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Health-related Quality of Life in Patients with Previously Treated Advanced Urothelial Carcinoma from EV-301: A Phase 3 Trial of Enfortumab Vedotin Versus Chemotherapy

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Abstract

Background and objective: In comparison to chemotherapy, enfortumab vedotin (EV) prolonged overall survival in patients with previously treated advanced urothelial carcinoma in EV-301. The objective of the present study was to assess patient experiences of EV versus chemotherapy using patient-reported outcome (PRO) analysis of health-related quality of life (HRQoL).

Methods: For patients in the phase 3 EV-301 trial randomized to EV or chemotherapy we assessed responses to the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline, weekly for the first 12 wk, and then every 12 wk until discontinuation. We analyzed the QLQ-C30 change from baseline to week 12, the confirmed improvement rate, and the time to improvement or deterioration.

Key findings and limitations: Baseline PRO compliance rates were 91% for the EV arm (n = 301) and 89% for the chemotherapy arm (n = 307); the corresponding average rates from baseline to week 12 were 70% and 67%. Patients receiving EV versus chemotherapy had reduced pain (difference in change from baseline to week 12: −5.7, 95% confidence interval [CI] −10.8 to −0.7; p = 0.027) and worsening appetite loss (7.3, 95% CI 0.90–13.69; p = 0.026). Larger proportions of patients in the EV arm reported HRQoL improvement from baseline than in the chemotherapy arm; the odds of a confirmed improvement across ten QLQ-C30 function/symptom scales were 1.67 to 2.76 times higher for EV than for chemotherapy. Patients in the EV arm had a shorter time to first confirmed improvement in global health status (GHS)/QoL, fatigue, pain, and physical, role, emotional, and social functioning (all $p < 0.05$). EV delayed the time to first confirmed deterioration in GHS/QoL (p = 0.027), but worsening appetite loss occurred earlier (p = 0.009) in comparison to chemotherapy.

Conclusions and clinical implications: HRQoL with EV was maintained, and deterioration in HRQoL was delayed with EV in comparison to chemotherapy. Better results with EV were reported for some scales, with the greatest difference observed for pain. These findings reinforce the EV safety and efficacy outcomes and benefits observed in EV-301.

Patient summary: Patients with previously treated advanced cancer of the urinary tract receiving the drug enfortumab vedotin maintained their HRQoL in comparison to patients treated with chemotherapy.

The EV-301 trial is registered on ClinicalTrials.gov as NCT03474107 and on EudraCT as 2017-003344-21.

Keywords

Antineoplastic agents; Cancer pain; Immunoconjugates; Patient-reported outcome; measures; Urinary bladder neoplasms

1. Introduction

Despite therapeutic advances in the treatment of locally advanced/metastatic urothelial carcinoma (la/mUC), outcomes remain poor. Long-term survival may be limited by resistance to chemotherapy [1–3]. During the past 5 yr, novel therapies have improved outcomes in the metastatic setting [4]; as these therapies are integrated into clinical practice, systematic evaluation of their impact on health-related quality of life (HRQoL) has become important [5–8]. Prospective data on the effects of chemotherapy and immunotherapy for UC on QoL parameters (eg, disease-related symptoms, functioning, overall HRQoL) are emerging, but data describing patient-reported outcomes (PROs) beyond immunotherapy (particularly for antibody-drug conjugates) are limited [9–12].

Enfortumab vedotin (EV) is an antibody-drug conjugate comprising a fully human monoclonal antibody directed against nectin-4, and monomethyl auristatin E, a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker [13,14]. The phase 3 EV-301 trial demonstrated that EV significantly improved overall survival versus chemotherapy in patients with la/mUC with disease progression/relapse after platinum-containing chemotherapy and (PD-1/PD-L1 inhibitor treatment [15]. Incidence

rates for treatment-related adverse events (EV, 94%; chemotherapy, 92%) and grade ≥3 adverse events (EV, 51%; chemotherapy, 50%) were similar between the groups. After adjustment for treatment exposure, event rates per patient year were lower for EV than for chemotherapy (2.4 vs 4.3) [15].

PRO data were collected in EV-301 to measure the patient experience during treatment and further contextualize the benefits and risks of EV versus standard chemotherapy regarding disease-related symptoms and HRQoL in patients with la/mUC. HRQoL outcomes for prespecified secondary and post hoc exploratory endpoints are reported here.

2. Patients and methods

In the global, open-label, phase 3 EV-301 trial, adults were randomized 1:1 to EV 1.25 mg/kg administered on days 1, 8, and 15 of each 28-d cycle or to standard chemotherapy with the investigator's choice of paclitaxel, docetaxel, or vinflunine (on the basis of a previously published approach [16]; use of vinflunine was capped at 35% of patients because of unavailability in some countries where EV-301 was conducted) on day 1 of each 21-d cycle. Patients received the study treatment until investigator-assessed radiological disease progression, death, or other discontinuation criteria were met.

Patients with histologically or cytologically confirmed UC, radiologically documented locally advanced/metastatic disease, and radiographic progression or relapse during or after treatment with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy for locally advanced or metastatic disease (or the neoadjuvant/adjuvant setting for chemotherapy) were included. Detailed descriptions of the EV-301 methods and a CONSORT diagram have previously been reported [15].

2.1. PRO assessments

PRO data were prospectively collected via validated patient self-reported instruments, namely the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [17] and the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire (Supplementary Table 1) [18]. PROs were prespecified secondary endpoints. The QLQ-C30 is a 30-item questionnaire assessing functioning scales (role, physical, emotional, social, and cognitive functioning), GHS/QoL, and symptom scales (pain, fatigue, dyspnea, nausea/vomiting, insomnia, appetite loss, diarrhea, and constipation) for patients with cancer and has been used in recent trials evaluating treatments in the mUC setting [9,10]. The key objective of the PRO analysis was to assess patients' experiences of EV versus chemotherapy. Data obtained via the QLQ-C30 are reported here. EQ-5D-5L visual analog scale findings are provided in the Supplementary material.

Patients completed the EORTC QLQ-C30 version 3 for measurement of HRQoL at baseline, weekly for the first 12 wk, then every 12 wk, and at the end-of-treatment and follow-up visits. Questionnaires were completed by patients on electronic devices at home, and the responses were transferred electronically to a central website at predefined intervals. An outcome variable scored from 0 to 100 was derived for each QLQ-C30 scale; lower

symptom scores indicate a better health state, while higher GHS/QoL and functioning scores indicate better health status or function.

2.2. Statistical analyses

PRO data were analyzed for patients randomized to treatment. PRO compliance rates (adjusted) were calculated for each assessment point as the number of patients who completed at least one scale, divided by the number of patients expected to have PRO assessments at that specific time point (ie, patients still enrolled and able to complete questionnaires). Completion rates (unadjusted) were calculated for each assessment point as the number of patients meeting the minimum requirements for scoring at least one scale of the instrument, divided by the number of patients randomized to study treatment. Descriptive analyses were conducted for items and scales.

2.2.1. Longitudinal comparisons over 12 wk—Longitudinal analysis of changes in PRO scores from baseline was conducted using a mixed-model repeated measures approach (missing observations were assumed to be missing at random). The change from baseline at week 12 and at each postbaseline assessment was calculated for each scale score. Week 12 was selected as the analysis point to minimize the impact of missing data; the median progression-free survival was 4 mo (according to previous sample-size calculations), so approximately half of the patients in the chemotherapy arm were expected to have disease progression by approximately week 12. In addition, PRO data were collected weekly for the first 12 wk to provide a timeframe with the most granular data. Patients with a baseline score and at least one postbaseline score were included. Covariates included as fixed effects were treatment group (EV vs chemotherapy), time point (week), baseline PRO score, and stratification factors. Covariates included as interaction terms were baseline score × time, and treatment group × time. The difference in scores over time was further investigated post hoc by evaluating variance for estimates of the adjusted change from baseline across the first 12 wk of treatment between the two arms using an F test.

2.2.2. Responder analyses: improvement rate—Changes in QLQ-C30 scores from baseline were categorized as an improvement, stable, or a deterioration using prespecificed threshold values reflecting clinically meaningful changes for patients, which were set using previously identified cutoffs (Supplementary Table 2) [19].

The confirmed improvement rate was defined as the number of patients with two consecutive assessments showing a clinically meaningful improvement at any time point during the study. Patients with baseline values allowing for an improvement in the assessment were included in this responder analysis. The confirmed improvement rate was summarized by treatment group and compared using logistic regression with stratification.

2.2.3. Time-to-event analyses: improvement and deterioration—A post hoc evaluation of time-to-event endpoints was also conducted to explore improvement and deterioration. Time to the first confirmed clinically meaningful improvement or deterioration was defined as the time from randomization to the first improvement or deterioration, respectively, in PRO score of at least one threshold unit in comparison to the baseline

score; confirmation (of a sustained clinically meaningful improvement/deterioration) at the next consecutive scheduled visit was also required. If the patient subsequently dropped out of the study, deterioration was concluded and was considered to be confirmed. Additional analyses of time to improvement or deterioration (ie, time to first improvement and time to first/definitive deterioration) were also conducted. Methods for these additional analyses are reported in the Supplementary material.

For time-to-event analyses, improvement and deterioration were defined on the basis of two sets of thresholds (primary and sensitivity threshold consisting of the next higher threshold; Supplementary Table 3). The primary threshold was based on threshold values identified previously [19]. Sensitivity analyses were performed using the primary threshold to define deterioration and included death from any cause as an event. Further sensitivity analyses were performed using the primary and sensitivity threshold to define deterioration. Statistical comparisons were made using two-sided tests at the 0.05 significance level; no adjustments for multiple comparisons were conducted. Kaplan-Meier curves were generated for time-to-event analyses for improvement and deterioration, and a stratified log-rank test was used to compare the distribution of time-to-event results between the two treatment arms. Further comparisons between the EV and chemotherapy arms were conducted using stratified Cox regression models. PRO analyses reported here were prespecified before database lock, with the exception of Kaplan-Meier estimates for time-to-event analyses. All patients were included in the time-to-event analyses; patients not showing an improvement or deterioration were censored at the date of the last available PRO assessment. Data were analyzed using SAS v9.4.

2.3. Ethical approval and informed consent

EV-301 was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. Written informed consent was obtained from patients before screening.

3. Results

Of 608 randomized patients (EV, $n = 301$; chemotherapy, $n = 307$), 79% in the EV arm and 76% in the chemotherapy arm were male. The median age in both groups was 68 yr (interquartile ranges: EV, 62–73 yr; chemotherapy, 62–74 yr). Additional patient and disease characteristics were presented previously [15].

For the QLQ-C30 instrument, baseline PRO compliance rates were 91% for the EV arm and 89% for the chemotherapy arm, with corresponding average rates during the study PRO assessment period of interest of 70% and 67% (Supplementary Table 4). QLQ-C30 completion rates from week 2 to 12 ranged from 44% to 62% for the EV arm and from 34% to 52% for the chemotherapy arm (Supplementary Table 5). Baseline QLQ-C30 scores were similar between the groups (Table 1).

3.1. Longitudinal comparisons over 12 wk

At week 12, changes in scores from baseline for HRQoL and functioning domains were similar in the EV and chemotherapy arms. Point estimates for changes in GHS/QoL,

physical functioning, and role functioning did not significantly differ between the arms, but favored EV over chemotherapy. Patients in the EV arm reported a significant reduction in pain symptoms (difference in change from baseline to week 12 between EV and chemotherapy: −5.7, 95% confidence interval [CI] −10.8 to −0.7; $p = 0.027$) and significant worsening of appetite loss (difference 7.3, 95% CI 0.9–13.7; $p = 0.026$; Fig. 1 and Supplementary Table 6).

Scores over time showed greater variation in the chemotherapy arm (greater deterioration in the week following dosing at weeks 1, 4, 7, and 10) than in the EV arm (Fig. 2 and Supplementary Table 7). Analysis of variance in the adjusted change from baseline revealed significant differences in GHS/QoL scores over 12 wk of treatment between chemotherapy and EV ($p = 0.02$). Weekly results for other QLQ-C30 scales were variable (Supplementary Fig. 1 and Supplementary Table 7).

3.2. Responder analyses: improvement rate

More patients in the EV arm than in the chemotherapy arm reported confirmed clinically meaningful improvement for ten of the 15 QLQ-C30 scales (ORs ranging from 1.67 to 2.76), including all functioning scales, fatigue, pain, dyspnea, and constipation (Fig. 3 and Supplementary Table 8). The greatest difference in confirmed improvement was reported for pain: patients in the EV arm had 2.76 times higher odds of achieving a clinically meaningful reduction in pain in comparison to the chemotherapy arm.

3.3. Time-to-event analyses: improvement and deterioration

Patients in the EV arm experienced a confirmed clinically meaningful improvement earlier than patients in the chemotherapy arm for GHS/QoL (Fig. 4A), fatigue, and pain (2/8 symptom scales), and for physical, role, emotional, and social functioning (4/5 functioning scales; Fig. 4B and Supplementary Table 9). No differences were observed for the remaining scales. Results for time to the first clinically meaningful improvement are shown in Supplementary Fig. 2 and Supplementary Table 10; additional details are provided in the Supplementary material.

In comparison to chemotherapy, EV significantly delayed the time to first confirmed clinically meaningful deterioration in GHS/QoL (Fig. 5A), although deterioration for appetite loss occurred earlier with EV (Fig. 5B and Supplementary Table 11). For the remaining functioning and symptom scales, results were similar for the two treatment arms. Sensitivity analyses showed similar results. Results for time to the first clinically meaningful deterioration favored EV versus chemotherapy for GHS/QoL and physical, role, and emotional functioning (Supplementary Fig. 3 and Supplementary Table 12). For time to definitive deterioration, results for physical, role, emotional, and social functioning and nausea/vomiting, pain, and dyspnea favored EV (Supplementary Fig. 4 and Supplementary Table 13). Results for the EQ-5D-5L visual analog scale were generally consistent with QLQ-C30 results (Supplementary Table 14).

4. Discussion

HRQoL was maintained with EV versus chemotherapy throughout EV-301. Patients in the EV arm reported a greater reduction in pain but greater worsening of appetite loss in comparison to patients in the chemotherapy arm. Patient-level responder analyses demonstrated that more patients experienced a confirmed improvement across all functioning and most symptom scales in the EV arm than in the chemotherapy arm. These PRO data complement the safety and efficacy outcomes in EV-301 and can be used to contextualize potential risks and benefits of EV and assist in shared decision-making in clinical practice.

A strength of this analysis is the frequency of PRO data collection. Whereas prior PRO evaluations of treatments in phase 3 trials for patients with advanced UC generally collected assessments in line with treatment administration (ie, every 3 wk) [9,10,20], EV-301 captured PROs once weekly for at least the first 12 wk, permitting real-time capture of changes occurring over time. This also aligns with the EORTC QLQ-C30 recall period, with assessment of symptoms or function “during the past week” for most items. Interestingly, GHS/QoL declined each week following chemotherapy administration, whereas GHS/QoL remained more stable during each EV treatment, suggesting better tolerability or potentially less dysfunction with EV relative to the chemotherapy options used in the trial (administered every 3 wk).

Pain is among the most common and debilitating symptoms associated with UC or its treatment [21,22]. In a realworld study of PROs for patients with UC, pain was reported as one of the top five most frequent symptoms during treatment with chemotherapy or immunotherapy and is an important contributor to overall HRQoL [11]. Patients treated with EV had reductions in pain symptoms in comparison to chemotherapy-treated patients across different analyses. In addition to improvements in average scores and the proportion of patients achieving confirmed clinically meaningful improvements, the time to improvement in pain symptoms was also shorter with EV than with chemotherapy. Patients receiving weekly administered EV reported less pain, suggesting a reduction in tumor burden [23]. These results are consistent with the higher response and disease control rates observed with EV versus chemotherapy in EV-301 [15].

Patients in the EV arm had significantly more appetite loss than patients in the chemotherapy arm. For EV, worsening of appetite increased from baseline to week 3 and fluctuated throughout the remaining weeks, consistent with adverse event rates for decreased appetite (EV, 30.7% vs chemotherapy, 23.4%) and dysgeusia (EV, 24.3% vs chemotherapy, 7.2%) [15]. On the basis of these data, it is important that loss of appetite occurring in patients receiving EV is not misinterpreted as disease progression [24,25].

This study has several limitations. EV-301 was an open-label trial and was impacted by declining yet similar compliance rates between the groups. Although a minimal effect of patients’ knowledge of their treatment assignment on patient-reported symptoms, functioning, or health status was observed in trials in other cancer types [26], patients in EV-301 were aware of their assigned treatment, which potentially could have influenced

their perceptions and experiences. Although the study design may not impact PRO completion rates or baseline scores, the impact on any change in score or study exit scores is unknown [27]. Declining completion rates because of patients who died or experienced disease progression may bias interpretation in favor of responders; however, this is a problem that generally affects oncology trials and was observed in another HRQoL study of patients with previously treated advanced UC [9]. Site administrators for EV-301 were trained to oversee PRO questionnaires; the convenience of an electronic option may have improved completion rates. Second, PRO analyses were secondary or exploratory outcomes and relevant differences may have been undetected; adjustments for multiple testing and sample size differences between groups were not conducted. The increasing number of deaths over time may limit the accuracy of interpreting outcomes in time-to-event analyses. In addition, since enrolled patients had a baseline Eastern Cooperative Oncology Group performance status score of 0 or 1, the results may not apply to patients with poor performance status. Patients in EV-301 showed better role and social functioning, less dyspnea, and more appetite loss and pain at baseline in comparison to reference patients with genitourinary cancer [28]. Thus, the magnitude of the improvement in QLQ-C30 scores in comparison to baseline in this population may have been limited. Because data were obtained while the study was being conducted, patient-reported findings pertaining to symptoms/functioning may be difficult to generalize to patient experiences in broader practice settings [29]. Although weekly monitoring could capture more immediate changes in comparison to less frequent monitoring, the effects of a response shift (ie, whereby a patient's self-evaluation may change over time because of psychological adaptation, such as value for different areas of functioning) should also be considered [30,31]. Lastly, while most of the analyses were prespecified, survival curves for time-to-event analyses were post hoc.

5. Conclusions

In EV-301, HRQoL was maintained during EV treatment. At week 12, there were similar changes in HRQoL and functioning domains from baseline in the EV and chemotherapy arms. However, more patients in the EV arm had a confirmed improvement for the majority of scales, and the odds of confirmed clinically meaningful improvement across all functioning and most symptom scales were 1.67 to 2.76 times higher with EV than with chemotherapy. The time to GHS/QoL improvement was also consistently shorter and the time to deterioration was consistently longer in the EV arm than in the chemotherapy arm. Taken together, results from these analyses complement the clinically meaningful improvements in overall survival, progression-free survival, and overall response rate demonstrated for EV in EV-301. These PRO data provide further evidence of areas of benefit as perceived by patients for EV (eg, pain) versus chemotherapy in previously treated la/mUC.

These results were presented in part at the 2021 American Society of Clinical Oncology Annual Meeting; The 2021 Australian and New Zealand Urogenital and Prostate Cancer Trials Group Annual Scientific Meeting; and Congrès Français d'Urologie 2021.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement:

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellassponsored clinical trials at www.clinicalstudydatarequest.com. Astellas criteria on data sharing can be viewed at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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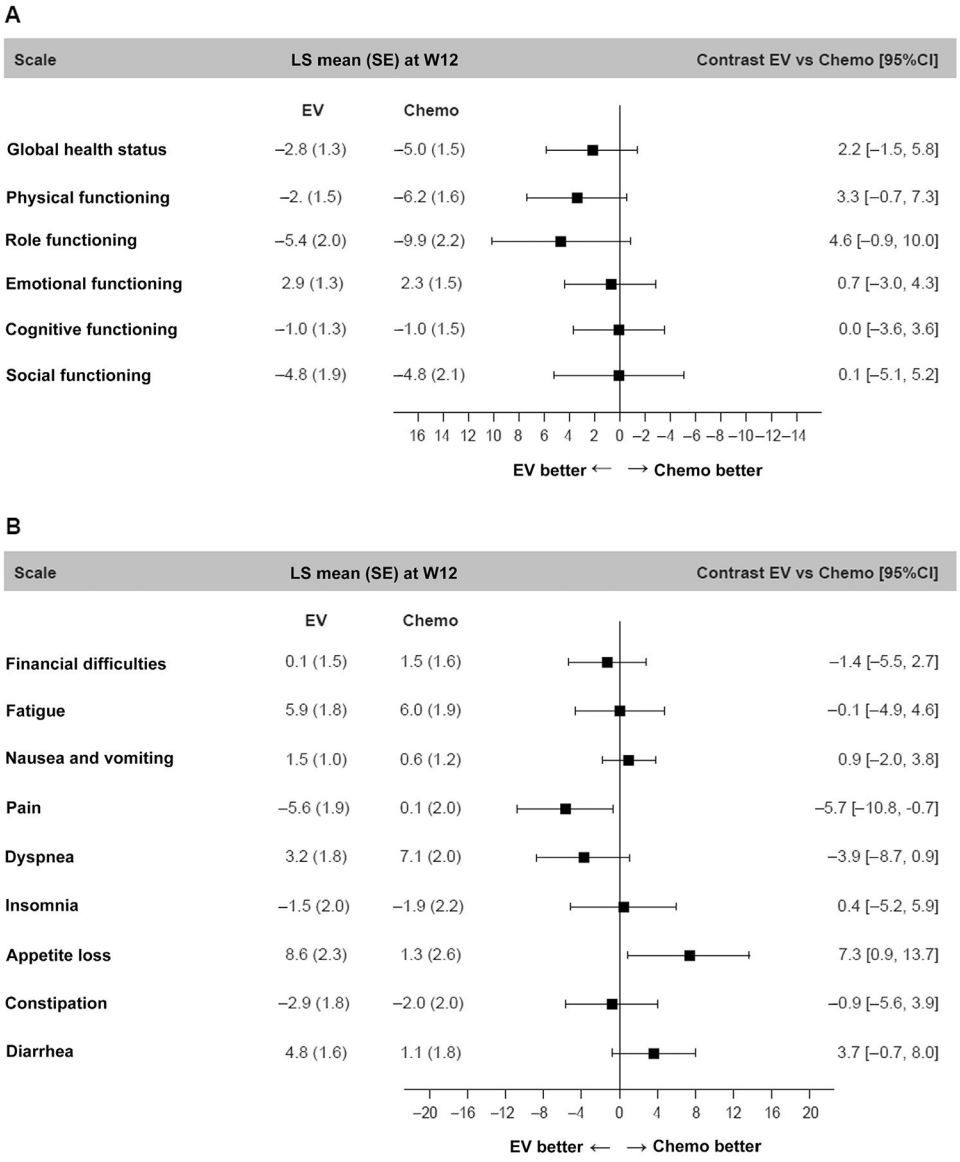

Fig. 1 –.

Quality of Life Questionnaire Core 30 scores at week 12 by treatment group. (A) Global health status/quality of life and functioning scales. (B) Symptom scales. For functioning scales, negative numbers indicate that chemotherapy is better than EV. For symptom scales, negative numbers indicate EV is better than chemotherapy. Chemo = chemotherapy; CI = confidence interval; EV = enfortumab vedotin; LS = least squares; SE = standard error; W12 = week 12.

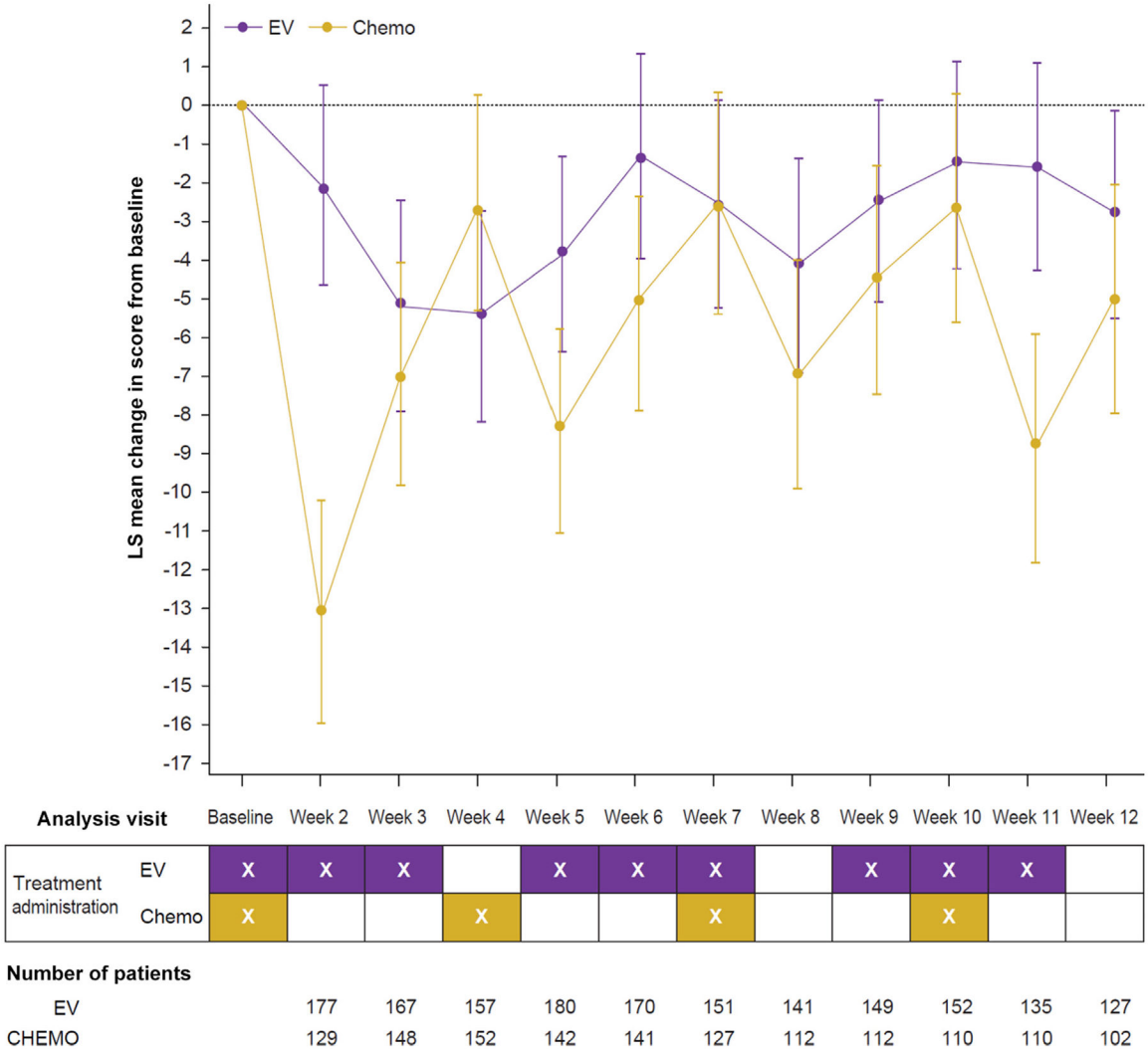

Fig. 2 –.

Adjusted least-squares mean change in Quality of Life Questionnaire Core 30 global health status score from baseline with 95% confidence interval by treatment group. EV = enfortumab vedotin; LS = least squares. [a]An additional post hoc analysis (*F* test) revealed that the variance in estimates of the adjusted change from baseline across the first 12 wk of treatment between the two arms was significantly different ($p = 0.02$), supporting considerable variability for the chemotherapy arm.

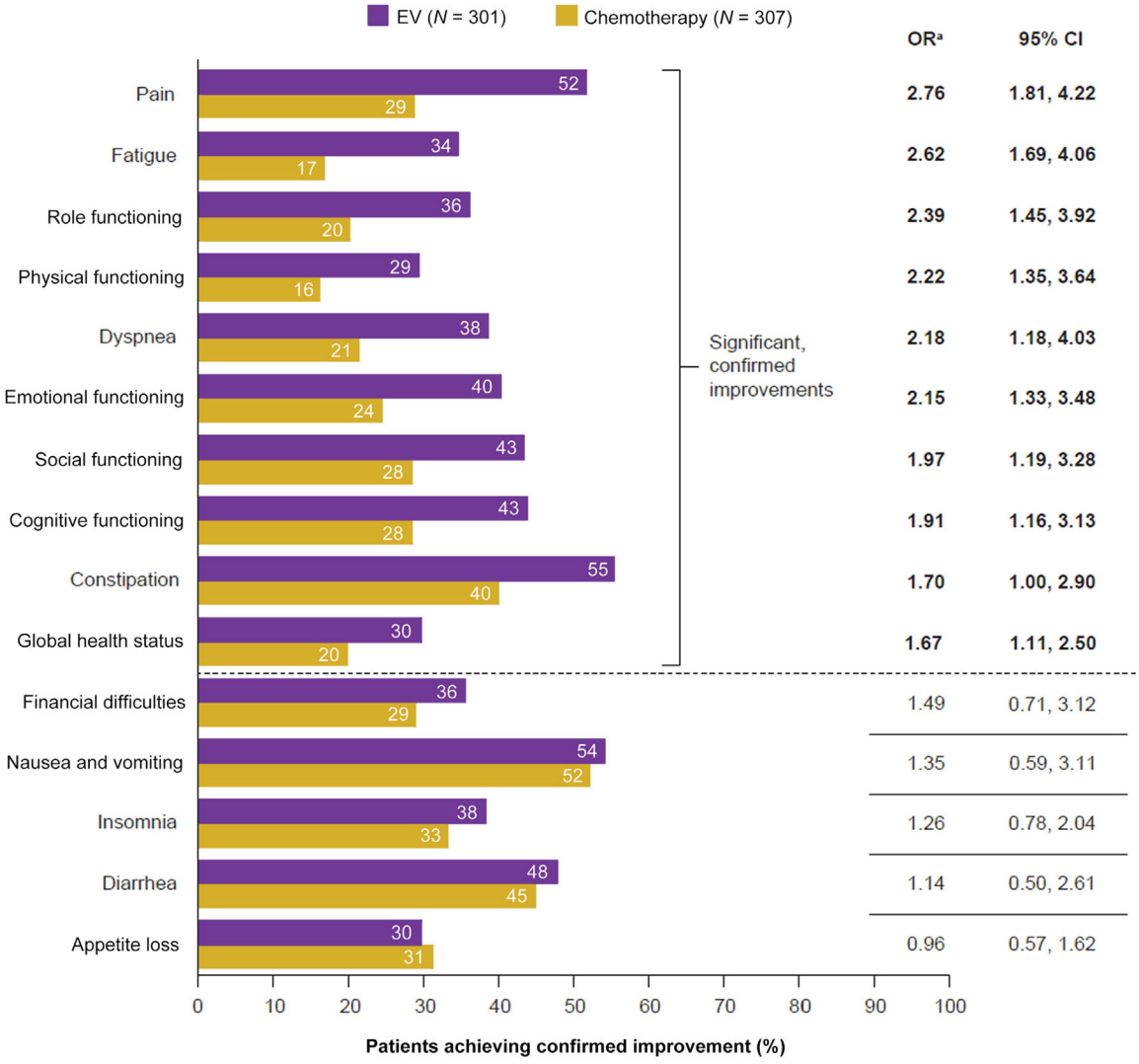

Fig. 3 –.

Confirmed improvements in scores for Quality of Life Questionnaire Core 30 scales. CI = confidence interval; EV = enfortumab vedotin; OR = odds ratio. Only patients with baseline values allowing for an improvement in score for the respective scale were included in the responder analysis. [a]OR > 1.00 favors EV versus chemotherapy.

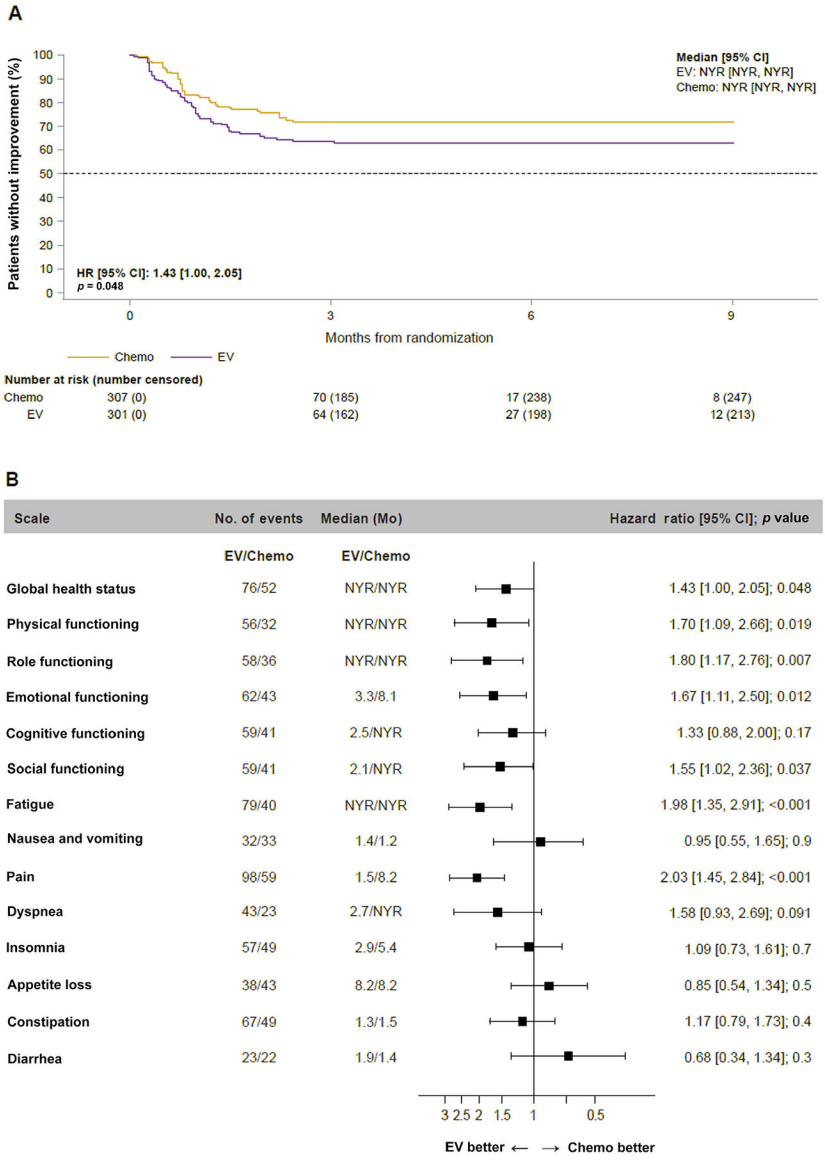

Fig. 4 –.

Time to first confirmed clinically meaningful improvement. (A) Estimate of global health status/quality of life. (B) Results for Quality of Life Questionnaire Core 30 scales based on primary thresholds. Scores for financial difficulties were not included, as estimates were large because of the small number of events. Chemo = chemotherapy; CI = confidence interval; EV = enfortumab vedotin; HR = hazard ratio; NYR = not yet reached.

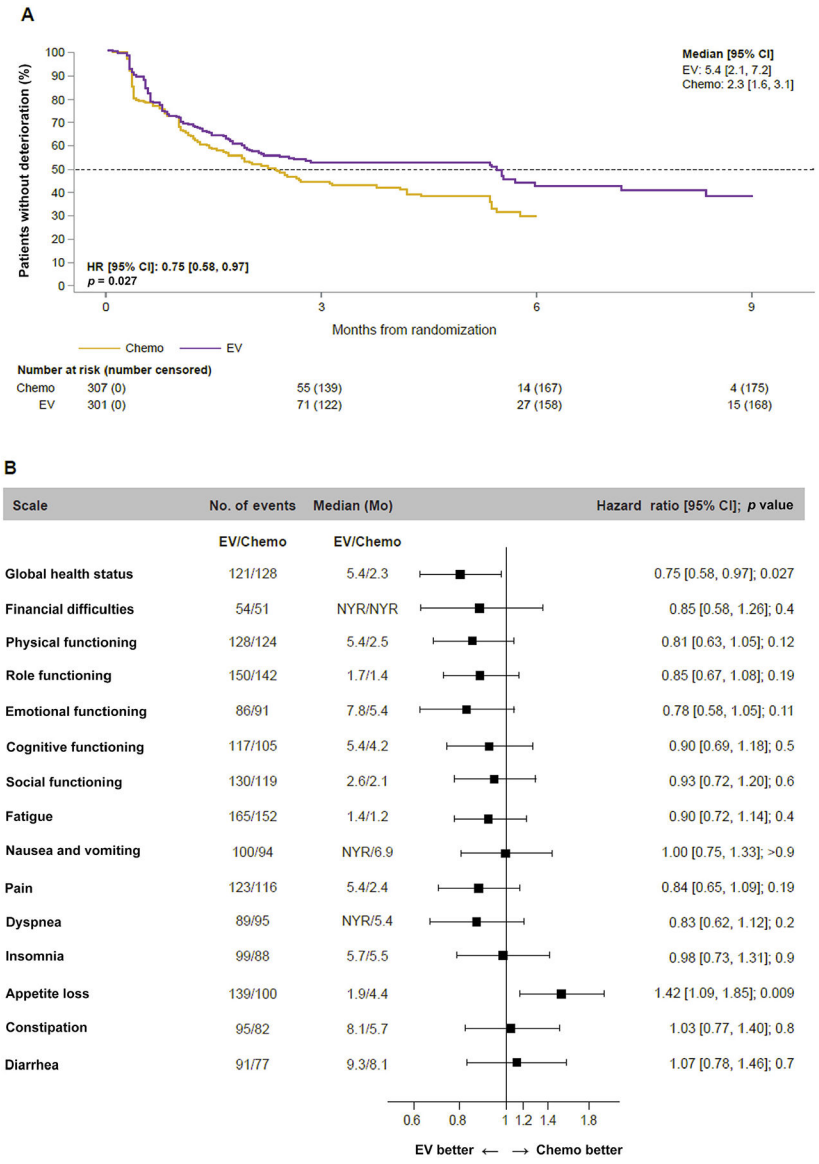

Fig. 5 –.

Time to first confirmed clinically meaningful deterioration. (A) Estimate of global health status/quality of life. (B) Results for Quality of Life Questionnaire Core 30 scales based on primary thresholds. Chemo = chemotherapy; CI = confidence interval; EV = enfortumab vedotin; HR = hazard ratio; NYR = not yet reached.

Table 1 –

EORTC QLQ-C30 scores at baseline

Scale	Mean score (SD)	
	EV	CTx
Global health status	64 (20)	65 (19)
Physical functioning	75 (22)	75 (21)
Role functioning	74 (28)	72 (27)
Emotional functioning	79 (21)	77 (20)
Cognitive functioning	86 (18)	84 (20)
Social functioning	80 (25)	80 (24)
Fatigue	34 (25)	35 (24)
Pain	31 (28)	32 (27)
Nausea and vomiting	6 (14)	7 (14)
Dyspnea	17 (23)	17 (23)
Insomnia	25 (27)	25 (27)
Appetite loss	22 (28)	24 (28)
Constipation	21 (27)	22 (28)
Diarrhea	7 (16)	7 (17)
Financial difficulties	12 (21)	11 (20)

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EV = enfortumab vedotin; CTx = chemotherapy; SD = standard deviation.