

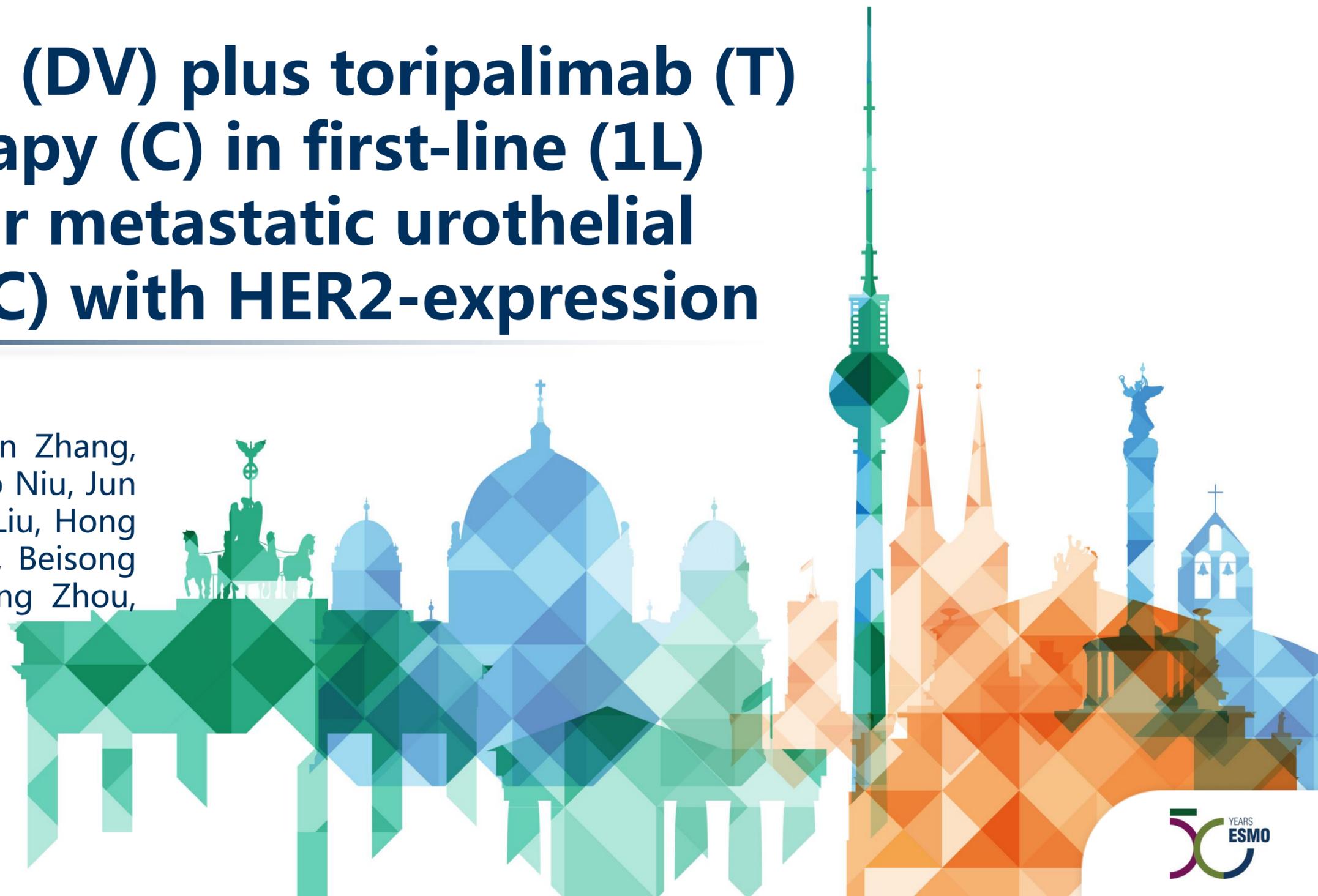


# Disitamab vedotin (DV) plus toripalimab (T) versus chemotherapy (C) in first-line (1L) locally advanced or metastatic urothelial carcinoma (la/mUC) with HER2-expression

## Phase III RC48-C016 study

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Presenter: Jun Guo, MD  
October 19, 2025



# 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).<sup>1-2</sup>
- ◆ 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.<sup>3</sup>
- ◆ HER2 expression is highly prevalent in UC, with HER2 IHC  $\geq 1+$  accounting for up to 70% of UC.<sup>4-7</sup>
- ◆ 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.

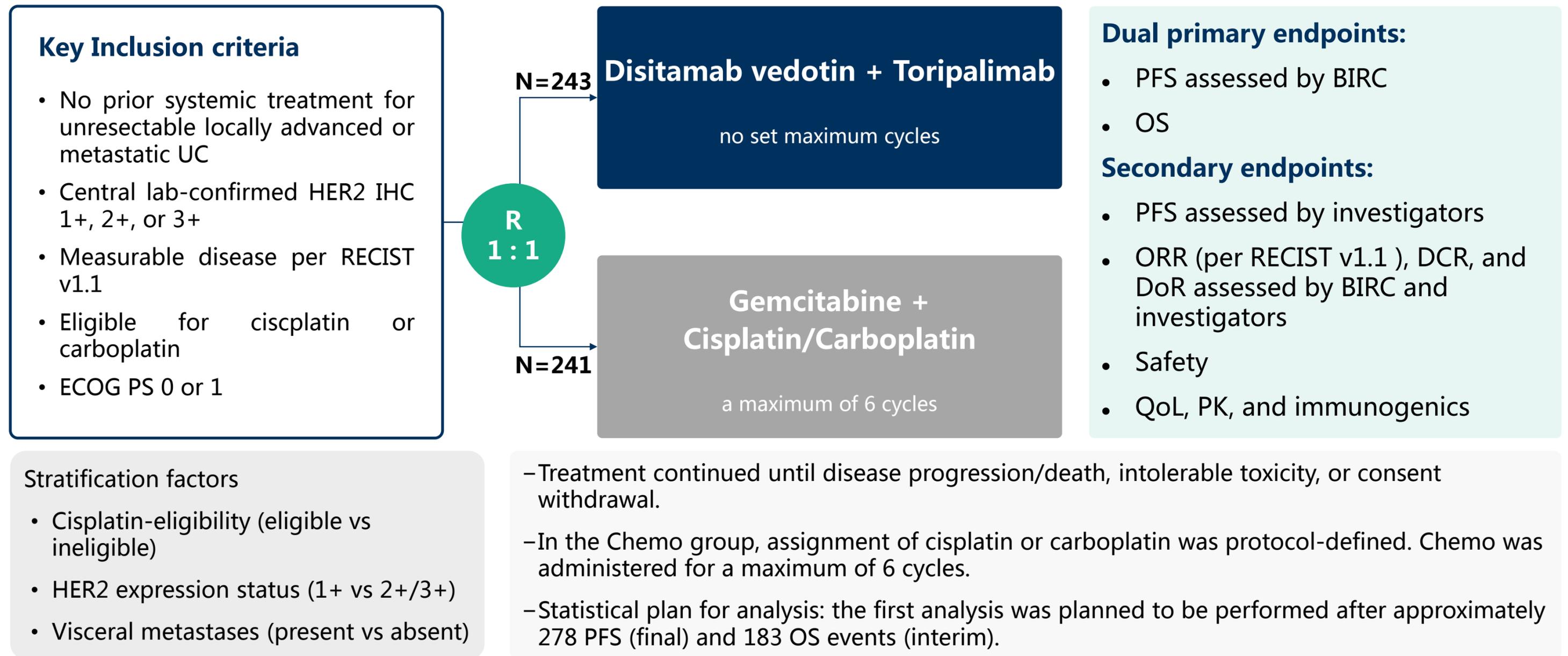
Abbreviations: ORR: objective response rate; PFS: progression-free survival; IHC: immunohistochemistry; la/mUC, locally advanced or metastatic urothelial carcinoma.

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)



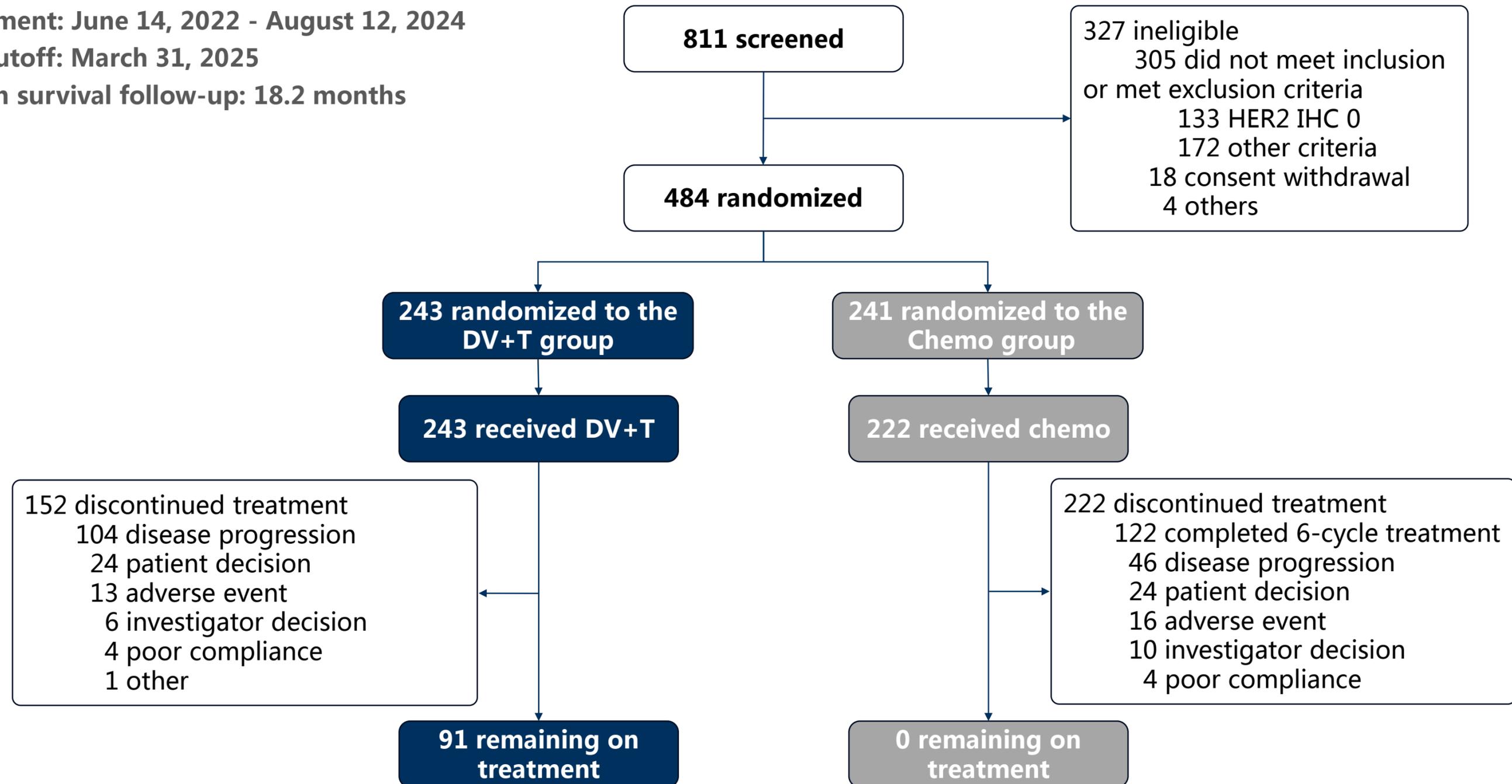
DV (2.0 mg/kg) and toripalimab (3.0 mg/kg) were administered intravenously (IV) every 2 weeks. Gemcitabine (1000mg/m<sup>2</sup> d1, d8) and cisplatin (70mg/m<sup>2</sup>, d1)/Carboplatin (AUC=4.5, d1) were administered IV every 3 weeks. DV dose cited here is based on calculations using BSA-based extinction 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 Independent 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

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

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

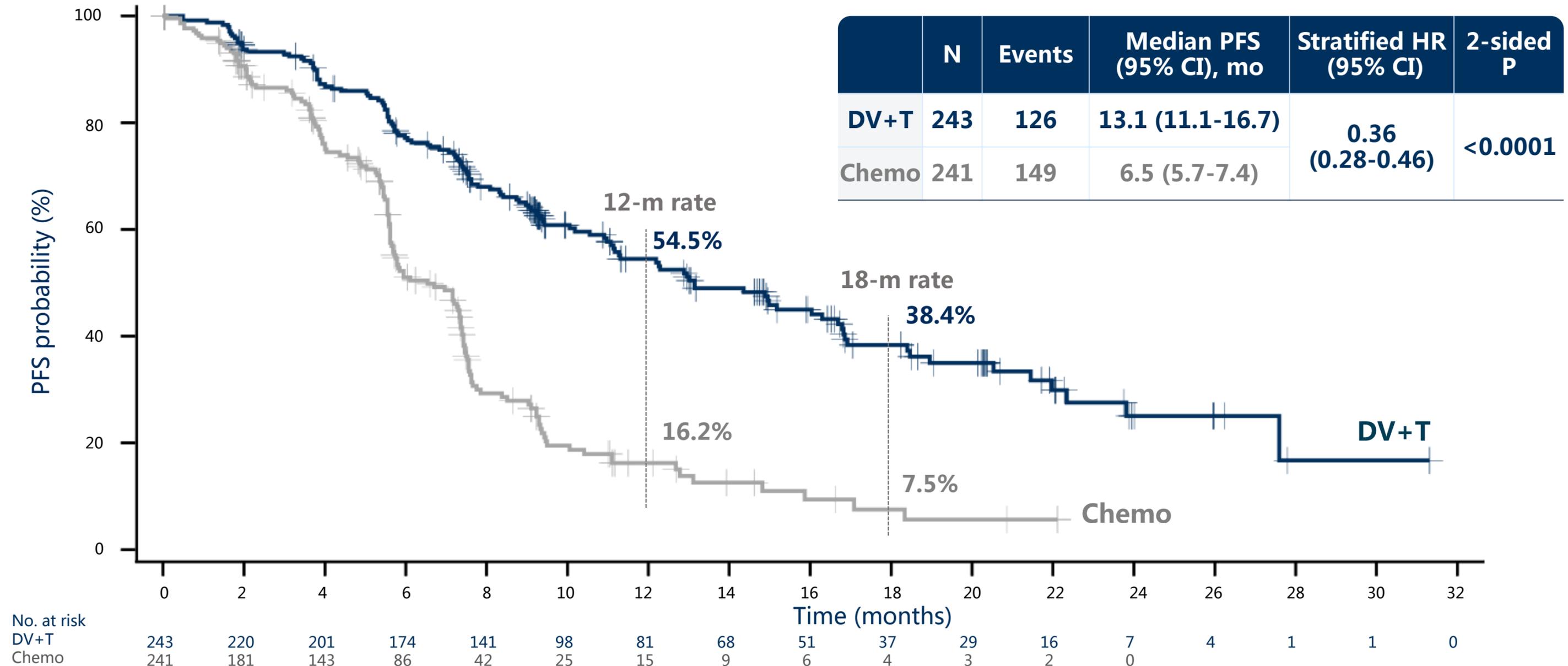
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# Progression-free Survival according to BIRC

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



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

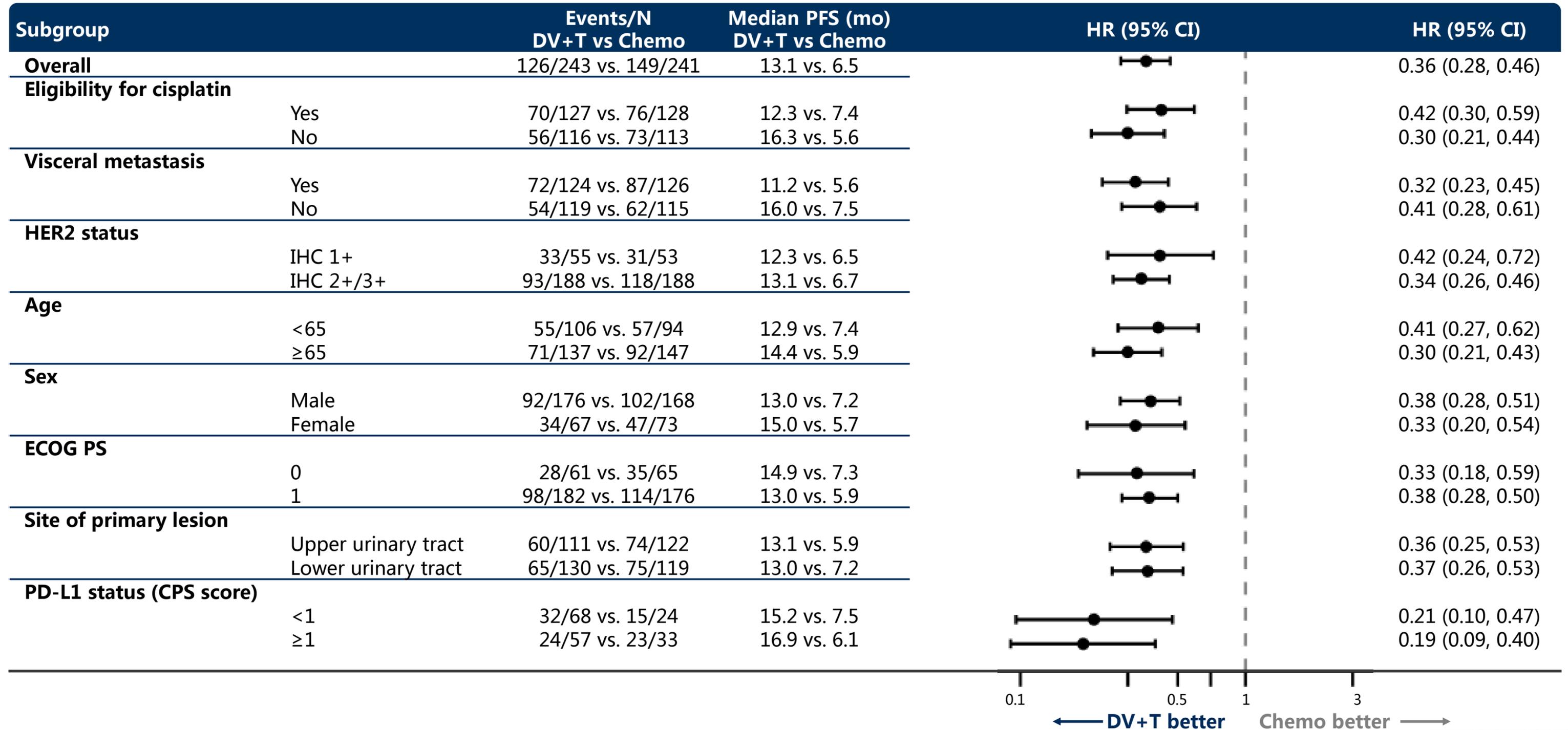
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# PFS Subgroup Analysis according to BIRC

PFS benefit was consistent across all prespecified subgroups



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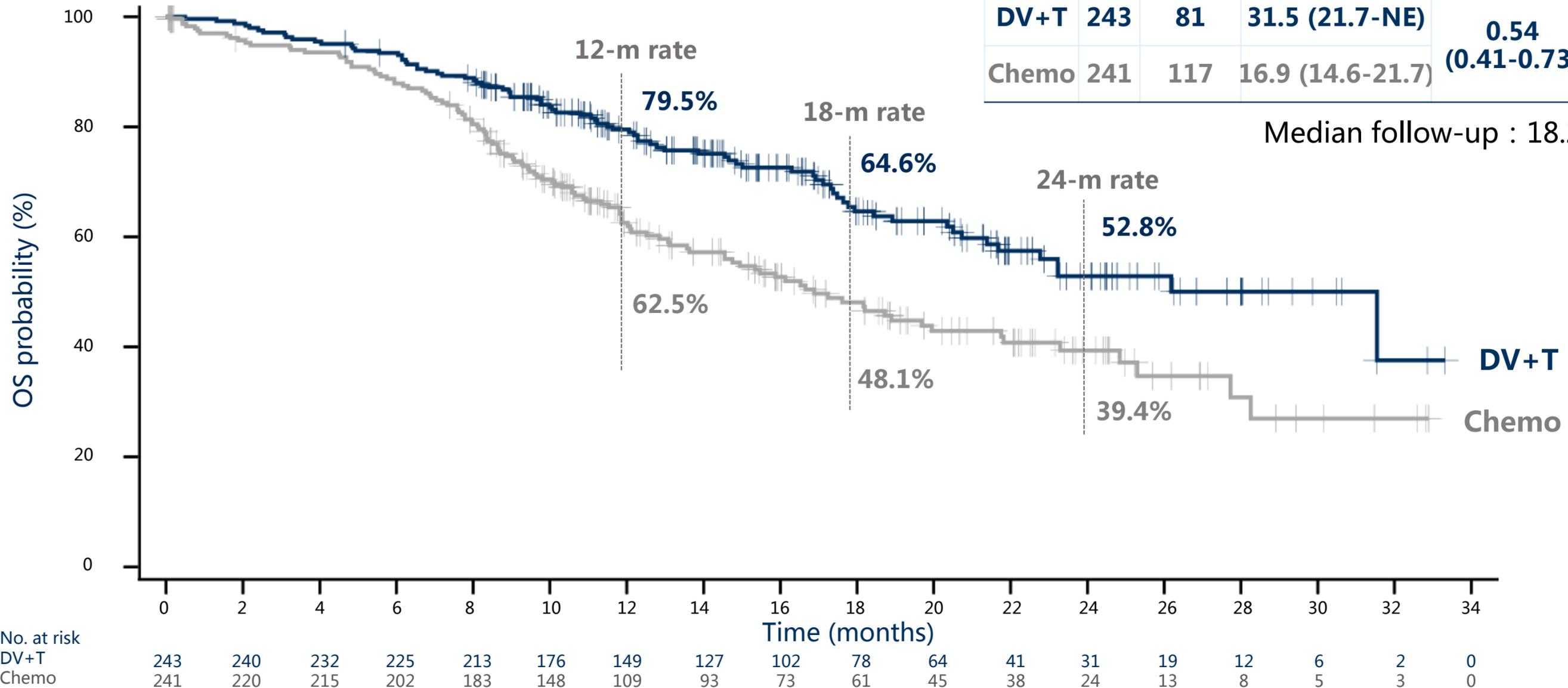
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# Overall Survival

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



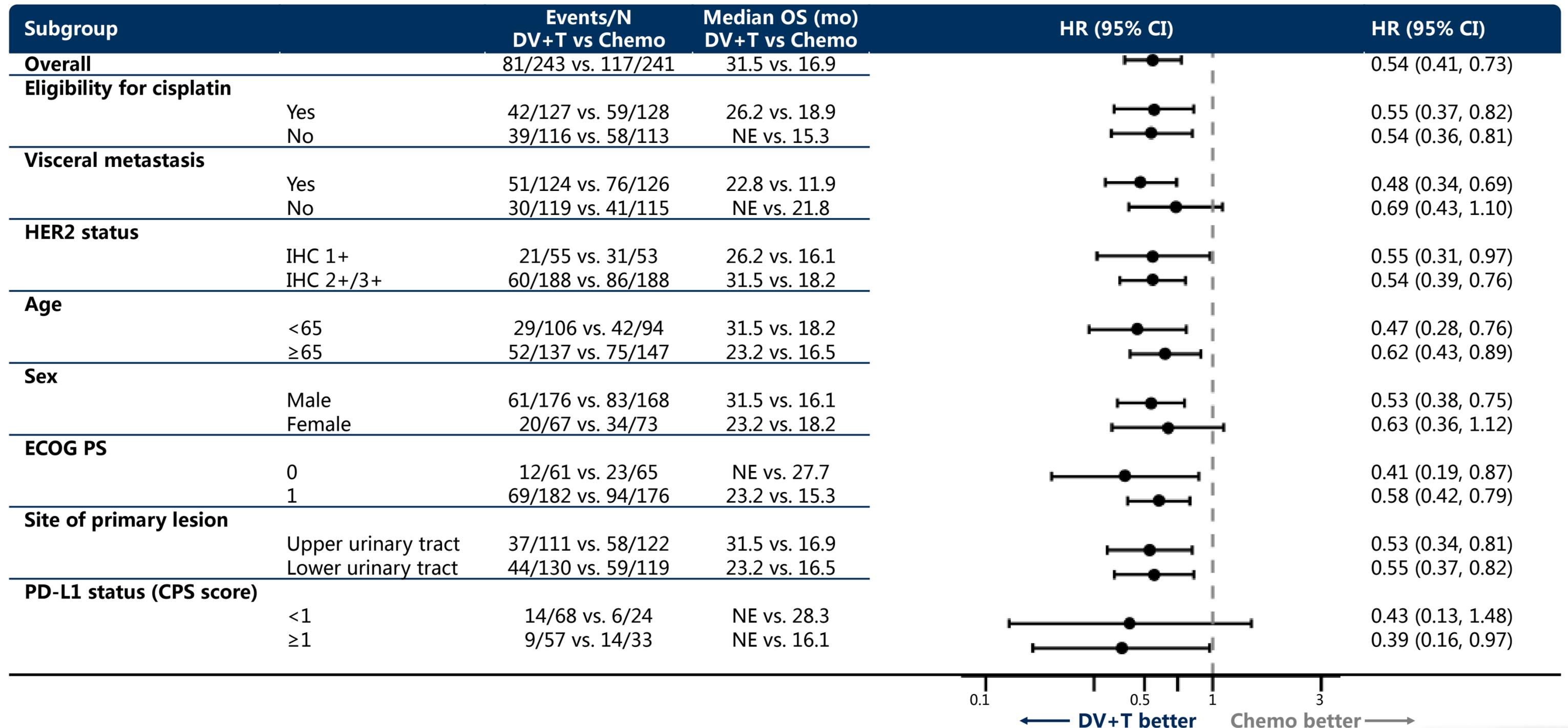
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# OS Subgroup Analysis

OS benefit was consistent across all prespecified subgroups



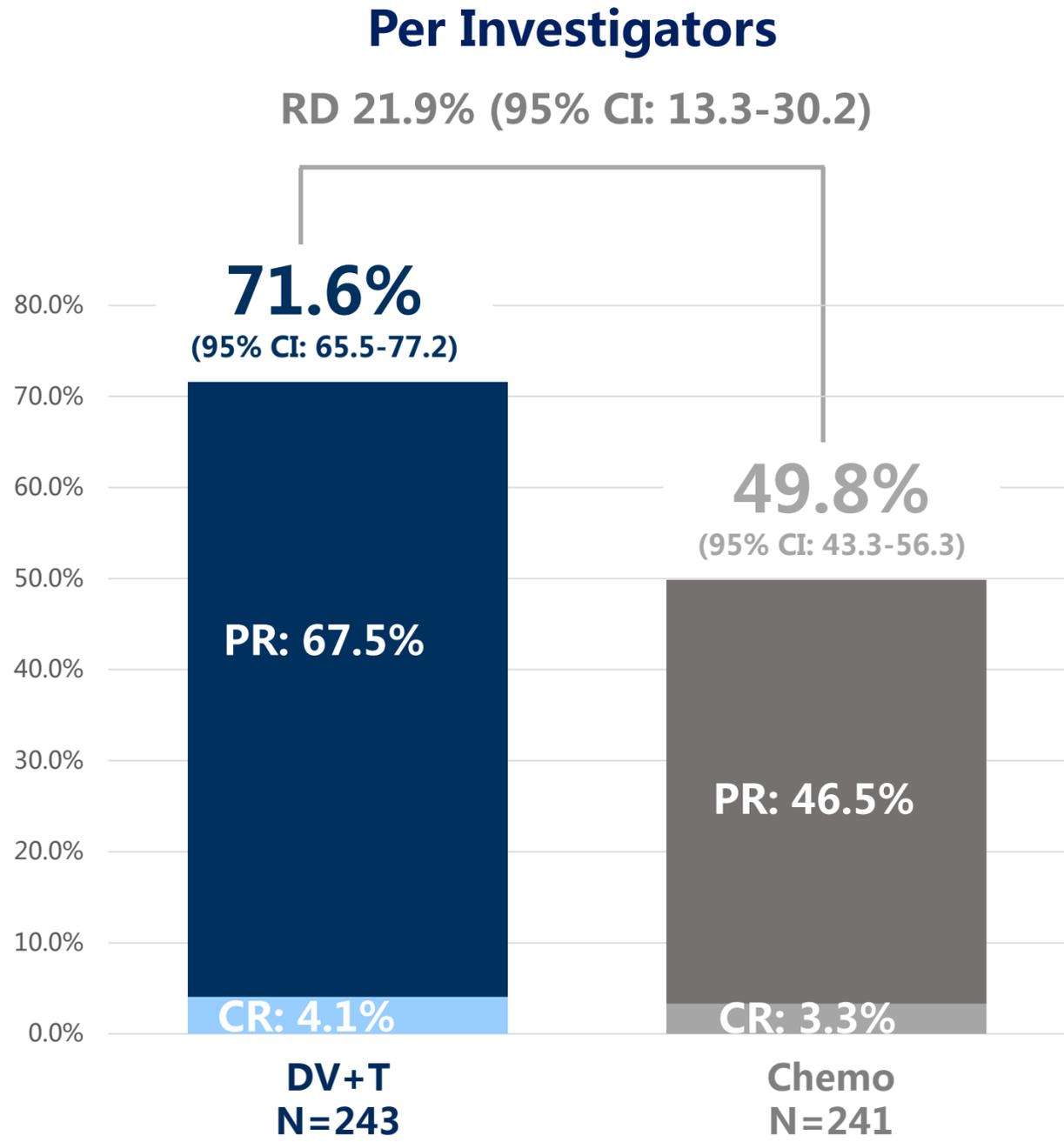
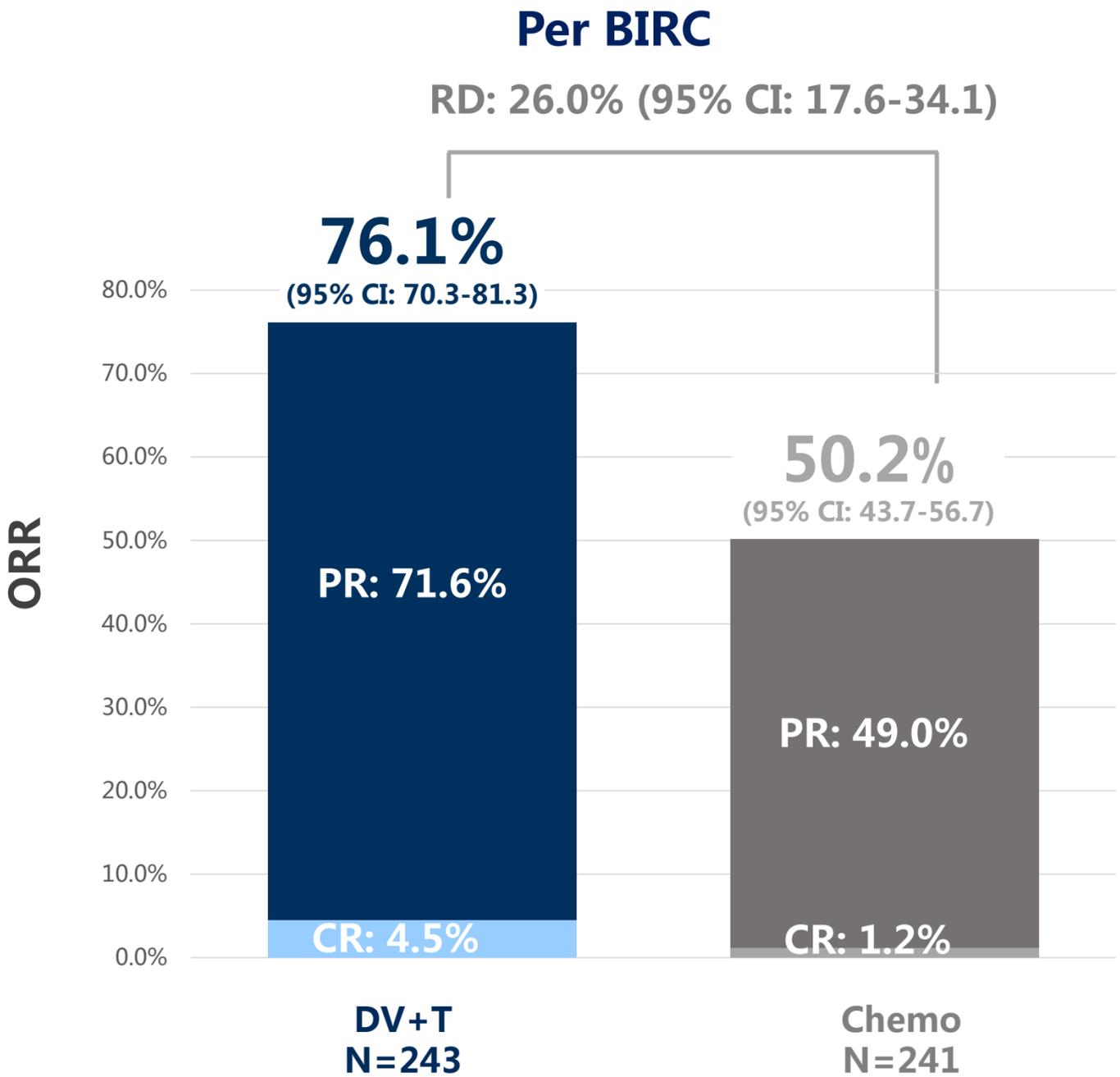
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# Tumor Response

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



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

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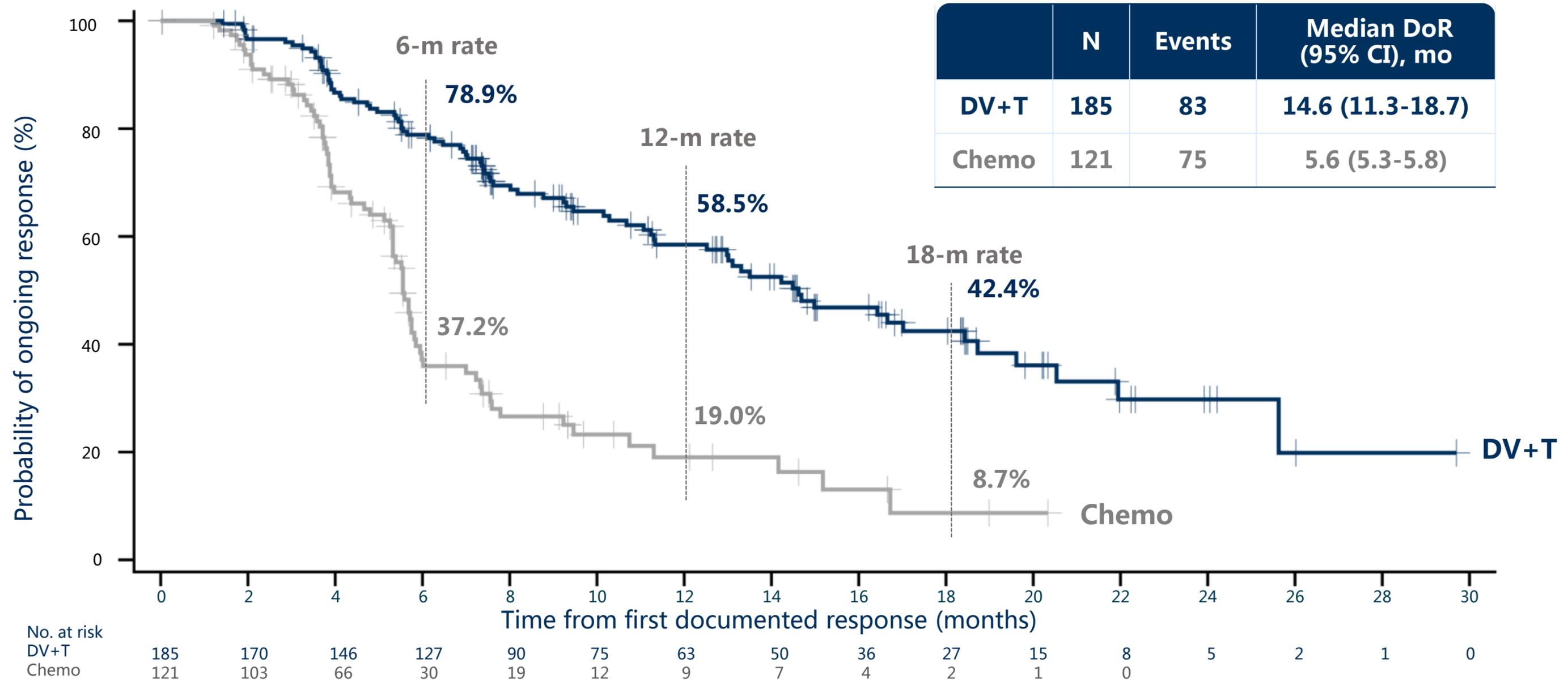
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# Duration of Response

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



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

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# 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)
<b>Patients with at least one subsequent systemic anticancer treatment</b>	<b>66 (27.2)</b>	<b>156 (64.7)</b>
<b>Anti-HER2-containing therapy</b>	<b>5 (2.1)</b>	<b>97 (40.2)</b>
DV-containing therapy	4 (1.6)	91 (37.8)
<b>PD-1/PD-L1 inhibitor-containing therapy</b>	<b>26 (10.7)</b>	<b>121 (50.2)</b>
<b>Both anti-HER2-containing therapies and PD-1/PD-L1 inhibitor therapies</b>	<b>2 (0.8)</b>	<b>75 (31.1)</b>
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.

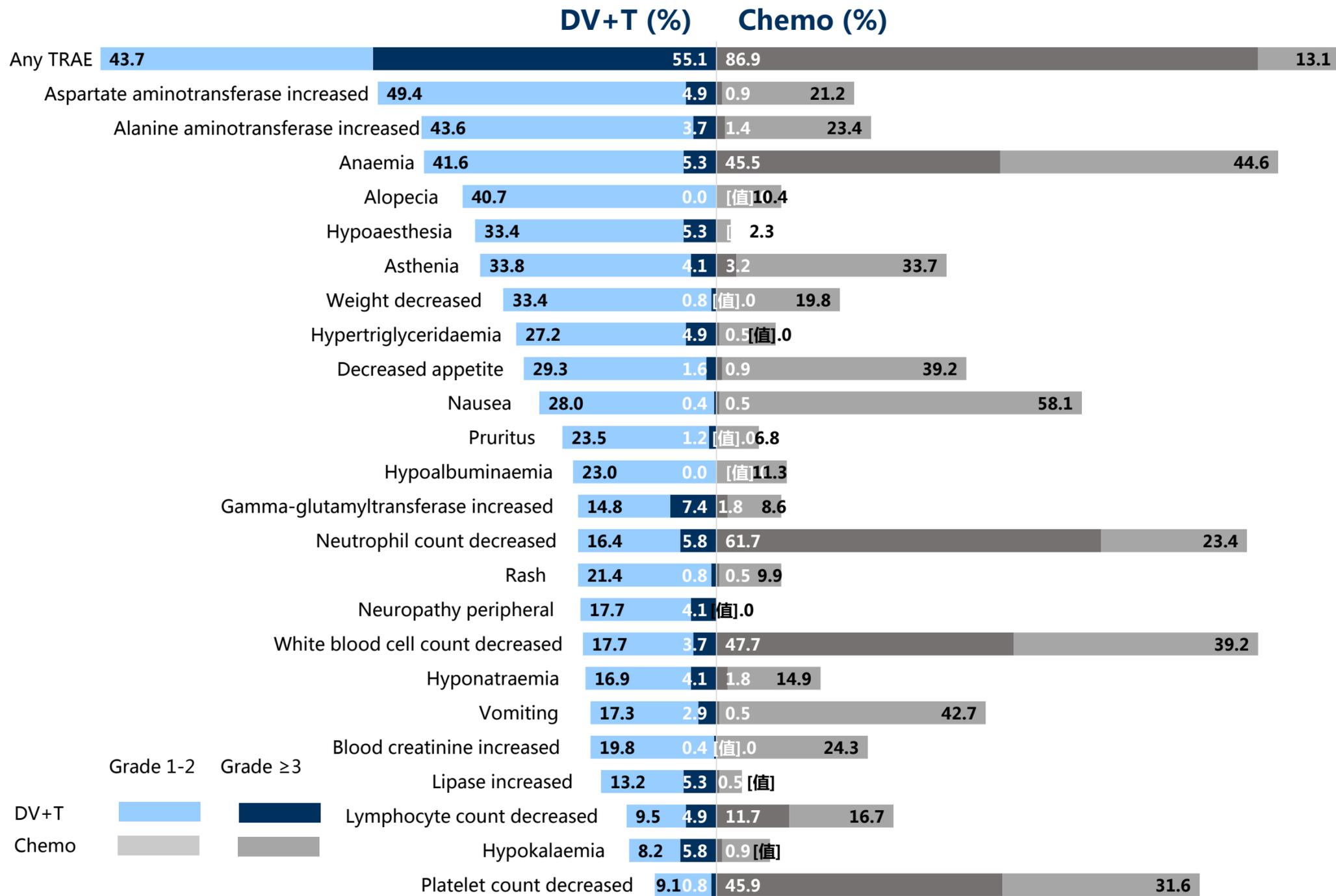
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# Safety Summary

Incidence of grade  $\geq 3$  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 $\geq 3$ 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 $\geq 3$	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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# 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  $\geq$ 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.

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Participating sites	Investigators	Participating sites	Investigators	Participating sites	Investigators
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• Hunan Cancer Hospital	Shusuan Jiang, Gongqian Zeng	• General Hospital of Ningxia Medical University	Xiangming Jin	• The First Affiliated Hospital of Guangzhou Medical University	Yongda Liu
• Peking University First Hospital	Zhisong He, Cuijian Zhang	• Harbin Medical University Cancer Hospital	Hui Chen	• The First Affiliated Hospital of Nanchang University	Ting Sun
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for the RC48-C016 Trial Investigators\*



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