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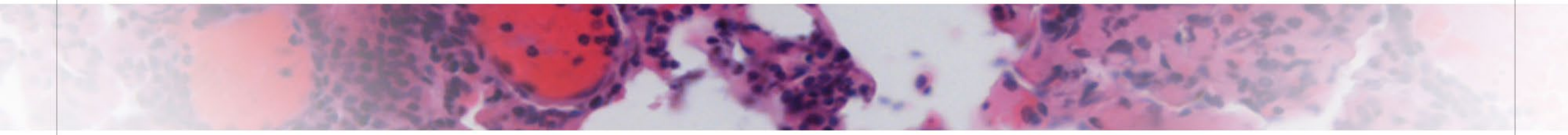

Results from the Completed Dose Escalation Portion of the Phase 1 Study of HPN217, a Half-Life Extended Tri-Specific T Cell Activating Construct (TriTAC®) Targeting B Cell Maturation Antigen (BCMA) for Relapsed/Refractory Multiple Myeloma (MM)

Authors

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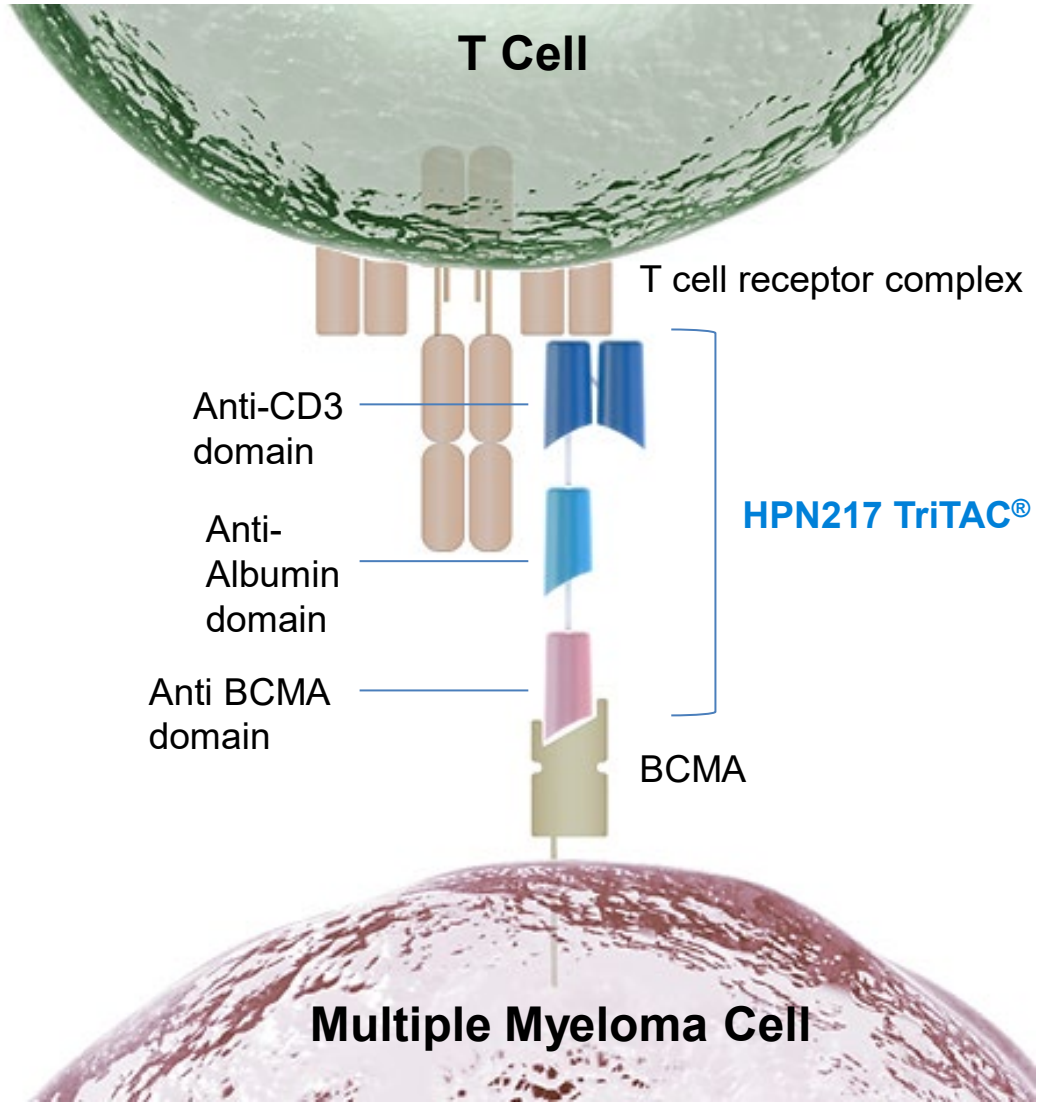
Background

- HPN217 is a BCMA-targeting T cell engager
- Redirects T cells to kill BCMA expressing multiple myeloma cells
- 3 binding domains
  - BCMA (for multiple myeloma cell binding)
  - CD3 (for T cell engagement)
  - Albumin (for half-life extension)
- Absence of Fc domain avoids Fc receptor binding
  - Minimizes T cell activation in the absence of Target cells
  - Designed to increase the therapeutic window
- Here we present the results from HPN 217-3001, the first in-human study



HPN217-3001 Trial Design

Primary Objectives

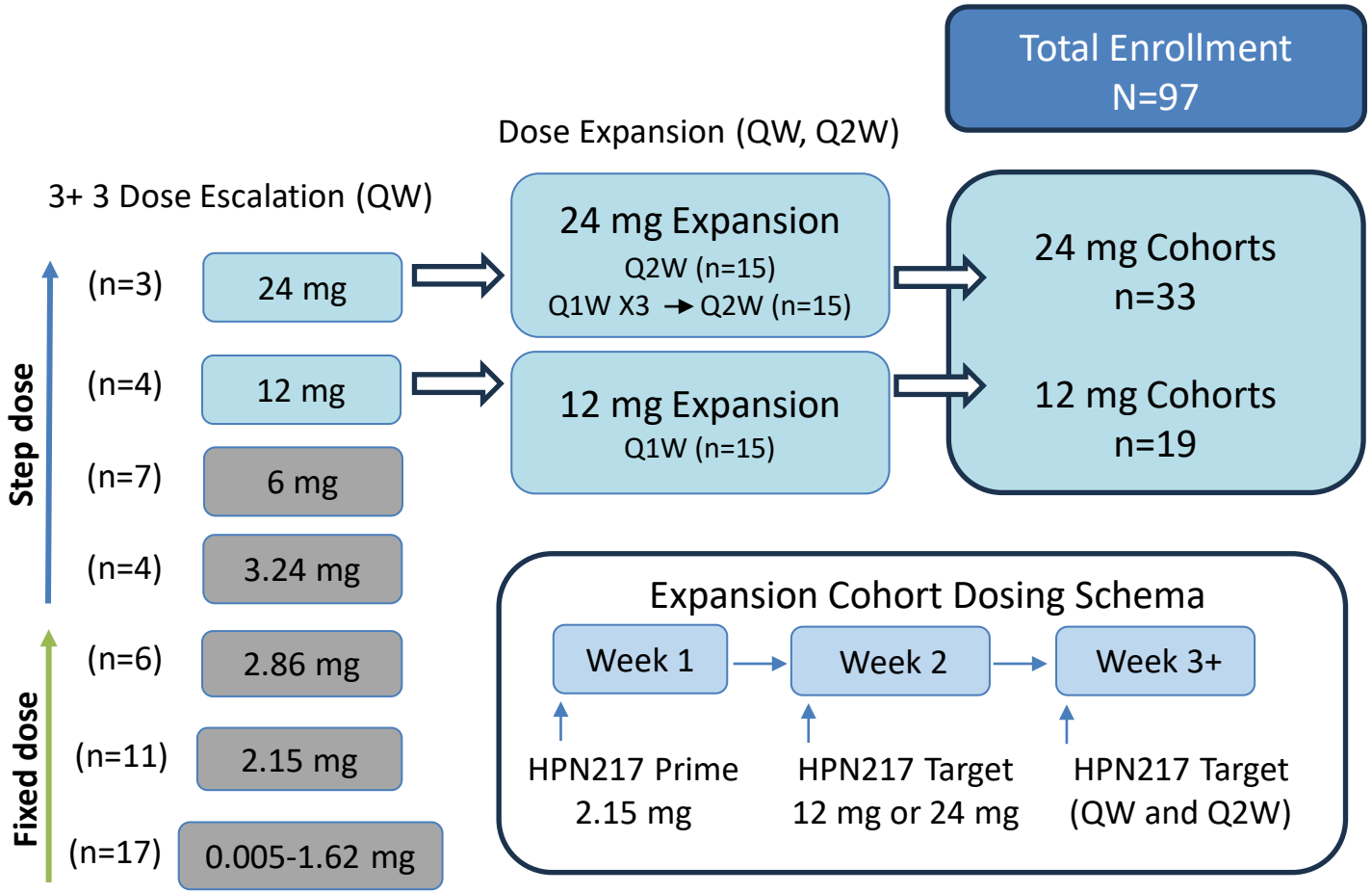
- Safety and tolerability
- Estimate MTD and/or identify RP2D

Key Secondary Objective

- Preliminary efficacy per IMWG

Key Eligibility Criteria

- Relapsed/refractory multiple myeloma
- ≥ 3 prior therapies including a PI, IMiD, an anti-CD38 antibody
- Prior treatment with BCMA targeted therapies allowed



Study Population

Baseline Characteristics	All Patients (N = 97)	12mg Target Dose (N=19)	24mg Target Dose (N=33)
Age (yr), Median (range)	69 (38-85)	69 (46-83)	68 (51-85)
Age ≥ 75 years, n (%)	23 (24)	7 (37)	7 (21)
Time Since Initial MM Diagnosis (yr), Median (range)	6.8 (0.6 - 20.2)	4.8 (0.6 - 12.1)	6.8 (1.0-19.4)
Baseline sBCMA (ng/mL), Median (range)	249 (0 – 3000)	204 (0 – 2363)	236 (27 - 1345)
ECOG, n (%)			
0	23 (24)	1 (5)	9 (27)
1	71 (73)	17 (90)	23 (70)
2	2 (2)	1 (5)	1 (3)
Missing	1 (1)	0	0
Revised ISS Stage at Study Entry, n (%)			
I	24 (25)	2 (11)	9 (27)
II	32 (33)	10 (53)	13 (39)
III	37 (38)	7 (37)	8 (24)
Missing	4 (4)	0	3 (9)
Cytogenetic Status, n (%)			
High risk [a]	18 (19)	4 (21)	8 (24)
Standard risk or none	49 (51)	7 (37)	21 (64)
Unknown	30 (31)	8 (42)	4 (12)

	All Patients (N = 97)	12mg Target Dose (N=19)	24mg Target Dose (N=33)
Plasmacytoma at baseline, yes (%)	10 (10)	1 (5)	5 (15)
Prior Systemic Regimens, Median (range)	6 (2-19)	5 (2-9)	4 (2-14)
Prior Transplantation, n (%)	71 (73)	13 (68)	20 (61)
Exposure Status, n (%)			
Triple-class[b] exposed	97 (100)	19 (100)	33 (100)
Penta-drug[c] exposed	64 (66)	11 (58)	18 (55)
BCMA Exposed	20 (21)	4 (21)	5 (15)
Relapsed/Refractory Status, n (%)			
Triple-class[b] refractory[d]	76 (78)	14 (74)	23 (70)
Penta-drug[c] refractory[d]	37 (38)	6 (32)	9 (27)
BCMA refractory	14 (14)	1 (5)	3 (9)
Last Line of Therapy	85 (88)	14 (74)	29 (88)

[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)

Note: Unaudited patient data are based on entries provided in open clinical database as of 10/17/23

Adverse Events in ≥ 20% of Subjects Regardless of Relationship

Adverse Event[a]	All Patients (N=97)		12mg Target Dose (N=19)		24mg Target Dose (N=33)	
	All Grades	≥Gr 3	All Grades	≥Gr 3	All Grades	≥Gr 3
Hematologic n(%)						
Anaemia[b]	43 (44)	33 (34)	9 (47)	6 (32)	11 (33)	9 (27)
Neutropenia[b]	39 (40)	33 (34)	9 (47)	9 (47)	15 (46)	11 (33)
Thrombocytopenia[b]	27 (28)	17 (18)	6 (32)	4 (21)	10 (30)	6 (18)
Non-hematologic n(%)						
Fatigue	39 (40)	6 (6)	9 (47)	1 (5)	11 (33)	3 (9)
Cough	30 (31)	0	9 (47)	0	11 (33)	0
CRS [c]	29 (30)	2 (2)	3 (16)	0	14 (42)	2 (6)
Nausea	29 (30)	0	4 (21)	0	13 (39)	0
Arthralgia	26 (27)	1 (1)	3 (16)	0	13 (39)	0
Diarrhoea	26 (27)	1 (1)	5 (26)	0	12 (36)	0
Headache	25 (26)	0	4 (21)	0	11 (33)	0
Hypokalemia	23 (24)	4 (4)	7 (37)	2 (11)	7 (21)	0
Hypophosphatemia	23 (24)	4 (4)	6 (32)	0	11 (33)	0
Transaminases increased[b]	25 (26)	15 (16)	5 (26)	1 (5)	10 (30)	7 (21)
Back pain	21 (22)	1 (1)	3 (16)	0	9 (27)	0

[a] Grading per CTCAE v5.0; [b] Includes grouped terms; [c] Cytokine release syndrome (CRS) Grading per ASTCT 2019 Criteria

Note: Unaudited patient data are based on entries provided in open clinical database as of 10/17/23

Additional Adverse Events of Interest

Dose Limiting Toxicity

- Fixed Dose Escalations Cohorts
  - 2.86 mg (n=2): Gr 3-4 Transaminitis
  - ➢ Fixed Dose MTD: 2.15 mg
- Step Dose Escalation Cohorts
  - No DLTs; MTD not reached

Neurological Toxicity[a]

- n= 21 (22%)- All Grade 1-2
- ICANS (n=3); All Grade 1
  - 2.15 mg (n=1)
  - 24 mg (n=2)
- Other
  - Headache (n=9), Confusional state (n=2), Paresthesia (n=2), Peripheral neuropathy (n=2), Insominia, Neuro symptom, Akathisia, Hypoasthesia, Dysgeusia, Dizziness, Tremor (n=1 each)

Infections

- All grades (n=57 [59%])
- ≥ Grade 3 (n= 24 [25%])
  - Pneumonia[b] (n=10), Sepsis[b] (n=8), Influenza/parainfluenza (n=3), Bacteremia (n=2), Urinary tract infection, Pyelonephritis, C.diff, Medical device infection (n=1 each)

Grade 5 AEs

- Treatment related (n=1)
  - Traumatic subdural hematoma (in setting of CRS, ICANS, and thrombocytopenia)
- Not treatment related (n=4)
  - Myeloma progression (n=2), Global health deterioration (n=1), Cardiac event (n=1; occurred after PD and initiation of subsequent therapy)

[a] Related AEs in neuro/psych System Organ Class, [b] Grouped term

Note: Unaudited patient data are based on entries provided in open clinical database as of 10/17/23

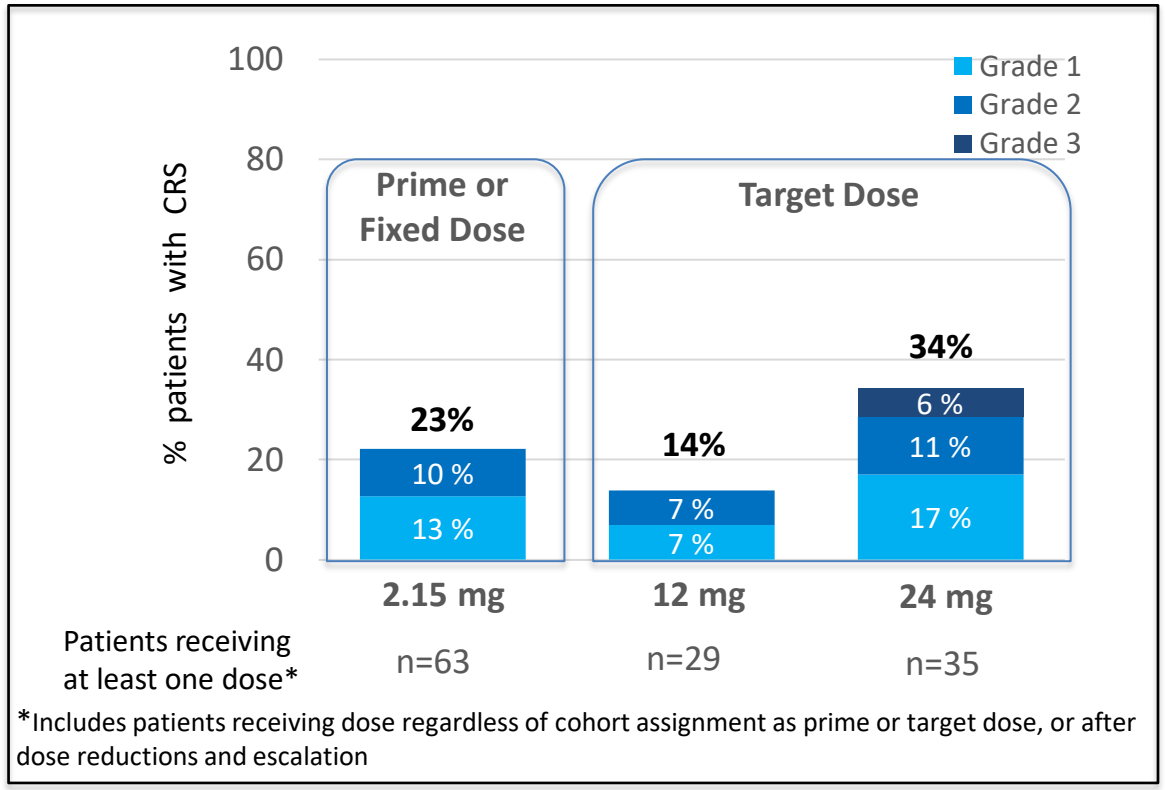
Cytokine Release Syndrome

CRS by Dose Cohort

	All Patients (N=97)	12 mg Cohorts (N=19)	24 mg Cohorts (N=33)
Patients with CRS, n (%)	29 (30)	3 (16)	14 (42)
Grade 1	16 (17)	1 (5)	7 (21)
Grade 2	11 (11)	2 (11)	5 (15)
Grade 3*	2 (2)	0	2 (6)
Patients with > 1 CRS event	8 (8)	2 (11)	5 (15)
Received supportive measures for CRS, n (%)			
Tocilizumab	9 (9)	2 (11)	5 (15)
Dexamethasone	1 (1)	0	0

*No G4/G5 CRS

CRS by Most Recent Dose Received

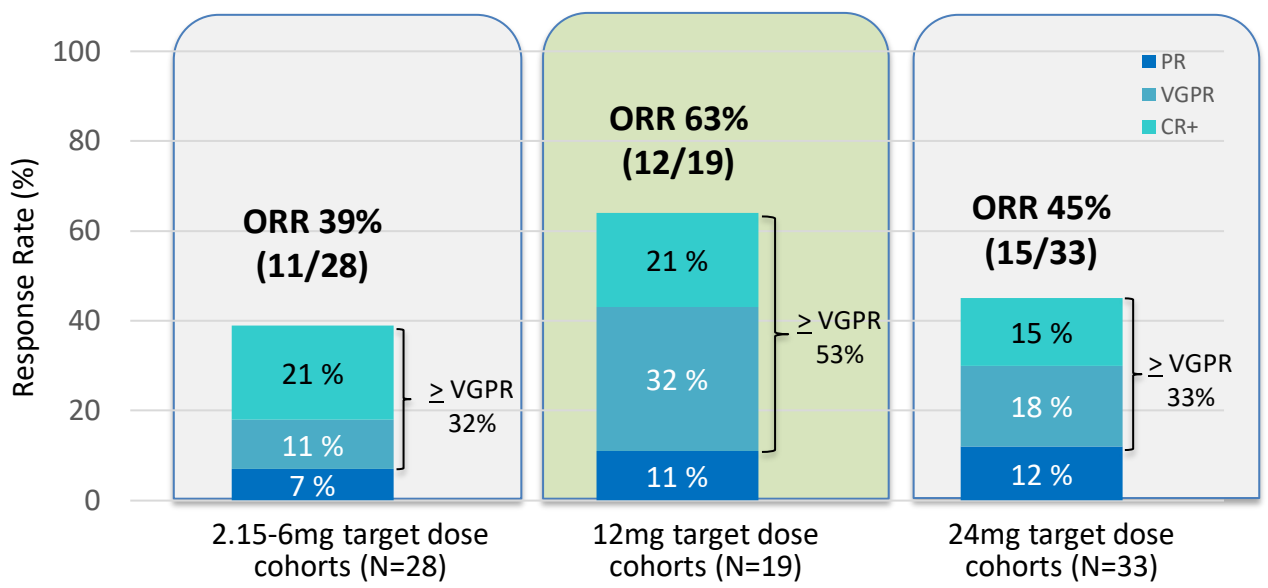


*Includes patients receiving dose regardless of cohort assignment as prime or target dose, or after dose reductions and escalation

12 mg target dose associated with lowest rates of CRS

Note: Unaudited patient data are based on entries provided in open clinical database as of 10/17/23

Response Assessment



[a] Efficacy evaluable population includes all patients who had received ≥1 dose of HPN217 and opportunity for first disease assessment at C1D15

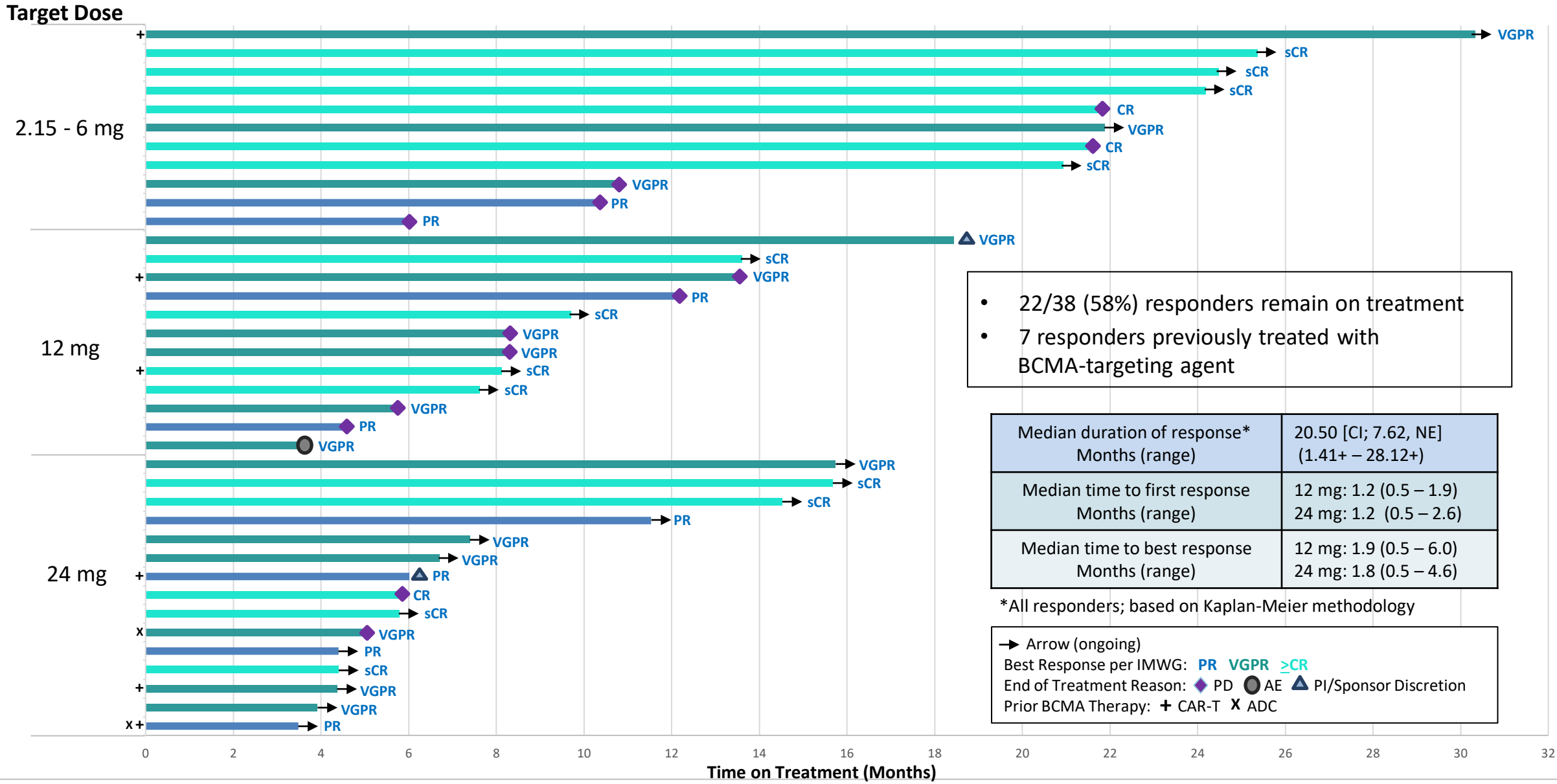
12 mg cohorts showed numerically higher response rates compared to lower dose cohorts and 24 mg cohorts

- 12 mg Target dose cohorts
  - ORR: 63% (95% CI: 38.4, 83.7)
  - ≥ VGPR 53%
- 24 mg Target dose cohorts
  - ORR: 45% (95% CI: 28.1, 63.6)
  - ≥ VGPR 33%
  - 1 additional PR after data cut increases ORR to 48%

Note: Updated responses in 24 mg cohorts post data cut (not reflected graph): One patient with PR (previously SD) and one patient with sCR (previously VGPR)

Note: Unaudited patient data are based on entries provided in open clinical database as of 10/17/23

Responder Time on Treatment (N=38)



- 22/38 (58%) responders remain on treatment
- 7 responders previously treated with BCMA-targeting agent

Median duration of response* Months (range)	20.50 [CI; 7.62, NE] (1.41+ – 28.12+)
Median time to first response Months (range)	12 mg: 1.2 (0.5 – 1.9) 24 mg: 1.2 (0.5 – 2.6)
Median time to best response Months (range)	12 mg: 1.9 (0.5 – 6.0) 24 mg: 1.8 (0.5 – 4.6)

*All responders; based on Kaplan-Meier methodology

→ Arrow (ongoing)
Best Response per IMWG: PR VGPR ≥CR
End of Treatment Reason: ◆ PD ● AE ▲ PI/Sponsor Discretion
Prior BCMA Therapy: + CAR-T X ADC

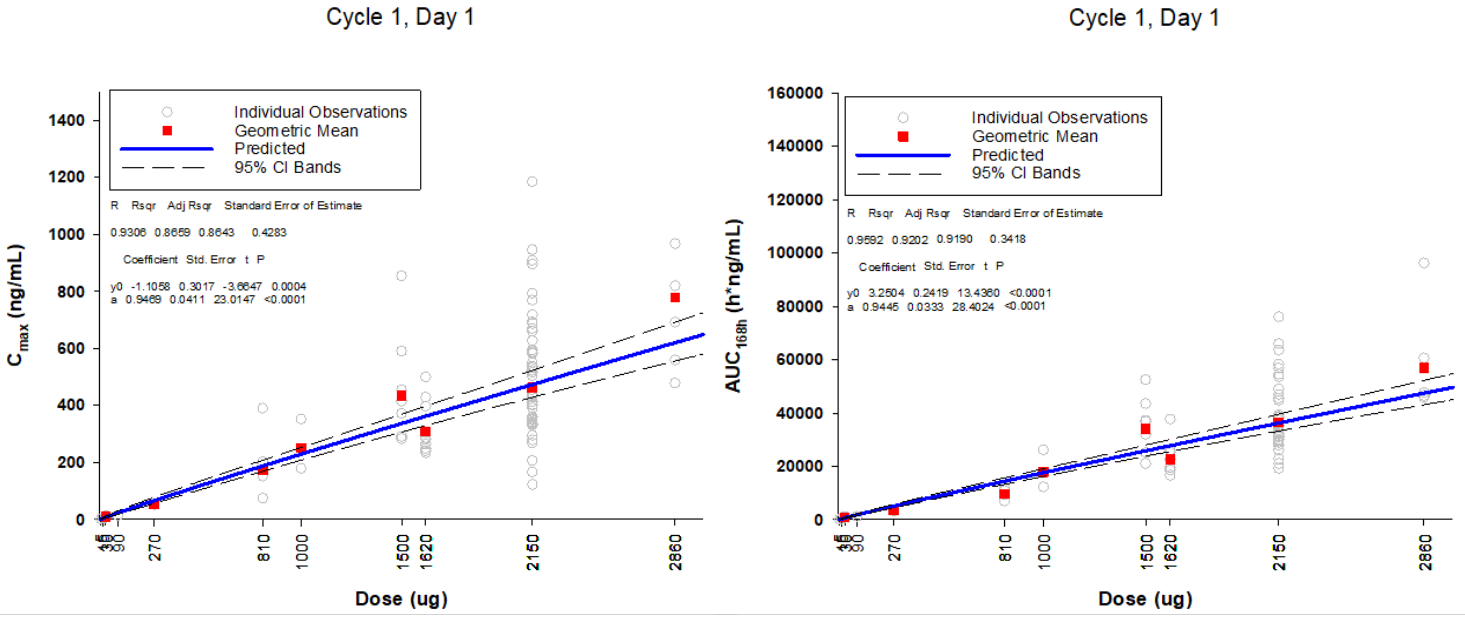
Note: Updated responses in 24 mg cohorts post data cut (not reflected graph): One patient with PR (previously SD) and one patient with sCR (previously VGPR)

Pharmacokinetics and Pharmacodynamics

Linear PK; Step Dosing Reduces Post-Infusion Cytokine Spikes

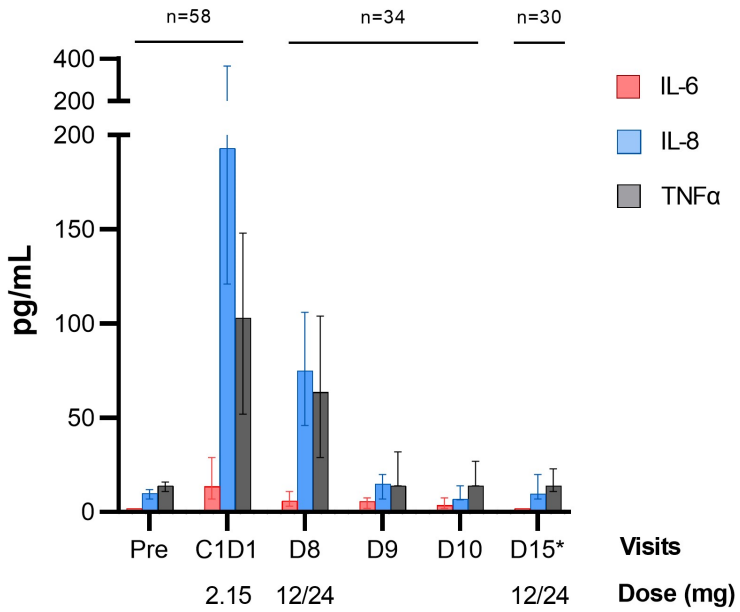
- HPN217 exhibited dose proportional PK with median $t_{½}$ 68 hours
  - *Similar PK between 12 mg Q1W & 24 mg Q2W dose groups*
- No apparent impact of ADA (6/86 patients ~7%) on PK

Dose Proportionality Assessment of HPN217 Cmax and AUC_{168h}



- Cytokine spikes following target doses lower than after priming doses
- Step dosing strategy enables administration of higher target doses without increased risk of CRS

Changes in Cytokine Levels in Response to 2.15/12 mg or 2.15/24 mg Step-dosing



Conclusions

- **HPN217 was well tolerated and demonstrated clinical activity at doses of ≥ 2.15 mg in heavily pre-treated patients including patients with prior exposure to BCMA-targeted therapy**

- **Comparison between the highest dose levels administered indicates optimal activity and safety profile at the 12 mg dose**
  - CRS was reported in only 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
  - 12 mg has been declared the RP2D

- **The data supports further clinical development using a 12 mg target dose with a step-up approach**

Acknowledgements

- Thank you to the patients who participated in this study and their caregivers; and all the investigators and their clinical site staff who continue to make this trial possible

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