A Phase 1 Study of Enoblituzumab in Combination with Pembrolizumab in Patients with Advanced B7-H3 Expressing Cancers

ASCO 2016
Abstract 165034

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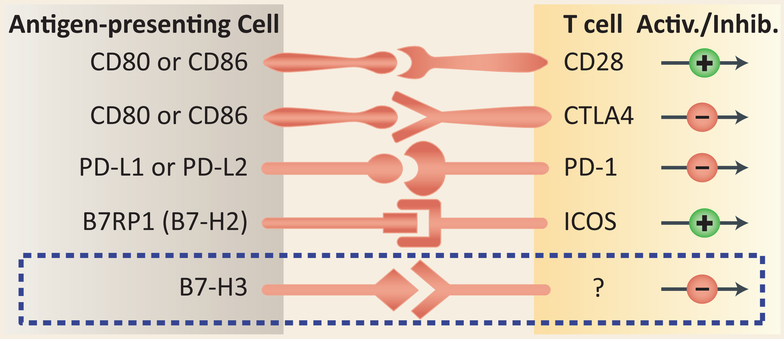
NCT02475213

Background

B7-H3: Member of B7 Family of Immune Regulators[1]

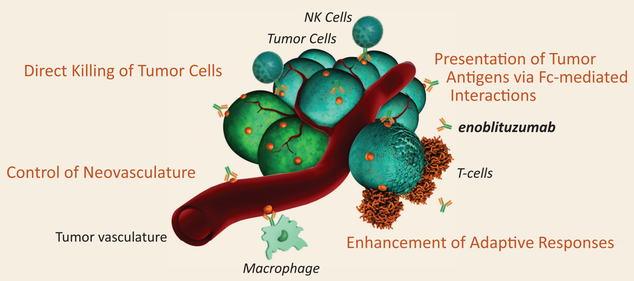


- B7-H3 Expressed on broad range of tumors and tumor vessels
- Minimal expression on normal cells
- High expression correlates with advanced disease, metastases, inferior patient survival[7]

Multiple Roles for B7-H3 in Cancer

- **Immunosuppressive role**
  - Expression drives immune escape/invasiveness of glioblastoma in mice[2]
  - Expression on lung cancer and macrophages suppresses T-cell mediated anti-tumor immune response[3]
  - B7-H3-positive myeloid-derived suppressor cells present in tumor microenvironment[4]
- **Metastatic enhancing role**
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines[5]
  - Enhances metastatic potential of melanoma cells[6]

Enoblituzumab Potential Mechanisms of Action



Enoblituzumab (MGA271)

- 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 inhibitory FcγRIIB (CD32B) receptors
- Single agent Enoblizumab anti-tumor activity observed in Phase I trial[11]

Pembrolizumab

- Humanized monoclonal antibody: blocking interaction between PD-1 and its ligands, PD-L1 and PD-L2

Key Study Objectives

Primary Objective:

Characterize the safety, tolerability, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) or maximum administered dose (MAD) of enoblituzumab when given in combination with pembrolizumab to patients with unresectable, locally advanced or metastatic B7-H3-expressing melanoma, squamous cell carcinoma of the head & neck (SCCHN), non-small cell lung cancer (NSCLC), or urothelial cancer (UC)

Secondary Objectives:

- Characterize pharmacokinetics (PK), immunogenicity and pharmacodynamic (PD) activity of the combination
- Investigate preliminary anti-tumor activity of the combination using both:
  - Conventional Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
  - Immune-related response criteria (irRC)

Exploratory Objectives:

- Explore relationships between PK, PD, safety, and anti-tumor activity of the combination
- Investigate immune-regulatory activity of combination in peripheral blood and tumor biopsies
- Assess relationships between membranous expression of B7-H3 and PD-L1 on tumor cells, immune cell infiltration within biopsy specimens, and anti-tumor activity

Rationale

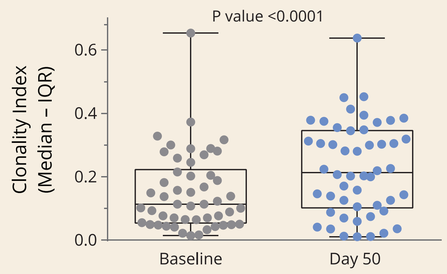
Rationale for Combining Enoblituzumab and an Anti-PD-1 Checkpoint Inhibitor

Exploits Both Complementary and Unique Mechanisms of Action Against Tumors

- Combination of two molecules targeting B7 pathways can synergize clinically (e.g., anti-CTLA-4/anti-PD-1)
- Coordinate engagement of innate and adaptive immunity by combining agents that modulate T-cell function and potentiate ADCC
- Limited B7-H3 expression on normal cells appears to limit disruption of self tolerance

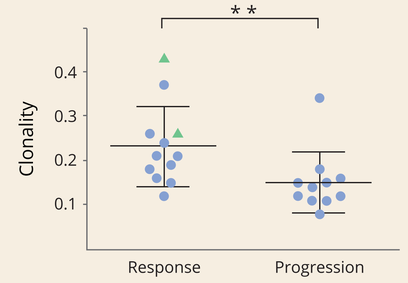
Enoblituzumab Increases T-cell Clonality

Population Clonality



- Treatment with enoblituzumab increases the T-cell repertoire clonality in the peripheral blood[8]

PD-1 Blockade: Response Correlates with Enhanced Clonality of Tumor-associated T Cells at Baseline[10]

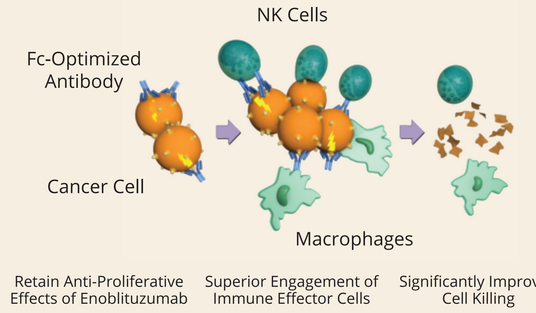


- Consistent with the hypothesis of enhancing pre-existing anti-tumor specific T-cell response

Potential For Increased Activated / Focused T-cells in Tumor

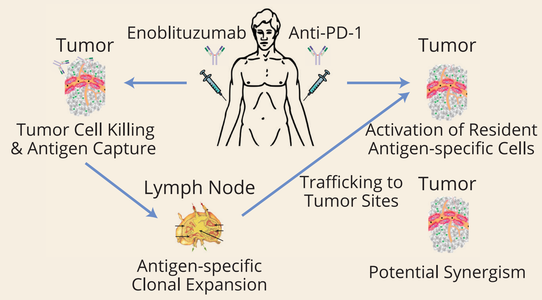
Enoblituzumab: Induces ADCC

Fc-engineered Antibody Maximizes Effector Cell Activity

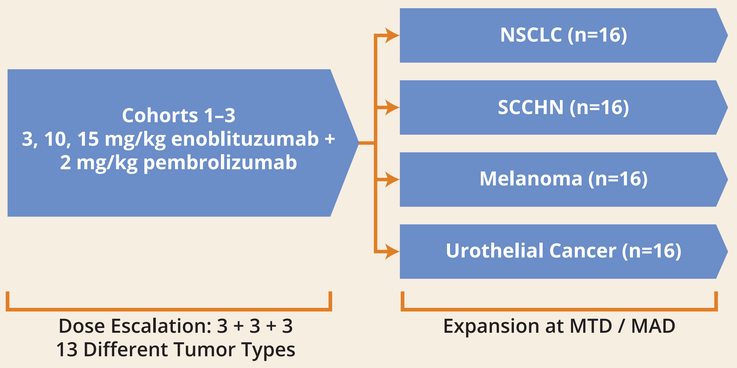


Combination Immunotherapy: Enoblituzumab + Anti-PD-1

Potential for Enhanced Tumor Killing

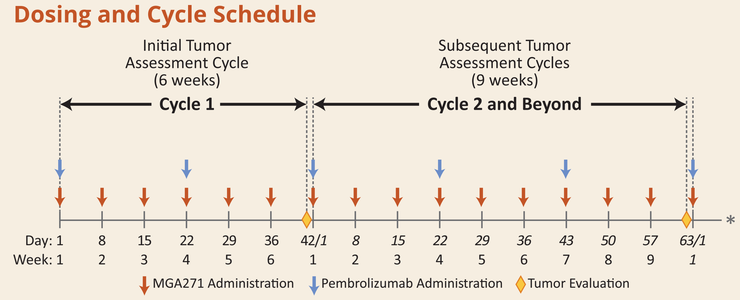


Study Design



- Multi-center Phase 1, open-label, 3+3+3 design dose escalation and cohort expansion study
- **Enoblituzumab** enrolled at escalating doses of 3, 10, and 15 mg/kg administered IV weekly
- **Pembrolizumab** administered at 2 mg/kg IV every 3 weeks
- MTD for combination: Dose level at which <33% of patients experience a drug-related DLT during the initial 6-week DLT evaluation period
- Patient management according to IR principles and may receive up to 6 cycles of enoblituzumab + pembrolizumab

Dosing and Cycle Schedule



- Efficacy follow-up period: up to 96 weeks after last dose of either drug

Entry Criteria

Key Inclusion Criteria

- Histologically-proven, unresectable, locally advanced or metastatic cancers that express B7-H3. Patients who are intolerant of or have refused treatment with standard cancer therapy will be allowed to enroll
- Progression during or following at least 1-2 and up to 3-5 prior therapeutic regimens, depending on tumor type; not inclusive of experimental therapies
- Measurable disease per RECIST 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 with acceptable laboratory parameters and adequate organ reserve

Key Exclusion Criteria

- Patients with symptomatic central nervous system metastases must have been treated and be asymptomatic, with certain exceptions
- History of autoimmune disease with certain exceptions
- Treatment with systemic cancer therapy within 4 weeks; radiation within 2 weeks; history of clinically-significant cardiovascular disease, gastrointestinal perforation, gastrointestinal bleeding, acute pancreatitis or diverticulitis within 4 weeks

References

1. Pardoll D, et al., Nature Reviews Cancer 2012; 12 (4): 252-264. **2.** Lemke D, et al., Clin Cancer Res 2012; 18(1): 105-117. **3.** Chen C, et al., Exp Cell Res 2013; 19(1): 96-102. **4.** Zhang G, et al., Oncoimmunology 2015; 4(2): e977164. **5.** Chen YW, et al., Cur Cancer Drug Targets 2008; 8(5): 404-413. **6.** Tekle C, et al., Int J Cancer 2012; 130 (10): 2282-2290. **7.** Loos M, BMC Cancer 2009; Yamato I, Br J Cancer 2009. **8.** Data from ongoing clinical trial CP-MGA271-01: NCT01391143. **9.** Pembrolizumab Package Insert 2015. **10.** Tumeh PC, et al., Nature 2014; 515(7528): 568-71. **11.** Powderly D, et al., Journal for ImmunoTherapy of Cancer 20153 (Suppl 2):O8.

Presented at The 2016 ASCO Annual Meeting, June 3–7, 2016, Chicago, IL