A multicenter, randomized, controlled, open-label, Phase III confirmatory clinical study comparing the efficacy and safety of IMC002 with investigator's choice of therapy in adult subjects with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have received at least two prior lines of therapy and are positive for CLDN18.2 expression.

Clinical research protocol

Project number:	IMC002-RT02-RCT
Solution version number:	V 2.1
Version Date:	September 27, 2025

Sponsor: Suzhou Immunofoco Biotechnology Co., Ltd.

Principal Investigator's Protocol Signature Page

I have read this trial protocol (Version Number : V 2.1 Version Date: September 27, 2025) and confirm that I agree to conduct this study in accordance with this protocol. I agree to perform my duties in accordance with the Declaration of Helsinki, GCP, other applicable regulations, and this study protocol.

This study may only be conducted after obtaining approval from the Ethics Committee. During the implementation of the study, I will strictly adhere to the requirements of this protocol. If the protocol needs to be modified, it may only be implemented after notifying the researcher and obtaining their consent, and after re-approval or filing of the Ethics Committee, unless measures are necessary to protect the safety, rights, and interests of the subjects.

At the same time, as the principal investigator of this trial, I coordinate the overall progress of the trial.

Research Unit: _____

Name: _____

sign: _____

date: _____

Sponsor 's proposal signature page

Our company will conscientiously fulfill its sponsor responsibilities in accordance with Chinese Good Clinical Practice (GCP) regulations and will be responsible for initiating, applying for, organizing, and funding this clinical trial. We will assume legal liability for the medical expenses and appropriate financial compensation for any trial-related injuries or deaths incurred by subjects during the clinical trial, and will provide legal guarantees to the investigators. We agree to design and conduct this clinical trial in accordance with this protocol (Version Number: V 2.1 , Version Date : September 27 , 2025) .

Sponsor: Suzhou Yimufeng Biotechnology Co., Ltd.

Name: _____

sign: _____

date: _____

Description of major changes to the plan

Solution version number	Plan version date	Main changes and reasons
V1.0	March 18, 2025	not applicable.
V1.1	April 28, 2025	1. The research background section of the protocol updates the results of the IMC002 Phase I/ IIa study; 2. The inclusion criteria were increased to include "if the first-line treatment used three drugs including taxanes (or anthracyclines), platinums and fluorouracils at the same time, and the disease progression was assessed by the researchers, the patient could also be included as an eligible subject."
V1.2	June 18, 2025	Randomization stratification factors were modified according to changes in the treatment landscape.
V2.0	August 18, 2025	1. Based on communication with the CDE, the original co-primary endpoints of ORR and PFS were changed to a single endpoint of PFS; 2. Considering the changes in clinical practice, multiple PD-1/PD-L1 inhibitors have been approved as first-line and second-line drugs for advanced gastric cancer, and nivolumab has been removed from the comparator drug selection; 3. Based on the requirement of at least 100 cases in the CDE trial group, the sample size calculation was adjusted from 105 to 150 cases; 4. PFS2 was deleted as an exploratory endpoint; 5. Improved the description of the objectives and endpoints of the translational medicine section of the exploratory indicators; 6. Added descriptions of companion diagnostics; 7. Added life scale measurement; 8. Increase the possible adverse reactions and treatment of control drugs.

V2.1	September 27, 2025	1. The inclusion criteria include the addition of intolerance criteria, the addition of dose adjustments of control drugs due to safety reasons and the discontinuation of treatment due to intolerance. 2. In the bridging therapy and control drug section, add the selection of marketed drugs with gastric cancer indications or recommended by guidelines. 3. It is clear that the number of subjects in the experimental group is no less than 100. 4. According to the CDE's opinion, OS was selected as the key secondary endpoint, and OS-related sample size calculation was performed; relevant descriptions of the interim analysis were added. 5. After the disease progresses in the control group, patients have the right to choose subsequent salvage treatment that is in their own interests.

Head record

Project Summary

Protocol Name: A multicenter, randomized, controlled, open-label, Phase III confirmatory clinical study comparing the efficacy and safety of IMC002 with investigator's choice of therapy in adult subjects with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have received at least two prior lines of therapy and are positive for CLDN18.2 expression.
Protocol number: IMC002-RT0 2-RCT
Version number and date: V2.1 , September 27, 2025
Research phase : Phase III clinical study
Sponsor: Suzhou Immunofoco Biotechnology Co., Ltd.
Research **centers:** approximately 30
Study drug: Autologous CAR-T cell injection targeting CLDN18.2 (hereinafter referred to as CLDN18.2 CAR-T cells or CAR-T cells , codenamed IMC002), specification: 30 mL/bag.
Subject population: Adult subjects with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who are positive for CLDN18.2 expression .
Number of cases: Approximately 150
Study objectives and endpoints: **Research objectives:** ● **Main Purpose:** To evaluate the progression-free survival (PFS) of IMC002 compared with investigator's choice of therapy (ICT) as third-line or higher-line treatment for inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma that is CLDN18.2 positive . ● **Secondary objectives:** 1) To evaluate the efficacy of IMC002 compared with ICT as a third-line or higher treatment for inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma that is positive for CLDN18.2 . 2) Describe the security features of IMC002 . 3) Cell kinetics were evaluated in subjects infused with IMC002. ● **Exploratory purpose:**

1) be conducted including immunogenicity analysis, lentiviral insertion site analysis, and replication-competent lentivirus (RCL).
2) To evaluate the changes in cytokines before and after administration of IMC002 and their correlation with efficacy and safety.
3) To evaluate the correlation between biomarker changes before and after IMC002 administration and its efficacy and safety.
4) To evaluate the phenotypic changes of CAR-T cells before and after IMC002 administration.
5) To evaluate the correlation between changes in the tumor microenvironment of tumor tissue samples before and after IMC002 administration and its efficacy and safety.
6) To evaluate the effectiveness of subsequent IMC002 treatment in subjects in the control group.
7) To evaluate the effects of IMC002 and ICT on the quality of life of subjects.

Study endpoints:

- **Primary study endpoint:**

Progression-free survival (PFS) assessed by a blinded independent imaging review committee (BIRC).

- **Key secondary study endpoints:**

Overall survival (OS).

- **Secondary endpoints:**

1) Based on investigator-assessed PFS, objective response rate (ORR), disease control rate (DCR) , duration of response (DOR), and time to response (TTR) based on BIRC and investigator evaluation .
2) According to NCI CTCAE 5.0 (except CRS /ICANS , according to 2019 ASTCT CRS /ICANS grading criteria were used to evaluate the type, frequency, and severity of treatment -emergent adverse events (TEAEs) and treatment- related adverse events (TRAEs) , as well as changes in laboratory values, vital signs, and ECG.
3) Cell kinetic indicators include analysis of the number of CAR-T cells and CAR copy number in peripheral blood : such as C_{max} , T_{max} , AUC, C_{last} , T_{last} , C_{max}/T_{max} , and maximum survival time.

- **Exploratory endpoints:**

1) ADA immunogenicity analysis, lentivirus insertion site analysis, and replication-competent lentivirus (RCL) detection were performed.

2) cytokines (such as IL-2, IL-6, TNF - α, INF- γ, etc.) before and after IMC002 administration were detected.

3) Additional exploratory testing may be conducted in research centers with appropriate conditions to support the evaluation of changes in biomarkers (such as CLDN18.2, etc.) before and after administration of IMC002.

4) Additional exploratory testing can be performed at research centers with appropriate conditions to support the evaluation of changes in CAR-T cell phenotype before and after IMC002 administration (at time points with CAR-T expansion, such as if there are surplus samples).

5) In research centers with corresponding conditions, additional exploratory tests can be carried out to support the CAR-T expansion, immune cell composition (CD4+/CD8+ ratio, memory cell phenotype, etc.) and changes in patient tumor tissues.

6) subsequent IMC002 treatment for subjects in the control group, including ORR , etc.

7) The European Organisation for Research and Treatment of Cancer (EORTC) quality of life scale was used to assess the subjects' quality of life .

- **Study Design:**

This study is a multicenter, randomized, active-controlled, open-label, confirmatory clinical study to evaluate the efficacy and safety of IMC002 compared with ICT as third-line or higher-line treatment for subjects with advanced gastric/esophagogastric junction adenocarcinoma who are positive for CLDN18.2 expression .

Subjects meeting the eligibility criteria will be randomly assigned to either the experimental or control group in a 2 :1 ratio. Following randomization, subjects in the experimental group will undergo peripheral blood mononuclear cell (PBMC) collection (abbreviated as apheresis), bridging therapy (if necessary), lymphoproliferative conditioning (abbreviated as CLEA), and a single infusion of IMC002. Subjects in the control group will undergo apheresis and ICT treatment until intolerable toxicity, progressive disease (PD), initiation of new anticancer therapy, or death. In the control group, if PD or intolerable toxicity develops after ICT treatment, eligible subjects, after full evaluation by the investigator, may receive CLEA and IMC002 treatment.

Randomization stratification factors included:

- Eastern Cooperative Oncology Group performance status (ECOG PS): 0 or 1
- Liver metastasis: yes or no
- Previous lines of systemic therapy: 2 lines * or ⩾3 lines

* Patients who received only first-line treatment with a combination of taxanes (or anthracyclines), platinums, and fluorouracils and whose disease progressed as assessed by the investigator were considered to

have failed the second-line regimen.

Both groups of subjects will undergo relevant examinations according to the established visits in the trial flow chart to evaluate their efficacy, safety and cell dynamics.

A BIRC will be established in this study to evaluate the tumor status and treatment response of the subjects according to the BIRC charter.

An independent data monitoring committee (IDMC) has been established for this study, which will dynamically evaluate the clinical trial data in accordance with the IDMC charter requirements to assess the drug's efficacy, safety, and trial execution.

In this study, the protein expression level of Claudin18.2 will be detected in the central laboratory using the cell tight junction protein (Claudin) 18.2 antibody reagent (immunohistochemistry method) companion diagnostic kit.

Study population:

Subjects must meet all the following inclusion criteria and not all exclusion criteria to be enrolled.

Inclusion criteria

1. The age at randomization was at least 18 years old , and both men and women were eligible.
2. histologically or cytologically confirmed inoperable locally advanced or metastatic gastric/ gastroesophageal junction adenocarcinoma who have failed at least two previous lines of therapy :

   a. Radiographic progression or clinical worsening of symptoms during second-line treatment (if first-line treatment includes three drugs including taxanes [or anthracyclines], platinums, and fluorouracils, and the disease progression is assessed by the investigator, the patient may also be enrolled as an eligible subject; disease progression within 6 months after the end of neoadjuvant/adjuvant treatment is also considered a first-line treatment failure).

   b. Patients with intolerance to second-line treatment may also be enrolled in the study after full evaluation by the investigator. The definition of intolerance to previous treatment is as follows:

   - any Grade ⩾ 3 (according to NCI CTCAE v5.0 criteria) hematologic toxicity that has not recovered to Grade 1 or pre-treatment levels after 14 days of best supportive care;
   - any Grade ⩾ 3 (according to NCI CTCAE v5.0 criteria) non-hematologic toxicity (excluding alopecia and asymptomatic laboratory abnormalities) that has not resolved after 14 days of best supportive care.

3. Tumor tissue specimens (primary or metastatic, archived or newly collected) from subjects

are expected to be available and tested by a central laboratory, indicating positive histological staining for CLDN18.2 (defined as a positive tumor cell rate ≥40% and a staining intensity ≥2+) . If the subject has previously received other CLDN18.2-targeted therapies, tumor tissue specimens collected after that treatment are required to retest and evaluate CLDN18.2 expression levels .

4. The subject's expected survival period is ≥12 weeks.
5. According to the RECIST 1.1 standard, there must be at least one stably measurable target lesion or evaluable lesion, and the longest diameter of the largest lesion (or the shortest diameter if it is a lymph node lesion) should be ⩽5 cm .
6. ECOG performance status score is 0-1.
7. The subject must have adequate organ and bone marrow function. Laboratory screening must meet the following criteria. All laboratory test results should be within the stable ranges described below, and there should be no ongoing supportive treatment. If any laboratory test result is abnormal based on the following criteria , the test can be repeated within 1 week. If the test results still do not meet the following criteria , the patient has failed the screening.
   a) Blood tests [no enhanced blood transfusion (≥ 2 times within 1 week), platelet transfusion, or cell growth factor (except recombinant erythropoietin) within 7 days before the examination]: neutrophil count ≥ 1.5×10^{9}/L; platelet count (PLT) ≥ 75×10^{9}/L; hemoglobin content (Hb) ≥ 8.0g/dL; lymphocyte (LYM) ≥ 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 patients with liver metastasis, AST and ALT < 5×ULN;
   c) Renal function: Serum creatinine ≤ 1.5 × ULN. If serum creatinine is > 1.5 × ULN, creatinine clearance > 50 mL/min (according to the Cockcroft-Gault formula); qualitative urine protein ≤ 1+; if qualitative urine protein is ≥ 2+, a 24-hour urine protein quantitative test is required (a 24-hour urine protein quantitative test < 1 g is acceptable);
   d) Amylase and lipase ≤ 1.5 × ULN; alkaline phosphatase (ALP) ≤ 2.5 × ULN. For patients with bone metastases, ALP < 5 × ULN.
8. All toxic reactions caused by previous anti-tumor therapy have been alleviated to Grade 0-1 (according to NCI CTCAE Version 5.0) or to a level acceptable to the inclusion/exclusion criteria. This excludes other toxicities such as alopecia and vitiligo that the investigator believes do not pose a safety risk to the subjects.
9. Reproductive status: Female patients of childbearing age or male patients whose sexual partners are female patients of childbearing age are willing to take medically approved and highly effective contraceptive measures , such as intrauterine devices or condoms, from the

time the informed consent is signed until 12 months after cell infusion (female patients of childbearing age include premenopausal women and women within 24 months of postmenopause).

10. The subjects must sign and date the written informed consent form.
11. Subjects must be willing and able to comply with the scheduled treatment regimen, laboratory tests, follow-up and other study requirements.

Exclusion criteria

Subjects who meet any of the following conditions will not be included in this study;

1. Pregnant and breastfeeding women.
2. Positive human immunodeficiency virus (HIV) antibody; hepatitis B virus infection (HBsAg positive and/or HBc antibody positive, and HBV-DNA positive); acute or chronic active hepatitis C (HCV antibody positive and HCV-RNA positive); positive syphilis antibody; Epstein-Barr virus infection (IgM positive); cytomegalovirus (CMV) infection (IgM positive) ; positive human T- lymphotropic virus (HTLV); positive for novel coronavirus (COVID-19) and not reverting to negative within 7 days . The above pathogen test results are subject to the central laboratory test results.
3. Known HER2 expression is positive (defined as IHC 3+, or IHC 2+ and FISH+).
4. Active or clinically poorly controlled serious infection.
5. Patients had uncontrollable pleural effusion, pericardial effusion, and ascites before enrollment.
6. Extensive or diffuse lung metastases or extensive or diffuse liver metastases or extensive or diffuse bone metastases .
7. Blood oxygen saturation is ≤ 95% without oxygen inhalation.
8. Other serious pulmonary 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. Patients with deep and large ulcers of the primary lesion, or recurrence of the anastomotic site with tumor infiltration of the entire layer, or tumor lesions infiltrating large blood vessels, who are judged by the researchers to be at high risk of bleeding or perforation, were included in the CT/MRI or combined gastroscopy examinations.
10. Patients with known past or current hepatic encephalopathy requiring treatment; patients with current or history of central nervous system diseases, such as epileptic seizures, cerebral ischemia /hemorrhage, dementia, cerebellar disease, or any autoimmune disease involving the central nervous system; patients with central nervous system metastasis or

meningeal metastasis who are judged by the investigator to be unsuitable for inclusion.

11. unstable heart disease that requires treatment or heart disease that cannot be controlled after treatment, or hypertension that is poorly controlled as determined by the researchers (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 after standard treatment (fasting blood glucose ≥ 10.2 mmol/L).
12. Any of the following cardiac clinical symptoms or diseases within 6 months before cell infusion:
    a) Left ventricular ejection fraction (LVEF) < 50%;
    b) Myocardial infarction within 1 year; or unstable angina; or history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); use of pacemaker;
    c) Resting electrocardiogram (ECG) with QTc F >450 ms (male) or QTc F >470 ms (female);
    d) Resting electrocardiogram reveals clinically significant abnormalities (such as abnormalities in heart rate, conduction, or morphological characteristics), complete left bundle branch block, third- degree atrioventricular block, or a PR interval greater than 250 ms.
13. Evidence of a significant coagulopathy or other significant bleeding risk, including:
    a) clinically significant coagulation abnormalities;
    b) A history of intracranial hemorrhage or spinal cord hemorrhage;
    c) Patients whose tumor lesions invade large blood vessels and have a significant risk of bleeding;
    d) Patients with current unstable or active ulcers or active gastrointestinal bleeding;
    e) An embolic event occurred within 6 months before cell transfusion;
    f) Clinically significant hemoptysis or significant bleeding in tumor lesions occurred within 1 month before cell transfusion;
    g) Major trauma or major surgery within 1 month before enrollment;
    h) The presence of any bleeding disorders, such as hemophilia, von Willebrand disease, etc.;
    i) Use of anticoagulant therapy (except low molecular weight heparin) for therapeutic purposes within 2 weeks before cell transfusion;
    j) Patients are currently receiving conventional anticoagulant therapy (such as warfarin or heparin). Patients require long-term antiplatelet therapy (aspirin ⩾ 100 mg/day;

clopidogrel ⩾ 75 mg/day); dipyridamole, ticlopidine, or cilostazol.

14. Receipt of systemic steroids equivalent to >15 mg/day of prednisone for more than 3 days within 2 weeks before apheresis, excluding inhaled steroids.
15. Subjects requiring systemic treatment with corticosteroids or other immunosuppressive drugs during treatment. Subjects with any active autoimmune disease, or a history of autoimmune disease with expected recurrence (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 fully resolved in childhood and does not require any intervention in adulthood; or other subjects whose condition is not expected to relapse in the absence of external triggers.
16. Patients with previous or concurrent malignancies, with the following exceptions:
    a) Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing was required before study enrollment);
    b) Carcinoma in situ of cervical or breast cancer who has undergone curative treatment and has no signs of recurrence for at least 3 years before the study;
    c) The primary malignancy has been completely resected and remains in complete remission for ≥ 5 years.
17. Subjects who have previously received other gene therapies, including but not limited to CAR-T therapy and TCR-T therapy .
18. Received the following treatments or drugs before cell infusion: received chemotherapy, targeted therapy, biological therapy, endocrine therapy, immunotherapy and other anti-tumor treatments (except for treatments used in accordance with the protocol requirements before infusion, such as lymphoproliferative conditioning and bridging therapy) , less than 28 days or less than 5 half-lives (whichever is shorter) from the first infusion of treatment in this study ; received traditional Chinese medicine treatment with anti-tumor indications within 2 weeks before cell infusion.
19. There is a history of other severe allergies such as anaphylactic shock.
20. Subjects with severe mental disorders.
21. If a subject develops a new arrhythmia, including but not limited to arrhythmias that cannot be controlled with medication; hypotension requiring pressor medication; or bacterial, fungal, or viral infection requiring intravenous antibiotics , the investigator may determine that the subject is unsuitable for participation in the trial . Subjects who are taking antibiotics to prevent infection may continue to participate in the trial at the investigator's discretion.
22. Participation in other interventional clinical studies and use of study drug within 1 month

before the planned IMC 002 infusion .

23. The investigator assesses that the subject is unable or unwilling to comply with the requirements of the study protocol.
24. 4 weeks before the planned apheresis time or plan to receive a live attenuated vaccine during the study.
25. Subjects with gastrointestinal obstruction or obstructive jaundice are deemed unsuitable for participation in this trial by the investigator .
26. Subjects with any other concurrent serious and/or uncontrolled medical conditions who are deemed unsuitable for participation in this trial by the investigator.

Reassessment before apheresis

Subjects who are confirmed to be qualified by screening examination can undergo leukocyte apheresis.

Seven days before apheresis, the researcher needs to conduct relevant examinations (if the screening examination is no more than 7 days away from the apheresis, there is no need to re-examine, unless the researcher assesses that there are clear reasons that may cause the test values to change during this period). The patient should be re-evaluated and the subject must meet the following criteria: neutrophil count $\geqslant 1.5\times10^{9}$/L; platelet count PLT $\geqslant 75\times10^{9}$/L; hemoglobin content Hb $\geqslant$ 8.0 g/dL; lymphocyte LYM $\geqslant 0.5\times10^{9}$/L.

Evaluation before lympholysis pretreatment and IMC002 infusion

Pre-treatment assessment of leaching

If the subject meets any of the following criteria before lymphoproliferative pretreatment and is judged by the researcher to be unsuitable for subsequent trial procedures, lymphoproliferative pretreatment cannot be continued or needs to be delayed , and infusion cannot be performed or needs to be delayed.

1. ECOG performance status score $\geqslant$2 points;
2. Active infection: If the subject requires systemic anti-infective treatment or has a body temperature of $\geqslant 38^{\circ}$C within 7 days before lymph node clearance pretreatment, the investigator must discuss this with the sponsor before starting lymph node clearance pretreatment;
3. Patients are assessed by the investigator to have a high risk of bleeding or perforation;
4. with known or suspected central nervous system metastasis;
5. Surgery, interventional therapy, radiotherapy or immunotherapy for the disease underwent within 2 weeks before lympholysis pretreatment;
6. Blood test: Neutrophil count < 1.5×10^{9}/L; Platelet count (PLT) < 75×10^{9}/L; Hemoglobin

content (Hb) < 8.0 g/dL;

7. Liver function: Alanine aminotransferase (ALT) > 2.5×ULN, aspartate aminotransferase (AST) > 2.5×ULN, serum total bilirubin (TB) > 2×ULN; for patients with liver metastasis, AST and ALT > 5×ULN;

8. Renal function: Creatinine clearance < 50 mL/min (according to the Cockcroft-Gault formula);

9. Amylase and lipase > 1.5 × ULN; alkaline phosphatase (ALP) > 2.5 × ULN; for patients with bone metastases, ALP > 5 × ULN ;

10. international normalized ratio (INR) and partial prothrombin time (APTT) > 1.5 × ULN;

11. Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen)

12. Patients who have used systemic glucocorticoids within 7 days before lymph node clearance pretreatment and whose cumulative dose exceeds 70 mg of prednisone (except those who used inhaled or topical glucocorticoids);

13. Any toxic reactions caused by bridging therapy have not recovered to CTCAE grade 2 or below;

14. failure to complete the bridging therapy washout period;

15. Other complications or toxicities may place the subject at inappropriate risk for lymphoproliferative conditioning and IMC002 cell infusion, including but not limited to the development of new arrhythmias in the subject that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient's presence of major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the matter with the sponsor's medical department.

IMC002 Pre-infusion Assessment

Before IMC002 infusion, the subject's clinical status should not be significantly worse than that at the time of enrollment screening as assessed by the investigator, which would increase the risk of IMC002 infusion. On the scheduled IMC002 infusion day, if the subject meets any of the following criteria, IMC002 infusion should be delayed:

1. ECOG performance status score ≥ 2

2. Active infection: If the subject requires systemic anti-infection treatment or has a body temperature ≥38° C, the infusion cannot be given or needs to be delayed;

3. CTCAE grade 3 or higher non-hematologic toxicity (excluding grade 3 nausea, vomiting, diarrhea, or constipation) occurring after lympholysis pretreatment;

4. Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen);

5. Other complications or toxicities may place the subject at inappropriate risk for IMC002 cell infusion, including but not limited to the subject experiencing new arrhythmias that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient to have major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the medical situation with the sponsor.

For subjects who have completed cell preparation but do not meet the reinfusion criteria and need to delay infusion, if their body temperature does not return to normal within 7 days after the lymphatic ablation pretreatment or other toxicity does not recover to ≤ Grade 1, the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment. If for any reason the cell infusion is delayed for more than 7 days after the lymphatic ablation pretreatment, the infusion cannot be performed , or the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment to delay the infusion. It is recommended that the interval between two lymphatic ablations be no less than 4 weeks .

Treatment

- **experimental group**

Trial interventions and treatments : including apheresis, bridging therapy (if necessary), lymphoblastic leukorrhea clearance, and IMC002 infusion.

After randomization , the subjects will begin apheresis. Before apheresis and lymphoproliferative pretreatment, the researchers will judge the subject's status and consider bridging therapy based on the subject's clinical benefits and risks. The purpose of bridging therapy is to stabilize the subject's current disease status or reduce the subject's current tumor burden. The preferred drugs are those with gastric cancer indications in the instructions, or after the researchers combine clinical practice and the patient's previous medication status, irinotecan monotherapy can be used for 1-2 courses (recommended dose: irinotecan 150 mg/m ^{2} , intravenous drip, single dose) or FOLFIRI regimen (recommended dose: irinotecan 130-150 mg/m ^{2} , 5-fluorouracil 2400 mg/m ^{2} , intravenous drip, single dose) or paclitaxel (recommended dose: paclitaxel 135 mg/ m^2 , intravenous infusion, single dose) as bridging therapy. The use of bridging therapies other than the recommended regimen requires medical confirmation from the investigator and the sponsor. Bridging therapy must be completed 7 days prior to lymphoproliferative conditioning , or a washout period of at least five half-lives of the bridging agent from the time of lymphoproliferative conditioning (whichever is longer) . Once the IMC002 product has been prepared and meets the inspection and release specifications, and if

the subject meets the cell reinfusion criteria, IMC002 cell infusion can be performed. Subjects will receive a single infusion of two bags of IMC002 , for a total dose of 2.5×10^{8} ^{CAR} -T cells per subject.

Lymphocyte depletion pretreatment: This is lymphocyte depletion chemotherapy. This pretreatment is performed before IMC002 infusion to increase T cell counts and survival in vivo. Each subject will receive lymphocyte depletion pretreatment according to the following regimen before cell infusion. The specific dosage can be adjusted at the investigator's discretion. The lymphocyte depletion pretreatment regimen consists of fludarabine, cyclophosphamide, and nab-paclitaxel (FNC) . If a subject is allergic to or intolerant of nab-paclitaxel, the investigator may administer fludarabine combined with cyclophosphamide (FC), depending on the subject's condition.

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

Fludarabine 25 mg/m ^{2} /day × 2 days (day 1 and day 2 for clearing urethritis)

Cyclophosphamide 250 mg/m ^{2} /day × 3 days (lymph clearance on the first, second, and third days)

nab-paclitaxel 100 mg (2nd day after clearing stranguria)

If the subject is allergic to or intolerant to albumin-paclitaxel, the researcher may choose the following FC lympholysis pretreatment regimen based on the subject's condition.

(2) FC regimen: Fludarabine combined with cyclophosphamide

Fludarabine 20-25 mg/m ^{2} /day × 2 days

Cyclophosphamide 500 mg/m ^{2} /day × 2 days

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

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

If the researcher needs to use a lymphoproliferative conditioning regimen for a subject beyond the protocol, this should be discussed with the sponsor. CAR-T cell infusion can begin 1-2 days after the subject has received the lymphoproliferative conditioning regimen.

IMC002 Infusion : Subjects who have successfully prepared the IMC002 injection and have undergone lymphoproliferative pretreatment and are assessed by the investigator as eligible will continue to receive the IMC002 infusion . Prior to cell infusion, sufficient backup medications (e.g., at least two doses of tocilizumab) should be available, and emergency facilities and equipment should be readily available for prompt treatment in the event of a severe allergic reaction, severe hypotension, or other emergency. Thirty to sixty minutes before cell infusion, investigators may consider pre-treating subjects to prevent infusion reactions based on clinical experience , such as with histamines such as acetaminophen (300-1000 mg orally), promethazine

hydrochloride (25 mg intramuscularly), or diphenhydramine (50 mg). Following infusion, each subject is recommended to remain hospitalized for 14 days, or the investigator may determine the time of discharge based on the subject's condition .

- **Control group:**

After randomization, subjects will undergo single-dose sampling before receiving the investigator's selected treatment. Comparator drugs include apatinib mesylate, paclitaxel alone, docetaxel alone, or irinotecan alone. Drugs with gastric cancer indications in the package insert are preferred, or selected by the investigator based on clinical experience and the patient's previous medication history. Dose adjustments are permitted based on the subject's tolerance. This continues until toxic intolerance, disease progression, initiation of new anti-cancer therapy, or death, whichever occurs first. The trial center is responsible for drug storage and distribution, and the investigator will conduct safety and efficacy assessments on the subjects according to the established visits.

Apatinib mesylate: 850 mg, orally, once a day.

Paclitaxel alone: Paclitaxel 80 mg/m ^{2} , intravenous drip, on day 1, day 8, day 15, and repeat every 28 days.

Docetaxel alone: docetaxel 75-100 mg/m ^{2} , intravenous drip, on day 1, repeated every 21 days.

Irinotecan monotherapy: 150-180 mg/m ^{2} by intravenous drip on day 1, repeated every 14 days.

For subjects in the control group who have undergone apheresis and successfully prepared IMC002, if they develop PD or toxic intolerance after receiving ICT drug treatment, the researcher, after fully evaluating the subject's overall condition, believes that subsequent treatment with IMC002 is in the best interest of the subject and may recommend that the subject consider subsequent treatment with IMC002. Patients also have the right to choose subsequent salvage treatment that is in their best interests. If the subject is willing to receive this product, a further assessment of their condition before lymphoblastic leukemia and IMC002 cell infusion will be required, using the same assessment criteria as the experimental group. Those who meet the assessment criteria can begin the lymphoblastic leukemia and IMC002 treatment process, using the same treatment plan as the experimental group.

Research Assessment

Safety will be assessed by adverse events, ECOG performance status score , vital sign measurements, physical examination results , laboratory test results , electrocardiogram , and echocardiogram .

Tumor assessments will be conducted by the BIRC and the investigator according to RECIST 1.1 criteria . Starting from post-randomization apheresis, the first tumor assessment will

be conducted at week 8 ± 7 days (for the IMC002 trial group, this must also be at least 4 weeks post-infusion). Tumor assessments will be conducted every 6 weeks ± 7 days thereafter until disease progression, as determined by the investigator and confirmed by the BIRC , initiation of new anti-cancer therapy, death, loss to follow-up, or study withdrawal, whichever occurs first. For patients in the control group who receive IMC002 infusion after progression, the first post-infusion tumor assessment will be conducted at week 4 ± 2 days post-infusion. Tumor assessments will be conducted every 6 weeks ± 7 days thereafter until disease progression, as determined by the investigator, initiation of new anti-cancer therapy, death, loss to follow-up, or study withdrawal, whichever occurs first.

Survival status was collected every 12 weeks after entering the survival follow-up.

Tissue, blood, and serum samples will be collected from the subjects to evaluate characteristic information such as the expression ratio and intensity of the CLDN18.2 target, changes in biomarkers related to the tumor immune microenvironment characteristics and the body's overall immune characteristics, and cytokine level analysis, IMC002 cell dynamics, and immunogenicity analysis will be performed.

Sample size and statistical methods

Sample size:

This study used BIRC-assessed PFS as the primary endpoint. Early study data indicate that the median PFS (mPFS) observed in the IMC002 trial arm is approximately 6.9 months, while historical data indicate that the mPFS in the control arm (investigator's choice of treatment) ranges from 1.6 to 2.6 months. This study assumed mPFS of 5.2 and 2.6 months in the trial and control arms, respectively, and a true PFS hazard ratio (HR: IMC002 vs. investigator's choice of treatment) of 0.5. With a power of 85%, a one-sided type I error rate of 0.025, and a 2:1 randomization ratio between the trial and control arms , the final analysis required approximately 86 events.

Assuming complete enrollment within 12 months, the minimum follow-up is 3 months .

The sample size was also calculated based on the key secondary endpoint of OS . Assuming an exponential distribution for OS, the median OS in the control group was approximately 6 months, and the true OS hazard ratio (HR: IMC002 vs. investigator-selected treatment) was 0.56. OS will be tested at a one-sided 0.025 test level. With an assumed power of 80 % , the final analysis of OS will be conducted approximately 10 months after the last randomized subject, when approximately 112 events have been observed.

Considering a 20% dropout rate, approximately 150 subjects need to be enrolled. The trial group should enroll at least 100 subjects.

Interim analysis:

The interim analysis of OS will be conducted at the same time as the final analysis of PFS . The O'Brien-Fleming spending function (Lan-Demets algorithm) will be used to calculate the significance level for both the interim and final analyses of OS. Gate keeping will be used to control type I error. Hypothesis testing for the key secondary endpoint of OS will only be conducted if the hypothesis test for the primary endpoint of PFS is significant .

Analysis set:

Intention-to-treat (ITT) analysis set included all randomized subjects.

Modified intention-to-treat analysis set (mITT): all subjects who were randomized and received at least one dose of study treatment (IMC002 or ICT).

Per-Protocol Set (PP): Subjects in the ITT set who did not experience major protocol violations that affected the efficacy evaluation and who had at least one efficacy evaluation. Major protocol violations that affected the efficacy evaluation will be determined after discussion in the blind review meeting before the database is locked.

Safety Analysis Set (SS): includes all subjects who were randomized and received at least one dose of study treatment. Subjects will be analyzed based on the study treatment they received (IMC002 or ICT).

Cell Kinetics Set (PKS): All subjects who received IMC002 cell infusion, had at least one valid PK data, and did not experience protocol deviations that seriously affected the PK evaluation will be used for PK analysis.

Pharmacodynamic analysis set: All subjects who received IMC002 cell infusion and had baseline and at least one post-baseline evaluable pharmacodynamic index examination results.

Immunogenicity analysis set: All subjects who received IMC002 cell infusion and had at least one post-dose ADA result. This dataset was used for immunogenicity analysis.

Crossover Analysis Set: The crossover analysis set includes subjects randomly assigned to the control group who crossed over to receive IMC002 cell infusion. All analyses of safety and efficacy parameters collected after subjects received crossover treatment were performed using this analysis set.

Statistical analysis:

Demographics and other baseline characteristics:

will be summarized by treatment group using descriptive statistics in the ITT . Relevant medical history and current medical conditions at baseline will be summarized by system organ class and preferred term, as well as by treatment group.

Efficacy analysis:

Details of data processing, statistical methods, and result presentation will be described in detail in the Statistical Analysis Plan (SAP). The final version of the SAP will be finalized before

the database is locked. All statistical analyses will be performed using SAS version 9.4 or later. Generally, continuous variables will be described using the number of cases, mean, median, standard deviation, minimum, and maximum values; categorical and ordinal variables will be described using the frequency and percentage of each category or level. Time-to-event metrics will be analyzed separately using the Kaplan-Meier method. The median, 25th and 75th percentiles, and their 95% confidence intervals will be calculated for each cohort, and Kaplan-Meier curves will be plotted. Unless otherwise specified, missing values will not be included in the calculation of percentages.

The primary endpoint of this study was progression -free survival (PFS), as assessed by the BIRC. PFS was defined as the time from the date of randomization to the first documented disease progression (as assessed by the BIRC according to RECIST 1.1) or death from any cause . PFS analysis was based on the ITT dataset. If two or more consecutive tumor assessments were missed before the PFS event date, PFS was censored to the date of the last evaluable tumor assessment before the missed assessment . The Kaplan-Meier method was used to calculate the median PFS, quartiles, and 95% confidence intervals (CIs) for each group. Censorship was summarized, and KM curves were plotted. A stratified log-rank test was used to compare PFS between the two groups. A stratified proportional hazards regression model (the exact method was used for identical event times) was used to estimate the hazard ratio (HR) and 95% CI for the experimental group versus the control group. Stratification factors were used at randomization. Sensitivity analyses were also performed using data from the mITT and PP datasets.

The primary estimated objective PFS analysis will take into account different concomitant events as follows:

- Discontinuation of study treatment: PFS analysis will take into account all tumor assessments and deaths, regardless of discontinuation of study treatment for any reason (treatment strategy)
- Patients who underwent a crossover (for patients in the control group) or started a new anticancer treatment (for all patients) were treated with a hypothetical strategy whereby PFS would be censored at the date of the last adequate assessment or the date of randomization before the crossover or start of new anticancer treatment if no PFS event was observed before the crossover or start of new anticancer treatment.
- Any unforeseen concomitant events, such as those arising from public health emergencies, will be addressed through therapeutic strategies.

Treatment of missing values not related to concurrent events

The censoring rules for PFS follow the RECIST 1.1 guidelines and will be further detailed in the statistical analysis plan (SAP).

Sensitivity analysis

As a sensitivity analysis, the two treatment groups will be compared using a nonstratified log-rank test. A nonstratified Cox model will be used to generate the PFS hazard ratio and 95% confidence interval based on BIRC review. The sensitivity analysis estimates are the same as the key secondary estimates. Additional sensitivity analyses and estimates, if any, will be detailed in the SAP.

Supporting analysis

In the ITT, investigator-assessed PFS will be analyzed using a stratified Cox model, as in the primary efficacy analysis, and the treatment effect will be summarized as the hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians, and 95% confidence intervals will be provided for each treatment group.

In the ITT, hazard ratios and 95% confidence intervals for PFS based on BIRC review will be obtained from stratified and covariate-adjusted Cox models including sex and age. The final list of covariates included in the model will be provided in SAP.

If statistical significance is achieved in the primary analysis of PFS, subgroup analyses will be performed to assess the homogeneity of the treatment effect across demographics and baseline disease characteristics. Different thresholds or variables used for subgroup analyses will be detailed in the SAP. The number of subjects censored in the PFS analysis and the reasons for censoring will be summarized by treatment group.

Analyses supporting secondary objectives

Secondary efficacy endpoints will be assessed using ITT.

The key secondary endpoint, OS, was defined as the interval from the date of randomization to the date of documented death from any cause. For subjects whose deaths were not documented, those who had not died by the analysis cutoff date were censored at the time of last contact. The analysis will be based on data from the ITT population. The OS analysis will provide Kaplan-Meier curves, medians, and 95% confidence intervals for OS in each treatment group . A stratified Cox model will be used to calculate the hazard ratio (HR) and its 95% confidence interval for OS .

Disease control rate (DCR) is defined as the proportion of subjects who achieve BOR: CR , PR , SD , or non -CR/ non- PD . DCR will be analyzed using the same conventional analysis methods as ORR .

ORR is defined as the proportion of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR). The tumor response status was assessed by BIRC according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). Confirmation must be made by repeated assessment at least 4 weeks after the CR and PR response criteria were first achieved. For ORR, the chi-square test or Fisher's exact test was used to compare the difference between the two groups, and the difference in ORR and its 95% confidence interval were calculated. The analysis was based on the ITT set and included all randomized subjects,

regardless of whether they complied with the protocol or withdrew from the trial. Stratified analysis can be performed to assess the difference in efficacy between different subgroups, in which the stratification factors used at the time of randomization were used. Sensitivity analysis was also performed on data based on the mITT and PP sets.

Duration of response (DOR) was defined as the duration from the date of the first documented response (CR or PR) to the date of the first documented disease progression or all-cause death. If a patient had no events, the DOR was censored at the date of the last adequate tumor assessment. Subjects whose BOR never achieved a CR or PR were excluded from the analysis. The Kaplan-Meier method was used to estimate the DOR distribution function. The median DOR and its 95% CI are presented by treatment group .

Time to response (TTR), defined as the time from the date of randomization to the date of the first documented response (CR or PR , which must then be confirmed), was analyzed descriptively.

The above analyses will be performed based on BIRC assessment and local investigator assessment (according to RECIST 1.1).

The BOR for each subject was determined in order of overall response according to the following rules :

• CR = at least two CRs before disease progression , with at least 4 weeks between the two CRs .

• PR = at least two PRs before disease progression , with at least 4 weeks between the two PRs (and not meeting CR criteria).

• SD = SD in at least one assessment > 5 weeks after randomization (and does not meet CR or PR criteria).

• Non- CR/ non- PD = non- CR/ non- PD in at least one assessment > 5 weeks after randomization (and does not meet CR , PR , or SD criteria).

• PD = disease progression after randomization (and does not meet CR , PR , SD , or non-CR/ non- PD criteria).

• Not evaluable = all other lesions (i.e., not meeting confirmed CR or PR criteria or non-CR/ non- PD after > 5 weeks and no SD , or no early progression)

Analysis time point

The final analysis of PFS efficacy will be performed approximately 3 months after completion of enrollment when at least 86 PFS events have been observed. The interim analysis of OS will be performed at the time of the final analysis of PFS. The final analysis of OS efficacy will be performed approximately 10 months after the last subject is randomized when at least 112 deaths have been observed.

Security Analysis

All listings and tables are presented by treatment group using the safety set.

Exposure to each study drug was summarized descriptively, including the number of cycles received (number and percentage of patients), duration of exposure (days), total cumulative dose per patient, dose intensity, and relative dose intensity.

Adverse events (AEs) were coded verbatim to Medical Dictionary for Drug Regulatory Activities (MedDRA ®) terms according to NCI CTCAE 5.0 (except CRS and ICANS, which were coded according to 2019 ASTCT All treatment -emergent adverse events (TEAEs) were summarized .

Identify outliers in clinical laboratory data. Selected laboratory data are summarized by level. Changes in vital signs are also summarized by visit number.

Cell kinetic analysis

This study will collect PK samples according to the evaluation plan.

The main pharmacokinetic parameters of each subject were calculated using the non-compartmental model of WinNonlin 8.2 (or newer version) pharmacokinetic software, including peak concentration (C_{max}), time to peak concentration (T_{max}), area under the concentration-time curve (AUC), observed final concentration (C_{last}), last detectable time (T_{last}), C_{max}/T_{max}, etc.

Cellular kinetic analysis was performed based on PKS. Descriptive statistical analysis of blood CAR copy number versus time data was performed according to the planned sampling time. The arithmetic mean, standard deviation, median, maximum, minimum, coefficient of variation, and geometric mean of blood CAR copy number at each time point were calculated. Individual and mean blood CAR copy number versus time curves were plotted.

Pharmacodynamic 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 value, maximum value, geometric mean, and geometric mean coefficient of variation were reported.

If necessary, additional PD analyses can be performed.

Exposure-response (efficacy or safety endpoint) analyses may be performed if supported by data.

Immunogenicity analysis

Immunogenicity samples will be collected for this study as described in the evaluation plan.

Immunogenicity results will be summarized by number of patients and percentage using descriptive statistics. The incidence of positive ADA in patients with detectable ADA will be

reported. If data allow, the impact of immunogenicity on PK, efficacy, and safety will be assessed.

Other translational research analyses

This study will conduct translational research to analyze the correlation between changes in cytokines, biomarkers, and tumor microenvironment and clinical outcomes, as well as lentiviral insertion site analysis, replication-competent lentivirus (RCL) analysis, and CAR-T cell phenotypic changes .

Analysis of the correlation between companion diagnostic reagents and drug efficacy

using the Claudin 18.2 protein expression results detected by the cell tight junction protein (Claudin) 18.2 antibody reagent (immunohistochemistry method) to evaluate the effectiveness of IMC002 in treating patients with gastric or gastroesophageal junction adenocarcinoma with positive Claudin 18.2 expression.

period : Expected to be from May 2025 to May 2027

Abbreviations

Abbreviations	Chinese definition/explanation
ADA	Antidrug antibodies
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BIRC	Blinded Independent Imaging Review Committee
CABG	Coronary artery bypass grafting
CAR	Chimeric antigen receptor
CD3ζ	Cluster of differentiation 3 ζ chain , TCR complex component, CD3 intracellular signaling region ζ chain, also known as zeta, abbreviated as Z
CDx	Companion diagnostics
Claudin	A family of proteins whose role is to maintain tight junctions that control the exchange of molecules between cells
Claudin 18.2	A subtype of the Claudin protein family, a highly selective molecule, referred to as CLDN18.2
CLDN18.2 CAR-T cells	Autologous T cells modified with chimeric antigen receptors targeting CLDN18.2
C_{max}	Peak concentration
CMV	Cytomegalovirus
Cr	Creatinine
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTL	Cytotoxic T lymphocytes
DCR	Disease control rate
DLT	Dose -limiting toxicity
DOR	Duration of remission
EORTC	European Organization for Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice Guidelines for Drug Clinical Trials
GMP	Good Manufacturing Practice for Pharmaceuticals
GVHD	Graft-versus-host disease
Hb	Hemoglobin content
HER2	human epidermal growth factor receptor 2
HTLV	Human T-lymphotropic virus
ICANS	Immune cell therapy-related neurotoxicity syndrome
IDMC	Independent Data Monitoring Committee

IFN-γ	Interferon-gamma
IL	interleukins
ICT	Investigator's choice of treatment
LVEF	Left ventricular ejection fraction
LYM	lymphocytes
MRI	Nuclear magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
PCI	Percutaneous coronary intervention
PD	Disease progression
PDX	Human tissue xenotransplantation
PFS	Progression-free survival
PK	Pharmacokinetics
PBMC	peripheral blood mononuclear cells
P LT	platelets
RCL	Replication-competent lentivirus
RP2D	Recommended Phase II dose
SAE	Serious adverse events
scFv	single-chain antibody fragments
SD	Stable disease
SMC	Safety Monitoring Committee
TCR	T cell receptor
Tmax	Peak time
TNF-α	Tumor necrosis factor-α
TRAE	Treatment-related adverse events
TTR	Time to relief
ULN	Upper limit of normal
WBC	leukocyte

1. Introduction

1.1 Disease Background

According to Global Cancer Statistics 2022 [1], gastric cancer is the fifth most common malignant tumor in terms of morbidity and mortality worldwide, with approximately 970,000 cases per year, accounting for 4.9% of the total number of new cancer patients, and approximately 660,000 deaths per year, accounting for 6.8% of the global cancer deaths. Due to differences in lifestyle, gastric cancer is more prevalent in Asia: 71.4% of cases and 70.1% of deaths are from Asia. In China, the number of new cases of gastric cancer accounts for 37% of the global total, and the number of deaths accounts for 39% of the global total. It is a common malignant tumor in China, with approximately 360,000 new cases of gastric cancer per year, ranking fifth in the incidence of malignant tumors in China, and approximately 260,000 deaths. The mortality rate is second only to lung cancer and liver cancer, ranking third in the mortality rate of malignant tumors, accounting for approximately 10.1% of all malignant tumor deaths, and the 5-year survival rate is 26.4%. The burden of gastric cancer in China is severe and needs to be addressed urgently.

According to the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) gastric cancer diagnosis and treatment guidelines, it is currently recognized that for patients with no chance of surgical cure or metastatic gastric cancer, comprehensive treatment with systemic anti-tumor drugs as the main treatment should be adopted [2] [3]. In China, the current drug treatment for gastric cancer includes chemotherapy drugs, molecular targeted drugs and immune checkpoint inhibitors. The overall prognosis of advanced gastric cancer is poor, the effect of chemotherapy alone has entered a bottleneck period, the selection of targeted drugs is limited, and the efficacy of immunotherapy alone in the overall population is poor. PD-1/PD-L1 monoclonal antibody combined with chemotherapy has become the first-line treatment recommendation. Fluorouracil, platinum and taxane are the main chemotherapy drugs for advanced gastric cancer. Usually, the first-line chemotherapy regimen is based on fluorouracil drugs, combined with platinum and/or taxane drugs to form a two-drug or three-drug chemotherapy regimen. In China, the two-drug combination regimen of fluorouracil and platinum drugs is more recommended [3].

First-line treatment of gastric cancer: Patients with advanced gastric cancer or esophagogastric junction adenocarcinoma are divided into three categories according to human epidermal growth factor receptor 2 (HER2) positive, HER2 negative, and dMMR/MSI-H, regardless of HER2 status, to determine the first-line treatment plan. For patients with HER2-negative disease (IHC 0 or 1+, or 2+ but FISH-), if the PD-L1 CPS is ≥5, the first-line treatment recommendation is FOLFOX/XELOX combined with nivolumab, or XELOX combined with sintilimab (1A), or XELOX combined with sugemalimab. If the PD-L1 CPS is ≥10, XELOX or FP combined with pembrolizumab is also recommended. If the PD-L1 TAP is ≥5%, XELOX or FP combined with tislelizumab is recommended. If there is no PD-L1 CPS score, the recommended two-drug combination chemotherapy regimens are oxaliplatin/cisplatin + fluorouracil (5-FU or

capecitabine or tegafur) (1A), or paclitaxel/docetaxel combined with fluorouracil (5-FU or capecitabine or tegafur) (2A). In addition, canidolizumab combined with XELOX is also approved for the first-line treatment of HER2-negative advanced gastric cancer regardless of PD-L1 expression status. For patients with dMMR/MSI-H, regardless of HER2 status, there is no Class I recommendation. Class II recommendations include nivolumab combined with ipilimumab or pembrolizumab alone (2B), or Class III recommendations include PD-1 monoclonal antibody combined with chemotherapy (2B). Second-line treatment for gastric cancer: For second-line treatment of HER2-negative advanced gastric cancer, Class I recommendations include paclitaxel combined with ramucirumab (1A) or single-agent chemotherapy (paclitaxel/docetaxel, irinotecan) (1A). For patients with dMMR/MS-H, regardless of HER2 status, if they have not previously received PD-1/PD-L1 monoclonal antibodies, envolizumab (2A), tislelizumab (2A), or serotonin (2A) are recommended. If they have previously received PD-1/PD-L1 monoclonal antibodies, the second-line treatment option is based on HER2 status (Class 3). The phase III RAINBOW global study showed that the ORR for second-line paclitaxel + ramucirumab and paclitaxel + placebo was 28% vs. 16%, the median PFS was 4.4 months vs. 2.9 months, and the median OS was 9.6 months and 7.4 months, respectively . [4] The RAINBOW-ASIA study , which was mainly conducted in the Chinese population , showed similar results. The ORR for second-line paclitaxel + ramucirumab and paclitaxel + placebo was 27% vs. 22%, the median PFS was 4.1 months vs. 3.5 months, and the median OS was 8.7 months and 7.9 months, respectively . [5] The WJOG4007 [6] and KCSG ST1001 [7] studies conducted in Japan and South Korea showed that the ORR of irinotecan and paclitaxel as second-line chemotherapy for gastric cancer was approximately 14% to 21%, with a median PFS of 2.1 to 3.6 months and a median OS of 7.0 to 9.5 months. There is still a serious unmet clinical need for second-line treatment of advanced gastric cancer, and more effective treatment options for gastric cancer need to be actively explored clinically.

Third-line treatment for gastric cancer: The third-line treatment for advanced gastric cancer is the targeted therapy drug apatinib alone (1A) (HER2 positive or negative). In a placebo-controlled study, the ORR of apatinib alone for the third-line treatment of advanced gastric cancer was only 2.84%, with a median PFS of 2.6 months vs. 1.8 months and a median OS of 6.5 months vs. 4.7 months [8] . Or nivolumab alone is recommended for third-line use only when PD-1/PD-L1 monoclonal antibodies have not been used before (1A). In a placebo-controlled study, the ORR of nivolumab for the third-line treatment of advanced gastric cancer was 11.2% , with a median PFS of 1.61 months vs. 1.45 months and a median OS of 5.26 months vs. 4.14 months. With the approval of multiple first-line immunotherapy indications for gastric cancer, it is rarely used in third-line treatment in clinical practice. Third-line chemotherapy for advanced gastric cancer only involves small sample studies, but the benefit of chemotherapy is unclear. Therefore, clinically, there is still a need to actively explore more effective treatment options for gastric cancer.

Gastroesophageal junction adenocarcinoma and gastric cancer share similar underlying pathogenesis and genomic alterations and are often discussed as a single cancer type.

CLDN18.2 (also known as Claudin 18.2, later unified as CLDN18.2) is a tight junction protein,

which is an isoform produced by alternative splicing of the CLDN18 gene. The human CLDN18 gene has two different exons 1. After transcription, alternative splicing ultimately produces two protein isoforms CLDN18.1 and CLDN18.2 with different sequences only at the N-terminus. The two isoforms differ by only eight amino acids in the extracellular loop 1. The isoform CLDN18.1 is only expressed in lung tissue in normal tissues, while CLDN18.2 is expressed in gastric tissue. Except for gastric tissue, it is almost not expressed in other normal tissues, and is specifically expressed in solid tumor cells such as the stomach, esophagus, pancreas, ovary and lung cancer [9]. The expression of CLDN18.2 in normal tissues is limited to differentiated gastric mucosal epithelial cells, but not in the gastric stem cell area. When cancer occurs, CLDN18.2 is expressed in primary gastric cancer and its metastatic lesions. According to reports, CLDN18.2 is positively expressed in approximately 80% of gastric cancer tissues and moderately to strongly expressed in approximately 50% of gastric cancer tissues [9] [10]. Therefore, CLDN18.2 is an ideal target for the treatment of CLDN18.2-positive digestive system tumors.

Because the high specificity of CLDN18.2 helps T cells recognize tumors, it is used in chimeric antigen receptor T (CAR-T) cell therapy. Although CAR-T cell therapy has encountered setbacks in solid tumors, breakthroughs may be made because human tissue xenograft (PDX) models can verify in vivo efficacy compared with standard therapies, proving that CLDN18.2-specific CAR-T cells can serve as a promising treatment strategy for other potential CLDN18.2-positive tumors.

Currently, the types of products targeting CLDN18.2 worldwide include monoclonal antibodies, bispecific antibodies, CAR-T, and ADC. The high specificity of CLDN18.2 helps T cells recognize tumors and is used for chimeric antigen receptor T (CAR-T) cell therapy. Compared with standard therapy, CLDN18.2-specific CAR-T cells can be used as a promising treatment strategy for CLDN18.2-positive tumors, especially gastric cancer [11].

Currently, several companies in China are researching CAR-T products targeting CLDN18.2. Legend Biotech's LCAR-C18S and Casci Biopharmaceuticals' CT041 are among the most advanced. Both are CAR-T products targeting CLDN18.2. Legend Biotech's LCAR-C18S is currently in Phase I studies. Casci Biopharmaceuticals' CT041 is currently conducting multiple studies and has submitted and received a marketing authorization application in China.

The final analysis data of the reported CT041 IIT study showed that 98 patients with advanced digestive system tumors received CT041 infusion, of which 89 patients received 2.5×108^{CAR}-T cells/patient, 6 and 3 patients received $3.75\times108^{and}5\times108^{CAR}$-T cells/patient, respectively. No dose-limiting toxicity (DLT), treatment-related death or immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in the study. Cytokine release syndrome (CRS) occurred in 96.9% of patients, all of which were grade 1-2. Gastric mucosal damage was reported in 8 patients (8.2%). CT041 was generally well tolerated and had controllable safety risks. In terms of efficacy, a total of 59 patients with gastric cancer / gastroesophageal junction adenocarcinoma who had failed at least one first-line treatment received CT041 monotherapy, of which 51 had

target lesions at baseline. The ORR and DCR were 54.9% (28/51) and 96.1% (49/51), respectively. The median PFS and median OS of all 59 patients with gastric cancer / gastroesophageal junction adenocarcinoma were 5.8 months (95% CI : 4.1 , 8.0) and 9.0 months (95% CI : 7.0 , 11.9), respectively. In the population of gastric cancer/gastroesophageal junction adenocarcinoma patients who had previously failed first-line treatment, the median PFS and median OS were 9.3 months (95% CI : 3.7, 14.6) and 11.1 months (95% CI : 6.9, 17.8), respectively. There were 26 patients with gastric cancer / gastroesophageal junction adenocarcinoma who had failed second-line treatment , with median PFS and median OS of 7.1 months (95% CI : 3.8 , 8.4) and 10.1 months (95% CI : 6.7 , 20.4), respectively . There were 11 patients with gastric cancer / gastroesophageal junction adenocarcinoma who had failed third-line or higher treatment , with median PFS and median OS of 4.1 months (95% CI : 2.2 , 5.3) and 5.7 months (95% CI : 2.6 , 8.0) , respectively.), and in the third cohort of 5 patients with gastric cancer / gastroesophageal junction adenocarcinoma, CT041 was used as a sequential treatment after first-line treatment. The median PFS and median OS were 15.2 months (95% CI : 6.8 , not yet reached) and 16.4 months (95% CI : 7.0 , not yet reached), respectively. The results of this clinical study showed that CT041 has a good safety profile and has a good clinical efficacy when combined with the Baizi Qinglin regimen in the $2.5\times 108^{\text{dose}}$ group [12] .

IMC002, an autologous cell therapy developed independently by Suzhou Imufeng Biotechnology Co., Ltd. (Imufeng), is an infusion of autologous T cells modified with a chimeric antigen receptor targeting CLDN18.2. It is produced from the patient's own genetically engineered T cells and is a single-patient, single-batch specialty drug. This product received Orphan Drug Designation (ODD) from the FDA for the treatment of advanced gastric cancer on July 18, 2022 , and Fast Track Designation (FTD) from the FDA on December 6, 2024, for the treatment of patients with unresectable, locally advanced, recurrent, or metastatic CLDN18.2-positive gastric cancer . The clinical trial application for this product (Acceptance Number: CXSL2300041, Protocol Number: IMC002-RT01) received implicit approval from the CDE on April 6, 2023. The first patient was enrolled in August 2023. Dose-escalation and dose-expansion studies have been completed, demonstrating excellent safety and efficacy data.

Binding data from nonclinical studies of IMC002 demonstrated that the extracellular VHH domain of the IMC002 CAR specifically binds to the CLDN18.2 antigen and its positive cells with strong affinity. Furthermore, this VHH fragment does not bind to CLDN18.1-positive cells, demonstrating excellent specificity. Upon stimulation with CLDN18.2-positive cells, the IMC002 CAR-T cells secrete high levels of IFN-γ, TNF-α, and IL-2, and exhibit dose-dependent cytotoxicity against CLDN18.2+ (NUGC4) cells . In vivo pharmacodynamic studies demonstrated that IMC002 significantly inhibited tumor growth in an immunodeficient mouse subcutaneous NUGC4-luc tumor-bearing model at doses ranging from 1 to 5×10^{6} CAR-T cells/mouse. Furthermore, in a PDX model, which more closely reflects the patient's tumor landscape, IMC002 CAR-T cells demonstrated significant inhibition of the growth of subcutaneous gastric cancer xenografts. Results from preliminary tissue distribution experiments demonstrated that CAR-T

cells possess excellent tumor targeting. Single-dose toxicity studies revealed that IMC002 CAR-T cells did not cause significant weight loss at a dose of 5×10^{6} CAR-T cells/mouse. Histopathological examinations at the study endpoint revealed no significant tissue toxicity in the IMC002-treated group compared to control T cells, and a better safety profile than competing products. These findings suggest that IMC002 has the potential to treat CLDN18.2-positive advanced digestive system tumors.

CLDN18.2 is a target for digestive system tumors. Drugs targeting the same target have shown good clinical trial results in the past. The CAR-T product CT041 targeting CLDN18.2 and the monoclonal antibody product Zolbetuximab have both shown good safety and preliminary efficacy in clinical trials [13] [14].

In summary, CLDN18.2 may become a promising target for the treatment of CLDN18.2-positive advanced digestive system tumors.

1.2 Preclinical Study Results of IMC002

1.2.1 Overview of IMC002 Preclinical Studies

Existing nonclinical data indicate that CLDN18.2 is rarely expressed in normal tissues other than gastric tissue; however, it is specifically expressed in solid tumor cells such as those in the stomach, esophagus, and pancreas, making CLDN18.2 an ideal target for these tumors. Binding data from nonclinical studies of IMC002 demonstrate that the extracellular VHH domain of the IMC002 CAR specifically binds to the CLDN18.2 antigen and its positive cells with strong affinity. Furthermore, this VHH fragment does not bind to CLDN18.1-positive cells, demonstrating high specificity. Upon stimulation with CLDN18.2-positive cells, IMC002 secretes high levels of IFN-γ, TNF-α, and IL-2, and exhibits a dose-dependent cytotoxic effect against CLDN18.2+ cells (NUGC4). Further in vivo pharmacodynamic studies demonstrated that IMC002 significantly inhibited tumor growth in the NUGC4-luc subcutaneous tumor-bearing model in immunodeficient mice at doses of 1-5×10^{6} CAR-T cells/mouse and 1.5-5×10^{8} CAR - T cells/kg mouse body weight. Furthermore, in a PDX animal model, which better reflects the real-world tumor state in patients, IMC002 significantly inhibited the growth of subcutaneous gastric cancer xenografts. Preliminary tissue distribution studies and final experiments demonstrated that IMC002 CAR-T cells, developed using the IND process, achieved the highest tumor exposure. Results from a formal GLP single-dose toxicity study showed that IMC002 administered intravenously to NOG tumor-bearing mice at doses of 1.5×10^{CAR} - T cells/kg and $5.0^{\times10}$ CAR - T cells/kg primarily revealed test article-related gastric squamous epithelial hyperplasia, atypical glandular regeneration, and erosions/ulcers. Other findings were due to mononuclear cell infiltration caused by GVHD. The HNSTD (highest non-serious toxic dose) of IMC002 was 5.0×10^{CAR} - T cells/kg. Toxicity studies demonstrated a favorable safety profile and tolerability, indicating that IMC002 has the potential to treat CLDN18.2-positive solid tumors. A summary of existing nonclinical study data is provided below **.**

1.2.2 IMC002 Exists Preclinical Research Data

Suzhou Immofeng Biotechnology Co., Ltd. conducted in vitro functional characterization and proof-of-concept studies for IMC002, as well as comprehensive preclinical GLP safety, efficacy, and pharmacokinetic evaluations. To evaluate the preclinical in vivo efficacy of IMC002, an immunodeficient tumor-bearing mouse model was designed and utilized. Key preclinical data are summarized below:

(1) **Pharmacological research**

a) In vitro pharmacodynamic studies:

The binding properties of the IMC002 CAR were evaluated using the CLDN18.2-specific VHH antibody BC008 as a surrogate molecule. In vitro binding studies demonstrated that BC008 exhibited high specific binding affinity for recombinant human CLDN18.2 (KD of 0.592 nM) and cell-surface expressed CLDN18.2 (EC50 range: 10.37 nM to 60.39 nM), while no binding was detected for the related splice variant CLDN18.1. Consistent with the findings at the protein level, IMC002 induced potent cytotoxicity against CLDN18.2-positive cells (293T-CLDN18.2 and NUGC4-luc) in a dose-dependent manner, accompanied by high levels of cytokine release (IL-2 , IFN-γ, and TNF-α). On the other hand, IMC002 failed to induce cytotoxicity or cytokine production in cells expressing CLDN18.1 or CLDN18-negative cells, suggesting that IMC002 has minimal off-target toxicity in non-gastric tissues.

IMC002 cross-reacts with mouse CLDN18.2 (mCLDN18.2) as demonstrated by dose-dependent killing of cells expressing mCLDN18.2 and high levels of IFN- γ production ; therefore, mice are considered a pharmacologically relevant species.

b) In vivo pharmacodynamic studies:

IMC002 was evaluated in two mouse xenograft models . The first model was a cell-derived xenograft model established by subcutaneously inoculating 1.5×10^{8} human gastric cancer cells, NUGC4-luc , in the right axilla of immunodeficient mice . Furthermore, the antitumor effect of IMC002 was confirmed in an immunodeficient mouse model bearing a patient-derived gastric cancer xenograft (PDX). Antitumor activity was assessed by measuring the relative tumor volume between the test and control groups and expressing it as tumor volume inhibition (TGI). Vehicle-treated mice served as a basal control for tumor growth. The in vivo antitumor effects of IMC002 are summarized in **Table 1** .

Table 1 In vivo anti-tumor effects of IMC002 in various tumor xenograft models

dose (× 10 ^{8} CAR-T cells /kg)	TGI (%)				
	NUGC4-luc			PDX	
	Exp1	Exp2	Exp3	Exp1	Exp2
0.25 (F)	-	23.43	-	-	-
0.75 (F)	-	0.54	-	-	-
1 (F)	-	-	-	-	99.82
1.25 (F)	-	-	-	44.56	-

dose (× 10 8 CAR-T cells /kg)	TGI (%)				
	NUGC4-luc			PDX	
	Exp1	Exp2	Exp3	Exp1	Exp2
1.5 (M/F)	-	-	68.8 (M) 30.1 (F)	-	-
2.5 (F)	100	73.14	-	-	-
3 (F)	-	-	-	-	99.61
5 (M/F)	-	-	92.2 (M) 48.3 (F)	-	-

Note: All in vivo pharmacodynamic studies were conducted by intravenous injection with a single-dose schedule; M: male; F: female.

IMC002 well . No animal deaths, severe weight loss, or clinical symptoms related to the test substance were observed in mice given IMC002 at doses up to 5 × 10 8 CAR-T cells /kg. Dose-dependent effects were observed in individual studies of the NUGC4-luc xenograft model, but not in the PDX model. In female animals in Exp2 , the anti-tumor activity of IMC002 against NUGC4-luc gradually increased with increasing doses from 0.75 × 10 8 to 2.5 × 10 8 CAR-T cells /kg , and in Exp3 with increasing doses from 1.5 × 10 8 to 5 × 10 8 CAR-T cells /kg . In the PDX model, IMC002 had a significant effect at 1 × 10 8 CAR - T cells /kg . The dose range of ∼3 × 10 8 cells /kg demonstrated robust anti-tumor effects without dose dependence. A comprehensive consideration of all models tested indicated that doses of 2.5 × 10 8 CAR-T cells /kg and above were effective.

c) Secondary pharmacodynamics:

The IMC002 CAR portion consists of an extracellular VHH domain that targets CLDN18.2 . The parental anti-human CLDN18.2 antibody BC008 , derived from the IMC002 VHH domain , was evaluated for binding to over 6,000 human membrane proteins using the Membrane Proteome Array (MPA).

20 μg /mL of BC008 among 6,000 membrane proteins (over 94% of the human membrane proteome) identified potential membrane protein targets as CLDN18.2 , FCGR2B , and FCGR3B (Uniprot Nos . P56856-2 , P31994 , and O75015 , respectively). FCGR2B and FCGR3B encode Fcγ receptors IIb and IIIb , respectively, which are low- affinity inhibitory receptors for the Fc region of immunoglobulin (IgG) γ (NCBI gene report 10/2022). Non - specific binding between BC008 and FCGR2B/FCGR3B is likely mediated through their Fc regions, which are absent in the IMC002 CAR . Therefore, these non-specific binding events are absent in cells, demonstrating the high target specificity and low off-target binding of IMC002 .

(2) Animal pharmacokinetic studies

Results from a study of the IND-developed IMC002's CAR-T persistence in the blood and in vivo distribution in immunodeficient tumor-bearing mice showed that after a single intravenous administration of 5×10 CAR-T cells/kg of IMC002 to male and female NOG mice bearing subcutaneous tumors (human gastric cancer cell lines, NUGC4-Luc), a certain amount of CAR

gene DNA copy number was detected in the whole blood and several tissues of the mice. CAR gene DNA copy number first peaked in total DNA in tumor and lung tissues of the tumor-bearing mice on Day 7 after administration, and in total DNA in gastric tissue on Day 14 after administration. After reaching peak concentrations, concentrations in all tissues gradually decreased before gradually increasing over time until the end of observation (Day 70 after administration). IMC002 exposure was highest in the tumor, with some exposure observed in highly vascularized tissues such as the lung and liver, as well as in target immune organs such as the stomach and spleen. These results demonstrate that IMC002 exhibits good tumor targeting in animals.

(3) Toxicology studies

a) Pharmacodynamics and GLP toxicity studies of IMC002 after a single intravenous injection into NOG tumor-bearing mice

The results of the study showed that IMC002 was administered intravenously to NOG tumor-bearing mice (subcutaneously transplanted with the human gastric cancer cell line NUGC4-Luc) at a single dose of 1.5×10^{8} CAR T cells/kg and 5.0×10^{8} CAR T cells/kg, respectively. The main visible manifestations were test article-related gastric squamous epithelial hyperplasia and atypical glandular regeneration and erosion/ulceration. Other manifestations were multi-organ/tissue mononuclear cell infiltration due to GVHD, increased number of splenic white myeloid cells, increased number of bone marrow (sternum and femur) granulopoietic hematopoietic cells, and anti-tumor effects (such as increased IFN-γ production). The HNSTD (highest non-severe toxicity dose) of IMC002 was 5.0×10^{8} CAR T cells/kg.

b) Viral insertion site analysis

Viral insertion site analysis was performed on batches of samples from the IND process. Results from five sample batches have shown that no insertion sites of potential clinical significance were detected in IMC002 under the IND process. Yimufeng also rigorously monitored the safety of lentiviral vectors during the development of IMC002, including the following: 1) strict control of the CAR gene copy number in the final product; 2) rapid release testing of the RCL of the CAR-T product using qPCR, with subsequent retrospective analysis of the RCL using a co-culture assay; 3) lentiviral insertion site analysis of the final CAR-T product in process confirmation batches; and 4) RCL testing and lentiviral insertion site analysis of peripheral blood samples from subjects at protocol-specified follow-up time points after product infusion.

c) In vitro tumorigenicity studies

The in vitro tumorigenicity test of the IND process IMC002 CAR-T was studied through the soft agar cell clone formation ability experiment. The results showed that under the experimental conditions, the test product IMC002 could not form clones in soft agar, indicating that it does not have tumorigenicity in vitro.

d) In vitro hemolysis test results

Under the experimental conditions, IMC002 at a theoretical concentration of 5.0×10^{7} cells/mL had no hemolytic effect on human erythrocytes in vitro and did not cause erythrocyte aggregation.

Through the above studies, we have fully evaluated the in vivo and in vitro efficacy, tissue distribution characteristics, and safety risks of this product to prove that this product is safe and effective, which can support the clinical trials of IMC002.

1. 3 IMC002 early clinical study results

Our company has initiated a Phase I/IIa clinical study titled "An Open-label, Multicenter, Dose-Escalation Study to Evaluate the Safety and Preliminary Efficacy of IMC002 in Subjects with Advanced Digestive System Cancers Positive for CLDN18.2 Expression" (Study Number: IMC002-RT01). The study aims to evaluate the safety and preliminary anti-tumor efficacy of IMC002 in patients with advanced digestive system cancers positive for CLDN18.2 expression, including but not limited to advanced gastric cancer/GEJ adenocarcinoma and advanced pancreatic cancer. This study assesses the safety, tolerability, efficacy, cellular metabolism kinetics, and pharmacodynamics of IMC002 in the treatment of advanced digestive tract cancers, including gastric cancer / GEJ adenocarcinoma and pancreatic cancer. The dose-escalation phase utilized a classic "3+3" dose-escalation strategy, with three doses (1.0×10^{8}, 2.5×10^{8}, and 5.0×10^{8} CAR - T cells/ subject, hereafter referred to as the low, medium, and high doses) completed . The Safety Monitoring Committee (SMC) discussed and decided to simultaneously initiate a dose expansion at the medium dose. As of April 3, 2025, a total of 24 subjects had received IMC002 in this clinical study, including 16 with gastric cancer (11 with advanced gastric cancer in the medium-dose group and 5 with advanced gastric cancer in the high-dose group at the RP2D) and 8 with pancreatic cancer (3, 4, and 1 with advanced pancreatic cancer in the low-dose, medium-dose, and high-dose groups, respectively). All 9 patients in the dose-escalation phase (3 patients in each dose group , low, medium, and high) completed DLT observation and were DLT-evaluable cases. The median follow-up time for all 24 patients in the dose-escalation and dose-expansion phases was 4.4 months (95% CI, 3.3, 7.7).

In the IMC002-RT01 study, IMC002 demonstrated a manageable overall safety profile, with a favorable safety profile across all three doses. No DLTs were reported during the dose-escalation phase across all three doses. Treatment-related adverse events (TRAEs) with an incidence of 30% or greater included pyrexia, cytokine release syndrome (CRS), decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, hypoalbuminemia, hypokalemia, increased gamma-glutamyl transferase, increased alanine aminotransferase, hypocalcemia, hypertriglyceridemia, increased aspartate aminotransferase, increased alkaline phosphatase, anemia, decreased platelet count, vomiting, increased fibrinogen degradation products, hypophosphatemia, nausea, decreased appetite, and abnormal electrocardiogram T waves. A total of 20 patients (83.3%, 20/24) experienced grade ≥3 TRAEs ; grade ≥3 TRAEs were mainly blood cell counts caused by lympholysis pretreatment, including decreased white blood cell count (58.3%, 14/24), decreased lymphocyte count (58.3%, 14/24), decreased neutrophil count (37.5%, 9/24),

increased γ-glutamyl transferase (29.2%, 7/24), hypokalemia (16.7%, 4/24), anemia (12.5%, 3/24), increased lipase (12.5%, 3/24), decreased platelet count (8.3%, 2/24), as well as upper gastrointestinal bleeding, peripheral edema, infectious pneumonia, increased blood creatine phosphokinase, increased interleukin level, hyperkalemia, coronary artery atherosclerosis, gastritis, respiratory failure and decreased fibrinogen in 1 patient (4.2%, 1/24). A total of 4 patients (18.8% , 3/16) experienced investigator-assessed treatment-related serious adverse events (SAEs) during the study: upper gastrointestinal bleeding (4.2%, 1/24 patients), gastritis (4.2%, 1/24 patients), peripheral edema (4.2%, 1/24 patients), and hypokalemia (4.2%, 1/24 patients). All CRS were grade 1-2 , with no grade 3 CRS , and all resolved with treatment. Acute gastric mucosal injury / gastrointestinal bleeding occurred in 37.5 % of patients , mostly of CTCAE grade 1-2 severity, with an incidence of grade 3 events in 8.3 % . These events resolved with appropriate symptomatic treatment, and the risk of acute gastric mucosal injury / gastrointestinal bleeding was manageable. The cytopenias observed in this study were primarily related to pre-treatment with lymphadenopathy. The toxicity of IMC002 cell infusion on cytopenias was manageable, with no risk of prolonged cytopenias. IMC002-related cardiac events were reported in 4 patients (16.7%, 4/24), including sinus tachycardia (4 cases, 16.7%, 4/24), heart failure (2 cases, 8.3%, 2/24), and palpitations (1 case, 4.2%, 1/24). No other CAR-T therapy-related events, including ICANS , cerebral edema, tumor lysis syndrome, HLH/MAS , DIC , infusion reactions, or allergic reactions, were observed in the study.

In summary, IMC002 has an acceptable and manageable safety profile for patients with CLDN18.2 -positive locally advanced or metastatic gastric / GEJ adenocarcinoma. Reported adverse events were well characterized and generally reversible.

Preliminary clinical data show that IMC002 has a highly effective anti-tumor effect on advanced gastric cancer. As of April 3, 2025, among 16 gastric cancer patients who failed at least two lines of systemic treatment (all patients had received PD-1/PD- L1 inhibitors, and 8 of them had failed at least three lines of systemic treatment), 8 achieved PR , with an overall ORR of 50 % (95% CI : 24.7, 75.3). Among a total of 11 patients with advanced gastric cancer at a medium dose, 5 achieved PR, with an ORR of 45.5% (95% CI : 16.7, 76.6), which are numerically much higher than the currently available third-line treatments apatinib and nivolumab (2.84% and 11.2% , respectively). Following the approval of multiple first-line immunotherapy indications for gastric cancer, their use in third-line treatment is rare in clinical practice. All 16 gastric cancer patients enrolled in this study had received prior PD-1/PD-L1 inhibitors. The median duration of response (DOR) was immature (95% CI : NA , NA). Of the eight patients who achieved a PR , only two had disease progression, while the remaining six showed ongoing tumor responses, with the potential for more durable responses with extended follow-up. The median progression-free survival (mPFS) of 6.9 months was achieved in all 16 patients and 11 patients receiving the RP2D mid-dose . This significantly prolongs the mPFS of currently available third-line treatments for advanced gastric cancer, including apatinib and nivolumab (2.6 and 1.61 months, respectively), and even the median PFS of currently available second-line treatments for advanced gastric cancer

(2.1-4.4 months). IMC002 is used for the third-line or higher treatment of patients with CLDN18.2 -positive locally advanced or metastatic gastric cancer. Compared with existing third-line treatments or even second-line treatments, IMC002 significantly improved the objective response rate, showed the potential for durable response, and prolonged PFS.

1.4 Risks and Benefits

According to 2022 Global Cancer Statistics , gastric cancer is the fifth most common malignant tumor in terms of morbidity and mortality worldwide, with approximately 970,000 cases and 660,000 deaths annually . In China, gastric cancer accounts for 37% of the global total in new cases and 39% of deaths . It is a common malignant tumor in China, with approximately 360,000 new cases each year , ranking it fifth in the incidence of malignant tumors in China. There are also approximately 260,000 deaths , and the mortality rate ranks third among malignant tumors, after lung cancer and liver cancer, accounting for approximately 10.1% of all malignant tumor deaths . The five- year survival rate is 26.4% . The burden of gastric cancer in China is severe and urgently needs to be addressed.

According to the National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) gastric cancer diagnosis and treatment guidelines, it is generally recognized that patients with incurable or metastatic gastric cancer should receive comprehensive treatment, primarily systemic anti-tumor drug therapy. In China, current drug treatments for gastric cancer include chemotherapy, molecularly targeted drugs, and immune checkpoint inhibitors. The overall prognosis of advanced gastric cancer is poor, and the efficacy of chemotherapy alone has reached a bottleneck. Targeted drug options are limited, and immunotherapy alone has poor efficacy in the general population . PD-1/PD-L1 monoclonal antibody combined with chemotherapy has become the preferred first-line treatment. For second-line treatment of HER2-negative advanced gastric cancer, the Class I recommendation is paclitaxel combined with ramucirumab (1A) or single-agent chemotherapy (paclitaxel/docetaxel, irinotecan) (1A). The global phase III RAINBOW study showed ORRs of 28% and 16% for second-line paclitaxel plus ramucirumab and paclitaxel plus placebo, respectively. Median PFS was 4.4 months versus 2.9 months, and median OS was 9.6 months and 7.4 months, respectively. The RAINBOW-ASIA study, conducted primarily in China, showed similar results: ORRs of 27% and 22% for second-line paclitaxel plus ramucirumab and paclitaxel plus placebo, respectively. Median PFS was 4.1 months versus 3.5 months, and median OS was 8.7 months and 7.9 months, respectively. The WJOG4007 and KCSG ST1001 studies, conducted in Japan and South Korea, showed that single-agent irinotecan and paclitaxel chemotherapy as second-line treatment for gastric cancer achieved ORRs of approximately 14% to 21%, median PFS was 2.1 to 3.6 months, and median OS was 7.0 to 9.5 months. There is still a serious unmet clinical need for second-line treatment of advanced gastric cancer, and clinically there is still a need to actively explore more effective treatment options for gastric cancer.

CLDN18.2 is specifically expressed in gastric, esophageal, and pancreatic tumor cells and is not expressed in normal tissues except for gastric mucosal epithelial cells. Binding data from

nonclinical studies of IMC002 demonstrated that the extracellular VHH domain of the IMC002 CAR specifically binds to the CLDN18.2 antigen and its positive cells with strong affinity. Conversely, this VHH fragment does not bind to CLDN18.1 - negative cells. Upon stimulation with CLDN18.2 -positive cells, the IMC002 CAR-T cells secreted high levels of IFN-γ , TNF-α , and IL-2 , and exhibited dose-dependent cytotoxicity against CLDN18.2+ cells (NUGC4). Furthermore, IMC002 CAR-T cells demonstrated excellent tumor growth inhibition and safety in in vivo models. Therefore, CLDN18.2 is an ideal target for the treatment of advanced solid tumors positive for CLDN18.2 .

Publicly published data on the same target also suggest that CLDN18.2 is a promising target for the treatment of CLDN18.2 -positive advanced digestive system tumors, including gastric and pancreatic cancer . Currently, global product lines targeting CLDN18.2 include monoclonal antibodies, bispecific antibodies, CAR-T cells, and ADCs . Among these, zolbetuximab has the largest number of monoclonal antibodies in development and is the most advanced. It has been approved for first-line combination therapy with chemotherapy for the treatment of advanced gastric cancer. Several ADCs have also entered pivotal registration studies, with monotherapy being used as second- or third-line treatments for advanced gastric cancer. The high specificity of CLDN18.2 facilitates T cell tumor recognition and is used in chimeric antigen receptor T (CAR-T) cell therapy. Compared with standard therapies, CLDN18.2 -specific CAR-T cells offer a promising treatment strategy for CLDN18.2 -positive tumors, particularly gastric cancer. Currently, CT041 , developed by Cogen Biosciences, is making rapid progress in China. CT041 is currently undergoing multiple Phase I studies and has completed a pivotal Phase II clinical trial in China. Its application for marketing approval has been accepted and submitted in China. Published studies have demonstrated a tolerable safety profile and promising anti-tumor activity in patients with advanced gastric cancer / esophagogastric junction adenocarcinoma, demonstrating significant patient benefit.

The IMC002-RT01 study evaluated the safety, tolerability, efficacy, cellular metabolism dynamics, and pharmacodynamics of IMC002 in the treatment of advanced gastrointestinal cancers, including gastric cancer / GEJ adenocarcinoma and pancreatic cancer. Preliminary clinical data demonstrated that IMC002 was safe, tolerable, and highly effective in treating advanced gastric cancer. Furthermore, as a CAR-T product, IMC002 requires only a single dose, offering greater convenience compared to traditional intravenous drug therapies, reducing hospital visits for follow-up medication. IMC002 demonstrated an acceptable and manageable safety profile in patients with CLDN18.2 -positive locally advanced or metastatic gastric cancer / GEJ adenocarcinoma. Reported adverse events were well characterized and generally reversible.

In summary, based on the safety and efficacy results observed in the Phase I/IIa clinical study, the proposed recommended Phase II dose (RP2D) is safe and well-tolerated. Preliminary efficacy data demonstrate significant anti-tumor activity compared to existing treatments . IMC002 demonstrates clear benefits that outweigh its risks, supporting further confirmatory clinical trials in China to confirm the benefit advantage. The proposed confirmatory clinical study is for patients

with inoperable locally advanced or metastatic gastric cancer and gastroesophageal junction adenocarcinoma who are CLDN18.2 -positive and have failed at least two lines of systemic therapy (disease progression or intolerance). This clinical study will also fully investigate the risks of CLDN18.2 CAR-T therapy and develop strategies for managing treatment-related adverse events. A product manual for hospital-based apheresis and reconstitution has also been developed to guide standardized procedures. Overall, IMC002 (CLDN18.2 CAR-T) has an acceptable benefit-risk ratio for the treatment of inoperable locally advanced or metastatic gastric cancer and gastroesophageal junction adenocarcinoma that are CLDN18.2 -positive and have failed at least two lines of systemic therapy (disease progression or intolerance).

1.5 Basis for dose selection

this Phase Ⅲ clinical study (2.5x108 ^{CAR} -T cells/subject, single infusion) was selected based on data from an ongoing Phase I/IIa clinical study titled "An open-label, multicenter, dose-escalation clinical trial to evaluate the safety and preliminary efficacy of IMC002 in subjects with advanced digestive system tumors that are positive for CLDN18.2 expression" (Study No.: IMC002-RT01).

Safety: IMC002 was well tolerated across all three dose groups, with no DLTs observed . Among the 24 subjects, no IMC002 -related adverse events resulted in death. The incidence of CRS was 100% , limited to Grades 1-2, with no Grade 3 CRS . All resolved within approximately one week after treatment , demonstrating a manageable safety profile. Four IMC002 -related SAEs occurred : gastritis, upper gastrointestinal bleeding, bilateral lower extremity edema, and hypokalemia. These adverse reactions resolved with symptomatic treatment. These adverse reactions are related to the on-target mechanism of action of IMC002 and are manageable. No significant differences in safety were observed between dose groups, demonstrating an overall good and manageable safety profile.

Efficacy: Among 24 patients, 9 achieved a best response (PR) , with an overall ORR of 37.5% (95% CI : 18.8, 59.4). Eight of 16 patients with gastric cancer achieved a PR , with an overall ORR of 50 % (95% CI : 24.7, 75.3). $^{In\ the}$ 2.5×10^{-1} dose group, 5 of 11 patients with gastric cancer achieved a PR , with an ORR of 45.5% (95% CI : 16.7, 76.6). In the 5.0×10^{-1} dose group, 3 of 5 patients with gastric cancer achieved ^{a} PR , with an ORR of 60.0% (95% CI : 14.7, 94.7). Both the mid- and high-dose groups demonstrated superior efficacy compared to existing therapies.

As of April 3, 2025, among 16 gastric cancer patients, one additional patient in the medium-dose group achieved a PR. Excluding one patient without target lesions in the medium-dose group, 9 of 15 evaluable patients achieved a PR , for an overall ORR of 60%. Among 10 evaluable gastric cancer patients in the medium-dose group , 6 achieved a PR , for an ORR of 60 % . This demonstrates robust ORR efficacy data.

Cellular kinetics: Clinical pharmacology studies found that among all 16 subjects, ^{the} overall median Cmax was 1467.2 copies/μg gDNA ; the median Cmax for the three subjects in the low-

dose group was 611.4 copies/μg gDNA ; the median Cmax for the 10 subjects in the medium-dose group was 1467.2 copies/μg gDNA ; and the median Cmax for the three subjects in the high-dose group was 1589.5 copies/μg gDNA . Among six subjects with pancreatic cancer, the Cmax in the low-dose group was 611.4 copies/μg gDNA ; the median Cmax in the medium-dose group was 2467.4 copies/μg gDNA , with the medium-dose group exhibiting a higher median Cmax than the low-dose group. Among 10 subjects with gastric cancer, the median Cmax was 1467.2 copies/ μ g gDNA in 7 subjects receiving the medium dose , and 1589.5 copies / μg gDNA in 3 subjects receiving the high dose . There was no significant difference in median Cmax between the medium and high doses . Overall, the low-dose group had the lowest median Cmax, while there was no significant difference in median Cmax between the medium and high-dose groups . There were no statistically significant differences between cancer types and dose groups.

Pharmacodynamics: The main pharmacodynamic indicator, cytokine median Cmax , showed an upward trend in the medium-dose group, but no significant difference was found in the summary. For example, the median Cmax of IL-6 in the low-dose group was 559.1 pg/mL , the median Cmax of the medium-dose group was 1247.6 pg/mL , and the median Cmax of the high-dose group was 420.4 pg/mL ; the median Cmax of IFN-γ in the low-dose group was 1687.4 pg/mL , the median Cmax of the medium-dose group was 2416.5 pg/mL , and the median Cmax of the high-dose group was 1122.3 pg/mL ; the median Cmax of IP-10 in the low-dose group was 2981.2 pg/mL , the median Cmax of the medium-dose group was 5101.2 pg/mL , and the median Cmax of the high-dose group was 5191.9 pg/mL ; the median Cmax of MCP -1 in the low-dose group was 1050.6 pg/mL , the median Cmax of the medium-dose group was 1219.3 pg/mL , and the median Cmax of the high-dose group was The median C_{max} of IL -8 in the low-dose group was 54.1 pg/mL , the median C_{max} of the medium-dose group was 119.6 pg/mL , and the median C_{max} of the high-dose group was 47.3 pg/mL .

Based on the safety, efficacy, and clinical pharmacology data observed in the Phase I/IIa clinical trial of IMC002-RT01, the mid-dose group demonstrated favorable safety and efficacy, with no significant differences in safety or efficacy observed between the mid- and high-dose groups. No significant differences in PK parameters were observed between the mid- and high-dose groups, but post-administration cytokine levels were significantly elevated in the mid-dose group compared with the high-dose group. Considering that CAR-T cells are living cellular therapeutics and will proliferate after infusion, there is no inherent correlation between dose and in vivo PK/PD parameters. Furthermore, considering production cost control and production success rates, and considering that the SMC recommends the mid-dose as the recommended dose for subsequent studies, the recommended clinical dose for this Phase III study was determined to be 2.5×10^{8} CAR-T cells per subject, administered as a single infusion, for further Phase III clinical trials to confirm the clinical efficacy and safety of subjects at this dose level.

2. Study objectives , study endpoints and estimated targets

2.1 Research Objectives

Main Purpose:

To evaluate progression-free survival (PFS) of IMC002 compared with investigator's choice of therapy (ICT) as third-line or higher-line treatment for patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who are CLDN18.2 positive .

Secondary objectives:

1) To evaluate the efficacy of IMC002 compared with ICT as a third-line or higher treatment for inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma that is positive for CLDN18.2 .
2) Evaluate the safety of IMC002 and ICT .
3) The metabolic kinetics of subjects infused with IMC002 were evaluated.

Exploratory purpose:

1) Long-term follow-up including immunogenicity analysis, lentiviral insertion site, and replication-competent lentivirus (RCL) was performed.
2) To evaluate the changes in cytokines before and after administration of IMC002 and their correlation with efficacy and safety.
3) To evaluate the correlation between biomarker changes before and after IMC002 administration and efficacy and safety.
4) To evaluate the phenotypic changes of CAR-T cells before and after IMC002 administration.
5) To evaluate the correlation between changes in the tumor microenvironment of tumor tissue samples before and after IMC002 administration and its efficacy and safety.
6) To evaluate the effectiveness of subsequent IMC002 treatment in subjects in the control group.
7) To evaluate the effects of IMC002 and ICT on the quality of life of subjects.

2.2 Study Endpoints

Primary study endpoint:

PFS assessed by a blinded independent imaging review committee (BIRC) .

Key secondary endpoints:

Overall survival (OS).

Secondary study endpoints:

1) PFS based on investigator assessment, objective response rate (ORR), disease control rate (DCR) , duration of response (DOR), and time to response (TTR) based on BIRC and investigator evaluation .

2) According to NCI CTCAE 5.0 (except CRS /ICANS , according to 2019 ASTCT CRS /ICANS grading criteria were used to evaluate the type, frequency, and severity of treatment -emergent adverse events (TEAEs) and treatment- related adverse events (TRAEs) , as well as changes in laboratory values, vital signs, and ECG.

3) PK indicators include analysis of the number of CAR-T cells and CAR copy number in peripheral blood : such as C_{max} , T_{max} , AUC, C_{last} , T_{last} , C_{max}/T_{max} , and maximum survival time.

Exploratory endpoints:

1) ADA immunogenicity analysis, lentivirus insertion site analysis, and replication-competent lentivirus (RCL) detection were performed.

2) The changes in cytokines (such as IL-2, IL-6, TNF-α , INF-γ , etc.) before and after IMC002 administration were detected before and after treatment.

3) Additional exploratory testing may be conducted in research centers with appropriate conditions to support the evaluation of changes in biomarkers (such as CLDN18.2, etc.) before and after administration of IMC002.

4) Additional exploratory testing can be performed in research centers with appropriate conditions to support the evaluation of changes in CAR-T cell phenotype before and after IMC002 administration (at time points with CAR-T expansion, such as if there are surplus samples).

5) In research centers with corresponding conditions, additional exploratory tests can be carried out to support the CAR-T expansion, immune cell composition (CD4+/CD8+ ratio, memory cell phenotype, etc.) and changes in patient tumor tissues.

6) The effectiveness of subsequent IMC002 treatment for subjects in the control group, including ORR, etc.

7) Health-related quality of life was assessed using the parameters of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-OG25 questionnaires.

2.3 Estimation Target

2.3.1 Main estimation objectives

The target estimate is a precise description of the treatment effect and reflects the strategy for dealing with events that occur during the trial that may affect the interpretation of the trial results (such as premature discontinuation of treatment).

The primary clinical question of interest in this study was the relative effect of IMC002 as third-line or higher therapy in prolonging time to death or radiographic disease progression (per RECIST 1.1) compared with the control arm, ICT, in subjects with inoperable locally advanced or

metastatic gastric or GEJ adenocarcinoma who were CLDN18.2 positive, regardless of discontinuation of study treatment but before receiving off-study treatment after study entry, based on BIRC review .

The primary objective was to capture treatment effect data regardless of discontinuation of study treatment while avoiding the confounding effect of any new anticancer therapy that was not part of the originally assigned treatment. During the course of this study, other clinical trials of drugs targeting CLDN18.2 were ongoing, and new drugs targeting CLDN18.2 were anticipated to be approved. Given the open-label nature of this study, it is possible that subjects in the control group could have switched to these newly approved or investigational therapies before disease progression, with the potential for this practice to affect treatment efficacy. Therefore, the primary focus was on assessing treatment efficacy in the absence of non-study treatment.

The characteristics of the main estimation targets are as follows:

1. Population: Adult patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have previously received first-line therapy and are positive for CLDN18.2. For further details on this population, see Section 4. Study Population .
2. Objective variable: BIRC-assessed progression-free survival (PFS) was defined as the time from the date of randomization to the date of first radiographic disease progression (based on BIRC assessment according to RECIST 1.1) or death from any cause.
3. Treatment of Interest: The assigned IMC002 or ICT treatment in the control group (regardless of whether study treatment was discontinued). For more details on the study treatment and control treatment, see Section 5. Study Treatment .
4. Treatment of associated events:

- Discontinuation of Study Treatment: PFS will take into account all tumor assessments and death, regardless of discontinuation of study treatment for any reason (treatment strategy).
- Patients who underwent a crossover (for patients in the control group) or started a new anticancer treatment (for all patients) were treated with a hypothetical strategy in which PFS would be censored at the date of the last adequate assessment or at the date of randomization before the crossover or start of a new anticancer treatment.
- Any unforeseen concomitant events, such as those arising from public health emergencies, will be addressed through therapeutic strategies.

5. HR) between the two treatment groups . This HR will be estimated using a Cox proportional hazards model stratified by the randomization stratification factor . PFS will be tested using the log-rank test stratified by the randomization stratification factor.

3. Study Design

3.1 Overview of Research Design

This study is a multicenter, randomized, active-controlled, open-label, confirmatory clinical study to evaluate the efficacy and safety of IMC002 compared with ICT as third-line or higher-line treatment for subjects with advanced gastric/esophagogastric junction adenocarcinoma who are positive for CLDN18.2 expression .

A schematic diagram of the study design is shown in Figure 1 .

Subjects meeting the inclusion criteria will be randomly assigned to the experimental or control group in a 2:1 ratio. Following randomization, subjects in the experimental group will undergo peripheral blood mononuclear cell (PBMC) collection (abbreviated as apheresis), bridging therapy (if necessary), lymphoproliferative conditioning (abbreviated as lysozyme), and a single infusion of IMC002. Subjects in the control group will undergo apheresis and then receive investigator-selected treatment (ICT) until intolerable toxicity, progressive disease (PD), initiation of new anti-cancer therapy, or death. In the control group, if PD or intolerable toxicity develops after ICT treatment, eligible subjects who have been fully evaluated may receive lysozyme and IMC002 treatment.

Randomization stratification factors included:

- Eastern Cooperative Oncology Group performance status (ECOG PS): 0 or 1
- Liver metastasis: yes or no
- Previous lines of systemic therapy: 2 lines * or ⩾3 lines

*Patients who received only first-line treatment with a combination of taxanes (or anthracyclines) , platinum, and fluorouracil and whose disease progressed as assessed by the investigator were considered to have failed the second-line treatment.

Both groups of subjects will undergo relevant examinations according to the established visits in the trial flow chart to evaluate their efficacy, safety and cellular pharmacokinetics.

A BIRC will be established in this study to evaluate the tumor status and treatment response of the subjects according to the BIRC charter.

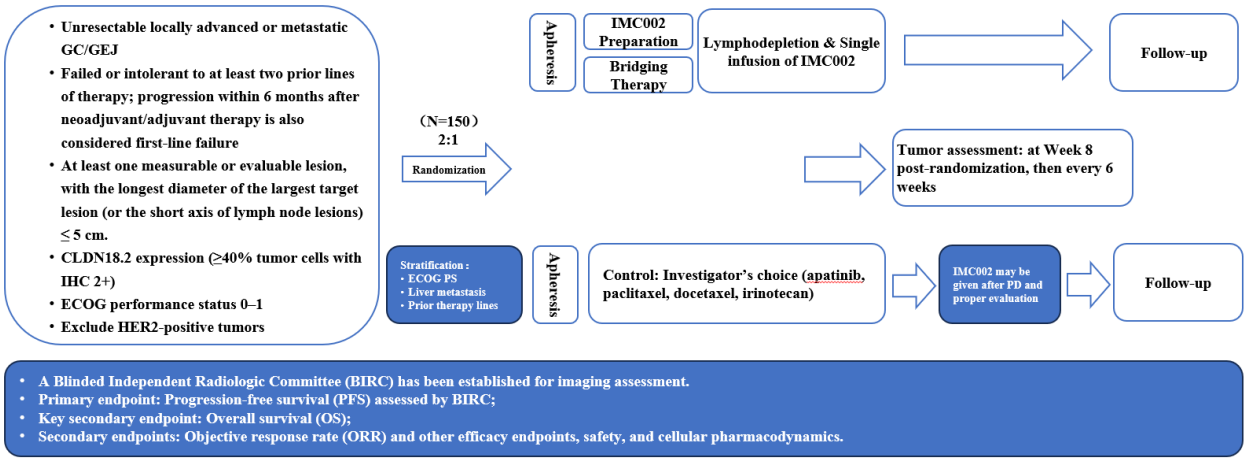

Figure 1 Schematic diagram of the study design

Experimental group:

Trial interventions and treatments : including apheresis, bridging therapy (if necessary), lymphoblastic leukorrhea clearance, and IMC002 infusion.

After randomization, the subjects will begin apheresis. Before apheresis to lymphoproliferative pretreatment, the researchers will judge the subject's status and consider bridging therapy based on the subject's clinical benefits and risks. The purpose of bridging therapy is to stabilize the subject's current disease status or reduce the subject's current tumor burden. The preferred drugs are those with gastric cancer indications in the instructions, or after the researchers combine clinical practice and the patient's previous medication status, irinotecan monotherapy can be used for 1 to 2 courses (recommended dose: irinotecan 150 mg/m ^{2}, intravenous drip, single dose) or FOLFIRI regimen (recommended dose: irinotecan 130-150 mg/m ^{2}, 5-fluorouracil 2400 mg/m ^{2}, intravenous infusion, single dose) or paclitaxel (recommended dose: paclitaxel 135 mg/m ^{2}, intravenous infusion, single dose) as bridging therapy. The use of bridging therapies other than the recommended regimen requires medical consultation and confirmation with the sponsor. Bridging therapy must be completed 7 days prior to lymphoproliferative conditioning, or a washout period of at least five half-lives of the bridging drug must be allowed (whichever is longer). Once the IMC002 product has been prepared and meets the inspection and release quality standards, if the subject meets the cell reinfusion criteria, IMC002 cell infusion can be performed. Subjects will receive a single infusion of two bags of IMC002 at a dose of 2.5×10 ^{8} CAR-T cells per subject.

Control group:

After randomization, subjects will undergo single-dose sampling before receiving the investigator-selected treatment. Comparator drugs include apatinib mesylate, paclitaxel alone, docetaxel alone, or irinotecan alone. Drugs with gastric cancer indications in their package inserts are preferred, or selected by the investigator based on clinical experience and the patient's previous medication history. Dose adjustments are permitted based on the subject's tolerance.

Apatinib mesylate: 850 mg, orally, once a day.

Paclitaxel alone: 80 mg/m $^{2\ \text{of paclitaxel}}$, intravenous drip, on day 1 , day 8 , day 15 , and repeated

every 28 days.

Docetaxel alone: docetaxel 75 to 100 mg/m ^{2} by intravenous drip on day 1 , repeated every 21 days.

Irinotecan alone: 150-180 mg/m ^{2} by intravenous drip on day 1 , repeated every 14 days .

Until intolerable toxicity, disease progression, initiation of new anti-cancer therapy, or death, whichever occurs first. The trial center is responsible for drug storage and distribution, and the investigator will conduct safety and efficacy assessments on the subjects according to the established visits.

For subjects in the control group who have undergone apheresis and successfully prepared IMC002, if they develop PD or toxic intolerance after receiving ICT drug treatment , the researcher, after fully evaluating the subject's overall condition, believes that subsequent treatment with IMC002 is in the best interest of the subject and may recommend that the subject consider subsequent treatment with IMC002. Patients also have the right to choose subsequent salvage treatment that is in their best interests. If the subject is willing to receive this product, a further assessment of their condition before lymphoblastic leukemia and IMC002 cell infusion will be required, using the same assessment criteria as the experimental group. Those who meet the assessment criteria can begin the lymphoblastic leukemia and IMC002 treatment process, using the same treatment plan as the experimental group.

Before a patient with PD, as assessed by the researcher, plans to receive IMC002 treatment, the BIRC-assessed PD auxiliary confirmation process must be initiated. For subjects whose PD is not confirmed by BIRC, their efficacy status judgment and treatment decision must be comprehensively evaluated and handled by the researcher.

Subjects in both groups will undergo molecular pre-screening and related examinations according to the established visits in the trial flow chart to evaluate their efficacy, safety and cell dynamics (CAR copy number detection and cell metabolic dynamics-related assessments will only be performed on subjects receiving IMC002 infusion).

A BIRC will be established in this study to evaluate the tumor status and treatment response of the subjects according to the BIRC charter.

3.2 Random Methods

After the subject signs the molecular pre-informed consent form, researchers from each trial center will pre-assign a screening number to each screened subject in order of priority. After passing the screening, the subject will fill out the screening information and obtain a random number. Each subject will have a unique random number.

This study used a stratified block randomization method. Participants who met the inclusion criteria were randomly assigned to the experimental group and the control group in a 2:1 ratio. Randomization stratification factors included: (1) Eastern Cooperative Oncology Group performance status (ECOG PS): 0 or 1 ; (2) liver metastasis: yes or no; (3) number of previous

systemic treatment lines: 2 lines * or ⩾3 lines.

* Patients whose first-line treatment used three drugs simultaneously, including taxanes (or anthracyclines), platinums, and fluorouracils, and whose disease progressed as assessed by the investigator were considered to have failed the second-line treatment.

3.3 Research Methods

3.3.1 Molecular Pre-screening Phase

CLDN18.2 IHC detection:

all subjects signed the molecular pre-screening informed consent form, they used the companion diagnostic reagent Claudin 18.2 antibody reagent (immunohistochemistry) to perform CLDN 18.2 target screening and related molecular biological characteristics. If the central laboratory test results did not meet the CLDN 18.2 expression level required by the protocol , the pre-screening was considered a failure and subsequent screening was discontinued.

CDx Development:

Claudin18.2 expression in tumor tissue will be assessed using a companion diagnostic reagent, the Claudin 18.2 Antibody Reagent (Immunohistochemistry). The results will be used in clinical trial screening to evaluate the efficacy of IMC002 in the treatment of patients with gastric or GEJ adenocarcinoma positive for Claudin18.2. This companion diagnostic kit utilizes immunohistochemistry, performed on a Leica BOND-III stainer and accompanied by complementary reagents (such as the Bond Polymer Refine Detection immunochromatographic reagent). The kit will detect Claudin18.2 protein expression in 10% neutral formalin-fixed, paraffin-embedded (FFPE) tissue sections from gastric or GEJ adenocarcinoma. This testing will be performed at a central laboratory, and all subjects must submit FFPE tissue for Claudin18.2 expression testing prior to enrollment.

3.3.2 Screening period

subjects with inoperable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose central laboratory test results meet the protocol-required CLDN 18.2 expression levels may enter the screening period after signing the master informed consent form. Subjects meeting the eligibility criteria will be randomly assigned to the experimental or control group in a 2:1 ratio. The screening period is defined as the period from signing the master informed consent form until subject randomization .

3.3.3 Treatment period

3.3.3.1 Experimental Group

After randomization, subjects in the experimental group will begin apheresis, bridging therapy (if necessary), lymphoblastic leukemia removal, and IMC002 infusion.

Single collection:

After randomization, subjects will begin apheresis for IMC002 preparation.

Bridging therapy:

Before the pretreatment of lymphoproliferative apheresis to lymphoproliferative depletion, the researcher shall judge the subject's condition and consider giving bridging therapy based on the subject's clinical benefits and risks. The purpose of bridging therapy is to stabilize the subject's current disease status or reduce the subject's current tumor burden. The preferred drugs are those with gastric cancer indications in the instructions, or after the researcher combines clinical practice and the patient's previous medication status, 1 to 2 courses of irinotecan alone (recommended dose: irinotecan 150 mg/m ^{2}, intravenous drip, single dose) or FOLFIRI regimen (recommended dose: irinotecan 130-150 mg/m 2 mg/m ^{2}, 5-fluorouracil 2400 Recommended dose: paclitaxel 135 mg/m ^{2}, intravenous infusion, single dose) or paclitaxel (recommended dose: paclitaxel 135 mg/m^2, intravenous infusion, single dose) as bridging therapy. The use of bridging therapy other than the recommended regimen requires medical consultation and confirmation with the sponsor. Bridging therapy must be completed within 7 days of lymphoproliferative conditioning, or a washout period of at least five half-lives of the bridging drug must elapse from the time of lymphoproliferative conditioning (whichever is longer).

If the subject receives bridging therapy or the investigator believes the subject's disease condition requires reassessment, appropriate examinations may be performed, including but not limited to: imaging assessment, tumor biomarkers, blood routine, biochemistry and coagulation function, etc. If the subject experiences rapid hyperprogression, the investigator will need to assess the risks and benefits of the subject's subsequent trial process and determine whether the subject should undergo subsequent lymphoproliferative conditioning and infusion. If the subject achieves complete remission, no subsequent lymphoproliferative conditioning and infusion will be required.

Pretreatment of rinsing:

When the IMC002 product is prepared, if the subject meets the lymph node clearance pretreatment criteria, lymph node clearance pretreatment will be performed.

- **Drainage pretreatment assessment**

If the subject meets any of the following criteria before lymphoproliferative pretreatment and is judged by the researcher to be unsuitable for subsequent trial procedures, lymphoproliferative pretreatment cannot be continued or needs to be delayed, and infusion cannot be performed or needs to be delayed.

1. ECOG performance status score ≥2 points;
2. Active infection: If the subject requires systemic anti-infective treatment or has a body temperature of ≥38° C within 7 days before lymph node clearance pretreatment, the investigator must discuss this with the sponsor before starting lymph node clearance pretreatment;

3. Patients are assessed by the investigator to have a high risk of bleeding or perforation;
4. with known or suspected central nervous system metastasis;
5. Surgery, interventional therapy, radiotherapy or immunotherapy for the disease underwent within 2 weeks before lympholysis pretreatment;
6. Blood tests: neutrophil count $<1.5 \times 10^9$ /L; platelet count (PLT) $<75 \times 10^9$ /L; hemoglobin content (Hb) < 8.0g /dL;
7. Liver function: Alanine aminotransferase (ALT) >2.5×ULN, aspartate aminotransferase (AST) >2.5 × ULN, serum total bilirubin (TB) >2 × ULN; for patients with liver metastasis, AST and ALT >5×ULN;
8. Renal function: creatinine clearance < 50 mL /min (according to the Cockcroft-Gault formula);
9. Amylase and lipase > 1.5 × ULN; alkaline phosphatase (ALP) > 2.5 × ULN; for patients with bone metastases, ALP > 5 × ULN;
10. International normalized ratio (INR) and partial prothrombin time (APTT) >1.5 × ULN;
11. Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen);
12. Systemic glucocorticoids were used within 7 days before the lymph node clearing pretreatment, and the cumulative dose exceeded 70 mg prednisone equivalent dose of glucocorticoids (except for those using inhaled or topical glucocorticoids);
13. Any toxicity caused by bridging therapy has not recovered to CTCAE grade 2 or below;
14. failure to complete the bridging therapy washout period;
15. Other complications or toxicities may place the subject at inappropriate risk for lymphoproliferative conditioning and IMC002 cell infusion, including but not limited to the development of new arrhythmias in the subject that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient's presence of major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the matter with the sponsor's medical department.

- **Pretreatment plan for clearing leucoderma:**

lympholysis conditioning regimen consists of fludarabine, cyclophosphamide, and nab-paclitaxel (FNC) . If a subject is allergic to or intolerant of nab-paclitaxel, the investigator may administer fludarabine combined with cyclophosphamide (FC) based on the subject's condition.

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

Fludarabine 25 mg/m ^{2} /day × 2 days (day 1 and day 2 for clearing urethritis)

Cyclophosphamide 250 mg/m ^{2} /day × 3 days (lymph clearance on the first, second, and third days)

Albumin-paclitaxel 100 mg (on the second day of lymph node clearance)

If the subject is allergic to or intolerant to albumin-paclitaxel, the researcher may choose the following FC lympholysis pretreatment regimen based on the subject's condition.

(2) FC regimen: Fludarabine combined with cyclophosphamide regimen

Fludarabine 20-25 mg/m ^{2} /day × 2 days

Cyclophosphamide 500 mg/m ^{2} /day × 2 days

The body surface area of the subjects was calculated according to the Stevenson formula

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

If the researcher needs to use a lymphoproliferative conditioning regimen for a subject beyond the protocol, this should be discussed with the sponsor. CAR-T cell infusion can begin 1-2 days after the subject has received the lymphoproliferative conditioning regimen.

IMC002 cell infusion:

After successful preparation of IMC002 injection and lymph node clearance pretreatment, subjects who are assessed by the researchers as qualified will continue to receive subsequent IMC002 infusion treatment .

Pre-infusion assessment:

Before IMC002 infusion, the subject's clinical status should not be significantly worse than that at the time of enrollment screening, as assessed by the investigator, which would increase the risk of IMC002 infusion. On the scheduled IMC002 infusion day, if the subject meets any of the following criteria, IMC002 infusion should be delayed:

1. ECOG performance status score ≥2 points ;
2. Active infection: If the subject requires systemic anti-infection treatment or has a body temperature ⩾38° C, the infusion cannot be given or needs to be delayed;
3. CTCAE grade 3 or higher non-hematologic toxicity (excluding grade 3 nausea, vomiting, diarrhea, or constipation) occurring after lympholysis pretreatment;
4. Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen);
5. Other complications or toxicities may place the subject at inappropriate risk for IMC002

cell infusion, including but not limited to the subject experiencing new arrhythmias that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient to have major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the medical situation with the sponsor.

For subjects who have completed cell preparation but do not meet the reinfusion criteria and need to delay infusion, if their body temperature does not return to normal within 7 days after the lymphatic ablation pretreatment or other toxicity does not recover to ≤ Grade 1, the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment. If for any reason the cell infusion is delayed for more than 7 days after the lymphatic ablation pretreatment, the infusion cannot be performed , or the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment to delay the infusion. It is recommended that the interval between two lymphatic ablations be no less than 4 weeks .

IMC002 feedback:

After successful preparation of IMC002 injection and lymph node clearance pretreatment, subjects who are assessed by the researchers as qualified will continue to receive subsequent IMC002 infusion treatment.

Before cell infusion, sufficient backup medications (e.g., at least two doses of tocilizumab) should be available, and emergency facilities and equipment should be readily available to ensure prompt treatment in the event of a severe allergic reaction, severe hypotension, or other emergency. Thirty to sixty minutes before cell infusion , investigators may consider pre-treating subjects to prevent infusion reactions based on clinical experience , such as with histamines such as acetaminophen (300-1000 mg orally), promethazine hydrochloride (25 mg intramuscularly), or diphenhydramine (50 mg). Following infusion, each subject is recommended to remain hospitalized for 14 days, or the investigator may decide on the discharge date based on the subject's condition .

3.3.3.2 Control Group

Single collection:

After randomization, subjects will be administered a single dose of IMC002 before receiving the investigator's selected treatment.

Control treatment:

Comparator drugs include apatinib mesylate, paclitaxel alone, docetaxel alone, or irinotecan alone. Drugs with a gastric cancer indication in the package insert are preferred, or selected by the investigator based on clinical experience and the patient's previous medication history. Dose adjustments are permitted based on the subject's tolerance. The trial will continue until toxic intolerance, disease progression, initiation of new anticancer therapy, or death, whichever occurs

first. The trial center is responsible for drug storage and distribution, and the investigator will conduct safety and efficacy assessments on the subjects according to scheduled visits.

Apatinib mesylate treatment:

850 mg, orally, once a day.

Paclitaxel alone (only for subjects with contraindications to ramucirumab):

Paclitaxel 80 mg/m ^{2}, intravenous drip, on day 1, day 8, day 15, and repeat every 28 days.

Docetaxel alone (only for subjects with contraindications to ramucirumab):

Docetaxel 75-100 mg/m ^{2}, intravenous drip, on day 1, repeated every 21 days.

Irinotecan alone:

150-180 mg/m ^{2}, intravenous drip, on day 1, repeated every 14 days.

For subjects in the control group who have undergone apheresis and successfully prepared IMC002 and develop PD or intolerable toxicity after a thorough evaluation, the BIRC assessment process for PD confirmation must be initiated before the investigator-assessed PD is confirmed and IMC002 treatment is planned. For subjects whose PD is not confirmed by the BIRC, the efficacy status assessment and treatment decision must be comprehensively evaluated by the investigator and medically confirmed with the sponsor. If the investigator fully evaluates the subject's overall condition and determines that subsequent IMC002 treatment is in the best interest of the subject, the investigator may recommend that the subject consider IMC002 treatment. Patients also have the right to choose subsequent salvage treatment that is in their best interests. If the subject is willing to receive this product, a further assessment of the subject's status before lymphoblastic ablation and IMC002 cell infusion will be required, using the same criteria as for the experimental group. Those who pass the assessment can begin the lymphoblastic ablation and IMC002 treatment process, using the same treatment plan as the experimental group.

3.3.4 Follow-up period

Tumor assessments will be conducted by the BIRC and investigators according to RECIST 1.1 criteria. Starting from post-randomization apheresis, the first tumor assessment will be conducted at Week 8 ± 7 days (for patients in the IMC002 trial group, this must also be at least 4 weeks after infusion). Tumor assessments will be conducted every 6 weeks ± 7 days thereafter until disease progression, as determined by the investigator and confirmed by the BIRC, initiation of new anti-cancer therapy, death, loss to follow-up, or study withdrawal, whichever occurs first. For patients in the control group who receive IMC002 infusion after progression, the first post-infusion tumor assessment will be conducted at Week 4 ± 2 days after infusion. Thereafter, tumor assessments will be conducted every 6 weeks ± 7 days until disease progression, as determined by the investigator, initiation of new anti-cancer therapy, death, loss to follow-up, or study withdrawal, whichever occurs first. Survival status will be collected every 12 weeks after entering

survival follow-up.

Tissue, blood, and serum samples will be collected from the subjects to evaluate characteristic information such as the expression ratio and intensity of the CLDN18.2 target, changes in biomarkers related to the tumor immune microenvironment characteristics and the overall immune characteristics of the body, and cytokine level analysis, cell dynamics, and immunogenicity analysis of IMC002 will be performed.

3. 4 Study Suspension, Termination, and Withdrawal

3.4.1 Study Suspension and Termination

The sponsor has the right to suspend or terminate the clinical study early at any time. The reasons for suspending or terminating the study early may include, but are not limited to, the following:

Unexpected, significant, or unacceptable risks occur to the enrolled subjects;

The sponsor decides to suspend or stop the development of the drug.

3.4.2 Termination of study treatment

Discontinuation of study treatment means the permanent cessation of study treatment by a subject for any reason (before the completion of planned study drug administration, if any) and may be initiated by the subject or the investigator.

If the investigator believes that continuing the study treatment may have an adverse effect on the subject's health, the investigator must terminate the study treatment for the subject.

The current group study treatment should be terminated in the following cases:

- Subject decision
- The researcher decided
- pregnancy
- Other anti-tumor treatments prohibited in the " Prohibited Treatments " section were used during the study , including but not limited to radiotherapy, chemotherapy, immunotherapy, surgical treatment, etc.
- Any situation where continued participation in the study may result in safety risks
- If a subject in the experimental group shows rapid hyperprogression before receiving treatment, the researcher needs to evaluate the risks and benefits of the subject's subsequent trial process and determine whether the subject should undergo subsequent lymphoproliferative pretreatment and infusion. If the control group shows disease progression according to RECIST 1.1 (confirmed by BIRC assessment)
- Adverse events requiring permanent discontinuation of study treatment

- Protocol deviations that pose a significant risk to the safety of the subjects
- Withdrawal of informed consent and withdrawal from the study
- Sponsor terminates study
- die
- Lost to follow-up

If study treatment is terminated, the investigator should make every effort to understand the subject's main reason for termination of study treatment and record this information.

Subjects who discontinued study treatment agreed to return for end-of-treatment and follow-up visits as indicated in the assessment schedule.

If a subject is unable or unwilling to attend any further visits, site staff should maintain regular telephone contact with the subject or a person designated by the subject in advance. Telephone contact is preferred according to the study visit schedule.

at least a brief visit should be performed by office visit or telephone / email contact to collect the following data:

- New / combination treatment
- AE/SAE

The investigator must also contact the randomized registration system to register information about subjects who discontinued study treatment.

subjects who discontinue study treatment due to reasons other than documented disease progression, death, loss to follow-up, or withdrawal of informed consent , tumor assessments must continue according to the assessment schedule until BIRC determines disease progression, death, loss to follow-up, or withdrawal of informed consent according to RECIST 1.1 .

3.4.3 Withdrawal from the Study

Study withdrawal was defined as the time at which a subject permanently stopped receiving study treatment for any reason and any further evaluation or follow-up required by the protocol.

or withdraw informed consent at any time . Withdrawal of informed consent may affect further contact with the subject and the collection of follow-up data (e.g., responses to data inquiries). Therefore, it is important to ensure accurate documentation of withdrawal from the study and discontinuation of study treatment, as defined in the protocol. If a subject requests withdrawal from the study, the investigator should make every effort to determine the subject's primary reason for withdrawal through various means (e.g., telephone, email, letter) and document this information.

Once a subject confirms withdrawal from the study, study treatment must be discontinued and no further assessments will be performed. Data that should have been collected at subsequent visits will be considered missing. No further attempts to contact the subject will be permitted unless

safety concerns arise and communication or follow-up is required. If the subject agrees, a final assessment will be conducted at the time of withdrawal, as detailed in the Assessment Schedule.

Subjects who did not complete the study protocol (including cell reinfusion and follow-up assessments) were considered to have terminated the study prematurely.

for withdrawal must be recorded in the CRF and kept within the prescribed time according to GCP requirements.

Reasons for subjects to withdraw from the study included:

1) The subject died.
2) The subject was lost to follow-up.
3) The subject requested to withdraw from the study.
4) IMC002 preparation failed and is not suitable for re-apheresis (only applicable to the experimental group) .
5) Termination of a project initiated by the sponsor, principal investigator, ethics committee, or regulatory agency.

for withdrawal must be recorded in the CRF and kept within the prescribed time according to GCP requirements.

3.4.4 Lost to follow-up

If a subject fails to attend study visits or respond to any contact attempts by the research center and does not clarify his or her intention to discontinue study treatment or withdraw from the study or withdraw informed consent, and thus his or her status cannot be known, the investigator should record the steps for contacting the subject in the original documents, such as the date of the phone call or registered mail, as a demonstration of due diligence. The subject should not be considered lost to follow-up until due diligence is completed.

4. Study Population

All subjects in this study must provide their informed consent (ICF) before undergoing any study-related procedures. Subjects must meet all the following inclusion criteria and do not meet all exclusion criteria to be included.

4.1 Inclusion Criteria

1) The age at randomization was at least 18 years old , and both men and women were eligible.
2) histologically or cytologically confirmed inoperable locally advanced or metastatic gastric/esophagogastric junction adenocarcinoma who have failed at least two prior lines of therapy :
    a. Radiographic progression or clinical worsening of symptoms during second-line

treatment (if first-line treatment includes three drugs including taxanes (or anthracyclines), platinums, and fluorouracils, and the disease progression is assessed by the investigator, the patient may also be enrolled as an eligible subject; disease progression within 6 months after the end of neoadjuvant/adjuvant treatment is also considered a first-line treatment failure);

b. Patients with intolerance to second-line treatment may also be enrolled in the study after full evaluation by the investigator. The definition of intolerance to previous treatment is as follows:

- any Grade ⩾ 3 (according to NCI CTCAE v5.0 criteria) hematologic toxicity that has not recovered to Grade 1 or pre-treatment levels after 14 days of best supportive care;
- any Grade ⩾ 3 (according to NCI CTCAE v5.0 criteria) non-hematologic toxicity (excluding alopecia and asymptomatic laboratory abnormalities) that has not resolved after 14 days of best supportive care.

3) Tumor tissue specimens (primary or metastatic, archived or newly collected) from subjects are expected to be available and tested by a central laboratory, indicating positive histological staining for CLDN18.2 (defined as a positive tumor cell rate ≥40% and a staining intensity ≥2+) . If the subject has previously received other CLDN18.2-targeted therapies, tumor tissue specimens collected after that treatment are required to retest and evaluate CLDN18.2 expression levels .

4) The subject's expected survival period is ≥12 weeks.

5) According to RECIST 1.1, there should be at least one stably measurable target lesion or evaluable lesion, and the longest diameter of the largest lesion (or the shortest diameter if it is a lymph node lesion) should be ⩽5 cm .

6) ECOG performance status score is 0-1.

7) The subject must have adequate organ and bone marrow function. Laboratory screening must meet the following criteria. All laboratory test results should be within the stable ranges described below, and there should be no ongoing supportive treatment. If any laboratory test result is abnormal based on the following criteria , the test can be repeated within 1 week. If the test results still do not meet the following criteria , the patient has failed the screening.

   a) Blood tests [no enhanced blood transfusion (≥ 2 times within 1 week), platelet transfusion, or cell growth factor (except recombinant erythropoietin) within 7 days before the examination]: neutrophil count ≥ 1.5×10^{9}/L; platelet count (PLT) ≥ 75×10^{9}/L; hemoglobin content (Hb) ≥ 8.0 g/dL; lymphocyte (LYM) ≥ 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

patients with liver metastasis, AST and ALT < 5×ULN;

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

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

8) All toxic reactions caused by previous anti-tumor therapy have been alleviated to Grade 0-1 (according to NCI CTCAE Version 5.0) or to a level acceptable to the inclusion/exclusion criteria. This excludes other toxicities such as alopecia and vitiligo that the investigator believes do not pose a safety risk to the subjects.

9) Reproductive status: Female patients of childbearing age or male patients whose sexual partners are female patients of childbearing age are willing to take medically approved and highly effective contraceptive measures , such as intrauterine devices or condoms, from the time the informed consent is signed until 12 months after cell infusion (female patients of childbearing age include premenopausal women and women within 24 months of postmenopause).

10) The subjects must sign and date the written informed consent form.

11) Subjects must be willing and able to comply with the scheduled treatment regimen, laboratory tests, follow-up and other study requirements.

4.2 Exclusion criteria

Subjects who meet any of the following conditions will not be included in this study;

1) Pregnant and breastfeeding women.

2) Positive human immunodeficiency virus (HIV) antibody test; hepatitis B virus infection (HBsAg positive and/or HBc antibody positive, and HBV-DNA positive); acute or chronic active hepatitis C (HCV antibody positive and HCV-RNA positive); positive syphilis antibody test; Epstein-Barr virus infection (IgM positive); cytomegalovirus (CMV) infection (IgM positive) ; human T- lymphotropic virus (HTLV) positive; positive for novel coronavirus (COVID-19) and not reverting to negative within 7 days . The above pathogen test results are subject to the central laboratory test results.

3) Known HER2 expression is positive (defined as IHC 3+, or IHC 2+ and FISH+).

4) Active or clinically poorly controlled serious infection.

5) Patients had uncontrollable pleural effusion, pericardial effusion, and ascites before enrollment.

6) Extensive or diffuse lung metastases or extensive or diffuse liver metastases or extensive or diffuse bone metastases .

7) Blood oxygen saturation is ≤ 95% without oxygen inhalation.

8) Other serious pulmonary 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) Patients with deep and large ulcers of the primary lesion, or recurrence of the anastomotic site with tumor infiltration of the entire layer, or tumor lesions infiltrating large blood vessels, who are judged by the researchers to be at high risk of bleeding or perforation, were included in the CT/MRI or combined gastroscopy examinations.

10) Patients with known past or current hepatic encephalopathy requiring treatment; patients with current or history of central nervous system diseases, such as epileptic seizures, cerebral ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease involving the central nervous system; patients with clinical symptoms of central nervous system metastasis or meningeal metastasis, or other evidence indicating that the patient's central nervous system metastasis or meningeal metastasis has not been controlled, who are judged by the investigator to be unsuitable for inclusion.

11) unstable heart disease that requires treatment or heart disease that cannot be controlled after treatment, or hypertension that is poorly controlled as determined by the researchers (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 after standard treatment (fasting blood glucose ≥ 10.2 mmol/L).

12) Any of the following cardiac clinical symptoms or diseases within 6 months before cell infusion:

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

    b) Myocardial infarction within 1 year; or unstable angina; or history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); use of pacemaker;

    c) Resting electrocardiogram (ECG) with QTc F >450 ms (male) or QTc F >470 ms (female);

    d) Resting electrocardiogram reveals clinically significant abnormalities (such as abnormalities in heart rate, conduction, or morphological characteristics), complete left bundle branch block, third- degree atrioventricular block, or a PR interval greater than 250 ms.

13) Evidence of a significant coagulopathy or other significant bleeding risk, including:

a) clinically significant coagulation abnormalities;

b) A history of intracranial hemorrhage or spinal cord hemorrhage;

c) Patients whose tumor lesions invade large blood vessels and have a significant risk of bleeding;

d) Patients with current unstable or active ulcers or active gastrointestinal bleeding;

e) An embolic event occurred within 6 months before cell transfusion;

f) Clinically significant hemoptysis or significant bleeding in tumor lesions occurred within 1 month before cell transfusion;

g) Major trauma or major surgery within 1 month before enrollment;

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

i) Use of anticoagulant therapy (except low molecular weight heparin) for therapeutic purposes within 2 weeks before cell transfusion;

j) Patients are currently receiving conventional anticoagulant therapy (such as warfarin or heparin). Patients require long-term antiplatelet therapy (aspirin ⩾ 100 mg/day; clopidogrel ⩾ 75 mg/day); dipyridamole, ticlopidine, or cilostazol.

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

15) Subjects requiring systemic treatment with corticosteroids or other immunosuppressive drugs during treatment. Subjects with any active autoimmune disease, or a history of autoimmune disease with expected recurrence (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 fully resolved in childhood and does not require any intervention in adulthood; or other subjects whose condition is not expected to relapse in the absence of external triggers.

16) Patients with previous or concurrent malignancies, with the following exceptions:

a) Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing was required before study enrollment);

b) Carcinoma in situ of cervical or breast cancer who has undergone curative treatment and has no signs of recurrence for at least 3 years before the study;

c) The primary malignancy has been completely resected and remains in complete remission for ≥ 5 years.

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

18) Received the following treatments or drugs before cell infusion: received chemotherapy, targeted therapy, biological therapy, endocrine therapy, immunotherapy and other anti-tumor treatments (except for treatments used in accordance with the protocol requirements before infusion, such as lymphoproliferative conditioning and bridging therapy) , less than 28 days or less than 5 half-lives (whichever is shorter) from the first infusion of treatment in this study ; received traditional Chinese medicine treatment with anti-tumor indications within 2 weeks before cell infusion.

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

20) Subjects with severe mental disorders.

21) If a subject develops a new arrhythmia, including but not limited to arrhythmias that cannot be controlled with medication; hypotension requiring pressor medication; or bacterial, fungal, or viral infection requiring intravenous antibiotics , the investigator may determine that the subject is unsuitable for participation in the trial . Subjects who are taking antibiotics to prevent infection may continue to participate in the trial at the investigator's discretion.

22) Participation in other interventional clinical studies and use of study drug within 1 month before the planned IMC 002 infusion .

23) The investigator assesses that the subject is unable or unwilling to comply with the requirements of the study protocol.

24) 4 weeks before the planned apheresis time or plan to receive a live attenuated vaccine during the study.

25) Subjects with gastrointestinal obstruction or obstructive jaundice are deemed unsuitable for participation in this trial by the investigator .

26) Subjects with any other concurrent serious and/or uncontrolled medical conditions who are deemed unsuitable for participation in this trial by the investigator.

4.3 Re-evaluation of subjects before apheresis

Subjects who are confirmed to be qualified by screening examination can undergo leukocyte apheresis.

Seven days before apheresis, the researcher needs to conduct relevant examinations (if the screening examination is no more than 7 days away from the apheresis, there is no need to re-examine, unless the researcher assesses that there are clear reasons that may cause the test values to change during this period) . The patient should be re-evaluated and the subject must meet the following criteria: neutrophil count $\geq 1.5\times10^{9}$/L; platelet count PLT $\geq 75\times10^{9}$/L; hemoglobin content Hb $\geq$ 8.0g/dL; lymphocyte LYM $\geq 0.5\times10^{9}$/L.

Pre-dose Assessment of Subjects with Lymphatic Clearance Pretreatment

If the subject meets any of the following criteria before lymphoproliferative pretreatment and is judged by the researcher to be unsuitable for subsequent trial procedures, lymphoproliferative pretreatment cannot be continued or needs to be delayed , and infusion cannot be performed or needs to be delayed.

1) ECOG performance status score ≥2 points;
2) Active infection: If the subject requires systemic anti-infective treatment or has a body temperature of ≥38° C within 7 days before lymph node clearance pretreatment, the investigator must discuss this with the sponsor before starting lymph node clearance pretreatment;
3) Patients are assessed by the investigator to have a high risk of bleeding or perforation;
4) with known or suspected central nervous system metastasis;
5) Surgery, interventional therapy, radiotherapy or immunotherapy for the disease underwent within 2 weeks before lympholysis pretreatment;
6) Blood tests: neutrophil count < 1.5×10^{9} /L; platelet count (PLT) < 75×10^{9} /L; hemoglobin content (Hb) < 8.0 g/dL;
7) Liver function: Alanine aminotransferase (ALT) > 2.5×ULN, aspartate aminotransferase (AST) > 2.5×ULN, serum total bilirubin (TB) > 2×ULN; for patients with liver metastasis, AST and ALT > 5×ULN;
8) Renal function: creatinine clearance < 50 mL/min (according to the Cockcroft-Gault formula);
9) Amylase and lipase > 1.5 × ULN; alkaline phosphatase (ALP) > 2.5 × ULN; for patients with bone metastases, ALP > 5 × ULN ;
10) international normalized ratio (INR) and partial prothrombin time (APTT) > 1.5 × ULN;
11) Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen)
12) Patients who have used systemic glucocorticoids within 7 days before lymph node clearance pretreatment and whose cumulative dose exceeds 70 mg of prednisone (except those who used inhaled or topical glucocorticoids);
13) Any toxic reactions caused by bridging therapy have not recovered to CTCAE grade 2 or below;
14) failure to complete the bridging therapy washout period;
15) Other complications or toxicities may place the subject at inappropriate risk for lymphoproliferative conditioning and IMC002 cell infusion, including but not limited to

the development of new arrhythmias in the subject that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient's presence of major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the matter with the sponsor's medical department.

4.5 Subject Pre-Infusion Assessment

Before IMC002 infusion, the subject's clinical status should not be significantly worse than that at the time of enrollment screening, as assessed by the investigator, which would increase the risk of IMC002 infusion. On the scheduled IMC002 infusion day, if the subject meets any of the following criteria, IMC002 infusion should be delayed:

1) ECOG performance status score ≥2 points;
2) Active infection: If the subject requires systemic anti-infection treatment or has a body temperature ≥38° C, the infusion cannot be given or needs to be delayed;
3) Non-hematologic toxicity of CTCAE grade 3 or higher (excluding grade 3 nausea, vomiting, diarrhea, or constipation) occurring after lympholysis pretreatment ;
4) Oxygen supplementation is required to maintain blood oxygen saturation > 95% (referring to pulse oxygen);
5) Other complications or toxicities may place the subject at inappropriate risk for IMC002 cell infusion, including but not limited to the subject experiencing new arrhythmias that cannot be controlled by medication; hypotension requiring pressors; the researcher assesses the patient to have major organ dysfunction (such as severe heart disease, uncontrolled hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis, etc.). If necessary, it is recommended to discuss the medical situation with the sponsor.

For subjects who have completed cell preparation but do not meet the reinfusion criteria and need to delay infusion, if their body temperature does not return to normal within 7 days after the lymphatic ablation pretreatment or other toxicity does not recover to ≤ Grade 1, the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment. If for any reason the cell infusion is delayed for more than 7 days after the lymphatic ablation pretreatment, the infusion cannot be continued, or the investigator will evaluate whether the subject should receive another lymphatic ablation pretreatment to delay the infusion. It is recommended that the interval between two lymphatic ablations be no less than 4 weeks.

4.6 Review and rescreening

If a subject's screening test value fails the test during the first screening, and the researcher suspects that it may be caused by non-disease reasons, a maximum of one re-examination of the

failed indicator is allowed.

If a subject fails the initial screening due to an unsatisfactory screening test value, and the investigator subsequently determines that the test value may have recovered to meet the requirements of this protocol, the subject may be rescreened once. During the rescreening, the subject should be assigned a new screening number.

5. Research therapeutic drugs

5.1 Basic Information of Study Drug

The drug used in this study is an autologous T cell injection modified with a chimeric antigen receptor targeting CLDN18.2, code-named IMC002 , produced by Suzhou Yimufeng Biotechnology Co., Ltd.

IMC002 is an injection consisting of 0.9% sodium chloride injection, 20% human serum albumin (HSA) resuspended in a 3:1 ratio, and then an equal volume of CryoStor® ^{CS10} cryopreservation solution. The final formulation specification is 30 mL/bag. The CAR-T cell content in each bag is shown in Table 2 below .

Table 2 IMC002 information table

Number of CAR-T cells per patient	2.5×10^{8}
Number of bags per dose	2
Number of CAR-T cells per bag	1.25×10^{8}

IMC002 is a cell preparation cryopreserved in liquid nitrogen vapor phase. It is a white to reddish, clear to turbid liquid with no visible foreign particles. Storage and transportation conditions are liquid nitrogen vapor phase, cryopreserved and transported below -150°C .

5.2 Packaging and labeling

5.2.1 Investigational Drug IMC002

The drug label of IMC002 shall include at least: product name, protocol number, subject screening number, subject's initials, the words " For autologous transfusion in clinical research only , patient identity must be confirmed before use , cell product, not irradiated" , subject number, production batch number, specifications, manufacturer, storage and transportation conditions, expiration date, route of administration, etc.

5.2.2 Bridging drugs, lymphoproliferative pretreatment drugs, and CRS treatment drugs

Bridging drugs, lymphoproliferative pretreatment drugs, and CRS treatment drugs will preferably be available at the research center. If these are not available at the research center, the sponsor will purchase them from the manufacturer in commercially available packaging and affix a label indicating that they are for clinical research use only.

5.3 Dosage of the drug

A single infusion of two bags is used, with a dose of 2.5×10^{8} CAR-T cells per subject. The

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

5.4 Preparation before reinfusion

5.4.1 Preparation

IMC002 is packaged and labeled in a cell infusion bag, with the outer packaging serving as the reconstitution bag. After the packaging integrity is verified by the quality department, it is stored in a liquid nitrogen vapor phase. Prior to infusion, the product is placed in a vapor phase liquid nitrogen tank and transported to the clinical research center at low temperature. If reconstitution is acceptable, the liquid nitrogen tank is unpacked and reconstitution is performed. If reconstitution is not possible, the liquid nitrogen tank is returned to the manufacturer .

5.4.2 Reconstitution of cells at the clinical research center

The frozen product will be transported to the research center in a vapor phase liquid nitrogen tank. After receiving the IMC002 product, the clinical research center must review the label information, the integrity of the transport packaging, and the transport temperature curve of the IMC002 product. Only qualified products will be accepted. Before rethawing, the label information, the appearance and integrity of the packaging bag must be reviewed. After confirmation of compliance, the product will be rethawed in a warm water bath at 36℃~38℃. The rethawing steps are as follows:

Completely immerse the double-wrapped product in a warm water bath, reconstitute one bag at a time, and gently massage the bag until the cells are just thawed. Reconstituted product is considered complete when no unthawed clumps remain in the infusion bag. Store the reconstituted product at room temperature and infuse as quickly as possible. The time from reconstitution of the first bag of cells to the completion of the infusion should not exceed 2 hours.

5.4.3 Recheck and prepare before re-transfer

If the outer packaging containing IMC002 is damaged or leaking, but the inner packaging bag is confirmed to be intact after careful inspection, it can still be infused. If the cell infusion bag is damaged, it should not be returned for infusion and should be destroyed.

IMC002 is administered intravenously via a transfusion device at the research center. Each bag of transfused cells will be labeled " For Autologous Transfusion Only for Clinical Research Use " and at least two unique identifiers , such as the subject's initials and screening number . Prior to transfusion, two individuals will independently verify all subject information to ensure it is correctly matched to the participating subjects.

Before cell infusion, sufficient backup medications (e.g., at least two doses of tocilizumab) should be available, and emergency facilities and equipment should be readily available to provide prompt treatment in the event of a severe allergic reaction, severe hypotension, or other emergency. Thirty to sixty minutes before cell infusion, investigators may consider pre-treating subjects based on clinical experience, such as with antihistamines such as acetaminophen (300–1000 mg orally),

promethazine hydrochloride (25 mg intramuscularly), or diphenhydramine (20 mg intramuscularly) . These medications will be provided by the research hospital pharmacy.

5.5 Intravenous Infusion and Monitoring

The subjects will be given the study drugs by researchers at the research center, and the researchers will truthfully record the number of cells used in the study product , infusion time, special circumstances during the infusion process, etc. based on the cell number and infusion conditions on the quality inspection report.

5.5.1 Reinfusion process

1) Choose superficial veins suitable for puncture and blood transfusion, and thicker veins in the upper limbs are recommended ;
2) Use disposable blood transfusion sets for reinfusion, and do not mix the infusion lines with other drugs ;
3) Before reinfusion, confirm again that the subject meets the infusion criteria and has no infection;
4) Before reinfusion, drip normal saline intravenously to lubricate the infusion tube. If the normal saline solution flows smoothly, replace it with an IMC002 cryopreservation bag for reinfusion ;
5) reconstitution of the first bag of cells to the completion of infusion of IMC002 injection should not exceed 2 hours. It is recommended that each bag of cells be infused within 30 minutes (at a drip rate of approximately 3 mL/minute). If cell fluid leakage occurs during the reinfusion process, the reinfusion should be stopped and the remaining product should be destroyed as specified in the protocol.
6) After the reinfusion is completed, at least 50 mL of normal saline should be used to flush the cells attached to the wall of the transfusion tube to ensure that as many cells as possible are reinfused into the subject's body. The time when the last bag is flushed is regarded as the end time of all reinfusions.
7) If severe infusion reaction occurs during the reinfusion, the reinfusion should be stopped immediately and the IMC002 cryopreservation bag should be sealed and kept for inspection;
8) Continuous ECG monitoring should be performed for at least 4 hours from the start of the reinfusion to the end of the reinfusion.

For detailed procedures for reinfusion, please refer to the product manual. If a subject experiences an infusion-related reaction during the reinfusion process, the infusion can be temporarily stopped or the infusion rate reduced. The specific treatment will be evaluated by the investigator.

5.5.2 Post-infusion monitoring

After transfusion, each subject is recommended to be hospitalized for 14 days or the researcher may decide the discharge time based on the subject's condition. During hospitalization after transfusion , body temperature should be monitored at least twice a day, with at least 8 hours between each time. If the body temperature is ≥ 38°C, CRS should be considered. Closely monitor for suspected CRS, neurotoxicity or other adverse reaction symptoms, and provide timely and appropriate treatment for any adverse conditions.

IMC002 injection is released for reinfusion based on the results of the rapid sterility test. If the pharmacopoeial sterility test report is positive after cell reinfusion , refer to the "Reporting and Handling of Positive Sterility Test Reports after Cell Infusion" for handling.

5.6 Storage, distribution and recycling

5.6.1 Storage

IMC002 products for long-term storage will be stored in vapor-phase liquid nitrogen tanks at the preparation center. IMC002 for infusion will be transported to the clinical research center in vapor-phase liquid nitrogen tanks before infusion, and temporarily stored in vapor-phase liquid nitrogen tanks before infusion, with the temperature recorded.

5.6.2 Reconstitution and Infusion of Investigational Drug

The clinical research center will record the IMC002 shipping temperature, packaging bag appearance, and packaging bag integrity. Reconstitute the cells in a warm water bath at 37±1°C. Reconstitute and infuse according to the instructions in Sections 5.4 Pre-infusion Preparation and 5.5 Intravenous Infusion and Monitoring of this protocol .

5.6.3 Recall and Destruction of Investigational Drugs

If the cell infusion bag is damaged, it should not be reinfused and should be destroyed.

The reasons for recalling IMC002 products include but are not limited to:

1) Deviations, OOS investigations, adverse drug reaction complaints, stability study results, supplementary traditional sterility and mycoplasma testing, etc., indicate that the product has quality and safety risks;

2) The subject's condition is not suitable for infusion;

3) The subject refused the infusion.

5.7 Issuance and Receipt, Recovery, and Destruction of Study Drugs

The management, distribution, and recovery of IMC002 in this trial are the responsibility of dedicated personnel. Researchers must ensure that all IMC002 is used only for subjects participating in this clinical study, and its usage and dosage comply with the trial protocol. Remaining cells are returned to the sponsor, and IMC002 must not be transferred to any non-clinical study participants.

CAR - T cells should be cryopreserved at or below -150°C until thawed for use. Upon receipt of IMC002 cells, a two-signature cell receipt form must be signed. The clinical research unit will retain the original, while the collaborating unit will retain a scanned copy. The issuance and receipt of each IMC002 cell should be promptly recorded on a dedicated record sheet.

Any unused IMC002 or cells suspected of quality issues requiring analysis will be returned to the sponsor in a vapor phase liquid nitrogen tank, which will then organize analysis or destruction. Entire bags of IMC002 that do not need to be returned to the sponsor, as well as the post-infusion cell product bag, infusion tubing, and any other items that came into contact with the product, will be disposed of in accordance with the waste management regulations for medical institutions.

5.8 Control Group Drugs

Comparator drugs, i.e., apatinib mesylate, paclitaxel alone, docetaxel alone, or irinotecan alone, are preferably drugs with gastric cancer indications in the instructions , or selected by the investigator based on clinical practice and the patient's previous medication history. Dose adjustment is allowed based on the subject's tolerance. The trial center is responsible for the storage and distribution of the drugs, and the investigator will conduct safety and efficacy assessments on the subjects according to the established visits.

5.8.1 Principles of Dose Adjustment and Discontinuation

If a subject experiences a drug-related adverse event that is clinically significant and has not recovered to CTCAE ≤ Grade 1 or baseline before the next dose, medication may be suspended for up to 14 days (calculated based on the scheduled date of medication). "Clinically significant" and "related" are based on the investigator's judgment. For example, hair loss may be determined to be drug-related, but may not be evaluated as clinically significant. When clinically significant toxicity related to the study drug recovers to Grade 1 or baseline, the subject may continue to use the study drug. During the recovery period, changes in toxicity should be evaluated weekly. The subject's continued medication should maintain the same dose or reduce the dose according to the instructions of the control group drug, or the dosage can be adjusted according to the subject's specific situation.

If the subject still experiences clinically significant drug-related adverse events after the dose is reduced and does not recover to a level that allows continued dosing within 14 days (calculated based on the scheduled medication time), the subject is assessed as intolerant to ICT drug treatment and is advised to terminate treatment.

5.9 Prohibited Drugs and Concomitant Medications

5.9.1 Contraindicated concomitant therapy

During treatment, any anti-tumor treatment not specified in the study protocol is not permitted, including radiotherapy (except for local palliative radiotherapy), chemotherapy, anti-tumor Chinese medicine, immunotherapy, surgical treatment, and other anti-tumor treatments (except for

bridging treatment permitted in the study protocol). Immunostimulants, including interferon, thymosin, injectable RNA, lentinan, and ganoderma lucidum polysaccharide, are not permitted during IMC002 treatment (as they can enhance the immune system's ability to phagocytose and kill CAR-T cells).

corticosteroids exceeding 10 mg/day of prednisone or equivalent is prohibited except for the management or prevention of adverse events .

live or live attenuated vaccines during treatment and within 2 years of IMC002 infusion .

Subjects receiving IMC002 cell infusion should avoid using drugs that may damage the gastric mucosa and cause a higher incidence of gastrointestinal bleeding: non-steroidal anti-inflammatory drugs, glucocorticoids, antiplatelet/anticoagulant drugs, etc.

5.9.2 Permitted concomitant treatment

This study allows the use of medications solely for supportive care (e.g., antipyretics, analgesics, antibiotics, antiemetics, antidiarrheals, hepatoprotective drugs, emergency medications, and medications for adverse events). Blood products are also permitted. Transfusion-associated graft-versus-host disease (TA-GVHD) (an immune response in which transfused immunocompetent lymphocytes attack and destroy host cells and tissues) has been reported in subjects receiving fludarabine after transfusion of non-irradiated blood. This condition, which can be fatal, is associated with a risk of TA-GVHD. To reduce the risk of TA-GVHD, all blood transfusions (including platelets, whole blood, and red blood cells) during study treatment and for three months after FNC conditioning should be irradiated. If irradiation is not feasible due to specific circumstances, transfusions should be performed using an leukolytic transfusion set.

Hypotension may occur during cell reinfusion. Therefore, subjects who have previously used antihypertensive drugs may consider suspending the use of antihypertensive drugs within 12 hours before reinfusion, and closely monitor the subject's blood pressure.

The 3 days before IMC002 infusion and 4 weeks after IMC002 infusion are a period of close observation, and the prophylactic use of proton pump inhibitors and gastric mucosal protective agents is recommended.

In addition to the treatment according to the study protocol, if the subject has disease progression (PD), the subject is discharged from the group and the researcher may adopt any appropriate treatment plan.

to the initial signing of the principal informed consent form until the end of the study should be recorded (excluding infusion solutions, flushing solutions, softeners, excipients, etc. used in routine clinical procedures). The following concomitant medication information should be recorded in the original medical record and entered into the electronic case report form: generic name, route of administration, method of administration, start date, end date, and indication. Any dose adjustment of concomitant medications or changes in treatment regimens must be recorded. At each post-dosing visit, the investigator will ask the subject about their concomitant medication

use, and this information should be recorded in the original medical record and entered into the electronic case report form.

6. Study process and visit arrangements

6.1 Research Process

The specific process of this study is shown in the table below .

surface 3. Study flow chart of experimental groups

Study period / visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Drainage pretreatment			28 days after infusion								Main follow-up period								Follow-up	Exit Treatment Visit [13]	Survival visit
				Pre-drainage assessment [3]	Clearing the bowels	Before infusion Assessment [4]	Infusion	Follow-up within 28 days after infusion																	
Visit time	~D42	D-42~ D-1	D0	Before shower 7 days	$D_{infusion}$ -5d~ -3d	$D_{infusion}$ - 1 day	$D_{infusion}$	$D_{infusion}$ + 1d	$D_{infusion}$ + 3d	$D_{infusion}$ + 7d	$D_{infusion}$ + 9 days	$D_{infusion}$ + 14d	$D_{infusion}$ + 21d	$D_{infusion}$ + 28d	W8	W14	W20	W26	W32	W38	W44	W50	W56~ [12]		Every 12 weeks
Time Window			+3 days						±1d			±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	+ 7d	±14d
Sign the molecular pre-screening informed consent form	X																								
Sign the informed consent form		X																							
Inclusion/Exclusion Criteria		X																							
Demographic data	X	X																							
Tumor diagnosis and treatment history		X																							
Tumor staging and pathology during screening		X																							
History of non-study illnesses		X																							

Study period / visit	**Molecular pre-screening phase**	**Screening Period [1]**	**Single sampling [2]**	**Drainage pretreatment**			**28 days after infusion**								**Main follow-up period**								**Follow-up**	**Exit Treatment Visit [13]**	**Survival visit**
				Pre-drainage assessment [3]	**Clearing the bowels**	**Before infusion Assessment [4]**	**Infusion**	**Follow-up within 28 days after infusion**																		
Visit time	**~D42**	**D-42~ D-1**	**D0**	**Before shower 7 days**	**$D_{infusion}$ -5d~ -3d**	**$D_{infusion}$ - 1 day**	**$D_{infusion}$**	**$D_{infusion}$ + 1d**	**$D_{infusion}$ + 3d**	**$D_{infusion}$ + 7d**	**$D_{infusion}$ + 9 days**	**$D_{infusion}$ + 14d**	**$D_{infusion}$ + 21d**	**$D_{infusion}$ + 28d**	**W8**	**W14**	**W20**	**W26**	**W32**	**W38**	**W44**	**W50**	**W56~ [12]**		**Every 12 weeks**
Time Window			**+3 days**						**±1d**			**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+ 7d**	**±14d**
/allergies/current medical conditions																									
Previous non-study disease treatment [5]		X																							
Claudin 18.2 Detection [6]	X																								
ECOG score		X		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Vital signs		X		X	X	X	X [20]	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	X	X		X	
Blood oxygen saturation		X		X		X	X [20]	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Height /body surface area		X		X																					
weight		X		X						X		X	X	X	X	X	X	X	X	X	X	X		X	
Complete blood count		X	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Urinalysis		X		X				X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	

Study period / visit	**Molecular pre-screening phase**	**Screening Period [1]**	**Single sampling [2]**	**Drainage pretreatment**			**28 days after infusion**								**Main follow-up period**								**Follow-up**	**Exit Treatment Visit [13]**	**Survival visit**
				Pre-drainage assessment [3]	**Clearing the bowels**	**Before infusion Assessment [4]**	**Infusion**	**Follow-up within 28 days after infusion**																		
Visit time	**~D42**	**D-42~ D-1**	**D0**	**Before shower 7 days**	**$D_{infusion}$ -5d~ -3d**	**$D_{infusion}$ - 1 day**	**$D_{infusion}$**	**$D_{infusion}$ + 1d**	**$D_{infusion}$ + 3d**	**$D_{infusion}$ + 7d**	**$D_{infusion}$ + 9 days**	**$D_{infusion}$ + 14d**	**$D_{infusion}$ + 21d**	**$D_{infusion}$ + 28d**	**W8**	**W14**	**W20**	**W26**	**W32**	**W38**	**W44**	**W50**	**W56~ [12]**		**Every 12 weeks**
Time Window			**+3 days**						**±1d**			**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+ 7d**	**±14d**
Stool routine and occult blood test		X		X				X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Blood biochemistry		X		X		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Coagulation function		X		X		X		X	X	X		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	X	X	X	X	X		X	
C-reactive protein		X		X				X	X	X		X	X	X	X	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	X	
Peripheral blood ferritin		X		X				X	X	X		X	X	X	X	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	X	
Pregnancy test [7]		X		According to clinical signs, if women of childbearing age who are fertile experience amenorrhea, morning sickness, abdominal pain, vaginal bleeding, or other symptoms suspected of pregnancy, they should be reviewed promptly.																					
fasting blood sugar		X		Diabetic patients should undergo timely review according to clinical needs																					
Infectious disease examination		X																							
Gastroscopy [8]		X																							

Study period / visit	**Molecular pre-screening phase**	**Screening Period [1]**	**Single sampling [2]**	**Drainage pretreatment**			**28 days after infusion**								**Main follow-up period**								**Follow-up**	**Exit Treatment Visit [13]**	**Survival visit**
				Pre-drainage assessment [3]	**Clearing the bowels**	**Before infusion Assessment [4]**	**Infusion**	**Follow-up within 28 days after infusion**																		
Visit time	**~D42**	**D-42~ D-1**	**D0**	**Before shower 7 days**	**D infusion -5d~ -3d**	**D infusion - 1 day**	**D infusion**	**D infusion + 1d**	**D infusion + 3d**	**D infusion + 7d**	**D infusion + 9 days**	**D infusion + 14d**	**D infusion + 21d**	**D infusion + 28d**	**W8**	**W14**	**W20**	**W26**	**W32**	**W38**	**W44**	**W50**	**W56~ [12]**		**Every 12 weeks**
Time Window			**+3 days**						**±1d**			**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+ 7d**	**±14d**
12-lead electrocardiogram		X		X		X	X [11]	X [11]		X		X	X	X	X	X	X	X	X	X	X	X		X	
echocardiography		X		Based on clinical signs, if symptoms or signs suggestive of heart failure occur, a follow-up examination should be conducted promptly.																					
Tumor markers		X												X	X	X	X	X	X	X	X	X	X	X	
Imaging examination9		X													X	X	X	X	X	X	X	X	X	X	
Tumor Assessment10		X													X	X	X	X	X	X	X	X	X	X	
Random [2]			X																						
Leukocyte apheresis			X																						
Lymph effusion pretreatment					X																				
IMC002 Feedback							X																		
CAR copy number [15]				X		X	X		X	X	X	X		X	X	X		X				X	X	X	
CAR-T cells Subgroup/Phenotype [15]				X		X	X		X	X	X	X		X	X	X		X				X	X	X	

Study period / visit	**Molecular pre-screening phase**	**Screening Period [1]**	**Single sampling [2]**	**Drainage pretreatment**			**28 days after infusion**								**Main follow-up period**								**Follow-up**	**Exit Treatment Visit [13]**	**Survival visit**
				Pre-drainage assessment [3]	**Clearing the bowels**	**Before infusion Assessment [4]**	**Infusion**	**Follow-up within 28 days after infusion**																		
Visit time	**~D42**	**D-42~ D-1**	**D0**	**Before shower 7 days**	**$D_{infusion}$ -5d~ -3d**	**$D_{infusion}$ - 1 day**	**$D_{infusion}$**	**$D_{infusion}$ + 1d**	**$D_{infusion}$ + 3d**	**$D_{infusion}$ + 7d**	**$D_{infusion}$ + 9 days**	**$D_{infusion}$ + 14d**	**$D_{infusion}$ + 21d**	**$D_{infusion}$ + 28d**	**W8**	**W14**	**W20**	**W26**	**W32**	**W38**	**W44**	**W50**	**W56~ [12]**		**Every 12 weeks**
Time Window			**+3 days**						**±1d**			**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+ 7d**	**±14d**
Cytokine [15]				X		X	X		X	X	X	X		X	X	X		X				X		X	
Immunogenicity testing[16]				X										X		X		X				X	X	X	
RCL detection [17]						X										X		X				X	X	X	
Lentiviral genome Insertion site [18]						X										X		X				X	X	X	
Exploratory indicator testing	X								Based on the actual clinical sample availability and visit points, the researcher will decide whether to conduct an exploratory study with informed consent.																
Combination drug /non-drug treatment		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC Quality of Life Scale [19]		X													X	X	X	X	X	X	X	X	X	X	
Adverse event records		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Living conditions																									X
Antitumor therapy after																									X

Study period / visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Drainage pretreatment			28 days after infusion								Main follow-up period								Follow-up	Exit Treatment Visit [13]	Survival visit
				Pre-drainage assessment [3]	Clearing the bowels	Before infusion Assessment [4]	Infusion	Follow-up within 28 days after infusion																	
Visit time	~D42	D-42~ D-1	D0	Before shower 7 days	$D_{infusion}$ -5d~ -3d	$D_{infusion}$ - 1 day	$D_{infusion}$	$D_{infusion}$ + 1d	$D_{infusion}$ + 3d	$D_{infusion}$ + 7d	$D_{infusion}$ + 9 days	$D_{infusion}$ + 14d	$D_{infusion}$ + 21d	$D_{infusion}$ + 28d	W8	W14	W20	W26	W32	W38	W44	W50	W56~ [12]		Every 12 weeks
Time Window			+3 days						±1d			±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	+ 7d	±14d
study treatment discontinuation																									

Note:

1. Subjects must complete all required visits according to the visit schedule during the screening period. The primary and subsequent follow-up visits are calculated based on the randomization date (D0). Pre-infusion extensions due to CAR-T cell preparation, bridging therapy, or other factors will not be recorded as protocol deviations. If necessary, screening examinations may be performed concurrently with molecular screening . In this case, patients must sign both the molecular pre-screening informed consent form and the primary informed consent form.

2. The date of randomization is designated as D0. Subjects randomized into the trial group will undergo apheresis on the day of randomization or the day following, after the investigators have initially assessed their eligibility. Routine blood test results, if available within 7 days prior to leukocyte apheresis, can be used to assess the safety and standard of apheresis . If the last routine blood test has been performed more than 7 days prior to leukocyte apheresis, or if the investigators determine that the subject's hematological parameters may have changed, a routine blood test should be performed within 7 days prior to apheresis .

3. Within 7 days before the lymph node clearance pretreatment, the researcher will conduct another examination based on the subject's disease condition, including but not limited to: routine examination and occult blood in blood, urine and stool, blood biochemistry, pancreatic function, coagulation function, electrocardiogram, etc. Subjects judged by the researcher to be in a qualified condition will undergo lymph node clearance pretreatment.

4. Prior to cell reinfusion, the investigator must re-evaluate the subject. Only subjects who meet the cell reinfusion criteria may undergo the infusion. If the subject does not meet the cell reinfusion criteria, the infusion may be delayed for no more than 7 days . If the delay exceeds 7 days , the investigator will assess whether the subject should undergo a repeat baseline examination and lymphadenopathy pretreatment procedure. Following cell reinfusion, the subject is recommended to remain hospitalized for 14 days, or the investigator may determine the discharge date based on the subject's condition. Extended hospitalization due to standard medical procedures will not be recorded as a SAE.

5. All medications (including nutritional supplements such as vitamins, therapeutic solvents or solvents) and non-drug treatments used within 30 days before the first signing of the principal informed consent form should be recorded.

6. Potentially eligible subjects will sign the molecular pre-screening informed consent form and undergo CLDN18.2 target screening and related molecular biological characterization testing. Subjects are required to provide a tumor tissue specimen (paraffin block or section). If a tumor tissue specimen is unavailable, a biopsy will be performed during the molecular pre-screening period for central laboratory screening of CLDN18.2 expression. Sample requirements include: formalin-fixed, paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable), fresh biopsy tissue, or at least 6-10 freshly cut, 4-5 μm thick, unstained tissue sections.

7. Blood pregnancy tests are only for female subjects of childbearing age who are fertile. Urine or blood pregnancy tests may be performed during the study if deemed necessary by the investigator. Testing should be performed during the screening period. Women of childbearing age include premenopausal women and women within 24 months of menopause. Infertile women are defined as: 1. Postmenopausal women (amenorrhea for at least one year); 2. Women who have undergone bilateral oophorectomy or hysterectomy.

8. Gastroscopy is required during the screening period. For subjects who have undergone total gastrectomy, the researcher will determine whether gastroscopy is necessary.

9. ① Imaging examinations include enhanced MRI of the head, enhanced CT or MRI of the chest, abdomen, and pelvis , and bone scan results (if bone metastases or signs of bone metastases are present). Subjects with contrast agent allergies may undergo conventional CT /MRI examinations . Enhanced MRI of the head is mandatory during the screening period and optional during the follow-up period at the investigator's discretion if no abnormalities are present . ② Imaging examinations required for enrollment assessments may be performed within 28 days prior to signing the primary informed consent form. Additionally, an imaging assessment must be performed within 14 days prior to randomization as the baseline for this study . ③ During the primary and subsequent follow-up periods, enhanced CT or MRI imaging examinations will be performed according to the trial schedule. Based on the subject's clinical signs, if a subject is suspected of achieving complete remission or disease progression, the investigator may determine whether to increase the frequency of testing based on actual circumstances . ④ The examination methods for the same subject and the same site during the baseline and follow-up periods should remain consistent .

10. Tumor Assessment: Imaging assessment within 14 days before randomization served as the baseline of this study. Starting from the post-randomization apheresis, the first tumor assessment was performed at 8 weeks ± 7 days (the trial group must also meet the requirement of at least 4 weeks after infusion). Tumor assessments were performed every 6 weeks ± 7 days thereafter until disease progression was determined by the investigator and confirmed by BIRC, or the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

on the infusion day and 1 day after infusion are not required .

1 2. After W56 (inclusive), return to the research center for relevant examinations every 6 weeks, with a visit window period of ±7 days, until PD, death, or withdrawal from the trial (whichever occurs first).

13. If a subject withdraws from treatment for any reason, the withdrawal visit will be completed within 7 days of withdrawal and before starting any new anti-cancer treatment. Subjects who have completed the required assessment within 7 days before withdrawal do not need to undergo a repeat examination. Imaging examinations that have already been performed within 4 weeks and do not require reconfirmation do not need to be repeated (if a corresponding safety follow-up examination has been performed during this period, a repeat examination is not required).

14. Researchers may decide whether to conduct this test based on actual circumstances .

15. Blood samples for CAR copy number, CAR-T cell subsets/phenotypes, and cytokines were collected before lymphoblastic effusion (within 7 days), before cell infusion after lymphoblastic effusion ($D_{infusion}$-1), 30 minutes ± 5 minutes after cell infusion on the infusion day, 3 days, 7 days, 9 days, 14 days, 28 days, W8 after randomization, W14 (± 7 days), W26 (± 7 days), W50 (± 7 days), W98 (± 7 days), and at the exit visit. Blood samples were collected every 6 months for 2 years after cell infusion. Blood samples were collected until disease progression, two consecutive undetectable CAR copy numbers after peak detection, death, or other reasons for patient withdrawal from the study (whichever occurred first).

16. Immunogenicity testing will be performed at the pre-lympholysis assessment (within 7 days), 28 days after cell infusion, 14 weeks after randomization, 26 weeks after randomization, 50 weeks after randomization, 98 weeks after randomization, and at the exit visit. If the CAR copy number is still detectable in peripheral blood 2 years after cell infusion, then it will be tested every 6 months thereafter. No further testing will be performed after week 14 if the CAR copy number is undetectable for two consecutive times (including testing before week 14), in the event of death, withdrawal of informed consent, 15 years after cell infusion, or trial termination (whichever occurs first).

17. RCL testing should be performed before lymphoblastic leukemia cell infusion ($D_{Infusion}$-1) , at 14, 26, 50, and 98 weeks after randomization, and annually for 2 years after cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion, or trial termination (whichever occurs first). If the RCL test is negative within 26 weeks after randomization and there are no clinical signs of abnormal lentiviral expansion, blood samples collected after 26 weeks can be retained and not tested.

18. The time points for lentiviral genome insertion site detection are before cell infusion after lympholysis ($D_{infusion}$-1) , 14 weeks , 26 weeks, 50 weeks and 98 weeks after randomization and the exit visit , and once a year after 2 years of cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion or trial termination (whichever occurs first).

19. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires: Assessments were performed during the screening period, 8 weeks ± 7 days after randomization, and every 6 weeks ± 7 days thereafter until the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

20. Physical examination and blood oxygen saturation: Monitor within 1 hour before infusion and within 1 hour after infusion. Additional monitoring may be performed after infusion at the investigator's discretion.

surface 4. Control group study flow chart (apatinib mesylate/paclitaxel monotherapy)

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period									Exit Treatment Visit [9]	Survival follow-up
				C1 (28 days)			C2 (28 days)			Subsequent treatment cycle [12]				
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**	**Within 30 days after the last dose**	**±14d**
Sign the molecular pre-screening informed consent form	X													
Sign the informed consent form		X												
Inclusion/Exclusion Criteria		X												
Demographic data	X	X												
Tumor diagnosis and treatment history		X												
Tumor classification and staging during screening		X												
History of non- study illnesses /allergies/current medical conditions		X												
Previous treatment [3]		X												
Claudin 18.2 Detection [4]	X													
ECOG score		X		X			X			X			X	
Vital signs		X		X			X			X			X	
Physical examination		X		X			X			X			X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period									Exit Treatment Visit [9]	Survival follow-up
				C1 (28 days)			C2 (28 days)			Subsequent treatment cycle [12]				
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**	**Within 30 days after the last dose**	**±14d**
Blood oxygen saturation		X		X	X	X	X	X	X	X		X	X	
Height/body surface area		X												
weight		X		X			X			X			X	
Complete blood count		X	X	X	X	X	X	X	X	X		X	X	
Urinalysis		X		X	X	X	X	X	X	X		X	X	
Stool routine and occult blood test		X		X	X	X	X	X	X	X		X	X	
Blood biochemistry		X		X	X	X	X	X	X	X		X	X	
Coagulation function		X		X	X	X	X	X	X	X		X	X	
Amylase and lipase		X		X			X			X			X	
C-reactive protein		X		X	X	X	X	X	X	X		X	X	
Peripheral blood ferritin		X												
Pregnancy test [5]		X	According to clinical signs, if women of childbearing age who are fertile experience amenorrhea, morning sickness, abdominal pain, vaginal bleeding, or other symptoms suspected of pregnancy, they should be reviewed promptly.											
fasting blood sugar		X		Diabetic patients should undergo timely review according to clinical needs										
Infectious disease examination		X												
Gastroscopy [6]		X												
12-lead electrocardiogram		X		X			X			X			X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period									Exit Treatment Visit [9]	Survival follow-up
				C1 (28 days)			C2 (28 days)			Subsequent treatment cycle [12]				
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**	**D1**	**D 8**	**D 15**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**		**± 3 days**	**± 3 days**	**Within 30 days after the last dose**	**±14d**
echocardiography		X		Based on clinical signs, if symptoms or signs suggestive of heart failure occur, a follow-up examination should be conducted promptly.										
Tumor markers		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days									X	
Imaging examination[7]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days									X	
Tumor Assessment[8]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days									X	
Random [2]			X											
Leukocyte apheresis			X											
Control group treatment [10]				X	X	X	X	X	X	X	X	X		
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	
EORTC Quality of Life Scale [11]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days										
Recording adverse events		X	X	X	X	X	X	X	X	X	X	X	X	
Living conditions														X
Other anti-tumor treatments														X

Note:

1. Subjects must complete all required visits according to the visit schedule during the screening period. The primary and subsequent follow-up visit windows are calculated based on the randomization day (D0). If necessary, screening tests can be performed simultaneously with molecular screening tests . In this case, patients must sign both the molecular pre-screening informed consent form and the primary informed consent form.

2. The date of randomization is designated as D0. Subjects randomized into the trial group will undergo apheresis on the day of randomization or the day following, after the investigators have initially assessed their eligibility. Routine blood test results, if available within 7 days prior to leukocyte apheresis, can be used to assess the safety

and standard of apheresis. If the last routine blood test has been performed more than 7 days prior to leukocyte apheresis, or if the investigators determine that the subject's hematological parameters may have changed, a routine blood test should be performed within 7 days prior to apheresis .

3. All medications (including nutritional supplements such as vitamins, therapeutic solvents or solvents) and non-drug treatments used within 30 days before the first signing of the principal informed consent form should be recorded.

4 . Potentially eligible subjects will sign the molecular prescreening informed consent form and undergo CLDN18.2 target screening and related molecular biological characterization tests. Subjects are required to provide a tumor tissue specimen (paraffin block or section). If a tumor tissue specimen is unavailable, a biopsy will be performed during the molecular prescreening period for central laboratory screening of CLDN18.2 expression. Sample requirements include: formalin-fixed, paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable), fresh biopsy tissue, or at least 6-10 freshly cut, 4-5 μm thick, unstained tissue sections.

5. Blood pregnancy tests are only applicable to female subjects of childbearing age who are fertile. Urine or blood pregnancy tests may be performed during the study if deemed necessary by the investigator. Testing should be performed during the screening period. Women of childbearing age include premenopausal women and women within 24 months of menopause. Infertile women are defined as: 1. Postmenopausal women (menopause for at least one year); 2. Women who have undergone bilateral oophorectomy or hysterectomy.

6. Gastroscopy is required during the screening period . For subjects who have undergone total gastrectomy, the researcher will determine whether gastroscopy is necessary.

7. ① Imaging examinations include enhanced MRI of the head, enhanced CT or MRI of the chest, abdomen, and pelvis, and bone scan results (if bone metastases or signs of bone metastases are present). Subjects with contrast agent allergies may undergo conventional CT/MRI examinations. Enhanced MRI of the head is mandatory during the screening period and optional during the follow-up period at the investigator's discretion if no abnormalities are present. ② Imaging examinations required for enrollment assessments can be performed within 28 days prior to signing the informed consent form. Additionally, an imaging assessment must be performed within 14 days prior to randomization as the baseline for this study. ③ During the primary and subsequent follow-up periods, enhanced CT or MRI imaging examinations will be performed according to the trial schedule. Based on the subject's clinical signs, if the subject is suspected of achieving CR or disease progression, the investigator may determine whether to increase the frequency of testing based on actual circumstances. ④ The examination methods for the same subject and the same site during the baseline and follow-up periods should remain consistent.

8. Tumor Assessment: Imaging assessment within 14 days before randomization served as the baseline of this study. Starting from the single collection after randomization, the first tumor assessment was performed at 8 weeks ± 7 days, and then every 6 weeks ± 7 days until disease progression was determined by the investigator and confirmed by BIRC, or the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

9. If a subject withdraws from treatment for any reason, the withdrawal visit will be completed within 30 days of the last dose and before starting any new anti-cancer therapy. If the subject has completed the required assessment within 7 days before withdrawal, no repeat examination is required. Imaging examinations that have been performed within 4 weeks and do not require reconfirmation do not need to be repeated (if the corresponding safety follow-up examination has been performed during this period, the examination does not need to be repeated).

10. Apatinib mesylate: 850 mg, orally, once a day; paclitaxel: 80 mg/m^2, intravenous drip, on day 1, day 8, day 15, repeated every 28 days.

11. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires : Assessments were performed during the screening period, 8 weeks ± 7 days after randomization, and every 6 weeks ± 7 days thereafter until the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

12. During subsequent treatment cycles, physical examination, vital signs, ECOG score, blood routine test, and blood biochemistry test should be performed within 3 days before the first medication of each cycle. Coagulation function, C-reactive protein, urine routine test, stool routine test and occult blood test, blood oxygen saturation, and electrocardiogram test should be performed within 3 days before the first medication of every 2 treatment cycles (i.e., the 3rd, 5th, 7th, and 9th cycles, and so on).

surface 5. Control group study flow chart (docetaxel alone)

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (21 days)		C2 (21 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Sign the molecular pre-screening informed consent form	X									
Sign the informed consent form		X								
Inclusion/Exclusion Criteria		X								
Demographic data	X	X								
Tumor diagnosis and treatment history		X								
Tumor classification and staging during screening		X								
History of non-study illnesses/allergies/current medical conditions		X								
Previous treatment [3]		X								
Claudin 18.2 Detection [4]	X									
ECOG score		X		X		X		X	X	
Vital signs		X		X		X		X	X	
Physical examination		X		X		X		X	X	
Blood oxygen saturation		X		X	X	X	X	X	X	
Height/body surface area		X								
weight		X		X		X		X	X	
Complete blood count		X	X	X	X	X	X	X	X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (21 days)		C2 (21 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Urinalysis		X		X	X	X	X	X	X	
Stool routine and occult blood test		X		X	X	X	X	X	X	
Blood biochemistry		X		X	X	X	X	X	X	
Coagulation function		X		X	X	X	X	X	X	
Amylase and lipase		X		X		X		X	X	
C-reactive protein		X		X		X		X	X	
Peripheral blood ferritin		X								
Pregnancy test [5]		X	According to clinical signs, if women of childbearing age who are fertile experience amenorrhea, morning sickness, abdominal pain, vaginal bleeding, or other symptoms suspected of pregnancy, they should be reviewed promptly.							
fasting blood sugar		X		Diabetic patients should undergo timely review according to clinical needs						
Infectious disease examination		X								
Gastroscopy [6]		X								
12-lead electrocardiogram		X		X		X		X	X	
echocardiography		X		Based on clinical signs, if symptoms or signs suggestive of heart failure occur, a follow-up examination should be conducted promptly.						
Tumor markers		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	
Imaging examination[7]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	
Tumor Assessment[8]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (21 days)		C2 (21 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Random [2]			X							
Leukocyte apheresis			X							
Control group treatment [9]				X		X		X		
Concomitant medication		X	X	X	X	X	X	X	X	
Quality of Life Scale [11]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days						
Recording adverse events		X	X	X	X	X	X	X	X	
Living conditions										X
Other anti-tumor treatments										X

Note:

1. Subjects must complete all required visits according to the visit schedule during the screening period. The primary and subsequent follow-up visits are calculated based on the randomization date (D0). If necessary, screening tests can be performed simultaneously with molecular screening tests . In this case, patients must sign both the molecular pre-screening informed consent form and the primary informed consent form.

2. The date of randomization is designated as D0. Subjects randomized into the trial group will undergo apheresis on the day of randomization or the day following, after the investigators have initially assessed their eligibility. Routine blood test results, if available within 7 days prior to leukocyte apheresis, can be used to assess the safety and standard of apheresis. If the last routine blood test has been performed more than 7 days prior to leukocyte apheresis, or if the investigators determine that the subject's hematological parameters may have changed, a routine blood test should be performed within 7 days prior to apheresis .

3. All medications (including nutritional supplements such as vitamins, therapeutic solvents or solvents) and non-drug treatments used within 30 days before the first signing of the principal informed consent form should be recorded.

4 . Potentially eligible subjects will sign the molecular prescreening informed consent form and undergo CLDN18.2 target screening and related molecular biological characterization tests. Subjects are required to provide a tumor tissue specimen (paraffin block or section). If a tumor tissue specimen is unavailable, a biopsy will be performed during the molecular prescreening period for central laboratory screening of CLDN18.2 expression. Sample requirements include: formalin-fixed, paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable), fresh biopsy tissue, or at least 6-10 freshly cut, 4-5 μm thick, unstained tissue sections.

5. Blood pregnancy tests are only applicable to female subjects of childbearing age who are fertile. Urine or blood pregnancy tests may be performed during the study if deemed necessary by the investigator. Testing should be performed during the screening period. Women of childbearing age include premenopausal women and women within 24 months of menopause. Infertile women are defined as: 1. Postmenopausal women (menopause for at least one year); 2. Women who have undergone bilateral oophorectomy or hysterectomy.

6. Gastroscopy is required during the screening period . For subjects who have undergone total gastrectomy, the researcher will determine whether gastroscopy is necessary.

7. ① Imaging examinations include enhanced MRI of the head, enhanced CT or MRI of the chest, abdomen, and pelvis , and bone scan results (if bone metastases or signs of bone metastases are present). Subjects with contrast agent allergies may undergo conventional CT /MRI examinations . Enhanced MRI of the head is mandatory during the screening period and optional during the follow-up period at the investigator's discretion if no abnormalities are present . ② Imaging examinations required for enrollment assessments may be performed within 28 days prior to signing the informed consent form. Additionally, an imaging assessment must be performed within 14 days prior to randomization as the baseline for this study . ③ During the primary and subsequent follow-up periods, enhanced CT or MRI imaging examinations will be performed according to the trial schedule. Based on the subject's clinical signs, if a subject is suspected of achieving complete remission or disease progression, the investigator may determine whether to increase the frequency of testing based on actual circumstances . ④ The examination methods for the same subject and the same site during the baseline and follow-up periods should remain consistent .

8. Tumor Assessment: Imaging assessment within 14 days before randomization served as the baseline of this study. Starting from apheresis after randomization, the first tumor assessment was performed at 8 weeks ± 7 days, and tumor assessments were performed every 6 weeks ± 7 days thereafter until disease progression determined by the investigator and confirmed by BIRC, or the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

9. Docetaxel alone 75-100 mg/m ^{2}, intravenous drip, on day 1, repeated every 21 days.

10. If a subject withdraws from treatment for any reason, the withdrawal visit will be completed within 30 days of the last dose and before starting any new anti-cancer therapy. Subjects who have completed the required assessment within 7 days prior to withdrawal do not need to undergo a repeat examination. Imaging examinations that have already been performed within 4 weeks and do not require reconfirmation do not need to be repeated (if appropriate safety follow-up examinations have already been performed during this period, repeat examinations are not required).

11. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires: Assessments were performed during the screening period, 8 weeks ± 7 days after randomization, and then every 6 weeks ± 7 days until the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

12. During subsequent treatment cycles, physical examination, vital signs, ECOG score, blood routine test, and blood biochemistry test should be performed within 3 days before the first medication of each cycle. Coagulation function, C-reactive protein, urine routine test, stool routine test and occult blood test, blood oxygen saturation, and electrocardiogram test should be performed within 3 days before the first medication of every 2 treatment cycles (i.e., the 3rd, 5th, 7th, and 9th cycles, and so on).

surface 6. Control group (irinotecan alone)

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (14 days)		C2 (14 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Sign the molecular pre-screening informed consent form	X									
Sign the informed consent form		X								
Inclusion/Exclusion Criteria		X								
Demographic data	X	X								
Tumor diagnosis and treatment history		X								
Tumor classification and staging during screening		X								
History of non-study illnesses/allergies/current medical conditions		X								
Previous treatment [3]		X								
Claudin 18.2 Detection [4]	X									
ECOG score		X		X		X		X	X	
Vital signs		X		X		X		X	X	
Physical examination		X		X		X		X	X	
Blood oxygen saturation		X		X	X	X	X	X	X	
Height/body surface area		X								
weight		X		X		X		X	X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (14 days)		C2 (14 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Complete blood count		X	X	X	X	X	X	X	X	
Urinalysis		X		X	X	X	X	X	X	
Stool routine and occult blood test		X		X	X	X	X	X	X	
Blood biochemistry		X		X	X	X	X	X	X	
Coagulation function		X		X	X	X	X	X	X	
Amylase and lipase		X		X		X		X	X	
C-reactive protein		X		X		X		X	X	
Peripheral blood ferritin		X								
Pregnancy test [5]		X	According to clinical signs, if women of childbearing age who are fertile experience amenorrhea, morning sickness, abdominal pain, vaginal bleeding, or other symptoms suspected of pregnancy, they should be reviewed promptly.							
fasting blood sugar		X		Diabetic patients should undergo timely review according to clinical needs						
Infectious disease examination		X								
Gastroscopy [6]		X								
12-lead electrocardiogram		X		X		X		X	X	
echocardiography		X		Based on clinical signs, if symptoms or signs suggestive of heart failure occur, a follow-up examination should be conducted promptly.						
Tumor markers		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	
Imaging [examination7]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	

Study period/visit	Molecular pre-screening phase	Screening Period [1]	Single sampling [2]	Treatment period					Exit Treatment Visit [10]	Survival follow-up
				C1 (14 days)		C2 (14 days)		Subsequent treatment cycle [12]		
Visit time	**~D42**	**D-42~D-1**	**D0**	**D1**	**D 8**	**D1**	**D 8**	**D1**		**Every 12 weeks**
Time Window			**± 3 days**		**± 3 days**		**± 3 days**		**Within 30 days after the last dose**	**±14d**
Tumor Assessment[8]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days						
Random [2]			X							
Leukocyte apheresis			X							
Control group treatment [9]				X		X		X		
Concomitant medication		X	X	X	X	X	X	X	X	
EORTC Quality of Life Scale [11]		X		First time: 8 ± 7 days, then every 6 weeks ± 7 days					X	
Recording adverse events		X	X	X	X	X	X	X	X	
Living conditions										X
Other anti-tumor treatments										X

Note:

1. Subjects must complete all required visits according to the visit schedule during the screening period. The primary and subsequent follow-up visits are calculated based on the randomization date (D0). If necessary, screening tests can be performed simultaneously with molecular screening tests . In this case, patients must sign both the molecular pre-screening informed consent form and the primary informed consent form.

2. The date of randomization is designated as D0. Subjects randomized into the trial group will undergo apheresis on the day of randomization or the day following, after the investigators have initially assessed their eligibility. Routine blood test results, if available within 7 days prior to leukocyte apheresis, can be used to assess the safety and standard of apheresis. If the last routine blood test has been performed more than 7 days prior to leukocyte apheresis, or if the investigators determine that the subject's hematological parameters may have changed, a routine blood test should be performed within 7 days prior to apheresis .

3. All medications (including nutritional supplements such as vitamins, therapeutic solvents or solvents) and non-drug treatments used within 30 days before the first signing of the principal informed consent form should be recorded.

4 . Potentially eligible subjects will sign the molecular prescreening informed consent form and undergo CLDN18.2 target screening and related molecular biological characterization tests. Subjects are required to provide a tumor tissue specimen (paraffin block or section). If a tumor tissue specimen is unavailable, a biopsy will be

performed during the molecular prescreening period for central laboratory screening of CLDN18.2 expression. Sample requirements include: formalin-fixed, paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable), fresh biopsy tissue, or at least 6-10 freshly cut, 4-5 μm thick, unstained tissue sections.

5. Blood pregnancy tests are only applicable to female subjects of childbearing age who are fertile. Urine or blood pregnancy tests may be performed during the study if deemed necessary by the investigator. Testing should be performed during the screening period. Women of childbearing age include premenopausal women and women within 24 months of menopause. Infertile women are defined as: 1. Postmenopausal women (menopause for at least one year); 2. Women who have undergone bilateral oophorectomy or hysterectomy.

6. Gastroscopy is required during the screening period . For subjects who have undergone total gastrectomy, the researcher will determine whether gastroscopy is necessary.

7. ① Imaging examinations include enhanced MRI of the head, enhanced CT or MRI of the chest, abdomen, and pelvis , and bone scan results (if bone metastases or signs of bone metastases are present). Subjects with contrast agent allergies may undergo conventional CT /MRI examinations . Enhanced MRI of the head is mandatory during the screening period and optional during the follow-up period at the investigator's discretion if no abnormalities are present . ② Imaging examinations required for enrollment assessments may be performed within 28 days prior to signing the informed consent form. Additionally, an imaging assessment must be performed within 14 days prior to randomization as the baseline for this study . ③ During the primary and subsequent follow-up periods, enhanced CT or MRI imaging examinations will be performed according to the trial schedule . Based on the subject's clinical signs, if a subject is suspected of achieving complete remission or disease progression, the investigator may determine whether to increase the frequency of testing based on actual circumstances . ④ The examination methods for the same subject and the same site during the baseline and follow-up periods should remain consistent .

8. Tumor Assessment: Imaging assessment within 14 days before randomization served as the baseline of this study. Starting from apheresis after randomization, the first tumor assessment was performed at 8 weeks ± 7 days, and tumor assessments were performed every 6 weeks ± 7 days thereafter until disease progression determined by the investigator and confirmed by BIRC, or the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

9 . Irinotecan monotherapy: 150-180 mg/m ^{2} , intravenous drip, on day 1, repeated every 14 days.

10. If a subject withdraws from treatment for any reason, the withdrawal visit will be completed within 30 days after the last dose and before starting any new anti-cancer treatment. Subjects who have completed the required assessment within 7 days before withdrawal do not need to undergo a repeat examination. Imaging examinations that have been performed within 4 weeks and do not require reconfirmation do not need to be repeated (if a corresponding safety follow-up examination has been performed during this period, a repeat examination is not required).

11. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires: Assessments were performed at screening, 8 weeks ± 7 days after randomization, and every 6 weeks ± 7 days thereafter until the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

12. During subsequent treatment cycles, physical examination, vital signs, ECOG score, blood routine test, and blood biochemistry test should be performed within 3 days before the first medication of each cycle. Coagulation function, C-reactive protein, urine routine test, stool routine test and occult blood test, blood oxygen saturation, and electrocardiogram test should be performed within 3 days before the first medication of every 2 treatment cycles (i.e., the 3rd, 5th, 7th, and 9th cycles, and so on).

Table 7 Flowchart of the control group receiving subsequent IMC002 treatment

Study period/visit	Drainage pretreatment			the infusion day and within 28 days after infusion								Main follow-up period							Follow-up	Exit Treatment Visit [8]	Survival visit
	Pre-drainage assessment (baseline) [1]	Clearing the bowels	Pre-infusion assessment [2]	Infusion		Follow-up within 28 days after infusion															
Visit time	Before shower 7 days	- D 5~- D3	-D1	D0	D1	D 3	D 7	D9	D 14	D 21	D 28	W1 0	W 16	W 22	W 28	W3 4	W4 0	W 46	W 52 ~ [7]		Every 12 weeks
Time Window						±1d			±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
Verify inclusion and exclusion criteria	X																				
ECOG score	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Vital signs	X	X	X	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	X	X		X	
Blood oxygen saturation	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Height/body surface area	X																				
weight	X						X		X	X	X	X	X	X	X	X	X	X		X	
Complete blood count	X		X	X [11]	X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Urinalysis	X				X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Stool routine and occult blood test	X				X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Blood biochemistry	X		X		X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Coagulation function	X		X		X	X	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	X	X		X	
C-reactive protein	X				X	X	X		X	X	X	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]	(X) [14]		X	
Peripheral blood ferritin	X				X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Tumor markers	X										X	X	X	X	X	X	X	X	X	X	
Pregnancy test [3]	According to clinical signs, if women of childbearing age who are fertile experience amenorrhea, morning sickness, abdominal pain, vaginal bleeding, or other symptoms suspected of pregnancy, they should be reviewed promptly.																				
fasting blood sugar	X		Diabetic patients should undergo timely review according to clinical needs																		

Study period/visit	Drainage pretreatment			the infusion day and within 28 days after infusion								Main follow-up period							Follow-up	Exit Treatment Visit [8]	Survival visit
	Pre-drainage assessment (baseline) [1]	Clearing the bowels	Pre-infusion assessment [2]	Infusion		Follow-up within 28 days after infusion															
Visit time	Before shower 7 days	- D 5~- D3	-D1	D0	D1	D 3	D 7	D9	D 14	D 21	D 28	W1 0	W 16	W 22	W 28	W3 4	W4 0	W 46	W 52 ~ [7]		Every 12 weeks
Time Window						±1d			±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
Infectious disease examination	X																				
12-lead electrocardiogram	X		X	X [6]	X [6]		X		X	X	X	X	X	X	X	X	X	X		X	
echocardiography	Based on clinical signs, if symptoms or signs suggestive of heart failure occur, a follow-up examination should be conducted promptly.																				
Imaging examination[4]	X										X	X	X	X	X	X	X	X	X	X	
Tumor Assessment [5]	X										X	X	X	X	X	X	X	X	X	X	
Lymph effusion pretreatment		X																			
IMC002 Feedback				X																	
CAR copy number [9]	X		X	X		X	X	X	X		X	X	X		X				X	X	
CAR-T cells Subgroup/Phenotype [9]	X		X	X		X	X	X	X		X	X	X		X				X	X	
Cytokine [9]	X		X	X	X	X	X	X	X		X	X	X		X				X	X	
Immunogenicity testing[10]			X								X		X		X				X	X	
RCL test [11]			X										X		X				X	X	
Lentiviral genome insertion site [12]			X										X		X				X	X	
Exploratory indicator testing	Based on the availability of actual clinical samples, the researcher will decide whether to conduct exploratory research with informed consent.																				
EORTC Quality of Life Scale [13]	X										X	X	X	X	X	X	X	X		X	
Concomitant medication	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	

Study period/visit	Drainage pretreatment			the infusion day and within 28 days after infusion								Main follow-up period							Follow-up	Exit Treatment Visit [8]	Survival visit
	Pre-drainage assessment (baseline) [1]	Clearing the bowels	Pre-infusion assessment [2]	Infusion		Follow-up within 28 days after infusion															
Visit time	Before shower 7 days	- D 5~- D3	-D1	D0	D1	D 3	D 7	D9	D 14	D 21	D 28	W1 0	W 16	W 22	W 28	W3 4	W4 0	W 46	W 52 ~ [7]		Every 12 weeks
Time Window						±1d			±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
Recording adverse events	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Living conditions																					X
Other anti-tumor treatments																					X

Note:

1. Within 7 days before lymphoproliferative pretreatment, the investigator will conduct another examination based on the subject's disease status, including but not limited to routine blood and urine tests, blood biochemistry, pancreatic function, coagulation function, and electrocardiogram (ECG) . The inclusion criteria will be verified before lymphoproliferative pretreatment . Subjects deemed qualified by the investigator will undergo lymphoproliferative pretreatment. The visit time in this visit form is calculated based on the day of IMC002 infusion as day 0. Any extension of the pre-infusion time window due to factors such as CAR-T cell preparation or bridging therapy will not be recorded as a protocol deviation.

2. Before cell infusion, the investigator must re-evaluate the subject. Only subjects who meet the cell infusion criteria can undergo cell infusion. If the subject does not meet the cell infusion criteria, the infusion can be delayed for no more than 7 days . If the delay exceeds 7 days , the investigator will evaluate whether the subject should repeat the baseline examination and lymphadenopathy pretreatment process. At least 14 days of hospitalization and observation should be completed from the date of cell infusion. The 15-28 days of hospitalization and observation should be based on local diagnosis and treatment standards. If the hospitalization period is extended due to diagnosis and treatment standards, it will not be recorded as an SAE.

3. Blood pregnancy tests are only applicable to female subjects of childbearing age who are fertile. Urine/blood pregnancy tests may be performed during the study if deemed necessary by the investigator. Testing should be performed during the screening period. Women of childbearing age include premenopausal women and women within 24 months of menopause. Infertile women are defined as: 1. Postmenopausal women (amenorrhea for at least one year); 2. Women who have undergone bilateral oophorectomy or hysterectomy.

4. ① Imaging examinations include enhanced MRI of the head, enhanced CT or MRI of the chest, abdomen, and pelvis , and bone scan results (if bone metastases or signs of bone metastases are present). Subjects with contrast agent allergies may undergo conventional CT /MRI examinations . Enhanced MRI of the head is mandatory

during the screening period and optional during the follow-up period at the investigator's discretion if no abnormalities are present . ② Imaging examinations required for enrollment assessments may be performed within 28 days prior to signing the informed consent form. Additionally, an imaging assessment must be performed within 14 days prior to randomization as the baseline for this study . ③ During the primary and subsequent follow-up periods, enhanced CT or MRI imaging examinations will be performed according to the trial schedule. Based on the subject's clinical signs, if a subject is suspected of achieving complete remission or disease progression, the investigator may determine whether to increase the frequency of testing based on actual circumstances . ④ The examination methods for the same subject and the same site during the baseline and follow-up periods should remain consistent .

5. Tumor Assessment: Imaging assessment before lympholysis was used as the baseline; the infusion day was designated as D0, and the first tumor assessment was performed on the 4th week ± 2 days after infusion. Tumor assessment was performed every 6 weeks ± 7 days thereafter until disease progression determined by the investigator occurred, or the patient started new anti-tumor treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

6. If the patient has ECG monitoring after infusion, ECG examinations on the infusion day and 1 day after infusion may not be performed .

7. After W52 (inclusive), return to the research center for relevant examinations every 6 weeks, with a visit window period of ±7 days, until PD, death , or withdrawal from the trial (whichever occurs first).

8. If a subject withdraws from treatment for any reason, the withdrawal visit will be completed within 7 days of withdrawal and before starting any new anti-cancer treatment. If the subject has completed the required assessment within 7 days before withdrawal, no repeat examination is required. Imaging examinations that have been performed within 4 weeks and do not require reconfirmation do not need to be repeated (if corresponding safety follow-up examinations have been performed during this period, repeat examinations are not required).

9. Blood samples for CAR copy number, CAR-T cell subsets/phenotypes, and cytokines should be collected before lymphoblastic effusion (within 7 days), before IMC002 infusion, 30 minutes ± 5 minutes after cell infusion, 3 days, 7 days, 9 days, 14 days, 28 days, W10, W16 (± 7 days), W28 (± 7 days), W52 (± 7 days), W94 (± 7 days), and at the exit visit. Blood samples should be collected every 6 months for 2 years after cell infusion. Blood samples should be collected until disease progression, 2 consecutive undetectable CAR copy numbers after peak detection, death, or patient withdrawal from the study due to other reasons, whichever occurs first.

10. Immunogenicity testing will be performed at the pre-lympholysis assessment (within 7 days), day 28 after cell infusion, week 16, week 28, week 52, and week 94 after cell infusion, as well as at the exit visit. If the CAR copy number is still detectable in peripheral blood 2 years after cell infusion, then testing will be performed every 6 months thereafter. If the CAR copy number is undetectable for two consecutive times after week 16 (including testing before week 14), or in the event of death, withdrawal of informed consent, 15 years after cell infusion, or trial termination (whichever occurs first), no further testing will be performed.

11. RCL testing should be performed before IMC002 infusion, at Weeks 16, 28, 52, and 94 after cell infusion, and at the withdrawal visit. Blood samples should be collected annually two years after cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion, or terminates the trial (whichever occurs first). If the RCL test is negative within 28 weeks after IMC002 infusion and there are no clinical signs of abnormal lentiviral expansion, blood samples collected after 28 weeks can be retained and not tested.

12. The time points for lentiviral genome insertion site detection are before IMC002 infusion , 16 weeks , 28 weeks, 52 weeks , and 94 weeks after cell infusion , and at the exit visit . Data will be collected once a year after 2 years of cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion, or the trial is terminated (whichever occurs first).

13. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires: Assessments were conducted before lymphoblastic leukemia, on day 28 ± 2 days after infusion, and every 6 weeks ± 7 days thereafter until the patient started new anti-cancer treatment, died, was lost to follow-up, or withdrew from the study, whichever occurred first.

14. Researchers may decide whether to conduct this test based on actual circumstances.

6.2 Visit Arrangements

6.2.1 Molecular Prescreening Period (~ D- 42)

Potentially eligible subjects will sign the molecular prescreening informed consent form and undergo CLDN18.2 target screening and related molecular biological profiles (such as the tumor immune microenvironment and tumor mutational burden (TMB)) . Subjects are required to provide a tumor tissue specimen (paraffin block or section). If a tumor tissue specimen is unavailable, a biopsy will be performed during the molecular prescreening period for central laboratory screening of CLDN18.2 expression. Sample requirements include: formalin-fixed, paraffin-embedded tumor tissue block (paraffin blocks within 2 years are acceptable), fresh biopsy tissue, or at least 6–10 freshly cut, 4–5 μm thick, unstained tissue sections. If subjects have received other CLDN18.2-targeted therapies, they must provide a post-treatment tumor tissue specimen before enrollment to reassess CLDN18.2 expression levels.

using a companion diagnostic reagent, Claudin 18.2 antibody reagent (immunohistochemistry) , which the sponsor will simultaneously use for companion diagnostic reagent (CDx) development.

If the central laboratory test results do not meet the protocol-required CLDN 18.2 expression level, the patient will be considered a pre-screening failure and will not be considered for subsequent screening. For subjects who fail pre-screening and do not sign the primary informed consent form, the EDC must record the subject's demographic information and the time the pre-screening informed consent form was signed.

6.2.2 Screening period (D- 42 to D-1)

advanced gastric cancer who meet the protocol requirements for CLDN 18.2 expression as determined by central laboratory testing may enter the screening phase after signing the Master Informed Consent Form. All patients participating in the screening phase must sign the Master Informed Consent Form . If necessary, screening can be performed concurrently with molecular screening . In this case, patient screening must begin after signing the Molecular Pre-Screening Informed Consent Form and the Master Informed Consent Form. After signing the Master Informed Consent Form, patients will undergo screening phase examinations and assessments, including:

Screening period:

1) Signed Master Informed Consent (obtained before any study-related tests or procedures other than molecular screening tests)
2) Demographic data collection
3) Tumor diagnosis and treatment history, tumor stage and pathology (including previous and current anti-tumor treatments)
4) Non-tumor medical history, concomitant diseases, and previous treatment history

5) History of non-study illnesses/allergies/current medical conditions
6) Previous treatment for non-study disease
7) Claudin 18.2 test results (Central Laboratory)
8) ECOG score
9) Vital signs
10) Physical examination
11) Blood oxygen saturation (pulse oxygen)
12) Height/ body surface area (Body surface area is calculated based on the patient's height and weight only during the lymph node clearance period)
13) weight
14) Complete blood count
15) Urinalysis
16) Stool routine and occult blood test
17) Blood biochemistry
18) Coagulation tests
19) Blood amylase and lipase
20) C-reactive protein
21) Peripheral blood ferritin
22) Blood pregnancy test (needed for women of childbearing age, defined as those who have not yet menopausal or have been menopausal for less than 2 years)
23) fasting blood sugar
24) Infectious disease testing (central laboratory testing)
25) Gastroscopy (gastroscopy is required during the screening period, and the researcher will determine whether gastroscopy is necessary for subjects who have undergone total gastrectomy)
26) 12-lead electrocardiogram
27) Echocardiography (including LVEF)
28) Tumor markers
29) Imaging tests and tumor assessments (imaging tests required for enrollment assessment can be performed within 28 days before signing the informed consent form. At the same time, imaging assessments must be performed within 14 days before randomization as the baseline of this study)

30) European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires

31) Combination drug/non-drug treatment

32) Adverse event records

For detailed examination items, please refer to **Table 3, the study flow chart of the experimental group , for screening period examinations** . Researchers can add relevant tests based on the actual situation of the patients.

After completing all the aforementioned screening tests , the inclusion/exclusion criteria for the screening period will be verified. Subjects meeting all inclusion criteria and none of the exclusion criteria will be enrolled and undergo leukocyte apheresis . After apheresis, the blood is transported to the cell production site at 2-8° C. For review and research purposes by the National Medical Products Administration (NMPA), the initial PBMCs are also collected and refrigerated. The cell product is expected to be ready for research use approximately 2-3 weeks later.

6.2.3 Randomization (D0)

Subjects who meet the inclusion criteria will be randomly assigned to the experimental group and the control group in a ratio of 2:1.

6.2.4 Study Treatment Period Visits

6.2.4.1 Trial Group Visit Arrangements

6.2.4.1.1 Study Intervention (Before Lymph Circulation Treatment)

Subjects randomized into the trial group will undergo single collection on the day of randomization or within 3 days after the researcher's preliminary assessment that they meet the requirements.

Before apheresis to lymphoproliferative pretreatment, the researcher will judge the subject's condition and, based on the subject's clinical benefits and risks, may consider administering bridging therapy. The purpose of bridging therapy is to stabilize the subject's current disease status or reduce the subject's current tumor burden. For bridging therapies other than the recommended regimen, the researcher must discuss and confirm with the sponsor's medical department. Bridging therapy must be completed 7 days before lymphoproliferative pretreatment, or at least 5 half-lives of the bridging drug before lymphoproliferative pretreatment as a washout period (whichever is longer).

7 days before the lymph node clearing pretreatment , the researcher will conduct relevant examinations required to determine the condition of the subject based on the subject's specific condition, including :

Pre-drainage assessment:

1) ECOG score

2) Vital signs

3) Blood oxygen saturation (pulse oxygen)

4) Height/body surface area (body surface area is calculated based on the patient's height and weight only during the lymph node clearance period)

5) Weight

6) Complete blood test

7) Urinalysis

8) Routine stool examination and occult blood test

9) Blood biochemistry

10) Coagulation function test

11) Blood amylase and lipase

12) C -reactive protein

13) Peripheral blood ferritin

14) Collect blood samples for CAR copy number, CAR-T cell subsets/phenotypes, and cytokine testing

15) 12 -lead electrocardiogram

16) Combined drug/non-drug treatment

17) Adverse event records

Detailed examination items are listed in **Table 3 , the study flow chart for the trial group** . Researchers may add relevant tests based on the patient's actual situation to assess the eligibility of the subject before lymphoproliferative pretreatment. Subjects assessed by the researcher as qualified may receive the lymphoproliferative pretreatment regimen .

6.2.4.1.2 Lymphatic drainage pretreatment (5 to 3 days after infusion)

To ensure optimal survival and stable expansion of autologous IMC002 within the subject, ensuring its anti-tumor activity, a lymphoablation pretreatment protocol will be implemented after successful IMC002 production and prior to infusion. This pretreatment should be performed 3-5 days prior to IMC002 infusion (the specific number of days will be determined by the investigator based on clinical circumstances), after the investigator assesses the patient's condition for suitability. CAR-T cell infusion can begin 1-2 days after the lymphoablation protocol. If IMC002 production is confirmed to be unsuccessful, the investigator may assess the need for repeat apheresis or preparation based on the subject's condition. If the subject is unsuitable for apheresis, they may withdraw from the study and receive other anti-tumor treatment .

6.2.4.1.3 IMC002 Infusion

After the completion of the lymphoproliferative pretreatment and within one day before the reinfusion, the investigator will conduct relevant laboratory tests based on the subject's condition, including but not limited to routine blood and urine tests, blood biochemistry, and coagulation function tests (see Table 3 for details **of the study flow chart for the experimental group**) . The investigator will then reassess the subject's eligibility. Subjects who meet the assessment criteria can undergo the IMC002 reinfusion.

The following tests need to be completed on the day of infusion:

1) Vital signs (monitored within 1 hour before infusion/1 hour after infusion , and additional testing may be performed after infusion at the investigator's discretion)
2) Blood oxygen saturation (pulse oximetry) testing (monitored within 1 hour before infusion/1 hour after infusion , and additional testing may be performed after infusion at the investigator's discretion)
3) Complete blood test (can be tested after infusion unless deemed necessary by the researcher)
4) 12-lead electrocardiogram (this item can be omitted if there is an electrocardiogram monitor after infusion)

For detailed examination items, please refer **to the research flow chart of the experimental group in Table 3.** Researchers can add relevant tests based on the actual situation of the patients.

6.2.4.1.4 Follow-up period within 28 days after infusion (infusion day + 28 days)

1) The following tests are required on day 1, day 3 (±1 day), day 7, day 9, day 14 (±2 days), day 21 (±2 days), and day 28 (±2 days) after cell infusion :
2) ECOG score (performed on D1/D3/D7/D14/D21/D28 after infusion)
3) Vital signs (D1/D3/D7/D14/D21/D28 after infusion)
4) Physical examination (performed on D1/D3/D7/D14/D21/D28 after infusion)
5) Blood oxygen saturation (pulse oxygen) test (D1/D3/D7/D14/D21/D28 after infusion)
6) Body weight (D7/D14/D21/D28 after infusion)
7) Complete blood test (performed on D1/D3/D7/D14/D21/D28 after infusion)
8) Urinalysis (performed on D1/D3/D7/D14/D21/D28 after infusion)
9) Stool routine and occult blood test (performed on D1/D3/D7/D14/D21/D28 after infusion)
10) Blood biochemistry (performed on D1/D3/D7/D14/D21/D28 after infusion)
11) Coagulation test (performed on D1/D3/D7/D14/D21/D28 after infusion)
12) Amylase and lipase (performed on Day 1/D3/D7/D14/D21/D28 after infusion)

13) C-reactive protein (measured on D1/D3/D7/D14/D21/D28 after infusion)

14) Peripheral blood ferritin (performed on D1/D3/D7/D14/D21/D28 after infusion)

15) 12-lead electrocardiogram (performed on D1/D7 /D14 /D28 after infusion ; D1 can be omitted if an ECG monitor is used after infusion)

16) Echocardiogram (including LVEF) (Based on clinical signs, if the subject develops symptoms or signs of heart failure, the examination should be repeated promptly)

17) Tumor markers (performed on D28 after infusion)

18) Collect blood samples for monitoring of cytokines, CAR copy number, and CAR-T cell subsets/phenotypes (D3/D7/D9/ D14 /D28 after infusion) until the CAR copy number test results are negative or below the detection limit for two consecutive times .

19) Anti-CAR anti-drug antibody (ADA) detection (D28 after infusion)

For detailed examination items, please refer to **the research flow chart of the experimental group in Table 3.** Researchers can add relevant tests based on the actual situation of the patients , and can also decide whether to conduct exploratory studies on characteristic detection of tumor immune microenvironment based on the accessibility of clinical samples and informed consent.

6.2.4.1.5 Follow-up period (W8 after randomization)

(± 7 days) after randomization (the trial group must also meet the requirement of at least 4 weeks after infusion). If the W8 visit after randomization overlaps with a visit within 28 days after the first infusion, all examinations within 28 days after infusion and the W8 visit must be completed simultaneously (if there are repeated examination items, they do not need to be repeated). The following tests are required :

1) ECOG score

2) Vital signs

3) Physical examination

4) Blood oxygen saturation (pulse oxygen) detection

5) weight

6) Complete blood count

7) Urinalysis

8) Stool routine and occult blood

9) Blood biochemistry

10) Coagulation tests

11) Amylase and lipase

12) C-reactive protein

13) Peripheral blood ferritin
14) 12-lead electrocardiogram
15) Echocardiogram (including LVEF) (Based on clinical signs, if the subject develops symptoms or signs of heart failure, the examination should be repeated promptly)
16) Tumor markers
17) Imaging and tumor assessment
18) European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires
19) Collect blood samples for monitoring of cytokines, CAR copy number, and CAR-T cell subsets/phenotypes until the CAR copy number test results are negative or below the detection limit for two consecutive times.

For detailed examination items, please refer to **the research flow chart of the experimental group in Table 3.** Researchers can add relevant tests based on the actual situation of the patients , and can also decide whether to conduct exploratory studies on characteristic detection of tumor immune microenvironment based on the accessibility of clinical samples and informed consent.

6.2.4.1.6 Main follow-up period (W14-W50)

Subsequent follow-up visits are based on W14, W20, W26, W32, W38, W44, and W50, with patients returning to the research center every 6 weeks for corresponding examinations . The visit window period is ±7 days, and the following tests must be performed:

1) ECOG score
2) Vital signs
3) Physical examination
4) Blood oxygen saturation (pulse oxygen) detection
5) weight
6) Complete blood count
7) Urinalysis
8) Stool routine and occult blood
9) Blood biochemistry
10) Coagulation tests
11) Amylase and lipase
12) Peripheral blood ferritin (researchers can decide whether to conduct this test based on actual conditions)

13) C-reactive protein (researchers can decide whether to conduct this test based on actual conditions)

14) 12-lead electrocardiogram

15) Echocardiography (based on clinical signs; if symptoms or signs of heart failure develop, follow up promptly)

16) Tumor markers (every 6 weeks, i.e. W14, W20, W26, W32, W38, W44, W50)

17) Imaging examination and tumor assessment (performed every 6 weeks , i.e., W14, W20, W26, W32, W38, W44, and W50)

18) European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OG25 questionnaires (administered every 6 weeks, i.e., W14 , W20 , W26 , W32 , W38 , W44 , and W50)

19) Blood samples were collected for cytokine, CAR copy number, CAR-T cell subset/phenotype , and ADA monitoring (W14 / W26 / W50) until the CAR copy number test results were negative or below the detection limit for two consecutive times. If the CAR copy number was undetectable for two consecutive times after W14, ADA testing was not performed at W26 and W50. RCL and lentiviral genome insertion site detection was performed (W14 / W26 / W50) .

For detailed examination items, please refer to **the research flow chart of the experimental group in Table 3.** Researchers can add relevant tests based on the actual situation of the patients , and can also decide whether to conduct exploratory studies on characteristic detection of tumor immune microenvironment based on the accessibility of clinical samples and informed consent.

6.2.4.1.7 Follow-up (W 56~)

After W56 (inclusive) , patients should return to the research center for examinations every 6 weeks . The visit window period is ±7 days until PD , death, or withdrawal from the trial (whichever occurs first). The following tests must be performed:

1) Tumor markers

2) Imaging tests and tumor assessment

3) Blood samples were collected for CAR copy number, CAR-T cell subset/phenotype , and ADA monitoring (performed on W9 8) until two consecutive test results were negative or below the detection limit; RCL and lentiviral genome insertion site detection was performed (W9 8)

For detailed examination items, please refer to **the research flow chart of the experimental group in Table 3.** Researchers can add relevant tests based on the actual situation of the patients , and can also decide whether to conduct exploratory studies on characteristic detection of tumor immune microenvironment based on the accessibility of clinical samples and informed consent.

6.2.4.2 Arrangements for visits to the control group

6.2.4.2.1 Single collection

After the researchers make a preliminary assessment that the subjects who are randomized into the control group meet the requirements, they will undergo single collection before receiving the treatment drugs selected by the researchers. The single collection process is the same as that of the experimental group.

6.2.4.2.2 The first and second treatment cycles

On the day of the first dose, test results from the three days prior to the first dose are acceptable, unless the investigator deems it necessary to conduct additional tests. All tests should be completed within three days prior to the start of treatment cycle D1 (the second cycle). Investigators may add additional tests based on the patient's specific circumstances . Detailed tests are based on the different dosing regimens and are described in the control group study flow charts 4 , 5, and 6 .

6.2.4.2.3 Subsequent treatment cycles

All examinations should be completed within 3 days before the start of the subsequent treatment cycle D1. Researchers can add relevant tests based on the actual situation of the patient . Detailed examinations should refer to the control group study flow chart Table 4 Table 5 Table 6 according to different medication regimens .

6.2.4.2.4 The control group subsequently received IMC002 infusion

6.2.4.2.4.1 Baseline of Control Group Received IMC002 Infusion

was completed within 7 days before the urinary tract infection .

If significant abnormalities are found and the patient does not meet the criteria for clearing stranguria, the patient cannot proceed with the clearing stranguria test. A retest result may be accepted.

6.2.4.2.4.2 Pretreatment of leaching

Same as 6.2.4.1.2 rinsing pretreatment

6.2.4.2.4.3 IMC002 Infusion

Same as 6.2.4.1.3 First infusion of IMC002

6.2.4.2.4.4 Follow-up period within 28 days after infusion

The following tests are required on day 1, day 3 (±1 day), day 7, day 9, day 14 (±2 days), day 21 (±2 days), and day 28 (±2 days) after cell infusion:

1) ECOG score (performed on D1/D3/D7/D14/D21/D28 after infusion)
2) Vital signs (D1/D3/D7/D14/D21/D28 after infusion)
3) Physical examination (performed on D1/D3/D7/D14/D21/D28 after infusion)

4) Blood oxygen saturation (pulse oxygen) test (D1/D3/D7/D14/D21/D28 after infusion)
5) Body weight (D7/D14/D21/D28 after infusion)
6) Complete blood test (performed on D1/D3/D7/D14/D21/D28 after infusion)
7) Urinalysis (performed on D1/D3/D7/D14/D21/D28 after infusion)
8) Stool routine and occult blood test (performed on D1/D3/D7/D14/D21/D28 after infusion)
9) Blood biochemistry (performed on D1/D3/D7/D14/D21/D28 after infusion)
10) Coagulation test (performed on D1/D3/D7/D14/D21/D28 after infusion)
11) Amylase and lipase (performed on Day 1/D3/D7/D14/D21/D28 after infusion)
12) C-reactive protein (measured on D1/D3/D7/D14/D21/D28 after infusion)
13) Peripheral blood ferritin (performed on D1/D3/D7/D14/D21/D28 after infusion)
14) 12-lead electrocardiogram (performed on D1/D7/D28 after infusion ; D1 can be omitted if an ECG monitor is used after infusion)
15) Echocardiogram (including LVEF) (Based on clinical signs, if the subject develops symptoms or signs of heart failure, the examination should be repeated promptly)
16) Tumor markers (performed on D28 after infusion)
17) Imaging examination and tumor assessment (performed on day 28 after infusion)
18) Blood samples were collected for monitoring of cytokines, CAR copy number, and CAR-T cell subsets/phenotypes (D3/D7/D9/D14/D28 after infusion) until the CAR copy number test results were negative or below the detection limit for two consecutive times.

Table 7 for detailed examination items . Researchers can add relevant tests based on the actual situation of the patients , or decide whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

6.2.4.2.4.5 Primary follow-up period

should be conducted every 6 weeks at W10, W16, W22, W28, W34, W40, and W46 after infusion. The visit window is ±7 days and the following tests should be performed:

1) Physical examination
2) Vital signs
3) Blood oxygen saturation (pulse oxygen) detection
4) weight
5) ECOG score

6) Complete blood count
7) Urinalysis
8) Stool routine and occult blood
9) Blood biochemistry
10) Coagulation tests
11) Amylase and lipase
12) Peripheral blood ferritin
13) C-reactive protein (optional at the investigator's discretion)
14) 12-lead electrocardiogram
15) Echocardiography (during the screening period and based on clinical signs; if symptoms or signs of heart failure develop, follow up promptly)
16) Tumor markers (every 6 weeks, i.e. W10, W16, W22, W28, W34, W40, W46)
17) Imaging examination and tumor assessment (performed every 6 weeks, W10, W16, W22, W28, W34, W40, W46)
18) Blood samples were collected for cytokine, CAR copy number, CAR-T cell subset/phenotype, and ADA monitoring until disease progression, undetectable CAR copy number for two consecutive times after peak detection, death, or other reasons for exclusion from the study (whichever occurred first); RCL and lentiviral genome insertion site detection were performed.

Table 7 for detailed examination items . Researchers can add relevant tests based on the actual situation of the patients , or decide whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

6.2.4.2.4.6 Follow-up

52 (inclusive), follow-up will be conducted every 6 weeks , with a visit window of ± 7 days , until PD, death, or withdrawal from the trial (whichever occurs first). Follow-up must include the following tests:

1) Tumor markers
2) Imaging tests and tumor assessment
3) Blood samples were collected for cytokine, CAR copy number, CAR-T cell subset/phenotype, and ADA monitoring until disease progression, undetectable CAR copy number for two consecutive times after peak detection, death, or other reasons for exclusion from the study (whichever occurred first); RCL and lentiviral genome insertion site detection were performed.

Table 7 for detailed examination items REF _Ref190869082 \h * MERGEFORMAT . Researchers can add relevant tests based on the actual situation of the patients , or decide whether to conduct exploratory studies on characteristics such as tumor immune microenvironment based on the availability of clinical samples and informed consent.

6.2.5 Unplanned Visits

All unplanned visits occurring during or after the study must be recorded in the original medical records and CRFs. During unplanned visits, relevant adverse reactions and their changes, concomitant medications and treatments, and any other information deemed necessary by the investigator should be recorded.

6.2.6 Exit Treatment Visit

Subjects will complete the exit visit within 7 days of discontinuing treatment and before starting any new anti-cancer therapy (see Tables 4-8 for detailed examinations). Subjects who have completed the required assessment within 7 days before discontinuing treatment do not need to undergo a repeat examination. Imaging examinations that have been performed within 4 weeks and do not require reconfirmation do not need to be repeated.

6.2.7 Survival Visit

All subjects will enter the survival follow-up period after completing safety follow-up and efficacy follow-up (whichever is longer) after treatment discontinuation. Survival status will be collected every 12 weeks (±14 days), regardless of the reason for treatment discontinuation (except withdrawal of informed consent or loss to follow-up), until the subject dies, is lost to follow-up, or withdraws informed consent for survival follow-up.

If an interim assessment requires an update of survival status to meet safety or regulatory requirements, additional survival assessments may be performed beyond the planned 12- week follow-up.

Survival information can be obtained by telephone, clinic visit or letter , and the information will be recorded in the original documents and related eCRF . The following data will continue to be collected during the survival visit :

All subsequent anti-tumor treatments were recorded until the subject's death or the end of the study;

1) Survival status was recorded until the subject's death or the end of the study.

2) SAEs related to the trial drug included the occurrence of secondary tumors.

For patients receiving IMC002 infusion (including those in the experimental group and those who crossed over to the control group and received IMC002 infusion) , ADA, RCL, and lentiviral genome insertion site samples will be collected annually for 2 years after cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion, or trial termination (whichever occurs first). If the RCL test is negative within 28 weeks after

randomization and there are no clinical signs of abnormal lentiviral expansion, blood samples collected after 28 weeks can be retained and not tested .

7. Research Evaluation

7.1 Effectiveness Evaluation

7.1.1 Efficacy evaluation indicators

Efficacy evaluation indicators:

The RECIST1.1 standard was used to evaluate efficacy. The effectiveness indicators included objective response rate (ORR), progression-free survival (PFS), disease control rate (DCR), duration of response (DOR) , time to response (TTR) and overall survival (OS) .

Objective response rate (ORR): defined as the proportion of subjects with a confirmed response of CR or PR; also defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR). Tumor response status was assessed by the BIRC according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Confirmation was required by repeat assessment at least 4 weeks after the initial achievement of CR or PR response criteria.

Progression-free survival (PFS): defined as the interval from the date of randomization to disease progression or death from any cause, whichever occurs first. For subjects without documented disease progression or death, the last censored date is used as the cutoff date.

Disease control rate (DCR): the proportion of subjects confirmed to have CR, PR, or SD (RECIST 1.1) .

Duration of response (DOR): The interval from the first assessment of CR or PR to the first assessment of PD or death from any cause (the percentage of subjects with DOR ≥6 months, ≥9 months, and ≥12 months will be reported).

Time to response (TTR): defined as the time from the date of randomization to the first evaluation of the subject as CR or PR (whichever occurs first) .

Overall survival (OS) was defined as the interval from the date of randomization to the date of death from any cause. For subjects whose death was not recorded, those who had not died by the analysis cutoff date were censored at the time of last contact.

7.1.2 Efficacy evaluation criteria

This study will establish a BIRC and assess each subject's tumor status and treatment response (CR, PR, SD, or PD) using RECIST 1.1 criteria . If a PR or CR is achieved, the subject must undergo a confirmation evaluation no less than 4 weeks after the initial evaluation. Regular imaging assessments will be performed until PD is confirmed.

Tumor efficacy assessment:

screening assessments can be performed within 28 days prior to signing the informed consent

form. Imaging assessments can be performed using plain and contrast-enhanced MRI or CT, with the specific examination site determined by the investigator based on the patient's condition. An imaging assessment is required within 14 days prior to randomization as the study baseline . Thereafter , imaging (plain and contrast-enhanced MRI or CT) and tumor marker monitoring will be performed at scheduled visits as outlined in Section 6. Study Procedures and Visits until disease progression , death, or trial withdrawal (whichever occurs first) .

7.2 Safety Assessment

7.2.1 Safety evaluation indicators

According to NCI CTCAE 5.0 (except CRS and ICANS, according to 2019 ASTCT The CRC /ICANS grading standard was used to evaluate the type, incidence, and severity of adverse events after IMC -002 cell infusion , including abnormal clinically significant laboratory test results, abnormal physical examination results, and immunogenicity results after treatment.

The relevance of adverse events to the IMC002 CAR-T treatment regimen will be assessed by the investigator according to the attribution assessment criteria specified in the protocol.

7.2.2 Safety evaluation projects

Clinically significant abnormal laboratory test values should be reported as AEs, except during the molecular pre-screening and screening periods. Blood samples for safety assessment may be repeated if necessary. Clinically significant results meet one or more of the following conditions:

- Examination results and accompanying symptoms;
- Leading to changes in study medication (such as dose changes, interruptions, or permanent discontinuation);
- The test results require additional diagnostic testing or medical/surgical intervention;
- Requires significant increase in concomitant medication or other treatment;
- The investigators believe that this test result should be reported as an adverse event.

An examination performed solely to review an abnormality that does not meet any of the above criteria is not considered an adverse event. Any abnormal test result that is determined to be an error does not need to be reported as an adverse event.

7.2.2.1 ECOG activity score

The Eastern Cooperative Oncology Group (ECOG) has developed a simplified activity status score, which categorizes patients' activity status into six levels, ranging from 0 to 5. For details, see Appendix 4 of 14.4 ECOG Performance Status Score .

7.2.2.2 Vital signs

Vital signs will be assessed according to the study flow chart 2 :

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

After the subject rests in the supine position for 5 minutes, vital signs will be checked. Investigators will assess whether abnormal values are clinically significant.

7.2.2.3 Blood oxygen saturation

The non-invasive pulse oximetry is used to measure the arterial oxygen saturation at the finger site to characterize the cerebral oxygen saturation .

7.2.2.4 Physical examination

will be examined according to the scheduled visits in Section 6. Study Procedures and Visit Schedule : general appearance, head (ears, nose, throat, eyes), respiratory system, abdomen, genitourinary system, musculoskeletal system, nervous system, lymphatic system, and skin.

7.2.2.5 Routine laboratory tests

The indicators of routine laboratory examinations are described below, and the specific indicators of each center may be slightly adjusted.

- Routine blood tests include: 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 content, and platelets;
- Urinalysis includes: specific gravity, pH, bilirubin, urine protein, glucose, ketones, urobilinogen, nitrite, red blood cells and white blood cells;
- Routine stool and occult blood examination include: color, shape, white blood cells, red blood cells, and occult blood tests.
- Blood biochemistry tests include: Blood biochemistry needs to be tested in a fasting state, and the test items include: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (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; total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, sodium, potassium, chloride, calcium, magnesium; if the research center's creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and other tests are not included in the biochemical test, they need to be tested separately.

- Pancreatic function tests include: serum amylase, serum lipase;
- Coagulation function tests include: prothrombin time, activated partial thromboplastin time, thrombin time and international normalized ratio (INR), fibrinogen, fibrin degradation products, and DD dimer.

7.2.2.6 Infectious disease inspection (pathogen detection)

During the screening period, pathogen testing will be conducted. Indicators include HBsAg, HBsAb, HBeAg, HBcAb, HBeAb, HCV antibody, HIV antibody, syphilis antibody, Epstein-Barr virus, cytomegalovirus (CMV), human T- lymphotropic virus (HTLV) , and the novel coronavirus . Both HBsAg and hepatitis B core antibody should be negative. If any of these tests are positive, peripheral HBV DNA testing will be required. Enrollment will only be possible if the HBV DNA level is below the detection limit. HCV antibody-positive subjects should undergo HCV RNA testing, and only those with negative RNA levels will be eligible for enrollment. The results of these pathogen testing are subject to the central laboratory test results .

7.2.2.7 C - reactive protein

High-sensitivity C-reactive protein is the first choice. If detection is difficult, conventional C-reactive protein can be considered.

7.2.2.8 Electrocardiogram

will be performed according to the study procedures described in Section 6. Study Procedures and Visit Arrangements . The subject should rest in the supine position for 5 minutes and then be examined while awake. Sleeping patients should be examined 5 minutes after being awakened and repositioned. All ECGs must be evaluated by a qualified physician. ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QTc.

7.2.2.9 Echocardiography

Echocardiography uses the principle of ultrasonic ranging to measure the cyclical movement of underlying structures, including the heart wall, ventricles, and valves, by transmitting pulsed ultrasound waves through the chest wall and soft tissue. The images are displayed on a monitor as curves showing the relationship between the movement of each structure and time. Recording these curves with a recorder constitutes an echocardiogram. Essential test item: Left ventricular ejection fraction (LVEF).

7.2.2.10 Tumor markers

Tumor markers include AFP (alpha-fetoprotein), CEA (carcinoembryonic antigen) , CA724 , and other tumor marker tests that researchers believe need to be added (such as CA19-9 , CA125 , etc.) .

7.2.3 Adverse events and serious adverse events

7.2.3.1 Definition of adverse events

Adverse events (AEs) are defined as any adverse medical events that occur to clinical trial subjects after they sign informed consent, regardless of whether they are causally related to the study drug. AEs include but are not limited to the following:

- Exacerbation of existing medical conditions/diseases (before entering the clinical trial) (including aggravation of symptoms, signs, and abnormal examinations);
- Any new adverse medical condition (including symptoms, signs, and newly diagnosed diseases);
- Abnormal test results of significant clinical significance.

Medical conditions/diseases that existed before signing the informed consent will be recorded as AEs only if they worsen after signing the informed consent. Any clinically significant abnormal laboratory or other abnormal safety assessment related to the underlying disease will not be recorded as an AE unless the investigator determines that the patient's condition is more severe than expected. Clinically significant laboratory test results during the screening period should be recorded as medical history and not as AEs unless the investigator believes that the abnormality is caused by the study procedure . Symptoms and signs related to the tumor at baseline should be recorded as adverse events if they worsen in severity or increase in frequency during the study. However, disease progression assessed by imaging methods to measure cancer lesions should not be reported as an adverse event unless it is more severe than expected or the investigator believes that tumor progression is related to study medication or study procedures. If a new primary malignant tumor occurs, such events are considered adverse events.

7.2.3.2 Definition of Serious Adverse Events

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

- resulting in death.
- an AE that may cause death if the event worsens).
- Resulting in hospitalization or prolonged hospitalization, excluding the following:
  - ✓ Hospitalization or prolonged hospitalization not related to worsening of an AE is not an SAE in itself , for example, hospitalization for management reasons (such as physical examinations), hospitalization specified in the clinical trial protocol, etc.
  - ✓ Hospitalization or prolonged hospitalization due to the need for close attention or specific medical procedures (including but not limited to examination purposes, physical conditioning, apheresis, lympholysis, infusion, and intensive monitoring) of the subject is not considered an SAE .

- ✓ Elective hospitalization not related to worsening of adverse events (e.g., elective surgery).

- Resulting in permanent or severe disability or loss of function.
- Cause congenital anomalies or birth defects.

Other important medical events 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 outcomes defined above, such as intensive treatment of allergic bronchospasm in the emergency room or at home; cachexia or convulsions not requiring hospitalization; and ongoing drug dependence or abuse.

7.2.3.3 Grading of adverse events

Investigators should evaluate AEs according to the CTCAE 5.0 criteria (except for CRS and ICANS , which should be evaluated according to the 2019 ASTCT CRC/ICANS grading criteria, see 15.3 Appendix 3 ASTCT CRS grading and ICANS grading for details) and assess the severity of AEs. Severity grading of CTCAE 5.0 version:

Grade 1 : Mild; asymptomatic or mildly symptomatic; clinical or diagnostic findings only; no treatment required

Grade 2 : Severe; minor, local, or noninvasive treatment indications required; age-appropriate instrumental activities of daily living (ADLs) limited (instrumental ADLs include cooking, buying groceries or clothes, using the telephone, managing finances, etc.)

Grade 3 : Severe or medically significant, but not immediately life-threatening; leading to hospitalization or prolonged hospitalization; causing disability; limited self-care activities (ADLs) (self-care ADLs include bathing, dressing and undressing, eating, using the toilet, taking medications, etc., and are not bedridden)

Grade 4 : Life-threatening; urgent treatment required

Grade 5: AE -related death

7.2.3.4 Determination of causal relationship of adverse events

Investigators should use a dichotomous approach to assess the possible association between the AE and the study drug, assessing whether the AE is reasonably related to the study drug and recording this in the CRF : No (not related) or Yes (related). When assessing causality, the following aspects should be considered:

- The temporal relationship between the adverse event and the administration of the trial drug (including the sequence and reasonable time interval)
- Are other medications or treatments associated with adverse events?
- Whether the adverse event is consistent with the mechanism of action of the investigational drug

- Whether the subject's indications or other underlying diseases/comorbidities may lead to the occurrence of adverse events
- Whether the adverse event improves or resolves after dose reduction or discontinuation of the trial drug (if applicable)
- After recovery from the adverse event, whether the adverse event recurs when the trial drug is used again (if applicable)

7.2.3.5 Outcome of adverse events

It can be described as follows:

- Recovered: The subject returned to baseline.
- Recovering: The event has not yet been fully resolved, but the subject is in the recovery stage.
- Unrecovered: The event is ongoing, e.g., an irreversible congenital malformation.
- Recovered with sequelae: Only if the subject will have long-lasting or lifelong sequelae, such as hemiplegia caused by a stroke.
- Fatal: The event resulted in the subject's death, and the date of death was the end date of the event .
- Unknown: The investigator cannot obtain information on the AE outcome, such as the subject being lost to follow-up.

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

7.2.3.6 Collection of adverse events

All adverse events (AEs) should be collected from the signing of the primary informed consent form until the 48-week visit after the subject completes the cell infusion or receives new anti-cancer treatment (whichever occurs first). For subjects who underwent leukapheresis but did not receive CAR-T cell transfusion, only adverse events reported within 30 days of the relevant procedure or treatment (e.g., leukapheresis, lympholysis pretreatment) or the start of new anti-cancer treatment, whichever occurs first, should be collected. Serious adverse events occurring after this collection period and judged by the investigator to be related to the study procedures and/or study treatments should also be collected and recorded.

If adverse events or serious adverse events occurred between the signing of the molecular prescreening consent form and the signing of the master informed consent form and were related to the prescreening tumor biopsy procedure , these AEs or SAEs needed to be recorded.

Disease progression is defined as a worsening of the subject's condition due to the primary tumor targeted by the investigational drug. Symptoms and signs of disease progression do not need

to be recorded as AEs/SAEs.

7.2.3.7 Follow-up of adverse events

Adverse events should be followed up until recovery to normal/baseline levels, the subject is lost to follow-up or dies, or the investigator deems follow-up unnecessary for reasonable reasons (e.g., stabilization of the AE). If an adverse event does not resolve, a reasonable explanation should be documented 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 CRF and medical record. Changes in the severity of the adverse event, its causal relationship to the study drug, measures taken to address the study drug, therapeutic interventions administered, and outcomes should be assessed at each visit (more frequent visits may be necessary).

7.2.3.8 Serious Adverse Event Reporting

All SAEs occurring during the study, regardless of whether they are related to the study drug, should be reported to the ethics committee as soon as possible upon learning of them, in accordance with the requirements of the local ethics committee. Investigators must complete the Serious Adverse Event Report Form and submit it to the sponsor within 24 hours of learning of the SAE . Serious adverse reactions to active control drugs should be reported to the National Center for Drug Evaluation by the clinical trial institution.

The first reported SAE should contain at least the following information:

- Identifiable subject (e.g., subject number);
- Suspicious research drugs;
- Identifiable source of the report (name of the researcher/reporter or institution);
- Other AE related information for reference:
  - If the diagnosis is known, record it as a single disease or syndrome; if the diagnosis is unknown, report signs and / or symptoms, avoiding colloquialisms and abbreviations;
  - Dates of onset and resolution of the event;
  - severity;
  - Determination of the relationship with the investigational drug;
  - Actions taken and results obtained with the investigational drug;
  - Treatment / remedial measures for the subject 's AE ;
  - Description of the adverse event process (including information on concomitant medication, etc.).

When reporting for the first time, try to complete all the information in the SAE report form. The SAE must be recorded and filed with the ethics committee.

When filling in the adverse event form of the CRF, researchers will use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5.0) to judge the severity of adverse events (CRS and ICANS according to the 2019 ASTCT The severity of the adverse event should be assessed using the CRC /ICANS grading criteria , and the grading should be recorded in the CRF. If the severity of the adverse event changes, the original record information should be updated promptly .

7.2.3.9 Suspected and Unexpected Serious Adverse Reactions (SUSAR)

suspected and unexpected serious adverse reactions whose nature and severity exceed the information already provided in the study brochure of the investigational drug.

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

7.2.3.10 Adverse events of special concern and their management principles

The trial site must be equipped with necessary medical rescue equipment, emergency medications, and emergency measures. If necessary, establish an emergency medical incident response team to handle emergency medical incidents and unexpected disasters in accordance with relevant standard operating procedures. Closely monitor potential adverse events, especially unexpected adverse events, and promptly analyze and communicate them. Complete an adverse event observation log. Establish liaison procedures with the hospital's intensive care unit for subject transfer and care. Establish communication and exchange between researchers, laboratories, and collaborating institutions to ensure timely communication and handling of potential adverse events.

Adverse events associated with CAR-T therapy reported in the literature include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cerebral edema, cytopenia, cardiac toxicity, tumor lysis syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), disseminated intravascular coagulation (DIC), off-target toxicity, hypogammaglobulinemia, infectious complications, infusion reactions, and allergic reactions.

Adverse events that may be related to the CLDN18.2 target include acute gastric mucosal injury/gastrointestinal bleeding.

Appendix 5 lists the treatment and response measures for the common adverse events mentioned above, which can be used as a reference for researchers. However, they are subject to the researchers' actual clinical operations and should be recorded truthfully.

Non-serious adverse events of special concern do not need to be reported to the sponsor in a timely manner.

7.2.3.11 Pregnancy

Pregnancy itself is not considered an AE. If a subject or their partner becomes pregnant between the start of study drug administration and W48 of follow-up, regardless of whether the subject withdraws from the trial early, the subject should notify the investigator. The investigator must complete the " Pregnancy Report Form " and submit it to the sponsor within 24 hours of learning of the pregnancy.

Researchers should provide counseling to female subjects and discuss the risks of continuing the pregnancy and the possible effects on the fetus and nursing infant.

Investigators should follow up on pregnancy outcomes until one month after delivery/termination of pregnancy and report the results to the sponsor. If the pregnancy outcome is stillbirth, spontaneous abortion, or fetal malformation, it is considered a SAE and must be reported according to the SAE timeline requirements.

7.3 Cellular Kinetics Assessment

7.3.1 Cellular kinetics evaluation indicators

PK parameters (PK) were assessed using ddPCR and flow cytometry to assess the expansion and persistence of CLDN18.2 CAR-T cells in peripheral blood after IMC002 infusion . Key evaluation indicators included: CAR-T cell peak (peak CAR copy number and peak CAR-T cell number in peripheral blood after cell infusion), time to peak (days to peak CAR copy number and peak CAR-T cell number after cell infusion) , AUC (area under the curve of CAR copy number in peripheral blood versus visit time from day 0 to 28) , T_{last} (the last time CAR copy number became detectable) , final observable concentration (C_{last}), expansion rate (C_{max}/T_{max}), and persistence (from the end of infusion, qPCR was used to measure CAR copy number in peripheral blood at each visit until any two consecutive test results were negative or below the limit of detection). The duration of IMC002 persistence was recorded from the day of infusion to the first negative result or the time when the result fell below the limit of detection .

7.3.2 Cytokinetic Blood Sample Collection and Testing

Blood samples were collected before lymphoblastic leukemia (PLL) clearance (within 7 days), before IMC002 infusion, 30 minutes ± 5 minutes, 3 days, 7 days, 9 days , 14 days, and 28 days after cell infusion, and at W8 , W14 (±7 days), W26 (±7 days), W50 (±14 days), and W98 (±14 days) after randomization. Blood samples were collected every 6 months for 2 years after cell infusion . Blood samples were collected until disease progression, undetectable CAR copy number for two consecutive days after CAR-T cell monitoring reached its peak , death, or other reasons for patient withdrawal (whichever occurred first).

7. 4 Pharmacodynamic evaluation

7.4.1 Pharmacodynamic evaluation indicators

The peak concentration and time to peak of cytokines before and after treatment will be

evaluated , and the corresponding concentration-time curves will be drawn.

7.4.2 Pharmacodynamic blood sample collection and testing

inflammatory factors in the blood before and after treatment , including but not limited to IL-2, IL-6, TNF-α, INF-γ, acute phase response-related factors CRP, ferritin, etc.

Pharmacodynamic blood collection is consistent with PK blood collection , with the addition of sampling before lympholysis .

7.5 Immunogenicity Evaluation

Immunogenicity evaluation : Changes in anti-CAR anti-drug antibodies (ADA) in the blood before and after IMC002 treatment.

ADA testing : Testing should be performed before lymphoblastic effusion (within 7 days of purging lymphoblastic effusion), on day 28 after cell infusion , and on days 14 (±7 days), 26 (±7 days), 50 (±14 days) , and 98 (±14 days) after randomization . If CAR copies are still detectable in peripheral blood 2 years after cell infusion , ADA testing should be performed every 6 months thereafter. If CAR copies are undetectable for two consecutive times after W14 (including testing before W14) , in the event of death, withdrawal of informed consent, 15 years after cell infusion , or trial termination (whichever occurs first) , ADA testing will not be performed again .

7.6 RCL detection

Replication-competent lentivirus testing (RCL testing) : Testing should be performed before infusion, at Weeks 14 (±7 days), 26 (±7 days), 50 (±14 days) , and 8 (±14 days) after randomization. Blood samples should be collected annually for 2 years after cell infusion until the subject is lost to follow-up, dies, withdraws informed consent, 15 years after cell infusion, or trial termination (whichever occurs first). If the RCL test is negative within 26 weeks after randomization and there are no clinical signs of abnormal lentiviral expansion, blood samples collected after Week 24 can be retained and not tested.

7.7 Lentiviral genome insertion site detection

Lentiviral genome insertion site detection was performed after IMC002 treatment to assess lentiviral insertion site events. Testing was performed before infusion, and at W1 4 (±7 days), W2 6 (±7 days), W50 (±14 days) , and W9 8 (±14 days) after randomization. Data were collected annually for 2 years after cell infusion until the subject was lost to follow-up, died, withdrew informed consent, 15 years after cell infusion, or trial termination (whichever occurred first).

7.8 Other exploratory research indicator tests

Other exploratory translational medicine indicators include:

• Detect changes in cytokines (such as IL-2 , IL-6 , TNF-α , INF-γ , etc.) before and after IMC002 administration before and after treatment .

- Additional exploratory testing may be conducted in research centers with appropriate

conditions to support the evaluation of changes in biomarkers (such as CLDN18.2, etc.) before and after administration of IMC002.

- Additional exploratory testing can be performed in research centers with appropriate conditions to support the evaluation of changes in CAR-T cell phenotype before and after IMC002 administration (at time points with CAR-T expansion, such as if there are surplus samples).
- In research centers with corresponding conditions, additional exploratory tests can be carried out to support the CAR-T expansion, immune cell composition (CD4+/CD8+ ratio, memory cell phenotype, etc.) and changes in patient tumor tissues.

Quality of Life Questionnaire C30

The EORTC-QLQ-C30 is a 30-item cancer-specific questionnaire consisting of five functional scales (physical functioning, role functioning, emotional functioning, social functioning, and cognitive functioning) , nine symptom scales/items (fatigue, nausea/vomiting, general pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) , and an overall health status scale. Higher scores on the functional scales indicate better functioning, while higher scores on the symptom scales/items indicate worse symptoms.

Esophageal-gastric module 25

The EORTC QLQ-OG25 questionnaire is a 25-item tool that assesses symptoms associated with gastric and GEJ cancer. This module includes six scales : dysphagia (3 items) , dietary restriction (4 items) , regurgitation (2 items) , odynophagia (2 items) , pain and discomfort (2 items) , and anxiety (2 items) , as well as 10 individual items : eating in the presence of others, dry mouth, taste disturbance, body image, saliva swallowing disorder, choking when swallowing, coughing, difficulty speaking, weight loss, and hair loss. For each symptom scale/item, higher scores indicate worse symptoms.

8. Statistical Analysis

Details of data processing, statistical methods, and result tabulation will be described in detail in the Statistical Analysis Plan (SAP). The final version of the SAP will be finalized before the database is locked.

8.1 Statistical analysis population

8.1.1 Subject enrollment information

The number and percentage of subjects enrolled and completing the study will be calculated for each treatment group. The reasons for withdrawal from the study before and after enrollment will be summarized.

8.1.2 Deviation from the plan

by dose group and listed by subject.

8.1.3 Rejection criteria

Before statistical analysis of the data, the statisticians and the principal investigator will discuss and determine whether to exclude individual cases. In the following situations, the statisticians and the investigators should make a comprehensive judgment based on factors such as the degree of completion of the trial and the reason for withdrawal, and whether to exclude the subject from the per-protocol set, and provide relevant explanations:

1) Subjects who are found to not meet the inclusion criteria or exclusion criteria after participating in the trial and are judged to have committed major protocol violations;

2) Failure to comply with the trial plan during the trial (poor compliance, such as not having used IMC002 or ICT , or samples that cannot be evaluated for efficacy and safety as required by the trial protocol, and no data, etc.);

3) In addition to the above situations, there are other major deviations or violations of the protocol during the trial that affect the efficacy and safety of IMC002.

8.1.4 Analysis Set

Intention-to-treat (ITT) analysis set included all randomized subjects.

Modified intention-to-treat analysis set (mITT): all subjects who were randomized and received at least one dose of study treatment (IMC002 or ICT).

Per-Protocol Set (PP): Subjects in the ITT set who did not experience major protocol violations that affected the efficacy evaluation and who had at least one efficacy evaluation. Major protocol violations that affected the efficacy evaluation will be determined after discussion in the blind review meeting before the database is locked.

Safety Analysis Set (SS): includes all subjects who were randomized and received at least one dose of study treatment. Subjects will be analyzed based on the study treatment they received (IMC002 or ICT).

Cell Kinetics Set (PKS): All subjects who received IMC002 cell infusion, had at least one valid PK data, and did not experience protocol deviations that seriously affected the PK evaluation will be used for PK analysis.

Pharmacodynamic analysis set: All subjects who received IMC002 cell infusion and had baseline and at least one post-baseline evaluable pharmacodynamic index examination results.

Immunogenicity analysis set: All subjects who received IMC002 cell infusion and had at least one post-dose ADA result. This dataset was used for immunogenicity analysis.

Crossover analysis set: The crossover analysis set included subjects randomized to the control group who crossed over to receive IMC002 cell infusion. All analyses of safety parameters collected after subjects received crossover treatment were performed using this analysis set.

8.2 General principles

All statistical analyses will be performed using SAS version 9.4 or later. Generally, continuous variables will be described using the number of cases, mean, median, standard deviation, minimum, and maximum values; categorical and ordinal variables will be described using the frequency and percentage of each category or level. Time-to-event metrics will be analyzed using the Kaplan-Meier method. The median, 25th and 75th percentiles, and their 95% confidence intervals will be calculated for each cohort, and Kaplan-Meier curves will be plotted. Unless otherwise specified, missing values will not be included in the calculation of percentages.

8.3 Demographics , medical history, baseline characteristics, and concomitant medications

The FAS will be used to summarize demographic information and baseline characteristics. Demographic information and baseline characteristics, 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 Medical Dictionary for Regulatory Activities (MedDRA); concomitant medications will be coded according to the World Health Organization Drug Dictionary Enhanced (WHO-DDE) based on the Anatomical Therapeutic and Chemical Classification (ATC) system. Medical history and concomitant medications will be summarized in the FAS.

The version of the dictionary used for encoding shall be described in the CSR.

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

8.3.1 Subject demographics

The demographic information of the subjects included: age, height, weight, ethnicity, and gender.

8.3.2 Medical and treatment history

Medical history: This refers to the subject's previous history of cancer and cancer treatment history. Treatment includes but is not limited to surgical treatment, chemotherapy, radiotherapy, drug therapy, and other treatments. In addition to cancer history, other past medical history or treatment history that the researcher considers important may also be recorded as appropriate.

Treatment history: Tumor diagnosis and treatment history, including cancer-related medical history and treatment history, as well as previous biomarker expression; a complete history of past medical history, current medical history, and treatment history was collected during the screening period. Only new medical history was recorded during follow-up visits.

The subject's previous surgical history or non-tumor chronic disease, which has been cured or recovered to a state of no clinical significance during the screening period, will be recorded as past medical history.

Allergy history: Previous allergy to immunotherapy, allergy to related drugs such as tocilizumab, cyclophosphamide, fludarabine, or albumin-paclitaxel, allergy to IMC002 components such as albumin, DMSO, etc., or other severe allergic history.

8.3.3 Concomitant diseases and concomitant medications

Concomitant diseases and concomitant medications that existed in the subjects and still existed after entering the trial, excluding tumor-related diseases and treatments.

Any non-tumor chronic disease suffered by the subject that is still clinically significant during the screening period or any clinically significant abnormal symptoms, signs, laboratory or auxiliary examination abnormal results related to non-study diseases discovered after the signing of the ICF and before the subject is enrolled in the study for leukocyte apheresis should be recorded as a concomitant disease: Abnormal results during the screening period caused by the study procedures should be recorded as AEs.

8.4 Medication Adherence

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

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

8.5 Efficacy analysis

The primary endpoint of this study was progression -free survival (PFS), as assessed by BIRC. PFS was defined as the time from the date of randomization to the first documented disease progression (as assessed by BIRC according to RECIST 1.1) or death from any cause . PFS analysis was based on the ITT cohort. If two or more consecutive tumor assessments were missed before the date of a PFS event, PFS was censored to the date of the last evaluable tumor assessment before the missed assessment. The Kaplan-Meier method was used to calculate the median PFS, quartiles, and 95% confidence intervals (CIs) for each group. Censorship was summarized, and KM curves were plotted.

The stratified log-rank test was used to compare PFS between the two groups. A stratified proportional hazards regression model (Cox Proportional Hazards Regression Model) was used to estimate the hazard ratio (HR) and its 95% CI for the experimental group versus the control group (with the exact method used for identical event times). The stratification factors used were the same as those used at randomization. Sensitivity analyses were also performed using data from the mITT and PP sets.

The final analysis of PFS efficacy was performed approximately 3 months after the completion of enrollment of the subjects when at least 86 PFS events were observed.

The primary estimated objective PFS analysis will take into account different concomitant events as follows:

- Discontinuation of study treatment: PFS analysis will take into account all tumor

assessments and deaths, regardless of discontinuation of study treatment for any reason (treatment strategy)

• Patients who cross treatment (for patients in the control group) or start new anticancer treatment (for all patients) will be treated using a hypothetical strategy whereby PFS will be censored at the last adequate assessment date or the date of randomization before the cross treatment or start of new anticancer treatment if no PFS event was observed before the cross treatment or start of new anticancer treatment.

• Any unforeseen concomitant events, such as those arising from a public health emergency, will be addressed through therapeutic strategies.

Treatment of missing values not related to concurrent events

The censoring rules for PFS follow the RECIST 1.1 guidelines and will be further detailed in the statistical analysis plan (SAP).

Sensitivity analysis

As a sensitivity analysis, the two treatment groups will be compared using a nonstratified log-rank test. A nonstratified Cox model will be used to generate the PFS hazard ratio and 95% confidence interval based on BIRC review. The sensitivity analysis estimates are the same as the key secondary estimates. Additional sensitivity analyses and estimates, if any, will be detailed in the SAP.

Supporting analysis

Investigator-assessed PFS will be analyzed in the ITT using a stratified Cox model, and treatment effects will be summarized as hazard ratios with 95% confidence intervals. Kaplan-Meier curves, medians, and 95% confidence intervals will be provided for each treatment group.

In the ITT, hazard ratios and 95% confidence intervals for PFS based on BIRC review will be obtained from stratified and covariate-adjusted Cox models including sex and age. The final list of covariates included in the model will be provided in SAP.

If statistical significance is achieved in the primary analysis of PFS, subgroup analyses will be performed to assess the homogeneity of the treatment effect across demographics and baseline disease characteristics. Different thresholds or variables used for subgroup analyses will be detailed in the SAP. The number of subjects censored in the PFS analysis and the reasons for censoring will be summarized by treatment group.

Analyses supporting secondary objectives

Secondary efficacy endpoints will be assessed using ITT.

OS is defined as the interval from the date of randomization to the date of recorded death from any cause. For subjects whose deaths were not recorded, those who had not died by the analysis cutoff date were censored at the time of last contact. The analysis will be based on data

from the ITT population. The OS analysis will provide Kaplan-Meier curves, medians, and 95% confidence intervals for OS in each treatment group . A stratified Cox model will be used to calculate the hazard ratio (HR) for OS and its 95% confidence interval.

The ORR is defined as the proportion of subjects achieving a best overall response (BOR) of complete response (CR) or partial response (PR). Tumor response status was assessed by the BIRC according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Confirmation was required by repeat assessment at least four weeks after the initial achievement of CR or PR response criteria. The disease control rate (DCR) was defined as the proportion of subjects achieving a BOR of CR, PR, SD, or non-CR/non-PD. DCR was analyzed using the same conventional analysis methods as ORR .

Duration of response (DOR) was defined as the duration from the date of the first documented response (CR or PR) to the date of the first documented disease progression or all-cause death. If a patient had no events, the DOR was censored at the date of the last adequate tumor assessment. Subjects whose BOR never achieved a CR or PR were excluded from the analysis. The Kaplan-Meier method was used to estimate the DOR distribution function. The median DOR and its 95% CI are presented by treatment group.

Time to response (TTR), defined as the time from the date of randomization to the date of the first documented response (CR or PR, which must then be confirmed), was analyzed descriptively.

The above analyses will be performed based on BIRC assessment and local investigator assessment (according to RECIST 1.1).

The BOR for each subject was determined according to the order of overall response (lesion) as follows:

• CR = at least two CRs before disease progression, with at least 4 weeks between the two CRs.

• PR = at least two PRs before disease progression, with at least 4 weeks between the two PRs (and not meeting CR criteria).

• SD = SD in at least one assessment > 5 weeks after randomization (and not meeting CR or PR criteria).

• Non-CR/non-PD = non-CR/non-PD (and does not meet CR, PR, or SD criteria) in at least one assessment > 5 weeks after randomization.

• PD = progressive disease after randomization (and not meeting CR, PR, SD, or non-CR/non-PD criteria).

• Not evaluable = all other lesions (i.e., not meeting confirmed CR or PR criteria or non-CR/non-PD after > 5 weeks and no SD, or no early progression)

Analysis Timing: The final analysis of PFS efficacy will be performed approximately 3

months after completion of enrollment when at least 86 PFS events have been observed . The interim analysis of OS will be performed at the time of the final analysis of PFS. The final analysis of OS efficacy will be performed approximately 10 months after the last subject is randomized when at least 112 deaths have been observed.

8.6 Security Analysis

All listings and tables are presented by treatment group using the safety set.

Exposure to each study drug was summarized descriptively, including the number of cycles received (number and percentage of patients), duration of exposure (days), total cumulative dose per patient, dose intensity, and relative dose intensity.

Adverse events (AEs) were coded verbatim using Medical Dictionary for Drug Regulatory Activities (MedDRA®) terms and graded according to NCI CTCAE 5.0 (except for CRS and ICANS, which were assessed according to the 2019 ASTCT CRS/ICANS grading criteria). All treatment-emergent adverse events (TEAEs) were summarized.

Identify outliers in clinical laboratory data. Selected laboratory data are summarized by level. Changes in vital signs are also summarized by visit number.

8.7 Cell kinetic analysis

The main cellular kinetic parameters of each subject, including peak concentration (C_{max}), time to peak (T max), area under the concentration-time curve (AUC), final observable concentration (C_{last}), last detectable time (T_{last}), and expansion rate (C_{max}/T_{max}), were calculated using the non-compartmental model of WinNonlin 8.2 (or newer) pharmacokinetic software.

Cellular kinetic analysis was performed based on PKS. Descriptive statistical analysis of blood CAR copy number versus time data was performed according to the planned sampling time. The arithmetic mean, standard deviation, median, maximum, minimum, coefficient of variation, and geometric mean of blood CAR copy number at each time point were calculated. Individual and mean blood CAR copy number versus time curves were plotted.

8.8 Pharmacodynamic 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 value, maximum value, geometric mean, and geometric mean coefficient of variation were reported.

If necessary, additional PK analyses can be performed.

Exposure-response (efficacy or safety endpoint) analyses may be performed if supported by data.

8.9 Immunogenicity analysis

Immunogenicity samples will be collected for this study as described in the evaluation plan.

Immunogenicity results will be summarized by number of patients and percentage using descriptive statistics. The incidence of positive ADA and neutralizing ADA will be reported in patients with detectable ADA. The impact of immunogenicity on PK, efficacy, and safety will be assessed if data permit.

8.10 Translational Research

Translational studies will be conducted to analyze relevant biomarkers and their correlation with clinical outcomes.

8.11 Analysis of Correlation between Companion Diagnostic Reagents and Drug Efficacy

Claudin 18.2 protein expression was detected using a Claudin 18.2 antibody reagent (immunohistochemistry) to conduct a drug efficacy analysis to evaluate the effectiveness of IMC002 in treating patients with gastric or gastroesophageal junction adenocarcinoma that is positive for Claudin 18.2 expression.

8.12 Sample Size and Interim Analysis

8.12.1 Sample size

This study used BIRC-assessed PFS as the primary endpoint. Early study data indicate that the median PFS (mPFS) observed in the IMC002 trial arm is approximately 6.9 months, while historical data indicate that the mPFS in the control arm (investigator's choice of treatment) ranges from 1.6 to 2.6 months. This study assumed mPFS of 5.2 and 2.6 months in the trial and control arms, respectively, and a true PFS hazard ratio (HR: IMC002 vs. investigator's choice of treatment) of 0.5. With a power of 85%, a one-sided type I error rate of 0.025, and a 2:1 randomization ratio between the trial and control arms , the final analysis required approximately 86 events.

Assuming complete enrollment within 12 months, the minimum follow-up is 3 months.

The sample size was also calculated based on the key secondary endpoint of OS . Assuming an exponential distribution for OS, the median OS in the control group was approximately 6 months, and the true OS hazard ratio (HR: IMC002 vs. investigator-selected treatment) was 0.56. OS will be tested at a one-sided 0.025 test level. With an assumed power of 80 % , the final analysis of OS will be conducted approximately 10 months after the last randomized subject, when approximately 112 events have been observed.

Considering the 20% dropout rate of subjects, approximately 150 subjects need to be enrolled, with at least 100 subjects in the trial group.

8.12.2 Interim Analysis

The interim analysis of OS will be conducted at the same time as the final analysis of PFS . The O'Brien-Fleming spending function (Lan-Demets algorithm) will be used to calculate the significance level for both the interim and final analyses of OS. Gate keeping will be used to control type I error. Hypothesis testing for the key secondary endpoint of OS will only be conducted if the hypothesis test for the primary endpoint of PFS is significant .

8.12.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be established for this study. The IDMC will consist of at least three experts, including clinical and statisticians. Interim analyses will be conducted by the IDMC. The IDMC will evaluate the efficacy and safety data at the interim analysis in accordance with its protocols and make recommendations to the sponsor regarding trial continuation, protocol modification, or trial termination.

9. Data quality and management

9.1 Data Quality Assurance

The sponsor or its designated personnel will conduct an on-site visit to the research center to verify the qualifications of the investigator, inspect the center facilities, and inform the investigator of the responsibilities and procedures to be followed to ensure the completeness and accuracy of the records.

The investigator should fully and accurately record study-related observations and other data for each subject in the medical record. All information recorded in the CRF should be consistent with the subject's source documents (e.g., medical records).

9.1.1 Data management and quality control

All data collected by the research center and its laboratories will be recorded in the CRF. Once the clinical data in the CRF is transferred to the data management party and the database is frozen, changes to the data will be recorded as an audit trail. The reason for the change, the name of the person who made the change, and the time and date of the change will be recorded as an audit trail record.

During routine monitoring, the relevant monitor or data manager will raise questions regarding the CRF. Authorized personnel at the research center will respond to the questions sent to the investigator. The name of the person who responded to the question, along with the time and date of the response, should be recorded. Once all raw data have been verified and all questions have been resolved, the monitor or data manager will freeze the database.

9.2 Case Report Form and Source Documents

All data obtained during the study should be entered into the CRF promptly. The source files for all data entered into the CRF should be kept in the medical record. These source files typically include laboratory tests, electrocardiograms, and echocardiography. Data entered directly into the CRF will be considered raw data. Clinical monitors will verify the raw data entered into the CRF with the source files during site monitoring. After completing the verification, the clinical monitor will discuss missing and unexplained data with the investigator.

9.2.1 Data Collection

The researcher (and appropriate authorized personnel) will be given access to the CRF, and only the researcher and authorized personnel can enter and correct data on the CRF.

The investigator (or appropriately authorized personnel) should complete a CRF for each enrolled subject, reflecting their findings from the most recent study observation. Therefore, the CRF should be completed as soon as possible after the subject completes a visit or assessment. The investigator should verify the accuracy of the data entered on the CRF. If some assessments cannot be performed, or if specific information is unavailable, inapplicable, or unknown, the investigator should indicate this in the CRF.

The researcher must sign the CRF upon completion.

The amount of study drug used by each subject and any dose changes will be recorded on the CRF.

9.3 Monitoring of raw data

During the study, the monitor will conduct site visits to verify protocol compliance, CRF entry, subject medical history, medication counts, and compliance with relevant regulatory requirements. CRF entries will be reconciled with the original data. This medical history verification will be conducted in a manner that protects subject confidentiality.

CRF entries are reviewed for completeness and clarity and compared with the original data to monitor study progress. Additionally, regulatory authorities and the EC's clinical quality assurance department may review the original data and/or conduct on-site audits or inspections at the site. Audits or inspections provide direct access to the original data; parties with direct access will take every measure to ensure data and medical confidentiality.

9.4 Data Processing

The data review and data handling plan includes specific requirements for verifying the consistency and authenticity of the data, as well as principles for handling data with obvious errors. The database will be updated based on signed corrections.

Previous medications and concomitant medications will be coded according to WHO-DDE using ATC categories, and past/present medical history and AEs will be coded according to MedDRA.

The version of the encoding dictionary will be described in the CSR.

9.5 Archiving of research records

Researchers should retain clinical research data for 5 years after the completion of the clinical study. Sponsors should retain clinical research data for 5 years after the study drug is approved for marketing.

9.6 Good Practices for Clinical Trials of Drugs

This study protocol will be carried out in accordance with GCP, the Declaration of Helsinki (2008) and local regulatory requirements.

9.7 Informed Consent

In accordance with local laws and regulations, a signed and dated ICF will be obtained from the subject before any study-related procedures begin. The researcher will retain the original signed ICF as a study document. The signing date of the ICF will be recorded in the CRF.

If the protocol needs to be amended, the ICF may need to be amended to reflect the updated information in the protocol. If the ICF is amended, it must be submitted to the EC and approved in writing, and signed by the subjects who will be subsequently enrolled and are currently in the study.

9.8 Plan Approval and Amendment

In accordance with local regulations, the study protocol and/or other relevant documents will be approved by the EC/competent authority before the study begins, ensuring that all ethical and regulatory requirements are met before the first subject is enrolled.

This study will be conducted strictly in accordance with this protocol. Any amendments to the protocol must be approved in writing by the relevant personnel and submitted to the EC/IRB/competent authority for approval before implementation.

Changes in management (that do not affect the benefit/risk ratio for the subjects) do not require a formal protocol amendment. Each version of the protocol amendment will be distributed to all protocol recipients with corresponding instructions.

9.9 Research cycle

The completion of this study period was defined as the last subject completing the last visit specified in the protocol.

Completion of the study cycle for each subject is defined as the completion of the last visit specified in the protocol. After signing the master informed consent form, each subject, based on treatment group, will undergo a screening period, treatment and follow-up period, exit visit, and survival/long-term follow-up.

9.10 Early Termination of the Study

If the investigator, sponsor, or monitor becomes aware of a situation or event that could endanger the subjects if the study continues, the study may be terminated after discussion among the relevant personnel.

The study may be terminated early for the following reasons, but is not limited to:

- Unexpected, significant or unacceptable risks to enrolled subjects
- The sponsor decides to suspend or stop the development of the drug

9.11 Confidentiality

All findings and documents related to the study will be treated as confidential. The researcher and his/her research team members shall not disclose such information without the written consent of the sponsor.

Ensure that research subjects remain anonymous. Subjects should be identified in CRFs and submissions by subject number, initials, and/or date of birth, but not by their names. Researchers should maintain confidentiality regarding documents that do not need to be shared but that identify the subject (e.g., signed ICFs).

9.12 Liability and Insurance

The sponsor will provide insurance for the subjects participating in this study in accordance with legal requirements and will bear the cost of treatment and corresponding financial compensation for the subjects who suffer damage related to the study drugs or research process.

9.13 Publishing Policy

By signing this study protocol, the investigator agrees that the results of this study may be used for domestic or international registration applications, publication, or disclosure to medical professionals. If necessary, the investigator's name, address, qualifications, and responsibilities in the study will be disclosed to regulatory authorities.

10. Research Monitoring and Project Management

10.1 Study Monitoring Plan

The study will be monitored according to the monitoring plan. Investigators will allocate sufficient time to cooperate with monitoring activities. Investigators will also ensure that the monitor or other quality assurance reviewers have access to all study-related documents and methods for accessing study-related facilities (such as pharmacies, diagnostic laboratories, etc.), as well as sufficient space for on-site monitoring.

10.2 Audit and Inspection

The researcher will allow the research-related ethics committee, government regulatory agencies, and quality assurance groups to monitor, review, and inspect all research-related documents (such as source documents, regulatory documents, data collection tools, research data, etc.). The researcher will ensure the capacity of research-related facilities (such as pharmacies, diagnostic laboratories, etc.).

Research participation in this study means that it will be subject to inspection by government regulatory agencies and relevant quality assurance offices.

10.3 Clinical Monitor

The clinical monitor will conduct routine site monitoring and review all CRFs and corresponding source documents for each subject at a mutually convenient time during and after the study. During site monitoring, the monitor will ensure that the site has appropriate study-related

documentation, provides training and GCP guidance to investigators and other staff involved in the study, and ensures that appropriate facilities and sufficient professional staff are available.

Regular monitoring during the study allows researchers to assess study progress and identify potential issues. The monitor will ensure that submitted data is accurate and consistent with source documents; review and properly store research products; obtain and archive informed consent from subjects; confirm that subjects entering the study meet the study inclusion and exclusion criteria; and ensure that all necessary documents required by GCP are properly stored.

11. Ethical Standards and Informed Consent

1.1 . Review by the Ethics Committee

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

Before the study begins, researchers /institutions should obtain written approval from the independent ethics committee for the study protocol, informed consent form, subject recruitment procedures, and other written materials to be provided to subjects. During the study, any additions or revisions to the study protocol, informed consent form, etc. must be approved in writing by the independent ethics committee or filed.

11.2 Informed Consent

During the clinical research process, if any serious adverse events or unexpected adverse events related to clinical research safety occur and may affect the safety of the subjects and the implementation of the research, the researcher must inform the ethics committee in accordance with relevant regulatory requirements.

The researcher is responsible for explaining to each subject the study's objectives, methods, procedures, benefits and potential risks, available treatment options, and their rights and obligations. The researcher should inform each subject that they have the right to withdraw from the study at any time without any personal harm. The researcher will recommend alternative treatments based on their individual circumstances.

Before any study-related procedures begin, written informed consent must be obtained from the subject. Before obtaining informed consent, the researcher or their designee should provide the subject with sufficient time and opportunity to inquire about the details of the study and sufficient time 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 subject, their legal guardian or proxy, and the researcher conducting the informed consent process. One original copy of the signed informed consent form should be retained by the subject and one by the study center.

If any information related to the subject's willingness to continue participating in the study is obtained during the study, the subject must be notified in a timely manner to confirm whether the subject is willing to continue participating.

The revised informed consent form needs to obtain ethical approval before it can be provided to the subjects.

By signing the informed consent form, the subjects must also agree to allow the drug regulatory authorities, auditors and authorized clinical monitors to verify the original data and information obtained about the clinical research, and the reviewers must abide by the confidentiality statement.

11.3 Confidentiality of subjects

In this study, researchers must protect the privacy of the subjects. Data protection and privacy regulations must be followed when collecting, transmitting, processing, and storing subject data. After signing a written informed consent form, the subject will be given a unique screening number, which will serve as the subject's identifier in the study and database. All subject data collected in the study will be stored according to the subject number. Researchers can link study data to individual subjects using the identity information stored at the center. Monitoring, audit, and drug regulatory authorities must ensure that they have access to each subject's original medical data during inspections, while strictly protecting the subject's privacy.

1 2． Paper publication

As the sponsor, IMUF holds exclusive rights to this study. The authors and manuscript reflect collaboration among multiple researchers, research centers, and IMUF staff. Authorship was determined in consultation with the researchers before the manuscript was written. Researchers should not disclose trial results in any form without the sponsor's consent.

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14. Appendix

1 4 .1 Appendix 1 RECIST 1.1 criteria for evaluating response to treatment in solid tumors

The following translation is 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.

1. **Measurement of tumor lesions**

1. Definition of baseline tumor lesions

Tumor lesions were categorized as measurable lesions (at least one measurable lesion) at baseline: lesions that could be accurately measured using conventional techniques, with a diameter ≥ 20 mm or ≥ 10 mm on spiral CT. Non-measurable lesions were defined as all other lesions (including small lesions with a 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, lymphangitic carcinomatosis of the skin or lung, and abdominal masses and cystic lesions that could not be diagnosed or followed up by imaging.

2. Measurement method

1) The same techniques and methods were used to assess lesions at baseline and follow-up.
2) Clinically superficial lesions such as palpable lymph nodes or skin nodules can be considered measurable lesions, and color photographs with a ruler should be used for skin lesions.
3) Chest X-ray: A clearly defined lesion can be used as a measurable lesion, but CT scan is best used.
4) CT and MRI: CT and MRI are currently the best and most repeatable methods for identifying measurable target lesions and evaluating treatment efficacy. For the chest, abdomen, and pelvis, CT and MRI scans are performed using 10 mm or thinner slices, while spiral CT scans are performed using 5 mm continuous slices. Special protocols are used for the head, neck, and other specific 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. It can also be used to confirm the complete disappearance of superficial lesions after clinical examination.
6) Endoscopy and laparoscopy: As objective tumor response assessments, they have not yet been widely and adequately used and are only used in controversial lesions or in high-level research centers with clear validation purposes. Biopsy specimens obtained with these methods can confirm pathologically confirmed CR.
7) Tumor markers: They cannot be used alone to determine efficacy. However, if tumor markers

were elevated before treatment, all markers must return to normal for clinical evaluation of a complete response (CR). Disease progression requires that an increase in tumor markers be accompanied by visible lesion progression.

8) Cytology and histopathology: In rare cases, cytology and histopathology can be used to differentiate between complete response (CR) and partial response (PR) and to distinguish between benign lesions after treatment and residual malignant lesions. Any effusion that occurs during treatment requires cytology to differentiate between remission, stability, and progression of the tumor.

II. Evaluation of Tumor Response

1. Baseline evaluation of tumor lesions

To establish the overall tumor burden at baseline, against which subsequent measurements will be compared, at least one target lesion should be measurable, with limited, isolated lesions requiring histopathological confirmation.

1) Measurable target lesions should represent all affected organs, with a maximum of two lesions per organ and a maximum of five lesions total. These lesions should be measured and recorded at baseline. Target lesions should be selected based on their long diameter size and reproducible measurability. The sum of the diameters of all target lesions (including the longest diameter of non-nodal lesions and the short diameter of nodal lesions) will be reported as the baseline diameter sum. If lymph node diameters are included, as mentioned above, only the short diameter will be included. The baseline diameter sum will serve as the reference value for the baseline disease level.

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

2. Criteria for remission

1) Evaluation of target lesions:

- **Complete remission (CR)** : After treatment, all target lesions of the subject 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 response (PR**): After treatment, the sum of the target lesion diameters of the subject is reduced by ≥30% compared with the baseline level.
- **Progressive disease (PD)** : After treatment, the subject develops ≥1 new lesion or the minimum sum of the diameters of all target lesions is used as a reference, and the relative increase in the sum of diameters is ≥20% (if the baseline measurement value is the smallest, the baseline value is used as a reference); in addition, the absolute increase in the sum of diameters must be ≥5 mm.

- **Stable disease (SD)** : After treatment, the degree of reduction and increase of target lesions in the subjects is between PD and PR, and the minimum sum of diameters can be used as a reference.

2) Evaluation of non-target lesions:

- **CR** : All non-target lesions disappear, tumor marker levels return to normal, and all lymph nodes are non-pathological in size (short diameter <10 mm).
- **SD** : One or more non-target lesions and/or tumor markers persist above normal levels.
- **PD** : appearance of one or more new lesions and/or progression of non-target lesions.

3. Overall efficacy evaluation

The best overall response is the best response documented from the beginning of the trial to the end of the trial, taking into account any necessary conditions for confirmation. Sometimes a response occurs after the end of treatment, so the protocol should clarify whether a response after the end of treatment is considered in the best overall response. The protocol must clarify how any new treatment before progression affects the best response. The patient's best response depends primarily on the results of the target and non-target lesions and the manifestation of new lesions. It also depends on the nature of the trial, protocol requirements, and outcome measures. Specifically, in non-randomized trials, the response is the primary goal, and confirmation of a PR or CR is necessary to determine which is the best overall response.

- **Time point reaction**

It was assumed that a response would occur at the specific time points for each regimen. Appendix Table 1 provides a summary of the overall response at each time point for patients with measurable disease at baseline. For patients without measurable disease (no target lesions), assessments can be found in Appendix Table 2 .

Assessment of Best Overall Response When Confirmation of Complete or Partial Response is Required: A complete or partial response can be declared only if each subject meets the trial-specified criteria for a partial or complete response and a subsequent confirmation of response is performed as specifically mentioned in the protocol at a later time point (generally four weeks later). In this case, the best overall response is described in Table 3 in the Appendix .

Appendix Table 1Time Point Response: Subjects with Target Lesions (Including or Excluding Non-Target Lesions)

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluable	No	PR

PR	Non-progressive or not fully evaluable	No	PR
SD	Non-progressive or not fully evaluable	No	SD
Not fully evaluable	Non-progressive	No	NE
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD

Abbreviations:

CR = Complete Response PR = Partial Response SD = Stable Disease PD = Progressive Disease NE = Not Evaluable

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR or non-PD	No	Non-CR/Non-PD
Cannot be assessed	No	Not Evaluable
Indeterminate PD	Yes or No	PD
Any	Yes	PD

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

Appendix Table 3Best overall response required for confirmation of CR and PR efficacy

First Time Point Response	Subsequent Time Point Response	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	If SD lasts long enough → SD; otherwise → PD
CR	PD	If SD lasts long enough → SD; otherwise → PD
CR	NE	If SD lasts long enough → SD; otherwise → NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts long enough → SD; otherwise → PD
PR	NE	If SD lasts long enough → SD; otherwise → NE
NE	NE	NE

Note: CR means complete remission, PR means partial remission, SD means stable disease, PD means progressive disease, and NE means not evaluable. Superscript "a": If a CR actually occurs at the first time point, and any disease appears at a subsequent time point, then even if the subject's efficacy meets the PR criteria relative to baseline, the efficacy evaluation at the subsequent time point will still be PD (because the disease will reappear after CR). The best response depends on whether SD occurs within the shortest treatment interval.

However, sometimes the first evaluation is CR, but scans at subsequent time points show that small lesions seem to still appear, so the subject's efficacy at the first time point should actually be PR rather than CR. In this case, the first CR judgment should be revised to PR, and the best response is PR.

1. Best Relief Assessment

The best response assessment refers to the smallest measurement recorded from the start of treatment until disease progression/recurrence (the smallest measurement serves as a guide for progression). Discontinuation of treatment due to systemic deterioration, even in the absence of PD, should be considered "symptomatic worsening," and detailed documentation of objective tumor progression should be obtained after discontinuation of treatment. Patients with early progression, early death, and those who cannot be evaluated should be identified. In some cases, it may be difficult to distinguish residual tumor lesions from normal tissue. When a complete response is assessed based on these circumstances, examination of residual lesions (fine needle aspiration / biopsy) is recommended to confirm the complete response . When residual imaging abnormalities are thought to be fibrosis or scarring , FDG PET can be used to confirm CR , similar to biopsy .

2. Frequency of tumor re-evaluation

The frequency of tumor reassessment depends on the treatment regimen. In reality, the duration of treatment benefit is unclear. Reassessment every two cycles (6-8 weeks) is reasonable, but shorter or longer intervals may be adjusted in special circumstances. The need for tumor reassessment after treatment is determined by the clinical study endpoint, whether it is response rate or time to event (TTE), also known as time to progression/death (TTP/TTD). If TTP/TTD is the endpoint, regular repeat assessments are required; there is no strict standard for the interval between reassessments.

3. Confirm

The goal of objective efficacy confirmation is to avoid overestimating the RR. Changes in tumor measurements for CR and PR must be repeatedly assessed and confirmed, with reconfirmation required at least 4 weeks after the initial evaluation. Longer confirmation times, as determined by the trial protocol, are also appropriate. Patients with SD should have at least one lesion measurement demonstrating SD at least 6-8 weeks after treatment. Clinical studies using progression-free survival (PFS) and overall survival (OS) as endpoints do not require repeated confirmation of changes in tumor size.

4. Remission period

It is measured from the time of first CR or PR until the first disease relapse or progression.

5. Stable period

It is the time from the start of treatment to disease progression. The correlation between SD stage and clinical symptoms varies with different tumor types and different degrees of

differentiation.

The remission period, stable period and PFS are affected by the follow-up frequency after baseline evaluation. Due to the influence of multiple factors such as disease type, stage, treatment cycle and clinical practice, the basic follow-up frequency has not yet been determined, which to some extent affects the accuracy of the trial endpoints.

IV. Results Report

All patients, including those who deviated from the treatment plan or were ineligible, were assessed for response to treatment (ITT). Each patient was categorized as complete response (CR), partial response (PR), sustained death (SD), progressive death (PD), death from cancer, death from toxicity, death from other cancers, or unknown (insufficient data for evaluation). All eligible patients were included in the risk ratio (RR) analysis, and all PD and death were considered treatment failures. Conclusions were based on eligible patients, and further analyses were conducted in different patient subgroups, providing 95% confidence intervals.

1 4 .2 Calculation formulas involved in Appendix 2 scheme

- **Renal function assessment: Cockcroft-Gault formula**

  Creatinine is expressed in mg/dL:

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

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

  Creatinine unit is μ mol/L:

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

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

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

- **Fridericia -corrected QTcF calculation formula:**

QTcF(ms) = QT(ms)/ (RR^0.33)

Note: ECG does not include RR (RR=60/heart rate)

- **Standard Stevenson formula :**

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

Note: BSA: body surface area.

1 4 .3 Appendix 3 ASTCT CRS and ICANS classifications

1 4 .3.1 ASTCT CRS classification

CRS parameters	Level 1	Level 2	Level 3	Level 4
fever *	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
and				
low blood pressure	none	No boost required	Requires vasopressors with or without vasopressin	Requirement of multiple vasopressors (excluding vasopressin)
and/or †				
Hypoxia	none	Low-flow nasal cannula oxygen required ‡	Requires high-flow nasal cannula oxygen ‡ , face mask, non-rebreather mask, or Venturi mask	Requirement for positive pressure ventilation (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Note: Organ toxicities associated with CRS can be graded according to CTCAE 5.0, but they do not affect the CRS grade.

*: Fever is defined as a temperature ≥ 38°C not attributable to any other cause. In patients who have had CRS and subsequently received antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade the severity of subsequent CRS. In this setting, CRS grade is due to hypotension and/or hypoxia.

†: CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring a low-flow nasal cannula is classified as Grade 3 CRS.

‡: Low-flow nasal cannula is defined as oxygen delivered at a rate of ≤6 L/min. Low flow also includes insufflation oxygen, which is sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at a rate of >6 L/min.

Reference: Lee DW et al. / Biol Blood Marrow Transplant 25 (2019) 625-638.

1 4 .3.2 ASTCT ICANS classification

Neurotoxicity	Level 1	Level 2	Level 3	Level 4
ICE score *	7~9	3~6	0~2	0 (patient cannot be awakened)
Low level of consciousness †	spontaneous awakening	Awakened by sound	Awakens only to tactile stimulation	The patient cannot be aroused or requires strong or repeated tactile stimulation to arouse; coma or stupor
epileptic seizures	not applicable	not applicable	Any clinically focal or generalized seizure, nonconvulsive seizure that resolves rapidly on EEG or with intervention	Life-threatening, prolonged seizures (> 5 minutes), repetitive clinical or electrical seizures, without recovery to baseline
Exercise Results ‡	not applicable	not applicable	not applicable	Deep focal motor weakness, such as hemiparesis or paraparesis
Increased intracranial pressure/cerebral edema	not applicable	not applicable	regional edema on neuroimaging§	Diffuse cerebral edema, decerebrate rigidity, cranial nerve VI palsy, papilledema, or Cushing's triad on neuroimaging

Note: The ICANS rating is determined by the most severe incident that cannot be attributed to any other cause.

*: A patient with an ICE score of 0 may be classified as a Grade 3 ICANS if they have global aphasia when awake, but may be classified as a Grade 4 ICANS if they cannot be aroused.

†: Not attributable to other causes (e.g., absence of sedative medication).

‡ Tremor and myoclonus associated with immune effector cell therapy can be graded according to the CTCAE 5.0 scale, but they do not affect the ICANS grade.

§: Intracranial hemorrhage with or without edema is not considered a neurotoxic feature and is not included in the ICANS classification. It can be graded according to the CTCAE 5.0 scale.

ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, effector cell-associated encephalopathy; ICP, intracranial pressure.

1 4 .4 Appendix 4 ECOG Performance Status Score

Grading	Physical condition
Level 0	The ability to move is completely normal, with no difference from the ability to move before the onset of the disease.
Level 1	Able to move around freely and engage in light physical activities, including general housework or office work, but not able to engage in heavy physical activities.
Level 2	Able to move around freely and take care of themselves, but have lost the ability to work and can be out of bed and active for at least half of the day.
Level 3	He can only partially take care of himself and spends more than half of the day in bed or in a wheelchair.
Level 4	Bedridden and unable to take care of himself .
Level 5	die

1 4 .5 Appendix 5 Possible risks and treatment measures

The risks associated with lympholysis pretreatment mainly include cytopenia and infection. For treatment measures, please refer to IMC002 Treatment measures for cytopenia and infection.

IMC002Possible risks and treatment measures

Possible risks	Treatment measures
Immune effector cell-associated hematotoxicity (ICAHT)	• The risk of immune effector cell-associated hematologic toxicity (ICAHT) was assessed according to the CAR-HEMATOTOX scoring table in the CSCO Guidelines for CAR-T Cell Therapy for Hematologic Malignancies. • Administer concentrated red blood cell/platelet transfusions based on the subject's risk profile (pay attention to irradiation of blood products). • Subjects with high-risk features for ICAHT received prophylactic G-CSF (starting on day +2). • Severe neutropenia (ANC < 500/ul) with or without infection should be treated with G-CSF.
Cytokine release syndrome (CRS)	**Level 1 CRS processing** • Symptomatic supportive treatment (antipyretic, fluid replacement, etc.) . • Exclude infection (if the patient also has agranulocytosis, give prophylactic antibiotics, use G-CSF, and contraindicate GM-CSF). • If the fever persists (> 3 days) or is refractory , tocilizumab (8 mg/kg) can be given . If the symptoms do not improve, it can be repeated after 8 hours. It is recommended not to exceed 3 times. If CRS does not improve after 24 hours of treatment, dexamethasone 5-10 mg qd can be given or upgraded to level 2 treatment. **Level 2 CRS processing** • Symptomatic supportive treatment, low-flow oxygen inhalation, and anti-infection. • If tocilizumab has not been used, tocilizumab can be given, using the same instructions as in level 1. • For patients who are unresponsive to tocilizumab, dexamethasone 10 mg every 12 hours or once a day for 1-3 days should be administered, and the dose should be reduced as soon as symptoms improve. • There was no improvement after 24 hours of dexamethasone treatment and the patient was treated according to level 3. **3-level CRS processing** • Consider transfer to the ICU for treatment. • Symptomatic supportive treatment, high-flow oxygen inhalation, pressor drugs, and strong anti-infection drugs. • If tocilizumab has not been used, tocilizumab can be given, using the same instructions as in level 1. • Dexamethasone 10-20 mg every 6 hours for 1-3 days; reduce the dose as soon as symptoms improve. **4-level CRS processing** • Transferred to the ICU, mechanical ventilation, and multiple drugs to increase blood pressure . • Symptomatic supportive treatment, potent anti-infection, and tocilizumab treatment are the same as those for level 3. • High-dose glucocorticoid therapy is used until symptoms are relieved to grade 1, after which the dose can be reduced, such as methylprednisolone 1 g/d for 3 consecutive days, followed by 250 mg

	every 12 hours for 2 consecutive days, 125 mg every 12 hours for 2 consecutive days, and 60 mg every 12 hours for 2 consecutive days.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	**Level 1 ICANS processing** • Without concurrent CRS: Strengthen symptomatic supportive treatment . • Concurrent CRS: Tocilizumab can be given , with the same usage as CRS . • If swallowing function is affected, oral medications and nutrition should be changed to intravenous infusion. • Please consult the neurology department and perform examinations such as ophthalmoscopy, cranial imaging, lumbar puncture, and electroencephalogram. • If it is assessed that the subject may subsequently develop severe neurotoxicity, 5-10 mg of dexamethasone and levetiracetam may be administered to prevent epileptic seizures. **Level 2 ICANS Processing** • Symptomatic treatment and corresponding examinations are the same as those for level 1. • Patients without CRS or with ineffective anti-IL6 treatment were given dexamethasone (10 mg/kg, Every 6 to 12 hours) or methylprednisolone equivalent (1 mg/kg, once every 12 hours) , and quickly reduce the dose after it drops to level 1 . • Patients with CRS were treated with tocilizumab, with the same usage as level 1. • Patients with CRS grade ⩾2 are recommended to be transferred to the ICU. **Level 3 ICANS Processing** • Symptomatic treatment and examination are the same as those for level 1. • It is recommended to transfer to the ICU . • Patients with CRS can be treated with tocilizumab, with the same usage as level 1. • Dexamethasone 20 mg q6h was administered until symptoms improved to grade 1, after which the dose was rapidly reduced. • Repeat imaging studies every 2 – 3 days . **Level 4 ICANS Processing** • Symptomatic treatment and examination are the same as those for level 1. • Transferred to the ICU and mechanically ventilated . • The principles of anti-IL6 treatment and imaging examinations are the same as those for level 3. • High-dose glucocorticoid therapy is used until symptoms are relieved to grade 1, after which the dose can be reduced, such as methylprednisolone 1 g/d for 3 consecutive days, followed by 250 mg every 12 hours for 2 consecutive days, 125 mg every 12 hours for 2 consecutive days, and 60 mg every 12 hours for 2 consecutive days . • If there is no response to corticosteroids, consider anakinra (an IL-1 receptor antagonist) .

Tumor lysis syndrome (TLS)	• Provide adequate intravenous hydration. • Allopurinol or febuxostat is given to lower serum uric acid. • Sodium bicarbonate is given intravenously to alkalinize the urine. • Closely monitor electrolytes and renal function, and actively correct electrolyte imbalances.
Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)	**First-line treatment** • Anakinra (adults: 200-800 mg/day) and/or corticosteroids (adults: dexamethasone 10-40 mg/day or methylprednisolone 1000 mg/day). **Second-line treatment** • If remission is not achieved after 48 hours, the dose of first-line treatment is increased and dual therapy (anakinra + corticosteroids) is used. A JAK-2 inhibitor (such as ruxolitinib 5-10 mg/day) may be considered. **Third-line treatment** • In addition to JAK-2 inhibitors, gamma interferon monoclonal monomers (Imazol), CTLA-4 agonists (such as abatacept), and CD52 antibodies (alemtuzumab) can be considered. • Etoposide is effective in both pHLH and sHLH, with a preferred dose of 50-100 mg/ m^2 • In rapidly progressive/life-threatening high-grade IEC-HS, TKIs (eg, dasatinib) may be considered as a third-line treatment option after failure of first- and second-line therapy.
CAR-T associated coagulation disorder (CARAC)	• Regularly monitor blood routine and coagulation indicators to detect abnormal coagulation function in time. • The main treatment measures include platelet and coagulation factor supplementation, appropriate use of anticoagulant or antifibrinolytic drugs, etc. • Patients with APTT values >1.5 times the upper limit of normal should receive fresh frozen plasma. • When blood fibrinogen is <1.0 g/L, transfuse blood products such as cryoprecipitate and/or fibrinogen.
Hypogammaglobulinemia	• Supplement immunoglobulin therapy to restore serum immunoglobulin levels to normal levels. The researcher will refer to the treatment plan and make appropriate arrangements based on the patient's condition .
Infect	**Any level** • Prophylactic antiviral and Pneumocystis jiroveci pneumonia treatment until 6 – 12 months after CAR-T cell infusion and/or CD4 cell count > 200 cells/ μl . • Antifungal drugs should be considered in high-risk patients. • G-CSF is recommended for patients with persistent neutropenia for >7 days after CRS . **Level 1** • Provide supportive care. • If fever occurs, empirical anti-infective treatment is recommended. **Level 2** • Start oral antibiotics according to the course of treatment. **Level 3** • Intravenous antibiotics were started. **Level 4** • Intensive care supportive treatment .
Allergic reaction	• Use anti-allergy drugs prophylactically . • Treat the symptoms. When a severe allergic reaction occurs,

	researchers should immediately provide emergency treatment according to relevant diagnosis and treatment routines.
Abnormal proliferation of CAR-T cells	• Glucocorticoids and other immunosuppressants (eg, antithymocyte globulin or anti-CD52 antibodies) . • Severe patients may use two or more immunosuppressants.
Acute gastric mucosal injury/gastrointestinal bleeding	According to the severity of the disease and the risk of death, patients are divided into dangerous acute gastric mucosal lesion (AGML) patients and non-risk AGML patients. Patients with AGML accompanied by high-risk underlying diseases or severe gastrointestinal bleeding (including AGML patients with abnormal coagulation mechanism and difficult to stop bleeding) or even perforation are classified as dangerous AGML patients, otherwise they are non-risk AGML patients. • In this clinical study, strict inclusion and exclusion criteria must be adhered to, excluding patients at high risk for gastrointestinal bleeding. Prophylactic use of proton pump inhibitors and gastric mucosal protective agents can be administered during the three days before cell infusion and the four-week intensive observation period after cell infusion. Gastric protection, antiemetics, and nutritional support can also be administered as appropriate. Before and after cell infusion, fecal occult blood, routine blood tests, coagulation function, cytokines, CAR copy number, and imaging studies should be closely monitored. For patients with a higher risk of bleeding due to the primary tumor site, changes after tumor treatment should be closely monitored. Drugs that may damage the gastric mucosa and increase the incidence of gastrointestinal bleeding should be avoided. • Treatment principles for dangerous AGML and non-dangerous AGML: The main "risks" of dangerous AGML come from, on the one hand, large blood loss or difficult-to-control gastrointestinal bleeding, secondary hemorrhagic shock, multiple organ dysfunction and failure; on the other hand, they also come from gastrointestinal perforation and bacterial translocation that occur in dangerous AGML, which lead to disease progression and multiple organ dysfunction and failure. The focus of early treatment is on emergency organ function assessment and emergency organ function resuscitation and support. Only in the later stage will AGML be treated in a targeted manner. The treatment principles for non-dangerous AGML are, first, to inhibit factors that damage the gastric mucosa, such as inhibiting gastric acid and increasing the pH value in the stomach; second, to strengthen the protective mechanism of the gastric mucosa; and third, to adjust the coagulation function to prevent worsening of gastrointestinal bleeding. • When acute gastric mucosal injury or gastrointestinal bleeding occurs, it is

	recommended to refer to the "Chinese Expert Consensus on Emergency Treatment of Acute Gastric Mucosal Lesions", "Guidelines for the Diagnosis and Treatment of Acute Non-varicose Upper Gastrointestinal Bleeding", and "Guidelines for the Diagnosis and Treatment of Lower Gastrointestinal Bleeding" for treatment according to the condition. If necessary, please consult and implement the treatment in collaboration with relevant disciplines. • For subjects diagnosed with acute gastrointestinal bleeding, the bleeding site, urgency, cause, and volume should be assessed as soon as possible. For subjects diagnosed with acute upper gastrointestinal bleeding, active treatment should include withholding water, high-dose proton pump inhibitors for acid suppression, fluid replacement, infusion, and vasoactive medications. The severity and prognosis can be assessed using the GBS or Rockall scoring systems. Signs of bleeding should also be closely monitored, including recording the frequency, color, nature, frequency, and total volume of vomiting, melena, and hematochezia. Red blood cell (RBC), hemoglobin, hematocrit, and blood urea nitrogen should be regularly checked, and vital signs and circulatory status should be monitored. For subjects unresponsive to medical treatment, endoscopic hemostasis should be initiated as soon as possible, and surgery or interventional embolization may be necessary if necessary. For subjects diagnosed with lower gastrointestinal bleeding, the basic principles of management include rapid assessment, hemodynamic stabilization, localization and qualitative diagnosis, and treatment as needed. Treatment options include supportive care, medical therapy, endoscopic therapy, vascular embolization, and surgical intervention. When grade 3 to 4 gastrointestinal bleeding occurs, the researcher should decide whether to suspend or stop the trial drug based on the patient's condition.

Possible risks and treatment measures of important adverse reactions of apatinib mesylate

Possible risks	Treatment measures
hypertension	Blood pressure should be monitored regularly during medication. If necessary, antihypertensive treatment or dosage adjustment should be initiated under the guidance of a specialist. If Grade 3/4 blood pressure elevation occurs, medication suspension/dose adjustment or discontinuation is recommended, depending on the specific circumstances. For patients experiencing hypertensive crisis, this product should be discontinued during this period.
proteinuria	Patients are advised to have their urine routine and renal function checked regularly during medication. Seek medical attention promptly if proteinuria occurs. If grade 2 or higher proteinuria occurs, medication should be suspended. If necessary, the dosage should be adjusted or the medication should be discontinued based on the specific circumstances.
Bleeding	Prothrombin time and international normalized ratio should be closely monitored during medication. Once severe (grade 3/4) abnormalities occur, consideration should be given to suspending the medication, adjusting the dose, or discontinuing the medication based on the specific circumstances.
Skin toxicity	If hand-foot syndrome occurs, necessary symptomatic supportive treatment can be taken under the guidance of a physician. If hand-foot syndrome of grade 2 or higher occurs three times in a row and worsens, it is recommended to suspend medication; if necessary, adjust the dose or discontinue the medication.
Hepatotoxicity	When patients experience grade 3/4 elevation of transaminase or total bilirubin, it is recommended to suspend medication and monitor serum transaminase and total bilirubin until their levels drop significantly before resuming medication. If the adverse reaction reappears after resuming medication or persists, it is recommended to stop the medication.
Cardiotoxicity	Close monitoring of electrocardiogram (ECG) and cardiac function should be performed during medication. If a grade 3/4 adverse reaction occurs, medication suspension is recommended. If the adverse reaction recurs after resumption or persists, dose adjustment or drug discontinuation is recommended based on the specific circumstances. Discontinuation of medication is recommended for patients with grade III-IV heart failure or a left ventricular ejection fraction <50% as determined by cardiac ultrasound.

Possible risks and treatment measures of important adverse reactions of paclitaxel

Possible risks	Treatment measures
Myelosuppression	The complete blood count should be closely monitored during medication, and symptomatic supportive treatment should be taken in a timely manner according to the degree of bone marrow suppression.
Allergic reaction	All patients should receive pre-treatment with corticosteroids (such as dexamethasone), diphenhydramine, and an H2 receptor antagonist (such as cimetidine or ranitidine) before paclitaxel treatment, and undergo ongoing safety monitoring, including the occasional occurrence of chills, shock, and back pain associated with allergic reactions.
Cardiovascular toxicity	Vital sign monitoring is recommended during paclitaxel treatment, especially within one hour of paclitaxel infusion.

Possible risks and treatment measures of important adverse reactions of docetaxel

Possible risks	Treatment measures
Hematological toxicity	neutrophil counts <1500 cells/mm³ · Frequent blood counts should be performed in all patients receiving docetaxel to monitor for the development of neutropenia and prevent it from developing into a severe infection. Dosage adjustments should be made according to the labeling.
Allergic reaction	Equipment for treating hypotension and bronchospasm should be readily available. Close monitoring of key functional indicators is recommended during medication use. Unless contraindicated, patients should receive prophylactic medication prior to docetaxel treatment.
Hepatotoxicity	Docetaxel should be avoided in patients with bilirubin levels above the upper limit of the recommended daily limit (ULN) or AST and/or ALT levels >1.5×ULN combined with alkaline phosphatase levels >2.5×ULN. Patients with elevated bilirubin or abnormal transaminases with elevated alkaline phosphatase are at increased risk for grade 4 neutropenia, febrile neutropenia, infection, severe thrombocytopenia, severe gastritis, severe skin toxicity, and toxic mortality. Therefore, bilirubin, AST or ALT, and alkaline phosphatase should be measured before starting docetaxel each cycle.
Gastrointestinal reactions	Particular caution should be exercised in patients with neutropenia, particularly those at risk for gastrointestinal complications. Enterocolitis can occur at any time and can be fatal within the first day of illness. Patients should be closely monitored for early clinical manifestations of severe gastrointestinal toxicity.
Fluid retention	Unless contraindicated, patients should receive prophylaxis before docetaxel treatment to reduce the incidence and severity of fluid retention and to reduce the severity of allergic reactions.
Skin and subcutaneous tissue diseases	Patients should be informed of the signs and symptoms of severe skin manifestations and monitored closely. If adverse skin reactions are observed, discontinuation of treatment should be considered.

Possible risks and treatment measures of important adverse reactions of irinotecan hydrochloride injection

Possible risks	Treatment measures
Contraindications	It is contraindicated in patients with chronic inflammatory bowel disease and/or intestinal obstruction, bilirubin exceeding 3 times the upper limit of normal value; severe bone marrow suppression: patients with WHO performance status score greater than 2 points.
diarrhea	65 years or older are more likely to develop early-onset diarrhea and should be monitored more closely. Late-onset diarrhea may last longer and may lead to dehydration, electrolyte imbalance, or infection, and may even be fatal. If late-onset diarrhea occurs, prompt treatment with Imodium is necessary. Patients should be instructed to have Imodium available and to start treatment with Imodium if they experience unformed or loose stools or increased bowel movement frequency. Prophylactic administration of Imodium is not recommended. Patients with diarrhea must be closely monitored. If dehydration occurs, water and electrolytes should be supplemented. If intestinal obstruction, fever, or severe neutropenia occurs, antibiotics should be administered. Medication should be suspended, dosage adjusted, and hospitalization may be necessary depending on the specific situation.
Hematologic toxicity	If febrile neutropenia occurs or the absolute neutrophil count falls below 1.5×10^9 /L, irinotecan hydrochloride chemotherapy should be suspended. A new course of chemotherapy should be initiated after the granulocyte count returns to $>1.5 \times 10^9$ /L. After the patient recovers, the subsequent irinotecan hydrochloride dose should be reduced based on the patient's neutropenia. Routine administration of colony-stimulating factor (CSF) is not required, but physicians may consider administering CSF to patients with neutropenia.

Hepatotoxicity	Patients should undergo regular laboratory evaluation of liver function.
Immunosuppressant effects / increased susceptibility to infection	Administration of live or live-attenuated vaccines to patients who are immunocompromised due to chemotherapy, including irinotecan hydrochloride, may result in serious or fatal infections. Live vaccines should be avoided in patients taking irinotecan hydrochloride. Killed or inactivated vaccines are acceptable, but their effectiveness may be reduced.

14.6 Appendix 6 Central Laboratory Information

Central Laboratory 1: Tissue section - Claudin 18.2 detection; Whole blood - CAR copy number, CAR-T cell subsets/phenotype, immunogenicity detection, RCL detection, lentiviral genome insertion site; Serum - cytokines

Name of testing and analysis unit: Guorui Yikang Medical Laboratory (Shanghai) Co., Ltd.

Unified social credit code: 91310118MA1JL5119D

Address: 2nd and 3rd Floor, Block B, 14th Building, South District, E-Tong World, No. 685, Huaxu Road, Xujing Town, Qingpu District, Shanghai

Name of the remaining sample processing unit: Shanghai Solid Waste Disposal Co., Ltd.

Unified Social Credit Code: 913101147294906145

Address: No. 2491, Jiazhu Road, Jiading District, Shanghai

Central Laboratory II: Serum-Infectious Disease Testing (HBsAg, HBsAb, HBeAg, HBcAb, HBeAb, HCV Antibody, Syphilis Antibody, HIV Antibody, HBV-DNA, HCV-RNA, EBV IgM Antibody, CMV IgM Antibody, HTLV Antibody, SARS-CoV-2 Antibody (IgM))

Name of testing and analysis unit: Wuxi Guanhe Medical Laboratory Co., Ltd.

Unified Social Credit Code: 91320214MA20PUKD2P

Address: 1st and 5th Floor, Building A, Xingye Building, No. 99 Linghu Avenue, Xinwu District, Wuxi City, Jiangsu Province

Name of the remaining sample processing unit: Hangzhou Dadi Weikang Medical Environmental Protection Co., Ltd.

Unified Social Credit Code: 913301057544069124

Address: Room 325, Building 2, No. 28, Xiangyuan Road, Gongshu District, Hangzhou, Zhejiang Province