Research Article

A real-world study of diverse RC48-based regimens across disease stages of urothelial carcinoma

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Abstract

Background: RC48, a human epidermal growth factor receptor 2 (HER2)-targeting antibody–drug conjugate (ADC), has been approved in China for the treatment of HER2-positive metastatic urothelial carcinoma. **Objective:** This study evaluated the efficacy and safety of various RC48-based regimens in patients with urothelial carcinoma across disease stages in real-world settings. **Methods:** We retrospectively analyzed data from 56 patients at different disease stages who were treated at the Second Hospital of Lanzhou University between March 2023 and June 2024. RC48-ADC was administered as a monotherapy or in combination with immunotherapy until discontinuation due to disease progression, intolerable toxicity, death, or other reasons. **Results:** Outcomes included the objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs). The median patient age was 67.5 years, with 83.9% being male. Of all patients, 14 (25.0%) received RC48-ADC monotherapy, and 42 (75.0%) received RC48-ADC combined with immunotherapy. Response rates were as follows: 15 patients (26.8%) achieved complete remission, 21 (37.5%) attained partial remission, 14 (25.0%) had stable disease, and 6 (10.7%) suffered from disease progression. The overall ORR was 64.3%, with rates of 70.0% and 60.0% in first-line and second-line treatment groups, respectively. The median PFS lasted for 6 months (range: 5–7 months), whereas the median OS was not reached. The most common TRAEs were peripheral sensory neuropathy (58.9%), fatigue (48.2%), decreased appetite (42.9%), and weight loss (37.5%). **Conclusion:** No increased incidence of TRAEs was observed in patients with poor performance status or impaired kidney function. RC48-ADC demonstrated efficacy and safety in patients with urothelial carcinoma, providing clinical benefits regardless of performance status or renal function.

Keywords: RC48, Antibody–drug conjugate, PD-1 inhibitor, Locally advanced or metastatic urothelial carcinoma, Efficacy and safety

1. Introduction

Bladder cancer represents one of the most common malignancies of the urinary system, with over 90% of cases being urothelial carcinoma (UC).[1] Owing to its unclear pathogenesis and high recurrence rates, the overall prognosis for patients with UC remains poor.[2] Surgical intervention is the cornerstone of UC treatment. This encompasses transurethral resection of bladder tumor, employed for early-stage diagnosis and treatment, and radical cystectomy, which typically involves urinary diversion and is reserved for more advanced disease.[3] Chemotherapy, including gemcitabine and cisplatin, forms the basis of UC treatment and is given as either pre-operative neoadjuvant therapy or post-operative adjuvant therapy, depending on timing.[4] Immunotherapy (programmed cell death protein 1 [PD-1], programmed death-ligand 1 [PD-L1]), and targeted therapy (nectin-4 and human

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epidermal growth factor receptor 2 [HER2]) has provided more options for patients with bladder cancer.[5] However, only roughly 20% of patients respond to immune checkpoint inhibitors, and their safety warrants further investigation and validation.[6]

Antibody–drug conjugates (ADCs) consist of antigen-specific antibodies, chemotherapeutic drugs, and cleavable linker agents.[7] These conjugates combine the targeted antigen recognition of antibodies with the antitumor effects of chemotherapeutics, potentially mitigating adverse effects by preferentially delivering their payload to the tumor site.[8] HER2 is a transmembrane receptor-like protein with tyrosine kinase activity that plays a critical role in cellular signal transduction, affecting cell growth, differentiation, and survival.[9] HER2 is overexpressed in approximately 30% of UC cases, and this overexpression is closely associated with tumor progression and unfavorable prognosis.[10] RC48-ADC is a HER2-targeted ADC composed of anti-HER2 antibodies conjugated with monomethyl auristatin E.[11]

Recent studies have demonstrated the efficacy and safety of RC48-ADC in patients with locally advanced or metastatic urothelial carcinoma (La/mUC).[12] A phase II, open-label, multicenter, single-arm study reported an objective response rate (ORR) of 51.2% for RC48-ADC in mUC, indicating promising efficacy and manageable safety.[13] Another real-world study recorded an ORR of 50.5% for RC48-ADC in mUC, further supporting its strong safety profile.[14] In high-risk UC, elevated HER2 expression is inversely associated with the efficacy of intravesical Bacillus Calmette–Guérin (BCG) therapy. A single-arm, dose-escalation phase I trial demonstrated that intravenous administration of RC48-ADC enhanced the therapeutic effect of BCG against HER2-overexpressing UC.[15] However, few real-world studies explored the combination of RC48-ADC with anti-PD-1/PD-L1 monoclonal antibodies in patients with La/mUC. The present study aimed to evaluate and compare the efficacy and safety of RC48-ADC with and without anti-PD-1/PD-L1 antibodies in a real-world setting, focusing on their combined use in La/mUC cases.

2. Materials and methods

2.1. Study design and patients

This study, involving human participants, was reviewed and approved by the Medical Ethics Committee of the Second Hospital of Lanzhou University, Lanzhou, China. In this real-world study, we retrospectively analyzed data from 56 patients with UC who received RC48-ADC-based treatment at Lanzhou University Second Hospital between March 2023 and March 2024.

The inclusion criteria were as follows: (i) UC confirmed by biopsy, with or without histological variations; (ii) having received treatment with RC48-ADC alone or in combination with immunotherapy; (iii) La/mUC cases, including lymphatic, skeletal, or visceral metastasis; (iv) availability for at least one response assessment; and (v) adequate baseline hematological, hepatic, and cardiac functions. RC48-ADC was administered at a dose of 2.0 mg/kg through intravenous infusion every 2 weeks until discontinuation due to disease progression, intolerable toxicity, death, or other factors.

Clinical data were collected on demographics, Eastern Cooperative Oncology Group (ECOG) performance status, imaging results (enhanced computed tomography [CT] and magnetic resonance imaging [MRI]), laboratory tests, pathological findings, HER2 expression, treatment strategies, and treatment-related adverse events (TRAEs).

2.2. Outcomes and assessments

Progression-free survival (PFS) was defined as the time from RC48-ADC treatment initiation to disease progression or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Tumor response was categorized as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease. The ORR was defined as the proportion of patients achieving CR or PR, whereas the disease control rate (DCR) was defined as the proportion of patients with CR, PR, or SD. Follow-up duration was calculated from the start of treatment to death or the last known follow-up.

Tumor response was evaluated against the response evaluation criteria in solid tumors version 1.1, using CT or MRI.[16] TRAEs were based on patient self-reported and laboratory test results and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. All patients were followed up every 12 weeks through telephone consultation or outpatient visits after their final treatment.

2.3. Statistical analysis

Categorical and continuous variables were analyzed using the Chi-square test. ORRs were estimated using the Clopper–Pearson method with 95% confidence intervals (CIs). Time-to-event endpoints, including PFS and OS, were analyzed using the Kaplan–Meier method. The log-rank test and multivariate Cox regression analysis were applied to identify prognostic factors. All statistical analyses were performed using SPSS version 19 (IBM, United States of America), with a $p<0.05$ considered statistically significant.

3. Results

3.1. Baseline characteristics

This study recruited 56 patients who had received RC48-ADC-based treatment. Demographic information is detailed in Table 1. Among these patients, 47 were male and 9 were female, with a median age of 67.5 years (range: 46–89 years). In terms of age distribution, 13 patients (23.2%) were <60 years old, 28 (50%) were between 60 and 75 years, and 15 (26.8%) were aged >75 years. Considering the baseline creatinine clearance rate (CCR), 32 patients (57.1%) had a CCR of ≥60 mL/min, 19 (33.9%) had a CCR of 30–60 mL/min, and 5 (8.9%) had a CCR of <30 mL/min. ECOG performance status was 0 in 6 patients (10.7%), 1 in 35 (62.5%), and ≥2 in 15 (26.8%).

In 41 patients (73.2%), the primary tumors were located in the bladder, whereas in 15 (26.8%) patients, their primary lesions were situated in the upper urinary tract. Metastatic sites included the lymph nodes, lungs, bones, liver, prostate, and adrenal glands. Pathologically, 4 patients (7.1%) were diagnosed with low-grade UC, 22 (39.3%) with high-grade UC, 26 (46.4%) with invasive high-grade UC, and 4 (7.1%) were of unknown pathological types. As to HER2 status, 5 patients (9.0%) were HER2-negative, 7 (12.5%) were weakly HER2-positive, 32 (57.1%) were HER2-positive, 8 (14.3%) were strongly HER2-positive, and 4 (7.1%) had unknown HER2 expression.

With regard to surgical history, 29 patients (51.8%) had undergone transurethral resection of bladder tumors, 7 (12.5%) had had radical cystectomy, 14 (25.0%) had received radical nephrectomy, and 6 (10.7%) had not been surgically treated. Regarding chemotherapy history, 10 patients (17.9%) had received bladder instillation chemotherapy and 21 (37.5%) had been subjected to systemic chemotherapy or immunotherapy. As for RC48-ADC treatment, 5 (8.9%) had received it as neoadjuvant therapy, 20 (35.7%) as the first-line therapy due to ineligibility for platinum-based chemotherapy or refusal to be on chemotherapy, 30 (53.5%) as the second-line therapy, and 1 (1.8%) as the third-line therapy. Overall, 14 patients (25.0%) had received RC48-ADC monotherapy, while 42 (75.0%) had been treated with RC48-ADC plus immunotherapy.

3.2. Efficacy

In total, 15 patients (26.8%) achieved CR, 21 (37.5%) attained PR, 14 (25.0%) had SD, and 6 (10.7%) experienced disease deterioration. The overall ORR was 64.3% (36/56), and the DCR was 89.3% (50/56). Among patients who received RC48-ADC as first-line therapy, the ORR was 70.0% (14/20), whereas the ORR for those who received it as the second-line therapy was 60.0% (18/30). The ORR was 57.1% (8/14) for RC48-ADC monotherapy and 66.7% (28/42) for RC48-ADC

Table 1. Demographic and clinical features of UC patients receiving RC48-antibody–drug conjugate-based therapy

Parameter	*n* (%)
Total	56
Male	47 (83.9)
Age (years)	67.5 (46–89)[a]
≤7.	13 (23.2)
60–75	28 (50)
≥8	15 (26.8)
Creatinine (μmol/L)	87 (36.3–356)[a]
Baseline creatinine clearance rate	
≥60 mL/min	32 (57.1)
30–60 mL/min	19 (33.9)
<30 mL/min	5 (9.0)
BMI (kg/m^2)	23.85 (17.7–39.8)[a]
ECOG score	
0	6 (10.7)
1	35 (62.5)
≥2	15 (26.8)
Primary lesion	
Bladder	41 (73.2)
Renal pelvis/ureter	15 (26.8)
Pathological type	
LGUC	4 (7.1)
HGUC	22 (39.3)
IHGUC	26 (46.4)
Other	4 (7.1)
HER2 expression	
0	5 (9.0)
1+	7 (12.5)
2+	32 (57.1)
3+	8 (14.3)
Unknown	4 (7.1)
Surgery	
TURBT	29 (51.8)
RC	7 (12.5)
RN	14 (25.0)
No	6 (10.7)
Prior chemotherapy/immunotherapy	
Bladder infusion	10 (17.9)
Systemic chemotherapy	21 (37.5)
No	25 (44.6)
Treatment lines	
First line	20 (35.7)
Second line	30 (53.5)
Third line	1 (1.8)
Neoadjuvant	5 (9.0)
Treatment	
RC48 alone	14 (25.0)
RC48+immunotherapy	42 (75.0)
Follow-up time (months)	8 (3–12)[a]

Note: [a]Expressed as median (range). Abbreviations: BMI: Body mass index; ECOG: Eastern cooperative oncology group; HER2: Human epidermal growth factor receptor 2; HGUC: High-grade urothelial carcinoma; IHGUC: Invasive high-grade urothelial carcinoma; LGUC: Low-grade urothelial carcinoma; RC: Radical cystectomy; RN: Radical nephrectomy; TURBT: Transurethral resection of bladder tumor.

combined with immunotherapy.

The ORRs by age group were as follows: 53.8% (7/13) in patients ≤60 years, 64.3% (18/28) in those aged 60–75 years, and 73.3% (11/15) in those ≥75 years. The ORR was 57.9% (22/38) in patients with ECOG performance scores of 0–1 and was 80.0% (12/15) in those who scored ≥2. Among patients with impaired renal function, the ORR was 56.3% (18/32) for those with a CCR ≥60 mL/min, 73.7% (14/19) for those with a CCR of 30–60 mL/min, and 80.0% (4/5) for those with a CCR <30 mL/min. Patients with higher ECOG scores or lower CCRs tended to receive treatment regimens with fewer side effects, which may have contributed to the increased ORRs in these groups. ORRs by pathological type were as follows: 100.0% (4/4) for low-grade UC, 54.5% (12/22) for high-grade UC, and 65.4% (17/26) for invasive high-grade UC. ORRs by HER2 expression level were 44.4% (4/9) for HER2-negative or HER2-unknown patients, 57.1% (4/7) for weakly HER2-positive, 56.3% (18/32) for HER2 positive, and 87.5% (7/8) for strongly HER2-positive patients.

The median follow-up duration lasted for 14.0 months (range: 9.0–18.0 months). At the final follow-up, 6 patients (10.7%) had died. The median OS was not reached, whereas median PFS was 6.0 months (range: 5.0–7.0 months; Figure 1). PFS was significantly longer in patients with HER2-positive and strongly HER2-positive expression than in those with HER2-negative and weakly HER2-positive expression (p=0.048; Figure 2A). PFS was also longer in patients receiving RC48-ADC combined with anti-PD1/PD-L1 antibodies as the first-line therapy compared to those receiving it as second- or third-line therapy (p=0.003). Nonetheless, there was no significant difference in PFS between RC48-ADC monotherapy and combination therapy (p=0.71; Figure 2B and C). In addition, PFS was shorter in patients aged ≥70 years than in those aged <70 years (p=0.032; Figure 2D). No significant difference in PFS was observed between patients with ECOG scores of 0–1 and those with scores ≥2 (p=0.66; Figure 2E).

3.3. Safety

All patients developed TRAEs of varying severities. The most common TRAEs were peripheral sensory neuropathy (58.9%), weakness (48.2%), decreased appetite (42.9%), weight loss (37.5%), hair loss (35.7%), anemia (33.9%), and nausea and vomiting (32.1%). Overall, 13 patients (23.3%) experienced grade 3–4 TRAEs (Table 2).

The incidence of grade 2 TRAEs by age group was 23.0% (3/13) in patients aged ≤60 years, 75.0% (21/28) in those aged 60–75 years, and 66.7% (10/15) in those aged ≥75 years. By ECOG performance status, the incidence was 53.7% (22/41) in patients with ECOG scores of 0–1 and 80% (12/15) in those with ECOG scores ≥2. By renal function, incidence was 100% (5/5) in patients with a CCR of <30 mL/min, 63.2% (12/19) in those with a CCR of 30–60 mL/min, and 50% (16/32) in those with a CCR of ≥60 mL/min.

The incidence of grade 3–4 TRAEs was 7.1% (1/14) in the RC48-ADC monotherapy group and 28.6% (12/42) in the combination therapy group. Neurological disorders were mostly grade 1–2, with 6.0% (2/33) of patients experiencing grade 3 events, and no patients suffering from grade 4 neurological TRAEs. TRAEs led to treatment discontinuation in 17.9% (10/56) of patients. Notably, no deaths were attributed to TRAEs during RC48-ADC treatment.

4. Discussion

This study employed a prospective cohort design to systematically evaluate the clinical efficacy and safety of RC48-ADC in 56 patients with La/mUC. Key outcomes included a median PFS of 6.0 months, an ORR of 64.3%, and a DCR of 85.7%. Notably, no new safety signals emerged during treatment, and TRAEs were predominantly grade 1–2. Importantly, consistent efficacy and safety profiles were maintained in elderly patients (>70 years), those with renal insufficiency (CCR <60 mL/min), individuals with ECOG performance status scores ≥2, and vulnerable subgroups with significant comorbidities. These findings provide a robust foundation for the application of RC48-ADC in complex clinical scenarios.

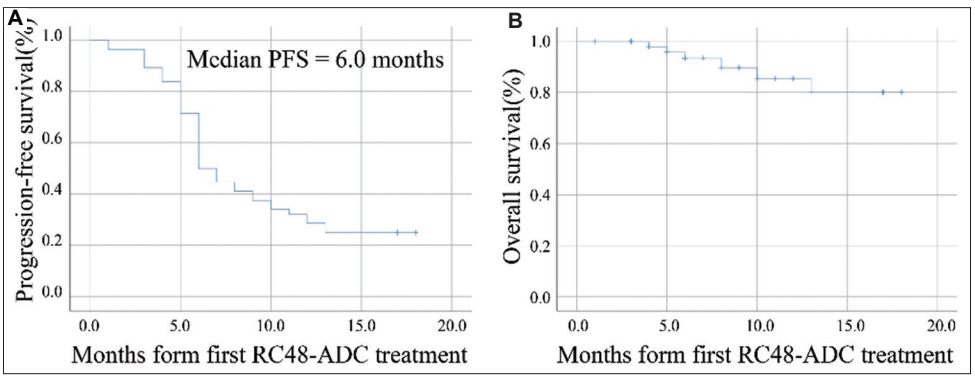

Figure 1. Progression-free survival (PFS) (A) and overall survival (B) of the patients receiving RC48-antibody–drug conjugate (ADC)

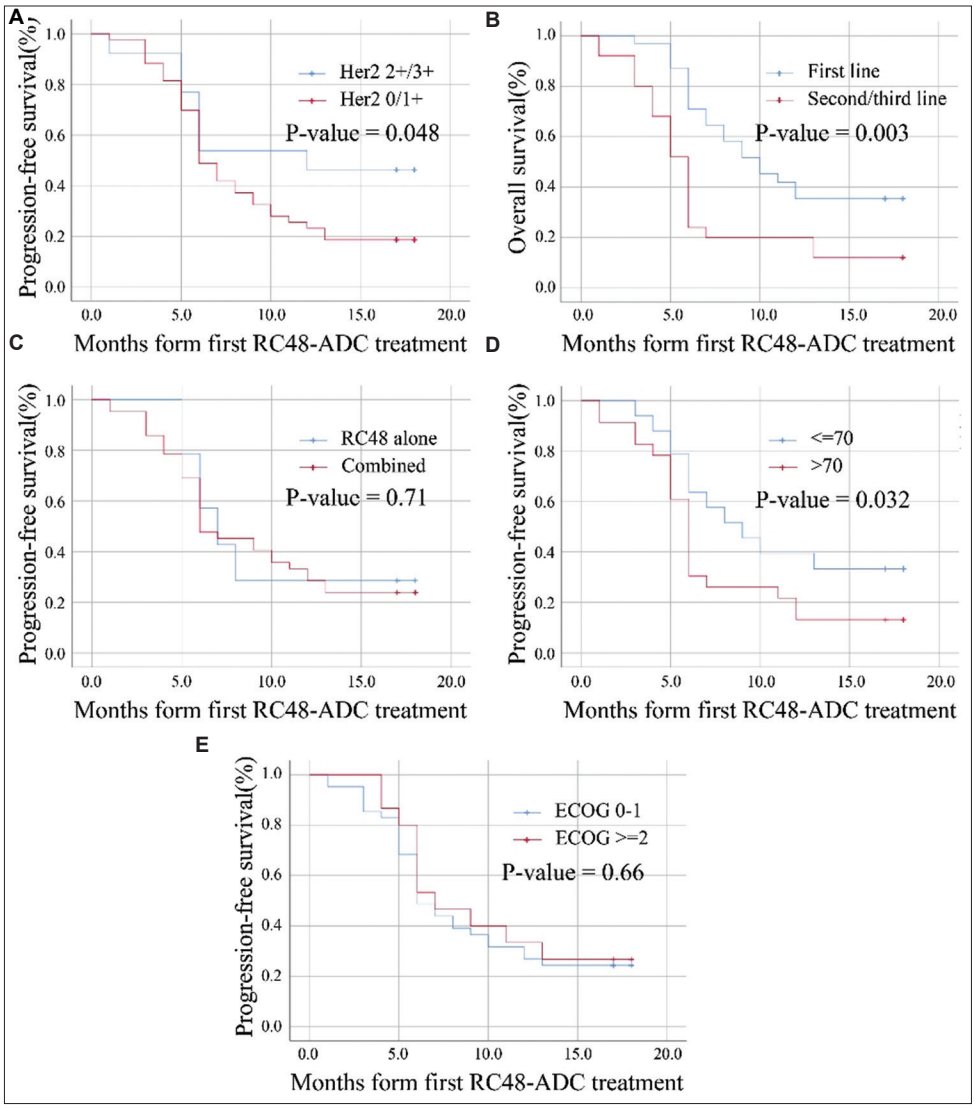

Figure 2. Stratified progression-free survival comparisons. (A) HER2 1+ versus HER2 2+/3+. (B) First-line versus second-/third-line therapy. (C) RC48-antibody–drug conjugate (ADC) monotherapy versus combination therapy. (D) Age ≤70 years versus >70 years. (E) ECOG 0/1 versus ≥2.
Notes: HER2 1+: Weakly HER2-positive; HER2 2+: HER2-positive; HER2 3+: Strongly HER2-positive.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; HER2: Human epidermal growth factor receptor 2.

The current findings demonstrated robust alignment with multiple pivotal clinical trials across the globe.[17,18] A joint analysis of two phase II, open-label, multicenter, single-arm studies (RC48-C005 and RC48-C009), including 107 patients, revealed an overall ORR of 50.5% (95% CI: 40.6–60.3%), a median PFS of 5.9 months (95% CI: 4.3–7.2 months), and a median OS of 14.2 months (95% CI: 9.7–18.8 months).[12] Similarly, in a study of 43 patients with mUC receiving RC48-ADC, Sheng *et al*.[13] reported an ORR of 51.2% (95% CI: 35.5–66.7%), a median PFS of 6.9 months (95% CI: 5.6–8.9 months), and a median OS of 13.9 months (95% CI: 9.1–not evaluated months). Another real-world data analysis showed that RC48-ADC combined with PD-1 inhibitors may enhance bladder preservation rates in muscle-invasive bladder cancer patients, particularly in primary and T2-stage tumors, with a favorable safety profile.[19]

Real-world studies have reported comparable findings. Xu *et al*.[17] reported an overall ORR of 63.2% (95% CI: 47.1–79.2%) and a DCR of 89.5% (95% CI, 79.3%–99.7%) in 38 patients with La/mUC receiving RC48-ADC monotherapy or in combination with PD-1 inhibitors, with a median PFS of 8.2 months (95% CI: 5.9–10.5 months); although median OS was not reached, the 12-month OS rate was 76.7%. Similarly, Chen *et al*.[20] reported an ORR of 38.9%, a DCR of 69.4%, and a median PFS of 5.4 months in 36 patients with mUC receiving RC48-ADC; median OS was also not accomplished, but the 12-month OS was 79.6%. Another study involving 103 patients with mUC receiving RC48-ADC alone or in combination with immunotherapy, in which 2 patients achieved CR, 50 attained PR, and 30 showed SD, reported an ORR of 50.5% and a median PFS of 6 months (95% CI: 3.9–8.1 months); the median OS was not reached.[14]

Table 2. Summary of TRAEs in UC patients receiving RC48-antibody–drug conjugate

Adverse event	Any grade	Grade ≥3
Peripheral sensory neuropathy	58.9% (33/56)	3.6% (2/56)
Alopecia	48.2% (27/56)	1.8% (1/56)
Weakness	42.9% (24/56)	1.8% (1/56)
Decreased appetite	37.5% (21/56)	0
Weight loss	35.7% (20/56)	0
Anemia	33.9% (19/56)	0
Nausea and vomiting	32.1% (18/56)	3.6% (2/56)
Elevated levels of aspartate aminotransferase	30.4% (17/56)	0
Pruritus	28.6% (16/56)	0
Leukopenia	28.6% (16/56)	0
Elevated levels of alanine aminotransferase	26.8% (15/56)	1.8% (1/56)
Elevated blood triglycerides	25.0% (14/56)	0
Neutropenia	23.2% (13/56)	0
Elevated blood glucose	23.2% (13/56)	1.8% (1/56)
Decreased platelet count	23.2% (13/56)	1.8% (1/56)
Elevated blood bilirubin	21.4% (12/56)	1.8% (1/56)
Decreased albumin levels	21.4% (12/56)	3.6% (2/56)
Hypoproteinemia	21.4% (12/56)	3.6% (2/56)

The efficacy of RC48-ADC in our study is consistent with that reported by these prior reports. A multicenter real-world analysis of 102 muscle-invasive bladder cancer patients evaluated clinical characteristics and pathological responses to neoadjuvant RC48-ADC combined with immunotherapy. Results indicated promising efficacy for this combination regimen.[21]

The synergistic effect of RC48-ADC and PD-1 inhibitors results from the integration of two antitumor mechanisms: (i) targeted killing, in which RC48-ADC specifically recognizes tumor cell surface antigens through an anti-HER2 monoclonal antibody, is internalized, and cells release the cytotoxic payload monomethyl auristatin E to induce tumor cell death; and (ii) immune microenvironment remodeling, whereby PD-1 inhibitors block the PD-L1 immune checkpoint pathway, reverse T-cell exhaustion, and enhance antitumor immune responses.[22,23] Clinical studies have reported a median PFS of 5.4 months in patients receiving RC48-ADC monotherapy, against 8.5 months in those receiving combination therapy.[20] An ongoing phase Ib/II clinical trial investigating RC48-ADC combined with PD-1 monoclonal antibodies as a first-line treatment for advanced HER2-positive UC has shown promising results.[24] In our study, the ORR was 57.1% in patients receiving RC48-ADC monotherapy and 66.7% in those receiving combination therapy, although PFS did not differ significantly between the two treatments.

HER2 expression status significantly influences RC48-ADC efficacy.[25] Studies have shown that patients with HER2-positive or strongly HER2-positive expression tend to respond better, in whom ORRs being generally higher than in their counterparts with weakly HER2-positive or HER2-negative expression.[26] In patients with advanced cancer, HER2-positive individuals often exhibit better therapeutic responses to targeted therapies or ADCs, and overall treatment efficacy correlates positively with HER2 expression levels.[25] Research suggests that the ORR in HER2-positive or strongly HER2-positive patients can exceed 40%, whereas in weakly HER2-positive or HER2-negative patients, it tends to remain below 20%. Importantly, the safety profile in HER2-positive patients is comparable to that in HER2-negative ones, with no significant difference found in TRAEs.[20] Overall, HER2-positive patients demonstrated significantly better efficacy relative to HER2-negative patients, without experiencing a higher incidence of TRAEs.

Differential analysis of clinically relevant subgroups yielded the following results: (i) no significant differences in ORR (65.6% vs. 63.2%) or PFS (6.2 vs. 5.8 months) were found between patients with CCR ≥60 mL/min (n = 32) and those with CCR 30–59 mL/min (n = 19) (p>0.05). Notably, even in the severe renal insufficiency subgroup (CCR < 30 mL/min, n = 5), no dose-limiting toxicities or compromised efficacy occurred.[27] (ii) ECOG performance status did not significantly affect RC48-ADC efficacy.[28] In our study, 26.8% and 73.2% of patients had ECOG scores of ≥2 and 0–1, with ORRs of 80.0% and 57.9% observed in groups. However, there were no differences in PFS or TRAE incidence. (iii) Stratified analysis in terms of age revealed that PFS was longer in patients aged ≤70 years than in those aged >70 years, although the difference was not statistically significant. This difference may be attributed to age-related comorbidities and lower physical fitness in elderly patients.[18] Our findings suggest that RC48-ADC remains safe and effective regardless of ECOG status, whereas age may influence efficacy and side effects, indicating that caution should be exercised when elderly populations are considered for the treatment.

Although patients with renal insufficiency may face additional treatment challenges, RC48-ADC demonstrated consistent efficacy and safety across different levels of renal function. In this study, ORR and PFS were comparable between patients with normal renal function and those with mild renal insufficiency, and no increase in TRAEs was observed in the latter group. Despite the small sample size of the patients with severe renal insufficiency, no significant differences in efficacy or safety were observed. Overall, RC48-ADC remained safe and efficacious regardless of renal function status.

The combination of RC48-ADC with immunotherapy enhances treatment efficacy through complementary mechanisms.[29] As an HER2-targeting ADC, RC48-ADC directly targets and kills HER2-positive tumor cells, while immunotherapy strengthens the immune response by overcoming tumor immune evasion.[30] Clinical studies in patients

with La/mUC receiving RC48-ADC plus immunotherapy have reported significant improvement in efficacy without an increase in the burden of adverse events.[17] Most TRAEs were grade 1 or 2, and no severe adverse events were reported, reinforcing the combination therapy's strong safety profile. This is particularly relevant for patients with La/mUC, who are often ineligible for traditional cisplatin-based chemotherapy due to advanced age or comorbidities. Our findings support RC48-ADC combined with immunotherapy as a promising first-line treatment for mUC, highlighting its efficacy and safety, especially for patients ineligible for cisplatin-based chemotherapy. Further clinical studies are needed to confirm its role in treating mUC and to facilitate broader clinical adoption.

This study has several limitations, including its retrospective design and potential bias resulting from heterogeneous baseline characteristics and treatment regimens. In addition, only 10 of the 56 patients underwent next-generation sequencing, underscoring the need for more genomic data in future research. However, the study's strength lies in its analysis of RC48-ADC efficacy and safety, both as a monotherapy and in combination with immunotherapy, particularly in patients with La/mUC and renal dysfunction. Prospective clinical trials with larger cohorts are necessary to validate these findings.

5. Conclusion

RC48-ADC demonstrated strong antitumor activity in patients with La/mUC, including those with moderate or severe renal insufficiency. A phase III randomized controlled trial comparing RC48-ADC monotherapy with combination immunotherapy is warranted. Overall, this retrospective study confirms that RC48-ADC is both effective and well-tolerated in patients with La/mUC, aligning with previous findings. Moreover, our findings suggest that RC48-ADC maintains high efficacy and tolerability in patients with poor prognostic factors.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

This study was reviewed and approved by the Medical Ethics Committee of the Second Hospital of Lanzhou University (approval ID: 2024A-576). Oral consent was obtained from each participant to participate in this study.

Consent for publication

Oral consent was obtained from each participant for the publication of their data. All information that could potentially reveal the identity of the patients has been concealed.

Data availability statement

The data obtained in this study are available from the corresponding author upon reasonable request.

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