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Quality of Life, Functioning, and Symptoms in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma From EV-301: A Randomized Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy

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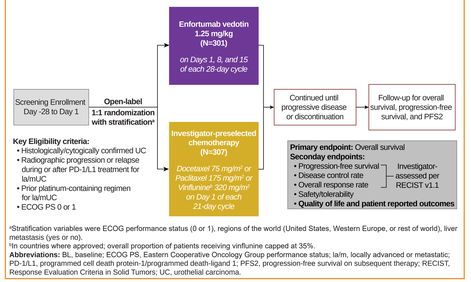
Background

- Enfortumab vedotin (EV) is an antibody-drug conjugate comprised of 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[1]
- EV received accelerated approval from the United States Food and Drug Administration in 2019 for the treatment of adults with locally advanced/metastatic urothelial carcinoma (la/muC) who have previously received a programmed cell death protein-1/programmed death-ligand 1 (PD-1/L1) inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting[2]
- In the phase 3, randomized EV-301 trial (NCT03474107), EV prolonged median overall survival by 3.9 months and significantly reduced the risk of death by 30% when compared with standard chemotherapy in patients with previously treated la/muC[3]
- Characterizing patient-reported outcomes (PRO) using a systematic process with a validated instrument provides evidence to support informed decision-making by patients, physicians, policy makers, and payers[4,5]
- Examining patient perspectives and experiences is important to further contextualize the risks and benefits of EV compared with standard chemotherapy
- Here, we report key prespecified PRO endpoints, a secondary objective of the EV-301 trial, measuring quality of life (QoL), functioning, and symptoms

Methods

Figure 1. Study Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, Western Europe, or rest of world), liver metastasis (yes or no).
[b]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; la/m, locally advanced or metastatic; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; PFS2, progression-free survival on subsequent therapy; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

- Patients completed the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline (Day -7 to -1), on Day 1 of each week for the first 12 weeks, and then every 12 weeks until discontinuation
- The QLQ-C30 assesses the following domains:
  - Global health status (GHS)/QoL (two items)
  - Functional scales
    - Physical functioning (five items)
    - Role functioning (two items)
    - Emotional functioning (four items)
    - Cognitive functioning (two items)
    - Social functioning (two items)
  - Symptom scales/items
    - Fatigue (three items)
    - Nausea and vomiting (two items)
    - Pain (two items)
    - Dyspnea, insomnia, appetite loss, constipation, and diarrhea (one item each)
  - Financial impact (one item)

Statistical Analyses

- **Descriptive statistics:** to summarize instrument completion and compliance rates, item and scale scores, and proportions of patients with improvement, stability, or deterioration
  - Completion (unadjusted) rates were calculated as the number of patients meeting the minimum requirements for scoring at least one domain divided by the number of patients that were randomized
  - Compliance (adjusted) rates were calculated as the number of patients at each visit who completed at least one domain divided by the number of patients who were expected to have PRO assessments
  - Change in domain scores from baseline were categorized as improvement, stable, or deterioration using prespecified threshold values (Table 1) that connote clinically meaningful changes for patients
  - In addition to the primary thresholds, a sensitivity threshold of 10 was used to define one threshold unit for all domains and used for comparability
  - For categorical data, statistical comparisons were made using two-sided tests at the α=0.05 significance level unless otherwise stated and no adjustments for multiple comparisons were made
- **Mixed model repeated measures:** to evaluate longitudinal changes from baseline at Week 12, adjusted for covariates
  - Missing data are handled under the missing at random assumption wherein missingness is independent of unobserved values
- **Logistic regression models:** to assess confirmed improvement, defined as clinically meaningful improvement (as per Table 1) over two consecutive visits
- **Kaplan-Meier methods, stratified log-rank test, and stratified Cox proportional hazards model:** to evaluate time to first clinical deterioration in symptoms, functioning, and health-related QoL

Table 1. Primary Thresholds for Defining Deterioration, Stability, and Improvement on QLQ-C30 Domains

Higher scores mean "better"
Lower scores mean "better"

Domain\Change Value of	Primary Threshold		
	Deterioration	Stable	Improvement
Global Health Status	<-10	-10 to +8	>+8
Physical Functioning	<-10	-10 to +7	>+7
Role Functioning	<-14	-14 to +12	>+12
Emotional Functioning	<-12	-12 to +9	>+9
Cognitive Functioning	<-7	-7 to +7	>+7
Social Functioning	<-11	-11 to +8	>+8
Fatigue	>+10	+10 to -9	<-9
Pain	>+11	+11 to -9	<-9
Nausea and Vomiting	>+11	+11 to -9	<-9
Dyspnea	>+11	+11 to -9	<-9
Insomnia	>+9	+9 to -9	<-9
Appetite Loss	>+14	+14 to -13	<-13
Constipation	>+15	+15 to -10	<-10
Diarrhea	>+15	+15 to -11	<-11
Financial Difficulties	>+10	+10 to -3	<-3

Abbreviation: QLQ-C30, Quality of Life Questionnaire Core 30.

Results

Baseline Characteristics and Questionnaire Compliance/Completion Rates

- Of the 608 randomized patients (EV, n=301; SC, n=307), 77.3% were male, median age was 68 (range: 30-88), and 30.9% had liver metastasis (Table 2)

Table 2. Patient and Disease Characteristics

Parameter		Enfortumab Vedotin N=301 n (%)	Chemotherapy N=307 n (%)
Sex	Male	239 (79.1)	232 (75.6)
	Female	63 (20.9)	75 (24.4)
Age	<65	108 (35.9)	111 (36.2)
	≥65 to <75	141 (46.8)	128 (41.7)
	≥75	52 (17.3)	68 (22.1)
ECOG PS	0	120 (39.9)	124 (40.4)
	1	181 (60.1)	183 (59.6)
Liver Metastasis	No	208 (69.1)	212 (69.1)
	Yes	93 (30.9)	95 (30.9)

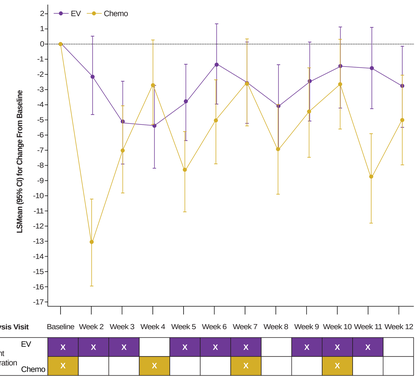
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

- Questionnaire completion and compliance rates
  - Completion rate was 60% for EV and 43% for chemotherapy on Day 8; rates fell to 44% and 34% at Week 12, respectively
  - Compliance rates at baseline were ~90% in both groups; during the study, average rates were 70.2% for EV and 66.9% for chemotherapy
- Baseline QLQ-C30 scores were similar between groups

Longitudinal Comparisons at Week 12

- At Week 12, scores on the GHS scale were similar between groups, but chemotherapy was associated with numerically greater deterioration and variability in QoL over the first 12 weeks (Figure 2)

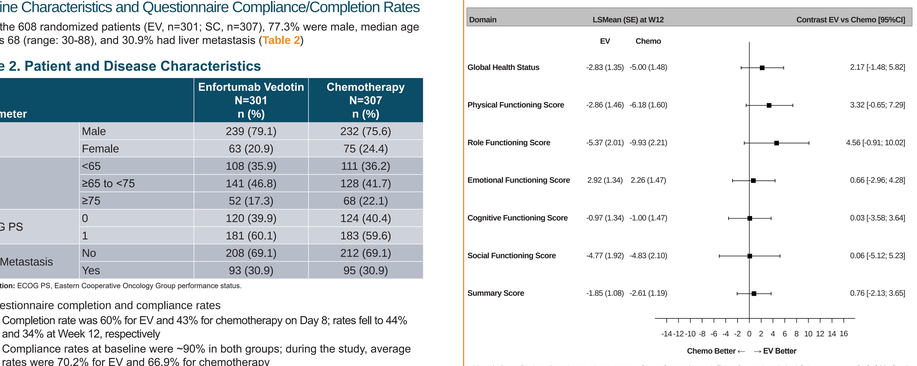
Figure 2. Adjusted Least Squares Mean Change From Baseline on QLQ-C30 Global Health Status by Treatment Group



Abbreviations: chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; LS, least squares; QLQ-C30, Quality of Life Questionnaire Core 30.

- Numerical benefits were observed for EV on global health, physical functioning, and role functioning (Figure 3)

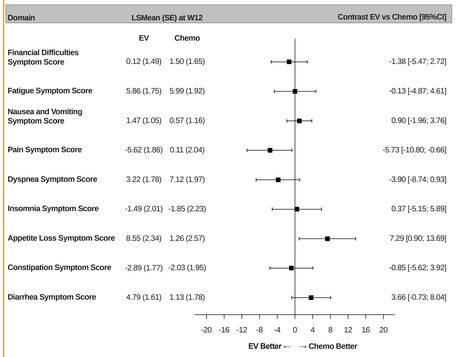
Figure 3. QLQ-C30 Functioning Domains at Week 12 by Treatment



Abbreviations: BL, baseline; chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; LS, least squares; QLQ-C30, Quality of Life Questionnaire Core 30; SE, standard error; W, week.

- Patients receiving EV had significant (P=0.0268) reduction in reported pain symptoms but significant (P=0.0256) worsening of appetite loss compared with chemotherapy (Figure 4)

Figure 4. QLQ-C30 Symptom Scales at Week 12 by Treatment

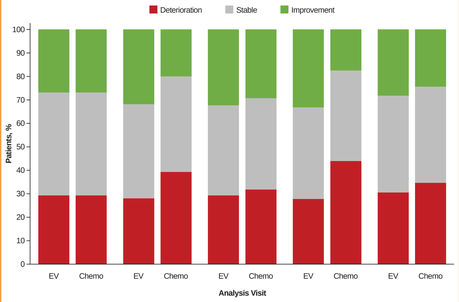


Abbreviations: BL, baseline; chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; LS, least squares; QLQ-C30, Quality of Life Questionnaire Core 30; SE, standard error; W, week.

Responder Status

- Higher proportions of patients improved and lower proportions of patients worsened across domains and symptoms with EV compared with chemotherapy, including GHS (Figure 5)
  - This was consistent across all domains except for appetite loss

Figure 5. Proportion of Patients Responding on Global Health Status by Treatment Group During Week 8-12[a]



[a]This figure is a snapshot of the descriptive analyses and shown as a sample of trends, not to represent all data.
Abbreviations: chemo, chemotherapy; EV, enfortumab vedotin; QLQ-C30, Quality of Life Questionnaire Core 30.

References

1. Rosenberg J, et al. *J Clin Oncol*. 2020;38(10):1041-1049. **2.** Center for Drug Evaluation and Research. Application number: 761137Orig1s000 Approval Letter. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761137Orig1s000Approv.pdf. Updated December 18, 2019. Accessed September 3, 2020. **3.** Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135. **4.** Basch E, et al. *J Clin Oncol*. 2012;30(34):4249-4255. **5.** Giesinger JM, et al. *J Clin Epidemiol*. 2016;69:79-88.

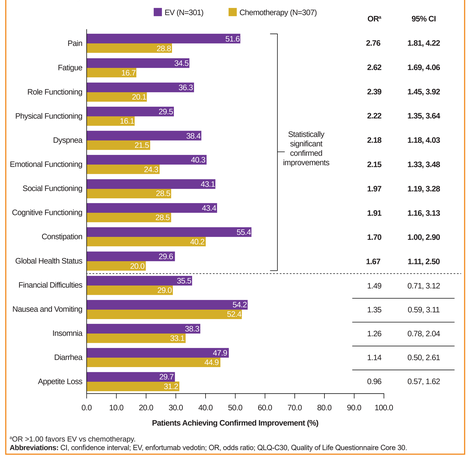
Conclusions

- **QoL was maintained across the course of study treatment with patients receiving EV**
- **EV-treated patients had statistically significant reductions in pain symptoms compared with chemotherapy-treated patients; however, EV-treated patients had significantly more appetite loss**
- **Significantly more patients had confirmed improvement in the majority of domains, with clinically meaningful improvements 1.6 to 2.7 times higher across all functioning and most symptom scores**

Confirmed Improvement

- Significantly more patients reported a confirmed improvement on EV versus chemotherapy in 10 out of 15 domains; clinically meaningful improvement was 1.6 to 2.7 times higher with EV across all functioning and most symptom domains (Figure 6)
- The greatest difference in confirmed improvement was reported for pain which showed that patients had a 2.7 times higher likelihood of achieving a clinically meaningful reduction in pain with EV compared with chemotherapy

Figure 6. Confirmed Improvements on QLQ-C30 Subscales Based on Primary Thresholds



*OR >1.00 favors EV vs chemotherapy.
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; OR, odds ratio; QLQ-C30, Quality of Life Questionnaire Core 30.

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Disclosures

CV, DC, and SS held a consulting or advisory role with Astellas Pharma, Inc. ID held a consulting or advisory role with Seagen Inc. RM, JR, TP, GS, YL, MH, and DP held a consulting or advisory role with Astellas Pharma, Inc./Seagen Inc. MH reports travel, accommodations, expenses from Astellas Pharma, Inc. YL reports travel, accommodations, expenses from Astellas Pharma, Inc./Seagen Inc. GS reports other from Astellas Pharma, Inc. ID and JL received honoraria from Astellas Pharma, Inc. TP received honoraria from Astellas Pharma, Inc./Seagen Inc. ID, NM and JB received research funding from Astellas Pharma, Inc. JL received research funding from Seagen Inc. JR, TP, MH, and DP received research funding from Astellas Pharma, Inc./Seagen Inc. CW and CM are employees of Astellas Pharma, Inc. ZH is an employee of Seagen Inc.

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