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The addition of fludarabine to cyclophosphamide for lymphodepleting chemotherapy enhances the persistence of infused NY-ESO-1 TCR anticancer therapy TBI-1301.

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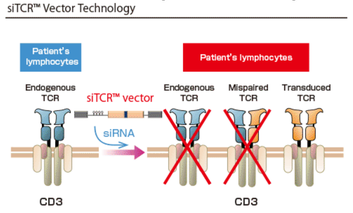
BACKGROUND

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. 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. In this study, we examined a repeat infusion of TBI-1301 and the addition of fludarabine to cyclophosphamide for pre-infusion lymphodepletion.

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.



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 of single/repeat dosing of TBI-1301 administered following cyclophosphamide +/- fludarabine pre-treatment
- To determine the recommended phase II (RP2D) dose of TBI-1301

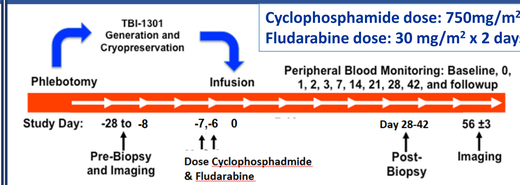
Secondary:

- 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



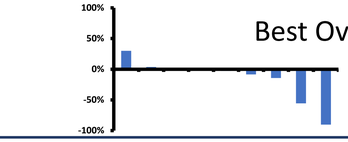
Cyclophosphamide dose: 750mg/m²/d x 2 days
Fludarabine dose: 30 mg/m² x 2 days

Cohort A: Single treatment of TBI-1301
Cohort B: Retreatment for patients who have persisting disease following NY-ESO-1 directed TCR T cell therapy
Cohort C: Double treatment of TBI-1301 on Days 0 and 14

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 m²
- 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: Cohort A



CLINICAL RESULTS

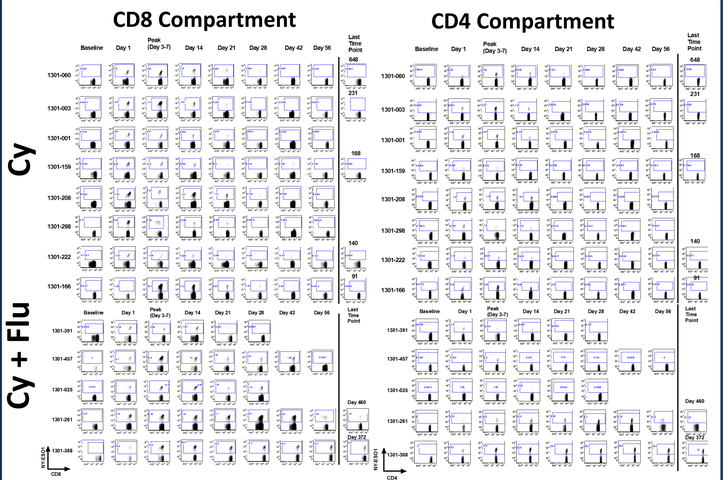
Pt	Age/Sex/Dx	Prior Tx	NYESO1 Expr	# Cells (x10^9)	CRS	Toci Tx	BOR	Time to Prog (mo)
060	40/F – Endometrial	CT, aPI3K, P, xrt	<5%	5.0	None	N	SD 3.6%	3.6
159	49/M – Synovial Sarc	D/If, xrt	>75%	2.14	Grade 2; fever, n/v, tumor pain	Y	SD -2.7%	5.5
208	38/M – Synovial Sarc	xrt, D/If	>75%	5.0	Grade 1; fever	N	PR -90.3%	6.2
003	30/F – Synovial Sarc	xrt, D/If, trem/durva	>75%	5.0	Grade 1; fever	N	PR -55.7%	10.5
109	60/F – Melanoma	TT; P/C/T; N/aLAG3	>75%	5.0	None	N	SD 2.2%	4.5
001	64/F – Melanoma	N; I; TT, CT	<5%	5.0	None	N	PD 30%	1.7
298	28/F – Synovial Sarc	D/If, xrt; GT; pazopanib	>75%	5.0	Grade 1; fever, tumor pain	N	SD -14.3%	7.3
222	50/M – Melanoma	TT; I/N; pemb/aICOS; aPDL1/tebe	<5%	5.0	None	N	SD 1.3%	4.8
166	79/F – Ovarian Ca	CT; CG; doxil/aPDL1; wkly T; C	5-25%	5.0	Grade 2; fever, SVT	Y	SD -8.5%	4.7
391	17/M – Synovial Sarc	D/If; xrt; paz; olaparib/DTIC	50-75%	5.0 x2	Grade 2; fever	Y	SD -3.9%	2.3
457	40/M – Melanoma	I/N; xrt; TT	5-25%	5.0 x2	Grade 2; fever	Y	PD 30.7%	1.4
025	40/M – Melanoma	Interferon; DTIC; I; P; CT; TIL; xrt	>75%	5.0 x2	None	N	PD -2.2%	0.7
261	50/F – Synovial Sarc	MAGEA4 TCR-T	>75%	5.0 x2	Grade 2; fever	Y	SD -29.1%	10.5
368	61/M – Synovial Sarc	Epirubicin/If; MAGEA4 TCR-T	>75%	5.0 x1	None	N	SD 0%	4.2

Abbreviations: carboplatin (C), doxorubicin (D), ifosphamide (If), ipilimumab (I), gemcitabine (G), nivolumab (N), pazopanib (paz), pembrolizumab (P), targeted therapy (TT), taxol (T), tebentafusp (tebe). Patients indicated in upper and lower sections were treated in cohort A and C, respectively. Patients underlined were treated in cohort B.

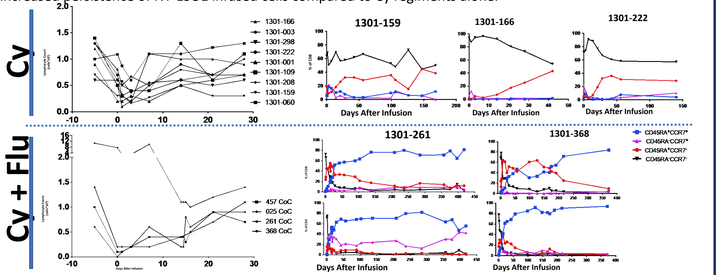
CONCLUSIONS

- Repeated infusion of TBI-1301 is well tolerated and induces clinical responses in HLA-A*0201+ patients with NY-ESO-1+ tumors
- Addition of fludarabine may contribute to longer persistence of NY-ESO-1 TCR-T cells
- Persisting NY-ESO-1 TCR-T following cyclophosphamide/fludarabine lymphodepletion have less differentiated phenotype
- Further characterization of long persisting TBI-1301 cells is ongoing

BIOMARKER CORRELATES



Detection of NY-ESO1 specific CD4 and CD8 T cells in Peripheral Blood. The percentage of NY-ESO1 specific cells peaked between 3 and 7 days after infusion. Patients undergoing Cy+Flu lymphodepletion regiment showed increased persistence of NY-ESO1 infused cells compared to Cy regiments alone.



Absolute Lymphocyte Count (ALC) and Persisting Cell Phenotype. The ALC decrease following cyclophosphamide or the combination of cyclophosphamide and fludarabine therapies is shown. Persisting TBI-1301 cells have high CD45RA and CCR7 expression.