Poster 746

Characterization of patients responding to enfortumab vedotin plus pembrolizumab (EV+P): exploratory analysis from the phase 3 EV-302 trial of EV+P vs chemotherapy in previously untreated locally advanced or metastatic urothelial carcinoma

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Objective

- To present additional data from an exploratory analysis of efficacy and safety results for responders (patients who achieved confirmed CR or PR based on tumor response) and those who achieved a CR in the EV-302 study, with ≈2.5 years of median follow-up

Conclusions

- Among patients who achieved a response (CR+PR) or CR, improvements in DOR and OS were seen in the EV+P arm vs the chemotherapy arm
  - Durable responses were seen regardless of cisplatin eligibility
- Most patients with CR achieved PR before converting to CR; conversion to CR occurred more rapidly and in more than twice as many patients in the EV+P than in the chemotherapy arm
- The safety profile of EV+P in patients with CR+PR and those with CR was consistent with that in the overall population, and no new safety signals were identified with longer treatment duration
- These data, including long-term outcomes for patients who achieved CR or PR as best response, reinforce the use of EV+P as the preferred SOC for 1L treatment of la/mUC until disease progression

Abbreviations

1L, first line; AESI, adverse event of special interest; AEOSI, adverse event of special interest; BICR, blinded independent central review; CPS, combined positive score; CR, complete response; DOCR, duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; HR, hazard ratio; INV, investigator; IV, intravenous; ITT, intent-to-treat; la/mUC, locally advanced or metastatic urothelial cancer; NE, not estimable; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; TRAE, treatment-related adverse event.

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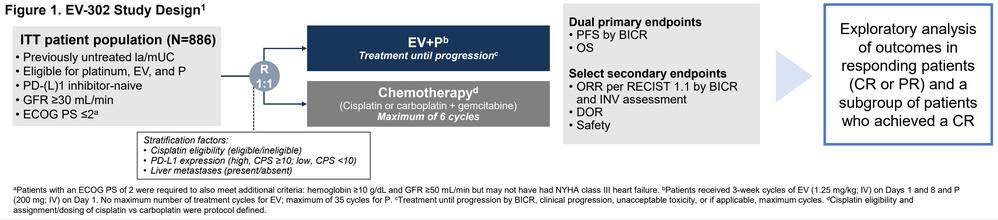
Background

- The global, open-label, randomized, phase 3 EV-302/KEYNOTE-A39 study (NCT04223856) demonstrated significant improvements in PFS and OS with EV+P compared with platinum-based chemotherapy[1]
  - These data resulted in global approvals for EV+P and established it as SOC for the 1L treatment of patients with la/mUC and a preferred option recommended by major international medical guidelines[1-7]
- Updated results after ≈2.5 years of median follow-up confirmed sustained efficacy benefits[8,9]
  - In a previously reported exploratory analysis of responders, the confirmed objective response rate (CR+PR) by BICR was greater in the EV+P arm than in the chemotherapy arm (67.5% vs 44.2%; P<0.00001), and the proportion of patients achieving CR was twice that in the EV+P arm than in the chemotherapy arm (30.4% vs 14.5%)[8]
    - For patients with CR, efficacy outcomes similarly favored EV+P vs chemotherapy; median OS was NE in both arms, and median duration of CR was NE in the EV+P arm vs 15.2 months in the chemotherapy arm[9]
    - Safety remained consistent with the previously reported primary analysis,[1] with no new safety signals[8]
- To further characterize responders in EV-302, we present additional data from an exploratory analysis of outcomes in patients achieving an objective response (CR or PR) and in the subgroup of patients with a CR (**Figure 1**)

Methods

Figure 1. EV-302 Study Design[1]



[a]Patients with an 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. No maximum number of treatment cycles for EV; maximum of 35 cycles for P. [c]Treatment until progression by BICR, clinical progression, unacceptable toxicity, or if applicable, maximum cycles. [d]Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol defined.

Results

Overview of the Patient Population

- A total of 886 patients were randomized: 442 to the EV+P arm and 444 to the chemotherapy arm
- At data cutoff (Aug 8, 2024), median follow-up in the ITT population was 29.1 months
- Baseline characteristics among complete and partial responders in the EV+P arm were generally consistent with those of the ITT population (**Table 1**)

Efficacy Outcomes: Responders (CR+PR)[9]

- Among responders, the probability of maintained response at 24 months was ≈50% with EV+P and 24% with chemotherapy (**Figure 2A**)
  - DOR by BICR among all responders favored EV+P vs chemotherapy, irrespective of cisplatin eligibility (**Figure 2B, 2C**)
- Median OS among all responders was 39.3 months (95% CI: 36.5, NE) with EV+P and 32.1 months (95% CI: 26.8, NE) with chemotherapy (**Figure 3**)

Time to Response and Conversion From PR to CR

- Median time to objective response (CR or PR) was 2.1 months with both EV+P and chemotherapy; median time to CR was 4.3 months with EV+P and 4.2 months with chemotherapy (**Table 2**)
- In the EV+P and chemotherapy arms, 88/437 (20.1% of the response-evaluable set) and 38/441 (8.6%), respectively, achieved PR then converted to CR
  - In patients achieving CR initially experiencing PR (88/133 with EV+P and 38/64 with chemotherapy), median time from first PR to CR was 4.5 months with EV+P and 6.1 months with chemotherapy (**Table 2**)

Table 1. Key Demographic and Baseline Disease Characteristics[9]

	EV+P arm ITT[1,8] (n=442)	EV+P arm responders (n=295)
Age, median (range), y	69.0 (37-87)	69.0 (37-87)
ECOG PS, n (%)		
0	223 (50.5)	160 (54.2)
1	204 (46.2)	129 (43.7)
2	15 (3.4)	6 (2.0)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	90 (30.5)
Lower tract	305 (69.0)	204 (69.2)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	201 (68.1)
Liver	100 (22.6)	59 (20.0)
Lymph node–only disease	103 (23.3)	79 (26.8)
Cisplatin eligibility status, n (%)		
Eligible	244 (55.2)	172 (58.3)
Ineligible	198 (44.8)	123 (41.7)

Table 2. Summary of Time to CR

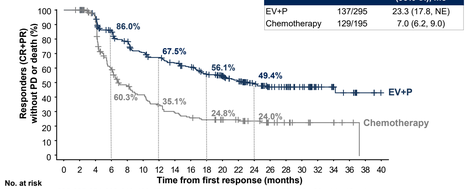
	EV+P arm (n=437)	Chemotherapy arm (n=441)
Patients achieving CR, n (%)	133 (30.4)	64 (14.5)
Patients achieving CR directly	45 (10.3)	26 (5.9)
Patients achieving CR after PR	88 (20.1)	38 (8.6)
Median time from randomization to CR[a] (range), months	4.3 (2-22)	4.2 (2-27)
Median time from PR to CR[b] (range), months	4.5 (2-20)	6.1 (2-25)

[a]Time from randomization to first CR that is subsequently confirmed; n=133 and n=64 in the EV+P and chemotherapy arms, respectively. [b]Time from first PR to first CR that is subsequently confirmed; n=88 and n=38 in the EV+P and chemotherapy arms, respectively.

Figure 2. Duration of Response by BICR in Responders (CR+PR)[9]

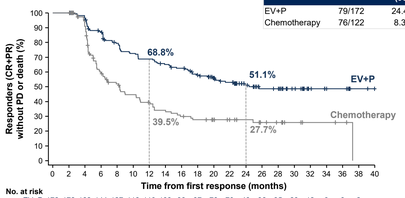
A) All patients with CR+PR

	Events/N	Median DOR (95% CI), mo
EV+P	137/295	23.3 (17.8, NE)
Chemotherapy	129/195	7.0 (6.2, 9.0)



B) Cisplatin-eligible patients

	Events/N	Median DOR (95% CI), mo
EV+P	79/172	24.4 (17.8, NE)
Chemotherapy	76/122	8.3 (5.9, 10.8)



C) Cisplatin-ineligible patients

	Events/N	Median DOR (95% CI), mo
EV+P	58/123	21.9 (15.7, NE)
Chemotherapy	53/73	6.6 (5.5, 9.3)

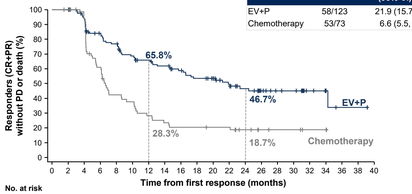
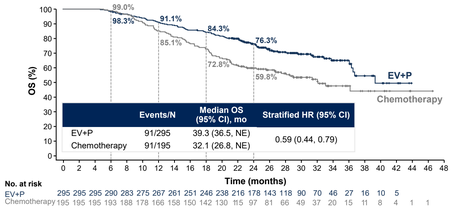
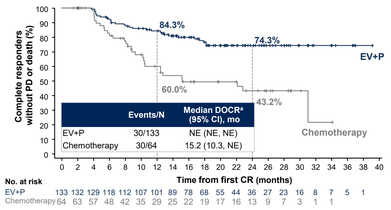


Figure 3. OS in All Patients With CR+PR



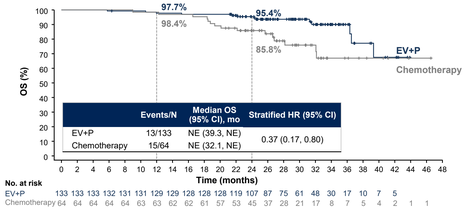
	Events/N	Median OS (95% CI), mo	Stratified HR (95% CI)
EV+P	91/295	39.3 (36.5, NE)	0.59 (0.44, 0.79)
Chemotherapy	91/195	32.1 (26.8, NE)	

Figure 4. Duration of Response by BICR in Patients Achieving CR[9]



	Events/N	Median DOCR[a] (95% CI), mo
EV+P	30/133	NE (NE, NE)
Chemotherapy	30/64	15.2 (10.3, NE)

Figure 5. OS in Patients Achieving CR[9]



	Events/N	Median OS (95% CI), mo	Stratified HR (95% CI)
EV+P	13/133	NE (39.3, NE)	0.37 (0.17, 0.80)
Chemotherapy	15/64	NE (32.1, NE)	

Efficacy Outcomes in Patients Achieving CR[9]

- The probability of maintained CR 2 years after the first documentation of CR was 74.3% with EV+P and 43.2% with chemotherapy (**Figure 4**)
- Median OS was NE (95% CI: 39.3 months, NE) in the EV+P arm and NE (95% CI: 32.1 months, NE) in the chemotherapy arm for patients achieving CR (**Figure 5**)

Safety

- Among responders (CR+PR) in the EV+P arm, the median number (range) of cycles was 12 (1-54) for EV and 17 (1-35) for P[9]
- An overall summary of TRAEs is shown in **Table 3**
- Treatment-related AESIs for EV were primarily low grade (**Table 4**)
  - The most common treatment-related AESIs in the EV+P arm in all responders (CR+PR) and in patients who achieved CR were peripheral neuropathy (77.6% and 80.5%, respectively), skin reactions (76.6% and 82.7%, respectively), and ocular disorders (25.4% and 21.8%, respectively)
- Severe skin reactions (any grade: 20.3% for responders, 21.1% for CR), hypothyroidism (any grade: 13.9% for responders, 19.5% for CR), and pneumonitis (any grade: 11.9% for responders, 12.0% for CR) were the most common treatment-emergent AEOSIs for P in the EV+P arm (not shown)
- A summary of dose modifications for EV and P is shown in **Figure 6**

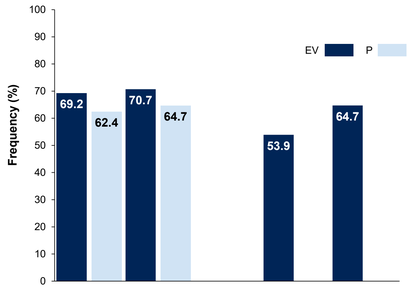
Table 3. Overall Summary of TRAEs

n (%)	Responders (CR+PR) EV+P (n=295)	Responders (CR+PR) Chemotherapy (n=195)	Patients achieving CR EV+P (n=133)	Patients achieving CR Chemotherapy (n=64)
Any TRAE	293 (99.3)	189 (96.9)	133 (100)	62 (96.9)
Any Grade ≥3 TRAE	181 (61.4)	129 (66.2)	82 (61.7)	46 (71.9)
Any serious TRAE	83 (28.1)	27 (13.8)	33 (24.8)	9 (14.1)
Any TRAE leading to discontinuation of any study treatment	157 (53.2)	32 (16.4)	86 (64.7)	15 (23.4)
Any TRAE leading to death	2 (0.7)	0	0	0

Table 4. Treatment-Related AESIs for EV (EV+P Arm)

n (%)	Responders (CR+PR) (n=295) Any grade	Responders (CR+PR) (n=295) Grade ≥3	Patients achieving CR (n=133) Any grade	Patients achieving CR (n=133) Grade ≥3
Peripheral neuropathy	229 (77.6)	29 (9.8)	107 (80.5)	13 (9.8)
Sensory events	217 (73.6)	19 (6.4)	102 (76.7)	9 (6.8)
Motor events	39 (13.2)	12 (4.1)	22 (16.5)	4 (3.0)
Skin reactions	226 (76.6)	53 (18.0)	110 (82.7)	28 (21.1)
Rash	208 (70.5)	51 (17.3)	101 (75.9)	27 (20.3)
Hyperglycemia	47 (15.9)	22 (7.5)	26 (19.5)	11 (8.3)
Ocular disorders	75 (25.4)	0	29 (21.8)	0
Dry eye	67 (22.7)	0	27 (20.3)	0
Corneal disorder	9 (3.1)	0	2 (1.5)	0
Blurred vision	16 (5.4)	0	6 (4.5)	0
Infusion-related reactions	8 (2.7)	0	4 (3.0)	0

Figure 6. Dose Modifications (EV+P Arm)[9]



[a]Dose interruption includes dose elimination (scheduled dose being skipped) and dose delay (dose not occurring on the scheduled dosing day) as collected on the case report form. [b]No dose reduction was permitted for P.