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Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

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abstract

PURPOSE Locally advanced or metastatic urothelial carcinoma is an incurable disease with limited treatment options, especially for patients who were previously treated with platinum and anti–programmed death 1 or anti–programmed death ligand 1 (PD-1/L1) therapy. Enfortumab vedotin is an antibody–drug conjugate that targets Nectin-4, which is highly expressed in urothelial carcinoma.

METHODS EV-201 is a global, phase II, single-arm study of enfortumab vedotin 1.25 mg/kg (intravenously on days 1, 8, and 15 of every 28-day cycle) in patients with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum chemotherapy and anti–PD-1/L1 therapy. The primary end point was objective response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by blinded independent central review. Key secondary end points were duration of response, progression-free survival, overall survival, safety, and tolerability.

RESULTS Enfortumab vedotin was administered to 125 patients with metastatic urothelial carcinoma. Median follow-up was 10.2 months (range, 0.5 to 16.5 months). Confirmed objective response rate was 44% (95% CI, 35.1% to 53.2%), including 12% complete responses. Similar responses were observed in prespecified subgroups, such as those patients with liver metastases and those with no response to prior anti–PD-1/L1 therapy. Median duration of response was 7.6 months (range, 0.95 to 11.30+ months). The most common treatment-related adverse events were fatigue (50%), any peripheral neuropathy (50%), alopecia (49%), any rash (48%), decreased appetite (44%), and dysgeusia (40%). No single treatment-related adverse events grade 3 or greater occurred in 10% or more of patients.

CONCLUSION Enfortumab vedotin demonstrated a clinically meaningful response rate with a manageable and tolerable safety profile in patients with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum and anti–PD-1/L1 therapies.

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ASSOCIATED CONTENT

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Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Locally advanced or metastatic urothelial carcinoma of the renal pelvis, ureters, bladder, or urethra is an incurable disease with poor long-term survival.[1] Platinum-based therapies are the first-line treatment for most patients, with objective response rates of 41% to 50% and median progression-free survival of 7.6 months.[2-4] In the postplatinum setting, phase III studies of anti–programmed death 1 or anti–programmed death ligand 1 (PD-1/L1) therapy demonstrated objective response rates of 21% and 13%, respectively, with an overall survival advantage compared with second-line chemotherapy demonstrated in one of two studies conducted to date.[5,6]

For patients who have experienced progression after platinum-based therapy and anti–PD-1/L1 therapy, treatment options are limited to chemotherapies that have modest activity.[7] Thus, there is an urgent need for effective and tolerable therapies in patients with locally advanced and metastatic urothelial carcinoma after treatment with platinum and anti–PD-1/L1 therapies.

Enfortumab vedotin is an investigational antibody–drug conjugate that is comprised of a fully human monoclonal antibody conjugated to the clinically validated microtubule-disrupting agent, monomethyl auristatin E (MMAE), via a protease-cleavable linker.[8,9] Enfortumab vedotin targets Nectin-4, a transmembrane protein that belongs to the Nectin family of cell

adhesion molecules involved in cellular processes associated with oncogenesis.[8,10-12] Nectin-4 is highly expressed in several solid tumors, including urothelial, breast, gastric, and lung carcinomas. Expression is weak to moderate in normal skin.[8,13-16] Enfortumab vedotin binds to cells that express Nectin-4 with high affinity, triggering the internalization and release of MMAE in target cells. MMAE disrupts microtubule networks, leading to cell-cycle arrest and apoptotic death of Nectin-4–expressing cells.

The phase I dose escalation and expansion study EV-101 (ClinicalTrials.gov identifier: NCT02091999) demonstrated that enfortumab vedotin, administered on days 1, 8, and 15 of every 28-day cycle, has antitumor activity in previously treated patients with metastatic urothelial carcinoma, including those who received platinum-based chemotherapy and anti–PD-1/L1 therapy.[17] Pharmacokinetic data from this study demonstrate a half-life of approximately 2 days, which supports this dosing schedule.[18] EV-201, a two-cohort, single-arm, phase II study, was designed to establish the efficacy and safety of enfortumab vedotin in patients with locally advanced or metastatic urothelial carcinoma who were previously treated with anti–PD-1/L1 therapy. Cohort 1 enrolled patients who were previously treated with both platinum chemotherapy and an anti–PD-1/L1 therapy, whereas Cohort 2 continues to enroll patients who were previously treated only with an anti–PD-1/L1 therapy. Here, we report results from EV-201 Cohort 1.

METHODS

Study Participants

Patients with locally advanced or metastatic urothelial carcinoma who were previously treated with anti–PD-1/L1 therapy and age 18 years or older were eligible to enroll if they experienced progression during or after their most recent therapy, had an Eastern Cooperative Oncology Group performance status score of 1 or less, and had adequate baseline organ function. Patients with ongoing sensory or motor neuropathy grade 2 or greater, active CNS metastases, or uncontrolled diabetes were excluded. Uncontrolled diabetes was defined as hemoglobin A1C of 8% or greater or hemoglobin A1C of 7% to less than 8% with associated diabetes symptoms—polyuria or polydipsia—that were not otherwise explained. There were no limits for prior lines of therapy, including taxanes. Full eligibility criteria are available in the protocol (Data Supplement).

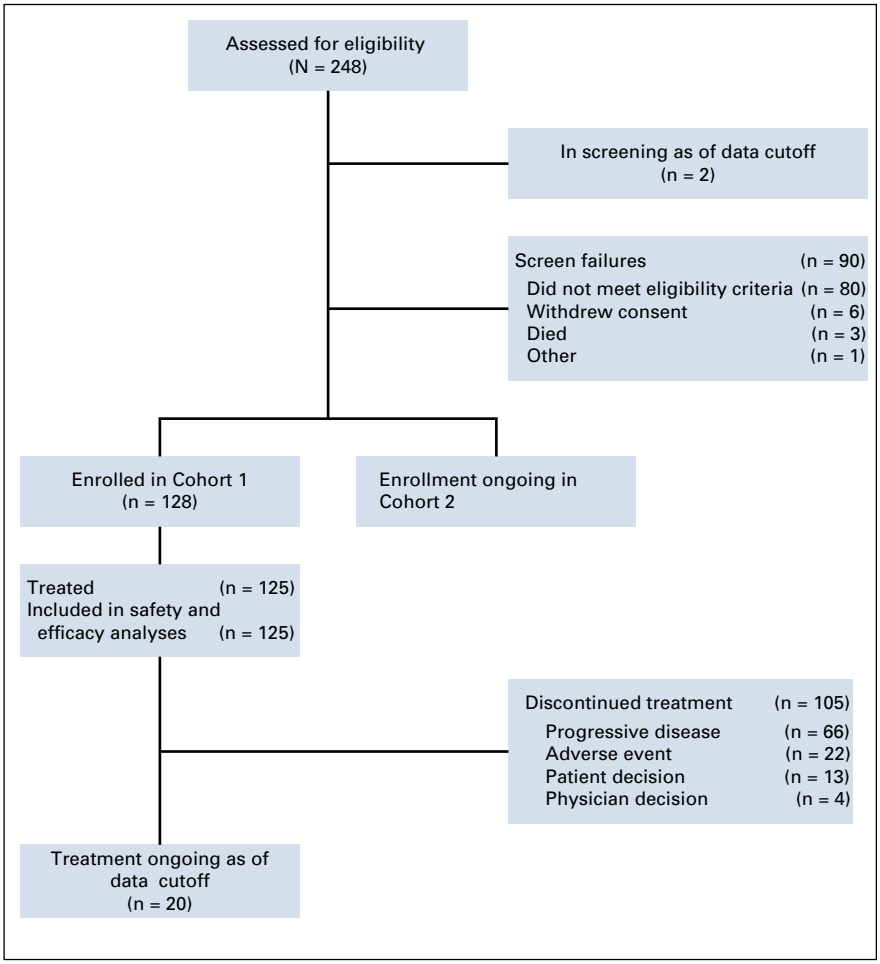

FIG 1. CONSORT diagram. Three patients were discontinued from the study before receiving study treatment; 1 due to clinical deterioration, 1 per patient decision, and 1 due to low hemoglobin levels after screening and enrollment. This latter patient met all eligibility criteria, including adequate hemoglobin level and was enrolled in the study; however, the patient's hemoglobin levels were subsequently found to be low and the investigator withdrew the patient from the study as a result.

Trial Design

EV-201 is a global, single-arm, two-cohort, phase II multicenter study that was designed to assess the efficacy and safety of enfortumab vedotin (Fig 1). Cohort 1 enrolled platinum- and anti–PD-1/L1–treated patients with Eastern Cooperative Oncology Group performance status scores of 1 or less. Platinum treatment was defined as platinum-containing chemotherapy in the neoadjuvant and/or adjuvant setting with recurrent or progressive disease within 12 months of completion, or platinum in the locally advanced or metastatic setting.

Treatment

Patients received enfortumab vedotin 1.25 mg/kg intravenously over approximately 30 minutes on days 1, 8, and 15 of each 28-day cycle. Weight-based dosing was calculated using the patient's actual body weight, with a maximum dose of 125 mg. Dose modifications were permitted to manage treatment-related hematologic and nonhematologic toxicities and are outlined in the protocol (Data Supplement). Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or investigator decision. Additional details are provided in the protocol.

Assessments

Efficacy of enfortumab vedotin was assessed by appropriate imaging (computed tomography or magnetic resonance imaging) every 8 weeks (± 1 week), then every 12 weeks (± 1 week) after 1 year. Time points for response assessments were calculated from cycle 1, day 1. Complete or partial responses, as defined by RECIST version 1.1,[19] were confirmed with repeat scans 4 to 5 weeks after initial response and assessed by blinded independent central review (BICR) and investigator.

Safety assessments included physical and eye examinations, routine chemistry, and hematologic laboratory tests. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Per protocol, certain adverse events observed in the EV-201 study were prespecified for assessment and analysis as composite terms and were observed until resolved, returned to baseline, or became chronic and adequately characterized. These events are summarized here in composite terms of peripheral neuropathy, rash, infusion-related reactions, and hyperglycemia. Expression levels of Nectin-4 and PD-L1 were assessed using validated immunohistochemical assays in archival or fresh tumor samples (Data Supplement).

End Points

The Primary end point was confirmed objective response rate as assessed by BICR. Data cutoff was to be at least 6 months after the last patient in Cohort 1 received his or her first dose. Key secondary end points were duration of response and progression-free survival by BICR and investigator; objective response rate by investigator; and overall survival, safety, and tolerability.

Trial Oversight

The EV-201 trial was designed by the sponsors, with contributions from a steering committee of study investigators. Study protocol and amendments were approved by site independent review boards or ethics committees and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Committee on Harmonization. Written informed consent was obtained from all patients. Safety was monitored by an independent data-monitoring committee and the sponsor. Data were analyzed by sponsor statisticians and interpreted by authors and the sponsor.

Statistical Analysis

Objective response rate and its two-sided 95% CI were calculated using the Clopper-Pearson method. For time-to-event end points, median survival time was estimated using the Kaplan-Meier method and the associated 95% CI was calculated using the complementary log-log transformation.

With 100 patients in Cohort 1, there is a 98% chance of observing ORR with lower-limit of the exact 95% CI excluding a historical response rate of 10%,[20] if the true ORR is 25%. The complete statistical analysis plan is available along with the protocol in the Data Supplement.

RESULTS

Study Participants

There were 51 sites in the United States and Japan during the enrollment of Cohort 1 (October 8, 2017 to July 2, 2018). A total of 128 patients with metastatic urothelial carcinoma who were previously treated with platinum and anti–PD-1/L1 therapy were enrolled. Three patients withdrew before treatment and 125 were treated with enfortumab vedotin. As of March 1, 2019, median follow-up was 10.2 months (range, 0.5 to 16.5 months). Twenty patients (16%) remain on treatment and 45 patients (36%) are in follow-up for progression or survival. Median duration of treatment was 4.6 months, and maximum duration was 15.6 months and ongoing at data cutoff. All patients who were treated had metastatic disease. Demographic and disease characteristics were representative of patients with metastatic urothelial carcinoma (Table 1 and Appendix Table A1, online only). Median age was 69 years (range, 40 to 84 years), with 27% age 75 years or older. Eighty-one percent of patients had one or more adverse prognostic factor.[21] Visceral metastases were present in 90% of patients and 40% had liver metastases. Patients were heavily pretreated, with a median of three systemic therapies (range, one to six therapies) for locally advanced or metastatic disease; 26% received taxanes. Patients with only one previous therapy received platinum and anti–PD-1/L1

TABLE 1. Demographic and Disease Characteristics at Baseline

Characteristic	Patients (N = 125)
Male sex	88 (70)
Age, years	
Median	69
Min, max	40, 84
Age group, years	
< 75	91 (73)
≥ 75	34 (27)
Region	
North America	117 (94)
Asia	8 (6)
ECOG performance status*	
0	40 (32)
1	85 (68)
Primary tumor location	
Bladder/other	81 (65)
Upper tract†	44 (35)
Histology type	
Urothelial carcinoma only	84 (67)
Urothelial carcinoma with squamous differentiation	15 (12)
Urothelial carcinoma with other histologic variants	26 (21)
Current extent of disease	
Metastatic	125 (100)
Metastasis sites	
Lymph nodes only	13 (10)
Visceral disease‡	112 (90)
Bone	51 (41)
Liver	50 (40)
Lung	53 (42)
No. of prior systemic therapies in locally advanced or metastatic setting§	
Median	3
Min, max	1, 6
≥ 3	63 (50)
Best response to PD-1/L1–containing therapy	
Responder	25 (20)
Nonresponder	100 (80)
PD-L1 status by combined positive score‖	
< 10	78/120 (65)
≥ 10	42/120 (35)

(continued on following page)

therapy in combination. Additional details are available in Appendix Table A1. Most patients (80%) did not respond to prior anti–PD-1/L1 therapy. All tumor biopsy samples from the 120 patients who had adequate tissue for testing had detectable Nectin-4 expression.

Efficacy

Confirmed objective response rate was 44% (95% CI, 35.1% to 53.2%) as assessed by BICR, including a 12% complete response rate (Table 2). Median time to response was 1.84 months (range, 1.2 to 9.2 months), with most responses identified by the first disease assessment. Median duration of response was 7.6 months (range, 0.95 to 11.30+; 95% CI, 4.93 to 7.46; Appendix Fig A1, online only). At the time of analysis, 44% of all responders had ongoing responses. Duration of response ranged from 3.6+ to 11.3+ months for patients with complete responses (Fig 2A). Investigator-assessed responses, including objective response rate, duration of response, tumor reduction, and progression-free survival, were similar to those assessed by BICR (Data Supplement; Appendix Table A2, online only; and Appendix Figs A2, A3, and A4, online only).

Responses across all subgroups analyzed were consistent with overall study results. Objective responses occurred regardless of patients' responses to prior anti–PD-1/L1 therapy (56% in responders and 41% in nonresponders). Similar responses were observed in patients with poor prognostic characteristics, including liver metastases (38%), and three or more prior lines of therapy (41%; Fig 3).

Target lesions were reduced in a majority of evaluable patients (84%; Fig 2B). Estimated median progression-free survival was 5.8 months (95% CI, 4.9 to 7.5 months; Appendix Fig A5, online only), and estimated median overall survival was 11.7 months (95% CI, 9.1 months to not reached; Appendix Fig A6, online only).

Safety

The most common treatment-related adverse events were fatigue (50% all grade and 6% grade ≥ 3), alopecia (49% all grade), decreased appetite (44% all grade and 1% grade ≥ 3), dysgeusia (40% all grade and none grade ≥ 3), and peripheral sensory neuropathy (40% all grade and 2% grade ≥ 3; Table 3). The most common grade 3 or greater treatment-related adverse events were neutropenia (8%), anemia (7%), and fatigue (6%). Febrile neutropenia (4%) was the most common serious treatment-related adverse event; there was no routine growth factor use. A full listing of adverse events is available in Appendix Tables A3 and A4 (online only). Treatment-related adverse events led to dose reductions in 32% of patients and discontinuation in 12% of patients. Peripheral sensory neuropathy was the most common treatment-related adverse event that led to dose reduction (9%) and discontinuation (6%).

TABLE 1. Demographic and Disease Characteristics at Baseline (continued)

Characteristic	Patients (N = 125)
Nectin-4 expression level, H-score‖¶	
Median	290
Max, min	14, 300

NOTE. Data are represented as No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; PD-1/L1, programmed death 1 or programmed death ligand 1.

*ECOG performance status scale ranges from 0 to 5, with 0 indicating that the patient is fully active with no restrictions, 1 that the patient is ambulatory and able to carry out work of a light or sedentary nature but restricted in physically strenuous activity, and higher numbers indicating greater disability.

†Including renal pelvis, ureter, and kidney.

‡A patient may have metastatic disease in more than one location.

§Including anti-PD-1/L1–containing therapy in the neoadjuvant/adjuvant setting with progression or recurrence within 3 months after therapy completion, or platinum-based therapy in the neoadjuvant/adjuvant setting with progression or recurrence within 12 months after therapy conclusion.

‖Five patients did not have tumor samples evaluable for PD-L1 or Nectin-4 expression levels.

¶Nectin-4 levels were assessed by immunohistochemistry in tumor biopsies. Immunohistochemistry images were scored by a pathologist using the H-score method (H-score = [percentage of strong positive tumor cells × 3] + [percentage of moderate positive tumor cells × 2] + [percentage of weak positive tumor cells × 1]). A score of 0 indicates no expression and a score of 300 indicates the maximum possible expression with this assay.

TABLE 2. Summary of Responses Per Blinded Independent Central Review

Response	Patients (N = 125)
Objective response rate	55 (44)
95% CI*	35.1 to 53.2
Best overall response†	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable‡	12 (10)

NOTE. Data are presented as No. (%).

*Computed using the Clopper-Pearson method.[22]

†Best overall response according to RECIST v1.1.

‡Includes 10 patients who did not have any response assessment postbaseline, one patient who had uninterpretable postbaseline assessment, and one patient whose postbaseline assessment did not meet the minimum interval requirement for stable disease.

Peripheral neuropathy, rash, hyperglycemia, and infusion-related reactions were prespecified for analysis as composite terms (Appendix Table A5, online only). A summary of time to onset and time to resolution for these events is available in Appendix Table A6 (online only). Treatment-related peripheral neuropathy occurred in 50% of patients, almost all (94%) of which were grade 2 or less. Peripheral sensory neuropathy was more common (44%) than motor neuropathy (14%). Of the 42 patients with peripheral neuropathy at enrollment, 20 (48%) did not experience worsening from baseline. Most patients (76%) with peripheral neuropathy had resolution or ongoing grade 1 peripheral neuropathy at last follow-up.

Treatment-related rash—as a composite term—occurred in 48% of patients, most of which were low grade (75% grade ≤ 2) with onset in the first treatment cycle. Two patients discontinued treatment as a result of rash, one of whom experienced a grade 3 rash reported as Stevens-Johnson syndrome. Onset of symptoms for this event was 4 days after the initial dose and the rash resolved after the discontinuation of enfortumab vedotin and treatment with systemic corticosteroids. Of all patients who experienced rash, 73% experienced complete resolution and 20% had some improvement at last follow-up. Most patients (75%) with ongoing rash had grade 1 at last follow-up. Three patients had infusion site extravasation, of which two cases were considered serious. All patients with extravasation recovered completely and were able to continue treatment.

Treatment-related hyperglycemia occurred in few patients (11%), regardless of known hyperglycemia at baseline. Nineteen patients had hyperglycemia at baseline and, of these, 68% did not develop treatment-related events. Of patients without hyperglycemia at baseline, 8% developed treatment-related hyperglycemia. Hyperglycemia in seven of 14 patients with these events was grade 2 or less. The single patient with grade 4 hyperglycemia did not have known baseline hyperglycemia and, per protocol, treatment was discontinued. The patient later recovered and had no ongoing need for insulin or oral hypoglycemic agents. This was the only discontinuation as a result of hyperglycemia. Among patients who experienced hyperglycemia, 57% achieved complete resolution and 14% experienced some improvement.

There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment related. This death was confounded by prolonged high-dose corticosteroid use and suspected *Pneumocystis jiroveci* pneumonia.

DISCUSSION

In patients with metastatic urothelial carcinoma who were previously treated with both platinum chemotherapy and anti–PD-1/L1 therapy, enfortumab vedotin treatment led to a 44% objective response rate, including a 12% complete response rate and a 7.6-month duration of response. Most responses to enfortumab vedotin occurred rapidly.

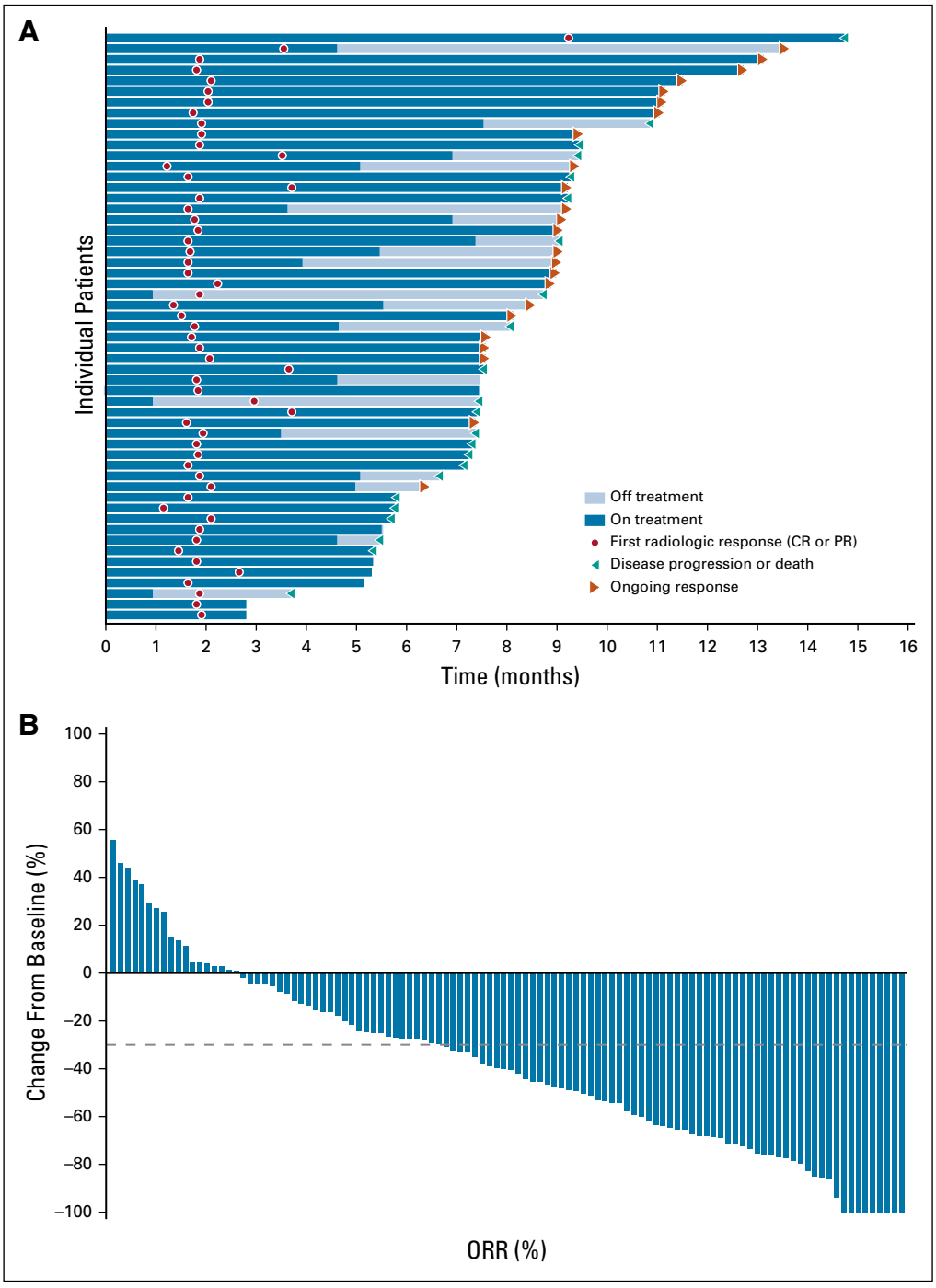

FIG 2. Response among patients with metastatic urothelial carcinoma per blinded independent central review. (A) Swimmer plot of the objective responses (n = 55) (according to RECIST v1.1.) from the start of treatment to disease progression, as determined by blinded independent central review, or death. At the time of analysis, 44% of responders had ongoing responses. (B) Waterfall plot of the best percentage of change from baseline in the sum of the diameters of target lesions as identified per RECIST v1.1. Target lesions were reduced in 84% of patients (92 of 110) who were evaluable—that is, had target lesions and adequate postbaseline assessment). Dashed line indicates threshold for partial response (−30%), but is not necessarily indicative of response. CR, complete response; ORR, overall response rate; PR, partial response.

Although this was a single-arm study, which limits interpretation, responses observed here with enfortumab vedotin were remarkably consistent with the prior phase I study EV-101.[17]

In the control arms of recent randomized phase III trials in the postplatinum setting, objective response rates in patients who were treated with antimicrotubule agents ranged from 11% to 13%, including 3% complete responses.[5,6] Unlike these phase III trials, which primarily enrolled patients with only prior platinum therapy, patients who received enfortumab vedotin in this study were more heavily pretreated, with one half of patients receiving three or more lines of therapy, one of which was an anti-PD-1/L1 therapy. In a subset of patients who were previously treated with both platinum and anti–PD-1/L1 therapy from a randomized phase III trial, docetaxel had a 10.5% response rate.[23] Although the single-arm nature of EV-201 limits the ability to compare the activity of enfortumab vedotin with standard antimicrotubule chemotherapy, differences in observed response rates (44%) and complete response rates (12%), as well as the consistent results across EV-101 and EV-201, suggest that enfortumab vedotin possesses

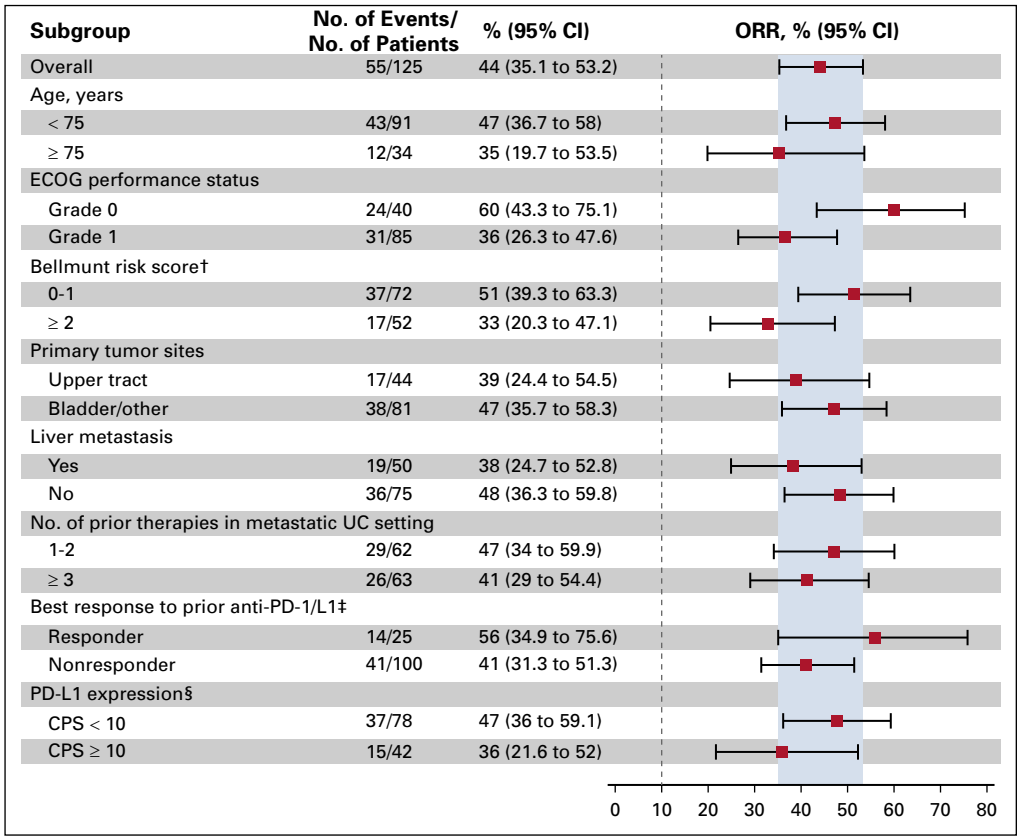

FIG 3. Objective response in key prespecified subgroups per blinded independent central review. This prespecified subgroup analysis was performed on the full analysis set of all patients who received any amount of enfortumab vedotin (N = 125). Historical control response rate is 10%, as indicated by dashed line.[20] The programmed death ligand 1 (PD-L1) combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression of the total number of tumor cells. The upper tract was defined as the renal pelvis, ureter, and kidney. Data are given as No. (%), unless otherwise noted. (†) Bellmunt risk score was not available for 1 patient. (‡) Anti-PD-1 or anti-PD-L1 therapy. (§) Five patients did not have tumor samples evaluable for PD-L1 expression levels. ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; UC, urothelial carcinoma.

antitumor effects significantly beyond conventional chemotherapy. In fact, the objective response rate of enfortumab vedotin monotherapy in this study is similar to that of gemcitabine and carboplatin in the first-line setting, which suggests that treatment earlier in the disease course should be explored in clinical trials.[3]

Enfortumab vedotin also had consistent clinical activity across all subgroups analyzed, including patients with traditionally challenging features, such as liver metastases or other poor prognostic factors. Responses were observed regardless of previous response to anti–PD-1/L1 therapy. These data demonstrate the ability of enfortumab vedotin to elicit responses across a broad range of patients with different disease characteristics.

Enfortumab vedotin was generally well tolerated in this patient population; most treatment-related adverse events were of mild to moderate severity. No single treatment-related adverse event grade 3 or greater occurred in 10% or more of patients, and there were relatively few discontinuations because of a treatment-related adverse event. One treatment-related death occurred outside of the safety reporting period and there were no other treatment-related deaths.

Peripheral neuropathy observed with enfortumab vedotin was generally low grade and manageable. Most patients who developed peripheral neuropathy had either resolution or symptoms ongoing at grade 1 at last follow-up. Peripheral neuropathy is a known toxicity associated with MMAE-containing antibody–drug conjugates, such as brentuximab vedotin[24]; however, these two MMAE-containing antibody–drug conjugates have distinct targets in different patient populations. Therefore, on-target toxicities are expected to differ.

Because enfortumab vedotin targets Nectin-4, which is expressed in skin,[8] rash is an anticipated on-target toxicity. Rashes observed with enfortumab vedotin were generally low grade and manageable, often demonstrating a maculopapular and diffuse appearance. Management included topical corticosteroids, oral antihistamines, and, in some cases, systemic corticosteroids, as well as enfortumab

TABLE 3. Summary of Adverse Events in Patients Receiving Enfortumab Vedotin

Variable	Patients (N = 125)	
Any adverse event	125 (100)	
Treatment-related adverse events	117 (94)	
Grade ≥ 3 treatment-related adverse events	68 (54)	
Treatment-related serious adverse events	24 (19)	
Treatment-related adverse events resulting in treatment discontinuation	15 (12)	
Treatment-related adverse events leading to death*	0 (0)	
Treatment-related adverse events occurring in ≥ 20% (preferred term)	Any Grade	Grade ≥ 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

NOTE. Data are presented as No. (%).

*There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment related.

vedotin dose reductions and delays. Nearly all patients with rash had resolution or improvement and most ongoing treatment-related rashes were grade 1 at last follow-up. The one reported case of Stevens-Johnson syndrome may have been confounded by the direct effects of enfortumab vedotin on Nectin-4 in skin. Hyperglycemia was much less common than rash or peripheral neuropathy, and most patients experienced resolution or improvement at last follow-up. Treatment-related hyperglycemia occurred regardless of known hyperglycemia at baseline and the underlying etiology remains unclear but is not likely to be an on-target effect.

An ongoing phase III trial comparing enfortumab vedotin monotherapy with single-agent chemotherapy in patients with prior platinum and anti-PD-1/L1 therapy may establish the survival benefit of enfortumab vedotin in this patient population (EV-301; ClinicalTrials.gov identifier: NCT03474107). The EV-201 study is also actively enrolling a second cohort (Cohort 2) of patients who have received prior anti–PD-1/L1 therapy and are cisplatin ineligible without prior platinum treatment to determine if a similar benefit will be observed. In addition, enfortumab vedotin is being evaluated in a broader population of patients with urothelial carcinoma, including in the first-line setting where it is being studied in combination with anti–PD-1 and/or platinum-based therapies (EV-103; ClinicalTrials.gov identifier: NCT03288545). In this study, enfortumab vedotin is administered on days 1 and 8 of a 21-day cycle to coincide with the administration of the other agents. Nectin-4 is also expressed in other tumor types, and enfortumab vedotin may be explored in other solid tumors.[8]

In conclusion, enfortumab vedotin is the first antibody–drug conjugate targeting Nectin-4 in clinical development, and the antitumor activity observed in EV-201 validates Nectin-4 as a therapeutic target in urothelial carcinoma. In Cohort 1 patients who previously received platinum and anti–PD-1/L1 therapies, enfortumab vedotin has a 44% objective response rate and a 12% complete response rate. Data reported here demonstrate that enfortumab vedotin has the potential to change the treatment landscape of metastatic urothelial carcinoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

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No other potential conflicts of interest were reported.

APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

EV-201 Investigators

The following investigators (listed by country) participated in the EV-201 study:

France: Yohann Loriot; **Germany:** Jens Bedke; **Italy:** Andrea Necchi; **Japan:** Satoshi Fukasawa, Satoshi Fukasawa, Yasuhiro Hashimoto, Junichi Inokuchi, Hiro-omi Kanayama, Takahiro Kojima, Ryuichi Mizuno, Kazuo Nishimura, Wataru Obara, Yoshihiko Tomita, Yoshiaki Yamamoto, Akira Yokomizo, and Kazuhiro Yoshimura; **the Netherlands:** Michiel van der Heijden; **South Korea:** Yu Jung Kim, Hyo Jin Lee, Jae Lyun Lee, Se Hoon Park, and Sang Joon Shin; **Spain:** Ignacio Duran; **United States:** Leonard Appleman, Arjun Balar, Britt Bolemon, John Burke, Daniel Chong, Jorge Darcourt, Nancy Davis, Christopher DiSimone, Robert Dreicer, Nicholas Farrell, Mark Fleming, Chunkit Fung, Matthew Galsky, Noah Hahn, Elisabeth Heath, Thomas Hutson, William Kelly, Nataliya Mar, Bradley McGregor, Megan McNamara, Amir Mortazavi, Samuel Myrick, Peter O'Donnell, Moshe Ornstein, Chong-Xian Pan, Daniel Petrylak, Joel Picus, David Quinn, Arash Rezazadeh, Jonathan Rosenberg Ian Schnadig, David Shaffer, Parminder Singh, Mark Stein, Jennifer Suga, Nicholas Vogelzang, Jeffrey Yorio, Evan Yu, and Jingsong Zhang.

Methods

Patient populations for analysis. The full analysis set (FAS) included all patients who were enrolled in the study who received any amount of enfortumab vedotin. The FAS was used as the primary analysis set for efficacy end points. The safety analysis set included all patients who received any amount of enfortumab vedotin and was therefore used for all safety analyses.

Biomarker assessments. Samples for exploratory biomarkers were collected at protocol-specified timepoints defined in the schedule of events. Biomarker assessments were not used for patient selection.

Nectin-4 levels were assessed by immunohistochemistry in tumor biopsies. Immunohistochemistry images were scored by a pathologist using the H-score method (H-score = [percentage of strong positive tumor cells $\times$ 3] + [percentage of moderate positive tumor cells $\times$ 2] + [percentage of weak positive tumor cells $\times$ 1]). All evaluable patients (120 of 120) had detectable Nectin-4 on archival or fresh tumor samples by immunohistochemistry as determined by H-score. Nectin-4 expression was high, with a median H-score of 290 (range, 14 to 300).

Programmed death ligand 1 levels were assessed in tumor-infiltrating immune cells using DAKO 22C3 immunohistochemistry to determine PD-L1 combined positive score of less than 10 versus 10 or greater in archival or fresh tumor samples. Overall, 78 (65%) of 120 evaluable patients had a programmed death ligand 1 combined positive score of less than 10.

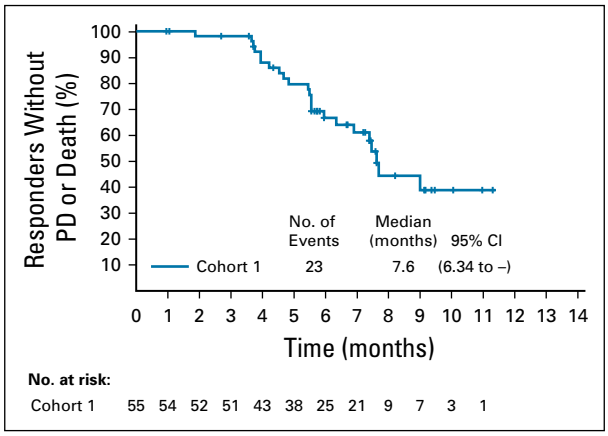

FIG A1. Kaplan-Meier estimate of duration of response for responders per blinded independent central review. PD, progressive disease.

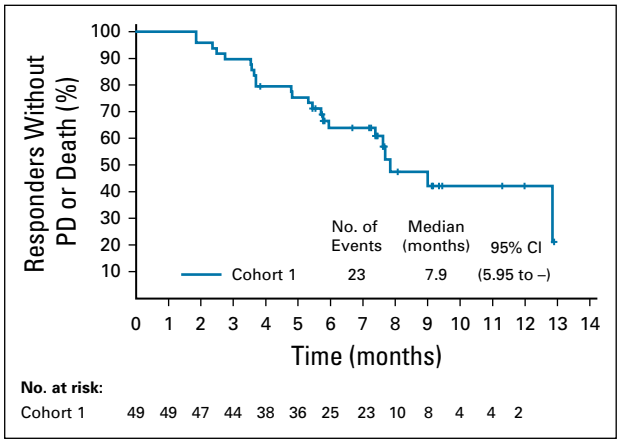

FIG A2. Kaplan-Meier estimate of duration of response for responders per investigator assessment. PD, progressive disease.

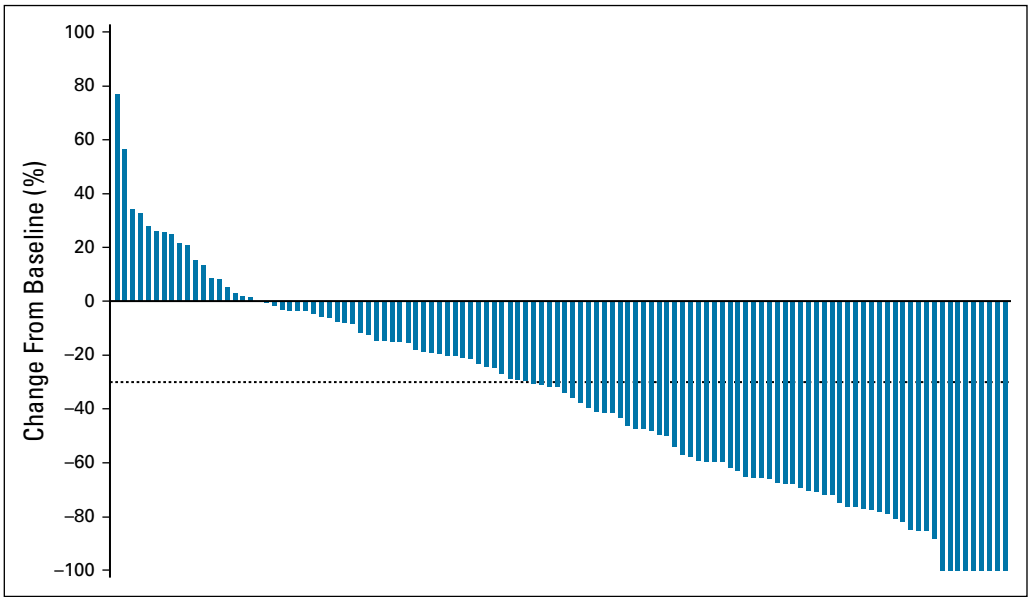

FIG A3. Waterfall plot of the best percentage change from baseline of target lesions per investigator. Waterfall plot of the best percentage of change from baseline in the sum of the diameters of target lesions according to RECIST,[19] version 1.1, per investigator. Overall, 114 patients were evaluable for target lesion response, and 11 patients were not evaluable. Dashed line indicates approximate threshold for partial response (−30%), but is not necessarily indicative of response. ORR, overall response rate.

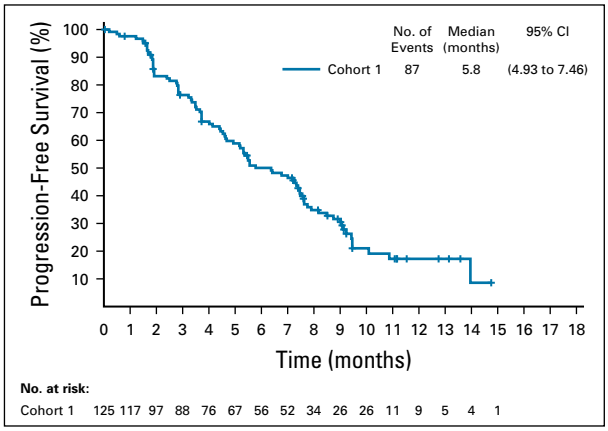

FIG A4. Kaplan-Meier estimate of progression-free survival per investigator in the full analysis set.

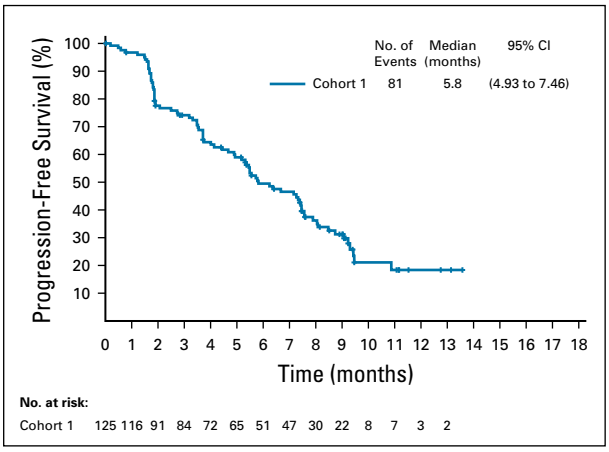

FIG A5. Kaplan-Meier estimate of progression-free survival per blinded independent central review in the full analysis set.

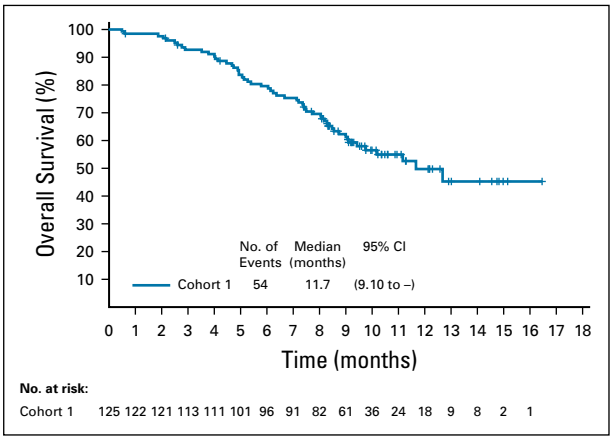

FIG A6. Kaplan-Meier estimate of overall survival in the full analysis set.

TABLE A1. Summary of Demographics and Disease Characteristics at Baseline

Characteristic	Patients (N = 125)
Age, years	
Median	69
Min, max	40, 84
Age group, years	
< 65	45 (36)
≥ 65	80 (64)
< 75	91 (73)
≥ 75	34 (27)
Sex	
Male	88 (70)
Female	37 (30)
Race	
White	106 (85)
Asian	11 (9)
Black or African American	2 (2)
Other	1 (1)
Not reportable	5 (4)
Region	
North America	117 (94)
Asia	8 (6)
Ethnicity	
Hispanic or Latino	5 (4)
Not Hispanic or Latino	118 (94)
Not reportable	2 (2)
Smoking status	
Smoker[a]	82 (66)
Nonsmoker	43 (34)
Height, cm	
Median	172.7
Min, max	146, 193
Weight, kg	
Median	76.1
Min, max	45, 115
> 100	4 (3)
Body mass index, kg/m^2	
Median	25.3
Min, max	17, 40
Body mass index, kg/m^2	
< 25	58 (46)
25 to < 30	46 (37)
≥ 30	21 (17)

(continued in next column)

TABLE A1. Summary of Demographics and Disease Characteristics at Baseline (continued)

Characteristic	Patients (N = 125)
ECOG performance status,[b]	
0	40 (32)
1	85 (68)
Primary tumor location	
Bladder/other	81 (65)
Upper tract[c]	44 (35)
Histology type	
Urothelial carcinoma only	84 (67)
Urothelial carcinoma with squamous differentiation	15 (12)
Urothelial carcinoma with other histologic variants	26 (21)
Time from diagnosis of metastatic disease to enrollment,[d] months	
No.	124
Median	15.4
Min, max	1, 85
Metastasis sites	
Lymph nodes only	13 (10)
Visceral disease[e]	112 (90)
Bone	51 (41)
Liver	50 (40)
Lung	53 (42)
Renal function on the basis of creatinine clearance, mL/min	
Normal (≥ 90)	26 (21)
Mild decrease (≥ 60 and < 90)	51 (41)
Moderate decrease (≥ 30 and < 60)	47 (38)
Severe decrease[f] (≥ 15 and < 30)	1 (1)
HbA1c	
No.	119
Median, %	5.60
Min, max, %	4.2, 7.2
Percent HbA1c	
< 6.5	110 (88)
≥ 6.5	9 (7)
Hemoglobin, g/dL	
< 10	35 (28)
≥ 10	89 (71)
Missing	1 (1)

(continued on following page)

TABLE A1. Summary of Demographics and Disease Characteristics at Baseline (continued)

Characteristic	Patients (N = 125)
No. of Bellmunt risk factors[g]	
0	23 (18)
1	49 (39)
2	35 (18)
3	17 (14)
Missing	1 (1)
No. of systemic therapies in locally advanced or metastatic settings[h]	
Median	3.0
Min, max	1, 6
1	4 (3)
2	58 (46)
≥ 3	63 (50)
Prior treatment	
PD-1/L1–containing therapies	125 (100)
Nivolumab	18 (14)
Pembrolizumab	59 (47)
Atezolizumab	62 (50)
Avelumab	1 (1)
Durvalumab	6 (5)
Prior platinum-based therapies	125 (100)
Cisplatin-based therapies	92 (74)
Carboplatin-based therapies	43 (34)
Taxane	32 (26)
Premetrexed	7 (6)
FGFR inhibitor	3 (2)
Time from completion/discontinuation of most recent prior therapy to first study dose, months	
Median No.	1.54
Min, max	0.5, 14.3
≤ 3	101 (81)
> 3	24 (19)
Best response to PD-1/L1–containing therapy	
Responder	25 (20)
Nonresponder	100 (80)
PD-L1 status by combined positive score[i]	
< 10	78/120 (65)
≥ 10	42/120 (35)
First-line therapy received	
Platinum-based	105 (84)
PD-1/L1 monotherapy	11 (9)
PD-1/L1 + platinum	8 (6)
Other	1 (1)
Time from completion/discontinuation of most recent PD-1/L1–containing therapy to first study dose, months	
Median No.	2.33
Min, max	0.5, 39.6
≤ 3	73 (58)
> 3	52 (42)
Setting of PD-1/L1–containing therapy	
Neoadjuvant/adjuvant	1 (1)
Metastatic/locally advanced	124 (99)
PD-1/L1 as most recent therapy	86 (69)
Nectin-4 expression level, H-score[i,j]	
No.	120
Median	290
Min, max	14, 300

(continued in next column)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; HbA1c, hemoglobin A1C; max, maximum; min, minimum; PD-1/L1, programmed death 1 or programmed death ligand 1.

[a]Smokers include both current and former smokers.

[b]ECOG performance status scale ranges from 0 to 5, with 0 indicating that the patient is fully active with no restrictions, 1 that the patient is ambulatory and able to carry out work of a light or sedentary nature but restricted in physically strenuous activity, and higher numbers indicating greater disability.

[c]Including renal pelvis, ureter, and kidney.

[d]One patient in the platinum-treated cohort had an incomplete date of diagnosis (month and day are unknown); therefore, time from diagnosis to enrollment cannot be calculated.

[e]A patient may have metastatic disease in more than one location.

[f]On the basis of a baseline central laboratory assessment after screening and enrollment.

[g]Bellmunt risk factors include ECOG performance status > 0, hemoglobin < 10 g/dL, and presence of liver metastasis.[21]

[h]Including PD-1/L1–containing therapy in the neoadjuvant/adjuvant setting with progression or recurrence within 3 months after therapy completion, or platinum-based therapy in the neoadjuvant/adjuvant setting with progression or recurrence within 12 months after therapy conclusion.

[i]Five patients were not evaluable for PD-L1 or Nectin-4 expression levels.

[j]Nectin-4 levels were assessed by immunohistochemistry in tumor biopsies. Immunohistochemistry images were scored by a pathologist with the H-score method (H-score = [percentage of strong positive tumor cells × 3] + [percentage of moderate positive tumor cells × 2] + [percentage of weak positive tumor cells × 1]). A score of 0 indicates no expression and a score of 300 indicates the maximum possible expression with this assay.

TABLE A2. Summary of Responses Per Investigator in the Full Analysis Set

Response	Patients (N = 125)
Objective response rate	49 (39)
95% CI*	30.6, 48.3
Best overall response,†	
Complete response	9 (7)
Partial response	40 (32)
Stable disease	48 (38)
Progressive disease	17 (14)
Not evaluable‡	11 (9)

NOTE. Data are presented as No. (%).

*CI was computed using the Clopper-Pearson method.[22]

†Best overall response according to RECIST v1.1.

‡Includes 10 patients who did not have any response assessment postbaseline and one patient whose postbaseline assessment did not meet the minimum interval requirement for stable disease.

TABLE A3. Treatment-Related Adverse Events Occurring in ≥ 10% of Patients

	Patients (N = 125)	
Common Adverse Event (preferred term)	Any Grade	Grade ≥ 3
All adverse events	117 (94)	68 (54)
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0
Rash maculopapular	27 (22)	5 (4)
Dry eye	24 (19)	0
Anemia	22 (18)	9 (7)
Pruritus	21 (17)	0
Vomiting	18 (14)	3 (2)
Lacrimation increased	18 (14)	0
AST increased	17 (14)	4 (3)
Constipation	15 (12)	0
Vision blurred	15 (12)	0
Rash erythematous	14 (11)	4 (3)
Edema peripheral	14 (11)	1 (1)
Neutropenia	13 (10)	10 (8)
Hyperglycemia	12 (10)	5 (4)
Amylase increased	12 (10)	3 (2)
Pruritus generalized	12 (10)	2 (2)
ALT increased	12 (10)	2 (2)

NOTE. Data are presented as No. (%).

TABLE A4. All Adverse Events Occurring in ≥ 10% of Patients

	Patients (N = 125)	
Common Adverse Events (preferred term)	Any Grade	Grade ≥ 3
All adverse events	125 (100)	91 (73)
Fatigue	69 (55)	7 (6)
Decreased appetite	65 (52)	3 (2)
Alopecia	63 (50)	0
Nausea	56 (45)	4 (3)
Peripheral sensory neuropathy	54 (43)	2 (2)
Diarrhea	52 (42)	4 (3)
Dysgeusia	52 (42)	0
Anemia	39 (31)	17 (14)
Weight decreased	39 (31)	2 (2)
Constipation	35 (28)	1 (1)
Dry skin	33 (26)	0
Dry eye	29 (23)	0
Edema peripheral	29 (23)	2 (2)
Rash maculopapular	28 (22)	5 (4)
Urinary tract infection	23 (18)	6 (5)
Vomiting	23 (18)	3 (2)
Cough	20 (16)	2 (2)
Dizziness	20 (16)	0
Dyspnea	20 (16)	3 (2)
AST increased	19 (15)	4 (3)
Back pain	19 (15)	3 (2)
Hyperglycemia	19 (15)	9 (7)
Vision blurred	19 (15)	0
Lacrimation increased	18 (14)	0
Hyponatremia	17 (14)	7 (6)
Insomnia	17 (14)	0
Pyrexia	17 (14)	0
Hypokalemia	16 (13)	2 (2)
Rash erythematous	15 (12)	4 (3)
Lipase increased	14 (11)	5 (4)
Neutropenia	14 (11)	11 (9)
Pain in extremity	14 (11)	0
ALT increased	13 (10)	2 (2)
Skin hyperpigmentation	13 (10)	0
Amylase increased	12 (10)	3 (2)
Fall	12 (10)	1 (1)
Hematuria	12 (10)	2 (2)
Muscular weakness	12 (10)	1 (1)
Pruritus generalized	12 (10)	2 (2)
Urinary tract infection	23 (18)	6 (5)
Vomiting	23 (18)	3 (2)

NOTE. Data are presented as No. (%).

TABLE A5. Search Terms Used for Composite Adverse Events

Search Term
Hyperglycemia
Acquired lipoatrophic diabetes
Blood 1,5-anhydroglucitol decreased
Blood glucose abnormal
Blood glucose fluctuation
Blood glucose increased
Diabetes complicating pregnancy
Diabetes mellitus
Diabetes mellitus inadequate control
Diabetes with hyperosmolarity
Diabetic arteritis
Diabetic coma
Diabetic hepatopathy
Diabetic hyperglycemic coma
Diabetic hyperosmolar coma
Diabetic ketoacidosis
Diabetic ketoacidotic hyperglycemic coma
Diabetic metabolic decompensation
Fructosamine increased
Fulminant type 1 diabetes mellitus
Gestational diabetes
Glucose tolerance impaired
Glucose tolerance impaired in pregnancy
Glucose urine present
Glycosuria
Glycosuria during pregnancy
Glycosylated hemoglobin increased
Hyperglycemia
Hyperglycemic hyperosmolar nonketotic syndrome
Hyperglycemic seizure
Hyperglycemic unconsciousness
Impaired fasting glucose
Insulin resistance
Insulin resistance syndrome
Insulin resistant diabetes
Insulin-requiring type 2 diabetes mellitus
Ketoacidosis
Ketonuria
Ketosis
Latent autoimmune diabetes in adults
Metabolic syndrome
Monogenic diabetes
Neonatal diabetes mellitus

(continued in next column)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Pancreatogenous diabetes
Type 1 diabetes mellitus
Type 2 diabetes mellitus
Type 3 diabetes mellitus
Urine ketone body present
Infusion-related reactions
Administration-related reaction
Administration site extravasation
Allergic reaction to excipient
Anaphylactic reaction
Anaphylactic shock
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Bronchospasm
Catheter site extravasation
Chemotherapy extravasation management
Documented hypersensitivity to administered product
Drug eruption
Drug hypersensitivity
Epiglottic edema
Extravasation
Face edema
Fixed eruption
Hypersensitivity
Immediate postinjection reaction
Implant site extravasation
Infusion related reaction
Infusion site abscess sterile
Infusion site anesthesia
Infusion site atrophy
Infusion site bruising
Infusion site calcification
Infusion site coldness
Infusion site cyst
Infusion site dermatitis
Infusion site discharge
Infusion site discoloration
Infusion site discomfort
Infusion site dryness
Infusion site dysesthesia
Infusion site eczema

(continued on following page)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Infusion site erosion
Infusion site erythema
Infusion site exfoliation
Infusion site extravasation
Infusion site fibrosis
Infusion site granuloma
Infusion site hematoma
Infusion site hemorrhage
Infusion site hyperesthesia
Infusion site hypersensitivity
Infusion site hypertrichosis
Infusion site hypertrophy
Infusion site hypoesthesia
Infusion site induration
Infusion site inflammation
Infusion site injury
Infusion site irritation
Infusion site ischemia
Infusion site joint discomfort
Infusion site joint effusion
Infusion site joint erythema
Infusion site joint inflammation
Infusion site joint movement impairment
Infusion site joint pain
Infusion site joint swelling
Infusion site joint warmth
Infusion site laceration
Infusion site lymphadenopathy
Infusion site macule
Infusion site mass
Infusion site mobility decreased
Infusion site necrosis
Infusion site nerve damage
Infusion site nodule
Infusion site edema
Infusion site pain
Infusion site pallor
Infusion site papule
Infusion site paresthesia
Infusion site phlebitis
Infusion site photosensitivity reaction
Infusion site plaque
Infusion site pruritus
(continued in next column)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Infusion site rash
Infusion site reaction
Infusion site recall reaction
Infusion site scab
Infusion site scar
Infusion site streaking
Infusion site swelling
Infusion site thrombosis
Infusion site ulcer
Infusion site urticaria
Infusion site vasculitis
Infusion site vesicles
Infusion site warmth
Injection-related reaction
Injection site extravasation
Laryngeal edema
Laryngospasm
Laryngotracheal edema
Lip swelling
Mast cell degranulation present
Medical device site extravasation
Pharyngeal edema
Red man syndrome
Stoma site extravasation
Swelling face
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Throat tightness
Tongue edema
Type I hypersensitivity
Peripheral neuropathy
Acute painful neuropathy of rapid glycemic control
Acute polyneuropathy
Amyotrophy
Angiopathic neuropathy
Antiganglioside antibody positive
Antimyelin-associated glycoprotein antibodies positive
Antimyelin-associated glycoprotein associated polyneuropathy
Areflexia
Autoimmune neuropathy
Autonomic failure syndrome
Autonomic neuropathy
Axonal neuropathy
(continued on following page)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Biopsy peripheral nerve abnormal
Burning feet syndrome
Burning sensation
Decreased nasolabial fold
Decreased vibratory sense
Demyelinating polyneuropathy
Dysesthesia
Electromyogram abnormal
Formication
Gait disturbance
Genital hypoesthesia
Guillain-Barré syndrome
Hereditary motor and sensory neuropathy
Hypoesthesia
Hyporeflexia
Hypotonia
Ischemic neuropathy
Loss of proprioception
Miller Fisher syndrome
Mononeuritis
Mononeuropathy
Mononeuropathy multiplex
Motor dysfunction
Multifocal motor neuropathy
Muscle atrophy
Muscular weakness
Myelopathy
Nerve conduction studies abnormal
Nerve degeneration
Neuralgia
Neuritis
Neuromuscular pain
Neuromuscular toxicity
Neuromyopathy
Neuronal neuropathy
Neuropathic muscular atrophy
Neuropathy peripheral
Neuropathy vitamin B_6 deficiency
Neurotoxicity
Notalgia paraesthetica
Paresthesia
Paresthesia ear
Peripheral motor neuropathy

(continued in next column)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Peripheral nerve lesion
Peripheral nerve palsy
Peripheral nerve paresis
Peripheral nervous system function test abnormal
Peripheral sensorimotor neuropathy
Peripheral sensory neuropathy
Peroneal nerve palsy
Phrenic nerve paralysis
Polyneuropathy
Polyneuropathy chronic
Polyneuropathy idiopathic progressive
Radiation neuropathy
Sensorimotor disorder
Sensory disturbance
Sensory loss
Skin burning sensation
Small fiber neuropathy
Synkinesis
Temperature perception test decreased
Tick paralysis
Tinel's sign
Toxic neuropathy
Ulnar neuritis
Vulvovaginal hypoesthesia
Rash
Acquired epidermolysis bullosa
Acute generalized exanthematous pustulosis
Autoimmune dermatitis
Blister
Blister rupture
Blood blister
Bromoderma
Bullous impetigo
Butterfly rash
Coma blister
Conjunctivitis
Corneal exfoliation
Cutaneous vasculitis
Dennie-Morgan fold
Dermatitis
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous

(continued on following page)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Dermatitis contact
Dermatitis diaper
Dermatitis exfoliative
Dermatitis exfoliative generalized
Dermatitis herpetiformis
Diabetic bullosis
Drug eruption
Drug reaction with eosinophilia and systemic symptoms
Dyshidrotic eczema
Eczema
Eczema asteatotic
Eczema infantile
Eczema nummular
Eczema vesicular
Eczema weeping
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Erythema
Erythema ab igne
Erythema elevatum diutinum
Erythema multiforme
Erythema toxicum neonatorum
Exfoliative rash
Fixed eruption
Flagellate dermatitis
Fracture blisters
Generalized erythema
Genital ulceration
Hand dermatitis
Herpes gestationis
HLA-B*1502 assay positive
HLA-B*5801 assay positive
Hypopharyngeal synechiae
Intertrigo
Linear IgA disease
Lip exfoliation
Lupus miliaris disseminatus faciei
Mazzotti reaction
Morbihan disease
Mouth ulceration
Mucocutaneous rash
Mucocutaneous ulceration
(continued in next column)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Mucosa vesicle
Mucosal erosion
Mucosal exfoliation
Mucosal necrosis
Mucosal ulceration
Necrolytic migratory erythema
Neurodermatitis
Nikolsky's sign
Nodular rash
Noninfective conjunctivitis
Occupational dermatitis
Oculomucocutaneous syndrome
Oral mucosal blistering
Oral mucosal exfoliation
Oral papule
Oropharyngeal blistering
Palmar erythema
Palmar-plantar erythrodysaesthesia syndrome
Paraneoplastic pemphigus
Paraneoplastic rash
Pemphigoid
Pemphigus
Penile exfoliation
Periarticular thenar erythema with onycholysis
Perivascular dermatitis
Plantar erythema
Prurigo
Pseudocellulitis
Pseudoporphyria
Rash
Rash erythematous
Rash generalized
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Rebound atopic dermatitis
Rebound eczema
(continued on following page)

TABLE A5. Search Terms Used for Composite Adverse Events (continued)

Search Term
Red man syndrome
Sea bather's eruption
Seborrhoeic dermatitis
Skin erosion
Skin exfoliation
Skin irritation
Skin necrosis
Staphylococcal scalded skin syndrome
Stasis dermatitis
Stevens-Johnson syndrome
Stomatitis
Symmetrical drug-related intertriginous and flexural exanthema
Systemic lupus erythematosus rash
Tongue exfoliation
Toxic epidermal necrolysis
Toxic erythema of chemotherapy
Toxic skin eruption
Transient neonatal pustular melanosis
Umbilical erythema
Vaginal exfoliation
Vaginal ulceration
Vulval ulceration
Vulvovaginal rash
Vulvovaginal ulceration

NOTE. Listed are all search terms used to identify events considered to be indicative of hyperglycemia, infusion-related reactions, peripheral neuropathy, or rash on the basis of standardized terms in the Medical Dictionary for Regulatory Activities (version 20.0).

TABLE A6. Summary of Time to Onset, Improvement, and Resolution for Treatment-Related Adverse Events of Interest

Adverse Event	No. of Patients With Any-Grade Event	Total No. of Any-Grade Events*	Median Time to Onset of First Event,* Months (range)	Median Time to Improvement of Any Event,† Months (range)	Median Time to Resolution of Any Event,‡ Months (range)
Peripheral neuropathy	63	80	2.43 (0.03-7.39)	1.18 (0.26-4.86)	1.48 (0.23-11.60)
Rash	60	110	0.53 (0.03-7.39)	0.72 (0.03-2.66)	0.72 (0.03-7.20)
Hyperglycemia	14	16	0.58 (0.26-9.23)	0.89 (0.59-1.18)	1.12 (0.26-6.47)

*Patients could have had more than one event.

†Improvement defined as at least one grade improvement from the worst grade at the last assessment.

‡Resolution defined as a return to baseline grade or better at the last assessment.