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: 698P

European Society for Medical Oncology
16–21 September 2021
Virtual Congress

Analysis of Hard-to-Treat Subgroups From EV-301, a Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy for Previously Treated Advanced Urothelial Carcinoma

Jonathan E Rosenberg[1], Thomas Powles[2], Guru P Sonpavde[3], Yohann Loriot[4], Ignacio Duran[5], Jae Lyun Lee[6], Nobuaki Matsubara[7], Christof Vulsteke[8], Daniel Castellano[9], Ronac Mamtani[10], Srikala S Sridhar[11], Helle Pappot[12], Howard Gurney[13], Jens Bedke[14], Michiel van der Heijden[15], Mary Campbell[16], Chunzhang Wu[17], Maria Matsangou[17], Daniel P Petrylak[18]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [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]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [11]Princess Margaret Cancer Center, Toronto, Ontario, Canada; [12]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [13]Macquarie University, Sydney, Australia; [14]University Hospital Tübingen, Tübingen, Germany; [15]Netherlands Cancer Institute, Amsterdam, The Netherlands; [16]Seagen Inc., Bothell, WA, USA; [17]Astellas Pharma, Inc., Northbrook, IL, USA; [18]Smilow Cancer Center, Yale School of Medicine, New Haven, CT, USA

Background

- Effective therapies are critically needed for previously treated patients with locally advanced or metastatic urothelial carcinoma (la/mUC), particularly those considered hard-to-treat with poor prognostic factors, including the presence of liver metastasis, advanced age, upper tract disease, and nonresponse to prior programmed cell death protein-1 or programmed death-ligand 1 (PD-1/L1) inhibitor[1-5]
- Enfortumab vedotin (EV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody directed against Nectin-4, and monomethyl auristatin E (MMAE), a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker[6]
- In the confirmatory, randomized, phase 3 EV-301 trial (NCT03474107), EV showed superior overall survival (OS) compared with standard chemotherapy (SC) in patients with previously treated la/mUC[7]
- Subsequently, in July 2021, EV received regular approval from the United States Food and Drug Administration for the treatment of adults with la/mUC who have previously received a PD-1/L1 inhibitor and platinum-containing chemotherapy and is under accelerated assessment by the European Medicines Agency based upon the global EV-301 trial[6,8,9]

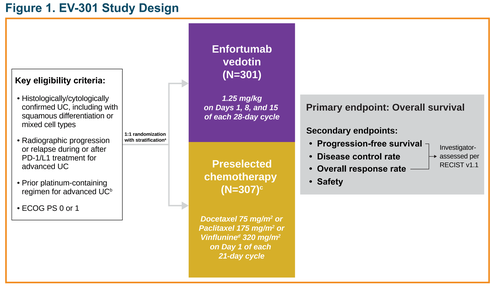
Aim/Objective

- To evaluate the efficacy and safety of EV compared with SC for patients from the EV-301 study with advanced la/mUC who are considered "hard-to-treat"

Methods

- In this open-label, phase 3 trial, la/mUC patients previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor were randomized to EV or investigator's choice of SC (Figure 1)
  - The study design has been described in a previously published article[7]

Figure 1. EV-301 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]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion. [c]Investigator selected prior to randomization. [d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

- Subgroup analyses were prespecified for the primary endpoint of OS and secondary endpoints of investigator-assessed progression-free survival (PFS) and overall response rate (ORR) per RECIST v1.1
- The following subgroups were characterized as the "hard-to-treat" subgroups, including those with poor prognostic factors:
  - Age ≥65 years
  - Presence of liver metastasis
  - Primary upper tract disease
  - Nonresponse to prior PD-1/L1 inhibitor
- Statistical analyses included the following:
  - Kaplan-Meier analyses and log-rank test to compare OS and PFS
  - Cox proportional hazards model to estimate hazard ratios
  - Cochran-Mantel-Haenszel test to compare response and disease control rates between groups

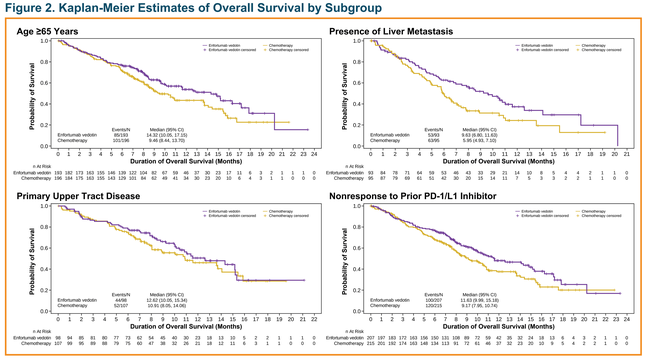
Results

Efficacy

- A total of 301 patients were randomized to EV and 307 patients to SC in EV-301; median follow-up was 11.1 months
- OS benefit for EV was retained across the majority of subgroups; for primary upper tract disease, the median OS was longer for EV versus SC and consistent with the median OS for the overall population (Table 1, Figure 2)

Table 1. Subgroup Analysis of Overall Survival

	Enfortumab Vedotin N=301			Chemotherapy N=307			
	Events		Median	Events		Median	
Subgroup	n/N	%	(months)	n/N	%	(months)	HR (95% CI)
All	134/301	44.5	12.88	167/307	54.4	8.97	0.702 (0.556, 0.886)
Age ≥65 years	85/193	44.0	14.32	101/196	51.5	9.46	0.745 (0.558, 0.995)
Presence of liver metastasis	53/93	57.0	9.63	63/95	66.3	5.95	0.660 (0.456, 0.957)
Primary upper tract disease	44/98	44.9	12.62	52/107	48.6	10.91	0.848 (0.567, 1.269)
Nonresponse to prior PD-1/L1 inhibitor	100/207	48.3	11.63	120/215	55.8	9.17	0.757 (0.580, 0.988)



Data analyzed in all randomized patients.
Abbreviations: CI, confidence interval; HR, hazard ratio; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1.

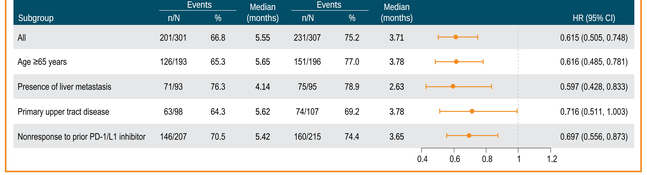
Figure 2. Kaplan-Meier Estimates of Overall Survival by Subgroup

Abbreviations: CI, confidence interval; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1.

- PFS benefit for EV was retained across the majority of subgroups; for primary upper tract disease, the median PFS was longer for EV versus SC and consistent with the median PFS for the overall population (Table 2, Figure 3)

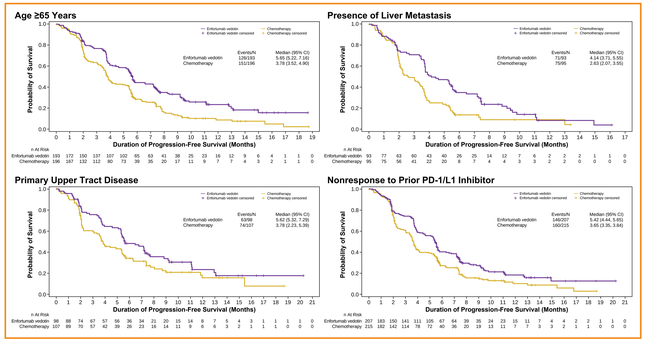
Table 2. Subgroup Analysis of Progression-Free Survival

	Enfortumab Vedotin N=301			Chemotherapy N=307			
	Events		Median	Events		Median	
Subgroup	n/N	%	(months)	n/N	%	(months)	HR (95% CI)
All	201/301	66.8	5.55	231/307	75.2	3.71	0.615 (0.505, 0.748)
Age ≥65 years	126/193	65.3	5.65	151/196	77.0	3.78	0.616 (0.485, 0.781)
Presence of liver metastasis	71/93	76.3	4.14	75/95	78.9	2.63	0.597 (0.428, 0.833)
Primary upper tract disease	63/98	64.3	5.62	74/107	69.2	3.78	0.716 (0.511, 1.003)
Nonresponse to prior PD-1/L1 inhibitor	146/207	70.5	5.42	160/215	74.4	3.65	0.697 (0.556, 0.873)



Data analyzed in all randomized patients.
Abbreviations: CI, confidence interval; HR, hazard ratio; PD-1/L1, programmed cell death protein 1 or programmed death-ligand 1.

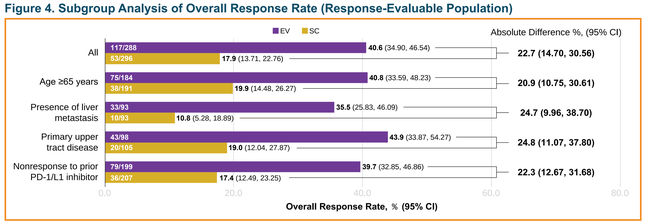
Figure 3. Kaplan-Meier Estimates of Progression-Free Survival by Subgroup



Abbreviations: CI, confidence interval; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1.

- The overall response rate was consistently higher for EV relative to SC across all subgroups (Figure 4)

Figure 4. Subgroup Analysis of Overall Response Rate (Response-Evaluable Population)

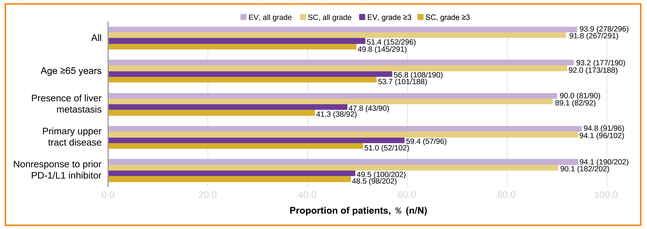


Data analyzed in all randomized patients with measurable disease at baseline. Numbers in white indicate patients with complete or partial response (numerator) of all randomized patients with measurable disease at baseline (denominator). Absolute differences favor EV.
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1; SC, standard chemotherapy.

Safety/Tolerability

- Overall rates of adverse events (AEs) were similar between EV vs SC among subgroups
  - Age ≥65 years: 97.4% vs 98.9%
  - Presence of liver metastasis: 97.8% vs 96.7%
  - Primary upper tract disease: 99.0% vs 99.0%
  - Nonresponse to prior PD-1/L1 inhibitor: 97.5% vs 99.5%
- Treatment-related AEs were comparable between treatments across subgroups (Figure 5)

Figure 5. Treatment-Related Adverse Events (Safety Population)



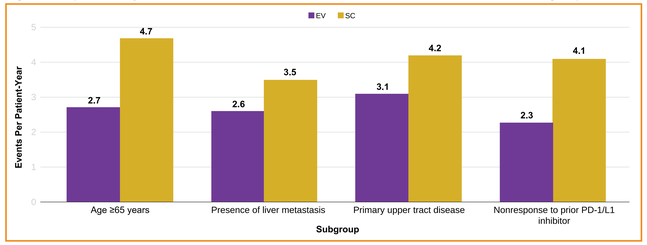
Evaluated in all patients who received any amount of trial drug.
Abbreviations: EV, enfortumab vedotin; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1; SC, standard chemotherapy.

Conclusions

- **Similar to the results from the overall EV-301 population,[7] patients with la/mUC who are considered hard-to-treat had consistently longer OS and PFS and higher ORR with EV than with SC**
- **Safety profiles for study treatments were consistent with those of prior studies and with the overall EV-301 study population; no new safety signals were observed**
- **These data support the consistency of EV effects and use in previously treated patients with la/mUC, including those with poor prognostic factors**

- When adjusted for treatment exposure, grade ≥3 treatment-related AEs occurred less frequently in the EV versus SC group across all subgroups (Figure 6)

Figure 6. Exposure-Adjusted Grade ≥3 Treatment-Related Adverse Events in Hard-To-Treat Subgroups



Abbreviations: EV, enfortumab vedotin; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1; SC, standard chemotherapy.

- The incidence of grade ≥3 treatment-related AEs that were reported at a rate of >5% in either treatment arm in each subgroup was similar to that of the overall EV-301 safety population (Table 3)

Table 3. Incidence of Grade ≥3 Treatment-Related Adverse Events[a] (Safety Population)

	All		Age ≥65 Years		Presence of Liver Metastasis		Primary Upper Tract Disease		Nonresponse to Prior PD-1/L1 Inhibitor	
Adverse Event	EV N=296	SC N=291	EV N=190	SC N=188	EV N=90	SC N=92	EV N=96	SC N=102	EV N=202	SC N=202
Maculopapular rash	22 (7.4)	0	14 (7.4)	0	8 (8.9)	0	10 (10.4)	0	19 (9.4)	0
Fatigue	19 (6.4)	13 (4.5)	15 (7.9)	12 (6.4)	5 (5.6)	5 (5.4)	9 (9.4)	5 (4.9)	10 (5.0)	5 (2.5)
Decreased neutrophil count	18 (6.1)	39 (13.4)	14 (7.4)	26 (13.8)	5 (5.6)	7 (7.6)	9 (9.4)	18 (17.6)	10 (5.0)	27 (13.4)
Neutropenia	14 (4.7)	18 (6.2)	7 (3.7)	15 (8.0)	5 (5.6)	4 (4.3)	6 (6.3)	7 (6.9)	9 (4.5)	10 (5.0)
Anemia	8 (2.7)	22 (7.6)	5 (2.6)	15 (8.0)	3 (3.3)	3 (3.3)	6 (6.3)	5 (4.9)	6 (3.0)	12 (5.9)
Decreased white blood cell count	4 (1.4)	20 (6.9)	4 (2.1)	14 (7.4)	0	3 (3.3)	1 (1.0)	9 (8.8)	2 (1.0)	15 (7.4)
Febrile neutropenia	2 (0.7)	16 (5.5)	2 (1.1)	11 (5.9)	2 (2.2)	6 (6.5)	2 (2.1)	7 (6.9)	2 (1.0)	10 (5.0)

[a]Events occurring in at least 5% of patients in either treatment group from the total EV-301 safety population.
Abbreviations: EV, enfortumab vedotin; PD-1/L1, programmed cell death protein-1 or programmed death-ligand 1; SC, standard chemotherapy.

References

1. Ruiz-Banobre J, et al. *ESMO Open*. 2021;6(2):100090. **2.** Gomez de Liano Lista A, et al. *Eur Urol*. 2020;77(2):269-276. **3.** Roupret M, et al. *Eur Urol*. 2018;73(1):111-122. **4.** National Cancer Institute Surveillance, Epidemiology, and End Results Program, Cancer stat facts: bladder cancer Web site. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed July 22, 2021. **5.** Bellmunt J, et al. *J Clin Oncol*. 2010;28(11):1850-1855. **6.** PADCEV® (enfortumab vedotin-ejfv) for injection prescribing information https://astellas.us/docs/PADCEV_label.pdf. Updated July 2021. Accessed July 20, 2021. **7.** Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135. **8.** FDA grants regular approval to enfortumab vedotin-ejfv for locally advanced or metastatic urothelial cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-enfortumab-vedotin-ejfv-locally-advanced-or-metastatic-urothelial-cancer. Updated July 9, 2021. Accessed July 20, 2021. **9.** European Medicines Agency accepts marketing authorization application for enfortumab vedotin. https://www.astellas.com/system/files/news/2021-03/20210326_en_5.pdf. Updated March 26, 2021. Accessed August 6, 2021.

Acknowledgments

This study is sponsored by Astellas Pharma, Inc. and Seagen Inc. Writing and editorial assistance was provided by Stephanie Phan, PharmD, Cheryl Casterline, MA, and Elizabeth Hermans, PhD, from Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by the study sponsors.

Disclosure

Jonathan E Rosenberg reports personal fees from Adicet Bio, Astellas Pharma, Inc., AstraZeneca, BioClin, Bristol-Myers-Squibb (BMS), Boehringer Ingelheim, Chugai Pharma, Eli Lilly, EMD Serono/Pfizer, Fortress Biotech, GSK, Gilead, Janssen Oncology, Merck, Mirati, QED Therapeutics, Roche/Genentech, Seagen, and Western Oncolytics; non-financial support from Astellas Pharma, Inc. and Seagen; and other from Astellas Pharma, Inc., AstraZeneca, Bayer, Novartis, Roche/Genentech, and Seagen.