in heavily pre-treated patients**
  - 77% (10/13) ORR observed across highest doses (12 and 24 mg)
  - Responses occurred early, were durable, and deepened over time
  - Majority of responders had decreases in sBCMA by week 2 on treatment, deepening over time
- **Continued evidence of clinical activity and tolerable safety profile support ongoing dose optimization and further clinical development**
  - Dose-proportional increase in drug exposure with a median half-life of 66 hours, supporting less frequent dosing regimens
  - Assessment of Q2W dosing schedule is ongoing

ACKNOWLEDGEMENTS

Thank you to our clinical site staff, patients, and their families who continue to make this trial possible

Publication #3240 Note: Unaudited patient data based on entries provided in open clinical database as of 10/17/2022, subject to change **Presented at the American Society of Hematology Annual Meeting; December 11, 2022**

Contact the author at aabdallah@kumc.edu for questions or comments