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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**Backgr**

HPN328 is a three specific anti-DLL3-CD3 engager derived from the TCMVA platform.

HPN328 contains 3 binding domains, engineered to redirect T cells to anti-DLL3 expressing cells:

- anti-DLL3 (for target engagement)
- anti-CD8 (to half life extension)
- anti-CD3 (for T cell engagement)

HPN328 is constructed as a small, globular protein, a DCSA to enable efficient tumor penetration with prolonged half-life.

HPN328 binds monovalently to CD3 and DLL3, mimicking non-activated T cell activation.

**Trial Design**

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

**Baseline Characteristics**

Table 1. Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category  A</th>
<th>Category  B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Median 55</td>
<td>Median 56</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Male 45</td>
<td>Male 46</td>
</tr>
<tr>
<td>ECOG (%)</td>
<td>0 50</td>
<td>0 50</td>
</tr>
<tr>
<td>Prior Systemic Treatments (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
<tr>
<td>Prior Radiation (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
<tr>
<td>Prior Surgery (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
<tr>
<td>Prior Brain Metastases (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
<tr>
<td>Prior Liver Metastases (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
<tr>
<td>Prior Spleen Metastases (%)</td>
<td>2 80</td>
<td>2 80</td>
</tr>
</tbody>
</table>

**Pharmacody**

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

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Grade</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Skin</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Other</td>
<td>Grade 1</td>
<td>3 (17%)</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

**Target population**

SCLC response after platinum chemotherapy: other malignancies with high grade neuroendocrine features behaved refractory to standard of care (SOC) or no SOC available.

**Trial objectives**

- Assess safety and tolerability
- Determine PK and PD
- Characterize PK and PD
- Assess tumor activity
- Assess clinical activity

**Dosing and Administration**

- Dose escalation followed by expansion
- Dose escalation: 1, 3, 5, and 7 mg
- Expansion: 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 mg

**Results**

- Maximum tolerated dose (MTD) not reached
- No Dose limiting toxicities (DLTs) observed
- Grade 2-3 DLTs observed in 3 (21%) patients; No Grade 4 DLTs
- No SAEs
- No patients discontinued study treatment due to adverse events

**ADVERSE EVENTS**

**Onset**

- Maximum tolerated dose (MTD) not reached
- No Dose limiting toxicities (DLTs) observed
- Grade 2-3 DLTs observed in 3 (21%) patients; No Grade 4 DLTs
- No SAEs
- No patients discontinued study treatment due to adverse events

**Pharmacodynamics**

- T cell migration and activation was observed, consistent with target engagement.
- Small tumor increase in median 2 weeks, 12 weeks on treatment.
- No new or increased target activity.
- First dose effect observed relative to repeat or target dose.
- More tumor migration was observed in prolonged half-life.
- Higher mean cytokine/chemokine concentrations

**Target engagement**

- 7 of 18 (39%) had at least 1 PR or above on target lesion diameters (SCLC, NEC, NEPC, CDX, Hyper tyroid controlled).
- 2 confirmed partial responses (PRs) ongoing treatment at 32 weeks.
- 2 of 12 (17%) of patients across all disease had >10% decrease in sum of target lesion diameters.
- 4 of 18 (22%) SCLC patients treated at ≤12 weeks had >10% decrease in sum of target lesion diameters.
- 17 of 31 (56%) SCLC patients with brain metastases remained stable at 26 weeks.

**Survival**

- Overall Survival (OS) at 12 months: Median 10.3 months
- Progression-free survival (PFS) at 12 months: Median 5.0 months
- Patients received 39 cycles, 211 treatment weeks

**SUMMARY**

HPN328 is a novel half-life extended DLL3-targeting T-cell engager that is well tolerated and activated T cells with target engagement. HPN328 has demonstrated tumor activity and is currently in clinical development for treatment of small cell lung cancer and other neuroendocrine malignancies.