Efficacy and Safety of Low-dose Radiation Combined With Neoadjuvant Chemotherapy and Immunotherapy in Locally Advanced Esophageal Squamous Cell Carcinoma

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Research Background

1. Current Status of Esophageal Cancer Treatment

According to the 2020 GLOBOCAN data, esophageal cancer ranks fifth in incidence among all malignant tumors in China, with as many as 324,000 new cases and 301,000 deaths annually. These figures indicate a significant burden of esophageal cancer in China, representing 55% of global esophageal cancer patients. Unlike Western countries, the majority of esophageal cancer patients in China have squamous cell carcinoma, and 40% of patients are diagnosed at an advanced stage. Surgery is a crucial treatment method for locally advanced esophageal cancer patients, but those who receive neoadjuvant therapy before surgery may achieve better clinical outcomes. However, the prognosis for these patients remains relatively poor. Between 2009 and 2015, the overall 5-year relative survival rate for esophageal cancer was 21.4%. Specifically, the 5-year relative survival rate for localized tumors was 46.7%, for regional metastasis was 25.1%, and for distant metastasis was only 4.8%.

The CROSS study, a randomized controlled trial spanning over a decade, has clearly demonstrated the significant survival advantage of neoadjuvant chemoradiotherapy in the treatment of locally advanced esophageal cancer compared to surgery alone. According to this study, patients had an absolute survival benefit of 13% over 10 years. Furthermore, pathologic subtype stratification analysis conducted in this study indicated that squamous cell carcinoma patients derived greater benefit from neoadjuvant chemotherapy compared to adenocarcinoma patients. Among the squamous cell carcinoma subgroup, patients treated with neoadjuvant concurrent chemoradiotherapy followed by surgery achieved a median overall survival of 82 months, whereas the control group receiving surgery alone had a median overall survival of 21 months.

2. Application of Albumin-Bound Paclitaxel in Esophageal Cancer

In this study, albumin-bound paclitaxel and platinum-based chemotherapy are used as chemotherapy agents, with albumin-bound paclitaxel being used off-label. In terms of safety, albumin-bound paclitaxel mostly induces grade 1-2 adverse reactions during chemotherapy application, within a manageable range. Regarding efficacy, a study compared albumin-bound paclitaxel combined with platinum-based chemotherapy (nabTP) versus paclitaxel combined with platinum-based chemotherapy (TP) along with PD-1 inhibitors (ICI) as neoadjuvant therapy for locally advanced resectable esophageal squamous cell carcinoma (ESCC). The results showed that the pCR rate of the ICI-nabTP group compared to the ICI-TP group was 36.7% versus 21.4%, respectively. The ICI-nabTP group improved postoperative pathological outcomes, providing a more viable treatment option for ESCC patients undergoing neoadjuvant therapy. In a study reported in the ASCO journal in 2022, comparing the efficacy and safety of albumin-bound paclitaxel combined with cisplatin followed by surgery versus direct surgery in ESCC patients, the treatment group showed a major pathological response (MPR) of 33.33%, a pathological complete response rate (pCR) of 20.83%, and a downstaging rate of 58.33%. There were statistically significant differences in survival rates between the two groups, with the treatment group showing higher 1-year disease-free survival (DFS) rate (88.90% vs. 75.58%) and 2-year DFS rate (88.99% vs. 66.13%), as well as higher 1-year overall survival (OS) rate (93.21% vs. 75.32%) and 2-year OS rate (86.56% vs. 75.32%). Moreover, the most common adverse events were hematologic toxicities, including neutropenia (16.13%), with no Grade IV adverse events reported. These results indicate that albumin-bound paclitaxel combined with cisplatin treatment for ESCC has

good efficacy and safety, prolonging both DFS and OS compared to surgery alone.

3. Exploration of Immunotherapy (Tislelizumab) in Esophageal Cancer

In recent years, immunotherapy has demonstrated significant survival benefits in patients with advanced esophageal cancer. Immunotherapy combined with chemotherapy has now become the standard first-line treatment for advanced esophageal cancer. Currently, there is considerable interest in the research field of introducing immunotherapy as neoadjuvant treatment in locally advanced esophageal cancer. Many studies are underway involving the combined application of neoadjuvant chemotherapy and immunotherapy, as well as the combined strategy of neoadjuvant chemoradiotherapy and immunotherapy.

Han et al. incorporated the anti-PD-L1 monoclonal antibody, Toripalimab, into neoadjuvant CP chemotherapy in 18 cases of esophageal squamous cell carcinoma, achieving a disease control rate (DCR) of 100% after two cycles of neoadjuvant treatment. Among the 16 patients who underwent surgical treatment according to the trial design, the R0 resection rate was 87.5%, the pCR rate was 18.8%, and the MPR rate was 43.8%. Recently, Tan Lijie et al. from Zhongshan Hospital, affiliated with Fudan University, explored for the first time the safety and preliminary efficacy of PD-L1 monoclonal antibody, Atezolizumab, as a neoadjuvant monotherapy for resectable ESCC, and conducted in-depth research on the mechanisms of sensitivity/resistance, providing solid evidence for personalized treatment selection for immunotherapy populations. This project utilizes the immunotherapeutic agent Tislelizumab, involving its off-label use. The domestically produced PD-1 inhibitor Tislelizumab has obtained approvals for ten indications domestically and is widely used in our hospital and other hospitals in China. The 2023 version of the CSCO Esophageal Cancer Diagnosis and Treatment Guidelines has added "Tislelizumab combined with chemotherapy (Class IA evidence) as a Grade I recommendation for first-line treatment of advanced esophageal cancer." In terms of safety, Tislelizumab is similar to similar foreign drugs, mostly inducing grade 1-2 adverse reactions within a manageable range. Our center's preliminary research results have indicated that Tislelizumab can be used as neoadjuvant immunotherapy for esophageal squamous cell carcinoma with good perioperative safety.

It's worth noting that recent research reports have shown a significant heterogeneity in the pathological complete response (PCR) rate ranging from 17% to 22% in small-sample studies of neoadjuvant chemotherapy combined with immunotherapy. Recently, a study by Chinese scholars published in the prestigious academic journal "Nature Medicine" demonstrated that using PD-L1 antibodies for immunotherapy as neoadjuvant treatment combined with surgery resulted in a PCR rate of only 8%. However, its long-term survival outcomes were comparable to traditional chemoradiotherapy. This further underscores the vast potential of neoadjuvant immunotherapy compared to traditional neoadjuvant chemoradiotherapy. Nevertheless, the efficacy of immunotherapy alone or in combination with chemotherapy for local control remains unsatisfactory, which may affect the curative effect of surgery and long-term survival of patients. Therefore, combining immunotherapy with more effective local treatment modalities is undoubtedly a more promising therapeutic option.

4. Exploration of Low-Dose Radiotherapy (LDRT) in Esophageal Cancer

Low-dose radiotherapy (LDRT) is typically defined as radiation therapy with each treatment not exceeding 2 Gy, totaling no more than 10 Gy, and is considered non-ablative therapy. The low toxicity of LDRT makes it a treatment option for lesions unsuitable for site-directed radiation

therapy. Additionally, although LDRT cannot directly kill tumor cells, it can promote tumor regression by readjusting the tumor immune microenvironment.

LDRT damages cell DNA, exposing tumor antigens that were previously hidden or difficult to identify on the cell surface. This change promotes the cross-presentation of tumor-specific antigens, increases lymphocyte infiltration into the tumor site, enhances tumor-specific immune responses, and further improves the efficacy of immune checkpoint inhibitors. Moreover, preoperative immunotherapy can activate the patient's immune system, enabling it to recognize tumor antigens and establish immune memory. This allows the immune system to continue its immune surveillance after surgical tumor resection. Currently, the main focus of clinical research is on maximizing the synergistic effects between different treatment modalities to achieve the best survival outcomes for locally advanced esophageal cancer patients while minimizing treatment side effects.

This study is a phase IIA clinical trial focusing on preliminary efficacy and safety. The study proposes comprehensive treatment combining neoadjuvant low-dose radiotherapy with chemotherapy plus immunotherapy (chemoimmunotherapy). By reducing the radiation dose, this approach aims to improve local control efficacy while minimizing adverse reactions from combination therapy. Therefore, the study plans to conduct neoadjuvant low-dose radiotherapy combined with chemoimmunotherapy in patients with locally advanced esophageal squamous cell carcinoma, adjusting the radiation dose from 40 Gy/20 fractions to 4 Gy/2 fractions. The study aims to evaluate the efficacy and safety of this treatment modality and provide more evidence for the neoadjuvant treatment mode for locally advanced esophageal cancer patients. Additionally, exploratory analysis will be conducted based on tissue and blood samples collected from patients before and after surgery to understand the impact of preoperative low-dose radiotherapy combined with immunotherapy on the esophageal cancer immune microenvironment and identify suitable biomarkers to identify the optimal beneficiary population.

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Research Objectives

Primary Objective:
Evaluate the safety and pathological complete response (pCR) rate of participants receiving neoadjuvant low-dose radiotherapy (4 Gy/2f) combined with domestically-produced PD-1 inhibitor (toripalimab) and chemotherapy as neoadjuvant treatment.

Secondary Objectives:
Assess the major pathological response (MPR) of participants receiving neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy as neoadjuvant treatment.
Evaluate the R0 resection rate of participants receiving neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy as neoadjuvant treatment.
Assess the 1-year/2-year event-free survival (EFS) of participants receiving neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy as neoadjuvant treatment.
Investigator-assessed objective response rate (ORR) of preoperative neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy.

Exploratory Objectives:
Evaluate the overall survival (OS) of participants receiving neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy as neoadjuvant treatment.
Assess the potential correlation between biomarkers and clinical effectiveness in participants receiving neoadjuvant low-dose radiotherapy combined with toripalimab and chemotherapy as neoadjuvant treatment.

Research Design, Methods, and Procedures

Study Design:
This study is a single-arm, single-center, prospective, open-label, phase IIA clinical cohort study initiated by the investigators. The aim is to evaluate the impact of neoadjuvant low-dose radiotherapy combined with domestically-produced PD-1 inhibitor (toripalimab) and chemotherapy on the pathological complete response (pCR) rate in esophageal cancer patients. Based on previous studies and anticipated effects, we set the expected pCR rate of this neoadjuvant regimen at 40%, higher than the effect of immunotherapy combined with chemotherapy as neoadjuvant therapy (approximately 20%). To ensure sufficient statistical power (80%) with a significance level set at 20%, we calculated the required sample size using statistical methods. Considering a possible data loss rate of 10%, we determined that approximately 30

participants are needed for this study. This sample size is set to minimize both type I errors (incorrectly assuming treatment effectiveness) and type II errors (incorrectly assuming treatment ineffectiveness), while also considering the feasibility of the study. Through this approach, we hope to accurately assess the potential value of combined low-dose radiotherapy and immunotherapy in improving the pCR rate of esophageal cancer patients and provide reliable evidence to support future clinical practice.

Study Methods:

Study Cohort (30 cases): Patients receiving neoadjuvant low-dose radiotherapy (4 Gy/2f) combined with domestically-produced PD-1 inhibitor (toripalimab) and chemotherapy as neoadjuvant treatment will be enrolled.

The study will evaluate the safety and efficacy of reduced-dose radiotherapy during the neoadjuvant treatment phase.

Neoadjuvant Treatment Phase:

During the neoadjuvant treatment phase, patients will receive two cycles of low-dose radiotherapy combined with chemotherapy and immunotherapy, with each cycle lasting 21 days. The specific treatment regimen is as follows: Day 1/2: Low-dose radiotherapy (4 Gy/2f); Day 3: Toripalimab at a fixed dose of 200mg; Albumin-bound paclitaxel 260mg/m2; Cisplatin 75mg/m2 or carboplatin AUC = 5. The interval between radiotherapy and chemotherapy should not exceed 3 days. Drug infusion will be administered in the order of toripalimab → albumin-bound paclitaxel → cisplatin/carboplatin, with at least 30 minutes between each infusion.

At the end of the neoadjuvant treatment, patients will undergo surgical treatment 6-8 weeks after the last treatment.

Postoperative Treatment:

After surgery, based on the degree of postoperative pathological response, the following adjuvant treatment strategies will be adopted:

Patients who did not achieve complete pathological response: Adjuvant immunotherapy is recommended for 4-8 weeks postoperatively, using a fixed dose of 200mg every 3 weeks, continuing for 12 months postoperatively.

Patients who achieved complete pathological response: Follow-up every three months within two years postoperatively, then every six months thereafter.

Radiotherapy Protocol:

Simulation and Target Definition:

Patients will be positioned using commonly used immobilization devices at each study center, with the patient in supine position. Gross target volume (GTV) and planning gross target volume (PGTV) need to be delineated and determined on each CT slice. CT scanning should be performed with the patient in a quiet, normal breathing state, covering from the cricoid cartilage to the lower edge of L2 vertebral body, with a slice thickness of 3mm. The entire target area should have a scan thickness ≤ 5mm to generate dose-volume histograms for the lung, spinal cord, heart, and esophagus. Patients should start radiotherapy within 1 week after the positioning CT scan.

LDRT Target Volume Definition:

Gross target volume (GTV): Named GTVLDRT, visible tumors shown on CT, PET scan, esophagography, gastroscopy, etc. The clinical radiation oncologist can select appropriate LDRT lesions based on the actual situation.

Planning target volume (PTV): Named PTVLDRT, considering the target movement and daily positioning errors, the PTVLDRT will appropriately expand the GTVLDRT. Generally, the GTVLDRT will expand outward by 0.5 ~ 1cm in all directions. After confirming the GTVLDRT motion range with X-ray fluoroscopy or 4DCT, the expansion range of PTVLDRT can be appropriately reduced. If the patient is positioned with 4DCT, the ITV can be generated by the planning system and then expanded appropriately to generate PTVLDRT. The expansion range and generation method of PTVLDRT are determined by the researcher and need to be documented in writing.

LDRT Dose Prescription:

Radiotherapy begins on the first day, once daily, with a dose of 2Gy per fraction, until the target dose reaches 4Gy/2f (rescheduled in case of weekends or holidays).

LDRT Plan Evaluation:

The doses at the maximum and minimum points within the PTV should be registered. The dose distribution inside and outside the PTV should be evaluated, and dose deviations should be differentiated and adjusted accordingly.

No deviation: ≥ 99% of the PTV receives at least 95% of the prescription dose, and no volume ≥ 1cm3 within the PTV receives > 110% of the prescription dose.

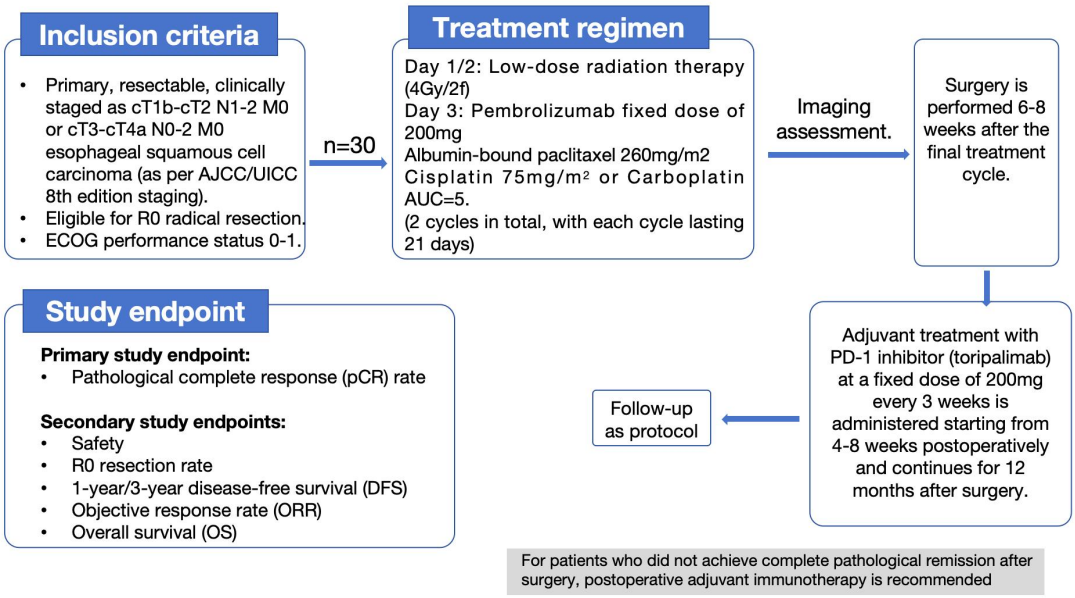
Minor deviation (acceptable but should be avoided as much as possible): ≤ 99% but ≥ 95% of the PTV receives at least 95% of the prescription dose, and there are volumes > 1cm3 within the PTV receiving > 110% but ≤ 115% of the prescription dose.

Severe deviation (not acceptable): < 95% of the PTV receives at least 95% of the prescription dose, and there are volumes > 1cm3 within the PTV receiving > 115% of the prescription dose.

Surgical Phase:

After completing neoadjuvant treatment, the resectability of the lesion will be reassessed, and study participants will undergo surgical treatment within 6-8 weeks after completing the last immunotherapy treatment. Pathological response (MPR and pCR) assessment will be performed on surgical specimens.

Research Steps:



Patient Selection

Inclusion Criteria:

1. Histopathological and Clinical Staging Confirmation: Confirmed histologically as thoracic esophageal squamous cell carcinoma, clinically staged as:
cT1b-cT2 N1-2 M0 or cT3-cT4a N0-2 M0 (according to AJCC/UICC Esophageal Cancer Staging, 8th edition).
2. Suitability for R0 Radical Resection: Able to undergo R0 radical resection.
3. ECOG Performance Score:ECOG performance score 0-1.
4. Age and Gender:Male or female ≥18 years old and ≤75 years old.
5. Vital Organ and Bone Marrow Function: Blood routine parameters: WBC count ≥ 3.5×10^9/L, ANC ≥ 1.5 ×10^9/L, PLT ≥ 100×10^9/L, HGB ≥ 9g/dL.
Pulmonary function assessed by a radiation oncologist: FEV1/FVC≧70%, FEV1≧50% of normal value, DLCO > 80% of predicted value.
Hepatic function: TBIL ≤ 1.5 × ULN, ALT and/or AST ≤ 2.5 × ULN, ALB ≥ 3g/dL.
Renal function: Serum creatinine ≤ 1.5×ULN or creatinine clearance rate ≥ 60ml/min (calculated by Cockcroft/Gault formula).
6. Voluntary Participation and Compliance: Willingness to participate voluntarily, sign informed consent, and comply with protocol-specified visits and procedures.
7. Expected Survival: Expected survival > 6 months.
8. Acceptance of Surgery, Radiotherapy, Chemotherapy, and Immunotherapy: Willingness to undergo surgical treatment, radiotherapy, chemotherapy, and immunotherapy.
Pregnancy Status and Contraception:
9. Women of childbearing potential must have a negative pregnancy test within 7 days before starting treatment and agree to use appropriate contraception methods during the trial and for 8 weeks after the last dose of the investigational drug.
10. Absence of Esophageal Perforation, Active Esophageal Bleeding, Tracheal Invasion, or Invasion of Major Blood Vessels.
11. Measurable Lesions According to RECIST 1.1.

Exclusion Criteria:

1. Ineligibility for Specified Immunotherapy and Chemotherapy.
2. History of Prior Treatment for ESCC.
3. History of Primary Tumor Infiltration Causing Fistula.
4. High Risk or Presence of Fistula Symptoms.
5. Requirement for Systemic Corticosteroid Therapy within 14 Days Before the First Dose of Study Drug.
6. Active Autoimmune Disease or History of Autoimmune Disease with Potential for Recurrence.
7. Interstitial Lung Disease, Non-Infectious Pneumonia, or Poorly Controlled Lung Disease.
8. Need for Systemic Antibacterial, Antifungal, or Antiviral Therapy for Infection.
9. Recent Severe Infection Within 4 Weeks Before the First Dose of Study Drug.
10. Recent Therapeutic Oral or Intravenous Antibiotic Use Within 2 Weeks Before the First Dose of Study Drug.
11. Known Solid Organ Transplantation or Allogeneic Hematopoietic Stem Cell Transplantation.
12. Known Allergy to Investigational Drug or Active Ingredients/Excipients of Chemotherapy.
13. Presence of Significant and Symptomatic Abnormalities on Resting Electrocardiogram.

Criteria for Study Termination

Participants may discontinue study treatment for reasons including but not limited to:

Completion of treatment
Disease progression (assessed by radiographic or clinical progression)
Adverse events
Participant's decision
Pregnancy
Any medical condition identified by the investigator or sponsor that may jeopardize participant safety if study treatment continues
Concurrent use of any anti-tumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, or standard or investigational agents)
Participant non-compliance
Participant withdrawal of informed consent, loss to follow-up, death, or study termination by the sponsor, whichever occurs first.

Procedures After Study Termination

Compensation Terms:
Participants in this study will receive corresponding exemptions and compensation, provided by Suzhou Shengdiya Biomedical Co., Ltd., including two cycles of free infusions of toripalimab and a travel subsidy of 100 yuan per trip, as well as the purchase of clinical trial insurance for 500 yuan per case. Blood collection compensation of 200 yuan per collection will be reimbursed from the project leader's research funds.
Indemnity Terms: Clinical trial insurance will be purchased for each patient in the study for 500 yuan per case, providing security for patient treatment. In the event of a serious adverse event (SAE) related to toripalimab treatment during the clinical trial, which must be judged by the

investigator to be possibly or definitely related to the investigational drug, the subject can apply for compensation from the insurance company for losses incurred due to the treatment of SAEs. The insurance company will make payments according to the terms and conditions of the policy after obtaining responsibility determination from authoritative departments. The maximum compensation limit is one million yuan (¥2,000,000.00) in total and one million yuan (¥2,000,000.00) per incident.

Establishment of Compensation Committee: A dedicated compensation committee will be established to evaluate applications and provide compensation based on factual circumstances, including but not limited to medical expenses and loss of income. The compensation committee will consist of personnel from Suzhou Shengdiya Biomedical Co., Ltd., project research members, and relevant personnel from the insurance company.

5. Alternative Treatment Options

Participants may choose to receive alternative treatments such as neoadjuvant synchronous chemoradiotherapy or neoadjuvant chemotherapy.

6. Criteria for Efficacy Assessment

Efficacy Analysis:

Primary Efficacy Analysis: Safety and Pathological Complete Response (pCR) rate of participants receiving neoadjuvant low-dose radiotherapy (4Gy/2f) combined with domestically produced PD-1 inhibitor (toripalimab) and chemotherapy as neoadjuvant treatment will be evaluated.

Safety Analysis: All adverse events will be assessed for safety using NCI-CTCAE v5.0 grading. Safety analysis will also consider laboratory test results (e.g., hematology, clinical biochemistry, urine analysis), vital signs, ECG, and physical examination. All safety data in the safety analysis will be analyzed using descriptive statistics.

Secondary Efficacy Analysis: Pathological Response Rate (MPR), R0 Resection Rate, 1-year/3-year Disease-Free Survival (DFS), and Objective Response Rate (ORR) will be evaluated.

7. Observation, Recording, and Management of Adverse Events

Adverse events (AEs) will be reported using MedDRA coding in the case report form (CRF). Treatment-emergent adverse events (TEAEs) are defined as AEs that occur from the first dose of the study drug until 30 days after the discontinuation of the study drug or initiation of new anti-tumor therapy, whichever comes first. TEAE classification also applies to immune-related adverse events recorded within 90 days after discontinuation of toripalimab, regardless of whether the patient starts new anti-tumor therapy. AE records will continue until 30 days after the last administration of the study treatment or until the initiation of other anti-tumor therapy, whichever comes first. Immunotherapy-related AE records will continue until 90 days after the last administration of toripalimab, regardless of whether the participant starts new anti-tumor therapy. The investigator should record all drug-related SAEs until the participant's death, withdrawal of informed consent, or loss to follow-up.

Statistical Analysis

Data Management: Data entry and management will be conducted using SPSS 22.0 database with double data entry verification.

Statistical analysis of research data will be performed using SPSS 22.0 software.

Descriptive statistics including mean, standard deviation, median, minimum, maximum,

frequencies, and percentages will be used to describe continuous and categorical variables, respectively. When necessary, 95% confidence intervals will be calculated.

Analysis Sets: Evaluability Analysis Set (EE): Includes all participants who undergo surgery after receiving neoadjuvant treatment. This will be the primary analysis set for efficacy analysis.
Intention-to-Treat Analysis Set (ITT): Includes all enrolled participants in the study.
Safety Analysis Set (SAF): Includes all enrolled participants who have received ≥ 1 treatment. This will be the primary analysis set for safety analysis.
Primary Efficacy Analysis:

pCR Rate: The primary endpoint of the study. It evaluates the Pathological Complete Response (pCR) rate of participants receiving neoadjuvant low-dose radiotherapy (4Gy/2f) combined with domestically produced PD-1 inhibitor (toripalimab) as neoadjuvant treatment. The pCR rate is defined as the proportion of participants with no residual tumor in the primary tumor and all resected lymph nodes after completion of neoadjuvant treatment, and the Clopper-Pearson 95% confidence interval (CI) will be calculated. pCR rate analysis will be conducted in the EE analysis set after completion of pathological response assessment for all participants.
Safety Analysis:

Safety assessment will be conducted by monitoring and recording all adverse events according to NCI-CTCAE v5.0 grading. Laboratory test results, vital signs, ECG, and physical examinations will also be considered. Descriptive statistics will be used for all safety data analysis.
Secondary Efficacy Analysis:

MPR Rate: Defined as the proportion of participants with residual viable tumor ≤ 10% in the primary tumor and all resected lymph nodes after completion of neoadjuvant treatment and surgery. MPR rate in the EE analysis set will be summarized.
R0 Resection Rate: Defined as the proportion of participants with R0 resection. R0 resection rate will be summarized in the EE analysis set.
1-year/3-year Disease-Free Survival (DFS) Rate: DFS rate is defined as the proportion of participants without disease events at the 1st and 3rd year after the first recorded disease-free date. DFS is calculated from the first recorded disease-free date to local or distant recurrence or death for any reason (whichever occurs first). Kaplan-Meier method will be used to estimate DFS rate, and 95% CI will be estimated using Greenwood's formula.
Objective Response Rate (ORR): Defined as the proportion of participants with complete or partial response assessed by RECIST 1.1 criteria among all participants with measurable lesions at baseline in the ITT analysis set.
Exploratory Efficacy Analysis:

Overall Survival (OS): Defined as the total survival period of participants after enrollment. Data of participants who have not reported death at the time of analysis will be censored at the last known survival date.