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

Naiyer Rizvi, Deryk Loo, Jan Baughman, Soyoun Yu, Francine Chen, Paul A. Moore, Ezio Bonvini, James Vasselli, Jon Wigginton, Roger B. Cohen, Charu Aggarwal, Anthony Tolcher

Columbia University Medical Center, New York, NY; *MacroGenics, Inc., Rockville, MD; 1University of Pennsylvania/Abramson Cancer Center, Philadelphia, PA; South Texas Accelerated Research Therapeutics (START), San Antonio TX

NCT02475213

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

**Background**

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

- An antigen-presenting cell (APC) of the immune system
- Engagement of B7-H3 with T cells and innate immune cells
- Constitutes a checkpoint on a broad range of tumor types

- **Immunoactive role**
  - Expression on T cells: enhances T cell function
  - Expression on B cells: enhances B cell function

- **Fixed role**
  - Expression on tumor cells: facilitates tumor growth and evasion

- **Metastatic enhancing role**
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines

**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)
  - Decreased affinity for inhibitory Fcγ receptors (CD32B receptors)
- Single agent Enoblituzumab anti-tumor activity observed in Phase I trial

**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) 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 (irCR)

**Exploratory Objectives:**
- Explore relationships between PD, safety, and anti-tumor activity of the combination
- Investigate immune-related 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 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**

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

**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

**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**