Clinical Research Protocol

Title: Clinical study of CLDN 18.2-targeting chimeric antigen receptor-modified autologous T cells for CLDN 18.2-positive advanced solid tumors

Protocol No.: IMC002-CT01

Version: V2.0

Version date: 2022-01-25

Protocol synopsis

Title: Clinical study of CLDN 18.2-targeting chimeric antigen receptor-modified autologous T cells for CLDN 18.2-positive advanced solid tumors.
Protocol No.: IMC002-CT01
Version and date: Version 2.0; January 25, 2022
Type of study: IIT study (investigator-initiated trial)
Research Centers: 3
Investigational drug: chimeric antigen receptor-modified autologous T cells targeting CLDN 18.2 (hereinafter referred to as "CLDN 18.2 CAR-T" or "CAR-T" cells), codenamed IMC002 **Dosage form and specification:** Injection, 5×10^{7} ～ 3.5×10^{8} CAR-T positive live cells
Mode of administration: Intravenous infusion
Indications: Advanced solid tumors with positive CLDN18.2 expression (including advanced gastric cancer/gastroesophageal junction cancer, advanced pancreatic cancer, and advanced ovarian cancer).
Number of cases: 10 to 30 cases
Research objectives **Primary objective:** 1) To observe and evaluate the safety and tolerability of advanced solid tumors patients with positive CLDN18.2 expression treated with intravenous infusion of IMC002. **Secondary objectives:** 1) To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) according to dose-limiting toxicity and clinical response including possible side effects after IMC002 treatment of advanced solid tumors patients with positive CLDN18.2 expression.

2) To evaluate the correlation of pharmacodynamic (PD) biomarkers with clinical efficacy to IMC002; the correlation of in vivo expansion and persistence of IMC002 and pharmacodynamic (PD) biomarkers and adverse events.

3) To evaluate the preliminary antitumor efficacy of IMC002 in patients with advanced solid tumors with positive CLDN18.2 expression using objective response rate (ORR), duration of response (DOR), disease control rate (DCR) and progression-free survival are used Phase (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST1.1), Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST).

4) Incidence of treatment-related adverse events.

Exploratory Purpose:

1) To assess changes in immune status after IMC002 treatment.

Study design:

This study is a multicenter, single-arm, open-label, dose-escalation clinical study to evaluate the safety and preliminary anti-tumor efficacy of IMC002 treatment of CLDN18.2-positive advanced solid tumors.

This study plans to recruit 10 to 30 patients with advanced solid tumors with positive CLDN18.2 expression for autologous CAR-T cell therapy.

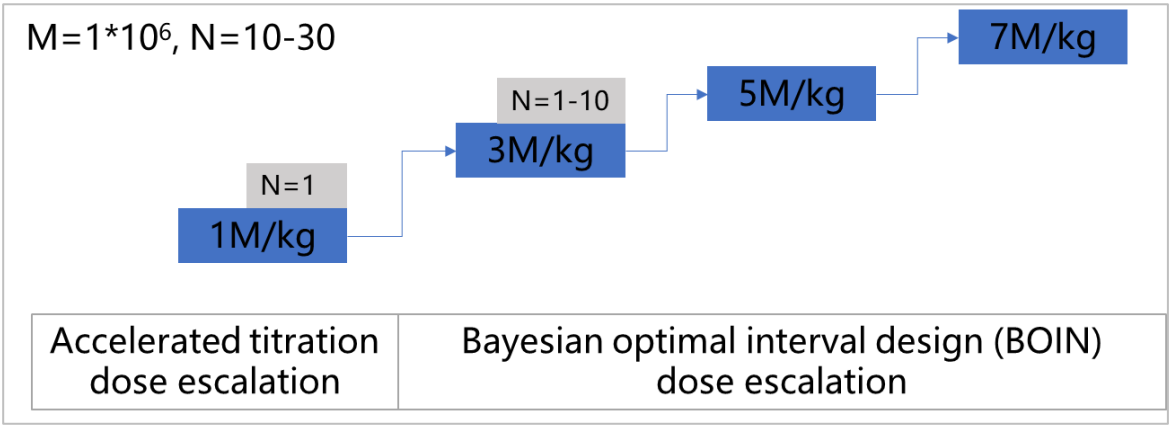

Figure 1. IMC002 Dose Escalation Design

Starting dose and dose escalation settings:

In this study, the accelerated titration and Bayesian optimal interval design (BOIN) is adopted, the starting dose is 1×106 cell s/kg, and sequential doses are 3×10^6, 5×10^6, and 7×10^6 cells/kg, a total of 4 dose levels will be used.

1. Accelerated titration dose escalation:

The accelerated titration group is set as the first dose group, the dose is 1×10^6 cells/kg, and one subject will be enrolled and observed after administration, during the DLT observation period:

- If the subject has no ≥ grade 2 toxicity related to the study drug, the dose group will not be enrolled in other subjects and will be directly escalated to the next dose group.

2. Bayesian optimal interval design (BOIN) dose escalation

Step 1: Enroll 1-10 subjects in the low dose group (3×10^6 cells/kg), and then observe the number of subjects with DLT during the DLT observation period.

Step 2: Calculate the incidence of DLT, denoted by p, and compare it with the boundary values λe and λd given before the experiment. The dose level for the next cohort of subjects to be enrolled is determined.

The incidence of DLT (p) = the number of subjects with DLT at the current dose level / the total number of subjects enrolled at the current dose level.

λe and λd are calculated by the target toxicity probability DLT.

BOIN设计的剂量递增和递减边界

	Target toxicity rate for the MTD						
Boundary	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**
λ_e	0.078	0.118	0.157	0.197	0.236	0.276	0.316
λ_d	0.119	0.179	0.238	0.298	0.358	0.419	0.479

The DLT rate in this study is set between 16% and 33%.

DLT率在30%的剂量递增表格

	The number of patients treated at the current dose																	
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
De-escalate if# of DLTs ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7

In the dose escalation phase, each dose group needs to complete the DLT observation before entering the next dose group; when the first subject in the same dose group has no DLT observed for at least 14 days after cell infusion, subsequent subjects can perform cell infusion.

If a subject withdraws from the study for reasons other than toxicity and does not complete the DLT observation period, the subject will be replaced to meet the requirements of the number of observation cases in each dose group.

The final dose should also consider the actual number of CAR-T cells produced and record the actual number of cells infused.

DLT observation time is 28 days after IMC002 infusion.

After the first CAR T cell infusion, if the investigator judges that the benefits of continued treatment outweigh the risks, based on the existing safety, CAR-T DNA copy number, and efficacy data, the investigator may consider continuing to give the subject IMC002 infusion more than one time (provided that there are enough qualified and quality CAR T cells to be used, and the infusion interval is 6-12 weeks), if appropriate, the next higher dose of IMC002 injection can be used.

For subjects who eligible for multiple infusion, if there are not enough qualified or quantity CAR T cells, the process of PBMC re-apheresis (if applicable), lymphodepletion, infusion procedures and safety visit procedures is the same with the first circle.

For patients who are judged by the investigator to be eligible for multiple infusions between 6-12 weeks, and ADA should be tested before IMC002 infusion.

Definition of Dosing Limiting Toxicity (DLT):

Adverse events (AEs) that occur during the study will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE 5.0), but a modified grading scale will be used to evaluate cytokine release syndrome as described in the protocol text.

The DLT for the dose escalation portion is defined as the following events possibly or definitely related to IMC002 that occurred within 28 days of infusion:

Hematological toxicity

- CLDN 18.2 CAR-T cell therapy-related hematological toxicity of grade ≥4 and cannot be recovered to grade ≤2 after 14 days of treatment (except for lymphocyte and leukopenia, non-febrile neutropenia).
- CLDN 18.2 CAR-T cell therapy-associated hemophagocytic lymphohistiocytosis (HLH)/hemophagocytic syndrome (HPS).

Non-hematological toxicity

- grade ≥4 non-hematological toxicity associated with CLDN 18.2 CAR-T cell therapy.
- CLDN 18.2 CAR-T cell therapy-related cytokine release syndrome ≥ grade 3 cannot be controlled to grade ≤ 2 after 7 days of treatment.
- CLDN 18.2 CAR-T cell therapy-related grade 3 and above CAR-T cell therapy-related encephalopathy (CRES)/immune cell therapy-related neurotoxicity syndrome (ICANS).
- CLDN 18.2 CAR-T cell therapy-related grade 3 other non-hematologic toxicity persisting for more than 7 days, except:

1) ≤grade 3 fever or >grade 3 fever recovered within 48 hours after adequate intervention to ≤grade 3;
2) ≤ Grade 2 within 48 hours after adequate intervention;
3) Grade 3 fatigue;
4) Other laboratory abnormalities (such as alopecia) without significant clinical significance.

Definition of MTD:

BOIN design needs to be based on isotonic regression to estimate MTD after synthesizing subject information at each dose level. Statisticians can use the select.mtd of the R software BOIN package function to achieve, the specific procedure is as follows: select.mtd (target=0.3), npts =c (3,3,15,9,0), ntox =c (0,0,4,4,0)) / inside the numbers can be adjusted according to the actual situation.

Efficacy evaluation:

Efficacy evaluation will be based on RECIST 1.1 and iRECIST 1.1 for treatment response evaluation in solid tumors until 96 weeks after IMC002 infusion or disease progression, whichever occurs first.

Safety Assessment:

The study will collect all adverse events from the time the subjects sign the informed consent form until the subjects are discharged or other anti-tumor treatments are started, whichever occurs first. For subjects who have undergone leukapheresis but failed to reinfuse IMC002, only all adverse events reported within 30 days after the relevant operation or treatment (such as leukapheresis, pretreatment chemotherapy) or the initiation of a new antitumor therapy are collected, whichever occurs first.

The investigators will collect all serious adverse events and ≥ grade 3 cytokine release syndrome (CRS) events from the time the subjects signed the informed consent form until the subjects are discharged or other anti-tumor therapy is started, whichever occurs first. For subjects who failed screening, or who had undergone leukapheresis but failed to reinfuse IMC002, the report is only collected within 30 days after the last procedure or treatment (such as screening tests, leukopheresis, pretreatment chemotherapy) or until the start of new All serious adverse events and grade ≥3 CRS events on antitumor therapy, whichever occurred first. Serious events or grade ≥3 CRS events determined by the investigator to be related to IMC002 should be reported regardless of the time of occurrence.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 5.0, except that cytokine release syndrome (CRS) will be graded according to the 2019 ASTCT CRS grading scale.

Inclusion /Exclusion Criteria, Early withdraw Criteria

Subjects must meet all the following inclusion criteria and none of the exclusion criteria in order to be enrolled.

Inclusion Criteria:

1. Ages ranged from 18 to 70 years (including cut-off values), both male and female.
2. Subjects with previously histologically or cytologically confirmed advanced CLDN 18.2 positive malignant solid tumors (including advanced gastric or esophagogastric junction adenocarcinoma, advanced pancreatic cancer, and metastatic ovarian cancer without standard treatment).
3. Tumor histopathological specimens within 24 months before signing the informed consent, or fresh biopsy specimens collected within 6 months before cell infusion should be available; biopsy tumor tissue specimens are histologically stained positive for CLDN 18.2 (defined as staining intensity ≥ 1+, positive rate ≥ 10%), the recommended antibody for detection is: Anti-Claudin18.2 antibody.
4. Subject's expected survival period ≥ 12 weeks.
5. According to RECIST1.1 criteria, subjects participating in dose escalation must have at least one target lesion that can be stably assessed.
6. ECOG performance status score of 0 to 1.
7. Subjects have adequate organ and bone marrow function. Laboratory screening must meet the following criteria (with reference to NCI CTCAE 5.0). All laboratory test results should be within the stable ranges described below, and there is no ongoing supportive care.
    a) Blood test: white blood cell (WBC)≥1.5×10^9/L; platelet count (PLT)≥100×10^9/L; hemoglobin content (Hb)≥9.0g/dL; lymphocyte (LYM)≥0.4×10^9/L.
    b) Liver function: serum total bilirubin≤1.5×ULN, alanine aminotransferase (ALT)≤1.5×ULN, aspartate aminotransferase (AST)≤1.5×ULN.
    c) Renal function: Serum creatinine≤1.5 ×ULN, if serum creatinine >1.5×ULN, creatinine clearance rate>50mL/min (according to Cockcroft-Gault formula: ([140-age]×body weight[kg]×0.85, only For women])/72× creatinine (mL/dL)); urine

protein qualitative ≤ 1+; if urine protein qualitative ≥ 2+, 24-hour urine protein quantitative test is required (eligible if 24-hour urine protein quantitative test <1g);

d) Amylase and lipase≤1.5 × ULN.

e) Coagulation function: International normalized ratio (INR) ≤ 1.5 × ULN, activated partial thromboplastin time (APTT) ≤ 1.5 × ULN.

8. All toxicities caused by previous antitumor therapy are relieved to grade 0-1 (according to NCI CTCAE version 5.0) or to acceptable levels for inclusion/exclusion criteria. Except for other toxicities such as alopecia and vitiligo that the researchers believe do not pose a safety risk to the subjects.

9. Fertility status: Female patients of childbearing age or male patients whose sexual partners are females of childbearing age are willing to take medically approved high-efficiency contraceptive measures such as intrauterine device or contraception from the time of signing the informed consent to 6 months after the last cell infusion (women of childbearing age include premenopausal women and women within 24 months after menopause).

10. Subjects must sign and date written informed consent.

11. Subjects must be voluntary and able to comply with predetermined treatment regimens, laboratory tests, follow-up and other study requirements.

Exclusion criteria:

Subjects who meet any of the following conditions are not eligible for this study:

1. Pregnant and lactating women.

2. Known history of human immunodeficiency virus (HIV) infection; acute or chronic active hepatitis B (HBsAg positive or HBsAb positive, and HBV-DNA positive); acute or chronic active hepatitis C (HCV antibody positive, and HCV-RNA is positive). Syphilis antibody positive; EB virus DNA quantification >500 copies (or according to the positive standard detected by each research center); cytomegalovirus (CMV) infection (IgM positive).

3. Serious infections that are active or poorly controlled clinically.

4. Existing cardiac disease requiring treatment or poorly controlled hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure >90 mmHg after standardized antihypertensive medication) in the judgment of the investigator.

5. The presence of any of the following clinical cardiac symptoms or diseases within 6 months prior to cell infusion:

a) New York Heart Association (NYHA) ≥ grade II cardiac insufficiency; or 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 a pacemaker;

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

d) Resting-state ECG findings of clinically significant abnormalities (such as heart rate, conduction, morphological features) or complete left bundle branch block or third-degree heart block or PR interval >250ms;

e) Presence of factors that increase the risk of QTc prolongation, abnormal heart rate, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or sudden unexplained death in an immediate family member under 40 years of age, or concomitant prolonged interval medication.

6. Evidence of a major coagulation disorder or other significant bleeding risk, including:

a) A history of intracranial hemorrhage or intraspinal hemorrhage;

b) Tumor lesions invade large blood vessels and have obvious bleeding risk;

c) Thrombotic or embolic events occurred within 6 months before cell infusion ;

d) Clinically significant hemoptysis or tumor hemorrhage occurred within 1 month before cell infusion;

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

f) Presence of any bleeding disorder such as hemophilia, von Willebrand disease;

g) Anticoagulant therapy for therapeutic purposes (except low molecular weight heparin) has been used within 2 weeks before cell infusion;

h) The patient is receiving conventional anticoagulation therapy (eg, warfarin or heparin). Patients require long-term antiplatelet therapy (aspirin, dose >300mg/day; clopidogrel, dose > 75mg /day); dipyridamole, ticlopidine or cilostazol.

7. Subjects requiring systemic therapy with corticosteroids or other immunosuppressive drugs during the treatment period. Presence of any active autoimmune disease, or history of autoimmune disease expected to recur (including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, need for bronchodilators asthma subjects undergoing medical intervention, except for the following: type 1 diabetes; skin conditions not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia); hypothyroidism requiring only hormone replacement

therapy; complete childhood asthma in remission without any intervention in adulthood; or others not expected to relapse in the absence of external triggers).

8. Blood oxygen saturation (pulse oxygen detection) ≤95% before treatment.
9. Diffuse lung metastases.
10. Previous history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis, and symptomatic interstitial lung disease or active pneumonitis on chest CT scan within 4 weeks prior to first study drug treatment.
11. There is uncontrolled pleural effusion, pericardial effusion, and ascites effusion before enrollment.
12. Poorly controlled diabetes (glycated hemoglobin $HbA_{1c} \geq 8\%$).
13. Daily prednisone dose>15mg within 2 weeks prior to apheresis, excluding inhaled steroids.
14. Subjects developed new arrhythmias prior to lymphadenectomy, including but not limited to uncontrolled arrhythmias, hypotension requiring vasopressors, bacterial, fungal, or viral infections requiring intravenous antibiotics. Subjects using investigational antibiotic to prevent infection are at the discretion of the investigator to continue participating in the trial.
15. Known prior or current hepatic encephalopathy requiring treatment; patients with current or history of central nervous system disorders such as seizures, cerebrovascular ischemia/bleeding, dementia, cerebellar disease, or any autoimmunity with CNS; CNS metastases or meningeal metastases with clinical symptoms, or there is other evidence that the patient's central nervous system metastases or meningeal metastases have not been controlled, and are judged not suitable for inclusion by the investigator.
16. Previous or concomitant malignancies of other systems, with the following exceptions:
    - Adequately treated basal cell or squamous cell carcinoma (requires adequate wound healing prior to study entry);
    - Carcinoma in situ of cervical cancer or breast cancer, after curative treatment, with no evidence of recurrence for at least 3 years prior to the study;
    - primary malignancy has been completely resected and has been in complete remission for ≥5 years.
17. Received other CAR-T therapy or TCR-T therapy in the past.
18. Received the following treatments or drugs prior to cell infusion:

- Received anti-tumor therapy such as chemotherapy, biological therapy, endocrine therapy, and immunotherapy within 28 days before the infusion of cells (except for the treatment that meets the requirements of the plan before infusion, such as bridging therapy), or any unmarketed experimental drug treatment; received traditional Chinese medicine treatment with anti-tumor indications within 2 weeks before infusion.

19. Subjects who have received other gene therapy in the past.
20. Subjects with severe mental disorders.
21. Participated in other clinical studies within the past 1 month.
22. The investigator assesses the subject's inability or unwillingness to comply with the requirements of the study protocol.
23. Subjects withdrew from the study for various reasons and could not participate in the study again.

The following criteria need to be re-evaluated before lymphodepletion and before the infusion of IMC002 (CLDN18.2 CAR-T cells):

Before lymphodepletion and 3 days before IMC 002 infusion, if the investigator judges that the subject has significant abnormalities; or the investigator judges that the subject has rapid disease progression compare to the screening time; or the investigator assesses that the patient has significant organ dysfunction (such as severe heart disease, uncontrollable hypertension or diabetes, severe liver or kidney damage, pulmonary edema, severe lung infection, brain metastasis); and it is not suitable for follow-up test procedures, then the lymphodepletion cannot be continued or should be delayed; the CAR T cells should not be infused or the infusion should be delayed.

If the infusion of cells is delayed for more than 5 days after lymphodepletion for any reason, the infusion is not allowed or needs to be delayed.

Withdrawal criteria:

- Subjects may withdraw from the study at any time of their choice.
- Subjects who did not complete the study protocol, including cell infusion and follow-up assessments, are considered to have terminated the study early.
- The reason for termination must be recorded in the CRF and maintained for the specified period of time as required by GCP.
- Subjects may be withdrawn from the study at any time during the study at the discretion of the investigator for reasons of subject safety, behavior, or management reasons, including:

1) Disease progression confirmed by imaging and iRECIST criteria.

2) The cumulative treatment reached 96 weeks (no radiographic progression).

3) The subjects experienced serious adverse reactions.

4) Subject died.

5) Subject is pregnant.

6) Major protocol deviation included, but not limited to:

   a) Mistaken for failing to meet inclusion/exclusion criteria

   b) Concomitant use of prohibited drugs in this protocol

   c) The subjects did not cooperate with the treatment and follow-up, are lost to the follow-up, or the subjects did not come to the hospital for more than two follow-up visits on time.

7) The disease progressed rapidly before the cell infusion, and the investigators determined that other treatment regimens needed to be used based on the maximum benefit of the subjects.

8) In the absence of efficacy, the investigator determined that the subject did not benefit from the trial treatment, and continued participation in the study may put the patient at unacceptable risk.

9) The production of IMC002 (CLDN 18.2 CAR-T cells) failed and a sufficient clinical dose of cells that met quality standards could not be obtained.

10) Safety reasons considered by the investigator.

Test Drug Dosage and Administration

Test drug: IMC002 (CLDN 18.2 chimeric antigen receptor T cell injection).

Codename: IMC002

Route of Administration: Intravenous infusion

Dosage:

Initial dose and dose escalation: this study adopted the dose escalation design of accelerated titration and Bayesian optimal interval design (BOIN). Four dose levels of 1×10^6, 3×10^6, 5×10^6, and 7×10^6 cells/kg will be dose-escalated sequentially.

The final dose should also consider the actual number of CAR-T cells produced and record the actual number of cells infused.

Elimination criteria:

Before the statistical analysis of the data, the statistician and the principal investigator should discuss and judge whether the individual case is excluded. In the following cases, statisticians and investigators should comprehensively judge whether to exclude this subject based on factors such as the subject's degree of completion of the trial and the reasons for withdrawal, and not to be included in the set of compliance with the protocol, and make relevant explanations:

1） After participating in the trial, the subjects do not meet the inclusion criteria or meet the exclusion criteria or are judged to be major protocol deviations.

2） Not compliance with the protocol plan during the trial (poor compliance, such as IMC002 cells have not been used, or samples that cannot be evaluated for efficacy or safety according to the requirements of the trial protocol, without any data).

In addition to the above-mentioned cases, subjects who have other major deviations or violations of the protocol during the trial and have an impact on the efficacy and safety of IMC002 cells.

Criteria for early study termination:

Criteria for early termination of this study include but are not limited to the following:

1. Unexpected, significant, or unacceptable risk to enrolled subjects.
2. Enrollment is very slow and frequent protocol deviations.
3. Suspension or discontinuation of drug development.

Study endpoints and evaluation indicators

Primary endpoint: Safety and tolerability 28 days after a single infusion, to determine DLT and MTD.

Secondary endpoints: Engraftment endpoints after infusion of IMC002 (CLDN 18.2 CAR-T cells), i.e., copy number and sustained survival time of cells in vivo.

The “engraftment endpoint” is defined as the number of copies of CLDN 18.2 CAR-T DNA in peripheral blood detected by q-PCR at each visit point from the end of the infusion until any 2 consecutive test results are negative or below the detection limit. The time from the day of infusion to the first negative result or below the lower limit of detection is recorded as the survival time of IMC002 (CLDN 18.2 CAR-T cells).

Safety endpoints: The incidence of DLT is assessed according to NCI CTCAE 5.0 and its correlation with investigational product, lymphodepletion and leukopheresis.

Other safety endpoints:

- The type, incidence, and severity of adverse events, including abnormal clinically significant laboratory test results, abnormal physical examination and blood test results, bone marrow test results, and immunogenicity results after treatment. AE/SAE is assessed according to NCI CTCAE version 5.0. The association of adverse events with the IMC002 CAR-T treatment regimen will be assessed by the investigator according to the attribution evaluation criteria specified by the protocol.
- Grade 3-4 laboratory tests and their association with investigational products, lymphodepletion, and leukopheresis.

Efficacy evaluation endpoints:

Efficacy is evaluated using RECIST1.1 and iRECIST1.1. For each subject, the same technique must be used to obtain tumor imaging during the trial. For subjects first determined to be in complete remission (CR) or partial remission (PR), the assessment results should be confirmed by repeat imaging scans at least 4 weeks later.

Efficacy endpoints include tumor objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Objective response rate (ORR) is defined as the proportion of subjects with confirmed response as CR or PR; tumor response status is assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST1.1).

Duration of response (DOR) interval from first assessment as CR or PR to first assessment as PD or death from any cause (percentage of subjects with DOR ≥24 weeks, ≥36 weeks, ≥48 weeks will be reported).

Disease control rate (DCR) percentage of patients who confirmed as CR or PR or SD (RECIST1.1).

Progression-free survival (PFS) is defined as the time interval from the subject's first infusion of IMC002 to disease progression or death from any cause, whichever occurred first. For subjects with no documented disease progression or death, the cutoff date is the date of the last examination.

Overall survival (OS) is defined as the time interval between subjects receiving the first infusion of IMC002 and the recording of death from any cause. For subjects whose death is not recorded, subjects who did not die by the analysis cut-off date are censored with the last contact time.

For subjects with advanced solid tumors with positive CLDN18.2 expression, after 4 weeks of treatment, the treatment effect of the target lesions is evaluated using the RECIST1.1 and iRECIST1.1: treatment effect = (CR+ PR)/total number of cases ×100%.

Metabolic kinetic endpoints:

The expansion and persistence of CLDN 18.2 CAR-T cells in peripheral blood will be detected by q-PCR. The main evaluation indicators: peak CAR-T cells (the highest number of CAR+ peripheral blood mononuclear cells in serum after cell infusion), Time to peak (days after cell infusion to peak CAR-T cells) and AUC0-28 (area under the curve plotted from days 0 to 28 as the number of CAR-T cells in serum versus visit time).

Exploratory endpoints:

Detection of cytokine levels in blood before and after treatment, including but not limited to pro-inflammatory and immunomodulatory cytokines IL-6, TNFα, IL-8, IL-1rα, IL-10, IL-12, IL-2Rα, GM-CSF, IL-15, IFNγ, immune effector molecule granzyme B, acute phase response-related factors CRP, Ferritin, VCAM-1, and chemokines MCP-1, IP-10.

The level of ADA in blood will be detected before and after treatment.

Explore the correlation of biomarkers with efficacy and safety.

Tumor efficacy evaluation:

During the screening period, imaging (unenhanced and enhanced nuclear magnetic resonance MRI or CT, the specific examination site shall be determined by the investigator according to the patient's condition) and tumor markers should be examined. The imaging results 28 days before cell infusion can be set as study baseline. Imaging (unenhanced and contrast-enhanced MRI or CT) and tumor markers are then performed at the scheduled visits of the study protocol until Week 96, disease progression, subject lost to follow-up, withdrawal of informed consent, or death (whichever occurs first).

Imaging assessments are based on RECIST1.1 until confirmed disease progression.

Pseudoprogression may occur with IMC002 treatment due to infiltration of IMC002 autologous CAR-T cells or other mechanisms resulting in a significant increase in existing tumor volume. If the investigator suspects pseudoprogression of disease according to RECIST1.1, the assessment should be confirmed by repeat imaging after at least 4 weeks (no later than 8 weeks). The criteria for confirming progression are on the basis of the imaging results of the last suspected progression, the sum of the target lesion measurements has further increased by at least 5 mm, or the progression of non-target lesions, or the number of new lesions has further increased or increased in number. If the efficacy assessment reaches CR, PR, and SD compared with the baseline according to the RECIST1.1, the previously suspected

progression cannot be confirmed; as long as the suspected progression is not confirmed, subsequent imaging examinations can be performed for confirmation.

Statistical Analysis:

All statistical analyses will be done with SAS 9.4 or above. In general, continuous variables will be described using the number of cases, mean, median, standard deviation, minimum and maximum values; categorical and rank variables will be statistically described using frequencies and percentages for each category or rank; missing values are not included in the calculation of percentages unless otherwise stated. All statistical tests will use a two-sided test with α=0.05, and a two-sided 95% confidence interval (CI) will be calculated.

Demographics and other baseline characteristics

Demographic data and other baseline characteristics are summarized using descriptive statistics.

Analysis of safety indicators

The primary safety endpoint of this study is the DLT observed at 28 days post-infusion, which will be used to determine the MTD.

All adverse events after infusion will be performed in the safety analysis population.

Efficacy endpoints analysis

According to the RECIST1.1, the progression-free survival (PFS) and overall survival (OS) of each dose and all patients within 96 weeks after IMC002 treatment are evaluated, and 12 months after IMC002 infusion will be counted and calculated. PFS and OS are achieved within the period, and their bilateral 95% exact confidence intervals are calculated to analyze the dose-efficacy relationship.

Statistical analysis of dose-response relationship

Descriptive statistical analysis is performed on the indicators, and median Tmax, Cmax, as well as the survival rate and cell number of CAR-T cells in peripheral blood within 96 weeks after IMC002 infusion are provided. The relevant parameters should be analyzed separately for responders and non-responders and compared. Descriptive statistical analysis is performed on the cytokine dose-response relationship, and the median peak value of each cytokine within 4 weeks of CAR-T cell infusion, and the median time to return to baseline or normal range are provided.

The differences in the dose-response relationship of patients in different dose groups are compared.

Ethics:

The protocol (including the informed consent form) must be approved by an independent ethics committee before start. This study strictly follows the protocol and GCP to fully protect the legitimate rights and interests and safety of the subjects.
Research period: Expected from December 2021 to December 2024