Poster 3073P

Enfortumab vedotin (EV) + pembrolizumab (P) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC): An exploratory analysis in older patients and those with comorbidities from EV-302

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Objective

- To provide insights into clinical outcomes in patients treated with EV+P who are older, and those with diabetes and renal impairment

Conclusions

- OS and PFS benefits in patients treated with EV+P vs chemotherapy were maintained across patients aged ≥75 years and those with clinically challenging comorbidities of diabetes and renal impairment
- In these subgroups, the overall safety profile of EV+P was consistent with the overall population
- These data reinforce EV+P as the standard of care for the 1L treatment of patients with la/mUC, when administered according to protocol-defined criteria, and further demonstrate that clinical benefit with EV+P in all key subgroups assessed to date is consistent with the overall population

Abbreviations

1L, first line; AE, adverse event; AESI, adverse event of special interest; AEOSI, adverse events of special interest; BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c, INV, investigator; ITT, intention-to-treat; IV, intravenous; la/mUC, locally advanced or metastatic urothelial carcinoma; NE, not estimable; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

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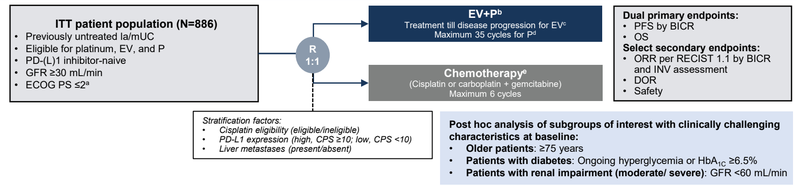
Background

- The pivotal, phase 3 EV-302 study (NCT04223856) is a global, open-label, randomized study comparing the efficacy and safety of EV+P versus platinum-based chemotherapy in patients with previously untreated la/mUC (**Figure 1**)[1]
  - Results from EV-302, demonstrating significant improvements in PFS and OS with EV+P compared with chemotherapy,[1] led to global approvals of EV+P as 1L treatment for patients with la/mUC[2-5]; EV+P has now become the new standard of care in this setting[6,7]
- Updated results from EV-302 after ≈2.5 years of median follow-up showed that the OS and PFS benefits in patients treated with EV+P were maintained, with median OS of 33.8 months (95% CI, 26.1-39.3 months)[8]
  - In the EV-302 updated analysis, clinical benefit of EV+P was consistent between the ITT population and prespecified subgroups, including age (<65 or ≥65 years) and renal function (normal, mildly impaired, or moderately/severely impaired)[8]
- Here, we present a subgroup analysis of clinical outcomes for EV+P in patients with clinically challenging characteristics at baseline:
  - Older patients (≥75 years)
  - Diabetes: ongoing hyperglycemia or HbA_{1c} ≥6.5%
  - Renal impairment (moderate or severe): GFR <60 mL/min

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 had 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]Treatment until protocol-defined study discontinuation due to disease progression by BICR, clinical progression or unacceptable toxicity. [d]Treatment until disease progression by BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles. [e]Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol defined.

Results

Patients and treatment

- A total of 886 patients were randomized: 442 to the EV+P arm and 444 to the chemotherapy arm
- Baseline characteristics across the subgroups are shown in **Table 1**
- At data cutoff (August 8, 2024), median follow-up for the ITT population was 29.1 months (95% CI, 28.5-29.9)
- In the EV+P arm, the median (range) treatment duration of EV+P by subgroup was:
  - 10.0 cycles (1-39) in patients aged ≥75 years
  - 17.5 cycles (1-45) in patients with diabetes (ongoing hyperglycemia or HbA_{1C} ≥6.5%)
  - 12.0 cycles (1-50) in patients with renal impairment (GFR <60 mL/min)

Efficacy

- Efficacy data in the evaluated subgroups were consistent with those in the ITT population
- Confirmed ORR (**Figure 2**) was higher in the EV+P treatment arm than in the chemotherapy arm across all evaluated subgroups:
  - 66.3% vs 38.3% for patients ≥75 years at baseline
  - 69.9% vs 35.4% for patients with diabetes at baseline
  - 66.3% vs 38.2% for patients with renal impairment at baseline (GFR <60 mL/min)
- PFS (by BICR) and OS benefits in patients treated with EV+P vs chemotherapy were maintained across all evaluated subgroups (**Figures 3** and **4**)

Safety

- Safety data in the evaluated subgroups were generally consistent with those in the overall safety analysis population[8]
- Frequency of grade ≥3 TRAEs was lower in the EV+P arm than in the chemotherapy arm across all subgroups (**Table 2**)
- In the EV+P arm, treatment-related AESIs for EV were primarily low grade across subgroups, for majority of the AESIs (**Figure 5A**)
  - Treatment-related AESIs leading to discontinuation are shown in **Table 3.** Among patients in the EV+P arm with baseline diabetes, grade ≥3 treatment-related hyperglycemia occurred in 15.5%, none of which resulted in treatment discontinuation
- Severe skin reactions were the most common treatment-emergent AEOSIs for P in the EV+P arm (**Figure 5B**)

Table 1. Key demographic and baseline disease characteristics

Characteristic	ITT population[1]		Age ≥75 years[a]		Diabetes[a]		GFR <60 mL/min[a]	
	EV+P n=442	Chemo n=444	EV+P n=102	Chemo n=108	EV+P n=85	Chemo n=97	EV+P n=193	Chemo n=187
Age								
Median (range), years	69 (37-87)	69 (22-91)	79.0 (75-87)	78.0 (75-91)	70.0 (45-86)	70.0 (48-91)	72.0 (40-86)	73.0 (47-91)
Sex, n (%)								
Male	344 (77.8)	336 (75.7)	73 (71.6)	77 (71.3)	70 (82.4)	78 (80.4)	132 (68.4)	134 (71.7)
Female	98 (22.2)	108 (24.3)	29 (28.4)	31 (28.7)	15 (17.6)	19 (19.6)	61 (31.6)	53 (28.3)
Race, n (%)								
White	308 (69.7)	290 (65.3)	73 (71.6)	78 (72.2)	59 (69.4)	61 (62.9)	117 (60.6)	124 (66.3)
ECOG PS, n (%)								
0	223 (50.5)	215 (48.4)	43 (42.2)	42 (38.9)	43 (50.6)	44 (45.4)	89 (46.1)	81 (43.3)
1	204 (46.2)	216 (48.6)	52 (51.0)	59 (54.6)	38 (44.7)	49 (50.5)	100 (51.8)	97 (51.9)
2	15 (3.4)	11 (2.5)	7 (6.9)	6 (5.6)	4 (4.7)	3 (3.1)	4 (2.1)	7 (3.7)
Primary tumor location, n (%)								
Upper tract	135 (30.5)	104 (23.4)	32 (31.4)	26 (24.1)	22 (25.9)	18 (18.6)	74 (38.3)	53 (28.3)
Lower tract	305 (69.0)	339 (76.4)	70 (68.6)	81 (75.0)	62 (72.9)	79 (81.4)	119 (61.7)	134 (71.7)
Metastatic category, n (%)								
Visceral metastases	318 (71.9)	318 (71.6)	76 (74.5)	77 (71.3)	61 (71.8)	69 (71.1)	138 (71.5)	144 (77.0)
Lymph node–only disease	103 (23.3)	104 (23.4)	20 (19.6)	28 (25.9)	18 (21.2)	23 (23.7)	44 (22.8)	36 (19.3)

[a]Comorbidity subgroups are not mutually exclusive.

Table 2. Overall summary of TRAEs across subgroups

	Overall EV-302 safety population[9]		Age ≥75 years		Diabetes		GFR <60 mL/min	
	EV+P n=440	Chemo n=433	EV+P n=102	Chemo n=105	EV+P n=84	Chemo n=96	EV+P n=192	Chemo n=181
Any treatment-related AE, n (%)	428 (97.3)	414 (95.6)	99 (97.1)	101 (96.2)	83 (98.8)	92 (95.8)	185 (96.4)	173 (95.6)
Any grade ≥3 treatment-related AE, n (%)	252 (57.3)	301 (69.5)	60 (58.8)	77 (73.3)	54 (64.3)	67 (69.8)	119 (62.0)	141 (77.9)
TRAE leading to dose interruption of EV, n (%)	263 (59.8)	--	62 (60.8)	--	51 (60.7)	--	118 (61.5)	--
TRAE leading to dose interruption of P, n (%)	223 (50.7)	--	57 (55.9)	--	42 (50.0)	--	98 (51.0)	--
TRAE leading to dose reduction of EV, n (%)[a]	189 (43.0)	--	47 (46.1)	--	39 (46.4)	--	86 (44.8)	--

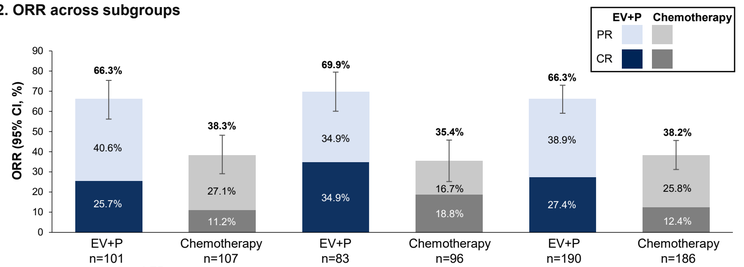
[a]No dose reduction was permitted for pembrolizumab.

Table 3. Treatment-related AESIs for EV leading to treatment discontinuation[a,b,c]

	Age ≥75 years EV+P n=102			Diabetes EV+P n=84			GFR <60 mL/min EV+P n=192		
	EV	P	Any drug	EV	P	Any drug	EV	P	Any drug
Peripheral neuropathy, n (%)	19 (18.6)	4 (3.9)	19 (18.6)	17 (20.2)	1 (1.2)	17 (20.2)	26 (13.5)	2 (1.0)	26 (13.5)
Sensory events	17 (16.7)	3 (2.9)	18 (17.6)	15 (17.9)	0	15 (17.9)	25 (13.0)	2 (1.0)	26 (13.5)
Motor events	2 (2.0)	1 (1.0)	2 (2.0)	2 (2.4)	1 (1.2)	2 (2.4)	1 (0.5)	0	1 (0.5)
Skin reactions, n (%)	5 (4.9)	5 (4.9)	6 (5.9)	4 (4.8)	2 (2.4)	4 (4.8)	9 (4.7)	6 (3.1)	11 (5.7)
Rash	5 (4.9)	5 (4.9)	6 (5.9)	3 (3.6)	1 (1.2)	3 (3.6)	9 (4.7)	6 (3.1)	11 (5.7)
Severe cutaneous adverse reactions	1 (1.0)	2 (2.0)	2 (2.0)	2 (2.4)	2 (2.4)	2 (2.4)	1 (0.5)	2 (1.0)	2 (1.0)

[a]AESIs for EV may be labeled as related to pembrolizumab per investigator judgment. [b]There were no discontinuations due to hyperglycemia, ocular disorders (grouped term that includes dry eye, corneal disorder, and blurred vision) or infusion related reactions. [c]In the overall EV-302 safety population, the most frequent treatment-related AESI for EV leading to discontinuation of EV was peripheral sensory neuropathy (in 17.3% of patients) in the EV+P arm.

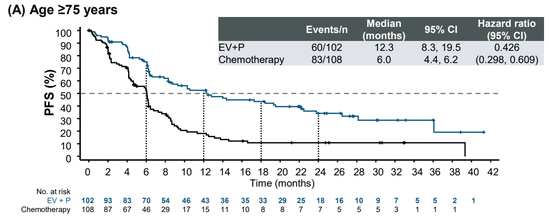
Figure 2. ORR across subgroups



	Age ≥75 years		Diabetes		GFR <60 mL/min	
ORR, n (%)	67 (66.3)	41 (38.3)	58 (69.9)	34 (35.4)	126 (66.3)	71 (38.2)
Median DOR (95% CI), months	20.2 (12.2, NE)	7.1 (5.5, 10.8)	34.2 (24.4, NE)	12.4 (6.1, NE)	17.2 (12.5, 34.2)	7.0 (6.1, 10.3)

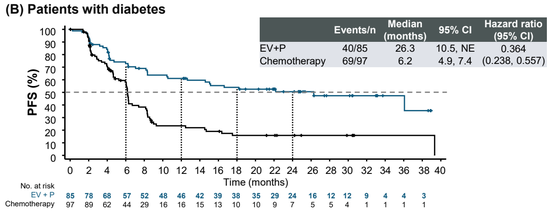
Figure 3. PFS by BICR for patients in select subgroups

(A) Age ≥75 years



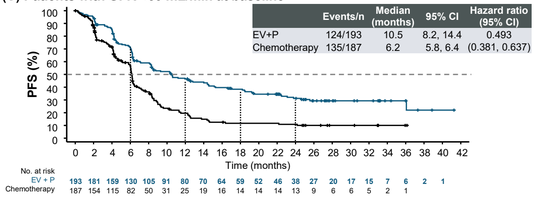
	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	60/102	12.3	8.3, 19.5	0.426 (0.298, 0.609)
Chemotherapy	83/108	6.0	4.4, 6.2	

(B) Patients with diabetes



	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	40/85	26.3	10.5, NE	0.364
Chemotherapy	69/97	6.2	4.9, 7.4	(0.238, 0.557)

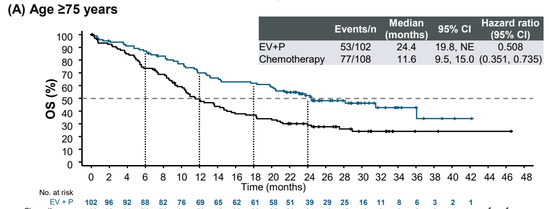
(C) Patients with GFR <60 mL/min at baseline



	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	124/193	10.5	8.2, 14.4	0.493
Chemotherapy	135/187	6.2	5.8, 6.4	(0.381, 0.637)

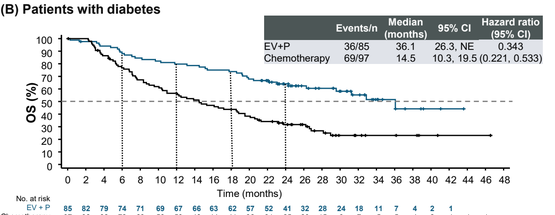
Figure 4. OS for patients in select subgroups

(A) Age ≥75 years



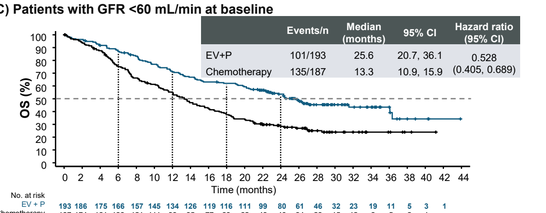
	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	53/102	24.4	19.8, NE	0.508
Chemotherapy	77/108	11.6	9.5, 15.0	(0.351, 0.735)

(B) Patients with diabetes



	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	36/85	36.1	26.3, NE	0.343
Chemotherapy	69/97	14.5	10.3, 19.5	(0.221, 0.533)

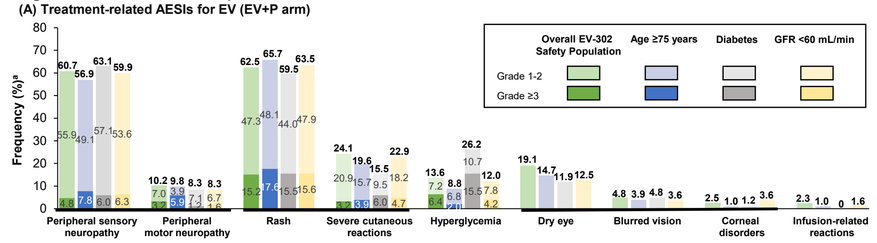
(C) Patients with GFR <60 mL/min at baseline



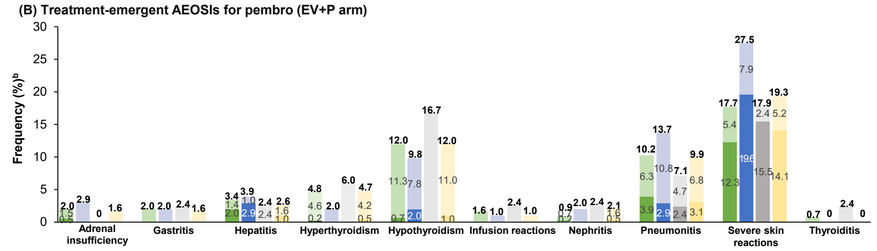
	Events/n	Median (months)	95% CI	Hazard ratio (95% CI)
EV+P	101/193	25.6	20.7, 36.1	0.528
Chemotherapy	135/187	13.3	10.9, 15.9	(0.405, 0.689)

Figure 5. Adverse events of special interest

(A) Treatment-related AESIs for EV (EV+P arm)



(B) Treatment-emergent AEOSIs for pembro (EV+P arm)



Due to rounding, percentages may not equal total.
[a]AESIs for EV in the EV+P arm are shown by medical concept.
[b]AEOSIs for P that occurred in ≥2% of patients in the EV+P arm in any of the subgroups are shown by medical concept. In the overall population, colitis also occurred in ≥2% of patients (2.7%).