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 11.3 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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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. Nectin-4 is highly expressed in several solid tumors, including urothelial, breast, gastric, and lung carcinomas. Expression is weak to moderate in normal skin. 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. Pharmacokinetic data from this study demonstrate a half-life of approximately 2 days, which supports this dosing schedule. 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
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 11.3 months; 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

| 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 scoreII           |                    |
| < 10                                                | 78/120 (65)        |
| ≥ 10                                                | 42/120 (35)        |

(continued on following page)
some improvement at last follow-up. Most patients (75%) had ongoing rash and 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. 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.

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**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.

†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.

§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.

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

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.

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

**TABLE 2.** Summary of Responses Per Blinded Independent Central Review

| Response                | Patients (N = 125) |
|-------------------------|--------------------|
| Objective response      | 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. (%).

§Computation 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.
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...
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. 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; 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, 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 vedotin.

| Subgroup                        | No. of Events/No. of Patients | % (95% CI) ORR, % (95% CI) |
|--------------------------------|-------------------------------|---------------------------|
| Overall                        | 55/125                        | 44 (35.1 to 53.2)         |
| Age, years                     |                               |                           |
| < 75                           | 43/91                         | 47 (36.7 to 58)           |
| ≥ 75                           | 12/34                         | 35 (19.7 to 53.5)         |
| ECOG performance status        |                               |                           |
| Grade 0                        | 24/40                         | 60 (43.3 to 75.1)         |
| Grade 1                        | 31/85                         | 36 (26.3 to 47.6)         |
| Bellmunt risk score†           |                               |                           |
| 0-1                            | 37/72                         | 51 (39.3 to 63.3)         |
| ≥ 2                            | 17/52                         | 33 (20.3 to 47.1)         |
| Primary tumor sites            |                               |                           |
| Upper tract                    | 17/44                         | 39 (24.4 to 54.5)         |
| Bladder/other                  | 38/81                         | 47 (35.7 to 58.3)         |
| Liver metastasis               |                               |                           |
| Yes                            | 19/50                         | 38 (24.7 to 52.8)         |
| No                             | 36/75                         | 48 (36.3 to 59.8)         |
| No. of prior therapies in metastatic UC setting |                            |                           |
| 1-2                            | 29/62                         | 47 (34 to 59.9)           |
| ≥ 3                            | 26/63                         | 42 (29 to 54.4)           |
| Best response to prior anti-PD-1/L1‡ |                          |                           |
| Responder                      | 14/25                         | 56 (34.9 to 75.6)         |
| Nonresponder                   | 41/100                        | 41 (31.3 to 51.3)         |
| PD-L1 expression§              |                               |                           |
| CPS < 10                       | 37/78                         | 47 (36 to 59.1)           |
| CPS ≥ 10                       | 15/42                         | 36 (21.6 to 52)           |

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. 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.
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). 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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**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.
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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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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 = \[\text{percentage of strong positive tumor cells \times 3} + \text{percentage of moderate positive tumor cells \times 2} + \text{percentage of weak positive tumor cells \times 1}\]). 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,\textsuperscript{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 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/m²                | Median 25.3, Min, max 17, 40 |
| (continued in next column)            |                    |

| Characteristic                        | Patients (N = 125) |
|---------------------------------------|--------------------|
| 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) |
| Time from diagnosis of metastatic disease to enrollment, ⁴ months | No. 124, Median 15.4, Min, max 1, 85 |
| Metastasis sites                       | Lymph nodes only 13 (10), Visceral disease 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 (< 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^a                      |                    |
| 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^b |        |
| 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                                              | 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^c           |                    |
| < 10                                                | 78/120 (65)        |
| ≥ 10                                                | 42/120 (35)        |
| First-line therapy received                         |                    |
| Platinum-based                                      | 105 (84)           |
| PD-1/L1 monotherapy                                 | 11 (9)             |

(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.

^aSmokers include both current and former smokers.

^bECOG 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.

^cIncluding renal pelvis, ureter, and kidney.

^dOne 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.

^eA patient may have metastatic disease in more than one location.

^fOn the basis of a baseline central laboratory assessment after screening and enrollment.

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

^hIncluding 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.

^iFive patients were not evaluable for PD-L1 or Nectin-4 expression levels.

^jNectin-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.

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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.†
†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

| Common Adverse Event (preferred term) | Patients (N = 125) |
|--------------------------------------|--------------------|
| 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                        | 18 (14) 4 (3)      |
| Constipation                         | 17 (14) 0          |
| Vision blurred                       | 15 (12) 0          |
| Rash erythematos                     | 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

| 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)     |
| Back pain                             | 19 (15)   | 3 (2)     |
| Hyperglycemia                         | 19 (15)   | 9 (7)     |
| Vision blurred                        | 19 (15)   | 0         |
| Lacrimation increased                 | 18 (14)   | 0         |
| Hypokalemia                           | 17 (14)   | 7 (6)     |
| Insomnia                              | 17 (14)   | 0         |
| Pyrexia                               | 17 (14)   | 0         |
| Hypokalemia                           | 16 (13)   | 2 (2)     |
| Rash erythematos                      | 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 lipoatrophy 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)

#### Search Term (continued)

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

| Search Term                                      | Search Term                                      |
|--------------------------------------------------|--------------------------------------------------|
| Biopsy peripheral nerve abnormal                  | Peripheral nerve lesion                         |
| Burning feet syndrome                             | Peripheral nerve palsy                           |
| Burning sensation                                 | Peripheral nerve paresis                         |
| Decreased nasolabial fold                         | Peripheral nervous system function test abnormal |
| Decreased vibratory sense                         | Peripheral sensorimotor neuropathy               |
| Demyelinating polyneuropathy                      | Peripheral sensory neuropathy                    |
| Dysesthesia                                       | Peroneal nerve palsy                             |
| Electromyogram abnormal                           | Phrenic nerve paralysis                           |
| Formication                                       | Polynuropathy                                    |
| Gait disturbance                                  | Polyneuropathy chronic                           |
| Genital hypoesthesia                              | Polyneuropathy idiopathic progressive            |
| Guillain-Barré syndrome                           | Radiation neuropathy                             |
| Hereditary motor and sensory neuropathy           | Sensorimotor disorder                            |
| Hypoesthesia                                      | Sensory disturbance                              |
| Hyporeflexia                                      | Sensory loss                                     |
| Hypotonia                                         | Skin burning sensation                           |
| Ischemic neuropathy                               | Small fiber neuropathy                           |
| Loss of proprioception                            | Synkinesis                                       |
| Miller Fisher syndrome                            | Temperature perception test decreased            |
| Mononeuritis                                      | Tick paralysis                                   |
| Mononeuropathy                                    | Tinel’s sign                                     |
| Mononeuropathy multiplex                          | Toxic neuropathy                                 |
| Motor dysfunction                                 | Ulnar neuritis                                   |
| Multifocal motor neuropathy                       | Vulvovaginal hypoesthesia                        |
| Muscle atrophy                                    | Rash                                             |
| Muscular weakness                                 | Acquired epidermolysis bullosa                   |
| Myelopathy                                        | Autoimmune dermatitis                            |
| Nerve conduction studies abnormal                 | Blister                                          |
| Nerve degeneration                                | Blister rupture                                  |
| Neuralgia                                         | Blood blister                                    |
| Neuritis                                          | Bromoderma                                       |
| Neuromuscular pain                                | Bullous impetigo                                 |
| Neuromuscular toxicity                            | Butterfly rash                                   |
| Neuromyopathy                                     | Coma blister                                     |
| Neuronal neuropathy                               | Conjunctivitis                                   |
| Neuropathic muscular atrophy                      | Corneal exfoliation                              |
| Neuropathy peripheral                             | Cutaneous vasculitis                             |
| Neuropathy vitamin B<sub>6</sub> deficiency        | Dennie-Morgan fold                               |
| Neurotoxicity                                     | Dermatitis                                       |
| Notalgia paraestheticica                          | Dermatitis allergic                              |
| Paresthesia                                       | Dermatitis atopic                                |
| Paresthesia ear                                   | Dermatitis bullous                               |
| Peripheral motor neuropathy                       |                                                 |

(continued in next column)
### TABLE A5. Search Terms Used for Composite Adverse Events

(continued)

| Search Term                                      |
|-------------------------------------------------|
| Dermatitis contact                              |
| Dermatitis diaper                               |
| Dermatitis exfoliative                          |
| Dermatitis exfoliative generalized              |
| Dermatitis herpetiformis                        |
| Diabetic bullous                                |
| Drug eruption                                   |
| Drug reaction with eosinophilia and systemic symptoms |
| Dyshidrotic eczema                              |
| Eczema                                          |
| Eczema asteatotic                               |
| Eczema infantil                                 |
| 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                                                                 |
|-----------------------------------------------------------------------------|
| 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.