Informed Consent Form

Project Name: A Clinical Study of Disitamab Vedotin for Injection Combined With Penpulimab Injection in Neoadjuvant Therapy for Patients With HER2-expressing Cisplatin-intolerant cT2-T4aNxM0 Bladder Urothelial Carcinoma

Sponsor: Sun Yixian Memorial Hospital, Sun Yat-sen University

Version number: V1.0

Version date: 2022/5/1

Informed consent informed page

Dear Ms/Mr ：

After the doctor examines you, you have been diagnosed with bladder cancer with myometrial invasion. We will invite you to voluntarily participate in the "A Clinical Study of Disitamab Vedotin for Injection Combined With Penpulimab Injection in Neoadjuvant Therapy for Patients With HER2-expressing Cisplatin-intolerant cT2-T4aNxM0 Bladder Urothelial Carcinoma". This study was initiated by Sun Yixian Memorial Hospital of Sun Yat-sen University and the main researcher was Professor Lin Tianxin. This study has been approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, the unit leader.

I. research background

Bladder cancer is a common malignant tumor worldwide. According to the clinical TNM staging of bladder cancer, bladder cancer can be divided into non-muscle layer invasive bladder cancer (NMIBC) and muscle layer invasive bladder cancer (MIBC). Treatment options for different stages of bladder cancer are different. NMIBC can be treated by transurethral resection of the bladder, combined with intravesical instillation of BCG. Neoadjuvant chemotherapy based on platinum drugs and radical cystectomy were the preferred treatments for MIBC. Intravenous chemotherapy based on platinum is an option for patients with mBC.

However, there is currently no standard therapeutic regimen for neoadjuvant therapy in platinum-intolerant bladder cancer patients, and immune checkpoint inhibitors (ICIs) have become a new option for the treatment of bladder cancer. A study of 114 patients with MIBC(T2-4aN0M0) showed a complete pathologic response rate (CRR) of 37% with three courses of neoadjuvant immunotherapy with 200 mg Pembrolizumab prior to radical resection. A single-arm phase II clinical trial included 95 patients with MIBC who received 2 cycles of Atezolizumab before radical resection. Approximately 31% of the patients experienced complete pathological response during radical resection. The pathological stage of more than half of the patients was reduced to NMIBC, and the one-year recurrence-free survival rate (RFS) was 79%. The above studies have demonstrated that neoadjuvant immunotherapy based on ICIs is a therapeutic option for patients with MIBC, especially those who are intolerant to chemotherapy. Studies confirm that neoadjuvant immunotherapy continues to trigger a stronger immune response, predominantly CD8+ T lymphocytes, in patients after tumor resection, leading to longer survival. Furthermore, the surgical safety of radical resection after neoadjuvant immunotherapy is not significantly different from other methods. Although ICIs can

benefit more patients with MIBC than neoadjuvant chemotherapy, the use of ICIs still faces many challenges. First, there are no biomarkers that can predict the sensitivity of patients with MIBC to new ICIs-based adjuvant immunotherapy. The guidelines point out that PD- L1 expression and tumor mutation burden may predict the pathological response of ICIs treatment in some patients, but it is still not recommended as the basis of treatment selection. Second, some patients lost the chance of radical surgery due to the adverse events caused by ICIs treatment. Finally, there is still controversy over whether ICIs alone or in combination with other immune and chemotherapy regimens is optimal.

A C014 study published on ASCO 2021 showed excellent anti-tumor activity with the combination of vidicon and tripril monoclonal antibody, with a therapeutic ORR of 94.1% in 17 evaluable patients. The ORR of the combination regimen was also 100% in 10 new patients. Further analysis revealed that the combination regimen achieved excellent efficacy regardless of the expression status of HER2 and PD-L1 in patients. In addition, the combination of viteximab and tripril mab worked quickly, and a treatment response was observed in 88.2% of patients at the first evaluation (8 1 weeks).

Disitamab Vedotin for Injection (RC48-ADC), an antibody-coupled drug targeting HER2, was approved in June 2021 for the treatment of advanced gastric cancer positive for HER2 in China. Advanced urothelial cancer approved for first-line treatment progression in January 2022. Its C005 study was a Phase II, open-label, multicenter, single-arm study of patients with locally advanced or mUC HER2(IHC state 3+ or 2+) and included 43 patients who had at least one systemic chemotherapy failure, with an ORR of 51.2%, and a prespecified subgroup should be observed, such as liver metastasis and patients who had been treated with PD-1/PD-L1 in the past. The median PFS and OS were 6.9 months (95%CI, 5.6 – 8.9) and 13.9 months (95% CI, 9.1 – NE), respectively, with good safety and no Grade 4 or 5 TRAE.

As the fifth domestic anti-PD-1 antibody drug marketed, Penpulimab Injection has obvious differentiation advantages, and is the only new PD-1 monoclonal antibody in the world that adopts IgG1 subtype and modifies Fc segment, thus avoiding the problems of self-aggregation of IgG4 subtype PD-1 monoclonal antibody and binding to in vivo anti-tumor IgG1; At the same time, the IgG1 subtype is easy to be purified, which can reduce host cell residue and the occurrence of fever and infusion reaction. The Ampley monoclonal antibody utilizes genetic engineering technology to carry out amino acid mutation in the Fc segment of the heavy chain to form FC silencing, thereby

remarkably reducing effector T cell depletion. On the other hand, Fc-segment modification also reduced ADCR effect, reduced IL-8 release, enhanced curative effect, and reduced IL-6 release, thereby reducing irAE, and significantly improving the clinical safety of Ampley monoclonal antibody. Crystal structure analysis showed that Ampley monoclonal antibody had unique PD-1 binding epitope, which dissociated more slowly with PD-1 and permanently blocked PD-1/PD-L1 binding. Different from other PD-1 products already on the market, it is possible that the efficacy and safety of Ampley monoclonal antibody are better.

In this study, we intended to obtain the efficacy and safety indicators of cisplatin-intolerant patients with locally advanced urothelial carcinoma of the bladder treated with combination immunotherapy, so as to provide guidance for the follow-up Phase III clinical trials and clinical applications.

II. purpose of the study

To evaluate the efficacy and safety of neoadjuvant treatment with Disitamab Vedotin for Injection combined with Penpulimab Injection in patients with cisplatin-intolerant cT2-T4aNxM0 bladder urothelial carcinoma expressing HER2.

III. Introduction to clinical research projects

This is a single-armed, open-label exploratory clinical trial to evaluate the efficacy and safety of neoadjuvant treatment with vidicon and Ampley monoclonal antibody in patients with urothelial carcinoma of the bladder (cT2-T4aNxM0) who are resistant to HER2-expressed cisplatin. In the absence of active withdrawal of the subject from the trial, intolerable drug-induced toxic and side effects, or the investigator's belief that the subject was not suitable for further trials, each subject will undergo four cycles of surgery following neoadjuvant treatment with vidicon combined with Ampley monoclonal antibody, with efficacy evaluation and follow-up at each cycle. A total of 48 eligible patients with cisplatin-intolerant urothelial carcinoma of the bladder were planned to be enrolled in the study for a total of 46 months, with an enrollment period of 18 months and a follow-up period of 28 months.

Inclusion criteria:

Each patient eligible for participation in this study must meet the following criteria:

1. Those who voluntarily participated in this study and were able to sign a written informed consent form, and understand and agree to comply with the requirements of this study and the

evaluation schedule.

2. The insured is 18 – 75 years old on the date of signing the informed consent form.

3. In the case of a patient with bladder urothelial carcinoma of cT2-T4aNxM0 based on AJCC Version 8 bladder cancer TNM staging, histologic diagnosis and imaging evaluation, in which the investigator believes there is a residual lesion after the TURBT surgery; Patients with histologically mixed tumors require urothelial carcinoma to dominate (at least 50%).

4. The patient who is intolerant or does not accept cisplatin drug treatment must be determined for the researcher. Patients who are intolerant to cisplatin chemotherapy must meet at least one of the following criteria:

A. The physical status of ECOG was > 1;

b. Creatinine clearance < 60 mL/min;

c. Hearing loss ≥ Grade 2 in the National Cancer Institute Generic Term Standard for Adverse Events (NCI-CTCAE) Version 5;

D. Peripheral neuropathy grade 2 or higher in NCI-Ctcae Version 5;

e. With new york Heart Association Grade III or above heart failure.

5. The investigator assesses that the radical cystectomy needs to be performed after the neoadjuvant treatment, and the indications for radical surgery are met, so the investigator is willing to undergo the surgery.

6. HER2 detection in local laboratory using pre-treatment tumor specimen: HER2 expression confirmed after IHC result (defined as: IHC 1+ 2+ 3+).

7. ECOG physical status 0~1.

8. The patient's organ function was good, as measured by the following screening laboratory values obtained ≤14 days before enrollment:

A. Patients should not use growth factor support ≤14 days prior to sample collection when screening for:

I. Absolute neutrophil count ≥1.5×109/L;

Ii. Platelet ≥100×109/L;

Iii. Hemoglobin ≥90g/L;

B. The international standardized ratio or activated partial thromboplastin time ≤1.5 upper limit of normal (ULN);

C. Total serum bilirubin ≤1.5×ULN;

D. AST, ALT and alkaline phosphatase ≤2.5×ULN;

F. Calculated creatinine clearance is greater than 30 mL/min;

9. Women who are not pregnant or have fertility must be willing to use high-potency contraception during the study and ≥120 days after the last dose of vidicon or Ampley mab, whichever occurs later, and have a negative urine or serum pregnancy test result within ≤7 days prior to enrollment.

10. The male who is not sterilized must be willing to use efficient contraceptive methods during the study and up to 120 days after the last dose of vidicon or pie Ampley monoclonal antibody (whichever is later).

Exclusion criteria

Patients who met any of the following criteria did not meet the enrollment requirements:

1. Patients who have previously received therapies targeting PD-1, PD-L1, PD-L2, CTLA4, and Her2, or other antibodies or drugs that specifically target T cell co-stimulation or checkpoint channels.

2. Receiving other approved systemic anti-cancer treatments or systemic immunomodulators (including but not limited to interferon, interleukin-2 and tumor necrosis factor) within 28 days before enrollment.

3. Patients who have received radiotherapy for bladder cancer in the past.

4. Patients who have received medical treatments targeting tumors in the past, with the following exceptions:

A. In patients who have previously received systemic chemotherapy, a treatment-free interval of at least 12 months from the last treatment to the start of neoadjuvant therapy;

B. Local intravesical chemotherapy or immunotherapy is completed at least 1 week before initiation of study neoadjuvant therapy.

5. Major surgery has been performed or major trauma has occurred within 28 days before enrollment (implantation of vascular access device and TURBT are not considered as major surgery).

6. Severe infections requiring systemic anti-bacterial, anti-fungal or anti-viral treatment within 14 days prior to enrollment (HBV infection is performed as described in exclusion criterion

12).

7. Live vaccines have been administered within 28 days prior to enrollment (Seasonal influenza vaccines are usually inactivated and are therefore allowed to be administered. Intranasal vaccine is a live vaccine, so it is not allowed to be used).

8. Anyone who has received any Chinese herbal medicine or proprietary Chinese medicine for the control of cancer within 14 days before enrollment.

9. Active autoimmune diseases requiring systemic treatment that the researchers assess as having an impact on study treatment.

10. The need for long-term use of large amounts of hormones or the use of other immunosuppressive agents, the researchers assessed that there is an impact on the study of treatment.

11. The history of potassium, sodium, calcium abnormalities or hypoalbuminemia, interstitial lung disease, non-infectious pneumonia or other uncontrolled systemic diseases that the researchers determined might affect treatment, including diabetes, hypertension, and cardiovascular diseases (such as the active heart diseases existing within the six months prior to enrollment, including severe/unstable angina pectoris, myocardial infarction, symptomatic congestive heart failure and ventricular arrhythmia requiring drug treatment), etc.

12. Treatment-naive subjects with chronic hepatitis B or hepatitis B virus (HBV) carriers with HBV DNA ≥ 500 IU /mL (2500 copies/mL) were excluded from the study. Note: Patients with inactive hepatitis B surface antigen carriers or stable active HBV infection (HBV DNA < 500 IU/mL [2500 copies /mL]) after continuous antiviral therapy may be enrolled. HBV DNA testing is only performed in patients who are positive for antibodies to hepatitis B surface antigen.

13. patients with active hepatitis c shall not be included in the group. Patients who were negative for HCV antibody during the Screening Period or negative for HCV RNA after a positive HCV antibody test were enrolled. Only patients with positive HCV antibody testing require HCV RNA testing.

14. Has a history of immunodeficiency (including HIV-positive human immunodeficiency virus, and other acquired or congenital immunodeficiency diseases), or a history of allogeneic stem cell transplantation or organ transplantation.

15. allergies to other monoclonal antibodies are known.

16. Known to be allergic to any study drugs or excipients.

17. Concurrently enrolled in another therapeutic clinical study.

IV. Procedures of clinical research

1、 Sign informed consent form

2、 Inclusion screening for clinical studies

3、 Treatment options:

VIDITUOM: 2.0mg/kg, iv drip, q3w every 21 days for 4 cycles;

Ampley monoclonal antibody: 200mg, iv drip, q3w, in a cycle of 4 cycles every 21 days.

Order of use: Vidicidone monoclonal antibody → PyAmpley monoclonal antibody.

Radical cystectomy was performed 4 weeks after the neoadjuvant treatment.

4、 Visit

During the study, you also had responsibilities such as arriving at the hospital on time to receive the protocol-mandated tests until the end of the study. You need a total of 9 follow-up visits, 1 visit per treatment cycle for the neoadjuvant treatment phase, a total of 4 visits; Follow-up visits were made 5 times every 3, 6, 12, 18, and 24 months postoperatively. At each follow-up, your doctor will arrange for you to have the following follow-up examinations (list of examinations required by the protocol):

- Medical History, Physical Examination
- Blood biochemistry, routine blood test, urine routine test, thyroid function, myocardial enzyme spectrum
- Imaging: Computed tomography (CT) of the chest, whole abdomen and pelvis

5、 Collection and testing of remaining samples

In the process of this study, your doctor will, with your consent, collect blood, tissues and other samples remaining from your routine diagnosis and treatment. The use of these samples will not affect your disease diagnosis and treatment. Your sample will be sent to our central laboratory for the detection of HER2 immunohistochemical protein expression and PD-L1 expression. The results of the tests above may help to better understand your condition.

6、 Other items that need your cooperation to complete

During the study, you are responsible for reporting to your doctor any changes in your body and spirit that occurred during the course of the study, whether or not related to the study. Be sure to tell your

doctor about any other medications you are taking and will take during the study. Please do not use any other medicine for the treatment of muscle-layer invasive bladder cancer during the study. For other treatments, please contact your doctor in advance to obtain formal medical guidance.

7、 During the course of the study, you also have certain responsibilities, such as visiting the hospital on time and receiving tests. You are also responsible for reporting to your doctor any changes in your body and spirit that occurred during the course of the study, whether or not related to the study. Be sure to tell your doctor about any other medications you are taking and will take during the study. Please do not use any other medicine for the treatment of bladder urothelial carcinoma during the study. For other treatments, please contact your doctor in advance for formal medical guidance.

V. Alternative Treatment:

- Maximize TURBT+ concurrent chemoradiotherapy
- Systemic chemotherapy
- Partial cystectomy
- Simple radiotherapy

VI. Possible benefits

There may or may not be a direct benefit to you if you agree to participate in this study. Such benefits include the possibility of remission of your condition, and your participation in and cooperation with the completion of this study, whose information may provide reference and assistance in the treatment of other individuals with the same condition. Medical units will provide you with active diagnosis and treatment throughout the clinical study. Your study doctor will be informed promptly of any discomfort that occurs to you during the study, or new changes in your condition, or any unexpected circumstances, whether drug-related or not, that will lead to your doctor's judgment and medical treatment.

VII. Expenses related to this study

If you are qualified through screening and successfully enrolled in the group, you will be responsible for the follow-up medication expenses and examination expenses necessary to maintain the normal treatment and examination. The vidicon and Ampley mab will be provided by this study free of charge. Therefore, no additional treatment and examination expenses were incurred in this study, and partial free treatment medication could be provided.

VIII. Possible risks

Any medical treatment may bring you discomfort and unpredictable risks.

ADC drugs have various degrees of toxic reactions, such as bone marrow suppression, gastrointestinal reactions, functional impairment of vital organs such as liver and kidney, alopecia, and even life-threatening.

PD-1 antibody can cause different degrees of immune-related adverse reactions, including immune-related skin toxicity, immune-related pneumonia, liver and kidney damage, and myocardial damage.

Pregnancy risk: Due to ignorance of the effects of study drugs on the fetus and on breastfed infants, it is important that you are not during pregnancy or lactation when enrolled in the study and that you are not pregnant during the course of the study. You will not be allowed to participate in this study if you are pregnant, preparing to become pregnant, or breastfeeding.

If you are a fertile female subject, your study doctor will ask for a urine sample for a pregnancy test before you begin the study.

If you are a female subject, are fertile, and must use reliable methods of contraception during the study. Your study doctor will tell you which contraceptive methods are acceptable. The following contraceptive methods are recommended: condoms with or without spermicide (a sperm-killing drug), vaginal diaphragms or cervical caps with spermicide, or intrauterine devices (small contraceptive devices installed in a woman's uterus). Emergency contraception, such as the emergency contraceptive pill, following the occurrence of an unprotected sex cannot be used as a routine method of contraception. If you find a positive pregnancy test result while participating in the study, you should immediately inform the study doctor. You will need to discontinue study drug immediately and agree to undergo further follow-up testing. • if your pregnancy is confirmed, terminate the study and terminate the pregnancy at your own expense; If you continue to be pregnant, you will be solely responsible for all consequences arising therefrom.

If you are a male subject: Participation in this study may cause damage to your sperm and to the children you gave birth to during the study. The damage is currently unpredictable. If you have sex, you must agree to use a medically approved contraceptive method during the course of the study. Medically acceptable contraceptive methods are: surgical contraception (e.g., vasectomy) or spermicide condoms. Emergency contraception, such as the emergency contraceptive pill, following

the occurrence of an unprotected sex cannot be used as a routine method of contraception. Please inform your partner of the risk this medication poses to the unborn child. She should know that you need to tell your study doctor right away if she is pregnant and she should tell her doctor right away. You will need to discontinue study drug immediately and agree to undergo further follow-up testing. • if your partner is confirmed to be pregnant, terminate the study and terminate the pregnancy at your own expense; If your partner continues to be pregnant, you will be solely responsible for all consequences arising therefrom.

IX. Compensation for research-related damages

If any adverse event occurs that is really caused by the study drugs, the diagnostic tests and treatments required by the study protocol, and causes injury to you, the sponsor will buy the corresponding insurance in accordance with the law to bear part of the compensation, and the doctor will provide active treatment to you at the same time. If a medical event occurs, it shall be handled according to the medical event procedure.

X. Measures for confidentiality

The results of this clinical study are for scientific purposes only, so that your participation in the study and your personal data during the study will be confidential and will be protected in accordance with the law against disclosure of your name and identity, and your name will not appear in any study reports and public publications. Hospital ethics committee and researchers shall have the right to access all your research materials, including clinical observation forms and test data, as required due to work needs.

XI. Rights

This clinical study has been reviewed and approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and the scheme design meets the ethical requirements, which will ensure that your rights and interests are not violated in this study.

Your participation in this clinical study is entirely voluntary, and you can refuse to participate or withdraw at any time without discrimination or retaliation, and your medical treatment and rights will not be affected. If you withdraw from a clinical study, you should complete some appropriate medical tests upon withdrawal for safety reasons. If during the study the doctor determines that you are not

suitable to continue participating in the study, in order to protect your interests, the doctor has the right to decide to suspend you from continuing to participate in this clinical study. In addition, you will have access to information related to study drugs at all times during the study. We will also keep you informed of any updated information regarding this study so that you may decide to continue participating in the study.

Inform your study doctor immediately if any discomfort or exacerbation occurs during the clinical study and we will take appropriate medical action in a timely manner; If you follow the protocol, the investigator will actively treat any study-related adverse event that occurs.

XII. Contact details

If you have any concerns or questions about participating in this study, or if you experience any unusual reactions while participating in this study, or if an emergency occurs, you should contact:

Doctor: phone number:

If you have any complaints or concerns about the way in which the study physician conducted the study or questions your rights as a study subject, you can contact the following ethics committee members:

E-mail: sysyxllwyh@163.com Tel: 020-81332587

Informed consent consent consent signature page

Subject Statement

1、I have read the Informed Consent Form carefully, and the researchers have given me a detailed explanation and answered my relevant questions. I am fully aware of the following:

（1） As a subject, I will voluntarily participate in this study in accordance with the instructions to subjects, and fully cooperate with the researchers to provide the researchers with the health status and relevant information before participating in this study faithfully and objectively.

（2） The results of this clinical study are only for scientific research purposes, except for the ethics committee and the researcher. My personal data obtained from participating in the study and during the study are confidential and will be protected in accordance with the laws and regulations.

（3） I volunteered for this study and will be properly and actively treated for any study-related

adverse reactions that occur in clinical studies.

（4） My participation in this clinical study is entirely voluntary, and I can refuse to participate in or withdraw from the study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

（5） If I am a woman of childbearing age or my spouse is a woman of childbearing age, I will use one or more contraceptive methods during the study to avoid pregnancy. If I become pregnant, the clinical study will be discontinued and the pregnancy will be terminated. If the pregnancy continues, the consequences will be borne by me.

At the same time, I declare:

（1） I am willing to follow the study process;

（2） During the research period, I am willing to cooperate with the doctor to visit the doctor within the stipulated time and make corresponding examination.

（3） This informed consent form has been received.

Subject Signature: Contact information:

Date:

Signature of subject's guardian (if necessary): Contact information:

Date:

Signature of witness (if necessary): Contact information:

Date:

Investigator Statement

2. I have fully explained and illustrated the purpose of this clinical study, study methods, operating procedures and the possible risks and potential benefits for the subject to participate in this study to the subject, and answered all relevant questions of the subject with satisfaction.

Signature of the investigator (person who notified the subject): Contact information:

Date: