A Phase 1, Open-label, Dose Escalation Study of MGA271 (Enoblituzumab) in Pediatric Patients with B7-H3-Expressing Relapsed or Refractory Solid Tumors

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Abstract TPS2596

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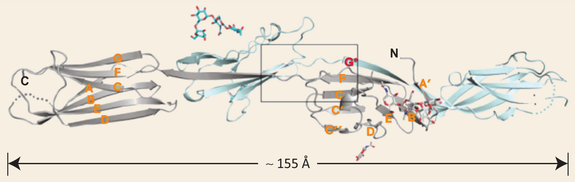
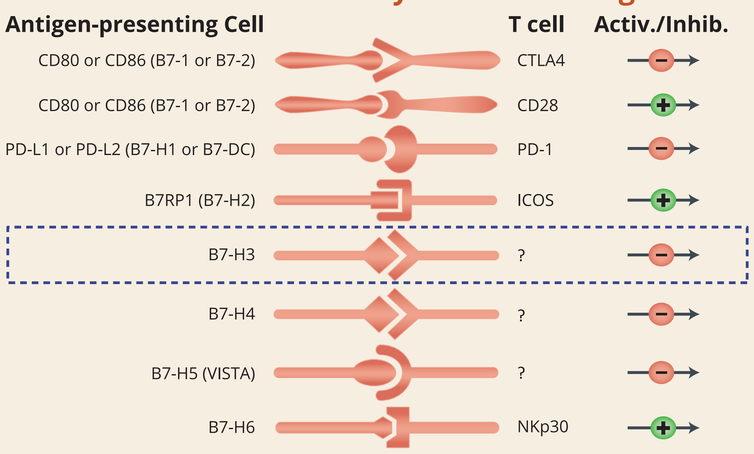
Background

B7-H3 Crystal Structure: T-cell Inhibitory Domain Mapped[1]



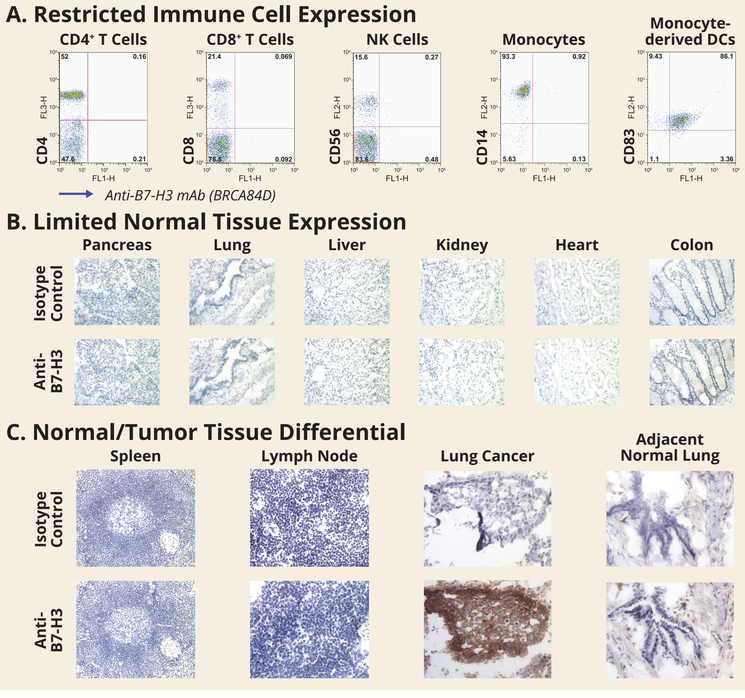
B7-H3: Member of B7 Family of Immune Regulators[2]



Multiple Roles for B7-H3 in Cancer

- **Immunosuppressive role**
  - Expression drives immune escape/invasiveness of glioblastoma in mice[3]
  - Expression on lung cancer and macrophages suppresses T-cell mediated anti-tumor immune response[4]
  - B7-H3-positive myeloid-derived suppressor cells present in tumor microenvironment[5]
- **Tumor autonomous role**
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines[6]
  - Enhances metastatic potential of melanoma cells[7]

B7-H3 Displays Favorable Tumor/Normal Differential



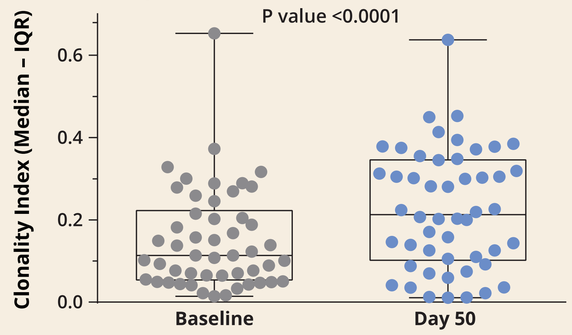
Enoblituzumab

- 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 cytotoxicity (ADCC)
  - Increased affinity for activating Fcγ receptor IIIA (FcγRIIIA, or CD16A)[8]
  - Decreased affinity for the inhibitory FcγRIIB (CD32B) receptors

Rationale

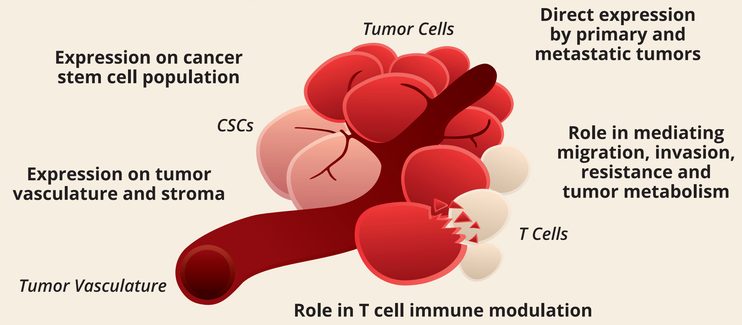
Enoblituzumab Increases T-cell Clonality

Population Clonality



- Treatment with enoblituzumab increases the T-cell repertoire clonality in the peripheral blood (Adaptive Biotechnologies)

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

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:

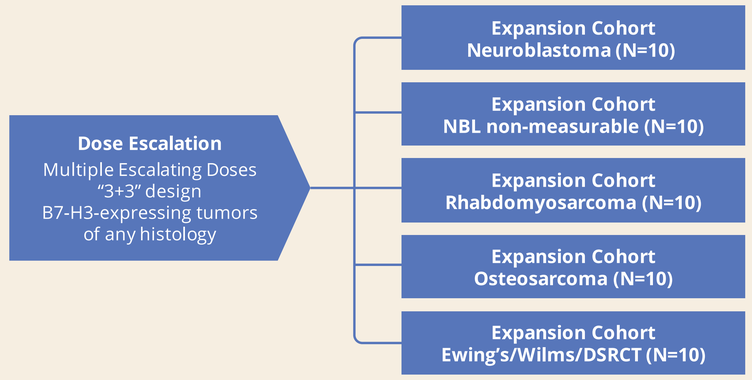
- Characterize pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD)
- Investigate preliminary anti-tumor activity using RECIST, immune-related (ir) RECIST, and overall response criteria for neuroblastoma

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

Study Design

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	5
Cohort 1 (Starting Dose)	10
Cohort 2	15

- Enoblituzumab administered IV weekly
- DLT evaluation period is the time following administration of first dose to the 5th planned dose of enoblituzumab (29 days)
- Enoblituzumab MTD: Dose at which <33% of patients experience a drug-related DLT during the DLT evaluation period
- If no MTD defined, highest dose level will be designated as MAD
- Patient management according to IR principles; may receive up to 96 doses of enoblituzumab
- Dose escalation cohorts complete
- Expansion cohorts open at 15 mg/kg

Entry Criteria

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 neuroblastoma)
- 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 >1.5 x ULN for age
  - QTcB prolongation >480 msec
  - Measured LVSF <28%

References

1. Vigdorovich V, et al. Structure 2013; 21(5): 707-717. **2.** Adapted from Pardoll D, et al. Nature Reviews Cancer 2012; 12 (4): 252-264. **3.** Lemke D, et al. Clin Cancer Res 2012; 18(1): 105-117. **4.** Chen C, et al. Exp Cell Res 2013; 19(1): 96-102. **5.** Zhang G, et al. Oncoimmunology 2015; 4(2): e977164. **6.** Chen YW, et al. Cur Cancer Drug Targets 2008; 8(5): 404-413. **7.** Tekle C, et al. Int J Cancer 2012; 130 (10): 2282- 2290. **8.** Data from ongoing clinical trial CP-MGA271-01.

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