EV-302/KEYNOTE-A39: Open-Label, Randomized Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab vs Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

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Background

- There are approximately 200,000 deaths worldwide from advanced urothelial carcinoma annually[1]; prognosis is poor with low 5-year survival rates[2]
- Platinum-based chemotherapy has been the standard 1L treatment for la/mUC for decades
  - While avelumab is approved as maintenance therapy in a subset of patients whose disease has not progressed following 1L platinum-based chemotherapy, high unmet need remains[3-6]
  - Two previously published trials of chemotherapy in combination with PD-1/PD-L1 inhibitors have failed to improve survival in la/mUC[7,8]
- Enfortumab vedotin, a Nectin-4 directed antibody-drug conjugate, and pembrolizumab, a PD-1 inhibitor (EV+P), have individually demonstrated a survival benefit in previously treated la/mUC[9-11]
- The combination was granted accelerated approval in the US by the FDA for the treatment of patients with la/mUC who are ineligible for cisplatin[13]
- In EV-302/KEYNOTE-A39 (NCT04223856) EV+P was compared with chemotherapy in patients with previously untreated la/mUC regardless of cisplatin eligibility and PD-L1 expression status

1L, first-line treatment; **EV+P**, enfortumab vedotin + pembrolizumab; **FDA**, Food and Drug Administration; **la/mUC**, locally advanced or metastatic urothelial carcinoma; **PD-1**, programmed cell death protein 1; **PD-L1**, programmed death-ligand 1.

1. Bray F. CA Cancer J Clin 2018;68:394-424. **2.** SEER Cancer Stat Facts: Bladder Cancer. Bethesda, MD: National Cancer Institute; 2021. **3.** Flaig TW. J Natl Compr Canc Netw 2020;18:329-54.**4.** Bloudek L. Current Oncology 2023;30:3637-47.**5.** Witjes JA. Eur Urol 2020;77:223-50.**6.** Powles TB. Ann Oncol 2020;31:S552-3 **7.** Powles T. Lancet Oncol 2021;22(7):931-45. **8.** Galsky MD. Lancet. 2020;395(10236):1547-57. **9.** O'Donnell PH. J Clin Oncol 2021;39;Abstract 4508. **10.** Powles T. N Engl J Med 2021;384:1125-35. **11.** Rosenberg JE. J Clin Oncol 2019;37:2592-600. **12.** Yu EY. Lancet Oncol 2021;22:872-82.**13.** PADCEV [package insert]. Northbrook, IL: Astellas US Pharma, Inc. Accessed Sep 25,2023.
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EV-302/KEYNOTE-A39 (NCT04223856)

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30[a]
- ECOG PS ≤2[b]

N=886

R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Dual primary endpoints:

- **PFS by BICR**
- **OS**

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; 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

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **EV**, enfortumab vedotin; **FPI,** first person initiated into trial; **GFR**, glomerular filtration rate; **LPI**, last person initiated into trial; **IV**, intravenous; **la/mUC,** locally advanced or metastatic urothelial carcinoma; **ORR**, overall response rate; **OS**, overall survival; **P**, pembrolizumab; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors.

[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine.

[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure.

[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023
FPI: 7 Apr 2020
LPI: 09 Nov 2022

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Key Demographic and Baseline Disease Characteristics

Balanced between treatment arms and representative of 1L la/mUC population

	EV+P (N=442)	Chemotherapy (N=444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Age (years), median (range)	69.0 (37,87)	69.0 (22,91)
Race, n (%)		
White	308 (69.7)	290 (65.3)
Asian	99 (22.4)	92 (20.7)
Geographic location, n (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of World	167 (37.8)	162 (36.5)
ECOG PS, n (%)		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)

	EV+P (N=442)	Chemotherapy (N=444)
Cisplatin eligible[a], n (%)	240 (54.3)	242 (54.5)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Lymph node only disease	103 (23.3)	104 (23.4)
PD-L1 expression[b], n/N (%)		
High (CPS ≥ 10)	254/438 (58.0)	254/439 (57.9)
Low (CPS < 10)	184/438 (42.0)	185/439 (42.1)

1L, first-line treatment; **CPS**, combined positive score; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EV+P**, enfortumab vedotin + pembrolizumab; **FPI,** first person initiated into trial; **IHC**, immunohistochemistry; **la/mUC**, locally advanced or metastatic urothelial carcinoma; **LPI**, last person initiated into trial; PD-L1, programmed death-ligand 1.

[a]Represents eligibility at time of randomization.

[b]CPS status was determined using the validated PD-L1 IHC 22C3 pharmDx assay at Neogenomics and Labcorp; 4 patients in the EV+P arm and 5 patients in the chemotherapy arm had samples that were of inadequate tissue quality for analysis.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

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Summary of Disposition

33% of patients in EV+P arm remain on treatment at time of analysis

	EV+P (N=442)	Chemotherapy (N=444)
Patients randomized, n (%)	442 (100)	444 (100)
Patients who received any amount of study drug, n (%)	440 (99.5)	433 (97.5)
Patients on treatment	144 (32.6)	0
Patients on study, n (%)	296 (67.0)	203 (45.7)
Primary reason for study treatment discontinuation[a], n (%)		
Completed treatment	8 (1.8)[b]	244 (55.0)
Progressive disease	153 (34.6)	73 (16.4)
Adverse event	97 (21.9)	62 (14.0)
Physician/Patient decision	31 (7.0)	52 (11.7)
Other[c]	7 (1.6)	2 (0.5)

EV, enfortumab vedotin; **EV+P**, enfortumab vedotin + pembrolizumab; **FPI,** first person initiated into trial; **LPI**, last person initiated into trial; **P**, pembrolizumab.
[a]Patients in EV+P arm received EV until disease progression or toxicity (per protocol, there was no maximum number of EV cycles) or completion of maximum cycles (35 cycles for P); chemotherapy could be given for a maximum of 6 cycles.
[b]Patients completed 35 cycles of P and had discontinued EV prior to P.
[c]7 patients on EV+P: Death (n=3), Grade 3 Asthenia outside of protocol reporting period (n=1), Lost to follow-up (n=1), Chronic Lymphatic Leukemia (n=1), general deterioration (n=1); 2 patients on Chemotherapy: Respiratory failure (n=1), Patient insurance would not cover chemotherapy treatment on clinical trial (n=1).
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

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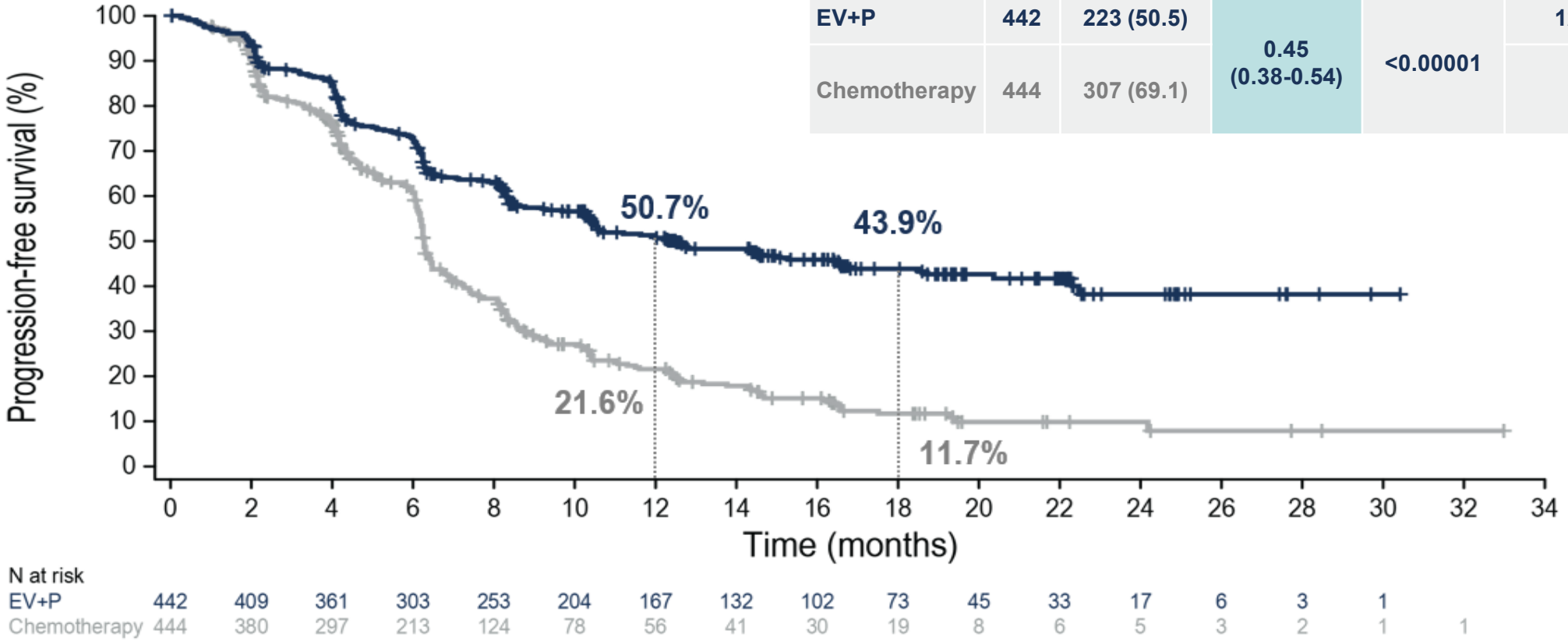
Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



BICR, blinded independent central review; **CI**, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mPFS**, median progression-free survival. mPFS at 12 and 18 months as estimated using Kaplan-Meier method.

[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.

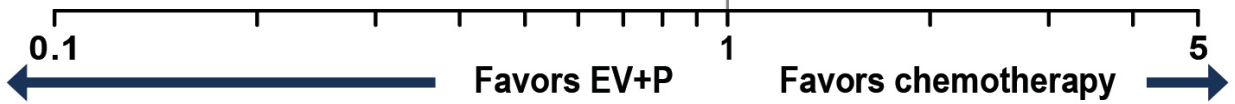
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

Subgroup Analysis of PFS per BICR

PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



BICR, blinded independent central review; **CPS**, Combined Positive Score; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EV+P**, enfortumab vedotin + pembrolizumab; **la/mUC**, locally advanced or metastatic urothelial carcinoma; **PD-L1**, Programmed death-ligand 1; **PFS**, progression-free survival.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

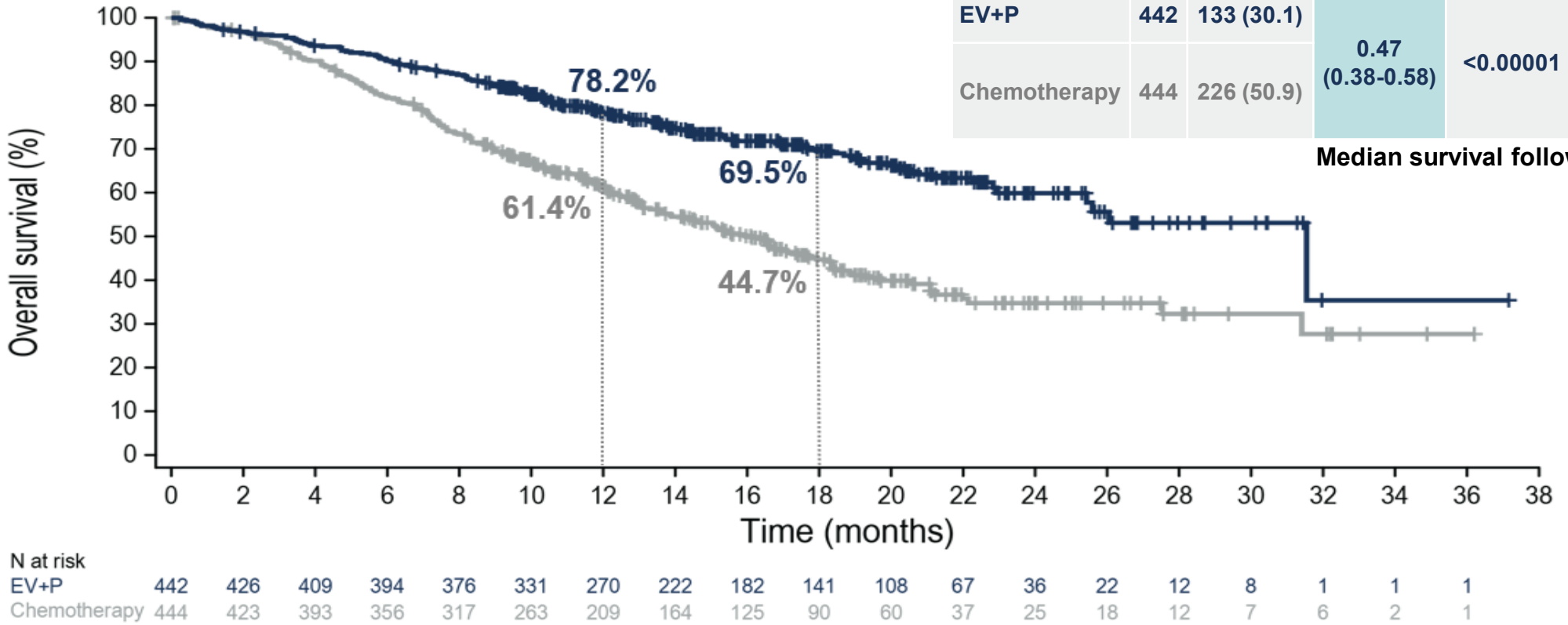
Data cutoff: 08 Aug 2023

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



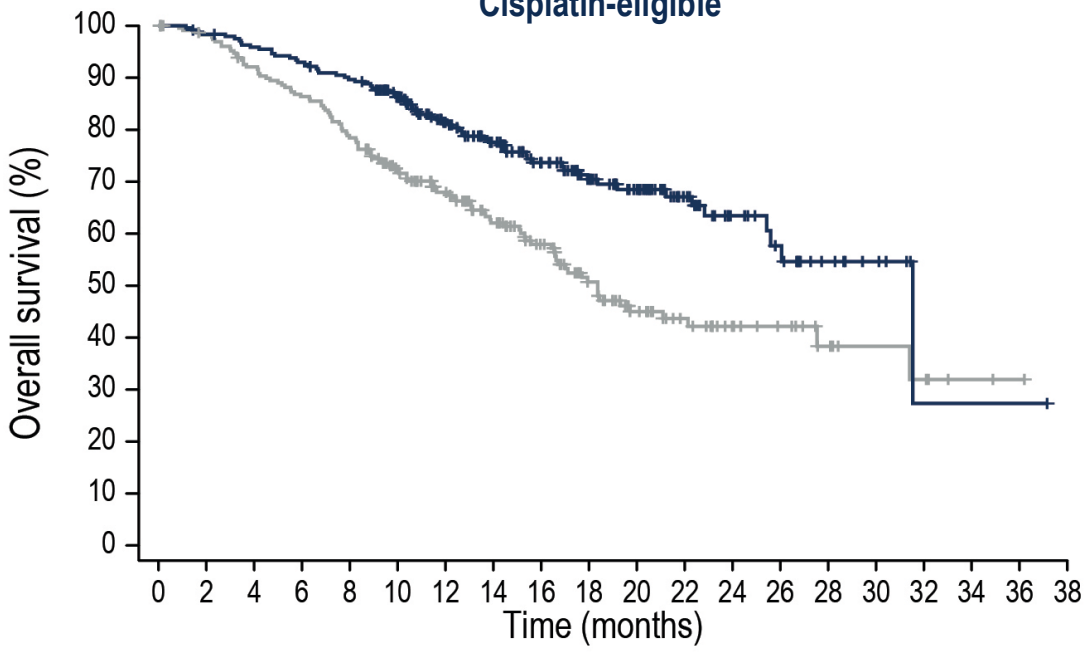
CI, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mOS**, median overall survival; **NR**, not reached; **OS**, overall survival.
OS at 12 and 18 months as estimated using Kaplan-Meier method.
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility

Cisplatin-eligible

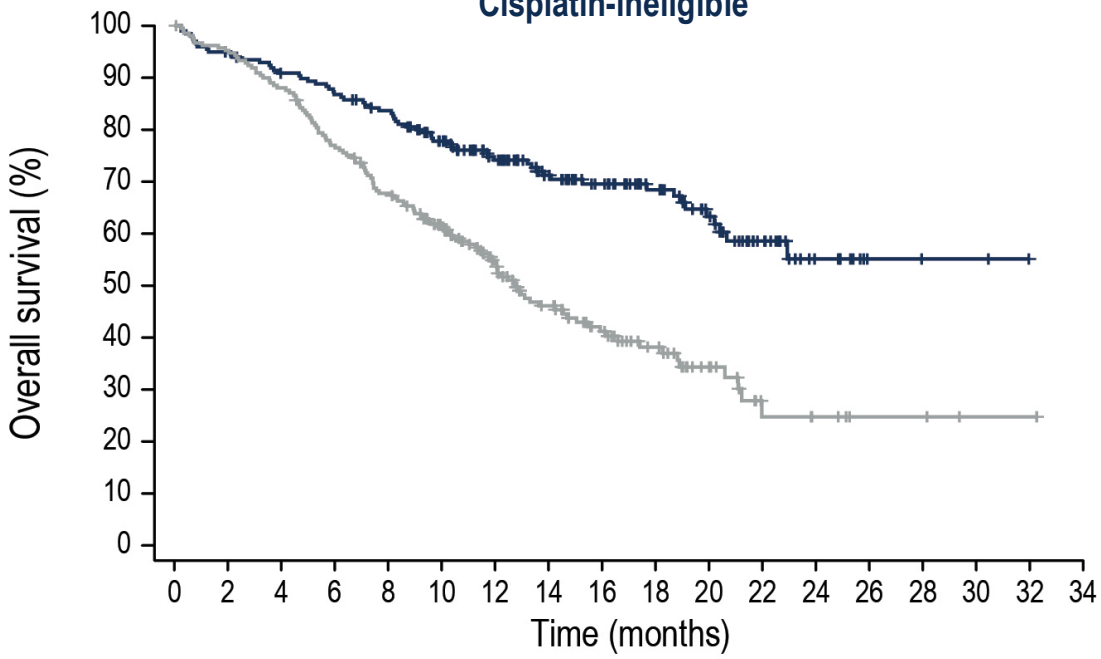


N at risk

EV+P	244	239	232	225	216	193	155	131	105	80	64	42	25	19	10	6	1	1	1
Chemotherapy	234	224	209	196	178	147	123	101	79	57	40	29	19	15	9	6	5	2	1

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)

Cisplatin-ineligible



N at risk

EV+P	198	187	177	169	160	138	115	91	77	61	44	25	11	3	2	2	
Chemotherapy	210	199	184	160	139	116	86	63	46	33	20	8	6	3	3	1	1

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

CI, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mOS**, median overall survival; **OS**, overall survival.

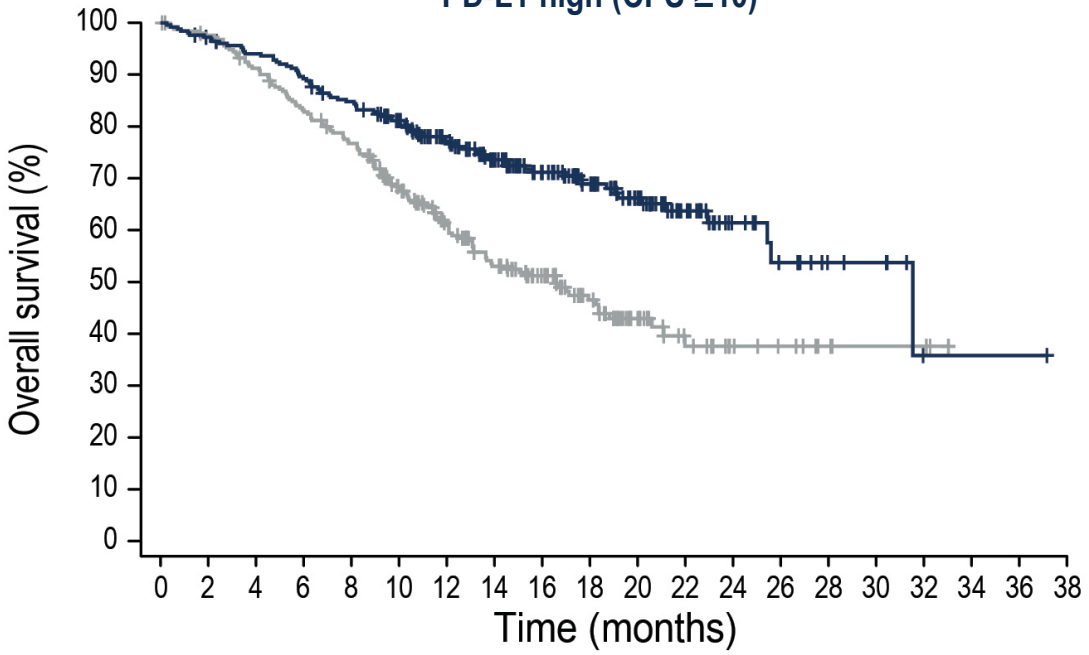
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status

PD-L1 high (CPS ≥10)

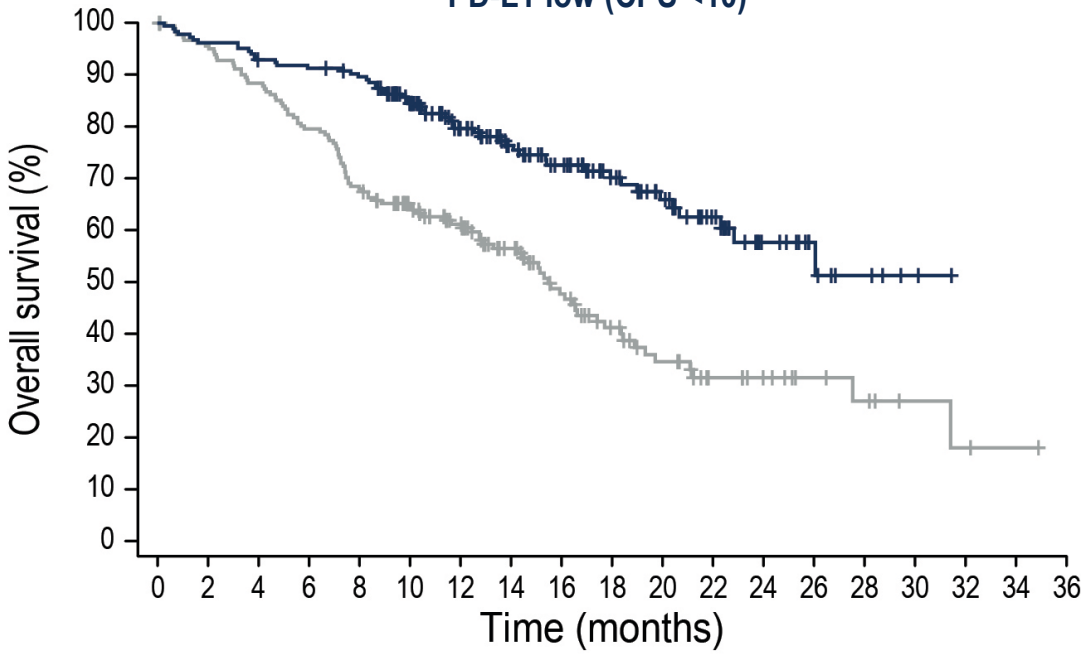


N at risk

EV+P	254	245	235	223	210	189	162	136	111	87	65	37	20	13	7	6	1	1	1
Chemotherapy	254	245	228	207	189	155	122	97	76	54	33	19	12	9	5	3	3		

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)

PD-L1 low (CPS <10)



N at risk

EV+P	184	177	170	167	162	139	106	86	71	54	43	30	16	9	5	2		
Chemotherapy	185	173	160	144	123	103	84	65	47	34	25	16	12	8	6	3	2	1

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

CI, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mOS**, median overall survival; **OS**, overall survival; **PD-L1**, Programmed death-ligand 1.

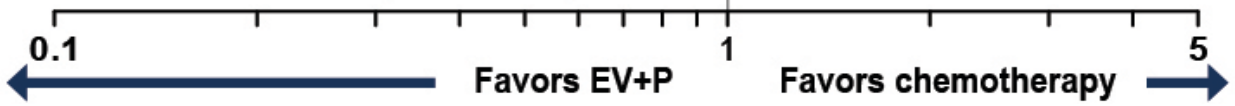
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



CPS, Combined Positive Score; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **EV+P**, enfortumab vedotin + pembrolizumab; **OS**, overall survival; **PD-L1**, Programmed death-ligand 1.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

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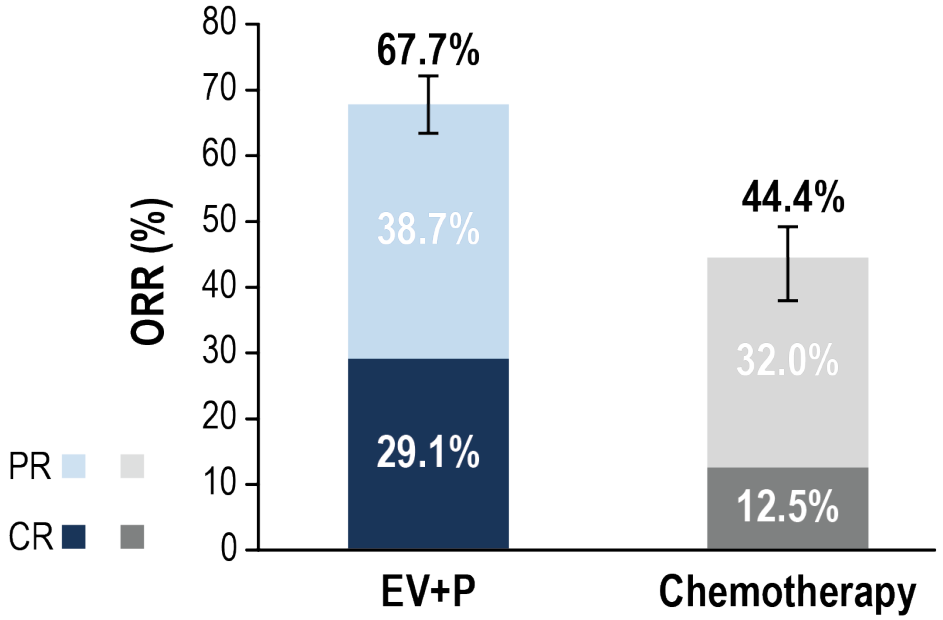
Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

BICR, blinded independent central review; **CI**, confidence interval; **CR**, complete response; **DOR**, duration of response; **EV+P**, enfortumab vedotin + pembrolizumab; **NR**, not reached; **ORR**, overall response rate; **PR**, partial response.

[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response.

[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

Summary of Subsequent Systemic Therapy

59% of patients in chemotherapy arm received subsequent PD-1/L1 inhibitors

	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28.9)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy	0	143 (32.2)
Avelumab maintenance	0	135 (30.4)
PD-1/L1 inhibitor-containing therapy following progression	7 (1.6)	117 (26.4)
Other	11 (2.5)	17 (3.8)

[a]144 (32.6%) patients in the EV+P arm remain on treatment at time of analysis.

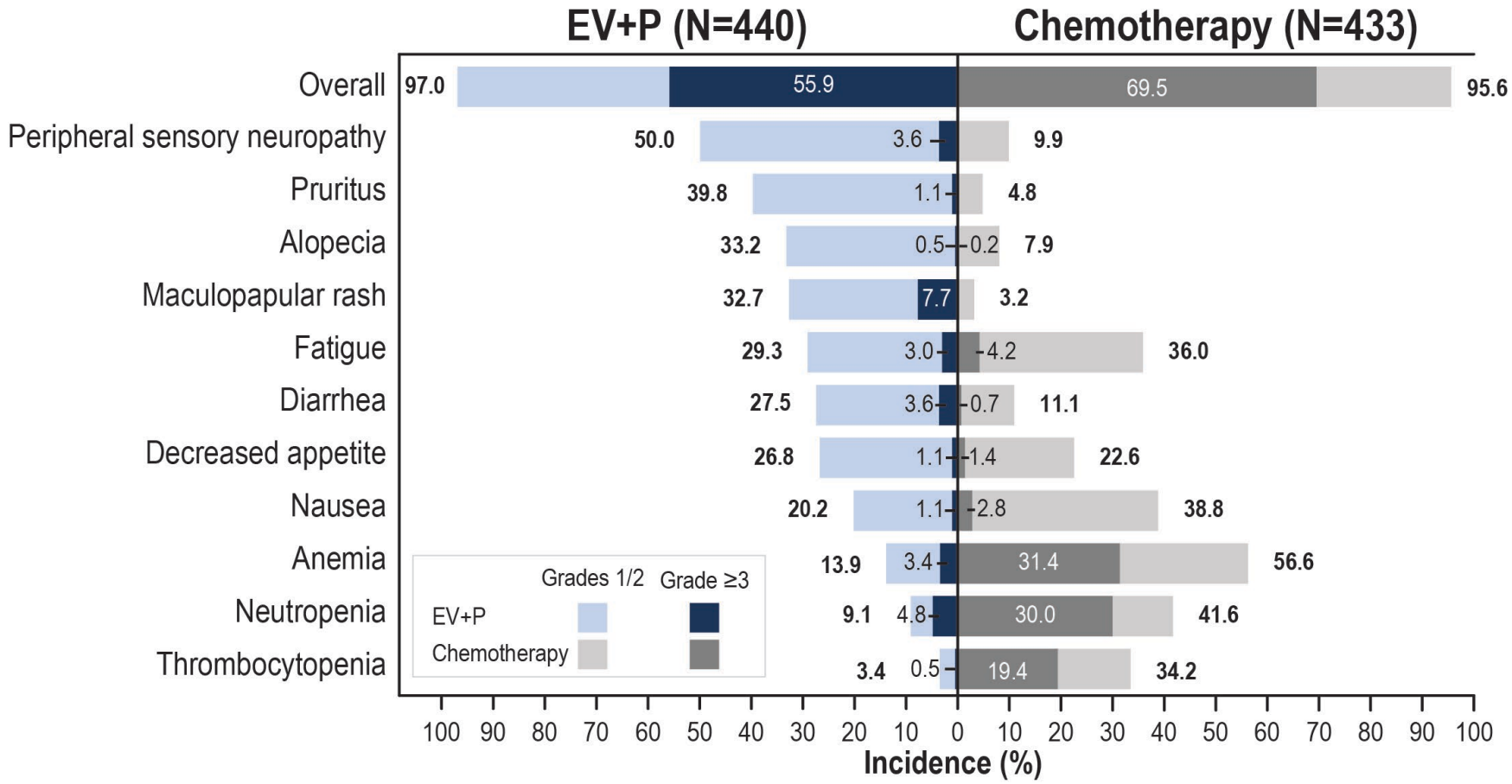
EV+P, enfortumab vedotin + pembrolizumab; **PD-1**, programmed cell death protein 1; **PD-L1**, programmed death-ligand 1.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

EV+P, enfortumab vedotin + pembrolizumab; **TRAEs,** treatment-related adverse events.
TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

AESI, adverse event of special interest; **EV**, enfortumab vedotin; **EV+P**, enfortumab vedotin + pembrolizumab; **P**, pembrolizumab; **TRAEs,** treatment-related adverse events.
*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively.
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Pembrolizumab Treatment-Emergent Adverse Events of Special Interest*

AEOSIs any grades by preferred term in ≥1% of patients	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Severe skin reactions	75 (17.0)	52 (11.8)	2 (0.5)	0
Hypothyroidism	47 (10.7)	2 (0.5)	3 (0.7)	0
Pneumonitis	42 (9.5)	16 (3.6)	1 (0.2)	1 (0.2)
Hyperthyroidism	20 (4.5)	1 (0.2)	2 (0.5)	0
Hepatitis	14 (3.2)	8 (1.8)	2(0.5)	0
Colitis	12 (2.7)	7 (1.6)	0	0
Gastritis	9 (2.0)	0	3 (0.7)	0
Adrenal insufficiency	7 (1.6)	2 (0.5)	0	0
Infusion reactions	6 (1.4)	0	6 (1.4)	1 (0.2)
Pancreatitis	5 (1.1)	4 (0.9)	1 (0.2)	1 (0.2)

AEOSI, adverse event of special interest; **AESI**, adverse event of special interest; **EV**, enfortumab vedotin; **P**, pembrolizumab; **TEAE**, treatment-emergent adverse event.
*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively.
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Authors' Summary & Conclusions

- EV-302/KEYNOTE-A39 is the first time that platinum-based chemotherapy has been surpassed in OS in patients with previously untreated la/mUC
- EV+P showed statistically significant and clinically meaningful improvement in efficacy over chemotherapy
  - PFS HR: 0.45; OS HR: 0.47
  - mPFS and mOS were nearly doubled in the EV+P arm compared with chemotherapy
  - Benefit in prespecified subgroups and stratification factors was consistent with the overall population
- The safety profile of EV+P was generally manageable, with no new safety signals observed
- These results support EV+P as a potential new standard of care for 1L la/mUC

1L, first-line treatment; **EV+P**, enfortumab vedotin + pembrolizumab; **la/mUC**; locally advanced, metastatic urothelial cancer; **HR**, hazard ratio; **mOS,** median overall survival**; mPFS,** median progression-free survival**; OS**, overall survival; **PFS**, progression-free survival.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Plain Language Summary

Why was this research needed?

- Platinum-based chemotherapy is the standard first treatment for locally advanced or metastatic urothelial cancer. However, as there is a very low survival rate, there is a strong need to improve survival for these patients.
- Previously, EV+P showed responses that were quick in onset and durable and side effects were generally manageable.
- The EV-302/KEYNOTE-A39 study compared EV+P with chemotherapy in patients who had not received treatment for la/mUC.

What were the results and why are the findings meaningful?

- In patients with la/mUC who had not received prior treatment, EV+P showed statistically significant and clinically meaningful improvement in survival compared with patients who received treatment with chemotherapy, nearly doubling the median overall survival.
- In this larger study, the safety profile of EV+P was generally manageable. There were no new side effects or risks seen from EV+P.
- Results from this study support having EV+P as a potential new standard first treatment for patients with la/mUC.

Where can I find more information?

https://www.clinicaltrials.gov/study/NCT04223856

EV+P, enfortumab vedotin + pembrolizumab; **la/mUC**; locally advanced, metastatic urothelial cancer.

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