

Informed Consent Form · Information Sheet

(Version: V1.0, Date: 2026.2.2)

Dear Subject:

You are invited to participate in a prospective, multicenter, randomized controlled study of neoadjuvant PD-1 inhibitor combined with SOX chemotherapy plus short-course radiotherapy (omitting regional lymph node irradiation) for locally advanced upper gastric/gastroesophageal junction adenocarcinoma. The Principal Investigator of this study is Prof. Hu Junbo, Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology. The study protocol has been reviewed and approved by the Medical Ethics Committee of Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology, and permission has been granted to conduct this clinical research.

Before you decide whether to participate in this study, please read the following content as carefully as possible. It will help you understand the study, why it is being conducted, the procedures and duration, as well as the potential benefits, risks, and discomforts. You may also discuss it with your relatives and friends, or ask the doctor for further explanation to help you make a decision.

If you are currently participating in another clinical study, please be sure to inform your study doctor or research staff. Thank you for supporting this study.

I. Background and Purpose of the Study

1. Disease Burden and Current Treatment Status

Gastric cancer and gastroesophageal junction adenocarcinoma are among the malignant tumors with high incidence and mortality rates in China. For patients diagnosed with "locally advanced" disease, the tumor is often large, or imaging suggests possible involvement of regional lymph nodes. Even if radical surgical resection with standard lymph node dissection is performed, some patients still experience recurrence or metastasis after surgery. One important reason for recurrence is that at the time of surgery, there may already be "micro-metastases" invisible to the naked eye, which cannot be completely eliminated by surgery alone. Therefore, both

international and domestic authoritative guidelines generally recommend that for eligible patients with locally advanced disease, a comprehensive treatment strategy of "systemic drug treatment first, then surgery" – i.e., neoadjuvant therapy before surgery – should be adopted to reduce the risk of recurrence and improve overall treatment outcomes.

Evidence from high-quality clinical studies conducted in China, such as the RESOLVE study, shows that standardized systemic drug therapy before surgery can bring several benefits: first, it can help shrink the tumor, down-stage the disease, and thereby increase the chance of complete (R0) resection; second, it can treat potential micrometastases early through the bloodstream before surgery; third, the treatment response helps doctors better judge tumor sensitivity to drugs, providing a basis for subsequent treatment decisions. At present, in Chinese clinical practice, the SOX regimen (commonly consisting of S-1 plus oxaliplatin) is one of the important backbone regimens for perioperative treatment. However, a real-world problem is also observed: despite the effectiveness of SOX and other chemotherapy regimens, a considerable proportion of patients still have residual viable tumor cells in the tumor tissue at the time of surgery; and the rate of pathological complete response (i.e., no residual tumor cells detected microscopically after surgery) is relatively low with chemotherapy alone. It is generally believed that achieving a deeper pathological response suggests a more robust treatment effect, but this does not equate to "cure" nor guarantee that recurrence will not occur.

In recent years, immunotherapy represented by PD-1 inhibitors has brought new advances in gastric cancer treatment. Immunotherapy is different from chemotherapy: it does not directly "kill all tumor cells", but rather helps the body's immune cells better recognize and attack the tumor by relieving the immunosuppression imposed by the tumor. Large clinical studies such as KEYNOTE-585 have suggested that adding immunotherapy to chemotherapy can increase the depth of pathological response, including the proportion of pathological complete response, in some patients. However, it must also be objectively recognized that not all patients derive equal benefit from immunotherapy, and in some studies, improved pathological response

did not necessarily translate into long-term survival benefit. This suggests that simply "adding an immune drug to chemotherapy" may not be sufficient, and more rational, targeted combination strategies need to be explored to achieve deeper and more durable treatment responses in more patients.

Radiotherapy is a commonly used local treatment modality that kills local tumor cells and reduces the risk of local recurrence. Recent basic and translational research has also found that, in addition to its local killing effect, radiotherapy can induce changes in tumor immunogenicity: tumor cells undergo death after irradiation and release certain "signals" that may help the immune system better "see" the tumor, thereby creating more favorable conditions for immunotherapy. This can be understood as radiotherapy potentially converting the tumor from a "more hidden, less immune-recognizable" state to a "more easily recognized and attacked by the immune system" state, while immunotherapy further helps the immune system function. It must be clarified, however, that this synergistic effect does not necessarily occur for all tumors or all radiotherapy regimens; it is closely related to the timing, fractionation, and field of radiotherapy, and therefore needs to be validated through well-designed clinical studies.

In the field of gastric cancer, previous classic preoperative chemoradiotherapy regimens often had a long treatment course (e.g., lasting about 5 weeks) and relatively large irradiation fields, routinely including regional lymph nodes in the prophylactic irradiation volume. While such strategies may indeed enhance local control and increase the depth of pathological response, they also have significant practical drawbacks: a long treatment course means more hospital visits, potentially longer waiting time for surgery, and increased burdens of accommodation, transportation, caregiving, and lost work time. At the same time, large-field irradiation also affects more normal tissues and may increase treatment-related adverse effects. In the era of immunotherapy, whether an overly large irradiation field or overly long treatment course might to some extent affect immune system function has also become an important scientific question. Based on these considerations, this study aims to explore a radiotherapy integration strategy that is "lower burden", easier to coordinate

with systemic therapy, and more conducive to immune synergy.

The radiotherapy strategy used in this study has two core features. The first is "short-course radiotherapy", i.e., delivering radiotherapy within a concentrated short period (typically completing all fractions within about 1 week) to reduce travel frequency, shorten overall treatment time, alleviate the burden on patients and their families, and improve the feasibility of consistent implementation across multiple centers. The second is "omission of prophylactic regional lymph node irradiation", meaning that radiotherapy mainly targets the primary tumor area without routine prophylactic irradiation to regional lymph nodes that are not suspected of metastasis on imaging. One scientific basis for this design is that lymph nodes are not only associated with tumor metastasis but are also important sites for immune cell priming and expansion; some animal studies suggest that including tumor-draining lymphoid tissue in the prophylactic irradiation field may affect the establishment of immune responses and thus be detrimental to the synergy between radiotherapy and immunotherapy. On the other hand, in standard treatment for upper gastric and gastroesophageal junction adenocarcinoma, the oncological management of regional lymph nodes does not rely solely on radiotherapy; standard radical surgery includes D2 lymph node dissection, and systemic drug therapy also acts simultaneously on possible micrometastases. Therefore, this study does not "ignore lymph node management" but rather, under rigorous screening and quality control, relies primarily on standard surgical dissection and systemic therapy for regional lymph node control, while allowing radiotherapy to focus more on "primary tumor control and immune synergy". To further ensure safety and consistency, the study strictly restricts enrollment to patients with upper gastric and gastroesophageal junction adenocarcinoma to reduce variability in treatment fields and perioperative risk.

Before launching this study, our research team accumulated relevant exploratory experience: we conducted an exploratory study using long-course radiotherapy combined with PD-1 inhibitors and chemotherapy in a similar patient population. The data indicated that such combination therapy was safe, some patients achieved deep pathological responses, and all patients underwent R0 resection. It must be

emphasized, however, that such exploratory studies had small sample sizes and lacked randomization, making it difficult to definitively prove that this regimen is superior to current standard treatment. Meanwhile, our team's animal experiments observed that short-course radiotherapy combined with PD-1 inhibitors was more advantageous than long-course fractionation, and that sequencing radiotherapy followed by immunotherapy was superior to immunotherapy followed by radiotherapy. Our preliminary experimental data demonstrate the potential of this regimen, but clinical validation in humans through well-designed clinical trials is still required.

Based on the above background, this study intends to compare two preoperative neoadjuvant treatment strategies: all enrolled patients will receive the currently clinically used neoadjuvant therapy of SOX chemotherapy plus PD-1 inhibitor and undergo planned radical surgery; one group of patients will additionally receive short-course, regional-node-sparing radiotherapy before the same neoadjuvant chemoimmunotherapy. The primary objective of the study is, under rigorous safety monitoring and standardized perioperative management, to evaluate whether adding this radiotherapy strategy can further increase the rate of pathological complete response. To ensure objective and reliable comparisons, the study uses randomization – i.e., allocating subjects fairly to different treatment groups by a method similar to "drawing lots" – to avoid bias from human selection. Regardless of which group you are assigned to, you will receive standardized comprehensive treatment and close follow-up. Participating in the study does not guarantee additional benefit, but we hope that through a more scientifically optimized combination, more patients can achieve better treatment responses and improved long-term control without significantly increasing the overall burden.

2. Purpose of this Study

Primary objective: To compare the efficacy and safety of neoadjuvant treatment with short-course, regional-node-sparing radiotherapy followed by chemoimmunotherapy versus chemoimmunotherapy alone in patients with locally advanced upper gastric/gastroesophageal junction adenocarcinoma.

Secondary objective: To explore screening indicators for sensitive populations to neoadjuvant radiotherapy combined with chemoimmunotherapy in locally advanced upper gastric/gastroesophageal junction adenocarcinoma.

3. Study Groups

This study is a prospective, open-label, multicenter, randomized controlled clinical trial. It plans to enroll previously untreated, operable patients with locally advanced upper gastric/gastroesophageal junction adenocarcinoma. After signing informed consent and meeting eligibility criteria, enrolled patients will be randomized into two cohorts: Cohort 1 (experimental group): regional-node-sparing SCRT followed by 4 cycles of SOX plus serplulimab as neoadjuvant therapy, then surgery; Cohort 2 (control group): 4 cycles of SOX plus serplulimab as neoadjuvant therapy, then surgery. Both cohorts will continue with 4 cycles of adjuvant SOX plus serplulimab after surgery, followed by serplulimab maintenance therapy until 1 year after surgery.

4. Treatment Regimen and Drugs

Cohort 1: regional-node-sparing SCRT → 4 cycles serplulimab + SOX neoadjuvant → surgery → 4 cycles serplulimab + SOX adjuvant → serplulimab maintenance (until 1 year post-surgery)

Cohort 2: 4 cycles serplulimab + SOX neoadjuvant → surgery → 4 cycles serplulimab + SOX adjuvant → serplulimab maintenance (until 1 year post-surgery)

Regional-node-sparing SCRT regimen: 25 Gy, delivered in 5 fractions of 5 Gy each, completed within one week.

CTV delineation: Using image-guided intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT) technique. The CTV is defined on CT images and includes only the tumor and stomach. To ensure quality, treatment delineation atlases will be provided and planning reviews performed. All delineations will be centrally reviewed before treatment initiation and corrected if necessary.

Regional-node-sparing SCRT followed by serplulimab + SOX therapy starts one week after completion of radiotherapy.

Serplulimab + SOX regimen: Each combined therapy cycle is 3 weeks (21 days).

Sequence on day 1 (if administered on the same day):

- Immune checkpoint inhibitor: PD-1 4.5 mg/kg IV drip d1; Q3W
- Oxaliplatin: 130 mg/m² IV drip, d1; Q3W
- S-1: 40-60 mg/dose, orally, bid, d1-14; Q3W

II. Who will be invited to participate in this study?

1. Who is eligible to participate

1. Voluntary participation, ability to sign informed consent, and good compliance;
2. Age 18-75 years (at time of signing informed consent), both genders;
3. Histologically and/or cytologically confirmed adenocarcinoma, diagnosed as locally advanced per AJCC 8th edition, cT3-4 or N+ M0 on endoscopic ultrasound or contrast-enhanced CT/MRI, willing to receive neoadjuvant therapy, and assessed by the investigator as resectable or potentially resectable; planned for radical resection with standard D2 lymphadenectomy after MDT evaluation;
4. Primary tumor location restrictions:
 - 1) Gastroesophageal junction adenocarcinoma: Siewert type II-III;
 - 2) Upper gastric cancer: lower margin of tumor located within the upper 1/3 of the gastric body, mainly involving the cardia, fundus, or upper gastric body;
5. No prior systemic treatment for the current disease, including anti-tumor radiotherapy/chemotherapy/immunotherapy;
6. ECOG performance status 0-1;
7. Expected survival ≥ 6 months;
8. Preoperative chest, abdominal, pelvic CT and FAPI-PET or PET-CT rule out distant metastasis;
9. Adequate major organ function, meeting the following criteria:
 - 1) Hematology (within 14 days without blood transfusion or hematopoietic growth factors): Hemoglobin (Hb) ≥ 90 g/L; Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L; Platelets (PLT) $\geq 80 \times 10^9$ /L;
 - 2) Biochemistry: ALT and AST $\leq 2.5 \times \text{ULN}$; Total bilirubin (TBIL) $\leq 1.5 \times \text{ULN}$; Serum creatinine (Cr) $\leq 1.5 \times \text{ULN}$, or creatinine clearance ≥ 60 mL/min;

- 3) Coagulation: APTT, INR, PT $\leq 1.5 \times \text{ULN}$;
- 4) Echocardiography: Left ventricular ejection fraction (LVEF) $\geq 50\%$;
- 10. Clinically judged by the physician to have adequate organ function;
- 11. Fertile subjects must use appropriate contraception during the study and for 120 days after study completion; negative serum pregnancy test within 7 days before enrollment; must not be breastfeeding.

2. Who is not suitable to participate

- 1. Radiotherapy within 4 weeks before enrollment, or radionuclide therapy within 8 weeks;
- 2. Within 6 months before enrollment: gastroesophageal varices, severe ulcer, unhealed wound, gastrointestinal perforation, fistula, intestinal obstruction, intra-abdominal abscess, or acute gastrointestinal bleeding;
- 3. Diagnosis of another malignancy other than gastric cancer within 5 years before first dose (excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or carcinoma in situ that has been curatively resected);
- 4. Presence of distant metastasis (M1), including but not limited to: peritoneal metastasis (confirmed by imaging or laparoscopy), ascites or positive peritoneal lavage cytology, liver/lung/bone or other organ metastases; imaging evidence of para-aortic lymph node (No.16) metastasis;
- 5. High regional lymph node burden on imaging: suspicious/positive lymph nodes involving ≥ 3 anatomical stations; or multiple matted nodes; or any lymph node with short axis ≥ 15 mm;
- 6. Tumor with high bleeding tendency (e.g., active deep ulcer, history of hematemesis or melena within 2 months before signing informed consent, high risk of gastrointestinal bleeding judged by investigator) or blood transfusion within 4 weeks before study treatment;
- 7. Inability to swallow oral medication, malabsorption syndrome, or other conditions affecting gastrointestinal absorption;
- 8. Currently participating in an interventional clinical trial treatment, or received

another investigational drug or device within 4 weeks before first dose;

9. Prior systemic or local anti-tumor therapy for gastric cancer, including curative surgery, chemotherapy, radiotherapy, immunotherapy (e.g., immune checkpoint inhibitors, agonists, or cell therapy), biologics, or small-molecule targeted drugs;

10. Received systemic treatment with Chinese patent medicines with anti-tumor indication or immunomodulatory drugs (including thymosin, interferon, interleukin, except for local use to control pleural effusion) within 2 weeks before first dose;

11. Active autoimmune disease requiring systemic treatment (e.g., disease-modifying drugs, corticosteroids, or immunosuppressants) within 2 years before first dose. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroids for adrenal or pituitary insufficiency) is not considered systemic treatment;

12. Receiving systemic corticosteroids (excluding intranasal, inhaled, or other local routes) or any other form of immunosuppressive therapy within 7 days before first dose; Note: physiologic doses of corticosteroids (≤ 10 mg/day of prednisone or equivalent) are permitted; short-course corticosteroids for chemotherapy antiemesis, contrast allergy premedication, or other short-term medically necessary uses are permitted;

13. Known allogeneic organ transplant (except corneal transplant) or allogeneic hematopoietic stem cell transplant;

14. Known allergy to any drug used in this study;

15. Peripheral neuropathy $\geq$ grade 2;

16. Known history of HIV infection (i.e., HIV1/2 antibody positive);

17. Active hepatitis B or hepatitis C (HBsAg positive with HBV DNA above ULN; HCVAb positive with HCV RNA above ULN; Note: HBsAg-positive subjects willing to receive antiviral therapy throughout the study and already started before enrollment may be considered on a case-by-case basis with infectious disease consultation);

18. Received live vaccine within 30 days before first dose (Cycle 1, Day 1); inactivated influenza vaccine for seasonal flu is allowed within 30 days before first

dose; live attenuated intranasal influenza vaccine is not allowed;

19. Pregnant or breastfeeding women;

20. Presence of any severe or uncontrolled systemic disease, such as:

1) Significant and symptomatic abnormalities in rhythm, conduction, or morphology on resting ECG, e.g., complete left bundle branch block, second-degree or higher atrioventricular block, ventricular arrhythmia, or atrial fibrillation;

2) Unstable angina, congestive heart failure, NYHA class ≥ 2 chronic heart failure;

3) Any arterial thrombotic, embolic, or ischemic event within 6 months before enrollment, e.g., myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack;

4) Poorly controlled long-standing hypertension (systolic BP >160 mmHg, diastolic BP >100 mmHg);

5) History of non-infectious pneumonitis requiring corticosteroid therapy within 1 year before first dose, or currently active clinical interstitial lung disease;

6) History of significant bleeding disorder or coagulopathy; current or long-term anticoagulation therapy (e.g., atrial fibrillation with CHADS2 score ≥ 2);

7) Active pulmonary tuberculosis;

8) History of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) or chronic diarrhea;

9) Major surgery or major trauma within 30 days before treatment; minor local surgery within 3 days before treatment (excluding peripheral venous central catheter placement);

10) Active or uncontrolled infection requiring systemic therapy;

11) Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction;

12) Uncontrolled comorbidities including but not limited to decompensated cirrhosis, nephrotic syndrome, uncontrolled metabolic disorders, severe active peptic ulcer or gastritis, or psychiatric/social conditions that would interfere with protocol adherence or informed consent;

- 13) Poorly controlled diabetes (fasting blood glucose >10 mmol/L);
- 14) Urinalysis showing protein $\geq +$, with confirmed 24-hour urine protein >1.0 g;
21. Known history of psychiatric disorder, substance abuse, alcoholism, or drug addiction;
22. History or evidence of disease, treatment, or laboratory abnormality that might interfere with study results or prevent full participation, or any other condition deemed unsuitable for enrollment by the investigator, including tumor-related local or systemic disease, high medical risk, or unfavorable prognosis (e.g., leukemoid reaction with WBC $>20 \times 10^9/L$, cachexia, >10% weight loss within 3 months before screening, or BMI ≤ 18).

III. Study sites and planned number of participants

Lead site: Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology

Participating sites:

Beijing Cancer Hospital

Fudan University Shanghai Cancer Center

Renji Hospital, Shanghai Jiao Tong University School of Medicine

Second Affiliated Hospital, Zhejiang University School of Medicine

Planned enrollment: 146 subjects.

IV. What will you need to do if you participate?

1. Screening period

In addition to routine diagnostic imaging and other tests, written informed consent must be obtained before any study-specific additional examinations or medical procedures. However, CT/MRI results obtained before signing informed consent and within 28 days before starting study treatment can be used for screening tumor evaluation.

The following observations and assessments must be completed within 28 days before the start of treatment (Day -28 to Day -1):

- Sign informed consent before any screening procedures.
- Collect demographic data, weight, height, medical history, and other past

history.

- Collect prior medications/treatments within 28 days before first study drug administration.

- Collect previous pathological results.

- Perform physical examination.

- Perform blood routine, blood biochemistry, tumor markers (CEA, CA19-9, etc.), urinalysis, coagulation function, thyroid function, 12-lead ECG, echocardiography (results from the study site are acceptable if obtained within 28 days before first study drug administration). Pregnancy test for women of childbearing potential (serum pregnancy test within 7 days before first dose).

- Perform serum virology: hepatitis B panel, HBV DNA quantitative (if HBsAg positive), HCV antibody, HCV RNA quantitative (if HCVAb positive), HIV antibody. Results within 28 days before first study drug administration are acceptable.

- Tumor assessment: chest, abdomen, pelvis, and other sites suspected of metastasis per investigator's judgment – contrast-enhanced CT or MRI; FAPI-PET or PET-CT. Results obtained within 28 days before first dose at the study site are acceptable if the same method as during the study is used. Bone scan results within 42 days before enrollment may be used.

- ECOG performance status.

- Quality of life questionnaires: EORTC QLQ-C30 (version 3), EORTC QLQ-STO22, EQ-5D-5L.

- Nutritional assessment: including body mass index (BMI), fat-free mass index (FFMI), blood biochemical markers (e.g., albumin, transferrin), and Patient-Generated Subjective Global Assessment (PG-SGA).

- All enrolled patients will be tested for HER2, Claudin18.2, MRD, PD-L1 expression level (CPS score), and microsatellite instability status. If tissue allows, exploratory testing of tumor mutational burden (TMB), whole-exome sequencing of tumor tissue, etc.

2. Neoadjuvant treatment period

Subjects should undergo corresponding examinations and assessments at the study site. Control group: 4 cycles of SOX + serplulimab. Experimental group: regional-node-sparing short-course radiotherapy (5 fractions) + 4 cycles of SOX + serplulimab. Surgery is to be performed within 3-4 weeks after neoadjuvant therapy.

- CTV delineation: Using IMRT/VMAT technique. CTV is defined on CT images and includes only the tumor and stomach, without prophylactic regional lymph node irradiation. All delineations will be centrally reviewed before treatment initiation and corrected if necessary.

- Administer protocol-specified drug doses (chemotherapy calculated by body surface area; immunotherapy by body weight).

- Within 7 days before first dose: vital signs, weight measurement, ECOG performance status, physical examination, blood routine, blood biochemistry, urinalysis. If screening tests were done within 7 days before first dose of Cycle 1, they need not be repeated.

- Within 3 days before doses 2-4: vital signs, weight, ECOG, physical exam, blood routine, blood biochemistry, urinalysis.

- Imaging: chest, abdomen, pelvis plain + contrast CT or plain + contrast MRI; other sites suspected of metastasis per clinical indication – plain + contrast CT or MRI; brain CT or MRI (if clinically indicated); bone scan (if clinically indicated). Performed every 6 weeks (± 3 days) from first dose date. Preoperative imaging for surgery decision should be done within 14 days before planned surgery.

- Tumor assessment per RECIST 1.1 (every 6 weeks ± 3 days from first dose).

- Collect concomitant medications/treatments and adverse event information.

3. Surgery

- Gastric resection margin: For Borrmann types I and II, at least 3 cm proximal margin is recommended; for Borrmann types III and IV, at least 5 cm proximal margin is recommended. If the above principles cannot be achieved, frozen section examination of the proximal margin is recommended. For tumors invading the esophagus, a margin of 2-4 cm or frozen section examination is recommended to achieve R0 resection.

- Lymph node dissection: In principle, all subjects should undergo radical resection and achieve D2 lymphadenectomy. If not achieved due to anatomical/safety reasons, the reason should be documented in detail as a protocol deviation, and will be included in quality control and sensitivity analysis. Lymph node dissection extent can be graded as D1, D1+, or D2 according to D-grade criteria. The lymph nodes to be dissected are defined based on the gastric resection type. Additional or omitted nodal stations may be recorded as D1 (+No.8a) or D2 (–No.12a). However, when entering data into the database, the D grade must be strictly determined. If any node that should have been removed is omitted such that a certain D grade is not met, downgrade accordingly. For example, D2 (–No.12a) should be recorded as D1+. If D1 lymphadenectomy is not met, record as D0.

- Proximal radical gastrectomy: Recommended lymph node stations No.1, 2, 3, 7, 8a, 9, 11p, 11d; if tumor invades ≥ 3 cm of esophagus, add stations 19, 20, 110.

- Total radical gastrectomy: Recommended lymph node stations No.1-7, 8a, 9, 11p, 11d, 12a. If tumor invades ≥ 3 cm of esophagus, add stations 19, 20, 110.

- Reconstruction: For proximal radical gastrectomy, double-tract anastomosis is recommended; other methods may be used based on surgeon's preference. For total radical gastrectomy, Roux-en-Y anastomosis is recommended.

- Surgical record includes operation time, procedure name, type, anastomosis method, and lymph node dissection extent.

- Pathological response assessment.

- Collect perioperative (30-day safety follow-up) complications.

4. Adjuvant treatment period

Adjuvant treatment should start within 6 weeks after surgery: 4 cycles of SOX + serplulimab, then serplulimab maintenance until 1 year after surgery. Patients should come to the study site for corresponding examinations and assessments before starting adjuvant treatment.

- Administer protocol-specified drug doses (chemotherapy by BSA; immunotherapy by body weight).

- Within 7 days before first dose: vital signs, weight, ECOG, physical exam,

blood routine, blood biochemistry, urinalysis. If screening tests were done within 7 days before first dose of Cycle 1, they need not be repeated.

- Within 3 days before each subsequent dose: vital signs, weight, ECOG, physical exam, blood routine, blood biochemistry, urinalysis.

- Imaging: chest, abdomen, pelvis plain + contrast CT or plain + contrast MRI to assess for disease recurrence or metastasis (once before first adjuvant treatment, and then every 3 months during adjuvant treatment).

- Collect concomitant medications/treatments and adverse event information.

V. Potential Benefits of Participation

If you agree to participate in this study, you may receive direct medical benefit. Although we cannot promise that you will definitely obtain superior outcomes compared to conventional treatment, based on the study's design and current medical evidence, participation may offer the following potential benefits:

1.Opportunity for tumor down-staging and deeper response:** This study represents an optimization exploration on top of current standard treatment. Regardless of which group you are assigned to, you will receive high-standard neoadjuvant therapy. Preoperative treatment (especially the addition of short-course, immune-synergistic radiotherapy in the experimental group) aims to shrink or down-stage your tumor before surgery, thereby increasing the chance of complete (R0) resection. Some patients may achieve deeper pathological responses, even pathological complete response (i.e., no residual tumor cells under the microscope). Although pCR does not equate to 100% cure, it generally indicates a favorable treatment response, which may translate into longer survival and lower recurrence risk.

2.Reduced treatment burden and toxicity risk (for experimental group):** This study specifically adopts a "short-course" and "regional-node-sparing" radiotherapy design. If assigned to the experimental group, your radiotherapy course will be shortened from the traditional 5 weeks to about 1 week, significantly reducing travel frequency and family caregiving burden. At the same time, the precise smaller-field technique aims to maximally protect your normal lymphoid tissue and immune

function, theoretically lowering some side effects associated with conventional radiotherapy.

3.Close medical monitoring and expert team support:** Throughout the study, you will be placed on a "fast track" with more standardized, intensive follow-up than routine care. A multidisciplinary expert team will follow your condition throughout. Such high-frequency monitoring helps detect treatment responses and potential adverse events earlier, allowing timely professional management, thereby providing additional safety assurance.

4.Reduced financial burden (drug support):** During the study, eligible subjects may receive support for the study drug (serplulimab) through patient assistance programs, which will reduce some of your treatment expenses. (Note: The specific scope, quantity, and eligibility for drug assistance are subject to the policies issued by the drug supplier at study initiation and the "Fees" section of the informed consent form. Should the assistance policy change, the study team will inform you promptly.)

5.Contribution to medical progress:** Your participation will help doctors scientifically evaluate the efficacy and safety of this new regimen. The valuable data you provide will become an important basis for future treatment standards for gastric cancer. This means that your efforts may not only benefit you but also help explore more effective, lower-burden treatment options for other gastric cancer patients like you.

VI. Potential Adverse Reactions, Risks, Discomforts, and Inconveniences

Adverse reactions may occur during the study. If you experience any discomfort, change in condition, or any unexpected event – whether or not related to the study – you should promptly inform your doctor, who will assess and provide appropriate medical management. The investigator will take necessary measures (e.g., dose adjustment, temporary interruption, or discontinuation) based on the condition. In case of serious adverse events, necessary actions will be taken to ensure subject safety.

Most adverse reactions are predictable, reversible, and manageable. By adjusting drug doses, temporarily interrupting treatment, or providing symptomatic supportive

care, the vast majority can be alleviated; however, rarely, severe (grade 3 or higher) or even life-threatening adverse reactions may occur. Specific risks include:

1. Radiotherapy-related complications:** If assigned to receive short-course radiotherapy, the radiation, while killing tumor cells, may cause some irritation or damage to the stomach and surrounding tissues. During and shortly after radiotherapy, you may experience nausea, vomiting, mild upper abdominal pain, acid reflux, or eating discomfort. In rare cases, radiotherapy may cause gastric or intestinal injury, increasing the risk of bleeding or perforation.

2. Chemotherapy- and immunotherapy-related complications:** Regardless of group assignment, you will receive SOX chemotherapy plus serplulimab (PD-1 inhibitor). Common adverse reactions include:

- Myelosuppression (hematologic toxicity):** Chemotherapy may temporarily suppress bone marrow function, leading to neutropenia (increased infection risk), thrombocytopenia (increased bleeding tendency), or anemia (fatigue). Management: We will monitor blood counts regularly. If clinically significant declines occur, doctors will use G-CSF, thrombopoietin, transfusions, etc., according to standard practice, and may delay or adjust chemotherapy doses if necessary.

- Gastrointestinal reactions:** Nausea, vomiting, decreased appetite, diarrhea, oral mucositis, or constipation.

- Peripheral sensory neuropathy:** A common oxaliplatin reaction, presenting as numbness, paresthesia, or cold-induced sharp pain in fingers and toes. Usually reversible, but may last several months after treatment ends.

- Hand-foot syndrome:** S-1 may cause redness, swelling, peeling, pain, or hyperpigmentation on palms or soles.

- Immune-related adverse events (irAEs):** Serplulimab activates the immune system to fight cancer. While enhancing anti-tumor effects, the activated immune cells may, very rarely, attack normal body tissues. Potentially involved organs: thyroid (hypo- or hyperthyroidism), lung (immune pneumonitis), liver (immune hepatitis), gut (immune colitis), or skin (rash). Special note: Although severe irAEs are uncommon, they can progress rapidly. If you develop dyspnea, severe diarrhea, or non-specific

profound fatigue, tell your doctor immediately.

3. Surgery-related complications: Regardless of group assignment, you will undergo planned radical gastrectomy. Surgical risks are the same as for conventional radical gastrectomy, including:

- Intraoperative risks: Bleeding, inadvertent injury to surrounding organs (e.g., spleen, pancreas).

- Postoperative complications: Anastomotic leak, reflux, abdominal infection, delayed wound healing, deep vein thrombosis, or pulmonary embolism.

Additionally, neoadjuvant treatment (especially radiotherapy) may cause edema or fibrosis of tissues around the tumor, which theoretically could increase surgical difficulty. The study team will operate with meticulous technique based on intraoperative findings and will ensure adequate recovery time before surgery to maximize safety.

4. Reproductive toxicity and pregnancy risk: The drugs and radiation used in this study have definite reproductive toxicity and may cause fetal malformation or miscarriage. Women of childbearing potential must have a negative pregnancy test before enrollment. During the entire study and for at least 6 months after the last dose, highly effective contraception must be used. Male subjects must also use effective contraception to avoid partner pregnancy during the study and for a period after treatment ends.

5. Potential inconveniences: To ensure your safety, the trial requires more intensive follow-up than routine care. You will need to come to the hospital at protocol-specified time points for blood draws, imaging (CT/MRI), and completing quality-of-life questionnaires. This may take your personal time and involve additional travel arrangements.

We understand that these risk descriptions may cause you concern. Your safety is always our highest priority. We will grade and record all reactions strictly according to the CTCAE criteria. If an adverse reaction occurs, doctors will immediately assess and provide appropriate medical therapy. If intolerable toxicity occurs, we will reduce doses, delay treatment, or discontinue study treatment per protocol. You have the right

to withdraw from the study at any time, for any reason (including inability to tolerate side effects), without affecting your subsequent standard care. Please read the above carefully before signing this consent form, discuss it fully with your family or study doctor, and weigh the benefits and risks of participation.

VII. Costs

Before you decide to participate, please read the following cost information carefully. We understand that medical expenses are an important concern, and we will explain transparently which costs are covered by the study and which you (or your insurance) must bear.

1. Free tests and support provided by the study: To evaluate treatment efficacy and explore biomarkers, the study will provide the following specific tests free of charge: pathology and genetic tests – pathological response assessment (MPR), PD-L1 expression level (CPS/TPS). Note: These tests are often expensive; participation saves you these costs and provides more precise molecular information about your tumor

2. Cost of the immunotherapy drug (serplulimab): For the immunotherapy drug involved in this study, the study team will assist you in applying for patient assistance. Qualification, quantity, and specific scope of drug assistance will be based on the policy issued by the drug supplier at study initiation. Special note: While we will do our best to assist, the assistance policy is not an absolute commitment of this study. If force majeure or manufacturer policy changes cause changes in the assistance program, the study team will inform you promptly, and subsequent treatment costs may need to be borne by you or through insurance.

3. Costs you need to bear yourself: This study is an optimization exploration on top of standard care. Therefore, costs that fall under routine clinical care are your responsibility (or reimbursable by your insurance). These include, but are not limited to:

- Drugs and tests: Short-course radiotherapy, SOX chemotherapy drugs (oxaliplatin, S-1), routine preoperative tests (blood routine, biochemistry, ECG, etc.), and imaging.

- Surgery and hospitalization: Radical surgery fees, anesthesia, hospital bed fees,

nursing fees.

- Complication management: Routine treatment-related complications (e.g., infection, anastomotic leak) or treatment of other underlying diseases.

- Other expenses: Transportation, accommodation, meals, caregiving (unless specified otherwise in the informed consent form regarding travel allowance).

4. Compensation for study-related injury: Study doctors will follow medical standards to prevent adverse events as much as possible. If, during participation, an injury occurs that is judged to be directly related to study procedures or study drugs (i.e., "study-related injury"), we will provide prompt free treatment. If such injury results in temporary or permanent disability or death, we will provide economic compensation in accordance with Chinese laws, regulations, and expert determination. Health damage due to natural progression of your disease (e.g., tumor recurrence, metastasis), routine treatment-related complications (e.g., infection, anastomotic leak), other underlying diseases, or non-adherence (e.g., self-discontinuation of medication, missed follow-up) is not covered by the study sponsor.

5. Privacy and personal information protection: We highly respect your privacy. Your personal information and medical records will be kept strictly confidential and used only for this study. When publishing study results, we will remove your name, ID number, and other identifying information, using only coded identifiers. If your personal sensitive information is leaked due to sponsor error, causing substantial impact, reputational harm, or psychological distress, you have the right to claim compensation under applicable laws, including the Personal Information Protection Law of China.

VIII. Confidentiality of Personal Information

Your medical records (study files, CRFs, lab reports, etc.) will be kept intact at the hospital where you are treated. The doctor will record laboratory and other test results in your medical record. The investigator, ethics committee, and regulatory authorities will be permitted to access your medical records. Any public report of the study results will not disclose your personal identity. We will make every effort within legal limits to protect the privacy of your personal medical information.

Per medical research ethics, except for personal private information, study data may be made publicly available and shared, limited to web-based electronic databases, ensuring that no personal private information is disclosed.

IX. How to Obtain More Information?

You may ask any questions about this study at any time and receive appropriate answers.

If any important new information becomes available during the study that could affect your willingness to continue participation, your doctor will inform you promptly.

X. Voluntary Participation and Withdrawal

Whether to participate is entirely your choice. You may refuse to join or withdraw at any time without affecting your relationship with your doctor or any loss of medical benefits or other interests.

For your best interest, the doctor or investigator may discontinue your participation at any time during the study.

If you withdraw, for your health benefit, you may be asked about your use of study drugs, and if the doctor deems it necessary, physical examination and laboratory tests may be performed – this will be beneficial to your health.

If your condition changes and you need any other treatment, you may receive such treatment at any time; please truthfully inform the doctor afterwards.

XI. What to Do Now?

Whether to participate in this study is a decision for you (and your family). Before deciding, please ask your doctor as many questions as you need.

Thank you for reading the above information. If you decide to participate, please tell your doctor, who will arrange all study-related matters. Please keep this document.

XII. How to Contact the Responsible Person in an Emergency?

In case of any emergency during the study, you may contact the Principal Investigator: Hu Junbo, Tel: 13647218935.

For questions regarding your rights and interests, you may contact the Ethics Committee of Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology. Address: No. 1095 Jiefang Avenue, Wuhan, Hubei Province, China, Zip code: 430030, Tel/Fax: 027-83662379.

Informed Consent Form · Signature Page

Project Title: A prospective, multicenter, randomized controlled study of neoadjuvant PD-1 inhibitor combined with SOX chemotherapy plus short-course radiotherapy (omitting regional lymph node irradiation) for locally advanced upper gastric/gastroesophageal junction adenocarcinoma

Site: Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology

Consent Statement

I have read the above introduction to this study, and have had the opportunity to discuss it with the doctor and ask questions. All my questions have been answered satisfactorily.

I understand the potential risks and benefits of participating in this study. I am aware that participation is voluntary, and I confirm that I have had sufficient time to consider it, and I understand that:

- I may ask the doctor for more information at any time.
- I may withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.
- I agree that the ethics committee or regulatory authorities may access my study records.
- I will receive a signed and dated copy of this informed consent form.
- Finally, I decide to voluntarily agree to participate in this study and will try my best to follow the doctor's instructions.

Subject signature: _____ Date: _____ year _____ month _____ day

Phone number: _____

I confirm that I have explained the details of this study to the subject, including their rights and potential benefits and risks, and have given them a signed copy of the

informed consent form.

Investigator signature: _____ Date: _____ year _____ month _____ day

Phone number: _____