Adaptive transfer of T cell receptor (TCR) gene-engineered T cells can induce durable anti-cancer responses. Post-infusion cytokine release syndrome (CRS) has been associated with clinical response. Pre-infusion lymphodepletion may influence CRS, granzyme, and clinical responses. While the optimal lymphodepletion regimen is yet not defined, most include both cyclophosphamide (CY) and fludarabine (FLU). TBI-1301 is a novel gene therapy produced by engineering autologous lymphocytes to express an NY-ESO-1-specific TCR using a retrovirus vector that encodes siRNA to silence endogenous TCR. Since less intense lymphodepletion may be sufficient with the use of this novel vector, we are conducting a study where patients are treated with TBI-1301 following lymphodepletion with CY alone.

**BACKGROUND**

**TY 1301**

- **gene name (TCA1301)**: New York esophageal squamous cell carcinoma 1 (TCA1301) is a cancer testis antigen that is expressed in 80% of synovial sarcoma, 33% of esophageal cancer, 43% of ovarian cancer, 45% of malignant melanoma, 31-60% of multiple myeloma, and 24% of head and neck cancers. CT antigens have restricted expression during development to germ cells and placental tissue. However, they can be expressed in tumor cells making them an ideal target for immunotherapy. While little is known about the biological function of NY-ESO-1, it has been suggested that it may play a critical role in cell cycle progression and cellular differentiation.

**TBI-1301**

- **gene-modified T cell product (i.e.: TCR-T)**: TBI-1301 is a gene-modified T cell product (i.e.: TCR-T) where autologous lymphocytes are induced to express a TCR which specifically recognizes tumor cells expressing NY-ESO-1 protein in the context of HLA-A2 and NY-ESO-1. The retroviral vector used to generate TBI-1301, MS3II-NYESO1, also encodes siRNAs (small interfering RNA) that are homologous to the Constant (C)-region sequence of endogenous, but not transduced, TCR.

**Inclusion Criteria TBI-1301 for study treatment:**

- A TCA1301 or HLA-A02:06 positive.
- TCA1301 expression by immunohistochemistry (IHC).
- SCOG Performance Status ≤1.
- If approved and funded standard anti-cancer therapy is available, subjects must have failed, be intolerant to, or have refused treatment.
- Age ≥16 years on consent.
- No anti-cancer chemotherapy or radiation therapy within 28 days of the first dose of TBI-1301.
- Life expectancy greater than 3 months.
- Has not developed a condition that, in the opinion of the investigator, would interfere with the evaluation of TBI-1301 or interpretation of subject safety or study results.

**EXCLUSION CRITERIA**

- Treatment within 6 weeks of the first dose of TBI-1301: (i.e.: intravenous immunoglobulin, high-dose corticosteroids, or chemotherapy).
- Co-morbid conditions that interfere with the evaluation of TBI-1301 or interpretation of subject safety or study results.

**CLINICAL RESULTS**

**BIOMARKER CORRELATES**

- **Lymphocyte Count**
- **CRP**

**CONCLUSIONS**

- Adoptive T cell therapy with TBI-1301 is well tolerated and induces clinical responses in HLA-A02+ patients with NY-ESO-1+ tumors.
- Long-term persistence of NY-ESO-1 TCR-T cells observed.
- **Cytokine Release Syndrome (CRS)** is observed in patients with high NY-ESO-1 expressing tumors.
- **CRP** with increased CRP and IL-6 occurs after minimal lymphodepletion with cyclophosphamide 750mg/m2 once 2 days (without fluidics).
- Investigation of strategies to enhance progression free survival are underway.