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Patient-Reported Outcomes in Patients With Advanced Urothelial Cancer Who Are Ineligible for Cisplatin and Treated With First-Line Enfortumab Vedotin Alone or With Pembrolizumab

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ABSTRACT

PURPOSE Locally advanced/metastatic urothelial cancer (la/mUC) affects patients' quality of life (QOL) and functioning. We describe the impact of first-line (1L) enfortumab vedotin (EV) alone or with pembrolizumab (P) on QOL/functioning/symptoms in patients with la/mUC who were cisplatin-ineligible from EV-103 Cohort K.

METHODS In this phase Ib/II trial, patients were randomly assigned 1:1 to EV + P or EV monotherapy (mono). Exploratory patient-reported outcomes (PROs) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30) and Brief Pain Inventory Short Form (BPI-SF) at baseline, once per week for cycles 1-3, and then in every cycle through the end of treatment. Changes in scores from baseline to week 24, reported as least squares mean (standard error), were assessed by mixed models for repeated measures. There were no formal statistical comparisons between treatment arms.

RESULTS Of 149 patients treated, 65 (EV + P) and 63 (EV mono) comprised the PRO analysis set. For EV + P, EORTC QLQ-C30 QOL was maintained through week 24 with improvements in emotional functioning, pain, and insomnia. Clinically meaningful improvements were seen in EORTC QLQ-C30 pain after EV + P at weeks 12 (−14.41 [3.14]) and 24 (−14.99 [3.56]) and BPI-SF worst pain at week 24 (−2.07 [0.37]). For EV mono, EORTC QLQ-C30 QOL remained stable with clinically meaningful improvements in EORTC QLQ-C30 pain (−12.55 [4.27]), insomnia (−14.46 [4.69]), and constipation (−10.09 [4.35]) at week 24. There were small-to-moderate improvements in BPI-SF worst pain at week 24.

CONCLUSION EV + P in patients with la/mUC who were cisplatin-ineligible was associated with preservation or improvement of QOL/functioning/symptoms. Improvement in pain was seen in both PRO instruments and treatment arms. These data complement clinical outcomes of 1L EV + P.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Locally advanced/metastatic urothelial cancer (la/mUC) is an aggressive and incurable disease in which patients have a poor prognosis with an estimated 5-year survival rate of 8% in the United States.[1] la/mUC is associated with a high symptom burden, which negatively affects quality of life (QOL) and functioning in patients.[2,3]

Cisplatin-based chemotherapy followed by immunotherapy maintenance is the preferred first-line (1L) treatment option for eligible patients with la/mUC.[4-6] However, approximately 50% of patients are considered unfit for 1L cisplatin-based chemotherapy because of impaired renal function, poor performance status, and/or comorbidities.[7-9] There is a need for effective 1L treatment options for patients with la/mUC who are cisplatin-ineligible.

CONTEXT

Key Objective

What is the impact of first-line enfortumab vedotin (EV) with or without pembrolizumab (P) on quality of life (QOL), functioning, and symptoms in patients with locally advanced/metastatic urothelial cancer (la/mUC) who are cisplatin-ineligible?

Knowledge Generated

In patients with la/mUC who were cisplatin-ineligible in Cohort K of the EV-103 trial, EV with or without P was associated with preservation or improvements in QOL, emotional functioning, and insomnia. Treatment was associated with clinically meaningful improvements in pain at week 24.

Relevance *(M.A. Carducci)*

This summary provides information important to patients as they evaluate treatment options for advanced urothelial cancer with their providers. This study incorporated the patient perspective in the early phase development stage of this novel therapeutic gathering such data early to help with patient counseling and correlation with patient benefit.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD, FACP, FASCO.

In phase Ib/II EV-103 study Cohort K, the efficacy and safety of enfortumab vedotin (EV) with/without pembrolizumab (P) were assessed in 1L or previously untreated patients with la/mUC who were cisplatin-ineligible. EV + P showed a confirmed objective response rate (ORR) of 64.5% (95% CI, 52.7 to 75.1) and a manageable safety profile with fatigue, peripheral sensory neuropathy, alopecia, and maculopapular rash as the most common side effects.[10] Data from the EV-103 Cohort K and dose escalation/cohort A results[11] led to US Food and Drug Administration–accelerated approval of EV + P for this patient population.[12] In EV-103 Cohort K, EV monotherapy (mono) also demonstrated efficacy (ORR, 45.2% [95% CI, 33.5 to 57.3]) and a tolerable safety profile (most common side effects were peripheral sensory neuropathy, fatigue, and decreased appetite),[10] which were consistent with previous results in previously treated la/mUC.[13,14]

For patients with la/mUC who are cisplatin-ineligible, worsening pain and impaired emotional functioning have been reported as salient symptoms/impacts compared with patients with other advanced malignancies.[15] There are limited data from patient-reported outcomes (PROs), including the impact on pain severity, with 1L therapies in this patient population.[3]

Using two well-defined and validated PRO instruments to capture QOL, functioning, and symptoms, including pain in cancer (the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire [EORTC QLQ-C30] and Brief Pain Inventory Short Form [BPI-SF]),[3,16,17] we describe the impact of 1L EV + P or EV mono on QOL, functioning, and symptoms in patients with la/mUC who are cisplatin-ineligible in Cohort K of the EV-103 trial.

METHODS

Study Design and Participants

Cohort K is a cohort of the ongoing, open-label, multicohort EV-103 study assessing the efficacy and safety of EV alone (EV mono) or in combination with P (EV + P) in patients with la/mUC who are cisplatin-ineligible. The Protocol (online only) was approved by independent review boards or ethics committees, and the trial was conducted in agreement with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice Guidelines and registered on ClinicalTrials.gov (identifier: NCT03288545). All participants provided written informed consent.

The methodology for the EV-103 study has been published previously.[10] Briefly, eligible patients were 18 years and older with previously untreated la/mUC who were cisplatin-ineligible (on the basis of Galsky criteria[8]), had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2, and were eligible for P therapy. See Appendix 1 (online only) for more details.

Study Treatment

Patients were randomly assigned 1:1 to receive EV mono (1.25 mg/kg once daily, intravenously) on days 1 and 8 or EV + P (200 mg once daily, intravenously) on day 1 of 3-week cycles. Random assignment was stratified by ECOG PS (0 *v* 1 or 2) and the presence versus absence of liver metastasis.

Study Assessments

The impact on QOL, functioning, and symptoms from the patient perspective was an exploratory end point in the study,

which used a validated methodology to conduct PRO analyses in patients with la/mUC. The EORTC QLQ-C30[18] has been validated in patients with la/mUC and was used as a standard approach in key trials[19-22] including KEYNOTE-052 in patients with la/mUC who were considered platinum-ineligible.[23] The EORTC QLQ-C30[18] is a 30-item questionnaire that assesses QOL in patients with cancer categorized into five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global QOL/health status score. All domain scores are converted to a 0-100 scale. For symptom scales and items, higher scores represent greater symptom burden. For functioning scales and QOL, higher scores indicate better functioning and QOL.[24] The BPI-SF[3,25,26] is an eight-item questionnaire that has been validated in la/mUC to assess severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; location of pain; pain medications; and pain interference with daily functioning. Pain severity (worst, least, average, and right now) and interference (in general activity, mood, walking activity, normal work, relations with others, enjoyment of life, and sleep) items are scored using a 10-point Likert scale (0-10): higher scores represent more pain or greater interference. EuroQoL five dimensions, five labels assessment was also performed as described in Appendix 1 and 2.[27]

Patients completed the EORTC QLQ-C30 and BPI-SF via an electronic device (or on paper or via telephone if the use of an electronic device was not feasible or available; Appendix 1) at baseline (day 1; postrandomization and predose), once per week for cycles 1-3, once every cycle through the end of treatment (EOT), and once at each follow-up visit (every 9 weeks until 1 year and every 12 weeks thereafter through long-term follow-up). PRO questionnaires were also completed at EOT (Appendix Fig A1). Data captured through only EOT were analyzed.

Clinically meaningful improvements in QOL, functioning, and symptom scores were identified using predefined meaningful change thresholds (MCTs). On the basis of a previously validated approach for the EORTC QLQ-C30,[28] a 10-point change from baseline in PRO scores at the patient level was an appropriate threshold indicating moderate change.[28] For the mean group change, a lower threshold of approximately 5-10 points was applied to indicate mild/moderate improvement.[29,30] For the BPI-SF, a validated 2-point change from baseline was applied to indicate meaningful changes.[31-33]

Time to sustained improvement was evaluated using the Kaplan–Meier method and was defined as the time from the start of treatment to sustained improvement, as defined by derived MCTs, where clinically meaningful improvement was sustained for two or more consecutive assessments. In a subgroup of patients with moderate-to-severe pain at baseline, defined as those who scored ≥5 on BPI-SF worst pain (moderate pain, 5-6; severe pain, 7-10), time to improvement analyses were replicated for a selection of EORTC QLQ-C30 scales (QOL, physical/role/emotional functioning) and symptoms (fatigue and pain) and BPI-SF items (worst pain and pain interference) considered meaningful to patients.

Statistical Analysis

All analyses were performed on the patient-reported outcome population (PRP), unless otherwise specified, using SAS Version 9.4 or higher (SAS Institute, Inc, Cary, NC). The PRP consisted of patients who completed at least one question of any PRO questionnaire at baseline. On the basis of the prespecified statistical plan and trial design, no formal statistical comparisons between the EV + P and EV mono arm were planned. For these PRO analyses, no adjustments in statistical significance testing for multiple comparisons were performed.

For each questionnaire, compliance was defined as the proportion of patients who completed the PRO instrument of the number of patients expected at that visit, on the basis of the treatment end date; the number of patients who remained on treatment within the study at each assessment was used as the denominator.

For the longitudinal modeling of PRO end points, mixed models for repeated measures[34] (MMRM; least squares [LSs] mean defined as the mean difference in scores between baseline and follow-up timepoints, standard error [SE]) not adjusted for multiplicity were used to estimate change from baseline until week 24 for all EORTC QLQ-C30 and BPI-SF scales. An MMRM approach was applied to manage missing data, using all available observations and yielding unbiased estimates by assuming that missing data follow the same distribution as the observed data, conditional on observed data. Weeks 8-12, 24, and 51 were prespecified timepoints of interest; analyses at week 51 were not conducted because of limited data.

RESULTS

Patient Disposition and Baseline Characteristics

At data cutoff (June 10, 2022), 151 patients were randomly assigned and 149 were treated with either EV + P (n = 76) or EV mono (n = 73). Baseline demographics and clinical characteristics are summarized in Table 1. Of 76 and 73 patients who received EV + P and EV mono, respectively, 65 and 63 patients completed at least one question of any PRO questionnaire at baseline and comprised the PRP.

PRO Questionnaires' Compliance Rates

For the EORTC QLQ-C30, compliance rates were 85.5% (65 of 76) and 83.6% (61 of 73) for EV + P and EV mono, respectively, at baseline and generally remained above 67.0% and 63.0% through week 24; for the BPI-SF, these values were 81.6% (62 of 76) and 80.8% (59 of 73) at baseline and generally remained above 73.0% and 68.0% until week 24.

TABLE 1. Baseline Demographics and Clinical Characteristics Among Previously Untreated Patients With la/mUC Who Were Cisplatin-Ineligible in Cohort K of the EV-103 Study (ITT population)

Baseline Demographic and Clinical Characteristic	EV + P (n = 76)	EV Mono (n = 73)
Male sex, No. (%)	54 (71.1)	56 (76.7)
Age, years, median (range)	71 (51-91)	74 (56-89)
Race, No. (%)		
White	61 (80.3)	55 (75.3)
Black or African American	5 (6.6)	5 (6.8)
Asian	5 (6.6)	6 (8.2)
Other	1 (1.3)	0
Unknown	3 (3.9)	1 (1.4)
Not reported	1 (1.3)	6 (8.2)
Geographic region,[a] No.		
North America	73	66
Europe	3	7
Patient meeting ≥1 Galsky criteria, No. (%)		
CrCL <60 and ≥30 mL/min[b]	48 (63.2)	44 (60.3)
Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
ECOG PS of 2[c]	6 (7.9)	9 (12.3)
CrCL <60 and ≥30 mL/min and grade ≥2 hearing loss	7 (9.2)	7 (9.6)
CrCL <60 and ≥30 mL/min and ECOG PS of 2	4 (5.3)	1 (1.4)
Patient considered cisplatin-ineligible by the investigator although not meeting Galsky criteria,[d] No. (%)	0	1 (1.4)
Metastasis disease sites,[e] No. (%)		
Bone	19 (25.0)	21 (28.8)
Liver[c]	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, No. (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[f]	2 (2.6)	1 (1.4)

Abbreviations: CrCL, creatinine clearance; ECOG PS; Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ITT, intent-to-treat; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; P, pembrolizumab.

[a]Patients were enrolled into Cohort K from 71 study sites across North America (including Canada and Puerto Rico) and Europe (France, Spain, and Italy).

[b]Estimated creatinine clearance per Cockcroft-Gault formula, or 24-hour urine collection, or modification of diet in renal disease equation.

[c]Patients were stratified by ECOG PS (0 *v* 1 or 2) and the presence versus absence of liver metastasis.

[d]One patient in the EV mono arm was considered cisplatin-ineligible by the investigator because of age and grade 1 hearing loss.

[e]Patients might have experienced metastatic disease in at least one location.

[f]Patients had locally advanced disease without metastasis to lymph nodes or distant organs.

EORTC QLQ-C30 and BPI-SF Baseline PRO Scores

For the EORTC QLQ-C30, fatigue, sleep disturbances, and pain were the most burdensome symptoms at baseline, as reflected in the highest mean scores (Table 2). For the BPI-SF, 17.7% (11 of 62) and 27.4% (17 of 62) of patients had moderate and severe worst pain at baseline, respectively, in the EV + P group; for the EV mono group, these values were 19.0% (11 of 58) and 17.2% (10 of 58).

EORTC QLQ-C30 QOL, Functioning, and Symptom Scales

For overall QOL, adjusted LS (SE) mean scores for the EV + P arm were stable through week 8 (−0.82 [2.73]), 12 (−1.88 [2.50]), and 24 (1.59 [2.84]) versus baseline. In terms of functioning, emotional functioning demonstrated a consistent pattern of mild-to-moderate improvement at week 8 (5.96 [2.35]), with a clinically meaningful improvement at week 24 (10.20 [2.43]) relative to baseline. Mild-to-moderate transient worsening of QOL, role, and physical and social functioning were observed at week 3 (≤−8.82), but all returned to baseline levels thereafter (Fig 1A). Regarding symptoms, a mild-to-moderate improvement in pain was seen at week 8 (−8.05 [3.42]) compared with baseline; clinically meaningful improvements in pain were seen at weeks 12 (−14.41 [3.14]) and 24 (−14.99 [3.56]) versus baseline. A clinically meaningful improvement in insomnia was also observed at weeks 12 and 24 (−12.95 [3.47] and −15.22 [3.92], respectively), as was a

TABLE 2. EORTC QLQ-C30 and BPI-SF Scores at Baseline

EORTC QLQ-C30 or BPI-SF Scale/Item	EV + P (n = 65)	EV Mono (n = 61)
EORTC QLQ-C30,[a] mean (SD)		
Global health status/QOL	64.5 (23.9)	63.1 (26.5)
Functioning scales[b]		
Physical functioning	74.1 (23.2)	78.4 (22.2)
Role functioning	70.0 (30.9)	74.6 (30.1)
Emotional functioning	77.2 (19.7)	79.5 (22.6)
Cognitive functioning	86.4 (15.6)	87.7 (17.5)
Social functioning	79.0 (23.1)	78.4 (28.4)
Cancer-related symptom scales and items[b]		
Fatigue	34.5 (28.5)	33.3 (26.5)
Nausea/vomiting	10.0 (22.6)	3.6 (14.0)
Pain	32.8 (32.4)	35.3 (28.1)
Dyspnea	14.4 (20.4)	16.9 (27.6)
Sleep disturbances	33.8 (32.5)	33.9 (33.0)
Appetite loss	27.2 (35.5)	22.4 (29.0)
Constipation	19.5 (24.2)	22.4 (30.9)
Diarrhea	8.7 (21.5)	5.5 (12.4)
BPI-SF worst pain,[c] No. (%)	n = 62	n = 58
No/mild pain (score range, 0-4)	34 (54.8)	37 (63.8)
Moderate pain (score range, 5-6)	11 (17.7)	11 (19.0)
Severe pain (score range, 7-10)	17 (27.4)	10 (17.2)

NOTE. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline.

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; mono, monotherapy; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life; SD, standard deviation.

[a]A 30-item questionnaire to assess QOL in patients with cancer; scores range from 0 to 100.

[b]Higher symptom domain score indicates a greater symptom burden and a less favorable outcome; higher functional score indicates greater functioning and a more favorable outcome.

[c]An eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10.

mild-to-moderate improvement in constipation (−9.14 [3.02] and −8.01 [3.54]) versus baseline. Fatigue, appetite loss, and dyspnea worsened at week 3 from baseline, with clinically meaningful worsening of diarrhea at week 3 (12.57 [2.73]). However, all returned to baseline levels thereafter (Fig 1B).

In the EV mono arm, adjusted LS (SE) mean scores for overall QOL were stable through weeks 8 (2.70 [2.81]), 12 (−0.62 [2.73]), and 24 (2.03 [3.42]) relative to baseline. In terms of functioning, a mild-to-moderate improvement in emotional functioning was demonstrated at weeks 8 and 24 (6.88 [2.43] and 5.49 [2.89], respectively) versus baseline. While mild-to-moderate transient worsening of QOL, role, and physical and social functioning was observed at week 3 (≤−7.61) compared with baseline, all improved over time (Fig 2A). Regarding symptoms, a clinically meaningful improvement in pain was found at week 8 (−10.11 [3.52]), 12 (−10.55 [3.42]), and 24 (−12.55 [4.73]) relative to baseline (Fig 2B). At week 24, a clinically meaningful improvement in insomnia and constipation (−14.46 [4.69] and −10.09 [4.35], respectively) was also found relative to baseline. Fatigue, appetite loss, dyspnea, nausea, and vomiting showed transient worsening around week 3 from baseline, and clinically meaningful worsening in diarrhea was observed at weeks 3, 6, and 7 versus baseline (15.18 [2.74], 11.38 [2.88], 11.38 [2.84], respectively). However, all retuned to baseline levels shortly thereafter (Fig 2B).

BPI-SF Worst Pain and Pain Interference

BPI-SF MMRM analyses in the EV + P arm showed a clinically meaningful improvement in adjusted LS (SE) mean scores for worst pain at week 24 (−2.07 [0.37]) versus baseline (Fig 3A). From weeks 8 to 24, consistent improvements in average pain (−0.66 [0.30] to −1.38 [0.31]), pain interference (−0.52 [0.32] to −1.32 [0.33]; Fig 3B), and pain severity (−0.62 [0.29] to −1.16 [0.30]) were observed relative to baseline.

In the EV mono arm, BPI-SF worst pain (Fig 4A), average pain, pain interference (Fig 4B), and pain severity remained

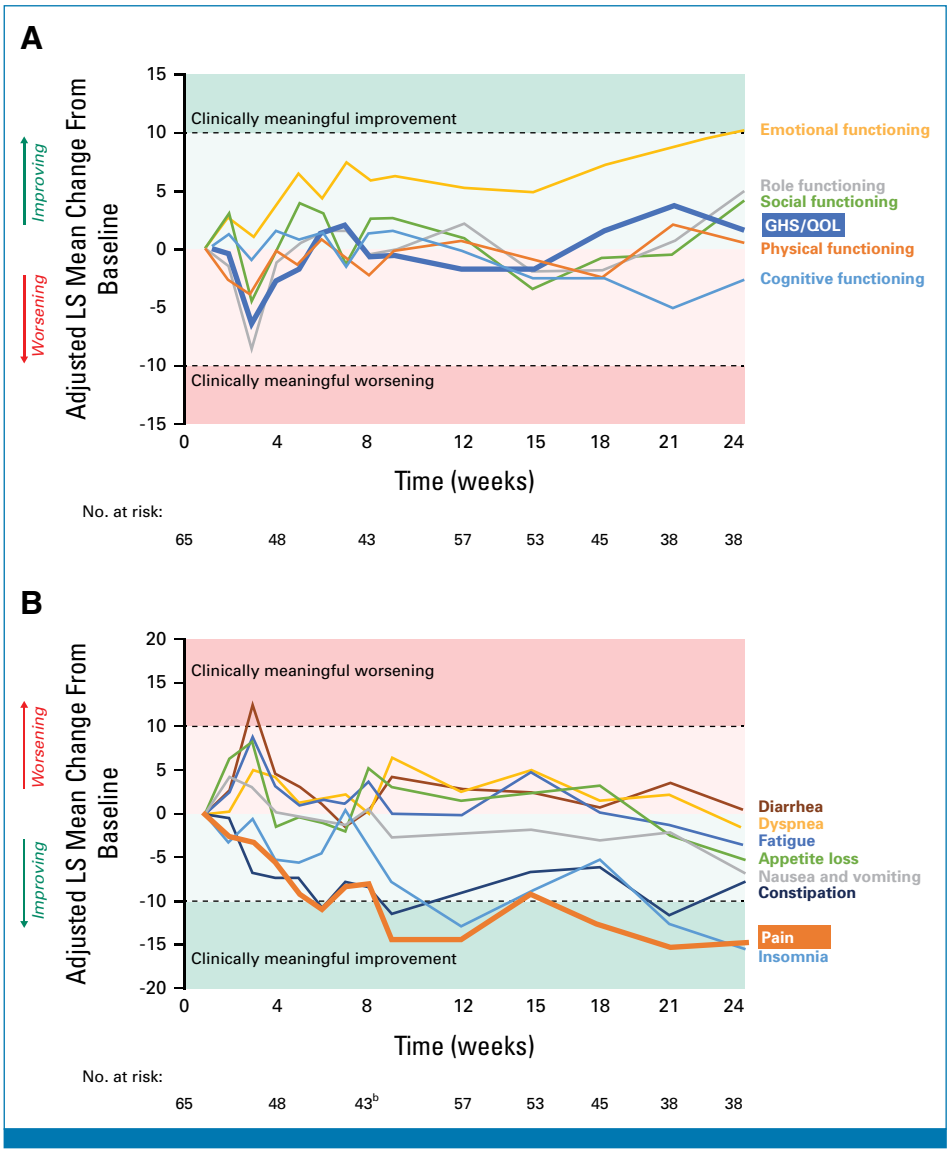

FIG 1. (A) EORTC QLQ-C30[a] QOL and functioning scales and (B) EORTC QLQ-C30 symptom scales in the EV + P arm over a 24-week follow-up period. [a]For MMRM analyses, treatment and time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. Line plots show adjusted LS means of predicted change from baseline for all postbaseline assessments. Clinically meaningful improvements were identified using a predefined threshold (10-point change) for the EORTC QLQ-C30. [b]For appetite loss, n = 42 at week 8. ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; GHS, global health status; la/mUC, locally advanced/metastatic urothelial cancer; LS, least square; MMRM, mixed models for repeated measures; P, pembrolizumab; PRO, patient-reported outcome; QOL, quality of life.

stable over time, with small-to-moderate improvements observed at weeks 8, 12, and 24 versus baseline.

Time to Sustained Improvement for the EORTC QLQ-C30 Pain

In the EV + P arm, 76.7% experienced a sustained improvement of pain, with a median time to improvement of 1.2 months (95% CI, 0.7 to 1.8; Appendix Table A1); in the EV mono arm, 65.4% reported a sustained improvement, with a median time to improvement of 1.0 months (95% CI, 0.5 to 2.4; Appendix Table A2).

Among a subset of patients in the EV + P arm (n = 28) with moderate-to-severe pain at baseline, 82.1% experienced a sustained improvement in pain, with a median time to improvement of 1.1 months (95% CI, 0.7 to 1.2; Appendix Table A1); in the EV mono arm (n = 21), 81.0% reported a sustained improvement, with a median time to improvement of 0.9 months (95% CI, 0.5 to 2.4; Appendix Table A2).

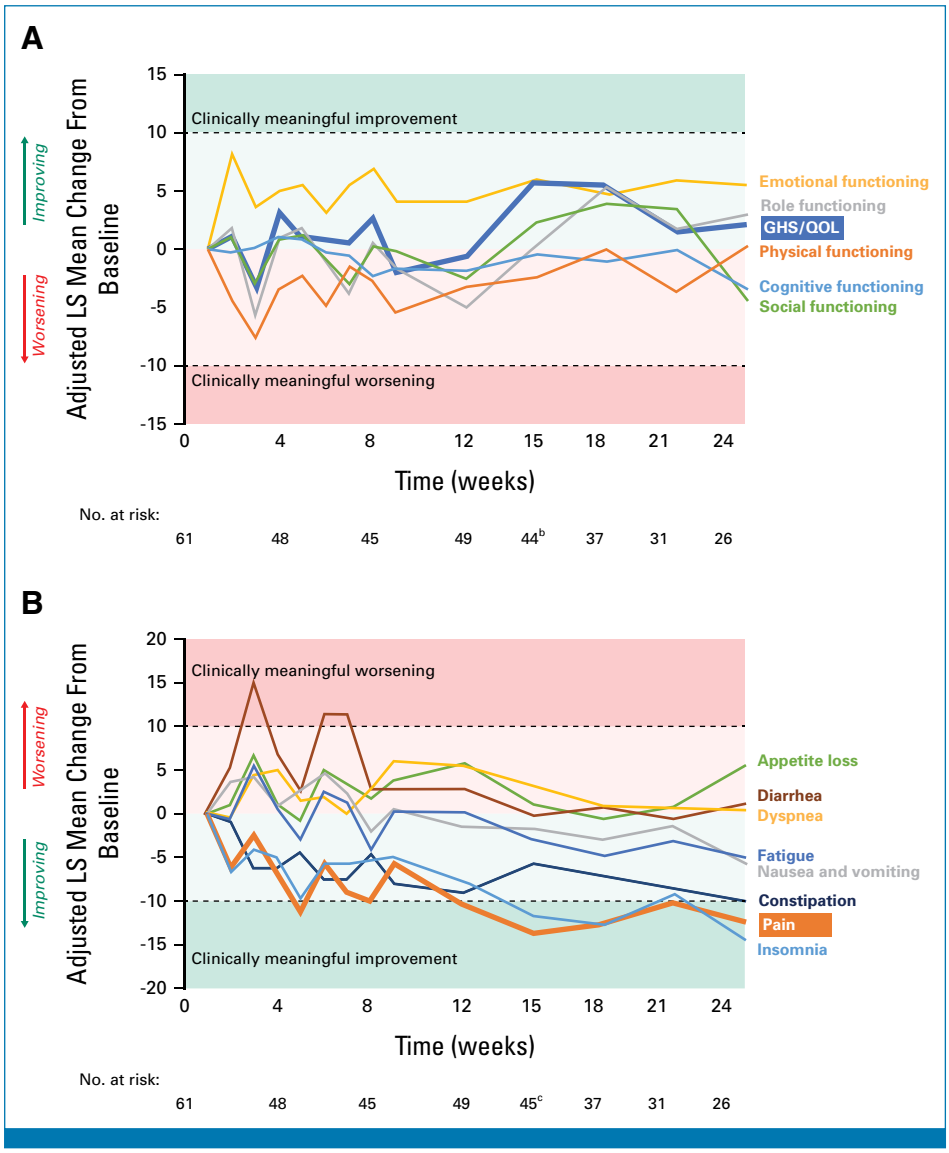

FIG 2. (A) EORTC QLQ-C30[a] QOL and functioning scales and (B) EORTC QLQ-C30 symptom scales in the EV mono arm over a 24-week follow-up period. [a]For MMRM analyses, treatment and time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. Line plots show adjusted LS means of predicted change from baseline until week 24. Clinically meaningful improvements were identified using a predefined threshold (10-point change) for the EORTC QLQ-C30. [b]For physical functioning and role functioning, n = 45 at week 15. [c]For diarrhea, n = 44 at week 15. ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; GHS, global health status; LS, least square; MMRM, mixed models for repeated measures; mono, monotherapy; PRO, patient-reported outcome; QOL, quality of life.

Time to Sustained Improvement for BPI-SF Worst Pain

In the EV + P arm, 73.9% of patients experienced an improvement in worst pain with a median time to improvement of 1.1 months (95% CI, 0.7 to 1.4; Appendix Table A1); in the EV mono arm, 47.7% experienced a sustained improvement in worst pain with a median time to improvement of 1.4 months (95% CI, 0.5 to not estimable [NE]; Appendix Table A2).

In the EV + P arm, among patients with moderate-to-severe pain at baseline, 85.7% experienced a sustained improvement, with a median time to improvement of 1.1 months (95% CI, 0.5 to 1.2; Appendix Table A1). Among the same patient population for the EV mono arm, 61.9% reported a sustained improvement, with a median time to improvement of 1.4 months (95% CI, 0.5 to NE; Appendix Table A2).

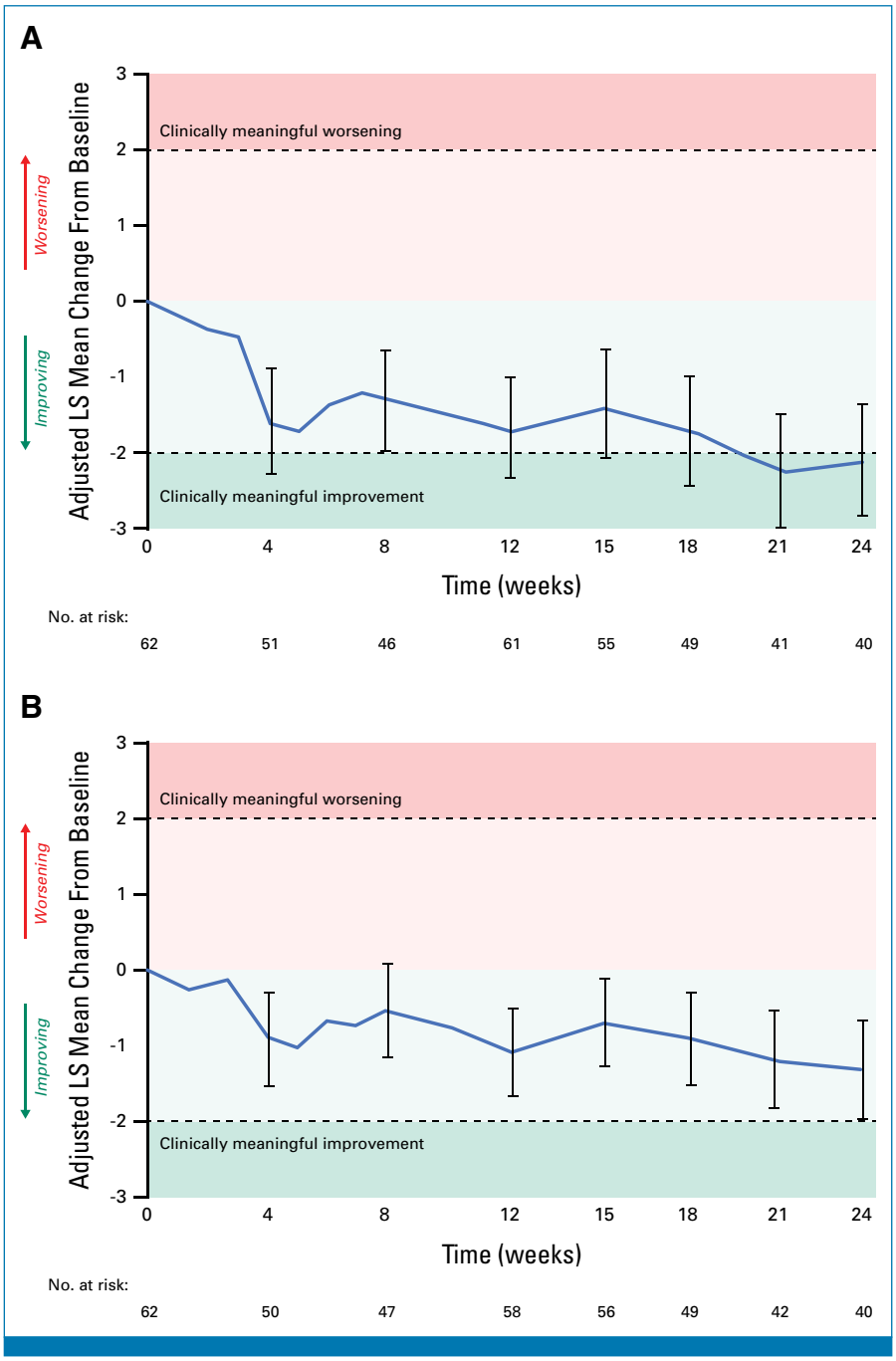

FIG 3. (A) BPI-SF worst pain scores[a] and (B) pain interference in the EV + P arm over a 24-week follow-up period. [a]For MMRM analyses, treatment and time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. Line plots show adjusted LS means of predicted change from baseline for all postbaseline assessments. Clinically meaningful improvements were identified using a predefined threshold (2-point change) for the BPI-SF. BPI-SF, Brief Pain Inventory Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; LS, least square; MMRM, mixed models for repeated measures; P, pembrolizumab; PRO, patient-reported outcome.

DISCUSSION

In Cohort K of the EV-103 trial, longitudinal PRO data showed that EV + P was associated with preservation or improvement of QOL, functioning, and symptoms. Clinically meaningful improvements in EORTC QLQ-C30 pain were observed as early as week 12 and through week 24. Similar findings were observed for BPI-SF worst pain. In a subset of patients with

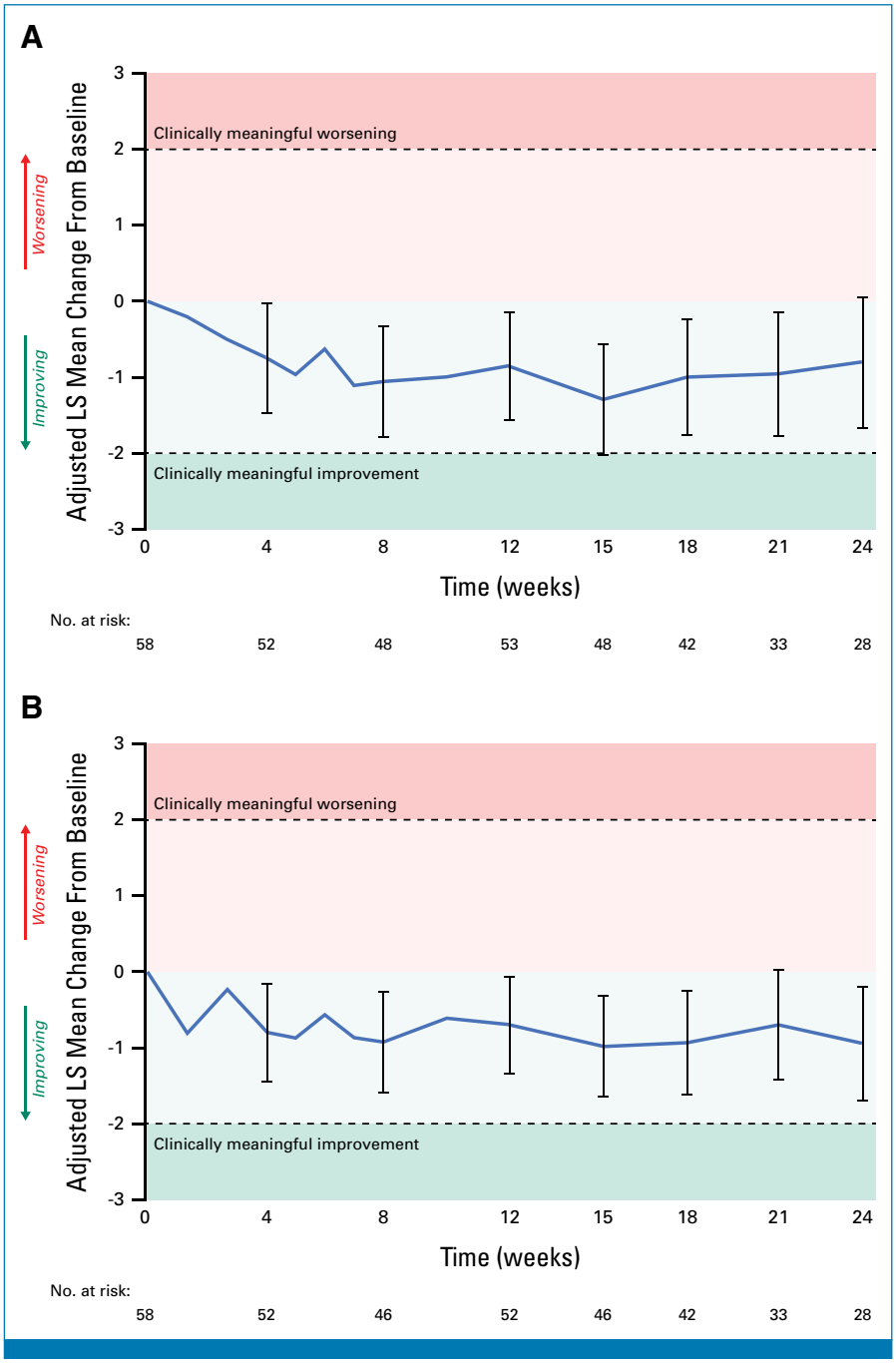

FIG 4. (A) BPI-SF worst pain scores[a] and (B) pain interference in the EV mono arm over a 24-week follow-up period. [a]For MMRM analyses, treatment and time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. Line plots show adjusted LS means of predicted change from baseline for all postbaseline assessments. Clinically meaningful improvements were identified using a predefined threshold (2-point change) for the BPI-SF. BPI-SF, Brief Pain Inventory Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; LS, least square; MMRM, mixed models for repeated measures; mono, monotherapy; PRO, patient-reported outcome.

moderate-to-severe pain at baseline, 85.7% reported a sustained improvement in pain approximately 1 month after initiation of EV + P.

While QOL, role functioning, and social functioning were preserved over time in both treatment arms, transient worsening was observed at week 3, which may suggest that

patients are adapting to treatment over time. Clinically meaningful worsening of diarrhea was also observed at week 3 but returned to baseline levels around week 6.

Despite advances in pain relief, inadequate pain assessment and management continue to affect patients with advanced/metastatic cancer.[35] A key finding was that in both treatment arms, similar trends in the rapid improvement of pain were demonstrated by both PRO instruments. EORTC QLQ-C30 pain scores showed clinically meaningful improvements as early as week 12 through week 24. These data were comparable with those from the phase III IMvigor130 trial evaluating atezolizumab with/without platinum-based therapy in patients with previously untreated la/mUC where a mean pain score change of approximately 10 points was observed in patients treated with atezolizumab plus platinum-based chemotherapy at week 24.[36] Using the validated BPI-SF worst pain item,[3] we also observed a clinically meaningful improvement after EV + P treatment and in patients experiencing moderate-to-severe pain at baseline, where most experienced sustained pain improvement.

For EV mono, PRO analyses showed preservation of QOL and functioning, with improvement in symptoms, such as insomnia and constipation. Clinically meaningful improvements in EORTC QLQ-C30 pain scores were observed at weeks 8, 12, and 24. EV mono data in the 1L setting were also consistent with reports on QOL in later-line trials such as EV-301[2] and EV-201.[20] In EV-301, EV mono was associated with preservation of QOL and statistically confirmed improvement in pain at week 12 versus chemotherapy.[2]

Patients with la/mUC often experience a significant emotional burden.[37] A recent real-world study of social media posts written by patients and caregivers on their insights and experiences with la/mUC over 6 years identified the high psychological impact of la/mUC.[38] In our study, a clinically meaningful improvement in emotional functioning was observed with EV + P.

Our findings also showed clinically meaningful improvement in insomnia over time in both treatment arms. Insomnia can have a profound effect on patients with cancer and result in worsening of fatigue, psychological and cognitive functioning, and increased pain,[39,40] all of which can significantly affect QOL.

There are several limitations in our study. This study was not designed to compare outcomes between treatment arms. The open-label study design may lead to bias and influence reporting of patients' symptoms and functions. Because of a lack of device availability, most patients completed questionnaires on paper at the start of the study and then transitioned to electronic patient reported outcomes devices, which might explain the lower-than-expected compliance rates; declining compliance rates may also bias data interpretation at later timepoints. However, longitudinal modeling of PRO end points allowed the use of all available data and included adjustments for covariates by MMRM. Neither the EORTC QLQ-C30 nor BPI-SF was designed to identify the cause of pain; therefore, we were not able to assess the direct impact of peripheral neuropathy (PN) on PROs, and data showing associations between experienced PN and PRO outcomes were unavailable. QOL or symptoms might have been influenced by intervening events, for example, use of pain medications. However, although pain medication use remained stable over time, the impact on overall QOL and symptoms was not evaluated. PRO data captured beyond week 24 were not described, so it was not possible to comment further on the longitudinal impact of EV + P and EV mono. This is particularly notable for PN in that timing of PN might not have occurred or was only beginning to develop during the reporting timeframe, and therefore, the longitudinal impact of PN on QOL might not have been captured within the 24-week follow-up period.

In conclusion, data on PROs in patients with la/mUC who are cisplatin-ineligible are limited. Here, we report PROs in a patient population with advanced UC who were cisplatin-ineligible and received EV + P or EV mono in the 1L setting. PRO findings showed that EV + P was associated with preservation or improvement of QOL, emotional functioning, pain, insomnia, and constipation, with transient worsening in some symptoms observed at week 3. In both treatment arms, similar trends in rapid improvement of pain were observed. These PRO data are supportive of the use of EV + P as a 1L therapy option for patients who are cisplatin-ineligible. A randomized phase III study (EV-302) is ongoing to assess efficacy and safety and to evaluate PROs in patients with previously untreated la/mUC treated with 1L EV + P or cisplatin-/carboplatin-based regimens (ClinicalTrials.gov identifier: NCT04223856).

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DATA SHARING STATEMENT

Deidentified patient-level trial data that underlie the results reported in this publication will be made available on a case-by-case basis to researchers who provide a methodologically sound proposal. Additional documentation may also be made available. Data availability will begin after approval of the qualified request and end 30 days after the receipt of data sets. All requests can be submitted to CTDR@seagen.com and will be reviewed by an internal review committee. Note that the data sharing policy of this clinical study's sponsor, Seagen Inc, requires all requests for clinical trial data be reviewed to determine the qualification of the specific request. This policy is available at https://www.seagen.com/healthcare-professionals/clinical-data-requests and is aligned with BIO's Principles on Clinical Trial Data Sharing (available at https://www.bio.org/blogs/principles-clinical-trial-data-sharing-reaffirm-commitment).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient-Reported Outcomes in Patients With Advanced Urothelial Cancer Who Are Ineligible for Cisplatin and Treated With First-Line Enfortumab Vedotin Alone or With Pembrolizumab

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APPENDIX 1. SUPPLEMENTARY METHODS

Study Design and Participants

Patients with previously untreated locally advanced/metastatic urothelial cancer were classed as ineligible for cisplatin-based chemotherapy at enrollment on the basis of at least one of the following: impaired renal function, grade ≥2 hearing loss, an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2, or New York Heart Association (NYHA) class ≥III heart failure. Patients with an ECOG PS of ≥2 met the following additional criteria: hemoglobin ≥10 g/dL, glomerular filtration rate ≥50 mL/min, and no NYHA class III heart failure. Patients treated with previous systemic treatment and with ongoing grade ≥2 sensory or motor neuropathy, clinically significant toxicity associated with previous treatment, active CNS metastases, or uncontrolled diabetes were excluded from the analyses.[10]

Mode of Questionnaire Administration

Where access to a device to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30), Brief Pain Inventory Short Form (BPI-SF), and EuroQoL five dimensions, five labels (EQ-5D-5L) questionnaires was not feasible or available at the start of the study, patients (n = 94) completed questionnaires on paper and transitioned to electronic patient reported outcomes devices during the study.

Responder Analysis

In responder analyses, the patient-reported outcome population was classified into the proportion of patients who improved (change from baseline score suggesting improvement ≥meaningful change threshold [MCT]), worsened (change from baseline score suggesting deterioration ≥MCT), or stabilized (absolute value of change <MCT) and was identified using the aforementioned threshold values for the EORTC QLQ-C30 and BPI-SF; data were presented for all postbaseline assessments.

EQ-5D-5L Assessment

The EQ-5D-5L consists of a five-item questionnaire evaluating mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five grades of problem severity for each item. Responses to the five items are transformed into a health utility score on the basis of data from the general population,[27] where 0 is considered death and 1 is good health. Participant's self-rated health status on a visual analog scale (VAS; score range, 0-100) is also assessed, and a higher score indicates more favorable patient outcomes.

Statistical Analysis

For the longitudinal modeling of PRO end points, treatment and time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model.

APPENDIX 2. SUPPLEMENTARY RESULTS

Responder Analysis

In patients who received enfortumab vedotin (EV) + pembrolizumab (P), responder analysis for BPI-SF worst pain showed that a higher proportion of patients reported improved rather than worsened pain scores, with the majority of patients remaining stable over time. At week 9 (when patients received their first tumor-response radiologic assessment), 15 of 41 patients experienced pain improvement versus 3 of 41 who experienced pain worsening; similar findings were found at week 24 (17 of 36 and 3 of 36, respectively; Appendix Fig A2).

A similar trend was found in the EV mono arm with a higher proportion of patients reporting pain improvement (12 of 33) than pain worsening (4 of 33) at week 9 as measured by BPI-SF worst pain, with a similar pattern observed for week 24 (8 of 24 and 5 of 24, respectively; Appendix Fig A3).

Opioid Medication Use at Baseline

On the basis of 65 patients treated with EV + P, 28.3% (15 of 53), 30.6% (11 of 36), 16.7% (7 of 42), and 15.4% (4 of 26) of patients who provided a response to the pain medication question reported opioid use at baseline, week 8, week 12, and week 24, respectively. Among 28 patients with moderate-to-severe pain at baseline, 65.2% (15 of 23 with medication data) reported receiving opioid medication at baseline (Appendix Table A3).

Of 63 patients in the EV mono arm, 32.7% (16 of 49), 32.4% (11 of 34), 22.5% (9 of 40), and 29.2% (7 of 24) answered the pain medication question and reported opioid use at baseline, week 8, week 12, and week 24, respectively. Of 21 patients with moderate-to-severe pain at baseline, 61.1% (11 of 18 with medication data) reported receiving opioid medication at baseline (Appendix Table A3).

EQ-5D-5L

For the EQ-5D-5L, compliance rates were 73.7% (56 of 76) and 74.0% (54 of 73) for EV + P and EV mono, respectively, at baseline and generally remained above 67.0% and 56.0% at week 24. Overall health VAS from the EQ-5D-5L at baseline (mean [standard deviation, SD], 71.98 [20.91] and 70.87 [21.86] for EV + P and EV mono, respectively) was similar to that reported at week 24 (mean [SD], 76.37 [15.91] and 80.14 [13.17], respectively).

APPENDIX 3

TABLE A1. Time to Sustained Improvement for the EORTC QLQ-C30 and BPI-SF in the EV + P Arm

	EV + P (n = 65)		Subgroup of Patients With Moderate-to-Severe Pain at Baseline[a] (n = 28)	
EORTC QLQ-C30 and BPI-SF Scores	No. of Events, No./n (%)	Median, Months (95% CI)	No. of Events, No./n (%)	Median, Months (95% CI)
EORTC QLQ-C30[b]				
QOL	23/52 (44.2)	13.4 (3.0 to NE)	17/28 (60.7)	3.0 (1.4 to 10.3)
Physical functioning	20/45 (44.4)	NE (1.2 to NE)	13/26 (50.0)	2.7 (1.2 to NE)
Emotional functioning	26/41 (63.4)	4.2 (1.0 to 6.3)	14/21 (66.7)	4.2 (0.7 to 4.4)
Role functioning	24/39 (61.5)	1.6 (1.0 to NE)	16/26 (61.5)	1.6 (1.0 to NE)
Fatigue	23/51 (45.1)	10.3 (1.4 to NE)	16/28 (57.1)	1.6 (0.7 to NE)
Pain	33/43 (76.7)	1.2 (0.7 to 1.8)	23/28 (82.1)	1.1 (0.7 to 1.2)
BPI-SF[c]				
Worst pain	34/46 (73.9)	1.1 (0.7 to 1.4)	24/28 (85.7)	1.1 (0.5 to 1.2)
Pain interference	18/31 (58.1)	1.3 (1.0 to 3.9)	17/24 (70.8)	1.2 (0.9 to 1.8)

NOTE. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline. A Kaplan-Meier estimator was used to estimate time to sustained improvement, which was defined as the number of months from the start of treatment to time of sustained improvement, where meaningful improvement was considered if a change in score increased from baseline by at least one MCT and was sustained for at least two consecutive assessments among patients who were not within one MCT of best possible score at baseline.

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; MCT, meaningful change threshold; NE, not estimable; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life.

[a]Moderate-to-severe pain was defined as a baseline BPI-SF worst pain score of ≥5.

[b]A 30-item questionnaire to assess QOL in patients with cancer; scores range from 0 to 100. Higher QOL and functioning scores represent better QOL and functioning, whereas higher symptom scores represent greater symptom burden; a 10-point MCT was applied. For QOL and functional scores, an improvement was defined as an increase in score from baseline by at least one MCT, stable was defined as a change in score from baseline within one MCT, and worsening was defined as a decrease in score from baseline by at least one MCT. For symptom scores, an improvement was defined as the decrease in score from baseline by at least one MCT, stable was defined as a change in score from baseline within one MCT, and worsening was defined as an increase in score from baseline by at least one MCT.

[c]An eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. Higher scores are associated with more pain; a 2-point MCT was applied. An improvement in pain was defined as a decrease in score from baseline by at least one MCT, pain reported as stable was defined as a change in score from baseline within one MCT, and a worsening in pain was defined as an increase in score from baseline by at least one MCT.

TABLE A2. Time to Sustained Improvement for the EORTC QLQ-C30 and BPI-SF in the EV Mono Arm

EORTC QLQ-C30 or BPI-SF Scale/ Item	EV Mono (n = 63)		Subgroup of Patients With Moderate-to-Severe Pain at Baseline[a] (n = 21)	
	No. of Events, No./n (%)	Median, Months (95% CI)	No. of Events, No./n (%)	Median, Months (95% CI)
EORTC QLQ-C30[b]				
QOL	24/49 (49.0)	1.4 (0.95 to NE)	13/20 (65.0)	1.2 (0.5 to NE)
Role functioning	19/36 (52.8)	1.6 (0.7 to NE)	10/15 (66.7)	1.4 (0.5 to NE)
Physical functioning	15/39 (38.5)	NE (1.6 to NE)	7/16 (43.8)	NE (0.7 to NE)
Emotional functioning	21/33 (63.6)	1.1 (0.5 to 3.2)	10/12 (83.3)	0.9 (0.3 to 3.2)
Fatigue	30/53 (56.6)	2.4 (1.4 to 4.9)	14/20 (70.0)	1.4 (0.7 to 4.9)
Pain	34/52 (65.4)	1.0 (0.5 to 2.6)	17/21 (81.0)	0.9 (0.5 to 2.4)
BPI-SF[c]				
Worst pain	21/44 (47.7)	1.4 (0.5 to NE)	13/21 (61.9)	1.4 (0.5 to NE)
Pain interference	14/30 (46.7)	2.6 (0.5 to NE)	11/18 (61.1)	0.7 (0.3 to NE)

NOTE. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline. A Kaplan-Meier estimator was used to estimate time to sustained improvement, which was defined as the number of months from the start of treatment to time of sustained improvement, where meaningful improvement was considered if a change in score increased from baseline by at least one MCT and was sustained for at least two consecutive assessments among patients who were not within one MCT of best possible score at baseline.

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; MCT, meaningful change threshold; mono, monotherapy; NE, not estimable; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life.

[a]Moderate-to-severe pain was defined as a baseline BPI-SF worst pain score of ≥5.

[b]A 30-item questionnaire to assess QOL in patients with cancer; scores range from 0 to 100. Higher QOL and functioning scores represent better QOL and functioning, whereas higher symptom scores represent greater symptom burden; a 10-point MCT was applied. For QOL and functional scores, an improvement was defined as an increase in score from baseline by at least one MCT, stable was defined as a change in score from baseline within one MCT, and worsening was defined as a decrease in score from baseline by at least one MCT. For symptom scores, an improvement was defined as the decrease in score from baseline by at least one MCT, stable was defined as a change in score from baseline within one MCT, and worsening was defined as an increase in score from baseline by at least one MCT.

[c]An eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. Higher scores are associated with more pain; a 2-point MCT was applied. An improvement in pain was defined as a decrease in score from baseline by at least one MCT, pain reported as stable was defined as a change in score from baseline within one MCT, and a worsening in pain was defined as an increase in score from baseline by at least one MCT.

TABLE A3. Opioid Medication Use on the Basis of Responses to Question 7 of the BPI-SF Over the 24-Week Follow-Up Period in the EV + P and EV Mono Arms

Timepoint	EV + P (n = 65)	EV Mono (n = 63)
Overall population, No./n (%)		
Baseline	15/53 (28.3)	16/49 (32.7)
Week 8	11/36 (30.6)	11/34 (32.4)
Week 12	7/42 (16.7)	9/40 (22.5)
Week 24	4/26 (15.4)	7/24 (29.2)

NOTE. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline. Sample sizes for some analyses are smaller because of missing data. The BPI-SF is an eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. Question 7 of the BPI-SF is "What treatments or medications are you receiving for your pain?".

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; EV, enfortumab vedotin; mono, monotherapy; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population.

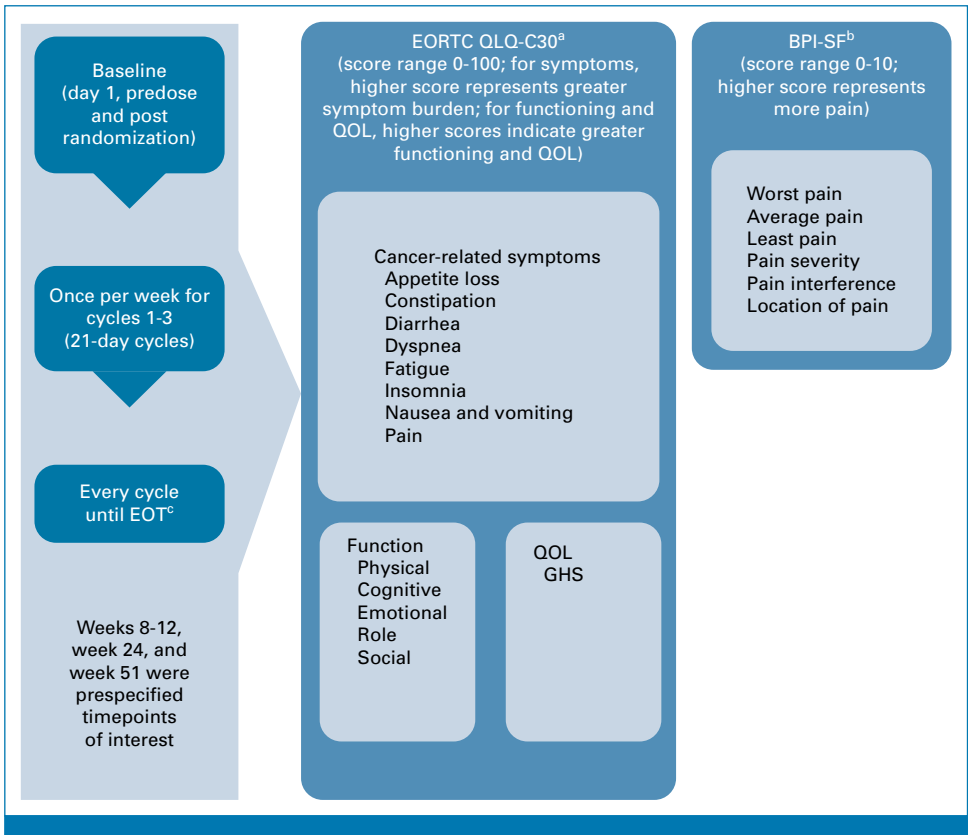

FIG A1. PRO instruments and assessment schedule for the PRP. All analyses were conducted in the PRP unless otherwise specified. The PRP included any patients who completed at least one question of the PRO questionnaire at baseline. [a]A 30-item questionnaire to assess QOL in patients with cancer; scores range from 0 to 100. [b]An eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. [c]After EOT, patients completed PROs once every 9 weeks until 1 year and then every 12 weeks thereafter through long-term follow-up; those data are not presented here. BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EOT, end of treatment; GHS, global health status; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life.

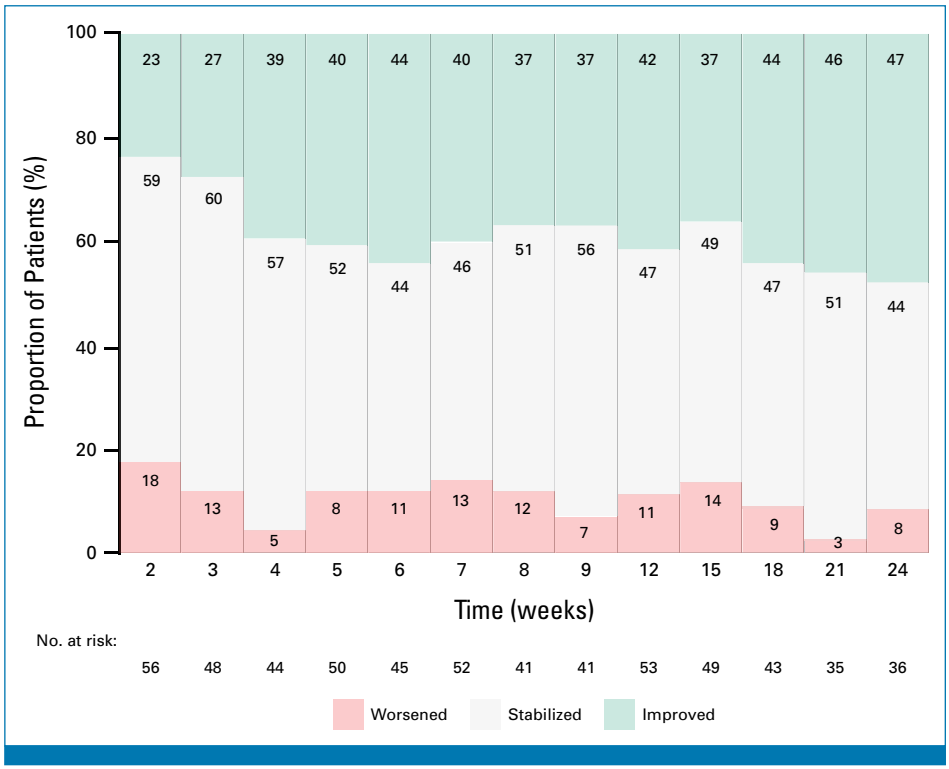

FIG A2. Responder analysis for BPI-SF worst pain over the 24-week follow-up period in the EV + P arm. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline. Sample sizes for some analyses are smaller because of missing data. An improvement in pain was defined as a decrease in score from baseline by at least one MCT, pain reported as stable was defined as a change in score from baseline within one MCT, and a worsening in pain was defined as an increase in score from baseline by at least one MCT. The BPI-SF is an eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. Higher scores are associated with more pain; a 2-point MCT was applied. BPI-SF, Brief Pain Inventory Short Form; EV, enfortumab vedotin; MCT, meaningful change threshold; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population.

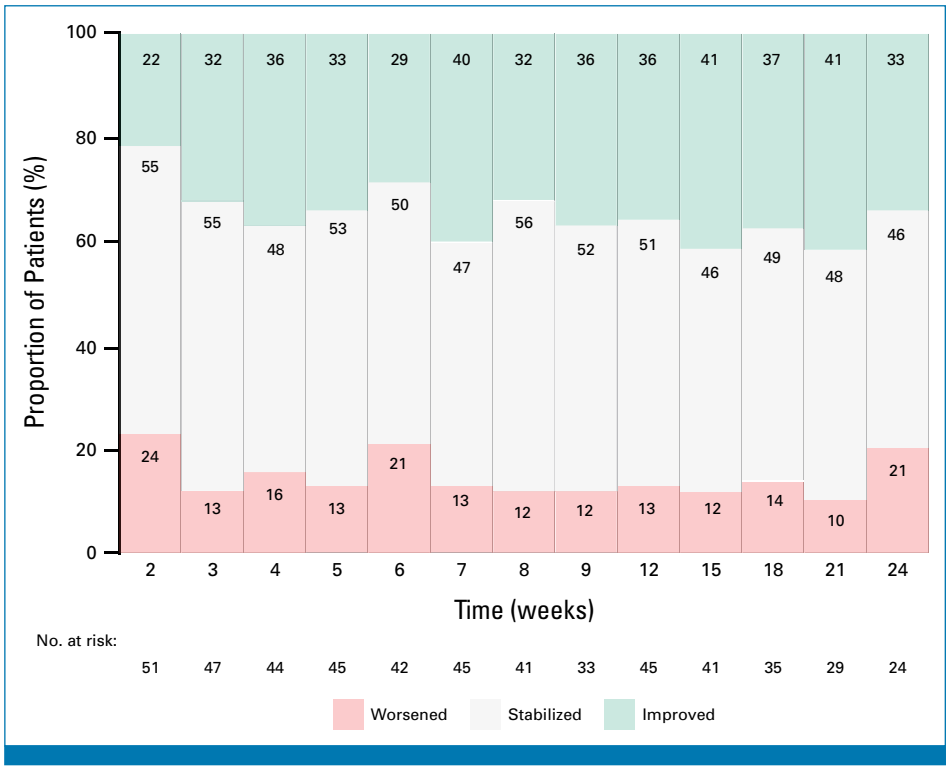

FIG A3. Responder analysis for BPI-SF worst pain over the 24-week follow-up period in the EV mono arm. All analyses were conducted in the PRP unless otherwise specified; the PRP included patients who completed at least one question of the PRO questionnaires at baseline. Sample sizes for some analyses are smaller because of missing data. An improvement in pain was defined as a decrease in score from baseline by at least one MCT, pain reported as stable was defined as a change in score from baseline within one MCT, and a worsening in pain was defined as an increase in score from baseline by at least one MCT. The BPI-SF is an eight-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the past 24 hours; scores range from 0 to 10. Higher scores are associated with more pain; a 2-point MCT was applied. BPI-SF, Brief Pain Inventory Short Form; EV, enfortumab vedotin; MCT, meaningful change threshold; mono, monotherapy; PRO, patient-reported outcome; PRP, patient-reported outcome population.