Number: LBA7

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Disitamab vedotin (DV) plus toripalimab (T) versus chemotherapy (C) in first-line (1L) locally advanced or metastatic urothelial carcinoma (la/mUC) with HER2-expression

Phase III RC48-C016 study

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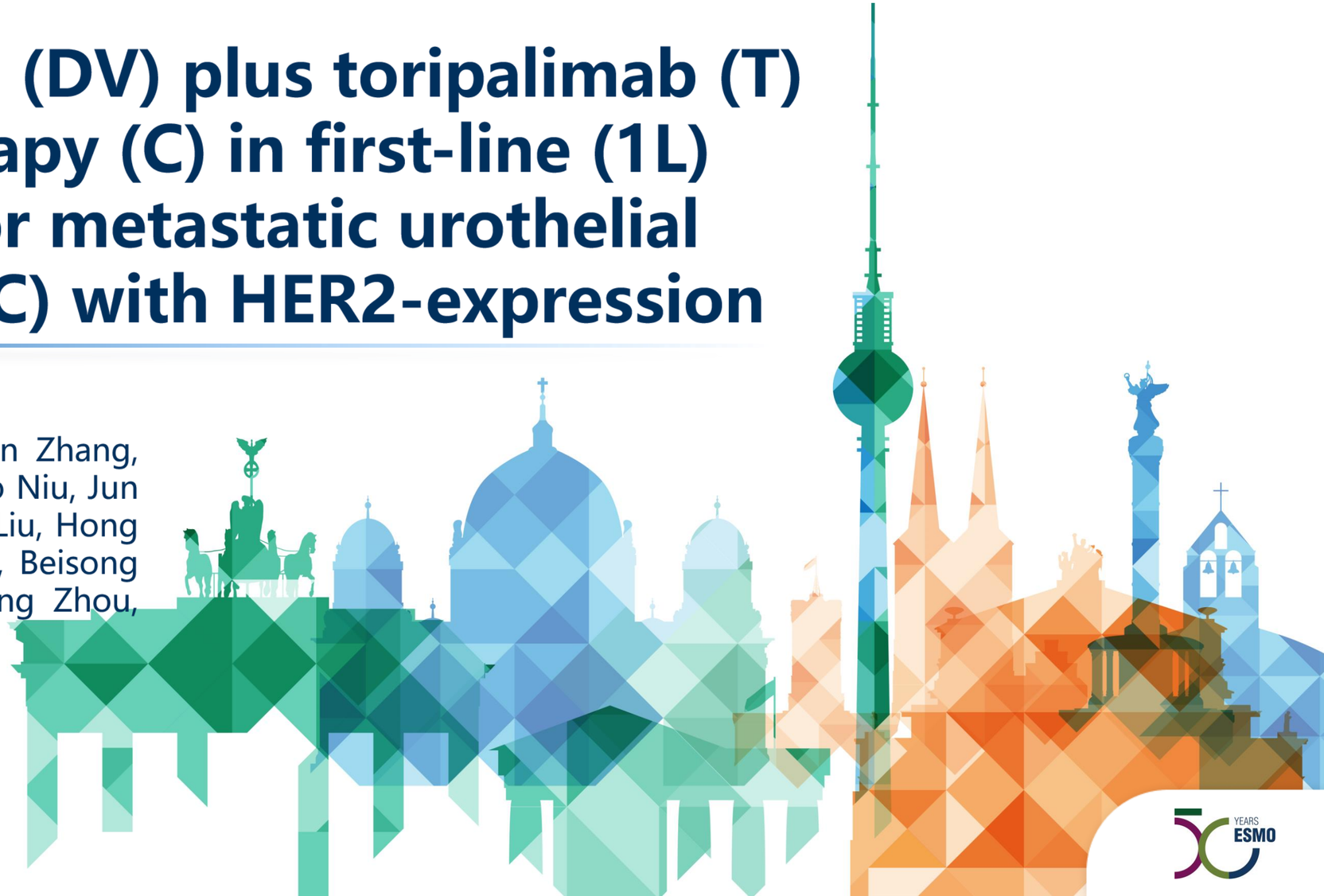

Presenter: Jun Guo, MD
October 19, 2025

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Declaration of Interests

- As a member of the advisory board/ consultant: MSD, Roche, Pfizer, Bayer, Novartis, Simcere, RemeGen, Shanghai Junshi Bioscience, and Oriengene.

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Background

- HER2-targeted antibody-drug conjugate monotherapy has demonstrated efficacy in the post-chemotherapy setting for HER2-positive UC and is approved in both China (disitamab vedotin) and the USA (T-DXd).[1-2]
- An ORR of 76.3% and median PFS of 9.3 months were observed with DV plus toripalimab (a humanized anti-PD-1 monoclonal antibody) in patients with previously untreated or chemotherapy-refractory HER2-expressing (IHC 1+, 2+, or 3+) la/mUC based on the previous phase Ib/II RC48-C014 study.[3]
- HER2 expression is highly prevalent in UC, with HER2 IHC ≥1+ accounting for up to 70% of UC.[4-7]
- The RC48-C016, an open-label, multicenter, randomized phase 3 trial, was conducted to evaluate DV+T vs chemotherapy in the 1L treatment of patients with HER2-expressing la/mUC in China. We report the prespecified final PFS analysis and interim OS analysis.

Abbreviations: ORR: objective response rate; PFS: progression-free survival; IHC: immunohistochemistry; la/mUC, locally advanced or metastatic urothelial carcinoma.
Reference:. 1. Sheng X, et al. J Clin Oncol 2024;42(12):1391-402. 2. Meric-Bernstam F, et al. J Clin Oncol 2024;42(1):47-58. 3. Zhou L, et al. Ann Oncol 2025; 36(3):331-339. 4. Koshkin VS, et al. JCO Precis Oncol 2025;9:e2400879. 5. Zhou L, et al. Oncologist 2023;28(8):e617-24. 6. Uzunparmak B, et al. Ann Oncol 2023;34(11):1035-46. 7. Zhu X, et al. Oncologist 2024;29(8):e1094-7

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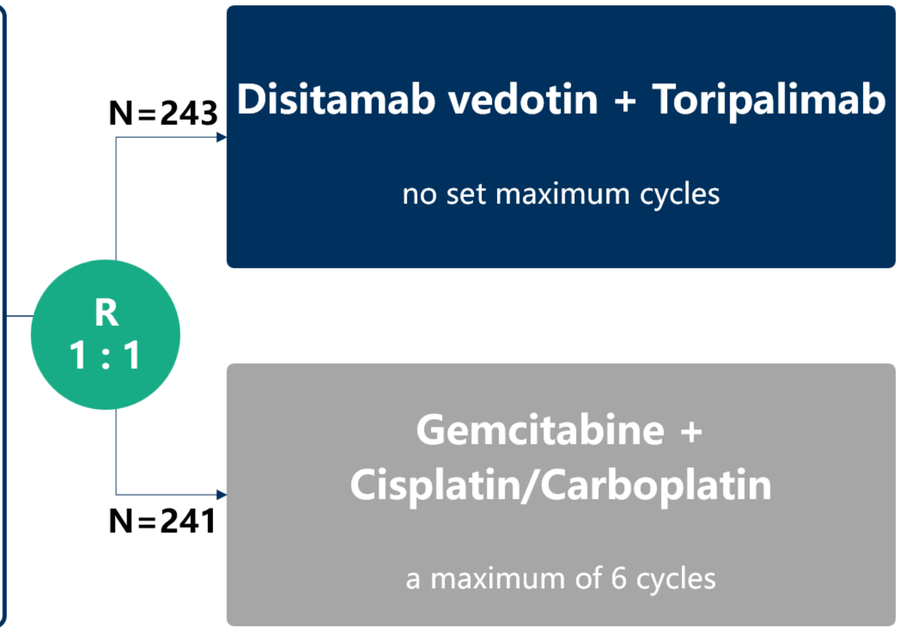
RC48-C016 Study Design (NCT05302284)

Key Inclusion criteria

- No prior systemic treatment for unresectable locally advanced or metastatic UC
- Central lab-confirmed HER2 IHC 1+, 2+, or 3+
- Measurable disease per RECIST v1.1
- Eligible for ciscplatin or carboplatin
- ECOG PS 0 or 1



Dual primary endpoints:

- PFS assessed by BIRC
- OS

Secondary endpoints:

- PFS assessed by investigators
- ORR (per RECIST v1.1), DCR, and DoR assessed by BIRC and investigators
- Safety
- QoL, PK, and immunogenics

Stratification factors

- Cisplatin-eligibility (eligible vs ineligible)
- HER2 expression status (1+ vs 2+/3+)
- Visceral metastases (present vs absent)

- Treatment continued until disease progression/death, intolerable toxicity, or consent withdrawal.
- In the Chemo group, assignment of cisplatin or carboplatin was protocol-defined. Chemo was administered for a maximum of 6 cycles.
- Statistical plan for analysis: the first analysis was planned to be performed after approximately 278 PFS (final) and 183 OS events (interim).

DV (2.0 mg/kg) and toripalimab (3.0 mg/kg) were administered intravenously (IV) every 2 weeks. Gemcitabine (1000mg/m^2 d1, d8) and cisplatin (70mg/m^2, d1)/Carboplatin (AUC=4.5, d1) were administered IV every 3 weeks. DV dose cited here is based on calculations using BSA-based extinction coefficient (EC) implemented in China. Outside of China, DV dose calculation is based on DV EC which is equivalent to 1.07 (BSA-based EC) ÷ 1.41 (DV-based EC) X BSA-based EC dose. Equivalent to dose cited outside of China of 1.5 mg/kg derived by DV-based EC. Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; R: randomized; BIRC: Blinded Idependent Review Committee; RECIST v1.1:Response Evaluation Criteria in Solid Tumors version 1.1; OS: overall survival; DCR: disease control rate; DoR: duration of response; QoL: Quality of life.

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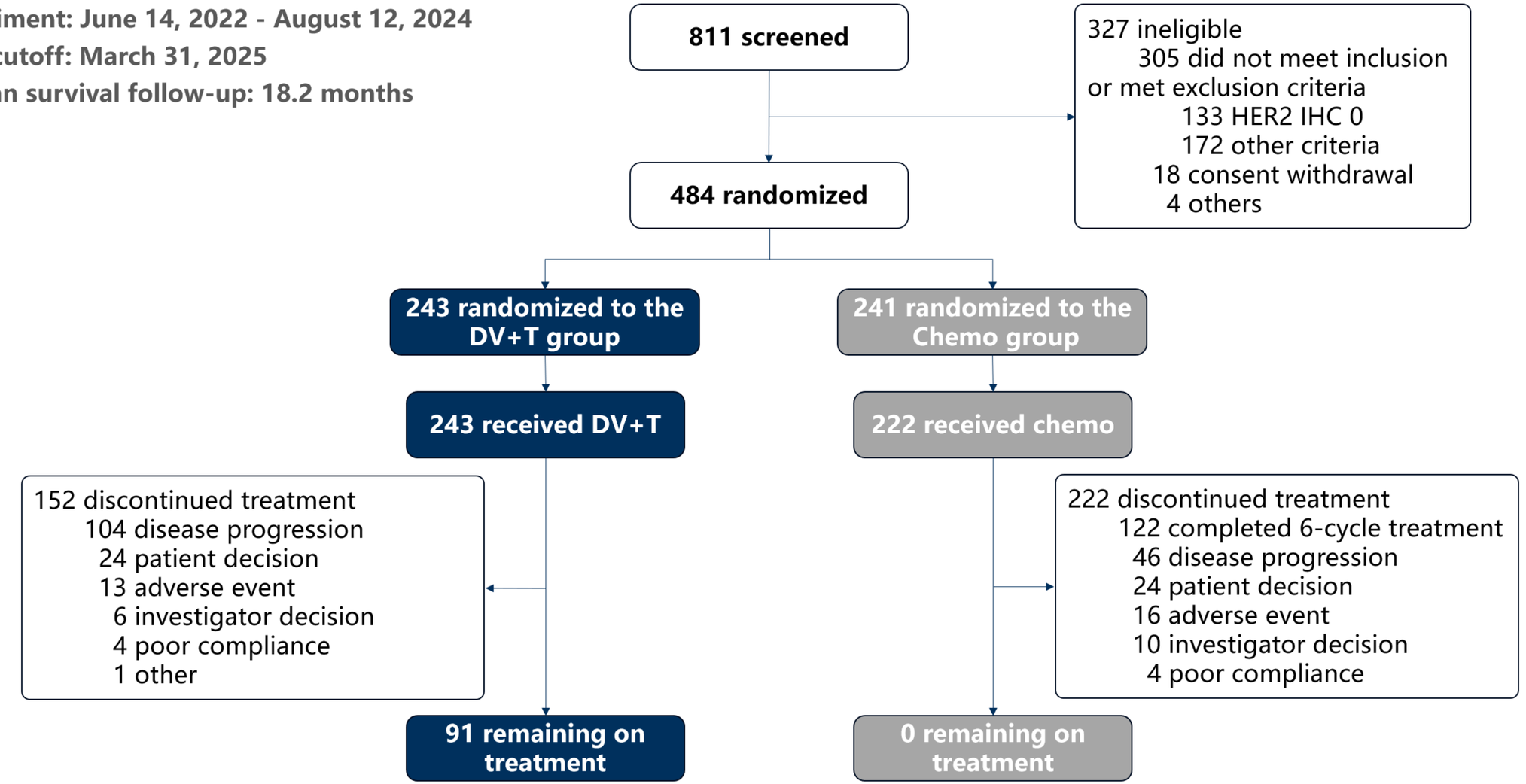
Patients Flow

- **Recruiment: June 14, 2022 - August 12, 2024**
- **Data cutoff: March 31, 2025**
- **Median survival follow-up: 18.2 months**



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Baseline Characteristics

Balanced between the DV+T and Chemo groups

		DV + T (N = 243)	Chemo (N = 241)
Median (yrs), median (range)		66.0 (39-84)	67.0 (33-85)
Age ≥65 years, n (%)		137 (56.4)	147 (61.0)
Sex, n (%)	Male	176 (72.4)	168 (69.7)
	Female	67 (27.6)	73 (30.3)
ECOG performance status score, n (%)	0	61 (25.1)	65 (27.0)
	1	**182 (74.9)**	**176 (73.0)**
Clinical stage, n (%)	III	10 (4.1)	8 (3.3)
	IV	**233 (95.9)**	**233 (96.7)**
Primary site of origin of urothelial cancer, n (%)	**Upper tract**	**111 (45.7)**	**122 (50.6)**
	Lower tract	130 (53.5)	119 (49.4)
	Other	2 (0.8)	0

		DV + T (N = 243)	Chemo (N = 241)
Visceral metastases, n (%)	Absent	119 (49.0)	115 (47.7)
	Present	**124 (51.0)**	**126 (52.3)**
HER2 expression, n (%)	IHC 1+	55 (22.6)	53 (22.0)
	IHC 2+ or 3+	**188 (77.4)**	**188 (78.0)**
	IHC 2+	127 (52.3)	142 (58.9)
	IHC 3+	61 (25.1)	46 (19.1)
Cisplatin eligibility status, n (%)	Eligible	127 (52.3)	128 (53.1)
	Ineligible	**116 (47.7)**	**113 (46.9)**
PD-L1 expression, n (%)*	CPS <1	68/125 (54.4)	24/57 (42.1)
	CPS ≥1	57/125(45.6)	33/57 (57.9)

Percentages may not total 100% because of rounding. *PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Inc; CA 93013 United States). CPS was defined as the total number of PD-L1-staining cells divided by the total number of viable tumor cells, multiplied by 100. PD-L1 test was included since protocol version 4.0; a total of 182 patients provided samples for the PD-L1 expression test. Abbreviations: ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; PD-L1, programmed death ligand 1; CPS, combined positive score.

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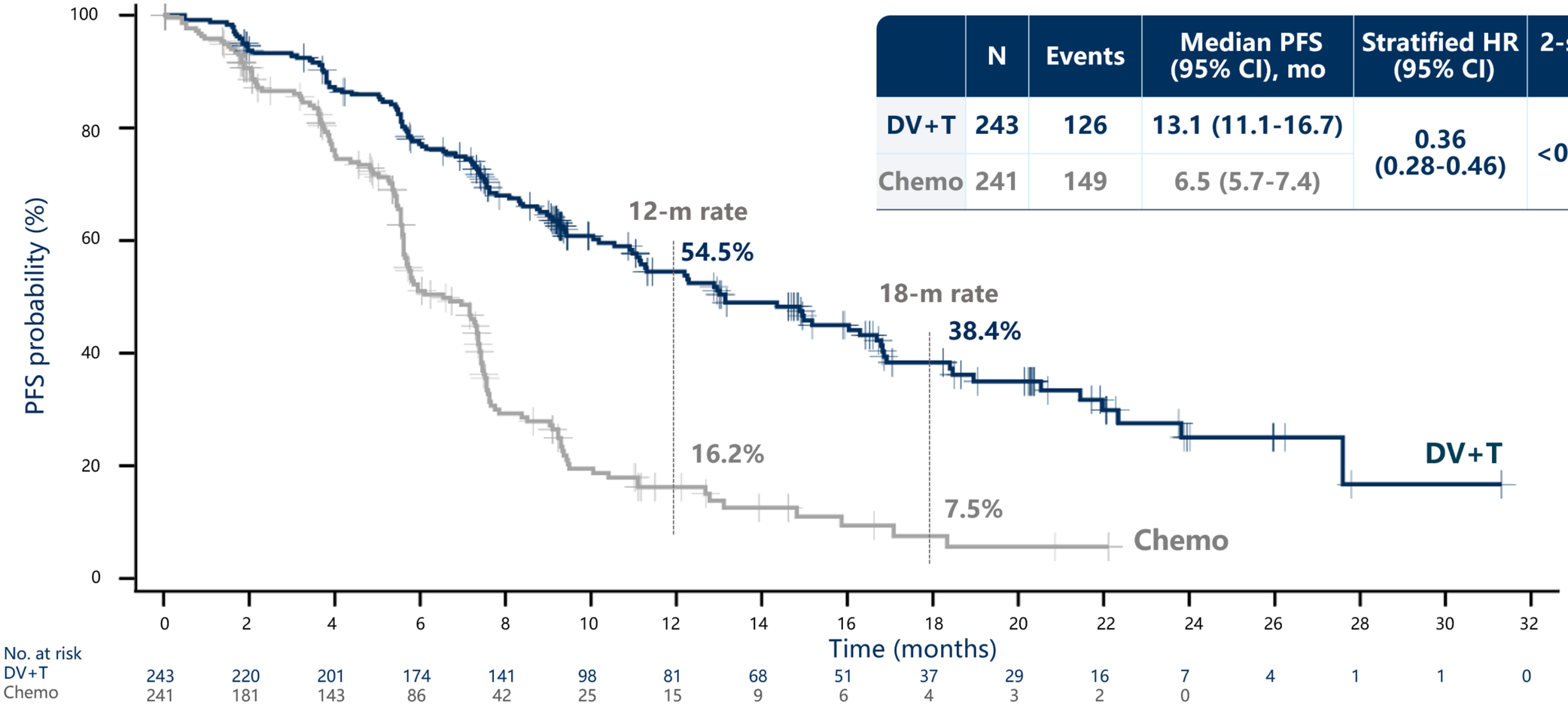
Data cutoff date: March 31, 2025

Progression-free Survival according to BIRC

Clinically meaningful reduction in the risk of progression or death by 64% with DV+T

	N	Events	Median PFS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	126	13.1 (11.1-16.7)	0.36 (0.28-0.46)	<0.0001
Chemo	241	149	6.5 (5.7-7.4)		



- The investigator assessment (median: 12.3 vs 6.2 months; stratified HR: 0.36 [95% CI: 0.28-0.46]) was consistent with BIRC.

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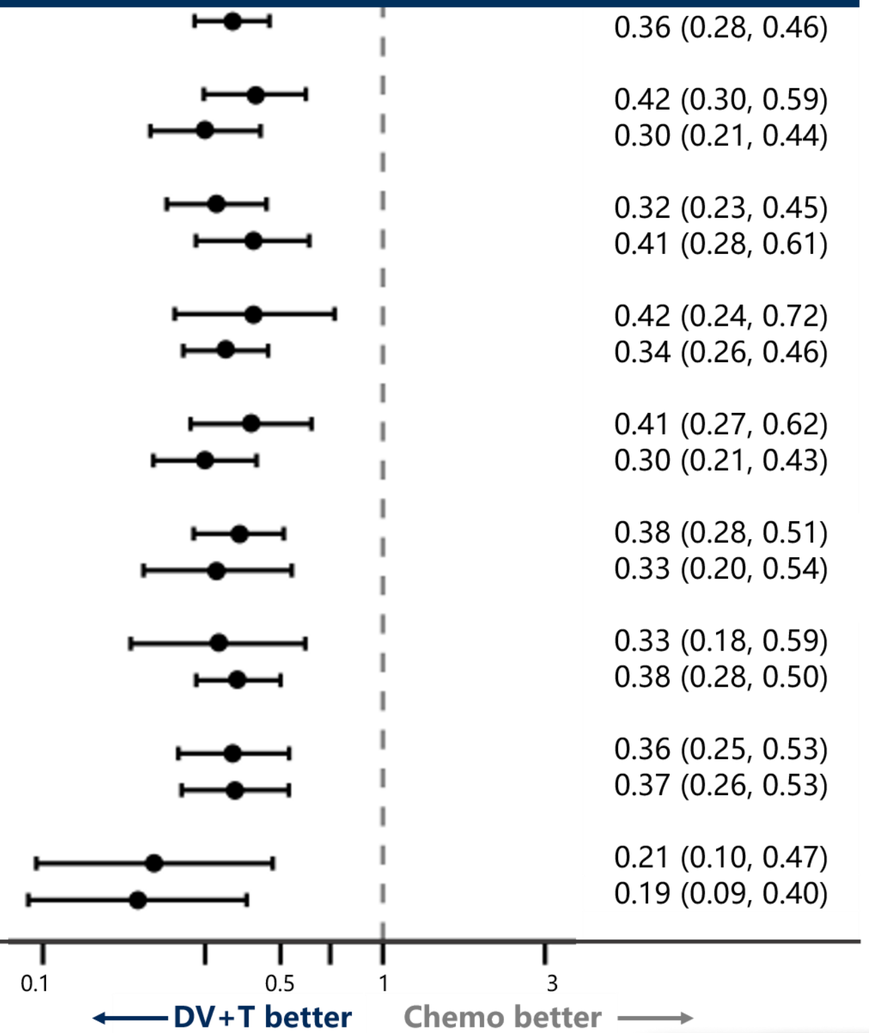
Data cutoff date: March 31, 2025

PFS Subgroup Analysis according to BIRC

PFS benefit was consistent across all prespecified subgroups

Subgroup		Events/N DV+T vs Chemo	Median PFS (mo) DV+T vs Chemo	HR (95% CI)
Overall		126/243 vs. 149/241	13.1 vs. 6.5	0.36 (0.28, 0.46)
Eligibility for cisplatin				
	Yes	70/127 vs. 76/128	12.3 vs. 7.4	0.42 (0.30, 0.59)
	No	56/116 vs. 73/113	16.3 vs. 5.6	0.30 (0.21, 0.44)
Visceral metastasis				
	Yes	72/124 vs. 87/126	11.2 vs. 5.6	0.32 (0.23, 0.45)
	No	54/119 vs. 62/115	16.0 vs. 7.5	0.41 (0.28, 0.61)
HER2 status				
	IHC 1+	33/55 vs. 31/53	12.3 vs. 6.5	0.42 (0.24, 0.72)
	IHC 2+/3+	93/188 vs. 118/188	13.1 vs. 6.7	0.34 (0.26, 0.46)
Age				
	<65	55/106 vs. 57/94	12.9 vs. 7.4	0.41 (0.27, 0.62)
	≥65	71/137 vs. 92/147	14.4 vs. 5.9	0.30 (0.21, 0.43)
Sex				
	Male	92/176 vs. 102/168	13.0 vs. 7.2	0.38 (0.28, 0.51)
	Female	34/67 vs. 47/73	15.0 vs. 5.7	0.33 (0.20, 0.54)
ECOG PS				
	0	28/61 vs. 35/65	14.9 vs. 7.3	0.33 (0.18, 0.59)
	1	98/182 vs. 114/176	13.0 vs. 5.9	0.38 (0.28, 0.50)
Site of primary lesion				
	Upper urinary tract	60/111 vs. 74/122	13.1 vs. 5.9	0.36 (0.25, 0.53)
	Lower urinary tract	65/130 vs. 75/119	13.0 vs. 7.2	0.37 (0.26, 0.53)
PD-L1 status (CPS score)				
	<1	32/68 vs. 15/24	15.2 vs. 7.5	0.21 (0.10, 0.47)
	≥1	24/57 vs. 23/33	16.9 vs. 6.1	0.19 (0.09, 0.40)



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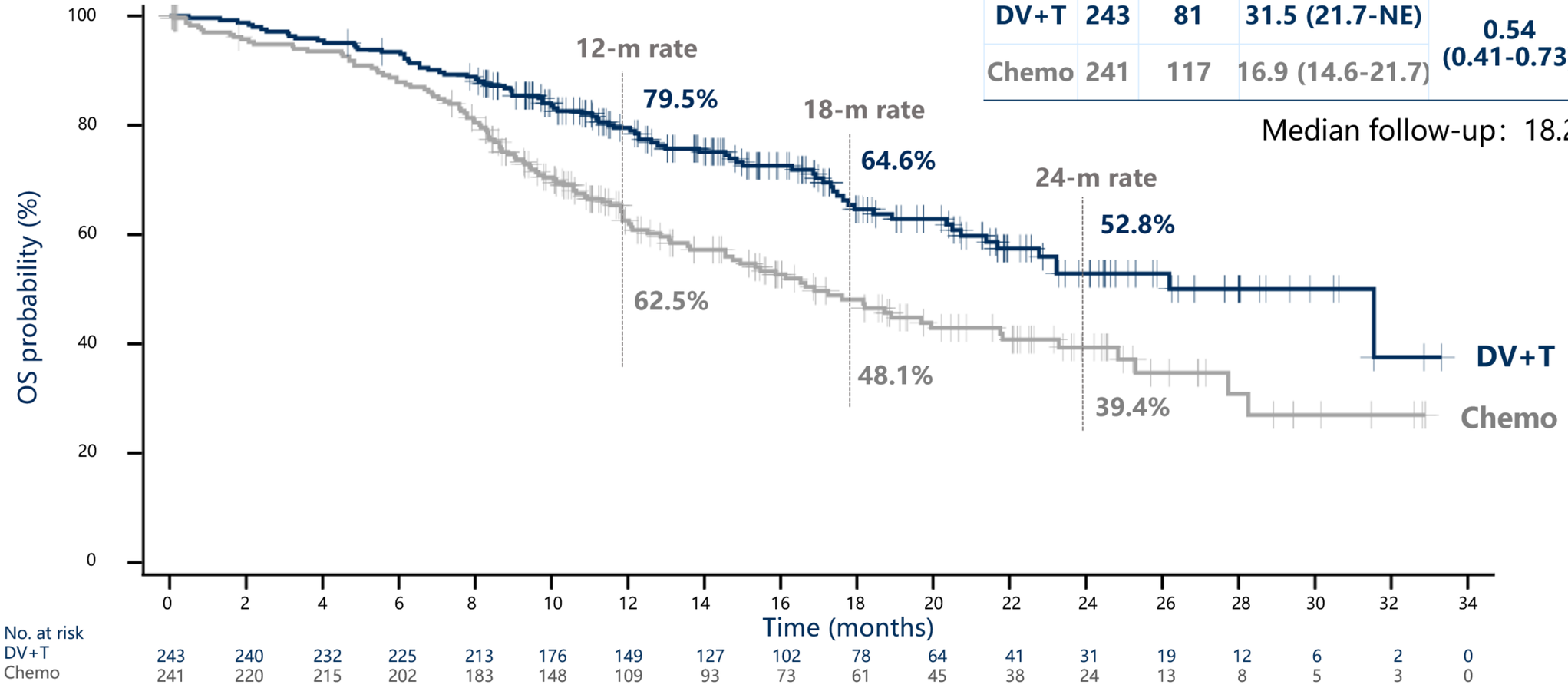
Data cutoff date: March 31, 2025

Overall Survival

Clinically meaningful reduction in the risk of death by 46% with DV+T

	N	Events	Median OS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	81	31.5 (21.7-NE)	0.54 (0.41-0.73)	<0.0001
Chemo	241	117	16.9 (14.6-21.7)		

Median follow-up: 18.2 months



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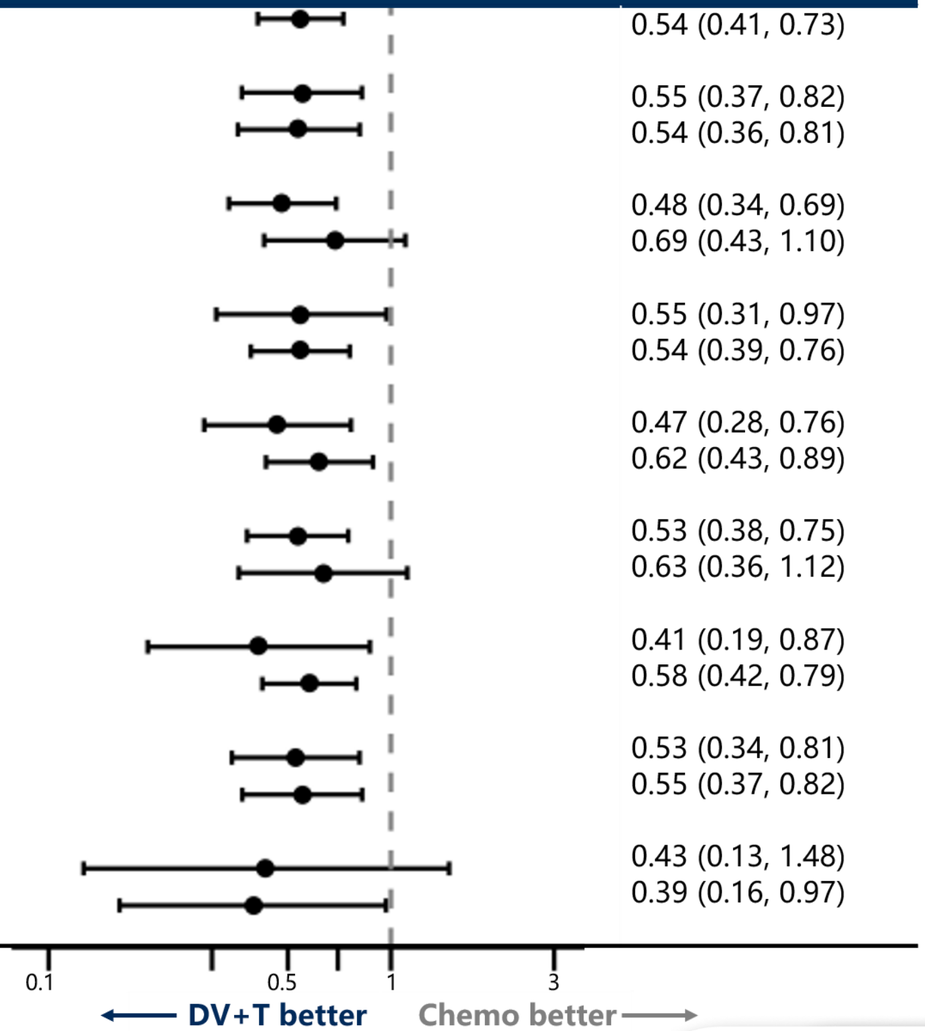
Data cutoff date: March 31, 2025

OS Subgroup Analysis

OS benefit was consistent across all prespecified subgroups

Subgroup		Events/N DV+T vs Chemo	Median OS (mo) DV+T vs Chemo	HR (95% CI)	HR (95% CI)
Overall		81/243 vs. 117/241	31.5 vs. 16.9		0.54 (0.41, 0.73)
Eligibility for cisplatin					
	Yes	42/127 vs. 59/128	26.2 vs. 18.9		0.55 (0.37, 0.82)
	No	39/116 vs. 58/113	NE vs. 15.3		0.54 (0.36, 0.81)
Visceral metastasis					
	Yes	51/124 vs. 76/126	22.8 vs. 11.9		0.48 (0.34, 0.69)
	No	30/119 vs. 41/115	NE vs. 21.8		0.69 (0.43, 1.10)
HER2 status					
	IHC 1+	21/55 vs. 31/53	26.2 vs. 16.1		0.55 (0.31, 0.97)
	IHC 2+/3+	60/188 vs. 86/188	31.5 vs. 18.2		0.54 (0.39, 0.76)
Age					
	<65	29/106 vs. 42/94	31.5 vs. 18.2		0.47 (0.28, 0.76)
	≥65	52/137 vs. 75/147	23.2 vs. 16.5		0.62 (0.43, 0.89)
Sex					
	Male	61/176 vs. 83/168	31.5 vs. 16.1		0.53 (0.38, 0.75)
	Female	20/67 vs. 34/73	23.2 vs. 18.2		0.63 (0.36, 1.12)
ECOG PS					
	0	12/61 vs. 23/65	NE vs. 27.7		0.41 (0.19, 0.87)
	1	69/182 vs. 94/176	23.2 vs. 15.3		0.58 (0.42, 0.79)
Site of primary lesion					
	Upper urinary tract	37/111 vs. 58/122	31.5 vs. 16.9		0.53 (0.34, 0.81)
	Lower urinary tract	44/130 vs. 59/119	23.2 vs. 16.5		0.55 (0.37, 0.82)
PD-L1 status (CPS score)					
	<1	14/68 vs. 6/24	NE vs. 28.3		0.43 (0.13, 1.48)
	≥1	9/57 vs. 14/33	NE vs. 16.1		0.39 (0.16, 0.97)



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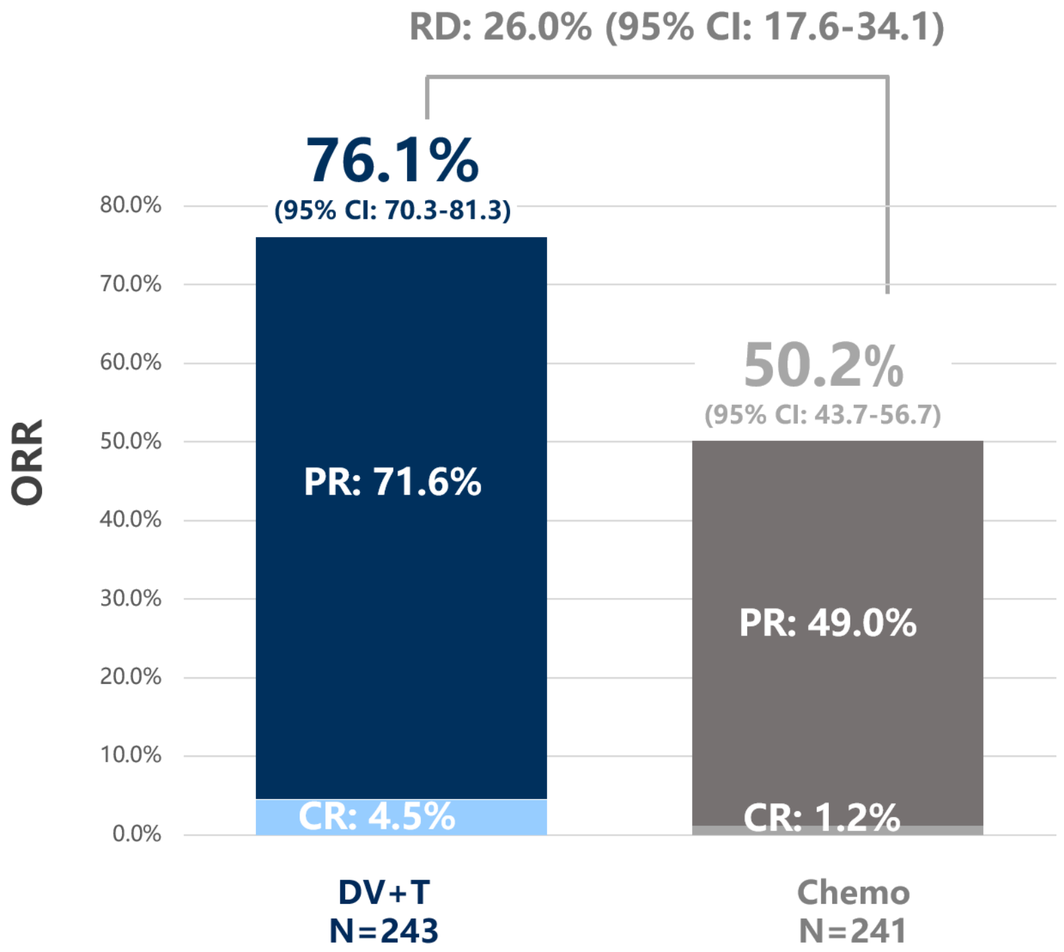
Data cutoff date: March 31, 2025

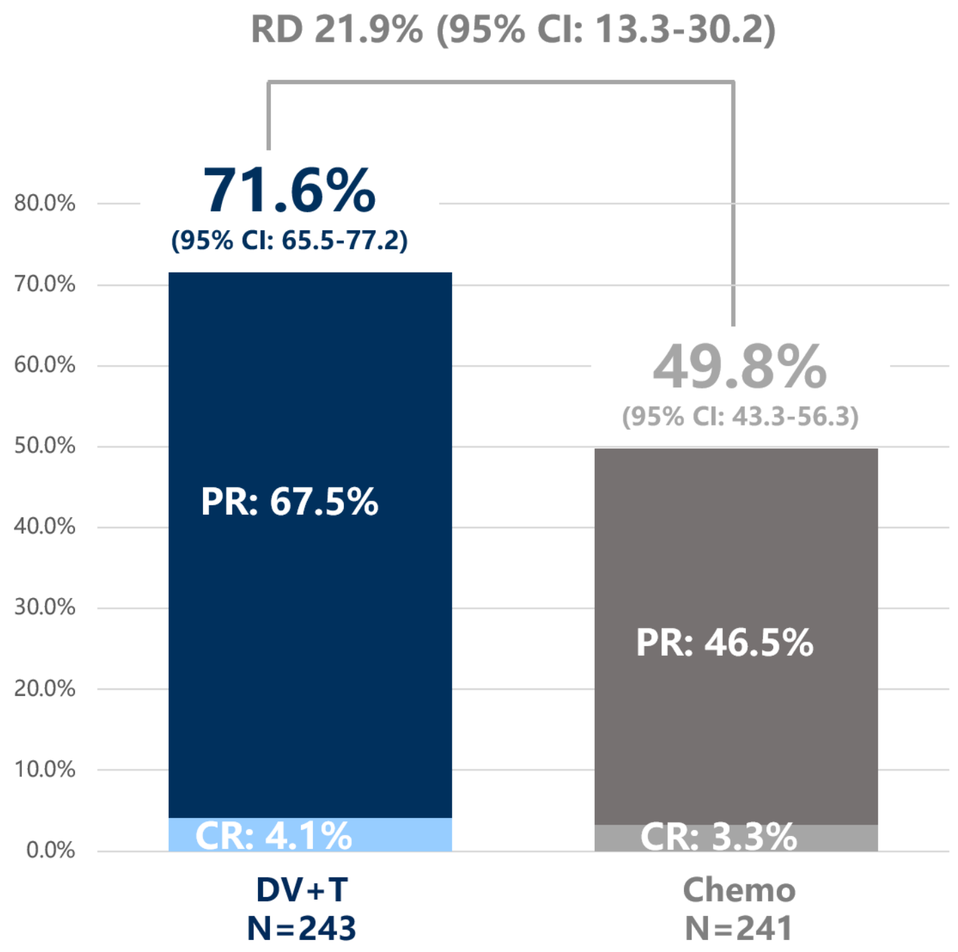
Tumor Response

Significant improvement in tumor response in patients with DV+T by BICR and investigators

Per BIRC



Per Investigators



RD (rate difference) and it's corresponding 95%CI was calculated using a stratified Miettinen-Nurminen method. Abbreviations: CR, complete response; PR, partial response.

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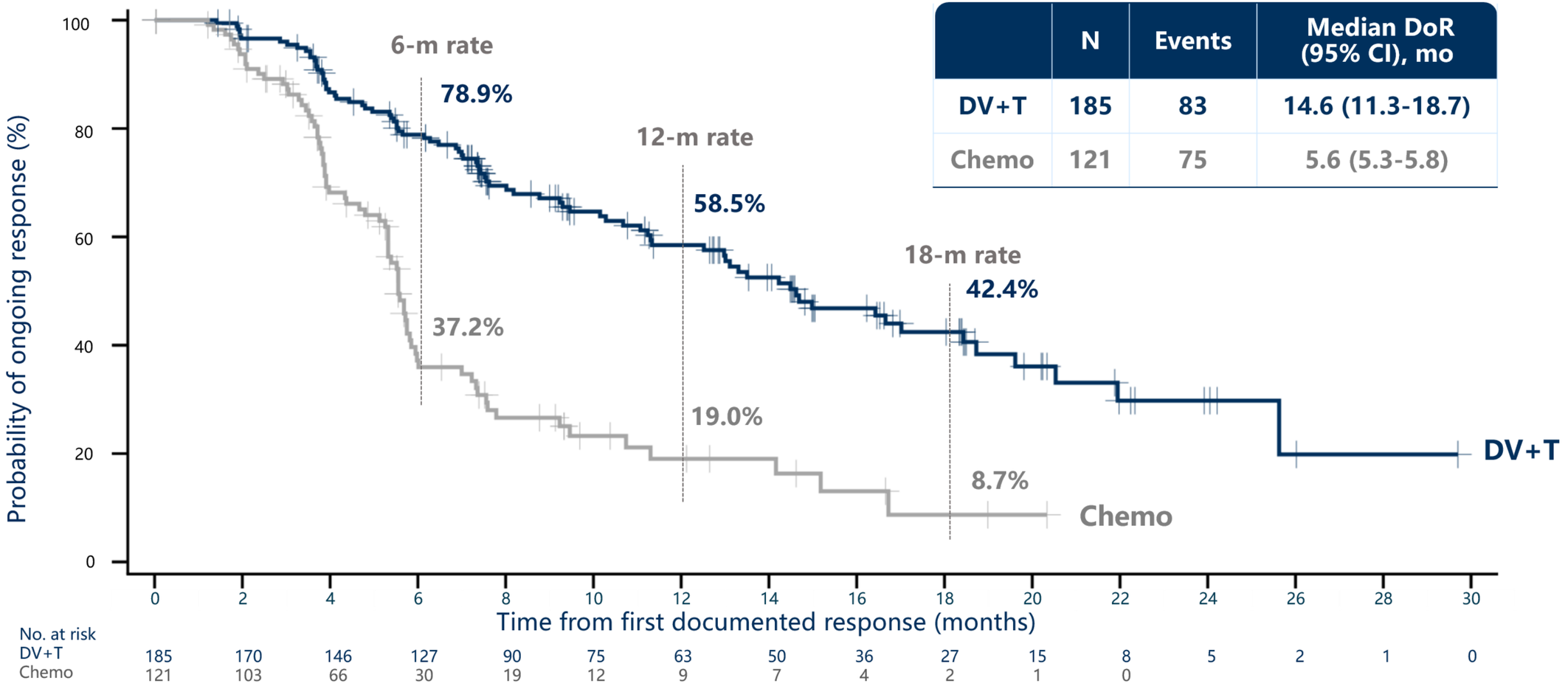
Duration of Response

Significant improvement in DoR in patients with DV+T by BICR and investigators

	N	Events	Median DoR (95% CI), mo
DV+T	185	83	14.6 (11.3-18.7)
Chemo	121	75	5.6 (5.3-5.8)



- The investigator assessment (median: 13.1 vs 5.5 months) was consistent with BIRC.

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Data cutoff date: March 31, 2025

Subsequent Systemic Treatment

64.7% patients in Chemo group had subsequent treatment, and 40.2% chose anti-HER2 therapy

n (%)	DV + T (N = 243)	Chemo (N = 241)
Patients with at least one subsequent systemic anticancer treatment	**66 (27.2)**	**156 (64.7)**
Anti-HER2-containing therapy	**5 (2.1)**	**97 (40.2)**
DV-containing therapy	4 (1.6)	91 (37.8)
PD-1/PD-L1 inhibitor-containing therapy	**26 (10.7)**	**121 (50.2)**
Both anti-HER2-containing therapies and PD-1/PD-L1 inhibitor therapies	**2 (0.8)**	**75 (31.1)**
Both DV and PD-1/PD-L1 inhibitor therapies*	2 (0.8)	72 (29.9)
Chemotherapy	57 (23.5)	19 (7.9)
Others	16 (6.6)	43 (17.8)

*Patients received subsequent DV and PD-1/PD-L1 inhibitor, either in combination or as sequential monotherapy.

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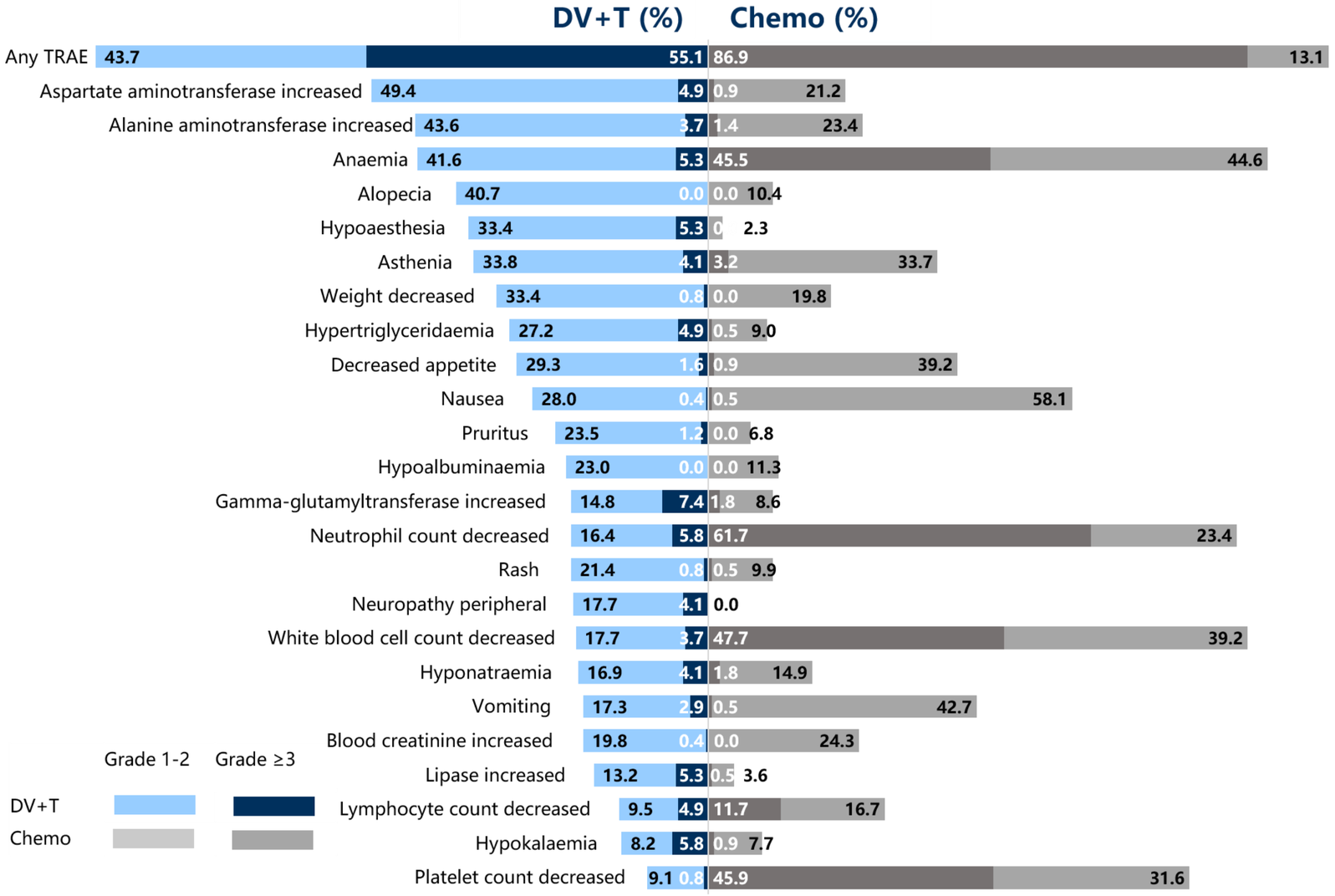
Data cutoff date: March 31, 2025

Safety Summary

Incidence of grade ≥3 TRAEs: 55.1% with DV+T vs 86.9% with chemo



n (%)	DV+T (N = 243)	Chemo (N = 222)*
Treatment-emergent adverse events (TEAEs)	243 (100)	222 (100)
Treatment-related adverse events (TRAEs)	240 (98.8)	222 (100)
Grade ≥3 TRAEs	134 (55.1)	193 (86.9)
Grade 3	107 (44.0)	93 (41.9)
Grade 4	24 (9.9)	97 (43.7)
Grade 5	3 (1.2)	3 (1.4)
Serious TRAEs	69 (28.4)	90 (40.5)
Immune-related adverse events		
Any grade	114 (46.9)	/
Grade ≥3	46 (18.9)	/
TRAE leading to discontinuation of any study treatment	30 (12.3)	23 (10.4)

*19 patients in the chemo group did not receive the assigned treatment after randomization and were excluded from safety analysis.

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Data cutoff date: March 31, 2025

Conclusions

- The Phase III RC48-C016 study demonstrated for the first time superiority of an anti-HER2 antibody drug conjugate plus an anti-PD1 inhibitor in a biomarker-selected patient population with la/mUC.

- DV+T led to a clinically meaningful and statistically significant prolongation of PFS and OS versus chemo in patients with previously untreated HER2-expressing la/mUC.
  - **PFS (per BIRC): median, 13.1 versus 6.5 months; HR, 0.36 (95% CI: 0.28-0.46); P<0.0001.**
  - **OS: median, 31.5 versus 16.9 months; HR, 0.54 (95% CI: 0.41-0.73); P<0.0001.**
  - **PFS and OS benefits are consistent across HER2 expression levels and other prespecified subgroups**

- The safety profile of DV+T was consistent with each agent, and it was more favorable than chemo.
  - **Incidence of grade ≥3 TRAEs: 55.1% with DV+T vs 86.9% with chemo.**

- DV+T offers a valuable new treatment option and represents a potential new standard of care for the 1L treatment of patients with HER2-expressing la/mUC.

Presented by Dr. Jun Guo

Acknowledgement

- We thank all patients who participated in this study and their families, as well as all investigators involved in this study for their contributions.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

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