Patient-reported outcomes in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer treated with enfortumab vedotin alone or in combination with pembrolizumab in the Phase 1b/2 EV-103 Cohort K study

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Background

- Patients with la/mUC have a poor prognosis
  - 5-year survival rate of ~7.7%[1]
  - High symptom burden/pain negatively impacts QOL and functioning[2,3]
- 1L therapeutic options are an unmet need for patients with la/mUC who are cisplatin ineligible[4-7]
- There are limited PRO data available for 1L therapies in the cisplatin-ineligible patient population
- These data describe the impact of 1L EV+P or EV monotherapy on QOL, functioning, and symptoms from the patient perspective

1L, first-line; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; P, pembrolizumab; PRO, patient-reported outcome; QOL, quality of life.

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Bladder Cancer. National Institutes of Health; 2021. Accessed Jan 30, 2023. https://seer.cancer.gov/statfacts/html/urinb.html; **2.** Mamtani R, et al. *J Clin Oncol*. 2021;39(suppl 15):4539. **3.** Martin S, et al. *Bladder Cancer*. 2022;8(1):45-53; **4.** Dash A, et al. *Cancer*. 2006;107(3):506-513; **5.** Galsky MD, et al. *Bladder Cancer*. 2018;4(2):227-238; **6.** Galsky MD, et al. *J Clin Oncol*. 2011;29(17):2432-2438; **7.** Galsky MD, et al. *Ann Oncol*. 2012;23:406-410.

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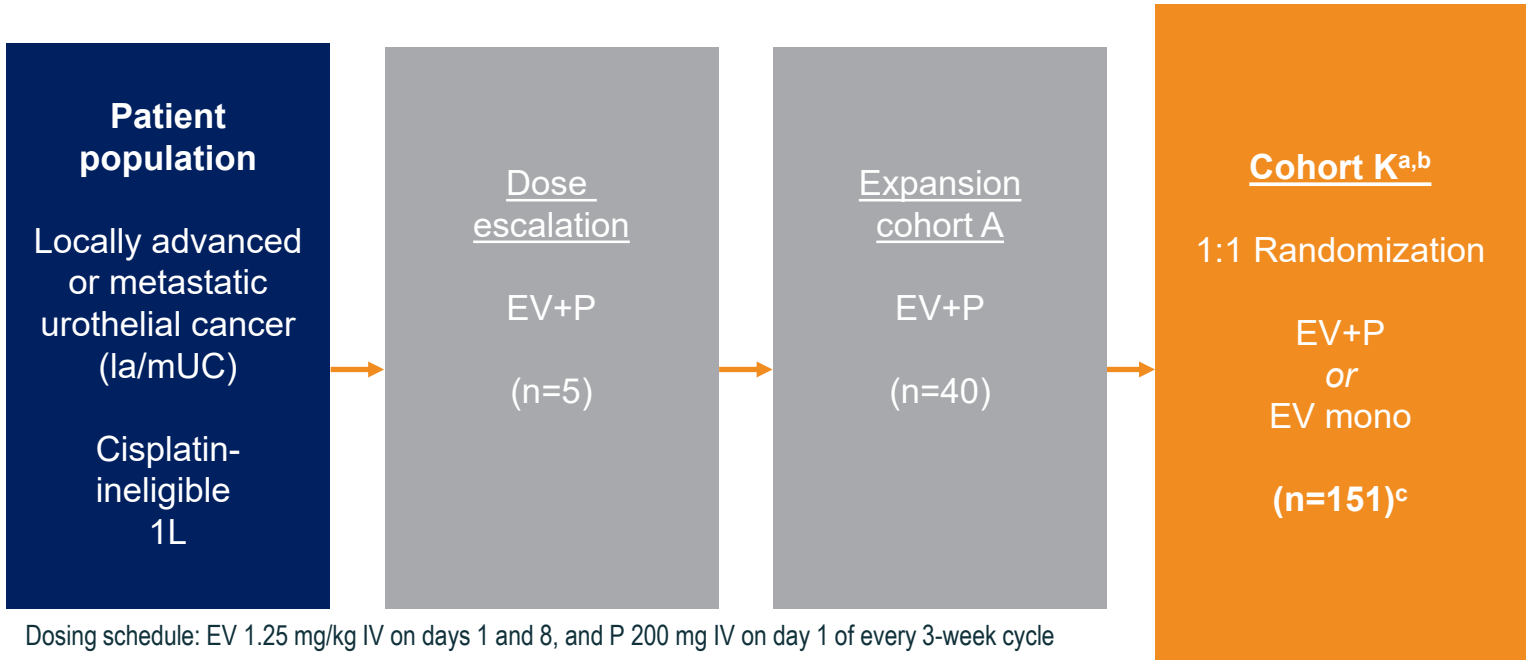
EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with la/mUC



Dosing schedule: EV 1.25 mg/kg IV on days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle

[a]Cohort K Stratification factors: liver metastases (present/absent) and ECOG PS (0 or 1/2); the sample size was based on precision of the estimate for ORR characterized by 95% CIs.
[b]Cohort K completed enrollment on 11 Oct 2021; data cutoff was 10 Jun 2022.
[c]The full analysis set included all patients who enrolled in the study and received study treatment. Of 151 patients who were randomized, 149 were treated; 2 patients were randomized but not treated and so were not included in the safety and efficacy analyses.

Study endpoints

- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities
- **Exploratory endpoints:** PK, biomarkers, PFS2, **PROs (EORTC QLQ-C30, BPI-SF**, EQ-5D-5L, HRU)

Statistical considerations

- No formal statistical comparisons between the two treatment arms

1L, first-line; BICR, blinded independent central review; BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; DCR, disease control rate; DOR, duration of response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EQ-5D-5L, EuroQol-5 dimension-5 level; EV, enfortumab vedotin; HRU, healthcare resource utilization; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P, pembrolizumab; PK, pharmacokinetics; PROs, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumours.

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Key demographic and baseline disease characteristics[a]

Renal impairment was the main reason for cisplatin-ineligibility

	EV+P (n=76)	EV mono (n=73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Age, median (range), y	71 (51-91)	74 (56-89)
White race, n (%)	61 (80.3)	55 (75.3)
Met ≥1 Galsky criteria[b], n (%)		
CrCL <60 and ≥30mL/min	48 (63.2)	44 (60.3)
Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
ECOG PS of 2	6 (7.9)	9 (12.3)
CrCL <60 and ≥30mL/min and Grade ≥2 hearing loss	7 (9.2)	7 (9.6)
CrCL <60 and ≥30mL/min and ECOG PS of 2	4 (5.3)	1 (1.4)
Metastasis disease sites[c], n (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis disease sites[c], n (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable	2 (2.6)	1 (1.4)

[a]ITT population.
[b]Patients may have experienced metastatic disease in ≥1 location.
[c]One patient in the EV mono arm was considered cisplatin-ineligible by the investigator due to age and Grade 1 hearing loss

Previously presented in part at ESMO 2022, Rosenberg et al. Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC).
1L, first-line; 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.

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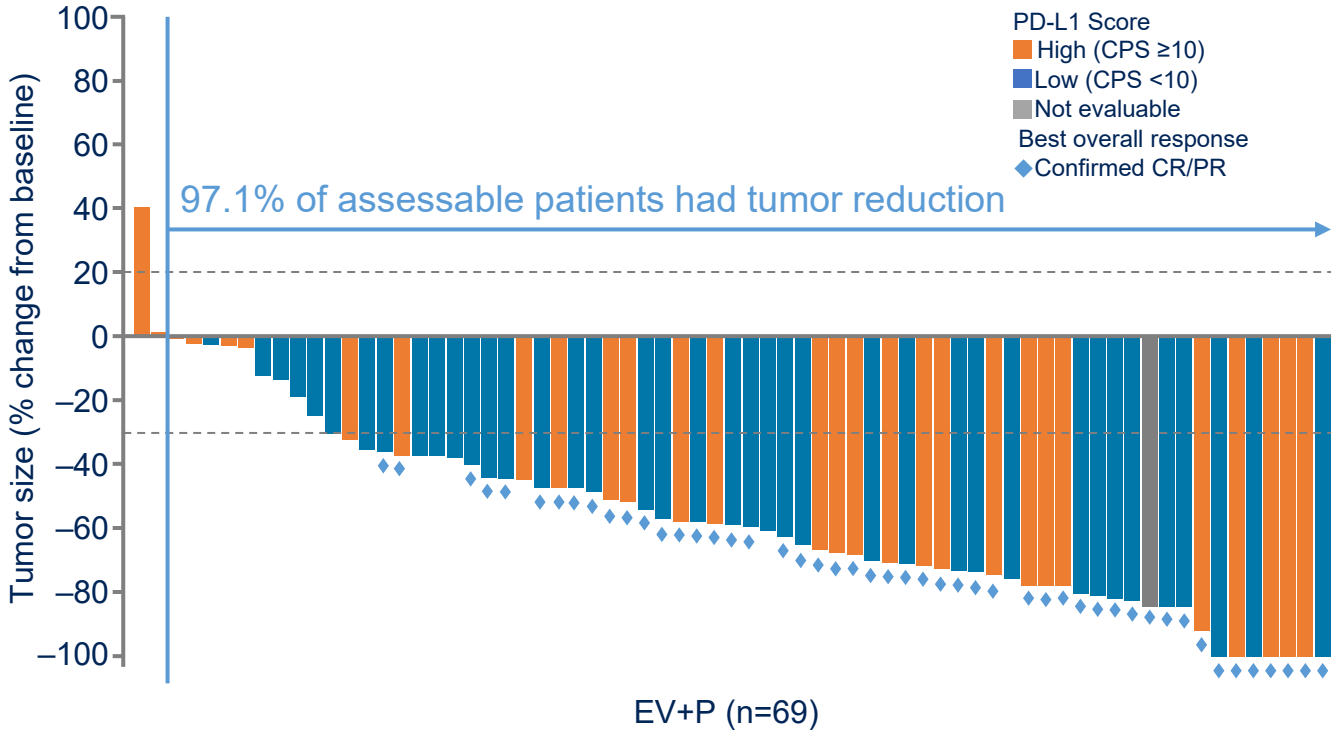
ORR by BICR and safety profile



Data cutoff: 10 Jun 2022.

[a]Of 76 patients in the EV+P arm, seven patients were not assessable due to non-measurable disease (n=4), post-baseline assessment that was not evaluable (n=2), and lack of post-baseline assessment (n=1).

[b]There were no formal statistical comparisons between treatment arms.

	EV+P[b] (n=76)	EV mono[b] (n=73)
cORR, n (%) (95% CI)	49 (64.5) (52.7-75.1)	33 (45.2) (33.5-57.3)
Median time to objective response (range), mo	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	11.0 (1-29)	8.0 (1-33)

EV+P

- 42/49 (85.7%) of responses observed at first assessment (week 9±1 week)
- Most common AEs were fatigue, peripheral sensory neuropathy, alopecia, and maculopapular rash

EV mono

- Activity is consistent with prior results in 2L+ la/mUC
- Safety profile consistent with previous studies

Previously presented at ESMO 2022, Rosenberg et al. Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC).

1L, first-line; AEs, adverse events; BICR, blinded independent central review; CPS, combined positive score; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; ORR, overall response rate; P, pembrolizumab.

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PRO instruments and assessment schedule

EORTC QLQ-C30 and BPI-SF were used to assess PROs in patients with la/mUC[a]

Baseline
(Day 1, predose and postrandomization)

Weekly for cycles 1-3
(21-day cycles)

Every cycle until EOT[d]

Weeks 8-12, Week 24, and Week 51 were prespecified timepoints of interest

EORTC QLQ-C30[b]
(score range 0-100; higher score represents greater symptom burden, higher functioning, and higher QOL)

Cancer-related symptoms
- Appetite loss
- Constipation
- Diarrhea
- Dyspnea
- Social
- Fatigue
- Insomnia
- Nausea and vomiting
- Pain

Function
- Physical
- Cognitive
- Emotional
- Role
- Social

QOL
- GHS

BPI-SF[c]
(score range 0-10; higher score represents more pain)
- Worst pain
- Average pain
- Least pain
- Pain severity
- Pain interference
- Location of pain

- Descriptive analyses included change from baseline (as measured using a Mixed Model for Repeated Measures [MMRM]) and time to sustained improvement

[a]All analyses were conducted in the PRP unless otherwise specified. The PRP included any patients who completed ≥1 question of the PRO questionnaire at baseline.
[b]A 30-item questionnaire to assess QOL in patients with cancer; score range 0-100.
[c]An 8-item questionnaire assessing the severity of pain and its impact on functioning in terms of worst, least, and average pain in the last 24 hours; score range 0-10.
[d]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; la/mUC, locally advanced/metastatic urothelial cancer; MMRM, mixed model for repeated measures; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life.

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EORTC QLQ-C30 baseline scores[a]

Pain, sleep disturbances, and fatigue were the most burdensome symptoms at baseline

EORTC-QLQ-C30	EV+P (n=65)	EV mono (n=61)
QOL, mean (SD)	64.5	63.1

Cancer-related symptom scales and items,[b] mean (SD) *Higher scores indicate greater symptom burden*		
Fatigue	34.5 (28.5)	33.3 (26.5)
Sleep disturbances	33.8 (32.5)	33.9 (33.0)
Pain	32.8 (32.4)	35.5 (28.1)
Appetite loss	27.2 (35.5)	22.4 (29.0)
Constipation	19.5 (24.2)	22.4 (30.9)
Dyspnea	14.4 (20.4)	16.9 (27.6)
Nausea/vomiting	10.0 (22.6)	3.6 (14.0)
Diarrhea	8.7 (21.5)	5.5 (12.4)

[a]All analyses were conducted in the PRP unless otherwise specified. The PRP included any patients who completed ≥1 question of the PRO questionnaire at baseline.
[b]All EORTC QLQ-C30 scale scores range from 0-100.

EORTC-QLQ-C30	EV+P (n=65)	EV mono (n=61)
Functioning scales,[b] mean (SD) *Higher scores indicate higher functioning*		
Cognitive functioning	86.4 (15.6)	87.7 (17.5)
Social functioning	79.0 (23.1)	78.4 (28.4)
Emotional functioning	77.2 (19.2)	79.5 (22.6)
Physical functioning	74.1 (23.2)	78.4 (22.2)
Role functioning	70.0 (30.9)	74.6 (30.1)

- Of 76 and 73 patients treated with EV+P and EV mono, respectively, 65 and 61 completed the questionnaire at baseline; for both treatment arms, compliance rates were ≥84% through Week 24
- Scores in both treatment arms were typical of that reported for patients with la/mUC[1]

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; P, pembrolizumab; PRO, patient-reported outcome; PRP, patient-reported outcome population; QOL, quality of life; SD, standard deviation.

1. O'Donnell PH, et al. *Cancer*. 2020;126(2):432-443.

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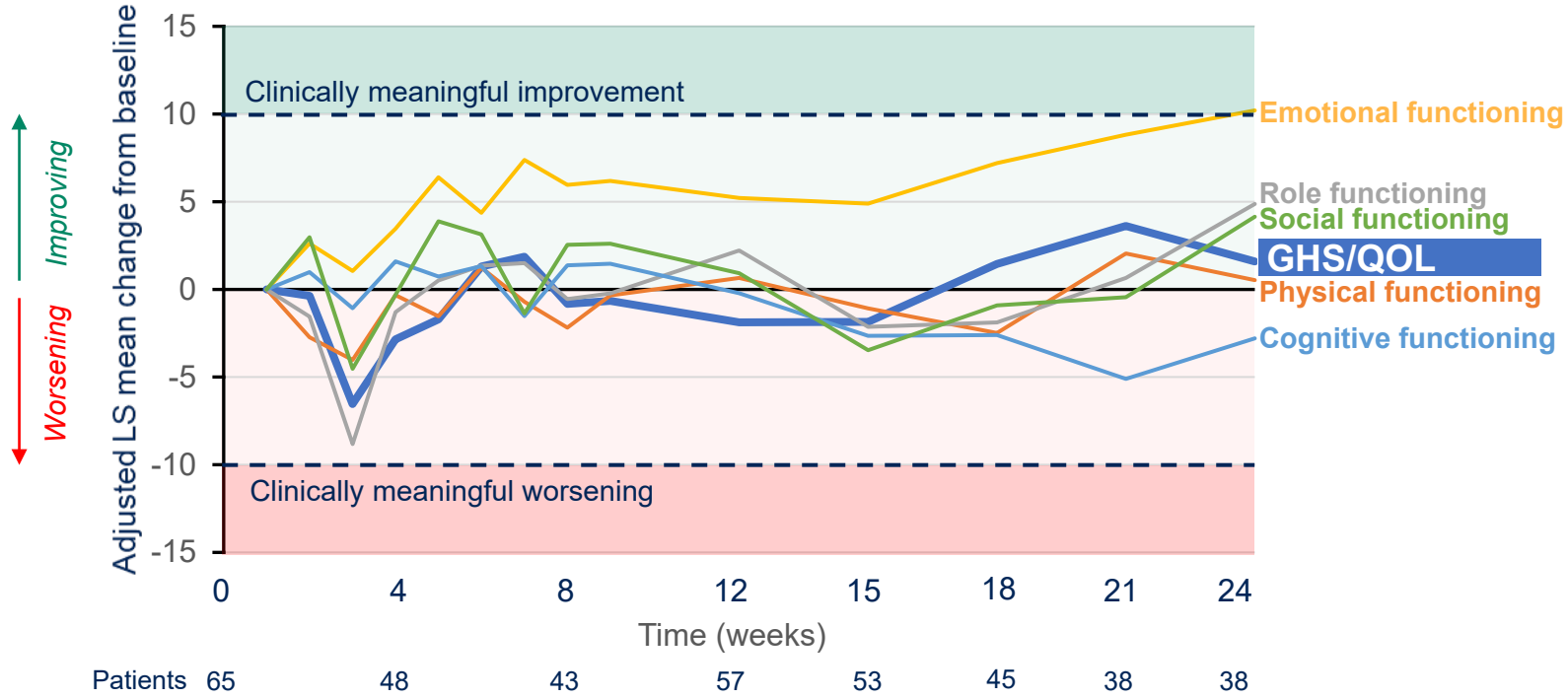
EORTC QLQ-C30[a] QOL and functioning scales

EV+P was associated with preservation or improvement in QOL and functioning scale scores

EORTC QLQ-C30 QOL and functioning scales EV+P



- Emotional functioning demonstrated a consistent pattern of mild/moderate improvement[1] (range of 5-10 points)
- Mild/moderate, transient worsening in QOL, role, and social functioning were observed at Week 3 then returned to baseline where they were maintained

[a]For MMRM analyses, treatment, time, their interaction, baseline PRO, liver metastases, and ECOG PS were included in the model. LS means were reported; line plots show adjusted mean of predicted change from baseline until Week 24. Clinically meaningful improvements were identified using a predefined threshold (10-point change)[2] for the EORTC QLQ-C30.

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 effect models for repeated measures; P, pembrolizumab; QOL, quality of life.

1. Staunton H, et al. *J Patient Rep Outcomes*. 2019;3(1):16. doi:10.1186/s41687-019-0100-y. **2.** Osoba D, et al. *J Clin Oncol*. 1998;16(1):139-144.

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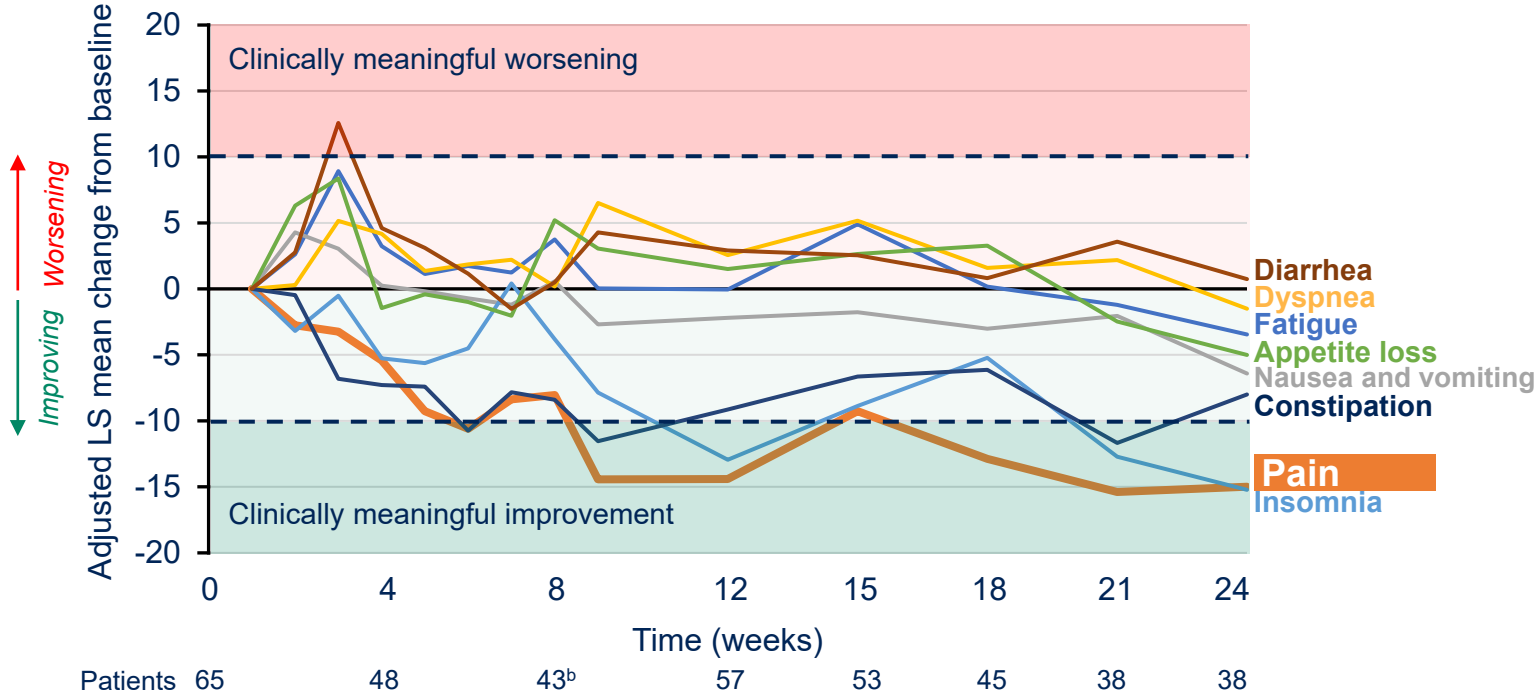
EORTC QLQ-C30[a] symptom scales

EV+P was associated with preservation or improvement in symptom scale scores

EORTC QLQ-C30 symptom scales EV+P



- Clinically meaningful improvements in pain were seen at Week 12 (-14.41 [3.14]) versus baseline and persisted through Week 24 (-14.99 [3.56])
- Insomnia and constipation demonstrated a consistent pattern of mild/moderate improvement[1] (range of 5-10 points) versus baseline
- Diarrhea worsened at Week 3 but returned to baseline levels at Week 8 and 24
- As the EORTC QLQ-C30 does not capture the cause of pain, it was not possible to determine neuropathic pain specifically

[a]For MMRM analyses, treatment, time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. LS means are reported; line plots show adjusted mean of predicted change from baseline until Week 24. Clinically meaningful improvements were identified using a predefined threshold (10-point change)[2] 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; la/mUC, locally advanced/metastatic urothelial cancer; LS, least square; MMRM, mixed effect models for repeated measures; P, pembrolizumab.

1. Staunton H, et al. *J Patient Rep Outcomes*. 2019;3(1):16. doi:10.1186/s41687-019-0100-y. **2.** Osoba D, et al. *J Clin Oncol*. 1998;16(1):139-144.
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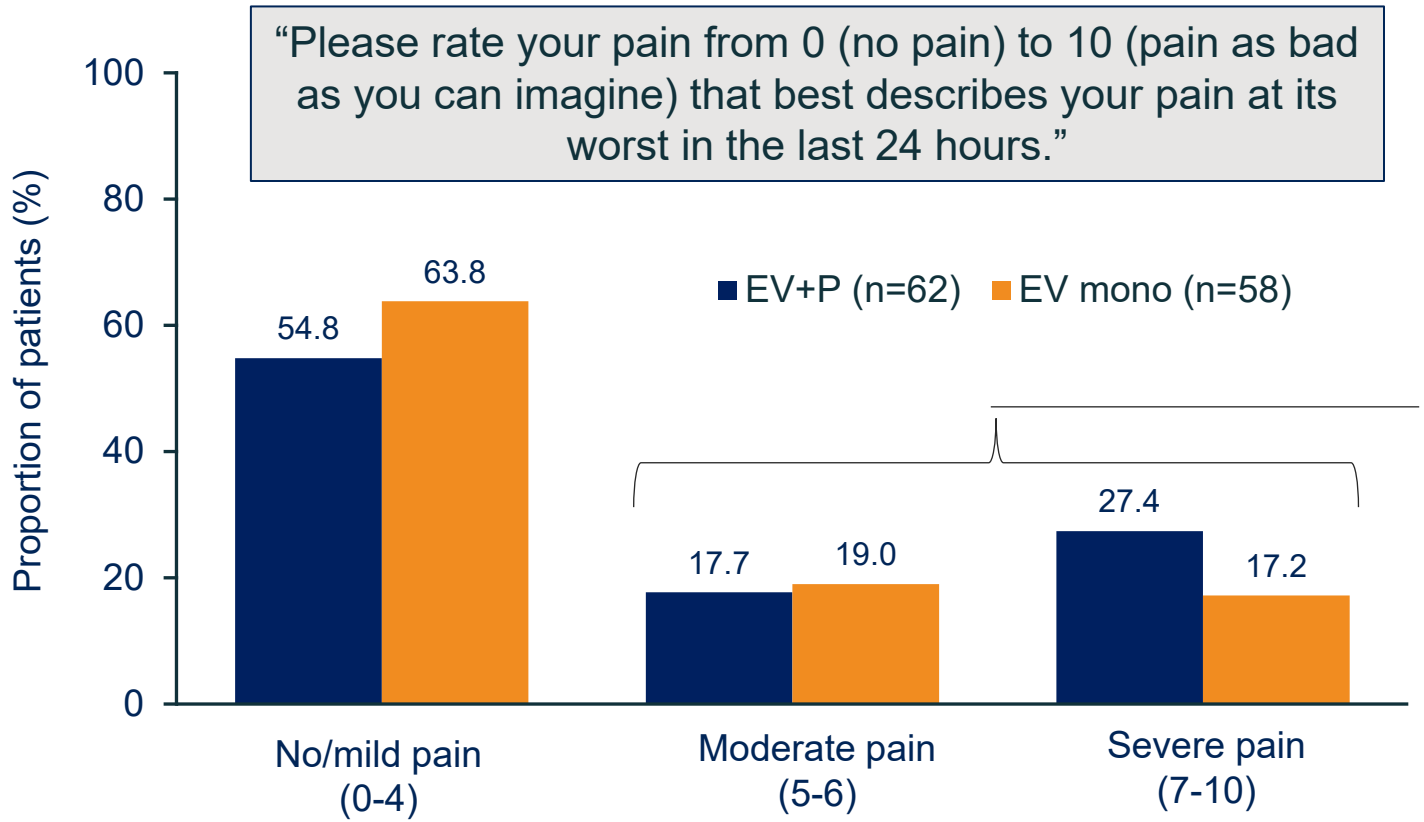
BPI-SF baseline scores[a]

More than one-third of patients had moderate to severe pain at baseline



28 of 62 (45.2%) and 21 of 58 (36.2%) patients treated with EV+P and EV mono, respectively, had moderate to severe worst pain at baseline

[a]All BPI-SF scale scores range from 0-10; higher scores indicate higher pain levels.
[b]For the EV Mono group, n=57 for pain severity.

BPI-SF, Brief Pain Inventory Short Form; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; P, pembrolizumab; SD, standard deviation.

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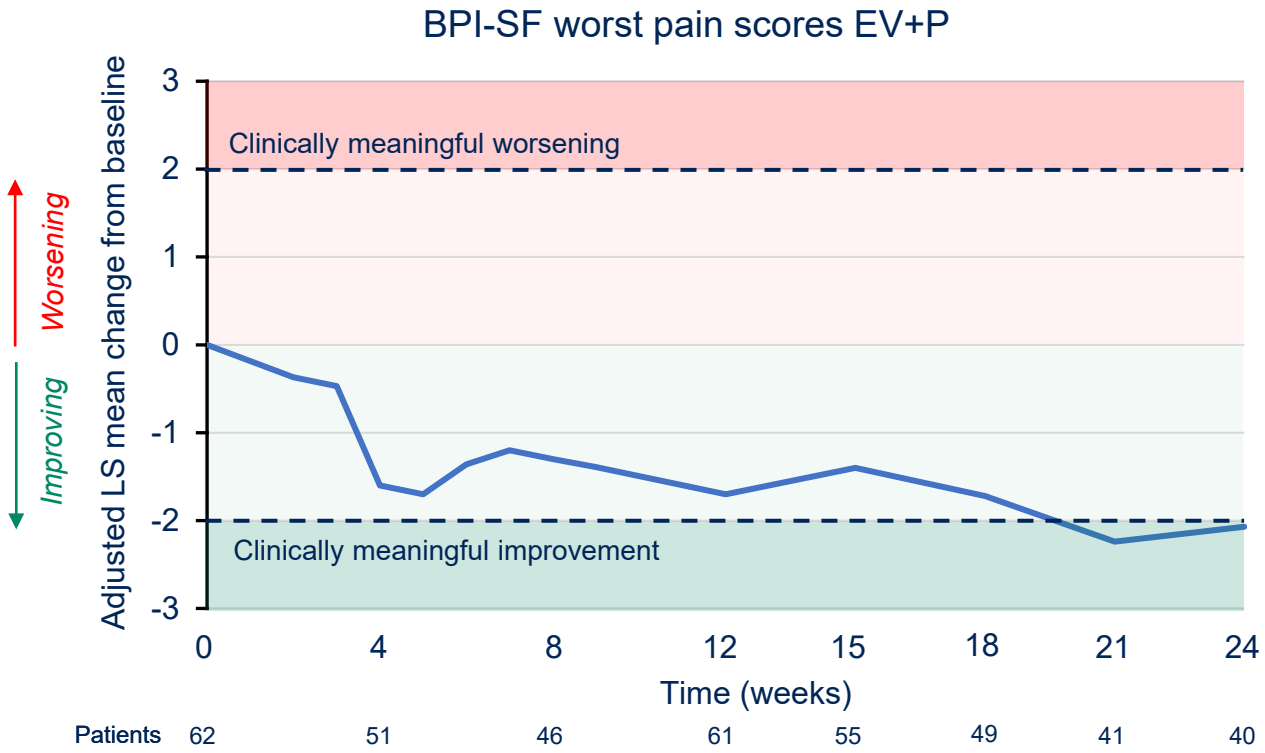
BPI-SF[a] scores

Improvement in worst pain was demonstrated in the EV+P treatment arm



[a]For MMRM analyses, treatment, time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. LS means are reported; line plots show adjusted mean of predicted change from baseline for all post-baseline assessments. Clinically meaningful improvements were identified using a predefined threshold (2-point change)[1] for the BPI-SF.

- A clinically meaningful improvement in worst pain was observed at Week 24 (-2.07 [0.37])
- Worst pain, average pain, pain interference, and pain severity consistently showed improved scores from Week 4-24

BPI-SF, Brief Pain Inventory Short Form; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EV, enfortumab vedotin; MMRM, mixed effect models for repeated measures; P, pembrolizumab.

1. Mathias SD, et al. *J Support Oncol*. 2011;9(2):72-78.

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BPI-SF time to improvement[a] among patients with moderate to severe pain[b] at baseline

A majority of patients presenting with moderate to severe pain experienced sustained improvement

Parameters	EV+P N = 28 of 65 (43.1%)
Rate of sustained improvement,[c] n (%)	24 (85.7%)
Time to sustained improvement,[d] median (95% CI)	1.1 (0.5-1.2) months
25th percentile (95% CI)	0.5 (0.3-0.7) months
75th percentile (95% CI)	1.4 (1.2-7.9) months
Censored observations, n (%)	3 (11.1%)

[a]An improvement in BPI-SF domain and items scores was defined as a decrease in score from baseline by ≥1 MCT, while a deterioration was defined as an increase in score from baseline by ≥1 MCT; otherwise, patients were categorized as stable.
[b]Moderate to severe pain was defined as a baseline BPI-SF worst pain score of ≥5.
[c]Defined as improvement as identified by a 2-point change in BPI-SF pain scores.
[d]Time to sustained improvement was defined as the number of months from start of treatment to sustained improvement, where meaningful improvement was considered if a change in score increased from baseline by ≥1 MCT and was sustained for ≥2 consecutive assessments among patients who were not within 1 MCT of best possible score at baseline.

BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; EV, enfortumab vedotin; MCT, meaningful change threshold; P, pembrolizumab.

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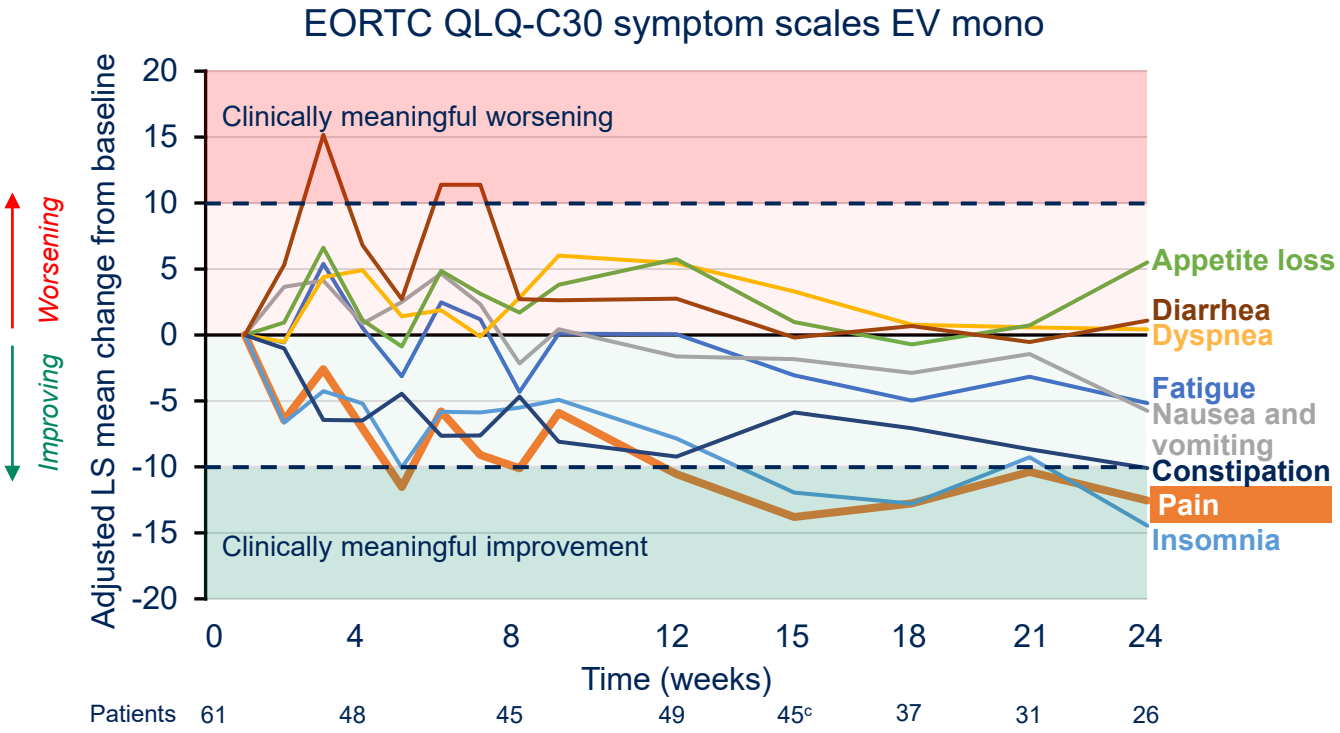
Impact of EV mono on PROs

QOL, functioning, and pain scores for EV mono were consistent with those for EV+P



EORTC QLQ-C30 QOL, functioning, and symptom scale scores[a]

- QOL, functioning, and symptom scale scores were directionally similar with that of the EV+P treatment arm
  - Clinically meaningful improvements in pain were observed at Week 24 (-12.55 [4.27])
  - Clinically meaningful improvements in insomnia were observed at Week 24 (-14.46 [4.70])

BPI-SF pain scores

- Consistent small to moderate improvements in the BPI worst pain, average pain, and pain severity were observed

BPI-SF time to improvement[b]

- 21 of 58 (36.2%) patients had moderate to severe worst pain at baseline
  - 13 of 21 (61.9%) patients experienced sustained improvement
  - Median time to sustained improvement of worst pain was 1.4 months

[a]For MMRM analyses, treatment, time (and their interaction), baseline PRO, liver metastases, and ECOG PS were included in the model. LS means are reported; line plots show adjusted mean of predicted change from baseline until Week 24. Clinically meaningful improvements were identified using predefined thresholds (10-point change and 2-point change for EORTC QLQ-C30 and BPI-SF, respectively).
[b]Time to sustained improvement was defined as the number of months from start of treatment to sustained improvement, where meaningful improvement was considered if a change in score increased from baseline by ≥1 MCT and was sustained for ≥2 consecutive assessments among patients who were not within 1 MCT of best possible score at baseline.
[c]For diarrhea, n=44 at Week 15.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EV, enfortumab vedotin; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; GHS, global health status; la/mUC, locally advanced/metastatic urothelial cancer; LS, least square; MMRM, mixed effect models for repeated measures; mono, monotherapy; P, pembrolizumab; PRO, patient-reported outcome; QOL, quality of life.

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Author's Conclusions

- Overall, PRO data showed that EV+P in cisplatin-ineligible patients with la/mUC was associated with preservation or improvement of QOL, functioning, and symptoms;
  - Transient worsening in some symptoms was observed at Week 3 that returned to baseline within 1-2 weeks
- In both treatment arms, similar trends in rapid improvement of pain were demonstrated
- EV+P is the first regimen in the 1L setting to show clinically meaningful improvements in pain in cisplatin-ineligible patients with la/mUC
- PRO results for EV mono were directionally similar with that of the EV+P arm
- These PRO data complement the efficacy and safety profile of EV+P in 1L cisplatin-ineligible patients with la/mUC[1]
- A confirmatory randomized phase 3 study (EV-302) is ongoing to assess efficacy, safety and evaluate PROs in patients with previously untreated la/mUC treated with 1L EV+P or cisplatin/carboplatin–based regimens (NCT04223856)

1L, first-line; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; P, pembrolizumab; PRO, patient-reported outcome; QOL, quality of life.

1. Rosenberg JE, et al. *Annals of Oncology*. 2022;33(suppl 7):S808-S869.

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