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Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin monotherapy or in combination with pembrolizumab in previously untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC)

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Declaration of Interests

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Commercial Interest(s)	Nature of Relationship
Bayer, Seagen, AstraZeneca, Roche/Genentech, Astellas, QED Therapeutics	Consulting fees, trial funding
Alligator Biosciences, BMS, Merck, Pfizer, Pharmacyclics, Boehringer Ingelheim, GSK, Infinity, Janssen, Mirati, EMD-Serono, Gilead, Lilly, Tyra Biosciences, Pharmacyclics, Imvax, Hengrui	Consulting fees
Research to Practice, MJH Life Sciences, Medscape, Uptodate, Clinical Care Options, OncLive	CME
EMD-Serono, Pfizer	Honoraria

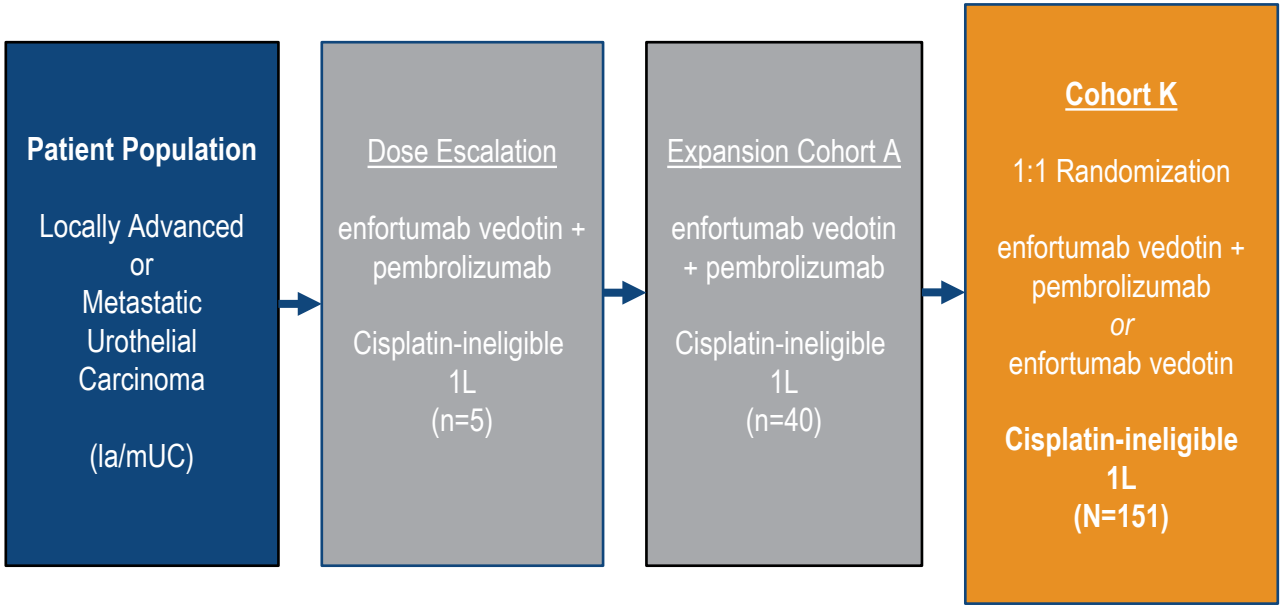
Background

- First-line (1L) therapeutic options remain an unmet need for patients with la/mUC who are cisplatin-ineligible
  - Avelumab maintenance therapy is only available to patients who do not progress after gemcitabine-carboplatin
  - PD-1/L1 inhibitor monotherapy is available to only select patients
- Enfortumab vedotin (EV) and pembrolizumab (P) as monotherapy have each shown antitumor activity with a survival benefit in pre-treated patients with la/mUC[1-4]
- EV+P was previously evaluated in EV-103 Dose Escalation/Cohort A and showed encouraging safety and efficacy results[5]
- We present the results of EV-103 Cohort K to further investigate EV+P combination and EV monotherapy in 1L cisplatin-ineligible patients

1.Powles T, et al. N Engl J Med 2021;384:1125-35; 2. Yu EY, et al. Lancet Oncol 2021;22:872-82; 3. Balar AV, et al. Lancet Oncol 2017;18:1483-92; 4. Fradet Y, et al. Ann Oncol 2019;30:970-6; 5. Hoimes CJ, et al. JCO 2022 (In press).

EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with urothelial carcinoma



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

Statistical considerations

- The sample size was based on precision of the estimate for ORR characterized by 95%CIs
- No formal statistical comparisons between the 2 treatment arms

Stratification factors: Liver metastases (present/absent) and ECOG PS (0 or 1/2); **Exploratory endpoints**: pharmacokinetics, antitherapeutic antibody, biomarkers of activity including baseline PD-L1 status and Nectin-4 expression, progression-free survival on subsequent therapy by investigator, patient reported outcomes; **Cohort K** completed enrollment on 11 Oct 2021; **Data cutoff was 10 Jun 2022**

Reasons for Cisplatin-Ineligibility

Renal impairment was the main reason for cisplatin-ineligibility

	EV+P (N=76) n (%)	EV Mono (N=73) n (%)
Patient meeting at least one of the following Galsky criteria	76 (100%)	72 (98.6)
CrCL <60 and ≥30mL/min[1]	48 (63.2)	44 (60.3)
Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
ECOG PS of 2	6 (7.9)	9 (12.3)
CrCL <60 and ≥30mL/min[1] and Grade ≥2 hearing loss	7 (9.2)	7 (9.6)
CrCL <60 and ≥30mL/min[1] and ECOG PS of 2	4 (5.3)	1 (1.4)
Patient considered cisplatin-ineligible by the investigator although not meeting Galsky criteria[2]	0	1 (1.4)

CrCL: Creatinine Clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Mono: Monotherapy
[1]Estimated creatinine clearance per Cockcroft-Gault formula or 24-hr urine collection or MDRD equation.
[2]One patient in the EV Mono arm was considered cisplatin-ineligible by the investigator due to age and Grade 1 hearing loss.

Key Demographic and Baseline Disease Characteristics

Representative of the 1L cisplatin-ineligible la/mUC population

	EV+P (N=76)	EV Mono (N=73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Age (yrs), median (range)	71 (51, 91)	74 (56, 89)
White race, n (%)	61 (80.3)	55 (75.3)
ECOG PS, n (%)		
0	33 (43.4)	28 (38.4)
1	33 (43.4)	35 (47.9)
2	10 (13.2)	10 (13.7)
Primary tumor location, n (%)		
Lower tract	46 (60.5)	51 (69.9)
Upper tract	30 (39.5)	21 (28.8)

	EV+P (N=76)	EV Mono (N=73)
Metastasis disease sites, n (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, n (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[1]	2 (2.6)	1 (1.4)
PD-L1 status by combined positive score,[2] n (%)		
CPS<10	44 (57.9)	38 (52.1)
CPS≥10	31 (40.8)	28 (38.4)
Not Evaluable	1 (1.3)	7 (9.6)

CPS: Combined Positive Score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Mono: monotherapy; PD-L1: Programmed death-ligand 1

[1]Patients had locally advanced disease without metastasis to lymph nodes or distant organs.

[2]PD-L1 tested using the PD-L1 IHC 22C3 pharmDx assay from Agilent

Summary of Disposition

Disease progression was the main reason for treatment discontinuation

	EV+P (N=77)	EV Mono (N=74)
Patients on treatment, n (%)	25 (32.5)	8 (10.8)
Patients off treatment, n (%)	51 (66.2)	65 (87.8)
Reason for treatment discontinuation, n (%)		
Progressive disease	33 (42.9)	40 (54.1)
Adverse event	12 (15.6)	18 (24.3)
Patient decision	4 (5.2)	3 (4.1)
Physician decision	1 (1.3)	3 (4.1)
Other	1 (1.3)	1 (1.4)
Patients off study, n (%)	23 (29.9)	28 (37.8)
Reason for study discontinuation, n (%)		
Patient withdrawal of consent	2 (2.6)	1 (1.4)
Death	20 (26.0)	26 (35.1)
Other	1 (1.3)	1 (1.4)

Overall Response Rate by BICR

EV+P: 64.5% confirmed ORR with rapid responses

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

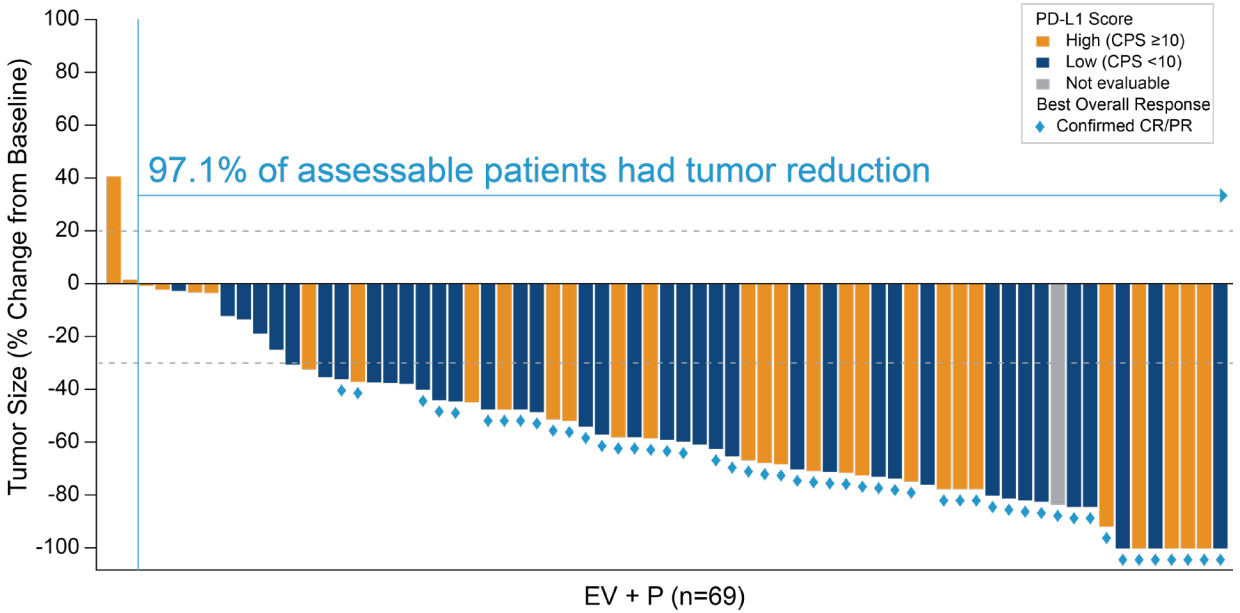
EV+P

- 41/49 (85.7%) of responses observed at first assessment (week 9±1 wk)
- cORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) cORR observed in patients with liver metastases

EV monotherapy

- Activity is consistent with prior results in 2L+ la/mUC

EV+P: Maximum Percent Reduction from Baseline of Target Lesion by BICR

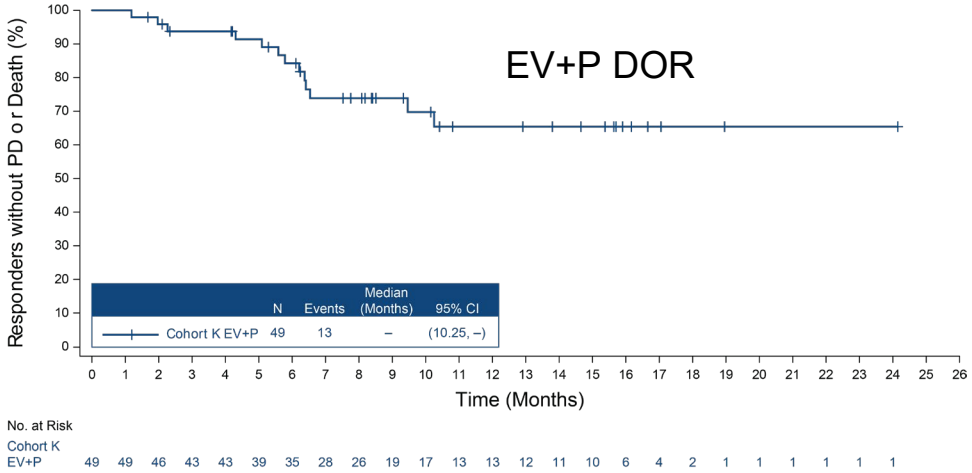


BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

Duration of Response per BICR

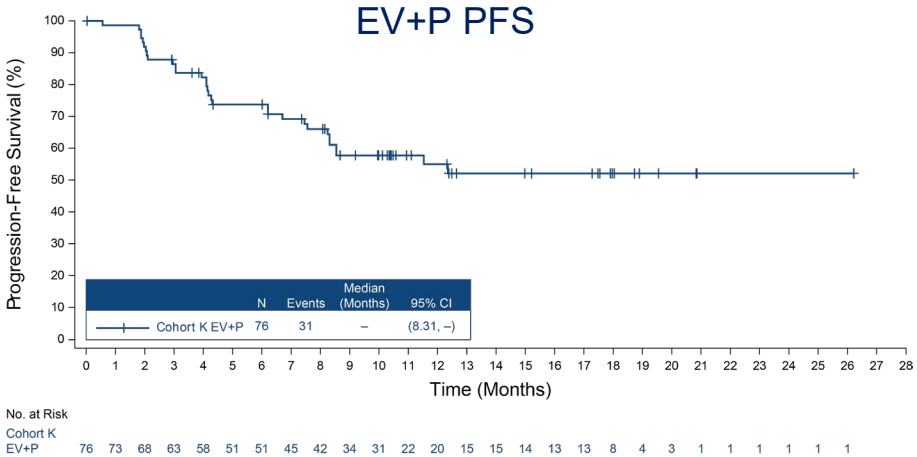
Median DOR for EV+P was not reached; 65.4% of responders were still responding at 12 months

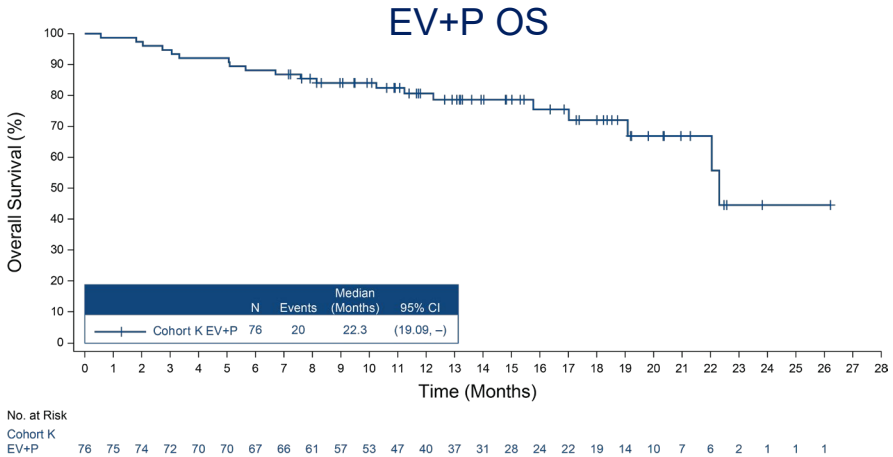


	EV+P (N=76)	EV Mono (N=73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), mos	- (10.25, -)	13.2 (6.14, 15.97)
DOR ≥12 mos, %	65.4%	56.3%

Progression-Free Survival per BICR and Overall Survival

PFS and OS for EV+P with data expected to continue to evolve with follow-up



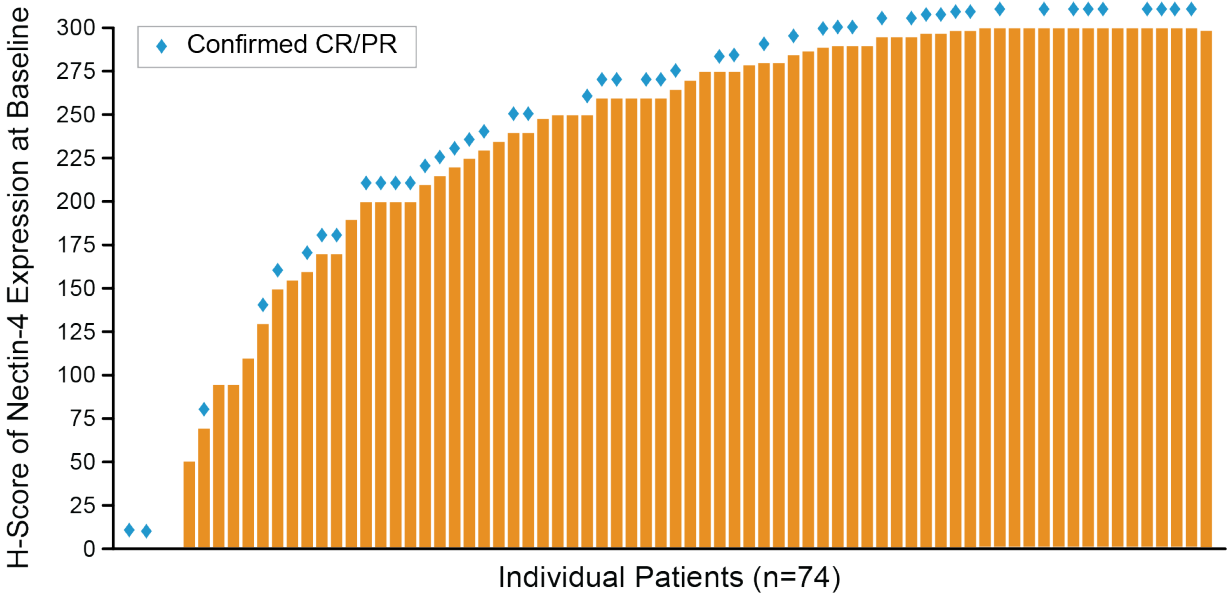


	EV+P (N=76)	EV Mono (N=73)
PFS events, n	31	38
mPFS (95% CI), mos	- (8.31, -)	8.0 (6.05, 10.35)
PFS at 12 mos, %	55.1%	35.8%

	EV+P (N=76)	EV Mono (N=73)
OS Events, n	20	26
mOS (95% CI), mos	22.3 (19.09, -)	21.7 (15.21, -)
OS at 12 mos, %	80.7%	70.7%
Median follow-up time, mos	14.8	15.0

EV+P: Nectin-4 Expression and Best Overall Response

Activity seen regardless of Nectin-4 expression level



- Nectin-4 was detected in tumor tissue from 94.6% of patients who had adequate tissue for testing

Treatment-Related Adverse Events (TRAEs)

Most common AEs with EV+P were fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	**EV+P (N=76) n (%)**		**EV Mono (N=73) n (%)**	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

Serious TRAEs
- 18 (23.7%) EV+P
- 11 (15.1%) EV Mono

TRAEs leading to death (per investigator)
- 3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)
- 2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)

EV Treatment-Related Adverse Events of Special Interest*

The majority of treatment-related AESIs were grade ≤2

	EV+P (N=76)		EV Mono (N=73)	
	Any Grade n (%)	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	18 (23.7)	0	9 (12.3)	0
Blurred vision	9 (11.8)	0	10 (13.7)	0
Corneal disorders	0	0	4 (5.5)	0
Hyperglycemia	11 (14.5)	5 (6.6)	8 (11.0)	7 (9.6)
Infusion-related reactions	3 (3.9)	0	4 (5.5)	0

- Skin reactions were observed more frequently with EV+P
  - No serious skin reactions occurred
- Peripheral neuropathy remain the most common reason for treatment-related discontinuations

*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and pembro TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and pembro monotherapies, respectively

Pembrolizumab Treatment-Emergent Adverse Events of Special Interest*

	EV+P (N=76)	
	Any Grade n (%)	Grade ≥3 n (%)
Severe skin reactions	21 (27.6)	15 (19.7)
Hypothyroidism	10 (13.2)	0
Pneumonitis	7 (9.2)	4 (5.3)
Adrenal insufficiency	3 (3.9)	0
Colitis	3 (3.9)	1 (1.3)
Hyperthyroidism	3 (3.9)	0
Infusion reactions	3 (3.9)	0
Hepatitis	2 (2.6)	2 (2.6)
Myasthenic syndrome	2 (2.6)	2 (2.6)
Myositis	2 (2.6)	0
Pancreatitis	2 (2.6)	1 (1.3)
Hypophysitis	1 (1.3)	0
Myocarditis	1 (1.3)	0
Nephritis	1 (1.3)	1 (1.3)
Thyroiditis	1 (1.3)	0

- Pembrolizumab TEAEs were consistent with previously observed results with pembrolizumab monotherapy, except for severe skin reactions, which were reported with a higher incidence in this study.

*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and pembro TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and pembro monotherapies, respectively

Summary and Conclusions

- In this patient population with a high unmet need, EV+P showed encouraging activity in 1L cisplatin-ineligible patients with la/mUC in EV-103
  - high ORR by BICR (64.5%) and rapid responses; median DOR not reached
  - promising PFS and OS expected to continue to evolve
  - safety profile for EV+P was manageable, including skin reactions and peripheral neuropathy
  - no new safety concerns emerged
- EV+P results were consistent with those previously reported in Dose Escalation/Cohort A[5]
- EV monotherapy results were generally consistent with prior results in 2L+ la/mUC[1-4]
- EV+P is being further investigated in three ongoing phase 3 trials in 1L la/mUC (EV-302) and MIBC (KN-B15 and KN-905)
- EV+P combination has the potential to become a 1L therapeutic option for cisplatin-ineligible patients with la/mUC

1.Powles T, et al. N Engl J Med 2021;384:1125-35; 2. Yu EY, et al. Lancet Oncol 2021;22:872-82; 3. Balar AV, et al. Lancet Oncol 2017;18:1483-92; 4. Fradet Y, et al. Ann Oncol 2019;30:970-6; 5. Hoimes CJ, et al. JCO 2022 (In press)

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