©(2021) by Dr Jonathan E. Rosenberg. Contents not to be distributed, reproduced, presented, or otherwise shared without permission. All rights reserved by copyright holder.

This includes use for the following relevant business purposes:

- Communication and storage within Astellas for business and/or scientific purposes
- Preparation and use of training materials within Astellas
- External communication to regulatory authorities
- External meetings, such as advisory board, steering committee, or investigator meetings (provided that a confidential disclosure agreement is in place with attendees prior to use)
- Responses by Medical Science Liaison and/or Medical Information Department to unsolicited requests by health care providers (as allowed by local regulations)

Contains prepublication or embargoed material

Poster Number: 4516
ASCO 2022
June 3–7, 2022
Chicago, IL, and virtual

Long-Term Outcomes in EV-301: 24-Month Findings From the Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy in Patients With Previously Treated Advanced Urothelial Carcinoma

Jonathan E. Rosenberg, MD[1]; Thomas Powles, MD[2]; Guru P. Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Duran, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Daniel Castellano, MD[9]; Ronac Mamtani, MD[10]; Chunzhang Wu, PhD[11]; Maria Matsangou, MD[11]; Mary Campbell, MD[12]; Daniel P. Petrylak, MD[13]

[1]Department of Medicine, Division of Solid Tumor Oncology, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Barts Cancer Institute, CRUK Experimental Cancer Medicine Centre, London, UK; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [4]Gustave Roussy, Université Paris-Saclay, Villejuif, France; [5]Hospital Universitario Marques de Valdecilla, IDIVAL, Cantabria, Spain; [6]Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Center for Oncological Research (CORE), University of Antwerp, Integrated Cancer Center Ghent, Ghent, Belgium; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [11]Astellas Pharma, Inc., Northbrook, IL; [12]Seagen Inc., Bothell, WA; [13]Yale Cancer Center, New Haven, CT

Background

- Long-term outcomes are poor for metastatic bladder cancer, with a 5-year relative survival rate of ≈8% in US patients[1]
- Enfortumab vedotin (EV), an antibody–drug conjugate directed against Nectin-4, demonstrated overall survival (OS) and progression-free survival (PFS) benefit in patients with locally advanced or metastatic (la/m) urothelial carcinoma (UC) in the open-label, confirmatory phase 3 EV-301 trial at the prespecified interim analysis[2]
  - Interim analysis (data cutoff date of July 15, 2020) was planned when 285 (65% of total planned) events had occurred; 301 deaths had actually occurred at this time
  - Median OS rates were 12.88 months for EV and 8.97 months for chemotherapy (hazard ratio [HR] 0.70 [95% CI, 0.56–0.89]; *P*=0.001)
  - Median PFS rates were 5.55 months for EV and 3.71 months for chemotherapy (HR 0.62 [95% CI, 0.51–0.75]; *P*<0.001)
- We present efficacy and safety data for EV compared with chemotherapy over a median follow-up period of ≈2 years

Aim/Objective

- To demonstrate long-term sustained and consistent efficacy and safety for EV vs chemotherapy

Methods

- In EV-301 (NCT03474107), patients with la/mUC who previously received platinum-containing chemotherapy and had disease progression during or after programmed cell death protein-1 programmed death-ligand 1 inhibitor treatment were randomized to EV or investigator-chosen standard chemotherapy (**Figure 1**)

Figure 1. Study design

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumours; UC, urothelial carcinoma.
[a]If used in the adjuvant/neoadjuvant setting, progression must be ≤12 mo of completion. [b]Stratification variables were ECOG PS, regions of the world, and liver metastasis. [c]Investigator selected prior to randomization. [d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.

- Statistical analyses
  - Prespecified final OS analysis (1-sided 0.02332 significance level) was planned when the total planned events of 439 deaths had occurred
  - OS crossed the efficacy boundary (1-sided value of 0.00679) at the interim analysis (1-sided *P*=0.00142); thus, the interim analysis served as the final analysis for EV-301
- Here, we report efficacy and safety findings with a cutoff date of July 30, 2021, ≈1 year after interim and final analysis (July 15, 2020)[1] and when the number of deaths prespecified in the protocol had occurred

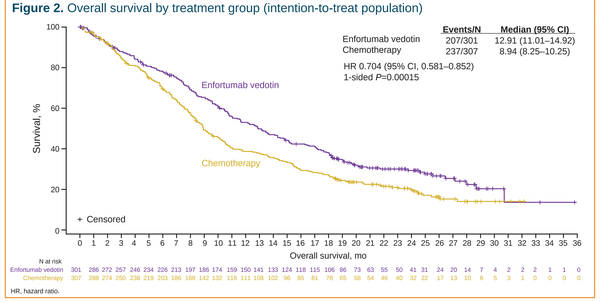
Results

- Overall, 608 patients with la/mUC were randomized to EV (n=301) or chemotherapy (n=307)
- As of July 30, 2021, a total of 444 deaths had occurred (EV, n=207; chemotherapy, n=237)

Overall Survival

- With a median follow-up period of 23.75 months, median OS was prolonged by 3.97 months with EV compared with chemotherapy (HR 0.704 [95% CI, 0.581–0.852]; 1-sided *P*=0.00015; **Figure 2**)

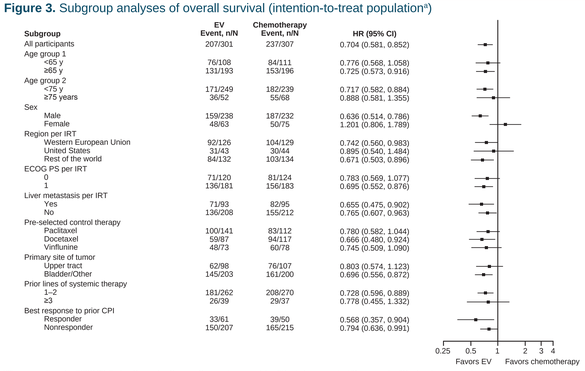
Figure 2. Overall survival by treatment group (intention-to-treat population)



HR, hazard ratio.

- Consistent with the interim analysis,[1] OS benefit of EV was observed in the majority of prespecified subgroups (**Figure 3**)

Figure 3. Subgroup analyses of overall survival (intention-to-treat population[a])

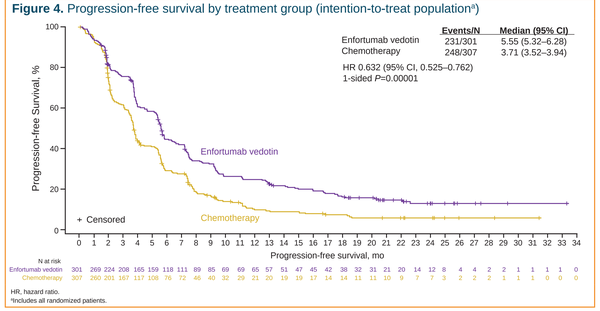


CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; HR, hazard ratio; IRT, interactive response technology.
[a]Includes all randomized patients.

Progression-Free Survival

- PFS was improved with EV vs chemotherapy, consistent with the interim analysis (HR 0.632 [95% CI, 0.525–0.762]; 1-sided *P*<0.00001; **Figure 4**)

Figure 4. Progression-free survival by treatment group (intention-to-treat population[a])

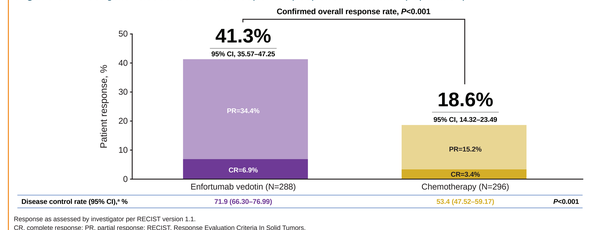


HR, hazard ratio.
[a]Includes all randomized patients.

Clinical Response

- Confirmed overall response rate (ORR) was higher in the EV group than the chemotherapy group (**Figure 5**)

Figure 5. Investigator-assessed clinical response (response evaluable population)



Response as assessed by investigator per RECIST version 1.1.
CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Proportion of patients with best overall response of confirmed CR, PR, or SD (≥7 wk); enfortumab vedotin vs chemotherapy.

Safety Profile/Tolerability

- In the safety population, median durations of treatment were 4.99 months (range, 0.5–29.9) in the EV group and 3.45 months (range, 0.2–26.4) in the chemotherapy group
- Rates of treatment-related adverse events (TRAEs) were unchanged from the interim analysis
  - As previously reported in the interim analysis, rates of TRAEs were comparable between treatment groups (**Table 1**)
  - Rates of grade ≥3 TRAEs were ≈50% in both groups

Table 1. Summary of Treatment-Related Adverse Events (Safety Population[a])

Adverse event, n (%)	Enfortumab vedotin (N=296)	Chemotherapy (N=291)
Any	278 (93.9)	267 (91.8)
Serious	67 (22.6)	68 (23.4)
Grade ≥3	155 (52.4)	147 (50.5)
Leading to withdrawal of treatment	45 (15.2)	36 (12.4)
Leading to death	7 (2.4)	3 (1.0)
Leading to death, excluding PD	7 (2.4)	3 (1.0)

PD, progressive disease.
[a]Included all patients receiving any study treatment.

- Grade ≥3 TRAEs of decreased neutrophil count, decreased white blood cell count, and anemia were more common in the chemotherapy vs EV group, and maculopapular rash, fatigue, and peripheral sensory neuropathy were more common in the EV group (**Table 2**)

Table 2. Treatment-Related Adverse Events[a] (Safety Population[b])

Adverse event, n (%)	Enfortumab vedotin (N=296) Any grade	Enfortumab vedotin (N=296) Grade ≥3	Chemotherapy (N=291) Any grade	Chemotherapy (N=291) Grade ≥3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	NR
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white blood cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

NR, not reported.
[a]Occurring in ≥20% of patients in either treatment group or grade ≥3 treatment-related adverse events occurring in ≥5% of patients in either treatment group. [b]Included all patients receiving any study treatment.

- Compared with the interim analysis, no additional TRAEs leading to death were observed in either treatment group
- Since the interim analysis, 3 additional patients reported treatment-related rash in the EV group (two grade 2, one grade 3); no additional severe cutaneous adverse reactions were reported in either group (**Table 3**)
  - Proportions of patients with other TRAEs of special interest were consistent with the primary analysis

Table 3. Treatment-Related Adverse Events of Special Interest[a] (Safety Population[b])

Adverse event, n (%)	Enfortumab vedotin (N=296) Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Chemotherapy (N=291) Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	133 (44.9)	41 (13.9)	48 (16.2)	43 (14.5)	1 (0.3)	NR	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	NR
Severe cutaneous adverse reaction	60 (20.3)	20 (6.8)	25 (8.4)	14 (4.7)	1 (0.3)	NR	22 (7.6)	12 (4.1)	8 (2.7)	2 (0.7)	0	NR
Peripheral neuropathy	142 (48.0)	36 (12.2)	84 (28.4)	22 (7.4)	NR	NR	92 (31.6)	43 (14.8)	41 (14.1)	8 (2.7)	NR	NR
Peripheral neuropathy sensory events	135 (45.6)	35 (11.8)	82 (27.7)	18 (6.1)	NR	NR	89 (30.6)	42 (14.4)	39 (13.4)	8 (2.7)	NR	NR
Peripheral neuropathy motor events	23 (7.8)	6 (2.0)	11 (3.7)	6 (2.0)	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Dry eye	48 (16.2)	34 (11.5)	12 (4.1)	2 (0.7)	NR	NR	9 (3.1)	6 (2.1)	2 (0.7)	1 (0.3)	NR	NR
Blurred vision	13 (4.4)	11 (3.7)	2 (0.7)	0	NR	NR	6 (2.1)	5 (1.7)	0	1 (0.3)	NR	NR
Corneal disorders	2 (0.7)	2 (0.7)	NR	NR	NR	NR	0	0	NR	NR	NR	NR
Infusion-related reaction	27 (9.1)	12 (4.1)	11 (3.7)	4 (1.4)	NR	NR	14 (4.8)	7 (2.4)	7 (2.4)	0	NR	NR
Systemic infusion-related reaction event	24 (8.1)	11 (3.7)	9 (3.0)	4 (1.4)	NR	NR	9 (3.1)	4 (1.4)	5 (1.7)	0	NR	NR
Local infusion-related reaction event	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Infusion site reaction	2 (0.7)	0	2 (0.7)	0	NR	NR	5 (1.7)	4 (1.4)	1 (0.3)	0	NR	NR
Extravasation site reaction	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR
Hyperglycemia	20 (6.8)	3 (1.0)	4 (1.4)	12 (4.1)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.
[a]Adverse events of special interest to enfortumab vedotin. Events represent listings by preferred term and are sponsor-specific query/customized medical queries or standard MedDRA queries. Order of adverse events is as it appears in the Supplementary Appendix to the EV-301 primary publication (Powles, et al. *N Engl J Med*. 2021;384:1125-1135). [b]Patients receiving any study treatment.

Conclusions

- **After a median follow-up period of ≈2 years, EV maintained a clinically meaningful and significant OS benefit versus chemotherapy consistent with findings from the primary efficacy results (which had occurred at the interim analysis)**
  - **PFS and ORR results were consistent with what was observed in the interim and final analysis**
- **Safety and tolerability of EV and chemotherapy were consistent with findings from the interim analysis**
  - **EV adverse events continued to be manageable and no new safety signals were observed**
- **These data showed continued survival benefit of EV vs chemotherapy, including a sustained magnitude of benefit, in patients with previously treated la/mUC**

References

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed April 25, 2022.
2. Powles T, et al. *N Engl J Med*. 2021;384:1125-1135.

Funding

This study was funded by Astellas Pharma, Inc. and Seagen Inc.

Acknowledgments

Medical writing/editorial support was provided by Stephanie Phan, PharmD, and Sherri Damlo, ELS, from Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by the study sponsor.