HPN424, a half-life extended, PSMA/CD3-specific TriTAC for the treatment of metastatic prostate cancer

Bryan Lemon, Wade Aaron, Richard Austin, Patrick A. Baeuerle, Adrie Jones, Susan D. Jones, Kathryn Kwant, Che-Leung Law, Harpoon Therapeutics, South San Francisco, CA.

**Rationale**
- Metastatic, castration-resistant prostate cancer (mCRPC) kills 27,000 patients in the US each year.
- Once mCRC has metastasized beyond regional lymph nodes, the 5-year survival rate is 20%.
- Abietorine and enzalutamide have improved the treatment options for mCRC, but no curative treatment is available and new therapies are urgently needed.
- PSMA is expressed in >90% of malignant lesions of mCRPC patients.
- In normal tissues, PSMA expression outside the central nervous system is largely restricted to the prostate.
- HPN424 is engineered to direct T cells to kill prostate cancer cells.

**Introduction**
HPN424 is a PSMA-targeting TriTAC.
- Single domain antibody targets cancer cells expressing PSMA/FOG12.
- Single domain antibody binds albumin to extend serum half-life.
- Anti-CD3ε isoform engages T cells.

**Biophysical Characterization**

**In Vitro Binding**
HPN424 binding to human and cyno PSMA, ALB, and CD3ε by biolayer interferometry.

**In Vitro Pharmacology**
- PSMA-dependent activation of T cells by HPN424.
- Induction of CD3ε expression on T cells in presence of UNCAf cells with HPN424 but not with an aGFPA-TTAC.
- HPN424 induction of TcRε expression by T cells in presence of UNCAf cells but not PSMA-negative HCT116 cells.

**In Vivo Pharmacology**
Adoptive 5 x 10^9 human PBMC + 22Rv1 prostate cancer cells, 4D.
- HPN424 potently inhibits growth of 22Rv1 xenografts.
- PK results suggest once or twice weekly dosing in humans.
- HPN424 has a half-life of ~3.3 days in cynomolgus monkeys.

**Pharmacokinetics**
HPN424 has a half-life of ~3.3 days in cynomolgus monkeys.
- HPN424 is highly tolerated with repeat dosing in cynomolgus monkeys.
  - No observed adverse effect level was 3 mg/kg, 4xkd.
  - Similar results observed with 0.1 mg/kg and 0.3 mg/kg qd doses.
  - CD3 and albumin binding domains contribute with synergistic effects.
- Minimal binding of HPN424 to recombinant cyno PSMA.
- Pharmacodynamic effects consistent with T cell engagement.
  - Transient reduction in circulating T cells, NK cells, and monocytes.
  - Transient increase in cytokine markers (C507, TNFα, and IFNγ) with 1st dose, no increase with 2nd or 3rd dose.
- Transient, dose-dependent increases in IL-6 and IL-10 as similarly reported with other bispecific T cell therapies.

**Safety**
HPN424 is highly tolerated with repeat dosing in cynomolgus monkeys.
- No adverse histopathology findings.
- HPN424 induces transient T lymphocyte margination and activation.
- Rapid decline of circulating T cells within 48 hrs post dose.
- Much less lymphocyte margination after 4th and final dose.
- HPN424 induces limited cytokines, no evidence of cytokine release syndrome.

**Summary**
- HPN424 TriTAC is a stable, manufacturable, single chain molecule that binds with high affinity and specificity to PSMA, CD3 and albumin.
- HPN424 potently activates and redirects T cells to kill PSMA expressing cells in both in vitro and in vivo prostate cancer models.
- HPN424 has a long serum half life and was very well tolerated, even at high doses, in cynomolgus monkeys.
- With its small size, HPN424 is anticipated to be more able to penetrate solid tumors than antibodies.
- HPN424 is expected to be safe, effective, and convenient treatment for patients with metastatic castration-resistant prostate cancer.
- HPN424 is anticipated to enter the clinic in 2018.

**Abstract 1773 AACR Annual Meeting 2018**