

COVER PAGE

Informed Consent Form

Official Title

A Multicenter Exploratory Clinical Study of Targeted NK
Cell Inhibition for Transplant Kidney Chronic Active
Antibody-Mediated Rejection (caABMR): Single Induction
with CD38 Monoclonal Antibody Followed by Sequential
Maintenance with Azathioprine

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INFORMED CONSENT FORM

Study Title:

CD38 Monoclonal Antibody Single Induction, Azathioprine
Replacement of Mycophenolate Sequential Maintenance
for Targeted NK Cell Inhibition in the Treatment of
Transplant Kidney Chronic Active Antibody-Mediated
Rejection (caABMR): A Multicenter Exploratory Clinical
Study

Protocol Version: 3.0 (May 28, 2026)

Informed Consent Form Version: 3.1 (June 14, 2026)

Research Institution: The First Affiliated Hospital, Zhejiang University School
of Medicine

Principal Investigator: Wu Jianyong, MD

Introduction

You are being invited to participate in a clinical research study. This informed consent form provides you with information to help you decide whether to participate. Please take time to read the following content carefully. If you have any questions or unclear terms, you may discuss them with the study physician.

Your participation in this study is entirely voluntary. This study has been reviewed and approved by the hospital's Clinical Research Ethics Committee.

Study Background

You have previously undergone kidney transplantation. Kidney transplantation is currently the most effective treatment for uremia (end-stage renal disease) and the method that best improves quality of life. However, even if the surgery is successful, your immune system may still attack the transplanted kidney as "foreign tissue." This condition is called rejection.

Among rejections, there is a chronic, persistent, antibody-mediated rejection medically known as **chronic active antibody-mediated rejection (caABMR)**. It is one of the main causes of gradual loss of transplant kidney function and eventual graft failure.

1. How does caABMR occur?

Your immune system produces donor-specific antibodies (DSA). These antibodies bind to the blood vessels of the transplanted kidney, continuously activating inflammatory cells (especially plasma cells and NK cells), causing microvascular injury and glomerulosclerosis in the transplant kidney, ultimately leading to a gradual decline in kidney function. This process is insidious, slow, and continuously progressive. Early stages may have no obvious discomfort, but it will cause long-term damage to the transplanted kidney.

2. What treatment options are currently available clinically?

Current guideline-recommended and commonly used treatments for caABMR include:

1. Intensification or adjustment of conventional immunosuppressants (e.g., steroids, tacrolimus, mycophenolate).
2. Plasmapheresis / immunoadsorption (to remove antibodies).
3. Intravenous immunoglobulin (IVIG).
4. Anti-CD20 monoclonal antibody (e.g., rituximab).
5. Other targeted agents such as bortezomib and C5 inhibitors.
6. Long-term maintenance therapy with CD38 monoclonal antibody.

3. What are the disadvantages of existing treatments?

Limited efficacy: Most can only temporarily stabilize the condition and have difficulty truly reversing existing kidney damage. Long-term outcomes are unsatisfactory.

Easy recurrence: Antibody levels often rise again after declining, and rejection recurs.

Many side effects: Intensified immunosuppression significantly increases risks of infection, tumor, bone marrow suppression, and liver/kidney toxicity.

High cost: Some new drugs or biologics are expensive and not covered by regular medical insurance.

Lack of standardized regimen: Currently, no drug worldwide has been formally approved for the treatment of caABMR.

In simple terms: Existing treatments have suboptimal efficacy, notable side effects, and high costs. It remains one of the most challenging problems in the field of kidney transplantation.

4. Why is this study being conducted?

CD38 monoclonal antibody is a mature drug already on the market for the treatment of multiple myeloma, with known safety. Recent domestic and international studies have found that:

CD38 monoclonal antibody can deplete antibody-producing plasma cells.

It simultaneously inhibits NK cells that cause kidney injury.

It significantly reduces donor-specific antibody (DSA) levels.

It improves transplant kidney function and related pathological damage.

Although CD38 monoclonal antibody is a relatively mature drug clinically and several studies in the kidney transplant field have confirmed benefit in some patients, its use in kidney transplantation remains off-label, and patients must pay out-of-pocket. The drug is prone to recurrence after discontinuation, and long-term use alone is expensive and may increase infection risk.

Therefore, this study designed a regimen of **"single induction with CD38 monoclonal antibody + long-term sequential maintenance with azathioprine replacing mycophenolate"**:

First use CD38 monoclonal antibody to control rejection and lower NK cells.

Then use azathioprine (already used in kidney transplantation for decades, safe, inexpensive, and well-tolerated) to maintain NK cell suppression, achieve long-term immune balance, protect the transplanted kidney, and avoid long-term use of expensive biologics.

Study Objective: To explore the efficacy and safety of the "CD38 monoclonal antibody induction + azathioprine sequential replacement of mycophenolate" regimen in kidney transplant recipients with caABMR, providing scientific evidence for wider clinical application and ultimately helping to solve the treatment dilemma of caABMR.

Study Process: This is a multicenter, prospective study involving 6 major transplant centers across China. It plans to enroll 20 eligible patients to evaluate the efficacy (kidney function, transplant kidney biopsy pathology scores, DSA quantity and MFI), safety (injection reactions, infection rates), and immunological changes (peripheral blood immune cell profile) of CD38 monoclonal antibody induction followed by azathioprine sequential therapy for caABMR.

Inclusion Criteria

1. Voluntary written informed consent.
2. Age ≥ 18 years.
3. Kidney transplant (living or deceased donor) ≥ 180 days prior.
4. eGFR ≥ 30 mL/min/1.73 m² (CKD-EPI formula).
5. Currently receiving stable triple immunosuppression (e.g., tacrolimus/cyclosporine + mycophenolate + steroid) for ≥ 4 weeks, with no severe immunosuppression-related adverse reactions.
6. Positive HLA Class I and/or Class II donor-specific antibodies.

7. Transplant kidney pathology consistent with Banff 2022 chronic active AMR (caABMR).

8. TPMT/NUDT15 genotyping: non-homozygous mutant.

Exclusion Criteria

1. Currently participating in another clinical trial.

2. Age < 18 years.

3. Female participants who are pregnant or breastfeeding, or not using appropriate contraception.

4. ABO blood group incompatible transplant.

5. TPMT/NUDT15 genotyping homozygous mutant.

6. Transplant kidney biopsy showing any of the following: T-cell mediated rejection, new or recurrent severe thrombotic microangiopathy, or polyomavirus nephropathy.

7. Received anti-acute rejection treatment within 3 months before screening.

8. Used other immunomodulatory monoclonal/polyclonal antibodies (e.g., anti-CD20, bortezomib, anti-C5, anti-IL-6/IL-6R) within 3 months.

9. Total bilirubin > 2× upper limit of normal, or ALT/AST > 2.5× upper limit of normal.

10. Hemoglobin < 8 g/dL.

11. Platelets < 100×10⁹/L.

12. White blood cells < 3×10⁹/L or neutrophils < 1.5×10⁹/L.

13. Hypogammaglobulinemia: serum IgG < 400 mg/dL.

14. Active viral, bacterial, or fungal infection.

15. Active malignancy requiring intensified immunosuppression.

16. Latent or active tuberculosis.

17. Received live vaccine within 6 weeks after screening.

18. History of alcohol or illicit drug abuse.
19. Severe medical or psychiatric illness that may affect study participation.
20. Active hepatitis B.
21. Hypersensitivity to CD38 monoclonal antibody, azathioprine, or related study drug components, or history of severe drug allergy.

Study Procedures

After successful enrollment, participants will receive:

A single subcutaneous injection of CD38 monoclonal antibody 1800 mg.

Immediate switch from mycophenolate mofetil to azathioprine.

Continued triple immunosuppression with steroid + azathioprine + tacrolimus (target trough 5–7 ng/mL) or cyclosporine (target trough 150–250 ng/mL).

Azathioprine starting dose is based on TPMT/NUDT15 genotype:

Normal metabolizer: 2.0–3.0 mg/kg/day, once daily in the morning.

Intermediate metabolizer: 30–80% of normal metabolizer dose (0.6–2.4 mg/kg/day).

Dose will be adjusted according to bone marrow suppression and disease status. NK cell count will be monitored starting from Week 1, with target $< 20/\mu\text{L}$.

Follow-up visits and tests will be conducted at Weeks 0, 1, 2, 4, 8, 12, 16, 20, 24, and 28, including blood routine, liver/kidney function, electrolytes, drug levels, urine routine, HLA antibody quantification, infection markers, lymphocyte subsets, and a protocol transplant kidney biopsy at Week 28.

Important Note on Costs:

CD38 monoclonal antibody, azathioprine, HLA antibody testing, pharmacogenomic testing, and immune status dynamic assessment fees will be covered by the study team (approximately 40,000 RMB per participant). Other routine hospitalization, laboratory, and examination costs will be borne by the participant.

Risks and Discomforts of Participation

Risks related to CD38 monoclonal antibody:

Infusion/injection-related reactions (most common): fever, chills, fatigue, nausea, headache, etc. (most occur during or within 24 hours of the first dose; premedication with dexamethasone + antihistamine is used for prevention).

Hematologic abnormalities: neutropenia, thrombocytopenia, anemia.

Increased infection risk (CMV, BKV, bacterial/fungal).

Gastrointestinal reactions, fatigue, etc.

Risks related to Azathioprine:

Bone marrow suppression (most important to monitor): leukopenia, neutropenia, thrombocytopenia, anemia.

Liver injury.

Gastrointestinal discomfort.

Slightly increased long-term infection and malignancy risk (low at transplant doses).

Transplant kidney biopsy risks: Local pain, hematuria, perinephric hematoma (rare serious complications < 1%).

The study team will closely monitor all risks and provide timely intervention.

Potential Benefits of Participation

Free provision of CD38 monoclonal antibody, azathioprine, and key monitoring tests (value ~40,000 RMB).

Close medical monitoring and management during the study.

Potential stabilization or improvement of transplant kidney function.

Contribution to scientific knowledge that may benefit future patients with similar conditions.

Important Note: This is an exploratory clinical study. The efficacy of the regimen has not been fully confirmed. Participation does not guarantee personal clinical improvement.

Alternative Treatments

You may choose not to participate and continue with currently available standard treatments for caABMR (as listed in the background section). Your physician can discuss these options with you.

Costs and Compensation

Costs covered by the study team: CD38 monoclonal antibody, azathioprine, HLA antibody testing, pharmacogenomic testing, and immune status monitoring (approximately 40,000 RMB per participant).

Other routine medical costs will be your responsibility.

There is no direct financial compensation for participation. The study has purchased clinical trial liability insurance. If you experience study-related serious adverse events, you may receive corresponding medical treatment and economic compensation according to insurance terms and national laws after medical assessment.

Right to Withdraw

You may withdraw from the study at any time without giving a reason. Withdrawal will not affect your normal medical care or any rights you are entitled to.

Privacy and Confidentiality

Your personal information will be kept strictly confidential. Study data will be de-identified. Only authorized study personnel, ethics committee members, and regulatory authorities may access your records for study-related purposes. Results may be published, but your identity will not be disclosed.

Contact Information

If you have questions about the study, please contact:

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Ethics Committee Contact:

The First Affiliated Hospital, Zhejiang University School of Medicine

Ethics Committee Office

Phone: +86-571-87233418

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Consent to Participate

I have read and understood the above information. I have had the opportunity to ask questions and have received satisfactory answers. I understand that my participation is voluntary and that I may withdraw at any time without penalty.

I agree to participate in this clinical research study.

Participant Name (Print): _____

Participant Signature: _____

Date: _____

Legal Representative / Guardian (if applicable):

Name: _____

Relationship: _____

Signature: _____

Date: _____

Witness (if participant cannot read):

Name: _____

Signature: _____

Date: _____

Investigator Declaration:

I have explained the nature, purpose, risks, and benefits of this study to the participant (or legal representative). I have answered all questions to the best of my ability.

Investigator Name (Print): _____

Investigator Signature: _____

Date: _____

This is a faithful English translation of the original Chinese Informed Consent Form Version 3.1 dated June 14, 2026. In case of any discrepancy, the Chinese version shall prevail for regulatory and ethical purposes in China.

End of Informed Consent Form