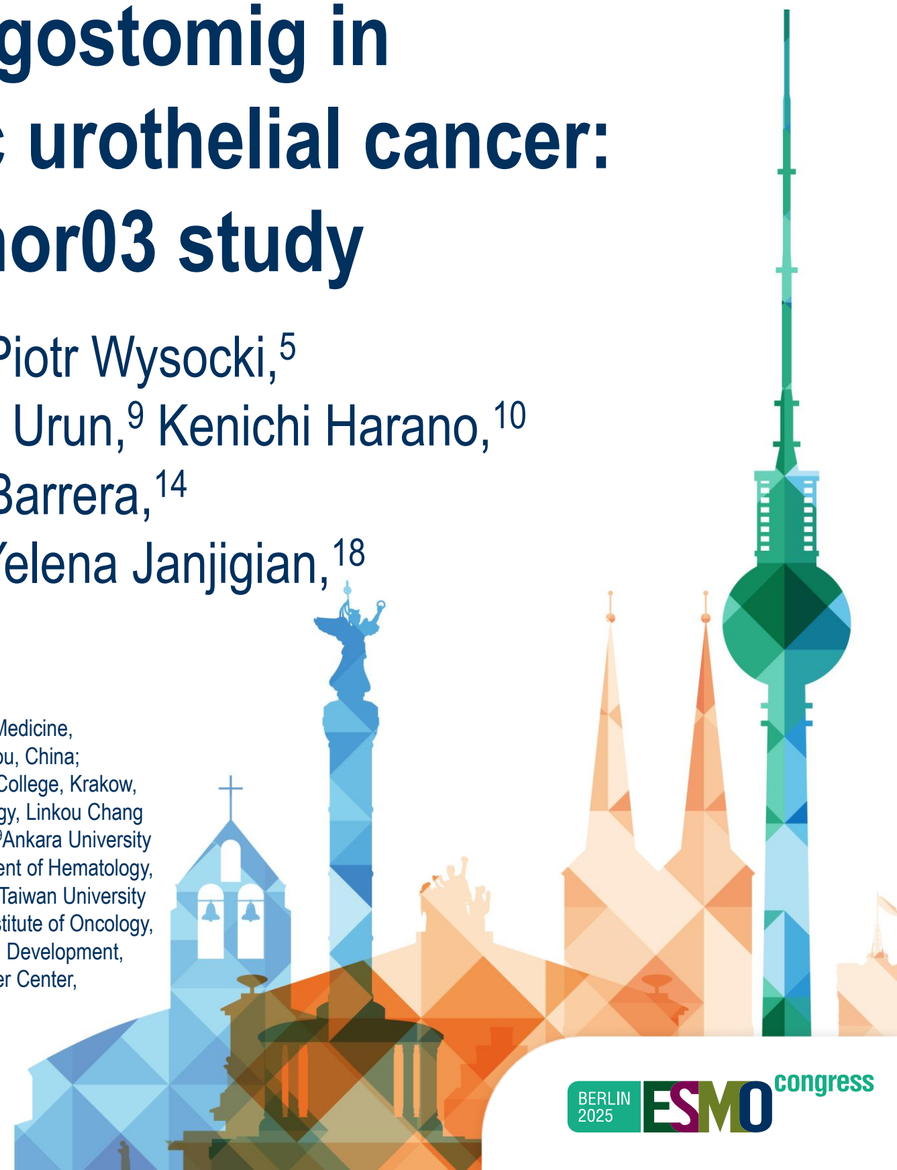
Datopotamab deruxtecan (Dato-DXd) + rilvegostomig in patients with locally advanced or metastatic urothelial cancer: Results from the phase 2 TROPION-PanTumor03 study

Sun Young Rha,[1] Sung Hee Lim,[2] Fangjian Zhou,[3] Kyung Hae Jung,[4] Piotr Wysocki,[5] Katarzyna Drosik-Rutowicz,[6] Jen-Shi Chen,[7] Hiroya Taniguchi,[8] Yuksel Urun,[9] Kenichi Harano,[10] Salvatore Siena,[11] Chia-Chi Lin,[12] Chi-Feng Chung,[13] Rafael Morales-Barrera,[14] Srikanth Gajavelli,[15] Dakshayini Kulkarni,[16] Shamim Gharagoozloo,[17] Yelena Janjigian,[18] Funda Meric-Bernstam[19]

[1]Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea; [3]Department of Urology, Sun Yat-Sen University Cancer Center, Guangzhou, China; [4]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]Department of Oncology, Jagiellonian University Medical College, Krakow, Poland; [6]Radiation and Clinical Oncology Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland; [7]Department of Hematology-Oncology, Linkou Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan; [8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [9]Ankara University School of Medicine, Department of Medical Oncology, Ankara, Türkiye; [10]Department of Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [11]Department of Hematology, Oncology, and Molecular Medicine, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, University of Milano, Milan, Italy; [12]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [13]Department of Medical Oncology, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; [14]Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d' Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [15]Clinical Development, Oncology R&D, AstraZeneca, New York, NY, USA; [16]Clinical Development, Oncology R&D, AstraZeneca, Cambridge, UK; [17]Biostatistics, Oncology R&D, AstraZeneca, Macclesfield, UK; [18]Memorial Solid Tumor Group, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [19]Department of Investigational Cancer Therapeutics, M.D. Anderson Cancer Center, University of Texas, Houston, TX, USA.



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Declaration of Interests

Sun Young Rha has the following disclosures:

- **Consultant or advisor for** Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eisai, Indivumed, LG Chem, MSD Oncology, Ono Pharmaceutical, Toray Industries

- **Speaker for** Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb/Ono, Daiichi Sankyo/UCB Japan, Eisai, MSD Oncology

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Background

- Both 1L and 2L treatment for la/m UC have evolved; however, a need for novel therapies remains[1–3]
- Dato-DXd, a TROP2-directed ADC, is approved for the treatment of HR+/HER2- advanced breast cancer and recently received accelerated approved in the US for the treatment of la/m *EGFR*-mutated lung cancer[4–6]
  - Dato-DXd has also demonstrated antitumour activity in patients with heavily pre-treated la/m UC[7,8]
- Rilvegostomig, an Fc-reduced, monovalent, bispecific IgG1 antibody against PD-1 and TIGIT receptors,[a] has demonstrated enhanced activity in freshly isolated NSCLC tumours compared with anti–PD-L1 or anti–TIGIT treatment (alone or in combination) and also showed encouraging efficacy in patients with advanced or metastatic NSCLC[9,10]
- Combining ICIs with therapies with broad antitumour activity, such as ADCs, has shown improved clinical efficacy in patients with la/m UC[11]
- Here, we present initial results from patients with la/m UC who received Dato-DXd + rilvegostomig in the phase 2 TROPION-PanTumor03 study (NCT05489211)

[a]The anti-TIGIT component of rilvegostomig is derived from COM902 developed by Compugen Ltd.

1L, first line; 2L, second line; ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; la/m, locally advanced or metastatic; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TROP2, trophoblast cell-surface antigen 2; UC, urothelial cancer; US, United States.

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TROPION-PanTumor03 Study Design

Phase 2, open-label study evaluating Dato-DXd ± various anticancer agents across several tumour types

- Here, we present initial results of Dato-DXd + rilvegostomig in patients with Ia/m UC (cohort 6B)

Key eligibility

- Histologically confirmed unresectable, Ia/m UC[a]
- No prior anti-PD-(L)1, anti-CTLA-4, anti-TIGIT, enfortumab vedotin, or TROP2-targeted or deruxtecan-based ADCs

***Either* 1L cisplatin-ineligible**

- No prior systemic therapy in the Ia/m setting[b]
- Cisplatin-ineligible (investigator's opinion) and met one of the following:
  - ECOG PS 0–2
  - CrCl ≥30mL/min but ≤ 60 mL/min
  - NCI CTCAE v5.0 grade ≥2 hearing loss
  - NCI CTCAE v5.0 grade ≥2 peripheral neuropathy

***Or* 2L platinum-treated**

- Previously treated with platinum-based chemotherapy in the Ia/m setting[c]
- ECOG PS 0 or 1

N=40

Dato-DXd
6 mg/kg IV Q3W
+
Rilvegostomig
750 mg Q3W[d]

Endpoints

Primary
- ORR (by investigator, per RECIST v1.1)
- Safety and tolerability

Secondary
- DCR, DoR and PFS (by investigator, per RECIST v1.1)

NCT05489211. Data cut-off: June 27, 2025

[a]Transitional cell or mixed transitional/non-transitional cell histologies of the urothelium, including the renal pelvis, ureters, urinary urothelial, and urethra; [b]Progression >12 months after platinum-based neoadjuvant or adjuvant therapy was allowed; [c]Patients who progressed <12 months after platinum-based neoadjuvant or adjuvant therapy were eligible; patients who progressed >12 months after platinum-based neoadjuvant or adjuvant therapy should have received one line of platinum-based chemotherapy in the Ia/m setting; [d]Patients received treatment until they met one of the discontinuation criteria, including: disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Per protocol, a daily oral care plan was provided to all patients prior to initiation of Dato-DXd; the use of a steroid-containing mouthwash for stomatitis prophylaxis was highly recommended. Patients were also advised to use artificial tears and to avoid use of contact lenses as a preventative measure for ocular surface events.

CrCl, creatinine clearance; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluable Criteria in Solid Tumours version 1.1.

Baseline Characteristics and Demographics

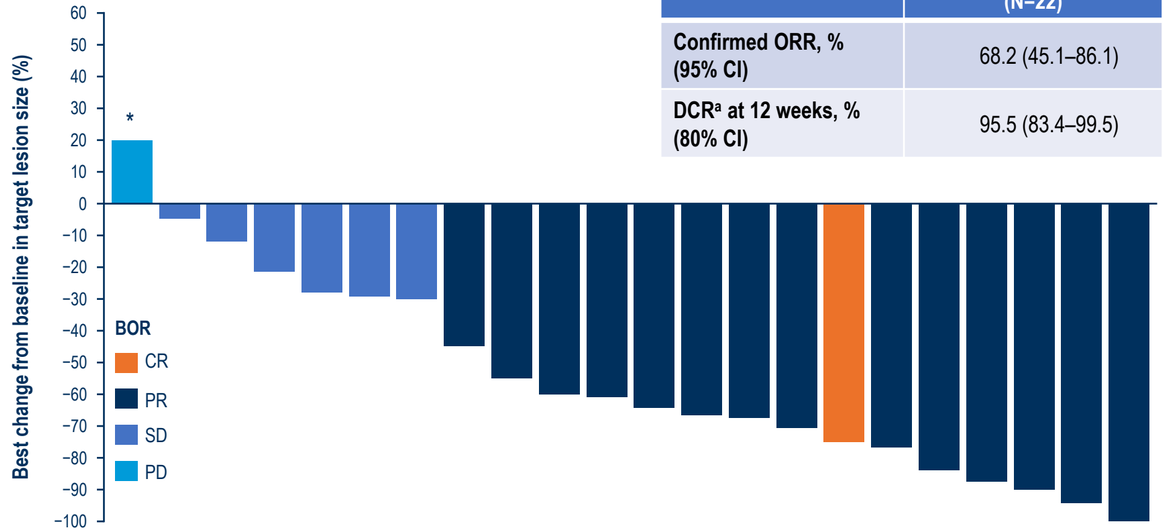
	1L cisplatin-ineligible (N=22)	2L (N=18)
Age, median (range), years	71 (53–85)	66 (56–78)
Sex, n (%)		
Male	17 (77.3)	15 (83.3)
Female	5 (22.7)	3 (16.7)
ECOG PS, n (%)		
0	17 (77.3)	13 (72.2)
1	5 (22.7)	5 (27.8)
AJCC stage, n (%)		
III	3 (13.6)[a]	2 (11.1)
IV	19 (86.4)[a]	16 (88.9)
Previous lines of therapy, n (%)		
No prior treatment	19 (86.4)	0
Adjuvant/neoadjuvant[b]	3 (13.6)	6 (33.3)
1L	0	11 (61.1)
2L+	0	1 (5.6)[c]
Prior therapy, n (%)		
Radiotherapy	0	2 (11.1)[e]
Chemotherapy		
Carboplatin	0	5 (27.8)[c,d]
Cisplatin	3 (13.6)	16 (88.9)[e]

[a]Following data cutoff, 5 and 17 patients were categorised as stage III and IV, respectively; [b]Patients whose disease progressed <12 months after platinum-based neoadjuvant or adjuvant therapy are counted as a line of therapy;
[c] One patients received carboplatin administered as 2L treatment; [d]Two patients switched from cisplatin to carboplatin due to toxicity; [e]Two patients received adjuvant chemoradiotherapy with cisplatin.
AJCC, American Joint Committee on Cancer.

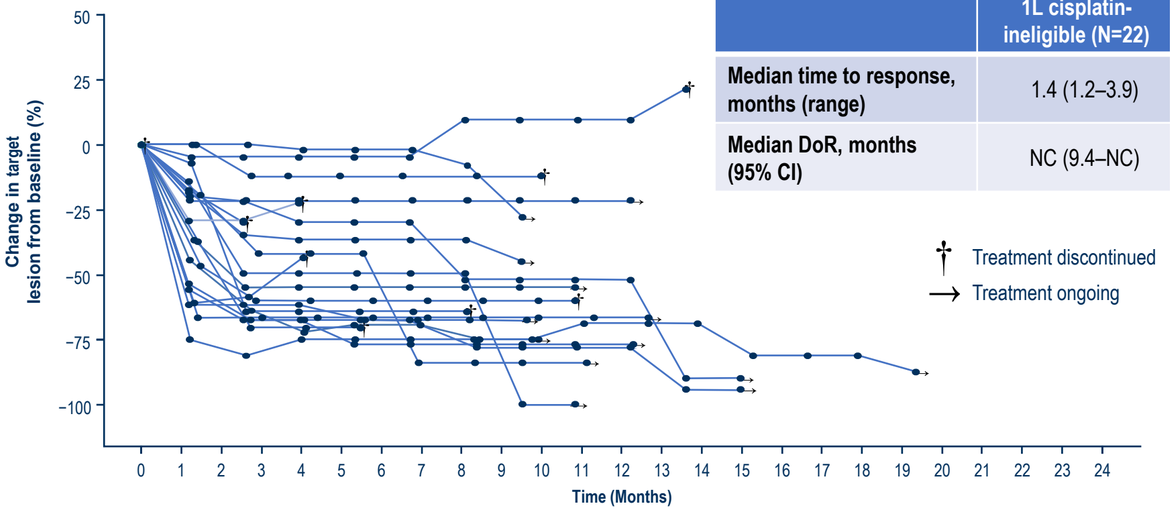
Objective Response Rate and Duration of Response (Investigator Assessed)

1L cisplatin-ineligible (N=22)

	1L cisplatin-ineligible (N=22)
Confirmed ORR, % (95% CI)	68.2 (45.1–86.1)
DCR[a] at 12 weeks, % (80% CI)	95.5 (83.4–99.5)

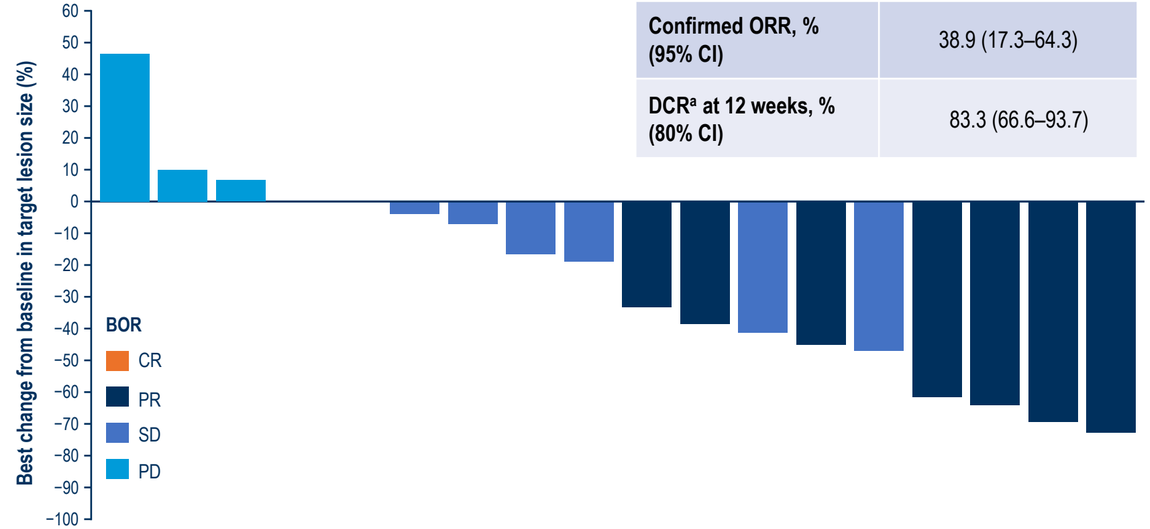


	1L cisplatin-ineligible (N=22)
Median time to response, months (range)	1.4 (1.2–3.9)
Median DoR, months (95% CI)	NC (9.4–NC)

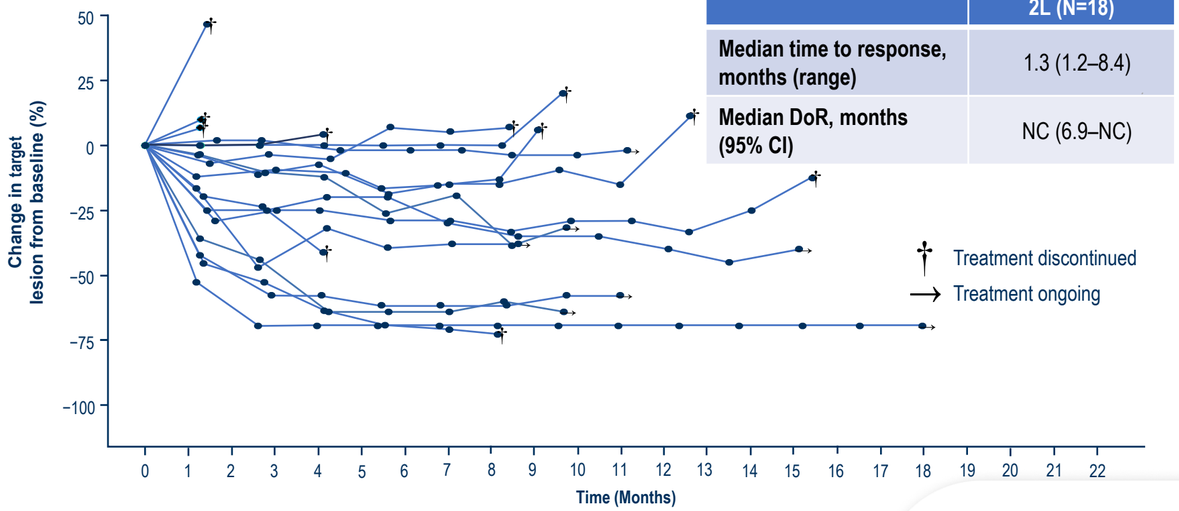


2L (N=18)

	2L (N=18)
Confirmed ORR, % (95% CI)	38.9 (17.3–64.3)
DCR[a] at 12 weeks, % (80% CI)	83.3 (66.6–93.7)



	2L (N=18)
Median time to response, months (range)	1.3 (1.2–8.4)
Median DoR, months (95% CI)	NC (6.9–NC)



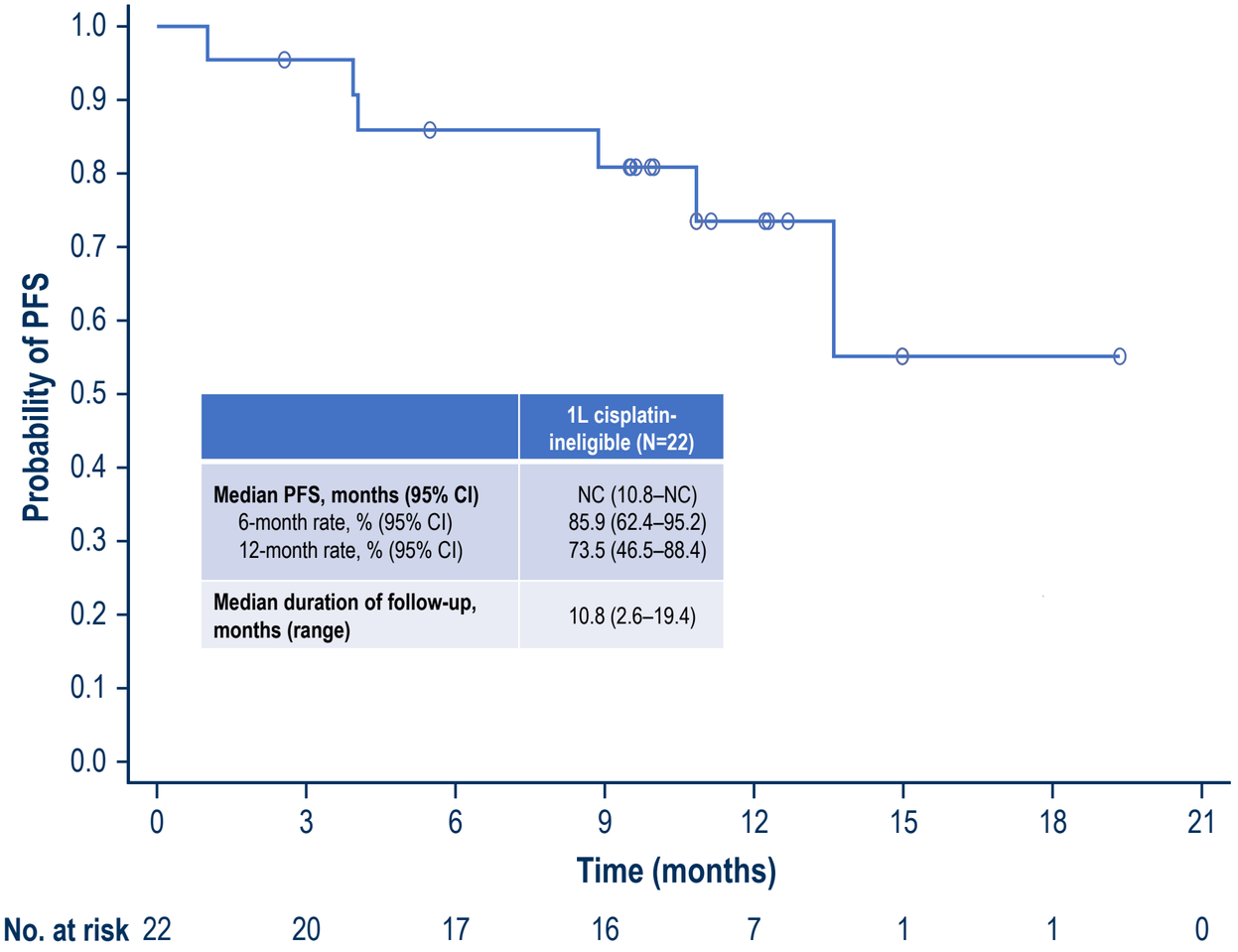
*A value of 20% is imputed as patient has no post-baseline assessment and died less than 13 weeks after first dose.

[a]Defined as the percentage of patients who achieved a CR or PR in the first 13 weeks or who had SD for at least 11 weeks after start of treatment per RECIST 1.1 as assessed by the investigator.

BOR, best overall response; CI, confidence interval; CR, complete response; NC, not calculable; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-Free Survival (Investigator Assessed)

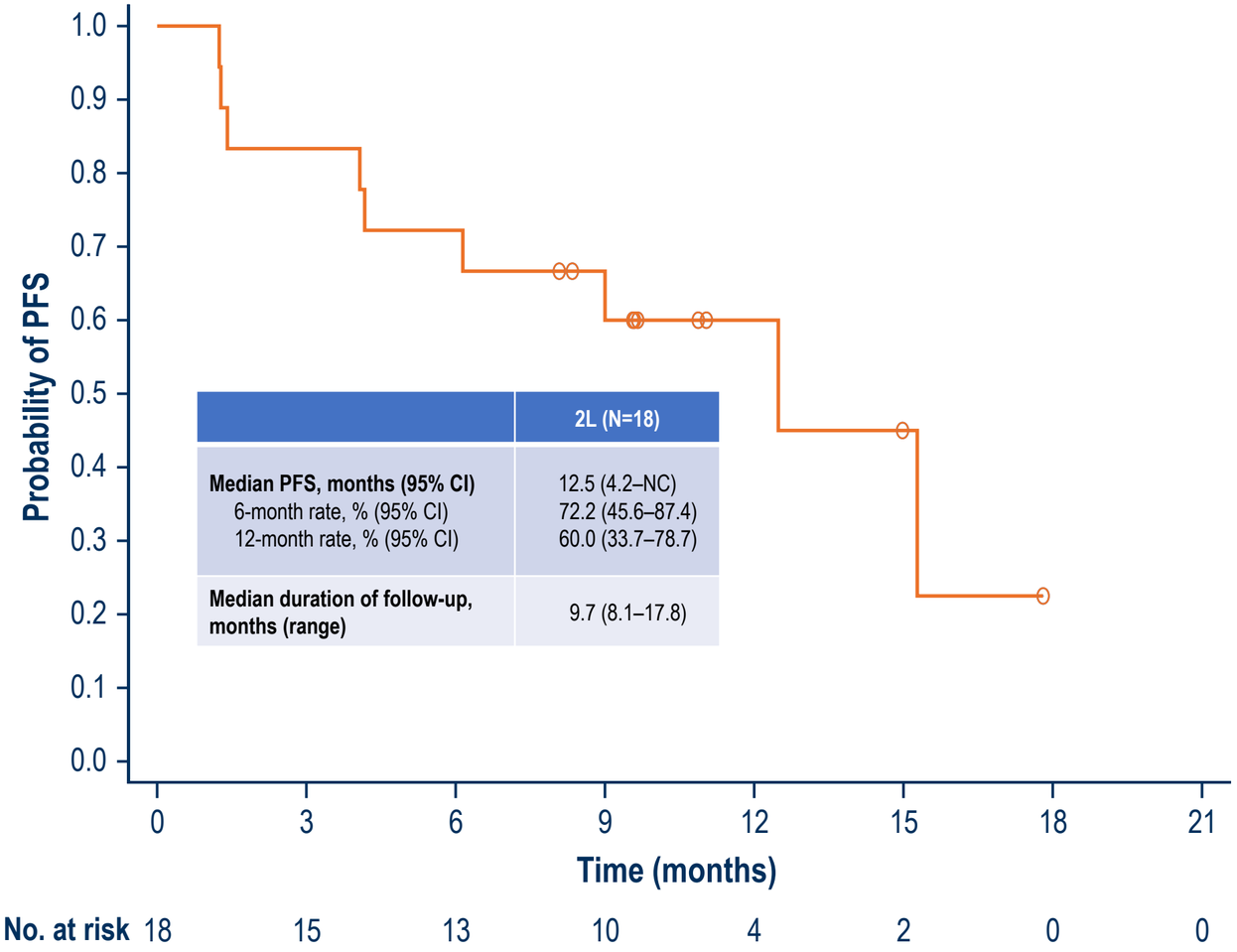
1L cisplatin-ineligible (N=22)



	1L cisplatin-ineligible (N=22)
Median PFS, months (95% CI) 6-month rate, % (95% CI) 12-month rate, % (95% CI)	NC (10.8–NC) 85.9 (62.4–95.2) 73.5 (46.5–88.4)
Median duration of follow-up, months (range)	10.8 (2.6–19.4)

No. at risk	22	20	17	16	7	1	1	0

2L (N=18)



	2L (N=18)
Median PFS, months (95% CI) 6-month rate, % (95% CI) 12-month rate, % (95% CI)	12.5 (4.2–NC) 72.2 (45.6–87.4) 60.0 (33.7–78.7)
Median duration of follow-up, months (range)	9.7 (8.1–17.8)

No. at risk	18	15	13	10	4	2	0	0

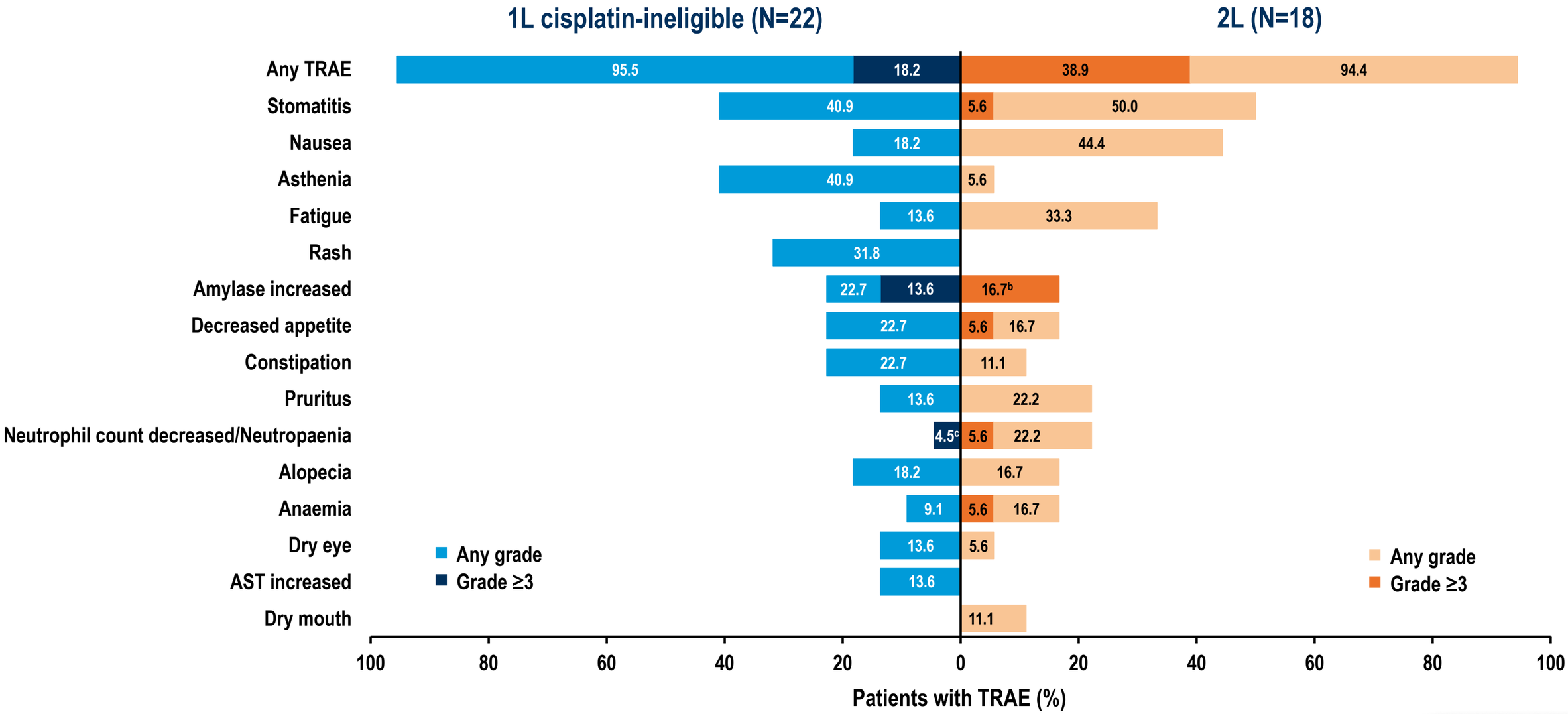
Overall Safety Summary

	1L cisplatin-ineligible (N=22)	2L (N=18)
TRAEs[a] leading to:		
Dose reduction of any treatment	14 (63.6)	4 (22.2)
Dose interruption of any treatment	10 (45.5)	6 (33.3)
Discontinuation of any treatment	2 (9.1)	3 (16.7)
Death	0	0

	1L cisplatin-ineligible (N=22)		2L (N=18)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
TRAEs[a]	21 (95.5)	4 (18.2)	17 (94.4)	7 (38.9)
Serious TRAEs[a]	0	0	3 (16.7)	3 (16.7)
AESIs for Dato-DXd				
Oral mucositis/stomatitis[b]	9 (40.9)	0	11 (61.1)	1 (5.6)
Ocular surface events[b]	4 (18.2)	0	4 (22.2)	0
Adjudicated drug-related ILD/pneumonitis[b,c]	1 (4.5)	0	2 (11.1)	0
AESIs for rilvegostomig				
Hepatic events[b]	3 (13.6)	0	1 (5.6)	1 (5.6)
Diarrhoea/colitis[b]	1 (4.5)	0	1 (5.6)	0
Dermatitis/rash[b]	11 (50.0)	0	8 (44.4)	0
IRR/hypersensitivity reaction[b]	2 (9.1)	0	0	0

[a]Related to either treatment; assessed to be possibly related by the investigator; [b]Grouped terms defined by a range of medically relevant MedDRA preferred terms; [c]All cases of possible ILD/pneumonitis are subject to review by an independent adjudication committee.
AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; TRAEs, treatment-related adverse events.

Most Common TRAEs[a] (≥10% of Patients)



[a]≥10% of all-grade TRAEs by MedDRA preferred term. Related to either treatment; assessed to be possibly related by the investigator.

[b]16.7% for both any grade and grade ≥3.

[c]4.5% for both any grade and grade ≥3.

AST, aspartate aminotransferase.

Conclusions

- The combination of Dato-DXd + rilvegostomig demonstrated promising efficacy in patients with la/m UC who were cisplatin-ineligible and patients who had progressed on prior platinum-based chemotherapy

- The safety profile of Dato-DXd + rilvegostomig was consistent with previous reports of this combination. No new safety signals were identified

- These results warrant further exploration of Dato-DXd + rilvegostomig in the 1L la/m UC setting

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Via Ginevra 4, CH-6900 Lugano
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Datopotamab deruxtecan (Dato-DXd) + rilvegostomig in patients with locally advanced or metastatic urothelial cancer: the phase 2 TROPION-PanTumor03 study

Plain Language Summary

Why did we perform this research?

- People with urothelial cancer (a type of cancer in the cells lining the bladder) that has grown through the bladder wall or has spread only to lymph nodes (locally advanced), has spread to other parts of the body (metastatic), or worsened after treatment often have limited treatment options
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) and an anticancer drug (DXd), joined via a plasma-stable cleavable linker. Dato-DXd binds to TROP2 on the surface of cancer cells and is then taken inside the cell, where the linker detaches and releases DXd to kill the cancer cells
- Dato-DXd has shown promising antitumour activity in people with locally advanced or metastatic urothelial cancer who had already received multiple treatments[1–3]
- Rilvegostomig is a drug that blocks both PD-1 and TIGIT proteins to help the immune system kill cancer cells. Rilvegostomig has shown potential in treating people with non-small cell lung cancer that had spread to other parts of the body or was in advanced stages[4]
- TROPION-PanTumor03 is a clinical study in which Dato-DXd is being assessed as treatment alone or in combination with other anticancer drugs, across several different cancer types
- Here, the results of the safety and efficacy analysis of Dato-DXd in combination with rilvegostomig in people with locally advanced or metastatic urothelial cancer are presented

How did we perform this research?

- The study included 40 people with urothelial cancer. All participants had cancer that was locally advanced or metastatic. The study included two subgroups: a group of 22 people who could not receive cisplatin (a platinum-based chemotherapy), known as the cisplatin-ineligible group, and 18 people who had previously received platinum-based chemotherapy for advanced cancer, known as the platinum-treated group
- Participants received Dato-DXd every 3 weeks and rilvegostomig until their cancer worsened or they experienced unacceptable side effects

What were the findings of this research?

- Overall, the side effects experienced by people in this study were manageable and consistent with what is known from other studies of Dato-DXd and rilvegostomig
  - The most common side effect was inflammation of the lining in the mouth (stomatitis), which was mostly mild
  - Few side effects led to people stopping treatment and no deaths were caused by treatment
- The combination of Dato-DXd and rilvegostomig showed promising antitumour activity in both groups
  - In the cisplatin-ineligible group, 68.2% of people had their tumours shrink
  - In the platinum-treated group, 38.9% of people had their tumours shrink

What are the implications of this research?

These findings demonstrate that Dato-DXd in combination with rilvegostomig has promising efficacy in people with locally advanced or metastatic urothelial cancer who cannot receive cisplatin or whose cancer has worsened after platinum-based chemotherapy

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329-40; 2. Lisberg A, et al. J Clin Oncol 2024;42(4_suppl):abstract 603; 3. Meric-Bernstam F, et al. J Clin Oncol 2025;43(5_suppl);abstract 663;
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