Efficacy and Safety of Serplulimab Combined with SOX and Nab-paclitaxel as Neoadjuvant Treatment for Locally Advanced Gastric cancer or Adenocarcinoma of Esophagogastric junction: A Multicenter Randomized Controlled Trial

CLINICAL STUDY PROTOCOL

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Abbreviations

Abbreviations	Full names
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BIL	Bilirubin
BSA	Body surface area
BUN	Blood urea nitrogen
CCr	Creatinine Clearance
CFDA	China Food and Drug Administration
CI	Confidence interval
Cr	Creatinine
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTC AE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DRQ	Data Request
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EORTC	The European Organization for Research and Treatment for Cancer
FAS	Full Analysis Set
Fbg	Fibrinogen
GC	Gastric cancer
GCP	Good Clinical Practice

Glu	Glucose
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard Ratio
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IQR	Interquartile range
IRB	Institutional Review Board
irAE	Immune-related adverse event
ITT	Intention-to-treat
LAGC	Locally advanced gastric cancer
MPR	Major pathological response
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NMPA	National Medical Products Administration
NTAX	Nanoparticle albumin-bound-paclitaxel
NSCLC	Non-small Cell Lung Cancer
OB	Occult blood
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PD	Progression disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal Investigator
PLT	Platelets

PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell
RCCEP	Reactive cutaneous capillary endothelial proliferation
RECIST	Response Evaluation Criteria in Solid Tumor
RR	Respose Rate
SAE	Serious adverse event
SAS	Safty Analysis Set
SCr	Serum Creatinine
SD	Stable disease
TRG	Tumor regression grade
TSH	Thyroid-stimulating hormone
TT	Thrombin time
ULN	Upper limits of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell

SYNOPSIS

Title	Efficacy and Safety of Serplulimab Combined with SOX and Nab-paclitaxel as Neoadjuvant Treatment for Locally Advanced Gastric or Esophagogastric junction Cancer: A Multicenter Randomized Controlled Trial
Study Subjects	Patients with locally advanced gastric cancer (LAGC) or adenocarcinoma of esophagogastric junction (AEG)
Study Design	Multicenter, double-blind, randomized phase 2 clinical trial
Study Objectives	**Primary endpoint** ➢ Pathological complete response rate (pCR), postoperative pathological response according to the Mandard tumor regression grading system (TRG), TRG 1 is pCR. **Secondary endpoints** ➢ ORR，MPR, etc. ➢ R0 resection rate ➢ 1/3-year PFS and OS ➢ Safety of study drugs according to the NCI-CTCAE, version 5.0 ➢ Surgical safety: including morbidity, mortality, hospital stay, etc. ➢ Patient reported outcomes: EORTC QLQ-C30 and QLQ-STO22
Number of Patients	58 patients per group
Inclusion	● Age older than 18 and younger than 80 years ● Primary GC or AEG (Siewert II/III)confirmed pathologically by endoscopic biopsy ● Clinical stage T3/T4N+M0 disease as assessed by CT/MRI, PET-CT, and laparoscopy, if feasible ● At least one measurable lesion according to the RECIST, version 1.1 ● Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Criteria	● Surgical treatment after neoadjuvant chemotherapy is planned according to clinical staging criteria. ● Life expectancy of at least 3 months ● Acceptable bone marrow, hepatic, and renal function, including: 1.Blood routine examination(No blood transfusion within 14 days; No granulocyte colony-stimulating factor (G-CSF) or other hematopoietic stimulating factors were used): white blood cell count ≥3.5 ×10^9/L, neutrophils ≥1.5 × 10^9/L, platelet count >100 × 10^9/L, and hemoglobin ≥90 g/L; 2. Hepatic function: alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ALT and AST≤2.5×ULN; total bilirubin (TBIL) ≤1.5×ULN (Gilbert syndrome patients, ≤3×ULN); 3. Renal function: serum creatinine (Cr) ≤1.5×ULN or creatinine clearance (Ccr) ≥60mL/ min; 4. Coagulation function: activated partial thromboplastin time (APTT), international standardized ratio (INR), prothrombin time (PT) ≤1.5×ULN; ● Written informed consent
Exclusion Criteria	● Squamous cell carcinoma, adenosquamous cell carcinoma, small cell carcinoma, and undifferentiated gastric cancer were confirmed by pathology ● Positive Her-2 detection (IHC3+ or IHC2+ amplified by FISH detection) ● Prior chemotherapy, radiotherapy, hormone therapy, targeted therapy, or immunotherapy ● Contraindications for surgical treatment or chemotherapy ● Presence of distant metastasis ● History of other malignant disease within the past 5 years, except: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that have been

	treated radically and have shown no signs of disease for at least 5 years ● Any active or history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy ● History of immunodeficiency diseases, including human immunodeficiency virus (HIV), or other acquired or congenital immune-deficient disease, or transplantation ● Severe mental disorder ● Presence of digestive tract obstruction, jaundice, acute infectious diseases, inflammatory bowel disease, Crohn's disease, ulcerative colitis, chronic diarrhea, active tuberculosis ● Immunosuppressive drugs are required for 2 weeks or within 2 weeks or during the study period, excluding the following: a) intranasal, inhaled, topical or topical steroid injections (e.g. intra-articular injections); b) Physiological dose of systemic corticosteroids (≤10mg/ day prednisone or equivalent dose); c) Short-term (≤7 days) use of steroids for the prevention or treatment of non-autoimmune allergic diseases; ● Patients who have undergone major surgery or received live virus vaccine within 4 weeks ● Pregnant or breast-feeding women, subjects who are unwilling to receive effective contraception during treatment and within 6 months after the end of treatment (including male subjects who have the ability to impregnate women and female subjects and their male partners) ● Evidence of bleeding tendency or receiving thrombolytics or anticoagulants ● According to the criteria of the term Common Adverse Events (NCI-CTCAE V5.0), the corresponding symptoms have been diagnosed;

	● Hepatitis B or hepatitis C virology tests at the time of screening meet any of the following: a) HBsAg positive and HBV-DNA titer ≥104 copy number /mL or ≥2000IU/mL (hepatitis B carriers should ask researchers for appropriate antiviral treatment); b) Active hepatitis C: HCV antibody positive and HCV-RNA higher than the lower detection limit of the assay; ● Allergic to study drugs ● The investigator believes that the subjects have other conditions that may affect their adherence to the protocol and evaluation of the study indicators, and the subjects are not suitable to participate in the study.
Drop out/removal criteria	● Use of NMPA-approved modern traditional Chinese medicine agents for the treatment of gastric cancer ● Concurrent radiotherapy or other local treatments during the study periods ● Medication, dosing, and treatment methods do not follow the study protocol
Treatment end/termination Criteria	● The patient has completed the treatment prescribed in the protocol; ● Withdrawn of the informed consent ● Progression disease (PD) or death ● Unbearable toxicity after dose reductions ● When an adverse event (AE) or serious adverse event (SAE) occurs, the patient does not wish to continue treatment or has an unexpected and unacceptable adverse drug reaction; ● Loss to follow up ● Investigator's decision that stopping treatment was in the best interest of the patient
Study Duration	● Planned start date: September 1, 2024 ● Planned enrollment completion date: September 1, 2025 ● Planned study end date: September 31, 2025

Treatment Regimens

Neoadjuvant treatment

Treatment group (S-P-SOX):

- Serplulimab, 4.5 mg intravenously on day 1;
- Nap-paclitaxel, 260 mg/m^2 intravenously on days 1;
- Oxaliplatin (OXA), 130mg/ /m^2, intravenously on days 1;
- Tigio (S-1), 40-60 mg orally twice daily on days 1 to 14.

Control group (P-SOX):

- Nap-paclitaxel, 260 mg/m2 intravenously on days 1;
- Oxaliplatin (OXA), 130mg/ m2, intravenously on days 1;
- Tigio (S-1), 40-60 mg orally twice daily on days 1 to 14.

The dose of S-1 is based on body surface area (BSA):

BSA	Dose
< 1.25m^2	40mg× 2/day
1.25m^2 - 1.5m^2	50mg× 2/day
> 1.5m^2	60mg× 2/day

The above treatments will be administered every 3 weeks for three preoperative cycles. Dose adjustment is not allowed and delayed dosing is allowed.

Surgery

Surgery was scheduled 3 to 4 weeks after completion of the last cycle of neoadjuvant treatment. All surgical procedures are performed according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer.

Adjuvant treatment

Adjuvant treatment started 3 to 8 weeks after surgery. Patients will receive three to five 3-week cycles of adjuvant treatment with S-P-SOX or P-SOX according to the preoperative regimen.

Statistical Consideration	Full analysis set (FAS) included all patients who are randomly assigned according to the intention-to-treat (ITT) principle. This population will be used for the efficacy analyses. Baseline data were analyzed by FAS. Per-protocol set (PPS) included patients in the ITT population who did not present major deviations from the protocol. We pre-specified that participants who received surgery after administration of neoadjuvant S-P-SOX or P-SOX are included in this set. This population will be also used for the efficacy analyses. Safety analysis set (SAS) included patients who received at least one dose of allocated treatment. This population will be also used for the safety analyses.
Sample size determination	Based on results and data from previous similar studies, the pCR rate of nap-paclitaxel combined with SOX is known to be 7%, and the pCR rate of the Serplulimab combined with nap-paclitaxel and SOX is expected to be 25%. A sample size of 58 patients per group was required to detect improvement with 80% power and a one-sided alpha level of 0.05, including a 15% dropout rate.
Version	1.1

Study Plan

Items	Screening Period		Randomization	Neoadjuvant Treatment Period					Surgery		Adjuvant Treatment Period		Follow-up[16]
				Cycle 1	Cycle 2		Cycle 3		Before 1 week of surgery	After 1 week of surgery	Cycle 4-6		
	Before 2 weeks of enrollment	Before 1 week of enrollment		Day 14	Day 1	Day 14	Day 1	Day 14			Day 1	Day 14	
Baseline characters													
Informed consent	√												
Demographics data	√												
Medical history		√											
Vital signs and physical[1]		√		√	√	√	√	√	√	√	√	√	√
Assessments													
Blood routine[2]		√		√	√	√	√	√	√	√	√	√	√
Urinary routine[3]		√			√		√		√		√		
Fecal routine		√			√		√		√		√		
Biochemistry[4]		√		√	√	√	√	√	√	√	√	√	√
Coagulation test[5]		√			√		√		√		√		
Thyroid function test[6]		√							√				
Tumor markers[7]		√			√		√		√	√	√		√
Myocardial zymogram		√							√				
Pituitary-adrenal axis examination[8]		√											
HBV/HCV/HIV[9]		√							√				
Tumor sample[10]		√								√			
Gastroduodenoscopy		√											
12-lead ECG		√			√		√		√		√		
Echocardiography[11]		√							√				
Imaging examination[12]	√								√				√
ECOG status		√		√	√	√	√	√	√	√	√	√	
Blood pressure monitoring[13]		√		√	√	√	√	√	√	√	√	√	
Adverse events[14]				√	√	√	√	√	√	√	√	√	

Others														
Concomitant treatments	√			√	√	√	√	√	√	√	√	√	√	
Drug compliance					√		√		√		√		√	
Surgical record[15]											√			
Drug suspension and dose adjustment				√	√	√	√	√	√		√	√		
Pathological efficacy evaluation											√			

[1] Including vital signs (blood pressure, pulse, and temperature), height (at baseline only), weight, and physical examination (especially abdominal examination).

[2] Including hemoglobin, hematocrit, RBC, WBC, ANC, and platelet count.

[3] Including urinary protein and urine occult blood.

[4] Including bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, blood urea nitrogen (BUN), glucose, calcemia, sodium, and potassium.

[5] Including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen.

[6] Including thyroid-stimulating hormone (TSH), free T3, and free T4.

[7] Including carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, CA125, CA153, etc.

[8] Pituitary-adrenal axis examination: adrenocorticotropin, cortisol

[9] Including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).

[10] Central evaluation of programmed death-ligand 1 (PD-L1) expression and microsatellite instability (MSI) in pretreatment specimens, tumor regression grade in surgical specimens, and exploring the the mechanisms of response and resistance to S-P-SOX.

[11] Echocardiography must be examined during screening. During the study period, ECG abnormalities of significant clinical significance should be supplemented by Echocardiography

[12] Including chest, abdomen and pelvis CT or MRI.

[13] Blood pressure monitoring is completed by the patient and recorded in a diary card. Blood pressure should be measured at least 3 times a week for the first 3 cycles. For patients with abnormal blood pressure, blood pressure should be measured every day. At each visit, blood pressure should be measured by the investigator. Each blood pressure measurement should be taken ipsilateral.

[14] Adverse events are recorded from randomization until 30 days after the last dose of the investigational product. During follow-up, all adverse events that occur previously and are ongoing, and newly occurring adverse events related with the investigational product or determined by the investigator as having a reasonable possibility of being caused by the investigational product are recorded, and of these, serious adverse events are all reported. Serious adverse events ongoing at the time of completion of the investigational product administration will be followed during the follow-up period until resolved or stabilized irrespective of the relationship with the investigational product.

[15] Surgical record: including operative time, intraoperative bleeding, surgical approach, postoperative complications, postoperative outcomes, surgical costs, and pathological result.

[16] Patients are followed up postoperatively by physical examination, laboratory tests, and imaging examination every 3 months for 2 years, every 6 months during years 3-5, and annually thereafter. Endoscopy is recommended annually.

1. Background

Gastric Cancer (GC) is the fifth most common malignancy globally and the third leading cause of cancer death. Half of the world's cases occur in eastern Asia [1], which has the highest mortality rate. According to the latest data released by the National Tumor Registration Center, it is estimated that in 2015, there were 679,000 new cases of gastric cancer in China, and 498,000 deaths, ranking second in both incidence and fatality rate among malignant tumors [2]. The overall prognosis is poor, posing a serious threat to human health.

Environmental and genetic factors play an important role in the development of gastric cancer, with common risk factors including age, male gender, smoking, radiation and family history. Specific risk factors for gastric cancer include Helicobacter pylori infection and dietary factors [3]. Helicobacter pylori (H.pylori) infection often leads to chronic gastritis, gastric atrophy, and then intestinal metaplasia, abnormal hyperplasia and gastric cancer [4-6]. Dietary factors include low intake of fruits and vegetables, high salt, and intake of smoked foods.

Radical surgical resection is still the main treatment for non-metastatic gastric cancer, but the postoperative recurrence and metastasis rate is as high as 40-80%, and the 5-year survival rate is 30-60%[7-8]. The treatment mode of neoadjuvant chemotherapy + surgery + adjuvant chemotherapy (perioperative treatment) is an important part of the comprehensive treatment of gastric cancer at present. A number of studies have proved that compared with surgery alone, this treatment mode can reduce the tumor stage, increase the R0 resection rate, and improve the overall survival, without increasing postoperative complications and mortality. The purpose of neoadjuvant chemotherapy is to reduce tumor load and increase the possibility of R0 resection [9], so as to improve the pathological complete response rate. Neoadjuvant chemotherapy can measure a patient's sensitivity to chemotherapy drugs and therefore predict a patient's response to subsequent chemotherapy. At present, it has been confirmed that pathological complete response rate is correlated with overall survival [10]. On September 28, 2019, at the ESMO Conference , Chinese scholars announced the results of the RESOLVE Phase III study on perioperative treatment of locally

advanced gastric cancer [11], adding new evidence-based medical evidence for perioperative treatment of such patients. The RESOLVE study is A three-arm, randomized, multicenter, open-label Phase III trial comparing the efficacy and safety of using XELOX (Group A) or SOX (Group B) after radical D2 surgery versus perioperative use of SOX (group C). Finally, 1022 cases of ITT population were included in the analysis. In the perioperative group (group C), the R0 resection rate (92.88%) and the proportion of D2 lymph node dissection (95.59%) showed an increasing trend. The R0 removal rates of group A and group B were 86.47% and 87.83%, respectively. In patients with locally advanced gastric cancer, SOX chemotherapy during perioperative period improved 3-year disease-free survival (62.02% vs 54.78%, P=0.045, HR=0.79, 95%CI 0.62-0.99) compared with XELOX adjuvant. Results of a multicenter Phase III clinical study in France [12] showed that preoperative neoadjuvant chemotherapy with PF regimen significantly increased R0 resection rate compared with surgery alone (84% vs 73%, P=0.04). For initially treated locally advanced gastroesophageal cancer, XELOX regimen has been proven to be as effective as cisplatin combined with fluorouracil regimen [13]. Results of a Chinese study showed that for patients with advanced gastric cancer, the ORR of neoadjuvant chemotherapy with FOLFOX regimen was 70%[14], and the R0 resection rate was significantly improved compared with surgery alone (86% vs 55%, P=0.011). A study from Japan showed [15] that neoadjuvant chemotherapy with SP protocol is safe and effective for stage II and III gastric cancer with lymph node metastasis, with ORR of 75.5% and R0 removal rate of 87.8%. Chinese researchers have found [16] that SOX neoadjuvant application in advanced gastric cancer has an ORR of 68.5%, and the R0 removal rate is also significantly higher than that of operation alone (81.3%vs 73.5%, P=0.040). The results of the recent FLOT4 study [17] showed that the perioperative regimen of 5-fluorouracil + docetaxel + oxaliplatin + calcium folinate (FLOT) was superior to the perioperative regimen of epirubicin + cisplatin + 5-fluorouracil or capecitabine (ECF/ECX) in terms of R0 removal rate (85% vs 78%). P=0.0162).

At present, the recommended preoperative chemotherapy for gastric cancer mainly includes: Epirubicin combined with Cisplatin and fluorouracil (ECF) and its modification, cisplatin combined with fluorouracil (PF), oxaliplatin combined with

capecitabine (XELOX), oxaliplatin combined with fluorouracil (FOLFOX), Cisplatin combined with S-1 (SP), oxaliplatin combined with S-1 (SOX), FLOT (5-fluorouracil + docetaxel + oxaliplatin + calcium folinate).

The evaluation of neoadjuvant chemotherapy regimen and cycle selection as well as clinical efficacy for advanced gastric cancer is summarized as follows. For whether combined immunotherapy drugs are needed, further randomized controlled trials are needed to verify their advantages and value.

Table 1 Phase II clinical trials of neoadjuvant chemotherapy for advanced GC

Items	sample	treatment	Cycle	cRR	pRR
Chen et al.	113	OXA /5-FU/ calcium folinate	/	/	17/87(19)
		Epirubicin/OXA/capecitabine	/	/	10/26(38)
Yoshiaki et al.	49	S-1/ cisplatin	2	25/49(51)	23/49(47)
Takaki et al.	83	S-1/ cisplatin	2/4	19/41(46)	17/41(42）
		paclitaxel / cisplatin		11/42(26)	14/42(33)
				2 cycles 14/42(33)	15/42(36)
				4 cycles 16/41(39)	16/41(39)
Migita et al.	59	S-1/ cisplatin / Docetaxel	1-2	44/59(74)	42/59(71)
Aoyama et al.	132	S-1/ cisplatin	2/4		12/62(19）
		S-1/ cisplatin / Docetaxel			10/65(15)
					2 cycles 10/64(15)
					4 cycles 12/63(19)

As a highly heterogeneous malignant tumor, gastric cancer is an extremely complex process in which the immune microenvironment plays an important role, and the inhibitory immune microenvironment and immune escape have received more and more attention. programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1) belong to the B7/CD28 superfamily and are very important negative co-stimulatory molecules discovered in recent years. It can negatively regulate the activity of immune cells [18]. PD-1 is the main immunosuppressive molecule on the surface of T cells and B cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is widely

expressed in activated T cells, B cells, macrophages, dendritic cells, and tumor cells. PD-L1 expressed by tumor cells and PD-1 expressed by tumor Infiltrating Lymphocytes (TILs) (mainly CD8+T cells) bind to activate the PD-1/PD-L1 signaling pathway and inhibit the activation of tumor infiltrating lymphocytes. Reduced T cell reactivity leads to T cell incapacitated, induces T cell apoptosis, provides a suitable microenvironment for the development of tumor cells, mediates tumor immune escape, and promotes tumor growth [19]. Blocking the PD-1/PD-L1 signaling pathway can reverse the tumor immune microenvironment and enhance the endogenous anti-tumor immune effect. PD-L1 is highly expressed in various solid malignant tumors [20-21], including non-small cell lung cancer, melanoma, renal cell carcinoma, prostate cancer, breast cancer, stomach cancer, etc., and its expression level varies according to different tumor types. At present, the relationship between PD-L1 expression and prognosis in gastric cancer is still controversial.

In December 2018, the Phase II trial results of the Asian Attract-04 study [22] were published. The study was designed to explore the safety and efficacy of Nivolumab in combination with SOX (Ticeo and oxaliplatin) or XELOX (capecitabine and oxaliplatin) in first-line treatment of advanced, unresectable, or recurrent gastric/gastroesophageal junctional adenocarcinoma. The randomized ratio was 1:1, and the median OS follow-up was not reached in the FAS population (NR (11.9, NR) and NR (11.2, NR), respectively). Median PFS were 9.7 months (5.8-NR) and 10.6 months (5.6-12.5), respectively. The ORR of Nivolumab combined with SOX was 57.1%, and that of Nivolumab combined with XELOX was 76.5%.

In March 2019, the results of KEYNOTE-059 study [23] Cohort 2 and cohort 3 Phase II clinical trials were published. The study cohort 2 and cohort 3 were designed to explore the safety and efficacy of Pembrolizumab± chemotherapy in first-line treatment of advanced gastric or gastroesophageal junction adenocarcinoma. In cohort 2, 25 patients received Pembrolizumab combined with chemotherapy. All patients had an ORR of 60.0%, including 73.3% ORR in the PD-LI positive group and 37.5% ORR in the PD-LI negative group, with a median OS of 13.8 months (8.6-NR). The median PFS was 6.6 months (5.9-10.6). In cohort 3, 31 PD-L1 positive (CPS $\geqslant$ 1) patients who

received Pembrolizumab monotherapy had an ORR of 25.8%, a median OS of 20.7 months (9.2-20.7), and a median PFS of 3.3 months.

At the American Society of Clinical Oncology Symposium (ASCO) in June 2019, Merck presented the results of the KEYMAT-062 Phase III study [24], which randomized untreated PD-L1-positive advanced gastric or gastroesophageal junction adenocarcinoma into three groups, group 1 being Pembrolizumab monotherapy (Group P). Pembrolizumab combined with chemotherapy in group 2 (P+C) and placebo combined with chemotherapy in group 3 (C) had primary endpoints of PFS in people with PD-L1 CPS≥1 and OS in people with PD-L1 CPS≥1 and CPS≥10. The results suggest that Pembrolizumab combined with chemotherapy is not superior to chemotherapy for OS and PFS in any population. From the perspective of ORR alone, in patients with CPS≥1, the ORR in group P vs group C vs group P+C was 14.8% vs 37.2% vs 48.6%; In patients with CPS≥10, the ORR in group P vs C vs P+C was 25.0% vs 37.8%vs 52.8%. In terms of safety, the P vs C group had better safety, with the incidence of any grade of AE in the P+C vs C group being 94% vs 92%, and the incidence of grade 3-4 TRAE being 71% vs 68%, with no unexpected adverse events.

On November 5, 2022, at the CSCO Annual Meeting, Professor Huang Jing reported on the research related to the treatment of advanced esophageal cancer with Srulizumab - ASTRO-007: In the whole population, the median PFS in the srulizumab and placebo groups was 5.8 months vs5.3 months (HR=0.60, P < 0.0001), and the median OS was 15.3 months vs 11.8 months (HR=0.68, P=0.0020). Among those with PD-L1 CPS≥10, the median PFS for both groups was 7.1 months vs 5.3 months (HR=0.48, P < 0.0001), and the median OS was 18.6 months vs 13.9 months (HR=0.59, P=0.0082). The study also confirmed the significance of srulizumab combined with chemotherapy in the first-line treatment of advanced esophageal cancer, especially in those with CPS > 10.

Table 2 First-line PD-1 antibody combined with chemotherapy for GC

Items	Treatment	Sample	ORR
ATTRACTION-04	SOX	21	57.1
	XELOX	18	76.5

KEYNOTE-062	CPS≥1	257	48.6
	CPS≥10	99	52.8
KEYNOTE-059	Cohort 2	25	60.0
Innovent	F cohort	20	85
HOTWELL		43	44

In other cancers, such as triple negative breast cancer and head and neck squamous cell carcinoma, Pembrolizumab combined with neoadjuvant chemotherapy has shown promising antitumor activity and clinical efficacy. At present, immunotherapy is also being explored in the perioperative period of gastric cancer, such as the phase III clinical study of KEYKEYNOTE 585 perioperative chemotherapy for gastric cancer combined with or without PD-1 inhibitor, and the clinical study of mFOLFOX combined with PD-1 inhibitor for the treatment of gastroesophageal conjoint adenocarcinoma or gastric adenocarcinoma in perioperative period (NCT03488667), etc. In order to provide a new clinical thinking for the treatment of locally advanced gastric cancer.

2. Objectives

2.1 Primary Objective

To assess the efficacy of Serplulimab combined with nab-paclitaxel plus SOX versus nab-paclitaxel plus SOX alone as neoadjuvant treatment for locally advanced GC or AEG, as measured by pCR according to the the Mandard tumor regression grading criteria.

2.2 Secondary Objectives

To assess and compare the followings between the two groups:

- ORR，MPR, etc.
- R0 resection rate
- 1/3-year PFS and OS
- Safety of study drugs according to the NCI-CTCAE, version 5.0
- Surgical safety: including morbidity, mortality, hospital stay, etc.
- Patient reported outcomes: EORTC QLQ-C30 and QLQ-STO22

2.3 Exploratory Objective

To assess the associations between the primary endpoint and several tumor biomarkers (including but not limited to PD-L1 expression and MSI status), and explore the mechanisms of response and resistance to S-P-SOX.

2.4 Randomization, Blinding, and Unblinding

A randomized, double-blind design is employed in this trial. This study employed block randomization to allocate subjects in a 1:1 ratio to either the experimental or control group. To ensure balance in sample size between the groups, the randomization sequence was generated using SAS 9.4 software. The randomization list was generated by an independent statistician and securely stored in a password-protected computer system, with corresponding envelopes prepared. The research team remained blinded to the group assignments, and subjects were instructed to open the envelopes according to their enrollment order.:

- Arm A (S-P-SOX): Serplulimab + Nap-paclitaxel + S-1 + Oxaliplatin
- Arm B (P-SOX): placebo + Nap-paclitaxel + S-1 + Oxaliplatin

During the study, the subjects, the investigator, the sponsor, and the designees are not aware of the randomized allocation, except in the event of emergency unblinding.

During the course of treatment with the study drug, if the investigator determines that the study drug is related to a life-threatening situation of the subject, and the investigator considers that knowing the medication of the subject is conducive to the handling of adverse events, an emergency unblinding is allowed. The decision to unblind in an emergency is the responsibility of the investigator and will not be delayed or declined by the sponsor; however, the investigator may contact the sponsor or its designees to discuss the unblinding and the protocol that is in the best interest of the subject prior to unblinding. The investigator shall ensure that unblinding is performed in strict accordance with the protocol. The investigator shall inform the sponsor of the circumstances of and reasons for emergency unblinding as soon as possible, and record these details clearly on the subject's source document. Two sets of sealed blind envelopes were prepared. In the event of an emergency unblinding, the identification number will be used to open the retained envelope to complete the unblinding process. If deemed necessary, the unblinding shall only apply to the affected subject.

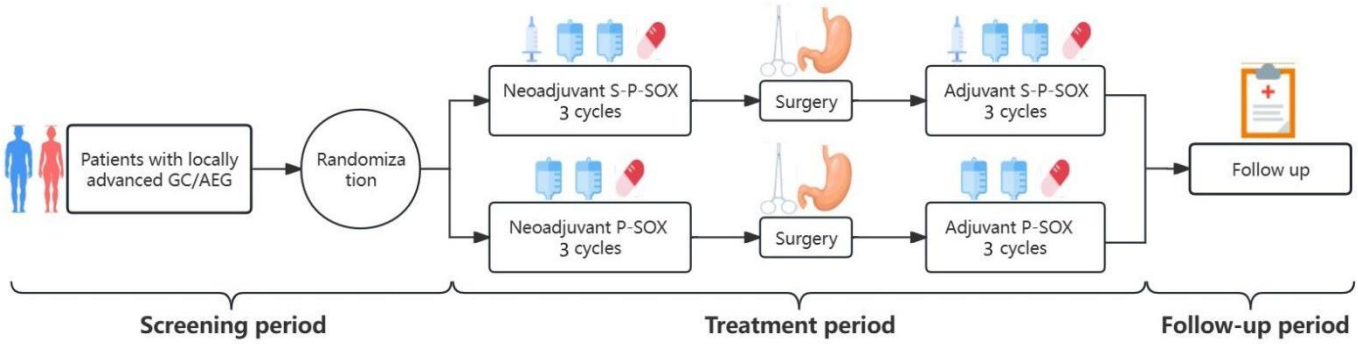
The study will be unblinded overall after the last subject completed the study visit. The study shall remain blinded unless there is an emergency medical condition (emergency treatment is only possible when being informed of the randomized medication) or unblinding is requested by the regulatory authorities. Only when all data have been input into the database, all data queries have been resolved and subjects have been allocated into analysis sets, can the random codes be unblinded.

3. Study Design and Sample Size

3.1 Study Design

This is a multicenter, double-blind, randomized, phase 2 trial to investigate the efficacy and safety of Serplulimab combined with nab-paclitaxel plus SOX versus nab-paclitaxel plus SOX alone as neoadjuvant treatment for locally advanced GC or AEG. It will be conducted in 5 medical centers in China. Eligible patients were randomly assigned to receive Serplulimab (4.5 mg intravenously on day 1) combined with chemotherapy (nap-paclitaxel 260 mg/m^2 intravenously on days 1, OXA 130mg/ /m^2, intravenously on days 1, and S-1 40 to 60 mg orally twice daily depending on BSA on days 1 to 14) or chemotherapy alone every 3 weeks for 3 preoperative cycles followed by 3-5 postoperative cycles. All patients will be followed for survival.

3.2 Study Schema



3.3 Study Duration

The total duration for enrollment is expected to be 12 months, beginning with the first patient in September 1, 2024, and ending with the last patient in September 1, 2025. The initial analyses for the primary endpoint are planned in September 31, 2025. The total duration of the study is expected to be 4 years, including a follow-up period of 3

years. The final analyses for OS and PFS are planned in the third quarter of 2028.

3.4 Sample Size

Based on results and data from previous similar studies, the pCR rate of nap-paclitaxel combined with SOX is known to be 7%, and the pCR rate of the Serplulimab combined with nap-paclitaxel and SOX is expected to be 25%. A sample size of 58 patients per group was required to detect improvement with 80% power and a one-sided alpha level of 0.05, including a 15% dropout rate.

4. Study Population

4.1 Inclusion Criteria

- Age older than 18 and younger than 80 years
- Primary GC or AEG (Siewert II/III)confirmed pathologically by endoscopic biopsy
- Clinical stage T3/T4N+M0 disease as assessed by CT/MRI, PET-CT, and laparoscopy, if feasible
- At least one measurable lesion according to the RECIST, version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Surgical treatment after neoadjuvant chemotherapy is planned according to clinical staging criteria.
- Life expectancy of at least 3 months
- Acceptable bone marrow, hepatic, and renal function, including: a)Blood routine examination(No blood transfusion within 14 days; No granulocyte colony-stimulating factor (G-CSF) or other hematopoietic stimulating factors were used): white blood cell count ≥3.5 ×109/L, neutrophils ≥1.5 × 109/L, platelet count >100 × 109/L, and hemoglobin ≥90 g/L; b)Hepatic function: alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ALT and AST≤2.5×ULN; total bilirubin (TBIL) ≤1.5×ULN (Gilbert syndrome patients, ≤ 3×ULN); c)Renal function: serum creatinine (Cr) ≤1.5×ULN or creatinine clearance (Ccr) ≥ 60mL/ min; d)Coagulation function: activated partial thromboplastin time (APTT), international standardized ratio (INR), prothrombin time (PT) ≤1.5×ULN;
- Written informed consent

4.2 Exclusion Criteria

- Squamous cell carcinoma, adenosquamous cell carcinoma, small cell carcinoma, and undifferentiated gastric cancer were confirmed by pathology
- Positive Her-2 detection (IHC3+ or IHC2+ amplified by FISH detection)
- Prior chemotherapy, radiotherapy, hormone therapy, targeted therapy, or immunotherapy
- Contraindications for surgical treatment or chemotherapy

- Presence of distant metastasis
- History of other malignant disease within the past 5 years, except: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that have been treated radically and have shown no signs of disease for at least 5 years
- Any active or history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy
- History of immunodeficiency diseases, including human immunodeficiency virus (HIV), or other acquired or congenital immune-deficient disease, or transplantation
- Severe mental disorder
- Presence of digestive tract obstruction, jaundice, acute infectious diseases, inflammatory bowel disease, Crohn's disease, ulcerative colitis, chronic diarrhea, active tuberculosis
- Immunosuppressive drugs are required for 2 weeks or within 2 weeks or during the study period, excluding the following: a) intranasal, inhaled, topical or topical steroid injections (e.g. intra-articular injections); b) Physiological dose of systemic corticosteroids ($\leqslant$ 10mg/ day prednisone or equivalent dose); c) Short-term ($\leqslant$7 days) use of steroids for the prevention or treatment of non-autoimmune allergic diseases;
- Patients who have undergone major surgery or received live virus vaccine within 4 weeks
- Pregnant or breast-feeding women, subjects who are unwilling to receive effective contraception during treatment and within 6 months after the end of treatment (including male subjects who have the ability to impregnate women and female subjects and their male partners)
- Evidence of bleeding tendency or receiving thrombolytics or anticoagulants
- According to the criteria of the term Common Adverse Events (NCI-CTCAE V5.0), the corresponding symptoms have been diagnosed;
- Hepatitis B or hepatitis C virology tests at the time of screening meet any of the following: a) HBsAg positive and HBV-DNA titer $\geqslant$104 copy number /mL or $\geqslant$2000IU/mL (hepatitis B carriers should ask researchers for appropriate antiviral treatment); b) Active hepatitis C: HCV antibody positive and HCV-RNA higher than the lower detection limit of the assay;
- Allergic to study drugs
- The investigator believes that the subjects have other conditions that may affect their adherence to the protocol and evaluation of the study indicators, and the subjects are not suitable to participate in the study.

4.3 Drop Out/Removal Criteria

- Use of NMPA-approved modern traditional Chinese medicine agents for the treatment of gastric cancer
- Concurrent radiotherapy or other local treatments during the study periods
- Medication, dosing, and treatment methods do not follow the study protocol

4.4 Treatment end/termination Criteria

- The patient has completed the treatment prescribed in the protocol;
- Withdrawn of the informed consent
- Progression disease (PD) or death
- Unbearable toxicity after dose reductions
- When an adverse event (AE) or serious adverse event (SAE) occurs, the patient does not wish to continue treatment or has an unexpected and unacceptable adverse drug reaction;
- Loss to follow up
- Investigator's decision that stopping treatment was in the best interest of the patient

5. Study Treatments

5.1 Handling and Storage

Study drugs must be stored in a secure area under the appropriate physical conditions. Access to and administration of the study drugs will be limited to the investigators and authorized site staff. The investigators must complete storage, handling, dispensing, and infusion information for the study drugs in time. The trial agents were not allowed to be used in other treatments.

The management, distribution and withdrawal of drugs in this study shall be the responsibility of the investigator designated person, and the investigator must ensure that all drugs in the study are only used for participants in the clinical study, and their dosage and administration are in accordance with the trial protocol. Surplus or expired drugs should be returned to the pharmaceutical company for destruction, and clinical drugs should not be transferred to any non-clinical study participants.

A drug receipt must be signed at the time of drug receipt, signed by two persons and kept by the research center. When the remaining drugs are recovered, both parties sign a drug recovery form. Each drug release and recall should be recorded in a timely manner on a special record sheet.

5.2 Treatment

The study drugs that are used in this trial are outlined below in **Table 3**.

Table 3. Study drugs.

Product name	Serplulimab	Nap-paclitaxel	S-1	Oxaliplatin
Dosage form	Lyophilized powder	Lyophilized powder	Capsule	Lyophilized powder
Unit dose strength	4.5 mg	100 mg	20 mg	50 mg
Route of administration	IV infusion	IV infusion	Oral	IV infusion
Storage requirements	2-8℃. Protect from light and freezing.	<25℃. Protect from light.	20-30℃. Protect from light.	<25℃. Protect from light.

Treatment will be assigned to eligible patients after signed consent forms:

- Serplulimab is to be administered initially at 4.5 mg as a 60-minute IV infusion every 3 weeks for 2 preoperative cycles followed by 6 postoperative cycles.
- Nap-paclitaxel is to be administered initially at 260 mg/m^2 as a 30-minute IV infusion every 3 weeks for 2 preoperative cycles followed by 6 postoperative cycles.
- Oxaliplatin is to be administered initially at 130 mg/m^2 as a 120-minute IV infusion every 3 weeks for 2 preoperative cycles followed by 6 postoperative cycles.
- S-1 is to be administered initially at 40-60 mg orally twice daily on days 1 to 14 every 3 weeks for 2 preoperative cycles followed by 6 postoperative cycles.

Table 4. Dose of S-1 depending on BSA.

BSA	**Dose**
< 1.25m^2	40mg× 2/day
1.25m^2 - 1.5m^2	50mg× 2/day
> 1.5m^2	60mg× 2/day

5.3 Dose Modification

Dose modification will be performed based on the severity of toxicities according to the NCI-CTCAE, version 5.0. Reasons for dose interruption, delay, or reduction, the supportive measures, and the outcomes will be documented. Dose interruptions are permitted for reasons apart from toxicities, such as medical/surgical events or logistical reasons (e.g., unrelated medical events or elective surgery).

For participants treated with S-P-SOX, if a toxicity is considered to be due solely to one investigational agent (i.e., Serplulimab or chemotherapeutic agents), the dose of that agent should be interrupted or delayed in accordance with the guidelines below and the treatment with other agents can continue as scheduled at the discretion of the investigator. When the attribution of toxicity is uncertain, interruption of

chemotherapeutic agents is done first. If one agent is discontinued due to unacceptable toxicity, patients are able to continue the study with the other agent.

5.3.1 Dose Modification for Serplulimab

Toxicities associated or possibly associated with Serplulimab may represent an immunologic etiology. For suspected immune-related AEs (irAEs), ensure adequate evaluation to confirm etiology or exclude other causes.

In general, administration of Serplulimab may be continued in the presence of most grade 1 irAEs. For grade 2-4 irAEs, Serplulimab is usually discontinued and can be resumed once irAEs resolve to ≤grade 1. Serplulimab should be permanently discontinued if the irAE cannot resolve within 12 weeks of the last dose or corticosteroids cannot be reduced to ≤10 mg/day prednisone or equivalent within 12 weeks. Permanent discontinuation of Serplulimab should be considered for any severe or life-threatening events.

The use of corticosteroids is the mainstay of management of irAEs. For severe and life-threatening irAEs, corticosteroids should be initiated intravenously first followed by oral administration. With improvement to ≤grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids within 3-5 days.

Dose reduction is not permitted for Serplulimab. Dose modification is shown in table 5.

Table 5. Dose modification guidelines for Serplulimab.

Toxicity	Grade	Timing for Resumption	Toxicity Treatment
Pneumonitis	Grade 2	Withhold Serplulimab	Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents.
	Grade 3	Resolution for ≤grade 2 toxicity	Administer corticosteroids at a dose of 2-4 mg/kg/day prednisone equivalents followed by corticosteroid taper.
	Grade 4 or reoccurrence	Permanently discontinue	
Diarrhea and colitis	Grade 2	Resolution for ≤grade 1 toxicity	Administer corticosteroids at a dose of 0.5-1 mg/kg/day prednisone equivalents followed by corticosteroid taper for colitis of more than 5 days duration.

			if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1-2 mg/kg/day prednisone equivalents.
	Grade 3	Resolution for ≤grade 1 toxicity	Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents followed by corticosteroid taper for grade 3-4 colitis.
	Grade 4 or reoccurrence	Permanently discontinue	
Hepatitis	Grade 2	Resolution for ≤grade 1 toxicity	Administer corticosteroids at a dose of 0.5-1 mg/kg/day prednisone equivalents for grade 2 transaminase elevations.
	Grade 3	Resolution for ≤grade 1 toxicity	Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents followed by corticosteroid taper for grade 3-4 transaminase elevations, with or without concomitant elevation in total bilirubin.
	Grade 4 or reoccurrence	Permanently discontinue	
Nephritis and Renal Dysfunction	Grade 2-3	Resolution for ≤grade 1 toxicity	Administer corticosteroids at a dose of 0.5-1 mg/kg/day prednisone equivalents for grade 2-3 increased serum creatinine.
			if worsening or no improvement occurs, increase dose of corticosteroids to 1-2 mg/kg/day prednisone equivalents.
	Grade 4	Permanently discontinue	Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents followed by corticosteroid taper.
Endocrinopathies	Grade 2-3	Resolution for ≤grade 1 toxicity	Administer hormone-replacement therapy for hypothyroidism
			Initiate medical management for control of hyperthyroidism.
			Other endocrinopathies include hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, etc. Monitor patients for signs and symptoms and provide specialist treatment.
	Grade 4	Permanently discontinue	specialist treatment
Skin Adverse Reactions	Grade 3	Resolution for ≤grade 2 toxicity	Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone

	Grade 4	Permanently discontinue	equivalents followed by a corticosteroid taper.
Other Immune-mediated Adverse Reactions	Grade 3 or 4 serum amylase or lipase elevation Grade 2 or 3 pancreatitis Grade 2 myocarditis Other adverse reactions that occur for the first time in grade 2 or 3	Resolution for ≤grade 1 toxicity	Based on the severity of the adverse reaction, administer high-dose corticosteroids, upon improvement to ≤grade 1, initiate corticosteroid taper and continue to taper over at least 1 month.
	Grade 4 pancreatitis or any grade of reoccurrence pancreatitis Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Other adverse reactions that occur for the first time at grade 4	Permanently discontinue	specialist treatment
Infusion Reactions	Grade 1-2	Symptom relief	Interrupt or slow the rate of infusion in patients
	Grade 3-4	Resolution for ≤grade 2 toxicity	Suspension or delay of administration

5.3.1 Dose Modification for chemotherapeutic agents

For intolerable grade 2 AEs, chemotherapeutic agents (nap-paclitaxel, oxaliplatin, and S-1) should be interrupted until resolution to ≤grade 1. For grade 3-4 AEs, chemotherapeutic agents should be interrupted until resolution to ≤grade 1 or 2, then resume treatment with one dose or two dose reductions, or permanently discontinue treatment which is based on investigator judgement. A maximum of two dose reductions are permitted for chemotherapeutic agents. Permanently discontinue chemotherapeutic agents in the presence of grade 3 or 4 AEs after two dose reductions. However, exception will be permitted in the best interest of the patients. Dose escalation is not permitted. Dose modification of chemotherapeutic agents guidelines are provided in **Table 5**. The dose modifications must be performed as clinically indicated at the discretion of the investigator.

Table 5. Dose modification guidelines for chemotherapeutic agents.

Toxicity	Grade	Timing for Resumption	Toxicity Treatment
Hematological toxicity	Grade 3-4	Resolution for ≤grade 1 toxicity	1st occurrence: 75% of Nap-paclitaxel starting dose 75% of Oxaliplatin starting dose 75% of S-1 starting dose
			2nd occurrence: 50% of Nap-paclitaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose
Mucositis/stomatitis, diarrhea, and anorexia	Grade 2	Resolution for ≤grade 1 toxicity	1st occurrence: maintain the same dose
			2nd occurrence: 75% of Oxaliplatin starting dose 75% of S-1 starting dose
			3rd occurrence: 50% of Oxaliplatin starting dose 50% of S-1 starting dose
	Grade 3	Resolution for ≤grade 1 toxicity	1st occurrence: 75% of Oxaliplatin starting dose 75% of S-1 starting dose
			2nd occurrence: 50% of Oxaliplatin starting dose 50% of S-1 starting dose
	Grade 4	Resolution for ≤grade 1 toxicity	1st occurrence: 50% of Oxaliplatin starting dose and 50% of S-1 starting dose or permanently discontinue
Peripheral neuropathy	Grade 2 (cannot resolve to ≤grade 1 despite supportive care	Resolution for ≤grade 1 toxicity	1st occurrence: 75% of Nap-paclitaxel starting dose
			2nd occurrence: 50% of Nap-paclitaxel starting dose
	Grade 3-4	Resolution for ≤grade 1 toxicity	1st occurrence: 75% of Nap-paclitaxel starting dose
			2nd occurrence: 50% of Nap-paclitaxel starting dose
Other non-hematological toxicity	Grade 2	Resolution for ≤grade 1 toxicity	1st occurrence: maintain the same dose
			2nd occurrence: 75% of Nap-paclitaxel starting dose 75% of Oxaliplatin starting dose 75% of S-1 starting dose

			3rd occurrence: 50% of Nap-paclitaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose
	Grade 3	Resolution for ≤grade 1 toxicity	1st occurrence: 75% of Nap-paclitaxel starting dose 75% of Oxaliplatin starting dose 75% of S-1 starting dose
			2nd occurrence: 50% of Nap-paclitaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose
	Grade 4	Resolution for ≤ grade 1 toxicity	1st occurrence: 50% of Nap-paclitaxel, Oxaliplatin, and S-1 starting dose or permanently discontinue

5.4 Concomitant Therapy

Concomitant therapy refers to any type of treatment continued from 14 days before randomization, during the study administration period, and until 30 days after the last dose, or all treatment initiated since the first dose of study drugs. Such treatment should be carefully and accurately documented in the Case Report Forms (CRFs).

6. Study Procedure

6.1 Screening Period

The following items are completed within 2 weeks before randomization:

- Demographics data: age, gender, date of birth, height, weight, etc.
- Tumor data: date of diagnosis, histological classification, clinical stage, etc.
- Medical history: comorbidities, previous medication/surgery, etc.
- Imaging examination: chest, abdomen and pelvis CT or MRI.

After admission, patients who meet the eligibility criteria are screened out. For these patients, the investigator introduces this trial in detail, and the patients sign informed consent if they agree to participate.

The following items are completed within 1 week before randomization:

- ECOG performance status.
- Vital signs: heart rate, breathing rate, temperature, and blood pressure.
- Physical examination: head, skin, lymph nodes, eyes, ears, nose, throat, mouth,

respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, and nervous system.

- Blood routine: hemoglobin, hematocrit, RBC, WBC, ANC, and platelet count.
- Urinary routine: urinary protein and urine occult blood, and a 24-hour urinary protein quantification test should be performed in the presence of urine protein ≥2+.
- Stool routine: fecal occult blood.
- Biochemistry: bilirubin, ALT, AST, ALP, creatinine, BUN, glucose, calcemia, sodium, and potassium.
- Coagulation test: PT, APTT, TT, and fibrinogen.
- Thyroid function test: TSH, fT3, and fT4.
- Pituitary-adrenal axis examination: adrenocorticotropin, cortisol.
- Myocardial zymogram
- Tumor markers: CEA, CA 19-9, CA125, CA153, etc.
- HBV, HCV, and HIV tests.
- Pretreatment tumor samples.
- 12-lead ECG.
- Echocardiography.

6.2 Treatment Period

6.2.1 Neoadjuvant Treatment Period

Administration of the neoadjuvant treatment is initiated within 7 days after randomization. The following items are completed during the neoadjuvant treatment:

- Physical examination, vital signs, ECOG performance status, tumor markers, Urinary routine, Fecal routine, Coagulation test, and ECG are performed on day 1 of cycles 2 and 3. If cardiac pains or palpitations occur, myocardial enzyme spectrum (creatine kinase, lactate dehydrogenase), and cardiac ultrasound should be immediately performed.
- Blood routine and biochemistry are performed on day 14 of cycle 1 and days 1, 14 of cycles 2 and 3.
- Imaging examination is performed after completion of cycle 3 and before 1 week of surgery.
- AEs during the treatment period should be recorded and graded according to the CTCAE, version 5.0.
- ECOG status and blood pressure monitoring are performed by the patient and recorded in a diary card.

6.2.2 Preoperative Assessments and Surgery

After completion of the last cycle of neoadjuvant treatment, 1 week before surgery, blood routine, biochemistry, stool routine, urine routine, 12-lead ECG, echocardiography, coagulation test, thyroid function test, myocardial zymogram, tumor markers, and imaging examination are performed. Without clear surgical contraindications and with the patients' consent, surgery will be performed. If the disease progresses, laparoscopic exploration is recommended. The following items are completed after surgery:

- Blood routine, biochemistry, tumor markers.
- Surgical outcomes: operation time, intraoperative bleeding, surgical approach, intraoperative complications (e.g. major bleeding), postoperative complications and management, postoperative hospital stay, etc.
- Tumor data: tumor regression grade, residual tumor (R) classification, etc.
- Surgical specimens.

6.2.3 Adjuvant Treatment Period

Adjuvant treatment started 3-8 weeks after surgery. The following items are completed during the adjuvant treatment:

- Physical examination, vital signs, ECOG status, urinary routine, fecal routine, coagulation test, tumor markers, and ECG are performed on day 1 of cycles 4-6. If cardiac pains or palpitations occur, myocardial enzyme spectrum (creatine kinase, lactate dehydrogenase), and cardiac ultrasound should be immediately performed.
- Blood routine and biochemistry are performed on days 1, 14 of cycles 4-6.
- Imaging examination is performed every 3 months.
- AEs during the treatment period should be recorded and graded according to the NCI-CTCAE, version 5.0.
- Blood pressure monitoring is performed by the patient and recorded in a diary card.

6.3 Follow-up Period

After completion of the last administration of study drugs, patients enter follow-up period. All patients are followed up with every 3 months (± 2 weeks) during the first 2 years and then every 6 months (± 2 weeks) beyond the third year. Data on survival

status and disease progression are recorded in the follow-up tables.

Assessments during the follow-up period include physical examination, blood routine, biochemistry, tumor markers, abdominal ultrasound, and chest, abdomen and pelvis CT. Gastroscopy is recommended to performed once a year.

6.4 Progression of Disease

If any of the following criteria is met, it is defined as the progressive disease:

- Determination as PD according to the RECIST, version 1.1 during the neoadjuvant treatment
- Reporting of a distant metastasis from pathology
- R1 or R2 resection
- Finding of a recurrence/distant metastasis during follow-up after R0 resection

For a subject determined to have disease progression, administration of the study drugs will be discontinued and other anti-tumor treatment will be administered at the discretion of the investigator.

7. Efficacy Assessments

- **Pathological Response**

TRG is evaluated centrally using the Mandard regression criteria, which are based on the percentage of vital tumor cells in the tumorous area and include the following categories: TRG 1 (no residual tumor cells, including lymph nodes, staging ypT0N0-M0), TRG 2 (Only single or small focal residual tumor cells), TRG 3 (residual tumor less than fibrotic interstitium tissue), TRG 4 (residual tumor more than fibrotic interstitium tissue), and TRG 5 (tumor did not change or even progress). The pCR rate is defined as the proportion of patients with TRG1 in resection specimens. More details are provided in **Appendix 1**.

- **Radiologic Response**

Radiologic response is evaluated using RECIST (version 1.1), which is based on CT or MRI findings and includes complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients with CR and PR, and the disease control rate (DCR) was defined as the proportion of patients with CR, PR, and SD. More details are provided in **Appendix 4**.

In a comparison between the pretreatment and posttreatment clinical staging, T

downstaging, N downstaging are compared between the two groups based on the CT findings.

- **Surgical Margin**

Tumor condition is explained according to the residual tumor (R) classification:

- R0: No residual cancer (negative cross-section)
- R1: Microscopically observed residual cancer (positive cross-section)
- R2: Macroscopically observed residual cancer

R0 resection rate is defined as the proportion of patients who achieve the R0 resection.

- **Survival**

OS is defined as the time between randomization and the death date. Patients alive at last report will be considered censored at the endpoint. Alive patients will be censored at the last date known to be alive, either during study treatment period or during follow-up period.

PFS is defined as the time between disease progression (see **Section 6.4**) or death irrespective of cause and censored at the date of last contact.

8. Safety Assessments

8.1 Safety Endpoints

Data on all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

The investigator will collect information on the following variables and record in the CRFs:

- **Surgical safety:** operation time, blood loss, intraoperative complications, postoperative morbidity, mortality, postoperative hospital stay, time to ambulation, time to first flatus, and time to first liquid intake etc.

Postoperative morbidity is evaluated according to the Clavien-Dindo classification (**Appendix 6**)

- **Study drug safety:** AEs and serious AEs (SAEs)

All AEs should be recorded by it duration, regulatory seriousness criteria, suspected relationship to the study drug, and actions taken. AEs are evaluated according to the CTCAE, version 5.0.

- **Details on drug modification caused by AEs**

See 5.3 for details.

8.2 Definition of Adverse Event and Serious Adverse Event

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drugs, whether or not considered related to the study drugs. The causal relationship to study drug is determined by a physician and should be used to assess all AEs.

The **casual relationship** can be one of the following:

- Definitely: An AE which has a timely relationship to the administration of the study drugs, follows a known pattern of response, for which no alternative cause is present.

- Probably: An AE, which has a timely relationship to the administration of the study drugs, follows a known pattern of response, but for which a potential alternative cause may be present.

- Unlikely: An AE which does not have a timely relationship to the administration of the study drugs, follows no known pattern of response, does not reappear or worsen after re-administration of the study drugs (if applicable), and for which there is evidence that it is related to a cause other than the study drugs.

- Unrelated: An AE, for which there is evidence that it is definitely related to a cause other than the study drugs. In general, there is no timely relationship to the administration of the study drugs, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

A **SAE** is an AE not classified as serious that, at any time, fulfills one or more of the following criteria:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Any important medical event that may not be immediately life threatening or

result in death or hospitalization but, based upon appropriate medical judgment, may endanger the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

- Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

Events initially reported as an AE may also become serious.

8.3 Recording and Follow-up of (Serious) Adverse Events

AEs and SAEs will be recorded from time of signature of informed consent, throughout the treatment period and including 30 days after the last dose of study drugs (SAEs will be collected for 90 days after discontinuation of treatment). During the course of the study all AEs and SAEs should be followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion.

The investigator is requested to assess the relationship between the study drugs and the occurrence of each (S)AE. The investigator will use clinical judgment to determine the relationship. Alternatives causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

All SAEs occurring to any patient on this study, regardless of attribution, should be reported to the Institutional Review Board and regulatory authority within 24 hours of the investigator’s knowledge of the events. The report of SAE should be consistent with standard SAE reporting guidelines.

9. Statistical Analysis Plan

9.1 Sample Size Considerations

Based on results and data from previous similar studies, the pCR rate of nap-paclitaxel combined with SOX is known to be 7%, and the pCR rate of the Serplulimab combined with nap-paclitaxel and SOX is expected to be 25%. A sample size of 58 patients per group was required to detect improvement with 80% power and a one-sided alpha level of 0.05, including a 15% dropout rate.

9.2 Analysis Sets

FAS included all patients who are randomly assigned according to the ITT principle. This population will be used for the efficacy analyses. Baseline data were analyzed by FAS.

PPS included patients in the ITT population who did not present major deviations from the protocol. We pre-specified that participants who received surgery after administration of neoadjuvant S-P-SOX or P-SOX are included in this set. This population will be also used for the efficacy analyses.

SAS included patients who received at least one dose of allocated treatment. This population will be also used for the safety analyses

9.3 Statistical Analysis

Baseline characteristics and demographic variables will be summarized in the mITT set. Surgical and pathology results will be summarized in the per-protocol set. Nonsurgical AEs will be summarized in the safety analysis set. Continuous variables are presented as medians and interquartile ranges (IQRs) or means and standard deviations (SDs) and are compared using the Wilcoxon rank sum test or t test. Categorical variables are presented as frequencies and percentages and are compared using the $\chi 2$ test or Fisher's exact test.

The efficacy analysis will be performed using both the mITT and per-protocol sets. The efficacy endpoints, including the pCR rate, R0 resection rate, ORR, DCR, and survival, are compared using the Fisher's exact test. The pCR rate, R0 resection rate, ORR, and DCR will be summarized (i.e., number of patients [%]) and 95% confidence intervals (CIs) for the objective response rate will be provided. Medians and 95% CIs for OS and PFS will be calculated. Kaplan-Meier plots of OS and PFS will be presented. Hazard ratio assessment and the corresponding 95% CIs can be presented using the Cox proportional hazard model.

The relationship between biomarkers (including but not limited in PD-L1 expression and MSI status) and the pCR rate will be presented for a subset of patients in the efficacy evaluable population who are available for these biomarkers.

The safety analysis will be done on the safety analysis set. All AEs will be presented as frequencies and percentages in each category. If a patient experiences the same AE multiple times during the treatments, the event will be counted only once and

by the greatest severity.

10. Data Management

10.1CRF Completion Guidelines

For each participant, CRF should be completed by the investigator. The investigator is responsible for ensuring that data recorded in the CRFs are complete, accurate, and legible. The CRF will be served as the original records, and should not be changed. Any correction must not be made on the original records, but an additional narrative can be used for recording the change, the investigator should sign and date for any change made. All data in the CRFs must come from and be consistent with the source documents, i.e. patient's file or medical records.

The CRFs should be completed before reviewing by the Monitor. For any questionable data in the case report form, the Monitor will issue the Data Request (DRQ) to query the investigator, the investigator should answer it as soon as possible and return.

10.2Data Lock

After validating the data correction under blinding review, the principle investigator and statistical analysis personnel will lock the data. The locked database is no longer to be changed.

10.3Quality Control and Quality Assurance

Investigational personnel must be physicians through training of clinical study and who will work under the guidance of the principal investigator.

Prior to the study initiation, the pre-study qualification is needed to ensure the facility is equipped with all rescue equipment and meets the standard requirements.

Recommendations to study nurses who will administer study medications to subjects, have a good understanding of the drug administration, and ensuring the compliance of study subjects.

Each study center must strictly conduct in accordance with the study protocol, and complete CRFs faithfully.

The Monitor will monitor the clinical study according to the Good Clinical Practice and the Standard Operating Procedure, ensure the data recording and reporting is correct and intact, all CRFs will be completed correctly and be verified with the

original documents, and ensure the study can be conducted according to the study protocol.

11. Ethics and Regulatory Considerations

11.1Local Regulations / Helsinki Declaration

The study was performed in accordance with the Helsinki Declaration of 1964 and later versions, Guidelines for Good Clinical Practice, and Chinese law.

11.2Informed Consent

The investigator must explain to subjects that their participation is voluntary and that they may withdraw at any study stage at any time, and will not affect their medical treatment and interest; they also can continue to receive other kind of treatments after withdrawal. Subjects must be informed that their participation and their personal information in the study are confidential. Subjects must be informed of the study nature, the study objectives, anticipated benefits, potential hazards or inconveniences, other available treatments, and subject rights and obligations that meet the Declaration of Helsinki, etc. Subjects should be given sufficient time to consider whether or not they will participate the trial. The signature of the participant is needed on the informed consent form. If new safety information changes the risk/benefit assessments, the informed consent may be modified as necessary. If any modification is made, all subjects (including those who have received treatment) will be notified of the new information and given a revised consent form to continue their participation in the study.

11.3Independent Ethics Committee/Institutional Review Board

Before the study begins, all participating centers should submit the study protocol and relevant documents (CRFs, consent forms, and other documents that may be required) to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The study can only start after obtaining approval from the IEC/IRB. Any amendments to the study protocol must be submitted to the IEC/IRB in accordance with local laws and regulations.

11.4Confidentiality Agreement

Data obtained by this study is confidential, and disclosure to third parties other

than the regulatory authority, the principle investigator, and study personnel is prohibited.

11.5Record Storage

The investigator should arrange for the storage of the research files until the end of the study. All records and documents pertaining to the conduct of this study and the distribution of the study drugs, including CRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the principal investigator for at least 5 years.

11.6Study Interruption

The principal investigator can decide to discontinue this study at any time and for any reason; the decision to discontinue the study will be communicated in writing to the participating researchers. Likewise, if other participating researchers decide to withdraw from the study, they must notify the company in writing.

11.7Protocol Modification

Any modification to the protocol will be recorded in a written revision and signed by the principal investigator. A signed, revised version will be attached to the last version of the protocol.

11.8Protection of participants' Rights and Interests

Ethics committee and informed consent are the main organizations and measures to protect the rights and interests of subjects. Before the clinical study starts, the research plan must be reviewed and approved by the Ethics Committee of Cancer Hospital of Chinese Academy of Medical Sciences and signed before it can be implemented. During the clinical study, any changes to the study protocol should be approved by the Ethics Committee before implementation.

Clinical investigators must explain to subjects that participation in clinical research is voluntary, and at any stage of the study have the right to withdraw from the study at any time without discrimination and retaliation, their medical treatment and rights will not be affected, and they can continue to receive other treatment methods and treatment means. Subjects must be made aware that personal data relating to and participating in the study are confidential. Subjects should also be informed of the nature of the clinical

study, the purpose of the study, the expected possible benefits and possible risks and inconveniences, the alternative treatment options available to them, and the rights and obligations of the subjects in accordance with the Declaration of Helsinki, so that the subjects have sufficient time to consider whether they are willing to participate in the study and sign the informed consent.

References

[1] Cutsem E V, Sagaert X, Topal B, et al. Gastric cancer[J]. Lancet, 2016, 388(10060):2654–2664.

[2] Chen W , Zheng R , Baade P D , et al. Cancer statistics in China, 2015[J]. CA: A Cancer Journal for Clinicians, 2016, 66(2):115-132.

[3] Karimi P, Islami F, Anandasabapathy S, et al., Gastric Cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomark Prev 2014;23:700-13.

[4] Murakami TT, Scranton RA, Brown HE, et al.Management of helicobacter pylori in the united states: results from a national survey of gastroenterology physicians. Prev Med 2017;100: 216-22.

[5] Uemura N, Okamoto S, Yamamoto S, et al.Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784-9.

[6] Plummer M,Franceschi S,Vignat J,et al.Global burden of gastric cancer attributable to Helicobacter pylori.Int J Cancer 2015;136:487-90.

[7] Brar S, Law C, Mcleod R, et al. Defining surgical quality in gastric cancer: a RAND/UCLA appropriateness study.[J]. J Am Coll Surg, 2013, 217(2):347-357.e1.

[8] Karimi P, Islami F, Anandasabapathy S, et al. Gastric Cancer: Descriptive Epidemiology, Risk Factors, Screening, and Prevention[J]. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2014, 23(5):700-13.

[9] Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet*. 2020;396(10251):635-648.

[10]Li Z, Shan F, Wang Y, et al. Correlation of pathological complete response with survival after neoadjuvant chemotherapy in gastric or gastroesophageal junction cancer treated with radical surgery: A meta-analysis[J]. Plos One, 2018, 13(1):e0189294.

[11]LBA42-Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus

postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE trial) (ID 3635).

[12]Ychou M , Boige V , Pignon J P , et al. Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial[J]. Journal of Clinical Oncology, 2011, 29(13):1715-1721.

[13]Sumpter K, Harperwynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF.[J]. British Journal of Cancer, 2005, 92(11):1976-1983.

[14]Li Z Y, Koh C E, Bu Z D, et al. Neoadjuvant chemotherapy with FOLFOX: improved outcomes in Chinese patients with locally advanced gastric cancer[J]. Journal of Surgical Oncology, 2012, 105(8):793-799.

[15]Kochi M , Fujii M , Kanamori N , et al. Phase II Study of Neoadjuvant Chemotherapy With S-1 and CDDP in Patients With Lymph Node Metastatic Stage II or III Gastric Cancer[J]. American journal of clinical oncology, 2014, 40(1):17-21.

[16]Li T, Chen L. [Efficacy and safety of SOX regimen as neoadjuvant chemotherapy for advanced gastric cancer][J]. Zhonghua wei chang wai ke za zhi = Chinese journal of gastrointestinal surgery, 2011, 14(2):104-106.

[17]Salah-Eddin, Al-Batran, et al. Perioperative chemotherapy with docetaxel , oxaliplatin , and fluorouracil/leucovorin (FLOT) versus epirubicin , cisplatin , and fluorouracil or capecitahine (ECF/ECX) for resectable gastric and EGJ cancer , ASCO ZO17 . Abstract 4004.

[18]Dzik S. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin

[19]Lote H, Cafferkey C, Chau I. PD-1 and PD-L1 blockade in gastrointestinal malignancies.[J]. Cancer Treatment Reviews, 2015, 41(10):893-903.

[20]Sun S, Fei X, Mao Y, et al. PD-1(+) immune cell infiltration inversely correlates with survival of operable breast cancer patients.[J]. Cancer Immunol Immunother, 2014, 63(4):395-406.

[21]Hawkes E A, Grigg A, Chong G. Programmed cell death-1 inhibition in

lymphoma[J]. Lancet Oncology, 2015, 16(5):e234-e245.

[22]N. Boku, M.-H. Ryu, K. Kato, et al.,Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4).Annals of Oncology 2019;30: 250-258.

[23]Yung-Jue Bang,Yoon-Koo Kang,Daniel V. Catenacci,et al.,Pembrolizumab alone or in combination with chemotherapy as firstline therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study.Gastric Cancer. 2019 Mar 25.

[24]Josep Tabernero, et al.2019 ASCO. Oral Abstract Session:LBA4007.

[25]Chen D S, Mellman I. Elements of cancer immunity and the cancer-immune set point.[J]. Nature, 2017, 541(7637):321-330.

[26]Zheng C, Zheng L, Yoo J K, et al. Landscape of Infiltrating T Cells in Liver Cancer Revealed by Single-Cell Sequencing[J]. Cell, 2017, 169(7):1342-1356.

[27]Azizi E, Carr A J, Plitas G, et al. Single-Cell Map of Diverse Immune Phenotypes in the Breast Tumor Microenvironment[J]. Cell, 2018, 174(5):págs. 1293-1308.

[28]Zhang L , Yu X , Zheng L , et al. Lineage tracking reveals dynamic relationships of T cells in colorectal cancer[J]. Nature, 2018.

Appendix 1 Mandard Regression Criteria

Mandard Regression Criteria

Grade	Characteristic
TRG 1	Complete tumor regression without residual tumor
TRG 2	Only single or small focal residual tumor cells
TRG 3	Residual tumor less than fibrotic interstitium tissue
TRG 4	Residual tumor more than fibrotic interstitium tissue
TRG 5	tumor did not change or even progress

Note: The Mandard regression criteria are based on the comparison of residual tumor cells and the degree of fibrosis in the cancer foci after neoadjuvant chemotherapy as a grading index, which can describe the morphological changes of tumor treatment response semi-quantitatively, and can objectively evaluate the degree of tumor regression after treatment. TRG has a good performance in evaluating the efficacy of neoadjuvant chemotherapy for gastric cancer.

Appendix 2 Pathological Staging System

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach (8th ed, 2017)

- **Definition of Primary Tumor (T)**

T_x Primary tumor cannot be assessed

T_0 No evidence of primary tumor

Tis Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia

T_1 Tumor invades lamina propria, muscularia mucosa or sub-mucosa

T_{1a} Tumor invades the lamina propria or muscularis mucosae

T_{1b} Tumor invades the sub-mucosa

T_2 Tumor invades the muscularis propria

T_3 Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures

T_4 Tumor invades the serosa (visceral peritoneum) or adjacent structures

T_{4a} Tumor invades the serosa (visceral peritoneum)

T_{4b} Tumor invades adjacent structures/organs

- **Definition of Regional Lymph Node (N)**

N_x Regional lymph node(s) cannot be assessed

N_0 No regional lymph node metastasis

N_1 Metastasis in one or two regional lymph nodes

N_2 Metastasis in three to six regional lymph nodes

N_3 Metastasis in seven or more regional lymph nodes

N_{3a} Metastasis in seven to 15 regional lymph nodes

N_{3b} Metastasis in 16 or more regional lymph nodes

- **Definition of Distant Metastasis (M)**

M_0 No distant metastasis

M_1 Distant metastasis

Post-Neoadjuvant Therapy (ypTNM)

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
AnyT	AnyN	MI	IV

Appendix 3 Surgical Manual

In this study, the basic purpose of surgery is curative resection. Curative resection

is defined as follows:

- No distant metastasis.
- No infiltration to surrounding organs, or in case of infiltration, curative combined resection should be performed.
- No macroscopic residual cancer.
- D2 or greater resection is necessarily required.
- No infiltration of cancer cells on both margins from histopathology.

Selection of gastrectomy The standard surgical procedure for clinically node-positive (cN+) or T2-T4a tumors is either total or distal gastrectomy. Distal gastrectomy is selected when a satisfactory proximal resection margin (see below) can be obtained. When obtaining proximal resection margin is not possible, total gastrectomy is selected.

Resection margin A sufficient resection margin should be ensured when determining the resection line in gastrectomy with curative intent. Proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (types 1 and 2) and 5 cm for those with an infiltrative growth pattern (types 3 and 4). When these rules cannot be satisfied, it is advisable to examine the whole thickness of proximal resection margin by frozen section. For tumors invading the esophagus, resection margin >5 cm is not necessarily required, but frozen section examination of the resection line is preferable to ensure an R0 resection.

Definition of the D levels

- **Total gastrectomy**

D0: Lymphadenectomy less than D1.

D1: No. 1-7.

D1+: D1 + No. 8a, 9, 11p.

D2: D1 + No. 8a, 9, 11p, 11d, 12a.

For tumors invading the esophagus, resection of No.110 should be added to D1+, and resection of Nos. 19, 20, 110 and 111 to D2.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1

Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

• 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

• 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

- **Evaluation of target lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study。

- **Evaluation of non-target lesions**

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions.

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Appendix 5 ECOG Performance Status

According to the simplified performance status score scale developed by the ECOG, the patients' performance status can be classified into 6 levels, namely 0-5, as follows:

ECOG Performance Status

Grade	Characteristic
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. In total, confined to bed or chair.
5	Dead.

Note: Patients at levels 3, 4 and 5 are generally considered to be unsuitable for surgical

treatment or chemotherapy.

Appendix 6 Classification of Surgical Complications

Clavien-Dindo Classification

Grade	Characteristic
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
	Requiring surgical, endoscopic or radiological intervention
Grade III	**Grade IIIa:** Intervention not under general anesthesia
	Grade IIIb: Intervention under general anesthesia
	Life-threatening complication requiring ICU management
Grade IV	**Grade IVa:** Single organ dysfunction (including dialysis)
	Grade IVb: Multiorgan dysfunction
Grade V	Death of a patient.

Efficacy and Safety of Serplulimab Combined with SOX and Nab-paclitaxel as Neoadjuvant Treatment for Locally Advanced Gastric cancer or Adenocarcinoma of Esophagogastric junction: A Multicenter Randomized Controlled Trial

SUMMARY OF CHANGES.

Protocol Version History

Version Number	Version Date	Scientific and Substantive Revisions
v1.0	July 7, 2024	● Initial protocol
v1.1	Oct 8, 2024	● Add secondary objectives: Patient reported outcomes: EORTC QLQ-C30 and QLQ-STO22