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ENFORTUMAB VEDOTIN (EV) ALONE OR IN COMBINATION WITH PEMBROLIZUMAB (P) IN PREVIOUSLY UNTREATED CISPLATIN-INELIGIBLE PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER (la/mUC): SUBGROUP ANALYSES OF CONFIRMED OBJECTIVE RESPONSE RATE (cORR) FROM EV-103 COHORT K

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Background

- Efficacious and tolerable first-line therapeutic options remain a high unmet need for patients with la/mUC who are cisplatin-ineligible
- Enfortumab vedotin (EV) and pembrolizumab (P) monotherapy have each shown survival benefits in previously treated patients with la/mUC[1–4]
- EV in combination with P was previously evaluated in EV-103 (NCT03288545) Dose Escalation/Cohort A
  - Results showed a tolerable and manageable safety profile with encouraging efficacy results[5]

EV-103 Cohort K Design

Patient Population

Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

→

Cohort K

1:1 Randomization[a]

enfortumab vedotin + pembrolizumab or enfortumab vedotin Cisplatin-ineligible 1L (N=151)[b]

- **Dosing:** EV 1.25 mg/kg on Days 1 and 8, and P 200 mg on Day 1 of every 3-week cycle
- **Primary endpoint:** confirmed ORR per RECIST v1.1 by BICR[c]
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS by BICR and investigator, OS, safety/ tolerability, and lab abnormalities

Cohort K completed enrollment on 11 Oct 2021; Data cutoff was 10 Jun 2022

a Randomization was stratified by ECOG PS (0 vs 1 or 2) and liver metastases (present or absent)
b Sample size was based on precision of the estimate for ORR characterized by 95% CIs; of 151 patients, 149 were treated and included in the analyses
c There were no formal statistical comparisons between the two treatment arms

EV-103 Cohort K Summary

- In EV-103 Cohort K, EV+P showed encouraging antitumor activity in first-line cisplatin-ineligible patients with la/mUC[6]
  - High ORR by BICR (64.5%) and rapid responses; median DOR not reached
  - Promising PFS and OS expected to continue to evolve
  - Manageable safety profile; no new safety concerns emerged
- EV-103 Cohort K EV+P results were consistent with those previously reported in EV-103 Dose Escalation/Cohort A[5]
- EV monotherapy results were generally consistent with prior EV monotherapy results in second-line or beyond for la/mUC
- Here we report results of an analysis of prespecified EV-103 Cohort K subgroups that are representative of the first-line cisplatin-ineligible la/mUC population; we also report additional safety information

EV-103 Cohort K Subgroup Analysis

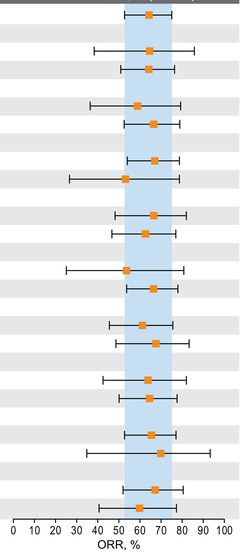
- Confirmed ORR subgroup analysis was performed in prespecified subgroups indicative of prognosis in the la/mUC patient population
- Age (≥65 years, <65 years)
- Sex (Male, Female)
- Race (White, Non-white)
- ECOG PS (Grade 0, Grade 1–2)
- Liver metastasis (Yes, No)
- PD-L1 expression level (CPS <10, CPS ≥10)
- Bajorin risk factors[a] (0, 1)
- Metastatic disease site at baseline (Visceral metastases, Lymph nodes only disease)
- Primary disease site of origin (Lower tract, Upper tract)

a Bajorin risk factors include visceral metastases (bone, lung, liver) and ECOG PS >2; patients with ECOG PS >2 were not eligible for this study

EV + Pembrolizumab: Subgroup Analyses of cORR

EV+P (N=76)

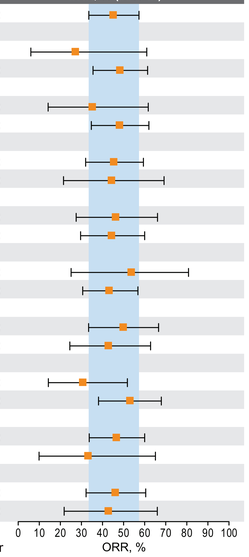
Subgroup	n/N	% (95% CI)	ORR, % (95% CI)
Overall	49/76	64.5 (52.7, 75.1)	
Age			
<65 years	11/17	64.7 (38.3, 85.8)	
≥65 years	38/59	64.4 (50.9, 76.4)	
Sex			
Female	13/22	59.1 (36.4, 79.3)	
Male	36/54	66.7 (52.5, 78.9)	
Race			
White	41/61	67.2 (54.0, 78.7)	
Non-white	8/15	53.3 (26.6, 78.7)	
ECOG PS			
Grade 0	22/33	66.7 (48.2, 82.0)	
Grade 1–2	27/43	62.8 (46.7, 77.0)	
Liver metastasis			
Yes	7/13	53.8 (25.1, 80.8)	
No	42/63	66.7 (53.7, 78.0)	
PD-L1 expression			
CPS <10	27/44	61.4 (45.5, 75.6)	
CPS ≥10	21/31	67.7 (48.6, 83.3)	
Bajorin risk factors			
0	16/25	64.0 (42.5, 82.0)	
1	33/51	64.7 (50.1, 77.6)	
Metastatic disease site at baseline			
Visceral metastases	42/64	65.6 (52.7, 77.1)	
Lymph nodes only disease	7/10	70.0 (34.8, 93.3)	
Primary disease site of origin			
Lower tract	31/46	67.4 (52.0, 80.5)	
Upper tract	18/30	60.0 (40.6, 77.3)	



EV Monotherapy: Subgroup Analyses of cORR

EV Monotherapy (N=73)

Subgroup	n/N	% (95% CI)	ORR, % (95% CI)
Overall	33/73	45.2 (33.5, 57.3)	
Age			
<65 years	3/11	27.3 (6.0, 61.0)	
≥65 years	30/62	48.4 (35.5, 61.4)	
Sex			
Female	6/17	35.3 (14.2, 61.7)	
Male	27/56	48.2 (34.7, 62.0)	
Race			
White	25/55	45.5 (32.0, 59.4)	
Non-white	8/18	44.4 (21.5, 69.2)	
ECOG PS			
Grade 0	13/28	46.4 (27.5, 66.1)	
Grade 1–2	20/45	44.4 (29.6, 60.0)	
Liver metastasis			
Yes	7/13	53.8 (25.1, 80.8)	
No	26/60	43.3 (30.6, 56.8)	
PD-L1 expression			
CPS <10	19/38	50.0 (33.4, 66.6)	
CPS ≥10	12/28	42.9 (24.5, 62.8)	
Bajorin risk factors			
0	8/26	30.8 (14.3, 51.8)	
1	25/47	53.2 (38.1, 67.9)	
Metastatic disease site at baseline			
Visceral metastases	28/60	46.7 (33.7, 60.0)	
Lymph nodes only disease	4/12	33.3 (9.9, 65.1)	
Primary disease site of origin			
Lower tract*	24/52	46.2 (32.2, 60.5)	
Upper tract	9/21	42.9 (21.8, 66.0)	



*One patient had primary disease at both bladder and ureter

Median duration of treatment for EV+P arm was 11 cycles, EV monotherapy arm was 8 cycles

Overview of TRAEs

	EV + P (N=76) n (%)	EV Monotherapy (N=73) n (%)
Grade ≥3 TRAEs	48 (63.2)	35 (47.9)
Serious TRAEs	18 (23.7)	11 (15.1)
TRAEs leading to death	3 (3.9)[a]	2 (2.7)[b]

a Three patients died due to a TRAE in the EV+P arm; one each from respiratory failure, pneumonitis, and sepsis
b Two patients died due to a TRAE in the EV monotherapy arm; one each from multiple organ dysfunction syndrome and respiratory failure

- EV TRAEs of special interest in the EV+P arm included peripheral neuropathy (46 of 76 patients, 60.5%), skin reactions (51 of 76 patients, 67.1%), and hyperglycemia (11 of 76 patients, 14.5%)
- Pembrolizumab Treatment-Emergent AEs of Special Interest in the EV+P arm included severe skin reactions (21 of 76 patients, 27.6%), hypothyroidism (10 of 76 patients, 13.2%), and pneumonitis (7 of 76 patients, 9.2%)
- Comprehensive safety data were previously presented[6]

TRAEs[a] Leading to Dose Interruption of Either Enfortumab Vedotin and/or Pembrolizumab

Event	EV+P (N=76) n (%)	EV Monotherapy (N=73) n (%)
Overall	52 (68.4)	26 (35.6)
Peripheral sensory neuropathy	14 (18.4)	7 (9.6)
Rash maculo-popular	11 (14.5)	2 (2.7)
Fatigue	5 (6.6)	1 (1.4)
Neutropenia	5 (6.6)	1 (1.4)
Pneumonitis	5 (6.6)	1 (1.4)
Diarrhea	4 (5.3)	1 (1.4)

a Treatment-relatedness was determined by the investigator, including causality to EV and/or pembrolizumab as applicable

- For EV in combination with pembrolizumab:
  - 68.4% of patients had TRAEs leading to interruption of either EV or P
  - 48.7% of patients had TRAEs leading to EV dose reduction
  - 47.4% of patients had TRAEs[a] leading to discontinuation of either EV or P
    - 25.0% of patients had TRAEs leading to discontinuation of EV only
    - 22.4% of patients had TRAEs leading to discontinuation of P only
    - 5.3% of patients had TRAEs leading to discontinuation of both EV and P

a TRAEs leading to discontinuation of EV, pembro, or both, are not mutually exclusive. A patient can be counted in multiple categories.

Summary and Conclusions

- EV+P showed promising cORR in 1L cisplatin-ineligible patients with la/mUC
  - While underpowered to draw definitive conclusions, pre-specified subgroup analyses show activity of EV+P across a broad range of patients, including PD-L1 subgroups and subgroups with poor prognosis
- EV+P TRAEs were manageable with close monitoring and appropriate dose modifications
  - Although dose interruptions and modifications were common, patients received a median of 11 treatment cycles
- EV monotherapy results were generally consistent with prior results in previously treated la/mUC
- EV+P has the potential to address high unmet needs in the 1L la/mUC cisplatin-ineligible patient population
- EV+P is being further evaluated in la/mUC in patients that are both eligible and ineligible for cisplatin and in MIBC in 3 ongoing Phase 3 trials (NCT04223856, NCT04700124, NCT03924895)

Abbreviations

1L, first-line; BICR, blinded independent central review; CI, confidence interval; cORR, confirmed objective response rate; CPS, combined positive score; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Score; EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial carcinoma; mg/kg, milligrams/kilogram; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST v1.1; Response Evaluation Criteria in Solid Tumors version 1.1; TRAE, treatment-related adverse event

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