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Datopotamab deruxtecan in advanced/ metastatic urothelial cancer: Results from the phase 1 TROPION-PanTumor01 study

Aaron Lisberg,[1a] Alexandra Drakaki,[1ab] Funda Meric-Bernstam,[2] Omar Alhalabi,[3] Takahiro Kojima,[4] Manabu Kato,[4] Alexander Spira,[5] Mohamad A. Salkeni,[5] Rebecca Heist,[6] Xin Gao,[6] Manali Bhave,[7] Gunnar Klauss,[8] Hayato Sakaki,[9] Yasuyuki Kakurai,[10] Takahiro Kogawa[11]

[a]Indicates co-first authors; [b]Indicates presenting author

[1]Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Urology, Aichi Cancer Center, Nagoya, Japan; [5]Virginia Cancer Specialists (VCS) Research Institute, Fairfax, VA, USA; [6]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Department of Hematology/Oncology, Emory University, Atlanta, GA, USA; [8]Global Oncology, R&D, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [9]Clinical Science, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [10]Data Intelligence, Daiichi Sankyo, Co., Ltd., Tokyo, Japan; [11]The Cancer Institute Hospital of Japanese Foundation For Cancer Research, Tokyo, Japan.

Objective

- To assess the safety, tolerability, and antitumor activity of Dato-DXd 6 mg/kg in patients with advanced/metastatic urothelial cancer treated with ≥1 prior line of therapy (including a checkpoint inhibitor) in the advanced setting

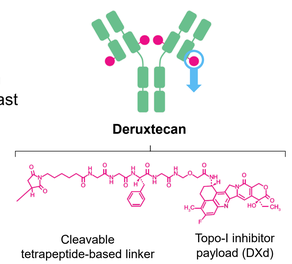
Conclusions

- In this interim analysis of the ongoing Phase 1 TROPION-PanTumor01 study, Dato-DXd demonstrated encouraging antitumor activity and a manageable safety profile in patients with pretreated advanced/metastatic urothelial cancer
  - Confirmed ORR was 19.2% ([95% CI, 6.6–39.4]1 CR and 4 PR) in all response-evaluable patients regardless of follow-up time and 22.7% (95% CI 7.8–45.4) in patients with at least 2 post-baseline tumor assessments
  - Tumor burden reduction was observed in 82% of evaluable patients
- TEAEs were primarily grade 1 or 2; stomatitis, nausea, and fatigue were the most frequently reported
- Enrollment in this cohort is now complete, and updated efficacy and safety data will be presented at a future meeting
- Dato-DXd is being further evaluated as a monotherapy and in combination in patients with urothelial cancer in the phase 1/2 TROPION-PanTumor02 (NCT05460273) and the phase 2 TROPION-PanTumor03 (NCT05489211) studies[7,8]

Introduction

- Dato-DXd is an ADC composed of a TROP2-directed IgG1 monoclonal antibody covalently linked to a highly potent cytotoxic topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- In the Phase 1 TROPION-PanTumor01 study, Dato-DXd has previously shown encouraging antitumor activity and a manageable safety profile in patients with HR+/HER2- breast cancer, triple-negative breast cancer, and advanced/ metastatic NSCLC[2–4]
- Dato-DXd demonstrated significant improvements in PFS vs SOC in two Phase 3 trials:
  - TROPION-Lung01 (NCT04656652) met the primary endpoint of PFS, showing significant improvement vs docetaxel in patients with previously-treated advanced NSCLC[5]
  - TROPION-Breast01 (NCT05104866) met the primary endpoint of PFS, showing significant improvement vs investigator's choice of chemotherapy in patients with previously treated metastatic HR+/HER2- breast cancer[6]
- Here, we present the first interim results from patients with advanced/metastatic urothelial cancer in this actively enrolling cohort of TROPION-PanTumor01

Dato-DXd: Humanized anti-TROP2 IgG1 mAb



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Plain language summary

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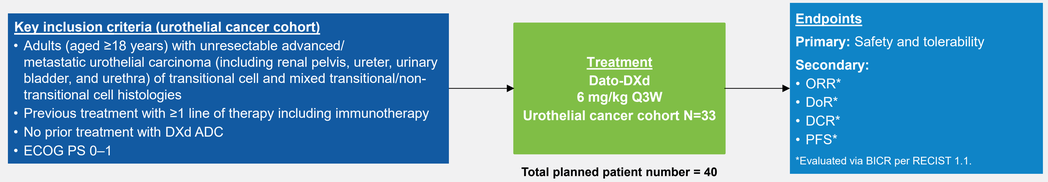
Corresponding author email address: ADrakaki@mednet.ucla.edu

Methods

Study design

- TROPION-PanTumor01 (NCT03401385) is an ongoing phase 1, multicenter, open-label, 2-part dose-escalation and -expansion study evaluating Dato-DXd in patients with previously treated advanced solid tumors, including urothelial cancer (renal pelvis, ureters, urinary bladder, and urethra)
- The study design for this patient cohort is shown in **Figure 1**
- The response evaluable population in this ongoing study included patients who received at least one dose of Dato-DXd and had tumor assessments at both baseline and post-baseline; patients who discontinued Dato-DXd and had baseline tumor assessment but lacked post-baseline assessment were also included

Figure 1. TROPION-PanTumor01 study design



Results

Patients

Table 1. Baseline characteristics and prior treatments

Characteristic	All patients (N=33)
Age, median (range), years	67 (46–83)
Female, n (%)	7 (21)
ECOG PS, n (%)	
0	18 (55)
1	15 (46)
Site, n (%)	
USA	21 (64)
Japan	12 (36)
Number of prior lines of therapy, n (%)[a]	
1	1 (3)
2	6 (18)
≥3	25 (76)
Prior systemic treatment, n (%)	32[a] (97)
Immune checkpoint inhibitors	31 (94)
Platinum-based chemotherapy	27 (82)
Taxanes	5 (15)
Enfortumab vedotin	26 (79)
History of brain metastasis, n (%)	
Yes	1 (3)
No	31 (94)

[a]Data for one patient was missing at DCO. The maximum number of prior therapies was 6.

- At data cut-off (DCO, September 14, 2023), thirty-three patients were enrolled and treated with Dato-DXd 6 mg/kg Q3W (**Table 1**)
- Sixteen (49%) patients had treatment ongoing, and 17 (52%) patients had discontinued, primarily due to disease progression
- The median study duration was 9.0 (range, 0–21) months and the median treatment duration was 2.8 (range, 0.7–12.8) months

Efficacy

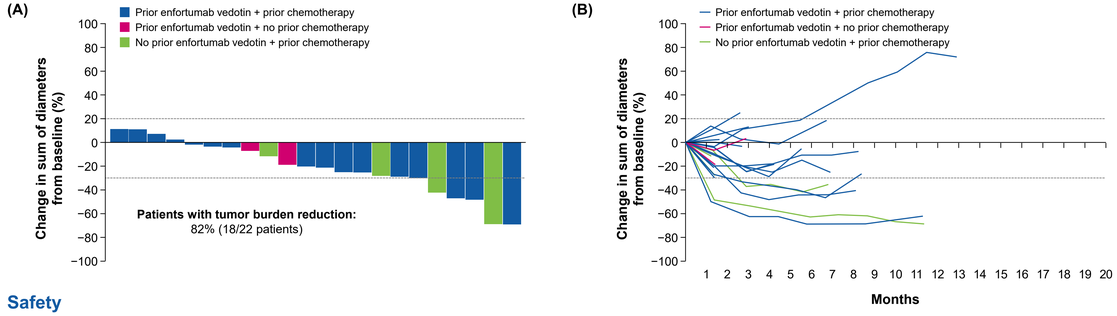
Table 2. Tumor response by BICR

Response, n (%)	All response-evaluable patients (N=26)[a]	Patients with 2 post-baseline scans (N=22)[b]
ORR (confirmed)	5 (19.2)	5 (22.7)
(95% CI)	(6.6, 39.4)	(7.8, 45.4)
CR	1 (3.8)	1 (4.5)
PR	4 (15.4)	4 (18.2)
Non-CR/non-PD	1 (3.8)	1 (4.5)
SD	15 (57.7)	11 (50.0)
DCR	21 (80.8)	17(77.3)
(95% CI)	(60.6, 93.4)	(54.6, 92.2)
PD	3 (11.5)	3 (13.6)
NE	2 (7.7)[c]	2 (9.1)[c]

[a]7 patients without tumor assessment at baseline and/or a post-baseline were excluded from the response-evaluable population. [b]Patients who discontinued study treatment before 2 scans were also included. [c]NE due to no adequate post-baseline tumor assessment.

- The abstract (ASCO GU 2024, abstract #603), presented efficacy from 18 patients who were enrolled and response-evaluable at the May 18, 2023, DCO. Confirmed ORR was 27.8% (95% CI, 9.7–53.5; 5/18 patients)
- At the September 14, 2023, DCO presented in this poster, among 26 response-evaluable patients (regardless of follow-up time), the confirmed ORR was 19.2% (95% CI, 6.6–39.4; **Table 2**)
  - Duration of response ranged from 2.6 to 10.1+ months (+ indicates ongoing treatment at DCO)
  - In total, 80% (95% CI, 20–97) of responders had ongoing responses for ≥6 months per Kaplan-Meier estimate
- Among 22 patients with at least 2 post-baseline tumor assessments, ORR was 22.7% (95% CI, 7.8–45.4)
- Tumor burden reduction was observed in 82% of evaluable patients (**Figure 2A**)

Figure 2. Change in tumor burden from baseline per BICR (A) Best change (N=22) and (B) Change over time (N=22)



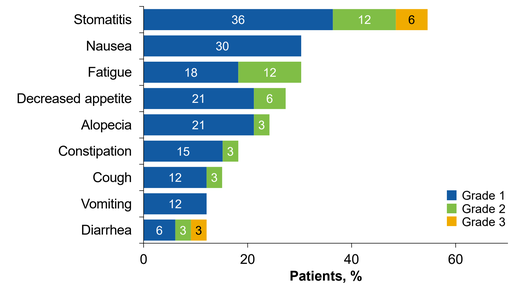
Safety

Table 3. Safety summary

TEAE, n (%)	All patients (N=33)
TEAEs	
Any grade	30 (91)
Grade ≥3	11 (33)
Drug-related	29 (88)
Grade ≥3	3 (9)
Serious TEAEs	
Any grade	7 (21)
Grade ≥3	6 (18)
Drug-related	0
Dose adjustments due to TEAEs	
Dose reduction	5 (15)
Dose interruption	9 (27)
Treatment discontinuation	2 (6)
TEAEs associated with death	0

- Any grade and grade ≥3 TEAEs were observed in 30 (91%) and 11 (33%) patients, respectively (**Table 3**)
  - No TEAEs associated with death were observed
- Drug-related TEAEs of any grade and grade ≥3 occurred in 29 (88%) and 3 (9%) patients
  - No drug-related serious TEAEs were reported
  - Nine (27%) patients had a TEAE associated with dose interruption and 5 (15%) patients had a TEAE associated with dose reduction

Figure 3. All-cause TEAEs occurring in ≥10% of patients[a]



[a]Owing to rounding, summed rates may not reflect total percentage of TEAEs.

- The most common TEAEs were stomatitis (55%), nausea (30%), and fatigue (30%) (**Figure 3**)
  - The most common grade ≥3 TEAEs were stomatitis (6%) and diarrhea (3%)
- The majority of TEAEs were grade 1–2; no grade 4 or 5 TEAEs were reported
- 61% of patients experienced an AESI, the majority of which were grade 1–2 (**Table 4**)

Table 4. AESI[a]

	AESIs				AESIs leading to:		
n (%)	Any grade	Grade 1	Grade 2	Grade 3[b]	Dose reduction	Dose interruption	Treatment discontinuation
Oral mucositis/stomatitis[a]	18 (55)	12 (36)	4 (12)	2 (6)	1 (3)	1 (3)	0
Ocular surface events[b]	5 (15)	3 (9)	2 (6)	0	1 (3)	2 (6)	0
IRR	2 (6)	1 (3)	1 (3)	0	0	1 (3)	0
Adjudicated drug-related ILD[c]	1 (3)	0	1 (3)	0	0	1[c] (3)	0

[a]Events included the selected PTs oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. [b]Ocular surface events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. [c]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).

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Abbreviations

ADC, antibody-drug conjugate; AESI, adverse event of special interest; BICR, blinded independent central review; CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IgG1, immunoglobulin G1; ILD, interstitial lung disease; IRR, infusion-related reaction; mAb, monoclonal antibody; NE, non-evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PT, preferred terms; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event; Topo-I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

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