A Phase 1b Dose-Escalation Study of TRC105 in Combination with Nivolumab in Patients with Metastatic Non-Small Cell Lung Cancer

Abstract # 8386

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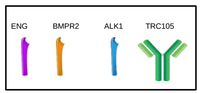
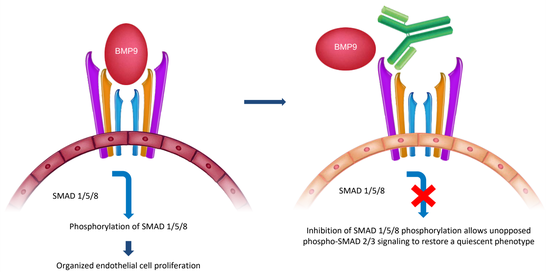
INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is densely expressed by proliferating endothelial cells in solid tumors (Seon 2011), and is upregulated following VEGF inhibition
- Endoglin is also expressed on myeloid derived suppressor cells (MDSCs), a cell type unaddressed by immune checkpoint inhibition (Farsaci 2016)
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2014)
- TRC105 is a chimeric IgG1 monoclonal antibody with high avidity (K_D = 5 pM) that inhibits endoglin binding to bone morphogenic protein (BMP9) to interrupt signal transduction, causes telangiectasia, and potentiates PD-1 inhibition in preclinical models
- TRC105 treatment decreased T regulatory cells among CD4-positive T cells and increased PD-1 expression on peripheral blood CD8-positive T cells in genitourinary cancer patients (Karzai 2015; Apolo 2016)





STUDY RATIONALE

- Nivolumab is an antibody that binds the programmed death receptor (PD-1) and promotes anti-cancer immunity by sensitizing tumors to T cell immune surveillance
- Nivolumab is approved for the treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed following platinum-based chemotherapy, based on improved overall survival versus docetaxel in squamous cell NSCLC (median OS of 9.2 months versus 6.0 months, respectively) and in non-squamous NSCLC (median OS of 12.2 versus 9.4 months, respectively)
- Nivolumab had limited activity in NSCLC following first-line treatment (15 to 20% response rate), and assessment of concurrent endoglin and PD-1 blockade is of significant clinical interest
- Endoglin is expressed on activated MDSCs (Farsaci, 2014), a cell type that inhibits cancer immune surveillance by a mechanism of action distinct from that targeted by nivolumab
- TRC105 and nivolumab have distinct and non-overlapping toxicity profiles
- By targeting MDSCs, TRC105 has the potential to complement nivolumab and improve clinical efficacy over that seen with single agent nivolumab

STUDY DESIGN

- Multicenter, open-label, nonrandomized, dose-escalation study with a dose expansion cohort at the RP2D (N=18) of nivolumab dosed at 240 mg q2wk and TRC105 dosed at 8 or 10 mg/kg weekly for 4 weeks and then given at 15 mg/kg q2wk
- Primary Endpoint:
  - Evaluate the safety and tolerability and determine a RP2D for TRC105 when added to standard dose nivolumab in patients with metastatic NSCLC
- Secondary Endpoints:
  - Assess preliminary evidence of antitumor activity when TRC105 is added to nivolumab, by assessing response rate and progression-free survival
  - Characterize the pharmacokinetic profile of TRC105 when given with nivolumab
  - Evaluate the frequency of TRC105 anti-product antibodies (APA)
- Exploratory Endpoint:
  - Explore effects of TRC105 and nivolumab on tumor immune effector cells

Dose Level 1 (Starting Dose)
- TRC105 8 mg/kg weekly for 4 weeks then 15 mg/kg q2wk IV
- Nivolumab 240 mg q2wk IV
- N = 3 - 6

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Dose Level 2
- TRC105 10 mg/kg weekly for 4 weeks then 15 mg/kg q2wk IV
- Nivolumab 240 mg q2wk IV
- N = 3 - 6

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Expansion Cohort
- RP2D of TRC105
- Nivolumab 240 mg q2wk IV
- N=Up to 12

Eligibility

Inclusion Criteria:
- Histologically confirmed metastatic NSCLC with disease recurrence or progression during or after prior platinum containing doublet chemotherapy regimen
- Programmed death ligand 1 (PD-L1) expression on ≥ 1% of tumor cells by validated immunohistochemistry assay on formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides
- ECOG ≤ 1
- Measurable disease by iRECIST
- Resolution of all acute adverse events resulting from prior cancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 or baseline (except alopecia or neuropathy).

Exclusion Criteria:
- Autoimmune disease
- Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment
- Prior T-cell therapy, including immune checkpoint inhibition
- Immunosuppression
- Receipt of systemic anticancer therapy, including investigational agents, within 28 days prior to study treatment

Study design details are located at https://clinicaltrials.gov/ct2/show/NCT03181308

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