

A prospective, multicenter, randomized controlled study of neoadjuvant PD-1 inhibitor combined with SOX chemotherapy with or without short-course radiotherapy (omitting regional lymph node irradiation) for locally advanced upper gastric/gastroesophageal junction adenocarcinoma

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I. Study Background

This study focuses on patients with locally advanced, resectable upper gastric and gastroesophageal junction adenocarcinoma. Against the backdrop of continuous progress in perioperative systemic therapy, the pathological complete response (pCR) rate has not yet reached a satisfactory level. In addition to its traditional local cell-killing effect, radiotherapy has the potential to induce tumor immunogenic changes and promote anti-tumor immune responses. Therefore, it is necessary to explore a radiotherapy integration strategy that imposes a lower burden on patients and the healthcare system while being more conducive to immune synergy, characterized by short-course, reduced irradiation volume, and sparing of prophylactic regional lymph node irradiation.

Gastric cancer remains an important public health problem in China. Based on the latest national cancer registry and model estimates, there were approximately 358,700 new cases and 260,400 deaths from gastric cancer in China in 2022, ranking among the top in terms of common malignant tumor burden, with heavy social impact and room for clinical improvement [1]. Proximal gastric cancer and gastroesophageal junction (GEJ) adenocarcinoma, due to their special anatomical location, complex lymphatic drainage pathways, and limited safe margins for local resection, often face a difficult balance and challenge between achieving adequate down-staging, ensuring R0 resection, and reducing regional recurrence risk. Even with standard surgery and systemic therapy, there remains a non-negligible risk of recurrence and an urgent need for further efficacy improvement. For reasons of target reproducibility, perioperative pathway consistency, and safety, this study population is strictly limited to upper gastric and GEJ adenocarcinoma, excluding cases with esophageal invasion >2 cm, to reduce treatment pathway variability, target uncertainty, and perioperative risk caused by excessive esophageal extension, thereby improving the consistency and controllability of multicenter implementation.

Perioperative chemotherapy remains an important cornerstone for locally advanced resectable gastric cancer, but its “effective but with limitations” status constitutes the realistic starting point for further optimization strategies. In Western

populations, the FLOT4 randomized trial demonstrated that perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) was superior to an anthracycline-based triplet regimen in terms of overall survival: the hazard ratio for OS was 0.77 (95% CI 0.63–0.94), median OS was prolonged (50 months vs. 35 months), and the pCR rate was higher (16% [95% CI 10–23] vs. 6% [95% CI 3–11]; $p=0.02$), suggesting that intensified chemotherapy can indeed increase the proportion of pathological response [2]. In Asian and Chinese clinical practice, S-1-based regimens are more accessible and implementable across multiple centers. The Chinese RESOLVE randomized phase III study provided high-quality evidence for perioperative SOX (S-1 plus oxaliplatin) in a strictly D2-dissected population: perioperative SOX significantly improved overall survival compared to postoperative CapOx (5-year OS 60.0% vs. 52.1%; HR 0.79, 95% CI 0.62–1.00; $p=0.049$), and postoperative adjuvant SOX also showed an OS benefit (5-year OS 61.0%; HR 0.77, 95% CI 0.61–0.98; $p=0.033$), thus establishing the rationality and generalizability of SOX as an important perioperative treatment “backbone” in Asian populations [3]. Nevertheless, from the perspective of overall treatment outcomes, even with intensified chemotherapy, a considerable proportion of patients still fail to achieve ideal pathological response and long-term control, indicating that systemic chemotherapy alone is insufficient to adequately avoid local residual and regional recurrence risk in this key population, and further exploration of new systemic regimens and more precise local intensification strategies is warranted.

Immunotherapy has become an important direction in perioperative treatment in recent years. Randomized studies conducted in Chinese populations, which are closer to real-world chemotherapy backbones, provide direct evidence that “chemoimmunotherapy can significantly deepen pathological response”. The NEOSUMMIT-01 randomized phase II study compared perioperative SOX/XELOX alone versus adding the PD-1 inhibitor toripalimab in patients with resectable cT3-4aN+ M0 gastric/GEJ cancer. The results showed that the proportion of the primary endpoint TRG0/1 (pathological complete or near-complete response) was significantly higher in the chemoimmunotherapy group (44.4% [24/54] vs. 20.4%

[11/54]; $P=0.009$), and the pCR (ypT0N0) rate was also higher (22.2% [12/54] vs. 7.4% [4/54]; $P=0.030$), while surgical complications (11.8% vs. 13.5%) and grade 3-4 treatment-related adverse events (35.2% vs. 29.6%) were generally similar, suggesting that perioperative chemoimmunotherapy can significantly improve deep pathological response signals with a manageable safety profile [4]. However, the improvement in pathological response with perioperative immunotherapy does not necessarily translate into long-term outcome benefits, a fact that underscores the need for continued optimization of combination strategies and treatment modules.

KEYNOTE-585 evaluated the value of adding pembrolizumab to perioperative chemotherapy in locally advanced resectable gastric/GEJ adenocarcinoma. The results published in *The Lancet Oncology* showed that the pCR rate was significantly higher in the pembrolizumab group (12.9% [56/435] vs. 2.0% [9/454]), but although event-free survival (EFS) was prolonged (median 44.4 months vs. 25.3 months; HR 0.81, 95% CI 0.67-0.99; $P=0.0198$), it did not reach the prespecified significance boundary ($\alpha=0.0178$), and overall survival also showed no statistically significant difference (median 60.7 months vs. 58.0 months; HR 0.90, 95% CI 0.73-1.12; $P=0.174$) [5]. A subsequent final analysis published in the *Journal of Clinical Oncology* further highlighted the complexity of the evidence in this field: median OS was 71.8 months vs. 55.7 months (HR 0.86, 95% CI 0.74-1.00; $P=0.044$), and EFS also showed a trend toward improvement (HR 0.81, 95% CI 0.67-0.98; $P=0.019$), but the authors reported that the prespecified significance level was not met [6].

Meanwhile, ATTRACTION-05, which evaluated adjuvant nivolumab in patients with pathological stage III gastric/GEJ cancer after D2 radical gastrectomy, did not demonstrate a relapse-free survival benefit: 3-year RFS rate was 68.4% vs. 65.3% (HR 0.90, 95.72% CI 0.69-1.18; $P=0.44$) [7]. These high-quality studies collectively point to a key fact: perioperative chemoimmunotherapy has consistently improved pathological response metrics, but long-term outcomes have not always improved in parallel, suggesting that simply “adding immunotherapy to chemotherapy” may not be sufficient to fully unleash the potential of immunotherapy in the resectable setting, and that additional local modules capable of enhancing primary tumor immune

priming and synergizing with systemic immunity are needed.

Radiotherapy can induce immunogenic cell death, promote tumor antigen release and inflammatory signal amplification, enhance antigen presentation, and improve the tumor immune microenvironment, thereby converting local irradiation into an “in situ immune priming” process. The combination of radiotherapy and immunotherapy, owing to its clear mechanism and cross-tumor clinical translational evidence, has gained increasing attention in the perioperative setting. Classic reviews have systematically articulated the conceptual framework of radiotherapy as an immune adjuvant that promotes systemic anti-tumor immune responses, pointing to a theoretical and practical synergistic basis with immune checkpoint inhibitors [8]. At the more detailed molecular and cellular level, radiation-related cytoplasmic DNA can be recognized by innate immune pathways and trigger type I interferon responses. Deng et al. published in *Immunity* showed that the STING-related pathway plays a critical role in radiation-induced type I interferon-dependent antitumor immunity, emphasizing the importance of dendritic cell-mediated T cell priming as a key component of the radiation immune effect [9]. Moreover, the immune effect induced by radiotherapy is closely related to dose fractionation: Vanpouille-Box et al. published in *Nature Communications* suggested that when the single-fraction dose exceeds a certain threshold, it can induce upregulation of the DNA exonuclease TREX1, which degrades cytoplasmic DNA, attenuates STING pathway activation, and limits radiation-induced immunogenicity, providing clear experimental evidence that “radiotherapy regimens need to be designed for immune synergy” [10].

Seminal basic research on the synergy between radiotherapy and immune checkpoint inhibitors has provided further empirical support for this combination. Twyman-Saint Victor et al. published in *Nature* demonstrated that combining radiotherapy with immune checkpoint blockade can activate complementary anti-tumor immune mechanisms and suggested that in the context of specific immune escape, more rational combination strategies are needed to overcome limited T cell function, thereby providing important insights for using radiotherapy to reshape the immune microenvironment and then using checkpoint inhibitors to relieve

suppression in the clinic [11]. Furthermore, the irradiation volume is not merely a technical parameter but may directly affect immune synergy. Marciscano et al. published in *Clinical Cancer Research* pointed out that prophylactic irradiation of clinically negative tumor-draining lymph nodes may suppress adaptive immune responses and attenuate long-term immune memory and overall efficacy of combined radiotherapy and immunotherapy, suggesting that the necessity and extent of prophylactic regional lymph node irradiation warrant re-evaluation in the immunotherapy era [12].

At the clinical level, the integration of radiotherapy-based treatment pathways with immunotherapy has shown the potential to translate into long-term benefits across multiple tumor types. The PACIFIC study established the standard of consolidation durvalumab after concurrent chemoradiotherapy in unresectable stage III non-small cell lung cancer, with 5-year OS of 42.9% vs. 33.4% and 5-year PFS of 33.1% vs. 19.0%, indicating that the “definitive radiotherapy + immunotherapy” model can generate sustained survival benefits [13]. In the esophageal/GEJ cancer population, the CheckMate 577 study, targeting patients with high recurrence risk due to residual disease after neoadjuvant chemoradiotherapy and surgery, showed that adjuvant nivolumab significantly prolonged disease-free survival (median 22.4 months vs. 11.0 months; HR 0.69, 96.4% CI 0.56-0.86; $P < 0.001$), providing direct evidence for a clinically verifiable association between radiation-induced immunogenic changes and subsequent immunotherapy benefit [14]. It must be emphasized that the clinical benefit of combining radiotherapy and immunotherapy does not occur automatically; its effect is influenced by tumor type, systemic backbone regimen, radiation fractionation, irradiation volume, and treatment sequence. For precisely this reason, in resectable upper gastric/GEJ adenocarcinoma – a setting with a clear need for local control and an urgent need to improve deep responses and long-term outcomes – a prospective validation of a radiotherapy integration strategy centered on “hypofractionated short-course, reduced volume, immune-sparing” has clear biological rationale and clinical value.

In the exploration of perioperative comprehensive treatment for gastric and GEJ adenocarcinoma, radiotherapy has long been placed within the framework of “traditional local intensification”: predominantly long-course fractionation, relatively large irradiation volumes, and routine inclusion of regional lymph nodes in the target volume to cover potential subclinical metastatic deposits. The AGITG-TOPGEAR regimen clearly exemplifies this paradigm: preoperative chemoradiotherapy uses long-course fractionation of 45 Gy/25 fractions, with the target volume covering the whole stomach, perigastric tumor extension, and regional lymph nodes, and continuous infusion fluorouracil as concurrent chemotherapy (200 mg/m²/day on weekdays) [15]. Such designs have clear oncological rationale in the era when “chemotherapy was the systemic backbone,” but their costs are equally evident: longer radiotherapy courses, higher time-related costs, and potential immunological costs (especially in the current era when synergy with immunotherapy is desired) all suggest that the “traditional chemoradiotherapy paradigm” may not be the optimal integration model to be directly carried over into the immunotherapy era.

More importantly, recent high-level randomized evidence suggests that adding traditional preoperative chemoradiotherapy to a “pure perioperative chemotherapy” framework, while significantly deepening pathological response, may not necessarily improve overall survival.

The TOPGEAR randomized trial, published in The New England Journal of Medicine, enrolled patients with resectable gastric or GEJ adenocarcinoma and compared perioperative chemotherapy alone with perioperative chemotherapy plus preoperative chemoradiotherapy (45 Gy/25 fractions + weekday fluorouracil 200 mg/m²/day). The results showed that the pCR rate was higher in the chemoradiotherapy group (17% vs. 8%, $P < 0.001$), but at a median follow-up of 67 months, there was no improvement in overall survival: median OS was 46 months vs. 49 months (HR 1.05, 95% CI 0.83-1.31, $P = 0.62$); progression-free survival was also similar: median PFS was 31 months vs. 32 months (HR 1.07, 95% CI 0.86-1.32, $P = 0.59$) [15]. The key insight from this result is that the traditional chemoradiotherapy pathway is not “without local effect”, but the local response

advantage it brings may not translate into long-term survival benefit, suggesting that the role of the radiotherapy module may need to be redefined and redesigned in the context of new systemic treatments.

As the perioperative systemic backbone evolves from “chemotherapy alone” to “chemotherapy plus immunotherapy”, the role of radiotherapy may shift from mere “local dosimetric intensification” to a functional module more aligned with immunotherapy mechanisms: “immune priming/sensitization of the primary tumor”. In this context, whether radiotherapy should still maintain the previous long-course fractionation and large volumes becomes a question that must be re-examined: if the goal is not only local cell kill but also the induction of a higher-quality, more sustainable anti-tumor immune response, then the fractionation, volume, and sequence of integration with systemic therapy may directly affect whether “pathological response” can ultimately be translated into “long-term benefit”.

Traditional preoperative chemoradiotherapy often requires a continuous treatment course of about 5 weeks (e.g., 45 Gy/25 fractions), with patients needing frequent visits to the radiotherapy center. The prolonged radiotherapy course itself also extends the total time from diagnosis to the next stage of systemic treatment or surgery. Non-local patients require longer caregiving arrangements and accommodation, and costs of travel, short-term rental, lost work, and caregiving accumulate with longer courses, potentially negatively affecting treatment adherence and completion rates. A systematic review has shown that patients receiving radiotherapy experience significant regional variations in travel distance and access to care, with treatment center distribution, patient residence, and treatment modality affecting travel burden [16]. In contrast, short-course radiotherapy (SCRT) can be completed within about 1 week (e.g., 25 Gy/5 fractions). Real-world data studies have quantified the significant reduction in patient burden from shorter courses: for example, a survey of breast and prostate cancer radiotherapy patients found that 43% of respondents came from outside the area, with an average one-way distance of several hundred kilometers; hypofractionated regimens resulted in quantifiable transportation cost savings (estimated in US dollars at the hundred-dollar level for

different tumors, even greater for out-of-area patients)[17]. Although tumor types and regional backgrounds differ, the common message is clear: in solid tumors requiring long-term multidisciplinary treatment, reducing the number of radiotherapy fractions greatly reduces burden and improves accessibility. Such short-course fractionation has also appeared in research protocols for preoperative radiotherapy in gastric cancer: NCT04162665 (“Pre-operative Adaptive SCRT in Gastric Cancer”) explicitly uses adaptive 25 Gy/5 fractions (5 Gy/fraction, once daily) as the preoperative radiotherapy module, suggesting that in a challenging site like gastric cancer with significant organ motion and target stability issues, a short-course, rapidly sequenced radiotherapy strategy is feasible and researchable. This is expected to significantly reduce the socioeconomic burden on patients and families and improve treatment adherence and completion rates.

Beyond short-course, the strategy of minimizing irradiation volume and omitting prophylactic regional lymph node irradiation is also critical in the immune-combination setting. From an immunological mechanistic standpoint, tumor-draining lymph nodes (TDLNs) are not only anatomical channels for tumor metastasis but also important sites for the priming, expansion, and maintenance of tumor-specific T cells and immune surveillance. A Cancer Cell review points out that increasing evidence suggests anti-tumor immunotherapy responses can be driven and amplified in lymph nodes, making a “node-sparing” strategy a potential direction for advancing next-generation precision integration of chemoradiotherapy and immunotherapy [18]. Several clear preclinical lines of evidence support that elective nodal irradiation (ENI) may attenuate the systemic effect of radiotherapy × immunotherapy. A classic mouse study published in Clin Cancer Res compared immunological outcomes of irradiating only the primary tumor versus primary tumor plus draining lymph nodes: when combined with immune checkpoint blockade, adding ENI reduced intratumoral chemokine expression, limited antigen-specific CD8+ effector T cell infiltration, and adversely affected survival when combined with immune checkpoint inhibitors, indicating that “irradiation technique and volume” themselves affect radiotherapy-immune synergy [12]. In settings such as head and

neck cancer, where ENI has traditionally been widely used to reduce regional recurrence risk, a study published in Nature Communications similarly suggested that ENI may attenuate the local and systemic immune effects generated by combination radiotherapy and immunotherapy, pointing to the potential value of “irradiating only the primary tumor or minimizing exposure of draining lymphoid tissue” [19]. Further research even suggests that if oncological reasons cannot permanently avoid addressing the draining lymph node area, then “timing” may be a compromise strategy: in a mouse metastatic model, concurrent draining lymph node irradiation abrogated the benefit of radio-immunotherapy combination, whereas delayed (adjuvant-phase) draining lymph node irradiation partially overcame this adverse effect, with mechanistic explanations involving disruption of the CCR7-CCL19/CCL21 homing axis [20]. These cross-model, cross-tumor types of evidence collectively indicate that when radiotherapy is used for “immune priming/sensitization” purposes, minimizing prophylactic irradiation of draining lymphoid tissue may be a key step to improving the quality of radiotherapy × immune synergy.

At the clinical translation level, “node-sparing” has begun to enter clinical trials, but the strategy still needs to be validated and rigorously quality-controlled in specific tumor settings. For example, NCT06980389 uses “node-sparing short-course radiotherapy” as a core concept to explore integrating node-sparing SCRT with chemotherapy and PD-1 blockade in unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma to improve 2-year PFS. Although the population and treatment intent differ from the resectable perioperative setting, it also indicates that “volume-reduced / minimizing exposure of draining lymphoid tissue” radiotherapy strategies are becoming a research trend in the immunotherapy context. At the same time, reducing ENI does not equate to denying the importance of regional lymph node control; especially in diseases such as head and neck cancer where regional recurrence risk is high and ENI has clear oncological value, the discussion about whether abandoning ENI in the immunotherapy era should be cautious has been raised, emphasizing the need to seriously assess regional recurrence risk and salvage

difficulty while pursuing immune preservation [18]. In the specific setting of gastric/GEJ adenocarcinoma, the oncological safety premise for “sparing prophylactic regional lymph node irradiation and reducing volume” is that regional lymph node management does not have to rely solely on radiotherapy: standardized radical surgery and systemic therapy remain the cornerstones of regional control. The Japanese Gastric Cancer Treatment Guidelines clearly state that D2 lymphadenectomy is indicated for potentially curable cT2-T4 tumors and cT1N+ tumors, reflecting the consensus basis of D2 as the standard procedure for regional node control [21]. Therefore, under conditions of rigorous imaging staging, strict risk control, and anticipated high-quality surgical dissection, shifting the radiotherapy volume strategy from “prophylactically covering regional lymph nodes” to “focusing on the primary tumor and minimizing volume” has clear mechanistic rationale and cross-tumor evidence support in the immune-combination setting, and also meets the practical needs of reducing treatment burden and improving accessibility.

Our research team has previously conducted an exploratory perioperative integration of radiotherapy and immunotherapy in the GEJ adenocarcinoma population: a single-center, single-arm, prospective study evaluating the safety and early efficacy signals of PD-1 inhibitor (toripalimab) combined with preoperative chemoradiotherapy, along with biomarker exploration, focusing on continuous monitoring and grading of treatment-related adverse events, perioperative complication assessment, and immune-related indicator analysis based on tissue and peripheral blood samples. Preoperative radiotherapy used IMRT and lasted about 5 weeks, integrated concurrently with SOX chemotherapy, and toripalimab was administered at fixed cycles throughout the preoperative chemoradiotherapy phase, preoperative waiting period, and postoperative adjuvant phase. The study observed a 100% R0 resection rate, a 33.3% complete response rate (CR), and a 72.2% major pathological response (MPR) rate, with no grade ≥ 3 immune-related complications, preliminarily confirming that toripalimab combined with concurrent chemoradiotherapy for resectable GEJ adenocarcinoma achieves significant pathological responses and good safety. However, in the course of this study, practical

challenges of perioperative integration of “long-course, larger-volume” radiotherapy emerged: prolonged treatment duration, increased medical burden, significant radiation resource utilization, and complexity of screening and pathways, all of which could affect enrollment efficiency and multi-center replicability. These experiences provide direct feasibility support and optimization directions for the present study – to further reduce the time and volume burden of the radiotherapy module and optimize its sequencing with systemic therapy while ensuring oncological safety boundaries and perioperative implementability.

Unpublished preclinical data from our research team further provide strong preliminary support for a strategy of “short-course radiotherapy first, rapidly sequenced with immunotherapy”. In two mouse subcutaneous xenograft models, YTN16 gastric cancer and MC38 colorectal cancer, we compared the anti-tumor effects of different radiotherapy fractionation schedules combined with PD-1 antibody. The results consistently showed that short-course radiotherapy combined with PD-1 antibody had superior tumor inhibition compared to long-course fractionation combined with PD-1 antibody; when further comparing treatment sequences under the same combination framework, radiotherapy followed by immunotherapy induced significantly greater tumor regression than immunotherapy followed by radiotherapy. This suggests that both fractionation and the temporal sequence of radiotherapy and immunotherapy are not merely procedural choices but may be important biological variables affecting the quality of immune synergy and ultimate efficacy.

Based on our previous clinical experience with perioperative chemoradiotherapy-immunotherapy integration and the above preclinical evidence, this study plans to use S-1 plus oxaliplatin (SOX) plus a PD-1 inhibitor as the neoadjuvant systemic backbone, introduce short-course radiotherapy as a local immune priming/sensitization module, and adopt “sparing prophylactic regional lymph node irradiation and minimizing irradiation volume” as the volume optimization direction, to test whether this strategy can significantly increase the postoperative pCR rate with a manageable safety profile. The pCR rate in the control group is provisionally assumed to be 15% based on our center’s previous clinical

observation, which will serve as the realistic baseline for defining the research question and the effect size framework for subsequent statistical design. The core hypothesis of this study is that, on top of the same neoadjuvant chemoimmunotherapy backbone, the sequential integration of short-course radiotherapy can bring a clinically meaningful increase in pCR rate, thereby providing a solid foundation for further exploring long-term outcome benefits and identifying subpopulations that may derive benefit.

In summary, after perioperative chemoimmunotherapy has gradually become an important backbone for resectable upper gastric/GEJ adenocarcinoma, there is a clear mechanistic rationale and cross-tumor clinical translational evidence for synergy between radiotherapy and immunotherapy. However, the traditional long-course, large-volume perioperative chemoradiotherapy pathway has not consistently translated into overall survival benefit in gastric cancer populations, suggesting that the radiotherapy module needs to be optimized with immune synergy and real-world implementability as guiding principles. Supported by our previous clinical experience with perioperative chemoradiotherapy-immunotherapy integration and unpublished preclinical data, this study proposes an immune-friendly combination strategy characterized by short-course radiotherapy, minimized irradiation volume, and sparing of prophylactic regional lymph node irradiation, and will validate its value in improving pCR and safety through a randomized controlled trial, thereby providing high-quality, generalizable evidence for optimizing perioperative comprehensive treatment pathways and identifying potential benefit populations.

II. Study Objectives

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.

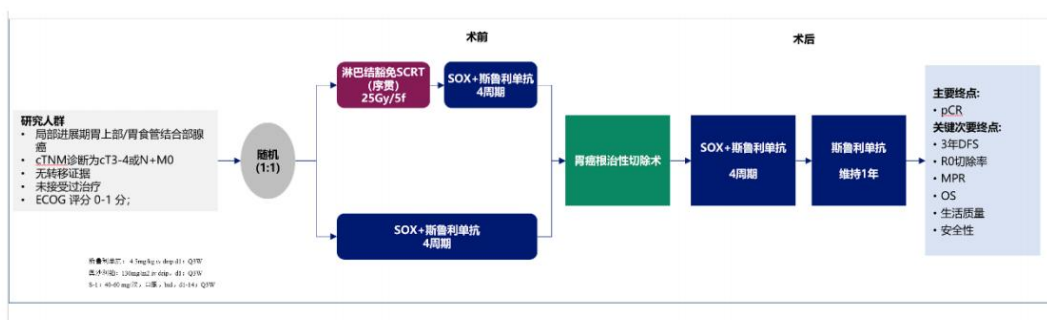
Secondary objective: To explore screening indicators for populations sensitive to neoadjuvant radiotherapy combined with chemoimmunotherapy in locally advanced upper gastric/gastroesophageal junction adenocarcinoma.

III. Study Design

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. After surgery, both cohorts will continue with 4 cycles of adjuvant SOX plus serplulimab, followed by serplulimab maintenance therapy for 1 year. If a patient does not meet the criteria for radical gastrectomy, the MDT team will discuss and decide on a change to conservative treatment or other surgical approaches. The study aims to evaluate the efficacy and safety of SOX plus serplulimab and SCRT followed by SOX plus serplulimab as neoadjuvant therapy followed by radical gastrectomy. All enrolled patients will undergo testing for PD-L1 expression level (CPS score, TPS score), microsatellite instability status (MSI-H population). If tissue quantity and center conditions permit, exploratory testing for MRD (before initial treatment, after neoadjuvant therapy, after surgery, after adjuvant therapy), tumor mutational burden (TMB), and whole-exome sequencing of tumor tissue will be performed.

Imaging assessments will be performed every 3 months (± 1 week) for the first 2 years after surgery, then every 6 months (± 2 weeks) until year 5, and annually thereafter until disease recurrence. After recurrence, survival follow-up will be performed every 3 months. Safety visits: from the first dose until 30 days after the last dose or the start of new anti-tumor therapy.

Study flow chart:



IV. Study Endpoints

Primary endpoint:

- Pathological complete response (pCR) rate.

Secondary endpoints:

- 3-year event-free survival (EFS);
- 3-year disease-free survival (DFS);
- Major pathological response (MPR) rate;
- R0 resection rate;
- Overall survival (OS);
- Safety: including perioperative complications, incidence of adverse events (AEs) and serious adverse events (SAEs), postoperative quality of life, and nutritional status.

V. Participating Study Sites

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

VI. Subject Selection

1. Inclusion Criteria

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. Exclusion Criteria

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).

VII. Sample Size Estimation

This trial uses a superiority design to evaluate the difference in efficacy between different neoadjuvant treatment strategies in patients with locally advanced upper gastric/gastroesophageal junction adenocarcinoma. Based on literature reports and clinical expert consensus, the pCR rate in the chemoimmunotherapy group (Cohort 2)

is set at $p_1 = 15\%$. Our team's previous clinical data showed that the pCR rate for LCRT concurrent chemoimmunotherapy in locally advanced upper gastric and GEJ cancer could reach 33-42%. Previously reported literature on locally advanced rectal cancer without node-sparing SCRT followed by chemoimmunotherapy showed superior pCR rates compared to LCRT concurrent chemoimmunotherapy. Based on our team's preliminary data, literature reports, and clinical expert consensus, the pCR rate in the node-sparing SCRT followed by chemoimmunotherapy group (Cohort 1) is set at $p_2 = 40\%$. The superiority margin is set at 0 (null hypothesis $H_0: p_1 - p_2 \leq 0$; alternative hypothesis $H_1: p_1 - p_2 > 0$). The comparison will use a one-sided, two-sample Z-test (unpooled), with a type I error rate $\alpha = 0.025$. Power $(1-\beta) = 90\%$. Considering a dropout rate of 15%, each group will have 73 subjects, for a total sample size of 146. Sample size was calculated using PASS 2025 (version 25.0.2).

VIII. Study Procedures

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. Randomization

The randomization numbers for subjects in this study will be generated using block randomization.

An independent statistician not involved in the study statistics will select appropriate block lengths, specify a random seed, and use SAS 9.4 statistical software to generate a randomization sequence assigning subjects to treatment groups (Cohort 1, Cohort 2) in a 1:1 ratio, producing randomization numbers 001-146 and their corresponding treatment allocations, i.e., the randomization table for this study.

The randomization sequence, along with parameters such as the random seed and block length, will be sealed and kept by the sponsor. No one may unseal the randomization table until enrollment is complete.

3. 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. The 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.

4. 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.

5. 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.

6. End of Treatment Visit

End of treatment (EOT) visit: within 30 days after stopping study treatment / last dose. If a subject experiences disease progression, intolerable toxicity, voluntary withdrawal, pregnancy, starts new anti-tumor therapy, or the investigator terminates the study during the neoadjuvant phase, the subject will undergo an end-of-treatment visit and safety visit. For subjects who discontinue neoadjuvant treatment due to disease progression or intolerable toxicity but undergo surgery, postoperative safety visits are required, and if the investigator judges that continued adjuvant treatment would be beneficial, they may enter the adjuvant phase.

7. Follow-up Period

After subjects discontinue study drug for any reason, they enter the follow-up period and will undergo the following follow-up until completion of survival follow-up:

- Safety follow-up: Within 30 ± 7 days after the last dose of study drug or first discharge after surgery, or until initiation of other anti-tumor therapy (whichever comes first), AEs, concomitant medications, and treatments will be assessed.

- Survival follow-up: After the safety follow-up, enter survival follow-up. Starting from the last safety follow-up, follow-up will be performed every 6 months

(± 2 weeks) (including telephone follow-up) to collect information on whether the subject has received other anti-tumor therapy since the previous follow-up. If other treatment is used, the regimen, number of cycles, best response, and time to progression must be recorded. Follow-up continues until subject death, recording cause and date of death to obtain overall survival (OS). Note: If the subject does not have a 30-day safety visit, survival follow-up should be calculated from the end of treatment.

8. Adverse Event Follow-up

Adverse events that have not resolved at the time of study drug discontinuation should be tracked and finally assessed. All subjects should be followed for 30 days after the last dose to detect any new adverse events.

9. Early Withdrawal

Subjects who withdraw early due to intolerance of adverse events or other reasons should complete all assessments required for the end-of-treatment visit, including a complete tumor imaging assessment (unless performed within the prior 30 days). Thereafter, with the subject's consent, imaging should be continued as much as possible until disease progression/death/initiation of new anti-tumor therapy (whichever occurs first).

10. Loss to Follow-up

If a subject fails to attend required visits and/or the study site cannot contact the subject, the following procedures will be followed:

- The study site must attempt to contact the subject and reschedule the missed visit. If contact is made, the subject should be informed of the importance of maintaining the protocol-specified visit schedule.

- For each missed visit, the investigator or designee must make every effort to re-establish contact with the subject (e.g., by phone and/or registered mail). These contact attempts should be documented in the subject's medical record.

11. Unscheduled Visits

If a subject requires an unscheduled visit due to an adverse event during the trial, the following should be recorded:

- Record concomitant medications/treatments;
- Record adverse events;
- Record relevant examinations performed (including imaging and tumor markers, if any).

IX. Data Collection and Statistical Analysis

1. CRF Completion and Transfer

Case report forms (CRFs) will be completed by the investigator. Each enrolled subject must have a completed CRF. Completed CRFs will be reviewed by the clinical research associate (CRA) and then transferred to the data manager for data entry and management.

2. Data Entry and Modification

Data entry and management will be performed by the data management unit. The data manager will be responsible for data entry and management. To ensure data accuracy, any queries regarding the CRFs will be written into a Data Query Form (DRQ) and sent to the investigator via the CRA. The investigator should answer as soon as possible and return it. The data manager will then modify, confirm, and enter the data based on the investigator's responses, and may issue another DRQ if necessary.

3. Data Review and Database Lock

Before database lock, the study team will summarize all protocol deviations that occurred during the trial and hold a data review meeting. Decisions made at the data review meeting must be documented.

After all data have been reviewed and approved, the database will be locked with confirmation from the investigator, study site, and statistician. Once locked, the data file cannot be altered. The locked data will be properly stored for future reference.

4. Data Archiving

The storage and management of trial documents must comply with GCP requirements.

5. Analysis Populations

To ensure reliable interpretation of results, the primary analyses of this trial will be based on the ITT, mITT, and SS sets. Results from the three analysis sets should be consistent; otherwise, potential reasons for differences should be discussed.

1) Intention-to-treat (ITT): Includes all randomized subjects, followed, evaluated, and analyzed according to the group to which they were assigned, regardless of whether they complied with the planned process.

2) Modified intention-to-treat (mITT): mITT is a subset of ITT, including all randomized subjects who underwent surgery.

3) Safety set (SS): Includes all subjects who received neoadjuvant chemotherapy, used for safety analysis.

6. Statistical Analysis Plan

6.1 Descriptive statistical content:

1) Normality testing: If not normally distributed, modify statistical methods or perform data transformation.

2) Outliers: Assess statistically and professionally to determine inclusion/exclusion.

3) Missing values: If a primary efficacy measure is missing for a subject, use last observation carried forward (LOCF).

4) Dropout rate: Should not exceed 15%; otherwise, provide explanation.

5) Descriptive statistics: Continuous data described by mean, standard deviation, median, interquartile range; categorical data described by frequency (proportion).

6.2 Statistical analysis methods:

1) Continuous data: Between-group comparisons using independent t-test or Wilcoxon rank-sum test; within-group comparisons using paired t-test or signed-rank test.

2) Categorical data: Chi-square test, Fisher's exact test, etc.; ordinal data: rank-sum test, CMH-chi-square test.

3) Multi-center analysis: CMH-chi-square test for categorical data; analysis of covariance (ANCOVA) for continuous data adjusting for center effect and baseline.

4) Analytical models: ANCOVA, Cox regression.

6.3 Statistical presentation:

Results will be presented using internationally common three-line tables, with appropriate headings and column labels.

Descriptive results will be described using a combination of text and tables.

The primary efficacy endpoint will be tested for superiority. All other statistical tests will be two-sided. A P value ≤ 0.05 will be considered statistically significant.

6.4 Statistical software:

SAS 9.4 will be used.

6.5 Statistical analysis content:

1) Distribution of subjects between the two groups: comparison of dropout/withdrawal rates, listing of subjects who dropped out/withdrew.

2) Comparability analysis: Comparison of demographic and other baseline variables to assess balance between groups.

3) Efficacy analysis: Because this is a multicenter trial, the analysis should account for center effect on efficacy outcomes. For long-term outcomes such as 3-year DFS, first use Kaplan-Meier method to plot survival curves for experimental and control groups, then use log-rank test to compare survival curves, and finally use Cox regression model to estimate HR and two-sided 95% CI, analyzing the effect of multiple factors on survival. Describe changes in disease-related laboratory parameters before and after treatment. Use ANCOVA to compare the change from baseline between the two groups for laboratory parameters at end of treatment, with baseline as covariate and adjusting for center and group effects. Perform consistency testing with a significance level of 0.10.

4) Safety analysis: Use chi-square test or Fisher's exact test to compare adverse event rates between groups, and list all adverse events that occurred during the trial. Changes in laboratory parameters from normal to abnormal before and after treatment, and their relationship with surgical procedure.

5) Stratified analysis: Stratify based on baseline CPS score (preferentially using central laboratory uniform testing and interpretation; if both central and investigator

interpretations exist, central results will prevail).

Patients will be stratified using CPS <5 and CPS $\geq$ 5 as cut-offs, and treatment effects will be assessed within each CPS stratum: for time-to-event outcomes (e.g., EFS/DFS/OS), a Cox proportional hazards model will be used to estimate stratum-specific HR and 95% CI, including treatment, CPS stratum, and their interaction (treatment $\times$ CPS), adjusting for key covariates (e.g., stage, tumor location, center) if necessary; for binary outcomes (e.g., pCR/MPR/R0 rate), logistic regression will be used to estimate OR and 95% CI, also including treatment, CPS stratum, and interaction.

X. References

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