Updated results from first-in-human phase 1 dose-escalation trial of TAK-102, a GPC3-targeted armored CAR-T cells, in patients with advanced solid tumors

2543

Takako Eguchi Nakajima,[1] Yasutoshi Kuboki,[2] Masaru Fukahori,[1] Yutaka Shimazu,[1] Shunsuke Kondo,[3,4] Yuki Katsuya,[3] Masafumi Ikeda,[5] Tomoyuki Satake,[5] Hideaki Kagehara,[6] Takenori Akaike,[6] Aman P Singh,[7] Kondala Atkuri,[8] Petar Pop-Damkov,[7] Koji Tamada,[9] Takafumi Koyama[3]

[1]Department of Early Clinical Development, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan; [3]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [4]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [6]Oncology Cell Therapy and Therapeutic Area Unit, Takeda Pharmaceutical Company Limited, Osaka, Japan; [7]Oncology Cell Therapy Precision and Translational Medicine, Takeda Pharmaceuticals, Cambridge, MA, USA; [8]Oncology Drug Development Unit, Takeda Pharmaceuticals, Cambridge, MA, USA; [9]Department of Immunology, Yamaguchi University Graduate School of Medicine, Ube, Japan

ePoster

Supplementary information

Background

- TAK-102 is a GPC3-targeted autologous CAR-T cell immunotherapy. IL-7 and CCL19 are incorporated into the CAR construct to generate 'armored' CAR-T cells. This is expected to support the persistence of CAR-T cells and expansion of memory subsets.[1]
- TAK-102 is hypothesized to overcome the challenges associated with an immunosuppressive tumor microenvironment,[1] which is one of the resistance mechanisms limiting the activity of non-armored CAR-T cell therapies in solid tumors.
- The antitumor activity of TAK-102 was confirmed in a preclinical study of a xenograft mouse model engrafted with GPC3-positive human HepG2 cells.[2]
- The interim results of this phase 1 study (data cutoff: August 22, 2022) demonstrated an encouraging safety profile of TAK-102 and favorable cellular kinetics at lower dose levels in patients with advanced solid tumors.[3]
- Here we present the updated results (data cutoff: March 25, 2024).

Objectives

- This phase 1 study aimed to evaluate the safety and tolerability of TAK-102 administered intravenously in patients with GPC3-expressing solid tumors that are refractory or intolerant to standard treatments. Additionally, we aimed to characterize the expansion and persistence of TAK-102.

Methods

- **Study population:** patients who are adults (≥ 18 years old) and have GPC3-positive solid tumors that are refractory or intolerant to standard treatments, and adequate organ function (determined by clinical laboratory evaluation).
- **Lymphodepleting chemotherapy:** fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily on days –5, –4 and –3 before TAK-102 infusion.
- **TAK-102 dose escalation:** a Bayesian optimal interval design was used.
  - Three patients were recruited for each fixed dose level (DL) cohort. Additional patients could be recruited as deemed appropriate by sponsor representatives and the investigators.
- **Primary endpoints:** incidence of DLTs and TEAEs (coded using MedDRA Version 26.1 and graded using CTCAE version 5.0).
  - CRS and ICANS were graded using the American Society for Transplantation and Cellular Therapy consensus.[4]
- **Secondary endpoints:** objective response (based on investigator's assessment using the RECIST 1.1 criteria) and cellular kinetics.
- **Exploratory endpoint:** biomarker expression.

Results

Patient demographics

- As of March 25, 2024, 11 Japanese patients were enrolled and received a TAK-102 infusion (**Table 1**).
  - The median age was 62 (range 37–74) years and most patients were men (73%).
  - Data presented after a median follow-up duration of 8.8 months.
  - All patients had prior anticancer therapy.

Safety and tolerability

- No DLTs were observed.
  - One patient in the DL3 group was not evaluable for DLT owing to early study discontinuation.
- Patients experienced a total of 143 TEAEs of any grade (**Table 2**).
  - Nine patients had TEAEs that were related to TAK-102.
  - All patients experienced TEAEs that were related to lymphodepletion chemotherapy.
  - Seven TEAE-related deaths were reported; none were related to TAK-102 or lymphodepleting chemotherapy.
- TEAEs observed in more than four patients are listed in **Table 3**.
  - No patients experienced ICANS.
  - Six patients experienced mild CRS (grade 1: n = 5; grade 2: n = 1); all cases were manageable.

Table 1. Patient demographics and baseline characteristics

	DL1: 1 × 10^7 CAR+ cells/body (n = 3)	DL2: 1 × 10^8 CAR+ cells/body (n = 3)	DL3: 5 × 10^8 CAR+ cells/body (n = 5)	Overall (N = 11)
Diagnosis, n (%)				
Hepatocellular carcinoma	1 (33)	2 (67)	5 (100)	8 (73)
Liposarcoma	1 (33)	1 (33)	0	2 (18)
Gastric carcinoma	1 (33)	0	0	1 (9)
Time since diagnosis, months, median (range)[a]	17.5 (17.5–31.3)	99.4 (93.2–157.4)	29.0 (20.3–112.3)	31.3 (17.5–157.4)
Disease stage, n (%)				
II	0	0	1 (20)	1 (9)
IIIA	0	0	1 (20)	1 (9)
IIIB	0	0	1 (20)	1 (9)
IV	3 (100)	1 (33)	1 (20)	5 (46)
IVA	0	1 (33)	0	1 (9)
IVB	0	1 (33)	1 (20)	2 (18)
ECOG PS at baseline, n (%)				
0	3 (100)	2 (67)	3 (60)	8 (73)
1	0	1 (33)	2 (40)	3 (27)
Number of prior anticancer therapies, n (%)				
1	0	0	2 (40)	2 (18)
2	2 (67)	2 (67)	0	4 (36)
3	1 (33)	0	1 (20)	2 (18)
≥ 4	0	1 (33)	2 (40)	3 (27)
Bridging therapy, n (%)				
Chemotherapy	1 (33)	0	0	1 (9)
Radiotherapy	0	0	2 (40)	2 (18)
Surgery	0	0	1 (20)	1 (9)
Time since leukapheresis, days, median (range)[b]	43 (42–57)	49 (34–56)	42 (36–48)	43 (34–57)
GPC3 H-score, median (range)[c]	3 (2–40)	110 (36–170)	92 (2–300)	40 (2–300)

[a]Calculated as the date of TAK-102 infusion minus the date of initial diagnosis plus 1 day and then divided by 30.44.
[b]Calculated as the date of TAK-102 infusion minus the date of leukapheresis plus 1 day.
[c]Calculated as the sum of ($H_x \times N_x$)/sum of N_x. H = GPC3 H-score; N = percentage of tumor proportion; n = location number of formal GPC3.
CAR, chimeric antigen receptor; DL, dose level; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GPC3, glypican-3.

Antitumor activity

- Five (46%) patients achieved stable disease (**Figure 1**).
- One patient with HCC in the DL2 group who achieved a maximum of 26.1% tumor shrinkage demonstrated durable antitumor activity and also had corresponding decreases in AFP levels of up to 52% (**Figure 2**).

Cellular kinetics

- Cellular kinetic profiles were assessed by quantitative PCR (**Figure 3**, **Table 4**) and flow cytometry (**Figure S1**).
  - Increases in TAK-102 exposure (C_{max}, $AUC_{0\text{-}28}$) were observed with escalating dose levels. There was also a decrease in the time to C_{max} (T_{max}) with increasing dose levels (**Table 4**).

Biomarkers

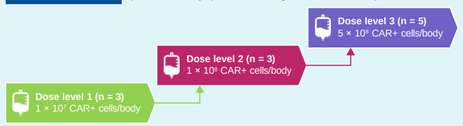
- IL-7 spiked following lymphodepletion chemotherapy but showed no further increases after TAK-102 infusion across all DL cohorts (**Figure 4**, **Figure S2**).
- CCL19 levels increased by nearly two- and three-fold at DL2 and DL3, respectively, compared with pre-infusion levels (**Figure 4**, **Table 4**, **Figure S2**).
- Dose-dependent increases in IFN-γ and IL-6 levels were observed (**Figure 5**, **Figure S3**).

Conclusions

- TAK-102, an armored CAR-T cell immunotherapy, had a manageable safety profile, including grade 1/2 CRS.
- There were some signs of antitumor activity, which will require further study.
  - One patient with HCC demonstrated a 6-month durable antitumor response and tumor shrinkage.
- Improvements in TAK-102 cellular kinetics were observed with escalating doses.
- A dose-dependent relationship was also observed for the biomarkers CCL19, IFN-γ and IL-6, indicating increased TAK-102 activity with escalating doses.
- However, our small sample sizes warrant caution when interpreting these data.
- Four patients are now being followed up in a long-term safety study.

Question — Is TAK-102 a well-tolerated CAR-T cell immunotherapy for patients with GPC3-expressing solid tumors that are refractory or intolerant to standard treatments?

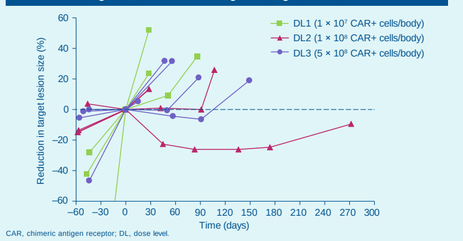
Study design — Open-label, non-randomized, first-in-human, dose-finding, phase 1 study (ClinicalTrials.gov NCT04405778).



Results

- Enrolled patients had HCC (n = 8), liposarcoma (n = 2) and gastric carcinoma (n = 1).
- No DLTs or ICANS were observed.
- Six patients (55%) experienced CRS at the higher dosing levels of TAK-102.
- CCL19, IFN-γ and IL-6 exhibited dose-dependent expression.

Figure 1. Individual changes in target lesion size



CAR, chimeric antigen receptor; DL, dose level.

Key takeaways — TAK-102, an armored CAR-T cell immunotherapy, demonstrated a manageable safety profile and some early signs of antitumor activity.

Table 2. Safety summary of TAK-102

	DL1: 1 × 10^7 CAR+ cells/body (n = 3)		DL2: 1 × 10^8 CAR+ cells/body (n = 3)		DL3: 5 × 10^8 CAR+ cells/body (n = 5)		Overall (N = 11)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Any TEAE	35		3 (100)	55	3 (100)	53	5 (100)	143	11 (100)
Related to TAK-102	3		2 (67)	12	3 (100)	9	4 (80)	24	9 (82)
TEAE related to lymphodepletion chemotherapy	22		3 (100)	38	3 (100)	25	5 (100)	85	11 (100)
Grade ≥ 3 TEAE	14		3 (100)	27	3 (100)	24	5 (100)	68	11 (100)
Related to TAK-102	1		1 (33)	5	2 (67)	0	0	6	3 (27)
Serious TEAE	4		3 (100)	5	2 (67)	8	4 (80)	17	9 (82)
Related to TAK-102	0		0	1	1 (33)	0	0	1	1 (9)
TEAE resulting in death	3	3 (100)		2	2 (67)	2	2 (40)	7	7 (64)
TEAE resulting in TAK-102 dose modification									
Drug withdrawn	0		0	1	1 (33)[a]	0	0	1	1 (9)
Dose rate reduced	0		0	0	0	0	0	0	0
Dose infusion interrupted	0		0	0	0	0	0	0	0

[a]This patient had ≥ 90% of the planned infusion volume of TAK-102, which was considered evaluable for DLT.
CAR, chimeric antigen receptor; DL, dose level; DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Table 3. Incidences of TEAEs (≥ 4 patients overall)

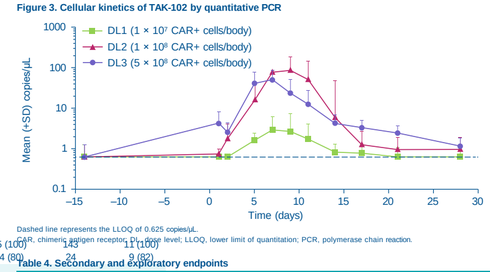
	DL1: 1 × 10^7 CAR+ cells/body (n = 3)	DL2: 1 × 10^8 CAR+ cells/body (n = 3)	DL3: 5 × 10^8 CAR+ cells/body (n = 5)	Overall (N = 11)
Any TEAE, n (%)	3 (100)	3 (100)	5 (100)	11 (100)
Neutrophil count decreased	2 (67)	3 (100)	4 (80)	9 (82)
White blood cell count decreased	3 (100)	3 (100)	3 (60)	9 (82)
CRS	0	2 (67)	4 (80)	6 (55)
Nausea	2 (67)	2 (67)	2 (40)	6 (55)
Anemia	0	1 (33)	4 (80)	5 (46)
Platelet count decreased	1 (33)	2 (67)	2 (40)	5 (46)
Alopecia	1 (33)	1 (33)	2 (40)	4 (36)
Malignant neoplasm progression	1 (33)	2 (67)	1 (20)	4 (36)
TEAE related to TAK-102, n (%)	2 (67)	3 (100)	4 (80)	9 (82)
CRS	0	2 (67)	4 (80)	6 (55)
Grade ≥ 3 TEAE, n (%)	3 (100)	3 (100)	5 (100)	11 (100)
White blood cell count decreased	3 (100)	3 (100)	3 (60)	9 (82)
Neutrophil count decreased	2 (67)	3 (100)	3 (60)	8 (73)
Platelet count decreased	0	2 (67)	2 (40)	4 (36)
Malignant neoplasm progression	1 (33)	2 (67)	1 (20)	4 (36)

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DL, dose level; TEAE, treatment-emergent adverse event.

Figure 2. Changes in AFP levels in a patient with tumor shrinkage

AFP, alpha fetoprotein.

Figure 3. Cellular kinetics of TAK-102 by quantitative PCR



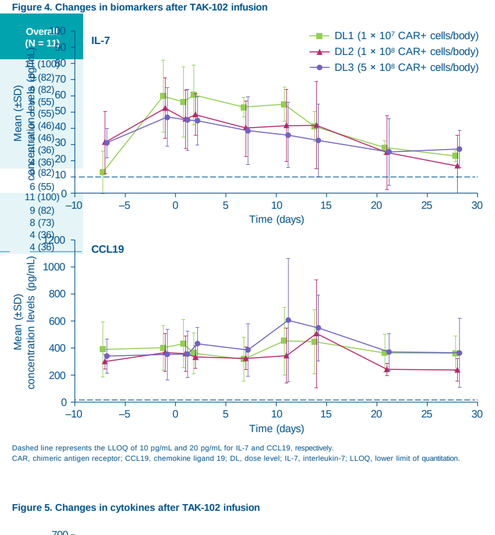
Dashed line represents the LLOQ of 0.625 copies/μL.
CAR, chimeric antigen receptor; DL, dose level; LLOQ, lower limit of quantitation; PCR, polymerase chain reaction.

Table 4. Secondary and exploratory endpoints

Parameters (mean ± SD)	DL1: 1 × 10^7 CAR+ cells/body (n = 3)	DL2: 1 × 10^8 CAR+ cells/body (n = 3)[a]
Cellular kinetics		
C_{max}, copies/μL	4.6 ± 4.4	109.2 ± 97.3
$AUC_{0\text{-}28}$, copies/μL·day	39.5 ± 25.4	724.2 ± 754.9
T_{max}, days	8.3 ± 1.2	9
Biomarkers[b]		
IL-7 fold change	1.1 ± 0.1	1.1 ± 0.1
CCL19 fold change	1.2 ± 0.1	1.8 ± 1.2

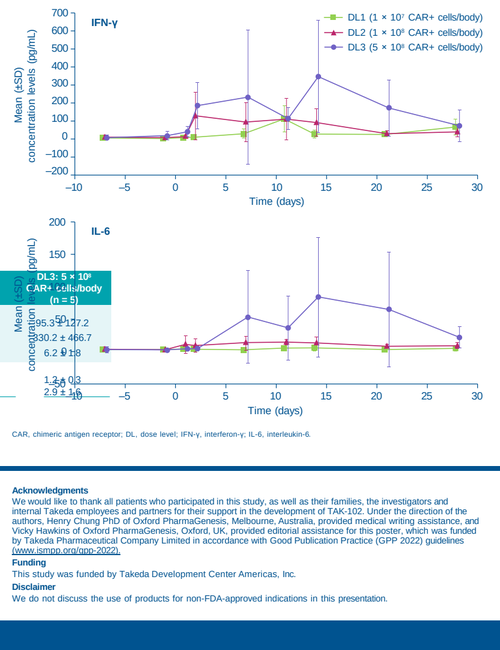
[a]Cellular kinetic parameters were calculated based on two of the three patients in DL2.
[b]Fold changes were calculated using the ratio of C$_{max}$ to the pre-infusion baseline value.
$AUC_{0\text{-}28}$, area under the time–concentration curve from day 0 to 28; CAR, chimeric antigen receptor; CCL19, chemokine ligand 19; C_{max}, maximum observed concentration; DL, dose level; IL-7, interleukin-7; SD, standard deviation; T_{max}, time to C_{max}.

Figure 4. Changes in biomarkers after TAK-102 infusion



Dashed line represents the LLOQ of 10 pg/mL and 20 pg/mL for IL-7 and CCL19, respectively.
CAR, chimeric antigen receptor; CCL19, chemokine ligand 19; DL, dose level; IL-7, interleukin-7; LLOQ, lower limit of quantitation.

Figure 5. Changes in cytokines after TAK-102 infusion



CAR, chimeric antigen receptor; DL, dose level; IFN-γ, interferon-γ; IL-6, interleukin-6.

References

1. Adachi K *et al. Nat Biotechnol* 2018;36:346–51. 2. Data on file. Takeda Pharmaceuticals Company Limited.
3. Koyama T *et al. J Immunother Cancer* 2022;10:A737. 4. Lee DW *et al. Biol Blood Marrow Transplant* 2019;25:625–38.

Abbreviations

AFP, alpha fetoprotein; $AUC_{0\text{-}28}$, area under the time–concentration curve from day 0 to 28; CAR, chimeric antigen receptor; CCL19, chemokine ligand 19; C_{max}, maximum observed concentration; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DL, dose level; DLT, dose-limiting toxicity; FDA, Food and Drug Administration; GPC3, glypican-3; HCC, hepatocellular carcinoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN-γ, interferon-γ; IL, interleukin; IV, intravenous; LLOQ, lower limit of quantitation; MedDRA, Medical Dictionary for Regulatory Activities; PCR, polymerase chain reaction; RECIST, Response Evaluation Criteria in Solid Tumours; TEAE, treatment-emergent adverse event; T_{max}, time to C_{max}.

Disclosures

TEN: consultant/advisor for Rebirthel and Thyas; honoraria for Bristol Myers Squibb Japan, Chugai Pharma, Daiichi Sankyo/UCB Japan, Nobelpharma, Ono Pharmaceutical, Parexel, Pfizer and Taiho Pharmaceutical; and research funding from AbbVie, Chugai Pharma, Eli Lilly Japan, KBBM, Novartis, Otsuka, Taiho Pharmaceutical, Taisho Pharmaceutical Holdings, Takeda and Zymeworks. YKu: consultant/advisor for AbbVie, Amgen, Boehringer Ingelheim, Incyte, Janssen Oncology and Takeda; travel/accommodation/expenses from Amgen, Chugai Pharma and Incyte; honoraria from Eli Lilly Japan, Taiho Pharmaceutical and Takeda; and research funding from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Carna Biosciences, Chugai Pharma, Daiichi Sankyo/UCB Japan, Eli Lilly, Genmab, GlaxoSmithKline, Incyte, Janssen Oncology, Jiangsu Hengrui Pharmaceuticals, Merck Serono, Novartis, Ono Pharmaceutical, Taiho Pharmaceutical and Takeda. SK: honoraria from Chugai Pharma, Eisai and Sanofi; speaker fees from Chugai Pharma and Eisai; and research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, Chugai Pharma, Eisai, Eli Lilly and Incyte. MI: consultant/advisor for Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Chugai Pharma, Eisai, Guardant Health, MSD, Novartis, Roche and Servier; honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, Chugai Pharma, Eisai, Eli Lilly Japan, Fujifilm, Guardant Health, Incyte, MSD, Nihon Kayaku, Nobelpharma, Novartis, Ono Pharmaceutical, Servier, Taiho Pharmaceutical, Taisho Pharmaceutical Holdings, Takeda, Teijin Pharma and Yakult Pharmaceutical; and research funding from AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim, Bristol Myers Squibb, Chiome Bioscience, Chugai Pharma, Delta-Fly Pharma, Eisai, Eli Lilly Japan, Invitae, J-Pharma, Merck, Merus NV, MSD, Nobelpharma, Novartis, Ono Pharmaceutical, Rakuten Medical Japan, Servier and Syneos Health. TS: honoraria from AstraZeneca; and research funding from Nihon Servier. HK, APS and PPD: employment and stock/other ownership interests from Takeda. TA: employed by Takeda. KA: employment, stock/other ownership interests, research funding, patents/royalties/other intellectual property and travel/accommodation/expenses from Takeda. KT: leadership and stock/other ownership interests from Noile-Immune Biotech Inc.; honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Gilead Sciences K.K., Kyowa Kirin, Merck, MSD, Novartis, Ono Pharmaceutical and Takeda; consultant/advisor for Daiichi Sankyo, Kyowa Kirin and Ono Pharmaceutical; and research funding from Chugai Pharma and Noile-Immune Biotech Inc. TK: consultant/advisor for Amgen; honoraria from Chugai Pharma and Sysmex; research funding from Chugai Pharma, Daiichi Sankyo RD Novare, Eli Lilly, Novartis, PACT Pharma, Pfizer, Takeda and Zymeworks. MF, YS and YKa: no conflicts of interest to disclose.

For questions or comments, please contact Dr Takako E Nakajima: tnakajima@kuhp.kyoto-u.ac.jp

Acknowledgments

We would like to thank all patients who participated in this study, as well as their families, the investigators and internal Takeda employees and partners for their support in the development of TAK-102. Under the direction of the authors, Henry Chung PhD of Oxford PharmaGenesis, Melbourne, Australia, provided medical writing assistance, and Vicky Hawkins of Oxford PharmaGenesis, Oxford, UK, provided editorial assistance for this poster, which was funded by Takeda Pharmaceutical Company Limited in accordance with Good Publication Practice (GPP 2022) guidelines (www.ismpp.org/gpp-2022).

Funding

This study was funded by Takeda Development Center Americas, Inc.

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 31–June 4, 2024, Chicago, IL, USA