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Study Protocol

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

Protocol Version: 3.0

Protocol Date: May 28, 2026

NCT Number: To be assigned

Document Type: Study Protocol

Document Date: July 11, 2026

Sponsor-Investigator

Wu Jianyong, MD

Director, Nephrology Center

The First Affiliated Hospital, Zhejiang University School of Medicine

79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, China 310003

Email: wujianyong1964@zju.edu.cn

Phone: +86-13906523095

STUDY PROTOCOL

CD38 Monoclonal Antibody Single Induction Followed by Azathioprine 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

Version Date: May 28, 2026

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

Principal Investigator: Wu Jianyong, MD

1. Study Background and Rationale

Chronic active antibody-mediated rejection (caABMR) is the leading cause of late kidney allograft loss. Current treatments (plasmapheresis, IVIG, rituximab, bortezomib, long-term CD38 monoclonal antibody) have limited efficacy, high recurrence rates, significant side effects, and high costs, with no globally approved standard therapy.

CD38 monoclonal antibodies can deplete antibody-producing plasma cells and pathogenic NK cells, rapidly reducing donor-specific antibodies (DSA) and microvascular inflammation. However, long-term monotherapy is expensive and may increase infection risk.

This study proposes a novel sequential regimen: **single-dose CD38 monoclonal antibody (1800 mg subcutaneous) induction** to control rejection and lower NK cells, followed by **long-term maintenance with azathioprine** (replacing mycophenolate mofetil). Azathioprine is safe, inexpensive, widely used in transplantation, and effectively suppresses NK cell activity. TPMT/NUDT15 genotyping enables personalized dosing, with serial NK cell monitoring targeting $<20/\mu\text{L}$.

This approach aims to provide an effective, safe, and cost-effective treatment strategy for caABMR while minimizing the risks and costs associated with prolonged biologic therapy.

2. Study Objectives

Primary Objective

To evaluate the efficacy of CD38 monoclonal antibody single induction followed by azathioprine sequential maintenance in stabilizing or improving graft function in kidney transplant recipients with caABMR, as measured by the slope of eGFR decline over 28 weeks.

Secondary Objectives

To assess changes in peripheral blood NK cell, T cell, and B cell subsets.

To evaluate changes in DSA levels (MFI).

To evaluate changes in transplant kidney pathology (Banff 2022 scores) at 28 weeks.

To assess patient and graft survival.

To evaluate safety, including infection rates (BKV, CMV) and neutropenia.

3. Study Design

Design: Multicenter, prospective, open-label, single-arm, exploratory clinical study

Number of Centers: 6 (China)

Sample Size: 20 participants

Duration per Participant: 28 weeks active treatment + follow-up

Overall Study Duration: Approximately June 2026 – January 2028

4. Study Population

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 2021 formula).
5. Currently receiving stable triple immunosuppression (CNI + MMF + steroid) for ≥ 4 weeks.
6. Positive HLA Class I and/or Class II donor-specific antibodies (DSA).
7. Transplant kidney biopsy consistent with Banff 2022 chronic active antibody-mediated rejection (caABMR).
8. TPMT/NUDT15 non-homozygous mutant genotype.

Exclusion Criteria

1. Participating in another clinical trial.
2. Age < 18 years.
3. Pregnant, breastfeeding, or inadequate contraception in females.
4. ABO-incompatible transplant.
5. TPMT/NUDT15 homozygous mutant genotype.
6. Biopsy shows any of: T-cell mediated rejection (TCMR), new/recurrent severe thrombotic microangiopathy, or polyomavirus nephropathy.
7. Received anti-rejection therapy in prior 3 months.
8. Received other immunomodulatory monoclonal/polyclonal antibodies (anti-CD20, bortezomib, anti-C5, anti-IL-6/IL-6R) in prior 3 months.
9. Total bilirubin $> 2 \times \text{ULN}$ or ALT/AST $> 2.5 \times \text{ULN}$.
10. Hemoglobin < 8 g/dL.

11. Platelets $<100 \times 10^9/L$.
12. WBC $<3 \times 10^9/L$ or neutrophils $<1.5 \times 10^9/L$.
13. Hypogammaglobulinemia: IgG <400 mg/dL.
14. Active bacterial, viral, or fungal infection.
15. Active malignancy requiring intensified immunosuppression.
16. Latent or active tuberculosis.
17. Live vaccine within 6 weeks of screening.
18. History of alcohol or illicit drug abuse.
19. Severe medical or psychiatric illness likely to impair study participation.
20. Active hepatitis B.
21. Known hypersensitivity to CD38 mAb, azathioprine, or study drug components, or severe drug allergy history.

5. Study Intervention

Intervention Arm (Single Group):

All participants will receive:

Day 0: Single subcutaneous injection of CD38 monoclonal antibody 1800 mg.

Immediate switch: Mycophenolate mofetil → Azathioprine (dose based on TPMT/NUDT15 genotype and adjusted to achieve NK cell count $<20/\mu L$).

Maintenance immunosuppression: Corticosteroid + Azathioprine + Tacrolimus (trough 5–7 ng/mL) or Cyclosporine (trough 150–250 ng/mL).

Drug Accountability: All study drugs (CD38 mAb and Azathioprine) and key monitoring tests will be provided free of charge by the study team (approximately 40,000 RMB per participant).

Study Endpoints

Primary Endpoint

Slope of eGFR decline from baseline to Week 28 (calculated using 2021 CKD-EPI formula from serial serum creatinine measurements every 4 weeks).

Key Secondary Endpoints

1. Change in NK cell, T cell, and B cell subset counts and percentages (flow cytometry).
2. Change in eGFR and urine protein/creatinine ratio at Week 28.
3. Change in DSA MFI at Weeks 8 and 28.
4. Change in Banff 2022 pathology scores at Week 28 protocol biopsy.
5. Incidence of acute rejection, patient survival, and graft survival at Week 28.
6. Incidence of BKV infection, CMV infection, and neutropenia through Week 28.

7. Study Procedures and Visit Schedule

Intensive monitoring from Week 0 to Week 28, including:

Blood routine, biochemistry, drug levels, DSA quantification, lymphocyte subsets, infection markers (BKV, CMV, EBV).

Protocol transplant kidney biopsy at Week 28.

Adverse event monitoring and recording.

8. Statistical Considerations

Sample Size: 20 participants (exploratory study).

Analysis Populations: Intent-to-Treat (ITT) and Per-Protocol (PP).

Primary Analysis: Linear mixed-effects model or ordinary least-squares regression for eGFR slope.

Safety Analysis: Descriptive statistics for adverse events.

9. Safety Monitoring and Adverse Events

All adverse events will be collected, graded, and reported according to protocol. Serious adverse events will be reported to the sponsor-investigator and ethics committee within required timelines. The study has clinical trial liability insurance coverage.

10. Ethical Considerations

The study has been approved by the IIT Ethics Review Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (Approval No. IIT20260074C-R1, modified approval June 10, 2026). All participants will provide written informed consent. The study will be conducted in accordance with the Declaration of Helsinki, GCP, and applicable Chinese regulations.

11. Data Management and Quality Assurance

Data will be collected using electronic Case Report Forms (eCRF). Source data verification and monitoring will be performed. All data will be handled confidentially.

12. Publication Policy

Study results will be published in peer-reviewed journals. The sponsor-investigator and participating centers will be acknowledged appropriately.

End of Protocol

References

(Full list of 23 references with verified PMIDs is available in a separate document.)

Contact for Further Information

Coordinating Investigator: Wei Chunhuan, MD

Phone: +86-13738053172

Email: 1514050@zju.edu.cn

This English protocol is a faithful translation and summary of the original Chinese Protocol Version 3.0 dated May 28, 2026.