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First-in-human phase 1 study of IT1208, a defucosylated humanized anti-CD4 depleting antibody, in patients with advanced solid tumors

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Presenter Disclosure Information

Kohei Shitara

The following relationships exist related to this presentation:

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Background and Study Design

- Transient CD4$^+$ T cell depletion led to the proliferation of tumor-specific CD8$^+$ T cells in the draining lymph node and increased infiltration of PD-1$^+$CD8$^+$ T cells into the tumor, which resulted in strong anti-tumor effects in tumor-bearing mice (*Ueha S, et al. Cancer Immunol Res. 2015;3:631-40*).
- Here we report a first-in human study of IT1208, a defucosylated humanized anti-CD4 monoclonal antibody engineered to exert potent antibody-dependent cellular cytotoxicity.
- Patients(pts) with advanced solid tumors were treated with iv. IT1208 at doses of 0.1 or 1.0 mg/kg.
- The first patient(pt) in each cohort received a single administration on day 1, and the other pts received two administrations on days 1 and 8.

- Advanced solid tumors resistant to standard therapy
- ECOG PS 0-1
- Adequate organ functions
- Pts who had previously received immune checkpoint inhibitors were eligible

Clinical trial identifier:
UMIN000026564

IT1208 IV Infusion at 2 to 4 hours
0.1 mg/kg (level 1, N=4)
or 1.0 mg/kg (level 2, N=7)

1 dose on day1 (1st pt)
2 dose on day1 and 8 (other pts)

Tumor biopsy

Although no DLT was observed at 1.0 mg/kg, we did not further escalate the dose because clear depletion of CD4$^+$ T cells in PBMCs was seen

DLT evaluation until day29

Safety and Efficacy follow up

Tumor biopsy

Baseline characteristics and adverse events

Baseline characteristics

Characteristics		Patients (*n* = 11) N	%
Age, years	Median (range)	65 (35–79)	–
Sex	Male	8	73
ECOG PS	0	11	100
Cancer types	Gastric or GEJ	6	55
	Colorectal	4	36
	Esophageal	1	9
	Pancreas	1*	9
MSI status	MSS	9	82
	Unknown	2	18
Previous treatment line	Median (range)	5 (2–11)	–
Previous anti-PD1/PDL1	Yes	4	36

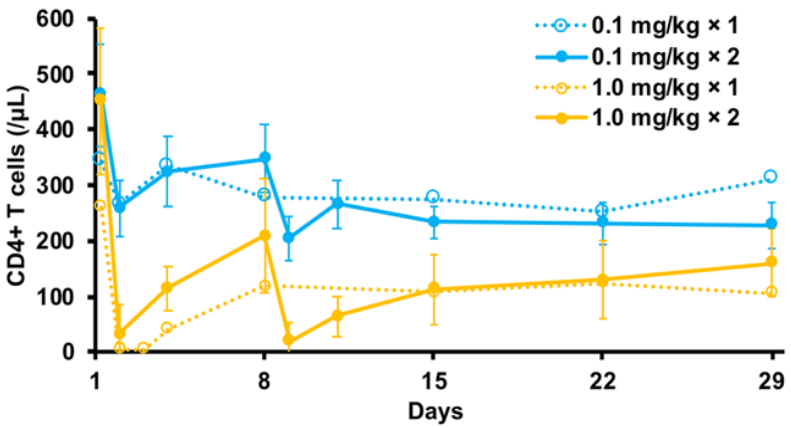
*With simultaneous colon cancer

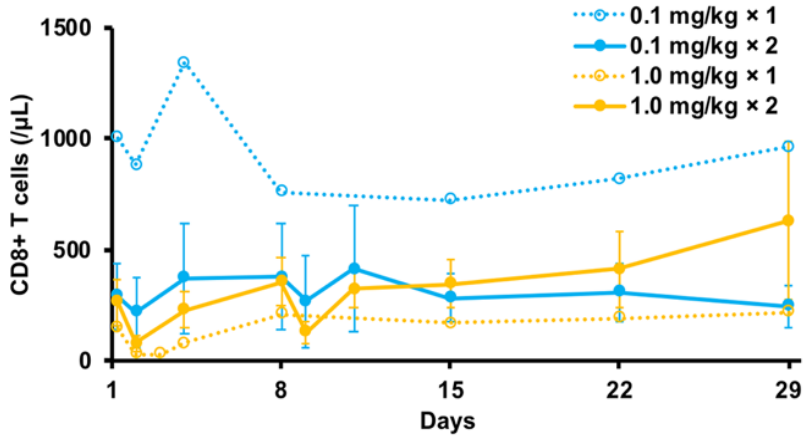
IT1208-related adverse events

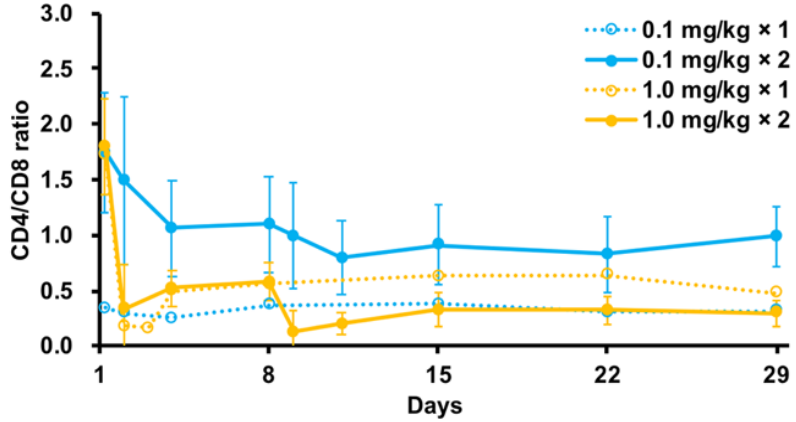
Adverse event	Dose level 1 (*n* = 4)				Dose level 2 (*n* = 7)			
Grade	1	2	3	4	1	2	3	4
Infusion-related reactions	4	0	0	0	1	6	0	0
Fever	4	0	0	0	0	4	0	0
Diarrhea	0	0	0	0	1	1	0	0
Nausea	0	0	0	0	0	3	0	0
Vomiting	0	0	0	0	0	3	0	0
Tumor pain	0	0	0	0	0	1	0	0
Decreased oxygen saturation	0	0	0	0	0	1	0	0
Hypotension	0	0	0	0	0	1	0	0
Flushing	0	0	0	0	0	1	0	0
Chills	0	0	0	0	0	6	0	0

Pharmacodynamics in PBMC

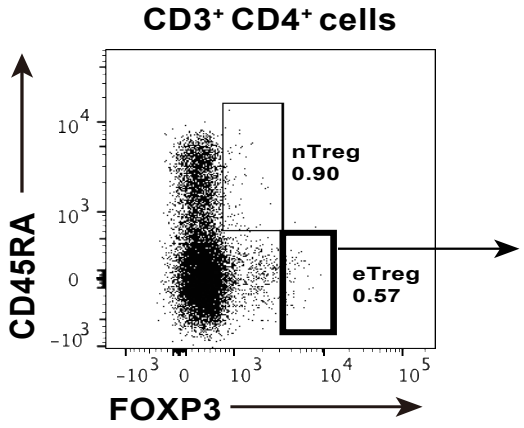
Mean peripheral counts of CD4+ and CD8+ T cells at each dose level.

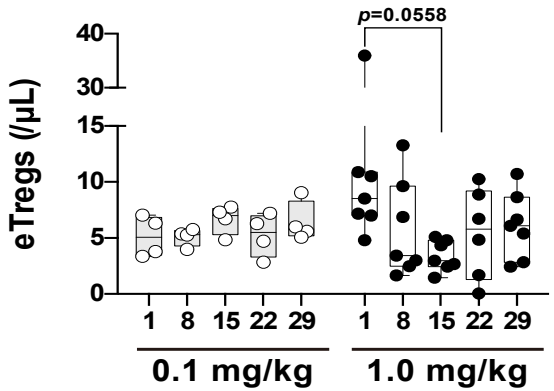


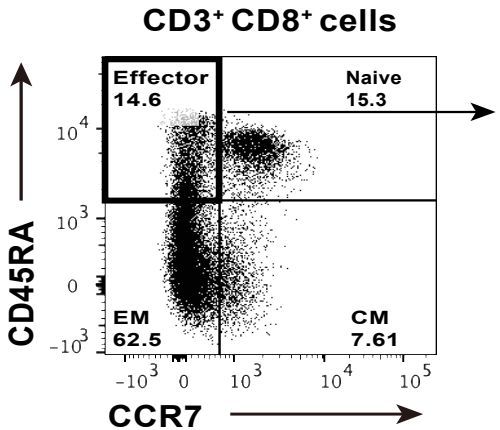


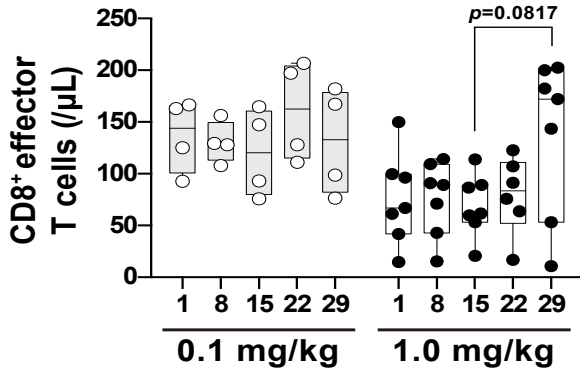


eTregs and effector CD8+ T cells in PBMCs



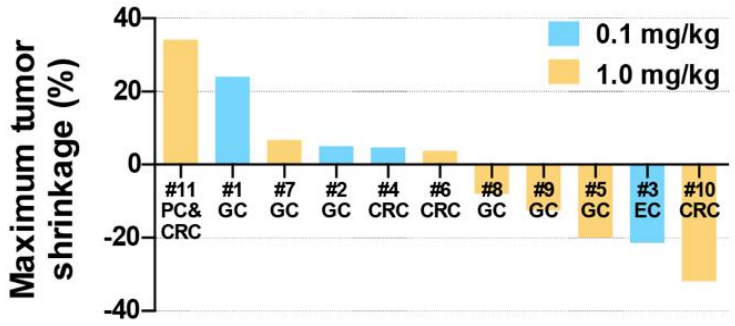


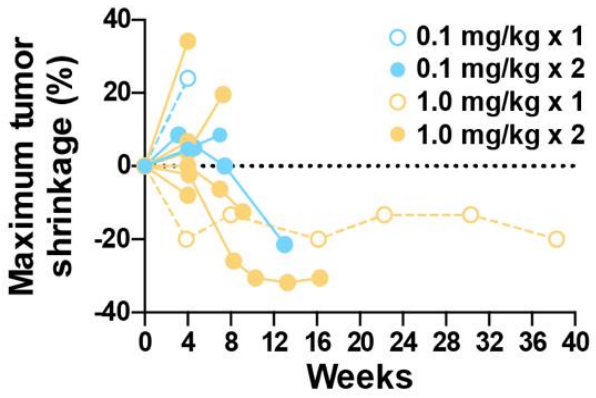


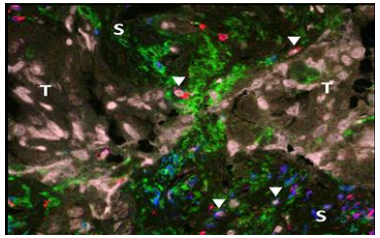


The eTregs were identified as $CD4^+CD45RA^-FoxP3^{high}$ and effector $CD8^+$ T cells were identified as $CD8^+CD45RA^+CCR7^-$, respectively. The results of the cell number of each subset are presented as Box-and Whiskers plots. The ordinary one-way ANOVA (by Prism7) was used to multiple comparisons of the means of cell numbers among the time periods, in day.

Antitumor Activity and biomarker analysis

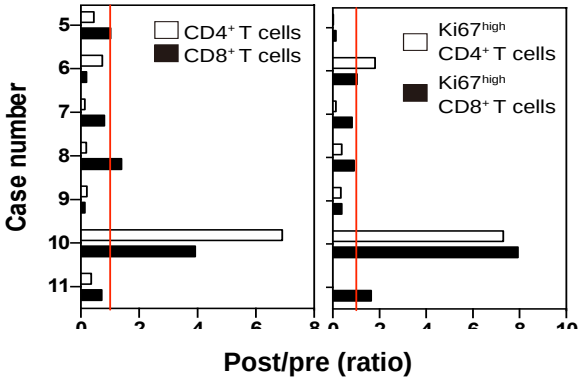




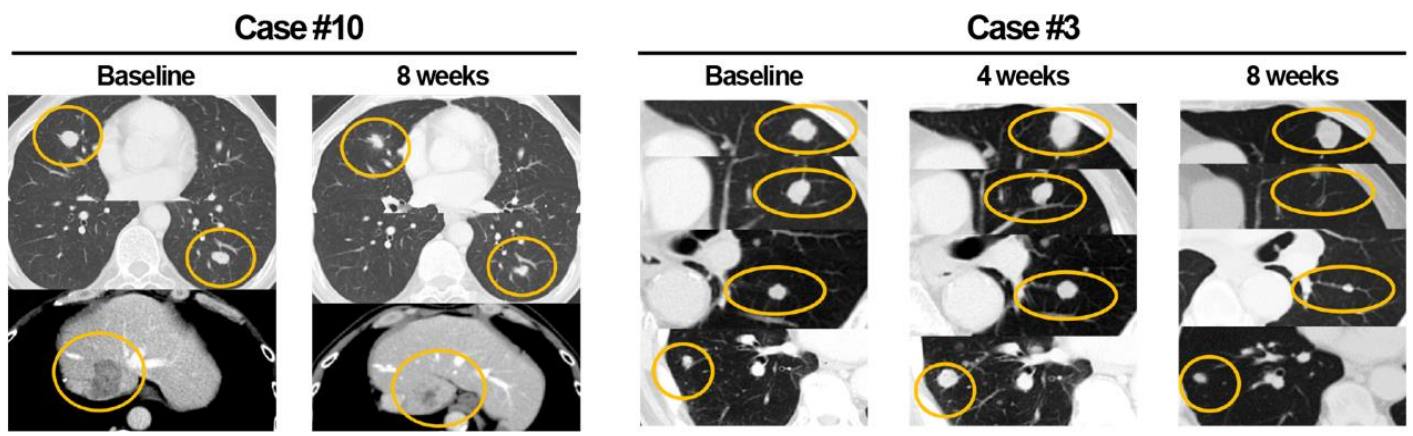


CD3 CD4 CD8 CK Ki67

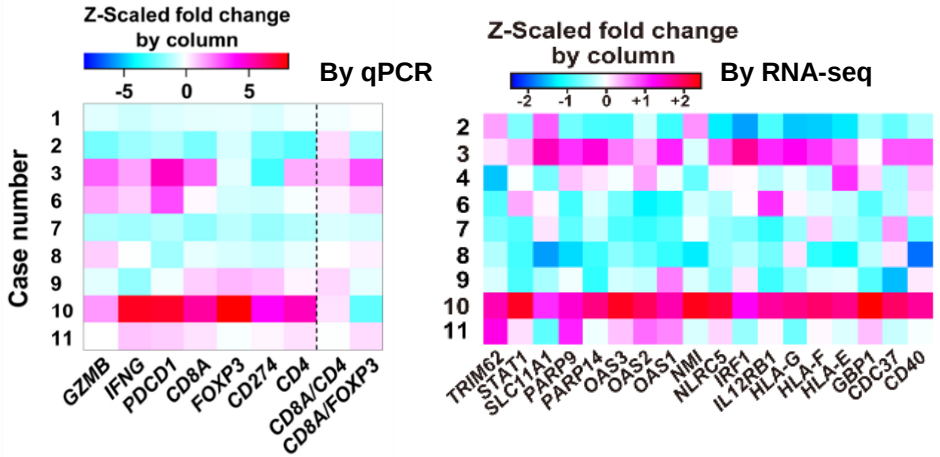
T; tumor, S; stroma,
▼; $CD3^{+}CD8^{+}Ki67^{high}$ cells



Representative image of biopsy specimens stained using mFIHC. Changes in T cell subsets after IT1208 treatment were histologically evaluated.



GC; gastric cancer, CRC; colorectal cancer, EC; esophageal cancer, PC; pancreas cancer
Case 10 is CRC with liver and lung metastases. Pt experienced a PR (32% shrinkage of target lesions) at two months after IT1208 treatment. Tumor response have been maintained more than 3 months at the data cut off. Case 3 with esophageal squamous cell cancer also showed tumor shrinkage (21%) with PFS of 3.1 months



Heat map of the changes in T cell response- and interferon-related gene expression in the tumor biopsies following IT1208 treatment.

Summary

- In this FIH study, IT1208 successfully depleted $CD4^+$ T cells with a manageable safety profile and encouraging preliminary efficacy signals.
- Decreased $CD4^+$ T cells were observed in all pts and especially in those receiving two administrations of 1.0 mg/kg.
- One MSS CRC pt achieved durable PR showing increased infiltration of both $CD4^+$ and $CD8^+$ T cells into the tumor after IT1208. This observation was more prominent when Ki67 expression in T cells was used as an activation marker. Moreover, transcriptomic profiling of the liver metastasis of the pt revealed upregulation of the expression of interferon-stimulated genes, T cell activation-related genes, and antigen presentation-related genes after IT1208.
- Two additional pts with gastric or esophageal cancer achieved stable disease lasting at least 3 months.
- These results warrant further investigations especially in combinations with immune check point inhibitors