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

Informed consent form

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Research center： Sun Yat-sen University Cancer Center

Subject's initials：_____ Subject Screening No.：___

Dear Sir/Madam：

We invite you to participate in ”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”.

This study will be carried out in about 10 research centers nationwide, and about 33 subjects with locally advanced or metastatic genitourinary small cell carcinoma.

Please read the information below carefully before deciding whether to participate in this research study.

[Research Background and Introduction of Drugs]

Genitourinary small cell carcinoma is very rare, and common sites include bladder, prostate, ureter, etc. Among them, small cell carcinoma of the bladder accounts for about 1% of bladder tumors. According to the SEER database, the incidence of small cell carcinoma of the bladder(SCCB) is increasing, from 0.05/100,000 in 1991 to 0.14/100,000 in 2005. Most patients with SCCB are often at an advanced stage when they are diagnosed, and are prone to distant metastasis. Compared with urothelial carcinoma, SCCB is more aggressive and has a worse prognosis. 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 are mixed with adenocarcinoma components, and the rest are pure small cell carcinoma. The effect of comprehensive treatment is not good, and the median survival is less than one year. 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 at the time of diagnosis. The median survival time varies greatly between different case reports. In summary, genitourinary small cell carcinoma is rare and has a poor prognosis.

There is no treatment recommendation based on randomized clinical trials for

genitourinary small cell carcinoma. There are only some retrospective studies exploring treatment options. Some scholars believe that small cell carcinoma outside the lung can be treated with similar chemotherapy regimens for small cell lung cancer, including etoposide combined with cisplatin (EP) regimen. Although patients with metastatic small cell carcinoma of the bladder and small cell carcinoma of the prostate can obtain a high remission rate, the median survival time is only 7-13 months. However, the remission period of patients is often very short, most patients will relapse after treatment, and data on genitourinary small cell carcinoma receiving chemotherapy are limited. A prospective trial included 12 patients with stage IV small cell carcinoma of the bladder at the time of diagnosis, who received IA regimen (ifosfamide + doxorubicin) and EP regimen alternately, and three of these patients achieved complete remission and underwent consolidation surgery. The median overall survival (OS) of this cohort was 13 months, but only 1 patient remained disease-free at 28 months after initial treatment. A French multicenter retrospective study found that the first-line EP regimen in advanced metastatic patients had longer overall survival than the etoposide combined carboplatin (EC) regimen, but only 3 patients received immunotherapy in this study, Therefore, the role of immunotherapy in SCCB 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. Genetic profiling analysis found that small cell carcinoma of the prostate and small cell carcinoma of the bladder have some similarities, and the treatment is mostly combined with radiotherapy and chemotherapy based on small cell lung cancer. 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. Therefore, for patients with effective EP, an appropriate maintenance regimen to delay disease progression needs to be further explored.

Immunotherapy has been explored in bladder urothelial carcinoma and small cell

lung cancer. The KEYNOTE-045 study enrolled 542 patients with advanced urothelial carcinoma who had relapsed or progressed after platinum-based chemotherapy to compare the efficacy of pembrolizumab with chemotherapy (paclitaxel, docetaxel, vinblastine) , the results showed that the median OS in the pembrolizumab group was 10.3 months, and the ORR was 21.1%; the median OS in the chemotherapy group was 7.4 months, and the ORR was 11.0%, and the differences were statistically significant; The Checkmate-275 study found that the second-line overall ORR of nivolumab in patients with advanced urothelial carcinoma was 19.6%, and the median OS was 8.74 months. Anti-PD-L1 drugs also have a certain effect on patients with metastatic urothelial carcinoma, and the median OS of second-line treatment with atezolizumab is 7.9 months. 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 anti-PD-L1 drugs (atezolizumab, durvalumab) has been confirmed by a large number of studies to improve the OS of patients. Moreover, maintenance therapy with anti-PD-L1 drugs 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 extrapulmonary small cell carcinoma, there is not much evidence for immunotherapy combined with chemotherapy, and the choice of immune checkpoint inhibitors needs further exploration. Toripalimab is an anti-PD-1 drug independently developed by our country. It has been approved by the Chinese FDA for the first-line and later-line treatment of recurrent and metastatic nasopharyngeal carcinoma and melanoma. The exploration of toripalimab in other cancers such as esophageal cancer is in progress.

Based on the current domestic and foreign literature, immunotherapy combined

with chemotherapy has achieved great success in lung cancer, nasopharyngeal carcinoma, etc., and other tumor types are also exploring its efficacy through clinical trials. Therefore, this study aims to explore an effective salvage chemotherapy regimen for genitourinary small cell carcinoma, 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 genitourinary small cell carcinoma.

[Study design and study process]

This study focuses on patients with locally advanced/metastatic genitourinary small cell carcinoma (small cell carcinoma originating in the kidney, ureter, bladder, urethra, and prostate), and it aims to explore the efficacy and safety of toripalimab combined with EP or EC. If you are eligible and agree to participate in the study, you will start treatment with toripalimab plus EP (etoposide, cisplatin) or EC (etoposide, carboplatin). The research process includes three parts: screening period, treatment period and follow-up period.

- Screening period

If you agree to take part in this clinical trial, your doctor or a member of the research team will first evaluate whether this study is right for you. To determine this, you will undergo a comprehensive medical examination prior to enrollment, including:

- Medical History: Your doctor will ask questions about your medical condition and general health, as well as any recent medicines or other treatments you have taken. It is important to tell your doctor about all the medicines or other treatments you are taking, including any medicines you have bought yourself.

- Physical examination: Your doctor will perform a physical examination, including measurements of height, weight, heart rate, and blood pressure. Your doctor will also evaluate your activities of daily living.

- Laboratory tests: Your doctor will prescribe you a laboratory test list based on blood tests, including blood routine, biochemistry, urine routine, coagulation function, thyroid function, tumor markers and virology. You need to cooperate with the nurse to complete blood drawing and stool sample collection.

- Your doctor will likely look at your heart with an electrocardiogram or echocardiogram of the heart.

- Imaging: Your doctor will analyze your CT, MRI, bone scan and other imaging examination results to clarify the location and size of your lesion and other related information.

- If you are a woman of childbearing potential, you will be given a urine or blood pregnancy test 7 days before the start of study treatment to make sure you are not pregnant.

If the results of these tests suggest that participating in this clinical study may put your health at risk, your doctor will not advise you to enter this study and discuss other treatment options with you. However, if these test results show that you are suitable for the study, you can choose to join the clinical study.

➢ Treatment period

If you agree to participate in this study, you will receive toripalimab combined with EP (etoposide, cisplatin) or EC (etoposide, carboplatin) treatment, a course of treatment every 3 weeks. The drug administration can be suspended after 4 to 6 cycles. If you tolerate it well, you can continue chemotherapy after the investigator judges. You may be advised to increase the cycle of combination therapy. After chemotherapy is suspended, you can continue toripalimab maintenance therapy until your disease progresses or unacceptable adverse events/reactions occur, and

toripalimab can be used for up to 24 months.

- Physical examination: Your doctor will perform a physical examination, including measurements of height, weight, heart rate, and blood pressure. Your doctor will also evaluate your activities of daily living.

- Blood test: Before the start of each course of treatment, your doctor will issue you a test sheet for blood tests, including blood routine, blood biochemistry, urine routine, coagulation function, thyroid function, tumor markers, etc. You need to cooperate with the nurse to complete blood drawing and stool sample collection.

- Imaging: From the time of the first administration, tumor imaging evaluations (CT, MRI, orthopedics) were performed every 2 courses (6 weeks ± 7 days) for the first 6 courses. Subsequently, tumor imaging evaluation (CT, MRI, bone scan, etc.) will be performed every (9 weeks ± 7 days) to clarify your disease condition and the effect of drug treatment. The study doctor will make appropriate treatment decisions based on the results of the tumor assessment until your first objective imaging evidence of disease progression (PD).

- Your doctor may order an electrocardiogram to see how your heart is doing.

- Concomitant treatments: Your doctor will ask about recent medications or other treatments. It is important to tell your doctor about all the medicines or other treatments you are taking, including any medicines you have bought yourself.

- Record adverse events: Your doctor will ask you about any discomfort you have had since your last chemotherapy treatment, including when and how much it started, and whether it has gotten better.

➢ Follow-up period

The follow-up period starts when you finish the trial treatment. Follow-up for safety needs to be completed 90 days (±7 days) after the end of the trial treatment, including rechecking your blood routine, biochemistry, urine routine, electrocardiogram, CA199, thyroid function, taking stool samples, etc., as well as vital

sign measurements and a physical examination to assess the safety of your medication. After the end of the trial treatment, imaging examinations will be performed about every 90 days (±7 days) to evaluate the efficacy until your disease progresses, other anti-tumor treatments are used or the study ends, whichever occurs first. If your disease progresses or you start a new anti-tumor treatment, you will have a survival visit every 90 days (±7 days) to learn about your current disease status, follow-up treatment and survival information.

[Benefits and Risks]

What are the possible benefits of participating in this study?

Your medical condition may or may not improve with toripalimab plus EP (etoposide, cisplatin) or EC (etoposide, carboplatin)(At present, there is no sufficient evidence to prove that genitourinary small cell carcinoma chemotherapy combined with PD-1 monoclonal antibody therapy is superior to chemotherapy alone). Your tumor may or may not decrease in size.

You will not receive any additional compensation for taking part in this research study. After participating in this clinical study, all toripalimab drugs will be given away, and the chemotherapy drugs for EP (etoposide, cisplatin) or EC (etoposide, carboplatin) will be borne by you.

Your participation in this clinical study will provide important information for medical scientific research, including the efficacy and safety of triplumab combined with EP (etoposide, cisplatin) or EC (etoposide, carboplatin) in the treatment of locally advanced / metastatic genitourinary small cell carcinoma, which may help benefit the general population of genitourinary small cell carcinoma patients in the future.

What are the risks of this study?

As you know, medication usually produces adverse reactions, which need to be reported to your doctor immediately. The occurrence of adverse reactions is caused

by the mechanism of action of the drug itself, which does not mean that there is no curative effect, nor does it absolutely mean that the treatment should be terminated. You can also consult your responsible doctor about the situation. The research doctor will closely monitor your condition, and if there is an adverse reaction, you must inform your doctor in time, and your doctor will determine if you have any side effects. and other drugs will be used to treat you to reduce side effects or discomfort.

Adverse reactions of etoposide: reversible myelosuppression, including leukopenia and thrombocytopenia, mostly occurred 7-14 days after treatment and returned to normal after 20 days. Anorexia, nausea, vomiting, stomatitis and other digestive tract reactions, hair loss is also common. If the intravenous drip is too fast (< 30 minutes), there may be hypotension, laryngospasm and other allergic reactions.

Common adverse reactions of cisplatin: Cumulative and dose-related renal impairment is the main dose-limiting toxicity of cisplatin. If multiple courses of drugs are used repeatedly, nephrotoxicity will be prolonged and more severe. Neurotoxicity, characterized by peripheral neuropathy, both sensory and motor, can occur in some patients. Myelosuppression can occur in patients taking cisplatin; cisplatin causes severe nausea and vomiting in almost all patients. Nausea and vomiting usually begin 1-4 hours after treatment and can last up to a week after treatment. Hyperuricemia can occur in patients taking cisplatin. Mainly due to drug-induced nephrotoxicity. Hyperuricemia can be more significant in patients with doses > 50mg/m3, and it can reach the bee level 3-5 days after administration. Allopurinol can be used to reduce serum uric acid levels. Hypomagnesemia and hypocalcemia can occur after cisplatin treatment or discontinuation. Hypomagnesemia and/or hypocalcemia may manifest as muscle irritation or twitches, clonus, tremors, tetany, or tonic convulsions. Serum electrolyte levels should be monitored regularly and supplemented as necessary.

Common adverse reactions of carboplatin:

Hematological toxicity: Myelosuppression is the dose-limiting toxicity of carboplatin. The white blood cells and platelets are reduced to the minimum 14-24

days after injection, and generally return to normal levels in 35-41 days. For white blood cells below 4000mm3 and platelets below 80,000/mm3, it should be used with caution or in reduced doses. Generally, patients with poor physical fitness, ⩾65 years old and retreated patients with intensive chemotherapy will have more severe myelosuppression and last longer. Combination of carboplatin with other myelotoxic drugs or radiotherapy will aggravate myelosuppression, but as long as the application is reasonable and appropriate, myelosuppression is reversible and will not produce cumulative effects.

Gastrointestinal toxicity: About 15% of patients experienced nausea and 65% experienced vomiting after treatment with carboplatin, and one-third of patients experienced severe vomiting. Nausea and vomiting usually disappeared within 24 hours after treatment. Antiemetics can effectively prevent and treat carboplatin-induced nausea and vomiting. Abdominal pain, diarrhea, constipation, and loss of appetite have also been reported.

Nephrotoxicity: Generally, the nephrotoxicity of carboplatin is not dose-dependent. About 15% of patients had elevated BUN or plasma creatinine levels; 25% of patients had creatinine clearance rates below 60ml/min; in renal impairment, the incidence and severity increased. When renal failure occurs, regardless of whether hydration can prevent nephrotoxicity, the dose of carboplatin should be reduced or discontinued first.

Allergic reaction: According to reports, about 2% of patients developed rash within a few minutes after administration, without other obvious causes of fever, itching, hives, erythema and rarely bronchospasm, hypotension and other allergic reactions. Similar to allergic reactions caused by other platinum compounds.

Ototoxicity: Asymptomatic high-frequency hearing loss occurs first, and only 1% develops symptomatic ototoxicity, including most patients with tinnitus.

Neurotoxicity: low incidence of peripheral neuropathy, such as sensory abnormalities or reduction of deep tendon reflexes. Patients with previous sensory

abnormalities, especially those caused by cisplatin, may persist or worsen during treatment with carboplatin.

Others: In patients with normal liver function, mild to moderate liver function abnormalities occur after carboplatin treatment, but most cases will automatically return to normal during treatment. Occasionally, hypogeusia, hair loss, fever without infection or allergic reaction, chills, respiratory, cardiovascular, mucous membrane, genitourinary, skin, musculoskeletal and other side effects occurred in less than 5%. Although deaths from cardiovascular side effects have been reported, it is unclear whether the deaths were related to chemotherapy.

Common adverse reactions of toripalimab:

The incidence of adverse reactions in all levels of monotherapy was 93.8%. The adverse reactions with an incidence of more than 10% were anemia, elevated ALT, fatigue, elevated AST, rash, fever, elevated blood thyrotropin, decreased white blood cell count, cough, pruritus, hypothyroidism, decreased appetite, elevated blood glucose and elevated blood bilirubin. Most of the adverse reactions were mild to moderate (grade 1-2). The incidence of adverse reactions of grade 3 and above was 29.4%. The incidence of ⩾ 1% was anemia, hyponatremia, infectious pneumonia, elevated amylase, elevated lipase, elevated ALT, fatigue, elevated AST and thrombocytopenia. Autoimmune-related adverse reactions, such as rash, hemangioma, fatigue, immune-related thyroid dysfunction, enteritis, pneumonia, hepatitis, myocarditis and so on.

If you are enrolled in clinical research, any adverse reactions you have should be reported to us. Any drug has unavoidable adverse reactions, especially chemotherapy drugs. Some of these adverse reactions are common, preventable or treatable, and some are rare or even unreported. The doctor in charge will also prevent common adverse reactions in advance, or adjust the dosage and change the treatment plan based on your own adverse reactions. At present, advanced tumors are still incurable diseases, and any treatment may progress or the treatment effect will be poor. In addition, due to the possible impact of therapeutic drugs on the fetus and pregnant women, it is necessary for you to take appropriate contraceptive measures during the

period of taking the drug, and you should also use contraception for a period of time after the completion of the study or the early termination of the study.

[Alternative treatment options]

Whether you participate or not participate in this clinical study is entirely based on your own wishes. Participation in this study is not your only option for treatment. If you do not participate in this clinical study, your doctor will recommend appropriate treatment methods to you according to your actual physical condition, such as radiotherapy and chemotherapy, targeted drugs, immunotherapy, supportive treatment, etc. or participate in other clinical studies. You can discuss other treatment options with your doctor before taking part in this study.

[Collection, processing and preservation measures of biological samples]

In order to explore factors that may affect or predict the efficacy (including effectiveness and safety), your doctor or his research team members will retain your tumor tissue and blood samples for exploratory analysis. After you sign the informed consent form, you need to keep 15 pieces of wax block or paraffin white film of the primary tumor or metastatic tumor. 10 ml of peripheral blood was collected during the screening period, efficacy evaluation, and tumor progression out of the group. The main measurement content is immune-related indicators, including PD-L1 expression, etc.

After the final report for this study is completed, all remaining biological samples and any isolates from you will be destroyed.

[Engagement/termination principle]

Your participation in this study is completely voluntary. If you are unwilling to participate or continue to participate in this study, your rights and interests will not be affected in any way. You can withdraw from this study at any time, and you will not be discriminated against or retaliated against after withdrawing from the study, and any of your medical treatment and rights will not be affected.

You may also be asked by your doctor and investigator to withdraw from the study if you do not follow your doctor's advice or if it is in the interests of your health

or well-being to do so. If the doctor thinks it is necessary, please continue to cooperate with the relevant laboratory tests and physical examinations at the end of the study.

During the study period, your doctor will notify you if there is any important information about the disease or any medicine that will affect your decision whether to continue participating in the study.

You can keep abreast of the information and research progress related to this research at any time. If you have any questions related to this research, or if you have any discomfort or injury during the research process, or have questions about the rights and interests of participants in this research , you can contact the doctor in charge. You can also consult the ethics committee of our hospital.

[Relevant costs]

After enrollment, toripalimab will be given to you for free. The cost of chemotherapy and adjuvant therapy drugs, as well as examination-related costs are borne by you personally.

[Indemnification Clause]

This study has purchased clinical trial liability insurance. If you experience any discomfort during the study, or new changes in your condition, or any unexpected situation, regardless of whether it is related to the clinical study, you should notify your doctor in time, and he/she will make a judgment and treat it medically. If any adverse event related to this clinical study occurs during the clinical trial, we will compensate for it in accordance with Chinese laws and regulations and relevant insurance regulations.

[Information confidentiality]

Your right to privacy will be protected and all personal data about your participation in this study will be kept confidential. Your and other information that could identify you will be removed and replaced with a number that is linked to your

identifying information. During the course of this clinical research, your personal data, especially the medical results, are collected, stored and evaluated. The Ethics Committee, the sponsor and its entrusted representatives, and the State Drug Administration may consult your information when necessary for their work. Research results, including laboratory tests and other test data, may be published, but this is done for research purposes only and your name will not appear in any research reports or public publications.

After the conclusion of this clinical study, data obtained from this study may also be used in other studies or data analysis again, confidentiality as listed above.

Signature Page of Informed Consent

Statement of Consent: I have carefully read and understood all the information in this informed consent form for clinical research. I confirm that I have had sufficient time to consider whether to participate in this clinical trial, and that all questions have been satisfactorily answered and that I have the right to be consulted at any time and will be answered. I know that participating in this clinical research is voluntary, and I have the right to decide to withdraw from this research at any time without discrimination or retaliation, and my medical treatment and rights will not be affected. I will be given a signed and dated copy of this consent form. Finally, I am willing to participate in this study and follow the doctor's advice.

Subject signature:

Date of signature:

Legal agent (if applicable)

Signature of legal representative:

Date of signature: Relationship to subject:

Investigator statement: I confirm that I have explained and informed the subject in detail about the nature, purpose, requirements and possible risks of this research, and answered all the relevant questions of the subject. The subjects voluntarily agreed to participate in this study. The subjects have received a signed informed consent form. According to national laws and regulations and the research plan, I will accurately implement the clinical research and take necessary measures to protect the rights and safety of the above-mentioned subjects.

Investigator's signature：_____ _

Date of signature: