Exploratory Study of Anti-BCMA–CD19 CAR-T Cell Therapy in Relapsed or Refractory IgG4-Related Disease

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Informed Consent Form

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Dear Mr./Ms. _____:

We invite you to participate in an investigator-initiated exploratory clinical study entitled “Anti-BCMA-CD19 CAR-T Cell Injection for the Treatment of Relapsed/Refractory IgG4-Related Disease.”

This Informed Consent Form provides information to help you decide whether to participate. Please take sufficient time to read it carefully. It contains the study background, objectives, methods, possible benefits and risks, and your rights and protections. If you have any questions or do not understand certain terms, please discuss them with the study doctor to ensure you fully understand.

If you agree to participate, please sign this Informed Consent Form and keep a copy signed by both parties. Participation is entirely voluntary. This study has been reviewed and approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

1. Why is this study being conducted?

Background:

Immunoglobulin G4–related disease (IgG4-RD) is an increasingly recognized immune-mediated chronic fibroinflammatory disorder that can involve nearly any organ system in the body, including the pancreas (autoimmune pancreatitis), bile ducts, salivary glands, lacrimal glands, orbits, retroperitoneum, lungs, kidneys, aorta, and lymph nodes. The disease is characterized pathologically by dense lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and marked tissue infiltration by IgG4-positive plasma cells.

Although glucocorticoids are typically effective as first-line induction therapy, a considerable proportion of patients relapse upon tapering or discontinuation (up to 30%–50%). Long-term use of glucocorticoids (GCs) carries the risk of serious adverse effects (e.g., metabolic disorders, osteoporosis, increased infection risk),

which is a major clinical challenge. This is particularly concerning because the patient population is predominantly middle-aged to elderly, with common comorbidities such as diabetes mellitus and osteoporosis that exacerbate GC-related toxicity.

To reduce steroid exposure, maintain long-term disease remission, and improve prognosis, it is crucial to identify safe and effective alternative or adjunctive therapies. Given that the immunopathogenesis of IgG4-RD is heavily dependent on B lymphocytes and plasma cells, existing research has demonstrated that rituximab (an anti-CD20 monoclonal antibody) is an effective first-line treatment option. Rituximab depletes CD20+ B cells, effectively inducing remission and significantly reducing GC requirements. However, some patients relapse during the B-cell reconstitution phase after rituximab therapy, suggesting that residual B-cell subsets or pathogenic B-cell precursors may reignite inflammation and tissue damage after treatment cessation. Thus, despite the benefits of B-cell depletion therapy, IgG4-RD remains challenged by high relapse rates after drug withdrawal and suboptimal responses in some patients.

CAR-T cell therapy has emerged as a potent and targeted therapeutic strategy, with its rationale based on several key points:

1. **Plasmablasts express CD19** – Plasmablasts are critical pathogenic cells in IgG4-RD and generally express the CD19 surface antigen. Rituximab targets CD20, which is present on mature B cells and some plasmablasts (although CD20 is lost in many plasmablasts), but is ineffective against CD19-positive plasmablasts and more differentiated long-lived plasma cells that are CD20-negative. Targeting CD19 may enable more complete elimination of CD19+ plasmablasts.
2. **Pathogenic long- and short-lived plasma cells express BCMA** – B-cell maturation antigen (BCMA) is highly expressed on terminally differentiated plasma cells, including long-lived plasma cells (primarily in the bone marrow) and short-lived plasma cells (at peripheral inflammatory sites). In IgG4-RD, IgG4 production within affected tissues primarily derives from short-lived plasma cells differentiated from plasmablasts. These IgG4-secreting plasma cells usually have low or absent CD19 expression but high BCMA expression. Targeting BCMA can effectively deplete these cells, which continuously produce pathogenic IgG4 antibodies.

Anti–BCMA–CD19 CAR-T cell therapy enables deep and sustained B-cell depletion. While rituximab cannot eliminate all IgG4-producing plasmablasts and plasma cells (especially CD19−CD20−BCMA+ plasma cells), dual-target CAR-T therapy can eradicate both CD19+ plasmablasts and BCMA+ long-/short-lived plasma cells. With strong tissue penetration, it can achieve profound depletion of the pathogenic B-cell lineage, cutting off abnormal IgG4 secretion at its source. Furthermore, CAR-T cells can persist in vivo for months or even years, providing ongoing immune surveillance to eliminate regenerating pathogenic B-cell clones, potentially achieving longer-lasting remission and reducing relapse rates. Deep depletion of pathogenic B cells/plasma cells may also disrupt the self-reactive T–B cell cycle, allowing reconstitution of a healthier immune system.

In recent years, there have been multiple reports worldwide of CAR-T cell therapy in autoimmune diseases, with some patients experiencing symptom improvement or sustained remission.

In summary, cellular immunotherapy has become one of the innovative approaches for autoimmune disease treatment, offering controllable safety and durable efficacy, and warrants further clinical investigation.

2. Study Objectives

This is a prospective, exploratory clinical trial conducted in patients with relapsed or refractory IgG4-related disease (IgG4-RD).

If eligible for infusion, participants will receive anti-BCMA–CD19 CAR-T cells at a starting dose of 1×10^6 CAR-T cells/kg (with a permissible total cell count variation of ±20%).

The objective of this study is to evaluate the safety and efficacy of anti-BCMA–CD19 CAR-T cell injection in the treatment of relapsed/refractory IgG4-RD.

Cyclophosphamide is a commonly used immunosuppressive agent in autoimmune diseases, with a well-recognized adverse event profile (e.g., nausea) and good patient acceptance. In the field of cell therapy, cyclophosphamide is typically used for lymphodepleting preconditioning, in combination with fludarabine, to enhance lymphodepletion and reduce immune rejection. Previous studies have shown that cyclophosphamide plus fludarabine is well tolerated and effective for lymphodepletion in various immune-mediated diseases. Therefore, this study adopts a cyclophosphamide–fludarabine combination as the lymphodepletion regimen.

The main study period consists of:

- **Screening phase:** Day −45 to Day −21
- **Autologous CAR-T cell manufacturing phase:** Day −20 to Day −6
- **Lymphodepletion chemotherapy and rest/observation phase:** Day −5 to Day −1
- **Cell infusion and primary endpoint observation phase:** Day 0 to Week 26 post-infusion

After completion of the main study (end of study, EOS), participants may enter an **extension observation phase** (Week 27 to Week 52 post-infusion) according to their preference.

3. Study Content

This is a prospective exploratory clinical trial in patients with relapsed/refractory IgG4-RD.

If eligible, you will receive 1×10^6 CAR-T cells/kg as the starting dose (±20% variation allowed).

Cyclophosphamide plus fludarabine will be used for lymphodepletion prior to infusion.

4. Study Procedures

This study has a total duration of approximately 1 year, with a follow-up period ranging from 6 months to 1 year. There will be 19 scheduled visits during which you will be required to undergo examinations, attend follow-up visits as scheduled, and report any changes in your condition.

The main study procedures are divided into five phases:

1. **Screening period**
2. **Autologous CAR-T cell manufacturing period**
3. **Lymphodepletion chemotherapy (if applicable) and rest/observation period (if applicable)**
4. **Cell infusion and primary endpoint observation period**
5. **Follow-up period**

After the main study concludes (end of study, EOS), you may choose to enter an **extension observation period** at your discretion.

Screening period:

Demographic information, medical history/treatment history/medication history, height, and weight will be collected. You will also undergo vital signs measurement, physical examination, IgG4-RD Responder Index assessment, pulse oximetry, and laboratory testing (including infection screening, complete blood count, serum chemistry, coagulation profile, urinalysis, serum pregnancy test, inflammatory markers, cardiac enzymes, B-cell CD19 and BCMA expression, lymphocyte subsets, immunoglobulin levels, complement C3 and C4). Additional assessments include immune reconstitution, dominant clone detection, echocardiography, and 12-lead electrocardiogram (ECG).

Based on the investigator's judgment, you may also undergo ESR, autoantibody testing, chest CT, pulmonary function tests, CT/MRI/PET-CT/B-ultrasound of affected sites, and other imaging assessments. Eligibility will be confirmed according to inclusion and exclusion criteria. Participants meeting all criteria will proceed to lymphodepletion and observation/cell infusion; those not meeting criteria will be informed of the reasons and alternative treatment options will be discussed.

Autologous CAR-T cell manufacturing period:

Tests performed within 2 weeks before or after leukapheresis may be accepted as baseline without repetition. During this period, vital signs, physical examination (if needed), pulse oximetry, IgG4-RD Responder Index, cytokine testing, pharmacokinetic (PK) sampling, and laboratory tests (CBC, chemistry, coagulation, urinalysis, inflammatory markers, cardiac enzymes, lymphocyte subsets, immunoglobulin, C3/C4, ESR if needed) will be performed, as well as ECG.

Lymphodepletion and rest/observation period:

You will be hospitalized. Prior to lymphodepletion, weight, vital signs, CBC, physical examination (if needed), and IgG4-RD Responder Index will be performed.

Chemotherapy doses will be calculated according to your height and weight. After lymphodepletion, you will have a 2-day rest/observation period, during which vital signs, physical examination (if needed), pulse oximetry, cytokines, PK sampling, and laboratory tests (CBC, chemistry, coagulation, urinalysis, inflammatory markers, cardiac enzymes, lymphocyte subsets, immunoglobulin, C3/C4, autoantibodies, ESR if needed), ECG, and ICE score will be collected.

Cell infusion and primary endpoint observation period:

You will receive a single intravenous infusion of BCMA–CD19 CAR-T cells, followed by 26 weeks of treatment observation. On the day of infusion, vital signs and

pulse oximetry will be measured pre- and post-infusion; a physical examination may also be performed as clinically indicated.

At Days 4, 7, 10, 14, 21, 28, Weeks 8, 12, 16, 20, and 26 post-infusion: physical examination (if needed), vital signs, pulse oximetry, laboratory tests (CBC, inflammatory markers, cardiac enzymes, lymphocyte subsets), cytokines, PK sampling (if needed), immune reconstitution, and dominant clone assessment (if needed).

ICE scores will be assessed on Days 7, 14, 21, and 28. On Days 14, 28, Weeks 8, 12, 16, 20, and 26, additional labs will include chemistry, coagulation, urinalysis, immunoglobulin, C3/C4, ECG, pulmonary function (if needed), ESR (if needed), chest CT (if needed), autoantibodies (if needed), and efficacy evaluation. Imaging of lesions will be performed at Weeks 8 and 12.

Extension observation period:

If you opt to participate, at Weeks 38 and 52 post-infusion, physical examination (if needed), vital signs, IgG4-RD Responder Index, laboratory tests (cardiac enzymes, CBC, chemistry, coagulation, urinalysis, inflammatory markers, autoantibodies, immunoglobulin, C3/C4, lymphocyte subsets), immune reconstitution, dominant clone (if needed), ECG, cytokines (if needed), PK sampling (if needed), pulmonary function (if needed), ESR (if needed), chest CT (if needed), imaging of lesions, ICE score (if needed), and efficacy evaluation will be conducted.

Early termination procedures:

If you withdraw, physical examination, vital signs, ECG, laboratory tests (cardiac enzymes, CBC, chemistry, coagulation, urinalysis, inflammatory markers, autoantibodies, immunoglobulin, C3/C4, lymphocyte subsets, pregnancy test [women of childbearing potential]), pulmonary function (if needed), chest CT (if needed), KL-6 (if needed), ESR (if needed), PK sampling (if needed), cytokines, lesion imaging (CT/MRI for IgG4-RD), efficacy evaluation, and ICE score (if needed) will be performed.

Special procedures:

At Week 26 post-infusion or at peripheral B-cell reconstitution, you may undergo bone marrow aspiration and lesion biopsy. If feasible and deemed appropriate by the investigator, bone marrow sampling may also be performed within 14 days after infusion.

Throughout the study, a series of examinations and assessments will be conducted to monitor your response to the investigational product and your overall health status.

5. Other Treatment Options

Participation may or may not improve your condition. If you choose not to participate, you may receive standard treatments such as glucocorticoids, immunosuppressants, or NSAIDs. Your doctor will recommend options suitable for you.

6. Potential Effects of the Study

You may find the required visits and procedures inconvenient or uncomfortable.

Prohibited medications: Immunosuppressants other than study lymphodepletion regimen are not allowed during the study.

Contraception: Women of childbearing potential must use effective contraception; certain methods may be prohibited—consult your study doctor.

No participation in other clinical trials during this study.

7. Risks and Adverse Reactions

Risks from the study drug:

- Cytokine Release Syndrome (CRS)
- Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)
- Cytopenias
- Infections
- Allergic reactions
- Infusion reactions
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- Abnormal proliferation of BCMA-CD19 CAR-T cells
- Immunogenicity concerns

Risks from study procedures:

- Venipuncture
- ECG
- Imaging radiation exposure

Other risks:

- Risks from lymphodepletion chemotherapy (cyclophosphamide ± fludarabine), e.g., nausea, alopecia, bone marrow suppression, infection, hepatic/renal impairment, hemorrhagic cystitis.

8. Potential Benefits

You may not directly benefit, but your participation will help advance knowledge about BCMA-CD19 CAR-T therapy and may benefit future patients.

9. Handling and Use of Biological Samples and Medical Information

Remaining samples will be stored per testing facility requirements. Your medical information (name, address, phone number, medical history, study visit data) will be kept confidential. Regulatory authorities and the ethics committee may review your records without disclosing your identity.

10. Your Rights and Obligations

You may take time to consider and ask questions. Whether or not you participate will not affect your medical care. You may withdraw at any time. If new information arises that may affect your willingness to continue, the study team will inform you promptly.

11. Study-Related Costs

You will not be charged for the study drug or study-related procedures

12. Compensation or Reimbursement

You will receive 200 RMB travel reimbursement per visit (estimated 8–10 visits in main study, 2 visits in extended follow-up).

13. Management of Study-Related Injury

If you are injured due to study participation, notify the study doctor immediately. You may receive free treatment and/or compensation according to Chinese law.

14. Confidentiality

Your personal data will be kept confidential. Records will be coded, and only the study doctor and authorized personnel will have access.

15. Voluntary Participation

Participation is voluntary; you may refuse or withdraw at any time without penalty.

16. Study Contacts

For questions about the study, contact your study doctor at: _____.

For questions about your rights, contact the Medical Ethics Committee, Chinese PLA General Hospital, Tel: +86-10-66937166.

Informed Consent Signature Page

Participant Statement:

I have read and understood this Informed Consent Form, including the purpose, procedures, risks, and benefits of this study. My questions have been answered satisfactorily. I agree to cooperate fully and understand that I may withdraw at any time without affecting my future care. I understand that relevant authorities may review my records under confidentiality. I voluntarily agree to participate.

Select one (only one box may be checked):

☐ **Main study**

☐ **Extended follow-up**

Participant Signature: _____

Printed Name: _____

Telephone: _____

Date: _____

Legal Representative Signature (if applicable):

Relationship: _____

Reason for signing: _____

Date: _____

Witness Signature (if applicable):

Printed Name: _____

Telephone: _____

Date: _____

Investigator Statement:

I confirm that I have explained the study details, risks, and benefits to the participant, and have provided a signed copy of this form to the participant.

Investigator Signature: _____

Printed Name: _____

Telephone: _____

Date: _____