Toripalimab plus etoposide and Platinum-based chemotherapy in first-line treatment of locally advanced or metastatic genitourinary small cell carcinoma：A multicenter, prospective, open label, single-arm, phase II study

Research center：Sun Yat-sen University Cancer Center

Principal Investigator： Shi yanxia

Phone number：020-87343874

Version：1.0

Version date：2022.10.15

Sun Yat-sen University Cancer Center

2022.10.15

1 Background

1.1 Background

Small cell carcinoma of the urinary system is very rare, including bladder, prostate, ureter, etc. Among them, small cell carcinoma of the bladder accounts for about 1% of bladder tumors. According to the US SEER database, the incidence of small cell carcinoma of the bladder is increasing, from 0.05/100,000 in 1991 to 0.14/100,000 in 2005[1].Most patients with small cell carcinoma of the bladder are often at an advanced stage of the disease when they are diagnosed, and are prone to distant metastasis. Compared with urothelial carcinoma, small cell carcinoma of the bladder is more aggressive and has a worse prognosis[2]. Small cell carcinoma of the prostate is a rare prostate tumor with high malignancy and strong invasiveness. About 50% of small cell carcinoma of the prostate is mixed with adenocarcinoma, and the rest are pure small cell carcinoma.The effect of comprehensive treatment is not good, and the median survival time is less than one year[3]. Small cell carcinoma of the ureter is also very rare, accounting for about 0.5% of ureteral tumors. Its onset is insidious, and it is usually advanced when it is diagnosed. The median survival time varies greatly among different case reports.[4]. In summary, small cell carcinoma of the urinary system is rare but has a poor prognosis.

Small cell carcinoma of the urinary system has no treatment recommendations based on randomized clinical trials, only a few retrospective studies have explored treatment options, and some experts believe that small cell carcinoma outside the lung can be treated with similar chemotherapy regimens as small cell lung cancer[5], Including the combination of etoposide and cisplatin (EP) regimen. Although patients with metastatic small cell carcinoma of the bladder and small cell carcinoma of the prostate can achieve a high response rate, the median survival time is only 7-13 months[6]. However, the remission period of patients is often very short-lived, most patients will relapse after treatment, and the data on chemotherapy for small cell carcinoma of the urinary system are limited. A prospective trial included 12 patients with stage IV small cell carcinoma of the bladder at the time of diagnosis. These

patients received IA regimen (ifosfamide + doxorubicin) and EP regimen alternately, and 3 patients completely recovered. Remission, and received surgical consolidation therapy. Median OS in this cohort was 13 months, but only 1 patient remained disease-free at 28 months after initial treatment[7].A French multicenter retrospective study found that the first-line EP regimen in advanced metastatic patients had longer overall survival than etoposide combined with carboplatin (EC) regimen[8], However, only 3 patients received immunotherapy in this study, therefore, the role of immunotherapy in SCBC remains to be further explored. The treatment of small cell carcinoma of the prostate and small cell carcinoma of the ureter is mostly based on case reports and analysis. Gene profile analysis has found that small cell carcinoma of the prostate and small cell carcinoma of the bladder have certain similarities. Most of them refer to small cell lung cancer for comprehensive treatment based on radiotherapy and chemotherapy[9]. After EP treatment, there is no standard maintenance treatment plan. Currently, there is no second-line recommended plan for patients with disease progression after EP treatment. Some treatment centers have published relevant treatment experience, but only case reports with a small sample size[10]. Therefore, for patients with effective EP, the appropriate maintenance regimen to delay disease progression needs further exploration.

Immunotherapy has been explored in urothelial carcinoma of the bladder and small cell lung cancer. The KEYNOTE-045 study enrolled 542 patients with advanced urothelial carcinoma who had relapsed or progressed after prior platinum-based chemotherapy, and compared the efficacy of pembrolizumab with chemotherapy (paclitaxel, docetaxel, vinblastine) , the results showed that the median OS of the pembrolizumab group was 10.3 months, and the ORR was 21.1%; the median OS of the chemotherapy group was 7.4 months, and the ORR was 11.0%, the differences were statistically significant[11]；The Checkmate-275 study found that the second-line overall ORR of nivolumab in patients with advanced urothelial cancer was 19.6%, and the median OS was 8.74 months[12]. PD-L1 monoclonal antibody also has certain curative effect on patients with metastatic urothelial carcinoma, and

the median OS of atezolizumab second-line treatment is 7.9 months[13]. In the exploration of first-line combination chemotherapy, PD-1 and PD-L1 immunotherapy have also achieved encouraging results in urothelial carcinoma. At present, nivolumab, pembrolizumab, and atezolizumab have been approved abroad for the first-line treatment of metastatic urothelial carcinoma. However, no immunotherapy has been explored in non-urothelial carcinoma. In extensive-stage small cell lung cancer, chemotherapy combined with PD-L1 monoclonal antibody (atezolizumab, durvalumab) has been confirmed by a large number of studies to improve the overall survival of patients[14, 15]. It has been confirmed by a large number of studies that it can improve the overall survival of patients. Maintenance therapy with PD-L1 monoclonal antibody after combination therapy has filled the gap in maintenance therapy for small cell lung cancer and is one of the major advances in the treatment of small cell lung cancer in recent years. However, in small cell carcinoma outside the lung, there is not much evidence for immune combination chemotherapy, and the choice of immune checkpoint inhibitors needs further exploration. Toripalimab is a PD-1 antibody independently developed by my country, which has been approved by the Chinese FDA for the first-line and later-line treatment of recurrent and metastatic nasopharyngeal carcinoma and melanoma[16, 17], Exploration of toripalimab in other cancers such as esophageal cancer is underway[18].

According to the current domestic and foreign literature, immunotherapy combined with chemotherapy has achieved great success in lung cancer, nasopharyngeal carcinoma and other tumor types, and other tumor types are also exploring its efficacy through clinical trials. Therefore, this study aims to explore an effective salvage chemotherapy regimen for small cell carcinoma of the urinary system, using the standard EP regimen combined with toripalimab, which is expected to increase the efficacy of the EP regimen and provide options for subsequent maintenance therapy for patients. For patients whose EP regimen is effective, toripalimab is used as maintenance therapy until disease progression or unacceptable side effects, which further provides a new way to improve the curative effect of

patients with small cell carcinoma of the urinary system.

1.2 Research Principles

According to the clinical dose data of triplatin, etoposide and cisplatin / carboplatin in small cell cancer, we selected the doses of 240mg/, etoposide 100mg/m2, D1-3 and cisplatin 25mg/m2, D1-3 as the dose of this study, every 21 days as a course of treatment.

For patients with cisplatin intolerance, we use carboplatin instead of cisplatin. The criteria for cisplatin intolerance are as follows:

(1) Renal dysfunction calculated serum creatinine clearance < 30-60mL/min according to CG formula (Annex 2);

(2) ECOG score is 2;

(3) Hearing impairment: difficulty in communication due to hearing aids, or hearing loss greater than 25 decibels twice in a row.

(4) Other concomitant diseases are not suitable for cisplatin chemotherapy.

Note: if the patient is accompanied by two or more of the above conditions, the researchers need to evaluate in detail whether they can tolerate combined chemotherapy.

For patients with cisplatin intolerance, EC regimen combined with toripalimab was used for treatment, toripalimab 240mg/time, etoposide 100mg/m2, d1-3, Carboplatin is calculated according to AUC=5 (ivgtt, d1) based on renal function

After entering the group, the patients were treated with triplizumab combined with EP or EC for 4 to 6 courses, and the efficacy was evaluated by imaging every 2 courses. If there is a chance of local treatment, they will participate in a multidisciplinary discussion to determine the next step of treatment. After local treatment, they will continue to use triplizumab to maintain treatment until the disease progresses or intolerable toxicity occurs, and the maximum duration of maintenance treatment is 2 years. If the patient's efficacy was evaluated as complete remission (CR), partial remission (PR) or disease stability (SD) after 4 to 6 courses of treatment, maintenance therapy with triplizumab 240mg/ every 21 days until the disease

progressed or intolerable toxicity developed for up to 2 years. If the patient has disease progression or intolerable side effects in the course of treatment, the patient will be withdrawn from the group. The patients in the withdrawal group entered the follow-up period.

1.3 Risk/Benefit

1.3.1 Risk

Subjects will receive toripalimab, etoposide, and cisplatin/carboplatin therapy after enrollment. According to preclinical and clinical research reports and a large number of clinical application evidences, treatment with toripalimab, etoposide, cisplatin, and carboplatin may cause myelosuppression, hair loss, rash, peripheral neurotoxicity, blurred vision, fatigue, and nausea , anemia, decreased appetite, fever, diarrhea, constipation, vomiting, back pain, increased blood thyroid-stimulating hormone, decreased white blood cell count, cough, itching, hypothyroidism, decreased appetite, increased blood sugar, and increased blood bilirubin , transaminase elevation and other toxic reactions; in addition, due to possible leakage of chemotherapy drugs during administration (varies from person to person), serious adverse events such as skin damage or even necrosis around the injection port may occur. During the trial, the researchers will closely monitor any adverse events and risks that may occur to ensure that the subjects receive timely examination and treatment, and if necessary, reduce or stop the use of related drugs, or even terminate the subjects from continuing to participate in the trial.

1.3.2 Benefit

Subjects will receive good medical services during the study period. According to relevant clinical research reports, subjects may benefit from drug effects such as delayed disease progression and life extension, but we cannot guarantee or promise that all subjects will benefit. In addition, if the subjects are successfully enrolled, they will receive good medical treatment. After the subjects are successfully enrolled, participating in this study will receive free medicines for all courses of toripalimab, and the costs of chemotherapy drugs and related examinations will be borne by the

subjects themselves.

2 Research purposes and assumptions

2.1 Research purposes

2.1.1 Main purpose

•To observe the curative effect of toripalimab, etoposide, cisplatin/carboplatin in the treatment of small cell carcinoma of urinary system

2.1.2 Secondary Purpose

•To observe the safety and tolerability of toripalimab, etoposide, and cisplatin/carboplatin in the treatment of small cell carcinoma of the urinary system

2.2 Research Hypotheses

Test hypothesis: P0: the single-arm test group is invalid; P1: the single-arm test group is effective.

3 Design

3.1 Design outline

3.1.1 Subject Population/Treatment Assignment

This study is a prospective, multicenter, open-label, single-arm phase II clinical trial. A single-arm experimental group of toripalimab, etoposide, and cisplatin/carboplatin was designed to evaluate its efficacy and safety in small cell carcinoma of the urinary system.

After meeting the enrollment conditions, they received combination therapy: toripalimab 240 mg, administered on the first day of each cycle, and a cycle of administration every 3 weeks. Etoposide 100mg/m2, d1-3, cisplatin 25mg/m2, d1-3 or carboplatin AUC=5 d1, administered on the first day of each cycle, a cycle of administration every 3 weeks. Toripalimab combined with etoposide and cisplatin/carboplatin was used for 4 to 6 courses of treatment. Evaluate the curative effect with imaging every 2 courses. If there is an opportunity for local treatment after chemotherapy, participate in multidisciplinary discussions to decide the next step of treatment. For patients who can be treated with local treatment (surgery, radiotherapy)

after treatment, the investigator will receive maintenance treatment with toripalimab 240 mg/time, every 21 days, until the disease progresses or unacceptable toxicity occurs. If the curative effect evaluation of the patient is complete remission (CR), partial remission (PR) or stable disease (SD) after 4 to 6 courses of treatment, maintenance therapy with toripalimab 240mg/time, every 21 days, until the disease progression or intolerable toxicity. The maximum duration of maintenance treatment is 2 years. Subjects who finished treatment entered the follow-up period and received safety follow-up and survival follow-up.

3.1.2 Efficacy variables

3.1.2.1 Main Efficacy Parameters

• Progression-free survival (PFS)

3.1.2.2 Secondary Efficacy Parameters

- Complete Response Rate (CRR)
- Duration of Response (DOR)
- Objective Response Rate (ORR)
- Overall Survival (OS)

3.1.3 Security variable

- Adverse events and serious adverse events
- Symptoms and signs
- laboratory tests
- Treatment-emergent adverse events leading to dose adjustments, dosing interruptions, delays, non-dosing, and/or study drug discontinuation

3.1.4 Assessment of Quality of Life

EQ-5D (Euro QoL five-dimensions questionnaire) and EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30) scale and Functional Assessment of Cancer Therapy questionnaire were used to evaluate the quality of life.

3.2 Trial period

The trial is planned to be enrolled for 24 months and followed up for 12 months.

From the enrollment of the first subject to data analysis, the trial is expected to last for 36 months. During the trial, if the subjects do not stop treatment (see 11 for details), they will receive 4-6 cycles of complete combined treatment and maintenance treatment. Except for the occurrence of progression or death, the subjects should complete the visit plan specified in the protocol.

3.2 Study endpoint

3.2.1 Efficacy Evaluation Criteria

Evaluation was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, see Appendix 1 for details.

3.2.2 Primary Endpoint

- Progression-free survival (PFS)

3.2.3 Secondary Endpoints

- Complete Response Rate (CRR)
- Duration of Response (DOR)
- Objective Response Rate (ORR)
- Overall Survival (OS)
- Safety and tolerability (type, frequency, severity, relationship of adverse events to study treatment, physical examination, vital signs, laboratory tests, concomitant medications/treatments, and dose adjustments)
- Patient's quality of life assessment

3.2.4 Exploratory Molecular Marker Research

The collected and preserved tumor samples (primary tumor and/or metastatic tumor), blood, urine, and stool samples will be used for future exploratory research on factors that may affect or predict efficacy (including efficacy and safety). The main measurement contents are as follows (but not limited to):

- ◆ Immune-related indicators: PD-L1 expression, etc.
- ◆ Serological tumor markers (NSE, CEA, CA199, etc.)
- ◆ Other biomarkers (SPARC, ERCC1, etc.), gene detection, homologous recombination repair defect (HRD) detection, etc.

3.3 Efficacy evaluation

3.3.1 Time for efficacy evaluation

Before drug administration in this study, after the 2nd, 4th, and 6th courses of chemotherapy, and every 2 courses of maintenance, the curative effect evaluation was performed, and all patients were required to undergo curative effect evaluation when completing or withdrawing.

3.3.2 The means of evaluating the curative effect

Efficacy evaluation before administration, after the 2nd, 4th, and 6th cycles of chemotherapy, and during maintenance therapy. Visceral lesions should be evaluated by CT, MRI or PET-CT, and surface lesions should be evaluated by a physician's physical examination and recorded in the original medical records as objective evidence. Chest X-ray or B-ultrasound can be used to screen the suspected invasion site, but CT, MRI or PET-CT must be used for evaluation after the lesion is confirmed.

Because toripalimab is an immune checkpoint inhibitor, according to the experience of similar drugs, some subjects will experience delayed or early tumor pseudo-progression after receiving immunotherapy drugs. Therefore, this study allowed subjects whose response assessment was indeterminate response (IR) to continue treatment until PD was confirmed by the next imaging evaluation.

4 Experimental population

4.1 Clinical Trial Center

Sun Yat-sen University Cancer Center

4.2 Number of cases

Based on the characteristics of the population of patients with small cell carcinoma of the urinary system and the statistical needs of the centers participating in the trial, this trial is expected to enroll 33 subjects with small cell carcinoma of the urinary system within 24 months.

4.3 Inclusion criteria

Patients should meet the following criteria to be enrolled in the trial:

1) Participate voluntarily and sign the informed consent;

2) Age ≥ 18 years old;

3) Life expectancy ≥ 3 months;

4) Physical condition score ECOG 0-2;

5) Pathologically diagnosed as genitourinary small cell carcinoma (recommended central consultation for difficult pathology), including small cell carcinoma primary in the kidney, ureter, bladder, urethra, and prostate. The stage is locally advanced or advanced (stage IIIA or above, that is, cT3 or above N0 M0, or cT1-4a N1-3 M0, or cT4b any N M0, or any T any N M1), or the investigator judges that local treatment is not suitable for the time being (surgery, radiotherapy) patients.

6) Patients whose pathology is mixed small cell carcinoma can be included, and the small cell carcinoma component is ≥50%.

7) Have not received systemic treatment before, or the time interval from the last adjuvant treatment is more than 6 months;

8) There are measurable or/and evaluable lesions (non-radiotherapy target areas) (lesion evaluation according to Recist1.1 standard);

9) No serious organ (main organs: heart, lung, liver, kidney) dysfunction (refer to the respective standards);

10) Blood routine indicators: white blood cell (WBC) ≥ 3 × 109/L; absolute neutrophil count (ANC) ≥ 1.5 × 109/L; platelet (PLT) ≥ 100 × 109/L; hemoglobin (Hgb) ≥ 8g /dL;

11) Blood biochemical indicators: AST (SGOT), ALT (SGPT) ≤ 2.5 × upper limit of normal value (ULN) (in the case of no liver invasion) or ≤ 5 × upper limit of normal value (ULN) (in the case of liver invasion); total bilirubin (TBIL) ≤ ULN; serum creatinine clearance calculated according to the CG formula > 30 mL/min

12) Coagulation function: prothrombin time (PT), international normalized ratio (INR) ⩽ 1.5 × ULN (unless warfarin is being used for anticoagulation);

13) Able to comply with the research visit plan and other program requirements;

14) All patients of childbearing age must agree to take effective contraceptive measures during the study period and within 6 months of stopping treatment, and the urine pregnancy test of female patients of childbearing age must be negative before treatment.

4.4 Exclusion Criteria

Patients will be excluded from this study if they meet any of the following criteria:

1) Received treatment for small cell carcinoma of the urinary system within 2 weeks before enrollment;

2) Once diagnosed with prostate adenocarcinoma, received endocrine therapy (such as enzalutamide, apalutamide, abiraterone, etc.) and chemotherapy (docetaxel) for prostate adenocarcinoma, and is currently considering neuroendocrine differentiation of prostate cancer ;

3) Mixed small cell carcinoma, in which the small cell carcinoma component is less than 50%.

4) Medical history and comorbidities:

[1] Anti-tumor vaccine or cellular immunotherapy has been used before the first dose of the study drug;

[2] Previously received systemic therapy for metastatic lesions;

[3] The patient is participating in other interventional clinical studies or less than 4 weeks before the end of the previous clinical study;

[4] Those who have been less than 4 weeks away from the last anti-tumor treatment (radiotherapy, chemotherapy, targeted therapy, immunotherapy or local-regional treatment). The adverse reactions related to anti-tumor treatment (except hair loss) after the previous systemic anti-tumor treatment have not recovered to NCI-CTC AE

≤level 1;

[5] Live vaccines have been vaccinated within 4 weeks before administration of the study drug. Inactivated virus vaccines for seasonal influenza and injection are allowed, but attenuated live influenza vaccines for intranasal administration are not allowed;

[6] The subject has any active, known or suspected autoimmune disease. Subjects who are in a stable state and do not require systemic immunosuppressant therapy are allowed to be enrolled;

[7] Subjects who required systemic treatment with corticosteroids (>10 mg/day of prednisone or equivalent doses of other glucocorticoids) or other immunosuppressants within 14 days before the first dose of study drug. Steroid replacement with inhaled or topical steroids and curative doses of prednisone at doses > 10 mg/day is permitted in the absence of active autoimmune disease;

[8] Patients with a known history of interstitial pneumonia or highly suspected interstitial pneumonia; or patients who may interfere with the detection or treatment of suspected drug-related pulmonary toxicity;

[9] Other active malignant tumors that require simultaneous treatment;

[10] Has a history of malignant tumors. Patients with basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or cervical carcinoma in situ who underwent potentially curative therapy and had no disease recurrence within 5 years from the end of treatment were excluded.

[11] Known history of organ transplantation and allogeneic hematopoietic stem cell transplantation;

[12] Subjects who have undergone major surgery or severe trauma have less than 14 days before enrollment;

[13] Patients with active pulmonary tuberculosis should be excluded. Patients suspected of having active pulmonary tuberculosis should be checked for chest X-ray, sputum, and ruled out by clinical symptoms and signs. Patients with a history of active tuberculosis infection within the previous 1 year, even if treated, should be excluded; patients with a history of active tuberculosis infection more than 1 year ago

should also be excluded. Unless it is proven that the duration and type of antituberculosis treatment previously used was appropriate;

[14] Severe acute or chronic infection requiring systemic therapy

[15] Heart failure (New York Heart Association Class III or IV) despite appropriate medical therapy. Patients with poorly controlled coronary artery disease or poorly controlled arrhythmia, or a history of myocardial infarction within 6 months prior to screening.

5) Neutrophil count <1.0 × 109/L, or hemoglobin <80g/L, or platelet count <90 × 109/L. Hepatic insufficiency not related to tumor (transaminase more than 3 times the upper limit of normal value and/or blood bilirubin greater than 2.0mg/dl). Renal insufficiency not related to tumor (serum creatinine clearance <30 mL/min calculated according to the CG formula).

6) Known history of positive human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);

7) Untreated active hepatitis (hepatitis B: HBsAg positive and HBV DNA ⩾ 500IU/mL; hepatitis C: HCV RNA positive and abnormal liver function); co-infected with hepatitis B and C;

8) Allergy to any study drug;

9) Pregnant and breastfeeding women;

4.5 Rejection criteria

For those who have been selected into this clinical study and fall into one of the following situations, they will be counted as excluded cases:

1) After the subjects are selected, it is found that there are cases that do not meet the case selection criteria;

2) Those who have taken less than 2 consecutive medications after being selected, and cannot evaluate the objective curative effect (but can evaluate adverse reactions);

3) Patients who violate the requirements of the trial protocol.

4.6 Exit Criterion

Patients can withdraw from clinical trials at any time and for any reason. When the researchers think that it is not appropriate to continue the drug, they can also ask the patient to withdraw from the interest of the patient.

If one of the following situations occurs to the subject during the trial, the investigator should arrange for the subject to discontinue treatment and withdraw from the trial:

1) The subject's compliance is poor, and the medication cannot be taken on time and in the right amount;

2) The use of other anti-tumor treatments affects the judgment of the results;

3) Adverse reactions occur, and the investigator judges that it is not appropriate to continue this clinical study;

4) The subject is unwilling to continue the clinical study and withdraws voluntarily.

Before withdrawing from the trial, the latest follow-up and evaluation of various indicators of efficacy and adverse reactions must be completed, and the reason and date of withdrawal of the withdrawn patient must be recorded in detail.

5 Research Flow Chart

project	Baseline assessment before enrollment (within 2 weeks before enrollment)	Toripalimab combined with etoposide, cisplatin/carboplatin therapy (1-6 courses of treatment)	Inspection at the end of 2, 4, 6 courses of combined treatment	Toripalimab maintenance therapy
Imaging examination	X		X	X
Pathological examination/consultation	X			
eligibility criteria	X			
Sign the informed consent	X			
Demographics	X			
Detailed medical history and complete physical examination	X	X	X	X
Clinical biochemistry, urine, and stool laboratory tests	X	X	X	X
routine blood test	X	X	X	X
serum tumor markers	X	X	X	X
urine pregnancy test	X			
electrocardiogram	X	X	X	X
tumor specimen	X			
Blood samples, urine samples, stool samples	X	X		X
ECOG score	X	X	X	X
Abdomen, pelvis, chest CT/MRI or PET-CT	X		X	X
Etoposide, cisplatin/carboplatin administration		X		

Administration of toripalimab		X		X
Adverse event		X	X	X
Accompanying treatment records		X	X	X
quality of life assessment	X	X		X
Confirmation of tumor progression and survival status		X	X	X

6 Research Steps

6.1 Screening

The researchers gave informed consent to the subjects who met the enrollment conditions, and only when the subjects signed the latest version of the informed consent form could the next step of the research be carried out.

According to the inclusion/exclusion criteria of the protocol, the researchers conducted or approved imaging data (tumor histopathology, abdominal and pelvic CT/MRI plain scan + enhancement, endoscopic ultrasonography can be used as a supplementary method of CT, PET/ CT scan is not used as a routine method) to evaluate the tumor characteristics of the subjects. The evaluation content includes tumor location, number, size, degree of invasion of large blood vessels, tumor thrombus, extent of invasion of surrounding tissues, etc., and needs to be recorded in the medical record. If the imaging examination cannot be obtained or is not recognized by the researcher within two weeks before the subject's enrollment, it is recommended that he undergo another CT in our hospital, and the researcher will re-evaluate and record according to this examination.

6.2 Baseline

Prior to enrollment, the following will be reviewed to ensure inclusion/exclusion criteria are met and baseline data obtained:

- Chest + abdomen + pelvic CT (plain scan + enhanced)
- Blood tumor markers
- Tumor histopathology or cytology
- If the subject has relevant abnormal clinical symptoms or signs, and the investigator suspects that it is caused by distant metastasis of the tumor, relevant imaging examinations and/or laboratory examinations may be performed:
    - ○ Suspect brain and nervous system metastases, MRI examination
    - ○ Skeletal invasion is suspected, and ECT examination is performed
- Blood routine, urine routine, stool routine + occult blood test, electrocardiogram

- Liver function (AST, ALT, γ -glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function (creatinine), electrolytes, blood glucose, blood amylase
- Clotting function (prothrombin time)
- Urine pregnancy test (female subjects of childbearing potential)
- Vital signs, height, weight, physical examination
- ECOG score
- Collect the subject's past diabetes, treatment history, and allergy history, and record them in the medical record

According to the imaging report, combined with other laboratory tests and symptoms and signs, the researcher judges whether the subject has disease progression, and records it in the medical record.

6.3 Enter the group

According to the inclusion/exclusion criteria, the investigators will judge whether the subjects meet the enrollment conditions based on the results of the baseline examination, third-party imaging and pathological results(test code). For successfully enrolled subjects, the researchers need to obtain a copy of their ID card for archiving.

6.4 Treatment

6.4.1 Treatment execution

After successful screening of subjects, the dosing plan is shown in Table 1. The first dose of study drug will be administered within 72 hours of enrollment. All patients will be continuously monitored for adverse events. Treatment revisions (eg, dose withholding, reduction, interruption, or discontinuation) will be based on specific laboratory and AE criteria. In each cycle, toripalimab will be given before chemotherapy drugs.

Patients should receive antiemetics according to local standard treatment and manufacturer's instructions. Because of the immunomodulatory effects of steroids, their use as prechemotherapy should be limited when clinically feasible. It is

recommended to use the standard antiemetic regimen, and the optional antiemetic drugs include 5-HT3 receptor antagonists alone or in combination with NK-1 receptor antagonists (fosaprepitant, aprepitant, etc.), determined by the investigator .

In exceptional circumstances (e.g., dosing is withheld due to the need to manage an AE or infusion-related reaction), dosing of subsequent study drug may be delayed until the second day of each cycle.

Table 1 Dose selection and administration time for each patient

Table 1A Doses of cisplatin if tolerated

Study Drug	dosage	frequency of dosing	Route of administration
Toripalimab	240mg	Day 1 of each 21-day cycle	IV drip
Etoposide	100mg/m^2	Day 1 to Day 3 of each 21-day cycle	IV drip
Cisplatin	25mg/m^2	Day 1 to Day 3 of each 21-day cycle	IV drip

Table 1B Doses when cisplatin is not tolerated

Study Drug	dosage	frequency of dosing	Route of administration
Toripalimab	240mg	Day 1 of each 21-day cycle	IV drip
Etoposide	100mg/m^2	Day 1 to Day 3 of each 21-day cycle	IV drip
Carboplatin	AUC 5	Day 1 of each 21-day cycle	IV drip

6.4.2 Cycle Time Settings

In this experiment, 4-6 courses of chemotherapy were used. Relevant inspections were required before and after each course of treatment to evaluate safety events, and imaging review was performed every 2 courses of treatment during the course of treatment. After 4-6 courses of treatment, if there is no disease progression or unacceptable toxicity, maintenance treatment will be initiated, and imaging reexamination will be performed every 2 courses during the maintenance treatment to evaluate the disease progression. For patients who are evaluated by the investigator

for local treatment (surgery, radiotherapy) after treatment, maintenance treatment can be started after the end of local treatment.

6.4.3 Pre-treatment operation

The following operations need to be completed within one week before medication:

- Chest, abdomen, pelvic CT (plain scan + enhanced)
- Blood tumor markers
- Blood routine, urine routine, stool routine + occult blood test, electrocardiogram
- Liver function (AST, ALT, γ -glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function (creatinine), electrolytes, blood glucose, blood amylase
- Clotting function (prothrombin time)
- Urine pregnancy test (female subjects of childbearing potential)
- Vital signs, height, weight, physical examination
- ECOG score
- Collect subjects' previous diabetes history, treatment history, and allergy history, and record them in medical records

6.4.4 Treatment administration

The subjects were administered according to the prescribed cycle. The researchers decided whether to administer chemotherapeutic drugs and to adjust the dosage according to the subjects' previous treatment and pre-medication laboratory test results. When the subject has intolerable chemotherapy toxicity, the investigator can reduce or stop the administration of chemotherapy (refer to the dose adjustment regulations), but the investigator needs to record the reason for the reduction or withdrawal in the medical record.

Common toxicities of chemotherapy drugs include nausea, vomiting, abdominal pain, diarrhea, decreased blood cells (WBC, RBC, PLT, ANC, etc.), abnormal liver

and kidney function. If leakage occurs during the administration of chemotherapy drugs, it may cause skin damage or even necrosis. Any adverse event that occurs during the study, regardless of whether it is related to the study drug or not, should be monitored and treated accordingly and recorded truthfully in the medical record.

6.4.5 Post-treatment inspection

Relevant laboratory tests need to be completed after the end of the study drug (can overlap with the next pre-treatment test):

- Blood routine, urine routine, stool routine + occult blood test, electrocardiogram
- Liver function (AST, ALT, γ -glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function (creatinine), electrolytes, blood glucose, blood amylase
- Clotting function (prothrombin time)
- Blood tumor markers

6.5 Follow up

After the subject received the study drug treatment (the end of the course of treatment or early termination due to any reason, except for death), CT was re-examined every 2 courses of treatment (6 weeks) during the medication period; CT was re-examined every 3 months after drug withdrawal until the disease relapsed , progression or metastasis, and then changed to telephone visits for survival follow-up, every 3 months until the death of the patient or the second study analysis of the trial (whichever occurs earlier). Tumor progression and death events need to be recorded, as well as concomitant related treatments. All anti-cancer treatments received by the subjects before death shall be recorded in the follow-up records.

6.6 Clinical Trial Completion

Before the second study analysis condition is met, the subject has a progression/death event, and the trial is considered to be completed. When the

conditions for the second analysis are met, no recurrence/transfer/death occurs, and the trial is also considered to be completed. The test completion time is stipulated as follows:

- If a progressive condition has occurred but study drug was not stopped immediately, the last time study drug was given is the completion date of the study
- If the experiment was terminated because the second analysis was reached, fill in the date of completion of the experiment, which is the time when the second analysis was reached
- In case of death, the date of completion of the trial is the time of death of the subject

6.7 Discontinuation of the trial visit

Once a trial-terminating event occurs, the following assessments should be completed at the same time as withdrawal, if possible. If the subject terminates the trial due to an adverse event, the subject needs to be followed up as much as possible until the investigator determines that the adverse event has recovered, stabilized, or cannot be changed.

The following procedures will be performed at the termination trial visit:

- The investigator must inform the subjects that they need to withdraw from the trial and the reasons for withdrawal
- Record in detail the reason for the subject's early withdrawal from the trial and the date of withdrawal in the scientific medical record and case report form (CRF)
- A safety assessment is required, including:
    - Physical examination
    - Weight and vital signs
    - Blood routine, urine routine, stool routine + occult blood test, electrocardiogram
    - Blood tumor markers
    - Liver and kidney function, prothrombin time

○ ECOG score

○ Concomitant medication and adverse event report

• Regular follow-up of subjects by investigators or authorized persons

How to record when the trial was terminated:

• Terminate test on date of positive urine pregnancy test if pregnancy occurs

• If the combined treatment violates the protocol, the trial date will be terminated with the start date of the combined treatment

• If due to adverse events or non-compliance, the subject's last imaging/laboratory evaluation date in the study will be the termination time of the trial

• If the subject is lost to follow-up, the trial will be terminated on the date of the last follow-up with clear survival information

• If the subject or his legal representative requests or should withdraw from the study at the specific request of the research party, the date when the subject or his legal representative or the research party makes the request shall be the termination time of the trial

6.8 Plan deviation

Researchers should conduct research in accordance with the protocol and corresponding laws and regulations. Prior to implementing protocol deviation operations, written approval from the principal investigator is required.

The protocol deviation should be documented and explained by the investigator or authorized personnel. If the subject is not eligible for enrollment or receives the wrong dose of trial treatment, and has used the study drug at least once, for the sake of safety, it is necessary to collect relevant data and notify the ethics committee of the deviation according to relevant procedures.

6.9 Lab test

During the test, blood, urine, and feces samples were collected multiple times before each cycle of medication. The following specific parameters need to be

determined:

- WBC/ANC/RBC/PLT/Hb
- Aspartate aminotransferase/alanine aminotransferase/gamma-glutamyl transpeptidase/total bilirubin/albumin/prealbumin/electrolytes/creatinine
- Prothrombin time
- CA19-9 and other tumor markers
- Blood tumor markers
- Routine urine/stool + occult blood test
- Glucose/amylase
- urine pregnancy test

All laboratory examinations are carried out in the Laboratory Department of the hospital, and the relevant procedures of the hospital are followed, and the inspection reference values of the hospital are used as the reference for examination indicators. The investigator must review the results and sign off. For laboratory results to be clinically significant, they must be reported as medical history or adverse events.

6.10 Imaging examination

Re-examination of imaging examination is required before every 2 cycles of treatment, and re-examination every 3 months after the end of medication. include:

- Chest + abdomen + pelvic CT (plain scan + enhanced)

7 Experimental drug

7.1 Experimental Drugs and Preparations

7.1.1. Toripalimab

Toripalimab is a monoclonal antibody in the form of intravenous injection in a single-use vial containing 6mL of solution containing a total of 240mg of antibody.

7.1.2 Etoposide

Etoposide is a cytotoxic drug, which is in the form of intravenous injection and packed in single-use vials, each bottle contains 5mL solution and 100mg drug.

7.1.3 Cisplatin

Cisplatin is a cytotoxic drug, it is in the form of intravenous injection, and it is packed in a single-use medicine bottle, each bottle contains 6mL solution and 30mg drug.

7.1.4 Carboplatin

Carboplatin is a cytotoxic drug, which is in the form of intravenous injection, packed in single-use vials, each bottle contains 10mL solution and 100mg drug.

7.2 Labeling and Packaging

Etoposide, cisplatin, carboplatin, and toripalimab are already on the market, and the labels and packaging are the same as the product specifications. The label is printed with the following marks: [drug name], [drug number], [serial number], [product batch number], [expiration date].

7.3 Storage conditions

Investigators are responsible for the drug counts in clinical trials. All test drugs must be stored according to relevant standards and meet temperature control requirements.

8 Treatment and Restraint

8.1 Treatment

8.1.1 Treatment rules and duration

Before the progress of the subject, the subjects must take the medication according to the protocol until the completion of the course of treatment, and follow-up as required after the course of treatment until the end of the second research analysis.

After the progress of the subject, the investigator will decide whether to continue the experimental drug treatment according to the condition of the subject, and if continue to use the experimental drug. Can be stopped at any time before the end of the trial at the investigator's discretion. After the course of treatment is over, the subjects do not need to continue to use the study drugs as required.

8.1.2 Dosage adjustment

Dose withholding was defined as an interruption of the treatment regimen (i.e., delaying drug administration beyond the visit window). Dose interruption was defined as infusion interruption.

Every effort should be made to administer study drug according to the planned dose and schedule. In the event of severe toxicity, dosing may be delayed and/or reduced according to the guidelines outlined below. Reasons for dose adjustments or delays, supportive measures taken, and outcomes will be documented in the patient's medical record.

The dose adjustment guidelines in this section are not a substitute for clinical judgment. The investigator may temporarily suspend or adjust the dose due to other reasons (such as adverse events, weight loss, laboratory findings).

Dosing interruptions were permitted if due to medical/surgical events or logistical reasons unrelated to study treatment (eg, unrelated medical events, patient leave, and/or vacation). However, patients are advised to continue study treatment within 3 weeks of planned discontinuation.

8.1.2.1 General Guidance Regarding Dose Adjustments

Dosage adjustments for toripalimab and etoposide, cisplatin, and carboplatin should be made according to the prescribing information and local practice, based on the clinical judgment of the treating physician (Table 2).

- For AEs that have occurred at baseline, dose adjustments will be made based on changes in toxicity grade, at the investigator's discretion. For example, if a patient had Grade 1 asthenia at baseline and it rose to Grade 2 during treatment, it would be considered a change from Grade 1, and the dose adjustment would be aimed at downgrading to Grade 1 toxicity.
- When several toxicities of varying severity occur concurrently, dose adjustments should be based on the highest level observed.
- If the investigator believes that the toxicity is due to only one part of the study treatment, and the dose of this part has been suspended or adjusted

according to the following guidelines, the other part can continue to be administered if there are no contraindications.

- If chemotherapy-related toxicity occurs, chemotherapy will be withheld until the toxicity reaches baseline or ≤ Grade 1 (whichever is more severe) before the next dose of chemotherapy. Except for hair loss, grade 2 fatigue, or other adverse events that the investigator believes will not affect the safety assessment of the study drug. Toripalimab should continue to be administered as planned. If the AE resolves within 10 days, chemotherapy will be administered. Dosing of chemotherapy and toripalimab will be resynchronized in the next cycle, which will be scheduled according to the chemotherapy dose administration dates. If the AE does not resolve within 10 days, no chemotherapy will be given for this cycle. If the AE resolves within 21 days, chemotherapy and toripalimab will be administered as originally scheduled on Day 1 of the next treatment cycle.
- If toripalimab-related toxicity occurs, toripalimab dosing will be withheld. The next dose of toripalimab could not be continued until the toxicity reached baseline level or ≤ grade 1 (whichever was more severe). Except for hair loss, grade 2 fatigue, or other adverse events that the investigator believes will not affect the safety assessment of the study drug. Chemotherapy should be carried out as scheduled. If the AE resolves within 10 days, toripalimab will be administered. Dosing of chemotherapy and toripalimab will be resynchronized in the next cycle, which will be scheduled according to the chemotherapy dose administration dates. If the AE did not resolve within 10 days, toripalimab should not be administered during the current cycle. If the AE resolves within 21 days, toripalimab and chemotherapy will be continued as originally planned on the first day of the next treatment cycle.

8.1.2.2 Suspension or dose adjustment of toripalimab

The dose of toripalimab was not reduced in this study.

If the patient develops toxic side effects that are considered to be related to toripalimab, and the drug needs to be suspended, the study treatment can be temporarily suspended. If the dosing delay is ≤10 days, toripalimab will be administered. If the hold-off is longer than 10 days, toripalimab will be omitted for this cycle and the next cycle will be administered as planned as long as the AE resolves within 21 days.

Patients should resume toripalimab treatment as soon as possible after the adverse event resolves to baseline levels or grade 1, whichever is more severe, and within 12 weeks of the last dose of toripalimab . If a patient cannot resume toripalimab within 12 weeks of the last dose of toripalimab, the patient should discontinue treatment.

If the patient meets the discontinuation criteria, but is still able to benefit from the study treatment, the study treatment can be resumed.

Dose adjustments for irAEs and infusion-related reactions are described in Appendix 3 and Section 10.3.6, respectively.

8.1.2.3 Dose suspension, interruption, or modification of etoposide, cisplatin, and carboplatin

Dose adjustment guidelines for etoposide, cisplatin, and carboplatin, as described below, depend on the severity of the toxicity and the risk-benefit assessment for the patient, with the goal of maximizing patient compliance and access to supportive care.

The required etoposide, cisplatin, and carboplatin doses were calculated using baseline body weight. If a patient's weight changes ≥10% from baseline (the newly recorded weight will be the new baseline weight), a dose adjustment will be required. If the weight change is <10%, no chemotherapy dose adjustment is necessary.

Study drug-related toxicity must subside to baseline levels or ≤ Grade 1 (whichever is more severe) before the next dose, except for hair loss or Grade 2 fatigue or other adverse events that the investigator believes will not affect the safety evaluation of the study drug .

During the treatment, if the patient develops severe neutropenia (ANC<0.5x 109/L for 1 week or more), the treatment dose of the subsequent course of treatment should be reduced by 20%. If the above-mentioned severe neutropenia occurs again, then reduce the subsequent treatment dose by 20%-25%. If the chemotherapy drug has been suspended for more than 2 cycles (6 weeks) from the expected treatment date, or if 2 doses are reduced into intolerance, the chemotherapy regimen should be permanently stopped (as shown in Table 3).

Table 2 Guidelines for Dose Adjustment Levels

	Starting dose	Dose level-1	Dose level-2	Dose level-3
Toripalimab	240mg	not allowed	not allowed	not allowed
Etoposide	100mg/m^2	Decrease 20%-25%	Decrease 20%-25%	stop drug
Cisplatin	25mg/m^2	Decrease 20%-25%	Decrease 20%-25%	stop drug
Carboplatin	AUC 5	Decrease 20%-25%	Decrease 20%-25%	stop drug

Table 3 Chemotherapy dose adjustments for cytotoxicity of etoposide, cisplatin, and carboplatin

adverse events		**treatment**
neutropenia	grade 3 (0.5-0.99×10^9/L)	Chemotherapy withheld until recovery to ≤Grade 1 (≥1.5 x 109/L); restart at full dose
	grade 4	1. Chemotherapy withheld until recovery to ≤ grade 1; all

	(＜0.5×10^9/L) (for 1 week or more)	subsequent doses reduced by 1 dose level 2. If it occurs for the second time after the dose reduction, the subsequent doses are all reduced by 1 dose level 3. If the third time occurs, stop chemotherapy.
Thrombocytopenia	grade 2	1. Chemotherapy withheld until back to normal; restart at full dose
	⩾ grade 3	1. Chemotherapy withheld until recovery to ⩽ grade 1; all subsequent doses reduced by 1 dose level 2. If it occurs for the second time after the dose reduction, the subsequent doses are all reduced by 1 dose level 3. If the third time occurs, stop chemotherapy.
Renal insufficiency	⩾ grade 3	1. Chemotherapy withheld until recovery to ⩽ grade 2; all subsequent doses reduced by 1 dose level 2. If it occurs for the second time after the dose reduction, the subsequent doses are all reduced by 1 dose level 3. If the third time occurs, stop chemotherapy.

Note: The investigator may decide to use supportive measures/treatment and/or secondary prevention in the next cycle instead of lowering the dose if the patient's best interest is considered and consistent with local practice. Dose adjustment recommendations are provided for informational purposes only.

8.1.3 Treatment Allocation and Blinding

8.1.3.1 ID code

After the subjects sign the informed consent form, the researcher will assign an

identification code to them according to the order of enrollment. The code consists of 3 digits and represents the serial number of the subject. The researcher will fill in the identification code in the "Subject Identification Code Table" and save. This test is an open study without blinding.

8.1.3.2 Enrollment randomization

All subjects in this trial were included in the single-arm trial group, and no randomization control was required.

8.1.4 Compliance Control

In this trial, all subjects were required to return to the hospital as scheduled to complete all medication cycles and related inspections in accordance with the requirements of the protocol. The number of drug cycles, the amount and duration of the test drug actually received by the subject in each cycle, and the reasons for violating the treatment plan should be recorded in the original medical records and CRF to judge the compliance of the subject. The researchers need to maintain close contact and communication with the subjects, and try to explain the subjects' doubts about any medical operation and medical event during the research process. At the same time, inform that low compliance may be required to withdraw from the trial to improve the compliance of the subjects.

8.2 Experimental constraints

8.2.1 Permitted concomitant medications and treatments

- Can receive usual standard supportive care
- Acceptable treatment for any underlying medical condition (including diabetes)

8.2.2 Prohibited concomitant medications and treatments

- No other clinical investigational drugs are allowed during the study
- Chemotherapy drugs other than those specified in this protocol are not allowed to be used during the study
- Other systemic anti-tumor treatments are not allowed before progression, including chemotherapy, radiotherapy, radiofrequency ablation, molecular targeted therapy, etc.

8.2.3 Necessary concomitant medications and treatments

• Correspondingly sensitive antibiotics must be used in case of infection

• For information on other drugs that may interact with the study drug and affect its metabolism, pharmacokinetics, or excretion, refer to the relevant drug leaflet

• Any concomitant medication or treatment during the study should be accurately documented in the medical record and CRF

8.2.4 Subject constraints

• Must return to the hospital on time to complete all inspections and laboratory tests required by the plan

• Cannot leave the hospital during inpatient treatment

• Need to promptly report any discomfort to the investigator

• Women of childbearing age are required to take appropriate contraceptive measures throughout the treatment period of the trial and for 6 months after the end of the trial.

9 Treatment Evaluation

9.1 Screening Period Evaluation

Enrollment assessments must be completed within 14 days prior to study drug administration. After obtaining informed consent, the investigator will conduct a corresponding clinical assessment of the subject (see 6.1 and 6.2).

9.2 Evaluation during treatment

Corresponding clinical assessments (see 6.4.4 and 6.4.6) are required for the subjects before the start of each treatment cycle and within 3 days after the completion of the treatment cycle, so as to make a correct efficacy assessment (see below).

9.3 Efficacy Evaluation

9.3.1 Efficacy variables

- see 3.4.3

9.3.2 Procedure description

- see 3.2.2

9.4 End of Study Treatment (EOT) Assessment

An EOT assessment should be performed on all patients who complete study treatment, and the following procedures will be completed:

- Physical examination, weight, vital signs, ECOG score
- Concomitant medications and concomitant therapy evaluation
- Serum EBV DNA copy number
- Blood routine, liver and kidney function, blood sugar
- Imaging studies based on follow-up time
- Evaluation for peripheral neuropathy
- Assessment of adverse events (see 10.3)

9.5 Follow-up of disease recurrence and metastasis

See 6.5, 6.6, 6.7

9.6 Follow-up of overall survival

See 6.5, 6.6, 6.7

10 Safe variables

10.1 Variables and Procedure Descriptions

- Symptoms and signs
- laboratory tests
- Adverse Events (AEs) and Serious Adverse Events (SAEs)

Any abnormal symptoms, signs (including laboratory test results with clinical significance) or medical diagnosis recorded by the medical staff from the enrollment to the trial drug treatment of the subjects must be recorded in the medical records and CRF.

After enrollment, the researchers need to conduct corresponding laboratory tests according to the protocol, and record the results in the medical records and CRF. Abnormal results with clinical significance should be recorded as adverse events.

10.2 Symptoms and signs

10.2.1 Medical History and Concomitant Medications

A complete medical history of the subject needs to be recorded. All concomitant medications from the first day of cycle 1 to 30 days after the last use of the test drug need to be recorded, including changes in dosage and reasons for use, etc.

10.2.2 Physical examination and weight

A complete physical examination should include, but is not limited to, evaluation of the vital organs of the body:

- Head, ears, eyes, nose, throat
- Lungs and respiratory system
- Cardiovascular System
- Gastrointestinal system
- Central Nervous System
- skin
- lymphatic system
- musculoskeletal system
- Endocrine and metabolic system

All discrepancies from the baseline examination should be documented in the medical record and CRF.

10.2.3 ECG

ECGs were performed before and after each treatment cycle, including a baseline ECG assessment prior to the first treatment cycle. Any clinically significant change from baseline should be reported as an adverse event and recorded in the subject's medical record and CRF.

10.2.4 Imaging examination

Imaging evaluations, including CT scans, should be performed according to protocol requirements, including baseline CT examinations before the first treatment cycle. Any clinically significant change from baseline should be reported as an adverse event and recorded in the subject's medical record and CRF. If additional imaging evaluations are performed as part of the subject's routine examination, they will also need to be evaluated and determined to be an adverse event.

10.3 Adverse Events

10.3.1 Definition

Any undesired treatment-related or unrelated medical event after the use of a drug by a subject in a clinical trial is an adverse event. It can be any unfavorable and unexpected signs, symptoms, abnormal results of laboratory tests, whether related to drugs or not. All adverse events should be recorded in the CRF form. The intensity of adverse events was graded according to the grading method recommended by the NCI Common Toxicity Criteria Grading System.

During site visits, clinical monitors must systematically collect and verify information on adverse events when reviewing patients' clinical records (raw data check). Unresolved adverse events at the time of assessment require continued follow-up until resolution. For adverse events that cannot be resolved during the clinical possible observation period (such as blindness, neurotoxicity, loss of limbs, etc.), the investigators will rate them as permanent unresolved events, and the resolution time of the event in the CRF table will be left blank.

10.3.2 Adverse Event Correlation

Investigators should evaluate the possible association between adverse events, study drugs and combined drugs, and evaluate according to the following 5-level classification criteria:

(1) Definitely related: the reaction appears in a reasonable time sequence after administration, and the reaction conforms to the known reaction type of the suspected drug; it improves after stopping the drug, and the reaction reappears after repeated administration.

(2) Possibly related: the reaction appears in a reasonable time sequence after administration, and the reaction is consistent with the known reaction type of the suspected drug; the patient's clinical status or other treatment methods may also produce the reaction.

(3) Possibly irrelevant: the reaction does not conform to the reasonable time sequence after the drug, and the reaction does not conform to the known reaction type of the suspected drug; the patient's clinical status or other treatment methods may produce the reaction.

⑷ Irrelevant: The reaction does not conform to the reasonable time sequence after drug administration, and the reaction is consistent with the known reaction type of the non-test drug; the patient's clinical state or other treatment methods may produce the reaction, and the disease state improves or other treatment methods are discontinued. , repeated use of other treatment methods to respond.

(5) Unable to assess: The occurrence of the reaction has no clear relationship with the time sequence after the drug, and is similar to the known reaction type of the drug, and other drugs used at the same time may also cause the same reaction.

The above items (1), (2) and (5) were recorded as the adverse reactions of the drugs in this study.

Incidence rate of adverse reactions = number of adverse reactions/total number of cases × 100%.

10.3.3 Serious Adverse Events

A serious adverse event was defined as an unexpected adverse event at any drug dose that met any of the following criteria: 1) resulting in death; 2) life-threatening due to the trial drug; 3) resulting in hospitalization or Prolonged hospital stay; 4) permanent or significant loss of function/disability; 5) teratogenic or carcinogenic.

Some events requiring hospitalization or prolonged hospitalization may not be reported as serious adverse events, including: 1) hospitalization due to social reasons rather than adverse events; 2) hospitalization for elective surgery, examination or other treatment that has been booked before entering the study. 3) Tumor progression and related events.

10.3.4 Report Form

Reporting of serious adverse events requires the use of the SAE reporting form.

10.3.5 Serious Adverse Event Reporting – Investigator Procedures

Reporting of serious adverse events requires the use of the SAE reporting form. When a serious adverse event occurs (drug-related or not), the investigator should send the completed initial report to the team leader unit, Sun Yat-sen University Cancer Center Ethics Committee (Tel: 020-87343363) within 24 hours (Guangzhou Sun Yat-Sen University Cancer Prevention and Control Center, Tel: 020-87343363),

and report the final report (including the outcome of serious adverse events, etc., if the serious adverse event is death, there is no need to post the final report) as soon as possible and report to the above department again .

10.3.6 Assessment and recording of immune-related adverse events

Because of the potential for autoimmune disease with anti-PD-1 therapy, the investigators considered immune-related AEs to be classified as immune-related AEs (irAEs) and identified as irAEs on the CRF AE page until day 90 after treatment discontinuation .

Investigators should refer to Appendix 3 for guidelines on the diagnostic evaluation and management of irAEs, which are commonly seen with the use of immune checkpoint inhibitors.

An exhaustive list of potential irAEs is presented in Table 5. Individual conditions similar to the listed irAEs should be evaluated to determine whether these are irAEs according to a diagnostic process similar to the reactions described in more detail in Appendix 3.

10.3.6.1 Management of Adverse Events of Special Attention

As a routine precaution, patients must be monitored for at least 1 hour in an area equipped with resuscitation equipment and rescue medication after the toripalimab infusion on Day 1 of Cycle 1 and Cycle 2. Beginning with cycle 3, monitoring is required for at least 30 minutes in an area equipped with resuscitation equipment and first aid medication.

According to the NCI-CTCAE, the management of infusion-related reactions, severe hypersensitivity reactions, and irAEs is outlined below.

- **Infusion-related reactions**

Symptoms of infusion-related reactions include fever, chills/rigidity, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia,

dizziness, or hypertension. Severe reactions can include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be monitored closely for such reactions. If an infusion-related reaction occurs, immediate admission to an intensive care unit or equivalent setting and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be administered.

Table 4 Treatment Modifications for Study Drug-Induced Infusion Reaction Symptoms

NCI-CTCAE level	**Treatment adjustments for toripalimab**
Grade 1 - Mild Mild transient reaction; does not indicate interruption of infusion; does not indicate intervention	Infusion speed decreased by 50%. All deterioration should be closely monitored. Medical management as needed. Subsequent infusions should be performed after the administration of the prechemotherapy drug, and the infusion should be completed at a reduced infusion rate.
Grade 2 - Moderate Indicates interruption of therapy or infusions, but responds rapidly to symptomatic therapy (eg, antihistamines, NSAIDs, narcotics, IV fluids); suggests prophylaxis for ≤ 24 hours	Stop the infusion. If the infusion-related reaction has resolved or the severity has been reduced to Grade 1, the infusion can be resumed at 50% of the previous rate. All deterioration should be closely monitored. Proper medical management should be planned as described below. Subsequent infusions should be performed after the administration of the prechemotherapy drug, and the infusion should be completed at a reduced infusion rate.
Grade 3 - Severe Prolonged (eg, lack of rapid response to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; clinical sequelae suggestive of hospitalization.	Stop the infusion immediately. Proper medical management should be planned as described below. Patients should suspend study medication.
Grade 4 - life-threatening	Stop the infusion immediately. Proper medical management

Life-threatening consequences; prompt urgent medical attention.	should be planned as described below. Patients should suspend study medication. Hospitalization is recommended.

If the toripalimab infusion rate is reduced by 50% or suspended due to an infusion-related reaction, the reduced rate must be maintained and chemotherapy premedication administered for all subsequent infusions. If the patient experiences a second infusion-related reaction (≥Grade 2) with a slower infusion rate, the infusion should be discontinued and toripalimab therapy should be discontinued in the patient.

NCI-CTCAE Grade 1 or 2 Infusion Reactions: Appropriate medical management should be instituted based on the type of reaction. These include, but are not limited to, antihistamines (eg, diphenhydramine or equivalent), antipyretics (eg, paracetamol or equivalent), and if consideration suggests oral or intravenous use, corticosteroids, epinephrine , bronchodilators and oxygen. In the next cycle, patients should receive an oral antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent) as prechemotherapy and should be closely monitored for clinical signs and symptom.

NCI-CTCAE Grade 3 or 4 Infusion Reactions: Immediately institute appropriate medical management measures based on the type and severity of the reaction. These include, but are not limited to, oral or intravenous antihistamines, antipyretics, corticosteroids, epinephrine, bronchodilators, and oxygen.

- **Severe allergic reactions and flu-like symptoms**

If hypersensitivity reactions occur, patients must be treated according to best available medical practice as described in the Complete Guidelines for the Emergency Management of Anaphylaxis developed by the Resuscitation Council (UK) Working Group. Patients should be instructed to report any delayed reactions to the investigator immediately.

If systemic / rapid anaphylaxis occurs (typically within minutes of drug / antigen administration, it is characterized by respiratory distress; laryngeal edema; and / or

intense bronchospasm; and is usually followed by vascular collapse or shock, and previous dyspnea disappears; skin manifestations, such as itching and urticaria with / without edema. And gastrointestinal manifestations, such as nausea, vomiting, spasmodic abdominal pain and diarrhea), infusion must be stopped immediately and the patient must be arranged to withdraw from the study.

If anaphylaxis is observed, the patient will receive an injection of epinephrine and an infusion of dexamethasone, followed by immediate monitoring of the patient and notification to the intensive care unit, which may require transfer if necessary.

To prevent flu-like symptoms, 25 mg of indomethacin or an equivalent dose of NSAIDs (i.e., 600 mg ibuprofen, 500 mg naphthalene Proprietary Sodium). Alternative treatment for fever (ie, paracetamol) may be given to the patient at the investigator's discretion.

- **Immune-related adverse events**

Immune-related AEs deserve special attention in this study. If the following events or similar events occur, the investigator should rule out other explanations (such as co-medication, infectious disease, metabolic, toxin, PD, or other neoplastic causes) and perform appropriate diagnostic tests, including but not limited to serology, immunology and histological (biopsy) data. If other causes have been ruled out, the AE requires the use of systemic steroids, other immunosuppressants, or endocrine therapy; and the AE is consistent with an immune-mediated mechanism of action, the irAE index in the AE CRF should be checked.

A list of potential irAEs is presented in Table 5 below. In patients receiving toripalimab, all conditions similar to those listed should be evaluated to determine whether they are immune-related.

Based on the guidelines of the European Society of Medical Oncology and the American Society of Clinical Oncology, recommendations on diagnostic evaluation and management of irAEs are given. Common immune-related toxicities are listed in Appendix 3. For all adverse events not included in Appendix 3, please refer to the American Society of Clinical Oncology Clinical Practice Guidelines for further

guidance on the diagnostic evaluation and management of immune-related toxicities.

Table 5 Immune-related adverse events

body organ system affected	event
Skin (mild-common)	Pruritus or maculopapular rash; Vitiligo
skin (moderate)	Folliculitis or urticarial dermatitis; erythematous/lichenoid rash; acute febrile neutropenic dermatosis
Skin (severe-rare)	Full Thickness Necrolysis/Stevens-Johnson Syndrome
gastrointestinal tract	Colitis (including diarrhea with abdominal pain or endoscopic/radiological evidence of inflammation); pancreatitis; hepatitis; elevated transaminases (ALT/AST); bowel perforation
endocrine	Thyroiditis, hypothyroidism, hyperthyroidism, hypophysitis with features of hypopituitarism such as fatigue, weakness, weight gain, insulin-dependent diabetes mellitus, diabetic ketoacidosis, adrenal insufficiency
breathe	Noninfectious pneumonia/diffuse alveolitis
eyes	Episcleritis; Conjunctivitis; Conjunctivitis/Uveitis
neuromuscular	Arthritis, arthralgia, myalgia, neuropathy, Guillain-Barre syndrome, aseptic meningitis, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myositis
blood	Anemia, leukopenia, thrombocytopenia
kidney	Interstitial nephritis, glomerulonephritis, acute renal failure
heart	Pericarditis, myocarditis, heart failure

Recommendations for the management of irAEs are detailed in Appendix 3.

Study drug was discontinued if toxicity did not decrease to Grade $\leqslant$1 within 12 weeks. Treatment should be permanently discontinued in patients who recur with an event of the same or greater severity.

10.4 Pregnancy Events in Clinical Trials

Any subject participating in the trial should notify the organizer if a pregnancy

event occurs. Although pregnancy is strictly speaking not an AE, all pregnancy situations need to be followed up to the end for results to be judged. This information is of great relevance to drug safety and public health. It is the investigator's responsibility to report all pregnancies in the trial using the pregnancy event reporting form.

If a pregnancy event occurs within 30 days of using the test drug or stopping the test drug, the investigator or his partner should contact the superior competent authority to discuss the management of the subject. The content of the report of the pregnancy event includes the expected date of delivery, and the report form of the pregnancy event shall be submitted within 24 hours after the occurrence of the pregnancy event according to the procedure for reporting the SAE. If the pregnancy needs to be terminated, the estimated time of termination is required.

If the spouse of the subject has a pregnancy event instead of the subject himself, the completion of the pregnancy event report form needs to include the subject's screening number, initials, and date of birth. Details about the spouse need to be recorded in the Narrative section of the Pregnancy Event Report form. Subjects/spouses should be followed up until the end of the trial. If the pregnancy is terminated before the expected date of delivery, the investigator needs to truthfully record this situation. After the pregnancy is over, the investigator needs to record and determine the pregnancy results.

11 Withdrawal and Discontinuation of Research Regulations

11.1 patient withdrawal

Patients can withdraw from clinical trials at any time and for any reason, and it will not affect the rights of researchers to treat their diseases. From the perspective of the interests of the subjects, the researchers have the right to ask the subjects to withdraw for any reason, including concomitant diseases, adverse events or treatment failure. The Clinical Research Core Group reserves the right to ask subjects to withdraw due to protocol violations, administrative reasons, or other valid and ethical reasons.

Although the withdrawal of subjects should be avoided as much as possible, it is necessary to know that withdrawals of subjects will occur in clinical research. Regardless of when the subject withdraws from the study for any reason, the subject's final study assessment must be completed and the reason for withdrawal must be indicated. All documentation on the subject must be as complete as possible. As long as the patient did not withdraw his consent, these withdrawn patients were followed up and the disease was recorded as if they had not withdrawn.

Investigators must follow up those who drop out due to poor compliance to obtain reasons for non-attendance. When a patient withdraws, the study will do its best to complete and report observations as comprehensively as possible. As long as the patient does not withdraw his consent, these patients will continue to be followed if possible and their disease recorded as if they had not withdrawn.

Withdrawals due to concomitant diseases or adverse events must be documented in detail on the observation form, along with all other appropriate and valuable information.

11.2 Early Termination of Study

Reasons for early termination may include external events, recurrence of serious adverse events, increased treatment-related mortality, or insufficient enrollment in clinical trials. All investigators will be notified in writing when the clinical study is terminated early. Any researcher who wants to stop participating in this clinical study must immediately inform the principal investigator of his/her decision.

11.2.1 Study follow-up

11.2.2 follow-up time

Subjects were followed up after the end of treatment or withdrawal from the study for other reasons, and the follow-up was once every three months, and changed to once every six months after two years, until the end of the whole study.

11.2.3 Follow-up content

Subject follow-up includes collection of subject complaints, physical examination, blood and urine routine, biochemical routine and tumor evaluation. The above-mentioned follow-up visits were recorded in the original medical records. The

content of tumor evaluation should be filled in the CRF form.

12 Statistical analysis

12.1 Statistical analysis population

- Full analysis population (FAS): includes all subjects who entered randomization and received at least one study drug (experimental drug or control drug). The FAS is the primary data set for the evaluation of the primary and secondary efficacy measures.
- Population according to the protocol (PPS): including all those in the analysis set who did not have major protocol deviations, completed the study according to the protocol or observed the second analysis endpoint of the trial, did not receive other combined treatments that may affect the efficacy of the study drug during the period, and maintained Subjects with good compliance. The division standard is determined by the research party and the statistical party before data analysis.
- Safety Analysis Population (SS): Include all subjects who have received the study drug once and have safety records after administration.

12.2 Statistical method

After the test plan is determined, professional statisticians and the main researchers will negotiate to formulate a statistical analysis plan. SPSS 18.0 statistical software was used. All statistical tests used one-sided or two-sided tests as needed, and a P value less than 0.05 was considered statistically significant. The description of quantitative indicators will calculate the mean, standard deviation, median, minimum value, maximum value, lower quartile, upper quartile, and classification indicators describe the number of cases and percentages of each category. The comparison of the general conditions of the two groups will use corresponding analysis methods according to the type of indicators, and the comparison of quantitative data between groups will use paired sample t test or Wilcoxon rank sum test. Chi-square test or Fisher's exact probability method was used for categorical data, and Wilcoxon rank sum test or CMH test for hierarchical data.

12.2.1Enrollment and completion

In principle, all patients who meet the inclusion/exclusion criteria can be enrolled, and the number of enrollment and completion is summarized, and a list of dropped cases is listed. Different data set size, case distribution, total dropout rate comparison, and detailed list of termination reasons for each group. Describe the patient's demographic characteristics (age, height, vital signs, etc.), medical history, and medication history, and compare the age, height, and weight of the two groups to measure the comparability of the data.

12.2.2 Adherence analysis

- Medication compliance analysis: Follow up whether the patient is using the test drug on time and in the right amount, and whether the drug and food prohibited in the protocol are not used
- Combined drug analysis: It is necessary to count the number of combined drugs and make a detailed list to statistically analyze the potential impact of combined drugs on the efficacy of experimental drugs

12.2.3 Baseline Data Analysis

According to the baseline check indicators listed in 6.2, the n value, mean, standard deviation, median, minimum value, and maximum value will be described for continuous data, and the frequency and percentage of each group will be described for categorical data.

12.2.4 Efficacy analysis

The analysis objects are FAS and PPS

12.2.4.1 Primary efficacy analysis

Progression-free survival (PFS) will be analyzed using Kaplan-Meier curves depicting the change in the experimental group during the analysis. Subjects who withdraw from the trial early before the study analysis will be censored at the time of the last tumor imaging assessment or the last follow-up visit (whichever is later).

12.2.4.2 Secondary efficacy analysis

The objective response rate (ORR) is the proportion of subjects with complete remission and partial remission according to the efficacy evaluation to the total number of subjects. Overall survival (OS) will be analyzed using Kaplan-Meier

curves depicting the changes in the experimental groups during the analysis. Subjects who withdraw from the trial early before the study analysis will be censored at the time of the last tumor imaging assessment or the last follow-up visit (whichever is later).

12.2.5 Safety Analysis

Including monitoring and recording all AEs and SAEs (including the number of events and the incidence of subjects), routine blood and biochemical indicators, body weight, vital signs, physical examination, and all treatments and concomitant medications. Safety indicators include: body weight, vital signs, clinical laboratory parameters, AE, etc. For laboratory parameters, actual values at each assessment, values changed from baseline, and abnormal classification (below, normal, or above reference range) will be tabulated by treatment group, over time. For body weight and vital signs, the actual value and baseline change value at each evaluation will be tabulated according to the treatment group and the change over time.

The ratio of the number of subjects with AEs during treatment to the number of subjects eligible for safety evaluation was used

To represent the incidence of AE. AE rates will be summarized using the Study Data Coding System (MedDRA) organ class and standard terminology. AEs that occurred during treatment were defined as AEs that occurred on or after the day of the first dose to the day of or before the last dose + 30 days or the day when the treatment was terminated. The severity of toxic reactions was graded according to NCI-CTCAE version 5.0. When analyzing by subject, subjects with the same event occurring more than once are only counted once, and the worst CTCAE grade event is selected.

All AEs are listed and described in detail in terms of type, grade, frequency of occurrence, severity, duration, relationship with trial drugs, treatment measures and outcomes, etc.

12.3 Sample size calculation

This study is a single-arm design. According to the existing clinical data, the

parameters for calculating the sample size are as follows:

1. Enrollment time = 24 months, follow-up time = 12 months (the overall time is 36 months), referring to the previous research results and the historical comparison of our center, the PFS of chemotherapy alone = 5 months, assuming that the PFS of chemotherapy combined with immunotherapy increased to 10 months.

2. α =0.05 (two-sided).

3. The test has a power of 90%.

Based on the above parameter considerations, according to the logrank test of single-arm PFS, 30 subjects are required. Considering the dropout rate of 10% during the study, 33 subjects were finally required to be enrolled.

13 Regulatory matters

13.1 Ethics and compliance with GCP

All researchers must comply with the requirements of the International Conference on Harmonization (ICH) Guideline E6 in terms of Good Clinical Practice (GCP) on drug clinical research management practices, ethical regulations, and research protocols to implement research.

- Institutional Review Board/Ethics Committee (IRB/EC) Approval: Investigators should obtain IRB approval of the study protocol, revisions to the study protocol, informed consent, investigator brochure, and any File approval is required.
- Ethical considerations for research implementation: research protocols and SOPs must comply with the GCP requirements and the Declaration of Helsinki on human medical research ethics.
- Subject Information and Informed Consent: The Principal Investigator or his authorized person will be responsible for obtaining informed consent. The context of the study and the benefits and risks of participating in the study should be clearly explained. The subjects will obtain a copy of the signed and dated informed consent form, and the researcher will keep the original. Confirmation of informed consent should be recorded in the subject's medical records before any testing or intervention (including screening and evaluation) is performed according to the research protocol.

• Subject data protection: Subjects shall not be identified by name in any study report. Research reports are for research purposes only. Every effort will be made to ensure the confidentiality of subjects' personal medical data.

13.2 Responsibilities of the researcher

• Ensure that staff assisting with the study are fully aware of the protocol, revisions, study treatments, and study-related responsibilities and functions. The Investigator shall maintain a list of Assistant Investigators and other qualified personnel who have been assigned significant research-related responsibilities.

• Responsible for maintaining records of all patients who have signed informed consent and been screened for study entry. For patients who fail screening, the reason must be documented in the patient's source file.

• During monitoring visits, investigators or their authorized personnel must review data, resolve queries, and allow direct access to patient records (medical records, study-related charts, etc.) for primary data reconciliation. Investigators must complete the CRF in a timely and accurate manner.

13.3 Informed consent

Before subjects are enrolled in the trial, the researchers must explain to them the purpose, methods, possible benefits, potential risks and possible discomforts of the trial. Inform the subjects that participation in the trial is voluntary, that they can withdraw at any time, and that participation in the trial has no effect on the treatment of their disease. The privacy of the subjects will be protected. The subjects or guardians should have enough time to read the informed consent form and ask questions. Before being selected, the subjects or their guardians must sign the informed consent form, and the subjects keep a copy of the informed consent form.

13.4 Good Clinical Practice (GCP)

This clinical study will be conducted in accordance with the "Declaration of Helsinki" and China's Good Clinical Practice (GCP). The research protocol must be approved by the Ethics Committee of the clinical research unit before it can be

implemented. The researchers will ensure that the clinical research is carried out in compliance with the laws, regulations, scientific and ethical standards of the People's Republic of China on medical research. If it is found that the research protocol needs to be revised during the research process, the revised research protocol must be submitted to the ethics committee of the responsible unit for record/approval before implementation. If important new information related to the research drug is found, the informed consent must be revised in writing and sent to the ethics committee of the responsible unit for approval, and the subject’s consent must be obtained again.

13.5 Confidentiality of Subject Personal Data

In this trial, only the information needed for research on the effectiveness and safety of the drug was collected. When collecting and using these data, relevant laws and regulations on the protection of privacy will be complied with.

13.6 Plan revision

If necessary during the research process, the research protocol can be revised to guide the next step of the research. The revision of the protocol must comply with the relevant regulations of GCP. The researchers and the organizers will formulate a revised draft of the protocol according to the progress of the research, and it must be reviewed and approved by the ethics committee before it can be implemented. Protocol revisions approved by the ethics committee must be part of the revised protocol.

13.7 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the study begins, the study protocol, informed consent form, and any other corresponding documents will be submitted to the IRB/EC with a cover or form listing the submitted documents, date of issue, and the research center to be approved. Documentation will also be submitted to regulatory agencies as required by local law, if applicable.

13.8 Research Progress Plan

- Trial start date: December 2022
- Trial end date: December 2024

14 Data Management and Record Keeping

14.1 Data handling

14.1.1 Data handling

The researcher needs to fill in the data of the enrolled subjects into the CRF, and the patients who fail the screening do not need to fill in. Researchers should ensure that the data filled in the CRF is accurate and complete, and at the same time keep the original records intact. The CRF filling of each enrolled subject must be completed on time. After the completed CRF was reviewed, it was handed over to the data administrator of this trial for data entry and management.

14.1.2 Data input

The data entry and management are in the charge of the designated data management unit. Data administrators use computer software to compile data entry programs for data entry and management. In order to ensure the accuracy of the data, it should be proofread by others after the input is completed.

14.1.3 Medical Information Coding

Coding of medical information will use the following tools:

- MedDRA 11.0 (Medical History and Adverse Events)
- WHO Drug 2008.03 (concomitant medication)
- NCI-CTCAE 5.0 (Toxic Reaction)

14.1.4 Data audit

The main researchers, data managers, and statistical analysts will review the established database, and lock the database after confirming the research data set and statistical analysis plan.

14.2 Record keeping

According to the GCP guidelines, the principal investigator must keep all data

related to the clinical trial, such as the subject's medical records, drug disposal records, signed informed consent, and approval documents from the ethics committee, for 5 years after the termination of the clinical trial.

14.3 Privileges for raw data/documents

Any observations and inspection results in clinical trials should be recorded in the medical records and correctly filled in the CRF by the researchers in a timely, accurate, complete, standardized, and truthful manner. It is not allowed to be changed arbitrarily. If it is really due to a mistake, the researcher should keep the original record clear and legible when making any correction, and the corrector should sign the name and time. Raw data/documents must be properly kept in the research center in accordance with the requirements of ICH GCP and local regulations.

The higher-level competent department and the drug supervision and management department can monitor, inspect, and inspect the clinical trial implementation process and original data/source documents. Inspectors, inspectors, and regulatory authorities have the right to check all original data/source documents related to the test, but have no right to modify them. If a problem is found, the researcher must be notified to make corrections and sign.

15 Specimen Collection and Storage

15.1 Specimen Collection Standard Operating Procedures

Subject specimens were collected according to the standard operating procedures (SOP) for the collection of blood samples and tumor tissue specimens in the tissue bank of our hospital.

15.2 Specimen storage

Subject specimens are stored by the principal investigator. After the patients signed the informed consent to enroll in the group, their postoperative tumor tissue will routinely retain paraffin and frozen specimens. After all subjects are enrolled, the tumor specimens (paraffin) will be made into tissue chips. After the blood sample is centrifuged, the serum and blood cells are stored separately.

16 Quality Control and Quality Assurance

16.1 Data Quality Assurance

In order to ensure the integrity, accuracy and reliability of the data, the following measures were taken in this study: Qualified and experienced research units and researchers were selected. Before the start of the study, use lectures and written materials to introduce the content of the research plan to the researchers in detail, and jointly formulate solutions to possible problems; the completeness and accuracy of the data are regularly checked by the inspector; if the data is found to be in doubt , should be communicated with the researchers in a timely manner and confirmed or corrected; in the statistical stage, the data should be checked blindly. If there is a deviation, it will be confirmed or corrected by the researcher.

16.2 Monitor

16.2.1 Purpose of inspection

Ensure that clinical trials are carried out in strict accordance with the protocol and relevant regulations, ensure data integrity, reliability and consistency of multi-center data, and coordinate the uniformity of trial progress.

16.2.2 The content of the audit

Supervisors regularly visit clinical research units to monitor and report on the progress of the trial. Supervisors have the right to check the original data of all patients related to this study. The monitoring content mainly includes: whether the subjects meet the inclusion criteria; whether the filling of the case report form (CRF) is timely, accurate, complete, and credible; whether the methods and doses of the subjects' medication meet the requirements of the protocol. Whether all adverse events are recorded in the CRF form; at the same time, ensure that all errors or omissions are corrected, and are signed and dated by the researcher.

Inspectors are also responsible for transmitting various forms of data, including normal value data of clinical tests, to ensure that there is a scientific and consistent clinical testing system between the participating units and the team leader unit.

If there are serious adverse events or deaths (including chemotherapy-related deaths) related or unrelated to this study during the clinical trial, the managing doctor

or the hospital shall take appropriate measures immediately.

17 Inspect

The sponsor may have representatives visit the research unit to check all the research records of this trial, including original documents, and compare them with the CRF form. Before the audit, the research unit will be notified to make appropriate preparations. Drug regulatory agencies may conduct similar inspections. In this case, the investigator should notify the sponsor immediately.

18 Post Policy

The results of this study can be published in medical journals, journals or used for teaching purposes. In addition, this study and its results may be submitted for inclusion in all appropriate health agency registries of research and published on health agency research registry websites (eg, ClinicalTrials.gov), as required by local health agency regulations. The first author is selected based on several considerations, including but not limited to: research participation, contribution to protocol development, and analysis and input in the research manuscript, relevant abstracts and presentations.

19 Clinical Trial Management Information

19.1 Organizational Units

Unit: Sun Yat-sen University Cancer Center

Address: No. 651, Dongfeng East Road, Guangzhou

Tel: 020-87343088

Zip code: 510060

20 参考文献

1. Koay, E., et al., *A Surveillance, Epidemiology, and End Results analysis of small cell carcinoma of the bladder: epidemiology, prognostic variables, and treatment trends.* 2011. **117**(23): p. 5325-33.
2. Nagumo, Y., et al., *Prognostic significance of non-urothelial carcinoma of bladder: analysis of nationwide hospital-based cancer registry data in Japan.* 2020. **50**(9): p. 1068-1075.
3. Furtado, P., et al., *Review of small cell carcinomas of the prostate.* 2011. **2011**: p. 543272.
4. Farci, F., et al., *Primary small cell carcinoma of the ureter: Case report and review of the literature.* 2018. **97**(24): p. e11113.
5. Mukesh, M., et al., *Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network.* 2009. **103**(6): p. 747-52.
6. Ismaili, N., et al., *Outcome of recurrent and metastatic small cell carcinoma of the bladder.* 2009. **9**: p. 4.
7. Siefker-Radtke, A., et al., *Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer.* 2009. **27**(16): p. 2592-7.
8. Sroussi, M., et al., *Neuroendocrine Carcinoma of the Urinary Bladder: A Large, Retrospective Study From the French Genito-Urinary Tumor Group.* 2020. **18**(4): p. 295-303.e3.
9. Priemer, D., et al., *Small-cell Carcinomas of the Urinary Bladder and Prostate: TERT Promoter Mutation Status Differentiates Sites of Malignancy and Provides Evidence of Common Clonality Between Small-cell Carcinoma of the Urinary Bladder and Urothelial Carcinoma.* 2018. **4**(6): p. 880-888.
10. Choong, N., J. Quevedo, and J.J.C. Kaur, *Small cell carcinoma of the urinary bladder. The Mayo Clinic experience.* 2005. **103**(6): p. 1172-8.
11. Bellmunt, J., et al., *Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.* 2017. **376**(11): p. 1015-1026.
12. Sharma, P., et al., *Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial.* 2017. **18**(3): p. 312-322.
13. Powles, T., et al., *Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial.* 2018. **391**(10122): p. 748-757.
14. Horn, L., et al., *First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer.* 2018. **379**(23): p. 2220-2229.
15. Paz-Ares, L., et al., *Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial.* 2019. **394**(10212): p. 1929-1939.
16. Tang, B., et al., *Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients.* 2019. **12**(1): p. 7.
17. Wang, F., et al., *Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02).* 2021: p. JCO2002712.
18. Zheng, Y., et al., *A phase III study on neoadjuvant chemotherapy versus neoadjuvant*

toripalimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: Henan Cancer Hospital Thoracic Oncology Group 1909 (HCHTOG1909). 2021. **9**(1): p. 73.

21 Declaration of investigator

I would like to sign my name and agree to the following:

I have read the protocol, I agree to the protocol and acknowledge all necessary details to be carried out during the study described in the protocol. I will implement the program design and specific regulations and try to complete the research within the specified time. Under my management/supervision, I will give a copy of the protocol and related information to the researchers involved in the trial. I discuss these documents with them to make sure they fully understand the study protocol and study steps. I will inform them that this information is confidential and belongs to the research center and that it will not be disclosed to third parties. I understand that the ethics committee, the higher authorities, or the drug regulatory department may terminate or stop the recruitment at any time for any reason, or if I think it is necessary to protect the best interests of the subjects. I agree to conduct this research in full compliance with the requirements of the State Food and Drug Administration, the Ethics Committee, and ICH GCP.

Investigator's signature	Date