phase I/IIa clinical trial evaluating the safety and efficacy of IMC001 in patients with advanced epithelial solid tumors.

Clinical Study Protocol

Scheme Number: IMC001-RT02

Version number: V1.1

Version date: 2025-09-30

Sponsor: Chengdu Yimufeng Biotechnology Co., Ltd.

Suzhou Yimufeng Biotechnology Co., Ltd.

principal investigators

Signature Page

I have read this experimental protocol (version number : V1.1 , version date : September 30 , 2025) and confirm my agreement to conduct this study in accordance with this protocol. I agree to fulfill my responsibilities in accordance with the Declaration of Helsinki, GCP , other applicable regulations, and this research protocol.

This study can only be conducted after obtaining approval from the ethics committee. During the study, I will strictly adhere to the requirements of this protocol. Any modifications to this protocol will only be implemented after notifying the researchers and obtaining their consent, and after further approval or filing with the ethics committee, unless measures are necessary to protect the safety, rights, and interests of the participants.

Meanwhile, as the principal investigator of this experiment, I coordinated the overall progress of the experiment.

Research Unit: _____

Name: _____

sign: _____

date: _____

Sponsor

Signature Page

I will diligently fulfill my responsibilities as sponsor in accordance with Chinese GCP regulations, and will be responsible for initiating, applying for, organizing, and funding this clinical trial. I will bear legal responsibility for related medical expenses and provide appropriate financial compensation to subjects who suffer trial-related harm or death during the clinical trial, and will provide legal guarantees to the researchers. I agree to conduct this clinical trial in accordance with the design and provisions of this protocol (Version No .: V1.1 , Version Date : September 14 , 2025) .

Applicant: Chengdu Yimufeng Biotechnology Co. , Ltd.

Suzhou Yimufeng Biotechnology Co., Ltd.

Name: _____

sign: _____

date: _____

Revision Summary

Summary of protocol Revisions for Versions V1.0 -V1.1

Contents	Summary of Revisions	Reasons for revision
Enrolled population and sample size	• EpCAM- positive epithelial solid tumors such as biliary tract cancer, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors . • Phase I was adjusted to 7-15 subjects, with each dose group expanded to approximately 10 subjects; for stage IIa, approximately 6-20 subjects were observed for each tumor type .	EpCAM is a broadly expressed target, and increasing the sample size and indications will help to explore safety and preliminary efficacy.
Phase I dose escalation strategy	• Accelerated titration (ATD) was used in combination with a 3+3 design, and subjects with evaluable lesions were allowed to enroll in the low-dose group. • Clarify the definition of "significant toxicity" and the rules for determining the escalation / cessation of ATD (Acute Tolerance Treatment).	Optimize the dose escalation strategy to improve safety and escalation efficiency.
Inclusion / Exclusion Criteria	• Define the criteria for positive EpCAM expression (≥ 10% positive rate of tumor cells, intensity ≥ 1+). • Adjust the lower limit of platelet count to 100× 10^9 /L and the lower limit of hemoglobin to 8.0g/dL to ensure safety. • Increase the criteria for excluding extensive bone metastases; break down the criteria for central nervous system metastases. • For multiple primary EpCAM- positive tumors, the inclusion restrictions should be appropriately relaxed.	Revise according to the protocol design
Study follow-up and exploratory endpoints	• Long-term follow-up was adjusted to 15 years after IMC001 infusion or at the end of the trial (whichever comes first), including immunogenicity, lentiviral insertion site (RCL), etc. • Clearly assess the correlation between CAR-T phenotypic changes, cytokines, and the tumor microenvironment and efficacy and safety. Increase exploratory studies involving biopsies before and after CAR-T therapy.	Adjust in accordance with the regulatory requirements for cell therapy
Bridging therapy and imaging assessment	• Added recommendations for bridging therapy and descriptions of secondary infusions. • Imaging assessments can be performed using results from examinations within 28 days prior to infusion; reassessment is required if the patient is receiving bridging therapy.	The protocol design has been updated to achieve better benefit for participants.

Other updates	• Update the study design diagram, flowchart, visit schedule, major adverse events section, and RECIST 1.1 calculation formula. • Supplement and update preclinical organoid (PDO) research data and IIT safety and efficacy data.	Data update

* This table is a simplified summary of the revised plan comparison table.

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Abbreviations

English abbreviations	Chinese definition
ADA	Antidrug antibodies
AE	Adverse events
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cell Therapy
ATD	Accelerated titration
AUC	Area under the curve
$AUC_{0\text{-}28d}$	Area under the curve from 0 to 28 days
BUN	urea nitrogen
CAR	Chimeric antigen receptor
CD	Cluster differentiation antigen
CD3ζ	TCR complex component, CD3 intracellular signaling region ζ chain, also known as zeta, abbreviated as Z.
CI	Confidence interval
CK	Creatine kinase
C_{max}	Peak concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission
CRF	Case Report Form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	X- ray computed tomography
CTC	Peripheral blood circulating tumor cells
CTCAE	Standard Terminology for Adverse Events
CTL	Cytotoxic T cells
DBIL	direct bilirubin
DLT	Dose-limiting toxicity
DNA	DNA
DOR	Duration of relief
ECG	electrocardiogram
ECOG	Physical fitness score
EDC	Electronic data acquisition system
EpCAM CAR-T	Chimeric antigen receptor-modified autologous T cells targeting EpCAM
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GC	Stomach cancer
GCP	Good Clinical Practice for Drug Clinical Trials
GEJ	Adenocarcinoma of the esophagogastric junction
GMP	Good Manufacturing Practices for Pharmaceuticals
HbcAb	Hepatitis B virus core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic lymphohistiocytosis
English abbreviations	**Chinese definition**
HPS	Hemophagocytic syndrome
ICANS	Immunotherapy-related neurotoxicity syndrome
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
Ig	Immunoglobulins
IHC	Immunohistochemistry
IL	Interleukin
INR	International Normalized Ratio
IV	Intravenous injection
LD	Pretreatment of shower
LDH	lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MedDRA	Standard Medical Terminology for Pharmaceutical Administration
MRI	Nuclear magnetic resonance
ORR	Objective response rate of tumor
OS	Overall Survival
PCR	Polymerase chain reaction
PD	Disease progression
PFS	Progression-free survival

PK	Pharmacokinetics
PR	Partial relief
PT	Preferred terminology
qPCR	Real-time quantitative polymerase chain reaction
English abbreviations	**Chinese definition**
QTc	QT interval
RCL	Replicating Lentiviral
RNA	Ribonucleic acid
RP2D	Recommended Phase II dosage
SAE	Serious adverse events
scFv	Single-chain antibody fragments
SD	Disease Stable
SOP	Standard Operating Procedures
SMC	Safety Inspection Committee
TBIL	Total bilirubin
TCR	T cell receptors
T_{max}	Peak time
TRAE	Treatment-related adverse events
ULN	Upper limit of normal value
VCN	Carrier copy number
WHO	World Health Organization

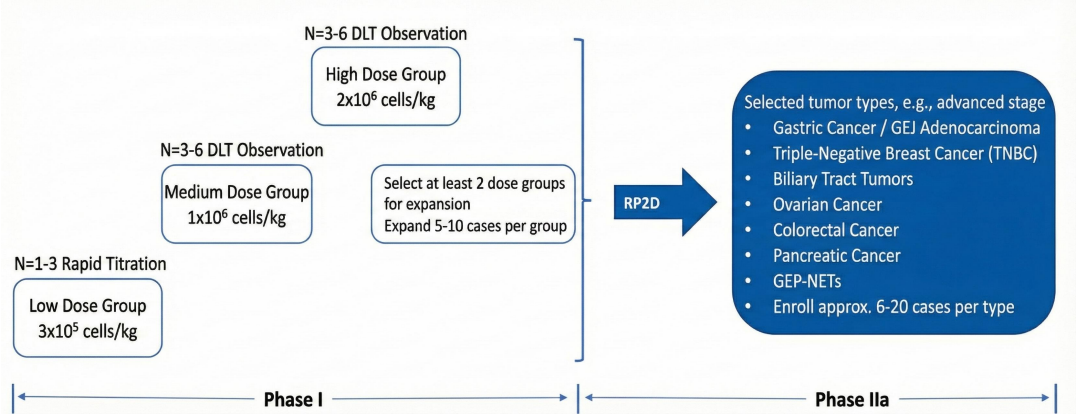
1. Solution Overview

1.1 summary

Research Title	A phase I/IIa clinical trial evaluating the safety and efficacy of IMC001 in patients with advanced epithelial solid tumors.
Research Number	IMC001-RT0 2
applicant	Chengdu Yimufeng Biotechnology Co., Ltd. / Suzhou Yimufeng Biotechnology Co., Ltd.
Research drugs	Autologous CAR-T cell injection targeting EpCAM Code name: IMC001
Research nature	Phase I /IIa
Research Center	1
Number of cases	Phase I : 7-15 subjects in the dose escalation phase ; in the expansion phase, select at least 2 dose groups for expansion, with 5-10 subjects in each group (combined with the escalation phase, expand each dose group to about 10 subjects) . 6-20 subjects for each selected epithelial tumor . Enrollment for Stage IIa will be further expanded within the selected tumors, with the protocol revised and sample size determined based on statistical assumptions and regulatory requirements.
Subject population	Advanced epithelial solid tumors who have failed standard treatment , including but not limited to subjects with advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors .
Study phases	Each participant followed the same study treatment plan and procedural requirements. Each participant experienced a screening period, leukapheresis, bridging therapy (if applicable), lymphocyte clearance conditioning (LD) period, treatment period, a 16-week primary follow-up period, and a 2- year long-term follow-up period. Exploratory endpoints such as immunogenicity testing, RCL testing, and lentiviral genome insertion site testing were followed up for a final period of 15 years after IMC001 infusion or at trial termination (whichever occurs first).
Research Objective	**Phase I:** Main purpose

	• Assess the safety and tolerability of IMC001 to determine the recommended dose for entering Phase IIa (RP2D). Secondary objective • Evaluation of the preliminary antitumor activity of IMC001 • Evaluation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IMC001 **Phase IIa** Main purpose • the efficacy of IMC001 in subjects with solid tumors who have failed standard therapy. Secondary objective • Assess the safety and other efficacy endpoints of IMC001 • Evaluation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IMC001 Exploratory objectives (applicable to Phase I and IIa studies) • Immunogenicity analysis, lentiviral genome insertion sites, and long-term follow-up of replicating lentiviruses (RCLs) were conducted . • To assess changes in cytokines before and after administration of IMC001 and their correlation with efficacy and safety. • Evaluation of IMC001 The correlation between changes in biomarkers before and after drug administration and efficacy and safety. • To assess changes in CAR-T cell phenotype before and after administration of IMC001. • Evaluation of IMC00 1 The correlation between changes in the tumor microenvironment of tumor tissue samples before and after drug administration and efficacy and safety. • Explore the correlation between the above-mentioned and other relevant biomarkers and efficacy and safety.
Study endpoints	**Phase I** Primary endpoint: safety and tolerability • Incidence, duration, and severity of treatment-related adverse events (TEAEs) (according to CTCAE v5.0 classification) • Incidence and severity of dose-limiting toxicities (DLTs) within 28 days after IMC001 infusion. • Following IMC001 treatment, the recommended Phase II dose (RP2D) is determined based on dose-limiting toxicities (DLT) and clinical response, including potential side effects.

	Secondary endpoints: preliminary efficacy endpoints and pharmacokinetic/pharmacodynamic indicators • Efficacy endpoints: Efficacy was assessed using RECIST 1.1 criteria, including objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). • PK indicators: The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry. The main evaluation indicators included Cmax , Tmax , AUC $_{0-28}$, Tlast , Clast , Cmax / Tmax $_{and}$ other relevant PK parameters. • PD indicators: The levels of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ . **Phase IIa** Primary endpoint • Objective response rate (ORR) of tumors was assessed according to RECIST 1.1. Secondary endpoint • Safety: Incidence, duration, and severity of adverse events (AEs), and changes in safety assessments (such as physical examination results, laboratory tests, vital signs, and electrocardiograms). • Efficacy endpoints: Efficacy was assessed using RECIST 1.1 criteria, including disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) , and overall survival (OS). • PK indicators: The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry. The main evaluation indicators included Cmax , Tmax , AUC $_{0-28}$, Tlast , Clast , Cmax / Tmax $_{and}$ other relevant PK parameters. • PD indicators: The levels of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ . **Exploratory endpoints (applicable to Phase I and IIa studies)** • Long-term follow-up of lentiviral genome insertion sites, replicating lentiviruses (RCLs), etc. • IMC001 CAR-T cells , lymphocyte subsets/phenotypes , etc. before and after treatment • EpCAM target expression ratio and intensity, etc.

	• Changes and quantitative analysis of biomarkers related to tumor immune microenvironment characteristics and overall immune characteristics of the body • Immunogenicity: Changes in anti- EpCAM CAR-T antibodies (ADA) in the blood before and after IMC001 treatment .
Research Design	This is an open -label phase I /IIa study designed to evaluate the safety and efficacy of IMC001 in patients with advanced epithelial solid tumors. The study comprises two parts: a phase I dose-escalation phase and a phase IIa phase to further explore and validate efficacy . See study design (**Figure 1**).  **Figure 1 IMC001-RT02 Phase I /IIa Study Design Diagram** **Phase I dose escalation + extension** In the Phase I dose-escalation phase of this study, approximately 7–15 subjects with advanced epithelial solid tumors will be recruited to evaluate the safety and tolerability of autologous IMC001 treatment . In the expansion phase, at least two dose groups will be selected , each recruiting 5 – 10 subjects. Combined with the subjects from the escalation phase, each dose group will be expanded to approximately 10 subjects to determine the recommended RP2D dose for progression to Phase IIa . DLT (digestive tract aging) assessment will be performed on subjects in each cohort within 28 days of IMC001 infusion . The definition of DLT is detailed below. Dose escalation design: This study employed accelerated titration (ATD) combined with a 3 +3 design for dose escalation. Starting dose level (3×10^{5} ^{CAR} -T cells/kg) 1. Entry method and rhythm Using a sentinel + staggered ATD approach: one sentinel subject is enrolled first; only after a safety review is completed ⩾28 days after the infusion of the sentinel subject can the second subject be considered for enrollment .

	The maximum number of patients enrolled in this dose group is 3 (ATD total sample size limit = 3). 2. Increment/Cessation Determination During ATD (Applicable Only to This Dosage) Rapid escalation criteria: If no DLT is observed in enrolled ATD subjects and no "significant toxicity" as defined in the protocol (see below) occurs, the dose group can be terminated directly after the minimum observation requirement is met in the first or second case and the next dose level can be started, without having to complete the count to 3 in the dose group. Complete the observation criteria: If a single case of "significant toxicity" occurs, the dose group can be expanded to a maximum of 3 subjects to complete safety confirmation; if no DLT is found after completing the observation criteria, the dose group can be terminated and the next dose can be started. "Significant toxicity" is defined as a treatment-related adverse event (TRAE) below the DLT threshold, but sufficient to raise safety concerns and affect dose escalation decisions. It can only be confirmed by the investigator, medical monitor, and SMC. Significant toxicity includes the following situations: ➢ Persistent or recurrent grade 2 or higher unintended toxicity, which, although not reaching the DLT threshold, still affects the overall tolerability of the subject or delays subsequent dosing despite adequate supportive care; ➢ Rapidly progressing or worsening toxic reactions, even if they do not meet the definition of DLT, suggest a potential serious safety hazard (such as progressive worsening of CRS or ICANS). ➢ Events requiring clinical intervention and having a significant impact on exposure to the investigational drug, such as the need to delay or reduce subsequent treatment for safety reasons; ➢ Other treatment-related toxicities that researchers and medical monitors deem to be of safety concern and require submission to the SMC for discussion. Stop/Safety Review Criteria: If any DLT occurs in an ATD subject, do not proceed to the 3+3 escalation in this dose group; immediately halt escalation and convene a safety review meeting (SMC, composed of the sponsor, clinical experts, clinical pharmacology experts, and statisticians). The review will determine whether: a) After adjusting the treatment (such as adjusting the lowest dose cohort, prophylactic medication, or hospitalization monitoring), maintain the established "starting 3+3 for the next dose group"; or b) start a lower dose for further exploration using the ATD method; or c) terminate the escalation/revision protocol. Subsequent dose levels ($1 \times 10^{6\ CAR}$ -T cells/kg and $2 \times 10^{6\ CAR}$ -T cells/kg) The classic 3+3 design was adopted. The specific rules are as follows: At each dose level, 3 subjects were initially enrolled. If 0/3 subjects experienced dose-limiting toxicity (DLT), the next dose level could be advanced; if 1/3 subjects experienced DLT , 3 more subjects were

enrolled at the same dose level (i.e., expanded to 6 subjects); if 6 subjects... If ⩽ 1 case shows DLT , the next dose level can be advanced; if in the initial 3 subjects ... ⩾ 2 subjects had DLT , or 6 subjects after expansion If DLT occurs in ⩾ 2 subjects , the dose level is considered to be non-tolerated , and escalation is terminated. Dose reduction should be considered if necessary. Furthermore, if DLT occurs in the first 2 subjects at any dose level , there is no need to enroll a third subject; the dose level is directly deemed to be intolerant, and further enrollment at that dose level is terminated.

For any other exploratory dose (if applicable), the initial sample size is set at 3 – 6 subjects, and the same criteria for tolerability assessment as for the starting dose are used.

To ensure the safety of participants, a sentinel group is established during dose escalation. At each new dose level, the first participant will serve as the sentinel subject. Sentinel subjects must complete at least 28 days of safety monitoring after infusion. Subsequent participants can only be enrolled in that dose group after investigators and medical monitors confirm that there are no unacceptable safety risks.

Each dose level requires a 28-day DLT observation period, followed by review by the Safety Oversight Committee before a decision can be made on whether to proceed to the next dose level.

Based on the results of the SMC meeting, 2-3 dose levels will be selected for expansion to 5-10 subjects (excluding dose escalation subjects) to further evaluate safety and preliminary efficacy and determine the recommended dose for entering Phase IIa (RP2D).

The Safety Monitoring Committee (SMC) will comprehensively evaluate all available data, including the ongoing IMC001 study, and make recommendations for subsequent studies. Based on the safety results of completed dose escalation studies and all available safety, pharmacokinetic/ pharmacodynamic (PK/PD) and efficacy data, the SMC will assess the overall benefit/risk and determine the R- P2D before the study can proceed to Phase IIa.

Phase IIa study

the RP2D is determined , approximately 6-20 subjects will be initially enrolled at this dose for each selected tumor type to further explore the efficacy and safety of autologous IMC001 for this indication. Subsequently, the protocol may be revised based on statistical hypotheses and regulatory requirements to continue enrolling subjects in the selected tumor types to further validate the efficacy and safety in specific tumor types.

Definition of dose-limiting toxicity (DLT)

Adverse events (AEs) occurring during the study will be classified according to NCI CTCAE 5.0. However, CRS and ICANS will be classified and evaluated according to the 2019 ASTCT standards. Section 6.8 of this protocol describes detailed information on CRS/ICANS classification and management.

In this study, DLT was defined as: the following IMC001-related events occurring within 28 days after IMC001 cell infusion, according to FDA guidance (FDA, 2022):

Hematologic toxicity

- IMC 001 treatment-related grade ≥4 hematologic toxicities that cannot be reduced to grade ≤2 after 7 days of treatment (including neutropenia, anemia without bleeding evidence, and thrombocytopenia).
- Grade 3 or lower platelet count, complicated by bleeding;
- IMC 001 treatment associated with hemophagocytic lymphohistiocytosis (HLH)/ hemophagocytic syndrome (HPS).

Non-hematologic toxicity

- IMC 001 treatment-associated grade ≥3 cytokine release syndrome (CRS) that cannot be controlled to grade ≤2 after 7 days of treatment;
- IMC00 1 Treatment-related ≥ Grade 3 ICANS;
- IMC 001 treatment-related grade 3 non-CRS toxicity of the heart, liver, lungs, and kidneys, which cannot be recovered to grade ≤2 within 7 days after treatment;
- Except for other non-hematologic toxicities of grade 3 treatment-related IMC 001 lasting more than 7 days:
  - Grade 2 within 48 hours after adequate intervention ;
  - Level 3 fatigue;
- IMC 001 treatment-related grade ≥4 other non-hematologic toxicities, excluding:
  - Fever of grade ≥4 recovers to grade ≤3 within 48 hours after adequate intervention;
  - Grade 4 nausea, vomiting, diarrhea, and constipation recover to grade ≤2 within 48 hours after adequate intervention;
  - Hepatotoxicity recovered to grade ≤3 within 72 hours after adequate intervention .

Subject replacement

Phase I dose escalation: The number of subjects in each dose group must be at least 3. If a subject in any dose group withdraws from the study for reasons other than DLT and fails to complete the DLT observation, that subject will be replaced to meet the requirement of the number of subjects observed in each dose group (≥3 , except for the accelerated titration group).

Phase IIa study: Not applicable .

Research completed

the date on which the last participant completes a two-year follow-up visit, is lost to follow-up, withdraws informed consent, or dies (whichever occurs first) . It is important to note that for long-term follow-up programs such as ADA, RCL, and VIS (up to 15 years), which require protocol-based follow-up, these follow-ups will be conducted continuously according to protocol and regulatory requirements. However, the actual study participation time for each participant

	will vary depending on screening requirements, response to treatment, long-term follow-up arrangements, and survival status .
Main selection criteria	Subjects must meet all of the following inclusion criteria to be enrolled: 1) to provide a signed and dated informed consent form before conducting any research-related procedures , and willing and able to comply with all research procedures. 2) Applicants must be 18 years of age or older and 75 years of age or younger; both male and female applicants are welcome . 3) Subjects with histologically or cytologically confirmed locally advanced/metastatic epithelial solid tumors , including but not limited to subjects with advanced gastric cancer/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, gastrointestinal and pancreatic neuroendocrine tumors, etc. 4) Disease progression or intolerance to standard systemic therapy , including: • Gastric cancer and gastroesophageal junction adenocarcinoma that have failed or are intolerant of at least two lines of standard systemic therapy. If first-line three-drug combination therapy has failed or is intolerant, enrollment may be made after thorough investigator evaluation. • Triple-negative breast cancer: Subjects with unresectable locally advanced or metastatic triple-negative breast cancer who have failed at least two lines of standard systemic therapy. All subjects must have previously received taxane therapy, regardless of the stage of disease at the time of treatment. • Other subjects with epithelial solid tumors who have failed or are intolerant of standard treatment. 5) Tumor tissue samples (primary or metastatic, archived or newly collected) from the expected subjects, tested by the central laboratory, are EpCAM histologically positive (defined as tumor cell positivity ⩾10% and staining intensity ⩾1+). 6) The expected survival period of the subjects is ≥12 weeks . 7) According to RECIST 1.1 criteria, there should be at least one stably measurable target lesion (where the largest lesion should be ⩽4). In the 3×10^{5} ^{CAR}-T cells/kg dose group, subjects with evaluable lesions (unmeasurable lesions) can be admitted. 8) ECOG performance status score 0-1 . 9) The subject has adequate organ and bone marrow function. Laboratory screening must meet the following criteria: all laboratory test results should be within the stable ranges outlined below, and there should be no ongoing supportive treatment. If any laboratory test result is abnormal according to the following criteria, a repeat test may be performed within one week. If the test results still do not meet the following criteria, the subject's screening has failed.

	a) Blood tests [No intensive blood transfusions (≥2 times within 1 week), platelet transfusions, or cell growth factor injections (excluding recombinant erythropoietin)) within 7 days prior to the test]: Neutrophil count (ANC) ≥1.5×10^9/L; Platelet count (PLT) ≥100 × 10^9/L; Hemoglobin content (Hb) ≥9.0g / dL; Lymphocyte count (ALC) ≥0.5× 10^9/L ; b) Liver function: alanine aminotransferase (ALT) ≤ 2.5 × ULN, aspartate aminotransferase (AST) ≤ 2.5 × ULN, serum total bilirubin (TB) ≤ 2 × ULN; for subjects with liver metastases, AST and ALT < 5 × ULN ; c) Kidney function: Serum creatinine ≤1.5×ULN; if serum creatinine >1.5×ULN, creatinine clearance rate >50mL/min is required (according to the Cockcroft-Gault formula); qualitative urine protein ≤1+; if qualitative urine protein ≥2+, a 24-hour urine protein quantification test is required (if the 24-hour urine protein quantification test is <1g, it is acceptable). d) Amylase and lipase ≤1.5×ULN; alkaline phosphatase (ALP) ≤2.5×ULN, and for subjects with bone metastases, ALP <5×ULN ; e) Coagulation function: Activated partial thromboplastin time ≤ 1.5 ULN, prothrombin time ≤ 1.5 × ULN ; 10) All toxicities resulting from prior antitumor therapy were reduced to grade 0–1 (according to NCI CTCAE version 5.0) or to a level acceptable to the inclusion criteria. Other toxicities, such as alopecia and vitiligo, which the investigators deemed not to pose a safety risk to the subjects, were excluded . 11) Reproductive status: Female subjects of reproductive age or male subjects whose sexual partners are women of reproductive age, who are willing to use medically approved and highly effective contraceptive methods, such as intrauterine devices or condoms, from the time they sign the informed consent form until 12 months after cell infusion (women of reproductive age include premenopausal women and women within 24 months after menopause) .
Main exclusion criteria	Subjects must not meet any of the following conditions: 1) Pregnant and breastfeeding women . 2) Positive for human immunodeficiency virus (HIV) antibodies; hepatitis B virus infection (if the subject is positive for hepatitis B surface antigen, regardless of whether the core antibody is negative or positive, they can also be enrolled if the viral DNA load is negative, and prophylactic antiviral treatment should be considered); acute or chronic active hepatitis C (positive for HCV antibodies); positive for syphilis antibodies; Epstein-Barr virus (EBV) infection (positive for IgM or known EBV infection); cytomegalovirus (CMV) infection (positive for IgM); positive for human T-lymphotropic virus (HTLV). The results of the above pathogen tests are subject to the results of the central laboratory .

	3) Severe infections that are in an active phase or poorly controlled clinically . 4) The patients had uncontrollable pleural effusion, pericardial effusion, and ascites before enrollment . 5) Extensive or diffuse lung metastases , extensive or diffuse liver metastases , extensive or diffuse bone metastases . 6) Subjects with intestinal obstruction or obstructive jaundice who are deemed unsuitable for participation in this trial by the researchers . 7) Blood oxygen saturation ≤95% without oxygen supplementation . 8) Patients with other serious lung diseases that may limit their participation in this study, such as pulmonary embolism, chronic obstructive pulmonary disease, symptomatic or poorly controlled interstitial lung disease, or clinically significant abnormalities in pulmonary function tests . 9) Subjects with a known history or current hepatic encephalopathy requiring treatment; subjects with a current or history of central nervous system disorders, such as seizures, cerebral ischemia/hemorrhagic disease, dementia, cerebellar disease, or any autoimmune disease involving the central nervous system . 10) Central nervous system metastasis or meningeal metastasis . 11) Currently, patients have unstable heart disease requiring treatment or heart disease that cannot be controlled by treatment, or hypertension that is poorly controlled according to investigators (defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure >100 mmHg after standard antihypertensive drug treatment); or diabetes that is poorly controlled despite standard treatment (fasting blood glucose ≥10.2 mmol/L) . 12) If any of the following cardiac clinical symptoms or conditions exist within 6 months prior to cell infusion: a) Left ventricular ejection fraction (LVEF) < 50%; b) History of myocardial infarction within the past year; or unstable angina; or percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); or use of a pacemaker; c) Resting electrocardiogram examination: QTc F > 450ms (male) or QTc F > 470ms (female); d) An electrocardiogram at rest reveals clinically significant abnormalities (such as abnormalities in heart rate, conduction, or morphological characteristics) or complete left bundle branch block or third-degree atrioventricular block or a PR interval >250 ms. 13) Evidence of a significant coagulation disorder or other obvious risk of bleeding, including: a) Abnormal coagulation function that is clinically significant;

	b) History of intracranial hemorrhage or spinal cord hemorrhage; c) Patients with tumor lesions invading major blood vessels and posing a significant risk of bleeding; d) Subjects who currently have unstable or active ulcers or active gastrointestinal bleeding; e) An embolic event occurred within 6 months prior to cell reinfusion; f) Within one month prior to cell reinfusion, there has been clinically significant hemoptysis or obvious bleeding from tumor lesions; g) Had a major trauma or major surgery within one month prior to enrollment; h) The presence of any bleeding disorder, such as hemophilia, von Willebrand disease, etc.; i) The patient has received anticoagulation therapy (excluding low molecular weight heparin) for therapeutic purposes within 2 weeks prior to cell reinfusion. j) Subjects are receiving routine anticoagulation therapy (such as warfarin or heparin). Subjects require long-term antiplatelet therapy (aspirin >300 mg/day; clopidogrel >75 mg/day); dipyridamole, ticlopidine, or cilostazol, etc. 14) The patient has received systemic steroids equivalent to >15 mg/day of prednisone for more than 3 days within 2 weeks prior to apheresis, excluding inhaled steroids . 15) Subjects requiring systemic therapy with corticosteroids or other immunosuppressive drugs during treatment. Subjects with any active autoimmune disease, or a history of autoimmune disease with anticipated relapse (including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, and asthma requiring medical intervention with bronchodilators). Exceptions include: type 1 diabetes; skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis); alopecia; hypothyroidism requiring only hormone replacement therapy; asthma that was completely remitted in childhood and requires no intervention in adulthood; or other conditions not expected to relapse in the absence of external triggers . 16) Subjects with a prior or concurrent history of other malignant tumors, except in the following circumstances: a) Basal cell or squamous cell carcinoma that has undergone adequate treatment (sufficient wound healing is required before enrollment in the study). b) Cervical cancer or breast cancer in situ, cured and with no signs of recurrence for at least 3 years prior to the study; c) The primary malignant tumor has been completely removed and has been in complete remission for ≥5 years ; d) The concurrent malignant tumor was an epithelial tumor that expressed EpCAM .

	17) Subjects who have previously received other gene therapies, including but not limited to CAR-T therapy and TCR-T therapy . 18) The following treatments or medications were received before cell reinfusion: chemotherapy, targeted therapy, biotherapy, endocrine therapy, immunotherapy, or other anti-tumor treatments (excluding treatments that meet the protocol requirements before reinfusion, such as lymph node pretreatment and bridging therapy); less than 28 days or less than 5 half-lives since the first infusion treatment in this study (whichever is shorter); or traditional Chinese medicine treatment with anti-tumor indications received within 2 weeks before cell reinfusion . 19) of severe allergies, such as anaphylactic shock . 20) Subjects with severe mental disorders . 21) Subjects who develop new cardiac arrhythmias, including but not limited to arrhythmias that cannot be controlled by medication; hypotension requiring vasopressors; or bacterial, fungal, or viral infections requiring intravenous antibiotics. Subjects receiving antibiotics to prevent infection may continue to participate in the trial at the investigator's discretion . 22) The patient had participated in other interventional clinical studies and used investigational drugs within one month prior to the planned infusion of IMC001 . 23) Subjects who received a live attenuated vaccine within 4 weeks prior to the planned single-donor administration or who are scheduled to receive a live attenuated vaccine during the study. 24) Subjects with any other concurrent serious and /or uncontrolled medical conditions that the investigators deem unsuitable for participation in this trial. 25) Researchers assessed that participants were unable or unwilling to comply with the requirements of the research protocol .
Assessment before lymph node cleansing and reinfusion	**Pre-collection assessment :** Subjects who pass the screening tests can receive leukocyte apheresis. Seven days prior to apheresis, researchers must conduct relevant examinations (if the screening examination is within 7 days of apheresis, no further examination is required unless the researcher assesses that there is a clear reason that could cause a change in the test values during this period). Patients must be reassessed, and subjects must meet the following criteria: neutrophils $\geqslant 1.5 \times 10^{9}/L$; platelet count (PLT) $\geqslant 75 \times 10^{9}/L$; hemoglobin (Hb) $\geqslant$ 8.0 g/dL; lymphocyte count (LYM) $\geqslant 0.5 \times 10^{9}/L$. **The following criteria must be reassessed before pretreatment with the scrubbing solution and before IMC00 1 infusion:** , before urine sample preparation and 3 days before IMC00 1 infusion, the investigator determines that a subject has significant abnormalities (such as a new arrhythmia, including but

	not limited to arrhythmias that cannot be controlled by medication; hypotension requiring vasopressors; bacterial, fungal, or viral infections requiring intravenous antibiotics , and the investigator determines that the subject is unsuitable for this trial ; subjects using antibiotics to prevent infection may continue to participate in the trial , as determined by the investigator) ; or the investigator determines that the subject has experienced rapid disease progression relative to the screening time; or the investigator assesses that the subject has significant organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney dysfunction, pulmonary edema, severe lung infection, brain metastases, etc.); and the investigator determines that the subject is unsuitable for subsequent trial procedures, then urine sample preparation should not continue or should be delayed , and infusion should not be performed or should be delayed. If cell infusion is delayed for any reason beyond 7 days after pre-treatment with hysterosalpingography, infusion is not possible or may require further hysterosalpingography followed by a delayed infusion. **Subjects must meet the following criteria before undergoing pretreatment with a urinary tract infection.** If a subject receives bridging therapy after leukapheresis, relevant baseline tests must be performed again after bridging therapy , and the investigator must assess that complete remission (CR) was not achieved after bridging therapy . 1) 2 days before cell infusion . 2) No new arrhythmias were found, including but not limited to arrhythmias that could not be controlled by medication . 3) No subjects of hypotension requiring the use of vasopressors were observed . 4) No bacterial, fungal, or viral infections requiring intravenous antibiotics were found prior to the pretreatment of the urinary tract . 5) According to the researchers' assessment, the subjects had no other conditions that made them unsuitable for pretreatment with urine stream cleaning . **Prior to IMC001 infusion, the subject must meet the following criteria:** 1) It must meet the standards for pretreatment of shower water . 2) If blood oxygen saturation (via fingertip pulse oximeter) is ≥95%, no oxygen supplementation is required . 3) the left ventricular ejection fraction (LVEF) was ≥50% within 6 months prior to cell reinfusion . 4) Researchers determined that there was no serious active infection . 5) The pregnancy test was negative in the woman of childbearing age .

	6) According to the researchers' assessment, there were no other circumstances that would make the subjects unsuitable for IMC001 infusion . For subjects who have completed cell preparation but do not meet the criteria for reinfusion and require delayed infusion, such as those whose body temperature does not return to normal or whose other toxicities do not recover to ⩽ Grade 1 within 7 days after urinary tract pretreatment , the investigator will assess whether the subject should receive urinary tract pretreatment again. If any reason causes a delay in cell infusion beyond 7 days after urinary tract pretreatment, infusion is not permitted, or the investigator will assess whether the subject should undergo urinary tract pretreatment again for delayed infusion. It is recommended that the interval between two urinary tract pretreatments be no less than 4 weeks.
Other treatments	**Bridging therapy** Before the pretreatment phase from apheresis to lymphoma clearance, the investigator assesses the subject's condition and, considering the clinical benefit and risks, may consider bridging therapy. The goal of bridging therapy is to stabilize the subject's current disease state or reduce the current tumor burden. Drugs with gastric cancer indications listed in the drug's package insert are preferred. Alternatively, based on clinical practice and the patient's prior medication history, the investigator may choose 1-2 cycles of irinotecan monotherapy (recommended dose: irinotecan 150 mg/m2, intravenous infusion, single dose), the FOLFIRI regimen (recommended dose: irinotecan 130-150 mg/m2, 5-fluorouracil 2400 mg/m2, intravenous infusion, single dose), or paclitaxel (recommended dose: paclitaxel 135 mg/m2, intravenous infusion, single dose) as bridging therapy. For bridging therapies other than those recommended, the investigator must confirm the decision with the sponsor. Bridging therapy must be completed 7 days prior to lymph node decongestion pretreatment, or at least 5 half-lives of the bridging drug should be allowed as the washout period (whichever is longer) . Subjects who have undergone bridging therapy will be assessed for tumors by investigators before lymph node decongestion pretreatment. If the bridging therapy efficacy assessment indicates complete remission, subsequent lymph node decongestion and IMC001 cell product infusion will not be performed. **Lymphocyte ablation chemotherapy, also known as lymphocyte pretreatment (LD) FNC regimen.** • Cyclophosphamide 250 mg/ m^2 Intravenous infusion was administered on days 1, 2, and 3 of the lymph node dissection. • Fludarabine 25 mg/m^2 was administered intravenously on day 1 and day 2 of lymph node cleansing. • Albumin-bound paclitaxel 100 mg was administered intravenously on the second day of lymphadenopathy .

	If the subject has a history of intolerance to albumin-bound paclitaxel, the FC regimen containing fludarabine and cyclophosphamide will be used only: fludarabine 20-25 mg/m² and cyclophosphamide 500 mg/m² will be administered intravenously for two consecutive days . The subject's body surface area was calculated using Stevenson's formula: Body surface area (m2) = 0.0061 × height (cm) + 0.0128 × weight (kg) - 0.1529 **Secondary reinfusion** Researchers may consider administering the drug again to subjects who they believe could benefit from reinfusion, after discussions with the sponsor, provided that there are sufficient CAR-T cells remaining from the previous production and that the subject meets the reinfusion criteria. **Early single sampling** At the researchers' discretion, to ensure successful enrollment in the study even after disease progression, leukocyte apheresis may be performed before disease progression during first-line treatment. This advance apheresis is solely a preparatory step for potential subsequent reinfusion and does not constitute formal enrollment or the start of treatment. In this case, leukocyte apheresis must still meet the aforementioned hematological and infectious disease criteria, and the sample must be transported and stored under specified conditions. EpCAM target expression must meet the protocol's enrollment requirements in this situation.
Research Evaluation	**Security assessment** Researchers will collect all adverse events (AEs), serious adverse events (SAEs), critical illness syndromes (CRS), and ICANS events from the signing of the primary informed consent form to the subject's discharge from the study or the initiation of other anti-tumor treatments (whichever occurs first). AEs occurring during the study period include DLT, CRS, ICANS, and clinically significant laboratory test results, abnormal physical examinations, and immunogenicity results. Results during the screening period are not counted as AEs. The type, incidence, duration, and severity of adverse events should be recorded in detail, including clinically significant abnormal laboratory test results, abnormal physical examination results, and immunogenicity results. For subjects who failed the screening, or subjects who underwent apheresis/lymphatic flushing but did not receive IMC001 infusion, only new AEs, SAEs, CRSs and ICANS occurring within 28 days after the last study treatment/study procedure (such as screening, apheresis or lymphatic flushing) were collected. AEs are classified according to the National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE 5.0), but CRS and ICANS will be classified according to the 2019 ASTCT classification criteria.

Evaluation of tumor treatment efficacy

This study used RECIST 1.1 criteria to assess objective efficacy of cancer treatment, including ORR, DCR, DOR, PFS , and OS. If PR or CR was achieved, confirmation was required at least 4 weeks after the initial evaluation. Patients underwent regular imaging assessments at scheduled appointment times according to the study protocol until a confirmed PD was achieved, 2 years (96 weeks) after infusion , loss to follow-up, withdrawal of informed consent, or death (whichever occurred first).

Imaging results required for enrollment assessment can be obtained within 28 days prior to signing the informed consent form. Imaging assessment can be performed using plain MRI or CT scans with contrast enhancement; the specific sites to be examined will be determined by the investigator based on the patient's condition. Imaging assessment must be performed within 28 days prior to cell infusion therapy as the baseline for this study. If the patient received bridging therapy prior to infusion, this imaging assessment should be performed after the bridging therapy and before lymph node dissection pretreatment.

If a subject receives bridging therapy or the investigator deems the subject's condition requires reassessment, appropriate examinations may be performed, including but not limited to: imaging assessment, tumor biomarkers, complete blood count, biochemistry, and coagulation function. If a subject experiences rapid hyperprogression, the investigator must assess the risks and benefits of the subsequent trial procedures to determine whether the subject should undergo further lymph node dissection and infusion; if the subject achieves complete remission, further lymph node dissection and infusion will not be performed.

PK index

The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry. The main evaluation indicators included Cmax , Tmax , AUC_{0-28}, longest survival time and other relevant PK parameters.

PD index

The levels of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α , and IFN-γ .

Exploratory research indicators

RCL testing before and after IMC001 treatment will be conducted at baseline, at W16 and W48 after IMC001 infusion, and annually thereafter until the subject is lost to follow-up, dies, withdraws informed consent, reaches 2 years (96 weeks) after cell reinfusion, or the trial is terminated (whichever occurs first). Monitoring will also be conducted during an additional 15-year long-term follow-up. Long-term follow-up will also include monitoring of lentiviral insertion sites.

IMC001 CAR-T cell lymphocyte subsets/phenotypes before and after treatment .

	Ep CAM target expression ratio and intensity, etc. Changes and quantitative analysis of biomarkers related to tumor immune microenvironment characteristics and overall immune characteristics of the body. Changes in anti-EpCAM CAR-T anti-antibody (ADA) levels in the blood before and after IMC001 treatment;
Statistical analysis	All statistical analyses will be performed using SAS 9.4 or later. Generally, continuous variables will be described using the number of subjects, mean, median, standard deviation, minimum, and maximum; categorical and ordinal variables will be described using the frequency and percentage of each category or ordinal. Unless otherwise specified, missing values will not be included in the percentage calculation. All statistical tests will use a two-tailed test with α=0.05, and the two-tailed 95% confidence interval (CI) will be calculated. Demographic and other baseline characteristics Demographic data and other baseline characteristics will be summarized using descriptive statistics. Safety Index Analysis AEs will be coded using the latest version of the Standard Medical Terminology for Pharmaceutical Administration (MedDRA) by system organ class (SOC) and preferred term (PT). The number of subjects experiencing AEs and the incidence of AEs, as well as post-cell infusion SAEs and adverse events of particular concern, will be summarized by dose group, SOC, and PT, and a list of relevant AEs will be provided. In addition, the severity of post-cell infusion AEs (according to the NCI CTCAE5.0 classification) will also be categorized and summarized by group, SOC, and PT. CRS and ICANS will summarize and analyze the data according to severity (based on the 2019 ASTCT grading criteria). Therapeutic Indicator Analysis According to the RECIST 1.1 criteria for evaluating treatment response in solid tumors, ORR, DCR, DOR, PFS, and OS were evaluated for each dose and for all subjects treated with IMC001 over 48 weeks post-infusion. The 95% exact confidence intervals for ORR and DCR were calculated using the Clopper-Pearson method . If data permit, the median and 95% confidence intervals for OS, as well as PFS and DOR, were estimated using the Kaplan-Meier method. Cell kinetic analysis of each subject were calculated using the non-compartmental model of WinNonlin 8.2 (or later) pharmacokinetic software, including Cmax , Tmax , AUC , Clast , Tlast , and Cmax / Tmax , and blood drug concentration-time curves were plotted .

	Pharmacokinetic analysis Based on the pharmacodynamic analysis set, descriptive statistical analysis was performed on the pharmacodynamic indicators at each visit time point, and the mean, standard deviation, median, minimum, maximum, geometric mean, and geometric mean coefficient of variation were reported , and the indicator concentration-time curves were plotted . Statistical analysis of dose-response relationship Descriptive statistical analysis was performed on all indicators, including median Tmax and Cmax, as well as the survival rate and cell count of peripheral blood CAR-T cells within 12 weeks after IMC001 infusion . Parameters were analyzed separately for responders and non-responders. Descriptive statistical analysis was also performed on the dose-response relationship of cytokines, providing the median peak values of each cytokine within 4 weeks of CAR-T cell infusion, and the median time to recovery to baseline or normal range. If necessary, the differences in dose-response relationships among subjects in different dose groups will be compared.

1.2 Research Process Diagram

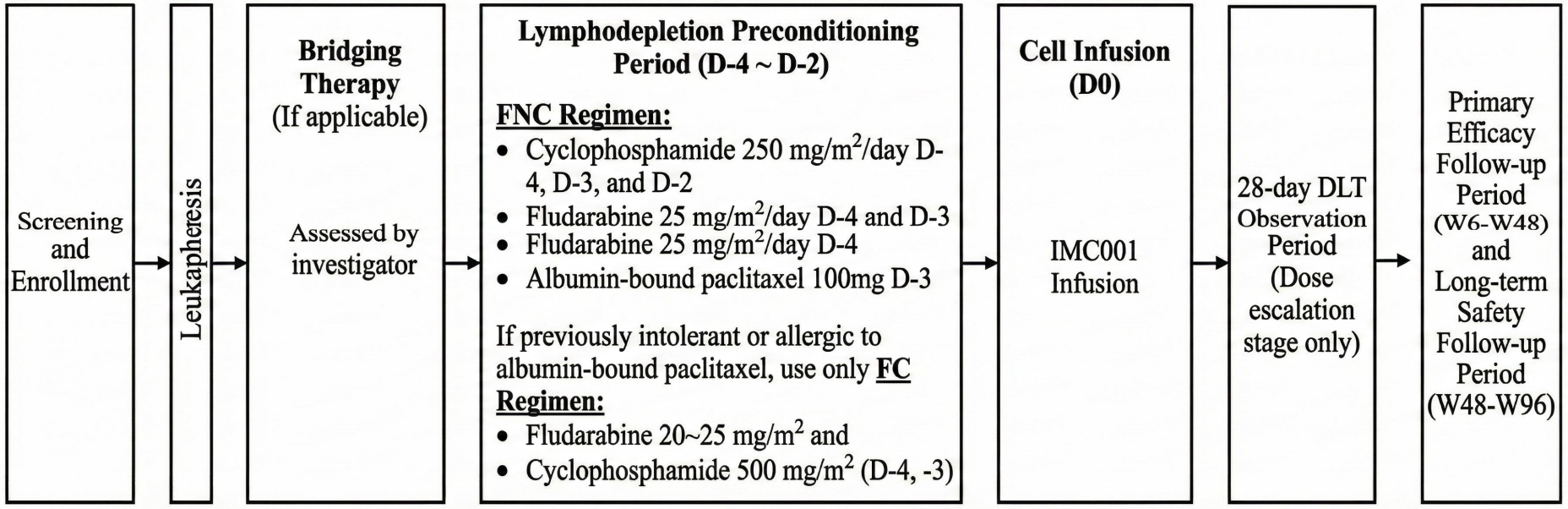


Figure 2 Study phased diagram

1.3 Research Flowchart

Table 1 Research Flowchart

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	4 days **before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
Signing the Molecular Pre-screening Informed Consent Form	X																		
Signing the Informed Consent Form		X																	
Inclusion/Exclusion Criteria		X																	
Pre-infusion assessment of lymph node dissection				X															
Demographic data	X	X																	

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	4 days **before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
History of tumor diagnosis and treatment		X																	
Tumor staging and pathology during the screening period		X																	
EpCAM detection [7]	X																		
Detection of tumor immune microenvironment characteristics, etc. [8]		X		Based on the availability of clinical samples, exploratory studies will be conducted with informed consent.															
Previous non-research disease treatment [9]		X																	
Pregnancy test [10]		X				←								→					X

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	**4 days before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
Infectious disease screening (pathogen detection)		X																	
ECOG rating		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs [11]		X		X	X	X	X	X	X	X		X	X	X	X	X	X		X
Physical examination		X			X	X	X	X	X	X		X	X	X	X	X	X		X
blood oxygen saturation		X		X	X	X	X	X	X	X		X	X	X	X	X	X		X
Height/Weight/Body Surface Area		X				X				X		X	X	X	X	X			
Blood routine		X	X		X	X	X [10]	X	X	X		X	X	X	X	X	X		X
Urinalysis		X		X		X		X	X	X		X	X	X	X	X	X		X

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	**4 days before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
Stool routine and occult blood test		X		X		X		X	X	X		X	X	X	X	X	X		X
C-reactive protein [1 and 2]		X				X		X	X	X		X	X	X	X	X	X		X
Peripheral serum ferritin [1 2]		X				X		X	X	X		X	X	X	X	X	X		X
Coagulation function [1 2]		X				X		X	X	X		X	X	X	X	X	X		X
amylase and lipase		X				X		X	X	X		X	X	X	X	X	X		X
fasting blood glucose		X																	
Tumor markers						X	X	X	X	X		X	X	X	X	X	X	X	X
CAR-T copy number [1 3]						X	X [1 4]	X	X	X	X	X	X	X	X	X	X	X	X

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	**4 days before cell infusion**	**Treatment period**							**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
CAR-T cell subsets/phenotypes [1 and 3]						X	X [1 4]	X	X	X	X	X	X	X	X	X	X	X	X
Cytokine [1 and 3]						X	X [1 4]	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity testing						X								X		X			X [1 5]
RCL detection [1 6]						X										X	X	X	X
Lentiviral genome insertion site analysis [1 7]						X										X	X	X	X
12-lead electrocardiogram		X		X		X	X	X	X	X		X	X	X	X	X	X		X
Echocardiography		X		←												→			

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	**4 days before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
Imaging examinations [1] [8]		X		←	←	←	←	←	←	←	←	←	←	←	←	←	←	X	X
Tumor assessment [1] [9]		X		X		→	→	→	→	→	→	→	→	→	→	→	→	(X)	X
Leukocyte apheresis			X																
Dredging Pretreatment Drug Administration					X														
IMC001 return							X												
Concomitant drugs/subsequent anti-tumor therapy Treatment documentation (if available)		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	(X)	X

During the research period/visit	**Molecular pre-screening period**	**Filter** [1]	**Leukocyte apheresis** [2]	**Before rinsing Assessment** [3]	**Pretreatment of shower**	**4 days before cell infusion**	**Treatment period**								**main Treatment follow-up**		**Long-term follow-up**		**Early Exit** [5]
Time point/time window	~D-43	D-42 to D- 18		Qinglin Within the first 7 days	D-7~D-2	D-1	D0	D1	D3	D7	D9	D14	D21	D28	W 6	W1 2	W1 2 ~W48 Q 6 W	W48~ W96 [6] Q12W	After the subject decided to withdraw early Within 7 days
					±1d		Cell infusion	-	±1d			±2d	±2d	±2d	+7 days	±7d	±7d	±14d	
Recording of adverse events		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	(X)	X
ICE rating							X	X	X	X		X	X	X	X	X	X	(X)	
Survival follow-up															X	X	X	X	X

1. During the screening period, subjects completed the corresponding visit examinations according to the visit schedule. Subsequent visit time windows are calculated from the cell infusion day (D0). If the time window before infusion is extended due to reasons such as CAR-T cell preparation or bridging therapy, it will not be recorded as a deviation from the protocol.
2. 7 days prior to apheresis , it can be used to assess the safety and standards of the apheresis. If the last CBC was performed more than 7 days prior to apheresis, or if the investigator determines that the subject's hemodynamics have changed, a CBC should be performed within 7 days prior to apheresis.
3. Within 7 days prior to the urine scrub pretreatment, the researchers will conduct further examinations based on the subjects' medical conditions, including but not limited to: complete blood count, blood biochemistry, urinalysis, stool routine and occult blood test, and electrocardiogram. Subjects whose condition is deemed acceptable by the researchers will undergo urine scrub pretreatment.

4. Before cell reinfusion, researchers must reassess the subjects. Only subjects meeting the criteria for cell reinfusion can receive the infusion. If a subject does not meet the criteria, reinfusion may be delayed, but the delay should not exceed 7 days . If the delay exceeds 7 days , researchers will assess whether the subject needs to undergo baseline examination and lymph node dissection again. A 14-day hospital stay is recommended from the date of cell reinfusion. Hospital stays of 15-28 days should be conducted according to local treatment guidelines. Extensions required by treatment guidelines will not be recorded as SAEs.

   Note: This study uses the results of the above examinations that are closest to the time of reinfusion as the baseline.
5. Participants who withdraw from the study early will have an exit visit within 7 days of withdrawal and before starting any new anti-tumor treatment. Participants should complete the required assessments within 7 days before withdrawal; no repeat examinations are necessary.
6. Long-term follow-up intervals were every 6 weeks for W1 2 -W48 and every 12 weeks for W48- W96 .
7. After signing the informed consent form, participants must provide a tumor tissue specimen (paraffin block or slide). If a tumor tissue specimen cannot be provided, a biopsy must be performed during the screening period to detect EpCAM expression. Sample requirements are: formalin-fixed paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable) or fresh biopsy tissue or at least 5 freshly cut, 4-5 μm thick, unstained tissue slides. If a participant cannot meet any of the above requirements for special reasons, they may participate in the screening with the sponsor's consent.
8. Provided that clinical feasibility and accessibility of biological samples are met, and after the subjects have signed informed consent, exploratory analyses can be conducted. These analyses are primarily based on paired tumor tissue samples before and after treatment to characterize the composition and dynamic changes of the tumor immune microenvironment.
9. All medications (including nutritional supplements such as vitamins, and solvents or solvents with therapeutic effects) and non-drug treatments used within 30 days prior to signing the informed consent form should be recorded.
10. Blood pregnancy tests are only applicable to women of reproductive age who are capable of having children. Urine/blood pregnancy tests may be performed during the study if deemed necessary by the researchers. Testing will be conducted during the screening period. Women of reproductive age include premenopausal women and women within 24 months of menopause. Women who are infertile are defined as: 1. Postmenopausal women (who have stopped menstruating for at least 2 years), 2. Women who have had both oophorectomies or hysterectomies removed.
11. If the subject is under cardiac monitoring on days 0 and 1 after infusion, vital signs do not need to be checked. A complete blood count is not performed before infusion on day 0; however, the researcher may perform the necessary checks after infusion if deemed necessary.
12. Subjects who develop CRS should have their C-reactive protein, peripheral blood ferritin, and coagulation function monitored daily. Subjects suspected of developing hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should have their peripheral blood ferritin and triglycerides monitored dynamically.

13. after cell reinfusion to measure CAR-T cell copy number, CAR-T cell subsets/phenotype, and cytokines until disease progression, or after two consecutive undetectable CAR copy numbers following peak detection , cell death, or other reasons for cell withdrawal (whichever occurs first) . Cytokines measured included, but were not limited to, pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ .
14. Blood samples for CAR-T copy number, CAR-T cell subsets/phenotype, and cytokines were collected on the infusion day (D0) and D1 at time windows of 30 minutes ± 5 minutes after cell reinfusion on the infusion day (D0) and 24 hours ± 30 minutes after reinfusion on D1, respectively.
15. Immunogenicity testing (ADA) for subjects who withdraw early should be repeated at a later time point (W16) if the last test at the time of withdrawal was positive . If CAR copy number is still detectable in peripheral blood 2 years after cell infusion, it should be repeated every 6 months thereafter 2 years after cell infusion. If CAR copy number is not detectable for two consecutive times after week 14 (including tests prior to week 14), or if the subject dies, withdraws informed consent, is discharged 15 years after cell infusion, or the trial is terminated (whichever occurs first), no further samples will be collected.
16. RCL testing: During the W6-W48 follow-up period, RCL sampling points are W24 and W48; during the W48- W96 follow-up period, RCL sampling points are collected annually until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell reinfusion, or the trial is terminated (whichever occurs first) .
17. Viral insertion site analysis: During the W6-W48 follow-up period, the sampling points for lentiviral insertion site analysis were W24 and W48; during the long-term follow-up period from W48 to W96 , the sampling points for lentiviral insertion site analysis were collected annually until the subject was lost to follow-up, died, withdrew informed consent, 15 years after cell reinfusion, or the trial was terminated (whichever occurs first) .
18. ① Imaging examinations include enhanced CT or MRI scans of the chest, abdomen, and pelvis. The examination sites can be determined by the researchers based on the subject's condition. ② Enhanced MRI/CT scan of the head (this examination is mandatory during the screening period and optional during the follow-up period. CT scans can be used for those with contraindications to MRI, and conventional MRI/CT scans can be performed for subjects with contrast agent allergies). ③ Imaging examinations during the screening period: imaging examinations within 28 days prior to signing the informed consent form; simultaneously, imaging examinations must be performed within 28 days prior to cell infusion as the baseline for this study. If the subject received bridging therapy before infusion, this imaging examination should be performed after the bridging therapy is completed. ④ Based on the subject's clinical signs, if it is suspected that the subject has achieved CR or that disease progression has occurred, a follow-up examination should be performed promptly. The researchers can determine whether to increase the frequency of examinations based on the actual situation.
19. Tumor assessment: The baseline assessment time point is 28 days prior to infusion, requiring imaging examinations. Infusions are performed every 6 weeks between W12 and W48, and every 12 weeks between W48 and W96 , until disease progression, other anti-tumor treatments, loss to follow-up, death, withdrawal of informed

consent (whichever occurs earlier), or withdrawal/discontinuation (within 30 days of withdrawal/discontinuation). If subjects are receiving bridging therapy, tumor assessment should be performed after the completion of bridging therapy.

2 background

2.1 Indications and target introduction

2.1.1 Epidemiology of the disease and unmet clinical needs

April 2024, the International Agency for Research on Cancer (IARC) of the World Health Organization reported the global statistics for malignant tumors in 2022. In 2022 , there were 19.965 million new cases of malignant tumors and 9.737 million deaths worldwide. The top five cancers globally were lung cancer (2.48 million, 12.4%), breast cancer in women (2.296 million, 11.5%), colorectal cancer (1.926 million, 9.6%), prostate cancer (1.467 million, 7.3%), and stomach cancer (0.968 million, 4.9%). The top five cancers causing cancer death are lung cancer (1.817 million, 18.7%), colorectal cancer (904,000 , 9.3%), liver cancer (758,000 , 7.8%), breast cancer in women (666,000 , 6.9%), and stomach cancer (660,000 , 6.8%). Based on current demographics, it is estimated that by 2050 , there will be more than 35 million new cases of malignant tumors worldwide (Zhang Xi et al., 2024). In 2024, the National Cancer Center of China released an analysis of the 2022 prevalence of malignant tumors in China: the estimated number of new cases of malignant tumors in China in 2022 was 4.8247 million, of which 2.5339 million were male and 2.2908 million were female; the overall standard incidence rate of malignant tumors was 208.58/100,000, with 212.67/100,000 for males and 208.08/100,000 for females. In 2022, the top five cancers in terms of incidence were lung cancer (1,060,600 cases), colorectal cancer (517,100 cases), thyroid cancer (466,100 cases), liver cancer (367,700 cases), and breast cancer in women (357,200 cases), accounting for 57.4% of all malignant tumors. The top five malignant tumors in terms of mortality were lung cancer (733,300 cases), liver cancer (316,500 cases), stomach cancer (260,400 cases), colorectal cancer (240,000 cases) , and esophageal cancer (187,500 cases), accounting for 67.5% of all deaths (Zheng Rongshou et al., 2024) .

EpCAM is a type I transmembrane glycoprotein that is uniformly and highly expressed on the membranes of various human epithelial tumors, including esophageal cancer, colorectal cancer, pancreatic cancer, ovarian cancer, lung cancer, gastric cancer , and breast cancer (P Went, 2018 ; Carlo P, 2012). In normal tissues, EpCAM expression is relatively lower than in tumor tissues (GEPI, cancer-pku.cn) , thus it is considered a potential therapeutic target with potential value in treating various epithelial tumors .

Triple-negative breast cancer : According to the Chinese Clinical Diagnosis and Treatment Guidelines for Advanced Triple-negative Breast Cancer (2024 Edition), triple-negative breast cancer originates from the mammary ductal epithelium and is characterized by negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). Specifically, ER and PR expression are both <1%, and HER-2 is negative. It is prone to distant metastasis to the lungs, bones, and brain. In 2022, there were 357,200 new cases of breast cancer in Chinese women, accounting for 15.6% of all female solid tumors, with triple-

negative breast cancer accounting for approximately 15%-20%. Compared to other breast cancer subtypes, triple-negative breast cancer is a highly heterogeneous disease, commonly occurring in young women. It is characterized by poor differentiation, high invasiveness, earlier onset, and a higher likelihood of recurrence and metastasis; more than one-third of triple-negative breast cancer patients will experience recurrence or distant metastasis. Recurrent or metastatic triple-negative breast cancer usually has a poor prognosis, with a 5-year survival rate of less than 15%, significantly lower than the overall 5-year survival rate of breast cancer patients (31%). The main goal of its treatment is to slow disease progression, prolong survival time, and improve patients' quality of life.

for advanced triple-negative breast cancer . For patients who have failed previous anthracycline therapy, monotherapy or combination therapy based on taxanes (such as paclitaxel, docetaxel, and albumin-bound paclitaxel) is usually the first choice. For patients who have failed both anthracycline and taxane therapy, there is currently no standard chemotherapy regimen, but monotherapy or combination chemotherapy can be considered. Immunotherapy for PD-L1-positive advanced triple-negative breast cancer can be an option for these patients, but immune checkpoint inhibitors have not yet been approved for the treatment of advanced triple-negative breast cancer in China. A large-scale Chinese study on germline mutations in breast cancer susceptibility genes showed that approximately 11% of triple-negative breast cancer patients have BRCA1/2 germline mutations. Olaparib significantly prolonged progression-free survival (PFS) compared to chemotherapy (7 months vs. 4.2 months), but olaparib is currently not approved for the treatment of advanced triple-negative breast cancer in China, limiting drug accessibility.

For second-line and later-line treatment of triple-negative breast cancer, goxatuzumab, as a Trop2 ADC, can be considered a recommended treatment option for these patients. In a study of 80 Chinese patients who received goxatuzumab monotherapy as a fourth-line treatment, the median progression-free survival (PFS) was 5.6 months (95% *CI* : 4.1 – 8.3 months), and the median overall survival (OS) was 14.7 months (95% *CI* : 10.3 – 18.3 months). For patients with advanced triple-negative breast cancer exhibiting low HER-2 expression, T-DXd is an option. Other monotherapy or combination chemotherapy regimens (including eribulin, utidelon, capecitabine, vinorelbine, gemcitabine, etc.) besides first-line treatment can also be considered as second-line and later-line treatment options. Overall efficacy remains unsatisfactory.

Gastric cancer : Gastric cancer refers to malignant tumors of epithelial origin originating in the stomach. According to the latest data from China in 2020, gastric cancer ranks third in both incidence and mortality among all malignant tumors. Globally, there are approximately 1.2 million new cases of gastric cancer each year, with China accounting for about 40% of these. Early-stage gastric cancer accounts for a very low percentage in China, only about 20%, and most cases are diagnosed at an advanced stage, with an overall 5-year survival rate of less than 50% (National Health Commission Medical Administration Bureau, 2022).

The overall strategy for treating gastric cancer is comprehensive treatment with surgery as the primary approach. For patients with no surgical chance or metastatic gastric cancer, the current consensus is to adopt comprehensive treatment with systemic drug therapy as the main approach. The "Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Primary Gastric Cancer 2022" classifies patients with advanced gastric cancer or esophagogastric junction adenocarcinoma into three categories: human epidermal growth factor receptor 2 (HER2) positive, HER2 negative, and dMMR/MS-H regardless of HER2 status, and recommends treatment regimens accordingly. For HER2 positive (IHC3+ or 2+ and FISH+) patients, the first-line treatment regimen is trastuzumab + oxaliplatin or cisplatin + fluorouracil or capecitabine or tegafur (I). For HER2-negative subjects with PD-L1 CPS ≥ 5, first-line treatment is FOLFOX/XELOX combined with nivolumab, or XELOX combined with sintilimab (I); if there is no CPS score, a two-drug combination chemotherapy regimen of oxaliplatin/cisplatin + fluorouracil (5-FU or capecitabine or tegafur) (I), or paclitaxel/docetaxel combined with fluorouracil (5-FU or capecitabine or tegafur) (I) is recommended. For dMMR/MSI-H subjects regardless of HER2 status, pembrolizumab monotherapy (2A) or PD-1 monoclonal antibody combined with chemotherapy is recommended (2B).

For second-line treatment of advanced gastric cancer, single-agent chemotherapy regimens are generally recommended. For HER2-positive and HER2-negative subjects, single-agent chemotherapy (paclitaxel/docetaxel, irinotecan) (I) or paclitaxel combined with ramucirumab (I) is recommended. For HER2-positive subjects who have not previously used trastuzumab, other second-line chemotherapy regimens besides anthracyclines can be chosen (Category 3), or participation in clinical trials is encouraged, referring to the second-line chemotherapy drug selection for HER2-negative gastric cancer. For dMMR/MS-H subjects regardless of HER2 status, envorimab (2B) or pembrolizumab monotherapy (2B) is recommended. The phase III AINBOW study showed that the median overall survival (OS) for second-line paclitaxel + ramucirumab and paclitaxel + placebo were 9.6 months and 7.4 months, respectively.

For third-line treatment of advanced gastric cancer, apatinib monotherapy (I) (HER2-positive or HER2-negative) or nivolumab monotherapy (I) are recommended; vidicetuzumab (2A) is also an option. In previous studies, drugs such as pembrolizumab (KEYNOTE-059 study) and nivolumab (ATTRACTION 2 study) demonstrated ORRs of 11.2% and 13.3%, respectively, with mPFS of approximately 1.6-2.6 months and mOS not exceeding 6 months (Charles S. Fuchs, 2019; Yoon-Koo Kang, 2017). Third-line chemotherapy for advanced gastric cancer has only been studied in small sample sizes, and its benefit is unclear (Chinese Society of Clinical Oncology Guidelines Working Committee, 2022).

Esophagogastric junction adenocarcinoma (GEJ) shares similar underlying pathogenesis and genomic alterations with gastric cancer and is often discussed as a single cancer type.

Biliary tract tumors : Biliary tract tumors mainly include cholangiocarcinoma (intrahepatic and extrahepatic cholangiocarcinoma), gallbladder cancer, and periampullary cancer, which are malignant tumors originating from the bile duct epithelium. According to data from the National Cancer Center in 2022, the incidence of biliary tract tumors in China is showing an increasing trend year by year, with cholangiocarcinoma being the most common. Many patients are diagnosed at a time when the disease is already unresectable or metastatic. The overall 5-year survival rate is less than 20%.

For locally advanced and metastatic BTC, systemic drug therapy is the primary treatment, with gemcitabine plus cisplatin being the internationally recognized first-line standard regimen (the ABC-02 study showed a median overall survival (OS) of approximately 11.7 months). For patients whose disease has progressed after the gemcitabine regimen, there is currently no globally unified second-line standard; fluorouracil-based second-line chemotherapy can be selected (such as the FOLFOX regimen, with an median OS of 6.2 months vs. 5.3 months in the ABC-06 study).

Molecular typing studies have identified approximately 10% – 15% of BTC patients with FGFR2 fusions/rearrangements and approximately 5% – 10% with IDH1 mutations. Related targeted therapies (such as Pemigatinib and Ivosidenib) have been approved in some countries for patients who have failed previous treatments, but their accessibility in China is limited. Immunotherapy (PD-1/PD-L1 inhibitors) as monotherapy or in combination with chemotherapy has also shown some efficacy, but it remains in the exploratory stage.

Ovarian cancer : Ovarian cancer is a common malignant tumor of the female reproductive system, with epithelial ovarian cancer being the most common, accounting for 85% – 90% of all ovarian cancers. According to data from the National Cancer Center of China in 2022, there are approximately 57,000 new cases of ovarian cancer and about 37,000 deaths annually, with a high proportion of advanced-stage cases. Approximately 70% of patients are diagnosed at stage III – IV, and the 5-year survival rate is less than 40%.

The standard first-line treatment for advanced ovarian cancer is combination chemotherapy based on taxanes (such as paclitaxel) and platinum (such as carboplatin) plus bevacizumab. After surgical debulking and first-line chemotherapy, maintenance therapy can be with bevacizumab or a PARP inhibitor. Approximately 15% – 20% of ovarian cancer patients carry BRCA1/2 germline mutations. PARP inhibitors (olaparib, niraparib, etc.) can significantly prolong PFS in BRCA-mutated or HRD-positive patients during maintenance therapy (SOLO-1 study showed no mPFS vs. 13.8 months). Second-line and subsequent-line treatment for relapsed or refractory ovarian cancer is based on previous platinum sensitivity, choosing a platinum-based combination regimen or monotherapy. For platinum-resistant /refractory patients, monotherapy chemotherapy (such as liposomal doxorubicin (PLD), gemcitabine, vinorelbine, topotecan, etc.) or combination therapy with targeted drugs can be chosen, but the efficacy is limited.

Colorectal cancer : Colorectal cancer is the third most common malignant tumor worldwide. In 2022, there were approximately 550,000 new cases of colorectal cancer and about 280,000 deaths in China. About 20% of these patients were diagnosed with metastatic disease at initial diagnosis, and about 50% developed distant metastases during the course of the disease. The overall 5-year survival rate is approximately 50%, while the 5-year survival rate for metastatic CRC (mCRC) patients is less than 20%.

For treatment, combination chemotherapy based on fluorouracil (5-FU or capecitabine) + oxaliplatin (FOLFOX/XELOX) or irinotecan (FOLFIRI) remains the first-line standard regimen. Bevacizumab or EGFR monoclonal antibodies (cetuximab or panitumumab) can be added depending on the RAS/BRAF mutation status. For MSI-H/dMMR patients, PD-1 inhibitors can be used (the KEYNOTE-177 study showed that pembrolizumab as first-line mPFS was 16.5 months vs. chemotherapy 8.2 months). Second-line or later-line patients can choose to switch to another platinum-based/irinotecan regimen or combine it with targeted therapy; third-line options include multi-target tyrosine kinase inhibitors such as regorafenib or fruquintinib, and significant unmet clinical needs remain.

Pancreatic cancer : Pancreatic cancer has one of the worst prognoses among malignant tumors of the digestive system, with pancreatic ductal adenocarcinoma (PDAC) being the most common, accounting for more than 90% of all pancreatic cancers. According to the 2022 Global Cancer Statistics, pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide, with a 5-year survival rate of less than 10%. China accounts for approximately 26% of global cases.

Approximately 80% of patients have lost the opportunity for radical surgical treatment at the time of diagnosis. First-line standard treatment for unresectable or metastatic pancreatic cancer includes the FOLFIRINOX regimen (mOS 11.1 months in the PRODIGE 4/ACCORD 11 study) or gemcitabine + albumin-bound paclitaxel (mOS 8.5 months vs. gemcitabine 6.7 months in the MPACT study). Second-line treatment may involve changing the mechanism of action based on the first-line regimen; a typical regimen is nanoliposome irinotecan (nal-IRI) + 5-FU/LV (NAPOLI-1), or other sequential regimens based on fluoropyrimidine/platinum. Pancreatic cancer as a whole has limited response to immune checkpoint inhibitors; only patients with the dMMR/MSI-H subtype benefit.

Gastrointestinal and pancreatic neuroendocrine tumors (NETs): These tumors originate from neuroendocrine cells in the gastrointestinal tract and pancreas. They are a group of tumors with diverse biological behaviors, slow progression, but the potential for distant metastasis. The global incidence of NETs continues to rise. While precise epidemiological data in China is limited, it is reported to account for approximately 2% – 3% of gastrointestinal tumors. Common metastatic sites for GEP-NETs are the liver and lymph nodes.

Gastrointestinal and pancreatic neuroendocrine tumors are classified into G1, G2, and G3 grades based on differentiation and the Ki-67 index. Treatment strategies depend on the grade, stage, and functional status. Surgical resection remains the first-line treatment for localized patients. For advanced or metastatic G1/G2 NETs, long-acting somatostatin analogs (SSAs, such as octreotide LAR and lanreotide) can be used to delay disease progression (PROMID study mTTP 14.3 months vs. placebo 6.0 months). For patients with disease progression, targeted therapy (such as everolimus and sunitinib) or peptide receptor radionuclide therapy (PRRT) can be considered. For G3 grade or high-proliferative-index NEC patients, platinum-based chemotherapy combined with cytotoxic chemotherapy regimens such as etoposide is recommended. Overall prognosis varies considerably; low-grade NETs can survive for many years, while high-grade NECs have a median overall survival (OS) of only about 1 year.

In summary, China has a high incidence and mortality rate of advanced solid tumors. Solid tumors that relapse or progress to the terminal stage after existing standard treatments, such as advanced gastric cancer/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors, have limited existing treatment options and efficacy, and there is a great unmet clinical need for new and effective therapies.

2.1.2 Introduction to EpCAM targets

EpCAM is a type I transmembrane glycoprotein that is uniformly and highly expressed on the membranes of various human epithelial tumors, including esophageal cancer, colorectal cancer, pancreatic cancer, ovarian cancer, lung cancer, gastric cancer, and breast cancer (P Went, 2018 ; Carlo P, 2012). In normal tissues, EpCAM expression is relatively lower than in tumor tissues (GEPI, cancer-pku.cn). In one study, EpCAM expression was not observed in any of 129 normal gastric mucosa samples, but it was observed in 77% of gastric cancers, with 56% showing moderate to high expression (Feride K, 2013). Another study showed that 100% of patients with metastatic breast cancer expressed EpCAM (Gilbert Spizzo , 2011). In normal tissues, EpCAM is thought to be confined to the basolateral aspect of epithelial cells, making it difficult for immune cells to enter EpCAM (Agnieszka M, 2016). Following malignant transformation, EpCAM expression shifts from the basal layer to uniform expression on the cell membrane surface (Agnieszka M, 2016), making it more readily acquired by CAR-T cells. Therefore, EpCAM is considered a potential therapeutic target with clinical value in cancer treatment.

There have been various attempts at drug development targeting EpCAM. To investigate the safety of EpCAM×CD3 bispecific antibodies in treatment, MarI A et al. constructed a bispecific antibody alternative molecule, MuS110, targeting mouse EpCAM. At a dose of 5 μg/Kg, it effectively cleared mouse tumors, and no significant toxicity was observed even when the dose was increased to 400 μg/mL. Therefore, bispecific antibodies targeting EpCAM have a large therapeutic window (MarI A, 2008).

In summary, although EpCAM is expressed in normal tissues, it has shown a certain therapeutic window in preclinical models and can serve as a potential target for tumor therapy.

epithelial-derived tumors, EpCAM has a certain amount of clinical research experience with drugs targeting the same target. The CD3 bispecific antibody Catumaxomab , targeting EpCAM , was approved in the EU in 2009 for the treatment of patients with malignant ascites and EpCAM-positive tumors; it can effectively prolong the time required for ascites aspiration. This product was later withdrawn from the market, but recently, it has been undergoing clinical development for multiple indications in China . For example, Lingteng 's intraperitoneal instillation of Catumaxomab for the treatment of advanced gastric cancer with peritoneal metastasis was a phase I/III study (CTR20201246); and non-muscle-invasive bladder cancer that has failed or is intolerant to BCG treatment was a phase I/II study (CTR20210616). In addition, the studies registered by Youzhiyou include a phase II study (CTR20211787) evaluating the efficacy of intraperitoneal injection of recombinant anti-EpCAM and CD3 chimeric bispecific antibody M701 combined with systemic therapy versus intraperitoneal chemotherapy combined with systemic therapy in subjects with advanced epithelial solid tumors and malignant ascites; a phase III study (CTR20240712) evaluating the efficacy of intraperitoneal infusion of M701 compared with peritoneal puncture drainage in subjects with malignant ascites caused by advanced epithelial solid tumors; and a phase I study (CTR20232278) of Tianmaiyuanhe 's recombinant anti- EpCAM -CD3 antibody injection A-337 for malignant solid tumors . All of these studies are ongoing .

EpCAM -based CAR-T drugs have been registered in hospital IIT clinical trials, such as NCT02915445 for advanced solid tumors, NCT03563326 for peritoneal metastases of gastric cancer, NCT03013712 for advanced solid tumors, and NCT02725125 for advanced gastric cancer. However, no clinical results have been reported, nor have any registration applications been submitted.

2.1.3 IMC001 Overview

IMC001 is a genetically engineered drug produced from the patient's own T cells, and is a single-person, single-batch specialty drug. IMC001 is a cell preparation cryopreserved in liquid nitrogen vapor phase; it is a white to reddish, clear to cloudy liquid, free of visible exogenous particles. Its preparation principle is as follows: PBMCs (human peripheral blood mononuclear cells) are obtained from a single blood collection of the patient's leukocytes. T cells are then sorted and activated, transduced using a lentiviral vector encoding the EpCAM antigen-antibody recognition region, and subsequently expanded and cultured to obtain CAR-T cells that recognize EpCAM .

IMC001 CAR-T cells are autologous T cells modified with EpCAM -specific chimeric antigen receptor (CAR) . EpCAM CAR is a chimeric molecule mainly composed of an extracellular recognition region, a transmembrane region, and an intracellular signaling region.

The extracellular recognition region is a humanized single-chain antibody that specifically recognizes EpCAM; the transmembrane region is the transmembrane region of CD28; and the intracellular signaling region includes the intracellular signaling regions of CD28 and CD3ζ.

The intracellular signaling domains of IMC001 include the intracellular CD28 and CD3ζ domains. Binding of the CAR extracellular domain to the target site leads to the formation of a non-classical immune synapse (Benmebarek, 2019). Furthermore, the intracellular CD3ζ and CD28 signaling domains work together to activate T cell proliferation and effector capacity. CD3ζ is a chain of the TCR/CD3 complex containing three immune receptor tyrosine activation motifs (ITAMs). When CAR-T cells bind to the target antigen, CD3ζ can activate the effector capacity of T cells to kill target cells (Benmebarek, 2019). The addition of CD28 can significantly enhance IL2 release, T cell proliferation, and the ability of CAR-T cells to resist TGF-β in the tumor microenvironment by activating Lck (Maher, 2002; Golumba-Nagy, 2018). Similar to the physiological functions of CD28, studies have shown that the CD28-CD3ζ structure can induce signaling pathways such as NF-κB, Akt, ERK, and NFAT, and has been shown to activate the PI3K signaling pathway (Stegen, 2015). Simultaneously, cytokines and chemokines secreted by CAR-T cells can further improve the tumor microenvironment, recruit and activate other anti-tumor immune cells, thereby inhibiting tumor growth (Restifo, 2012).

The IMC001 CAR molecule is composed of the sequences described above, linked together in series. Its structure is shown in Figure 3. This CAR molecule is integrated into a lentiviral vector and transduced into autologous T cells, which are then expanded in vitro to obtain IMC001 CAR-T cells.

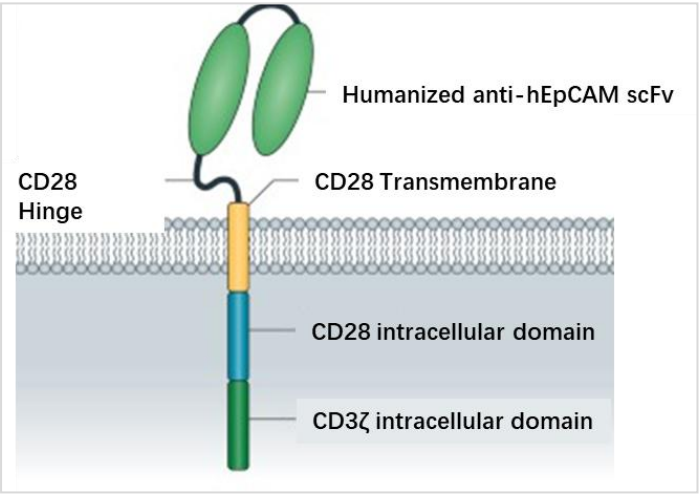


Figure 3 Schematic diagram of IMC001 CAR-T structure

Non-clinical research data on IMC001 show that the extracellular domain of the IMC001 CAR can specifically bind to EpCAM antigen and its positive cells with strong affinity; EpCAM can kill EpCAM-positive tumor cells in a dose-dependent manner without killing EpCAM-negative tumor cells; the killing ability of IMC001 target cells is positively correlated with the expression level of

EpCAM on the target cells; after stimulation by EpCAM-positive target cells, IMC001 CAR-T cells can secrete high levels of IFN-γ, TNF-α, and IL-2. In subject-derived organoid (PDO) studies, IMC001 showed significantly higher cytotoxicity against colorectal cancer PDOs in vitro than against adjacent normal colon PDOs. In vivo experiments showed that IMC001 can significantly inhibit the growth of gastric cancer tumors and triple-negative breast cancer xenografts , and no toxic reactions were observed in mice.

2.2 Summary of non-clinical studies

2.2.1 Preclinical pharmacodynamics

Non-clinical pharmacological data indicate that the extracellular binding domain of IMC001 (IMC001-scFv) specifically binds to EpCAM antigen and EpCAM-positive target cells. Human membrane proteomic array analysis shows that IMC001-scFv specifically binds to human EpCAM, but not to other human membrane proteins. In vitro pharmacodynamic studies demonstrate that IMC001 kills various EpCAM-positive tumor cells in a dose-dependent manner, while simultaneously secreting large amounts of cytokines, including IFN-γ, IL2, and TNF-α. The killing ability and cytokine release capacity of IMC001 are positively correlated with the expression level of EpCAM on target cells. Co-incubation of IMC001 with EpCAM-negative cells showed no killing effect or cytokine secretion capacity, indicating that IMC001 CAR-T has good EpCAM specificity. In vivo pharmacodynamic studies have shown that a single dose of $0.3 - 3 \times 10^{6}$ CAR-T cells/ IMC001 significantly inhibited the growth of gastric cancer cell NCI-N87 xenografts and triple-negative breast cancer cell MDA-MB-468 xenografts in a dose-dependent manner.

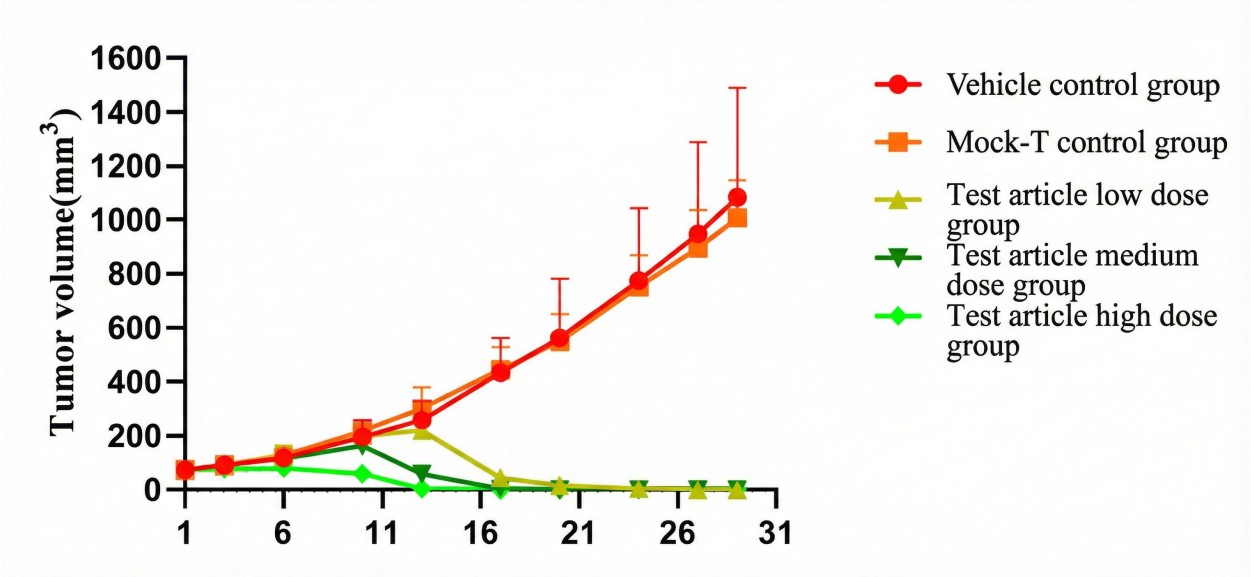


Figure 4-1 Tumor proliferation curve of NPG mouse NCI-N87 subcutaneous xenograft tumor treated with IMC001

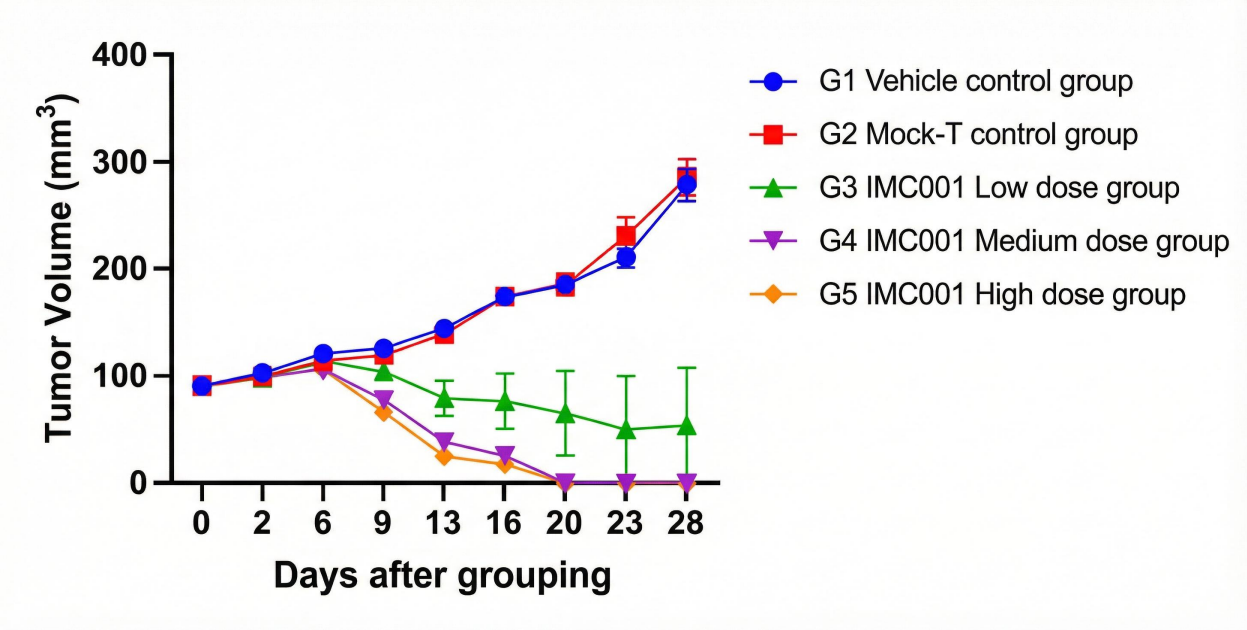


Figure 4-2 Tumor proliferation curves of subcutaneous xenograft MDA-MB-468 triple-negative breast cancer in NCG mice treated with IMC001 .

2.2.2 Pharmacokinetics/Biodistribution and Metabolism

The applicant conducted tissue distribution studies on IMC001 in tumor-bearing mice and the tissue distribution studies on the alternative molecule IMC001 -G8.8 in non-tumor-bearing mice. In tumor-bearing mice, a single administration of $3 \times {}^{10^6}$ CAR-T cells/ mouse of IMC001 resulted in the highest exposure in tumor tissue, indicating its good tumor targeting ability. IMC001 concentrations in tumor tissue and most other tissues peaked at D15 or D22 , then decreased to a low point before amplifying again to the study endpoint at D43 , where IMC001 was detected at various tissue levels . In non-tumor-bearing mice, a single administration of 3×10^6 CAR -T cells/ mouse of IMC001 -G8.8 resulted in the highest exposure in the lungs , followed by the liver and spleen. After reaching a peak in all tissues at day 8 , the number of CAR-T cells decreased. CAR-T cells expanded again at day 22, and IMC001 - G8.8 was detectable in all tissues at days 28 and 43. The widespread distribution of CAR-T cells in various tissues during the later stages of the study is attributed to GvHD caused by different cell species, which is not expected to occur in humans .

2.2.3 Preclinical safety and toxicology

1) Single-dose toxicity study

The applicant conducted a complete toxicological study on test substance I MC001 . To better identify potential target-related risks of tumor degeneration, the applicant also conducted a single-dose toxicity study on the alternative molecule I MC001-G8.8 . In tumor-bearing mice, a single

administration of 3 × 10^6 CAR-T cells/ mouse of I MC001 mainly resulted in multi-organ mononuclear cell/inflammatory cell infiltration induced by GvHD. In non-tumor-bearing mice, a single administration of 1 × 10^6 ^{CAR} -T cells/mouse of I MC001... The alternative CAR-T product IMC001 -G8.8 , which targets E pCAM in mice with 3 × 10^6 ^{CAR} -T cells/ mouse , mainly showed mild to moderate hepatocellular necrosis and abnormalities in liver function-related blood biochemical indicators in some mice in the high-dose administration group; other reactions were considered to be caused by immune responses induced by GvHD or CAR-T administration and were not toxicologically significant. During the experiment, no deaths or near-death experiences were observed in any of the IMC001 or IMC001-G8.8 injection groups; no significant abnormalities related to the test substance were observed in general condition, administration site, body weight, ophthalmological examination, respiration, behavior, or nervous system indicators in any group of animals. Based on the above results, under the conditions of this experiment, the highest non-serious toxicity dose (HNSTD) of IMC001-G8.8 in non- NPG tumor-bearing mice and IMC001 in NPG tumor -bearing mice is greater than or equal to 3 × 10^6 CAR - T cells/ mouse. Based on a dose of 2.5 g per mouse , the human equivalent dose is 1.2 × 10^8 ^{CAR} T cells/ kg body weight. The HNSTD is 120 times and 60 times the clinical starting dose (3 × 10^5 ^{CAR} T cells/ kg body weight) and the planned maximum dose (2 × 10^6 CAR T cells/ kg body weight) , respectively , which has a large safety margin .

2) Genotoxicity

IMC001 is an autologous T-cell therapy product. During its preparation, a lentiviral vector is used to stably integrate the EpCAM CAR gene into the T-cell genome . The applicant analyzed the viral insertion sites of three batches of IMC001 products produced under the IND process , using statistical indicators to measure the diversity of insertion site distribution across the genome. The Shannon index of the three samples ranged from 6.98 to 9.03, indicating that the insertion site distribution exhibited polyclonal characteristics. Most lentiviral insertion sites were located in introns and intergenic regions of the genome, consistent with the typical distribution patterns of lentiviral insertion sites. Furthermore, the distribution near repeat regions, CpG islands, and TSS sites was similar to the trend of HIV-1 insertion sites. Detected insertion sites were more biased towards high-GC regions of the genome. No insertion bias was observed for cancer-related gene exons during the lentiviral insertion process , and no clinically significant insertion sites were found. In summary, the integration site characteristics of IMC001 are similar to those of HIV and other lentiviral vectors, and there is no potential genotoxicity.

3) Carcinogenicity

ICH guidelines stipulate that treatment regimens intended for patients with advanced cancer may be exempt from reproductive toxicity and carcinogenicity studies (ICH Guidance for Industry: S9 Nonclinical Evaluation of Anticancer Pharmaceuticals, 2010). Based on an overall nonclinical

safety assessment, the applicant evaluated the in vitro tumorigenicity of this product, IMC001 , using cytokine-independent amplification assays and soft agar cloning assays .

The applicant first conducted an in vitro soft agar clonal assay on IMC001 injection solutions from three different donors to observe the colony-forming ability of the test cells after inoculation on soft agar, and to evaluate its potential for transformation and tumorigenicity in animals, providing reference information for assessing the safety of clinical use. The results showed that IMC001 injection solutions from all three donors failed to form colonies on soft agar and did not exhibit in vitro tumorigenicity.

To investigate whether IMC001 CAR-T cells possess uncontrolled expansion capabilities, we cultured IMC001 CAR-T cells from three different donors under varying conditions for extended periods , fully validating their safety . The results showed that the addition of the cytokine IL- 2 significantly improved the survival time and expansion level of IMC001 CAR-T cells. However, under all culture conditions, IMC001 CAR-T cells gradually declined and died after reaching a certain level of expansion, indicating that IMC001 CAR-T cells do not possess uncontrolled expansion capabilities, do not exhibit tumorigenicity, and demonstrate good safety .

4) In vitro hemolysis test

Given that IMC001 is an intravenous injectable, the applicant conducted an in vitro hemolysis test to support its safety for intravenous infusion. This study used an in vitro tube method to observe the effect of the test product (IMC001) on the lysis and aggregation of human erythrocytes. Based on the clinically intended maximum total viable cell concentration of 2.22×10^7 cells / mL, this study used IMC001 at a concentration of 2.5×10^7 cells/mL . The results showed that under the conditions of this study, the viable cell concentration of IMC001 injection at 2.5×10^7 cells /mL had no hemolytic or agglutinatory effect on human erythrocytes, and the in vitro hemolysis test result was negative.

5) Tissue crossover experiment

Given that EpCAM is expressed in multiple human tissues, the applicant conducted tissue cross-reactivity studies using the extracellular recognition region of I MC001 to elucidate its binding in vivo. This study will also provide data support for utilizing I MC001 - G8.8 to target mEpCAM as an alternative molecule.

The applicant first constructed the extracellular region of I MC001 into I MC001- scFv - Fc, and then expressed and purified it to obtain the fusion protein. The results showed that I MC001- scFv - Fc binds weakly to EpCAM on the cell membrane, showing only slight to mild staining on alveolar epithelial cells and fallopian tube epithelial cells. In tissues such as the bladder, breast, colon, fallopian tube (mucosal epithelium), small intestine, kidney, liver, pancreas, pituitary gland, prostate, testis, thymus, thyroid gland, cervix, and uterus, only cytoplasmic staining was observed . Further supplementary experiments revealed that I MC001- scFv - Fc showed mild to significant

cell membrane and cytoplasmic staining in tumor tissues derived from human gastric cancer cells. These results indicate that I MC001 can specifically bind to the EpCAM antigen on the tumor cell membrane, while binding weakly or not at all to the cell membranes of normal tissues. Furthermore, in the study of subject-derived organoids (PDOs), IMC001 showed a significant cytotoxic effect on colorectal cancer PDOs, while having almost no effect on adjacent normal PDOs , indicating that IMC001 may have good safety profiles during in vivo application.

2.3 Clinical summary

2.3.1 Brief Introduction to IIT Research Designs Conducted by IMC001

IMC001 has initiated two IIT studies: IMC001-CT03 (ChiCTR2100047129) and IMC001-CT04 (NCT05028933). Information on the two IIT studies is shown in Table 2 .

surface 2. Information on IIT research already conducted

Research Topic	Clinical research on the use of chimeric antigen receptor-modified autologous T cells targeting EpCAM in advanced gastric cancer.	Clinical research on the use of chimeric antigen receptor-modified autologous T cells targeting EpCAM for advanced gastrointestinal malignancies.
Research Number	IMC001-CT03	IMC001-CT04
type	IIT	IIT
main Researchers	Shanghai Changhai Hospital Gastrointestinal Surgery - Professors Luo Tianhang and Lu Zhengmao	The First Affiliated Hospital of Zhejiang University School of Medicine Department of Medical Oncology - Professor Fang Weijia
Research Objective	The safety and tolerability of IMC001 were observed and evaluated in subjects with advanced gastric cancer who received intravenous infusion therapy.	The safety and tolerability of IMC001 were observed and evaluated in subjects with advanced gastrointestinal malignancies.
Study population	Advanced gastric cancer	Advanced malignant tumors of the digestive system (gastric cancer, colorectal cancer, pancreatic cancer, liver cancer)
Sample size	12 subjects	8 subjects
Subject distribution	3×10^{5} CAR-T cells/kg 4 subjects	3×10^{5} CAR-T cells/kg 4 subjects

	1× 10 6 CAR-T cells/kg 5 subjects 3× 10 6 CAR-T cells/kg 3 subjects	1× 10 6 CAR-T cells/kg 3 subjects 3× 10 6 CAR-T cells/kg 1 case
Research Design	The multicenter, single-arm, open-label, dose-escalation clinical trial started with a dose of 3 × 10^5 CAR -T cells /kg, and then escalated according to the 3+3 dose-escalation principle, with doses increased to 3 × 10^5 · 1 × 10^6 , and 3 × 10^6 CAR-T cells /kg respectively ·	The study was a multicenter, single-arm, open-label, dose-escalation clinical trial, which was divided into two phases: IMC001 monotherapy dose escalation (phase one) and IMC001 combined with local radiofrequency/microwave ablation therapy (phase two). The initial dose for the first phase is 3 × 10^5 · CAR-T cells/kg, with dose escalation following the 3+3 dose escalation principle. Trials were performed at 3×10^5 · 1× 10^6 · and 3× 10^6 · Increasing the dose of CAR-T cells/kg. The second phase used a fixed dose of 1× 10^6 CAR-T cells/kg.
Study endpoints	Safety and tolerability 28 days after a single infusion, determining DLT and MTD	Safety and tolerability 28 days after a single infusion, determining DLT and MTD
SMC	Both studies established the same safety oversight committee composed of researchers to regularly discuss and make decisions regarding dose escalation, data safety, and research implementation.	

2.3.2 Results of IIT studies conducted by IMC001

From August 18, 2021 to April 30, 2023, enrollment for the Phase I dose-escalation portion of the CT03 and CT04 studies was completed. Eighteen subjects received IMC001 CAR-T cell infusions in CT03 (12 subjects) and CT04 (8 subjects).

The study involved escalating doses of 3 × 10^5 , 1 × 10^6 , and 3 × 10^6 CAR-T cells/kg. The distribution of participants was as follows:

- 3 × 10^5 CAR-T cells/kg (low - dose group): CT03 and CT04 each consisted of 4 subjects .
- 1 × 10^6 CAR-T cells/kg (medium-dose group): CT03 was Five subjects , CT0 4 was Three subjects .
- 3 × 10^6 CAR-T cells/kg (high-dose group): CT03 consisted of 3 subjects, and CT04 consisted of 1 subject ·

As of April 30, 2023, all enrolled subjects (12 subjects , 100.0%) withdrew from IMC001 treatment ahead of schedule.

Nine out of 12 subjects (75 %) completed the CT03 study, and six out of 8 subjects (75%) completed the CT04 study.

(1) Demographic and disease baseline characteristics

The following are the demographic and disease baseline characteristics of the participants in the IMC 001-CT03 and CT04 studies.

CT03 Study:

Of the 12 participants , 8 were male and 4 were female; the median age was 53 years ; the ECOG score was 0 (7 , 58.3 %) and ECOG score was 1 (5 , 41.7 %).

This study included 12 patients with advanced gastric cancer who expressed EpCAM, all of whom had adenocarcinoma (12/12, 100%). All patients were in advanced stages at enrollment (12/12, 100%). Regarding past treatment history, 11 patients (91.7%) had undergone tumor surgery. Most patients had received second-line systemic anti-tumor therapy (9/12, 75%), and one patient (8.3%) had received third-line therapy. At baseline, 10 patients (83.3%) had ≤2 metastases, and 2 patients (16.7%) had ≥3 metastases. Common sites of metastasis include lymph nodes (9/12, 75%), liver (3/12, 25%), abdominal cavity (4/12, 33.3%), peritoneum (4/12, 33.3%), pancreatic neck (2/12, 16.7%), and pelvic cavity (2/12, 16.7%).

CT04 Study:

All participants were male ; median age was 52 years; ECOG score was 0 (7, 87.5%) , and ECOG score was 1 (1, 12.5%) .

This study included 8 patients with advanced solid tumors expressing EpCAM, including 7 with colorectal cancer and 1 with gastric cancer; all were adenocarcinoma (8/8, 100%). All subjects were in advanced cancer stage at enrollment (8/8, 100%). The vast majority of patients had previously undergone surgical treatment for cancer (7/8, 87.5%). Regarding prior systemic therapy, 3 patients (37.5%) received second-line anti-tumor therapy, 3 patients (37.5%) received third-line therapy, and 2 patients (25%) received more than three lines of therapy. At baseline, 2 patients (25%) had ≥3 metastatic organs, and 6 patients (75%) had ≤2 metastatic organs. Common metastatic sites included the liver (6/8, 75%), lungs (5/8, 62.5%), peritoneum (3/8, 37.5%), pelvis (2/8, 25%), and lymph nodes (2/8, 25%).

(2) Safety assessment

Adverse events

TEAE is defined as any adverse event that occurs during or after CAR-T infusion, while TRAE is defined as a drug-related adverse event. Table 3 summarizes all AEs.

The incidence of TEAEs was the same for both CT03 and CT04, at 100%. The incidence of drug-related adverse events (TRAEs) was 100% and 62.5%, respectively.

In the CT03 study, the incidence of grade ≥3 TEAE and grade ≥3 TRAE was 100%; in the CT04 study, the incidence of grade ≥3 TEAE and grade ≥3 TRAE was 100% and 12.5%, respectively.

In the CT03 study, the incidence of SAEs during treatment was 30%, with no SAEs related to the study drug; in the CT04 study, the incidence of SAEs during treatment and SAEs related to the study drug were 25% and 12.5%, respectively.

In the CT03 study, two TEAEs (20%) resulted in death; no TRAEs resulted in death. The CT04 study had neither fatal TEAEs nor fatal TRAEs.

In the CT03 study, the overall incidence of CRS was 40%, with 0%, 66.7%, and 66.7% in the low, medium, and high dose groups, respectively. The CRS rate for ASTCT ≥ grade 3 was 30%, with 0%, 33.3%, and 66.7% in the low, medium, and high dose groups, respectively.

In the CT04 study, the overall incidence of CRS was 50%, with 25%, 66.7%, and 100% in the low, medium, and high dose groups, respectively. No CRS with ASTCT grade ≥3 was observed.

Table 3 Summary table of all Account Executives (SS) (N=18)

	CT03				CT04			
project	**3× 10^5/kg (N=4) Number of subjects (%)**	**1× 10^6/kg (N= 5) Number of subjects (%)**	**3× 10^6/kg (N=3) Number of subjects (%)**	**Total (N=1 2) Number of subjects (%)**	**3× 10^5/kg (N=4) Number of subjects (%)**	**1× 10^6/kg (N=3) Number of subjects (%)**	**3× 10^6/kg (N=1) Number of subjects (%)**	**Total (N=8) subjects (%)**
DLT	0	0	2 (66.7)	**2 (16.7)**	0	0	0	**0**
TEAE [1]	4 (100)	5 (100)	3 (100)	**1 2 (100)**	4 (100)	3 (100)	1 (100)	**8 (100)**
Adverse drug reactions (TRAE) [2]	4 (100)	5 (100)	3 (100)	**1 2 (100)**	2 (50.0)	2 (66.7)	1 (100)	**5 (62.5)**
CTCAE ≥ Level 3 TEAE	4 (100)	5 (100)	3 (100)	**1 2 (100)**	4 (100)	3 (100)	1 (100)	**8 (100)**
CTCAE Level 3 or higher TRAE	4 (100)	5 (100)	3 (100)	**1 2 (100)**	1 (25.0)	0	0	**1 (1 2.5)**
CRS	0	3 (60)	2 (66.7)	**5 (41.7)**	1 (25.0)	2 (66.7)	1 (100)	**4 (50.0)**
CRS with ASTCT ≥ 3 [3]	0	1 (33.3)	2 (66.7)	**3 (25)**	0	0	0	**0**
Serious adverse events during treatment (TESAE)	1 (25.0)	1 (33.3)	1 (33.3)	**3 (25)**	1 (25.0)	1 (33.3)	0	**2 (25.0)**
Research drug-related insurance (TRSAE)	0	0	0	**0 (0)**	1 (25.0)	0	0	**1 (12.5)**
The TEAE that led to the death [4]	1 (25.0)	0	1 (33.3)	**2 (16.7)**	0	0	0	**0**

TRAE that caused death	0	0	0	**0**	0	0	0	**0**

Note: (1) Percentages are calculated with the number of subjects in each group as the denominator.

(2) Treatment-related adverse events (TEAEs): adverse events that occur after the first CAR-T therapy.

(3) Adverse drug reactions (TRAEs) : adverse events during treatment that are definitely related to, possibly related to, or whose relationship to the study drug is uncertain.

(4) CRS is classified according to ASTCT, and other AEs are classified according to CTCAE.

(5) TEAEs leading to the death of the subject: TEAEs that resulted in the subject's death.

Summary of safety results

In CT03, high dose (3×10^6) CAR-T cells Two subjects of DLT occurred per kg (S0118, grade 4 immune hepatitis; S0122, grade 4 CRS (with COVID-19) and grade 4 immune-related pancreatitis); no DLT events occurred in the CT04 study.

Twenty subjects (100.0%) experienced at least one TEAE; TEAEs with an incidence of ≥20% included decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, decreased platelet count, fever, increased C-reactive protein, abdominal distension, vomiting, anemia, increased aspartate aminotransferase, increased alanine aminotransferase, cytokine release syndrome, immune-related hepatitis, interstitial lung disease, and skin changes (maculopapular rash and epidermolysis).

In the CT03 study, 12 subjects (100%) experienced ≥ Grade 3 TEAEs; ≥ Grade 3 TEAEs with an incidence of ≥20% included decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, decreased platelet count, anemia, cytokine release syndrome, immune-related hepatitis, and interstitial lung disease. In the CT04 study, 8 subjects (100%) experienced ≥ Grade 3 TEAEs; ≥ Grade 3 TEAEs with an incidence of ≥20% included decreased lymphocyte count, decreased white blood cell count, and decreased neutrophil count.

Of the 17 subjects (85 %), at least one TRAE occurred. In CT03, TRAEs with an incidence ≥20% included decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, decreased platelet count, fever, anemia, elevated C-reactive protein, cytokine release syndrome, immune-related hepatitis, and epidermal lysis. In CT04, TRAEs with an incidence ⩾20% included cytokine release syndrome and immune-related hepatitis.

In the CT03 study, 12 subjects (100%) experienced a grade ≥3 TRAE; grade ≥3 TRAEs with an incidence of ≥20% included decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, decreased platelet count, increased C-reactive protein, cytokine release syndrome, and immune-related hepatitis. In the CT04 study, 1 subject (12.5%) experienced a grade

≥3 TRAE, including immune-related hepatitis and decreased white blood cell count; there were no grade ≥3 TRAEs with an incidence of ≥20%.

As of December 10, 2024 , in the CT03 study, 11 participants (60%) died. Of these, 2 participants (20%) experienced fatal TEAEs (1 in the low-dose group, respiratory failure and disseminated intravascular coagulation; 1 in the high-dose group, infectious pneumonia), but these were considered by the investigators to be unrelated or possibly unrelated to the study drug. In the CT04 study, 6 participants (75%) died. There were no fatal TEAEs.

In the CT03 study, 3 subjects (25 %) experienced treatment-related autoimmune diseases (SAEs): 1 in the low-dose group (25%), 1 in the medium-dose group (20 %), and 1 in the high-dose group (33.3%). These resulted in TESAEs (2 subjects in the low-dose group , 1 with respiratory failure and disseminated intravascular coagulation ; 1 case in the medium-dose group , pancreatitis; and 1 case in the high-dose group , infectious pneumonia). No drug-related SAEs were reported. In the CT04 study, 2 subjects (25%) experienced TESAEs . These resulted in TESAEs (1 case in the low-dose group, autoimmune hepatitis; 1 case in the medium-dose group, bowel obstruction); 1 subject experienced a TRSAE (low-dose group, autoimmune hepatitis).

Other adverse events of concern related to drug treatment:

CRS: A total of 9 subjects (9/20 , At least one CRS occurred in 4-5% of the participants. Five participants were in CT03 and four in CT04. CRS occurred in all low-, medium-, and high-dose groups in both studies. In IMC001-CT03, one case of grade 3 CRS (S0107) occurred in the medium-dose group, and two subjects of grade 4 CRS (S0118 and S0122) occurred in the high-dose group. In CT04, the CRS subjects in all groups were mainly grade 1-2. No CRS-related SAEs were observed in either study.

Immune-related hepatitis: A total of 6 subjects (6/20 , 30 %) experienced at least one instance of immune-related liver injury. In the CT03 study, 2 subjects in the low-dose group and 2 subjects in the high-dose group experienced immune-related liver injury. In the CT04 study, 2 subjects in the low -high - dose group experienced immune-related liver injury .

In IMC001-CT03, one case of grade 2 immune-related hepatitis (S0107) and one case of grade 3 immune-related hepatitis (S0113) occurred in the medium-dose group, while one case of grade 4 immune-related hepatitis (S0118) and one case of grade 3 immune-related hepatitis (S0122) occurred in the high-dose group .

In IMC001-CT04, one case of grade 3 immune-related hepatitis (SAE) occurred in the low-dose group (S0105). One case of grade 2 immune-related hepatitis (SAE) occurred in the high-dose group (S0116).

Skin toxicity: Three subjects experienced at least one instance of drug-related skin toxicity. All three subjects occurred in the CT03 study. In the medium-dose group, one case (S0113) of

grade 1 rash occurred, and in the high-dose group, one case (S0118) of grade 2 epidermolysis and one case (S0122) of grade 2 epidermolysis and grade 2 maculopapular rash occurred. No subjects were observed in any of the dose groups in IMC001-CT04. No skin toxicity- related DLT or SAE was found in either study .

As of April 30, 2023, the high-dose regimen of this study was 3×10^{6} · CAR - T Two patients in the cells/kg group experienced DLT (digestive tract infection) and could not tolerate it; the MTD (medium dose) should be a dose lower than that of the high-dose group; however, the medium-dose group in this study had a dose of 1×10^{6} · CAR - T None of the three subjects in the cells/kg regimen developed DLT. Since the protocol did not specify a dose between the medium and high dose groups, the MTD has not yet been determined.

(3) Evaluation of therapeutic effect

The efficacy was evaluated only in two patients with advanced gastric cancer (GC) during the dose escalation phase of the CT03 study .

As of the data cutoff date (April 30, 2023), the median follow-up time was 3.3 months (range 2.2-15.9).

Overall objective response rate (ORR)

Tumor remission was observed in the 3×10^{5} CAR -T cells / kg and 1×10^{6} CAR -T cells/kg dose groups. The investigator-assessed overall response rate (ORR) was 25 % (3/12) according to RECIST 1.1 , with an ORR of 40 % (2/5) in the intermediate-dose group . The disease control rate (DCR) (DCR = CR + partial response + stable disease) was 70% . [95% CI 34.8%-95.3%]. See Table 4 for details .

Table 4 Objective response rate of the CT03 study (ORR) and disease control rate (DCR) SS (N=12)

project	3×10^{5} /kg (N=4)	1×10^{6} /kg (N= 5)	3×10^{6} /kg (N=3)	Total (N=1 2)
Best efficacy assessment				
Partial remission (PR)	1 (25.0%)	2 (40 %)	0	3 (20.0%)
Disease stable (SD)	2 (50.0 %)	2 (40 %)	2 (66.7%)	6 (58.3 %)
Disease progression (PD)	0	1 (33.3%)	0	1 (10.0%)
No assessment performed (NA)	1 (25.0%)	0	1 (25.0%)	2 (20.0%)

Objective remission rate	1/4	2/5	0/3	3/12
Objective response rate (ORR) (95% CI) [2]	4.5 % , 69.9 %	11.7 %, 76.9 %	0 %, 56.1%	4.5 %, 69.9 %
Disease control rate (CR+PR+SD)	3/4	4/5	2/3	9/12
Disease control rate (DCR) (95% CI) [3]	30.0 %, 95.4 %	37.5 %, 96.3 %	20.7 %, 93.8 %	30.0 %, 95.4 %

Note: (1) Percentages are calculated with the number of subjects in each group as the denominator.
(2) Objective response rate (ORR): The proportion of subjects who were confirmed to have a complete response (CR) or a partial response (PR).
(3) Disease control rate (DCR): The proportion of subjects who were confirmed to have CR, PR, or SD (RECIST V1.1).

Treatment duration

As of December 10 , 2024 , all enrolled subjects (12 subjects , 100.0%) had withdrawn from IMC001 treatment. See Figure 5 for details .

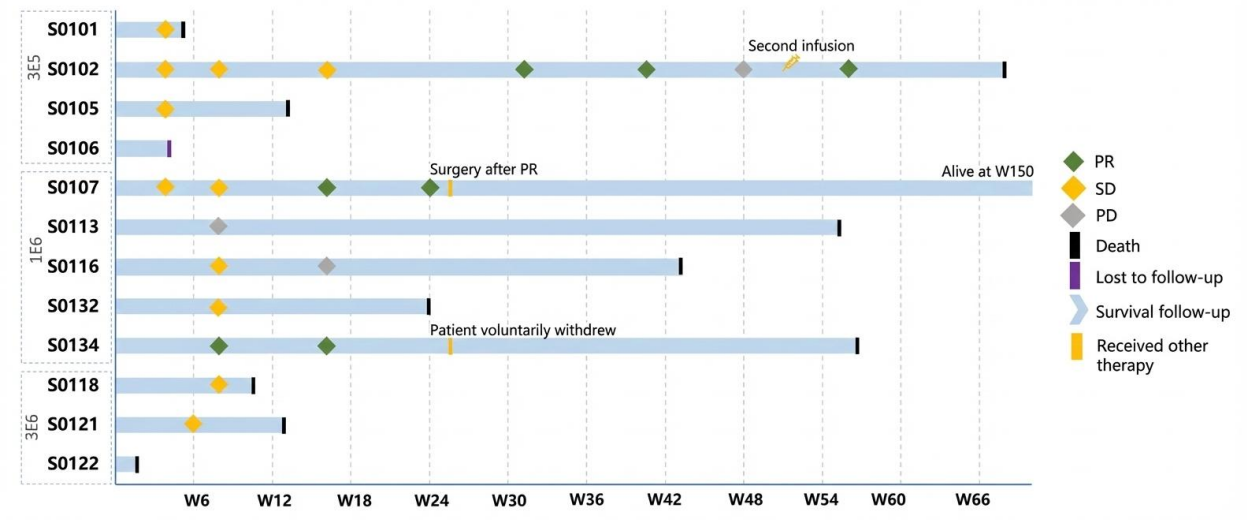


Figure 5. Swimming image of subjects evaluating tumor treatment efficacy - CT03

Details of continued treatment for subjects who achieved tumor remission in the low-dose group (S0102) and the medium-dose group (S0107) are as follows:

- 1×10^{6} ^{CAR} -T cells/kg achieved partial remission (PR) at week 16. After PR was confirmed at week 24, the lesion was converted to an operable target lesion (stomach), and the subject remained alive at week 150 post-surgery. Another subject (S0134) achieved partial remission at both week 8 and week 16 tumor assessments.
- 3×10^{5} ^{CAR} -T cells/kg achieved partial remission (PR) at week 32, which was confirmed at week 40. After a second cell infusion following a tumor progression (PD) assessment at week 48, the tumor was assessed as stable (SD) at week 8 (i.e., week 56).

Total Survival (OS) :

As of December 10, 2024 , a total of 11 participants had died (1 case was lost to follow-up in the low-dose group). The median progression-free survival (mPFS) was 4.5 months, and the median overall survival (mOS) was 13.8 months.

(4) Pharmacokinetics / Pharmacodynamics

Pharmacokinetics

The sampling points for the PK analysis were before lymph node cleansing (baseline), before reinfusion (Day 1), and on days 0 (the day of reinfusion) , 1, 3, 5, 7, 9, 11, 14, and 28 after reinfusion, as well as at 1.5, 3, 6, 9, 12, and 24 months. The dosage groups were 3×10^{5} CAR -T cells/kg for the low-dose group and 1×10^{6} CAR-T cells /kg for the medium-dose group. /kg and high-dose group 3×x10 ^{6} CAR-T cells /kg. Following a single infusion of IMC001 EpCAM CAR-T, CAR -T amplification was detectable in the peripheral blood of three different dose groups in both studies , exhibiting a distinct biphasic characteristic . In the CT03 study, the detection rate of CAR-T amplification was 90 % in subjects , with the peak amplification range from Day 7 to Day 28 ; in the CT04 study, this rate was 75 % , with the peak amplification range from Day 9 to Day 14. The duration of IMC001 CAR-T in peripheral blood is generally 4 weeks, but in some subjects, the duration can reach 12 weeks.

$_{0\text{-}28d}$ and Cmax $_{)}$ of IMC001 EpCAM CAR-T may be strongly correlated with changes in cytokines and the occurrence of DLT.

This may be very different from the situation in CAR-T therapy for hematologic malignancies. In the two subjects with PR response, there was no direct correlation between the amplification level of CAR-T and the change in cytokine levels in the peripheral blood.

Pharmacodynamics:

Serum biomarkers, including cytokines, chemokines, and other immune-related biomarkers, generally peak within 7 days after IMC001 EpCAM CAR-T infusion. The vast majority of biomarkers return to baseline levels within 4 weeks, and clinically observed CRS events are correlated with the rise in biomarkers. In the CT03 and CT04 studies, the proportions showing significant changes in cytokine levels were 60% and 38%, respectively.

Following IMC001 EpCAM CAR-T infusion, compared to grade 2 and grade 1 CRS, the occurrence of grade 3 and above CRS was associated with higher fold changes in IFN-γ, IL-6, IP-10, IL-2, and IL-10.

In one case, the response of a PR participant was unrelated to the CRS event.

The occurrence of DLT events is associated with higher levels of CRS and biomarkers IFN-γ, IL-6, IL-2 and IL-10.

No neurotoxic events were observed in any level of CRS occurrence.

Because the number of cases is currently small, it is speculated that, unlike hematologic malignancies, the occurrence of CRS in EpCAM CAR-T therapy for advanced gastric and colorectal cancer solid tumors may not be directly related to the amplification of CAR-T in peripheral blood.

2.4 Dosage selection criteria

Based on the results of the single-dose toxicity study , under the conditions of this study, the highest non-serious toxic dose (HNSTD) of IMC001-G8.8 in non-tumor-bearing NPG mice and IMC001 in tumor- bearing NPG mice was greater than or equal to 3×10^{6} CAR - T cells / mouse. Extrapolating from 2.5 g per mouse , the human equivalent dose of this dose is 1.2×10^{8} CAR T cells/ kg body weight. The HNSTD is 360 times and 60 times the clinical starting dose (3×10^{5} CAR T cells/ kg body weight) and the planned maximum dose (2×10^{6} CAR T cells/ kg body weight) , respectively , indicating a large safety margin .

In the two IIT studies conducted on IMC001 (detailed data are provided in Section 2.3.2), the low-dose group (3×10^{5}) and the medium-dose group (1×10^{6} CAR -T cells/kg) were well-tolerated, with no cases of disease-limiting lesions (DLT). Other adverse events (AEs) of grade 3 or higher potentially related to IMC001 infusion, including chronic renal failure (CRS) and abnormal liver function, returned to normal after symptomatic treatment. Two cases of DLT occurred in the high-dose group (3×10^{6} CAR -T cells/kg), meeting the protocol's criteria for discontinuing dose escalation. Regarding preliminary efficacy, the IIT IMC001-CT03 study in gastric cancer showed that one subject in each of the low-dose and medium-dose groups achieved partial response (PR) in tumor assessment after IMC001 administration . The other two subjects in the medium-dose group, although their best tumor assessment result was stable disease (SD), were still alive as of the protocol's finalization date and had survived for more than 8 months. PK study data showed that after IMC001 cell infusion, the maximum concentration of CAR+ cells in the blood circulation reached approximately 5-7 days; significant release of multiple cytokines such as IFN-γ, IL-6, IP-10, IL-2, and IL-10 was detected in the low- and medium-dose groups. Based on these results, subsequent IIT studies were also conducted in the 1×10^{6} CAR -T cells/kg dose group .

The reported study doses of EpCAM CAR-T cell therapy were all at 1×10^{6} CAR-T cells. The dosage was above /kg. For example, Wei Wang of Sichuan University used EpCAM CAR-T at a dose of 2×10^{8} - 2×10^{9} in a phase I study of advanced solid tumors (NCT02915445). Chengdu Medical College used a dose of 1-10×10^{6} EpCAM CAR+ T cells/kg in a phase I/II study of EpCAM-expressing tumors（NCT03013712）. JIn-Kun Hu of West China Hospital used intraperitoneal perfusion of EpCAM CAR-T combined with chemotherapy for advanced gastric cancer with peritoneal metastasis, but the cell dose was not disclosed (NCT03563326).

In conclusion, the starting dose of 3×10^{5} CAR-T cells/kg used in this study is reasonable. Furthermore, the dose escalation in Phase I of this study was designed to allow for the exploration of lower doses if the starting dose is not tolerated, aiming to ensure the safety of subjects while achieving initial therapeutic effects.

After completing dose escalation in the Phase I study, the recommended dose for the Phase IIa study will be determined based on the results, and further follow-up studies will be conducted at that dose.

2.5 Research basis

This is an open -label , phase I /IIa study (designated IMC001-RT02) designed to evaluate the safety and efficacy of IMC001 in patients with advanced epithelial solid tumors (including but not limited to advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors). These patients with solid tumors have limited and ineffective treatment options after standard therapy, necessitating new and effective treatments. The study comprises a phase I dose-escalation phase and a phase IIa phase. The phase I study involves dose escalation at different doses to preliminarily determine the safety of IMC001 and clarify the recommended dose for subsequent studies. The phase IIa phase expands enrollment to specific tumor types at the recommended dose to validate the efficacy and safety of IMC001.

EpCAM is uniformly and highly expressed on the membranes of various human epithelial tumors (P Went, 2018 ; Carlo P, 2012). In normal tissues, its expression is relatively lower than in tumor tissues (GEPI, cancer-pku.cn) . Drugs targeting EpCAM are already on the market, and others are in clinical development, including the EpCAM-CD3 bispecific antibody Catumaxomab, the Yuzhiyou anti-EpCAM and CD3 chimeric bispecific antibody M701, and Tianmaiyuan's recombinant anti-EpCAM-CD3 antibody A-337. Preclinical studies show that IMC001 has significantly higher killing power against organoids derived from cancer tissue than against paired organoids derived from normal tissue . In vitro killing and animal studies have shown that IMC001 has potential efficacy against triple-negative breast cancer, gastric cancer, and other solid tumors. Toxicology studies have shown no significant abnormalities of toxicological significance related to the test substance, and the safe dosage range is wide.

The IMC001-CT03 and CT04 studies showed that subjects with advanced gastric and colorectal cancer tolerated IMC001 well at low doses (3×10^5) and medium doses (1×10^6 CAR-T cells/kg), with the 1×10^6 CAR - T cells /kg dose showing better efficacy and significantly prolonged survival. In the high-dose group (3×10^6 CAR - T cells/kg), two subjects developed deep vein thrombosis (DLT) after IMC001 administration, and other related adverse events (AEs) also showed a trend of increased incidence and severity. Meanwhile, from a pharmacodynamic perspective, compared to the low-dose group, PK data showed that the proportion of subjects with detected CAR-T amplification in peripheral blood in the medium-dose group was significantly higher than that in the low-dose group, and one subject in the medium-dose group had sustained PR efficacy. Although CAR-T amplification was detected in peripheral blood in all subjects in the high-dose group, and the amplification peak was relatively high, the occurrence of DLT events made the selection of low or medium doses more consistent with the mechanism of action of CAR-T. Secondly, from a safety perspective, compared to the high-dose group, PD data showed that the overall proportion of adverse reactions in the medium-dose group was lower than that in the high-dose group, but slightly higher than that in the low-dose group. This is because the CAR-T killing process is accompanied by the release of cytokines, which may suggest that a moderate increase in biomarkers such as cytokines in peripheral blood indicates the function of CAR-T. In summary, considering both safety and efficacy, a low dose of 3×10^5 CAR-T cells/kg is recommended as the starting dose for subsequent studies .

Based on the above background and data, the IMC001 study will be conducted in subjects with solid tumors, including but not limited to advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal pancreatic neuroendocrine tumors. The study will start with a dose of 3×10^5 CAR-T cells/kg and conduct rapid titration and a 3+3 dose escalation design. Subsequently, efficacy exploration studies will be conducted at the recommended dose to further clarify the safety and efficacy of IMC001.

3 Research objectives and endpoints

Table 5. Study Objectives and Relevant Endpoints

Research Objective	Study endpoints
Phase I	
Main purpose: • Assess the safety and tolerability of IMC001 to determine the recommended Phase IIa dose (RP2D).	**Primary endpoint:** • Incidence, duration, and severity of treatment-related adverse events (TEAEs) (according to CTCAE v5.0 classification) • Incidence and severity of dose-limiting toxicities (DLTs) within 28 days after IMC001 infusion • Following IMC001 treatment, the recommended Phase II dose (RP2D) is determined based on dose-limiting toxicities (DLT) and clinical response, including potential side effects.
Secondary objective : • Evaluation of the preliminary antitumor activity of IMC001 • Evaluation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IMC001	**Secondary endpoint:** • Efficacy endpoints: Efficacy was assessed using RECIST 1.1 criteria, including objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). • PK indicators : The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry . The main evaluation indicators included Cmax , Tmax , AUC , Tlast , Clast , Cmax /Tmax , and other relevant PK parameters . • PD indicators: The levels of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ .
Phase IIa	
Main purpose : • the efficacy of IMC001 in subjects with solid tumors who have failed standard therapy.	**Primary endpoint:** • According to RECIST 1.1, the objective response rate (ORR) for tumors...
Secondary objective :	**Secondary endpoint:**

• Assess the safety and other efficacy endpoints of IMC001 • Evaluation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IMC001	• Safety: Incidence, duration, and severity of adverse events (AEs), and changes in safety assessments (such as physical examination results, laboratory tests, vital signs, and electrocardiograms). • Efficacy endpoints: Efficacy was assessed using RECIST 1.1 criteria, including disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) , and overall survival (OS). • PK indicators: The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry. The main evaluation indicators included Cmax , Tmax and AUC , Tlast , Clast , Cmax / Tmax and other relevant PK parameters. • PD indicators: The levels of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ .
I and Phase IIa	
Exploratory objectives (applicable to Phase I and IIa studies) : • Immunogenicity analysis, lentiviral genome insertion sites, and long-term follow-up of replicating lentiviruses (RCLs) were conducted. • To assess changes in cytokines before and after IMC001 administration and their correlation with efficacy and safety. • To assess the correlation between changes in biomarkers before and after IMC001 administration and efficacy and safety. • To assess changes in CAR-T cell phenotype before and after IMC001 administration.	**Exploratory endpoints: (Applicable to Phase I and IIa studies)** • Long-term follow-up of lentivirus insertion sites, replicating lentiviruses (RCLs), etc. • Before and after treatment, IMC001 CAR-T cells, lymphocyte subsets / phenotypes, etc. • EpCAM target features. • Changes and quantitative analysis of biomarkers related to tumor immune microenvironment characteristics and overall immune characteristics of the body. • Immunogenicity: Changes in anti- EpCAM CAR-T antibodies (ADA) in the blood before and after IMC001 treatment .

• To assess the correlation between changes in the tumor microenvironment of tumor tissue samples before and after IMC001 administration and their efficacy and safety. • Explore the correlation between the above-mentioned and other relevant biomarkers and efficacy and safety.	

4 Research Design

4.1 Overall research design

This is an open -label phase I /IIa study designed to evaluate the safety and efficacy of IMC001 in patients with advanced epithelial solid tumors (including but not limited to patients with advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors). The study includes a phase I dose-escalation phase and a phase IIa efficacy exploration and confirmation phase . See study design (Figure 6).

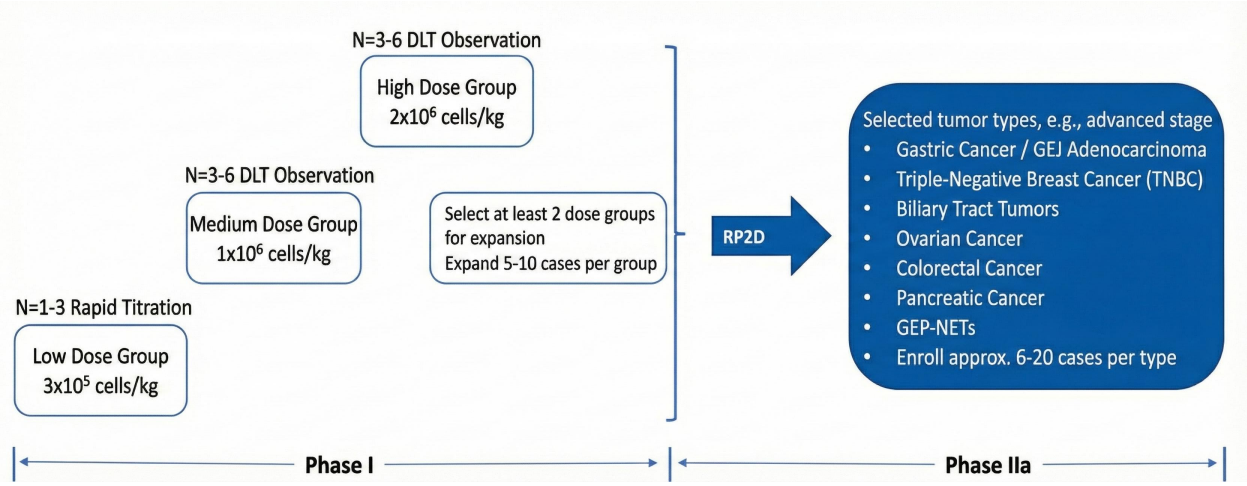


Figure 6. Schematic diagram of the IMC001-RT02 I/IIa study design

In the Phase I dose-escalation phase of this study, approximately 7 – 15 subjects with advanced epithelial solid tumors will be recruited to evaluate the safety and tolerability of autologous IMC001 treatment. DLT (digestive-thickness assessment) will be performed on subjects in each cohort within 28 days after IMC001 infusion; the definition of DLT is detailed below. The expansion phase will select at least two dose groups, each recruiting 5 – 10 subjects (in conjunction with the escalation phase, expanding each dose group to approximately 10 subjects), to determine the recommended RP2D dose for progression to Phase IIa.

The starting dose is set at 3×10^5 CAR-T cells/kg. If the starting dose is assessed as safe and tolerable, higher dose groups will be explored. If the starting dose is not tolerated, lower doses may be explored.

The Safety Monitoring Committee (SMC) will comprehensively evaluate all available data, including the ongoing IMC001 study, and make recommendations for subsequent studies. Based on the completed Phase I dose-escalation DLT assessment and all available safety, pharmacokinetic/pharmacodynamic (PK/PD) and efficacy data, the SMC will assess the overall benefit/risk to determine the RP2D, allowing the study to proceed to Phase IIa.

4.1.1 Phase I dose escalation

In the Phase I dose-escalation phase of this study, approximately 7 – 15 subjects with advanced epithelial solid tumors will be recruited to evaluate the safety and tolerability of autologous IMC001 treatment. In the expansion phase, at least two dose groups will be selected, each recruiting 5 – 10 subjects . Combined with the subjects from the escalation phase, each dose group will be expanded to approximately 10 subjects to determine the recommended RP2D dose for progression to Phase IIa. DLT assessment will be performed on subjects in each cohort within 28 days of IMC001 infusion.

Dosage escalation design: This study employed accelerated titration (ATD) combined with a 3+3 design for dose escalation.

Starting dose level (3×10^5 CAR -T cells/kg)

1. Entry method and rhythm

The sentinel + staggered ATD approach was adopted: one sentinel subject was enrolled first ; after a safety review was completed ⩾28 days from the date of infusion, a second subject could be considered for enrollment ; the second and third subjects were staggered by at least 72 hours.

The maximum number of patients enrolled in this dose group is 3 (maximum total number of ATD samples = 3).

2. / Cessation Determination During ATD (Applicable Only to This Dosage)

DLT is observed in enrolled ATD subjects and no "significant toxicity" as defined in the protocol (see below) occurs, the dose group can be terminated directly after the minimum observation requirement is met in the first or second case , and the next dose level can be started without having to complete the count to 3 in the dose group .

Complete the observation criteria: If a single case of "significant toxicity" (not reaching DLT) occurs, the dose group can be expanded to a maximum of 3 subjects to complete signal confirmation; if no DLT is found after expansion and no clustering risk is observed, the dose group can be terminated and the next dose can be started. "Significant toxicity" is defined as a treatment-related adverse event (TRAE) below the DLT threshold, but sufficient to raise safety concerns and affect dose escalation decisions. It must be confirmed jointly by the investigator, medical monitor, and SMC before it can be identified.

Significant toxicity includes the following situations:

- Persistent or recurrent grade 2 or higher unintended toxicity, which, although not reaching the DLT threshold, still affects the overall tolerability of the subject or delays subsequent dosing despite adequate supportive care;

- Rapidly progressing or worsening toxic reactions, even if they do not meet the definition of DLT , suggest a potential serious safety hazard (such as progressive worsening of CRS or ICANS).
- Events requiring clinical intervention and having a significant impact on exposure to the investigational drug, such as the need to delay or reduce subsequent treatment for safety reasons;
- treatment-related toxicities that researchers and medical monitors deem to be of safety concern and require submission to the SMC for discussion.

Stop / Safety Review Criteria: If any DLT occurs in an ATD subject , do not proceed to the 3+3 escalation in the current dose group; immediately halt escalation and convene a Safety Review Committee (SMC) meeting (composed of the sponsor, clinical experts, clinical pharmacology experts, and statisticians). The review will determine whether to: a) adjust the treatment (e.g., adjust the lowest dose cohort, administer prophylactic medication, or provide inpatient monitoring) and maintain the established "next dose group starting 3+3 "; or b) start a lower dose for ATD re-exploration; or c) terminate the escalation / revision protocol.

Subsequent dose levels ($1 \times 10^{6\ CAR}$ -T cells/kg and $2 \times 10^{6\ CAR}$ -T cells/kg)

The classic 3+3 design was adopted. The specific rules are as follows: At each dose level, 3 subjects were initially enrolled. If 0/3 subjects experienced dose-limiting toxicity (DLT), the next dose level could be advanced; if 1/3 subjects experienced DLT , 3 more subjects were enrolled at the same dose level (i.e., expanded to 6 subjects); if 6 subjects... If $\leqslant$ 1 case shows DLT , the next dose level can be advanced; if in the initial 3 subjects... $\geqslant$ 2 subjects had DLT , or 6 subjects after expansion If DLT occurs in $\geqslant$ 2 subjects , the dose level is considered to be non-tolerated , and escalation is terminated. Dose reduction should be considered if necessary. Furthermore, if DLT occurs in the first 2 subjects at any dose level , there is no need to enroll a third subject; the dose level is directly deemed to be intolerant, and further enrollment at that dose level is terminated.

For any other exploratory dose (if applicable), the initial sample size is set at 3–6 subjects, and the same criteria for tolerability assessment as for the starting dose are used.

To ensure the safety of participants, a sentinel group is established during dose escalation. At each new dose level, the first participant will serve as the sentinel subject. Sentinel subjects must complete at least 28 days of safety monitoring after infusion. Subsequent participants can only be enrolled in that dose group after investigators and medical monitors confirm that there are no unacceptable safety risks.

Each dose level requires a 28- day DLT observation period, followed by review by the Safety Oversight Committee before a decision can be made on whether to proceed to the next dose level.

For any other exploratory dose (if applicable), the initial sample size is set at 3 – 6 subjects, and the same criteria for tolerability assessment as for the starting dose are used.

Based on DLT monitoring results, two to three dose levels will be selected for expansion, with five to ten subjects planned for each expansion cohort, to further evaluate safety and preliminary efficacy and determine the recommended dose for entering Phase IIa (RP2D).

The Safety Monitoring Committee (SMC) will comprehensively evaluate all available data, including the ongoing IMC001 study, and make recommendations for subsequent studies. Based on the safety results of completed dose escalation studies and all available safety, pharmacokinetic/pharmacodynamic (PK/PD) and efficacy data, the SMC will assess the overall benefit/risk to determine the RP2D, at which point the study can proceed to Phase IIa.

Please refer to the dose escalation guidance in section 6.2.1 for details.

4.1.2 IIa efficacy exploration

Once the RP2D is determined, approximately 6-20 subjects will be initially enrolled at this dose for each selected tumor type to further explore the efficacy and safety of autologous IMC001 for this indication. Subsequently, the protocol may be revised based on statistical hypotheses and regulatory requirements to continue enrolling subjects in the selected tumor types to further validate the efficacy and safety in specific tumor types (such as patients with advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors).

Treatment period

Each participant in this study followed the same study treatment plan and operational requirements (see Chapter 7 for details). Each participant will experience the following phases:

- Screening period
- Leukocyte apheresis
- Bridging therapy (if applicable)
- Leachate pretreatment (LD) period
- Treatment period
- 16-week primary follow-up period
- Follow-up period

4.2 Sample size

I dose-escalation phase of this study , approximately 7-15 participants with advanced epithelial solid tumors will be recruited. The expansion phase will select at least two dose groups, recruiting 5-10 participants per group (expanding each dose group to approximately 10 participants in conjunction with the dose-escalation phase). Phase IIa will enroll approximately 6-20 participants per tumor type. Further expansion of enrollment within the selected tumor types is possible in subsequent Phase IIa phases, with the sample size adjusted based on statistical hypotheses and regulatory requirements.

4.3 Research Exit

Participants may withdraw from the study or retract their informed consent at any time at their own discretion . Participants who do not complete the study protocol (including cell reinfusion and subsequent evaluation) are considered to have withdrawn from the study early. The reason for withdrawal must be recorded in the EDC and kept in accordance with GCP requirements for the specified time.

Reasons for participants withdrawing from the study include:

1) The subject died.
2) Subjects were lost to follow-up.
3) The participant requested to withdraw from the study.
4) Projects terminated upon the request of the sponsor, principal investigator, ethics committee, or regulatory body.

4.4 Research terminated

If researchers, sponsors, or monitors become aware that certain conditions or events could endanger participants if the study continues, the study may be terminated after discussion among the relevant personnel.

Early termination of a study may be due to, but is not limited to, the following reasons:

- Unexpected, significant, or unacceptable risks to enrolled subjects
- The sponsor decides to suspend or halt drug development.

5 Study population

Phase I dose escalation phase: Subjects with advanced epithelial solid tumors who have failed standard therapy , including but not limited to subjects with advanced gastric/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors .

Stage IIa: Subjects with specific types of epithelial solid tumors, including but not limited to those with advanced gastric / esophageal junction adenocarcinoma who have failed or are intolerant of at least two lines of standard therapy (subjects who have failed or are intolerant of first-line three-drug combination therapy may also be enrolled after thorough investigator evaluation), and those with triple-negative breast cancer who have failed at least two lines of standard systemic therapy (all subjects must have previously received taxane therapy) . Other subjects with epithelial solid tumors who have failed or are intolerant of standard therapy.

5.1 Selection criteria

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

1) Willing and able to provide a signed and dated informed consent form before conducting any research-related procedures, and willing and able to comply with all research procedures.
2) Applicants must be 18 years of age or older and 75 years of age or younger; both male and female applicants are welcome.
3) histologically or cytologically confirmed locally advanced / metastatic epithelial solid tumors, including but not limited to advanced gastric cancer/gastroesophageal junction adenocarcinoma, triple-negative breast cancer, biliary tract tumors, ovarian cancer, colorectal cancer, pancreatic cancer, and gastrointestinal neuroendocrine tumors;
4) Disease progression or intolerance to standard systemic therapy, including:

   • Gastric cancer and gastroesophageal junction adenocarcinoma that have failed or are intolerant of at least two lines of standard systemic therapy. Those who have failed or are intolerant of first-line three-drug combination therapy may also be enrolled after thorough investigator evaluation.
   • Triple-negative breast cancer: Subjects with unresectable locally advanced or metastatic triple-negative breast cancer who have failed at least two lines of standard systemic therapy. All subjects must have previously received taxane therapy, regardless of the stage of disease at the time of treatment;
   • Other subjects with epithelial solid tumors who have failed or are intolerant of standard treatment.

5) Tumor tissue samples (primary or metastatic, archived or newly collected) from the expected subjects, tested by the central laboratory, are EpCAM histologically positive (defined as tumor cell positivity ≥10% and staining intensity ≥1+).

6) The expected survival period of the subjects is ≥12 weeks.

7) According to RECIST 1.1 criteria, there should be at least one stably measurable target lesion (with the largest lesion being ≤ 4 cm). Subjects with evaluable lesions (non-measurable lesions) can be admitted in the 3×10^5 CAR-T cells/kg dose group.

8) ECOG performance status score 0-1 .

9) The subject has adequate organ and bone marrow function. Laboratory screening must meet the following criteria: all laboratory test results should be within the stable ranges outlined below, and there should be no ongoing supportive treatment. If any laboratory test result is abnormal according to the following criteria, a repeat test may be performed within one week. If the test results still do not meet the following criteria, the subject's screening has failed.

   a) Blood tests [No intensive blood transfusions (≥ 2 times within 1 week), platelet transfusions, or cell growth factor injections (excluding recombinant erythropoietin) within 7 days prior to the test]: Neutrophil count (ANC) ≥ 1.5×10^9 / L ; Platelet count (PLT) ≥ 100×10^9 / L ; Hemoglobin level (Hb) ≥ 9.0 g/dL ; lymphocyte count (ALC) ≥ 0.5×10^9 /L ;

   b) Liver function: Alanine aminotransferase (ALT) ≤ 2.5×ULN , aspartate aminotransferase (AST) ≤ 2.5×ULN , serum total bilirubin (TB) ≤ 2×ULN ; for subjects with liver metastases, AST and ALT < 5×ULN ;

   c) Renal function: Serum creatinine ≤ 1.5×ULN ; if serum creatinine > 1.5×ULN , creatinine clearance rate > 50 mL/min (according to the Cockcroft-Gault formula); qualitative urine protein ≤ 1+ ; if qualitative urine protein ≥ 2+ , a 24-hour urine protein quantification test is required (if the 24-hour urine protein quantification test is <1g , it is acceptable).

   d) Amylase and lipase ≤ 1.5×ULN ; alkaline phosphatase (ALP) ≤ 2.5×ULN , and for subjects with bone metastases, ALP < 5×ULN ;

   e) Coagulation function: Activated partial thromboplastin time ≤ 1.5 ULN, prothrombin time ≤ 1.5 × ULN.

10) All toxicities resulting from prior antitumor therapy were mitigated to grade 0–1 (according to NCI CTCAE version 5.0) or to a level acceptable to the inclusion criteria. Other toxicities ,

such as alopecia and vitiligo , which the investigators deemed not to pose a safety risk to the subjects, were excluded.

11) Reproductive status: Female subjects of reproductive age or male subjects whose sexual partners are women of reproductive age, who are willing to use medically approved and highly effective contraceptive methods, such as intrauterine devices or condoms, from the time they sign the informed consent form until 12 months after cell infusion (women of reproductive age include premenopausal women and women within 24 months after menopause) .

5.2 Exclusion criteria

Subjects must not meet any of the following conditions:

1) Pregnant and breastfeeding women.

2) for human immunodeficiency virus (HIV) antibodies; hepatitis B virus infection (if the subject is positive for hepatitis B surface antigen, regardless of whether the core antibody is negative or positive, they can be enrolled if the viral DNA load is negative, and prophylactic antiviral treatment should be considered); acute or chronic active hepatitis C (positive for HCV antibodies); positive for syphilis antibodies; Epstein-Barr virus (EBV) infection (positive for IgM or known EBV infection); cytomegalovirus (CMV) infection (positive for IgM); positive for human T - lymphotropic virus (HTLV). The results of the above pathogen tests are subject to the results of the central laboratory.

3) Severe infections that are in an active phase or poorly controlled clinically.

4) The patients had uncontrollable pleural effusion, pericardial effusion, and ascites before enrollment.

5) Extensive or diffuse lung metastases, extensive or diffuse liver metastases, extensive or diffuse bone metastases.

6) Subjects with intestinal obstruction or obstructive jaundice who are deemed unsuitable for participation in this trial by the researchers.

7) Blood oxygen saturation $\leqslant$95% without oxygen supplementation.

8) Patients with other serious lung diseases that may limit their participation in this study, such as pulmonary embolism, chronic obstructive pulmonary disease, symptomatic or poorly controlled interstitial lung disease, or clinically significant abnormalities in pulmonary function tests.

9) Subjects with a known history or current hepatic encephalopathy requiring treatment; subjects with a current or history of central nervous system disorders, such as seizures, cerebral ischemia / hemorrhagic disease, dementia, cerebellar disease, or any autoimmune disease involving the central nervous system.

10) Central nervous system metastasis or meningeal metastasis.

11) Currently, patients have unstable heart disease requiring treatment or heart disease that cannot be controlled by treatment, or hypertension that is poorly controlled according to investigators (defined as systolic blood pressure ⩾160 mmHg and / or diastolic blood pressure > 100 mmHg after standard antihypertensive drug treatment); or diabetes that is still poorly controlled with standard treatment (fasting blood glucose ⩾10.2 mmol/L).

12) 6 months prior to cell infusion :

a) Left ventricular ejection fraction (LVEF) < 50% ;

b) History of myocardial infarction within the past year; or unstable angina; or history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); or use of a pacemaker;

c) Resting electrocardiogram examination: QTc > 450ms (male) or QTc > 470ms (female);

d) An electrocardiogram at rest reveals clinically significant abnormalities (such as abnormalities in heart rate, conduction, morphological characteristics, etc.) or complete left bundle branch block or third-degree atrioventricular block or PR interval > 250ms .

13) Evidence of a significant coagulation disorder or other obvious risk of bleeding, including:

a) Abnormal coagulation function that is clinically significant;

b) History of intracranial hemorrhage or spinal cord hemorrhage;

c) Tumor lesions that invade major blood vessels and pose a significant risk of bleeding;

d) Subjects who currently have unstable or active ulcers or active gastrointestinal bleeding;

e) An embolic event occurred within 6 months prior to cell reinfusion ;

f) Within one month prior to cell reinfusion , there has been clinically significant hemoptysis or obvious bleeding from tumor lesions;

g) Had a major injury or major surgery within one month prior to enrollment ;

h) The presence of any bleeding disorder, such as hemophilia, von Willebrand disease, etc.;

i) Within 2 weeks prior to cell reinfusion , the patient has received anticoagulation therapy for therapeutic purposes (excluding low molecular weight heparin).

j) Subjects are receiving routine anticoagulation therapy (such as warfarin or heparin). Subjects require long-term antiplatelet therapy (aspirin > 300 mg/ day; clopidogrel > 75 mg/ day); dipyridamole, ticlopidine, or cilostazol, etc.

14) has received systemic steroids equivalent to > 15 mg/ day of prednisone for more than 3 days within 2 weeks prior to apheresis , excluding inhaled steroids.

15) Subjects requiring systemic treatment with corticosteroids or other immunosuppressants during treatment. Subjects with any active autoimmune disease, or a history of autoimmune disease with anticipated relapse (including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, and asthma requiring medical intervention with bronchodilators). Exceptions include: type 1 diabetes; skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis); alopecia; hypothyroidism requiring only hormone replacement therapy; asthma that was completely remitted in childhood and requires no intervention in adulthood; or other conditions not expected to relapse in the absence of external triggers.

16) Subjects with a prior or concurrent history of other malignant tumors, except in the following circumstances:

a) Basal cell or squamous cell carcinoma that has undergone adequate treatment (sufficient wound healing is required before enrollment in the study).

b) Cervical cancer or breast cancer in situ, cured and with no signs of recurrence for at least 3 years prior to the study;

c) The primary malignant tumor has been completely removed and in complete remission for $\geqslant$ 5 years.

d) The concurrent malignant tumor was an epithelial tumor that expressed EpCAM.

17) Subjects who have previously received other gene therapies, including but not limited to CAR-T therapy and TCR-T therapy.

18) The following treatments or medications were received before cell reinfusion: chemotherapy, targeted therapy, biotherapy, endocrine therapy, immunotherapy, or other anti-tumor treatments (excluding treatments that meet the protocol requirements before reinfusion, such as lymph node pretreatment and bridging therapy); less than 28 days or less than 5 half-lives since the first infusion treatment in this study (whichever is shorter); or traditional Chinese medicine treatment with anti-tumor indications received within 2 weeks before cell reinfusion .

19) There is a history of other severe allergies, such as anaphylactic shock.

20) Subjects with severe mental disorders.

21) Subjects who develop new cardiac arrhythmias, including but not limited to arrhythmias that cannot be controlled by medication; hypotension requiring vasopressors; or bacterial, fungal, or viral infections requiring intravenous antibiotics. Subjects receiving antibiotics to prevent infection may continue to participate in the trial at the investigator's discretion .

22) The patient had participated in other interventional clinical studies and used investigational drugs within one month prior to the planned infusion of IMC001 .

23) 4 weeks prior to the planned single-donor administration or who are scheduled to receive a live attenuated vaccine during the study.

24) Subjects with any other concurrent serious and / or uncontrolled medical conditions that the investigators deem unsuitable for participation in this trial.

25) Researchers assessed that participants were unable or unwilling to comply with the requirements of the research protocol .

5.3 Pre-collection assessment

Subjects who pass the screening tests can receive leukocyte apheresis.

Seven days prior to apheresis, researchers must conduct relevant examinations (if the screening examination is within 7 days of apheresis, no further examination is required unless the researcher assesses that there is a clear reason that could cause a change in the test values during this period). Patients must be reassessed, and subjects must meet the following criteria: neutrophils $\geqslant 1.5 \times 10^9$ / L; platelet count (PLT) $\geqslant 75 \times 10^9$ / L; hemoglobin (Hb) $\geqslant$ 8.0 g/dL; lymphocyte count (LYM) $\geqslant 0.5 \times 10^9$ / L.

5.4 Evaluation criteria for rinsing pretreatment

If a subject receives bridging therapy after leukapheresis, relevant baseline testing must be performed again after bridging therapy, and the subject must be assessed by the investigator as having not achieved complete remission (CR).

If, before the urine test and 3 days before IMC001 infusion, the investigator determines that a subject has a significant abnormality (such as a new arrhythmia, including but not limited to arrhythmias that cannot be controlled by medication; hypotension requiring vasopressors; bacterial, fungal, or viral infection requiring intravenous antibiotics, and the investigator determines that the subject is unsuitable for this trial; subjects using antibiotics to prevent infection may continue to participate in the trial as determined by the investigator); or the investigator determines that the subject has experienced rapid disease progression relative to the screening time; or the investigator assesses that the subject has significant organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney dysfunction, pulmonary edema, severe lung infection, brain metastases, etc.); and the investigator determines that the subject is unsuitable for subsequent trial procedures, then urine test should not be continued or should be delayed, and infusion should not be performed or should be delayed.

If cell infusion is delayed for any reason beyond 7 days after pre-treatment with hysterosalpingography, infusion is not possible or may require further hysterosalpingography followed by a delayed infusion.

Before initiating lymph node pretreatment and IMC001 infusion, researchers will ensure that cell infusion is safe. Subjects must meet the following criteria prior to lymph node pretreatment:

1) Pretreatment with urinary tract infection should be completed within 5 days prior to cell infusion.
2) No new arrhythmias were reported, including but not limited to arrhythmias that could not be controlled by medication.
3) No cases of hypotension requiring vasopressors were observed.
4) No bacterial, fungal, or viral infections requiring intravenous antibiotics were observed prior to the pretreatment of the scrub irrigated area.
5) There were no other circumstances, in the researchers' judgment, where the subjects were unsuitable for pretreatment with a urinary tract infection.

5.5 IMC001 pre-infusion evaluation criteria

Prior to IMC001 cell infusion, subjects must meet the following criteria:

1) It must meet the standards for pretreatment of shower water.
2) Blood oxygen saturation (via fingertip pulse oximeter) ≥95%, no need for supplemental oxygen.
3) the left ventricular ejection fraction (LVEF) was ≥50% within 6 months prior to cell infusion.
4) Researchers determined there was no serious active infection.
5) Negative pregnancy test in women of childbearing age
6) According to the researchers' assessment, there were no other circumstances that would make the subject unsuitable for IMC001 infusion.

Once the above criteria are met, the subject may continue IMC001 infusion. If the IMC001 infusion is delayed by more than 2 weeks, the pretreatment with urinary tract infection should be repeated (see Section 7.5).

6 Research on treatment

6.1 Dosing regimen

surface 6 Dosage and administration regimen

Research drugs	IMC001: Chimeric antigen receptor-modified autologous T cells targeting EpCAM
pharmaceutical preparations	IMC001 (EpCAM CAR-T cells) is formulated according to the following prescription, aliquoted into one or more packaging bags for cryopreservation, and each infusion

	package contains: • EpCAM CAR-T cells • 0.9% Sodium Chloride Injection • Human serum albumin • CS10 cryopreservation solution
Dosage form	cell suspension
route of administration	Intravenous infusion
dose *	3×10^5 CAR-T cells/kg , (1 bag) 1×10^6 CAR-T cells/kg , (1 bag) 2×10^6 CAR-T cells/kg , (2 bags)
Dosage frequency	Single cell infusion #

Note: *The permissible dosage range is 3×10^5 CAR -T cells/kg to 2×10^6 CAR -T cells/kg. The final dosage should also take into account the actual number of CAR-T cells produced and record the actual number of cells infused.

#If researchers determine that a subject could benefit from reinfusion, they may consider administering the drug again after discussing with the sponsor, provided that there are sufficient CAR-T cells remaining from the previous production and the subject meets the reinfusion criteria.

Dosage instructions :

Qualified subjects received IMC001 cell infusion after urinary tract cleansing pretreatment.

1) Preventive medication: 30 to 60 minutes before IMC001 infusion, administer 650 mg of acetaminophen orally and 12.5 mg of diphenhydramine intravenously (or 25 to 50 mg orally).

2) Transportation: IMC001 cells are stored and transported in gaseous liquid nitrogen and delivered to the clinical research center in gaseous liquid nitrogen perfusion at -150°C or below.

3) Remelting: Remelt according to the standard operating procedure (SOP) or product manual.

4) Cell infusion: Infuse according to the product manual. If the outer packaging containing IMC001 is damaged or leaked, but the inner packaging bag is carefully inspected and the cells are confirmed to be undamaged, infusion may still proceed. If the cell infusion bag is damaged, it should not be reinfused and should be disposed of.

5) Emergency equipment (such as at least two doses of tocilizumab) should be readily available during cell infusion to address severe allergic reactions, severe hypotension, or other adverse events. Vital signs (temperature, respiratory rate, heart rate, blood pressure) should be measured 15 ± 3 minutes before infusion, at the start of infusion, within one hour after infusion (every 15 ± 3 minutes), and thereafter every 30 minutes until 4 hours after infusion. Abnormal vital signs should be monitored until measurements stabilize.

6.2 Subject treatment allocation

This is an open-label study, without blinding or randomization. Participants will be assigned to the appropriate dose group in the order of enrollment. The day a participant receives the designated single dose of IMC001 infusion is designated as D0.

6.2.1 Dosage escalation guidance

The starting dose is 3×10^5 CAR-T cells/kg.

of this study , approximately 7 – 15 subjects with advanced epithelial solid tumors will be recruited to evaluate the safety and tolerability of autologous IMC001 treatment. The expansion phase will select at least two dose groups, each recruiting 5 – 10 subjects (in conjunction with the escalation phase, expanding each dose group to approximately 10 subjects), to determine the recommended RP2D dose for progression to Phase IIa. DLT assessment will be performed on subjects in each cohort within 28 days of IMC001 infusion.

The initial dose will be escalated using a combination of accelerated titration and a 3+3 design. One subject will be rapidly enrolled in the $3\times10^{5\ CAR}$-T cells/kg group for initial safety assessment. If no DLT or significant toxicity (e.g., grade ≥2 treatment-related adverse events) occurs, the dose will be rapidly escalated to the next level.

Dosage escalation design: This study employed accelerated titration (ATD) combined with a 3+3 design for dose escalation.

Starting dose level ($3 \times 10^{5\ CAR}$-T cells/kg)

1. Group entry method and pace

Using a sentinel + staggered ATD approach: one sentinel subject is enrolled first; only after a safety review is completed ≥28 days after the infusion of the sentinel subject can the second subject be considered for enrollment.

The maximum number of patients enrolled in this dose group is 3 (ATD total sample size limit = 3).

2. Determination of escalation/cessation during ATD (applicable only to this dose)

Rapid escalation criteria: If no DLT is observed in enrolled ATD subjects and no "significant toxicity" as defined in the protocol (see below) occurs, the dose group can be terminated directly after the minimum observation requirement is met in the first or second case and the next dose level can be started, without having to complete the count to 3 in the dose group.

Complete the observation criteria: If a single case of "significant toxicity" (not reaching DLT) occurs, the dose group can be expanded to a maximum of 3 cases to complete signal confirmation; if no DLT is found after expansion and no clustering risk is observed, the dose group can be terminated and the next dose can be started. "Significant toxicity" is defined as a treatment-related adverse event (TRAE) below the DLT threshold, but sufficient to raise safety concerns and affect dose escalation decisions. It must be confirmed by the investigator, medical monitor, and SMC before it can be identified.

Significant toxicity includes the following situations:

- Persistent or recurrent grade ≥2 unexpected toxicity, even if it does not reach the DLT threshold, still affects the overall tolerability of the subject or delays subsequent dosing after adequate supportive treatment;
- Rapidly progressing or worsening toxic reactions, even if they do not meet the definition of DLT, suggest a potential serious safety hazard (such as progressive worsening of CRS or ICANS).
- Events requiring clinical intervention and having a significant impact on exposure to the investigational drug, such as the need to delay or reduce subsequent treatment for safety reasons;
- Other treatment-related toxicities that researchers and medical monitors deem to be of safety concern and require submission to the SMC for discussion.

Stop /Safety Review Criteria: If any DLT occurs in an ATD subject, do not proceed to the 3+3 expansion in the current dose group; immediately halt escalation and convene a Safety Review Committee (SMC) meeting (composed of the sponsor, clinical experts, clinical pharmacology experts, and statisticians). The review will determine whether to: a) adjust the treatment (e.g., adjust the lowest dose cohort , administer prophylactic medication, or provide inpatient monitoring) and maintain the established "next dose group starting 3+3"; or b) initiate a lower dose for ATD re-exploration; or c) terminate the escalation/revision protocol.

Subsequent dose levels (1×10^{6} ^{CAR} -T cells/kg and 2×10^{6} ^{CAR} -T cells/kg)

The classic 3+3 design was adopted. The specific rules are as follows: At each dose level, 3 subjects were initially enrolled. If 0/3 subjects experienced dose-limiting toxicity (DLT), the next dose level could be advanced; if 1/3 subjects experienced DLT, 3 more subjects needed to be enrolled at the same dose level (i.e., expanded to 6 subjects); if ≤1 out of 6 subjects experienced

DLT, the next dose level could be advanced; if ⩾2 out of the initial 3 subjects experienced DLT, or if ⩾2 out of the expanded 6 subjects experienced DLT, the dose level was deemed to be a non-tolerated dose level, and the escalation was terminated there, with dose reduction considered if necessary. Furthermore, if DLT occurred in the first 2 subjects at any dose level, there was no need to enroll a 3rd subject; the dose level was directly deemed intolerant, and further enrollment at that dose level was terminated.

For any other exploratory dose (if applicable), the initial sample size is set at 3 – 6 subjects, and the same criteria for tolerability assessment as for the starting dose are used.

To ensure the safety of participants, a sentinel group is established during dose escalation. At each new dose level, the first participant will serve as the sentinel subject. Sentinel subjects must complete at least 28 days of safety monitoring after infusion. Subsequent participants can only be enrolled in that dose group after investigators and medical monitors confirm that there are no unacceptable safety risks.

For any other exploratory dose (if applicable), the initial sample size is set at 3 – 6 subjects, and the same criteria for tolerability assessment as for the starting dose are used.

Based on DLT monitoring results, two to three dose levels will be selected for expansion, with five to ten subjects planned for each expansion cohort, to further evaluate safety and preliminary efficacy and determine the recommended dose for entering Phase IIa (RP2D).

The Safety Monitoring Committee (SMC) will comprehensively evaluate all available data, including the ongoing IMC001 study, and make recommendations for subsequent studies. Based on the safety results of completed dose escalation studies and all available safety, pharmacokinetic/pharmacodynamic (PK/PD) and efficacy data, the SMC will assess the overall benefit/risk to determine the RP2D, at which point the study can proceed to Phase IIa.

Determination of the recommended phase IIa dose (RP2D)

R P2D is defined as the recommended dose level of IMC001 for further Phase IIa clinical studies.

The Safety Monitoring Committee (SMC) will comprehensively evaluate all available safety, pharmacokinetic/pharmacodynamic (PK/PD), and efficacy data after the dose escalation phase DLT observations are completed. Based on the overall benefit/risk assessment, the final R- P2D will be determined , and the study may proceed to Phase IIa for further efficacy exploration.

Safety Oversight Committee (SMC)

To ensure safety monitoring and sponsor oversight of the study, a Safety Management Committee (SMC) will be established. The SMC, comprised of representatives from the sponsor, clinical experts, clinical pharmacology experts, and statisticians, will oversee all safety issues

related to the study. As needed, the SMC may convene a safety discussion meeting after DLT observations are completed in a dose group during dose escalation to review all available safety, efficacy, PK/PD data, accumulated information from the ongoing IMC001 study, and any new preclinical information, and to make recommendations regarding dose escalation, maximum study decisions, and participant safety. All SMC decisions will be documented in written meeting minutes and distributed to all research centers. The SMC will operate according to pre-established protocols.

6.2.2 Study drug adherence

Treatment adherence : IMC001 is administered via intravenous infusion. Any infusion failure or incomplete infusion for any reason should be recorded in detail in the electronic data capture system (EDC).

Drug management responsibility

The investigational drug will be stored at the study site in accordance with Good Clinical Practice (GCP) and GMP requirements, as well as the requirements of the sponsor's clinical supplies department (or its affiliates/Clinical Research Organization [CRO]). Access to the investigational drug is prohibited to unauthorized personnel. Complete records of specific storage conditions, batch numbers, and expiration dates are kept in the relevant research documentation. The research center shall record and maintain transportation and receipt records for the investigational drug, and shall immediately report any defects or problems found in the quality, quantity, or cold chain transportation of the investigational drug to the sponsor. The research center shall also maintain detailed cell preparation records. Sponsor monitors may review these records during monitoring visits. Only personnel authorized by the principal investigator of this clinical study are permitted to use the investigational drug in accordance with the requirements of this protocol. The receipt, distribution, return, and disposal (if any) of the investigational drug must be recorded in accordance with the standard operating procedures established by the sponsor. If there is a risk of potential contamination during drug management, the drug must be returned or recycled in accordance with the relevant safety procedures/guidelines.

6.2.3 Definition of DLT

Adverse events (AEs) occurring during the study will be classified according to NCI CTCAE 5.0. However, CRS and ICANS will be evaluated according to the 2019 ASTCT CRS classification. Section 6.8 of this protocol describes in detail the CRS/ICANS classification and management.

In this study, DLT was defined as: the following IMC001-related events occurring within 28 days after IMC001 cell infusion, according to FDA guidance (FDA, 2022):

Hematologic toxicity

- IMC001 treatment-related grade ≥4 hematologic toxicities that cannot be reduced to grade

≤2 after 7 days of treatment (including neutropenia, anemia without bleeding evidence, and thrombocytopenia).

- Grade 3 or lower platelet count, complicated by bleeding;
- IMC001 treatment for hemophagocytic lymphohistiocytosis (HLH)/hemophagocytic syndrome (HPS).

Non-hematologic toxicity

- IMC001 treatment-associated grade ≥3 cytokine release syndrome (CRS) that cannot be controlled to grade ≤2 after 7 days of treatment;
- IMC001 treatment-related ICANS grade 3 and above;
- IMC001 treatment-related grade 3 non-CRS toxicity of the heart, liver, lungs, and kidneys that cannot be recovered to grade ≤2 within 7 days after treatment;
- Except for other non-hematologic toxicities of grade 3 treatment-related IMC001 lasting more than 7 days:
  - Grade 3 nausea, vomiting, diarrhea, and constipation recover to grade ≤2 within 48 hours after adequate intervention;
  - Level 3 fatigue;
- Except for other non-hematologic toxicities of grade 4 or above related to IMC001 treatment:
  - Fever of grade ≥4 recovers to grade ≤3 within 48 hours after adequate intervention;
  - Grade 4 nausea, vomiting, diarrhea, and constipation recover to grade ≤2 within 48 hours after adequate intervention;
  - Hepatotoxicity recovered to grade ≤3 within 72 hours after adequate intervention.

The following factors also need to be considered when evaluating DLT:

(1) Subjects may receive supportive treatment (such as packed red blood cells, G-CSF) in accordance with local institutional guidelines;

(2) Take full account of the contraindicated drugs listed in this treatment plan and provide the best supportive care for vomiting or diarrhea in accordance with institutional guidelines;

(3) Grade 3 or 4 electrolyte abnormalities lasting for 72 hours without clinical complications, which can resolve spontaneously or respond to routine medical interventions, are not considered DLT.

6.2.4 Subject replacement

During the dose escalation phase of this study, unless a subject withdraws due to dose-dependent leukemia (DLT), a replacement will be considered if a subject drops out before completing the DLT observation. For other reasons (4 weeks post-infusion), such as CAR-T cell production failure, CAR-T cell count not meeting the dosage error range required by product quality standards, or cases where the subject was infused for efficacy considerations, a replacement will be provided to ensure sufficient subjects in each dose group for preliminary efficacy and safety evaluations. Subject replacement is generally not permitted during the Phase IIa efficacy exploration phase .

6.2.5 Other treatments (bridging therapy and lymph node dissection)

For bridging therapy, refer to Chapter 7.3 of this protocol; for pretreatment of lymph node dissection, refer to Chapter 7.5 of this protocol.

6.3 Treatment period

The treatment period in this study was defined as the 28-day period following a single infusion of IMC001 into the cell line.

6.4 Dosage adjustment

6.4.1 Overall considerations

not applicable .

6.4.2 Dosage adjustment and delayed administration

Prior to lymph node dissection (LD), relevant criteria should be assessed. If a subject does not meet the criteria for LD, LD may be delayed for up to 6 weeks until the subject meets the criteria for LD.

Subjects must be evaluated before IMC001 infusion. Those deemed eligible for IMC001 infusion by the investigator will receive IMC001. If a subject does not meet the criteria for IMC001 infusion, the infusion may be delayed for up to 2 weeks. If the delay exceeds 2 weeks, the investigator will assess whether the subject should undergo the standard pre-LD assessment again and/or repeat the LD.

may be permitted after thorough discussion with the sponsor and a comprehensive assessment of the safety of the investigational drug and the participants' condition, provided that product release and clinical infusion standards are met .

6.5 CAR-T cell management

6.5.1 Dosage and administration of medication

The starting dose for the dose escalation phase of this study was 3×10^5 CAR-T cells/kg. This phase employed a 3+3 dose escalation design, with the intermediate -dose group receiving 1×10^6 CAR-T cells/kg and the high- dose group receiving 2×10^6 CAR -T cells/kg. CAR-T cells/kg.

Phase IIa will be determined by SMC based on the results of previous studies.

The final dosage should also take into account the actual number of CAR-T cells produced and record the actual number of cells infused.

6.5.2 Preparation before reinfusion

IMC001 is packaged in an inner cell infusion bag with a label, and an outer reconstitution bag. After the packaging integrity is confirmed by the quality department, it is stored in a liquid nitrogen vapor phase. Before reconstitution , the product is placed in a liquid nitrogen vapor phase tank and transported at low temperature to the clinical research center. Reconstitution and infusion are performed within 2 hours (from the completion of reconstitution to the completion of infusion) , or the product is temporarily stored in a liquid nitrogen vapor phase tank at the clinical research center, depending on the needs.

6.5.3 Reconstituted cells

The frozen product will be transported to the research center in a gaseous liquid nitrogen tank. Upon receiving the IMC001 product, the clinical research center must verify the label information, the integrity of the transport packaging, and the transport temperature profile. Acceptance is only permitted after verification of these verifications . Before thawing, the label information and the appearance and integrity of the packaging bag are verified. After confirmation of compliance, thawing is performed using a 37 ±1 ℃ water bath. The thawing steps are as follows:

Completely immerse the product, packaged in double-layered bags, in a warm water bath, one bag at a time, thawing each bag individually. Gently rub the bags until the cells are just thawed and there are no unthawed clumps in the infusion bag. Infuse the reconstituted product within 2 hours. Store the reconstituted product at room temperature and infuse it as soon as possible.

6.5.4 Double-check and prepare before re-input

If the outer packaging containing IMC001 is damaged or leaked, but the inner packaging bag is carefully inspected and confirmed to be intact and the cells should be undamaged, infusion may still proceed. If the cell infusion bag is damaged, it should not be reinfused and should be disposed of.

IMC001 was administered intravenously via transfusion set at the research center. Each bag of transfused cells was labeled with "For Clinical Research Use Only" and included at least two unique identifiers, such as the subject's initials and subject number. Prior to transfusion, two individuals independently verified the information of all subjects to ensure a correct match between the information and the participating subjects.

Before cell reinfusion, prepare sufficient backup medications (such as at least two doses of tocilizumab) and ensure that relevant emergency equipment is available for timely treatment in case of severe allergic reactions, severe hypotension, or other emergencies. 30-60 minutes before cell reinfusion, researchers may consider pre-treatment of subjects based on clinical experience, such as administering acetaminophen (300-1000 mg orally), promethazine hydrochloride (25 mg intramuscularly), or diphenhydramine (50 mg). These medications are provided by the research hospital pharmacy.

6.5.5 Intravenous infusion and monitoring

Subjects will be given the study drug by researchers at the research center. The researchers will record the amount of study product used, the infusion time, and any special circumstances during the infusion process based on the cell count and infusion details in the quality inspection report.

6.5.6 Reinfusion process

Choose a superficial vein suitable for puncture and transfusion; a larger vein in the upper limb is recommended.

Use disposable blood transfusion sets (without filters) for reinfusion, and do not mix infusion tubing with other medications.

Before reinfusion, it was confirmed again that the subject met the infusion criteria and was free from infection.

Before reinfusion, administer 15–30 mL of normal saline intravenously to flush the infusion tubing. If the saline solution flows smoothly, the tubing can be replaced with an IMC001 cryopreservation bag for reinfusion.

From the completion of reconstitution to the completion of infusion of IMC001 injection, no more than 2 hours should pass. It is recommended to complete the infusion within 30 minutes (drip rate approximately 3 mL/min). If extracellular fluid leakage occurs during reinfusion, stop the infusion and dispose of any remaining product according to the protocol.

each bag of infusion is completed, the cells adhering to the transfusion set wall are flushed with 15-30 mL of normal saline to ensure that as many cells as possible are returned to the subject. The time when the last bag of IMC001 injection solution is flushed is taken as the end time of infusion.

If a severe infusion reaction occurs during the reinfusion, the infusion should be stopped immediately, and the IMC001 cryopreservation bag should be sealed and kept for inspection.

Continuous ECG monitoring for at least 4 hours from the start to the end of the infusion.

For detailed instructions on reinfusion, please refer to the product manual. If a subject experiences an infusion-related reaction during the reinfusion process, the infusion may be temporarily stopped or the infusion rate may be reduced. The specific treatment shall be assessed by the investigator.

6.5.7 Post-infusion monitoring

After reinfusion, each subject should be hospitalized for 14 days in principle, or the investigator should decide the discharge time based on the subject's condition. During the DLT observation period (dose escalation phase) after reinfusion, body temperature should be monitored at least twice a day, with an interval of at least 8 hours between each monitoring. If the body temperature is ≥38°C, CRS should be considered as a possible symptom. Closely monitor for any suspected CRS, neurotoxicity or other adverse reactions, and treat any adverse conditions promptly and appropriately.

6.5.8 Research on drug packaging and labeling

The drug label for IMC001 must include at least the following information: product name, the words "For clinical research use only", subject number, production batch number, specifications, manufacturer, storage conditions, expiration date, and route of administration.

6.6 Research on drug packaging, distribution , recycling, and disposal.

In this trial, the management, distribution, and retrieval of IMC001 cell products are the responsibility of designated personnel. Researchers must ensure that all IMC001 is used only by subjects participating in this clinical study, and that its usage and dosage comply with the trial protocol. Any remaining cells must be returned to the sponsor, and IMC001 must not be transferred to any non-clinical study participants.

Cells should be cryopreserved at -150°C or below until thawed for use . A cell reception form must be signed upon receiving IMC001 cells, with two signatures required. The original should be kept by the clinical research unit, and a scanned copy by the sponsor. Each issuance and receipt of an IMC001 cell should be promptly recorded on a dedicated log sheet.

Any unused IMC001 cells or cells suspected of having quality issues requiring analysis will be transported back to the sponsor in a gas-phase liquid nitrogen tank for analysis or disposal. Whole bags of IMC001 cells that do not need to be returned to the sponsor, as well as IMC001 packaging bags after infusion, will be disposed of according to the research center's medical waste disposal principles and recorded.

6.6.1 Drug storage

Long-term stored IMC001 products will be stored in a gas-phase liquid nitrogen tank at the preparation center. IMC001 intended for infusion will be transported to the clinical research center

under gas-phase liquid nitrogen conditions before infusion, where it will be temporarily stored in a gas-phase liquid nitrogen tank and the temperature will be recorded.

6.6.2 Recall and destruction of investigational drugs

If the cell infusion bag is damaged, reinfusion is prohibited and the bag should be destroyed.

There are several reasons for recalling the IMC001 product, including but not limited to:

- Products with incorrect labels
- The packaging bag is damaged or leaking, or there is other damage.
- The subject's condition was not suitable for infusion.
- Subject refused infusion

6.7 Combination therapy

Concomitant medication records should be kept from the date of signing the ICF until the completion of the primary safety follow-up period, loss to follow-up, or withdrawal from the study (whichever occurs first). Concomitant medications should be recorded in the EDC . For subjects entering the long-term follow-up period, concomitant treatments for AEs/SAEs related to IMC001 should be recorded in the EDC .

6.7.1 Research prohibits concomitant treatments

1) Except for treatment of adverse events or after the absence of detectable IMC001 cells in vivo, the use of systemic corticosteroids at doses equivalent to 5 mg/day of prednisone or higher, including prednisone, dexamethasone, or any other corticosteroid, is prohibited during the study period. Any other circumstances requiring steroid use should be discussed with the investigator. Inhaled, topical, intranasal, or local injection of corticosteroids is permitted.
2) During the study, patients are prohibited from receiving any other anticancer treatments concurrently (except for bridging therapy/lymph node flushing therapy specified in the protocol).
3) The use of immune enhancers is prohibited during the study (as immune enhancers can increase the immune system's phagocytosis and killing effect on CAR-T cells), including interferon, thymosin, injectable ribonucleic acid, lentinan, and Ganoderma lucidum polysaccharide.
4) During the study period and for two years following IMC001 reinfusion, patients are prohibited from receiving live or attenuated live vaccines.
5) The use of any other investigational new drugs is prohibited during the study.

6) The use of other treatments that the investigators believe may affect the study evaluation is prohibited during the study period.

6.7.2 Research-permitted concomitant treatment

1) This study allows bridging therapy after apheresis in subjects with high tumor burden or rapid progression.

2) This study allows for standard treatment for pre-existing conditions (excluding the study disease). Hypotension may occur during cell reinfusion; therefore, subjects previously using antihypertensive medication may consider discontinuing their medication for 12 hours prior to reinfusion, while closely monitoring their blood pressure.

3) This study allows the use of medications intended solely for supportive care (such as antipyretics, analgesics, antibiotics, antiemetics, antidiarrheals, hepatoprotective agents, emergency treatment medications, and medications for treating adverse events), and also allows the use of blood products.

6.8 specific toxic reactions

Adverse reactions following CAR-T therapy are very common. These adverse events include, but are not limited to: CRS, ICANS, infection (bacterial, fungal, viral), viral reactivation, grade ≥3 hematologic or organ dysfunction toxicity (such as hematologic toxicity, coagulation disorders, hypogammaglobulinemia, etc.), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), appearance of replicating lentiviruses, uncontrolled T cell proliferation, tumorigenicity risk, acute infusion reactions, or allergic reactions to excipients.

6.8.1 Cytokine release syndrome (CRS)

Level 1 CRS processing

- Assess fever, perform culture monitoring, and administer antibiotics according to the center's guidelines.
- Closely monitor organ dysfunction, including regular neuropsychiatric examinations.
- Daily testing of C-reactive protein, peripheral blood ferritin, and coagulation function.
- Symptomatic and supportive treatment (e.g., antipyretics).
- If fever persists for more than 96 hours after CAR-T cell infusion, especially if CRP and ferritin levels rise rapidly, consider administering tocilizumab 8 mg/kg intravenously every 24 hours, plus dexamethasone.
- If fever (≥38.5℃) occurs within 96 hours after CAR-T cell infusion, it is recommended to administer tocilizumab 8 mg/kg intravenously every 24 hours for 1-2 times, combined with dexamethasone 10 mg (or equivalent) twice daily for at least 3 days or until CRS or any

clinically manifested neurotoxicity symptoms are controlled. Prophylactic administration of levetiracetam for seizures is also recommended.

Level 2 CRS processing

- Close monitoring upon admission until fever and symptoms subside, including neuropsychiatric assessment.
- Symptomatic treatment, blood pressure regulation and respiratory support
- Administer antiepileptic drugs for prophylaxis (such as levetiracetam), and consider electrocardiogram (EEG) monitoring.
- Tocilizumab 8 mg/kg is recommended for intravenous (IV) administration, and can be repeated every 24 hours if necessary.
- If fever and hypotension persist for more than 96 hours and progress rapidly after CAR-T cell infusion, at least one of the following conditions must be present:
  - ✓ Progressive hypotension
  - ✓ Neurological symptoms
  - ✓ and/or a rapid increase in CRP within 96 hours
  - ✓ The initial fever progresses rapidly.
  - ✓ Symptoms did not improve after the first administration of tocilizumab (refractory).
- We recommend combining dexamethasone 20 mg IV Q12h or 10 mg IV Q6h with tocilizumab 8 mg/kg IV Q24h 1-2 times.
- If grade 2 CRS with fever (≥38.5℃) occurs within 96 hours after CAR-T cell infusion, dexamethasone 20mg BID or 10mg IV Q6h can be administered, along with tocilizumab 8mg/kg IV Q24h 1~2 times.

Level 3 CRS processing

- ICU-level monitoring until the patient's condition stabilizes, including neuropsychiatric examinations.
- Symptomatic treatment, blood pressure regulation and respiratory support
- Administer antiepileptic drugs for prophylaxis (such as levetiracetam), and consider EEG monitoring.
- Tocilizumab 8 mg/kg IV is recommended, and can be repeated every 24 hours if necessary.
- Dexamethasone 10mg IV every 12-24 hours

If CRS progresses rapidly, dexamethasone 20 mg IV every 12 hours is recommended, and/or an IL-6 antagonist may be added.

Level 4 CRS processing

- ICU-level monitoring until the condition stabilizes, including neuropsychiatric examinations.
- Symptomatic treatment, blood pressure regulation, and respiratory support.
- Administer antiepileptic drugs for prophylaxis (such as levetiracetam), and consider EEG monitoring.
- Tocilizumab 8 mg/kg IV is recommended, and can be repeated every 24 hours if necessary.
- Dexamethasone 10-20 mg IV (or equivalent) Q6h-Q12h
- If grade 2 CRS is not cured or does not improve within 48 hours, and/or life-threatening neurotoxicity is observed, high-dose corticosteroids are recommended, and the addition of an IL-6 antagonist should be considered.
- Consider using cyclophosphamide to deplete CAR-T cells.

6.8.2 Immune effector cell-associated neurotoxicity syndrome (ICANS)

Level 1 ICANS processing

- No CRS: Enhanced supportive care
- For concurrent CRS: Tocilizumab 8 mg/kg intravenously over 1 hour (not exceeding 800 mg/dose), repeated every 8 hours. A maximum of 3 to 4 doses may be administered within 24 hours. Caution should be exercised when repeating tocilizumab doses in ICANS subjects; corticosteroids may be administered after the first tocilizumab injection.

Level 2 ICANS processing

- No CRS: Provide supportive care as per Grade 1; for higher-grade subjects, consider reassessment after two intravenous doses of dexamethasone 10 mg. If there is no improvement, repeat every 6–12 hours. Once symptoms improve to Grade 1, reduce the hormone dose as soon as possible.
- Concurrent CRS: If ICANS is associated with grade >2 CRS, consider ICU transfer; administer tocilizumab as grade 1; if tocilizumab is ineffective on the first administration, administer dexamethasone (10 mg/kg IV, every 6–12 hours) or methylprednisolone equivalent (1 mg/kg IV, every 12 hours). Continue corticosteroids until improvement to grade 1, then rapidly reduce the corticosteroid dosage.

Level 3 ICANS processing

- All Level 3 participants: Transfer the patient to the ICU.

- No CRS: Administer dexamethasone (10 mg IV every 6–12 hours) or methylprednisolone (1 mg/kg IV every 12 hours).
- For CRS: Administer tocilizumab as Grade 1; if tocilizumab is ineffective on the first administration, administer dexamethasone (10 mg/kg IV, every 6–12 hours) or methylprednisolone equivalent (1 mg/kg IV, every 12 hours). Continue corticosteroid administration until improvement to Grade 1, then rapidly reduce the corticosteroid dosage.

Level 4 ICANS processing

- All Level 4 subjects were transferred to the ICU and given mechanical ventilation to protect their airways.
- No CRS: Administer 1000mg of methylprednisolone intravenously once or twice daily for 3 consecutive days; if there is no improvement, consider 1000mg of methylprednisolone twice or three times daily or alternating treatment; continue using hormones until the condition improves to grade 1, and reduce the hormone dosage as needed;
- Concurrent CRS: In addition to methylprednisolone, administer tocilizumab according to the grade 1 criteria, combined with methylprednisolone 1000mg once or twice a day for 3 consecutive days; if there is no improvement, consider 1000mg methylprednisolone IV 2-3 times a day or alternative therapy.
- Continue using hormones until improvement reaches grade 1, then gradually reduce the dosage.

6.8.3 Immune-related hepatitis

Immune- related liver toxicity is mainly manifested by elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), with or without elevated bilirubin.

Generally, there are no specific clinical manifestations. Sometimes, it is accompanied by nonspecific symptoms such as fever, fatigue, decreased appetite, and early satiety. When bilirubin is elevated, yellowing of the skin and sclera and tea-colored urine may occur.

IMH is mainly classified into three types: hepatocellular, cholestatic, and mixed. Cholestatic IMH typically presents with elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Most IMH cases are hepatocellular, with cholestatic cases accounting for only a minority. Diagnosis of IMH requires ruling out active viral hepatitis, liver damage caused by other diseases (such as fatty liver, alcoholic liver disease, etc.), liver damage caused by other drugs, autoimmune hepatitis, progression of primary liver tumors or liver metastases, and biliary obstruction from various causes.

Before the first immunotherapy, a comprehensive assessment of liver function should be conducted to identify and screen for underlying liver diseases, including viral hepatitis, fatty liver,

alcoholic liver disease, autoimmune hepatitis, etc. Immunotherapy is not recommended after liver transplantation.

Most participants recovered well after treatment, with the liver damage caused by immunotherapy being reversed. However, the prognosis for participants with cirrhosis is currently unclear. Treatment of these participants should be approached with caution, and multidisciplinary consultations and close monitoring of their condition are essential.

Countermeasures:

Treatment should begin with reducing or discontinuing other medications that may cause liver damage. IMH has a relatively good prognosis, is usually responsive to steroid therapy, and has a low incidence of liver failure and death. Most subjects recover to baseline liver function within 1-3 months. Cholestatic IMH has a relatively poor prognosis and is not sensitive to steroid and immunosuppressant therapy. If glucocorticoid therapy is ineffective, mycophenolate mofetil can be added; if the effect is still poor, low-dose tacrolimus (5-7 ng/dL) can be substituted. Newer treatments include budesonide, anti-thymoglobin (ATG), and plasma exchange, which can be used cautiously in experienced centers. Infliximab is not recommended for use in subjects with IMH due to its potential hepatotoxicity. Cholestatic IMH can be treated with ursodeoxycholic acid (UDCA).

6.8.4 cytopenia

Prior to CAR-T therapy, lymphocyte pre-clearance is performed to reduce the number of regulatory T cells, increase the availability of cytokines, especially IL-2, and reduce immune rejection, thereby enhancing the effect of CAR-T. Fludarabine and cyclophosphamide are the most commonly used regimens, but their toxicities include hematologic toxicity such as neutropenia, leukopenia, anemia, and thrombocytopenia, and they also increase the risk of infection. The duration of CAR-T therapy can vary significantly depending on prior treatment and the subject's hematopoietic reserve.

Response measures: For cytopenia lasting more than 28 days after CAR-T infusion, in addition to standard examinations, bone marrow biopsy and bone marrow aspiration should be performed to assess the response and etiology, including assessment of pathogens; for long-term neutropenia, i.e. neutropenia lasting more than 3 weeks after CAR-T cell injection, myeloid cell growth factor can be considered after any cytokine release syndrome (CRS) has been resolved.

6.8.5 Interstitial pneumonia

During the IIT study IMC001-CT03 , the high-dose group (3×10^6 CAR-T cells/kg) Two cases of interstitial pneumonia were observed . However, due to the overlap of enrollment and study commencement with the COVID-19 pandemic, a correlation between the occurrence of interstitial pneumonia and IMC001 cannot be definitively established . Preclinical mouse toxicology studies

revealed that the mouse EpCAM- targeting IMC001 substitute molecule IMC001-G8.8 resulted in mononuclear cell and mixed inflammatory cell infiltration in the lungs and other blood-rich organs and lymphoid tissues after administration. This response was determined to be primarily related to the accumulation of GvHD and CAR-T cells in these organs, with no significant toxicological significance. No interstitial pneumonia was observed in clinical studies of the EpCAM-targeting monoclonal antibody Adecatumumab, the EpCAM × CD3 bispecific antibodies Catumaxomab and MT110, the EpCAM-targeting ADC drug Oportuzumab Monatox, or EpCAM-targeting CAR-T drugs.

Response measures: After cell reinfusion, closely monitor the subject's blood oxygen saturation and for symptoms such as shortness of breath, cough, chest pain, and dyspnea. Perform complete blood counts and pathogen testing to rule out underlying lung diseases, concurrent pulmonary infections, and CRS . Conduct a comprehensive assessment of pulmonary imaging findings, and consult with respiratory and infectious disease specialists if necessary. Actively administer symptomatic treatment. If clinical symptoms appear or worsen, administer hormone therapy. If infection cannot be ruled out, consider adding empirical anti-infective therapy. If hormone therapy does not significantly improve the condition, consider administering tocilizumab, infliximab, or mycophenolate mofetil. Closely monitor the patient's condition and conduct multidisciplinary consultations.

6.8.6 Immune pancreatitis

During the IIT study IMC001-CT03, one case of potentially related immune pancreatitis was observed in the high-dose group (3×10^6 /kg), and one case of pancreatitis unrelated to IMC001 was observed in the low-dose group . No significant pancreatic toxicity was observed in preclinical data. In a phase II clinical trial (M. Schmidt, 2009) of the monoclonal antibody Adecatumumab targeting EpCAM in patients with metastatic breast cancer, transient grade 4 elevations in lipase and amylase were observed (13% and 7% in the low-dose and high-dose groups, respectively), with no related symptoms in the subjects.

Management: Regularly monitor pancreatic lipase and amylase levels in the subjects, and perform thin-section enhanced CT scans or MRCP tests of the pancreas if necessary, based on the subjects' clinical symptoms. If immune pancreatitis is diagnosed, actively implement symptomatic supportive care and drug treatment for pancreatitis, closely monitor changes in the condition, and consult with gastroenterologists/ICUs if necessary. If pancreatitis symptoms and signs progress rapidly or reach CTCAE grade 3 or higher, consider adding hormones or combining hormones with mycophenolate mofetil.

6.8.7 Skin toxicity

Two cases of epidermolysis were observed in the high-dose group (3×10^6 /kg) during the IIT study IMC001-CT03 . No significant skin toxicity was observed in preclinical data. Previous

clinical studies of bispecific anti-epidermal drugs targeting EpCAM and CD3 have observed rashes, erythema, and pruritus, but no reports of epidermolysis have been found. A clear correlation between epidermolysis and IMC001 cannot yet be established.

Management: Closely monitor subjects' clinical symptoms. Provide prompt symptomatic and supportive treatment if rashes or itching occur. Consult a dermatologist if necessary and consider a skin biopsy to confirm the diagnosis. If blisters appear, administer potent corticosteroids and request an urgent dermatology consultation. For subjects diagnosed with bullous dermatitis or epidermolysis bullosa , if hormone therapy is ineffective, consider adding rituximab and further intensify monitoring.

6.8.8 Secondary tumors

possible mechanism	The increased incidence of secondary tumors may be due to the disease itself, and/or immunosuppression and/or genotoxicity caused by treatments including pretreatment chemotherapy. Other possible mechanisms include viral vectors, i.e., RCRs, where viral vectors recombine with endogenous retroviral components to produce replicating retroviruses that integrate into the genome associated with the transcription of specific genes, leading to secondary tumors. Currently, there are no reports of CAR-T therapy-related secondary tumors.
illustrate	Cytopenia was one of the most common grade ≥3 adverse events reported in the JULIET, ZUMA-1, ZUMA-2, and ELINA trials. For newer products, such as BCMA-targeted bb2121, cytopenia was the most common grade ≥3 event, including neutropenia (85% of subjects), leukemia (58%), anemia (45%), and thrombocytopenia (45%). Real-world follow-up data showed an increased incidence of secondary tumors after CAR-T cell therapy. Among 1223 LBCL subjects treated with axi-cel, 37 subjects developed secondary tumors, including 18 cases of myelodysplastic syndrome. This may be related to the fact that the subjects had previously received multiple chemotherapy regimens, but the influence of cell therapy cannot be ruled out.
manage measure	• Information on the occurrence of second primary tumors in subjects was collected during the study; • receiving CAR-T cell therapy will be followed up for 15 years in a separate long-term follow-up study .

6.8.9 Immunogenicity

possible mechanism	The mechanisms of immunogenicity include immune activation mediated by humoral and cellular immunity, potentially encompassing immunogenic responses and type I hypersensitivity immune responses. Immunogenicity includes cell-mediated immune responses against novel CAR protein-associated immune epitopes, as well as immune responses to mouse scFv or residual impurities in fetal bovine serum and bovine serum albumin from the preparation process. Immunogenicity is unlikely to be caused by EpCAM CAR-T or lymphocyte-sparing pretreatment chemotherapy, and there are currently no reports of CAR-T therapy for solid tumors.
illustrate	IMC001 (EpCAM CAR-T) is composed of genetically modified autologous T cells, which are stably integrated into the T cell genome using the γ-retroviral vector EpCAM CAR-T during its preparation. Considering the differences between animal models and clinical subjects, EpCAM CAR-T may readily induce immunogenicity in animals, but this does not guarantee that it will induce similar immunogenicity in humans.
manage measure	Immunogenicity testing was performed on subjects who received CAR-T cell therapy .

6.8.10 Infect

Immunosuppression secondary to lymphocyte depletion is an expected toxicity associated with CAR-T cell therapy. Targeted killing of B cells through emerging therapies such as CD19-targeted CAR-T cell products and BCMA-targeted CAR-T cells for multiple myeloma may further weaken the immune defenses of subjects. Bacteremia, fungal infections, recurrent urinary tract infections, and viral infections such as influenza, respiratory syncytial virus, and herpes zoster have all been reported after CAR-T therapy. Activation and reactivation of cytomegalovirus (CMV), EBV, and human herpesvirus 6 are also of concern. The routine dosing regimens for prophylactic antibacterial, antiviral, and antifungal drugs vary by center for subjects receiving CAR-T cell therapy.

Infections can improve with symptomatic treatment, but in rare cases they may be life-threatening. Measures to prevent risks include ruling out contraindications, strictly following treatment procedures and guidelines, closely monitoring the vital signs and various indicators of the subjects, and having doctors handle the situation according to the condition and provide symptomatic treatment.

Countermeasures:

Infections can improve with symptomatic treatment, but in rare cases they may be life-threatening. Measures to prevent risks include ruling out contraindications, strictly following treatment procedures and guidelines, closely monitoring the vital signs and various indicators of the subjects, and having doctors handle the situation according to the condition and provide symptomatic treatment.

- If a subject develops fever and has a positive bacterial blood culture before infusion, appropriate antibiotics should be administered, and CAR-T cell infusion should be delayed until the subject is fever-free and has a negative culture for at least 48 hours.
- If a fungal infection is suspected, lymphocyte removal chemotherapy should not be performed until appropriate antifungal medication is started and the fungal infection is under control.
- If the nasal wash is positive for an active viral infection, but the subject's symptoms are not severe, treatment can continue after the symptoms improve.
- All subjects should receive prophylaxis against Pneumocystis pneumonia.
- Preventing HSV/VZV reactivation (i.e., using low-dose acyclovir) can be considered.
- The decision to administer antimicrobial, antiviral, and/or antifungal drugs prophylactically should be risk-adjusted based on subject characteristics (i.e., pediatric versus adult subjects, prior myelosuppression therapy, and history of infection).
- If a subject has a high-risk medical history, such as long-term use of steroids or active use of high-dose corticosteroids, or is receiving high-dose lympholytic or anti-cytokine therapy, antimicrobial and antifungal prophylaxis should be strongly considered.
- Subjects who develop persistent neutropenia should receive antimicrobial and antifungal prophylaxis.
- Subjects with active influenza infection should receive antiviral treatment and continue intravenous infusion until the main symptoms disappear.

For subjects receiving CAR-T cell therapy, the routine dosing regimens for prophylactic antibacterial, antiviral, and antifungal drugs vary from center to center.

6.8.11 Cardiovascular toxicity

Common definitions of cardiovascular toxicity include heart failure symptoms and/or a decrease in left ventricular ejection fraction (LVEF): a decrease in LVEF from symptomatic to <55% or from asymptomatic to <55%. Other definitions include increased serum troponin, a greater decrease in LVEF, and a reduction in overall longitudinal strain >15%. CTCAE classifies cardiotoxicity based on symptoms, imaging abnormalities, and biomarker measurements, including troponin.

Common cardiovascular and cardiac toxicities reported with CAR-T cell therapy include hypotension, new heart failure, worsening of pre-existing heart failure, and new arrhythmias (atrial fibrillation/atrial flutter are common).

Countermeasures:

- Baseline cardiac tests prior to CAR-T cell therapy should include echocardiography, serum troponin, and NT-proBNP/BNP ratio. Subjects with ASTCT grade 2 or higher CRS should have troponin and LVEF monitored. Serum troponin and LVEF testing should be considered for subjects with any grade of CRS when additional risk stratification is required.
- Subjects deemed high cardiac risk at baseline may require early intervention with tocilizumab and/or steroids at the onset of CRS. Early intervention should be considered with IL-6 blockers and/or steroids or escalation of current treatment if there is evidence of cardiotoxicity, elevated troponin, decreased LVEF, or significant arrhythmias; evidence of malignant arrhythmias or severe left ventricular dysfunction indicating severe end-organ damage necessitates escalation of intervention.
- Medications that should be discontinued before CAR-T cell therapy include antiplatelet drugs such as aspirin and clopidogrel. Subjects using therapeutic anticoagulants should be switched from long-acting to short-acting formulations whenever possible. Long-acting anticoagulants can significantly increase the risk of bleeding during CRS. Dual-acting anticoagulants should be discontinued if the subject's platelet count is below 100,000/μL; all anticoagulants should be discontinued if the platelet count is below 50,000/μL unless the subject has recently experienced thrombosis; if the platelet count is below 50,000/μL and the subject has recently experienced thrombosis, anticoagulants may continue, but the dose should be reduced or platelet transfusions should be administered.
- during CAR-T cell therapy include beta-blockers, angiotensin II receptor blockers, calcium channel blockers, and ACE inhibitors. If feasible, these drugs should be switched from long-acting to short-acting formulations.

6.8.12 Replicating Lentiviral Virus (RCL)

Possible mechanisms	Retroviral vectors are genetically engineered to remove their replication ability; however, during the preparation process, replication-capable retroviruses may be generated through homologous or non-homologous recombination between the transfer vector, packaging components, and endogenous retroviral components of the production cells.
illustrate	IMC001 involves genetically modifying and in vitro expanding autologous T cells from the patient to express EpCAM CAR. In its manufacturing process,

	IMC001 uses a recombinant, replication-deficient lentiviral vector to introduce the EpCAM CAR gene into T cells. The transduced T cells are further expanded in vitro and released after passing EpCAM CAR transduction rate testing before final formulation. Although IMC001 uses a replication-deficient viral vector system to genetically modify T cells, to further ensure product safety and ensure that the viral vector has not regained its self-replication ability during vector production and the IMC001 manufacturing process, a highly sensitive and specific real-time quantitative PCR method is used to detect any proviruses that may be replicating lentiviruses. The acceptable standard is that the amount of replicating lentivirus should be below the limit of detection (1×10^4 copies /mL). The presence of a limit of detection (RCL) indicates a safety risk and is a critical quality attribute.
Management Measures	It is recommended that lentivirus operations be performed under BSL2-compliant laboratory conditions. Proper and standardized procedures are perhaps the most basic and crucial guarantee of safety. • RCL was measured in blood samples from subjects who received CAR-T cell therapy . • 15- year follow-up study will be conducted in a separate long-term follow-up study .

6.8.13 Tumor lysis syndrome (TLS)

Possible mechanisms	Tumor lysis syndrome (TLS) refers to the phenomenon where tumor cells rapidly lyse after being attacked by CAR-T cells, releasing a large number of bioactive molecules that alter the microenvironment and disrupt normal physiological processes. If left untreated, TLS can progress to acute renal failure, arrhythmias, epilepsy, and even death.
illustrate	Both lymphocyte-depleting chemotherapy and relma-cel treatment can lead to lymphoma-related TLS in subjects with high lymphoma burden. Currently, there is no epidemiological data on TLS associated with CAR-T therapy for solid tumors. TLS : high potassium, high uric acid, high phosphorus, low calcium. Symptoms of TLS include nausea and vomiting, shortness of breath, irregular heartbeat, cloudy urine, drowsiness, and/or joint discomfort. High-risk characteristics of TLS:

	• Histological types include Burkitt lymphoma and lymphoblastic lymphoma, occasionally occurring in DLBCL and CLL patients. • Spontaneous TLS • Elevated white blood cell count • Bone marrow involvement • Elevated uric acid levels already exist. • Allopurinol is ineffective • Kidney disease or kidney metastasis from tumors.
Management Measures	If TLS can be anticipated and treatment can begin before chemotherapy, TLS can be effectively prevented and controlled. • Key treatments include: ➢ Strict intravenous infusion ➢ Treatment of hyperuricemia ➢ Closely monitor electrolytes and actively correct electrolyte imbalances. • First-line treatment and retreatment for hyperuricemia: Allopurinol is administered 2-3 days before chemotherapy and continued for 10-14 days. • Subjects with any of the following risk factors may receive symptomatic treatment: ➢ Any high-risk characteristics present ➢ Patients with large masses urgently need to begin treatment. ➢ In cases where adequate intravenous infusion may be difficult or impossible ➢ Acute renal failure

6.8.14 Reduced product activity due to improper infusion preparation

Possible mechanisms	IMC001 must be handled, prepared, and used in accordance with the relevant guidelines. Failure to do so may theoretically lead to a decrease in product viability.
illustrate	There are currently no reports of drugs for treating advanced malignant tumors experiencing reduced product efficacy due to improper infusion

	preparation, nor are there any relevant epidemiological studies.
Management Measures	This potential risk can be reduced by handling, preparing, and using the product in accordance with regulations.

6.8.15 Infectious pathogens can be transmitted through products.

Possible mechanisms	Subjects carrying HIV, HBV, and HCV may also use IMC001. The use of autologous cells from these infected subjects poses potential risks to production personnel and medical workers.
illustrate	Unless the subject uses blood products or drugs made from blood-derived materials, such as blood transfusions, albumin, and immunoglobulins, the transmission of infectious pathogens through products is extremely rare. There are currently no reports of solid tumor patients contracting pathogens through traditional non-blood product drugs, nor are there any related epidemiological studies. Exposure to IMC001 via needles or other means (broken skin) is a major risk factor. At-risk groups include production workers and healthcare workers handling patient cells.
Management Measures	Knowing the subject's infection status in advance helps in prevention (testing is recommended before leukocyte apheresis). Adhering to GMP and local biosafety guidelines, including the use of personal protective equipment (gloves, goggles), can mitigate risks. All materials (solid and liquid waste) that have come into contact with IMC001 should be treated and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

7 Visit Arrangements and Assessment

7.1 Research process and visit arrangements

Table 1, the research workflow chart (see section 1.3 for details), lists all assessments in the study and marks them with an "X" in the corresponding visit grid. All data obtained from these assessments must be supported by original documents.

7.2 Molecular pre- screening period (before screening period)

After signing the informed consent form for molecular pre-screening, participants will undergo EpCAM target screening and related molecular biological characteristics (such as tumor immune microenvironment, tumor mutational burden (TMB), etc.). Participants must provide tumor tissue specimens (paraffin blocks or sections). If tumor tissue specimens cannot be provided, a biopsy will be performed during the screening period for screening EpCAM expression at the central laboratory. Sample requirements are: formalin-fixed paraffin-embedded tumor tissue blocks (paraffin blocks within 2 years are acceptable) or fresh biopsy tissue or at least 6 freshly cut 4-5 μm thick unstained tissue sections.

the EpCAM expression level required by the protocol, the pre-screening is considered a failure, and further screening will not proceed. Information on subjects who failed pre-screening and did not sign the primary informed consent form must be recorded in the EDC (Education Data Center) along with their demographic information and the date they signed the pre-screening informed consent form.

7.3 Screening period (D-42~D-18)

Subjects can enter the screening period after signing the informed consent form. The screening period is defined as the period from signing the primary informed consent form to the subject's white blood cell apheresis.

Screening: Subjects sign informed consent forms and undergo a series of laboratory and non-laboratory tests to assess their preliminary eligibility.

(including informed consent forms for molecular target screening and primary informed consent) prior to any screening procedure . Screening assessments will be conducted between 42 and 18 days prior to the infusion of the investigational drug . During the screening period, archived tumor tissue samples or fresh samples will be obtained from the participants, along with relevant medical history and demographic data. All medications (including nutritional supplements such as vitamins, therapeutic solvents or carbides) and non-pharmacological treatments used within 30 days prior to signing the primary informed consent form should be documented. If the assessment is performed as part of a participant's routine clinical evaluation and is not specific to this study, it does not need to be repeated after signing the ICF. However, the assessment must meet the study requirements and should be performed within the specified timeframe. Tumor imaging assessments performed 28 days prior to signing the ICF may be acceptable for screening, but baseline imaging must be performed within 28 days prior to cell infusion. Only one retest is permitted during the screening period for abnormal screening values that led to exclusion (to reassess eligibility). The final results obtained before the infusion of the investigational drug will be used to determine eligibility. Measurements collected closest to the start of drug administration but prior to that will be defined as baseline values for safety assessment and treatment decisions.

Screening, white blood cell collection, and cell preparation should be completed within 6 weeks prior to the infusion of IMC001 into the subject. If the first subject enrolled in a certain dose plan is waiting for the overall safety results of the previous dose, and the screening-related procedures exceed the time window allowed by the protocol, they will not be included in the protocol deviation.

During the screening period, subjects completed the corresponding visit examinations according to the visit schedule. Subsequent visit time windows are calculated from the cell infusion day (D0). If the time window before infusion is extended due to reasons such as CAR-T cell preparation or bridging therapy, it will not be recorded as a deviation from the protocol.

Screening period checks:

1) Sign the primary informed consent form (obtained before any research-related examinations or procedures other than molecular screening tests).

2) Collection of demographic data

3) Tumor diagnosis and treatment history, tumor stage and pathology (including previous and current anti-tumor treatments)

4) Non-tumor medical history, comorbidities, and previous treatment history

5) Collection of allergy history

6) Blood pregnancy test (required for women of reproductive age, defined as women who have not yet gone through menopause or who have gone through menopause for less than 2 years)

7) Infectious disease screening (central laboratory testing)

8) ECOG score

9) Vital signs

10) Physical examination

11) Blood oxygen saturation (referring to pulse oxygen)

12) Height / weight, body surface area (body surface area is calculated based on the patient's height and weight only during the clearing stage).

13) Complete blood count

14) Urinalysis

15) Stool routine examination and occult blood test

16) Blood biochemistry

17) Coagulation function test

18) Blood amylase and lipase

19) Fasting blood glucose

20) C- reactive protein

21) Peripheral serum ferritin

22) Tumor markers

23) 12 -lead electrocardiogram

24) Chest CT (If the researcher suspects that the subject has lung metastases, a chest CT scan may be performed .)

25) Echocardiography (including LVEF)

26) Imaging examinations (Imaging examinations required for enrollment assessment can be performed within 28 days prior to signing the informed consent form. Simultaneously, imaging assessments must be performed within 28 days prior to cell infusion therapy as the baseline for this study.)

27) Combine drug / non-drug and adverse event records

28) Review of inclusion and exclusion criteria: The review of inclusion / exclusion criteria during the screening period is conducted after all screening tests are completed. Subjects must meet all inclusion criteria and not meet any exclusion criteria to be enrolled.

Filtering failed

If a participant is found to be ineligible to participate in the study after signing the informed consent form, the screening process is considered a failure, and the same method is used to collect data in such cases.

The reasons for screening failure will be recorded in the subject's medical record and simultaneously entered into the EDC electronic system . Demographic information, informed consent, and inclusion/exclusion information for failed screening subjects must also be completed. Because the subject failed screening, no other data needs to be entered into the clinical database; however, serious adverse events (SAE reports are detailed in Chapter 8 of this protocol) and SAEs that may be related to the study protocol that occurred during the screening period also need to be recorded in the EDC .

7.4 Leukocyte apheresis

Apheresis: Eligible subjects who pass the initial assessment will undergo apheresis to enrich white blood cells. Subjects' hematological examinations should meet certain standards, including a platelet count (PLT) $\geq 75 \times 10^9$ / L, a hemoglobin level (Hb) ≥ 8.0 g/dL, and a lymphocyte count (LYM) $\geq 0.5 \times {}^{10^9}$ /L, with the lymphocyte count preferably not lower than 0.5×10^9 / L. Infectious

disease screening (hepatitis B, hepatitis C, HIV, syphilis, EBV-IgM, and CMV-IgM) should be negative. Apheresis is performed at the clinical research center by clinical research center personnel using qualified apheresis equipment. The processed whole blood volume is typically no less than 1.5 whole blood volumes, with the addition of an appropriate amount of anticoagulant. The total collected white blood cells are no less than 5×10^9（minimum 3.5×10^9）, in a volume of 40–130 mL. Leukocyte single-sample bags should be refrigerated immediately and placed in a validated cold chain transport container, and transported to the cell preparation center at a temperature of 2°C to 8°C. The time from completion of single-sample collection to start of preparation should not exceed 48 hours.

At the researcher's discretion, to ensure successful enrollment in the study even after disease progression, leukocyte apheresis may be performed before disease progression during first-line treatment. This advance apheresis is solely a preparatory measure for potential subsequent reinfusion and does not constitute formal enrollment or the start of treatment. In this case, leukocyte apheresis must still meet the aforementioned hematological and infectious disease criteria, and the sample must be transported and stored under specified conditions. The subject's EpCAM expression must meet the enrollment criteria in this situation.

7.5 Bridging therapy (if applicable)

Based on the investigator's assessment of the participant's condition and considering the clinical benefits and risks, bridging therapy may be considered after leukapheresis and before lymphocyte clearance pretreatment. The aim of bridging therapy is to stabilize the participant's current disease state or reduce their current tumor burden.

Bridging therapy must be completed 7 days prior to lymphocyte ablation chemotherapy; or at least 5 half-lives of the bridging drug prior to lymphocyte ablation pretreatment (whichever is longer). If bridging therapy is performed, baseline tumor assessment must be repeated before lymphocyte ablation pretreatment. Subjects who achieve complete remission after bridging therapy are not permitted to undergo lymphocyte ablation pretreatment and cell reinfusion.

Bridging therapy should be chosen based on regimens with fewer adverse reactions. Its goal is not to achieve disease remission, but rather to prevent disease progression leading to organ dysfunction or any other complications that may hinder lymph node debridement and CAR-T cell reinfusion (such as infection, bleeding, etc.). If the expected turnover time of CAR-T cells is very short, bridging therapy can be omitted if the disease is stable and the tumor burden is low. If, during CAR-T cell preparation, the researcher determines that tumor progression in the subject may affect cell reinfusion, bridging therapy may be considered. It is recommended to select previously effective drugs based on the subject's response to previous treatments; the bridging therapy regimen should not be too aggressive, otherwise adverse reactions may affect subsequent lymph node debridement and cell reinfusion; subjects who achieve complete remission (CR) with

bridging therapy should not proceed to the lymph node debridement phase. Immunotherapy drugs with long half-lives should be avoided to prevent affecting CAR-T cell expansion and survival. Bridging therapy regimens can include chemotherapy, targeted therapy, immunotherapy, and radiotherapy.

7.6 Evaluation before rinsing pretreatment

The pretreatment assessment should be performed within 7 days prior to the pretreatment, but vital signs and physical examination should be performed within 1 day prior to the pretreatment.

Pre-treatment assessment of tumor burden within 14 days prior to initiation of lymph node dissection (LHD). Subjects must meet the LHD criteria to receive LHD (see Section 5.3 of this protocol for details) .

To ensure better survival and stable expansion of autologous IMC001 in the subjects and to maximize its anti-tumor function, a lymph node debridement pretreatment protocol was implemented after enrollment and before infusion. This pretreatment was conducted 1–4 days prior to IMC001 infusion (the exact number of days was determined by the investigator based on clinical practice), and was implemented after the investigator assessed the subject's condition as suitable. CAR-T cell infusion could begin 1–2 days after the lymph node debridement protocol was implemented.

For subjects who have been screened and confirmed as eligible, within 7 days prior to the urine cleansing pretreatment, after the IMC001 is prepared, researchers will conduct relevant examinations to assess the subject's condition, including but not limited to: ECOG score, vital signs, weight/body surface area (body surface area is calculated based on height and weight only during the urine cleansing period), blood oxygen saturation, routine blood and urine tests, routine stool tests and occult blood test, blood biochemistry, coagulation function, 12-lead electrocardiogram, etc., to evaluate the subject's eligibility before the urine cleansing pretreatment. If the subject has received bridging therapy, imaging examinations must be performed before the urine cleansing as a baseline. Subjects who are deemed eligible by the researchers can receive the urine cleansing pretreatment protocol.

For detailed examination items, please refer to the protocol flowchart 1. Researchers may add relevant tests based on the actual situation of the subjects , or determine whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent .

7.7 Pretreatment of shower

Subjects who are deemed eligible by the investigator may receive a lymph node pretreatment protocol, the specific protocol of which may be provided by the investigator according to local clinical practice standards.

Shower pretreatment flow:

Before receiving IMC001 infusion , subjects will undergo 2-3 days of lymph node cleansing pretreatment to increase the copy number and survival time of CAR T cells in vivo . Each subject will undergo lymph node cleansing pretreatment according to the following protocol before cell infusion. The detailed dosage may be adjusted according to the investigator's judgment.

(1) FNC regimen: Fludarabine (F) combined with cyclophosphamide (C) + albumin-bound paclitaxel (N) regimen

- Fludarabine 25 mg/m² / day x 2 days ; administered intravenously on day 1 and day 2 of lymphadenopathy.
- Cyclophosphamide 250 mg/m² / day × 3 days ; administered intravenously on days 1, 2, and 3 of lymph node cleansing.
- Albumin-bound paclitaxel 100mg Intravenous injection ; intravenous infusion on the second day after lymph node dissection.

If the subject is allergic to or intolerant to albumin-bound paclitaxel, or if the investigator may choose the following FC lymph node pretreatment regimen based on the subject's condition.

(2) FC regimen: Fludarabine combined with cyclophosphamide regimen

- Fludarabine 20-25 mg/m² / day ; administered intravenously on day 1 and day 2 of lymphadenopathy .
- Cyclophosphamide 500 mg/m² / day ; administered intravenously on day 1 and day 2 of lymphadenopathy .

The subject's body surface area was calculated using Stevenson's formula:

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

The specific lymph node dissection pretreatment protocol will be selected and implemented by the investigator based on the subject's underlying diseases and previous treatments. Before and after implementing the lymph node dissection pretreatment protocol, investigators should closely monitor the subject's complete blood count (paying close attention to changes in white blood cell and lymphocyte counts), various blood biochemical indicators, and urine output. If oliguria occurs, the attached hydration and alkalization protocol should be repeated, and records should be kept. Clinicians should implement various protective measures for the subject (such as wearing masks, reducing personnel movement, etc.) to strictly prevent opportunistic infections. CAR-T cell infusion can begin 1-2 days after the subject implements the lymph node dissection pretreatment protocol.

During the study, subjects will be assessed for the safety, transplantation status, and survival of IMC001 through blood tests. Subpopulations of IMC001 in peripheral blood will be measured and compared with baseline samples at different time points after infusion.

7.8 Pre-infusion assessment of cells

All results of the pre-infusion assessment visit should be evaluated before IMC001 infusion to ensure that the subject meets the infusion criteria in Section 5.4 of this protocol . Detailed examination items are listed in Table 1 of the protocol flowchart. Investigators may add relevant tests based on the subject's actual situation , and may also determine whether to conduct exploratory studies on characteristics such as the tumor immune microenvironment based on clinical sample availability and informed consent.

If, 3 days prior to IMC001 infusion, the investigator determines that the subject has a significant abnormality; or the subject has an active infection requiring systemic antimicrobial treatment or a body temperature ≥38°C before reinfusion; or the investigator determines that the subject has experienced rapid disease progression relative to the screening time; or the investigator assesses that the subject has significant organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney dysfunction, pulmonary edema, severe lung infection, brain metastases, etc.); and the investigator determines that the subject is unsuitable for subsequent trial procedures, then infusion should not be performed or should be delayed.

If cell infusion is delayed for any reason beyond 7 days after urine cleansing pretreatment, infusion should not be performed, or the investigator will assess whether the subject should undergo urine cleansing pretreatment again for delayed infusion. An interval of at least 4 weeks between two urine cleansing treatments is recommended.

7.9 Cell infusion (D0)

Subjects are advised to receive an IMC001 infusion on day 0 and be hospitalized.

are advised to be hospitalized for 14 days after the infusion . All examinations listed in the flowchart must be completed on the day of the IMC001 infusion.

The following checks need to be completed on the day of infusion (D0):

1) Vital signs (monitored within 1 hour before infusion and within 1 hour after infusion; additional monitoring may be performed after infusion as determined by the researcher)

2) Blood oxygen saturation (pulse oxygen) monitoring (monitoring within 1 hour before infusion and within 1 hour after infusion; additional monitoring may be performed after infusion as determined by the researcher).

3) Complete blood count (can be performed after infusion unless the researcher deems it necessary)

4) 12-lead electrocardiogram (this step can be omitted if there is cardiac monitoring after infusion)

5) Collect blood samples for monitoring cytokines and overall immune status markers, CAR cell copy number, and CAR-T cell subsets/phenotypes.

For detailed examination items, please refer to Table 2/Table 3 of the protocol flowchart. Researchers may add relevant tests based on the patient's actual condition.

For detailed examination items, please refer to the protocol flowchart 1. Researchers may add relevant tests based on the actual situation of the subjects , or determine whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

7.10 Treatment period (D0 to D28)

Subjects will be followed up according to the protocol flowchart in Table 1. During the dose escalation phase, all subjects will undergo DLT observation within 28 days after infusion .

The following tests should be performed on days 1 , 3 (±1 d), 5 (±2 d), 7 , 9 , 14 (±2 d), 21 (±2 d), and 28 (±2 d) after cell infusion:

1) ECOG scoring (performed on D1/D3/D7/D14/D21/D28)

2) Vital signs (D1/D3/D7/D14/D21/D28)

3) Physical examination (conducted on days 1/3/7/14/21/28)

4) Blood oxygen saturation (pulse oxygen) measurement (D1/D3/D7/D14/D21/D28)

5) Weight (measured on days 7/14/21/28)

6) Complete blood count (performed on days 1/3/7/14/21/28)

7) Urinalysis (performed on days 1/3/7/14/21/28)

8) Stool routine examination and occult blood test (performed on days 1/3/7/14/21/28)

9) Blood biochemistry (performed on days 1/3/7/14/21/28)

10) Coagulation tests (performed on days 1/3/7/14/21/28)

11) Amylase and lipase (proceded on D1/D3/D7/D14/D21/D28)

12) C - reactive protein (D1/D3/D7/D14/D21/D28)

13) Peripheral serum ferritin (administered on D1/D3/D7/D14/D21/D28)

14) 12 -lead electrocardiogram (performed on D1/D7/D28 ; if there is ECG monitoring after infusion, this step can be omitted on D1).

15) Echocardiography (including LVEF) (Based on clinical signs, if the subject develops symptoms or signs of heart failure, a follow-up examination should be performed promptly).

16) Tumor markers (d28)

17) Collect blood samples for monitoring cytokines and overall immune status markers, CAR cell copy number, and CAR-T cell subsets / phenotypes (D1/D3/D5/D7/D9/D14/D28) until two consecutive test results are negative or below the detection limit.

18) Anti- CAR anti-drug antibody (ADA) detection (performed on day 28)

For detailed examination items, please refer to the protocol flowchart 1. Researchers may add relevant tests based on the actual situation of the subjects , or determine whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

7.11 Research Exit

In this study, the standard treatment regimen was a single infusion, and the study treatment was considered complete upon completion of the study cell infusion at Day 0. Subjects who withdraw early will undergo a withdrawal visit within 7 days of withdrawal and before initiating any new anti-tumor treatment. If the required assessments are completed within 7 days prior to withdrawal, no repeat examination is necessary. Where feasible and with fully informed consent, tumor tissue biopsies may be performed on subjects who received IMC001 cell infusions to obtain specimens for EpCAM testing.

Even after a participant withdraws from the study, relevant data should continue to be collected with their consent, including blood tests for RCL at weeks 16 and 48. Blood tests for ADA or CAR copy number may continue if necessary. Furthermore, participants should be contacted every 3 months by phone, outpatient visit, or mail to record all subsequent anti-tumor treatments, secondary tumors, survival status, etc., until week 48. However, data will no longer be collected in the following situations:

- Lost to visit
- die
- Subject refused
- Researchers decided
- Early termination of the entire study requested by the principal investigator, sponsor, ethics committee, or regulatory agency.

If the reason for early withdrawal from the study is either the subject's request to withdraw from subsequent follow-up or the researcher's decision, and the subject has not yet completed the 28-day follow-up after the treatment infusion, the subject should be encouraged to complete the visit examination as soon as possible.

Regardless of the reason, participants who withdraw from the study should have their information entered into the EDC .

Subjects who are unable to receive an IMC001 infusion do not need to withdraw/withdraw from the visit.

7.12 Follow-up period

7.12.1 Note the follow-up period at week 6 (D42±7d).

6 weeks ± 7 days after cell infusion :

1) ECOG score

2) Vital signs

3) Physical examination

4) Blood oxygen saturation (pulse oxygen) test

5) Weight

6) Complete blood count

7) Urinalysis

8) Stool routine examination and occult blood test

9) Blood biochemistry

10) Coagulation test

11) Amylase and lipase

12) C- reactive protein

13) Peripheral serum ferritin

14) 12 -lead electrocardiogram

15) Tumor markers

16) Tumor assessment

17) Collect blood samples and monitor cytokines and overall immune status markers, CAR cell copy number, and CAR-T cell subsets / phenotypes until two consecutive test results are negative or below the detection limit.

For detailed examination items, please refer to Table 2/Table 3 of the protocol flowchart. Researchers may add relevant tests based on the patient's actual situation, or conduct exploratory studies on tumor immune microenvironment and other characteristics based on the availability of clinical samples and informed consent.

7.12.2 Follow-up period from 12 weeks to 48 weeks after infusion (W12~W48, including week 12)

From week 12 to week 48 post-cell infusion, visits should be conducted every 6 weeks, with each visit window lasting ± 7 days. Specifically, the following tests should be performed at weeks 12, 18, 24, 30, 36, 42, and 48:

1) Physical examination

2) Vital signs

3) Blood oxygen saturation (pulse oxygen) measurement

4) Weight

5) ECOG

score

6) Complete blood count

7) Urinalysis

8) Stool routine examination and occult blood test

9) Blood biochemistry

10) Coagulation test

11) Amylase and lipase

12) Peripheral serum ferritin

13) C-reactive protein (detection may be selective based on the researcher's judgment)

14) 12-lead electrocardiogram

15) Echocardiography (during the screening period, and should be repeated promptly if symptoms or signs of heart failure appear, based on clinical signs).

16) Tumor markers (performed every 6 weeks, i.e., W12/W18/W24/W30/W36/W42/W48)

17) Imaging examinations and tumor assessment (every 6 weeks, W12/W18/W24/W30/W36/W42/W48)

18) Collect blood samples and monitor cytokines and overall immune status markers, CAR cell copy number, and CAR-T cell subsets/phenotypes (W6/W12/W24/W48) until two

consecutive test results are negative or below the detection limit; perform ADA, RCL, and lentiviral genome insertion site detection (W12/W24/W48).

For detailed examination items, please refer to Table 2/Table 3 of the protocol flowchart. Researchers may add relevant tests based on the patient's actual situation, or conduct exploratory studies on tumor immune microenvironment and other characteristics based on the availability of clinical samples and informed consent.

7.12.3 Follow-up period from 48 weeks to 96 weeks after infusion (W48~W96)

Follow-up should be conducted every 12 weeks from week 48 (excluding the W48 visit) to week 96 after cell infusion, with each visit window lasting ±14 days. The following tests must be completed at the W60/W72/W84/W96 follow-up visits:

1) Physical examination

2) Vital signs

3) Blood oxygen saturation (pulse oxygen) measurement

4) Weight

5) ECOG score

6) Complete blood count

7) Urinalysis

8) Stool routine examination and occult blood test

9) Blood biochemistry

10) Peripheral serum ferritin

11) Coagulation test

12) Amylase and lipase

13) 12-lead electrocardiogram

14) Echocardiography (including LVEF)

15) Tumor markers

16) Imaging examination and tumor assessment

17) Collect blood samples and monitor CAR copy number and CAR-T cell subset/phenotype (W96) until two consecutive test results are negative or below the detection limit; perform ADA, RCL, and lentiviral genome insertion site detection (W96).

The detailed examination items are listed in the protocol flowchart. Researchers can add relevant tests based on the patient's actual situation, and can also determine whether to conduct

exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

If CAR copy number is still detectable in peripheral blood 2 years after cell infusion, then ADA testing will be performed every 6 months thereafter 2 years after cell infusion. If CAR copy number is not detected for two consecutive times after week 12, or if the individual dies, withdraws informed consent, is discharged 15 years after cell infusion, or the trial is terminated (whichever occurs first), no further ADA testing will be performed.

RCL testing: During the W6-W48 follow-up period, RCL sampling points were W24 and W48; during the W48-W96 follow-up period, RCL sampling points were collected annually until the subject was lost to follow-up, died, withdrew informed consent, 15 years after cell reinfusion, or the trial was terminated (whichever occurs first).

Viral insertion site analysis: During the W6-W48 follow-up period, the sampling points for lentiviral insertion site analysis were W24 and W48; during the long-term follow-up period of W48-W96, the sampling points for lentiviral insertion site analysis were collected annually until the subject was lost to follow-up, died, withdrew informed consent, 15 years after cell reinfusion, or the trial was terminated (whichever occurs first).

7.12.4 Survival follow-up

For subjects experiencing disease progression or initiating new anti-tumor therapy, a survival follow-up phase will commence, with follow-ups conducted every 12 weeks (±14 days) via telephone (telephone, outpatient visit, or mail) until the subject dies, is lost to follow-up, requests withdrawal from further follow-up, or the program is terminated at the request of the principal investigator, ethics committee, or regulatory agency, whichever occurs first. The following data will continue to be collected during survival follow-up:

1) Record all subsequent anti-tumor treatments;

2) Record survival status;

3) Detection of ADA, RCL and lentiviral genome insertion sites.

7.13 Unplanned visits

visits during and after the study should be recorded in the EDC (Educational Data Sheet). During unplanned visits, vital signs, physical examination, adverse events, concomitant medications and treatments, and any changes deemed necessary by the investigator should be recorded, depending on the purpose of the visit. If a subject withdraws from the study during an unplanned visit, the above information should also be recorded in the EDC .

All unplanned visits occurring during the study or after the study treatment period must be recorded in the original medical record and EDC . During unplanned visits, record any relevant

adverse reactions and their changes, concomitant medications and treatments, and any other information deemed necessary by the investigator.

7.14 Assessment type

7.14.1 Therapeutic effect evaluation

Imaging assessments (plain and enhanced MRI or CT scans, specific sites to be examined, within 28 days prior to IMC001 infusion) can serve as a baseline. If the subject receives bridging therapy after apheresis, the subject will be assessed after bridging therapy. If the investigator assesses that the subject has achieved CR, IMC001 infusion will not be permitted. Imaging assessments will then be performed at scheduled visits according to the imaging assessment schedule in Table 7, until disease progression, 2 years (96 weeks) post-infusion , loss to follow-up, withdrawal of informed consent, or death (whichever occurs first).

Table 7 Imaging Assessment

operate	Screening/Baseline	Treatment/Follow-up Period
Contrast-enhanced CT or MRI (chest, abdomen, pelvis)	Must be completed	Follow the visit form 1 .
Whole body bone scan	If clinical indications exist	not applicable
Head CT or MRI	Must be completed	If clinical indications exist
Bone X-ray or CT/MRI (only applicable to subjects with bone lesions)	If a bone scan shows punctate areas of concentrated radioactivity	If bone lesions are found during the screening period, they should be monitored every 8 weeks (±7 days).
Color Doppler imaging of the skin (only applicable to subjects with skin lesions)	If skin lesions are found during the screening period, then the procedure must be completed.	If skin is found during the screening period

Tumor efficacy was assessed by the research center according to the RECIST version 1.1 criteria for evaluating efficacy in solid tumors (see Annex 2) . The assessment results from the research center investigators will be used for primary endpoint analysis and treatment decisions.

The assessment time points are as follows: imaging examinations must be performed within 28 days prior to infusion as the baseline for this study; assessments should be performed at W4, W8, W16, and thereafter every 8 weeks (every 3 months after 48 weeks) until disease progression, other anti-tumor treatments, loss to follow-up, death, withdrawal of informed consent (whichever occurs first), and withdrawal /discontinuation (within 30 days of withdrawal/discontinuation). See

Table 1 for details REF _Ref149643164 \h * MERGEFORMAT . Imaging assessments following unplanned confirmation of efficacy assessments should be performed according to the original assessment schedule. The assessment methods and techniques used to determine tumor and report lesion characteristics for each subject should be the same at baseline and during follow-up.

All subjects will undergo chest, abdominal, and pelvic CT/MRI scans at screening/baseline, followed by visits as scheduled in Table 1. If a subject has contraindications to intravenous contrast agents for CT at baseline or during the study, evaluation may be performed using plain chest CT scans combined with contrast-enhanced abdominal and pelvic MRI.

Subjects with clinical evidence of bone metastasis must undergo a whole-body bone scan at baseline, in accordance with the research center's treatment guidelines. If a punctate area of radioactive concentration is found on the baseline whole-body bone scan but not on a chest, abdominal, or pelvic CT (or MRI) scan, a local CT, MRI, or X-ray should be performed at baseline and followed up at a subsequent scheduled visit. A repeat whole-body bone scan is not required after baseline unless clinically indicated.

Color photography should be used to document baseline skin lesions, including a ruler to help confirm lesion size in the photographs. Skin lesions already documented during screening should be documented again during subsequent tumor assessments. If subcutaneous masses or lymph nodes are palpable (e.g., large in size) and can be evaluated clinically and by imaging techniques, CT or MRI should be used.

7.14.2 Safety and tolerability assessment

The following assessment methods will be used in the study to monitor drug safety:

Safety monitoring indicators include: adverse events, clinical laboratory test results (routine blood and urine tests, blood biochemistry, coagulation function, etc.), vital signs, physical examination, echocardiography, 12-lead electrocardiogram, and physical examination findings (including weight and ECOG performance status score). Safety will be comprehensively evaluated based on the type, frequency, and severity of adverse events.

Except for the CRS and ICANS classification according to the 2019 ASTCT CRS/ICANS classification criteria, the clinical safety of the study treatment was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE 5.0) throughout the study period.

At each visit, the subject's adverse events (AEs) must be assessed. The EDC should record the start and end times of the AE, severity level, relevance to the study drug and its therapeutic effect, whether there is any concomitant treatment, and the outcome.

7.14.2.1 Physical examination

according to Table 1 .

According to the schedule, physical examinations will be conducted at different times, including general condition, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, limbs, blood vessels, and nervous system. If indicated by medical history and/or symptoms, examinations of the rectum, external genitalia, breasts, and pelvis will be scheduled.

Researchers can increase the frequency of physical examinations based on clinical needs.

7.14.2.2 Blood oxygen saturation (referring to pulse oxygen)

The oxygen saturation of the brain can be characterized by measuring the arterial oxygen saturation of the finger using a non-invasive pulse oximetry method.

7.14.2.3 vital signs

Perform vital sign checks as shown in Table 1 .

Vital signs include pulse, respiratory rate, blood pressure, and body temperature. Pulse, respiratory rate, and blood pressure are measured after the subject has been sitting still for 5 minutes. Systolic and diastolic blood pressure are measured using an appropriately sized cuff. If the results are abnormal, the measurement is repeated or a different instrument is used to confirm the result.

When vital signs measurements are performed concurrently with PK or other blood sample collection, the vital signs measurements will be performed before blood sample collection to maximize the accuracy of blood sample collection timing and minimize the potential impact of blood sample collection on safety assessment records.

On the day of cell infusion (D0) and the following day (D1), if the subject is under electrocardiographic monitoring, no additional vital signs checks are required.

7.14.2.4 ECOG physical fitness status

ECOG performance status should be assessed at each visit as specified in the visit schedule and procedures (Table 1 , Appendix 1), and it is recommended that the same investigator conduct the assessment each time.

7.14.2.5 Height and weight

Measure height (cm) and weight (with underwear on, shoes off, accurate to 0.1kg).

7.14.2.6 Laboratory assessment

The specific time points for laboratory tests are detailed in Table 1. Researchers may increase the frequency of tests based on clinical indications. Specific assessment items are shown in Tables 8 and 9. The tests listed in Table 8 are conducted in the research center laboratory. The tests listed in Table 9 are performed by the central laboratory.

surface 8 Research Center Clinical Laboratory Tests

Inspection Classification	**Check Name**
Blood routine	White blood cell count, absolute lymphocyte count, absolute neutrophil count, absolute monocyte count, absolute eosinophil count, absolute basophil count, neutrophil percentage, lymphocyte percentage, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin level, platelets.
Urinalysis	Specific gravity, pH value, bilirubin, urine protein, glucose, ketone bodies, urobilinogen, nitrite, red blood cells, and white blood cells
Stool routine and occult blood test	Includes: color, shape, white blood cells, red blood cells, and occult blood test.
Blood biochemistry	The blood biochemistry test must be performed on an empty stomach and includes the following tests: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (γ-GT), Total bilirubin (TBIL), Direct bilirubin (D-BIL), Indirect bilirubin, Alkaline phosphatase (AKP or ALP); Glucose, Total protein (TP), Albumin (ALB), Globulin (G), Albumin/Globulin (A/G) ratio; Urea, Creatinine, Uric acid; Lactate dehydrogenase (LDH), Creatine kinase (CK), Creatine kinase isoenzyme (CK-MB), Troponin, C-reactive protein (CRP), Ferritin; Total cholesterol, Triglycerides, High-density lipoprotein, Low-density lipoprotein, Sodium, Potassium, Chloride, Calcium, Magnesium; If the research center's creatine kinase (CK) and creatine kinase isoenzyme (CK-MB) tests are not included in the biochemistry tests, they will need to be performed separately.
Coagulation function test	This includes: prothrombin time, activated partial thromboplastin time, thrombin time and international normalized ratio (INR), fibrinogen, fibrin degradation products, and DD dimer.
Serological virology test	Pathogen testing will be conducted during the screening period, including HBsAg, HBsAb, HBeAg, HBcAb, HBeAb, HCV antibody testing, HIV antibody testing, syphilis antibody testing, EBV testing, CMV testing, and human T-lymphotropic virus (HTLV) testing. HBsAg and hepatitis B core antibody should both be negative. If any of these are positive, peripheral HBV-DNA testing is required, and enrollment is only permitted if HBV-DNA levels are below the detection limit. Subjects who are HCV antibody positive should undergo HCV-RNA testing; only those with negative RNA results are eligible for enrollment. All pathogen testing results are subject to confirmation by the central laboratory.
pancreatic function	Serum amylase, serum lipase;

Tumor markers	This includes AFP (alpha-fetoprotein), CEA (carcinoembryonic antigen), and other tumor markers that researchers believe need to be added (such as CA19-9).

surface 9 central laboratory tests

Inspection Classification	Check Name
Serological virology test	Pathogen testing will be conducted during the screening period, including HBsAg, HBsAb, HBeAg, HBcAb, HBeAb, HCV antibody testing, HIV antibody testing, syphilis antibody testing, EBV testing, CMV testing, and human T-lymphotropic virus (HTLV) testing. HBsAg and hepatitis B core antibody should both be negative. If any of these are positive, peripheral HBV-DNA testing is required, and enrollment is only permitted if HBV-DNA levels are below the detection limit. Subjects who are HCV antibody positive should undergo HCV-RNA testing; only those with negative RNA results are eligible for enrollment. All pathogen testing results are subject to confirmation by the central laboratory.
tumor specimen	EpCAM expression

7.14.2.7 12-lead electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed during the screening period and subsequent visits. Subjects should rest in a supine position for 5 minutes before the ECG. ECG assessments will be performed according to the assessment schedule (Table 1). The frequency of assessments may be increased by the investigator based on clinical indications during the study.

Standard ECG parameters, including heart rate, QRS complex, PR, RR, and QT interval, will be measured. The heart rate-corrected QTc interval (QTcF) will be calculated using the FRP2Derica formula (Appendix 2).

7.14.2.8 Cardiac imaging examination (echocardiography)

Echocardiographic assessments will be performed according to the assessment schedule (Table 1). This includes left ventricular ejection fraction (LVEF) and diagnosis. Throughout the study, it is recommended that the same technician use the same equipment to perform LVEF assessments for each subject whenever possible.

7.14.2.9 Pregnancy and fertility assessment

will be conducted according to the assessment schedule in Table 1. Women of childbearing age are not required to undergo pregnancy testing, but these female participants must meet the criteria for childbearing age status in Section 5.1, Clause 11 of this protocol. Upon pregnancy, the participant must immediately discontinue the study drug and withdraw from the study; this event must be recorded in the Clinical Study Pregnancy Form.

7.14.3 Pharmacokinetic assessment

7.14.3.1 Blood sample collection and testing

must be entered into the EDC . At the date and time of biomarker and pharmacokinetic blood sample collection, a pharmacokinetic sample must be collected first.

Blood samples were collected for PK analysis, see Table 1 .

Blood samples for PK assessment will be collected and processed according to the instructions in the Laboratory Manual.

7.14.3.2 Pharmacokinetic assessment

PK indicators: The expansion and survival of EpCAM CAR-T cells in peripheral blood after IMC001 infusion were detected by qPCR and flow cytometry. The main evaluation indicators included Cmax , Tmax , AUC_{0-28} , longest survival time and other relevant PK parameters.

7.14.4 Pharmacokinetic assessment

PD index: The level of cytokines in peripheral blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines such as IL-2, IL-6, IL-10, TNF-α , and IFN-γ .

7.14.5 Exploratory endpoint assessment

Follow-up of lentiviral insertion sites and replicating lentiviruses (RCLs) , changes in anti-EpCAM CAR-T antibodies (ADAs) in the blood before and after IMC001 treatment, characteristics of IMC001 CAR-T cell lymphocyte subsets / phenotypes before and after treatment, expression ratios and intensities of EpCAM targets, changes and quantitative analysis of biomarkers related to tumor immune microenvironment and overall immune characteristics, etc.

8 Adverse events

8.1 Definition of adverse events

An adverse event (AE) is defined as any adverse medical event that occurs to a clinical trial participant after they have signed an informed consent form, regardless of whether it is causally related to the investigational drug. AEs include, but are not limited to, the following:

- the original (pre-clinical) medical condition / disease (including the aggravation of symptoms, signs, and abnormal examination results);
- Any new adverse medical condition (including symptoms, signs, or newly diagnosed diseases);
- Abnormal test results with significant clinical significance.

Medical conditions/diseases predating informed consent are only recorded as adverse events (AEs) if they worsen after informed consent is signed. Any clinically significant abnormalities in laboratory or other safety assessments related to the underlying disease are not recorded as AEs unless the investigator determines the patient's condition is more severe than expected. Clinically significant laboratory test results during the screening period should be recorded as medical history,

not as AEs, unless the investigator believes the abnormality is due to the study procedure. Symptoms and signs relevant to the tumor at baseline should be recorded as adverse events if their severity or frequency increases during the study. However, disease progression assessed by imaging methods of cancer lesions should not be reported as an adverse event unless it is more severe than expected or the investigator believes the tumor progression is related to the study drug administration or study procedure. New-onset primary malignancy is considered an adverse event.

8.2 Reporting and follow-up of adverse events

A serious adverse event (SAE) is an adverse event that meets at least one of the following criteria:

- Caused death
- an event that would only cause death if the event were to escalate)
- The following situations will result in hospitalization or prolonged hospitalization, excluding:
  - ✓ Hospitalization or prolonged hospitalization that is not related to the worsening of AE is not itself an SAE . Examples include hospitalization for management reasons (such as physical examinations) and hospitalization as required by clinical trial protocols.
  - ✓ Hospitalization or prolonged hospitalization due to the need for close monitoring of the subject or specific medical procedures (including but not limited to examination purposes, recuperation, apheresis, lymph node dissection, infusion, and enhanced monitoring) is not considered SAE .
  - ✓ Elective hospitalization (e.g., elective surgery) unrelated to the worsening of adverse events.
- Causes permanent or severe disability or loss of function
- Causes congenital abnormalities or birth defects
- Other significant medical events that may not be immediately life-threatening or result in death or require hospitalization, but may endanger the subject or require intervention to prevent any of the consequences defined above. Examples include intensive treatment of anaphylactic bronchospasm in the emergency room or at home; cachexia or seizures that do not require hospitalization; and progressive drug dependence or substance abuse.

8.3 Classification of adverse events

Researchers should assess adverse events (AEs) according to the CTCAE 5.0 standard (except for CRS and ICANS, which should be evaluated according to the 2019 ASTCT CRC/ICANS grading standard, see Appendix 3, 15.3, ASTCT CRS and ICANS grading) to determine the severity of the AEs. CTCAE 5.0 severity grading:

- 1 : Mild; asymptomatic or with mild symptoms; clinically or diagnostically detectable only; no treatment required.
- 2 : Severe; requires minor, local or non-invasive treatment; age-appropriate limitations in instrumental activities of daily living (ADL) (instrumental ADL includes cooking, grocery shopping or dressing, using the telephone, managing finances, etc.)
- 3 : Serious or medically significant, but not immediately life-threatening; requires hospitalization or prolongs hospitalization; causes disability; limited independent living abilities (independent living abilities refer to bathing, dressing and undressing, eating, toileting, taking medication, etc., not being bedridden).
- 4 : Life-threatening; requires emergency treatment.
- 5 : Deaths related to AE (Adventure Effect).

8.4 Determining the causal relationship of adverse events

Researchers should use a dichotomy to assess the potential association between adverse events (AEs) and the investigational drug, evaluating whether the AE is reasonably relevant to the investigational drug and recording this in the Emergency Data Sheet (EDC): No (not relevant), Yes (relevant). When assessing causality, the following aspects should be considered:

- The time correlation between adverse events and administration of the investigational drug (including the order and reasonable time intervals).
- Do adverse events conform to the mechanism of action of the investigational drug?
- Do other medications or treatments lead to adverse events?
- Whether the subject's indications or other underlying/comorbid diseases could lead to the occurrence of adverse events.
- Whether adverse events improved or resolved after dose reduction or discontinuation of the investigational drug (if applicable).
- After recovery from an adverse event, whether the adverse event recurs upon re-administration of the investigational drug (if applicable).

8.5 Outcome of adverse events

It can be described in the following ways:

- Recovery complete: Subjects have returned to baseline status.
- Recovery in progress: The incident is not yet fully resolved, but the subjects are in the recovery phase.
- Unrecovered: The event is in progress, such as an irreversible congenital malformation.
- Recovery with sequelae: only when the subject has long-lasting or lifelong sequelae, such as hemiplegia caused by stroke.
- Fatal: The event resulted in the death of the subject, and the date of death was the end date of the event.

- Unknown: Researchers are unable to obtain information on adverse event (AE) outcomes, such as loss to follow-up of participants.

If the outcome of an adverse event (AE) is "recovered", "recovered with sequelae", or "fatal", the AE end date must be recorded.

8.6 Collection of adverse events

All adverse events (AEs) should be collected from the date of signing the informed consent form until the subject's 48-week follow-up visit after cell infusion or the commencement of new anti-tumor therapy (whichever occurs first). For subjects who underwent apheresis but were not able to receive CAR-T cell infusion, only all adverse events reported within 30 days of the relevant procedure or treatment (e.g., apheresis, lymphocyte pretreatment) or the commencement of new anti-tumor therapy should be collected and reported, whichever occurs first. Serious adverse events occurring after the above collection period, which the investigator deems related to the study procedure and/or study treatment, should also be collected and recorded. Any AEs or SAEs directly related to the pre-screening procedure (i.e., fresh tumor biopsy) should be reported. If adverse events or serious adverse events occurring between the signing of the pre-screening consent form and the primary informed consent form are unrelated to the pre-screening tumor biopsy procedure, these AEs or SAEs do not need to be recorded.

Disease progression is defined as a deterioration in the subject's condition caused by the primary tumor targeted by the investigational drug. Symptoms and signs of disease progression do not need to be recorded as adverse events/severe illnesses (AEs) or adverse events (SAEs).

8.7 Follow-up of adverse events

Adverse events should be followed up until they return to normal/baseline levels, or until the subject is lost to follow-up or dies, or until the investigator deems follow-up unnecessary for a reasonable reason (e.g., stable AE). If an adverse event is irreversible, a reasonable explanation must be recorded in the original medical record, regardless of whether it is related to the study drug. The recovery status and date of the subject's AE or SAE should be recorded in the EDC and medical record. Furthermore, changes in the severity of the adverse event, its causal relationship with the study drug, measures taken with the study drug, treatment interventions administered, and outcomes should be assessed at each follow-up visit (the frequency of follow-up may be increased if necessary).

8.8 Serious adverse event reporting

All SAEs occurring during the study period, regardless of whether they are related to the investigational drug, should be reported to the local ethics committee as soon as possible upon becoming aware of them, in accordance with the committee's requirements. Researchers must complete a Serious Adverse Event Report Form and submit it to the sponsor within 24 hours of becoming aware of the SAE.

The first SAE report should include at least the following information:

- Identifiable subjects (e.g., subject ID);
- Suspicious research drugs;
- Identifiable source of the report (name of the researcher/reporter or research institution);
- Other relevant information about After Effects is provided for reference:
  - ✓ If the diagnosis is known, record it as a single disease or syndrome; if the diagnosis is unknown, report the signs and / or symptoms, avoiding colloquialisms and abbreviations.
  - ✓ The dates of the event's occurrence and resolution;
  - ✓ Severity;
  - ✓ Determining the relationship with the test drug;
  - ✓ The measures taken and the results regarding the investigational drug;
  - ✓ Treatment / rescue measures for adverse events (AEs) in subjects ;
  - ✓ Description of the adverse event process (including information on accompanying medications, etc.).

For the initial report, all information in the SAE report form should be completed to the greatest extent possible. The SAE must record this information and file it with the ethics committee. In reports involving death, researchers should provide our company and the ethics committee with any other necessary information, such as the autopsy report and the final medical report.

When completing the adverse event form in the EDC, researchers will use the National Cancer Institute Commonly Used Terminology Standard for Adverse Events (NCI CTCAE 5.0) to determine the severity of adverse events (CRS and ICANS are assessed according to the 2019 ASTCT CRC/ICANS grading standards), and record the grading in the EDC. If the severity of an adverse event changes, the original record information must be updated promptly.

8.9 Suspected and unexpected serious adverse reactions

SUSAR refers to a suspected and unexpected serious adverse reaction whose clinical manifestations exceed the information available in the investigational drug study manual.

All SUSARs that occur during the study period should be reported to the ethics committee as soon as possible, in accordance with the requirements of the local ethics committee, upon becoming aware of them.

8.10 pregnancy

Pregnancy itself is not considered an adverse event (AE). Any pregnancy that occurs in a subject or their partner between the start of the study drug treatment and a follow-up period of W48, regardless of whether the subject withdraws from the trial early, must be reported to the investigator. The investigator must complete a Pregnancy Report Form and submit it to the sponsor within 24 hours of learning of the pregnancy.

Researchers should advise female participants to discuss the risks of continuing the pregnancy and the potential impact on the fetus and breastfed infant.

Researchers must follow up on the pregnancy outcome until one month after delivery or at the end of the pregnancy, and report the results to the sponsor. If the pregnancy outcome is stillbirth, miscarriage, or fetal malformation, it is considered a SAE and must be reported according to the SAE timeline requirements .

9 Data collection and management

9.1 Data confidentiality

In this study, researchers must protect the privacy of the participants. Data protection and privacy regulations must be followed when collecting, transmitting, processing, and storing participant data. After explaining the following matters to the participants as required, written informed consent must be obtained from them:

- What protected health information (PHI) needs to be collected from the participants in this study?
- The researchers, departments, institutions that can obtain this information, and the reasons why;
- Researchers, departments, and institutions that may use or disclose this information;
- Participants have the right to withdraw their authorization to use their PHI at any time during the study.

If a subject withdraws their authorization and no longer consents to the collection or use of their PHI, the researchers are still permitted to use all information collected prior to the withdrawal of authorization, as per regulations. For subjects who have withdrawn their authorization and no longer allow researchers to collect or use their PHI, researchers should endeavor to obtain the subject's consent to collect at least the information regarding their vital status (i.e., whether the subject is alive or dead) for the scheduled study period.

The data acquisition system used in this study has robust security features, encrypting all transmitted data to prevent unauthorized access to the participants' confidential information. Authorized researchers access the system using a unique user code and password, ensuring that only authorized personnel who have completed the necessary training can access the system.

When entering critical and sensitive personally identifiable information (initials of the subject's name and exact date of birth), the system will prompt the research center to confirm whether this data collection is permissible. If the research center reports that such data collection is not permitted under national laws or ethics committee standards, the system will no longer require the initials of the subject's name. The system will then require the subject's month and year

of birth (instead of the exact date of birth) to assess whether the subject meets the protocol's age requirements and to ensure that laboratory test results are placed within the appropriate age-related normal range when evaluating them.

9.2 Research monitoring

Before the research begins, at the center's kick-off meeting or researcher meeting, staff from EmoFeng (or its designated CRO) will work with the research center staff to explain the research plan and EDC .

During the study, clinical monitors will visit the center regularly to ensure that the submitted data is accurate and conforms to the source documents; review and properly store the study products; correctly obtain and file informed consent forms from participants; confirm that participants entering the study meet the study inclusion and exclusion criteria; record SAEs as required; and determine the proper storage of all necessary documents required by GCP.

Researchers must allocate sufficient time to cooperate with monitoring activities. Researchers will also ensure that monitors or other quality assurance reviewers have access to all the aforementioned research-related documents and methods of accessing research-related facilities (such as pharmacies, diagnostic laboratories, etc.), and that there is sufficient space for on-site monitoring.

During the study, researchers must retain the source files for each participant, and all data obtained during the study should be promptly entered into the EDC (Early Data Center). The source files for all data entered into the EDC should be kept in the patient's medical history; these source files typically include laboratory tests, imaging studies, electrocardiograms, and echocardiograms. Researchers must retain the participant's original signed ICF (providing a copy to the participant), and the signing date of the ICF will be recorded in the EDC . Data directly entered into the EDC will be considered raw data.

During central monitoring, clinical monitors will verify the original data entered into the EDC against the source files. After completing the verification, the clinical monitors will discuss missing and unexplained data with the investigators.

9.3 Data collection

Researchers (and appropriate authorized personnel) will be granted access to the EDC (Electronic Data Center). Only researchers and authorized personnel can enter and correct data on the EDC . Other research center staff who have not received training are not allowed to access the EDC system.

an EDC (Educational Data Sheet) for each enrolled participant to reflect findings from their most recent study observations. Therefore, the EDC should be completed as soon as possible after a participant completes a visit or assessment . Researchers should verify the accuracy of the data

entered into the EDC . If some assessments could not be performed, or certain information was unavailable, inapplicable, or unknown, the researcher should note this in the EDC .

During the study, samples (tissues) for PK and biomarker research were collected from the research center and analyzed by a laboratory designated by EMUFENG. Research center staff designated by the investigator entered the required information from the study protocol into the PK and biomarker sample collection EDC and the designated CRO application form. Clinical monitors reviewed the accuracy and completeness of the relevant EDCs and, together with research center staff, corrected any discrepancies as required. Clinical monitors also reviewed the completeness of the application forms.

9.4 Data management and quality control

EmoFeng staff (or designated CRO) will review the completeness and accuracy of data entered by research center staff. During routine monitoring, relevant monitors or data management personnel will raise questions regarding the EDC . Authorized personnel at the research center will respond to the questions posed to researchers and make necessary modifications to the data. The names of the personnel who responded to the questions, as well as the time and date of their responses, will be recorded.

Medical history will be coded according to the MedDRA (Medical Terminology Standards for Pharmaceutical Administration); concomitant medications will be coded according to the WHO-DDE (World Health Organization Drug Dictionary Enhanced Version) which uses the Anatomical Therapeutic and Chemical Classification (ATC) system. Medical history and concomitant medications will be summarized in the FAS (Fluid Medical Information System).

Centralized processing of PK sampling and biomarker samples and/or data, and sending the results via email to Emufeng Company (or a designated CRO).

At the end of the study, all deviations from the study protocol will be confirmed. After these measures are completed and the completeness and accuracy of the data are verified, the database will be locked for data analysis. Any modifications to the locked data must first obtain joint written authorization from the biostatistics and data management lead and the clinical research lead. For EDC studies, after the database is locked, researchers will receive a CD-ROM or paper copy of the participant data, which will be stored at the research center.

10 Statistical analysis

10.1 General principles of statistical analysis

The statistical considerations summarized in this chapter only outline the plan for the data analysis of this study; the statistical methods will be described in detail in a separate Statistical Analysis Plan (SAP).

All statistical analyses will be performed using SAS 9.4 or later. Typically, continuous variables will be described using the number of cases, mean, median, standard deviation, minimum, and maximum; unless otherwise specified, categorical and ordinal variables will be described using the frequency and percentage of each category or rank. Missing values will not be included in percentage calculations. All statistical tests will be performed using a two-tailed test with α=0.05, and two-tailed 95% confidence intervals (CIs) will be calculated.

10.2 Sample size determination

of this study , 7-15 subjects were enrolled. In the expansion phase, at least two dose groups were selected, with 5-10 subjects expanded in each group (in conjunction with the escalation phase, each dose group was expanded to approximately 10 subjects) . In the Phase IIa efficacy exploration phase , approximately 6-20 subjects were enrolled for each tumor type . Further expansion of enrollment may be conducted in the selected tumor types in subsequent Phase IIa phases, with the protocol revised and sample size determined based on statistical hypotheses and regulatory requirements.

10.3 Statistical Analysis Set

Enrollment Set : Contains all participants who have signed up for the ICF . The enrollment set will be used for describing and listing the participants' enrollment status.

Full Analysis Set (FAS): Includes all eligible subjects who received IMC001 cell infusion after enrollment. FAS is used for summarizing basic subject information and primary efficacy analysis.

The evaluable efficacy set (ES) includes subjects who received IMC001 cell infusion, had measurable lesions at baseline, and had at least one post-dose efficacy assessment. ES is used for supportive efficacy analyses.

Safety Dataset (SS): This dataset contains all subjects who underwent safety evaluations for the investigational drug. The SS dataset will be used for all safety analyses .

DLT analysis set: Subjects who received IMC001 cell infusion during the dose escalation phase and underwent a DLT observation period of at least 28 days, or who experienced a DLT event during the DLT observation period. The DLT analysis set was used for DLT analysis.

Pharmacokinetic Set (PKS): All enrolled subjects who received IMC001 cell infusions, had at least one valid PK data point, and did not experience any protocol deviations that would significantly affect PK evaluation. These will be used for PK analysis.

Pharmacodynamic analysis set (PDS): Subjects who received partial or full planned total doses of IMC001 cell infusion therapy, and who had baseline and at least one post-baseline assessable pharmacodynamic endpoint.

Immunogenicity Analysis Set: This set includes subjects who received IMC001 cell infusion therapy and had at least one post-treatment ADA result. This dataset was used for immunogenicity analysis.

10.4 Demographic information, medical history, baseline characteristics and concomitant medications

FAS will be used to summarize demographic information and baseline characteristics. Demographic information and baseline characteristics data, medical history, and concomitant medications will be analyzed using descriptive statistics (number of cases [n], mean, SD, median, minimum, and maximum) or frequency tables.

Medical history will be coded according to the MedDRA (Medical Terminology Standards for Pharmaceutical Administration); concomitant medications will be coded according to the WHO-DDE (World Health Organization Drug Dictionary Enhanced Version) which uses the Anatomical Therapeutic and Chemical Classification (ATC) system. Medical history and concomitant medications will be summarized in the FAS (Fluid Medical Information System).

The version of the dictionary used for encoding will be described in the summary report (CSR).

Demographic information and baseline characteristics are only included in the information collected/assessed during the screening period/baseline.

10.4.1 Subject demographic information

The participants' demographic information included: age, height, weight, ethnicity, and gender.

10.4.2 Past medical history and treatment history

Past medical history: This refers to the subject's past cancer history and cancer treatment history, including but not limited to surgical treatment, chemotherapy, radiotherapy, drug treatment and other treatments. Other past medical history or treatment history that the researchers consider important, in addition to cancer history, may also be recorded as appropriate.

Treatment history: Tumor diagnosis and treatment history includes cancer-related medical history and treatment history, as well as previous biomarker expression; during the screening period, complete past medical history, present medical history, and treatment history are collected. Subsequent visits only record newly emerging medical history.

If a subject's previous surgical history or non-tumor chronic disease has been cured or has recovered to a clinically insignificant state during the screening period, it will be recorded as past medical history.

Allergy history: history of allergy to immunotherapy, allergy to related drugs such as tocilizumab, cyclophosphamide, fludarabine or albumin-bound paclitaxel, allergy to IMC001 components such as albumin, DMSO or other serious allergies.

10.4.3 Concomitant diseases and concomitant medications

Concomitant diseases and medications that the subject had and continued to have after entering the trial, excluding tumor-related diseases and treatments.

All clinically significant abnormal symptoms, signs, laboratory or auxiliary examination results that are not related to the study disease and are found after ICF signing and before the subject's enrollment for leukocyte apheresis should be recorded as comorbidities. Abnormal results during the screening period caused by the study procedure should be recorded as adverse events (AEs).

10.5 Medication adherence

Treatment adherence was summarized using descriptive statistics (number of cases [n], mean, SD, median, minimum and maximum) and/or frequency tables.

Medication adherence (%) will be calculated as actual dosage / planned dosage × 100%.

10.6 Validity analysis

Efficacy analysis was conducted based on the full analysis set and the efficacy evaluable set.

ORR and DCR were analyzed, describing the number of cases and percentages, and the 95% two-sided confidence intervals for ORR and DCR were estimated using the Clopper-Pearson method.

The Kaplan-Meier method was used to analyze up to the end of the event time, including DOR, PFS, and OS, and Kaplan-Meier plots of the corresponding metrics were drawn.

Graphical analysis includes waterfall plots (for the best percentage change in the sum of the diameters of the target lesions relative to the baseline).

10.7 Security Analysis

Based on the DLT analysis set, descriptive statistics on the occurrence of DLT events in each dose group were performed, and the number and percentage of DLT events were summarized by dose level. A preliminary safety assessment of each dose group was then conducted based on the occurrence data.

According to the SS set, all AEs will be listed by subject. The number and percentage of subjects experiencing TEAEs will be calculated by system organ classification, preferred terminology, and group. SAEs, including deaths, and TEAEs leading to study cessation will be summarized.

Laboratory findings, vital signs, echocardiographic changes including LVEF, and changes relative to baseline (if any) were described by group. Other safety parameters were described using a similar methodology and by subject list.

10.8 Pharmacokinetic analysis

$_{Cmax}$, Tmax , and AUC $_{0-28}$, were calculated using a non-compartmental model of WinNonlin 8.2 (or later) pharmacokinetic software.

Pharmacokinetic analysis was performed based on PKS. Descriptive statistical analysis was conducted on blood drug concentration-time data according to the planned sampling time, calculating the arithmetic mean, standard deviation, median, maximum, minimum, coefficient of variation, and geometric mean of blood drug concentrations at each time point. Individual and mean blood drug concentration-time curves were then plotted.

Descriptive statistical analysis was performed on the pharmacokinetic parameters of different dose groups, and the arithmetic mean, standard deviation, coefficient of variation, median, maximum, minimum and geometric mean of the pharmacokinetic parameters of each dose group or different cohorts were calculated.

10.9 Pharmacokinetic analysis

Based on the pharmacodynamic analysis set, descriptive statistical analysis was performed on the pharmacodynamic indicators at each visit time point, and the mean, standard deviation, median, minimum, maximum, geometric mean, and geometric mean coefficient of variation were reported.

10.10 Exploratory indicator analysis

Descriptive statistical analysis will be used to determine the distribution of lentiviral gene insertion sites and the proportion of subjects with positive or negative RCL test results.

Descriptive statistical analysis will be used to analyze changes in IMC001 CAR-T cell lymphocyte subsets/phenotypes, as well as the expression ratio and intensity of EpCAM targets, tumor immune microenvironment characteristics, and biomarkers related to overall immune characteristics before and after treatment .

Descriptive statistical analyses will be used to calculate the presence and antibody titer and quantity of anti-EpCAM CAR-T antibodies, and the percentage of subjects who will report producing anti-EpCAM CAR-T antibodies. If sufficient data are available, the impact of anti-EpCAM CAR-T antibodies on pharmacokinetics, safety, and efficacy can also be assessed.

11 Ethical norms and management procedures

11.1 Compliance with laws and ethics

This study was conducted in accordance with Good Clinical Practice (GCP), the current Declaration of Helsinki, relevant regulations, and the opinions of the ethics committee.

11.2 Responsibilities of Researchers and Ethics Committees

Before the study begins, researchers/research institutions should obtain written approval from the ethics committee regarding the research protocol, informed consent form, participant recruitment procedures, and other written materials to be provided to participants. During the study, any additions or revisions to the research protocol, informed consent form, etc., should again be obtained in writing from an independent ethics committee or filed with the committee.

11.3 Informed consent procedure

During clinical research, if any serious or unexpected adverse event occurs that is related to the safety of the clinical research and may affect the safety of the subjects and the implementation of the research, the researchers must inform the ethics committee in accordance with the relevant regulations.

Researchers are responsible for explaining to each participant the purpose, methods, procedures, benefits, potential risks, alternative treatment options, and their rights and obligations. Participants should be informed that they have the right to withdraw from the study at any time without any loss of personal benefit. Researchers will recommend alternative treatments based on their individual circumstances. Women of childbearing age should be informed that if they become pregnant during the study, the investigational drugs may pose risks to the fetus, and these risks are currently unclear; therefore, if they participate in the study, they must adhere to the study's contraceptive requirements throughout the study period. Contraception is required for 12 months after cell infusion or before survival follow-up, whichever occurs later. If there is any doubt regarding a participant's adherence to the study protocol, that participant cannot participate in the study.

Before any research-related procedures can begin, a written informed consent form signed by the participant must be obtained. Prior to obtaining informed consent, the researcher or their designated representative should provide participants with sufficient time and opportunity to inquire about the details of the research and to decide whether to participate. The informed consent process must be documented in the original medical record. The informed consent form must be dated and signed by each participant or their legal guardian or representative, as well as the researcher who conducted the informed consent process. One original copy of the signed informed consent form should be retained by both the participant and the research center.

If any information is obtained during the study that relates to a participant's willingness to continue participating, the participant must be notified promptly to confirm their willingness to continue.

The revised informed consent form must be ethically approved before it can be provided to the participants.

By signing an informed consent form, participants must also agree to allow drug regulatory authorities, auditors, and authorized clinical monitors to review the original data obtained regarding the clinical study, and the reviewers must comply with the confidentiality statement.

11.4 Terminate research

EmoFeng has the right to terminate this study under the conditions stipulated in the clinical research agreement. An overview of the conditions for early termination of the study is provided in Section 4.4.

11.5 Paper publication

As the sponsor, Yimufeng has exclusive rights to this research. The authors and manuscript will reflect collaboration between multiple researchers and staff from the research center and Yimufeng. Authors will be determined in discussions with researchers before manuscript writing. Researchers should not disclose experimental results in any form without the sponsor's consent.

11.6 Research document record preservation

As required by the sponsor, researchers are required to maintain up-to-date and complete clinical research-related documents. As part of research monitoring, the sponsor will review these documents. Financial information is not subject to regulatory scrutiny and should be kept separately.

In addition, researchers must retain research records and original documents until their destruction is approved in writing by the sponsor. If a researcher retires, leaves the organization, or ceases to be responsible for maintaining research records for any other reason, the sponsor must be notified, and appropriate arrangements must be made for the retention of research records and original documents in accordance with national regulations (5 years after the completion of the clinical study). The sponsor should also retain clinical trial data for 5 years after the investigational drug is approved for marketing. Documents should be retained for a longer period if required by regulatory authorities or otherwise specified by the sponsor. The sponsor is responsible for informing researchers of the specific retention period for documents.

11.7 Deviation of plan

Researchers must read and comply with the protocol in its entirety , except in emergency situations where the researcher or a professional designated by the researcher (i.e., an assistant researcher) determines that intervention is necessary to protect the rights of the participants .

In the event of a significant deviation from the protocol due to an emergency, accident, or negligence, the researcher or designated personnel must contact the monitor as soon as possible. This allows the researcher and sponsor to make a joint decision early on regarding whether the participant should continue the study.

11.8 Research monitoring

Following prequalification and/or initiation of the clinical research center visit, the sponsor or its designated personnel will conduct regular monitoring visits and closing visits. In accordance with the guidelines for managing clinical trials of drugs issued by the Chinese and International Harmonisation Conferences (HCIC), investigators must provide adequate assistance to monitors, allocating sufficient time and space for them to examine original subject records, EDCs , inquiry forms, laboratory normal range collections (if applicable), records of investigational drug use, and regulatory documents.

The purpose of the study and monitoring is to verify the following:

- Protect the rights and welfare of research participants.
- The accuracy and completeness of the reported data are verified by original documents.
- All data is collected, tracked, and submitted by the research center to the sponsor or designated personnel, including unplanned visits and missed evaluations.
- The reported data is consistent with all raw data (e.g., laboratory test values, safety data, clinical database data).
- The trial will be conducted in accordance with the currently approved protocol, amendments, GCP, and applicable regulations.

If required by the National Medical Products Administration (NMPA) or other applicable regulatory agencies, researchers must allow them to inspect the research site and records. If the NMPA or other relevant regulatory agencies notify researchers of a required inspection related to this research, researchers must immediately notify the sponsor.

11.9 Inspection and supervision

Authorized representatives of the sponsor, regulatory agencies, and ethics committees may conduct audits or inspections of the research center, including verification of source data. Investigators will allow auditors from the sponsor, representatives from regulatory agencies, or ethics committees to inspect the storage area for the investigational drug, the inventory of the

investigational drug, drug counting records, participant records, and source documents and other records related to the clinical study. The purpose of the audit or inspection is to systematically and independently examine all activities and documents related to the clinical study and to determine whether clinical study activities are being conducted as scheduled, and whether relevant data are being recorded, analyzed, and accurately reported, in accordance with the clinical trial protocol, ICH GCP guidelines, and any applicable regulatory requirements. If an investigator is notified by a regulatory agency of an upcoming inspection, they should immediately notify the sponsor.

11.10 Plan revision

According to ICH GCP guidelines, researchers may not deviate from or change the protocol without the sponsor's consent and the written approval of the Ethics Committee (EC), except for necessary protocol revisions to immediately eliminate serious harm to the study participants , or changes that only involve logistical or administrative changes to the study (such as changes to monitors or telephone numbers).

Any changes to the protocol must be handled as a protocol revision , and any potential revisions must be approved by the sponsor. Written revisions must be submitted to the relevant regulatory authorities and the ethics committee of the research center . Researchers may only implement the changes after the ethics committee has approved the protocol revision , except for necessary changes to eliminate serious harm to subjects immediately . In such cases, the ethics committee must be notified within 5 days of implementing the changes.

All revisions to the protocol must be approved in writing by the relevant regulatory authorities and the ethics committee, except for administrative revisions, which only require notification and not written approval. Each revised version of the protocol will be distributed to all recipients, along with corresponding explanations.

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13 appendix

13.1 Appendix 1 ECOG Performance Status

Classification	Physical condition
Level 0	The patient's mobility is completely normal, with no difference from that before the onset of the illness.
Level 1	They can move around freely and engage in light physical activities, including general housework or office work, but cannot engage in heavier physical activities.
Level 2	They can move around freely and take care of themselves, but have lost their ability to work. They can get up and move around for at least half of the day.
Level 3	He can only partially take care of himself and spends more than half of his daytime hours in bed or in a wheelchair.
Level 4	Bedridden and unable to take care of himself.
Level 5	die

13.2 Appendix 2 RECIST 1.1 Criteria for Evaluating Treatment Response in Solid Tumors

The following translation is provided for researchers' reference.

Original English text : Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST Guideline (version1.1). Eur J Cancer. 2009 Jan; 45(2): 228-47.

I. Measurement of Tumor Lesions

1. Definition of baseline tumor lesions

The baseline of tumor lesions is divided into measurable lesions (at least one measurable lesion) : using conventional techniques, the diameter and length of the lesion... Lesions that can be precisely measured are ⩾ 20 mm or ⩾ 10 mm on spiral CT . Unmeasurable lesions include all other lesions (including small lesions, i.e., long diameter < 20 mm on conventional techniques or < 10 mm on spiral CT) , including bone lesions, meningeal lesions, ascites, pleural effusion, pericardial effusion, inflammatory breast cancer, carcinomatous lymphangitis of the skin or lung, abdominal masses and cystic lesions that cannot be definitively diagnosed or followed up on imaging.

2. Measurement Method

1) The same techniques and methods were used to assess lesions at baseline and during follow-up.

2) Superficial lesions, such as palpable lymph nodes or skin nodules, can be considered measurable lesions. Skin lesions should be photographed using color photographs with a ruler size.
3) Chest X- ray: Clear and well-defined lesions can be used as measurable lesions, but CT scan is preferred.
4) CT and MRI : For assessing measurable target lesions and evaluating treatment efficacy, CT and MRI are currently the best methods with repeatable follow-up. For the chest, abdomen, and pelvis, CT and MRI use 10 mm or thinner slices, while spiral CT uses continuous 5 mm slices. Special protocols are required for the head and neck and other special areas.
5) Ultrasound examination: When the endpoint of the study is objective tumor efficacy, ultrasound cannot be used to measure tumor lesions. It can only be used to measure superficial palpable lymph nodes, subcutaneous nodules and thyroid nodules, and can also be used to confirm the complete disappearance of superficial lesions after clinical examination.
6) Endoscopy and laparoscopy: While not yet widely and adequately used for objective evaluation of tumor treatment efficacy, they are primarily employed in controversial lesions or high-level research centers with clear validation objectives. Biopsy specimens obtained using these methods can confirm complete remission (CR) on pathological tissue .
7) Tumor markers: They cannot be used alone to judge treatment efficacy. However, if tumor markers are higher than normal before treatment, all markers must return to normal for clinical evaluation of complete remission (CR) . For disease progression to be considered, an increase in tumor markers must be accompanied by visible lesion progression.
8) Cytology and histopathology: In a few cases, cytology and histopathology can be used to differentiate between complete remission (CR) and partial remission (PR) , and to distinguish between benign lesions after treatment and residual malignant lesions. Any exudation that occurs during treatment requires cytological differentiation to indicate tumor remission, stabilization, or progression.

II. Evaluation of Tumor Response

1. Evaluation of baseline tumor lesions

To establish the baseline total tumor burden, this must be compared in subsequent measurements. There must be at least one measurable target lesion, and if it is a limited, isolated lesion, it must be confirmed by histopathology.

1) Measurable target lesions: These should represent all affected organs, with a maximum of two lesions per organ and a maximum of five lesions in total. These should be measured and recorded at baseline. Target lesions should be selected based on their long diameter and the accuracy and repeatability of measurement. The calculated sum of the diameters of all target lesions (including the longest diameter of non-nodular lesions and the shortest diameter of nodular lesions) will be reported as the baseline diameter sum. If lymph node diameters are

included, as mentioned above, only the shortest diameter will be counted. The baseline diameter sum will serve as a reference value for the disease baseline level.

2) Non-target lesions: All other lesions should be treated as non-target lesions and recorded at baseline. Lesions that do not require measurement should be monitored for their presence or disappearance during follow-up.

2. Standards for Relief

1) Evaluation of target lesions:

- Complete remission (CR): After treatment, all target lesions disappear, the short diameter of all pathological lymph nodes (including target nodules and non-target nodules) must be reduced to < 10 mm , and tumor markers return to normal.
- Partial remission (PR): After treatment, the sum of the diameters of the target lesions decreased by ⩾ 30% from the baseline level .
- Disease progression (PD): After treatment, the subject is considered to have ⩾ 1 new lesion or the minimum sum of diameters of all target lesions as a reference, with a relative increase of ⩾ 20% in the sum of diameters (or the baseline value if the baseline measurement is the minimum); in addition, the absolute increase in the sum of diameters must be ⩾ 5 mm .
- Disease stability (SD): After treatment, the degree of reduction or increase in target lesions in the subject is between PD and PR , and the minimum value of the sum of diameters can be used as a reference.

2) Evaluation of non-target lesions:

- CR : All non-target lesions disappeared, and tumor marker levels returned to normal. All lymph nodes were of non-pathological size (short diameter < 10 mm).
- SD : One or more non-target lesions and / or tumor markers that are elevated to normal and persist.
- PD : The appearance of one or more new lesions and / or the presence of non-target lesions.

III. Overall Evaluation of Therapeutic Effect

Optimal overall response evaluation is the record of the best response from the start to the end of the trial, taking into account any necessary conditions for confirmation. Sometimes a response occurs after treatment ends; therefore, the protocol should clearly state whether the post-treatment response evaluation is considered within the scope of optimal overall response evaluation. The protocol must clearly define how any new treatments prior to progression affect the optimal response. A patient's optimal response depends primarily on the results of both target and non-target lesions, as well as the presentation of new lesions. Furthermore, it depends on the nature of the trial, protocol requirements, and outcome measurement criteria. Specifically, in non-randomized trials, response is the primary objective, and confirmation of PR or CR is essential to determine which constitutes the optimal overall response.

- **Time point reaction**

It is assumed that a therapeutic response will occur at each specific time point for each regimen. Appendix Table 1 provides a summary of the overall therapeutic response at each time point for a patient population with measurable disease at baseline. If the patient has no measurable lesions (no target lesion), the assessment can be found in Appendix Table 2 .

When a study requires confirmation of a complete or partial response, the assessment of optimal overall response is as follows: A complete or partial response can only be declared if each subject meets the trial's criteria for partial or complete response and, as specifically mentioned in the protocol, undergoes a follow-up confirmation at a subsequent time point (usually four weeks later). In this case, the optimal overall response is explained in Appendix Table 3 .

Appendix Table 1. Time point response: Subjects with target lesions (including or excluding non-target lesions).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not Evaluable	No	PR
PR	Non-PD or not fully evaluable	No	PR
SD	Non-PD or not fully evaluable	No	SD
Not fully evaluable	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=Complete Response	PR=Partial Response	SD=Stable Disease	PD=Progressive Disease

NE = Cannot be evaluated

Appendix Table 2 Time Point Responses - Subjects with Only Non-Target Lesions

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR or Non-PD	No	Non-CR or Non-PD
Not Evaluable	No	Not Evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: For non-target lesions, "non-CR/non-PD" refers to efficacy superior to SD. Since SD is increasingly used as an endpoint for evaluating efficacy, the non-CR/non-PD efficacy standard was established to address situations where no lesions are specified for measurable progression. For unclear progression findings (e.g., very small, indeterminate new lesions; cystic changes or necrotic lesions of existing lesions), treatment can continue until the next assessment. If disease progression is confirmed in the next assessment, the progression date should be the date of the previously suspected progression.

Appendix Table 3. The optimal overall response needs to be confirmed for CR and PR efficacy.

Overall Response at First Time Point	Overall Response at Subsequent Time	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD if SD lasts for a sufficient duration, otherwise PD
CR	PD	SD if SD lasts for a sufficient duration, otherwise PD
CR	NE	SD if SD lasts for a sufficient duration, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if SD lasts for a sufficient duration, otherwise PD
PR	NE	SD if SD lasts for a sufficient duration, otherwise NE
NE	NE	NE

Note: CR stands for complete remission, PR for partial remission, SD for stable disease, PD for disease progression, and NE for non-evaluable response. Superscript "a": If CR truly occurs at the first time point, any disease that recurs at subsequent time points will still be rated as PD at later time points, even if the subject's response relative to baseline meets the PR criteria (because the disease will recur after CR). Optimal response depends on whether SD occurs within the shortest possible treatment interval. However, sometimes the initial evaluation is CR, but subsequent scans suggest that small lesions may still be present, so the subject's actual response at the first time point should be PR rather than CR. In this case, the initial CR assessment should be revised to PR, and the best response is PR.

1. Optimal Relief Assessment

Optimal response assessment refers to the minimum measurement recorded from the start of treatment until disease progression/relapse (the minimum measurement is used as a reference for progression). Even without evidence of disease progression (PD), patients who discontinue treatment due to worsening general condition should be considered to have "symptom deterioration," and the objective progression of the tumor should be recorded in detail after treatment cessation. Early progression, early death, and patients who cannot be evaluated should be identified. In some cases, it is difficult to distinguish between residual tumor lesions and normal tissue. When evaluating complete response based on such situations, it is recommended to examine residual lesions (fine-needle aspiration / biopsy) to confirm whether it is a complete response . When residual imaging abnormalities are considered to be fibrosis or scarring , FDG PET can be used, similar to a biopsy, to confirm whether it is a complete response (CR).

2. Frequency of tumor re-evaluation

The frequency of tumor re-evaluation depends on the treatment regimen. In reality, the duration of treatment benefit is unclear, and re-evaluation every two cycles (6-8 weeks) is reasonable. In special circumstances, this should be adjusted to a shorter or longer interval. Re-evaluation after treatment depends on the clinical trial endpoint: whether it's the response rate or the time to event (TTE), i.e., the time to progression/death (TTP/TD). If it's TTP/TD, routine repeat evaluation is necessary, and there are no strict guidelines for the interval between re-evaluations.

3. Confirm

The purpose of objective efficacy confirmation is to avoid inflated response rate (RR). Changes in tumor measurements for complete response (CR) and partial response (PR) must be repeatedly assessed and confirmed, and must be re-verified at least 4 weeks after the initial evaluation. Longer confirmation periods, as determined by the trial protocol, are also appropriate. For patients with disease stagnation (SD), there should be at least one SD measurement at least 6-8 weeks after treatment. Repeated confirmation of changes in tumor size is not necessary for clinical studies with progression-free survival (PFS) and overall survival (OS) as endpoints.

4. Remission period

It is from the first measurement of CR or PR until the first recurrence or progression of the disease.

5. Stable period

The time from the start of treatment to disease progression is called SD (sickness-prone) stage. The relevance of SD stage to clinical outcomes varies depending on the type of tumor and the degree of differentiation.

The remission period, stable period, and PFS are affected by the follow-up frequency after

baseline evaluation. Due to the influence of various factors such as disease type, stage, treatment cycle, and clinical practice, the basic follow-up frequency cannot be determined to date, which to some extent affects the accuracy of the trial endpoint.

IV. Results Report

All patients, including those who deviated from their treatment regimen or were ineligible, must undergo an intervention-to-treatment (ITT) assessment. Each patient must be categorized as follows: CR, PR, SD, PD, death from cancer, death from toxicity, death from other cancers, or unknown (insufficient data for assessment). All eligible patients should be included in the RR analysis, and all PD and deaths should be considered treatment failures. Conclusions are based on eligible patients, and further analyses can be conducted in different patient subgroups, providing 95% confidence intervals.

13.3 Appendix 3 Calculation formulas involved in the protocol

- QTcF calculation formula FridriricI formula

$$QTcF=\frac{QT}{\sqrt[3]{RR}}$$

QT refers to the interval between the start of the Q wave and the end of the T wave.

RR refers to the time interval between the occurrence of a QRS group and the occurrence of the next QRS group.

- The standard formula for calculating body surface area is Stevenson's formula .

BSA = 0.0061 × height (cm) + 0.0128 × weight (kg) − 0.1529

Note: BSA: Body Surface Area.

- Kidney function assessment: Cockcroft-Gault formula

Creatinine is measured in mg/dl.

For men: Creatinine clearance (ml/min) = (140 - age) × weight / (72 × Scr)

For women: Creatinine clearance (ml/min) = (140 - age) × weight × 0.85 / (72 × Scr)

Creatinine is measured in μmol/L.

For men: Creatinine clearance (ml/min) = (140 - age) × weight / 0.818 × Scr

For women: Creatinine clearance (ml/min) = (140 - age) × weight × 0.85 / 0.818 × Scr

Note: Scr: serum creatinine (mg/dl); age is in years; weight is in kilograms (kg).