ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

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ABSTRACT

BACKGROUND

Patients with advanced urothelial carcinoma have poor overall survival after platinum-containing chemotherapy and programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor treatment.

METHODS

We conducted a global, open-label, phase 3 trial of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-containing chemotherapy and had had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor. Patients were randomly assigned in a 1:1 ratio to receive enfortumab vedotin (at a dose of 1.25 mg per kilogram of body weight on days 1, 8, and 15 of a 28-day cycle) or investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine), administered on day 1 of a 21-day cycle. The primary end point was overall survival.

RESULTS

A total of 608 patients underwent randomization; 301 were assigned to receive enfortumab vedotin and 307 to receive chemotherapy. As of July 15, 2020, a total of 301 deaths had occurred (134 in the enfortumab vedotin group and 167 in the chemotherapy group). At the prespecified interim analysis, the median follow-up was 11.1 months. Overall survival was longer in the enfortumab vedotin group than in the chemotherapy group (median overall survival, 12.88 vs. 8.97 months; hazard ratio for death, 0.70; 95% confidence interval [CI], 0.56 to 0.89; P=0.001). Progression-free survival was also longer in the enfortumab vedotin group than in the chemotherapy group (median progression-free survival, 5.55 vs. 3.71 months; hazard ratio for progression or death, 0.62; 95% CI, 0.51 to 0.75; P<0.001). The incidence of treatment-related adverse events was similar in the two groups (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group); the incidence of events of grade 3 or higher was also similar in the two groups (51.4% and 49.8%, respectively).

CONCLUSIONS

Enfortumab vedotin significantly prolonged survival as compared with standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-based treatment and a PD-1 or PD-L1 inhibitor. (Funded by Astellas Pharma US and Seagen; EV-301 ClinicalTrials.gov number, NCT03474107.)

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The standard of care for advanced urothelial carcinoma includes platinum-based chemotherapy and programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors, administered as frontline, second-line, or maintenance therapy.[1-4] Despite advances in treatment, this disease remains aggressive and generally incurable.[5-7] Unfortunately, urothelial cancers are associated with intrinsic and acquired resistance to chemotherapy.[8,9] Although immunotherapy has a more acceptable side-effect profile and is associated with a longer duration of response than chemotherapy, a minority of patients have a durable response.[5,6,8,10-12] The median overall survival with these therapies is only 10 to 14 months.[5,6,13,14]

Nectin-4 is a cell-adhesion molecule that is highly expressed in urothelial carcinoma and may contribute to tumor-cell growth and proliferation.[15-19] Enfortumab vedotin, an antibody–drug conjugate directed against nectin-4, is composed of a fully human monoclonal antibody specific for nectin-4 and monomethyl auristatin E (an agent that disrupts microtubule formation).[16] Targeted delivery of monomethyl auristatin E results in cell-cycle arrest and apoptosis.[16,17]

EV-301 was a global, open-label, phase 3 trial that evaluated enfortumab vedotin as compared with chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who had previously received treatment with a platinum agent and a PD-1 or PD-L1 inhibitor. Single-group clinical studies have shown that enfortumab vedotin resulted in an objective response in more than 40% of patients with advanced urothelial carcinoma who had progression after previous treatment.[16,17] This trial was designed to confirm the clinical benefit of enfortumab vedotin as compared with standard chemotherapy by assessing overall survival in patients with advanced urothelial carcinoma who had previously received treatment.

Methods

Trial Participants

Eligible patients were 18 years of age or older, had histologically or cytologically confirmed urothelial carcinoma (including differentiation in squamous cells or in multiple cell types), radiologically documented metastatic or unresectable locally advanced disease at baseline, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (scores range from 0 to 4, with higher scores indicating greater disability). Patients must have had radiographic progression or relapse during or after PD-1 or PD-L1 inhibitor treatment. In addition, patients must have previously received a platinum-containing regimen. For patients who had received platinum chemotherapy as neoadjuvant or adjuvant therapy, progression must have occurred within 12 months after completion of treatment.

Patients were excluded from the trial if they had preexisting grade 2 or higher sensory or motor neuropathy or ongoing clinically significant toxic effects associated with previous treatment, active central nervous system metastases, uncontrolled diabetes, or active keratitis or corneal ulcerations or if they had received more than one previous chemotherapy regimen for locally advanced or metastatic urothelial carcinoma, including neoadjuvant or adjuvant treatment. Full eligibility criteria are provided in the trial protocol, available with the full text of this article at NEJM.org.

Randomization and Treatments

Enrolled patients were randomly assigned in a 1:1 ratio to receive enfortumab vedotin or chemotherapy. Randomization was stratified according to ECOG performance-status score (0 or 1), geographic region (Western Europe, United States, or rest of the world), and the presence or absence of liver metastasis at baseline. Enfortumab vedotin was administered at a dose of 1.25 mg per kilogram of body weight by means of intravenous infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Chemotherapy was selected by the investigator before randomization and was one of the following: docetaxel at a dose of 75 mg per square meter of body-surface area, administered intravenously over 60 minutes; paclitaxel at a dose of 175 mg per square meter, administered intravenously over 3 hours; or vinflunine (in regions where it is approved for treatment of urothelial carcinoma) at a dose of 320 mg per square meter, administered intravenously over 20 minutes. The use of vinflunine was capped at 35% of the patients in this trial. The chemotherapy treatments were administered on day 1 of a 21-day cycle. Patients who received enfortumab vedotin or vinflunine re-

quired no premedication, whereas all patients who received paclitaxel or docetaxel received premedication to prevent hypersensitivity reactions or fluid retention. Dose modifications and interruptions were permitted for management of adverse events on the basis of prespecified criteria (Table S1 in the Supplementary Appendix, available at NEJM.org).

TRIAL OVERSIGHT

The trial was designed by the sponsors in collaboration with an advisory committee. Data were collected by the trial investigators, analyzed by statisticians employed by Astellas Pharma US, and interpreted by all authors. The trial received approval from independent institutional review boards and independent ethics committees and was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient before trial entry.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors had access to the data used in the preparation of the manuscript. The authors, with writing and editorial support funded by the trial sponsors, developed and approved the manuscript.

END POINTS AND ASSESSMENTS

The primary end point was overall survival. Key secondary efficacy end points, evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, included investigator-assessed progression-free survival and clinical response. The safety profile was also a secondary end point. Investigator-assessed adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Radiographic imaging was performed at baseline and every 8 weeks. Bone scintigraphy was performed in all patients at screening; repeat scanning was performed at least every 8 weeks in patients with a positive scan. Imaging of the brain was performed, if clinically indicated, at baseline and throughout the trial. Patients were followed until radiographic disease progression, until discontinuation criteria were met (see the protocol), or until trial completion. Patients who discontinued treatment before disease progression underwent imaging assessments every 8 weeks until documented disease progression or initiation of a different anticancer treatment, whichever occurred earlier. After radiographic disease progression had occurred, patients entered the long-term follow-up phase and were followed at least every 3 months from the date of the follow-up visit for vital status until death, loss to follow-up, withdrawal of consent, or termination of the trial. Quality of life, patient-reported outcomes, and additional exploratory efficacy end points were assessed but are not reported here.

STATISTICAL ANALYSIS

Overall and progression-free survival were estimated for each treatment group with the use of the Kaplan–Meier method, and comparisons between groups were conducted with the use of the stratified log-rank test. Sensitivity analyses were also planned. Stratified Cox proportional-hazards models were used to estimate hazard ratios and corresponding 95% confidence intervals. Analyses of overall survival and progression-free survival included all patients who underwent randomization. The percentage of patients with an overall response (a best overall response of confirmed complete or partial response according to RECIST, version 1.1) and disease control (a best overall response of confirmed complete response, confirmed partial response, or stable disease according to RECIST, version 1.1) were compared with the use of a stratified Cochran–Mantel–Haenszel test to estimate differences between groups. The duration of response was analyzed with the use of the Kaplan–Meier method. Overall response and disease control were assessed in all patients who underwent randomization and had measurable disease at baseline. The randomization stratification factors were used in all stratified efficacy analyses.

Safety analyses, which were performed with the use of descriptive statistics, included patients who received any amount of trial drug. Prespecified subgroup analyses were conducted, with subgroups defined according to demographic and baseline disease characteristics. All analyses were performed with the use of SAS software, version 9.2 or higher (SAS Institute).

The trial used a group-sequential design with two planned analyses (an interim and a final analysis). The primary end point and selected

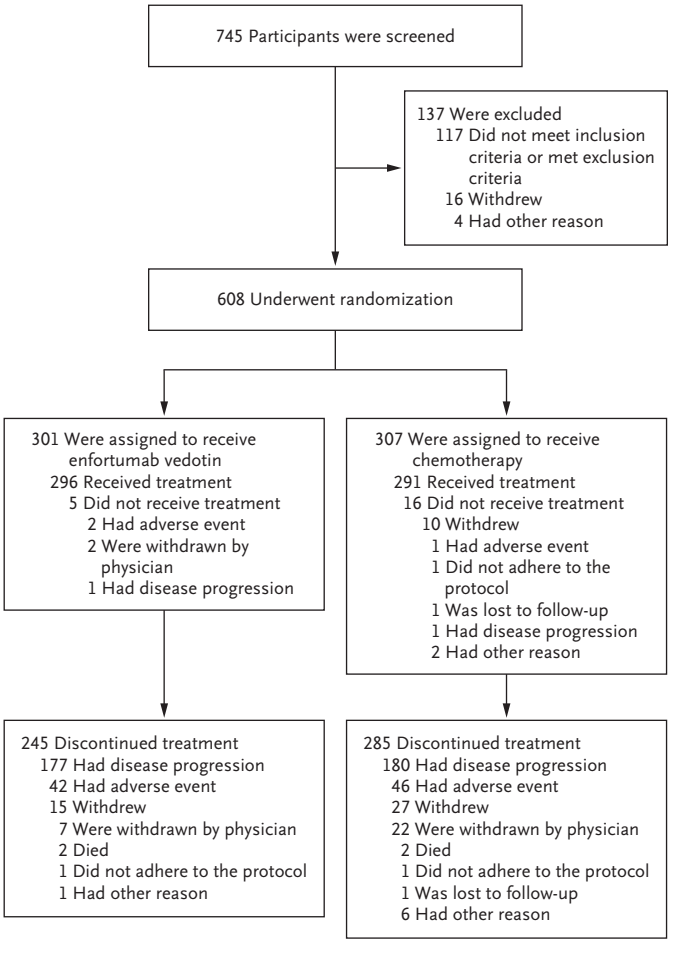


Figure 1. Screening, Randomization, and Treatment.

key secondary end points (progression-free survival, overall response, and disease control) were tested with the hierarchical gatekeeping procedure (Supplementary Appendix). Prespecified multiplicity-adjustment methods were used to control the overall one-sided type I error rate at 0.025. Efficacy boundaries were calculated on the basis of the information fraction at the time of analysis. The reported 95% confidence intervals describe the precision of the point estimates and may not correspond to the significance of the test. We calculated that a sample size of approximately 600 patients would give the trial 85% power to detect a significant difference in the primary outcome between treatment groups at an overall one-sided type I error rate of 0.025, assuming a hazard ratio for death of 0.75, a median overall survival of 8 months with chemotherapy, and 10% of the patients leaving the trial prematurely. A final analysis was planned for when 439 deaths had occurred, and one interim analysis would be conducted when 65% of patients had died. The interim analysis was performed by the independent data analysis center and was reviewed by an independent data and safety monitoring committee. If the interim analysis showed that the efficacy of enfortumab vedotin was significantly better than that of chemotherapy, the trial would be stopped and concluded.

At the interim analysis, overall survival was tested at a one-sided significance level of 0.00541 for efficacy (adjusted to 0.00679 on the basis of 301 observed deaths) according to the O'Brien–Fleming stopping boundary with the use of the Lan–DeMets alpha-spending function. On the basis of the results of the interim analysis, our trial met the superiority threshold, and the results are reported here. Because outcomes were determined with the use of tests associated with stopping rules, data are reported with one-sided P values. Full statistical methods are provided in the statistical analysis plan, which is available with the protocol.

RESULTS

RANDOMIZATION AND BASELINE CHARACTERISTICS

A total of 608 patients at 191 centers in 19 countries were randomly assigned to receive enfortumab vedotin (301 patients) or chemotherapy preselected by the investigator (307 patients) (Fig. 1). Of the patients assigned to receive chemotherapy, 117 received docetaxel, 112 received paclitaxel, and 78 received vinflunine. A total of 296 patients in the enfortumab vedotin group and 291 patients in the chemotherapy group received any amount of study drug.

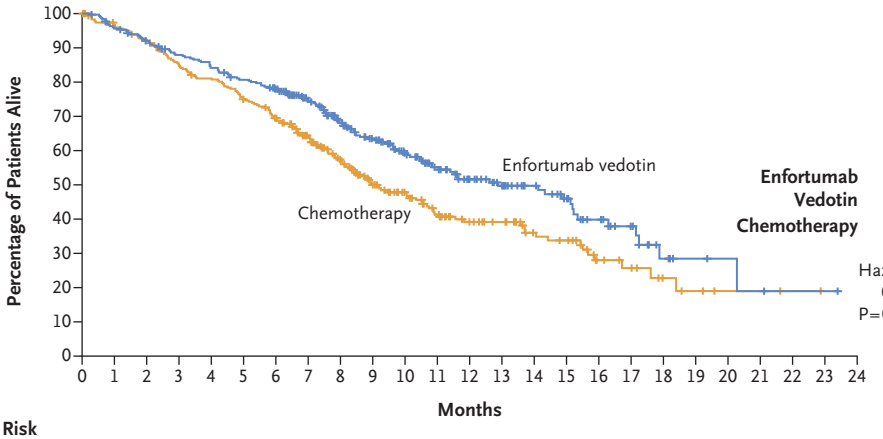
Baseline characteristics were generally balanced between the two groups (Table 1). The median age was 68 years (range, 30 to 88), and 77.3% of patients were men. Visceral disease was present in 77.7% of patients in the enfortumab vedotin group and in 81.7% in the chemotherapy group. The number of patients who had liver metastasis was similar in the two groups. At the date of data cutoff (July 15, 2020), the median duration of treatment was 5.0 months (range, 0.5 to 19.4) in the enfortumab vedotin group and

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Enfortumab Vedotin (N=301)	Chemotherapy (N=307)
Median age (range) — yr	68.0 (34.0–85.0)	68.0 (30.0–88.0)
Age ≥75 yr — no. (%)	52 (17.3)	68 (22.1)
Sex — no. (%)		
Male	238 (79.1)	232 (75.6)
Female	63 (20.9)	75 (24.4)
Geographic region — no. (%)		
Western Europe	126 (41.9)	129 (42.0)
United States	43 (14.3)	44 (14.3)
Rest of the world	132 (43.9)	134 (43.6)
Tobacco use — no. (%)		
Former user	167 (55.5)	164 (53.4)
Current user	29 (9.6)	31 (10.1)
Never used	91 (30.2)	102 (33.2)
Not reported or unknown	14 (4.7)	10 (3.3)
History of diabetes or hyperglycemia — no. (%)	56 (18.6)	58 (18.9)
ECOG performance-status score — no. (%)†		
0	120 (39.9)	124 (40.4)
1	181 (60.1)	183 (59.6)
Bellmunt risk score — no. (%)‡		
0–1	201 (66.8)	208 (67.8)
≥2	90 (29.9)	96 (31.3)
Not reported	10 (3.3)	3 (1.0)
Origin site of primary disease — no. (%)		
Upper urinary tract	98 (32.6)	107 (34.9)
Bladder or other site	203 (67.4)	200 (65.1)
Histologic type at initial diagnosis — no./total no. (%)		
Urothelial or transitional-cell carcinoma	229/301 (76.1)	230/305 (75.4)
Urothelial carcinoma, mixed types	45/301 (15.0)	42/305 (13.8)
Other§	27/301 (9.0)	33/305 (10.8)
Sites of metastasis — no./total no. (%)		
Lymph node only	34/301 (11.3)	28/306 (9.2)
Visceral site	234/301 (77.7)	250/306 (81.7)
Liver	93/301 (30.9)	95/307 (30.9)
Previous systemic therapies — no. (%)		
1–2	262 (87.0)	270 (87.9)
≥3	39 (13.0)	37 (12.1)
Best response among patients who previously received checkpoint inhibitor treatment — no. (%)¶		
Response	61 (20.3)	50 (16.3)
No response	207 (68.8)	215 (70.0)
Median time since diagnosis of metastatic or locally advanced disease (range) — mo	14.8 (0.2–114.1)	13.2 (0.3–118.4)

* Percentages may not total 100 because of rounding.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 4, with higher scores indicating greater disability.
‡ Bellmunt risk scores range from 0 to 3 according to the presence of the following risk factors: a hemoglobin level of less than 10 g per deciliter, an ECOG performance-status score of greater than 0, and liver metastasis.
§ Other histologic types include adenocarcinoma, squamous-cell carcinoma, and pseudosarcomatic differentiation.
¶ The best response among patients who had a response was defined as a confirmed complete or partial response; among patients who did not have a response, the best response was defined as stable disease or progressive disease.

A Overall Survival According to Treatment Group



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Enfortumab Vedotin	134/301	12.88 (10.58–15.21)
Chemotherapy	167/307	8.97 (8.05–10.74)

Hazard ratio for death, 0.70 (95% CI, 0.56–0.89)
P=0.001

No. at Risk

Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

B Deaths According to Subgroup

Subgroup	Enfortumab Vedotin	Chemotherapy	Hazard Ratio (95% CI)
	no. of deaths/no. of patients		
All patients	134/301	167/307	0.70 (0.56–0.89)
Age group			
<65 yr	49/108	66/111	0.68 (0.47–0.99)
≥65 yr	85/193	101/196	0.75 (0.56–1.00)
<75 yr	109/249	128/239	0.69 (0.53–0.89)
≥75 yr	25/52	39/68	0.91 (0.55–1.51)
Sex			
Male	101/238	132/232	0.61 (0.47–0.79)
Female	33/63	35/75	1.17 (0.72–1.89)
Geographic region			
Western Europe	57/126	72/129	0.76 (0.53–1.07)
United States	25/43	25/44	0.88 (0.51–1.54)
Rest of the world	52/132	70/134	0.64 (0.45–0.92)
ECOG performance-status score			
0	40/120	46/124	0.81 (0.53–1.24)
1	94/181	121/183	0.67 (0.51–0.87)
Liver metastasis			
Yes	53/93	63/95	0.66 (0.46–0.96)
No	81/208	104/212	0.73 (0.55–0.98)
Preselected chemotherapy			
Paclitaxel	63/141	59/112	0.71 (0.49–1.01)
Docetaxel	41/87	67/117	0.71 (0.48–1.04)
Vinflunine	30/73	41/78	0.77 (0.48–1.24)
Primary site of tumor			
Upper urinary tract	44/98	52/107	0.85 (0.57–1.27)
Bladder or other site	90/203	115/200	0.67 (0.51–0.88)
Previous systemic therapies			
1–2	115/262	147/270	0.69 (0.54–0.88)
≥3	19/39	20/37	0.88 (0.47–1.64)
Best response among patients who previously received CPI treatment			
Response	18/61	23/50	0.63 (0.34–1.17)
No response	100/207	120/215	0.76 (0.58–0.99)

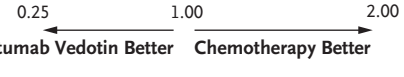


Figure 2 (facing page). Overall Survival in the Intention-to-Treat Population and Analyses in Key Subgroups.

The primary end point of overall survival was defined as the time from randomization to the date of death, assessed in the intention-to-treat population, which included all patients who underwent randomization. Panel A shows the Kaplan–Meier estimates of overall survival according to treatment group. Tick marks indicate censored data. Panel B shows a forest plot of the analyses in prespecified key subgroups in the intention-to-treat population. The dashed line indicates a hazard ratio of 1.00. The hazard ratio for death in all patients was calculated on the basis of an analysis stratified according to the following factors: geographic region (Western Europe, United States, or rest of the world), Eastern Cooperative Oncology Group (ECOG) performance-status score (0 or 1), and the presence or absence of liver metastasis recorded at randomization. The best response among patients who had a response was defined as a confirmed complete or partial response; among patients who did not have a response, the best response was defined as stable disease or progressive disease. In each subgroup, the hazard ratio for death was estimated with the use of unstratified Cox proportional-hazards models. Under an assumption of proportional hazards, a hazard ratio of less than 1.00 favors enfortumab vedotin treatment. CPI denotes checkpoint inhibitor.

3.5 months (range, 0.2 to 15.0) in the chemotherapy group.

OVERALL SURVIVAL

At the time of data cutoff, a total of 301 deaths had occurred (134 in the enfortumab vedotin group and 167 in the chemotherapy group). After a median follow-up of 11.1 months, the risk of death was 30% lower with enfortumab vedotin than with chemotherapy (hazard ratio, 0.70; 95% confidence interval [CI], 0.56 to 0.89; P=0.001), indicating significantly longer overall survival with enfortumab vedotin. Results of sensitivity analyses were consistent with those of the primary analysis (Table S2). The median overall survival was 12.88 months (95% CI, 10.58 to 15.21) in the enfortumab vedotin group and 8.97 months (95% CI, 8.05 to 10.74) in the chemotherapy group (Fig. 2A). The estimated percentage of patients alive at 12 months was 51.5% (95% CI, 44.6 to 58.0) in the enfortumab vedotin group and 39.2% (95% CI, 32.6 to 45.6) in the chemotherapy group. An overall survival benefit of enfortumab vedotin was also observed in most subgroup analyses (Fig. 2B).

PROGRESSION-FREE SURVIVAL

Treatment with enfortumab vedotin resulted in significantly longer progression-free survival than chemotherapy and a 38% lower risk of progression or death (hazard ratio, 0.62; 95% CI, 0.51 to 0.75; P<0.001). The median progression-free survival was 5.55 months (95% CI, 5.32 to 5.82) in the enfortumab vedotin group and 3.71 months (95% CI, 3.52 to 3.94) in the chemotherapy group (Fig. 3). The results of subgroup analyses show that a progression-free survival benefit with enfortumab vedotin was present across multiple subgroups (Fig. S1).

CLINICAL RESPONSE

The confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group (40.6% [95% CI, 34.9 to 46.5] vs. 17.9% [95% CI, 13.7 to 22.8]; P<0.001) (Table S3). The results of subgroup analyses were consistent with those of the primary analysis (Fig. S2). A complete response was observed in 4.9% of the patients (14 of 288) in the enfortumab vedotin group and in 2.7% of the patients (8 of 296) in the chemotherapy group. Disease control was observed in 71.9% (95% CI, 66.3 to 77.0) and 53.4% (95% CI, 47.5 to 59.2), respectively (P<0.001). In patients who had a complete or partial response, the median duration of response was 7.39 months in the enfortumab vedotin group and 8.11 months in the chemotherapy group (Fig. S3).

SAFETY PROFILE

The incidence of treatment-related adverse events was high overall but was similar in the two groups (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group) (Table 2). Treatment-related adverse events of grade 3 or higher occurred in 51.4% of patients in the enfortumab vedotin group and in 49.8% in the chemotherapy group. After adjustment for treatment exposure, the rate was 2.4 and 4.3 events per patient-year in the enfortumab vedotin group and the chemotherapy group, respectively (Table S4). Grade 3 or higher treatment-related adverse events that occurred in at least 5% of patients included maculopapular rash (7.4%), fatigue (6.4%), and decreased neutrophil count (6.1%) in the enfortumab vedotin group and decreased neutrophil count (13.4%), anemia (7.6%), decreased white-cell count (6.9%), neutropenia

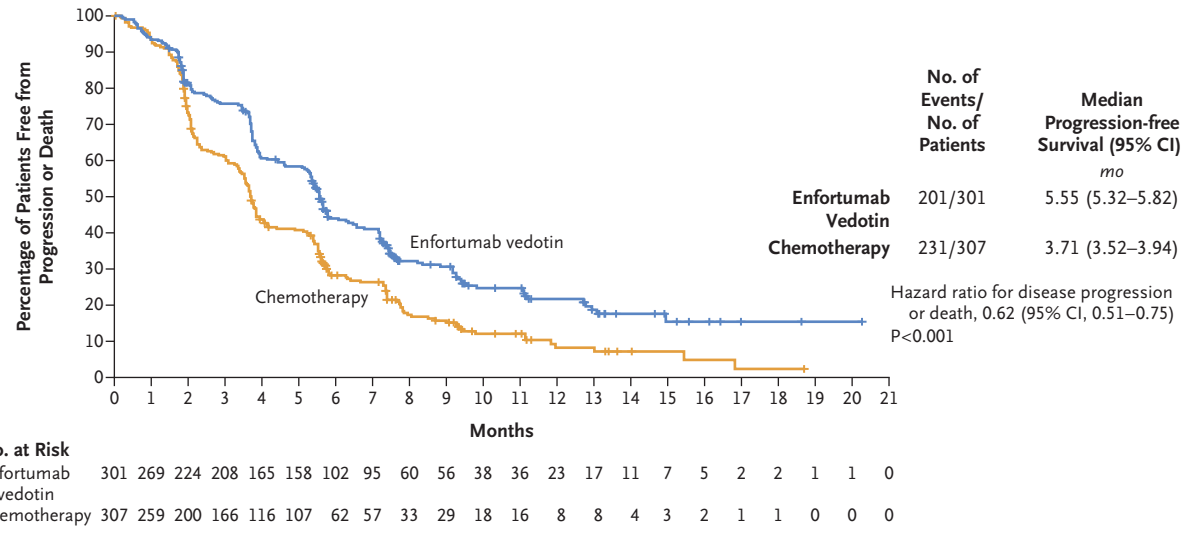


Figure 3. Progression-free Survival in the Intention-to-Treat Population.

Shown are the Kaplan–Meier estimates of progression-free survival according to treatment group. The secondary end point of investigator-assessed progression-free survival was defined as the time from randomization to the date of radiologically confirmed disease progression (according to Response Evaluation Criteria in Solid Tumors, version 1.1) or death from any cause, assessed in the intention-to-treat population, which included all patients who underwent randomization. If the patient did not have disease progression and did not die, data for the patient were censored at the date of the last radiologic assessment. Data for patients who received any further anticancer therapy for urothelial carcinoma before radiologic disease progression were censored at the date of the last radiologic assessment before the new anticancer therapy was initiated. Tick marks indicate censored data.

(6.2%), and febrile neutropenia (5.5%) in the chemotherapy group. Treatment-related adverse events resulting in dose reduction, interruption of treatment, or withdrawal of treatment occurred in 32.4%, 51.0%, and 13.5% of patients in the enfortumab vedotin group, respectively, and in 27.5%, 18.9%, and 11.3% in the chemotherapy group, respectively (Table S5). Exposure-adjusted values are provided in the Supplementary Appendix. All adverse events that occurred during the treatment period are listed in Table S6.

Skin reactions and peripheral neuropathy were the most frequent treatment-related adverse events of special interest with enfortumab vedotin (Table S7). Treatment-related rash occurred in 43.9% of patients who received enfortumab vedotin (grade 1, 13.9%; grade 2, 15.5%; grade 3, 14.2%; grade 4, 0.3%) and in 9.6% of patients who received chemotherapy (grade 1, 7.2%; grade 2, 2.1%; grade 3, 0.3%). Treatment-related peripheral neuropathy, manifesting predominantly as sensory events, occurred in 46.3% of patients in the enfortumab vedotin group and in 30.6% in the chemotherapy group. Grade 1, 2, and 3 peripheral sensory neuropathy occurred in 14.5%, 25.7%, and 3.7% of patients in the enfortumab vedotin group, respectively, and in 15.1%, 12.0%, and 2.4% in the chemotherapy group, respectively. Peripheral sensory neuropathy was the most common treatment-related adverse event that resulted in dose reduction (7.1%), interruption of treatment (15.5%), or withdrawal of treatment (2.4%) in the enfortumab vedotin group.

Treatment-related hyperglycemia occurred in 6.4% (19 patients) in the enfortumab vedotin group and in 0.3% (1 patient) in the chemotherapy group. In the enfortumab vedotin group, 7 patients had grade 1 or 2 hyperglycemia, 11 had grade 3 hyperglycemia, and 1 died. Hyperglycemia occurred more frequently in patients with hyperglycemia at baseline or with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher. The time to the onset of adverse events, the incidence of peripheral neuropathy and hyperglycemia according to baseline status, and the

Table 2. Treatment-Related Adverse Events (Safety Population).*

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

* The safety population included all patients who received any amount of trial drug. Included are treatment-related adverse events that occurred in at least 20% of patients in either treatment group or treatment-related adverse events of grade 3 or higher that occurred in at least 5% of patients in either treatment group. Treatment-related adverse events are those for which there is a reasonable possibility that they were caused by the trial treatment, as assessed by the investigator. If data regarding the relationship to treatment were missing, the event was considered to be related to treatment.

† A total of 113 patients (55 in the enfortumab vedotin group and 58 in the chemotherapy group) had preexisting peripheral neuropathy.

management of selected adverse events are reported in Tables S7 through S9.

Adverse events, regardless of relationship to treatment, that resulted in death (excluding disease progression) during the treatment period occurred in 11 patients in each group; the incidence remained the same after adjustment for treatment exposure. Investigator-assessed treatment-related adverse events that resulted in death occurred in 7 patients (2.4%) in the enfortumab vedotin group (multiorgan dysfunction syndrome [in 2 patients] and abnormal hepatic function, hyperglycemia, pelvic abscess, pneumonia, and septic shock [each in 1 patient]) and in 3 patients (1.0%) in the chemotherapy group (neutropenic sepsis, sepsis, and pancytopenia [each in 1 patient]). The demographic characteristics of the patients in the enfortumab vedotin group who died are provided in Table S10.

DISCUSSION

Enfortumab vedotin showed superior efficacy over chemotherapy in patients with advanced urothelial carcinoma who had previously received treatment with platinum-based chemotherapy and PD-1 or PD-L1 inhibitors. There are limited and largely ineffective treatment options for patients who have disease progression after treatment with platinum chemotherapy and PD-1 or PD-L1 inhibitors. Single-agent chemotherapy is the currently accepted practice, despite limited prospective data and modest outcomes with respect to response and duration of survival.[7,20-24]

Enfortumab vedotin treatment resulted in a 30% lower risk of death than chemotherapy, indicating significantly longer overall survival. The benefit of enfortumab vedotin was observed in most subgroups, including patients with liver

metastasis. Although subgroup analyses did not show an advantage with enfortumab vedotin in female patients, only 22.7% of the patients in the trial were women, which reflects the demographic profile of this disease. Future work would be needed to further explore enfortumab vedotin treatment in specific subgroups.

Progression-free survival, overall response, and disease control with enfortumab vedotin were also superior to those of chemotherapy. Outcomes in the chemotherapy group were as expected in patients with refractory disease after treatment with a platinum-containing agent,[5-7,24] and outcomes in the enfortumab vedotin group were consistent with overall survival and response rates in phase 1 and 2 studies.[16,17] Although tissue samples were obtained for use in exploratory outcomes, nectin-4 expression was not required for entry into the EV-301 trial, since high expression has been observed in the vast majority of patients with advanced urothelial carcinoma in previous studies.[16,17]

The overall incidence of treatment-related adverse events was similar in the two groups. The incidence of treatment-related adverse events was also similar in the two groups after adjustment for exposure and in a comparison of events of grade 3 severity or higher. Skin reactions, frequently manifesting as maculopapular rash, are likely related to nectin-4 expression in the skin.[15,16] The incidence of peripheral neuropathy was higher in the enfortumab vedotin group than in the chemotherapy group. In phase 1 and 2 studies,[16,17] peripheral neuropathy occurred in 49 to 50% of patients; of the 50% of patients who received enfortumab vedotin and had treatment-related peripheral neuropathy in the phase 2 study, 76% had resolution of symptoms or grade 1 symptoms at the last follow-up.[17] Hyperglycemia, an adverse event observed in previous studies,[16,17] occurred in a higher percentage of patients in the enfortumab vedotin group than in the chemotherapy group, although the precise mechanism remains unidentified. Although most adverse events were mild to moderate in severity in this trial, some patients who receive treatment with enfortumab vedotin may have serious adverse events and should be monitored for rash, peripheral neuropathy, and hyperglycemia. The incidence of treatment-related deaths in the enfortumab vedotin group was similar to that observed in previous trials involving patients with advanced, platinum-refractory urothelial carcinoma.[6,25,26] Disease characteristics, preexisting conditions, coexisting conditions, and poor prognostic factors were potential confounders among patients who died in the two groups. Because of the superior overall survival benefit observed at the planned interim analysis, the EV-301 trial was stopped early. Future analyses of quality-of-life data from this trial will further contextualize the efficacy and safety results.

The efficacy data from this trial suggest that enfortumab vedotin may play a role in the treatment of advanced urothelial carcinoma. In light of recent data that support maintenance treatment with the PD-L1 inhibitor avelumab after platinum-containing chemotherapy for advanced urothelial carcinoma, enfortumab vedotin may be considered at the time of the first relapse after maintenance immunotherapy.[27] Phase 2 data for enfortumab vedotin in combination with pembrolizumab as first-line treatment for metastatic disease have resulted in a Breakthrough Therapy designation from the Food and Drug Administration[28] on the basis of high response rates and duration of response.[29] Additional evaluations of regimens containing enfortumab vedotin in the first-line (ClinicalTrials.gov numbers, NCT04223856 and NCT03288545) and perioperative (NCT03924895) contexts are ongoing.

Although skin reactions, peripheral neuropathy, and hyperglycemia were common with enfortumab vedotin, these events were commonly mild to moderate in severity. In patients with advanced urothelial carcinoma who had relapse of disease after platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor, enfortumab vedotin resulted in significantly longer overall survival and progression-free survival and a higher overall response than chemotherapy.

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