NCT04223856

EV-302: Long-term subgroup analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC)

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Objective

- To provide long-term efficacy and safety results from the EV-302/KEYNOTE-A39 (NCT04223856) study in subgroups of patients of clinical interest, including those defined by primary disease site of origin and metastatic site

Conclusions

- EV+P continues to demonstrate superior efficacy versus chemotherapy across prespecified subgroups after a median of ≈2.5 years of follow-up, with a magnitude of benefit aligned with the overall population
- AE frequencies across subgroups were generally consistent with those in the overall population
- These data reinforce EV+P as the standard of care for the 1L treatment of patients with la/mUC

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Abbreviations

1L, first line; AE, adverse event; AESI, adverse event of special interest; AEOSI, adverse event of special interest; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CPS, combined positive score; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; gem, gemcitabine; GFR, glomerular filtration rate; HR, hazard ratio; INV, investigator; IV, intravenously; ITT, intent to treat; la/mUC, locally advanced or metastatic urothelial cancer; LN, lymph node; M, metastasis; mets, metastases; N, nodes; NE, not estimable; NYHA, New York Heart Association; OS, overall survival; ORR, overall response rate; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; plat, platinum; PR, partial response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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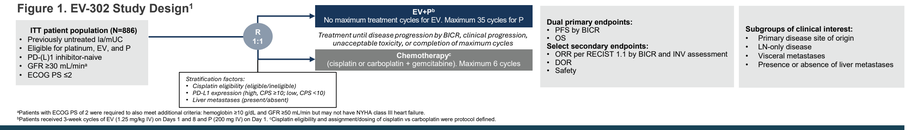
Background

- The pivotal, phase 3 EV-302 study demonstrated significant improvements in PFS, OS, and ORR for EV+P versus chemotherapy in patients with previously untreated la/mUC[1]
- Results from EV-302 led to EV+P becoming the new 1L standard of care for la/mUC[2,3]
- Updated OS results from EV-302 after a median of ≈2.5 years of follow-up showed a median OS of 33.8 months in patients treated with EV+P[4]
- In the EV-302 primary analysis, clinical benefit of EV+P was consistent between the ITT population and all prespecified subgroups[1]
- Here, we present updated longer-term efficacy and safety analyses in prespecified subgroups of clinical interest after a median of ≈2.5 years of follow-up, including those defined by primary disease site of origin and metastatic site (lymph node–only disease, visceral metastases, and liver metastases)

Methods

Figure 1. EV-302 Study Design[1]



[a]Patients with ECOG PS of 2 were required to also meet additional criteria: hemoglobin ≥10 g/dL and GFR ≥50 mL/min but may not have NYHA class III heart failure.
[b]Patients received 3-week cycles of EV (1.25 mg/kg IV) on Days 1 and 8 and P (200 mg IV) on Day 1. [c]Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol defined.

Results

Patients

- A total of 886 patients were randomized: 442 to the EV+P arm and 444 to the chemotherapy arm
- At data cutoff (August 8, 2024), median follow-up was 29.1 months (95% CI, 28.5, 29.9)
  - 54 patients (12%) remained on EV+P treatment, and no patients remained on chemotherapy
  - 218 patients (49%) in the EV+P arm and 131 patients (30%) in the chemotherapy arm remained on study

Baseline characteristics

- Baseline characteristics are shown in **Table 1**

Efficacy in prespecified subgroups

- PFS by BICR, OS, ORR, and DOR continued to demonstrate sustained benefit of EV+P versus chemotherapy across prespecified subgroups after longer-term follow-up (**Figures 1-3; Supplementary online content**)

Overall TRAEs across prespecified subgroups

- TRAE frequencies across subgroups (**Table 2**) were generally consistent with the ITT population[1] (**Supplementary online content**)
  - For EV+P, any-grade TRAEs occurred in 96.0%-98.5% and Grade ≥3 TRAEs in 53.4%-60.7% of patients across prespecified subgroups
  - For chemo, any-grade TRAEs occurred in 94.8%-96.9% and Grade ≥3 TRAEs in 66.7%-74.0% of patients across prespecified subgroups

Treatment-related AESI for EV

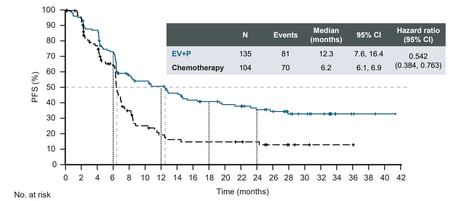
- In the EV+P arm, treatment-related AESIs for EV were primarily low grade (**Table 3**)

Treatment-emergent AEOSI for P

- In the EV+P arm, treatment-emergent AEOSIs for P were primarily low grade (**Table 4**)

Figure 2. PFS by BICR in Subgroups of Interest

(A) Primary Disease Site of Origin in the Upper Tract

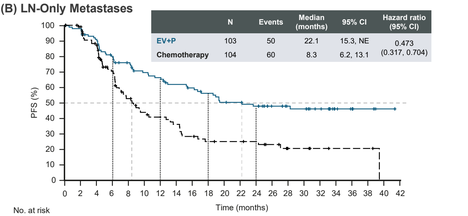


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	135	81	12.3	7.6, 16.4	0.542 (0.384, 0.763)
Chemotherapy	104	70	6.2	6.1, 6.9	

No. at risk

EV+P	135	124	112	92	69	64	59	51	46	42	39	36	32	28	21	18	15	4	3	2	1	0
Chemotherapy	104	86	65	51	26	18	13	11	10	10	10	9	8	5	3	2	1	1	0	0	0	0

(B) LN-Only Metastases

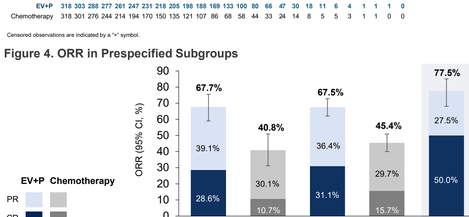


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	103	50	22.1	15.3, NE	0.473 (0.317, 0.704)
Chemotherapy	104	60	8.3	6.2, 13.1	

No. at risk

EV+P	103	101	90	78	72	64	60	55	52	48	43	42	39	31	27	26	20	11	7	5	2	0
Chemotherapy	104	95	76	52	37	29	26	23	18	15	14	14	13	10	5	5	3	2	2	2	0	0

(C) Presence of Visceral Metastases



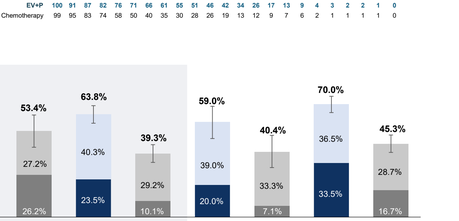
	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	318	203	10.4	8.3, 12.7	0.477 (0.393, 0.579)
Chemotherapy	318	242	6.2	6.0, 6.3	

No. at risk

EV+P	318	287	251	211	170	148	129	118	112	103	93	80	64	48	33	30	22	11	7	5	2	0
Chemotherapy	318	263	201	144	77	49	36	29	27	22	20	18	15	11	9	8	5	3	2	1	1	0

Censored observations are indicated by a "+" symbol.

(D) Presence of Liver Metastases



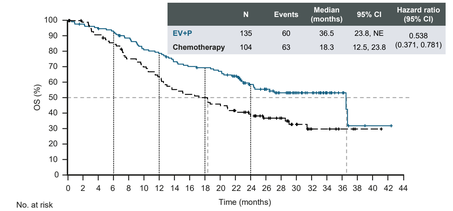
	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	100	74	8.1	6.1, 12.0	0.548 (0.392, 0.766)
Chemotherapy	99	80	6.0	4.4, 6.3	

No. at risk

EV+P	100	91	87	82	76	71	66	61	55	51	46	42	34	26	17	13	9	4	3	2	2	1
Chemotherapy	99	95	83	74	58	50	40	35	30	28	26	19	13	12	9	7	6	2	1	1	1	0

Figure 3. OS in Subgroups of Interest

(A) Primary Disease Site of Origin in the Upper Tract

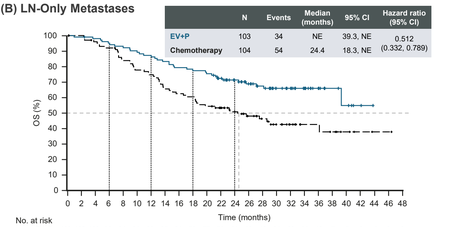


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	135	60	36.5	23.8, NE	0.538 (0.371, 0.781)
Chemotherapy	104	63	18.3	12.5, 23.8	

No. at risk

EV+P	135	131	126	123	116	106	103	95	91	89	86	77	57	50	41	32	25	13	7	2	1	1	0
Chemotherapy	104	97	89	83	72	67	61	53	50	48	44	37	32	25	21	13	7	6	3	1	1	0	0

(B) LN-Only Metastases

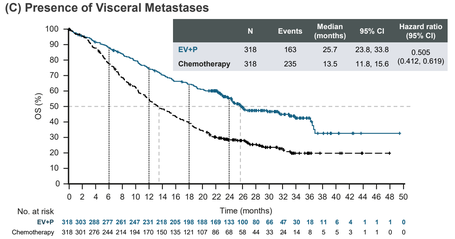


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	103	34	NE	39.3, NE	0.512 (0.332, 0.789)
Chemotherapy	104	54	24.4	18.3, NE	

No. at risk

EV+P	103	102	100	96	94	91	88	85	81	79	77	70	61	52	46	34	30	21	13	7	5	2	0	0
Chemotherapy	104	101	96	92	83	77	74	65	62	60	54	47	39	32	26	20	15	9	9	7	4	2	1	1

(C) Presence of Visceral Metastases

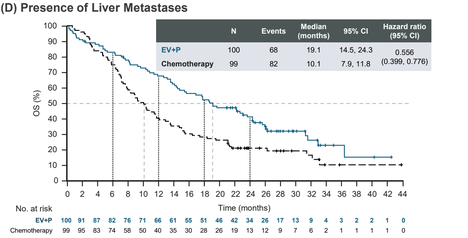


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	318	163	25.7	23.8, 33.8	0.505 (0.412, 0.619)
Chemotherapy	318	235	13.5	11.8, 15.6	

No. at risk

EV+P	318	303	288	277	261	247	231	218	205	198	188	169	133	100	80	66	47	30	18	11	6	4	1	1	1	0
Chemotherapy	318	301	276	244	214	194	170	150	135	121	107	86	68	58	44	33	24	14	8	5	5	3	1	1	0	0

(D) Presence of Liver Metastases



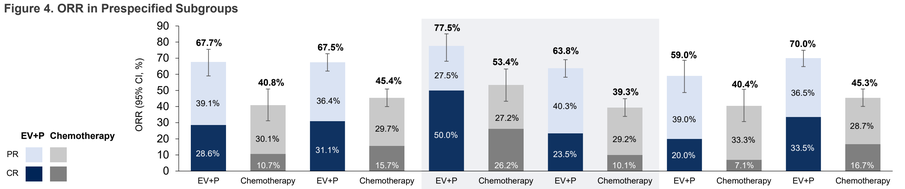
	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	100	68	19.1	14.5, 24.3	0.556 (0.399, 0.776)
Chemotherapy	99	82	10.1	7.9, 11.8	

No. at risk

EV+P	100	91	87	82	76	71	66	61	55	51	46	42	34	26	17	13	9	4	3	2	2	1	1	0
Chemotherapy	99	95	83	74	58	50	40	35	30	28	26	19	13	12	9	7	6	2	1	1	1	1	0	0

Censored observations are indicated by a "+" symbol.

Figure 4. ORR in Prespecified Subgroups



	Upper tract		Lower tract		LN-only mets		Visceral mets present		Liver mets present		Liver mets absent	
	EV+P n=133	Chemotherapy n=103	EV+P n=302	Chemotherapy n=327	EV+P n=102	Chemotherapy n=101	EV+P n=315	Chemotherapy n=318	EV+P n=99	Chemotherapy n=96	EV+P n=337	Chemotherapy n=340
ORR, n (%)	90 (67.7)	42 (40.8)	204 (67.5)	153 (45.4)	79 (77.5)	55 (53.4)	201 (63.8)	125 (39.3)	59 (59.0)	40 (40.4)	236 (70.0)	155 (45.3)
DOR, median (95% CI), months	23.3 (12.6, NE)	6.2 (4.9, 12.5)	23.9 (17.3, NE)	7.0 (6.2, 10.2)	NE (19.9, NE)	12.4 (8.6, 24.9)	20.2 (14.7, 25.6)	6.1 (5.4, 6.9)	12.9 (8.4, 20.2)	5.0 (4.3, 6.2)	34.2 (21.5, NE)	8.4 (6.6, 10.4)

Table 1. Key Baseline Demographics and Disease Characteristics

Characteristic	Upper tract		Lower tract		LN-only mets		Visceral mets present		Liver mets present		Liver mets absent	
	EV+P n=135	Chemotherapy n=104	EV+P n=305	Chemotherapy n=339	EV+P n=103	Chemotherapy n=104	EV+P n=318	Chemotherapy n=318	EV+P n=100	Chemotherapy n=99	EV+P n=342	Chemotherapy n=345
Age												
Median (range), years	68.0 (40, 84)	68.0 (45, 86)	69.0 (37, 87)	69.0 (22, 91)	68.0 (37, 87)	69.0 (35, 91)	69.0 (40, 86)	69.0 (22, 87)	69.0 (40, 86)	69.0 (22, 86)	69.0 (37, 87)	69.0 (32, 91)
Sex, n (%)												
Male	88 (65.2)	70 (67.3)	254 (83.3)	265 (78.2)	80 (77.7)	76 (73.1)	246 (77.4)	246 (77.4)	82 (82.0)	82 (82.8)	262 (76.6)	254 (73.6)
Female	47 (34.8)	34 (32.7)	51 (16.7)	74 (21.8)	23 (22.3)	28 (26.9)	72 (22.6)	72 (22.6)	18 (18.0)	17 (17.2)	80 (23.4)	91 (26.4)
ECOG PS, n (%)												
0	74 (54.8)	49 (47.1)	148 (48.5)	166 (49.0)	58 (56.3)	63 (60.6)	156 (49.1)	139 (43.7)	46 (46.0)	41 (41.4)	177 (51.8)	174 (50.4)
1	59 (43.7)	52 (50.0)	145 (47.5)	164 (48.4)	42 (40.8)	39 (37.5)	150 (47.2)	168 (52.8)	48 (48.0)	53 (53.5)	156 (45.6)	163 (47.2)
2	2 (1.5)	3 (2.9)	12 (3.9)	7 (2.1)	3 (2.9)	1 (1.0)	12 (3.8)	10 (3.1)	6 (6.0)	5 (5.1)	9 (2.6)	6 (1.7)
Primary tumor location, n (%)												
Upper tract	135 (100.0)	104 (100.0)	0	0	20 (19.4)	19 (18.3)	109 (34.3)	82 (25.8)	31 (31.0)	23 (23.2)	104 (30.4)	81 (23.5)
Lower tract	0	0	305 (100.0)	339 (100.0)	82 (79.6)	85 (81.7)	208 (65.4)	235 (73.9)	69 (69.0)	75 (75.8)	236 (69.0)	264 (76.5)
Metastatic category, n (%)												
Visceral metastases	109 (80.7)	82 (78.8)	208 (68.2)	235 (69.3)	0	0	318 (100.0)	318 (100.0)	100 (100.0)	99 (100.0)	218 (63.7)	219 (63.5)
Bone	21 (15.6)	23 (22.1)	60 (19.7)	78 (23.0)	0	0	81 (25.5)	102 (32.1)	25 (25.0)	34 (34.3)	56 (16.4)	68 (19.7)
Liver	31 (23.0)	23 (22.1)	69 (22.6)	75 (22.1)	0	0	100 (31.4)	99 (31.1)	100 (100.0)	99 (100.0)	0	0
Lung	66 (48.9)	50 (48.1)	104 (34.1)	107 (31.6)	0	0	170 (53.5)	157 (49.4)	40 (40.0)	39 (39.4)	130 (38.0)	118 (34.2)
LN-only disease*	20 (14.8)	19 (18.3)	82 (26.9)	85 (25.1)	103 (100.0)	104 (100.0)	0	0	0	0	103 (30.1)	104 (30.1)

*LN-only disease is defined as participants with metastatic disease only in the lymph nodes. Due to the limitation of AJCC staging, patients with bladder cancer that have LN-only disease will have a specific M1a stage, but patients with UC from other primary disease sites may have different M/N stages.

Table 2. Overall Summary of TRAEs Across Subgroups

	Upper tract		Lower tract		LN-only mets		Visceral mets present		Liver mets present		Liver mets absent	
	EV+P n=135	Chemotherapy n=97	EV+P n=303	Chemotherapy n=335	EV+P n=103	Chemotherapy n=102	EV+P n=316	Chemotherapy n=309	EV+P n=99	Chemotherapy n=96	EV+P n=341	Chemotherapy n=337
Any TRAE, n (%)	133 (98.5)	92 (94.8)	293 (96.7)	321 (95.8)	100 (97.1)	98 (96.1)	307 (97.2)	295 (95.5)	95 (96.0)	93 (96.9)	333 (97.7)	321 (95.3)
Any Grade ≥3 TRAE, n (%)	82 (60.7)	69 (71.1)	170 (56.1)	231 (69.0)	55 (53.4)	68 (66.7)	185 (58.5)	219 (70.9)	55 (55.6)	71 (74.0)	197 (57.8)	230 (68.2)
Any serious TRAE, n (%)	39 (28.9)	13 (13.4)	90 (29.7)	71 (21.2)	26 (25.2)	18 (17.6)	95 (30.1)	64 (20.7)	32 (32.3)	16 (16.7)	97 (28.4)	69 (20.5)

Table 3. Treatment-Related AESIs for EV in the EV+P Arm

	Upper tract (n=135)		Lower tract (n=303)		LN-only mets (n=103)		Visceral mets present (n=316)		Liver mets present (n=99)		Liver mets absent (n=341)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Peripheral neuropathy, n (%)[a]	89 (65.9)	10 (7.4)	193 (63.7)	23 (7.6)	72 (69.9)	9 (8.7)	196 (62.0)	22 (7.0)	53 (53.5)	6 (6.1)	230 (67.4)	27 (7.9)
Sensory events	88 (65.2)	8 (5.9)	178 (58.7)	13 (4.3)	67 (65.0)	7 (6.8)	185 (58.5)	13 (4.1)	49 (49.5)	4 (4.0)	218 (63.9)	17 (5.0)
Motor events	8 (5.9)	2 (1.5)	37 (12.2)	12 (4.0)	16 (15.5)	2 (1.9)	28 (8.9)	11 (3.5)	9 (9.1)	3 (3.0)	36 (10.6)	11 (3.2)
Skin reactions, n (%)	96 (71.1)	28 (20.7)	199 (65.7)	42 (13.9)	78 (75.7)	14 (13.6)	203 (64.2)	54 (17.1)	64 (64.6)	12 (12.1)	232 (68.0)	58 (17.0)
Rash	92 (68.1)	27 (20.0)	182 (60.1)	40 (13.2)	68 (66.0)	14 (13.6)	193 (61.1)	51 (16.1)	59 (59.6)	11 (11.1)	216 (63.3)	56 (16.4)
Hyperglycemia, n (%)	13 (9.6)	8 (5.9)	47 (15.5)	20 (6.6)	17 (16.5)	7 (6.8)	39 (12.3)	19 (6.0)	9 (9.1)	6 (6.1)	51 (15.0)	22 (6.5)
Ocular disorders, n (%)	29 (21.5)	0	65 (21.5)	0	24 (23.3)	0	65 (20.6)	0	20 (20.2)	0	75 (22.0)	0
Dry eye	24 (17.8)	0	59 (19.5)	0	21 (20.4)	0	57 (18.0)	0	16 (16.2)	0	68 (19.9)	0
Corneal disorder	3 (2.2)	0	8 (2.6)	0	4 (3.9)	0	7 (2.2)	0	3 (3.0)	0	8 (2.3)	0
Blurred vision	8 (5.9)	0	13 (4.3)	0	2 (1.9)	0	19 (6.0)	0	6 (6.1)	0	15 (4.4)	0
Infusion-related reactions, n (%)	2 (1.5)	0	8 (2.6)	0	3 (2.9)	0	6 (1.9)	0	1 (1.0)	0	9 (2.6)	0

[a]Peripheral neuropathy standardized MedDRA queries (broad scope).

Table 4. Treatment-Emergent AEOSIs for P in the EV+P Arm

	Upper tract (n=135)		Lower tract (n=303)		LN-only mets (n=102)		Visceral mets present (n=316)		Liver mets present (n=99)		Liver mets absent (n=341)	
	Any grade[a]	Grade ≥3	Any grade[a]	Grade ≥3	Any grade[a]	Grade ≥3	Any grade[a]	Grade ≥3	Any grade[a]	Grade ≥3	Any grade[a]	Grade ≥3
Adrenal insufficiency, n (%)	4 (3.0)	0	5 (1.7)	2 (0.7)	2 (1.9)	1 (1.0)	6 (1.9)	1 (0.3)	2 (2.0)	1 (1.0)	7 (2.1)	1 (0.3)
Arthritis, n (%)	1 (0.7)	0	2 (0.7)	0	1 (1.0)	0	2 (0.6)	0	1 (1.0)	0	2 (0.6)	0
Colitis, n (%)	2 (1.5)	1 (0.7)	10 (3.3)	6 (2.0)	1 (1.0)	0	10 (3.2)	6 (1.9)	3 (3.0)	2 (2.0)	9 (2.6)	5 (1.5)
Gastritis, n (%)	2 (1.5)	0	7 (2.3)	0	3 (2.9)	0	6 (1.9)	0	1 (1.0)	0	8 (2.3)	0
Hepatitis, n (%)	4 (3.0)	2 (1.5)	11 (3.6)	7 (2.3)	4 (3.9)	2 (1.9)	11 (3.5)	7 (2.2)	4 (4.0)	2 (2.0)	11 (3.2)	7 (2.1)
Hyperthyroidism, n (%)	5 (3.7)	0	16 (5.3)	1 (0.3)	6 (5.8)	0	14 (4.4)	1 (0.3)	5 (5.1)	0	16 (4.7)	1 (0.3)
Hypophysitis, n (%)	1 (0.7)	0	2 (0.7)	0	1 (1.0)	0	2 (0.6)	0	0	0	3 (0.9)	0
Hypothyroidism, n (%)	17 (12.6)	2 (1.5)	36 (11.9)	1 (0.3)	17 (16.5)	1 (1.0)	30 (9.5)	2 (0.6)	7 (7.1)	0	46 (13.5)	3 (0.9)
Infusion reactions, n (%)	1 (0.7)	0	6 (2.0)	0	2 (1.9)	0	4 (1.3)	0	0	0	7 (2.1)	0
Myocarditis, n (%)	1 (0.7)	0	2 (0.7)	1 (0.3)	0	0	3 (0.9)	1 (0.3)	2 (2.0)	1 (1.0)	1 (0.3)	0
Myositis, n (%)	2 (1.5)	1 (0.7)	2 (0.7)	0	0	0	3 (0.9)	1 (0.3)	0	0	4 (1.2)	1 (0.3)
Nephritis, n (%)	1 (0.7)	0	3 (1.0)	1 (0.3)	3 (2.9)	1 (1.0)	1 (0.3)	0	0	0	4 (1.2)	1 (0.3)
Pancreatitis, n (%)	2 (1.5)	1 (0.7)	5 (1.7)	5 (1.7)	1 (1.0)	1 (1.0)	6 (1.9)	5 (1.6)	4 (4.0)	3 (3.0)	3 (0.9)	3 (0.9)
Pneumonitis, n (%)	14 (10.4)	6 (4.4)	31 (10.2)	11 (3.6)	11 (10.7)	2 (1.9)	32 (10.1)	14 (4.4)	4 (4.0)	2 (2.0)	41 (12.0)	15 (4.4)
Sarcoidosis, n (%)	0	0	2 (0.7)	1 (0.3)	1 (1.0)	1 (1.0)	1 (0.3)	0	0	0	2 (0.6)	1 (0.3)
Severe skin reactions, n (%)	22 (16.3)	17 (12.6)	56 (18.5)	37 (12.2)	19 (18.4)	8 (7.8)	57 (18.0)	45 (14.2)	18 (18.2)	13 (13.1)	60 (17.6)	41 (12.0)

*Occurring in ≥1% of patients in at least one subgroup.

NCT04223856

EV-302: Long-term subgroup analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC)

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Objective

- To provide long-term efficacy and safety results from the EV-302/KEYNOTE-A39 (NCT04223856) study in subgroups of patients of clinical interest, including those defined by primary disease site of origin and metastatic site

Conclusions

- EV+P continues to demonstrate superior efficacy versus chemotherapy across prespecified subgroups after a median of ≈2.5 years of follow-up, with a magnitude of benefit aligned with the overall population
- AE frequencies across subgroups were generally consistent with those in the overall population
- These data reinforce EV+P as the standard of care for the 1L treatment of patients with la/mUC

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Abbreviations

1L, first line; AE, adverse event; AESI, adverse event of special interest; AEOSI, adverse event of special interest; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CPS, combined positive score; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; gem, gemcitabine; GFR, glomerular filtration rate; HR, hazard ratio; INV, investigator; IV, intravenously; ITT, intent to treat; la/mUC, locally advanced or metastatic urothelial cancer; LN, lymph node; M, metastasis; mets, metastases; N, nodes; NE, not estimable; NYHA, New York Heart Association; OS, overall survival; ORR, overall response rate; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; plat, platinum; PR, partial response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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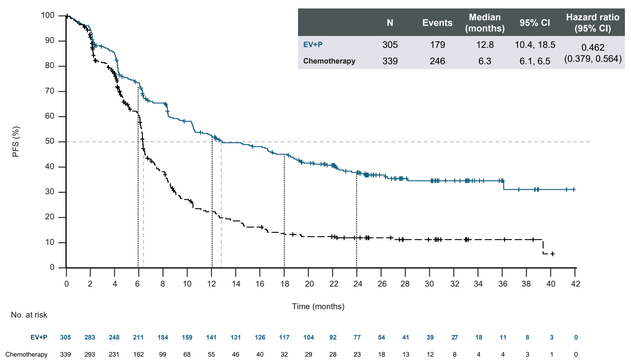
Supplementary Results

Table S1. Overall Summary of TRAEs in the ITT population

	ITT
	EV+P N=440
Any TRAE, n (%)	428 (97.3)
Any Grade ≥3 TRAE, n (%)	252 (57.3)

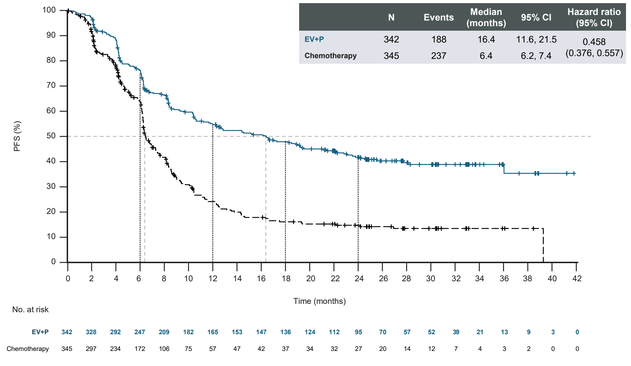
Figure S1. PFS by BICR in Subgroups of Interest

(A) Primary Disease Site of Origin in the Lower Tract



	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	305	179	12.8	10.4, 18.5	0.462 (0.379, 0.564)
Chemotherapy	339	246	6.3	6.1, 6.5	

(B) Absence of Liver Metastases

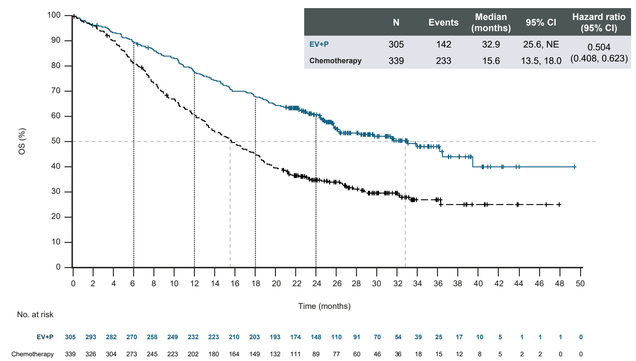


	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	342	188	16.4	11.6, 21.5	0.458 (0.376, 0.557)
Chemotherapy	345	237	6.4	6.2, 7.4	

Censored observations are indicated by a "+" symbol.

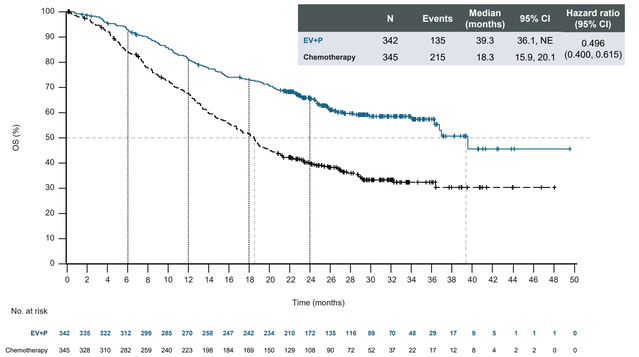
Figure S2. OS by BICR in Subgroups of Interest

(A) Primary Disease Site of Origin in the Lower Tract



	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	305	142	32.9	25.6, NE	0.504 (0.408, 0.623)
Chemotherapy	339	233	15.6	13.5, 18.0	

(B) Absence of Liver Metastases



	N	Events	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	342	135	39.3	36.1, NE	0.496 (0.400, 0.615)
Chemotherapy	345	215	18.3	15.9, 20.1	

Censored observations are indicated by a "+" symbol.