RC48-ADC combined with tislelizumab as neoadjuvant treatment in patients with HER2 positive locally advanced muscle-invasive urothelial bladder cancer—A multi-center phase Ib/II study (HOPE-03)

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Study protocol

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Abstract

Background

Bladder cancer with Human Epidermal Growth Factor Receptor 2 (HER2) high expression is related to pathological malignancy and poor prognosis. The standard care for muscle-invasive urothelial bladder cancer (MIBC) is neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) with pelvic lymph node dissection. For HER2 positive MIBC, the efficacy of cisplatin-based NAC is unsatisfactory, and adverse reactions are inevitable or even intolerable. New regimens with higher efficiency and lower toxicity are needed to be explored in the neoadjuvant setting for this population.

Methods

HOPE-03 is a multi-center, open-label, single-arm, phase Ib/II study, aiming to evaluate the safety and efficacy of RC48-ADC (Distamab Vedotin, DV), a humanized anti-HER2 antibody conjugated with monomethyl auristatin E, and tislelizumab (PD-1 antibody) as a novel neoadjuvant treatment combination in patients with HER2 positive locally advanced urothelial MIBC. Fifty-one patients with cT2-4bN0-3M0-1a pathological and imaging diagnosed HER2 positive (Immunohistochemistry status 3+ or 2+ or 1+) MIBC will be recruited. Of them, 6 patients are enrolled in the dose-escalation phase (3 patients in RC48-ADC 1.5kg/m2 group and 3 patients in 2.0mg/kg group), and 45 patients enter into phase II study (the expected recommended phase II dose for RC48-ADC is 2.0mg/kg). Patients without disease progression will receive radical cystectomy or bladder-sparing therapies as their will after neoadjuvant treatment. The primary endpoints are clinical complete remission rate (cCR, T0/Ta/Tis), pathological complete remission rate (pCR) and safety. The secondary endpoints are overall survival (OS), local recurrence free survival (LRFS), distant metastasis free survival (DMFS) and quality of life.

Discussion

HOPE-03 trial will give a description about the safety profile of RC-48 and tislelizumab combination in the neoadjuvant treatment of HER2 positive locally advanced urothelial MIBC, and the efficacy will be explored as well in this population.

Background

Bladder cancer is the tenth commonly diagnosed malignancy all over the world, with an estimated 573,278 new cases and 212,536 deaths occurred globally in 2020[1]. It is more common in males than in females, with respectively estimated incidence rate and mortality rate ranking fourth and eighth among all the cancer types in the United State men in 2022[2]. Urothelial carcinoma accounts for about 90% bladder cancer, and more than 30% bladder cancers are muscle-invasive urothelial bladder cancer (MIBC) [3]. Platinum-containing neoadjuvant chemotherapy (NAC) followed by radical cystectomy and pelvic
lymph node dissection is a widely used standard treatment for urothelial MIBC, with a 5-year overall survival (OS) rate of approximately 50%-70% [4].

Not with standing, the established position of NAC in urothelial MIBC, there are many challenges in the implementation process. On the one hand, the compliance of clinical guidelines in daily practice is as low as 20%; On the other hand, about 50% of patients are not eligible for cisplatin nor for neoadjuvant treatment because of risk comorbidities, such as impaired renal function, heart failure, hearing loss[4, 5]. The situation becomes more complicated when it comes to human epidermal growth factor receptor-2 (HER2) positive urothelial MIBC patients.

HER2, as a member of epidermal growth factor receptor family, plays an important role in cell proliferation and differentiation though the tyrosine kinase activity[6]. As we know, the amplification of HER2 gene resulted in overexpression of HER2 protein, which is related with the growth of several tumors, such as breast cancer, gastrointestinal cancer and ovarian cancer. Therefore, HER2 is a promise target in clinical cancer treatment. The HER2 overexpression in urothelial bladder cancer varies from 4–76%, which is one of the most prevalent carcinomas[7–10]. It is verified that the overexpression of HER2 protein is related to tumor progression and poor prognosis in bladder cancer, and the efficacy of cisplatin-based NAC in HER2 positive urothelial bladder cancer is unsatised[11–13]. However, the explore of antitumor efficacy of HER2 antibodies and tyrosine kinase inhibitors(TKIs) in HER2 positive urothelial carcinoma(UC) has encountered dilemmas[14, 15]. Hence, new regimens with better efficiency and lower toxicity are needed to be explored in the neoadjuvant setting for this population.

RC48-ADC (Distamab Vedotin, DV), a humanized HER2 targeting antibody conjugated with monomethyl auristatin E(MMAE), been granted as a breakthrough treatment for metastatic UC by FDA in 2020 based on the results of RC48-C005 and RC48-C009 studies, in which RC48-ADC demonstrated a promising efficacy with a manageable safety profile in HER2-positive locally advanced or mUC patients who failed to platinum-based chemotherapy[3].

Meanwhile, immune checkpoint inhibitors(ICI s) targeting programmed cell death protein 1 (PD-1) and programmed cell death–ligand1 (PD-L1) have significantly changed the treatment landscapes of locally advanced / unresectable or metastatic UC[16]. Previous studies showed the combination of RC48-ADC and PD-1 antibody may have synergistic antitumor effect, because ADC linking to MMAE elicits immunogenic cell death (ICD) and has a direct effect on DC maturation and activation, which may enhance antitumor immunity[17, 18]. Moreover, combination of RC-48-ADC and PD-1 antibody confirmed an promising objective response rate (ORR) of 73.9% for metastatic UC patients without previous system treatment and a good tolerance in RC48-C014 trial [19]. However, the efficacy of this combination in the local advanced HER2 positive urothelial bladder cancer is still unknown.

Therefore, the present study aims to evaluate the safety and efficacy of RC48-ADC and tislelizumab (PD-1 antibody) as a novel neoadjuvant treatment combination in patients with HER2 positive locally advanced urothelial MIBC. And whether this setting can achieve better efficacy and safety profile than platinum-
based NAC in the neoadjuvant treatment of HER2 positive MIBC patients will be further explored indirectly.

Materials And Methods

Study design

This is a Ib/II, multi-center, open-label, single-arm study. Patients with cT2-4bN0-3M0-1a pathological and imaging diagnosed HER2 positive (Immunohistochemistry status 3+ or 2+ or 1+) MIBC are eligible. Of them, 6 patients are enrolled in the dose-escalation phase (3 patients in RC48-ADC 1.5kg/m2 group and 3 patients in 2.0mg/kg group), and 45 patients enter into phase II study (the expected recommended phase II dose for RC48-ADC is 2.0mg/kg). RC48-ADC is given every 2 weeks with a maximum dose of 120mg, meanwhile tislelizumab is given every three weeks at the dose of 200mg. Treatment efficacy will be performed by imaging and transurethral multi-point biopsy after the neoadjuvant therapy. Patients without disease progression will receive radical cystectomy or bladder-sparing therapies as their will thereafter. For patients receiving radical cystectomy, tislelizumab will be given to one year totally for patients with ypT2-4a or ypN+, and adjuvant radiotherapy will be considered in selected patients (ypT3-4, positive nodes/ margins). For patients with bladder-sparing will, pelvic radiotherapy will be given, and tislelizumab will be continued to one year in total. Patients who suffer from disease progression during the neoadjuvant treatment will receive second-line treatment. The flow-chart of the study is presented in Fig. 1.

Study organization, ethics approval and drug supply

The current trial is principal- investigator mainly initiated by West China Hospital, Sichuan University, and three other institutions take part in the study, including Sichuan Provincial People's Hospital, Affiliated Hospital of Southwest Medical University, Affiliated Hospital of North Sichuan Medical College. The treatment protocol was approved by the medical ethics committee of West China Hospital, Sichuan University and Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20210564). Signed informed consent is required before eligible patient is enrolled. Additionally, the study was performed in accordance with the ethical standards put forth in the 1964 Declaration of Helsinki. RC48-ADC and Tislelizumab are provided free of charge by RemeGen Ltd. and BeiGene Ltd. for clinical trial subjects, respectively.

Study population

The patients with HER2 positive urothelial MIBC will be selected according to the inclusion criteria and exclusion criteria (Table 1). HER2 status of 1+, 2+, 3+ by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) can be included in this study. And the status of HER2 and PD-L1 expression can be stratifies analysis factors. The study was opened on December 24, 2021.
Table 1
Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. Pathological confirmed urothelial cancer</td>
<td>1. Female with pregnancy or breast-feeding</td>
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<tr>
<td>2. Imaging diagnosed cT2-4bN0-3M0-1a muscle-invasive urothelial bladder cancer</td>
<td>2. Uncontrolled infection disease needs systemic therapy</td>
</tr>
<tr>
<td>3. Immunohistochemistry status of HER2 is 3+ or 2+ or 1+</td>
<td>3. Diagnosed with other malignancies within 5 years</td>
</tr>
<tr>
<td>4. No prior systemic chemotherapy</td>
<td>4. History of previous anti-tumor treatment, including chemotherapy, immune checkpoint inhibitors regimes, radiotherapy, etc</td>
</tr>
<tr>
<td>5. Age ≥ 18 years old, male and female</td>
<td>5. Active autoimmune disease or immunodeficiencies, organ transplantation history or systematic use of immunosuppressive drugs</td>
</tr>
<tr>
<td>6. ECOG physical status 0 or 1</td>
<td>6. Current severe cardiac disease, renal and/or liver dysfunction</td>
</tr>
<tr>
<td>7. Sufficient functions of heart, bone marrow, liver, kidney and other organs</td>
<td>7. Severe neurological or mental illness</td>
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<tr>
<td>8. Good compliance and signed the consent form</td>
<td>8. History of acute cardiac infarction or cerebral ischemic stroke occurred within 6 months</td>
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<td>9. Human immunodeficiency virus (HIV) infection (i.e., HIV 1 to 2 antibody positive), active syphilis infection, active pulmonary tuberculosis infection</td>
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<tr>
<td></td>
<td>10. Active Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection</td>
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<td></td>
<td>11. Allergic to any component of the regimens</td>
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<td></td>
<td>12. Insufficient patient's compliance</td>
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</table>

Study endpoints and assessment

The primary endpoints are clinical complete remission rate (cCR, T0/Ta/Tis), pathological complete remission rate (pCR) and safety. The secondary endpoints are overall survival (OS), local recurrence free survival (LRFS), distant metastasis free survival (DMFS) and quality of life.

Imaging evaluation will be performed based on the response evaluation criteria in solid tumors (RECIST v.1.1) and immune response evaluation criteria in solid tumors (iRECIST). For patients with radical cystectomy, pCR is used as the main endpoint, namely, no evidence of tumor cells in resected specimens. And for patients with bladder-sparing treatment, cCR is applied as the primary endpoint, defined as undetectable tumor existence after NAC by chest and abdominal computed tomography (CT), bladder magnetic resonance (MR) and cystoscopy of multi-point biopsy, which includes the clinical efficacy of T0 /Ta /Tis.

Adverse effects will be evaluated every cycle of treatment and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. OS is defined as time from enrollment to death. For
patients achieving pCR or cCR, LRFS and DMFS will be recorded, defining as time from evidence of no existence of tumor to local recurrence or distant metastasis of disease per RECIST 1.1 or death, respectively. Patients’ quality of life will be evaluated based on FACT-G scales at the end of the neoadjuvant therapy and during every follow-up visit.

**Sample size**

The main research purpose of this trial is the cCR rate and it is proposed to adopt a non-randomized controlled observation study. With reference to the data in published clinical studies or the treatment data of our institution previously, the cCR rate of HER2 positive urothelial MIBC patients who received gemcitabine and cisplatin combination with or without immunotherapy as a new adjuvant treatment is about 23%. We expect that the cCR rate of this research scheme can be increased to 40%, and β value of 0.2, α value of 0.05 are applied in Single Stage Phase Ib/II Clinical Trials with PASS. The estimated lost interview rate is 10%. As a result, 51 patients will be enrolled, including 6 patients in Phase Ib stage, 3 patients in the RC48-ADC 1.5mg/kg combined tislelizumab group, and 3 patients in the RC48-ADC 2.0mg/kg combined tislelizumab group; and 45 patients will be enrolled in stage II. The planned enrollment time is 1–2 years. Considering the interference of other factors, we will include as many patients as possible who meets the inclusion criteria.

**Follow-up**

Based on the study protocol, patients will receive regular examinations at the baseline and end of the whole neoadjuvant therapy and at every visit during the follow-up. Regular examinations are consisted of chest and abdominal CT, bladder MR, cystoscopy of multi-point biopsy, blood cells counting, liver and kidney function test, urine routine test and FISH test. For patients after cystectomy or radiotherapy, regular visit will be applied every three months in the first two years, and every 6 months in the next three years.

**Discussion**

Bladder cancer, as one of the common malignancies, carries a large societal burden in the worldwide. About half locally advanced MIBC patients will ultimately develop distant disease after radical cystectomy and pelvic lymph node dissection because of the micro-metastases in the blood[20, 21]. Hence, NAC followed by local therapy plays a key role in reducing recurrence rate and metastatic rate, as well as prolonging the overall survival[22]. Gemcitabine and cisplatin (GC) and dose dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) have been widely used in clinical practice as systematic treatment of locally advanced MIBC, with a pCR rate varying from 36%-42%[23]. In the past 10 years, development of sequencing technologies has deepened the understanding of pathogenesis of bladder cancer and widened the potential treatment options[4]. On the basis of high mutation burden of bladder cancer genomic characterization, ICIs have been recommended in the first-line and second-line treatment of selected advanced urothelial cancer patients. Moreover, the expanded applications in neoadjuvant, adjuvant and bladder-sparing treatments have been evaluated in advanced
bladder cancer patients, in which durable responses in a subset of patients have been achieved. The pCR rate for single-agent ICI or two ICIs combinations in the neoadjuvant setting varied from 7–46%, including 42% of pembrolizumab in PURE-01 trial, 27% of atezolizumab in ABACUS trial, and 43% of durvalumab plus tremelimumab in the first reported dual ICIs setting [24–26]. Besides, the combination of chemotherapy and ICIs as an optional neoadjuvant also has been explored with pCR rates varied from 7–46%.

Additionally, with the discovery of commonly expressed molecular targets in bladder cancer, targeted therapies have been developed, such as antibody-drug conjugates of HER2 and fibroblast growth factor receptor inhibitors. Several studies showed that the overexpression of HER2 was associated with tumor progression and poor prognosis[7]. Besides, compared with HER2 negative MIBC patients, HER2 overexpression patients showed therapeutic resistance to regular chemoradiation treatment[13]. Based on the real-world study of chemotherapy plus immunotherapy versus chemotherapy alone as neoadjuvant treatment guided bladder-sparing therapy for localized MIBC of our group, we found the cCR rate was about 23% for HER2 positive urothelial MIBC patients who received GC chemotherapy with or without immunotherapy as a new adjuvant treatment, and related adverse reactions were inevitable or even intolerable [27]. Therefore, new regimens with higher efficiency and lower toxicity are needed to be explored in the neoadjuvant setting for this population.

Though the unsuccessful clinical explorations of antibodies and TKIs of HER2 in urothelial cancer, the advent of ADCs changes the treatment landscape of advanced bladder cancer. ADCs is consisted of a monoclonal-antibody, a protease-cleavable linker, and chemotherapeutic drug. After the interaction of antibody and antibody target expressed on the surface of tumor cell, the cytotoxic agent will be released inside the cells after the internalization of ADCs and cleavage of lysosomal linker, which leads to the delivery of high dose of the chemotherapy agent. Until now, several proteins have been investigated as the ADCs’ targets, including SLITRK6, Nectin-4, Trop-2, and Her-2[28–30].

RC-48-ADC, with a highly selective HER2 affinity, elicited promising anti-tumor effect in HER2 positive advanced or metastatic urothelial cancer patients with disease progression of at least one line treatment[3]. In addition, the combination of RC-48-ADC and PD-1 antibody (Toripalimab) achieved a satisfied ORR of 73.9% in metastatic UC patients without previous system treatment. It is worth to verify the disease control ability of RC48-ADC and ICI combination in the neoadjuvant treatment of locally advanced MIBC patients.

The current HOPE-03 trial, is an open-label, multi-center, phase lb/II study, designing to figure out the safety and efficacy of RC48-ADC and tislelizumab combination as neoadjuvant treatment in patients with HER2 positive locally advanced urothelial MIBC. Pathological and imaging diagnosed HER2 positive (Immunohistochemistry status 3 + or 2 + or 1+) cT2-4bN0-3M0-1a MIBC patients with will be recruited, and the sample size is 52. The enrollment is currently ongoing, and 6 patients are included until now. The median age was 62 years old with clinical stages of T3-4aN0-3M0. Five patients were HER2(2+), and 1 patient was HER2(1+). Among them, 4 patients received the primary efficacy evaluation by now. Three
patients achieved T0, and 1 patient was Tis. Hence the cCR rate was 100%. Only one patient suffered from immune-related grade 2 myositis and grade 1 elevated transaminase adverse event, which led to treatment interruption. Besides, RC48-ADC related toxicities were found in 3 patients, including Grade 1 elevated transaminase, Grade 1 erythra and Grade 1 paresthesia. Up to now, no treatment related dose reduction happened. From the perspective of toxicity, the RC48-ADC combination seems safer than other ADCs, which gives us great confidence.

To conclude, neoadjuvant RC48-ADC combined with tislelizumab in patients with HER2 positive locally advanced urothelial MIBC initially shows satisfied efficacy and manageable toxicities in the preliminary result, which will be verified by the final analysis of this phase Ib/II, multi-center study. With the implementation of HOPE-03, we want to find an optimal neoadjuvant treatment for HER2 positive patients, which underlines the need for further phase III clinical trials.

**Declarations**

**Ethics approval and consent to participate**

The treatment protocol was approved by the medical ethics committee of West China Hospital, Sichuan University and Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20210564). Signed informed consent is required before eligible patient is enrolled. Additionally, the study was performed in accordance with the ethical standards put forth in the 1964 Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Availability of Data and Material (ADM)**

Not applicable in this study protocol. The data after the trial accomplishment is available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare no competing interests.

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**Authors' contributions**

Prof. Yali Shen and Peng Zhang contributed the concept and design of the study. Feng Wen and Tianhai Lin involved in the organization of the trial and drafting the manuscript. All authors have given final
approval of the version of the protocol, and it was also approved by local investigators at the participating centers.

Acknowledgment

We would like to thank RemeGen Ltd. and BeiGene Ltd. for providing clinical trial subjects RC48-ADC and Tislelizumab free of charge, respectively.

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Figures

**Ib/II, multi-center, open-label, single-arm study**

**Figure 1**

The flow-chart of the HOPE-03 study.

* Patients who suffer from disease progression during the neoadjuvant treatment will receive second-line treatment.