Adoptive T cell Therapy with TBI-1301 results in Gene-engineered T cell persistence and Anti-tumor Responses in Patients with NY-ESO-1 Expressing Solid Tumors

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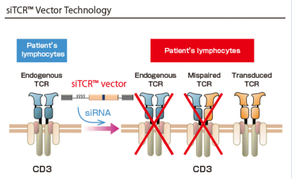
Background

Adoptive T cell therapy (ACT) has shown the ability to induce meaningful, long-term clinical responses in patients with cancer. We are conducting an investigator initiated, single site Phase IB study with TBI-1301 which is adoptively transferred to patients with NY-ESO1 expressing solid tumors. TBI-1301 is produced by engineering autologous lymphocytes to express an affinity-enhanced NY-ESO-1-specific TCR using a proprietary retrovirus vector that encodes siRNA to silence endogenous TCR expression.

Downregulation of endogenous TCR expression promotes efficient expression of the introduced TCR and reduces the risk of unknown side effects caused by the TCR mispairing. Using flow cytometry analysis we can track the persistence and phenotype of the infused cells for months after initial infusion.



Clinical Trial Design

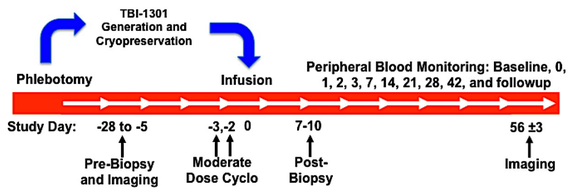


Figure 1. Schematic for TBI-1301 trial. HLA-A*02:01+ or HLA-A*02:06+ patients with NY-ESO-1 expressing tumor undergo phlebotomy at least 6 weeks prior to the planned infusion. Autologous lymphocytes are then transduced to express NY-ESO-1 specific TCR. The retroviral vector used to generate TBI-1301, MS3II-NYESO1-siTCR, encodes TCR α and β chains that specifically recognize an NY-ESO-1 derived peptide that is presented in the context of HLA-A*02:01 or HLA-A*02:06 molecules. The vector also encodes siRNA (small interfering RNA) that are homologous to the constant (C)-region sequence of endogenous, but not transduced, TCR α and β chain mRNAs (5-7). Patients undergo lymphodepleting chemotherapy with 750mg/m2/d of Cyclophosphamide on Days -3 and -2 before being infused with 5x10^9 cells on Day 0. Radiographic imaging of sites of tumor was performed preinfusion and on Day 56 and every 3 months thereafter.

Methods

Tumour NY-ESO-1 expression by immunohistochemistry was determined as negative, <5%, 5-25%, 25-50%, 50-75%, or >75%. Response was determined using RECIST v1.1. 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; additional samples were taken as follow up every 3 months post infusion. Lymphocytes were isolated from the blood through ficolling and stained with A2/NY-ESO-1-specific multimer and 5 panels of antibodies including CD3, CD4, CD8, CD56, CD19, CD45RA, HLA-DR, CD27, CD57, CCR7, PD1, CTLA-4, PD-L1, TIGIT, 4-1BB, CD28, LAG3, CD103, CD107, Granzyme, Perforin, IL-2, IFNg, Ki67, CD25, CD127, FoxP3 and Helios. Patient's serum was analyzed for IFN-γ, IL-6, IL-8 and IP-10, using the BioRad 27-plex Human Cytokine Immunoassay.

Results

Table 1. Characteristics of the Patients and Clinical Outcomes.

Patient	Age/Sex - Diagnosis	Prior Treatment	NY-ESO-1 Expression by Tumour	# Infused Cells	Grade of CRS	Best Overall Response (RECIST)	Time to Progression
060	40/F - Endometrial	Carbo/Tax, PI3K inh, Pembrolizumab, xrt	<5%	5.0	None	SD (3.6%)	3.6 month
159	49/M - Synovial	Doxo/Ifos, xrt	>75%	2.14	Grade 2 (tocilizumab)	SD (-2.7%)	5.5 month
208	38/M - Synovial	Doxo/Ifos	>75%	5.0	Grade 1	PR (-90.3%)	6.2 month
003	30/F - Synovial	Doxo/Ifos, Treme/Durva	>75%	5.0	Grade 1	PR (-55.7%)	10.5 month
001-B	64/F - Melanoma	Nivo, Ipi, Dab/Tram, Carbo/Taxol	<5%	5.0	None	PD (+30%)	1.7 month
109	60/F/ - Melanoma	Encora/Binimetinib; Pembro/Carbo/Tax	>75%	5.0	None	SD (2.2%)	4.5 month
298	28/F – Synovial Sarcoma	doxo/ifos, xrt; gem/tax; pazopanib	>75%	5.0	Grade 1	SD (14.3%)	7.3 month
222	50/M – Melanoma	encor/bini; ipi/nivo; pemb/aICOS; durv/IMCgp100	<5%	5.0	None	SD (1.3%)	4.8 month
166	79/F – Ovarian Carcinoma	carbo/tax; carbo/gem; doxil/aPDL1; wkly tax; phase 1; carbo	5-25%	5.0	Grade 2 (tocilizumab)	SD (8.5%)	4.7 month

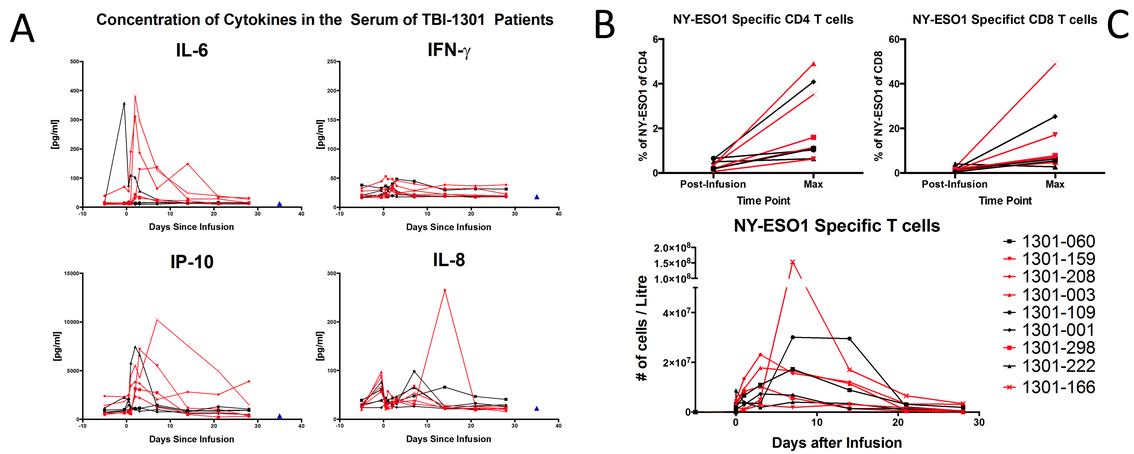
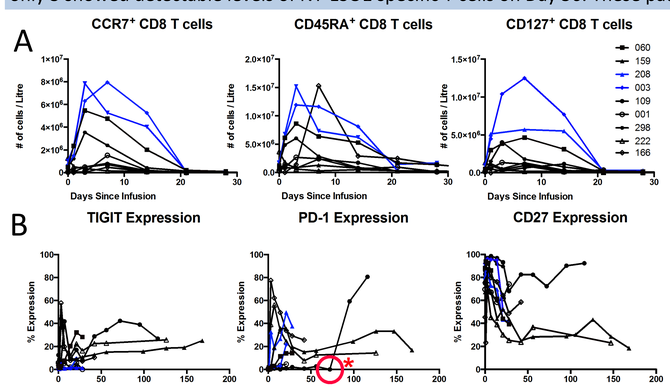


Figure 2. Detection of NY-ESO-1 specific CD4 and CD8 T cells in Peripheral Blood. (A) Patients experiencing AE (coloured in red) had elevated levels of IL-6 as well as IP-10 following the infusion. However, concentrations of IFN-γ and IL-8 were comparable to healthy donor levels and remained unchanged. **(B)** Percent of CD4 and CD8 T cells that are specific for A2/NY-ESO-1 is shown. Additionally, total number of NY-ESO-1 specific CD4 and CD8 T cells was calculated based on the total number of lymphocytes. **(C)** Persistence of infused cells was monitored for all patients, however only 3 showed detectable levels of NY-ESO1 specific T cells on Day 56. These patients continue to show detectable levels of the infused cells more than 100 days after infusion.



* Patient was receiving pembrolizumab therapy before TBI-1301 enrollment and received atezolizumab 70 days after TBI Infusion

Figure 3. Phenotype of NY-ESO-1 specific CD8 T cells detected in the periphery. (A) Absolute number of cells expressing CD45RA, CCR7 and CD127 was calculated based on lymphocyte counts and percentage of NY-ESO-1 specific CD8 T cells in the periphery. Patients who responded to the treatment (coloured in blue) showed higher number of cells expressing those markers, compared to patients who did not (coloured in black) suggesting a role for the cells in tumor recognition. **(B)** Long-term persisting NY-ESO-1 specific CD8 T cells show substantial expression of TIGIT and PD1 markers.

Summary

1. Adoptive transfer of TBI-1301, T cells engineered to express an A2/NY-ESO-1 TCR, can induce clinical responses and cytokine release syndrome.
2. Three patients showed detectable levels of NY-ESO-1-specific T cells in the periphery for greater than 100 days post infusion.
3. Immunophenotyping experiments are ongoing: patients responding to the treatment appear to have increased number of CD45RA, CCR7 and CD127 positive CD8 T cells.
4. Biomarker analysis of persisting TBI-1301 cells in peripheral blood showed increased expression of CD27, PD-1 and TIGIT cells.

Disclosures/Acknowledgements

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