



# Efficacy and biomarker analysis of neoadjuvant disitamab vedotin (RC48-ADC) combined immunotherapy in patients with muscle-invasive bladder cancer: A multi-center real-world study

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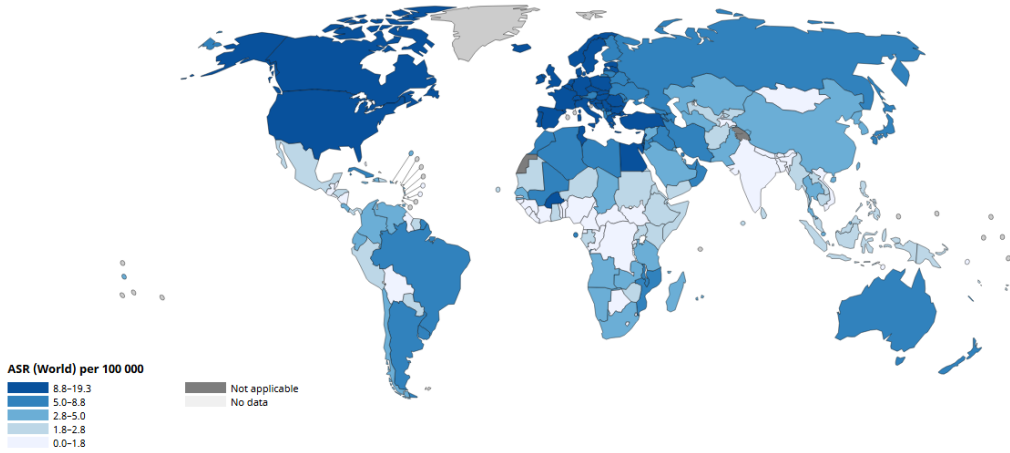
Hu, Jiao, Luzhe Yan, Jinhui Liu, Minfeng Chen, Peihua Liu, Dingshan Deng, Chaobin Zhang, et al. 2025. “Efficacy and biomarker analysis of neoadjuvant disitamab vedotin (RC48-ADC) combined immunotherapy in patients with muscle-invasive bladder cancer: A multi-center real-world study.” *iMeta* 4: e70033.

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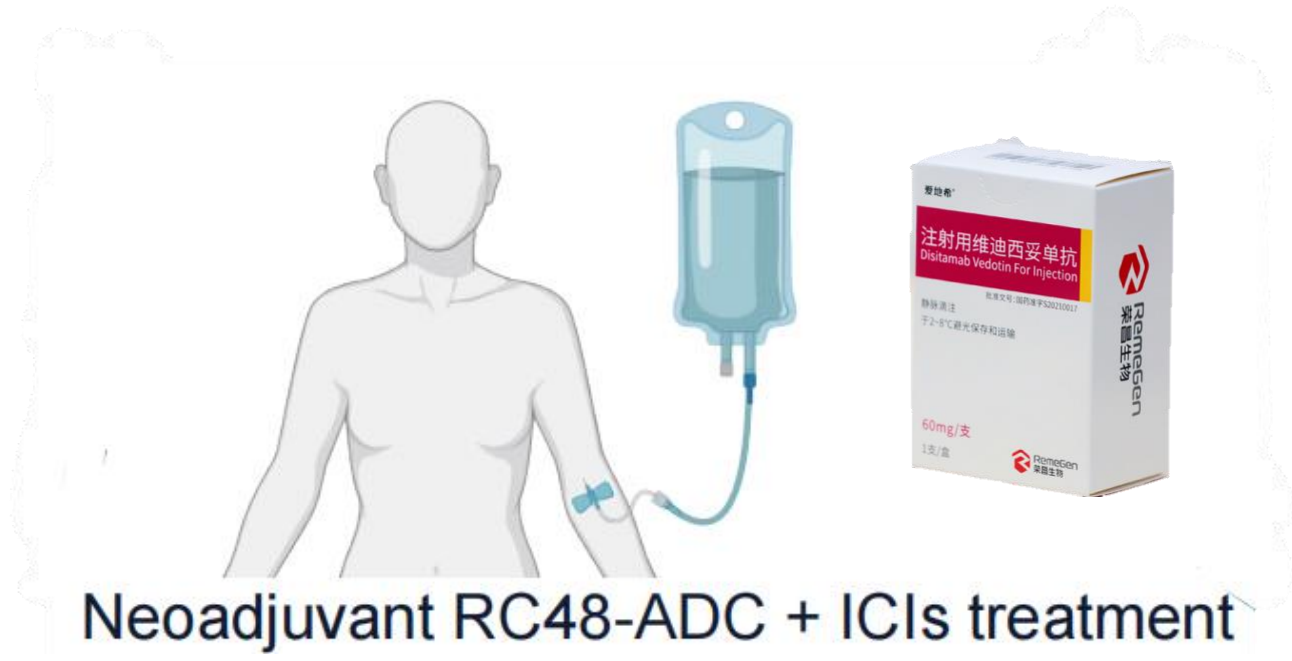
# Background

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022  
Bladder



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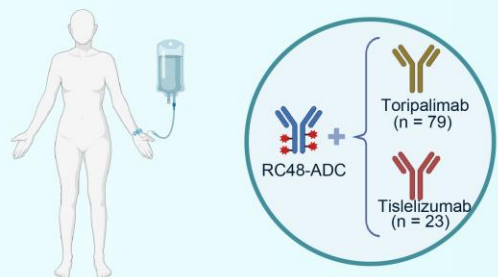
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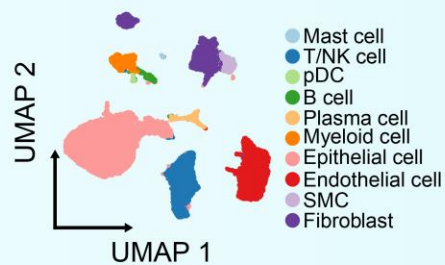
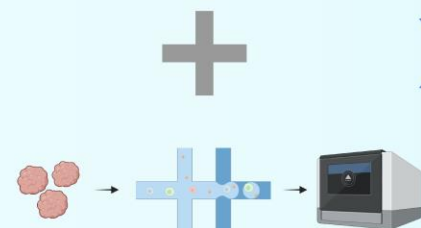
- ❑ Bladder cancer is the tenth most common cancer globally.
- ❑ More than half of patients with MIBC cannot benefit from neoadjuvant chemotherapy.
- ❑ In recent years, RC48-ADC have shown excellent clinical benefits in advanced MIBC patients.
- ❑ However, there is still a lack of research on using RC48-ADC as neoadjuvant therapy.



# Highlight

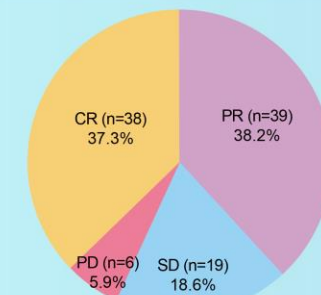
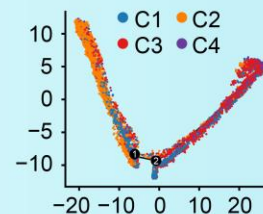
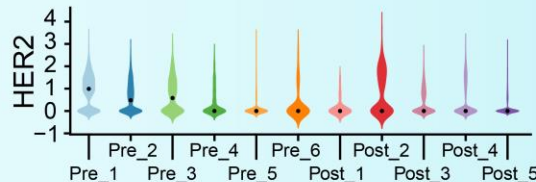
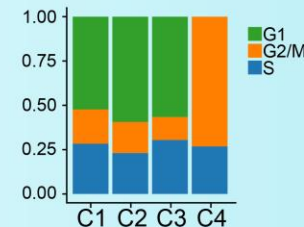
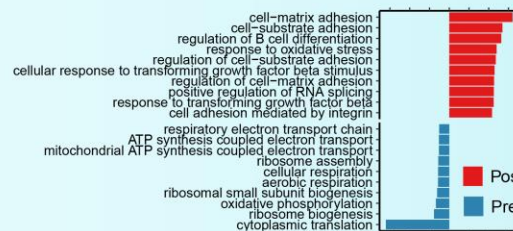
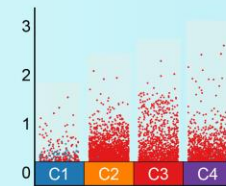
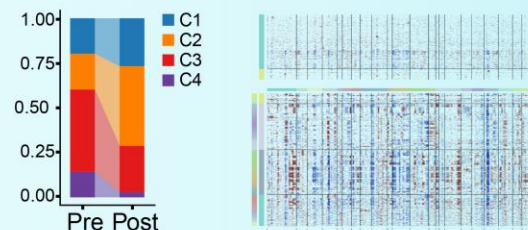


Neoadjuvant RC48-ADC + ICIs

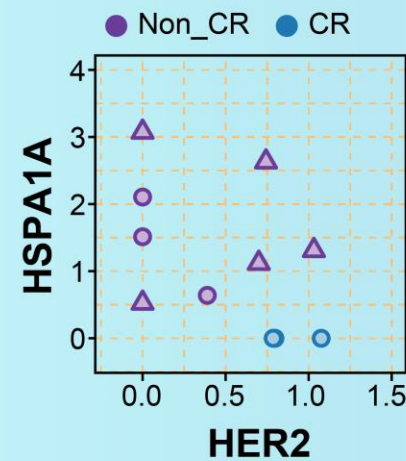
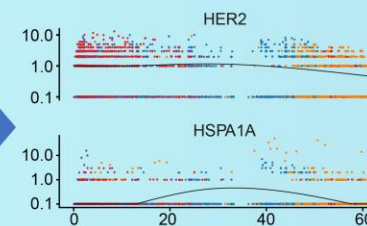


**UMAP plot:**  
45,603 high-quality single cells were defined as 10 cell populations by classic markers.

Term	Univariate analysis	p value	Multivariable analysis	p value
HER2				
Low expression				
Overexpression		0.944		0.319
Clinical Stage				
T2N0M0				
>T2N0M0		<0.001		<0.001
Histology variants				
Pure UC				
UC with variants		0.002		0.005
Globulin		0.01		0.118
ALG		0.009		0.746



Responder (CR + PR): n=77 (75.5%)  
Non-responder (SD + PD): n=25 (24.5%)



# Outcome

## Study design, outcomes and participants selection

124 patients with MIBC were included

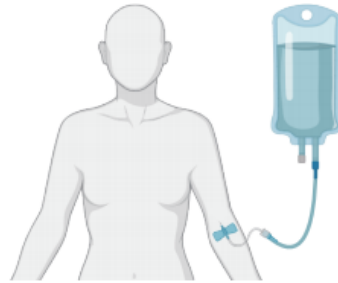


22 excluded :

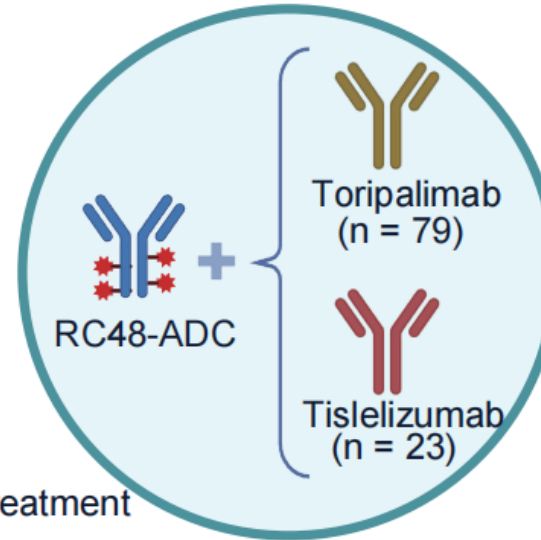
- Previous treatments (n = 2)
- Incomplete treatment (n = 12)
- Distant metastasis (n = 3)
- Complicated with UTUC (n = 5)




102 met inclusion criteria



Neoadjuvant RC48-ADC + ICIs treatment



 Outcomes

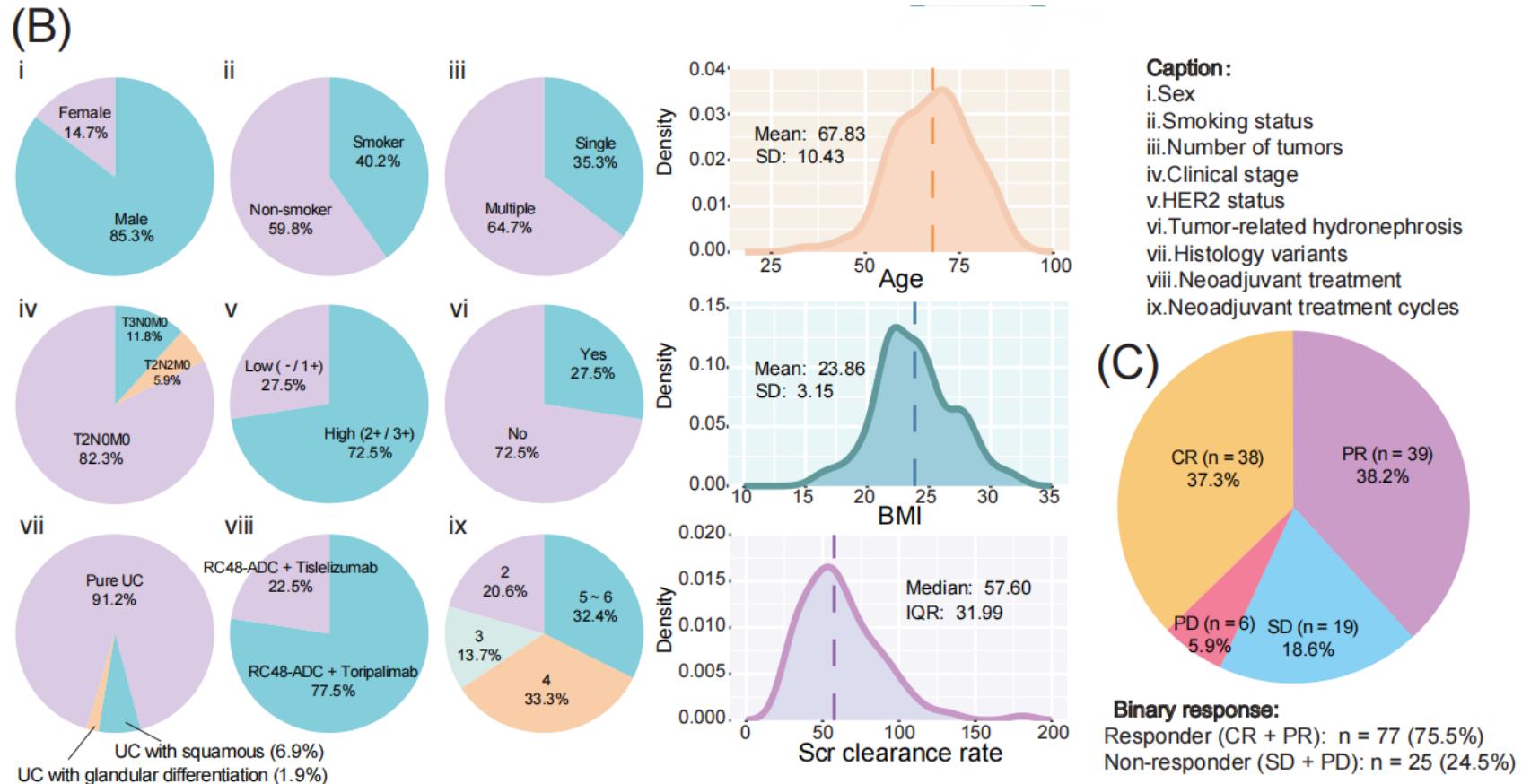
Primary :  
Pathological response  
(pCR/PR/SD/PD)

Secondary :  
Disease free survival  
(DFS)



# Outcome

## Efficacy of neoadjuvant RC48-ADC combined with ICIs

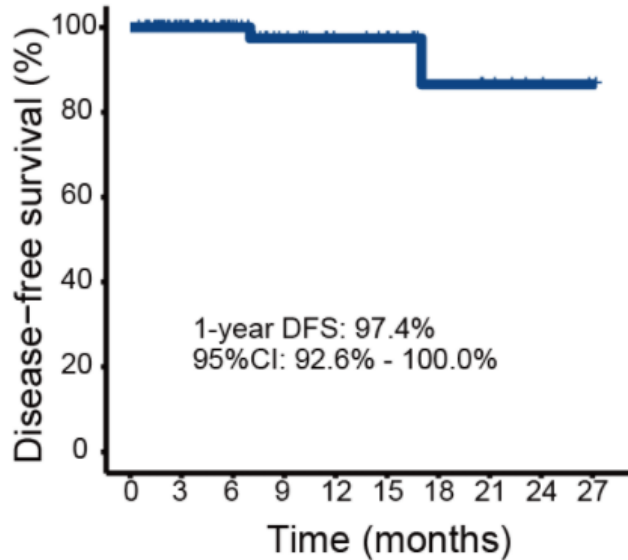


**(B) Patients baseline characteristics. (C) Pathologic response.**

# Outcome

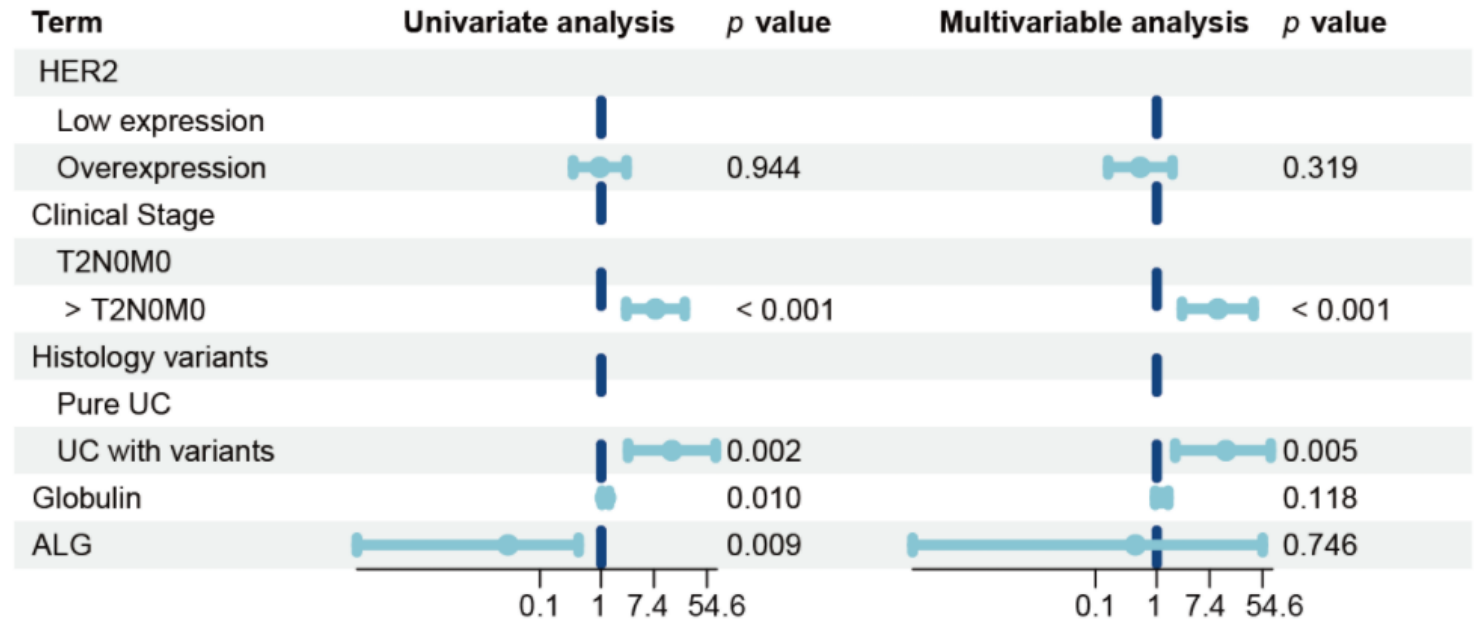
## Relationships between clinicopathological features and pathological response

(D)



**(D) Kaplan-Meier estimates of 1-year DFS.** Two patients underwent intravesical recurrence: One patient (T2N0M0, HER2: 1+) achieved PR after receiving two cycles of neoadjuvant treatment plus maximal TURBT and had a recurrence at 7 months. The other patient (T2N0M0, HER2: 2+) reached SD after six cycles of neoadjuvant treatment plus maximal TURBT and had a recurrence at 17 months.

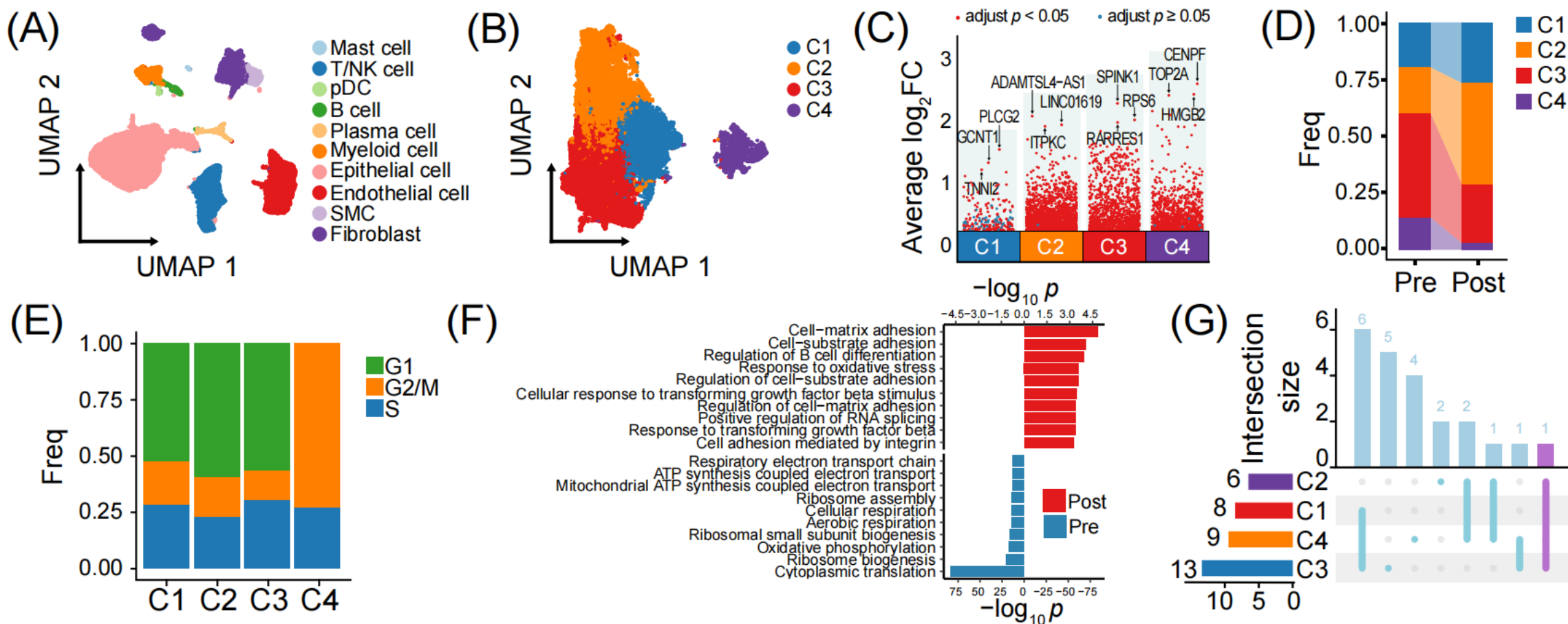
(E)



**(E) Uni- and multivariable logistic regression of pathological response-related factors.**

# Outcome

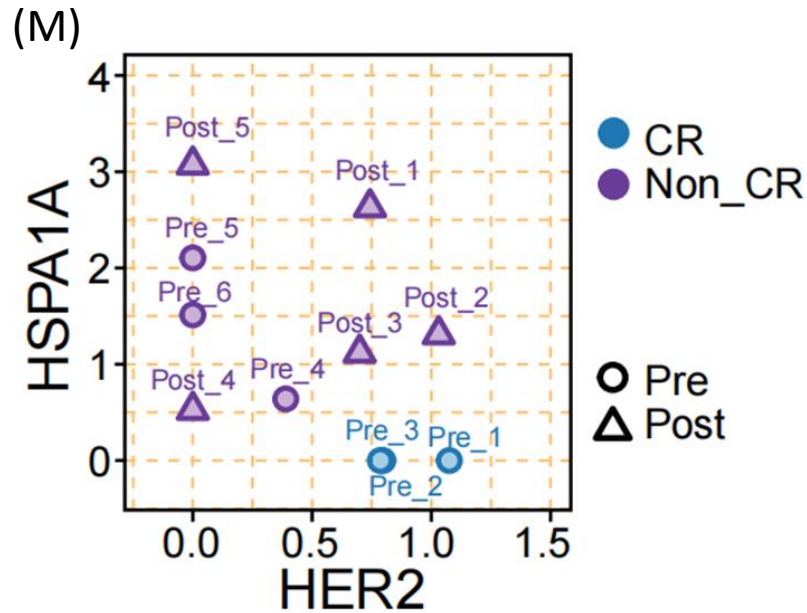
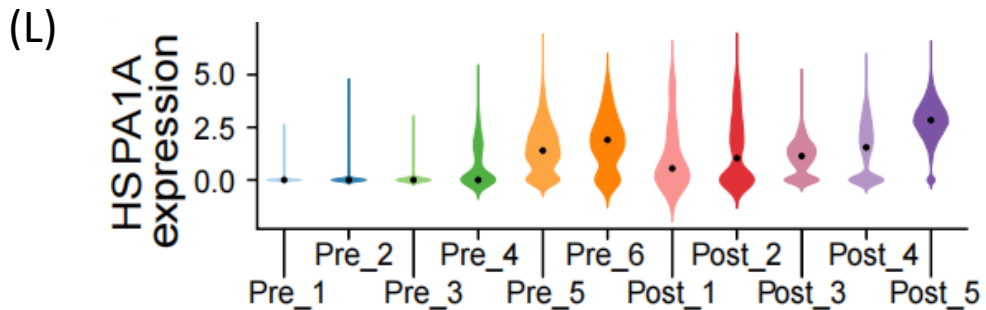
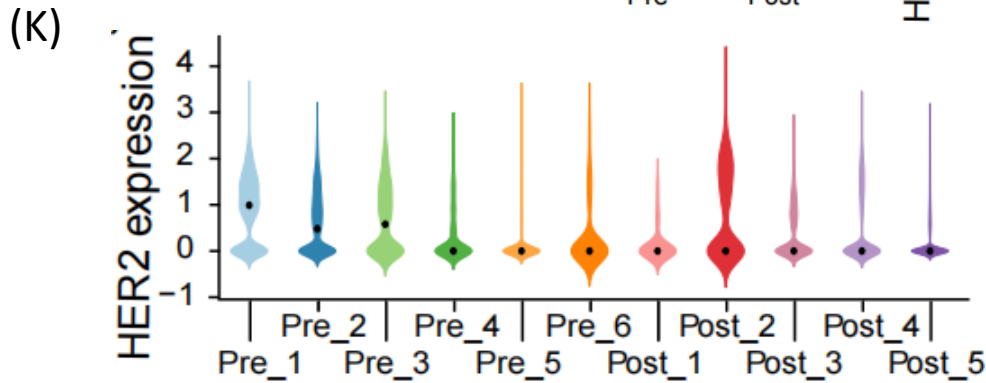
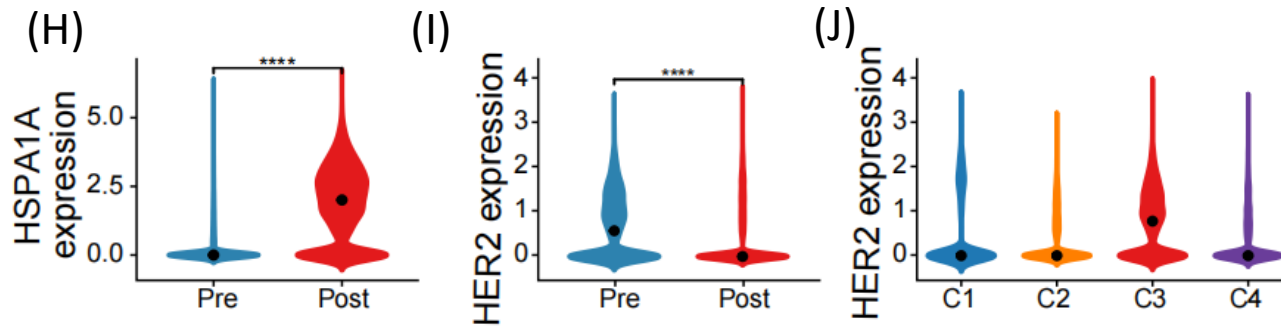
## Single-cell map of tumor microenvironment (TME) before and after neoadjuvant RC48-ADC combined with ICIs



**(A)**UMAP plot of all single cells profiled in the presenting work. **(B)**UMAP plot of subclusters of BLCA epithelial cells. **(C)**The highly expressed marker genes specific to each subcluster, shown by manhattan plot. **(D)**Histogram illustrated the differences in BLCA epithelial cell population proportions before and after treatment. **(E)**Histogram illustrated the differences in BLCA cell cycle phases proportions of four subclusters. **(F)**Functional enrichment analysis highlighted the most significantly enriched pathways for all subclusters before and after treatment. **(G)**UpSet plot showed the intersection of overexpressed genes across four subclusters after treatment.

# Outcome

## HER2 and HSPA1A can be used in combination as efficacy prediction biomarkers

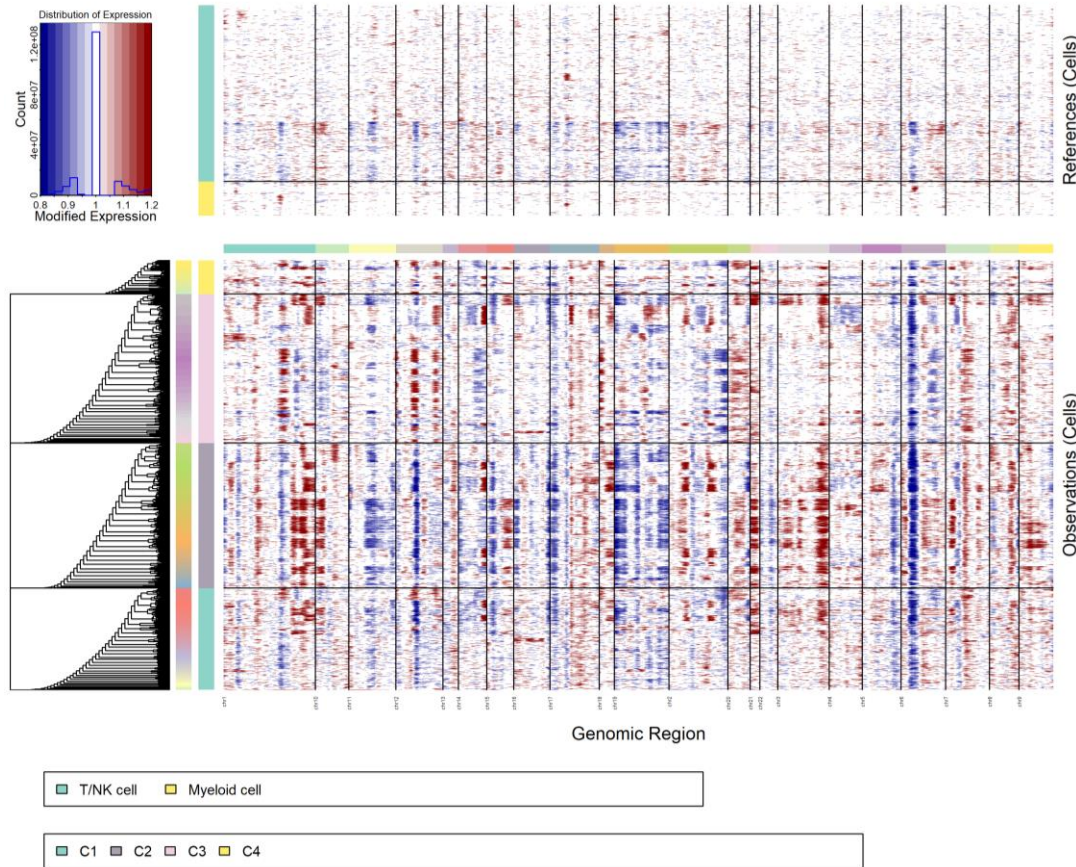


(H) Violin plot compared the expression of HSPA1A in all BLCA epithelial cells before and after treatment. (I) Violin plot compared the expression of HER2 in all BLCA epithelial cells before and after treatment. (J) The violin plot showed the expression of HER2 in four subclusters. (K) The violin plot showed the expression of HER2 in each sample. (L) The violin plot showed the expression of HSPA1A in each sample. (M) The scatter plot showed the median values of HER2 and HSPA1A in C3 BLCA epithelial cells of each sample, and it could be seen that patients who achieved CR had the characteristics of HSPA1A-HER2+.

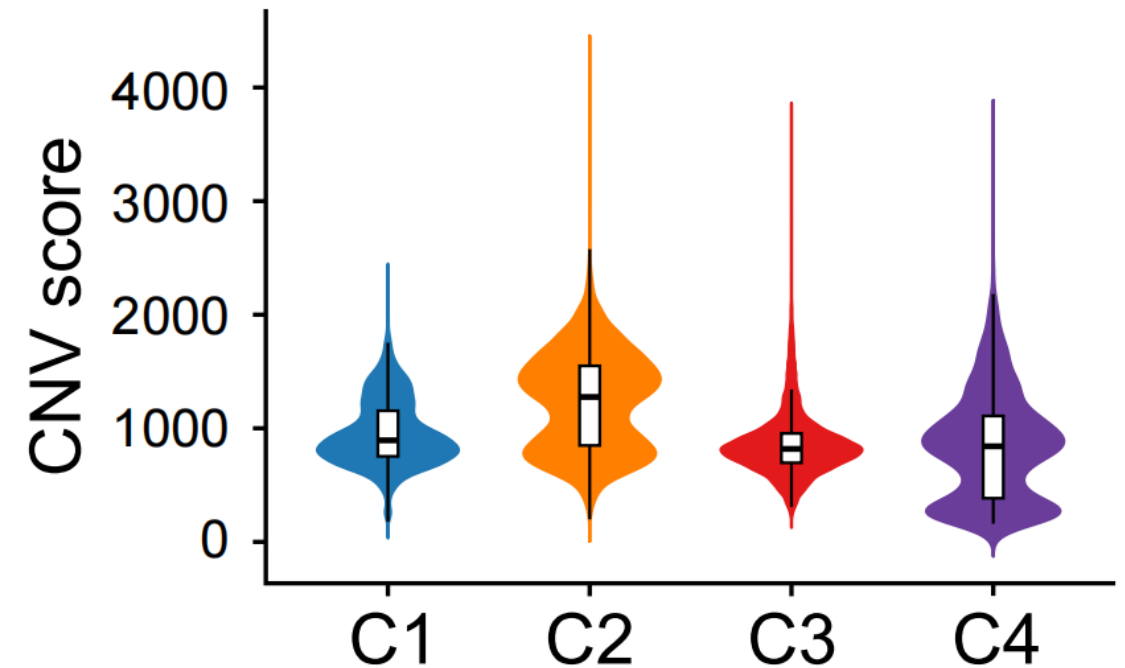


# Outcome

## CNV analysis



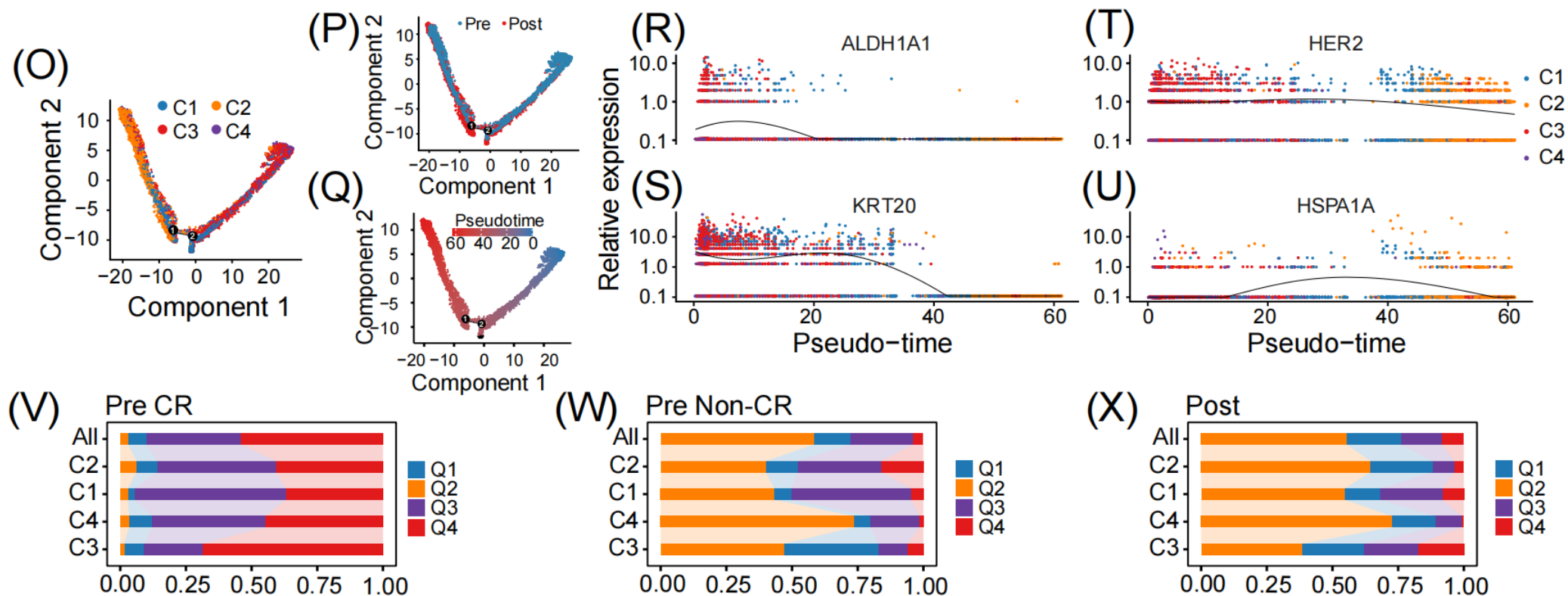
Heatmap represented the CNV analysis for all BLCA epithelial cells.



The violin plot indicated the CNV score of four subclusters.

# Outcome

## C3 plays a dominant role in the emergence of drug-resistance characteristics during the evolution of BLCA epithelial cells



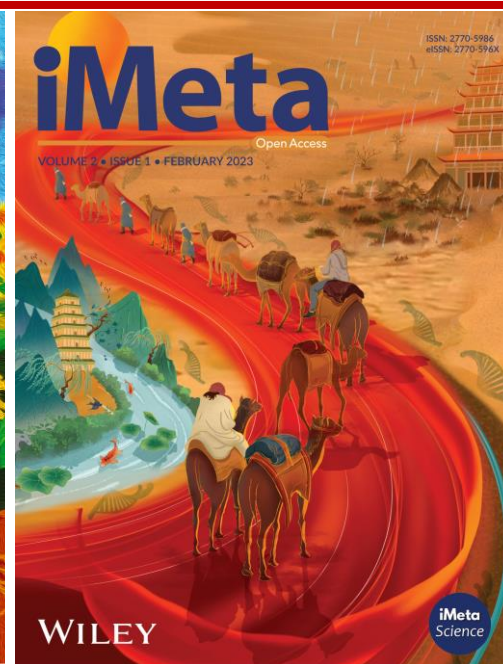
**(O)-(Q)** Pseudo-time analysis of BLCA epithelial cells for all samples. BLCA epithelial cell subclusters (O), treatment groups (P) and pseudo-temporal ordering (Q) were labeled by colors. **(R)-(S)** The expression of tumor stem cell markers ALDH1A1 (R) and KRT20 (S) during the evolutionary process of BLCA epithelial cells. **(T)-(U)** The expression of HER2 (T) and HSPA1A (U) during the evolutionary process of BLCA epithelial cells in Pre-CR group. **(V)-(X)** Histogram illustrated the proportion in four quadrants segmented based on the expression of HER2 and HSPA1A in all epithelial cells and subclusters in Pre-CR group (V), Pre-NonCR group (W) and Post group (X).



# Summary




- ❑ This is the first study to evaluate the efficacy and biomarkers of neoadjuvant RC48-ADC combined with immunotherapy for bladder cancer.
- ❑ Neoadjuvant RC48-ADC combined with ICIs showed promising efficacy in patients with MIBC.
- ❑ Predicting treatment efficacy based on single-cell RNA sequencing is feasible.
- ❑ This study will expand neoadjuvant treatment strategies for patients who are ineligible for neoadjuvant chemotherapy.


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