Study Design: Phase 1 Dose Escalation, Multi-tumor Study to Assess Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4 SPEAR T-cells in HLA-A2^{+} Subjects with MAGE-A4^{+} Tumors (NCT03132922)

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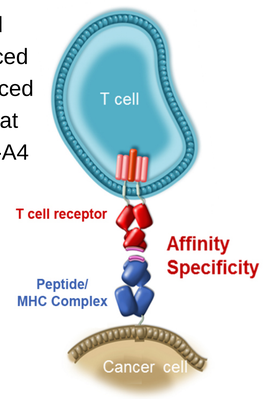
BACKGROUND

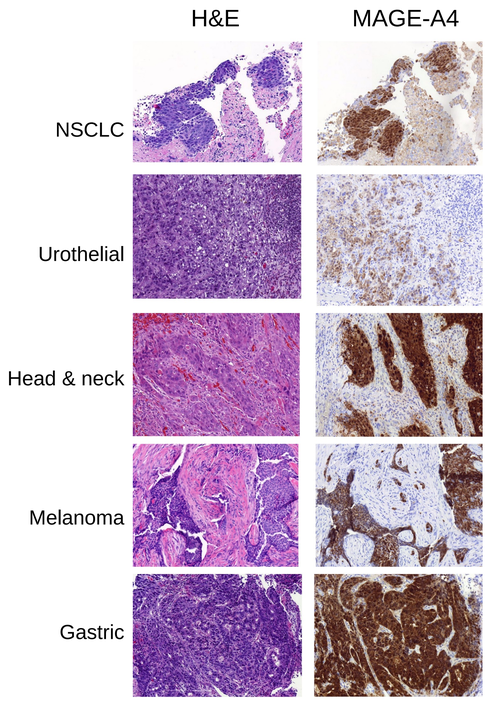
MAGE-A4 is a cancer/testis antigen that has been identified by immunohistochemistry in 13-48% of non-small cell lung cancer (NSCLC), urothelial, melanoma, head and neck, ovarian, gastric and esophageal tumors. This study will evaluate the safety and tolerability of genetically engineered autologous specific peptide enhanced affinity receptor (SPEAR) T-cells (MAGE-A4^{c1032}T-cells) directed towards a MAGE-A4 peptide expressed on tumors in the context of HLA-A*02. Antitumor activity will also be assessed.

MAGE-A4 SPEAR T-CELLS

Autologous CD4^{+} and CD8^{+} T-cells transduced with an affinity enhanced MAGE-A4^{c1032}TCR that recognize the MAGE-A4 specific HLA-A*02 restricted peptide: *GVYDGREHTV*



ANTIGEN EXPRESSION



- Examples of immunohistochemistry staining of tumor tissues for the MAGE-A4 antigen
- Criteria for inclusion: MAGE-A4 at ≥1+ intensity in ≥ 10% of tumor cells

STUDY OBJECTIVES & ENDPOINTS

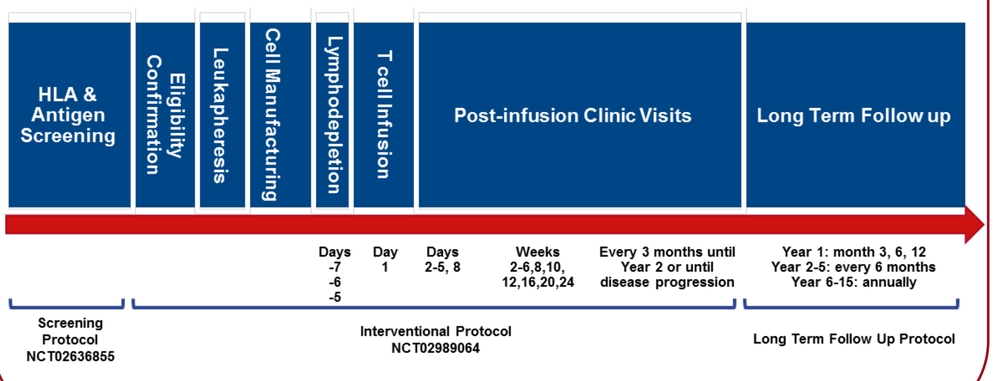
Objectives	Endpoints
Primary • To evaluate the safety and tolerability of autologous genetically modified MAGE-A4 SPEAR T-cells in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors Secondary • To evaluate the anti-tumor activity of MAGE-A4 SPEAR T-cells Exploratory • To explore potential mechanisms of response and resistance to MAGE-A4 SPEAR T-cells • To evaluate germline polymorphisms in cytokine genes and their association with cytokine release syndrome (CRS)	Primary • Adverse events, including serious adverse events • Laboratory assessments • Incidence of dose limiting toxicities (DLTs) and determination of optimally tolerated dose range • Persistence of MAGE-A4 SPEAR T-cells Secondary • Overall response rate, best overall response, time to response, duration of response, duration of stable disease, progression-free survival, overall survival Exploratory • Measurement of persistence, phenotype and functionality of MAGE-A4 SPEAR T-cells in the blood • Measurement of changes in MAGE-A4 SPEAR T-cell subsets, immunosuppressive cell populations and clonal outgrowth of T cell populations in the blood • Evaluation of the tumor microenvironment and measurement of immune cell markers and clonal outgrowth of T cell populations in tumor pre- and post-infusion • Assess DNA for polymorphisms in cytokine genes including those previously associated with CRS

STUDY DESIGN

- An open-label study of autologous genetically modified MAGE-A4-specific T cells in urothelial cancer (transitional cell cancer of the bladder, ureter or renal pelvis), melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, NSCLC (squamous, adenosquamous, or large cell), esophageal (squamous and adenocarcinoma) or gastric cancer
- Subjects must screen positive for relevant HLA alleles and MAGE-A4 antigen expression
- Eligible subjects will undergo leukapheresis and their T cells will be isolated, genetically engineered and expanded ex vivo
- This dose escalation study utilizes a modified 3+3 design (see table below)
- Expansion at optimal dose range up to 20 subjects across tumors
- If 1 out of 3 subjects experiences a DLT, expansion of additional 3 subjects will occur in that dose group
- Lymphodepletion is with fludarabine at 30 mg/m^2 and cyclophosphamide at 600 mg/m^2 for 3 days
- Subjects discontinue "interventional phase" at disease progression
- Long term follow up to 15 years post T cell infusion

Group	Subjects	Transduced cells	Safety Review Interval
1	3 – 6	0.1x10^9 (±20%)	21 days*
2	3 – 6	1x10^9 (±20%)	7 days
3	3 - 6	5x10^9 (>1.2 - 6x10^9)	7 days

*If, in Group 1 or Group 2, 1 out of 3 subjects experiences a DLT requiring expansion of an additional 3 subjects (n=6), the subsequent observation period in Group 2 or Group 3 will be increased from 7 days to 14 days for the respective groups.



KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
• Designated cancer type and prior therapies in Table below • HLA-A*02 and MAGE-A4 positive • ≥ 18 years of age • Anticipated life expectancy >3 months • ECOG performance status 0-1 • Left ventricular ejection fraction ≥50% • Adequate organ function	• HLA-A*02:05 positive in either allele; HLA-A*02:07 or *02 null allele as sole A*02 allele • Previous anti-cancer therapy toxicity must have recovered to ≤ Grade 1 • History of chronic or recurrent severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments • Major surgery within 4 weeks prior to lymphodepletion • Symptomatic CNS metastases • Inadequate pulmonary function: <60% predicted FEV1 and DLCO, interstitial lung disease (pneumonitis), history of pneumonectomy or COPD, chronic systemic or inhaled therapy for respiratory disease • Other malignancy within 3 years • ECG showing clinically significant abnormality • Active infection with HIV, HBV, HCV or HTLV

Tumor Type	Requirements
Urothelial Cancer	Inoperable or metastatic (advanced)
	Has received, is intolerant, or refused a platinum containing regimen in the adjuvant or metastatic setting; may have received atezolizumab and/or other immunotherapies
Melanoma	Inoperable or metastatic (advanced)
	Has received, is intolerant, or refused a CTLA-4 inhibitor (ipilimumab) or a PD-1 inhibitor (nivolumab or pembrolizumab) as monotherapy or a combination of ipilimumab and nivolumab
	Has received or is intolerant of a BRAF inhibitor or the combination of BRAF and MEK inhibitors for BRAFv600 mutant melanoma
Squamous Cell Head and Neck Cancer	Inoperable or metastatic (advanced)
	Has received a platinum containing chemotherapy for treatment of primary tumor in adjuvant, locally advanced, or metastatic settings, is intolerant, or refused such treatment. May have received prior immunotherapy
Ovarian, Primary Peritoneal or Fallopian Tube Carcinoma	Inoperable or metastatic (advanced)
	Has received platinum containing chemotherapy and has platinum refractory or resistant disease
	If platinum sensitive disease, should have received ≥2 lines of chemotherapy
	May have received PARP inhibitors, bevacizumab, or immunotherapy
NSCLC	Histologically or cytologically confirmed diagnosis of advanced (stage IIIB or IV) or recurrent disease
	Has squamous cell, adenosquamous or large cell carcinoma
	Subjects whose tumors are known to have EGFR mutations or ALK gene rearrangements must have failed (progressive disease or unacceptable toxicity) prior EGFR inhibitor or ALK tyrosine kinase inhibitor, respectively
	Subjects with ROS-1 positive tumors must have failed an ALK inhibitor (crizotinib)
	May have received PD-1 inhibitors. There is no limit on lines of prior anti-cancer therapies
Adenocarcinoma and Squamous Cell of the Esophagus, Gastro-esophageal Junction or Gastric Cancer	Inoperable or metastatic (advanced)
	Has received, is intolerant, or refused at least one 5-FU and/or platinum containing regimen
	Subjects whose tumors are known to have Her2neu amplification must have failed (progressive disease or unacceptable toxicity) or refused trastuzumab
	May have received ramucirumab

SITES & INVESTIGATORS

This study is open and currently enrolling

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center	MD Anderson Cancer Center, Houston, TX	David S Hong, MD
SARAH CANNON Fighting Cancer Together	Sarah Cannon Research Institute, Nashville, TN	Melissa Johnson, MD
FOX CHASE CANCER CENTER TEMPLE HEALTH	Fox Chase Cancer Center, Philadelphia, PA	Anthony J Olszanski, MD
UHN Princess Margaret Cancer Centre	Princess Margaret Cancer Centre, Toronto, ON, Canada	Marcus Butler, MD

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