



Clinical Study Protocol

NCT Number: NCT05164666

Title: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-103 in Adult Patients with Mesothelin-Expressing Advanced or Metastatic Solid Tumors

Study Number: TAK-103-1001

Document Version and Date: Amendment 4 / 5 April 2024

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PROTOCOL

An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-103 in Adult Patients with Mesothelin-Expressing Advanced or Metastatic Solid Tumors

Sponsor: Takeda Pharmaceutical Company Limited
1-1 Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan

Study Number: TAK-103-1001

EudraCT Number: Not Applicable

Compound: TAK-103

Date: 5 April 2024 **Amendment Number:** 05

Amendment History:

Date	Amendment Number	Region
26 August 2021	Initial protocol	Japan
16 September 2021	01	Japan
17 February 2022	02	Japan
30 June 2022	03	Japan
20 April 2023	04	Japan
5 April 2024	05	Japan

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the Takeda trial clinician and the Takeda medical expert are in the protocol annex.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

_____ Global Clinical Lead, Oncology Cell Therapy and Therapeutic Area Unit	Date _____	_____ Global Translational Lead, Precision & Translational Medicine, Oncology Cell Therapy and Therapeutic Area Unit	Date _____
_____ Study Clinical Science Lead, Oncology Cell Therapy and Therapeutic Area Unit	Date _____	_____ Statistician, Statistical & Quantitative Sciences	Date _____
_____ Clinical and Quantitative Pharmacology Lead, Cell Therapy Clinical Pharmacology and Modeling, Precision and Translational Medicine, Oncology Cell Therapy and Therapeutic Area Unit	Date _____		Date _____

1.3 Protocol Amendment 05 Summary of Changes

This section describes the changes to the protocol incorporating Amendment 05. The primary reasons for this amendment are to:

- Reduce assessments/measurements in Secondary Follow-up phase.
- Allow earlier discontinuation of sample collection and its test by sponsor's decision

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Updated information on Takeda organization and person in charge.	To update name of Takeda's Clinical Science and Pharmacology function and a change of person in charge of Statistician.	Section 1.2 Approval
Added explanation that in Secondary Follow-up phase, the immunophenotyping for lymphoma/leukemia will be done at a local laboratory when clinically indicated.	Changed in consideration of the current state of the study.	Section 9.4.18 Flow Cytometry Assay
Added explanation that in Secondary Follow-up phase, the following sample collection and testing may be stopped at the discretion of the sponsor if TAK-103 cells are undetectable on 2 consecutive ddPCR tests: <ul style="list-style-type: none">• Droplet Digital Polymerase Chain Reaction and Flow Cytometry• T-cell Receptor (TCR)	To reduce patient's burden.	Sections 9.4.23.1 Droplet Digital Polymerase Chain Reaction and Flow Cytometry, 9.4.24.3 T-cell Receptor (TCR), Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up

Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Added explanation that in Secondary Follow-up phase, the following sample collection and testing at Month 4 and beyond may be stopped at the discretion of the sponsor: <ul style="list-style-type: none"> • [REDACTED] • Proteins • Immunogenicity Sample Collection 	To reduce patient's burden.	[REDACTED]
Added explanation that in Secondary Follow-up phase, sample collection and testing at Month 5 and beyond of immunophenotyping may be stopped at the discretion of the sponsor.	To reduce patient's burden.	Section 9.4.24.4 Immunophenotyping, Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up
Added explanation that in Secondary Follow-up phase, sample collection and testing at Month 7 and beyond of ctDNA and/or RNA will be stopped.	To reduce patient's burden.	Section 9.4.24.6 ctDNA and/or RNA, Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up
Added explanation of study termination by the sponsor.	To clarify applicable cases.	Section 9.6 Completion of Study (for Individual Patients)
Added explanation to the footnote of SOE for Primary Follow-up phase that collection of plasma sample for ctDNA testing may be stopped at the discretion of the sponsor during Primary Follow-up phase.	To reduce patient's burden.	Appendix A Schedule of Events (SOE), Schedule of Events for Primary Follow-up
Revised the SOE for Secondary Follow-up phase to delete measurements at Month 7 and beyond of investigation items below: <ul style="list-style-type: none"> • Weight • Thyroid hormone • Coagulation • Urinalysis • Plasma sample for ctDNA 	To reduce patient's burden.	Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up
Deleted tumor and normal tissue biopsy time points in the SOE for Secondary Follow-up phase.	To reduce patient's burden.	Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up

Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Revised the footnote of SOE for Secondary Follow-up phase to add explanation that hematology/chemistry at Month 19 and beyond may be stopped.	To reduce patient's burden.	Appendix A Schedule of Events (SOE), Schedule of Events for Secondary Follow-up

CCL19: chemokine (C-C motif) ligand 19; ctDNA: circulating tumor DNA; ddPCR: droplet digital polymerase chain reaction; IL: interleukin; TCR: T-cell receptor; SOE: Schedule of Events

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	Compound: TAK-103
Title of Protocol: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-103 in Adult Patients with Mesothelin-Expressing Advanced or Metastatic Solid Tumors	EudraCT No.: Not Applicable
Study Number: TAK-103-1001	Phase: 1
Study Design: <p>This is an open-label, nonrandomized, phase 1, first-in-human study to evaluate the safety and tolerability of TAK-103 administered intravenously (IV) in patients with mesothelin- expressing advanced or metastatic solid tumors with no standard therapeutic alternative with established clinical benefit. Ovarian cancer, mesothelioma, gastric cancer and non-small lung cell cancer (NSCLC) are the target population for TAK-103. Up to 21 dose-limiting toxicity (DLT) evaluable patients will be treated with TAK-103 in 1 of the 5 proposed dosing cohorts. Dose escalation will be guided by the Bayesian Optimal Interval (BOIN) design which is based on the observed DLT rate for each dose level. Dose escalation/de-escalation decisions will be determined within the recommended dose by BOIN, taking into account safety other than DLTs, efficacy and cellular kinetics (CK), and be made jointly by the sponsor and the investigator at meetings, including the cohort management meetings. Additional emerging translational data (e.g., soluble mesothelin, Cancer Antigen 125 [CA125]) may also be used, when feasible, to aid decision-making of dosing additional patients at a given dose level. Recommended phase 2 dose (RP2D) will be determined based on aggregated observations of safety, efficacy, CK and biomarker assessments at each dose-level. In any Cohorts, infusion of TAK-103 of every patient will be separated by 28 (or more) days. Dose cohorts will be separated by a minimum of 28 days (from the last TAK-103 infusion in the precedent cohort to the first TAK-103 infusion in the subsequent cohort). Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) will be evaluated according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus.</p> <p>This study consists of the Prescreening, Screening, Pretreatment, Treatment and Primary Follow-up, and Secondary Follow-up phases. The Prescreening phase may begin on the date the patient signs the institutional review board/independent ethics committee (IRB/IEC)-approved informed consent form (ICF) for the assessment of mesothelin expression in tumor cells. The Screening phase starts with the date when one of procedures in the Screening phase take place. The patient is provided with a study-specific patient number on the date of Prescreening ICF or the date of Main ICF, whichever comes first. The Screening phase includes confirmation of eligibility and enrollment into the study, and ends with the start of leukapheresis procedures. The Pretreatment phase is defined as the period from the start of leukapheresis procedures through the completion of conditioning chemotherapy until the start of TAK-103 infusion. During the Pretreatment phase, leukapheresis, bridging therapy, and conditioning chemotherapy will be performed. The Treatment and Primary Follow-up phase begins with TAK-103 administration and continues up to Month 13. Secondary Follow-up phase begins with the end of the Treatment and Primary Follow-up period and continues up to Month 37. In the Pretreatment, the Treatment and Primary Follow-up and Secondary Follow-up phases, patients may complete study participation due to death, consent withdrawal, or other predefined situations.</p> <p>Patients must be followed according to the visit schedule to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. Patients may voluntarily withdraw from the Treatment and Primary Follow-up phase or be dropped from it at the discretion of the investigator at any time. It is anticipated that patients may leave the Primary Follow-up and move to Secondary Follow-up due to reasons including:</p>	

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<ul style="list-style-type: none"> • Disease progression • Patient voluntary withdrawal from the Primary Follow-up <p>Patients who discontinue the Treatment and Primary Follow-up phase before Month 13 will continue to be followed in the Secondary Follow-up phase in order to collect data requested from health authority (e.g. protocol defined AEs) up to 3 years after TAK-103 infusion.</p> <p>The first visit in the Secondary Follow-up phase is determined according to the time when the patient discontinued in the Treatment and Primary Follow-up phase. For example, if the patient discontinues from the Treatment and Primary Follow-up phase at Month 7, the first visit in the Secondary Follow-up phase will be Month 10.</p>	
Primary Objectives: <ul style="list-style-type: none"> • To evaluate the safety and tolerability of TAK-103. • To determine the RP2D of TAK-103. 	
Secondary Objectives: <ul style="list-style-type: none"> • To evaluate the antitumor activity of TAK-103. • To characterize the CK of TAK-103. • To determine the number and percent of cases with replication competent retrovirus (RCR)-positive test results. 	
Subject Population: Patients with mesothelin-expressing advanced or metastatic solid tumors	
Number of Subjects: Up to 21 DLT evaluable patients	Number of Sites: Approximately 4 sites in Japan
Dose Levels: The following cohorts with ascending TAK-103 dose levels are to be tested: <ul style="list-style-type: none"> • Cohort (-2): 1×10^6 chimeric antigen receptor (CAR) (+) cells/body [starting dose at resumption]. • Cohort (-1): 3×10^6 CAR (+) cells/body. • Cohort 1: 1×10^7 CAR (+) cells/body [starting dose]. • Cohort 2: 1×10^8 CAR (+) cells/body. • Cohort 3: 5×10^8 CAR (+) cells/body. 	Route of Administration: Intravenous
Duration of Treatment: Single IV infusion. Conditioning chemotherapy precedes TAK-103 treatment. (Cohorts where conditioning chemotherapy is not administered may be tested.)	Period of Evaluation: Maximum of 15 years <ul style="list-style-type: none"> • Enrollment duration: approximately 1 to 2 years • Primary Follow-up: 1 year • Secondary follow-up: 2 years • Long-term follow-up: 12 years (via enrollment in a planned long-term follow-up study).

Main Criteria for Inclusion:

1. Male or female patients aged ≥ 18 years or meeting country definition of adult, whichever is older, at the time of signing informed consent.
2. Histologically or cytologically confirmed advanced or metastatic solid tumors who have no option with or are intolerant of standard therapies with a proven clinical benefit.
3. Mesothelin-expression ($\geq 50\%$ positive on viable tumor cells) must be determined on the tumor by immunohistochemistry using a validated assay, scoring and staining confirmed by the sponsor prior to leukapheresis procedures.
4. Life expectancy ≥ 12 weeks.
5. Eastern Cooperative Oncology Group performance status of 0 or 1.
6. Adequate organ function as confirmed by clinical laboratory values as specified below:
 - a) Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll with direct bilirubin $\leq 3 \times$ ULN of the direct bilirubin. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed.
 - b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be $< 3 \times$ ULN. AST and ALT may be elevated up to $5 \times$ ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in the liver.
 - c) Calculated creatinine clearance > 50 mL/min (Cockcroft-Gault formula).
 - d) Hemoglobin must be ≥ 9 g/dL.
 - e) Neutrophil count must be > 1000 /mm³.
 - f) Absolute lymphocyte count must be > 500 /mm³.
 - g) Platelet count must be $> 75,000$ /mm³.
7. Patients must have radiographically measurable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).
8. Female patients who:
 - a) Are postmenopausal (natural amenorrhea) for at least 1 year before the screening visit, OR
 - b) Are surgically sterile, OR
 - c) If they are of childbearing potential, agree to practice 1 highly effective nonhormonal method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
 - d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
9. Male patients, even if surgically sterilized (i.e., postvasectomy), who:
 - a) Agree to practice effective barrier contraception from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
 - b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
10. Voluntary written consent must be given before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
11. Willingness and ability to comply with scheduled visits and study procedures.

Main Criteria for Exclusion:

1. Active systemic infections.
2. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection. Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.
3. Coagulation disorders, or other major medical illnesses including respiratory or immune system disease.
4. Patients with high tumor burden at the disease assessment at screening. The tumor burden is determined by the threshold set for each type of cancer.
5. Patients with current or history of interstitial lung disease.
6. Patients with current or history of significant immune-related adverse events (irAEs) related to treatment with immune checkpoint inhibitors. Patients with current or history of the following adverse events (AEs) can be enrolled after careful discussion between the investigator and sponsor: hyperglycemia/diabetes mellitus, thyroid disorder, hypopituitarism, hypoadrenocorticism, asymptomatic elevation in amylase/lipase, and Grade 1 or 2 skin toxicity.
7. Patients with known cardiovascular and cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, myocardial infarction, congestive heart failure, Left Ventricular Ejection Fraction (LVEF) <45 %, impaired respiratory function, baseline oxygen saturation <93% on room air. A well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion.
8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
9. Patients with any signs of lymphoma and/or leukemia.
10. Patients who are diagnosed with or treated for another malignancy within 3 years before leukapheresis procedures. Patients with non-melanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) would be included if they were adequately treated.
11. Any disease requiring systemic steroid treatment.
12. Any prior use of cell and gene therapy(ies).
13. Treatment with any investigational products (except for cell or gene therapy) within 14 days before leukapheresis procedures or 28 days before treatment with conditioning chemotherapy/TAK-103.
14. Systemic anticancer therapy (including immuno-oncology therapies) and treatment with radiotherapy within 14 days before leukapheresis procedures or treatment with conditioning chemotherapy/TAK-103.
15. Treatment with major surgery within 28 days before leukapheresis procedures or treatment with conditioning chemotherapy/TAK-103 (minor surgical procedures such as catheter placement are not exclusionary criteria).
16. Previous treatment with any mesothelin-targeted therapy.
17. Any unresolved toxicity of Grade 3 or higher from previous anticancer therapy.
18. Patients with risk of bleeding as judged by the investigator.
19. Presence of central nervous system metastasis or other significant neurological conditions (patient with central nervous system metastases that have been effectively treated where necessary and stable can be enrolled).
20. Patients with human immunodeficiency virus (HIV) seropositive and/or human T- cell lymphotropic virus (HTLV) seropositive.
21. Patients with a history of organ transplantation or awaiting organ transplantation.
22. Patients with severe immediate hypersensitivity to any of the agents including cyclophosphamide, fludarabine, or streptomycin.
23. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

24. Live vaccine ≤ 6 weeks prior to start of conditioning regimen.
25. Female patients who are breastfeeding or have a positive serum pregnancy test (urine pregnancy test is allowed before treatment with conditioning chemotherapy and TAK-103).
Note: Female patients who are lactating will be eligible if they discontinue breastfeeding before preconditioning therapy and the treatment with TAK-103. For those who undergo bridging therapy, lactation should be terminated in compliance with the package insert of the drug.

Main Criteria for Evaluation and Analyses:

Primary endpoints:

- Incidence of dose-limiting toxicities (DLTs).
- Incidence of treatment-emergent AEs (TEAEs).
- Incidence of AEs of clinical interest including severe ICANS, CRS, hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and tumor lysis syndrome (TLS).

Secondary endpoints:

- Overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), and progression-free survival (PFS) as assessed by the investigator according to RECIST 1.1 and iRECIST.
- Overall survival (OS).
- CK-related parameters evaluated by CAR vector copy number (C_{max} [maximum (peak) observed in peripheral blood drug concentration after single dose administration], t_{max} [time of first occurrence of maximum observed peripheral blood concentration], C_{last} [last observed quantifiable concentration in peripheral blood], t_{last} [persistence: time of last observed quantifiable concentration in peripheral blood (days)]; AUC [area under the blood concentration-time curve]).
- Number and percentage of cases with RCR-positive test results.

Statistical Considerations:

The incidence and percentage of DLTs and TEAEs will be summarized by System Organ Class and Preferred Term of the International Council for Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) and by grade. In addition, the following events will be summarized with the same method.

- Treatment-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher treatment-related TEAEs.
- Serious adverse events (related and regardless of relationship).

The AEs of clinical interest and RCR will be summarized by counts and percentages.

For the secondary efficacy endpoints, point estimate and the 2-sided 95% exact binominal confidence intervals will be computed for binary endpoints and time-to-event endpoints will be analyzed descriptively using Kaplan-Meier method.

CK parameters will be summarized using descriptive statistics. Individual TAK-103 concentration-time data and individual CK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

Sample Size Justification:

It is anticipated that up to 21 DLT evaluable patients will be enrolled in this study. The study will use BOIN design to inform dose escalation/de-escalation decisions, taking into account safety other than DLTs, efficacy, CK, and biomarker assessments.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 List of Abbreviations

ACT	adoptive cell transfer
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
BSA	body surface area
BOIN	Bayesian Optimal Interval
CA125	Cancer Antigen 125
CA19-9	Cancer Antigen 19-9
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T cell
CARTOX	CAR-T-cell-therapy-associated TOXicity
CCL19	chemokine (C-C motif) ligand 19
CEA	Carcinoembryonic Antigen
CK	cellular kinetics
C _{last}	last observed quantifiable concentration in peripheral blood (CAR copies/μg of gDNA or CAR+ cells/μL)
C _{max}	maximum (peak) observed in peripheral blood drug concentration after single dose administration (CAR copies/μg of gDNA or CAR+ cells/μL)
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DC	dendritic cell
DCR	disease control rate
ddPCR	droplet digital polymerase chain reaction
DLT	dose-limiting toxicity
DOR	duration of response
DMC	Data Monitoring Committee
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EOPF	end of primary follow-up
EOS	end of study
FCM	flow cytometry
FDA	Food and Drug Administration [United States]
FDG-PET	fluorodeoxyglucose-position emission tomography
FFPE	formalin-fixed, paraffin-embedded
FIH	first in human
GCP	Good Clinical Practice
GvHD	graft versus host disease
gDNA	genomic DNA
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAbs	hepatitis C virus antibody
HEK	human embryonic kidney (cell line)
HepG2	human hepatocellular carcinoma (cell line)
HepG2-Red-FLuc	luciferase-expressing HCC cell line derived from HepG2
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune-confirmed progressive disease
iCR	immune complete response
IEC	independent ethics committee
IFNg	interferon gamma
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
I/O	immuno-oncology
iPR	immune partial response
irAE	immune-related adverse event
iRECIST	immune Response Evaluation Criteria in Solid Tumors (a modified Response Criteria in Solid Tumors Version 1.1 for immune-based therapeutics)
IRB	institutional review board
iSD	immune stable disease

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iUPD	immune-unconfirmed progressive disease
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
J-non-IMP	Japan Drug, Product, or Device Used in the Clinical Trial other than IMP
kDa	kilodalton
LAM-PCR	linear amplification-mediated polymerase chain reaction
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MPF	megakaryocyte potentiating factor
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MTV	mean tumor volume
NCI	National Cancer Institute
NK	natural killer cell
NLNT	new lesion-non-target
NLT	new lesions-target
NSG	NOD SCID Gamma
ORR	overall response rate
OS	overall survival
PMPA	plasma membrane protein array
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffer saline
PET	position emission tomography
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]
PT	prothrombin time
PR	partial response
Pr	probability
PRIME CAR-T	proliferation-inducing and migration-enhancing CAR-T
RCR	replication competent retrovirus
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
rm	recombinant mouse
RNAseq	ribonucleic acid sequencing
RP2D	recommended phase 2 dose
SAE	serious adverse event

SC	subcutaneously
scFv	single-chain variable fragment
SD	stable disease
SMRP	soluble mesothelin-related peptides
SOC	standard of care
SOE	schedule of events
SpO ₂	percutaneous oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TF	total flux
TGI	tumor growth inhibition
t _{last}	time of last observed quantifiable concentration in peripheral blood (days)
TLS	tumor lysis syndrome
TMB	tumor mutational burden
t _{max}	time of first occurrence of maximum observed CAR-T cell concentration (C _{max}) in peripheral blood
TTP	time to progression
TV	tumor volume
ULN	upper limit of the normal range
UPENN	University of Pennsylvania
US	United States
UTD	untransduced
WBC	white blood cell
WHO	World Health Organization

3.3 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC	Takeda Development Center

4.0 INTRODUCTION

4.1 Background

4.1.1 Scientific Background

Adoptive cell-transfer (ACT) and gene-transfer techniques have been developed over 30 years, and autologous CD19-targeted chimeric antigen receptor T cell (CAR-T) therapies have dramatically improved the clinical outcomes of patients with relapsed/refractory diffuse large B cell lymphoma and B cell precursor acute lymphoblastic leukemia [1-4]. Chimeric antigen receptors (CARs) are synthetic receptors that typically consist of an extracellular single-chain variable fragment (scFv) to direct specificity in human leukocyte antigen (HLA)-independent manner, a transmembrane domain, an intracellular CD3 ζ signaling domain, and usually 1 or 2 costimulatory domains, such as CD28/4-1BB, which enhance proliferation, cytokine production, and T cell persistence in vivo.

CAR-T cell therapies in some types of hematological malignancy have surpassed expectations; however, no definite therapeutic effects of CAR-T cell therapy have been demonstrated in solid tumors. This may be a consequence of impaired T cell trafficking in tumors, tumor heterogeneity related to targeted antigen expression, and limited CAR-T cell expansion and persistence [5]. Strategies designed to facilitate delivery to solid tumors and favorably modulate immunosuppressive pathways may improve outcomes for nonhematologic indications [6, 7]. Typical adverse events (AEs) associated with CAR-T cell therapy include on-target off-tumor toxicity, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is characterized by fevers, hypotension, capillary leak, coagulopathy, and several organ dysfunctions. ICANS comprises presentations such as dysgraphia, speech disturbance, headache, delirium, focal neurological deficits, seizures and cerebral edema.

On-target off-tumor toxicity is an AE that occurs when the surface antigen, which is targeted by the CAR-T cells, is also expressed in normal tissue, because CAR-T cells recognize their target and damage or destroy these normal tissue cells. Compared to CD19-targeted CAR-T cells in hematologic malignancies, this toxicity has been limited in recent trials in solid tumors. In a messenger RNA (mRNA)-based anti-mesothelin CAR-T trial, patients with mesothelioma received 1×10^8 cells/m² for the first infusion followed by 1×10^9 cells/m² for the second infusion 1 week later. After safety monitoring for a minimum of 1 month, patients received 1×10^8 cells/m² 3 times per week for 1 week followed by 1 week of rest and then 1×10^9 cells/m² administered 3 times per week for 1 week [8]. Of note, 1 of 3 patients developed anaphylaxis and cardiac arrest within minutes of completing the third infusion in the trial. However, investigators were able to determine that the patient had developed anaphylaxis and cardiac arrest, due to development of anti-mouse IgE antibodies specific to the CAR-protein (scFv), which was of murine origin. The patient experienced a rapid recovery and was discharged to home 10 days after the events [9]. One of 3 patients developed a partial response (PR) after receiving the third infusion, followed by disease progression 6 months later.

A subsequent study led by the same group from the University of Pennsylvania (UPENN) using the same mRNA-based mesothelin-targeting CAR-T cells approach found no dose-limiting toxicities (DLTs) or on-target off-tumor toxicities after infusing 6 patients with pancreatic cancer systemically with 1×10^8 cells/ m^2 3-times a week for 3 weeks (i.e., a total of 9 infusions). The best overall response was stable disease (SD) with 2 patients out of 6 patients and the total metabolic active volume decreased by 69.2% in 1 of those patients. In this patient, all liver lesions had a complete reduction in ^{18}F -2-fluoro-2-deoxy-D-glucose uptake at 1 month compared to baseline, although there was no effect on the primary pancreatic ductal adenocarcinoma [10]. A single case of confirmed on-target- off-tumor toxicity was observed in 1 patient with ovarian cancer who received 3 intraperitoneal infusions of 1×10^8 mesothelin-targeting CAR-T cells (MCY-M11) and presented with Grade 2 pericarditis 2 days after receiving the third infusion. The patient recovered without recurrence of pericarditis after clinical treatment with ibuprofen and colchicine. Five patients achieved SD as the best response: 3 in 5×10^7 cells/dose and 2 in 1×10^8 cells/dose among 9 evaluable patients (1×10^7 cells/dose for 2, 5×10^7 cells/dose for 3 and 1×10^8 cells/dose for 2 patients) [11]. Noteworthy is that TAK-103 is constructed with the same P4 scFv and 4-1BB costimulatory domains as were used in the MCY-M11 clinical trial.

The largest mesothelin-targeting CAR-T clinical study reported to date from Memorial Sloan Kettering Cancer Center has reported no on-target off-tumor toxicities observed in 27 patients with mostly mesothelioma, who received various doses of intrapleural mesothelin-targeting CAR-T cells infusions (highest dose of 6×10^7 cells/kg). Among 16 patients who received cyclophosphamide as a conditioning chemotherapy, followed by treatment with CAR-T cells and at least 3 doses of anti-programmed death receptor-1 (PD1) antibody, 3 patients with complete response (CR) and 7 patients with PR were observed [12].

Lastly, another cell therapy consists of autologous, genetically engineered T cells (gavocabtagene autoleucel [gavo-cel]; TC-210) expressing a single-domain antibody against mesothelin, which is incorporated into the endogenous T cell receptor (TCR) complex. The preliminary report from a phase 1 study of gavo-cel in patients with refractory solid tumors (i.e., malignant mesothelioma, ovarian cancer, cholangiocarcinoma, or non-small cell lung cancer) did not observe any on-target off-tumor toxicities in 8 patients with mesothelioma or ovarian cancer: 7 patients received a single infusion of 5×10^7 cell/ m^2 body surface area (BSA) and 1 patient received 1×10^8 cell/ m^2 BSA. Three patients achieved PR, and 5 patients achieved SD as best overall response [13].

As noted above, experience with solid tumors in general has been limited. Mesothelin-targeting autologous CAR-T cell therapies have reversible and tolerable safety profiles and show some evidence of clinical activity, although some on-target off-tumor toxicities have been observed [9, 11, 14]. As such, there is precedent for safety with systemic infusion of unarmored anti-mesothelin CAR-T; this study will assess the tolerability of an armored anti-mesothelin product.

4.1.2 TAK-103 Description

Noting the hypothesis that the insufficient therapeutic effect of CAR-T cell therapy against solid tumors could be attributable to the difficulties of CAR-T to infiltrate and survive in the local microenvironments of the tumor [15], the cytokine and chemokine-producing CAR-T cells (i.e.,

proliferation-inducing and migration-enhancing CAR-T; defined as PRIME CAR-T) were developed. PRIME CAR-T cells are autologous T cells transduced with a CAR construct that encodes the *IL7* and *CCL19* genes, in addition to targeting a specific antigen (e.g., mesothelin) and to express cytokine IL-7 and chemokine CCL19, respectively. T cells transfected with these genes can produce the corresponding proteins, with IL-7 and CCL19 contributing to T cell proliferation and survival in tumor sites, and to accumulation of T cells and dendritic cells (DCs) in the tumor sites, respectively. In a study with immunocompetent DBA/2 and C57BL/6 mice with preestablished solid tumors formed by subcutaneous inoculation of P815-hCD20, 3LL-hCD20, and PAN02 cell lines, PRIME CAR-T cells were shown to have greater antitumor effects than conventional CAR-T cells. In addition, not only the CAR-T cells, but also the host T cells and DCs showed increased infiltration into tumors, demonstrating the induction of CAR independent immune reactions [16].

TAK-103 is a cell therapy product consisting of human (autologous) mesothelin-targeting T cells prepared by transducing cultured autologous T cells isolated from the patient's blood. The transgene in TAK-103 has a structure in which a P4 scFv recognizes and binds mesothelin which is fused to hinge and transmembrane regions of CD8, an intracellular region of 4-1BB, and an intracellular region of CD3 ζ , followed by IL-7, and CCL19 genes that are each bound via a self-cleaving linker P2A sequence. These genes are translated from a single transcription product and are believed to involve ribosomal skipping to make independent proteins and are therefore designed to enable expression of soluble IL-7 and CCL19 and anti-mesothelin CAR.

The sequence of the scFv region for TAK-103 CAR T construct was fully humanized [17], suggesting a lower risk of immunogenicity in humans compared to a murine-derived binder. Target-selectivity of binder scFv used in TAK-103 was evaluated with a plasma membrane protein array (PMPA) assay (Retrogenix Ltd., Chinley, High Peak, United Kingdom). Among the 5,855 human proteins tested, the vast majority of which are cell surface membrane proteins, the only specific interaction observed for the P4 scFv of TAK-103 was for mesothelin. No P4 scFv-mediated specific off-target binding was identified in this study, indicating high target specificity of TAK-103.

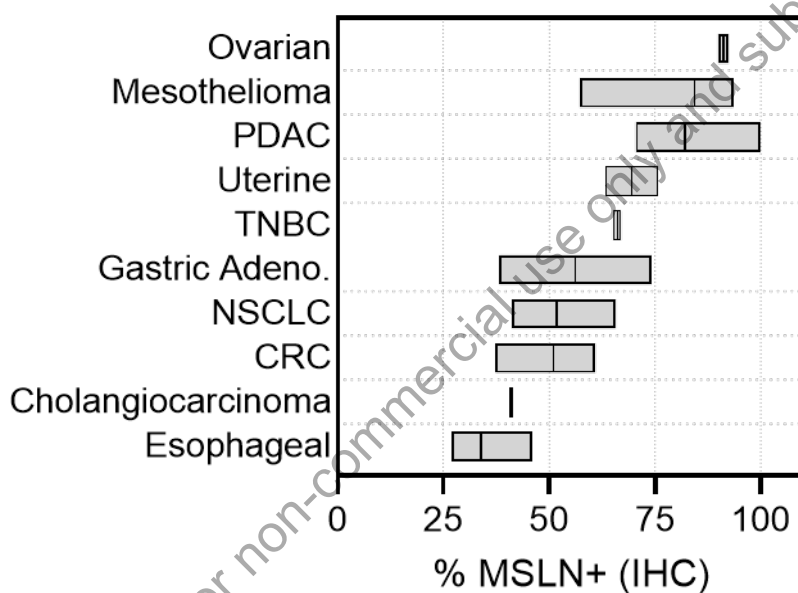
Human mesothelin is a glycosylphosphatidylinositol-anchored membrane glycoprotein, which was first described as a membrane-bound protein expressed on mesothelioma, ovarian, and pancreatic cancer cells as well as some normal cells [18]. *MSLN* gene encodes a precursor cell-surface protein of 69 kDa that is processed to a soluble 32-kDa N-terminal fragment named megakaryocyte potentiating factor (MPF), and 40 kDa C-terminal membrane-bound mesothelin protein by furin protease. A soluble form of the protein, often referred to as soluble mesothelin-related protein (SMRP), is also generated by either alternative splicing or proteolytic cleavage of the mesothelin mature form [19].

The biological function for mesothelin is yet to be fully uncovered, and in knockout studies mice exhibited normal development [20]. Mesothelin is expressed on normal mesothelial cells in the pleura, pericardium, and peritoneum, and in epithelial cells on the surface of the ovaries, tunica vaginalis, rete testis, fallopian tubes, and tonsils, in trace amounts [21]. Some preclinical studies have suggestive evidence that aberrant mesothelin expression could promote cancer cell

proliferation, and enhance malignant transformation and tumor aggressiveness, by activating the nuclear factor- κ B (NF- κ B), mitogen-activated protein kinase (MAPK), and phosphoinositide 3 (PI3)-kinase intracellular pathways [22]. In addition, an increase in tumor burden and poor overall survival are associated with elevated mesothelin expression, according to clinical observations in early-stage lung adenocarcinoma and triple negative breast cancer [23, 24]. Furthermore, the high-affinity interaction between mesothelin and Cancer Antigen 125 (CA-125, also known as mucin 16 [MUC16]) is believed to lead to heterotypic cell adhesion, which facilitates metastasis of ovarian cancer cell lines and can promote metastatic invasion [25, 26].

Expression of mesothelin on malignant cells has been reported by several groups (using 5B2 antibody for immunohistochemistry [IHC] with no predefined cutoff), and an overview of solid tumor tissues with a mesothelin expression prevalence of greater than 25% is presented in Figure 4.a.

Figure 4.a Mesothelin Expression in Solid Tumor Tissues With >25% Prevalence



Adeno: adenocarcinoma; CRC: colorectal cancer; IHC: immunohistochemistry; MSLN: mesothelin; NSCLC: non-small-cell lung adenocarcinoma cancer; PDAC: pancreatic ductal adenocarcinoma; TNBC: triple-negative breast cancer

Many clinical studies have been conducted with the use of mesothelin-targeting investigational drugs and CAR-T cell therapies. Hence, mesothelin is considered to be a promising target for solid tumor CAR-T cell therapy.

4.1.3 Preclinical Experience

A series of in vitro (including biochemical or cell-based functional assays) and in vivo (with immunocompromised mice bearing HepG2 [a human hepatocellular carcinoma (HCC) cell line] or HepG2-Red-FLuc [a luciferase-expressing HCC cell line derived from HepG2] xenografts) studies have been conducted to evaluate the mechanism of action (MOA), efficacy, and safety profiles of the mesothelin-targeting CAR-T cell therapy TAK-103. CAR expression and target cell killing activity against engineered human mesothelin-expressing human embryonic kidney (HEK)293 cells and mesothelin-expressing HepG2 tumor cells were confirmed in vitro as the key functions of TAK-103. In vitro secretion and functional activity of IL-7 and CCL19 were demonstrated by enzyme-linked immunosorbent assay (ELISA) and reporter assays. In vivo antitumor activity was confirmed using mesothelin-expressing HepG2 or HepG2 Red-FLuc xenograft models.

In the first integrated in vivo safety and efficacy study, NOD SCID gamma (NSG) mice implanted subcutaneously (SC) with HepG2 HCC cells were injected intravenously (IV) with low dose (2×10^6 cells/mouse) or high dose (5×10^6 cells/mouse) TAK-103 CAR-positive (CAR (+)) T cells, phosphate buffer saline (PBS; vehicle control), or untransduced (UTD) T cells as a control and tumor volume (TV) was measured twice weekly by calipers. The TAK-103 5×10^6 CAR(+) T cells group was removed early from the study (Day 25) due to lack of tolerability, the remainder of the animals survived to the scheduled necropsy on Day 31. While mice receiving 5×10^6 CAR(+) T cells did not demonstrate a difference in mean tumor volume (MTV) from the UTD T cells group on Day 25, mice receiving 2×10^6 CAR(+) T cells exhibited a not statistically significant, modest MTV reduction and tumor growth inhibition (TGI) compared to the UTD T cells group, with a complete remission in 2 out of 8 mice on Day 31. Despite the lack of significant impact on MTV and %TGI after administration of TAK-103 at both dose levels, microscopically there was a lack of viable tumor cells and infiltration of engrafted human CD3(+) mononuclear cells consistent with pseudoprogression-driven efficacy.

In the second integrated in vivo safety and efficacy study, with the same study design as described above for the first study, TAK-103 CAR(+) T cells manufactured from a different T cell donor (than the one used in the first integrated in vivo safety and efficacy study) were evaluated with increased numbers of animals per group. Both dose groups receiving TAK-103 were removed early from the study (the 5×10^6 CAR(+) T cells group by Day 18, and the 2×10^6 CAR(+) cell group by Day 21) due to lack of tolerability. The xenografted tumors in animals receiving TAK-103 at both doses transiently grew rapidly in size as compared to those in animals receiving vehicle and UTD T cells, attributed to pseudoprogression. In mice receiving TAK-103 at both doses, MTVs began to decrease after Day 14; however, MTV was not significantly lower than control animals by Day 18 (5×10^6 CAR(+) T cells) or 21 (2×10^6 CAR(+) T cells). Despite the lack of significant impact on TV in animals receiving TAK-103, microscopic evaluation of tumors in mice at both dose levels demonstrated mononuclear cell inflammation (confirmed to be engrafted human CD3(+) cells) and necrosis of tumor cells, with a lack of viable intact tumor cells in all animals, indicative of an antitumor effect.

Additionally, TAK-103 was evaluated in an in vivo efficacy study with female NSG mice implanted SC with HepG2-Red-FLuc HCC cells. Total flux (TF), which is a measure of the luminescence of HepG2-Red-FLuc cells, is proportional to the number of tumor cells present in the animal and was used to evaluate antitumor efficacy. Mice injected IV with a single dose of 2×10^6 or 5×10^6 TAK-103 CAR(+) T cells demonstrated a sustained TF reduction from Day 7 after TAK-103 administration through Day 21, the end of the study. Although TV, measured by calipers, increased in both groups administered TAK-103 when compared to groups receiving UTD T cells, the significant reduction in mean TF indicated in vivo antitumor activity of TAK-103 against mesothelin-expressing tumor cells.

Further confirmation of the efficacy and MOA of TAK-103 was established through blood cellular kinetics (TAK-103 CAR copy number) and IL-7/CCL19 serum concentrations in the integrated efficacy and safety study of HepG2-bearing female NSG mice after single administration of TAK-103. TAK-103 CAR copy number and IL-7/CCL19 concentrations increased over time in a correlative manner.

The safety of TAK-103 was evaluated in the 2 integrated in vivo safety and efficacy studies in the HepG2 mouse xenograft model, through in vitro models of tumorigenicity and clonal expansion, and in in vitro assessments of on- and off-target binding. Stand-alone toxicity studies were not performed with TAK-103 due to the expected difficulty of continuous safety assessment as a result of the development of graft versus host disease (GvHD) in animal models treated with human CAR-T products. Additionally, standalone nonclinical safety assessments of IL-7 and CCL19 were determined to be irrelevant based on lack of translatability to humans as administration of recombinant mouse (rm) IL-7 or rmCCL19 would not recapitulate the kinetics of IL-7/CCL19 produced by the CAR-T and the similarity of IL-7 and CCL19 biological function between mouse and human has not been confirmed. No commercially available mouse tumors have been identified that express mesothelin, so mouse syngeneic models with a mouse surrogate for TAK-103 would underestimate IL-7 and CCL19 production due to lack of target-induced CAR-T activation.

In the 2 integrated in vivo efficacy and safety studies with female NSG mice implanted SC with HepG2 hepatocarcinoma cells, mice were injected IV with a single dose of TAK-103 at 2×10^6 or 5×10^6 CAR(+) T cells, PBS (vehicle control), or UTD T cells as a control. TAK-103 manufactured from 2 different T-cells donors and UTD T cells manufactured in the same procedure were independently evaluated in these 2 studies. Mortality, moribundity, body weight loss, and/or adverse clinical signs in animals receiving TAK-103 at 5×10^6 cells/mouse ($n = 8$ or 16) resulted in early removal (Day 18 or Day 25) of the groups from both studies. In one of the integrated safety and efficacy studies, mortalities ($n = 3$ out of 16) and abnormal clinical signs were observed in the animals receiving TAK-103 at 2×10^6 cells/mouse, which resulted in the removal of this group from the study on Day 21. Microscopic evaluation of limited tissues in these studies did not identify target organs; however, findings were consistent with GvHD (an expected occurrence in mice administered human cell products), including adverse clinical observations, body weight loss and a characteristic pattern of mononuclear cell inflammation in tissues, were observed in animals receiving TAK-103, and the poor tolerability in these animals was attributed to GvHD. Mice receiving UTD T cells did not demonstrate the lack of tolerability as noted after administration of

TAK-103 and had similar microscopic findings consistent with GvHD, but of lower severity; this may reflect the armoring of TAK-103 and a more robust response to the release of IL-7 and CCL19.

In the first integrated in vivo safety and efficacy study, a subcutaneous mass in the right shoulder in 1 animal receiving TAK-103 at 5×10^6 cells/mouse was first observed on Day 23, collected and determined to be a human T cell lymphoma. Further investigation of the subcutaneous mass determined it could be attributed to an underlying transformed cell population specific to the donor T cells that were utilized to manufacture TAK-103 product for this study. In the second integrated in vivo safety and efficacy study, with TAK-103 manufactured from a different T cell donor, related findings were not observed in any of the mice. This donor-specific finding is considered to have negligible risk for patients receiving TAK-103 manufactured from their own (autologous) T cells.

In vivo tumorigenicity studies were not conducted with TAK-103 because (1) the in vivo studies are confounded by GvHD which prevents a longer term tumorigenicity assessment, and (2) it is conjectured that the risk of in vivo postdose malignant transformation of TAK-103 in human is low because TAK-103 is derived from differentiated T cells in human blood. Therefore, the tumorigenicity assessment of TAK-103 was performed in vitro, including an IL-2 independent proliferation test and a linear amplification mediated polymerase chain reaction (LAM-PCR) assessment of clonality and insertion site-driven mutagenesis. Consistent with a low risk of malignant transformation, TAK-103 did not demonstrate IL-2 independent proliferation ability. In a clonality analysis, LAMPCR for insertion site monitoring revealed that the transfected T cells were not in a genetically clonal state and that the transgene (i.e., the replication incompetent gene transfer virus vector with the CAR construct) underwent nonspecific insertion into patients' autologous T cell genome. Overall, these results indicate that TAK-103 has a low potential for tumorigenicity.

To assess potential off-target binding of TAK-103, a PMPA assay was performed to evaluate binding to 5855 human plasma membrane proteins covering the majority of plasma proteins that have an extracellular domain available for CAR-T cell binding. The scFv of TAK-103 specific to human mesothelin (P4 scFv) exhibited highly specific binding only to mesothelin. No P4 scFv-specific off-target interactions were identified in the PMPA assay, suggesting the risk for off-target binding and toxicity is minimal. A cross reactivity study was performed in cryosections from a full panel of normal human tissues with P4 scFv to evaluate the potential of TAK-103 for on-target off-tumor toxicity. Binding with P4 scFv in the human tissue panel was limited to the membrane and cytoplasm of mesothelial cells lining the lung, spleen, and stomach and surface epithelial cells of the ovary. No unexpected cross reactivity was observed with P4 scFv in the human tissue panel examined.

Additionally, target (mesothelin) distribution analysis was performed via IHC with a commercial antibody to evaluate the potential for on-target off-tumor toxicity (ie, TAK-103 CAR(+) T cells binding to mesothelin [on-target] that is not located on the tumor [off-tumor]) of TAK-103 to normal human tissues. The expression of mesothelin is consistent with published literature [21, 27, 28] and identifies potential mesothelin-targeting of TAK-103 to the mesothelial lining of the

peritoneum, pericardium, and pleura. Additional tissues/organs with membranous labeling include epithelium, glandular and/or ductular structures in reproductive tissues, kidney (Bowman's capsule), tonsil, and trachea.

4.1.4 Clinical Experience

This is the first-in-human (FIH) study of TAK-103. One patient with malignant pleural mesothelioma has been dosed with TAK-103 and died 25 days after study drug administration (Day 26) due to Grade 5 pneumonitis. Both CRS and pneumonitis in this patient were considered related to study product by the investigator, and pneumonitis was considered a DLT.

This patient developed hypoxia; a contrast-enhanced computed tomography (CT) of the chest revealed patchy ground-glass opacities 8 days after administration (Day 9), and the patient was diagnosed with CRS (Grade 2). Tocilizumab and dexamethasone were administered. In addition, the patient tested positive for cytomegalovirus (CMV) antigen and was treated with ganciclovir. On Day 17, the ground-glass opacities and reticular opacities became faint and improved. However, on Day 21, the respiratory symptoms worsened, as well as the ground-glass opacities and reticular opacities, leading to a diagnosis of pneumonitis. Steroid pulse therapy was ineffective and the patient died on Day 26. The patient was previously treated with nivolumab in March 2020 and subsequently developed pneumonitis.

Autopsy of the lung showed malignant mesothelioma measuring 12 cm from the right pleura to the chest wall, with multiple metastatic foci in the lung field and hilum. Inflammatory cell infiltration mainly consisting of CD8+ T cells was conspicuous in the background lung. In addition, fibrosis accompanied with a part of hyaline membrane spread, and it is considered to be the exudative stage to organizing stage of diffuse alveolar damage.

The sponsor analyzed tumor tissue, normal tissue, and tissue with pneumonitis lesions obtained by autopsy using immunofluorescence test, etc. In the examination of the autopsied lungs at the site of pneumonitis, high infiltration of CD3-positive T-cells, with minimal to no CAR-positive cells was observed. In contrast, the autopsied tumor sections that strongly expressed mesothelin showed infiltration of a large number of CAR-positive T-(CD3+) cells, which were activated and proliferating. These findings suggest that the CD8-positive T-cells involved in pneumonitis were predominantly CAR-negative T-cells and that the CAR-positive cells selectively acted on only tumor cells in the lung that highly express mesothelin in the patient.

4.1.5 Potential Risks and Benefits

Since TAK-103 has been administered to only 1 patient, the clinical benefits or risks of TAK-103 in humans have not yet been determined. However, potential risks of treatment with TAK-103 are listed below and are based on the known and potential risks of currently approved CAR-T therapies, including CAR-T procedures and/or manufacturing, as well as current understanding of mesothelin targeting and on-target/off-tumor effects.

Known risks associated with CAR-T therapies:

- CRS

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- Hemophagocytic lymphohistiocytosis (HLH)
- Macrophage activation syndrome (MAS)
- ICANS
- Tumor lysis syndrome (TLS)
- Hypersensitivity reaction.

Potential risks associated with CAR-T therapies:

- Generation of replication competent retrovirus (RCR)
- Secondary malignancies
- Immunogenicity

Potential risks associated with mesothelin expression in normal tissues, as well as product labeling from currently approved CAR-T therapies:

- Effects on fetus or female reproductive function due to mesothelin expression in fallopian tube, endometrium, cervix, uterus, and placenta
- Effects of male reproductive function due to mesothelin expression in tunica vaginalis and rete testis
- Effects on cardiopulmonary function due to mesothelin expression in pleura and pericardium
- Pleuritis, peritonitis or pericarditis due to normal low level mesothelin expression on these serosal surfaces

Known risks associated with CAR-T therapy procedures, conditioning chemotherapy, and/or manufacturing:

- Hepatitis B virus (HBV) reactivation
- Lymphopenia
- Transmission of infectious agents during apheresis

Potential risks associated [REDACTED]:

- Transaminase elevation
- Hypertension and chest pain
- Lymphadenopathy, fever, rash, and fatigue
- Hypophosphataemia

Potential risks associated [REDACTED]:

- T-cell lymphoma

- Pneumonitis

4.2 Rationale for the Proposed Study

This study will investigate the safety, CK, and preliminary efficacy of TAK-103 and determine the recommended phase 2 dose (RP2D) in adult patients with mesothelin-expressing advanced or metastatic solid tumors. The selection of study population is based on a use of mesothelin as a marker because it is overexpressed in number of solid tumors such as pancreas, stomach, and colon, where there is no gene target associated to solid tumors.

4.2.1 Rationale for Starting Dose

The starting dose of TAK-103 will be 1×10^7 CAR (+) cells/body. Given the complex biology of cell therapies, animal models used to determine preclinical activity of CAR-T cell therapies may not predict clinical efficacy or safety in humans. Therefore the starting dose was based on the following considerations: 1) Retrospective analysis on the administered starting dose-levels and dose-escalation cohorts for mesothelin targeted cell therapy clinical trials in the literature, and 2) Observed AEs, on-target/off-tumor and other DLTs in mesothelin-targeted cell-therapy trials.

A retrospective meta-analysis on dose-ranges for 17 different unarmored and armored mesothelin-targeted cell therapy clinical studies (source: ClinicalTrials.gov, literature) resulted in the median starting flat dose (based on the average body weight of 60 kg and BSA of 1.62 m^2) of 1.6×10^7 ($1.3\text{--}6.0 \times 10^7$, 25th–75th percentile) CAR (+) cells/body and median highest dose of 4.9×10^8 ($1.6\text{--}6.0 \times 10^8$, 25th–75th percentile) CAR (+) cells/body (Table 4.a). Our proposed starting dose and dose-escalation steps are within clinically investigated dose-ranges for mesothelin-targeted CAR cell therapies.

An IV administered unarmored mesothelin CAR-T study from UPENN [29] evaluated dose-levels of 4.9×10^7 (Dose Level [DL1]) and 4.9×10^8 (DL2) CAR (+) cells/body with presence or absence of lymphodepleting regimen. Within their study consisting of 15 patients (4 cohorts), besides one patient experiencing DLT at cohort 1 (DL1, no lymphodepletion), there were no significant CRS, ICANS, or on-target/off-tumor toxicity observations. Our proposed IV administered starting dose of TAK-103 (1×10^7) is 4.9-fold lower than the one investigated in UPENN study [29].

After the start of the study, a patient with malignant pleural mesothelioma enrolled in Cohort 1 developed pneumonitis (Grade 5) (see Section 4.1.4 Clinical Experience) and this event was determined as a DLT. To ensure the safety of the participants after resumption of the study, a new Cohort (–2) for a lower dose, 1×10^6 CAR(+) cells/body was added, and the starting dose at resumption was set as 1×10^6 CAR(+) cells/body.

Table 4.a Mesothelin-Targeted Cell Therapy Clinical Studies

Sponsor	Route of administration	Additional information	Dose (10 ⁸ cells/body)		NCT number	Reference
			Min	Max		
China Meitan Hospital	IV		0.03	6	NCT02930993	[30]
Chinese PLA General Hospital	Unknown	PD-1 gene-knocked out	0.6	30	NCT03747965	[31]
Shanghai Cell Therapy Research Institute	IV	Anti-CTLA4/PD-1 antibodies expressing	12	30	NCT03182803	[32]
Shanghai Cell Therapy Research Institute	IV	Anti-PD-1 antibodies expressing	3	60	NCT03615313	[33]
Shanghai GeneChem	Unknown		0.6	6	NCT02706782	[34]
Shenzhen BinDeBio	IV		0.162	4.86	NCT03638193	[35]
Shanghai Cell Therapy Group	IV	Anti-PD-1 antibodies expressing	0.06	1.8	NCT04503980	[36]
Shanghai 6th People's Hospital	Unknown			3	NCT03814447	[37]
NCI	IV	With IL-2 infusion	0.01	1	NCT01583686	[38]
Allife Medical Science and Technology	Unknown		0.3	1.8	NCT03692637	[39]
UPENN	IV	RNA transfection	1.62	4.86	NCT01897415	[40]
UPENN	IV		0.162	4.86	NCT02465983	[41]
UPENN	IV		0.162	0.486	NCT03323944	[42]
UPENN	IV		0.486	4.86	NCT02159716	[29]
UPENN	IV		0.162	0.486	NCT03054298	[43]
UPENN	intrapleural		0.162	0.486	NCT03054298	[44]
MSKCC	intrapleural		0.18	6	NCT02414269	[45]
MaxCyte	intraperitoneal	RNA transfection	0.1	5	NCT03608618	[46]
Total	75% quantile		0.6	6.0		
	Median		0.16	4.9		
	25% quantile		0.13	1.6		

CTLA4: cytotoxic T lymphocyte antigen 4; IL-2: interleukin 2; IV: intravenous; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; PD-1: programmed death receptor-1; UPENN: University of Pennsylvania

Based on the body weight=60 kg and BSA=1.62 m² [47]

4.2.2 Rationale for Conditioning Chemotherapy

Clinical and preclinical evidence identify that administration of lymphodepleting conditioning chemotherapy prior to ACT of tumor-specific T lymphocytes plays a key role in enhancing

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treatment efficacy via transient elimination of regulatory T cells and competing cells of the immune system ('cytokine sinks').

The rationale for lymphodepletion prior to ACT is attributable the need to condition the host's immune system in order to render provision to the adoptively transferred cells an advantage over other competing immune cell populations. Lymphodepleting chemotherapy creates a favorable immune environment for ACT, improving infused therapeutic cells in vivo expansion, subsequent persistence, and clinical activity [48].

Lymphodepletion and ACT have not yet been tested in randomized studies. However, the results of recent clinical trials in CD19-expressing hematologic malignancies using these methods have rendered exceptional response rates in patients who have failed standard treatments. Animal studies postulate that lymphodepletion may enhance the effectiveness of adoptively transferred T cells [49]. This hypothesis has been clinically tested and confirmed in the setting of CD19/CD20-expressing B-cell malignancies in several series of heavily pretreated patients with refractory diffuse large cell non-Hodgkin lymphoma, transformed indolent non-Hodgkin lymphoma, acute and chronic lymphocytic leukemia, who received fludarabine-cyclophosphamide-based lymphodepleting chemotherapy conditioning prior to infusions of autologous CAR-T [1, 50-53].

Multiple mechanisms have been postulated to explain the remarkable tumor response rates in these patients. The size of the lymphoid compartment is tightly controlled via homeostatic mechanisms, including innate and adaptive regulatory cells as well as competition for cytokines such as IL-2, IL-7, IL-15, and IL-21 [54-56]. Lymphopenia-induced homeostatic proliferation of ACT is thought to be driven by these cytokines as well as exposure to cells expressing the specific antigen the CAR engages and exposure to self-peptides and other antigens. Further, tissue injury and a generalized inflammatory reaction may likely be a contributing factor which drives ACT activation and expansion in the setting of 'danger' signals [57, 58].

In this phase 1 study, patients may receive fludarabine (30 mg/m²/day) and cyclophosphamide (500 mg/m²/day) as the conditioning chemotherapy regimen before infusion of TAK-103. The potency of addition of fludarabine to cyclophosphamide alone has been suggested in some small non-randomized ACT studies [59, 60]. The regimen for conditioning chemotherapy in this study which consists of fludarabine and cyclophosphamide for consecutive 3 days at 5, 4, 3 days prior to TAK-103 infusion, is determined based on approved conditioning regimens for Kymriah, Yescarta, and Tecartus (Table 4.b) and recent reports from CAR-T studies [3, 4, 61, 62].

Table 4.b Approved Conditioning Regimens for Kymriah, Yescarta, and Tecartus

Product	Indication	Cyclophosphamide	Fludarabine
Kymriah	Relapsed/refractory B-cell precursor acute lymphoblastic leukemia	500 mg/m ² (2 days)	30 mg/m ² (4 days)
	Relapsed/refractory large B-cell lymphoma	250 mg/m ² (3 days)	25 mg/m ² (3 days)
Yescarta	Relapsed/refractory large B-cell lymphoma	500 mg/m ² (3 days)	30 mg/m ² (3 days)
Tecartus	Relapsed/refractory mantle cell lymphoma	500 mg/m ² (3 days)	30 mg/m ² (3 days)

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

- To evaluate the safety and tolerability of TAK-103.
- To determine RP2D of TAK-103.

5.1.2 Secondary Objectives

- To evaluate the antitumor activity of TAK-103.
- To characterize the cellular kinetics of TAK-103.
- To determine the number and percent of cases with replication competent retrovirus (RCR)-positive test results.

5.1.3 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

5.2 Endpoints

5.2.1 Primary Endpoints

- Incidence of dose limiting toxicities (DLTs).
- Incidence of treatment-emergent adverse events (TEAEs).
- Incidence of AEs of clinical interest including severe ICANS, CRS, HLH, MAS, and TLS.

5.2.2 Secondary Endpoints

- Overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), and progression-free survival (PFS) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (RECIST 1.1) [63] (see Appendix D) and immune RECIST (iRECIST) [64].

- ### 5.2.3 Exploratory Endpoints

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.0 STUDY DESIGN

6.1 Overview of Study Design

Study TAK-103-1001 is an open-label, non-randomized, phase 1, FIH study to evaluate the safety and tolerability of TAK-103 administered IV in patients with mesothelin-expressing advanced or metastatic solid tumors with no standard therapeutic alternative with established clinical benefit. Ovarian cancer and mesothelioma are the high priority target population for TAK-103, given the prevalence of high mesothelin expression and prior clinical evidence of mesothelin-targeting autologous CAR-T. NSCLC and gastric cancer patients are also hypothesized to benefit from TAK-103 due to reported mesothelin expression and clinical activity with immune checkpoint inhibitors (immune-sensitive).

The patient population will consist of adults with a diagnosis of solid tumors with confirmed mesothelin-expression determined on the tumor by IHC and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E). Patients must also have radiographically measurable disease as defined by RECIST 1.1 (see Appendix D). Eligibility must be confirmed, reviewed/reconfirmed before leukapheresis procedures and conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered), respectively.

Up to 21 DLT evaluable patients will be treated with TAK-103. Patients will be enrolled in the study and treated with TAK-103 starting with Cohort (-2) and sequentially to the next dosing cohort up to Cohort 3 in accordance with dose escalation schema. Dose levels between planned cohorts may also be tested following discussion between the sponsor and the investigators.

- Cohort (-2): 1×10^6 CAR (+) cells/body [starting dose at resumption].
- Cohort (-1): 3×10^6 CAR (+) cells/body.
- Cohort 1: 1×10^7 CAR (+) cells/body [starting dose].
- Cohort 2: 1×10^8 CAR (+) cells/body.
- Cohort 3: 5×10^8 CAR (+) cells/body.

Each patient will receive a single IV infusion of TAK-103 in this study.

Conditioning chemotherapy is started before TAK-103 infusion so that TAK-103 cells will be administered approximately 3 days after completion of the conditioning chemotherapy. TAK-103 infusion after conditioning chemotherapy may be delayed for up to 14 days based on medical judgement by the investigators. The regimen for conditioning chemotherapy consists of fludarabine (30 mg/m^2 IV daily for 3 doses on Days -5, -4 and -3) and cyclophosphamide (500 mg/m^2 IV daily for 3 doses starting with the first dose of fludarabine) (Section 8.4).

Cohorts where conditioning chemotherapy is not administered may be tested. For instance, the use of conditioning chemotherapy is concerning potential association with the development of AEs. If de-escalation of TAK-103 is necessary due to DLTs, TAK-103 infusion without conditioning

chemotherapy may be examined to confirm safety of TAK-103. As another potential scenario, TAK-103 is armored CAR-T, where there is a possibility of remarkable efficacy without conditioning chemotherapy. TAK-103 infusion without conditioning chemotherapy may be investigated once significant efficacy of TAK-103 infusion with conditioning chemotherapy is confirmed.

TAK-103 will be shipped to the clinical site in a proper container which can maintain and control cryopreserved condition (Section 8.11). TAK-103 is to be administered on Day 1 at approximately 5 mL/min within 60 minutes after being thawed (Section 8.4). The investigator should complete the administration as soon as possible to maintain the quality of the study product.

During the Pretreatment phase, bridging therapy may be performed with any approved regimen for the subject's malignancy. Immuno-oncology (I/O) medications (e.g., pembrolizumab or nivolumab) are not allowed as bridging therapy (Section 8.3). Patients cannot use medications including systemic steroids and anti-cancer treatments that can impact the product function or confound interpretation of immunologic correlates during the Treatment and Primary Follow-up phase and Secondary Follow-up phase unless there is medical need.

Dose escalation will be guided by the Bayesian Optimal Interval (BOIN) design. The BOIN design is based on the observed toxicity probabilities for each dose level. Dose escalation/de-escalation decisions will be determined within the recommended dose by BOIN, taking into account safety, efficacy, and CK (see Table 8.a for details), and be made jointly by the sponsor and the investigator at meetings, including the cohort management meetings. Additional emerging translational data (e.g., soluble mesothelin, CA125) may also be used, when feasible, to aid decision-making of dosing additional patients at a given dose level. RP2D will be determined based on aggregated observations of safety, efficacy, CK, and biomarker assessments at each dose level.

In any Cohorts, infusion of TAK-103 of every patient will be separated by 28 (or more) days. Dose cohorts will be separated by a minimum of 28 days (from the last TAK-103 infusion in the precedent cohort to the first TAK-103 infusion in the subsequent cohort).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 [65]. CRS and ICANS will be evaluated according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus [66]. The management of CRS and ICANS will follow the management procedures of the sites with CRS/ICNS management manual for this clinical trial provided by the sponsor. For management of HLH and MAS, CARTOX (CAR-T-cell-therapy-associated TOXicity) recommendations will be used [67] in principal. DLT will be defined as Grade 3 or higher toxicities that are considered by the investigator to be at least possibly related to therapy with TAK-103 during the 28 days immediately following TAK-103 infusion. Events which the investigator identifies as clinically significant may be considered as an additional DLT upon discussion with the sponsor.

The study consists of the Prescreening, Screening, Pretreatment, Treatment and Primary Follow-up, and Secondary Follow-up phases (Figure 6.a).

- The Prescreening phase may begin on the date the patient signs the institutional review board/independent ethics committee (IRB/IEC)-approved informed consent form (ICF) (Prescreening ICF) for the assessment of mesothelin expression in tumor cells. The patient is provided with a study-specific patient number on the date of Prescreening ICF.
- The Screening phase starts with the date when one of procedures in the Screening phase take place. If the patient's mesothelin expression status is already analyzed with the patient's archived tumor tissue sample using Takeda validated assay and the patient participates in the study from the Screening phase, a study-specific patient number is provided on the date of Main ICF. The Screening phase includes confirmation of eligibility and enrollment into the study, and ends with the start of leukapheresis procedures.
- The Pretreatment phase is defined as the period from the start of leukapheresis procedures through the completion of conditioning chemotherapy until the start of TAK-103 infusion. During the Pretreatment phase, leukapheresis, bridging therapy, and conditioning chemotherapy will be performed.
- The Treatment and Primary Follow-up phase begins with TAK-103 administration and continues up to Month 13.
- Secondary Follow-up phase begins with the end of the Treatment and Primary Follow-up period and continues up to Month 37.

In the Pretreatment phase, the Treatment and Primary Follow-up and Secondary Follow-up phases, patients may complete study participation due to death, consent withdrawal, or other predefined situations.

Patients must be followed according to the visit schedule to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. Patients may voluntarily withdraw from the Treatment and Primary Follow-up phase or be dropped from it at the discretion of the investigator at any time. It is anticipated that patients may leave the Primary Follow-up and move to Secondary Follow-up due to reasons including:

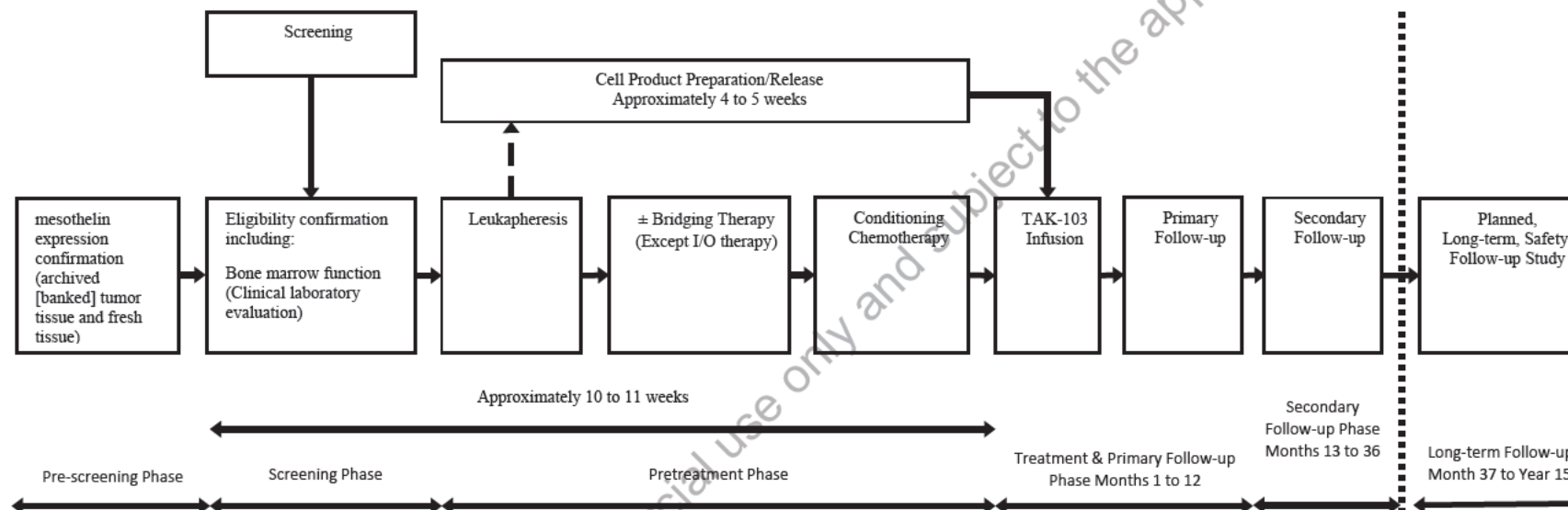
- Disease progression
- Patient voluntary withdrawal from the Primary Follow-up

Patients who discontinue the Treatment and Primary Follow-up phase before Month 13 will continue to be followed in the Secondary Follow-up phase in order to collect safety data requested from health authority (e.g., protocol defined AEs) up to 3 years after TAK-103 infusion.

The first visit in the Secondary Follow-up phase is determined according to the time when the patient discontinued in the Treatment and Primary Follow-up phase. For example, if the patient discontinues from the Treatment and Primary Follow-up phase at Month 7, the first visit in the Secondary Follow-up phase will be Month 10. Secondary Follow-up phase is set to evaluate long-term toxicity which is required by health authority. It is not considered to be a protocol deviation if patients refuse non-safety assessment (e.g., disease assessment, sampling for biomarker, CK, or pharmacodynamic assessment) during Secondary Follow-up phase.

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Figure 6.a Study Schematic for TAK-103-1001 Protocol



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6.2 Number of Patients

Up to 21 DLT evaluable patients.

6.3 Duration of Study

This study consists of the Prescreening, Screening, Pretreatment, Treatment and Primary Follow-up, and Secondary Follow-up phases.

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive a single infusion of TAK-103 and be followed for up to 15 years. The follow-up phase consists of the single infusion and 12-month Primary Follow-up, the 2-year Secondary Follow-up, and 12-year long-term follow-up phases. The long-term follow-up phase will be conducted via enrollment in a planned long-term study per a separate protocol.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion

The primary analyses for a clinical study report (CSR) will be conducted after all patients have completed the Treatment and Primary Follow-up phase or transferred to the Second Follow-up phase or the study.

Other Planned Analyses

The final analyses for a CSR will be conducted after all patients have completed the study (Section 9.6) or transferred to a separate, long-term, safety, follow-up study.

Study Completion

The estimated time frame for study completion is maximum of 5 years. The study will end at the time when all patients have completed the study or transferred to a separate, long-term, safety, follow-up study.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints in this study.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint *	Definition	Maximum Time Frame
Primary Endpoints:		
Incidence of DLTs	Refer to Section 8.5	Up to 28 days
Incidence of TEAEs	AEs that occur after administration of TAK-103	Up to 1 year ^a
Incidence of AEs of clinical interest	<ul style="list-style-type: none"> ICANS CRS HLH MAS TLS 	Up to 1 year ^a
Secondary Endpoints:		
Objective response	Objective tumor response based on the investigator's assessment using RECIST 1.1 and iRECIST (Refer to Section 13.1.3)	Up to 3 years
Tumor response parameters	Based on RECIST 1.1 and iRECIST (Refer to Section 13.1.3)	Up to 3 years
<ul style="list-style-type: none"> DOR DCR TTP PFS 		
OS	Refer to Section 13.1.3	Up to 3 years
CK-related parameters	Parameters evaluated by ddPCR based assay measuring CAR vector copy number in peripheral blood (C_{max} , t_{max} , C_{last} , t_{last} , AUC).	Up to 3 years
Number and percentage of cases with RCR-positive test results	RCR test results	Up to 3 years

AE: adverse event; AUC: area under the blood concentration-time curve; CAR: chimeric antigen receptor; CK: cellular kinetics; C_{last} : last observed quantifiable concentration in peripheral blood; C_{max} : maximum (peak) observed concentration in peripheral blood after single dose administration; CRS: cytokine release syndrome; DCR: disease control rate; DLT: dose-limiting toxicity; DOR: duration of response; HLH: hemophagocytic lymphohistiocytosis; ICANS: immune effector cell-associated neurotoxicity syndrome; iRECIST: immune Response Evaluation Criteria in Solid Tumors; MAS: macrophage activation syndrome; OS: overall survival; PFS: progression-free survival; RCR: replication competent retrovirus; RECIST 1.1: Response Evaluation Criteria in Solid Tumors Version 1.1; TEAE: treatment-emergent adverse event; t_{last} : persistence (time of last observed quantifiable concentration in peripheral blood [days]); TLS: tumor lysis syndrome; t_{max} : time of first occurrence of maximum observed in peripheral blood concentration; TTP: time to progression

* Some of the endpoints above will be followed during planned long-term follow-up study.

^a All SAEs (after the patient starts anti-cancer treatments following observation of PD, only SAEs related to study treatment and/or procedures must be reported) and the following AEs will be analyzed up to 3 years:

1) new malignancies, 2) new incidence or exacerbation of a preexisting neurologic disorder, 3) new incidence or exacerbation of a preexisting rheumatologic or other autoimmune disorder, 4) new incidence of a hematologic disorder, 5) AEs that are considered by the investigator to be at least possibly related to therapy with TAK-103, 6) Positive RCR test (always considered and reported to be an SAE).

6.3.4 Total Study Duration

The estimated time frame for study completion of the study is a maximum of 4 to 5 years consisting of approximately 1 to 2 years of enrollment, 1 year of primary follow up, and 2 years of secondary follow up. This study will be followed by a long-term 12 years of follow-up study by a separate protocol.

6.3.5 Posttrial Access

Posttrial access to TAK-103 is not planned for this study.

7.0 STUDY POPULATION

Each patient must meet all the inclusion criteria to be enrolled in the study and treated with study product. Patients meeting any of the exclusion criteria are not to be enrolled in the study or treated with study product.

Eligibility must be confirmed within 14 days before the day of the leukapheresis procedures (except for IHC test for mesothelin expression, virus test, and flow cytometry [FCM]) in the Screening phase and reviewed/reconfirmed within 3 days before the day of conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered) by the investigator, respectively.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study.

1. Male or female patients aged ≥ 18 years or meeting country definition of adult, whichever is older, at the time of signing informed consent.
2. Histologically or cytologically confirmed advanced or metastatic solid tumors who have no option with or are intolerant of standard therapies with a proven clinical benefit.
3. Mesothelin-expression ($\geq 50\%$ positive on viable tumor cells) must be determined on the tumor locally by immunohistochemistry using a validated assay, scoring and staining confirmed by the sponsor prior to leukapheresis procedures.
4. Life expectancy ≥ 12 weeks.
5. Eastern Cooperative Oncology Group performance status of 0 or 1.
6. Adequate organ function as confirmed by clinical laboratory values as specified below:
 - a) Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll with direct bilirubin $\leq 3 \times$ ULN of the direct bilirubin. Elevated indirect bilirubin due to posttransfusion hemolysis is allowed
 - b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be $< 3 \times$ ULN. AST and ALT may be elevated up to $5 \times$ ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in the liver.
 - c) Calculated creatinine clearance > 50 mL/min (Cockcroft-Gault formula).
 - d) Hemoglobin must be ≥ 9 g/dL.
 - e) Neutrophil count must be $> 1000/\text{mm}^3$.
 - f) Absolute lymphocyte count must be $> 500/\text{mm}^3$.
 - g) Platelet count must be $> 75,000/\text{mm}^3$.

7. Patients must have radiographically measurable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).
8. Female patients who:
 - a) Are postmenopausal (natural amenorrhea) for at least 1 year before the screening visit, OR
 - b) Are surgically sterile, OR
 - c) If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
 - d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
9. Male patients, even if surgically sterilized (i.e., postvasectomy), who:
 - a) Agree to practice effective barrier contraception from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
 - b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception
10. Voluntary written consent must be given before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
11. Willingness and ability to comply with scheduled visits and study procedures.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Active systemic infections.
2. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection. Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

3. Coagulation disorders, or other major medical illnesses including respiratory or immune system disease.
4. Patients with high tumor burden at the disease assessment at screening. The tumor burden is determined by the threshold set for each type of cancer (Refer to Appendix F).
5. Patients with current or history of interstitial lung disease.
6. Patients with current or history of significant immune-related AEs (irAEs) related to treatment with immune checkpoint inhibitors. Patients with current or history of the following AEs can be enrolled after careful discussion between the investigator and sponsor: hyperglycemia/diabetes mellitus, thyroid disorder, hypopituitarism, hypoadrenocorticism, asymptomatic elevation in amylase/lipase, and Grade 1 or 2 skin toxicity.
7. Patients with known cardiovascular and cardiopulmonary disease defined as unstable angina, clinically significant arrhythmia, myocardial infarction, congestive heart failure, left ventricular ejection fraction (LVEF) <45 %, impaired respiratory function, baseline oxygen saturation <93% on room air. A well-controlled atrial fibrillation would not be an exclusion whereas uncontrolled atrial fibrillation would be an exclusion.
8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
9. Patients with any signs of lymphoma and/or leukemia.
10. Patients who are diagnosed with or treated for another malignancy within 3 years before leukapheresis procedures. Patients with non-melanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) would be included if they were adequately treated.
11. Any disease requiring systemic steroid treatment.
12. Any prior use of cell and gene therapy(ies).
13. Treatment with any investigational products (except for cell or gene therapy) within 14 days before leukapheresis procedures or 28 days before treatment with conditioning chemotherapy/TAK-103.
14. Systemic anticancer therapy (including immuno-oncology therapies) and treatment with radiotherapy within 14 days before leukapheresis procedures or treatment with conditioning chemotherapy/TAK-103.
15. Treatment with major surgery within 28 days before leukapheresis procedures or treatment with conditioning chemotherapy/TAK-103 (minor surgical procedures such as catheter placement are not exclusionary criteria).
16. Previous treatment with any mesothelin-targeted therapy.
17. Any unresolved toxicity of Grade 3 or higher from previous anticancer therapy.
18. Patients with risk of bleeding as judged by the investigator.

19. Presence of central nervous system metastasis or other significant neurological conditions (patient with central nervous system metastases that have been effectively treated where necessary and stable can be enrolled).
20. Patients with human immunodeficiency virus (HIV) seropositive and/or human T-cell lymphotropic virus (HTLV) seropositive.
21. Patients with a history of organ transplantation or awaiting organ transplantation.
22. Patients with severe immediate hypersensitivity to any of the agents including cyclophosphamide, fludarabine, or streptomycin.
23. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
24. Live vaccine ≤ 6 weeks prior to start of conditioning regimen.
25. Female patients who are breastfeeding or have a positive serum pregnancy test (urine pregnancy test is allowed before treatment with conditioning chemotherapy and TAK-103).
Note: Female patients who are lactating will be eligible if they discontinue breastfeeding before preconditioning therapy and the treatment with TAK-103. For those who undergo bridging therapy, lactation should be terminated in compliance with the package insert of the drug.

8.0 STUDY DRUG

8.1 Leukapheresis

Leukapheresis is performed for an individual patient upon confirmation of eligibility in order to obtain CD3+ lymphocytes to manufacture TAK-103. If a patient undergoes bridging therapy(ies), leukapheresis must be performed prior to any bridging therapy (Section 8.3).

Leukapheresis procedures will follow clinical site standard operating procedures. Heparin is not allowed to be used as anti-coagulant during leukapheresis. Apheresate will be shipped to the manufacturing site under temperature control. Shipping materials will be provided by the sponsor. Study-specific requirements for leukapheresis procedures and details of apheresate handling are provided in the study manual.

8.2 TAK-103 Manufacturing

TAK-103 is a mesothelin-targeting CAR-T construct for expression of anti-mesothelin-CAR, IL-7 and CCL19 in patients' autologous T cells, being developed for autologous immunotherapy in patients with MSLN-expressing cancers. Autologous T cells from such patients are activated ex vivo, gene transduced with a retroviral vector for integrating the transgene, CAR-T cells are then expanded in cell culture, and formulated into infusible cryomedia. T cells that are enriched from a patient leukapheresis unit are expanded ex vivo using commercially available beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the retroviral vector. The residual non-integrated vector is washed away during the manufacturing process. TAK-103 cells expand ex vivo for several days. At the end of the culture, the TAK-103 cells are washed, concentrated, and cryopreserved.

TAK-103 cell product will be released toward the study site approximately 4 to 5 weeks after patient's leukapheresis, provided all required safety and quality release criteria have been met.

8.3 Bridging Therapy

The use of any additional chemotherapy as bridging therapy may be allowed if a patient experiences or is expected to have rapid disease progression following leukapheresis and before treatment with study product based on the investigator's assessment. I/O medications (e.g., pembrolizumab or nivolumab) are not allowed as bridging therapy.

8.4 Study Drug Administration

Prior to conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered), all inclusion/exclusion criteria must be reviewed and reconfirmed. If an enrolled patient becomes ineligible by not fulfilling any inclusion or exclusion criteria at the time of conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered), the investigator should consult with the Takeda trial clinician before proceeding to further study procedures.

TAK-103 infusion after conditioning chemotherapy may be delayed for up to 14 days based on medical judgement by the investigator. If the TAK-103 infusion is delayed more than 14 days, conditioning chemotherapy must be repeated. In all cases of TAK-103 infusion delays, or cases that conditioning chemotherapy regimen cannot be completed, the Takeda trial clinician must be contacted for guidance.

The regimen for conditioning chemotherapy consists of fludarabine (30 mg/m² IV daily for 3 doses on Days -5, -4, and -3) and cyclophosphamide (500 mg/m² IV daily for 3 doses starting with the first dose of fludarabine). Conditioning regimen may be modified upon discussion and agreement between the investigator and the sponsor according to emerging data. In this study, cohort where conditioning chemotherapy is not administered may be tested. For instance, the use of conditioning chemotherapy is concerning potential association with the development of AEs. If de-escalation of TAK-103 is necessary due to DLTs, TAK-103 infusion without conditioning chemotherapy may be examined to confirm safety of TAK-103. As another potential scenario, TAK-103 is armored CAR-T, where there is a possibility of remarkable efficacy without conditioning chemotherapy. TAK-103 infusion without conditioning chemotherapy may be investigated once significant efficacy of TAK-103 infusion with conditioning chemotherapy is confirmed.

Each patient will receive a single IV infusion of TAK-103 in any one of the following cohorts with ascending TAK-103 dose levels:

- Cohort (-2): 1×10^6 CAR (+) cells/body [starting dose at resumption].
- Cohort (-1): 3×10^6 CAR (+) cells/body
- Cohort 1: 1×10^7 CAR (+) cells/body [starting dose].
- Cohort 2: 1×10^8 CAR (+) cells/body.
- Cohort 3: 5×10^8 CAR (+) cells/body.

TAK-103 is to be administered at approximately 5 mL/min and completed within 60 minutes after being thawed at the clinical site. The investigator should complete the administration as soon as possible to maintain the quality of the study product.

Patients may be pre-medicated with antipyretics (e.g., acetaminophen) and antihistamine (e.g., diphenhydramine) to prevent hypersensitivity reaction/infusion-related reaction at the discretion of the investigator. Corticosteroids are not recommended as prophylaxis.

Treatment such as antihistamine or any other supportive therapy may be required in the event of hypersensitivity and/or infusion-related reaction. Patients should be evaluated and monitored carefully until the complete resolution of signs and symptoms.

If target dose of number of CAR (+) cells cannot be manufactured within release specification allowance, a lower dose level of TAK-103 product manufactured within the release criteria will be delivered to the patient for infusion. The patient may receive administration of TAK-103 at the

lower dose level under patient's consent and with the investigator's judgement. Such patient will be allocated in the analysis set of the cohort dose level of TAK-103 product which was actually administered and followed according to this study protocol. For instance, if a patient was enrolled in Cohort 3 (5×10^8 CAR (+) cells/body) and only 2 packages of 1×10^8 CAR (+) cells are available for the patient despite the plan that 3 packages of 5×10^8 CAR (+) cells are also manufactured for the patient, the patient may receive TAK-103 infusion of 1×10^8 CAR (+) cells under patient's consent and with the investigator's judgement; this patient will be allocated in the analysis set of Cohort 2.

8.5 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, version 5.0, effective 27 November 2017 [65] while CRS and ICANS will be evaluated according to ASTCT consensus [66].

Events which the investigator identifies clinically significant may be considered as additional DLT upon discussion with the sponsor.

DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with TAK-103 during the 28 days immediately after infusion of TAK-103:

- Any AEs requiring endotracheal intubation or tracheostomy.
- Any Grade 3 toxicities (lasting more than 3 days) other than AEs requiring intubation.
- Any Grade 4 toxicities.
- Any death.

The following events will not be considered DLT:

- Any Grade 3 neutropenia, and Grade 4 neutropenia lasting less than 21 days, when conditioning chemotherapy is administered.
- Any Grade 3 anemia, and Grade 4 anemia lasting less than 14 days, when conditioning chemotherapy is administered. Anemia requiring red blood cell transfusion is defined as DLT.
- Any Grade 3 thrombocytopenia, and Grade 4 thrombocytopenia lasting less than 35 days, when conditioning chemotherapy is administered. Thrombocytopenia requiring platelet transfusion is defined as DLT.
- Any other cytopenia excluding neutropenia, anemia, thrombocytopenia and febrile neutropenia (Grade 3 febrile neutropenia lasting more than 3 days and Grade 4 febrile neutropenia are defined as DLT).
- Aphasia/dysphasia or confusion/cognitive disturbance resolving to Grade ≤ 1 within 14 days and baseline within 28 days.
- Any Grade 3 fever, and Grade 4 fever lasting less than 4 days.

- Grade 3 immediate hypersensitivity reaction within 2 hours of infusion of TAK-103 reversible to Grade ≤ 2 within 24 hours.
- Asymptomatic non-hematological abnormal laboratory values recovering to baseline or Grade ≤ 1 within < 7 days.

Analyses on DLTs will be based on patients who have received any predetermined dose of TAK-103 and completed the assessment for DLT evaluation or experienced a DLT during the first 28 days following TAK-103 infusion. Patients who are withdrawn from the study or completed the study before reaching the end of the 28-day period may be replaced following discussion between the sponsor and the investigator. For definitions of study completion of individual subjects, refer to Section 9.6.

8.6 Dose Escalation Rules

Dose escalation/de-escalation will be guided by the BOIN design, which is based on the observed DLT rate at each dose level. Dose escalation/de-escalation decisions will be determined within the recommended dose by BOIN, taking into account safety other than DLTs, efficacy and CK (Table 8.a), and be made jointly by the sponsor and the investigator at meetings, including the cohort management meetings. Additional emerging translational data (e.g., soluble mesothelin, CA125) may also be used, when feasible, to aid decision-making of dosing additional patients at a given dose level. Basically, each patient will be treated with TAK-103 at any dose of Cohorts (-2) to 3 as listed below. For the purpose of overdose control, doses j and higher levels will be eliminated from the further examination if $\Pr(p_j > 0.3 | \text{data}) \geq 0.90$ and at least 3 evaluable patients have been treated at the dose level j , where p_j is the true DLT rate of the dose level j .

RP2D will be determined based on aggregated observations of safety, efficacy, CK, and biomarker assessments.

Below is the list of dose-levels to be evaluated at each cohort:

- Cohort (-2): 1×10^6 CAR (+) cells/body [starting dose at resumption].
- Cohort (-1): 3×10^6 CAR (+) cells/body.
- Cohort 1: 1×10^7 CAR (+) cells/body [starting dose].
- Cohort 2: 1×10^8 CAR (+) cells/body.
- Cohort 3: 5×10^8 CAR (+) cells/body.

The target DLT rate for this study is 0.3. The study was initiated with Cohort 1; however, it was suspended due to an occurrence of a DLT (grade 5 pneumonitis). At study resumption, Cohort (-2) will be used as a starting dose and the dose escalation and de-escalation rules for TAK-103 are described as follows (Table 8.b). The operating characteristics of the BOIN design were evaluated with simulations assuming various distributions of toxicity across dose levels (Appendix G).

1. Treat the patients at Cohort (-2) at study resumption.
2. To assign a dose to the next patient or cohort of patients,
 - a) If the observed DLT rate at the current dose level is ≤ 0.236 , escalate the dose.
 - The current dose level may also be expanded with additional patients in parallel with the dose escalation to better characterize the clinical activity profile if the set thresholds for clinical activity or cellular kinetics (as listed in Table 8.a) are met. The decision should be made jointly by the sponsor and the investigator at meetings. In this scenario, if additional DLT are identified during expansion, the dose escalation decision will be re-examined using the cumulative DLT rate at this dose level.
 - b) If the observed DLT rate at the current dose level is ≥ 0.359 , de-escalate the dose.
 - c) Otherwise, retain the current dose.
3. Repeat Step 2 until 1) the total is reached at 21, or 2) Cohort (-2) (1×10^6 CAR (+) cells/body) is eliminated. In the latter case, no dose should be selected as the maximum tolerated dose (MTD).

If the current dose level is also expanded with additional patients in parallel with the dose escalation, because the set thresholds for clinical activity or cellular kinetics (as listed in Table 8.a) are met, whenever DLTs are identified, the dose escalation decision will be re-examined using the cumulative DLT rate. For example, if patients are treated concurrently in the current dose cohort and the dose escalation cohort and 2 patients out of 6 patients in the current dose cohort experience DLTs, the dose escalation cohort should stop the enrollment immediately, and the current dose cohort should be further evaluated by enrolling additional patients. In addition, the total number of patients and the dose escalation/de-escalation decision will include the data of the first patient.

In any Cohorts, infusion of TAK-103 of every patient will be separated by 28 (or more) days. Dose cohorts will be separated by a minimum of 28 days (from the last TAK-103 infusion in the precedent cohort to the first TAK-103 infusion in the subsequent cohort).

Table 8.a Decision-Making Criteria for Dosing Additional Patients in a Given Cohort

Biological Parameter (Either Clinical response criteria OR Cellular kinetics)		Assessment	Sample	Proposed Criteria
Clinical response	Response	iRECIST	CT or MRI	≥1 iPR or iCR
Cellular kinetics*	Target engagement & Expansion of CAR-T cells	ddPCR	Blood	mean C _{max} >100-fold above baseline (DL(-2), DL(-1), DL1), >1000-fold (DL2 – DL3)
	Persistence of CAR-T cells	ddPCR	Blood	mean t _{last} ≥30 days

CAR-T: chimeric antigen receptor T cell; CT: computed tomography; ddPCR: droplet digital polymerase chain reaction; DL: dose level; iCR: immune complete response; iRECIST: immune Response Evaluation Criteria in Solid Tumors; iPR: immune partial response; MRI: magnetic resonance imaging

* Both expansion and persistence threshold should be met for the cellular kinetics criteria.

Table 8.b Dose Escalation/De-Escalation Rule for the BOIN Design

	Number of Evaluable Patients Treated at the Current Dose Level									
	1	2	3	4	5	6	7	8	9	10
Number of patients treated	1	2	3	4	5	6	7	8	9	10
Escalate if number of DLT ≤	0	0	0	0	1	1	1	1	2	2
De-escalate if number of DLT ≥	1	1	2	2	2	3	3	3	4	4
Eliminate* if number of DLT ≥	NA	NA	2	3	4	4	4	4	5	5

	Number of Evaluable Patients Treated at the Current Dose level							
	11	12	13	14	15	16	17	18
Number of patients treated	11	12	13	14	15	16	17	18
Escalate if number of DLT ≤	2	2	3	3	3	3	4	4
De-escalate if number of DLT ≥	4	5	5	6	6	6	7	7
Eliminate* if number of DLT ≥	6	6	6	7	7	8	8	8

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; NA: not applicable

* “Eliminate” means that the current and higher doses will be eliminated from the study to prevent treating any future patients at these doses due to toxicity.

8.7 Excluded Concomitant Medications and Procedures

During the Pretreatment phase, bridging therapy may be performed with any approved regimen for the subject's malignancy.

See Section 8.3 for details of the bridging therapy.

Patients cannot use the following medications that can impact the product function or confound interpretation of immunologic correlates during the Treatment and Primary Follow-up phase or the Secondary Follow-up phase unless there is medical need:

- Systemic steroids and any other immunosuppressive drugs
- Anti-cancer treatments, including investigational drugs/products

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- Checkpoint inhibitors
- Colony stimulating factors
- Live vaccines

Systemic steroids and any other immunosuppressive drugs are not allowed after initiation of conditioning chemotherapy, in addition to the Treatment and Primary Follow-up phase and the Secondary Follow-up phase.

COVID-19 vaccination is generally allowed for patients enrolled in the study with the exception of live vaccines. COVID-19 vaccination should follow local guidance and regulations. However, COVID-19 vaccination is not permitted from 28 days before the conditioning chemotherapy/TAK-103 infusion to completion of DLT evaluation period as this may confound the evaluation of safety and the determination of DLTs. Vaccination should be captured in the eCRF as a concomitant medication.

Use of the above treatments including anti-cancer treatments and checkpoint inhibitors are allowed after confirmation of single progressive disease (PD) according to RECIST 1.1 in not clinically stable patient, or confirmation of immune confirmed progressive disease (iCPD) according to iRECIST (Section 9.4.18). Prior to subsequent anti-cancer treatment, all study procedures outlined for the end of primary follow up (EOPF) visit will be completed as specified in the Schedule of Events (SOE) (Appendix A).

8.8 Precautions and Restrictions

Considering potential CAR-T-related toxicities (Section 4.1.5), appropriate safety measures should be taken when treating patients with TAK-103. Assessment and grading of CRS and ICANS will be performed as described in the SOE (Appendix A) following the definition provided in ASTCT consensus [66]. The management of CRS and ICANS will follow the management procedures of the sites with CRS/ICANS management manual for this clinical trial provided by the sponsor. Management of HLH and MAS should follow the CARTOX [67] in principal.

- The investigator will closely collaborate with intensive care unit by sharing dosing schedule as well as ensuring availability of beds and treating physicians prior to TAK-103 infusion.
- The investigator will ensure sufficient support by hematologists to monitor and treat CAR-T-related hematological AEs.
- The investigator is instructed to be well prepared for potential immediate reactions such as CRS and to ensure easy and immediate access to necessary medications such as anti-IL-6 receptor antibody (tocilizumab) and steroids.
- Monitoring of patients for any hypersensitivity or other acute infusion-related reaction such as fever, chills and/or nausea is conducted during and after administration of TAK-103. If the reaction is observed, anti-histamine drug, acetaminophen or supportive therapy may be given to patients and close monitoring of patients until complete resolution of signs and symptoms is conducted.

In view of the occurrence of pneumonitis following TAK-103 infusion, the following safety measures should be taken in addition to the above CAR-T related actions:

- The investigator must carefully monitor for dyspnea, cough, pyrexia, abnormal breathing sounds, percutaneous oxygen saturation (SpO₂), etc., perform imaging tests, serum marker tests, etc. as necessary, and if applicable, evaluate whether pneumonitis or interstitial lung disease has occurred.
- The investigator must monitor for clinical manifestations associated with concurrent pneumonia, systemic infection, and pulmonary edema according to standard procedures at the study site and take necessary treatment and possibly prophylactic measures.
- Prophylactic treatment for specific infections can be performed at the investigator's discretion, taking into consideration the patient condition and expected duration of immunosuppression after administration of lymphodepleting chemotherapy, referring to the institutional guidelines of CAR-T/stem cell transplant.
- The investigator can perform a rapid cytokine measurement in case of suspected symptoms or findings such as pneumonitis, CAR-T cell therapy-related AEs or irAEs. The timing of the measurements is described in the SOE (Appendix A). In addition, the results of measurement of CAR positive cell count will be obtained in a timely manner.
- In the event of an AE requiring careful attention [REDACTED], the sponsor will hold a meeting involving the investigators and specialists in hematology and relevant departments, etc.; [REDACTED]

[REDACTED] These treatment measures may include steroid pulse therapy or cyclophosphamide, extracorporeal cytokine adsorption, anti-thymocyte globulin (ATG), intravenous immunoglobulin (IVIG)[68], for treatment-resistant immune-related lung injury, steroid pulse therapy or other immunosuppressive medications (infliximab, cyclophosphamide, IVIG, mycophenolate mofetil, etc.[69]). The efficacy of these drugs has not been established. Details on holding the meeting will be described in the Cohort Management Plan.

It is not known what effects TAK-103 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner for 1 year after the dose of TAK-103. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below. Use of all contraceptive methods should be locally approved.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR

- If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception).

Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception from the time of signing the informed consent through at least 12 months following TAK-103 infusion, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception).

Before starting treatment, male patients may be advised to seek counseling on sperm storage, and female patients may be advised to seek counseling on egg storage.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Preparation, Reconstitution, and Dispensation of TAK-103

The final product of TAK-103 will be shipped to the clinical site as 1 or 2 bags of cryopreserved cells at appropriate concentration for administration without further manipulation, except for the final product for Cohorts 1, (-1) and (-2) that needs withdrawal of cell suspension from the bag before administration. Trained medical staff will thaw the product using appropriate equipment, connect the product to an injection or infusion set, and administer the product to the patients through IV injection/infusion.

TAK-103 will be shipped to the clinical site in a container which can maintain and control cryopreserved condition. Before administration, TAK-103 will be removed from the temperature-controlled container and thawed with appropriate equipment for approximately 5 minutes.

Upon removal from the container, cryopreserved IV bags should be visually inspected for any cracks or damages. Once thawed, the IV solution should be inspected visually before administration.

Details for preparation, reconstitution and dispensation of TAK-103 are described in the study manual.

8.11 Packaging and Labeling of TAK-103

The package of the product should include the patient-specific product label which includes sufficient patient identifying information to ensure chain of identity, and dose information (number of CAR-positive cells), and any other necessary product information. Details are described in the study manual.

8.12 Storage, Handling, and Accountability of TAK-103

The final product should be stored in the shipping container in which it is delivered. This container is designed and validated to maintain target temperature [REDACTED]. Details of storage, handling, and accountability are described in the study manual. If TAK-103 cannot be administered to the patient within the storage period described in the study manual, the clinical site must contact the sponsor immediately.

Once thawed, the product must be administered [REDACTED]. The investigator should complete the administration as soon as possible to maintain the quality of the study product. Details are described in the study manual.

8.13 Japan Drugs, Products and/or Devices Used in the Clinical Trial other than Investigational Medicinal Product (J-non-IMP)

Drugs used in the clinical trial other than investigational medicinal product (IMP) are fludarabine and cyclophosphamide, which will be prepared by the clinical sites. They will be managed by the on-site pharmacist (site designee) in accordance with site procedures ensuring appropriate handling, storage, management, and prescription. The investigators and/or the on-site pharmacist (site designee) must maintain up-to-date written records of dispensing activities at a site level. Accountability for the materials sourced by site and dispensed during the entire study are recorded for each patient on the accountability log.

The reference safety information for the J-non-IMP is the product package insert, which the sponsor has provided under separate cover to all investigators in Japan.

8.13.1 Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

8.13.2 Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda trial clinician and the Takeda medical expert, other third-party vendors, and the list of investigators can be found in the protocol annex.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/IEC.

9.3 Treatment Group Assignments

This is a phase 1, dose-escalation study. Patients will be assigned to a dose cohort on the basis of the dose escalation rules described in Section 8.6.

9.4 Study Procedures

This study consists of the Prescreening, Screening, Pretreatment, Treatment and Primary Follow-up, and Secondary Follow-up phases. Refer to the schedule of events (Appendix A) for timing of assessments in each study phase. Additional details are provided as necessary in the sections that follow.

9.4.1 Prescreening Phase

The Prescreening phase begins on the date the patient signs the IRB/IEC-approved ICF (Prescreening ICF) for the assessment of mesothelin expression in tumor cells. Patients must have mesothelin expression in tumor cells to be eligible for the study ($\geq 50\%$ positive on viable tumor cells). Adequate tumor tissue which must be either fresh biopsy or archived sample needs to be provided. Patients are required to sign Prescreening ICF to have their tumor tissue assessed of mesothelin expression using Takeda validated assay. The patient is provided with a study specific patient number on the date of Prescreening ICF. If fresh tumor tissue is collected for mesothelin expression analysis, part of the tumor tissue will be provided for biomarker analysis and normal tissue will also be collected at the same time.

After a patient signs the Prescreening ICF, virus tests and FCM can be performed at the discretion of the investigator.

Rescreened patients may reuse mesothelin expression status that was previously analyzed by Takeda validated assay for the Prescreening phase. In such case, the patients can begin with required study procedures in the Screening phase.

9.4.2 Screening Phase

The Screening phase starts with the date when one of procedures in the Screening phase takes place. The Screening phase includes confirmation of eligibility and enrollment into the study, and ends with the start of leukapheresis procedures.

Informed consent for study participation must be obtained before initiating any study-specific procedures. Procedures that are part of standard of care (SOC) are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility.

After written informed consent has been obtained, patients will be screened to confirm study eligibility and participation. Only patients who meet the eligibility criteria listed in Sections 7.1 and 7.2 will proceed to further study procedures. If at any time the patient fails to meet the eligibility criteria during the Screening phase, the patient should be designated as a screen failure on the patient screening log with the reasons for failing screening.

Evaluations during the Screening phase are to be conducted within 14 days before the leukapheresis procedures, except for [REDACTED] prior to leukapheresis. If leukapheresis is performed more than 3 months after obtaining consent by the Main ICF, investigators must reconfirm patient's will to continue participation in the study before performing leukapheresis procedures. Procedures and assessments to be conducted during the Screening phase are shown in the SOE (Appendix A).

Investigators should make sure that the patients do not have any signs of lymphoma and/or leukemia during the Screening phase. If any evidence of or concern for lymphoma and/or leukemia including abnormalities in hematological findings, physical examination or imaging is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist.

Patients who fail to meet the eligibility criteria will be allowed to rescreen 1 time. Patients will perform the assessment that initially resulted in the subject's failing screening including any other procedures that fell outside of the designated screening window (e.g., lab assessments).

9.4.3 Pretreatment Phase

The Pretreatment phase is defined as the period from the start of leukapheresis procedures through the completion of conditioning chemotherapy until the start of TAK-103 infusion. During the Pretreatment phase, leukapheresis, bridging therapy, and conditioning chemotherapy will be performed. Bridging therapy may consist of any approved regimen for the subject's malignancy.

Patient must meet all eligibility criteria prior to conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered). Patient will be hospitalized to receive conditioning chemotherapy, based on the investigator's judgement.

Procedures and assessments to be conducted during the Pretreatment phase are shown in the SOE (Appendix A).

9.4.4 Treatment and Primary Follow-up Phase

The Treatment and Primary Follow-up phase begins with TAK-103 administration.

Patients will be hospitalized for at least 28 days after TAK-103 infusion. The hospitalization can be shortened by the investigator's judgement that the patient's symptoms are stable based on physical examination, vital signs, and the safety laboratory assessments. Basically, patients can be discharged from the hospital if all TAK-103-related toxicities return to Grade ≤ 1 or baseline. Patients with noncritical and clinically stable or improving toxicities even of Grade ≥ 1 can be discharged if deemed appropriate by the investigator. However, the investigator must consult and agree with the sponsor in advance of discharge. The early discharges during the 28-day DLT period are only permitted on conditions that the study site and the patient have close contact, the study site ensures 24-hour admittance of the patient in emergency, and the patient lives or stays at a place that ensures quick visit to the study site.

Following the TAK-103 infusion, all patients will be followed for 12 months (up to Month 13) in this study. Procedures and assessments to be conducted during the Treatment and Primary Follow-up phase are shown in the SOE (Appendix A).

Investigators should carefully monitor the patients with available data (clinical symptoms, physical examination, hematological findings, CT, FDG-PET, etc.) to detect early signs of lymphoma and/or leukemia throughout the study. If any evidence of or concern for lymphoma and/or leukemia is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist and to perform intensive appropriate investigations and follow-up according to site standard practice.

It is anticipated that patients may leave the Primary Follow-up and move to Secondary Follow-up due to reasons including:

- Disease progression
- Patient voluntary withdrawal from the Primary Follow-up

Patients who discontinue the Treatment and Primary Follow-up phase before Month 13 will complete all study procedures for the EOPF visit and continue to be followed in the Secondary Follow-up phase in order to collect safety data requested from health authority (e.g., protocol defined AEs, see Section 10.3) up to 3 years after TAK-103 infusion.

9.4.5 Secondary Follow-up Phase

The Secondary Follow-up phase begins with the end of the Treatment and Primary Follow-up phase. All patients will be followed for 36 months (up to Month 37). Procedures and assessments to be conducted during the Treatment and Primary Follow-up phase are shown in the SOE for the Secondary Follow-up phase (Appendix A). Continued monitoring for the development of secondary malignancy including lymphoma/leukemia is expected.

The first visit in the Secondary Follow-up phase is determined according to the time when the patient discontinued in the Treatment and Primary Follow-up phase. For example, if the patient

discontinues from the Treatment and Primary Follow-up phase at Month 7, the first visit in the Secondary Follow-up phase will be Month 10.

Upon completion of the Secondary Follow-up phase of this study, patients will be enrolled in a planned 12-year long-term safety follow-up study.

9.4.6 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's SOC.

9.4.7 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during the Screening phase.

9.4.8 Medical History

During the Screening phase, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it and the best response achieved by each one. In addition, concomitant medications will be recorded as specified in Section 9.4.13.

Available tumor genomic information obtained at the site will be collected. Information collected will include previous DNA sequencing results for driver gene mutations (i.e., epidermal growth factor receptor for squamous NSCLC), as well as IHC staining results from pathology assessments (i.e., human papillomavirus for cervical cancer).

9.4.9 Physical Examination

A physical examination will be completed per SOC at the times specified in the SOE (Appendix A). Investigators must perform careful observation/palpation on superficial lymph nodes, skin, mucosa, etc. to look for any signs of lymphoma and/or leukemia. Any clinically relevant findings are to be documented.

9.4.10 Height and Weight

Height will be measured only during the Screening phase. Body weight will be measured at the times specified in the SOE (Appendix A).

9.4.11 Vital Signs

Vital sign measurements, including supine (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and body temperature will be assessed as specified in the SOE (Appendix A). SpO₂ will also be measured according to SOE (Appendix A).

9.4.12 Pregnancy Test

A serum beta-human chorionic gonadotropin pregnancy test will be performed for women of childbearing potential at screening. Urine pregnancy test is allowed for the rest of the visits. The results must be available and negative before leukapheresis and conditioning chemotherapy. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

9.4.13 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from the time of informed consent (the date of Prescreening ICF or the date of Main ICF, whichever comes first) through the EOPF visit. During the period between signing informed consent (the date of Prescreening ICF or the date of Main ICF, whichever comes first) and conditioning chemotherapy, medications and procedures associated with reported AEs, immunosuppressive drugs and vaccines will only be collected and recorded in the eCRF.

During the Secondary Follow-up phase, medications and procedures associated with reported AEs will be collected and recorded in the eCRF.

Section 8.7 provides a list of medications and therapies that are prohibited during the study.

9.4.14 Adverse Events

Monitoring of AEs, serious and non-serious, will be conducted throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0 [65]. CRS and ICANS will be evaluated according to ASTCT consensus [66]. Baseline brain MRI should be obtained according to the SOE (Appendix A) to rule out any central nervous system (CNS) disease.

Investigators should make sure that the patients do not have any signs of lymphoma and/or leukemia during Screening phase. If any evidence of or concern for lymphoma and/or leukemia including abnormalities in hematological findings, physical examination or imaging is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist.

Investigators should carefully monitor the patients with available data (clinical symptoms, physical examination, hematological findings, CT, FDG-PET, etc.) to detect early signs of lymphoma and/or leukemia throughout the study. If any evidence of or concern for lymphoma and/or leukemia is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist and to perform intensive appropriate investigations and follow-up according to site standard practice.

- During the period between signing Prescreening ICF and signing Main ICF, AEs listed below are collected.

- [REDACTED]
- [REDACTED]
- During the period between signing Main ICF and conditioning chemotherapy, AEs listed below and all SAEs are collected.

- [REDACTED]
- [REDACTED]
- [REDACTED]
- After initiation of conditioning chemotherapy, all AEs and SAEs will be collected by the time of EOPF visit. Positive RCR will always be considered and reported as an SAE.
 - During the Secondary Follow-up phase, all SAEs (after the patient starts anti-cancer treatments following observation of PD, only SAEs related to study treatment and/or procedures must be reported) and AEs listed below are collected and recorded in the eCRF:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.4.15 Enrollment

The enrollment occurs by the start of leukapheresis procedures after confirmation of eligibility. Procedures for completing enrollment information are described in the Cohort Management Plan.

9.4.16 Cardiac Monitoring

9.4.16.1 12-Lead ECGs

A single 12-lead standard safety ECG will be performed to assess eligibility and safety as specified in the SOE (Appendix A). ECG assessments are to be performed with the patient supine and rested for 5 minutes. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

9.4.16.2 *Cardiac Telemetry*

Cardiac telemetry will be performed at the onset of Grade 2 or higher CRS until resolution to Grade ≤ 1 and additionally as clinically indicated, as specified in the SOE (Appendix A).

9.4.17 **Clinical Laboratory Evaluations**

Clinical laboratory evaluations will be performed locally. Part of the laboratory evaluations can be skipped in cases where it is not feasible at clinical sites (e.g., holidays) on condition that investigators ensure safety of patient.

9.4.17.1 *Clinical Chemistry, Hematology, and Urinalysis*

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the SOE (Appendix A).

In addition to standard clinical chemistry, additional tests will be performed locally for HIV, human T-cell lymphotropic virus, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C virus antibody (HCVAb), and CMV DNA or CMV antigenemia according to the SOE (Appendix A). HBsAg, HBsAb or HBcAb positive patient will be monitored and managed according to Guideline for the Prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection by the Japan Society of Hepatology (JSH) [68].

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	GGT
Hemoglobin	ALP	Glucose
Leukocytes with differential	ALT	LDH
Platelet count	AST	Magnesium
Peripheral blood smear assessment by microscopy	Bilirubin (total)	Phosphate
	BUN	Potassium
	Calcium	Sodium
	Bicarbonate	Ferritin
	Chloride	Urate
	Standard CRP	Amylase
	Creatinine	Lipase
	CPK	
Coagulation	Hormone	
APTT	TSH	
Prothrombin time	FT3	
Fibrinogen	FT4	

ALP: Alkaline phosphatase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time, AST: aspartate aminotransferase; BUN: blood urea nitrogen; CPK: creatine phosphokinase; CRP: C-reactive protein; FT: free thyroxine; GGT gamma glutamyl transferase; LDH: lactate dehydrogenase; TSH: thyroid-stimulating hormone

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

On the visits for leukapheresis, conditioning chemotherapy and TAK-103 infusion, all tests should be completed before procedures/dosing. Microscopic analysis of urine sediment should be performed if significant abnormalities are detected in proteins, leukocytes, or blood.

Serum creatinine clearance is to be estimated using the Cockcroft-Gault formula as follows:

$$\text{Estimated creatinine clearance} = [(140 - \text{Age}) * \text{Mass}(\text{kg})] / [72 * \text{serum creatinine}(\text{mg/dL})]$$

For female patients, the result of the formula above should be multiplied by 0.85.

As a backup, creatinine clearance can be determined based on 12 hours or 24 hours collection of urine specimen. If creatinine clearance is measured for inclusion, it cannot be replaced by the calculated one, if it is more favorable.

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9.4.20 Disease Assessment

Patients will undergo CT and/or MRI scanning to assess disease response and progression, using RECIST 1.1 [63] and iRECIST [64] criteria. CT and/or MRI scans should be acquired with IV contrast. CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. If it is known or suspected that additional anatomy is affected by the disease, imaging should also include these areas. The imaging modalities used for a patient should remain consistent throughout the trial. If contrast enhanced CT scans are contraindicated for a particular patient, a non-contrast CT of the chest, abdominal cavity, and pelvis, in addition to contrast enhanced abdomen and pelvis MR images should be acquired, if possible. Objective assessments of target, non-target, and potential new lesions will be performed at each timepoint as described in the SOE (Appendix A). If any other ad hoc image assessments occur in addition to predefined timepoints described in the SOE, investigators should also record those objective assessments in eCRF. X-rays and bone scans should be collected as clinically indicated. In this study, FDG-PET must also be performed according to the SOE (Appendix A). When possible, the same qualified physician will interpret results to reduce variability. All radiographic images except for brain MRI at screening must be sent to the sponsor/designee. Determination of disease status will be based on local investigator assessment. CT and/or MRI and FDG-PET scans will be processed to calculate the tumor burden in a patient.

9.4.20.1 iRECIST and Treatment Beyond Progression

For patients who have initial radiological evidence of PD by RECIST 1.1 as determined by the site, the investigator may elect to continue a patient in Primary Follow-up period until repeated imaging is obtained according to the iRECIST-based management [64, 71]. This clinical judgment decision by the investigator should only be made if the patient is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. For such patients, an

imaging-based tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (e.g., CNS metastasis with potential for cord compression).

In determining whether or not the tumor burden has increased or decreased per iRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion.

iRECIST defines unconfirmed progressive disease (iUPD) on the basis of RECIST 1.1 principle; however, iUPD requires confirmation obtained by repeat imaging at least 4 weeks, but no longer than 8 weeks after.

Confirming Progression

Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

- A. Immune-confirmed progressive disease (iCPD) is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:
- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
 - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
 - Continued unequivocal progression in non-target disease with an increase in tumor burden.
 - Increase in size of previously identified new lesions (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

OR

- B. RECIST 1.1 progression criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or immune stable disease (iSD), immune partial response (iPR) or immune complete response (iCR) if those criteria are met

compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as new lesions-target (NLT) and new lesion-non-target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the eCRF.

PD is confirmed in the new lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT, an increase (but not necessarily unequivocal increase) in the size of NLNT lesions or the appearance of additional new lesions.

9.4.21 MRI

In the Screening phase, baseline brain MRI should be performed according to the SOE (Appendix A) to rule out any CNS disease.

9.4.22 Biomarker, Cellular Kinetic, and Pharmacodynamic Samples

9.4.22.1 Primary Specimen Collection

Primary specimen collection is shown in Table 9.c.

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sampling time points (Excluding Secondary Follow-up Phase)
Archival (banked) tumor tissue sample	FFPE block FFPE slides		Mesothelin evaluation	Baseline
Fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block FFPE slides	Mesothelin evaluation and biomarker measurements	Baseline, D15 and upon disease progression.
Fresh non-tumor tissue biopsy sample	Fresh tissue	FFPE block FFPE slides	Biomarker measurements	Baseline, D15 and upon disease progression.
Blood sample for TAK-103 transgenes (CK)	Blood	DNA	CK measurements	D1, D2, D4, D8, D11, D15, D18, D22, D29, M3, M4, M5, M7, M10, M13/EOPF

Blood sample for DNA (RCR)	Blood	DNA	DNA measurements	Before LCT, M4, M7, M13/EOPF
Blood sample for DNA (TCR)	Blood	DNA	Biomarker measurements	Before LCT, D15, D29, M3, M5, M7, M10, M13/EOPF
Blood sample for CK by FCM	Blood	PBMC	Biomarker measurements	Before LCT, D1, D2, D4, D8, D11, D15, D18, D22, D29, M3, M4, M5, M7, M10, M13/EOPF

Serum Sample for immunogenicity	Blood	Serum	Immunogenicity evaluation	Screening, D15, D29, M3, M4, M5, M7, M10, M13/EOPF
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9.4.22.2 Blood Sample Priority

Blood samples will be collected via venipuncture or indwelling catheter at the timepoints detailed in the SOE (Appendix A) for CK of TAK-103, plasma cytokine measurements, and biomarker assessments. If required, blood samples collected for secondary endpoints can be used for exploratory endpoint analyses only after final CK analysis has been completed. If under some circumstances of unmet blood collection, the prioritized assessments are listed in Table 9.d.

Details on sample handling, storage, shipment, and analysis are provided in the study manual.

Table 9.d Blood Specimen Collection Priority

Priority	Primary Specimen	Description of Intended Use
1	Blood sample for DNA	Blood sample for DNA (CK, RCR)
2		
3		
4		
5	Blood sample for CK by FCM and DNA	Blood sample for FCM Blood sample for DNA (TCR)
6		
7		

9.4.22.3 Biopsies

Serial biopsies on tumor and adjacent normal tissue are performed for biomarker measurements in addition to the assessments regarding mesothelin expression.

Biopsy samples are collected as a formalin-fixed, paraffin-embedded (FFPE) block or slide following the SOE (Appendix A). Patients undergoing biopsy procedures must meet the following criteria prior to the procedures.

- Platelet count $>75,000/\text{mm}^3$.
- ECOG performance status ≤ 1 .
- Use of no anticoagulant therapies or antiplatelet agents.
- Absence of any other known coagulation abnormalities that would contraindicate the tumor biopsy procedures.
- Absence of any other medical conditions that do not allow for biopsy at the investigator's discretion.

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The tumor biopsy procedures will be performed by core needle according to treating institution's guidelines under ultrasound, CT, or endoscopy guidance. Core needle biopsies will typically be performed with 18-gauge devices, but large cores may be elected by the treating clinician. Surgical approach may be allowed if intervention is intended for palliative care. Biopsy procedures should not be performed on target regions determined according to RECIST 1.1.

Minimal of 2 biopsies at screening for fresh biopsy and minimal of 2 tumor biopsies at other post-treatment timepoints are required. One adjacent normal tissue biopsy will also be performed at baseline and post-treatment timepoints with minimized invasion. Additional tumor biopsy is considered to obtain sufficient amount of tissue up to 5 passes of tumor biopsy and 1 normal tissue biopsy can be done at one time point of biopsy. Number of passes or biopsy procedures themselves may be averted based on medical judgement by the investigator. While obtaining the maximum number of biopsies may result in valuable information for patient management and overall impact of the study, clinical judgement regarding biopsy safety in each subject is the most important factor.

Prescreening biopsy (archived or fresh): Will be performed/used to confirm expression level of mesothelin in tumor cells to fulfill entry criteria prior to leukapheresis and will also be used to be retained as pretreatment comparison to evaluate changes in mesothelin expression and biomarkers following treatment with TAK-103 including the modulation of the tumor microenvironment.

If a patient has an archival sample, the sample can be used to confirm mesothelin expression for inclusion criteria and for biomarker assessment unless a fresh biopsy is recommended due to archival biopsy quality. A fresh biopsy can be performed at any time after obtaining informed consent and before conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered) for biomarker assessment, but it is not used to confirm mesothelin expression for inclusion criteria.

If a patient does not have an archival sample to confirm mesothelin expression, a fresh biopsy will be performed. The biopsy sample will also be used for biomarker assessment.

A separate ICF (Prescreening ICF) will be used to evaluate mesothelin expression on the archival tumor tissue sample or fresh tumor tissue biopsy sample prior to the Main ICF obtained from patients.

Posttreatment biopsy (fresh): Will be obtained on Day 15 after administration of TAK-103 and when disease progression is observed, unless prohibited by patient's safety. If the post-infusion biopsy cannot be obtained on Day 15 post-infusion, then the investigators would aim to obtain a biopsy within Day 15-22 timeframe, which are expected to yield significant insights on product mechanisms-of-action and tumor microenvironment. If the patient's medical condition does not allow for post-infusion biopsy collection between Day 15 and Day 22, then the investigators should try their best to collect the biopsy sample as soon as the patient's medical condition allows for the procedure within the Day 29 post-infusion timeframe.

9.4.23 Cellular Kinetic Measurements

9.4.23.1 Droplet Digital Polymerase Chain Reaction and Flow Cytometry

TAK-103 CK will be evaluated by a validated droplet digital polymerase chain reaction (ddPCR) method and reported as level of TAK-103 transgene copies/ μ g of genomic DNA (gDNA). For all subjects treated with TAK-103, the CK profile and the subsequently calculated CK parameters will be reported: C_{max} , t_{max} , C_{last} , t_{last} , and AUCs.

The assessment of TAK-103 CK will be used to examine the dose-exposure relationship, possible correlation of persistence and expansion of TAK-103 with safety and efficacy endpoints.

Additionally, the CK measurement by ddPCR will be utilized to monitor for the development of mono- or oligo-clonality. TAK-103 CAR-transgene allelic frequency will be assessed by ddPCR, and will serve as a surrogate marker for clonality. If TAK-103 CAR-transgene allelic frequency $\geq 1\%$ of total nucleated cells in a sample (estimated using a house-keeping gene) in peripheral blood at Month 7 and beyond post-infusion of TAK-103, then the patient will be asked to return for a confirmatory blood test prior to the next visit. If $\geq 1\%$ of the nucleated cells in the sample (estimated using a house-keeping gene) is positive upon the receipt of the confirmatory ddPCR result, then the TCR analysis (see Section 9.4.24.3) will be triggered, if samples have not been analyzed already as part of the T-cell repertoire exploratory analysis, for confirmation of T-cell clonal expansion. If TCR sequencing identifies a pattern of mono- or oligo-clonality an integration site analysis will be triggered to assess for vector integration sites at or near an oncogenic locus. Follow-up assessment for persistence will be scheduled within 3 months. In the event of persistent or expanding mono- or oligo- clonality and/or integration at or near an oncogenic locus, a monitoring plan, including follow-up molecular analyses, will be developed in collaboration between the investigator, sponsor, and health authorities if necessary, that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

Hence, samples for ddPCR will continue to be collected from all patients at no longer than 6 months intervals for the first 5 years post-treatment regardless of clinical outcomes. Additional blood samples will be archived annually for up to 15 years following treatment with TAK-103 and tested for CAR-T-cell clonality. Peripheral blood will be collected as indicated in the SOE (Appendix A) for these studies. In Secondary Follow-up phase, sample collection and testing may be stopped at the discretion of the sponsor if TAK-103 cells are undetectable on 2 consecutive ddPCR tests. Details of the sample collection procedures for these assays are provided in the study manual.

The timing, but not the total number of samples, may be modified during the study on the basis of emerging CK data if a change in sampling scheme is considered necessary to better characterize the CK. A protocol amendment is not necessary for such modifications.

9.4.24 Biomarker and Pharmacodynamic Measurements

In this study, several biomarkers and pharmacodynamic measurements will be assessed to test for correlations with safety and efficacy. These biomarkers will be used to identify potential

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pharmacodynamic activity in patients who have a greater likelihood of response or adverse reactions. The biomarker and pharmacodynamic specimen collection timepoints are displayed in the SOE (Appendix A). Details regarding the preparation, handling, and shipping of samples are provided in the study manual.

9.4.24.2 RCR

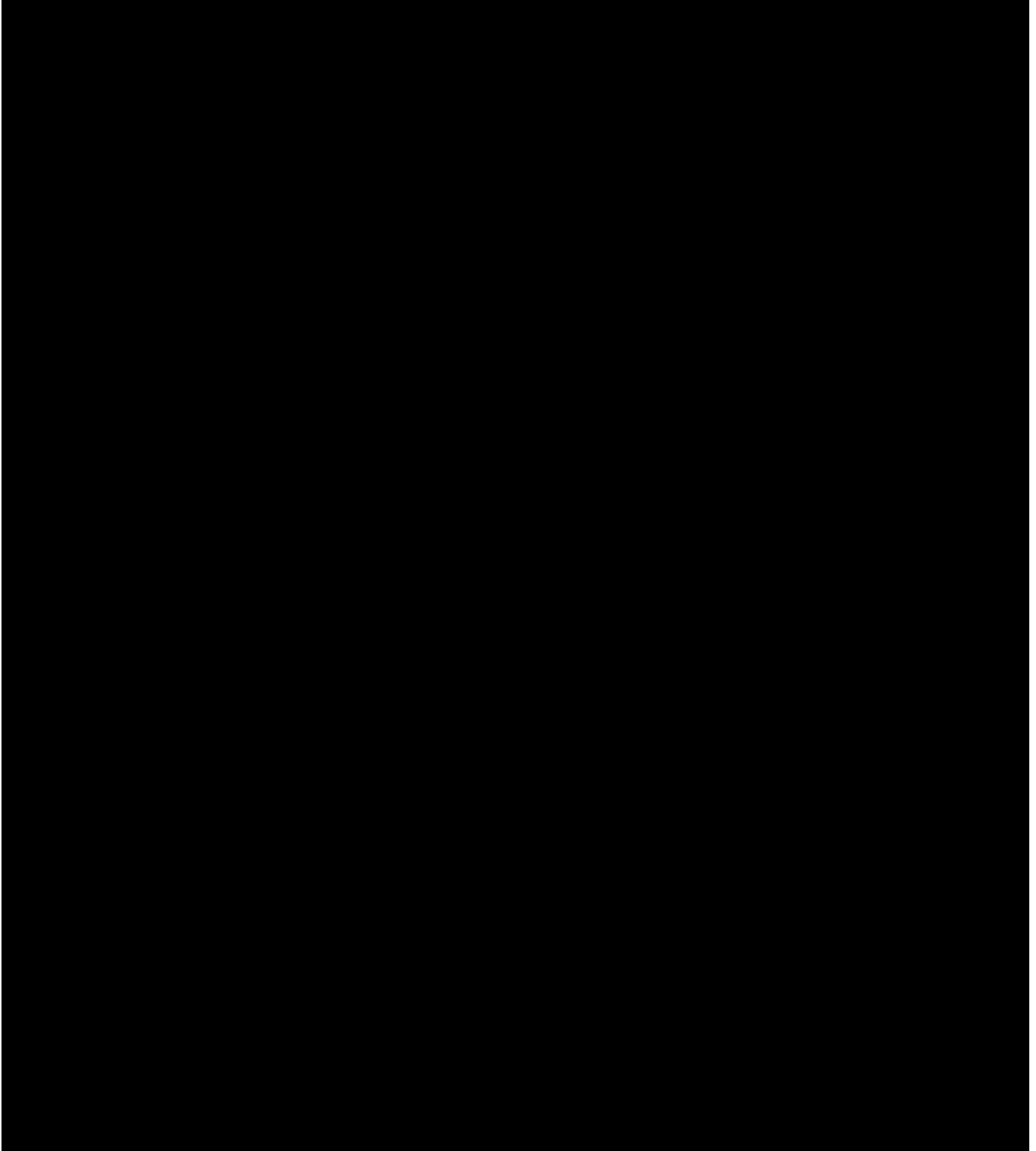
Blood samples will be collected to examine RCR during the course of the trial. If a positive RCR assay result is obtained from a patient blood specimen, the investigator will be informed, and the patient will be rescheduled for RCR retest. Positive RCR test will be reported as an SAE by the investigator. Additional blood samples will be archived annually for up to 15 years following therapy unless instructed to stop by the sponsor and tested only if RCR is detected within the first 1 year from treatment. Sample collection and testing may be stopped if no positive results are reported in the first year post-treatment.

9.4.24.3 T-cell Receptor (TCR)

T-cell repertoire in patient blood will be tracked using TCR sequencing to characterize patterns of T-cell repertoire changes as an exploratory surrogate for potential induction of an adaptive immune response.

Additionally, in the event that TAK-103 CAR-transgene allelic frequency of (surrogate marker of clonality) $\geq 1\%$ of the estimated total nucleated cells in a sample is positive upon the receipt of the confirmatory ddPCR result, T cell clonal expansion will be assessed utilizing TCR sequencing. If clonality is identified, this will trigger an integration site analysis as described in Section 9.4.23.1. Additional blood samples will be archived annually for up to 15 years following treatment with TAK-103 and tested for T-cell clonality. Testing may be stopped after 1 year post-treatment if TAK-103 cells are undetectable on 2 consecutive tests, although sample collection may continue. In Secondary Follow-up phase, sample collection and testing may be stopped at the discretion of the sponsor if TAK-103 cells are undetectable on 2 consecutive ddPCR tests.

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9.4.25 Possible Changes to Study Procedures Due to COVID-19 Pandemic

Possible changes of the study procedures that could be implemented for study participants or study sites are affected by the coronavirus disease 2019 (COVID-19) public health emergency should follow the guidance below. This guidance follows the Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 03 June 2020, and the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID-19 Pandemic, Version 3 (28 April 2020), and the Pharmaceuticals and Medical Devices Agency (PMDA) Guidance of Japan on Q&A regarding clinical trials of pharmaceuticals, medical devices, regenerative medicine products under the influence of the COVID-19, March 2020, updated 26 May 2020.

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

For this trial, procedural changes due to COVID-19 may include the following:

- ‘Remote visits’ may be performed as a safety check on subject well-being. When remote visits are necessary, due to COVID-19 pandemic restrictions, sites are permitted to conduct visits via telephone/video calls, including teleconferencing software.
- Deviations from the protocol-specified procedures (e.g., not collecting a protocol-specified specimen, such as postdose bloodwork, missed clinic visit) or subject withdrawals due to the COVID-19 will be recorded as related to COVID-19.

9.4.26 Patient Transfer

Designated clinical sites only recruit subjects and confirm mesothelin expression using Takeda validated assay as prescreening of this study. Potentially eligible patients will be then transferred to another participating clinical site for TAK-103 administration and subsequent follow-up. The

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investigator must obtain informed consent for study participation after explaining the transfer. Details are described in the study manual.

9.4.27 Sample Retention

Tumor tissue biopsy samples, peripheral blood mononuclear cells, serum, plasma, leukapheresis product, final product samples, and any other samples collected as part of the study will be stored up to 15 years after the date of study completion as identified in the CSR and may be used for research purposes. Samples will be destroyed by a third-party vendor per company standard operating procedures. Formalin-fixed tumor tissue biopsy samples will be stored at ambient temperature. Blood and plasma samples will be stored at -70°C. Apheresate and undosed CAR-T materials will be stored below -130°C. If patients withdraw consent, the samples will be discarded following the local procedure (i.e., where the sample resides at the time of withdrawal and the investigator needs to inform the sponsor of patient's intent to withdraw immediately). Test results should not be discussed with patients unless required by local law. The tests performed with these samples are not intended to make determinations about a patient's health or the likelihood that a patient will develop any disease, so no test results will be provided to the investigator or put into a patient's medical record.

9.4.28 Sample Use for Research Purposes

The function of CAR-T cells is not fully elucidated as CAR-T cell therapy in solid tumor is an evolving field. Tumor tissue biopsy samples, peripheral blood mononuclear cells, serum, plasma, leukapheresis product, final product samples, and any other samples collected as part of the study under sample retention section may be analyzed using new assays or platforms to test hypotheses relevant to disease, I/O and cell therapy outside of TAK-103 clinical study. Research analyses may include, but are not limited to, cell functional assays, targeted DNA and ctDNA, RNAseq, IHC, and/or flow cytometry.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they receive a dose of TAK-103.

9.6 Completion of Study (for Individual Patients)

In the Pretreatment, the Treatment and Primary Follow-up, or the Secondary Follow-up phase, patients may be considered to have completed the study if 1 or more of the following situations occur:

- Death.
- Consent withdrawal.
- Study terminated by the sponsor (applicable to Treatment and Primary Follow-up phase).
- Lost to follow-up.
- Transfer of patient to a long-term safety study.

If a patient discontinues the Treatment and Primary Follow-up phase, the patient will proceed directly to the EOPF visit and, where possible, be moved to the Secondary Follow-up phase. Patients who completed Month 13 assessments according to the SOE (Appendix A) will not proceed to EOPF visit because those patients are considered to have completed the Treatment and primary follow up phase with Month 13 assessments.

If completion of study participation occurs in the Secondary Follow-up phase, the patient will proceed directly to the EOS visit and, where possible, be followed for further long-term risk assessment in the planned long-term safety follow-up study. Patients who completed Month 37 assessments according to the SOE (Appendix A) will not proceed to EOS visit because those patients are considered to have completed the study with Month 37 assessments.

Subject withdrawals due to COVID-19 must be recorded. If a subject withdraws from study participation due to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Discontinuation of treatment is not applicable as this is a single infusion study. Patients who are withdrawn from the study or completed the study before reaching end of 28-day DLT period may be replaced.

9.8 Study Compliance

Study product will be administered or dispensed only to eligible patients under the supervision of the investigator. The appropriate study personnel will maintain records of study product receipt and dispensing.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AE Definition

AE means any untoward medical occurrence in a patient or subject enrolled in a study who has signed an ICF; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study product.

An abnormal laboratory value will not be assessed as an AE unless that value leads to therapeutic intervention or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization (after the initial treatment hospitalization period) or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of dependency or abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0 [65], while CRS and ICANS will be evaluated according to ASTCT consensus [66]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC count of $1000/\text{mm}^3$ to less than $2000/\text{mm}^3$ is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by calling, faxing, or e-mailing the SAE Form within 24 hours after becoming aware of the event. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information:



If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up SAE Form or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested. If the sponsor or designee requests provision of archived samples, tissues, etc. for a reasonable reason such as investigation of the cause of the event, the investigator will provide them after confirming that the consent of the subject (or the subject's legally acceptable representative if the subject has died) has been obtained.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before study product was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; e.g., surgery was performed earlier or later than planned. Extension of hospital admissions for 28-day follow-up after TAK-103 infusion is not considered an AE unless the condition deteriorated in an unexpected manner.

For both serious and non-serious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study product administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5 [65], ASTCT consensus [66], and CARTOX recommendations [67].

Relationship of the event to study product administration (i.e., its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study product? The investigator will also evaluate the relationship of each event with conditioning chemotherapy or other study procedure.

If the AE is related to product malfunctions, the details of the product malfunction will be recorded on the Product malfunction page of the eCRF. The procedures for collection and reporting of product malfunction are described in Section 10.6

10.3 Monitoring of AEs and Period of Observation

AEs will be collected and monitored throughout the study as follows:

- During the period between signing Prescreening ICF and signing Main ICF, AEs listed below are collected.

[REDACTED]

- During the period between signing Main ICF and conditioning chemotherapy, AEs listed below and all SAEs are collected.

[REDACTED]

- After initiation of conditioning chemotherapy, all AEs and SAEs will be collected by the time of end of EOPF visit. Positive RCR test is always considered and reported as an SAE.
- During the Secondary Follow-up phase, all SAEs (after the patient starts anti-cancer treatments following observation of PD, only SAEs related to study treatment and/or procedures must be reported) and AEs listed below are collected and recorded in the eCRF:

SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through the EOS visit and recorded in the eCRF. After patient starts anti-cancer treatments and/or checkpoint inhibitors following observation of PD, only SAEs related to study treatment and/or procedures must be reported to the sponsor. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illnesses.

AEs will be collected until the patient complete the study.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Overdose

An overdose is defined as a known deliberate or accidental administration of investigational product, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database.

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs and SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2, Procedures for Recording and Reporting AEs and SAEs.

In the event of overdose, the subject should be treated symptomatically.

10.6 Procedures for Reporting Product Malfunctions

All product malfunctions (e.g., a functional failure in the study product), regardless of presence or absence of AEs, will be recorded in the Product Malfunction page of the eCRF.

The following information will be documented for each event:

- Product identification number including patient identity.
- Event term.
- Date observed by the investigator.
- Presence or absence of AEs due to the malfunction.
- Presence or absence of a potential risk of health injury due to the malfunction (not applicable if any AEs have already occurred).
- Presence or absence of a potential risk that would lead to deaths or SAEs due to the malfunction (If there is such a risk, assumed health injury name must be provided. It is not applicable if any AEs have already occurred).

If an SAE occurred due to product malfunction, the SAE and the product malfunction should be reported as per Section 10.2 and the following procedure. If a product malfunction that may lead to death or SAE occurred without actual AE, it should be also reported according to the following procedure:

A product malfunction should be reported by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided in Section 10.2). This should be done by faxing calling or e-mailing the product malfunction report form within 24 hours after first onset or subject's notification of the event, such as SAE or product malfunction that may lead to death or SAE. A sample of the product malfunction report form may be found in study manual.

If information not available at the time of the first report becomes available at a later date, then the investigator will complete a follow-up product malfunction report or provide other documentation immediately within 24 hours of receipt.

The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event.
- Subject identification number.
- Investigator's name.
- Study product name.
- Presence or absence of AEs.

The sponsor will also evaluate whether there is a risk that would lead to deaths or SAEs due to the malfunction. As a result of the evaluation, the sponsor may ask the investigator for additional

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investigation. If additional investigation is required, the investigator should submit the completed product malfunction report form within 10 calendar days after the sponsor's request, including:

- Deaths and life-threatening cases.
- Cases that would require inpatient hospitalization or prolongation of existing hospitalization; cases that would lead to a persistent or significant disability/incapacity; other serious cases second to these cases or deaths/life threatening cases; and cases that would lead to a congenital anomaly/birth defect in later generation.

10.7 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, and/or the head of each study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

11.0 STUDY-SPECIFIC COMMITTEES

A Data Monitoring Committee (DMC) for this study will be established for the purpose of protecting the interests of the subjects in the study, and of those still to be entered, by review of accumulating safety and tolerability data generated in this study from a neutral standpoint during the trial period. In addition, regular and ad hoc meetings between the sponsor and the investigators are arranged to ensure safety of patients. Details on holding the meeting will be seen in DMC Charter and Cohort Management Plan respectively.

11.1 Data Monitoring Committee

The DMC will be composed of members who have the expertise necessary for the evaluation of the clinical trial and are independent of the sponsor and investigators. The DMC will review safety and tolerability data generated in this study at the timing of events such as before the study resumes, transition from the first patient to the second patient in each cohort, dose escalation, need evaluation of adverse events in each case etc. The DMC can also convene unscheduled meetings as necessary. The DMC will provide recommendations to the sponsor based on the review of data from this study.

11.2 Meeting for Careful Attention

In the event of an AE requiring careful attention such as [REDACTED], the sponsor will hold a meeting involving the investigators and specialists in hematology and relevant departments, etc.; and [REDACTED]

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs, including the audit trails, and detailed records of product disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any

source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility.

Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified product indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and/or the head of the institution and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The analysis sets will include the following:

- **Safety analysis set:** Patients who have received any dose of TAK-103. This set will primarily be used for safety analyses and for some efficacy analyses.
- **DLT analysis set:** Patients who have received any predetermined dose of TAK-103 and completed the assessment for DLT evaluation or experienced a DLT during the first 28 days following TAK-103 infusion. The DLT analysis set will be used to determine the MTD.
- **CK analysis set:** Patients who have received any dose of TAK-103 and have at least 1 CK parameter estimated will be used for CK analysis.
- **Response-evaluable analysis set:** Patients who have received any dose of TAK-103, have had measurable disease at baseline and at least 1 posttreatment evaluation, will be used for analyses of response.
- **Pharmacodynamic analysis set:** Patients from the safety analysis set who have baseline and at least 1 postbaseline sample assessment.
- **Immunogenicity-evaluable analysis set:** Patients from the safety analysis set who have a baseline and at least 1 postbaseline immunogenicity assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include gender, age, race and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts, and percentages will be provided. Categories for missing data will be presented as needed.

13.1.3 Efficacy Analysis

ORR, DCR, DOR, TTP and PFS as assessed by the investigator according to RECIST1.1 and iRECIST will be summarized descriptively. The OS will also be summarized. The summary may be generated by dose cohort. No formal statistical tests will be performed for these endpoints.

ORR is defined as the proportion of patients whose best overall response is complete response (CR/iCR) or partial response (PR/iPR) as determined by the investigator per RECIST 1.1 and iRECIST respectively.

DCR is defined as the proportion of patients whose best overall response is stable disease (SD/iSD) or better as determined by the investigator per RECIST 1.1 and iRECIST respectively. SD/iSD have to be maintained for at least 24 days (around 4 weeks) after the TAK-103 infusion.

DOR is defined as the time from the date of first documentation of a PR/iPR or better to the date of first documentation of disease progression per RECIST 1.1 and iRECIST respectively.

TTP is defined as the time from the TAK-103 infusion date to the date of first documented disease progression by the investigator per RECIST 1.1 and iRECIST respectively.

PFS is defined as the time from the TAK-103 infusion date to the date of disease progression per RECIST 1.1 and iRECIST respectively or death from any cause, whichever occurs first.

OS is defined as the time from the TAK-103 infusion date to the date of death from any cause.

Censoring for time-to-event efficacy endpoints will be detailed in the SAP.

DCR and ORR will be summarized using point estimate and the 2-sided 95% exact binomial confidence interval using the response-evaluable analysis set. ORR will also be summarized using the safety analysis set.

TTP, PFS, and OS will be analyzed descriptively using Kaplan-Meier method for safety analysis set. DOR will also be analyzed using Kaplan-Meier method for response-evaluable analysis set.

13.1.4 CK Analysis

13.1.4.1 CK Non-compartmental Analysis

CK parameters will be estimated using non-compartmental methods with WinNonlin Phoenix. The CK parameters (C_{max} , t_{max} , C_{last} , t_{last} , AUC) will be estimated from the DNA normalized concentration (copies/ μ g gDNA)-time profiles for the CK analysis set. The CK parameters will be determined, as permitted by data, by dose level, indication, and mesothelin expression levels (IHC, fresh, archived), and responder/non-responder (including CR, PR, SD, and PD).

CK parameters will be summarized using descriptive statistics. Individual TAK-103 concentration-time data and individual CK parameters will be presented in listings and also tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

13.1.4.2 CK Sampling Intended for Population PK Analysis

The CK data collected in this study are intended to contribute to future population CK analyses of TAK-103. These population CK analyses may additionally include data collected in other

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TAK-103 clinical studies. The plan for the population CK analysis will be defined separately and the results reported separately.

13.1.5 Pharmacodynamic Analysis

Pharmacodynamic analyses listed under Section 9.4.24 will be conducted on exploratory basis and may or may not be reported as part of the CSR. Peripheral blood, serum, plasma, and tumor biopsy collected at baseline and post administration of TAK-103 will be analyzed for: (1) expression pattern of surface bound or soluble mesothelin and other proteins, (2) CAR-Ts frequency and phenotype, (3) other immune-cell activation to establish evidence of pharmacodynamic modulation. The relationship between cytokines and activation of innate and/or adaptive immune response (as assessed by changes in immunophenotype and TCR clonality of peripheral blood and tumor) may also be explored.

13.1.5.1 Plasma Sample for Safety Biomarkers and Cytokines

Sample collections for plasma cytokines, inflammatory and safety biomarkers are mandated during the first 28 days following TAK-103 infusion.

13.1.5.2 Blood Sample for DNA (TCR)

T-cell repertoire in patient blood will be monitored using TCR sequencing to monitor potential induction of an adaptive immune response and patterns and changes in T cell repertoire.

13.1.5.3 Blood Sample for Flow Immunophenotyping

Blood samples will be collected for assessment of immunophenotypic changes induced by TAK-103. These blood samples will be analyzed for the presence and changes in immune cell state by FCM; including, but not limited to B and T lymphocytes, monocytes, NK cells, and DCs.

13.1.5.4 Serum Sample for Protein

Serum sample will be collected at baseline and on treatment for exploratory evaluation of pre- vs. post-treatment changes in soluble mesothelin, MPF, CA125, and other disease-relevant soluble biomarkers. The longitudinal assessment of soluble proteins may be used to monitor disease burden and/or assess biochemical responses to treatment with TAK-103.

13.1.5.5 Plasma Sample for Pharmacodynamics

Plasma based pharmacodynamic assessments will include serial sampling for proinflammatory cytokines. Additional soluble factor analyses can be conducted with emerging data.

13.1.5.6 Fresh Paired Tumor Biopsy

Paired biopsies will be used to evaluate TAK-103 tumor infiltration, activation, and changes in pharmacodynamic biomarkers following treatment with TAK-103 including the modulation of the tumor microenvironment. As part of the resistance mechanism assessment, RNA sequencing will

be performed on biopsy samples if feasible based on sample availability. Gene signatures will be calculated for association with CAR-T activity. Whole exome sequencing may also be performed to derive TMB.

13.1.5.7 Plasma Sample for ctDNA and/or RNA

ctDNA and/or exosome RNA measurements may be performed as an exploratory tumor-burden assessment that capture TAK-103-mediated changes in the tumor microenvironment. Plasma samples will be collected at baseline and on treatment for evaluation of tumor-associated genes and/or gene expressions changes, and as an exploratory measurement of disease burden. Correlative analysis will aim to track the kinetics of ctDNA and/or exosome RNA pre- and post-treatment with TAK-103.

13.1.6 CK/Pharmacodynamic Analysis

The relationship between TAK-103 systemic exposure and pharmacodynamic response (e.g., degree of immune activation, changes in cytokines/chemokines, gene expression changes, etc.) will be explored on an ongoing basis as CK and pharmacodynamic data become available to understand the CK-pharmacodynamic relationship of TAK-103 and to help in estimation of the efficacy based on pharmacodynamic markers. Data permitting, mathematical models may be used to describe this relationship and such models may be used to predict the dose/schedule of TAK-103 that provides the desired exposure and pharmacological response for future evaluation.

13.1.7 Immunogenicity Analyses

The proportion of subjects with humoral immunogenicity responses during the study will be summarized. The effect of immunogenicity on CK, safety, and efficacy will be examined if applicable.

13.1.8 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to study product will be tabulated.

AEs that occur after the date of prescreening ICF or the date of main ICF, whichever occurs first, will be tabulated.

TEAEs that occur after administration of TAK-103 will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Treatment-related TEAEs.
- Grade 3 or higher TEAEs.

- Grade 3 or higher treatment-related TEAEs.
- SAEs (related and regardless of relationship).

The incidence of DLTs will be tabulated using the DLT analysis set, and AEs of clinical interest will be tabulated using the safety analysis set.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled timepoint. ECOG performance status scores will be summarized using a shift table.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters), will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. For RCR, patient counts and percentages will be provided for all scheduled measurements over time.

Shift tables for laboratory parameters will be generated for changes in the NCI CTCAE grade from baseline to worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the TAK-103 safety profile.

All concomitant medications collected from the administration of study product throughout the study period will be classified to preferred terms according to the WHO Drug Dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-103.

13.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned in this study. The investigator and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort.

13.3 Determination of Sample Size

It is anticipated that up to 21 DLT evaluable patients will be enrolled in this study. The study will use BOIN design to inform dose escalation/de-escalation decisions, taking into account safety other than DLTs, efficacy, CK, and biomarker assessments.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without prior written agreement with the sponsor or prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and approval from IRB should be obtained.

The investigator should document all protocol deviations.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

Deviations from the protocol-specified procedures (e.g., not collecting a protocol-specified specimen, such as postdose bloodwork, missed clinic visit) due to the COVID-19 will be recorded as related to COVID-19.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the US Food and Drug Administration [FDA] and the

Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

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15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, i.e., before shipment of the sponsor-supplied product or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship product/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives product/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and before the subject enters into the study. The subject should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., US FDA and Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, e.g., subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact

information, along with facility name, investigator's city, country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study product or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events (SOE)

Schedule of Events for Primary Follow-up

Phase	Pre-screening	Screening	Pretreatment			Treatment and Primary Follow-up ^b															
Procedure	Pre-screening	Screening	LA	BT	LCT	D1		D2	D4	D8	D11	D15	D18	D22	D29	M3 ^d	M4	M5	M7	M10	M13/ EOPF ^y
		-14 D ^a			-3 D ^c	Pre	Post	0 D	±1 D	±1 D	±1 D	±1 D	±1 D	±2D	±4 D	±7 D	±7 D	±7 D	±7 D	±7 D	±14 D
Informed consent	X ^{bb}																				
Inclusion/exclusion criteria		X ^x			X																
Medical history		X																			
Physical examination ^z		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																			
Weight		X			X	X				X		X		X	X	X	X	X	X	X	X
ECOG performance status		X			X	X				X		X		X	X	X	X	X	X	X	X
Vital signs		X	X		X	X ^e	X ^e	X ^e	X	X	X	X	X	X	X	X	X	X	X	X	X
SpO ₂		X			X	X ^e	X ^e	X ^e	X	X	X	X									
Fresh tumor and normal tissue biopsy	X ^f	X ^f									X ^h			Upon disease progression							
Archived (banked) tumor tissue	X ^g																				
Disease assessment ^j		X			X ⁱ										X	X		X	X	X	X
FDG-PET scan ^k					X ^{ee}											X	As clinically indicated				
MRI (brain)		X				As clinically indicated															
Cardiac telemetry						At the onset of Grade 2 or higher CRS until resolution to Grade ≤1, and additionally, as clinically indicated															
12-lead ECG		X			X	As clinically indicated									X	As clinically indicated					
LVEF assessment by ECHO		X				As clinically indicated															
CRS assessment and grading						X ^e	X ^e	X ^e	X	X	X	X	X	X	X						
ICANS assessment and grading						X ^e	X ^e	X ^e	X	X	X	X	X	X	X						

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Schedule of Events for Primary Follow-up (continued)

Phase	Pre-screening	Screening	Pretreatment			Treatment and Primary Follow-up ^b															
Procedure	Pre-screening	Screening	LA	BT	LCT	D1		D2	D4	D8	D11	D15	D18	D22	D29 ^e	M3 ^d	M4	M5	M7	M10	M13/ EOPF ^y
		-14 D ^a			-3 D ^c	Pre	Post	0 D	±1 D	±1 D	±1 D	±1 D	±1 D	±1 D	±2D ^x	±4 D	±7 D	±7 D	±7 D	±7 D	±14 D
AE reporting	Continuously ^{m, x}																				
Monitoring of concomitant medications and procedures	Continuously ⁿ																				
Monitoring of anti-cancer therapies after TAK-103 infusion								Continuously													
Laboratory Assessments																					
Hematology/chemistry		X ^w			X ^w	X		X	X	X	X	X	X	X	X ^w	X ^w	X ^w	X ^w	X ^w	X ^w	X ^w
Flow cytometry	X ^p		As clinically indicated																		
Thyroid hormone						X ^o								X	X			X		X	
Coagulation		X			X	X ^o		X	X	X		X		X	X	X	X	X	X	X	X
Urinalysis		X			X	X				X		X		X	X	X	X		X		X
Virus tests (HIV, HTLV, HBsAg, HBsAb, HBcAb, HCVAb, HBV DNA ^{ff} , HCV RNA ^{ff} , CMV DNA or CMV antigenemia)	X ^p		As clinically indicated																		
Pregnancy tests ^q		X			X	As clinically indicated															
Rapid cytokine measurement (at baseline) ^{cc}					X		X		X												
Rapid cytokine measurement (as event occurred) ^{dd}						As clinically indicated															
Study Intervention																					
Leukapheresis procedures			X																		
Bridging therapy				X																	
Conditioning chemotherapy					X																
Treatment with TAK-103						X															

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Schedule of Events for Primary Follow-up (continued)

Phase	Pre-screening	Screening	Pretreatment			Treatment and Primary Follow-up ^b															
Procedure	Pre-screening	Screening	LA	BT	LCT	D1		D2	D4	D8	D11	D15	D18	D22	D29	M3 ^d	M4	M5	M7	M10	M13/EOFP ^y
		-14 D ^a			-3 D ^c	Pre	Post	0D	±1 D	±1 D	±1 D	±1 D	±1 D	±1 D	±2D ^b	±4 D	±7 D	±7 D	±7 D	±7 D	±14 D
Cellular Kinetics, Biomarker, Safety and Other Assessments																					
Blood sample for DNA (RCR)					X											X		X		X	
Blood sample for DNA (cellular kinetics) ^s						X	X ^u	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DNA (TCR)					X							X			X	X		X	X	X	X
Blood sample for flow cytometry (cellular kinetics)					X ^t	X	X ^u	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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receptor.

Unless otherwise noted, all tests must be completed before leukapheresis, conditioning chemotherapy and TAK-103 infusion on scheduled visits. Tests and procedures should be performed on schedule for all visits. For individual instances when assessments or procedures cannot be performed as defined in the protocol, the reasons for failing to perform those should be documented (e.g., identifying the specific limitation imposed by coronavirus disease 2019 that led to an inability to perform the protocol-specified visit, assessment, or procedure).

- a. Patient's eligibility must be confirmed within 14 days before the day of the leukapheresis procedures [REDACTED]. Signed informed consent must be obtained before performing any protocol-specific procedures. A separate consent may be obtained for the release of archival tumor tissue for the evaluation of mesothelin expression prior to screening. ICF may be signed more than 14 days before the day of leukapheresis procedures.
- b. Patients will be hospitalized for 28 days for the TAK-103 treatment.
- c. Within 3 days before the conditioning chemotherapy. For patients who do not receive the conditioning chemotherapy, the items that overlap with Day 1 pre-infusion can be skipped but other items must be performed within 3 days before TAK-103 administration.
- d. One month is defined as 30 days. M3 (Month 3) indicates M3D1.
- e. On Day 1, the assessments must be performed before and at the end of TAK-103 infusion (+30 minutes) and after 6 hours (± 1 hour) of TAK-103 infusion. On Day 2, the assessments must be performed twice daily with at least 9 hours apart.
- f. If a patient does not have an archival sample to confirm mesothelin expression, a biopsy will be performed and mesothelin expression is confirmed before proceeding to leukapheresis. The biopsy sample will also be used for biomarker assessment. Although archived biopsy samples are available, a fresh biopsy can be performed at any time after obtaining informed consent and before conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered) for biomarker assessment, but it is not used to confirm mesothelin expression for inclusion criteria.
- g. If a patient has an archival sample, the sample can be used to confirm mesothelin expression for inclusion criteria and for biomarker assessment unless a fresh biopsy is recommended due to archival biopsy quality.
- h. Biopsy will be performed at the earliest clinically feasible timepoint between Day 15 and Day 22. If the patient's medical condition does not allow for post-infusion biopsy collection between Day 15 and Day 22, then the investigators should try their best to collect the biopsy sample as soon as the patient's medical condition allows for the procedure within the Day 29 post-infusion timeframe.
- i. Within 14 days before the conditioning chemotherapy, or within 14 days before the TAK-103 infusion when conditioning chemotherapy is not administered.
- j. Contrast-enhanced CT or MRI should be performed 28 days, 2, 4, and 6 months after TAK-103 infusion for the first 6 months and every 3 months thereafter to 12 months, or more frequently if clinically indicated until the occurrence of iCPD or the start of subsequent antineoplastic therapy, whichever occurs first. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the medical record, and the further imaging of the patient may not be required. The same imaging modality (contrast enhanced CT or MRI and FDG-PET scan) should be used on a patient as at the screening visit and throughout the study. X-rays and bone scans may be performed on patients as clinically indicated. Response will be evaluated according to RECIST 1.1 and iRECIST.
- k. FDG-PET should be performed at pretreatment and 2 months after TAK-103 infusion (M3). After M3, PET can be acquired if clinically indicated until the occurrence of iCPD or the start of subsequent antineoplastic therapy, whichever occurs first. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the medical record, and the further imaging of the patient may not be required. The same imaging modality should be used on a patient as at the screening visit and throughout the study.
- l. (Not used.)
- m. All AEs and SAEs after initiation of LCT will be collected by the time of EOPF visit. During the period between signing Main ICF and LCT, [REDACTED] in the eCRF. [REDACTED] will be collected between the date of Prescreening ICF and the date of Main ICF.
- n. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent (the date of Prescreening ICF or the date of Main ICF, whichever comes first) through the EOPF visit. During the period between signing informed consent (the date of

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Prescreening ICF or the date of Main ICF, whichever comes first) and LCT, medications and procedures associated with reported AEs, immunosuppressive drugs and vaccines will only be collected and recorded in the eCRF.

o. Within 3 days before TAK-103 infusion

p. Within 28 days before the day of the leukapheresis procedures.

q. For women of childbearing potential, a serum beta-human chorionic gonadotropin pregnancy test will be performed at screening. A urine pregnancy test will be allowed for the rest of the visits. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

r. (Not used.)

s.

[REDACTED]

t. Sample collection can be skipped in case that LCT is not performed.

u. Sample will be collected 1 hour (± 0.5 hour) post-infusion.

v.

[REDACTED]

w. Peripheral blood smear assessment by microscopy will be performed at Screening, LCT(or Pre-TAK-103 Dose when preconditioning chemotherapy is not administered), D29, M3 and later visits.

x. Investigators should make sure that the patients do not have any signs of lymphoma and/or leukemia during Screening phase. If any evidence of or concern for lymphoma and/or leukemia including abnormalities in hematological findings, physical examination or imaging is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist. Investigators should carefully monitor the patients with available data (clinical symptoms, physical examination, hematological findings, CT, FDG-PET, etc.) to detect early signs of lymphoma and/or leukemia throughout the study. If any evidence of or concern for lymphoma and/or leukemia is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist and to perform intensive appropriate investigations and follow-up according to site standard practice.

y. The time window (± 7 days) applies to only Month 13. EOPF visit has no time allowance and is performed as soon as possible after discontinuation from Treatment and Primary Follow-up is decided.

z. Investigators must perform careful observation/palpation on superficial lymph nodes, skin, mucosa etc. to look for any signs of lymphoma and/or leukemia.

aa. Peritoneal or pleural fluids samples may be collected from patients that require drainage as clinically indicated. Up to 3 samples of fluids may be collected at any time when a procedure is being performed for a clinical indication. Optimal sample timepoints are 1 sample during screening/pre-treatment, 1 sample between D1-D29, and 1 sample in the M3-M4 timeframe. Fluid collection is at the discretion of the physician and should only be performed if clinically indicated as it should not be performed for the sole purpose of obtaining samples for this study.

bb. Obtain Prescreening ICF from patients when either archived sample or fresh biopsy will be used for the assessment of mesothelin expression in Prescreening phase. After a patient signs the Prescreening ICF, virus tests and FCM may be performed at the discretion of the investigator.

cc. Collect sample as baseline and measure as clinically indicated.

dd. Performed when an adverse event related to CAR-T therapy occurs or is suspected and clinically indicated.

ee. Within 28 days before the conditioning chemotherapy, or within 28 days before the TAK-103 infusion when conditioning chemotherapy is not administered.

ff. HBV DNA will be tested when positive HBcAb or HBsAb, and HCV RNA will be tested when positive HCVAb.

gg.

[REDACTED]

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Schedule of Events for Secondary Follow-up

Phase	Secondary Follow-up									
Procedure	M3 ^a	M4	M5	M7	M10	M13	M19	M25	M31	M37/ EOS ^a
	±7 D	±7 D	±7 D	±7 D	±14 D	±14 D	±14 D	±14 D	±14 D	±14 D
Physical examination ^o	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X							
ECOG performance status	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Fresh tumor and normal tissue biopsy										
Disease assessment ^b	X		X	X	X	X	X	X	X	X
FDG-PET scan ^c	X	As clinically indicated								
Brain MRI	As clinically indicated									
Cardiac telemetry	At the onset of Grade 2 or higher CRS until resolution to Grade ≤1, and additionally, as clinically indicated									
12-lead ECG	As clinically indicated									
AE reporting	Continuously ^{d,m}									
Monitoring of concomitant medications and procedures	Continuously ^e									
Monitoring of anti-cancer therapies after TAK-103 infusion	Continuously									
Laboratory Assessments										
Hematology/chemistry	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ^j	X ^j	X ^j	X ^j
Flow cytometry	As clinically indicated									
Thyroid hormone	X									
Coagulation	X	X	X							
Urinalysis	X	X								
Virus tests (HIV, HTLV, HBsAg, HBsAb, HBcAb, HCVAb, HBV DNA ^p , HCV RNA ^p , CMV DNA or CMV antigenemia)	As clinically indicated									
Pregnancy tests ^f	As clinically indicated									
Cellular Kinetics, Biomarker, Safety and Other Assessments										
Blood sample for DNA (RCR)		X		X		X	X ^j	X ^j	X ^j	X ^j
Blood sample for DNA (cellular kinetics) ^h	X	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q
Blood sample for DNA (TCR)	X		X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q

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Schedule of Events for Secondary Follow-up(continued)

Phase	Secondary Follow-up									
Procedure	M3 ^a	M4	M5	M7	M10	M13	M19	M25	M31	M37/ EOS ^a
	±7 D	±7 D	±7 D	±7 D	±14 D	±14 D	±14 D	±14 D	±14 D	±14 D
Blood sample for flow cytometry	X	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j

Unless otherwise noted, all tests must be completed before leukapheresis, conditioning chemotherapy and TAK-103 infusion on scheduled visits. Tests and procedures should be performed on schedule for all visits. For individual instances when assessments or procedures cannot be performed as defined in the protocol, the reasons for failing to perform those should be documented (e.g., identifying the specific limitation imposed by coronavirus disease 2019 that led to an inability to perform the protocol-specified visit, assessment, or procedure).

^a. One month is defined as 30 days. M3 (Month 3) indicates M3D1.

^b. Contrast-enhanced CT or MRI should be performed every 2 months from TAK-103 infusion for the first 6 months and every 3 months thereafter to 12 months, or more frequently if clinically indicated until the occurrence of iCPD or the start of subsequent antineoplastic therapy, whichever occurs first. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the medical record, and the further imaging of the patient may not be required. The same imaging modality (contrast enhanced CT or MRI and FDG-PET scan) should be used on a patient as at the screening visit and throughout the study. X-rays and bone scans may be performed on patients as clinically indicated. Response will be evaluated according to RECIST 1.1 and iRECIST.

^c. FDG-PET should be performed 2 months after TAK-103 infusion (M3). After M3, PET can be acquired if clinically indicated until the occurrence of iCPD or the start of subsequent antineoplastic therapy, whichever occurs first. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the medical record, and the further imaging of the patient may not be required. The same imaging modality should be used on a patient as at the screening visit and throughout the study.

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- d. During Secondary Follow-up phase, all SAEs (after the patient starts anti-cancer treatments following observation of PD, only SAEs related to study treatment and/or procedures must be reported) and the following AEs are collected and recorded in the eCRF:
1) new malignancies, 2) new incidence or exacerbation of a preexisting neurologic disorder, 3) new incidence or exacerbation of a preexisting rheumatologic or other autoimmune disorder, 4) new incidence of a hematologic disorder, 5) AEs that are considered by the investigator to be at least possibly related to therapy with TAK-103, 6) Positive RCR test (always considered and reported to be an SAE).
- e. During Secondary Follow-up phase, the concomitant medications and procedures associated with collected AEs are collected and recorded in the eCRF.
- f. A urine pregnancy test will be allowed for this phase. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.
- g. (Not used.)
- h. [REDACTED]
- i. (Not used.)
- j. Sample collection and testing may be stopped as directed by the sponsor.
- k. (Not used.)
- l. Peripheral blood smear assessment by microscopy will be performed at M3 and later visits.
- m. Investigators should carefully monitor the patients with available data (clinical symptoms, hematological findings, physical examination, CT, FDG-PET, etc.) to detect early signs of lymphoma and/or leukemia throughout the study. If any evidence of or concern for lymphoma and/or leukemia is detected, the investigators are encouraged to consult with a hematologist and/or dermatologist and to perform intensive appropriate investigations and follow-up according to site standard practice.
- n. The time window (± 14 days) applies to only Month 36. EOS visit has no time allowance and is performed as soon as possible after discontinuation from Secondary Follow-up is decided.
- o. Investigators must perform careful observation/palpation on superficial lymph nodes, skin, mucosa etc. to look for any signs of lymphoma and/or leukemia.
- p. HBV DNA will be tested when positive HBcAb or HBsAb, and HCV RNA will be tested when positive HCVAb.
- q. In Secondary Follow-up phase, sample collection and testing may be stopped at the discretion of the sponsor if TAK-103 cells are undetectable on 2 consecutive ddPCR tests.
- r. [REDACTED]

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Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (non-routine/non-standard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied products, and return all unused sponsor-supplied products to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D RECIST Version 1.1 and iRECIST

All sites of disease, target and non-target lesions, must be assessed at baseline. Objective disease status is to be recorded at each evaluation using the response categories and definitions provided in this section on the basis of RECIST 1.1[63] and iRECIST[64, 71].

All sites of measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target site of measurable lesions.

Disease Response Criteria for Target and Non-target Lesions

Evaluation of Target Lesions	
CR:	Disappearance of all target lesions.
PR:	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
PD:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
SD:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Evaluation of Non-target Lesions	
CR:	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/ SD:	Persistence of 1 or more non-target lesions or/and maintenance of tumor marker level above the normal limits.
PD:	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

Source: Eisenhauer et al. [63]

CR: complete response; LD: longest diameter; PD: progressive disease; PR: partial response; SD: stable disease.

The following table summarizes the overall response status calculation at each timepoint for patients who have measurable disease per RECIST 1.1 at baseline.

Timepoint Response: Patients With Target (± Non-target) Disease

Target Lesions	Nontarget Lesions	Unequivocal New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer et al. [63]

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

The following table summarizes the overall response status calculation at each timepoint for patients who have non-measurable (therefore non-target) disease at baseline.

Timepoint Response: Patients With Non-target Disease Only

Non-target Lesions	Unequivocal New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Source: Eisenhauer et al. [63]

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

^a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease because SD is increasingly used as endpoint for assessment of efficacy in some trial so to assign this category when no lesions can be measured is not advised.

Application of iRECIST[64, 71]: As described in Section 9.4.20, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue study treatment beyond initial RECIST 1.1-defined PD as long as they meet the criteria outlined in this section. All decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

The overall response according to iRECIST results from the combination of changes in target lesion (TL) and Non-TL, as well as the possible detection and change of new measurable and non-measurable tumor lesions. The objective response in the context of immunotherapy (with the prefix 'i' for immune-related) is differentiated into:

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- Complete Response (iCR), which describes the complete disappearance of TL and Non-TL as well as all new lesions. All lymph nodes must be non-pathological in size (< 10 mm in short axis diameter [SAD]).
- Partial Response (iPR), which occurs when the tumor load of the TL is reduced by $\leq 30\%$ compared to the baseline, or in the case of complete remission of the TL, when one or more Non-TL can still be distinguished.
- Stable Disease (iSD), which is to be determined if the criteria of iCR or iPR are not met and no tumor progression is present.

In case of a tumor progression, and in order to facilitate differentiation of true tumor progression from pseudoprogression in clinically stable patients, iRECIST proposes to determine first:

- unconfirmed Progressive Disease (iUPD) due to an increase in the sum of all TL by at least $\geq 20\%$ (but at least ≥ 5 mm) compared to the time point with the lowest TL sum (Nadir), or an unequivocal progression of Non-TL, or by the occurrence of new measurable and/or non-measurable tumor lesions.

This initially unconfirmed tumor progression might be confirmed by a subsequent follow-up where:

- confirmed Progressive Disease (iCPD) is present if further progress of the target sum (≥ 5 mm), or any further progress of the Non-TL, and/or progress of the new measurable and not measurable lesions either in number or in size (sum ≥ 5 mm).
if iUPD is not confirmed at subsequent timepoint and is interrupted by an iCR, iPR or iSD, the bar is reset and there needs to be another iUPD for iCPD to occur.

Comparison of definitions of RECIST 1.1 and iRECIST and assignment of timepoint response using iRECIST are provided in the tables below.

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥ 10 mm in diameter (≥ 15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥ 10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥ 5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

Source: Table 1 (modified), Seymour et al. [64]

iCPD: immune confirmed progression; iCR: immune complete response; iPR: immune partial response; iRECIST: immune Response Evaluation Criteria in Solid Tumors; iSD: immune stable disease; iUPD: immune unconfirmed progression; RECIST 1.1: Response Evaluation Criteria in Solid Tumors Version 1.1

“i” indicates immune responses assigned using iRECIST.

Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥ 5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥ 5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures > 5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥ 5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Source: Table 2, Seymour et al. [64]

iCPD: immune confirmed progression; iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progression; non-iCR/non-iUPD: criteria for neither CR nor PD have been met; iRECIST: immune Response Evaluation Criteria in Solid Tumors

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST.

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Appendix E ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, 1982 [72].

Appendix F Determination of High Tumor Burden

Patients with high tumor burden is determined according to the methods for each type of cancer shown below. The tumor burdens in patients with malignant peritoneal mesothelioma will be determined by the method for ovarian cancer.

1. Ovarian cancer

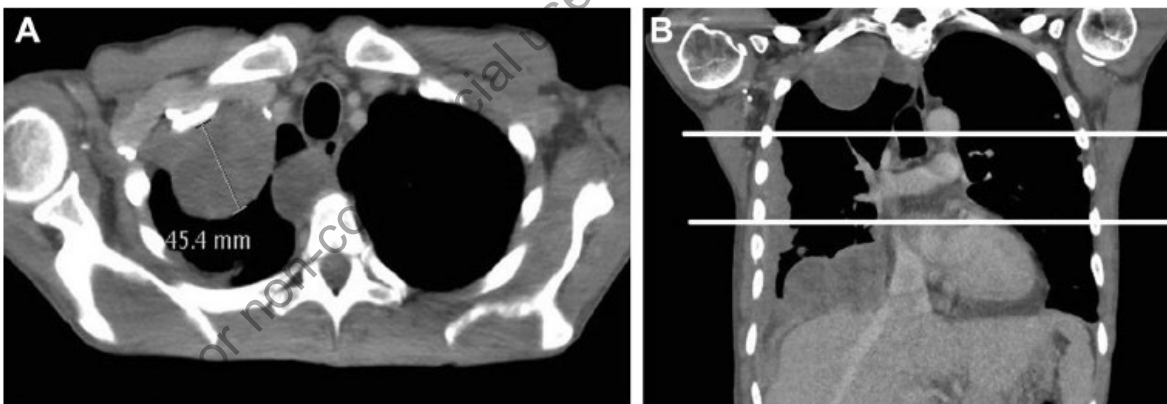
The maximum tumor diameter is greater than 6 cm among the radiographically measurable lesions as defined by RECIST 1.1.

2. Gastric cancer

The sum of the longest diameters of target lesions as defined by RECIST 1.1 is greater than 18 cm.

3. Malignant pleural mesothelioma

Axial (horizontal cross-section) CT images are used to measure the maximal tumor (pleura) thickness perpendicular to the chest wall or mediastinum. Measurement of the thickness of the tumor (pleura) is carried out for the upper third, the middle part, and the lower third of hemithorax. The upper part extends from the apex of the lung to the inferior margin of the arch of the aorta. The middle part is the pleura between the upper and lower parts. The lower part is pleural, including and inferior to the first image on which the left atrium is seen. The sum of the maximum tumor (pleura) thickness for each of the three parts is greater than 60 mm[73].



4. NSCLC

The sum of the longest diameters of target lesions as defined by RECIST 1.1 is greater than 21 cm.

Appendix G Bayesian Optimal Interval Design

The Bayesian Optimal Interval (BOIN) design will be used to guide the dose escalation decisions [74]. The dose escalation rules are detailed in Section 8.6.

The operating characteristics of the BOIN design are evaluated with simulations assuming various distributions of toxicity across dose levels shown in the table below.

Simulation Scenarios

Dose Level (CAR (+) cells/body)	True DLT rate						
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7
1×10^6 [starting dose at resumption]	0	0	0.1	0.2	0.3	0.4	0.4
3×10^6	0	0.1	0.2	0.3	0.45	0.5	0.4
1×10^7 [starting dose]	0.1	0.2	0.3	0.4	0.5	0.6	0.4
1×10^8	0.2	0.3	0.4	0.5	0.6	0.7	0.4
5×10^8	0.3	0.4	0.5	0.6	0.7	0.8	0.4

For each simulation, we suppose one patient treated in cohort 1 experienced DLT. And the size of each cohort is assumed to be 3, except 1) when patients are first treated in cohort 1 (the cohort size is assumed to be 4 in this case) and 2) when the number of remaining patients that can be enrolled is less than 3.

For the purpose of overdose control, doses j and higher levels will be eliminated from the further examination if $\Pr(p_j > 0.3 | \text{data}) > 0.90$ and at least 3 evaluable patients have been treated at the dose level j , where p_j is the true DLT rate of the dose level j .

1. Patients are treated at Cohort (-2) with at least 3 evaluable patients.
2. A dose is assigned to the next cohort of patients according to the rule below:
 - a) If the observed DLT rate at the current dose is ≤ 0.236 , escalate the dose to the next higher level.
 - b) If the observed DLT rate at the current dose is ≥ 0.359 , de-escalate the dose to the next lower dose level.
 - c) Otherwise, stay at the current dose.
3. Repeat Step 2 until 1) the maximum sample size (21 patients) is reached, or 2) Cohort (-2) (1×10^6 CAR (+) cells/body) is eliminated. In the latter case, no dose should be selected as the MTD.

The operating characteristics of the BOIN design are evaluated with 10,000 simulations of each scenario and presented in the following tables:

Operating Characteristics

	Scenario 1		Scenario 2		Scenario 3	
Dose Level (CAR (+) cells/body)	Selection %	# of Pts Treated	Selection %	# of Pts Treated	Selection %	# of Pts Treated
No MTD	0	-	0	-	2.8	-
1×10 ⁶ [starting dose at resumption]	0	3.00	2.8	3.42	12.7	5.69
3×10 ⁶	6.5	4.71	24.4	7.36	45.6	8.40
1×10 ⁷ [starting dose]	27.0	7.27	42.9	7.20	30.4	5.35
1×10 ⁸	30.0	3.53	18.4	2.18	5.9	0.90
5×10 ⁸	36.6	2.49	11.6	0.83	2.5	0.20
Expected # of Pts	21.0		21.0		20.53	

	Scenario 4		Scenario 5		Scenario 6		Scenario 7	
Dose Level (CAR (+) cells/body)	Selection %	# of Pts Treated	Selection %	# of Pts Treated	Selection %	# of Pts Treated	Selection %	# of Pts Treated
No MTD	11.5	-	30.7	-	58.0	-	57.2	-
1×10 ⁶ [starting dose at resumption]	32.0	8.54	50.8	10.97	34.3	9.76	27.9	8.99
3×10 ⁶	43.8	7.05	17.3	4.06	7.4	2.24	12.0	2.67
1×10 ⁷ [starting dose]	11.0	3.29	1.2	1.66	0.3	1.28	2.3	1.58
1×10 ⁸	1.4	0.25	0.1	0.04	0	0.00	0.4	0.07
5×10 ⁸	0.3	0.03	0.0	0.00	0	0.00	0.3	0.01
Expected # of Pts	19.17		16.73		13.28		13.33	

MTD: maximum tolerated dose

Appendix H Protocol History

Amendment History:

Date	Amendment Number	Region
5 April 2024	05	Japan
20 April 2023	04	Japan
30 June 2022	03	Japan
17 February 2022	02	Japan
16 September 2021	01	Japan
26 August 2021	Initial protocol	Japan

Protocol Amendment 04 Summary and Rationale:

The primary reasons for this amendment are to:

- Establish the Data Monitoring Committee and specify its role and responsibility.
- Set the time interval to separate each patient enrolled in every cohort as 28 days (or more) consistently.
- Add a new dose level cohort “Cohort (-2)” as a starting cohort at resumption and deleted the dose level cohort “Cohort 4: 1×10^9 CAR (+) cells/body.”
- Modify the dose escalation rule in accordance with the change of cohort structure.
- Add exclusion criteria to exclude patients with high tumor burden, current or history of interstitial lung disease, current or history of significant immune-related adverse events (irAEs), or impaired respiratory function.
- Add that cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) management will follow the management procedures of the sites with CRS/ICANS management manual for this clinical trial provided by the sponsor.
- monitoring instructions and rapid testing for pneumonitis, CAR-T cell therapy related adverse events (AEs) or irAEs and management including ad-hoc meeting between investigators and sponsor.
- Delete the restriction on the timing of archival tissue collection so that the tissue collected more than 6 months prior to leukapheresis can be used for mesothelin evaluation for the Prescreening Phase.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Deleted the language that patients with other cancer types than ovarian cancer, mesothelioma, gastric cancer or NSCLC may be enrolled.	Threshold to determine the high tumor burden for each type of cancer is set for those types of cancer and to minimize heterogeneity of types and to facilitate safety and efficacy assessment.	Sections 2.0 STUDY SUMMARY, 6.1 Overview of Study Design
Unified the time interval to separate each patient to be enrolled in each cohort and changed to 28 days (or more) from 14 days for first and second patients and 4 days for subsequent patients.	To secure time to adequately observe each and every patient in all cohorts before adding a next patient.	Sections 2.0 STUDY SUMMARY, 6.1 Overview of Study Design, 8.6 Dose Escalation Rules
Add a new lowest dose level cohort "Cohort (-2)" as a starting cohort at resumption, and deleted the highest dose level cohort "Cohort 4."	To better ensure safety of patients, especially at dosing resumption.	Sections 2.0 STUDY SUMMARY, 6.1 Overview of Study Design, 8.4 Study Drug Administration, 8.6 Dose Escalation Rules
Deleted the restriction on the timing of archival tissue collection so that the tissue collected more than 6 months prior to leukapheresis can be used for mesothelin evaluation for the Prescreening Phase.	To allow archival tissue to be available for mesothelin evaluation for eligibility regardless of the timing of its tissue collection.	Sections 2.0 STUDY SUMMARY, 7.1 Inclusion Criteria, 9.4.1 Prescreening Phase, 9.4.2 Screening Phase, 9.4.22.1 Primary Specimen Collection, 9.4.22.3 Biopsies, Appendix A Schedule of Events
Added criteria to exclude patients with high tumor burden at screening, current or history of interstitial lung disease, or current or history of history of significant irAEs related to treatment with immune checkpoint inhibitors. Patients with current or history of the following AEs can be enrolled after careful discussion between the investigator and sponsor: hyperglycemia/diabetes mellitus, thyroid disorder, hypopituitarism, hypoadrenocorticism, asymptomatic elevation in amylase/lipase, and Grade 1 or 2 skin toxicity. Modified the exclusion criterion on patients with cardiovascular and cardiopulmonary disease to exclude those with impaired respiratory function.	To exclude patients at risk of developing pneumonitis or irAEs.	Sections 2.0 STUDY SUMMARY, 7.2 Exclusion Criteria
Added new results from a toxicology study (cross reactivity study).	To update information on preclinical experience.	Section 4.1.3 Preclinical Experience

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Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Added a description on clinical experience of TAK-103 and a narrative of the patient enrolled thus far. Also, added pneumonitis to potential risks associated with TAK-103.	To update information on clinical experience and to include pneumonitis to potential risks associated with TAK-103.	Sections 4.1.4 Clinical Experience, 4.1.5 Potential Risks and Benefits
Added an explanation on the addition of a new lowest dose level cohort "Cohort (-2)" as a starting cohort at resumption.	To provide rationale for starting dose at resumption.	Section 4.2.1 Rationale for Starting Dose
Added language that CRS/ICANS management will follow the management procedures of the sites with CRS/ICANS management manual for this clinical trial provided by the sponsor.	To ensure CRS management be implemented properly at the site.	Sections 6.1 Overview of Study Design, 8.8 Precautions and Restrictions
Deleted language that CARTOX recommendations will be used for grading of toxicities associated with immune effector cell therapies.	The grading of CRS and ICANS follow ASTCT consensus.	Sections 8.5 Definitions of DLT, 9.4.14 Adverse Events, 10.1.2 SAE Definition
Changed the dose escalation rule.	To adjust to the change of cohort structure.	Section 8.6 Dose Escalation Rules
Added safety measures to be taken by the investigator against the possibility of occurrence of pneumonitis, CAR-T cell therapy related toxicities and irAEs following TAK-103 infusion.	To mitigate risk for occurrence of pneumonitis, CAR-T cell therapy related toxicities and irAEs after TAK-103 infusion and to provide additional information on management when they occur.	Section 8.8 Precautions and Restrictions, 16.0 REFERENCES
Added an instruction that final products for Cohort (-2), in addition to Cohorts (-1) and 1, should be administered after withdrawal of cell suspension from the bag.	To secure proper administration of final product for Cohort (-2).	Section 8.10 Preparation, Reconstitution, and Dispensation of TAK-103
Added language that patients who sign the prescreening ICF are allowed to undergo virus tests and flow cytometry during the Prescreening phase at the discretion of the investigator.	To allow flexibility of the timing of the tests for patients who sign the prescreening ICF.	Section 9.4.1 Prescreening Phase, Appendix A Schedule of Events

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Added CMV DNA or CMV antigenemia to virus tests at screening and when clinically indicated during the study.	To exclude patients with active CMV positive.	Section 9.4.17.1 Clinical Chemistry, Hematology, and Urinalysis, Appendix A Schedule of Events
Defined rapid cytokine measurement for safety purposes.	To enable the investigator to take immediate action against the event of or suspected pneumonitis, CAR-T cell therapy related toxicities, and irAEs.	Section 9.4.19 Rapid Cytokine Measurement (newly established section), Appendix A Schedule of Events
Removed FDG-PET at Day 29, Month 5, Month 7, and Month 13/ EOPF.	To ease the burden on patients to undergo FDG-PET.	Appendix A Schedule of Events
Added percutaneous SpO ₂ measurement on Day 11 and Day 15	To monitor SpO ₂ longer for pneumonitis.	Appendix A Schedule of Events
Excluded the results of brain MRI at screening from the radiographic images to be sent to the sponsor/designee.	To ease the administrative burden on the investigator.	Section 9.4.20 Disease Assessment
Updated specifications on the biopsy prior to preconditioning chemotherapy (or TAK-103 administration when preconditioning chemotherapy is not administered).	To clarify when/in what case a biopsy is needed.	Section 9.4.22.3 Biopsies, Appendix A Schedule of Events
Added sections for newly established committee and meeting and defined their purposes. Defined the details on the Data Monitoring Committee, e.g. the number of committee members and actions to be taken in the committee. Defined the details on the meeting, i.e., procedures to be taken in the event of an AE requiring careful attention.	To let the Data Monitoring Committee review the safety data and additional data. To manage AEs appropriately based on the available test results and expert opinion.	Sections 11.0 STUDY-SPECIFIC COMMITTEES, 11.1 Data Monitoring Committee, 11.2 Meeting for Careful Attention (newly established sections)
Modified the definition of CK analysis set; and newly defined "Immunogenicity-evaluable analysis set."	To clarify the definition of CK analysis set; and to enable immunogenicity evaluation.	Section 13.1.1 Analysis Sets
Added procedures for determination of high tumor burden that was newly added as an inclusion criterion of patients.	For the investigator to refer to the procedures when evaluating patient eligibility on the basis of patient's tumor burden.	Appendix F Determination of High Tumor Burden

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Changed the dose escalation rule.	To adjust to the change of cohort structure.	Appendix G Bayesian Optimal Interval Design

AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; CAR: chimeric antigen receptor; CAR-T: chimeric antigen receptor T cell; CARTOX: CAR-T-cell-therapy-associated TOXicity; CK: cellular kinetics; CMV: cytomegalovirus; CRS: cytokine release syndrome; DW-MRI: diffusion-weighted magnetic resonance imaging; EOPF: end of primary follow-up; FDG-PET: fluorodeoxyglucose-position emission tomography; ICANS: immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; irAE: immune-related adverse event; MRI: magnetic resonance imaging; NSCLC: non-small cell lung cancer; SpO₂: percutaneous oxygen saturation

Protocol Amendment 03 Summary and Rationale:

The primary reason for this amendment is to define Japan Drug, Product, or Device Used in the Clinical Trial other than IMP (J-non-IMP) to comply with the latest Japanese regulatory requirements.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 03		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Added investigational medicinal product (IMP) and Japan Drug, Product, or Device Used in the Clinical Trial other than IMP (J-non-IMP) to the abbreviations list.	To define the abbreviations that are to be used in the protocol to comply with the latest Japanese regulatory requirements.	Section 3.2 List of Abbreviations
Defined J-non-IMP and added instructions for its proper management at the clinical site. Added a description that the reference safety information for the J-non-IMPs is their package insert to be provided by the sponsor.	To comply with the latest Japanese regulatory requirements.	Section 8.13 Japan Drugs, Products and/or Devices Used in the Clinical Trial other than Investigational Medicinal Product (J-non-IMP)
Added a description on the procedure for the sponsors to obtain archived samples or tissues in the event of a serious adverse event with the confirmation of the consent of the subject or a subject's legally acceptable representative.	To clarify the procedure for the sponsors to obtain archived samples or tissues for reasonable reason in the event of a serious adverse event with the confirmation of the consent of the subject or a subject's legally acceptable representative.	Section 10.2 Procedures for Recording and Reporting AEs and SAEs

Protocol Amendment 02 Summary and Rationale:

The primary reason for this amendment is to include:

■ [REDACTED]

- procedures for patient transfer to another study site for TAK-103 administration and protocol-specified procedures thereafter.
- criteria for stopping sample collections for biomarker assessments.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		Sections Affected by Change
<i>Description</i>	<i>Rationale</i>	<i>Location</i>
Decreased age criterion for inclusion at enrollment.	To align with change in Adult Country Definition.	Sections 2.0 STUDY SUMMARY, 7.1 Inclusion Criteria
Reorganize the explanatory language for the reuse of archival tumor tissue sample obtained within 6 months prior to leukapheresis for rescreening.	To clarify that previous mesothelin assay result analyzed by Takeda validated assay using archival sample obtained within 6 months prior to leukapheresis is available for mesothelin evaluation for eligibility.	Section 9.4.1 Prescreening phase
Added “iRECIST” for another criteria to be used for disease assessment.	For clarification.	Section 9.4.19 Disease Assessment
Added a piece of literature for DW-MRI.	For clarification.	Sections 9.4.20 MRI, 16.0 REFERENCES
Deleted the description “biomarker assessment” from the intended use of archival tumor tissue sample.	To clarify that the archived sample is used not for biomarker assessment but for mesothelin evaluation.	Section 9.4.21.1 Primary Specimen Collection, Table 9.c
Changed the wording from “samples” to “samples for ddPCR.”	For clarification.	Section 9.4.22.1 Droplet Digital Polymerase Chain Reaction and Flow Cytometry
Added explanatory language for recruiting subjects and transferring potentially eligible patients to another site for part of protocol-specified procedures.	To recruit subjects who need to undergo part of protocol-specified procedures at another study site; and to clarify the procedures.	Section 9.4.25 Patient Transfer
Revised/added criteria for stopping sample collections for biomarker measurements (cytokines/chemokines, RCR, TCR, immunophenotyping, proteins, ctDNA/RNA, and immunogenicity).	To specify/clarify stopping rules of these biomarker samplings.	Sections 9.4.23 Biomarker and Pharmacodynamic Measurements, 9.4.28 Immunogenicity Sample Collection Appendix A Schedule of Events, Schedule of Events for Primary Follow-up (footnote “r”), Schedule of Events for Secondary Follow-up (footnotes “g, i, j, and k”)

CT: computed tomography; ctDNA: circulating tumor DNA; ddPCR: droplet digital polymerase chain reaction; DW-MRI: diffusion-weighted magnetic resonance imaging; FDG-PET: fluorodeoxyglucose-position emission tomography; iRECIST: immune Response Evaluation Criteria in Solid Tumors; MRI: magnetic resonance imaging; RCR: replication competent retrovirus; TCR: T-cell receptor

Protocol Amendment 01 Summary and Rationale:

The primary reason for this amendment is to incorporate recent feedback from the Pharmaceuticals and Medical Devices Agency (PMDA).

Several small changes are also included to resolve minor discrepancies between the text/table and Schedule of Events (SOE) in Appendix A; and between the SOE for Primary Follow-up and the SOE for Secondary Follow-up in Appendix A.

Changes in Amendment 01

- Added 'T -cell lymphoma' as a potential risk associated with TAK-103 in Section 4.1.5 "Potential Risks and Benefits."
- Deleted descriptions regarding subject's legally acceptable representative in Sections 15.2 "Subject Information, Informed Consent, and Subject Authorization" and Appendix B "Responsibilities of the Investigator."
- Added following modifications in Table 9.c in Section 9.4.21.1 "Primary Specimen Collection" to be aligned with the SOE (Appendix A):
 - Blood sample for TAK-103 transgenes (CK): Deleted 'Baseline' from the sampling time points.



- Blood sample for immunophenotyping: Replaced 'Pre-screening' with 'Screening' as a sampling time point.
- Serum Sample for immunogenicity: Replaced 'Pre-screening' with 'Screening' as a sampling time point.
- Plasma Sample for ctDNA: Replaced 'Pre-screening' with 'Screening' as a sampling time point and added D1.
- Added following modifications in the SOE for Secondary Follow-up to align with the SOE for Primary Follow-up:
 - Blood sample for DNA (RCR): Deleted 'X' from M3 and added 'X' to M4.
 - Blood sample for DNA (TCR): Added 'X' to M5 and M10.
 - Blood sample for immunophenotyping: Deleted 'X' from M4.