**BACKGROUND**

HPN424, a first-in-class, prostate-specific membrane antigen (PSMA)-targeting therapeutic (PSMA-Tt), is a target-engaging (Tt) engager designed for metastatic castration-resistant prostate cancer (mCRPC). HPN424 is a monoclonal antibody (mAb) engineered with two valence binding domains: Fc and anti-PSMA domain.

- **Valency**: allowance for two independent, simultaneously recruited target:antibody (Tt) complexes.
- **Size**: lower than the size of other current prostate-specific targets (data not shown)

**BASELINE DEMOGRAPHICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>71</td>
<td>48-87</td>
</tr>
<tr>
<td>Locals of Metastases</td>
<td>20</td>
<td>5-39</td>
</tr>
<tr>
<td>Time Since Diagnosis (Years)</td>
<td>5</td>
<td>1-16</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>7.6</td>
<td>3.6-100</td>
</tr>
<tr>
<td>n of Prior Novel Hormonal Therapies</td>
<td>2</td>
<td>1-4</td>
</tr>
<tr>
<td>% of patients with mCRPC</td>
<td>88</td>
<td>86-99</td>
</tr>
</tbody>
</table>

**TIME ON TREATMENT**

- **8 patients had PSA decreases from baseline ranging from -3.8% to -70%, including 3 patients with PSA decline >50% from baseline.**
- **PSA decline observed in patients across dose cohorts.**

**PSA CHANGES ON TREATMENT**

- **11 patients remain on treatment, patients discontinued study due to: PD (62%), Death due to PD (20%), Death due to other causes (6%), Other (14%).**

**EXAMINATION**

- **Mean Cytokine levels 5%**
- **Patients showed >10 pg/mL increase in C-reactive protein (CRP) and interleukin-6 (IL-6) at week 2.**

**BASELINE PROFILES**

- **Patient 002, 64-year old male, diagnosed December 2000**
- **Patient initiated HPN424 at 5640 kg with a 4-day term premedication (PA).**
- **Demonstration of a PSA decline followed by a single declining week 15.**
- **Patient remains on study after 28 weeks of treatment.**

**PHARMACOKINETICS**

- **Median clearance (CL) and volume of distribution (Vd) for HPN424 in the given dose range of 1.3 – 9.6 mg/kg appear to be dose independent, indicative of linear pharmacokinetics.**
- **Exposure to HPN424 following single dose and multiple doses is not associated with clinically significant interactions of HPN424 with CYP450 enzymes.**

**PHARMACODYNAMICS**

- **Dose-dependent, transient increases in peripheral cytokine and chemokine levels were observed post-dose on day 1 and persisted for 24 hours post-administration.**
- **Median cytokine/chemokine release eliminated with each successive dose over 3-5 cycles.**
- **Transient cytokine increases can be effectively managed with short-term premedication.**

**MEASURABLE DISEASE**

- **HPN424 demonstrated dose proportional increases in C-reactive protein (CRP) and acute-phase reactant (APR) levels.**

**SUMMARY**

- **HPN424 represents a novel half-life extended PSMA-targeting Tt engager that can be safely administered once weekly.**
- **Dose escalation is ongoing to identify dose for future phase 2 studies.**
- **Evidence of half-life extension supports once weekly HPN424 administration.**
- **Future studies will reduce in a subset of patients support target engagement.**
- **Adverse events have been minimal, manageable and consistent with expected exclusion of action.**
- **Future studies will be designed to observe, including patients on treatment for > 24 weeks of treatment.**
- **Dose escalation is ongoing to identify dose for future phase 2 studies.**