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PRIMARY RESULTS OF EV-301: A PHASE 3 TRIAL OF ENFORTUMAB VEDOTIN VS CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

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Current Treatment Landscape for Advanced Urothelial Carcinoma

Platinum-based chemotherapy, sequenced with programmed cell death protein-1/ programmed death-ligand 1 (PD-1/L1) inhibitors, is the standard of care for patients with advanced urothelial carcinoma (UC)[1-4]

Platinum-Based Chemotherapy	• Use in first line is associated with response rates of 36-64%[5-8] • Intrinsic and acquired resistance occurs[9,10]
PD-1/L1 Inhibitors	• Used in first line, first-line maintenance, and platinum-refractory disease[1,2,4] • Durable responses occur, but only in a minority of patients[11,12]

[1]Kamat AM, et al. *J Immunother Cancer.* 2017;5:68. [2]Warren M, et al. *Can Urol Assoc.* 2019;318-327. [3]Bellmunt J, et al. *Ann Oncol.* 2014;25(suppl 3):iii40-iii48. [4]Bladder Cancer (Version 6.2020), National Comprehensive Cancer Network. [5]Von der Maase H, et al. *J Clin Oncol.* 2000;18(17):3068-3077. [6]Sternberg CN, et al. *J Clin Oncol.* 2001;19(10):2638-2646. [7]Sternberg CN, et al. *Eur J Cancer.* 2006;42(1):50-54. [8]Linardou H, et al. *Urology.* 2004;64(3):479-484. [9]Höhn A, et al. *Oncotarget.* 2016;7(27):41320-41335. [10]Kersten K, et al. *Front Immunol.* 2015;6:516. [11]Bellmunt J, et al. *N Engl J Med.* 2017;376:1015-1026. [12]Powles T, et al. *Lancet.* 2018;391:748-757.

Treatment After Platinum-Based Chemotherapy and PD-1/L1 Inhibitors

Overall survival is limited and disease progression occurs in most patients1-3

Therapeutic options are limited for patients whose cancer has progressed after platinum-based chemotherapy and PD-1/L1 inhibitors

- Chemotherapy, such as taxanes, have generally been recommended globally in this population4-6
- Randomized trials supporting these treatment choices are lacking

In this setting, new therapeutic agents supported by randomized data are needed

[1]Black PC, et al. *Can Urol Assoc J.* 2020;14:E373-E382. [2]Nadal R, et al. *Cancer Treat Rev.* 2019;76:10-21. [3]Narayan V, et al. *Cochrane Database Syst Rev*. 2018;7(7):CD012838. [4]Kamat AM, et al. *J Immunother Cancer.* 2017;5:68. [5]Warren M, et al. *Can Urol Assoc.* 2019;318-327. [6]Bladder Cancer (Version 6.2020), National Comprehensive Cancer Network.

Enfortumab Vedotin

Enfortumab vedotin is an antibody-drug conjugate[1]

- Nectin-4 directed therapy
- It is comprised of a fully human monoclonal antibody and the microtubule-disrupting agent, monomethyl auristatin E (MMAE)

Nectin-4 is highly expressed in UC[1,2]

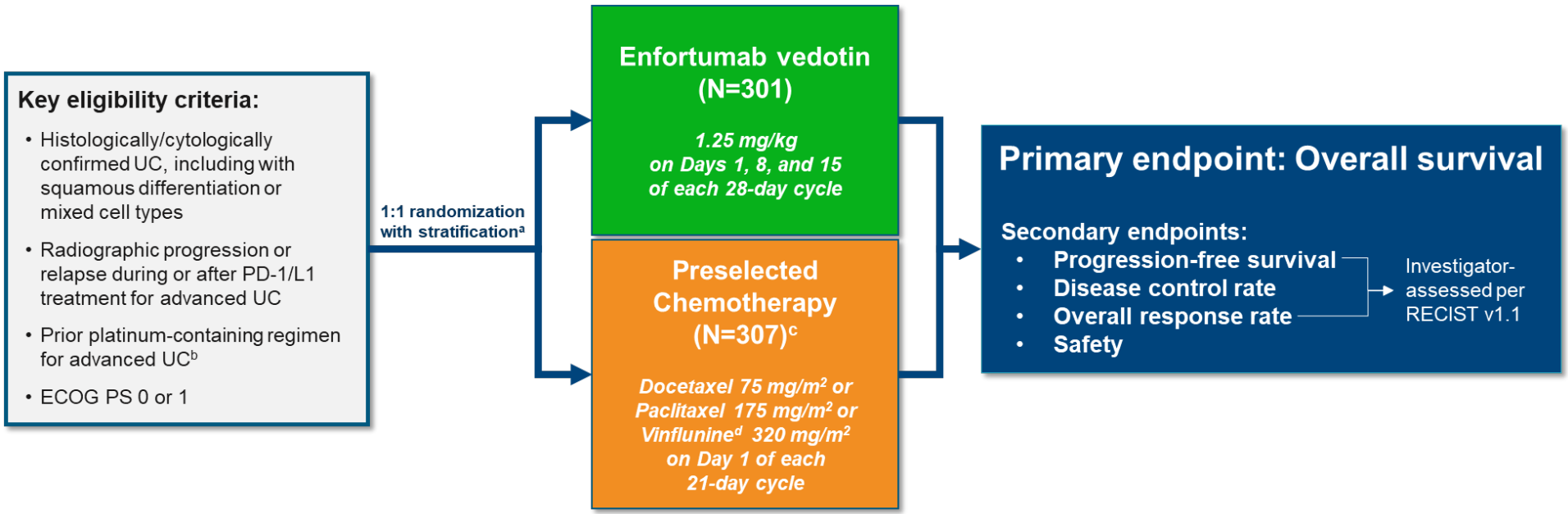
Phase 1 and 2 clinical trials demonstrated consistent clinical benefits[1,3]

- Durable clinical responses were achieved; objective response rates were >40%
- Received accelerated approval from the United States Food and Drug Administration in 2019[4]

The EV-301 trial (NCT03474107) was designed to confirm the benefit of enfortumab vedotin over chemotherapy after prior platinum-based chemotherapy and PD-1/L1 inhibitor in advanced urothelial carcinoma.

[1]Black PC, et al. *Can Urol Assoc J*. 2020;14:E373-E382. [2]Nadal R, et al. *Cancer Treat Rev*. 2019;76:10-21. [3]Narayan V, et al. *Cochrane Database Syst Rev*. 2018;7(7):CD012838. [4]Kamat AM, et al. *J Immunother Cancer*. 2017;5:68. [5]Warren M, et al. *Can Urol Assoc*. 2019;318-327. [6]Bladder Cancer (Version 6.2020), National Comprehensive Cancer Network.

EV-301 Open-Label Phase 3 Trial 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, advanced urothelial carcinoma.

Methods – Statistical Analyses

- Enrollment of ~600 patients provided 85% power to detect statistically significant difference at an overall 1-sided 0.025 type I error rate
  - Hazard ratio of 0.75
  - Median overall survival of 8 months for chemotherapy
  - Dropout rate of 10%

EV-301 was a group-sequential design

- Two analyses were planned
  - Final analysis at 439 deaths
  - Interim analysis at 285 (65%) deaths
- **At the interim analysis:** Overall survival was tested at a 1-sided significance of 0.00679 based on total number of observed deaths[a]
  - Interim analysis results are presented herein

[a]All reported *P*-values are 1-sided.

Statistical analyses also included:

- Kaplan-Meier methodology to estimate survival
- Stratified Cox proportional hazard model to estimate hazard ratios
- Stratified log-rank test to compare survival between groups
- Stratified Cochran-Mantel-Haenszel test to compare response and disease control rates between groups

Results – Demographics and Disease Characteristics

Parameter		Enfortumab Vedotin N=301	Chemotherapy N=307
Age, median		68 years	68 years
Male sex		79%	76%
Geographic region	Western Europe	42%	42%
	United States	14%	14%
	Rest of the world	44%	44%
ECOG performance status[b]	0	40%	40%
	1	60%	60%
Bellmunt risk score	0-1	67%	68%
	≥2	30%	31%
Liver metastasis[a]		31%	31%
Prior lines of systemic therapy	1-2	87%	88%
	≥3	13%	12%
Response to prior CPI		20%	16%

[a]Indicates stratification variables: ECOG performance status (0 or 1), regions of the world (US, western Europe, or rest of world), liver metastasis (yes or no).
Abbreviations: CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group.

Data cut-off: July 15, 2020

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Results – Patient Disposition

Parameter	Enfortumab Vedotin N=301	Chemotherapy N=307
Deaths at the data cut-off date[a]	n=134	n=167
Received study treatment	98%	95%
Median treatment exposure, months (range)	5.0 (0.5, 19.4)	3.5 (0.2, 15.0)
Median follow-up, months (95% CI)	11.1 (10.4, 11.9)	11.1 (10.0, 12.1)
Treatment discontinuation[b]	81%	93%
Progressive disease	59%	59%
Adverse event[c]	14%	15%
Withdrawal by patient	5%	9%
Physician decision	2%	7%

[a]A total of 301 deaths had occurred as of data cut-off date.
[b]Displaying reasons for treatment discontinuation occurring in ≥5% in either arm. Additional reasons for treatment discontinuation in EV vs chemotherapy arms included: death 0.7% vs 0.7%, protocol deviation 0.3% vs 0.3%; loss to follow-up 0% vs 0.3%; other 0.3% vs 2%.
[c]Represents treatment-emergent adverse events leading to treatment discontinuation.
Abbreviations: CI, confidence interval.

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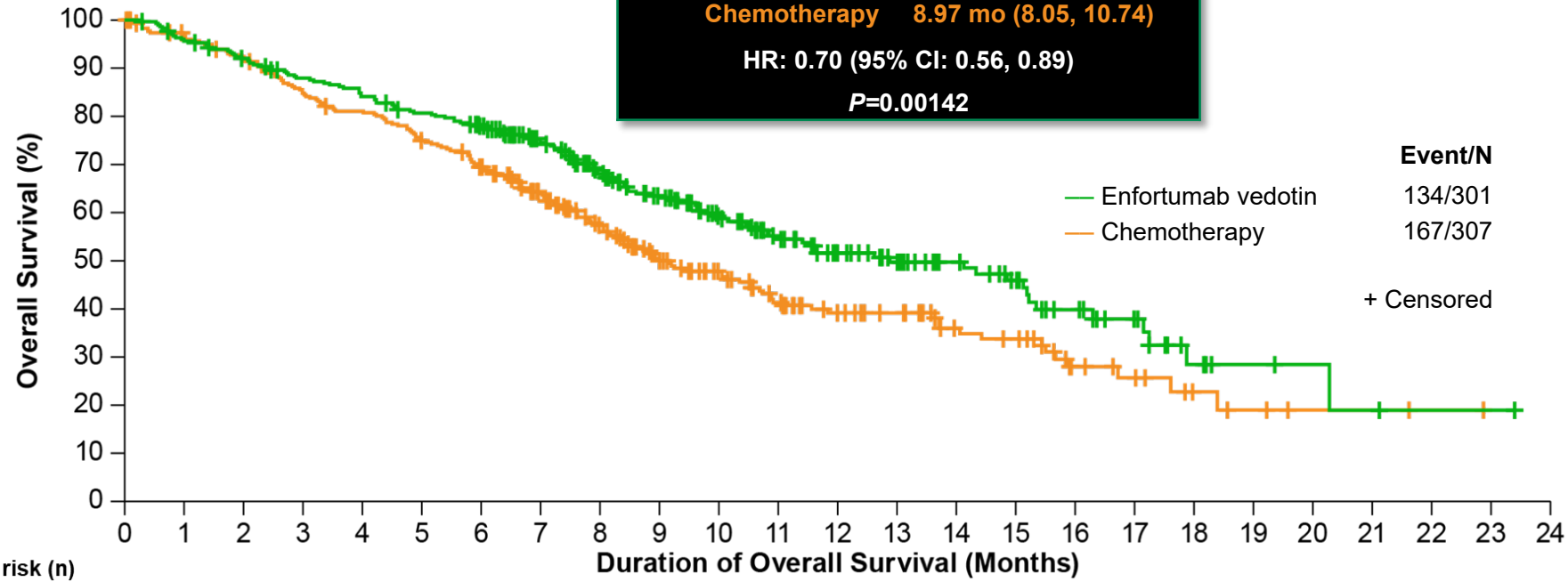
Overall Survival

Median OS

Enfortumab vedotin	12.88 mo (10.58, 15.21)
Chemotherapy	8.97 mo (8.05, 10.74)

HR: 0.70 (95% CI: 0.56, 0.89)

P=0.00142



Patients at risk (n)

Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

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Evaluated in the intent-to-treat population.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

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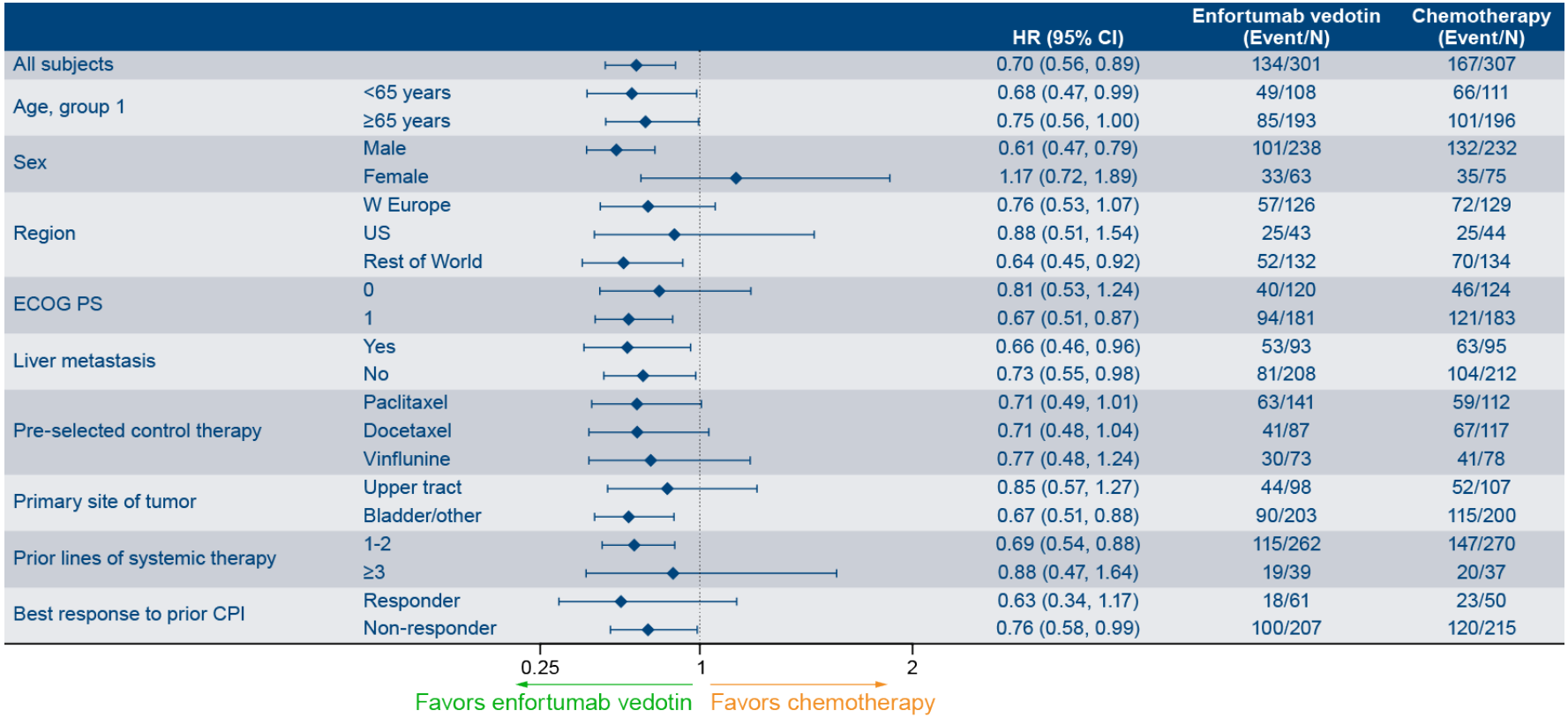
Overall Survival: Subgroup Analyses



		HR (95% CI)	Enfortumab vedotin (Event/N)	Chemotherapy (Event/N)
All subjects		0.70 (0.56, 0.89)	134/301	167/307
Age, group 1	<65 years	0.68 (0.47, 0.99)	49/108	66/111
	≥65 years	0.75 (0.56, 1.00)	85/193	101/196
Sex	Male	0.61 (0.47, 0.79)	101/238	132/232
	Female	1.17 (0.72, 1.89)	33/63	35/75
Region	W Europe	0.76 (0.53, 1.07)	57/126	72/129
	US	0.88 (0.51, 1.54)	25/43	25/44
	Rest of World	0.64 (0.45, 0.92)	52/132	70/134
ECOG PS	0	0.81 (0.53, 1.24)	40/120	46/124
	1	0.67 (0.51, 0.87)	94/181	121/183
Liver metastasis	Yes	0.66 (0.46, 0.96)	53/93	63/95
	No	0.73 (0.55, 0.98)	81/208	104/212
Pre-selected control therapy	Paclitaxel	0.71 (0.49, 1.01)	63/141	59/112
	Docetaxel	0.71 (0.48, 1.04)	41/87	67/117
	Vinflunine	0.77 (0.48, 1.24)	30/73	41/78
Primary site of tumor	Upper tract	0.85 (0.57, 1.27)	44/98	52/107
	Bladder/other	0.67 (0.51, 0.88)	90/203	115/200
Prior lines of systemic therapy	1-2	0.69 (0.54, 0.88)	115/262	147/270
	≥3	0.88 (0.47, 1.64)	19/39	20/37
Best response to prior CPI	Responder	0.63 (0.34, 1.17)	18/61	23/50
	Non-responder	0.76 (0.58, 0.99)	100/207	120/215

Abbreviations: CI, confidence interval; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; US, United States; W, western.

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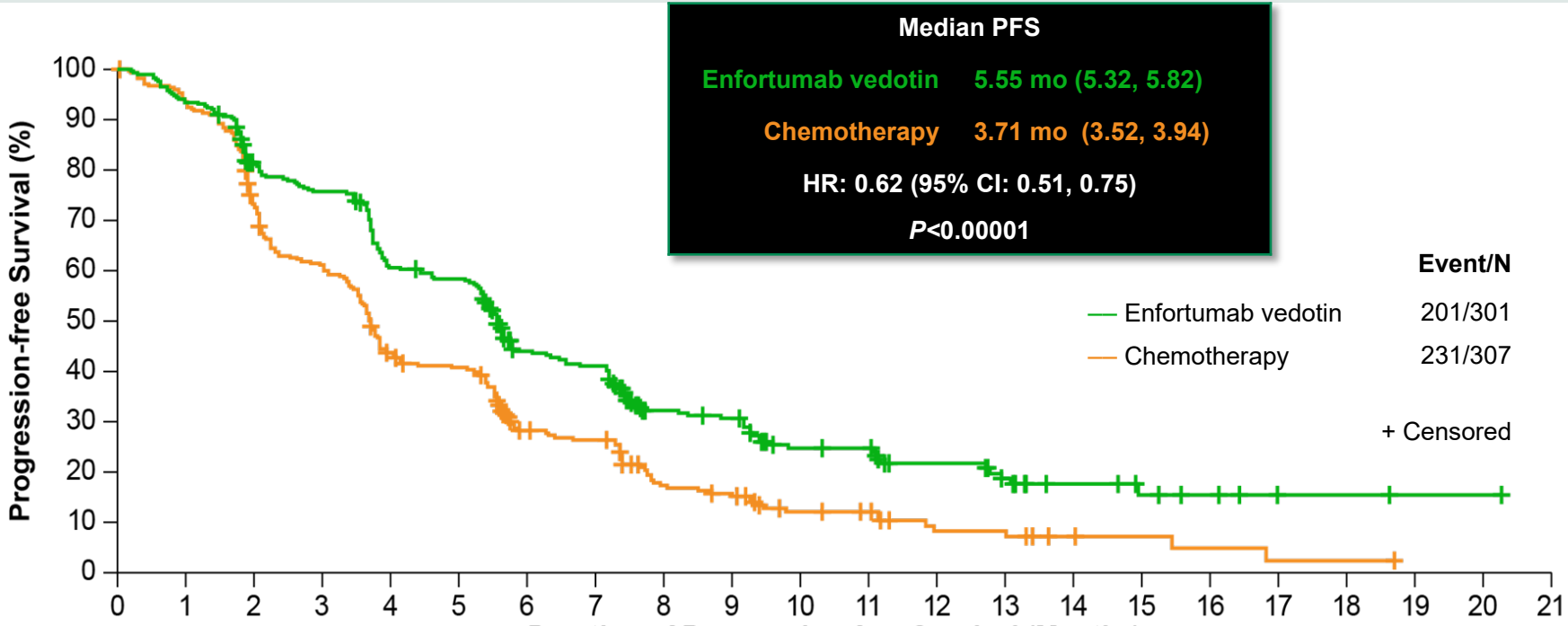
Progression-free Survival



Patients at risk (n)

Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

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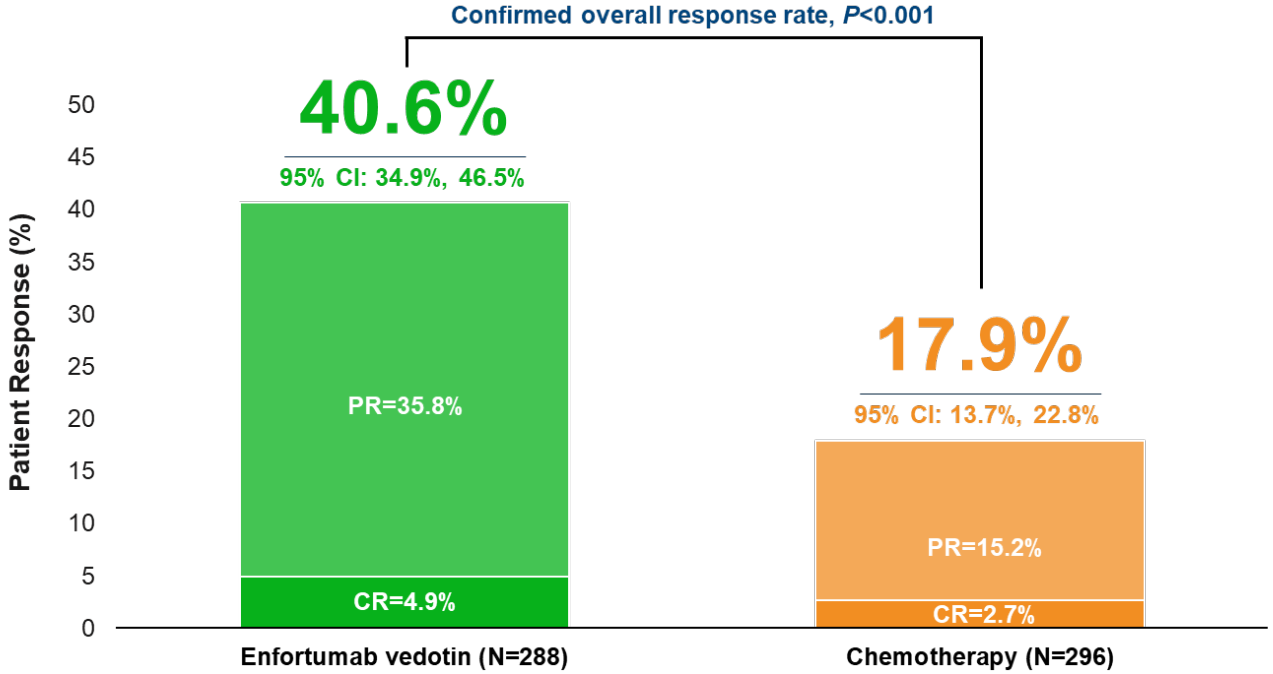
Investigator-Assessed Overall Response



Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	*P*<0.001

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Evaluated in the safety population; displaying adverse events (AEs) occurring in ≥20% or grade ≥3 AEs occurring in ≥5% of patients in either treatment group. Dashes indicate 'not applicable.'
Treatment-related AEs are events with a reasonable possibility of relationship to treatment (investigator-assessed) or missing relationship and are not time-adjusted.
[a]AEs that were deemed "serious" in the view of the investigator or sponsor and based upon predefined criteria.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; TRAEs, treatment-related adverse events.

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Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
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14

Adverse Events of Special Interest

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

Evaluated in the safety population; displaying selected TRAEs of special interest to EV. Differences between AE rates in current and prior slide may be due to preferred term groupings.
TRAE are events with a reasonable possibility of relationship to study treatment as assessed by the investigator or missing relationship.
[a]Encompasses rash and severe cutaneous adverse reactions.
[b]Severe cutaneous adverse reactions included the following (by Preferred Term): stomatitis, drug eruption, conjunctivitis, blister, dermatitis bullous, skin exfoliation, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.
[c]One patient had the TRAE that is listed.
Abbreviations: EV, enfortumab vedotin; TRAE, treatment-related adverse event.

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EV-301: Conclusions

Efficacy

Enfortumab vedotin had superior overall survival compared with chemotherapy in patients with advanced UC who had previously received platinum-based chemotherapy and a PD-1/L1 inhibitor

- Enfortumab vedotin showed superior progression-free survival and response rates compared with chemotherapy
- Subgroup analyses also broadly showed benefit in the enfortumab vedotin arm
- Results were consistent with phase 1 and 2 studies

Safety

Enfortumab vedotin demonstrated a tolerable safety profile

- No new safety signals were identified; safety profile was consistent with prior enfortumab vedotin studies
- Adverse events of special interest (eg, skin reactions, peripheral neuropathy, and hyperglycemia) were generally mild/moderate in severity and consistent with those reported in prior studies

Overall

Enfortumab vedotin is the first drug, beyond chemotherapy and immunotherapy, to show significant survival advantage in previously treated advanced UC

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