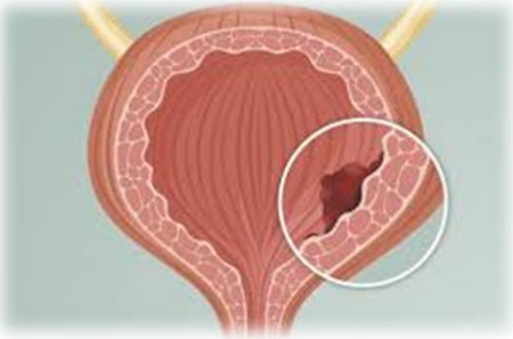
19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Novedades en cáncer de vejiga metastásico en primera línea

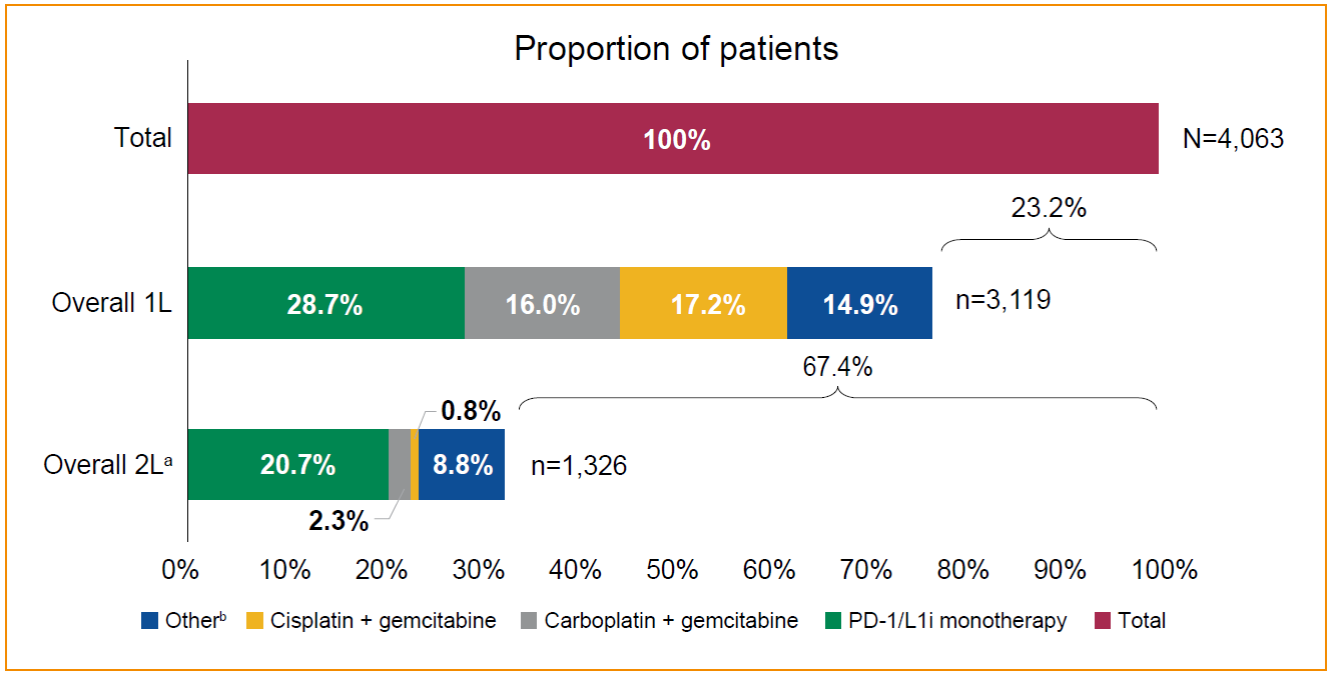


Teresa Alonso Gordoa
Servicio Oncología Médica
Hospital Universitario Ramón y Cajal

DISCLOSURES

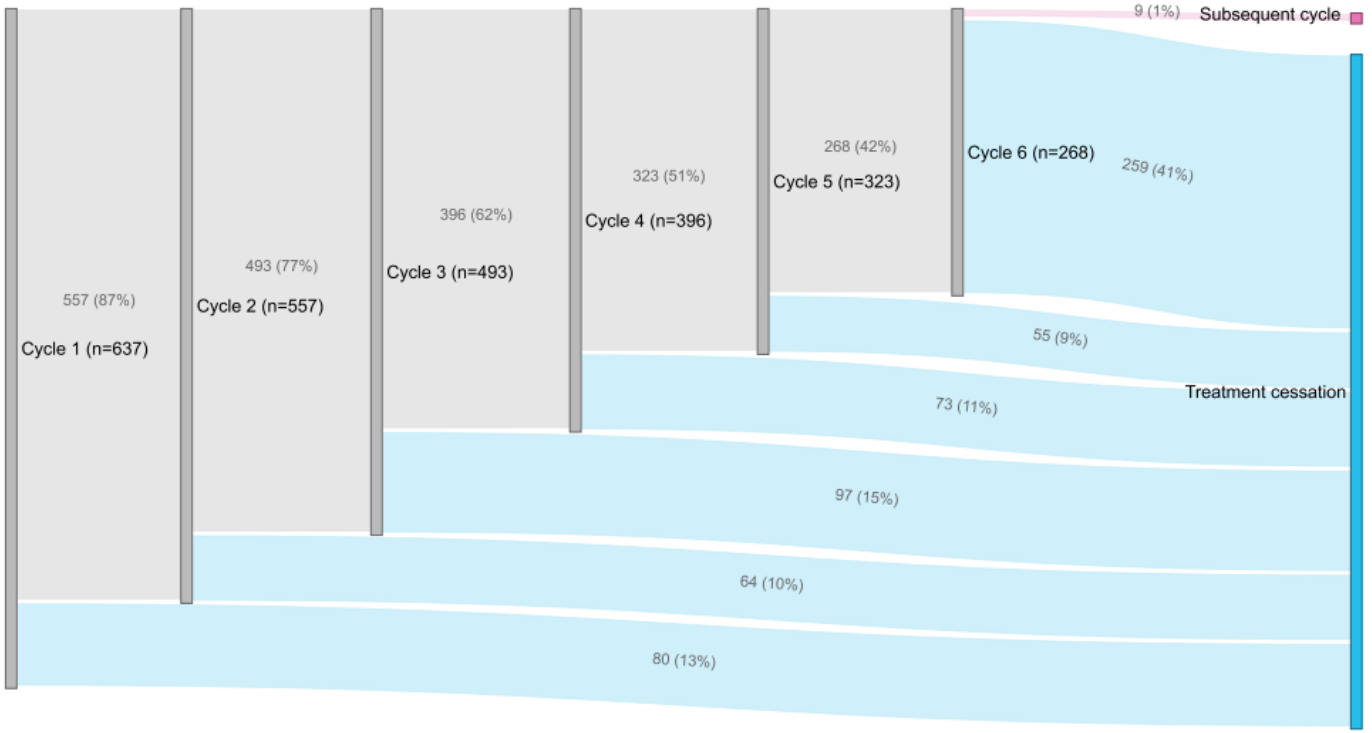
- Consultant or Advisory Role: IPSEN, Lilly, Bayer, Johnson & Johnson, Eisai, Astellas, MSD, Pfizer, Adacap.
- Speaking: Lilly, IPSEN, Pfizer, Astellas, Adacap, Johnson & Johnson, Roche, Eisai.
- Research Funding: Pfizer, Johnson & Johnson, IPSEN

EPIDEMIOLOGY



Morgans A, et al. Annals of Oncology (2021) 32 (suppl_5): S678-S724

EPIDEMIOLOGY

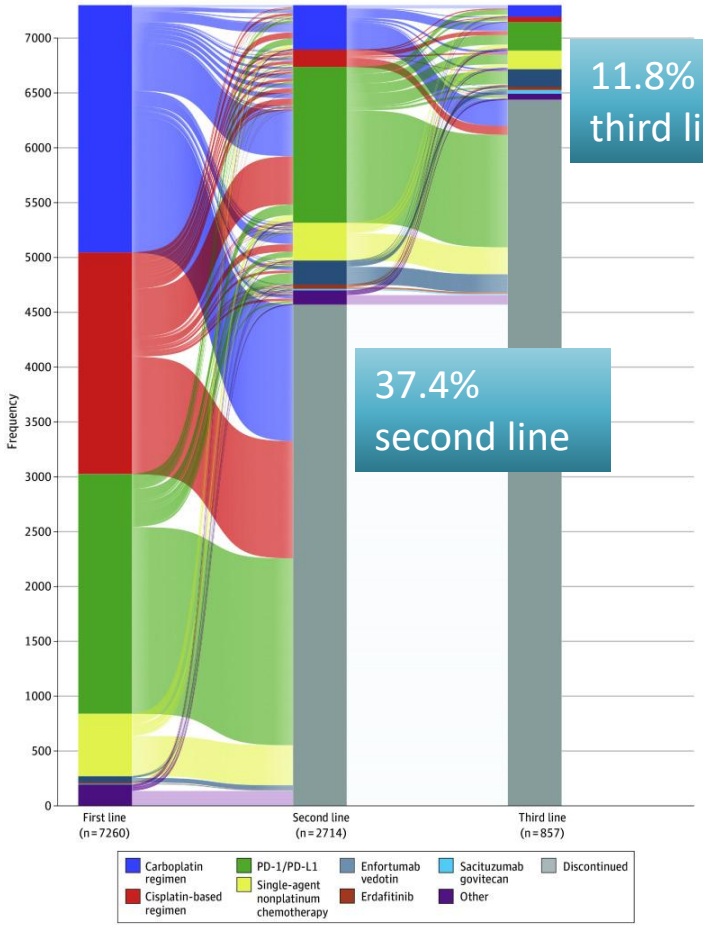


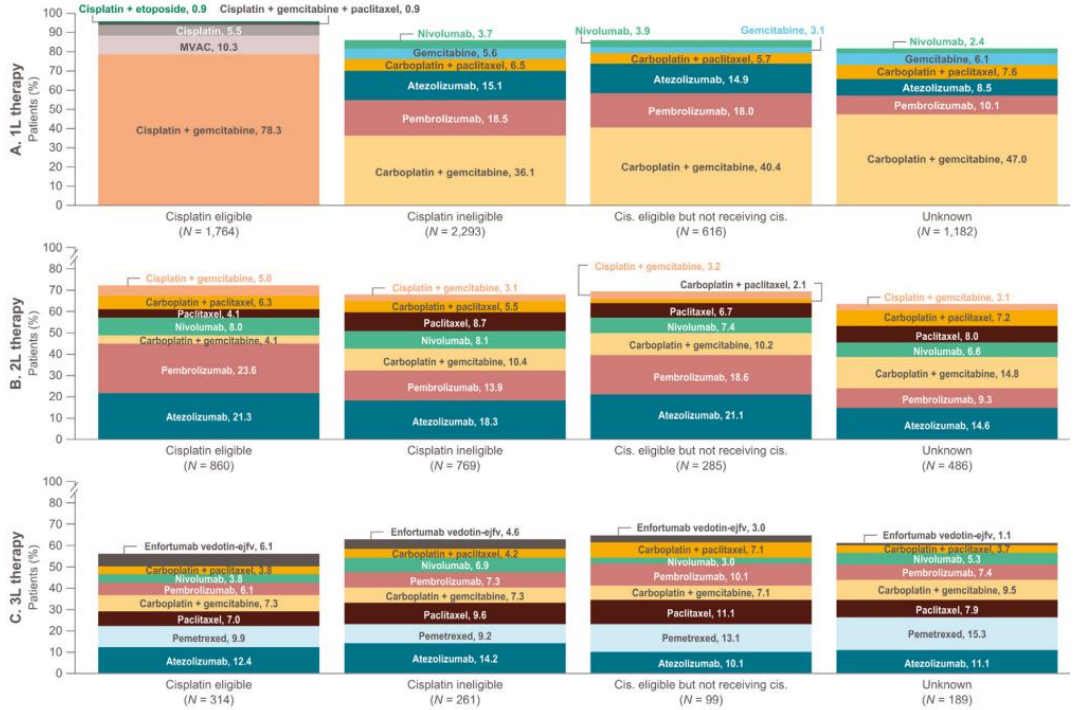
Slotman E, et al. Urologic Oncology: Seminars and Original Investigations 14 Nov 2024

EPIDEMIOLOGY

11.8%
third line

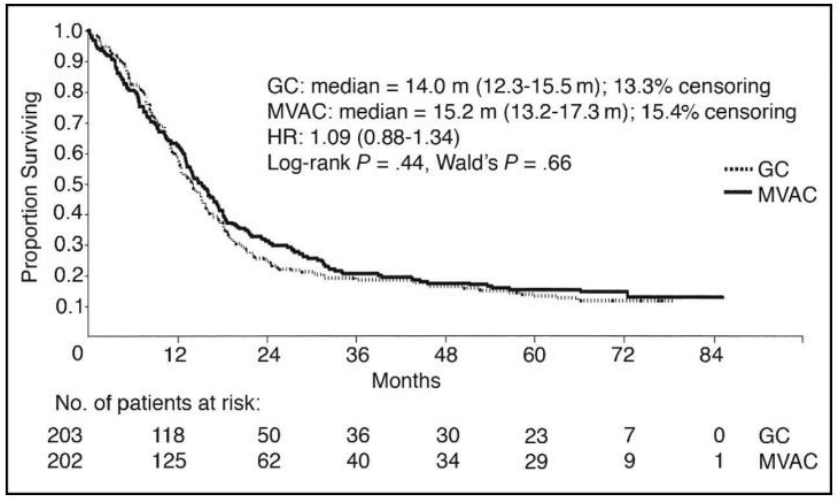
37.4%
second line

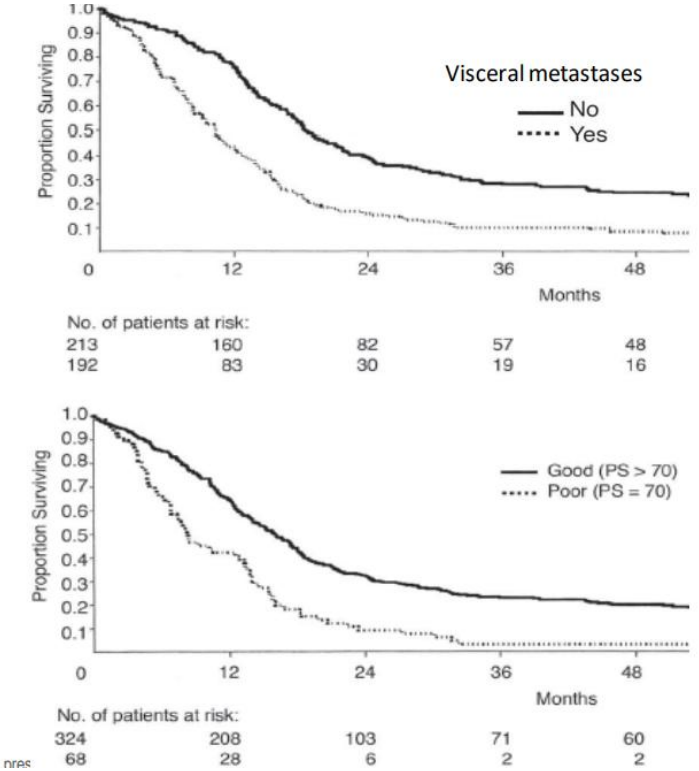




Mathew Thomas V, et al. JAMA Netw Open. 2024 May 1;7(5):e249417.
Morgans A, et al. Urol Oncol. 2023 Aug;41(8):357.e11-357.e21.

MVAC vs Gemcitabine + Cisplatin





von der Maase, et al. J Clin Oncol 2005

CISPLATIN VS CARBOPLATIN

	N	Complete response		Overall response		Survival	
		Cis-Pt	Carbo-Pt	Cis-Pt	Carbo-Pt	**Cis-Pt**	**Carbo-Pt**
MVAC vs MCaVi	47	17%	0%	52%	39%	**16 mo***	**9 mo***
MVEC vs MVECa	57	25%	11%	71%	41%	**13 mo**	**9 mo**
GemCis vs GemCa	110	23%	9%	66%	59%	**12.8 mo**	**9.8 mo**
MVAC vs PacCa	85	12.8%	2.6%	35.9%	28.2%	**15.4 mo**	**13.8 mo**

Bellmunt et al, Cancer 1997;80:1966-72
Petrioli et al, Cancer 1996;77:344-51
Dogliotti et al, Eur Urol 2007;52:344-51
Dreicer et al, Cancer 2004;100:1639-45

FIRST LINE IMMUNOTHERAPY (PD-1/PD-L1 inhbitors)

KEYNOTE 052

Patients (N = 350)
- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin based on ≥ 1 of the following:
  - CrCl <60 mL/min
  - ECOG PS 2
  - ≥ grade 2 neuropathy or hearing loss
  - NYHA class III CHF

→ **Pembrolizumab 200 mg Q3W**

→ **Primary Endpoints**
- ORR in all patients
- ORR in patients with PD-L1–positive tumors

First 100 patients included in this planned interim analysis
- **Evaluate ORR**
- **Determine the PD-L1–high expression cut point**

Secondary Endpoints: DOR, PFS, OS, and ORR in all patients, PD-L1 positive and PD-L1–high expressing patients; safety and tolerability; establish an assay cut point for high PD-L1 expression

Balar AV, Lancet Oncol. 2017 Nov;18(11):1483-1492

Imvigor 210: Cohort 1

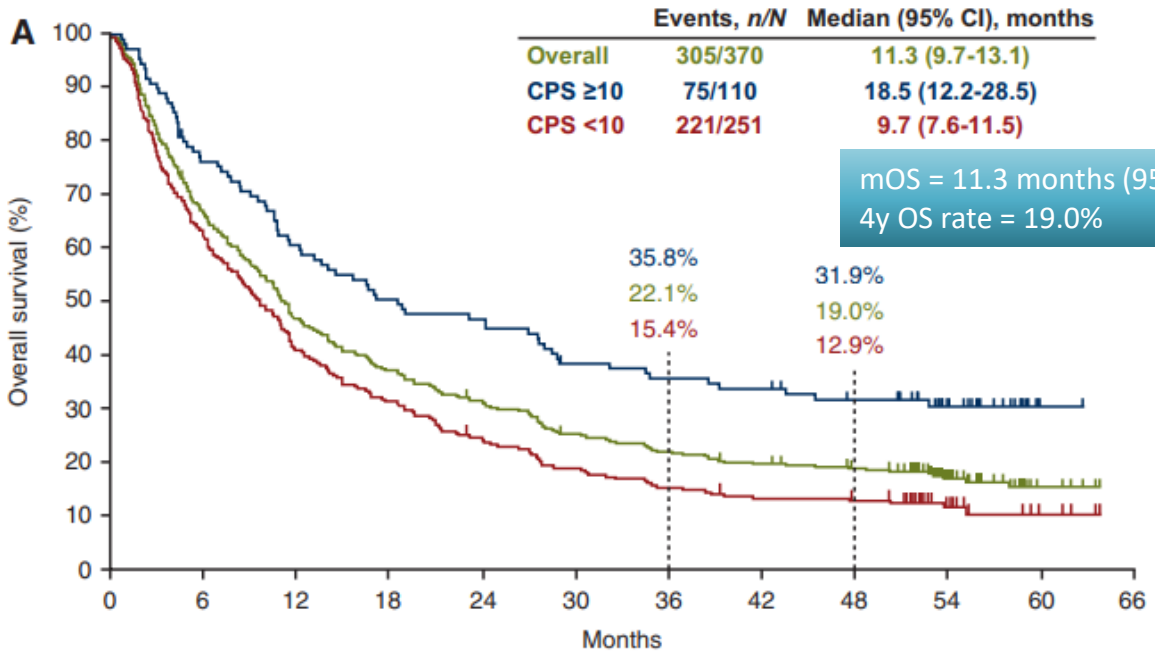
- Locally advanced or metastatic urothelial carcinoma
- Predominantly TCC histology
- Tumor tissue for PD-L1 testing[a]

→ Cohort 1 (N = 119) 1L cisplatin ineligible → *Cohort 1 presented earlier this morning*[1]

→ **Cohort 2** (N = 310) Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of benefit

Balar AV, et al. Lancet. 2017 Jan 7;389(10064):67-76

FIRST LINE IMMUNOTHERAPY (PD-1/PD-L1 inhbitors)



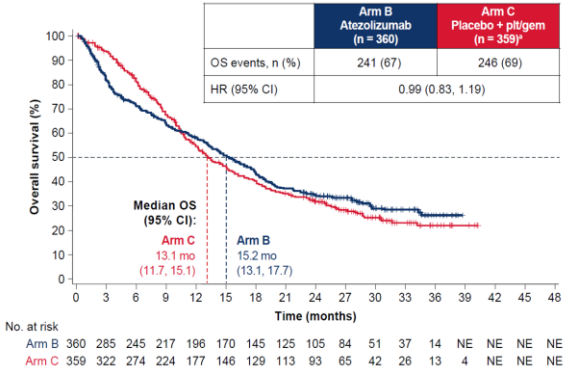
mOS = 11.3 months (95% CI 9.7-13.1 months)
4y OS rate = 19.0%

Balar AV, et al. Ann Oncol. 2023 Mar;34(3):289-299.

FIRST LINE IMMUNOTHERAPY (PD-1/PD-L1 inhbitors)

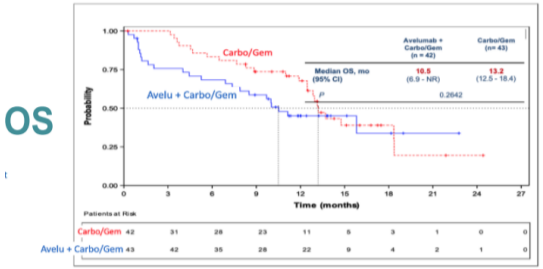
IMVIGOR 130: CT + IO

Davis ID. AACR 2021, abstract 5130



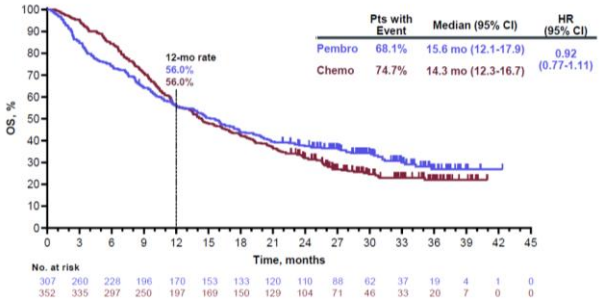
INDUCOMAIN: IO INDUCTION -> CT (cis-ineligible)

Perez Valderrama B, et al. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215



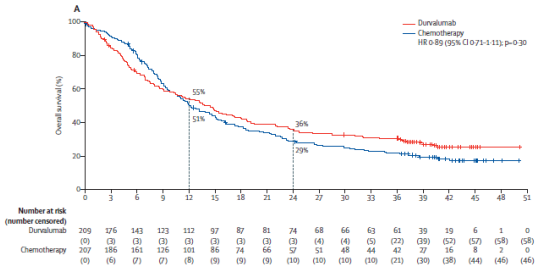
KEYNOTE 361: CT + IO

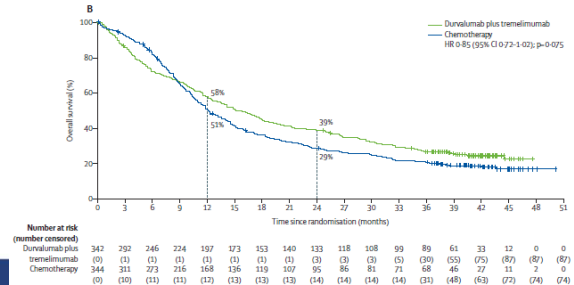
Powles T. Lancet Oncol. 2021 Jul;22(7):931-945.



DANUBE: IO/IO

Powles T. Lancet Oncol. 2020 Dec;21(12):1574-1588.





KEY ISSUE WHEN FIRST LINE IO

FIRST LINE COMBINATIONS (QT + IO)

Study	N	Treatment	Main Results, Primary endpoints
Imvigor 130 (NCT02807636)	1213	Arm A: Cisplatin/Carboplatin + Gem + Atezo Arm B: Atezo monotherapy Arm C: Cisplatin/Carboplatin + Gem	INV-assessed PFS (Arm A vs C ITT): 8.2m vs 6.3m (HR=0.82, 95%CI 0.70, 0.96) INV-assessed OS (Arm A vs C ITT): 16.1m vs 13.4m (HR=0.84, 95%CI 0.71, 1.00) OS (Arm B vs C ITT and PD-L1 IC2/3, hierarchical approach): 15.2m vs 13.1m (HR=0.99, 95%CI 0.83, 1.19) and 27.5m vs 16.7m (HR=0.67, 95%CI 0.45, 1.02)
KEYNOTE-361 (NCT02853305)	1010	Cisplatin/Carboplatin + Gem + Pembro Pembro Cisplatin/Carboplatin + Gem	PFS per RECIST v1.1 by BICR (CT+Pembro vs CT): 8.3m vs 7.1m (HR=0.78; 95%CI 0.65-0.93) OS (CT + Pembro vs CT): 17.0m vs 14.3m (HR=0.86; 95% CI 0.72-1.02)
DANUBE (NCT02516241)	1032	Durvalumab + Tremelimumab Durvalumab Cisplatin/Carboplatin + Gem	OS (Durva vs CT in high PD-L1 population): 14.4m vs 12.1m (HR= 0.89, 95% CI 0.71–1.11) OS (Durva + Treme vs CT in ITT population): 15.1m vs 12.1m (HR=0.85, 95% CI 0.72–1.02)

NEGATIVE TRIALS

Galsky MD. Lancet. 2020 May 16;395(10236):1547-1557; Galsky MD. AACR 2021, abstract 5253; Davis ID. AACR 2021, abstract 5130
Powles T. Lancet Oncol. 2021 Jul;22(7):931-945.
Powles T. Lancet Oncol. 2020 Dec;21(12):1574-1588.

PLATIN-BASED CHEMOTHERAPY AND IO SWITCH MAINTENANCE

13-15% progressive disease as best radiologic response

All endpoints measured post randomization (after chemotherapy)

- **CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)**
  - **– Cisplatin + gemcitabine or**
  - **– Carboplatin + gemcitabine**
- **Unresectable locally advanced or metastatic UC**

Treatment-free interval
4-10 weeks

N=700

R
1:1

Avelumab
10 mg/kg IV Q2W
+ BSC*
n=350

Until PD, unacceptable toxicity, or withdrawal

BSC alone*
n=350

Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

Powles T, et al. J Clin Oncol 38: 2020 (suppl; abstr LBA1)

Select baseline characteristics

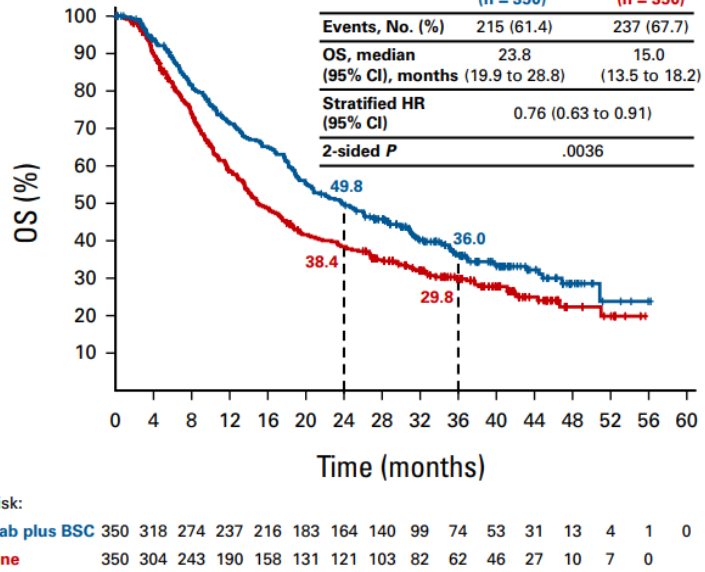
	Overall population (N=700)		PD-L1+ population (N=358)	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=169)
Median age, years	68	69	70	70
Site of primary tumor, %				
Upper tract (renal pelvis, ureter)	30	23	23	21
Lower tract (bladder, urethra, prostate gland)	70	77	77	79
Site of baseline metastasis, %				
Visceral	55	55	47	47
Nonvisceral*	45	45	53	53
PD-L1 status, %†				
Positive	54	48	100	100
Negative	40	38	0	0
Unknown	6	14	0	0
1st-line chemotherapy regimen, %				
Gemcitabine + cisplatin	52	59	53	58
Gemcitabine + carboplatin	42	35	39	32
Gemcitabine + cisplatin/carboplatin‡	6	6	7	9
Not reported	0	1	0	1
Best response to 1st-line chemotherapy, %				
CR or PR	72	72	74	76
SD	28	28	26	24

Powles T, et al. J Clin Oncol 38: 2020 (suppl; abstr LBA1)

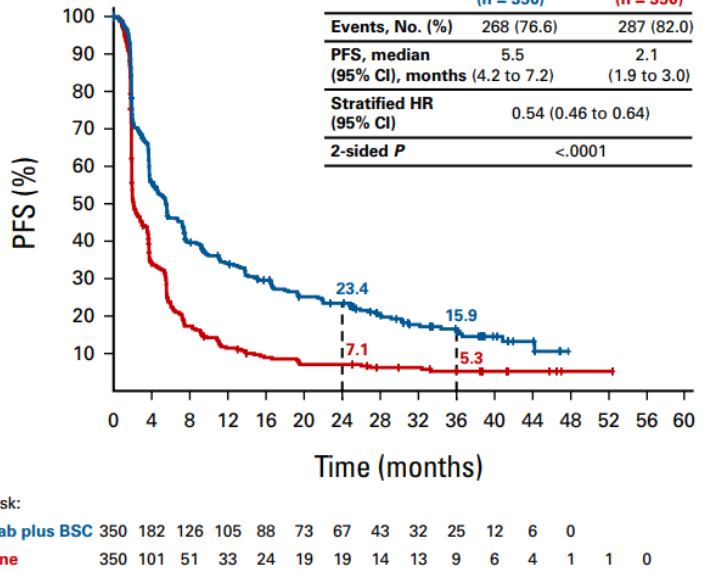
PLATIN-BASED CHEMOTHERAPY AND IO SWITCH-MAINTENANCE

Median FUP 38.0 months
(≥2 years in all patients)

A

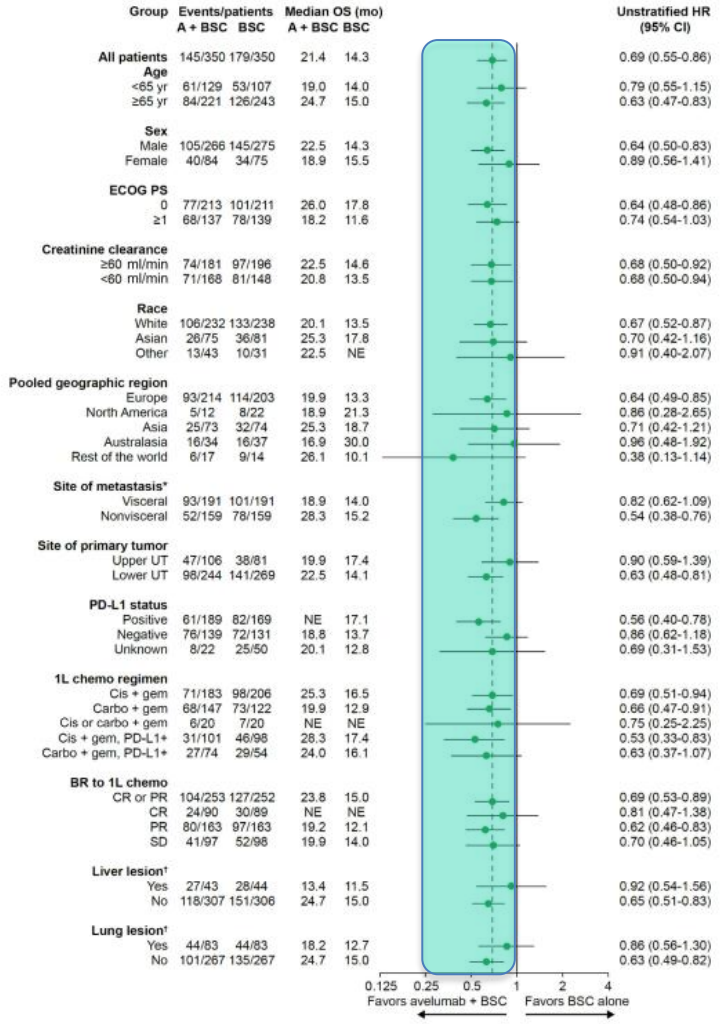


C



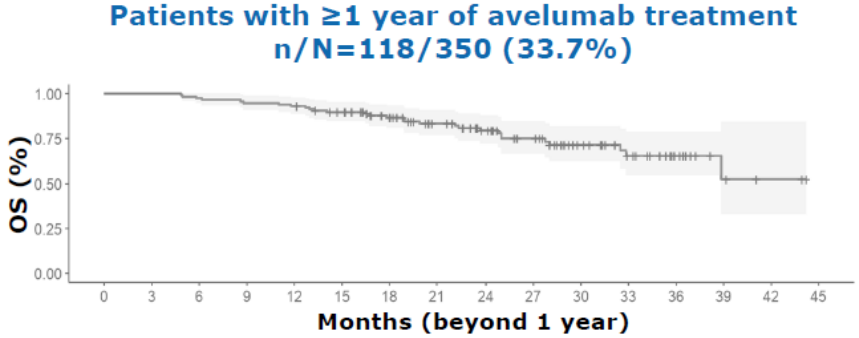
Powles T, Park SH, Caserta C, et al. J Clin Oncol. 2023;41(19):3486-3492

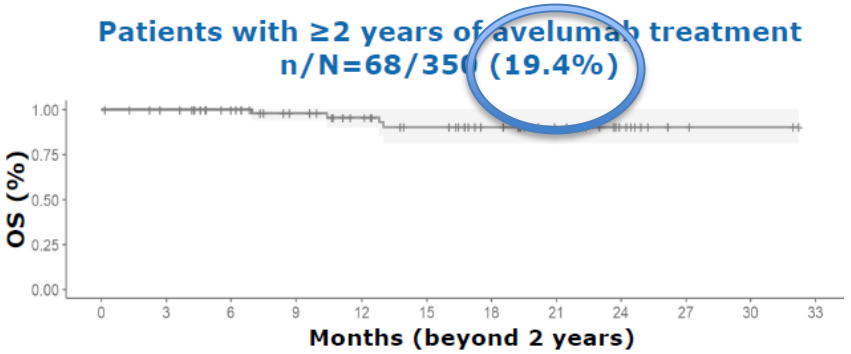
PLATIN-BASED CHEMOTHERAPY AND IO SWITCH-MAINTENANCE



Powles T, Park SH, Caserta C, et al. J Clin Oncol. 2023;41(19):3486-3492

PLATIN-BASED CHEMOTHERAPY AND IO SWITCH-MAINTENANCE





No. at risk

All	118	118	115	112	110	102	84	69	57	46	32	21	11	4	2	0

	Patients with ≥1 year of avelumab treatment (n=118)
Probability of additional OS beyond 1 year, % (95% CI)	
6 months	97.5 (94.7–100)
1 year	93.2 (88.8–97.9)
1.5 years	86.8 (80.8–93.3)
2 years	79.6 (72.0–88.0)

No. at risk

All	68	64	55	46	38	31	23	16	9	3	2	0

	Patients with ≥2 years of avelumab treatment (n=68)
Probability of additional OS beyond 2 years, % (95% CI)	
6 months	100 (100–100)
1 year	95.8 (90.2–100)
1.5 years	90.3 (81.6–99.9)

1L Cisplatin + Gemcitabine
Non visceral M1

Grivas P, et al. ESMO 2024

FIRST LINE COMBINATIONS (QT + IO)

Study/Clinicaltrials.gov	Population	N	Treatment
Imvigor 130 (NCT02807636)	1st line	1200	Cisplatin/Carboplatin + Gemcitabine + Atezolizumab vs Cisplatin/Carboplatin + Gemcitabine vs Atezolizumab
KEYNOTE-361 (NCT02853305)	1st line	990	Cisplatin/Carboplatin + Gemcitabine + Pembrolizumab vs Cisplatin/Carboplatin + Gemcitabine vs Pembrolizumab
DANUBE (NCT02516241)	1st line	1004	Durvalumab + Tremelimumab vs Durvalumab vs Cisplatin/Carboplatin + Gemcitabine
CA209-901 (NCT03036098)	1st line	897	Cisplatin/Carboplatin + Gemcitabine vs Cisplatin/Carboplatin + Nivolumab vs Nivolumab + Ipilimumab
NILE (NCT03682068)	1st line	885	Cisplatin/Carboplatin + Gemcitabine vs Cisplatin/Carboplatin + Gemcitabine + Durvalumab vs Cisplatin/Carboplatin + Gemcitabine + Durvalumab + Tremelimumab

THE ADDITION OF CTLA-4 INHIBITION TO PD-1/PDL-1 INHIBITION

CA209-901 (NCT03036098)

- Metastatic or unresectable UC
- Not previously treated for metastatic or surgically inoperable UC
- ECOG 0-1

N estimated = 1307

Cis-ineligible — R

- Arm A: Nivolumab + Ipilimumab q3w x 4c -> Nivolumab q4w
- Arm B: Cisplatin/Carboplatin Day 1+ Gemcitabine Day 1, 8 (up to 6 cycles)

Cis-eligible — R

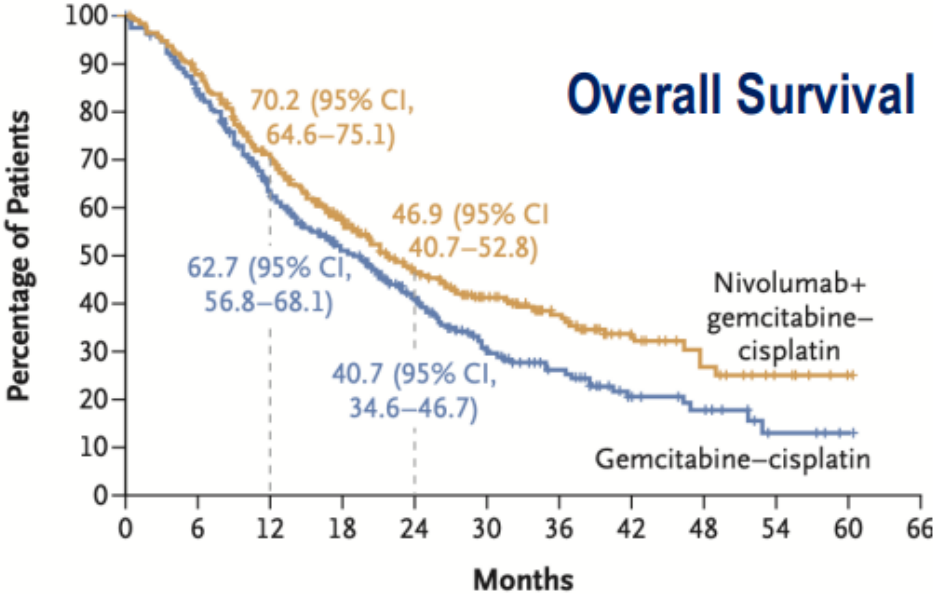
- Arm C: Nivolumab Day 1 + Cisplatin Day 1+ Gemcitabine Day 1, 8 (up to 6 cycles) -> Nivolumab
- Arm D: Cisplatin Day 1+ Gemcitabine Day 1, 8 (up to 6 cycles)

Closed 13 sept 2019

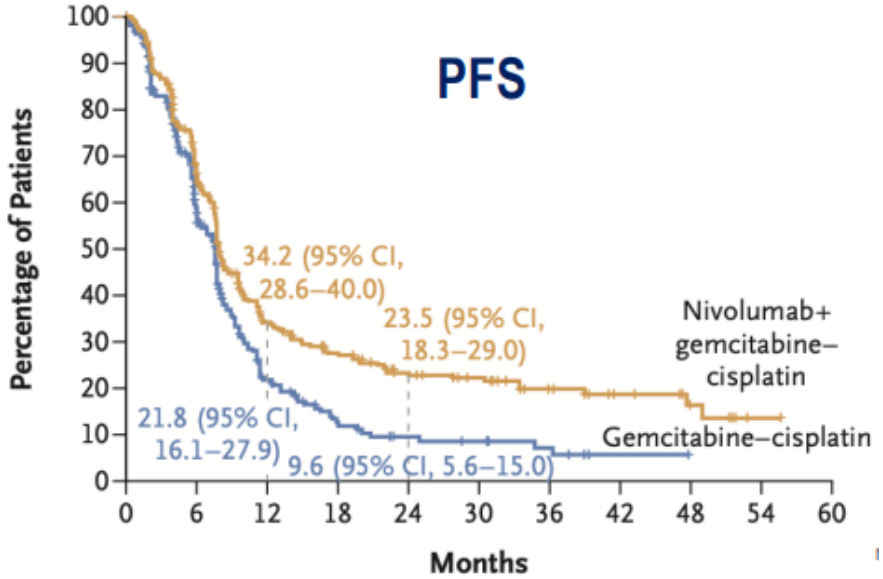
Primary endpoints:
1.OS in cisplatin-ineligible randomized participants
2.OS in PD-L1 positive (>=1%) randomized participants
3.PFS by BICR using RECIST 1.1 in cisplatin-eligible participants
4.OS in cisplatin-eligible participants

20% of pts in control arm received maintenance CPI

CA209-901: CISPLATIN-BASED CT + IO COMBINATION FIRST LINE



Median OS = 21.7m vs 18.9 m (0.78; 95%CI 0.63 to 0.96; P = 0.02)

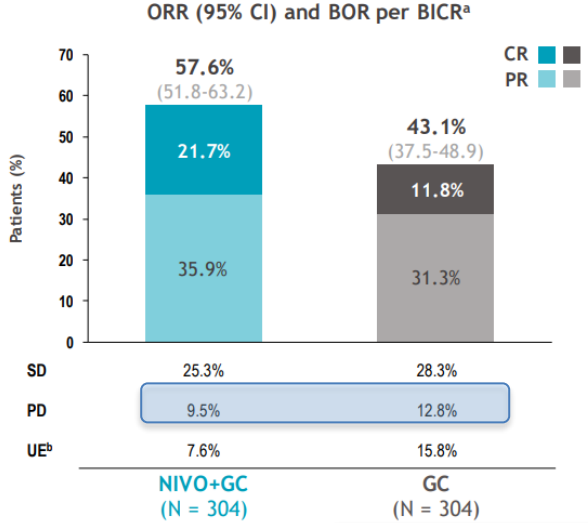


Median PFS = 7.9m vs 7.6m (0.72; 95% CI, 0.59 to 0.88; P = 0.001)

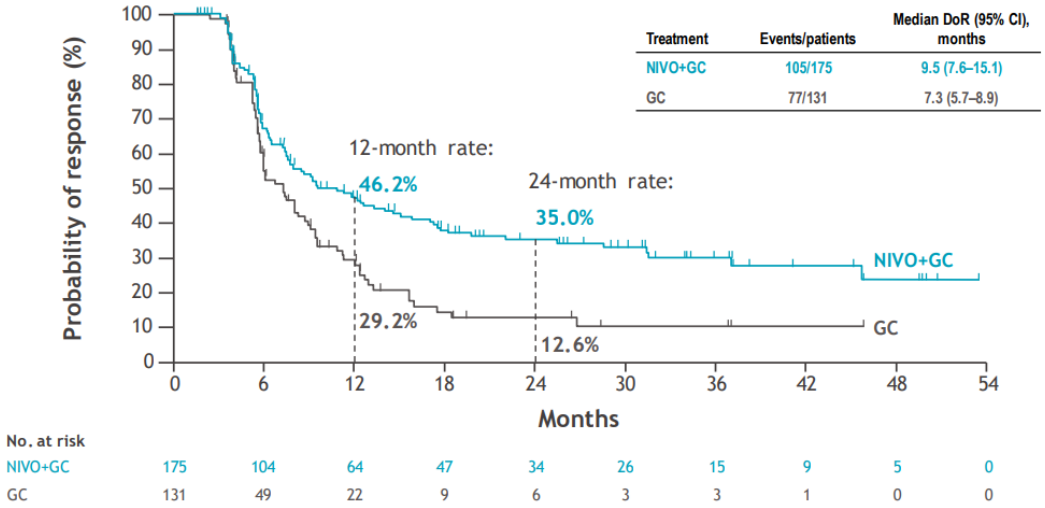
van der Heijden M, et al. ESMO 2023
van der Heijden M, et al. N Engl J Med. 2023 Nov 9;389(19):1778-1789.

CA209-901: CHEMO-IO COMBINATION FIRST LINE

Objective response outcomes



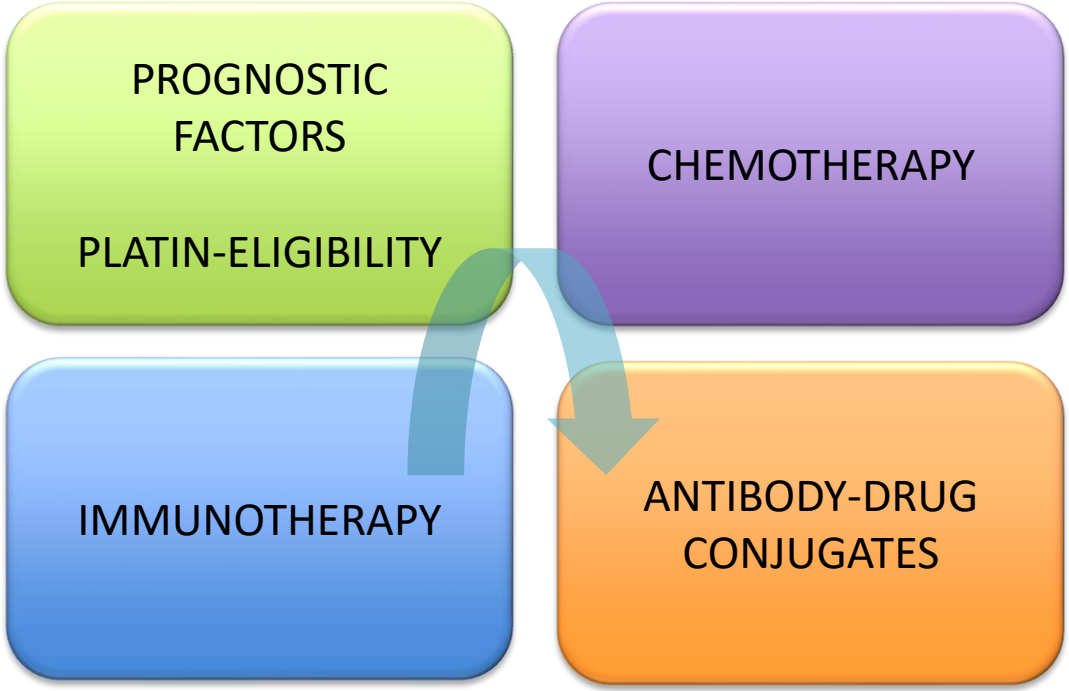
Duration of objective response per BICR



Treatment	Events/patients	Median DoR (95% CI), months
NIVO+GC	105/175	9.5 (7.6–15.1)
GC	77/131	7.3 (5.7–8.9)

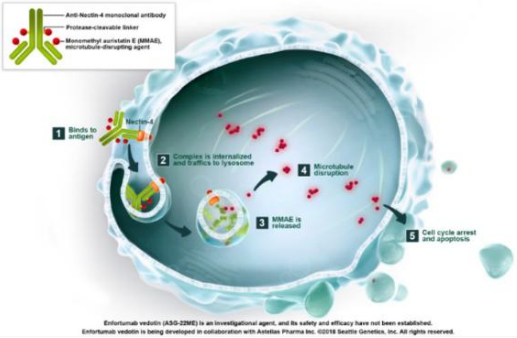
Avelumab maintenance
ORR: 14.3% (Combination vs Sequential PD-1/PD-L1 inh)
Lower PD as best response

van der Heijden M, et al. ESMO 2023


PROGNOSTIC FACTORS
PLATIN-ELIGIBILITY
CHEMOTHERAPY
IMMUNOTHERAPY
ANTIBODY-DRUG CONJUGATES

Enfortumab Vedotin: Nectin-4 Targeted Therapy

Proposed Mechanism of Action



A timeline of Enfortumab vedotin (EV) in mUC/LaUC

18 December 2019 ← **EV-201 Cohort 1**
Phase II, single-arm, multicentre
EV after post-ICI and platinum CT

- **Accelerated FDA approval** after failure to platinum CT and ICI

9 July 2021 ← **EV-201 Cohort 2**
Phase II, single-arm, multicentre
EV post-ICI in cisplatin-ineligible

- **FDA approval** in cisplatin-ineligible patients second-line, or after failure to platinum CT and ICI

3 April 2023 ← **EV-103 Cohort K**
Phase Ib/II
EV + pembrolizumab

- **Accelerated FDA approval for combination** EV + ICI in cisplatin-ineligible LA/mUC patients

13 April 2023 ← **EV-301**
Phase III, open-label
EV post-ICI and platinum CT

- **Full FDA/EMA approval** after failure to platinum CT and ICI

15 December 2023 ← **LBA6 EV-302/KEYNOTE-A39**
Randomised phase III, open-label
EV + Pembrolizumab vs chemotherapy

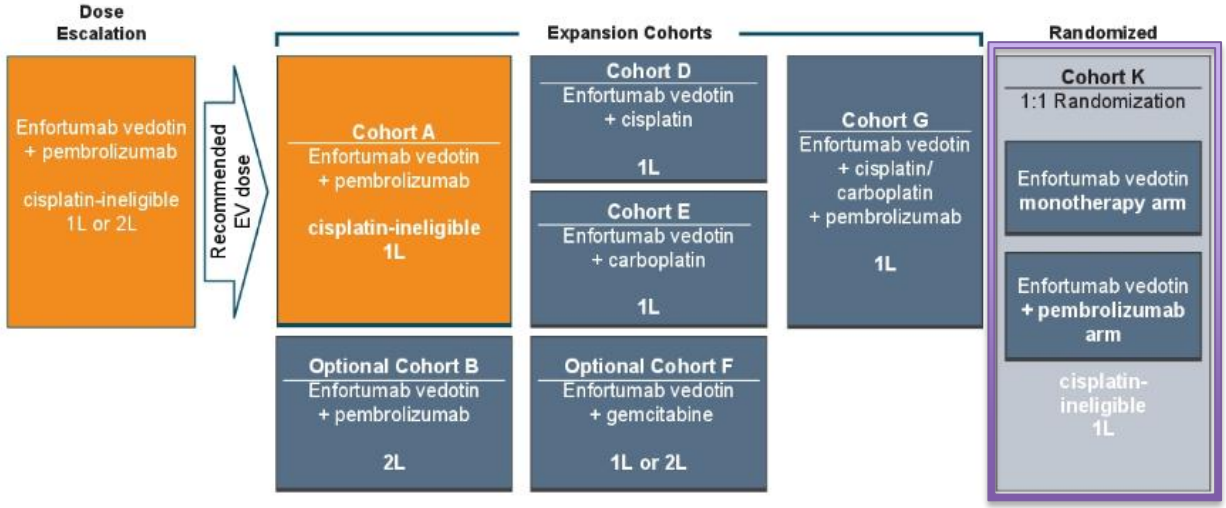
- Results published
- **Safety and efficacy** confirmed
- **Regular FDA approval** for combination EV + ICI

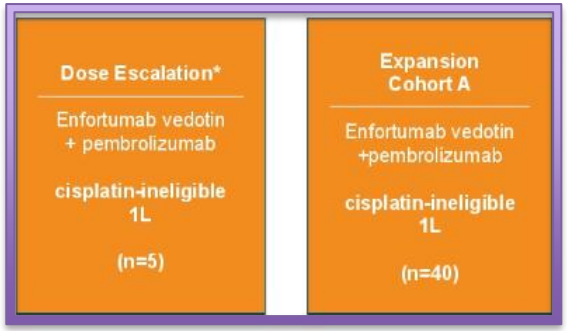
Nathan P et al. Current Oncol 2024

DEVELOPMENT OF ENFORTUMAB VEDOTIN IN 1L TREATMENT OF CIS-INELIGIBLE

EV-103 Clinical Trial

A multicohort study (NCT03288545)



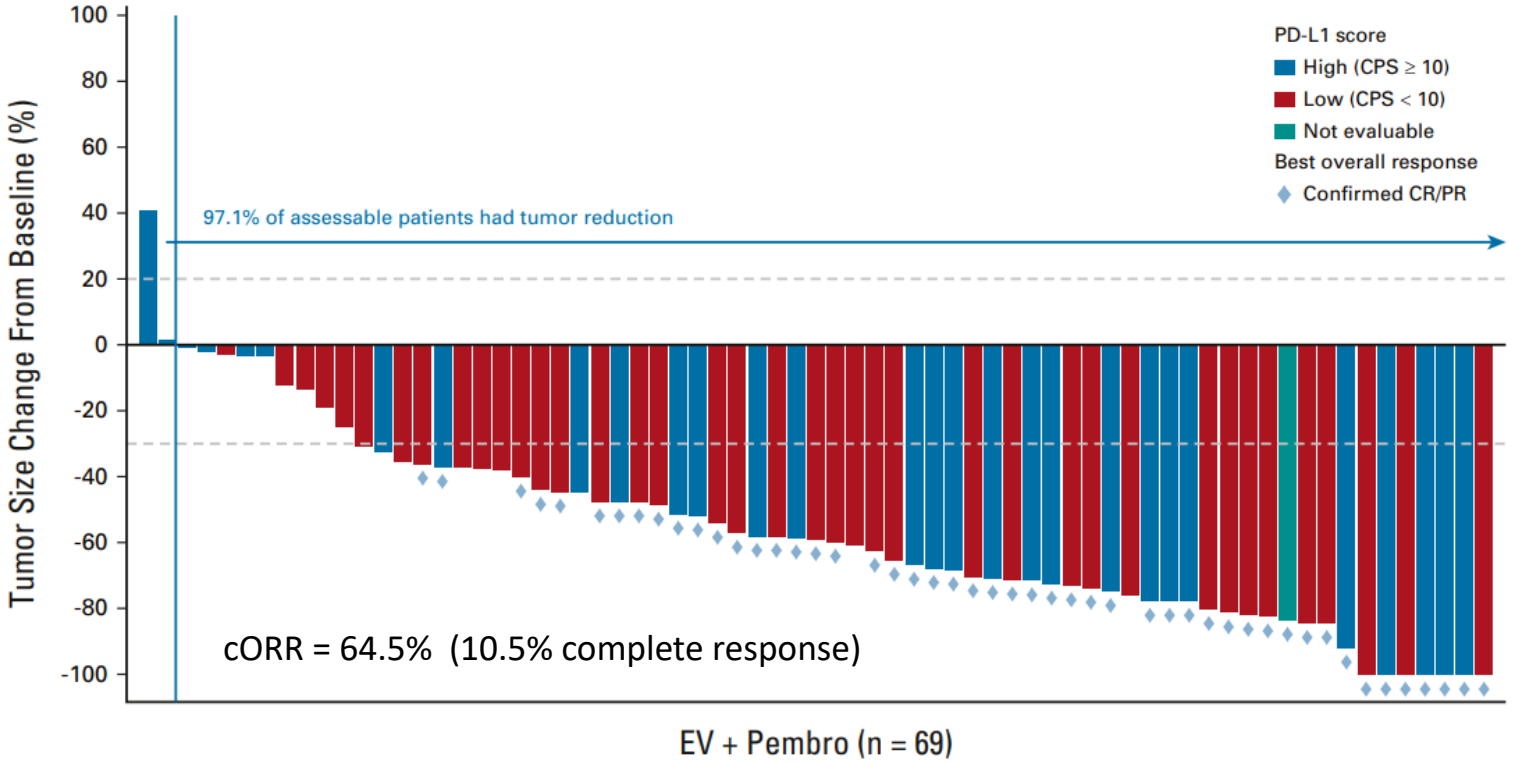


* Not included in the current analysis: three 1L patients treated with enfortumab vedotin 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with enfortumab vedotin 1.25 mg/kg + pembrolizumab 200 mg

Primary endpoints: Adverse Events, lab abnormalities
Key secondary endpoints: Dose-limiting toxicities, ORR, duration of response, PFS, OS

Rosenberg JE, et al. J Clin Oncol 38: 2020 (suppl; abstr 5044)

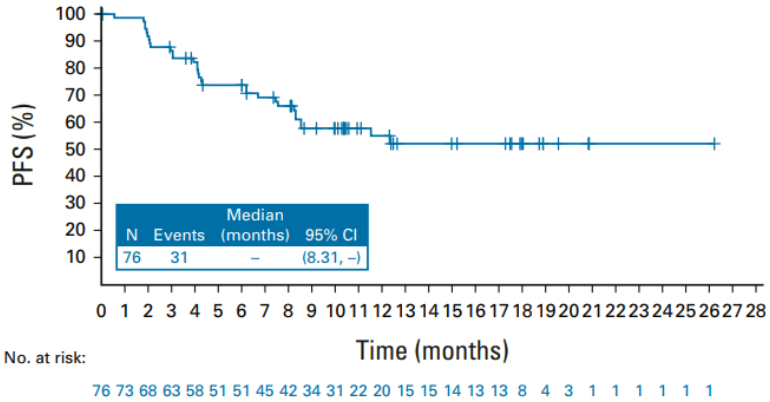
EV + Pembrolizumab (Cohort K, EV-103) 1L cisplatin ineligible

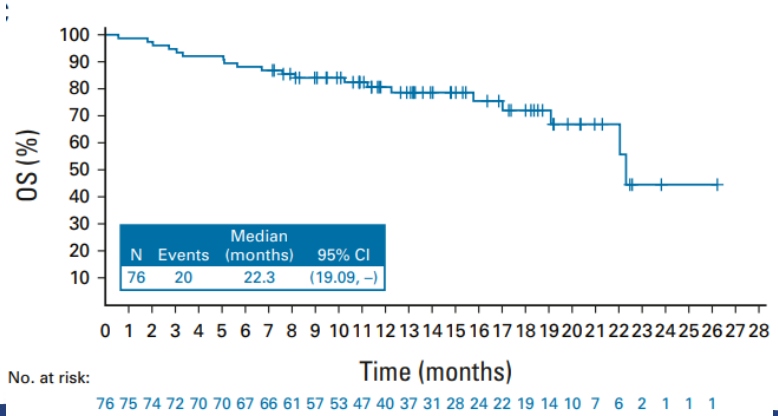


O´Donnell PH, et al. J Clin Oncol. 2023 Sep 1;41(25):4107-4117.

EV + Pembrolizumab (Cohort K, EV-103) 1L cisplatin ineligible

	EV + Pembro (N = 76)
PFS events, No.	31
PFS rate at 12 months, % 95% CI	55.1 (41.84, 66.48)
mPFS, months 95% CI	– (8.31, –)
OS events, No.	20
OS rate at 12 months, % 95% CI	80.7 (69.42, 88.13)
mOS, months 95% CI	22.3 (19.09, –)
Follow-up time, months, median 95% CI	14.8 (12.91, 17.28)





O´Donnell PH, et al. J Clin Oncol. 2023 Sep 1;41(25):4107-4117.

1Line EV + Pembrolizumab (EV-302)

EV-302/KEYNOTE-A39 (NCT04223856)

Patient population (N=886)
- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor-naive
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

R 1:1

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

Chemotherapy
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

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

Dual primary endpoints:
- PFS by BICR
- OS

Select secondary endpoints:
- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Prespecified subgroups:
- Stratification factors
  - Cisplatin eligibility (eligible, ineligible)
  - PD-L1 expression (low, high)
  - Liver metastases (present, absent)
- Age (<65, ≥65 years old)
- Region (North America, Europe, Rest of World)
- Sex (female, male)
- Race (white, other)
- ECOG PS at baseline (0, 1-2)
- Visceral metastases vs. lymph node only metastases
- Primary disease site of origin (upper tract, lower tract)
- Renal function (normal, mild, moderate, severe)

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

Maintenance therapy was permitted if deemed appropriate by the investigator following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 August 2023; FPI: 07 Apr 2020, LPI: 09 Nov 2022

[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 additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; NYHA, New York Heart Association; ORR, objective response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors

Powles T et al. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

1Line EV + Pembrolizumab (EV-302)

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

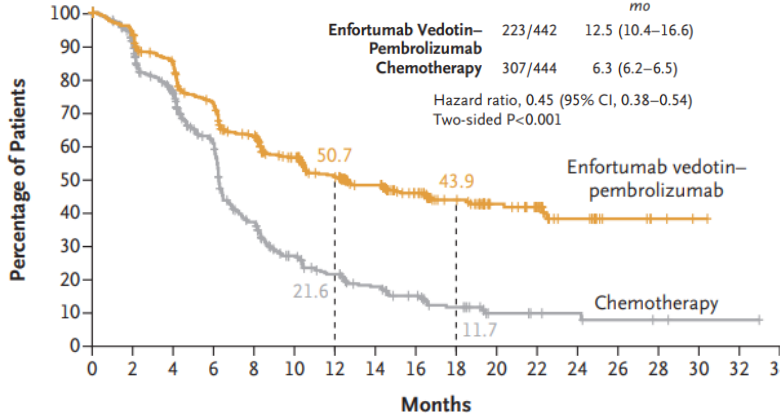
Powles T et al. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

1Line EV + Pembrolizumab (EV-302)

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

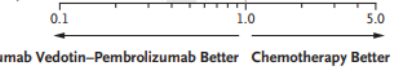


No. at Risk

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

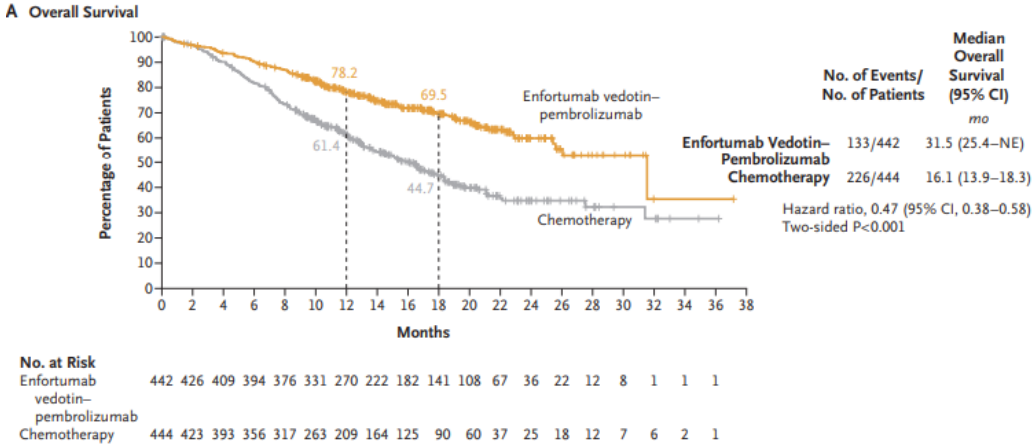
B Subgroup Analysis

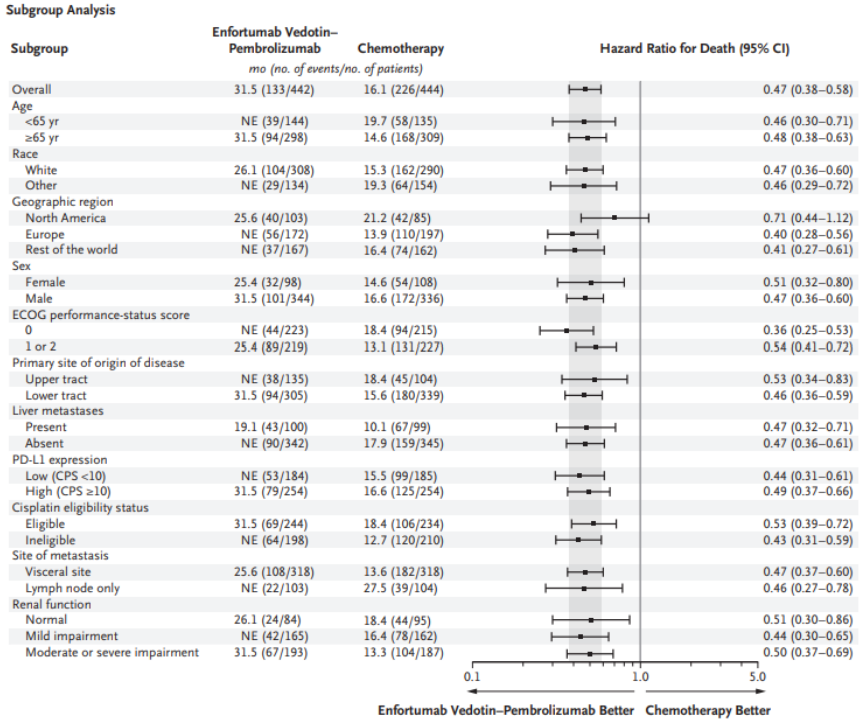
Subgroup	Enfortumab Vedotin–Pembrolizumab	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
	mo (no. of events/no. of patients)		
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
Age			
<65 yr	12.7 (75/144)	6.4 (88/135)	0.45 (0.32–0.62)
≥65 yr	12.0 (148/298)	6.2 (219/309)	0.45 (0.36–0.56)
Race			
White	10.4 (168/308)	6.2 (207/290)	0.48 (0.39–0.60)
Other	22.3 (55/134)	6.5 (100/154)	0.39 (0.27–0.55)
Geographic region			
North America	12.0 (58/103)	6.3 (55/85)	0.56 (0.38–0.82)
Europe	10.4 (94/172)	6.3 (144/197)	0.50 (0.38–0.66)
Rest of the world	NE (71/167)	6.2 (108/162)	0.35 (0.26–0.48)
Sex			
Female	10.4 (55/98)	6.1 (74/108)	0.49 (0.34–0.71)
Male	14.6 (168/344)	6.3 (233/336)	0.44 (0.36–0.54)
ECOG performance-status score			
0	22.3 (93/223)	6.7 (146/215)	0.36 (0.28–0.48)
1 or 2	9.3 (130/219)	6.1 (161/227)	0.53 (0.42–0.68)
Primary site of origin of disease			
Upper tract	12.7 (69/135)	6.2 (70/104)	0.50 (0.35–0.71)
Lower tract	12.5 (152/305)	6.3 (236/339)	0.44 (0.35–0.54)
Liver metastases			
Present	8.2 (66/100)	6.0 (78/99)	0.53 (0.38–0.76)
Absent	16.4 (157/342)	6.4 (229/345)	0.43 (0.35–0.52)
PD-L1 expression			
Low (CPS <10)	10.5 (105/184)	6.3 (127/185)	0.50 (0.38–0.65)
High (CPS ≥10)	18.5 (116/254)	6.2 (176/254)	0.42 (0.33–0.53)
Cisplatin eligibility status			
Eligible	14.6 (117/244)	6.5 (149/234)	0.48 (0.38–0.62)
Ineligible	10.6 (106/198)	6.1 (158/210)	0.43 (0.33–0.55)
Site of metastasis			
Visceral site	10.4 (176/318)	6.2 (238/318)	0.45 (0.37–0.55)
Lymph node only	NE (38/103)	8.3 (55/104)	0.40 (0.26–0.62)
Renal function			
Normal	18.7 (38/84)	6.7 (61/95)	0.46 (0.30–0.71)
Mild impairment	12.7 (79/165)	6.3 (114/162)	0.46 (0.34–0.62)
Moderate or severe impairment	10.5 (106/193)	6.2 (132/187)	0.47 (0.36–0.61)



Powles T, et al. N Engl J Med. 2024 Mar 7;390(10):875-888.

1Line EV + Pembrolizumab (EV-302)



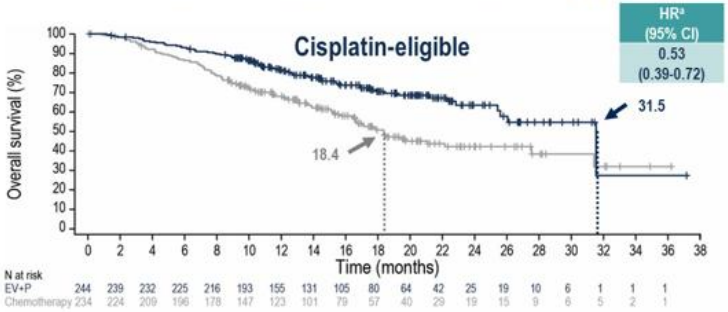


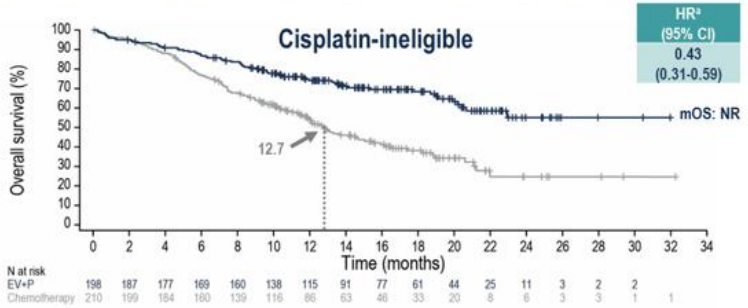
Powles T, et al. N Engl J Med. 2024 Mar 7;390(10):875-888.

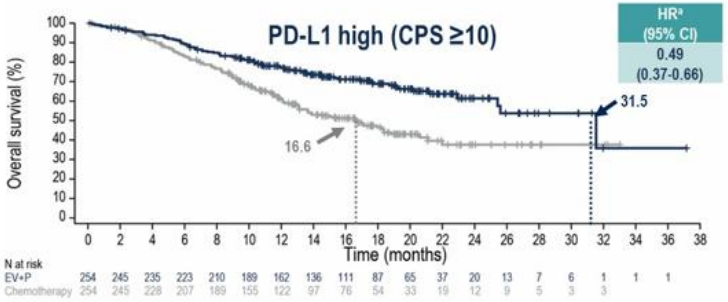
1Line EV + Pembrolizumab (EV-302)

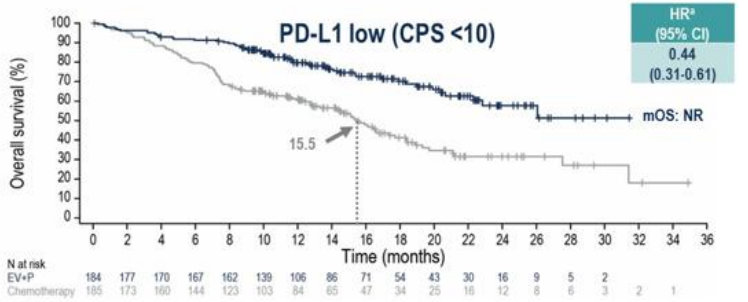
OS Subgroup Analysis: Cisplatin Eligibility and PD-L1 Expression

OS benefit was consistent with the overall population regardless of cisplatin eligibility or PD-L1 expression status









Data cutoff: 08 August 2023

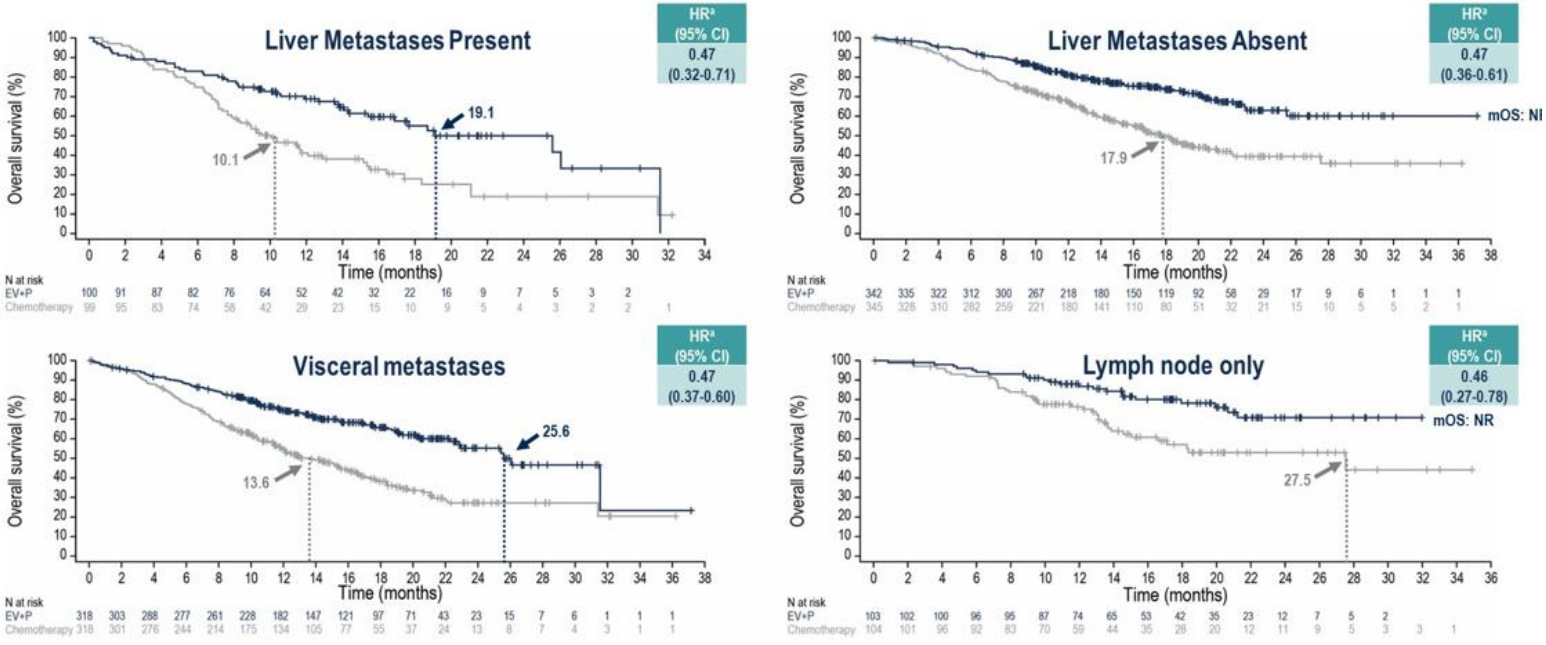
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

van der Heijden MS et al. ASCO GU 2024

1Line EV + Pembrolizumab (EV-302)

OS Subgroup Analysis: Liver Metastases and Metastatic Disease Site

OS benefit was consistent with the overall population regardless of the presence or absence of liver or visceral metastases



Data cutoff: 08 August 2023

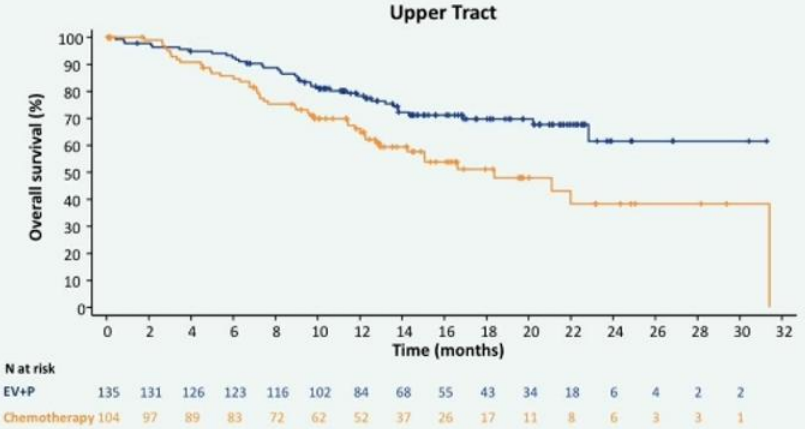
[a]Calculated using stratified Cox proportional hazards model, a hazard ratio <1 favors the EV+P arm

van der Heijden MS et al. ASCO GU 2024

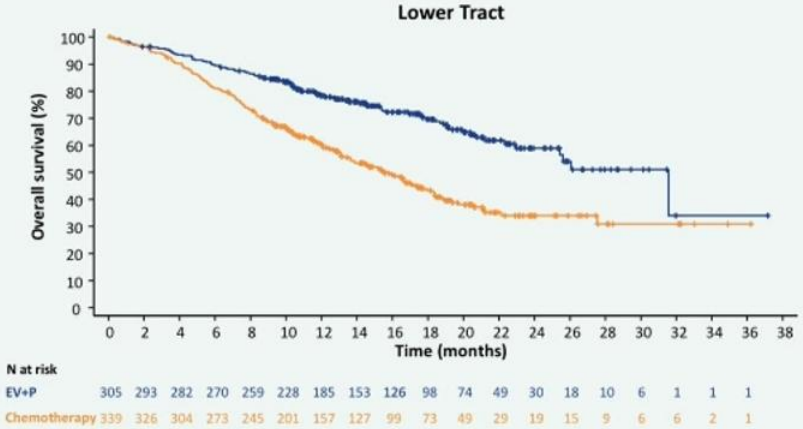
1Line EV + Pembrolizumab (EV-302)

New Data: OS Subgroup Analysis by Primary Disease Site

OS Benefit Was Consistent With Overall Population Regardless of Primary Disease Site



	Events, n	HR[a] (95% CI)	mOS (95% CI), months
EV+P	38	0.53 (0.34–0.83)	NR (22.8–NR)
Chemotherapy	45		18.4 (12.7–NR)



	Events, n	HR[a] (95% CI)	mOS (95% CI), months
EV+P	94	0.46 (0.36–0.59)	31.5 (25.4–NR)
Chemotherapy	180		15.6 (13.3–17.7)

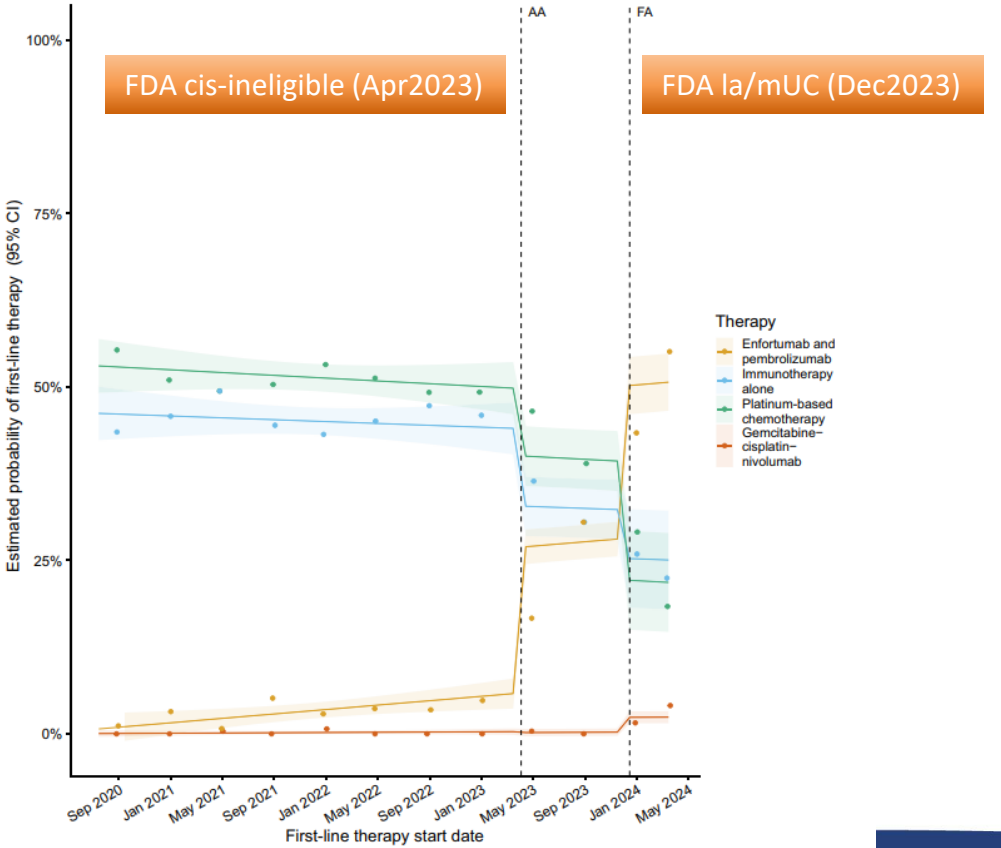
Data cutoff: 08 Aug 2023

Bedke J et al. EAU 2024

1Line EV + Pembrolizumab (EV-302)

Variable	Enfortumab Vedotin–Pembrolizumab (N=437)	Chemotherapy (N=441)
Confirmed best overall response — no. (%)		
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)
Could not be evaluated†	0	4 (0.9)
No assessment‡	21 (4.8)	32 (7.3)
Confirmed overall response (95% CI) — %§	67.7 (63.1–72.1)	44.4 (39.7–49.2)
Median time to response (range) — mo	2.1 (1.3–12.3)	2.1 (1.6–8.3)
Median duration of response (95% CI) — mo	Not reached (20.2–NE)	7.0 (6.2–10.2)

Bedke J et al. EAU 2024

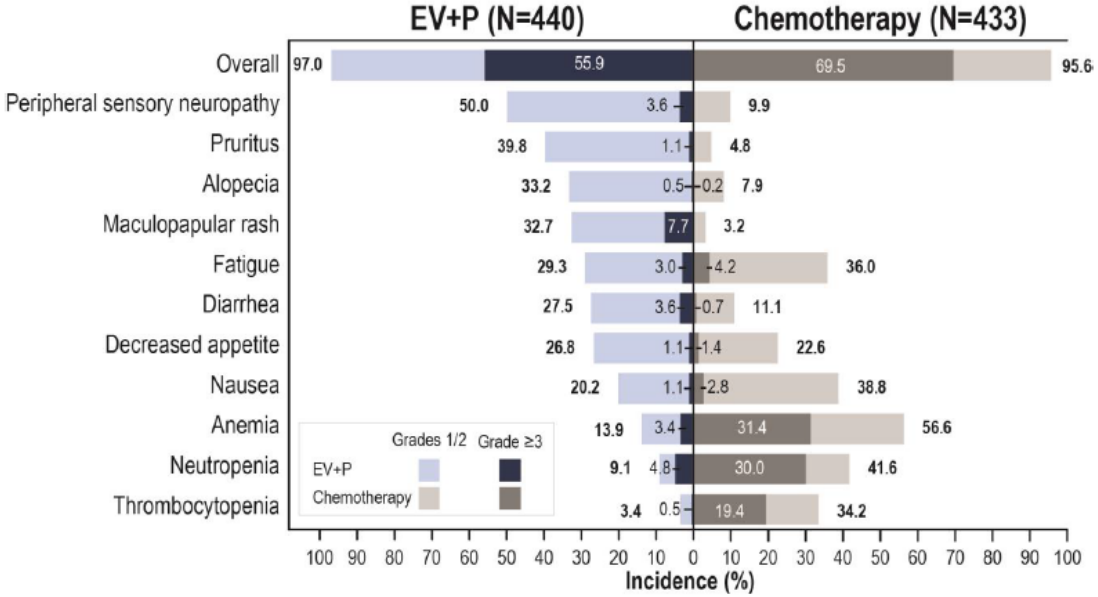


Mamtani R, et al. Eur Urol. 2024 Nov;86(5):474-476

1Line EV + Pembrolizumab (EV-302)

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

Powles T et al. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

EV-103 dose escalation/cohort A (DE/A): 5y follow-up

Treatment-related AESIs for EV

- Most events were of low grade (1 or 2) (**Table 4**)
- The most common treatment-related AESIs for EV of any-grade were skin reactions (66.7%)
- The most common Grade ≥3 treatment-related AESIs for EV were skin reactions (22.2%)

Table 4. Treatment-related AESIs for EV

	Dose Escalation/Cohort A (N=45)	
	Any grade n (%)	Grade ≥3 n (%)
Skin reactions	30 (66.7)	10 (22.2)
Peripheral neuropathy[a]	28 (62.2)	2 (4.4)
Ocular disorders	18 (40.0)	0
Dry eye	16 (35.6)	0
Blurred vision	5 (11.1)	0
Corneal disorders	1 (2.2)	0
Hyperglycemia	5 (11.1)	4 (8.9)
Infusion related reactions	3 (6.7)	1 (2.2)

There were no Grade 5 treatment-related AESIs for EV.
[a]Peripheral neuropathy Standardized MedDRA queries (broad scope). 8 patients had pre-existing peripheral neuropathy and 37 did not have pre-existing peripheral neuropathy. Pre-existing condition includes medical history and conditions ongoing at baseline.

Onset, improvement, and resolution for treatment-related AESIs for EV

- The majority of the EV treatment-related AESIs improved or resolved (**Table 5**)
- Median time to onset of skin reactions and hyperglycemia was 0.7 and 0.5 months, respectively, and median time to resolution was 1.2 and 1.6 months, respectively
- Median time to onset of peripheral neuropathy was 2.4 months, while median time to resolution was 8.6 months

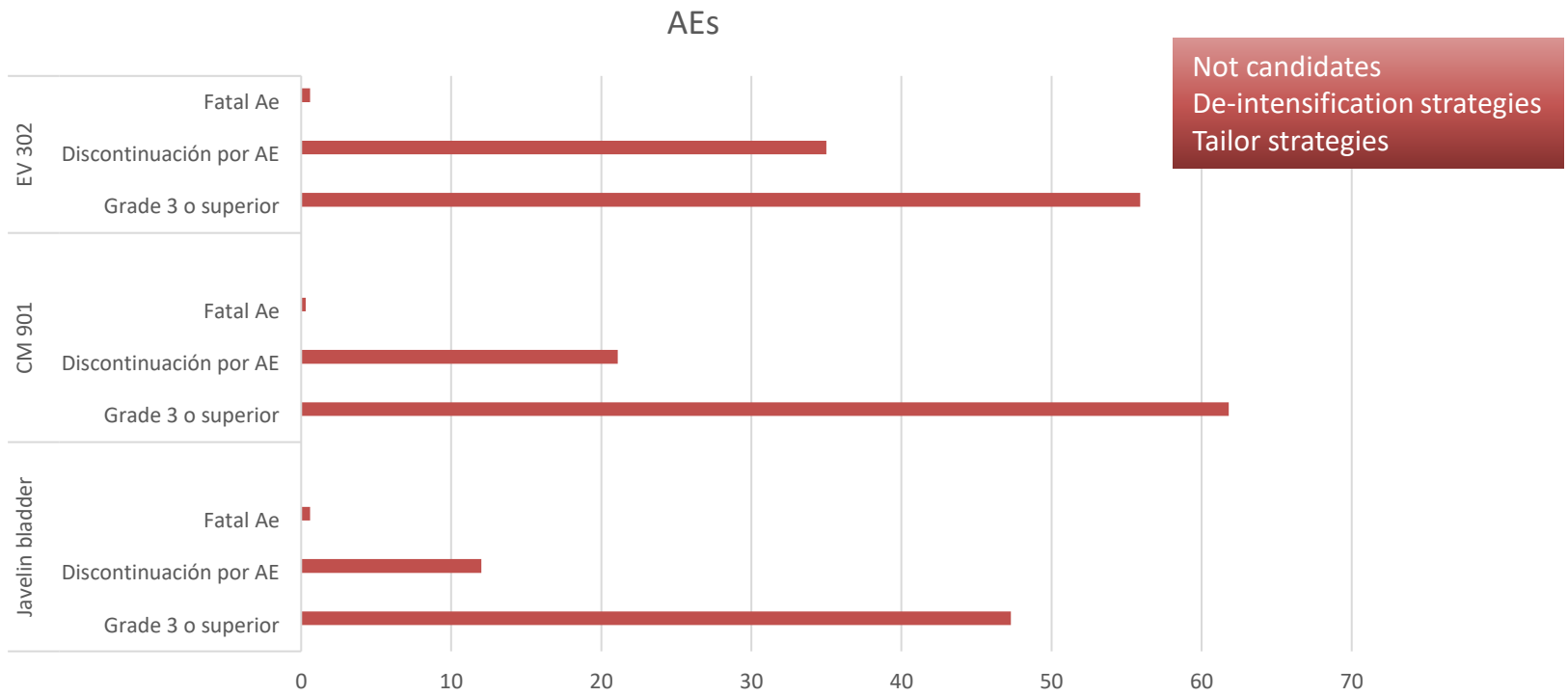
Table 5. Onset, improvement, and resolution for treatment-related AESIs for EV

	Total number of events[a] n	Events[a] with improvement n (%)	Events[a] with resolution n (%)	Median time to:		
				Onset of first event (range), mo	Improvement[b] (range), mo	Resolution[c] (range), mo
Skin reaction	66	2 (3.0)	59 (89.4)	0.7 (0.1-15.7)	0.7 (0.2-1.2)	1.2 (0.1-27.1)
Peripheral neuropathy	43	19 (44.2)	11 (25.6)	2.4 (0.7-12.5)	5.5 (0.3-27.4)	8.6 (3.5-56.7)
Hyperglycemia	7	1 (14.3)	6 (85.7)	0.5 (0.3-3.5)	0.5 (0.5-0.5)	1.6 (0.5-19.7)

[a]Patients could have had >1 event. [b]Improvement defined as at least 1 grade improvement from the worst grade at the last assessment. [c]Resolution defined as a return to baseline grade or better at the last assessment or recovered outcome.

Rosenberg J, et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169

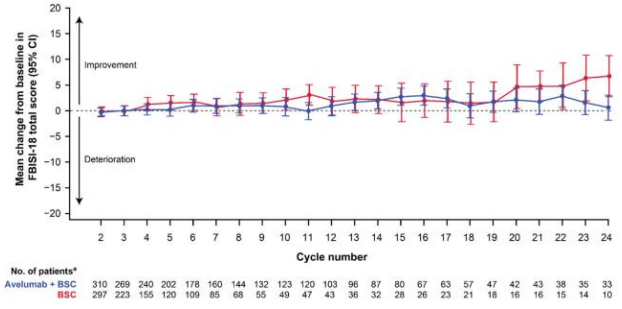
SAFETY IN THE 1 LINE



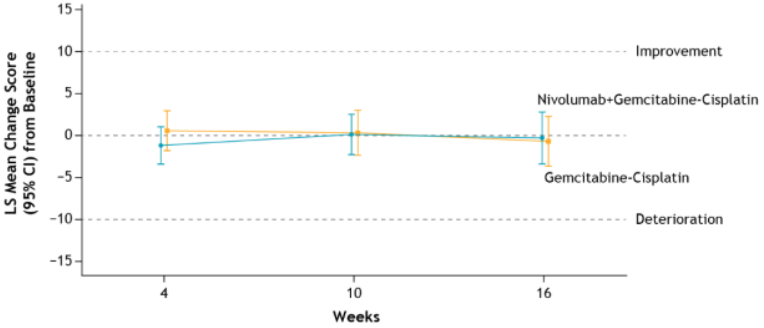
Powles T et al. NEJM 2021
van der Heijden MS et al. NEJM 2023
Powles T et al. NEJM 2024

QUALITY OF LIFE IN 1 LINE

Javelin bladder

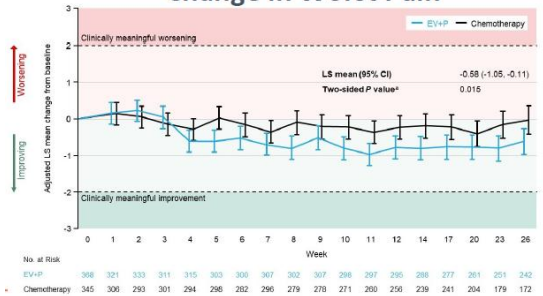


CM 901

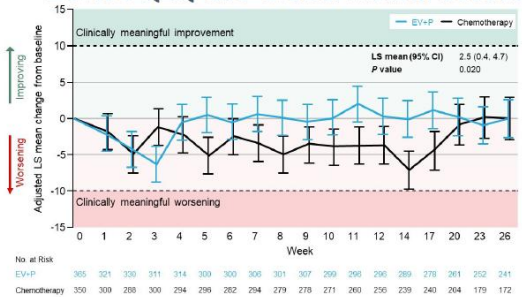


EV 302

Change in Worst Pain



EORTC QLQ-C30 Global Health Scores



Grivas P et al. Eur Urol 2023
van der Heijden MS et al. NEJM 2023
Milowsky M et al. JCO 2024

OVERALL SURVIVAL IN 1 LINE

CG: mOS: 14m
2yOS rate: 20%

Javelin bladder

HR: 0,69 (0,56-0,86) p 0.001

Platinum based QT+Avelumab — mOS: 21.4m, 2yOS rate: 50%

BSC — mOS: 14.3m

Selected population
No PG

CM 901

HR: 0,78 (0,63-0,96) p 0.02

Cisplatin/Gemcitabine/Nivolumab — mOS: 21.7m, 2yOS rate: 47%

Cisplatin/Gemcitabine — mOS: 18.9m

Only CIS elegible

20% received avelumab

EV 302

HR: 0,47 (0,38-0,58) p <0.001

Enfortumab vedotin/Pembrolizumab — mOS: 31.5m, 2yOS rate: 60%

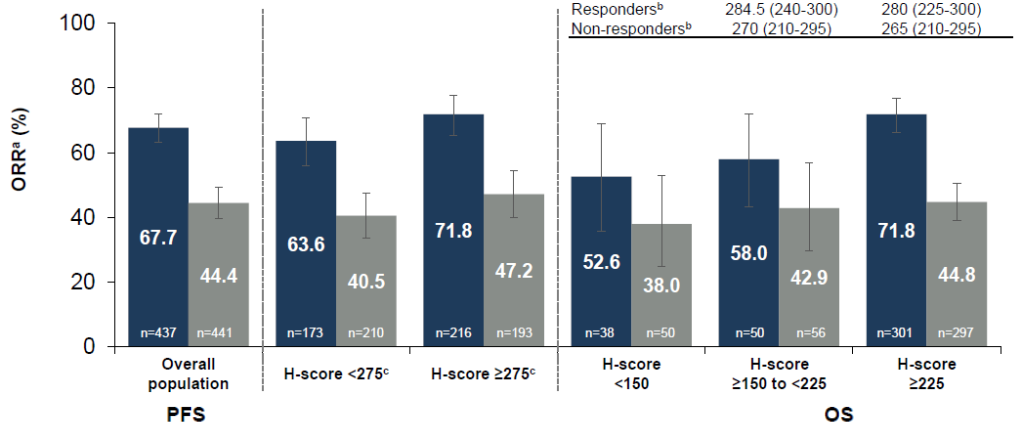
Platinum based QT ** — mOS: 16.1m

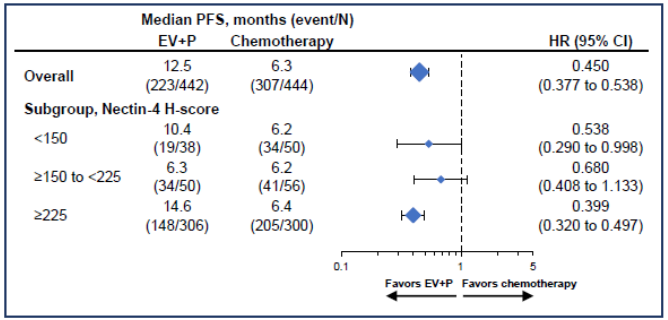
30,4% received avelumab

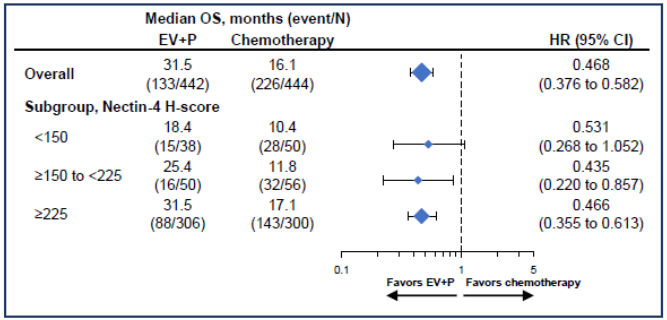
Powles T et al. NEJM 2021
van der Heijden MS et al. NEJM 2023
Powles T et al. NEJM 2024

Nectin-4 expression and response to 1L EV + P

Nectin-4 H-score, median (IQR)	EV+P n=437	Chemotherapy n=441
Responders[b]	284.5 (240-300)	280 (225-300)
Non-responders[b]	270 (210-295)	265 (210-295)







Powles T, et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169

FUTURE 1L: TARGETING HER2/FGFR

RC48G001 Cohort C Study Design

ITT Population (N=170)

Previously untreated HER2-positive/ HER2-low expressing la/mUC

Eligibility
- Age ≥18 years
- la/mUC
- HER2 status:[a]
  - HER2-positive: IHC 3+, ***or*** IHC 2+ and ISH-positive
  - HER2-low: IHC 2+ and ISH-negative, ***or*** IHC 1+
- ECOG PS of 0-2[b]

[a] HER2 IHC status will be determined by central laboratory.
[b] ECOG PS of 2 was allowed if hemoglobin ≥10 g/dL and CrCl ≥50 mL/min.

Part 1 (Safety Run-In)

Disitamab vedotin Q2W + pembrolizumab Q6W *6-week cycles*

N=20

Part 2 (Randomized; Currently Enrolling)

R 1:1

Disitamab vedotin Q2W + pembrolizumab Q6W *6-week cycles*

n=75

Disitamab vedotin Q2W *6-week cycles*

n=75

Primary Endpoint
- cORR per BICR

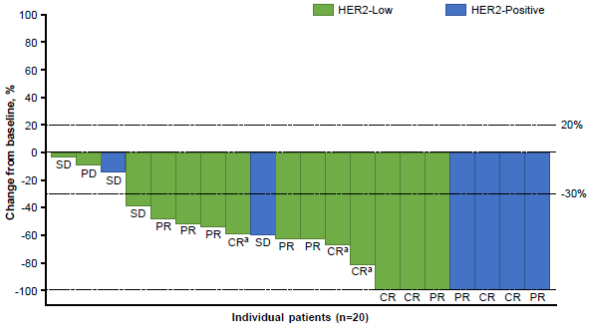
Secondary Endpoints
- cORR per investigator assessment
- DOR, PFS, DCR per BICR and investigator
- OS
- Safety

Disease assessments Q8W from C1D1 for 72 weeks, then Q12W until progression per BICR

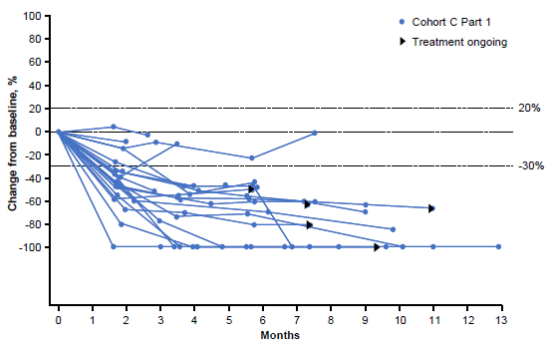
Overall Population	Cohort C N=20
Confirmed ORR, n (%)[a]	15 (75.0) [95% CI: 50.9-91.3]
Best overall response, n (%)[b]	
Complete response	7 (35.0)
Partial response	8 (40.0)
Stable disease	4 (20.0)
Progressive disease	1 (5.0)
HER2-Positive Group	**n=6**
Confirmed ORR, n (%)[a]	4 (66.7) [95% CI: 22.3-95.7]
HER2-Low Group	**n=14**
Confirmed ORR, n (%)[a]	11 (78.6) [95% CI: 49.2-95.3]

Median DOR was not reached (95% CI, 3.9 to NR)

Best Percent Change in Sum of Diameters From Baseline per BICR



Percent Change in Sum of Diameters From Baseline Over Time per BICR



Galsky M, et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169

FUTURE 1L: TARGETING HER2/FGFR

Treatment
Futibatinib 20 mg PO QD plus pembrolizumab 200 mg IV Q3W

Study population
- Age ≥18 years
- Histologically confirmed mUC
- No prior therapy for advanced/metastatic disease
- Unfit for or declining platinum-based chemotherapy[a]
- ECOG PS of 0 or 1

Safety lead-in[b]
(first 6 patients enrolled)
FGFR alteration agnostic

Cohort A (n=17)[c]
FGFR3 mutations or
FGFR1–4 rearrangements/fusions

Cohort B (n=26)
Wild-type or other *FGFR* / non–*FGFR*-aberrant tumors not included in Cohort A

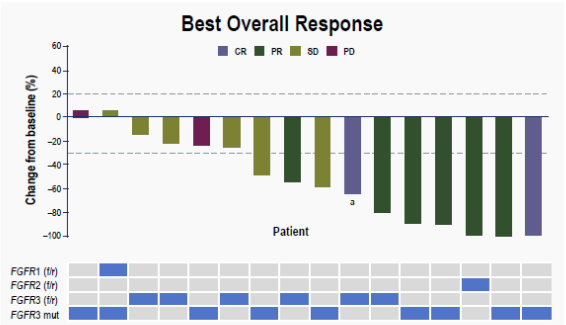
Treatment to continue until disease progression, unacceptable toxicity, or another criterion for discontinuation is met[d]

Primary endpoint
- Confirmed ORR

Secondary endpoints
- DCR
- DOR
- PFS
- OS
- Safety profile

- Global, two-cohort, noncomparative phase 2 study (NCT04601857)

Cohort A: *FGFR1–4* (fusions/rearrangements)/*FGFR3* mutations



- 14 (82.4%) of evaluable patients had a reduction in target lesions
- 3 (37.5%) patients had an ongoing response ≥6 months
- Median time to first response was 2.3 months

Data cut-off: March 8, 2024

[a]Patient had 1 lymph node measuring 22mm at baseline, which reduced to 8mm following treatment and was classified as CR per RECIST1.1. [b]Primary Reason Listed for End of Treatment: AE/SAE (n=3), disease progression (n=2), clinical disease progression (n=2), radiologic progression (n=4), death (n=1). cORR, confirmed objective response rate; CI, confidence interval; CR, complete response; DCR, disease control rate; fir, fusions/rearrangements; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mut, mutations; NA, not available; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Overall Efficacy Summary

Measure	Cohort A *FGFR1–4* (fir)/*FGFR3 mut* (n=17)
cORR, % (95% CI)	47.1 (23.0, 72.2)
CR	2 (11.8)
PR	6 (35.3)
SD	6 (35.3)
PD	2 (11.8)
NA	1 (5.9)
DCR, % (95% CI)	82.4 (56.6, 96.2)
Median follow-up, months	17.8
mDOR, months (95% CI)	12.3 (6.5, 24.0)
mPFS, months (95% CI)	8.3 (3.5, 18.5)
12-month PFS, %	49.2
mOS, months (95% CI)	NE (6.6, NE)
12-month OS, %	63.0
Median treatment duration, days (range)	
Futibatinib	196 (42–593)
Pembrolizumab	176 (1–576)
Discontinued treatment, n (%)[b]	12 (70.6)

Koshkin VS, et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169

CONCLUSIONS

Patients diagnosed with mUC:
25% do not reach the first line therapy
50% never get second-line therapy
75% never get 3rd line therapy

The relevance of giving the best therapy first.

Different treatment combination therapies have demonstrated a significant improvement in OS in the first-line/maintenance setting

- EV plus Pembrolizumab: considered the new SoC.
- Cisplatin-based chemotherapy plus Nivolumab
- Platinum-based chemotherapy → maintenance Avelumab

Novel trials on adjuvant and neoadjuvant including CT + IO combinations (and even ADC) will change the treatment sequence in those patients.