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Tumor responses and early onset cytokine release syndrome in synovial sarcoma patients treated with a novel affinity-enhanced NY-ESO-1-targeting TCR-redirected T cell transfer

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ABSTRACT

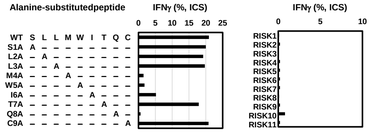
Background: Adoptive transfer of TCR-redirected T cells has been reported to exhibit efficacy in some of melanoma and sarcoma patients. However, there have not been well known about cytokine release syndrome (CRS) or its relations to tumor responses. This study evaluates clinical responses in association with the cell kinetics and CRSs after transfer of high-affinity HLA-A*02:01/*02:06 restricted NY-ESO-1 TCR-gene transduced T cells in NY-ESO-1-expressiong cancer patients with HLA-A*02:01 or A*02:06 (NCT02366546). Methods: We developed a novel-type affinity-enhanced NY-ESO-1-specific TCR and an originally-developed retrovirus vector that encodes siRNA to silence endogenous TCR creation. The NY-ESO-1/TCR sequence is mutated for high affinity with replacements of G50A and A51E in CDR2 region. This is a first-in-man clinical trial of the novel NY-ESO-1-specfic TCR-T cell transfer to evaluate the safety, in vivo cell kinetics and clinical responses. It was designed as a cell-dose escalation from 5 x10^8 to 5 x10^9 cells. NY-ESO-1-expressing refractory cancer patients were enrolled, with 3+3 cohort design. Cyclophosphamide (1,500mg/m^2) were administered prior to the TCR-T cell transfer as pre-conditioning. Results: 9 patients were treated with the NY-ESO-1/TCR-T cell transfer. The TCR-T cells expanded in peripheral blood with a dose-dependent manner, associated with rapid proliferation within 5 days after the cell transfer. 3 patients receiving 5x10^9 cells developed early-onset CRSs, with elevations of serum IL-6, IFN-γ. The CRSs developed on day1 or 2 after the cell transfer. They were well managed with tocilizumab treatment. 3 synovial sarcoma patients exhibited tumor shrinkages of partial responses, and they all had high-expression of NY-ESO-1 in the tumor samples, namely, 75% or more. Exploratory analysis revealed that multiple chemotactic cytokines including CCL2/MCP-1 and CCL7/MCP-3, and IL-3 increased in the serum from the patients with CRS. The proportions of effector-memory phenotype T cells in the infused cell-product were significantly associated with CRS development. Conclusions: The affinity-enhanced NY-ESO-1/TCR-T cell transfer exhibited early-onset CRS in association with in vivo cell proliferation and sequential tumor responses in the patients with high-NY-ESO-1-expressing synovial sarcoma.

METHODS

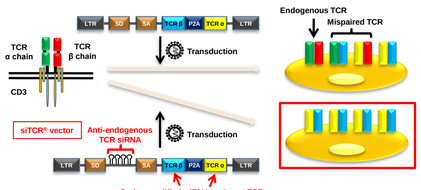
NY-ESO-1$_{157-165}$-specific-TCR is replaced with G50A and A51E in CDR2ß for high affinity[1].

TCR BV13	CDR2β 48	49	50	51	52	53	CDR3β 96	97	98	99	K_D (μM)	k_{on} (M^{-1} sec^{-1})	k_{off} (s^{-1})
WT (LAU155 BV13c1)	S	V	G	A	G	I	G	A	A	G	21.4	1.1×10^4	0.23
V49F[a]	S	I	G	A	G	I	G	A	A	G	n.a	n.a	n.a
G50A[a]	S	V	A	A	G	I	G	A	A	G	4.6	1.5×10^4	0.069
A51E[a]	S	V	G	E	G	I	G	A	A	G	7.1	1.7×10^4	0.12
G50A+A51E[a]	S	V	**A**	**E**	G	I	G	A	A	G	1.9	2.4×10^4	0.045
A97L[a]	S	V	G	A	G	I	G	L	A	G	2.7	2.3×10^4	0.061
G50A+A51E+A97L[a]	S	V	A	E	G	I	G	L	A	G	0.9	1.4×10^4	0.013
1G4 (36)[a]	S	V	G	A	G	I	G	N	T	G	14.2	1.2×10^4	0.17
wtc51 (modified)[c]	S	V	A	I	Q	T	G	A	A	G	0.015	8.5×10^4	0.0013

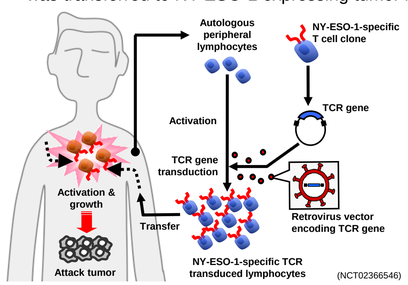
G50A+A51E TCR had low reactivity to analogous peptides searched by the BLAST database[2].



Retroviral vector encoding siRNA to silence endogenous TCR is adopted in TBI-1301[3].



Autologous T cells transduced with G50A+A51E TCR and silenced endogenous TCR (TBI-1301) was transferred to NY-ESO-1 expressing tumor bearing HLA-A*02:01 or A*02:06 patients.



(NCT02366546)

for 10-12 days		Day -3, -2 (Day -8〜-2)	Day 0	Day 28	Day 56
200mL blood	TCR-gene transduction & Culture	preconditioning Cy or (Cy+Flud)	TCR-T-cell transfer	Evaluation	Re-evaluation
Frozen, QC					
			Monitoring Safety & Cell kinetics		

Cohort	Preconditioning	TBI-1301
1	CY	5.0×10^8 cells
2	CY	5.0×10^9 cells
3	CY+Flud	5.0×10^9 cells

CY, cyclophosphamide: 750mg/m^2/day, 2 days
Flud, fludarabine: 20mg/m^2/day, 5 days

RESULTS

Patients who received adoptive transfer of TBI-1301

Cohort	Patient ID	Age	Sex	Cancer type	Tumor lesions at entry	Best tumor response
1	TBI1301-01	67	F	breast cancer	lung, lymph node	PD
	TBI1301-02	40	F	synovial sarcoma	lung	SD*
	TBI1301-03	73	M	malignant salivary tumor	primary lesion at parotid gland	SD
2	TBI1301-07	46	M	synovial sarcoma	soft tissue at femoral area, lung	PR
	TBI1301-09	61	M	melanoma	skin, liver, peritonium	SD
	TBI1301-08	70	M	synovial sarcoma	chest wall, soft tissue at inguinal area, bone	PR
	TBI1301-14	65	F	ovarian cancer	lymph node	SD*
	TBI1301-16	25	M	synovial sarcoma	lung	PR
	TBI1301-15	45	F	myxoid liposarcoma	retroperitonium	SD

*cases without measurable lesions

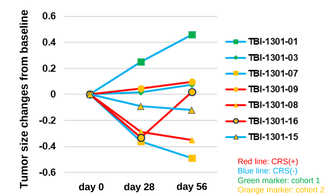
TBI-1301-related adverse events (AEs)

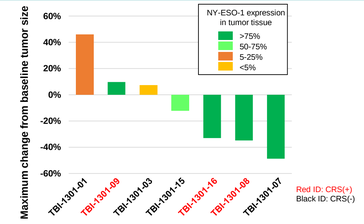
	Grade 1	Grade 2	Grade 3	Grade 4
Cytokine release syndrome		3		
Fever		3		
Fatigue	2			
Diarrhea		2		
Interstitial lung injury			1	
Appetite loss		1		
Constipation	1			
Hypoalbuminemia	1	1		
Edema		1		
Cancer pain		1		
Fibrinogen decrease		1		

(No. of patients)

- One case of ALT elevation, flush, proteinuria, purpura, platelet decrease, hyperkalemia, uric acid increase, ferritin increase, creatinine increase and tachycardia were also observed. Each AE was grade 1.
- Three patients developed CRS 13.5-28.5 hours after TBI-1301 infusion. They were treated with tocilizumab and resolved.
- No grade 4-5 AEs were observed.

TBI-1301 dose and NY-ESO-1 expression may be related with tumor response



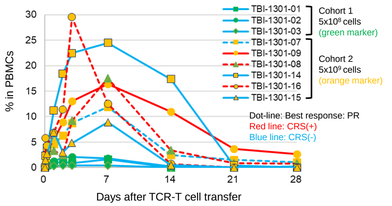


Diagnostic criteria and grade of CRS in this trial

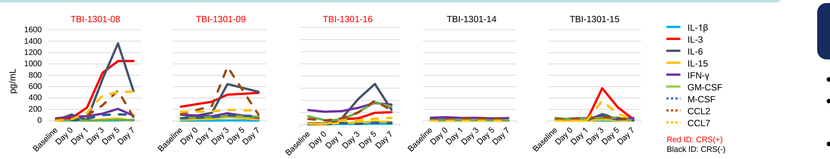
Fever (≥38 ℃) and
- Fatigue, Nausea, Vomiting, Appetite loss or
- Hypotension or
- Hypoxia or
- Tachycardia

Grade	Toxicity
1	Symptoms are not life threatening and require symptomatic treatment only
2	Symptoms require and respond to moderate intervention: Oxygen requirement <40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention: Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
4	Life-threatening symptoms: Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	Death

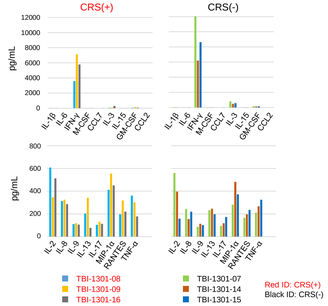
TBI-1301 kinetics



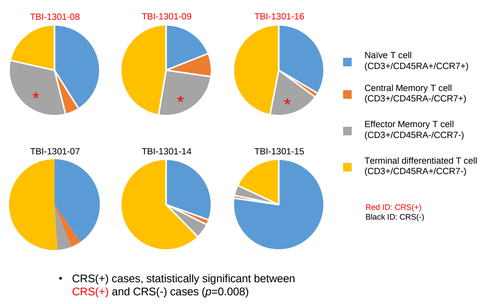
Serum cytokine levels in 5 patients: 3 from CRS(+) and 2 from CRS(-)



Cytokine secretion from TBI-1301 products after in vitro NY-ESO-1-peptide stimulation



CD8+ T cell Phenotype of TBI-1301 product



- CRS(+) cases, statistically significant between CRS(+) and CRS(-) cases (p=0.008)

The duration of response

CONCLUSIONS

- TBI-1301 was expanded in patients in a dose-dependent manner.
- In cohort 2, 3 patients developed CRS, but treatable with tocilizumab. Grade≥3 CRS was not observed.
- In CRS patients, serum CCL2, CCL7, IL-3 and IL-6 levels were elevated.
- TBI-1301 pre-infusion product showed similar cytokine secretion after in vitro stimulation. CCL2, CCL7 and IL-6 were not secreted by TBI-1301.
- The frequency of effector memory phenotype in TBI-1301 product may be related with CRS.
- TBI-1301 had 3 PR. NY-ESO-1 expression and TBI-1301 dose may be related with tumor response.

REFERENCES

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2. Y. Miyahara, Mie University. Unpublished data.
3. Cancer Res 69: 9003-11, 2009

ACKNOWLEDGEMENT

- We are grateful to members of TakaraBio Inc. for the preparation of TCR-T-cells and the analysis of the cell kinetics, and also to members of Takara Bio Inc. and FiveRings Co. for their support to the clinical trial management.
- This research is supported by the Medical Research and Development Programs Focused on Technology Transfer, Adaptable and Seamless Technology Transfer Program Through Target-driven R&D (A-STEP) from Japan Agency for Medical Research and development, AMED.

Poster presented at 2019 ASCO annual meeting, Chicago, IL

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