

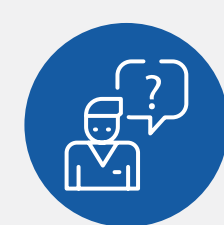
TROPION-Urothelial03: A Phase 2/3 study of datopotamab deruxtecan (Dato-DXd) + platinum chemotherapy vs gemcitabine + platinum chemotherapy in participants with locally advanced or metastatic urothelial carcinoma with progression on or after enfortumab vedotin + pembrolizumab

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Plain language summary



Why are we performing this research?

- The standard first treatment for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) is enfortumab vedotin (EV) combined with pembrolizumab. However, this therapy stops working for many patients^{1,2}
- Chemotherapy using platinum drugs may be recommended as the next treatment option, but only modest benefits are seen, and more effective and tolerable treatments are urgently needed³⁻⁵
- Datopotamab deruxtecan (Dato-DXd) is an antibody–drug conjugate that consists of an antibody (datopotamab) and an anticancer drug (DXd), joined via a stable cleavable linker⁶
- This study, called TROPION-Urothelial03, will compare Dato-DXd given with platinum-based chemotherapy versus a combination of chemotherapy in patients with la/mUC whose cancer has worsened while or after being treated first with EV and pembrolizumab⁷



How are we performing this research?

- The Phase 2 part of the study will determine the optimal dose of Dato-DXd to be used in the Phase 3 part of the study. In the Phase 3 part of the study, patients will receive either Dato-DXd with platinum-based chemotherapy or gemcitabine with platinum-based chemotherapy⁷
- The main aims of the study are to see how long patients who are given Dato-DXd stay alive overall and remain alive without their cancer growing or spreading⁷



Who will participate in this study?

- We are planning on enrolling approximately 630 patients with la/mUC whose cancer has worsened while receiving or after being treated first with EV and pembrolizumab⁷



Where can I access more information?

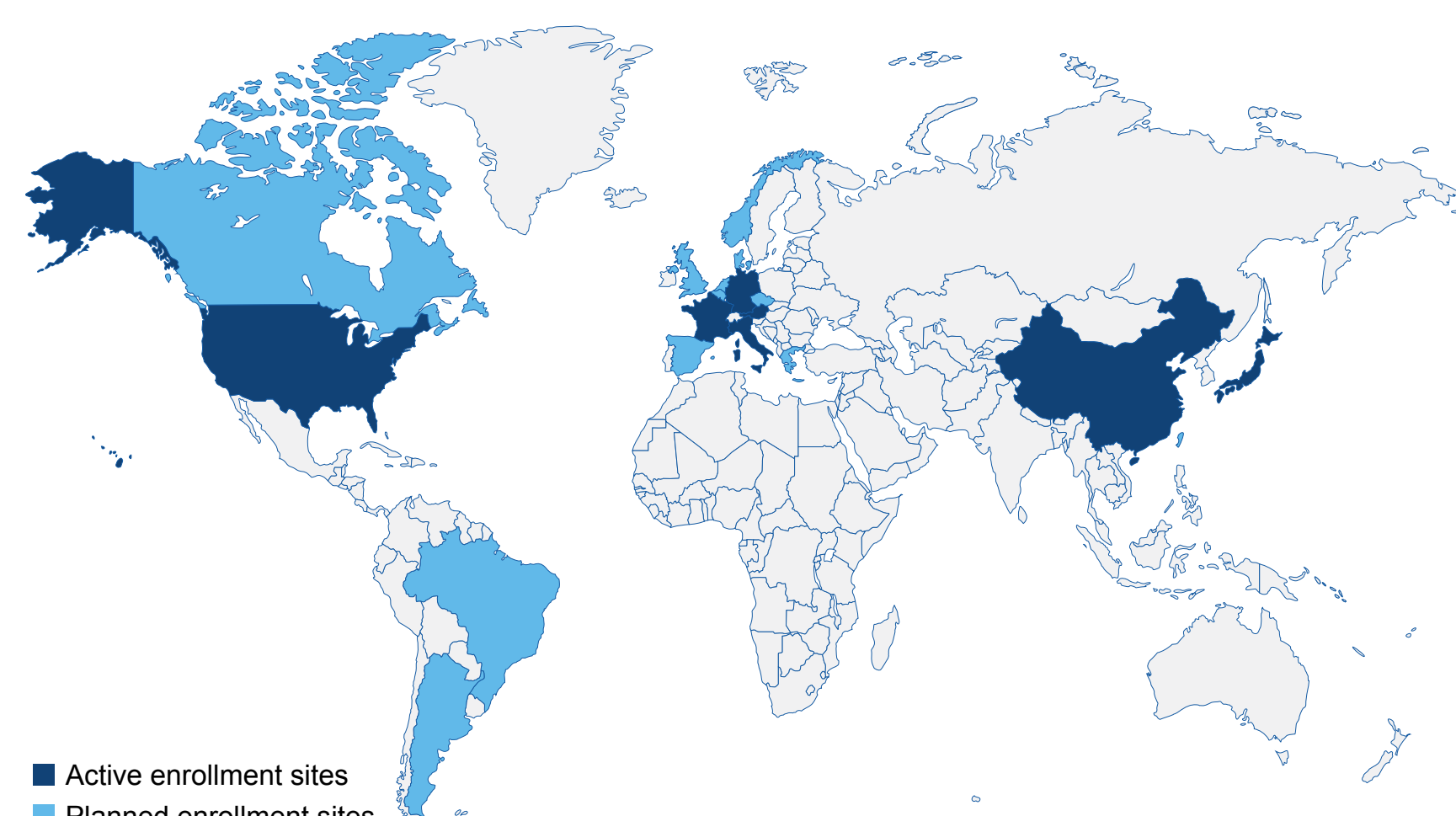
- The first results are expected to be available in mid-2029, with the study expected to end in 2030.⁷ For more information about TROPION-Urothelial03, please visit <https://clinicaltrials.gov/study/NCT07129993>. You may also speak to your doctor about clinical studies

1. Powles T, et al. *N Engl J Med*. 2024;390:875–888. 2. Stecca CE, et al. *Can Urol Assoc J*. 2024;18:379–390. 3. Powles T, et al. *Ann Oncol*. 2024;35:485–490. 4. Sternschuss M, et al. *J Clin Oncol*. 2025;43(Suppl 16). Abstract 4573. 5. Kim J, et al. *J Clin Oncol*. 2025;43(Suppl 16). Abstract 785. 6. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–2340. 7. ClinicalTrials.gov. <https://clinicaltrials.gov/study/NCT07129993>. Accessed May 13, 2026.

Background

- Although first-line (1L) therapy with the antibody–drug conjugate (ADC) enfortumab vedotin (EV) plus pembrolizumab has improved outcomes for patients with locally advanced or metastatic urothelial carcinoma (la/mUC),^{1–4} approximately half of patients experience disease progression within 2 years of initiating treatment^{1,5}
- While there is limited evidence to guide the optimal selection of second-line therapies post–disease progression on or after 1L EV plus pembrolizumab, current guideline recommendations include platinum-based chemotherapy,³ which has demonstrated modest efficacy in studies to date (complete response, 2.9–10.0%; median duration of response, 3.8 months; median progression-free survival, 3.4–4.4 months; median overall survival, 8.0–12.0 months)^{6,7}
- Trophoblast cell surface antigen 2 (TROP2) is a glycoprotein highly expressed in several epithelial tumors, including urothelial carcinoma^{8,9}
- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC comprising an anti-TROP2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload (DXd), designed to induce selective tumor-cell death and reduce systemic exposure to the payload¹⁰
- Dato-DXd has demonstrated durable efficacy and a manageable safety profile in patients with la/mUC both as monotherapy (TROPION-PanTumor01 [NCT03401385]) and in combination with immunotherapy (TROPION-PanTumor03 [NCT05489211])^{11,12}
- Here, we describe TROPION-Urothelial03, a Phase 2/3 trial comparing the efficacy and safety of Dato-DXd plus platinum chemotherapy (carboplatin or cisplatin) vs gemcitabine plus platinum chemotherapy in patients with la/mUC with disease progression on or after 1L EV plus pembrolizumab¹³

Enrollment start: September 2025 | Enrollment is ongoing



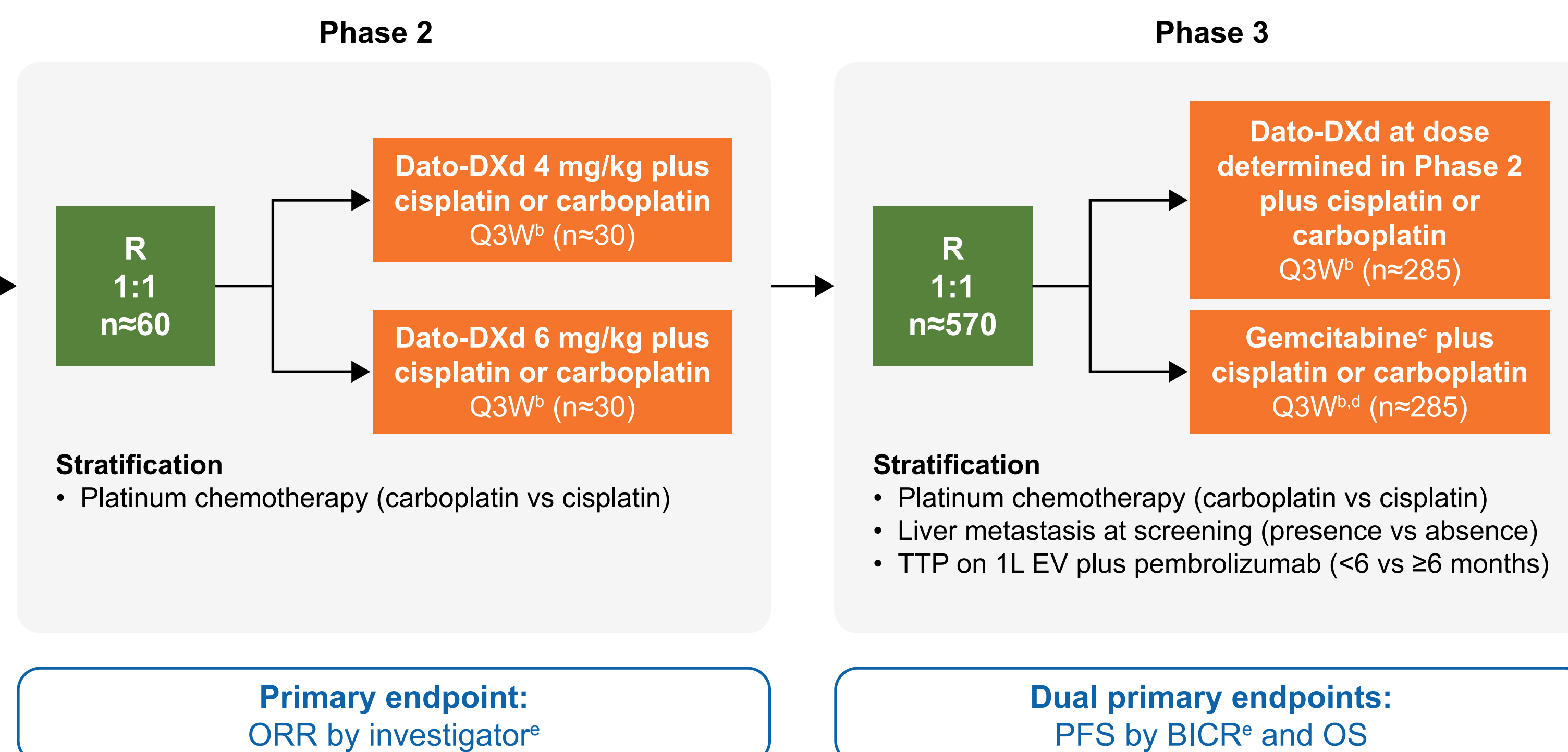
Countries with active or planned enrollment sites (~276 sites)

Active: Austria, China, France, Germany, Italy, Japan, United States
Planned: Argentina, Belgium, Brazil, Canada, Czech Republic, Denmark, Greece, Netherlands, Norway, Spain, Taiwan, United Kingdom

TROPION-Urothelial03 (NCT07129993): a Phase 2/3 global, multicenter, randomized, open-label study

Key inclusion criteria

- Unresectable la/mUC
- Measurable disease on CT/MRI per RECIST 1.1⁴
- ≥18 years of age or minimum legal adult age
- Radiographic progression or relapse during or after 1L EV plus pembrolizumab
- Tumor tissue sample of sufficient quantity from archival or newly obtained tissue
- Eligible to receive cisplatin- or carboplatin-containing chemotherapy
- Eastern Cooperative Oncology Group performance status of 0 or 1



^aAs assessed by investigator. ^bPlatinum treatment up to 6 cycles. After completing 6 cycles of Dato-DXd plus platinum chemotherapy, patients will continue Dato-DXd monotherapy Q3W. Before randomization, platinum chemotherapy (carboplatin or cisplatin) will be assigned per the investigator's assessment of cisplatin eligibility. Cisplatin-eligible patients will receive cisplatin. ^cDay 1 and Day 8. ^dGemcitabine plus cisplatin or gemcitabine plus carboplatin up to 6 cycles. Additional cycles may be allowed in the control group as per local guidelines or local practice. ^ePer RECIST 1.1.

1L, first-line; BICR, blinded independent central review; CT, computed tomography; Dato-DXd, datopotamab deruxtecan; EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial cancer; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTP, time to progression.

Key inclusion criteria

- Adults aged ≥18 years^a
- Histologically or cytologically documented unresectable la/mUC^b
- Tumor tissue sample of sufficient quantity from archival tissue^c or newly obtained pretreatment biopsy for exploratory biomarker testing
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Eligible to receive cisplatin- or carboplatin-containing chemotherapy
- Radiographic progression or relapse during or after 1L EV plus pembrolizumab
- Adequate treatment washout period prior to randomization^d
- Measurable disease on CT/MRI per RECIST 1.1 assessed by investigator
- Adequate organ function based on baseline laboratory testing

^aIf the legal age of consent is >18 years of age, local regulatory requirements will be followed. ^bPatients with la/mUC of the bladder, renal pelvis, ureter, or urethra. Patients with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible if histology is predominantly urothelial. ^cCollected after most recent anticancer treatment and within 12 months before informed consent date is preferred. ^dDefined as major surgery (≥3 weeks [or ≥2 weeks for low-invasive cases]); radiation therapy (≥4 weeks [or ≥2 weeks if palliative single site stereotactic radiation therapy without abdominal radiation]); antibody-based anticancer therapy (≥4 weeks); anticancer chemotherapy (non-antibody-based therapy) and/or retinoid therapy (≥2 weeks or 5 times the half-life of the chemotherapeutic agent, whichever is longer); chloroquine/hydroxychloroquine (>14 days).

1L, first-line; CT, computed tomography; EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial cancer; MRI, magnetic resonance imaging; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

Key exclusion criteria

- Prior systemic therapy other than the combination of EV plus pembrolizumab for la/mUC
- Prior allogeneic bone marrow or solid organ transplant
- Prior treatment with a TROP2-directed ADC
- Prior brain radiotherapy within 2 weeks or chest radiotherapy within 4 weeks of randomization
- Spinal cord compression or active and untreated CNS metastasis
- History of non-infectious ILD/pneumonitis that required steroids; current or suspected ILD/pneumonitis
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
- Uncontrolled or significant cardiovascular disease or cardiovascular events within 6 months prior to randomization

ADC, antibody–drug conjugate; CNS, central nervous system; EV, enfortumab vedotin; ILD, interstitial lung disease; la/mUC, locally advanced or metastatic urothelial cancer; TROP2, trophoblast cell surface antigen 2.

Abbreviations

1L, first-line; ADC, antibody–drug conjugate; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; EV, enfortumab vedotin; ILD, interstitial lung disease; la/mUC, locally advanced or metastatic urothelial carcinoma; MRI, magnetic resonance imaging; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TROP2, trophoblast cell surface antigen 2; TTP, time to progression; TTR, time to response.

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Disclosures

Matthew D. Galsky has served in a consulting or advisory role for AbbVie, Bristol Myers Squibb, EMD Serono, Gilead Sciences, Janssen, Merck, and Pfizer.

Study endpoints

Primary endpoints

Phase 2	Phase 3
ORR by investigator ^a	PFS by BICR ^a
	OS

Secondary endpoints

Phase 2	Phase 3
DOR ^b	PFS by investigator ^a
PFS ^b	ORR ^a
OS	DOR ^a
TTR ^b	TTR ^a
DCR ^{b,c}	DCR ^{a,e}
Safety ^d	Safety ^d
Immunogenicity of Dato-DXd (antidrug antibodies)	Immunogenicity of Dato-DXd (antidrug antibodies)
Pharmacokinetics	PROs ^f

^aPer RECIST 1.1. ^bBy investigator per RECIST 1.1. ^cProportion of patients with a best overall response of confirmed complete response, partial response, or stable disease. ^dIncluding treatment-emergent adverse events, serious adverse events, and adverse events of special interest (all graded according to the NCI-CTCAE v5.0); deaths; changes from baseline in vital signs; standard clinical laboratory parameters (graded according to the NCI-CTCAE v5.0); electrocardiogram parameters; echocardiogram/multigated acquisition scans; and ophthalmologic findings. ^eBy BICR and investigator per RECIST 1.1. ^fEuropean Organization for Research and Treatment of Cancer Quality of Life Questionnaire–muscle invasive bladder cancer 30 (disease symptoms, quality of life, and functioning).

BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTR, time to response.

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