**Background**

**B7-H3 Crystal Structure: T-cell Inhibitory Domain Mapped**

- Enoblituzumab increases T-cell clonality in the peripheral blood (Adaptive Biotechnologies)

**B7-H3: Member of B7 Family of Immune Regulators**

- **Immunosuppressive role**
  - Expression drives immune escape/invasiveness of glioblastoma in mice
  - Expression on lung cancer and macrophages suppresses T-cell mediated anti-tumor immune response
  - B7-H3-positive myeloid-derived suppressor cells present in tumor microenvironment
- **Tumor autonomous role**
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines
  - Enhances metastatic potential of melanoma

**Multiple Roles for B7-H3 in Cancer**
- **Expression on cancer cell surface**
  - CD80 or CD86 (B7-1 or B7-2)
- **Expression on immune cells**
  - CTLA4
  - CD28
- **Expression on stromal cells**
  - PD-1
  - ICOS
  - B7RP1 (B7-H2)
- **Expression on immune regulators**
  - B7-H3
  - B7-H4
  - B7-H5 (VISTA)
  - B7-H6
  - Nkp30

**B7-H3 Displays Favorable Tumor/Normal Differential**

- **A. Restricted Immune Cell Expression**
  - CD4 T Cells
  - CD8 T Cells
  - Monocytes
  - Monocyte-derived DCs
- **B. Limited Normal Tissue Expression**
  - Liver
  - Kidney
  - Heart
  - Colon
- **C. Normal/Tumor Tissue Differential**
  - Spleen
  - Lymph Node
  - Lung Cancer
  - Adjacent Normal Lung

**Enoblituzumab**

- Humanized IgG1 monoclonal antibody, Terminal Half Life = 3 weeks
- Recognizing human B7-H3 with high affinity (KD = 7 nM)
- Enhanced Fc function: Potential to increase antibody dependent cell-mediated cytoxicity (ADCC)
  - Increased affinity for activating FcY receptor IIa (FcYRIIA, or CD16A)
  - Decreased affinity for the inhibitory FcYRIIB (CD32B) receptors

**Rationale**

**Rationale for Targeting B7-H3 in Cancer**

- **High level of B7-H3 expression on neuroblastoma (NBL), rhabdomyosarcoma, osteosarcoma, Ewing’s sarcoma, Wilms tumor, and desmoplastic small round cell tumor (DSRCT)**
- **Rapidly accumulating evidence that checkpoint inhibitors may have anti-tumor activity in these tumors**
- **High level of unmet medical need for these pediatric patients with recurrent/refractory disease**
- **Enoblituzumab is well tolerated at doses up to 15 mg/kg administered weekly in adult patients with advanced cancer**

**Enoblituzumab Increases T-cell Clonality Population Clonality**

- Treatment with enoblituzumab increases the T-cell repertoire clonality in the peripheral blood

**Key Study Objectives**

**Primary Objective:**
- Characterize the safety, tolerability, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) or maximum administered dose (MAD) in children with B7-H3-expressing relapsed or refractory malignant solid tumors

**Secondary Objectives:**
- Characterize pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD)
- Investigate preliminary anti-tumor activity using RECIST, immune-related (ir) RECIST, and overall response criteria for neuroblastoma

**Exploratory Objectives:**
- Explore relationships between PK, PD and patient safety, and antitumor activity
- Investigate immune-regulatory activity of enoblituzumab in vivo (T cell function in blood)
- Explore relationship between Fc receptor genotype (CD16A, CD32A, CD32B) and anti-tumor activity
- Explore relationship between KIR and KIR ligand genotype and anti-tumor activity
- Determine the relationship between soluble B7-H3 and anti-tumor activity

**Multi-center Phase 1, Open-label, 3+3 Design Dose Escalation and Cohort Expansion Study**

- **Dose Escalation Schedule**
  - Dose-level Cohort Enoblituzumab Dose (mg/kg)
  - Cohort 1 (Starting Dose) 10
  - Cohort 2 15

**Study Design**

- **Key Inclusion Criteria**
  - Relapsed or refractory malignant solid tumors that express B7-H3 and for which no standard curative therapy is available
  - Age ≥21 at primary diagnosis (treatment age up to 30)
  - Measurable disease by RECIST 1.1 (except in non-measurable tumor)
  - Karnofsky (patients >16 years)/Lansky (patients ≤16 years) index ≥70
  - Systemic anticancer therapy ≥8 weeks post auto transplant, 4 weeks post chemo & post any biologic agent
  - Time after XRT – 2 weeks post focal, 4 weeks post large field radiation (e.g., whole lung, whole abdomen or pelvis) & 6 weeks after 131I-MIBG therapy
  - Life expectancy ≥12 weeks
  - Must meet laboratory criteria for organ function

**Key Exclusion Criteria**

- Corticosteroids (>0.2 mg/kg/day prednisone or equivalent) or other immune suppressive drugs within the 14 days
- Topical, ophthalmic, inhaled or nasal steroid administration allowed
- Symptomatic brain metastases or skull base lesions
- History of prior allogeneic bone marrow/stem cell or solid organ transplantation
- History of >Grade 3 drug related AE with previous CPI therapy
- History of clinically significant CV disease, including but not limited to:
  - Uncontrolled hypertension: systolic or diastolic BP consistently >15 x ULN for age
  - QTc prolongation >480 msec
- Measured LVSF <28%

**References**