Interim results of an ongoing Phase 1/2 study of HPN328, a tri-specific half-life extended DLL3-targeting T-cell engager, in patients with small cell lung cancer and other neuroendocrine cancers

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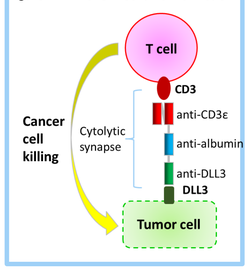
BACKGROUND

- HPN328 is a delta like canonical Notch ligand 3 (DLL3)-targeting T-cell engager derived from the TriTAC® platform
- HPN328 contains 3 binding domains, engineered to redirect T cells to kill DLL3-expressing cancer cells:
  - anti-DLL3 (for target engagement)
  - anti-albumin (for half-life extension)
  - anti-CD3 (for T-cell engagement)
- HPN328 is constructed as a small, globular protein (~50kDa) to enable efficient solid tumor penetration with prolonged half-life
- HPN328 binds monovalently to CD3 and DLL3, minimizing non-specific T-cell activation

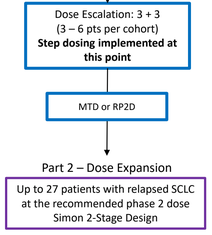
Figure 1. HPN328 Mechanism of Action



TRIAL DESIGN

Dose Escalation / Expansion, Safety & PK Study in patients with small cell lung cancer (SCLC) and other neuroendocrine malignancies

Figure 2. HPN328-4001 Trial Schema



- **Target population**
  - SCLC relapsed after platinum chemotherapy
  - Other malignancies with high grade neuroendocrine features relapsed/ refractory to Standard of Care (SOC) or no SOC available
- **Trial objectives**
  - Assess safety and tolerability
  - Determine RP2D and/or MTD
  - Characterize PK and PD
  - Evaluate preliminary anti-tumor activity
- **Dosing and administration**
  - Once weekly IV infusion of HPN328
  - Premedication with dexamethasone, acetaminophen, and histamine receptor blockers at initial dose(s)
- **Assessments**
  - Imaging every 9 weeks (RECIST v1.1)
  - Retrospective analysis of tumor tissue for DLL3 expression by IHC

BASELINE CHARACTERISTICS

- As of April 21st, 2022, 18 patients were enrolled and treated with HPN328

Table 1. Baseline Characteristics and Demographics

Age (Years)	
Median	61
Range	43-73
Race	n (%)
White	17 (94%)
Asian	1 (6%)
ECOG	n (%)
0	9 (50%)
1	9 (50%)

Diagnosis	n (%)
SCLC	11 (61%)
NEPC	2 (11%)
Other NENs[1]	5 (28%)
Baseline Brain / Liver metastases	
Brain metastases	7 (39%)
Liver metastases	9 (50%)
Best Response to Immediate Prior Therapy	
Progressive Disease	8 (44%)
Stable Disease	4 (22%)
Partial Response	1 (6%)
Unknown	5 (28%)

# Prior Therapies	n (%)
1	5 (28%)
2	5 (28%)
3	3 (17%)
4	3 (17%)
5	2 (11%)
Immune checkpoint inhibitor (αPD-1/αCTLA4, αPD-L1)	14 (78%) [SCLC: 11 (100%)]

NEPC = neuroendocrine prostate cancer (de-novo or treatment emergent)
NEN = neuroendocrine neoplasm
[1] *Other NENs: Retroperitoneal (unknown primary), Colon, Pancreas, Thymic, Bladder*

ADVERSE EVENTS

- Maximum-tolerated dose (MTD) has not been reached
- No Dose Limiting Toxicities (DLTs) have been observed
- Grade 1-2 CRS reported in 4 (22%) patients; No Grade ≥3 CRS
- No ICANS
- No patients discontinued study treatment due to adverse events

Table 2. Subject Incidence of Treatment Emergent Adverse Events (TEAEs) by Grade [a]

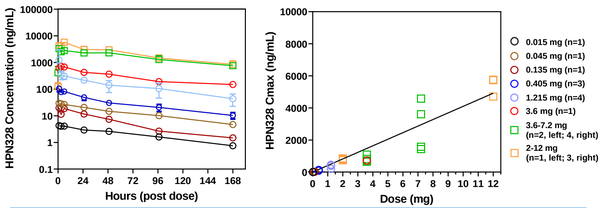
Adverse Events	All Grades, n (%)	Grade ≥3, n (%)
Any treatment-emergent AE	18 (100%)	10 (56%)
Any treatment-related AE	15 (83%)	1 (6%)[b]
Treatment-Emergent AEs in ≥15% of subjects (MedDRA preferred term)		
Dysgeusia	7 (39%)	-
Fatigue	7 (39%)	-
Hypotension	7 (39%)	1 (6%)
Constipation	6 (33%)	-
Hyponatraemia	6 (33%)	1 (6%)
Nausea	6 (33%)	-
Vomiting	6 (33%)	-
Anaemia	5 (28%)	2 (11%)
Chills	5 (28%)	-
Pyrexia	5 (28%)	-
Alanine aminotransferase increased	4 (22%)	1 (6%)
Aspartate aminotransferase increased	4 (22%)	1 (6%)
Cytokine release syndrome[c]	4 (22%)	-
Diarrhoea	3 (17%)	-
Dry skin	3 (17%)	-
Dyspnoea	3 (17%)	-
Headache	3 (17%)	-
Neutrophil count decreased / Neutropenia	3 (17%)	2 (11%)
Weight decreased	3 (17%)	-

[a] Grading per CTCAE v5.0, except Cytokine Release Syndrome (Grading per ASTCT 2019)
[b] Grade-3 treatment-related anemia reported in 1 patient
[c] Grade-2 CRS events occurred following C1D1 doses in 2/4 patients treated at 1.215mg, and in 1 patient receiving 3.6mg via intra-patient dose escalation. 1/4 patients treated with 3.6mg C1D1 experienced Grade-1 CRS.

PHARMACOKINETICS

- HPN328 exhibited linear PK, with dose-proportional increases in exposures at 0.135 to 12 mg
- Median half-life is 71 hours

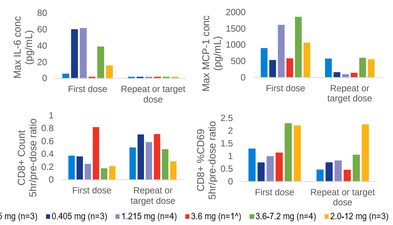
Figure 3. Mean (SD) HPN328 Concentration-Time Profile (left) and Individual C_{max} by Dose (right)



PHARMACODYNAMICS

- T-cell margination and activation was observed, consistent with target engagement.
- Small, transient increases in serum IL-6 and MCP-1 were observed up to 24 hours post dose.
- "First dose" effect observed relative to repeat or target dose:
  - More T-cell margination (as evidenced by decrease in peripheral T-cells)
  - More T-cell activation
  - Higher mean cytokine/chemokine concentrations

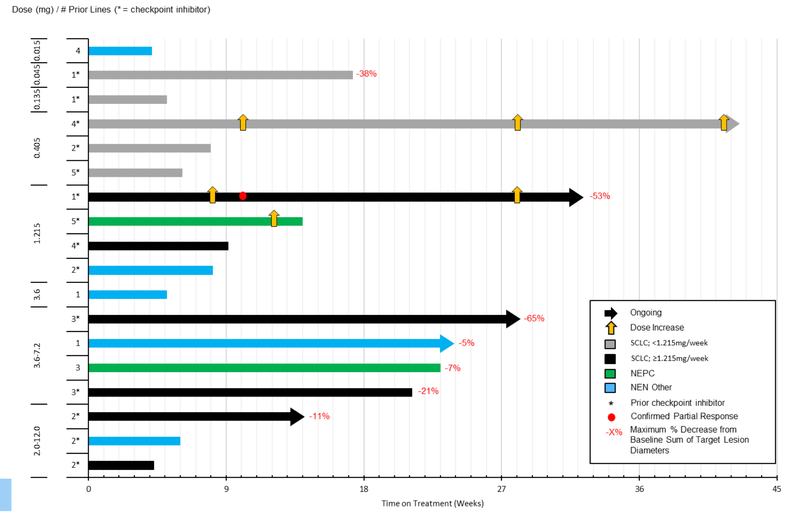
Figure 4. Mean Peripheral IL-6 (top left) and MCP-1 (top right) Concentrations, T-cell Margination (CD8+ count, bottom left) and T-cell Activation (CD8+ %CD69+, bottom right) after First and Repeat or Target Dose of HPN328



TIME ON TREATMENT

- Treatment duration ranged from 4.1 to 41.4 weeks
  - As of April 21st 2022, 5 patients on treatment (14.1, 22.1, 29, 33.1, 41.4 weeks and ongoing)
- 6/18 patients (33%) on treatment for ≥20 weeks
- Step-dosing initiated for target doses higher than 3.6 mg / week
- Highest target dose evaluated to-date: 12 mg / week

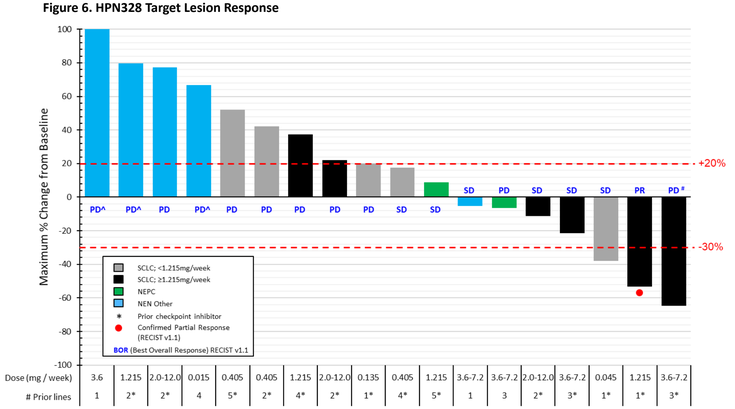
Figure 5. HPN328 Time on Treatment



TARGET LESION RESPONSE

- 7 of 18 (39%) had any decrease in sum of target lesion diameters (5 SCLC, 1 NEPC, 1 NEN [thymic atypical carcinoid])
- 1 Confirmed Partial Response (SCLC, 2L) ongoing treatment at 32 weeks
- 3 of 11 (27%) SCLC patients across all doses had >30% decrease in sum of target lesion diameters
- 4 of 6 (67%) SCLC patients treated at ≥1.215mg/week had decrease in sum of target lesion diameters
- 6 of 18 (33%) patients with best overall response of stable disease (4 SCLC, 1 NEPC, 1 NEN [thymic atypical carcinoid])

Figure 6. HPN328 Target Lesion Response



NEN Other includes: Pancreas, Retroperitoneal, Colon, Thymus, Bladder
New asymptomatic brain metastases identified at week 2. Overall response = PD; Target lesion response = PR
^ Retrospective IHC analysis of archival biopsies demonstrated 0% cells positive for DLL3 in 3/5 NEN patients

PATIENT PROFILES

Patient Case 1

- 61-year-old female with extensive-stage SCLC
- 1 prior line of treatment
- 100% cells positive for DLL3 on IHC analysis of archival biopsy
- Initiated treatment with 1.215mg HPN328, later dose escalated to 7.0 mg HPN328
- Confirmed Partial Response: 53% decrease in sum of target lesion diameters at Week 10
- Remains on treatment with HPN328, beyond 32 weeks

Table 3. Patient Case 1 Baseline Characteristics

Lesions	**TLs**: Lung, Liver x2, Lymph Nodes x2 **Non-TLs**: Lung x2, Liver	**Time on most recent prior treatment**	20.1 weeks
Prior Systemic Treatments	1) Carboplatin + Etoposide + Atezolizumab	**Best response to most recent prior treatment**	Stable Disease

Figure 7. CT Scans Showing Decrease in Diameter of Selected Target Lesions

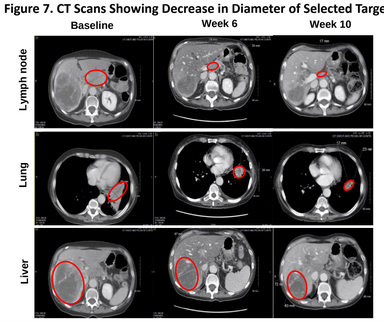
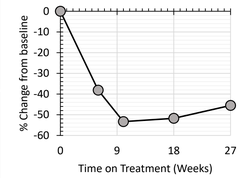


Figure 8. Sum of Target Lesion Diameters over Time



Patient Case 2

- 67-year-old male with extensive-stage SCLC
- 3 prior lines of treatment
- 60% cells positive for DLL3 on IHC analysis of archival biopsy
- 65% decrease in sum of target lesion diameters. Overall response: PD; Target Lesion response: PR
  - New asymptomatic brain metastases identified at week 2
- Deepening of response over >6 months of treatment
- Remains on treatment with HPN328, beyond 28 weeks

Table 4. Patient Case 2 Baseline Characteristics

Lesions	**TLs**: Liver x2, Lymph Nodes x2 **Non-TLs**: Liver, LN x2, Spleen, Bone, Brain	**Time on most recent prior treatment**	10.9 weeks
Prior Systemic Treatments	1) Carboplatin + Etoposide + Toripalimab 2) Cisplatin + Etoposide 3) Lurbinectedin	**Best response to most recent prior treatment**	Partial Response

Figure 9. CT Scans Showing Decrease in Diameter of Lymph Node Lesion

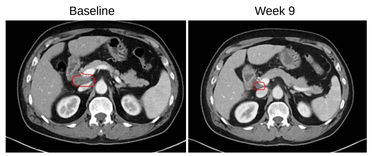
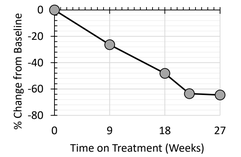


Figure 10. Sum of Target Lesion Diameters over Time



SUMMARY

- HPN328, a novel half-life extended DLL3-targeting T cell engager derived from the TriTAC platform, is clinically active and well tolerated
- T-cell margination and activation was observed, consistent with target engagement
- HPN328 has demonstrated anti-tumor activity
  - 3 of 11 SCLC patients had >30% decreases in sum of target lesion diameters, including 1 confirmed partial response (per RECIST v1.1)
  - 4 of 6 (67%) SCLC patients treated at ≥1.215mg/week had decrease in sum of target lesion diameters
- Treatment duration ≥ 20 weeks was observed in 6 of 18 (33%) patients
- CRS has been transient and manageable, with 22% of patients experiencing Grade 1-2 CRS; No Grade >=3 CRS has occurred
- Dose escalation is ongoing, MTD is not yet reached