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Enfortumab Vedotin + Pembrolizumab in Untreated Locally Advanced or Metastatic Urothelial Carcinoma: 2.5-Year Median Follow-up of the Phase III EV-302/KEYNOTE-A39 Trial

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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Enfortumab vedotin plus pembrolizumab in untreated locally advanced or metastatic urothelial carcinoma: 2.5-year median follow-up of the phase III EV-302/KEYNOTE-A39 trial☆

T. B. Powles[1*], M. S. Van der Heijden[2], Y. Loriot[3], J. Bedke[4], B. P. Valderrama[5], G. Iyer[6], E. Kikuchi[7], J. Hoffman-Censits[8,9], C. Vulsteke[10], A. Drakaki[11], S. Rausch[12], W. Arafat[13], S. H. Park[14], U. Swami[15], J.-R. Li[16], I. Duran[17], S. Gorla[18], B. Homet Moreno[19], X. Yu[20], Y.-T. Lu[20] & S. Gupta[21]

Platinum Combination Chemotherapy

- Platinum-based combination chemotherapy: standard of care 1L therapy for patients with locally advanced/metastatic urothelial carcinoma for nearly **4 decades**

- Major limitations:
  - Median overall survival only 15–16 months
  - Use is limited by platinum eligibility
    - Cisplatin eligibility

Timeline of Platinum Combination Chemo

1985: Use 1st reported at MSKCC

- Overall response rate: 72%
- CR rate: 36%
- Median OS: 14.8 months

2000: Ph 3 RCT of standard MVAC vs Gem-Cis in systemic therapy-naïve pts

- No difference in OS (13.8 mos GC vs 14.8 mos MVAC)
- MVAC more toxic:
  - Gr 3-4 neutropenia (82% vs 71%)
  - Neutropenic fever (14% vs 2%)
  - Sepsis (12% vs 1%)

2001: ddMVAC vs Standard MVAC

ddMVAC > MVAC for:

- ORR: 62% vs 50%
- PFS: 9.5 vs 8.1 mo (HR: 0.73)
- OS: 15.1 vs 14.9 mo (HR: 0.76)

Sternberg C, et al. J Urol, 1985.
Sternberg C, et al. Cancer, 1989.
Bajorin D, et al. JCO, 1999.
Von der Maase H, et al. JCO. 2000.
Sternberg C, et al. JCO, 2001.
Sternberg C, et al. Eur J Cancer, 2006.

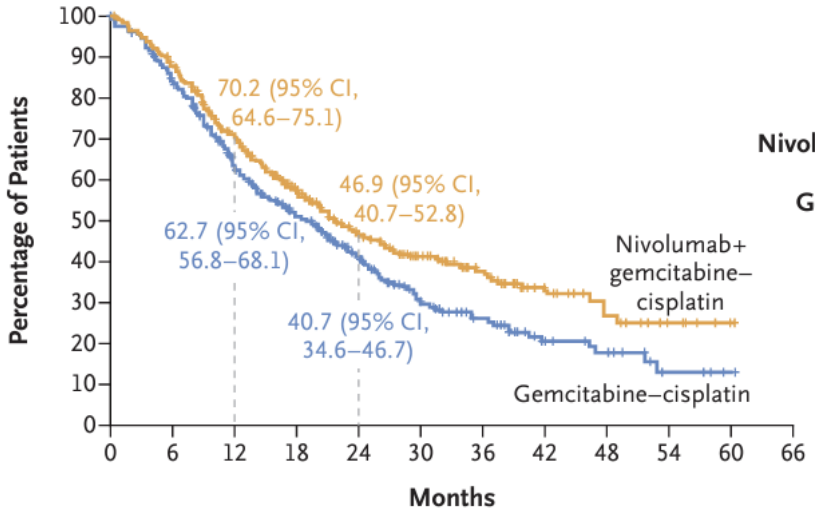
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

M.S. van der Heijden, G. Sonpavde, T. Powles, A. Necchi, M. Burotto, M. Schenker, J.P. Sade, A. Bamias, P. Beuzeboc, J. Bedke, J. Oldenburg, G. Chatta, Y. Ürün, D. Ye, Z. He, B.P. Valderrama, J.H. Ku, Y. Tomita, J. Filian, L. Wang, D. Purcea, M.Y. Patel, F. Nasroulah, and M.D. Galsky, for the CheckMate 901 Trial Investigators*

A Overall Survival



No. at Risk												
Nivolumab+gemcitabine–cisplatin	304	264	196	142	97	69	48	25	15	7	2	0
Gemcitabine–cisplatin	304	242	166	122	82	49	33	17	13	4	1	0

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+Gemcitabine–Cisplatin	172/304	21.7 (18.6–26.4)
Gemcitabine–Cisplatin	193/304	18.9 (14.7–22.4)

Hazard ratio for death, 0.78 (95% CI, 0.63–0.96)
P=0.02

Van der Heijden et al. NEJM, 2023

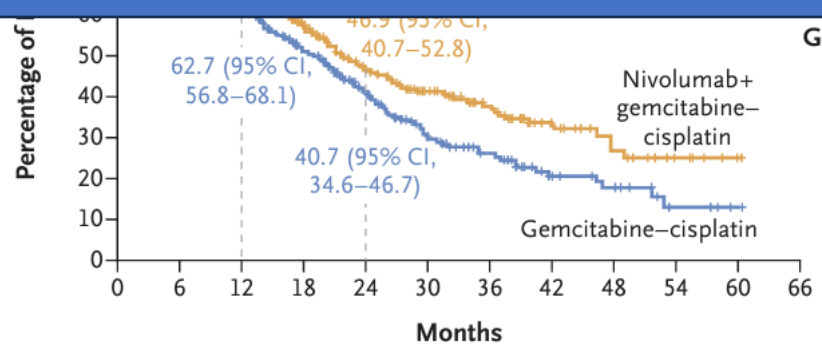
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

TAKE HOME MESSAGE:

No Significant Progress for 4 Decades!



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Gemcitabine–Cisplatin

193/304 18.9 (14.7–22.4)

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Van der Heijden et al. NEJM, 2023

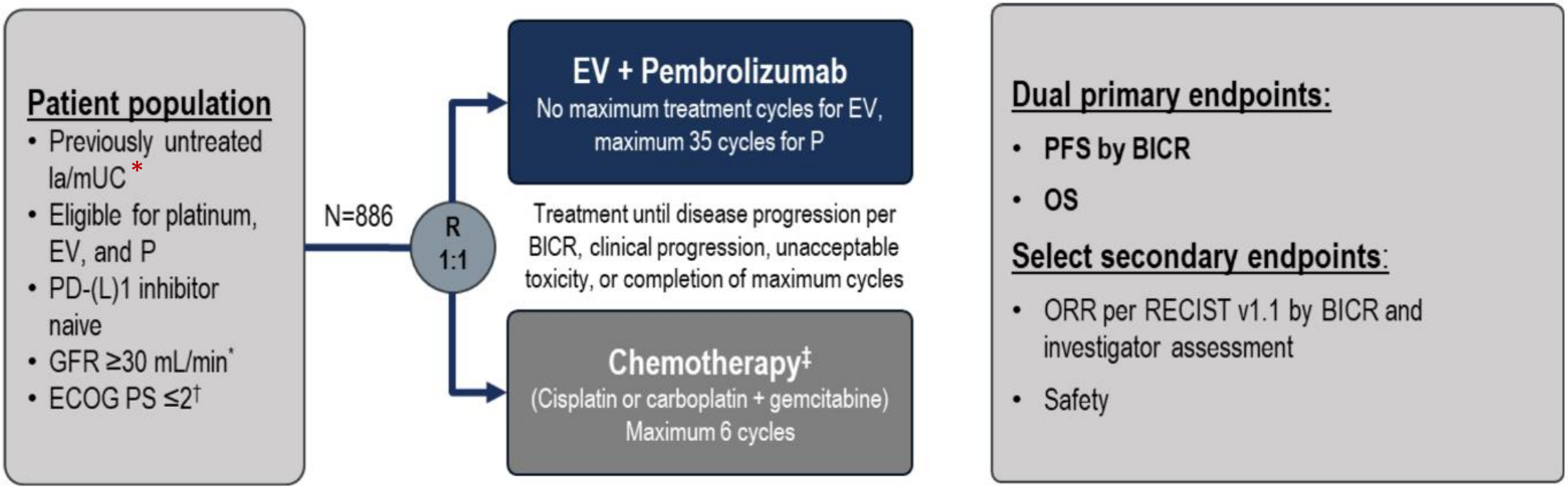
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 7, 2024 VOL. 390 NO. 10

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

T. Powles, B.P. Valderrama, S. Gupta, J. Bedke, E. Kikuchi, J. Hoffman-Censits, G. Iyer, C. Vulsteke, S.H. Park, S.J. Shin, D. Castellano, G. Fornarini, J.-R. Li, M. Gümüş, N. Mar, Y. Loriot, A. Fléchon, I. Duran, A. Drakaki, S. Narayanan, X. Yu, S. Gorla, B. Homet Moreno, and M.S. van der Heijden, for the EV-302 Trial Investigators*

Trial Design

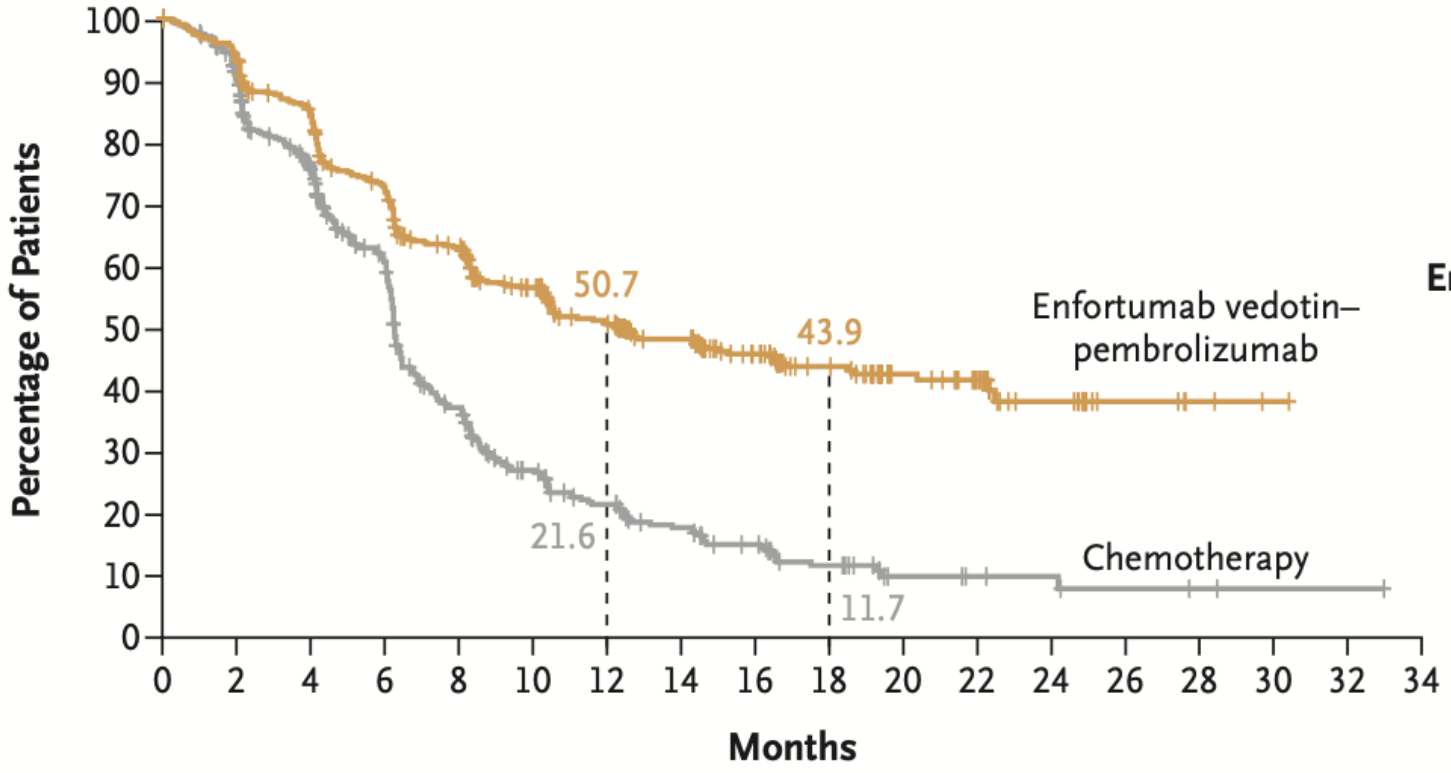


Includes patients with:

- Upper or lower tracts
- Pure UC, mixed type, or pure variant
- Unselected for nectin-4 and PD-L1 expression

Progression Free Survival

A **Progression-free Survival**



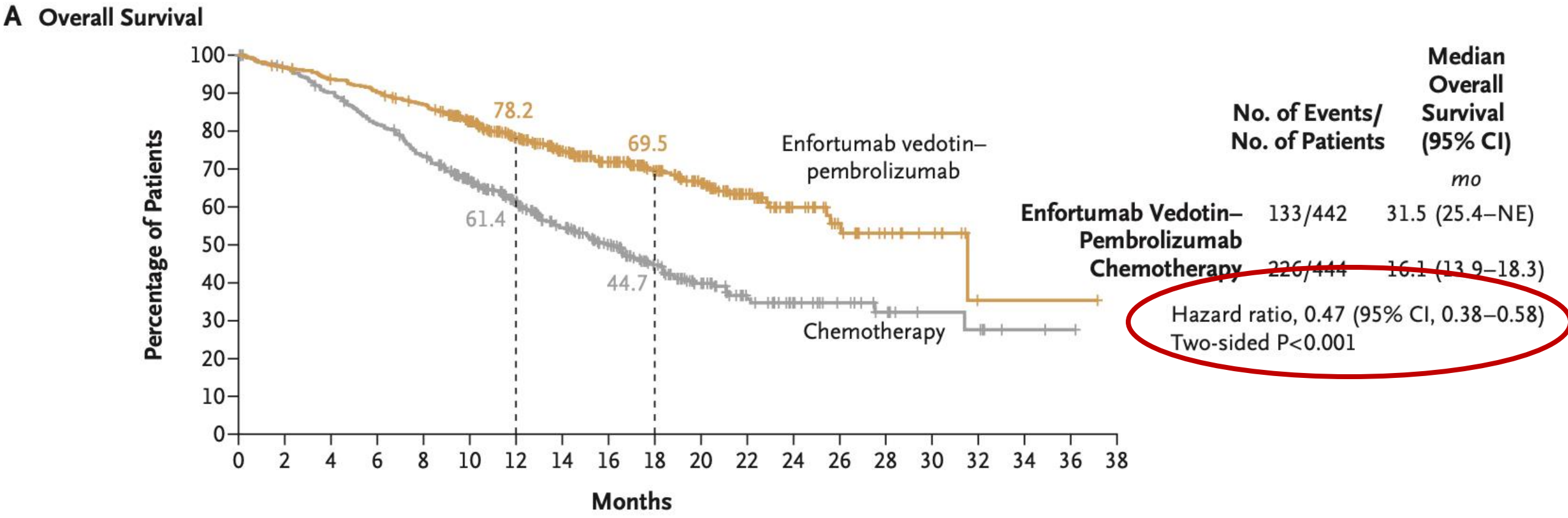
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

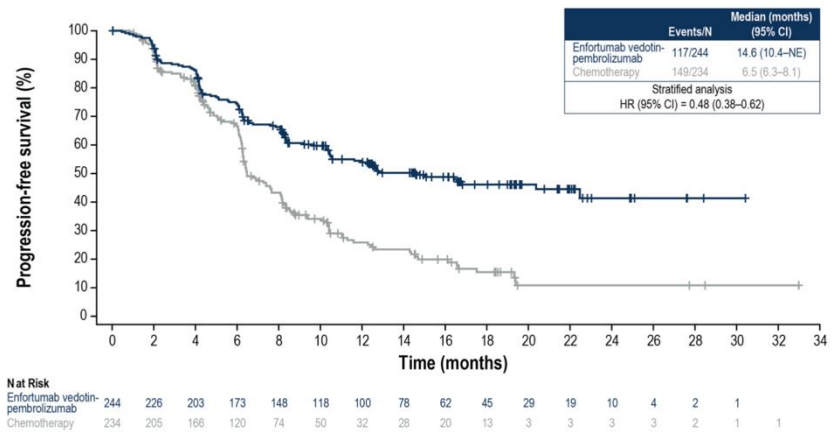
No. at Risk

Enfortumab vedotin–pembrolizumab	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

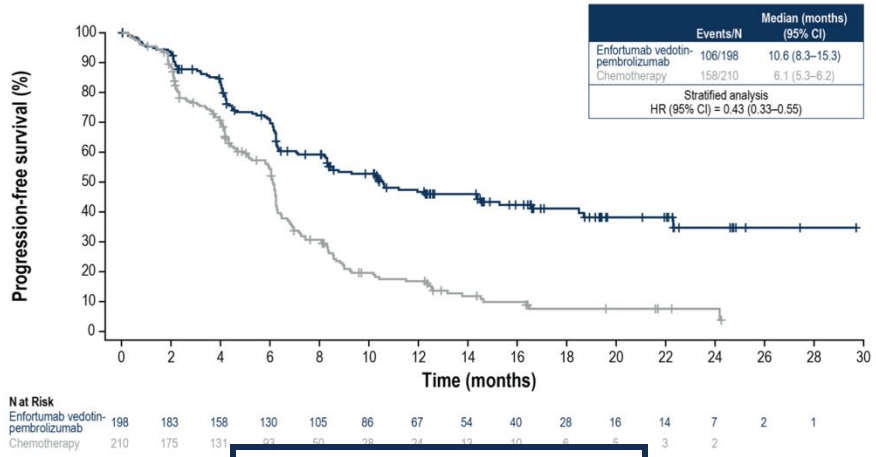
Overall Survival



Progression Free Survival

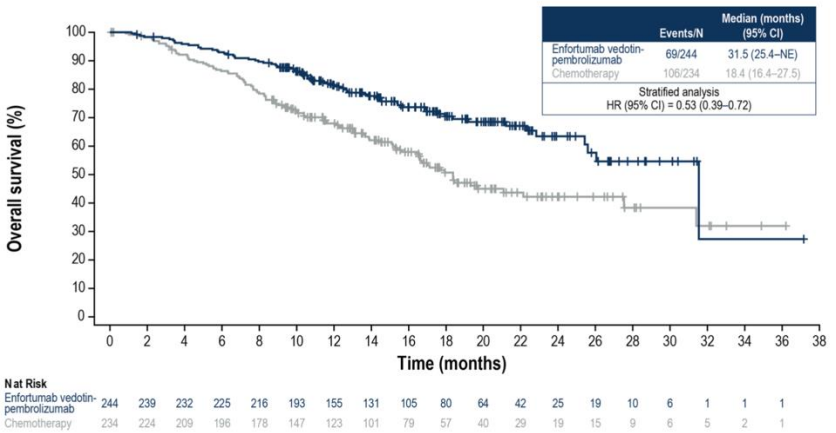


Cisplatin Eligible

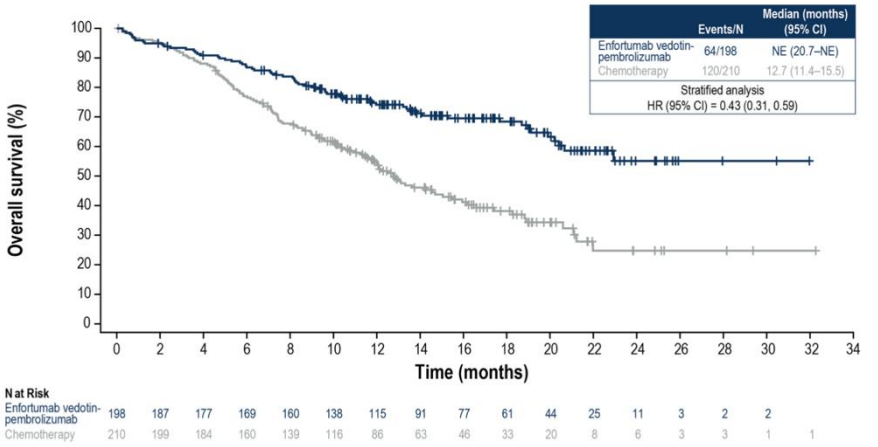


Cisplatin Ineligible

Overall Survival



Cisplatin Eligible



Cisplatin Ineligible

FDA approves enfortumab vedotin-ejfv with pembrolizumab for locally advanced or metastatic urothelial cancer

On December 15, 2023, the Food and Drug Administration (FDA) approved enfortumab vedotin-ejfv (Padcev, Astellas Pharma) in combination with pembrolizumab (Keytruda, Merck) for patients with locally advanced or metastatic urothelial cancer (la/mUC). FDA previously granted accelerated approval to this combination for patients with la/mUC who are ineligible for cisplatin-containing chemotherapy.

European Commission Approves Merck's KEYTRUDA® (pembrolizumab) Plus Padcev® (enfortumab vedotin-ejfv) as First-Line Treatment of Unresectable or Metastatic Urothelial Carcinoma in Adults

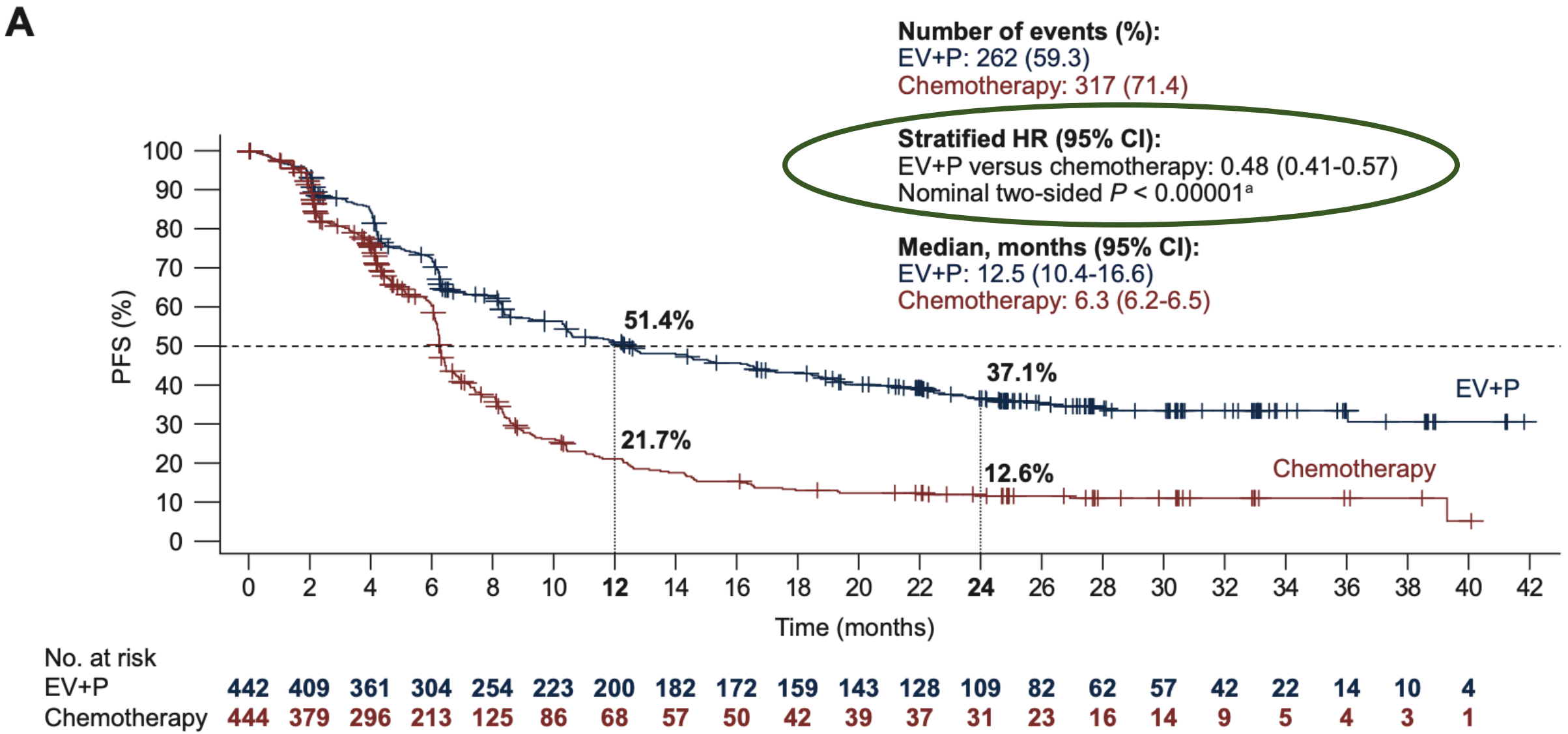
September 3, 2024 6:45 am ET

Study Objective

To report an updated analysis of **efficacy** and **safety** outcomes in the overall population with a median follow-up of 2.5 years

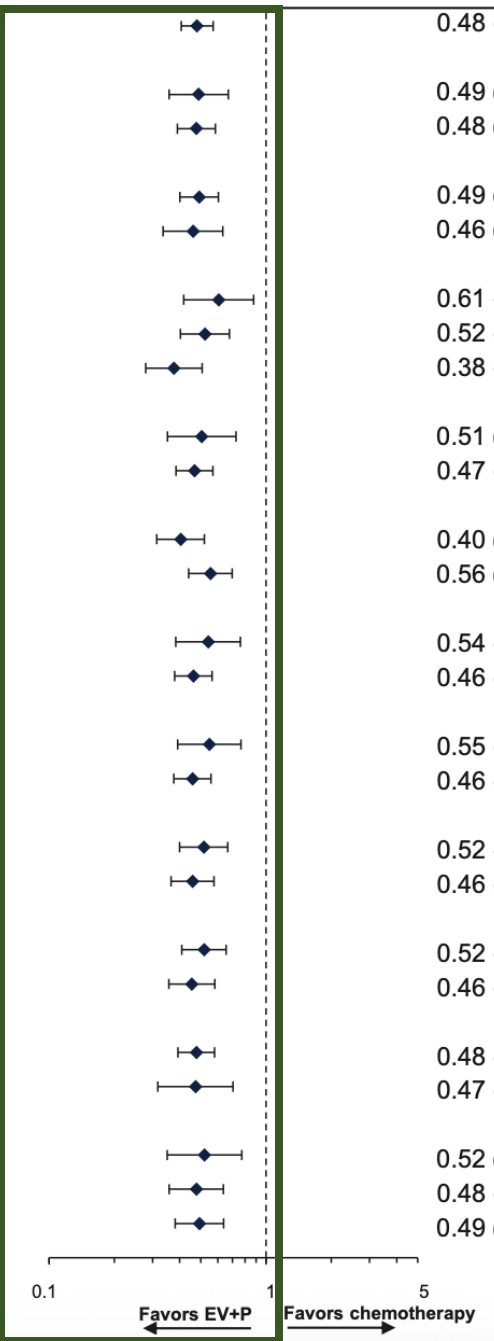
(1 yr additional f/u since primary analysis)

PFS by BICR Analysis



Forest Plot of PFS by BICR

	EV+P		Chemotherapy		
	Median PFS, months	events/*N*	Median PFS, months	events/*N*	HR (95% CI)
Overall	12.5	262/442	6.3	317/444	0.48 (0.41-0.57)
Age (years)					
<65	14.6	87/144	6.4	90/135	0.49 (0.36-0.67)
≥65	12.3	175/298	6.2	227/309	0.48 (0.39-0.59)
Race					
White	10.5	191/308	6.2	214/290	0.49 (0.40-0.60)
Other	19.2	71/134	6.5	103/154	0.46 (0.34-0.63)
Region					
North America	10.3	72/103	6.3	57/85	0.61 (0.42-0.88)
Europe	10.4	102/172	6.3	149/197	0.52 (0.40-0.68)
Rest of World	19.3	88/167	6.2	111/162	0.38 (0.28-0.51)
Sex					
Female	10.4	59/98	6.1	75/108	0.51 (0.35-0.73)
Male	14.0	203/344	6.3	242/336	0.47 (0.39-0.57)
ECOG PS					
0	17.3	121/223	6.7	151/215	0.40 (0.31-0.52)
1-2	9.3	141/219	6.1	166/227	0.56 (0.44-0.70)
Primary disease site of origin					
Upper tract	12.3	81/135	6.2	70/104	0.54 (0.38-0.76)
Lower tract	12.8	179/305	6.3	246/339	0.46 (0.38-0.56)
Liver metastases					
Present	8.1	74/100	6.0	80/99	0.55 (0.39-0.77)
Absent	16.4	188/342	6.4	237/345	0.46 (0.38-0.56)
PD-L1 expression					
Low (CPS <10)	10.5	122/184	6.3	131/185	0.52 (0.40-0.67)
High (CPS ≥10)	16.4	138/254	6.2	182/254	0.46 (0.37-0.58)
* **Cisplatin eligibility**					
Eligible	15.0	140/244	6.5	155/234	0.52 (0.41-0.66)
Ineligible	10.6	122/198	6.1	162/210	0.46 (0.36-0.58)
Metastatic disease site					
Visceral metastases	10.4	203/318	6.2	242/318	0.48 (0.39-0.58)
Lymph node only	22.1	50/103	8.3	60/104	0.47 (0.32-0.70)
Renal function[b]					
Normal	18.7	47/84	6.7	64/95	0.52 (0.35-0.77)
Mild	12.7	91/165	6.3	118/162	0.48 (0.36-0.64)
Moderate/severe	10.5	124/193	6.2	135/187	0.49 (0.38-0.64)



Overall Survival

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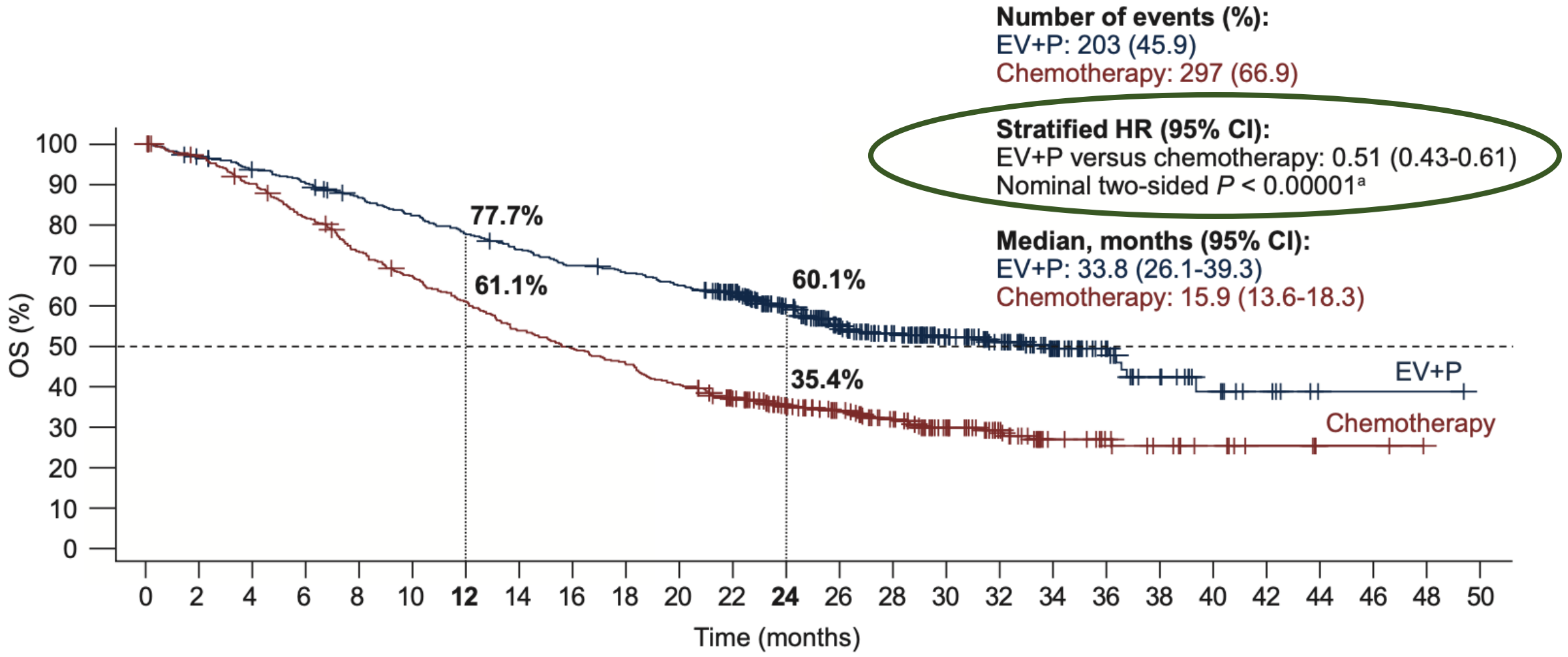

No. at risk

EV+P	442	426	409	394	375	356	336	319	302	293	280	252	206	161	133	102	79	52	32	19	11	6	1	1	1
Chemotherapy	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

Forest Plot of OS

	EV+P		Chemotherapy		
	Median OS, months	events/*N*	Median OS, months	events/*N*	HR (95% CI)
Overall	33.8	203/442	15.9	297/444	0.51 (0.43-0.61)
Age (years)					
<65	39.3	59/144	18.7	87/135	0.43 (0.31-0.61)
≥65	27.1	144/298	14.6	210/309	0.54 (0.44-0.67)
Race					
White	26.1	158/308	15.1	207/290	0.52 (0.42-0.64)
Other	36.3	45/134	19.1	90/154	0.44 (0.30-0.63)
Region					
North America	25.7	57/103	21.0	54/85	0.67 (0.45-1.00)
Europe	25.6	90/172	14.6	140/197	0.52 (0.40-0.69)
Rest of World	NR	56/167	15.5	103/162	0.39 (0.28-0.54)
Sex					
Female	25.4	46/98	14.6	70/108	0.55 (0.37-0.81)
Male	33.8	157/344	16.4	227/336	0.50 (0.41-0.62)
ECOG PS					
0	36.5	77/223	18.7	136/215	0.39 (0.30-0.52)
1-2	22.8	126/219	13.3	160/227	0.62 (0.49-0.79)
Primary disease site of origin					
Upper tract	36.5	60/135	18.3	63/104	0.54 (0.37-0.78)
Lower tract	32.9	142/305	15.6	233/339	0.50 (0.41-0.62)
Liver metastases					
Present	19.1	68/100	10.1	82/99	0.56 (0.40-0.78)
Absent	39.3	135/342	18.3	215/345	0.50 (0.40-0.62)
PD-L1 expression					
Low (CPS <10)	31.2	91/184	15.1	136/185	0.47 (0.36-0.62)
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Eligible	36.7	101/244	18.7	143/234	0.54 (0.42-0.70)
Ineligible	25.6	102/198	12.7	154/210	0.50 (0.39-0.64)
Metastatic disease site					
Visceral metastases	25.7	163/318	13.5	235/318	0.51 (0.41-0.62)
Lymph node only	NR	34/103	24.4	54/104	0.51 (0.33-0.79)
Renal function[b]					
Normal	39.3	33/84	18.6	61/95	0.50 (0.32-0.77)
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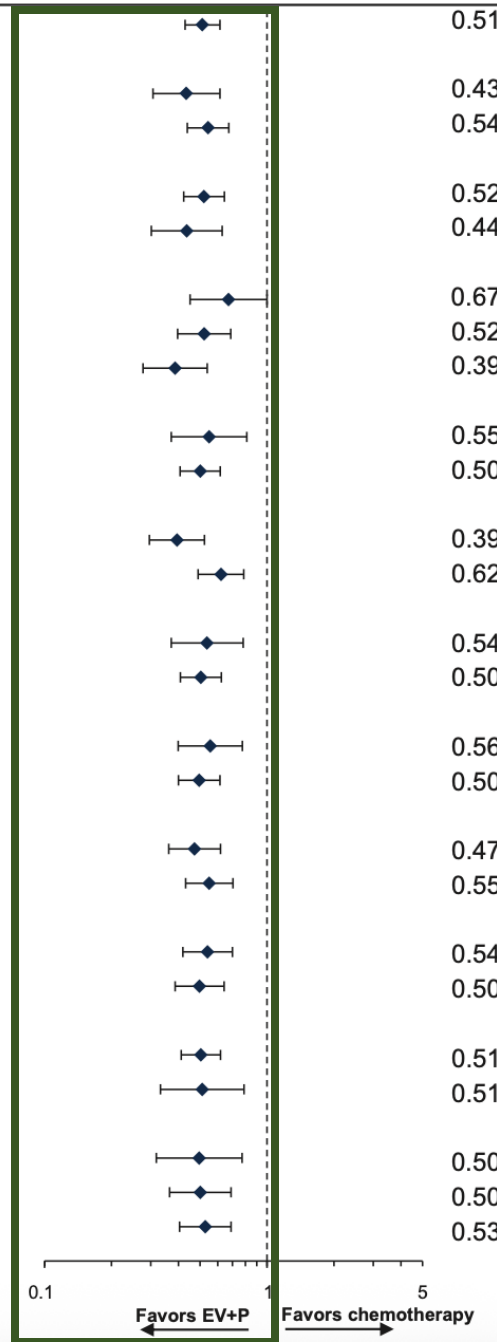
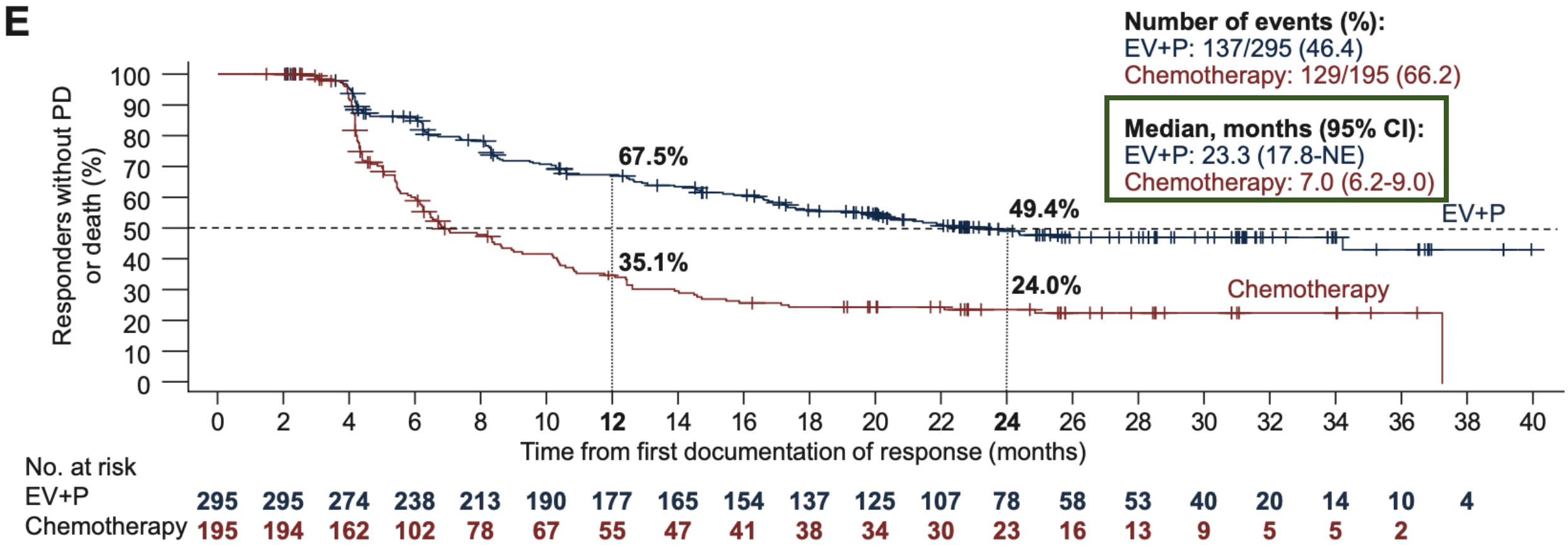
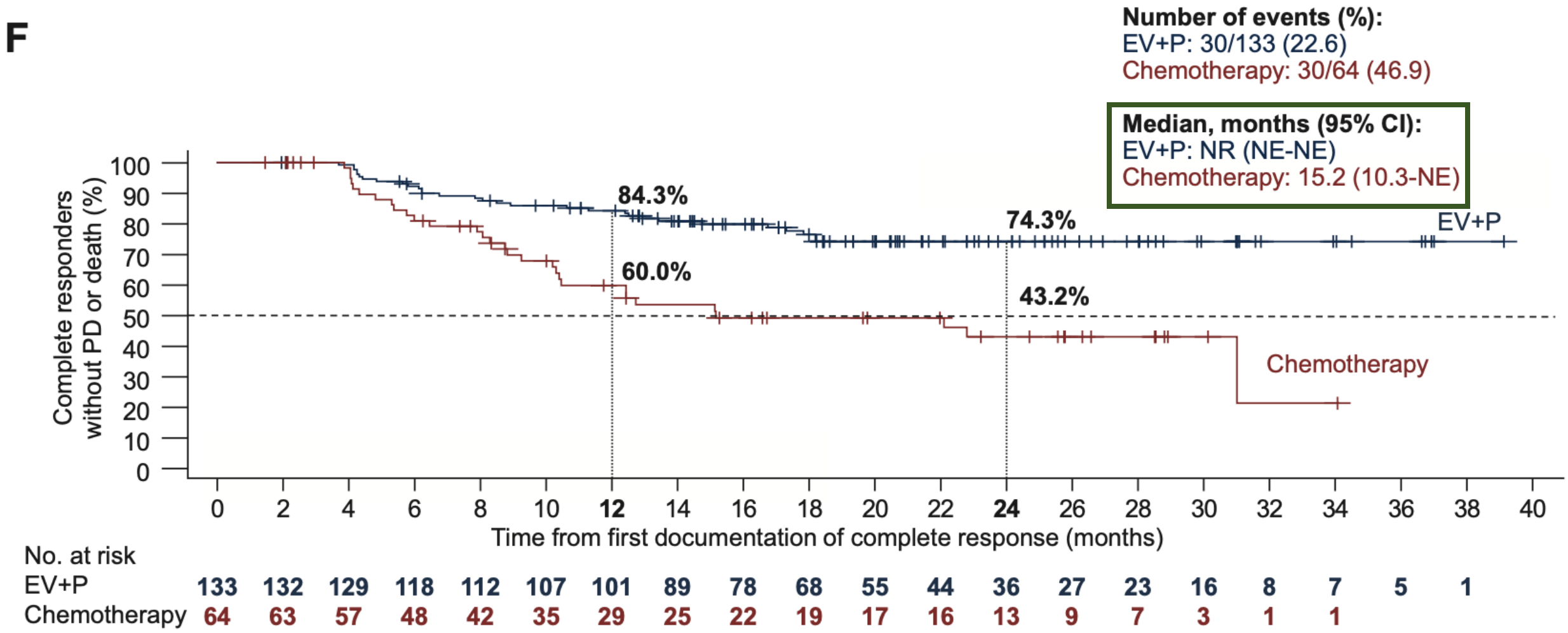


DOR per RECIST by BICR



Duration of CR per RECIST by BICR



Summary of TEAEs and TRAEs in the Safety Population

Patients with adverse event	Enfortumab vedotin plus pembrolizumab ($n = 440$), *n* (%)	Chemotherapy ($n = 433$), *n* (%)
TEAE	439 (99.8)	427 (98.6)
Grade ≥3 TEAE	331 (75.2)	341 (78.8)
Serious TEAE	234 (53.2)	169 (39.0)
TEAE leading to the discontinuation of enfortumab vedotin	186 (42.3)	NA
TEAE leading to the discontinuation of pembrolizumab	135 (30.7)	NA
TEAE leading to the discontinuation of any study drugs	212 (48.2)	93 (21.5)
TEAE leading to death	23 (5.2)	14 (3.2)
TRAE	428 (97.3)	414 (95.6)
Grade ≥3 TRAE	252 (57.3)	301 (69.5)
Serious TRAE	129 (29.3)	85 (19.6)
TRAE leading to the discontinuation of enfortumab vedotin	160 (36.4)	NA
TRAE leading to the discontinuation of pembrolizumab	109 (24.8)	NA
TRAE leading to the discontinuation of any study drugs	188 (42.7)	80 (18.5)
TRAE leading to death[a]	5 (1.1)	4 (0.9)

Specific TRAEs

Patients with adverse event	Enfortumab vedotin plus pembrolizumab (n = 440)		Chemotherapy (n = 433)	
	Any grade, n (%)	Grade ≥3, n (%)	Any grade, n (%)	Grade ≥3, n (%)
Overall	428 (97.3)	252 (57.3)	414 (95.6)	301 (69.5)
* Peripheral sensory neuropathy	228 (51.8)	18 (4.1)	43 (9.9)	0 (0)
Pruritus	179 (40.7)	6 (1.4)	21 (4.8)	0 (0)
Alopecia	146 (33.2)	2 (0.5)	34 (7.9)	1 (0.2)
* Rash maculopapular	144 (32.7)	34 (7.7)	14 (3.2)	0 (0)
Fatigue	131 (29.8)	14 (3.2)	156 (36.0)	18 (4.2)
Diarrhea	123 (28.0)	17 (3.9)	48 (11.1)	3 (0.7)
Decreased appetite	119 (27.0)	5 (1.1)	97 (22.4)	6 (1.4)
Nausea	93 (21.1)	5 (1.1)	168 (38.8)	12 (2.8)
* Anemia	65 (14.8)	16 (3.6)	245 (56.6)	136 (31.4)
* Neutropenia	43 (9.8)	23 (5.2)	180 (41.6)	130 (30.0)
* Thrombocytopenia	18 (4.1)	2 (0.5)	148 (34.2)	84 (19.4)
* Neutrophil count decreased	16 (3.6)	11 (2.5)	54 (12.5)	39 (9.0)
* Platelet count decreased	5 (1.1)	0 (0)	63 (14.5)	28 (6.5)

Discussion

- After a median F/U of ~2.5 yrs, 1L EV + P continued to demonstrate superior efficacy over chemotherapy
  - Holds true in a broad population including both cisplatin-eligible and cisplatin-ineligible patients
  - Nearly doubling the median PFS and more than doubling the median OS

- The response to EV + P was durable, with a median DOR of ~2 years in pts with a confirmed response
  - For pts achieving a clinical CR: 74.3% probability or remaining in clinical CR at 24 months

- No new safety signals for EV + P after an additional year of F/U:
  - Rate of grade 3+ peripheral sensory neuropathy:
    - Primary analysis: 3.6%
    - Additional F/U: 4.1%
  - Rate of grade 1-2 ocular disorders (no grade 3+):
    - Primary analysis: 21.4%
    - Additional F/U: 21.6%

Take Home Messages

- Updated efficacy and safety data with an additional year of F/U were consistent with the primary analysis
  - Represent the longest F/U duration for EV + P treated patients in a phase III setting

- These results are corroborated by 5-year F/U data from Cohort A of the phase Ib/II EV-103 study, which assessed EV + P in cisplatin-ineligible pts

- ***The continued survival benefit with EV + P vs chemotherapy from EV-302 reinforces EV + P as SOC for 1L treatment of mUC***