Project Source and Number：

A Study of the Safety and Efficacy of Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) in Patients with Refractory Membranous Nephropathy

Principal Investigator: He Lijie

Responsible Department: Department of Nephrology

Contact Phone: 029-89661611

Undertaking Institution: The First Affiliated Hospital of Air Force Medical University

Study Period: August 1, 2025 - July 31, 2028

Version No.: V3.0

Version Date: October 10, 2025

Table of Contents

Project Summary Project	Safety and Efficacy of Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T)in the Treatment of Refractory Membranous Nephropathy
Objectives	To preliminarily evaluate the safety and efficacy of CD19 CAR-T in refractory membranous nephropathy (rMN), with the aim of providing new insights for optimizing the treatment and management of the disease.
Study Design	This study is a single-center, prospective, exploratory Phase I clinical trial initiated by the team led by Associate Professor He Lijie from the Department of Nephrology, Xijing Hospital. Prior to receiving CAR-T cell therapy, patients will undergo lymphodepletion chemotherapy with cyclophosphamide (fludarabine will be added if necessary). After prophylactic administration of antihistamines and acetaminophen, patients will be infused with CD19 CAR-T cells at a dose of 1×10^6 cells/kg. In the subsequent 2 weeks, patients will be hospitalized for monitoring of vital signs and adverse reactions. The planned follow-up duration of this study is 1 years.
Total Number of Cases	5
Case Selection	Inclusion Criteria: （1）Confirmed diagnosis of primary membranous

	nephropathy (PMN) by renal biopsy; （2）Refractory membranous nephropathy (rMN) with moderate or high risk; （3）Patients aged ⩾ 18 years; （4）Estimated glomerular filtration rate (eGFR) ⩾ 30 ml/min/1.73m ^{2} , without severe cardiac, hepatic, or pulmonary dysfunction; （5）Signed written informed consent form.
	Exclusion Criteria: （1）Secondary membranous nephropathy; （2）Active bacterial, fungal, or viral (excluding common cold/flu) infections requiring intravenous antibiotic treatment, or active pulmonary tuberculosis, or positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Treponema pallidum (TP), Epstein-Barr virus (EBV), or cytomegalovirus (CMV)； （3）Severe comorbidities or underlying diseases; （4）History of malignant tumors; （5）Exclusion based on treatment history: meeting any of the following criteria:a. Previous receipt of any cell therapy (e.g., mesenchymal stem cells, etc.);b. Receipt of major surgery within 24 weeks prior to enrollment, or planned surgery within 24 weeks after enrollment;c. Planned kidney transplantation within 3 years;d. History of substance abuse;

	（6）Participation in other interventional clinical trials within 3 months prior to enrollment; （7）Pregnant or lactating women; （8）Inability to understand the study or provide informed consent (e.g., severe dementia, psychiatric disorders); （9）Any other conditions that the investigator deems may increase risks, interfere with evaluation, or affect compliance.
Interventions	The main intervention measures received include peripheral blood mononuclear cell (PBMC) collection, lymphodepleting chemotherapy, and autologous CAR-T cell infusion.
Assessment	Primary endpoint: Safety evaluation, with the type and incidence of dose-limiting toxicity (DLT) and adverse events (AE) after a single CAR-T infusion as the evaluation indicators.
	Secondary Endpoints: Efficacy Assessment：① Remission or relapse of rMN (renal Membranous Nephropathy). This includes the proportion of subjects who maintain complete remission or partial remission after cell infusion, the duration of remission, and the occurrence of relapse.② Changes in renal function, immune characteristics, and cellular dynamics, including changes in proteinuria, eGFR (estimated Glomerular Filtration Rate), serum anti-PLA2R (Phospholipase A2 Receptor) antibodies, infection markers, complement levels, immunoglobulin levels, cytokine levels, changes in peripheral blood immune cell subsets, and the expression level of CD19 on the surface of peripheral blood B cell subsets.

Statistical Methods	All statistical analyses will not account for cases such as poor subject compliance, premature withdrawal, or loss to follow-up.Due to the small sample size of this study, all data will be presented as individual values.The study will use descriptive statistical methods to report specific parameters during the baseline and follow-up periods.Statistical analyses and data visualization will be performed using SPSS Version 27.0 and GraphPad Prism Version 9.0.
Study Duration	August 2025 – July 2028

1. Background

Primary Membranous Nephropathy (PMN) is an autoimmune disease mediated by pathogenic antibodies produced by autoreactive B lymphocytes. These antibodies reach the kidneys through the bloodstream and bind to specific antigens on the glomerular basement membrane to form in-situ immune complexes. These complexes then trigger a series of pathological effects, ultimately leading to glomerular podocyte damage and massive proteinuria [1].Currently, the global incidence of PMN is approximately 8-10 cases per million people [2], while the incidence rate reported in China is 23.4% [3]. The specific etiology of PMN remains unknown, and the remaining cases are associated with drug use or underlying diseases such as systemic lupus erythematosus, hepatitis B virus infection, or malignant tumors.Although approximately one-third of patients may achieve spontaneous complete or partial remission through conservative treatment, another one-third of patients face an increased risk of disease progression, which may lead to end-stage renal disease within 10 years [4].

Over the past decade, significant progress has been made in research on the pathogenesis and therapeutic strategies of primary membranous nephropathy (PMN).More than ten target antigens associated with PMN have been identified so far, among which approximately 70% of cases are mediated by antibodies against phospholipase A2 receptor (PLA2R) [5].

Targeting the core pathological process of antibody production, the current main therapeutic strategy is to selectively eliminate B cells that produce autoantibodies and their terminally differentiated plasma cells [6].Anti-CD20 monoclonal antibodies, represented by Rituximab (RTX), are currently widely used targeted drugs in the clinical treatment of PMN. Their mechanism of action involves specific binding to the CD20 protein on the surface of B cells, thereby eliminating B cells. Although RTX and similar agents are considered safe and effective for PMN patients, their efficacy is still limited—about 30% of patients show no response. This insufficient response may be attributed to high titers of anti-PLA2R antibodies [7].In addition, some patients may develop anti-drug antibodies after receiving RTX treatment, which can also lead to accelerated drug clearance, reduced efficacy (drug resistance), or disease recurrence [8]. Patients with such refractory membranous nephropathy (rMN) — i.e., those non-responsive to RTX treatment (manifested as long-term unresolved proteinuria) — have a significantly increased risk of progressing to end-stage renal disease (ESRD) [9, 10].These patients are defined by the following characteristics:Positive anti-PLA2R antibodies at diagnosis, with persistently high or no significant changes in anti-PLA2R antibody titers after receiving adequate and full-course first-line immunosuppressive therapy;Persistently negative anti-PLA2R antibodies, but with unresolved nephrotic syndrome for more than 6

months despite continuous first-line immunosuppressive therapy.Therefore, it is necessary to explore alternative therapies with better efficacy.

Chimeric Antigen Receptor T-cell (CAR-T) therapy involves isolating mononuclear cells from peripheral blood via leukapheresis, followed by genetic engineering in vitro to express chimeric antigen receptors. Therefore, CAR-T cells can recognize specific antigens on target cells without the need for antigen processing and presentation. Once genetically modified, CAR-T cells undergo extensive proliferation in vitro; after lymphodepletion chemotherapy, these cells are reinfused into the patient's body. A key advantage of this therapy is that the body develops long-lived memory CAR-T cells, which can provide sustained efficacy against newly generated target cells without the need for repeated administration [11].

Due to the targeted effect of CAR-T therapy, its clinical application has gradually become widespread, and it has also shown promising application prospects in autoimmune diseases, including kidney diseases. In August 2021, the first case report was published about a patient with severe Systemic Lupus Erythematosus (SLE) who received CD19 CAR-T cell therapy and achieved favorable therapeutic effects [12]. Subsequently, in September 2022, the same research team reported another 5 cases of refractory SLE patients treated with CD19 CAR-T cells. All patients

experienced disease improvement, with lupus nephritis achieving clinical cure, and serum complement as well as double-stranded DNA antibodies returning to normal levels [13]. In February 2024, the team published the research results on CD19 CAR-T therapy for autoimmune diseases. This study enrolled 15 patients with autoimmune diseases, including 8 SLE patients, 4 systemic sclerosis patients, and 3 idiopathic myositis patients. These patients had signs of active organ involvement, had failed at least two immunotherapy regimens, and their diseases were severe with life-threatening potential. After 15 months of follow-up post-CAR-T therapy, all 8 SLE patients achieved disease remission, the disease activity index of the 4 systemic sclerosis patients decreased, and the disease of idiopathic myositis patients was also well-controlled [14].

In the treatment of autoimmune diseases, the adverse reactions of CAR-T therapy are consistent with those in hematological malignancies. The most prominent one is cytokine release syndrome (CRS), while other potential side effects include: immune effector cell-associated neurotoxicity syndrome (ICANS), immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), CAR-T-associated coagulopathy (CARAC), immune effector cell-associated hematotoxicity (ICAHT), B-cell deficiency or hypogammaglobulinemia, and infections [15].Existing studies have shown that the incidence of acute toxic reactions induced by CAR-T cell therapy

is low and the severity is mild, with favorable short-term safety. Particularly, it exhibits excellent tolerability in autoimmune diseases. The main risks are mild CRS and manageable infections, and there have been no treatment-related deaths or severe complications (e.g., no cases of disseminated intravascular coagulation, multiple organ failure, or the need for ventilator support) [13, 14, 16-18].In conclusion, the results from small-sample clinical studies of CAR-T cell therapy in autoimmune diseases conducted in the early stage indicate that this therapy holds broad application prospects in the treatment of autoimmune diseases.

Potential targets for MN antigen-specific therapeutic regimens include autoantibody production, antibody-antigen interaction, and immune-mediated podocyte injury [19]. In rMN, impeding antibody production is clearly of key significance. CAR-T cell therapy is a promising strategy that can not only eliminate specific pathogenic antigens and their epitopes (e.g., CD19+B cells) but also induce the generation of memory CAR-T cells in vivo, enabling the potential for long-term and sustained clearance [20].Therefore, the objective of our study is to preliminarily evaluate the safety and efficacy of CD19 CAR-T therapy in rMN through a prospective, small-sample clinical trial, with the aim of providing a better therapeutic strategy for rMN.

2. Research Objectives

Currently, rMN patients who do not respond to first-line

immunotherapy or targeted therapy have a significantly increased risk of progressing to end-stage renal disease. Therefore, there is still a need to further explore effective treatment methods for rMN. The achievements of CAR-T cells in clinical research on autoimmune diseases suggest that they may have good potential and application prospects in rMN. Thus, the objective of our study is to preliminarily explore the safety and efficacy of CAR-T therapy in rMN through a prospective, small-sample clinical trial, aiming to provide a better treatment strategy for rMN.

3. Study Design

Patients will undergo peripheral blood mononuclear cell (PBMC) collection 1-4 weeks prior to autologous CAR-T cell therapy. Shaanxi Yisaier Biotechnology Co., Ltd will be responsible for cell sorting and purification, T cell activation, CAR gene transduction, and in vitro expansion of CAR-T cells. After undergoing washing, formulation, cryopreservation, testing, and release procedures, the cells will be transported via cold chain to the laminar air flow ward for intravenous infusion.All patients will receive lymphodepleting chemotherapy 3-7 days before CAR-T cell therapy to reconstitute the immune environment. The preferred regimen is cyclophosphamide (CTX) 400 mg/day for two consecutive days. On the third day, the degree of peripheral blood lymphocyte depletion will be assessed. If the depletion effect is unsatisfactory, fludarabine (Flu) 25 mg/m^2 /day will be administered for

1-2 days. CD19 CAR-T cells (1×10^6/kg) will be infused more than 2 days after lymphodepleting chemotherapy. Before intravenous cell infusion, prophylactic antihistamines (such as chlorpheniramine or diphenhydramine) and acetaminophen will be administered.All patients will be hospitalized in the laminar air flow ward for at least 10 days of observation. For patients with severe adverse events such as grade 3 or higher cytokine release syndrome (CRS), the observation period will be extended to 14 days. The planned follow-up period for the entire study is 1 year, and long-term follow-up will continue after the study concludes.

During the study, the enrollment interval between each subject will be no less than 28 days.

4. Study population

4.1 Inclusion Criteria

1) Confirmed as primary membranous nephropathy (PMN) by renal biopsy;
2) Moderate-risk or high-risk rMN;
    a. Definition of moderate risk: eGFR $\geqslant$ 90 ml/min/1.73m^2, 24-hour urinary protein > 3.5g/d, and the reduction in urinary protein is no more than 50% within 6 months of receiving renin-angiotensin system inhibitors (RASi);
    b. Definition of high risk: eGFR < 60 ml/min/1.73m^2 and/or persistent proteinuria > 8g/d for more than 6 months; or

normal eGFR with proteinuria > 3.5g/d, and the reduction in urinary protein is no more than 50% within 6 months of receiving RASi, and at least one of the following conditions is met:

◆Serum albumin < 25g/L

◆PLA2Rab>50 RU/mI，

◆Urinary α1-microglobulin > 40 μg/min

◆Urinary IgG > 1 μg/min，

◆Urinary β2-microglobulin > 250 mg/d

◆Screening coefficient (IgG clearance/albumin clearance) > 0.20;

c. Definition of rMN: After receiving adequate and full-course (≥ 6 months) standard first-line immunosuppressive therapy (including but not limited to: glucocorticoid + cyclophosphamide (CTX) regimen, calcineurin inhibitor [CNI], or rituximab (RTX)), any of the following conditions is met:

◆Anti-PLA2R antibody remains persistently positive with high titer or shows no significant decrease.

◆For patients with negative anti-PLA2R antibody, they continuously present with nephrotic syndrome (24-hour urinary protein > 3.5g, serum albumin <

30g/L);

◆24-hour urinary protein reduction < 50%

3) Patients aged ≥ 18 years;

4) Key organ functions meet the following requirements:

◆Renal function: eGFR≥30 ml/min/1.73m² ;

◆Hepatic function: ALT and AST ≤2.5×upper limit of normal (ULN), total bilirubin ≤1.5×ULN;

◆Cardiac function: Left ventricular ejection fraction (LVEF) ≥ 50%; heart failure with NYHA functional class Ⅰ or Ⅱ; no clinically significant arrhythmias requiring intervention (e.g., ventricular tachycardia, ventricular [atrial] fibrillation, third-degree atrioventricular block, etc.). No acute coronary syndrome, stroke, aortic dissection, or other cardiovascular and cerebrovascular events within the past 6 months.

◆Respiratory function: Pulse oxygen saturation > 92% in a non-oxygen-dependent state.

5) Have a full understanding of the study's purpose, risks, and benefits, voluntarily participate in the study, and sign a written informed consent form (by the patient themselves and their legal guardian, if applicable).

4.2.Exclusion Criteria

1) Secondary membranous nephropathy (e.g., caused by SLE, tumors, drugs, infections, etc.);
2) Active bacterial, fungal, or viral (excluding common cold/influenza) infections requiring intravenous antibiotic treatment; active pulmonary tuberculosis; or positive viral serology, meeting any of the following criteria:
    - ◆HBsAg (+) and/or HBcAb (+) with HBV DNA > lower limit of detection;
    - ◆HCV Ab (+) and HCV RNA (+);
    - ◆HIV Ab (+);
    - ◆Active EBV/CMV infection: EBV IgM (+) or EBV-DNA > normal value; CMV IgM (+) or CMV-DNA > normal value;
    - ◆Treponema pallidum (TP) antibody positive (active infection needs to be evaluated).
3) Severe comorbidities/underlying diseases, such as: uncontrolled hypertension (e.g., persistent systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg); uncontrolled diabetes mellitus (HbA1c > 8% or random blood glucose ≥ 11.1 mmol/L) or diabetic nephropathy; history of symptomatic deep vein thrombosis or

pulmonary embolism within the past 6 months; history of active peptic ulcer and/or gastrointestinal bleeding within the past 6 months; congenital or acquired severe immunodeficiency (e.g., HIV, primary immunodeficiency diseases); severe central nervous system diseases (e.g., catastrophic antiphospholipid syndrome, uncontrolled epilepsy); or end-stage organ failure not caused by PMN;

4) History of malignant tumors: A history of malignant tumors within 5 years, except for cured basal/squamous cell carcinoma of the skin, cervical carcinoma in situ, and thyroid cancer;

5) Exclusion based on treatment history, meeting any of the following criteria:

◆Previous receipt of any cell therapy (e.g., mesenchymal stem cell therapy, hematopoietic stem cell transplantation, etc.)

◆Having undergone major surgery within 24 weeks before enrollment, or planning to undergo surgery within 24 weeks after enrollment;

◆Planning to undergo kidney transplantation within 3 years;

◆History of substance abuse

6) Having participated in other interventional clinical trials within 3 months before enrollment;
7) Pregnant or lactating women
8) Inability to understand the study or provide informed consent (e.g., severe severe severe dementia, mental illness);
9) Any conditions that, in the investigator's judgment, may increase risks, interfere with assessments, or affect compliance.

4.3.Criteria for Termination of the Study

Criteria for withdrawal of study subjects include:

1) Safety events: Occurrence of severe adverse events (SAEs) related to study treatment (e.g., lymphodepleting chemotherapy, CAR-T infusion) or intolerable toxicity, where the investigator determines that permanent discontinuation of treatment is necessary;
2) Subject's willingness: The subject or their legal guardian voluntarily requests to withdraw from the study;
3) Loss to follow-up or death of the subject.
4) Occurrence of severe complications unrelated to PMN (e.g., newly developed malignant tumors, severe infections) that require priority management.
5) Acute deterioration of PMN condition (e.g., acute kidney

injury requiring dialysis), where the investigator determines that continuation of the trial is inappropriate.

6) The investigator judges that continuing the study is not in the subject's best interest (e.g., ineffective treatment with increased risks) or that major protocol violations affect the assessment of primary endpoints.

7) Request for termination of the study by regulatory authorities or ethics committees.

Post-withdrawal management: The reasons for withdrawal, date, and details of the last treatment should be documented thoroughly. Standard treatment should be provided, and safety and efficacy should be followed up continuously (unless refused by the subject). Collected data will be used for statistical analysis under the premise of ethical compliance.

5.Research Methods and Technical Roadmap

5.1Intervention Measures

All patients will receive CD19 CAR-T cell therapy on the basis of standard symptomatic and supportive treatment.

（1）Symptomatic and supportive treatment

All patients will receive conservative treatment at the maximum tolerable level, mainly including:

① Drugs for blood pressure control and renal function protection, including but not limited to: renin-angiotensin-aldosterone system

inhibitors (RAASi), other first-line antihypertensive drugs (e.g., diuretics, β-blockers, CCBs, α-blockers, or centrally acting agents, etc.), and sodium-glucose cotransporter 2 inhibitors (SGLT-2i);

② Lipid-regulating drugs, including but not limited to: statins, fibrates, ezetimibe, and PCSK9 inhibitors, etc.;

③ Uric acid-lowering drugs, including but not limited to: febuxostat, allopurinol, etc.;

④Calcium and phosphorus metabolism regulators, including but not limited to: calcium supplements, calcitriol, etc.;

⑤Anti-anemic drugs, including but not limited to: iron supplements, folic acid, etc.;

⑥Other necessary non-immunosuppressive or regulatory drugs.

（2）CD19 CAR-T cell therapy

All patients will receive a single dose of 1×10^6/kg autologous CD19 CAR-T cell therapy, with the main procedures as follows:

①Peripheral blood mononuclear cell collection: Blood from patients will be collected using a blood component separator to isolate T cell-containing blood. The expected volume of collected blood is 120 ml, with a minimum of no less than 50 ml. During the collection process, the blood flow rate will be set at 50–70 ml/min; if necessary, the collection personnel will adjust the rate based on actual collection conditions, and the collection time is expected to be 2–4 hours.

②Lymphodepleting chemotherapy: The study will adopt the CTX± Flu regimen. After a comprehensive assessment of the patient's condition to confirm tolerance to lymphodepleting chemotherapy, CTX 400 mg/day will be administered intravenously for two consecutive days, with a total dose of 800 mg. On the third day, the degree of peripheral blood lymphocyte depletion will be tested; if the depletion effect is unsatisfactory, Flu 25 mg/m² /day will be added for 1–2 days.

③ Infusion of autologous CD19 CAR-T cell injection: Acetaminophen derivatives and antihistamines (e.g., chlorpheniramine or diphenhydramine) will be administered 30–60 minutes before infusion. The CD19 CAR-T cell injection will be infused intravenously using a non-filtered infusion tube to prevent loss of effective cellular components, which could reduce efficacy. The infusion procedure is as follows: flushing with 100 ml normal saline → cell infusion → flushing with 100 ml normal saline. The infusion rate will be controlled at 2–3 ml/min for the first 15 minutes to ensure patient tolerance; if no adverse reactions occur, the rate can be adjusted to 5–10 ml/min.

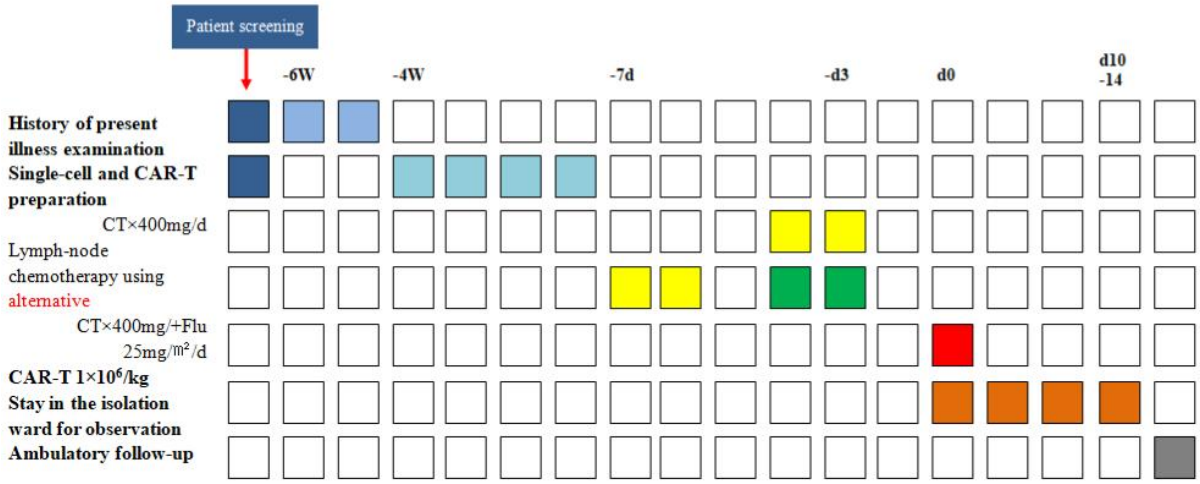

Figure 1 Main Interventions and Procedures of the Study

Table 1 Research Process Schedule

5.2Sample Size Determination

This study is a phase I clinical exploratory trial, with a preliminary plan to enroll 5 patients with rMN.

5.3Data Collection and Follow-up

5.3.1 Collected data

All subjects are required to complete the collection of data and

Stage	Time	Key Activities	Assessment Focus
Patient Screening	-6~-4w	Medical history review, laboratory tests, imaging examinations	Meet the criteria for refractory MN, organ function up to standard
Cell Preparation	-4~-1w	Patient assessment, leukapheresis, CAR-T modification, expansion, and quality inspection	Cell viability and safety compliance
Lymphodepleting Pretreatment	-7~-3d	Cyclophosphamide ± Fludarabine regimen	Lymphocyte depletion, infection prevention
CAR-T Infusion	Day 0	Intravenous infusion of CAR-T cells	Infusion reaction monitoring
In-hospital Monitoring	d0-d14	CRS/ICANS management, infection prevention, early efficacy assessment	Acute event control, B-cell depletion
Intensive Follow-up	≤3m	Monthly clinical assessment, laboratory tests	Renal response, immune indicators
Medium- and Long-term Follow-up	3~12m	Regular comprehensive assessment, immune reconstitution monitoring	Drug-free remission status, recurrence signs
Extended Follow-up	>12m	Recurrence rate, long-term side effect tracking	Long-term safety, quality of life

information such as signing of the informed consent form, medical history information, physical examination, electrocardiogram/echocardiography, renal assessment, routine tests, concomitant medication records, and endpoint outcome assessment at different study stages (Table 2). Such data and information include but are not limited to:

① Demographic data: including name, gender, date of birth, ethnicity, education level, occupation, marital status, current address, and contact information.

② Concomitant medication records: mainly including the usage of drugs related to blood pressure lowering, lipid regulation, blood glucose lowering, immunomodulation, adjuvant therapy, and vaccination, etc.

③ Vital signs: mainly including heart rate, blood pressure, body temperature, etc.

Table 2. Schedule of Study Activities and Assessments

Plan	Screening Period	CAR-T Preparation Period	Baseline Period	In-hospital Follow-up Period	Intensive Follow-up Period	Medium- and Long-term Follow-up	Follow-up at Study Completion	Follow-up after Study Completion (Extended Follow-up)
Time	**-6 to -4w**	**-4 to -1w**	**-2d to d0**	**d0 to d14**	**≤3m**	**3 to 12m**	**12y**	**>12m**
Informed Consent	×							
Inclusion and Exclusion Criteria	×							
Demographic	×							

Data								
Past Medical History	×							
Medication History	×							
Concomitant Medications	×	×	×	×	×	×	×	×
Physical Examination	×	×	×	×				
Weight, Height	×		×		×	×	×	×
Vital Signs	×	×	×	×	×	×	×	×
Electrocardiogram/Echocardiography	×		×					
Renal Ultrasound	×							
Laboratory Tests	×		×	×	×	×	×	×
Endpoint Assessment				×	×	×	×	×
AE Assessment				×	×	×	×	×

Study Procedures and Follow-up Plan

① Screening phase: Potential subjects will be screened according to the inclusion and exclusion criteria. Eligible subjects (or their legal representatives) will sign the informed consent form. Data including demographic information, past medical history, medication history, concomitant medications, physical examination results, and vital signs will be collected. A 12-lead electrocardiogram, echocardiography, and renal ultrasound will be performed. Routine tests (blood, urine, and stool), liver and kidney function, blood lipids, blood glucose, electrolytes, coagulation function, anti-PLA2R antibodies, infection screening (HBV, HCV, syphilis, HIV, EBV, CMV, etc.), urine microalbumin/creatinine

ratio (UACR), and urine protein quantification will be completed.

② CAR-T preparation phase: Data such as concomitant medications, physical examination results, and vital signs will be recorded. Routine tests (blood, urine, and stool), liver and kidney function, blood lipids, electrolytes, coagulation function, and infection screening (HBV, HCV, syphilis, HIV, EBV, CMV, etc.) will be completed.

③ Baseline phase: Data including concomitant medications, physical examination results, and vital signs will be recorded. Laboratory tests will be performed, including routine tests (blood, urine, and stool), liver and kidney function, blood lipids, blood glucose, electrolytes, coagulation function, C-reactive protein (CRP), procalcitonin (PCT), anti-PLA2R antibodies, ferritin, complements, immunoglobulins, cytokines, peripheral blood lymphocyte subsets, peripheral blood CD19 B cells, UACR, and 24-hour urine protein quantification. An electrocardiogram will also be conducted.

④ In-hospital follow-up phase: Data such as concomitant medications, physical examination results, and vital signs will be recorded. Laboratory tests will be completed, including routine tests (blood, urine, and stool), liver and kidney function, electrolytes, coagulation function, CRP, PCT, anti-PLA2R antibodies, ferritin, complements, immunoglobulins, cytokines, peripheral blood lymphocyte subsets, peripheral blood CD19 B cell expression, CAR copy parameters,

UACR, and 24-hour urine protein quantification.

⑤ Intensive follow-up phase: A total of 3 follow-ups are planned. The first post-discharge follow-up (Follow-up 1) will be conducted on Day 28 after infusion. Laboratory tests will include routine blood and urine tests, liver and kidney function, coagulation function, CRP, PCT, anti-PLA2R antibodies, ferritin, complements, immunoglobulins, cytokines, peripheral blood lymphocyte subsets, UACR, and 24-hour urine protein quantification. The second and third follow-ups (Follow-up 2 and 3) will be conducted at Month 2 and Month 3 after treatment, respectively. Planned laboratory tests include routine blood and urine tests, liver and kidney function, anti-PLA2R antibodies, complements, immunoglobulins, peripheral blood lymphocyte subsets, peripheral blood CD19 B cell expression, CAR copy parameters, UACR, and 24-hour urine protein quantification. Data such as concomitant medications and vital signs will also be recorded at each follow-up.

⑥ Medium- and long-term follow-up phase: From Month 3 to Month 12 after treatment, follow-ups will be conducted every 3 months, totaling 3 planned follow-ups: Follow-up 4 (Month 6 after treatment), Follow-up 5 (Month 9 after treatment), and Follow-up 6 (Month 12 after treatment), with Follow-up 6 also serving as the study completion follow-up. At each follow-up, laboratory tests will include routine blood and urine tests, liver and kidney function, anti-PLA2R antibodies,

complements, immunoglobulins, CAR copy parameters, UACR, and 24-hour urine protein quantification. Follow-up 4 will additionally include tests for peripheral blood lymphocyte subsets and peripheral blood CD19 B cell expression. Data such as concomitant medications and vital signs will be recorded at each follow-up.

⑦ Extended follow-up phase: This phase is a post-study follow-up with no strict scheduled plan. Patients are advised to undergo necessary laboratory and imaging tests at our center or local medical institutions every 3 to 6 months on their own initiative. The research team will continuously follow up on the patient’s basic vital signs and disease changes via phone calls, text messages, WeChat, etc.

5.3.2Data Integrity

① Data Collection for Routine Clinical Visits

This study will use paper-based Case Report Forms (CRFs) for data collection, the Epidata database for data management, and the double-entry comparison method for data entry and verification, with corresponding data validation and cleaning conducted. During the study period, researchers will, in principle, review the trial data once a month to ensure internal consistency.

② Sending Reminder Messages to Subjects

Automated reminder messages will be sent to subjects in advance via WeChat groups, text messages, or phone calls to minimize sample

loss caused by loss to follow-up and/or withdrawal.

5.4Technical Route Chart

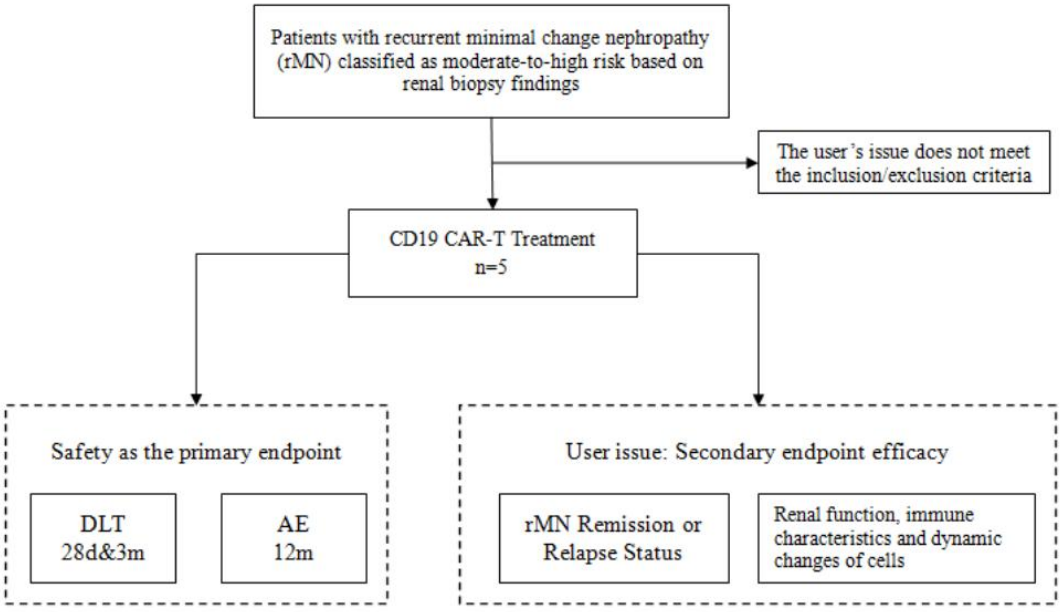

Figure 2 Technical Roadmap

6.Observation Items and Testing Time Points

6.1Primary Observation Endpoints

Safety is defined as the primary evaluation index of the study, including the type and incidence of dose-limiting toxicity (DLT) within 28 days and 3 months after a single CAR-T infusion, as well as the type and incidence of adverse events (AEs) within 12 months.

6.1.1Dose-Limiting Toxicity (DLT)

① Definition: The DLT evaluated in this study is assessed within two time windows: 28 days (Day 0 to Day 28) and 3 months (Day 28 to Month 3) after CAR-T cell infusion. These time windows are selected based on the typical timeline of CAR-T cell expansion, activity, and

potential occurrence of major toxicities in vivo.

The determination of DLT must meet all the following criteria:

- DLT must be an adverse event judged by the investigator as probably or definitely related to CAR-T cell infusion, and cannot be attributed to underlying diseases, comorbidities, or toxicities from concomitant medications;
- The adverse event must reach a severity grade of ⩾ Grade 3 (per CTCAE v5.0) or ⩾ Grade 3 specific toxicity grading criteria (e.g., IEC-HS grading).

② For AEs occurring within 28 days and 3 months, DLT is defined if any of the following conditions are met:

- Uncontrolled Grade 3 or ⩾ Grade 4 cytokine release syndrome (CRS);
- Uncontrolled Grade 3 or ⩾ Grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS);
- Death caused by CRS or ICANS of any grade;
- Any ≥ Grade 3 non-hematological toxicity, including but not limited to: Grade 3 or higher cardiac toxicity (myocarditis, heart failure), pulmonary toxicity (acute respiratory distress syndrome), hepatotoxicity, nephrotoxicity (acute kidney injury), allergic reactions, etc.;
- Persistent ≥ Grade 4 cytopenia lasting more than 28 days,

excluding other causes such as disease progression or bone marrow involvement. Examples include: white blood cells (WBC) < 1.0×10^9/L; neutrophils (NEU) < 0.5×10^9/L, etc.;

- Any fatal adverse event related to CAR-T therapy;
- Any CAR-T-related ≥ Grade 3 toxicity that cannot resolve or be controlled within 28 days;
- Any other severe toxicity deemed clinically significant by the investigator or sponsor, which would be sufficient to limit dose escalation in the future.

③ Toxicities that are expected in the study and easily manageable (even if reaching Grade 3 or higher) will not be defined as DLT. Excluded toxic events include:

- Controlled Grade 3 CRS: effectively controlled and reduced to ⩽ Grade 2 within 72 hours with standard supportive therapy (tocilizumab and/or corticosteroids);
- Controlled Grade 3 ICANS: effectively controlled and reduced to ⩽ Grade 2 within 72 hours with standard supportive therapy (corticosteroids);
- Transient and easily manageable laboratory abnormalities that resolve or are effectively controlled to ≤ Grade 2 within 28 days after treatment, such as transient Grade 3 cytopenia.

6.1.2 Adverse Events (AEs)

Severity grading is based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0:

Grade 1: Mild; asymptomatic or mild symptoms; only clinically or diagnostically detectable; no treatment required.

Grade 2: Moderate; requires minor, local, or non-invasive treatment; limitation in age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; results in hospitalization or prolongation of existing hospitalization; disabling; limitation in self-care activities of daily living.

Grade 4: Life-threatening; requires urgent treatment.

Grade 5: Death related to complications.

6.2.Secondary Endpoints

Secondary endpoints focus on efficacy evaluation, including the status of refractory membranous nephropathy (rMN) such as complete remission (CR), partial remission (PR), no remission (NR), or recurrence; the proportion of subjects maintaining CR or PR after cell infusion, duration of remission, and recurrence; as well as changes in renal function, immune characteristics, and cellular dynamics: proteinuria, estimated glomerular filtration rate (eGFR), serum anti-PLA2R antibodies, infection markers, complements, immunoglobulins, cytokine levels, blood cells, changes in peripheral blood immune cell subsets, and the expression level of CD19 on the surface of peripheral blood B cell

subsets, etc.

6.2.1Remission or recurrence of rMN

The proportion of subjects with maintained remission, partial remission, or no remission of rMN after cell infusion, the duration of rMN remission, and the recurrence of rMN.

① Definition of rMN CR: Disappearance of the patient’s clinical symptoms and signs; urine protein reduced to <0.3 g/day or UACR <300 mg/g; with normal levels of serum albumin (ALB) and serum creatinine (Scr).

② Definition of rMN PR: Improvement in clinical symptoms and signs; urine protein decreased by more than 50% compared with baseline, and reduced to 0.3–3.5 g/day or UACR 300–3500 mg/g.

③ Definition of rMN immunological remission: PLA2R antibody titer below the ELISA detection threshold (2 RU/mL) or negative result in indirect immunofluorescence assay.

④ Definition of rMN NR: Insufficient reduction or persistently high proteinuria, or deterioration of renal function, failing to meet the criteria for remission, partial remission, or immunological remission as mentioned above.

⑤ Definition of rMN recurrence: After NR or PR, the patient’s urine protein rises again to >3.5 g/day or UACR >3500 mg/g; frequent recurrence is defined as more than 2 recurrences within 6 months or more

than 4 recurrences within 12 months.

6.2.2 Changes in renal function, immune characteristics, and cellular dynamics

Changes in the subjects' serum urea (BUN), serum creatinine (Scr), cystatin C (CysC), estimated glomerular filtration rate (eGFR), urine protein, urine microalbumin/creatinine ratio (UACR), serum anti-PLA2R antibodies, complements, immunoglobulins, cytokine levels, blood cells, C-reactive protein (CRP), CAR copy parameters, peripheral blood immune cell subsets, and the expression level of CD19 on the surface of peripheral blood B cell subsets during the study period.

6.2.3 Testing Time Points

The testing time points for primary and secondary endpoints during the study are shown in Tables 3 and 4, respectively.

Table 3. Testing Time Points for Primary Endpoints (Safety)

Outcome Measurement	Measurement Description	Time Frame
Type and incidence of DLT in rMN subjects after a single infusion of CD19 CAR-T cells	Refer to the definition of DLT in the study protocol	28 days and 3 months after infusion
Type and incidence of AE in rMN subjects after a single infusion of CD19 CAR-T cells	Severity graded according to CTCAE V5.0	12 months after infusion

Table 4. Testing Time Points for Secondary Endpoints (Efficacy)

Outcome Measurement	Measurement Description	Time Frame
Overall response rate (CR+PR) in rMN subjects after cell infusion	CR+PR	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if

		applicable) after infusion
Proportion of rMN subjects achieving CR after cell infusion	Refer to the CR definition in the protocol	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Proportion of rMN subjects achieving PR after cell infusion	Refer to the PR definition in the protocol	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Proportion, frequency, and time of disease recurrence in rMN subjects after cell infusion	Refer to the recurrence definition in the protocol	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in eGFR from baseline in rMN subjects after a single infusion of CD19 CAR-T cells	Estimated glomerular filtration rate, calculated using the CKD-EPI 2021 formula	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in urine protein from baseline in rMN subjects after a single infusion of CD19 CAR-T cells	24-hour urine protein quantification	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in UACR from baseline in rMN subjects after a single infusion of CD19 CAR-T cells	Random urine	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in serum anti-PLA2R antibody from baseline in rMN subjects after a single infusion of CD19 CAR-T cells	Venous blood	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in serum renal function from baseline in rMN subjects after a single infusion of CD19 CAR-T cells	Venous blood, Scr, CysC	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in blood cells in rMN subjects after a single infusion of CD19 CAR-T cells	Venous blood, routine blood test	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if

		applicable), Month 24 (if applicable) after infusion
Change in CRP in rMN subjects after a single infusion of CD19 CAR-T cells	Venous blood	Day 2, Day 7, Day 10 or 14, Day 21, Day 28 (1 month) after infusion
Change in complements in rMN subjects after a single infusion of CD19 CAR-T cells	Serum complements C3, C4	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in immunoglobulins in rMN subjects after a single infusion of CD19 CAR-T cells	IgE、IgA、IgG、IgM	Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in CAR copy parameters in rMN subjects after a single infusion of CD19 CAR-T cells	Parameters related to CAR copy number	Day 2, Day 5, Day 7, Day 10 or 14, Day 21, Day 28 (1 month), Month 2, Month 3, Month 6, Month 9, Month 12, Month 18 (if applicable), Month 24 (if applicable) after infusion
Change in ferritin in rMN subjects after a single infusion of CD19 CAR-T cells	Ferritin level	Day 2, Day 7, Day 10 or 14, Day 21, Day 28 (1 month) after infusion
Change in cytokines in rMN subjects after a single infusion of CD19 CAR-T cells	Cytokine panel	Day 2, Day 7, Day 10 or 14, Day 21, Day 28 (1 month) after infusion
Change in peripheral blood lymphocyte subsets in rMN subjects after a single infusion of CD19 CAR-T cells	Peripheral blood lymphocyte subset count	Day 2, Day 5, Day 7, Day 10 or 14, Day 21, Day 28 (1 month) after infusion
Expression level of CD19 on the surface of peripheral blood B cell subsets in rMN subjects after a single infusion of CD19 CAR-T cells	Using flow cytometry method	Day 2, Day 5, Day 7, Day 10 or 14, Day 21, Day 28 (1 month) after infusion

7.Observation and Management of Adverse Events

7.1 Lymphodepletion Period

Lymphodepleting pretreatment (hereinafter referred to as "lymphodepletion") is required before CAR-T cell infusion to create a

favorable immune environment for CAR-T cells, enhance their expansion, persistence, and clinical activity, while reducing anti-CAR immune responses. Potential complications of lymphodepletion include pancytopenia, immunosuppression, infection, hemorrhagic cystitis, liver and kidney injury, etc. During this period, the subject's vital signs and 24-hour fluid intake/output will be monitored daily, and complete blood count, liver and kidney function, etc., will be monitored every 1–2 days.

7.2 After CAR-T Cell Infusion

After CAR-T cell infusion, patients require close clinical monitoring to evaluate the efficacy and safety of treatment. Common adverse reactions associated with CAR-T cell therapy include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), tumor lysis syndrome (TLS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), CAR-T cell-associated anaphylaxis (CARAC), immune complex-associated hemolytic transfusion (ICAHT), B-cell aplasia, hypogammaglobulinemia, infection, allergic reactions, and abnormal proliferation of CAR-T cells, etc. This study refers to the CSCO Guidelines for CAR-T Cell Therapy in Hematologic Malignancies (2024 Edition) and the Chinese Expert Consensus on Chimeric Antigen Receptor T-Cell Therapy for Refractory Autoimmune Neurological Diseases (2025 Edition) to assess potential CAR-T cell therapy-related

DLTs and AEs during the study, and formulate corresponding clinical prevention and management protocols.

7.2.1Cytokine Release Syndrome (CRS)

The possibility of CRS should be considered if any of the following 4 symptoms or signs appear: (1) Fever, with a body temperature ≥38°C; (2) Hypotension, with a systolic blood pressure <90 mmHg (1 mmHg = 0.133 kPa); (3) Arterial oxygen saturation <90%; (4) Presence of organ toxicity. For specific grading, refer to the CRS grading method of the American Society for Transplantation and Cellular Therapy [21].

Table 5. Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
Hypotension	None	Present, no vasopressor needed	Vasopressor ± vasopressin needed	Multiple vasopressors needed (excluding vasopressin)
Hypoxemia	None	Present, low-flow nasal cannula oxygen required	High-flow nasal cannula, face mask, or Venturi mask oxygen required	Positive-pressure ventilation needed (e.g., CPAP, BiPAP, intubation, or mechanical ventilation)

Note: CRS-related organ toxicity can be graded according to CTCAE v5.0 but does not affect CRS grading. Fever is defined as a body temperature ≥38°C and not attributed to any other causes. For CRS patients receiving antipyretic therapy or anti-cytokine treatments such as tocilizumab or steroids, subsequent CRS severity grading no longer requires the presence of fever. Low-flow nasal cannula oxygen: ≤6 L/min; high-flow nasal cannula oxygen: >6 L/min.

Table 6. Management Measures for CRS

Grade	Symptom or Sign	Management
1	Fever (body temperature ≥38°C)	• Fluid replacement • Symptomatic antipyretic therapy: physical cooling, drugs such as acetaminophen or ibuprofen • Rule out infection: blood/urine culture, chest imaging, etc. • If the patient has neutropenia, prophylactic antibiotics are given; G-CSF can be used, GM-CSF is contraindicated • If fever persists (>3 days) or is refractory, tocilizumab (8mg/kg) can be administered; if symptoms do not improve, it can be repeated after 8 hours (no more than 3 times recommended) • If CRS does not improve after 24 hours of treatment, dexamethasone 5~10mg qd can be administered or upgraded to Grade 2 management
2	Hypotension or hypoxemia	• Fluid replacement, anti-infection • If tocilizumab has not been used, it can be administered (same as Grade 1 usage) • If 1~2 doses of tocilizumab do not improve CRS, dexamethasone 10mg q12h or qd for 1~3 days, reduce the dose as soon as possible after symptom improvement • If no improvement after 24 hours of dexamethasone treatment, manage as Grade 3 • Low-flow oxygen inhalation (if needed) • Anti-infection treatment
3	Hypotension or hypoxemia	• Consider transfer to ICU • Fluid replacement, potent anti-infection • Vasopressors (if needed) • If tocilizumab has not been used previously, it can be administered (8mg/kg, same as Grade 1 usage) • Dexamethasone 10~20mg q.6h. for 1~3 days, reduce the dose as soon as possible after symptom improvement • High-flow oxygen inhalation (if needed)
4	Hypotension or hypoxemia	• Transfer to ICU • High-flow oxygen or mechanical ventilation • Fluid replacement, potent anti-infection • Multiple vasopressors (if needed) • High-dose glucocorticoid therapy (e.g., methylprednisolone 1g/d × 3 days, gradually reduce the dose) • Tocilizumab (if applicable) • Continuous monitoring and supportive treatment

Note: The maximum single dose of tocilizumab is 800 mg, and repeat administration is allowed. If CRS does not improve or even worsens within 24 hours

after treatment, the management measures should be escalated to the next grade. Early intervention with tocilizumab and steroids will not affect the expansion and efficacy of CD19 CAR-T cells in vivo.

7.2.2Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS presents with diverse clinical manifestations. Early symptoms often include decreased attention, language impairment, and reduced writing ability, among which testing writing ability is a relatively simple and sensitive method to assess ICANS progression. Most patients experience reversible ICANS symptoms, while a few may develop severe clinical manifestations such as seizures, confusion, and increased intracranial pressure. In the most severe cases, it can progress to acute cerebral edema, where patients may deteriorate from mild lethargy to unconsciousness within hours, and further progression can lead to death. For specific grading, refer to the ICANS grading method of the American Society for Transplantation and Cellular Therapy [21].

Symptoms and signs of ICANS typically appear 3–6 days after CAR-T cell infusion, peak on days 7–8, and gradually improve over time, with complete resolution within 2–3 weeks [22]. In this study, in addition to closely monitoring the patient's blood routine, blood biochemistry, coagulation function, ferritin, and cytokine levels, once investigators or clinicians suspect ICANS, cerebrospinal fluid examination, cranial CT/MRI, and electroencephalogram will be

performed based on the subject ' s condition after excluding contraindications.

Table 7. Grading of ICANS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7-9	3-6	0-2	0 (Patient is unarousable and unable to undergo ICE scoring)
Altered Level of Consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulation	Unarousable or requires vigorous/repeated stimulation; coma
Seizure ‡	N/A	N/A	Focal/generalized seizure with rapid resolution; or non-convulsive seizure (EEG) with resolution after intervention	Sustained seizure (>5 minutes) or recurrent seizures without return to baseline
Motor Impairment	N/A	N/A	N/A	Deep focal motor weakness (e.g., hemiparesis, paresis)
Increased Intracranial Pressure/Cerebral Edema§	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema; decorticate/decerebrate state; cranial nerve VI palsy; papilledema; Cushing's triad

Note: ICANS grading is determined by the most severe event not attributed to any other causes. Baseline ICE levels should be considered and scored before CAR-T infusion.

*Patients with an Immune Effector Cell-Associated Encephalopathy (ICE) score of 0 who have complete aphasia while awake are classified as Grade 3 ICANS, whereas patients with an ICE score of 0 who are unarousable are classified as Grade 4 ICANS. Detailed scoring criteria: Orientation (4 points): year, month, city, hospital;

Naming (3 points): 3 objects (e.g., clock, pen, button); Following commands (1 point): e.g., extending two fingers, closing eyes, and sticking out tongue; Writing (1 point): ability to write a standard sentence (e.g., "Our national flag is the Five-Star Red Flag"); Attention (1 point): counting backward from 100 by 10s.

†No other causes (e.g., no use of sedative drugs).

‡Tremors and myoclonus related to immune effector cell therapy can be graded according to CTCAE v5.0 but do not affect the score.

§Intracranial hemorrhage or cerebral infarction with or without edema is not considered a feature of neurotoxicity and is excluded from ICANS grading. It can be graded according to CTCAE v5.0.

Table 8. Management Measures for ICANS

Grade	Recommended Management Measures
1	• When swallowing function is impaired: switch oral medications and nutrition to intravenous infusion • For agitated patients: low-dose lorazepam or haloperidol for sedation • Neurology consultation • Funduscopic examination (to assess papilledema) • Cranial imaging (enhanced MRI/CT) • Optional lumbar puncture (to detect intracranial pressure, cytokines, CAR-T cell count) • Electroencephalogram (EEG) examination • Preventive treatment: - Dexamethasone 5-10mg (if likely to progress to severe neurotoxicity) - Levetiracetam (for seizure prevention) • When complicated with CRS: tocilizumab 8mg/kg (for those not previously treated with anti-IL-6 therapy), can be repeated after 8 hours (total ≤2-3 doses)
2	• Same symptomatic treatment and examinations as Grade 1 • When complicated with CRS: tocilizumab used as in Grade 1 • When anti-IL-6 is ineffective or not complicated with CRS: - Dexamethasone 10mg q6-12h or - Methylprednisolone 1mg/kg q12h (rapid dose reduction after symptoms decrease to Grade 1) • When complicated with ≥Grade 2 CRS: recommend transfer to ICU• Imaging examination: repeat every 2-3 days
3	• Same symptomatic treatment and examinations as Grade 1 • Immediately transfer to ICU with mechanical ventilation support• High-dose steroid therapy: - Methylprednisolone 1g/d × 3 days → gradual dose reduction (250mg q12h

	× 2 days → 125mg q12h × 2 days → 60mg q12h × 2 days) • Anti-IL-6 treatment principle same as Grade 3 • When glucocorticoids are unresponsive: consider anakinra (IL-1 receptor antagonist)

Note: Since tocilizumab binds to the IL-6 receptor, it causes an increase in serum free IL-6 levels and further elevates IL-6 concentration in the cerebrospinal fluid, which may exacerbate neurotoxicity. In the management of ICANS, the use of glucocorticoids is more important than that of tocilizumab.

7.2.3Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS)

IEC-HS is a syndrome of pathological and biochemical hyperinflammatory responses independent of CRS and ICANS, characterized by the following features:

(1) Manifesting characteristics of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH);

(2) Attributed to immune effector cell therapy;

Exacerbated or new-onset cytopenia, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminase abnormalities. Additionally, IEC-HS is generally considered a delayed manifestation following the management of CRS.

IEC-HS is defined as a syndrome based on pathological and biochemical hyperinflammatory states occurring after immune effector cell therapy, specifically macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH). The occurrence of IEC-HS is independent of CRS and ICANS, accompanied by new-onset or

exacerbated cytopenia, hyperferritinemia, coagulopathy with hypofibrinogenemia, and elevated transaminases, among other features. Furthermore, IEC-HS is generally regarded as a delayed manifestation following the management of CRS.

Table 9. Diagnostic Criteria for IEC-HS*

Common Findings†	• Elevated ferritin (>2×ULN or baseline at infusion) and/or rapidly rising (clinical assessment) • Exacerbated inflammatory response after initial improvement or resolution of CRS treatment • Elevated liver transaminases (>5×ULN with normal baseline)[§] or >5×baseline (with abnormal baseline)‡ • Hypofibrinogenemia (<150mg/dl or <LLN)# • Hemophagocytosis in bone marrow or other tissues# • New-onset, exacerbated, or refractory grade 4 cytopenia in ≥1 cell line&
Other Findings	• Elevated lactate dehydrogenase (>ULN) • Coagulation abnormalities (e.g., elevated PT/APTT) • Elevated direct bilirubin • New-onset splenomegaly • Fever（new-onset※or persistent#） • Central nervous system toxicity • Pulmonary manifestations (hypoxia, pulmonary infiltration, pulmonary edema) • New-onset renal insufficiency • Hypertriglyceridemia (fasting >265mg/dl)#

Note: ULN: upper limit of normal; LLN: lower limit of normal.

*Diagnosis is only made if it cannot be attributed to other etiologies (including CRS, infection, and/or disease progression).

†Refers to a cluster of symptoms occurring concurrently (e.g., all symptoms appear within 72 hours).

‡Although most IEC-HS cases are associated with CRS, this is not absolute.

§Meets the criteria for Grade 3 transaminase elevation in CTCAE v5.0.

#Refer to HLH-2004.

&Usually refers to Grade 4 cytopenia in at least one blood cell line (platelets, neutrophils, hemoglobin).

※Differentiate from initial onset or recurrence of CRS.

Table 10. Grading of IEC-HS

Grade	Severity of Symptoms and Intervention Measures
1	Asymptomatic or mild symptoms • Only observation and clinical assessment required • Continuous clinical monitoring
2	Mild to moderate symptoms • Medical intervention required (e.g.: - Immunosuppressive therapy (for IEC-HS) - Transfusion support for asymptomatic hypofibrinogenemia)
3	Severe symptoms (not immediately life-threatening) • Aggressive treatment required (e.g.: - Hemorrhagic coagulopathy requiring transfusion support - Hospitalization required due to new-onset acute renal injury/hypotension/respiratory distress)
4	Life-threatening symptoms requiring urgent intervention (e.g.: life-threatening bleeding or hypotension, respiratory distress requiring intubation, or acute renal injury requiring dialysis)
5	Death

Table 11. Management Measures for IEC-HS

Treatment Level	Recommended Regimen
First-line Treatment	• Anakinra (200–800mg/day) • With and/or glucocorticoids: - Dexamethasone 10–40mg/day - Or methylprednisolone 1000mg/day
Second-line Treatment	• If no remission within 48 hours: - Increase the dose of first-line drugs - Adopt dual-drug therapy (anakinra + glucocorticoid) - May add JAK-2 inhibitor (e.g., ruxolitinib 5–10mg/day)
Third-line Treatment	• Add JAK-2 inhibitor • May consider: - γ-interferon monoclonal antibody (emapalumab) - CTLA-4 agonist (e.g., abatacept) - CD52 antibody (alemtuzumab) • Etoposide (50–100mg/m²) is applicable for primary HLH and secondary HLH
Rescue Treatment	Rapidly progressive/life-threatening high-grade IEC-HS: - After failure of first/second-line treatment - May consider TKI (e.g., dasatinib) as a third-line option

Note: Due to the lack of prospective studies and data on IEC-HS treatment methods, treatment considerations are derived from expert consensus opinions. The

consensus mentions that there are currently multiple options for third-line and subsequent treatment regimens. Therefore, if IEC-HS occurs in the study, investigators or clinicians will adopt corresponding treatment methods based on the patient's specific conditions.

Table 12. Supportive Therapy for IEC-HS

Treatment Type	Recommended Management Measures
Monitoring	• Daily monitoring: - Complete blood count, coagulation function, fibrinogen - Routine assessment for patients with abnormal liver and kidney function • Infection monitoring: - Blood/urine/sputum cultures (bacteria, viruses, fungi) - Detection of other infection sources (e.g., bronchoalveolar lavage fluid, cerebrospinal fluid) • HLH-related parameters: - Soluble CD25, NK cell function, triglycerides - Bone marrow smear, IFN-γ, CXCL9/CXCL10, IL-10/IL-18
Cytopenia	• Maintain hemoglobin >7g/dl • Maintain platelets >50×10⁹/L (in case of active bleeding or coagulation dysfunction) • Consider G-CSF when ANC <0.5×10⁹/L (controversial) • Patients with menorrhagia are recommended to consult gynecology
Coagulation Dysfunction	• Maintain fibrinogen: - >100mg/dl (without bleeding) - >150mg/dl (with bleeding) • Supplement vitamin K when INR >1.5 • Administer cryoprecipitate and FFP when INR >2 • Use venous thromboembolism prophylaxis drugs with caution
Infection Management	• Empirical anti-infective therapy • Rule out infectious causes of sHLH • Prophylactic anti-infective therapy is required during immunosuppressive treatment • Regular infection monitoring

7.2.4 CAR-T-Associated Coagulopathy (CARAC)

CRS can cause coagulation dysfunction in patients. The principles of management include early identification, accurate assessment, removal of inducing factors, and stratified intervention based on CRS grading. The

reference management methods for CARAC are as shown in the following table.

Table 13. Management Measures for CARAC

CRS Grade	CARAC Management	Preventive and Supportive Treatment	Preventive/Anti-infective Treatment	Anti-inflammatory and Hepatoprotective Treatment	Promote Platelet Production
1	• Assess coagulation indicators: If normal: Observe. If abnormal: ① Increase the frequency of coagulation indicator monitoring ② WHO bleeding score③ Closely monitor CRS	√	√	√	√
2	• Assess coagulation indicators: If improved: Observe. If not improved: ① Increase monitoring frequency② WHO bleeding score + DIC score ② Control CRS (cytokine antagonists + glucocorticoids) ④ Alternative and anticoagulant treatment	√	√	√	√
3	• Assess coagulation indicators: If improved: Observe. If not improved: ① Increase monitoring frequency ② WHO bleeding score + DIC score ③ Strengthen CRS	√	√	√	√

	control (increase glucocorticoid dose/frequency) ④ Focus on alternative treatment ⑤ Adjust the plan in a timely manner				
4	• Assess coagulation indicators: If improved: Observe If not improved: ① Increase the monitoring frequency ② WHO bleeding score + DIC score ③ Strengthen CRS control (combination of multiple methods) ④ Replacement therapy + plasma exchange	√	√	√	√

7.2.5 Immune Effector Cell-Associated Hematotoxicity (ICAHT)

Some patients may experience pancytopenia, which can persist for half a year or even longer. Close attention should be paid to the increased risk of infection during the period of cytopenia. If necessary, hematopoietic stimulating factors should be administered, and blood products such as packed red blood cells and platelets should be transfused.

Table 14. Grading Criteria for ICAHT

Grading	Grade I	Grade II	Grade III	Grade IV
Early ICAHT ≤ 30 days				
ANC ≤ 500/μl	<7 days	>7–13 days	≥14 days	Never > 500/μl
ANC ≤ 100/μl	—	—	≥7 days	≥14 days
Late ICAHT > 30 days				
ANC ≤ 1 500/μl	√			
ANC ≤ 1 000/μl		√		

ANC ≤ 500/μl			√	
ANC ≤ 100/μl				√

Note: ANC, absolute neutrophil count, measured multiple times, not transient reduction.

Table 15. Risk Stratification Score for CAR-HEMATOTOX

Assessment Indicator	0 Point	1 Point	2 Points
Platelet Count	>175×10^9/L	75-175×10^9/L	<75×10^9/L
Absolute Neutrophil Count	>1.2×10^9/L	<1.2×10^9/L	—
Hemoglobin	>90g/L	<90g/L	—
C-Reactive Protein	<30mg/L	≥30mg/L	—
Ferritin	<650ng/ml	650-2,000ng/ml	>2,000ng/ml

Note: Low risk: 0–1 point; High risk: >2 points. Assess the incidence of hematotoxicity and infection based on results before lymphodepletion (–5 days, with a 3-day grace period). The incidence of hematotoxicity and infection is significantly increased in high-risk patients.

Table 16. Management Methods for Short-Term ICAHT Management

Management Measure	Time	Method	Precautions	Remarks
Infusion of Packed Red Blood Cells (pRBC) or Platelets	Based on the patient's specific cytopenia risk profile	For pRBC, consider using one product each time to reduce iron overload	Irradiate blood products or filter out white blood cells; start 7 days before apheresis and continue until at least 90 days after CAR-T administration	Flu may affect irradiated blood products
Prophylactic Use of G-CSF	High-risk ICAHT patients should use prophylactically on Day +2	G-CSF 5μg/kg qd	Low-risk ICAHT patients may not need G-CSF	Reduce the risk of febrile neutropenia (without increasing the risk of ≥Grade 3 CRS or ICANS)
Intermittent	When ANC <	5 μg/kg qd,	-	Neutropenic

Use of G-CSF	500/μl	consider 10 μg/kg if no response		patients with intermittent recovery respond rapidly, while aplastic patients have no response
Bacterial Prophylaxis	Consider prophylactic treatment when ANC < 500/μl	G- bacteria: third/fourth generation cephalosporins, enzyme inhibitors; G+ bacteria: vancomycin, teicoplanin, etc.	Pay attention to colonization of pathogens such as MRD and CRE	Adjust according to the bacterial epidemiology of the medical center and the patient's place of residence
Viral Prophylaxis	From the start of lymphodepletion conditioning until 1 year after CAR-T and/or $CD4^+$ > 0.2×10^9/L	Valacyclovir 500mg bid or Acyclovir 800mg bid	-	-
Pneumocystis Prophylaxis	From the start of lymphodepletion conditioning until 1 year after CAR-T and/or CD4 > 0.2×10^9/L	Cotrimoxazole 480mg qd or 960mg tiw	For allergic patients, pentamidine, dapsone or atovaquone can be selected	-
Fungal Prophylaxis	Neutropenia lasting 1-3 months	Posaconazole 300mg/d or Caspofungin 500mg i.v./d	Prophylaxis is recommended for patients with a history of invasive aspergillosis or long-term use of corticosteroids	–

Note: Subjects with baseline cytopenia, occurrence of grade >3 CRS or ICANS,

long-term use of glucocorticoids, and high-risk CAR-HEMATOTOX score may have a higher risk of infection.

7.2.6 B-cell Deficiency / Hypogammaglobulinemia

B-cell aplasia is defined as a disease caused by depletion or absence of B cells. The mechanism of CAR-T-induced B-cell aplasia is the on-target off-tumor effect and off-target effects of CD19-targeted CAR-T cell therapy. Usually, it is because the target is a shared target, which is also expressed in normal tissues and will be recognized and attacked by CAR-T, resulting in toxicity. This type of toxic side effect is relatively common in CAR-T, and its severity is related to the expression of the target in normal tissues and the criticality of its function. It can reduce B-cell count and the level of gamma immunoglobulins.

Currently, there are not many reported cases of off-target toxicity in CAR-T clinical practice. The possible reason is that most single-chain antibodies (scFv) used in CARs are high-affinity monoclonal antibodies, and many antibody drugs themselves have been used clinically, proving good safety, thus ensuring the safety of CAR-T. However, attention still needs to be paid to its off-target effects after CAR-T cell infusion. Studies have shown that hypogammaglobulinemia may occur at different time periods after CAR-T infusion, with an incidence of about 67% after 90 days, and a few patients even have it for several years. The main clinical manifestation is frequent infection.

(1) Calculation method of absolute B-cell count: Absolute B-cell

count = Total white blood cell count × Lymphocyte percentage × (CD19+ or CD20+) percentage.

Definition / Range: Absolute B-cell count < 61 cells/ml; IgG ⩽ 400 mg/dl.

(2) Management strategy: Intravenous infusion of human immunoglobulin (5g × 3 days, intravenous drip) for replacement therapy.

(3) Infusion frequency: Once a month after CAR-T infusion until B cells return to the normal range or 6 months after CAR-T infusion; high-risk populations continue once a month until high-risk factors are eliminated and globulin levels return to normal. For high-risk populations with IgG ⩽ 400 mg/dl accompanied by severe infection, persistent infection, or recurrent infection, pay attention to regular monitoring of serum IgG, IgM, IgA, and the number of (CD19+ or CD20+) B cells in peripheral blood, etc.

Table 17. Grading and Management Measures for B-cell Deficiency / Hypogammaglobulinemia

Grading	Management Measures
Any Grade	• It is recommended to receive influenza and COVID-19 vaccines • Viral prophylaxis and PCP prophylaxis (continue until 6-12 months after CAR-T infusion and/or CD4 cell count > 200/μl) • High-risk patients* consider antifungal prophylaxis (such as posaconazole), including those receiving corticosteroid therapy for CRS/ICANS
Grade 1(Asymptomatic)	• No special intervention required • Symptomatic supportive treatment
Grade	• Consider IVIG replacement therapy when IgG ≤ 400mg/dL

2(Symptomatic, Non-urgent)	• Targeted anti-infection treatment in case of infection
Grade 3(Requires Urgent Intervention)	
Grade 4(Life-threatening)	

*High-risk criteria for fungal infection (meeting ≥2 items): ANC ≤ 0.5×10^9/L before infusion, CAR-T dose > 2×10^7/kg.

7.2.7 Infection

The incidence of various types of infections after CAR-T cell therapy is approximately 55%, among which severe infections of grade >3 account for about 33%. Most infections occur within 1 to 2 years after CAR-T cell therapy, with the incidence reaching as high as 40% within 1 month after treatment. Depending on the infection site, non-specific symptoms such as fever, cough, expectoration, and hypotension may occur after CAR-T therapy; in severe cases, systemic symptoms like hypotension and hypoxia can develop.The increased risk of infection is associated with the following factors: number of previous treatments, infections within the recent 100 days, use of glucocorticoids or tocilizumab, febrile neutropenia, CD22-targeted CAR-T cell therapy, and hypogammaglobulinemia. Other potential risk factors for early severe infections include ICANS, as well as the use of tocilizumab and corticosteroids.

（1）Infection Screening

Table 18. Infection Screening to Be Completed Before Subject Enrollment / CAR-T Cell Infusion

	Items
Routine Examination	Medical history inquiry and physical examination, infectious diseases (invasive fungal disease, hepatitis, syphilis, AIDS, tuberculosis), and other important disease histories
Laboratory Examination	Routine blood, urine, and stool tests, ESR, liver and kidney functions, electrolytes, immunoglobulins, procalcitonin, C-reactive protein, detection of cytokines such as IL-6 (baseline)
Etiological Examination	HCV, HBV, HIV, TP, EBV, CMV, COVID-19 detection; add HSV/VZV, JCV, respiratory-related viruses, mycoplasma, G/GM test, Mycobacterium tuberculosis when necessary based on the patient's condition
Imaging Examination	High-resolution chest CT, abdominal ultrasound or CT, echocardiogram, cranial MRI (when necessary)

（2） Infection Prevention

The peak period of infection generally occurs within 8 weeks after CAR-T cell infusion, decreases with time, and can last for 1 to 2 years after treatment. The mortality rate of concurrent infection during the CRS phase is high; therefore, infection prevention and control is a top priority in CAR-T cell therapy.

The management of infections in subjects during this study mainly refers to the Chinese Expert Consensus on Prevention, Diagnosis, and Treatment of Infections Related to Chimeric Antigen Receptor T-Cell Therapy (2022 Edition). Acyclovir or valacyclovir is administered at the start of lymphodepletion, and the duration of medication is determined according to the recovery of immune function. From CAR-T cell infusion until granulocyte recovery, norfloxacin, triazole antifungals, and compound sulfamethoxazole tablets are given for infection prophylaxis (for patients allergic to quinolones, sulfonamides, etc., they can be replaced with penicillins, cephalosporins, or macrolide antibiotics).

Table 19. Infection Prophylaxis Regimen During CAR-T Therapy

Infection Type	Drugs and Dosage	Duration of Medication	Note
Bacterial	-	-	There is currently no evidence-based medicine to support routine bacterial prophylaxis during immunotherapy
Viral*	• Acyclovir 400mg q12h orally •Or 5mg/kg q12h intravenously	From the start of lymphodepletion conditioning until 6 months after CAR-T infusion; high-risk patients† extend to 1 year	•Routine prophylaxis •Strengthen monitoring for high-risk patients
Invasive Fungal	• Fluconazole 400mg qd •Filamentous fungal prophylaxis: – Posaconazole 200mg tid p.o. (suspension) –Or 300mg qd p.o. (tablet, bid on the first day) – Micafungin 50mg qd i.v.	Until neutrophil count returns to normal	• All patients: Fluconazole prophylaxis •High-risk patients:Add filamentous fungal prophylaxis
Pneumocystis	•First choice: Cotrimoxazole (TMP/SMX 160/800mg) bid twice a week •Alternative: Pentamidine 300mg nebulized once a month	Start 1 week before infusion until CD4 cell count > 200/μl	All patients need prophylaxis

*Monitoring of CMV and EBV: For patients with CMV and EBV serological IgG+, IgM-, viral PCR monitoring should be performed every 1-3 months during treatment. Patients with chronic HBV or HCV infection should be managed jointly with hepatologists to develop a reasonable management process.

†Recently received steroid/tocilizumab treatment.

（3） Infection Management

① Principles for managing infections during treatment.

Table 20. Principles for Managing Infections During CAR-T Therapy

Grading	Management Measures
Any Grade	• Prophylactic antiviral and Pneumocystis pneumonia prophylaxis (continue until 6-12 months after CAR-T infusion and/or CD4 cell count > 200/μl) •High-risk patients consider antifungal prophylaxis •G-CSF can be used in patients with neutropenia lasting >7 days after CRS
Grade 1(Mild Infection)	• Supportive treatment • Empirical anti-infection therapy when febrile: - Antibacterial: e.g., levofloxacin/ciprofloxacin - Antifungal: e.g., fluconazole - Antiviral: e.g., valacyclovir/acyclovir
Grade 2(Requires Oral Antibiotics)	• Oral antibacterial drugs for the full course of treatment
Grade 3(Severe Infection)	• Intravenous use of antibacterial drugs • Systemic anti-infection treatment
Grade 4(Life-threatening)	• Intensive care support

② Management of Infections Under Special Conditions During Treatment

a.Differentiation Between CRS and Infection

The two conditions share similar clinical manifestations, but there are currently no specific biomarkers to clearly distinguish them. Concurrent CRS and infection may also occur, so predicting their occurrence and development and grasping the timing of intervention are crucial. No significant differences in cytokine levels have been observed between CRS grades and infection severity. When CRS is complicated by severe infection, a secondary elevation in IL-6 levels may occur. Cytokines such as IL-8, IL-1 β , and IFN can be used to attempt differentiation, but sufficient clinical data and evidence are still lacking. If the two cannot be clearly distinguished, the guiding principle is

prophylactic anti-infection combined with CRS grade-based treatment.

b.Monitoring of Special Infections

Infections include tuberculosis, histoplasmosis, listeriosis, and nocardiosis. Investigators and clinicians should pay attention to medical history inquiry, especially when conventional anti-infection therapy is ineffective, and consider the possibility of infection with such special pathogens.

c.Patients Diagnosed with COVID-19

If a patient develops COVID-19 from enrollment to CAR-T cell infusion, CAR-T cell therapy should be postponed. For asymptomatic patients, CAR-T infusion should be postponed for ≥14 days from the date of the first positive nucleic acid test. For patients with mild symptoms, CAR-T infusion should be postponed for ≥14 days starting from the time when symptoms improve and fever resolves for at least 24 hours without the use of antipyretic drugs. If the patient has persistent positive nucleic acid tests, unrelieved or progressively worsening symptoms, they should withdraw from the study after evaluation by the research team.

7.2.8 Allergic Reactions

Allergic reactions usually present as rashes within 2 weeks after cell infusion, which fade when pressed and can resolve spontaneously in 3-5 days. In addition to allergies, the causes may include increased capillary

endothelial fragility induced by cytokine release, with or without thrombocytopenia, which requires comprehensive evaluation based on multiple indicators. Drug allergies may result from components of in vitro culture reagents during CAR-T production, viral vector impurities, or T cell activation caused by unresolved inflammatory background before CAR-T infusion.

Management measures for CAR-T-related allergic reactions during the study mainly include: excluding patients with hypersensitivity or allergic reactions at enrollment; strictly controlling procedures and reagents during CAR-T cell manufacturing; prophylactic use of anti-allergic drugs (such as diphenhydramine or promethazine); and close monitoring of patients' vital signs and symptoms within 14 days after CAR-T cell infusion.

7.2.9 Abnormal Proliferation of CAR-T Cells

Within 28 days after CAR-T cell infusion, the in vivo expansion of CAR-T cells in peripheral blood will be monitored. Blood samples will be collected every 2-3 days in the first week and then once a week. Specific time points are: Day 2, Day 5, Day 7, Day 10 or 14, Day 21, and Day 28 after infusion.

Diagnostic criteria for abnormal proliferation of CAR-T cells: peripheral blood white blood cell count >10×10^9/L; lymphocyte percentage in white blood cells ≥70%; absolute count of CAR-T

cells >600/μl.

When abnormal proliferation of CAR-T cells is suspected in a patient, glucocorticoids and other immunosuppressants (such as antithymocyte globulin or anti-CD52 antibody) should be administered. Patients with severe conditions may be treated with a combination of two or more immunosuppressants.

8.Quality Control and Quality Assurance of the Study

Investigators will be responsible for screening subjects in accordance with inclusion and exclusion criteria, recording study data in the Case Report Form (CRF), and entering study data into the electronic database. At the same time, they will maintain close contact with subjects in strict accordance with time nodes to avoid enrolling ineligible subjects, spontaneous withdrawal of subjects, or subjects not receiving treatment at all. Specialized personnel will independently conduct study monitoring, data management, safety monitoring, and statistical analysis. Once the quality assurance procedures are completed, the database will be locked.

9.Statistical Analysis

All statistical analyses will not consider factors such as poor subject compliance, premature withdrawal, or loss to follow-up. Due to the small sample size of this study, all data will be presented as individual values. Descriptive statistical methods will be used to report specific parameters at baseline and during follow-up. Statistical analyses and data

visualization will be performed using SPSS 27.0 and GraphPad Prism 9.0.

Baseline characteristics will be listed case by case by individual ID, including age, gender, pathological classification, baseline urinary protein, anti-PLA2R antibody level, etc.

Changes in continuous variables (e.g., laboratory indicators) will be recorded in individual follow-up value tables by subject ID and/or displayed as multi-time point line graphs (timeline graphs [from infusion day to D+n days]). Categorical variables will be labeled according to individual status (e.g., CR/PR/NR). Safety events will be listed by individual, including toxicity type, grade, onset time, duration, intervention measures, and outcome.

Since the sample size is only 5 cases, all findings are descriptive and do not represent generalizable inferences.

10.Ethics of Clinical Research

This clinical research will adhere to relevant regulations such as the World Medical Association's Declaration of Helsinki. Before the initiation of the study, the trial protocol must be approved by the Ethics Committee before the clinical research can be conducted. Prior to each subject's enrollment in this study, investigators are obligated to fully and comprehensively inform the subject or their legal representative of the purpose, procedures, potential benefits, and risks of the study, and obtain

a written informed consent form. Subjects should be made aware that they have the right to withdraw from the study at any time. The informed consent form shall be retained as a clinical research document for future reference. During the study, the personal privacy and data confidentiality of subjects will be protected.

11. Study Schedule

August 1, 2025 – October 31, 2025: Preliminary preparation, study protocol design, investigator meeting, ethics committee review, and trial registration.

November 1, 2025 – March 31, 2026: Trial initiation, patient enrollment and follow-up, monitor visits, data collection, management of blood samples and adverse adverse events.

April 1, 2026 – July 31, 2028: Data aggregation, data storage, statistical analysis and processing, manuscript writing and publication, and result reporting.

12.References

[1] DANTAS M, SILVA L B B, PONTES B T M, et al. Membranous nephropathy [J]. Jornal brasileiro de nefrologia, 2023, 45(2): 229-43.

[2] KERI K C, BLUMENTHAL S, KULKARNI V, et al. Primary membranous nephropathy: comprehensive review and historical perspective [J]. Postgrad Med J, 2019, 95(1119): 23-31.

[3] HOU J H, ZHU H X, ZHOU M L, et al. Changes in the Spectrum of Kidney Diseases: An Analysis of 40,759 Biopsy-Proven Cases from 2003 to 2014 in China [J]. Kidney diseases (Basel, Switzerland), 2018, 4(1): 10-9.

[4] WANG M, YANG J, FANG X, et al. Membranous nephropathy: pathogenesis and treatments [J]. MedComm (2020), 2024, 5(7): e614.

[5] SETHI S, BECK L H, JR., GLASSOCK R J, et al. Mayo Clinic Consensus Report on Membranous Nephropathy: Proposal for a Novel Classification [J]. Mayo Clin Proc, 2023, 98(11): 1671-84.

[6] ALSHARHAN L, BECK L H, JR. Membranous Nephropathy: Core Curriculum 2021 [J].

American journal of kidney diseases : the official journal of the National Kidney Foundation, 2021, 77(3): 440-53.

[7] DENG L, XU G. Update on the Application of Monoclonal Antibody Therapy in Primary Membranous Nephropathy [J]. Drugs, 2023, 83(6): 507-30.

[8] ROJAS-RIVERA J, FERVENZA F C, ORTIZ A. Recent Clinical Trials Insights into the Treatment of Primary Membranous Nephropathy [J]. Drugs, 2022, 82(2): 109-32.

[9] FERVENZA F C, APPEL G B, BARBOUR S J, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy [J]. N Engl J Med, 2019, 381(1): 36-46.

[10] GAUCKLER P, SHIN J I, ALBERICI F, et al. Rituximab in Membranous Nephropathy [J]. Kidney Int Rep, 2021, 6(4): 881-93.

[11] KITCHING A R, JAW J. Chimeric antigen receptor T (CAR T) cells: another cancer therapy with potential applications in kidney disease and transplantation? [J]. Kidney Int, 2018, 94(1): 4-6.

[12] ALBINGER N, HARTMANN J, ULLRICH E. Current status and perspective of CAR-T and CAR-NK cell therapy trials in Germany [J]. Gene Ther, 2021, 28(9): 513-27.

[13] MACKENSEN A, MULLER F, MOUGIAKAKOS D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus [J]. Nature medicine, 2022, 28(10): 2124-32.

[14] MULLER F, TAUBMANN J, BUCCI L, et al. CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up [J]. N Engl J Med, 2024, 390(8): 687-700.

[15] LI Y R, LYU Z, CHEN Y, et al. Frontiers in CAR-T cell therapy for autoimmune diseases [J]. Trends Pharmacol Sci, 2024, 45(9): 839-57.

[16] YANG C, SUN C, TAN B, et al. Allogeneic anti-CD19 CAR-T cells induce remission in refractory systemic lupus erythematosus [J]. Cell Res, 2025.

[17] WANG X, WU X, TAN B, et al. Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis [J]. Cell, 2024, 187(18): 4890-904 e9.

[18] WANG W, HE S, ZHANG W, et al. BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: a phase 1 open-label clinical trial [J]. Annals of the rheumatic diseases, 2024, 83(10): 1304-14.

[19] HOXHA E, REINHARD L, STAHL R A K. Membranous nephropathy: new pathogenic mechanisms and their clinical implications [J]. Nature reviews Nephrology, 2022, 18(7): 466-78.

[20] KOLLNER S M S, SEIFERT L, ZAHNER G, et al. Strategies Towards Antigen-Specific Treatments for Membranous Nephropathy [J]. Frontiers in immunology, 2022, 13: 822508.

[21] LEE D W, SANTOMASSO B D, LOCKE F L, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells [J]. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, 2019, 25(4): 625-38.

[22] LEUKEMIA, LYMPHOMA GROUP C S O H C M A, GROUP OF HEMATOPOIETIC STEM CELL T, et al. [Consensus of Chinese experts on the clinical management of chimeric antigen receptor T-cell-associated neurotoxicity (2022)] [J]. Zhonghua Xue Ye Xue Za Zhi, 2022, 43(2): 96-101.