

CT017 CAR T Protocol	Protocol No.: CT017-CG1010
Product No.: CT017	

CLINICAL TRIAL PROTOCOL

Protocol Title: Phase I Clinical Trial of Fourth-Generation Chimeric
Antigen Receptor T Cells Targeting Glypican-3(GPC3)
in the Treatment of Advanced Hepatocellular Carcinoma

Protocol No.: CT017-CG1010
Version: 3.0
Date: May 15, 2020
Principal Investigator: Tingbo Liang
Collaborator: CARsgen Therapeutics Co., Ltd.

CONFIDENTIALITY NOTICE

All information contained in this protocol is proprietary to the partner and, as such, will only be provided for review by the investigator, co-investigator, ethics committee, regulatory authorities and other relevant medical institutions. No information shall be disclosed to any third party not connected with this Trial without the written approval of the partner, except that necessary explanation is given to the subject who may participate in this Trial when signing an informed consent form.

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Principal Investigator

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PROTOCOL SIGNATURE PAGE

Principal Investigator agrees:

I confirm that I have read and understand this protocol, the Investigator 's Brochure, and any other product-related information provided by the partner. I agree to conduct this trial in accordance with the requirements of the protocol, while respecting the rights, security, privacy and well-being of the study subject, and in compliance with:

- Ethical principles in the Declaration of Helsinki.
- International Conference on Harmonisation/E6 (R2) Consolidated Guideline for Good Clinical Practice.
- Good Clinical Practice
- All applicable laws and regulations, including, without limitation, those governing privacy protection and disclosure of clinical trials.
- Regulatory requirements for reporting serious adverse events.

Principal Investigator Signature:

Date

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Protocol Signature Page

COLLABORATOR AGREES:

This trial will be conducted in compliance with the requirements of the clinical study protocol with the following regulations/guidelines and with the utmost respect for the subjects:

- Ethical principles in the Declaration of Helsinki.
- International Conference on Harmonisation/E6 (R2) Consolidated Guideline for Good Clinical Practice.
- Good Clinical Practice
- All applicable laws and regulations, including, without limitation, those governing privacy protection and disclosure of clinical trials.

CARsgen Therapeutics Co., Ltd.

Responsible Signature:

Date

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PROTOCOL SYNOPSIS

Protocol No. CT017-CG1010

Title: Phase I Clinical Trial of Fourth-Generation Chimeric Antigen Receptor T Cells Targeting Glypican-3(GPC3) in the Treatment of Advanced Hepatocellular Carcinoma

Version No./Date: V 3.0/May 15, 2020

Phase: Phase I

Principal Investigator: Prof. Tingbo Liang

Collaborator: CARsgen Therapeutics Co., Ltd.

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Table 1 Trial objectives and endpoints

Objectives		Endpoints
Primary objective	To evaluate the safety and tolerability of CT017 CAR-GPC3 T cells within 28 days following the first infusion of monotherapy dose-escalation phase in subjects with advanced hepatocellular carcinoma	<ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of Treatment-Related Adverse Events • Incidence of Adverse Events of Special Interest (AESI) • ECG, laboratory tests, vital sign changes, etc. • Identify DLTs and MTD
Secondary objectives	Evaluate the pharmacokinetics of CT017 CAR-GPC3 T cells	Peak time of cell expansion, Peak of amplification, Area Under the Curve (AUC), and Survival time after infusion of CT017 CAR-GPC3 T Cells
	Overall safety and tolerability in the monotherapy dose-escalation phase and the combination therapy expansion phase	<ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of Treatment-Related Adverse Events • Incidence of Adverse Events of Special Interest (AESI) • ECG, laboratory tests, vital sign changes, etc.
	To assess the preliminary efficacy of infusion of CT017 CAR-GPC3 T cells in the treatment of advanced hepatocellular carcinoma with positive GPC3 expression	<ul style="list-style-type: none"> • Objective response rate (ORR, response rate of PR and CR) • Duration of Response (DOR) • Disease Control Rate (DCR) • Disease Control Time (DDC) • Progression-free survival (PFS) • Overall survival (OS)

Trial design:

This is an open-label, monotherapy dose-escalation and combination therapy expansion phase I trial to observe the safety, tolerability, cellular pharmacokinetics and preliminary

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efficacy of CT017 CAR-GPC3 T cell therapy in advanced hepatocellular carcinoma subjects with positive GPC3 expression.

Stage 1. Monotherapy dose-escalation phase

In the monotherapy dose-escalation phase, three dose levels will be set (see 0) and 9-18 subjects who meet the inclusion and exclusion criteria will be enrolled.

The initial dose will start at Dose Level 0, ie, 2.5×10^8 cells, and subsequent dose groups will be increased up to Dose Level 1 (4×10^8) or decreased to Dose Level -1 (1.5×10^8) on a 3 + 3 principle. Three subjects are required to be included in each dose group for DLT evaluation. If 1 subject in a dose group develops DLT, three subjects will be added to this dose group. If $\geq 2/6$ subjects develop DLT, subjects will be increased to 6 at the previous low dose level. The dose with an incidence of $\leq 1/6$ DLTs was considered the maximum tolerated dose (MTD).

The DLT observation period was 28 days. Each dose group should complete DLT observation before entering the next dose group; if no DLT is observed 14 days after the first cell infusion for the first subject in the same dose group, cell infusion can be performed for subsequent subjects.

If the 4×10^8 dose level is not identified as the MTD, escalation to a higher dose may be decided by the investigator and collaborators, as well as dose determination for dose expansion phase.

During the trial, if 3 subjects in a dose group completed the first cell infusion and did not experience DLT after 28 days of observation and were well tolerated, the dose group could directly enter the expansion phase of combination therapy after discussion and evaluation by the investigator and collaborators.

Table 2 Single dose level

Group	Dose
Dose Level 0 (n = 3-6)	2.5×10^8 cells
Dose Level 1 (n = 3-6)	4.0×10^8 cells
Dose Level -1 (n = 3-6)	1.5×10^8 cells

Increase treatment cycles:

For subjects in monotherapy dose-escalation phase, if no DLT occurs after the completion of the DLT observation and the investigator considers that the subject may benefit, the cell infusion

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cycle can be increased for the subject according to dose expansion treatment method. Cell infusion may be performed again at 12 and 24 weeks after the first infusion (the specific reinfusion time is determined by the investigator after comprehensive consideration of the subject's safety, efficacy, pharmacokinetics or other factors) until the subject experiences disease progression, intolerable toxicity, requires other treatments, or has no cells available for infusion (whichever occurs earlier). The dose and method of subsequent infusions may be judged and adjusted by the investigator based on the subject's clinical benefit.

After subjects in monotherapy dose-escalation phase complete the first cycle of treatment, CT017 CAR-GPC3 T cells alone or in combination with other drugs that may benefit the subjects may be used in subsequent cycles, including but not completely limited to multi-kinase inhibitors such as sorafenib or PD-1/PD-L1 monoclonal antibody or other treatments that may benefit the subjects (including systemic chemotherapy (such as FOLFOX4, etc.) and local therapies such as intervention, ablation, radiotherapy, or other treatments).

If the investigator confirms that the subject may benefit from the combination therapy of drugs other than those recommended by NCCN Clinical Practice Guidelines for Hepatobiliary Tumors (current version) or Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (current version) (PD-1/PD-L1 monoclonal antibodies have been within the scope of combination therapy), they should be submitted to the Ethics Committee for filing before use in the subject.

If cell infusion cycles are added, the baseline period and follow-up schedule are not affected by the addition of treatment cycle, but safety and efficacy evaluation tests may be added according to the addition of treatment, as detailed in the schedule of study.

Stage 2. Combination Therapy Expansion Phase

Nine to 36 subjects will be enrolled into the combination therapy expansion phase. Subjects in this phase will enter the following treatment groups: combined sorafenib (or multi-kinase inhibitor of the same class) group; or combined PD-1/PD-L1 monoclonal antibody group or other treatment groups that may benefit subjects. The combination therapy will be performed according to the following way (the combination therapy methods are used as a reference, and the specific treatment method, time, frequency and drug dose are determined by the investigator according to the subject's comprehensive evaluation) until 52 weeks after the first treatment, intolerable toxicity, disease progression, withdrawal from the study, or discontinuation of the treatment at the

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investigator's discretion (whichever occurs earlier). Three to 12 subjects will be included in each group, and the number of subjects in each group will be determined by the investigator and collaborators based on the discussion of safety, pharmacokinetics and preliminary efficacy of the combination therapy.

Combined sorafenib (or similar multi-kinase inhibitor) group: sorafenib was started after apheresis, 200-400mg, orally, twice daily. Other similar multi-kinase inhibitors were administered according to this treatment prescription.

Combined PD-1/PD-L1 monoclonal antibody group: The combination therapy was started 2 weeks \pm 3 days after the first infusion of CT017 CAR-GPC3 T cells, and the specific administration time was determined by the investigator based on the overall consideration of the general condition of the subjects after infusion of CT017 CAR-GPC3 T cells. The specific drug dose and administration frequency were determined by the investigator.

Combined with other treatment groups that may benefit subjects: including systemic chemotherapy (such as FOLFOX4) and local therapy such as intervention, ablation and radiotherapy, or other treatments.

Each subject may receive cell infusion again at Week 12 and Week 24 after the first cell therapy (if it is found in monotherapy that the cells maintain in vivo for a long time, the dosing interval may be prolonged based on cell metabolism. It is determined by the investigator after comprehensive consideration of the subject's safety, efficacy and cell metabolism) until the subject develops intolerable toxicity, or has no cells available for treatment, or requires treatment termination at the investigator's discretion (whichever occurs earlier).

During the study, the investigator can adjust the dose of the combined therapy or cell therapy or make a decision on whether to continue the treatment based on the subject's tolerance and treatment response.

Dose reduction or discontinuation:

When > Grade 2 treatment-related **non-hematological AEs** persist for more than 14 days (except alopecia, fatigue and other AEs considered tolerable by the investigator), the investigator should reduce the dose of combined drug therapy to half the dose. If the half-dose drug combination therapy fails to reduce to grade 2 or less after 14 days and no further improvement is observed, the

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treatment will be suspended. Treatment will be terminated if the subject's treatment-related non-hematological AE does not recover to grade 1 or less by the next cell therapy (including pre-conditioning) (unless the investigator considers the subject tolerable).

When > Grade 3 treatment-related hematological AEs persist for more than 7 days (except decreased lymphocytes and white blood cells), the investigator should reduce the dose of combined drug therapy to half the dose. If the half-dose drug combination therapy fails to reduce to grade 3 or less after 7 days and no further improvement is observed, the treatment will be suspended. Treatment will be terminated if the subject's treatment-related non-hematological AE does not recover to grade 2 or less by the next cell therapy (including pre-conditioning).

Bridging regimen after apheresis and before cell infusion:

Subjects in the monotherapy dose-escalation phase were allowed to receive bridging therapy prior to the first cell infusion in this study. Bridging therapy may be sorafenib or a similar multi-kinase inhibitor, or systemic chemotherapy (eg, FOLFOX4, etc). PD-1 or PD-L1 monoclonal antibodies are contraindicated. Bridging therapy may be started after apheresis. Sorafenib or a similar multikinase inhibitor should be discontinued 1 week and systemic chemotherapy should be discontinued 2 weeks before pre-conditioning.

Pre-conditioning regimen before cell infusion:

Performed on Days 4-6 prior to cell infusion, subjects will receive fludarabine 25 mg/m² and cyclophosphamide 300 mg/m² once daily for 3 consecutive days. CT017 CAR-GPC3 T cell infusion will be performed 1-3 days after pre-conditioning, no later than 7 days. During pre-conditioning, the investigator may make some adjustment on the pre-conditioning regimen appropriately based on the subject 's response.

The day of the first cell infusion was D0, and subsequent visit times were calculated based on the first cell infusion.

Duration of trial:

Each subject will continue for a maximum of approximately 60 weeks (approximately 14 months) from signing of informed consent form, target prescreening, screening examination, apheresis, CT017 CAR-GPC3 T cell preparation, baseline examination, pre-conditioning, CT017 CAR-GPC3 T cell infusion and/or combination therapy to completing the trial.

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Trial completion is defined as 52 weeks after the last subject completes the first trial treatment, withdraws from the trial, lost to follow-up, withdraws consent, or dies.

During the trial, before subjects need to receive treatment with other anti-tumor drugs due to disease progression, efficacy and safety evaluation after cell infusion should be completed. The key information such as efficacy, safety data, concomitant therapy and survival status of subjects should be continuously collected with the consent of subjects.

Inclusion criteria:

Subjects must meet all of the following criteria to be enrolled:

1. Aged 18-75 years (inclusive), male or female;
2. Patients with pathologically confirmed advanced hepatocellular carcinoma who had recurrence after surgery or other local therapies, or who had progression or intolerance after previous standard systemic therapy (systemic therapy including but not limited to systemic chemotherapy (FOLFOX4 regimen), molecular targeted drug therapy (sorafenib, regorafenib, lenvatinib, etc.), etc.);
3. Stage C according to Barcelona Clinic Liver Cancer Criteria (BCLC) or Stage B not suitable for local therapy/local therapy progression;
4. Expression of GPC3 demonstrated by immunohistochemistry (IHC). Patients who had previously received targeted GPC3 treatment should be confirmed to have positive GPC3 target by pathological examination of tumor tissue after completion of previous treatment before enrollment;
5. At least one target lesion that can be evaluated according to RECIST 1.1, defined as non-lymph node lesions with the longest diameter ≥ 10 mm, or lymph node lesions with the short diameter ≥ 15 mm; intrahepatic lesions require enhanced arterial phase imaging;
6. Expected survival time > 12 weeks;
7. Child-Pugh score ≤ 7 ;
8. Adequate performance status defined as Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1;

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9. Subjects with positive HBsAg or positive HBcAb are required to have HBV-DNA < 2000 IU/ml. HBsAg positive subjects must receive antiviral treatment according to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (current version);
10. Subjects should meet the following test results at screening. If laboratory abnormalities do not meet the following criteria and they are allowed to be retested within one week. If the criteria are still not met, the screening is considered to have failed:
 - a. Hematology (no intensive blood transfusion, platelet transfusion, cell growth factor (except recombinant erythropoietin) and other supportive treatment within 7 days before the test): neutrophil count (ANC) $\geq 1.0 \times 10^9/L$; lymphocyte count $\geq 0.4 \times 10^9/L$; platelet count (PLT) $\geq 60 \times 10^9/L$; hemoglobin (Hb) $\geq 8.0g/dL$;
 - b. Blood biochemistry: endogenous creatinine clearance $\geq 50mL/min$ (using Cockcroft - Gault formula), alanine aminotransferase (ALT) $\leq 5 \times$ upper limit of normal(ULN); aspartate aminotransferase(AST) $\leq 5 \times$ ULN; alkaline phosphatase $\leq 5 \times$ ULN; total bilirubin $\leq 2 \times$ ULN;
 - c. Prothrombin time (PT): prolongation of prothrombin time ≤ 4 s;
11. Adequate venous access for mononuclear cell collection (referred to as apheresis) without other contraindications for apheresis (including but not limited to systemic bleeding disorders, puncture site infection or systemic infection, hemodynamic instability, and other conditions assessed by the investigator as contraindications to apheresis);
12. Female patients of childbearing potential must have a negative serum pregnancy test at screening and within 14 days prior to the start of study medication and are willing to use a reliable method of contraception during the trial (within 12 months after cell infusion (M12)). Male patients with partners of childbearing potential should have undergone sterilization or agree to use a reliable method of contraception during the trial;
13. Able to understand and sign informed consent form.

Exclusion Criteria:

Subjects meeting any of the following criteria will not be included in this trial:

1. Pregnant or lactating women;

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2. Human immunodeficiency virus (HIV) antibody, Treponema pallidum antibody positive or hepatitis C virus (HCV-RNA) positive;
3. Any active uncontrolled infection, including but not limited to patients with active tuberculosis;
4. Clinically significant thyroid dysfunction (serum thyroid hormone determination TT4, TT3, FT3, FT4 and serum thyroid-stimulating hormone TSH) assessed by the investigator as inappropriate for entry into the trial;
5. Prior or current hepatic encephalopathy;
6. Presence of clinically significant ascites, defined as those with positive physical examination signs of ascites or ascites that requires intervention (eg, paracentesis or medical therapy) to control (only those with imaging findings of ascites that do not require intervention may be included);
7. Imaging examination findings: the proportion of liver replaced by tumor $\geq 50\%$, or main portal vein tumor thrombus, or tumor thrombus invading the mesenteric vein/inferior vena cava;
8. Patients with known active autoimmune diseases requiring treatment with immunosuppressive drugs including biological agents;
9. Toxicities caused by previous treatment have not recovered to Common Terminology Criteria for Adverse Events (CTCAE) \leq Grade 1 (except alopecia, pigmentation, specific laboratory abnormalities that investigator believed would not affect or allowed in the protocol);
10. Systemic steroids, equivalent to > 15 mg/day prednisone within 14 days prior to apheresis, except inhaled steroids;
11. History of severe allergy, or allergy to excipients of CT017 CAR-GPC3 T cell fluid (eg, DMSO, albumin, etc.), or allergy to penicillin antibiotics;
12. Presence of untreated brain metastases or symptoms of brain metastases;
13. Maximum target lesion diameter > 5 cm or presence of central or extensive tumor lung metastases;

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14. Subjects with current unstable or active ulcers, gastrointestinal bleeding, or intolerance to proton pump inhibitors;
15. Subjects with history of organ transplantation or waiting for organ transplantation;
16. Received local-regional therapy for the lesion within 2 weeks prior to apheresis (ie, transarterial chemoembolization, transcatheter embolization, hepatic arterial infusion, radiotherapy, radioembolization, or ablation) or systemic oxaliplatin-based chemotherapy within 2 weeks prior to apheresis, or thymosin, interferon and other immunotherapies (see Section 18 for PD-1/PD-L1 monoclonal antibody requirements) or any Chinese herbal/patent medicine for the control of liver cancer within 1 week prior to apheresis; or received targeted drug therapy such as sorafenib, regorafenib, and lenvatinib within 1 week prior to apheresis;
17. Prior treatment with CAR T (refer to Inclusion Criteria 4 for CAR T requirement targeting GPC3) or TCR T;
18. Anti-PD-1/PD-L1 monoclonal antibody therapy within 4 weeks prior to apheresis;
19. Major surgical procedures or significant trauma within 4 weeks prior to apheresis or anticipation of the need for major surgery during the trial;
20. Other serious medical conditions that may limit the patient's participation in this trial (eg, poorly controlled diabetes mellitus (glycosylated hemoglobin [HbA1c]>8% after treatment), poorly controlled hypertension (systolic blood pressure>160 mmHg and/or diastolic blood pressure>100 mmHg), uncontrolled congestive heart failure (New York Heart Association Class III-IV), significantly prolonged QT interval (QTc \geq 500ms corrected by Bazetts's method is recommended, as evaluated by the investigator), left ventricular ejection fraction (LVEF)<50%, myocardial infarction or unstable arrhythmia or unstable angina within the past 6 months, pulmonary embolism, chronic obstructive pulmonary disease, interstitial lung disease, clinically significant pulmonary function test abnormalities);
21. Patients are unable or unwilling to comply with the protocol requirements assessed by investigator.

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The following criteria need to be assessed before pre-conditioning and/or before CT017 CAR-GPC3 T cell infusion (retesting within one week is allowed in case of laboratory abnormalities that do not meet the following criteria): patients with any of the following conditions will be excluded or require delayed pre-conditioning, no or delayed cell infusion.

1. Rapid disease progression relative to screening, as assessed by the investigator prior to pre-conditioning
2. Patients with any of the following conditions before pre-conditioning or prior to cell infusion, including but not limited to: new arrhythmia not controlled with drugs, hypotension requiring vasopressors; signs of central nervous system disease or clinically significant neurological abnormalities; assessed by the investigator to be inappropriate to continue the trial
3. Bacterial, fungal, or viral infections requiring intravenous antibiotics prior to pre-conditioning. Patients receiving antibiotics for infection prophylaxis may continue to receive CT017 CAR-GPC3 T cell infusion
4. Before pre-conditioning, blood routine: neutrophil count (ANC) $<1.0 \times 10^9/L$, platelet count (PLT) $<60 \times 10^9/L$, hemoglobin(Hb) $<8.0g/dL$
5. ECOG performance status ≥ 2 prior to pre-conditioning
6. Child-Pugh score >7 , creatinine clearance rate <50 mL/min prior to pre-conditioning
7. Oxygen saturation $<95\%$ (refers to pulse oxygen, low concentration oxygen is allowed) before pre-conditioning or cell infusion
8. Systemic steroids, equivalent to $>15mg/day$ prednisone within 3 days prior to pre-conditioning, except inhaled steroids
9. In addition to the requirements for combined therapy, molecular targeted therapy such as sorafenib or similar multi-kinase inhibitors was received within 1 week before pre-conditioning, systemic chemotherapy (such as FOLFOX4, etc.) or local therapy such as surgical therapy, interventional therapy, radiotherapy and ablation for liver cancer was received within 2 weeks before pre-conditioning
10. Cell infusion was delayed for > 7 days after pre-conditioning for any reason.

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Study treatment

Product Name: Fourth-generation humanized targeting Glypican-3(GPC3) modified autologous CAR T cell injection

Product short name: CT017 CAR-GPC3 T cells or CT017

Route of administration: CT017 CAR-GPC3 T cells will be infused intravenously through a blood transfusion device at the research center at a rate of approximately 2-5 mL/min. Cell infusion should be completed within 1 hour of cell resuscitation.

Number of Cases

About 18-54 subjects will be enrolled in the two phases of this study. During the study, the number of subjects may be adjusted by the investigator through negotiation with the collaborators according to the study design, study progress or the available safety, efficacy and pharmacokinetic data of CT017.

Study Assessments:

Safety Assessments :

Adverse events will be assessed according to CTCAE v5.0.

CRS/CRES will be assessed according to the CRS/CRES grading criteria.

In the monotherapy dose-escalation phase, patients experienced 1 or more of the following adverse events within 28 days after the first infusion of CT017 CAR-GPC3 T cells, defined as dose-limiting toxicities (DLTs):

Hematologic Toxicity

- CT017 CAR-GPC3 T cell-related \geq Grade 4 hematotoxicity (except lymphopenia and leukopenia) that fails to recover to \leq Grade 2 after 14 days of treatment
- CT017 CAR-GPC3 T cell therapy-related hemophagocytic lymphohistiocytosis syndrome (HLH)

Non-hematological toxicity

- CT017 CAR-GPC3 T cell treatment-related \geq Grade 3 bilirubin or ALT/AST increase that does not decrease to \leq Grade 2 after 14 days of treatment (except asymptomatic Grade 3 bilirubin or ALT/AST increase)

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- \geq Grade 3 cytokine release syndrome associated with CT017 CAR-GPC3 T cell therapy not controlled to \leq Grade 2 after 7 days of treatment
- CT017 CAR-GPC3 T-cell-related \geq Grade 3 CAR-T-cell-related encephalopathy syndrome (CRES)/immune cell therapy-related neurotoxicity syndrome (ICANS)
- CAR-GPC3 T-cell therapy-related other non-hematological toxicities \geq Grade 3 lasting more than 7 day, except: (1) Grade 3 fever, (2) laboratory abnormalities of no significant clinical significance, and (3) Grade 3 fatigue.

Pharmacokinetics Assessment:

The copy number of CT017 CAR-GPC3 DNA in peripheral blood will be detected by q-PCR.

Tumor Assessment:

Imaging (either enhanced CT or enhanced MRI) of the chest, abdomen and pelvis, and tumor marker examination should be obtained at baseline (before the first pre-conditioning). (Tumor assessments at each visit after cell infusion will be referenced to the baseline or the minimum after the first infusion). Evaluable imaging within 4 weeks prior to pre-conditioning may be accepted as the baseline for assessment. If patients receive bridging therapy after apheresis, baseline imaging is required at baseline. After the first cell infusion, tumor marker and imaging of the chest, abdomen, and pelvis (plain and contrast-enhanced CT or MRI of the head when central nervous system symptoms suggest possible brain metastases) are performed at the established visits (W4, W8, W12, W18, W24, W30, W36, W42, W48, and W52) until W52, disease progression, loss to follow-up, withdrawal from the trial, or death. Unscheduled examinations may be performed at other times if necessary.

Imaging evaluation According to RECIST 1.1 criteria and mRECIST criteria. Intrahepatic lesion visualization should be enhanced in the post-contrast arterial phase and stable measurements can be repeated until confirmed progressive disease (PD).

Statistical Analysis

Analysis Population

Enrolled Data Set: includes all enrolled subjects. Enrollment is defined as all meeting inclusion/exclusion criteria, apheresis samples shipped to the manufacturing preparation center and received, and baseline testing meeting assessment criteria to be able to undergo pre-conditioning.

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- **Safety Set (SS)** : All subjects receiving CT017 CAR -GPC3 T cell infusion. This analysis set will be used for secondary safety analyses and summaries of the baseline study population.
- **Dose Limiting Toxicity Analysis Set (DLTS):** In the monotherapy dose-escalation phase, all subjects who received CT017 CAR -GPC3 T cell infusion and completed the 28-day DLT assessment or developed a DLT within 28 days. This analysis set will be used for the primary safety analysis.
- **Cell Pharmacokinetics Analysis Set (CKS):** All subjects who received CT017 CAR - GPC3 T cell infusion and had at least one quantifiable copy of CT017 CAR-GPC3 DNA after infusion. This analysis set will be used for cellular pharmacokinetic analysis.
- **Modified Intention-to-Treat Set (mITT):** All subjects who received CT017 CAR-GPC3 T cell infusion and had measurable disease at baseline. This analysis set will be used for efficacy analysis.

Statistical analysis principles and methods

Continuous variables will be analyzed using descriptive statistics (e.g., number of cases, mean, median, standard deviation [SD], minimum, and maximum). Categorical variables will be analyzed using frequency tables (frequencies and percentages).

Safety analysis

All adverse events (AEs) will be classified according to the latest version of the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities MedDRA coding and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Frequency distribution, graphs or other descriptive indicators will be used for analysis. The number and percentage of subjects with treatment-related adverse events (TEAEs) will be calculated by system organ class, preferred term, and group.

Serious adverse events (SAEs) including deaths, TEAEs, adverse events of special interest (AESIs), and adverse events leading to discontinuation of trial treatment will be summarized.

Descriptive analyses were performed for laboratory tests, vital signs, ECG, and changes from baseline. Other safety measures will be described in a similar method.

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Metabolism Assessment of CT017 CAR-GPC3 T Cells

According to the Cell Pharmacokinetics Analysis Set, the list, plot and summary of CT017 CAR-GPC3 DNA copy number at different detection time points will be generated, and the peak time of cell expansion, peak value of expansion, area under the curve (AUC) and survival time after infusion of CT017 CAR-GPC3 T cells will be calculated.

Tumor response analysis

The efficacy endpoints of overall objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), time to disease control (DDC), and overall survival (OS) will be analyzed in the modified intention-to-treat(mITT) analysis set population.

Analysis Time Point

The safety analysis will be performed after the last subject completes the 28-day DLT observation period in the monotherapy dose-escalation phase.

In the combination therapy expansion phase, the last subject in each group will complete the 12-week, 24-week, and 52-week observation periods, and efficacy, safety, and cytokinetic analyses will be analyzed. The final analysis will be performed after the last subject completed 52 weeks of follow-up.

Schedule Study Procedures

The study procedures are described in [Table 3](#) and include: 1) Target Pre-screening (by signing the pre-screening informed consent form); 2) Screening Period: including apheresis and cell preparation; 3) Baseline Period; 4) Treatment Period (including pre-conditioning and CT017 CAR-GPC3 T cell infusion); and 5) Follow-up Period.

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Table 3 Schedule Study Procedures

	Pre-screening	Screening	Baseline	Treatment Period											Follow-up Period					Survival Follow-up ²⁶		
				Pre-conditioning	First Infusion							2 nd Infusion ^{18,19}		3 rd Infusion ^{18,19}								
Visits	V0	V1	V2 ¹⁸	V3 ^{18,19}	V4				V5	V6	V7	V8	V9	V10 ²⁰	V11 ²¹	V12 ²¹	V13 ²¹	V14	V15			
Visit Date	~ D-42	D-42 to D-9	D-8 to D-6	D-6 to D-1	D0 (W0)	D1	D3	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	D56 (W8)	D84 (W12)	D126 (W18)	D168 (W24)	D210 W30	D252 (W36)	D294 (W42)	D336 (W48)	D364 (W52)	Once every three months, until the fifth year	
Window (days)								± 1	± 1	± 2	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 14	
Target Pre-screening Informed Consent Form	X																				X	
Pathological tissue GPC3 detection ¹	X																					
Past medical history and treatment history		X	X																			
Demographic data		X																				
Concomitant diseases and medications		X	X																			
Signed informed consent		X																				
Check inclusion/exclusion criteria or reassessment criteria		X	X										X		X							
Physical Examination ²		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

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Visits	Pre-screening	Screening	Baseline	Treatment Period												Follow-up Period					Survival Follow-up ²⁶
				Pre-conditioning	First Infusion								2 nd Infusion ^{18,19}		3 rd Infusion ^{18,19}	V11 ²¹	V12 ²¹	V13 ²¹	V14	V15	
Visit Date	~ D-42	D-42 to D-9	D-8 to D-6	D-6 to D-1	D0 (W0)	D1	D3	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	D56 (W8)	D84 (W12)	D126 (W18)	D168 (W24)	D210 W30	D252 (W36)	D294 (W42)	D336 (W48)	D364 (W52)	Once every three months, until the fifth year
Window (days)								± 1	± 1	± 2	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 14
Vital Signs ³		X	X	X	X ²²	X	X	X	X	X	X		X ²²	X	X ²²	X	X	X	X	X	X
ECOG score		X	X					X	X				X	X	X	X	X	X	X	X	X
Child-Pugh score		X	X										X	X	X						
CT/MRI Examinations ⁴		X	X								X	X	X	X	X	X	X	X	X	X	X
Echocardiogram ⁵		X																			
Pulmonary function test ⁵		X																			
Glycosylated hemoglobin ⁵		X																			
Hepatitis B panel ^{5,6,7}		X																			
HBV DNA ^{6,7}		X						X		X	X	X	X	X	X	X	X	X	X	X	X
HIV syphilis test ⁵		X																			
HCV-RNA ⁵		X																			
Blood routine ^{5,7}		X	X	X ²³	X ²³	X	X	X	X	X	X	X	X ²³	X	X ²³	X	X	X	X	X	X
Blood chemistry ^{5,7}		X	X	X ²³		X	X	X	X	X	X	X	X ²³	X	X ²³	X	X	X	X	X	X
Tumor biomarkers ^{5,7,8}		X	X					X		X	X	X	X	X	X ²³	X	X	X	X	X	X
Electrolytes ^{5,7}			X	X ²³		X	X	X	X		X	X	X ²³	X	X ²³	X	X	X	X	X	X
Coagulation ^{5,7}		X	X	X ²³		X	X	X			X	X	X ²³	X	X ²³	X	X	X	X	X	X
C-reactive protein ^{5,7}			X		X ²³	X	X	X	X				X ²³		X ²³						
Ferritin ⁷			X		X ²³		X		X				X ²³		X ²³						

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Visits	Pre-screening	Screening	Baseline	Treatment Period												Follow-up Period					Survival Follow-up ²⁶
				Pre-conditioning	First Infusion								2 nd Infusion ^{18,19}		3 rd Infusion ^{18,19}	V11 ²¹	V12 ²¹	V13 ²¹	V14	V15	
Visits	V0	V1	V2 ¹⁸	V3 ^{18,19}	V4				V5	V6	V7	V8	V9	V10 ²⁰	V11 ²¹	V12 ²¹	V13 ²¹	V14	V15		
Visit Date	~ D-42	D-42 to D-9	D-8 to D-6	D-6 to D-1	D0 (W0)	D1	D3	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	D56 (W8)	D84 (W12)	D126 (W18)	D168 (W24)	D210 W30	D252 (W36)	D294 (W42)	D336 (W48)	D364 (W52)	Once every three months, until the fifth year
Window (days)								± 1	± 1	± 2	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 14
Urine routine ^{5,7}		X	X		X		X	X	X		X		X		X						
Fecal occult blood ^{5,7}		X	X		X		X	X	X		X		X		X						
Oxygen saturation (finger) ⁷			X		X ²²	X	X						X ²²		X ²²						
Electrocardiogram ^{5,7,9}		X	X		X			X			X		X		X						
Peripheral Blood T Cell Apheresis/CAR T Cell Preparation ¹⁰		X																			
Pre-conditioning ¹¹				X									X		X						
CT017 CAR-GPC3 T Cell Infusion					X								X		X						
CT017 CAR-GPC3 DNA Copy Number ¹²					X ²³	X	X	X	X	X	X	X	X ²³	X	X ²³	X	X				
Peripheral Blood Cytokines ¹³					X ²³	X	X	X	X	X	X	X	X ²³	X ²³	X	X	X				
Serum or urine pregnancy test (for women of		X	X										X		X	X	X	X	X	X	X

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Visits	Pre-screening V0	Screening V1	Baseline V2 ¹⁸	Treatment Period											Follow-up Period					Survival Follow-up ²⁶	
				Pre-conditioning V3 ^{18,19}	First Infusion D0 (W0)										2 nd Infusion ^{18,19} V8	V9	3 rd Infusion ^{18,19} V10 ²⁰	V11 ²¹	V12 ²¹		V13 ²¹
Visit Date	~ D-42	D-42 to D-9	D-8 to D-6	D-6 to D-1	D0 (W0)	D1	D3	D7 (W1)	D14 (W2)	D21 (W3)	D28 (W4)	D56 (W8)	D84 (W12)	D126 (W18)	D168 (W24)	D210 (W30)	D252 (W36)	D294 (W42)	D336 (W48)	D364 (W52)	Once every three months, until the fifth year
Window (days)								± 1	± 1	± 2	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 14
childbearing potential ¹⁴																					
Anti-drug antibody					X						X		X		X		X				X
Replicable lentivirus ¹⁵													X		X			X			X
Thyroid function ¹⁶		X											X		X		X				X
Combination Therapy ¹⁷		X ²⁴											X ²⁴	X ²⁴	X ²⁴	X ²⁴	X ²⁴	X ²⁴	X ²⁴	X ²⁴	X ²⁴
Documentation of adverse events and concomitant medications (including other anticancer therapies)		X	X	X	X ²⁵	X ²⁵	X ²⁵	X ²⁵	X	X	X	X	X ²⁵	X	X ²⁵	X	X	X	X	X	X
Survival Follow-up ²⁶																					X

Notes:

- At prescreening/screening, previous tissue samples or fresh puncture samples may be accepted; if the pathological diagnosis is confirmed, the screening period may be extended to D-49;
- A complete physical examination (including height, weight) of each system organ will be performed at Screening. Brief physical examination (including body weight) of the corresponding system and organ at other visit points;
- Vital signs: temperature, heart rate (or pulse), respiration, and blood pressure. Blood pressure should be measured in the same arm as far as possible using a cuff sphygmomanometer, and the subject rested for more than 5 minutes;

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4. Imaging examination: Enhanced CT/MRI scans of the chest, abdomen and pelvis and head MRI must be performed during the screening period [Enhanced CT may be performed for patients not suitable for MRI and vice versa] to rule out brain metastases. Results of evaluable tests performed 1 month prior to signing the ICF at screening are acceptable. For liver lesions, enhanced MR examination of the liver is recommended for subjects who have previously undergone TAE or TACE (except for subjects with contraindications to MR examination). Baseline imaging was acceptable for tumor assessment if there were evaluable imaging studies during the screening period within 4 weeks prior to pretreatment; baseline imaging was required if subjects received bridging therapy after apheresis. Subjects with complete response or partial response during the trial must have response confirmed after 4 weeks;
5. Laboratory test results within 1 week for subjects at this clinical site at screening; For laboratory parameters not meeting inclusion/exclusion criteria, reexamination within 1 week is allowed (other parameters may not be reexamined during reexamination and are not counted within the out-of-window PD range) ;
6. HBV DNA testing was required for subjects who were HBsAg positive and/or HBcAb positive at Screening and followed up according to visit requirements. Hepatitis B virus panel 5 and HBV DNA monitoring is not required during follow-up for subjects who are positive for HBsAb only in panel 5 at screening;
7. After pretreatment, unscheduled tests could be performed in case of abnormal parameters or clinical need; Electrolyte and coagulation function tests could be performed at W36 and later at the discretion of the investigator according to the patient 's condition;
8. Tumor biomarkers: AFP;
9. Except that ECG monitoring was used on the day of CT017 CAR-GPC3 T cell infusion (12-lead ECG may not be performed unless the investigator considered necessary), 12-lead ECG was used for other visits, and retest was performed as soon as possible in case of abnormalities;
10. Peripheral blood cell apheresis and CT017 CAR-GPC3 T cell preparation: Subjects who meet the inclusion criteria after preliminary screening will undergo mononuclear cell collection at the study site, and the apheresis will be transported to the partner for CT017 CAR-GPC3 T cell preparation, which takes about 3 weeks;
11. Conditioning regimen: Fludarabine 25 mg/m² + cyclophosphamide 300 mg/m² were administered intravenously once daily on Days -6, -5, and -4 before CT017 CAR-GPC3 T cell infusion; the investigator could appropriately adjust the conditioning drug according to the subject 's response; CT017 CAR-GPC3 T cells could also be infused without conditioning measures according to the subject' s cellular metabolism;
12. Blood samples will be collected until any 2 consecutive negative CT017 CAR-GPC3 DNA copy number tests are obtained; in case of reinfusion, CAR DNA copy number tests will be performed according to the corresponding visit time points until the results are negative or stable;
13. Collect blood samples and monitor cytokines, including IL-6, IL-10, IL-2, IL-8, IL-15, TNF- α , IFN- γ , TGF- β . If abnormal, perform unscheduled tests as needed until return to normal or baseline levels or 4 weeks after CT017 CAR-GPC3 T cell infusion, whichever occurs earlier; When clinically urgent, receive IL-2, IL-6, TNF- α and other tests in the laboratory of the study site, of which IL-6 is mandatory;
14. V1 during screening period, baseline during Cycle 1, and before pretreatment in Cycles 2-3: serum pregnancy test for female subjects of childbearing potential, and blood or urine pregnancy test for female subjects of childbearing potential during follow-up period ;
15. RCL monitoring: RCL blood samples were collected at W12, W24, W42, W52 after the first infusion of study treatment, and subjects entered long-term follow-up after W52 ;
16. Thyroid function test (determination of serum thyroid hormone TT4, TT3, FT3, FT4 and serum thyroid-stimulating hormone TSH) ;
17. Combination therapy includes: sorafenib or a similar multi-kinase inhibitor; or PD-1/PD-L1 monoclonal antibody; or other therapies that may benefit the subject ;
18. Permit D-6 to receive baseline examination on the same day, and start pretreatment medication on the same day; allow retest within 1 week for laboratory indicators that do not meet the reassessment criteria in the baseline examination; the details of the visits to be performed during Cycles 2 and 3 are the same as those in Cycle 1 (including the pre-pretreatment assessment and pretreatment 8 days in advance, and the visits to Day 14 after infusion) ;

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19. It is recommended that preconditioning status be monitored by performing the required tests on days 2-3 after the start of preconditioning and at other times as clinically indicated ;
20. Subjects who withdrew from the trial prior to W24 should be encouraged to complete the W24 visit process as much as possible; for subjects who did not want to visit W24, various examinations should be completed according to the W24 visit process, and imaging examinations may not be repeated if they have been performed within 4 weeks and do not require reconfirmation;
21. Subjects who withdraw from the trial between W24 and W52 should try to encourage them to complete the visit process at W52; for subjects who do not want to visit W52, various examinations should be completed according to the visit process at W52, and imaging examinations may not be repeated if they have been performed within 4 weeks and do not require reconfirmation ;
22. Subjects were monitored for vital signs (temperature, respiration, pulse (heart rate), and blood pressure) and oxygen saturation (finger) at least 15 minutes (\pm 5 minutes) before and at least 15 minutes (\pm 5 minutes) after the start of the CT017 CAR-GPC3 T cell infusion, and half an hour (\pm 5 minutes), 1 hour (\pm 5 minutes), 2 hours (\pm 5 minutes), 4 hours (\pm 5 minutes), 8 hours (\pm 10 minutes), and 24 hours (\pm 10 minutes) after the start of the infusion ;
23. Relevant blood tests (including cytokines, copy number of CT017 CAR-GPC3 DNA, ADA and hematology, etc.) on the day of infusion were drawn before CT017 CAR-GPC3 T cell infusion. Whether routine blood tests were performed between D-1 and D-3 before infusion was at the investigator 's discretion. Whether blood biochemistry, electrolytes and coagulation tests were performed on D0 was decided by the investigator according to the subject 's condition. The details of visits to be performed during Cycles 2-3 were the same as those in Cycle 1 (including pre-conditioning assessments and pre-conditioning performed 8 days earlier to visit 14 days after infusion). If the subject has obvious discomfort such as fever, the investigator may collect biological samples according to the patient 's condition for cytokine, CT017 CAR-GPC3 DNA copy number, blood routine test ;
24. In the monotherapy dose-escalation phase, the duration of sorafenib combination was 1 week \pm 3 days before the first cycle of conditioning, and whether sorafenib (or a similar multi-kinase inhibitor) or PD-1/PD-L1 monoclonal antibody or other treatments that may benefit the subjects were combined in Cycles 2 and 3 was decided by the investigator based on the safety and efficacy after the first infusion; the method of use was detailed in Section 3.3.3 of the text;
25. If CRS/CRES/neurotoxicity \geq Grade 2 occurs within 7 days after CT017 CAR-GPC3 T cell infusion, all parameters should be closely monitored and adverse event grades should be assessed daily until recovery to Grade 1. In case of grade 3 or higher CRS/CRES/neurotoxicity, transfer to ICU for close monitoring is recommended.
26. All subjects who completed the 52-week study visit or withdrew prematurely were followed for survival unless they withdrew consent, refused, were lost to follow-up, or died, or the program was terminated (as described in Section 6.8).

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ABBREVIATIONS TABLE

ADA	Anti-drug antibody
AE	Adverse Events
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
CAR T	Chimeric antigen receptor T
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRES	CAR T cell -related encephalopathy syndrome
ICANS	Immune cell therapy-related neurotoxicity syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HBV-DNA	HBV DNA
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphoid tissue cell hyperplasia syndrome
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
IRR	Infusion related reaction
LVEF	Left ventricular ejection fraction
NCCN	Integrated National Cancer Network Organization
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Disease progression

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PFS	Progression-free survival
PR	Partial response
PRES	Reversible posterior cerebral syndrome
RCL	Replication-competent lentivirus
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Events
SD	Stable disease
SUSAR	Suspected unexpected serious adverse event
SS	Safety Analysis Set
TEAEs	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
ULN	Upper limit of normal
WBC	White blood cell count

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1. STUDY BACKGROUND

1.1 DISEASE BACKGROUND

Primary liver cancer (PHC) is the fourth most common malignant tumor and the third leading cause of cancer death in China. About 400,000 people are diagnosed with PHC and 368,000 people die of PHC every year. The morbidity and mortality account for more than 50% of the world, seriously threatening the life and health of Chinese people^[1]. The etiology of liver cancer in China is different from carcinogenic factors in Europe and the United States, which is mainly chronic hepatitis virus infection, especially hepatitis B. Most of them are found in the middle and late stages of hepatocellular carcinoma, and the survival time is shorter than that in Europe and the United States.

Many factors should be considered for the treatment of primary liver cancer, such as tumor volume, tumor number, presence or absence of tumor spread, liver function reserve capacity, patient age and presence or absence of complications. Commonly used treatments include surgical resection of the liver, liver transplantation, ablation therapy (chemoablation, thermal ablation, and cryoablation), transcatheter arterial chemoembolization (TACE), radiation therapy, and systemic drug therapy. According to BCLC staging methods widely used at home and abroad, both Chinese Society of Clinical Oncology (CSCO) 2018 guidelines and National Comprehensive Cancer Network (NCCN) guidelines recommend that early liver cancer is mainly treated with surgery or ablation, and early detection and early treatment achieve radical results. However, patients with microvascular tumor emboli or satellite lesions have a high risk of recurrence, which limits the use of surgical treatment such as liver transplantation and hepatectomy for small lesions and small nodular liver cancer; TACE and ablation combined with systemic therapy are the main treatment methods for advanced hepatocellular carcinoma. Sorafenib^[2], lenvatinib^[3] as first-line therapy, or regorafenib as second-line therapy (sorafenib failure) in advanced disease subjects who are unresectable or locally treated can achieve clinical benefit of prolonging survival by 2-5 months^{[3][4]}. TACE alone, external radiotherapy, and seed

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embolization have some antitumor effects but do not have a clear clinical benefit of prolonged survival. Clinical studies with systemic chemotherapeutic agents have shown limited benefit and a narrow target population. An open-label, randomized, international multicenter Phase 3 clinical study (EACH study)^{[5][6]} included 371 subjects with advanced HCC who were ineligible for surgical or local therapy, of whom 75% were Chinese. The results showed that FOLFOX4 regimen significantly prolonged mPFS compared with doxorubicin alone (1.77 vs. 2.93 months, p 0.001), and analysis after follow-up to 7 months showed a benefit in OS in the FOLFOX4 group (6.47 vs. 4.90 months, p = 0.04). The incidence of neutropenia and neurotoxicity in the FOLFOX4 group was slightly higher than that in the control group. Although the therapeutic effect was limited, the current treatment for primary liver cancer was also limited. Oxaliplatin-based systemic chemotherapy was still recommended as the first-line treatment for advanced HCC by the CSCO guidelines for primary liver cancer (2018 V1).

In addition, with the exception of one cytokine-induced tumor killer cell^[7], the effect of systemic^[8] therapy as adjuvant therapy following partial hepatectomy or ablation has not been established whether recurrence rates can be reduced and survival time prolonged, and more effective and definitive treatments are urgently needed to maintain long-term survival of subjects.

The immune checkpoint inhibitors nivolumab and pembrolizumab achieved an objective response rate of 14-20% in subjects who failed or were intolerant to sorafenib, and therefore received marketing authorization in the United States for first-line and second-line systemic therapies, respectively, with nivolumab achieving a 9-month survival rate of 74% in the sorafenib failure population, which has the potential to significantly prolong survival time^[9]. In addition, nivolumab combined with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (Yervoy, ipilimumab) for second-line treatment of HCC that failed sorafenib achieved an ORR of 33%, and this combination has also been approved for second-line

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systemic treatment in the United States^[10] . Another phase III clinical study of PD-L1 monoclonal antibody atezolizumab (afatinib) combined with bevacizumab (bevacizumab) versus sorafenib as first-line treatment for advanced hepatocellular carcinoma (Imbrave 150 study)^[11] The results showed that both mPFS and mOS of atezolizumab combined with bevacizumab versus sorafenib reached statistical significance (6.8 months vs. 4.3 months, $P < 0.0001$; NE vs. 13.2 months, $P = 0.0006$), and significantly reduced the risk of death (56% reduction in the risk of death in Chinese patients and 42% reduction in the risk of death in global patients), and atezolizumab + bevacizumab has also been approved for first-line treatment of hepatocellular carcinoma in the United States. The objective response rate of domestic PD-1 monoclonal antibody carruzumab injection for second-line treatment of advanced HCC reached 14.7%, with a median survival of 13.8 months^[12] . Currently, it has been approved for second-line treatment of advanced liver cancer in China. These results suggest that immunotherapy and its combination therapy are very important for systemic treatment of patients with primary liver cancer.

As an adoptive immune cell therapy, the results of an open, phase 3 clinical trial of cytokine-induced killer T cell therapy showed that it could prolong the recurrence-free survival time after surgery in subjects with primary liver cancer as adjuvant therapy^[7] , and more clinical trial data are needed to support the clinical benefit of immunotherapy for prolonging the survival time of subjects with primary liver cancer.

Therapy with chimeric antigen receptor T cells (CAR T cells) genetically modified based on tumor-specific expressed antigens has been demonstrated as a promising cancer therapeutic strategy. CAR T cells can specifically recognize tumor-associated antigens without the limitation of major histocompatibility complex presentation to recognize tumor cells, potentially benefiting a wider subject population.

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Glypican-3 (GPC3-3) is a carcinoembryonic antigen belonging to the glycosylphosphatidylinositol-anchored heparan sulfate proteoglycan family involved in cell proliferation, differentiation, migration, and apoptosis^{[13][14][15]}, and several studies have shown that GPC3 is positively expressed at high rates in primary hepatocytes, but hardly expressed in normal tissues. Clinical studies have already been carried out with GPC3 monoclonal antibodies against this target, bifunctional antibodies against GPC3 and CD3, and GPC3 peptide vaccines (Fig. clinicaltrial.gov). Based on preclinical experimental and early clinical trial data, CARsgen will use CAR T cells independently developed to target GPC3 to conduct clinical studies in subjects with primary hepatocellular carcinoma with positive GPC3 expression and no alternative treatment to explore their preliminary safety and efficacy in humans.

1.2 INVESTIGATIONAL DRUG

The CT017 CAR-GPC3 T cells used in this study are fourth-generation CAR T cell products that co-express the transcription factor RUNX3 on second-generation CAR T cells targeting GPC3 (abbreviated as CT017 CAR-GPC3 T cells or CT017) as shown in [Figure 1](#). The structure diagram of CT017 CAR-GPC3/RUNX3 gene is shown in [Figure 2](#), in which CT017 CAR-GPC3 gene and RUNX3 are co-expressed through "self-cleaving polypeptide" F2A, and CT017 CAR-GPC3 gene is composed of the single-chain Fv antibody Y035 of GPC3 sequentially linked to the CD8 α hinge region, CD8 α transmembrane region, 4-1BB intracellular region signaling region, and CD3 ζ intracellular signaling region. CT017 CAR-GPC3 T cell injection was prepared by a partner at a GMP compliant preparation site.

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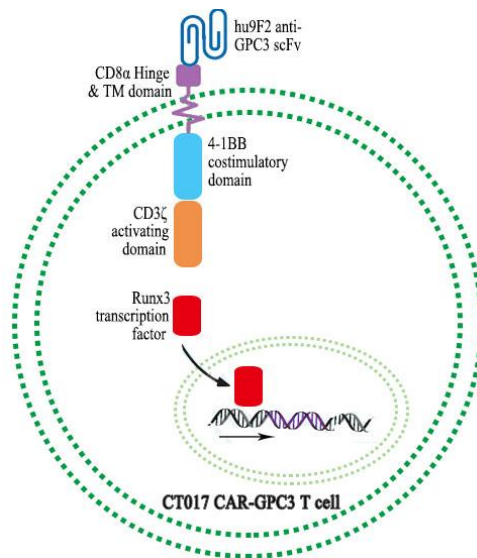


Figure 1 CT017 CAR-GPC3 T Cell Structure Diagram

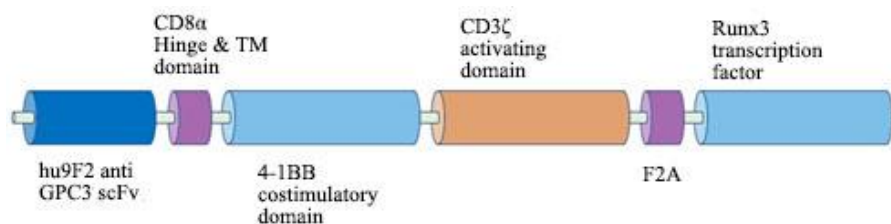


Figure 2 Structural diagram of CT017 CAR-GPC3/RUNX3 gene

1.3 GPC3-RELATED TRANSLATIONAL RESEARCH

Huh-7 cells, a hepatocellular carcinoma cell line with high expression of CT017 CAR-GPC3, were co-cultured with CT017 CAR-GPC3 T cells at different effector-to-target ratios of 2:1, 1:1, 1:2, and 1:4 for 17 h. The results showed that CT017 CAR-GPC3 T cell product had effective target-ratio gradient-dependent killing activity against GPC3-positive Huh-7 cells in vitro, and it was found that CT017 CAR-GPC3 T cells could secrete higher levels of IFN- γ and their secretion levels showed significant effector-to-target ratio gradient effect in co-culture with tumor cells at different effector-to-target ratios in vitro, indicating that this product has the ability to secrete IFN- γ cytokines in the process of killing tumor cells.

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In vivo pharmacodynamic results showed that the subcutaneous xenograft model of human hepatocellular carcinoma Huh-7 in NPG mice was randomized according to the tumor volume when the average volume of the xenograft was about $120 \text{ mm}^3 \sim 150 \text{ mm}^3$. Group 1 (vehicle control), 2 (CT017 CAR-GPC3 T, 2.0×10^6 cells/mouse), 3 (CT017 CAR-GPC3 T, 5.0×10^6 cells/mouse). During the treatment period, the animals were observed for general clinical signs every 2-3 days, and body weight and tumor diameter were measured twice weekly. During the whole test, the animals were in good mental state, without death or tumor ulceration; compared with the vehicle control group, significant tumor inhibition was observed in each group, with tumor inhibition rates of CT017 CAR-GPC3 T, 2×10^6 cells/mouse, 5×10^6 cells/mouse: 99.87%, 100%, tumor regression in 5/6 mice and 6/6 mice, respectively, with extremely significant difference compared with the vehicle control group ($P < 0.001$), showed that CT017 CAR-GPC3 T cells had a significant antitumor effect in NPG mice transplanted with human hepatocellular carcinoma Huh-7 cells at doses of $2 \sim 5 \times 10^6$ cells/mouse.

1.4 DOSE PRINCIPLE

1.4.1 Selection of starting dose

The results of tumor inhibition test of this product in NPG mouse model of Huh-7 showed that CT017 CAR-GPC3 T cells had a significant inhibitory effect on subcutaneous xenograft tumors in mice at $2 \sim 5 \times 10^6$ cells, without significant toxicity. The effective dose was assumed to be 1 to 2.5×10^8 cells/kg for mice based on 20 g, which translates to a human equivalent dose (HED) of 0.8 to 2×10^7 cells/kg, and approximately 4.8 to 12×10^8 cells per cell infusion based on 60 kg.

The second-generation CAR T cells targeting the same target as this product showed stronger efficacy of CT017 (fourth-generation) CAR-GPC3 T cells than CT011 (second-generation) CAR-GPC3 T cells at the same dose of cell level in vivo tumor inhibition experiments in mice (data unpublished, see CT017 CAR-GPC3 T cell Investigator's Brochure

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1.0). Preliminary data from the second-generation exploratory clinical trial of CAR-GPC3 T cells showed that $5-10 \times 10^8$ was a clinically intended dose and was safe and tolerable.

This study is the first-in-human trial of this product. In order to reduce the exposure of subjects to too low ineffective dose and ensure the safety of subjects, the initial dose is proposed to start at the fourth-generation CT017 CAR-GPC3 T cell dose from 2.5×10^8 .

1.4.2 Dose escalation intervals

The initial dose of this study starts from 2.5×10^8 cells, and subsequent dose groups will escalate upwards to Dose Level 1 (4×10^8) or decrease to Dose Level -1 (1.5×10^8) in the principle of 3+3. If the 4×10^8 dose level is not identified as the MTD, escalation to a higher dose may be decided by the investigator and collaborators.

During the trial, if 3 subjects in a certain dose group developed no DLT after completing a single cell infusion for 28 days and were well tolerated, the dose group could directly enter the expansion phase of combination therapy after discussion and evaluation by the investigator and collaborators.

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2. TRIAL OBJECTIVES AND ENDPOINTS

Table 4 Trial objectives and endpoints

Purpose of trial		Trial Endpoint Measures
Primary objective	To evaluate the safety and tolerability of CT017 CAR-GPC3 T cells in subjects with advanced hepatocellular carcinoma within 28 days after the first infusion of a monotherapy dose-escalation phase	<ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of Treatment-Related Adverse Events • Incidence of Adverse Events of Special Interest (AESI) • ECG, laboratory tests, vital sign changes, etc. • Identify DLTs and MTD
Secondary objectives	Evaluate the pharmacokinetics of infused CT017 CAR-GPC3 T cells	Time to Peak Cell Expansion, Peak Expansion, Area Under the Curve (AUC), and Survival Following Infusion of CT017 CAR-GPC3 T Cells
	Overall Safety and Tolerability in Monotherapy dose-escalation and Combination Therapy Expansion Phase	<ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of Treatment-Related Adverse Events • Incidence of Adverse Events of Special Interest (AESI) • ECG, laboratory tests, vital sign changes, etc.
	To assess the preliminary efficacy of infusion of CT017 CAR-GPC3 T cells in the treatment of advanced hepatocellular carcinoma with positive GPC3 expression	<ul style="list-style-type: none"> • Objective response rate (ORR, response rate of PR and above) • Duration of Response (DOR) • Disease Control Rate (DCR) • Disease Control Time (DDC) • Progression-free survival (PFS) • Overall survival (OS)

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3. TRIAL DESIGN

3.1 OVERALL DESIGN

This is an open-label, monotherapy dose-escalation and combination expansion phase I trial to observe the safety, tolerability, cellular pharmacokinetics and preliminary efficacy of CT017 CAR-GPC3 T cell therapy in subjects with advanced hepatocellular carcinoma with positive GPC3 expression.

3.1.1 Monotherapy dose-escalation phase

In the monotherapy dose-escalation phase, 3 dose levels will be set (see [Table 5](#)) to include 9-18 subjects who meet the inclusion and exclusion criteria.

The initial dose will start at dose level 0, ie, 2.5×10^8 cells, and subsequent dose groups will be escalated upward to dose level 1 (4×10^8) or down to dose level - 1 (1.5×10^8) using the 3+3 principle. Three subjects are required to be included in each dose group for DLT evaluation. If 1 subject in a dose group experiences DLT, 3 subjects will be added to this dose group. If $\geq 2/6$ subjects experience DLT, up to 6 subjects will be enrolled into the previous low dose level. The cellular dose that occurred in $\leq 1/6$ DLTs was considered as the maximum tolerated dose (MTD) (DLTs $\geq 2/6$ occurred at the higher dose of this dose level).

The DLT observation period was 28 days. Each dose group should complete DLT observation before entering the next dose group; no DLT was observed 14 days after the completion of cell infusion for the first subject in the same dose group before cell infusion for subsequent subjects.

If the 4×10^8 dose level is not identified as the MTD, escalation to a higher dose may be decided by the investigator and collaborators, as well as dose determination for dose expansion studies.

During the trial, if 3 subjects in a certain dose group developed no DLT after completing a single cell infusion for 28 days and were well tolerated, the dose group could directly enter

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the expansion phase of combination therapy after discussion and evaluation by the investigator and collaborators.

Table 5 Single dose level

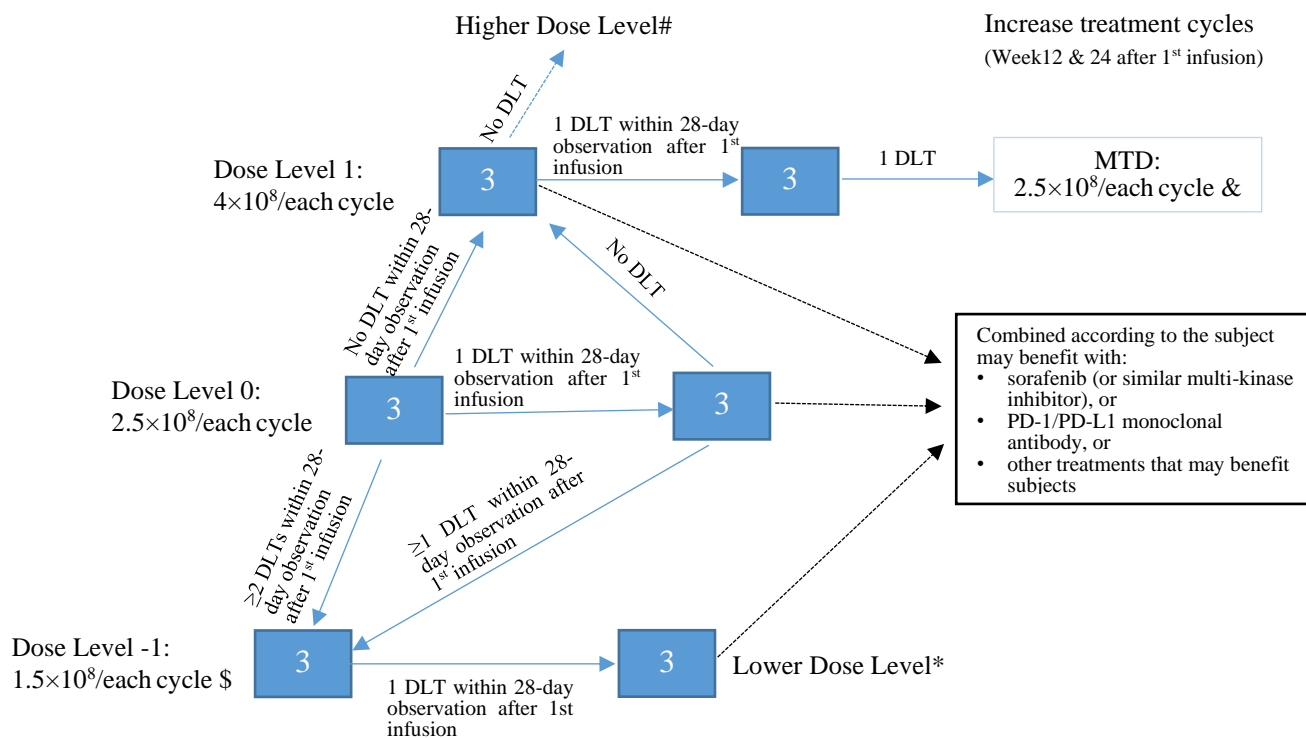
Group	Cell dose
Dose Level 0 (n = 3-6)	2.5×10^8 cells
Dose Level 1 (n = 3-6)	4×10^8 cells
Dose Level -1 (n = 3-6)	1.5×10^8 cells

Increase treatment cycles:

For subjects in monotherapy dose-escalation phase, after DLT observation is completed, if no DLT occurs, and the investigator considers that the subject may benefit, the cell infusion cycle may be increased for the subject according to dose expansion treatment, and cell infusion can be performed again at 12 and 24 weeks after the first infusion (the infusion interval is determined by the investigator according to the subject's safety, efficacy and cell metabolism and other factors) until the subject experiences disease progression, intolerable toxicity or requires other treatments, or there is no cell available for infusion (whichever occurs earlier). The dose and method of subsequent infusions may be judged and adjusted by the investigator based on the subject 's likely clinical benefit.

After all subjects in the monotherapy dose-escalation phase completed the first cycle of treatment, CT017 CAR-GPC3 T cells alone or in combination with other drugs that may benefit the subjects may be used in subsequent cycles, including but not completely limited to multi-kinase inhibitors such as sorafenib or PD-1/PD-L1 monoclonal antibody or other treatments that may benefit the subjects. The trial design is shown in [Figure 3](#).

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Note:

If the 4×10⁸ dose level is not identified as the MTD, escalation to a higher dose may be decided by the investigator and collaborators together.

& If up to 6 subjects are enrolled into the 2.5×10⁸ dose level, then this dose level will be defined as MTD; if only 3 subjects are enrolled into the 2.5×10⁸ dose level, then another 3 subjects will be enrolled into this dose level, and if there is ≤ 1 DLT, this dose level will be defined as MTD.

\$ If there is no DLT in 3 subjects of 1.5×10⁸ dose level, dose adjustment may be decided by the investigator and collaborators together.

* If there is no DLT in the newly added 3 subjects of 1.5×10⁸ dose level, this dose level will be defined as MTD; if there is one DLT in the newly added 3 subjects of 1.5×10⁸ dose level, dose reduction or administration method adjustment will be decided by the investigator and collaborators together.

Figure 3 Schematic of Monotherapy Dose-escalation Phase Design

If cell infusion cycles are added, the baseline period and follow-up schedule are not affected by the addition of treatment course, but safety and efficacy evaluation tests may be added according to the addition of treatment, as detailed in the schedule of study.

3.1.2 Combination Therapy Expansion Phase

During this phase, 9 to 36 subjects will be enrolled into the combination therapy expansion phase. Subjects in the expansion phase will enter the following treatment groups: combined sorafenib (or similar multi-kinase inhibitor) group; combined PD-1/PD-L1 monoclonal antibody group; or other treatment groups that may benefit subjects, combined treatment will be administered according to the following methods until 52 weeks after the first treatment, intolerable toxicity, disease progression, withdrawal of the subject from the study, or

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discontinuation of treatment at the investigator 's discretion, whichever occurs first. Three to 12 subjects per arm will be included and the number of subjects per arm will be determined by the investigator and collaborator based on discussion of the safety, cellular metabolism and preliminary efficacy of the combination. The trial design is presented in [Figure 4](#).

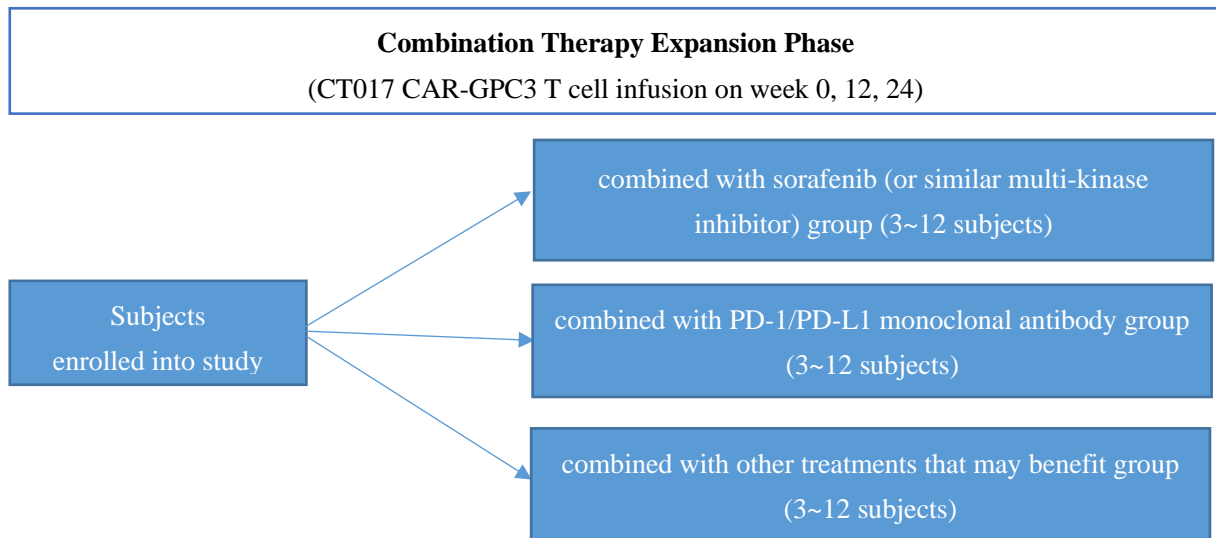


Figure 4 Schematic of Combination Therapy Expansion Phase Design

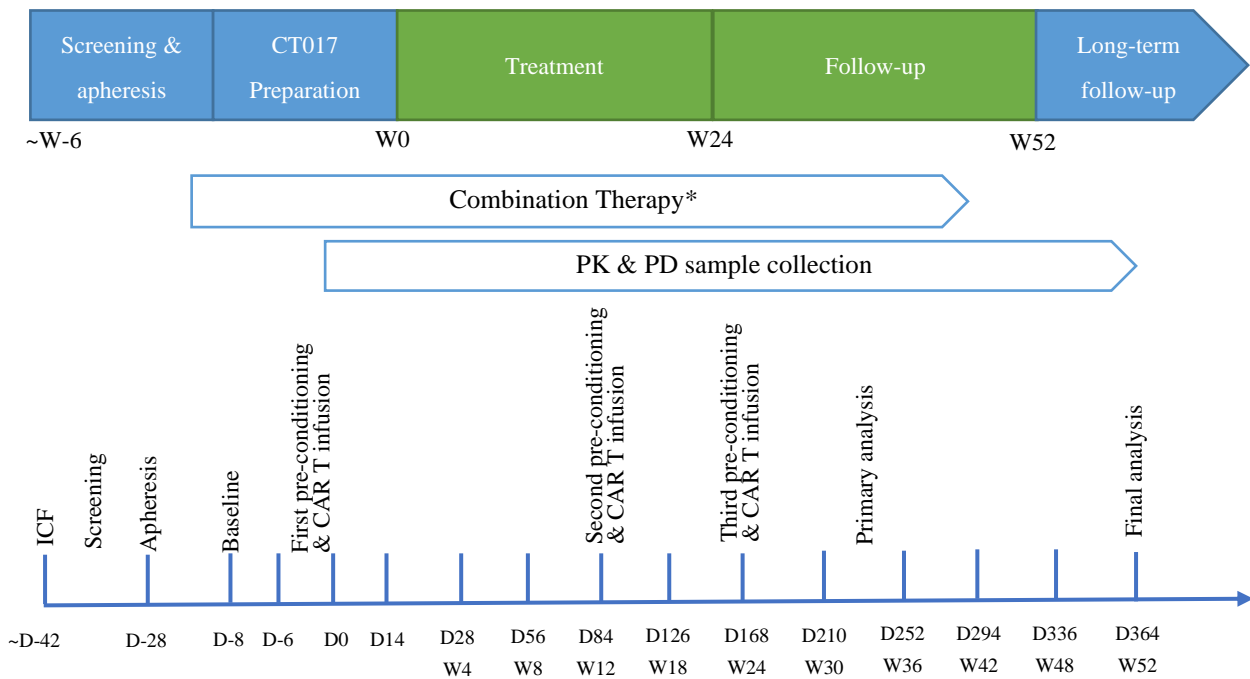


Figure 5 Trial Flow Diagram

* Combination therapy methods are detailed in Protocol Section 3.3.3

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3.2 DEFINITION OF DOSE LIMITING TOXICITY (DLT)

In the monotherapy dose-escalation phase, subjects experienced 1 or more of the following adverse events, defined as dose-limiting toxicities (DLTs), within 28 days after the first infusion of CT017 CAR-GPC3 T cells:

Hematologic Toxicity

- CT017 CAR-GPC3 T cell treatment-related \geq Grade 4 hematotoxicity (except lymphopenia and leukopenia) that cannot be recovered to \leq Grade 2 after 14 days of treatment;
- CT017 CAR-GPC3 T cell therapy-related hemophagocytic lymphohistiocytosis syndrome (HLH);

Non-hematological toxicities

- CT017 CAR-GPC3 T cell therapy-related \geq Grade 3 bilirubin or ALT/AST increase that cannot be reduced to \leq Grade 2 after 14 days of treatment (except asymptomatic grade 3 bilirubin or ALT/AST increase);
- \geq 3 Grade cytokine release syndrome associated with CT017 CAR-GPC3 T cell therapy that cannot be controlled to \leq Grade 2 after 7 days of treatment;
- CT017 CAR-GPC3 T-cell-related \geq Grade 3 CAR-T-cell-related encephalopathy syndrome (CRES)/immune cell therapy-related neurotoxicity syndrome (ICANS);
- CT017 CAR-GPC3 T cell therapy-related \geq Grade 3 other nonhematologic toxicities lasting more than 7 days. Exceptions were: (1) grade 3 fever; (2) laboratory abnormalities without significant clinical significance; and (3) grade 3 fatigue.

All adverse events (AEs) will be classified according to the latest version of the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities MedDRA coding and graded according to Common Terminology Criteria for Adverse Events

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(CTCAE) v5.0 using frequency distributions, graphs or other descriptive measures, and the number and percentage of subjects with TEAEs will be calculated by system organ class, preferred term, and group. Adverse events judged to be related to cytokine release syndrome (CRS), CAR-T cell-related encephalopathy syndrome (CRES), or CAR T cell therapy will also be graded and documented according to the CRS/CRES grading criteria and management recommended by Lee and the CARTOX Task Force.

3.3 STUDY TREATMENT

3.3.1 Investigational Product

Name of investigational product: Fourth-generation humanized anti-phosphatidylinositol proteoglycan-3 (GPC3) modified autologous CAR T cell injection

Product short name: CT017 CAR-GPC3 T cells or CT017

Route of administration: intravenous drip

3.3.2 Monotherapy Approach

3.3.2.1 Post-apheresis bridging therapy and conditioning regimen before cell infusion

Subjects in the monotherapy dose-escalation phase were allowed to receive bridging therapy prior to the first cell infusion in this study. Bridging therapy may be sorafenib or a similar multi-kinase inhibitor, or systemic chemotherapy (eg, FOLFOX4, etc); PD-1 or PD-L1 monoclonal antibodies are contraindicated. Bridging therapy may be started after apheresis; sorafenib or similar multikinase inhibitors should be discontinued 1 week before conditioning with clear lymphocytes, and systemic chemotherapy should be discontinued 2 weeks before conditioning with clear lymphocytes.

Conditioning was to be administered on Days 4-6 prior to cell infusion and subjects were to receive fludarabine 25 mg/m² and cyclophosphamide 300 mg/m² once daily for 3 consecutive days; CT017 CAR-GPC3 T cell infusions were to be administered 1-3 days after completion of

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conditioning, no later than 7 days. During pretreatment, the investigator may adjust the pretreatment medication appropriately based on the subject's response.

The day of the first cell infusion was D0, and subsequent visit times were calculated based on the first cell infusion.

3.3.2.2 CT017 CAR-GPC3 T Cell Therapy Approach

Resuscated CT017 CAR-GPC3 T cells were administered as an intravenous drip through a blood transfusion apparatus at the site at approximately 2-5 mL/minute. Promethazine 25 mg intramuscularly was administered within half an hour before infusion for anti-allergic (or equivalent) treatment and/or indomethacin suppositories 50 – 100 mg anal antipyretic and analgesic (or equivalent) treatment. Cell infusion was completed within 1 hour of cell resuscitation.

3.3.3 Combination Therapy Approach

After subjects in the monotherapy dose-escalation phase completed the first cycle of treatment, CT017 CAR-GPC3 T cells alone or in combination with other drugs that may benefit the subjects may be used in subsequent cycles, including but not completely limited to multi-kinase inhibitors such as sorafenib or PD-1/PD-L1 monoclonal antibody or other treatments that may benefit the subjects. Combined therapy with other agents will be administered as described below prior to the second infusion.

During the combination therapy expansion phase, subjects who meet the inclusion criteria as assessed at screening will receive one of the subsequent combination therapies at the investigator's discretion based on the subject's potential benefit.

Each subject may receive CT017 CAR-GPC3 T cell therapy again at Weeks 12 and 24 after the first cell therapy (if the cells are found to be maintained in vivo for a long time during monotherapy, the dosing interval may be extended based on cell pharmacokinetics) (the

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reinfusion time may be decided by the investigator after comprehensive consideration of the subject 's safety, efficacy and cell pharmacokinetics). Until 52 weeks after the first treatment, the subject developed intolerable toxicity, disease progression, withdrew from the study, or was judged by the investigator to require treatment termination, whichever came first. Whether to continue conditioning with FC regimen or adjust conditioning drugs after the first infusion will be judged by the investigator based on the subject 's response status (including but not limited to lymphocyte count, CT017 CAR-GPC3 DNA copy number, cytokine status, etc.). The investigator will also determine whether the subject is suitable for continued treatment based on the subject 's response to treatment.

Combination therapy is selected as follows (the following combination therapy is used as a reference, and the specific treatment method, treatment time, treatment frequency and drug dose are determined by the investigator according to the subject 's condition):

Combined Sorafenib (or equivalent multi-kinase inhibitor) therapy: Subjects in the monotherapy dose-escalation phase started combination therapy 1 week \pm 3 days prior to conditioning in Cycle 2; subjects in the combination expansion phase started combination therapy after apheresis. Sorafenib was administered orally at 200 mg to 400 mg twice daily; other similar multikinase inhibitors were administered according to this treatment prescription.

Combined PD-1/PD-L1 monoclonal antibody therapy: Subjects in the monotherapy dose-escalation phase started combination therapy 2 weeks \pm 3 days after the second cycle of CT017 CAR-GPC3 T cell infusion; subjects in the combination expansion phase started combination therapy 2 weeks \pm 3 days after the first infusion of CT017 CAR-GPC3 T cells. The specific administration time was determined by the investigator based on his/her comprehensive consideration of the subject 's general condition after infusion of CT017 CAR-GPC3 T cells; the specific drug dose and frequency of administration were determined by the investigator.

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Combined with other therapies that may benefit the subjects: including systemic chemotherapy (such as FOLFOX4), local therapy including intervention, ablation and radiotherapy, or other therapies.

When performing the above combined therapy, the specific treatment method, treatment time, treatment frequency and drug dose are determined by the investigator according to the comprehensive judgment of the subject. During the study, the investigator may adjust the dose of the combined therapy or cell therapy or make a judgment on whether to continue the treatment based on the subject 's tolerance and response to treatment.

If the investigator confirms that the combination therapy drugs that may benefit the subject are drugs other than those recommended by NCCN Clinical Practice Guidelines for Hepatobiliary Tumors (current version) or Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (current version) (PD-1/PD-L1 monoclonal antibodies have been within the scope of combination therapy), they should be submitted to the Ethics Committee for filing before use in the subject.

For combination therapies that require daily dosing, such as sorafenib, dosing will be at the discretion of the investigator during conditioning. No combination therapy was administered on the day of infusion of CT017 CAR-GPC3 T cells.

3.3.4 Cell/Combination Therapy Dose Reduction or Discontinuation

In case of > Grade 2 treatment-related **non-hematological AEs** lasting for more than 14 days (except alopecia, fatigue and other AEs considered tolerable by the investigator), the investigator should reduce the dose of combined drug therapy to half the original dose. If the dose of combined drug therapy cannot be reduced to \leq Grade 2 within 14 days after treatment and no further improvement is observed, the treatment will be suspended. If a subject 's treatment-related non-hematologic AE cannot recover to \leq Grade 1 (except for AEs that are

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considered tolerable by the investigator) prior to the next cell therapy (including conditioning), treatment will be discontinued.

When > Grade 3 treatment-related **hematological AEs** persisted for more than 7 days (except for lymphopenia and leukopenia), the investigator needed to reduce the dose of the combination drug to half the dose, and if it could not be reduced to \leq Grade 3 after the combination treatment with half the dose drug for 7 days and no further improvement was observed, the treatment was to be suspended. If a subject's treatment-related hematologic AE cannot recover to \leq Grade 2 before the next cell therapy (including conditioning), treatment will be discontinued.

3.4 DURATION OF TRIAL

3.4.1 Duration of Trial for Individual Subjects

Each subject may last up to approximately 60 weeks (approximately 14 months) from signing the Target Prescreening Informed Consent Form and/or Trial Informed Consent Form, Target Screening, Completion of Screening Checks, Apheresis, Cell Preparation, Baseline Checks, Conditioning, CT017 CAR-GPC3 T Cell Infusion and/or Combination Therapy through the completion of the trial.

3.4.2 Study Completed

Completion of this trial is defined as 52 weeks after the last subject completes the first trial treatment, withdraws from the trial, is lost to follow-up, withdraws consent or dies.

3.4.3 Criteria for trial termination

If the investigator finds that some conditions or events may endanger the subjects under the premise of continuing the trial, the trial may be terminated after discussion between the investigator and the partner.

Early termination of the trial may be for, but not limited to, the following reasons:

- Unexpected, significant, or unacceptable risk to enrolled subjects;
- Enrollment was slow.

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4. TRIAL POPULATION

In this study, 18 ~ 54 subjects with advanced HCC were planned to be enrolled in 1 ~ 3 clinical study sites in two phases, and the immunohistochemical detection of tumor tissue sections showed positive expression of GPC3 target.

All subjects and/or legal representatives must personally sign and date an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved informed consent form prior to performing the trial appropriate procedures. Infusions were not administered if pre-infusion exclusion criteria were met prior to administration of trial treatment. If a subject experiences a laboratory abnormality that does not meet the inclusion criteria, a retest is permitted to rule out laboratory testing error.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following criteria to be enrolled:

1. Aged 18-75 years (inclusive), male or female;
2. Patients with pathologically confirmed advanced hepatocellular carcinoma who had recurrence after surgery or other local therapies, or who had progression or intolerance after previous standard systemic therapy (systemic therapy including but not limited to systemic chemotherapy (FOLFOX4 regimen), molecular targeted drug therapy (sorafenib, regorafenib, lenvatinib, etc.), etc.);
3. Stage C according to Barcelona Clinic Liver Cancer Criteria (BCLC) or Stage B ineligible for local therapy/local therapy progression;
4. Expression of GPC3 demonstrated by immunohistochemistry (IHC). Patients who had previously received targeted GPC3 treatment should be confirmed to have positive GPC3 target by pathological examination of tumor tissue after completion of previous treatment before enrollment;

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5. At least one target lesion that can be evaluated according to RECIST 1.1, defined as non-lymph node lesions with the longest diameter ≥ 10 mm, or lymph node lesions with the short diameter ≥ 15 mm; intrahepatic lesions require enhanced arterial phase imaging;
6. Expected survival time > 12 weeks;
7. Child-Pugh score ≤ 7 ;
8. Adequate performance status defined as Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1;
9. Subjects with positive HBsAg or positive HBcAb are required to have HBV-DNA < 2000 IU/ml. HBsAg positive subjects must receive antiviral treatment according to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (current version);
10. Subjects should meet the following test results at screening. If laboratory abnormalities do not meet the following criteria and they are allowed to be retested within one week. If the criteria are still not met, the screening is considered to have failed:
 - a. Hematology (no intensive blood transfusion, platelet transfusion, cell growth factor (except recombinant erythropoietin) and other supportive treatment within 7 days before the test): neutrophil count (ANC) $\geq 1.0 \times 10^9/L$; lymphocyte count $\geq 0.4 \times 10^9/L$; platelet count (PLT) $\geq 60 \times 10^9/L$; hemoglobin (Hb) ≥ 8.0 g/dL;
 - b. Blood biochemistry: endogenous creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula), alanine aminotransferase (ALT) $\leq 5 \times$ upper limit of normal (ULN); aspartate aminotransferase (AST) $\leq 5 \times$ ULN; alkaline phosphatase $\leq 5 \times$ ULN; total bilirubin $\leq 2 \times$ ULN;
 - c. Prothrombin time (PT): prolongation of prothrombin time ≤ 4 s;

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11. Adequate venous access for mononuclear cell collection (referred to as apheresis) without other contraindications for apheresis (including but not limited to systemic bleeding disorders, puncture site infection or systemic infection, hemodynamic instability, and other conditions assessed by the investigator as contraindications to apheresis);
12. Female patients of childbearing potential must have a negative serum pregnancy test at screening and within 14 days prior to the start of study medication and are willing to use a reliable method of contraception during the trial (within 12 months after cell infusion (M12)). Male patients with partners of childbearing potential should have undergone sterilization or agree to use a reliable method of contraception during the trial;
13. Able to understand and sign informed consent form.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will not be included in this trial:

1. Pregnant or lactating women
2. Human immunodeficiency virus (HIV) antibody, Treponema pallidum antibody positive or hepatitis C virus (HCV-RNA) positive
3. Any active uncontrolled infection, including but not limited to patients with active tuberculosis
4. Clinically significant thyroid dysfunction (serum thyroid hormone determination TT4, TT3, FT3, FT4 and serum thyroid-stimulating hormone TSH) assessed by the investigator as inappropriate for entry into the trial
5. Prior or current hepatic encephalopathy

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6. Presence of clinically significant ascites, defined as those with positive physical examination signs of ascites or ascites that requires intervention (eg, paracentesis or medical therapy) to control (only those with imaging findings of ascites that do not require intervention may be included)
7. Imaging examination findings: the proportion of liver replaced by tumor $\geq 50\%$, or main portal vein tumor thrombus, or tumor thrombus invading the mesenteric vein/inferior vena cava
8. Patients with known active autoimmune diseases requiring treatment with immunosuppressive drugs including biological agents
9. Toxicities caused by previous treatment have not recovered to Common Terminology Criteria for Adverse Events (CTCAE) \leq Grade 1 (except alopecia, pigmentation, specific laboratory abnormalities that investigator believed would not affect or allowed in the protocol)
10. Systemic steroids, equivalent to > 15 mg/day prednisone within 14 days prior to apheresis, except inhaled steroids
11. History of severe allergy, or allergy to excipients of CT017 CAR-GPC3 T cell fluid (eg, DMSO, albumin, etc.), or allergy to penicillin antibiotics
12. Presence of untreated brain metastases or symptoms of brain metastases
13. Maximum target lesion diameter > 5 cm or presence of central or extensive tumor lung metastases
14. Subjects with current unstable or active ulcers, gastrointestinal bleeding, or intolerance to proton pump inhibitors
15. Subjects with history of organ transplantation or waiting for organ transplantation

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16. Received local-regional therapy for the lesion within 2 weeks prior to apheresis (ie, transarterial chemoembolization, transcatheter embolization, hepatic arterial infusion, radiotherapy, radioembolization, or ablation) or systemic oxaliplatin-based chemotherapy within 2 weeks prior to apheresis, or thymosin, interferon and other immunotherapies (see Section 18 for PD-1/PD-L1 monoclonal antibody requirements) or any Chinese herbal/patent medicine for the control of liver cancer within 1 week prior to apheresis; or received targeted drug therapy such as sorafenib, regorafenib, and lenvatinib within 1 week prior to apheresis
17. Prior treatment with CAR T (refer to Inclusion Criteria 4 for CAR T requirement targeting GPC3) or TCR T
18. Anti-PD-1/PD-L1 monoclonal antibody therapy within 4 weeks prior to apheresis
19. Major surgical procedures or significant trauma within 4 weeks prior to apheresis or anticipation of the need for major surgery during the trial
20. Other serious medical conditions that may limit the patient's participation in this trial (eg, poorly controlled diabetes mellitus (glycosylated hemoglobin [HbA1c]>8% after treatment), poorly controlled hypertension (systolic blood pressure>160 mmHg and/or diastolic blood pressure>100 mmHg), uncontrolled congestive heart failure (New York Heart Association Class III-IV), significantly prolonged QT interval (QTc \geq 500ms corrected by Bazetts's method is recommended, as evaluated by the investigator), left ventricular ejection fraction (LVEF)<50%, myocardial infarction or unstable arrhythmia or unstable angina within the past 6 months, pulmonary embolism, chronic obstructive pulmonary disease, interstitial lung disease, clinically significant pulmonary function test abnormalities)
21. Patients are unable or unwilling to comply with the protocol requirements assessed by investigator.

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The following criteria need to be reassessed before washing-out conditioning and/or before CT017 CAR-GPC3 T cell infusion (retesting within one week is allowed in case of laboratory abnormalities that do not meet the following criteria): i.e., patients with any of the following conditions will be excluded or require delayed pre-conditioning, no or delayed cell infusion:

1. Rapid disease progression relative to screening, as assessed by the investigator prior to pre-conditioning;
2. Patients with any of the following conditions before pre-conditioning or prior to cell infusion, including but not limited to: new arrhythmia not controlled with drugs, hypotension requiring vasopressors; signs of central nervous system disease or clinically significant neurological abnormalities; assessed by the investigator to be inappropriate to continue the trial;
3. Bacterial, fungal, or viral infections requiring intravenous antibiotics prior to pre-conditioning. Patients receiving antibiotics for infection prophylaxis may continue to receive CT017 CAR-GPC3 T cell infusion;
4. Before pre-conditioning, blood routine: neutrophil count (ANC) $<1.0 \times 10^9/L$, platelet count (PLT) $<60 \times 10^9/L$, hemoglobin(Hb) $<8.0g/dL$;
5. ECOG performance status ≥ 2 prior to pre-conditioning;
6. Child-Pugh score >7 , creatinine clearance rate <50 mL/min prior to pre-conditioning;
7. Oxygen saturation $< 95\%$ (refers to pulse oxygen, low concentration oxygen is allowed) before pre-conditioning or cell infusion;
8. Systemic steroids, equivalent to $>15mg/day$ prednisone within 3 days prior to pre-conditioning, except inhaled steroids;

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9. In addition to the requirements for combined therapy, molecular targeted therapy such as sorafenib or similar multi-kinase inhibitors was received within 1 week before pre-conditioning, systemic chemotherapy (such as FOLFOX4, etc.) or local therapy such as surgical therapy, interventional therapy, radiotherapy and ablation for liver cancer was received within 2 weeks before pre-conditioning;
10. Cell infusion was delayed for > 7 days after pre-conditioning for any reason;

4.3 CRITERIA FOR SUBJECT WITHDRAWAL AND REPLACEMENT

Subjects may withdraw from the trial during the course of the trial for one or more of the following reasons:

- Subjects may withdraw from the study at any time according to their own will, i.e., withdraw their informed consent;
- Disease progression was shown by imaging studies. If disease progression first occurs according to RECIST v1.1 criteria, confirmation is required after 4-6 weeks (except for rapid progression and significant clinical progression);
- Intolerable adverse reaction;
- Subject lost to follow-up or became pregnant;
- Subjects may be withdrawn from the study at any time at the investigator 's discretion for reasons related to subject safety, conduct, or management;
- The subject has received other anti-tumor therapies prohibited in this study, including but not limited to radiotherapy, chemotherapy and surgical treatment;
- CT017 CAR-GPC3 T cell production failed and sufficient cell doses for clinical use could not be obtained to meet specifications.

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When the safety parameters of CT017 CAR-GPC3 T cells all met the requirements, but some parameters that may be related to cell number, CAR T cell positivity, or cell viability failed to meet the pre-specified acceptance criteria, the subject 's cells could be released conditionally if the clinical comprehensive assessment concluded that the benefit of the subject' s infusion of cells may outweigh the risk, that is, the subject could receive CT017 CAR-GPC3 T cell infusion .

If a subject fails to complete the scheduled visit after receiving CT017 CAR-GPC3 T cells, the investigator shall make every effort to contact him/her and collect the efficacy, safety data, concomitant treatment, secondary tumor and survival status of the subject as far as possible. Unless a subject was lost to follow-up, died, refused, or was terminated by the principal investigator, ethics committee, or regulatory authority.

Criteria for Substitution of Subjects:

Subjects receiving CT017 CAR-GPC3 T cells who withdraw within 28 days of the first infusion will increase this group of subjects to obtain sufficient numbers of subjects to evaluate DLTs, excluding adverse events.

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5. INVESTIGATIONAL DRUG

5.1 IDENTITY OF INVESTIGATIONAL DRUG

CT017 CAR-GPC3 T cells are fourth-generation CAR T cell products that co-express the transcription factor RUNX3 on second-generation CAR T cells targeting GPC3. Among them, C T017 CAR-GPC3 protein is co-expressed by "self-cleaving polypeptide" F2A, and C T017 CAR-GPC3 protein is composed of a single-chain Fv antibody Y 035 of GPC3 sequentially linked to the CD8 α hinge region, CD8 α transmembrane region, 4-1BB intracellular region signaling region, and CD3 ζ intracellular signaling region. C T017 CAR-GPC3 T cells were cryopreserved in cytoprotective solution and dispensed in multiple pouches. Each pack contains a proportion of CryoStor Alpha commercial cryopreservation fluids and Human Albumin HSA.

CT017 product package According to the intended clinical dose and CT017 CAR-GPC3 T cell positive rate, each bag is packaged with the number of CT017 CAR-GPC3 positive T cells suitable for clinical infusion, with the packaging volume of 50 mL.

5.2 PROCEDURES FOR PERIPHERAL BLOOD COLLECTION, PREPARATION, QUALITY CONTROL AND TRANSPORTATION OF CT017 CAR-GPC3 T CELLS

CT017 CAR-GPC3 T cells were prepared and provided by CARsgen. Peripheral blood mononuclear cell collection (PBMC) was performed at the study site. CT017 CAR-GPC3 T cells were prepared, controlled, released and transported by CARsgen. The process is shown in [Figure 6](#).

After confirming that the subject met the inclusion and exclusion criteria, the investigator allowed the subject to be enrolled, signed the informed consent form and completed the relevant examinations, and submitted the proposed dose to the preparation center of CARsgen. Subjects will be arranged to collect PBMC and plasma, collect PBMC at least 2×10^9 , and ship the collected blood samples to CARsgen Preparation Center within 48 hours by cold chain logistics (2-8°C) to complete PBMC separation, autologous plasma extraction and inactivation treatment

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and testing. Appropriate amount of PBMC will be taken for T cell activation and CT017 CAR-GPC3 T cell transduction, and then completed cell production, sample collection, preparation, dispensing, labeling, encapsulation and cryopreservation, and can be released after quality inspection (The inspection items include sterility, mycoplasma, bacterial endotoxin, cell viability, CT017 CAR-GPC3 T cell positive rate, CT017 CAR-GPC3 T cell biological activity, CT017 CAR-GPC3 copy number, magnetic bead residue, etc.) are qualified. Released products are stored in CARsgen Biobank (vapor phase liquid nitrogen condition). Prior to infusion, the product will be shipped to the clinical site under vapor phase liquid nitrogen, and the shipping temperature, etc. of CT017 CAR-GPC3 T cells will be approved upon receipt at the clinical site.

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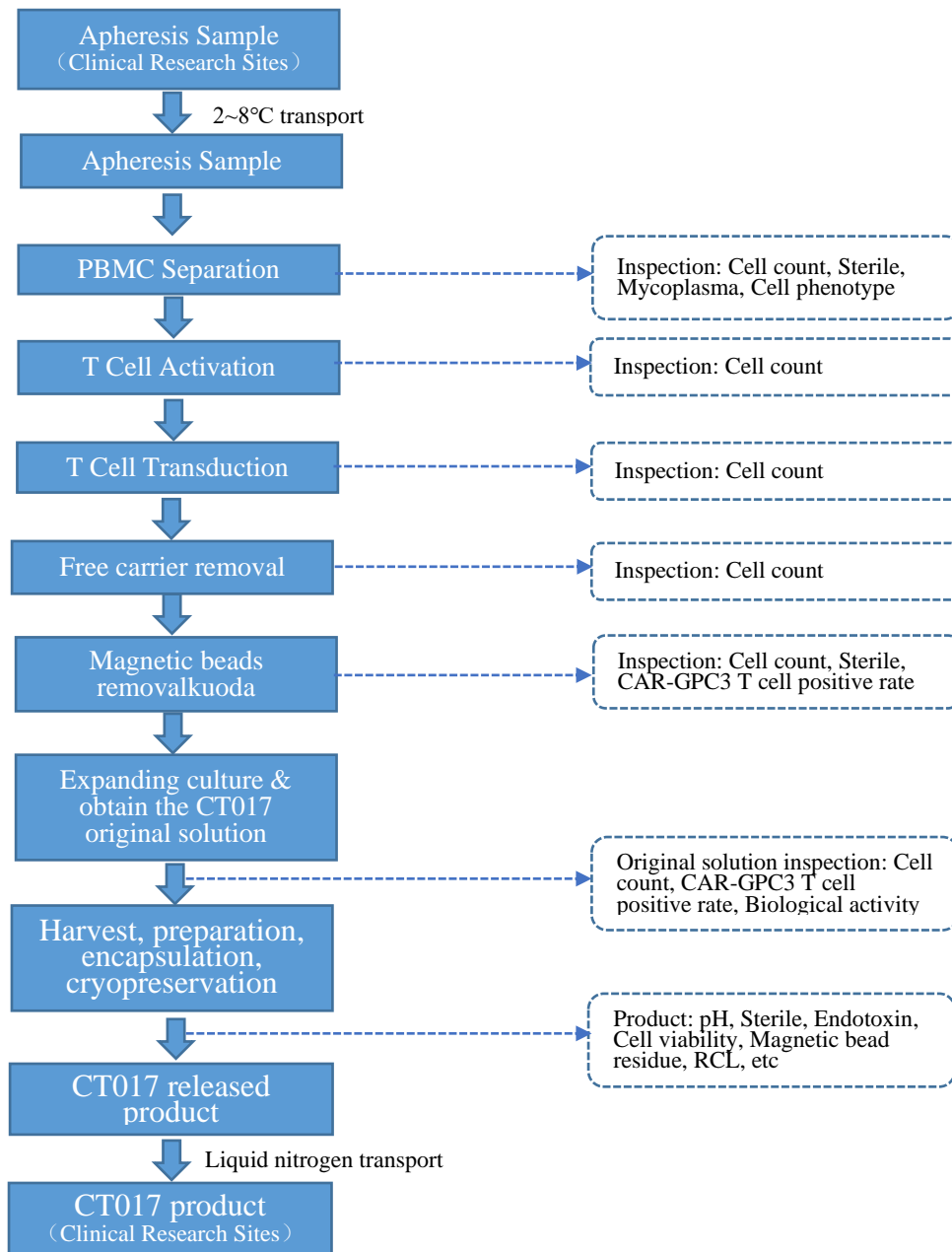


Figure 6 Flow Chart for Preparation and Transportation of Peripheral Blood Apheresis, CT017 CAR-GPC3 T Cells

5.3 PACKAGING

The CT017 product is packaged in two layers, a cryobag and a protective bag. The inner layer is a refrigerated bag and is in direct contact with the product; the outer layer is a protective bag and also plays a protective role in the refrigerated bag .

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5.4 LABELING

Each bag of infused cells will be accompanied by a label, including "For Autotransfusion Only" and unique identifying information, such as product number, subject name abbreviation, screening number, protocol number, site number, etc. Before infusion, two persons independently verified information from all subjects to determine that the information correctly matched the participating subjects. CT017 CAR-GPC3 T cell product label is placed in the center of the cryobag.

5.5 CELL RESUSCITATION AND INFUSION

The clinical site will record the shipping temperature, pouch appearance, and pouch integrity for CT017 CAR-GPC3 T cells. Cells were thawed using a warm water bath at approximately 37-40°C. Thawing steps are as follows:

Before thawing, confirm that the water bath is in normal working condition, set the temperature of water bath to 38°C, and ensure that the temperature of water bath is within 37 ~ 40°C. Remove the CT017 CAR-GPC3 T cell product from liquid nitrogen, quickly immerse the cell product (along with the protective bag) completely in a warm water bath, and gently shake the CT017 CAR-GPC3 T cell product in water until there is no visible residual ice in the cryobag. Immediately remove the CT017 CAR-GPC3 T cell product from the water bath and dry any remaining surface water spots with a sterile towel. Cut open the protective bag, remove the cryobag containing the CT017 CAR-GPC3 T cell product, gently mix the contents of the bag to disperse the cell pellet. If visible cell clumps remain, continue gently mixing the contents of the bag. Disinfect the outer surface of the cryobag and the infusion port with 75% alcohol cotton for future use.

In case of damage or flatulence of the protective bag during recovery, the protective bag should be discarded and taken out again after recovery and thawing in the water bath. If it is

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confirmed that the cryobag is intact, it will not affect the subsequent infusion and use after strengthening the disinfection of its external surface; if the cryobag is damaged or leaking, stop any use and handle it by referring to the Management Procedures for Nonconforming Products.

Resuscitation was performed by a trained person and the time and temperature of resuscitation were recorded. CT017 CAR-GPC3 T cells were administered intravenously at a rate of 2 to 5 mL/minute. Antiallergic treatment with intramuscular injection of promethazine 25 mg (or equivalent) and/or antipyretic and analgesic treatment with indomethacin suppositories 50 – 100 mg (or equivalent) was administered within half an hour before infusion. If an infusion-related reaction occurs, the infusion may be temporarily stopped or the infusion rate reduced, as assessed by the investigator. The start and end times of any changes to the infusion will be documented in the source documents. The recommended time from resuscitation to completion of infusion for the CT017 CAR-GPC3 T cell product is no more than 1 hour.

Finished recovered CT017 CAR-GPC3 T cells are stored at 2-8°C for up to 2 hours. Schedule the infusion as soon as possible at room temperature.

5.6 INVESTIGATIONAL PRODUCT STORAGE, DISPENSING, AND RECOVERY

5.6.1 Investigational Product Storage

Long-term stored CT017 CAR-GPC3 T cells will be stored in the gas phase liquid nitrogen storage bank of CARsgen. CT017 CAR-GPC3 T cells used for infusion were transported to the clinical site via gas-phase liquid nitrogen (below -175 ° C) prior to infusion and temporarily stored in a transport liquid nitrogen tank prior to infusion, and the temperature was recorded.

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5.6.2 Investigational Product Recovery and Destruction

CT017 CAR-GPC3 T cells may need to return to a partner for a variety of reasons, including, but not limited to:

- Mislabeled product;
- Damaged cryobag found;
- The subject 's condition is not suitable for infusion;
- Subject refused infusion.

Any unused CT017 CAR-GPC3 T cells or cells suspected of having quality issues requiring analysis will be returned to the partner in a liquid nitrogen environment for analysis or autoclaving for destruction. The entire bag of CT017 CAR-GPC3 T cells that did not need to be returned to the partner, as well as the infused bag of CT017 CAR-GPC3 T cells were destroyed according to the site 's medical waste disposal principles and documented.

5.6.3 Trial drug compliance

Subjects will be administered the CT017 CAR-GPC3 T cell investigational product at the site by study personnel, and if this investigational product fails to complete a full dose infusion, the reason and infusion information will be documented in the source documents. Medication compliance was calculated as the actual number of completed infusions/planned number of infusions.

5.7 CONCOMITANT TREATMENT

5.7.1 Permitted concomitant medications and treatments

In this trial, blood cell-related drugs that elevate blood cells are allowed after conditioning of the lymphocytes and after infusion of CT017 CAR-GPC3 T cells. Drugs used solely for supportive care (e.g., phenergan 25 mg intramuscularly (or equivalent) , indomethacin suppositories 50-100 mg (or equivalent) , antibiotic therapy, antiemetics, antidiarrheals, IL-6

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receptor monoclonal antibodies, etc.) were permitted before, during, and during the follow-up period after CT017 CAR-GPC3 T cell infusion. During the course of the trial, the necessity of blood products was assessed by the investigator. Because transfusion-related graft-versus-host disease (TA-GVHD), which is caused by the reaction of transfused immunocompetent lymphocytes to the host, has been found in patients receiving fludarabine after transfusion of non-irradiated blood, the disease has the potential to lead to death. To reduce the risk of TA-GVHD, blood transfusions (including platelets, whole blood, red blood cells) should be irradiated during study treatment and for 3 months after the last pretreatment with FC regimen. If irradiation is difficult to achieve due to special circumstances, it is necessary to use a whitened transfusion apparatus for infusion.

Subjects with liver cancer combined with HBsAg (+) and/or HBcAb (+) must receive long-term antiviral therapy with nucleos (t) ide analogues according to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (current version), with the first-line recommendation of nucleos (t) ide analogues entecavir or tenofovir. Interferon therapy is not permitted.

Dose:

Entecavir 0.5 mg once daily. Administered on an empty stomach (at least 2 hours before or after meals).

Tenofovir 300 mg once daily. Take with food.

If a subject is found to be HBsAg (+) and/or HBcAb (+) at Screening but has not previously taken antiviral treatment, antiviral treatment will be administered to the subject and ensure that it has been taken for at least 2 weeks prior to conditioning.

All concomitant medications (except vitamins , solvents, flushing tube and sealing liquid, PICC/PORT indwelling related drugs) and treatments from 1 month before signing the

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informed consent form to the end of the study should be recorded in the original medical record and eCRF, and the drug/non-drug name, reason for medication, dose, unit, frequency of administration, route, start date and end date of concomitant medications should be recorded in detail in the original medical record and eCRF; concomitant therapies should include: non-drug treatment name, treatment description, reason for treatment, start date and end date of treatment.

5.7.2 Prohibited concomitant medications and treatments

Intensive blood transfusion and growth factors (except recombinant erythropoietin), including granulocyte colony-stimulating factor (GCSF) and platelet growth factor, were prohibited within 7 days before blood routine tests before apheresis. During the trial, all anti-tumor therapies other than those specified in Protocol are prohibited, including modern Chinese herbal preparations with indications of liver cancer: Delisheng Injection, Kanglaite Injection/Soft Capsules, Aidi or Consaidi Injection, Elemene Injection/Oral Liquid, Huaier Granules, Cinobufotalin and Ganfule Capsules/Tablets. Immunopotentiators, including interferon, thymosin, ribonucleic acid for injection, lentinan, and ganoderma lucidum polysaccharide, should not be used during CT017 CAR-GPC3 T cell therapy.

Systemic corticosteroids were prohibited within 14 days prior to apheresis, use of trial treatment, and during the trial unless the subject developed an adverse event that required emergency medical care.

5.7.3 Other restrictions

Female subjects of childbearing potential were to practice strict contraception until 1 year after the last trial treatment and male subjects were not to donate sperm throughout the trial and until 1 year after receiving the last trial drug.

Male subject must agree that he and his spouse/partner will use reliable contraception from the start of the trial drug until 1 year or subject is not of childbearing potential.

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6. STUDY PROCEDURES

The trial procedures include: 1) target prescreening, 2) screening (including apheresis and cell preparation) , 3) baseline, 4) trial treatment period , and 5) follow-up period.

Trial procedures for specific visits are detailed in the Trial Flow Chart.

6.1 TARGET PRESCREENING (V0, ~ D-42)

Subjects who may meet the study protocol may have pathological sections of tumor tissues or fresh tissue samples tested after signing the pre-screening ICF, and the test results of GPC3 target expression should be positive.

6.2 SCREENING PERIOD (V1, D-42 TO D-9)

All subjects are required to undergo trial-related procedures after signing the informed consent . The screening period may be extended from D-49 to D-9 for definitive pathological diagnosis and other reasons.

Screening examination will be completed and inclusion/exclusion criteria will be reviewed, and detailed assessments will be provided in the trial flow chart. Eligible subjects will undergo peripheral blood mononuclear cell (PBMC) collection, at least 2×10^9 PBMC will be used to prepare CT017 CAR-GPC3 T cells, and cell products are expected to be ready for use in clinical trials in about 3 weeks. If sufficient PBMC are not collected on 1 occasion, additional collections may be performed.

6.3 BASELINE (V2, D-8 TO D-6)

The subject 's baseline condition should be assessed according to the flow chart within 3 days prior to preconditioning and baseline tests are not exempt. Imaging studies may be evaluated within 28 days prior to washing-lymphocyte conditioning; if subjects receive bridging therapy after apheresis, baseline imaging is required at baseline.

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Corresponding assessments were collected as baseline data within 3 days before pretreatment, including progress notes, laboratory tests, physical examinations, vital signs, ECOG scores, electrocardiograms, imaging tests, concomitant medications, and adverse events since informed consent. If significant abnormalities do not meet the screening and/or pretreatment criteria and are judged by the investigator to be inappropriate for subsequent trial procedures, pretreatment cannot be continued. In case of laboratory deviation, if the investigator considers it necessary to perform re-test, the re-test result once may be accepted.

6.4 TRIAL TREATMENT PERIOD

Cycle 1 Pretreatment (V3, D-6 to D-1)

In order to achieve better survival and stable expansion of reinfused CT017 CAR-GPC3 T cells in subjects and exert anti-tumor function, fludarabine and cyclophosphamide combination regimens were used for conditioning from D-6 to D-4 days before infusion.

Cycle 1 CT017 CAR-GPC3 T cell infusion and observation period (V4-6, D0 [W0] to D14 [W2] and W3, W4)

CT017 CAR-GPC3 T cell infusion was performed after completion of conditioning. The day of CT017 CAR-GPC3 T cell infusion was recorded as D0. CT017 CAR-GPC3 T cell infusion should be completed according to exclusion criteria before infusion, and the infusion can be performed only when the subject's condition is judged appropriate by the investigator.

Blood samples were collected before infusion for blood routine test, CT017 CAR-GPC3 DNA copy number, cytokines and anti GPC3 antibodies.

Subjects requiring hospitalization 7 to 14 days during and after infusion of CT017 CAR-GPC3 T cells will be closely observed, and the specific duration of hospitalization will be determined by the investigator based on the subject's condition and the presence or absence of

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unrecovered toxicity. Subjects should complete corresponding examinations and assessments on D1, D3, D7 and D14, D21, D28 as shown in the trial flow chart. Visit windows for Weeks 3 and 4 were ± 2 days. At least 2 weeks after discharge, it is recommended that the subject live in the same city near the hospital where he/she is participating in the study, and provide the subject with the site contact card, inform the subject to immediately contact the investigator if he/she is unwell, and return to the site as soon as possible for examination and treatment if necessary to ensure the safety of the subject.

Cancel CT017 CAR-GPC3 T cell infusion if it is not performed within 7 days of the last dose of conditioning drug. The need for baseline testing and re-conditioning will be confirmed based on the subject 's condition at the time of investigator assessment for consideration of infusion.

Subsequent treatment - Cycles 2 to 3 (V7 to V10, W8, W12, W18, W24)

If no DLT is observed in the first 28 days after the first infusion, retreatment at W12 and W24 may be continued or the dosing interval may be determined based on cellular pharmacokinetics, preliminary efficacy, and safety. The investigator will make a comprehensive judgment based on the subject 's condition and possible benefits as well as cell storage status to decide whether to continue to complete the subsequent Cycles 2-3. The dose and method of infusion are detailed in Section 3.3 and subsequent visits will occur at W24 with a visit window of ± 7 days from W8 to W24. Conditioning regimen prior to each infusion could be the same as Cycle 1, or CT017 CAR-GPC3 T cells could be infused without conditioning measures based on the subject 's cellular metabolism. Hematology, biochemistry, coagulation, electrolytes, C-reactive protein (CRP), electrocardiogram, and imaging (if necessary) were performed before pretreatment. The details of visits to be performed during Cycles 2-3 were the same as those in Cycle 1 (including pre-conditioning assessments and pre-conditioning performed 8 days earlier to visit 14 days after infusion). Subjects will complete each cycle of

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cell infusion according to the process specified in the trial flow chart and perform relevant test assessments, which will be recorded in the original medical record and eCRF.

Subjects will be hospitalized for 7 to 14 days after completion of Cycles 2 and 3 cell infusions, as determined by investigator assessment. Within at least 2 weeks after discharge, it is recommended that the subject live in the same city and be near the hospital where the subject participates in the study, and provide the subject with a site contact card to inform the subject that he/she should immediately contact the investigator if he/she is unwell and return to the site as soon as possible for examination and treatment if necessary to ensure the safety of the subject.

6.5 FOLLOW-UP PERIOD (V11 TO V15, W30, W36, W42, W48, W52)

The follow-up period was from W30 to W52, i.e., subjects were required to return to the hospital for visits at W30, W36, W42, W48, and W52, with a visit window of ± 7 days. Subjects are required to complete relevant tests and assessments according to the visit schedule and undergo relevant tests and assessments during the follow-up period as shown in the trial flow chart.

6.6 PREMATURE WITHDRAWAL FROM THE TRIAL AND COMPLETION OF VISITS

Subjects who prematurely withdraw from the trial will have an exit visit within 7 days of withdrawal from the trial and before the start of other new anticancer therapy, and subjects will complete assessments that should be done within 7 days before withdrawal from the trial without repeat testing.

If the subject withdraws from the trial before W24, the subject should be encouraged to complete the visit process at W24; for subjects who are unwilling to continue the visit, relevant examinations at W24 visit should be completed at the time of withdrawal. Subjects who withdraw from the trial between W24 and W52 will be encouraged to complete the visit

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procedures at W52, and subjects who are unwilling to continue the visit will be asked to complete relevant examinations at W52 visit at the time of withdrawal.

After a subject withdraws from the trial, unless the subject withdraws consent, refuses, is lost to follow-up, or dies, or the project is terminated, survival follow-up will continue and SAEs related to study treatment will continue to be collected for 3 months after the last cell infusion (or 52 weeks after the first cell infusion, whichever occurs later).

6.7 UNSCHEDULED VISIT

Unscheduled visits occurring during/after the trial will be documented in the original medical records and eCRF. Associated adverse events and changes, concomitant medications, and treatments were recorded at unscheduled visits, as well as those considered necessary by the investigator.

6.8 SURVIVAL FOLLOW-UP

All subjects who completed the 52-week study visit or withdrew prematurely will continue survival follow-up unless they withdrew consent, refused, were lost to follow-up, or died, or the program was terminated. RCL was monitored with blood samples collected annually until year 5 or death of the subject, whichever came first, and retained. Follow-up will occur every 3 months until 5 years after the first treatment or until the subject dies, whichever comes first. Poststudy survival was collected at each follow-up visit. If possible, information on subsequent anticancer therapies, tumor markers and imaging findings, and the presence or absence of secondary tumors should be collected as much as possible. Telephone contact is acceptable. For subjects who did not experience disease progression 52 weeks after the first treatment, tumor status assessments, including imaging and corresponding tumor marker tests, were performed as much as possible while survival information was collected every 3 months until progression or the addition of other antineoplastic agents, and information was subsequently collected according to routine long-term follow-up.

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7. STUDY ASSESSMENTS

7.1 DEMOGRAPHIC INFORMATION AND BASELINE CHARACTERISTICS

Demographic information and baseline characteristics only include information collected/assessed at Screening/Baseline.

Demographic information of subjects included: age, height, weight, race, gender, body surface area (BSA).

7.2 DISEASE HISTORY

The past and present medical history of the subject, including tumor history and treatment history, should be recorded.

7.3 PRIOR AND CONCOMITANT MEDICATIONS

Prior anticancer therapy should be collected and documented in the eCRF. All concomitant medications (except vitamins, solvents, flushing and sealing fluids, and drugs related to PICC/PORT indwelling) and treatments administered from 1 month before signing the informed consent form to the end of the study should be recorded in the original medical records and eCRF, and all concomitant treatments administered during the trial should be recorded in the eCRF. Coding can be found in the Drug Coding Dictionary WHO-DDE

7.4 EASTERN COOPERATIVE ONCOLOGY GROUP SCORE

ECOG performance status of each participant will be reviewed periodically and scored according to the criteria in [Appendix 2](#) . Scores were recorded on the subject 's eCRF.

7.5 TUMOR ASSESSMENT

Imaging (either enhanced CT or enhanced MRI) and tumor marker examination of the chest, abdomen, and pelvis were obtained at baseline (before the first pretreatment) and were performed at baseline for this trial (tumor assessments at each visit point after cell infusion were referenced to the baseline level or the minimum value after the first treatment). Assessable imaging within 4 weeks prior to washing-lymphocyte conditioning may be accepted as the

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baseline for imaging assessment; if subjects receive bridging therapy after apheresis, baseline imaging is required. Following the first trial treatment, imaging of the chest, abdomen, and pelvis (plain and enhanced CT or MRI of the head when there were central nervous system symptoms suggestive of possible brain metastases; bone scan when bone metastases were suspected) and tumor marker (AFP) were performed according to established visits (Screening, Baseline, W4, W8, W12, W18, W24, W30, W36, W42, W48, W52) until W52, disease progression, loss to follow-up, withdrawal from the trial, or death.

Imaging evaluation According to RECIST 1.1 criteria and mRECIST criteria, intrahepatic lesion opacification should be enhanced in the post-contrast arterial phase and stable measurements can be repeated until confirmed progressive disease (PD).

Objective tumor response assessments (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]) were performed according to RECIST 1.1 and mRECIST criteria, and subjects were required to confirm PR or CR no less than 4 weeks after the first evaluation.

- Objective response rate (ORR): defined as the percentage of evaluable subjects with confirmed PR or CR as best response, and confirmed PR or CR must be confirmed no less than 4 weeks after the first evaluation.
- Duration of response (DOR): defined as the time from the first tumor assessment of CR or PR to the first assessment of PD or death from any cause in subjects with a best response assessment of confirmed PR or CR.
- Progression-free survival (PFS): is defined as the time from the date of the first CAR T infusion to the date of the first documentation of tumor progression (regardless of treatment) or death from any cause, whichever occurs first.

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- Overall survival (OS): The time from the date of the first CAR-T infusion to the date of death due to any cause.
- Disease control rate (DCR): defined as the percentage of evaluable patients with confirmed response and stable disease (PR + CR + SD) based on best response assessment
- Time to Disease Control (DDC): defined as the time from the first tumor assessment of CR, PR, or SD to the first assessment of PD or death from any cause in subjects with best response assessment of SD or a confirmed response.

7.6 CT017 IN VIVO METABOLISM ASSESSMENT OF CAR-GPC3 T CELLS

Testing associated with CT017 CAR-GPC3 T cells included testing for copy number of CT017 CAR-GPC3 DNA.

From the first cell infusion, the copy number of CT017 CAR-GPC3 DNA in peripheral blood was detected by q-PCR at predetermined visit points in each cycle until any 2 consecutive tests were negative or below the lower limit of detection. Duration of CT017 CAR-GPC3 T cell survival was recorded from the day of infusion until the first negative result or below the lower limit of detection.

7.7 SAFETY MEASURES

7.7.1 Adverse Events

7.7.1.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward or untoward medical occurrence in a subject after signing informed consent, but which does not necessarily have to have a causal relationship with the use of the study drug. An AE can therefore be any sign, symptom, disease, or laboratory abnormality temporally associated with the use of a study drug, whether or not considered related to the study drug. Adverse events generally include the following :

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- Medical conditions/diseases present prior to signing of informed consent will be recorded as AEs only if worsening occurs after signing of informed consent (unequivocal signs or symptoms of progression of the tumor under study should not be recorded as AEs unless more severe than expected or the investigator believes that tumor progression is related to study drug administration or study procedures, and the rationale for judgment needs to be documented in the case. If a new primary malignancy developed, the event was considered an AE).
- New medical conditions/diseases emerging after informed consent
- Abnormal Clinically Significant Laboratory Findings
- Abnormal findings on physical examination
- Allergic reaction
- Drug dependence or drug abuse

In addition, adverse events may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawn;
- Drug interactions;
- Exposure during pregnancy;
- Exposure during lactation;
- Medication error

7.7.1.2 Collection and Reporting of Adverse Events

Adverse events were collected from the time the subject signed the informed consent until the subject completed the visit or withdrew from the study, whichever came first. Where the subject withdraws from the clinical trial within 3 months after the last infusion, all adverse events occurring within 3 months after the last infusion shall be recorded/reported.

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Serious adverse events occurring after this period should also be reported to the partner if the investigator considers them related to the study drug.

Adverse events may be collected by asking about signs or symptoms, laboratory tests, etc. The investigator or designee collected AEs using open and non-leading questions. The investigator ensured that all collected AEs were fully documented in the original medical records and eCRFs. The following adverse events should be recorded: medical term of the adverse event (diagnosis or symptom, if diagnosis is unknown, symptoms or signs can be recorded), date of onset and end of the adverse event, severity, need for treatment, action taken with the study drug, outcome of the adverse event, relatedness of the adverse event to the study drug, relatedness of the adverse event to lymphocyte pre-clearance treatment, and whether it is an SAE.

7.7.1.3 Adverse Event Severity Documentation

Investigators should judge the severity of AEs according to NCI-CTCAE Version v5.0. If a complete match code is not available in NCI-CTCAE v5.0, use the [Table 6](#) principle below.

Table 6 Severity of adverse reaction

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic findings only; treatment not indicated.
Grade 2:	Moderate degree; less , local, or noninvasive indication required; limiting age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.) .
Grade 3:	Serious or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, toileting, taking medications, and not bedridden) .
Grade 4:	Life-threatening; urgent treatment indicated .
Grade 5:	AE related death .

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7.7.1.4 Causal Relationship Determination of Adverse Events

Causal relationship between AEs and study drugs refers to whether there is a reasonable or possible correlation between the study drugs and AEs, which should be judged by the investigator after comprehensive consideration of clinical information. The investigator should evaluate possible relationship between AE and study procedures or study drug, and record this in EDC system. Causality assessment may be based on the following reference criteria:

Definitely related: refers to a medical event that has a reasonable temporal relationship to the administration of the study drug and cannot be explained by concurrent disease or other drugs or chemicals (ie, other possible medical explanations can be excluded).

Probable: refers to a medical event with a reasonable temporal relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possibly related: refers to a medical event with a reasonable temporal relationship to study drug administration, but which could also be explained by concurrent disease or other drugs or chemicals (ie, other factors may have contributed to the event).

Unlikely related: A medical event for which there is no likely causal relationship to the use of the study drug, but which can reasonably be explained by the underlying disease or other drugs or chemicals (ie, another plausible medical explanation exists).

Unrelated: refers to a medical event that does not have a reasonable temporal relationship to study drug administration and can be explained by the underlying disease or other drugs or chemicals (ie, definitely not causally related).

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Adverse events judged as definitely related, probably related, or possibly related will be judged as having "reasonable causal relationship" for expedited reporting.

7.7.1.5 Follow-up of Adverse Events

After the initial AE report, the investigator should proactively follow each subject and provide the partner with further information on the subject 's condition. All adverse events with documented last follow-up/contact information that are ongoing will continue to be assessed at the next follow-up/contact. All AEs experienced by a subject, whether considered related to study drug or not, were to be followed until the AE recovered or the condition stabilized, and the abnormal laboratory value returned to the baseline value or stabilized until the observed change could be reasonably explained, or until the subject was lost to follow-up or died. The investigator should ensure that the nature of the adverse event or its causal relationship with the study should be investigated and clarified as much as possible during subsequent follow-up visits, and additional laboratory tests, investigations, histopathological studies, or consultation with other health care professionals may be required.

7.7.2 Serious Adverse Events

A serious adverse event refers to an adverse event that meets at least one of the following serious criteria:

- Causing death;
- Life-threatening: refers to an event in which the subject was at risk of death during the event, rather than a hypothetical event that worsens in severity and could cause death;
- Results in hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability/incapacity loss ;
- Congenital anomaly/birth defect;

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- Important medical events that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the above definition. Important medical events should be reported as SAEs if it is determined that the event may jeopardize the subject or may require intervention to prevent various other adverse event consequences. Examples of such events are intensive treatment in the emergency room or at home for allergic tracheospasm; cachexia or convulsions, ongoing drug dependence or drug abuse. Clinical and scientific judgment is required in determining the seriousness of an event and whether expedited reporting is required.

Hospitalization or prolongation of hospitalization not associated with worsening of an AE is not in itself an SAE, eg, hospitalization for a pre-existing condition without new AE or worsening of a pre-existing condition; hospitalization for administrative reasons (eg, physical examination); hospitalization as specified in the clinical trial protocol; elective hospitalization not associated with worsening of an AE (eg, elective surgery); hospitalization for blood product use only, and the reason for blood product use does not meet seriousness criteria.

Diagnostic or therapeutic invasive (eg, surgical), noninvasive procedures should not be reported as AEs, but disease conditions that result in this procedure should be reported if they meet the definition of an AE, and acute appendicitis with onset during the AE reporting period should be reported as an AE, and appendectomy should therefore be recorded as the treatment for that AE.

Serious adverse events occurring after the end of the study or withdrawal of a subject from the trial were also to be reported to the partner if considered by the investigator to be related to the study drug. Adverse events were to be reported as SAEs when they met the DLT definition as specified in this protocol. Events meeting seriousness criteria caused by disease progression

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of the tumor under study in this protocol are not to be reported as SAEs, and the basis for judging the above disease progression should be recorded in the case.

7.7.3 Reporting of Serious Adverse Events (SAE)

The investigator should complete, sign and date the serious adverse event (SAE) report form within 24 hours after learning of the SAE, report to the partner's drug safety contact person, and report to the Ethics Committee and relevant units/departments according to the requirements of GCP.

Complete all information on the SAE Report Form as as possible at the time of the initial report. The first reported SAE should contain at least the following information:

- Name of person reporting the event (e.g. investigator's name and hospital)
- Subject information (e.g. screening/randomization number, gender, date of birth, etc.)
- Protocol No.
- Description of SAE
- Causality assessment (as far as possible)

7.7.4 Adverse Events of Special Interest and Handling Principles

Subjects in this study may experience fever, chills, nausea, neutropenia, thrombocytopenia, anemia and other myelosuppression conditions during and after infusion of CT017 CAR-GPC3 T cells, fever, hypoxia, tumor lysis syndrome, laboratory abnormalities (e.g., elevated CRP), cytokine release syndrome of varying severity (CRS), and CART treatment-related encephalopathy (CRES)/immune cell therapy-related neurotoxicity syndrome (ICANS) often occur during and after infusion of CAR-GPC3 T cells, and other CAR T cell therapies have also reported very rare hemophagocytic tissue cell hyperplasia syndrome (HLH). During the trial, close attention should be paid to these adverse events, and the occurrence, change and treatment process of such adverse events should be recorded in detail^{[18][20]}.

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The following AE is defined as a AE of special interest in this study, which requires the investigator to complete the "Serious Adverse Event Report Form" within 24 hours of awareness and report to the partner 's designated contact person.

- CT017 CAR-GPC3 T Cell Therapy-Associated Cytokine Release Syndrome Grade ≥ 3 ;
- CT017 CAR- GPC3 T cell therapy-related \geq Grade 3 infusion-related reactions;
- CT017 CAR- GPC3 T Cell Therapy-Associated Grade ≥ 3 CRES/ICANS ;
- Hemophagocytic lymphohistiocytosis syndrome (HLH);
- CT017 CAR- GPC3 T cell therapy-related grade ≥ 4 hematotoxicity that did not recover to grade ≤ 2 after 14 days of treatment (except lymphopenia and leukopenia);
- Hepatic impairment (see-12633904327.7.4.5)

7.7.4.1 Common general adverse reactions and treatment of CAR T

Common general adverse reactions after CT017 CAR- GPC3 T cell infusion mainly included transient fever, chills, fatigue, headache, myalgia and malaise. For subjects with mild fever following infusion of C T017 CAR-GPC3 T cells, subjects were advised to supplement necessary body fluids to aid in physical cooling. If the fever did not subside, indomethacin suppositories were used to assist in abatement of fever and applied until the symptoms were relieved or disappeared. If the subject remains unresolved with indomethacin suppositories, nonsteroidal anti-inflammatory drugs may be required, and attention should be paid to antipyretic dose and monitoring of liver function changes . If symptoms of hyperpyrexia continue to meet criteria for Grade 2 cytokine release syndrome (CRS), intervention with monoclonal antibody against IL-6R (tocilizumab) may be administered to subjects with 0 CRS treatment recommendations. For a small number of subjects with severe fever, it is recommended that hydrocortisone be administered at a starting dose of 100 mg when glucocorticoids must be used to manage serious adverse events.

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7.7.4.2 Management of infection

Neutropenia is often induced following clear lymphocyte pretreatment and may increase the risk of infection, CT017 CAR - GPC3 Subjects are at higher risk of infection within 10 days of T-cell infusion^[16]. Recommended according to China Neutropenia With Guidance for the Clinical Use of Antibacterial Drugs in Subjects with Fever (2016 Version)^[17] Protection against infection and sepsis. If a subject develops fever of unknown origin during the trial, body temperature > 38.3 ° C with concomitant neutropenia, recommended Etiological examination (e.g. Blood Culture, sputum culture AND URINE CULTURE et al) AND CHEST Imaging Evaluate infection and treat with broad-spectrum antibiotics and granulocyte colony-stimulating factor (GCSF)^[18], but the use of granulocyte-macrophage colony-stimulating factor (GM-CSF)^[19] is prohibited.

7.7.4.3 Identification, Grading, and Management of Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS), a non antigen specific toxic event, is caused by high levels of immune activation and occurs mostly within 2 weeks of receiving the infusion^[20]. In some cases treated with CAR T cells, CRS is a specific clinical syndrome characterized by hypoxia, neurological symptoms associated with markedly elevated serum levels of certain cytokines, and varying degrees of organ damage, as shown in [Table 7](#). The study will closely monitor the release of inflammatory factors for 28 days following the infusion.

Table 7 Cytokine release syndrome associated symptoms and clinical manifestations

Organ system	Symptoms and clinical manifestations
Whole body	Fever ± chills, discomfort, asthenia, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory Tract	Tachypnea, Blood oxygen decreased

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Cardiovascular	Tachycardia, pulse pressure increased, hypotension, cardiac output increased (early), potential cardiac output decreased (late)
Coagulation	D-dimer increased, hypofibrinogenemia ± hemorrhage
Kidney	Azotemia
Liver	Transaminase increased, Hyperbilirubinemia
Nerve	Headache, mental status changes, confusion, confusion, word finding difficulty or Frank aphasia, hallucinations, tremors, gait changes, seizures

CRS grading and management is managed, processed and documented using the following grading criteria as shown in [Table 8](#). The CRS start date was the date of persistent fever or first symptom of CRS judged by the investigator and could not be explained by other reasons. End date is defined as return to normal or stable symptoms or signs associated with CRS as judged by the investigator .

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Table 8 Grade of cytokine release syndrome (ASTCT (formerly ASBMT) consensus)

Grade	Toxicity
Grade 1	Body temperature * $\geq 38^{\circ}\text{C}$
Grade 2 §	Body temperature * $\geq 38^{\circ}\text{C}$, hypoxia requiring correction using only low flow nasal cannula oxygen & or insufflation No vasopressors required, effective hypotension with fluids
Grade 3 §	Body temperature * $\geq 38^{\circ}\text{C}$ requiring oxygen & with a high-flow nasal cannula and face mask, non-circulating expiratory mask or Venturi mask Hypotension requiring vasopressors with or without vasopressin
Grade 4 §	Body temperature * $\geq 38^{\circ}\text{C}$ requiring positive pressure oxygen therapy (eg CPAP, BiPAP, endotracheal intubation, mechanical ventilation) Hypotension requiring multiple vasopressors other than vasopressin

Source: Lee DW et al 2019.

Organ toxicities associated with CRS may be graded according to the Common Terminology Criteria for Adverse Events v5.0 guidelines (U.S. Department of Public Health, 2017).

* Fever is defined as a temperature $\geq 38^{\circ}\text{C}$ that requires exclusion of any other cause. Patients who develop CRS can be treated with antipyretics or anti-cytokine agents, such as tocilizumab or steroids, and fever no longer grades higher CRS severity. For CRS greater than Grade 2, the CRS grade is determined by hypotension and/or hypoxia.

& Nasal low-flow oxygen therapy is defined as delivering oxygen at a rate of $\leq 6\text{ L/min}$, and low-flow oxygen also includes insufflation oxygen, sometimes used in pediatrics. Nasal high-flow oxygen therapy is defined as delivering oxygen at $> 6\text{ L/min}$.

§ CRS was graded as determined by the more severe event, ie, excluding hypotension or hypoxia from any other cause. If the patient's body temperature was 39.5°C , vasopressin was used to raise blood pressure and low flow nasal cannula oxygen inhalation was classified as Grade 3 CRS.

CRS requires close monitoring, as recommended in the literature for^{[18][20][21][22][27]} management of toxicities resulting from CART treatment, the study physician should be informed immediately when the following situations are identified, and specific management measures are provided in [Table 9](#).

- Systolic blood pressure (SBP) $> 140\text{ mmHg}$ or $< 90\text{ mmHg}$; heart rate (or pulse) $> 120\text{ bpm}$ or $< 60\text{ bpm}$, or arrhythmia; respiratory rate $> 25\text{ breaths per minute}$ or $< 12\text{ breaths per minute}$;
- Arterial oxygen saturation $< 92\%$;

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- Urine output < 1,500 ml/day;
- Increased blood creatinine level or liver function ; tremors or astringent limb movements; altered mental status (alertness, orientation, speech, ability to write a sentence) .

Table 9 CRS Toxicity Management Recommendations

CRS Grade	Symptoms/Signs	Treatment Recommendations
Grade 1	Fever or organ toxicity *	<ul style="list-style-type: none"> • Indomethacin and physical cooling for fever • Ibuprofen may be a second treatment option for fever if there are no contraindications • Performing etiological examination (blood culture, sputum culture and urine culture etc.) as well as chest imaging to assess infection • Broad-spectrum antibiotics and G -CSF should be used if neutropenia develops • Maintenance of intravenous hydration • Management of Symptoms, Signs, and Organ Toxicity • Consider tocilizumab ^{&} 4 - 8 mg/kg intravenous drip for persistent (persisting > 3 days) or refractory fever
Grade 2	Hypotension	<ul style="list-style-type: none"> • 500-1000 ml normal saline via intravenous drip • Intravenous rehydration may be administered to keep systolic blood pressure (SBP) > 90 mmHg • Consider tocilizumab 4- 8 mg/kg ^{&} IV drip for treatment hypotension that is difficult to correct with fluid replacement; repeat tocilizumab after 6 hours if needed • If hypotension persists despite two fluid infusions and anti-IL-6 therapy, initiate vasopressors, consider transfer to the intensive care unit (ICU), obtain an echocardiogram, and initiate other hemodynamic monitoring methods • In subjects at high risk of severe C RS ¹ , methylprednisolone 1 mg/kg/IV drip or dexamethasone 10 mg IV every 6 hours may be administered if hypotension persists despite 1-2 doses of IL-6 antagonist therapy • Treat fever and corresponding symptoms and signs in a grade 1 manner

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CRS Grade	Symptoms/Signs	Treatment Recommendations
	Hypoxemia	<ul style="list-style-type: none"> • Supplemental oxygen • Treat with tocilizumab ± corticosteroids and supportive treatments as indicated for hypotension
	Organ toxicity *	<ul style="list-style-type: none"> • Organ toxicities were managed according to standard guidelines • Tocilizumab ± corticosteroids and supportive care if indicated for hypotension
Grade 3	Hypotension	<ul style="list-style-type: none"> • IV fluids as needed per Grade 2 CRS recommendation • If tocilizumab has not been used, use as recommended for Grade 2 CRS • Vasopressors as needed • Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring as in management of Grade 2 CRS • Intravenous drip of methylprednisolone 1 mg/kg/day, or intravenous injection of dexamethasone 10 mg every 6 hours. If refractory, the dose of methylprednisolone or dexamethasone may be increased appropriately according to the clinical situation • Treat symptoms and signs such as fever according to the recommended method for Grade 1 CRS
	Hypoxemia	<ul style="list-style-type: none"> • Supplemental oxygen, including high flow oxygen delivery and noninvasive positive pressure ventilation • As mentioned above, tocilizumab plus corticosteroids and supportive care
	Organ toxicity *	<ul style="list-style-type: none"> • Symptomatic management of organ toxicity according to standard guidelines • As mentioned above, tocilizumab plus corticosteroids and supportive care
Grade 4	Hypotension	<ul style="list-style-type: none"> • Intravenous fluids, anti-IL-6 therapy, vasopressors and hemodynamic monitoring as above • Methylprednisolone 0.5- 1 g/day ivgtt • Treat symptoms and signs such as fever according to the recommended method for Grade 1 CRS

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CRS Grade	Symptoms/Signs	Treatment Recommendations
	Hypoxemia	<ul style="list-style-type: none"> • Mechanical ventilation • As mentioned above, tocilizumab plus corticosteroids and supportive care
	Organ toxicity *	<ul style="list-style-type: none"> • Symptomatic management of organ toxicity according to standard guidelines • As mentioned above, tocilizumab plus corticosteroids and supportive care

* Organ toxicities and transaminase elevations graded according to CTCAE v5.0 .

& TOCILIZUMAB does not exceed 800 mg as a single dose and 2400 mg as a total daily dose.

¹ High risk factors for CRS include any of the following:

- High tumor burden
- Early Onset CRS (less than 3 days from cell infusion)
- With other concomitant diseases

Hypotension is a major factor in C RS ratings, and a clear baseline blood pressure value must be established prior to treatment that may lead to CRS and fluid replacement administered promptly when hypotension develops; vasopressors should be started if hypotension persists despite fluid replacement and anti-IL-6 therapy. Subjects with Grade 2 CRS require vigilant supportive care and close monitoring of heart, kidney and other organ functions. For patients with multiple complications and advanced age, tocilizumab treatment can be considered according to the criteria for Grade 3 CRS.

If the subject is judged to have Grade 3 or higher CRS reaction, it is recommended to transfer to ICU for treatment, closely monitor the organ function mainly including cardiac function, and perform echocardiographic monitoring for the subject suspected to have cardiac dysfunction. Tocilizumab and corticosteroids were recommended for all subjects with Grade 3 or higher CRS to prevent irreversible multi-organ failure.

Fever is the most prominent feature of CRS, and many features of CRS are similar to infection. Therefore, the possibility of infection should be considered in all subjects who develop symptoms of CRS, particularly fever and neutropenia, following appropriate etiologic investigations and empiric antibiotic therapy.

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Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurological toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. Of particular concern is cardiac dysfunction, which occurs rapidly and severely, but is usually reversible.

Neurological symptoms occurring in the setting of CRS vary widely among individuals and may co-occur with other symptoms of CRS. Symptoms of mild encephalitis (MERS) with reversible lesions in the splenium of the corpus callosum have been reported, and the mechanism may be related to increased IL-6 levels in the cerebrospinal fluid.

It has also been reported that CRS production is positively correlated with disease burden and the measured content of certain biomarkers in serum. For example, subjects with high levels of cytokines such as IFN- γ , MCP1, and IL-6 after administration or with a large disease burden have a greater probability of developing severe CRS, cytokine levels can be monitored during treatment to warn of possible CRS if necessary. If cytokine test results are not available in time, ferritin and CRP, as non-specific and sensitive inflammatory indicators, can reflect the release of cytokines to some extent.

CT017 For CRS \geq Grade 2 within 7 days of CAR-GPC3 T cell infusion, adverse event grades should be assessed at least daily until adverse event grade $<$ Grade 2.

In case tocilizumab is required, it is recommended to continue the use for 3 times . If there is no significant abnormality, except for decreased body temperature, other symptoms such as hypotension, hypoxemia, capillary leak syndrome, etc. are also significantly improved , the drug can be withdrawn for observation. For a small number of subjects with severe fever, if tocilizumab cannot control the clinical symptoms, the investigator considers it necessary to use hormones, timely use should be performed, and 1 mg/kg/day methylprednisolone is recommended as the initial dose.

7.7.4.4 Identification, grading and management of CART treatment-related

encephalopathy (CRES)

Neurotoxicity, also known as CART treatment-related encephalopathy (CRES)/immune cell therapy-related neurotoxicity syndrome (ICANS), is characterized by typical toxic encephalopathy with early symptoms of diminished attention, language impairment, and

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dysgraphia, as well as confusion, disorientation, agitation, aphasia, drowsiness, and chills. In severe CRES (> Grade 2), seizures, motor weakness, urinary incontinence, unresponsiveness, increased intracranial pressure, papilledema, and cerebral edema can occur. CRES manifestations can be biphasic, with the first phase occurring at the onset of fever and other signs of respiratory tract infection, usually in the first 5 days after cellular immunotherapy, the second phase occurring after fever, and other symptoms of CRS resolving, usually more than 5 days after cellular infusion. In particular, delayed neurotoxicity (seizures or confusion) occurs in about 10% of patients around the third or fourth week after CAR-T cell therapy. CRES usually lasts 2-4 days, but may last from a few hours to several weeks. In general, CRES that co-occur with CRS are of shorter duration and lower grade (grades 1 – 2) than CRES that occur after CRS, whereas CRES that occur after CRS are more frequently grade 3 and more persistent [Table 10](#), see for specific grading criteria. In addition, the severity of CRES may rapidly change and patients need to be closely monitored. Fatal cases of CRES have occurred rarely and are usually reversible^[18].

Subjects with "untreated brain metastases or symptoms of brain metastases" have been excluded from this clinical trial, and differential diagnosis is still required to guide treatment when they develop neurological symptoms. Treatment of neurotoxicity is usually symptomatic, including close monitoring and observation to ensure airway patency, prevention of seizures, and timely use of corticosteroids such as dexamethasone. Recognition of early signs and symptoms of neurotoxicity, as well as symptomatic treatment with corticosteroids, are ways to prevent more serious sequelae. Anti-IL-6 therapy reverses CRES/ICANS status in the first stage, but is usually ineffective in the second stage, whereas corticosteroids are the treatment of choice. Specific handling measures are listed in [Table 11](#).

Table 10 CRES/ICANS Grade (ASTCT (formerly ASBMT) Consensus)

Symptoms and signs	Grade 1	Grade 2	Grade 3	Grade 4
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ICE*	Mild (7-9)	Moderate (3-6)	Serious (0-2)	
				Patients with ICE score 0 due to inability to perform ICE assessment due to coma
Disturbance of consciousness +	Awake	Audible Awakening	Need to be aroused with tactile stimulation	The patient is unable to be aroused or requires intense or repetitive tactile stimulation to be aroused. Lethargy or coma.
Seizure	N/A	N/A	Rapidly resolving focal, generalized seizures, or electroencephalographically suggestive non-spastic seizures resolved after treatment	Life-threatening prolonged seizure (> 5 minutes); or repeated seizures or electrical seizures that do not return to baseline
Motor weakness &	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Increased intracranial pressure	—	—	Neuroimaging Findings of Focal/Localized Edema §	Neuroimaging diffuse brain edema; decerebrate or decorticate rigidity; or sixth cranial nerve palsy; or papilledema; Cushing's sign

ICE neurological assessment (scored 1 point for each task performed correctly: 10 points = normal):

Orientation: Name correctly Year, Month, City, Hospital: 4 points

Naming: Name 3 items correctly (identify clock, pen, button): 3 minutes

Commands: Perform simple commands correctly (e.g. "Extend 2 fingers", or "Close eyes and spit tongue"): 1 point

Writing: ability to write a standard sentence correctly (e.g., our flag is a five-star red flag): 1 point

Number inverted from 100 (10 intervals): 1 point

Source: Lee DW et al 2019.

The ICANS classification is determined by the most severe event (aphasia (ICE) score, level of consciousness, seizure, motor weakness, increased intracranial pressure/cerebral edema) and excludes any

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other cause; for example, a patient with a generalized seizure with an ICE score of 3 is classified as having ICANS Grade 3.

N/A means not applicable.

Patients with an ICE score of 0, with complete aphasia on awakening, will be summarized as having ICANS grade 3; if patients with an ICE score of 0 cannot be awakened, they will be classified as having ICANS grade 4.

+ Disturbance of consciousness caused by other causes should be excluded (e.g., sedative drugs are not used)

& Tremors and myoclonus associated with immune effector cell therapy may be graded according to CTCAE v5.0, but do not impact ICANS grading.

§ Intracranial hemorrhage with or without edema is not considered a neurotoxic feature and is not an ICANS grade, but may be graded according to CTCAE v5.0.

Table 11 CRES/ICANS Processing Recommendations (Integrated MD Anderson Cancer Center & ASTCT (formerly ASBMT) CAR-T Management of Therapeutic Toxicity)

Grading	Treatment
Grade 1	<ul style="list-style-type: none"> Careful use of supportive care; prevention of aspiration, avoidance of drugs that depress CNS function; intravenous fluids; Antiepileptic prophylaxis (levetiracetam 500 to 750 mg PO); Withhold oral intake of food/medication/fluids and assess swallowing ability and convert all oral medications and/or nutrients to intravenously administered medications and/or nutrients if swallowing ability is compromised; Patients who experience agitation may receive low doses of lorazepam (0.25 to 0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) and require careful monitoring; ICE neurological assessment daily, ophthalmoscopy for papilledema; brain MRI preferred, CT acceptable; diagnostic lumbar puncture with measurement of CSF pressure; spinal MRI if focally indicated; 30 minutes daily EEG; levetiracetam may be continued if no seizures are detected on EEG; if EEG shows nonconvulsive status epilepticus, treat as appropriate; Consider IL-6 antagonists if associated with comorbid CRS.
Grade 2	<ul style="list-style-type: none"> Supportive care and neurologic examinations were performed according to a Grade 1 approach; IL-6 antagonists were used if associated with comorbid CRS; CRES/ICANS treated with dexamethasone or methylprednisolone if not associated with CRS; Dexamethasone or methylprednisolone may also be used when refractory to IL-6 antagonists; transfer to the ICU may be considered if associated with Grade 2 or higher CRS.
Grade 3	<ul style="list-style-type: none"> Supportive care and neurologic examinations were performed according to a Grade 1 approach; Advise transfer of patient to ICU; IL-6 antagonist 1 may be used provided it is associated with comorbid CRS and has not been previously used; dexamethasone or methylprednisolone may be used throughout the day if symptoms worsen with IL-6 antagonist therapy. Continue corticosteroids until improvement to Grade 1, then taper or discontinue directly; Low grade (grade 1 or 2) papilledema with CSF pressure < 20 mmHg; If CRES/ICANS persists greater than or equal to grade 3, consider repeating

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	neuroimaging (CT or MRI) every 2-3 days.
Grade 4	<ul style="list-style-type: none"> • Supportive care and neurologic examinations were performed according to a Grade 1 approach; • ICU monitoring: Consider mechanical ventilation for airway protection; • IL-6 antagonist and repeat neuroimaging at grade 3; high-dose methylprednisolone; • Treatment of possible convulsive status epilepticus; indicated for high-grade (stage 3, 4, or 5) papilledema, CSF pressure ≥ 20 mmHg, or cerebral edema, refer to the appropriate management.

7.7.4.5 Management of hepatic impairment

Patients' liver function test values at any time after cell infusion that meet any of the following criteria and cannot be explained by other reasons, such as disease progression, cholestasis, acute viral hepatitis, pre-existing liver disease, or the use of other drugs or substances that may be hepatotoxic, will be reported as adverse events of special interest and SAEs and require further close monitoring and follow-up according to the following criteria:

For patients with AST or ALT and total bilirubin (TBIL) baseline values within the normal range, if their AST or ALT value was later ≥ 3 times the upper limit of normal (\times ULN), the TBIL value was $\geq^{[28]}$ $2 \times$ ULN without hemolysis, and alkaline phosphatase was not elevated or the value was $\leq 2 \times$ ULN.

For patients with previous ALT, AST, or TBIL values above the upper limit of normal, the following thresholds should be used in determining this:

For patients with a previous baseline AST or ALT value above the normal range: AST or ALT value ≥ 2 times the baseline value and $\geq 3 \times$ ULN, or $\geq 8 \times$ ULN, whichever is smaller. Also,

For patients with a previous TBIL value above the normal range: TBIL value at least $1 \times$ the upper limit of normal at baseline or a value $\geq 3 \times$ ULN, whichever is smaller.

When the above liver function abnormalities occur, the study drug should be stopped, and the relevant tests should be reexamined and perfected as soon as possible, and hepatologists should be consulted if necessary.

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Transient and reversible changes in ALT, AST, and TBIL in patients infused with CT017 CAR-GPC3 T cells were generally concurrent with cytokine release syndrome (CRS), and abnormalities in these liver function parameters were monitored until recovery to baseline values. Patients in this study could receive multiple infusions of CT017 CAR-GPC3 T cells with CRS generally occurring within 4 weeks of cell infusion, and if abnormal liver function test values were observed within 4 weeks of the last infusion and could be explained by CRS, they could be treated according to the corresponding CRS treatment measures. Abnormal liver function test values after infusion not explained by CRS or new liver function test abnormalities observed in patients after 4 weeks of infusion suggest potential hepatotoxicity if patients have marked liver enzyme elevations accompanied by marked total bilirubin elevations, with potential toxicity thresholds dependent on patients' baseline AST, ALT, and TBIL values. If immune hepatitis caused by CT017 CAR-GPC3 T cell therapy is considered in differential diagnosis, or hepatitis B virus reactivation and viral hepatitis activity, the following diagnosis and treatment measures can be referred to:

1) Immune hepatitis caused by CT017 CAR-GPC3 T cell therapy: it can be manifested as significantly increased transaminases, bilirubin, CRP, etc., and can be treated with liver protection according to the target organ toxicity level of cytokine release syndrome.

First, consult a hepatologist and actively use hepatoprotective, anti-inflammatory, and cholagogue drugs; if the above parameters continue to rise for more than 5 to 7 days or worsen: methylprednisolone 1-2 mg/kg/day treatment; if there is no remission within 2 to 3 days, mycophenolate mofetil 1000 mg twice a day may be considered. Monitor liver function every 3 to 7 days until liver function recovers to Grade 2. Corticosteroids were tapered for at least 1 month if liver function returned to grade 1. If the condition worsens further, transfer to ICU if necessary.

2) Hepatitis B virus reactivation and viral hepatitis activity:

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In this study, for liver cancer patients with combined HBsAg (+) and/or HBcAb (+), subjects were required to take long-term antiviral therapy with oral nucleos (t) ide analogues (entecavir or tenofovir) that are potent and have a high genetic resistance barrier.

To closely monitor hepatitis B virus activation, HBV DNA was monitored at the following time points: day 14, 28 days, 8 weeks, 12 weeks, 18 weeks, and 24 weeks within 26 weeks, and every 6 weeks after 24 weeks until 52 weeks.

If hepatitis B virus reactivation viral hepatitis activity occurs, liver disease specialists will be consulted to adjust antiviral drugs in a timely manner; at the same time, hepatoprotective, anti-inflammatory and cholagogue drugs will be actively used. Increased frequency of liver function, HBV - DNA monitoring and liver function every 3 days until liver function recovers to Grade 2. If liver function deteriorates further, close monitoring and transfer to ICU if necessary.

In general, no attempt should be made to re-initiate the medication in subjects with markedly elevated liver function tests as described above. If a subject has shown an important benefit to the investigational product and no other treatment options are available, consideration may be given to re-administering the investigational treatment once the patient 's liver function has returned to baseline or \leq Grade 1, and the extensive cumulative data on the investigational product do not suggest potential serious injury, after the investigator has adequately assessed the patient' s benefit-risk. If the subject resumes the medication, close attention and follow-up should be paid.

7.7.4.6 Capillary leak syndrome

Capillary leak syndrome (CLS) is a serious complication of systemic inflammatory response syndrome characterized by leakage of body fluids and proteins from blood vessels into the interstitial space, with clinical manifestations of systemic progressive edema, pleural

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and peritoneal effusion, oliguria, hypotension, hypoxemia, and hypoalbuminemia, which can affect multiple organs throughout the body, especially the lungs and kidneys.

The underlying cause of CLS is hypercytokinemia, a clinical manifestation of CRS. CLS can be clinically divided into two phases: leakage and recovery. The leakage phase is characterized by progressive anasarca, pleural and peritoneal effusion, gastrointestinal edema, non-cardiogenic pulmonary edema, hypoproteinemia, hypotension, and oliguria, and if not treated promptly, multiple organ dysfunction syndrome can occur due to tissue hypoperfusion. The recovery period is characterized by gradual regression of anasarca, increase in blood pressure and central venous pressure, and spontaneous increase in urine volume without diuretics, and non-cardiogenic pulmonary edema is likely to occur in this period.

After CT017 cell infusion, central venous pressure decreased (< 5 cmH₂O), serum albumin decreased significantly (< 25 g/L), oxygenation index decreased; chest imaging revealed pulmonary interstitial exudative changes; hematocrit increased; progressive systemic edema, accompanied by abdominal, pleural effusion, weight gain and other clinical manifestations, CLS diagnosis should be considered. It is also generally accompanied by symptoms such as fever in CRS.

CT017 treatment-emergent CLS refers to [Table 9](#) CRS toxicity management recommendations. Fluid therapy is the key link in the treatment of CLS. Artificial colloid can be used as resuscitation fluid in the leakage period of CLS. Pulsed fluid resuscitation can be performed. When the effect is not satisfactory, vasopressors, albumin, shock and high molecular weight starch can be given. In subjects who remain hypotensive despite adequate volume resuscitation, vasoactive agents may be used to increase blood pressure. Subjects in the recovery phase of CLS are prone to develop non-cardiogenic pulmonary edema, and to avoid massive fluid leakage, fluid restriction strategies are recommended, requiring reassessment of intravascular volume, lung water status, and tissue perfusion. Blood pressure remains stable

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and diuretics should be applied early to prevent pulmonary edema. In patients with volume overload, if hemodynamics are stable, loop diuretics are preferred to reduce volume load; if blood pressure is low and organ tissue perfusion is fair, albumin combined with diuretics can be used to reduce volume load. Glucocorticoids are effective in CLS induced by a variety of diseases, and hormones should be promptly intervened according to clinical symptoms. Renal replacement therapy is indicated in subjects with poor response to diuretics and acute kidney injury.

7.7.4.7 Hematotoxicity

Hematologic toxicities such as neutropenia, thrombocytopenia, and hemoglobin decreased may occur in subjects following fludarabine and cyclophosphamide-based conditioning and cell infusion and are expected adverse events.

For subjects with anemia, transfusion of suspended leukocyte-poor red blood cells and erythropoietin may be administered according to the severity of anemia and associated symptoms.

In case of neutropenia, recombinant human granulocyte stimulating factor (G-CSF) injection or leucogen can be considered for treatment to detect any possible infection symptoms and signs as early as possible. It is recommended to protect against infection and sepsis according to "Recommended Guidelines for Clinical Use of Antibacterial Drugs in Chinese Patients with Agranulocytosis and Fever (Guidelines for Clinical Use of Antibacterial Drugs in Patients with Fever (2016 Edit^[17]ion)" . During the trial, if the subject developed fever of unknown origin with body temperature > 38.3°C accompanied by neutropenia, blood and urine culture and chest X-ray were recommended to evaluate the infection, and broad-spectrum antibiotics and G-CSF could be used for prevention and treatment.

For subjects who develop thrombocytopenia, platelet stimulating factors, such as recombinant human thrombopoietin (rhTPO) and recombinant human interleukin-11 (rhIL-11),

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can be used and platelet transfusions can be given if necessary; when associated with severe leukopenia or anemia, they can be combined with G-CSF or recombinant human erythropoietin (rhEPO), respectively, and the above combination therapy is especially suitable for subjects with thrombocytopenia who do not meet the indications for platelet transfusions. Routine blood tests should be performed regularly during use, generally twice a week, every other day for special subjects according to the situation, and close attention should be paid to the subject's body weight and heart, lung, and kidney function during application. Dose reduction or discontinuation of drugs for thrombocytopenia should be promptly performed after platelet recovery^[24].

In this clinical trial, if any blood product (including platelets, whole blood, red blood cells or other components) is transfused within 3 months after the use of fludarabine, the transfused blood product should be irradiated before transfusion.

7.7.4.8 Infusion-related Reactions (IRRs)

CT017 is an autologous CAR T cell injection and may still cause infusion reactions. Infusion-related reactions may manifest as symptoms such as chills, rigors, increased body temperature, blood pressure fluctuations, and decreased oxygen saturation within 24 hours of infusion. Once an infusion reaction occurs, the infusion reaction can be treated according to the ESMO 2018 Clinical Practice Guideline: Managing Infusion Reactions in Systemic Anticancer Therapies, and the subject should be closely monitored until all symptoms completely disappear^[23].

Grade 1 infusion reactions may slow the rate of drug infusion or temporarily interrupt the infusion and continue after recovery is confirmed. Grade 2 infusion reactions may be treated with antihistamines, NSAIDs (eg, acetaminophen), or corticosteroids. If the subject who suspended the infusion is confirmed to recover after examination and the investigator considers that the subject can continue to participate in the trial, the infusion will be completed at half the

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original infusion rate. Once \geq Grade 3 infusion reactions occur during the infusion, the infusion should be stopped immediately, oxygen inhalation should be performed, NSAIDs, antihistamines (such as phenergan) and corticosteroids should be used for treatment, and bronchodilators and other symptomatic treatment should be given according to the actual situation; the subjects should permanently discontinue the study drug.

To prevent and reduce infusion-related reactions, this study requires administration of promethazine 25 mg intramuscularly for anti-allergic (or equivalent) treatment and/or indomethacin suppositories 50 – 100 mg anally for antipyretic and analgesic (or equivalent) treatment within half an hour before CT017 infusion.

7.7.4.9 Hemophagocytic lymphohistiocytosis (HLH)/hemophagocytic syndrome (HPS)

HLH is a severe or even fatal inflammatory state caused by the secretion of a large number of inflammatory factors by non-malignant proliferation of lymphocytes/macrophages and histiocytes. With regard to CAR T cell therapy, HLH may develop following CAR T cell infusion in subjects with increasing tumor burden. This may be accompanied by CRS, encephalopathy, pneumonia, pleural effusion, left ventricular dysfunction, pancytopenia, methaproteinaemia and direct hyperbilirubinaemia. Subjects who developed CRS following CAR T cell therapy had clinical features and laboratory findings similar to HLH/HPS and were likely to have excessive systemic inflammatory responses.

Subjects may have HLH if they have serum ferritin levels $> 10,000$ ng/ml during the phase of cytokine release syndrome (usually the first 5 days after cell infusion) following CT017 treatment and subsequently develop any two of the following:

- Grade ≥ 3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels;
- \geq Grade 3 oliguria or elevated serum creatinine;

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- \geq Grade 3 pulmonary edema;
- Hemophagocytosis was present in bone marrow or organs based on histopathological assessment of cytomorphology and/or CD68 immunohistochemistry.

Investigators should consider specialist consultation when unexplained tri-lineage decreases occur. For suspected HLH with organ toxicity, tocilizumab was administered according to the grading management principles of CRS, hormones were administered for intervention if necessary, and inflammatory factors, ferritin, lactate dehydrogenase, fibrinogen, transaminases, bilirubin and creatinine were monitored, and bone marrow aspiration was performed if necessary. If symptoms improve within 48 hours, continue intervention per CRS management principles. If not resolved within 48 hours, consider increasing etoposide 75 – 100 mg/m², which may be repeated 4 – 7 days later; intrathecal cytarabine with or without hydrocortisone should also be considered in subjects with HLH-related neurotoxicity.

7.7.4.10 Tumor lysis syndrome

Previous studies have shown that subjects with high tumor burden have a higher risk of developing TLS. TLS is characterized by hyperuricemia, hyperkalemia, hypocalcemia, and elevated LDH.

Therefore, close attention should be paid to such adverse events during the treatment with the investigational product, and countermeasures should be taken as early as possible. Investigators may enhance prophylaxis and serum uric acid monitoring in subjects at high risk for TLS. When a subject develops TLS, appropriate medical management including correction of electrolyte abnormalities, monitoring of renal function, balancing fluids, and other appropriate care must be instituted.

7.7.4.11 Lentiviral infections

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Currently lentiviral vector systems have been widely used in more than 300 clinical trials, and a large number of clinical data have demonstrated the safety and efficacy of lentiviral vectors^{[25][26]}. At present, there are no reports on RCL generation in CAR-T cell therapy. Exploratory clinical studies with second-generation CT011 CAR-GPC3T cells also used this third-generation self-inactivated lentiviral vector without events of RCL generation. Nevertheless, given the unknown possibility and characteristics of RCL, subjects will be followed for genetic safety for up to 5 years in this study.

RCL detection and confirmation: In the blood sample test for monitoring RCL after infusion of CAR T cells, if a positive HIV test result is found, the responsible physician of the clinical trial should be informed, and the suspected infected patient should be rescheduled for HIV genomic testing. If the second test remains positive, infusion of C T017 should be temporarily discontinued in other patients. Blood samples were collected from infected subjects to determine the source of the virus. If the sequence is from wild-type HIV, then other patients can continue to receive CAR T cell infusions and infected patients will be scheduled to receive anti-HIV therapy. If virus cannot be isolated from a blood sample from a suspected infected individual, the subject 's mononuclear cells should be recollected and subsequently tested for RCL to confirm the diagnosis of RCL.

At present, the probability of RCL production and the characteristics of RCL are unknown, and there are no appropriate guidelines to refer to. The consensus is that patients must be isolated immediately after they are diagnosed with RCL until the solution for infected patients is determined. Other relevant measures available include:

- Infected patients were followed up frequently and opinions were sought from gene therapy experts, clinical trial doctors, and experts from national regulatory authorities.
- Timely notify the health department, local CDC and relevant management units of the infected patients.

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- Identify the sexual partners of infected patients and provide them with corresponding counseling services, psychological counseling and preventive education.

7.7.4.12 Insertion Mutation and Risk of Secondary Tumors

For lentiviral vectors, so far, there have been no reports of adverse effects of carcinogenesis due to gene insertion mutations in a large number of lentivirus-based gene therapies and adoptive T cell clinical trials using lentiviral vector genetic engineering modifications. Nevertheless, in this study, for risk control, complete blood count (CBC) can be used to monitor T cell clonal growth; as well as abnormal expansion of XX cells analyzed by fluorescence quantification and/or flow cytometry. If after 6 weeks, the number of CAR T cells continues to expand abnormally, then high-throughput sequencing of the CAR T cell genome can be performed to assess whether it is a monoclonal or oligoclone at the same insertion site on the genome. If abnormal expansion of monoclonal or oligoclonal CAR T cells occurs, infusion of CT017 will be suspended in other patients; and the safety of the product will be further evaluated, and opinions from gene therapy experts, clinical clinicians, clinical data and safety supervisors, China Food and Drug Administration, National Health and Family Planning Commission and other regulatory authorities will be sought.

7.7.4.13 Target Detumorigination Toxicity

Previous studies have shown that CAR T may produce On-target off-tumor toxicity in the clinic. It has been reported that in a clinical study using CAR T cells targeting Her-2 to treat a patient with advanced colon cancer with lung metastases, the patient quickly developed respiratory distress syndrome and finally died of invalid rescue. Autopsy and other studies have found that there is a low level of Her-2 expression in normal lung tissues, and CAR T cells infiltrate a large number of lungs, so it is considered that CAR T cells recognize and attack Her-2-expressing lung tissues, thus causing respiratory distress syndrome. This kind of toxicity caused by attacking normal tissues expressing the same target antigen of CAR T cells is also

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considered to be the so-called toxicity of middle target debonding^{[29][30]}. Given the tumor specificity of the GPC3 target, there is little potential for on-target debonding toxicity for this target, but patients targeting the secretory phase of the menstrual cycle must still be closely monitored.

7.7.5 Pregnancy

Pregnancy itself was not considered an AE. Pregnancies occurring between the start of study drug administration and 52 weeks of follow-up in the subject or in the subject's partner, whether or not prematurely discontinued from the trial, were to be reported to the investigator who had to complete a Pregnancy Report Form within 24 hours of learning of the pregnancy.

The investigator should counsel the female subject on the risks of continuing the pregnancy and the possible effects on the fetus and nursing infant and the subject must be withdrawn from the study.

The investigator should follow up the pregnancy outcome until 1 month after delivery/termination of pregnancy and report the outcome to the partner. If the outcome of the pregnancy was stillbirth, abortion, fetal anomaly, it was considered an SAE and required reporting as an SAE.

7.7.6 Laboratory Abnormalities

Testing for anti-GPC3 antibodies (ADAs), cytokines, and RCLs will be performed at a central laboratory, and other laboratory tests related to safety will be performed at the site's laboratory. Samples will be collected, judged and analyzed according to local laboratory requirements. Clinically significant laboratory abnormalities should be reported as AEs according to NCI CTCAE v5.0 grading criteria, except for the screening period. Blood samples for safety assessments may be repeated if needed. Clinically significant results that meet one or more of the following:

- The examination results showed that accompanying symptoms occurred;

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- Resulting in a change in study medication (eg, dose change, interruption, or permanent discontinuation);
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Requires significantly increased concomitant medications or other treatments;
- The investigator or partner considers that this test result should be reported as an adverse event.

An adverse event is not defined if it is only to repeat an abnormal test and does not meet any of the above conditions. Any abnormal test result is not required to be reported as an adverse event if it is judged to be an error.

Laboratory abnormalities related to progression of the primary disease were not reported as AEs in this study (eg, abnormalities in total bilirubin).

Laboratory tests relevant to safety assessments include, but are not limited to:

- Blood routine, fecal occult blood, urine routine
- Liver function, renal function, HBV DNA (for subjects with hepatitis B), electrolytes, bleeding and coagulation time, CRP, ferritin
- Cytokine testing will be performed at the central laboratory, but in case of emergency, the investigator may test cytokines in the hospital as an aid for emergency treatment of the subject as clinically indicated.
- Reproducible lentivirus (RCL) detection: Peripheral blood samples were collected from subjects for detection of replicable lentivirus (RCL) using q - PCR (VSV-G qPCR).
- Anti-CAR-GCP3 Antibody (ADA): Detect anti- CAR-GPC3 antibodies in the serum of subjects using MSD method, and if the test result is positive, continuously monitor

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the persistence of anti- CAR-GPC3 antibodies for reference for clinical study protocol design adjustment.

7.7.7 Vital signs

Vital signs will be assessed according to the study flow chart:

- Blood pressure (systolic and diastolic; mmHg)
- Heart rate (or pulse) (beats per minute)
- Body temperature (° C)
- Respiratory rate (breaths per minute)

Vital signs were performed after the subject had rested for 5 minutes in the supine position. Abnormal values detected will be assessed by the investigator as clinically significant or not clinically significant.

7.7.8 ECG

A 12-lead ECG will be performed according to the study flow chart. Subjects should be reexamined in the awake state after resting in the supine position for 5 minutes. If the subject is asleep, the examination should be repeated 5 minutes after awakening to change position. All ECGs were to be assessed by a qualified physician. On the day of study drug infusion, subjects' cardiac rhythm status will be observed using electrocardiographic monitoring. If arrhythmia is found during the trial, it should be retested in time.

Any clinically significant finding (eg, QTc interval > 500 ms) was to be recorded as an AE by the investigator (except during screening).

7.7.9 Physical examination

The following body systems will be examined according to the study flow chart: general condition, head (ears, nose, throat, eyes), cardiovascular system, respiratory system, chest,

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abdomen, genitourinary system, musculoskeletal system, nervous system, lymphatic system, and skin.

7.7.10 Immunogenicity Testing

Blood samples (blood samples to detect CT017 CAR-GPC3 DNA copy number may be collected) for anti-drug antibodies prior to the first infusion and at Visits W 4 , W 12 , W 24 , W 36 , W 52 . Positive anti-drug antibodies were considered positive only once during the trial. If anti-drug antibodies are positive, tests are required to confirm neutralizing antibodies.

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8. STATISTICAL ANALYSIS

Detailed methods for summarization and statistical analysis of the data collected in this trial will be described in the Statistical Analysis Plan (SAP). The plan presented in this protocol may be modified appropriately in the SAP, but significant amendments involving the primary trial endpoints need to be reflected in the protocol amendment.

8.1 GENERAL PRINCIPLES

This section will briefly describe the statistical analysis methods used to analyze safety, pharmacokinetic efficacy, and efficacy endpoints. Details of handling data, data statistics and presentation of results will be described in detail in the Statistical Analysis Plan (SAP). Formal SAP will be finalized before locking the library. Statistical analysis will be calculated using SAS 9.4 or above statistical analysis software.

8.2 STATISTICAL ANALYSIS POPULATION

Enrolled Data Set: includes all enrolled subjects. Enrollment is defined as all meeting inclusion/exclusion criteria, single sample samples shipped to the manufacturing preparation site and received, and baseline testing meeting reassessment criteria to be able to undergo cleansing conditioning. Withdrawal prior to receiving clear lymphocyte conditioning was considered a screen failure.

- **Safety Set (SS)** : All subjects receiving C T017 CAR -GPC3 T cell infusion. This analysis set will be used for secondary safety analyses and summaries of the baseline study population.
- **Dose Limiting Toxicity Analysis Set (DLTS)**: In the monotherapy dose-escalation phase, all subjects who received C T017 CAR -GPC3 T cell infusion and completed the 28-day DLT assessment or developed DLT within 28 days. This analysis set will be used for the primary safety analysis.
- **Cell Pharmacokinetics Dataset (CKS)** : All subjects who received C T017 CAR -GPC3 T cell infusion and had at least one quantifiable CT017 C AR-GPC3 T cell data following infusion. This analysis set was used for cellular pharmacokinetic analysis.

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- **Adjusted Intent-to-Treat Set (mITT)** : All subjects who received C T017 C AR-GPC3 T cell infusion and had measurable disease at baseline. This analysis set was used for efficacy analysis.

8.3 STATISTICAL ANALYSIS METHODS

8.3.1 General principle of statistics

Listings containing all raw data will be generated, including all recorded data as well as all computationally generated data. Continuous variables will be analyzed using descriptive statistics (e.g., number of cases, mean, median, standard deviation [SD], minimum, and maximum). Categorical variables were analyzed using frequency tables (frequencies and percentages).

8.3.2 Demographic information, disease history, baseline characteristics and concomitant medications

The SS population will be used for summaries of demographic information and baseline characteristics. Demographic and baseline characteristics data, disease history, and concomitant medications will be analyzed using descriptive statistics (number of cases [n], mean, SD, median, minimum, and maximum) or frequency tables.

Disease history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA); concomitant medications will be coded according to World Health Organization Drug Dictionary Enhanced (WHO-DDE) using Anatomical Therapeutic Chemical (ATC) classification. Disease history and concomitant medications will be summarized in the safety analysis population.

8.3.3 Safety analysis

All adverse events (AEs) will be classified according to the latest version of the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities MedDRA coding and graded according to Common Terminology Criteria for Adverse Events

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(CTCAE) V5.0 using frequency distributions, graphs or other descriptive measures, and the number and percentage of subjects with TEAEs will be calculated by system organ class, preferred term, CTCAE grade, and group.

Serious adverse events (SAEs) including deaths, TEAEs, adverse events of special interest (AESIs), and adverse events leading to discontinuation of trial treatment were summarized.

Descriptive analyses were performed for laboratory tests, vital signs, including ECG, and changes from baseline, if any. Other safety measures will be described in a similar manner and listed by subject.

The same analysis method will be used to statistically analyze the above safety endpoints in the monotherapy dose-escalation phase and the expanded combination therapy phase, and all safety analyses will be based on the safety population.

8.3.4 CT017 In Vivo Metabolism Assessment of CAR-GPC3 T Cells

According to the cytodynamic analysis set, the time to peak cell expansion, peak amplification, area under the curve (AUC), and survival time after infusion of CT017 CAR-GPC3 T cells will be calculated by tabulating, plotting, and summarizing the copy number of CT017 CAR-GPC3 DNA at different time points tested.

8.3.5 Tumor response analysis

Efficacy analyses will be performed on the mITT analysis set. The efficacy endpoints of overall objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), time to disease control (DDC), and overall survival (OS) were analyzed in the mITT set population.

Estimate the incidence of ORR, DCR and its 95% confidence interval in the mITT population;

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Time to event type indicators such as DOR, DDC, PFS, OS, and their respective 25%, 50%, and 75% quantiles and their 95% confidence intervals were estimated using the Kaplan-Meier method in the mITT population; Kaplan-Meier survival curves were also plotted.

8.3.6 Analysis Time Point

The safety analysis will be performed after the last subject completes the 28-day DLT observation period in the monotherapy dose-escalation phase.

The combination therapy expansion phase will be conducted when the last subject in each group completes the 12-week, 24-week, and 52-week observation periods, and efficacy, safety, and cytokinetic analyses will be analyzed. The final analysis was completed after the last subject completed 52 weeks of follow-up.

Additional analyses are detailed in the Statistical Analysis Plan.

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9. DATA MANAGEMENT

9.1 DATA QUALITY ASSURANCE

The trial sponsor or sponsor 's designee will make on-site visits to each site to check the qualifications of the investigator at each site, inspect site facilities, inform the investigator of his or her responsibilities and procedures to be performed to ensure completeness and accuracy of the records.

The investigator at each site should completely and correctly record the observation indicators and other data related to the trial of each subject in the medical records. All information recorded on the eCRFs should be consistent with the subject 's source documents (eg, medical records).

9.2 DATA MANAGEMENT AND QUALITY CONTROL

All data obtained by the study site and its laboratory will be recorded in the eCRF, and changes to the data will be recorded as an audit trail. Reason for change, name of person making change, date and time of change will be recorded as audit trail record.

During routine monitoring, the relevant CRA or data manager designated by the trial sponsor will have questions about the eCRF. The relevant personnel at the study site will answer the questions sent to the investigator. The EDC system will record the name of the person answering the query, the time and date of the response. Once all source data verification is completed and all queries are resolved, the Data Manager freezes the database.

9.3 CASE REPORT FORMS (e CRFS) AND SOURCE DOCUMENTS

The data manager will establish the eCRFs in the EDC system. All data obtained during the trial should be entered into the eCRF in a timely manner. Different subjects will be identified only by an appropriate identification code (eg, subject number) on the eCRF. The eCRF is used to record the clinical trial data of subjects and is an integral part of the trial and relevant trial

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reports, so the entry must be accurate and complete. Data will be entered into the EDC system by the investigator or an authorized designee (to be identified on the Study Authorization Form). All data entries must be ensured complete and stored. The investigator must state that all information in the eCRF is true by electronic signature.

In clinical trials, eCRFs were completed after each visit to document the subject's condition.

Source documents for all data entered into the EDC will be maintained in the medical history record and will typically include laboratory tests, ECGs, and echocardiograms. The CRA will check the original data entered in the eCRF against the source documents during site monitoring.

9.4 DATA COLLECTION

Access to the eCRFs will be given to designated personnel at each site, and only authorized personnel will be able to enter and correct data on the eCRFs.

Authorized personnel will complete the eCRFs for each enrolled subject to reflect their findings from the most recent trial observation. Therefore, eCRFs should be completed as soon as possible after the subject completes the visit or assessment. The investigator should verify the accuracy of the data entered on the eCRF. If some assessments are not available, or certain specific information is unavailable, not applicable, or unknown, the investigator should indicate this in the eCRF.

Changes in the amount and dose of trial drug taken by each subject will be documented in the eCRF.

9.5 MONITORING OF RAW DATA

During the trial, the investigator must properly handle all data obtained during the clinical trial to ensure the rights and privacy of patients participating in the clinical trial. The CRA

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designated by the sponsor will conduct site visits to check protocol compliance, entry of eCRFs, subject 's medical history records, and to confirm that the trial is being conducted according to applicable regulatory requirements. Entry of the eCRFs will be checked against the source data. Medical history reconciliation will be performed in a manner that protects the subject 's privacy.

The eCRF entries were checked for completeness and clarity and were compared with the source data to monitor the progress of the trial. In addition, the regulatory authority and/or IEC may check the source data and/or visit the site for audit or inspection. Audits or inspections will have direct access to the source data and all parties who have direct access will take every measure to ensure data and medical confidentiality.

9.6 DATA PROCESSING

Data review and data processing protocols include specific requirements for consistency and authenticity verification of data, as well as principles for handling data with obvious errors.

Past medical history, non-drug therapies, and AEs will be coded according to the MedDRA dictionary and submitted as preferred term and system organ class. Prior medications and concomitant/concomitant medications will be coded using the World Health Organization Drug Dictionary.

During coding, DM will ask the investigator to verify and confirm any data problem that cannot be coded due to inappropriate, inaccurate and vague medical terminology.

Prior to database lock, medical coding report will be generated by data management and reviewed by investigators and collaborators.

Version of coding dictionary will be described in CSR.

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9.7 ARCHIVING OF TRIAL RECORDS

After the completion of the trial, the subject 's eCRFs will be stored on a non-rewritable compact disc (DVD), which will be submitted to each institution for archiving and audit.

The trial data shall be preserved and managed according to regulations. The investigator shall preserve the clinical trial data until 5 years after the end of the clinical trial or a longer period upon negotiation with the partner.

9.8 DATABASE LOCKING

Upon review and confirmation that the database meets the requirements for locking, the database will be locked by data management personnel. Locked databases are not allowed to be changed in principle.

According to the clinical trial protocol and eCRF, a statistical analysis plan was prepared for the clinical observation data, and the analysis plan was confirmed before analysis. The statistical analysis personnel then performed statistical analysis of the data in the database according to the statistical analysis plan.

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10. CLINICAL TRIAL MANAGEMENT

10.1 DECLARATION

This clinical trial will be conducted in compliance with the Declaration of Helsinki, China's GCP and drug clinical trial regulations.

By signing the protocol, the investigator will agree to follow the instructions and procedures described in the protocol and follow the principles of China Good Clinical Practice as well as all local regulations and principles for the management of medical research that are followed in accordance with this protocol.

10.2 ETHICS SECTION

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines, and each investigator will conduct the trial according to applicable regulatory requirements. The principal investigator or investigator of the clinical trial explained the purpose of the trial and all potential possibilities to the subjects, voluntarily agreed to participate in the clinical trial, and signed the informed consent form to become subjects.

Each investigator of the clinical trial and the investigators participating in the trial should correctly analyze and be familiar with the trial, abide by the contents specified in the protocol and carry out the trial according to the protocol, and be able to prepare measures in advance, such as countermeasures, required reports and adequate training in case of unexpected adverse events. Clinical investigators must comply with the regulations for clinical trials of investigational drugs when conducting clinical trials.

Investigators and personnel involved in the study should follow the protocol and scientifically maintain the currently accepted technical level in conducting the trial.

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According to national policies and regulations, the investigator will provide relevant trial documents to the Ethics Committee.

Ethics Committee approval documents must be accompanied by a list of all committee members involved in the discussion of the approval documents and their respective responsibilities.

Before the start of the clinical trial, approval must be obtained from the ethics committee and regulatory authorities.

The amendment to the study protocol shall be submitted to the Ethics Committee for review and approval.

During the course of the clinical trial, the investigator must inform the Ethics Committee of any serious adverse event.

10.3 QUALITY ASSURANCE AND AUDIT

Government regulatory authorities or ethics committees at each site may visit each site during the trial to ensure compliance with all aspects of the protocol. Source documents will be reviewed to verify data recorded on the eCRFs. Source documents are defined as original documents, data, and records. Investigators and institutions ensured access to source documents by government regulatory authorities and IRBs or IECs.

10.4 INFORMED CONSENT FORM

The investigator is responsible for explaining the objectives, methods, benefits and potential risks of this clinical trial, other alternative treatments and the rights and obligations of the subjects in accordance with the Declaration of Helsinki to each subject. Subjects should be informed that they have the right to withdraw from the trial at any time. A signed and dated ICF must be obtained from the subject prior to any operating procedures associated with the clinical

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trial. The investigator retained the original signed ICF as the trial data. The date the ICF was signed was to be recorded in the eCRF.

Verbal explanation must be given to the subject at the time of giving written informed consent. Informed consent must be dated and signed by each subject or his/her legal guardian or designee. The signed informed consent form and information sheet were retained by the subject and another signed informed consent form was retained and retained as a trial file.

The consent form must be agreed and signed by the subject or legal guardian or designee before any trial-related procedures are started. Before obtaining informed consent, the investigator or his/her designee was to give the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate. The informed consent process needs to be documented in the progress notes on the day of the screening visit.

All revised informed consent forms must be reviewed and signed by the subject or legal guardian or designee in the same manner as the original informed consent form, and the date the revised consent is obtained should be recorded in the subject 's medical record, and the subject should receive a copy of the revised informed consent form.

10.5 APPROVAL AND MODIFICATION OF CLINICAL PROTOCOL

The trial protocol and/or other relevant documentation will be approved by the IEC/competent authority before the start of the trial according to local regulations. The investigator was to ensure that all ethical and regulatory requirements were met prior to enrollment of the first subject. After the protocol is approved by the Ethics Committee, if there is any significant change to the trial protocol during the implementation, it will be timely reported to the Ethics Committee in accordance with the relevant national regulatory requirements.

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Administrative changes that do not affect the subject benefit/risk ratio may not require a formal protocol amendment. Each version of the protocol amendment will be distributed to all protocol recipients with appropriate instructions.

In order to protect the safety of all subjects in the study, the above requirements shall not prevent the investigator from taking any emergency measures. If the investigator considers that immediate changes to the protocol are necessary for safety reasons, the changes must be made in accordance with the ethical committee policy, local regulations and policies for the trial.

10.6 PROTOCOL DEVIATIONS

The investigator shall conduct this clinical trial in accordance with the clinical trial protocol approved by the Ethics Committee and in accordance with GCP. During the course of the trial, the investigator should not deviate from the protocol unless the immediate hazard to the subject is eliminated. If other unexpected circumstances arise that require deviation from protocol-specified procedures, the investigator should consult with the IRB or IEC, as necessary, to determine appropriate action.

The study site should record all protocol deviations in the subject 's original data, including but not limited to the occurrence time of protocol deviation, time of discovery, description of event and measures taken. In the event of a serious protocol deviation, the site should notify the IRB or IEC.

10.7 TRIAL MONITORING

During the course of the trial, the trial sponsor or its designated monitor will conduct on-site monitoring of the site on a regular basis, and the date of the visit will be documented on the site visit log for each monitoring.

Monitor activities for trial monitoring include:

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- Site initiation visit: collect and distribute necessary documents required before the trial; give instructions to the investigator and his/her site staff on the protocol, trial procedures and expectations; obtain the assurance that the investigator will conduct the trial according to the trial requirements and GCP guidelines, and introduce the trial materials to the investigator and corresponding study staff.
- Monitoring Visits: In accordance with GCP requirements, monitors participating in the current trial were fully aware of confidentiality issues and compared the data in the eCRF with data recorded in hospital or clinical records (source data). Before starting the trial, the CRA should discuss with the investigator the specific items required as the original data, and determine the nature and storage location of all original data, so as to ensure that the investigator knows the source of the original data used to complete the eCRF. The investigator authorizes the monitor to check and verify the right. All observations and findings during the monitoring process must be verified. If electronic records are maintained at the study site, the method of reconciliation must be discussed with the trial members.

Source data must be at least available to demonstrate:

- Subject identification, eligibility and participation;
- Appropriate informed consent procedures;
- Date of visit;
- Documentation of safety and efficacy parameters;
- Adequate reporting and follow-up of adverse events;
- Treatment with concomitant medication;
- Drug receipt/dispensing/return records;

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- Investigational product administration information;
- The subject completes treatment, terminates treatment or withdraws from the trial, and appropriate reasons;
- The data is true, accurate and complete;
- The safety and rights of subjects are protected;
- The investigator conducted the study in compliance with the currently approved protocol, GCP and all applicable regulatory requirements, etc.

During the trial, the CRA shall have direct access to all relevant documents with the consent of the Investigator, who shall ensure that he/she and relevant study personnel regularly meet with the CRA to discuss findings and any relevant issues during the visit.

10.8 INTELLECTUAL PROPERTY

All relevant personnel involved in the clinical trial must strictly keep confidential all information obtained from the trial sponsor and the trial collaborator and shall not disclose it to other personnel without prior consent of the trial sponsor and the collaborator.

10.9 CONFIDENTIALITY AGREEMENT AND SUBJECT PRIVACY

The investigator undertakes to keep confidential to third parties any confidential information obtained from the partner or from the company 's products or provided or disclosed in connection with the current contractual relationship and to use such information to the extent agreed in the agreement.

As long as the collaborators have reasonable and justified reasons to require the investigator to maintain a confidentiality agreement, this agreement shall be independent and valid during the existence of the contractual relationship between the parties.

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Study personnel must ensure that the privacy of clinical trial subjects is maintained. In all the documents submitted to the partners, only the subject code of the clinical trial can be used to identify the subject of the clinical trial, but the subject 's name and hospitalization number cannot be indicated. The Investigator must appropriately keep the names and addresses of clinical trial subjects and the enrollment forms corresponding to the codes of clinical trial subjects. These enrollment forms were kept strictly confidential by the investigator and could not be submitted to the partner.

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11.PAPER PUBLICATION

Authors and manuscripts of the paper will reflect collaboration between multiple investigators and sites and CARsgen. Authors should be identified before writing the manuscript. Unless agreed by the trial sponsor and CARsgen, no study site or individual will be allowed to write separately before the final report of the trial is completed. The manuscript and publication rights will be jointly decided by the trial sponsor and CARsgen through negotiation and subject to the execution of a contract.

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12.DATA ARCHIVING

12.1 MATERIALS RELATED TO THE ETHICS COMMITTEE

The person responsible for data storage at the study site must keep the minutes and abstracts of ethics committee meetings until 5 years after discontinuation or completion of the trial. If the partner wishes to retain for a longer period, the parties will discuss and decide on the retention time and method. If there is any change in the preservation of the documents by the study site, the person responsible for the preservation of the documents or the investigator needs to reach out to the partner.

12.2 MATERIALS RELATED TO STUDY IMPLEMENTATION

The person responsible for data storage at the study site must retain trial-related documents (including but not limited to the following) for up to 5 years after discontinuation or completion of the trial. If the partner wishes to retain for a longer period, the parties will discuss and decide on the retention time and method. If there is any change in the retention of documents by the site, the person responsible for the retention of the documents or the investigator needs to reach out to the partner.

- Original data;
- Original or photocopy of trial contract, informed consent form, notice on GCP and other materials related to GCP provided by collaborators or staff of study site;
- Protocol, GCP related data obtained from the Ethics Committee, or other GCP related data obtained;
- Investigational product management records, and other records related to the conduct of the trial;
- Auditing relevant records, or other relevant operational records;
- Data obtained in the trial;

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- Electronic Case Report Form;
- Original or copy of study report;
- Other relevant records as required by GCP.

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14.APPENDICES

APPENDIX 1 RECIST 1.1 CRITERIA

<http://www.eortc.be/recist/documents/RECISTGuidelines.pdf>

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable lesions:

Tumor lesions: must be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum length of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

10 mm by clinical routine examination instrument (tumor lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Chest X-ray 20 mm

Malignant lymph nodes: Pathologically enlarged and measurable lymph nodes must be \geq 15 mm in short axis on CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-measurable lesions:

All other lesions, including small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis \geq 10 mm to $<$ 15 mm) and non-measurable lesions. Lesions that could not be measured included: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitic carcinomatosis of the skin/lung, abdominal masses that could not be diagnosed and followed by imaging, and cystic lesions.

Special considerations regarding lesion measurement:

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Bone lesions, cystic lesions and lesions previously treated with local therapy need to be specified:

Bone lesions:

Bone scan, PET scan or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;

Lytic bone lesions or mixed lytic/osteoblastic lesions, with identifiable soft tissue components, that meet the definition of measurability described above may be considered measurable if they can be evaluated by cross-sectional imaging techniques such as CT or MRI;

Osteoblastic lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions since they are defined as simple cysts and are neither measurable nor non-measurable;

Cystic metastases that meet the definition of measurability described above may be considered measurable. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Locally treated lesions;

Lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are generally not measurable unless there has been unequivocal progression of the lesion. The protocol should detail the conditions under which such lesions would be considered measurable.

Lesion Measurements:

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All tumor measurements were recorded in metric notation at the time of clinical evaluation. All baseline assessments of tumor lesion size should be performed as close as possible to the start of treatment and must be performed within 14 days (2 weeks) before the start of treatment.

Evaluation method:

The same technique and method should be used for baseline assessment and subsequent measurement of lesions. All lesions must be evaluated by imaging except those that cannot be imaged but can only be evaluated by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter when measured (e.g. skin nodules). For subjects with skin lesions, documentation by color photography including a ruler to measure lesion size is recommended. When lesions are evaluated by both imaging and clinical examination, imaging evaluation should be selected whenever possible because imaging is more objective and can be reviewed repeatedly at the end of the trial.

Chest X-ray: When tumor progression is an important endpoint, chest CT is preferred because CT is more sensitive than X-ray, particularly for new lesions. Chest X-ray is indicated only when the measured lesion is well circumscribed and the lung is well ventilated.

CT, MRI: CT is currently the best available and reproducible method for response evaluation. This guideline defines measurability on CT scans based on the assumption that CT slice thickness is 5 mm or less. If CT slice thickness is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound should not be used as a method of measurement to measure lesion size. Because sonography is operation-dependent, it is not reproducible after the end of measurement and does not ensure the identity of techniques and measurements between

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different measurements. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. MRI may be used instead if radiation exposure from CT is taken into account.

Endoscopy, laparoscopy: The use of these techniques for objective tumor evaluation is not recommended, but they can be used to confirm CR when biopsies are obtained or to confirm relapse in trials where relapse following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to evaluate objective tumor response. However, if markers are present at baseline above the upper limit of normal, they must normalize for evaluation of a complete response. Because tumor markers vary by disease, this factor needs to be taken into account when writing the measurement criteria into the protocol. Specific criteria for CA-125 response (recurrent ovarian cancer) and PSA response (recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria, which are to be added to objective tumor evaluation criteria for first-line treatment regimens for ovarian cancer.

Cytological/histological techniques: These techniques may be used to identify PR and CR in protocol-specified specific situations (eg, residual benign tumor tissue in lesions of germ cell tumors). When effusions are known to be a potential adverse effect of treatment (e.g. with taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

Criteria for tumor response (target lesion assessment):

CR: Disappearance of all target lesions and short axis pathological lymph nodes (including target and non-target) must have decreased to < 10 mm.

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PR: At least a 30% decrease in the sum of diameters of target lesions compared with baseline.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study); in addition to the relative increase of at least 5 mm, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered PD).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Time point response: subjects with target lesions (including or excluding non-target lesions)

Target lesions	Non-target lesions	New Lesion	Total Assessments
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluable	No	PR
PR	Non-progressive or not fully evaluable	No	PR
SD	Non-progressive or not fully evaluable	No	SD
Not fully evaluated	Non-Progression	No	NE
PD	Any condition	Yes or No	PD
Any condition	PD	Yes or No	PD
Any condition	Any condition	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease NE = not evaluable

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Note: For non-target lesions, 'non-CR/non-PD' refers to efficacy superior to SD. Because SD is increasingly used as an endpoint to evaluate efficacy, a response of non-CR/non-PD is established to target when no lesions are measurable.

For equivocal findings of progression (eg, very small indeterminate new lesions; cystic degeneration or necrotic lesions in existing lesions), treatment may continue until the next assessment. If PD is confirmed at the next assessment, the date of progression should be the earlier date when progression was suspected.

Best overall response requiring confirmation for response of complete response (CR) and partial response (PR)

Overall response at first time point	Overall response at later time points	Best overall response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD provided SD persists for sufficient duration, otherwise PD
CR	PD	SD provided SD persists for sufficient duration, otherwise PD
CR	NE	SD provided SD persists for sufficient duration, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided SD persists for sufficient duration, otherwise PD
PR	NE	SD provided SD persists for sufficient duration, otherwise NE

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NE	NE	NE
<p>Note: CR means complete response, PR means partial response, SD means stable disease, PD means progressive disease, and NE means not evaluable. Superscript "a": If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease will reappear after CR). Best response depends on whether SD occurs within the shortest treatment interval. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. In this case, the first CR should be changed to PR and the best response is PR.</p>		

Confirmation of efficacy:

For non-randomized clinical studies where tumor response is the primary endpoint, confirmation of PR and CR is required to ensure that response is not the result of evaluation error. In studies where stable disease or PD are the primary endpoints, confirmation of efficacy is no longer required as it would not be valuable for the interpretation of trial results. In the case of SD, at least 1 measurement met the SD criteria as specified in the protocol at the minimum interval following the start of the trial (generally no less than 6-8 weeks).

Overall Response Period:

Overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded in the trial). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent or progressive disease is objectively documented.

Stable disease:

Time from start of treatment to PD (in randomized trials, from time of randomization), taking as reference the smallest sum in the trial (if the baseline sum is the smallest, this is the

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reference for calculation of PD). The clinical relevance of stable disease varies between studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint in a particular trial, the protocol should specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, stabilization, and PFS are influenced by the frequency of follow-up after baseline evaluation. Defining a standard follow-up frequency is outside the scope of this guideline. The frequency of follow-up should take into account many factors, such as disease type and stage, treatment cycle and standard practice. However, limitations in the accuracy of these endpoints should be taken into account if comparisons between trials are to be made.

PFS/TTP:

Many trials in advanced cancer have used PFS or TTP as the primary study endpoint. If the protocol requires that all subjects have measurable disease, evaluation of progression is relatively straightforward. An increasing number of trials allow subjects with measurable disease and those without measurable disease to enter the trial. In such cases, the clinical findings of PD in subjects without measurable disease must be clearly and thoroughly described. Because progression dates often have established deviations, the timing of observations should be the same for each trial arm.

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APPENDIX 2: ECOG PERFORMANCE STATUS ASSESSMENT

Grade	
0	Normal activities can be performed. Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work (eg, light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, more than 50% of waking hours spent in bed or chair.
4	Complete disability. Total loss of self-care ability. Completely ill lying in bed or wheelchair.
5	Death.

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**APPENDIX 3: CREATININE CLEARANCE CALCULATION FORMULA
(COCKROFT-GAULT FORMULA)**

Calculated creatinine clearance:

$$CL_{Cr} = \frac{(140 - \text{Age}(\text{year})) \times \text{Weight}(\text{kg})}{\text{creatinine} \left(\frac{\text{mg}}{\text{dL}} \right) \times 72} \times \text{Gender Correction Factor}(\text{Male: 1.00, Female: 0.85})$$

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APPENDIX 4: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 5.0

The NCI Common Terminology Criteria for AEs version 5.0 will be used to report AEs in this study. CTCAE version 5.0 can be downloaded from the homepage of the Cancer Therapy Evaluation Program CTEP. CTCAE v5.0 should be used at all relevant sites. Website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm ctc50

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APPENDIX 5: FORMULAS FOR CALCULATING BODY SURFACE AREA

Body surface area of the subjects was calculated according to the Stevenson formula:

$$\text{Body surface area (m}^2\text{)} = 0.0061 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.1529$$

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APPENDIX 6: BCLC STAGING

Phase	PS score	Tumor status		Hepatic Status
		Number of tumors	Tumor size	
Stage 0: Very early	0	Single	< 2 cm	No portal hypertension
Stage A: Early	0	Single		Child-Pugh A-B
		Within 3	< 3 cm	Child-Pugh A-B
Phase B: interim	0	Multinodular tumor	Any	Child-Pugh A-B
Stage C: Progressive	1-2	Portal invasion or N1, M1	Any	Child-Pugh A-B
Stage D: End Stage	3-4	Any	Any	Child-Pugh C

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APPENDIX 7: Child-Pugh Score

Indicators	Score		
	1	2	3
Total bilirubin (µmol/L)	< 34	34-51	> 51
Serum albumin (g/L)	> 35	28-35	< 28
Prothrombin time prolonged	1-3 seconds	4-6 seconds	> 6 seconds
Ascites	None	Mild	Moderate
Hepatic encephalopathy (grade)	None	1-2	3-4

Note: According to the scoring method, 5-6 points are classified as Grade A, 7-9 points are Grade B, and ≥ 10 points are classified as Grade C.