Effect of minimal lymphodepletion prior to ACT with TBI-1301, NY-ESO-1 specific gene-engineered TCR-T cells, on clinical responses and CRS.

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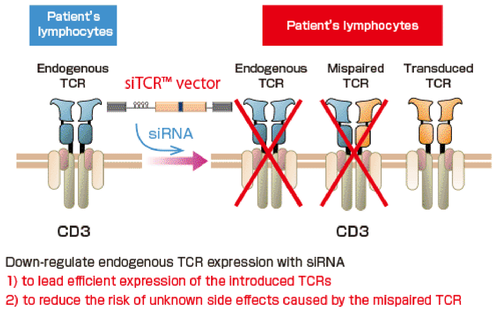
BACKGROUND

Adoptive 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 utility. Pre-infusion lymphodepletion may influence CRS, graft persistence, and clinical responses. While the optimal lymphodepletion regimen is not yet 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 intensive 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.

NY-ESO-1

NY-ESO-1 (gene name *CTAG1B*) or New York esophageal squamous cell carcinoma 1 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 cells; however, can be re-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.

siTCR™ Vector Technology



Down-regulate endogenous TCR expression with siRNA
1) to lead efficient expression of the introduced TCRs
2) to reduce the risk of unknown side effects caused by the mispaired TCR

TBI-1301

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 HLA-A2 and NY-ESO-1. The retroviral vector used to generate TBI-1301, MS3II-NYESO1-siTCR, encodes TCR α and β chains that specifically recognize an NY-ESO-1 derived peptide in the context of HLA-A*02:01 or HLA-A*02:06 molecules. The vector also encodes siRNAs (small interfering RNA) that are homologous to the Constant (C)-region sequence of endogenous, but not transduced, TCR α and β chain mRNAs. Incorporation of the siRNA sequences results in increased expression of the transduced TCR (http://www.takara-bio.com/medi_e/sitcr.html).

STUDY OBJECTIVES

Primary:

- To evaluate the safety profile of TBI-1301
- To determine the recommended phase II (RP2D) dose of TBI-1301 when administered following cyclophosphamide pre-treatment

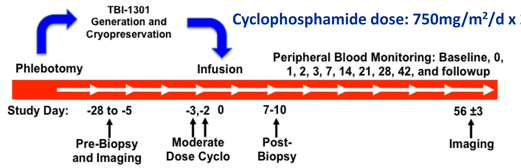
Secondary:

- To evaluate evidence of efficacy of TBI-1301 using RECIST v1.1.

Exploratory (Correlatives):

- Analysis of TBI-1301 tumor infiltration
- Analysis of NY-ESO-1 antigen-specific T cell persistence after TBI-1301 infusion by multimer analysis and cytokine production

TRIAL DESIGN AND KEY INCLUSION

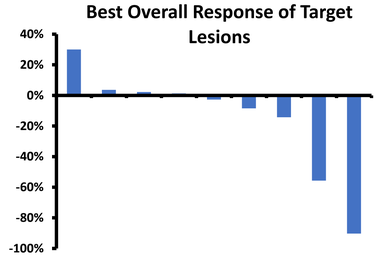


Inclusion Criteria TBI-1301 for study treatment:

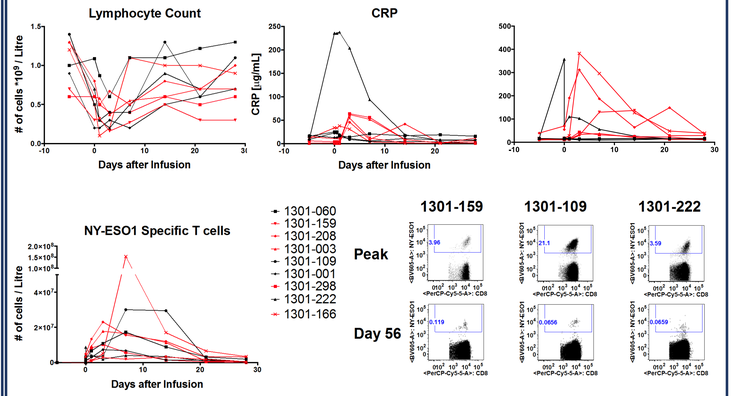
- o HLA-A*02:01 or HLA-A*02:06 positive.
- o Tumor NY-ESO-1 expression by immunohistochemistry (IHC).
- o ECOG Performance Status 0 or 1.
- o If approved and funded standard anti-cancer therapy is available, subjects must have failed, be intolerant to, be ineligible for, or have refused treatment.
- o Age ≥16 years on consent.
- o No anti-cancer chemotherapy or radiation therapy within 28 days of the first dose of cyclophosphamide. No immunotherapy within 6 weeks of the first dose of cyclophosphamide.
- o Life expectancy greater than 3 months.
- o The following laboratory requirements must be met within 7 days of first dose of cyclophosphamide: Absolute neutrophil count (ANC) ≥1.5 x10^9/L (1500/μL), WBC ≥ 2.5 x10^9/L (2,500/μl), Hgb ≥ 80 g/L, Plts ≥ 75 x10^9/L (75,000/μl), Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (≤2.5X if Gilbert's disease), AST and ALT <3.0 x ULN (< 5 x ULN with known liver metastases), Creatinine clearance ≥60 mL/min/1.73 m^2
- o No ongoing use of immunosuppressive medication within 30 days before study treatment, with the exceptions of intranasal or inhaled corticosteroids, or systemic corticosteroids at physiologic doses not to exceed 10mg/day of prednisone or equivalent. Oral steroid use as premedication to prevent allergic reactions to radiologic contrast is allowed.
- o 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.

CLINICAL RESULTS

Pt	Age/Sex/Dx	Prior Tx	NYESO1 Expr	# Cells (x10^9)	CRS	Toci Tx	BOR	Time to Prog (mo)
060	40/F – Endometrial CA	carbo/tax, αPI3K, pembro, xrt	<5%	5.0	None	N	SD 3.6%	3.6
159	49/M – Synovial Sarc	doxo/ifos, xrt	>75%	2.14	Grade 2; fever, n/v, tumor pain	Y	SD -2.7%	5.5
208	38/M – Synovial Sarc	xrt, doxo/ifos	>75%	5.0	Grade 1; fever	N	PR -90.3%	6.2
003	30/F – Synovial Sarc	xrt, doxo/ifos, trem/durva	>75%	5.0	Grade 1; fever	N	PR -55.7%	10.5
109	60/F – Melanoma	encor/bini; pemb/C/T; niv/αLAG3	>75%	5.0	None	N	SD 2.2%	4.5
001	64/F – Melanoma	nivo; ipi; dab/tram, carbo/tax	<5%	5.0	None	N	PD 30%	1.7
298	28/F – Synovial Sarc	doxo/ifos, xrt; gem/tax; pazopanib	>75%	5.0	Grade 1; fever, tumor pain	N	SD -14.3%	7.3
222	50/M – Melanoma	encor/bini; ipi/nivo; pemb/αICOS; durv/IMCgp100	<5%	5.0	None	N	SD 1.3%	4.8
166	79/F – Ovarian Ca	carbo/tax; carbo/gem; doxil/αPDL1; wkly tax; phase 1; carbo	5-25%	5.0	Grade 2; fever, SVT	Y	SD -8.5%	2.9+



BIOMARKER CORRELATES



Methods: Peripheral blood samples were taken on Day 0 before and after infusion as well as Days 1,2,3,7,14,21,28,42 and 56. Lymphocytes were extracted from the blood through ficolling and staining with mAb panels including NY-ESO-1 specific multimer, CD3, CD4, CD8. Samples are stained on BD Fortessa X-20 and analyzed using FlowJo 10.1. Cytokine analysis performed using a Luminex 24-plex cytokine panel. Graphs were generated using Graph Pad Prism V4.1.

CONCLUSIONS

- Adoptive cell therapy with TBI-1301 is well tolerated and induces clinical responses in HLA-A*0201+ 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
- CRS with increased CRP and IL-6 occurs after minimal lymphodepletion with cyclophosphamide 750mg/m^2/d x 2 days (without fludarabine)
- Investigation of strategies to enhance progression free survival are underway

Tumor Immunotherapy Program
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