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

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**Rationale**

- Metastatic, castration-resistant prostate cancer (mCRPC) kills 71,000 patients in the European Union each year.
- Once mCRPC has metastasized beyond regional lymph nodes, the 5-year survival rate is 30%.
- Abiraterone and enzalutamide have improved the treatment options for mCRPC, but no curative treatment is available.
- New therapies are urgently needed.
- PSMA is expressed in >90% of mCRPC lesions.
- 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.

**TriTAC Platform**

- Optimize for treatment of solid tumors.
- Small size for diffusion-controlled solid tumor penetration.
- Optimized CD3 binding to address T-cell-mediated clearance.
- Single polypeptide.
- Protein A purification.
- Robust stability.
- Albumin binding for extended serum half-life.

**Introduction**

HPN424 is a PSMA-targeting TriTAC.

- sPSMA
- sAB
- sCD3

HPN424 is a tri-specific single chain molecule of ~50 kDa.

**Biophysical Characterization**

- SDS-PAGE
- Western blot
- Flow cytometry

HPN424 Exhibits High Stability

- Optimal CD3 binding to address T-cell-mediated clearance.
- purification
- Robust stability.
- Albumin binding for extended serum half-life.

**In Vitro Pharmacology**

- HPN424 binds to cells expressing PSMA and CD3.
- HPN424 potently activates and redirects T cells to kill PSMA.

**Pharmacodynamics**

- PSMA-dependent activation of T cells by HPN424.
- HPN424 potently inhibits growth of 22Rv1 xenografts.

**Pharmacokinetics**

- HPN424 has a half-life of ~3.3 days in cynomolgus monkeys.

**Safety**

- No observed adverse effect level was 3 mg/kg, qdx.
- Similar results observed with 3 mg/kg and 0.1 mg/kg doses.
- CD3 and albumin binding domains cross-react with CD3 targets.
- Minimal binding of HPN424 to recombinant CD3 in vitro.

**Summary**

- HPN424 is highly tolerated with repeat dosing in cynomolgus monkeys.
- HPN424 potently activates and redirects T cells to kill PSMA.
- HPN424 is a tri-specific single chain molecule.
- HPN424 is highly tolerated with repeat dosing in cynomolgus monkeys.
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**In Vivo Pharmacology**

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