Results from phase I/II study of NY-ESO-1-specific TCR gene-transduced T cell therapy (TBI-1301: mipetresgene autoleucel) in patients with advanced synovial sarcoma.

Abstract # 11558

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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™ retroviral vector which expressed affinity-enhanced 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 / 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 therapy
  - 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 10^9 TBI-1301 cell suspension was divided and delivered by infusion of 2.5 x 10^9 cells on day 0 and day 1.
- Tocilizumab (8 mg/kg over 1 hour by IV administration) was made available in the event of cytokine release syndrome.

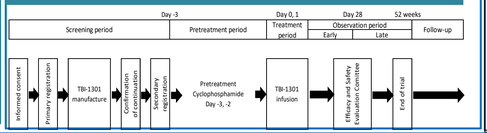
Manufacturing

- 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™ 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 progression-free 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



Results

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_{max} median (min, max) : 7.0 (6.8-9.9) days
  - T_{last} median (min, max) : 17.9 (8.9-58.9) days

Table 2 Summary of ≥ Grade 3 AEs

Events (MedDRA Preferred Term)	Total (N=8) Any relationship; n (%)	TBI-1301 related; n (%)	Cyclophosphamide 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

Figure 2 Maximum Change from Baseline

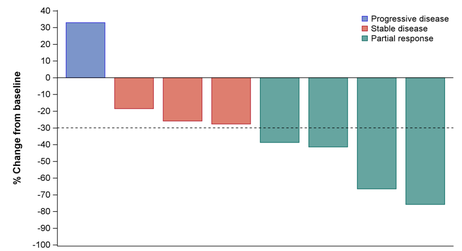


Figure 3 Change from Baseline in Sum of Target Lesion

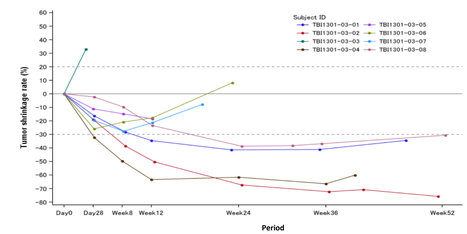


Figure 4 Duration and Type of Response for Individual Patients

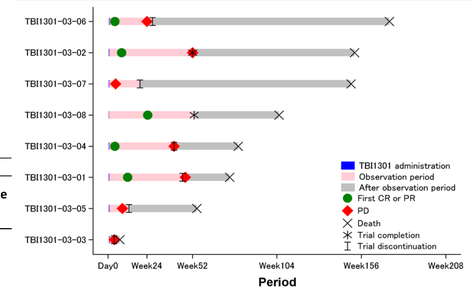


Figure 5 Kaplan-Meier Curve of PFS and OS

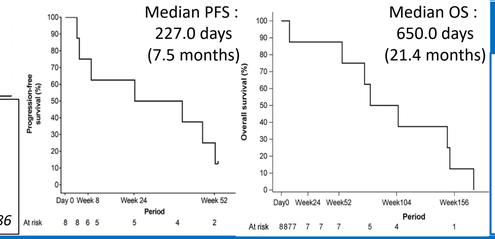
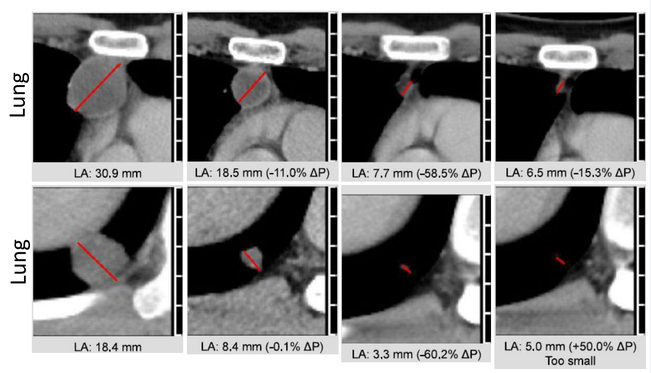


Figure 6 Representative CT scan images

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



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™ 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™ 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.

Acknowledgements

The authors thank all patients who participated in this study, their families and their caregivers.
And the authors also thank Dr. Hiroshi Shiku (Mie University) and Dr. Yasuo Ohashi (Chuo University). Dr. Shiku made a great contribution for his valuable and constructive suggestions during the development of TBI-1301. He passed away in 2022. Dr. Ohashi made a great contribution to the design of this study, especially to biostatistical field. He passed away in 2021.
This study was funded by Takara Bio Inc.