First-in-human, phase 1 study of HPN424, a tri-specific half-life extended PSMA-targeting T cell engager, in patients with metastatic castration-resistant prostate cancer (mCRPC)

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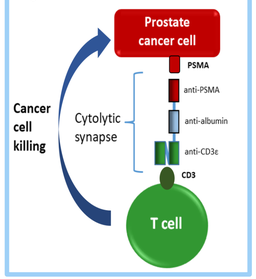
BACKGROUND

HPN424: PSMA-Targeting TriTAC®
(Tri-specific T cell-Activating Construct)

- HPN424, a first-in-class, prostate-specific membrane antigen (PSMA)-targeting T cell engager, is a recombinant polypeptide of ~50kDa, engineered with three binding domains:
  - PSMA (for tumor binding)
  - Albumin (for half-life extension)
  - CD3 (for T cell engagement)
- HPN424 is constructed as a small, globular protein to enable efficient solid tumor penetration with prolonged half-life and excellent stability
- HPN424 binds monovalently to CD3 and PSMA, minimizing non-specific T-cell activation

Figure 1. HPN424 Mechanism of Action

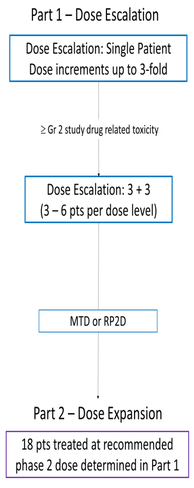


- These features are designed to increase the therapeutic index compared to earlier generations of T cell engagers by minimizing off-target toxicities
- HPN424 mediates potent target tumor cell killing in a PSMA-specific manner in vitro and in xenograft models in the presence of T cells, demonstrated at very low antigen densities
- A Phase I study was initiated to evaluate HPN424 in patients with mCRPC who progressed on ≥2 prior therapies, dose escalation is currently ongoing

TRIAL DESIGN

Dose Escalation / Expansion, Safety & PK Study

Figure 2. HPN424 Phase I Trial Design



Target Population
- Metastatic Castrate-resistant Prostate Cancer
- Disease progression on the prior systemic regimen
- Received ≥2 prior systemic therapies approved for mCRPC
- Prior chemotherapy allowed, but not required

Trial Design
- Key objectives include characterization of safety, pharmacokinetics, and identification of dose for expansion phase
- Tumor assessments performed every 9 weeks and include conventional CT and bone scans and PSA
- Additional assessments include cytokines, CTC

Dosing, Administration & Exposure
- HPN424 administered once weekly, one-hour IV infusion
  - One cycle is 3 weeks
- Starting dose of 1.3ng/kg established by minimally anticipated biological effect level
- As of May 11, 2020, 44 patients have been dosed across 11 cohorts (range 1.3 to 120ng/kg)

BASELINE DEMOGRAPHICS

- Median of 7 prior systemic therapies, median of 2 prior novel hormonal agents
- 73% of patients had prior chemotherapy in metastatic castrate-resistant setting

Table 1. Baseline Characteristics and Demographics (n=44)

Age (Years)	
Median	71
Range	44 - 91
Race	
White	34 (77%)
Black or African American	5 (11%)
Asian	1 (2%)
Other / Not reported	4 (9%)
ECOG Performance Status	
0	26 (59%)
1	18 (41%)
PSA (ng/mL)	
Mean	649
Median	244
Range	0.1 - 5000
LDH (U/L)	
Mean	402
Median	277
Range	126 - 1303
Location of Metastases	
Bone	42 (96%)
Lymph Node	20 (46%)
Liver	6 (14%)
Lung	6 (14%)
Other Visceral	7 (16%)

Time Since Diagnosis (Years)	
Mean	9.1
Median	7.8
Range	0.9 – 25.6
Reason for Entering Study	
PSA Progression	13 (30%)
PSA & Clinical Progression	1 (2%)
PSA & Radiographic Progression	3 (7%)
Radiographic Progression	13 (30%)
Unknown	14 (32%)
# of Prior Therapies	
Median (Range)	7 (2 – 16)
# of Prior Novel Hormonal Therapies	
Median (Range)	2 (1 – 3)
Prior Chemotherapy (in mCRPC setting)	
N	32 (73%)
Median (Range)	1 (0 – 3)

- Additional prior therapies include sipuleucel-T, radium-223, A2AR inhibitor, olaparib, rucaparib, pembrolizumab, nivolumab, durvalumab, ipilimumab, listeria vaccine, Lu177/Ac225-PSMA-617, other investigational agents

ADVERSE EVENTS

- All CRS events resolved and patients were successfully re-treated
- High-grade transaminitis was observed primarily in the setting of CRS; abnormalities were transient, no clinical sequelae
- Short-term premedication with steroids was effective in limiting CRS and allowing long-term treatment
- 1 DLT observed at 96ng/kg, Grade 3 lipase increase
- Treatment related SAEs: CRS (n=4), AST increase (n=3), ALT increase (n=2), IRR (n=2), myalgia (n=1), pneumonitis (n=1), seizure (n=1), syncope (n=1)

Table 2. Adverse Events ≥10% of Patients Regardless of Relationship

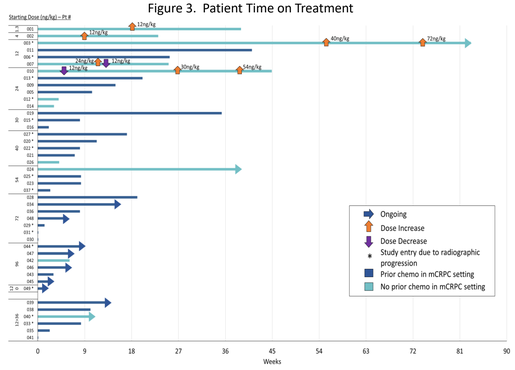
Event, n (%)	All Grades	Grade 3+
Cytokine-Related Adverse Events[a]		
Chills	32 (73%)	0 (0%)
Pyrexia	21 (48%)	0 (0%)
Cytokine release syndrome	14 (32%)	3 (7%)
Flushing	10 (23%)	0 (0%)
Hypotension	8 (18%)	1 (2%)
Infusion related reaction	6 (14%)	0 (0%)
All Other Adverse Events		
Fatigue	16 (36%)	2 (5%)
Anemia	14 (32%)	4 (9%)
Constipation	12 (27%)	0 (0%)
Nausea	11 (25%)	0 (0%)
Vomiting	8 (18%)	0 (0%)
Decreased appetite	8 (18%)	0 (0%)
Back Pain	8 (18%)	2 (5%)
Insomnia	7 (16%)	0 (0%)
Diarrhea	6 (14%)	0 (0%)
ALT increase	6 (14%)	2 (5%)
Arthralgia	6 (14%)	0 (0%)
Tachycardia	5 (11%)	0 (0%)
Asthenia	5 (11%)	0 (0%)
Blood creatinine increase	5 (11%)	1 (2%)
Pain in extremity	5 (11%)	0 (0%)
Hypertension	5 (11%)	2 (5%)

[a] Includes AEs that were reported as concurrent symptoms of the CRS events

TIME ON TREATMENT

- 11 of 28 pts (39%) with >18 weeks follow-up remained on study beyond week 18
- 8 of 26 (31%) patients remained on study >24 weeks
- Of the 8 patients on study >24 weeks, 7 patients (88%) continued on HPN424 treatment longer than the time on their most recent prior systemic regimen (data not shown)

Figure 3. Patient Time on Treatment

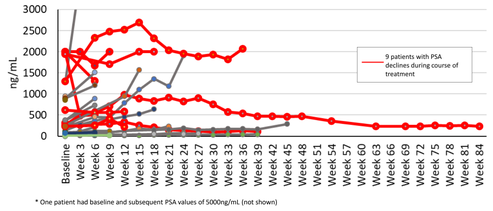


- 11 patients remain active, patients discontinued study due to: PD (63%), Death due to PD (9%), Death due to Unrelated AE (6%), Unrelated AE (3%), Other (18%)

PSA CHANGES ON TREATMENT

- Eight patients had PSA decreases from baseline ranging from -3.8% to -76%, including 2 patients with PSA decline >50% from baseline
- PSA declines observed in patients across dose cohorts

Figure 4. Patient PSA Values on Treatment



* One patient had baseline and subsequent PSA values of 5000ng/mL (not shown)

DEXAMETHASONE PREMEDICATION

- HPN424 was initiated at 1.3ng/kg with no dexamethasone (dex) premedication
- Dose-dependent, transient increases in serum cytokine and chemokines were observed in early cohorts (See Figure 8)

Cohort	Dose (ng/kg)	N	Dex Premed (mg)	Gr 3+ CRS, n
1	1.3	1	--	0
2	4	1	--	0
3	12	4	--	0
4a	24	3	--	2

- 2 patients who received 24ng/kg with no dex premed experienced Grade 3 CRS; patients were subsequently administered dex premedication weekly
- Dex taper was implemented at Cohort 5 based on the observation that peripheral cytokines attenuated with each successive dose
  - 6-Week Taper: Administered once weekly prior to HPN424 infusion for 2 cycles
  - 3-Week Taper: Administered once weekly prior to HPN424 infusion for 1 cycle

Cohort	Dose (ng/kg)	N	Dex Premed (mg)	Gr 3+ CRS, n
4b	24	4	10 mg weekly	1
5	30	3	10-10-4-4-2-2	0
6	40	3	10-10-4-4-2-2	0
6a	40	2	10-4-2	0
7	54	3	10-10-4-4-2-2	0
7a	54	1	10-4-2	0
8	72	6	10-10-4-4-2-2	0
8a	72	1	20-10-5	0
9	96	6	10-10-4-4-2-2	0
10	120	1	20-10-4-4-2-2	0

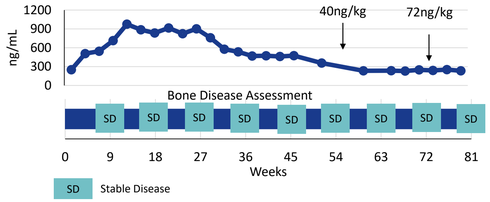
PATIENT PROFILES

- Patient 003, a 69-year old male, diagnosed March 2013

Baseline Characteristics			
ECOG	0	Reason for Study Entry	Radiographic Progression
PSA (ng/mL)	251	Location of Metastases	Bone
LDH (U/L)	530	Prior Therapies	ADT, sipuleucel-T, enzalutamide

- Patient initiated HPN424 at 12ng/kg and escalated twice to 40 then 72 ng/kg
- Patient demonstrated early rise in PSA followed by a steady decline starting Week 12, currently -9% PSA decline from baseline
- Drop in LDH from 2361 to 241 U/L observed, coinciding with PSA decline
- Patient remains on study after 84 weeks of treatment

Figure 5. Patient 003 PSA Values and Disease Assessment on Treatment

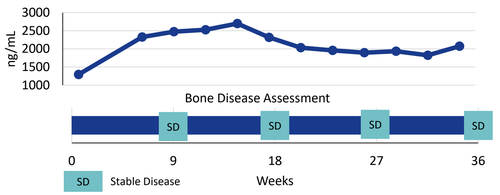


- Patient 024, a 76-year old male, diagnosed December 2009

Baseline Characteristics			
ECOG	1	Reason for Study Entry	PSA Progression
PSA (ng/mL)	1294	Location of Metastases	Bone
LDH (U/L)	187	Prior Therapies	ADT, docetaxel, sipuleucel-T, abiraterone, enzalutamide, nivolumab + rucaparib

- Patient initiated HPN424 at 54ng/kg with a 6-week dexamethasone premedication taper
- Pt demonstrated early rise in PSA followed by a slight decline starting Week 15
- Patient remains on study after 38 weeks of treatment

Figure 6. Patient 024 PSA Values and Disease Assessment on Treatment



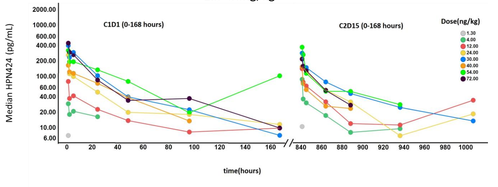
MEASURABLE DISEASE

- 18 patients of 44 (41%) had measurable disease at baseline, including 10 patients with ≥1 post-treatment protocol scheduled disease assessment
- In those 10 evaluable patients, sum of target lesions in 6 pts remained stable and 4 pts had disease progression as best response

PHARMACOKINETICS

- HPN424 demonstrated dose proportional increase in C_{max} and AUC with a geometric median $T_{1/2}$ of 24.9 hours (range: 9.0 – 312 hours)

Figure 7. Median Concentration Time Profile for HPN424 in the given dose range of 1.3- 96ng/kg



PHARMACOKINETICS

- Median clearance (CL) and volume of distribution (V_{ss}) for HPN424 in the given dose range of 1.3 – 96ng/kg appear to be dose independent, indicative of linear kinetics
- Of 27 patients measured for anti-drug antibodies (ADAs), one patient was ADA positive at baseline (neutralizing activity detected at C7D1 and beyond), two other patients developed ADA post-treatment (one was non-neutralizing, second was neutralizing at C4D1 and beyond)

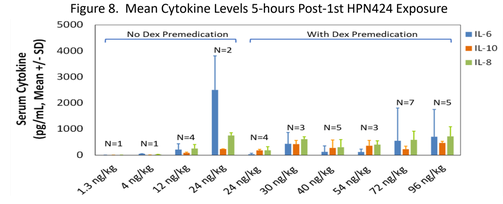
Table 3. Median PK parameters for HPN424 in the given dose range of 1.3 – 96ng/kg

Dose (ng/kg)	Half-life (hour)	Cmax (ng/mL)	CL (mL/hour*kg)	Vss (mL/kg)
1.3	NA	0.00704	NA	NA
4	94.6	0.0294	1.45	196
12	20.7	0.0969	5.52	256
24	40.4	0.262	5.76	152
30	18.7	0.4	3.69	97.2
40	25.3	0.166	8.19	263
54	50	0.321	4.82	257
72	22.1	0.450	8.93	275
96	24.5	0.590	6.41	206

PHARMACODYNAMICS

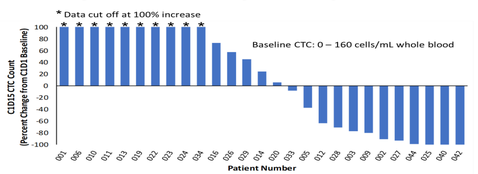
- Dose-dependent, transient increases in peripheral cytokine and chemokine levels were observed, peaking at 5 hours post infusion and returning to baseline 24 hours post-administration
- Maximal cytokine/chemokine release attenuated with each successive dose over 1st two cycles
- Transient cytokine increases can be effectively managed with short-term dexamethasone premedication

Figure 8. Mean Cytokine Levels 5-hours Post-1st HPN424 Exposure



- Reduction in circulating tumor cells (CTCs) was seen in 12 of 27 patients with available CTC counts collected on C1D1 predose (baseline) and C1D15 predose (after 2 doses of HPN424)

Figure 9. Post Treatment Changes in Circulating Tumor Cell



- Transient lymphocyte margination was observed post-HPN424 infusion across cohorts (data not shown)

SUMMARY

- HPN424 represents a novel half-life extended PSMA-targeting T cell engager that can be safely administered once weekly
- Dose escalation comprises a heterogeneous, heavily pretreated population
- Evidence of half-life extension supports once weekly HPN424 administration
- Cytokine increases indicate T-cell activation and CTC reductions in a subset of patients support target engagement
- Adverse events have been transient, manageable and consistent with expected mechanism of action
- Early clinical signals have been observed, including 8 patients on treatment > 24 weeks and PSA reductions in multiple patients
- Dose escalation is ongoing to identify dose for expansion phase

Abstract 5552
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