#4157

A novel affinity-enhanced NY-ESO-1-targeting TCR-redirected T cell transfer exhibited early-onset cytokine release syndrome and subsequent tumor responses in synovial sarcoma patients

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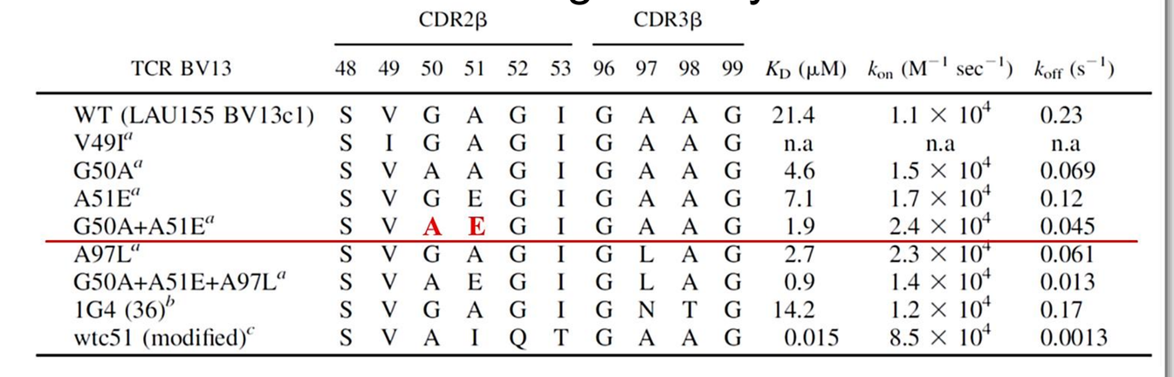
ABSTRACT

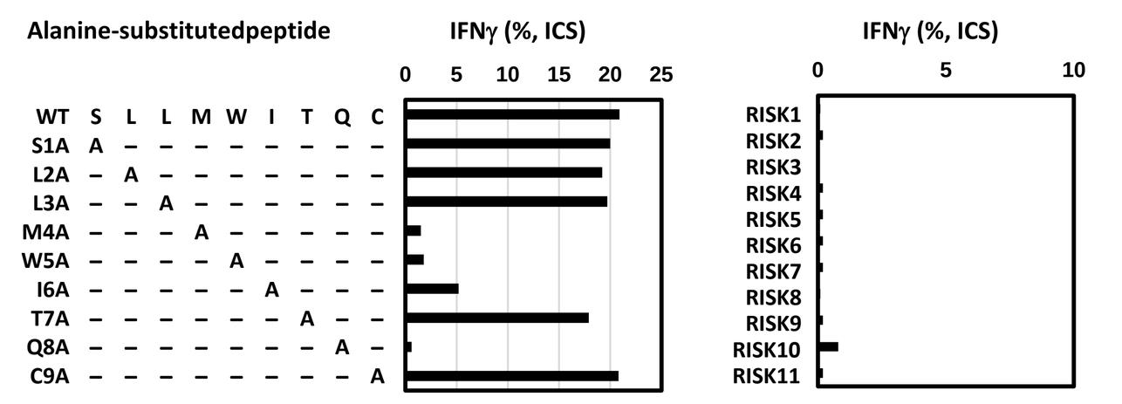
Background: Adoptive transfer of TCR-redirected T cells has been reported to exhibit efficacy in some patients with melanoma and sarcoma. However, cytokine release syndrome (CRS) or its relations to tumor response has not been well documented. This study aimed to evaluate clinical responses in association with the cell kinetics and CRSs after transfer of high-affinity NY-ESO-1 TCR-gene transduced T cells in cancer patients. (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 was mutated for high affinity with replacements of G50A and A51E in CDR2 region. This is a first-in-human 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: Nine patients were treated with the TCR-T cells that expanded in peripheral blood with a dose-dependent manner, associated with rapid proliferation within 5 days after infusion. Three patients receiving 5x10^9 cells developed early-onset CRSs, with elevated levels of serum IL-6, IFN-γ. The CRSs on day1 or 2 were well managed with tocilizumab treatment. Three synovial sarcoma patients exhibited tumor shrinkage and 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 and CCL7, 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.
Conclusion: 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

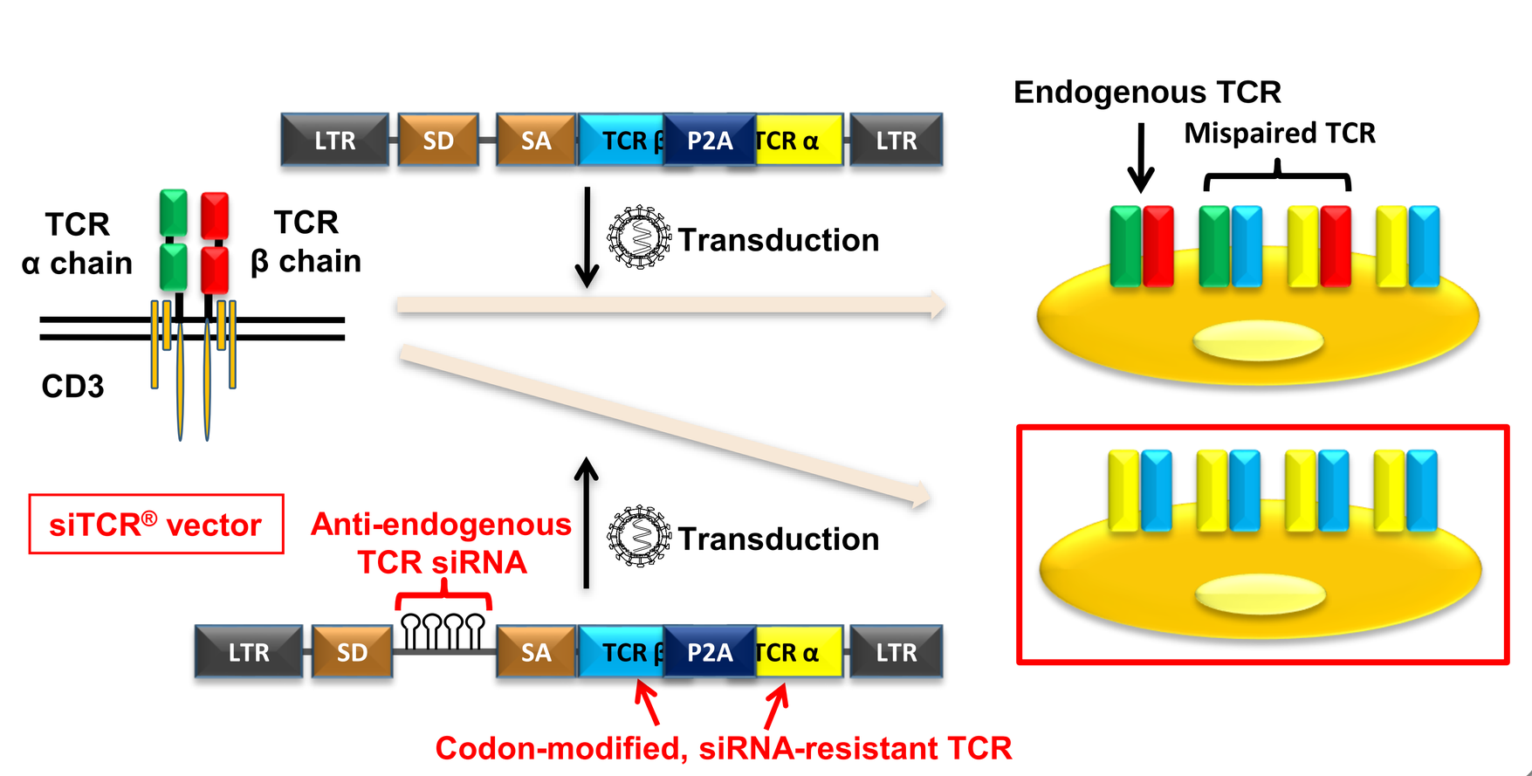
NY-ESO-1$_{157-165}$-specific-TCR is replaced with G50A and A51E in CDR2β for high affinity[1].



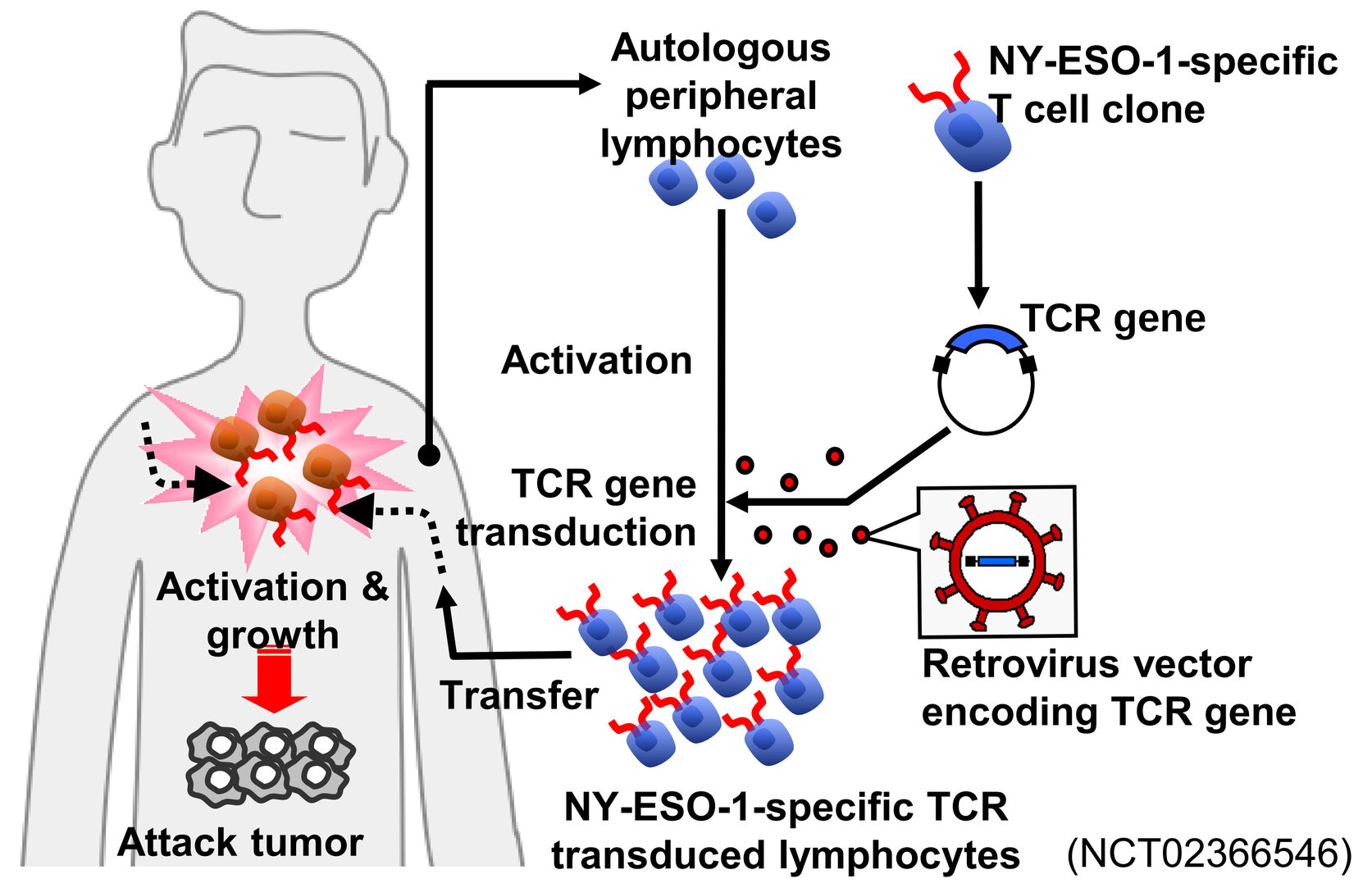
G50A+A51E TCR had low reactivity to analogous peptides searched by the BLAST database[2].



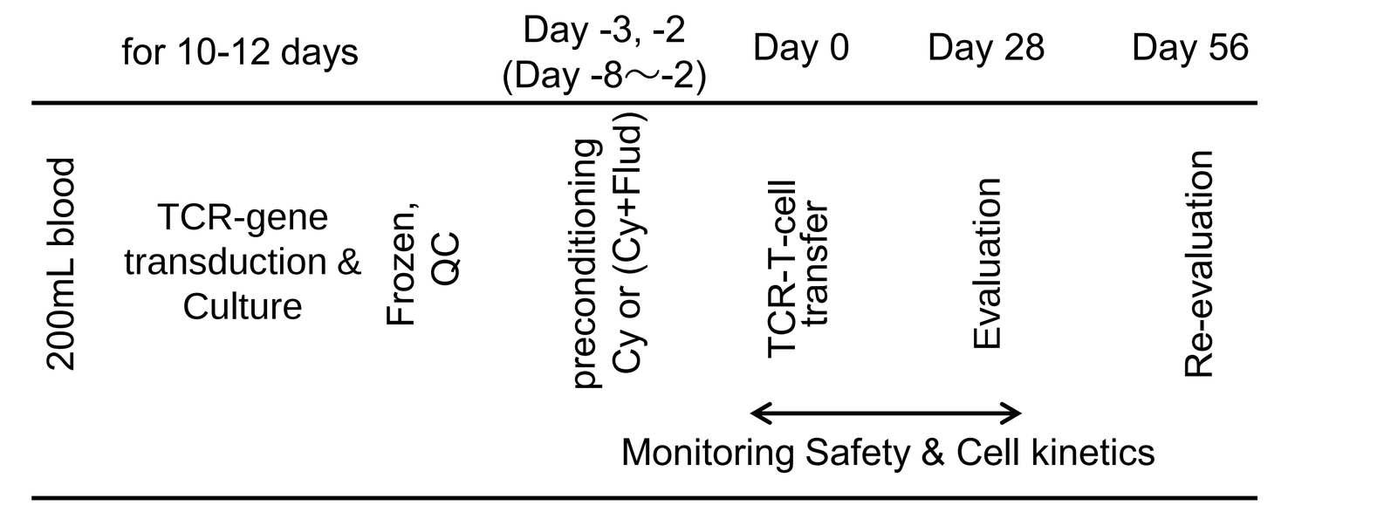
Retroviral vector encoding siRNA to silence endogenous TCR is adopted in TBI-1301[3].



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)



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	CRS	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	CRS*	SD
	TBI1301-08	70	M	synovial sarcoma	chest wall, soft tissue at inguinal area, bone	CRS*	PR
	TBI1301-14	65	F	ovarian cancer	lymph node	(-)	SD**
	TBI1301-16	25	M	synovial sarcoma	lung	CRS*	PR
	TBI1301-15	45	F	myxoid cell liposarcoma	retroperitonium	(-)	SD

* Tocilizumab was used to treat CRS. **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		

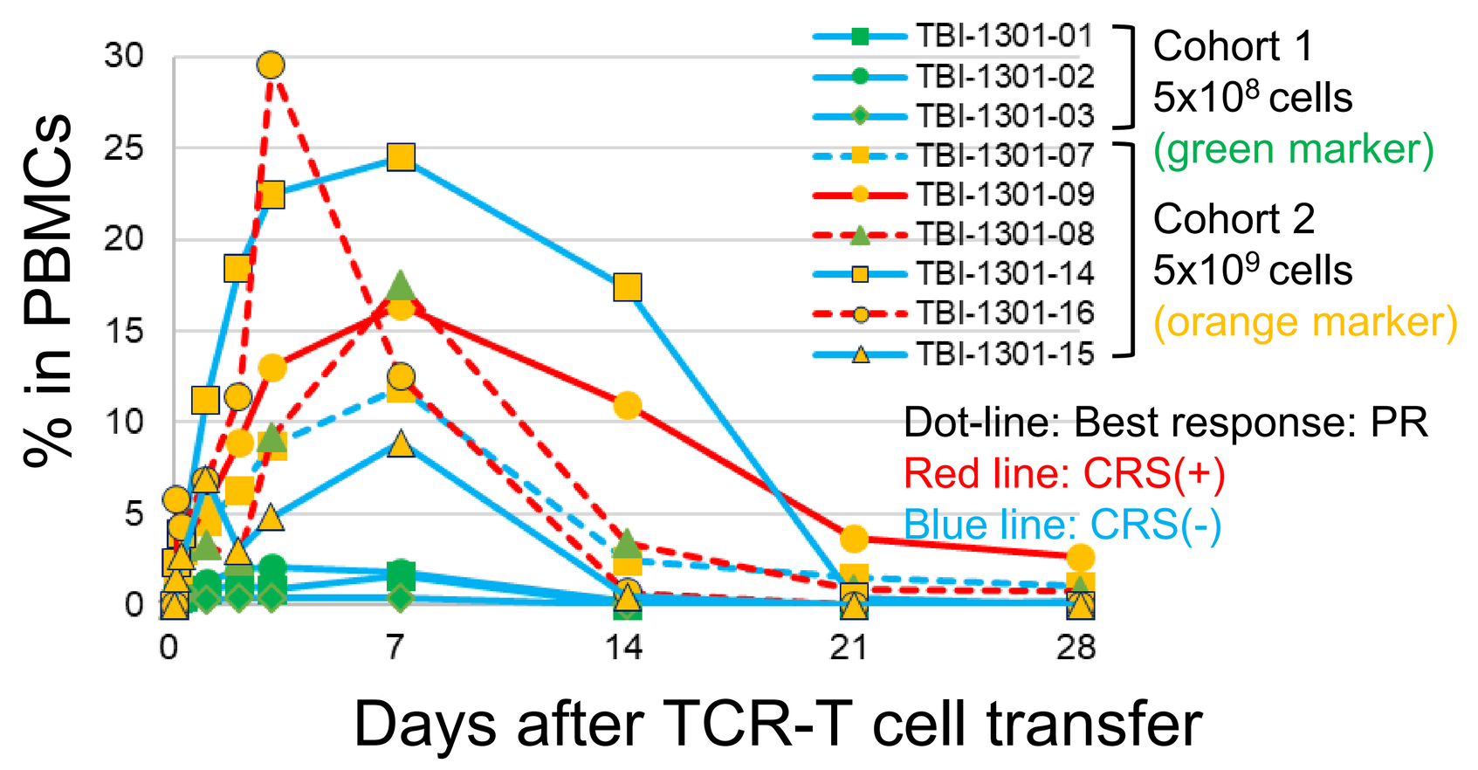
(No. of patients)

- 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.

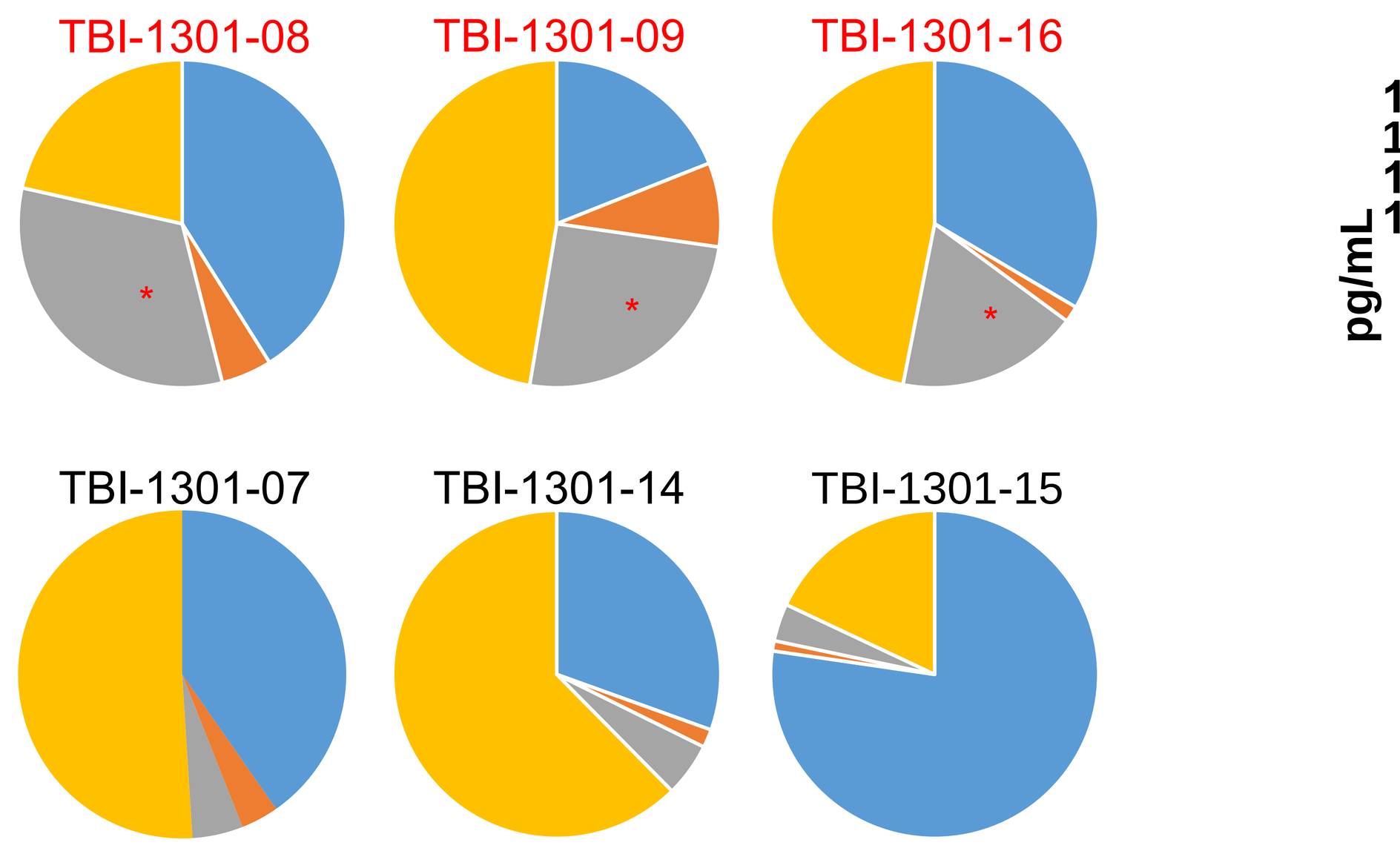
Diagnostic criteria of CRS in this trial

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

TBI-1301 kinetics


% in PBMCs
Days after TCR-T cell transfer
TBI-1301-01
TBI-1301-02
TBI-1301-03
TBI-1301-07
TBI-1301-09
TBI-1301-08
TBI-1301-14
TBI-1301-16
TBI-1301-15
Cohort 1
5x10⁸ cells
(green marker)
Cohort 2
5x10⁹ cells
(orange marker)
Dot-line: Best response: PR
Red line: CRS(+)
Blue line: CRS(-)

CD8+ T cell Phenotype of TBI-1301 product

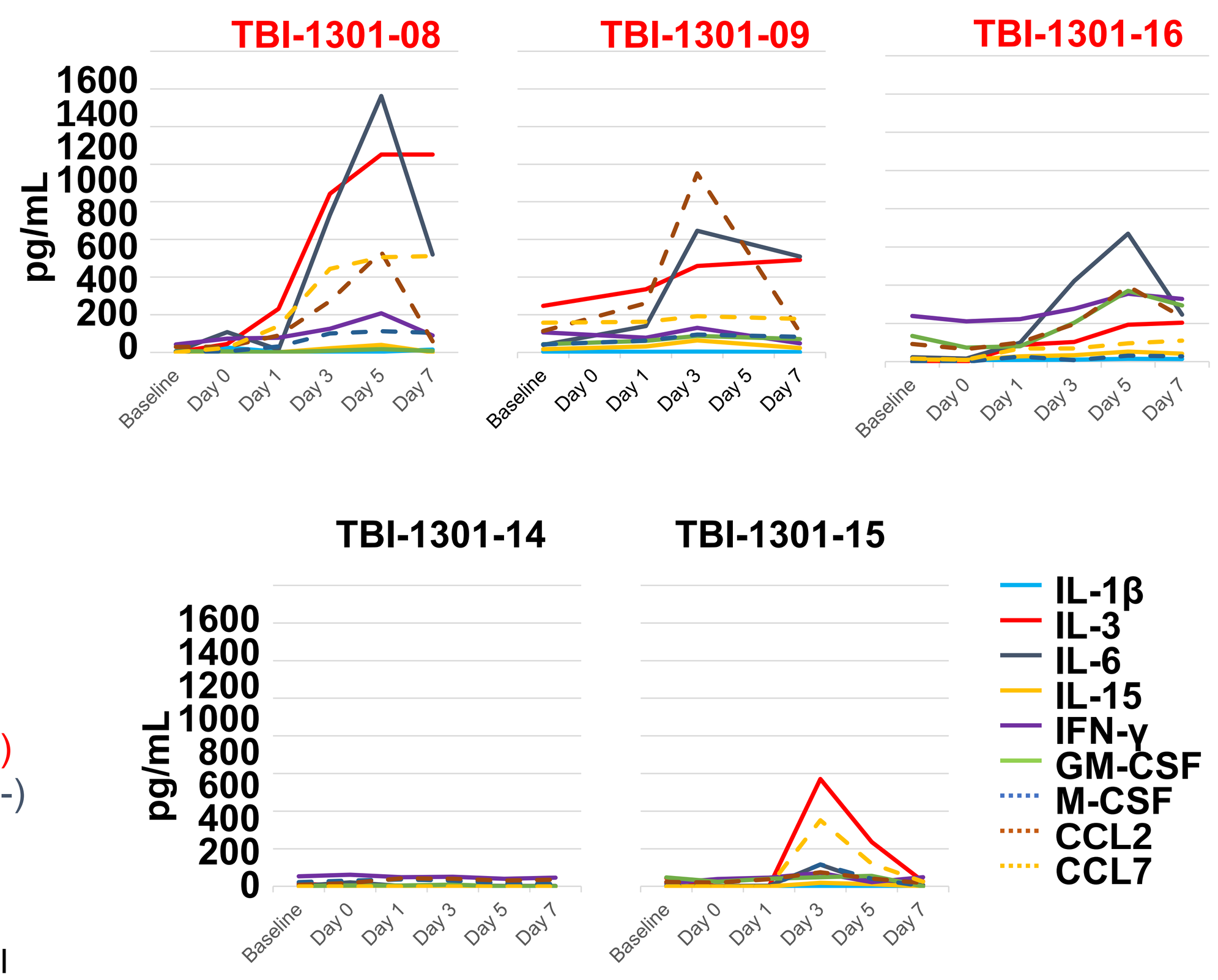


- CRS(+) cases, statistically significant between CRS(+) and CRS(-) cases (p=0.008)

Red ID: CRS(+)
Black ID: CRS(-)

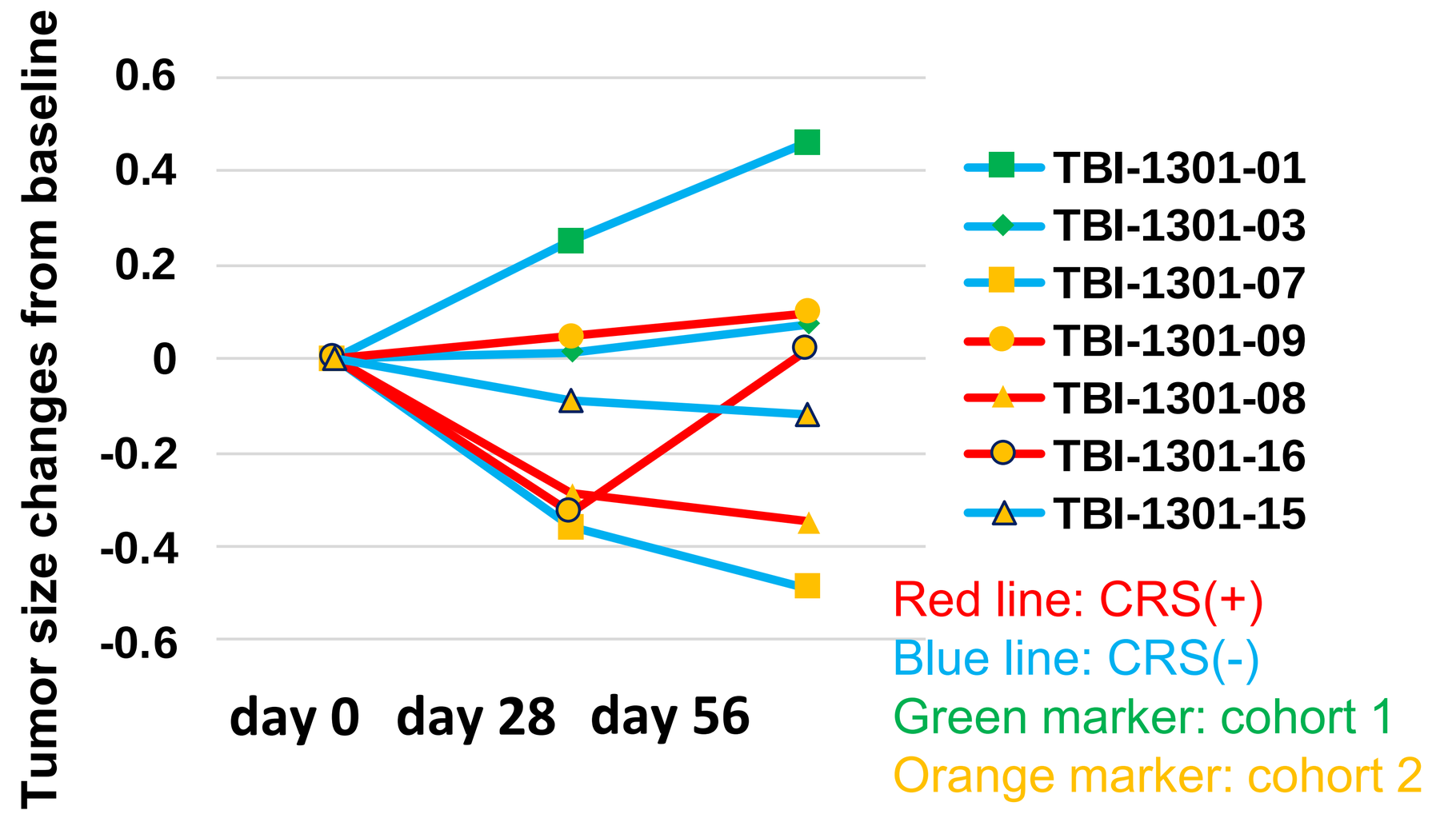
- Naïve T cell (CD3+/CD45RA+/CCR7+)
- Central Memory T cell (CD3+/CD45RA-/CCR7+)
- Effector Memory T cell (CD3+/CD45RA-/CCR7-)
- Terminal differentiated T cell (CD3+/CD45RA+/CCR7-)

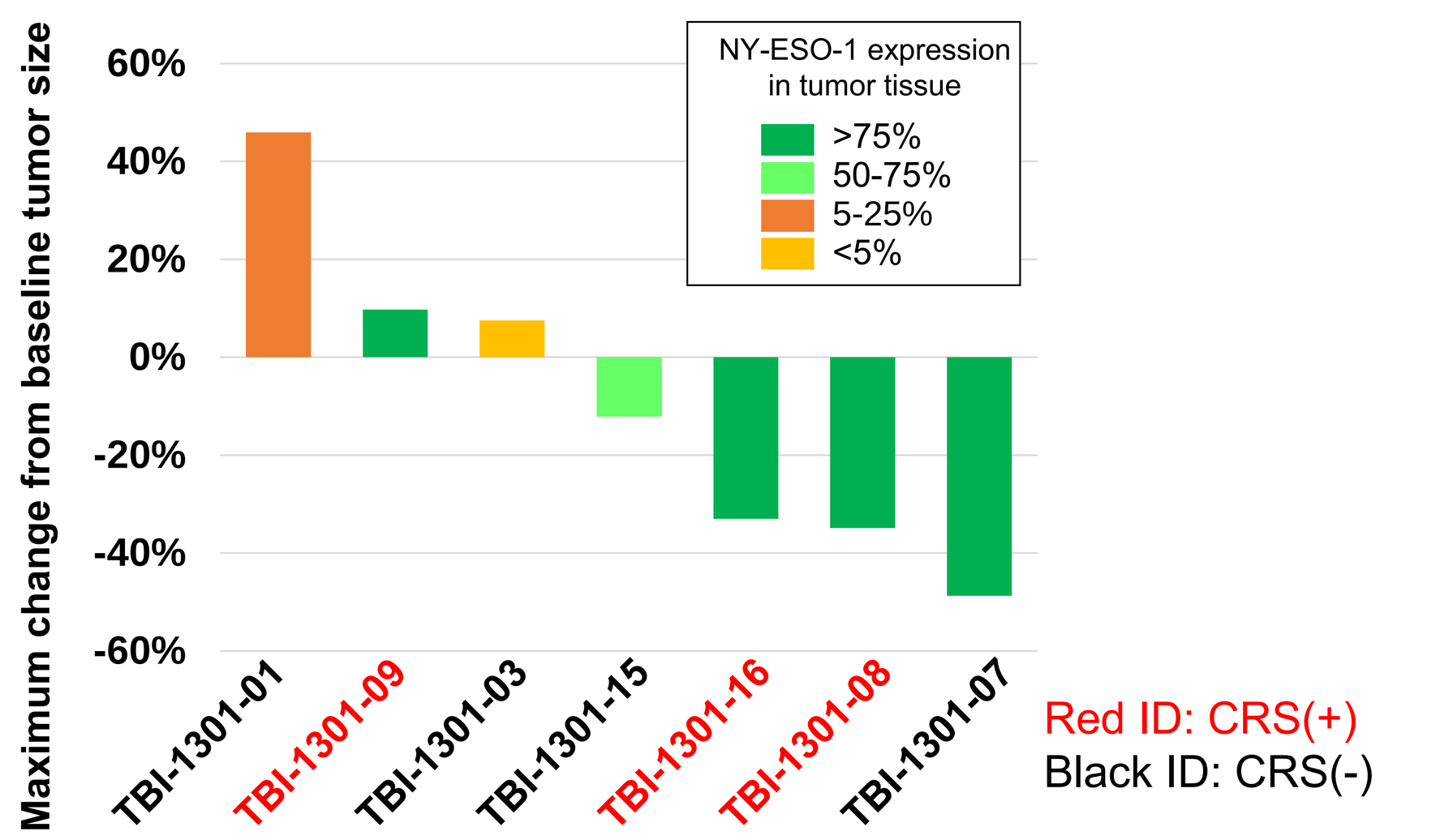
Serum cytokine levels in 5 patients: 3 from CRS(+) and 2 from CRS(-)



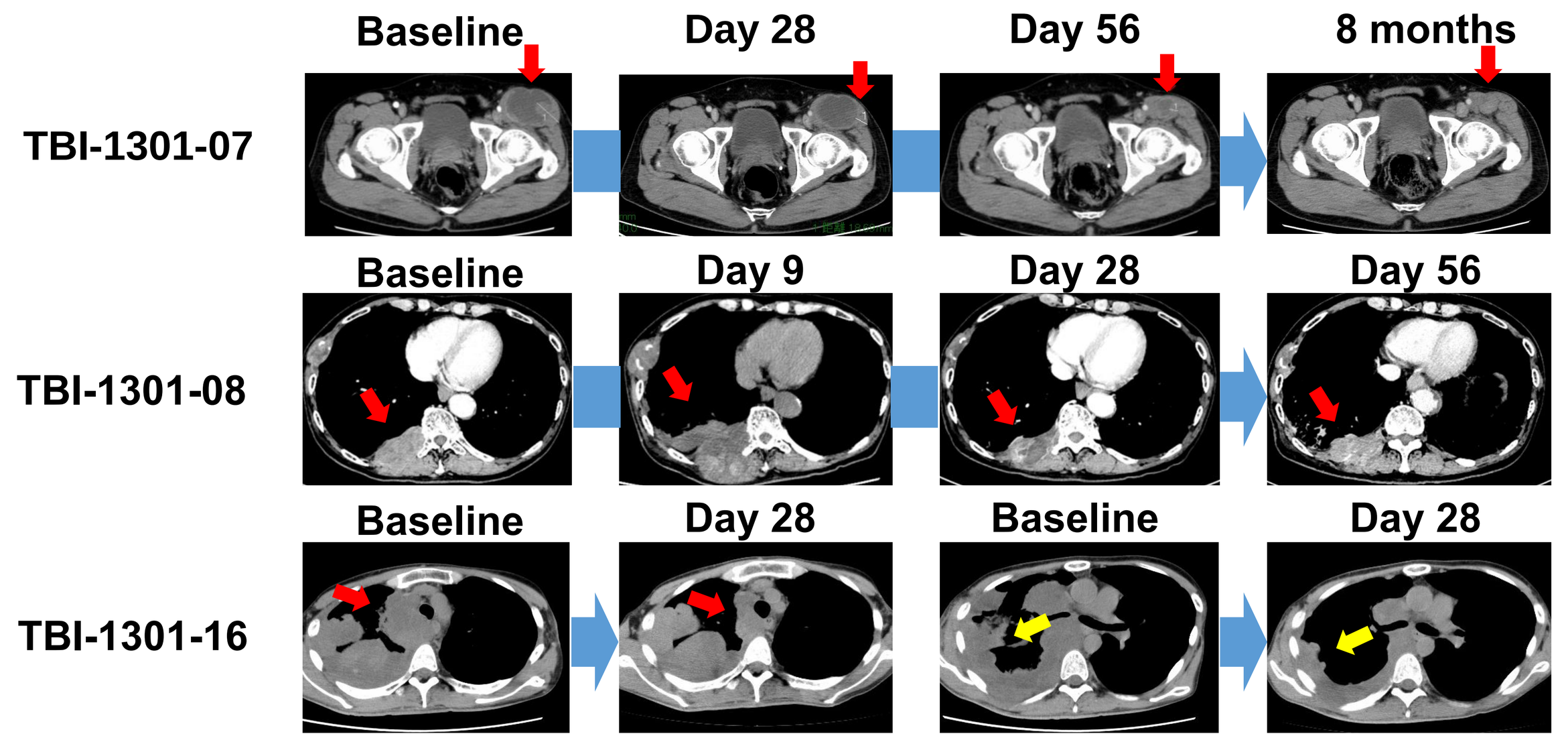
Red ID: CRS(+); Black ID: CRS(-)

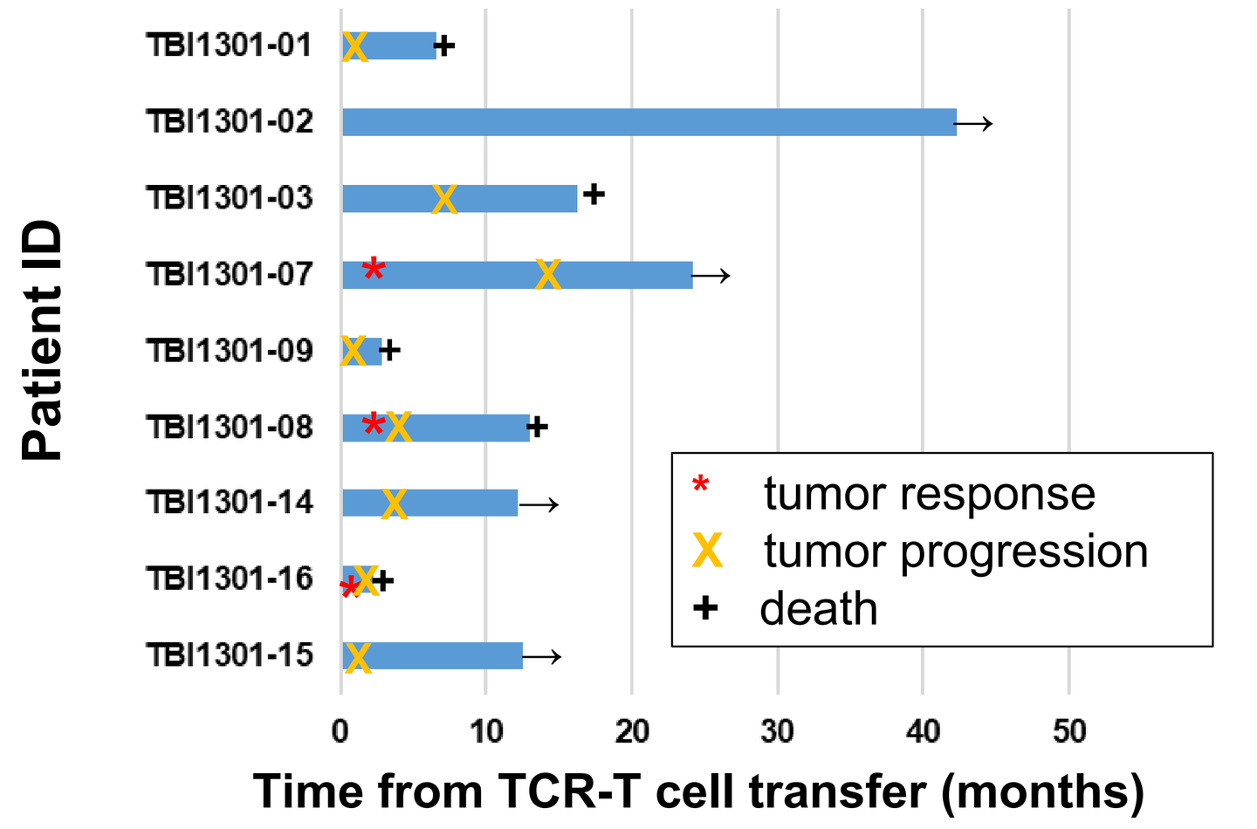
TBI-1301 dose and NY-ESO-1 expression may be related with tumor response





The duration of response





CONCLUSION

- 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.
- 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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3.Cancer Res 69: 9003-11, 2009

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Conflict of Interest Disclosure information, Lead presenter, Hiroyoshi Hattori, has No conflicts to disclose.

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