“Neoadjuvant treatment with Disitamab vedotin plus Perioperative Toripalimab in patient with MIBC with Her2neu expression”: Phase II

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Neoadjuvant treatment with disitamab vedotin plus perioperative toripalimab in patients with muscle-invasive bladder cancer (MIBC) with HER2 expression: updated efficacy and safety results from the phase II RC48-C017 trial

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Background: MIBC

- Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy is recommended for the cisplatin-eligible patients with muscle-invasive bladder cancer (MIBC).[1-4]
- Immunotherapy-based neoadjuvant therapy has a significant impact on the treatment of most cancers. The NIAGARA study demonstrated that neoadjuvant durvalumab plus chemotherapy significantly improved event-free survival and overall survival in operable MIBC.[5]
- Several clinical trials that combine immunotherapy with antibody-drug conjugates (ADCs) in the neoadjuvant setting are ongoing. However, none of these trials have yet published their findings.

1. Milowsky, et al. J Clin Oncol. 2016; 34(16): 1945-1952. 2. Witjes, et al. Eur Urol. 2021; 79(1): 82-104. 3. Pfister, et al. Eur Urol. 2021; 79(2): 214-221. 5. Powles, et al. N Engl J Med. 2024; 391:1773-1786.

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Background: DV

- HER2-targeting ADCs such as disitamab vedotin(DV) and trastuzumab deruxtecan (T-DXd) have emerged as effective treatment options for HER2 positive mUC who failed to chemotherapy and immunotherapy.[1-2]
- Disitamab vedotin(DV) plus Toripalimab (an anti-PD-1 inhibitor) has shown encouraging efficacy (confirmed objective response rate: 76.3%) in patients with HER2 expression (IHC 1+, 2+ or 3+) in a phase 1b/2 trial (RC48-C014).[3]
- The single-arm phase II RC48-C017 trial (NCT05297552) was conducted to evaluate the efficacy and safety of neoadjuvant DV plus perioperative toripalimab in patients with HER2-expression (IHC 1+, 2+ or 3+) MIBC.

1. Sheng, et al. J Clin Oncol. 2024;42(12):1391-1402. 2. Meric-Bernstam F et al. J Clin Oncol. 2024 Jan 1;42(1):47-58. 3. Zhou, et al. Ann Oncol. 2024.

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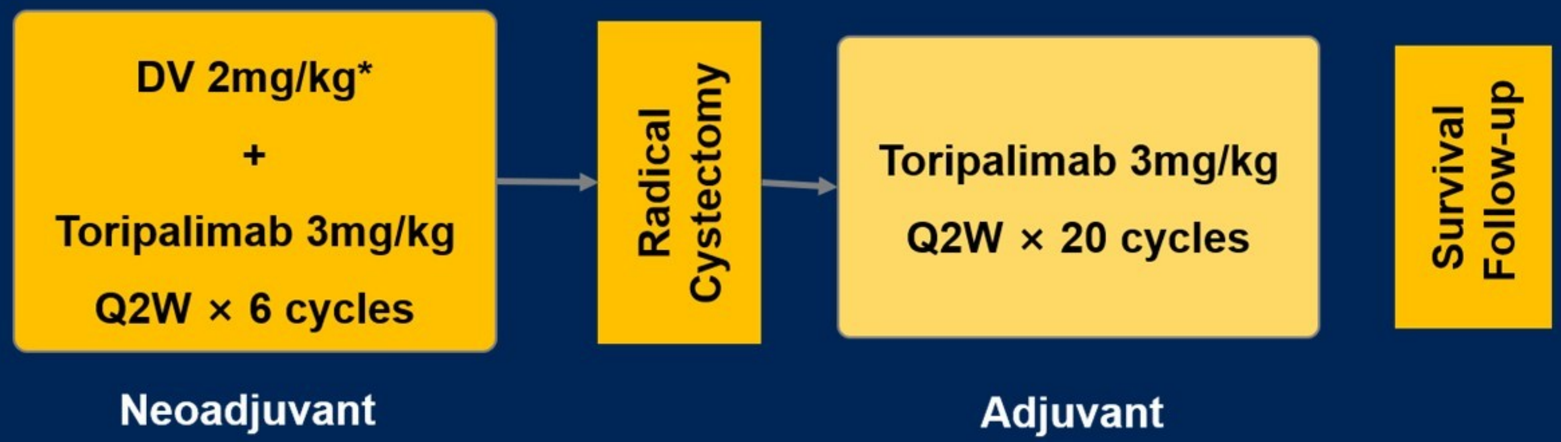
Study design

Key Eligible Criteria:

- Histologically confirmed urothelial carcinoma;
- MIBC at stage of cT2-T4a, N0-1, and M0;
- Eligible for radical cystectomy (RC) + pelvic lymph node dissection (PLND);
- HER2 expression: IHC 1+, 2+, or 3+.



- **Primary endpoint:** Pathologic complete response (pCR, defined as ypT0N0) rate.
- **Secondary endpoints:** Pathological response rate (defined as ≤ypT1N0M0)[#]; event-free survival (EFS); overall survival (OS)^; adverse events.

The preliminary results of this trial showed promising efficacy and acceptable safety.[1] Herein, we present updated results including the pathological response, event-free survival, safety, and other outcomes with a longer follow-up (data cutoff: Dec 3, 2024).

Pathological tumour response was assessed by the local pathologists and investigators based on the postoperative pathology. Radiological assessment was performed by the investigators per RECIST v1.1
*Equivalent to dose of 1.5 mg/kg using DV-based extinction coefficient outside of China. #Including complete or partial pathological response. ^OS data was not mature and not reported here. 1. Sheng, et al. J Clin Oncol. 2024, 42(16_suppl):4568.
Abbreviations: IHC=immunohistochemistry, Q2W=every two weeks, RECIST=Response Evaluation Criteria in Solid Tumors.

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Baseline Characteristics (ITT)

Demographics and baseline characteristics	Patients enrolled N=47
Median age (range), years	64.0 (30, 82)
Male, n (%)	34 (72.3)
Histology, n (%)	
Pure urothelial carcinoma (UC)	36 (76.6)
UC with other differentiation or variants	11 (23.4)
Squamous differentiation	3 (6.4)
Glandular differentiation	2 (4.3)
Micropapillary features	2 (4.3)
Clear cell	1 (2.1)
Sarcomatoid	1 (2.1)
Others (with 2 types variants)	2 (4.3)
ECOG performance status, n (%)	
0	25 (53.2)
1	22 (46.8)
Creatine clearance, n (%)	
<60 mL/min	12 (25.5)
>=60 mL/min	35 (74.5)

Demographics and baseline characteristics	Patients enrolled N=47
Baseline cTNM stage, n (%)	
cT2N0M0	19 (40.4)
cT3N0M0	14 (29.8)
cT4N0M0	6 (12.8)
cT2-4aN1M0	8 (17.0)
HER2 expression, n (%)	
IHC 1+	5 (10.6)
IHC 2+	27 (57.4)
IHC 3+	15 (31.9)
PD-L1 expression*, n (%)	
Negative	25 (53.2)
Positive	13 (27.7)
Not available	9 (19.1)

*PD-L1 positive status was defined as combined positive score ≥10 if examined by PD-L1 IHC 22C3 pharmDx assay, and, if tested by Ventana SP263 PD-L1 IHC assay, as PD-L1 staining in ≥25% of tumor cells, or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells present was >1% or ≤1% according to the consensus among Chinese Society of Pathology on IHC detection of PD-L1 (SP263) in bladder invasive UC.
Abbreviations: ECOG=Eastern Cooperative Oncology Group.

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Baseline Characteristics

63 patients screened

↓

47 enrolled and received neoadjuvant treatment

↓

33 underwent radical cystectomy
14 did not undergo cystectomy #
11 patients decision
2 distant metastases
1 adverse event

↓

16 received adjuvant treatment
17 did not receive adjuvant treatments
14 patients decision
3 investigator decision

11 patients refused RC (8 patients received TURBT and 5 of them achieved cT0); 1 patient did not recover from the AE within the operative window, then received TURBT and achieved cT0.

Demographics and baseline characteristics	Patients Received RC* N=33
Median age (range), years	64.0 (30, 81)
Male, n (%)	23 (69.7)
Histology, n (%)	
Pure urothelial carcinoma (UC)	24 (72.7)
UC with other differentiation or variants	9 (27.3)
Baseline cTNM stage, n (%)	
cT2N0M0	14 (42.4)
cT3N0M0	11 (33.3)
cT4N0M0	3 (9.1)
cT2-4aN1M0	5 (15.2)
HER2 expression, n (%)	
IHC 1+	4 (12.1)
IHC 2+	16 (48.5)
IHC 3+	13 (39.4)
PD-L1 expression, n (%)	
Negative	16 (48.5)
Positive	9 (27.3)
Not available	8 (24.2)

*RC：radical cystectomy

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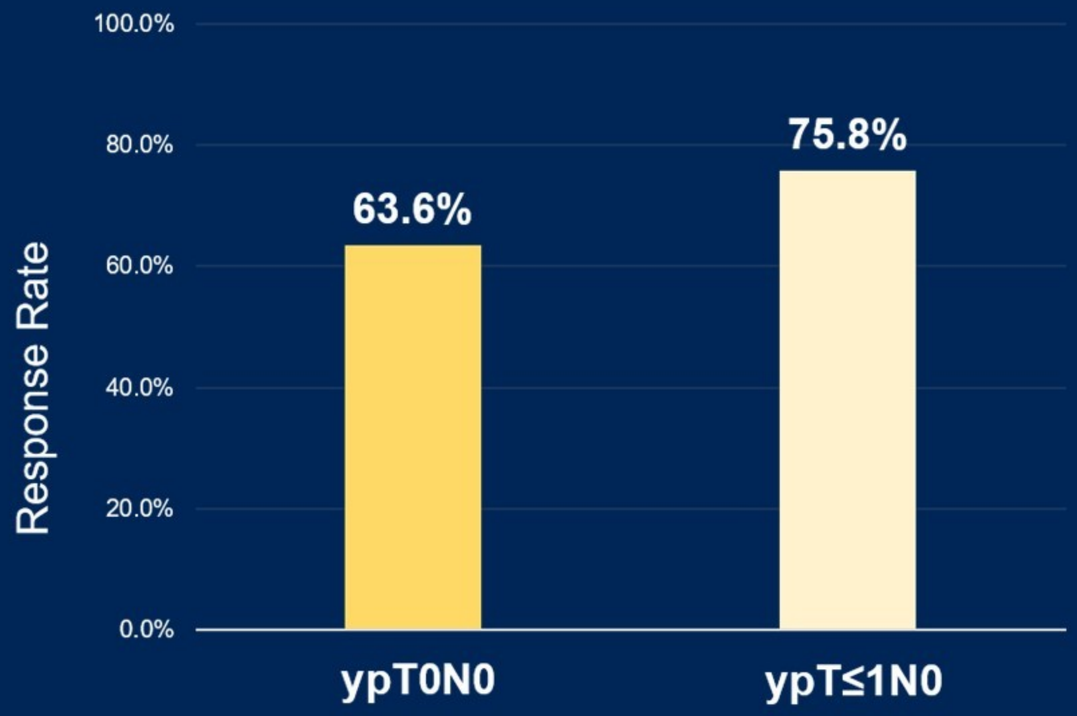
Pathological response

- Median time from end of neoadjuvant treatment to RC: 5.0 weeks (range: 2.6-13.1)

	Patients Received RC N=33
Pathological response	
pCR (ypT0N0), n (%)	**21 (63.6)**
95% CI	45.1-79.6
Pathological response (≤ypT1N0M0), n (%)	**25 (75.8)**
95% CI	57.7-88.9
Pathological staging, n (%)	
ypT0N0	21 (63.6)
ypT≤1N0	4 (12.1)
ypTisNx*	1 (3.0)
ypT2N0	4 (12.1)
ypT3N0	3 (9.1)
ypT4 or ypTanyN+	0

Pathological tumor response was assessed by the local pathologists based on the postoperative pathology.
*Pelvic lymph-node dissection was not performed.



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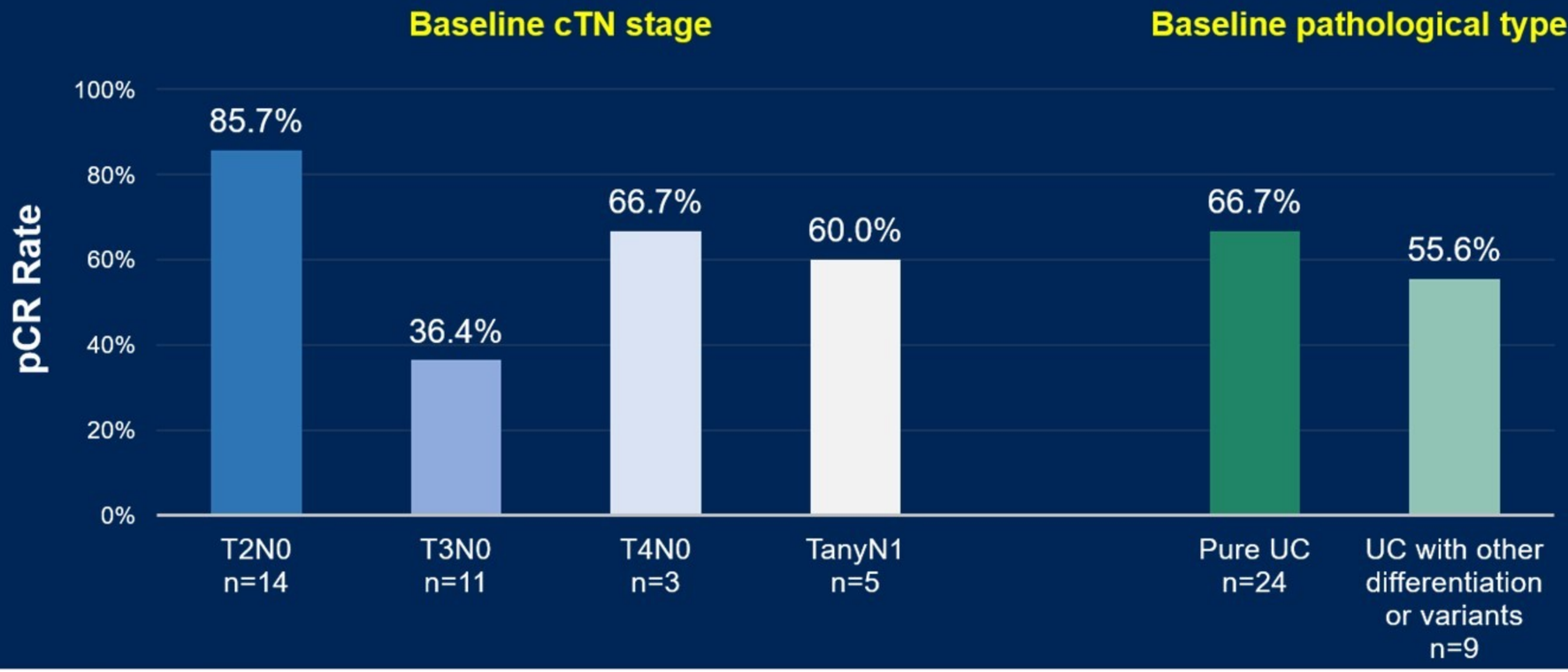
Subgroup analysis

- The pCR rate for the T2N0 patients appeared higher than those for the other subgroups.
- The pCR rates were generally consistent between patients with pure UC and patients with UC with other differentiation or variants.



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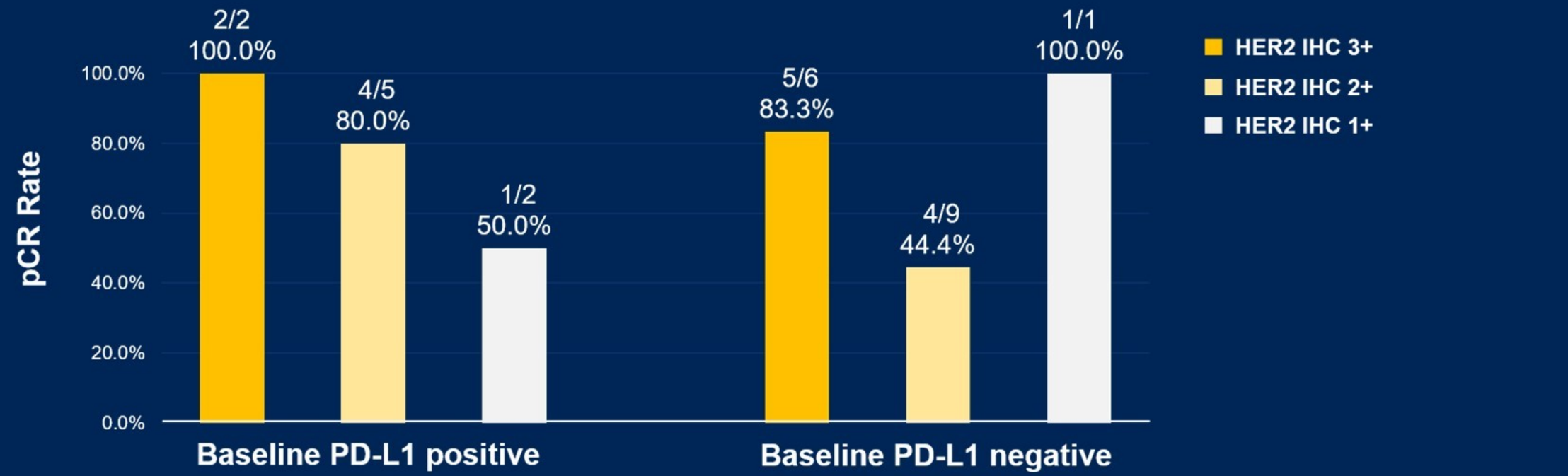
Subgroup analysis

- The pCR rate for the HER2 IHC 3+ subgroup was numerically higher than those for IHC 1+ and IHC 2+ subgroups regardless of PD-L1 status.



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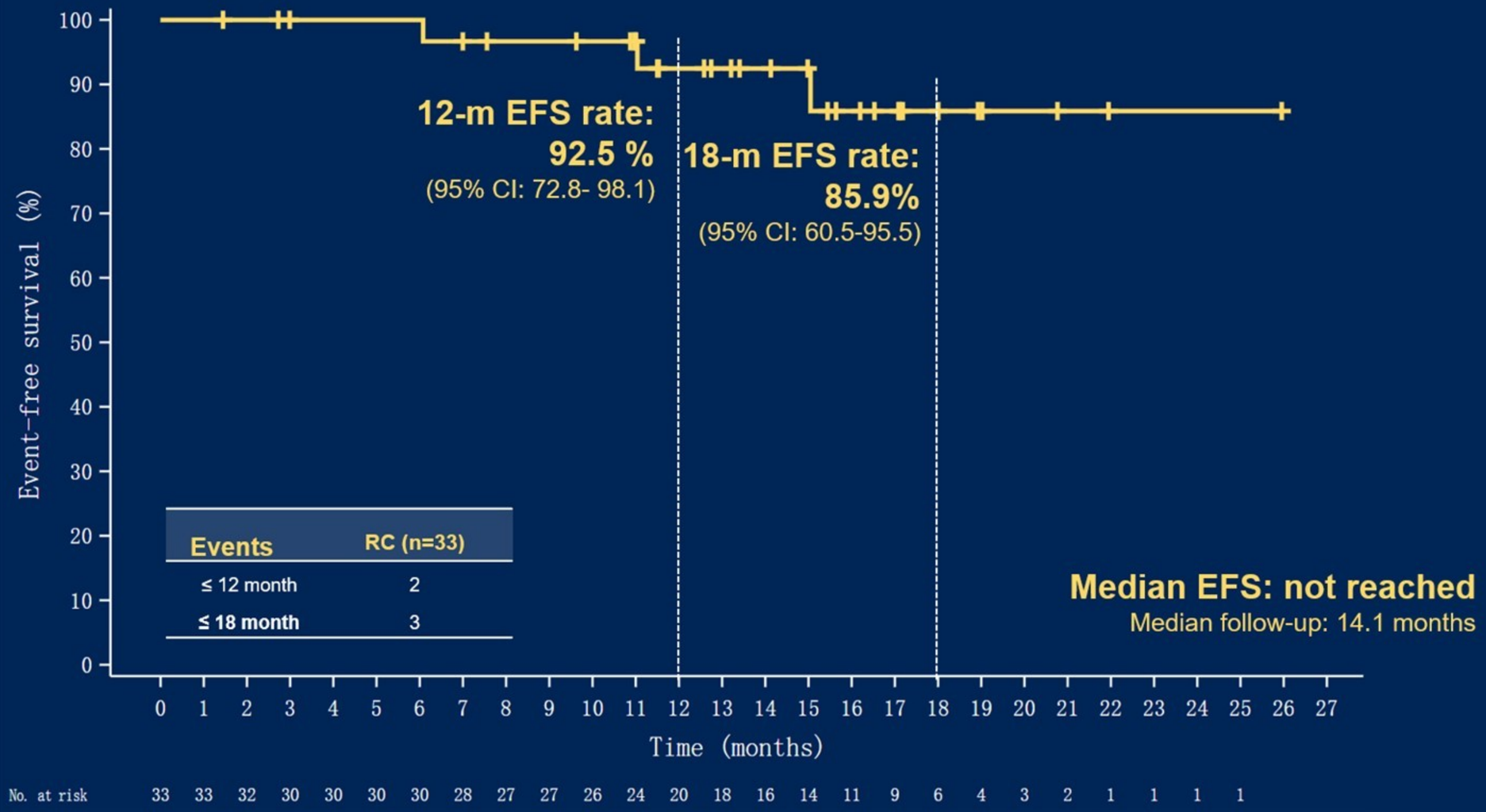
Event-free survival in the patients received RC



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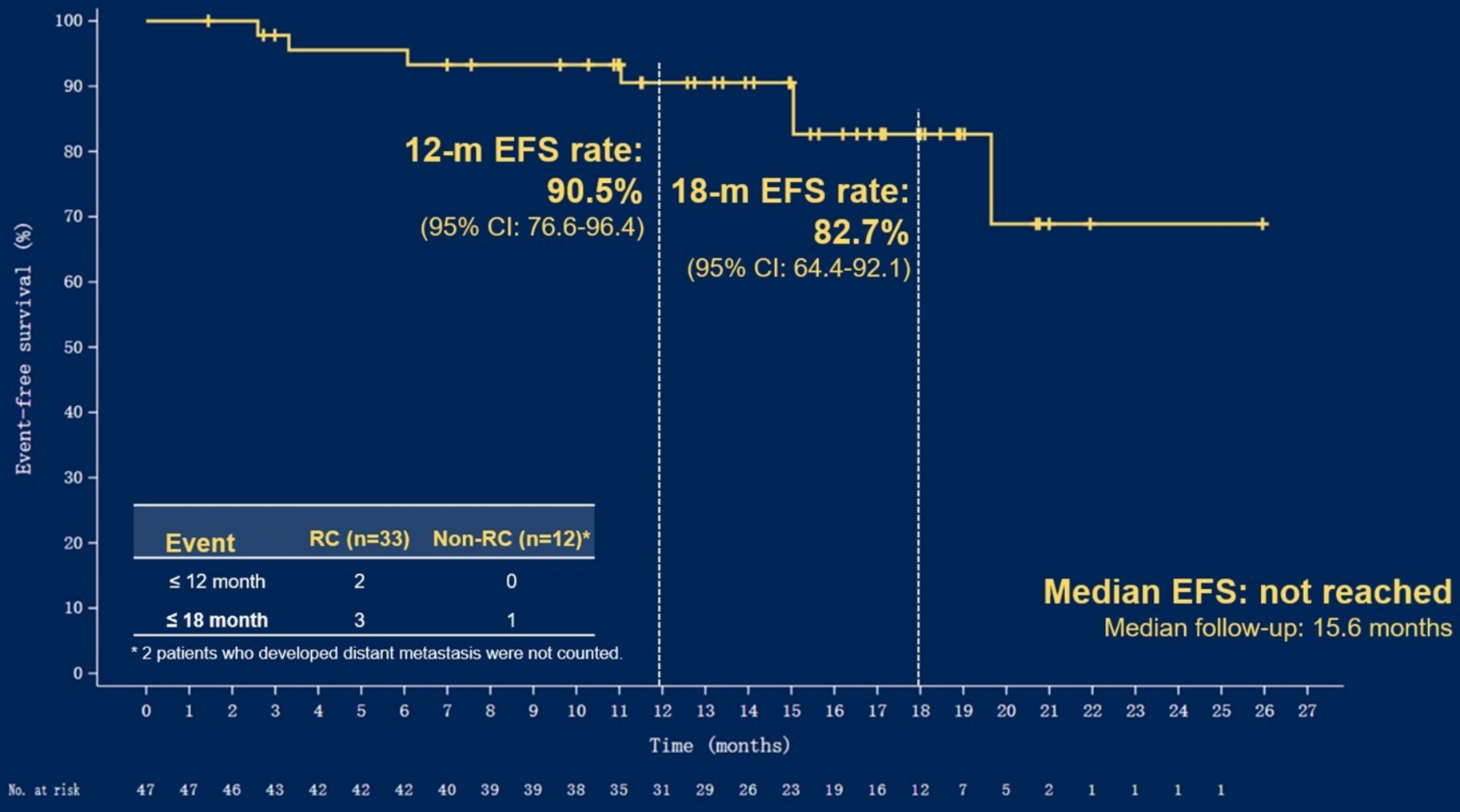
Event-free survival in ITT patients



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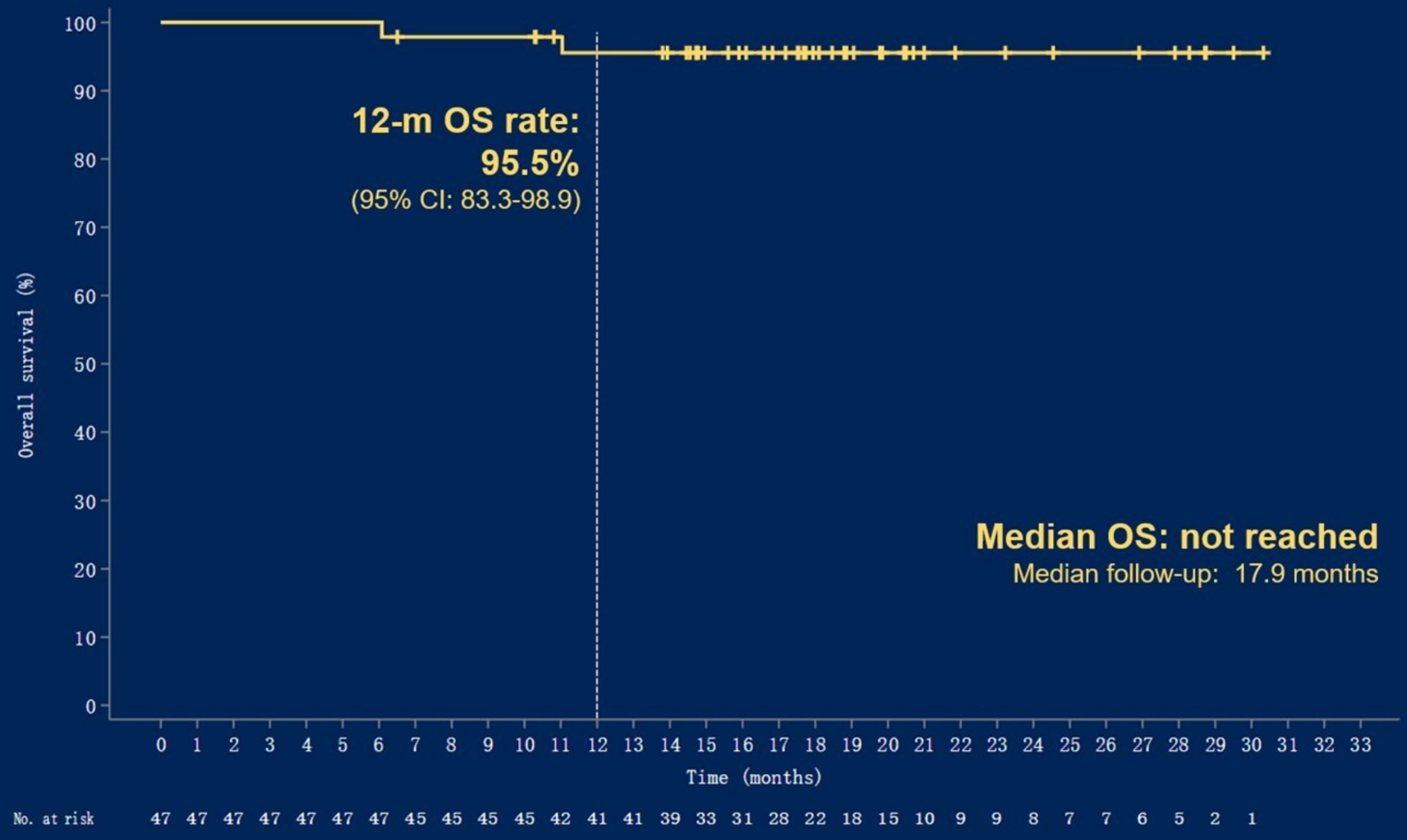
Overall survival in ITT patients



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Postoperative complications

Characteristic	Patients Received RC(N=33)
Postoperative complications (Clavien Dindo), n (%)	
Ⅰ	8 (24.2)
Ⅱ	5 (15.2)
Ⅲa	1 (3.0)
Ⅲb	1 (3.0)
Type of postoperative complications, n (%)	
Postoperative pain	4 (12.1)
Stoma site infection	5 (15.2)
Clotting disorder	1 (3.0)
Pyrexia	1 (3.0)
Pneumonia	1 (3.0)
Intestinal obstruction	1 (3.0)
Urinary tract infection	1 (3.0)
Hydronephrosis	1 (3.0)
Septic shock	1 (3.0)

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Safety summary in ITT patients

Overall study period (except otherwise specified)	All patients (N=47) n (%)
Treatment-emergent adverse events (TEAEs)	47 (100)
Grade ≥3	13 (27.7)
Grade ≥3 (neoadjuvant phase)	8 (17.0)
Grade ≥3 (adjuvant phase)	4/16* (25.0)
Serious adverse events	11 (23.4)
Leading to dose reduction	1 (2.1)
Leading to discontinuation of study treatment	8 (17.0)
Leading to discontinuation of neoadjuvant treatment	6 (12.8)
Leading to patient not undergoing radical cystectomy	1 (2.1)
Leading to discontinuation of adjuvant treatment	3/16* (18.8)
Treatment-related adverse events#	46 (97.9)
Grade ≥3	10 (21.3)
Serious adverse events	6 (12.8)

Safety information was collected from the first dosing until 28 days after last study treatment. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. *In patients who started adjuvant treatment. #Investigators assessed the causality.

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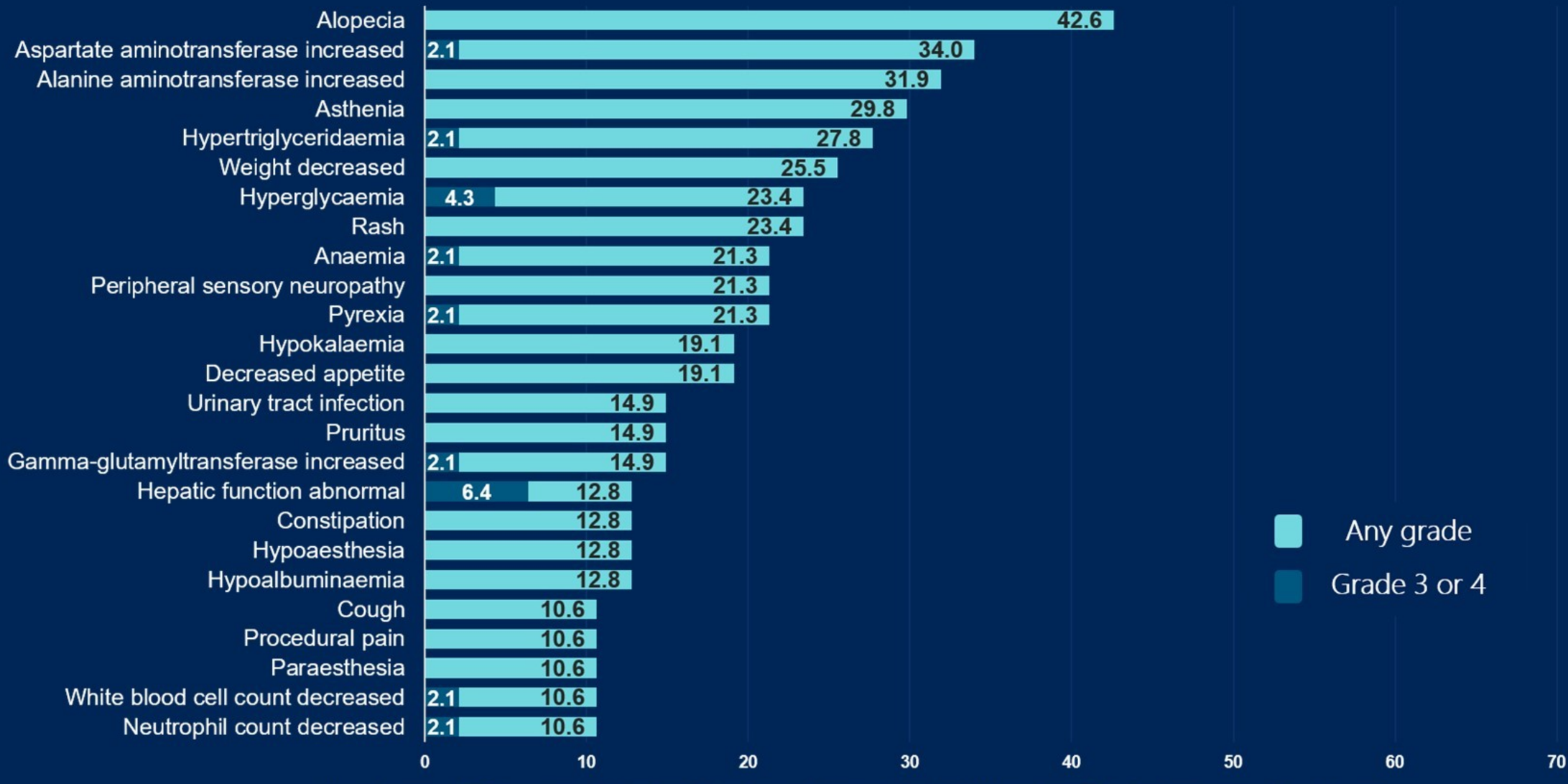
Most common TEAEs



The most common TEAEs occurring in ≥10% patients during the overall study period are listed. Abbreviations: TEAEs=treatment-emergent adverse events.

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Conclusion

- RC48-017 is the first prospective study showing that ADC in combination with a PD-1 inhibitor as perioperative treatment provided prominent outcomes in operable MIBC.
  - pCR rate: 63.6% (95% CI: 45.1-79.6)
  - 12-month EFS rate: 92.5% (95% CI: 72.8- 98.1)
- Neoadjuvant DV plus toripalimab did not delay RC procedures or impact patients' ability to undergo RC. Safety profile was manageable with no new safety signals.
- The results indicated that neoadjuvant DV plus perioperative toripalimab had promising efficacy and acceptable safety in patients with HER2-expressing MIBC, warranting further investigation.

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"The more we know , the more we realize we don't know"

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