ASCO® Genitourinary Cancers Symposium

Datopotamab deruxtecan (Dato-DXd) in locally advanced/metastatic urothelial cancer: updated results from the phase 1 TROPION PanTumor01 study

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Key Takeaway Points

- In this update from TROPION-PanTumor01, Dato-DXd continues to demonstrate encouraging activity in heavily pretreated patients with locally advanced/metastatic urothelial cancer
- The safety profile of Dato-DXd was consistent with previous studies; no new safety signals were observed
- Findings from this study support the ongoing evaluation of Dato-DXd in patients with urothelial cancer in the phase 2 TROPION-PanTumor03 (NCT05489211) trial[1]

1. ClinialTrials.gov. Available at: https://clinicaltrials.gov/study/NCT05489211. Accessed October 31, 2024.

Study Design

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- TROPION-PanTumor01 is an ongoing, phase 1, multi-cohort, multicenter, open-label, dose-escalation and dose-expansion study evaluating Dato-DXd in patients with several types of previously treated advanced solid tumors, including urothelial cancer

Key eligibility criteria

- Unresectable locally advanced/metastatic (stage III or IV) urothelial carcinoma (included renal pelvis, ureter, urinary bladder, and urethra)
- Previous treatment with ≥1 line of therapy including an immune checkpoint inhibitor
- ECOG PS 0–1
- Unselected for TROP2 expression
- No prior treatment with DXd-ADCs or TROP2-directed therapies

→ **Dato-DXd**
6 mg/kg Q3W
(N=40)

Primary endpoints

- Safety and tolerability

Secondary endpoints (by BICR[a])

- ORR
- DOR
- DCR
- PFS

BICR, blinded independent review committee; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; Q3W, every 3 weeks.
Data cut off: April 22, 2024. Median follow-up was 10.0 months (range, 5.0–28.2). [a]Evaluated per RECIST v1.1. 1. Okajima D, et al. Mol Cancer Ther. 2021;20:2329–40.

Demographics and Baseline Characteristics

Characteristic, n (%)	Dato-DXd (N=40)
Age, years, median (range)	66.5 (44–83)
Sex, male	31 (78)
ECOG PS	
0	19 (48)
1	21 (53)
Stage	
III	2 (5)
IV	33 (83)
History of brain metastases[a]	2 (5)
Time from diagnosis to study treatment, months, median (range)	24 (3–342)

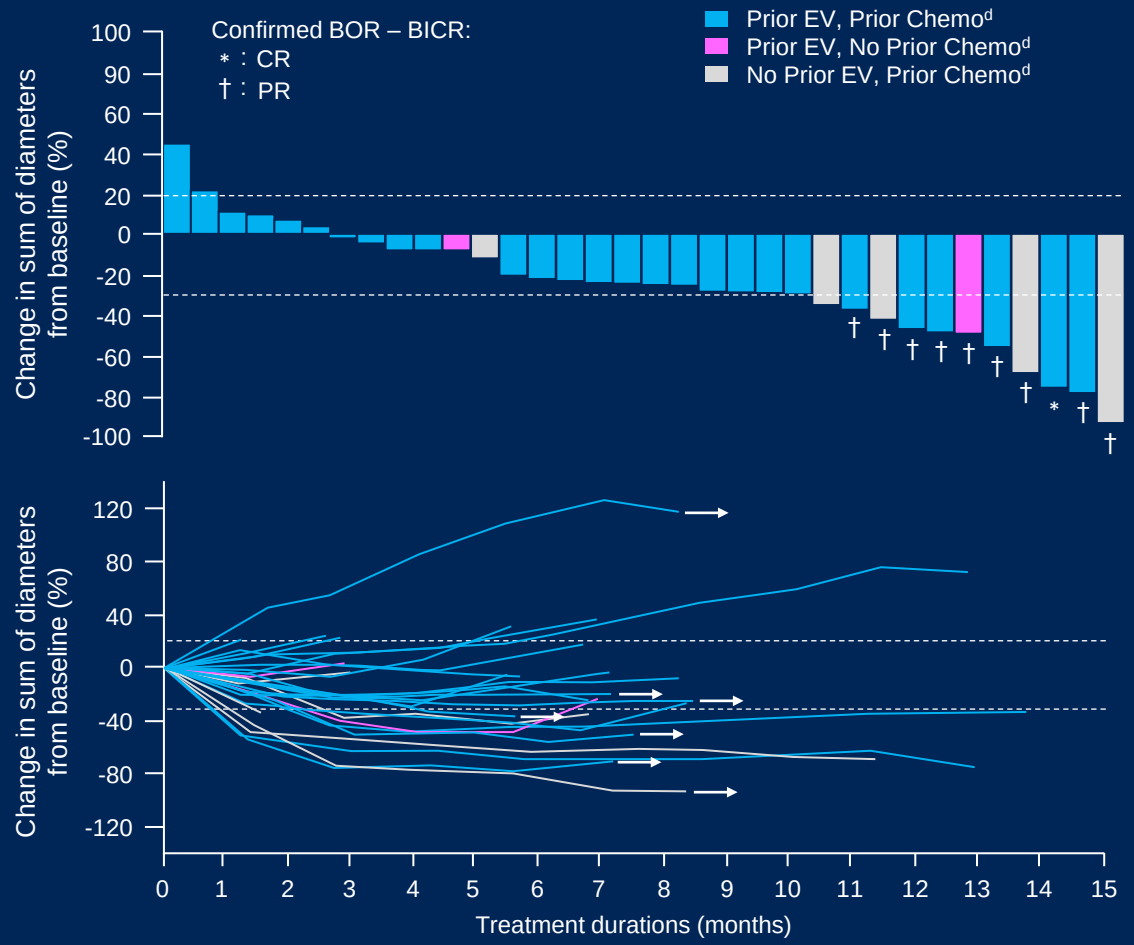
Characteristic, n (%)	Dato-DXd (N=40)
Number of prior lines of therapy (locally advanced/metastatic)	
1	5 (13)
2	11 (28)
≥3	24 (60)
Median (range)	3 (1–7)
Prior systemic treatment (any setting)	
Immunotherapy	40 (100)
Platinum-based chemotherapy	36 (90)
Taxane chemotherapy	7 (18)
Enfortumab vedotin[b]	33 (83)

Data cut off: April 22, 2024. [a]Patients with clinically inactive brain metastases and patients with treated brain metastases who are no longer symptomatic, require no treatment with steroids, and have recovered from radiotherapy, may be included in the study. [b]All patients received enfortumab vedotin in the locally advanced/metastatic setting except one patient that received it in the adjuvant setting (other clinical trial).

Response and Change in Tumor Burden

Response by BICR[a]	Dato-DXd (N=40)
ORR[b], n (%) [95% CI]	**10 (25.0)** [12.7–41.2]
DCR[c], n (%) [95% CI]	**31 (77.5)** [61.5–89.2]
BOR, n (%)	
CR	1 (2.5)
PR	9 (22.5)
SD	20 (50.0)
Non-CR/non-PD	1 (2.5)
PD	5 (12.5)
NE	4 (10.0)
DOR, median (95% CI)**, months**	NE (2.6–NE)
6-month DOR rate, % (95% CI)	76.2 (33.2–93.5)

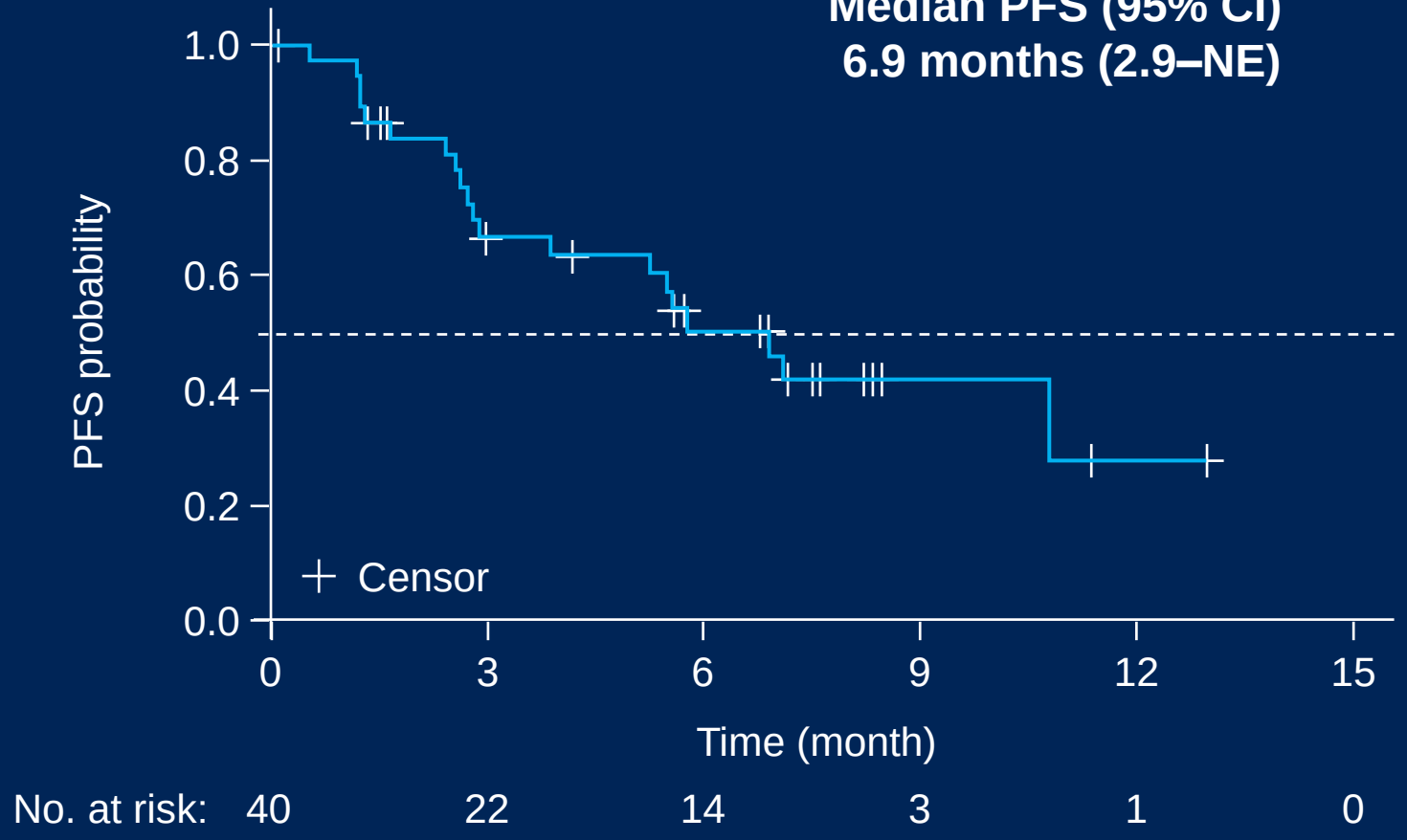
ORR by investigator was 30.0% (n=12); all were PR



BOR, best overall response; CI, confidence interval; CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Evaluated by BICR per RECIST v1.1. [b]Responses with confirmation of CR/PR. [c]CR + PR + SD + non-CR/non-PD. [d]All patients received prior immunotherapy.

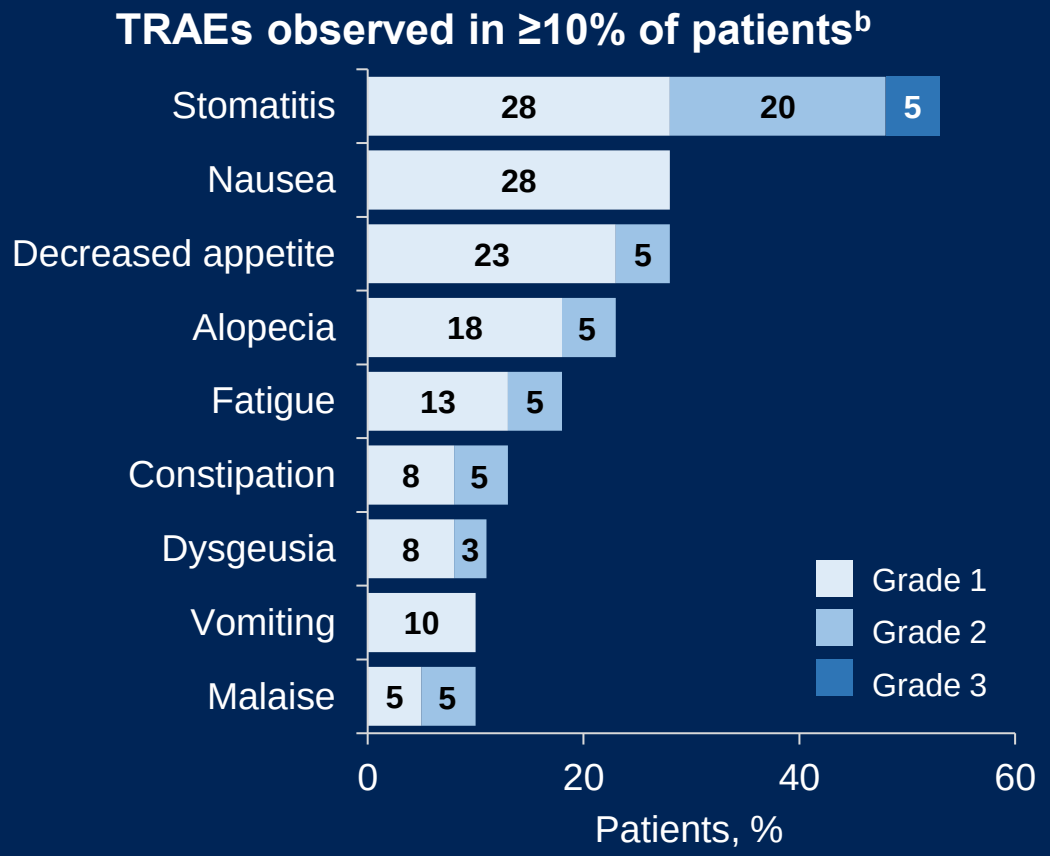
Progression-Free Survival

Median PFS (95% CI)
6.9 months (2.9–NE)



Safety

n (%)	Dato-DXd (N=40)[a]	
	Any Grade	Grade ≥3
TEAE	39 (98)	22 (55)
Treatment-related	35 (88)	4 (10)
Serious TEAE	17 (43)	16 (40)
Treatment-related	0	0
Dose adjustments due to TEAEs (any grade)		
Dose reduction	8 (20)	
Dose delay	14 (35)	
Treatment discontinuation	3 (8)	
TEAE associated with death	2 (5)	



- The two deaths were not related to the study drug
- No neuropathy events and only one cytopenia event (Grade 2 anemia) were observed

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]Median treatment duration was 6.2 (range, 0.7–14.3) months. [b]Owing to rounding, summed rates may not reflect total percentage of TRAEs.

Adverse Events of Special Interest

AESI, n (%)	AESIs[a]				AESIs associated with		
	Any grade	Grade 1	Grade 2	Grade 3	Dose reduction	Dose delay	Treatment discontinuation
Oral mucositis/stomatitis	22 (55)	11 (28)	9 (23)	2 (5)	3 (8)	1 (3)	0
Ocular surface events[b]	7 (18)	4 (10)	3 (8)	0	1 (3)	2 (5)	0
Adjudicated drug-related ILD	2 (5)	0	1 (3)	1 (3)	0	1 (3)	1 (3)

AESI, adverse event of special interest; ILD, interstitial lung disease.
[a]AESIs listed include all preferred terms defined by the medical concept. [b]Includes dry eye (7.5%), conjunctivitis (5.0%), keratitis, lacrimation increased, corneal toxicity, eye irritation, keratopathy, limbal stem cell deficiency, and visual impairment (2.5% each).

Conclusions

- In this update from TROPION-PanTumor01, Dato-DXd continues to demonstrate encouraging activity in heavily pretreated patients with locally advanced/metastatic urothelial cancer
  - Confirmed ORR by BICR was 25.0% and median PFS was 6.9 months
  - Median DOR was not reached at 10 months of follow-up; 76% of responders remained in response at 6 months
- The safety profile of Dato-DXd was consistent with previous studies; no new safety signals were observed
- These findings support the ongoing evaluation of Dato-DXd in patients with urothelial cancer in the phase 2 TROPION-PanTumor03 (NCT05489211) trial[1]

1. ClinialTrials.gov. Available at: https://clinicaltrials.gov/study/NCT05489211. Accessed October 31, 2024.

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Plain Language Summary

Why did we perform this research?

Therapies for patients with urothelial cancer only work for a limited period of time. Eventually, these drugs stop working and then patients need other therapies to treat their cancer. Datopotamab deruxtecan (Dato-DXd) is a new drug made up of a man-made antibody (datopotamab) linked to a chemotherapy drug (deruxtecan). The antibody binds to a protein found on cancer cells called TROP2, where it releases the chemotherapy to kill these cells. Since Dato-DXd attaches to cancer cells before the chemotherapy drug is released, the whole body sees lower drug levels, so the patient may have fewer side effects. Clinical trials of Dato-DXd in breast and lung cancer have shown promising results. This study is another clinical trial of Dato-DXd called TROPION-PanTumor01. Earlier findings from patients with urothelial cancer in this study have already been published. Here, we report new results after patients with urothelial cancer were followed for longer.

How did we perform this research?

Patients who took part in TROPION-PanTumor01 had urothelial cancer that could not be treated with surgery. They had also already received at least one therapy which had stopped working before joining this study. All patients received Dato-DXd in this study. The researchers wanted to find out what adverse events occurred, whether the patients' tumors shrank or disappeared, and how long patients received Dato-DXd for before their cancer got worse.

What were the findings of this research?

Dato-DXd made tumors shrink or disappear in one in four patients with urothelial cancer. After starting Dato-DXd, patients lived for an average of 6.9 months before their cancer got worse. Side effects ('adverse events') caused by Dato-DXd occurred in 88% of patients, but these were mostly either mild and not bothersome, or bothersome but not dangerous. Stomatitis (which is an inflamed and sore mouth) was the most common adverse event, occurring in 53% of patients. Nausea and decreased appetite were reported by 28% of patients. Nobody in the study died or had life-threatening adverse events because of treatment with Dato-DXd.

What are the implications of this research?

There is a need for new drugs to treat patients with urothelial cancer. This clinical study suggests that, in the future, patients with urothelial cancer could be treated with Dato-DXd after other cancer therapies stop working. However, more studies are needed before researchers will know whether Dato-DXd is better than other available treatment options. TROPION-PanTumor01 was a small study, so Dato-DXd needs to be tested in a larger patient population to see if the results are the same. Some types of adverse event were common, so doctors need to monitor their patients for signs of these adverse events and be educated on how to manage them.

Where can I access more information?

For more information about TROPION-PanTumor01, please visit https://clinicaltrials.gov/study/NCT04656652