Interim results from a phase 1/2 study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T-cell engager, in patients (pts) with neuroendocrine prostate cancer (NEPC) and other neuroendocrine neoplasms (NEN).

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**Background:** HPN328 is a delta-like canonical Notch ligand 3 (DLL3)-targeting T-cell engager. HPN328 has 3 binding domains including anti-DLL3 for target engagement, anti-albumin for T1/2 extension, and anti-CD3 for T cell engagement and activation. HPN328 treatment resulted in robust and specific anti-tumor activity in preclinical in vitro and in vivo DLL3-expressing NEPC models.

**Methods:** Patients (pts) with relapsed/refractory, metastatic NEPC, small cell lung cancer (SCLC), or other NEN associated with DLL3 expression are eligible. Verification of DLL3 expression is required for NEN other than SCLC or NEPC for eligibility. Primary objectives are safety, maximum tolerated dose (MTD), recommended dose(s) for expansion (RDE) determination, and pharmacokinetics (PK). Secondary objectives are immunogenicity and efficacy. HPN328 is administered IV weekly or biweekly with a priming dose preceding the target dose in higher dose cohorts. Adverse events (AEs) are graded (G) by CTCAE 5.0, and ASTCT for cytokine release syndrome (CRS).

**Results:** As of 21Aug23, 66 pts received HPN328 as a single agent at target doses of 0.015–24 mg across 14 dose escalation cohorts. Ten (10) pts had NEPC and 2 had small cell bladder cancer (SCBC). The remainder were SCLC or other NEN. Median number of prior regimens for all patients was 2 (1-6). Treatment is ongoing in 29 pts, with 3 from early escalation cohorts on study for more than a year. Treatment-related AEs in 10% of pts included CRS (52%), fatigue (35%), dysgeusia (33%), nausea (17%), vomiting and diarrhea (14% each), decreased appetite (12%), and pyrexia (11%). Nearly all CRS occurred after the initial priming dose and not with subsequent infusions. The most common G3 events were neutropenia (9%) and pneumonia and anemia (5% each). G3 CRS was a dose-limiting toxicity (DLT) in 2 pts at a priming dose of 2 mg; subsequent target dose escalation continued to 24 mg with a priming dose of 1 mg and no further DLTs of CRS; MTD at the target dose has not been reached. The 2 SCBC patients had confirmed partial responses (PR). Of the 10 NEPC patients, 3 of 6 with at least one imaging study had unconfirmed PRs. HPN328 exhibited linear PK with dose-proportional increases in exposure and a median T1/2 of 71 hrs. Transient increases in cytokines up to 24 hrs post-dose and T-cell activation were observed.

**Conclusions:** HPN328 is well tolerated and clinically active. MTD determination, dose escalation, and dose optimization are ongoing. Updated safety and efficacy results including recently enrolled NEPC and SCBC pts will be presented. Clinical trial information: NCT04471727. Research Sponsor: None.