Advanced Urothelial Cancer Recent Developments

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Faculty Disclosure

- I have served on advisory boards for, Astellas, Aveo, Bayer, Gilead, Hinova, Janssen, Merck, Pfizer, Seagen, Tavanta

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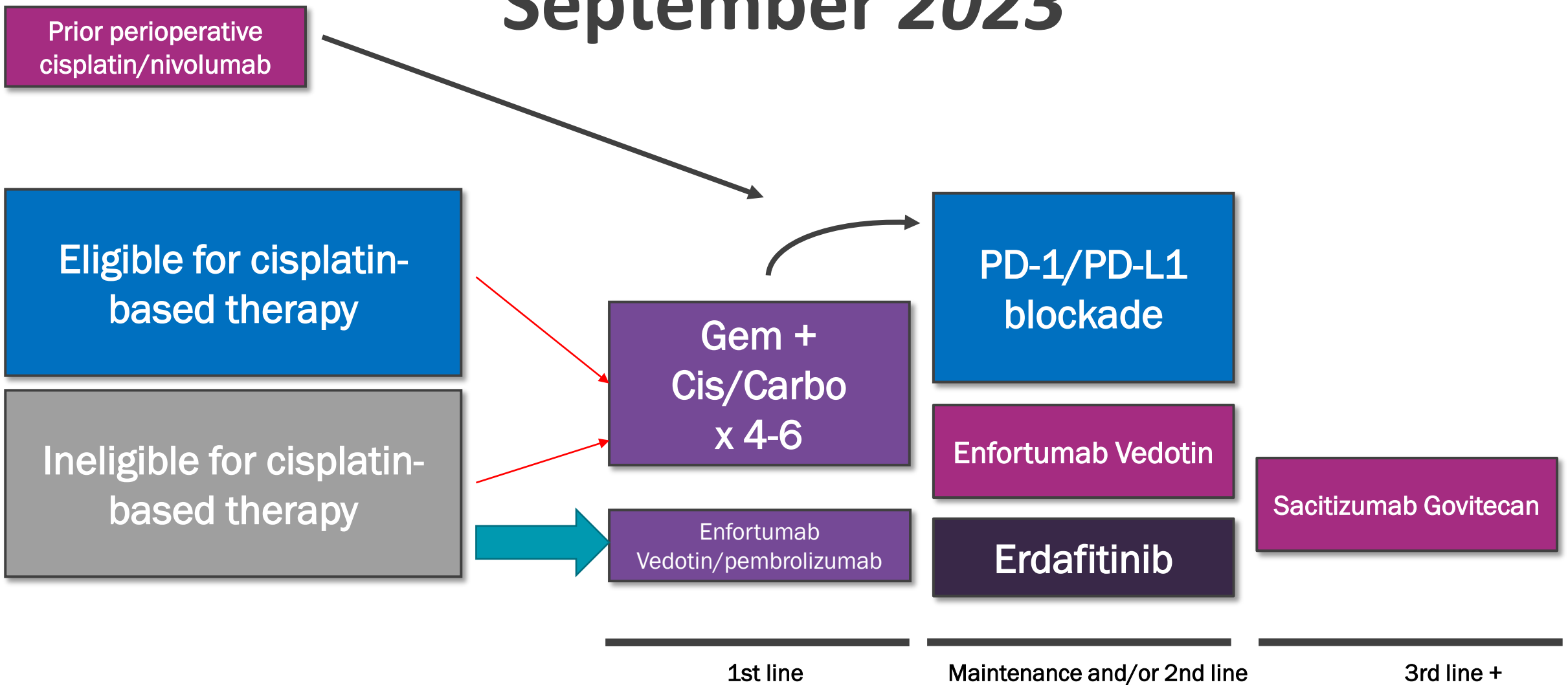
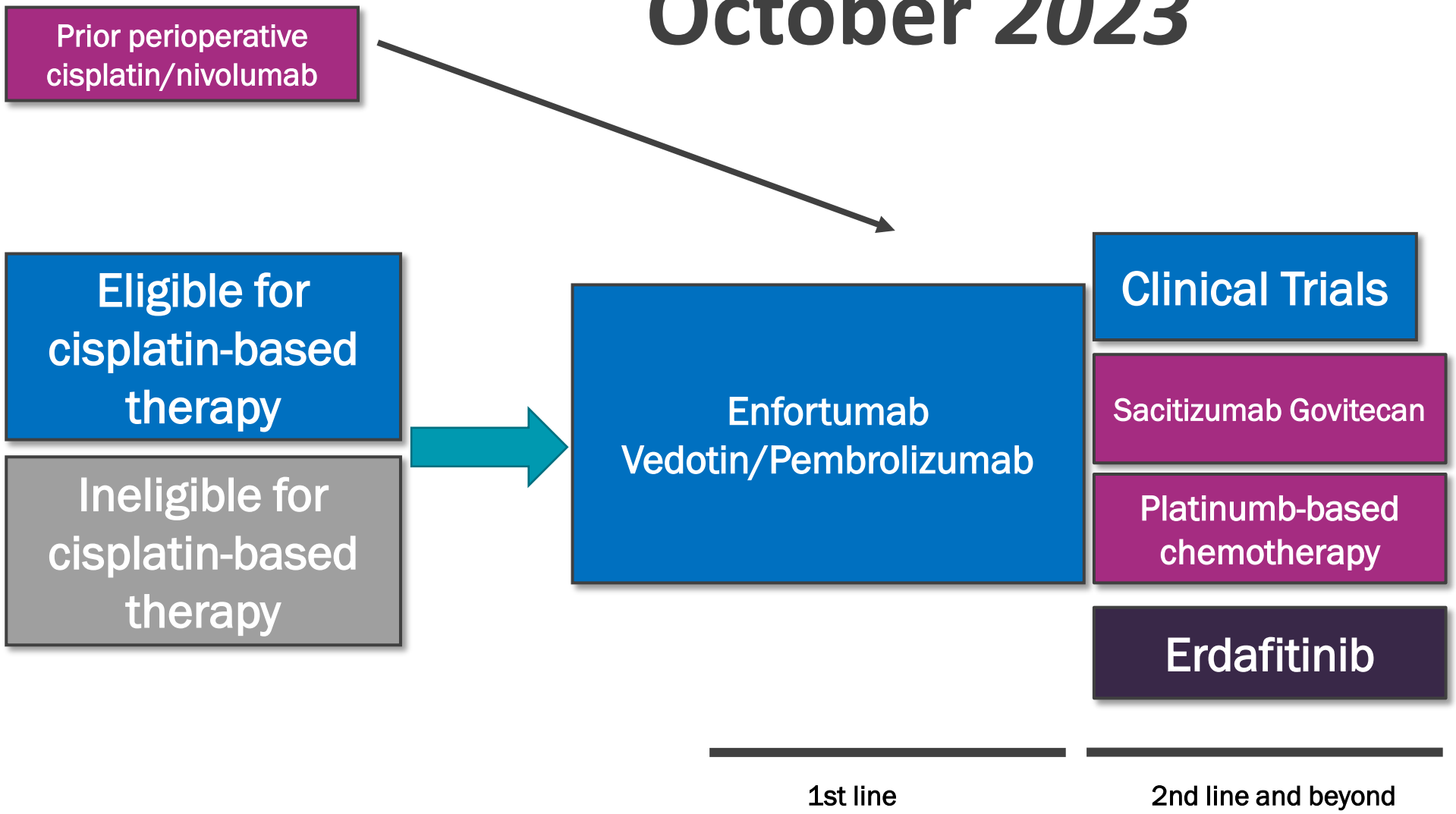
Advanced Urothelial Cancer
September *2023*



Advanced Urothelial Cancer
October *2023*



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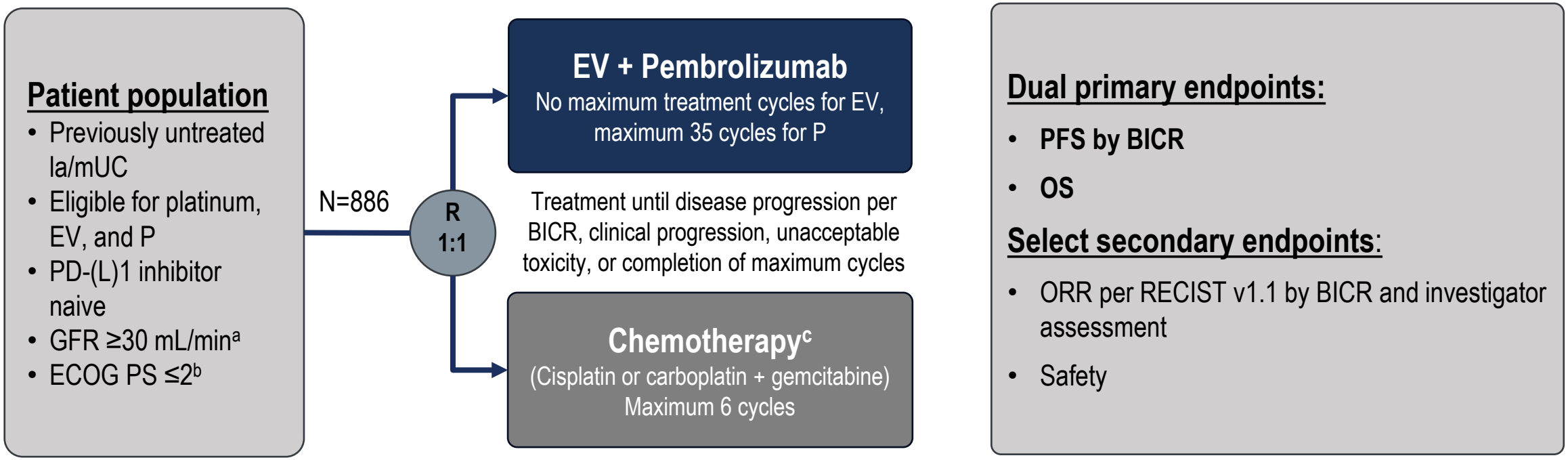
EV-302/KEYNOTE-A39: Open-Label, Randomized Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab vs Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, Begona Perez-Valderrama, Shilpa Gupta, Jens Bedke, Eiji Kikuchi, Jean Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Se Hoon Park, Sang Joon Shin, Daniel Castellano Gauna, Giuseppe Fornarini, Jian-Ri Li, Mahmut Gumus, Nataliya Mar, Sujata Narayanan, Xuesong Yu, Seema Gorla, Blanca Homet Moreno, Michiel Van der Heijden

FPN: LBA6

EV-302/KEYNOTE-A39 (NCT04223856)



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; GFR, glomerular filtration rate; ORR, overall response rate; 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

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

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 (yrs), 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)

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

CPS, combined positive score
[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

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)

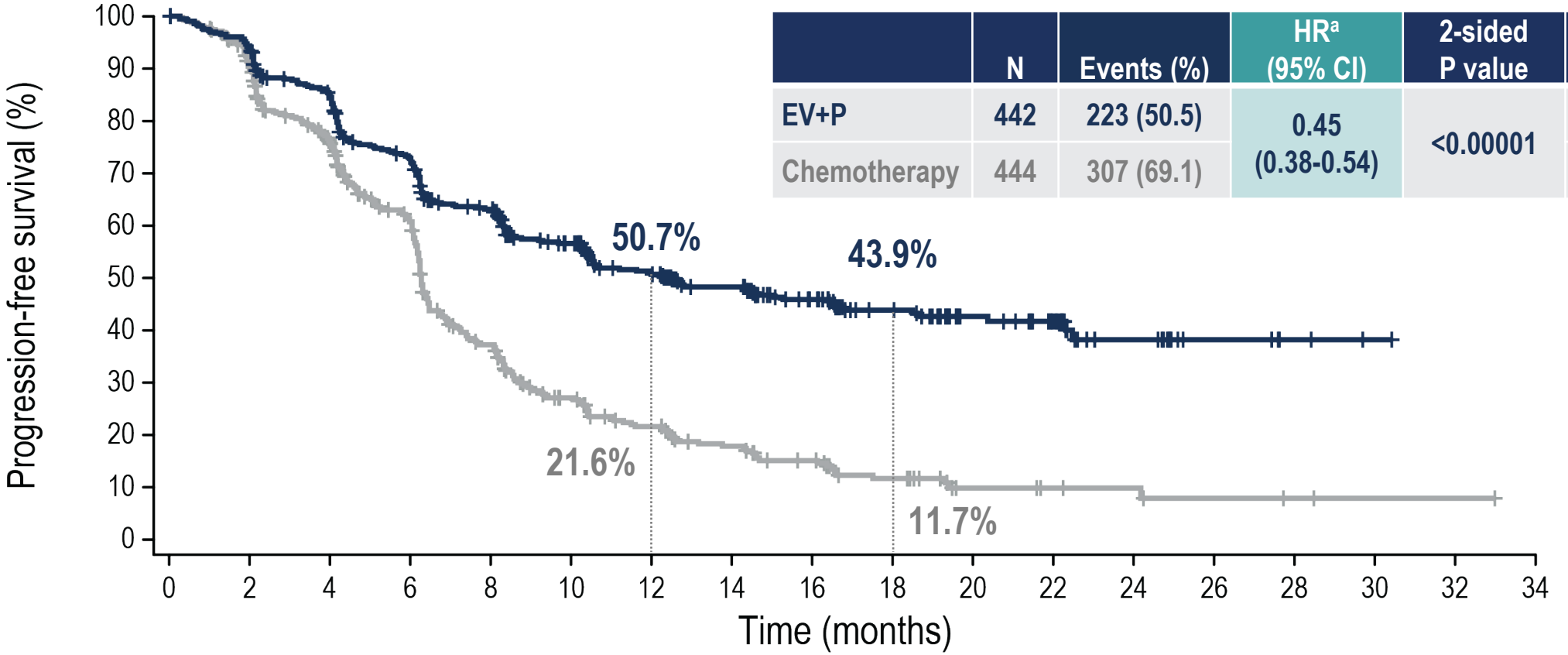
[a]Patients in EV+P arm received EV until disease progression or toxicity (per protocol, there was no maximum number of EV cycles) or completion of maximum cycles (35 cycles for P); chemotherapy could be given for a maximum of 6 cycles
[b]Patients completed 35 cycles of P and had discontinued EV prior to P
[c]7 patients on EV+P: Death (3), Grade 3 Asthenia outside of protocol reporting period (1), Lost to follow-up (1), Chronic Lymphatic Leukemia (1), general deterioration (1); 2 patients on Chemotherapy: Respiratory failure (1), Patient insurance would not cover chemotherapy treatment on clinical trial (1)

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

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)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

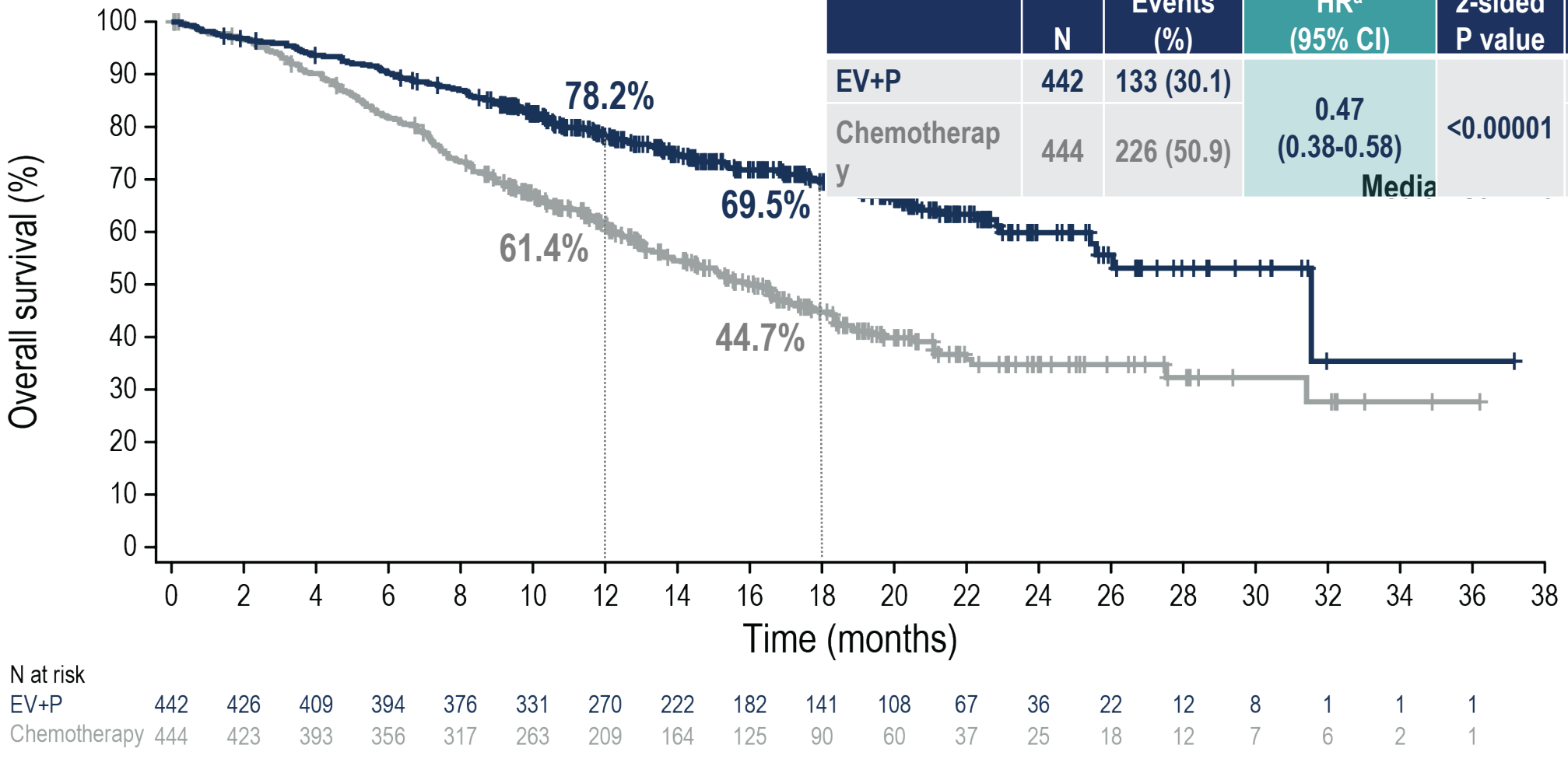
Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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)



N at risk

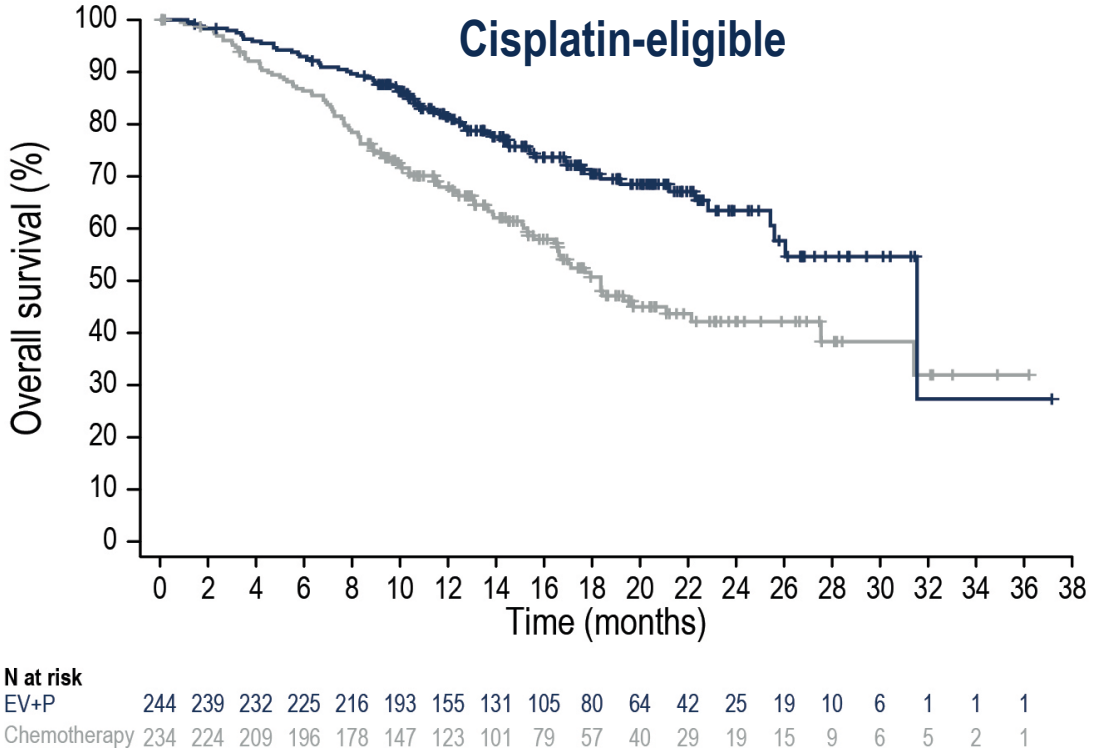
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

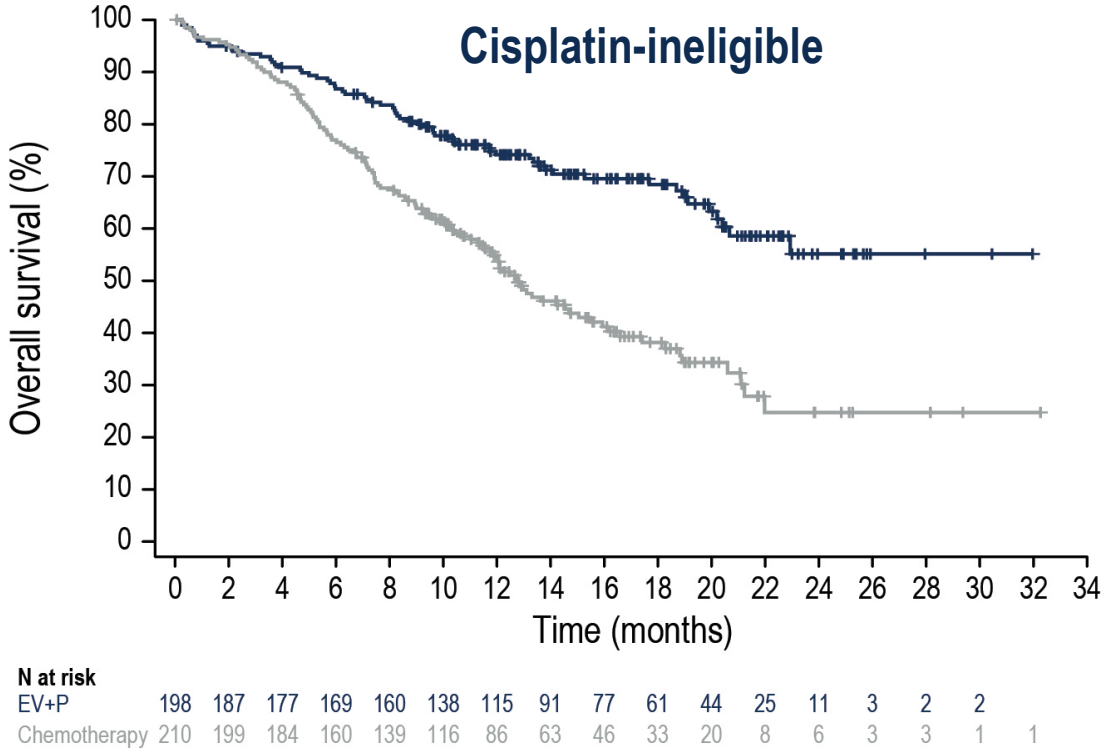
Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility





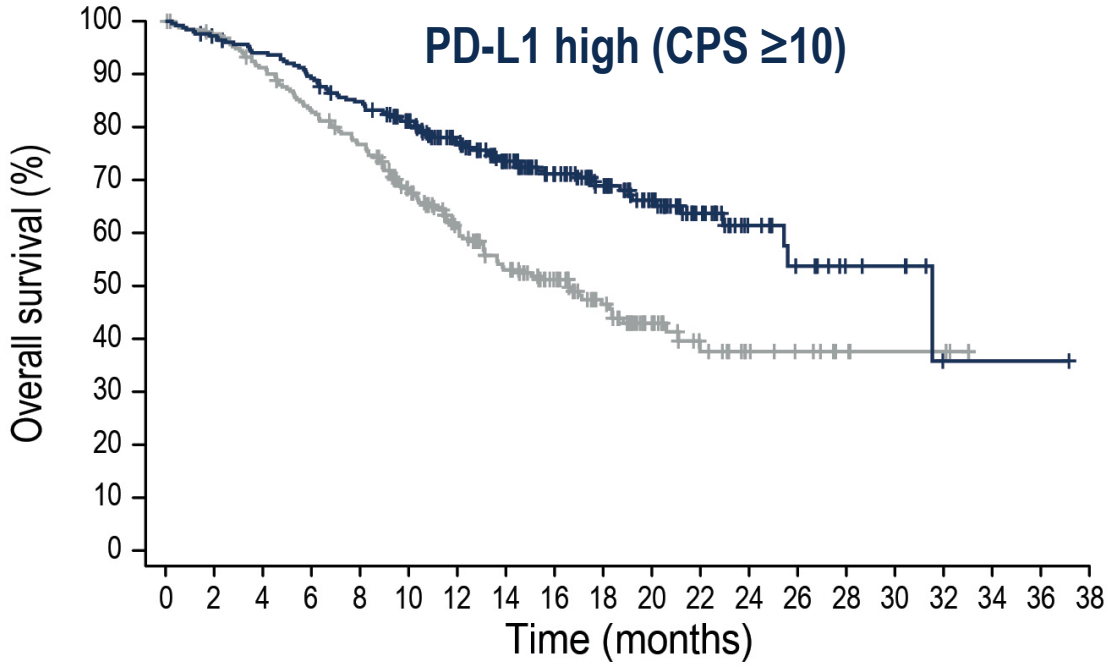
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)

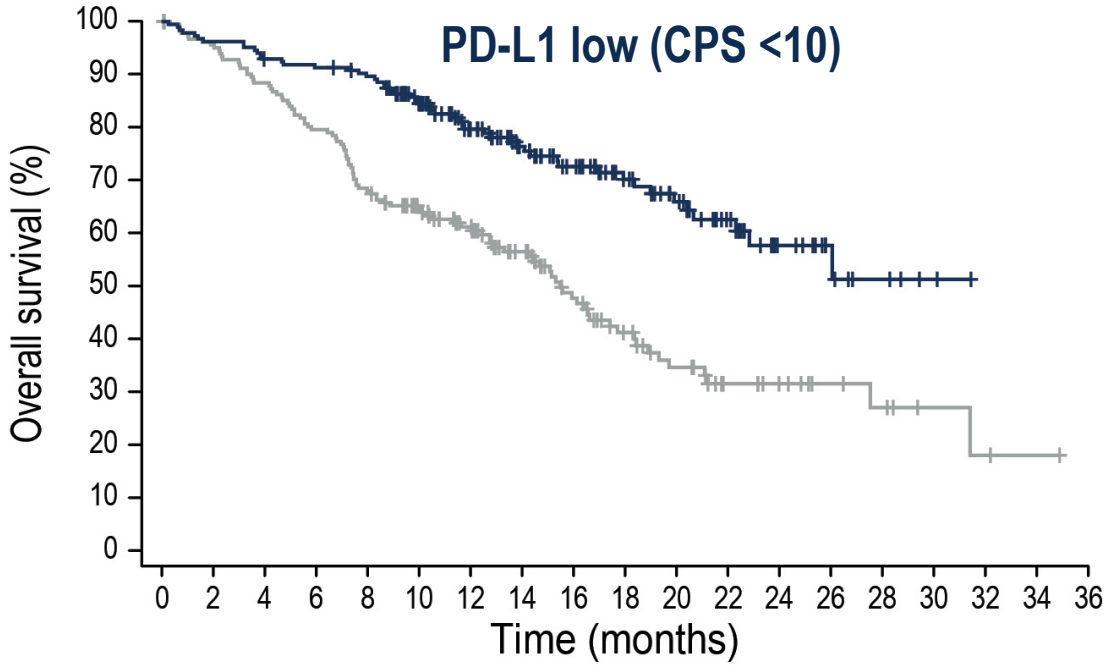
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

Data cutoff: 08 Aug 2023

OS Subgroup Analysis: PD-L1 Expression

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





	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)

	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)

Data cutoff: 08 Aug 2023

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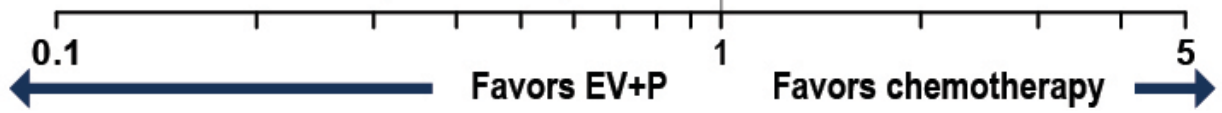
Subgroup Analysis of OS

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)



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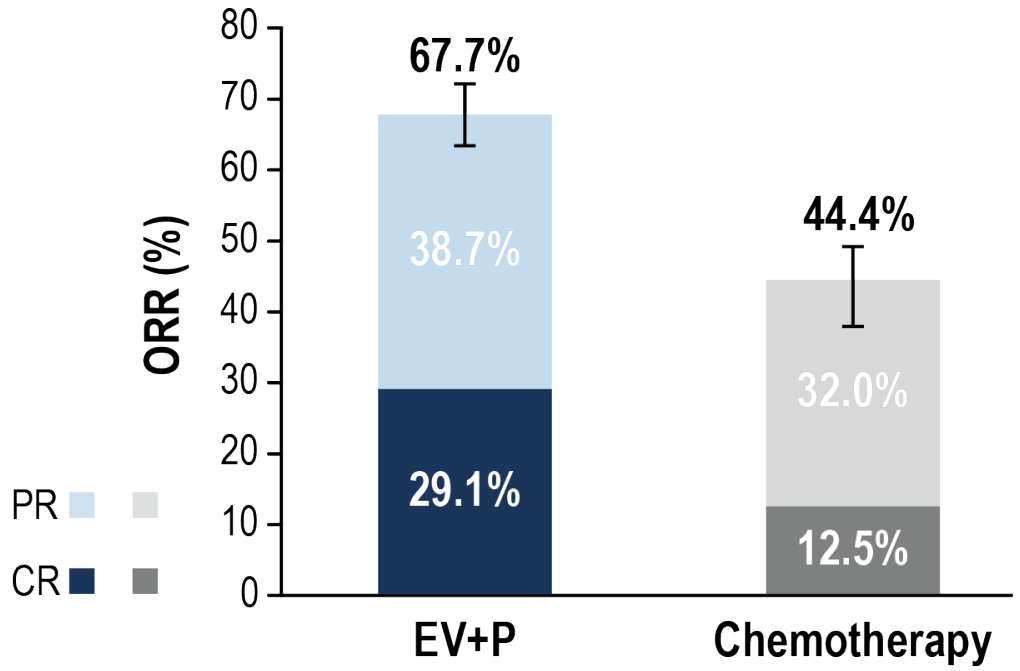
Confirmed Overall Response per BICR

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)

CR, complete response; DOR, duration of response; 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

Data cutoff: 08 Aug 2023

Summary of Subsequent Systemic Therapy

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

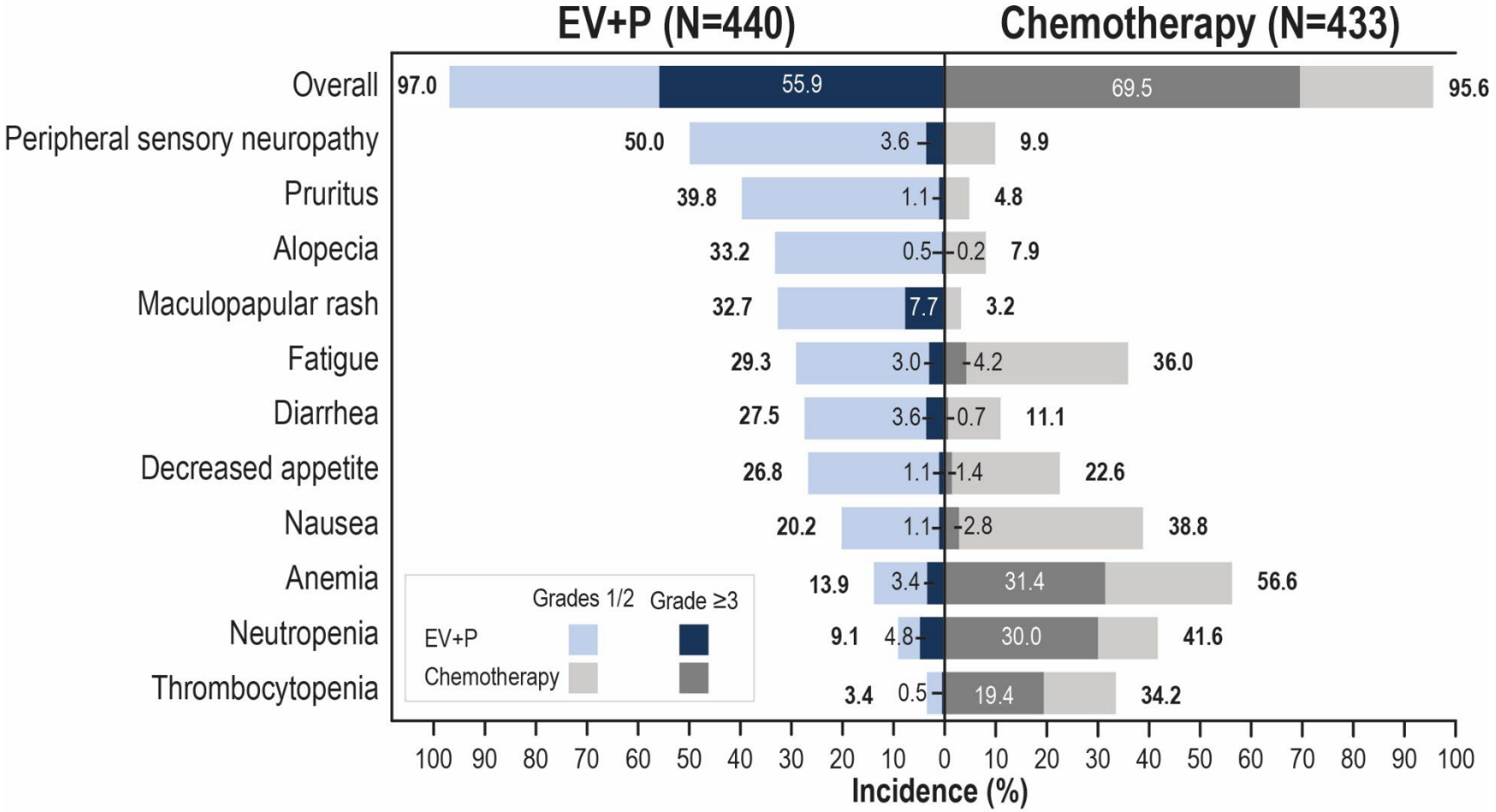
	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28.9)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy	0	143 (32.2)
Avelumab maintenance	0	135 (30.4)
PD-1/L1 inhibitor-containing therapy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

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

Data cutoff: 08 Aug 2023

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TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

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)

Data cutoff: 08 Aug 2023

*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
AESI, adverse event of special interest

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)

Data cutoff: 08 Aug 2023

*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
AEOSI, adverse event of special interest

Summary & Conclusions

- EV-302/KEYNOTE-A39 is the first time that platinum-based chemotherapy has been surpassed in OS in patients with previously untreated Ia/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 Ia/mUC

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Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: results from the phase 3 CheckMate 901 trial

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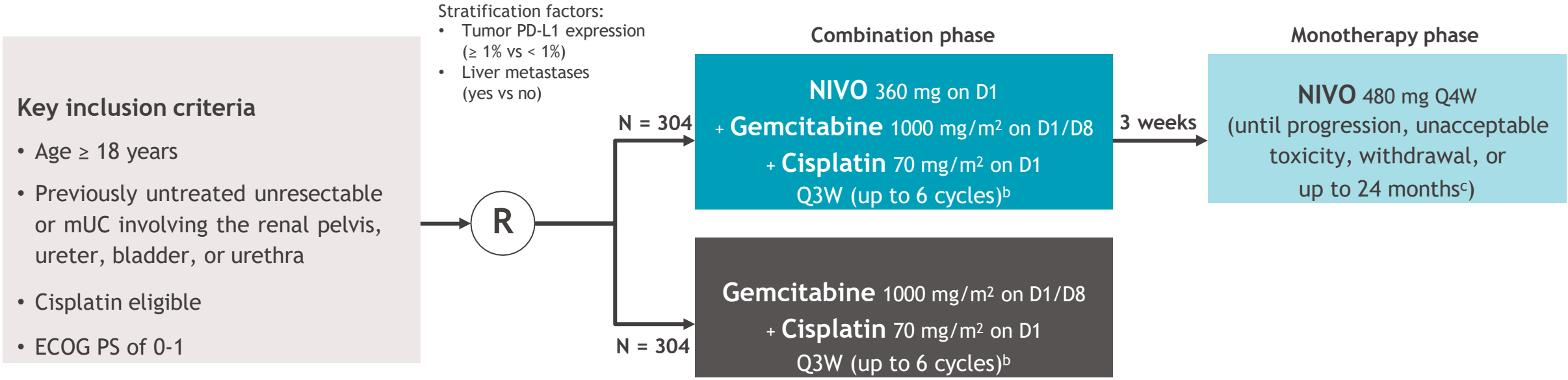
[a]Current affiliation is AdventHealth Cancer Institute and University of Central Florida, Orlando, FL, USA. [b]Current affiliation is IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy. [c]Current affiliation is Klinikum Stuttgart, Katharinenhospital, Stuttgart, Germany.

Presentation number LBA7

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]

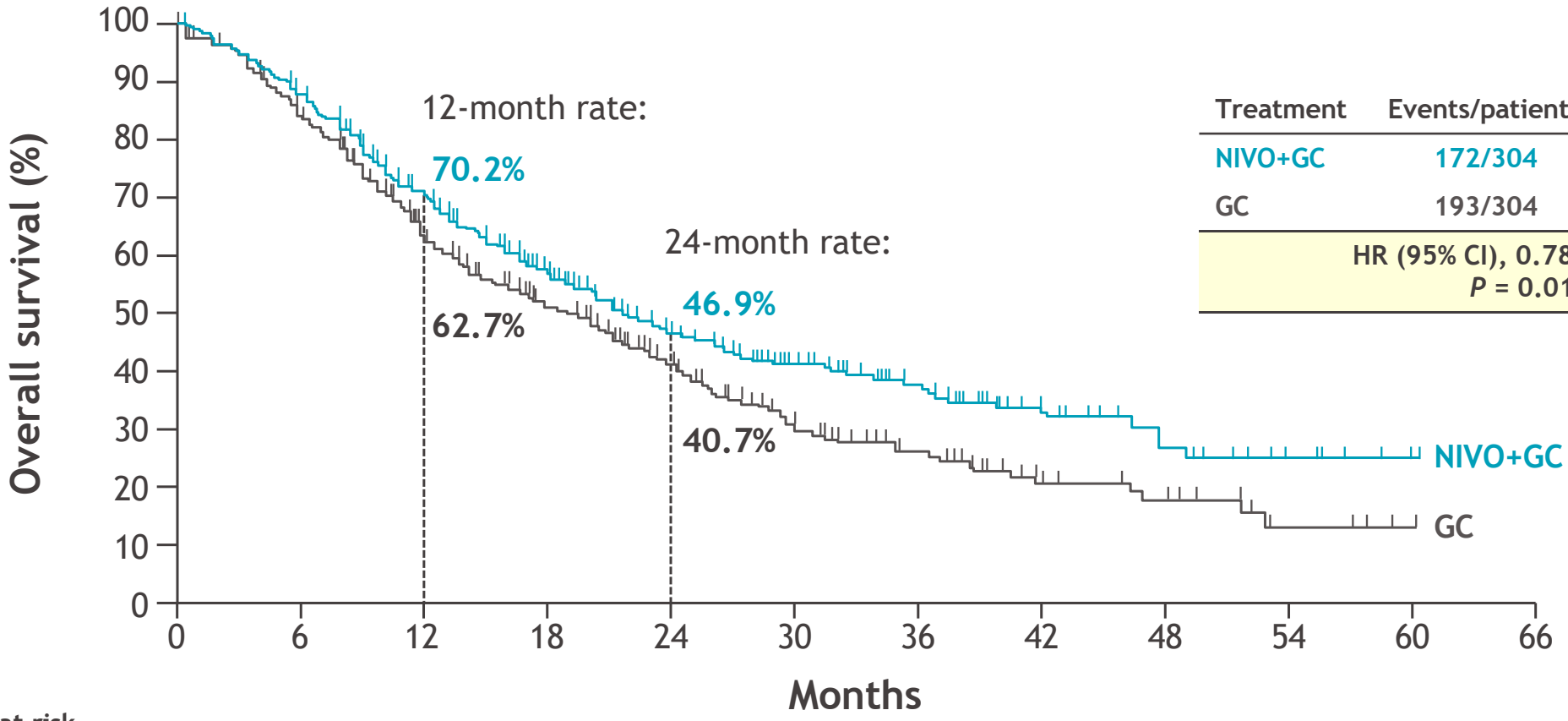


Median (range) study follow-up, 33.6 (7.4–62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

OS (primary endpoint)



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)

HR (95% CI), 0.78 (0.63-0.96)
P = 0.0171

No. at risk												
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4–62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at randomization.

Therapeutic Metaphysics In Advanced Neoplasms

- In the absence of level 1 evidence of sequence, you use the optimal therapy up-front and the rest of the drugs follow based upon patient factors, drug toxicity and clinical experience

Therapeutic Metaphysics In Advanced Urothelial Cancer

- In places where EVP is approved/available it is the SOC for initial therapy for metastatic urothelial cancer
- For those patients fit enough for second line therapy or beyond, patients not enrolled on trials will frequently (especially in community settings) receive platinum-based (and most often carboplatin) chemotherapy
  - For selected patients i.e. node only disease fit for cisplatin, there remains a potential curative window
  - Carboplatin-based chemotherapy at best would be considered palliative in intent i.e.

Therapeutic Metaphysics In Advanced Urothelial Cancer

- The role of sacituzumab govitecan and erdafitinib will evolve, the latter requiring a greater effort to acquire NGS data early to enable this as viable option
- Are there differences in patients who are primarily unresponsive to EVP vs those who progress later i.e. on pembrolizumab alone ?
- Impact of a follow-on paradigm shift if EVP in the “perioperative” setting moves the needle?
- Massive need for new drug development in newly created 2nd line and beyond setting
- Despite the challenges of “what to do next” the impact of EVP will mean there are fewer of these folks than in the past

“I told the team we could play with anybody in the country"
Shortly, I will tell them which country."
- Lou Holtz