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An investigator-initiated Phase I trial of an armored and GPC3-targeted autologous CAR T-cell infusion C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer

Principal Investigator:

Principal Study Institution:

Collaborator: Shanghai AbelZeta Ltd.

Clinical study protocol signature page

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Signature page (Collaborator)

I will strictly follow the Declaration of Helsinki, the principles of GCP, the principles of ICH-GCP and the established clinical study protocol, and earnestly fulfill my responsibilities as a collaborator. Agree with and be familiar with this protocol design and regulations to carry out this clinical study.

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I have been familiar with the clinical study protocol and confirm that the protocol includes the necessary contents for the protocol implementation. I will carry out this study and perform my investigator duties in strict accordance with the Declaration of Helsinki, GCP principles, ICH-GCP principles and established clinical study protocol.

Principal Investigator: signature: date:

Study Institutions:

Address:

Phone:

E-mail:

Brief Title:

A Phase I study to evaluate C-CAR031 in GPC3+ advanced/metastatic squamous cell lung cancer
Study Phase: I

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**

Overall Rationale for the Modification:

Not applicable.

Summary of Changes:

List of Substantial Modifications

Section # and name	Description of change	Brief rationale
not applicable		

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Special Term	Explanation
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic Lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
ANC	Absolute neutrophil count
Anti-HBc	Anti-hepatitis B core antibodies
Anti-HBs	Anti-hepatitis B surface antibodies
Anti-HCV	Anti-hepatitis C virus antibodies
ASTCT	American Society for Transplantation and Cellular Therapy
AST	Aspartate aminotransferase/transaminase
AUC	Area under the curve
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CAR	Chimeric antigen receptor
CBC	Complete blood cell count
CDE	Center for drug evaluation
CDx	Companion diagnostics
CI	Confidence interval
CK	Cellular kinetics
C_{last}	Last measurable concentration
C_{max}	Maximum observed concentration
CNS	Central nervous system
COA	Certificate of analysis
CPIs	Checkpoint inhibitors
CR	Complete response
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSCO	The Chinese Society of Clinical Oncology
CSP	Clinical study protocol

CSR	Clinical study report
ctDNA	Circulating tumor deoxyribonucleic acid
CTLA-4	Cytotoxic T lymphocyte associated protein 4
DB	Direct bilirubin
DCR	Disease control rate
DIC	Disseminated intravascular coagulation
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dnTGFβRII	Dominant-negative transforming growth factor-beta receptor II
DoR	Duration of response
DRR	Durable response rate
DUS	Disease under study
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMT	Epithelial mesenchymal transition
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
GCP	Good clinical practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPC3	Glypican-3
Hb	Hemoglobin
HBA1c	Haemoglobin A1c
HBS	Human biological sample(s)
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
HL	Hy's Law
HLH	Haemophagocytic lymphohistiocytosis
HR	Hazard ratio
IB	Investigator's brochure
ICF	Informed consent form
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell encephalopathy
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent review committee
IRR	Infusion-related reaction
ISH	In Situ Hybridization
IIT	Investigator initiated trial
IV	Intravenous
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
LDLE	Lymphoepithelioma-like carcinoma
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal to epithelial transition factor
MCV	Mean corpuscular volume
MS	Mass spectrometry
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Non evaluable
NIMP	Non-investigational Medicinal Product
NL	New lesion
NMPA	National Medical Products Administration

NOAEL	No Observed Adverse Effect Level
NSCLC	Non–small cell lung cancer
NTL	Non-target lesion
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PET	Positron emission tomography
PHL	Potential Hy's Law
PD	Progressive disease
PD	Pharmacodynamics
PD1	Programmed death 1
PD-L1	Programmed death ligand 1
PDX	Patient-derived xenograft
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLT	Platelet
PR	Partial response
PS	Performance status
PSMA	Prostate-specific membrane antigen
PT	Preferred term
PCR	Polymerase chain reaction
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumours
RCL	Replication-competent lentivirus
RMP	Risk management plan
RNA	Ribonucleic acid
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
scFv	Single chain variable fragment
SD	Stable disease
SIN	Self-inactivated
SoA	Schedule of activities
SoC	Standard of care
SOC	System organ class
SRC	Safety Review Committee

TBL	Total bilirubin
SUSAR	Suspected unexpected serious adverse reaction
TACE	Transarterial-chemoembolization
TEAE	Treatment-emergent adverse event
TGFβ	Transforming growth factor-beta
TKI	Tyrosine kinase inhibitors
TL	Target lesions
T_{last}	Time of last measurable concentration
TLS	Tumor lysis syndrom
T_{max}	Time to reach maximum concentration
TPS	Tumor proportion score
TRAE	Treatment-related adverse event
QTc	Corrected QT interval
TTR	Time to response
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

An investigator-initiated Phase I trial of an armored and GPC3-targeted autologous CAR T-cell infusion C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer

Brief Title:

A Phase I study to evaluate C-CAR031 in GPC3+ advanced/metastatic squamous cell lung cancer

Rationale:

Glypican-3 (GPC3) is present on non–small cell lung cancer (NSCLC) tumor cells (23% of expression), further studies have shown that the positive expression is significantly higher in squamous cell lung cancer (55% of expression) than that in adenocarcinoma (8% of expression) and virtually absent in normal adult tissues, making it an ideal target for chimeric antigen receptor (CAR) T-cell therapy (Aviel-Ronen et al 2008[1]). In addition, some studies have shown that GPC3 expression is significantly associated with poor prognosis of squamous cell lung cancer patients (Ning et al 2021[2]).

C-CAR031 is an autologous CAR T-cell product that expresses a CAR specific for GPC3 and a dominant-negative transforming growth factor-beta receptor II (dnTGFβRII) as an armoring strategy. Expression of dnTGFβRII can block TGFβ signaling, protecting CAR-T cells from the immunosuppressive effect of this cytokine. Early clinical data of C-CAR031 has shown promise in an ongoing, open label, investigator-initiated Phase I trial (NCT05155189) to evaluate the safety and efficacy C-CAR031 in patients with advanced hepatocellular carcinoma (HCC) (Zhang et al 2024[3]). C-CAR031 is well tolerated in all the dose levels being explored. No grade 5 treatment-related adverse event (TRAE), dose-limiting toxicity (DLT) and immune effector cell-associated neurotoxicity syndrome (ICANS) were observed. Cytokine release syndrome (CRS) was observed in 22 (91.7%) participants with only 1 (4.2%) Grade 3 CRS. All CRS events were started within the first week post the infusion and resolved within 3 to 6 days of onset. C-CAR031 mono therapy demonstrated an objective response rate (ORR) of 56.5% across all dose levels and the ORR in the 4.0 $\times 10^6$ CAR-T cells/kg dose cohort was 75% (6/8). The median target lesion reductions achieved 42.2% and the deep target lesion shrinkage can be observed in intra and extrahepatic lesions (70.8% of the participants have tumor lesions in lung). The median duration of response (DoR) was 7.4 months. Though there were 70.8% of participants had lung metastatic lesions, the pulmonary complications were not a safety concern in the HCC investigator-initiated trial (IIT). These data led to the hypothesis underlying this study: C-CAR031 mono therapy would provide clinical benefit with tolerable safety in GPC3 expression solid tumors which supports the exploration of C-CAR031 in squamous cell lung

cancer.

Objectives and Endpoints:

Table 1 Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Safety	• To assess the safety and tolerability of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer • To determine the RDE (Phase Ia)	• Incidence of AEs/SAEs/AESIs • Incidence and severity of DLTs (Safety run-in section of Phase Ia) • Changes from baseline in vital signs, physical examination, ECOG score, 12-lead ECGs, laboratory parameters that are abnormal and of clinically significance.
Secondary		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Efficacy	To estimate the anti-tumor activity of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• ORR, DCR, DoR, DRR, TTR, PFS and change in tumor size assessed by the investigator and evaluated according to RECIST 1.1 criteria • OS
Pharmacokinetics	To investigate the CK of C-CAR031 by PCR in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Quantification of CAR copies/μg DNA of C-CAR031 in peripheral blood • CK parameters of C-CAR031, including but not limited to T_{max}, C_{max}, $AUC_{0\text{-}28d}$, T_{last}, C_{last}, and AUC_{last}, as data allows
Safety	To assess the safety of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Presence of RCL in peripheral blood samples.
Exploratory		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Pharmacokinetics	To investigate the CK of C-CAR031 by flow cytometry in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Quantification of C-CAR031 CAR-T cells in peripheral blood • CK parameters of C-CAR031, including but not limited to T_{max}, C_{max}, $AUC_{0\text{-}28d}$, T_{last}, C_{last}, and AUC_{last} as data allows
Immunogenicity	To assess the immunogenicity of C-CAR031	• Evaluation of humoral immunogenicity against C-CAR031: incidence, and antibody levels as data allows.
Biomarkers	To assess intra-tumoral biomarkers of disease, pharmacodynamic biomarkers and biomarkers of clinical response to C-CAR031	• Presence or changes in tumoral biomarkers including, but not limited to levels of RNA, DNA, and protein analytes as well as imaging measurements. Specific assessments may include, but not be limited to expression of GPC3, immune markers (for example TGFβ, PD-L1, CD8) and CAR-T infiltration.

Biomarkers	To assess systemic biomarkers of disease, pharmacodynamic biomarkers and biomarkers of clinical response to C-CAR031	• Presence and changes in peripheral DNA, RNA, immune cell phenotype, and protein biomarkers, which may include, but not limited to ctDNA, soluble and cellular analytes, gene expression, and immune markers pre- and post-treatment or on disease progression.

AEs = adverse events; AESIs = adverse events of special interest; AUC_{last} = area under the curve from time 0 to the time of the last quantifiable concentration; AUC_{0-28d} = area under the curve 28 days after C-CAR031 infusion; CAR = chimeric antigen receptor; CD8 = cluster of differentiation 8; CK= cellular kinetics; C_{max} = maximum observed concentration; C_{last} = last measurable concentration; ctDNA = circulating tumour DNA; DCR = disease control rate; DLTs = dose-limiting toxicities; DNA= deoxyribonucleic acid; DoR = duration of response; DRR = durable response rate; ECG = electrocardiogram; ECOG= Eastern Cooperative Oncology Group; GPC3 = glypican-3; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PCR = polymerase chain reaction; RCL = replication-competent lentivirus; RDE = recommended dose for expansion; RECIST = Response Evaluation Criteria in Solid Tumours; RNA = ribonucleic acid; PD-L1= programmed death ligand 1; SAEs = serious adverse events; TGFβ = transforming growth factor-beta; T_{last} = Time of C_{last}; T_{max} = time to reach maximum concentration; TTR = time to response.

Overall Design Synopsis:

This single-arm, open-label, multicenter, Phase I study will evaluate the safety, tolerability, anti-tumor activity, pharmacokinetics (PK)/pharmacodynamics (PD), biomarker, and immunogenicity of C-CAR031 in adult participants with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of prior systemic treatment including immune checkpoint inhibitors (CPIs) and platinum-based doublet chemotherapy, concurrently or sequentially. The study will be divided into two sections: safety run-in and backfill phase (Phase Ia) and dose expansion phase (Phase Ib). Phase Ia will determine the recommended dose for expansion (RDE) to be used in Phase Ib (dose expansion) of the study and evaluate the safety and efficacy in participants with GPC3 expression. Phase Ib will further evaluate the safety, tolerability, cellular kinetics (CK), biomarker, immunogenicity and efficacy of C-CAR031 at the RDE.

The study will be conducted in the following steps: Participants will undergo pre-screening, screening, apheresis, bridging therapy (if appropriate) and lymphodepletion before receiving CAR T-cell (C-CAR031) infusion. Subsequent follow-up after C-CAR031 infusion is divided into three stages: Stage 1, 2, and 3.

In Stage 1, participants will be followed up to 6 months post C-CAR031 infusion. Participants who have not progressed, discontinued prematurely from the study or started a new anticancer regimen will continue the follow-up in Stage 2 for up to 12 months post C-CAR031 infusion or until disease progression, or discontinued prematurely from the study or started a new anticancer regimen, whichever occurs first. Stage 3 is considered long term follow up (LTFU) up to 15 years post C-CAR031 infusion based on the participants' willingness and will be offered to all participants who received any dose of C-CAR031 infusion.

Brief Summary:

The purpose of this study is mainly to evaluate the safety, tolerability, CK and anti-tumor efficacy of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer. The study is divided into: safety run-in and backfill phase (Phase Ia) and dose expansion

phase (Phase Ib).

Eligible participants will undergo apheresis, bridging therapy (if appropriate), and lymphodepletion before receiving one dose of C-CAR031 on Day 0. Following C-CAR031 infusion, participants will remain hospitalized for a minimum of 7days.

Participants will complete all assessments as indicated in the Scheme of Activity (SoA) through 6 months post C-CAR031 infusion, unless they experience disease progression, start a new anticancer regimen or discontinue due to participant or investigator decision, whichever occurs first (see Section 7.2.2). Participants who received C-CAR031 discontinue prematurely from the study in Stage 1 will undergo an early discontinuation visit (see SoA Table 2) and be offered to move to Stage 3 of the study (see SoA Table 3) for continued safety surveillance. The LTFU will start in Stage 3 of this study. After Stage 1 follow-up, participants who have not previously progressed, discontinued prematurely from the study or started a new anticancer regimen will continue to be followed in Stage 2 of the study for safety, efficacy, CK, immunogenicity and exploratory biomarkers up to 12 months post C-CAR031 infusion or until disease progression, start of new anticancer treatment, or discontinuation due to participant or investigator decision, whichever occurs first (see Figure 3, SoA Table 2, and Section 7.2.3). Participants who progress, start new anticancer treatment, or discontinue prematurely from the study in Stage 2 will undergo an early discontinuation visit and be offered to move to Stage 3 of the study (see SoA Table 3).

At the end of the main study, defined as 12 months after the last participant has received his/her dose of C-CAR031(or sooner if: all the participants have progressed or stated a new anti-cancer therapy or death occurred, or have either withdrawn or are lost to follow-up, or investigator and AbelZeta aligned to terminate the study), all study participants who received any dose of C-CAR031 infusion will be offered to transition to Stage 3 long-term follow-up up to 15 years post C-CAR031 based on their willingness.

Disclosure Statement: This is a multicenter, single-arm, open-label,treatment, Phase I study.

Number of Participants:

Approximately 47~62 GPC3+ squamous cell lung cancer participants (assuming 20% of dropout rate due to the failures in apheresis, lymphodepletion, and manufacturing processes, etc.) will be enrolled to yield approximately 37~49 evaluable participants (up to 25 in Phase Ia, which is finally based on the practical escalated dose, and approximately 12 each cohort in Phase Ib, which will be adjusted based on the results of Phase Ia).

Study Arms and Duration:

This is a single-arm study with one infusion of C-CAR031. Prior to receiving C-CAR031, participants will undergo prescreening and screening (which may occur in parallel), apheresis (see Section 6.1.1), bridging therapy (if appropriate; see Section 6.1.2) and lymphodepletion (see Sections 6.1.3). Following C-CAR031 infusion (see Section 6.1.4), participants will remain hospitalized for a minimum of 7 days. The dose-limiting toxicity (DLT) observation period in Phase Ia (safety run-in section) is 28 days post C-CAR031-infusion.

The follow-up period is divided into stage 1,2,3 which lasts for up to 6 months, 12 months and

15 years post C-CAR031 infusion (see Section 4.1).

Data Monitoring Committee/Other Committee: Yes

A safety review committee (SRC) will be appointed to review emerging data for the study.

Phase Ia (safety run-in): The first 1~6 participants of each dose level will be evaluated as safety run-in phase. The SRC will review the totality of all adverse events (AEs), serious adverse events (SAEs), and laboratory safety data for participants in the DLT period and all other available relevant data prior to adjudicating on dose-escalation decisions according to the protocol (see Section 6.6.1).

After each dose level during the safety run-in section (Phase Ia) of the study, once there are at least 3 evaluable participants (1 participant in dose level 1), the SRC will evaluate the safety, efficacy, tolerability, available CK and other available data of C-CAR031 to decide the dose for the next cohort of participants. SRC can suggest exploration of intermediate dose levels or additional higher or lower dose levels based on the available data but will not exceed the 3 times the current dose or the highest dose that has been determined safe by SRC (no more than 6.0 $\times 10^6$ CAR-T cells/kg). If 1 out of the first 3 participants or 2 out of the first 6 participants (the first participant of dose level 1) in a dose cohort experience the DLT, the SRC cannot recommend a dose escalation to doses exceed this current dose cohort.

Phase Ia (backfill): The SRC will evaluate the safety, efficacy, tolerability, available CK and other available data of C-CAR031 at not only the preset dose levels (0.75 $\times 10^6$ CAR-T cells/kg , 1.5 $\times 10^6$ CAR-T cells/kg and 4.0 $\times 10^6$ CAR- T cells/kg) but also the recommended additional intermediate/higher dose levels (Not exceeding 3 times the current dose or the highest dose that is determined safe by SRC) to determine the RDE of Phase Ib. Backfill will stop when up to 12 evaluable participants have been filled in each dose level. The SRC can decide the early termination of the backfill phase of each dose level after the evaluation of available data and/or further explore additional intermediate/higher dose levels. And if a new dose is to be explored, repeat the above steps of safety run-in of Phase Ia. The SRC will evaluate the safety, efficacy, tolerability, available CK and other available data of C-CAR031 at the new dose level to determine whether to continue to backfill phase.

The SRC will determine the RDE based on the safety, efficacy, tolerability, available CK and other available data of Phase Ia and further evaluate the safety and efficacy in participants with GPC3 expression squamous cell lung cancer in phase Ib.

Phase Ib (Dose expansion): Once RDE is determined by the SRC in Phase Ia, participants may be enrolled in Phase Ib at the RDE. If the SRC recommended more than one dose level as RDEs, approximately 12 evaluable participants will be enrolled in each RDE to further evaluate the safety, tolerability, CK, biomarker, immunogenicity and efficacy of C-CAR031 in squamous cell lung cancer participants with GPC3 expression.

The SRC will also be responsible for reviewing on a regular basis all safety data beyond the DLT period in the study and can determine the numbers of participants with different levels of GPC3

expression in each dose group based on enrollment.

Statistical Methods:

For purposes of analysis, the study populations are defined as provided in Table 20. Safety and tolerability will be assessed in terms of AEs/SAEs, adverse events of special interest (AESIs), DLTs (Phase Ia safety run-in only), vital signs, laboratory data, physical examinations and 12-lead electrocardiogram (ECG) changes, and replication-competent lentivirus (RCL) in peripheral blood. All safety analyses (other than DLT) will be performed on the safety analysis set (SS) and full analysis set (FAS). For the safety run-in phase in Phase Ia, DLTs analyses will be performed on the DLT evaluable analysis set (DLTAS).

The first cohort is treated with a starting dose which is considered safe based on extrapolation from other ongoing IIT, and the subsequent cohorts are treated at dose levels recommended by SRC which will not exceed 3 times the current dose level or the highest dose that is determined safe by SRC (no more than 6.0×10^6 CAR-T cells/kg). If 1 out of the first 3 participants or 2 out of the first 6 participants (the first participant of dose level 1) in a dose cohort experience the DLT, the SRC cannot recommend a dose escalation to doses exceed this current dose cohort.

For the backfill phase in Phase Ia and the dose-expansion cohorts in Phase Ib safety and preliminary efficacy will be assessed. The dose for further study in the future will be selected in consultation with SRC based on an assessment of safety and preliminary efficacy data and all relevant clinical and nonclinical data available at that time.

The assessment of efficacy endpoints will be conducted in efficacy analysis set (EAS), FAS and SS. Supplementary analysis will be performed in additional analysis sets as outlined in Table 20.

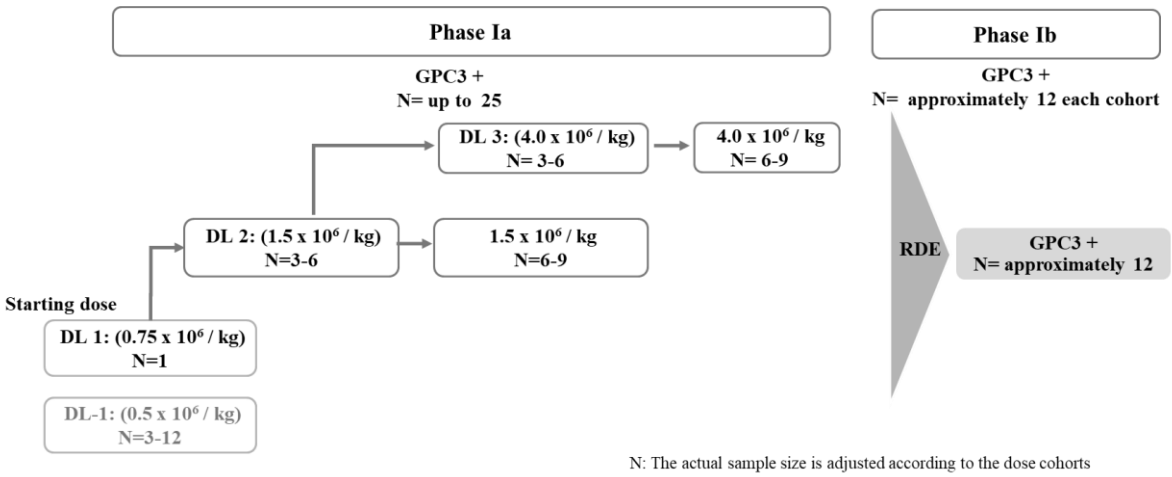
Data will be presented by dose level; No direct statistical comparisons will be made between any 2 dose levels.

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Time-to-event variables will be summarized using Kaplan-Meier estimates.

1.2 Schema

The study design is shown in Figure 1. Participants will flow through the study from pre/screening to CAR T-cell infusion and subsequent follow-up (see Figure 2). Participants will undergo follow-up for safety, efficacy, CK, immunogenicity and biomarker analysis as described in Figure 3.

Figure 1 Study Design

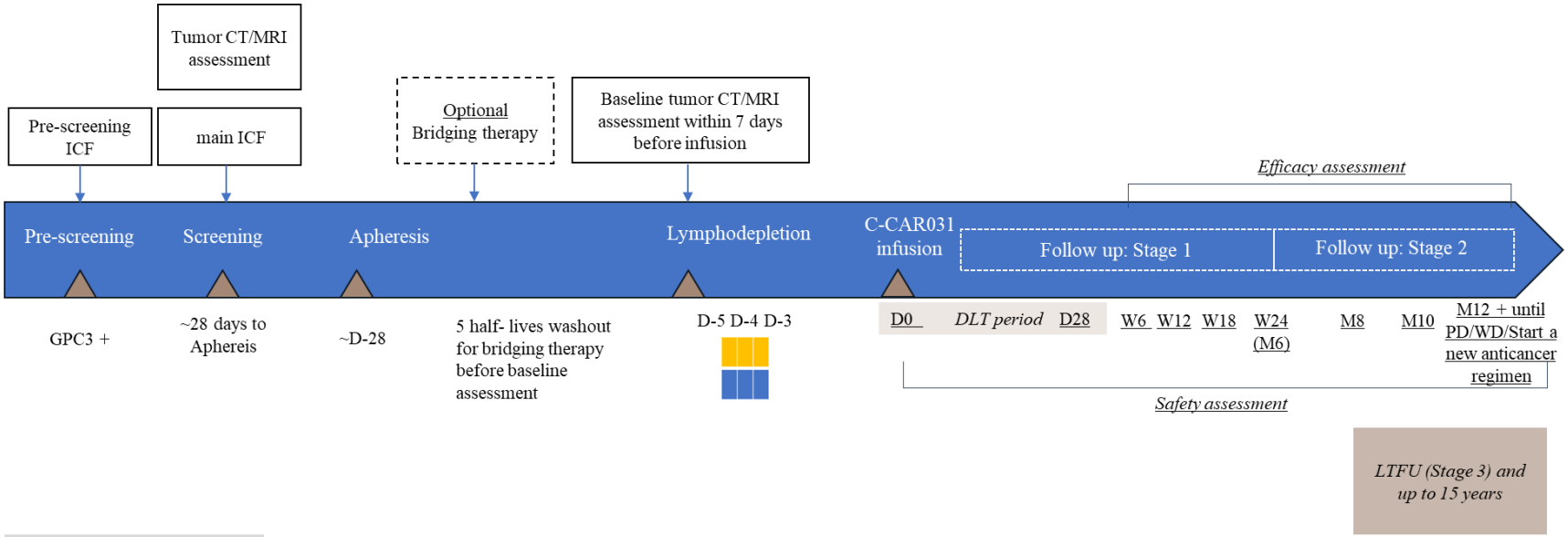


Note: Additional intermediate or higher dose level may be recommended by SRC.

More than one RDEs may be recommended by SRC.

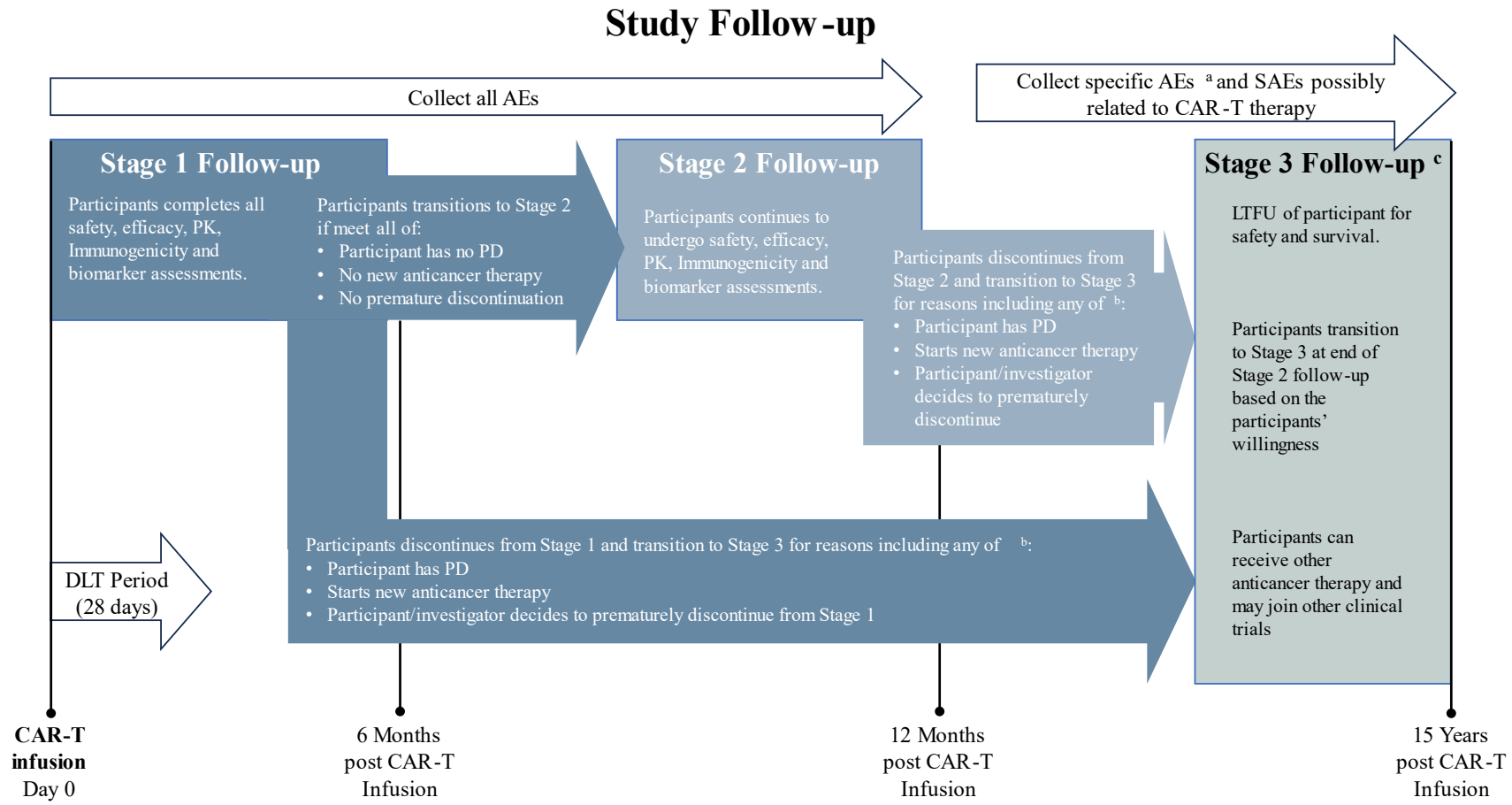
DL = dose level; GPC3 = glypican-3; N = the number of evaluable participants as defined by the protocol; RDE = recommended dose for expansion.

Figure 2 Participant Flow Through the Study – Phase Ia and Phase Ib



CT = computed tomography; D = day; DLT = dose-limiting toxicity; GPC3 = Glypican-3; ICF = informed consent; LTFU = long-term follow-up; M = month; MRI = magnetic resonance imaging; PD = progressive disease; W = week; WD = withdrawal.

Figure 3 Follow-up Schema for Stages 1-3



[a] For specific AEs, refer to Section 8.4.7
[b] Refer to Section 7.2.2 and Section 7.2.3 for full details on participant discontinuation from Stage 1 and 2 of the study
[c] LTFU commences in Stage 3 of the CSP. AEs = adverse events; CAR = chimeric antigen receptor; CSP = clinical study protocol; DLT = dose-limiting toxicity; LTFU = long-term follow-up; PD = progressive disease; SAE = serious adverse even.

1.3 Schedule of Activities

See Table 2 and Table 3 for the Schedule of Activities.

Table 2 Schedule of Activities - Pre-screening to Stage 2 Follow-up

Procedure/Schedule	Pre-Screening period	Screening	Apheresis	Baseline	LDC			Infusion eligibility	Cell Infusion	Stage 1 follow-up[1]										Stage 2 follow-up[1]			Early discontinuation[1]	Refer to CSP section
Study Day		≤28 days before Enrollment	Enrollment	D-7	D-5	D-4	D-3	D-2, D-1	D0	D1 (W1)	D4 (W1)	D7 (W1)	D10 (W2)	D14 (W2)	D21 (W3)	D28 (W4)	W6	W12	W18	M6	M8	M10	M12		
Procedure Window (days)	N/A	N/A	N/A	±2	0	0	0	N/A	N/A[2]	0	±1	±1	±1	±1	±2	±2	±7	±7	±7	±7	±14	±14	±14		
Enrollment																								
Informed pre-screening consent	×																							5.1.1 A2
Informed consent		×																						5.1.2 A2
Inclusion/Exclusion criteria		×	×[3]																					5
Pre-Assessment of Peripheral white blood cell collection[4]			×																					6.1.1
Pre-Assessment of Lymphodepleting Chemotherapy				×[5]																				6.1.3
Eligibility check prior to C-CAR031								×																6.1.4.1
Pre-screening																								
Tumor Sample for GPC3 IHC Test	×																							8.9.1.2
Baseline characteristics and medical history																								
Baseline characteristics		×																						8.1

Procedure/Schedule	Pre-Screening period	Screening	Apheresis	Baseline	LDC			Infusion eligibility	Cell Infusion	Stage 1 follow-up[1]										Stage 2 follow-up[1]			Early discontinuation[1]	Refer to CSP section
Study Day		≤28 days before Enrollment	Enrollment	D-7	D-5	D-4	D-3	D-2, D-1	D0	D1 (W1)	D4 (W1)	D7 (W1)	D10 (W2)	D14 (W2)	D21 (W3)	D28 (W4)	W6	W12	W18	M6	M8	M10	M12		
Procedure Window (days)	N/A	N/A	N/A	±2	0	0	0	N/A	N/A[2]	0	±1	±1	±1	±1	±2	±2	±7	±7	±7	±7	±14	±14	±14		
Medical/disease History		×																						8.1
Concomitant Medications		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	6.9
Study intervention																								
Apheresis			×																					6.1.1
Bridging Therapy			×[6]																					6.1.2
Lymphodepleting Chemotherapy					×	×	×																	6.1.3.2
Pre-C-CAR031 infusion medication									×[7]															6.1.4.1.2
C-CAR031 infusion									×															6.1.4.2
Physical assessment																								
Height/Weight[8]		×	×	×[5]				×								×[9]	×[9]	×[9]	×[9]	×[9]	×[9]	×[9]	×[9]	×[9]	8.3.1
Full physical examination		×		×[5]																			×	×	8.3.1
Brief physical examination			×		×	×	×	×	×[24]	×	×	×	×	×	×	×	×	×	×	×	×	×			8.3.1
Vital Sign		×	×[3]	×[5]	×[11]	×[11]	×[11]	×	×[10]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	8.3.3
Pulse Oximeter Oxygen Saturation		×		×[5]	×	×	×	×	×[24]	×	×	×	×	×											8.3.3
ECOG Performance Status		×		×[5]	×			×	×[24]							×	×	×	×	×			×	×	8.3.2

Procedure/Schedule	Pre-Screening period	Screening	Apheresis	Baseline	LDC			Infusion eligibility	Cell Infusion	Stage 1 follow-up[1]										Stage 2 follow-up[1]			Early discontinuation[1]	Refer to CSP section
Study Day		≤28 days before Enrollment	Enrollment	D-7	D-5	D-4	D-3	D-2, D-1	D0	D1 (W1)	D4 (W1)	D7 (W1)	D10 (W2)	D14 (W2)	D21 (W3)	D28 (W4)	W6	W12	W18	M6	M8	M10	M12		
Procedure Window (days)	N/A	N/A	N/A	±2	0	0	0	N/A	N/A[2]	0	±1	±1	±1	±1	±2	±2	±7	±7	±7	±7	±14	±14	±14		
ICE Score[12]								×	×[24]	×	×	×	×	×	×	×	×	As clinically indicated in case of suspected ICANS.							8.3.6.2
EEG										As clinically indicated in case of suspected ICANS.															8.3.6.3
Neuroimaging		As clinically indicated in case of suspected ICANS (Brain MRI or CT).																							8.3.6.1
Cardiac and pulmonary assessments																									
12-lead ECG		×		×[5]				×			×	×	×	×	×	×	×	×	×	×	×	×	×	×	8.3.4.1
Echocardiography		×		×[5]	As clinically indicated/Monitor in participants who develop CRS Grade ≥ 2.																				8.3.4.2
Serum troponin [13]		As clinically indicated																							8.3.5
NT-proBNP/BNP [13]		As clinically indicated																							8.3.5
Pulmonary Function Test		×	As clinically indicated																						8.3.4.3
Laboratory tests																									
Hematology[13]		×	×[3,14]	×[5]		×	×	×	×[24]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	8.3.5
Blood Chemistry Panel[13]		×	×[3]	×[5]				×	×[24]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	8.3.5
TSH		×		×[5]					×[24]								×								
Urinalysis		×		×[5]					×[24]			×		×		×	×	×	×	×					8.3.5
Coagulation parameters[13]		×		×[5]					×[24]	×	×	×	×	×	×	×	×	×	×	×					8.3.5

Procedure/Schedule	**Pre-Screening period**	**Screening**	**Apheresis**	**Baseline**	**LDC**			**Infusion eligibility**	**Cell Infusion**	**Stage 1 follow-up[1]**										**Stage 2 follow-up[1]**			**Early discontinuation[1]**	**Refer to CSP section**
Study Day		**≤28 days before Enrollment**	**Enrollment**	**D-7**	**D-5**	**D-4**	**D-3**	**D-2, D-1**	**D0**	**D1 (W1)**	**D4 (W1)**	**D7 (W1)**	**D10 (W2)**	**D14 (W2)**	**D21 (W3)**	**D28 (W4)**	**W6**	**W12**	**W18**	**M6**	**M8**	**M10**	**M12**		
Procedure Window (days)	**N/A**	**N/A**	**N/A**	**±2**	**0**	**0**	**0**	**N/A**	**N/A[2]**	**0**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**		
Inflammation (CRP, ferritin)[13]		×		×[5]					×[24]	×	×	×	×	×	×	×	×	×							**8.3.5**
Infectious Virological Test[15]		×	As clinical indicated																						**8.3.5**
Pregnancy Test [16]		×		×[5]				×								×	×	×	×	×	×	×	×	×	**8.3.5**
Disease and efficacy Assessments																									
Tumor Imaging[17]		×[18]		×[19]													×	×	×	×	×	×	×	×	**8.2.2 E**
Survival status										×															**8.2.3**
Collect anticancer medication										×															**8.2.4**
Cellular kinetics																									
Peripheral Blood CAR Transgene DNA Copy Number[20]				×							×	×	×	×	×	×	×	×	×	×	×	×	×	×	**8.5.1**
Peripheral CAR-T Flow Cytometry[21]				×							×	×	×	×	×	×	×	×	×	×	×	×	×	×	**8.5.1**
Immunogenicity																									
Blood Humoral Immunogenicity, ADA [22]				×					×[27]							×		×	×	×			×	×	**8.8**
Biomarkers																									
Cytokine[13,23]				×					×[27]		×	×	×	×	×	×	×	×						×	**8.9.1.1.2**

Procedure/Schedule	**Pre-Screening period**	**Screening**	**Apheresis**	**Baseline**	**LDC**			**Infusion eligibility**	**Cell Infusion**	**Stage 1 follow-up[1]**										**Stage 2 follow-up[1]**			**Early discontinuation[1]**	**Refer to CSP section**
Study Day		**≤28 days before Enrollment**	**Enrollment**	**D-7**	**D-5**	**D-4**	**D-3**	**D-2, D-1**	**D0**	**D1 (W1)**	**D4 (W1)**	**D7 (W1)**	**D10 (W2)**	**D14 (W2)**	**D21 (W3)**	**D28 (W4)**	**W6**	**W12**	**W18**	**M6**	**M8**	**M10**	**M12**		
Procedure Window (days)	**N/A**	**N/A**	**N/A**	**±2**	**0**	**0**	**0**	**N/A**	**N/A[2]**	**0**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**		
Soluble GPC3				×											×		×	×	×	×	×	×	×	×	**8.9.1.1.2**
RCL[25]				×														×		×			×	×	**8.7**
Lentiviral vector genome integration site														x			x			x			×	x	**8.9.1.1.1**
Blood immune associated genes signatures/ RNA seq				×										×	×		×	×	×	×	×		×	×	**8.9.1.1**
ctDNA			×[28]												×		×	×	×	×	×	×	×	×	**8.9.1.1.2**
Tumor Biopsy (optional)[26]																Post Treatment and/or On Progression biopsy									**8.9.2.1**
Safety assessments																									
Adverse events	Collect all AEs[29]																								**8.4**

The timing of C-CAR031 infusion (treatment) may be appropriately delayed (up to a maximum of 7 days) by the researcher based on the physical condition of the participant after receiving chemotherapy pretreatment. The day of infusion (treatment) will be redefined as "Day 0" (D0).

1. Early discontinuation: A participant who has received C-CAR031 and discontinues from the study in Stage 1 will be asked to undergo an early discontinuation visit and will be offered to transition to Stage 3 (see Table 3). Participants (from Stage 1) who have completed a scheduled study visit within 14 days of decision to continue follow-up in Stage 3 will not need to complete the early discontinuation visit (see Section 7.2.2). A participant who discontinues from Stage 2 will be asked to undergo an early discontinuation visit and will be offered to transition to Stage 3. Participants (from Stage 2) who have completed a scheduled study visit within 30 days of the decision to continue follow-up in Stage 3 will not need to complete the early discontinuation visit (see Section 7.2.3). Participants who received LDC but do not undergo C-CAR031 infusion will be required to be followed for a minimum of 30 days post the last dose of lymphodepletion and/or bridging therapy, if applicable (or until AEs have returned to a minimum Grade 2) (see Section 7.2.1), and be followed up only for AE, no blood samples to be collected unless clinical indicated. After Stage 1 follow-up, participants who have not previously progressed, discontinued prematurely from the study or started a new

anticancer regimen will continue to be followed in Stage 2 of the study for safety, efficacy, CK, immunogenicity and exploratory biomarkers up to 12 months post C-CAR031 infusion or until disease progression, start of new anticancer treatment, or discontinuation due to participant or investigator decision (see Figure 3 and Section 7.2.3).

2. For participants who do not meet the criteria for undergoing C-CAR031 infusion after 7 days of the last LDC dose, the investigator should contact the collaborator. Following discussion with the collaborator, these participants may receive C-CAR031 7-21 days after LDC completion as long as they fulfil infusion eligibility criteria. For further details refer to Section 6.1.4.2.
3. Pre apheresis (≤ 72h prior to start of apheresis), and if apheresis is performed > 14 days after main screening, chemistry laboratory assessments should be repeated. For participants who require repeat apheresis (see Section 6.1.1), screening assessments of weight, complete blood cell count (CBC) with differential and chemistry laboratory assessments, ECG (if clinically indicated), should be collected before the second apheresis.
4. The routine blood test results pre apheresis (≤ 72h prior to start of apheresis) can be used for pre-assessment of peripheral white blood cell collection.
5. After bridging therapy washout (if given) and ≤ 72h prior to first dose of LDC.
6. Post apheresis if agreed with the collaborator. For further details refer to Section 6.1.2.
7. See Table 11 for timings of pre-infusion medications.
8. Convert the measurement results into Body Surface Area (BSA) to calculate the drug dosage required for LDC (based on baseline measurement data on the day of LDC or no more than 3 days away from LDC) and the infusion dosage of C-CAR031 (based on measurement data no more than 3 days before apheresis). The calculation of BSA uses the Mosteller formula, BSA (m^2) = ([Height (cm) × Weight (kg)]/3600)1/2.
9. Weight only.
10. Vital signs: Perform at pre- C-CAR031 infusion (-15±5 min), start of C-CAR031 infusion (15±5 min), end of C-CAR031 infusion (+ 15±5 min), 1 hr (± 5 mins), and 2 hrs (± 5 mins) post C-CAR031 infusion.
11. Vital signs: Perform pre-LDC, post LDC.
12. If neurotoxicity is noted, ICE should be performed until ICANS is resolved.
13. These clinical laboratory parameters to also be monitored during CRS, or suspected CRS. In this case, it will be tested by clinically indicated in local laboratory.
14. The CBC and classification examination must be conducted ≤ 72h prior to apheresis，including the absolute lymphocyte count (ALC).
15. Infectious disease virology testing: Includes HCV antibody and RNA (Only if the HCV antibody is positive), HIV 1/2 antibody, and syphilis spirochete antibody (TP-Ab), HBV five items (HbsAg, HbsAb, HbeAg, HbeAb, HbcAb), HBV-DNA (only if the HbsAg is positive) and CMV DNA; HCV-RNA should be negative.
16. Pregnancy testing will be conducted at least 12 months after the infusion of C-CAR031 or as clinically indicated until blood C-CAR031 CAR transgene DNA is below the detectable level (end of exposure). Serum or urine tests are allowed.
17. If PD occurs a subsequent scan should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration).
18. Use dynamic enhanced MRI or dynamic enhanced CT scan, which must include chest, abdomen, pelvic cavity, head and neck, and whole-body bone scans. Qualified imaging results judged by investigator can be used for screening within 4 weeks before signing the informed consent form. For participants with asymptomatic, treated, and radiologically stable brain metastases at enrolment, a brain MRI should be conducted as indicated.
19. Scan can be done within 7 days of pre-C-CAR031 infusion as close as possible to infusion. Bone scan will be conducted if clinically indicated. Note, scan must be conducted after bridging therapy, if given. The baseline radiological assessments should be done after the washout of bridging therapy.
20. Peripheral blood CAR transgene DNA: Collect samples according to the SOA table and use the PCR method in the analysis laboratory to detect C-CAR031 transgene DNA in peripheral blood. The test results are not recorded in the EDC. If C-CAR031 CAR transgene DNA were < lower limit of quantification (LLOQ) in two consecutive assessments, then following sampling may be stopped. Patient should be tested in case of second malignancy.

21. Peripheral blood CAR-T cell percentage and the absolute number and immunophenotype: Collect samples according to the SoA table and detect by flow cytometry in the analysis laboratory. The detection results will not be recorded in the EDC. If two consecutive assessments of C-CAR031 CAR-T cells were < LLOQ, then following sampling of CAR-T flow cytometry may be stopped.
22. Immunogenicity: It will start before cell infusion and continue until withdrawal or completion of the main study.. The test results will not be recorded in the EDC.
23. Cytokine：Collect samples for testing including but not limited to blood TGFβ, IL-2, IL-4, IL-6, IL-10, IL-18, TNF-α and INF-γ according to the SoA table in the analysis laboratory. The test results will not be recorded in the EDC.
24. The test is done before the infusion.
25. RCL: It will be conducted until withdrawal of the study. Collection can be discontinued, if the testing results are all negative in the first year of infusion. If there were any clinical indication of suspected existence of RCL and at the diagnose of secondary malignancy. The test can be conducted per requirement and the results will not be recorded in the EDC.
26. Optional on-treatment tumor biopsy sample to be taken in a visit window of D29 to week 6 inclusive and/or on disease progression, as clinically indicated. Tumor biopsy sample and blood draw is indicated to determine if malignancy is secondary to cell therapy.
27. Can occur post last dose of LDC and ≤ 72h prior to C-CAR031 infusion.
28. Should occur ≤ 72 h prior to apheresis. Buffy coat (white blood cells) together with plasma will be collected.
29. Only AEs and SAEs related to study procedures will be collected in Pre-screening period from the pre-screening ICF signature.

Table 3 Schedule of Activities (Stage 3 Follow-up)

Study day (relative to C-CAR031 infusion)	M8[1] (± 14 days) [2]	Y1, Y2 (± 14 days) [2]	Y3, Y4, Y5 (± 3 months) [3]	Y6, Y7, Y8, Y9, Y10, Y11, Y12, Y13, Y14, Y15 (± 6 months) [3]	Refer to CSP Section
Assessment					
Informed consent	×[4]				A2
Collection of concomitant medication information for mutagenic agents or anticancer therapies	Document subsequent anticancer regimen post-CAR-T and/or mutagenic agents				8.2.4
Brief physical exam		×	Annual follow-up in-person	Annual follow-up via in-person or telephone visit	8.3.1
Peripheral Blood CAR DNA Copy Number[5]	×	×	×	×	8.5.1
Peripheral CAR-T Flow Cytometry [5]	×	×	×	×	8.5.1
Blood sample for RCL testing[6]	×	×	×	×	8.7
Lentiviral vector genome integration site		×			8.9.1.1.1
Tumor biopsy sample and blood draw to determine if malignancy is secondary to cell or gene therapy	To be collected if new malignancy is detected				8.9.2.1.1
AE/SAE reporting	Specific AEs (Section 8.4.7), and SAEs deemed by the investigator as possibly related to the C-CAR031				8.4
Efficacy assessment	Continue to collect as standard of care if progressive disease per applicable disease assessment criteria was not observed during the last disease assessment timepoint. Recommend to continue tumor evaluation in study site, if not applicable, every effort should be made to collect tumor evaluation result until disease progression or began new anticancer treatment.				8.2

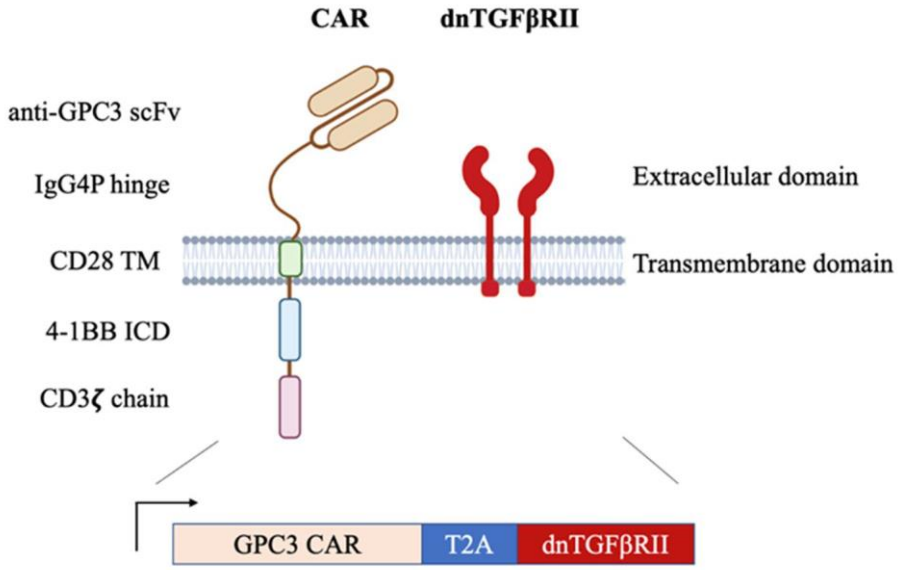
Study day (relative to C-CAR031 infusion)	M8[1] (± 14 days) [2]	Y1, Y2 (± 14 days) [2]	Y3, Y4, Y5 (± 3 months) [3]	Y6, Y7, Y8, Y9, Y10, Y11, Y12, Y13, Y14, Y15 (± 6 months) [3]	Refer to CSP Section
Survival status	×	× M12, M18, M24	Annual follow-up via in-person or telephone visit		8.2.3

1. For participants who discontinue prematurely from Stage 1 before the W12 (M3) visit, the assessments listed for M8 (Stage 3 Schedule of Activities) should be completed at W12 (M3) and W24 (M6) (including tumour biopsy if a new malignancy is suspected). For participants who discontinue from Stage 1 before the W24 (M6) visit, the assessments listed for M8 (Stage 3 Schedule of Activities) should be completed at W24 (M6).
2. For participants who received any dose of C-CAR031 and discontinue from or complete the stage 1 or stage 2 and are willing to enter stage 3.
3. If the participant decided to stop receiving medical care at the study site, every effort should be made to continue follow-up. When in person visits were not possible, assessments may be done via telephone, if there are no safety concerns.
4. Once participants receiving C-CAR031 infusion withdrew before stage 3 or complete the stage 2 follow up, the participants can independently decide to sign a separate ICF of the long-term follow up in stage 3. Participants who refused at the time but were willing to sign the ICF at any subsequent time, will also be included in the long-term follow-up as much as possible.
5. If two consecutive assessments of C-CAR031 blood CAR transgene DNA levels or blood CAR-T cell level were < LLOQ then following sampling may be stopped respectively. Patient should be tested for C-CAR031 blood CAR transgene DNA levels in case of second malignancy.
6. Collection can be discontinued, if the testing results are all negative in the first year of C-CAR-031 infusion. And patient should be tested in case of second malignancy.

2 INTRODUCTION

C-CAR031 is an autologous chimeric antigen receptor (CAR) T-cell product that expresses a CAR specific for Glypican-3 (GPC3) and a dominant-negative transforming growth factor-beta receptor II (dnTGFβRII) as an armouring strategy (see Figure 4). The GPC3-specific CAR construct consists of a scFv derived from a monoclonal antibody recognizing GPC3, an IgG4P hinge region, a CD28 transmembrane domain, and a 4-1BB and CD3ζ intracellular domain (Giardino Torchia et al 2022[4]). The armouring component dnTGFβRII is a truncated TGFβRII that lacks the intracellular domain necessary for downstream signalling (Chu et al 2022[5]). Expression of dnTGFβRII can block transforming growth factor-beta (TGFβ) signalling, protecting CAR-T cells from the immunosuppressive effect of this cytokine.

Figure 4 The C-CAR031 CAR Construct



GPC3 = Glypican-3; ICD = intracellular domain; scFv = single chain variable fragment; TM= transmembrane domain.

C-CAR031 is manufactured by Shanghai AbelZeta Ltd. It uses the patient's own fresh T cells, via a third-generation self-inactivated (SIN) lentiviral vector, in a serum-free culture process, utilizing a functionally closed system, such as the CliniMACS Prodigy® system (Miltenyi Biotec, Bergisch Gladbach, Germany). Semi-automated system is utilized in a strict Good Manufacturing Practice (GMP) environment.

This single-arm study will assess the safety, tolerability, anti-tumor activity, pharmacokinetics (PK), biomarker, and immunogenicity of C-CAR031.

2.1 Study Rationale

GPC3 is present on non–small cell lung cancer (NSCLC) tumor cells (23% of expression),

further studies have shown that the positive expression is significantly higher in squamous cell lung cancer (55% of expression) than that in adenocarcinoma (8% of expression) and virtually absent in normal adult tissues, making it an ideal target for CAR T-cell therapy (Aviel-Ronen et al 2008[1]). In addition, some studies have shown that GPC3 expression is significantly associated with poor prognosis of squamous cell lung cancer patients (Ning et al 2021[2]).

Early clinical data of C-CAR031 has shown promise in an ongoing, open label, investigator-initiated Phase I trial (NCT05155189) to evaluate the safety and efficacy C-CAR031 in patients with advanced hepatocellular carcinoma (HCC) (Zhang et al 2024[3]). C-CAR031 is well tolerated in all the dose levels being explored. No grade 5 treatment-related adverse event (TRAE), dose-limiting toxicity and immune effector cell-associated neurotoxicity syndrome (ICANS) were observed. Cytokine release syndrome (CRS) was observed in 22 (91.7%) participants with only 1 (4.2%) grade 3 CRS. All CRS events were started within the first week post the infusion and resolved within two to eight days of onset. C-CAR 031 mono therapy demonstrated an objective response rate (ORR) of 56.5% cross all dose levels and the ORR in the 4.0 ×106 CAR-T cells/kg dose cohort was 75% (6/8). The median target lesion reductions achieved 42.2% and the deep target lesion shrinkage can be observed in intra and extrahepatic lesions (70.8% of the participants have tumor lesions in lung). The median duration of response (DoR) was 7.4 months. Though there were 70.8% of participants had lung metastatic lesions, the lung complications were not a safety concern in the HCC IIT. These data support the exploration of C-CAR031 in squamous cell lung cancer.

This is a Phase I study designed to evaluate the safety, tolerability, anti-tumor activity and immunogenicity of C-CAR031 in adult participants with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of prior systemic treatment including immune checkpoint inhibitors (CPIs) and platinum-based doublet chemotherapy, concurrently or sequentially. The study will also characterize the cellular kinetics (CK)/pharmacodynamics (PD) of C-CAR031 and explore its potential biological activity.

The study will be divided into two sections: safety run-in and backfill phase (Phase Ia) and dose expansion phase (Phase Ib). Phase Ia will determine the recommended dose for expansion (RDE) to be used in Phase Ib (dose expansion) of the study and evaluate the safety and efficacy in participants with GPC3 expression. Phase Ib will further evaluate the safety, tolerability, CK, biomarker, immunogenicity and efficacy of C-CAR031 at the RDE.

To better understand clinical efficacy in this patient population, where GPC3 tumor expression levels will be determined by immunohistochemistry (IHC), correlation analysis on ORR, progression-free survival (PFS) and overall survival (OS) versus GPC3 baseline tumor expression levels and soluble GPC3 levels in blood at baseline and post treatment will then be performed.

The results from this study will inform decision-making regarding C-CAR031 CAR T-cell therapy in GPC3+ advanced/metastatic squamous cell lung cancer.

2.2 Background

2.2.1 Disease Background and Current Landscape

Lung cancer was identified as the first most common cancer in China and the world in 2022 representing an estimated 12.4% of all new cancer cases. It was also the most common cause of death from cancer, with 1.817 million deaths which account for 18.7% of the total. The 2022 global cancer statistics reported by the International Agency for Research on Cancer revealed that an estimated 1 060 600 new lung cancer diagnoses and 733 300 lung cancer-related deaths occurred in China in 2022 (Freddie et al 2024[6]). Non-small cell lung cancer (NSCLC) accounts for the majority of all lung cancers (80%), of which 20%-30% are the squamous subtype (Barta et al 2019[7]). Patients with metastatic squamous cell lung cancer have a lower driven mutation positive rate than those with metastatic non-squamous cell lung, including in EGFR (2.8%), ALK/ROS1 (1.3%), BRAF (1.5%), and MET amplification or exon 14 skipping (5.1%) (Lam et al 2019[8], Mazieres et al 2019[9]).

Up to two-thirds of NSCLC patients are diagnosed with advanced or metastatic NSCLC, and even among those with earlier stages of the disease, recurrence is frequent due to early micrometastatic dissemination (Passlick et al., 2001[10]).

In the past two decades, the advances of NSCLC drugs mainly focus on non-squamous cell lung cancer, including pemetrexed maintenance therapy, anti-vascular endothelial growth factor (VEGF) monoclonal antibody, and tyrosine kinase inhibitors (TKI) drugs. The research and development of drugs for squamous has been stagnating due to the specific epidemiological, histopathological, and molecular characteristics. Therefore, new treatment models and drugs are urgently needed for advanced squamous cell lung cancer to improve the efficacy and survival.

Platinum-based chemotherapy has been established as the classical treatment regimen for squamous cell lung cancer lacking driver gene mutations and exhibiting a performance status (PS) score of 0-1, often incorporating agents like gemcitabine or taxanes. In a randomized trial comparing two distinct chemotherapy regimens, cisplatin/gemcitabine demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to cisplatin/pemetrexed; both analyses revealed statistically significant results favoring the gemcitabine arm (Scagliotti et al., 2008[11]). Response rates have been documented in the range of 23-30%, with side effects such as thrombocytopenia and fatigue potentially necessitating treatment discontinuation (Langer et al., 2016[12]).

In addition to chemotherapy regimens, immunotherapy utilizing programmed death 1 (PD-1)/PD-L1 inhibitors has emerged as a first-line standard treatment for squamous cell lung cancer. The PD-1 protein is a co-inhibitory receptor expressed on activated T-cells, which, upon binding to its ligand PD-L1, suppresses T-cell antitumor activity within the tumor microenvironment (Mittal et al., 2016[13]).

Atezolizumab, an anti–PD-L1 monoclonal antibody, has been approved by the National Medical Products Administration (NMPA) as a first-line monotherapy for metastatic NSCLC, suitable for patients assessed as having ≥50% tumor cell PD-L1 staining positivity (TC≥50%) or tumor-infiltrating PD-L1 positive immune cells (IC) covering ≥10% of tumor area (IC≥10%). The approval of this clinical indication is based on analysis from the Impower 110 study, where atezolizumab significantly improves PFS (HR=0.63) and OS (HR=0.59) compared to chemotherapy in wild-type stage IV non-squamous or squamous cell lung cancer patients with high PD-L1 expression (TC≥50% or IC≥10%) (Herbst et al., 2020[14]).

Pembrolizumab efficacy in squamous cell lung cancer was supported in the open-label Phase III KEYNOTE-024 study, which enrolled 305 patients with advanced NSCLC (including adenocarcinoma and squamous cell carcinoma) who had PD-L1 tumor proportion score (TPS) ≥ 50% and wild-type EGFR/ALK. Pembrolizumab significantly prolonged PFS (hazard ratio [HR]=0.55 for adenocarcinoma subgroup and HR=0.35 for squamous cell carcinoma subgroup) and OS (HR=0.63) compared to chemotherapy, with a notably lower incidence of adverse reactions than the chemotherapy group (Reck et al., 2016[15]). Subsequently, the KEYNOTE-042 study further expanded the inclusion criteria to encompass patients with PD-L1 TPS ≥ 1%. The results indicated a 19% reduction in the risk of death with pembrolizumab compared to chemotherapy, although subgroup analyses suggested that the primary beneficiaries were patients with PD-L1 TPS ≥ 50% (Mok et al., 2019[16]). Based on the above results, theNMPA has approved pembrolizumab as a first-line therapy for NSCLC patients with PD-L1 TPS ≥ 1% in 2019. And the Chinese Society of Clinical Oncology (CSCO) 2023 guidelines have designated pembrolizumab as a first-tier recommendation.

In the KEYNOTE-407 study, 559 treatment-naive patients with metastatic squamous cell lung cancer were enrolled and randomized in a 1:1 ratio to receive pembrolizumab in combination with either carboplatin plus paclitaxel or nab-paclitaxel, or carboplatin plus paclitaxel/nab-paclitaxel alone. The results demonstrated that pembrolizumab in combination with chemotherapy significantly prolonged PFS (median, 6.4 months vs. 4.8 months, HR=0.56, P<0.001) and OS (median, 15.9 months vs. 11.3 months, HR=0.64, P<0.001), with no significant increase in adverse reactions (Paz-Ares et al., 2018[17]). Based on these results, NMPA has approved pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for first-line treatment of metastatic squamous cell lung cancer.

The RATIONALE 307 study demonstrated that in first-line treatment of advanced squamous cell lung cancer, compared to chemotherapy group, combination of tislelizumab with paclitaxel/nab-paclitaxel significantly prolongs the PFS of patients (Wang et al., 2021[18]). NMPA has approved the combination of tislelizumab with carboplatin and paclitaxel/nab-paclitaxel for first-line treatment of advanced squamous cell lung cancer.

Results from the CameL-sq study demonstrated that in comparison to chemotherapy, the combination of camrelizumab with paclitaxel and carboplatin significantly prolonged PFS of patients (median 8.5 months vs. 4.9 months, P<0.0001), with later follow-up indicating a median

OS of 27.4 months in the camrelizumab combination therapy group, extending almost a year beyond the chemotherapy group (Ren et al., 2022[19]). The GEMSTONE-302 study revealed that the combination of sugemalimab with carboplatin and paclitaxel significantly extends PFS (median 9.0 months vs. 4.9 months, HR=0.48, *P*<0.0001) compared to standard chemotherapy, with an increased objective response rate (63.4% vs. 40.3%) (Zhou et al., 2022[20]). These above treatments have all been approved by NMPA for first-line treatment of squamous cell lung cancer.

The first-line treatment with dual immunotherapy (PD-1 inhibitors combined with CTLA-4 inhibitors) have also been reported for positive results. The CheckMate-9LA study investigated the efficacy of nivolumab plus ipilimumab in combination with two cycles of chemotherapy compared to chemotherapy alone in advanced NSCLC. Results at a median follow-up of 13.2 months demonstrated a significant extension in PFS with the combination of dual immunotherapy and chemotherapy compared to chemotherapy alone, regardless of PD-L1 expression levels and tumor histology (median 6.7 months vs. 5.0 months, HR=0.68) (Paz-Ares et al., 2021[21]). In 2020, the FDA approved nivolumab plus ipilimumab with two cycles of chemotherapy for first-line treatment of advanced or recurrent NSCLC, but this indication has not yet been approved in China.

There is still a significant unmet medical need for most squamous cell lung cancer patients who have failed from or intolerant to previous CPIs and platinum-based doublet chemotherapy. Given the lack of randomized control trial evidence post CPI, the CSCO guidelines recommend second to late line therapy options for patients including nivolumab, tislelizumab, docetaxel, pembrolizumab, atezolizumab, afatinib and anlotinib.

The CheckMate-078 study, conducted in a Chinese population with squamous or non-squamous cell lung cancer that had progressed during/after platinum-based doublet chemotherapy, demonstrated that nivolumab significantly prolongs OS (median 12.0 months vs. 9.6 months, *P*=0.0006) and improve ORR (16.6% vs. 4.2%, *P*<0.0001) when compared to docetaxel. Among those with squamous histology, median OS was 12.3 months with nivolumab versus 7.9 months with docetaxel and ORR was 21.1% vs. 1.5%. (Wu et al., 2019[22]). Consequently, the NMPA approved nivolumab for second-line treatment of NSCLC in 2018.

Results from the RATIONALE 303 phase III clinical trial showed that compared to docetaxel, single-agent tislelizumab significantly extends OS in patients with advanced or metastatic squamous or non-squamous cell lung cancer in the second or third-line therapy (Zhou et al., 2023[23]). This second-line indication has also been granted approval by the NMPA.

Additionally, the KEYNOTE-010 study demonstrated that pembrolizumab provides superior OS benefit compared to docetaxel in late-stage CPIs naïve squamous or non-squamous cell lung cancer with positive PD-L1 expression. Subgroup analysis suggested that squamous cell lung cancer patients receiving pembrolizumab also significantly benefited in terms of OS (HR = 0.74) (Herbst et al., 2016[24]). Subgroup analysis of the OAK study showed a significant extension in median overall survival (8.9 months with atezolizumab vs. 7.7 months with docetaxel) with atezolizumab

as second-line treatment for patients with advanced squamous cell lung cancer (Rittmeyer et al., 2017[25]). Based on these findings, the FDA approved pembrolizumab for second-line treatment of PD-L1-positive (PD-L1 TPS ≥ 1%) CPIs naïve lung squamous cell carcinoma and atezolizumab for second-line treatment of CPIs naïve metastatic NSCLC following platinum-based chemotherapy or after EGFR/ALK-TKI therapy in sensitive mutation patients. However, these indications have not yet been approved by the NMPA.

Single-agent docetaxel is one of the options as second-line treatment approved based on the prolonged survival (7.0 months vs 4.6 months) compared with best supportive care. Grade 3 or 4 neutropenia occurred in more than 65% of patients treated with docetaxel (Shepherd, et al 2023[26] 错误!未找到引用源。).

In the third-line therapy, the ALTER 0303 study enrolled 439 patients with advanced NSCLC (including 86 cases of peripheral squamous cell lung cancer) post at least 2 lines of prior systemic therapies. The results indicated that anlotinib significantly prolonged PFS (median, 5.4 months vs. 1.4 months, *P*<0.001) and OS (median, 9.6 months vs. 6.3 months, P=0.002), and significantly increased the ORR (9.2% vs. 0.7%, *P*<0.001) ((Han et al., 2018[27])compared to placebo. Subgroup analysis showed that squamous cell lung cancer patients receiving anlotinib have benefits in terms of PFS (HR=0.37) only, no considerable OS improvement is seen. More patients experienced hypertension, hemoptysis, hand-foot syndrome in alotinib group. It can be considered as an optional regimen for third-line treatment of advanced NSCLC, limited to patients with peripheral squamous cell lung cancer.

Currently there is limited data to determine the best regimen and optimal sequence of late-line therapy, with treatment depending on patients' performance status, lung function, comorbidities and the choice of previous therapies. The outcome of CPIs naïve squamous cell lung cancer patients treated by CPI monotherapy or docetaxel is worse than that of non-squamous cell lung cancer patients. Checkmate-017 and checkmate-057 studies showed that two-year overall survival rates with nivolumab versus docetaxel were 23% versus 8% in squamous cell lung cancer and 29% versus 16% in non-squamous cell lung cancer. The median OS with nivolumab versus docetaxel were 9.2 months versus 6.0 months in squamous cell lung cancer and 12.2 months versus 9.5 months in non-squamous cell lung cancer (Horn et al 2017[28]).

Immunotherapy is becoming a pivotal role in the treatment of squamous cell lung cancer lacking driver gene mutations. But patients who experienced CPIs in prior lines are not recommended to received CPIs in later line, further limits the choice of patients who progressed from CPIs with/without platinum-based doublet chemotherapy. A huge unmet medical need still exists considering the moderate anti-tumor activity and significant toxicity of the recommended treatment options for 2L and beyond squamous cell lung cancer patients progressed from prior CPI and platinum-based doublet chemotherapy. Hence, there is an urgent need for innovative therapies in this disease setting to improve treatment outcome.

2.2.2 Glypican-3 as a Therapeutic Target in squamous cell lung cancer

GPC3 is present on NSCLC tumor cells (23% of expression). Further studies have shown that the positive expression is significantly higher in squamous cell lung cancer (55% of expression) than that in adenocarcinoma (8% of expression) and virtually absent in normal adult tissues, making it an ideal target for chimeric antigen receptor (CAR) T-cell therapy (Aviel-Ronen et al 2008[1]). In addition, some studies have shown that GPC3 expression is significantly associated with poor prognosis of squamous cell lung cancer patients (Ning et al 2021[2]).

2.2.3 Role of TGFβ in squamous cell lung cancer

TGFβ is a cytokine belonging to a family of growth factors that regulate a variety of cellular functions, such as growth, differentiation, and morphogenesis, which are essential for the homeostasis of tissues and organs. TGFβ ligands have three isoforms: TGFβ1, TGFβ2, and TGFβ3; TGFβ1 is the most abundant and is frequently upregulated in tumour cells (Dahmani and Delisle 2018[29]). A series of cell function experiments showed that GPC3 overexpression promoted the proliferation, migration, and invasion of squamous cell lung cancer cells (Ning et al 2023[30]). Some studies have demonstrated that TGFβ overexpression could be considered a potential predictive marker in lung cancer prognosis, and TGFβ inhibition has been shown to prevent lung cancer metastasis. Moreover, TGFβ inhibitors could be used in combination with chemo- and immunotherapy, thereby improving patient survival. (Ramundo et al 2023[31]). TGFβ is a potent immunosuppressive cytokine, and tumor-associated TGFβ inhibits T cell-mediated immune responses through a variety of mechanisms (Dahmani and Delisle 2018[29]). TGFβ can be blocked by using a dnTGFβRII, which is truncated and lacks the intracellular domain necessary for downstream signalling (Wieser et al 1993[32])

2.2.4 Preclinical and Clinical Evidence of TGFβ-armoured CAR T-Cell Activity Against Solid Tumors

Preclinical cell therapy studies have demonstrated that expression of the dnTGFβRII enhances antitumor immunity, and several clinical cell therapy studies using this armouring strategy are ongoing (NCT00368082, NCT04227275, NCT03089203, NCT02379520, NCT03198546, NCT04795882, NCT04526509, NCT03198052, NCT05489991, NCT05141253). One of these clinical trials (NCT00368082) testing the safety and efficacy of the dnTGFβRII receptor in Epstein-Barr virus-specific T cells for lymphoma, reported promising efficacy and no toxicity associated with the expression of this receptor (Bollard et al 2018[33]). In another study (NCT03089203), testing a dnTGFβRII-armoured Prostate-specific membrane antigen (PSMA) CAR T-cell product in 13 patients with prostate cancer, one patient experienced severe CRS and had a fatal outcome. This death occurred at a high dose and could have been impacted by multiple factors including normal tissue PSMA expression (Gastrointestinal [GI] tract, brain, liver and kidney), lymphodepleting chemotherapy (LDC), the aforementioned high CAR T-cell dose, and patient factors such as age and/or comorbidities (Narayan et al 2022[34]). In a second study NCT04227275 (McKean et al 2022[35]), with the same CAR T-cell product in 9 patients with prostate cancer, 2 deaths were reported. In the first patient, 2 Grade 5 events of ICANS and multi-organ failure with findings consistent with macrophage activation syndrome (MAS) were reported and in the second patient, severe immune mediated toxicity, with an equivocal cause of death with

contributing factors including metastatic prostate cancer, multi-organ failure and coagulopathy. Given a similar Grade 5 event was observed in an unarmoured PSMA CAR T cell trial NCT04249947 (Gergen 2020[36], Poseida 2020[37], Slovin et al 2022[38]), and the tolerability of dnTGFβRII armouring in NCT00368082 and NCT05155189 (G08Bz GPC3 CAR C-CAR031) studies (described in Section 2.2.5), it is unclear if the toxicities noted are more related to the PSMA target, armouring of the CAR T-cell product or other factors.

2.2.5 Summary of GPC3-Targeted CAR-T Clinical Trials Conducted to Date

CART-cell therapy has been highly effective in treating patients with relapsed/refractory B-cell malignancies and multiple myeloma; studies are ongoing across the globe to understand the best approaches to provide benefit to patients with solid tumors (Schroeder et al 2022[39]).

Several autologous GPC3 CAR T-cell products have been tested in the clinic in the solid tumor mainly HCC(see Table 4). To date no studies have been reported in squamous cell lung cancer. The safety profile, observed thus far, between the different GPC3 CAR T-cell products appears similar, with the major toxicity being CRS, as is expected from autologous CAR T-cell products, with no reports of notable on-target off-tumor toxicities, potentially reflecting the inherent tumor specificity of GPC3 expression. In addition, most GPC3 CAR T-cell products have reported antitumor activity, supporting the further exploration of GPC3 CAR T-cell products in the treatment of squamous cell lung cancer.

Table 4 GPC3-Targeted CAR T-Cell Clinical Trials

CAR T-cell therapy/clinical study/registry Number	Participants and CAR T-cell dose range	Safety findings (excl. haemalogical toxicities)	Efficacy/ response findings
Y035 CAR-GPC3 unarmoured NCT02395250, NCT03146234 (Shi et al 2020[40])	13 participants with GPC3+ advanced HCC 7.0×10^8 to 92.5×10^8 CAR-T cells Lowest dosed participant had a split infusion.	• Tolerable • ≥ Grade 3 AEs, including: • 1 DLT Grade 5 CRS (20×10^8 CAR-T) • 1 Grade 3 pyrexia • 1 Grade 4 and 1 Grade 3 bilirubin increase • 1 Grade 4 abnormal hepatic function • 1 Grade 3 blood albumin level decreased.	2/13 PRs: PFS of 111 days and 99 days
NCT03980288 Armoured (unknown) (Fang et al 2021[41])	6 participants with GPC3+ advanced HCC 2.5×10^8 CAR T-cells.	• Tolerable • No treatment-related SAEs or DLTs • ≥ Grade 3 toxicities included: ° 3 Grade 3 CRS ° 1 Grade 3 abnormal liver function.	1/6 PR

Ori-C101 armoured (unknown) ChiCTR1900028121 (Zhao et al 2021[42])	10 participants with GPC3+ advanced HCC via intravenous and intrahepatic routes. 0.9 to 3.0 × 10^8 CAR T-cells.	• ≥ Grade 4 non-haematological AEs included: ° 2 Grade 4 CRS ° 1 Grade 4 increased bilirubin ° 1 Grade 4 decreased fibrinogen ° 1 Grade 4 hypokalaemia • Other Grade 3 AEs included: LFT changes, blood chemistry changes, coagulation changes, fever, and other Grade 3 events, likely related to the patient's underlying condition.	4/9 PRs
TAK-102 (IL-7/CCL19 armoured GPC3 CAR-T, NCT04405778) (Koyama et al 2022[43])	4 participants with GPC3+ advanced solid tumors 1 × 10^7 to 1 × 10^8 CAR-T cells.	• Tolerable • No DLTs • ≥ Grade 3 AEs included: • 1 CD4 lymphocytes decrease • 1 hypersensitivity reaction • 1 gamma-glutamyl transferase increase • And events of disease progression.	0/4 PRs
CT0180; anti-GPC3 scFv-CD3ε engineered T cells NCT04756648 (Zheng et al 2023[44]) IIT	7 patients with hepatitis B virus-related HCC were treated with CT0180 (one patient each at 10×10^6 and 30×10^6 DLs, 3 at 100×10^6 DL, and 2 at 300×10^6 DL)	• Most common grade 3-4 AEs were hematologic toxicities, ie lymphopenia and neutropenia • No DTLs, immune effector cell-associated neurotoxicity syndrome, or treatment-related deaths occurred. • Grade 1 CRS was observed in 6 patients • tocilizumab was given in one patient and no glucocorticoids were used	2/7 PRs (30×10^6 and 300×10^6 DL) 3/7 SDs (10×10^6, 100×10^6 and 300×10^6 DL) 11.6 months median OS with 3 patients alive
C-CAR031; dnTGFβRII armoured GPC3 CAR-T NCT05155189 IIT	24 participants with GPC3+ HCC 0.75 × 10^6/kg to 4.0 × 10^6/kg	• Tolerable • Reported 28-day DLT period ° No DLTs ° 1 Grade 3 CRS ° No ICANS ≥ Grade 3 related AEs in 9 participants (37.5%, 9/24) included:Transient Grade 3 AST increases、Grade 3 Platelet count decreased, CRS and interstitial lung disease, the reported interstitial was considered CRS related and recovered from Grade 3 to Grade 2 within 6 days.	13/24 PR cross all dose levels; 6/8 PR at 4 × 10^6/kg

AE = adverse events; AST = Aspartate aminotransferase/transaminase; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DL = dose level; DLT = dose-limiting toxicity; GPC3+ = glypican-3 positive; dnTGFβRII = dominant-negative transforming growth factor-beta receptor II; HCC = hepatocellular carcinoma; ICANS = immune effector cell-associated neurotoxicity syndrome; IIT = Investigator-initiated trial; LDC =

lymphodepleting chemotherapy; LFT = liver function test; ORR = objective response rate; PFS = progression-free survival; PR = partial response; SAE = serious adverse event; SD = stable disease.

2.2.6 Summary of C-CAR031 preclinical study

According to the requirements of the *Technical Guidelines for the Studies and Evaluation of Cell Therapeutic Products (Tentative)* (2017 No. 216) issued by The former China Food and Drug Administration (CFDA, 2017[45]), the *Technical Guidelines for Non-Clinical Studies and Evaluation of Genetically Modified Cell Therapeutic Products (Tentative)* (2021 No. 49) and other relevant technical guidelines issued by Center for Drug Evaluation, National Medical Products Administration (NMPA, 2021[46]), as well as the studies evaluating the efficacy and safety of CAR-T products approved at home and abroad, the following non-clinical studies had been conducted for C-CAR031. Of note AZD5851 utilizes the same construct as C-CAR031, but uses a different manufacturing process.

Table 5 List of C-CAR031 Non-clinical Studies

Study type	Study title	Study number	GLP compliant
Main pharmacodynamics	Source and genetic payload of AZD5851 scFv	ONC5851-008	No
	C-CAR031 *in vitro* pharmacodynamics test	S000337-0311	No
	C-CAR031 *in vitro* antigen-specific proliferation test	S000337-0312	No
	AZD5851 *in vitro* functional identification	ONC5851-002	No
	AZD5851 *in vivo* efficacy and *in vitro* characterization	ONC5851-006	No
Pharmacokinetics	Methodological validation for fluorescence quantitative PCR (TaqMan probe method) for detecting C-CAR031 gene copy number in whole blood and tissues of NOG tumor-bearing mice	M23-S162-PKV	No
	Tissue distribution test of a single intravenous injection of C-CAR031 in NOG tumor-bearing mice	M23-S162-2PK	No
Single-dose toxicity	Toxicity study of a single intravenous injection of C-CAR031 in NOG tumor-bearing mice (subcutaneously transplanted with human hepatocellular carcinoma cell lines (Hep3B))	M23-S162-SD	Yes
Carcinogenicity	CAR-T cell lentiviral vector insertion site detection under the C-CAR031 project	RP-49204-04	No
	C-CAR031 *in vitro* soft agar clonal growth test	S000337-0313	No
	Evaluation of the functional gain of dnTGFβRII GPC3 CAR-T in IL-2-independent *in vitro* proliferation test	ONC5851-009	No
Local tolerability	*In vitro* hemolysis test of C-CAR031 on rabbit erythrocytes	O23-S162-HE	Yes
	Local irritation test	M23-S162-SD	Yes
Other toxicity studies	Expression of GPC3 in normal human tissues	ONC5851-010	No
	Assessment of GPC3 expression in 18 human primary cells or cell lines	ONC5851-0055	No
	Expression of Glypican-3 in adult peripheral nervous tissues	ONC5851-0057	No

Study type	Study title	Study number	GLP compliant
	Assessment of the binding properties of G08scFv-Fc using a human plasma membrane protein cell array	RP2113	No
	A study of tissue cross-reactivity of G08ScFv-hFc with normal human or NSG mouse tissues	20308687	Yes

GLP=Good Laboratory Practice; GPC3=glypican-3; PCR=polymerase chain reaction.
Note: AZD585, targeting GPC3-armored CAR-T cells, is identical with C-CAR031 in the CAR sequence and DnTGFβRII sequence; G08ScFv is the antigen recognition sequence of C-CAR031.

Among them, the single-dose toxicity study, in vitro hemolysis test, local irritation test and tissue cross-reactivity test were all completed under GLP conditions (Table 5); other studies were conducted under non-GLP conditions by qualified operators in accordance with standardized procedures, so that the results produced are authentic and reliable.

2.2.6.1 C-CAR031 preclinical efficacy study results

The specific scFv (clone number G08) targeting GPC3 in C-CAR031 is derived from the DP47 phage display library (Groves et al 2012[47]) The scFv in this library consists of fully humanized antibody variable domain sequences, with VH and VL being connected through a 15- residue linker sequence (GGGGS) 3. The single-chain variable region segment is transformed into scFv-Fc fusion protein, and its affinity with human and mouse GPC3 proteins is detected using surface plasmon resonance. It was observed in studies that the scFv recognizing GPC3 in C-CAR031 can bind to human and mouse GPC3 proteins, with a higher affinity to human GPC3 protein and the equilibrium dissociation constant (KD) of 73 nM and 138 nM, respectively.

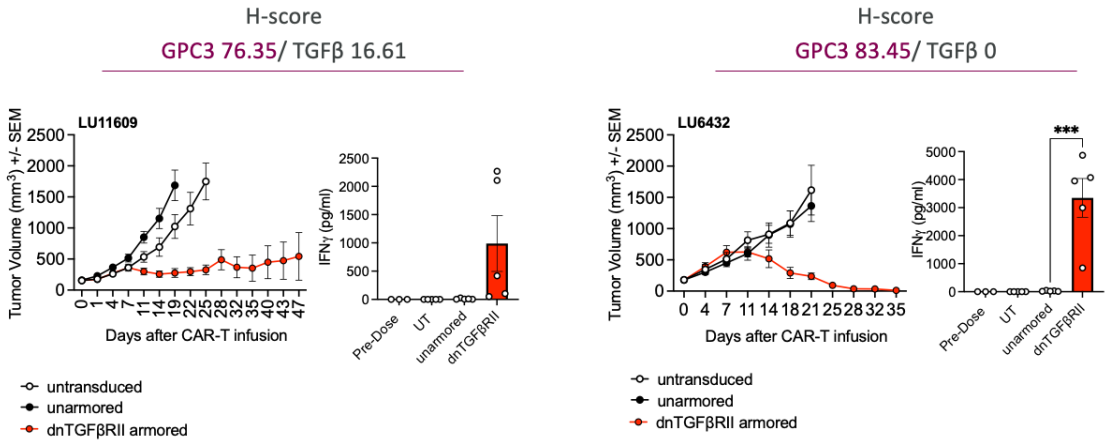
The specificity of CAR for the target antigen was evaluated in in vitro tests, including in vitro target antigen activation, cytokine secretion, antigen-dependent cell proliferation, and killing effect on GPC3-positive tumor cells. In addition, the blocking effect of dnTGFβRII on the TGFβ signaling pathway was evaluated. The test results showed that the lentiviral vector-transduced T cells co-expressed CAR and dnTGFβRII on their surface. Co-culture of CAR-T cells with a variety of tumor cells expressing GPC3 resulted in T cell activation, proliferation, production of IFN-γ and other effector cytokines, and target cytolysis. On the other hand, dnTGFβRII attenuates TGFβ-induced SMAD2/3 phosphorylation, thereby inhibiting the activity of the TGFβ signaling pathway. CAR-T cells armored with dnTGFβRII can maintain IL-2 transcription in the presence of TGFβ inhibitory molecules in the environment.

In vivo, armored GPC3 CAR-T were more efficacious compared to the unarmored GPC3 CAR-T cells in controlling the growth of a HCC cell line tumor model overexpressing TGFβ, achieving stronger and longer-lasting inhibitory effect even at low doses. On the Day 7 after treatment, a higher proportion of CAR-T cell infiltration was observed in tumor tissues of mice in the dnTGFβRII-armored CAR-T cell treatment group, indicating that armoring dnTGFβRII improved the infiltration ability of CAR-T cells in tumor tissues. Further flow cytometric analysis showed that compared with second-generation CAR-T cells, armored CAR-T cells expressed significantly lower levels of immunosuppressive molecules (e.g., LAG3 and PD1) in the tumor microenvironment, indicating the introduction of armoring dnTGFβRII enhanced the tolerability of CAR-T cells to immunosuppressive signals.

Furthermore, in vivo studies in HCC patient-derived xenograft (PDX) models showed that dnTGFβRII-armored CAR-T cell were able to control tumor growth of TGFβ positive tumors, while infusion of unarmored CAR-T cells did not result in significant tumor control. This shows that expression of dnTGFβRII does not affect the efficacy of GPC3 CAR-T cells in the absence of TGFβ but greatly improves it if TGFβ is present in the tumor.

The efficacy of dnTGFβRII-armored CAR-T cell in squamous cell lung cancer was tested in vivo using PDX models. Models were selected based on GPC3 and TGFβ expression, evaluated by IHC. Infusion of dnTGFβRII-armored CAR-T cell resulted in tumor control and production of IFNγ regardless of TGFβ expression, while infusion of unarmored CAR-T cells did not result in significant tumor control or IFNγ production (Figure 5).

Figure 5 Expression of dnTGFβRII increases CAR-T in vivo efficacy against TGFβ expressing tumors.



Average tumor volume and IFNγ concentration (day 7 post-CAR-T infusion) are shown for a TGFβ positive and a TGFβ negative PDX model. This demonstrates that dnTGFβRII-armored CAR-T cell are efficacious in vivo against squamous cell lung cancer and further evidenced the rationality and necessity of armoring with dnTGFβRII, providing strong support for the efficacy of armored CAR-T cell therapies.

2.2.6.2 C-CAR031 preclinical pharmacokinetic study results

Non-clinical pharmacokinetic study results showed that after a single caudal venous injection of 5×10^6 CAR-T cells/mouse of C-CAR031 into tumor-bearing mice, CAR- T cells had been detectable in mouse tumor tissues at 24 hours post-treatment and then increased over time; C-CAR031 in tumor tissues of male and female mice peaked on the Day 13 and Day 7 post-treatment, respectively, indicating that C-CAR031 cells could infiltrate into tumor tissues after entering the mice and further expand after activation by the target antigen. The copy numbers of C-CAR031 in various tissues also gradually increased over time; C-CAR031-specific DNA peaked on the Day 13 post-treatment in the kidney tissues of male animals and the lung and kidney tissues of female animals, and on the Day 21-Day 28 post-treatment in the remaining

tissues, and the distribution level of C-CAR031 was the highest in the spleen. The change patterns of C-CAR031 cells in various organs were consistent with those in tumor tissues, and showed a trend towards decreasing in different degrees after peaking.

Tissue distribution test results showed that after intravenous injection, C-CAR031 was mainly distributed in the spleen, lungs, whole blood, tumor tissues, liver, kidneys, and bone marrow, and the least distributed in the brain, gonads, heart and other tissues. It is worth noting that the spleen, lungs, liver, kidneys, bone marrow, etc. are all commonly affected organs in the mouse GvHD model. In the single-dose toxicity test, we also observed mononuclear cell infiltration in the histopathological examination of relevant tissues in animals in the T cell control group. Therefore, while the animal studies reflected the outcome, distribution and survival of C-CAR031 cells in the body to a certain extent, due to the limitations of the currently used animal models, it was not possible to distinguish GvHD-induced tissue distribution and cell proliferation of T cells in tumor-bearing mice in the studies, so that the study results may not be fully representative of the proliferation trend of this product in patients.

2.2.6.3 C-CAR031 results of preclinical safety studies

As required in the *Technical Guidelines for the Studies and Evaluation of Cell Therapeutic Products (Tentative)* (2017 No. 216) issued by The former China Food and Drug Administration (CFDA, 2017[45]), *the Technical Guidelines for Non-Clinical Studies and Evaluation of Genetically Modified Cell Therapeutic Products (Tentative)* (2021 No. 49), and other relevant technical guidelines issued by Center for Drug Evaluation, National Medical Products Administration (NMPA, 2021[46]), we conducted a single-dose toxicity study in tumor-bearing mice, lentiviral insertion site detection, in vitro soft agar clonal growth, IL-2-independent in vitro proliferation, in vitro hemolysis, and local irritation tests, as well as targeted studies including GPC3 expression in normal tissues, membrane protein array, and tissue cross-reactivity, etc. The primary toxicology study results are summarized as follows:

Table 6 Primary Toxicology Study Results of C-CAR031

Study type	Species / study system	Route of administration	Dosing cycle / frequency, dosage	Primary study results
Single-dose toxicity	NOG mice, Hep3B subcutaneous tumor model, half males and half males	Caudal venous injection	Single dose 1×10^6 CAR-T cells/animal 5×10^6 CAR-T cells/animal	During the 28-day observation period, no marked toxicities were observed other than the anti-tumor effects and GvHD-related reactions; The NOAEL was 5×10^6 CAR-T cells/animal
Lentivirus insertion site detection	3 batches of C-CAR031 prepared by the clinical process derived from healthy donors	*In vitro*	—	The numbers of insertion sites detected in the three samples were 20746, 23760, and 22721, respectively, and the Shannon indices were 9.68, 9.88, and 9.84, respectively, indicating polyclonality of insertion site distribution and random insertion. The insertion sites were mainly located in

				intronic regions of the genome, followed by intergenic and peri-gene regions. Insertion sites located in exon regions only accounted for 2.13% to 2.32% of any insertion sites, and no sites with integration preference were identified.
In vitro tumorigenicity	2 batches of C-CAR031 prepared by the clinical process derived from healthy donors	*In vitro*	Inoculated at the densities of 500, 5000, and 50,000 cells/well	Two batches of C-CAR 031 showed no colony formation within the 21-day culture period, indicating no *in vitro* tumorigenicity of C-CAR031
IL-2-independent *in vitro* proliferation test	3 batches of armored CAR-T prepared by the clinical process derived from healthy donors	*In vitro*	0.5×10^{6} cells/mL	In the absence of exogenous recombinant human IL-2, none of the three batches of armored CAR-T cells exhibited abnormal growth/expansion. Over time, the total cell number, viability, and number of proliferating cells decreased. The results indicated a low risk of abnormal expansion or clonal proliferation of armored CAR-T cells
In vitro hemolysis test	Rabbit red blood cells	*In vitro*	2.8×10^{7} cells/mL	The C-CAR031 preparation produced no hemolytic reaction *in vitro* at 2.8×10^{7} T cells/mL (higher than the maximum proposed clinical concentration)
Local tolerability	NOG mice, Hep3B subcutaneous tumor model, half males and half males	Caudal venous injection	Single dose, 6.76×10^{6} cells/mL and 3.38×10^{7} cells/mL	During the study, no local abnormalities at the administration site were observed in any animals; local irritation was not observed at the administration site in any animals upon pathological examination on D14 and D29
Off-target toxicity studies	Paraffin sections of 33 types of normal human tissues from 3 donors	*In vitro*	N/A	GPC3-positive staining was observed in the cell membrane/cytoplasm of the placental trophoblast; localized positive staining, mainly in the cell membrane, was observed in the anterior pituitary gland
	18 types of human primary cells or cell lines	*In vitro*	N/A	Compared with the hepatocellular carcinoma cell line HEP3B, the relative expression of GPC3 in motor neurons was low (9.52-13.0%), and the relative expression of GPC3 was all very low (<0.4%) in any other primary cells
	Paraffin sections of tongue, stomach, small intestine, large intestine, heart, skin, and dorsal root ganglion	*In vitro*	N/A	50% of the ganglion cells in the colon sample expressed low levels of cell membrane-localized GPC3 protein

	Retrogenix cell microarray (6101 human membrane proteins, cell model-anchored secreted proteins, and 396 human heterodimeric proteins)	*In vitro*	20 μg/mL	At the concentration of 20 μg/mL, the antigen recognition region of C-CAR031 only interacted specifically with GPC3 isoform 1, and no other interactions were observed.
	36 types of normal human frozen tissue sections from 3 donors	*In vitro*	0.5 μg/mL, 5 μg/mL	At the concentration of 5 μg/mL, the antigen recognition region of C-CAR031 exhibited staining specific to the cell membrane and cytoplasm of human placental trophoblast cells, and the cytoplasm of 1/3 of the donor's external cervical oriface, renal tubules, and anterior pituitary epithelial cells; considering that cell therapeutic products would not come into contact with the cytoplasm components in the body, these stains located in the cytoplasm would be associated with a low risk of causing off-target toxicity in clinical applications.

GPC3=glypican-3; IL-2=interleukin 2; NOAEL=No Observed Adverse Effect Level.

Toxicology studies showed that when C-CAR031 was given to NOG tumor-bearing mice by caudal venous administration at a dose of 1×10^6 CAR-T cells/ mouse and 5×10^6 CAR-T cells/ mouse, no marked toxicities other than the anti-tumor effects and GvHD-related reactions were observed, and the NOAEL was 5×10^6 CAR-T cells/animal, equivalent to the human dose of approximately 2×10^7 CAR-T cells/kg estimated based on the body surface area. Lentiviral insertion site detection for the 3 cases using C-CAR031 prepared with the clinical process showed that the insertion sites were mainly located in the intronic region of the genome, followed by intergenic and peri-gene regions, and the insertion sites located in the exon region accounting for only 2.13%-2.32% of any insertion sites; the distribution exhibited polyclonality, and no sites with integration preference were identified. C-CAR031 exhibited no tumorigenicity under *in vitro* culture conditions,and did not exhibit abnormal proliferation under culture conditions in the absence of exogenous recombinant human IL-2, indicating a low risk of abnormal expansion and clonal proliferation of C-CAR031 cells.

C-CAR031 produced no hemolytic reactions *in vitro* at 2.8×10^7 T cells/mL; when administered as a single caudal venous injection at the concentrations of 6.76×10^6 cells/mL and 3.38×10^7 cells/mL, C-CAR031 was observed with no local abnormalities at the administration site and no local irritation at the administration site upon pathological examination.Membrane protein array and tissue cross-reactivity tests indicated high specificity of the antigen recognition region of C-CAR031 and a low risk of causing off-target toxicity in clinical applications.

Expression of GPC3 in normal human tissues was investigated using a commercial mouse anti-GPC3 antibody (1G12 clone- Sigma-Aldrich®). Samples included 2 TMAs covering 32 different

organs, with tissue cores from 3 different donors per tissue (Study No.: ONC5851-010). Furthermore, a GLP tissue cross reactivity study was conducted assessing binding of the G08 binding part of CCAR031 to the full panel of 42 human tissues from 3 independent donors (Study No.:20308687). No binding to lung tissue was observed in any of these studies. Finally, a membrane protein array binding study (Retrogenix) was performed to assess any off-target binding of the G08 binding part. No off-target binding was observed. See Table 6 for list of studies assessing GPC3 expression and tissue/protein binding of the G08 binding part of C-CAR031.

In summary, the mechanism of action of C-CAR031 is well-established, the efficacy in terms of targeting GPC3-positive tumors *in vitro* and *in vivo* is well-documented, and armoring with dnTGFβRII improved the functioning of CAR-T cells in the immunosuppressive tumor microenvironment without increasing the safety risks (Bollard et al 2018[33], Narayan et al 2022[34]).

2.2.7 Summary of C-CAR031 clinical study

As of March 14, 2024, in the China IIT study of C-CAR031 for advanced HCC (NCT05155189), a total of 24 subjects had been infused in four dose cohorts of 0.75, 1.5, 2.5 and 4.0 (unit: $\times 10^6$ CAR-T cells/kg) as mono therapy in 1, 6, 9, and 8 participant, respectively, 70.8% participants had lung metastatic lesions. No DLT events were observed in all dose cohorts (0.75, 1.5, 2.5 and 4.0); The maximum tolerated dose (MTD) had not been reached. The median follow-up time was 9.03 months. As shown in Table 7, the 0.75, 1.5, 2.5 and 4.0 doses (unit: $\times 10^6$ CAR-T cells/kg) were safe and well tolerated, and the efficacy of the 1.5, 2.5 and 4.0 doses was better than that of the 0.75 dose. The ORR at 4.0 doses (75%) was higher than that in 1.5 and 2.5 doses (50%), the DCR was similar across dose cohorts. The median PFS and DoR at 4.0 doses was not mature by the data cutoff date, participants at 1.5 and 2.5 doses had the comparable median PFS (4.27m vs. 4.17m). The median DoR of 1.5 doses appeared to be longer than that of 2.5 doses numerically (7.36m vs. 4.44m, not compared statistically). 1 participant at 0.75 doses achieved a stable disease as the best of response, considered as a clinical benefit in this heavily treated patient population.

Table 7 Comparison of Safety and Efficacy Across Different Dose Groups (Safety Analysis Set)

Safety	0.75×10^6 /kg N=1 n (%)	1.5×10^6 /kg N=6 n (%)	2.5×10^6 /kg N=9 n (%)	4.0×10^6 /kg N=8 n (%)	Total N=24 n (%)
C-CAR031-related TEAEs	1 (100)	6 (100)	9 (100)	8 (100)	24 (100)
≥ Grade 3 C-CAR031-related TEAEs	0	3 (50.0)	3 (33.3)	3 (37.5)	9 (37.5)
TEAEs leading to withdrawal from study	0	0	0	0	0
SAEs	1 (100)	0	2 22.2)	2 (25.0)	5 20.8)
C-CAR031-related SAEs	0	0	1 (11.1)	1 (12.5)	2 (8.3)

TEAEs leading to death	1 (100)	0	0	0	1 (4.2)
Grade 1/2 CRS	1 (100)	5 (83.3)	8 (88.9)	7 (87.5)	21 (87.5)
≥ Grade 3 CRS	0	0	0	1 (12.5)	1 (4.2)
Median Days to CRS Onset day (range)	7 (7, 7)	3 (2, 3)	3 (2, 4)	2 (1, 3)	3 (1, 7)
Median Days to CRS Resolution day (range)	4 (4, 4)	6 (4, 8)	3 (2, 6)	5 (3, 8)	4 (2, 8)
ICANS	0	0	0	0	0
≥ Grade 3 infusion reactions	0	0	0	0	0
Efficacy	**N=1**	**N=6**	**N=8***	**N=8**	**N=23**
ORR	0	3 (50.0)	4 (50.0) *	6 (75.0)	13 (56.5)
DCR	1 (100)	5 (83.3)	8 (100)	7 (87.5)	21 (91.3)
Median DoR (months)	NE	7.36	4.44	NE	7.36
Median PFS (months)	NE	4.27	4.17	NE	4.30

Note: CRS = cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; NE=not evaluable yet; TEAE = treatment-emergent adverse events.

*Among the 24 participants, 1 (0921-02801C015) participantwas not included in efficacy analysis due to protocol deviations.

As classified by preferred term, the most common treatment-emergent adverse events (TEAEs) were hematologic toxicities and CRS, no ICANS reported. TEAEs with an incidence ≥ 20% included neutrophil count decreased (100%), lymphocyte count decreased (100%), white blood cell count decreased (100%), anemia (95.8%), CRS (91.2%, only 1 participant experienced G3 CRS), fibrin D dimer increased (70.8%), platelet count decreased (62.5%), cough (58.3%), hypokalaemia (50.0%), productive cough (45.8%), alopecia (45.8%), hypoalbuminaemia (41.7%), coagulation test abnormal (41.7%), aspartate aminotransferase increased (41.7%), hypoproteinemia (37.5%), proteinuria (37.5%), pyrexia (29.2%), hypotension (29.2%), blood glucose increased (29.2%), weight decreased (25.0%), myalgia (25.0%), nausea (25.0%), diarrhea (25.0%), pleural effusion (20.8%), hyponatremia (20.8%) and hepatitis B virus DNA increased (20.8%). 9 (37.5%) participants experienced ≥ Grade 3 TEAEs related to C-CAR031 infusion, including transient Grade 3 AST increases, Grade 3 Platelet count decreased, Grade 3 CRS and Grade 3 interstitial lung disease (ILD), the ILD was considered CRS related and recovered from Grade 3 to Grade 2 within 6 days.

A total of 2 (8.3%) participants experienced SAEs related to C-CAR031 infusion. 1 participant in 2.5 dose cohort experienced myelosuppression (Grade 4) assessed as definitely related to lymphodepleting chemotherapy and possibly related to C-CAR031 infusion. Another participant in 4.0 dose cohort experienced CRS and ILD (both Grade 3). The CRS post C-CAR031 infusion occurred more earlier at 1.5, 2.5 and 4.0 doses than in 0.75 doses (median onset days: 3, 3, 2 and 7), but the duration of CRS was similar (4-6 days). Though there were more than 70.8% of participants had lung metastatic lesions, the lung complications were not a safety concern based

on the safety data. Only 1 ILD was reported in 4.0 dose cohort, it was considered associated with Grade 3 CRS and recovered from Grade 3 to Grade 2 within 6 days.

After a single infusion of C-CAR031, the median T_{max} was 10 days (range: 7-21 days); the median C_{max} was 3.9×10^5 copies/µg gDNA (range: 7.1×10^3 , 8.3×10^5 copies/µg gDNA); the median $AUC_{0\text{-}28d}$ was 4.5×10^6 copies/µg·day (range: 1.3×10^6, 14.3×10^6 copies/µg·day); the median T_{last} was 125+ days (range: 42, 271+ days). The study results indicate that C-CAR031 can effectively expand in the body in a durable manner; no other adverse events of special interest, such as uncontrolled T cell expansion or new or secondary tumors, were observed.

2.3 Benefit/Risk Assessment

This section outlines the potential benefits, risks, and the mitigation strategies for this study. Table 8 identifies the risks associated with C-CAR031 and mitigates the impact of these risks, while aiming to maximize the chance of therapeutic benefit to participants. More detailed information about the potential benefits, and risks and reasonably anticipated adverse events (AEs) of C-CAR031 may be found in the C-CAR031 Investigator's Brochure (IB).

2.3.1 Risk Assessment

Risks related to the investigational intervention and study procedures with a brief description of strategies to mitigate these risks are summarized in Table 8.

Table 8 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk [a]	Mitigation strategy
Study intervention(s) C-CAR031		
CRS	CRS is an acute systemic inflammatory syndrome associated with immunotherapy including CAR T-cell therapy. Elevated inflammatory cytokine levels leading to fever, hypotension, hypoxia and/or other organ system toxicities.	• Participants with pre-existing autoimmune disorders (Section 5.2) • Pre-infusion medication (Section 6.1.4.1.2 and Table 11) • Mandatory hospitalization (minimum 7 days) post C-CAR031 infusion • Monitor closely for CRS, immediately hospitalize on first signs of CRS (such as fever), and follow the guidance for management of CRS (see RMP)
		• Access to ICU • Adequate supplies of supportive medications, including anti-IL-6 treatment (eg, tocilizumab), should be available on site prior to C-CAR031 infusion (Section 6.9.1) • A participant wallet card will be implemented (Section 6.1.4.1.1)

HLH/MAS	CAR T-cell therapy–induced HLH/MAS is a dysfunctional immune response leading to symptoms including fever, splenomegaly, lymphadenopathy, cytopenias, hyperferritinaemia. Considerable overlap with CRS symptoms.	• Mandatory hospitalization (minimum 7 days) post C-CAR031 infusion • Mitigations and clinical management mirrors the strategies used for managing CRS. Follow the guidance for management of HLH/MAS (see RMP) • A participant wallet card will be implemented (Section 6.1.4.1.1).
Neurological disorders including ICANS	Neurological complications including ICANS have been reported following CAR T-cell administration. A neurological condition characterized by confusion or delirium, expressive aphasia, weakness, tremor, seizures, and altered levels of consciousness.	• Participants with select neurological disorders and autoimmune conditions that impact the CNS will be excluded (see Section 5.2) • Mandatory hospitalization (minimum 7 days) post C-CAR031 infusion. Regular abbreviated neurological examination • Monitoring and management criteria for ICANS (see RMP) • A participant wallet card will be implemented (Section 6.1.4.1.1).
IRRs including hypersensitivity and anaphylaxis	Reaction to cell therapy product and/or excipients that may manifest as rash/erythema, hypotension, bronchospasm, and rarely anaphylaxis.	• Exclusion criteria (Section 5.2) • Participants should receive pre-medication (Table 11) and be treated urgently per institutional standard, appropriate clinical practice guidelines and society guidelines, avoiding corticosteroid use if possible • See RMP for suggested management of IRRs.
Transaminase elevation	Reactivity of C-CAR031 with GPC3 on liver metastatic tumor cells may cause elevation of liver transaminases. Transaminase elevation may also occur as part of CRS.	• Exclusion criteria of HBV, and HCV infection (Section 5.2) • Regular monitoring of liver transaminases • See RMP for suggested management.
New primary malignancy	Safety concern characterized by the risk of lentiviral induced insertional mutagenesis into a site that adversely affects the host cell genome, which could lead to genotoxicity and formation of new primary malignancy. Cases of new malignancies including T cell lymphomas have occurred following treatment with approved CAR-T products in haematological cancers.	• Routine pharmacovigilance (see Section 8.4). Monitoring to follow the recommendations set forth in the CDE Guidance for Industry (*Technical guidelines for conducting long-term follow-up in clinical studies of gene therapy products, 2021*) • New primary malignancies should be reported during the duration of the main study and LTFU study up to 15 years irrespective of when they occur.

Enteric Autonomic Neuropathy	Low levels of GPC3 expression on human colonic ganglia was detected by IHC with one antibody but the anti GPC3 scFv in C-CAR031 did not show reactivity. No toxicity or pathological findings were observed in the conducted safety study in mice. Reactivity of C-CAR031 may manifest with symptoms including constipation or diarrhea, but no AEs on colon related to C-CAR031 were reported in IIT to date.	• Exclusion of neurological autoimmune conditions • Regular clinical examination of participants • See RMP for suggested management of enteric autonomic neuropathy
Anterior pituitary dysfunction	Low levels of GPC3 expression in human anterior pituitary gland was detected with one antibody but the anti GPC3 scFv in C-CAR031 did not show reactivity. No toxicity or pathological findings were observed in the conducted safety study in mice. Reactivity of C-CAR031 may cause hormonal imbalance affecting e.g. thyroid function, but no AEs on anterior pituitary gland related to C-CAR031 were reported in IIT to date.	• Regular clinical examination of participants • Regular monitoring of TSH • See RMP for suggested management.
Infection with RCL	Risk of recombination event during manufacturing/post-infusion could generate pathogenic RCL variants.	• RCL testing of C-CAR031 product prior to release • Participant monitoring for RCL by mandatory viral testing (see Section 1.3, SoAs) • Monitoring of infections per local guidance.
Uncontrolled T-cell proliferation	Genetic engineering of participant T cells can increase the risk of T- cell clonal expansion or potentially malignant transformation via mechanisms such as insertional mutagenesis following lentiviral transduction or transgene expression.	• Test of the lentiviral vector genome integration site of C-CAR031 • Study participants will undergo regular blood sampling to monitor the proliferation of T cells.
Adverse effects on embryo-foetal development	GPC3 is expressed in human placenta and the mesodermal layer of the developing foetus. It is unknown if C-CAR031 has the potential to be transferred to the foetus.	• Exclusion criteria (Section 5.2), routine pharmacovigilance (Section 8.4), pregnancy testing and contraception guidelines (Section 5.1).

Immunogenicity of vector and transgene	Humoral and cellular responses against components of the CAR-T, which may limit the efficacy of the product.	• Routine pharmacovigilance (see Section 8.4) • Clinical monitoring for symptoms of immunogenicity; regular measurement of anti-drug antibodies and assessment after C-CAR031 infusion (see Section 8.8).
Study intervention(s): LDC associated with C-CAR031 therapy		
Cytopaenias	Low haematological cell counts (neutrophils, lymphocytes, platelets, erythrocytes, etc.) associated with lymphodepletion leading to increased risk of infection, bleeding, and/or fatigue.	• Participants with significant haematological imbalances are excluded (Section 5.2). • Frequent monitoring of haematological parameters and provision of supportive care (eg, irradiated blood and thrombocyte concentrates, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines.
Infections	Immunosuppression secondary to lymphodepletion leading to increased risk of bacterial, viral, and/or fungal infection. In CAR-T therapy, the pretreatment with cyclophosphamide and fludarabine can induce immunosuppression, which may be the main cause for HBV reactivation. 2 participants experienced virus reactivation post-infusion in HCC IIT to date. Both cases recovered to baseline levels within 4 weeks and 2 weeks, respectively, following antiviral treatment.	• Exclusion criteria of syphilis, HBV, HCV, CMV and HIV infection (Section 5.2) • Monitoring as clinically indicated; treatment as outlined by institutional guidelines • Prophylactic antimicrobial medication (including prophylaxis for pneumocystis jiroveci pneumonia) as clinically indicated and as outlined by institutional guidelines.
Other risks associated with lymphodepleting chemotherapy	• Fludarabine fevers, neurotoxicity, hemolysis. • Cyclophosphamide: haemorrhagic cystitis, myocarditis, pericarditis, pneumonitis, and neurotoxicity. Use of these agents may increase the risk of developing new primary malignancies; risk of fertility and embryo-fetal toxicity. Please see local product label for all product specific risks.	• Relevant exclusion criteria (see Section 5.2), including uncontrolled intercurrent illness. • Close monitoring and clinical examinations during and after the procedure according to local practice. • Supportive care as outlined by institutional guidelines and local product label • Exclusion: Pregnant or breastfeeding (see Section 5.1). • Pregnancy test prior to study intervention. • Contraception guidance (see Appendix F)
Study procedures		

Apheresis	Risks may include hypotension, faintness, blurry vision, dizziness, coldness, sweating, infection, abnormal blood clotting, allergic reaction, bleeding, seizures, abdominal cramps, and tingling in the limbs. Risks associated with placement of central venous catheter (if applicable) may include arterial puncture, pneumothorax, haemothorax, haematoma.	• Participants will have risks explained according to local practice by the investigator during the consent process • Close monitoring and clinical examinations during and after the procedure according to local practice.
Other		
Bridging therapy	Risk associated with anticancer drugs used in the bridging regimen. Product-specific risks as per local label.	• Participants will have risks explained by the investigator according to the local product information during the consent process • Close monitoring and clinical examinations during and after the procedure according to local practice • Supportive care as outlined by institutional guidelines and local product label.

[a] For a complete characterization for each risk associated with C-CAR031 refer to the C-CAR031 IB.
AEs = adverse events; CAR = chimeric antigen receptor; CDE = center for drug evaluation; CMV = cytomegalovirus; CNS = central nervous system; CRS = cytokine release syndrome; GPC3 = glypican-3; HBV = hepatitis C virus; HCV = hepatitis C virus; HIV = Human immunodeficiency virus; HLH = haemophagocytic lymphohistiocytosis; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; IL-6 = Interleukin- 6; IIT = investigator initiated trial; IRR = infusion-related reaction; LDC = lymphodepleting chemotherapy; LTFU = long-term follow-up; MAS = macrophage activation syndrome; RCL = replication-competent lentivirus; RMP = Risk Management Plan;; TSH = thyroid stimulating hormone.

2.3.2 Benefit Assessment

There remains a significant unmet need for additional treatment options for patients with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of systemic treatment including CPIs and platinum-based doublet chemotherapy, concurrently or sequentially (see Section 2.2.1). Early clinical data of C-CAR031 (Zhang et al 2024[3]) demonstrated promising safety and efficacy in other solid tumors support the exploration of C-CAR031 in patients with GPC3+ advanced/metastatic squamous cell lung cancer.

2.3.3 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize the risks to the participants of this study, the potential risks associated with C-CAR031 are justified by the anticipated benefits that may be afforded to participants with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of systemic treatment including CPIs and platinum-based doublet chemotherapy, concurrently or sequentially.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints are listed below in Table 9.

Table 9 Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Safety	• To assess the safety and tolerability of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer • To determine the RDE (Phase Ia)	• Incidence of AEs/SAEs/AESIs • Incidence and severity of DLTs (Safety run-in section of Phase Ia) • Changes from baseline in vital signs, physical examination, ECOG score, 12-lead ECGs, laboratory parameters that are abnormal and of clinically significance.
Secondary		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Efficacy	To estimate the anti-tumor activity of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• ORR, DCR, DoR, DRR, TTR, PFS and change in tumor size assessed by the investigator and evaluated according to RECIST 1.1 criteria • OS
Pharmacokinetics	To investigate the CK of C-CAR031 by PCR in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Quantification of CAR copies/μg DNA of C-CAR031 in peripheral blood • CK parameters of C-CAR031, including but not limited to T_{max}, C_{max}, $AUC_{0\text{-}28d}$, T_{last}, C_{last}, and AUC_{last}, as data allows
Safety	To assess the safety of C-CAR031 in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Presence of RCL in peripheral blood samples.
Exploratory		
Phase Ia: Safety run-in and backfill **Phase Ib: Dose expansion**		
Pharmacokinetics	To investigate the CK of C-CAR031 by flow cytometry in participants with GPC3+ advanced/metastatic squamous cell lung cancer	• Quantification of C-CAR031 CAR-T cells in peripheral blood • CK parameters of C-CAR031, including but not limited to T_{max}, C_{max}, $AUC_{0\text{-}28d}$, T_{last}, C_{last}, and AUC_{last} as data allows
Immunogenicity	To assess the immunogenicity of C-CAR031	• Evaluation of humoral immunogenicity against C-CAR031: incidence, and antibody levels as data allows.
Biomarkers	To assess intra-tumoral biomarkers of disease, pharmacodynamic biomarkers and biomarkers of clinical response to C-CAR031	• Presence or changes in tumoral biomarkers including, but not limited to levels of RNA, DNA, and protein analytes as well as imaging measurements. Specific assessments may include, but not be limited to expression of GPC3, immune markers (for example TGFβ, PD-L1, CD8) and

		CAR-T infiltration.
Biomarkers	To assess systemic biomarkers of disease, pharmacodynamic biomarkers and biomarkers of clinical response to C-CAR031	• Presence and changes in peripheral DNA, RNA, immune cell phenotype, and protein biomarkers, which may include, but not limited to ctDNA, soluble and cellular analytes, gene expression, and immune markers pre- and post- treatment or on disease progression.

AEs = adverse events; AESIs = adverse events of special interest; AUC_{last} = area under the curve from time 0 to the time of the last quantifiable concentration; $AUC_{0\text{-}28d}$ = area under the curve 28 days after C-CAR031 infusion; CAR = chimeric antigen receptor; CD8 = cluster of differentiation 8; CK= cellular kinetics; C_{max} = maximum observed concentration; C_{last} = last measurable concentration; ctDNA = circulating tumour DNA; DCR = disease control rate; DLTs = dose-limiting toxicities; DNA= deoxyribonucleic acid; DoR = duration of response; DRR = durable response rate; ECG = electrocardiogram; ECOG= Eastern Cooperative Oncology Group; GPC3 = glypican-3; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PCR = polymerase chain reaction; RCL = replication-competent lentivirus; RDE = recommended dose for expansion; RECIST = Response Evaluation Criteria in Solid Tumours; RNA = ribonucleic acid; PD-L1= programmed death ligand 1; SAEs = serious adverse events; TGFβ = transforming growth factor-beta; T_{last} = Time of C_{last}; T_{max} = time to reach maximum concentration; TTR = time to response.

4 STUDY DESIGN

4.1 Overall Design

This single-arm, open-label, multicenter, Phase I study will evaluate the safety, tolerability, anti-tumor activity, PK/PD, biomarker, and immunogenicity of C-CAR031 in adult participants with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of prior systemic treatment including CPIs and platinum-based doublet chemotherapy, concurrently or sequentially. The study will be divided into two sections: safety run-in and backfill phase (Phase Ia) and dose expansion phase (Phase Ib). Phase Ia will determine the recommended dose for expansion (RDE) to be used in Phase Ib (dose expansion) of the study and evaluate the safety and efficacy in participants with GPC3 expression. Phase Ib will further evaluate the safety, tolerability, CK, biomarker, immunogenicity and efficacy of C-CAR031 at the RDE.

The study will be conducted in the following steps: participants will undergo pre-screening, screening, apheresis, bridging therapy (if appropriate) and lymphodepletion before receiving C-CAR031 infusion and subsequent follow-up study schema is summarized in Figure 2 and Figure 3.

- **Study Consent:** Each potential participant will provide informed consent prior to starting any study-specific procedures. This study has a 3-step consent process, with separate informed consent forms (ICF).
- **Pre-screening:** Patients may consent to pre-screening only (see Section 5.1.1) Patients will be assessed for expression of GPC3 on the tumor via a validated IHC assay (performed at a central laboratory). The participant is required to provide tumor tissue sections (collection time requirements are detailed in the laboratory manual) or undergo a fresh tumor core biopsy for the testing of GPC3 expression.
- **Screening:** Main screening consent is then required to enter the treatment period of the study (see Section 5.1.2). During screening, all patients will provide written consent for study participation

and will be screened for study eligibility within 28 days prior to apheresis. All eligibility criteria must be met prior to starting apheresis. Prescreening and screening may occur in parallel.

- **Apheresis:** After meeting screening eligibility criteria, each participant will undergo apheresis for the collection of peripheral blood mononuclear cells (PBMCs). C-CAR031 will be generated from T cells selected from the apheresis. Participants for whom apheresis collection is unsuccessful or manufacturing is a failure may be allowed a second attempt at apheresis (see Section 6.1.1).
- **Bridging therapy:** Bridging therapy between apheresis and baseline assessment (allowing at least 5-half-lives washout of bridging therapy prior to baseline assessment) will be permitted when clinically indicated following a discussion with the collaborator (see Section 6.1.2).
- **Lymphodepletion:** After meeting eligibility criteria for receiving LDC (see Section 6.1.3.1), participants will be administered a conditioning regimen of IV cyclophosphamide 500 mg/m^2 and fludarabine 25 mg/m^2 daily for 3 days or per local standard (see Section 6.1.3.2).
- **C-CAR031 infusion:** C-CAR031 will be administered on Day 0, approximately 7 days after the last dose of LDC (see Sections 6.1.3.2 and 6.1.4.2 for more information on C-CAR031 dosing window), at the dose levels specified in Figure 1. Following C-CAR031 infusion, participants will remain as inpatients for a minimum of 7 days (inclusive of D0) and participants should be within an approximate 2-hour travel time from the study site for approximately 28 days following C-CAR031 infusion.

The study is divided into two sections: safety run-in and backfill phase (Phase Ia) and dose expansion phase (Phase Ib):

- **Phase Ia (safety run-in and backfill):** In each dose level of Phase Ia up to 12 evaluable participants with GPC3+ advanced/metastatic squamous cell lung cancer, who are not amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of prior systemic treatment including CPIs and platinum-based doublet chemotherapy, concurrently or sequentially will be evaluated. When enrolling is in progress, the eligible participant will preferentially be allocated to the 4.0 ×10^6 CAR -T cells/kg dose cohort if the two dose cohorts 1.5 ×10^6 CAR-T cells/kg and 4.0 ×10^6 CAR -T cells/kg are both open. This section aims to explore the RDE and consists of preset dose levels, with flexibility to explore additional intermediate/higher dose levels. See Section 6.6.1 for the proposed dose levels to be explored.
- **Phase Ib (dose expansion):** In Phase Ib approximately 12 evaluable participants each cohort at the RDE determined in Phase Ia will be evaluated to further evaluate the safety and tolerability, CK, biomarker, immunogenicity and explore efficacy of C-CAR031.
- **Follow-up and end of study:** Follow-up of participants is divided into 3 stages in the study as described below (see Table 2, Table 3 and Figure 3).
  - **Stage 1 Follow-up:** Participants will complete all assessments as indicated in the SoA through 6 months post C-CAR031 infusion unless they experience confirmed disease progression, start a new anticancer regimen or discontinue due to participant or investigator decision, whichever occurs first (see Section 7.2.2). For details of AE collection in Stage 1

see Table 17. Participants who received C-CAR031 discontinue prematurely from the study in Stage 1 will undergo an early discontinuation visit (see SoA Table 2) and be offered to move to Stage 3 of the study (see SoA Table 3) for continued safety surveillance. Participants who have completed a scheduled visit within 14 days of decision to be offered to move to Stage 3 will not need to complete the early study discontinuation visit.

- **Stage 2 Follow-up**: Participants who have not previously progressed, discontinued prematurely from the study or started a new anticancer regimen after Stage 1 follow-up, will continue to be followed in Stage 2 of the study for safety, efficacy, CK, immunogenicity and exploratory biomarkers up to 12 months post C-CAR031 infusion or until disease progression, start of new anticancer treatment, or discontinuation due to participant or investigator decision, whichever occurs first (see SoA Table 2 and Section 7.2.3). For AE collection in Stage 2 see Table 17.

  Participants who progress, start new anticancer treatment, or discontinue prematurely from the study in Stage 2 will undergo an early discontinuation visit and be offered to move to Stage 3 of the study (see SoA Table 3) for continued safety surveillance. Participants who have completed a scheduled visit within 30 days of decision to be offered to move to Stage 3 will not need to complete the early study discontinuation visit.

  The end of the main study is defined as 12 months after the last participant has received his/her dose of C-CAR031 (or sooner if: all the participants have progressed or stated a new anti-cancer therapy or death occurred, or have either withdrawn or are lost to follow-up, or investigator and AbelZeta aligned to terminate the study).

- **Stage 3 Follow-up (Long-term Follow-up)** – Once end of the main study is achieved (or before if appropriate follow-up has been completed),, all dosed with C-CAR031 participants will be offered to transition to, and continue to be monitored in stage 3 (the LTFU period) for up to 15 years from CAR-T infusion (see Figure 3) to assess for AEs as specified in Table 17, CK, RCL and OS (see Table 3). A separate ICF will be provided for the LTFU period.

4.2 Scientific Rationale for Study Design

CAR T-cell therapy has been highly effective in treating patients with relapsed/refractory B-cell malignancies and multiple myeloma; studies are ongoing across the globe to understand the best approaches to provide benefit to patients with solid tumors (Schroeder et al 2022[39]). Several autologous GPC3 CAR T-cell products against other solid tumors have been tested in the clinic (summarized in Section 2.2.5 and Table 4**)**. The safety profile observed thus far between the different GPC3 CAR T-cell products appears similar, with the major toxicity being CRS, as is expected from autologous CAR T-cell products, with no reports of notable on-target off-tumors toxicities. In addition, most GPC3 CAR T-cell products have reported anti-tumors activity, supporting the further exploration of differentiated GPC3 CAR T-cell products in the treatment of squamous cell lung cancer.

This is a single-arm study primarily designed to evaluate the safety, tolerability and efficacy of C-CAR031 in patients with GPC3 + advanced/metastatic squamous cell lung cancer, who are not

amenable to curative therapy and have progressed or are intolerant to no more than 3 lines of prior systemic treatment including CPIs and platinum-based doublet chemotherapy, concurrently or sequentially. The study will also characterize the PK/PD and immunogenicity of C-CAR031 and explore potential biological activity by assessing pharmacodynamic and exploratory biomarkers and antitumor activity. The statistical design for this study is provided in Section 9.

4.2.1 Rationale for Lymphodepletion Chemotherapy

LDC will be administered to all participants in this study prior to C-CAR031 infusion to induce lymphopenia to improve T-cell engraftment and persistence. Clinical studies of T-cell therapy for melanoma at the National Cancer Institute have demonstrated that administering LDC such as cyclophosphamide and fludarabine, or cyclophosphamide, fludarabine, and total body irradiation, prior to the transfer of 10^{10} to 10^{11} polyclonal melanoma-specific T cells improved the survival of a subset of the transferred T cells and antitumor efficacy (Dudley et al 2002[48], Dudley et al 2005[49], Dudley et al 2008[50]). The size of the T-cell pool is subject to homeostatic regulation and the induction of lymphopenia results in less competition for cytokines, such as IL-15 and IL-7, that promote lymphocyte proliferation and survival. Therefore, LDC leads to the proliferation of residual T cells, including those that are adoptively transferred. Lymphodepleting chemotherapy may also eliminate CD4+ and CD25+ regulatory T cells and activate antigen presenting cells that may promote the function of transferred T cells. Studies in murine models subsequently confirmed the human data indicating that lymphodepletion improves the persistence and antitumor efficacy of transferred effector T cells (Wrzesinski et al 2007[51]).

Additionally, multivariate analyses from studies of CD19 CAR T-cell therapy have shown that outcomes in patients with B-cell malignancies are improved with high-intensity LDC containing fludarabine/cytarabine and with the incorporation fludarabine into LDC (Hay et al 2019[52], Hirayama et al 2019[53]). Pre-conditioning with cyclophosphamide has also been shown to modify the tumor microenvironment and enhance solid tumor CAR T-cell efficacy (Murad et al 2021[54]).

These data suggest that lymphodepletion before CAR T-cell therapy effectively prolongs the persistence of infused cells and increases the effectiveness of the CAR-T cells in treating cancer.

4.3 Justification for Dose

4.3.1 Dose for LDC

Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily (for 3 days) is an often used LDC regimen and is used in many approved cell therapy products in the treatment of lymphoma (Kamdar et al 2022[55]) and multiple myeloma (Cohen et al 2022[56], Lin et al 2000[57], Munshi et al 2021[58], Usmani et al 2022[59]). In China IIT study of C-CAR031 against HCC, cyclophosphamide 500 mg/m^2 and fludarabine 25 mg/m^2 daily (for 3 days) were used and has shown to be safe, tolerable, and the promising antitumor activity of C-CAR031 for patients with GPC3+ advanced/recurrent HCC in the IIT trial. Based on this, cyclophosphamide 500 mg/m^2 and fludarabine 25 mg/m^2 doses will be used for LDC (daily for 3 days) in this study. Alternatively, local standards can also be followed, after discussion and alignment with the collaborator.

4.3.2 Dose for C-CAR031

The starting dose of C-CAR031 (DL1) for this study will be a single IV infusion of a dose of 0.75×10^6 CAR- T cells/kg. This is based on the clinical precedence from previous GPC3-targeted CAR-T therapies with active and safe doses evaluated in patients with advanced/recurrent HCC. This includes data from key trials summarized in Table 4 and below.

- As of March 14, 2024, in the China IIT study of C-CAR031for advanced HCC (NCT05155189), a total of 24 subjects had been infused in four dose cohorts of 0.75, 1.5, 2.5 and 4.0 (unit: $\times 10^6$ CAR-T cells/kg) as mono therapy in 1, 6, 9, and 8 participant, respectively, 70.8% participants had lung metastatic lesions. No DLT events were observed in all dose cohorts (0.75, 1.5, 2.5 and 4.0); The MTD had not been reached. The median follow-up time was 9.03 months. As shown in Table 7, the 0.75, 1.5, 2.5 and 4.0 doses (unit: $\times 10^6$ CAR-T cells/kg) were safe and well tolerated, and the efficacy of the 1.5, 2.5 and 4.0 doses was better than that of the 0.75 dose. The ORR at 4.0 doses (75%) was higher than that in 1.5 and 2.5 doses (50%), the DCR was similar across dose cohorts. The median PFS and DoR at 4.0 doses was not mature by the data cutoff date, participants at 1.5 and 2.5 doses had the comparable median PFS (4.27m vs. 4.17m). The median DoR of 1.5 doses appeared to be longer than that of 2.5 doses numerically (7.36m vs. 4.44m, not compared statistically). 1 participant at 0.75 doses achieved a stable disease as the best of response, considered as a clinical benefit in this heavily treated patient population. Though there were 70.8% of participants had lung metastatic lesions, the pulmonary complications were not a safety concern in the HCC IIT.
- Other trials evaluating GPC3 CAR-T cells were considered but, unlike C-CAR031, those do not use the same armouring, have unknown vectors and manufacturing and therefore, were given less weight in these considerations. Dose ranges administered in these trials: Ori-C101; ChiCTR1900028121 (0.9 to 3.0×10^8) and NCT02395250, NCT03146234 (7.0×10^8 to 92.5×10^8) were above the C-CAR031 starting dose and generally tolerated and demonstrated some signs of clinical activity. See Table 4 for further details.
- The incidence of ⩾Grade 3 pulmonary toxicity ranges 5-13.3% in CAR-T therapy for hematologic malignancy, the severe pulmonary complications are considered associated with CRS (Lee et al 2015[60] and Wudhikarn et al 2020[61]). Putting these available data of C-CAR031 and other similar products together, 0.75×10^6 CAR- T cells/kg is chosen as the starting dose in this IIT for squamous cell lung cancer.

Dose modifications are described in Section 6.6.

The decision to proceed to the next dose level of C-CAR031 (either an increase or a decrease) will be made by the SRC based on safety, tolerability, and preliminary CK data obtained in at least 3 participants at the prior dose level (1 participant in dose level 1). See Section 6.6.1 for additional details.

4.4 End of the Main Study Definition

The end of the main study is defined as 12 months after the last participant has received his/her

dose of C-CAR031 (or sooner if: all the participants have progressed or stated a new anti-cancer therapy or death occurred, or have either withdrawn or are lost to follow-up, or investigator and AbelZeta aligned to terminate the study). Once end of the main study is achieved (or before if appropriate follow-up has been completed), all ongoing participants will continue follow up in LTFU (Stage 3) (see also Section 4.1 and Figure 3) for monitoring based on their willingness. The total duration of follow-up for participants in both the main study and LTFU will be up to 15 years (± 6 months) post-infusion of C-CAR031. A separate ICF will be provided for the LTFU period.

A participant is considered to have completed the main study if he/she has received C-CAR031, completed Stage 2 follow-up and/or commenced Stage 3 (and continued to the point of the end of the main study as described above in Section 4.4).

4.4.1 Study Stopping Criteria

The principal investigator and collaborator reserve the right to temporarily suspend or permanently terminate this study or components of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include, but are not limited to the following:

- Any death related to study treatment occurring within 60 days of receiving investigational product.
- Occurrence of 2 or more participants with Grade 4 DLTs at a particular dose level that are not pre-existing or not due to the underlying malignancy, other concomitant medications, or another non drug related etiology.
- Unexpected and life-threatening events deemed related to study therapy.
- Principal investigator or collaborator decision that the study participants are placed at undue safety risk. See Section 6.6.1 and 6.6.2 for more details on pausing/stopping criteria for Phase Ia and Phase Ib, respectively.
- Participant enrolment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Principal investigator or collaborator decision to terminate development of the study intervention.

If the principal investigator or collaborator determines that temporary suspension or permanent termination of the study or components of the study is required, the principal investigator and collaborator will discuss and get alignment on the decision. The principal investigator and collaborator will discuss the reasons for taking such action with all participating investigators. When feasible, the principal investigator and collaborator will provide advance notice to all participating investigators of the impending action.

If the trial is on hold and LDC has been initiated for any participant, a risk/benefit assessment will be conducted on a case-by-case basis between the investigator and collaborator to determine the

next steps and discussions with the study participant will be documented. Participants who have already been treated with C-CAR031 will continue in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations for recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators should keep a record (ie, patient screening log) of participants who entered prescreening and screening.

Each participant must meet all the inclusion criteria and none of the exclusion criteria for this study prior to undergoing apheresis.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria are met at screening and up to the time of apheresis. The latest result obtained prior to apheresis will be used to determine eligibility. A participant will be considered 'on study' when they have passed the clinical eligibility criteria at screening and undergone apheresis.

5.1.1 Inclusion Criteria to be Met for Pre-screening

Tumor Tissue Sample

To enable timely analysis and treatment, patients will sign a pre-screening consent for potential participant eligibility prior to enrollment. During this phase, subjects consent to pre-screening only and will be assessed for expression of GPC3 on the tumor via a validated IHC assay performed at the central laboratory. See Section 8.9.1.2 and Appendix C for further details.

Criteria to be Met for Pre-screening:

1 Participant could reasonably be anticipated to be eligible in the study in the future based on medical / disease history.

2 Consent and provision of:

(a) Squamous cell lung cancer tumor material to assess GPC3 expression and other correlative biomarkers of an archival tumor sample, collection time requirements are detailed in the laboratory manual. If a suitable archival sample is not available, a fresh tumor core biopsy may be collected (see Section 8.9.1.2).

5.1.2 Inclusion Criteria to be Met for Screening

Participants will be eligible for the study only if all of the following criteria apply during screening and up until the time of apheresis:

1. The participant voluntarily participates in the study, and the individual or their legal guardian signs the ICF.

2. 18 - 75 years of age at the time of signing ICF.
3. Histologically or cytologically confirmed unresectable Stage IIIB ,IIIC or IV (Staging per American Joint Committee on Cancer [AJCC], Edition 8) squamous cell lung cancer (Histology according to 2021 WHO classification of thoracic tumor; adenosquamous carcinoma treated as squamous carcinoma is eligible), Lymphoepithelioma-like carcinoma (LELC) is excluded.
4. Confirmed to express GPC3, as assessed by immunohistochemistry at a central lab This can be tested on archived tissue if available, although preferred tumor specimen is a biopsy after the most recent therapy.
5. Participants who have progressed or intolerant to no more than three lines of prior systemic therapies for advanced/metastatic squamous cell lung cancer.
    a Must have been treated systemically with the immune checkpoint inhibitor and standard platinum-based doublet chemotherapy, concurrently or sequentially.
    b Previously received no more than two lines of systemic therapy containing cytotoxic regimen for advanced/metastatic squamous cell lung cancer .
    c If a systemic regimen of adjuvant/neoadjuvant therapy or part of multimodal (eg, chemoradiotherapy) treatment for locally advanced disease is also recommended as a standard care of systemic therapy for advanced/metastatic squamous cell lung cancer by guidelines of Chinese Society of Clinical Oncology (2024) and disease progression occurs within 6 months of the end of therapy, the systemic regimen is considered a line of therapy for advanced/metastatic squamous cell lung cancer.
6. At least one measurable target lesion (as defined by RECIST v1.1).
7. ECOG performance status score of 0 or 1.
8. Minimal life expectancy ≥12 weeks, per the investigator's discretion.
9. The left ventricular ejection fraction (LVEF) measured by echocardiography ≥50% and reported as non-impaired. Measure must be within 28 days prior to apheresis.
10. Sufficient pulmonary function：
    a. Oxygen saturation ≥ 92% without supplemental oxygen requirement.
    b. Forced expiratory volume in one second (FEV1) ⩾ 1.0 liter or ⩾ 50% of predicted normal value.
    c. Diffusing capacity of the lungs for carbon monoxide (DLCO) ⩾ 40% of predicted normal value.
11. The laboratory testing results meet the following study requirements.

    Hematology

    a *Absolute Neutrophil Count (ANC) $\geq 1.5\times10^9$/L.
    b Absolute Lymphocyte count $\geq 0.5\times10^9$/L.

c *Platelet count ≥ 100×10^9/L.

d Hemoglobin ≥ 90g/L.

**Hematological criteria cannot be met with ongoing or recent blood transfusions (within 28 days prior to screening; within 14 days prior to apheresis) or required growth factor support (within 28 days prior to screening; within 21 days prior to apheresis).*

Blood biochemistry

e Serum total bilirubin ≤ 1.5×ULN (upper limit of normal) in the absence of Gilbert's syndrome, or ≤ 3.0×ULN if the patient has Gilbert's syndrome or liver metastases.

f Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5×ULN, or ≤5.0×ULN if the patient has liver metastases.

g *Calculated creatinine clearance ≥30 ml/min.

**As determined by Cockcroft-Gault equation using actual body weight. (Cockcroft and Gault 1976[62]) or 24-hour urine creatinine clearance*

Coagulation

h Prothrombin time International normalized ratio (PT-INR) ≤1.5×ULN.

12. Female participants of childbearing potential must test negative for pregnancy in serum or urine; non-sterilized participants (males and females) agree to take effective contraceptive measures for at least 12 months and until CAR-T below lower limit of detection (LLOD) by PCR which occurs last after C-CAR031 infusion. (See details in section 5.3 and appendix F).

5.2 Exclusion Criteria

Any potential participant who meets any of the following criteria **up until apheresis** will be excluded from participating in the study:

1. known to harbor a driver mutation for which targeted standard therapy is recommended in accordance with local treatment guidelines.
2. Known life-threatening allergies, hypersensitivity, or intolerance to the CAR-T product or its excipients, including dimethyl sulfoxide (DMSO).
3. ~~Known allergies~~ Contraindication to lymphodepleting agents, including fludarabine and/or cyclophosphamide.
4. History of splenectomy or organ transplantation.
5. Prior treatment with:
   a) Any CAR-T therapy.

      OR

   b) Any therapy that is targeting GPC3.
6. Uncontrolled or intercurrent pulmonary disease, including but not limited to:

a) Chronic obstructive pulmonary disease with obvious symptoms,

b) Moderate or above persistent asthma,

c) Prior pneumonectomy,

d) Previous history of ILD requiring corticosteroid therapy or history of non-infectious pneumonia or current/suspected ILD or pulmonary infectious pneumonia,

e) History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to apheresis.

7. Clinically meaningful ascites, defined as any ascites requiring non-pharmacologic intervention (eg, paracentesis) to maintain symptomatic control, within 6 months prior to apheresis. Participants on stable doses of diuretics for ascites for ≥ 2 months prior to apheresis are eligible.

8. Uncontrolled pleural effusion or pericardial effusion requiring recurrent drainage procedures (once monthly or more frequently).

9. Cancer-related spinal cord compression, leptomeningeal disease, or

   a) brain metastases, unless asymptomatic, treated, and stable radiologically (defined as 2 brain images, [both after treatment], should both be obtained at least 4 weeks apart and show no evidence of intracranial progression) and resolved or stable clinically; not requiring continuous corticosteroids at a dose of > 10 mg/day prednisone or equivalent for at least 4 weeks prior to apheresis.

10. Received radiation therapy within 4 weeks of apheresis; or within 6 months or 3 half-lives (whichever is longer) if local radioactive particle implantation was performed.

Note: Palliative radiotherapy to localized sites outside the lung (eg, for palliation of pain from a bone metastasis) is allowed with investigator's approval if completed - ≥7 days prior to apheresis and no residual adverse effects >grade 1 attributed to the radiation.

11. Received local treatment (such as: surgery, ablation) within 4 weeks of apheresis, or existence of unhealed wound. Or has surgery planned during the study, or within a minimum of 4 weeks after study treatment administration. (Note: participants with planned surgical procedures to be conducted under local anesthesia may participate).

12. Received inactivated or live attenuated vaccine within 4 weeks prior to apheresis.

13. Blood transfusions within 14 days and/or growth factor support within 21 days prior to apheresis.

14. Received systemic treatment and did not meet the minimum requirement for washout before apheresis:

    a Immune checkpoint inhibitor: within 5 half-lives or 3 weeks (whichever is shorter).

    b Chemotherapy, small molecule targeted therapy: within 5 half-lives or 2 weeks (whichever is longer).

    c Experimental anticancer drugs or other anti-cancer systemic treatment including Chinese herbal medicine, Chinese patent drug: within 5 half-lives or 2 weeks (whichever is longer).

    d Systemic dosing of steroid(s) (excluding: intranasal, inhaled, topical steroids or local

steroid injections [eg, intra-articular injection]; systemic corticosteroids at physiologic doses not exceed 10mg/day of prednisone or its equivalent; steroids as premedication for hypersensitivity reaction [eg, computed tomography [CT] scan premedication]) or other immunomodulators (eg. Interleukins, interferons, thymosins, etc.): within 5 half-lives or 2 weeks (whichever is shorter).

15. History of another primary malignancy except for:

    (a) Malignancy treated with curative intent and with no known active disease within 3 years before the apheresis and of low potential risk for recurrence.

    (b) Adequately treated non-melanoma skin cancer or lentigo malignancy without evidence of disease.

    (c) Adequately treated carcinoma in situ without evidence of disease.

16. History of or with active autoimmune diseases (including but not limited to systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, myasthenia gravis, Graves' disease, pituitary inflammation, multiple sclerosis, neuromyelitis optica spectrum disorders, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy, etc.; The following are exceptions: patients with vitiligo or alopecia, patients with hypothyroidism who have stabilized after hormone replacement therapy, any chronic skin disease that does not require systemic treatment, and other diseases that deemed not clinically significant per the investigator’s discretion).

17. Patients with central nerve system (CNS) diseases:

    a. Stroke, intracranial haemorrhage, or seizure within 6 months prior to apheresis.

    b. Active uncontrolled epilepsy within 5 years prior to apheresis.

    c. Other diseases with obvious neurological symptoms (including mental illnesses).

18. Active infection, including:

    a HBV infection defined as HBsAg [hepatitis B surface antigen] positive, or HBcAb [hepatitis B core antibody] positive and HBV DNA detectable.

    b HCV infection defined as HCV antibody positive and HCV RNA positive.

    c CMV infection defined as CMV DNA detectable.

    d Syphilis infection defined as syphilis antigen and antibody positive.

    e HIV infection defined as HIV 1/2 antibody positive.

    f Other persistent or active infections requiring systemic treatment (prophylactic use of anti-infective drugs is allowed).

19. History of cardiac arrhythmia (such as multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment ; unless controlled by pacemaker or medical management (discussion with the medical monitor required); symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia; Fridericia formula-corrected QT interval (QTcF) $\geq$ 470 msec

20. Uncontrolled or intercurrent cardiac diseases, including but not limited to:
    a) Unstable angina,
    b) Severe arrhythmia,
    c) Severe non-ischemic cardiomyopathy history
    d) Myocardial infarction
    e) Cardiac vascular surgery treatment occurred within 6 months.
21. Heart failure: heart function of Class III or IV per the New York Heart Association (NYHA) heart function classification standards.
22. Patients using full-dose long acting oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose. Use of short acting direct oral anticoagulants for therapeutic and prophylactic purposes are permitted.
23. Obvious risk or tendency of bleeding or active bleeding (eg, clinically significant hemoptysis, tumor bleeding, etc.).
24. Being in pregnancy or lactation period, or having plan to conceive during the study period.
25. History or current evidence of any condition, therapy, or laboratory abnormality that, per the investigator's discretion, might confound the results of the study, interfere with the participant's safety and/or study compliance.
26. Any unresolved toxicity NCI CTCAE ≥ Grade 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and endocrine disorders stable on treatment. Participants with irreversible toxicity not reasonably expected to be exacerbated by treatment with study intervention including Grade 2 neuropathy maybe included after consultation with the collaborator.
27. Patients with alcohol or drug abuse.
28. Clear clinical evidence of dementia or changes in mental state.

5.3 Lifestyle Considerations

1 Cell therapy may have a major influence on the ability of the participant to drive or operate machinery or engage in hazardous occupations or activities. The participant should be advised to refrain from these activities for 8 weeks post C-CAR031 infusion.

2 After C-CAR031 infusion, participants should not donate blood, organ tissue or cells (including ova and sperm donations) from Day 0 to until 12 months after C-CAR031 infusion or until the C-CAR031 CAR T-cell DNA is no longer detectable by PCR test, whichever occurs last.

3 Contraceptive use by males and females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants:

(i) Use of a condom from enrolment until 12 months after the infusion of C-CAR031 and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last. This applies to all sexual partners.

(ii) Female partners of male participants, and of childbearing potential: use of one highly effective method of contraception (refer to Appendix F for definition) from enrolment of the male participant until 12 months after C-CAR031 infusion and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last.

(b) For male participants that receive LDC but do not receive C-CAR031:

(i) Use of a condom from enrolment, until 6 months after the last dose of LDC.

(ii) For female partners of male participants (that receive LDC but do not receive C-CAR031), and of childbearing potential: use of one highly effective method of contraception from enrolment of the male participant until 6 months after the last dose of LDC.

(c) Female participants:

(i) Females of childbearing potential (refer to Appendix F for definition) must have a negative urine or serum pregnancy test at screening, prior to LDC (within 72 hours of the first dose of LDC) and a negative urine or serum pregnancy test prior to C-CAR031 infusion (Day 1).

(ii) Female participants of childbearing potential who are sexually active with a nonsterilised male partner must agree to use one highly effective method of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly; as described in Appendix F), from enrolment, where the contraceptive method must be effective prior to the first dose of LDC, until at least 12 months after the infusion of C-CAR031 and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last. It is strongly recommended for the male partner of a female participant to also use a male condom (plus spermicide, if available) from enrolment of the female participant until 12 months after C-CAR031 infusion, and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last. Female participants who receive LDC but do not receive C-CAR031, who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly) for 6 months after the last dose of LDC.

5.4 Screen Failures

A pre-screen failure occurs where a patient is not eligible for the study screening. A screen failure occurs when a participant who has consented to participate in the clinical study, does not meet eligibility criteria at any point prior to apheresis and is not subsequently apheresed. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (pre-screening or screening failure) may be rescreened. Rescreening can be permitted in the study (after

agreement with the collaborator). Rescreened participants should be assigned the new participant number.

Participants who meet eligibility and who are enrolled in the study but from whom it is not possible to collect adequate apheresis material or not possible to have a product successfully manufactured will be considered discontinuations and not screen failures. All screening data will be collected on these participants.

Please note: pre-screen patients who do not sign the main ICF will have AEs and SAEs related to study procedures collected.

5.5 Criteria for Temporarily Delaying Enrolment/Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, investigational medical products (IMPs) and non-investigational medical products (NIMPs), medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Table 10 Study Intervention

	CAR-T cells	**Lymphodepletion**	
Intervention name	C-CAR031	Cyclophosphamide	Fludarabine
Type	Genetic. Autologous CAR T-cell therapy	Drug: Lymphodepleting chemotherapy	Drug: Lymphodepleting chemotherapy
Dose formulation	Cell suspension for infusion	Solution for infusion	Solution for infusion
Unit dose strength(s)	Number of CAR-positive viable T cells	As per label	As per label
Dosage level(s)	**Phase Ia (safety run-in and backfill):** Starting dose 0.75×10^6 CAR T cells/kg **Phase Ib (dose expansion):** cohort treated at RDE determined in Phase Ia	500 mg/m^2 or per local standards	25 mg/m^2 or per local standards
Route of administration	IV infusion	IV infusion	IV infusion

	CAR-T cells	Lymphodepletion	
Regimen	Single dose	Daily for 3 days	Daily for 3 days
Use	Experimental	Background intervention	Background intervention
IMP or NIMP/AxMP	IMP	NIMP	NIMP
Sourcing	Collaborator product and intellectual property, provided centrally by collaborator	Locally by the study site, subsidiary, or designee, or collaborator, if agreed.	Locally by the study site, subsidiary, or designee, or collaborator, if agreed.
Operation input	C-CAR031 will be provided in a CryoMACS Freezing Bag in an aluminum cassette. It will be labelled according to the local labelling guidelines and requirements. Each IMP should be accompanied by: 1 COA 2 IMP Packaging and Shipping Form It will be labelled as required per country requirement	Sourced from study site, no axillary labelling required	If sourced from study site, no axillary labelling required.
Current/former name(s) or alias(es)	C-CAR031	Cyclophosphamide	Fludarabine
Duration of infusion	As per IMP Handling Manual guidance	Per site's internal SOPs	Per site's internal SOPs
Order of infusion	N/A	Per site's internal SOPs	Per site's internal SOPs

AxMP = auxiliary medicinal product; CAR-T = chimeric antigen receptor T-cell; COA = Certificate of analysis; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; IV = intravenous; N/A = not applicable; RDE = Recommended dose for expansion; SOP = standard operating procedure.

6.1.1 Apheresis

Prior to apheresis, review of safety assessments should be completed per the SoA (Table 2). The

screening evaluation results of participants must meet the inclusion criteria and not meet the exclusion criteria. Vital signs, chemistry and hematology should be evaluated again within 3 days prior to apheresis. All the inclusion criteria of main screening (see Section 5.1.2) are met and none of the exclusion criteria of main screening (see Section 5.2) is met, and no other situations judged by investigator as unsuitable for apheresis, the participant can proceed to apheresis.

Apheresis should be performed according to institutional standards and following the instructions for processing and shipping apheresis product provided in the collaborator Apheresis Handling Manual.

If apheresis is performed > 14 days after main screening assessments, chemistry laboratory assessments should be repeated.

For participants who require a repeat apheresis, sites should first discuss this with the collaborator and the following screening assessments should be collected before the second apheresis:

- Weight
- CBC with differential
- Chemistry laboratory assessments
- ECG (if clinically indicated)

If the second apheresis falls outside of the 28-day screening window, all screening assessments (except tumor biopsy) must be repeated according to their applicable windows for completion.

6.1.2 Bridging Therapy

If appropriate, the participants are permitted to receive bridging therapy if it is necessary to provide disease control (this is not considered a line of therapy), during the period between apheresis and baseline assessment, while the participant is waiting to receive C-CAR031. The investigator must contact the collaborator for confirmation prior to administering bridging therapy. Bridging therapy will be administered according to Prescribing Information or treatment guidance in general use by the investigating site.

A treatment will be considered eligible as a bridging therapy if it meets the following criteria:

1 Favorable risk-benefit assessment for short duration of treatment, including no contraindications.
2 Bridging therapy with oral TKI locally approved for this indication e.g., afatinib (Half-life period is 8 days) may be utilized. Other agents are to be discussed with collaborator on a case-by-case basis. Long half-life drugs e.g., CPIs, antibodies, chemotherapy, TKIs with long half-life which couldn’t be eliminated within a short period (around 7 days) may not be used. Must ensure an adequate washout period between the administration of the bridging therapy and baseline assessment - at least 5-half-lives wash out of bridging therapy

prior to baseline assessment.

6.1.3 Lymphodepletion

Prior to infusion of C-CAR031, all participants will undergo lymphodepletion per rationale in Section 4.2.1.

6.1.3.1 Lymphodepletion Criteria

The investigator should contact the collaborator if evidence of rapid disease progression is observed between apheresis and lymphodepletion. Participants must meet the following criteria to proceed with lymphodepletion.

1. No presence of active infection per investigator's discretion. For participants requiring systemic anti-microbial treatment or with temperature ≥ 38.0 °C within 7 days prior to the first dose of lymphodepletion, the investigator must receive confirmation to proceed from the collaborator.
2. ECOG score 0~1.
3. Within 3 days before lymphodepletion, the laboratory test must meet the following requirements:

   a Hemoglobin (Hb) ≥90 g/L ; ANC ≥1.5×10^9/L ; Platelet (PLT) ≥100×10^9/L; White blood cell (WBC) > 1.0×10^9/L.

   b Total bilirubin (TBL) ≤ 1.5×ULN (≤3× for Gilbert's syndrome or liver metastases), ALT and AST ≤2.5×ULN, or ≤5.0×ULN if the patient has liver metastases.

   c Calculated creatinine clearance ≥30 mL/min.
4. Oxygen saturation ≥ 92% without supplemental oxygen use required.
5. The participant needs to complete the relevant examinations according to the visit schedule before the administration of lymphodepletion, and the examination results can proceed with lymphodepletion after being evaluated by the investigator.
6. C-CAR031 cells have been successfully prepared and meet the quality control standards.
7. Negative pregnancy test (serum or urine) for females of child-bearing potential within 72 hours prior to the first dose of lymphodepletion regimen.
8. A repeat echocardiogram scan may be required for participants who received bridging therapy that included agents with known cardiac toxicity and verification of non-impaired cardiac function (LVEF ≥ 50%) performed. Note: If given, to be performed after completion of bridging therapy and prior to the first dose of the lymphodepletion regimen.
9. No cumulative dose of corticosteroids equivalent to ≥ 70 mg prednisone within the 7 days prior to lymphodepletion. The collaborator should be contacted for confirmation if a participant receives corticosteroids at a dose > 10 mg per day in the week prior to the start of lymphodepletion.

10. No major surgery < 2 weeks prior to lymphodepletion.
11. No active Grade 3 toxicity to any bridging therapy.
12. No live attenuated vaccines within 30 days prior to lymphodepletion.
13. No new arrhythmia or other cardiac AEs unless controlled with medical management and approved by the collaborator.
14. There are no other situations judged by investigator(s) as unsuitable for lymphodepletion.

6.1.3.2 Administration of Lymphodepletion Regimen

The preferred regimen of cyclophosphamide 500 mg/m^2 and fludarabine 25 mg/m^2 daily for three days will lead to lymphodepletion and help promote C-CAR031 CAR T-cell expansion in the participant. Participants will receive three daily doses of cyclophosphamide and fludarabine-based lymphodepletion on Days -5, -4, and -3 prior to CAR T-cell infusion (Section 4.3.1).

Cyclophosphamide 500 mg/m^2 and fludarabine 25 mg/m^2 before C-CAR031 is consistent with the lymphodepletion regimen used in previous IIT study of C-CAR031. Alternatively, the dosage can also be adjusted per local standards after discussing and confirmation from collaborator.

After meeting eligibility criteria for undergoing lymphodepletion, all participants should receive the following conditioning regimen:

- Cyclophosphamide 500 mg/m^2/day IV on Days -5, -4 and -3
- Fludarabine 25 mg/m^2/day IV on Days -5, -4 and -3

Pre-medications for lymphodepletion should be given after confirmation with the collaborator per institutional standard.

If renal deficiency or hepatic impairment is observed, consider dose reduction of fludarabine and/or cyclophosphamide per the local institutional standard. In cases where the participants' hematological parameters do not meet the pre-specified laboratory criteria for undergoing lymphodepletion and/or the participant has a known intolerance to fludarabine or cyclophosphamide, the administration of alternative lymphodepletion regimens may be considered upon discussion with the collaborator.

Refer to Section 6.1.4.1 for the evaluation of participant health status prior to administration of C-CAR031. For those participants who do not meet the criteria for undergoing C-CAR031 infusion after 7 days of the last LDC dose, the investigator should contact the collaborator.

Following discussion with the collaborator, these participants can be dosed after 7 days of LDC completion. However, these participants may need to be replaced.

Of note, for participants with lymphocyte recovery, or 21 days post last dose of LDC, whatever is longer, administration of a repeat LDC course should be discussed with the collaborator (with

consideration to participant fitness, WBC count ≥ 1 × 10^9/L, and prior fludarabine exposure).

6.1.4 C-CAR031

6.1.4.1 Eligibility Check Prior to Administration of C-CAR031

Participants will be evaluated for safety within 48 hours prior to C-CAR031 infusion (within 2 days after the last dose of LDC). If a significant health status change (ie, clinical deterioration, rapidly progressing disease) occurs following the start of lymphodepletion, the investigator should contact the collaborator prior to C-CAR031 infusion.

Infusion of C-CAR031 must be delayed if any of the following events occur:

- Signs of active infection. Do not administer C-CAR031 to participants with active infection. For participants requiring systemic anti-microbial treatment, or with temperature ≥ 38.0 °C within 48 hours before C-CAR031 infusion, CAR T-cell infusion should be delayed until the infection has been successfully treated or controlled.
- Non-hematologic toxicities of lymphodepletion (except for Grade 3 nausea, vomiting, diarrhea, or constipation) not recovered to < Grade 3; Grade 4 neutropenia and Grade 4 thrombocytopenia not recovered to ≤ Grade 3. The investigator must consult with the collaborator prior to C-CAR031 dosing.
- Oxygen saturation < 92% without supplemental oxygen .
- ECOG score > 1.
- The investigator assesses that the participants are unable or unwilling to comply with the study protocol.

6.1.4.1.1 Participant Wallet Card

Before the infusion of C-CAR031 (ie, Day 0), participants will receive a participant wallet card that they must carry for a minimum of 56 days after the C-CAR031 infusion. The Participant Wallet Card is provided to increase participant awareness of the risks of CAR T-cell therapy, promote quick recognition and disclosure of any potential signs or symptoms during the study, and to inform participants about actions that must be taken if they are experiencing these symptoms or signs. At each on-site visit throughout the study, the investigators will ensure that the participant has the Participant Wallet Card with them.

6.1.4.1.2 Pre-infusion Supportive Therapy

Prior to C-CAR031 infusion, participants should receive premedication as noted in Table 11 to minimize the likelihood of an allergic reaction. Corticosteroids should not be used during pre- infusion.

Table 11 Pre-infusion Medications

Medication	Dose	Administration

Antihistamine	Diphenhydramine (50 mg) or equivalent	Oral – administer 1 hour (±15 minutes) prior to C-CAR031 OR IV or IM – start infusion/injection 30 minutes (±15 minutes) prior to C-CAR031 infusion.
Antipyretic	Acetaminophen (650 mg to 1000 mg) or equivalent	Oral or IV – administer 30 minutes (±15 minutes) prior to C-CAR031 infusion.

IM = intramuscular; IV = intravenous

6.1.4.2 C-CAR031 Administration

C-CAR031 will be administered within 7 days after the last LDC dose. Participants will be evaluated for safety within 48 hours prior to C-CAR031 infusion (as described in Section 6.1.4.1). For participants who do not meet the criteria for undergoing C-CAR031 infusion after 7 days of the last LDC dose, the investigator should contact the collaborator. Following discussion with the collaborator, these participants may receive C-CAR031 7-21 days after LDC completion.

C-CAR031 will be supplied by the collaborator for infusion and participants will receive 1 dose of C-CAR031. For details on dose preparation and administration please refer to the C-CAR031 IMP Handling Manual.

All planned assessments required for C-CAR031 administration (see SoA Table 2), including laboratory tests, must be completed and the results reviewed prior to the start of the C-CAR031 infusion. Treatment decisions will be based on safety and disease assessments performed at the local laboratory.

Following C-CAR031 administration, participants will remain hospitalized for a minimum of 7 days and should be within an approximate 2-hour travel time from the study site for approximately 28 days following C-CAR031 infusion.

In the event of an allergic reaction, the infusion must be immediately stopped, and antihistamine treatment initiated, as per institutional guidelines (see risk management plan [RMP]). Acute mild respiratory distress developing during or immediately after (within 48 hours) C-CAR031 infusion can be managed with supportive care (see RMP).

At the first signs of either CRS or neurotoxicity, participants should be hospitalized for monitoring and evaluation (see RMP).

6.1.5 Exceptional Release Criteria

In the event a CAR T-cell therapy product that did not meet pre-specified release criteria is produced during the manufacturing procedures, the collaborator will evaluate the risk/benefit for administration of the affected product, and determine if the supply of the product could be considered. If administration of the Exceptional Release IMP is considered appropriate by the collaborator, the investigator will evaluate the risk/benefit and confirm administration of the affected product is for the participant's interest. If the participant agrees, and it is filed or

approved by the Institutional Review Board or Independent Ethics Committee (IRB/IEC), the investigator should submit a formal request to collaborator including appropriate documentation required by health authorities (if required) prior to C-CAR031 infusion.

If required, collaborator will seek approval from the relevant health authorities for use of the product. If an Out-of-Specification product is administered to the patient, this information will be captured in the CRF.

6.2 Preparation, Handling, Storage, and Accountability

- The investigator or designee (eg, pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying collaborator (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by collaborator (or designated party).
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the C-CAR031 IMP Handling Manual.
- Refer to the C-CAR031 IMP Handling Manual for information on the procedure for product thawing and dose preparation.

6.3 Assignment to Study Intervention

This is an open-label study. Once participants have signed the main screen ICF at a site they will be assigned medication according to the agreed participant number.

6.4 Blinding

Not applicable.

6.5 Study Intervention Compliance

Apheresis, infusion of LDC, and infusion of C-CAR031 will be conducted in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. The details of apheresis, and administration of LDC and C-CAR031 will be recorded

in the source documents and recorded in the electronic Case Report Form (eCRF) (including date, dose, start, and stop times of the infusion, and volume infused). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Precautions associated with the use of the study treatment and concomitant medications will be reviewed by the collaborator.

Refer to the Apheresis Handling Manual and the C-CAR031 IMP Handling Manual for a description of the chain of identity and chain of custody procedures associated with the apheresis product and C-CAR031.

6.6 Dose Modification

6.6.1 Starting Dose, Safety run-in and backfill Scheme and Stopping Criteria

Starting Dose

The starting dose of C-CAR031 for this study will be a single IV infusion of a dose of 0.75×10^6 CAR T cells/kg (see Section 4.3).

Table 12 shows the Phase Ia scheme.

Table 12 C-CAR031 Phase Ia Scheme

Dose level cohort [a]	Planned dose (10^6 CAR- T cells/kg)
DL -1	0.5
DL 1	0.75
DL 2	1.5
DL 3	4.0

[a] Additional intermediate/higher dose levels can be explored based on the available clinical data and not exceed the 3 times the current dose or the highest dose that has been determined safe by SRC. (no more than 6.0×10^6 CAR-T cells/kg). CAR = chimeric antigen receptor; DL = Dose level.

The DLT observation period is from infusion to 28 days post-infusion of C-CAR031 (Day 0 to Day 28). DLT observation is for the first 1-6 evaluable participants of each dose level cohort. After DLT observation period is complete for a minimum of 3 evaluable participants (1 participant in dose level 1), relevant data will be reviewed by the SRC, and the SRC can approve to explore the next dose level and/or decide to start the backfill of current dose level; Or recommend to recruit 3 more evaluable participants in current dose level as safety run-in. The SRC can suggest exploration of intermediate or higher dose levels based on the available data. If 1 out of the first 3 participants or 2 out of the first 6 participants (the first participant of dose level 1) in a dose cohort experience the DLT, the SRC cannot recommend a dose escalation to doses exceed this current dose cohort.

- An DLT evaluable participant in the safety run-in phase should have received C-CAR031 per

protocol, with no substantial protocol violations and completed the DLT period (or have experienced a DLT before the end of DLT period). Non evaluable (NE) participants will be replaced.

- A minimum of 3 DLT evaluable participants are required in the dose level 2 and 3 unless unacceptable toxicity is encountered in the first 2 participants prior to enrolment of the third participant. For the dose level 1, 1 evaluable participant is required.

The first 1-6 participants of each dose level will be evaluated as safety run-in phase. Backfill will stop when up to 12 evaluable participants have been filled in each dose level. The SRC can decide to proceed to the backfill phase; the early termination of the backfill phase of each dose level after evaluation of available data; and /or further explore additional intermediate/higher dose levels. And if a new dose is to be explored, repeat the above steps of safety run-in phase of Phase Ia. The SRC will evaluate the safety, efficacy, tolerability, available CK and other available data of C-CAR031 at the new dose level to determine whether to continue to backfill phase.

To limit the number of participants who could be exposed to an unanticipated risk associated with C-CAR031 administration, a minimum of 14-days observation period between cell infusions for the first and second participant in each dose is required, if DLT occurred, all the other participants in this dose level will have minimum of 14-days observation period between each.

Staggered administration of C-CAR031 will not be required for:

- Dose levels assessed as tolerable by the SRC with a minimum of N = 3 evaluable participants (1 participant in dose level 1)
- Backfill and dose expansion phase

The RDE could be selected in consultation with the SRC based on an assessment of aggregate safety data and all relevant clinical and nonclinical data available at that time. The RDE for continued clinical development of C-CAR031 will be assessed as tolerable.

The dose for subsequent cohorts or a decision to stop recruitment to dose expansion (Phase Ib) of the study will be agreed upon by the SRC after review of the data from each cohort (See Section 6.6.5).

SRC can suggest starting the enrollment of dose-expansion cohort during Phase Ia, when:

1) The RDE has been determined safe in the Phase Ia.

2) The benefit/risk ratio supports the early dose expansion after the aggregate safety data and all relevant clinical and nonclinical data available at that time being evaluated by SRC.

Early dose-expansion and safety run -in to next dose level will be conducted in parallel in the circumstances. SRC will predefine the priority rules for participants allocation.

6.6.2 Dose Expansion

A dose-expansion phase, (Phase Ib) will begin at the RDE to confirm the safety, tolerability, CK/PD, efficacy of study intervention. Phase Ib dose expansion will investigate C-CAR031 in approximately 12 evaluable participants at each RDE.

Intermediate dose levels may be explored if warranted by emerging safety, CK/PD, and efficacy data. During dose expansion, participants will be monitored for safety using the same DLT criteria employed during safety run-in. If during the treatment period, ≥ 30% of participants experience safety events that would meet the criteria for a DLT in the safety run-in Phase of the study, the SRC will review the study data to determine whether additional monitoring, alternate dose levels, or treatment schedules should be evaluated prior to further enrolment.

Enrolment into the dose expansion cohort may be discontinued at the discretion of the investigator or collaborator or SRC based on emerging clinical or preclinical data suggest that continued treatment may not be beneficial to participants in a given cohort (see Section 4.4.1 for study stopping criteria, and Section 6.6.5 for details on the SRC).

Participants may be replaced if, for example, they are lost to follow-up, did not receive C-CAR031 per protocol, violated the protocol, did not have acceptable tumor measurements, or were non-compliant.

6.6.3 Definition of DLT

DLTs are defined as AEs that occur in the first 28 days after C-CAR031 infusion and meet the following criteria listed below.

For DLT criteria, ASTCT consensus Grading will be used for CRS and ICANS (Lee et al 2019[63]) and CTCAE v5.0 for all other events.

DLTs should be followed until improvement to full recovery (baseline, CTCAE Grade ≤ 1, or no further improvement expected).

The DLT definition **includes** any of the following conditions:

Hematologic Toxicities (not pre-existing, not related to underlying malignancy other concomitant medications, or another nondrug related etiology):

- Grade 3 or greater neutropenia lasting > 28 days with clinically significant complications.

  Note: If the Grade 3 event is not treated according to local guidance, the SRC will review the event and may determine the event as not a DLT despite being >28 days duration.
- Grade 4 febrile neutropenia lasting > 72 hours with clinically significant complications.
- Grade 3 febrile neutropenia > 14 days with clinically significant complications.

  Note: If the Grade 3 event is not treated according to local guidance, the SRC will review the event and may determine the event as not a DLT despite being >14 days duration.

- Grade 4 anemia lasting > 72 hours with clinically significant complications.
- Grade 3 or greater thrombocytopenia lasting > 28 days without clinically significant bleeding or requiring platelet transfusion.

  Note: if the Grade 3 event is not treated according to local guidance, the SRC will review the event and may determine the event is not a DLT despite being > 28 days duration.
- Grade 3 or greater thrombocytopenia with clinically significant bleeding.

Non-hematologic Toxicities (not pre-existing, not related to underlying malignancy other concomitant medications, or another nondrug related etiology):

- Any Grade 5 toxicity.
- Any treatment-emergent Grade 4 CRS.
- Any treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 7 days.
- Any treatment-emergent Grade 4 ICANS.
- Any treatment-emergent Grade 3 ICANS that does not resolve to ≤ Grade 2 within 72 hours.
- Any treatment-emergent autoimmune toxicity ≥ Grade 3.
- Grade 4 liver transaminase increase*.
- In participants without liver metastases, Grade 3 AST or ALT increase, do not resolve to ≤ Grade 2 within 10 days*.
- In participants with liver metastases, Grade 3 AST or ALT increase, do not resolve to ≤ Grade 2 within 10 days, if the baseline level was ≤1.5 × ULN*.
- In participants with liver metastases, AST or ALT increases > 3x but ≤ 10x baseline, do not downgrade to ≤ 3x baseline within 10 days, if the baseline level was > 1.5 × ULN; Or AST or ALT increases > 10x baseline*.

  *Note: Before defining a DLT, the SRC should review cases where AST meets the DLT criteria, but ALT remains < 3x ULN or < 2x baseline to determine whether AST release from other organ system injury is confounding the assessment of liver safety.
- Any confirmed Hy's Law case (see Appendix D).
- Grade 3 allergic reaction that does not downgrade to ≤ Grade 2 within 72 hours despite maximal supportive care (including systemic corticosteroids).
- Grade 4 allergic reaction related to C-CAR031 infusion.
- Any other Grade 3 treatment related AE that cannot resolve to ≤ Grade 2 within 7 days despite optimal supportive care (if event not otherwise specified as a DLT or a DLT exception).
- Any other Grade 4 treatment related AE that cannot resolve to ≤ Grade 2 within 3 days despite optimal supportive care (if event not otherwise specified as a DLT or a DLT exception), should be assessed by SRC to determine whether it is a DLT.
- Any other toxicity that is clinically significant and/or unacceptable and regarded to be a DLT by the SRC.

The DLT definition **excludes** any of the following conditions:

- Grade 3 or 4 lymphocytopenia of any duration.
- Grade 3 tumor lysis syndrome for < 14 days not associated with clinically significant complications.
- Grade 3 electrolyte disorders requiring intravenous fluids not associated with clinically significant complications.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy with resolution of the symptoms within 14 days after treatment onset.
- Concurrent vitiligo or alopecia of any AE grade.
- Fatigue of any AE grade.
- Grade 3 or 4 hypoalbuminemia not associated with clinically significant complications.
- Isolated Grade 3 laboratory abnormalities that are not associated with clinical signs or symptoms (eg, hyperlipasemia or hyperamylasaemia not associated with clinical signs or symptoms or radiographic features suggestive of pancreatitis).

6.6.4 Definition of DLT-Evaluable Participant

An DLT-evaluable participant is defined as a participant who has received C-CAR031, and either:

- has completed minimum safety evaluation requirements and has received at least 1 completed infusion of C-CAR031 per protocol during the first 28 days.

AND

- has completed the DLT observation period without major protocol deviations

  OR

- has experienced a DLT during the first 28 days post C-CAR031 infusion

6.6.5 Safety Review Committee

The members of SRC include the investigators, an independent clinician, an AbelZeta's medical delegate, and other relevant personnel may be added according to the specific needs of the study, including but not limited to the medical monitor, pharmacovigilance physician, clinical pharmacologist, statistician. All representatives from AbelZeta or other collaborators will be non-voting members.

A study specific SRC, in accordance with its charter, will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, efficacy, CK, and other relevant data. The SRC may also meet to review data at other time points (ie, in response to AEs assessed as medically relevant by the investigator). The SRC may also advise on modifications in study conduct, including whether hospitalization, local stay, or staggered dosing is required for

subsequent participants or stopping further enrolment if treatment-emergent toxicity is believed to result in an unfavorable risk-benefit profile. This committee will be responsible for making decisions regarding dose strategy and regarding further conduct of the study during all follow-up stages and parts of the study.

The SRC will review the totality of all AEs, SAEs, and laboratory safety data for participants in the DLT period and all other available relevant data prior to adjudicating on dose decisions based on the protocol.

After each dose level during the safety run-in (Phase Ia) section of the study, once there are at least 3 evaluable participants (1 participant in dose level 1), the SRC will evaluate the safety, efficacy, tolerability, available CK and other available data of C-CAR031 to decide the dose for the next cohort of participants:

- All available toxicity information (ie, AEs) and laboratory abnormalities in addition to the DLTs
- All available CK and other available data
- The dose recommendation
- Any dose interruptions and reductions will be taken into account.

The minimum data listed above will be extracted and confirmed for accuracy by the investigator ahead of the SRC.

The decision may be to:

- Proceed with dose escalation
- Start the backfill phase/continue the safety run-in of current dose level but not to exceed the total number of evaluable patients at a single dose
- De-escalate the dose either to a previous lower-dose level or to an intermediate lower-dose level
- Stop the dose-escalation part of the study (see Section 4.4.1 and 6.6.1) for more details on pausing/stopping rules)
- Initiate dose-expansion cohort(s).
- Explore a new dose level.

The SRC membership, purpose and frequency of SRC meetings, as well as the data and decision-making process to be used by the SRC are described in the SRC Charter and Appendix A 5. All decisions by this committee will be clearly documented and communicated to all SRC members as defined in the SRC Charter.

6.6.6 Risk Management Plan

The C-CAR031 RMP has been developed to assist investigators with the recognition and management of toxicities associated with use of C-CAR031. These RMPs are applicable to the management of participants receiving C-CAR031 as specified in the protocol.

The RMPs provide information for the management of CRS, ICANS, IRRs, and other reactions that may be observed with C-CAR031 treatment, with specific instructions for treatment interventions. These guidelines are provided as a recommendation to support investigators in the management of potential AEs. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with C-CAR031 treatment.

All AEs experienced will be graded for severity according to the NCI CTCAE v5.0 toxicity criteria with the exception of CRS and ICANS, which will be graded using ASTCT consensus grading (Appendix G).

6.7 Continued Access to Study Intervention After the End of the Study

No intervention is planned after the end of the study.

6.8 Treatment of Overdose

C-CAR031 CAR-T cells must be administered as a single dose by trained personnel at the investigational sites in this study. Infusion guidelines provided in the C-CAR031 IMP Handling

Manual must be strictly followed, including premedication, duration of infusion, and vital sign monitoring.

For this study, any dose of lymphodepleting agents or C-CAR031 greater than the defined dose will be considered an overdose.

The collaborator does not recommend specific treatment for an overdose of C-CAR031. Overdose with LDC medications should be managed as per local standard and the product label.

In the event of an overdose, the investigator/treating physician should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4.15 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

In the event of an LDC overdose, the investigator/treating physician should evaluate the participant to determine whether the dose should be reduced. The overdose should be assessed and managed as per local guidance and product label.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest eg,

corticosteroids that the participant (except for screen failures) is receiving should be recorded after screening commences, until completion of Stage 2 follow-up and must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route

The prohibited concomitant medications in the study are provided in Table 13. Permitted concomitant medications are provided in Table 14.

The collaborator should be contacted if there are any questions regarding concomitant or prior therapy.

Table 13 Prohibited Concomitant Medications

Supportive medication/ class of drug	Usage
Corticosteroids	Corticosteroid use should be avoided, except for the treatment of CRS or neurotoxicity or other adverse events where corticosteroids use is indicated. Dependent on timing of events relevant to CAR-T therapy and impact on potential efficacy, alternative therapies, if feasible, should be considered prior to corticosteroids.
Other immunosuppressants	Other immunosuppressant agents unless used as protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS).
Natural/herbal product	That may have immune-modulating effects, have unknown toxicities or anticancer effects (unless agreed by the collaborator).
GM-CSF	Must not be used for 28 days after C-CAR031 infusion or until CRS resolved (whichever is later).
Pegylated G-CSF	Long acting pegylated G-CSF should not be used within 21 days before apheresis and 28 days after C-CAR031 infusion or until CRS resolved (whichever is later).
G-CSF	Consider holding until 10 days after infusion of C-CAR031 or until CRS has resolved (whichever is later).
Any investigational therapy and anticancer therapy other than those under investigation in this study	Any chemotherapy, hormonal (except non-cancer conditions), targeted treatments, anticancer immunotherapy, or experimental therapy, (except protocol-specific therapies) should not be given concomitantly while the patient is in Stage 1 and 2 of the study. Participants can receive these agents in Stage 3 of the study.
Surgery and radiotherapy	During stage 1, non-emergency surgery or radiotherapy is generally prohibited, but may be allowed in the absence of disease progression. Cases must be discussed and approved by the investigator. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy). Participants can receive these agents in Stage 3 of the study.

Live/attenuated vaccinations	Should not be given within 30 days prior to lymphodepletion regimen, due to the immunosuppressed state of participants during this time frame, and for the 30 days following C-CAR031 infusion.

CRS = cytokine release syndrome; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.

Table 14 Permitted Concomitant Medications

Supportive medication/class of drug	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Table 13	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all participants
Hormonal therapy	Should be used for non-cancer-related conditions only (eg, hormone replacement therapy)
Growth factor support allowed with restrictions	See Table 13 for restrictions
Transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia	To be administered according to local standards of care.
Hydration	Should be used, when necessary, for all participants
Inactivated viruses, such as those in the influenza vaccine	Permitted
CYP450 substrates which have a narrow therapeutic window	Given the expected pharmacology of C-CAR031, the release of cytokines in the immediate period post the first administration of C-CAR031 may potentially lead to secondary alteration of CYP450 enzymes, with risk of subsequent drug-DDIs. Based upon the known mechanism of action of other CAR-T therapies, this risk is highest during the first week, or longer in the event of a prolonged event of CRS, after the first administration. Participants at highest risk for DDIs are those receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic window. As such, participants receiving medications fitting this description should be monitored closely and the dose adjusted as necessary.

DDI = drug-drug interaction; CRS = cytokine release syndrome

6.9.1 Rescue Medicine

CRS events that occur after C-CAR031 administration may require anti-IL-6 treatment (eg, tocilizumab) or corticosteroids. Emergency equipment must be available per participant prior to

infusion. Tumor necrosis factor-alpha antagonists are generally not recommended for management of CAR-T-associated CRS. In cases of CRS that is unresponsive to tocilizumab (or equivalent) or corticosteroids, additional interventions targeting cytokines may be considered based on institutional practice for management of unresponsive CRS. Refer also to RMP for further general supportive care guidance and for more information about management of CRS.

Before C-CAR031 infusion, the on-site pharmacy should confirm that adequate doses of supportive medications, including anti-IL-6 treatment (eg, tocilizumab or equivalent) are available on site and for administration for each participant within 2 hours after C-CAR031 infusion, if needed for CRS treatment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

C-CAR031 is administered as a one-time infusion and therefore discontinuation of study treatment is not applicable in this study. The following sections describe different scenarios under which participants may discontinue from participating in specific parts of the study. It is important to follow participants treated with C-CAR031 for the durations defined in Section 1.3 given the potential for delayed toxicities that may be associated with the administration of genetically modified cells.

7.2 Participant Discontinuation/Withdrawal From the Study

7.2.1 Discontinuation from the Study Between Apheresis and Prior to CAR T-Cell Infusion

Participants who are enrolled into the study may not receive the C-CAR031 for the following reasons:

- The investigator believes that for safety or tolerability reasons (ie, AEs, significant worsening of the participant's clinical status) it is in the best interest of the participant not to receive C-CAR031
- Participant decision
- Manufactured C-CAR031 is out-of-specification and not suitable for infusion
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study
- Investigator and AbelZeta aligned to termination of study for reasons including, but not limited to, unfavorable risk/benefit or change in drug development plan.

Participants who do not undergo C-CAR031 infusion will be required to be followed for a minimum of 30 days post the last dose of lymphodepletion and/or bridging therapy if applicable (or until AEs have returned to a minimum of Grade 2) for AEs. These participants will be followed up per local standard of care (SoC), will undergo an early discontinuation/completion visit, and

will not enter Stage 3 follow-up. See Table 2 and Table 3 for data to be collected at the time of early discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.2 Discontinuation from Stage 1 Follow-up

Participants may discontinue from Stage 1 of the study for the following reasons:

- Start of new anticancer treatment
- Disease progression (clinical or radiologically confirmed) as defined in Section 8.2
- Participant or investigator decision
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study
- Non-compliance with the CSP (investigator or participant)
- Investigator and AbelZeta aligned to termination of study for reasons including but not limited to unfavorable risk/benefit or change in drug development plan.

A participant who discontinues from the study in Stage 1 will be asked to undergo an early discontinuation visit and will be offered to transition to Stage 3 to assess for AEs as described in Table 17, CK, RCL, and OS (Stage 3 follow-up described in Table 3). Participants who have completed a scheduled study visit within 14 days of decision to continue follow-up in Stage 3 will not need to complete the early discontinuation visit.

Participants in Stage 3 are considered in long-term safety follow-up and will be allowed to start other anticancer treatments or other investigational clinical trials.

7.2.3 Discontinuation from Stage 2 Follow-up

Participants who enter Stage 2 may discontinue from this stage of the study and continue to be followed in Stage 3 for the following reasons:

- Disease progression (clinical or radiologically confirmed) as defined in Section 8.2
- Participant or investigator decision
- Non-compliance with the CSP (investigator or participant)
- Start of a new anticancer treatment
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study
- Investigator and AbelZeta aligned to termination of study for reasons including but not limited to unfavorable risk/benefit or change in drug development plan.

A participant who discontinues from Stage 2 will be asked to undergo an early discontinuation visit and will be offered to transition to Stage 3 of the study to assess for AEs as described in Table 17, CK, RCL, and OS. Participants who have completed a scheduled study visit within 30 days of the decision to continue follow-up in Stage 3 will not need to complete the early discontinuation visit.

Participants in Stage 3 are considered in long-term safety follow-up and will be allowed to start other anticancer treatments or other investigational clinical trials.

7.2.4 Participant Withdrawal from the Study

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records), and also the option to enter Stage 3 follow-up, which has limited assessments and allows the participant to start other anticancer treatments or other investigational clinical trials.
- If the participant withdraws consent for disclosure of future information, the investigator may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, the investigator may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation. See also Appendix C 2.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or continue in the study. Participants should be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records) and also the option to enter Stage 3 follow-up, which has limited assessments and allows the participant to start other anticancer treatments or other investigational clinical trials.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study/been lost to follow-up. Site personnel, or an independent third party, will attempt to collect specific AEs (as per Table 17 and Section 8.4.7) and survival status of the participant within legal and ethical boundaries for all participants who receive the study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Collaborator personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are provided in the following sections.

- Study procedures and their timing are summarized in the SoA Section 1.3. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with the collaborator immediately upon occurrence or awareness to determine if the participant should continue or discontinue (applicable for LDC only), study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants pre-screened and screened to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of Human biological sample(s) (HBS) will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS see Appendix C.
- The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical or other factors. Results of tests and procedures conducted as per SoC purposes prior to screening may be used for research purposes if conducted within the protocol-defined window prior to apheresis or LDC.
- If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood draw. Blood collections for biomarkers and CK assessments should be kept as close to the specified time

as possible. Actual dates and times of assessments will be recorded in the source documents and the laboratory requisition form.

- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the collaborator or the investigator, as per local health authority/ethics requirements.
- The amount of blood collected from each participant over the duration of the study may vary, however the maximum amount will not exceed 550 mL in an 8-week period.
- Safety laboratory assessments will be performed locally at each center's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Treatment decisions will be based on safety and disease assessments performed at the local laboratory.

8.1 Administrative and General/Baseline Procedures

Demographic data will include gender, age, race, and ethnicity. A complete medical history should include all relevant prior and current medical history, and should also include anticancer therapies.

Key baseline disease specific information including key clinical, histopathology, biomarkers, and key prognostic data will be collected including:

- Dates of diagnosis and disease staging
- Biomarker information (PD-L1/mutation testing and status/other)
- Smoking status
- Details of histopathological assessments performed including grade, if appropriate at diagnosis and most recent biopsy
- Tumor burden, ie, size, location, and number of tumors including CNS metastases at baseline
- Details of prior anticancer treatments (including systemic, locoregional, and radiotherapy), best response to prior treatment, and date of progression
- Dates and details of surgery, including lung resection

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the Section 1.3 SoA.

8.2.1 Efficacy Endpoints

Efficacy endpoints in the two parts of the study include ORR, durable response rate (DRR), DoR,

DCR, time to reponse (TTR), percentage change in tumor size, PFS, and OS. Please see Section 9.4.3 for detailed definitions of endpoints.

8.2.2 Tumor Assessments

RECIST 1.1 guidelines (Eisenhauer et al 2009[64]) for evaluating squamous cell lung cancer will be utilized for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumor response criteria are presented in Appendix E and will be performed according to the schedule presented in the SoA (Section 1.3).

Standard radiographic imaging using RECIST is used to assess both response (in participants with measurable disease) and progression. An ORR as per RECIST 1.1 criteria requires confirmation of PR and complete response (CR) and must occur no fewer than 4 weeks after initial documentation of PR or CR. Disease progression will be defined as per RECIST 1.1.

Throughout the research process, from the baseline period examination, the tumor imaging examination methods and parameters for the same participant must remain unchanged.

Patients who terminate the study prematurely due to reasons other than disease progression (such as toxicity) will continue to undergo tumor assessments as originally planned, until the participant begins subsequent anti-cancer treatment, disease progression occurs (assessed according to RECIST 1.1), consent is withdrawn, lost to follow -up, death occurs, or until the study is terminated, whichever occurs first.

All tumor assessments should include the following evaluations: physical examination and cross-sectional imaging using CT or Magnetic Resonance Imaging (MRI) scan.

Physical Examination

Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules, and palpable lymph nodes and spleen. Documentation by colour photography including ruler is recommended for estimating the size of skin lesions.

Imaging

Use dynamic enhanced CT scan or dynamic enhanced MRI, which must include chest, abdomen, pelvic cavity, head and neck, and whole-body bone scans. CNS imaging is optional unless disease is known to be present at baseline.

The preferred method of systemic disease assessment is CT with contrast; if CT with contrast is contraindicated, CT without contrast is preferred over MRI. The preferred method for CNS imaging is MRI; if CT scan is performed, CT with contrast is required. The same method should be followed for all subsequent tumor assessments.

CT Scans

CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI Scans

MRI scan is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations.

In addition to chest, abdomen, and pelvis cavity, head and neck, and whole-body bone scans, clinically indicated sites as determined by the treating investigator should be assessed at baseline.

Brain Scans

Brain scans are at the discretion of the investigator if CNS involvement is known/suspected. Post-baseline imaging of the brain will only be required in participants with brain metastases at baseline, while participants without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.

Assessment Schedule

To confirm eligibility a radiological assessment during the screening period should be performed no more than 28 days before the start of apheresis. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period are acceptable.

Baseline radiological assessments can be done anytime within 7 days prior to C-CAR031 infusion, ideally performed as close as possible to the start of study intervention on Day 0. If bridging therapy were conducted, the baseline radiological assessments should be done after the washout of bridging therapy.

The methods of assessment used at baseline should be used at each subsequent follow-up assessment through to radiologically objective progressive disease (PD), as defined by RECIST 1.1 and as determined by the investigator, or start a new anticancer treatment, or withdrawal of consent, lost to follow -up, death occurs, or until the study is terminated, whichever occurs first. Tumor assessments should be performed as per the SoA, until RECIST 1.1-defined radiological objective PD (see also Appendix E and Section 7.2). If scans are performed outside of scheduled visit window interval and the participant has not progressed, every attempt should be made to perform the subsequent scans at their scheduled visits. It is important to follow the SoA as closely as possible (see Section 1.3).

Tumor assessments should continue on schedule until RECIST 1.1-defined radiological progression followed by a subsequent scan, unless clinically unfeasible, evaluated by Confirmation of Radiological Progression criteria. The subsequent scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration). If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

8.2.2.1 Collection of Imaging Data for Secondary and Exploratory Analysis

Radiological examinations performed in the conduct of this study should be retained at site as source data. All treatment decisions will be based on site assessment of scans. Duplicates of all radiological examinations (redacted of personal identifiers to the participant) for participants must be available at the site in readiness to be sent for review, if requested by the collaborator. Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an collaborator-appointed CRO for quality control, storage, and, if deemed appropriate by the collaborator, for IRC evaluation Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the CRO is strongly encouraged. IRC evaluation of images will be performed at the discretion of collaborator. Results of these independent reviews will not be communicated to investigators, and results of investigator tumor assessments will not be shared with the central reviewers. Further details of the IRC evaluation will be documented in an Independent Review Charter. Guidelines for imaging collection and storage will be provided in a separate document.

8.2.3 Survival Follow-up

Participants will be followed up for survival status in this study as indicated in the SoA (Table 2 and Table 3) until death, withdrawal of consent, lost to follow-up or the end of the study. Survival information may be obtained via telephone contact, email or through a clinic visit with the participant or the participant's family, or by contact with the participant's current physician. If the site becomes aware that a participant has died prior to the final analysis, the relevant eCRF on the database should be completed at that time.

Additionally, other assessments, including subsequent anticancer therapy and time to second progression or death, are to be recorded.

In order to support key efficacy endpoints of OS analyses, the survival status of all participants in the Full Analysis Set should be re-checked for those participants who withdrew consent or are classified as "lost to follow-up."

- Participants lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status (the applicable eCRF modules will be updated)
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8.2.4 Subsequent Anticancer Treatment

The study site should maintain a record of the participant's exposure to subsequent anticancer therapies (including mutagenic agents for C-CAR031-treated participants) in the CRF. For C-CAR031-treated participants if they experience an AE (eg, new malignancy) that may either be possibly related to C-CAR031 treatment, a new anticancer regimen, or to exposure of a

mutagenic agent, then the site should enter the relevant treatment (ie, C-CAR031/mutagenic agent/anticancer therapy) into the appropriate CRF page.

8.2.5 Clinical Outcome Assessments

Not applicable.

8.3 Safety Assessments

Clinically relevant unfavorable changes occurring during the study must be recorded in the AE section of the eCRF. Clinically significant abnormalities persisting at the end of the study/withdrawal/study discontinuation will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Safety monitoring assessments may be performed more frequently, if clinically indicated.

Planned time points for all safety assessments are provided in the Section 1.3 SoA.

8.3.1 Physical Examinations

A complete physical examination will be performed at timepoints as specified in Section 1.3 SoA and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. Height and weight will be assessed at screening, apheresis, baseline and infusion eligibility, and weight only at follow-up.

A brief physical examination will be performed at timepoints as specified in Section 1.3 SoA and include assessments, at a minimum, of the following: neurological, skin, lungs, cardiovascular system, abdomen (liver and spleen), and lymph nodes.

8.3.2 ECOG Performance Status

Performance status will be assessed at timepoints as specified in Section 1.3 SoA according to ECOG criteria as follows:

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work.
- 2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.
- 5 = Dead.

Any significant change from baseline or screening must be reported as an AE.

8.3.3 Vital Signs and Oxygen Saturation

Vital signs will be performed at timelines as specified in the Section 1.3 SoA.

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, respiratory rate. Blood oxygen saturation will be measured at thetimepoints specified in Section 1.3 SoA. Three readings of blood pressure and pulse will be taken and should be averaged to give the measurement to be recorded in the eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.4.4.

Temperature should be checked at least twice a day by the participant after discharge until the end of the DLT period. Participants should be informed to contact their study doctor if any increase in temperature above 38 ^{o}C.

For any AEs of infusion-related reactions, the vital signs values should be entered into the eCRF.

8.3.3.1 Vital Signs and Oxygen Saturation to be Collected During CRS

Vital signs including body temperature and oxygen saturation should be monitored per institutional guidelines until values are normalized following a CRS event.

8.3.4 Cardiac and Pulmonary Safety Assessments

8.3.4.1 Electrocardiograms

12-lead ECG will be performed at timepoints as specified in the Section 1.3 SoA.

ECGs will be performed in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) and the mean value of the triplicate measurement will be recorded as the baseline value. At all other time points, a single ECG will be obtained. All ECG recordings will be made with the subject in a supine position having rested in this position for at least 5 minutes before the start of the ECG.

All ECGs will be recorded at a speed of 25 mm/second with amplitude recording of 100 mm/mV. At least 3 full complexes must be recorded. A multi-channel ECG machine should be used (equals 3 leads recorded simultaneously) and there must be amplitude index calibration for each lead. Digital copies of ECGs may be held centrally by a central ECG provider and stored for potential independent analysis during, or at the end of, the study at the collaborator’s discretion.

Electronic software will be used to assess the following parameters: pulse rate, RR, QRS, QT, and QTc time intervals. All ECGs must be reviewed by the principal investigator or a medically qualified designee before the start of C-CAR031 infusion (for time points prior to the infusion) and before the participant is permitted to leave the clinic (for post-infusion time points). In case of a clinically significant ECG abnormality (eg, occurrence of de- or re-polarization disorders, arrhythmic disorders), including QTc interval prolongation by Fridericia’s formula of > 500

milliseconds, a minimum of 2 additional 12-lead ECGs should be obtained over a brief interval (eg, 30 minutes) to confirm the abnormality based on manual over-read by a medically qualified person. Such abnormalities and any obvious changes in ECG parameters from baseline will be assessed by the principal investigator for clinical significance. If clinically significant, the ECG abnormality should be recorded as an AE in the eCRF. Clinical interpretation and any associated management of participants related to ECG abnormalities will be done locally and will be based on interpretation by a medically qualified person at the site.

8.3.4.2 Echocardiography (ECHO)

An ECHO to assess LVEF will be performed at the visits as shown in Section 1.3 SoA. The same modality should be used throughout the study for any given participant (ie, if ECHO is used for the screening assessment, then ECHO should also be used for subsequent assessments). Participants should also be examined using the same machine and operator whenever possible and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%). All ECHO scans performed will be evaluated for the change in LVEF from baseline.

If a participant has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which ECHO results should be reported as AEs are described in Section 8.4.4.

8.3.4.3 Pulmonary Function Test

A pulmonary function test that measures breathing and how well the lungs are functioning will be done during the screening and as clinical indicated.

8.3.5 Clinical Safety and Efficacy Laboratory Tests

- Blood and urine samples for determination of clinical chemistry, hematology, coagulation, urinalysis, serology, and pregnancy will be taken at the visits indicated in Section 1.3 SoA.
- Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.
- The clinical chemistry, hematology, coagulation, urinalysis, serology, pregnancy assessments will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured (see Table 15).

Table 15 Laboratory Safety and Efficacy Variables (Local Laboratories)

Hematology (whole blood [B]) [a]	**Blood chemistry (serum [S] or plasma [P]) [a]**	
B-Red blood count	S/P-Glucose	S/P-Alanine transaminase

B-White blood cell count with differential (including % neutrophils, B-Absolute lymphocyte, B-Absolute neutrophil, lymphocytes, monocytes, basophils, eosinophils)	S/P-Aspartate transaminase	S/P-Alkaline phosphatase
B-Platelet count	S/P-Gamma-glutamyl transpeptidase	S/P-Bilirubin, total (including direct)
B-Hemoglobin	S/P-Total protein	S/P-Albumin
B-Hematocrit		S/P-Creatinine
Urinalysis (U)	S/P-Uric acid	S/P-Urea
U-Ph	S/P-Creatine kinase and its isoenzymes	S/P–Lactate dehydrogenase
U-Ketones	S/P-Total cholesterol	S/P-triglycerides
U-Protein	S/P-Sodium	S/P-Potassium
U-Glucose	S/P-Calcium	S/P-Chlorine
U-Erythrocytes	S/P-Phosphorus	
U-White blood cell	S/P-Ferritin [a]	S/P-C-reactive protein [a]
U-Bilirubin	TSH	S-Troponin [a, b]
U-Bilinogen	NT-proBNP/BNP [a, b]	
Coagulation [a]	**Pregnancy test (females of childbearing potential only; local laboratories)**	
International normalized ratio	U-human chorionic gonadotropin	S/P-human chorionic gonadotropin
Activated partial thromboplastin time		
Prothrombin time	**Serology**	
Fibrinogen	Qualitative HBsAg, anti-HBc, anti-HBs, qualitative HBeAg, anti-HBs, Quantitative HBV-DNA, HCV, HCV RNA, anti-HCV, CMV DNA, and anti-HIV (1/2) serology, TPPA	
D-dimer		
Cytokine [a, c] (including but not limited to blood TGFβ, IL-2, IL-4, IL-6, IL-10, IL-18, TNF-α, INF-γ)		

a These clinical laboratory parameters to also be monitored during CRS, or suspected CRS.
b To be conducted only if clinically indicated.
c Cytokine will be tested in clinical sites when these clinical laboratory parameters are monitored during CRS, or suspected CRS.

CMV = cytomegalovirus; DNA = Deoxyribonucleic acid; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NT-proBNP= N-terminal pro-brain natriuretic peptide; TPPA = treponema pallidum particle assay.

Additional laboratory safety variables that may be added include triiodothyronine (T3), thyroxine (T4), adrenocorticotropic hormone, cortisol, prolactin, luteinizing hormone, follicle stimulating hormone, mean corpuscular volume (MCV) and hemoglobin A1c (HbA1c).

NB. In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2× ULN please refer to Appendix D, for further instructions and cases.

Table 16 Clinical Laboratory Parameters to be Monitored During CRS

Test category	Test name
Hematology	Platelets
Chemistry	Creatinine, LDH, ALT, AST, TBL
Coagulation	PT and INR, aPTT, d-dimer, fibrinogen
Inflammatory markers	CRP, ferritin
Cardiac	Serum troponin, NT-proBNP/BNP

ALT = alanine amino transferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = B type natriuretic peptide; CRP = C-reactive protein; CRS = cytokine release syndrome; INR = international normalized ratio; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro B-type natriuretic peptide; PT = prothrombin time; TBL = total bilirubin.

Minimal specific laboratory parameters described in Table 16 should be monitored following a CRS event until values are normalized. If multiple samples are taken, data from samples taken at key times in the CRS course should be entered into the EDC. At a minimum, the site should attempt to collect the laboratory parameters described in Table 16 at the beginning of CRS, at the peak of CRS symptoms, and after the resolution of CRS.

8.3.6 Neurological Examination

8.3.6.1 Brain MRI

Brain MRI (or CT scan if MRI is not feasible) or neurology consultation should be considered for all participants as part of apheresis eligibility screening, if pre-existing disease is expected. For participants with prior pertinent neurologic disease (ie, stroke, encephalitis) consider baseline MRI of brain and/or an electroencephalogram (EEG) as clinically appropriate. Brain MRI may be performed as clinically indicated thereafter. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. CAR-T cell-related neurotoxicity (ie, ICANS) should be graded using ASTCT consensus grading (see Appendix G). Neurotoxicity that is not temporarily associated with CRS, or any other neurological events that do not qualify as ICANS will be graded by CTCAE v 5.0 criteria only.

Findings from neurological testing that support CAR-T cell-related neurotoxicity (ie, ICANS) should be reported in the eCRF.

8.3.6.2 Immune Effector Cell Encephalopathy (ICE) Score

The ICE score will be collected as denoted in Section 1.3 SoA (Table 2). For ICE scoring see Appendix G. The ICE test was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR T products (Lee et al 2019[63]).

8.3.6.3 Electroencephalogram

In case of suspected ICANS, EEG will be conducted as clinically indicated after C-CAR031 infusion to the end of Stage 1 follow-up and findings reported in eCRF.

8.4 AEs, SAEs, and Other Safety Reporting

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) must notify the investigator or designees of any symptoms. These must then be assessed by the investigator and if considered an SAE it will be reported by the investigator immediately (within 24 hours regularly) after awareness of SAE.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- AE grade/changes in AE grade (ASTCT consensus grading for CRS and ICANS; CTCAE for other AEs)
- Whether the AE is SAE or not
- Whether the AE is an AESI (yes/no)
- Administration of treatment for the AE (yes/no)
- Investigator causality rating against any of: apheresis, LDC, bridging therapy (if given) or, the IMP (yes or no)
- Action taken with regard to IMP(s)
- AE caused participant's withdrawal from the study (yes/no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- SAE description
- At least one SAE seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Investigator causality rating against any of: apheresis, LDC, bridging therapy (if given), or the IMP (yes or no)
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Outcome
- CTCAE grade

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of signature of the study main ICF, throughout the treatment period and including the follow-up period. For patients who signed the pre-screening ICF, only AEs and SAEs related to study procedures will be collected during the pre-screening period. See AE/SAE collection requirements in Table 17 for details on collection window for AE/SAE, and see Appendix B 1 and B 2 for definitions of AE/SAE.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to the collaborator **within 24 hours**.

Table 17 Adverse Event Collection Window

AE collection period	AE collection requirements
Pre-screening period from the pre-screening ICF signature	Only AEs and SAEs related to study procedures will be collected
From study main ICF signature until 6 months post C-CAR031 infusion (Stage 1 follow-up)	Collect all AEs and SAEs. If the participant starts a new anticancer regimen, collect specific AEs (as described in Section 8.4.7) and any AE/SAE deemed by the investigator to be possibly related to C-CAR031
From 6 months to 12 months post C-CAR031 infusion (Stage 2 follow-up)	Collect all AEs and SAEs. If the participant starts a new anticancer regimen, collect specific AEs (as described in Section 8.4.7) and any AE/SAE deemed by the Investigator to be possibly related to C-CAR031

From 12 months to a maximum of 15 years post C-CAR031 infusion (Stage 3 follow-up)	Specific AEs (Section 8.4.7), and SAEs deemed by the investigator to be possibly related to the C-CAR031

- Any ongoing AEs should be followed to resolution (or if no resolution, until stabilization).
- If a participant does not receive infusion of C-CAR031 after bridging therapy or LDC, all AEs will be collected for 30 days post last dose or until start of new anticancer regimen, until the study discontinuation (whichever occurs first).

AE = adverse event; SAE = serious adverse event; ICF = informed consent form; LDC = lymphodepletion chemotherapy.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The collaborator retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. SAE Should be followed up until outcome of SAE was resolved, stable, death or participant was loss follow-up or the investigator could offer reasonable explanation.

8.4.3 Causality Collection

The investigator should assess causal relationship between the study intervention (apheresis, LDC, bridging therapy [if given] or C-CAR031) and each AE/SAE and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Disease progression and deterioration of an event, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of a study intervention and may require close monitoring and rapid communication to the collaborator by the investigator. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of a study intervention.

AESI will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AESI will be assessed by the investigator for severity, relationship to the study intervention, possible etiologies, and whether the event meets criteria for an SAE. If an AESI evolves into a condition that meets the regulatory definition of "serious," (see Appendix B for definitions) it will be reported as described in Section 8.4.10.

Based on the available preclinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, the following events are considered to be AESIs for C-CAR031:

- CRS
- Neurological disorders including ICANS
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- Any infection with RCL

- New primary malignancy

8.4.7 Specific AEs

Specific AEs are defined as AEs that fall into the following categories as per FDA and NMPA guidance for long term follow-up after administration of human gene therapy products (FDA 2020a[66], NMPA 2021[65]):

- New malignancy(ies)
- New incidence of infection (potentially product-related)
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder.

8.4.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of:

- AST or ALT ≥ 3 × ULN (if within normal range at baseline) together with TBL ≥ 2 × ULN (if within normal range at baseline*) or
- AST or ALT ≥ 3 × baseline value or ≥ 10 × ULN (if above normal range at baseline) together with TBL ≥ 2 × ULN (if within normal range at baseline*)

*If TBL is above normal range at baseline requires association with TBL ≥ 1.5 × baseline value with direct bilirubin (DB) ≥ 50% of the total, or any increase in DB ≥ 1 mg/dL over baseline may need to be reported as SAEs, unless caused by other underlying causes.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.9 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the Disease under study (DUS) and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AE/SAE during the study.

8.4.10 Reporting of SAEs

SAEs must be reported according to SAE reporting requirements in protocol whether or not considered causally related to the study intervention. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, the investigators or other site personnel need to conduct

timely emergency treatment to participants, filling in SAE/AESI form and inform the appropriate collaborator representatives immediately but no later than 24 hours and record in the eCRF .

For fatal or life-threatening SAEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform the collaborator representatives of, and record in the eCRF, any follow-up information on a previously reported SAE also reported according to SAE reporting process by filling in SAE/AESI form immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated collaborator representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate collaborator representative.

When the EDC is temporarily not accessible, the collaborator Study Representative should confirm that the investigator/site staff enters the SAE in the collaborator EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the collaborator IMP C-CAR031.

8.4.11 Pregnancy

Within 12 months post C-CAR031 infusion, and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last, all pregnancies and outcomes of pregnancy should be reported to the collaborator except if the pregnancy is discovered before the study participant has received any study intervention.

8.4.11.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects, stillbirth and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect, etc.) should be followed up and documented in the clinical trial pregnancy report form. Consent from the participant must be obtained before the Pregnancy Report Form is completed, even if the participant was discontinued from the study.

If any pregnancy occurs from the date of C-CAR031 infusion until 12 months after the infusion of C-CAR031 and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last, then the investigator or other site personnel fill in clinical trial pregnancy report form and informs

the appropriate collaborator representatives immediately but no later than 24 hours after he or she or he becomes aware of it.

The same timelines reporting apply when outcome information is available.

Female participants must not donate ova from the Day 0 until 12 months after C-CAR031 infusion and until the C-CAR031 CAR T-cell DNA is no longer detectable by PCR test, whichever occurs last.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the paper based PREGOUT module is used to report the outcome of the pregnancy.

8.4.11.2 Paternal Exposure

Male participants must not donate sperm from Day 0 until 12 months after C-CAR031 infusion and until the C-CAR031 CAR T-cell DNA is no longer detectable by PCR test, whichever occurs last.

Pregnancy data will be collected for all female partners of male participants from the infusion of C-CAR031. If a male participant's female spouse/partner becomes pregnant during the study, the same reporting procedure and timeline should be followed as mentioned in Section 8.4.11.1.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly, etc.), occurring from the date of C-CAR031 infusion until 12 months after the infusion of C-CAR031 and until CAR T-cell DNA is no longer detectable by PCR, whichever occurs last, should, if possible, be followed up and documented in the Pregnancy Report form. Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.4.12 New Primary Malignancies

The development of a new cancer, including hematological malignancy, should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study intervention, and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer. New cancers that arise that are not the primary reason for the administration of the study intervention will be considered as potential secondary malignancies that require additional follow-up.

8.4.13 Positive RCL Results

If any sample for RCL is positive, it must be reported to the collaborator according to SAE reporting process **within 24 hours**, and an ad hoc sample will be collected and analyzed to confirm the result. If the repeat test is also positive, this will be considered a confirmed positive result. The result of the repeat test, positive or negative, must be reported to the collaborator as a follow-

up **within 24 hours**.

8.4.14 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of C-CAR031, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the appropriate collaborator representatives and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE **within 24 hours after awareness**. It should also be documented in the eCRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Death with an unknown cause, or potentially related to C-CAR031, should always be reported as an SAE. It should also be documented in the eCRF. Autopsy may be helpful in the assessment of the cause of death, and if performed, a copy of the autopsy results should be forwarded to the collaborator or its representative within the usual time frames.

Additionally, the death eCRF is provided immediately after the occurrence or outcome of death is reported.

8.4.15 Reporting of Overdose

C-CAR031 T cells must be administered as a single dose by trained personnel at the investigational sites in this study. Infusion guidelines provided in the Product Handling Manual must be strictly followed, including premedication, duration of infusion, and vital sign monitoring.

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose of an IMP or collaborator NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate collaborator representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

If there is any untoward medical occurrence resulting from the overdose, associated AEs/SAEs will be recorded on the relevant modules in the eCRF (Section 8.4).

8.5 Pharmacokinetics

- Whole blood samples will be collected for measurement of whole blood concentrations, expansion, and persistence of C-CAR031 as specified in the Section 1.3 SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and collaborator, eg, for urgent safety reasons, and this will not be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough C-CAR031 concentrations) to ensure appropriate monitoring.
- Samples collected for analyses of C-CAR031 whole blood concentration, expansion, and persistence may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for CK see Appendix C.
- The CK (DNA copy number) samples can be hold 6 months after completion of CSR. CK samples for flow cytometry cannot be stored after analysis and the remaining samples will be destroyed after completing the analysis.
- Additional analyses may be conducted on the anonymized, pooled, or individual CK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Collection of Samples for Cellular Kinetics and Blood Cell Immunophenotyping

Blood samples will be collected for measurement of parameters listed in Table 18 at timepoints as listed in the SoA (Section 1.3).

Table 18 Description of Sample Collections for PK and Blood Cell Immunophenotyping

Sample name	Sample type	Purpose of collection
Cellular kinetics by PCR [a]	Whole blood	Characterization of expansion, and persistence of CAR-T product via detection of CAR transgene copies.
Cellular kinetics by flow cytometry [a]	Whole blood	Characterization of expansion, and persistence of CAR-T product via detection of CAR-T percentage and absolute counts.
Blood cell Immunophenotyping	Whole blood	Phenotyping of circulating lymphocytes; including but not limited to T cells, CAR T-cell subsets, B cells, and natural killer cells; and their relationship to clinical outcomes.

[a] For the sampling beyond M6, if two consecutive assessments of C-CAR031 sample concentrations are < LLOQ, then sampling may be stopped.

CAR-T = chimeric antigen receptor T-cell; CK = cellular kinetics; PCR = polymerase chain reaction; LLOQ = lower

limit of quantification.

8.5.2 Determination of C-CAR031 Blood Concentration

Samples for determination of the CAR transgene by PCR or blood CAR-T cell numbers by flow cytometry for C-CAR-031 will be analyzed by an analysis lab using appropriately validated bioanalytical methods. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

8.6 Pharmacodynamics

8.6.1 Collection of Samples for Pharmacodynamics

Tumor biopsies and peripheral blood will be collected to assess the pharmacodynamic activity of C-CAR031 (see Section 1.3).

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For additional details on storage, re-use, and destruction of pharmacodynamic samples, see Appendix C.

8.7 RCL Detection

The risk of infection with cell products manufactured with newer 2nd/3rd generation self-inactivating lentiviral vectors has been shown to be very low. For the safety of study participants, C-CAR031 will be tested for RCL as part of product release criteria before infusion.

Participants will also be tested for RCL at the baseline and following administration of C-CAR031. A whole blood sample will be collected to detect the presence of lentiviral agent by PCR at timepoints stated in the SoA (Table 2 and Table 3). Collection of RCL samples may be discontinued for a participant if all samples tested during the first year after C-CAR031 infusion are negative. All positive RCL results should be reported as a medically significant SAE (see Section 8.4.13).

Additionally, relevant clinical samples should be collected and tested for RCL if participants have AEs suggestive of a retroviral-associated disease, or if patients die of a suspected retroviral-associated disease or develop neoplasms within 15 years after C-CAR031 infusion.

8.8 Immunogenicity Assessments

- Blood samples for determination of humoral immunogenicity will be assayed by an analysis lab, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.
- For storage, re-use, and destruction of immunogenicity samples see and Appendix C.
- Remaining immunogenicity sample aliquots will be retained at the collaborator or its

designee for 1 year after completing CSR. Additional use includes but is not limited to further characterization of any immunogenicity, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.8.1 Collection of Samples for Immunogenicity Assessments

Blood samples will be collected for measurement of parameters per the timepoints listed in the SoA (Section 1.3).

Table 19 Blood Samples and Purpose of Collection for Immunogenicity Assessments

Sample name	Sample type	Purpose of collection
Humoral immunogenicity	Blood (serum)	Detection of anti-drug-antibody against and its impact on CK of CAR-T cells, and clinical efficacy and safety outcomes.

CAR = Chimeric antigen receptor; CK = cellular kinetics.

Further details on immunogenicity sample collection will be detailed in the Laboratory Manual.

8.9 Biomarkers

8.9.1 Mandatory Biomarker Sample Collection

Blood and tumor tissues samples for biomarker analyses are required and will be collected as specified in the SoA (see Section 1.3). By consenting to participate in the study, the participant consents to the mandatory research components of the study within the scope of the protocol-defined objectives (see Section 3 and below). Details regarding specimen collection, processing, and testing will be provided in the Laboratory Manual.

8.9.1.1 Collection of blood Samples

To assess systemic biomarkers of disease, pharmacodynamic biomarkers and biomarkers of clinical response to C-CAR031, presence of and changes in peripheral DNA, RNA, ctDNA, immune cell phenotype, and protein biomarkers, which may include, but not limited to, soluble and cellular analytes, gene expression, and immune markers pre- and post- treatment will be studied.

8.9.1.1.1 Collection of Blood for RNA and DNA

A peripheral blood sample will be collected for RNA and DNA sample preparation. Baseline and on-treatment whole blood RNA and DNA will be collected at timepoints indicated in the SoA. Samples may be tested to evaluate the pharmacodynamics, potential candidate predictive biomarkers, early biomarkers of response, potential resistance mechanisms, and lentiviral vector genome integration site when applicable.|

8.9.1.1.2 Collection of Serum and Plasma

A peripheral blood sample will be collected to provide serum and plasma for analysis of exploratory biomarkers, eg, ctDNA, soluble GPC3 and cytokines. Baseline and on-treatment serum and plasma will be collected at timepoints as specified in the SoA. For baseline ctDNA analysis, buffy coat (white blood cells) together with plasma will be collected. Details regarding specimen collection and processing will be provided in the Laboratory Manual.

Cytokines, including but not limited to IL-2, IL-4, IL-6, IL-10, IL-18, TNF-α, and IFN-γ, will be evaluated as potential pharmacodynamic markers for the activation of CAR-T cells.

Blood TGFβ levels will also be examined to assess its impact on armored CAR-T cells.

Soluble GPC3 baseline levels will be investigated to correlate with the baseline tumor expression levels of GPC3 and the clinical efficacy of C-CAR031, including ORR, PFS, and OS.

ctDNA will be collected to evaluation of association of baseline ctDNA levels and kinetics of ctDNA changes with clinical outcome measures. We will evaluate the correlation between tumor and plasma mutational status.

8.9.1.2 Collection of Pre-screening Tumor Samples

Provision of a tumor tissue at pre-screening is mandatory for all participants. Archived formalin-fixed paraffin-embedded (FFPE) sample (see Section 5.1 for detailed sample requirement) or fresh core needle or excisional biopsies are acceptable, fine needle aspirated are not acceptable.

Tumor Samples should have enough material to fulfil the requirements outlined in the Laboratory Manual. Where a participant has multiple existing tissue samples with sufficient tumor content available, the most recent sample is preferred.

If no sample is available, tumor tissue from a new biopsy must be collected following SoC procedures, if the participant is willing and it is deemed safe and feasible by the investigator and if the biopsy is not expected to present any additional risk to the health, safety, and welfare of the participant. The fresh biopsy at baseline is highly encouraged to assess whether GPC3 expression is maintained after previous treatments.

Expression of GPC3 will be evaluated in baseline tumor samples using a validated IHC assay in a central laboratory.

In addition to participant selection, submitted mandatory tumor samples, if available, will be used for the development of the GPC3 companion diagnostic (CDx) or diagnostics(including digital diagnostics) and further support the regulatory filing if needed.

Unstained tumor slides collected for GPC3 testing from participants will be repatriated or destroyed within 1 year of CSR completion. Stained tumor slides and IHC images will be stored for at least 5 years after clinical trial termination.

Residual tissue samples will be used to address the exploratory biomarker objectives described in

Section 3. Analyses may include assessments of RNA, DNA, and protein, including image analysis, aimed at assessing biomarkers of disease, evaluating pharmacodynamics of the response and identifying potential predictive biomarkers and resistance mechanisms. The tumor samples, and derived results, may also be used for future diagnostic test development and/or validation.

8.9.1.3 Mandatory Biomarker Sample Storage, Re-use and Destruction

For storage, re-use, and destruction of biomarker samples see Appendix C.

8.9.2 Optional Tumor Biopsy Sample Collection

Collection of optional samples for biomarker research is also part of this study as specified in Section 1.3 SoA and is subject to agreement to optional consent. Participants will only undergo optional biopsy sampling when the risks are considered medically acceptable by their treating physicians and when the procedure will not cause undue risk to the participant.

8.9.2.1 Tumor Biopsies

8.9.2.1.1 On-treatment Tumor Biopsies

On-treatment biopsies are critical to understanding whether C-CAR031 is able to infiltrate the tumor and mediating tumor killing. Assessment of intratumoral effects of C-CAR031 through on-treatment biopsies will enable further determination of whether pharmacodynamic effects in the periphery are indicative of pharmacodynamic effects within the tumor. On-treatment biopsies should be performed for participants as indicated in the SoA (Section 1.3).

For consenting participants, an on-treatment biopsy should be taken in a visit window of D29 to week 6 inclusive and/or on disease progression, as clinically indicated. Tumor biopsy sample and blood draw is indicated to determine if malignancy is secondary to cell therapy (see Section 1.3).

Participants providing fresh tumor biopsies that can be biopsied at acceptable risk as judged by the investigator on a non-target, non-lymph node lesion that can be biopsied and is ≥ 2 cm in longest diameter. Sites should confirm adequacy of tumor biopsy material at the time of the procedure. Associated pathology report(s) for fresh tumor samples will be required at screening and requested on-treatment for all participants enrolled into the study (details in the Laboratory Manual). Details for fresh tumor sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

Per institutional practice, image-guided fresh core needle tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator. Fine-needle aspirate specimens, bone specimens, or ascites are not acceptable.

Tumor biopsies will be stored with a vendor selected by the collaborator. Biopsies may be used for correlative biomarker studies including assessments of protein, RNA and DNA. Specific analyses may include, but not be limited to, presence of C-CAR031 as determined by PCR or ISH,

assessment of protein expression on tumor cells and other cells in the microenvironment by IHC or proteomic methods (for example GPC3, CD8, and PD-L1), tumor mutation analysis, gene expression analysis, and immunodiversity.

8.9.2.1.2 Disease Progression Tumor Biopsies

Where possible, an on-study tumor biopsy sample from the progressing lesion should be taken at the time of documented RECIST 1.1 progression in participants that have provided the additional optional consent. Biopsies at progression may be particularly valuable when there is a marked phenotypic change in a particular lesion.

The on-study provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care. The biopsied tumor must not be used as part of the RECIST 1.1 assessments. Participants will not be excluded from the study if these samples are not collected.

Refer to the Laboratory Manual for further details of on-study tumor tissue collection, shipping, and storage.

IHC study on changes in GPC3 expression levels, gene expression on TGFβ / Smad2/3 signaling pathway or other protein, RNA or DNA changes in tumor tissue before and after C-CAR031 infusion, and their relationship with efficacy may be studied.

8.10 Medical Resource Utilization and Health Economics

Not applicable

8.11 Study Participant Feedback Questionnaire

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

Approximately 47~62 GPC3+ squamous cell lung cancer participants (assuming 20% of dropout rate due to the failures in apheresis, lymphodepletion, and manufacturing processes, etc.) will be enrolled to yield 37~49 evaluable participants (up to 25 in Phase Ia, which is finally based on the practical escalated dose, and approximately 12 each cohort in Phase Ib, which will be adjusted based on the results of Phase Ia). Evaluability in the safety run-in section of Phase Ia will be determined based on inclusion in the DLT Evaluable Analysis Set (DLTAS), where participants who are not DLT evaluable may be replaced.

Evaluability in Phase Ib and backfill section of Phase Ia will be determined based on inclusion in

the Efficacy Analysis Set (EAS). Any participants deemed unevaluable may be replaced.

Phase Ia

The primary objective of study Phase Ia is to investigate the safety and tolerability and thereby identify the RDE of C-CAR031 for further evaluation. Hence the number of participants has been based on the desire to obtain adequate tolerability, safety, CK/PD, efficacy and biological data while exposing as few participants as possible to the investigational product and study procedures.

For the Phase Ia, up to 25 evaluable participants may be enrolled. Three dose levels are planned initially, with 1 participant in dose level 1 and 3 to 6 participants in dose level 2 and 3. Backfill will stop when up to 12 evaluable participants have been filled in each dose level to better characterize the safety, efficacy, and biological activity of C-CAR031 in these cohorts and explore the relationship between the efficacy and GPC3 expression levels. Assume 20% of patients will be non-evaluable or drop out. Approximately 32 patients will be enrolled.

The total number of participants will depend on the number of non-evaluable participants, the number of toxicities and efficacy observed in each cohort and hence the number of dose levels necessary. Similarly, if additional dose levels are explored, the sample size may increase accordingly.

Phase Ib

A sample size of approximately 15 GPC3+ squamous cell lung cancer participants (assuming 20% of dropout rate) is planned for the phase Ib. If the SRC recommended more than one dose level as RDEs, approximately 12 evaluable participants will be enrolled in each RDE to further evaluate the safety, tolerability and efficacy of C-CAR031 in squamous cell lung cancer participants with GPC3 expression.

9.3 Populations for Analyses

The analyses will be performed for Phase Ia and Phase Ib separately. Some analyses may pool data from both Phase Ia and Phase Ib (eg, participants who were treated at the same dose may be pooled for analyses). Analysis details will be provided in the statistical analysis plan (SAP) (refer to SAP).

For purposes of analysis, the study populations are defined as provided in Table 20.

Tabel 20 Study Populations

Population/analysis set	Description	Endpoint/output
Safety analysis set (SS)	All participants who receive C-CAR031 at any dose level	Baseline and demography (supportive) Exposure Safety PFS, OS ORR, DoR, DRR, DCR, TTR (supportive)

DLT evaluable analysis set (DLTAS)	Participants who received the target dose of C-CAR031 infusion without major protocol deviations and completed the 28-day DLT evaluation or experienced a DLT event. DLTAS is only used for safety run in section of phase Ia	DLT
Full analysis set (FAS) / apheresed set	All participants who undergo apheresis	Baseline and demography Feasibility Safety (supportive) OS (supportive) ORR, DRR, DCR (supportive)
Efficacy analysis set (EAS)	All participants who receive C-CAR031 infusion per protocol with measurable disease at baseline	ORR, DoR, DCR, DRR, TRR, change in tumor size, PFS, OS (supportive)
Pharmcokinetic and pharmacodynamic analysis set (PKPDS)	All participants who received C-CAR031 infusion per protocol, and have at least completed 28 day post-cell infusion pharmacokinetic data collections	CK/PD endpoints
Immunogenicity	All participants who receive C-CAR031 with baseline and at least 1 reportable post-baseline immunogenicity measurement.	Immunogenicity endpoints
Biomarker analysis set (BAS)	All participants who have received C-CAR031 with baseline biomarker measurement.	Biomarker endpoints

BAS = biomarker analysis set; DCR = disease control rate; DLT = dose-limiting toxicity; DLTAS = DLT evaluable analysis set; DoR = duration of response; DRR = durable response rate; FAS = full analysis set; ICF = informed consent form; LDC = lymphodepletion chemotherapy; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PKPDS= Pharmacokinetics and pharmacodynamic analysis set; EAS = Efficacy analysis set; TTR = time to response.

9.4 Statistical Analyses

The SAP will be finalized prior to the first SRC meeting and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, secondary and some exploratory endpoints.

9.4.1 General Considerations

Data will be presented by dose level. No direct statistical comparisons will be made between any 2 dose levels.

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated based on the population total, by dose level and by timepoint as appropriate.

SAS® version 9.4 (as a minimum) will be used for analyses presented in the SAP.

Baseline will be considered the last non-missing value prior to C-CAR031 infusion. Any information taken after the first dose of study intervention will be regarded as post-baseline information. Detailed rules for deriving baseline values will be described in the SAP.

Unless otherwise stated, 2 sided confidence intervals (CIs) will be produced at 95%.

Procedures for accounting for missing data, including missing dates, will be described in the SAP.

9.4.2 Safety Analyses

The primary objective of the study is safety and tolerability. Safety and tolerability will be assessed in terms of AEs, SAEs, AESIs, DLTs (the safety run-in section of Phase Ia only), laboratory data, vital signs, physical examinations and ECG changes and RCL in peripheral blood. The assessment of safety endpoints will be conducted in safety analysis set (SS) and FAS, and the evaluation of DLT in Phase Ia safety endpoints will also be conducted in DLTAS. The data will be summarized and/or listed according to the endpoint (see Section 8.4).

9.4.2.1 Analysis of AEs/SAEs/AESIs

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Assessment of severity of CRS and ICANS are per the ASTCT standard (2019 version). Assessment of severity of AEs other than CRS and ICANS are per NCI CTCAE (V5.0). AE including DLT, TEAE, Post-LDC AEs SAE, ≥grade 3 AE, serious drug adverse reactions (ADR), AESI, AE leading to permanent discontinuation of cell infusion during the cell infusion period, AE leading to temporary discontinuation of cell infusion during the cell infusion period, AE leading to withdrawal from the study, and AE leading to death are summarized and calculated for each dose group, each stage, and the overall incidence according to the System Organ Class (SOC) / Preferred Term (PT).

TEAEs are defined as:

- All AEs with onset or worsen in severity on or after the C-CAR031 infusion through 6 months after the C-CAR031 infusion or the start of subsequent anticancer therapy, whichever is earlier
- All specific AEs and AEs deemed by the investigator to be possibly related to C-CAR031 infusion that occurred on or after the start of subsequent cancer therapy or after 6 months of C-CAR031 infusion, whichever is earlier.

Post-LDC AEs are defined as:

- All AEs with onset or worsen in severity on or after the first dose of LDC but prior to C-CAR031

infusion.

- All AEs with onset or worsen in severity on or after the first dose of LDC up to 30 days after the last dose of LDC or until the study discontinuation whichever occurs first for patients not receiving C-CAR031 infusion.

AESI includes CRS, neurological disorders including ICANS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, any infection with RCL and new primary malignancy.

Describe the number of CRS measures, number of cases, and the incidence rate. Summarize the number and percentage of CRS cases and CRS cases with severity ≥ grade 3 by severity. Analyze the symptoms of CRS, calculate the number of cases, and the incidence rate. Perform descriptive statistics on the time to CRS onset and the duration of CRS. Analyze the treatment of CRS, including the use of tocilizumab, corticosteroids, and TNF-α inhibitors, and calculate the number of cases and incidence rate.

9.4.2.2 Analysis of Other Safety Data

Other AEs are statistically described and calculated for each AE's incidence rate by dose group, by stage, and overall. Other safety results will be summarized by the planned assessment time points, changes relative to baseline, and different categories of results, and assessed for clinical significance according to CTCAE grading (CRS and ICANS according to ASTCT, 2019 version). Abnormal and clinically significant results will be summarized and described for each assessment time point relative to baseline and the worst change. Data with only extreme evaluation results will be provided separately in the extreme analysis section.

RCL status of patients will be summarized.

9.4.3 Efficacy Analyses

The efficacy evaluation will be performed utilizing RECIST 1.1 (Eisenhauer et al 2009[64]) and assessed by the investigator.

The assessment of efficacy endpoints will be conducted in EAS, FAS and SS. A summary of the antitumor efficacy of C-CAR031 assessed according to RECIST v1.1 criteria will be provided, including ORR, DRR, DCR, TTR, DoR, and PFS. OS and OS rates and PFS rates at different time points after cell infusion will also be assessed.

The Clopper-Pearson method will be used to estimate the ORR and DCR and their 95% CI for each dose group. Time-to-event efficacy endpoints, such as DoR, PFS, and OS, will be plotted and described using the Kaplan-Meier method, providing the number and percentage of censored cases, median time and its 95% confidence interval, and survival rates at each assessment time point, as well as plotting the corresponding survival curves for each indicator.

The percentage of best change in tumor size compared to baseline will also be presented in a waterfall plot.

For further details on analyses, refer to the SAP.

9.4.3.1 Primary Endpoint(s)

Not applicable.

9.4.3.2 Secondary Endpoint(s)

Objective Response Rate (ORR)

The ORR is defined as the percentage of participants with a confirmed CR or PR per RECIST 1.1, with the denominator defined as the number of participants in the EAS. Objective response rate and its 95% CI will be summarized by dose level. Data obtained from infusion date until disease progression or the last evaluable assessment in the absence of progression, or initiation of subsequent anticancer treatment, will be included in the assessment of ORR.

Durable Response Rate (DRR)

DRR is defined as the percentage of participants who have a confirmed response (CR/PR) as determined by RECIST 1.1 with a duration of at least a specific number of months, the denominator is the number of participants in the EAS. Durable response will be summarized. The duration for DRR is from the date of first durable response to the date of first documented disease progression or the last evaluable assessment in the absence of progression or initiation of subsequent anticancer treatment prior to RECIST 1.1 progression. DRR and its 95% CIs will be summarized by dose level.

Duration of Response (DoR)

The DoR is defined as the time from the date of first documented objective response (which is subsequently confirmed) until date of first documented disease progression or the last evaluable assessment in the absence of progression or initiation of subsequent anticancer treatment prior to progression.

The analysis will include all participants in the EAS who have a confirmed response.

The measure of interest is the median and landmark estimates. DoR will be summarized using descriptive statistics and Kaplan-Meier plots, where there are sufficient numbers of responders. It may also be further summarized by best response (ie, CR and PR).

Disease Control Rate (DCR)

DCR is defined as the percentage of participants who have a best objective response of confirmed CR or PR or who have SD for at least 5 weeks after C-CAR031 infusion date per RECIST 1.1. Data obtained from infusion date up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR.

Participants with SD who receive any subsequent cancer therapy prior to week 5, will not be considered to have disease control in the analysis.

The analysis will include all participants in the EAS. DCR and its 95% CI will be summarized by dose level.

Time to Response (TTR)

TTR is defined as the time from infusion date until the date of first documented objective response, which is subsequently confirmed as assessed by the investigator per RECIST 1.1. Only participants who have achieved confirmed response in the EAS are evaluated for TTR.

TTR will be summarized by dose level using Kaplan-Meier method. Median TTR and it's 95% CI will be provided. Kaplan-Meier plots will be presented.

Percentage Change in Tumor Size

The best percentage change from baseline in tumor size is the largest decrease (or smallest increase) from baseline for a participant, using RECIST 1.1 assessments.

The analysis will include all participants in the EAS.

The percentage change in TL tumor size from baseline will be summarized using descriptive statistics by dose level and time point. Best percentage change will also be summarized.

Waterfall plots showing the best percentage change from baseline in sum of the diameters of TLs will be produced. Spider plots showing the percentage change from baseline in TL tumor size for each participant in a dose level over time will be produced.

Progression-free Survival (PFS)

PFS is defined as the time from C-CAR031 infusion until the date of objective disease progression or death (by any cause in the absence of progression). If participants receive another anticancer therapy, the PFS will be censored. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

The PFS time will always be derived, based on scan/assessment dates, not visit dates. RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined, based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.
- If the participant progresses or dies immediately after two or more consecutive missed

visits, the PFS will be censored at the time of the latest evaluable assessment prior to the two missed visits.

The analysis will include all participants in the SS, i.e. participants who receive C-CAR031 at any dose level.

PFS will be summarized by dose level and Kaplan-Meier plots will be provided. The measure of interest is the median and landmark estimates of PFS.

Overall Survival (OS)

OS is defined as the time from C-CAR031 infusion until death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

The analysis will include all participants in the SS.

The measure of interest is the median and landmark estimates. OS will be summarized by dose level and Kaplan-Meier plots will be provided.

9.4.4 Pharmacokinetic Analysis

Blood samples for determination of the level of CAR transgene by PCR and/or CAR-T blood concertation by flow cytometry for C-CAR031 will be tested by an analysis lab using appropriately validated bioanalytical methods. If data allows, CK parameters such as $AUC_{0\text{-}28d}$, C_{max}, T_{max}, T_{last}, C_{last} and AUC_{last} will be analyzed.

The calculation of CK parameters will use a non-compartmental model and actual sampling time. For data below the lower limit of cell concentration measurement, if it occurs before the first measurable concentration, it will be set as "0", otherwise, it will be set as 1/2 lower limit of quantification (LLOQ) (i.e., half of the LLOQ).

The main CK parameters will be statistically summarized by dose group and phase. The statistical summary will use descriptive statistical methods, including number of cases, mean, standard deviation, median, minimum, maximum, coefficient of variation between participants, geometric mean, and geometric coefficient of variation between participants, except for T_{max} and T_{last}. The statistical description of T_{max} and T_{last} only includes the number of cases, median, minimum, and maximum.

Relationship between CK parameters and efficacy/safety will be explored. CK parameter values will be described by category according to efficacy indicators whether clinical remission is achieved. CRS and ICANS will be classified by severity to evaluate the relationship between CK parameters and safety. Statistical charts for description will be applied where appropriate.

9.4.5 Exploratory Study Analyses

9.4.5.1 Immunogenicity

Humoral immunogenicity results will be analyzed descriptively by summarizing the number and percentage of participants who develop detectable ADAs. The potential impact on clinical efficacy and safety outcomes will be assessed if data allow.

9.4.5.2 Exploratory Biomarkers

Biomarker exploratory analyses may be described in a separate analysis plan and may be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

9.4.5.3 Long-term Data Analysis

Any data obtained after the end of the stage 3 follow-up will be analyzed as part of the LTFU data.

For further details on analyses, refer to the SAP.

9.5 Data Monitoring Committee

There will be no data monitoring committee for this study. A SRC will be appointed to review emerging data from each part of the study (refer to Section 6.6.5).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th World Medical Association (WMA) General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to collaborator of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Collaborator has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The collaborator will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and collaborator policy and forwarded to investigators as necessary.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from collaborator will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to collaborator of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate collaborator representatives immediately after he or she becomes aware of it.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to collaborator or delegated party, through the contacts (email address or telephone number) provided by collaborator.

A 2 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH

guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study centre.

- Of note for this study, consent is a 3-step process with a pre-screening, screening and stage 3 (the LTFU period) consent signature requirement. Pre-screening and screening may occur in parallel.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 3 Data Protection

- Participants will be assigned a unique identifier by the collaborator. Any participant records or datasets that are transferred to the collaborator will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the collaborator in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the collaborator, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of

personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 4 Committees Structure

The members of safety review committee (SRC) include the investigators, an independent clinician, an AbelZeta's medical delegate, and other relevant personnel may be added according to the specific needs of the study, including but not limited to the medical monitor, pharmacovigilance physician, clinical pharmacologist, statistician. All representatives from AbelZeta or other collaborators will be non-voting members.

The SRC membership should be recorded in the SRC Charter.

A 5 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to collaborator or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s) and contracts.
- Investigator or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical monitor Plan.
- Investigator or designee is responsible for the data management of this study including quality checking of the data.
- Investigator assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must

be retained by the investigator as required by local regulations. No records may be destroyed during the retention period without the written confirmation of collaborator. No records may be transferred to another location or party without written notification to collaborator.

A 6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator'ssite.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment or monitoring guidelines.

A 7 Study Closure

A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

AbelZeta may terminate support for study at any time and for any reason including, but not limited to scientific misconduct, AbelZeta disbarment, emerging safety findings, and discontinuation of further research on the compound by AbelZeta. In the event a study is terminated, the appropriate ethical considerations will be made for the participants in the study. Study may provide decision making data for the AbelZeta drug development program. Therefore, if a decision is made to withdraw AbelZeta support there should be full consultation with all pertinent parties, including but not limited to the review committee, the Product Team, investigator, and/or the Alliance Partner (if any) before proceeding. The investigator is responsible for all closure activities pertaining to their Regulatory Authority, IRB/IEC, research participants, safety reconciliation.

A 8 Publication Policy

- Collaborator shall have the right to make and control all scientific or other publications of any materials or information relating in any way to the Compound, Product, Development Activities or Development Results
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the collaborator before submission to gain consent from collaborator. This allows the collaborator to protect proprietary information and to provide comments.
- Collaborator will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the collaborator will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether it's considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and a deterioration of a pre-existing medical occurrence. An AE may occur at any time, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the study intervention and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered SAEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. Hospitalization or prolongation of existing hospitalization for study effectiveness assessment, hospitalization or prolongation of existing hospitalization for treatment of a disease covered by this study are not considered as SAE.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug (if applicable) does not mean that it is an important medical event; medical judgment must be used.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2.
On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised National Cancer Institute CTCAE version will be utilized for all events. This version will be used for the duration of the study. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by C-CAR031, and/or LDC and/or bridging therapy (if used).

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Investigator or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the collaborator-assigned biobanks or other sample archive facilities and will be tracked by the appropriate collaborator team for the remainder of the sample life cycle.

The immunogenicity sample should be retained 1 year after completing CSR. CK (DNA copy number) samples can be hold 6 months after completion of CSR. CK samples for flow cytometry cannot be stored after analysis and the remaining samples will be destroyed after completing the analysis.If required, collaborator will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

Investigator ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, the collaborator is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures the participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to the collaborator or delegate

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and collaborator is informed about the sample disposal.

Investigator or delegated representatives ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) cases and Hy's law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

In studies where laboratory data are not routinely collected, the investigator should be vigilant for cases of PHL from ad hoc laboratory tests or AEs. Additional safety samples for example, liver chemistry tests to determine PHL cases, may be collected if clinically indicated at the discretion of the investigator. During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory. The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with collaborator clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law

Table 21 Potential Hy's Law Definitions

Baseline lab values	ALT and/or AST in normal range	ALT and/or AST above ULN
TBL in normal range	AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, may need to be reported as SAEs.	AST or ALT ≥ 3 × baseline value or ≥ 10 × ULN, whichever occurs first, together with TBL ≥ 2 × ULN, may need to be reported as SAEs.

TBL above ULN	AST or ALT ≥ 3 × ULN, together with TBL ≥ 1.5 × baseline value with DB ≥ 50% of the total, or any increase in DB ≥ 1 mg/dL over baseline, may need to be reported as SAEs.	AST or ALT ≥ 3 × baseline value or ≥ 10 × ULN, whichever occurs first, together with TBL ≥ 1.5 × baseline value with DB ≥ 50% of the total, or any increase in DB ≥ 1 mg/dL over baseline, may need to be reported as SAEs.

ALT = Alanine Aminotransferase/Transaminase; AST = Aspartate Aminotransferase/Transaminase; DB = direct bilirubin; SAE = Serious Adverse Events; TBL = total bilirubin; ULN = upper limit of normal.

Hy's Law

Participants who have changes in transaminases and TBL/DBL in Table 21 above will be confirmed Hy's Law cases where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For Potential Hy's Law and Hy's Law the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination as detailed in Table 21.

Local Laboratories Being Used

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Determine whether the participant meets PHL criteria (Appendix D 2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the investigator will

- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

D 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study intervention (see Appendix D 6)
- Notify the collaborator representative who will then inform the Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion "Important Medical Event" and causality assessment "yes/related" according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change in the participant's condition.

- The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform investigations as discussed with the Study Physician.
  - Complete the eCRF as information becomes available.

A "significant" change in the participant's condition refers to a clinically relevant change in any of the individual's liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the medical monitor if there is any uncertainty.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the medical monitor contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The collaborator Clinical Lead or equivalent and Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made

and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the standard processes in protocol for AE/SAE reporting.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to standard processes in protocol for SAE reporting.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions Required When Potential Hy's Law Criteria are met Before and After Starting Study Intervention

This section is applicable to participants who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met, the investigator will determine if there has been a **significant change** in the participant's condition compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required
- If there is a significant change, notify the collaborator representative, who will inform the Study Team, then follow the subsequent process described in Appendix D 4.2.

D 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on study intervention visit as described in Section D 6

If **No**: follow the process described in Appendix D 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required
- If there is a significant change, follow the process described in Appendix D 4.2 for reporting PHL as an SAE.

D 8 Laboratory Tests

List of Hy's Law Laboratory tests

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HbsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA[b] IgM anti-HEV HEV RNA

Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate-deficient transferrin [c]
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] Carbohydrate-deficient transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio; LDH = lactate dehydrogenase; ribonucleic acid.

D 9 References

Aithal et al, 2011

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011; 89(6):806-15.

FDA Guidance for Industry, July 2009

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors v 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009[64]). iInvestigator assessments will use the RECIST 1.1 guidelines described in this appendix.

Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs, and NLs is provided in Table 22.

Table 22 Summary of Imaging Modalities for Tumor Assessment

Target lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) FDG-PET/CT

CT = Computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = Magnetic resonance imaging.

CT and MRI

Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality (although magnetic resonance imaging [MRI] with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoAs, see Section 1.3), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoAs. Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- IV contrast-enhanced CT or MRI of the head and neck
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred)

2 Chest CT without IV contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study

3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumors require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Isotopic Bone Scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed

equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that time point.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

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[1] A positive FDG-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

Other Tumor Assessments

Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and Cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of Tumor Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable Lesions at Baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[3])
- Previously irradiated lesions[4]
- Brain metastasis

Special Considerations Regarding Lesion Measurability at Baseline:

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

RECIST 1.1 TL Selection at Baseline:

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases for TL Assessment at Baseline:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

RECIST 1.1 NTL Selection at Baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are

not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumor Response and Progression

RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs (see also Table 23). The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special Cases for TL Assessment at Follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 case report form for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 23 RECIST 1.1 Evaluation of Target Lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir)—This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

CR = complete response; NA = not applicable; NE = not evaluable; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

RECIST 1.1 NTL Assessment at Follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline (see Table 24). Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator.

To achieve ‘unequivocal progression’ on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest ‘increase’ in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 24 RECIST 1.1 Evaluation of Non-target Lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when 1 or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if no NTLs present at baseline

CR = complete response; NE = not evaluable; NTL = non-target lesion; PD = progression of disease; TL = target lesion.

RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate disease progression.

RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 25.

Table 25 RECIST 1.1 Overall Visit Response

Target Lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR

PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.
Note: An overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable; NE = not evaluable; NED = no evidence of diseases;
PD = progressive disease; PR = partial response; SD = stable disease.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For patients with TLs (at baseline): complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), or not evaluable (NE)
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For patients with no disease at baseline: NED (no evidence of disease; available as an option in the eCRF), PD, or NE

Evaluation of Scans Subsequent to RECIST 1.1-defined Progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no later than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for patient management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer 2009[64]) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. If the follow-up scan acquired after a RECIST 1.1 PD scan meets *any* of the following criteria, it will be assigned an overall visit response of PD, and if the scan does not meet *any* of these 4 criteria, the timepoint assessment will be non-PD (ie, CR, PR, SD, or NE).

- ≥ 20% increase and at least a 5-mm increase in the sum diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm in the sum of diameters at the follow-up timepoint compared with the immediate prior timepoint
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional unequivocal brand-new lesions at the follow-up scan timepoint

Central Imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to a collaborator-appointed imaging Contract Research Organisation (iCRO) for quality control, storage, and for indepentent review committee (IRC) evaluation. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A IRC evaluation of images will be performed at the discretion of collaborator. Results of these independent reviews will not be communicated to investigators, and results of investigator tumor assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the tumor assessments conducted by the investigator. Further details of the IRC evaluation will be documented in an Independent Review Charter.

References

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Contraception Guidance

F 1 Definitions

Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.

Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly.

A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly.

F 2 Highly Effective Methods of Contraception

Table 26 Highly Effective Methods of Contraception

Non-hormonal methods	Hormonal methods
• Copper T intrauterine device • Levenorgestrel-releasing intrauterine system (eg, Mirena®) [a] • Bilateral tubal occlusion • Vasectomised sexual partner • Total sexual abstinence	• Implants ° Etonorgestrel-releasing implants (eg, Implanon® or Norplan®) • Intravaginal devices ° Ethinylestradiol/etonorgestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection ° Medroxyprogesterone injection: eg, Depo-Provera® • Combined pill ° Normal and low dose combined oral contraceptive pill • Patch ° Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill ° Progesterone based oral contraceptive pill using desogestrel ° Cerazette® is currently the only highly effective progesterone-based pill

[a] Also considered a hormonal method

Birth control methods that are NOT highly effective (failure rate of ≥ 1% per year) include: Male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide, or progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are not highly effective birth control methods.

The following are NOT acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female condom and male condom should not be used together.

Appendix G Grading of CRS, ICANS, and ICE Scoring

CRS grading criteria are presented in Table 27.

Table 27 American Society for Transplantation and Cellular Therapy Consensus Grading Criteria For CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [b]				
Hypoxia	None	Requiring low-flow nasal cannula [a] or blow-by	Requiring high-flow nasal cannula [c], face mask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

[a] Fever is defined as temperature 38°C not attributable to any other cause. In participants who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in paediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

Grading of CRS events is based on ASTCT consensus Grading (Lee et al 2019[63]).

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome;
CTCAE = Common Terminology Criteria for Adverse Events

ICANS grading criteria are presented in Table 28.

Table 28 American Society for Transplantation and Cellular Therapy Consensus Grading Criteria for ICANS in Adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score [a]	7-9	3-6	0-2	0 (participant is unarousable and unable to perform ICE assessment)
Depressed level of consciousness [b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalised that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings [c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated increased intracranial pressure/cerebral oedema [d]	N/A	N/A	Focal/local oedema on neuroimaging	Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilloedema; or Cushing's triad

[a] A participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[d] Intracranial hemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause; for example, a participant with an ICE score of 3 and a generalized seizure is classified as having grade 3 ICANS.
Grading of ICANS events is based on ASTCT consensus Grading (Lee et al 2019[63]).
ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune Effector Cell Encephalopathy; EEG = electroencephalogram; N/A = not applicable.

ICE scoring is presented in Table 29.

Table 29 Immune Effector Cell-associated Encephalopathy (ICE) Score

ICE assessment		**Score**
Orientation	Orientation to year, month, city, hospital	1 point each
Naming	Name 3 objects (eg, clock, pen, button)	1 point each
Following commands	(eg, show me 2 fingers, or close your eye and stick out your tongue)	1 point
Writing	Ability to write a standard sentence (eg, our national bird is the bald eagle)	1 point
Attention	Count backwards from 100 by 10	1 point
ICE scoring		
Score 10	No impairment	
Score 7-9	Grade 1 ICANS	
Score 3-6	Grade 2 ICANS	
Score 0-2	Grade 3 [a] ICANS	
Score 0 (due to participant unarousable and unable to perform ICE assessment)	Grade 4 ICANS	

[a] A participant with an ICE score of 0 may be classified as having Grade 3 ICANS if the participant is awake with global aphasia or may be classified as having Grade 4 ICANS if the participant is unarousable.

ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-associated Encephalopathy.

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