# Results from phase I/II study of NY-ESO-1-specific TCR gene-transduced T cell therapy (TBI-1301: mipetresgene autoleucel)

**Abstract # 11558** 

## in patients with advanced synovial sarcoma.

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#### BACKGROUND

#### Synovial sarcoma (SS) is a rare type cancer that accounts for approximately 5-10% of all soft-tissue sarcomas, and the incidence is around 70 cases per year in Japan.

- First-line anthracycline-based chemotherapy has limited efficacy, and also current second-line chemotherapy is not fully effective, so improved treatment is required.
- New York esophageal squamous cell carcinoma 1 (NY-ESO-1) antigen is a hydrophobic cancer-testis antigen and expressed in 50-80 % SS patients.
- TBI-1301 (mipetresgene autoleucel) is a novel gene engineered autologous T cell product with NY-ESO-1 siTCR<sup>TM</sup> retroviral vector which expressed affinityenhanced NY-ESO-1-specific TCR and siRNA to silence endogenous TCR.
- This study was conducted to assess the safety and efficacy of TBI-1301 in patients with advanced or recurrent SS not suitable for surgical resection and resistant to anthracycline (NCT03250325).

## PATIENTS CHARACTERISTICS

Eight of 17 patients who provided informed consent were eligible for primary registration and underwent blood sampling for TBI-1301 manufacturing. All 8 patients were eligible for secondary registration and received TBI-1301 infusion. Patients characteristics at primary registration are shown in Table 1. 1 patient (Patient ID: TBI1301-03-08) received a half dose of TBI-1301 due to the patient's systemic condition related to cytokine release syndrome (CRS).

TABLE 1 PATIENTS CHARACTERISTICS				
At primary registration		N=8		
Sex, n (%)	Male	7 (87.5)		
	Female	1 (12.5)		
Age, years, median (min, max)		53 (21, 61)		
HLA type, n (%)	HLA-A*02:01	4 (50.0)		
	HLA-A*02:06	3 (37.5)		
	HLA-A*02:01/	1 /12 5\		
	HLA-A*02:06	1 (12.5)		
NY-ESO-1 antigen expression, n (%)	Negative	0 (0.0)		
	<5%	1 (12.5)		
	5% to < 25%	0 (0.0)		
	25% to <50%	1 (12.5)		
	50% to <75%	2 (25.0)		
	≥75%	4 (50.0)		
Number of prior chemotherapy, n (%)	0	0 (0.0)		
	1	3 (37.5)		
	2	2 (25.0)		
	3	2 (25.0)		
	4	1 (12.5)		
Performance status, n (%)	0	4 (50.0)		
	1	4 (50.0)		
	2	0 (0.0)		
	3	0 (0.0)		

#### **METHODS**

#### Study design

- This study was an open label phase I/II study to evaluate safety, appearance of replication competent retrovirus (RCR), appearance of clonality, in vivo cell kinetics and clinical responses.
- This study comprised a screening, pretreatment, treatment, and observation period. Delayed toxicity information were collected during a follow-up period (Figure 1).

#### **Patients**

- Key eligibility criteria were as follows;
- 18 years or older at te time of consent
- Patients who had histologically diagnosed advanced or recurrent SS that was unable to be surgically resected
- Patients who had received between 1-4 systemic chemotherapy regimens, including anthracycline
- HLA type was either HLA-A\*02:01 or \*02:06 or both - NY-ESO-1 antigenic expression in the tumor tissue
- Key exclusion criteria were as follows;
- Patients who had serious complications
- Patients who had active autoimmune disorders that require systemic corticosteroids or immunosuppressants
- Patients who had active metastatic disease in the CNS

#### Interventions

- Lymphodepletion with intravenous cyclophosphamide 750 mg/m $^2$  once daily on days -3 and -2.
- 5 x 10<sup>9</sup> TBI-1301 cell suspension was divided and delivered by infusion of 2.5 x 10<sup>9</sup> cells on day 0 and
- Tocilizumab (8 mg/kg over 1 hour by IV administration) was made available in the event of cytokine release syndrome.

#### Manufacturing

- Peripheral blood mononuclear cells (PBMC) were obtained from blood (up to 200 mL) collected from each patient by Ficoll-Paque density gradient centrifugation without an apheresis process.
- PBMC were cultured and stimulated with anti-CD3 antibody and RetroNectin® and transduced with NY-ESO-1 siTCR<sup>™</sup> retroviral vector.

#### **Outcomes**

- Primary endpoints were safety and objective response rate (ORR) which was assessed according to RECIST version 1.1.
- Main secondary efficacy endpoints were progressionfree survival (PFS) and overall survival (OS).
- Tumor response was based on imaging diagnosis and assessed by the each investigator and by central review committee.

# FIGURE 1 STUDY DESIGN reatment Observation period Follow-up

#### Safety

- Adverse events occurred in all 8 patients.
- There were no deaths and no study discontinuation which were attributable to adverse events.
- Most grade 3 or higher adverse events were due to the pretreatment drug (Table 2).
- CRS occurred in 4 patients (50.0%) and consisted of 1 patient with grade 1 and 3 patients with grade 2. All patients recovered with prespecified treatment, in which 2 patients were treated with symptomatic therapy, 1 patient was treated with tocilizumab, and 1 patient was treated with both tocilizumab and corticosteroid.
- No patient had immune effector cell- associated neurotoxicity syndrome (ICANS).
- Neither RCR nor clonal dominance were detected in any patients throughout the study period and the follow-up period.

#### **Efficacy**

- ORR according to RECIST version 1.1 by central assessment was 50.0% (CR; 0, PR; 4, SD; 1, PD; 3).
- The median PFS according RECIST version 1.1 was 227.0 days. The median OS was 650.0 days. PFS and OS was calculated using the Kaplan-Meier method (Figure 5).
- Representative CT scan images of lung metastases that occurred in one patient (Patient ID: TBI1301-03-02) are shown in Figure 6.

#### TBI-1301 kinetics in peripheral blood

- The main pharmacokinetic parameters of TBI-1301 were as follows;
- T<sub>max</sub> median (min, max) : 7.0 (6.8-9.9) days
- T<sub>last</sub> median (min, max) : 17.9 (8.9-58.9) days

#### Table 2 Summary of ≥ Grade 3 AEs

Events (MedDRA Preferred Term)			
	Any relationship; n (%)	TBI-1301 related; n (%)	Cyclophosphamid related; n (%)
Febrile neutropenia	1 (12.5)	0 (0.0)	1 (12.5)
Acute cholangitis	1 (12.5)	1 (12.5)	0 (0.0)
Fall	1 (12.5)	0 (0.0)	0 (0.0)
Patella fracture	1 (12.5)	0 (0.0)	0 (0.0)
Decreased lymphocyte count	7 (87.5)	0 (0.0)	6 (75.0)
Decreased neutrophil count	7 (87.5)	1 (12.5)	7 (87.5)
Decreased platelet count	1 (12.5)	1 (12.5)	1 (12.5)
Decreased white blood cell count	6 (75.0)	0 (0.0)	6 (75.0)
Increased pancreatic enzymes	1 (12.5)	1 (12.5)	0 (0.0)
Hyperkalemia	1 (12.5)	0 (0.0)	0 (0.0)
Hyponatremia	1 (12.5)	0 (0.0)	1 (12.5)
Hypophosphatemia	1 (12.5)	1 (12.5)	1 (12.5)
Loss of appetite	1 (12.5)	0 (0.0)	1 (12.5)

#### [Reference data]

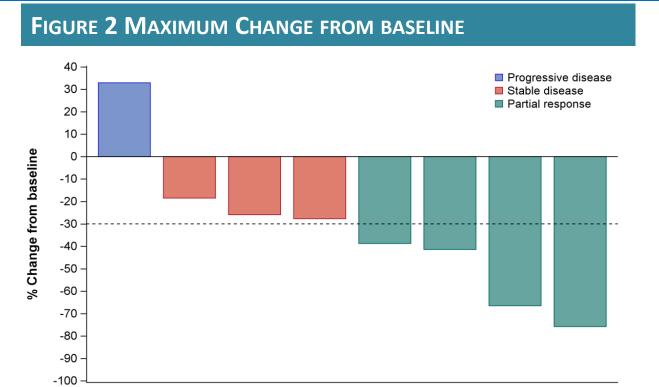
The efficacy of pazopanib in patients with soft-tissue sarcomas (PALETTE study)

- > ORR: 5.7 %
- Median OS: 12.5 months

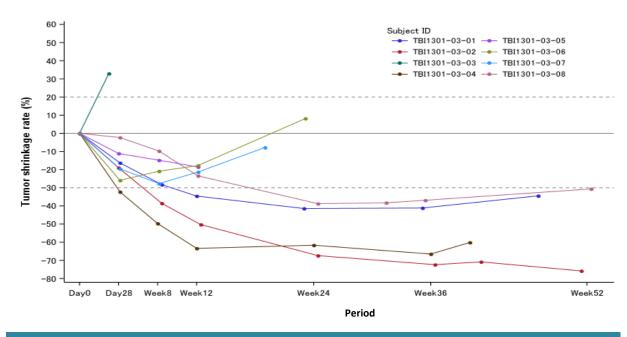
van der Graaf WT et al. Lancet 2012;379(9829):1879-86 | Atrisk

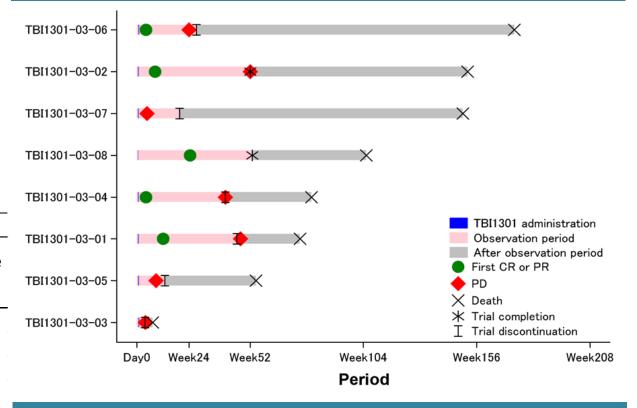
Total (N=8)

#### RESULTS

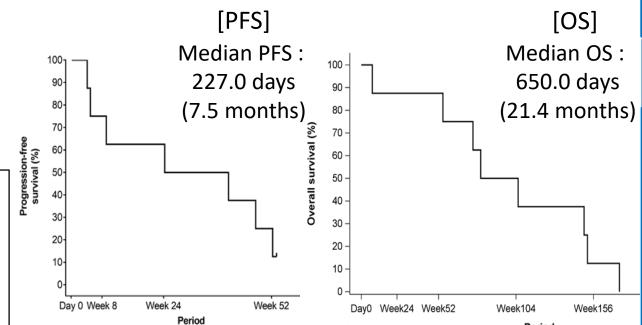


#### FIGURE 3 CHANGE FROM BASELINE IN SUM OF TARGET LESION





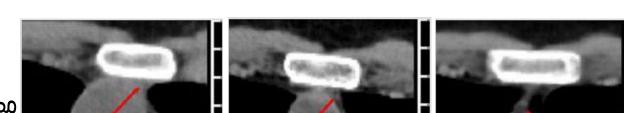
## FIGURE 5 KAPLAN-MEIER CURVE OF PFS AND OS



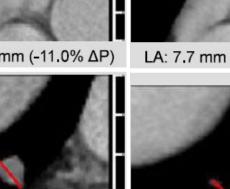
### FIGURE 6 REPRESENTATIVE CT SCAN IMAGES

[Patient ID: TBI1301-03-02; 21-year-old male]









Week 36

LA: 3,3 mm (-60,2% ΔP)

## Discussion/Conclusion

- Adoptive immunotherapy with TBI-1301 to selectively target NY-ESO-1 positive tumors will become a promising treatment for advanced or recurrent SS with acceptable toxicity.
- > ORR was 50.0% and median OS was 650.0 days.
- New technologies, including siTCR<sup>TM</sup> vectors and RetroNectin® were implemented in the manufacturing process of TBI-1301.
- Mispairing of the introduced TCR with endogenous TCR has potential risk to develop an auto-immune reaction. Using siTCR<sup>TM</sup> technology, it is possible to suppress the expression of endogenous TCR and avoid TCR mispairing. In fact, throughout the study, no symptoms suggestive of auto-immune reaction were observed.
- > Using a unique culture method incorporating RetroNectin®, TBI-1301 was manufactured from a small amount (200 mL) of collected blood without an apheresis process. As a result, the success rate of the TBI-1301 manufacturing in this study was 100%.
- Despite the milder lymphodepletion regimen, the efficacy was in line with results of other adoptive immunotherapy regimens directed against the NY-ESO-1 antigen that have been previously reported.

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