Two Phase I/II Open Label Clinical Trials Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 or MAGE-A10 in Subjects With Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NCT02588612/NCT02592577)

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ABSTRACT

Non-small cell lung cancer (NSCLC) accounts for 84% of lung cancer. Survival has recently been impacted by molecularly targeted therapies and checkpoint inhibitors (CPI), and the promising CPI results implicate a role for the immune system in NSCLC.

Between 10-40% of NSCLC express NY-ESO-1 or MAGE-A10 cancer/testis antigens. These studies will evaluate the safety and antitumor activity of genetically engineered affinity enhanced TCRs (NY-ESO-1c259T or MAGE-A10c796T) directed towards a NY-ESO-1 or MAGE-A10 derived peptide complexes with HLA-A*02. In addition, correlative studies to evaluate persistence, phenotype, functionality of engineered T cells, mechanisms of resistance and antigen spreading will be performed.

Methods

Patients are screened (NCT02636855) to identify those who have the relevant HLA-A*02 alleles and NY-ESO-1 or MAGE-A10 tumor expression. For entry into either treatment protocol, patients must have Stage IIIB or IV NSCLC, have failed at least one platinum-containing regimen (may have received CPIs), have measurable disease, ECOG 0-1, adequate organ function, and be without brain metastases, history of severe autoimmune disease or current uncontrolled illness.

Following apheresis, T cells are isolated and expanded with CD3/CD28 beads, transduced with a lentiviral vector containing the NY-ESO-1 c259TCR or MAGE-A10c796TCR, and infused into the patient following lymphodepleting chemotherapy with fludarabine and cyclophosphamide. The NY-ESO-1c259TCR study is a 10 patient study utilizing a dose of 1-6 x 10^9 transduced T cells. The MAGE-A10c796TCR first-in-human study is a modified 3+3 design in up to 28 subjects with escalating doses of 0.1, 1.0 and 1-6 x 10^9 transduced T cells, with staggered treatments to allow for safety review; dose escalation will be guided by the DLT observed and by safety review committee guidance. Response to treatment will be assessed by RECIST v1.1 at weeks 4, 8, 16, 24, every 3 months (for 2 yr) and every 6 months until disease progression.

STUDY OBJECTIVES & ENDPOINTS

Objectives

Primary

- To evaluate the safety and tolerability of autologous genetically modified T cells (NY-ESO-1c259T or MAGE-A10c796T)

Secondary

- To evaluate the efficacy of autologous genetically modified NY-ESO-1c259T/MAGE-A10c796T cells

Explorerary

- To evaluate the persistence, phenotype and functionality of NY-ESO-1c259T/MAGE-A10c796T cells

- To understand mechanisms of resistance to NY-ESO-1c259T/MAGE-A10c796T

- To evaluate antigen spreading as a mechanism of response

Endpoints

Primary

- Toxicity assessment, including dose limiting toxicities (DLT) (MAGE-A10 study only)

- Adverse events, including serious adverse events

- Correlate persistence of NY-ESO-1c259T/MAGE-A10c796T over time with safety parameters

- Correlate circulating cytokines with CRS

Secondary

- Overall response rate, best overall response, time to response, duration of response, duration of stable disease, progression-free survival, overall survival

Explorerary

- Correlate persistence, phenotype and functionality of genetically modified cells with response

- Correlate changes in immunosuppressive myeloid cells/Tregs with and without response

- Investigate the immune contexture of tumor and the mechanisms of tumor resistance, escape and response

- Determine whether loss of NY-ESO-1c259T/MAGE-A10c796T T antigen expression in tumor is a resistance mechanism

STUDY DESIGN

Open-label studies of autologous genetically modified T-cells in NSCLC

- Subjects must screen for relevant HLA alleles and NY-ESO-1/MAGE-A10 antigen expression

- The NY-ESO-1 study will treat 10 subjects; the MAGE-A10 study will treat 12-24 subjects in dose escalation phase + up to 10 subjects at selected target cell dose for a total of 28 subjects

- Eligible subjects will undergo leukapheresis, and their T cells will be isolated, genetically engineered and expanded ex vivo

- The MAGE-A10 study utilizes a modified 3+3 dose escalation design (see table below)

- The NY-ESO-1 dose is 1-6 x 10^9 transduced T cells

- Lymphodepletion is with fludarabine (Flu) at 30 mg/m² and cyclophosphamide (Cy) at 600 mg/m²

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ANTIGEN EXPRESSION

H&E NY-ESO-1 H&E MAGE-A10

SITES & INVESTIGATORS

Moffitt Cancer Center, Tampa, FL

Princess Margaret Cancer Centre, Toronto, ON, Canada

Massachusetts General Hospital, Boston, MA

Washington University in St. Louis, St. Louis, MO

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For more information visit www.ClinicalTrials.gov or www.adaptimmune.com

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