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Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

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ABSTRACT

BACKGROUND

No treatment has surpassed platinum-based chemotherapy in improving overall survival in patients with previously untreated locally advanced or metastatic urothelial carcinoma.

METHODS

We conducted a phase 3, global, open-label, randomized trial to compare the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma. Patients were randomly assigned in a 1:1 ratio to receive 3-week cycles of enfortumab vedotin (at a dose of 1.25 mg per kilogram of body weight intravenously on days 1 and 8) and pembrolizumab (at a dose of 200 mg intravenously on day 1) (enfortumab vedotin–pembrolizumab group) or gemcitabine and either cisplatin or carboplatin (determined on the basis of eligibility to receive cisplatin) (chemotherapy group). The primary end points were progression-free survival as assessed by blinded independent central review and overall survival.

RESULTS

A total of 886 patients underwent randomization: 442 to the enfortumab vedotin–pembrolizumab group and 444 to the chemotherapy group. As of August 8, 2023, the median duration of follow-up for survival was 17.2 months. Progression-free survival was longer in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (median, 12.5 months vs. 6.3 months; hazard ratio for disease progression or death, 0.45; 95% confidence interval [CI], 0.38 to 0.54; P<0.001), as was overall survival (median, 31.5 months vs. 16.1 months; hazard ratio for death, 0.47; 95% CI, 0.38 to 0.58; P<0.001). The median number of cycles was 12 (range, 1 to 46) in the enfortumab vedotin–pembrolizumab group and 6 (range, 1 to 6) in the chemotherapy group. Treatment-related adverse events of grade 3 or higher occurred in 55.9% of the patients in the enfortumab vedotin–pembrolizumab group and in 69.5% of those in the chemotherapy group.

CONCLUSIONS

Treatment with enfortumab vedotin and pembrolizumab resulted in significantly better outcomes than chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma, with a safety profile consistent with that in previous reports. (Funded by Astellas Pharma US and others; EV-302 ClinicalTrials.gov number, NCT04223856.)

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*A complete list of the investigators in the EV-302 trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

For decades, platinum-based chemotherapy has been the first-line standard therapy for locally advanced or metastatic urothelial carcinoma; however, treatment outcomes remain poor, with a relatively low 5-year survival rate.[1] Maintenance therapy with avelumab has been shown to result in longer overall survival than best supportive care alone,[2] but a notable proportion of patients do not receive maintenance therapy owing to disease progression or death.[3,4] Although a modest improvement in overall survival has recently been shown for nivolumab when added to gemcitabine–cisplatin,[5] other clinical trials in which a combination of chemotherapy and immune checkpoint inhibition was evaluated have not shown an improvement in overall survival in patients with locally advanced or metastatic urothelial carcinoma.[5-7]

Enfortumab vedotin, an antibody–drug conjugate directed against nectin-4, and pembrolizumab, a programmed death 1 (PD-1) inhibitor, have individually been associated with a survival benefit in patients with previously treated locally advanced or metastatic urothelial carcinoma.[7-11] In preclinical studies, the combination of enfortumab vedotin and a PD-1 inhibitor showed enhanced antitumor activity with lasting antitumor immunity, findings that suggest complementary mechanisms of action.[12] Enfortumab vedotin in combination with pembrolizumab received accelerated approval in the United States for use in patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy; this approval was based on the results of a phase 1b–2 study in which the combination resulted in high incidences of response and durable responses.[13,14]

EV-302 is a phase 3, global, open-label, randomized trial comparing the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma.

Methods

Patients

Eligible adult patients had radiologically documented, histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma (including differentiation in squamous cells or in multiple cell types); there was no preselection for biomarkers, including nectin-4 and programmed death ligand 1 (PD-L1) expression (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Various histologic types such as adenocarcinoma or squamous cell differentiation were included. Key exclusion criteria were previous PD-1 or PD-L1 inhibitor therapy or other systemic therapy (except for neoadjuvant or adjuvant chemotherapy after surgery with recurrence >12 months after the completion of therapy), uncontrolled diabetes, ongoing sensory or motor neuropathy of grade 2 or higher, and previous autoimmune disease for which the patient had received systemic treatment in the previous 2 years. Full eligibility criteria are described in the protocol, available at NEJM.org.

Trial Oversight

The trial was approved by the institutional review board or ethics committee at each site and was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and the policies of the trial sponsors regarding bioethics and human biologic samples. All the patients provided written informed consent before trial entry. The trial was sponsored by Astellas Pharma US; Merck Sharp and Dohme, a subsidiary of Merck; and Seagen. The trial was designed by the sponsors and select members of the steering committee. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript. Medical writers funded by the sponsors provided medical writing and editorial assistance with an earlier version of the manuscript in accordance with Good Publication Practice guidelines.

Trial Design and Treatment

Enrolled patients were randomly assigned in a 1:1 ratio to receive enfortumab vedotin and pembrolizumab (enfortumab vedotin–pembrolizumab group) or chemotherapy (gemcitabine and either cisplatin or carboplatin; chemotherapy group). Patients assigned to the enfortumab vedotin–pembrolizumab group received enfortumab vedotin as an intravenous infusion (at a dose of 1.25 mg per kilogram of body weight with a maximum of 125 mg per dose) on days 1 and 8

and pembrolizumab as an intravenous infusion (at a dose of 200 mg) after the enfortumab vedotin infusion on day 1 of each 3-week cycle. Patients assigned to the chemotherapy group received gemcitabine as an intravenous infusion (at a dose of 1000 mg per square meter of body-surface area) on days 1 and 8 and either cisplatin as an intravenous infusion (at a dose of 70 mg per square meter) or carboplatin as an intravenous infusion (at a dose equivalent to an area under the concentration–time curve of 4.5 to 5 mg per milliliter per minute, calculated by means of the Calvert formula) on day 1 of each 3-week cycle. Randomization was stratified according to eligibility to receive cisplatin (eligible or ineligible), PD-L1 expression status (high or low), and liver metastases (present or absent).

Patients in the chemotherapy group received either cisplatin or carboplatin on the basis of their eligibility to receive cisplatin therapy. Galsky criteria were used to determine cisplatin ineligibility, which was defined by a glomerular filtration rate of 30 to less than 60 ml per minute per 1.73 m^2 of body-surface area, hearing loss of grade 2 or higher, an Eastern Cooperative Oncology Group performance-status score of 2 (on a scale of 0 to 5, with higher scores indicating greater disability), or New York Heart Association class III heart failure at enrollment (Table S1). Patients were rigorously monitored to ensure that they received the protocol-defined platinum-based therapy.

Treatment was continued until the occurrence of disease progression (clinical progression or as confirmed by blinded independent central review), the start of a subsequent anticancer therapy, the occurrence of unacceptable toxic effects, or completion of the maximum number of treatment cycles (chemotherapy, 6 cycles; pembrolizumab, 35 cycles; enfortumab vedotin, no set maximum). The use of maintenance therapy was permitted in the chemotherapy group in geographic regions in which the maintenance therapy was available.

END POINTS

The trial had two primary end points: progression-free survival, which was defined as the time from randomization to the first occurrence of disease progression (as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause (whichever occurred first), and overall survival. Select secondary end points were overall response (defined as a complete or partial response according to RECIST, version 1.1) as assessed by blinded independent central review, the duration of response, the time to pain progression, and safety. Adverse events of special interest were defined for enfortumab vedotin and for pembrolizumab on the basis of previously described criteria unique to each drug.[14] Additional secondary and exploratory efficacy end points, quality of life, and other patient-reported outcomes were assessed but are not reported here.

ASSESSMENTS

Imaging studies were performed at baseline and every 9 weeks (within a 1-week window) after randomization for 18 months and then every 12 weeks (within a 1-week window) until the occurrence of disease progression according to RECIST, version 1.1. Antitumor activity was confirmed by computed tomography, performed after the administration of contrast material, at protocol-specified time points; if such imaging was contraindicated in a patient, an alternative imaging method (specified in the protocol) was used. For each patient, the same imaging method was used throughout the trial. Head imaging and bone imaging were required at screening and were repeated if clinically indicated. Patients were followed until the occurrence of radiologic disease progression, as confirmed by blinded review, or until other criteria were met (details are provided in the protocol). Data regarding patient-reported outcomes (e.g., time to pain progression) were collected by means of an electronic data capture device. The safety assessment included the monitoring and recording of adverse events (including serious adverse events) and adverse events of special interest that have previously been associated with enfortumab vedotin and with pembrolizumab. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

STATISTICAL ANALYSIS

The efficacy analyses were performed in the intention-to-treat population, which was defined as all the patients who had been randomly assigned to a treatment group. Progression-free survival and overall survival were compared in the two treatment groups with the use of a stratified log-rank test. All time-to-event end points were summarized with the use of the Kaplan–Meier method.

A stratified Cox proportional-hazards regression model was used to estimate the hazard ratio and corresponding 95% confidence intervals. Subgroup analyses were prespecified. The percentage of patients with an overall response was compared in the treatment groups with the use of the Cochran–Mantel–Haenszel test. The randomization stratification factors were used in stratified efficacy analyses. Overall response and duration of response were evaluated in patients with measurable disease at baseline. The time to pain progression was evaluated in patients who had received any amount of the trial treatment and had answered at least one question on the Brief Pain Inventory Short-Form questionnaire at baseline. The safety analyses included all the patients who had received any dose of the trial treatment and were performed with the use of descriptive statistics.

During the conduct of this trial, an amendment was instituted to define the use of maintenance therapy after discontinuation or completion of chemotherapy, such that it was not considered to be subsequent anticancer therapy. In addition, censoring rules for subsequent therapies in relation to the analysis of progression-free survival were revised so that the data from patients who received maintenance therapy as the first subsequent therapy in the chemotherapy group would not be censored.

One analysis of progression-free survival and two analyses of overall survival (one interim analysis at the time of the progression-free survival analysis and one final analysis) were planned. The efficacy boundaries for overall survival at the interim and final analyses were determined with the use of O'Brien–Fleming boundaries and the Lan–DeMets spending function. If the results of the two primary end-point analyses were significant, select secondary end points were to be tested with the use of a gatekeeping testing strategy; details are provided in the Supplemental Text section of the Supplementary Appendix. On the basis of the results of the interim analysis of overall survival, our trial met the superiority threshold, and the final results are reported here.

The trial was designed to provide at least 90% power to detect a difference between the groups in progression-free survival and overall survival at two-sided alpha levels of 0.005 and 0.045, respectively. To provide the trial with 90% power to show the superiority of enfortumab vedotin and pembrolizumab over chemotherapy with respect to progression-free survival, under the assumption of a hazard ratio of 0.70 and a median duration of progression-free survival of 7 months in the chemotherapy group, 526 events of disease progression or death would need to occur. A total of 489 deaths would need to occur to provide 93% power to show superiority with respect to overall survival, under the assumption of a hazard ratio of 0.73 and a median duration of overall survival of 15.3 months in the chemotherapy group. The random assignment of approximately 860 patients (430 patients per group) was planned. Detailed methods are provided in the Supplementary Appendix, the protocol, and the statistical analysis plan (provided with the protocol).

RESULTS

RANDOMIZATION AND BASELINE CHARACTERISTICS

A total of 886 patients were randomly assigned to receive enfortumab vedotin and pembrolizumab (442 patients) or chemotherapy (444 patients) (Fig. S2) at 185 sites in 25 countries. As of the data cutoff date (August 8, 2023), the median duration of follow-up for survival was 17.2 months.

The demographic and clinical characteristics of the patients at baseline were generally balanced in the two groups (Table 1) and were representative of the overall patient population with advanced urothelial carcinoma (Table S2). The median age was 69 years (range, 22 to 91), and 76.7% of the patients were men. A total of 67.5% were White, and 21.6% were Asian; Black patients were underrepresented in the trial population. The primary site of origin of the disease was the upper tract in 27.0% of the patients. At the time of the data cutoff, the median duration of treatment in the enfortumab vedotin–pembrolizumab group was 9.4 months (range, 0.3 to 31.9), with a median of 12 cycles (range, 1 to 46). The median duration of treatment with enfortumab vedotin was 7.0 months (range, 0.3 to 31.9), with a median of 9 cycles (range, 1 to 46), and the median duration of treatment with pembrolizumab was 8.5 months (range, 0.3 to 28.5), with a median of 11 cycles (range, 1 to 35). In the chemotherapy group, the median duration of treatment was 4.1 months (range, 0.0 to 7.7), with a median of 6 cycles (range, 1 to 6). In to-

tal, 94.0% of the patients who were eligible to receive cisplatin-based therapy and 97.6% of those who were eligible to receive carboplatin-based therapy according to the protocol received the respective therapy at the first cycle.

PROGRESSION-FREE SURVIVAL

Treatment with enfortumab vedotin and pembrolizumab resulted in longer progression-free survival than treatment with chemotherapy. Overall, 530 events of disease progression or death occurred: 223 in the enfortumab vedotin–pembrolizumab group and 307 in the chemotherapy group. The risk of disease progression or death was 55% lower in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (hazard ratio, 0.45; 95% CI, 0.38 to 0.54; P<0.001). The median duration of progression-free survival was 12.5 months (95% confidence interval [CI], 10.4 to 16.6) in the enfortumab vedotin–pembrolizumab group and 6.3 months (95% CI, 6.2 to 6.5) in the chemotherapy group (Fig. 1A). The results of the analyses of progression-free survival were consistent between the intention-to-treat population and all the prespecified subgroups, including those defined according to cisplatin eligibility status and PD-L1 expression status (Fig. 1B and Fig. S3A through D).

OVERALL SURVIVAL

At the time of the data cutoff, 359 deaths had occurred (133 in the enfortumab vedotin–pembrolizumab group and 226 in the chemotherapy group), which was 73.4% (359 of 489 events) of the required number of events for the final analysis of overall survival. The risk of death was 53% lower in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (hazard ratio, 0.47; 95% CI, 0.38 to 0.58; P<0.001). The median duration of overall survival was 31.5 months (95% CI, 25.4 to not reached) in the enfortumab vedotin–pembrolizumab group and 16.1 months (95% CI, 13.9 to 18.3) in the chemotherapy group (Fig. 2A). The estimated percentage of patients who were alive at 12 months was 78.2% (95% CI, 73.9 to 81.9) in the enfortumab vedotin–pembrolizumab group and 61.4% (95% CI, 56.6 to 65.9) in the chemotherapy group. The overall survival results were consistent between the intention-to-treat population and all the prespecified subgroups, including those defined according to cisplatin eligibility status and PD-L1 expression status (Fig. 2B and Fig. S4A through D).

OVERALL RESPONSE

The confirmed overall response was higher in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (67.7% [95% CI, 63.1 to 72.1] vs. 44.4% [95% CI, 39.7 to 49.2]; P<0.001) (Table 2). A complete response was observed in 29.1% (127 of 437) of the patients in the enfortumab vedotin–pembrolizumab group and in 12.5% (55 of 441) of those in the chemotherapy group. The results of the analysis of overall response were consistent between the intention-to-treat population and all the prespecified subgroups (Fig. S5). The median duration of response was not reached in the enfortumab vedotin–pembrolizumab group and was 7.0 months in the chemotherapy group (Table 2). The percentages of patients who were still in remission at 12 months and 18 months were 67.3% and 59.6%, respectively, in the enfortumab vedotin–pembrolizumab group and 35.2% and 19.3% in the chemotherapy group.

PATIENT-REPORTED OUTCOME

The median time to pain progression was 14.2 months in the enfortumab vedotin–pembrolizumab group as compared with 10.0 months in the chemotherapy group; the between-group difference in the time to pain progression was not significant (hazard ratio, 0.92; 95% CI, 0.72 to 1.17; P=0.48) (Fig. S6). Therefore, the additional patient-reported outcome in the statistical hierarchy was not formally tested.

SUBSEQUENT THERAPIES

As of the data cutoff, 32.6% (144 of 442) of the patients in the enfortumab vedotin–pembrolizumab group and none of the patients in the chemotherapy group were still receiving treatment; 31.7% (140 of 442) of the patients in the enfortumab vedotin–pembrolizumab group and 70.5% (313 of 444) of the patients in the chemotherapy group received subsequent anticancer therapies (Table S3). Among the patients in the enfortumab vedotin–pembrolizumab group who received subsequent therapies, 78.6% (110 of 140 patients) received platinum-based therapy as the first subsequent therapy. Seven patients (1.6%) in the enfortumab vedotin–pembrolizumab group and 260 patients (58.6%) in the chemotherapy group

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Enfortumab Vedotin–Pembrolizumab (N=442)	Chemotherapy (N=444)
Median age (range) — yr	69 (37–87)	69 (22–91)
Age ≥75 yr — no. (%)	102 (23.1)	108 (24.3)
Sex — no. (%)		
Male	344 (77.8)	336 (75.7)
Female	98 (22.2)	108 (24.3)
Race or ethnic group — no. (%)†		
Asian	99 (22.4)	92 (20.7)
Black	3 (0.7)	7 (1.6)
White	308 (69.7)	290 (65.3)
Other‡	5 (1.1)	8 (1.8)
Unknown or not reported	27 (6.1)	47 (10.6)
Geographic region — no. (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of the world	167 (37.8)	162 (36.5)
ECOG performance-status score — no. (%)§		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)
Data missing	0	2 (0.5)
Body-mass index — no. (%)¶		
<25	206 (46.6)	185 (41.7)
25 to <30	144 (32.6)	155 (34.9)
≥30	89 (20.1)	101 (22.7)
Data missing	3 (0.7)	3 (0.7)
Creatinine clearance — no. (%)‖		
≥60 ml/min	249 (56.3)	257 (57.9)
<60 ml/min	193 (43.7)	187 (42.1)
No. of Bajorin risk factors — no. (%)**		
0	179 (40.5)	183 (41.2)
1	263 (59.5)	259 (58.3)
Data missing	0	2 (0.5)
H score of nectin-4 expression††		
No. of patients tested	394	406
Median score (range)	280 (0–300)	270 (0–300)
Disease status at randomization — no. (%)		
Locally advanced	21 (4.8)	24 (5.4)
Metastatic	421 (95.2)	420 (94.6)

Table 1. (Continued.)

Characteristic	Enfortumab Vedotin–Pembrolizumab (N=442)	Chemotherapy (N=444)
Primary site of origin of disease — no. (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)
Unknown	2 (0.5)	1 (0.2)
Histologic type — no. (%)		
Urothelial carcinoma	379 (85.7)	373 (84.0)
Urothelial carcinoma, mixed types‡‡	50 (11.3)	53 (11.9)
Variant urothelial carcinoma only	4 (0.9)	7 (1.6)
Unknown	9 (2.0)	11 (2.5)
Sites of metastasis — no. (%)		
Lymph node only	103 (23.3)	104 (23.4)
Visceral site	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Cisplatin eligibility status — no. (%)		
Eligible	240 (54.3)	242 (54.5)
Ineligible	202 (45.7)	202 (45.5)
PD-L1 expression — no./total no. (%)§§		
High, CPS ≥10	254/438 (58.0)	254/439 (57.9)
Low, CPS <10	184/438 (42.0)	185/439 (42.1)

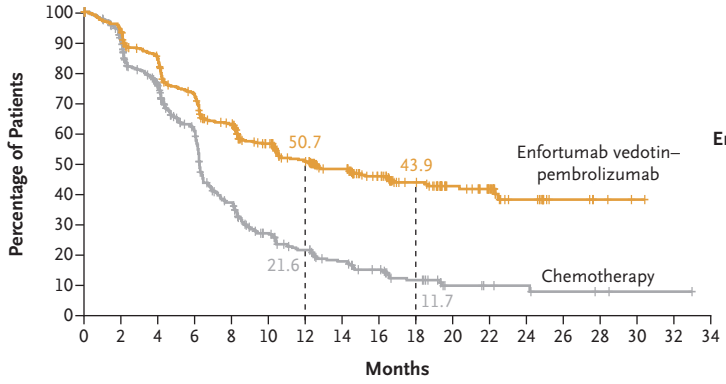
* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the patient.
‡ This category comprises other ethnic groups (including American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander) and multiple ethnic groups.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ To convert the values for creatinine clearance to milliliters per second, multiply by 0.01667.
** Bajorin risk factors include visceral metastases (metastases to the bone, lung, or liver) and an ECOG performance-status score of 3 or higher. Patients with an ECOG performance-status score of higher than 2 were not eligible for the trial.
†† Nectin-4 H scores were determined with the use of a validated Nectin-4 immunohistochemical assay performed at Q2 Solutions. H scores range from 0 to 300, with higher values indicating higher expression.
‡‡ This category included histologic types such as squamous, glandular, and micropapillary.
§§ Programmed death ligand 1 (PD-L1) expression was assessed with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumor and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

received PD-1 or PD-L1 inhibitor–containing therapy as the first subsequent systemic therapy, including 143 patients (32.2% total; 135 patients [30.4%] received avelumab) who received maintenance therapy.

SAFETY

Treatment-related adverse events of any grade occurred in 427 patients (97.0%) in the enfortumab vedotin–pembrolizumab group and in 414 patients (95.6%) in the chemotherapy group (Table 3). The

A Progression-free Survival



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

No. at Risk

Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

B Subgroup Analysis

Subgroup	Enfortumab Vedotin–Pembrolizumab	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
	mo (no. of events/no. of patients)		
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
Age			
<65 yr	12.7 (75/144)	6.4 (88/135)	0.45 (0.32–0.62)
≥65 yr	12.0 (148/298)	6.2 (219/309)	0.45 (0.36–0.56)
Race			
White	10.4 (168/308)	6.2 (207/290)	0.48 (0.39–0.60)
Other	22.3 (55/134)	6.5 (100/154)	0.39 (0.27–0.55)
Geographic region			
North America	12.0 (58/103)	6.3 (55/85)	0.56 (0.38–0.82)
Europe	10.4 (94/172)	6.3 (144/197)	0.50 (0.38–0.66)
Rest of the world	NE (71/167)	6.2 (108/162)	0.35 (0.26–0.48)
Sex			
Female	10.4 (55/98)	6.1 (74/108)	0.49 (0.34–0.71)
Male	14.6 (168/344)	6.3 (233/336)	0.44 (0.36–0.54)
ECOG performance-status score			
0	22.3 (93/223)	6.7 (146/215)	0.36 (0.28–0.48)
1 or 2	9.3 (130/219)	6.1 (161/227)	0.53 (0.42–0.68)
Primary site of origin of disease			
Upper tract	12.7 (69/135)	6.2 (70/104)	0.50 (0.35–0.71)
Lower tract	12.5 (152/305)	6.3 (236/339)	0.44 (0.35–0.54)
Liver metastases			
Present	8.2 (66/100)	6.0 (78/99)	0.53 (0.38–0.76)
Absent	16.4 (157/342)	6.4 (229/345)	0.43 (0.35–0.52)
PD-L1 expression			
Low (CPS <10)	10.5 (105/184)	6.3 (127/185)	0.50 (0.38–0.65)
High (CPS ≥10)	18.5 (116/254)	6.2 (176/254)	0.42 (0.33–0.53)
Cisplatin eligibility status			
Eligible	14.6 (117/244)	6.5 (149/234)	0.48 (0.38–0.62)
Ineligible	10.6 (106/198)	6.1 (158/210)	0.43 (0.33–0.55)
Site of metastasis			
Visceral site	10.4 (176/318)	6.2 (238/318)	0.45 (0.37–0.55)
Lymph node only	NE (38/103)	8.3 (55/104)	0.40 (0.26–0.62)
Renal function			
Normal	18.7 (38/84)	6.7 (61/95)	0.46 (0.30–0.71)
Mild impairment	12.7 (79/165)	6.3 (114/162)	0.46 (0.34–0.62)
Moderate or severe impairment	10.5 (106/193)	6.2 (132/187)	0.47 (0.36–0.61)

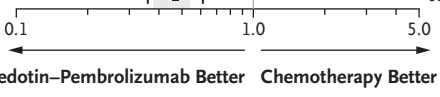


Figure 1 (facing page). Analysis of Progression-free Survival in Overall Population and in Prespecified Subgroups.

Panel A shows Kaplan–Meier estimates of progression-free survival according to treatment group in the intention-to-treat population. The dashed lines indicate progression-free survival at 12 and 18 months. The tick marks indicate censored data. Panel B shows a forest plot of the analyses of progression-free survival in all prespecified subgroups. The shaded area represents the 95% confidence intervals for the overall patient population. Race was reported by the patient. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumor and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. NE denotes could not be estimated.

most common treatment-related adverse events of any grade in the enfortumab vedotin–pembrolizumab group were peripheral sensory neuropathy (in 50.0% of patients), pruritus (in 39.8%), and alopecia (in 33.2%); the most common such events in the chemotherapy group were anemia (in 56.6%), neutropenia (in 41.6%), and nausea (in 38.8%).

Treatment-related adverse events of grade 3 or higher occurred in 55.9% of the patients in the enfortumab vedotin–pembrolizumab group and in 69.5% of those in the chemotherapy group. After adjustment for treatment exposure, the rate was 1.273 events per patient-year in the enfortumab vedotin–pembrolizumab group and 5.358 events per patient-year in the chemotherapy group (Table S4). The most common treatment-related adverse events of grade 3 or higher were maculopapular rash (in 7.7% of patients), hyperglycemia (in 5.0%), and neutropenia (in 4.8%) in the enfortumab vedotin–pembrolizumab group and anemia (in 31.4%), neutropenia (in 30.0%), and thrombocytopenia (in 19.4%) in the chemotherapy group.

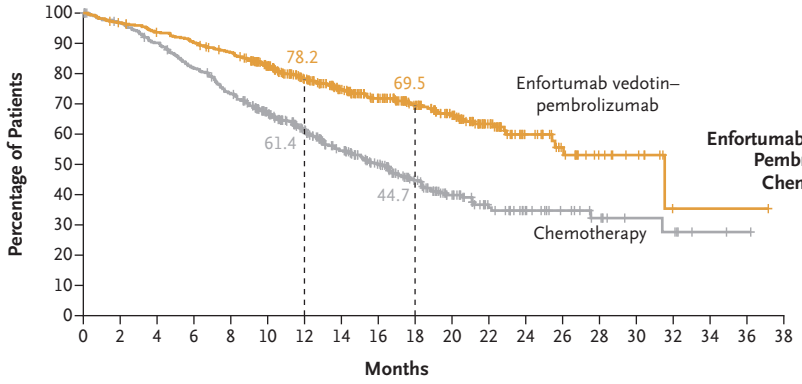
In the enfortumab vedotin–pembrolizumab group, the most common treatment-related adverse events of special interest of grade 3 or higher that have previously been associated with enfortumab vedotin were skin reactions (in 15.5% of patients), peripheral neuropathy (in 6.8%), and hyperglycemia (in 6.1%); of these events, only skin reactions occurred in the chemotherapy group (in 0.2% of patients) (Table S5). In the enfortumab vedotin–pembrolizumab group, the most common adverse events of special interest of grade 3 or higher that have previously been associated with pembrolizumab that occurred after the start of the trial treatment were severe skin reactions (in 11.8% of patients), pneumonitis (in 3.6%), and hepatitis (in 1.8%); of these events, only pneumonitis occurred in the chemotherapy group (in 0.2% of patients) (Table S6). Most of these adverse events of special interest were manageable with dose modifications.

Treatment-related adverse events resulting in dose reduction of any treatment occurred in 40.7% and 37.9% of the patients in the enfortumab vedotin–pembrolizumab and chemotherapy groups, respectively; treatment-related adverse events resulting in discontinuation of any treatment occurred in 35.0% and 18.5% of patients, respectively. In the enfortumab vedotin–pembrolizumab group, treatment-related adverse events led to the discontinuation of enfortumab vedotin in 29.5% of the patients and to the discontinuation of pembrolizumab in 21.4% of the patients. Discontinuation of enfortumab vedotin and discontinuation of pembrolizumab were not mutually exclusive; patients were permitted to continue treatment with either agent independently after discontinuation of the other. The most common treatment-related adverse event leading to discontinuation of any trial drug was peripheral sensory neuropathy (in 10.7% of patients) in the enfortumab–pembrolizumab group and anemia (in 2.8%) in the chemotherapy group (Table S7). Treatment-related adverse events that resulted in death occurred in 4 patients (<1.0%) in the enfortumab vedotin–pembrolizumab group (multiple organ dysfunction syndrome, immune-mediated lung disease, diarrhea, and asthenia; 1 patient each) and in 4 patients (<1.0%) in the chemotherapy group (sepsis, febrile neutropenia, neutropenic sepsis, and myocardial infarction; 1 patient each).

DISCUSSION

The EV-302 trial showed a significant and clinically meaningful benefit of enfortumab vedotin and pembrolizumab over chemotherapy with respect to progression-free survival and overall survival in patients with previously untreated locally advanced or metastatic urothelial carcinoma. The risk of disease progression or death in the

A Overall Survival



	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	133/442	31.5 (25.4–NE)
Chemotherapy	226/444	16.1 (13.9–18.3)

Hazard ratio, 0.47 (95% CI, 0.38–0.58)
Two-sided P<0.001

No. at Risk

Enfortumab vedotin–pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

B Subgroup Analysis

Subgroup	Enfortumab Vedotin–Pembrolizumab	Chemotherapy	Hazard Ratio for Death (95% CI)
	mo (no. of events/no. of patients)		
Overall	31.5 (133/442)	16.1 (226/444)	0.47 (0.38–0.58)
Age			
<65 yr	NE (39/144)	19.7 (58/135)	0.46 (0.30–0.71)
≥65 yr	31.5 (94/298)	14.6 (168/309)	0.48 (0.38–0.63)
Race			
White	26.1 (104/308)	15.3 (162/290)	0.47 (0.36–0.60)
Other	NE (29/134)	19.3 (64/154)	0.46 (0.29–0.72)
Geographic region			
North America	25.6 (40/103)	21.2 (42/85)	0.71 (0.44–1.12)
Europe	NE (56/172)	13.9 (110/197)	0.40 (0.28–0.56)
Rest of the world	NE (37/167)	16.4 (74/162)	0.41 (0.27–0.61)
Sex			
Female	25.4 (32/98)	14.6 (54/108)	0.51 (0.32–0.80)
Male	31.5 (101/344)	16.6 (172/336)	0.47 (0.36–0.60)
ECOG performance-status score			
0	NE (44/223)	18.4 (94/215)	0.36 (0.25–0.53)
1 or 2	25.4 (89/219)	13.1 (131/227)	0.54 (0.41–0.72)
Primary site of origin of disease			
Upper tract	NE (38/135)	18.4 (45/104)	0.53 (0.34–0.83)
Lower tract	31.5 (94/305)	15.6 (180/339)	0.46 (0.36–0.59)
Liver metastases			
Present	19.1 (43/100)	10.1 (67/99)	0.47 (0.32–0.71)
Absent	NE (90/342)	17.9 (159/345)	0.47 (0.36–0.61)
PD-L1 expression			
Low (CPS <10)	NE (53/184)	15.5 (99/185)	0.44 (0.31–0.61)
High (CPS ≥10)	31.5 (79/254)	16.6 (125/254)	0.49 (0.37–0.66)
Cisplatin eligibility status			
Eligible	31.5 (69/244)	18.4 (106/234)	0.53 (0.39–0.72)
Ineligible	NE (64/198)	12.7 (120/210)	0.43 (0.31–0.59)
Site of metastasis			
Visceral site	25.6 (108/318)	13.6 (182/318)	0.47 (0.37–0.60)
Lymph node only	NE (22/103)	27.5 (39/104)	0.46 (0.27–0.78)
Renal function			
Normal	26.1 (24/84)	18.4 (44/95)	0.51 (0.30–0.86)
Mild impairment	NE (42/165)	16.4 (78/162)	0.44 (0.30–0.65)
Moderate or severe impairment	31.5 (67/193)	13.3 (104/187)	0.50 (0.37–0.69)

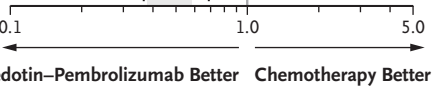


Figure 2 (facing page). Analysis of Overall Survival in Overall Population and in Prespecified Subgroups.

Panel A shows Kaplan–Meier estimates of overall survival according to treatment group in the intention-to-treat population. The dashed lines indicate overall survival at 12 and 18 months. Panel B shows a forest plot of the analyses of overall survival in all prespecified subgroups. Because the results of the interim analysis of overall survival were significant, the interim analysis was considered to be the final analysis.

enfortumab vedotin–pembrolizumab group was 55% lower than the risk in the chemotherapy group. Similarly, treatment with enfortumab vedotin and pembrolizumab resulted in a 53% lower risk of death than chemotherapy. The percentages of patients who had an overall response were also significantly higher with enfortumab vedotin and pembrolizumab than with chemotherapy. A majority of these responses were ongoing at 12 and 18 months in the enfortumab vedotin–pembrolizumab group, a finding that supports these efficacy results. The percentage of patients who had a complete response with enfortumab vedotin and pembrolizumab (29.1%) was higher than the percentage observed with chemotherapy and is higher than results reported previously.[5,6,15] The percentage of patients with a complete response in the chemotherapy group is similar to the percentages observed in the control groups of contemporary phase 3 trials in which patients received platinum-based chemotherapy.[5-7,15] The efficacy benefits were seen across all the prespecified subgroups, such as those defined according to the presence or absence of liver metastases, cisplatin eligibility status, and PD-L1 expression status. The trial showed a survival benefit of enfortumab vedotin and pembrolizumab over standard platinum-based chemotherapy in the first-line treatment of locally advanced or metastatic urothelial carcinoma both among patients who were eligible to receive cisplatin and among those who were ineligible to receive such treatment.[5-7,15]

The safety profile of the combination of enfortumab vedotin and pembrolizumab was consistent with that seen previously for this combination,[14] with no new safety signals identified. Despite the longer duration of treatment in the enfortumab vedotin–pembrolizumab group, the incidence of treatment-related adverse events of grade 3 or higher was lower than the incidence

Table 2. Overall Response and Duration of Response.*

Variable	Enfortumab Vedotin–Pembrolizumab (N=437)	Chemotherapy (N=441)
Confirmed best overall response — no. (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Could not be evaluated†	0	4 (0.9)
No assessment‡	21 (4.8)	32 (7.3)
Confirmed overall response (95% CI) — %§	67.7 (63.1–72.1)	44.4 (39.7–49.2)
Median time to response (range) — mo	2.1 (1.3–12.3)	2.1 (1.6–8.3)
Median duration of response (95% CI) — mo	Not reached (20.2–NE)	7.0 (6.2–10.2)

* Overall response and duration of response, as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were evaluated in all the patients in the intention-to-treat population who had measurable disease at baseline according to RECIST, version 1.1. NE denotes could not be estimated.
† Patients had a postbaseline assessment of response, but the best overall response could not be evaluated according to RECIST, version 1.1.
‡ Patients had no postbaseline assessment of response.
§ P<0.001.

Table 3. Treatment-Related Adverse Events.*

Adverse Event	Enfortumab Vedotin–Pembrolizumab (N=440)		Chemotherapy (N=433)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	Number of patients (percent)			
Any adverse event	427 (97.0)	246 (55.9)	414 (95.6)	301 (69.5)
Peripheral sensory neuropathy	220 (50.0)	16 (3.6)	43 (9.9)	0
Pruritus	175 (39.8)	5 (1.1)	21 (4.8)	0
Alopecia	146 (33.2)	2 (0.5)	34 (7.9)	1 (0.2)
Maculopapular rash	144 (32.7)	34 (7.7)	14 (3.2)	0
Fatigue	129 (29.3)	13 (3.0)	156 (36.0)	18 (4.2)
Diarrhea	121 (27.5)	16 (3.6)	48 (11.1)	3 (0.7)
Decreased appetite	118 (26.8)	5 (1.1)	98 (22.6)	6 (1.4)
Nausea	89 (20.2)	5 (1.1)	168 (38.8)	12 (2.8)
Anemia	61 (13.9)	15 (3.4)	245 (56.6)	136 (31.4)
Hyperglycemia	48 (10.9)	22 (5.0)	3 (0.7)	0
Neutropenia	40 (9.1)	21 (4.8)	180 (41.6)	130 (30.0)
Neutrophil count decreased	16 (3.6)	11 (2.5)	54 (12.5)	39 (9.0)
Thrombocytopenia	15 (3.4)	2 (0.5)	148 (34.2)	84 (19.4)
Platelet count decreased	3 (0.7)	0	63 (14.5)	28 (6.5)

* Included are treatment-related adverse events that occurred in at least 20% of the patients in either treatment group and treatment-related adverse events of grade 3 or higher that occurred in at least 5% of the 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. This analysis included all the patients who had received any dose of the trial treatment.

in the chemotherapy group. The most common adverse events of special interest of grade 3 or higher that have previously been associated with enfortumab vedotin were skin reactions, peripheral neuropathy, and hyperglycemia. The most common adverse events of special interest of grade 3 or higher that have previously been associated with pembrolizumab included severe skin reactions, pneumonitis, and hepatitis. Early recognition of adverse reactions through proactive monitoring and management of symptoms remains a cornerstone of patient care with enfortumab vedotin and pembrolizumab.

Treatment with enfortumab vedotin and pembrolizumab resulted in median durations of progression-free and overall survival that were nearly double those observed with chemotherapy. The median overall survival seen in the enfortumab vedotin–pembrolizumab group is at least as long as that seen in previous phase 2 trials; this result may be attributable to the inclusion of patients who were eligible to receive cisplatin in the EV-302 trial, given that this patient population generally has better survival outcomes than patients with locally advanced or metastatic urothelial carcinoma who are ineligible to receive cisplatin.[16] The magnitude of the survival benefit with enfortumab vedotin and pembrolizumab as compared with chemotherapy is stable, with approximately three quarters of the survival events for the final analysis having occurred. The delay in the patient-reported outcome, time to pain progression, did not differ significantly between the two groups. More detailed patient-reported analysis will be needed to contextualize the effect of these findings in patients.

The subsequent therapies in the chemotherapy group in this trial reflected the contemporary standard treatment that involves a high use of subsequent anti–PD-1 or anti–PD-L1 therapy (58.6% [260 of 444 patients]), including maintenance therapy with avelumab (30.4% [135 of 444 pa-

tients]). The percentage of patients who received maintenance therapy in the chemotherapy group is aligned with recent real-world observations, which showed that avelumab is used as maintenance therapy in 20 to 40% of patients who had previously received platinum-based chemotherapy.[17-20] The expected use of maintenance therapy with avelumab in clinical trials is unknown. At baseline, it was unclear which patients would be eligible to receive maintenance avelumab therapy; therefore, it is not possible to compare the subgroup of patients who received the maintenance avelumab therapy directly with the subgroup who received enfortumab vedotin and pembrolizumab. The combination of enfortumab vedotin and pembrolizumab was associated with a lower incidence of radiologic progression of primary disease than chemotherapy, and this finding may account for some of the benefits seen. At the time of data cutoff, 31.7% (140 of 442) of the patients in the enfortumab vedotin–pembrolizumab group had received subsequent anticancer therapies, with a majority of patients having received platinum-based chemotherapy as second-line therapy, and 32.6% (144 of 442) of the patients continued to receive the trial treatment.

This trial showed a significant survival benefit of enfortumab vedotin and pembrolizumab as compared with chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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