

Clinical Study Protocol

Protocol 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 Yat-sen Memorial Hospital, Sun Yat-sen University

Version number: V1.0

Version date: 2022.5.1

Signature confirmation of scheme:

Compliance Statement

In compliance with the Provisions of the Good Laboratory Practice Regulations, Administrative Measures for Investigator-initiated Clinical Studies in Medical and Health Institutions (for Trial Implementation) and the Declaration of Helsinki, participants pledged to conduct this study in accordance with this protocol. Participants must be trained to conduct the study after obtaining the written approval of the Ethics Committee and the informed consent of the subjects. Protocol modifications need to be re-approved.

I. programme summary

<p>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</p>
<p>Abbreviation of Scheme: RC48-C039</p>
<p>Test purpose:</p> <p>To evaluate the efficacy and safety of neoadjuvant treatment with Disitamab Vedotin for Injection Combined With Penpulimab Injection in patients with cT2-T4aNxM0 bladder urothelial carcinoma and HER2-expressing cisplatin intolerance.</p>
<p>Test brief:</p> <p>The single-armed, exploratory clinical study of vidicon monoclonal antibody combined with pie Ampley monoclonal antibody designed for cisplatin-intolerant patients with cT2-T4aNxM0 bladder urothelial carcinoma in this study confirmed the effectiveness and safety of the new adjuvant treatment of vidicon monoclonal antibody combined with pie Ampley monoclonal antibody for cisplatin-intolerant patients with cT2-T4aNxM0 bladder urothelial carcinoma, and finally provided new evidence-based evidence for new adjuvant treatment of such patients.</p>
<p>Sample size:</p> <p>This is a prospective clinical study. It is intended to collect 48 patients with cT2-T4aNxM0 bladder urothelial cancer who are HER2-expressing and cisplatin-intolerant, and all of them have received neoadjuvant treatment with vidicon monoclonal antibody in combination with pie Ampley monoclonal antibody.</p>
<p>research centre</p> <p>Sun yat-sen university memorial hospital The Third Affiliated Hospital of Sun Yat-sen University Southern hospital of southern medical university Zhujiang hospital of southern medical university The Third Affiliated Hospital of Southern Medical University</p>
<p>Efficacy evaluation</p> <p>Imaging evaluation by independent review experts according to the specific situation of patients, determine the evaluation time and evaluation method.</p>
<p>Data management and statistical analysis</p> <p>SAS 9.4 statistical software was used for statistical analysis. Unless otherwise specified, all statistical tests will use a one-sided test with $\alpha=0.05$ and the confidence intervals will use a one-sided 95% confidence interval.</p>
<p>Estimated Start and End Time: Start Time: June 2022; End: april 2026</p>

II. introduction

2.1 Research background

Bladder cancer is a common malignant tumor worldwide, and there are about 430,000 newly diagnosed patients every year [2]. According to the clinical TNM staging of bladder cancer, bladder cancer can be divided into non-muscular layer invasive bladder cancer (NMIBC) with high recurrence rate, muscular layer invasive bladder cancer (MIBC) with high metastasis risk, and metastatic bladder cancer (mBC) with high mortality. 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. MIBC's preferred treatments were radical cystectomy and neoadjuvant platinum-based chemotherapy; Intravenous chemotherapy is an option for patients with mBC, but it is intolerable to approximately 50% of patients due to inhibitory adverse events due to chemotherapeutic agents and/or delayed treatment in non-responders.

In recent years, 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 that a complete pathological response rate (CRR) of 37% was achieved with three courses of neoadjuvant immunotherapy with 200 mg Pembrolizumab before radical resection [3–4]. A one-arm second-stage clinical trial included 95 patients with MIBC who received two cycles of Atezolizumab before radical resection. About 31% of the patients experienced complete pathological reaction 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% [5]. 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 have confirmed that after tumor resection, neoadjuvant immunotherapy will continue to trigger a stronger immune response mainly by CD8⁺ T lymphocytes, leading to longer survival time for patients [6]. In addition, the surgical safety of radical resection after neoadjuvant immunotherapy is not significantly different from other methods [7]. Although ICIs can benefit more patients with MIBC than neoadjuvant chemotherapy, the use of ICIs still faces many challenges. First, there are currently 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 [8]. Second, some patients lose the opportunity of radical surgery due to adverse events caused by ICIs treatment [9]. 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 viteiximab and tripril mab worked quickly, and a treatment response was observed in 88.2% of patients at the first evaluation (8 1 weeks).

Vidicon monoclonal antibody (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 listed domestic PD-1 drug, Paxil Ampley monoclonal antibody injection has obvious differentiation advantages, and is the only new PD-1 monoclonal antibody adopting IgG1 subtype and modifying Fc segment in the world, which can avoid 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 mab 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 add immunotherapy to the treatment of patients with locally advanced urothelial carcinoma of the bladder who were intolerant to locally advanced cisplatin, so as to obtain the efficacy and safety indicators for the platinum-intolerant patients with locally advanced urothelial carcinoma of the bladder treated with the neoadjuvant therapy of vidicon combined with Ampley monoclonal antibody, and to provide guidance for the follow-up Phase III clinical trial and clinical application.

III. Study purpose and endpoint

1. Research purposes

1.1 Main research objectives:

To evaluate the pathological complete response rate (pCR rate) after radical cystectomy in patients with HER2 expression, cisplatin-intolerant cT2-T4aNxM0 vesical urothelial carcinoma treated with neoadjuvant therapy of vidicon combined with Ampley monoclonal antibody.

1.2 Secondary study objectives:

A) Evaluating the pathological descending rate;

B) Evaluating event-free survival (EFS);

C) Evaluating overall survival (OS);

D) To evaluate the safety of the new adjuvant therapy and its impact on radical cystectomy (evaluated according to NCI-CTCAE v5 and surgical complications according to Clavien-Dindo scoring criteria).

2. Analysis set:

2.1 Safety analysis set: Includes all patients who received at least 1 dose of any study drug (any component of neoadjuvant combination therapy).

2.2 Effectiveness analysis set: Includes all patients who received at least 1 dose of any study drug treatment (any component of neoadjuvant combination therapy) and had a radical cystectomy following that treatment.

3. Observation indicators

3.1 Main indicators:

Pathological complete response rate (pCR rate): the pathological stage after radical cystectomy was pT0N0 (based on effectiveness analysis)

3.2 Secondary indicators:

A) Pathological decline rate: the proportion of patients with pathological stage \leq pT1N0 (based on the efficacy analysis set) after radical cystectomy;

B) Safety: to evaluate the safety and impact on radical cystectomy of the new adjuvant therapy (evaluated according to NCI-CTCAE v5 and surgical complications according to Clavien-Dindo scoring criteria) (based on the safety analysis set);

C) Event-free survival (EFS): EFS is defined as the time from enrollment to disease progression, death from any cause, or new onset of another tumor.

D) Total survival (OS): Total survival was defined as the time from enrollment to death for any cause.

IV. Study population

1. Subjects

Patients diagnosed with bladder urothelial carcinoma of cT2-T4aNxM0 expressing HER2

through TURBT, cystoscopy biopsy and imaging evaluation were screened according to the entry and exit criteria.

1.1 Entry 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 fitness status of ECOG was > 1 ;
- b. Creatinine clearance < 60 mL/min;
- c. Hearing loss \geq 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 $\geq 1.5 \times 10^9/L$;

Ii. Platelet $\geq 100 \times 10^9/L$;

Iii. Hemoglobin $\geq 90g/L$;

B. The international standardized ratio or activated partial thromboplastin time ≤ 1.5 upper limit

of normal (ULN);

C. Total serum bilirubin $\leq 1.5 \times \text{ULN}$;

D. AST, ALT and alkaline phosphatase $\leq 2.5 \times \text{ULN}$;

E. 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).

1.2 Exclusions

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 investigator believes may affect treatment, including diabetes, hypertension, and cardiovascular diseases (such as active heart diseases including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure and ventricular arrhythmia requiring drug treatment within the six months prior to enrollment), etc.

12. Treatment-naïve subjects with chronic hepatitis B or hepatitis B virus (HBV) carriers with HBV DNA \geq 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.

1.3 exit criteria

Patient Discontinuation from Study Treatment: The patient has the right to discontinue study treatment at any time and for any reason. In addition, the investigator has the right to schedule the patient to discontinue study treatment at any time. Patients who discontinue study treatment should be followed if possible and the main reasons for discontinuation of study treatment should be documented on an appropriate electronic case report form (eCRF). Patients may discontinue study treatment for the following reasons, including but not limited to:

1. Pregnancy;

2. The investigator judges various medical conditions in which the safety of the patient under continuous treatment may be threatened;

3. The investigator judges that the operation timing is delayed, including but not limited to: disease progression occurs in the new adjuvant treatment stage or AE fails to complete 4 cycles of new adjuvant treatment, and the operation is not performed although it is assessed by the investigator to be in line with the indications for radical surgery;

4. Combined use of any anti-tumor therapy;

5. Patients fail to comply.

Patient withdrawal (individual patient ends the study): A patient may withdraw from the study for the following reasons, including but not limited to the following: 1. The patient withdraws informed consent; 2. Death; 3. Loss of follow-up.

V. research design

5.1 overall design

This is a multicenter, open-label, single-arm prospective clinical study to evaluate the efficacy and safety of neoadjuvant treatment with vidicon and Ampley monoclonal antibody in patients with cisplatin-intolerant cT2-T4aNxM0 urothelial carcinoma of the urinary bladder. In the absence of active withdrawal from the trial, intolerable drug-induced toxic and side effects, or findings that the subject was considered by the investigator to be unsuitable for further trials, each subject will undergo post-treatment surgery according to the following protocol, with efficacy evaluation and follow-up at each cycle.

5.2 Treatment

After completing all screening activities, patients confirmed to be eligible will enter the study and receive the following treatments and visits: new adjuvant treatment with vidicon combined with piAmpley monoclonal antibody (up to 4 dosing cycles), once every 3 weeks; The patient underwent radical cystectomy after neoadjuvant chemotherapy; The patient's complete pathological response rate, phase reduction rate, and regular follow-up of two years were detected postoperatively to evaluate the patient's drug/surgical safety and to evaluate the survival of the patient's radical resection after neoadjuvant immunization combined with chemotherapy.

New adjuvant regimens (up to 4 cycles administered): 2.0mg/kg, Vidisituzumab on Day 1, administered intravenously, Ampley monoclonal, 200mg, administered intravenously on Day 1 of each 21-day cycle. Order of use: Vidicide monoclonal antibody → PyAmpley monoclonal antibody.

Surgical scheme: radical cystectomy+urinary diversion.

Specific treatment and visit designs are as follows.

5.2.1 Screening period

Screening phase evaluation will be conducted within 28 days prior to enrollment and the patient has been diagnosed with transurethral resection of bladder tumor (TURBT) or cystoscopy biopsy; Patients who agree to participate in this study will sign an Informed Consent Form (ICF) prior to undergoing any screening procedures. Radical cystectomy must be performed at baseline at the investigator's discretion following neoadjuvant treatment. Screening assessment in the screening period can be repeated as needed; The investigator will initially assess the patient's eligibility based on the most recent screening assessments.

5.2.2 Drug treatment period

Upon completion of all screening activities, patients confirmed to be eligible will enter the study and receive treatment as follows: up to 4 cycles of administration of vidicon in combination with Ampley monoclonal antibody).

Imaging evaluation will be performed before the start of cycle 3 of new adjuvant therapy, and if the patient does not develop PD, treatment will be continued as planned; If the patient had PD, subsequent treatment would be administered at the discretion of the investigator.

5.2.3 Drug safety visit

Patients who stop/complete treatment for any reason during new adjuvant therapy are required to return to the hospital for a safety follow-up (28 days after the last dose [-7 to +21] and start the radical surgery, or before starting new anti-cancer therapy (surgery), whichever occurs first; In principle, return to the study center, but also in the local hospital for review). This visit can be combined with other visits. If routine laboratory tests (e.g., hematology, serum biochemistry) were performed prior to the safety visit, it is not considered necessary to repeat the same test in the investigator's experience. Imaging is not required at the safety follow-up if it is less than 28 days from the last imaging.

5.2.4 Surgical treatment

Preoperative evaluation will be performed prior to radical surgery, and if the patient meets the surgical indications, the investigator will perform radical cystectomy at an appropriate time as planned; If the patient is not suitable for surgery, the investigator decides to administer subsequent treatment. Disease progression occurs during the neoadjuvant treatment phase, or the AE fails to complete 4 cycles of neoadjuvant treatment (total neoadjuvant treatment duration does not exceed 15 weeks), but if the investigator assesses that the indication for radical surgery is met, surgery will be continued within the specified time frame and will still be considered eligible for treatment and evaluation for all study requirements. If the investigator determines that physical conditions preclude radical surgery, study treatment will be discontinued, an end-of-treatment visit will be given, and additional treatment selected by the investigator will be continued. If any of the conditions exceed the above time limits, but the investigator determines that the procedure is still acceptable, the team

leader unit will be contacted to determine whether or not they are eligible for study analysis. Patients who discontinue neoadjuvant therapy early due to disease progression or an intolerable adverse event (AE) before surgery and do not undergo surgery are given an end-of-treatment visit and will continue to receive other treatments selected by the investigator.

Patients who are amenable to surgery will receive the following treatment: radical cystectomy. Surgical procedures: Open, laparoscopic or robotic options are available. Resection range: According to the classical resection range, that is, the bladder and the surrounding adipose tissue, and the distal end of ureter. For male patients, the prostate and seminal vesicles should also be included, while for female patients, the uterus, bilateral appendices and part of the anterior vaginal wall should also be included (Note: Female patients are allowed to selectively retain pelvic organs according to the operator's experience and the patient's condition, but the reason should be recorded and explained). Lymph node dissection: The pelvic standard lymph node dissection was required, namely, the dissection of the bifurcation (proximal end) of the common iliac vessel, the genito-femoral nerve (lateral), the iliac circumflex vein and Cloquet lymph node (distal end), and the internal iliac vessel (posterior side), including the obturator lymph node (note: a wider lymph node dissection could be performed in accordance with the patient's condition during the operation, but the reason should be recorded and explained). Urinary diversion was selected according to the operator's experience and the patient's condition.

Perioperative drug use: Unless otherwise indicated as cautious or prohibited in this protocol, the investigator may reasonably use the drug according to experience and the patient's condition. Pathological staging after neoadjuvant therapy was assessed based on surgical samples after radical surgery.

5.2.5 Post-operative Follow-up/End of Surgical Treatment Visit (EOT)

These include one follow-up at week 1, one month, three months (EOT), six months, nine months, 12 months, 15 months, 18 months, 21 months, and 24 months after radical surgery, whichever occurs first, until the patient develops disease progression, dies, withdraws informed consent, loses follow-up, concludes the study follow-up, or begins new anticancer therapy (surgery).

End-of-surgical visit (EOT) was performed 90 days postoperatively (-14 to+28 days).

5.2.6 Study termination

Study termination was defined as the point in time when the final data from the clinical study was collected, that is, the point in time when the last study patient completed his/her last visit to the study center, and was expected to occur 2 years and 4 months after the last patient was enrolled in the study. The team leader unit has the right to terminate the study at any time. Reasons for early termination of the study may include, but are not limited to, 1) the incidence or severity of AEs in

this or other studies are suggestive of a health hazard to the patient; 2) The overall patient enrollment is unsatisfactory; 3) In the first stage (18 subjects), the effective cases with complete pathological response were less than 2.

If a decision is made to terminate the study, each investigator will be notified by the team leader unit. Patients who discontinue early should be viewed as soon as possible and scheduled for a drug safety/end-of-treatment visit, if necessary. The investigator may be notified to follow additional procedures to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board (IRB)/Independent Ethics Committee of the premature termination of the study.

5.3 Study evaluation and procedures.

Patient safety and tolerability will be closely monitored throughout the study. All evaluations of each patient should be performed and documented in the medical records. Dosing will only occur after review of clinical assessments and local laboratory values, which must be obtained before each dose, and when dosing conditions are met as directed by the study protocol.

5.3.1 Screening

Screening phase assessments will be conducted within 28 days prior to enrollment and patients who agree to participate will sign up for an ICF prior to undergoing any screening procedures. The screening period starts on the first day of the screening procedure. Screening evaluations can be repeated as needed during screening; The investigator will evaluate a patient's eligibility for inclusion based on the latest screening assessments. Standard tests or test results performed ≤ 28 days before informed consent are available for screening assessments and do not require repeat testing unless otherwise specified.

Demographic data and medical history of 5.3.1.1

Demographic data will include date of birth (or age), gender, and race/ethnicity reported by self. Medical history including a variety of clinically significant medical, surgical or cancer history; • Fertility status; And history of drinking and smoking. Radiographic findings prior to enrollment were collected.

Fertility Women and Contraception in 5.3.1.2

Fertility is defined as the ability to conceive physiologically. ◦

Informed consent and screening records in 5.3.1.3

Written informed consent to voluntarily participate in the study must be obtained prior to performing any study-specific procedures. The ICFs of all enrolled and screened but not enrolled patients will be maintained at the study center. All screening assessments must be completed and reviewed before patients are admitted to the group, confirming that they meet all eligibility criteria.

5.3.2 Entry

5.3.2.1 Qualification Confirmation

The investigator will evaluate the eligibility of each patient for inclusion. Results of all screening procedures and associated medical history must be obtained before eligibility is established.

5.3.2.2 Patient ID

After obtaining informed consent, study center staff will assign a unique patient number to a potential study subject.

5.3.3 Safety assessment

5.3.3.1 vital signs

Vital signs included measurement of body temperature (C), pulse, and blood pressure (systolic and diastolic). Height (baseline only) and weight should be measured and recorded in the eCRF. Patients will be advised of the possibility of a delay in symptoms following infusion and to contact their study doctor if they develop this condition.

5.3.3.2 Physical Examination

During the screening visit, a physical examination will be performed that includes assessment of 1) head, eyes, ears, nose, and throat, 2) cardiovascular, 3) skin, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, 7) nervous system, and 8) urinary system. Any abnormalities identified during screening will be graded according to NCI-CT Cae Version 5.0 and documented in eCRF using the appropriate disease/condition term.

Limited symptom-specific physical examinations will be performed at follow-up visits (and as clinically indicated). Changes from baseline will be recorded. New or worsening clinically significant abnormalities should be recorded as AEs in eCRF.

5.3.3.3 Eastern Cooperative Oncology Group (ECOG) Physical Status: The ECOG physical status was evaluated during the study.

Laboratory safety inspection in 5.3.3.4

Serum biochemistry, hematology, coagulation, urinalysis, fecal analysis, infectious disease testing, pregnancy testing, thyroid function (required before enrollment), and blood type will be evaluated at the discretion of the investigator in the local laboratory, with certain required components to be collected.

The investigator used the results from the local laboratory for eligibility assessment, safety monitoring, and dosing decisions. Table 1

Table 1: laboratory test items

Serum biochemical test	hematology	blood coagulation	Urine analysis
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Alkaline phosphatase	red blood cell	Prothrombin time	pH
Alanine aminotransferase	count	Partial thromboplastin time	specific gravity
aspartate amino transferase	hemoglobin	or activated partial thromboplastin time	glucose
albumin	hematokrit	international normalized ratio	albumen
Bicarbonate or total carbon dioxide i	white cell count		acetone/ketone body
Total bilirubin, direct bilirubin	platelet count	Infectious disease examination	occult blood
Blood urea nitrogen or urea	Neutrophil count	HIV antibody, hepatitis B two and a half	Fecal routine
Magnesium, chlorine, phosphorus, potassium, sodium, calcium	Eosinophil count	HCV antibody	Color, character
Creatinine, glucose	Basophil count	Thyroid function	Microscopic examination
Lactate dehydrogenase, total protein	Monocyte count	Free T3, free T4	of leukocytes
Creatine kinase (CK), CK-MBii	Lymphocyte count	Serum total thyroxine TT4	Microscopic red blood cell
		Serum total triiodothyronine TT3	Occult blood test
		Determination of thyroid stimulating hormone TSH	

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; I. If considered regional standard treatment, test for this. Ii. If CK-MB portion is not available, evaluate troponin I and/or troponin T instead.

5.3.3.5 electrocardiogram

For safety monitoring purposes, the investigator must review all 12-lead ECG records, and sign and date them. Paper or electronic copies of the ECG will be maintained at the study center as part of the patient's permanent study file.

5.3.3.6 echocardiography: echocardiography is optional.

5.3.3.7 pulmonary function: pulmonary function tests are optional and the tolerance to radical surgery is evaluated.

Adverse events in 5.3.3.8

Drug and radical surgical AEs will be graded and documented throughout the study according to the NCI-CTCAE, Version 5.0, and Clavien-Dindo scoring system. Toxicity will be characterized by severity, duration, and time to occurrence.

5.3.4 Tumor and Efficacy Evaluation

5.3.4.1 baseline neoplastic imaging will be performed prior to enrollment with multiparameter magnetic resonance imaging of the bladder (or pelvis) (which must be reassessed post-TURBT if TURBT) and computed tomography (CT) scans of the chest, whole abdomen, and pelvis (enhancement to be determined by the investigator if necessary).

While 5.3.4.2 is on treatment, multiparameter magnetic resonance imaging of the bladder (or pelvis) will be performed (with a conditional VI-RADS score) and computed tomography (CT) scans of the chest, whole abdomen, and pelvis (enhancement at the discretion of the investigator if

necessary) prior to and prior to the start of cycle 3 of neoadjuvant therapy according to RECIST version 1.1:

1. Assessed prior to the start of cycle 3 and continued treatment as planned if the patient did not develop PD; • if the patient has PD, subsequent treatment at the discretion of the investigator;

2. Pre-operative evaluation. If the patient meets the operation indication, the researcher shall select appropriate time to perform radical cystectomy according to the plan; If the patient is not suitable for surgery, the investigator decides to give subsequent treatment;

3. After radical surgery, the pathological stages after neoadjuvant treatment will be evaluated by the researchers based on the pathological results of surgical samples.

4. Computed tomography (CT) scans of the chest, whole abdomen, and pelvis are performed 3 months, 6 months, 12 months, 18 months, and 24 months after the radical resection (enhancement is judged by the researcher if necessary). The former shall prevail until the disease progression, death, withdrawal of informed consent, loss of follow-up, conclusion of study follow-up or initiation of new anti-cancer treatment (surgery) of the patient occur.

The investigator will evaluate the response using RECIST 1.1.

5.3.5 Visit window

All visits during neoadjuvant therapy were to be within the range of -3 to +7 days of the planned date, and postoperative visits were considered to be 14 days, unless otherwise noted. Evaluations scheduled for the day of study treatment dosing (Day 1) per cycle should be completed prior to study treatment infusion/dosing, unless otherwise noted. Laboratory and imaging results should be reviewed prior to dosing. Scheduling a study visit at a protocol-specified time point that is in conflict with a holiday, weekend, or other event/law will allow the visit to be scheduled to the nearest feasible date.

Visit schedule

	sift	Treatment period (one cycle every 21 days)				Drug safety follow-up r	operation		Postoperative follow-up				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4		Preoperative evaluation	Radical resection	1 week	1 month	3 months (EOT)	6, 12, 18, 24 months	9, 15, 21 months
fate (window)	-28 to -1	one	-3 to +7	-3 to +7	-3 to +7	28 after last dose (-3 to +7)	-7 to 0	28 - 42 after the last dose	±3	±7	±14	±14	±14
Informed consent a	X												
Demographic data/ Treatment historyb	X												
Physical examination/vital signs c	X	X	X	X	X	X	X		X	X	X	X	
ECOG assessment	X	X	X	X	X	X	X		X	X	X	X	
Surgical fitness evaluation	X						X						
Electrocardiogram d	X	X	X	X	X	X	X		X	X	X		
Hematology e	X	X	X	X	X	X	X		X	X	X	X	
Serum biochemistry e	X	X	X	X	X	X	X		X	X	X	X	
Urinalysis e	X	X	X	X	X	X	X		X	X	X	X	
Fecal analyse	X			X			X						

Coagulation e	X						X						
Pregnancy testf	X					X	X						
Hepatitis b two half qualitative g	X						X						
Hepatitis c qualitative g	X						X						
Venereal disease (HIV)g	X						X						
Marker screening (HER2 IHC)	X												
Thyroid functionh	X						X						
Chest CT plain scan i	X			X		X	X				X	X	
Total abdominal+pelvic CT plain scan+enhanced i	X			X		X	X				X	X	
Bladder (or pelvis) Multiparameter mri	X			X			X						
Bone scan i	X												
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse eventj	X	X	X	X	X	X	X	X	X	X	X	X	
Vidicon monoclonal antibody administration k		X	X	X	X								
Ampley monoclonal antibody administration l		X	X	X	X								
Radical resection and pathological evaluation m								X					
Archived/fresh tumor histon	X							X					
EQ-5D-5L/ EORTC QLQ-C30 o	X	X	X	X	X	X	X	X	X	X	X	X	X
Living condition	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CT: electronic computed tomography; MRI: magnetic resonance imaging; RECIST, evaluation criteria for efficacy of solid tumors; V, version; CTCAE: general term evaluation criteria for adverse events; EOT: end of treatment visit.

A. Written informed consent is required prior to any study-specific inspections or procedures. Standard treatment tests or workups performed prior to informed consent and within 28 days prior to enrollment that are available for screening evaluation do not need to be repeated unless otherwise specified.

B. including year of birth (or age), gender and race/ethnicity; Treatment history initially diagnosed, including prior medical therapy, local therapy, and surgical treatment. Information regarding imaging studies conducted prior to enrollment in the study may be collected for review by the investigator.

C Vital signs collected during the study included temperature, pulse, and blood pressure (systolic and diastolic) when the patient was at rest and at rest after 10 minutes. The patient's vital signs were recorded during the first 1 hour before, during, and 1 hour after the last two infusions of vidicon. For subsequent infusions, vital signs will be collected within 60 minutes prior to infusion and, if clinically indicated, during and 30 minutes after infusion. Patients should be asked by the investigator at each of the planned study visits during the treatment with vidicon for changes in vision, visual impairment, or ocular inflammation. Any change in vision should be referred to the appropriate specialist for further management guidance.

D. The patient should rest quietly for at least 10 minutes before undergoing ECG examination. If the ECG has significant clinical significance, color Dopplar ultrasound (LVEF) will be added for investigation, and such symptoms as precordial pain and palpitation will appear, together with myocardial enzyme spectrum.

E Hematology (routine blood and coagulation tests), serum biochemistry (including cardiac, hepatic, and renal function tests), urinalysis and fecal analysis will be evaluated in the local laboratory. Results should be viewed within 24 hours prior to each dose of study drug after the end of Cycle 1. Fecal analysis is required if clinically indicated during the follow-up period.

F. A urine pregnancy test will be performed on all fertile females. A weakly positive urine pregnancy test must be confirmed by an additional serum pregnancy test.

G serological tests including HBV/HCV/HIV (HBV halves, HCV antibodies, HIV antibodies) will be performed in the local laboratory. HBV DNA testing needs to be added if HbsAg is positive. Additional HCV RNA testing is required if HCV antibodies are positive.

H. In addition to the screening period and preoperative evaluation, the investigator determines whether a thyroid function test is required if clinically indicated.

I. Imaging examinations have been taken under standard treatment before obtaining the written informed consent, and the collection

time is within 28 days before inclusion. If the results meet the clinical requirements and are qualified, no repeated examination is required, but the multi-parameter MRI of bladder (pelvis) after TURBT must be guaranteed. All measurable and evaluable lesions need to be evaluated and documented at the screening visit. Chest, abdomen and pelvis-containing plain CT scan (enhancement at the discretion of the investigator if necessary) and multi-parameter MRI of bladder (pelvis) were selected for imaging examination (VI-RADS score was conducted when conditions were ripe). For each patient, the same imaging studies were used as far as possible throughout the study. The investigator must review the imaging results prior to the next cycle of dosing. During the follow-up period, imaging examinations were selected according to the pathological response of the patient or local medical guidelines. During the follow-up period, if imaging recurrence or metastasis occurs, no imaging examination will be conducted during the follow-up period covered by this study. Craniocerebral examinations and bone scans are required when symptoms appear, if clinically indicated.

J. AEs and laboratory abnormalities will be graded according to NCI-CT Cae Version 5.0 (drugs), and CLAVIEN-DINDO (surgery), and all AEs will be evaluated for severity. Only SAEs should be reported after informed consent has been signed but prior to initiation of study drug administration. After initiation of study drug, all AEs and SAEs, regardless of relationship of study drug and procedure, will be evaluated and documented until 28 days after the last dose (including chemotherapy) or initiation of new anticancer therapy (whichever occurs first). Assessment and documentation of surgery-related adverse events should be performed within 90 days after surgery.

K. VDT will be administered intravenously every 3 weeks. The infusion time for the first infusion (Cycle 1, Day 1) should be not less than 60 minutes; If well tolerated, subsequent infusions should take no less than 30 minutes, the shortest time allowed for an infusion. Patients must be monitored for at least 60 minutes in an area equipped with resuscitation equipment and emergency medications following the infusion of vidicon on the first day of Cycles 1 and 2. Beginning with cycle 3, a minimum of 30 minutes of monitoring is required in areas equipped with resuscitation equipment and emergency medications. VID should not be coadministered with any other drugs. At each cycle, vidicon will be administered prior to PD-1 drug administration.

L. PyAmpley monoclonal antibody will be administered intravenously every 3 weeks. Administration of the drug was on the same day as that of the vidicon.

M. After radical surgery, the pathological staging after neoadjuvant therapy will be evaluated by the investigator based on the pathological results of surgical samples.

N. During the screening stage, patients must provide tumor tissue samples of TURBT and relevant pathological report at the same time, and can choose to send fresh surgical tissue or pathological white sheet for biomarker analysis. Fresh tumor samples also need to be collected during radical surgery. Patients with disease progression will be asked if an optional biopsy has been performed (see central laboratory sample management manual).

O. Patients were required to complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires (Appendix 11, 12). Where feasible, patients are required to complete questionnaires prior to administration of study drug or any other procedure.

Q. Drug safety follow-up should be performed 28 days after the last dose of vidicon or Ampley monoclonal antibody (-3 to +7 days) and prior to initiating radical surgery, or prior to initiating new anti-cancer therapy, whichever occurs first. This visit can be combined with other visits as long as the drug safety visit occurs 28 days (-3 to +7 days) after the last dose. If routine laboratory tests (eg, hematology, serum biochemistry) were performed within 7 days prior to the drug safety visit, there is no need to repeat the same test. Imaging is not required at the drug safety follow-up if it is less than 28 days from the last imaging.

5.4 Statistical analysis

5.4.1 Sample size and calculation basis

The historical control pCR rate was assumed to be 10% based on recent clinical studies. The expected pCR estimate for this study was 25%, representing a clinically significant improvement.

The resulting zero and alternative assumptions are as follows:

The original assumptions to be tested were: h_0 : PCR rate = 25%

Corresponding alternative hypothesis: h_a : pcr rate > 25%

The Simon Phase II (Simon, 1989) design will be used to test the superiority of the combination

of neoadjuvant therapy with Ampley monoclonal antibody as compared with the historical control. The expected Class I error rate for the project (ineffective study drug but effective promotion) $\alpha=0.05$, with 80% confidence. An interim efficacy and safety analysis will be performed when 18 subjects are enrolled. Of the 18 subjects in the first phase, the second phase was not performed if < 2 effective cases of complete pathological response were achieved. If there were ≥ 2 valid cases in Phase 1, continue with Phase 2 until there are a total of 43 subjects. If the total effective cases in the first and second stages were not less than 7, it could be determined that the pCR of the new adjuvant therapy in this study was significantly improved compared with the historical control, thereby demonstrating the superiority and efficacy of the new adjuvant therapy in this study. A 10% dropout rate was considered for this study, which required the recruitment of a total of 48 subjects. The statistical design was calculated using an online statistical tool approved by the Design Department of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (<http://cancer.unc.edu/biostatistics/program/ivanova/simonstwestageDesign.aspx>) (Ivanova & Deal, 2016).

5.4.2 data analysis set

Safety analysis set: Includes all patients who received at least 1 dose of any study drug (any component of neoadjuvant combination therapy).

Efficacy analysis set: Includes all patients who received at least 1 dose of any study drug treatment (any component of neoadjuvant combination therapy) followed by radical cystectomy.

5.6.3 Statistical analysis plan.

5.4.3 Efficacy analysis

Analysis of primary effectiveness endpoint for 5.4.3.1

The primary endpoint, the pathological complete response rate (pCR rate), was defined as the proportion of patients in the efficacy analysis set who received radical cystectomy after completion of neoadjuvant therapy without residual tumor lesions as assessed by the investigator. Will be analyzed based on the validity analysis set.

5.4.3.2 secondary efficacy endpoint analysis

The pathological descending rate is determined according to the pathological results after surgery to determine whether the disease is descending to below T2. The percentages of CT2N0 \rightarrow PT0N0, CT3-4AN0 \rightarrow PT0N0, CT2N0 $\rightarrow \leq$ PT 1N0, CT3-4AN0 $\rightarrow \leq$ PT 1N0 were calculated respectively, and the 95% confidence interval (CI) of bilateral Clopper-Pearson for pathological stage reduction rate was calculated, to evaluate the accuracy of the estimate of pathological stage reduction rate. Will be analyzed based on the validity analysis set.

Event-free survival (EFS), is the time from the first neoadjuvant treatment until disease progression, death from any cause, or new onset of other tumors. The Kaplan-Meier(KM) method

will be used to estimate the no-event curve and the corresponding quantiles (including median values). If the two-sided 95% confidence interval for the median can be estimated, the generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982) was used. The KM method will be used to estimate EFS rates at 1 and 2 years from the first dose, and 1 and 2 years after surgery, with the corresponding 95% confidence interval estimated using Greenwood's formula (Greenwood, 1926). The EFS deletion criteria will be in compliance with the FDA Industry Guide: Clinical Trial Endpoints for Approval of Cancer Drugs and Biological Products (FDA 2007). EFS will be analyzed based on the security analysis set.

Overall survival (OS) was defined as the time from the start of treatment to death for any cause. OS will perform similar analyses using the KM method above for populations included in the safety and efficacy analysis sets, respectively. The time curve will be plotted against the KM estimate of OS. The median OS, OS rates 1 and 2 years from the first dose, and OS rates 1 and 2 years after surgery will be calculated and show a bilateral 95% CI.

5.4.4 safety analysis

Safety was evaluated by monitoring and documentation of all adverse events classified by NCI-CTCAE v5.0 or Clavien-Dindo. Laboratory values (eg, hematology, clinical biochemistry, urinalysis), vital signs, ECGs, and physical examinations will also be considered in evaluating safety. All safety data in the safety analysis set will be analyzed using descriptive statistics.

The safety analysis set was defined to include all patients who received ≥ 1 dose of neoadjuvant therapy from the study protocol. EFS rate, OS rate, and adverse events of drug exposure (including duration and dose) will be summarized by safety analysis set population. Adverse events will be described coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded according to NCI-CTCAE v5.0 or Clavien-Dindo.

Adverse events in 5.4.4.1

AE reporting terms (investigator description in eCRF) will be coded using the International Dictionary of Medical Terms (MedDRA). AEs were coded according to low-level terms, preferred terms, and major system organ class in MedDRA (version 20.0 or higher).

Vi. research interventions *

6.1 Administration Protocol

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: Vididone monoclonal antibody → PyAmpley monoclonal antibody.

Radical cystectomy was performed 4 weeks after the neoadjuvant treatment.

6.2 Combined treatment (permitted adjuvant, supplemental/alternative therapies)

All concomitant medications during the study (generic name of the drug, purpose of administration, dose administered, time of administration, etc.) must be detailed on the case report form. Other clinical trial drugs were prohibited during the study.

Combination therapies are prohibited as follows:

1) Similar anti-HER2 therapeutic drugs.

Drug-drug interaction studies with this product have not been formally conducted in patients. To characterize the potential drug-drug interaction of the free MMAEs, results from another drug-drug interaction study with an ADC drug coupled with the same cytotoxic monomethyl-Australian statin E(MMAE) are presented below:

2) the effect of other drugs on vidicon for injection:

CYP3A4 potent inhibitors: Other MMAE-coupled ADC drugs in combination with ketoconazole, a potent inhibitor of CYP3A4, will increase the exposure of free MMAEs by 25% in C_{max} and 34% in AUC; There is no effect on the ADC exposure. It is hypothesized that coadministration of this product with a potent inhibitor of CYP3A4 will have the same effect on exposure to free MMAE and bound antibodies as the ADC drug.

CYP3A4 potent inducers: Other MMAE-coupled ADC drugs in combination with rifampin, a potent inducer of CYP3A4, reduced exposure of free MMAEs by 44% in C_{max} and 46% in AUC; There is no effect on the ADC exposure. It is hypothesized that coadministration of this product with a potent inducer of CYP3A4 will have the same effect on exposure to free MMAE and bound antibodies as the ADC drug.

Other drug effects of vidicon mab for injection: CYP3A4 substrates: Other MMAE-coupled ADC drugs in combination with midazolam, a sensitive CYP3A4 substrate, did not affect midazolam exposure. It is also hypothesized that this product will not affect exposures of drugs metabolized by CYP3A4 enzymes.

VII. Study intervention discontinuation/subject discontinuation and withdrawal *

7.1 Test Termination/Suspension Criteria

The sponsor has the right to terminate/suspend this test. The Sponsor must notify the investigator, the Ethics Committee, and the State Food and Drug Administration with reasons prior to terminating/suspending a clinical trial. Resumption of the study following early termination/suspension of the study must be approved by the Ethics Committee review;

Termination/suspension requested by the ethics committee.

7.2 Provisions for Conclusion of Clinical Trials

The trial ended when all subjects:

1) All subjects complete a survival follow-up of at least 2 years;

2) or all subjects died, were lost to follow-up, or withdrew their informed consent.

VIII. Adverse events and unexpected events

8.1 Adverse Events

8.1.1 Definition of adverse event

An adverse event is any adverse medical event that occurs after the patient or subject has received a medication and is not necessarily causally related to treatment. Thus, an adverse event could be any adverse sign (including abnormal laboratory results), symptom, or disease temporally related to the use of study drug, regardless of whether a causal relationship with study drug was considered.

8.1.2 Classification of adverse events

Adverse events included Serious Adverse Event, (SAE) and non-serious adverse events.

8.1.3 serious adverse events

SAE refers to the medical events that need hospitalization or prolong hospitalization, cause disability, affect the ability to work, endanger life or death, and lead to congenital malformations in the process of clinical trials. Include the following medical events:

- 1) an event leading to death;
- 2) A life-threatening event (defined as a condition in which the subject was in immediate danger of death at the time of the event);
- 3) Events requiring hospitalization or prolonging hospitalization;
- 4) Events that can lead to permanent or severe disability/dysfunction/impact on work ability;
- 5) Congenital abnormality or birth defect;

Other important medical events (defined as events that endangered the subject or required intervention to prevent any of the above).

If the SAE of death occurs as a result of disease progression (at the discretion of the investigator), the SAE may be considered for non-escalation and dealt with in accordance with the medical practice at each center.

8.1.3 Evaluation of adverse events

(Severity of adverse event, relationship between adverse event and study, whether adverse event is known as adverse event of study intervention, etc.)

Severity will be assessed based on five criteria established by the NCI CT Cae Version 5.0:

Level 1, mild; No symptoms or slight signs; It is only for clinical or diagnostic observation and does not need medical intervention;

Level 2, moderate; • Age-appropriate limitations on activities of daily living (activities of daily living such as cooking, shopping, and making phone calls);

Grade 3, serious or medically important but not immediately life-threatening; Resulting in

hospitalization or prolonged hospitalization; Disability; Limited activities of daily living (activities of daily living refer to bathing, dressing, undressing, eating, going to the toilet, and taking medicine, but they are not bed-ridden);

Level 4, life threatening, requiring emergency treatment;

Level 5, AE-related death

8.1.4 Reporting of adverse events

Collection, reporting and handling of aes in 8.1.4.1

All AEs related to the protocol-specified procedures that occurred after the informed consent form was signed and prior to administration of the test article were recorded on the CRF.

Records of AEs should include a description of the AE and all associated symptoms, when it occurred, severity, duration, association with test article, action taken, and final outcome and outcome. The recording of AEs must use medical terminology, and if subject symptoms and signs can be summarized by a common etiology, the diagnosis should be recorded as much as possible. In addition to the indicators related to disease progression, all clinical events and clinically significant laboratory adverse reactions could be handled with reference to the Evaluation Standard for Common Adverse Reaction Events (CT cae) version 5.0; Post-surgical AEs were only evaluated by Clavien-Dindo classification. Treatment-emergent adverse reactions will be documented by the investigator.

Collection and reporting of SAEs in 8.1.4.2

All SAEs, regardless of cause or drug-related, that occurred between the time the subject signed the informed consent form and 4 weeks after completion of study dosing were reported using the SAE Reporting Form. In the event of SAE, the investigator shall immediately take appropriate treatment measures for the subject to ensure the safety of the subject, and report to the drug registration applicant, National Medical Products Administration, the Provincial Food and Drug Administration, the ethics committees of the corresponding clinical trial centers, and the Medical Department of Health and Sanitation Committee, Medical Administration and Hospital Authority within 24 hours and to the ethics committee of the team leader unit in a timely manner. The initial report should, to the extent possible, include the following: source of report, test article name, serious adverse events name, time of occurrence, severity, duration, relevance to the test article, action taken, and outcome.

IX. Data collection and management

9.1 Case Report Form

9.2 data management

The investigator should arrange for the retention of study documents until the end of the study.

In addition, investigators should follow specific local regulations/guidelines regarding the custody of patient records.

Unless otherwise stated in the investigator's agreement, it is recommended that the investigator preserve the study documentation for at least five years after study completion or discontinuation, in accordance with other criteria and/or local law.

X. Ethical requirements

This study was in compliance with the Provisions of Good Laboratory Practice (Good Laboratory Practice) and Administrative Measures for Investigator-sponsored Clinical Studies in Medical and Health Institutions (for Trial Implementation) and the Declaration of Helsinki. This study could be conducted only after the protocol was approved by the Ethics Committee of our hospital before the start of the trial. During the course of the study, if protocol revision is necessary, the revised protocol must be resubmitted to the Ethics Committee for review, and the investigator must wait for the consent of the Ethics Committee before implementing the new protocol.

An informed consent form must be signed by each enrolled patient. A copy of the informed consent form and contact information for the investigator and ethics committee must be provided to the requested patient *. The clinical data and personal information of the research subjects were collected by this research society for scientific research, which would involve the privacy rights of patients. Participants in the study and the data analysts signed a confidentiality agreement not to divulge the patient's personal information and disease-related information to any individual or institution not related to the study. The collected patient data are subject to unified management, so as to prevent personal privacy leakage.

References:

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- [3] NECCHI A, RAGGI D, GALLINA A, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with vari-ant histologies [J] . Eur Urol, 2020, 77 (4) : 439-446.
- [4] NECCHI A, ANICHINI A, RAGGI D, et al. Pembrolizumab as Neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (pure-01) : an open-la bel, single-arm, phase II study [J] . J Clin Oncol, 2018, 36 (34) : 3353-3360.
- [5] POWLES T, KOCKX M, RODRIGUEZ-VIDA A, et al. , Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial [J] . Nat Med, 2019, 25 (11) : 1706-1714.
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immunotherapy to eradicate meta-static disease [J] . Cancer Discov, 2016, 6 (12) : 1382-1399.

[7] BRIGANTI A, GANDAGLIA G, SCUDERI S, et al. Surgical safety of radical cystectomy and pelvic lymph node dissection following neoadjuvant pembrolizumab in patients with bladder cancer : prospective assessment of perioperative outcomes from the PURE-01 trial [J] . Euro Urol, 2020, 77 (5) : 576-580.

[8] He Wang, Jian Huang. One of the updated interpretations of the 2020 EAU bladder cancer guidelines [J].

grade	describe
I	Physical activity is not restricted. Daily activities do not cause excessive fatigue, palpitations, or dyspnea (shortness of breath).
II	<ul style="list-style-type: none"> Slightly limited physical activity. When there is no symptom during rest, daily activities can cause fatigue, palpitation and dyspnea (shortness of breath).
III	Physical activity is significantly limited. Rest asymptomatic, lighter than daily activities can cause

Chinese Journal of Urological Surgery, 2020,41 (7): 492-493.

[9] POWLES T, RODRIGUEZ-VIDA A, DURAN I, et al. A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS) [J] .J Clin Oncol, 2018, 36 (15 Suppl) : 4506-4506.

APPENDIX 1.ECOG PHYSICAL STATUS

grade	describe
0	Able to move freely, and carry out all activities before the disease without restrictions.
one	<ul style="list-style-type: none"> Limited physical activity for heavier tasks, but freedom to move about and engage in light or sedentary tasks, including general household or office work.
2	Able to move freely and live independently; But has lost the ability to work; Get up at least half the time during the day
3	Able to live only partially on his/her own, and stay in bed or wheelchair for more than half of the time during the day.
4	<ul style="list-style-type: none"> Complete disability; Inability to live independently; Bedridden or wheelchair-bound
5	die

Source: Okenmm, CREECH RH, TORMEY DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. AM J Clinoncol. 1982; 5(6):649-55.

APPENDIX 2. FUNCTIONAL CLASSIFICATION OF THE NEW YORK HEART ASSOCIATION

	fatigue, palpitations, or dyspnea.
IV	Do not engage in any physical activity without discomfort. Heart failure symptoms also occur during rest. After engaging in any physical activity, will increase discomfort.

From Dorgin M, AssociationNyh, Foxac, Gorlin R, Levinri, New York Heart Association. Criteria Committee.Nomenclature and criteria for diagnosis of diseases of the heart and great vessels.9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels.Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114

APPENDIX 3. PRE-EXISTING IMMUNODEFICIENCY OR AUTOIMMUNE DISEASE

Potential patients should be asked carefully to determine if they have a history of acquired or congenital immunodeficiency or autoimmune disease.

If you are unsure how to rule out immunodeficiency/autoimmune disease, contact the medical monitor.

Acute disseminated encephalomyelitis	Eddie is sick
ankylosing spondylitis	Antiphospholipid antibody syndrome
aplastic anaemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune pituitary inflammation	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombotic thrombocytopenic purpura	Behcet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Churg-Strauss syndrome/allergic granulomatous vasculitis	Crohn's disease
dermatomyositis	Familial autonomic nervous disorder syndrome
Acquired epidermolysis bullosa	Pemphigoid during pregnancy
giant cell arteritis	Goodall Pasture syndrome
Granulomatous polyangiitis	graves-disease
Guillain-Barre Syndrome	hashimoto's disease
Immunoglobulin A(IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
lambert eaton myasthenic syndrome,lems	lupus erythematosus
Lyme disease (chronic)	corneal ulcer
morphea	multiple sclerosis
myasthenia gravis	Neuromuscular rigidity
Ocular myoclonus syndrome	optic neuritis
Alder's thyroiditis	pemphigus
pernicious anemia	Nodular polyarthritis

Multiple arthritis	Multiple glandular autoimmune syndrome
Primary biliary cirrhosis	psoriasis
Wright's syndrome	rheumatoid arthritis
sarcoidosis	Schaeffering syndrome
Stiff person syndrome	Gao 'an arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 4. GUIDELINES FOR EFFICACY EVALUATION CRITERIA (RECIST) FOR SOLID TUMOR, VERSION 1.1

The following text is extracted from the following references:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-47.

definition

Mitigation and progress in this study will be evaluated using international standards proposed by the RECIST Committee (Version 1.1). Only the change in the longest diameter of the tumor lesion (one-dimensional measurement) was used in RECIST. -

Note: Pathological changes will be classified as measurable or non-measurable according to the criteria provided below. -the term "evaluable" used for reference scalability will no longer be used as it does not provide additional meaning or accuracy.

Measurable disease

Neoplastic lesions: at least one dimension not less than a low limit must be accurately measured:

- 10 mm with CT scan (regardless of scanner type) and MRI (not less than twice the slice thickness, at least 10 mm)
- 10 mm, measured with calipers on clinical examination (lesion on body surface)
- 20 mm, with chest X-ray (if well demarcated and surrounded by inflated lungs)-

Malignant lymph nodes: When evaluated with a CT scan (CT scan thickness is recommended to be no more than 5 mm), the short axis of the lymph node must be ≥ 15 mm to be considered pathologically enlarged and measurable. Only minor axis lengths were measured and tracked at baseline and at follow-up. -

An unmeasurable illness

All other lesions (or disease sites), including small lesions (conventionally ≥ 10 to < 15 mm in longest diameter or CT scan < 10 mm) were considered unmeasurable. Leptomeningeal disease, ascites, pleural or spiral pericardial effusion, inflammatory breast disease, lymphatic involvement of the skin or lungs, and abdominal masses/enlargement of abdominal organs determined by physical examination to be undetectable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scans, PET scans or plain films are not considered appropriate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
- If the soft tissue portions meet the above definition of measurability, lytic bone lesions or lytic-acute mixed lesions with identifiable soft tissues may be considered measurable when they can be evaluated by cross-imaging techniques such as CT or MRI. -
- Acute bone lesions are not measurable

Cystic lesions:

- Lesions that meet the criteria for simple cysts in the X-ray definition should not be considered malignant (measurable or not) because by definition they are simple cysts. -
- A "cystic lesion" that is considered to be a cystic metastasis may be considered measurable if it meets the above measurable definition

Quantitative lesions. However, if non-cystic lesions are present in the same patient at the same time, it is preferred that these are all targeted lesions. -

Lesions that have been locally treated:

- Tumor lesions previously located in the irradiated area or in an area under other local treatment are not generally considered measurable unless the lesion is demonstrated to be still present. The protocol should specify the conditions under which this lesion may be considered a measurable disease.

Target lesion

All measurable lesions (up to 2 lesions per organ for a total of 5 lesions) should be identified as target lesions and recorded and measured at baseline. The target lesion should be selected according to its size (the lesion with the longest diameter), be representative of all relevant organs, and in addition to this, be a lesion that facilitates repeated measurements.

Lymph nodes deserve special mention because they are normal anatomical structures that can be seen on imaging studies even in the absence of a tumor. Pathological nodules defined as measurable and identifiable as target lesions must meet the criteria of ≥ 15 mm in the short axis of the CT scan. The sum of the baseline was only obtained by summing the short axes of these nodules. The short axis of the nodule is the diameter that the radiologist usually uses to determine if the nodule is involved by a solid tumor. Nodule size is usually reported as two-dimensional data in the acquired image plane (for CT scans, the results are almost always axial; For MRI, that acquisition plane may be transverse, sagittal or coronal). The smaller of these measurements is the short axis. For example, an abdominal nodule measuring 20 mm \times 30 mm was reported, with a short axis of 20 mm, and was characterized as a malignant, measurable nodule. In this example, 20 mm should be recorded as the nodule measurement. All other pathologic nodules (with a short axis ≥ 10 mm but < 15 mm) should be considered non-target. Nodules with a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

The sum of the diameters of all target lesions (longest diameter for non-nodular lesions and short axis for nodular lesions) will be calculated and reported as the sum of baseline diameters. -if lymph nodes are included in the sum of diameters, then only minor axes are included in the sum of diameters as described above. The sum of the baseline diameters will be used as a reference to further characterize the various objective tumor responses in the measurable dimension of the disease.

Non-target lesion

All other lesions (or disease sites), including pathological lymph nodes, should be identified as non-target lesions and should be recorded at baseline. -No measurement is required and these lesions should be noted as "present", "absent", or in a few cases "clearly progressing" (see below for more details). In addition, multiple non-target lesions involving the same organ (for example, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases") can be recorded on a case history sheet.

Guideline for measurable disease assessment

All measurements should be recorded in units of metric symbols and measured with calipers for clinical evaluation. All baseline assessments must be performed as close as possible to treatment initiation and no later than 4 weeks prior to treatment initiation.

The same assessment methods and techniques should be used at baseline and at follow-up for each identified and reported lesion. -Except for lesions that can only be evaluated by clinical examination and are not applicable to image detection, all lesions must be evaluated by image detection, and cannot only be subjected to clinical examination.

Clinical lesions:

Clinical testing with calipers is considered only for superficial lesions below P10mm, such as skin nodules. The skin lesions are recommended to be recorded using color photographs with a scale measuring the size of the lesion. As mentioned above, imaging should be performed when the lesion is amenable to both clinical and imaging examination, as imaging is more objective and can be used for review of study endpoints after treatment.

- Chest X-ray: Chest radiograph and chest CT are used to measure the lesions, and chest CT is preferred, especially when an important treatment endpoint progresses, because CT is more sensitive than X-ray, especially in the detection of new lesions. -Of course, lesions with clear borders and surrounded by inflated lungs can also be detected using chest radiographs. -
- CT, MRI: CT is currently the most effective and repeatable test for evaluating the efficacy of a lesion. This guideline specifies whether a CT scan can be used to measure lesions based on whether the CT slice thickness is not more than 5 mm. When the thickness of the CT scan layer exceeds 5mm, the measurable lesion should be at least twice the layer thickness. MRI can also be used in some cases (such as a whole-body scan).
- Ultrasonography: Ultrasound should not be used to assess the size of a lesion and should not be used as a measurement. The ultrasound examination cannot be completely reproduced between two adjacent observations and the results depend on the operator, from one detection to the next, The use of the same technique and the same measurement results are not guaranteed. If new lesions are found by ultrasound during the course of the study, CT or MRI verification is recommended. If CT radiation is of concern, CT may be replaced with MRI in some cases.
- Endoscopy, laparoscopy: these techniques are not recommended for the evaluation of solid tumors. However, these examinations can be used when a biopsy confirms complete pathologic remission or to determine CR or recurrence after surgical resection.
- Tumor markers: Tumor markers cannot be used alone to evaluate the efficacy of solid tumors. If the marker is initially above the upper limit of normal, the marker must return to a standard level when the

patient is judged to be CR. Because tumor markers are disease-specific, measurement specifications should be noted in the protocol for a particular disease.

Special guidelines on CA-125 changes (ovarian cancer recurrence) and PSA changes (prostate cancer recurrence) have been published. In addition, the Gynecologic Oncology International Group has developed criteria for the progression of CA-125, which will be used in combination with objective tumor assessment for first-line studies of ovarian cancer.

- Cytology, histology: these techniques can be used to differentiate PR and CR in individual cases, if required by the protocol (e.g., residual lesions in tumors, such as germ cell tumors, where known residual benign tumors can be retained). When exudation is known to be a potential side effect of treatment (e.g., using certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the tumor origin of any exudate present or worsening may be considered during treatment if measurable tumors meet criteria of efficacy or disease stabilization to distinguish disease response (or disease stabilization) from PD.

Efficacy evaluation criteria

Therapeutic evaluation of target lesions

- Complete response (CR): All target lesions disappeared. The minor axis diameter of all pathological lymph nodes (whether target lesions or not) must be reduced to < 10 mm -
- Partial response (PR): a reduction of at least 30% in the sum of all target lesion diameters relative to the sum of baseline diameters
- Disease progression (PD): using the sum of the smallest diameters in the study as a reference, the sum of the diameters of the target lesions was increased by at least 20% (or the sum of baseline if it was the smallest diameter in the study). In addition to a relative increase of 20%, the sum must also show an increase in absolute value of at least 5 mm (Note that those with 1 or more new lesions will also be considered progressive).
- Stable Disease (SD): The extent of contraction did not meet the requirements of PR and the extent of increase did not meet the requirements of PD and was used as a reference for the sum of the minimum diameters during the study.
- Lymph nodes: If the target lesion is a lymph node, its actual short axis value (measured on the same anatomic plane as at baseline) should always be measured and recorded, even if the lymph node in question has resolved to less than 10 mm This means that when lymph nodes are also included in the target lesion, the "sum" of the lesions may not be zero even if the criteria for CR are met, since a normal lymph node is defined as having a short axis < 10 mm The case report was recorded separately, in which the short axis of each nodule had to be < 10 mm in order to meet the criteria for CR. For PR, SD, and PD, the actual short-axis measurement of the nodule will be included in the sum of the target lesions.

Target lesions that were "too small to be measured" In the study, all lesions recorded at baseline (nodular and non-nodular) should have their actual measurements recorded at each subsequent evaluation, even if they were very small (e.g., 2 mm). -however, sometimes lesions or lymph nodes recorded as target lesions at baseline become so vague on CT scans that the radiologist cannot comfortably assign accurate measurements and may report them as "too small to be measured."

When this occurs, it is important to record a measurement in the eCRF. If the radiologist believes the lesion may disappear, the measurement should be recorded as 0 mm If the lesion is considered to be present and faintly visible, but too small to be measured, a default value of 5 mm should be specified (note: this rule is unlikely to apply to lymph nodes, which usually have a definable size under normal circumstances and are often surrounded by fat, such as retroperitoneum; However, if lymph nodes are considered to be present and faintly visible but too small to be measured, the default value of 5 mm should also be specified in this case). The default value is based on the thickness of the 5 mm CT scan slice (the default value of 5 mm should not be changed if this thickness is changed). Measurements of this (too small to measure) lesion may lack repeatability, so giving this default value may prevent false efficacy or false progression due to measurement errors. -again, if the radiologist can give an actual measurement, even if it is less than 5mm, it should be recorded.

- Split or fused lesions on treatment: When a non-nodular lesion is "fragmented", the longest diameters of all fragments must be summed to calculate the sum of the target lesions (diameters). Similarly, if the lesions are fused, the plane between the lesions may remain unchanged before the merger, which contributes to obtaining the maximum diameter of each lesion. If the lesion is indeed fully fused and will not separate, the sagittal position of the longest diameter in this case should be the longest diameter of the "fused lesion".

Efficacy evaluation of non-target lesions

Although certain non-target lesions may in fact be measurable, special time points defined by the protocol may be non-measurable and qualitative.

- CR: All non-target lesions resolved and tumor marker levels normalized. -all lymph nodes must meet non-pathological criteria in size (i.e. short axis < 10 mm).
- PD: There has been definite progression of the non-target lesion (see below). (Note: The presence of one or more new lesions is also considered progressive.)

- Non -CR/ Non-PD: 1 or more non-target lesions persist and/or tumor marker levels remain above the upper limit of normal
- When patients simultaneously suffer from measurable diseases: in this case, in order to achieve a "definite progression" on the basis of non-target diseases, an overall level of substantial deterioration of the non-target diseases must occur, so that even in the presence of SD or PR in the target diseases, the overall tumor burden has increased to an extent sufficient to stop treatment. One or more non-target lesions were "increased" slightly in volume, but were generally insufficient to qualify as definitive progression. Therefore, if SD or PR occurs in a target disease, it will be extremely rare for the overall progression to be assigned solely based on the changes in the target disease in this setting.
- When a patient has only a non-measurable condition: this is generally the case in some Phase III trials where having a measurable condition is not a criterion for enrollment. As mentioned above, the same general concept applies here as well, but in this case, the lack of evaluation of measurable diseases can be used to explain the increase in the unmeasurable disease burden. -because the exacerbation of a non-target disease cannot be easily quantified (by definition: if all lesions are indeed unmeasurable), in assessing whether a patient has progressed definitively, if it is judged from the change in the unmeasurable disease that the overall disease burden increases to the extent necessary to determine the occurrence of PD in a measurable disease, a useful examination can be applied: that the increase in tumor burden represents an additional 73% increase in "volume" (which corresponds to a 20% increase in the measurable lesion diameter). -examples include the increase in pleural effusion from "trace" to "massive", the increase in lymphangitic disease from local to diffuse, or may be described in the protocol as "sufficient to warrant modified treatment". If "clear progression" is observed, the patient should be judged to have overall PD at that time point. While it would be desirable to apply objective criteria to an unmeasurable condition, the increase would have to be substantial because of the nature of the condition itself, which is unlikely to occur.

New lesion

The appearance of a new malignancy suggests PD, so it is important to discuss the detection of new lesions. Since there are no specific criteria for identifying new lesions on radiographs, the findings of new lesions should be very clear, for example not due to differences in scanning techniques, changes in imaging patterns or other findings other than tumor (e.g. some "new" bone lesions may simply be healing or emergent from pre-existing lesions). This is particularly important when a patient's baseline lesion presents as PR or CR. For example, hepatic necrosis may be reported as a "new" cystic lesion on the CT scan report card when it is not.

Anatomical locations where no lesion was detected on the baseline scan If a lesion was detected on the follow-up study, it can be considered a new lesion and indicates PD. -As an example of this, the patient had visceral disease at baseline and a CT or brain MRI examination showing metastases was scheduled at the time of study participation. Brain metastases in this patient can be considered evidence of PD development, although the patient did not undergo brain imaging at baseline.

If the new lesion is ambiguous, e.g. too small in size, continued treatment and subsequent evaluation will prove whether it represents a truly new disease. -If a repeat scan confirms the presence of a new lesion, the date of the initial scan should be used to announce progress.

Evaluation of best overall efficacy

Optimal overall response was the record of the best efficacy confirmed after consideration of various factors from the start of study treatment to the end of treatment. Sometimes efficacy is not recorded until after treatment is completed, so if posttreatment evaluation is considered in determining the best overall efficacy, this should be stated in the protocol. -The protocol must specify the designation of how the various new therapies introduced before progression will affect the best efficacy. The best overall response allocation for a patient is related to the discovery of both targeted and non-targeted lesions, and new lesions are considered. Also, due to the nature of the study itself and protocol requirements, certain measurements may be required. In particular, in non-randomized studies where efficacy is the primary endpoint, PR or CR need to be established as either "best overall efficacy."

Once all the patient's data are available, the best overall response can be determined. When determining the best efficacy in studies that did not require validation of CR or PR: The best efficacy in these studies was defined as the best efficacy at all time points (for example, 1 patient was determined to be SD in the first assessment, PR in the second assessment, PD in the last assessment, and his best overall response was PR). When disease stabilization is considered optimal, it must also meet the protocol minimum time from baseline. If the prescribed minimum time is not reached by keeping SD, but SD is indeed the best efficacy at the time point, and the best efficacy for patients depends on the subsequent evaluation. For example, if the patient was SD on the first evaluation and PD on the second evaluation, and there is no minimum required duration for SD, then PD is the best therapeutic outcome. The same patient was considered non-evaluable if lost to follow-up after the first SD evaluation.

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	no	CR

CR	Non -CR/ non -PD	no	PR
CR	Not evaluated	no	PR
PR	Non-PD or not all evaluated	no	PR
SD	Non-PD or not all evaluated	no	SD
Not all evaluations	Non -PD	no	NE
PD	various	Yes or no	PD
various	PD	Yes or no	PD
various	various	be	PD

Abbreviation: CR, complete remission; NE, cannot be evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

If the nodule lesion is included in the sum of the target lesions and the nodule size decreases to a "normal" size (< 10 mm), measurements are still reported on the scan log. These measurements should be recorded even if the nodules have recovered, and should be based on whether the nodule size has increased in order not to over-evaluate progression. As mentioned, this means that the sum of the patients who achieved CR may not be "zero".

In studies where efficacy needs to be determined, repeated "evaluable" time point assessments may complicate the determination of optimal efficacy. The analysis plan for the study must state how the missing data/assessments will be used to determine efficacy or progress. For example, PR- evaluable -PR is reasonable as a confirmed efficacy in most studies when considering a patient's efficacy at different time points.

Patients with deteriorating general health who require discontinuation of treatment but for whom there is no objective evidence of PD at this time point should be reported as having "symptomatic deterioration". Objective progression should be positively confirmed even after discontinuation of therapy. The worsening of the symptoms was not a description of an objective response: it was the reason for discontinuation of study treatment.

The conditions defining "early progression", "early death", and "non-evaluability" are study specific and should be clearly described in each protocol (depending on treatment duration, treatment cycle settings).

In some cases, it may be difficult to differentiate between residual lesions and normal tissue. When these results are needed to evaluate CR, it is recommended that the residual lesion be examined (by needle aspiration/biopsy) prior to concluding CR.

Since the progression of the findings is vague (e.g. a very small and uncertain new lesion; Cystic changes and necrosis of pre-existing lesions, etc.), the treatment can continue until the next scheduled evaluation point in time. If progress is confirmed in the next planned assessment, the date of progress should be earlier than the date when progress is suspected.

Confirmatory measurement/duration of response

Confirmation method

In non-randomized studies with efficacy as the primary endpoint, the identification of PR or CR requires the identification of efficacy as a result of a measurement error. Doing so would also enable appropriate interpretation of the results based on historical data, as in such cases such studies have traditionally required validation. However, in all other cases (such as randomized studies (Phase II or III) or studies with SD or progression as the primary endpoint), confirmation of efficacy may not be required because there is no added value to the interpretation of the study results. However, the elimination of the requirement for efficacy confirmation may make the central review of prevention deviation more important, especially in open-label studies.

For SD, there must be at least one measurement meeting SD criteria within the minimum time interval after entry into the study (typically not less than 6 weeks).

Overall duration of response

The DOR ranged from when the CR/PR time measure was first met, as recorded for the first time, to the first day on which recurrent or progressive disease was objectively recorded, using the smallest measure recorded in the study as the reference for PD.

The overall CR duration was from the first meeting of the CR time measurement criteria to the objective recording of the first day of disease relapse.

Duration of disease stabilization

The duration of disease stabilization was measured from the start of treatment (calculated from the date of enrollment) until criteria for progression were met, using the smallest sum in the study as a reference (if the baseline sum was the smallest, the baseline value would be used as a reference for PD calculations).

The clinical relevance of disease stabilization durations differs among studies and diseases. If the proportion of patients who achieve disease stabilization in the shortest time in a particular study is an important endpoint, the protocol should specify the shortest time interval required to determine disease stabilization twice.

Note: Frequency of follow-up after baseline assessment had an impact on DOR, duration of stabilization, and PFS. -defining standard follow-up frequencies is outside the scope of this guideline. -Frequency should take into account a number of parameters including disease type and stage, treatment cycle and standard practice. However, these limitations on the accuracy of measurement endpoints should be considered if comparisons are to be made between studies.

APPENDIX 5.COCKCROFT-GAULT FORMULA

Serum Creatinine Concentration (SCr) (in MG/DL) a

$$\text{Male C1cr(mL/min)} = \frac{(140 \text{ years old}) (\text{weight}) \text{ b}}{(72) (\text{SCr})}$$

$$\text{Female C1cr(mL/min)} = \frac{(0.85)(140 \text{ years}) (\text{weight}) \text{ b}}{(72) (\text{SCr})}$$

Serum Creatinine Concentration (SCr) (in mol/L) a

$$\text{Male C1cr(mL/min)} = \frac{(140 \text{ years old}) (\text{weight}) \text{ b}}{(0.81)(\text{SCr})}$$

$$(0.85)(140 \text{ years}) (\text{weight}) \text{ b}$$

$$\text{Female Cr(mL/min)} = \frac{\text{Cr(mL/min)}}{1.21} \times (0.81) \quad (\text{SCr})$$

- a Age is measured in years and weight in kilograms.
- b If the subject was obese (> 30% of ideal body weight), ideal body weight was used in calculating the estimated CLcr

APPENDIX 6. CLAVIEN-DINDO GRADING

The classification of surgery-related AEs as defined in Clavien-Dindo is as follows:

The severity of the complications was graded according to the Complication Score System (Clavien-Dindo scale) with a Grade IIIA or above as a serious complication.

- Level 1: Complications of unwanted medical, surgical, endoscopic, and reflex interventions after surgery, but including medication antiemetics, antipyretics, analgesics, diuretics, electrolytes, physical therapy, and open-label wound infection by the bed
- Level 2: patients requiring medication other than Level 1, including incision infections requiring antibiotic therapy, blood transfusions, and total parenteral nutrition
- Level 3: Surgical, endoscopic and radiological intervention required: Level 3a: No general anesthesia required; Class 3b: general anesthesia required
- Level 4: Life-threatening complications (including central nervous system complications) requiring intermittent or critical care: 4a: single organ dysfunction (including dialysis); 4b: Multiple organ dysfunction
- Level 5: Death

REFERENCES

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240(2):205-213.