TRC105 treatment decreased T regulatory cells among CD4-negative T cells in genitourinary cancer patients models.

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 to interrupt signal transduction, causes telangiectasia, and potentiates PD-1 inhibition in preclinical studies.

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 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.

By targeting MDSCs, TRC105 has the potential to complement nivolumab and improve clinical efficacy over that seen with single agent nivolumab.

TRC105 and nivolumab have distinct and non-overlapping toxicity profiles. 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 (15-20% response rate), and assessment of concurrent endoglin and PD-1 blockade is of significant clinical interest.

Nivolumab is densely expressed by proliferating endothelial cells 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 RECIST.

Resolusion 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).

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.

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 RECIST.
- Resolusion 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

References: