A Prospective, Single-Arm, Single-Center Phase II Clinical Trial of Iparomlimab and Tuvonralimab as Neoadjuvant Immunotherapy for Microsatellite Instability-High / Mismatch Repair-Deficient Locally Advanced Gastric Adenocarcinoma

CLINICAL STUDY PROTOCOL

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1. Protocol Synopsis

Protocol Title: A Prospective, Single-Arm, Single-Center Phase II Clinical Trial of Iparomlimab and Tuvonralimab as Neoadjuvant Immunotherapy for Microsatellite Instability-High / Mismatch Repair-Deficient Locally Advanced Gastric Adenocarcinoma.

Hypothesis, Objectives, and Endpoints:

Study hypothesis: Iparomlimab and tuvonralimab can significantly improve the perioperative therapeutic efficacy in patients with microsatellite instability-high / mismatch repair-deficient (MSI-H/dMMR) locally advanced gastric adenocarcinoma.

Purpose of the study:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of iparomlimab and tuvonralimab in improving perioperative treatment of MSI-H/dMMR locally advanced gastric adenocarcinoma.	Pathological complete response rate (pCR).
Secondary Objective	**Secondary Endpoints**
To evaluate the safety and long-term benefit of iparomlimab and tuvonralimab in improving perioperative treatment of MSI-H/dMMR locally advanced gastric adenocarcinoma.	Major pathological response (MPR), objective response rate (ORR), 3-year event-free survival (EFS) rate, 3-year disease-free survival (DFS) rate, overall survival (OS), and incidence of adverse events (including adverse reactions related to neoadjuvant and adjuvant therapy, and perioperative complications). Exploratory analyses of therapy-related biomarkers and mechanisms of resistance.

Study Phase	Phase II
Indication	Microsatellite instability-high / mismatch repair-deficient (MSI-H/dMMR) locally advanced gastric adenocarcinoma.
Eligibility Criteria	Inclusion Criteria: 1. Subjects voluntarily agree to participate in this study, are able to sign the informed consent form, and demonstrate good compliance. 2. Age 18 to 75 years (at the time of signing informed consent), regardless of sex. 3. Histologically confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma, diagnosed as locally advanced (clinical stage II to III by endoscopic ultrasound or contrast-enhanced CT/MRI according to the AJCC 8th edition), willing to undergo radical surgical resection, with the lesion assessed by the investigator as resectable; no prior systemic therapy for the current disease, including antitumor chemoradiotherapy or immunotherapy. 4. Biopsy of the lesion demonstrates dMMR status and concurrent MSI-H status. 5. ECOG performance status of 0 or 1. 6. Estimated life expectancy of at least 6 months.

7. Adequate function of major organs, meeting the following criteria:

• Complete blood count (without blood transfusion or hematopoietic stimulating factors within the prior 14 days): hemoglobin (Hb) ≥ 90 g/L; absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L; platelets (PLT) ≥ 100 × 10^9/L.

• 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; coagulation function: activated partial thromboplastin time (APTT), international normalized ratio (INR), and prothrombin time (PT) ≤ 1.5 × ULN.

• Doppler ultrasonography: left ventricular ejection fraction (LVEF) ≥ 50%.

8. Subjects of childbearing potential must use appropriate contraceptive methods during the study and for 120 days after the end of the study, must have a negative serum pregnancy test within 7 days prior to enrollment, and must not be breastfeeding.

Exclusion Criteria:

1. Diagnosis of any malignancy other than gastric cancer within 5 years prior to the first dose (excluding cured basal cell carcinoma of the skin, squamous cell carcinoma of the skin, radically resected carcinoma in situ, and papillary thyroid carcinoma cured by local treatment).

2. Currently participating in an interventional clinical trial, or having received another investigational drug or used an investigational device within 4 weeks prior to the first dose.

3. Systemic therapy with a proprietary Chinese medicine indicated for antitumor use or with an immunomodulatory agent (including thymosin, interferon, and interleukin, except for local use to control pleural effusion) within 2 weeks prior to the first dose.

4. Active autoimmune disease requiring systemic treatment (such as disease-modifying agents, corticosteroids, or immunosuppressants) within 2 years prior to the first dose. Replacement therapy (such as thyroxine, insulin, or physiological corticosteroids for adrenal or pituitary insufficiency) is not considered systemic treatment.

5. Systemic corticosteroid therapy (excluding intranasal, inhaled, or other forms of topical corticosteroids) or any other form of immunosuppressive therapy within 7 days prior to the first dose. Physiological doses of corticosteroids (≤ 10 mg/day of prednisone or equivalent) are permitted.

6. Known allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation.

7. Known allergy to any drug used in this study.

8. Peripheral neuropathy ≥ grade 2.

9. Known history of human immunodeficiency virus (HIV) infection (i.e., positive for HIV 1/2 antibodies).

10. Live vaccine administered within 30 days prior to the first dose (Cycle 1, Day 1). Inactivated seasonal influenza vaccine for injection is permitted within 30 days prior to the first dose; intranasal live attenuated influenza vaccine is not permitted.

11. Pregnant or breastfeeding women.

12. Presence of any severe or uncontrolled systemic disease, for example:

• Major and symptomatically severe, poorly controlled abnormalities of resting electrocardiogram in rhythm, conduction, or morphology.

• Unstable angina, congestive heart failure, or chronic heart failure of NYHA class ≥ 2.

	• Any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack. • History of non-infectious pneumonitis requiring corticosteroid therapy within 1 year prior to the first dose, or current clinically active interstitial lung disease. • Active pulmonary tuberculosis. • Active or uncontrolled infection requiring systemic therapy. • Clinically active diverticulitis, intra-abdominal abscess, or gastrointestinal obstruction. • Hepatic disease such as cirrhosis, decompensated liver disease, or acute or chronic active hepatitis. • Urinalysis showing urine protein ≥ ++ with confirmed 24-hour urine protein > 1.0 g. • Psychiatric disorders precluding cooperation with treatment. 13. History or evidence of disease, treatment, or laboratory abnormality that may interfere with the trial results or impede the subject's full participation, or any other condition deemed unsuitable for enrollment by the investigator, including other potential risks identified by the investigator.

Overall Design:

Study Type	Interventional
Specific Study Intervention	Neoadjuvant therapy: iparomlimab and tuvonralimab combination antibody 5 mg/kg, D1, every 3 weeks (q3w), for a total of 4 cycles. Radical surgical resection is performed within 4 to 8 weeks after the completion of the final neoadjuvant dose. Adjuvant therapy: iparomlimab and tuvonralimab combination antibody 5 mg/kg, D1, every 3 weeks (q3w), for a total of 4 cycles.
Estimated Study Duration	3 years.
Safety Assessment	Incidence and severity of adverse events (AE) and serious adverse events (SAE), and surgical safety.
Efficacy Assessment	Pathological complete response rate (pCR), major pathological response (MPR), objective response rate (ORR), 3-year event-free survival (EFS) rate, 3-year disease-free survival (DFS) rate, and overall survival (OS).
Statistical Analysis	Continuous data are summarized using mean, standard deviation, median, maximum, and minimum; categorical data are summarized using frequency and percentage, with 95% confidence intervals (CI) provided as necessary; time-to-event data are estimated using the Kaplan-Meier method, with survival curves plotted.

Number of Subjects: This is a single-arm, exploratory study; the primary efficacy endpoint is the pCR rate. Based on the 2024 Journal of Clinical Oncology Phase II study of sintilimab monotherapy and the 2023 BMC Cancer study of toripalimab monotherapy, the mean of the pCR rates reported in these two studies was adopted as the historical pCR rate of 28%. In this study, the iparomlimab and tuvonralimab regimen is expected to achieve a pCR rate of 50%. With a significance level α of 0.05 (one-sided) and a

power of 90%, calculation using PASS 15 software indicates that approximately 24 subjects are required. Considering a dropout rate of 15% and reserving an adequate sample size based on clinical practice (6 additional cases), a total of 30 subjects will be enrolled.

2. Study Background

2.1 Gastric Cancer is a Common Gastrointestinal Malignancy in China

According to the World Health Organization, gastric cancer ranks fifth in incidence and third in mortality among all malignancies worldwide, surpassed only by lung cancer and liver cancer in mortality [1]. China accounts for more than 40% of the world's newly diagnosed gastric cancer cases each year. Compared with the relatively low incidence in Europe and North America and the relatively high proportion of early-stage diagnoses in Japan and South Korea, China faces an extremely serious burden in combating gastric cancer [2]. Statistics indicate that East Asia accounts for 58% of the global incidence of gastric cancer, and the annual number of new cases in China approaches 400,000, with persistently high mortality. Nearly 90% of Chinese patients with gastric cancer have advanced-stage disease at the time of diagnosis, and the 5-year survival rate of advanced gastric cancer is only 10% to 49% [1, 3]. Therefore, the most important focus of gastric cancer treatment in China remains the effective management of locally advanced disease. How to improve the efficacy and ensure the safety of treatment for locally advanced gastric cancer will remain an arduous task for Chinese oncologists for a long period in the future.

Surgical resection of the tumor has long been considered the most effective and most established treatment for advanced gastric cancer. In 1881, Billroth performed the first successful gastric cancer resection [4]. Since then, surgical approaches for gastric cancer have continued to evolve. Following the publication of the 15-year follow-up results of the Dutch trial, D2 gastrectomy was ultimately established as the classical procedure for radical resection of gastric cancer, firmly consolidating the central role of surgery in gastric cancer treatment [5]. However, surgical treatment alone does not fully address the radical management of the tumor. Despite continuous advances in surgical techniques, instruments, and perioperative management, the local recurrence rate after gastric cancer surgery remains as high as 24% to 54%, and most patients with tumor recurrence die within 2 years; the outlook for surgery alone remains unsatisfactory [6].

Neoadjuvant treatment strategies have been widely applied in locally advanced gastric cancer with the aims of shrinking the tumor preoperatively, increasing the R0 resection rate, controlling micrometastases, and reducing postoperative recurrence and metastasis [7]. The National Comprehensive Cancer Network guidelines (United States), the European Society for Medical Oncology guidelines, the Japanese Gastric Cancer Association guidelines (5th edition), and the Chinese Society of Clinical Oncology guidelines all recommend neoadjuvant chemotherapy for patients with locally advanced gastric cancer [8, 9, 10, 11]. Studies have shown that neoadjuvant therapy can downstage the tumor and reduce tumor size, thereby improving treatment outcomes in locally advanced gastric cancer [7]. However, not all subtypes of gastric

cancer are suitable for conventional chemotherapy. The microsatellite instability-high / mismatch repair-deficient (dMMR/MSI-H) subtype in particular responds poorly to chemotherapy yet shows high sensitivity to immunotherapy, and more appropriate perioperative regimens are urgently needed [12].

2.2 Biological Characteristics and Therapeutic Challenges of dMMR/MSI-H Gastric Cancer

Microsatellite instability (MSI) refers to insertions or deletions in microsatellite repeat sequences caused by loss of mismatch repair (MMR) gene function, which may result from DNA methylation or genetic mutation [13]. Numerous studies have demonstrated that patients with MSI gastric cancer derive no benefit from chemotherapy, and the Chinese Society of Clinical Oncology guidelines do not recommend chemotherapy for these patients [11, 12]. Tumor cells with MSI are more readily recognized and eliminated by the immune system; therefore, blocking the immune evasion pathway with immunotherapeutic agents and restoring the sensitivity of the immune system can produce more substantial therapeutic efficacy [14]. To date, no consensus has been reached on perioperative adjuvant treatment for patients with MSI/dMMR locally advanced gastric cancer. The Chinese Society of Clinical Oncology guidelines recommend that these patients participate in immunotherapy clinical trials or undergo regular observation during the perioperative period [11].

2.3 Prospects for Immunotherapy in dMMR/MSI-H Gastric Cancer

Based on the high immunogenicity of MSI-H/dMMR gastric adenocarcinoma, immunotherapy has become the core therapeutic direction for this subtype and has made breakthrough progress in recent years, demonstrating broad clinical prospects. Immune checkpoint inhibitors, particularly PD-1 and PD-L1 inhibitors, can block the PD-1/PD-L1 pathway, release the inhibition of T lymphocytes by tumor cells, and activate the host antitumor immune response, thereby exerting antitumor effects [14]. The Phase II KEYNOTE-585 study (NCT03221426) [15] is one of the largest studies to date on neoadjuvant immunotherapy in MSI-H/dMMR locally advanced gastric adenocarcinoma. The study enrolled 82 patients treated with pembrolizumab (a PD-1 inhibitor) monotherapy as neoadjuvant therapy. The pCR rate reached 32.8%, the ORR reached 65.3%, and the 3-year postoperative progression-free survival (PFS) rate reached 78.5%, significantly superior to those of conventional neoadjuvant chemotherapy (pCR rate 12.3%; 3-year PFS rate 52.1%). A Phase II study of sintilimab monotherapy as neoadjuvant therapy (NCT04582345) enrolled 46 patients with MSI-H/dMMR locally advanced gastric adenocarcinoma; the pCR rate reached 34.2%, the major pathological response (MPR) rate reached 52.2%, and the incidence of grade 3 or higher treatment-related adverse events (TRAE) was only 8.7%, indicating a favorable safety profile.

Although the efficacy of PD-1 monotherapy is well established, single immune checkpoint blockade still has limitations. Exploring improved immunotherapy strategies, including dual-target combinations and bispecific antibodies, has therefore become a current research focus and is expected to further enhance treatment benefits in this population. The GERCOR NEONIPIGA trial showed that 58.6% of patients

with dMMR/MSI-H gastric cancer achieved pathological complete response (pCR) after neoadjuvant immunotherapy. In the INFINITY study, 18 patients with MSI-H/dMMR resectable gastric adenocarcinoma received preoperative tremelimumab combined with durvalumab for 3 months, achieving a pCR rate of 60% and an MPR rate of 80% [16]. The PANDA trial demonstrated that atezolizumab combined with chemotherapy as neoadjuvant treatment achieved an MPR rate of 70%, a pCR rate of 45%, and an R0 resection rate of 95% [17]. These results indicate that immunotherapy, particularly dual immune checkpoint inhibitor combinations, has significant advantages in the neoadjuvant treatment of dMMR/MSI-H gastric cancer, effectively reducing tumor volume, increasing surgical resection rates, and lowering postoperative recurrence risk [18].

2.4 Innovative Features and Clinical Advantages of Iparomlimab and Tuvonralimab (QL1706)

Iparomlimab and tuvonralimab (QL1706) is the world's first PD-1/CTLA-4 bifunctional combination antibody, developed on the MabPair® biotechnology platform, with distinctive pharmacological properties and clinical advantages. QL1706 consists of an anti-PD-1 antibody (iparomlimab) and an anti-CTLA-4 antibody (tuvonralimab) in a 2:1 ratio, and is capable of simultaneously blocking the PD-1/PD-L1 and CTLA-4 immune checkpoint pathways to achieve synergistic effects. Compared with the combined use of a PD-1 inhibitor and a CTLA-4 inhibitor as two separate agents, iparomlimab and tuvonralimab show more favorable pharmacokinetic characteristics with stronger target specificity, reduced off-target effects, and a lower incidence of adverse reactions, while offering a simpler administration regimen without the need for co-administration of two separate agents, thereby improving patient compliance [19].

Clinical data show that QL1706 exhibits excellent efficacy and safety across multiple tumor types. In cervical cancer, the DUBHE-C-206 study demonstrated that QL1706 monotherapy in patients with recurrent or metastatic cervical cancer who had failed prior platinum-containing chemotherapy achieved an ORR of 33.8%, a disease control rate (DCR) of 64.9%, and a median PFS of 5.4 months [20]. In hepatocellular carcinoma, the DUBHE-H-308 study showed that QL1706 combined with bevacizumab achieved an ORR of 40%, a median PFS of 8.1 months, and a 12-month OS rate of 73.3% [21]. In non-small cell lung cancer, cohort 5 of the Tianshu DUBHE-L-201 study evaluated a four-drug combination of QL1706 with bevacizumab, pemetrexed, and carboplatin, achieving a median PFS of 8.51 months and a median OS of 26.51 months, with grade 3 or higher TRAEs occurring in only 35.5% of patients, indicating substantial long-term survival benefit and a manageable safety profile [22].

2.5 Significance and Future Outlook of the Study

Conducting a prospective, single-arm, single-center Phase II clinical trial of iparomlimab and tuvonralimab as neoadjuvant immunotherapy for dMMR/MSI-H locally advanced gastric adenocarcinoma is of substantial significance. First, exploring the application of QL1706 in the neoadjuvant treatment of dMMR/MSI-H gastric cancer will provide new reference for clinical practice.

Second, by evaluating the performance of QL1706 in improving perioperative treatment efficacy and safety, this study can lay the groundwork for subsequent multicenter, randomized controlled Phase III studies. In addition, the exploration of therapy-related biomarkers and mechanisms of resistance will help to achieve precision treatment and improve individualized care. In the long term, this study is expected to drive a paradigm shift in the treatment of dMMR/MSI-H gastric cancer and may transform the current perioperative treatment model for this subtype, providing patients with dMMR/MSI-H gastric cancer with improved therapeutic options. Furthermore, exploring the possibility of an organ-preservation (surgery-sparing) strategy may offer some patients non-surgical treatment options, thereby reducing surgical trauma and complications and improving quality of life.

In summary, iparomlimab and tuvonralimab, as a novel dual immune checkpoint inhibitor combination antibody, is expected to provide a more effective perioperative regimen for patients with dMMR/MSI-H gastric cancer, based on its excellent performance in other tumor types and its distinctive pharmacological properties. This Phase II clinical trial will help evaluate the efficacy, safety, and long-term benefit of QL1706 in the neoadjuvant treatment of dMMR/MSI-H gastric cancer, providing new reference for clinical practice and promoting innovation and progress in gastric cancer treatment.

3. Study Objectives

Primary Study Objective: To evaluate the efficacy of iparomlimab and tuvonralimab in improving perioperative treatment of MSI-H/dMMR locally advanced gastric adenocarcinoma.

Secondary Study Objective: To evaluate the safety and long-term benefit of iparomlimab and tuvonralimab in improving perioperative treatment of MSI-H/dMMR locally advanced gastric adenocarcinoma.

Primary Study Endpoint:

Pathological complete response (pCR) rate: defined as the proportion of subjects in whom no viable tumor cells are microscopically present in the resected primary tumor specimen and all examined lymph nodes are negative, expressed as a percentage of all subjects.

Secondary Study Endpoints:

Major pathological response (MPR) rate: defined as the proportion of subjects in whom viable tumor cells account for ≤ 10% of the resected specimen, expressed as a percentage of all subjects.

Objective response rate (ORR): defined as the proportion of patients whose tumor volume is reduced to a prespecified extent and maintained for a minimum required duration, including complete response (CR) and partial response (PR).

3-year event-free survival (EFS) rate: the proportion of patients experiencing an event within 3 years among all enrolled patients. EFS is defined as the time from the start of treatment to the first occurrence of any of the following events: disease progression precluding surgery, local or distant recurrence, or

death from any cause.

3-year disease-free survival (DFS) rate: the proportion of patients without disease recurrence or death within 3 years among all patients who underwent radical surgery. DFS is defined as the time from surgery to the first radiologic recurrence of disease or death, whichever occurs first.

Overall survival (OS): the time from pathological diagnosis to death from any cause.

Exploratory analyses of therapy-related biomarkers and mechanisms of resistance.

Safety Assessment: Incidence and severity of adverse events (AE) and serious adverse events (SAE), and surgical safety. Drug-related adverse reactions are graded according to NCI-CTCAE version 5.0; surgical complications are defined and graded according to the Clavien-Dindo classification system.

Biological samples including peripheral blood, urine, and feces will be collected before treatment, after 2 cycles of treatment, before surgery, and 1 month after surgery. At each time point, 5 mL of peripheral blood, 10 mL of urine, and 10 g of feces will be collected. Peripheral blood will be used for circulating tumor cell detection. Biopsy and surgical tissue specimens will be used to screen for treatment-related biomarkers, with sample size approximately that of a red bean and on the condition that pathological diagnosis is not affected. Biological samples will be used solely for the exploration of biomarkers and mechanisms of resistance related to gastric cancer, and all samples will be destroyed within 3 years after the end of subject enrollment.

4. Study Design

4.1 Overall Design

This study is a prospective, single-arm, single-center Phase II clinical trial of iparomlimab and tuvonralimab as neoadjuvant immunotherapy for MSI-H/dMMR locally advanced gastric adenocarcinoma. Patients who meet the inclusion and exclusion criteria will, after being fully informed and signing the written informed consent form, be enrolled in this study. Patients will first receive 4 cycles of neoadjuvant immunotherapy with iparomlimab and tuvonralimab, followed by imaging assessment of tumor regression. All patients will subsequently undergo radical surgical resection. Postoperatively, patients will receive 4 cycles of adjuvant immunotherapy with iparomlimab and tuvonralimab. After completion of treatment, patients will enter the regular follow-up phase. This is a single-arm, exploratory study with pCR rate as the primary efficacy endpoint. Based on the 2024 Journal of Clinical Oncology Phase II study of sintilimab monotherapy and the 2023 BMC Cancer study of toripalimab monotherapy, the mean of the pCR rates reported in these two studies was adopted as the historical pCR rate of 28%. In this study, the iparomlimab and tuvonralimab regimen is expected to achieve a pCR rate of 50%. With a significance level α of 0.05 (one-sided) and a power of 90%, calculation using PASS 15 software indicates that approximately 24 subjects are required. Considering a dropout rate of 15% and reserving an adequate sample size based on clinical practice (6 additional cases), a total of 30 subjects will be enrolled.

4.2 Study Flow Chart

[Study flow chart to be inserted; same as in the original Chinese protocol.]

4.3 Study Procedures

4.3.1 Screening Period

With the exception of imaging examinations, written informed consent must be obtained before any trial-specified medical procedures are performed; however, CT/MRI scan results obtained prior to signing informed consent to participate may be used for tumor evaluation during the screening period (the examination must have been performed within 28 days before the start of study treatment). The window for observation indicators and examinations is 3 days, and all must be completed before the start of the treatment cycle.

Within 28 days before the start of the trial (Day -28 to Day -1), the following items will be observed and assessed:

- All enrolled subjects must sign the informed consent form prior to initiation of any screening procedure.
- Demographic characteristics, body weight, height, medical history and other prior history, and oncologic history will be collected.
- Concomitant medications and treatments received within 28 days prior to the first study drug administration will be recorded.
- Subjects' prior biopsy results for mismatch repair protein status and microsatellite status will be collected.
- Vital signs and physical examination will be performed.
- The following laboratory examinations will be performed: complete blood count; biochemistry including myocardial enzymes and amylase; urinalysis with urinary sediment; coagulation function; 8-item pituitary panel; 12-lead electrocardiogram; and echocardiography (results from previously performed examinations at the study center are acceptable, provided that the examination was completed within 28 days before the first study drug administration). Pregnancy testing (serum pregnancy test) will be performed within 7 days prior to the first dose.
- Serum virology testing will be performed: hepatitis B five-item panel; quantitative HBV-DNA (if HBsAg positive); hepatitis C antibody (HCVAb); quantitative HCV RNA (if HCVAb positive); and antibodies to human immunodeficiency virus (HIVAb). Results obtained within 28 days before the first study drug administration are acceptable.
- Tumor assessment: gastroscopy with biopsy for pathology and immunohistochemical staining; contrast-enhanced CT or MRI of the chest, abdomen, and pelvis, and of any other site suspected of metastasis based on the investigator's judgment. Results from the study center within 28 days before the first dose are acceptable, provided the same modality is used throughout the study.
- ECOG performance status.

4.3.2 Eligibility Criteria

Inclusion Criteria:

- Subjects voluntarily agree to participate in this study, are able to sign the informed consent form, and demonstrate good compliance.
- Age 18 to 75 years (at the time of signing informed consent), regardless of sex.
- Histologically confirmed gastric adenocarcinoma, diagnosed as locally advanced (clinical stage II to III by endoscopic ultrasound or contrast-enhanced CT/MRI according to the AJCC 8th edition), willing to undergo radical surgical resection, with the lesion assessed by the investigator as resectable; no prior systemic therapy for the current disease, including antitumor chemoradiotherapy or immunotherapy.
- Biopsy of the lesion demonstrates dMMR status and concurrent MSI-H status.
- ECOG performance status of 0 or 1.
- Estimated life expectancy of at least 6 months.
- Adequate function of major organs, meeting the following criteria:
    - Complete blood count (without blood transfusion or hematopoietic stimulating factors within the prior 14 days): hemoglobin (Hb) ≥ 90 g/L; absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L; platelets (PLT) ≥ 100 × 10^9/L.
    - 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; coagulation function: activated partial thromboplastin time (APTT), international normalized ratio (INR), and prothrombin time (PT) ≤ 1.5 × ULN.
    - Doppler ultrasonography: left ventricular ejection fraction (LVEF) ≥ 50%.
- Subjects of childbearing potential must use appropriate contraceptive methods during the study and for 120 days after the end of the study, must have a negative serum pregnancy test within 7 days prior to enrollment, and must not be breastfeeding.

Exclusion Criteria:

- Diagnosis of any malignancy other than gastric cancer within 5 years prior to the first dose (excluding cured basal cell carcinoma of the skin, squamous cell carcinoma of the skin, radically resected carcinoma in situ, and papillary thyroid carcinoma cured by local treatment).
- Currently participating in an interventional clinical trial, or having received another investigational drug or used an investigational device within 4 weeks prior to the first dose.
- Systemic therapy with a proprietary Chinese medicine indicated for antitumor use or with an immunomodulatory agent (including thymosin, interferon, and interleukin, except for local use to control pleural effusion) within 2 weeks prior to the first dose.
- Active autoimmune disease requiring systemic treatment (such as disease-modifying agents, corticosteroids, or immunosuppressants) within 2 years prior to the first dose. Replacement

therapy (such as thyroxine, insulin, or physiological corticosteroids for adrenal or pituitary insufficiency) is not considered systemic treatment.

- Systemic corticosteroid therapy (excluding intranasal, inhaled, or other forms of topical corticosteroids) or any other form of immunosuppressive therapy within 7 days prior to the first dose. Physiological doses of corticosteroids (≤ 10 mg/day of prednisone or equivalent) are permitted.
- Known allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation.
- Known allergy to any drug used in this study.
- Peripheral neuropathy ≥ grade 2.
- Known history of HIV infection (i.e., positive for HIV 1/2 antibodies).
- Live vaccine administered within 30 days prior to the first dose (Cycle 1, Day 1). Inactivated seasonal influenza vaccine for injection is permitted within 30 days prior to the first dose; intranasal live attenuated influenza vaccine is not permitted.
- Pregnant or breastfeeding women.
- Presence of any severe or uncontrolled systemic disease, for example:
    - Major and symptomatically severe, poorly controlled abnormalities of resting electrocardiogram in rhythm, conduction, or morphology.
    - Unstable angina, congestive heart failure, or chronic heart failure of NYHA class ≥ 2.
    - Any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack.
    - History of non-infectious pneumonitis requiring corticosteroid therapy within 1 year prior to the first dose, or current clinically active interstitial lung disease.
    - Active pulmonary tuberculosis.
    - Active or uncontrolled infection requiring systemic therapy.
    - Clinically active diverticulitis, intra-abdominal abscess, or gastrointestinal obstruction.
    - Hepatic disease such as cirrhosis, decompensated liver disease, or acute or chronic active hepatitis.
    - Urinalysis showing urine protein ≥ ++ with confirmed 24-hour urine protein > 1.0 g.
    - Psychiatric disorders precluding cooperation with treatment.
- History or evidence of disease, treatment, or laboratory abnormality that may interfere with the trial results or impede the subject's full participation, or any other condition deemed unsuitable for enrollment by the investigator, including other potential risks identified by the investigator.

4.3.3 Treatment Period

Neoadjuvant Treatment Period

During the treatment period, before the start of each new cycle, subjects should attend the study center for relevant examinations and assessments. After completion of 4 cycles of neoadjuvant therapy, surgery will

be performed within 4 to 8 weeks.

- The dose is calculated based on body weight and administered accordingly.
- Within 7 days prior to the first dose: vital signs, body weight measurement, ECOG performance status, physical examination, complete blood count, biochemistry including myocardial enzymes and amylase, urinalysis with urinary sediment, 8-item pituitary panel, tumor markers, and electrocardiogram. If screening examinations were completed within 7 days prior to the first dose of Cycle 1, they do not need to be repeated.
- On Days 8 and 15 after dosing, complete blood count will be repeated; if myelotoxicity occurs, dosing will be adjusted in a timely manner.
- Within 3 days prior to the second through fourth doses: vital signs, body weight measurement, ECOG performance status, physical examination, complete blood count, biochemistry including myocardial enzymes and amylase, urinalysis with urinary sediment, 8-item pituitary panel, and electrocardiogram.
- Imaging examinations: plain plus contrast-enhanced CT or MRI of the abdomen and pelvis; plain plus contrast-enhanced CT or MRI of any other site suspected of metastasis based on the investigator's judgment (per clinical indication); CT or MRI of the brain (per clinical indication); bone scan (per clinical indication). Imaging is performed every 6 weeks (± 3 days), calculated from the date of the first dose.
- Tumor assessment is performed according to RECIST 1.1 (every 6 weeks ± 3 days, calculated from the date of the first dose).
- Adverse event information will be collected.

Surgery

- Date of surgery, name and type of procedure.
- Perioperative complications will be collected.
- Pathological response assessment.

Adjuvant Treatment Period

During the treatment period, before the start of each new cycle, subjects should attend the study center for relevant examinations and assessments.

- The dose is calculated based on body weight and administered accordingly.
- Within 7 days prior to the first dose: vital signs, body weight measurement, ECOG performance status, physical examination, complete blood count, biochemistry including myocardial enzymes and amylase, urinalysis with urinary sediment, 8-item pituitary panel, and electrocardiogram.
- Within 3 days prior to the second through fourth doses: vital signs, body weight measurement, ECOG performance status, physical examination, complete blood count, biochemistry including myocardial enzymes and amylase, urinalysis with urinary sediment, 8-item pituitary panel, and electrocardiogram.

- Imaging examinations: plain CT of the chest; plain plus contrast-enhanced CT of the abdomen and pelvis, or abdominal and pelvic ultrasound, to assess for recurrence or metastasis, at the frequency recommended by current guidelines.
- Adverse event information will be collected.

4.3.4 Dose Modification

Every effort should be made to administer the study drug at the planned dose and on the planned schedule. In the event of grade II or higher adverse reactions, dosing may be delayed or reduced. When multiple adverse reactions occur simultaneously, dose modification should be based on the most severe adverse reaction observed. Subjects must be instructed to notify the investigator at the first occurrence of any adverse symptoms.

- Dose modification of iparomlimab and tuvonralimab (see Appendix 1).

4.3.5 Follow-up Period

Subjects who discontinue study drug administration for any reason will enter the follow-up period and undergo the following follow-up procedures until survival follow-up is completed:

Safety Follow-up: The safety follow-up period extends from the last dose of the study drug or from the date of surgery to 30 ± 7 days thereafter, or until the initiation of other antitumor therapy (whichever occurs first), during which AEs and concomitant medications and treatments will be assessed.

Survival Follow-up: After the safety follow-up, survival follow-up will be conducted. Using the last safety follow-up as the reference time point, follow-up will be performed every 6 months (± 2 weeks), including telephone follow-up, to record whether the subject has received any other antitumor therapy since the previous follow-up. If other treatment is received, the treatment regimen, number of cycles, best therapeutic response, and time to disease progression must be recorded. Follow-up will continue until the subject's death; the relevant cause and specific time of death will be recorded to determine overall survival (OS).

Note: If a subject does not have a 30-day safety visit, the survival follow-up will be calculated from the end of treatment.

4.3.6 Early Termination or Withdrawal

Withdrawal Criteria:

- Intolerable toxicity during treatment that prevents completion of the study treatment regimen.
- Receipt of antitumor therapy not specified in this protocol during the treatment period.
- Pyloric obstruction, gastric perforation, or gastric hemorrhage occurring after enrollment that requires emergency surgery.
- Tumor progression during the treatment period.
- Withdrawal at the request of the patient for any reason after enrollment.

- Inability of the patient to complete the study plan for any reason after enrollment.
- Subjects withdrawing from the study prematurely should complete one full tumor imaging examination (unless one has been performed within the previous 30 days). Thereafter, imaging examinations should continue whenever possible until the subject experiences disease progression, dies, or starts new antitumor therapy (whichever occurs first).

4.4 Statistical Analysis

4.4.1 Analysis Populations

Full Analysis Set (FAS): based on the intention-to-treat (ITT) principle, efficacy will be analyzed in all subjects who undergo surgery.

Per-Protocol Set (PPS): all subjects who comply with the trial protocol, demonstrate good compliance, do not take prohibited medications during the trial, and complete the required entries in the case report form. No imputation will be performed for missing data. Drug efficacy will be analyzed in both the FAS and PPS.

Safety Analysis Set (SAS): all enrolled subjects who have received at least one dose of the investigational drug and have post-dose safety records. This data set will be used for safety analysis.

In this study, baseline data will be analyzed using the FAS; all efficacy parameters will be analyzed using both the FAS and PPS; safety analysis will use the SAS.

4.4.2 Statistical Methods

Unless otherwise specified, data in this study will be summarized according to the following general principles:

Statistical analysis will be performed using SPSS software: continuous data will be summarized using mean, standard deviation, median, maximum, and minimum; categorical data will be summarized using frequency and percentage, with 95% confidence intervals (CI) provided as necessary; time-to-event data will be estimated using the Kaplan-Meier method, with survival curves plotted.

4.5 Efficacy and Safety Assessment

4.5.1 Efficacy Assessment

Efficacy Assessment Parameters

Primary endpoint: pathological complete response rate (pCR).

Secondary endpoints: major pathological response rate (MPR), objective response rate (ORR), 3-year event-free survival (EFS) rate, 3-year disease-free survival (DFS) rate, overall survival (OS), safety, and exploratory analyses of therapy-related biomarkers and mechanisms of resistance.

Efficacy Assessment Criteria

pCR and MPR will be assessed according to the Becker classification system; ORR will be assessed by imaging according to iRECIST 1.0. Tumor response assessment will include all known or suspected sites of disease. High-resolution CT with oral and intravenous contrast, or contrast-enhanced MRI, is the preferred imaging modality for assessing radiologic tumor response. For subjects allergic to CT contrast media, non-contrast chest and pelvic CT may be used, with non-contrast MRI of the upper abdomen and brain as substitutes.

4.5.2 Safety Assessment

Safety Assessment Parameters

Safety assessment parameters include: incidence and severity of adverse events (AE) and serious adverse events (SAE), and surgical safety.

Safety Assessment Standards

AE assessment includes type, incidence, severity, time of onset and resolution, classification as serious or not, adverse events of special interest, relationship to treatment/drug, and outcome.

4.6 Adverse Events and Serious Adverse Events

4.6.1 Adverse Events (AE)

Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical trial subject following administration of a pharmaceutical product, which does not necessarily have a causal relationship with treatment. An AE may be any unfavorable and unintended symptom, sign, laboratory abnormality, or disease, and includes at least the following situations:

1. Worsening of a preexisting medical condition or disease (existing before entry into the trial), including worsening of symptoms, signs, or laboratory abnormalities.

2. Any newly occurring AE: any new untoward medical condition (including symptoms, signs, or newly diagnosed disease).

3. Abnormal laboratory values or findings of clinical significance.

AE assessment includes type, incidence, severity (graded according to NCI-CTCAE version 5.0), time of onset and resolution, management measures, classification as serious or not, causality, and outcome.

AEs occurring during the study period, including signs and symptoms during the screening period, will be recorded on the AE page of the CRF.

Criteria for Assessing AE Severity

Severity will be graded according to NCI-CTCAE version 5.0. For AEs not listed in NCI-CTCAE version 5.0, the following reference criteria apply:

Reference criteria for the severity of AEs not listed in NCI-CTCAE version 5.0:

Grade	Clinical Description of Severity
1	Mild; asymptomatic or with mild symptoms; clinical or diagnostic observations only; no intervention indicated.
2	Moderate; requires minimal, local, or non-invasive intervention; limits age-appropriate instrumental activities of daily living (such as preparing meals, shopping for clothes, using the telephone, and managing money).
3	Severe or medically significant but not immediately life-threatening; results in hospitalization or prolongation of hospitalization; disabling; limits self-care activities of daily living (such as bathing, dressing, eating, using the toilet, and taking medications), but not bedridden.
4	Life-threatening; urgent intervention indicated.
5	Death related to the AE.

Postoperative adverse events mainly include early complications occurring within 30 days after surgery and the resulting prolonged hospitalization, reoperation, or readmission, as well as late complications occurring more than 30 days after surgery. When postoperative complications occur, the type, time of onset, and specific treatment regimen of each complication should be recorded in detail. Complications occurring after discharge, together with their type, time of onset, and specific treatment regimen, must be recorded in detail during readmission or follow-up.

Early postoperative complications (within 30 days after surgery): when early postoperative complications occur, patients will be classified by complication grade and treatment regimen for each complication.

Table: Definition and Grading of Complications (Clavien-Dindo Classification System)

Grade	Definition
I	Any deviation from the normal postoperative course without need for pharmacological treatment, surgical, endoscopic, or radiological interventions. Allowed therapeutic regimens are limited to antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requires pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusion and total parenteral nutrition are also included.
III	Requires surgical, endoscopic, or radiological intervention.
IIIa	Intervention not under general anesthesia.
IIIb	Intervention under general anesthesia.
IV	Life-threatening complications (including central nervous system complications) requiring intensive care unit management.
IVa	Single-organ dysfunction (including dialysis).
IVb	Multi-organ dysfunction.
V	Death of the patient.

Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" is added to the grade of the complication. This label indicates that follow-up is required to fully evaluate the complication.

Late postoperative complications (more than 30 days after surgery):

- Postoperative small bowel obstruction: abdominal pain occurring more than 30 days after surgery, diagnosed as intestinal obstruction by imaging examination, and requiring treatment.
- Postoperative anastomotic stricture: nausea occurring more than 30 days after surgery, confirmed as anastomotic stricture by endoscopy, and requiring treatment.
- Chronic incisional complications: chronic incisional complications, such as incisional hernia, occurring in the abdominal incision or trocar insertion sites more than 30 days after surgery.
- Other: other complications occurring more than 30 days after surgery that require treatment.

Assessment of Causality Between Adverse Events and Study Drug

The investigator should assess the potential association between an adverse event and the investigational drug. The following 5 criteria may be applied and judged as shown in the table below.

- Is there a reasonable temporal relationship between the start of drug administration and the onset of the adverse reaction?
- Is the suspected adverse reaction consistent with the known type of adverse reactions of the drug?
- Can the suspected adverse reaction be explained by the patient's underlying condition, concomitant medications, or concomitant or prior treatments?
- Does the adverse reaction improve or resolve after dose reduction or drug discontinuation?
- Does the same reaction recur upon re-exposure to the suspected drug?

	1	2	3	4	5
Definitely related	+	+	—	+	+
Probably related	+	+	—	+	?
Possibly related	+	+	±	±	?
Possibly unrelated	+	—	±	±	?
Definitely unrelated	—	—	+	—	—

Note: "+" denotes affirmative; "—" denotes negative; "±" denotes difficult to determine; "?" denotes unknown.

Cases judged as definitely related, probably related, or possibly related are counted as adverse drug reactions and used to calculate the incidence of adverse drug reactions.

Collection and Recording of Adverse Events

All adverse events must be recorded in the study records. For each adverse event, the investigator must

assess and record its severity, duration, relationship to surgery or drug treatment, measures taken, and outcome.

4.6.2 Serious Adverse Events (SAE)

Definition of Serious Adverse Events

A serious adverse event is a medical event occurring during a clinical study that requires hospitalization or prolongs hospitalization, causes disability, affects working ability, is life-threatening, results in death, or causes congenital malformation. SAEs include the following untoward medical events:

- Events resulting in death.
- Life-threatening events (defined as those in which the subject is at immediate risk of death at the time of the event).
- Events requiring hospitalization or prolongation of hospitalization.
- Events resulting in permanent or substantial disability/incapacity or affecting working ability.
- Other important medical events that may not immediately threaten life, cause death, or require hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (such as drug therapy or surgery) to prevent any of the outcomes listed in the definition above.

Reporting of Serious Adverse Events

The investigator must complete the serious adverse event report form within 24 hours of becoming aware of the SAE, and submit a written report to the Ethics Committee and the appropriate regulatory authority. The written report must include the time of occurrence, severity, duration, measures taken, and outcome of the SAE.

5. Benefit-Risk Assessment

5.1 Benefits

This study aims to provide a new therapeutic regimen for patients with MSI-H/dMMR locally advanced gastric adenocarcinoma. Subjects participating in this clinical trial may or may not receive direct medical benefit, including more thorough oncologic eradication and improved long-term survival. During the study, the study drug related to this research will be provided free of charge according to the protocol, which may reduce the economic burden on subjects to some extent. The laboratory and imaging examinations specified in this protocol are routine diagnostic and therapeutic examinations and do not impose additional burden or cost on patients. Relevant information and results obtained from this study will be provided to patients in due course. The information obtained from this study is intended to provide guidance for the future care of patients with gastric cancer.

5.2 Risks

5.2.1 Adverse Reactions Possibly Caused by Neoadjuvant and Adjuvant Therapy

The investigational drug iparomlimab and tuvonralimab is a marketed product. Drug-related adverse reactions are predominantly immune-related. Common types include hypothyroidism, hyperthyroidism, rash, and pruritus. Multi-system immune-related adverse reactions, including immune-related pneumonitis, diarrhea and colitis, hepatitis, myocarditis, pancreatitis, adrenal insufficiency, hyperglycemia, type 1 diabetes mellitus, thrombocytopenia, and nephritis, may also occur. Some adverse reactions may progress to grade 3 or higher; a small number of cases of fatal immune-related adverse events have been reported. The overall safety profile is consistent with that of other immune checkpoint inhibitors of the same class.

Among 666 patients who received this product as monotherapy, the incidence of adverse reactions of any grade was 77.5%. Adverse reactions with an incidence > 10% included: rash (19.8%), hypothyroidism (16.1%), hyperthyroidism (13.2%), pruritus (12.6%), fatigue (12.5%), anemia (12.5%), elevated aspartate aminotransferase (12.2%), and elevated alanine aminotransferase (11.3%). The incidence of grade 3 or higher adverse reactions was 25.4%, including the following events with an incidence > 1%: anemia (4.4%), decreased lymphocyte count (2.7%), pneumonitis (1.8%), elevated lipase (1.5%), decreased platelet count (1.5%), elevated aspartate aminotransferase (1.4%), infectious pneumonia (1.4%), rash (1.2%), elevated γ-glutamyl transferase (1.2%), decreased neutrophil count (1.2%), fatigue (1.1%), and elevated alanine aminotransferase (1.1%). With respect to immune-related adverse reactions, thyroid-related toxicities were the most common, with 105 cases of hypothyroidism (15.8%), 88 cases of hyperthyroidism (13.2%), and 7 cases of thyroiditis (1.1%). Immune-related cutaneous adverse reactions occurred in 72 cases (10.8%). Immune-related pneumonitis occurred in 24 cases (3.6%); immune-related hepatitis in 3 cases (0.5%); and immune-related myocarditis in 8 cases (1.2%). Other immune-related adverse reactions, such as immune-related gastrointestinal toxicity, pancreatic toxicity, hypophysitis, hypopituitarism, adrenal insufficiency, nephrotoxicity, hematologic toxicity, neurotoxicity, and ocular and oral toxicity, each occurred at an incidence below 1%. In addition, 55 cases of infusion-related reactions (8.3%) were reported, predominantly grade 1 to 2, most of which resolved with symptomatic treatment. The anti-drug antibody positivity rate of this product was 33.5% to 34.1%, with no significant impact on drug efficacy or safety.

5.2.2 Surgical Risks

During anesthesia, possible events include anesthetic drug allergy, cardiovascular and cerebrovascular complications, airway injury due to endotracheal intubation, and respiratory dysfunction. During the surgical procedure, possible events include intraoperative injury to important organs, vascular bleeding, and intra-abdominal infection. Postoperatively, possible complications include intra-abdominal bleeding, anastomotic leakage, duodenal stump leakage, anastomotic bleeding, intestinal obstruction, intra-abdominal or pelvic infection, respiratory tract infection, urinary tract infection, lower extremity venous thrombosis, pulmonary embolism, and incisional infection, fat liquefaction, dehiscence, or delayed healing.

5.2.3 Imaging Examination Risks

During imaging examinations, contrast media allergy may occur, including rash, asthma, hypotension, dizziness, and anaphylactic shock.

5.2.4 Risks of Blood Sampling

This study requires collection of 5 mL of peripheral venous blood at the following time points: before treatment, after 2 cycles of neoadjuvant therapy, before surgery, and 1 month after surgery. Study-related blood sampling will be performed together with routine blood sampling, with no separate venipuncture, although it may increase the patient's risk to some extent. Risks of venous blood sampling from the arm include transient discomfort and/or bruising. Although unlikely, infection, bleeding, clotting, or syncope may occur.

5.2.5 Risks for Subjects of Reproductive Age

The drugs used during treatment may be harmful to fetal development. Patients enrolled in this study are advised to use medically accepted effective contraceptive methods (including barrier contraception, surgical contraception, and abstinence) from the time of signing the informed consent form until 3 months after the last dose. Unintended pregnancy may cause harm to the fetus and may increase the risk of hereditary diseases in offspring. Drug treatment and surgical procedures may impair ovarian or testicular function, affect hormone levels, and thus have long-term effects on reproductive function and cause infertility; fertility preservation measures such as oocyte or sperm cryopreservation may be considered for patients with relevant needs.

5.2.6 Risk of Disease Progression

During neoadjuvant therapy for gastric cancer, tumor progression may occur if treatment is ineffective, and some patients may lose the opportunity for surgery. The study team will closely monitor the dynamic changes in tumor markers during treatment in conjunction with imaging examinations. If rapid elevation of tumor markers occurs during treatment, the team will convene a multidisciplinary team (MDT) discussion for timely intervention.

5.2.7 Unknown Risks

There may be currently unforeseen risks and adverse reactions.

6. Data Management and Record Retention

Data management in this study will be conducted using case report forms (CRF) for data collection and management. The data collection forms, study procedures, names of data forms, and data items to be collected will be designed in accordance with the protocol requirements, and corresponding data collection guidelines will be developed. The data administrator will design the CRF based on the study protocol and study records. After the trial is completed, CRFs will be retained for 7 years.

During the study period, patient information will be replaced by codes or numbers and kept strictly

confidential; only relevant physicians will be informed, and patient privacy will be well protected. Study results may be published in journals, but no personal patient information will be disclosed.

7. Ethical Considerations

7.1 Ethical Regulations and Policies

This study will be conducted in accordance with the Declaration of Helsinki, the Ethics Review Measures for Biomedical Research Involving Human Subjects, the Good Clinical Practice for Drug Clinical Trials, and other applicable laws, regulations, and international standards. Before the start of the trial, the relevant documents submitted to the Ethics Committee must be reviewed and approved by the Ethics Committee before the study can be initiated. Any modification of the study protocol during the clinical research must be approved by the Ethics Committee before implementation. Any event during the trial or research that may affect the safety of subjects or the continued conduct of the clinical trial must be submitted to the Ethics Committee for review or for documentation.

7.2 Informed Consent

Before participating in this study, each subject, or his or her legal guardian, must read the informed consent form. After detailed explanation by the study physician, sufficient time must be provided so that the subject or the guardian fully understands the details of the study and is fully informed. The subject has the right to voluntarily choose whether to participate or to withdraw at any time. Any revision of the informed consent form must be approved by the Ethics Committee of the participating institution before implementation; subjects who have not withdrawn must re-sign the updated informed consent form. The informed consent form must be voluntarily signed by the subject or his or her legal guardian.

7.3 Privacy Protection

Collection and processing of personal data of subjects enrolled in this study will be limited to the data necessary to achieve the study objectives. Adequate precautions must be taken when collecting and processing these data to ensure confidentiality and compliance with applicable data privacy regulations. Appropriate technical and organizational measures must be in place to prevent unauthorized disclosure or access to personal data, accidental or unlawful destruction of data, and accidental loss or alteration of data. Sponsor personnel who, in the course of their duties, are required to access personal data must agree to maintain the confidentiality of subjects' information. The informed consent of the subject (or legal guardian) includes explicit consent to the processing of personal data and explicit consent that the investigator and study institution may directly access the subject's original medical records (source data/documents) for purposes related to study monitoring, auditing, ethics committee review, and regulatory inspection. During the study, the subject's name, sex, and other personally identifiable information will be replaced by codes or numbers and kept strictly confidential; only relevant physicians will have access to the subject's personal information, and the subject's privacy will be well protected. Study results may be published in journals, but no personally identifiable information of any subject will

be disclosed.

7.4 Protocol Deviations

Investigators or trained study personnel must read the protocol in full and adhere to it strictly. Immediate emergency interventions taken based on considerations of subject protection, safety, and health may be considered exceptions. In the event of major protocol deviations caused by emergencies, accidents, or errors, the investigator or designated personnel must notify the Ethics Committee at the participating center and the sponsor as soon as possible.

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9. Appendices

Appendix 1: Dose Modification Schedule for Iparomlimab and Tuvonralimab

Immune-Related Adverse Reaction	Severity	Treatment Modification
Pneumonitis	Grade 2	Withhold dosing until the adverse reaction recovers to grade 0–1.
	Grade 3 or 4	Permanently discontinue.
Diarrhea and Colitis	Grade 2 or 3	Withhold dosing until the adverse reaction recovers to grade 0–1.
	Grade 4	Permanently discontinue.
Hepatitis (in patients without hepatocellular carcinoma)	Grade 2; AST or ALT 3–5 × ULN, or TBIL 1.5–3 × ULN	Withhold dosing until the adverse reaction recovers to grade 0–1 and prednisone is at ≤ 10 mg/day or equivalent.
	Grade 3 or 4; AST or ALT > 5 × ULN, or TBIL > 3 × ULN	Permanently discontinue.
Nephritis	Grade 2 increase in serum creatinine	Withhold dosing until the adverse reaction recovers to grade 0–1.
	Grade 4 or grade 3 increase in serum creatinine	Permanently discontinue.
Endocrine Disorders	Symptomatic grade 2 or 3 hypothyroidism, grade 2 or 3 hyperthyroidism, grade 2 or 3 hypophysitis, grade 2 adrenal	Withhold dosing until the adverse reaction recovers to grade 0–1.

	insufficiency, grade 3 hyperglycemia, or type 1 diabetes mellitus	
	Grade 4 hypothyroidism; grade 4 hyperthyroidism; grade 4 hypophysitis; grade 3 or 4 adrenal insufficiency; grade 4 hyperglycemia or type 1 diabetes mellitus	Permanently discontinue.
Cutaneous Adverse Reactions	Grade 3	Withhold dosing until the adverse reaction recovers to grade 0–1.
	Grade 4; Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue.
Thrombocytopenia	Grade 3	Withhold dosing until the adverse reaction recovers to grade 0–1.
	Grade 4	Permanently discontinue.
Other Immune-Related Adverse Reactions	Grade 3 or 4 increase in serum amylase or lipase; grade 2 or 3 pancreatitis; grade 2 myocarditis*; grade 2 or 3 first occurrence of other immune-related adverse reactions	Withhold dosing until improvement to grade 0–1.
	Grade 4 pancreatitis or recurrent pancreatitis of any grade; grade 3 or 4 myocarditis; grade 3 or 4 encephalitis; grade 4 first occurrence of other immune-related adverse reactions	Permanently discontinue.
Recurrent or Persistent Adverse Reactions	Recurrent grade 3 or 4 (excluding endocrine disorders); grade 2 or 3 adverse reaction not improving to grade 0–1 within 12 weeks after the last dose (excluding endocrine disorders); failure to reduce corticosteroids to ≤ 10 mg/day prednisone equivalent within 12 weeks after the last dose	Permanently discontinue.
Infusion Reactions	Grade 2	Reduce the infusion rate or withhold dosing; once symptoms resolve, resumption of dosing may be considered with close observation.
	Grade 3 or 4	Permanently discontinue.

Note: Severity of adverse reactions is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0), unless otherwise specified.

* The safety of resuming treatment with this product after recovery of myocarditis to grade 0–1 has not been established.

Appendix 2: List of Abbreviations

Abbreviation	Full Name
pCR	Pathological Complete Response
MPR	Major Pathological Response
ORR	Objective Response Rate
EFS	Event-Free Survival
DFS	Disease-Free Survival
OS	Overall Survival
AE	Adverse Event
SAE	Serious Adverse Event
AJCC	American Joint Committee on Cancer
ECOG	Eastern Cooperative Oncology Group
Hb	Hemoglobin
ANC	Absolute Neutrophil Count
PLT	Platelet
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ULN	Upper Limit of Normal
TBIL	Total Bilirubin
Cr	Creatinine
APTT	Activated Partial Thromboplastin Time
INR	International Normalized Ratio
PT	Prothrombin Time
LVEF	Left Ventricular Ejection Fraction
HIV	Human Immunodeficiency Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCVAb	Hepatitis C Virus Antibody
HCV RNA	Hepatitis C Virus RNA
dMMR	Deficient Mismatch Repair
MSI-H	Microsatellite Instability-High
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
OX-40	Tumor Necrosis Factor Receptor Superfamily Member 4

CD137	Tumor Necrosis Factor Receptor Superfamily Member 9
NYHA	New York Heart Association
FBG	Fasting Blood Glucose
BSA	Body Surface Area
PASS	Power Analysis and Sample Size
FAS	Full Analysis Set
PPS	Per-Protocol Set
SAS	Safety Analysis Set
Kaplan-Meier	Kaplan-Meier survival analysis method