STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN

Official Tiltle

Iparomlimab and Tuvonralimab Plus Paclitaxel and Platinum as Neoadjuvant Therapy for Locally Advanced Cervical Cancer: A Prospective Single-Arm Phase II Trial （QUARTZ-CC）

Study Protocol Synopsis (Full Protocol Available in Chinese upon Request)

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Outline

Research topic	Iparomlimab and Tuvonralimab Plus Paclitaxel and Platinum as Neoadjuvant Therapy for Locally Advanced Cervical Cancer: A Prospective Single-Arm Phase II Trial （QUARTZ-CC）
Research Objectives	1. To evaluate the efficacy and safety of epalolide tovorilimab combined with TP/TC neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer; 2. To investigate the feasibility of reducing surgical scope after neoadjuvant therapy for locally advanced cervical cancer; 3. Explore the possibility of reducing the probability of postoperative adjuvant radiotherapy; 4. To investigate the optimal population characteristics for benefiting from neoadjuvant immunotherapy combined with chemotherapy.
Research design	Prospective, single-arm, open-label Phase II clinical trial
Study endpoint	**Primary endpoint:** Pathological complete response rate (pCR) **Secondary endpoint:** ● Ideal Pathological Response Rate (MPR) ● Objective response rate (ORR) (complete response [CR] + partial response [PR], assessed according to RECIST 1.1 criteria) ● 3-year overall survival rate ● 3-year disease-free survival rate ● Neoadjuvant therapy-related adverse events (TRAEs and iTRAEs) ● Patient-reported outcomes (PRO) **Exploratory endpoints:** ● Biomarkers, tertiary lymph node architecture, and imaging features predictive of neoadjuvant therapy efficacy ● Changes in ovarian function before and after treatment in younger patients
Selection Criteria	(1) Age: 18 to 70 years; (2) Diagnosed with cervical cancer at stage IB3/IIA2. (3) Imaging studies revealed that the short diameter of the pelvic lymph nodes was less than 1.5 cm, as well as that of the para-aortic lymph nodes was less than 1.5 cm. (4) The pathological types are cervical squamous cell carcinoma, adenocarci-

	noma, or adenosquamous carcinoma; (5) No prior antitumor therapy received; (6) Eastern Cooperative Oncology Group (ECOG) score of 0–1.
Exclusion Criteria	(1) Patients with other malignant tumors; (2) Patients during pregnancy and the perinatal period; (3) Patients with a history of myocardial infarction or stroke, unstable angina, decompensated heart failure, or deep vein thrombosis; (4) Patients with NCI-CTCAE grade 5.0 or higher cardiac arrhythmias, atrial fibrillation of any grade, or clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention; (5) For patients with active hepatitis that has not resolved: those presenting with progressive loss of appetite, generalized weakness, nausea, acid reflux, aversion to fatty foods, abdominal distension, and other clinical manifestati- ons; or those exhibiting abnormal liver function accompanied by jaundice symptoms such as yellowing of the eyes or dark urine; specifically for hepatitis B cases, patients with a hepatitis B DNA level>1000 IU/mL. (6) Patients with hepatic dysfunction (aspartate/alanine aminotransferase>2.5 times the upper limit of normal); (7) Patients with renal insufficiency (serum creatinine>2 times the upper limit of normal); (8) A history of chronic pulmonary disease with restrictive respiratory dysfunction; (9) History of transplantation of vital organs or immune-mediated diseases; (10) History of severe mental disorders or cerebral dysfunction; (11) History of drug abuse or substance use; (12)The patient is undergoing immunosuppressive therapy or systemic corticosteroid treatment for immunosuppression (dose>10 mg prednisone or other equivalent potency corticosteroids) and continues to use these agents within 2 weeks prior to enrollment. (13)Coagulation abnormalities (INR>2.0, PT>16 s), presence of bleeding tendency, or ongoing thrombolytic/anticoagulant therapy; prophylactic use of low-dose aspirin or low molecular weight heparin is permitted. (14)Congenital or acquired immune deficiencies (e.g., in individuals with HIV infection); (l5) Administer the inactivated vaccine within 30 days prior to the first dose. (l6) Individuals who are unable or unwilling to sign an informed consent form or comply with study requirements.

Therapeutic regimen	**Neoadjuvant Treatment Regimen:** Paclitaxel 150–175 mg/m² , administered via intravenous drip (IV) over a duration exceeding 3 hours, with pre-drip antiallergic treatment. Cisplatin 70–75 mg/m² , intravenous drip (IV), infusion duration>1 hour, administered over two days; or carboplatin with AUC=5, IV, infusion duration>1 hour. Ipalotinib (tivolumab) 250 mg, intravenous drip, infusion duration exceeding 30 minutes After two courses of treatment, a clinical physician conducts a physical examination and assessment. If tumor enlargement or stabilization is detected during the evaluation, imaging studies are performed to determine whether radical surgery or radical radiotherapy should be administered; if tumor reduction is observed, treatment continues for another two courses followed by imaging evaluation of efficacy. Patients with complete remission (CR) on imaging are scheduled for cervical conization and sentinel lymph node biopsy (SLNB) or pelvic lymph node dissection (PLND). Those achieving optimal pathological response (OPR) on postoperative pathology undergo another two courses of the aforementioned regimen followed by eight cycles of maintenance therapy with epalolide plus torvolumab (hereinafter referred to as the QL1706 combination antibody), administered every 3 weeks. Patients who do not achieve OPR on postoperative pathology or exhibit partial remission (PR) on imaging undergo abdominal radical hysterectomy/cervical resection combined with SLNB/PLND. Postoperative adjuvant therapy is administered in accordance with the NCCN guidelines.
Sample size and Statistical method	This study employed a two-stage Simon design to estimate the sample size, with an alpha level of 0.05 (one-sided), a beta level of 0.2, and a power of 0.8. The primary endpoint was the rate of complete pathological response. The following assumptions were made: based on previous studies combining chemotherapy with monoclonal antibodies targeting immune checkpoints.The pathological complete response (pCR) rate for treatment was 30% (H0). As a historical reference, it is assumed that the pCR rate with the etoposide combination antibody regimen combined with the TP/TC regimen could reach 43% (H1). The first phase required enrollment of 33 patients; if more than 10 were effective, enrollment would proceed to the second phase, resulting in a total enrollment of 94 patients. With an estimated dropout rate of 10%, the total number of enrolled patients was projected to be 103.

一、Background

Research Significance

Cervical cancer remains the fourth most common malignancy among women worldwide. In 2022, approximately 660,000 new cases and 350,000 deaths were reported globally, with the heaviest burden observed in developing regions, particularly Asia, which accounts for nearly 60% of global cases and deaths. China alone contributes 22.8% of global incidence and 16% of global mortality.

Locally advanced cervical cancer (LACC, FIGO stages IB3 and IIA2) constitutes approximately 50% of all cervical cancer cases in China. Current standard of care is concurrent chemoradiotherapy (CCRT); however, 23.3%–34.4% of patients still experience disease recurrence or metastasis. Neoadjuvant chemotherapy (NACT) followed by radical surgery has been investigated as an alternative strategy, yet 9.8%–30.6% of patients fail to respond to NACT, potentially delaying effective local treatment. Moreover, over 30% of patients who undergo surgery require adjuvant radiotherapy, raising concerns regarding treatment burden and health economics.

In recent years, immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. AntiPD1/PDL1 and anti CTLA4 antibodies exert complementary mechanisms of action. PD1/PDL1 blockade reverses T cell exhaustion within the tumor microenvironment, whereas CTLA4 blockade enhances early T cell activation. Clinical guidelines have incorporated pembrolizumab plus chemotherapy as first line therapy for PDL1 positive advanced or recurrent cervical cancer, prompting further investigation of ICIs in the initial treatment setting.

Emerging evidence supports the combination of neoadjuvant chemotherapy and immunotherapy for LACC. In the PACS study (presented at ASCO 2024), 47 patients with newly diagnosed IB3-IIA2 cervical cancer received three cycles of paclitaxel, cisplatin, and sintilimab followed by radical surgery. The pathological complete response (pCR) rate was 36.2%, and the optimal pathological response rate (residual tumor <3 mm) was 53.2%. At a median follow up of 40 months, no

recurrences occurred among responders. Other studies, including NACI, MITO CERV3, and NATCI, have reported similarly encouraging pCR rates (38% in NACI) and reduced need for postoperative radiotherapy.Given the unmet medical need for more effective and less toxic neoadjuvant regimens, further evaluation of novel immunotherapy combinations such as the dual PD1/CTLA4 bispecific antibody iparomlimab and tuvonralimab (QL1706) in combination with platinum based chemotherapy is warranted to improve pCR rates, reduce the need for adjuvant radiotherapy, and ultimately improve outcomes for patients with LACC.

Drug Background

QL1706 is a novel therapeutic biologic agent developed by Qilu PuShang Biotech Co., Ltd., a wholly-owned subsidiary of Qilu Pharmaceutical Group, using the advanced MabPair™ technology platform. It consists of two engineered monoclonal antibodies (anti-PD-1 and anti-CTLA-4) expressed at a fixed ratio and produced as a single product from a single cell line.QL1706 targets and inhibits two immune checkpoint pathways: anti-PD-1 IgG4 and anti-CTLA-4 IgG1. Unlike bispecific antibodies that equally engage both targets, the MabPair product (e.g., QL1706) enables distinct pharmacokinetic (PK) profiles and antibody effector functions for each component. In QL1706, the anti-CTLA-4 IgG1 component may be key to reducing regulatory T cell function in the tumor microenvironment. Furthermore, both antibodies have been engineered to have different in vivo PK characteristics, aiming to achieve an optimal balance between therapeutic efficacy and toxicity.

A multicenter, open-label, single-arm Phase II trial enrolled 148 patients with recurrent/metastatic (R/M) cervical cancer who had failed first-line platinum-based chemotherapy (± bevacizumab) and had not received prior immunotherapy. Patients received QL1706 (5 mg/kg Q3W). At a median follow-up of 17.5 months, the objective response rate (ORR) was 33.3%, median progression-free survival (PFS) was 5.4 months, and median overall survival (OS) reached 17.1 months. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 27.0% of patients, with only

3.4% discontinuing treatment due to TRAEs. No treatment-related deaths were reported. Based on these results, QL1706 has received NMPA approval.An open-label, multicenter, non-randomized Phase II trial evaluating QL1706 plus different chemotherapy regimens with or without bevacizumab as first-line treatment for R/M cervical cancer (any PD-L1 expression). At a median follow-up of 14.0 months, the ORR was 81% (95% CI, 68.6%–90.1%), with a complete response (CR) rate of 10.3% and a disease control rate (DCR) of 98.3% (95% CI, 90.8%–100.0%). Median PFS was 14.3 months (95% CI, 9.2 months–not estimable). The results demonstrated significant benefit regardless of PD-L1 CPS status.

Given the above evidence, dual immune checkpoint inhibition combined with chemotherapy may offer improved outcomes for locally advanced cervical cancer. Given the increasing trend of younger patients with cervical cancer, neoadjuvant immunotherapy plus chemotherapy may shrink tumors, reduce circulating tumor cell residue, and enable less extensive surgery – potentially allowing uterine preservation and fertility preservation. Additionally, some patients may avoid adjuvant radiotherapy, reducing long-term toxicity and overall treatment costs.

This study (QUARTZ-CC) aims to investigate the efficacy and safety of Ipalotinib (Tivolumab) combined with TP/TC neoadjuvant chemotherapy in locally advanced cervical cancer, explore the feasibility of less extensive surgery after neoadjuvant therapy, evaluate the potential reduction in adjuvant radiotherapy, and identify the patient population most likely to benefit from this combination.

二、Study Design

This is a prospective, open-label, single-arm, phase II clinical trial. The study is designed to evaluate the efficacy and safety of iparomlimab and tuvonralimab (QL1706) combined with paclitaxel and either cisplatin or carboplatin (TP/TC regimen) as neoadjuvant therapy for patients with locally advanced cervical cancer (FIGO stage IB3 and IIA2).

三、Study Objectives

Primary Objective:

pathological complete response (pCR) rate following neoadjuvant immunochemotherapy

Secondary Objectives:

- major pathological response (MPR) rate
- objective response rate (ORR) per RECIST 1.1
- 3 years overall survival (OS) rate
- 3 years disease free survival (DFS) rate
- treatment related adverse events (TRAEs and iTRAEs),
- patient-reported outcomes (PROs).

Exploratory Objectives:

- Identify predictive biomarkers, tertiary lymphoid structures (TLS), and imaging features
- Compare changes in ovarian function in younger patients (anti-Müllerian hormone, AMH)

四、Study Population

Inclusion Criteria:

(1) Age: 18 to 70 years;

(2) Diagnosed with cervical cancer at stage IB3/IIA2 ;

(3) Imaging studies revealed that the short diameter of the pelvic lymph nodes was less than 1.5 cm, as well as that of the para-aortic lymph nodes was less than 1.5cm.

(4) The pathological types are cervical squamous cell carcinoma, adenocarci- noma, or adenosquamous carcinoma;

(5) No prior antitumor therapy received;

(6) Eastern Cooperative Oncology Group (ECOG) score of 0–1.

Exclusion Criteria:

(1) Patients with other malignant tumors;

(2) Patients during pregnancy and the perinatal period;

(3) Patients with a history of myocardial infarction or stroke, unstable angina, decompensated heart failure, or deep vein thrombosis;

(4) Patients with NCI-CTCAE grade 5.0 or higher cardiac arrhythmias, atrial fibrillation of any grade, or clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention;

(5) For patients with active hepatitis that has not resolved: those presenting with progressive loss of appetite, generalized weakness, nausea, acid reflux, aversion to fatty foods, abdominal distension, and other clinical manifestati- ons; or those exhibiting abnormal liver function accompanied by jaundice symptoms such as yellowing of the eyes or dark urine; specifically for hepatitis B cases, patients with a hepatitis B DNA level>1000 IU/mL.

(6) Patients with hepatic dysfunction (aspartate/alanine aminotransferase>2.5 times the upper limit of normal);

(7) Patients with renal insufficiency (serum creatinine>2 times the upper limit of normal);

(8) A history of chronic pulmonary disease with restrictive respiratory dysfunction;

(9) History of transplantation of vital organs or immune-mediated diseases;

(10) History of severe mental disorders or cerebral dysfunction;

(11) History of drug abuse or substance use;

(12)The patient is undergoing immunosuppressive therapy or systemic corticosteroid treatment for immunosuppression (dose>10 mg prednisone or other equivalent potency corticosteroids) and continues to use these agents within 2 weeks prior to enrollment.

(13)Coagulation abnormalities (INR>2.0, PT>16 s), presence of bleeding tendency, or ongoing thrombolytic/anticoagulant therapy; prophylactic use of low-dose aspirin or low molecular weight heparin is permitted.

(14)Congenital or acquired immune deficiencies (e.g., in individuals with HIV infection);

(l5) Administer the inactivated vaccine within 30 days prior to the first dose.

(l6) Individuals who are unable or unwilling to sign an informed consent form or comply with study requirements.

五、Sample Size and Statistical Considerations

The sample size is calculated using Simon's two-stage optimal design. With a one-sided alpha of 0.05 and power of 80%, the study tests the null hypothesis (H0: pCR = 30%) against the alternative hypothesis (H1: pCR = 43%). In the first stage, 33 patients will be enrolled. If 10 or more patients achieve pCR, the study proceeds to the second stage, enrolling additional patients to reach a total of 94 evaluable patients. Accounting for a 10% dropout rate, the total target enrollment is 103 patients. Statistical analyses will be performed using appropriate methods: pCR and ORR rates will be reported with 95% confidence intervals; survival endpoints (PFS, OS) will be estimated using Kaplan-Meier methodology; safety data will be summarized descriptively.

六、Intervention

Neoadjuvant Treatment Regimen (up to 4 cycles, every 3 weeks):

Paclitaxel: 150-175 mg/m² intravenously over at least 3 hours, with premedication for allergy prevention

Cisplatin: 70-75 mg/m² intravenously over at least 1 hour, administered over two days; OR Carboplatin: AUC=5 intravenously over at least 1 hour

Iparomlimab and tuvonralimab (QL1706): 250 mg intravenously over at least 30 minutes

Treatment Algorithm After Neoadjuvant Therapy:

After 2 cycles, clinical assessment is performed: If tumor enlargement or stability is observed: imaging evaluation is performed, and the investigator decides between radical surgery or radical radiotherapy;If tumor shrinkage is observed: the patient continues for 2 additional cycles (total 4 cycles) followed by imaging evaluation.

Subsequent Management Based on Imaging Response:

Complete response (CR) on imaging: cervical conization + sentinel lymph node biopsy (SLNB) or pelvic lymph node dissection (PLND)

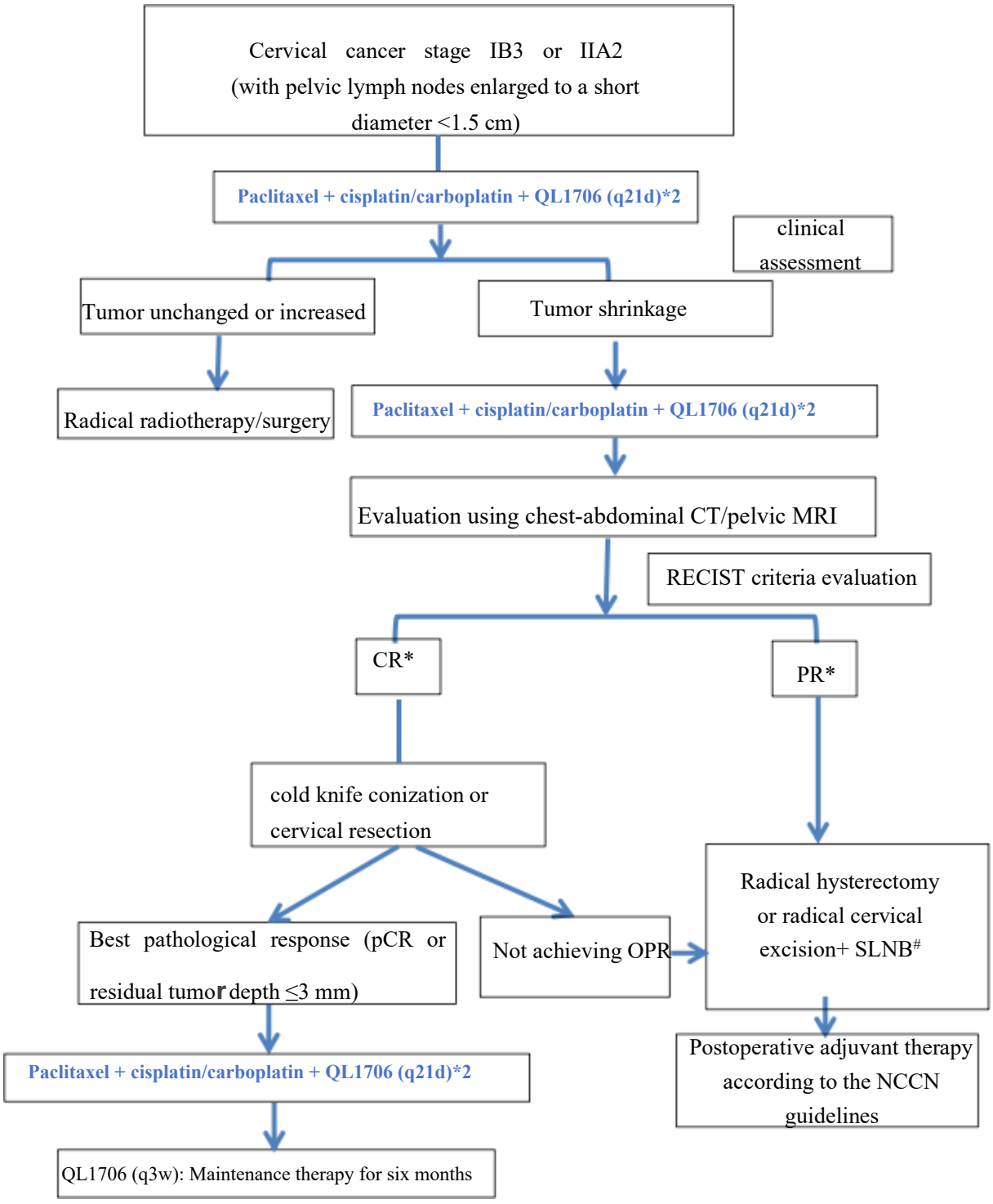
Partial response (PR) on imaging: radical hysterectomy/trachelectomy + SLNB/PLND

Optimal pathological response (OPR) after surgery: continuation of the same regimen for 2 additional cycles, followed by QL1706 maintenance therapy for 8 cycles (every 3 weeks)

Non optimal pathological response after surgery: adjuvant therapy according to NCCN guidelines

In this study, optimal pathological response (OPR) is defined as either pathological complete response (pCR) or residual tumor depth ≤3 mm in the surgically resected specimen following neoadjuvant therapy.During treatment, patients who cannot tolerate surgery or have contraindications to surgery will receive radical radiotherapy; for those in whom sentinel lymph nodes are not visualized, systematic lymph node dissection will be performed.

七、Research Flowchart



**During the course of treatment, patients who are unable to tolerate surgery or have contraindications to surgery will receive radical radiotherapy.*

#For patients in whom the sentinel lymph node is not visualized, systematic lymph node dissection will be performed.

SLNB:sentinel lymph node biopsy

八、Key Assessments

Baseline (within 3 weeks before enrollment):

CT chest/abdomen, pelvic MRI (+APTw), blood tests (CBC, chemistry, thyroid, tumor markers), tissue biopsy (for TLS, single-cell sequencing, PD-L1), blood for single-cell sequencing and AMH (≤45 years)

During treatment:

After cycle 2: clinical evaluation + tumor markers

After cycle 4: imaging (CT + MRI), AMH, blood/tissue for single-cell sequencing

After cycle 6: same as after cycle 4

Maintenance phase:

QL1706 every 3 weeks for 8 cycles; imaging every 3 months

Follow-up:

1 month post-treatment: CBC, chemistry, tumor markers, pelvic ultrasound

3 months to 2 years: every 3 months (CBC, chemistry, tumor markers, pelvic ultrasound), every 6 months (pelvic MRI + CT chest/abdomen)

2–5 years: every year (pelvic MRI + CT chest/abdomen)

九、Definition of Endpoints

pCR: No residual invasive tumor cells in primary tumor and lymph nodes after neoadjuvant therapy

MPR: Residual tumor depth ≤3 mm

ORR: CR + PR by RECIST 1.1

Safety: Incidence of TRAEs and iTRAEs (CTCAE v5.0)

PROs: EORTC QLQ-C30 and QLQ-CX24 at specified time points

十、Study Drug Information

Paclitaxel, cisplatin, carboplatin: Commercially available, paid by patient (standard of care)

QL1706 (iparomlimab + tuvonralimab): Provided free of charge by Qilu Pharmaceutical Co., Ltd.
Dose adjustments: Predefined for hematologic and non-hematologic toxicities; QL1706 dose cannot be adjusted (maximum interruption 12 weeks)

十一、Safety Monitoring

AEs and SAEs graded by CTCAE v5.0
SAE reporting within 24 hours to PI and GCP center
Immune-related AE (irAE) management based on ASCO guidelines
Study termination criteria: major SAE cluster, low efficacy, ethical or regulatory decision

十二、Data Management and Quality Control

Electronic data capture (EDC)
All pCR specimens centrally reviewed by the lead institution

十三、Data Monitoring

An independent Data Monitoring Committee (DMC) will be established to oversee patient safety and conduct periodic reviews of accumulating data. The DMC will have access to unblinded interim results and may recommend early termination of the study for efficacy, futility, or safety concerns.

十四、Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been approved by the Ethics Committee of Sun Yat-sen University Cancer Center. Written informed consent will be obtained from all participants prior to any study related procedures.

十五、Study Duration

The total study duration is approximately 36 months from first patient enrollment, including treatment, follow up, and data analysis phases. Each participant is expected to be on study for approximately 9-12 months, including neoadjuvant treatment, surgery, and maintenance therapy.

十六、References(key)

1.Li K, et al. Neoadjuvant camrelizumab plus chemothe rapy for locally advanced cervical cancer (NACI Study): A prospective, single-arm, phase II trial. Lancet Oncol.2024.

2.Sal utari V, Camarda F, Musacchio L, et al. TP003/#1533 MITO CERV3_phase II study on carboplatin-paclitaxel-pembro lizumab in neoadjuvant treatment of locally advanced cervical cancer. Int J Gynecol Cancer. 2022;32(Suppl 3):A224-A225.

3.Sheng J, Luo H, Liu X, et al. T isle lizumab (anti-PD-1) plus chemotherapy as neoadjuvant therapy for patients with stage IB3/IIA2 cervical cancer (NATIC): a prospective, single arm, phase II study. Signal Transduct Target Ther. 2025 Jul 4;10(1):215.

4.Lou H, Zhou Y, Li D, et al. 251 Efficacy and safety of iparomlimab and tuvonralimab in previously treated patients with recurrent or metastatic cervical cancer: a multicenter, open-label, single-arm, phase 2 clinical trial (DUBHE-C- 206). Int J Gynecol Cancer. 2024;34(Suppl 1):A5.1.