# Informed Consent

**Dear Sir/Madam:**

We invite you to participate in the "Sintilimab (PD-1 inhibitor) Combined with Ramucirumab (a VEGFR-2 antagonist) and Chemotherapy as First-line Treatment in Patients with Advanced Gastric Cancer with Liver Metastasis (RAMSINT): A Phase II, Single-center, Prospective Clinical Study" approved by Jiangsu Province Hospital. This study is led by Dr. Wu from the Gastric Cancer Center of our hospital and will be conducted at Jiangsu Province Hospital, with an estimated 39 participants voluntarily joining the study. Our center plans to enroll 39 participants. This research has been reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital), with ethics review approval number: 2024-SR-654.

**Why is this research being conducted?**

For patients with unresectable locally advanced, recurrent, or metastatic gastric and gastroesophageal junction adenocarcinomas, the five-year survival rate is only approximately 13.9%. The liver is the most common target organ for hematogenous metastasis of gastric cancer, with an incidence of liver metastasis ranging from 9.9% to 18.7%. Patients with gastric cancer liver metastasis have poor prognosis, with a five-year survival rate of less than 20%. In recent years, immunotherapy has achieved significant breakthroughs in the treatment of advanced gastric cancer. Multiple clinical trials have confirmed the substantial role of PD-1 monoclonal antibodies combined with chemotherapy in first-line treatment for advanced gastric cancer, and this combination has been included in the Class I recommendation of the 2023 CSCO Gastric Cancer Diagnosis and Treatment Guidelines for first-line treatment of advanced gastric cancer.

Although ICIs have been highly successful in the treatment of gastric cancer, not all advanced gastric cancer patients benefit from PD-1 inhibitor therapy. This is particularly true for populations with CPS < 5 or even CPS-negative cases, who show suboptimal responses to PD-1 inhibitors. How to further enhance efficacy in this group of patients has become a key concern for us. In 2014, Ramucirumab received FDA approval for second-line treatment of gastric cancer. Its ability to promote tumor vascular normalization can effectively modulate the immune microenvironment, having a "twice the effect with half the effort" on hypervascular liver metastases. In this study, we plan to use Sintilimab combined with Ramucirumab and chemotherapy as first-line treatment for patients with advanced gastric cancer and liver metastasis, observing the efficacy and safety of this treatment regimen. At the same time, by examining related indicators such as intratumoral microbial distribution, peripheral blood protein levels, and characteristics of gut microbiota, we aim to identify potential populations that can benefit from treatment, providing evidence for personalized and precise treatment for future patients with advanced gastric cancer and liver metastasis.

**Does this study involve the use of drugs beyond the approved indications?**

In this study, ramucirumab is used off-label. The approved indications for ramucirumab are: ramucirumab in combination with paclitaxel for the treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma whose disease has progressed during or after chemotherapy with fluoropyrimidine- or platinum-containing regimens. When used in combination with paclitaxel, the recommended dose of ramucirumab is 8mg/kg, administered as an intravenous infusion over approximately 60 minutes on days 1 and 15 of each 28-day cycle.

The updates of drug labels often lag behind the advances in clinical medicine. The Chinese drug label for ramucirumab does not cover its use as first-line therapy. However, the use of ramucirumab as first-line treatment for gastric cancer (10mg/kg, administered as an intravenous infusion over approximately 60 minutes on day 1 of each 21-day cycle) is supported by a rational basis in medical practice.

**Who should (or should not) participate in the study?**

**Inclusion criteria:**

1. Voluntary participation in the clinical study; full understanding and informed consent to this study by signing the Informed Consent Form (ICF); willingness to follow and ability to complete all trial procedures.

2. Gender is not restricted, and participants must be at least 18 years old when signing the ICF.

3. Patients with histologically or cytologically confirmed, unresectable, or who refuse surgical resection of locally advanced, recurrent, or metastatic gastric and gastroesophageal junction (GEJ) adenocarcinoma (including signet-ring cell carcinoma, mucinous adenocarcinoma, hepatoid adenocarcinoma, etc.). (Note: For patients who relapse after neoadjuvant/adjuvant therapy, the time from the end of neoadjuvant/adjuvant therapy to disease relapse must be more than 6 months.)

4. Patients, except those with recurrent disease after neoadjuvant/adjuvant therapy, must not have previously received systemic treatment.

5. Participants must be histologically confirmed as having HER2-negative gastric cancer, GEJ cancer, or esophageal adenocarcinoma.

6. There must be at least one measurable lesion in the liver assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) that can undergo repeat radiological evaluation; the radiological tumor assessment should be performed within 28 days prior to randomization.

7. The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0-2 within 7 days prior to the first dose of medication.

8. Expected survival greater than or equal to 3 months.

9. Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (HBcAb) negative. If HBsAg positive or HBcAb positive, hepatitis B virus deoxyribonucleic acid (HBV-DNA) must be less than 1000 copies/mL or less than 200 IU/mL or less than the upper limit of normal (ULN) at the research center for enrollment to occur.

10. HCV antibody negative.

11. Main organ functions must be normal, meeting the following criteria (no blood transfusions, albumin, recombinant human thrombopoietin, or colony-stimulating factor (CSF) treatments within

14 days prior to the first dose):

a. Hematological System

| | |
|---|---|
| White Blood Cells (WBC) | Normal range |
| Neutrophils (NE) | Normal range |
| Platelets (PLT) | ≥100 × 10^9/L |
| Hemoglobin (Hb) | ≥90 g/L |

b. Liver Function

| | |
|---|---|
| Total Bilirubin (TBIL) | ≤1.5 × ULN |
| Alanine Aminotransferase (ALT) | ≤5.0 × ULN |
| Aspartate Aminotransferase (AST) | ≤5.0 × ULN |
| Albumin | ≥30 g/L |

c. Renal Function

| | |
|---|---|
| Creatinine (Cr) | Normal range |

d. Coagulation Function

| | |
|---|---|
| Activated Partial Thromboplastin Time (APTT) | ≤1.5 × ULN |
| Prothrombin Time (PT) | ≤1.5 × ULN |
| International Normalized Ratio (INR) | ≤1.5 × ULN |

12. Availability of representative tumor tissue specimens, blood samples, and fecal samples for exploratory research.

**Exclusion criteria:**

1. History of other active malignancies within the past 5 years or currently having other active malignancies. Treated localized tumors, such as basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, prostate carcinoma in situ, cervical carcinoma in situ, and breast carcinoma in situ, are eligible for inclusion.

2. Underwent surgery within 4 weeks prior to the start of the study treatment.

3. Presence of central nervous system diseases or symptoms of central nervous system metastasis.

4. Patients preparing for or with a history of organ or bone marrow transplantation.

5. History or evidence of thrombosis or bleeding disorders within 6 months prior to the first study

treatment.

6. Diagnosis of active pulmonary tuberculosis.

7. History or presence of interstitial pneumonia, pneumoconiosis, radiation pneumonia, drug-induced pneumonia, or other conditions that may interfere with the detection and management of suspected drug-related pulmonary toxicity.

8. Uncontrolled hypertension (SBP ≥ 150 and/or DBP ≥ 100) or history of hypertensive crisis or cardiovascular diseases (≥ II degree or worse congestive heart failure, myocardial ischemia, unstable angina, stroke, or transient ischemic attack).

9. Patients with high-risk factors for gastrointestinal perforation (history of gastrointestinal fistula, perforation, abdominal abscess, partial or complete intestinal obstruction, or requiring total parenteral nutrition).

10. Patients with moderate to severe proteinuria.

11. Patients with non-healing wounds, ulcers, or fractures.

12. Presence of known active or suspected autoimmune diseases, except those who are in a stable condition at the time of enrollment (not requiring systemic immunosuppressive treatment).

13. Known history of severe allergy to any monoclonal antibodies or excipients.

14. Known history of substance abuse or drug addiction; patients who have stopped alcohol consumption can be included.

15. Patients with conditions that may increase the risk associated with the study drugs, or other severe, acute, and chronic diseases, as judged by the investigator, are deemed unsuitable for participation in the clinical study.

16. Previous use of PD-1 inhibitors, LAG-3 inhibitors, CTLA-4 inhibitors, or any other antibodies or drug treatments targeting T-cell co-stimulation or immune checkpoint pathways, including previous receipt of anti-tumor vaccines or other immunostimulatory anti-tumor therapies.

17. Previous exposure to VEGF (vascular endothelial growth factor) or VEGFR inhibitors or any anti-angiogenesis medications.

**What will you need to do if you participate in the study?**

If you agree to participate in this study, you will follow the treatment regimen of Sintilimab,

Ramucirumab and chemotherapy. The chemotherapy options include the following two combinations: the SOX regimen (oxaliplatin and S-1) and the XELOX regimen (oxalipatin and capecitabine) (your doctor will inform you about the indications and pros and cons of these two regimens, and you can choose the specific regimen based on your actual condition). You may receive up to 6 cycles of combined treatment, with each cycle lasting 21 days. After completing 6 cycles of combined treatment regimen, you will receive Sintilimab and oral chemotherapy agents (Capecitabine or S1) with or without Ramucirumab until disease progression. If disease progression or intolerable toxic reactions occur during treatment, the investigator will decide on the subsequent treatment plans.

The specific dosages and administration methods for the medications mentioned above are as follows:

Immunotherapy:

Sintilimab: 200 mg fixed dose, intravenous infusion on Day 1, repeated every 21 days.

Targeted Therapy:

Ramucirumab: 10 mg/kg intravenous infusion on Day 1, repeated every 21 days.

Chemotherapy: includes the following two combinations:

a. SOX regimen (Oxaliplatin 130mg/m² intravenous infusion on Day 1 and S1 40mg/m² orally, twice daily from Days 1 to 14, repeated every 21 days);

b. XELOX regimen (Oxaliplatin 130mg/m² intravenous infusion on Day 1 and Capecitabine 1000mg/m² orally, twice daily from Days 1 to 14, repeated every 21 days).

All participants will undergo imaging assessments (CT/MRI) before the first treatment and after every two cycles of treatment. Prior to the first treatment, tissue samples from endoscopy will be collected (paraffin sections) (5-20 pieces of surgical tissue [>1 cm²], or 20-25 pieces of puncture tissue); blood samples and fecal samples (a total of at least 3 times) will be collected prior to the first treatment, after every two treatment cycles, or at the time of disease progression. Blood samples (approximately 5 ml each) and fecal samples (mid-segment feces, approximately the size of a soybean [about 50 mg], 3 tubes each time) will be collected for analysis. The collected blood samples will undergo Olink proteomics testing through Jiangsu Simcere Diagnostics Co., Ltd, and the endoscopic tissue will be analyzed by 5R 16S rRNA sequencing and fecal samples will be

analyzed by 16S rRNA sequencing. The testing costs will be covered by us, and the results will be communicated to you if you wish. After testing, the samples will be immediately destroyed, and we assure you that samples will not be used for any other purposes. Additionally, we will conduct telephone follow-up for one year after the treatment concludes, including monthly follow-ups regarding your blood routine, liver and kidney function, tumor marker results, imaging outcomes (e.g., CT) every three months, and any related adverse events. Your involvement in this study will take approximately one year.

**What are the benefits of participating in the study?**

This study will not provide you with direct benefits; however, the clinical efficacy, safety, and tolerability of the explored treatment (Sintilimab, Ramucirumab combined chemotherapy as first-line treatment for advanced gastric cancer with liver metastasis) will bring societal benefits upon completion. Furthermore, by examining intratumoral microbial distribution, peripheral blood protein levels, and gut microbiota characteristics, we aim to identify potential populations that may benefit from treatment, providing evidence for personalized and precise therapies for future patients with advanced gastric cancer and liver metastasis.

This study may be terminated due to legal, regulatory requirements, or as requested by investigators or administrative authorities if significant safety issues arise, efficacy does not meet expectations, or clinical research is deemed unnecessary.

**What are the risks of participating in the study?**

All treatment medications may have side effects (the study describes the main side effects/adverse reactions of the treatment and informs about emergency measures). Medications such as S1, Capecitabine, and Oxaliplatin have certain toxicities/side effects, including low white blood cell count and liver/kidney function impairment. Ramucirumab may cause adverse reactions such as bleeding, gastrointestinal perforation, and arterial thromboembolism events. Risks associated with intravenous blood draws may include pain and/or bruising, and in rare cases, fainting or infection at the puncture site, though these usually resolve on their own. We will monitor potential side effects/adverse reactions caused by the study (medication treatment) through regular

blood tests and biochemical assessments and will take appropriate measures for prevention and treatment (providing risk control guidance, such as handling low blood sugar if necessary). If you experience any discomfort or adverse reactions, please contact the research physician promptly. Because the medications used in this study, such as S1, Capecitabine, and Oxaliplatin, are standard treatments for gastric cancer, these side effects/adverse reactions could occur even if you do not participate in this clinical study. Moreover, any treatment may not be effective, and disease progression may continue due to treatment failure or the presence of other concurrent conditions.

**Will there be any costs associated with participation?**

By participating in this study, you can receive Ramucirumab (buy two, get one free) at no cost. To compensate for any inconvenience caused by your participation, we will reimburse up to 100 RMB for your expenses related to transportation, parking, fuel, and time for each follow-up, which will be issued periodically. However, any treatments and tests required for other concurrent conditions, as well as the costs associated with switching to alternative treatments due to treatment failure, will not be covered. If any trial-related injuries occur, treatment and compensation will be provided in accordance with national regulations.

**Is personal information confidential?**

Your medical records will be kept at the hospital, and the researchers, research supervisory departments, and ethics committee will be allowed to access your medical records. Any public report regarding the results of this study will not disclose your personal identity. We will make every effort, within the bounds of the law, to protect the privacy of your personal medical information.

**What alternative treatment methods exist if you do not participate in this study?**

If you do not participate in this study or decide to withdraw from it mid-way, many alternative treatment options are available, such as chemotherapy combining Docetaxel with S1/Capecitabine.

**Is participation in the study mandatory?**

Participation in this study is entirely voluntary. You may refuse to participate or withdraw from the study at any time, and this will not affect the treatment provided by your physician. If you decide to withdraw from the study, please contact your doctor, and you may be asked to undergo relevant examinations that will benefit your health.

If you have any questions regarding your personal rights, please contact the ethics committee of this hospital at: 025-68306360.

**Participant Statement:**

I have read the introduction to this study above and fully understand the risks and benefits that may arise from participating in this research. I voluntarily agree to participate in this study. I will receive a signed copy of this informed consent form with my name and date.

I agree □ refuse □ other research to utilize my medical records and clinical samples related to this study.

Participant Signature: Date：__ __ __ __ Year __ __ Month __ __ Day

Participant's Phone Number: Mobile Number:

(If applicable) Legal Guardian/Witness Signature: Date: __ __ __ __ Year __ __ Month __ __ Day

Legal Guardian/Witness Phone Number: Mobile Number:

**Researcher Statement:**

I confirm that I have explained the details of this study to the participant, particularly the risks and benefits that may arise from participating in this research, and I have answered all of the participant's related questions. The participant has voluntarily agreed to participate in this study.

This informed consent form is made in duplicate; one signed copy is kept by the researcher and one by the participant.

Research Physician Signature: Date：__ __ __ __ Year __ __ Month __ __ Day

Research Physician's Work Phone Number: Mobile Number: