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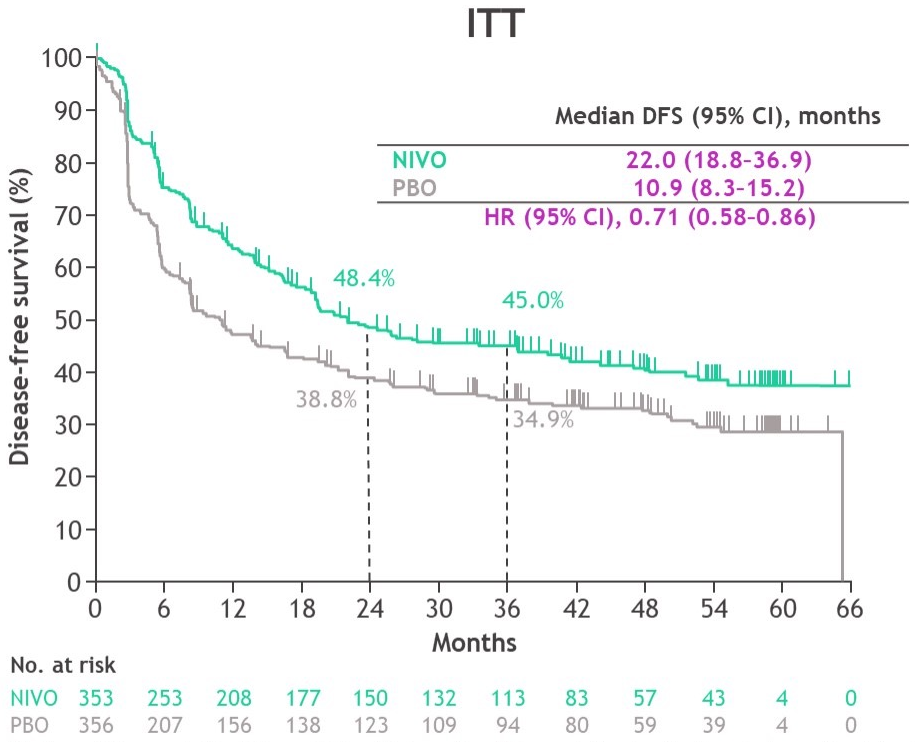
Updates on immunotherapy and ADCs in advanced urothelial cancers

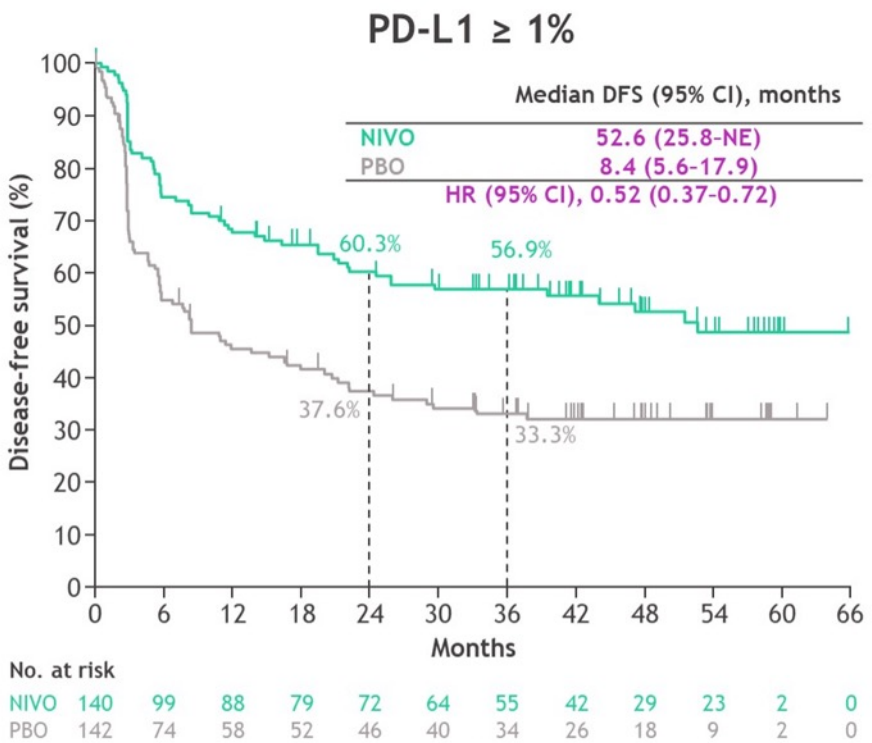
Jonathan Rosenberg, MD
Chief, Genitourinary Oncology Service
Enno Ercklentz Chair
Department of Medicine
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

Treatment Landscape of advanced UC

- Cisplatin-based neoadjuvant chemotherapy is standard for eligible muscle invasive UC patients
- Adjuvant immunotherapy is an option for patients
- Enfortumab vedotin and pembrolizumab approved for metastatic UC
- Platinum based chemotherapy is no longer the default option for metastatic UC patients
  - Role of avelumab maintenance is reduced in this new paradigm
- Patients who are not felt to be candidates for cytotoxic agents may receive pembrolizumab monotherapy

Adjuvant nivolumab improves continued disease-free survival in high-risk bladder cancer after cystectomy





Galsky et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA443)

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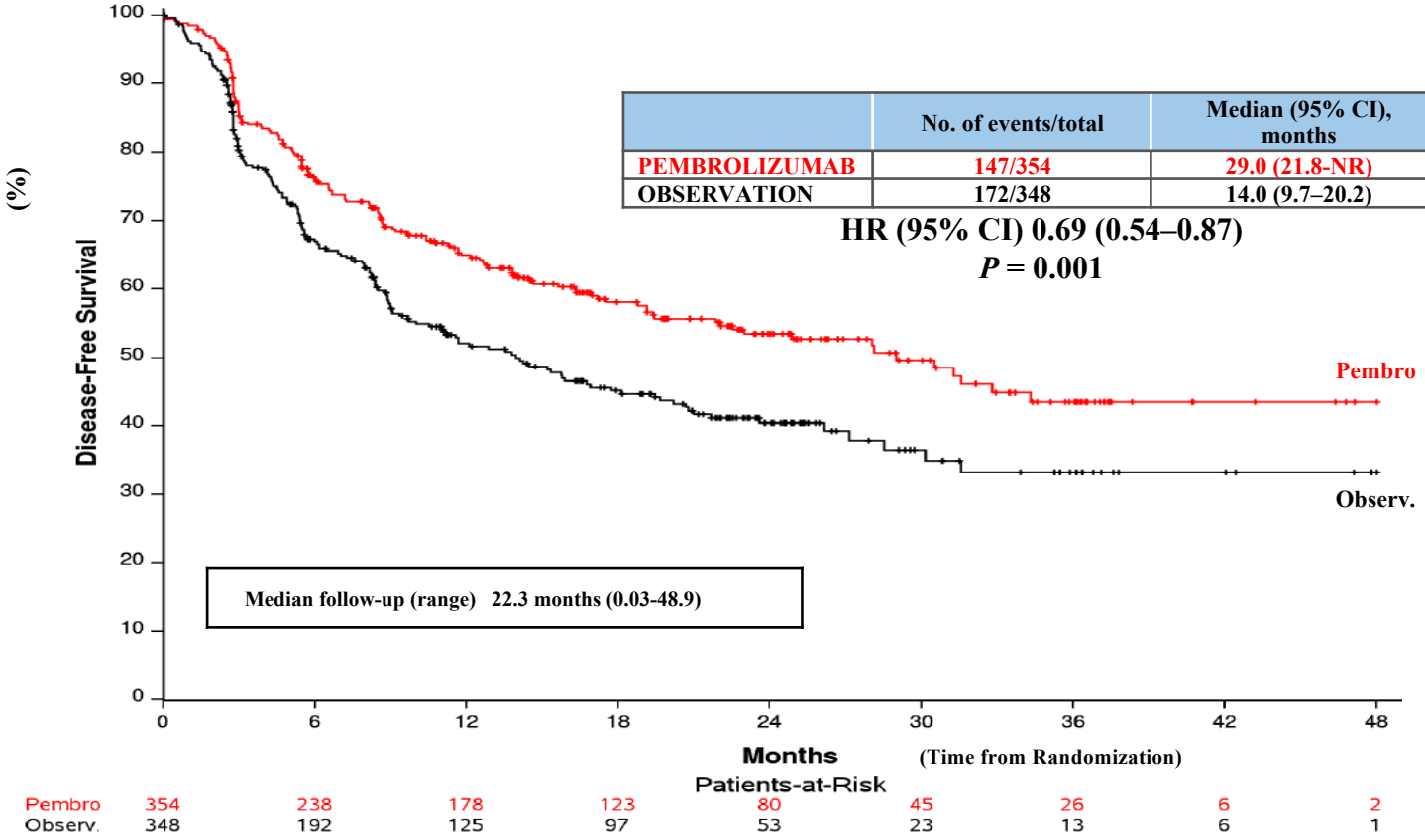
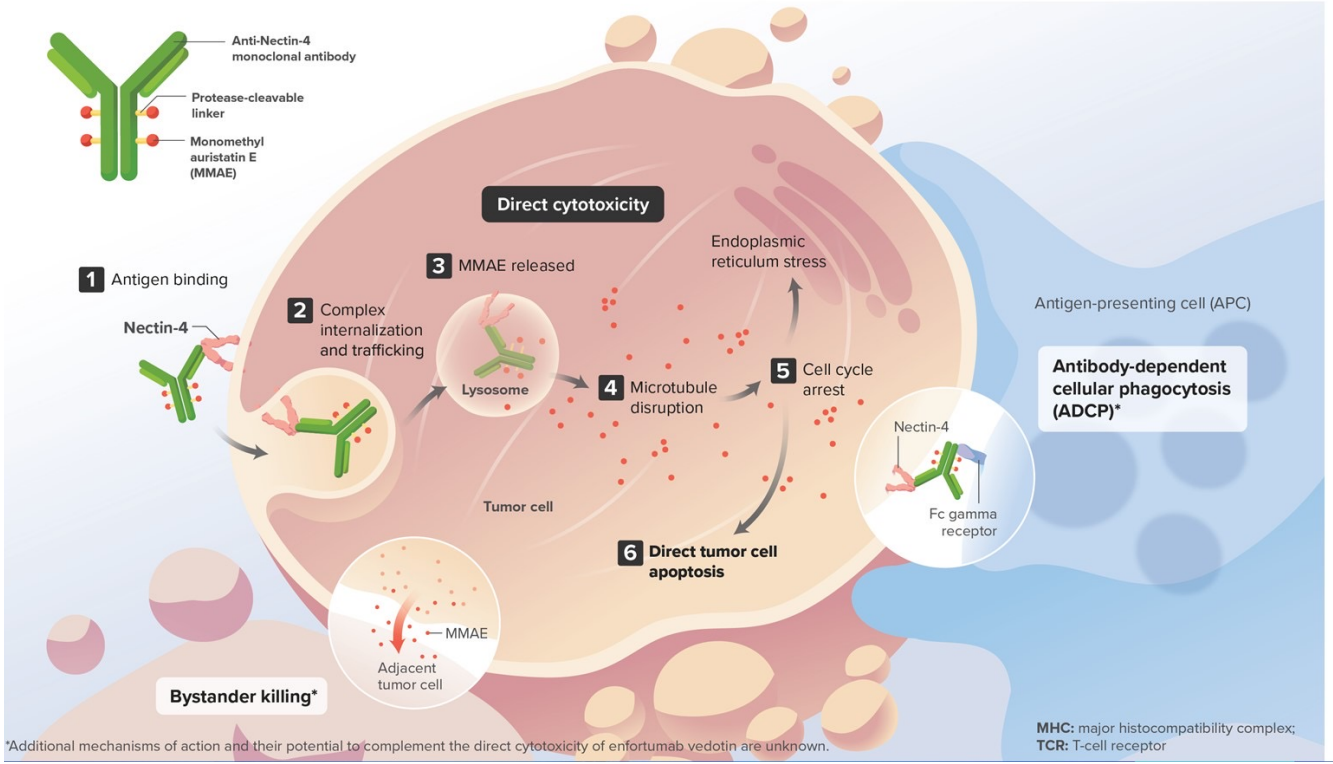
A031501 AMBASSADOR: Pembrolizumab Improves Disease-Survival Compared to Observation in high risk UC



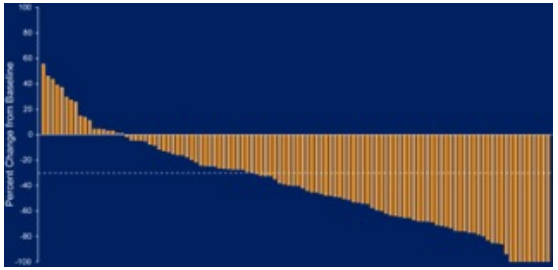
	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

Apolo et al. JCO 2024; 42 (supp 4) LBA531.

Metastatic UC: ADC Therapy with enfortumab vedotin



Targets Nectin-4 which is highly expressed in urothelial cancers



EV-201: post-IO/chemo

Rosenberg, et al. J Clin Oncol. 2019; 37(29):2592-2600.

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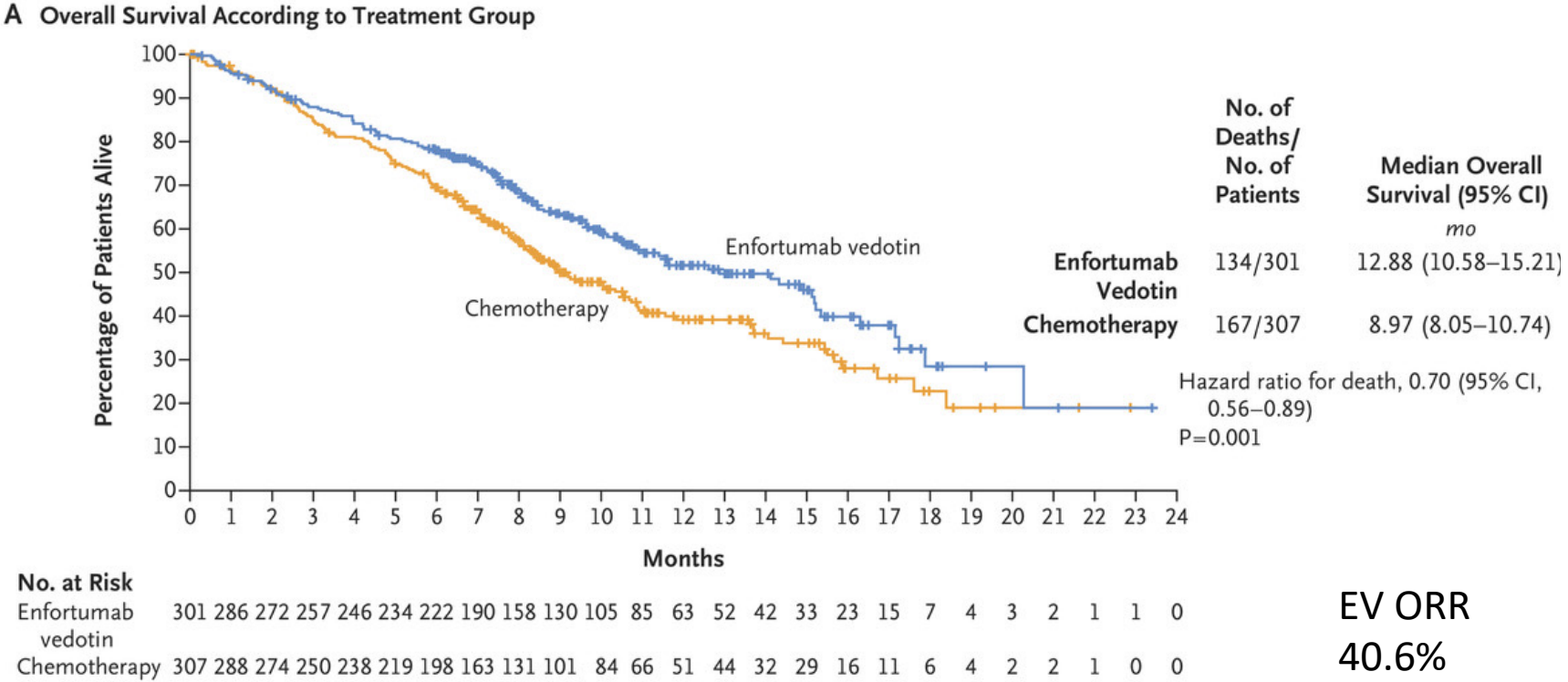
EV-301: EV improves survival compared to standard chemotherapy in platinum and CPI refractory patients



EV ORR 40.6%

PFS 5.55 vs. 3.71 months; hazard ratio for progression or death, 0.62; 95% CI, 0.51 to 0.75; P<0.001)

Powles, Rosenberg, et al. *NEJM* 2021

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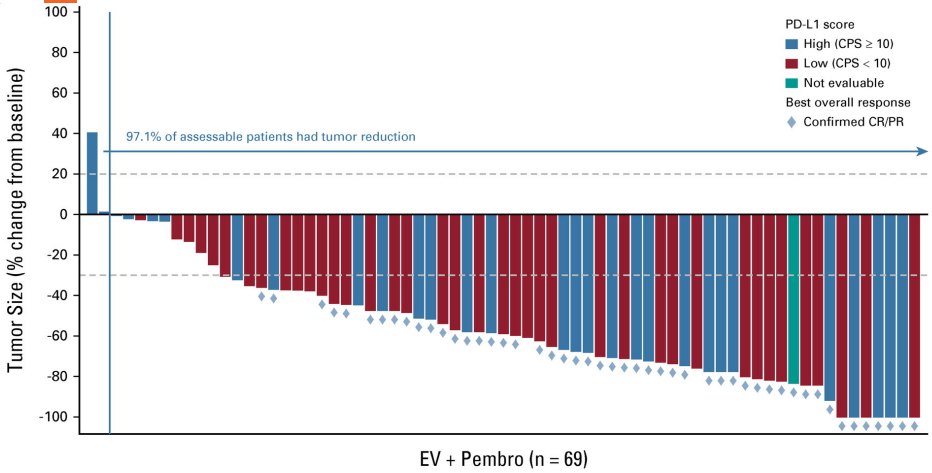
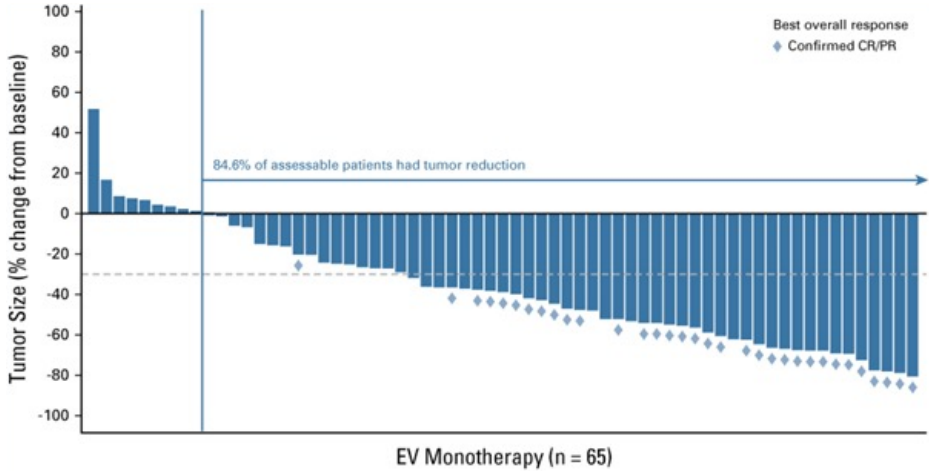
EV-103 Cohort K: EV +/- pembrolizumab



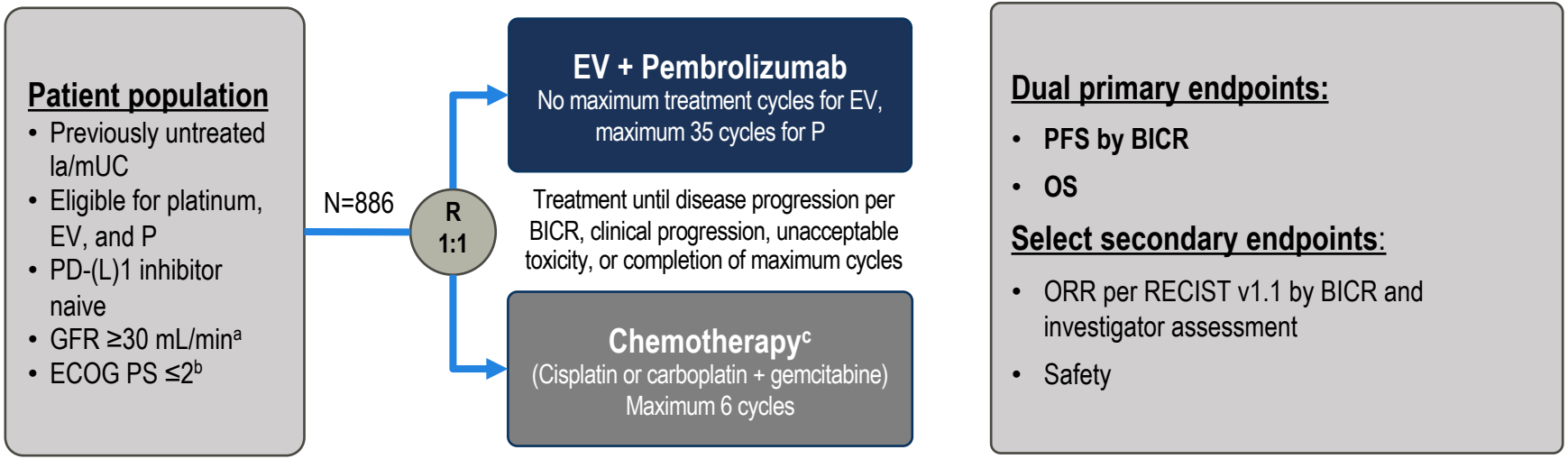


- EV/Pembro activity independent of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

	EV+Pembro (N=76)	EV Monotherapy (N=73)
Confirmed ORR (95% CI)	**64.5% (52.7-75.1)**	**45.2% (33.5-57.3)**
Complete response	10.5%	4.1%
Partial Response	53.9%	41.1%
Progressive Disease	7.9%	9.6%
Not evaluable or no assessment	5.3%	10.9%

O'Donnell et al. *JCO* 2023 41(25):4107-4117.

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

Adapted from Powles et al. ESMO 2023 LBA6

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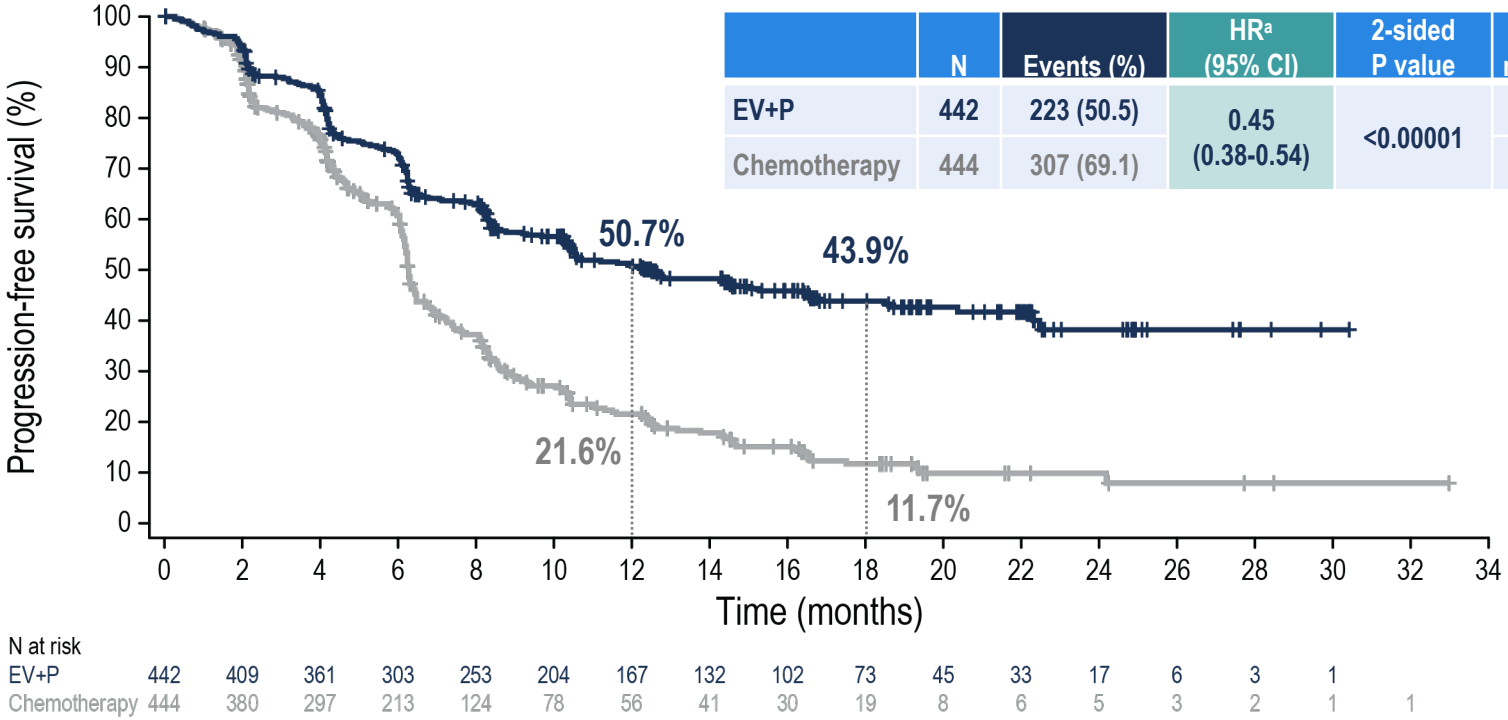
EV-302: Progression-Free Survival per BICR

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)



Adapted from Powles et al. ESMO 2023 LBA6

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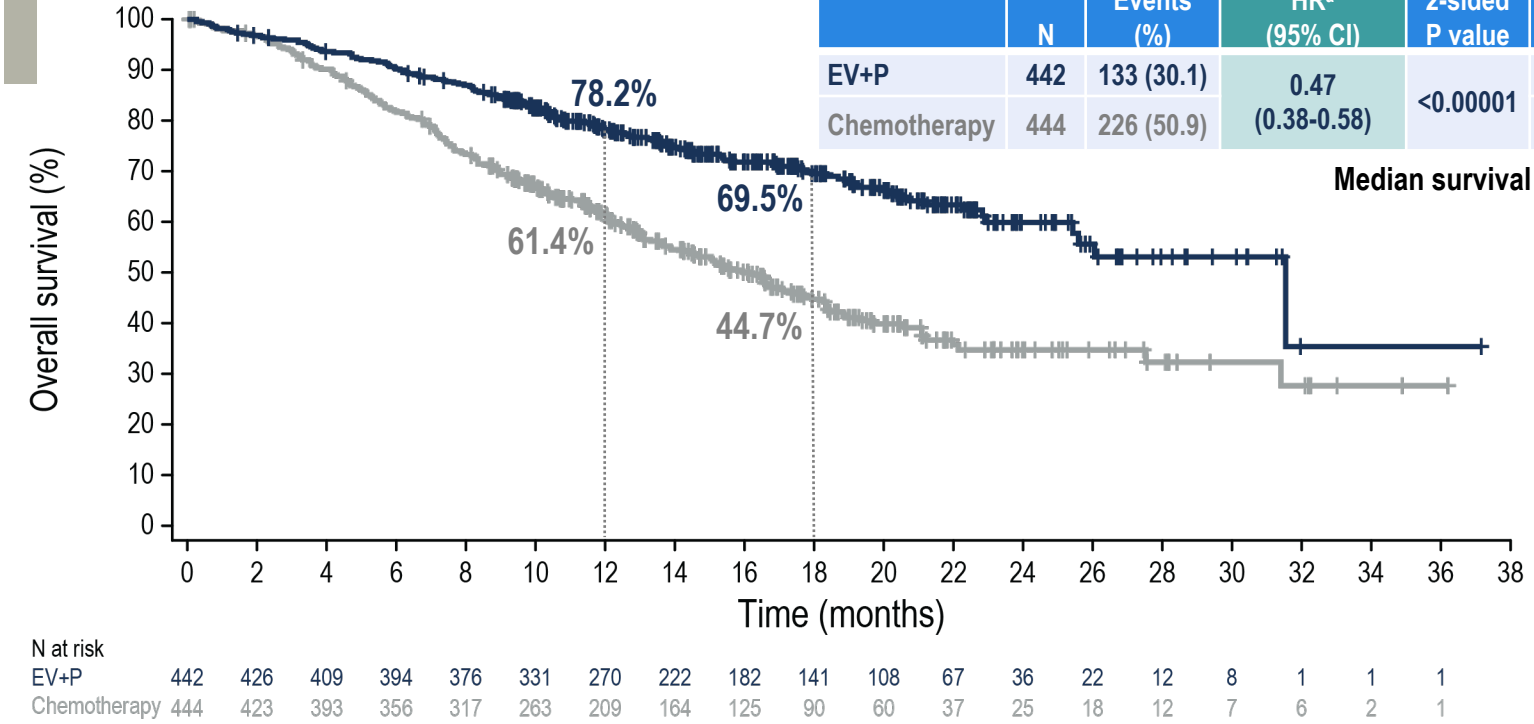
EV-302: Overall Survival

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



Adapted from Powles et al. ESMO 2023 LBA6

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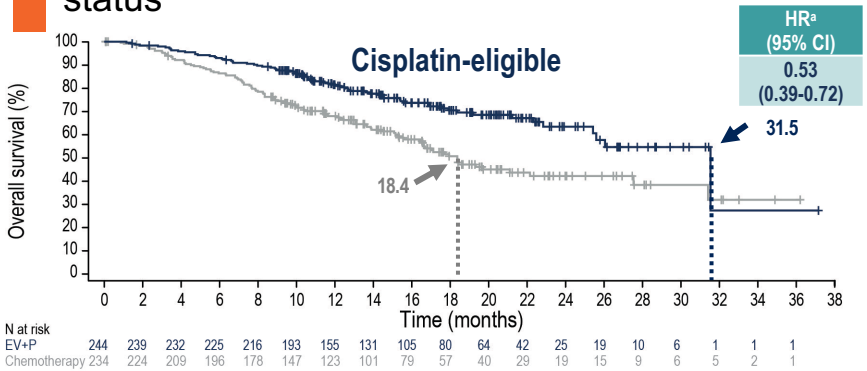
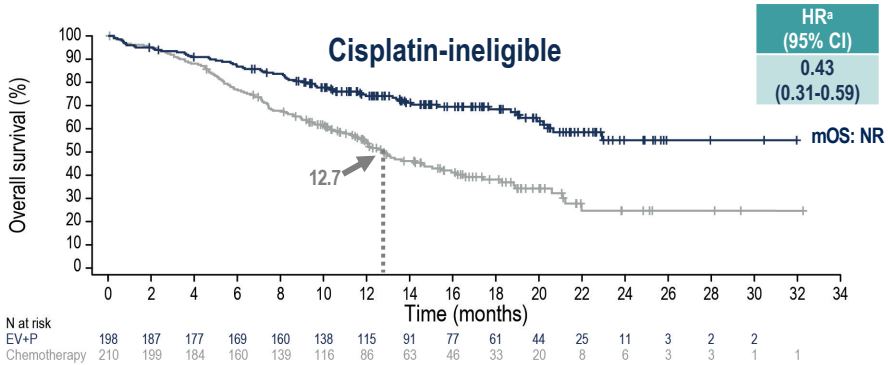
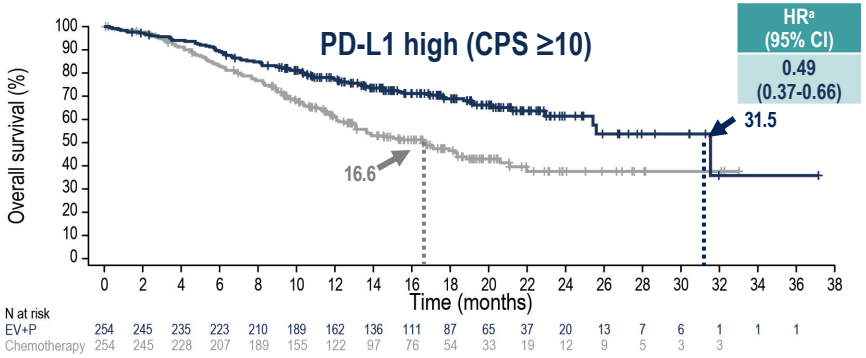
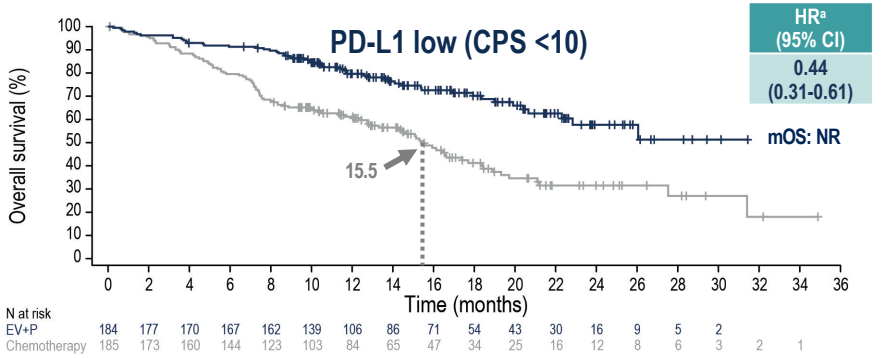
OS Subgroup Analysis: Cisplatin Eligibility and PD-L1 Expression

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. *J Clin Oncol* 42, 2024 (suppl 4; abstr LBA530)

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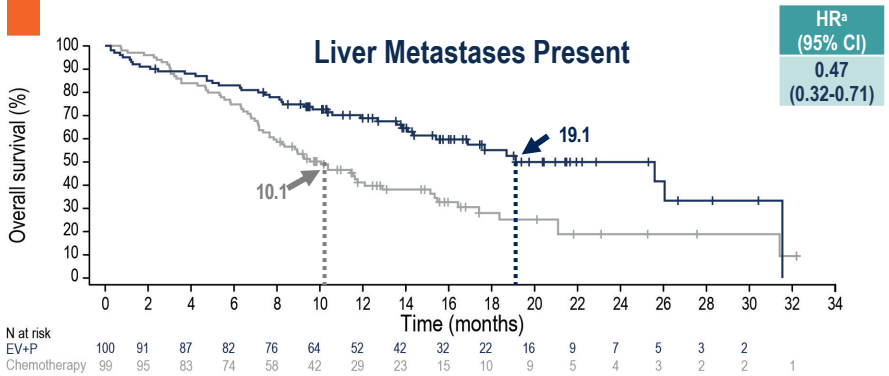
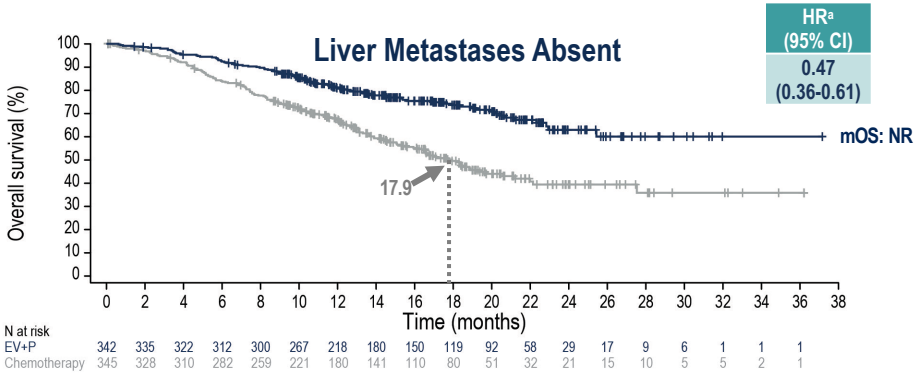
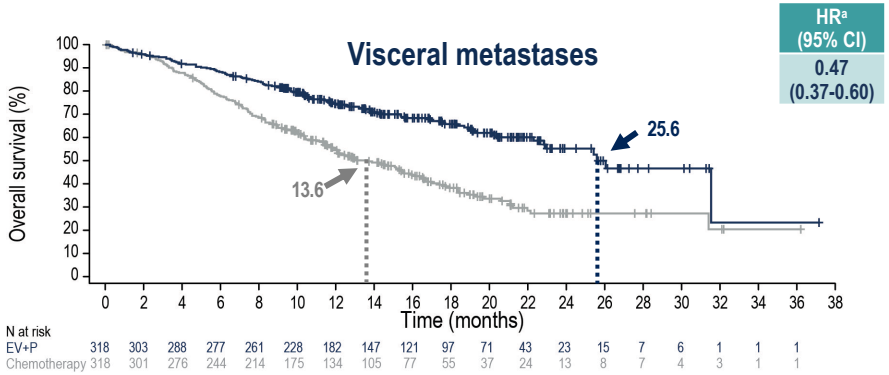
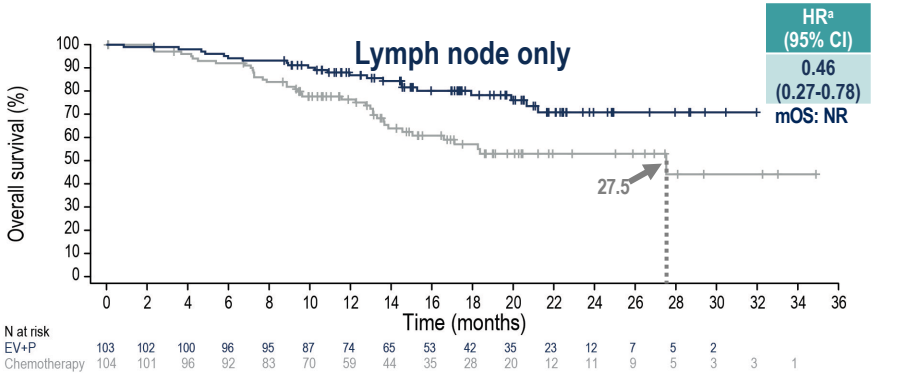
OS Subgroup Analysis: Liver Metastases and Metastatic Disease Site

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







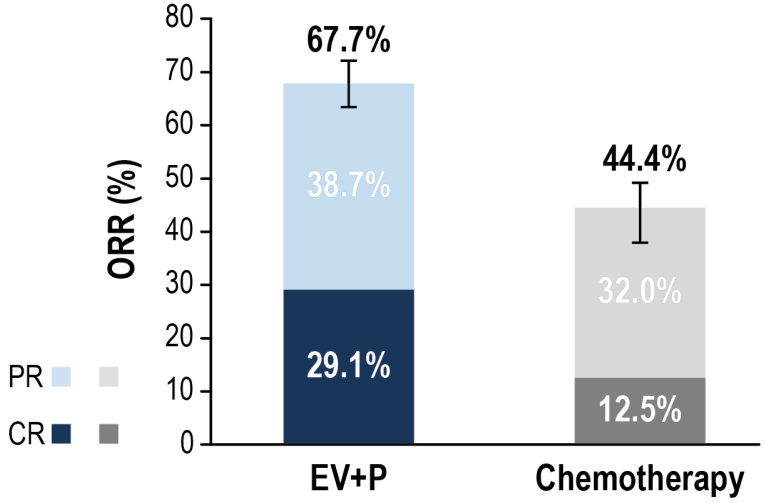


Data cutoff: 08 August 2023

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

EV-302: 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)

EV+P ORR is remarkably consistent across studies

Adapted from Powles et al. ESMO 2023 LBA6

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EV-302: Summary of Subsequent Systemic Therapy

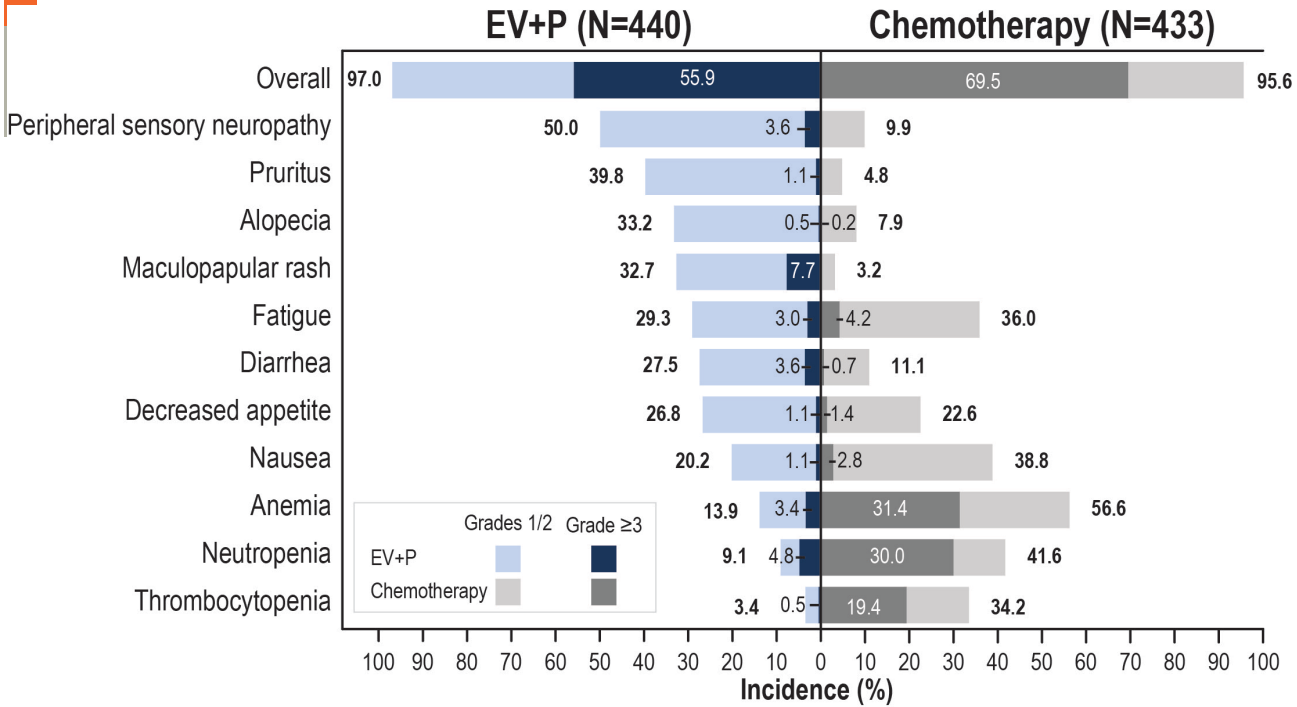
59% of patients in chemotherapy arm received subsequent PD-1/L1 inhibitors

	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)

Adapted from Powles et al. ESMO 2023 LBA6

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

Adapted from Powles et al. ESMO 2023 LBA6

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EV-302: EV Treatment-Related Adverse Events of Special Interest

Majority of treatment-related AESIs were low grade

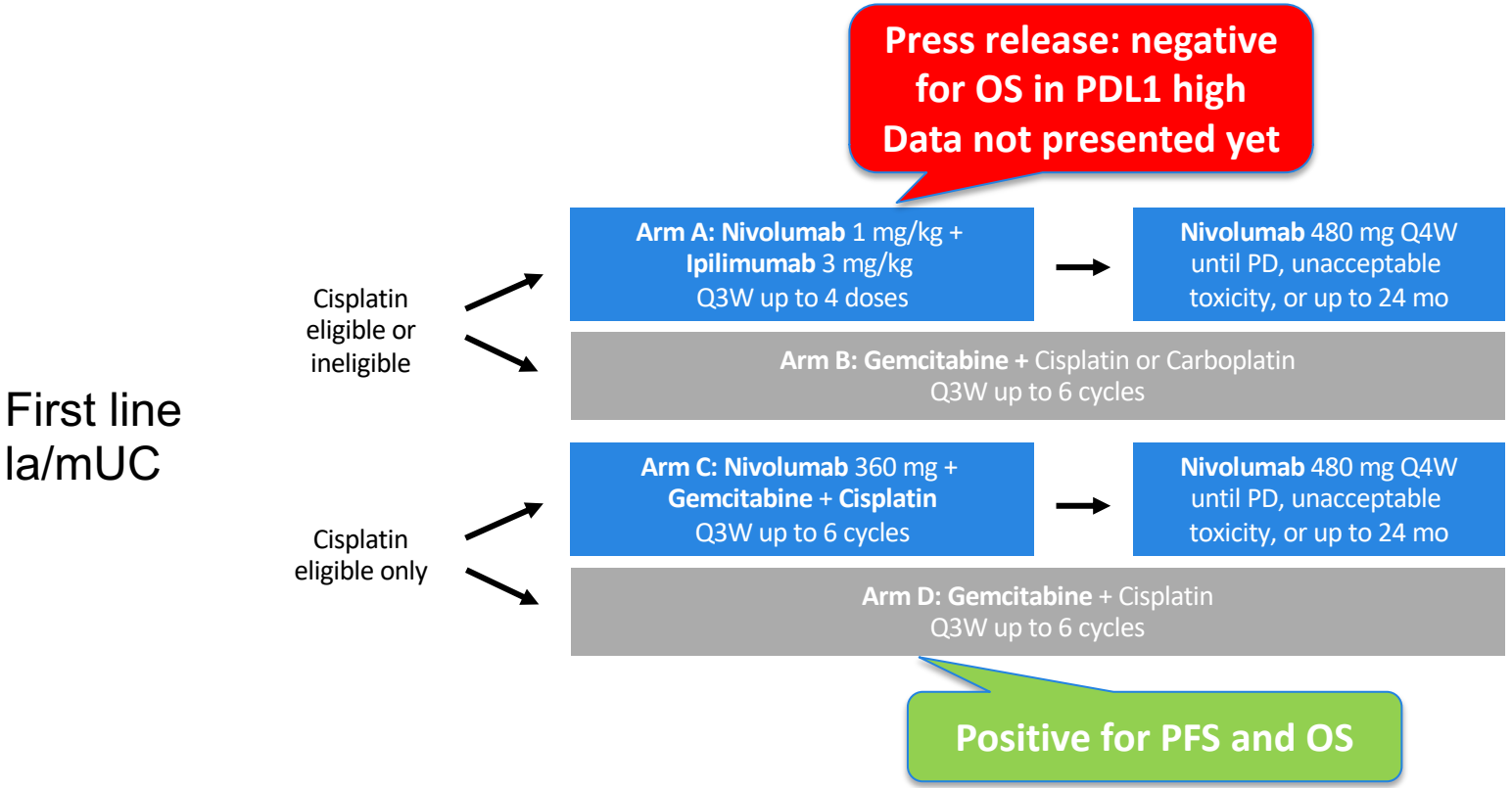
	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
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)

Adapted from Powles et al. ESMO 2023 LBA6

EV-302: Conclusions

- Risk of progression or death reduced by 55% with EV+P
- Risk of death reduced by 53% with EV+P
  - Median OS 31.5 months with EV+P
- All patient subsets seemed to benefit
- Confirmed ORR was 67.7% and 44.4% in the EV+P and chemo arms, respectively
  - 29% complete response rate!
- Transformative data
  - Replaces chemotherapy for most patients with mUC
  - Availability will be limited for some time in certain regions of the world

CheckMate-901: two phase 3 trials of immune checkpoint blockade



Galsky. ASCO 2018. Abstr TPS539. NCT03036098.

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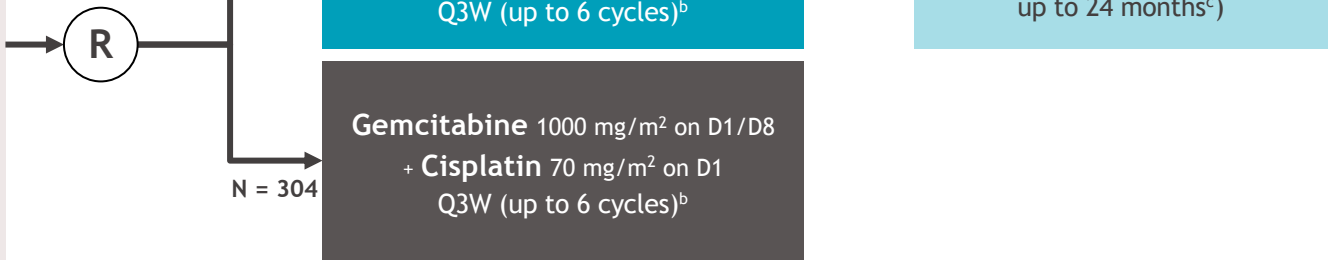
Checkmate 901: Study design

Does Nivolumab improve outcomes when added to gemcitabine-cisplatin?

Key inclusion criteria

- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible
- ECOG PS of 0-1

Stratification factors:
- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)

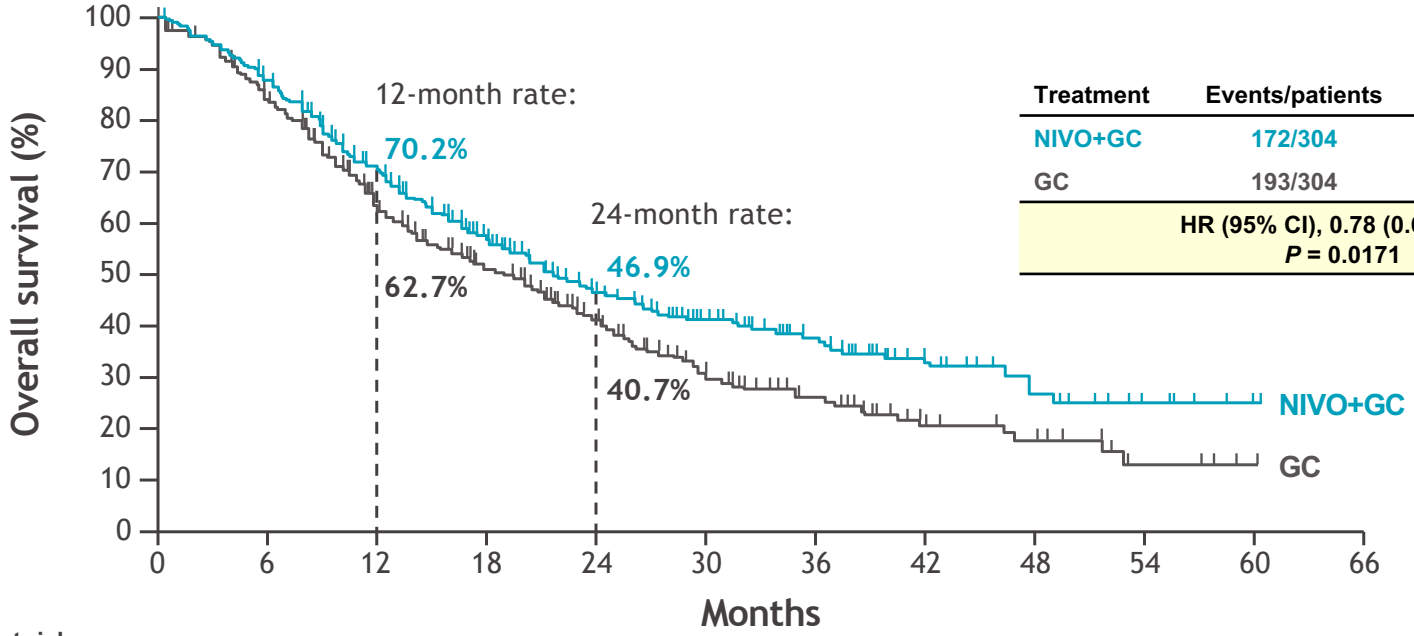


Median (range) study follow-up, 33.6 (7.4-62.4) months

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

Adapted from M van der Heijden; ESMO LBA7 2023

Checkmate 901: 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

Adapted from M van der Heijden; ESMO LBA7 2023

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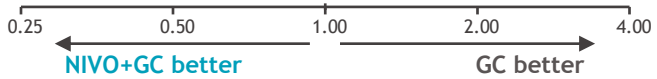
Checkmate 901: OS in subgroups

Subgroup	No. of patients	NIVO+GC *No. of events/no. of patients*	GC *No. of events/no. of patients*	Unstratified HR for death (95% CI)
Overall (N = 608)		172/304	193/304	0.78 (0.63-0.95)
Age, years				
< 65	298	85/150	100/148	0.69 (0.51-0.92)
≥ 65 and < 75	236	65/120	66/116	0.89 (0.63-1.26)
≥ 75	74	22/34	27/40	0.86 (0.49-1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60-0.97)
Female	138	39/68	46/70	0.82 (0.54-1.26)
Race				
White	436	123/211	145/225	0.80 (0.63-1.02)
Asian	138	38/75	36/63	0.71 (0.45-1.12)
Other	32	11/18	10/14	0.84 (0.35-1.97)
Region				
US	40	18/19	15/21	1.92 (0.95-3.88)
Asia	133	36/72	34/61	0.73 (0.46-1.17)
Europe	276	72/134	90/142	0.73 (0.53-0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49-1.08)
ECOG PS				
0	324	74/162	87/162	0.70 (0.51-0.95)
1	282	96/140	106/142	0.85 (0.64-1.11)
PD-L1 expression				
≥ 1%	221	64/111	67/110	0.75 (0.53-1.06)
< 1% or indeterminate	387	108/193	126/194	0.80 (0.62-1.04)
Liver metastases				
Yes	128	45/64	48/64	0.77 (0.51-1.16)
No	480	127/240	145/240	0.77 (0.61-0.98)
Previous systemic anticancer therapy				
Yes	156	44/88	41/68	0.90 (0.59-1.38)
No	452	128/216	152/236	0.76 (0.60-0.96)



No significant differences by subgroups

c/0 M van der Heijden; ESMO LBA 2023

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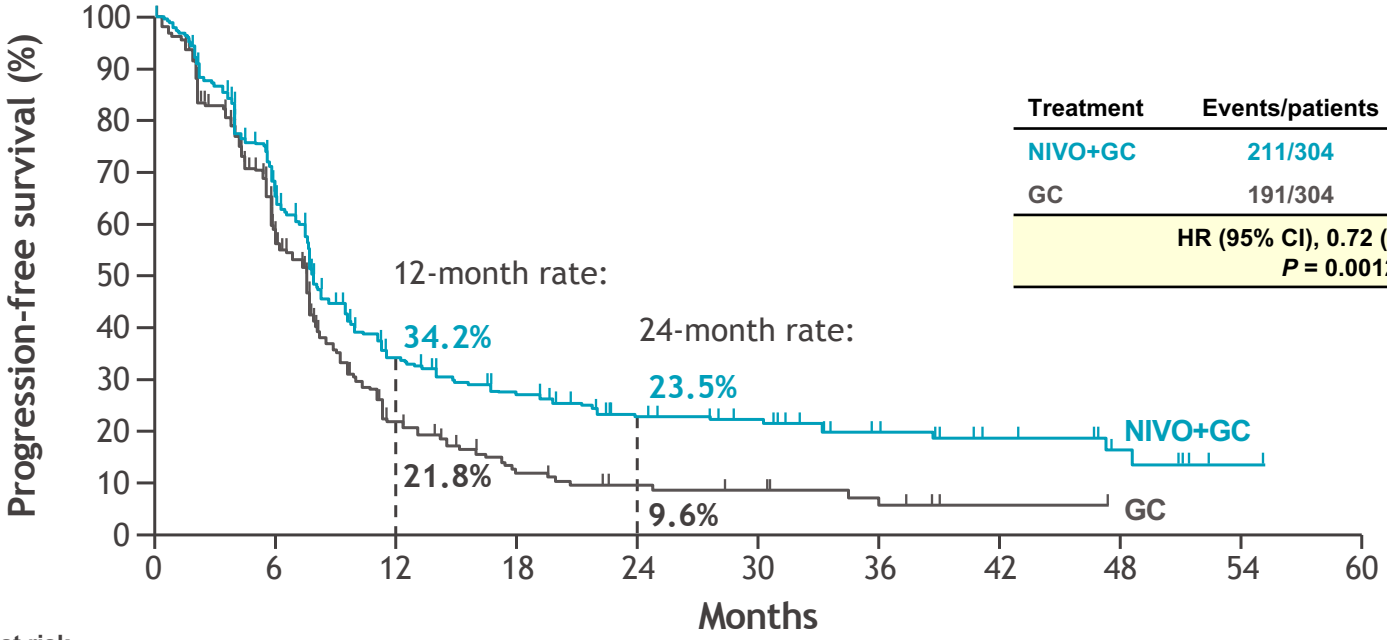
Checkmate 901: PFS per BICR (primary endpoint)



Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1–7.8)
HR (95% CI), 0.72 (0.59–0.88) *P* = 0.0012		

No. at risk											
NIVO+GC	304	179	82	57	41	31	19	11	6	1	0
GC	304	119	35	17	10	8	5	1	0	0	0

Adapted from M van der Heijden; ESMO LBA7 2023

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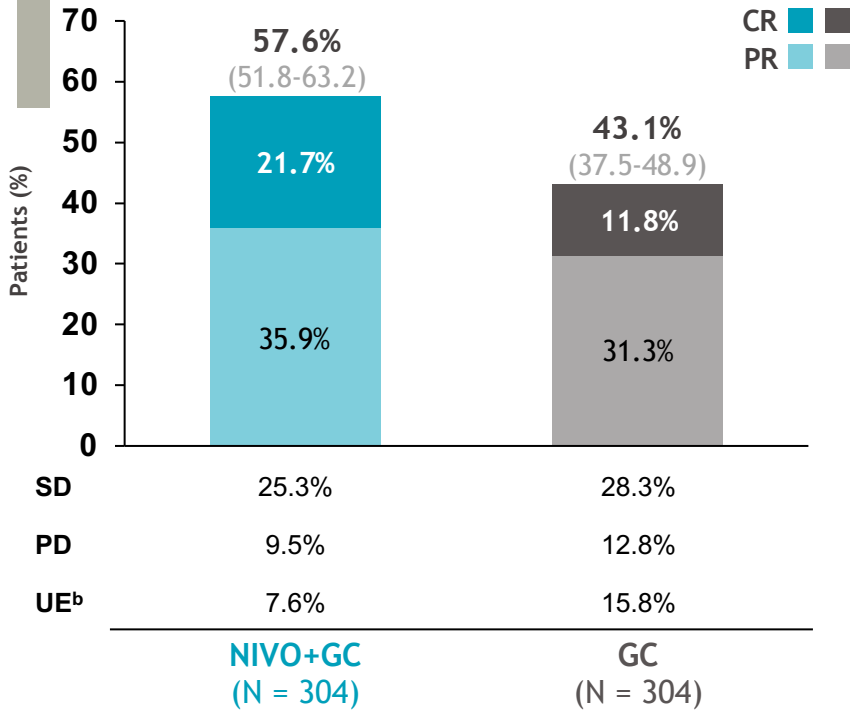
Checkmate 901: Objective response outcomes

ORR (95% CI) and BOR per BICR[a]



Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)

Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

Nivolumab associated with higher ORR, CR rate, and longer DOR

Adapted from M van der Heijden; ESMO LBA 2023

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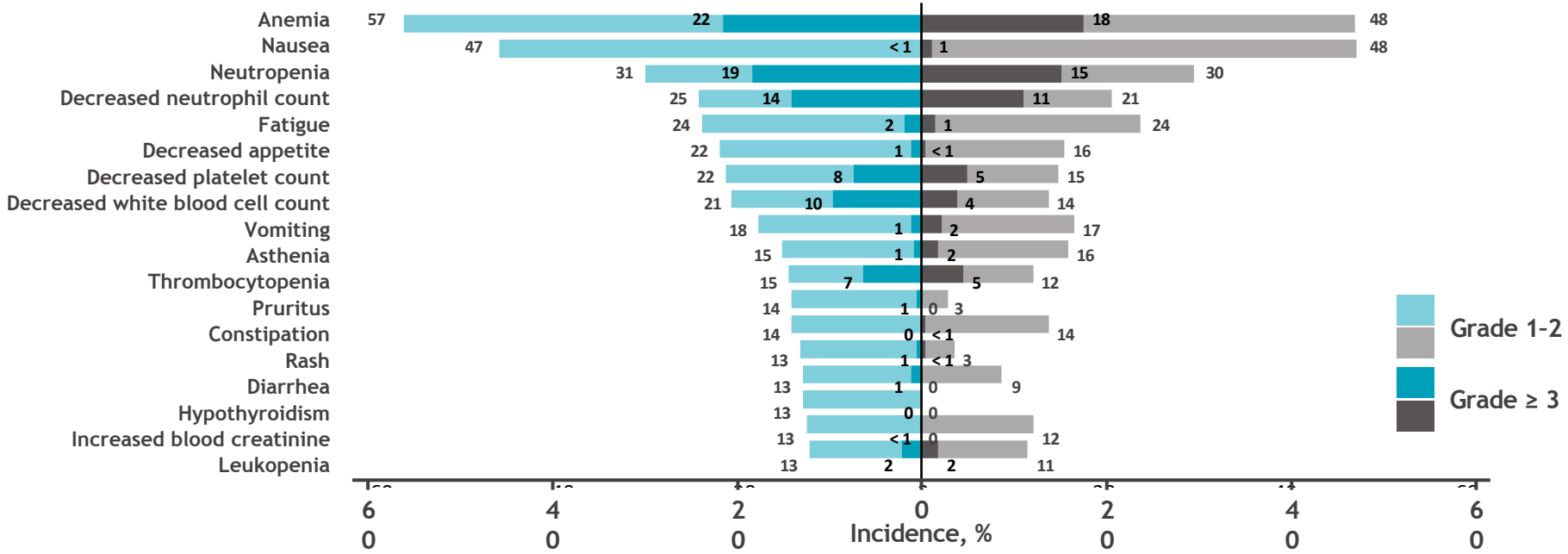
Checkmate 901: Treatment-related AEs in all treated patients

	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to discontinuation	21	11	17	8



Adapted from M van der Heijden; ESMO LBA 2023

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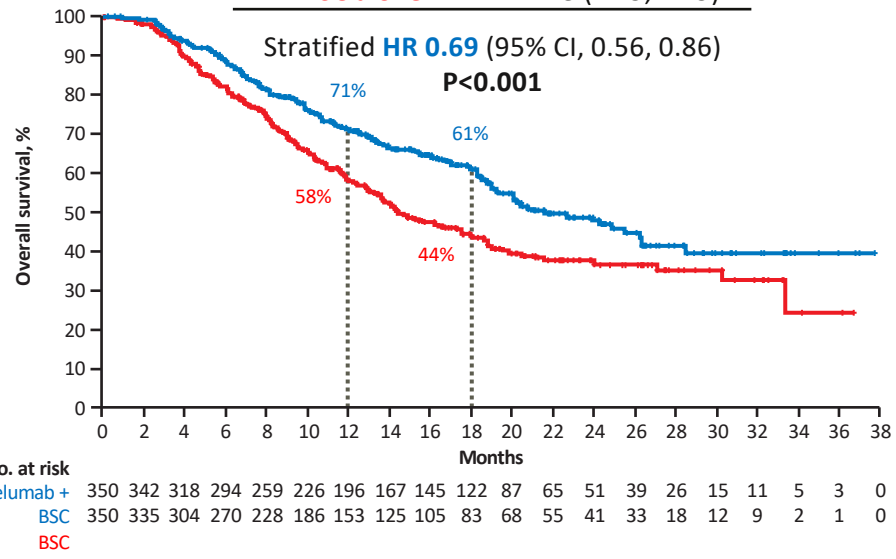
Modest increase in grade ≥3 toxicity

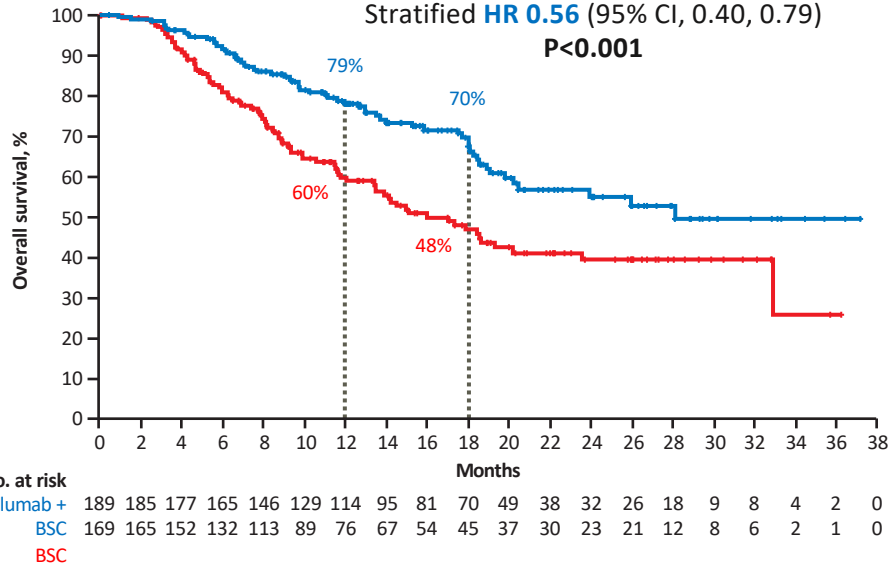
Javelin Bladder 100 trial: Avelumab as maintenance improves OS in the overall study population and PDL1+ population

Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)



ITT

Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)



PDL1+

Adapted from Powles et al. ASCO 2020

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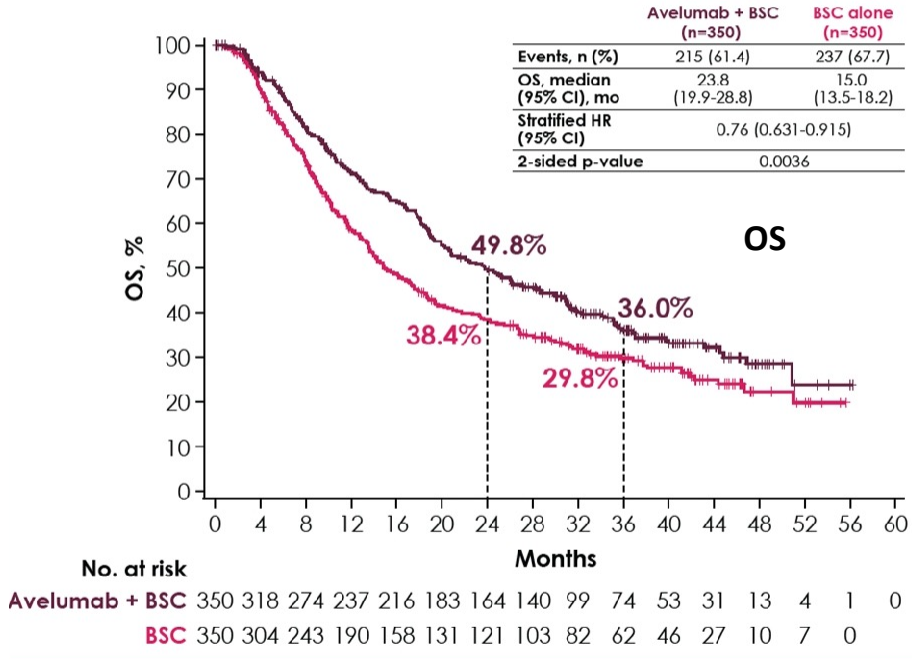
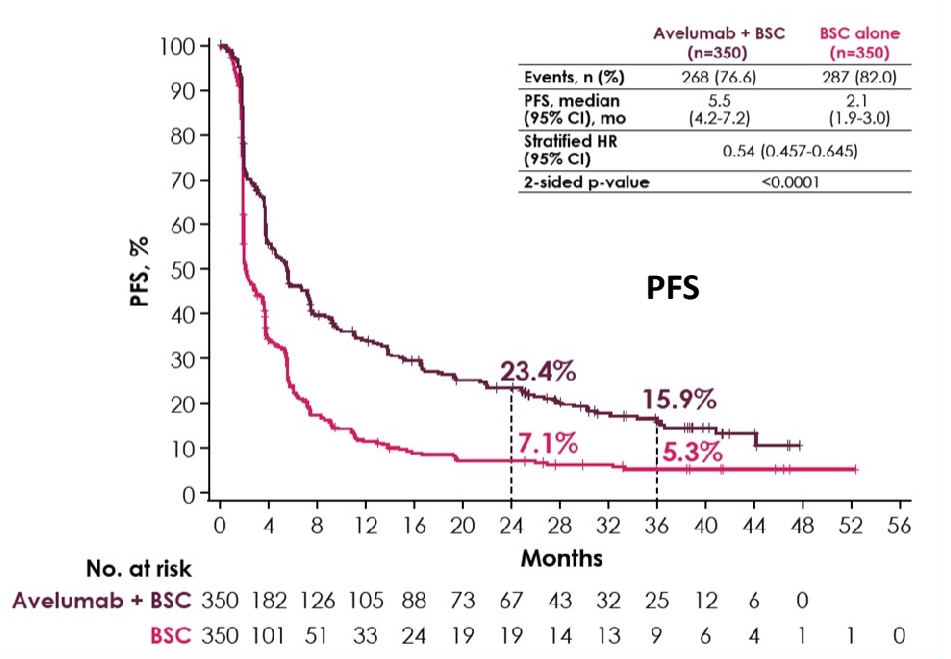
Javelin Bladder 100 trial: Longer term follow-up (≥ 2 years) confirms initial data





Powles, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 487)

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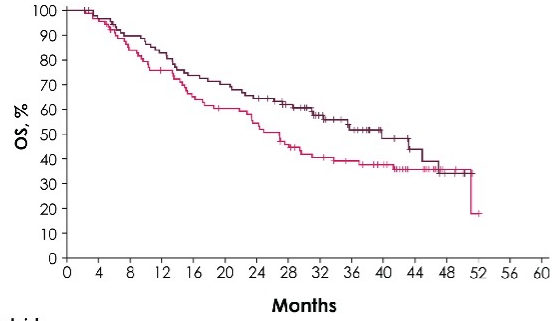
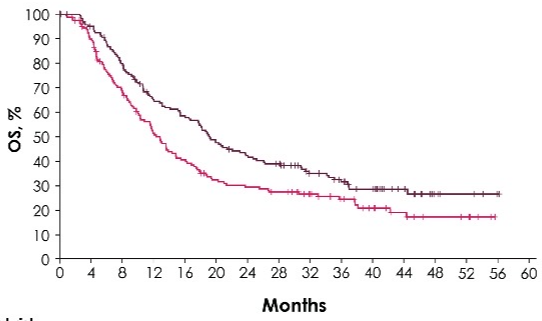
Overall, outcomes favor avelumab no matter prior chemo response

Complete response



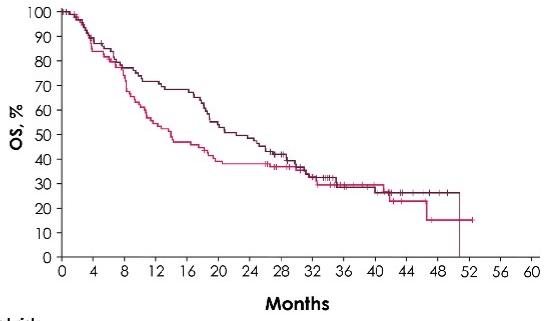
No. at risk														
Avelumab + BSC	90	85	78	72	64	61	56	47	34	24	14	9	4	0
BSC	89	86	72	64	55	50	45	37	30	26	21	13	3	1	0

Partial response



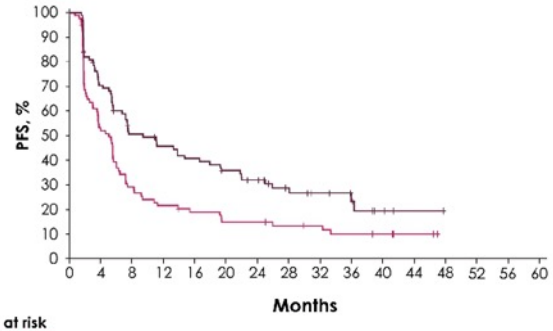
No. at risk																										
Avelumab + BSC	163	151	126	100	90	73	64	58	42	35	27	16	6	4	1	0
BSC	163	140	103	76	60	46	42	37	29	22	15	10	6	5	0

Stable disease



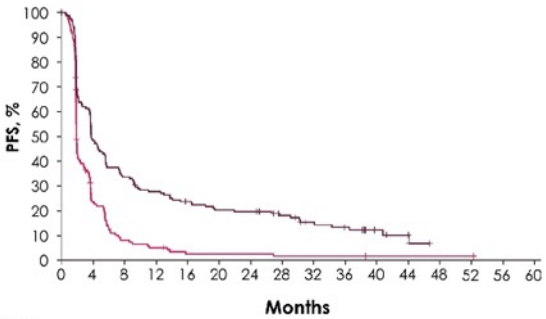
No. at risk														
Avelumab + BSC	97	82	70	65	62	49	44	35	23	15	12	6	3	0
BSC	98	78	68	50	43	35	34	29	23	14	10	4	1	1	0

Complete response



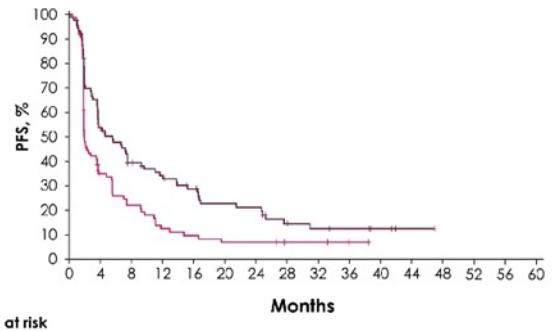
No. at risk													
Avelumab + BSC	90	61	42	37	33	28	24	14	11	7	3	1	0
BSC	89	42	23	17	14	11	11	9	8	6	5	3	0

Partial response



No. at risk														
Avelumab + BSC	163	75	52	42	35	30	29	21	15	13	6	4	0	
BSC	163	32	11	7	3	3	3	2	2	2	1	1	1	1	0

Stable disease



No. at risk													
Avelumab + BSC	97	46	32	26	20	15	14	8	6	5	3	1	0
BSC	98	27	17	9	7	5	5	3	3	1	0

Sridhar et al. ASCO 2022

Chemotherapy + IO in advanced UC

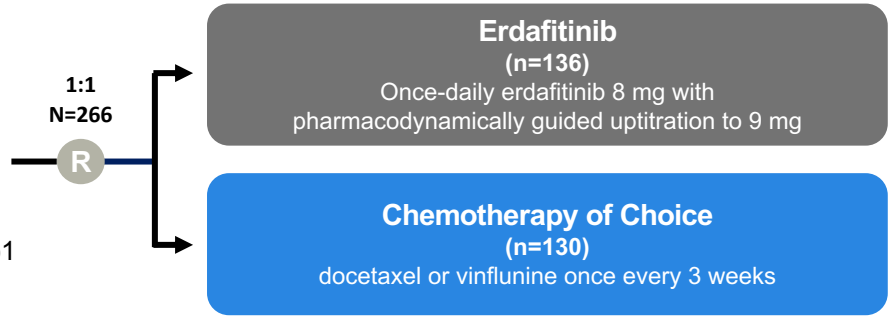
- Checkmate 901:
  - Higher ORR, DOR and CR rate with addition of nivolumab compared to gem/cis
  - Significantly longer PFS and OS
  - First study where chemotherapy + checkpoint inhibitor improved outcomes in mUC
  - Cisplatin and immunotherapy may have advantages over carboplatin-based combinations
- Javelin Bladder-100
  - Improvements in OS in patients who respond to first-line therapy compared to treatment at relapse
  - Would remain standard for EV and cisplatin-ineligible patients
  - Preferred to chemotherapy followed by observation
- Which is the better strategy?
  - Up-front therapy guarantees that all patients get a checkpoint inhibitor, rather than only those who benefit from chemotherapy, but may increase toxicity

Targeted therapy in advanced UC: FGFR3 inhibition

Phase 3 THOR Study Cohort 1: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Select *FGFR* Aberrations

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0-2



Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

Primary end point:

- OS

Key secondary end points:

- PFS
- ORR
- Safety

All Patients Received Anti–PD-(L)1 in the First- or Second-Line Setting

NCT03390504

Loriot Y et al. N Engl J Med 2023; 389:1961-1971

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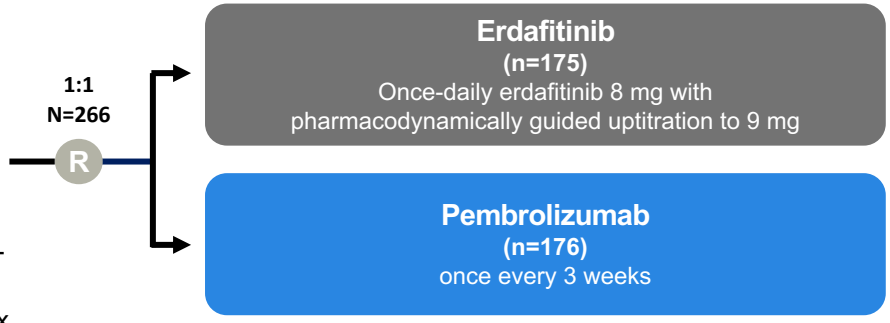
Phase 3 THOR Study Cohort 2: Erdafitinib Versus Pembrolizumab in Patients With Advanced Urothelial Cancer and Select *FGFR* Aberrations

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- No prior tx with anti–PD-(L)1
- 1 prior line of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0-2



Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

Primary end point:

- OS

Key secondary end points:

- PFS
- ORR
- Safety

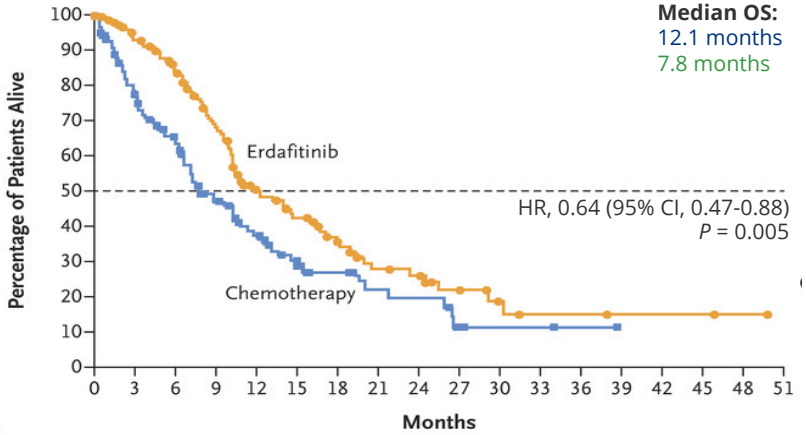
NCT03390504

Siefker-Radtke et al. Annals of Oncology 2024 (35): 107-117.

Memorial Sloan Kettering Cancer Center

Erdafinitinb in refractory mUC

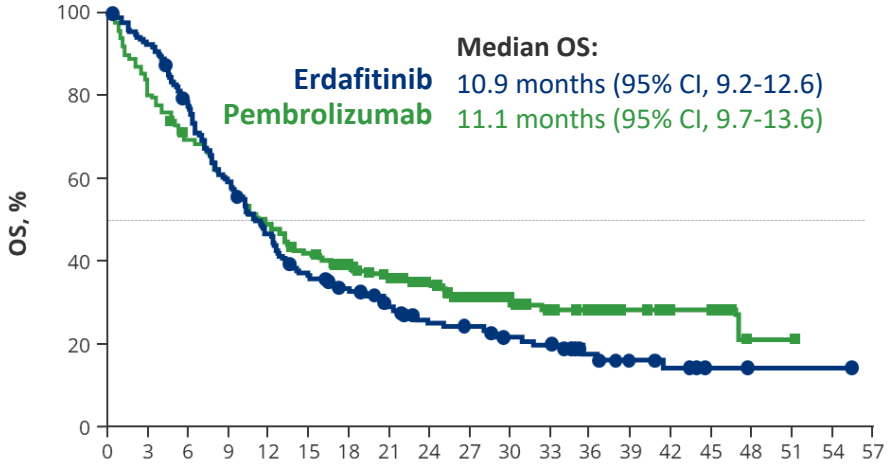
Cohort 1: Erdafitinib improves survival compared to taxane or vinflunine in IO-experienced patients



No. at Risk (no. with censored data)																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

Loriot Y et al. N Engl J Med 2023; 389:1961-1971

Cohort 2: Erdafitinib does not improve survival compared to pembrolizumab in IO-naïve patients



No. at risk																		
Erdafitinib	175	160	131	100	78	60	52	41	30	28	23	21	13	9	7	2	1	1	1	0
Pembrolizumab	176	148	119	103	84	72	60	52	43	34	29	23	19	11	8	8	1	1	0	0

Siefker-Radtke et al. Ann Oncol 2024 (35): 107-117.

Memorial Sloan Kettering Cancer Center

Adverse events associated with erdafitinb treatment

- Hyperphosphatemia is on-target effect and requires monitoring for dose up-titration at 14-21 days
- Gastrointestinal toxicity is common including stomatitis, dry mouth, and dysgeusia
- Skin and nail toxicity are frequent
- Grade 3 central serous retinopathy (in 2.2%) and other eye disorders (in 2.2%) were uncommon but require monitoring per package insert

Table 2. Adverse Events in the Safety Population.*

Event	Erdafitinib (N=135)				Chemotherapy (N=112)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
	number (percent)							
Hyperphosphatemia	108 (80.0)	70 (51.9)	31 (23.0)	7 (5.2)	0	0	0	0
Diarrhea	84 (62.2)	49 (36.3)	31 (23.0)	4 (3.0)	19 (17.0)	7 (6.2)	9 (8.0)	3 (2.7)
Stomatitis	65 (48.1)	22 (16.3)	32 (23.7)	11 (8.1)	14 (12.5)	4 (3.6)	8 (7.1)	2 (1.8)
Dry mouth	53 (39.3)	45 (33.3)	8 (5.9)	0	4 (3.6)	4 (3.6)	0	0
Palmar–plantar erythrodysesthesia syndrome	41 (30.4)	6 (4.4)	22 (16.3)	13 (9.6)	1 (0.9)	0	1 (0.9)	0
Dysgeusia	37 (27.4)	28 (20.7)	8 (5.9)	1 (0.7)	8 (7.1)	5 (4.5)	3 (2.7)	0
Alanine aminotransferase increased	37 (27.4)	24 (17.8)	9 (6.7)	4 (3.0)	4 (3.6)	2 (1.8)	1 (0.9)	1 (0.9)
Constipation	36 (26.7)	24 (17.8)	12 (8.9)	0	31 (27.7)	13 (11.6)	16 (14.3)	2 (1.8)
Decreased appetite	36 (26.7)	18 (13.3)	14 (10.4)	4 (3.0)	23 (20.5)	10 (8.9)	10 (8.9)	3 (2.7)
Anemia	35 (25.9)	10 (7.4)	15 (11.1)	10 (7.4)	36 (32.1)	8 (7.1)	19 (17.0)	9 (8.0)
Alopecia	34 (25.2)	29 (21.5)	4 (3.0)	1 (0.7)	27 (24.1)	16 (14.3)	11 (9.8)	0
Dry skin	31 (23.0)	23 (17.0)	6 (4.4)	2 (1.5)	5 (4.5)	4 (3.6)	1 (0.9)	0
Onycholysis	31 (23.0)	9 (6.7)	14 (10.4)	8 (5.9)	1 (0.9)	0	1 (0.9)	0
Weight decreased	30 (22.2)	12 (8.9)	15 (11.1)	3 (2.2)	3 (2.7)	3 (2.7)	0	0
Aspartate aminotransferase increased	29 (21.5)	21 (15.6)	5 (3.7)	3 (2.2)	3 (2.7)	2 (1.8)	1 (0.9)	0
Onychomadesis	28 (20.7)	9 (6.7)	17 (12.6)	2 (1.5)	2 (1.8)	1 (0.9)	1 (0.9)	0
Nail discoloration	24 (17.8)	16 (11.9)	7 (5.2)	1 (0.7)	2 (1.8)	1 (0.9)	1 (0.9)	0
Dry eye	23 (17.0)	20 (14.8)	3 (2.2)	0	2 (1.8)	1 (0.9)	1 (0.9)	0
Asthenia	20 (14.8)	6 (4.4)	12 (8.9)	2 (1.5)	28 (25.0)	9 (8.0)	15 (13.4)	4 (3.6)
Nausea	20 (14.8)	10 (7.4)	8 (5.9)	2 (1.5)	27 (24.1)	15 (13.4)	10 (8.9)	2 (1.8)
Neutropenia	0	0	0	0	22 (19.6)	1 (0.9)	5 (4.5)	16 (14.3)
Fatigue	20 (14.8)	12 (8.9)	8 (5.9)	0	21 (18.8)	13 (11.6)	4 (3.6)	4 (3.6)

* Listed are adverse events (of any cause) that emerged or worsened during treatment, according to preferred term and highest grade, and that were reported in more than 15% of the patients in either treatment group.

Novel ADCs in advanced UC: Trop2 and Her2 targeted therapies

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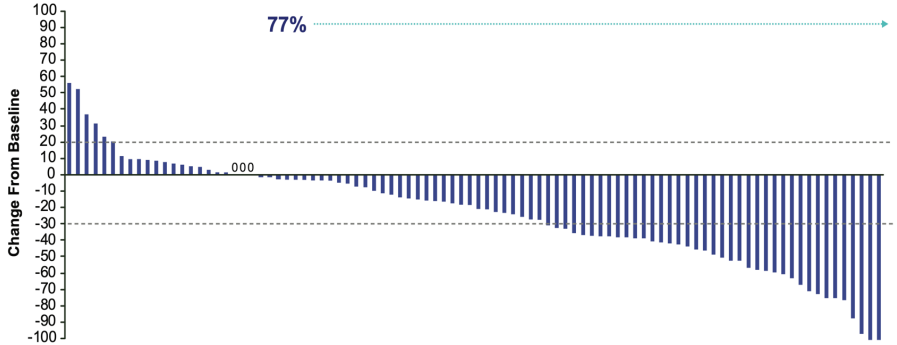
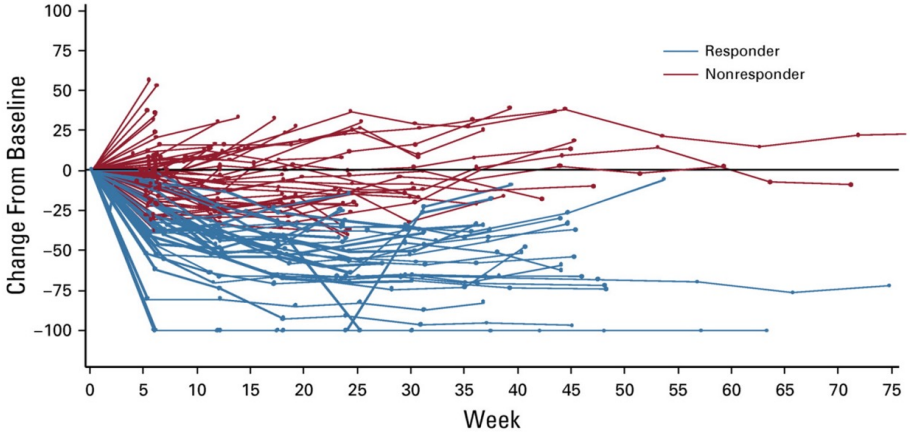
Sacitizumab govitecan:

Accelerated approval for mUC who progressed after prior platinum-based and CPI-based therapies





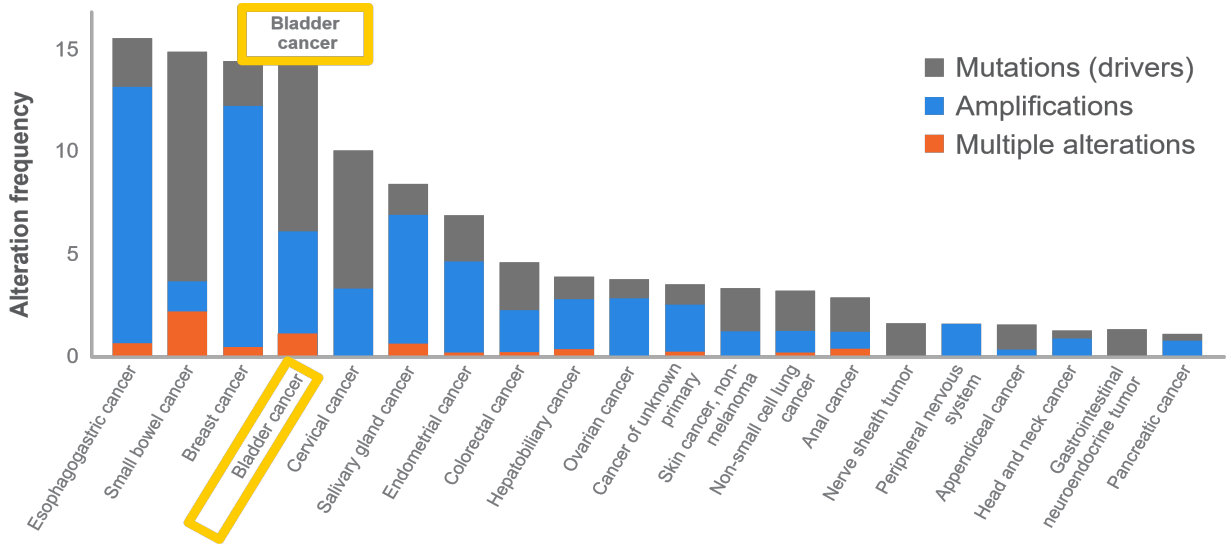
	(n=113)
Overall Response Rate	
ORR, % [95% CI]	27% [19.5, 36.6]
CR, % PR, %	5.3 22.1
Response duration	
mDOR, months	7.2

PFS: 5.4 months (95% CI 3.5, 7.2)
OS: 10.9 months (95% CI 9.0, 13.8)

Tagawa ST, et al. J Clin Oncol. 2021

Memorial Sloan Kettering Cancer Center

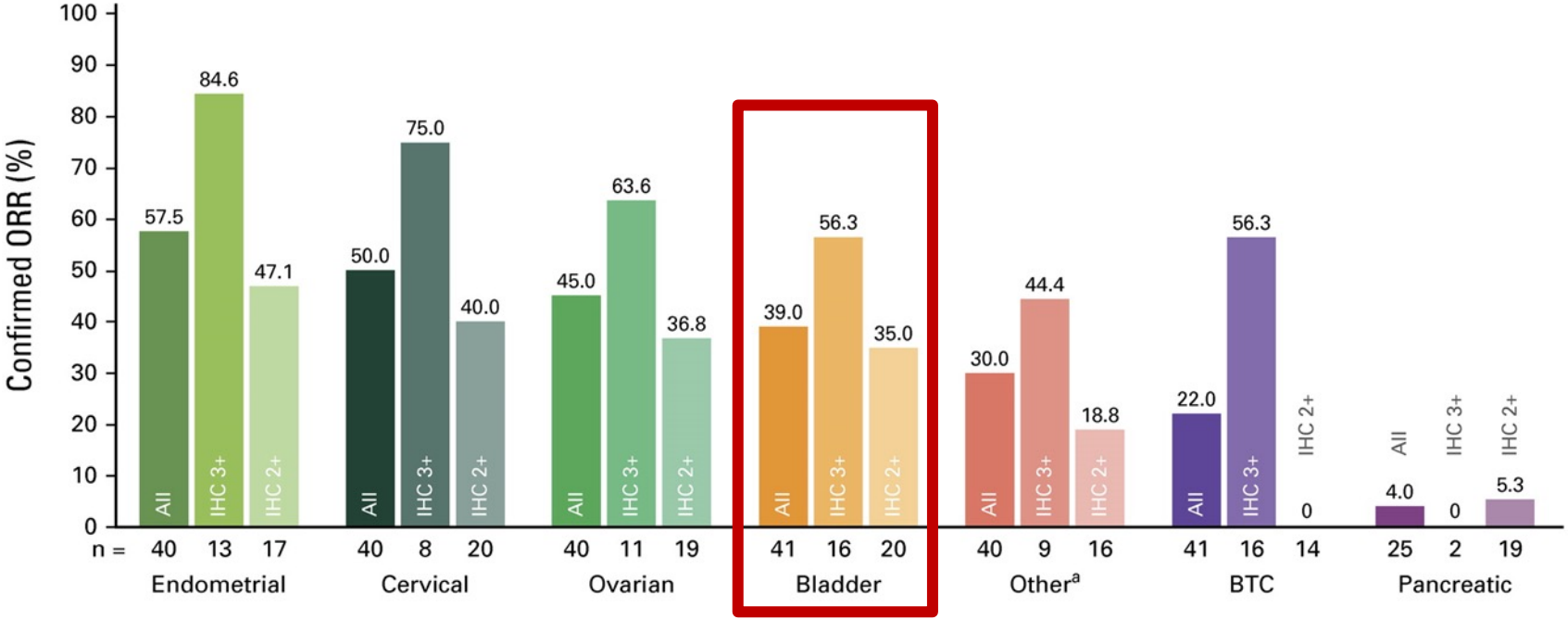
Frequency of *HER2* alterations is high in bladder cancer



- Mutations
  - 5-11% (higher frequency than breast and other cancer types)
- Amplifications
  - 6-9%
  - Can co-exist with mutations in a subset of tumors
- Overexpression in about 25-40% of UC tumors

Data source AACR GENIE Cohort v12.0-public, accessed 2022-08-04 via cBioPortal. Exclude alterations (mutations and copy number) of unknown significance, germline, and uncurated samples. MSK-IMPACT on 24,500 samples with mutation and CNA data. Filtered for minimal number of cases 200 per indication, and alteration frequency > 1%. Data on file.
AACR, American Association for Cancer Research; CNA, copy number aberrations.

Denstiny Pan-Tumor 02: Trastuzumab Deruxtecan leads to high response rates in HER2+ urothelial cancer



ORR 39%

Meric-Bernstam F. et al. *J Clin Oncol*. 2024 Jan 1;42(1):47-58.

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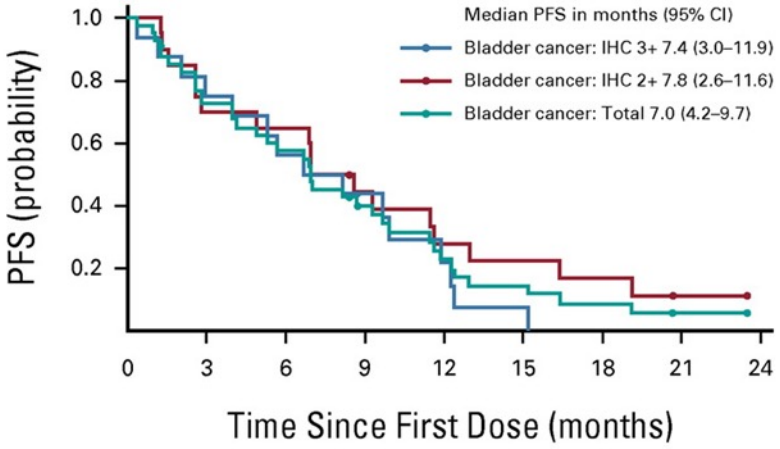
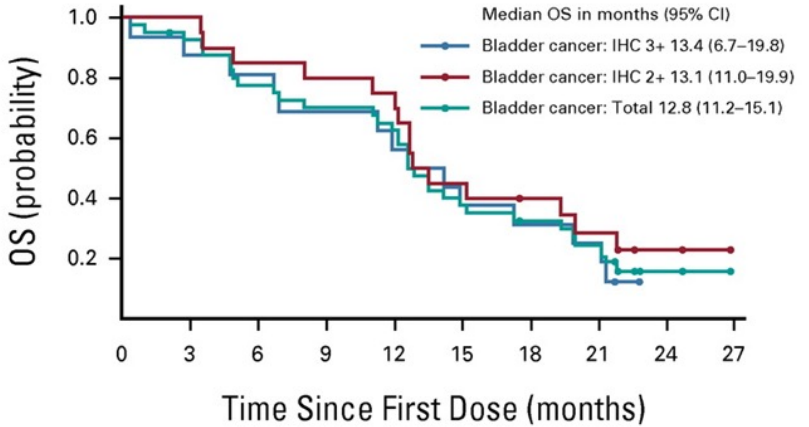
T-DxD outcomes by HER2 status



No. at risk:									
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

PFS



No. at risk:										
Bladder cancer: IHC 3+	16	14	13	11	9	6	5	4	0	
Bladder cancer: IHC 2+	20	20	17	16	15	9	7	5	2	0
Bladder cancer: Total	41	37	31	28	25	15	12	9	2	0

OS

Meric-Bernstam F. et al. *J Clin Oncol*. 2024 Jan 1;42(1):47-58.

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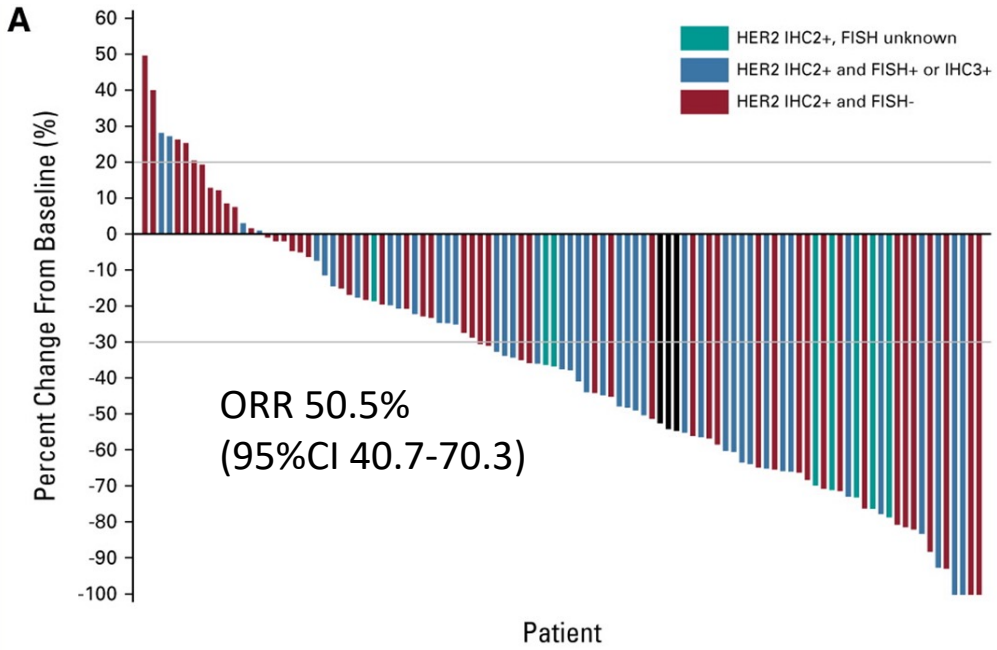
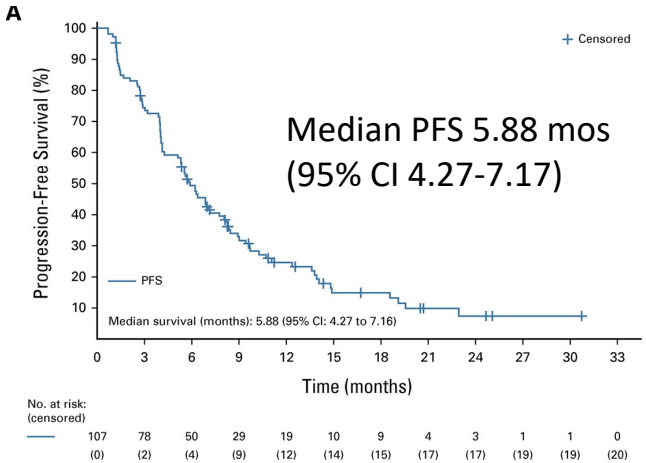
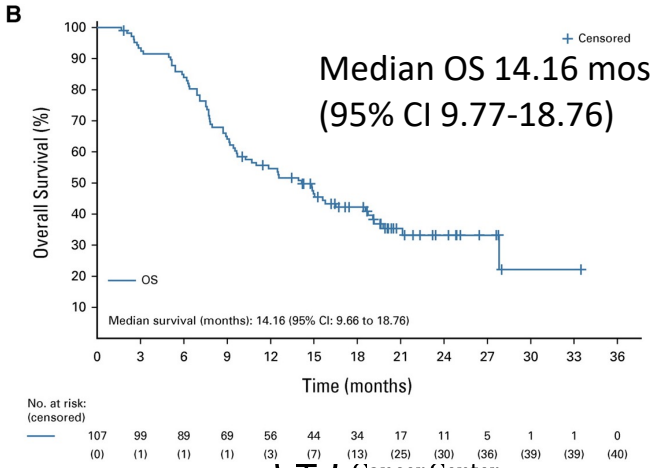
Disitamab vedotin: Combined analysis of two Phase 2 studies in refractory advanced UC

Study population:
- Locally advanced or metastatic UC
- PD after at least 1 prior line of therapy
- ECOG 0-1
- HER2 2/3+





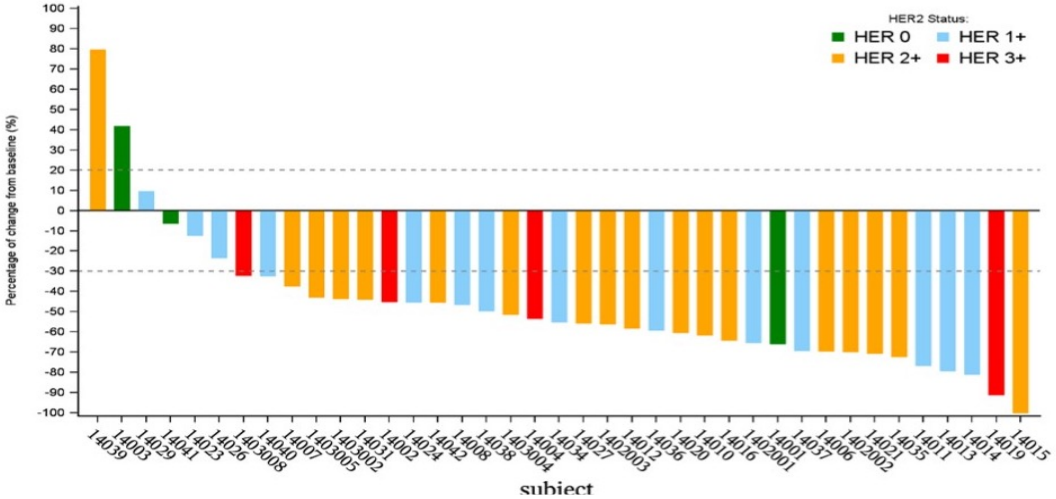


Sheng et al. *JCO*, epub ahead of print 2023

Disitamab vedotin + Toripalimab

(IgG4 anti-PD1 monoclonal antibody)

- Ph I/II study in patients with LA/mUC (n=41)
- HER2 2-3+ in 59% and PD-L1 positive in 32%
- RC48 at 1.5 or 2 mg/kg in combination with toripalimab 3 mg/kg every 2 weeks in dose escalation and expansion cohort
- TRAEs: Transaminitis, peripheral sensory neuropathy, asthenia, hypertriglyceridemia, decreased appetite
- No DLT observed and recommended dose of RC48 was 2 mg/kg



- Confirmed ORR 73.2% (95% CI 57.1, 85.8) including 9.8% CR
  - HER2 2-3+: 86.3%
  - HER2 1+: 57.1%
  - HER2 0: 33.3%
- Confirmed ORR PD-L1 positive: 66.6% ORR; PD-L1 negative: 74.1%
- Median PFS: 9.2 months; 2-year OS rate 63.2%

Sheng et al, *J Clin Oncol* 41, 2023 (suppl 16; abstr 4566)

First-line therapy for la/mUC is changing- finally!

- EV/pembro is now standard for metastatic UC patients in US
  - EV-302 markedly favors Ev/P: OS EV/P 31.5mo vs GP 16.1mo
- Addition of nivolumab to gem/cis improves PFS and OS (OS NGC 21.7mo vs GC 18.9mo)
  - GC+N is a first-line option for patients and likely used more frequently outside US where EV/P is not as readily available
- Pembrolizumab monotherapy for frail patients
- Avelumab maintenance checkpoint blockade following response to initial platinum-based chemotherapy
  - As landscape evolves and CPI is started at initial therapy for metastatic disease, its role will diminish but may remain an option for cisplatin- and EV-ineligible patients
- FGFR3 inhibition is now standard after 1-2 lines of therapy including checkpoint inhibition

Thank you!

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