Informed Consent Form

Project:	Safety and Efficacy of Chimeric Antigen Receptor T-CellImmunotherapy (CAR-T)in the Treatment of Refractory Membranous Nephropathy
Undertaking Institution:	Department of Nephrology, The First Affiliated Hospital of Air Force Medical University (Xijing Hospital)
Principal Investigator:	He Lijie
Study Period:	August 1, 2025 - July 31, 2028
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Dear Patient,

You are being invited to participate in a "single-center prospective exploratory clinical trial." This study is led by Associate Professor He Lijie. The research will strictly adhere to the Declaration of Helsinki and relevant laws and regulations of China.

Before you decide whether to participate in this clinical study, please read the following content carefully. It will help you fully understand the purpose of the study, the procedures and duration, as well as the potential benefits, risks, and discomforts that may arise from participating. You may discuss this with your relatives or friends and consult the doctor in charge of the study, who will explain any questions you have about the research to help you make a final decision.

1.Research Background

This study is a clinical research exploring the safety and efficacy of chimeric antigen receptor T-cell immunotherapy (CAR-T) in the treatment of refractory membranous nephropathy. The following is background information about the study, which we hope will help you understand its significance.

Membranous nephropathy is a common autoimmune kidney disease. Its fundamental cause is that the body's immune system (mainly B cells) produces autoantibodies that attack the kidneys, leading to kidney damage and severe proteinuria. Currently, first-line treatments for this disease, such as calcineurin inhibitors, cyclophosphamide, and rituximab, are all immunosuppressive drugs aimed at eliminating antibody-producing B cells. However, approximately one-third of patients respond poorly to existing treatments, becoming "refractory" cases and facing the risk of deteriorating renal function. Therefore, there is an urgent need to find new treatment options for this group of patients.

CAR-T therapy is a new type of precise immunotherapy. Its basic principle is to extract the patient's own T cells from their blood, modify them in vitro using genetic engineering technology to enable them to accurately recognize and eliminate specific abnormal cells in the body (such as B cells that produce harmful antibodies), and then infuse these modified cells back into the patient's body. An important potential advantage of this therapy is that the infused cells may survive long-term in the body, making it possible to achieve long-term efficacy with a single treatment.

In recent years, following its success in cancer treatment, CAR-T therapy has also been applied in the field of autoimmune diseases. Preliminary studies have shown that it has achieved encouraging results in the treatment of autoimmune diseases such as systemic lupus erythematosus, with an overall controllable safety profile. The most common adverse reaction is "cytokine release syndrome," which is usually mild to moderate.

Given that membranous nephropathy is also a B cell-mediated autoimmune disease, we hypothesize that CAR-T therapy may also bring hope to patients with refractory membranous nephropathy. Therefore, we plan to conduct this study to preliminarily evaluate the safety and efficacy of CAR-T therapy in the treatment of refractory membranous nephropathy.

2.Research Purpose

Currently, patients with refractory membranous nephropathy who are unresponsive to first-line immunotherapy or targeted therapy face a significantly increased risk of progressing to end-stage kidney disease. Therefore, there is an urgent need to further explore effective therapeutic approaches for this condition. The achievements of CAR-T cells in clinical studies of autoimmune diseases suggest their considerable potential and promising application prospects in refractory membranous nephropathy. Thus, the purpose of our study is to preliminarily investigate the safety and efficacy of CAR-T therapy in refractory membranous nephropathy through a prospective, small-sample clinical trial, aiming to provide a better therapeutic strategy for this disease.

3.Research Design

This study is a single-center, small-sample exploratory clinical trial initiated by the research team led by Associate Professor He Lijie from the Department of Nephrology, Xijing Hospital.

On the basis of receiving standard symptomatic and supportive therapy, you will undergo a single dose of autologous CD19 CAR-T cell therapy.You will need to undergo peripheral blood mononuclear cell (PBMC) collection 1-4 weeks prior to CAR-T cell therapy. The sorting, purification, T cell activation, CAR gene transduction,

and in vitro expansion of CAR-T cells will be performed by Shaanxi Yisaier Biotechnology Co., Ltd. After undergoing processes including washing, formulation, cryopreservation, testing, and release, the cells will be transported to the laminar air flow ward via cold chain for intravenous infusion.3-7 days before CAR-T cell therapy, you will receive lymphodepleting chemotherapy 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 tested. If the depletion effect is unsatisfactory, fludarabine (Flu) 25 mg/m² /day will be administered for 1-2 days.More than 2 days after lymphodepleting chemotherapy, you will receive CD19 CAR-T cell infusion at a dose of 1×10^{6} cells/kg. Prior to intravenous cell infusion, prophylactic administration of antihistamines (such as chlorpheniramine or diphenhydramine) and acetaminophen will be given. Subsequently, you will be hospitalized for observation in the laminar air flow ward for at least 10 days. If you experience severe adverse events such as grade 3 or higher cytokine release syndrome (CRS) during this period, the hospitalization time will be extended to 14 days.The planned follow-up period for the entire study is 1 year, and long-term follow-up after the study conclusion will be continued indefinitely.

3.1 Inclusion Criteria

(1) Diagnosed with primary membranous nephropathy (PMN) by renal biopsy;

(2) Refractory membranous nephropathy with intermediate or high risk;

(3) Patients aged ≥ 18 years old;

(4) Estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73m² , without severe abnormalities in cardiac, hepatic, or pulmonary function;

(5) Signed a written informed consent form.

3.2 Exclusion Criteria

(1) Secondary membranous nephropathy;

(2) Active bacterial, fungal, or viral infections (excluding common cold/influenza) requiring intravenous antibiotics, active pulmonary tuberculosis, or seropositivity 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 conditions:

a. Previous receipt of any cell therapy (e.g., mesenchymal stem cells);

b. 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 conditions deemed by the investigator to potentially increase risks, interfere with assessments, or affect compliance.

3.3 Criteria for Terminating the Study

The criteria for subject withdrawal from the study include:

(1) Occurrence of severe adverse events during the lymphocyte depletion phase;

(2) Severe intolerable reactions during CAR-T cell infusion;

(3) Subject loss to follow-up or death;

(4) Voluntary withdrawal request from the subject or their legal guardian;

(5) Assessment by researchers that continuation of the trial is inappropriate.

4.Study Process

1. Before you are enrolled in the study, the doctor will inquire about and document your medical history, and assess your condition. If you meet the inclusion criteria and

voluntarily agree to participate in the study, you will sign an informed consent form. If you choose not to participate, it will not result in any bias against you or affect your medical care.

2. If you voluntarily participate in the study, the process will proceed as follows:If you are eligible for inclusion, you may voluntarily participate in the study and sign the informed consent form. The physician will administer CAR-T cell therapy in accordance with standard procedures.

The main intervention measures include:

(1) Peripheral blood mononuclear cell (PBMC) collection. A blood component separator will be used to collect your blood and isolate the fraction containing T cells. The expected blood collection volume is 120 ml, with a minimum of no less than 50 ml. During the collection, the blood flow rate will be set at 50~70 ml/min. If necessary, the collection staff will adjust the flow rate based on actual collection conditions, and the entire collection process is expected to take 2~4 hours.

（2）Lymphodepleting chemotherapy. The study will adopt the cyclophosphamide ± fludarabine regimen. After a comprehensive assessment of your condition confirms that you can tolerate lymphodepleting chemotherapy, cyclophosphamide will be administered at a dose of 400 mg/d via intravenous injection for two consecutive days, with a total dose of 800 mg. On the third day, the degree of peripheral blood lymphodepletion will be tested. If the depletion effect is unsatisfactory, fludarabine may be added at a dose of 25 mg/m² /d for 1 – 2 days.

（3） Autologous CD19 CAR-T cell infusion. Acetaminophen derivatives and antihistamines (such as chlorpheniramine or diphenhydramine) will be administered 30 – 60 minutes prior to infusion. The CD19 CAR-T cell injection will be delivered via intravenous infusion using filter-free infusion tubing to prevent the loss of effective cellular components and subsequent reduction in therapeutic 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 your tolerance; if no adverse reactions occur, the rate can be adjusted to 5 – 10 ml/min.

Additionally, you will need to complete regular follow-up visits during the study period. The main follow-up schedule is as follows:

（1）Intensive Follow-up Phase. A total of 3 follow-up visits are planned. The first post-discharge follow-up (Follow-up 1) will be conducted on Day 28 after infusion. Planned laboratory tests include routine blood and urine tests, liver and kidney function tests, coagulation function tests, C-reactive protein (CRP), procalcitonin (PCT), anti-PLA2R antibodies, ferritin, complement, immunoglobulin, cytokines, peripheral blood lymphocyte subsets, urine albumin-to-creatinine ratio (UACR), and 24-hour urinary protein quantification. The subsequent second and third follow-up visits (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 tests, anti-PLA2R antibodies, complement, immunoglobulin, peripheral blood lymphocyte subsets, peripheral blood CD19 B-cell expression, CAR copy number, UACR, and 24-hour urinary protein quantification. Concomitant medications, vital signs, and other relevant data will also be recorded during each follow-up visit.

（2）Medium and Long-term Follow-up Phase. Between Month 3 and Month 12 after treatment, follow-up visits will be conducted every 3 months, totaling 3 planned visits: Follow-up 4 (Month 6 after treatment), Follow-up 5 (Month 9 after treatment), and Follow-up 6 (Month 12 after treatment). Follow-up 6 will also serve as the study conclusion visit. Planned laboratory tests for each follow-up include routine blood and urine tests, liver and kidney function tests, anti-PLA2R antibodies, complement, immunoglobulin, CAR copy number, UACR, and 24-hour urinary protein quantification. Additionally, peripheral blood lymphocyte subsets and peripheral blood CD19 B-cell expression detection will be performed at Follow-up 4. Concomitant medications, vital signs, and other relevant data will also be recorded during each follow-up visit.

（3）Extended Follow-up Phase. This phase is a post-study follow-up with no strict follow-up schedule. Patients are advised to voluntarily complete necessary laboratory and imaging examinations at our center or local medical institutions every 3 to 6 months. The research team will continuously follow up on patients' basic vital signs and disease changes via telephone, short message service (SMS), WeChat, and other means.

In addition, during different study phases, you will need to cooperate with the collection of data and information including but not limited to: signing of the informed consent form, medical history information, physical examination, electrocardiogram (ECG)/echocardiography, renal assessment, routine examinations, concomitant medication records, and endpoint outcome assessment.

（1）Demographic data. Including name, gender, date of birth, ethnicity, educational background, occupation, marital status, current address, and contact information.

（2）Concomitant medication records. Mainly including the use of drugs related to blood pressure lowering, lipid regulation, blood glucose lowering, immunomodulation, adjuvant therapy, and vaccination.

（3）Vital signs. Mainly including heart rate, blood pressure, body temperature, etc.

3. Other Matters Requiring Your Cooperation

During the conduct of the study, new information regarding the research methods may emerge. If new information becomes available, your study physician will promptly inform you and discuss with you whether you wish to continue participating in the study. If you decide to continue participating, you may be required to sign a new informed consent form. During the follow-up phase, the physician may obtain information about your condition through telephone calls, outpatient follow-up visits, or other means.

5.Risks and Discomforts

If you experience any discomfort, new changes in your condition, or any unexpected events during the study—whether related to the study or not—please promptly notify your study physician. He/she will make an assessment and provide appropriate medical treatment.

Prior to CAR-T cell infusion, lymphodepleting conditioning (hereinafter referred to as "lymphodepletion") is required. This creates a favorable immune environment for CAR-T cells, enhancing their expansion, persistence, and clinical activity while reducing anti-CAR immune responses. Potential complications of lymphodepletion include pancytopenia, immunosuppression, infection, hemorrhagic cystitis, and liver or kidney injury. During this period, your vital signs and 24-hour fluid intake/output will be monitored daily, and complete blood count (CBC), liver and kidney function tests, etc., will be performed every 1–2 days.

Common side effects after CAR-T cell infusion include cytokine release syndrome (CRS), 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/hypogammaglobulinemia, infection, allergic reaction, and abnormal CAR-T cell proliferation.

To date, severe adverse reactions have been reported infrequently in clinical trials of CAR-T cell therapy for patients with autoimmune diseases. No life-threatening or fatal cases have been reported, which may be related to the lower B-cell antigen load in patients with autoimmune diseases compared to those with B-cell malignancies. Nevertheless, current clinical trials and subjects of CAR-T cell therapy for glomerulonephritis, especially membranous nephropathy, remain very limited, and safety data need to be interpreted cautiously. For potential adverse reactions, this study has formulated corresponding clinical prevention and management protocols with reference to the Chinese Society of Clinical Oncology (CSCO) Guidelines for CAR-T Cell Therapy in Hematological Malignancies (2024 Edition) and the Expert Consensus on Chimeric Antigen Receptor T-Cell Therapy for Refractory Autoimmune Diseases of the Nervous System in China (2025 Edition). The research team will also closely monitor and assess dose-limiting toxicities and adverse reactions related to CAR-T cell therapy that you may experience during the clinical period, and provide active management.

6.Potential Benefits of Study Participation

Direct Benefits:If you participate in this study, your disease condition may improve after CAR-T therapy (though this is not guaranteed). You will also receive systematic observation and treatment follow-up, enabling timely assessment of your disease to maximize disease progression control and improve outcomes.

Indirect Benefits:We aim to leverage the information obtained from your participation to benefit future patients with the same condition. This will provide new insights and treatment options for optimizing the therapy and management of refractory membranous nephropathy.

7.Research Costs

If you agree to participate in this clinical trial, all costs incurred during peripheral blood mononuclear cell (PBMC) collection, lymphodepleting chemotherapy, CAR-T therapy, and hospitalization in the laminar air flow ward will be covered. This includes expenses for medications, nursing care, laboratory tests, and imaging studies. Within 12 months after CAR-T cell infusion, any additional costs beyond the routine clinical care plan that arise from the study will be borne by the researchers. These include fees for tests such as serum ferritin, complement, immunoglobulin, cytokines, peripheral blood lymphocyte subsets, peripheral blood CD19 B cell expression, and CAR copy number detection, as well as additional imaging studies in the follow-up plan (including echocardiography, renal/renal vascular color Doppler ultrasound, and chest CT).

For patients with refractory membranous nephropathy, adherence to standardized treatment and regular examinations is still required to maximize treatment effectiveness, even if they do not participate in the study. Costs such as examination fees, medication fees, and treatment fees incurred during routine clinical care will be paid by you in accordance with the hospital's billing procedures.

8.Compensation and Indemnification for Research

During the study period, physicians will make every effort to treat your disease and prevent or reduce complications. Regular follow-up is required both during the study and disease treatment. In the event of study-related harm, compensation will first be covered by the clinical trial liability insurance purchased by the researchers. Any excess amount beyond the insurance coverage will be compensated by Shaanxi Yisai'er Biotechnology Co., Ltd. in accordance with relevant laws and regulations.

9.Alternative Therapies

Participation in this study is not mandatory for the diagnosis and treatment of your disease. Alternative methods are available for such management, including other symptomatic and supportive treatments. Their benefits and risks are associated with the specific treatment plan — you may achieve control or relief of relevant complications, but may also experience common adverse reactions of the treatment. Your study physician will inform you of the specific examination or treatment options, explain the potential benefits and risks of accepting other alternatives, and answer all your questions.

10.Confidentiality of Personal Information

All information collected in this study will be kept confidential at the hospital. To protect your identity, any information related to you in the study documents will be labeled with a standardized code instead of your name. All collected and aggregated data from participants will have any personally identifiable information removed, ensuring that the information cannot be linked to a specific study participant.

The Ethics Committee and regulatory authorities may directly access participants' original medical records to verify clinical trial procedures and/or data, provided this complies with applicable laws and regulations and does not infringe on participants' privacy (the sponsor is not permitted to access such records). By signing the informed consent form, you or your legal representative authorize such access. To the extent permitted by applicable laws and/or regulations, records containing your identifying information will remain confidential and will not be disclosed to the public. Results of this study may be published in medical journals, shared for scientific purposes, or used by the sponsor for product research or improvement — however, your identity and personal information will never be revealed under any circumstances.

11.Withdrawal from the Research

During the study, the research physician will prioritize your best interests. If it is determined that you are no longer suitable to continue participating in the trial — including cases of disease recurrence, intolerable toxic reactions, severe adverse events, or if the sponsor, Ethics Committee, or national regulatory authorities require trial termination — the research physician will proactively explain the reasons to you and discontinue your participation. Your participation in this study is entirely voluntary. You have the right to choose not to participate, and you may withdraw at any time without penalty, loss of benefits, or any impact on your subsequent treatment. If you plan to withdraw from the study, please inform your research physician promptly. For your safety, they will conduct a comprehensive examination and provide necessary follow-up care. If the researchers obtain any information that may affect your continued participation in the trial, they will promptly notify you or your legal guardian.

12.Contact Person and Contact Information

You may obtain information and updates related to this study at any time. If any new safety information relevant to the study emerges, we will notify you promptly. If you have questions about the study, experience any discomfort or injury during

participation, or have inquiries regarding the rights and interests of study participants, you may contact Researcher He Lijie via phone at 13488317261.

13.Contact Information of the Ethics Committee

If you have any questions or requests regarding your rights, interests, or health related to participating in this study, you may contact the Ethics Committee of Xijing Hospital at the telephone number: 029-8477179.

Informed Consent Signature Page for Study Participants

I have carefully read the above Informed Consent Form and understand the purpose of the study, as well as the potential benefits and risks of participation. The researcher has clearly explained all medical terms contained herein. I have been given the opportunity to ask questions, and all my questions have been answered in a clear and understandable manner. I may choose not to participate in this study, or withdraw at any time by notifying the responsible physician, without any impact on my medical treatment or rights and interests. The responsible physician may terminate my continued participation in the study if I require other treatments, fail to comply with the study protocol, suffer study-related harm, or for any other legitimate reason.

I have read the above Informed Consent Form and received a copy, and my physician has provided me with a detailed explanation. I voluntarily participate in this clinical trial.

Subject's Full Name (in Regular Script)：__

Subject's Phone Number：_____

Subject's Signature：_____ Date：_____

Note: If the subject lacks capacity for civil conduct, the guardian shall sign; if the subject has limited capacity for civil conduct, both the subject and their guardian shall sign.

Guardian's Full Name in Block Letters：_____Relationship with the Subject：_____

Guardian's Signature：_____ Guardian's Telephone Number：____

Date：_____

Impartial Witness's Signature (if applicable)：_____Date：_____

Note: If the subject or their guardian is illiterate, an impartial witness shall be required to sign. The impartial witness shall read the Informed Consent Form and other written materials, and witness the informed consent process.

I confirm that I have fully explained the relevant content of this clinical trial to the patient, including the potential benefits and risks for the patient, and have answered all questions raised by the patient.

Investigator's Signature (Block Letters)：_____ Date：_____

Investigator's Telephone Number：_____Date：_____