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RC48-ADC monotherapy or in combination with immunotherapy for locally advanced or metastatic urothelial carcinoma with HER2 low and null expression: a multicenter, real-world, retrospective study

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Abstract

Background Approximately half of urothelial carcinoma (UC) patients exhibit low or null HER2 expression. Limited data are available on the efficacy of anti-HER2 RC48-ADC (Disitamab Vedotin) in HER2 low and null advanced UC.

Methods Patients with locally advanced or metastatic UC (la/mUC) with HER2 low (IHC 1+) and null (IHC 0) expression who received RC48-ADC monotherapy or in combination with programmed cell death protein 1 (PD-1) inhibitors were enrolled in this multi-center, retrospective study. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

Results A total of 27 patients were included, with a median age of 64 years, and 17 (63%) were male. Seven (26.0%) patients received RC48-ADC alone, and 20 (74.1%) received RC48-ADC combined with a PD-1 inhibitor. Eight (30.8%) patients achieved partial response (PR), and twelve (46.2%) exhibited stable disease (SD). The ORR was 30.8%, and DCR was 76.9%. The median PFS and OS were 7.4 months and 13.8 months, one-year PFS and OS rates were 29.1% and 57.2%, respectively. Both RC48 monotherapy and combination were well-tolerated. Grade 3 AEs occurred in 4 (14.8%) patients received combination treatment, including 2 cases of anemia, 1 case of increased serum creatinine, and 1 case of autoimmune encephalitis. No grade 3 or higher AEs were observed in RC48-ADC monotherapy.

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Conclusion RC48-ADC demonstrated favorable efficacy and manageable safety in la/mUC patients with HER2 low and null expression in real-world settings. Prospective studies with large sample size are warranted to validate this finding.

Keywords HER2 low and null expression, Locally advanced or metastatic urothelial carcinoma, RC48-ADC, PD-1 inhibitors, Real-world study

Introduction

Despite significant advances in the therapeutic landscape of metastatic urothelial carcinoma (mUC) in recent years, it remains a deadly disease with poor survival outcomes. Platinum-based chemotherapy (cisplatin or carboplatin) has been the standard first-line treatment for over 30 years, yet only 40–50% of patients respond to chemotherapy, with a median progression-free survival (PFS) of 6–7 months and overall survival (OS) of 9–15 months [1]. Immune checkpoint inhibitors (ICIs) were first approved as second-line therapy [2], and further evidence supports their use as maintenance therapy (avelumab) after chemotherapy, as well as first-line treatment either as monotherapy or in combination with cisplatin-based chemotherapy [3–5]. However, only a subset of patients benefits from ICIs. Additionally, some patients are ineligible for ICIs due to comorbidities or severe immune-related adverse events (AEs). Antibody-drug conjugates (ADCs) represent a new therapeutic approach for mUC. To date, four ADCs have been approved for mUC treatment. The first approved was the anti-Nectin-4 enfortumab vedotin (EV). In the phase III EV-301 trial, EV showed an objective response rate (ORR) of 41% and improved OS compared to treatment of physician's choice (TPC) in mUC patients who had progressed after platinum-based chemotherapy and ICIs [6]. First-line EV combined with pembrolizumab demonstrated a promising ORR of 68% and an OS of 31.5 months in the recent EV-302 trial [7], making it the new standard first-line treatment for eligible patients. However, EV is not yet available in many countries, including China. Moreover, severe toxicities, such as cutaneous adverse reactions, ocular toxicities, pneumonitis, and financial burden, limit its widespread use. The Trop2 ADC Sacituzumab Govitecan (SG) received accelerated FDA approval as later-line therapy based on the phase II TROPHY-U-01 study, which reported an ORR of 27.4% and a PFS of 5 months [8]. RC48-ADC (Disitamab Vedotin, DV), the first anti-HER2 ADC, was approved for the treatment of HER2-positive (IHC 2 + or 3+) locally advanced/metastatic urothelial carcinoma (la/mUC) in China. Two phase II studies, RC48-C005 and RC48-C009, showed that RC48-ADC monotherapy achieved an ORR of 50.5%, a disease control rate (DCR) of 82.2%, median PFS and OS of 5.9 and 14.2 months in HER2 overexpression la/mUC patients who had progressed on at least one systemic chemotherapy [9]. Another anti-HER2 agent, Trastuzumab deruxtecan (T-DXd), received accelerated FDA approval for unresectable or metastatic HER2 overexpression (IHC3+) solid tumors, including UC, based on the recent DESTINY-PanTumor 02 Trial [10].

According to the literature, the incidence of HER2 overexpression in UC ranges from 9.2% to 61.1%, meaning that approximately half of the patients exhibit HER2 low or null expression [11, 12]. Limited evidence supports the efficacy of RC48-ADC in la/mUC patients with HER2 low or null disease. The RC48-C011 study investigated RC48-ADC monotherapy in 19 patients with HER2 IHC 0 or 1 + la/mUC, reporting an ORR of 26.3%, DCR of 94.7%, and mPFS of 5.6 months [13]. All six patients with HER2 0 exhibited stable disease (SD). The combination of RC48-ADC and the PD-1 inhibitor toriplimab appeared more promising. The RC48-C014 trial showed that nine out of 14 (64.3%) patients with HER2 IHC 1 + and one out of three (33.3%) patients with HER2 0 achieved a response [14]. The RC48-G001 study also reported 14 patients with HER2 low (IHC1 + or IHC2+/non-amplified) mUC, RC48-ADC plus nivolumab achieved an ORR of 76.9% [15]. The purpose of this retrospective study was to use real-world data to evaluate RC48-ADC monotherapy or in combination with immunotherapy in metastatic UC with low or null HER2 expression (IHC 1+/0), providing additional evidence for clinical decision-making.

Materials and methods

Study design and patient enrollment

This multicenter, real-world, retrospective study included patients with la/mUC who had HER2 low/null disease and were treated with RC48-ADC at Sun Yat-Sen University Cancer Centre (SYSUCC), Zhujiang Hospital of the Southern Medical University, and Shenzhen Hospital between December 2021 and June 2024. The inclusion criteria were: (1) histologically confirmed UC; (2) unresectable la/mUC; (3) HER2 0 or 1 + by IHC; (4) treatment with RC48-ADC either as monotherapy or in combination with ICIs; and (5) available response assessment and/or toxicity data. The study protocol was approved by the ethical committee of SYSUCC (No. B2024-448).

Data collection and evaluation

Data were extracted frommedicalrecords, including patient demographics, tumor characteristics, treatments, standard laboratory tests, and imaging scans. Patients were typically treated with RC48-ADC at a

standardized dose of 2 mg/kg via intravenous infusion every 14 days, until disease progression, intolerable toxicity, or death. The dosing of PD-1 inhibitors is determined by the treating physician, treatment is determined by the treating clinician. Objective response was assessed using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Survival was measured from treatment initiation until the occurrence of an event (death or disease progression).

Table 1 Characteristics of the patients ($n=27$)

Characteristics	Values
Male sex, *n* (%)	17 (63)
Age (years)	
Median (range)	64(39–76)
ECOG PS	
0	1 (3.7)
1	20 (74.1)
2	6(22.2%)
Baseline creatinine clearance	
≥ 60 ml/min	14 (51.9)
30–60 ml/min	11 (40.7)
< 30 ml/min	2 (7.4)
Primary lesion, *n* (%)	
Renal pelvis	9 (33.3)
Ureter	11 (40.7)
Bladder	7 (26)
Histopathology, *n* (%)	
Pure UC	18 (66.6%)
UC with squamous differentiation	6 (22.2%)
UC with glandular differentiation	3 (11.11%)
Metastasis site, *n* (%)	
Lymph node metastasis	26 (96.3)
Lung	13 (48.1)
Bone	12 (44.4)
Liver	11 (40.7)
Local relapse	10 (37)
Peritoneal metastasis	7 (25.9)
Adrenal gland	2 (7.4)
Brain	2 (7.4)
HER2 IHC, *n* (%)	
0 *	8 (29.6)
1+	19 (70.4)
PD-L1 TC, *n* (%)	
≥ 1%	9 (33)
< 1%	10 (37)
NA	8 (30)
Treatment	
RC48	7 (25.9)
RC48 combined ICI	20 (74.1)
Prior therapy, *n* (%)	
Median (range)	2 (0–4)
Prior PD-1 immunotherapy	25 (92.6)
Prior platinum-based chemotherapy	25(92.6)
Prior locoregional curative treatments, *n* (%)	
Surgery	22 (81.5)
Radiotherapy	14 (51.9)
Prior neoadjuvant/adjuvant chemotherapy, *n* (%)b	
Yes	11 (40.7)
No	16 (59.3)

The primary endpoint was ORR. Secondary endpoints included DCR, PFS, OS, and adverse events (AEs). ORR was defined as the proportion of patients achieving CR or PR, DCR was defined as the proportion of patients achieving complete response (CR), partial response (PR), or stable disease (SD), PFS was defined as the time from enrollment to tumor progression or death, and OS as the time from enrollment to death from any cause. Side effects and their severity were assessed according to the World Health Organization (WHO) Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

HER2-testing

HER2 expression was determined by immunohistochemistry (IHC) assays, and IHC scores were assessed according to criteria of HER2 expression in breast cancer as recommended by clinical pathological expert consensus on HER-2 testing in urothelial carcinoma in China [16].

Statistical analysis

SPSS 27.0 (IBM, Armonk, NY, USA) and Prism 8.0.2 (GraphPad Software Inc., San Diego, CA, USA) were used for statistical analysis. Descriptive statistics summarized patient characteristics, treatment administration, antitumor activity, and safety. PFS and OS were analyzed using the Kaplan–Meier method and the log-rank test. A two-sided $P<0.05$ was considered statistically significant.

Results

Patients' characteristics and treatment

A total of 27 eligible patients were included. Patients' characteristics were shown in Table 1. The median age was 64 years (range 39–76), and 17 (63%) were male. The primary sites were ureteral UC in 11 (40.7%) patients, renal pelvis UC in 9 (33.3%) patients, and bladder UC in 7 (26%) patients. Visceral metastasis accounted for 18 (66.7%) of the cases. The median number of prior treatments for metastatic disease was 2, with 25 patients (92.5%) had previously received platinum-based chemotherapy and ICIs. Nineteen (70.4%) patients were diagnosed with HER2 IHC 1+, and 8 (29.6%) were HER2 IHC 0. Seven patients received RC48-ADC monotherapy, while 20 patients received RC48-ADC combined with a PD-1 antibody, including Toripalimab, Tislelizumab, Sintilimab, Pembrolizumab, and Nivolumab. Two patients received RC48-ADC combined with a PD-1 antibody as first-line therapy due to ineligibility for both cisplatin and carboplatin.

Efficacy

Treatment response could be assessed in 26 patients, with 18 (66.6%) showing a reduction in target lesions from baseline. According to RECIST v.1.1, 8 (30.8%) patients achieved PR and 12 (46.2%) showed SD (Fig. 1). The response of each individual patient are depicted in Fig. 2. The ORR was 30.8%, and the DCR was 76.9%. The ORR for patients treated with RC48 monotherapy and RC48 combined with PD-1 was 28.6% (2/7) and 31.6% (6/19), respectively. The ORR for patients with HER2 0 and HER2 1 + was 42.9% (3/8) and 26.3% (5/19). The ORR for upper urinary tract primary was 31.6% and 28.6% for bladder primary. The median follow-up time was 13.77 months. The median OS was 13.8 months (Fig. 3a), and the median PFS was 7.4 months (Fig. 3b). The 1-year PFS and OS rates were 29.1% and 57.2%, respectively. The median PFS for patients receiving RC48 combined with immunotherapy and those treated with RC48 monotherapy was 4.9 and 7.4 months (Fig. 3d). The median PFS for patients with HER2 IHC 0 and HER2 IHC 1 + was 4.6 and 7.4 months (Fig. 3f), respectively.

Among the eight patients with HER2 IHC 0 (Table 2), four had available tumor samples for reassessment of HER2 status, and one was found to have HER2 ultralow expression (< 10%) (Fig. 4)Two patients underwent NGS testing. One was detected to have a HER2 insertion mutation in exon 20 (Py772_A775dup), microsatellite Instability-Stable (MSS), and TMB 1.0/Mb. He received RC48 plus immunotherapy, experienced significant pain relief, and SD by CT scan. Another one is a solitary kidney patient with high-grade renal pelvis UC. NGS showed microsatellite Instability-Low (MSI-L), and TMB 7.7/Mb. Due to enlarged para-aortic lymph nodes, nephron-sparing surgery was not performed. She received 3 cycles of cisplatin plus gemcitabine chemotherapy, experienced disease progression, then switched to second-line RC48-ADC monotherapy and achieved PR (Fig. 5). Subsequent radiation was performed following tumor shrink, and had a PFS of 23.8 months. In addition, five patients underwent a second biopsy, and three showed a change in HER2 status. One patient had a change from HER2 1 + to 0, and two changed from HER2 1 + to 2+ (Table 3).

Toxicities

Toxicity profiles were available for all patients. All (100%) patients experienced at least one AE. In patients treated with RC48-ADC monotherapy, the most common AEs were peripheral neuropathy, hyponatremia, leukopenia and anemia. no grade 3 or higher AE occurred. In patients treated with RC48 combined with immunotherapy, the most common AEs were anorexia, fatigue, peripheral neuropathy and nausea, grade 3 AEs included 2 cases of anemia, 1 case of serum creatinine increase, and 1 case of autoimmune encephalitis (Table 4).

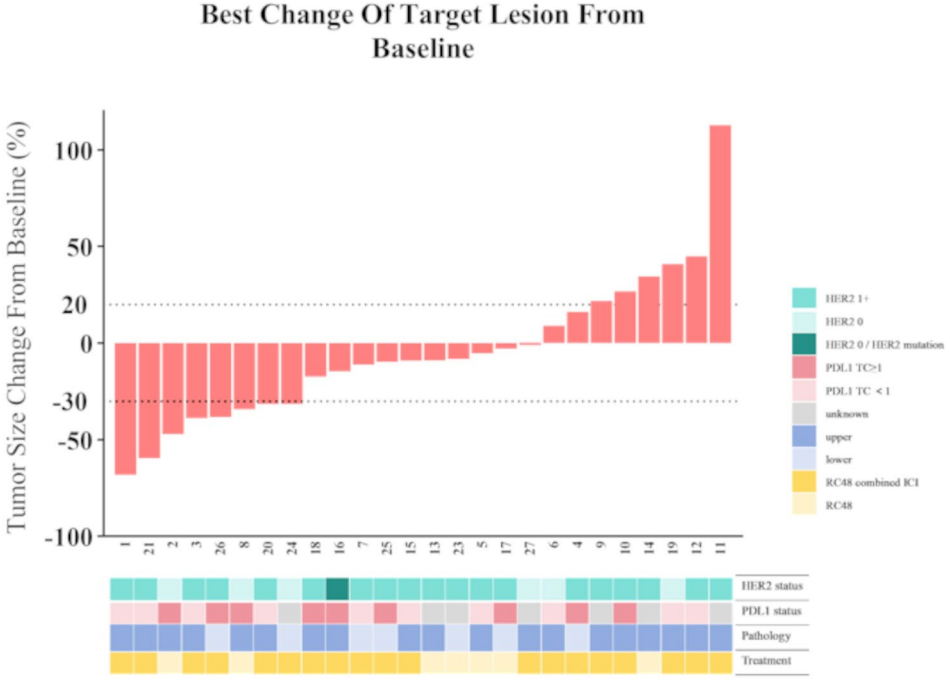

Fig. 1 Waterfall plot showing the best percentage change from baseline in the sum of the diameters of target lesions. Eighteen (69.2%) patients had a decrease in tumor size from baseline

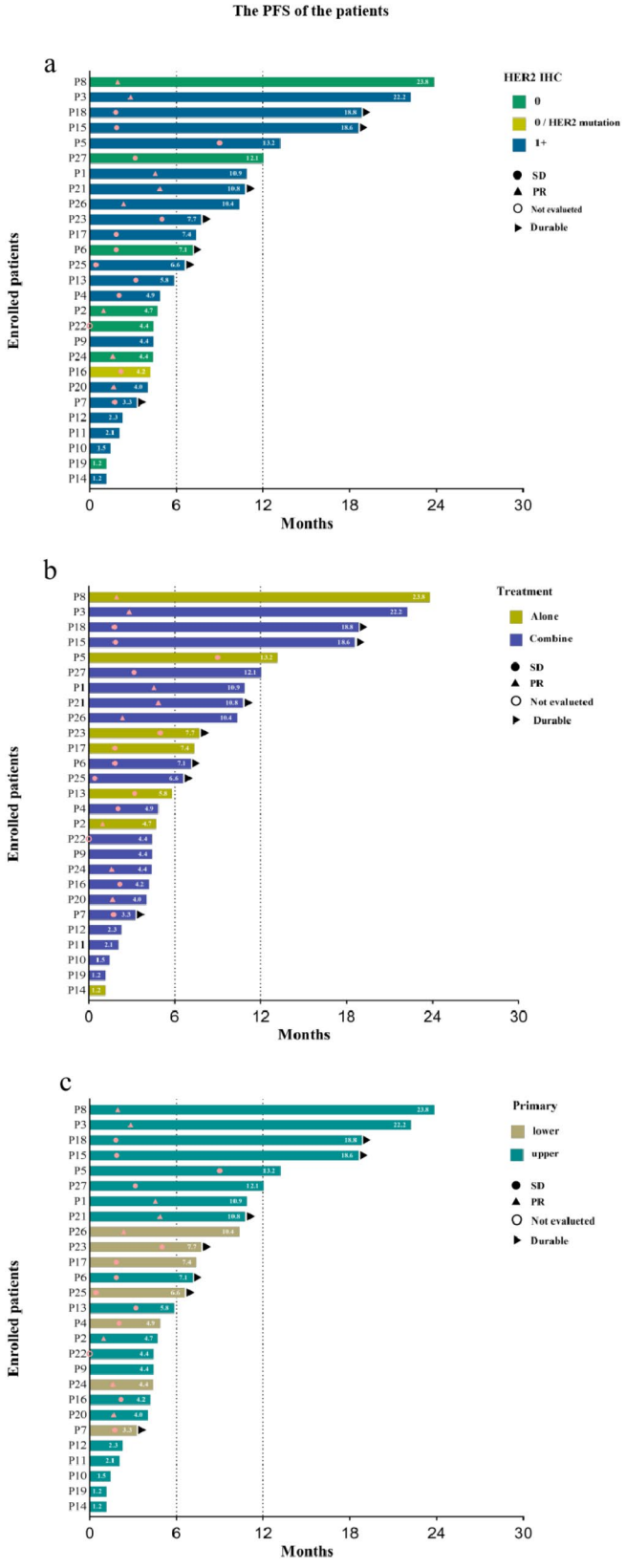

Fig. 2 Swimmer plot of patients' responses from the start of treatment to PD, death, or not evaluated. Swimmer plot of patients with different HER2 expressions (a). Swimmer plot of patients receiving RC48-ADC monotherapy versus combination with immunotherapy (b). Swimmer plot of patients with the primary site located in the lower and upper urinary tracts (c).

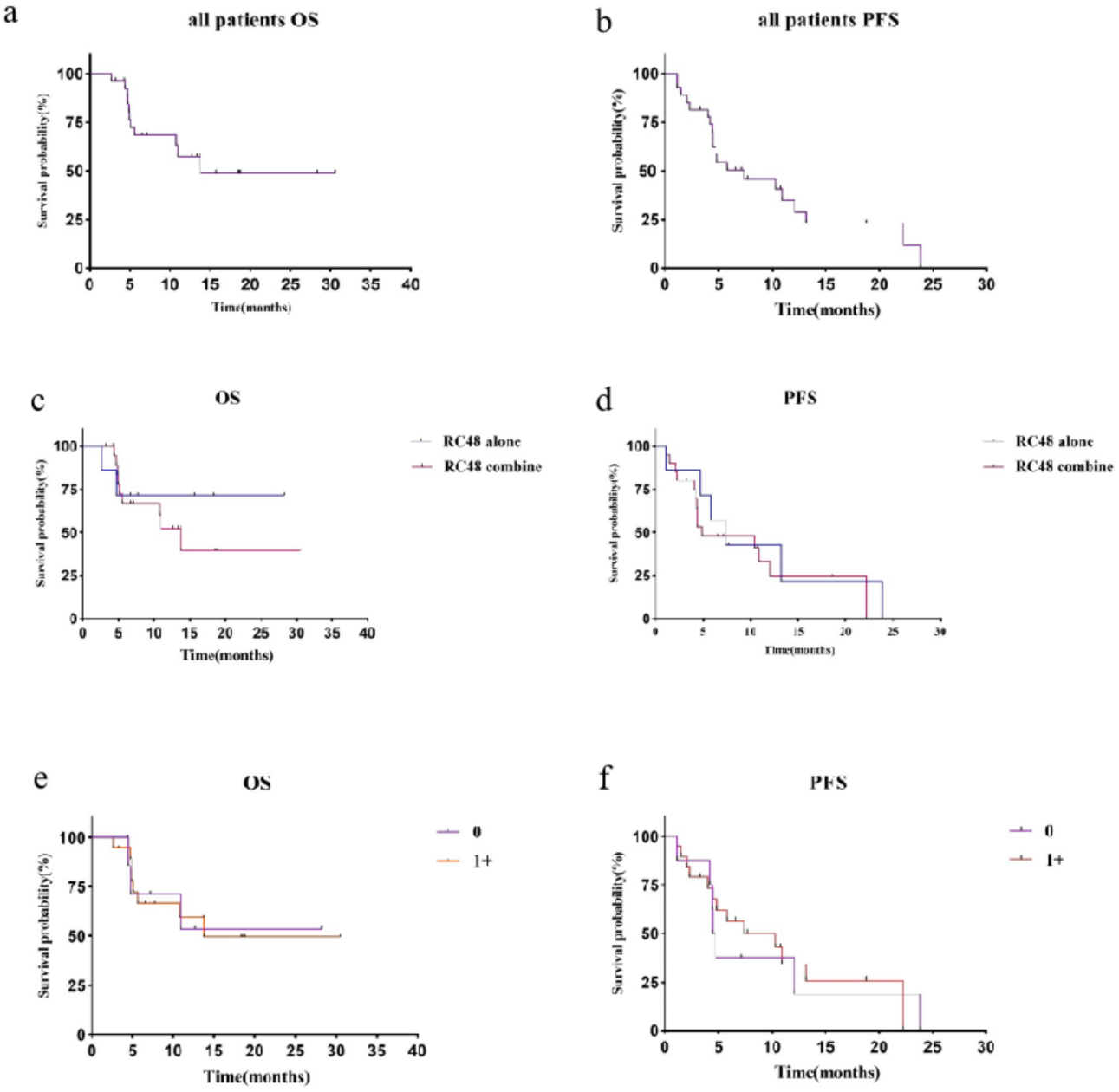

Fig. 3 Overall survival (OS) (a) and progression-free survival (PFS) (b). OS of patients receiving RC48-ADC monotherapy versus combination with immunotherapy (c). PFS of patients receiving RC48-ADC monotherapy versus combination with immunotherapy (d).OS of patients with HER2 1+ versus HER2 0 (e). PFS of patients with HER2 1+ versus HER2 0 (f).

Discussion

The current study confirmed the efficacy and safety of RC48-ADC, either as monotherapy or in combination with PD-1 inhibitors, in HER2 low and null la/mUC in a real-world setting. The ORR was 30.8% in the overall cohort, 26.3% (5/19) in HER2 IHC 1 + patients, and 42.9% (3/8) in HER2 IHC 0 patients. The efficacy data were consistent with those reported in the C011 and C014 trials [13, 14].

Accumulating evidence supports the promising efficacy of new-generation anti-HER2 ADCs in HER2 low expression solid tumors. For example, T-DXd demonstrated significant efficacy in HER2 low expression breast cancer (BC) patients (HER2 IHC 2+/in situ hybridization (ISH)- or IHC 1 + disease). Even in patients with HER2 IHC 0, approximately 30% achieved a response [17]. RC48 also demonstrated promising efficacy in HER2 low expression gastric/gastroesophageal cancers (GC/GEJC [18], suggesting the expanding application of anti-HER2 ADCs in HER2 low/null solid tumors.

There are several potential explanations for the efficacy of anti-HER2 ADCs in HER2 low and null tumors. One

Table 3 Demographics of 8 patients with HER2 IHC 0

Patient #	Re-evaluation HER2 status in primary tumor	HER2 status in recurrent tumor	Major NGS results	Treatment	Response	PFS
1	0	0	NA	RC48	PR	4.7
2	Ultra-low	NA	NA	RC48 + Toripalimab	SD	7.1
3	NA	NA	MSI-L, TMB-L, 7.74Muts/Mb NA	RC48	PR	23.8
4	NA	NA	MSS, TMB-L, HER-2exon 20 insertion mutation Py772_A775dup	RC48 + Tintilimab	SD	4.2
5	0	0	NA	RC48 + Toripalimab	PD	1.2
6	NA	NA	NA	RC48 + Toripalimab	NE	4.4
7	NA	NA	NA	RC48 + Toripalimab	PR	4.4
8	0	NA	NA	RC48 + Toripalimab	SD	12.1

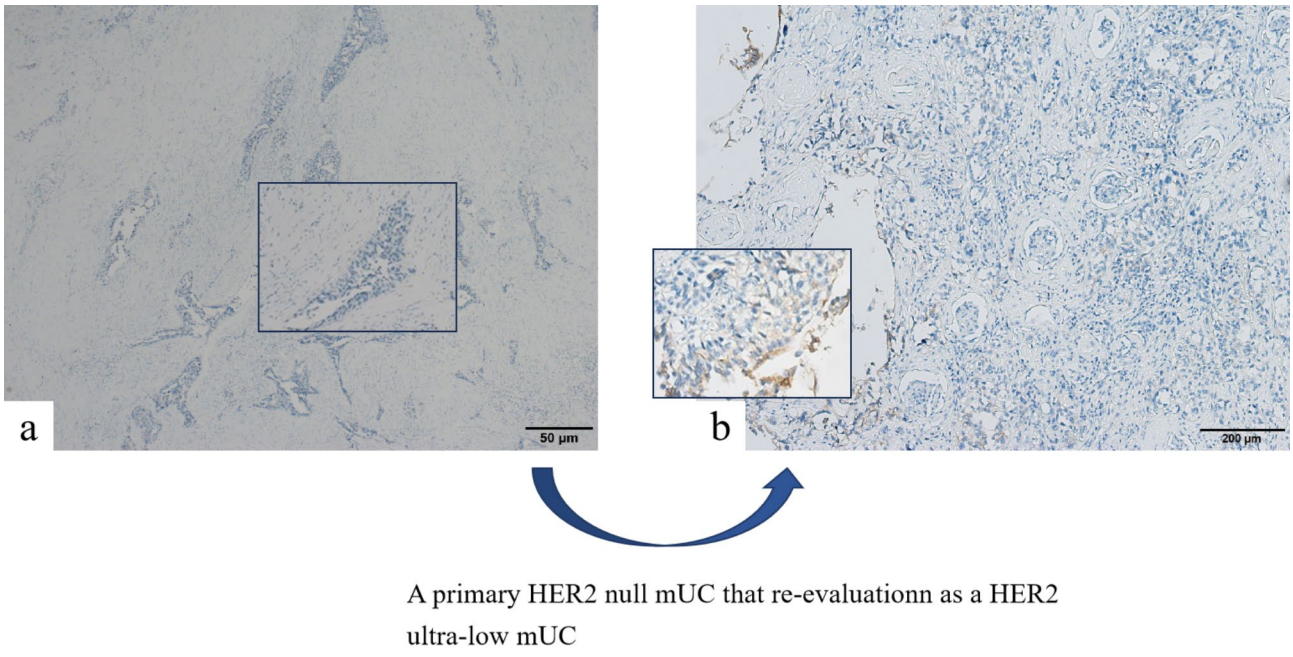

Fig. 4 An example of HER2 status evolution between primary urothelial carcinoma and re-evaluation of the primary tumor. On the left: primary tumor, which was HER2 null (0) at diagnosis, while re-evaluation HER2 immunostaining (IHC) of the primary tumor showed HER2 ultra-low expression (a, b: HER2 IHC).

key reason is the limitation of current HER2 IHC assessments, which are non-sensitive and semiquantitative. Although there is no standard criteria for HER2 testing in UC, most studies used the same criteria with BC [16], where HER2 IHC 1 + is defined as incomplete and faint membrane staining in ≥ 10% of invasive carcinoma cells, and HER2 IHC 0 is defined as ≤ 10% of cells showing incomplete and faint/weak membrane staining [19]. Since the new generation of anti-HER2 ADCs requires only minimal levels of HER2 to enter cancer cells, even low HER2 expression may be sufficient. Pathologists in BC have suggested further classifying HER2 IHC 0 BC into HER2-null (completely free of staining) and HER2 ultra-low (< 10% staining) [20]. In our study, one out of four patients with HER2 IHC 0 had HER2 ultra-low status, highlighting the need for more precise HER2 expression assessment by IHC in UC. Moreover, HER2 null expression by IHC does not necessarily indicate the complete absence of HER2. One study reported that 67% of BC cases with HER2 IHC 0 could detect HER2 expression using quantitative immunofluorescence [21]. Therefore, more sensitive and reliable methods are required to accurately identify the minimum threshold of HER2 expression for new-generation anti-HER2 ADCs. Another important issue is the spatial and temporal intratumoral heterogeneity of HER2 expression. Studies comparing tissue samples from primary and recurrent BC have shown bidirectional discordance in HER2 status. Approximately 14% of patients with HER2 low disease changed to HER2 IHC 0, while up to 15% changed from HER2 IHC

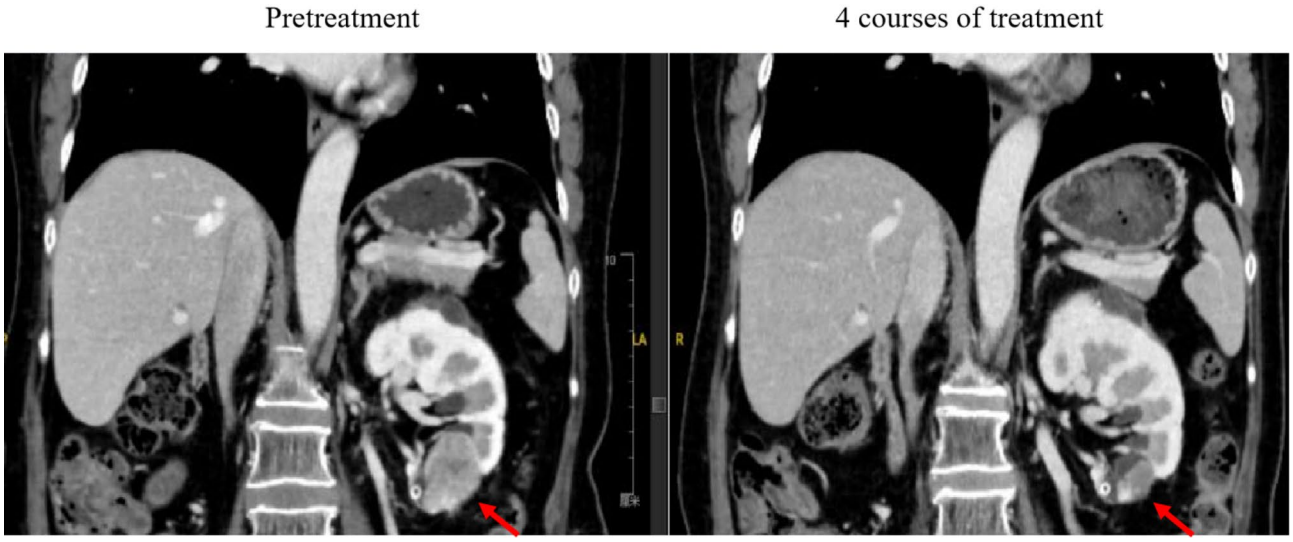

Fig. 5 A solitary kidney patient with high-grade renal pelvis urothelial carcinoma and HER2 0 disease achieved PR after second-line RC 48 monotherapy.

Table 3 Patients undergoing multiple biopsies

Patient#	Initial biopsy HER2 status	Secondary biopsy HER2 status	Treatment	Response	PFS (months)
1	0	0	RC48	PR	4.7
2	1	0	RC48 + Pembrolizumab	SD	4.9
3	1	2	RC48	PD	1.2
4	0	0	RC48 + Toripalimab	PD	1.2
5	1	2	RC48 + Toripalimab	PR	4.0

Table 4 Summary of the adverse events

	All patients (*n* = 27)		RC48 monotherapy (*n* = 7)		RC48 combination (*n* = 20)	
	All grades (*n*, %)	Grade ≥ 3 (*n*, %)	All grades (*n*, %)	Grade ≥ 3 (*n*, %)	All grades (*n*, %)	Grade ≥ 3 (*n*, %)
Any adverse event	27 (100)	4 (14.8)	7 (100.0)	0	20 (100)	4 (20)
Peripheral neuropathy	10 (37.0)	0	4 (57.2)	0	6 (30)	0
Anorexia	9 (33.3)	0	2 (28.6)	0	7 (35)	0
Nausea	8 (29.6)	0	2 (28.6)	0	6 (30)	0
Hyponatremia	8 (29.6)	0	3 (42.9)	0	5 (25)	0
Fatigue	8 (29.6)	0	1 (14.3)	0	7 (35)	0
Leukopenia	8 (29.6)	0	3 (42.9)	0	5 (25)	0
Anemia	7 (25.9)	2 (7.4)	3 (42.9)	0	4 (20)	2 (10)
Constipation	7 (25.9)	0	2 (28.6)	0	5 (25)	0
Hypoalbuminemia	6 (22.2)	0	2 (28.6)	0	4 (20)	0
Vomiting	5 (18.5)	0	1 (14.3)	0	4 (20)	0
Pruritus	5 (18.5)	0	1 (14.3)	0	4 (20)	0
Serum creatinine increased	4 (14.8)	1 (3.7)	1 (14.3)	0	3 (15)	1 (5)
Elevated transaminases	4 (14.8)	0	1 (14.3)	0	3 (15)	0
Urinary tract infection	4 (14.8)	0	1 (14.3)	0	3 (15)	0
Thrombocytopenia	2 (7.4)	0	1 (14.3)	0	1 (5)	0
Diarrhea	1 (3.7)	0	0	0	1 (5)	0
Autoimmune encephalitis	1 (3.7)	1 (3.7)	0	0	0	1 (5)
Hypoadrenocorticism	1 (3.7)	0	0	0	1 (5)	0
Hypothyroidism	1 (3.7)	0	0	0	1 (5)	0

0 to HER2 low in samples from the same patients [22]. Another study on BC demonstrated that the proportion of low HER2 expression increased with the number of biopsies. When ≥5 biopsies were performed, all cases previously classified as HER2 null shifted to low expression [23]. In our current study, three out of five patients who underwent a second biopsy showed a change in HER2 status—one changed from HER2 1+to 0, and two changed from HER2 1+to 2+. Lastly, the bystander effect of new-generation ADCs, including RC48-ADC, contributes to the penetration and efficacy against HER2 null cancer cells. Additional mechanisms independent of HER2 may also play a role [24]. For instance, a study demonstrated that HER2 low GEC had a significantly more robust tumor immune microenvironment (TIME) and higher immunogenicity compared to HER2-positive tumors [25], which may also explain the efficacy observed in patients with low HER2 expression when using a combination of anti-HER2 ADC and immunotherapy. These data suggest that screening for HER2 expression may not be necessary for RC48-ADC to ensure that all patients have access to effective treatment. Similar to EV and SG, both of which do not require biomarker selection, however, our sample size may not be sufficient to draw definitive conclusions, further studies are needed to confirm this hypothesis.Notably, our current study failed to demonstrate the superiority of RC48-ADC combined with a PD-1 inhibitor over RC48-ADC monotherapy. One reason might be the small sample size, particularly in the RC48-ADC monotherapy subgroup, which included only seven patients. Another possible explanation could be the later-line treatment. In the C014 trial, RC48-ADC combined with toriplimab showed better efficacy when used as a first-line treatment compared with later-line therapy. Our previous study also showed no benefit in adding a PD-1 inhibitor to RC48-ADC in a median of three treatment lines among a mixed population of both HER2-positive and HER2-negative patients [26]. Further studies should investigate the optimal timing for combining ADCs with immunotherapy.

In line with previous studies, the current study also showed favorable tolerability of RC48-ADC, either alone or in combination with immunotherapy. The toxicity profiles were consistent with previous reports, with no grade 4 or 5 AEs were observed. Two patients with baseline CrCl < 30 mL/min tolerated RC48-ADC well and maintained stable renal function. However, we observed one patient with a baseline CrCl of 47.2 mL/min and PS 2 who developed high creatinine levels after three cycles of RC48-ADC. Her renal function recovered two weeks after hemodialysis. The exact cause is unclear, but RC48-ADC-related toxicity cannot be excluded. Therefore, close monitoring for potential renal toxicity is recommended. The remaining five PS 2 patients tolerated RC48-based treatment very well.

Our study had several limitations, including its retrospective nature, limited sample size, incomplete NGS and PD-1 data, and heterogeneity in prior treatment regimens. Nevertheless, it adds to the evidence of the efficacy and safety of RC48-ADC for HER2 low and null UC in a real-world setting. Prospective clinical trials with larger sample sizes are needed.

In conclusion, this study provides evidence supporting the real-world effectiveness and safety of RC48-ADC either alone or in combination with immunotherapy in la/mUC patients with HER2 low and null expression. Further large-scale prospective studies are warranted to validate this finding.

Abbreviations

UC	Urothelial carcinoma
la/mUC	Locally advanced or metastatic urothelial carcinoma
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
CR	Complete response
SD	Stable disease
mOS	Median overall survival
mPFS	Median progression-free survival
ORR	Objective response rate
DCR	Disease control rate
PD-1	Programmed cell death protein 1
AEs	Adverse events
ICIs	Immune checkpoint inhibitors
ADCs	Antibody-drug conjugates
EV	Enfortumab Vedotin
DV	Disitamab Vedotin
SG	Sacituzumab Govitecan
TPC	Treatment of physician's choice
TRAE	Treatment emergent adverse event
CTCAE	Common terminology criteria for adverse events
RECIST	Response evaluation criteria in solid tumors
BC	Breast cancer

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Author contributions

XA, ZW and YS. Formal analysis and investigation: DW, MC, YZ, LB, MC, MN, QZ, KY, ZL, and XY. Date curation: DW, MC, YZ. Writing original draft preparation: DW, MC, YZ. Writing—review and editing: XA, ZW and YS. All authors contributed to the article and approved the submitted version.

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Data availability

Data is provided within the manuscript or supplementary information files， the datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by Th Sun Yat-sen University Cancer Center (file number: No. B2024-448). As this

study was retrospective, the Ethics Committee of the Sun Yat-sen University Cancer Center agreed to waive the informed consent of patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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