Ongoing 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 (MM)

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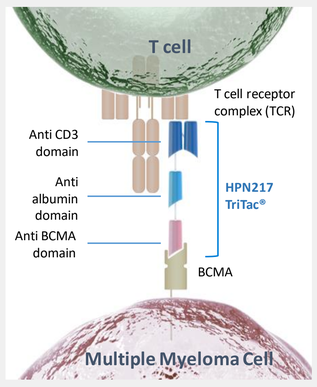
BACKGROUND

HPN217 Mechanism of Action



- HPN217 is a BCMA-targeting T cell engaging construct 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

INTERIM RESULTS

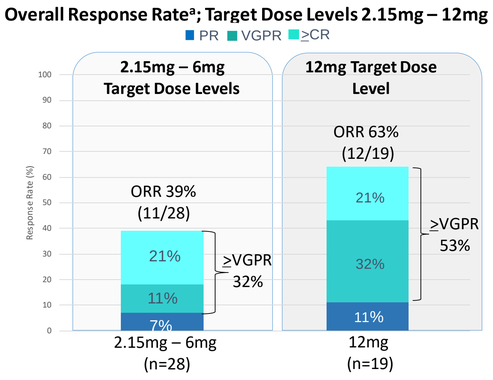
- **Enrollment recently completed, N = 97**
- **12mg is the highest target dose level with ≥6 months follow up**

Disposition	All Patients (N=97)
Treatment Ongoing, n (%)	33 (34%)
Median duration of treatment, weeks (range)	11.1 (0.1 - 119)
Discontinued Treatment, n (%)	64 (66%)
Disease Progression	52 (54%)
Adverse Event [a]	7 (7%)
Death [b]	2 (2%)
Other [c]	3 (3%)

[a] One patient (2.86mg) discontinued due to a study treatment related TEAE of G4 ALT/AST increase concurrent with G1 CRS; all other patients' AEs leading to study discontinuation were not related to study treatment; [b] One patient (2.15mg) died of general physical health deterioration (not treatment related) and one patient (24mg) died of traumatic subdural hematoma (treatment related); [c] Discontinued due to investigator discretion or patient request

RESPONSE ASSESSMENT

Overall Response Rate[a]; Target Dose Levels 2.15mg – 12mg

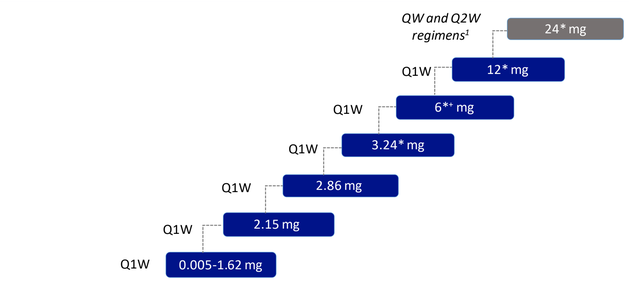


[a] Confirmed responses per investigator assessment, safety population includes all patients who had received ≥1 dose of HPN217

- 12mg cohorts showed improved efficacy compared to lower dose cohorts
- 13/23 responders remain on study treatment with sustained response

HPN217-3001 TRIAL DESIGN

Dose Escalation and Optimization



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

[1]*Cohorts recently enrolled with maturing data*

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

SAFETY

Treatment-Emergent Adverse Events (Regardless of Relationship), >20%

Adverse Event[a]	All Patients, % (N=97)		12mg Target Dose, % (N=19)	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Anemia	43 (44.3%)	32 (33%)	9 (47.4%)	6 (31.6%)
Fatigue	37 (38.1%)	5 (5.2%)	9 (47.4%)	1 (5.3%)
CRS[b]	29 (29.9%)	2 (2.1%)	3 (15.8%)	0
Cough	29 (29.9%)	0	9 (47.4%)	0
Nausea	27 (27.8%)	0	4 (21.1%)	0
Diarrhea	26 (26.8%)	1 (1.0%)	5 (26.3%)	0
Headache	25 (25.8%)	0	4 (21.1%)	0
Hypokalemia	23 (23.7%)	4 (4.1%)	7 (36.8%)	2 (10.5%)
Hypophosphatemia	23 (23.7%)	4 (4.1%)	6 (31.6%)	0
AST increased	22 (22.7%)	11 (11.3%)	4 (21.1%)	0
Arthralgia	21 (21.6%)	1 (1.0%)	2 (10.5%)	0
Neutrophil Ct. Dec.	21 (21.6%)	18 (18.6%)	4 (21.1%)	4 (21.1%)
Back Pain	20 (20.6%)	1 (1.0%)	2 (10.5%)	0

Dose Limiting Toxicity (n=2)[c]

- Fixed Dose: 2.86mg (n=2): Transaminitis (Gr 3, n=1; Gr 4, n=1)
- Step Dose: No DLTs; MTD not reached

Treatment related Neurologic/Psych Events[d]

- Reported in 20 (21%) patients
- All events G1 or G2
- Most common: Headache (n=9), ICANS (n=3); Confusion (n=2), Paresthesia (n=2)
- ICANS and confusion events were associated with CRS; none reported at the 12mg dose level.

Infections (regardless of relationship)[e]

- Reported in 53 (55%) patients; Gr ≥ 3 in 23 (24%) patients
- Most common: Pneumonia[f] (n=13), urinary tract infection[f] (n=10), COVID-19 (n=8), sepsis[f] (n=7), upper respiratory tract infection[f] (n=7), conjunctivitis (n=6), sinusitis[f] (n=6), skin infection[f] (n=5), and rhinovirus infection (n=5)

Grade 5 Events

- 1 treatment related G5 AE of traumatic subdural hematoma associated with CRS and thrombocytopenia (24 mg dose)

[a] Grading per CTCAE v5.0; [b] Cytokine release syndrome (CRS) Grading per ASTCT 2019 Criteria; [c] DLTs identified for dose escalation decisions; [d] SOC nervous system disorders and psychiatric disorders; [e] SOC infections and infestations; [f] includes grouped terms

TIME ON TREATMENT

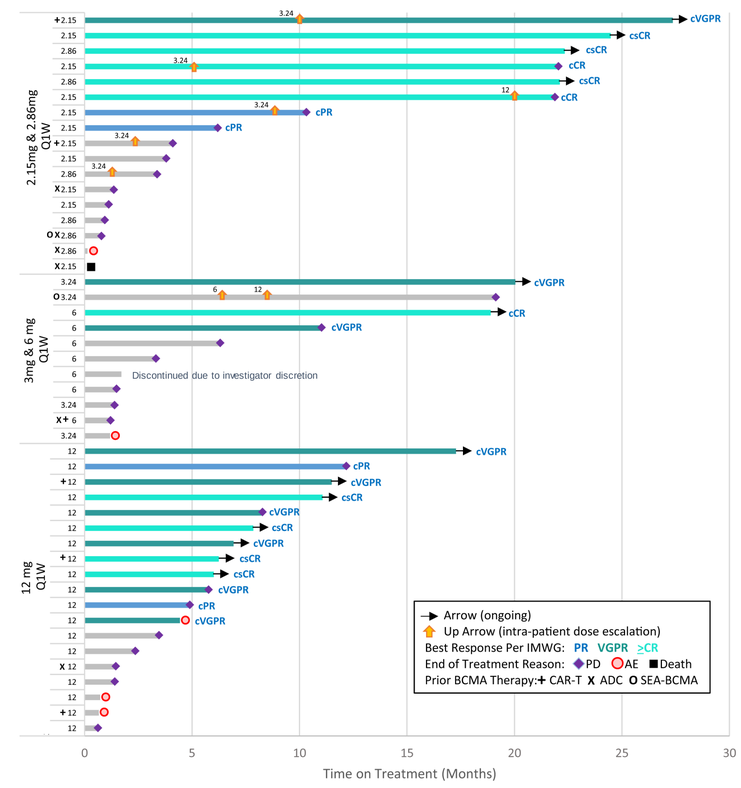
Prolonged time on treatment observed in responders

- 2.15 – 6mg cohorts: Median responder time on treatment: 21.8 months (10.4-27.5+)
- 12mg cohorts:
  - Median responder time on treatment: 8.3 months (6.0-17.3+)
  - 2 responders received prior BCMA CAR-T therapy

Time on treatment and duration of response data continue to mature

Dose levels 2.15 mg – 12 mg

All patients have at least 6 months of follow up



STUDY POPULATION

Baseline Characteristics and Prior Systemic Therapies

	All Patients (N = 97)	12mg Target Dose (N=19)
Age (yr), Median (range)	69 (38 – 85)	69 (46 – 83)
Age ≥ 75 years, n (%)	23 (23.7%)	7 (36.8%)
Time Since Initial MM Diagnosis (yr), Median (range)	6.8 (0.6 - 20.2)	4.8 (0.6 - 12.1)
Baseline sBCMA (ng/mL), Median (range)	239.7 (27.2 - 2444.2)	226.4 (54.4 - 2363.4)
ECOG, n (%)		
0, 1, 2, Missing	23 (23.7%), 71 (73.2%), 2 (2.1%), 1 (1.0%)	1 (5.3%), 17 (89.5%) 1 (5.3%), 0 (0%)
Revised ISS Stage at Study Entry, n (%)		
I, II, III, Missing	24 (24.7%), 32 (33%), 37 (38.1%), 4 (4.1%)	2 (10.5%), 10 (52.6%), 7 (36.8%), 0 (0%)
Cytogenetic Status, n (%)		
High risk[a]	18 (19%)	4 (21%)
Standard risk or none	48 (49%)	8 (42%)
Unknown	31 (32%)	7 (37%)
Plasmacytoma at baseline, yes (%)	10 (10.3%)	1 (5.3%)
Prior Systemic Regimens, Median (range)	6 (2 – 19)	5 (2 – 9)
Prior Transplantation, n (%)	70 (72.2%)	13 (68.4%)
Exposure Status, n (%)		
Triple-class[b] exposed	96 (99%)[e]	19 (100%)
Penta-drug[c] exposed	63 (64.9%)	11 (57.9%)
BCMA exposed	19 (19.6%)[f]	4 (21.1%)[f]
Refractory Status, n (%)		
Triple-class[b] refractory[d]	75 (77.3%)	14 (73.7%)
Penta-drug[c] refractory[d]	36 (37.1%)	6 (31.6%)
BCMA refractory	13 (13.4%)	1 (5.3%)
Last Line of Therapy	83 (85.6%)	14 (73.7%)

[a] t(4;14), t(14;16), del(17p); [b] IMiD, PI, and anti-CD38; [c] At least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 antibody; [d] No response to regimen or discontinued regimen due to progression, adapted from Rajkumar et al (Blood 2011); [e] one patient missing prior regimen data; [f] includes one patient with agent entered after data extract of 12-Aug

Note: Unaudited patient data are based on entries provided in open clinical database as of 08/12/2023

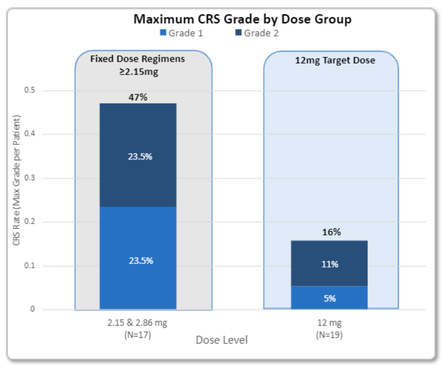
Contact the author at sumit.madan@bannerhealth.com for questions or comments

CYTOKINE RELEASE SYNDROME

CRS Summary

Parameter	All Patients (N=97)	12mg Target Dose (N=19)
Patients with CRS[a], n (%)	29 (29.9%)	3 (15.8%)
Grade 1	16 (16.5%)	1 (5.3%)
Grade 2	11 (11.3%)	2 (10.5%)
Grade 3[b]	2 (2.1%)	0
Patients with ≥ 1 CRS event	7 (7.2%)	2 (10.5%)
Received supportive measures for CRS, n (%)		
Tocilizumab	9 (9.3%)	2 (10.5%)
Dexamethasone	1 (1.0%)	0

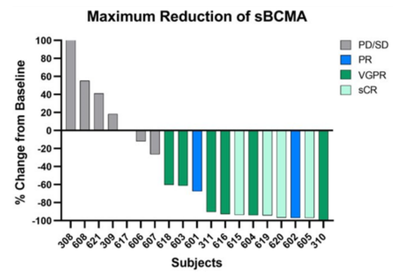
[a] Grading per ASTCT 2019 Criteria; [b] No G4/G5 CRS



Step dose approach with 12 mg target dose resulted in lower frequency of CRS compared to highest fixed dose cohorts

PHARMACODYNAMICS: SOLUBLE BCMA

Maximum Reduction of sBCMA During Treatment in Cohorts with 12 mg Target Dose



- Reduction in sBCMA during treatment is associated with clinical responses
- Majority of responders had decrease in sBCMA as early as 1 month on treatment

SUMMARY

- **HPN217-3001 enrolled heavily pre-treated patients with and without prior exposure to BCMA-targeted treatment**
- **Dose escalation has completed; Target dose MTD was not reached**
- **HPN217 was well tolerated and demonstrated clinical activity at doses of ≥ 2.15mg**
- **At 12mg target dose level, clinical activity and tolerable safety profile support further clinical development**
  - CRS was reported in 16% of patients; all events Grade 1-2
  - No events of ICANS reported
  - 63% ORR; 53% with VGPR or better
  - Responses were durable and occurred early
- **Follow-up of 24 mg dose cohorts is ongoing**
- **Dose optimization and duration of response data continue to mature**

ACKNOWLEDGEMENTS

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Poster #292

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