Appendix 1

Informed Consent

Dear Mr./Ms. _____:

You are invited to participate in a prospective, phase II clinical study titled "A Prospective, Multicenter, Single-Arm Phase II Study of Neoadjuvant Disitamab Vedotin (RC48) in Combination With Adebrelimab, Apatinib, and S-1 for Locally Advanced HER2-Positive Gastric Cancer," led by Jiangsu Province Hospital. This study expects to enroll 32 voluntary participants and will be conducted across seven research centers in Jiangsu Province, including Xuzhou Medical University Affiliated Hospital, Jiangsu Provincial Hospital of Chinese Medicine, Jiangsu Cancer Hospital, Taizhou People's Hospital, The First Affiliated Hospital of Soochow University, and Nanjing Jiangning Hospital. Jiangsu Province Hospital is the lead study center. This study has been reviewed and approved by the Ethics Committee of Jiangsu Province Hospital.

You may discuss your participation in this study with your family, friends, or your doctor. Participation is entirely voluntary, and you will have sufficient time to consider your decision. Even if you sign this consent form, you may withdraw from the study at any stage without providing a reason. If you agree to participate, you or your legal representative will receive a signed and dated copy of this consent form, approved by the Ethics Committee.

1. Background

In recent years, anti-HER2 therapies for HER2-positive advanced gastric cancer have shown promising clinical outcomes, with new anti-HER2 drugs and regimens increasingly applied in clinical practice. Perioperative anti-HER2 therapy for HER2-positive gastric cancer has also made progress, achieving a pathological complete response rate of approximately 9.6%–35%.

Preliminary results have been reported for combined anti-HER2 therapy with anti-angiogenic drugs and chemotherapy in HER2-positive gastric cancer. The Phase Ib/II HER-RAM study demonstrated that trastuzumab, ramucirumab, and paclitaxel as second-line treatment for HER2-positive advanced gastric cancer achieved an objective response rate (ORR) of 54%, a disease control rate (DCR) of 96%, a median progression-free survival (PFS) of 7.1 months, and an overall survival (OS) of 13.6 months. Another Phase II study of trastuzumab, bevacizumab, paclitaxel, oxaliplatin, and capecitabine as first-line treatment for HER2-positive advanced gastric cancer reported an ORR of 74.9%, a median PFS of 10.8 months, and an OS of 17.9 months.

Disitamab vedotin, an antibody-drug conjugate targeting HER2, achieved a 26% ORR in third-line treatment for HER2-positive gastric cancer and has been approved for this indication. Recent data from RC48+PD-1 as second-line treatment for HER2-positive advanced gastric cancer reported a 54% ORR, improving outcomes for second-line therapy. The combination of anti-angiogenic drugs and immunotherapy has also shown promising results in gastric cancer treatment. Our team's first-line study combining chemotherapy, immunotherapy, and anti-angiogenic drugs for advanced gastric cancer achieved a 76% ORR, significantly higher than chemotherapy plus immunotherapy alone.

Based on these advancements, this study aims to explore the efficacy and safety of disitamab vedotin combined with an immune checkpoint inhibitor (adebrelimab), an anti-angiogenic drug (apatinib), and chemotherapy (tegafur gimeracil oteracil potassium capsule) as neoadjuvant treatment for HER2-overexpressed locally advanced gastric cancer.

Inclusion and exclusion criteria

Inclusion criteria: Participants must meet all of the following criteria to be eligible for this study:

1. Voluntarily agree to participate, sign the informed consent form, and demonstrate good compliance.
2. Age 18–75 years at the time of signing the consent form, regardless of gender.
3. Histologically and/or cytologically confirmed gastric cancer or gastroesophageal junction adenocarcinoma, diagnosed as locally advanced per the AJCC 8th edition, with cTNM staging of >T2N0–3 or T0–4N+M0 based on endoscopic ultrasound or enhanced CT/MRI scans (with diagnostic laparoscopy if necessary), and agreement to undergo curative surgery with potentially resectable lesions as assessed by the investigator.
4. No prior systemic treatment (e.g., chemotherapy, radiotherapy, or immunotherapy) for the current disease.
5. Endoscopic biopsy confirming HER2 overexpression (IHC 2+ or 3+).

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6. ECOG performance status of 0–1.
7. Expected survival ≥6 months.
8. Adequate organ function, meeting the following criteria:
   8.1. **Hematology** (without transfusion or hematopoietic growth factor support within 7 days): hemoglobin (Hb) ≥80 g/L; absolute neutrophil count (ANC) ≥1.5×10^9/L; platelets (PLT) ≥80×10^9/L.
   8.2. **Biochemistry**: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× ULN; total bilirubin (TBIL) ≤1.5×ULN; serum creatinine (Cr) ≤1.5× ULN or creatinine clearance ≥60 mL/min.
   8.3. **Coagulation**: activated partial thromboplastin time (APTT), international normalized ratio (INR), and prothrombin time (PT) ≤1.5×ULN.
   8.4. **Cardiac function**: left ventricular ejection fraction (LVEF) ≥50% by Doppler ultrasound.
   8.5. Clinically assessed as having adequate organ function.
9. For participants with reproductive potential, effective contraception must be used during the study and for 120 days after its completion. Negative serum pregnancy test within 7 days before enrollment, and not breastfeeding.

Exclusion criteria: participants meeting any of the following criteria cannot enroll:

1. Concurrent malignant diseases other than gastric cancer (except cured early-stage tumors).
2. Tumors with bleeding tendencies (e.g., active ulcerative tumors with positive fecal occult blood, history of hematemesis or melena within 2 months before signing consent, or high risk of gastrointestinal bleeding as judged by the investigator) or receipt of blood transfusion within 4 weeks before study drug administration.
3. Inability to take oral medications.
4. Current participation in another interventional clinical study or receipt of other investigational drugs or devices within 4 weeks before the first dose.
5. Prior treatment with anti-HER2, anti-PD-1, anti-PD-L1, anti-PD-L2, or drugs targeting other T-cell receptors (e.g., CTLA-4, OX-40, CD137).
6. Active autoimmune disease requiring systemic treatment within 2 years before the first dose (e.g., disease-modifying drugs, corticosteroids, or immunosuppressants). Physiological doses of corticosteroids (≤10 mg/day prednisone or equivalent) or replacement therapies (e.g., thyroxine, insulin) are permitted.
7. Systemic treatment with antitumor-indicated Chinese herbal medicines or immunomodulatory drugs (e.g., thymalfasin, interferon, interleukin, except for local use to control pleural effusion) within 2 weeks before the first dose.
8. Known history of allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation.
9. Known hypersensitivity to study drugs.
10. Peripheral neuropathy ≥ Grade 2.
11. Known HIV infection (HIV 1/2 antibody positive).
12. Active hepatitis B or C.
13. Receipt of live vaccines within 30 days before the first dose. Inactivated seasonal influenza vaccines are permitted, but intranasal live attenuated influenza vaccines are not.
14. Pregnant or breastfeeding women.
15. Any severe or uncontrolled systemic diseases, including:
    15.1. Clinically significant and poorly controlled abnormalities in heart rhythm, conduction, or morphology (e.g., complete left bundle branch block, heart block ≥ Grade II, ventricular arrhythmia, or atrial fibrillation).
    15.2. Unstable angina, congestive heart failure, or chronic heart failure (NYHA ≥ Grade 2).
    15.3. Arterial thrombosis, embolism, or ischemia within 6 months before enrollment (e.g., myocardial infarction, unstable angina, stroke, or transient ischemic attack).
    15.4. Poorly controlled hypertension (systolic >140 mmHg, diastolic >90 mmHg).
    15.5. History of non-infectious pneumonitis requiring corticosteroids within 1 year before the first dose or active interstitial lung disease.
    15.6. Active tuberculosis.
    15.7. Active or uncontrolled infections requiring systemic treatment.

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15.8. Active diverticulitis, intra-abdominal abscess, or gastrointestinal obstruction.
15.9. Liver diseases such as cirrhosis, decompensated liver disease, or acute/chronic active hepatitis.
15.10. Poorly controlled diabetes (fasting blood glucose >10 mmol/L).
15.11. Urinalysis showing proteinuria ≥++ and 24-hour urine protein >1.0 g.
15.12. Mental disorders affecting treatment compliance.
16. Any condition that may interfere with study results, prevent full participation, or is deemed unsuitable by the investigator.

2. Treatment process

This study aims to evaluate the efficacy and safety of disitamab vedotin + adebrelimab + apatinib + tegafur gimeracil oteracil potassium capsule as neoadjuvant treatment for HER2-overexpressed locally advanced gastric cancer. If you agree to participate, you will receive the following treatment regimen:

- **Disitamab vedotin**: 2.5 mg/kg, intravenous infusion, day 1, every 3 weeks (Q3W).
- **Adebrelimab**: 1,200 mg, intravenous infusion, day 1, Q3W.
- **Tegafur gimeracil oteracil potassium capsule**: 50 mg for body surface area ≤1.5 m^2, 60 mg for >1.5 m^2, oral, twice daily, days 1–14, Q3W.
- **Apatinib**: 250 mg, oral, once daily, Q3W.

Adebrelimab will be administered first, followed by chemotherapy after at least a 30-minute interval. Neoadjuvant treatment will consist of 3–4 cycles, with apatinib administered for only 14 days in the final cycle. Patients with clinical benefit post-surgery may receive 4 cycles of adjuvant disitamab vedotin + adebrelimab + tegafur gimeracil oteracil potassium capsule (starting approximately 4 weeks post-surgery) or standard guideline-recommended adjuvant therapy.

Each treatment cycle lasts 21 days. Treatment will continue until intolerable toxicity, withdrawal of consent, or disease progression per RECIST v1.1.

This study complies with the *Good Clinical Practice Guidelines* of the People's Republic of China and the *Declaration of Helsinki*. Compensation for study-related harm will follow Chinese legal regulations.

During treatment, regular check-ups and data collection will include medical history, prior treatments, concomitant diseases, medications, allergies, vital signs, physical examinations, ECOG performance status, and clinical tests (e.g., blood pressure, blood tests, urinalysis, stool tests, ECG, blood chemistry, thyroid function, CT/MRI imaging). These are standard clinical procedures, and all efforts will be made to protect your personal medical information within legal limits.

3. Risks

The study drugs include disitamab vedotin, adebrelimab, apatinib, and tegafur gimeracil oteracil potassium capsule. Disitamab vedotin, developed by RemeGen Co., Ltd., is China's first approved antibody-drug conjugate. Adebrelimab is not approved for gastric cancer in China but is approved for small cell lung cancer, making its use off-label. Disitamab vedotin and apatinib are approved for third-line gastric cancer treatment.

Common adverse reactions from prior studies include leukopenia, neutropenia, anemia, elevated alanine aminotransferase, thrombocytopenia, elevated aspartate aminotransferase, loss of appetite, nausea, elevated γ-glutamyltransferase, fatigue, and hypothyroidism. The most common ≥ Grade 3 adverse reactions include neutropenia, leukopenia, thrombocytopenia, anemia, lymphopenia, elevated alanine aminotransferase, and hypertension. You may experience similar or unknown adverse reactions. Please contact the study doctor promptly if you experience discomfort or adverse reactions. Treatment may be ineffective, and disease progression may occur due to treatment failure or concurrent conditions.

If a serious adverse reaction occurs and is deemed related to the study drugs, RemeGen Co., Ltd. has purchased clinical trial insurance to cover treatment costs and legally mandated compensation.

4. Costs

During neoadjuvant treatment, disitamab vedotin (60 mg/vial, ~3 vials per dose), adebrelimab (600 mg/12 mL/vial, ~2 vials per dose), and apatinib (0.25 g/tablet, ~1 tablet daily, 14 tablets/box) will be provided free for 3–4 cycles (approximately 9–12 vials of disitamab vedotin, 6–8 vials of adebrelimab, 5–7 boxes of apatinib). Tegafur gimeracil oteracil potassium capsule is not covered. Post-surgery, patients with clinical benefit may receive 4 cycles of adjuvant therapy with disitamab vedotin +

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adebrelimab + tegafur gimeracil oteracil potassium capsule or standard adjuvant therapy, which must be self-funded. No subsidies for transportation or other expenses are provided.

5. Alternative treatment options

Besides this study, other treatment options for your condition include targeted therapies, chemotherapy, radiotherapy, and immunotherapy. Your study doctor will discuss the risks and benefits of these options. Participation in this study is not required to receive treatment. Alternative treatments include two- or three-drug regimens based on platinum, fluoropyrimidines, taxanes, or anti-HER2 therapies. Other options include:

- ❖ Other clinical studies known to your doctor.
- ❖ Best supportive care to minimize pain or discomfort.

Your doctor will discuss the risks and benefits of alternative treatments.

6. Potential benefits

Participation may not guarantee benefits, but this novel treatment regimen may provide favorable outcomes.

7. Confidentiality and privacy authorization

Your health information is protected under Chinese law. By signing this consent form, you authorize the study doctor and research center to collect, use, and share your health data. Your name will be anonymized with a study code. Your medical records (e.g., case report forms, lab results) will be securely stored at the hospital. Study investigators, the Ethics Committee, and regulatory authorities may access your records. Public reports on study results will not disclose your identity, and your privacy will be protected.

8. Voluntary participation/withdrawal

Participation is entirely voluntary. You may choose not to participate or withdraw at any time without affecting your medical care or rights, and you will not face discrimination from medical staff.

9. Questions and information

The study team will answer all your questions before you sign this consent form. You may contact the investigator with any questions, suggestions, or concerns after signing. You can access study-related information and progress updates at any time. For further inquiries, contact the Jiangsu Province Hospital Ethics Committee.

Investigator: _____ **Contact Number**: _____

Ethics Committee Address: 3rd Floor, Building 7, Jiangsu Province Hospital, Nanjing, China

Phone: 025-68306360

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Informed Consent Form - Consent Signature Page

The study's principal investigator or relevant research personnel has orally explained the details of this study to me, and I have also read the written information provided above.

I have been given sufficient opportunity to discuss the study and ask questions.

I agree to participate in this study, understanding that my participation is entirely voluntary, and I will fully cooperate with the study doctor.

I understand that I may withdraw from the study at any time, and my withdrawal will not affect my future medical care.

By signing this informed consent form, I agree that my personal information, including my medical data, will be used as described above.

I understand that I will receive a copy of this informed consent form.

Patient Name: _____

Patient Signature: _____

Date: _____ Year _____ Month _____ Day

Contact Number: _____

OR

Legal Representative Signature: _____

Date: _____ Year _____ Month _____ Day

(Applicable only if the participant lacks capacity)

Relationship to Patient: _____

Contact Number: _____

Investigator Signature: _____

Date: _____ Year _____ Month _____ Day

Contact Number: _____

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