Immunotherapy in Bladder and Kidney Cancer

Rohit Jain, MD, MPH
Assistant Member
Department of Genitourinary Oncology
H. Lee Moffitt Cancer Center
Tampa, FL

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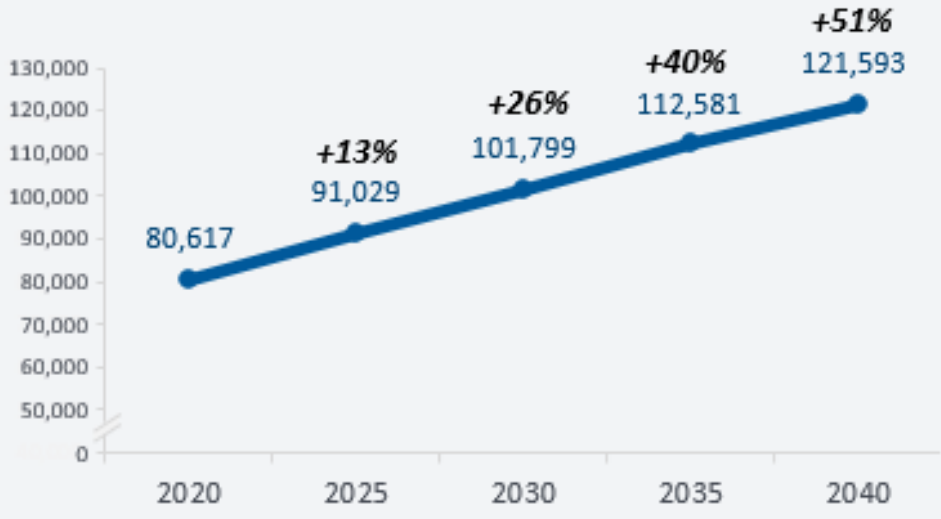
Bladder Cancer Is Projected to Be a Growing Health Problem in the US

Bladder cancer is estimated to be the 6th most common cancer in the United States[1]

		Estimated New Cases 2021	Estimated Deaths 2021
1	Breast cancer (female)	281,550	43,600
2	Prostate cancer	248,530	34,130
3	Lung and bronchus cancer	235,760	131,880
4	Colorectal cancer	149,500	52,980
5	Melanoma of the skin	106,110	7,180
6	**Bladder cancer**	**83,730**	**17,200**
7	Non-Hodgkin lymphoma	81,560	20,720
8	Kidney and renal pelvis cancer	76,080	13,780
9	Uterine cancer	66,570	12,940
10	Leukemia	61,090	23,660

In the United States, the incidence of bladder cancer is projected to increase[2]

Estimated incidence and increase compared with 2020[2,a]



[a]As with all estimates, cancer predictions for future years should be interpreted with due caution. The key assumptions are that national rates, as estimated in 2020, do not change in the prediction period 2020-2040 and that the national population projections are correct for these years.

1. National Cancer Institute. Cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed 06-08-2021.2. International Agency for Research on Cancer. Cancer tomorrow: bladder. http://gco.iarc.fr/tomorrow. Accessed 02-08-2021.

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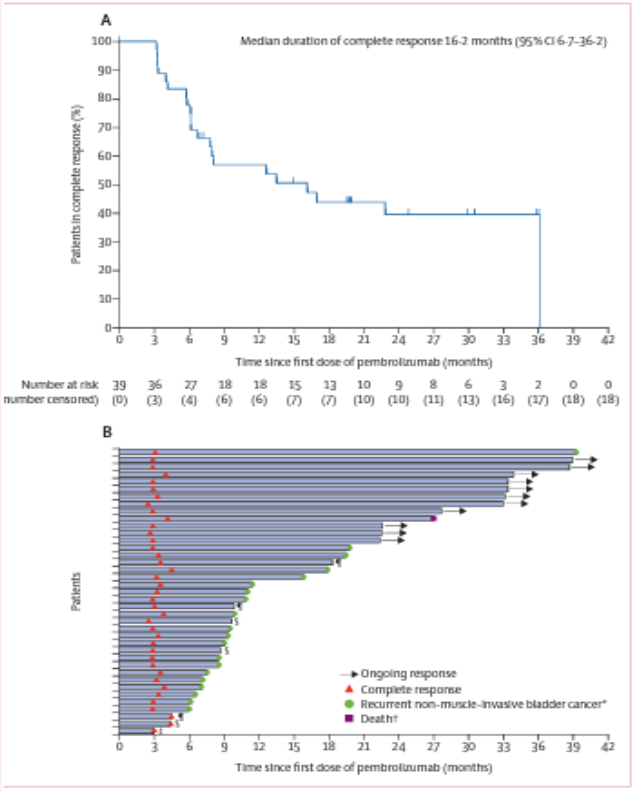
Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Prof Arjun V Balar, MD • Prof Ashish M Kamat, MD • Girish S Kulkarni, MD • Prof Edward M Uchio, MD • Joost L Boormans, MD • Mathieu Roumiguié, MD • et al. Show all authors

	Cohort A efficacy population (n=96)*
Complete response	39 (41%, 30·7–51·1)
Non-complete response	56 (58%, 47·8–68·3)
Persistent disease†‡	40 (42%, 31·7–52·2)
Recurrent disease	6 (6%, 2·3–13·1)
Non-muscle-invasive bladder cancer stage progression§	9 (9%, 4·4–17·1)
Non-bladder malignancy¶	1 (1%, 0·0–5·7)
Progression to muscle-invasive disease (T2)	0 (NA–NA)
Non-evaluable‖	1 (1%, 0·0–5·7)

Data are n (%, 95% CI). NA=not applicable. *Patients with high-risk non-muscle-invasive bladder cancer who received at least one dose of the study drug, had baseline evaluations, and had at least one post-baseline disease assessment. †Defined as patients with carcinoma in situ at baseline who also had carcinoma in situ with or without papillary tumour at month 3. ‡Defined as pathologically confirmed appearance of papillary tumour (high-grade Ta or T1) without carcinoma in situ at month 3. §Defined as an increase in stage from carcinoma in situ or high-grade Ta at baseline to T1 disease. ¶For this patient, new liver lesions were found on imaging; later, a second primary malignancy of pancreatic cancer was found. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer, and later scans showed metastases that were most likely from the pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer. ‖Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were not evaluable for efficacy and considered non-responders.

Table 2: **Best overall response at month 3 by central review in patients with BCG-unresponsive carcinoma in situ**



Balar A et al Lancet 2021

Muscle Invasive Bladder Cancer

Standard Treatment is Cisplatin-Based Neoadjuvant Chemotherapy

Neoadjuvant Single-agent IO and enfortumab vedotin is also effective in MIBC

	PURE-01[1]	ABACUS[2]	NABUCCO[3]	AURA[4]	MDACC[5]	DUTRENEO[6]
N	114	95	24 (14)	28	28	23
Immunotherapy	Pembrolizumab	Atezolizumab	Ipi/Nivo	Avelumab	Durval/Tremi	Durva/Tremi
Cisplatin eligible	✓	✓	✗	✗	✗	✗
pCR (pT0)	37%	31%	46%	36% *(includes Tis)	37.5%	34.8%
PFS	91% (1yr)	79% (1yr)	92% (1yr)	Not reported	82.8% (1yr)	Not reported

1Necchi et al, Eur Urol 2022, 2 Powles et al, Nat Med 2019, 3Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020, 4 Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019
5Gao J et al Nature Med 2020 6. Grande E et al. J Clin Oncol Suppl 5012 7. Petrylak D et al. ASCO GU 2022

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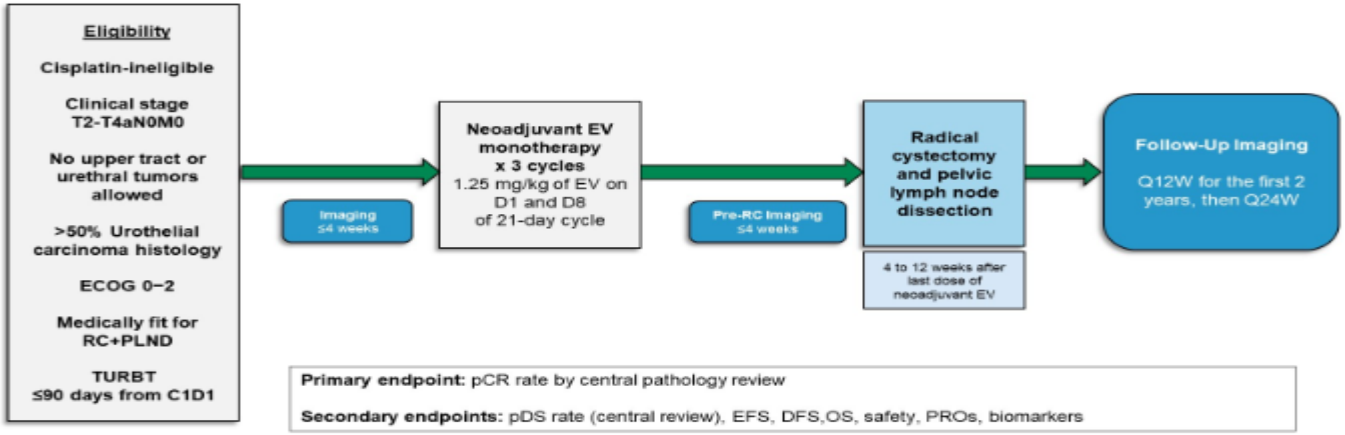
Enfortumab Vedotin

EV-103 Cohort H Study Design



Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Petrylak D et al
GU ASCO 2022

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Neoadjuvant Chemo-IO is effective in cis-eligible MIBC

	BLASST-1[1] (N = 41)	HCRN GU14-188[2] (N = 43)	LCCC1520[3] (N = 39)	MKSCC[4] (N = 39)	SAKK 06/17[5] (N = 53)
Immunotherapy	Nivolumab	Pembrolizumab	Pembrolizumab	Atezolizumab	Durvalumab
Chemotherapy	Gem-Cis	Gem-Cis	Split dose Gem-Cis	Gem-Cis	Gem-Cis
pCR (pT0), %	49% *(includes Tis)	44	39	38	34
RFS	85.4% (1yr)	Not reported	Not reported	Not reported	83.5% (2yr)

1. Gupta S et al. ASCO GU 2020. Abstract 439. 2. Holmes CJ et al. ASCO 2020. Abstract 5047. 3. Rose TL et al. J Clin Oncol. 2021;39:3140-3148. 4. Funt SA et al. J Clin Oncol. 2022;40:1312-1322. 5. Cathomas R et al. ASCO 2022. Abstract 4515

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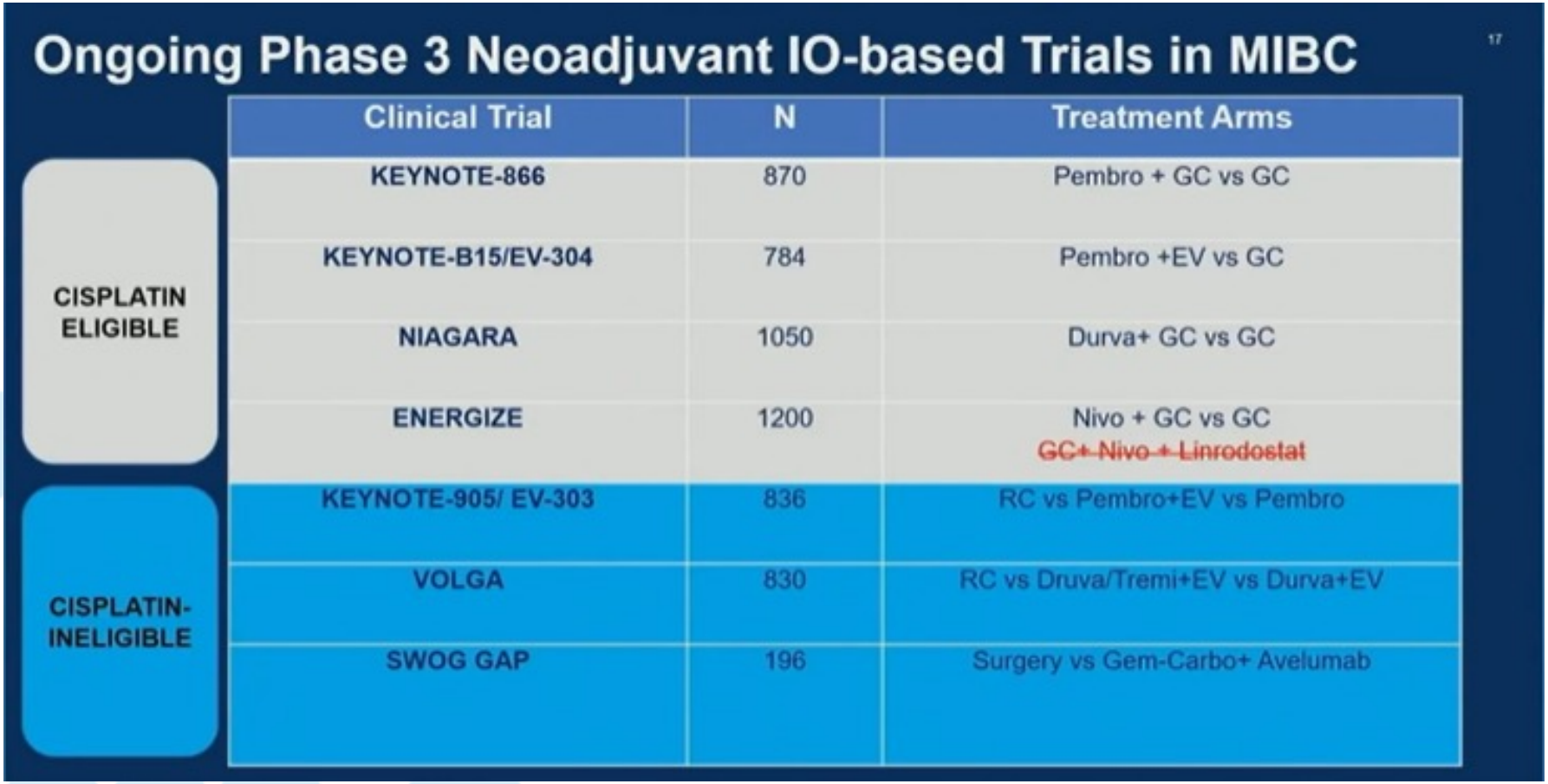
Ongoing Phase 3 trials



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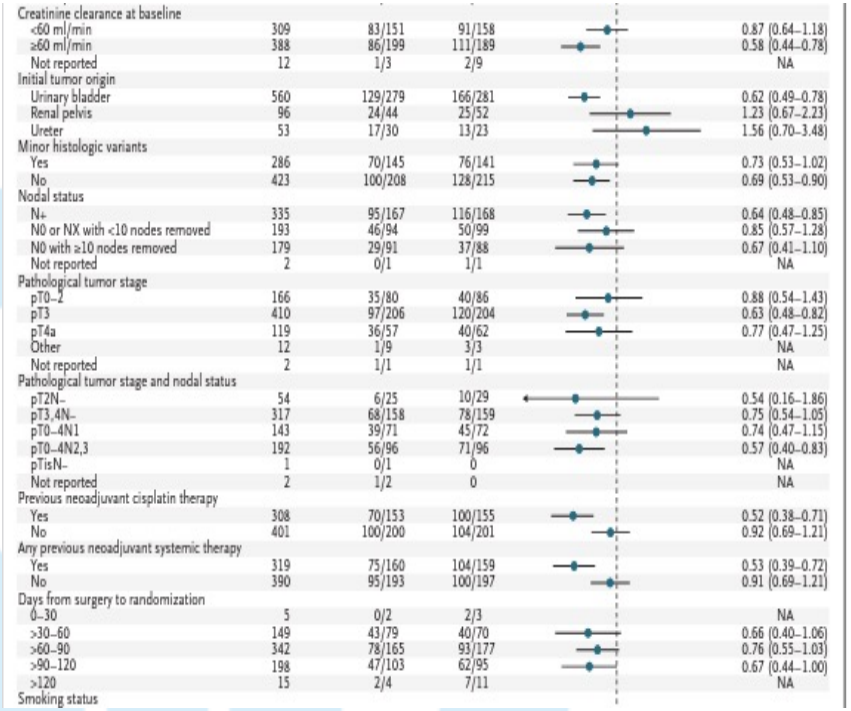
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

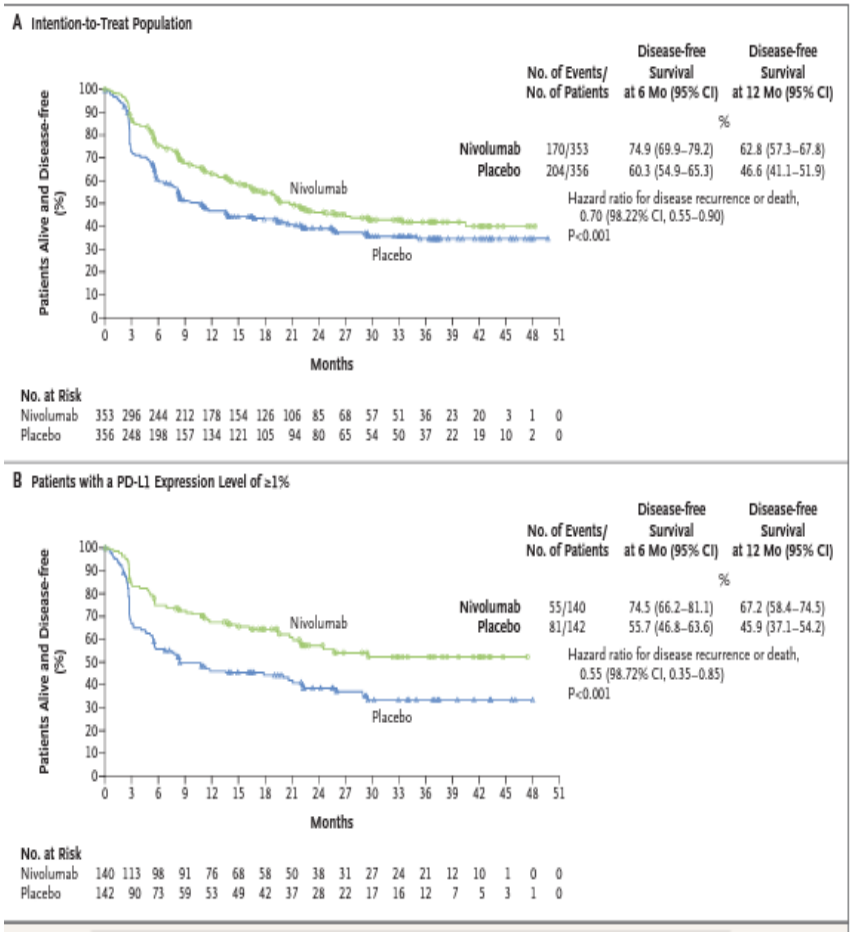
Dean F. Bajorin, M.D., J. Alfred Witjes, M.D., Jürgen E. Gschwend, M.D., Michael Schenker, M.D., Begoña P. Valderrama, M.D., Yoshihiko Tomita, M.D., Ph.D., Aristotelis Bamias, M.D., Thierry Lebret, M.D., Shahrokh F. Shariat, M.D., Se Hoon Park, M.D., Dingwei Ye, M.D., Mads Agerbaek, M.D., Deborah Enting, M.D., Ray McDermott, M.D., Pablo Gajate, M.D., Avivit Peer, M.D., Matthew I. Milowsky, M.D., Alexander Nosov, M.D., João Neif Antonio, Jr., M.D., Krzysztof Tupikowski, M.D., Laurence Toms, B.M., B.Ch., Bruce S. Fischer, M.D., Anila Qureshi, M.D., Sandra Collette, M.Sc., Keziban Unsal-Kacmaz, Ph.D., Edward Broughton, Ph.D., Dimitrios Zardavas, M.D., Henry B. Koon, M.D., and Matthew D. Galsky, M.D.

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing



Creatinine clearance at baseline				
<60 ml/min	309	83/151	91/158	0.87 (0.64–1.18)
≥60 ml/min	388	86/199	111/189	0.58 (0.44–0.78)
Not reported	12	1/3	2/9	NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)
Nodal status				
N+	335	95/167	116/168	0.64 (0.48–0.85)
N0 or NX with <10 nodes removed	193	46/94	50/99	0.85 (0.57–1.28)
N0 with ≥10 nodes removed	179	29/91	37/88	0.67 (0.41–1.10)
Not reported	2	0/1	1/1	NA
Pathological tumor stage				
pT0–2	166	35/80	40/86	0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
Pathological tumor stage and nodal status				
pT2N–	54	6/25	10/29	0.54 (0.16–1.86)
pT3,4N–	317	68/158	78/159	0.75 (0.54–1.05)
pT0–4N1	143	39/71	45/72	0.74 (0.47–1.15)
pT0–4N2,3	192	56/96	71/96	0.57 (0.40–0.83)
pTisN–	1	0/1	0	NA
Not reported	2	1/2	0	NA
Previous neoadjuvant cisplatin therapy				
Yes	308	70/153	100/155	0.52 (0.38–0.71)
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Days from surgery to randomization				
0–30	5	0/2	2/3	NA
>30–60	149	43/79	40/70	0.66 (0.40–1.06)
>60–90	342	78/165	93/177	0.76 (0.55–1.03)
>90–120	198	47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				



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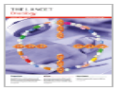
Bajorin, D NEJM 2021

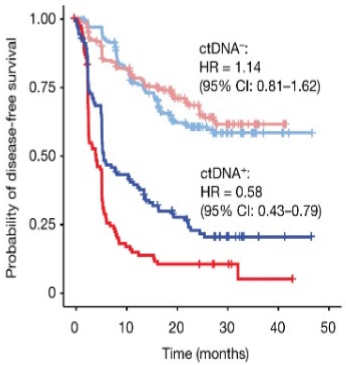
THE LANCET
Oncology
Volume 22, Issue 4, April 2021, Pages 525-537

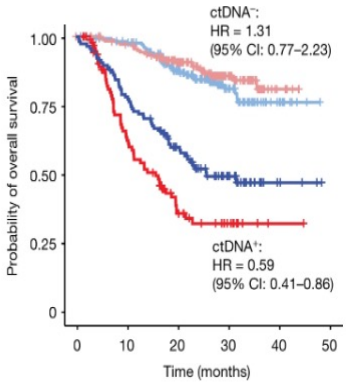


Articles

Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial

Joaquim Bellmunt MD [a], Prof Maha Hussain MD [b], Prof Jürgen E Gschwend MD [c], Prof Peter Albers MD [d], Prof Stephane Oudard MD [e], Daniel Castellano MD [f], Siamak Daneshmand MD [g], Prof Hiroyuki Nishiyama MD [h], Martin Majchrowicz MPH [i], Viraj Degaonkar PharmD [i], Yi Shi PhD [i], Sanjeev Mariathasan PhD [i], Petros Grivas MD [j k l], Alexandra Drakaki MD [m], Peter H O'Donnell MD [n], Prof Jonathan E Rosenberg MD [o p], Daniel M Geynisman MD [q], Prof Daniel P Petrylak MD [r], Jean Hoffman-Censits MD [s],





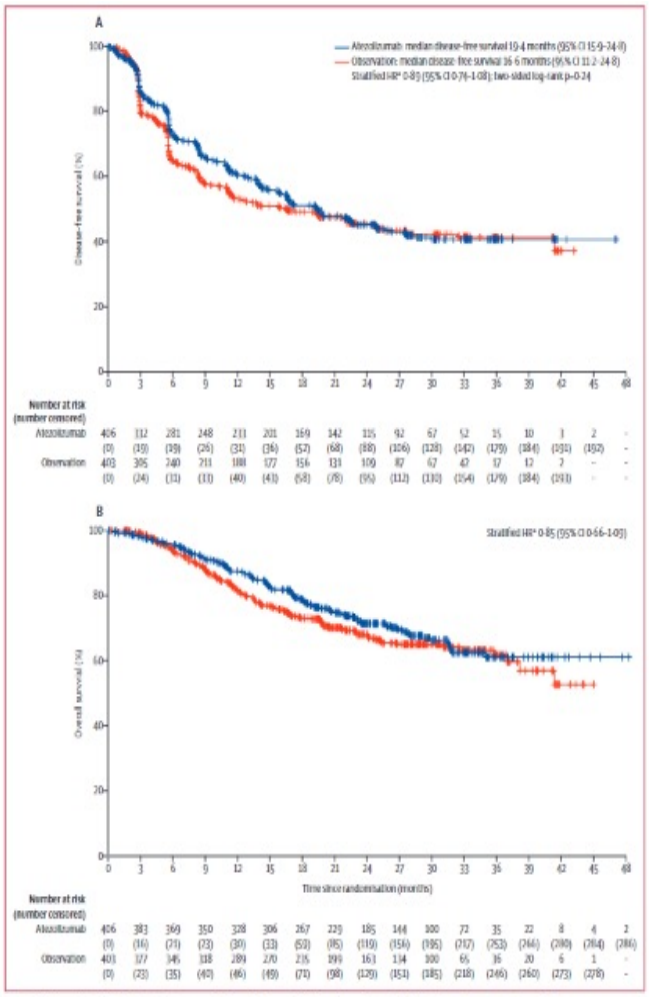


Figure 2: Kaplan-Meier plots for investigator-assessed disease-free survival (A) and overall survival (B) in the intention-to-treat population
HR=hazard ratio. *Stratified by post-resection tumour stage, nodal status, and PD-L1 status.

Bellmunt et al 2021 Lancet
Powles T et al 2021 Nature

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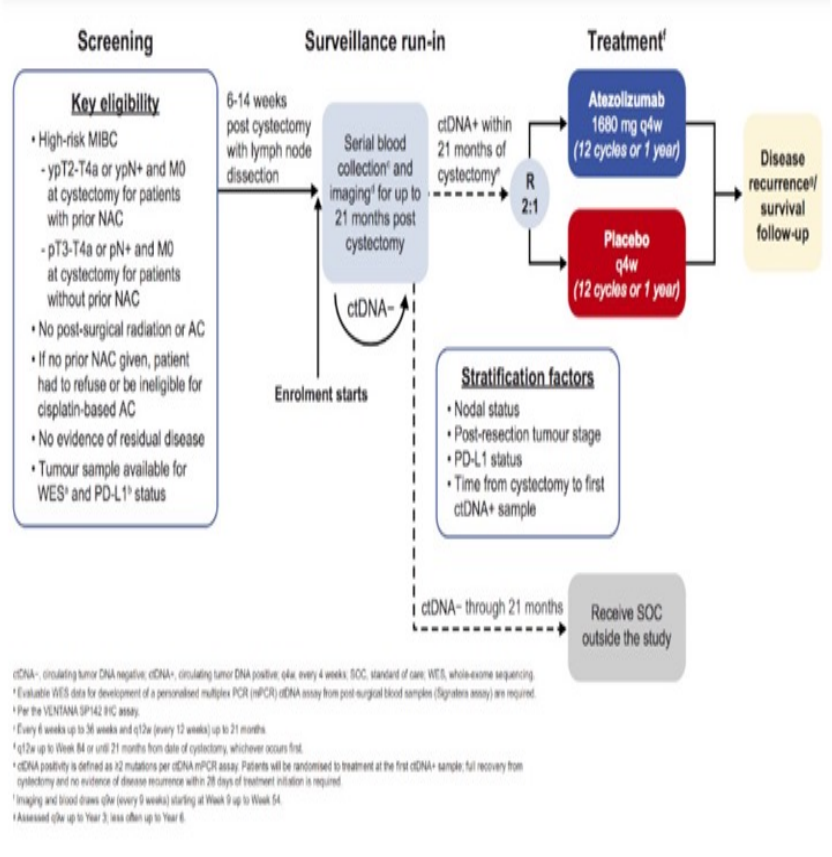
IMvigor 011



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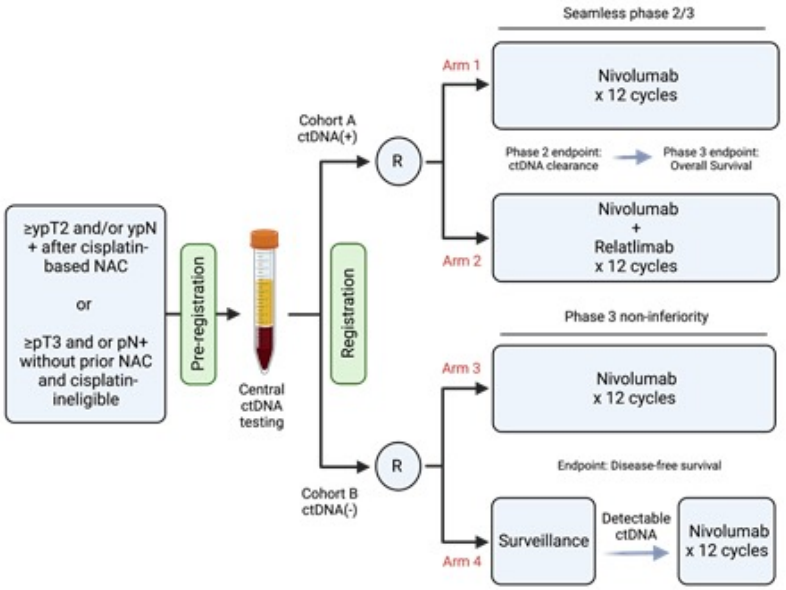

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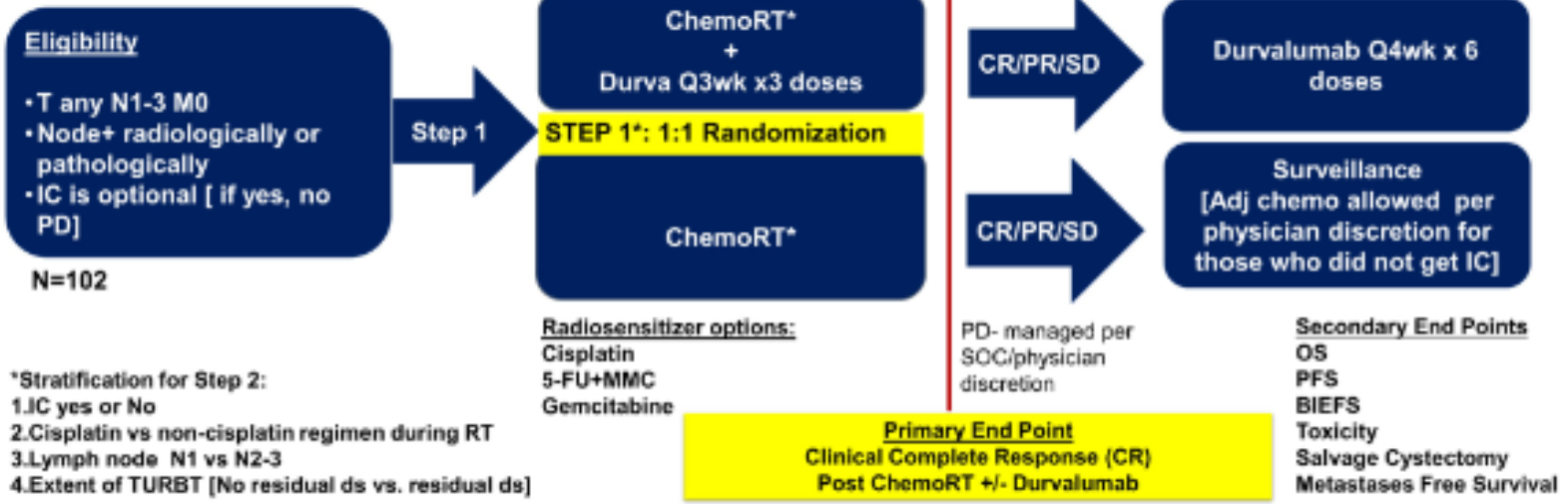
EA8185: Phase 2 study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node-positive urothelial carcinoma (INSPIRE), an ECOG-ACRIN/NRG collaboration.

Schema [Amendment # 4]:



Joshi M GU ASCO 2022, Shilpa Gupta GU ASCO 2023

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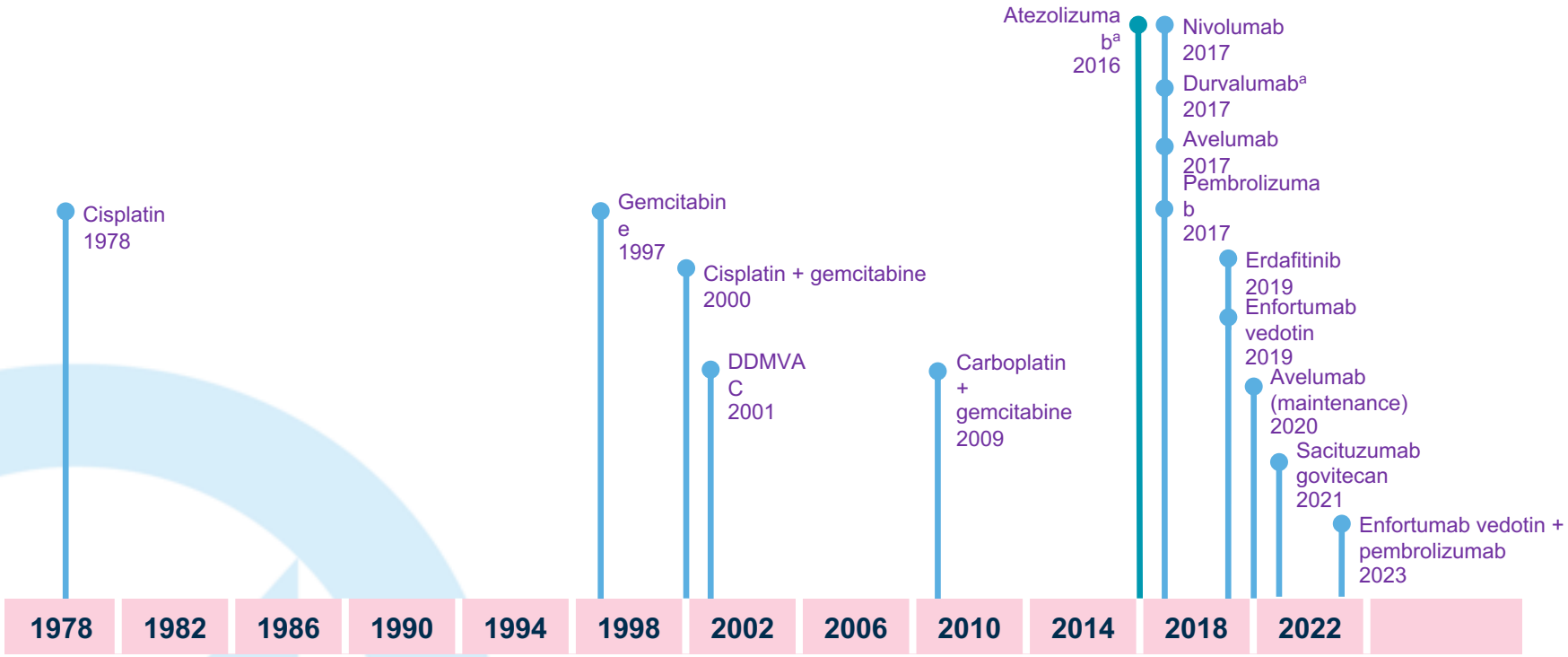
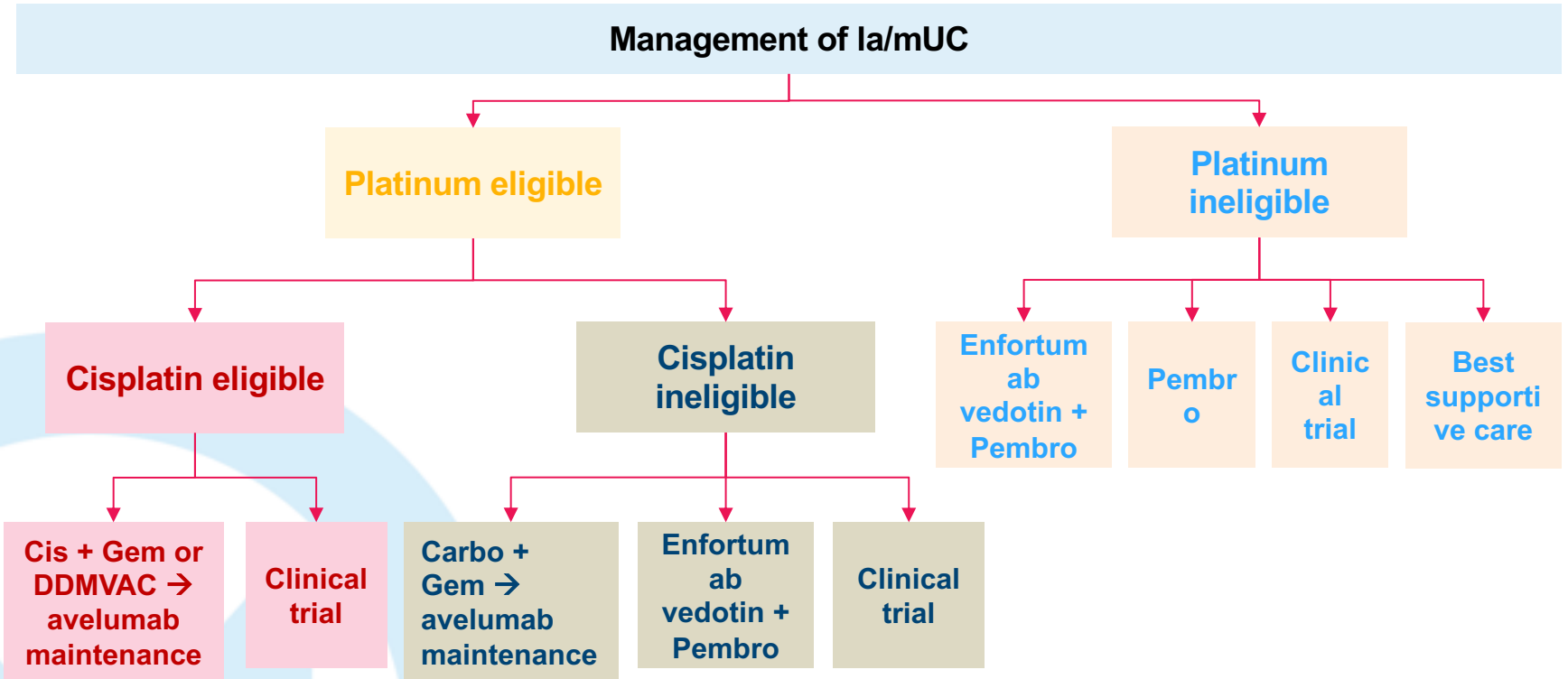
Treatment Landscape for Ia/mUC



[a] Not FDA approved; indication withdrawn.

First-Line Management of la/mUC



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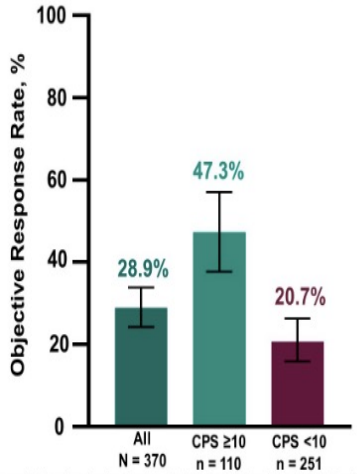
First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study

Arjun V Balar, Daniel Castellano, Peter H O'Donnell, Petros Grivas, Jacqueline Vuky, Thomas Powles, Elizabeth R Plimack, Noah M Hahn, Ronald de Wit, Lei Pang, Mary J Savage, Rodolfo F Perini, Stephen M Keefe, Dean Bajorin, Joaquim Bellmunt

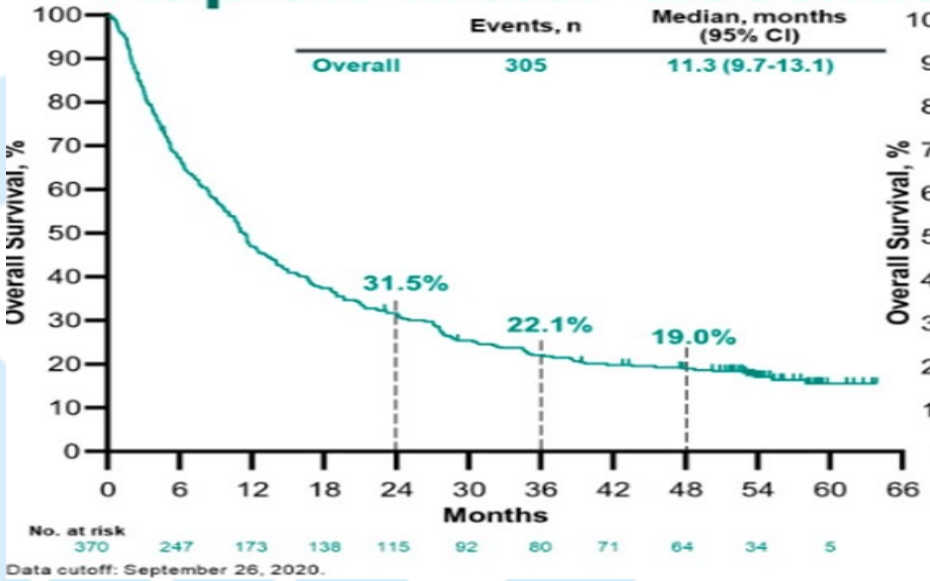
Confirmed ORR per RECIST v1.1

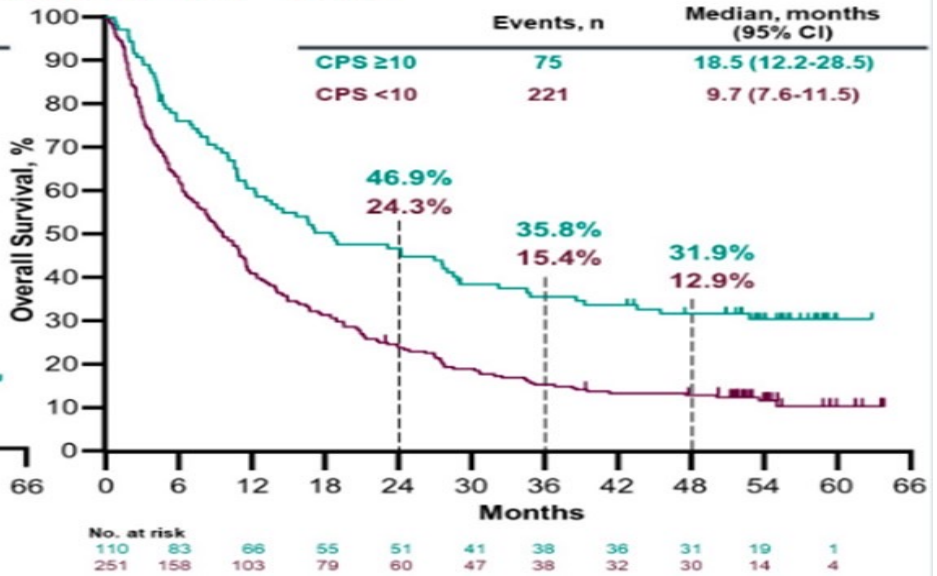


Best Response n (%)	All Patients N = 370	CPS ≥10 n = 110	CPS <10 n = 251
CR	35 (9.5)	23 (20.9)	10 (4.0)
PR	72 (19.5)	29 (26.4)	42 (16.7)
SD	67 (18.1)	22 (20.0)	44 (17.5)
PD	155 (41.9)	30 (27.3)	121 (48.2)
NA[a]	32 (8.6)	6 (5.5)	25 (10.0)
NE[b]	9 (2.4)	0 (0)	9 (3.6)

o available postbaseline imaging data. [b]Had postbaseline imaging, and best objective response was determined to be NE by RECIST v1.1. Data cutoff: September 26, 2020.

Kaplan-Meier Estimates of OS





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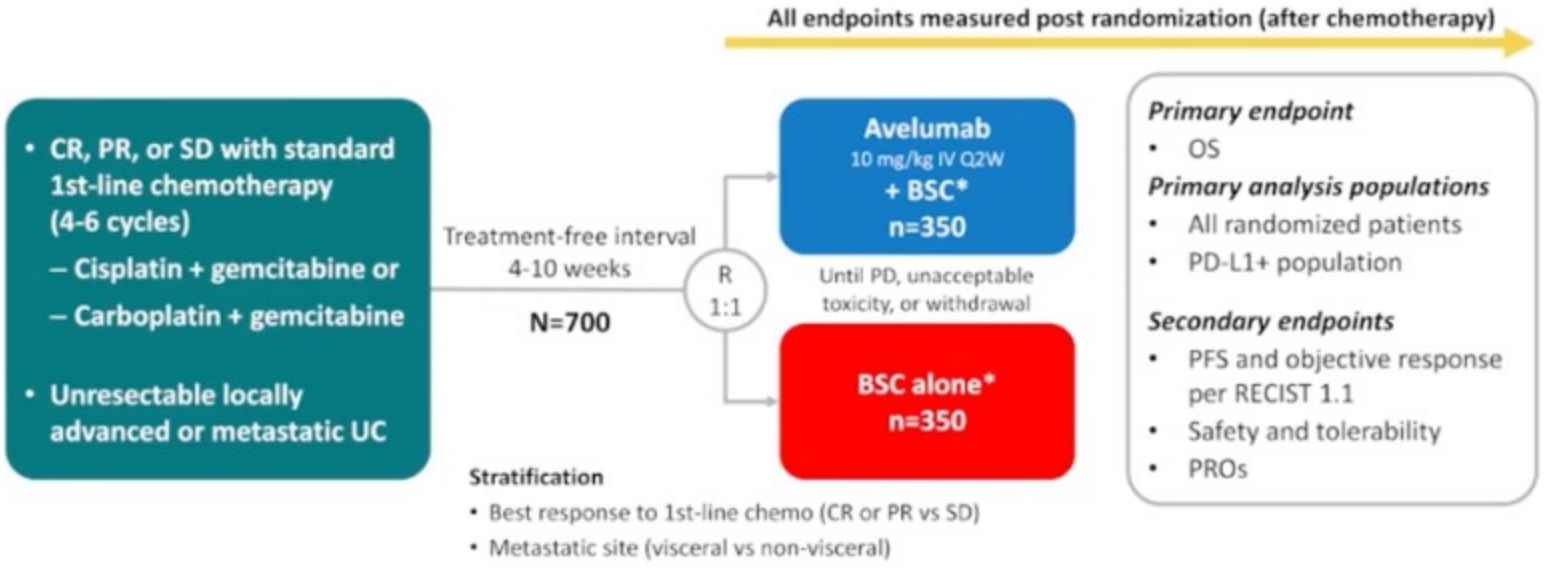
Balar et al 2017 Lancet oncology; O'Donell P. ASCO 2021

JAVELIN Bladder 100 study design (NCT02603432)



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

BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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

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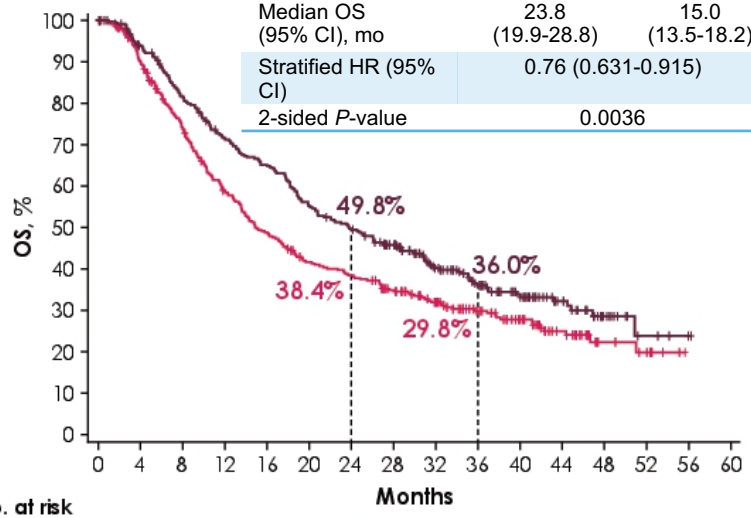
JAVELIN Bladder 100: Overall Survival

OS in the Overall Population

	Avelumab + BSC (n=350)	BSC alone (n=350)
Events	215 (61.4%)	237 (67.7%)
Median OS (95% CI), mo	23.8 (19.9-28.8)	15.0 (13.5-18.2)
Stratified HR (95% CI)	0.76 (0.631-0.915)	
2-sided *P*-value	0.0036	

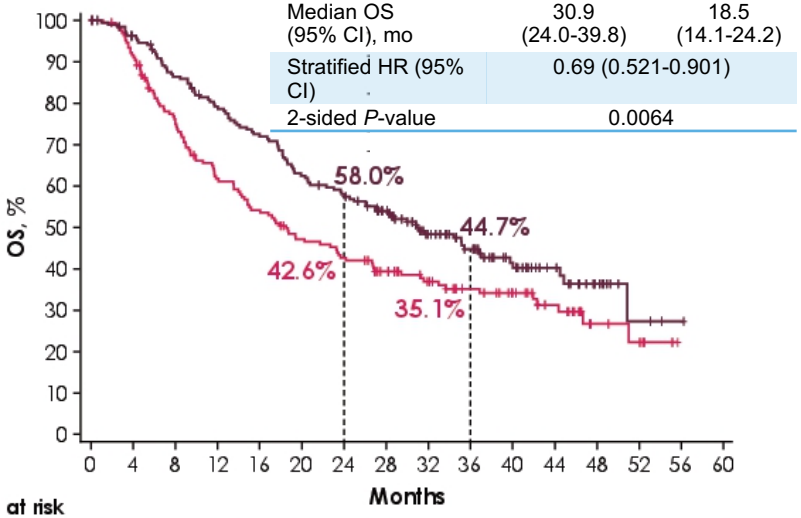


No. at risk

Avelumab + BSC	350	318	274	237	216	183	164	140	99	74	53	31	13	4	1	0
BSC	350	304	243	190	158	131	121	103	82	62	46	27	10	7	0	

OS in the PD-L1+ Population

	Avelumab + BSC (n=189)	BSC alone (n=169)
Events	102 (54.0%)	108 (63.9%)
Median OS (95% CI), mo	30.9 (24.0-39.8)	18.5 (14.1-24.2)
Stratified HR (95% CI)	0.69 (0.521-0.901)	
2-sided *P*-value	0.0064	



No. at risk

Avelumab + BSC	189	177	157	142	130	112	103	87	61	48	34	22	10	3	1	0
BSC	169	152	121	98	86	73	66	55	44	35	28	19	7	5	0	

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Powles T. ASCO GU 2022. Abstract 487.

EV-103 Dose Escalation and Cohort A: Phase 1b/2 Trial of Enfortumab Vedotin + Pembrolizumab

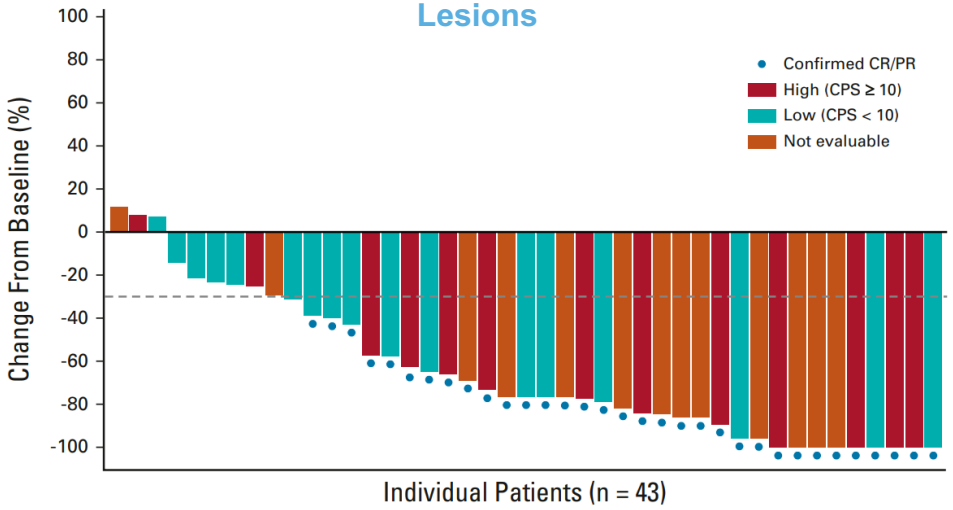
Patients With 1L Cisplatin-Ineligible la/mUC (N=45)

Dose escalation phase	**Dose expansion cohort A**
EV + Pembro (n=5)	EV + Pembro (n=40)

EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembro 200 mg on day 1 of a 3-week cycle

- 84% of patients had visceral disease and 31% had liver metastasis
- 31% of patients had PD-L1 CPS ≥10

Change From Baseline in the Sum of Diameters of Target Lesions



Confirmed ORR [95% CI]	**73.3%** (33/45) [58.1-85.4]
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

- 57.1% ORR in patients with liver metastases

Hoimes CJ, et al. *J Clin Oncol*. 2023;41(1):22-31.

MOFFITT CANCER CENTER

EV-103 Cohort K: Phase 1b/2 Trial of Enfortumab Vedotin + Pembrolizumab

Cohort K
- la/mUC
- Cisplatin ineligible
- No prior treatment for la/mUC

Primary endpoint: ORR per BICR

Key secondary endpoints: ORR per investigator assessment, DOR, disease control rate, PFS, OS, safety/tolerability, lab abnormalities

No formal statistical comparisons were conducted between the two treatment arms

R 1:1

N=76
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembro 200 mg on day 1 of a 3-week cycle

- EV + Pembro arm: 84% of patients had visceral disease and 17% had liver metastasis
- EV + Pembro arm: 41% of patients had PD-L1 CPS ≥10

N=73
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

Rosenberg JE, et al. ESMO 2022. Abstract LBA73.

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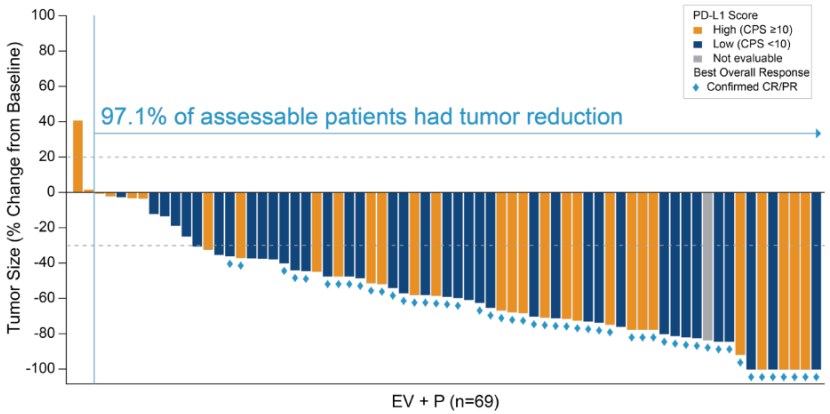
EV-103 Cohort K: Phase 1b/2 Trial of Enfortumab Vedotin + Pembrolizumab

	EV + Pembro N=76	EV Mono N=73
Confirmed ORR (95% CI)	49 (**64.5%**) (52.7-75.1)	33 (45.2%) (33.5-57.3)
Best overall response		
CR	8 (10.5%)	3 (4.1%)
PR	41 (53.9%)	30 (41.1%)
SD	17 (22.4%)	25 (34.2%)
PD	6 (7.9%)	7 (9.6%)
NE	3 (3.9%)	5 (6.8%)
No assessment	1 (1.3%)	3 (4.1%)
Median time to objective response, mo (range)	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	11.0 (1-29)	8.0 (1-33)

- EV + Pembro arm: 7/13 (53.8%) confirmed ORR observed in patients with liver metastases

EV + Pembro: Maximum Percent Reduction From Baseline of Target Lesion by BICR



	EV + Pembro N=76	EV Mono N=73
Median DOR, mo (95% CI)	NR (10.25-NR)	13.2 (6.14-15.97)
Median PFS, mo (95% CI)	NR (8.31-NR)	8.0 (6.05-10.35)
Median OS, mo (95% CI)	22.3 (19.09-NR)	21.7 (15.21-NR)

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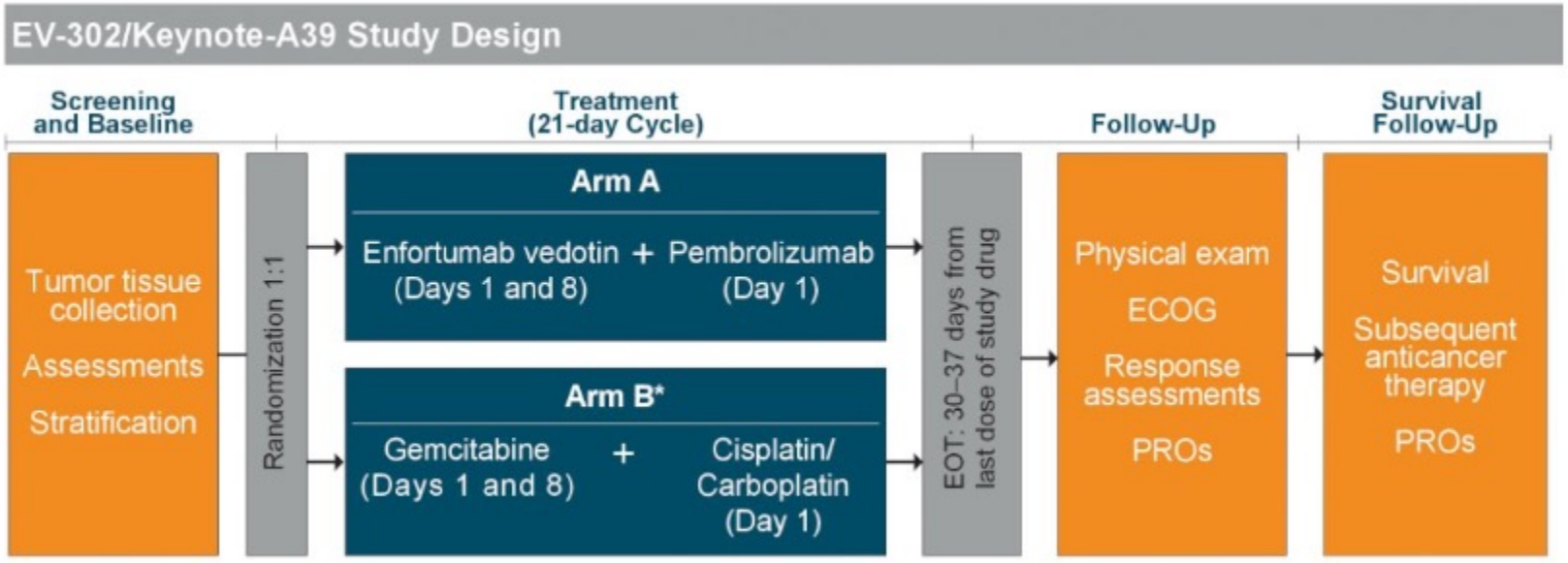
Rosenberg JE, et al. ESMO 2022. Abstract LBA73.

EV-302



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Second-Line Treatment Options Post-Platinum Treatment*

	KEYNOTE-045[1] Pembrolizumab Phase 3	IMvigor 210[2] Atezolizumab Phase 2	CheckMate 275[3] Nivolumab Phase 2	Study 1108[4] Durvalumab Phase 1/2	JAVELIN solid tumor [5] Avelumab Phase 1B
Patient number	542	310 (Cohort 2)	270	191	242
Study Arms	**Pembrolizumab** 200 mg (IV) q3w	**Atezolizumab** 1200 mg (IV) q3w	**Nivolumab** 3 mg/kg IV q2w	**Durvalumab** 10 mg/kg IV q2w	**Avelumab** 10 mg/kg q2w
Key Inclusion Criteria	• Metastatic or locally advanced urothelial cancer • Progression after 1 or 2 lines of platinum-based therapy • Measurable disease • ECOG PS 0-2	Cohort 2: • ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• Histologically confirmed solid tumors Locally advanced or mUC cohort: • Had progressed, on were ineligible for, or refused any number of prior therapies • ECOG PS 0-1	Solid tumors mUC cohort: • Had progressed post-platinum treatment or cisplatin-ineligible • Unselected for PD-L1 • ECOG PS 0-1
ORR (%)	• 21.1	• 15	• 19.6	• 20.4	• 16.1 (after ≥6 weeks follow-up)
Median PFS (months)	• 2.1	• 2.1	• 2.0	• NA	• NA
Median OS (months)	• 10.3	• 7.9	• 8.7	• NA	• NA

*No head-to-head studies have been conducted and direct comparisons cannot be made between these studies.

1. Bellmunt et al. N Engl J Med 2017; 376:1015-1026; 2. Loriot Y et al. Poster presentation at ESMO 2016. 783P; 3. Sharma P, et al. Lancet Oncol. 2017; 4. Powles T, et al. Poster presentation at ASCO GU. 286; 5. Patel M et al. Poster presentation at ASCO GU. 330.

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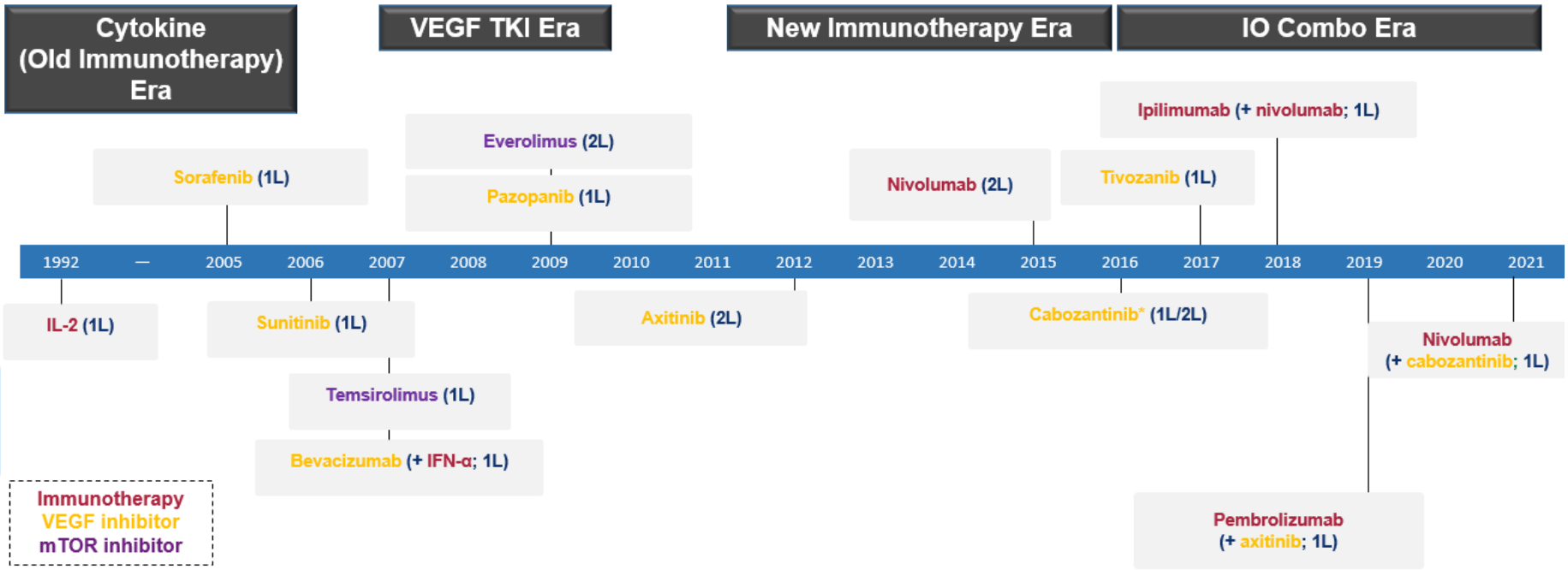
The Evolving Treatment Landscape in Metastatic Clear Cell RCC



Slide Courtesy to Sandy Srinivas, MD. 5th Annual Global Summit on Genitourinary Cancer, Banff 2022

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Studies of Adjuvant IO in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO 2021** **ASCO GU 2022**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	**ESMO 2022** **NS DFS** **HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**ESMO 2022** ***Part A (Nivo+Ipi)*** **NS DFS** **HR, 0.92; P=0.5347**
PROSPER RCC[4]	766	cT2Nx, cTxN1, cTxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	**ESMO 2022** **NS DFS** **HR, 0.97; P=0.43** **Trial stopped for futility**
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.

DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.

1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

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KEYNOTE 564

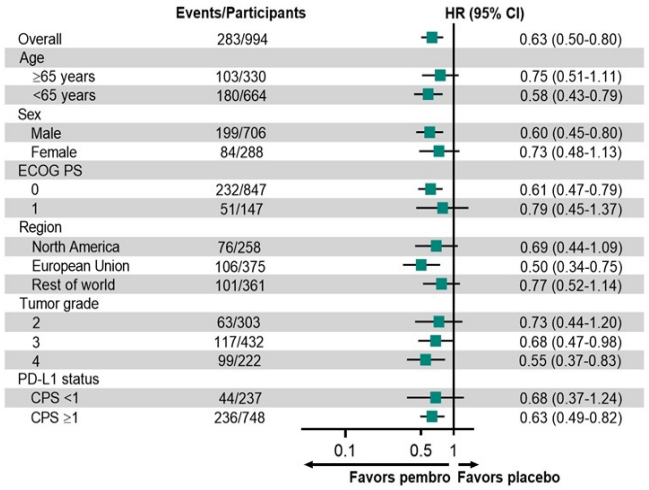
Key Eligibility Criteria
- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

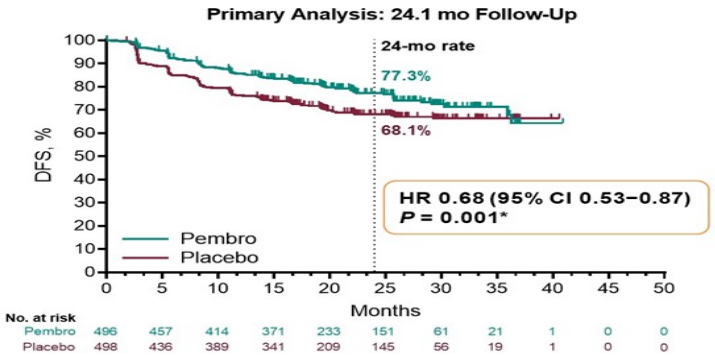
Stratification Factors
- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

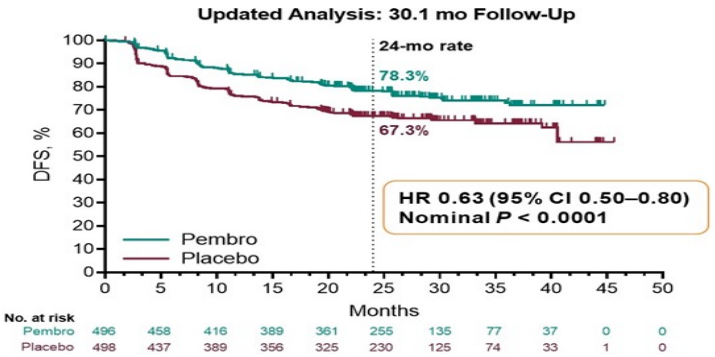
- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety





	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.
ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Data cutoff at updated analysis: June 14, 2021.

Powles T, et al. *Lancet Oncol*. 2022;23;1133-1144; Choueiri TK, et al. ASCO GU 2022. Abstract 290; Choueiri TK et al. *N Engl J Med*. 2021;385:683-694; Choueiri TK et al. 2021 ASCO Annual Meeting. Abstract LBA5.

Overview of Systemic Therapy in RCC Based on IMDC Risk Stratification

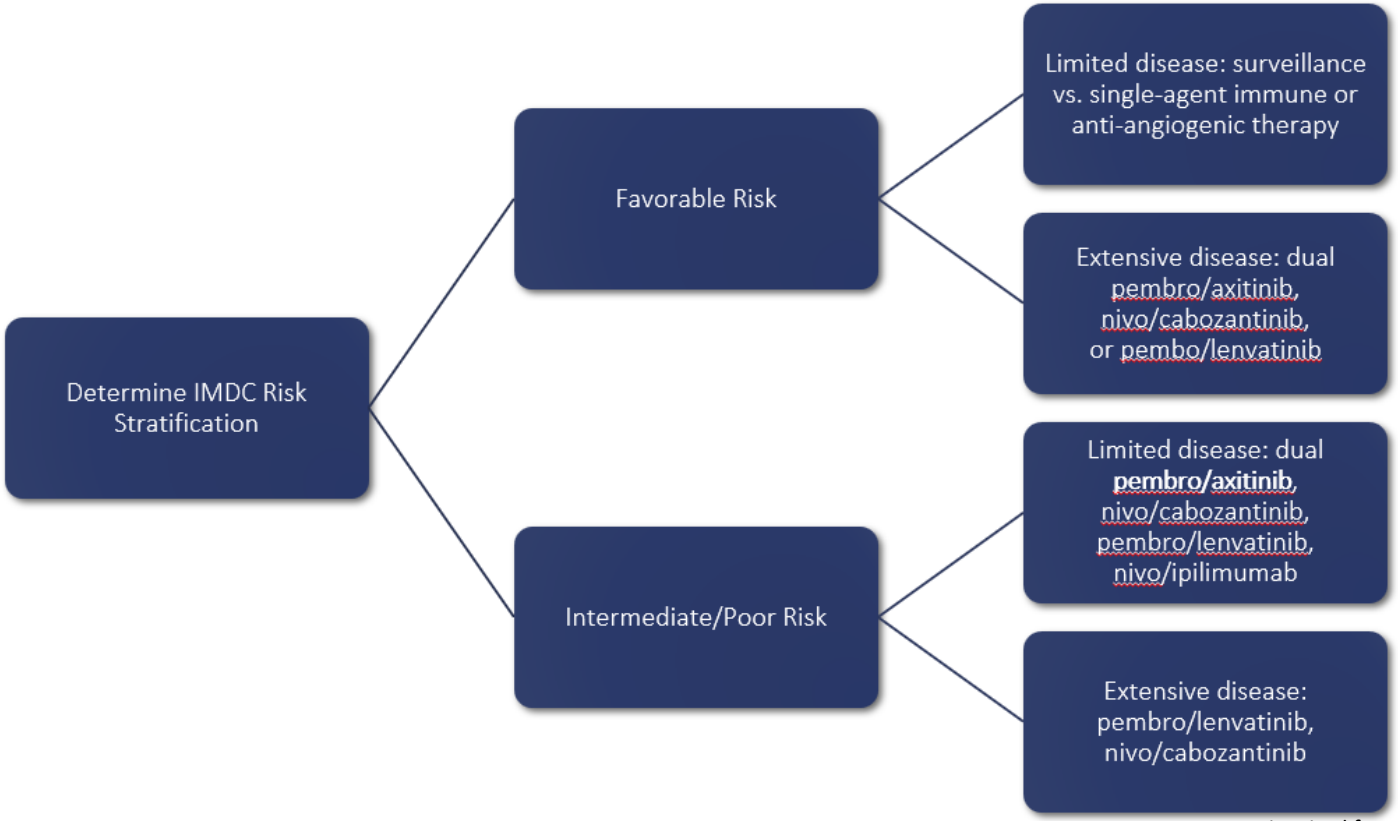


Image inspired from Atkins MB, UpToDate

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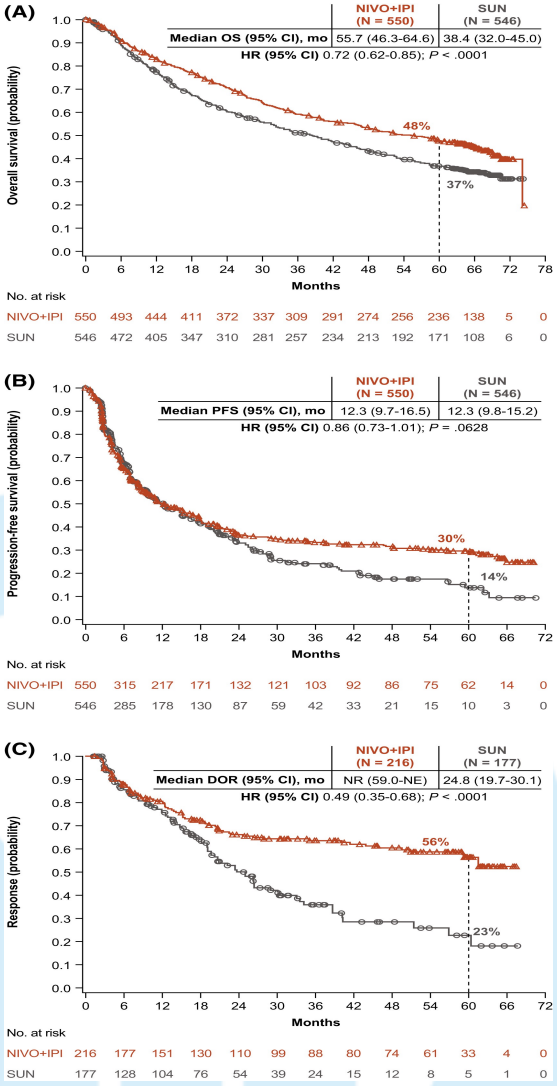
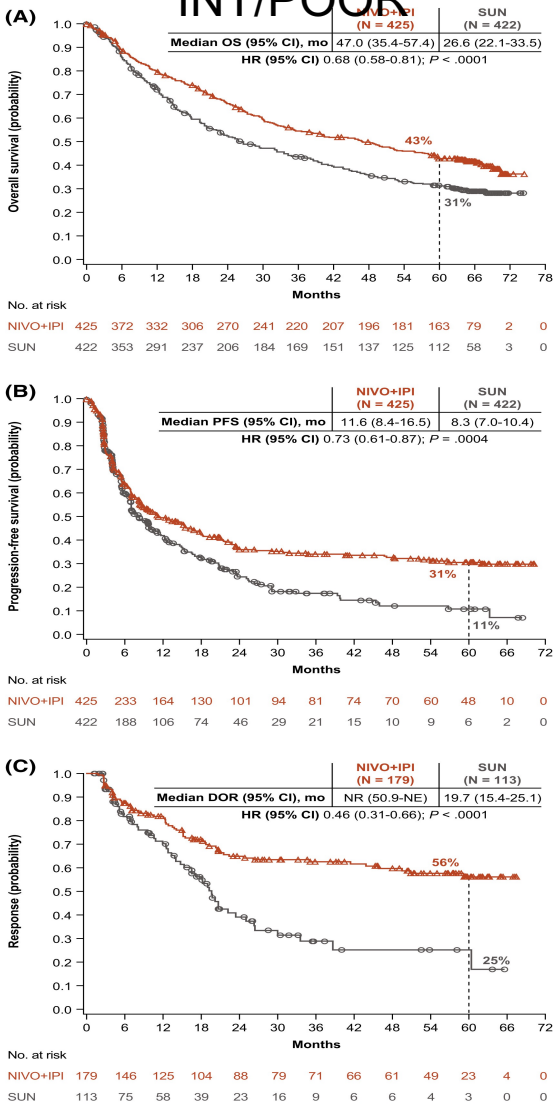
CheckMate 214: Nivo + IPI vs Sunitinib

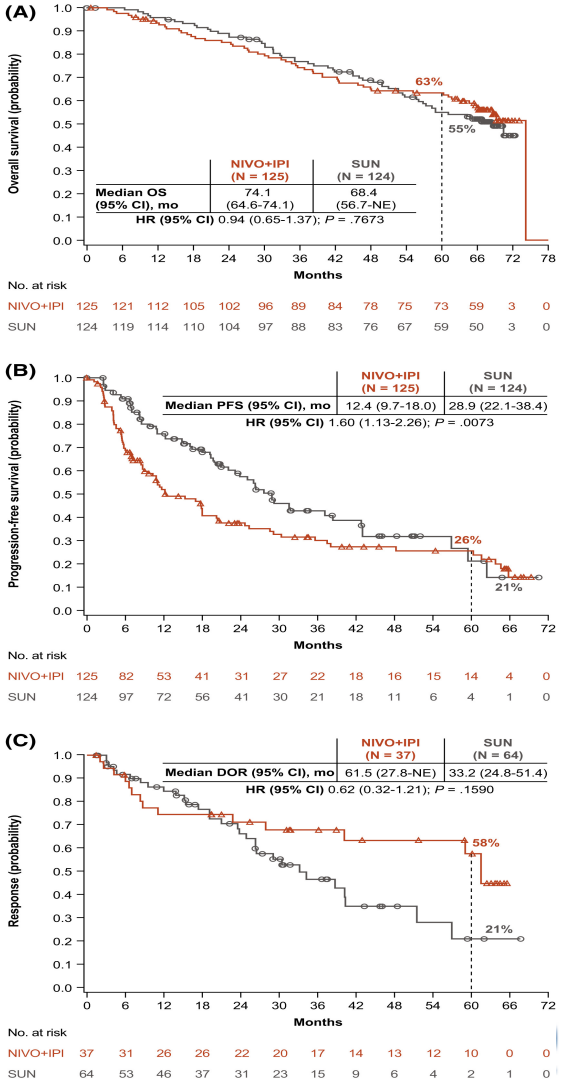
ITT



INT/POOR



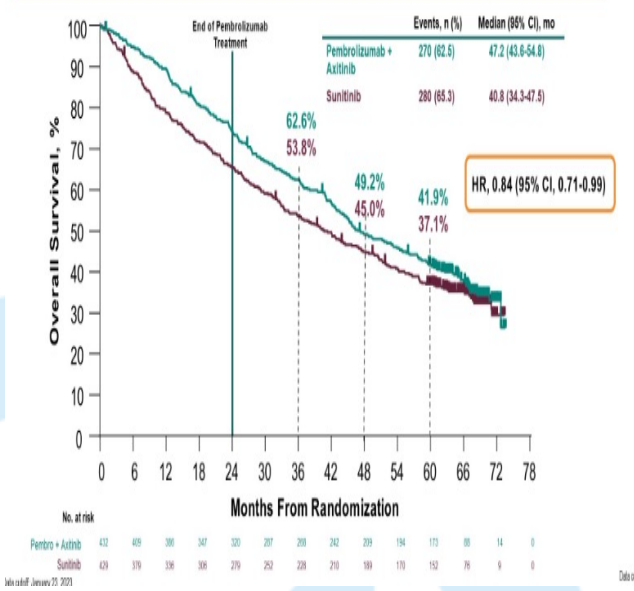
FAVOURABLE



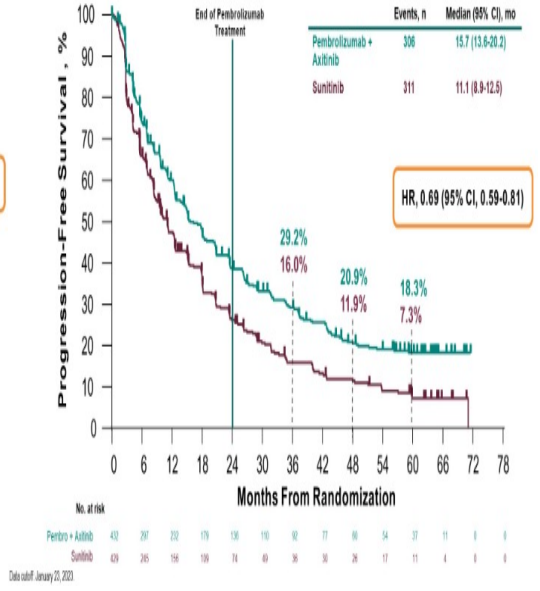
Motzer et al Cancer 2022

KEYNOTE 426: Pembrolizumab/Axitinib vs Sunitinib

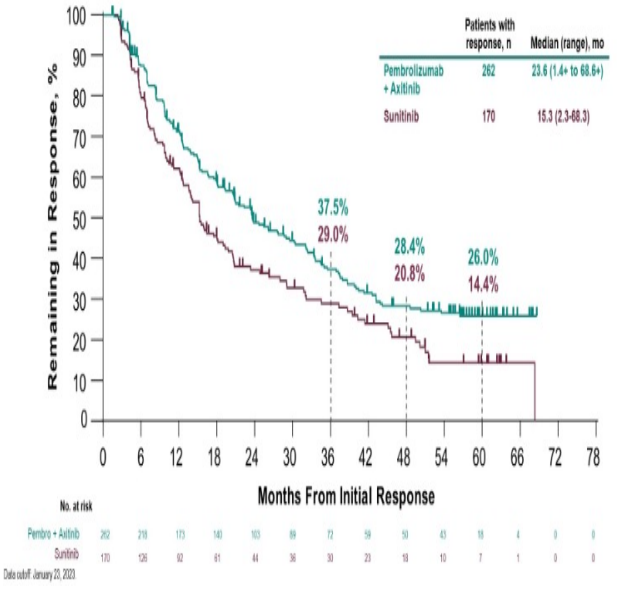
Overall Survival in the ITT Population



Progression-Free Survival in the ITT Population



Duration of Response in the ITT Population



Rini et al ASCO 2023

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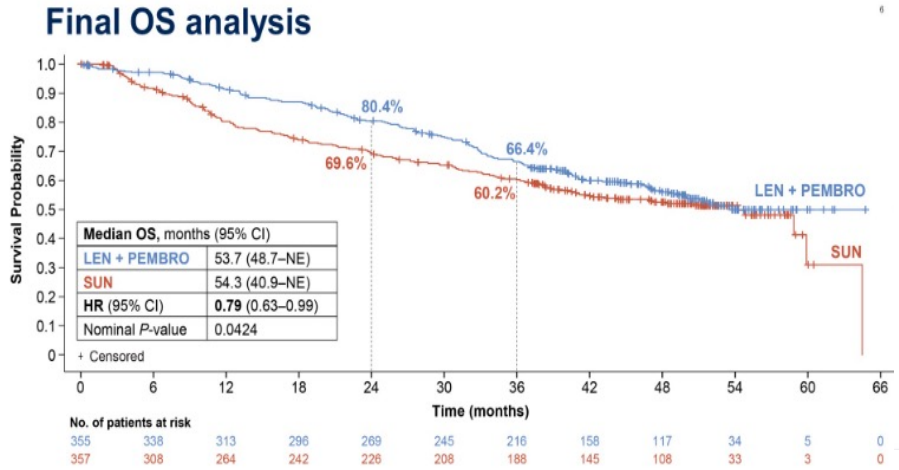
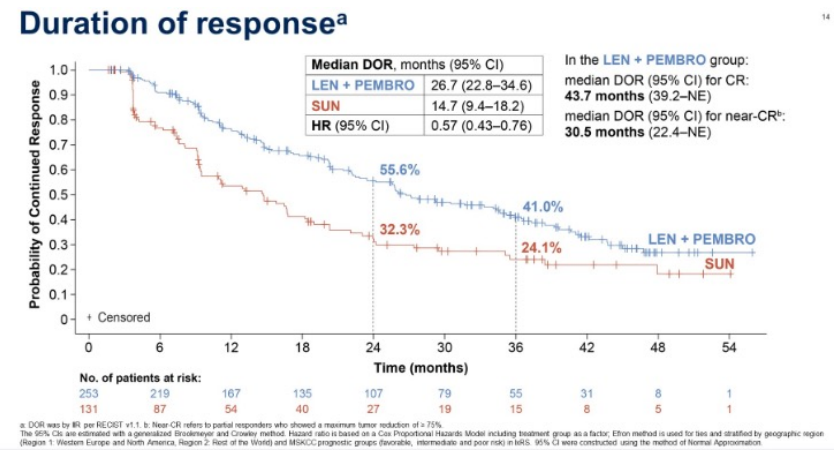
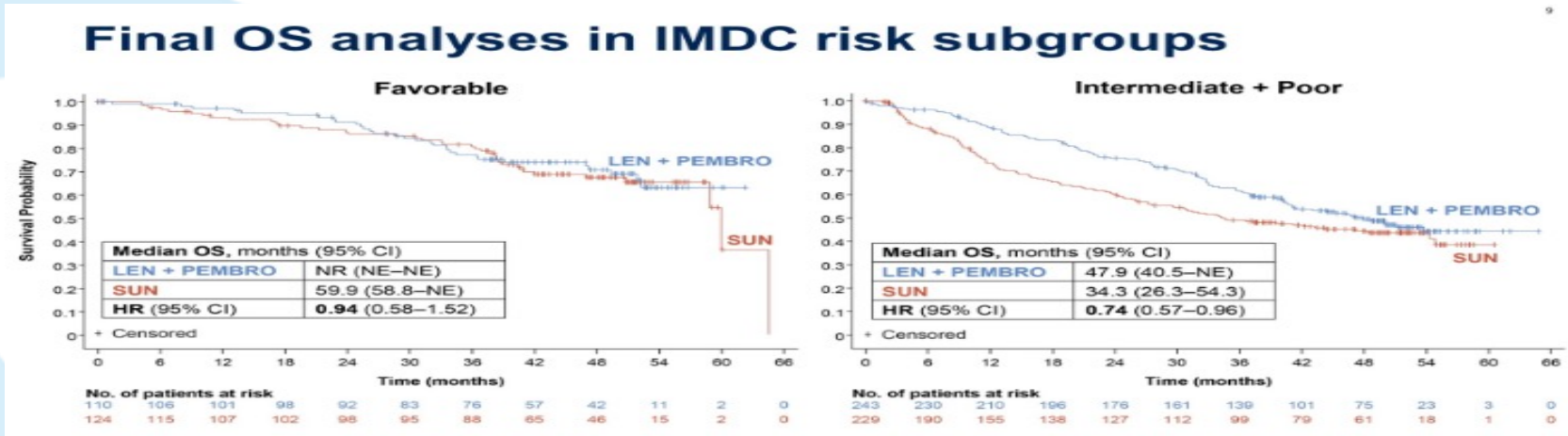
CLEAR: Lenvatinib + Pembro vs Sunitinib







Hudson et al ASCO 2023

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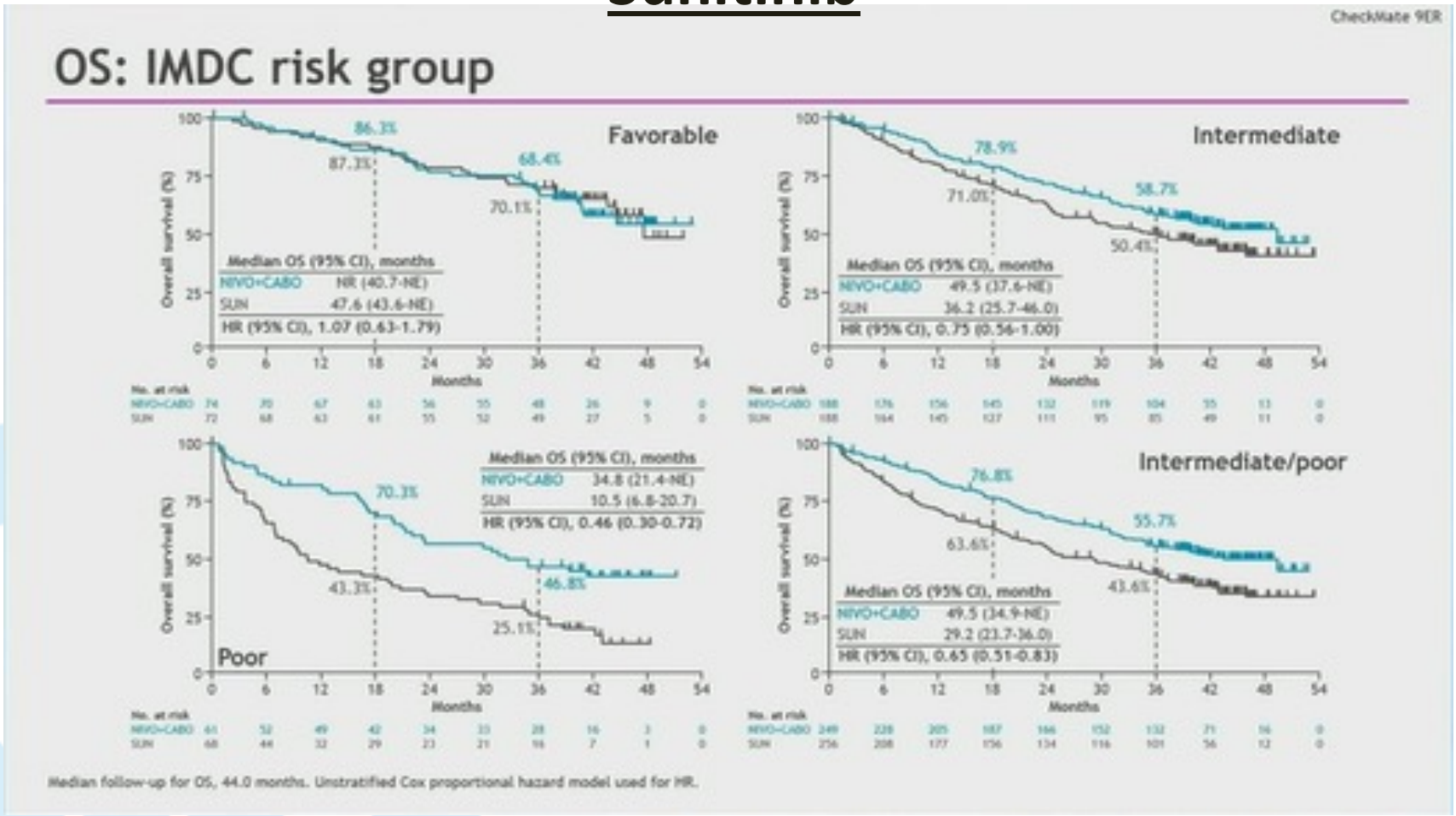
CheckMate 9ER: Nivolumab + Cabozantinib vs Sunitinib



Burotto M GU ASCO 2023

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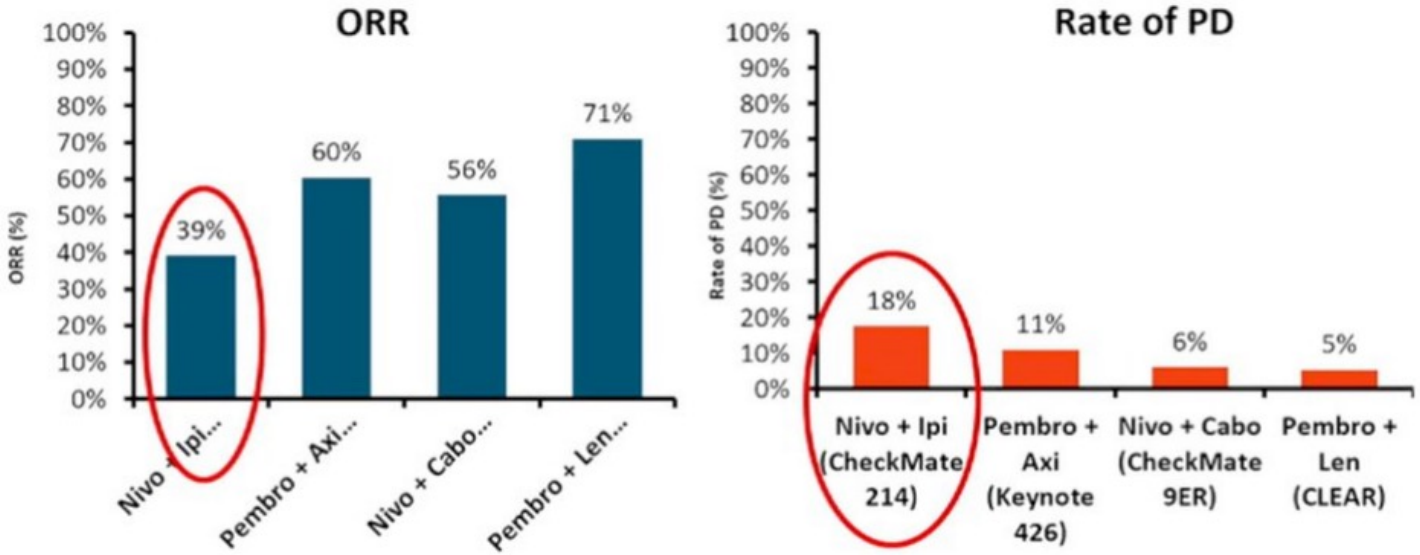
Cross-Trial Comparison of Response in ITT Population



- *Response rate may be a more immediately meaningful endpoint than survival measure.*
- *IO/IO has the lowest response rate and higher primary progressive disease.*
- *TKI containing therapy is more likely to control symptoms and may be prioritized.*

Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500; Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269. Pickering L, EIKCS 2022

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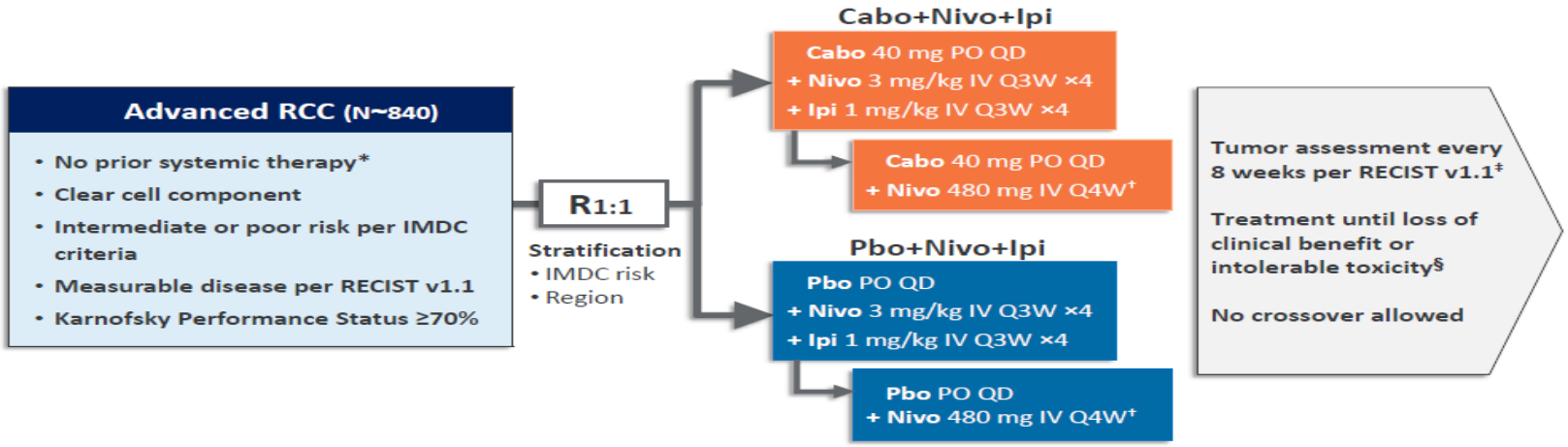
COSMIC-313

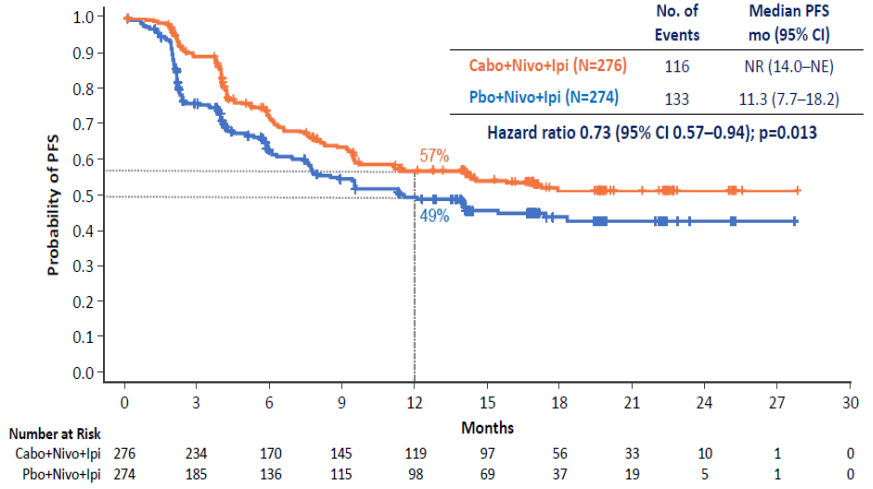
COSMIC-313 Study Design



Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Progression-Free Survival: Final Analysis (PITT Population)



Choueiri T. et al ESMO 2022

VEGF-IO in Refractory RCC

Phase III CONTACT-03 study

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R 1:1 N=522

- Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO
- Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

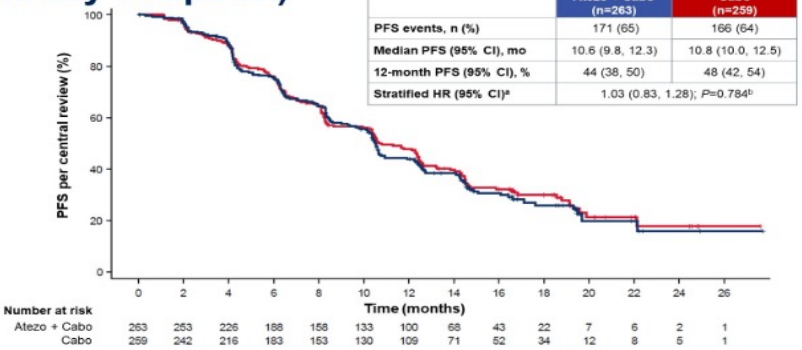
Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID: NCT04338269. IMDC: International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

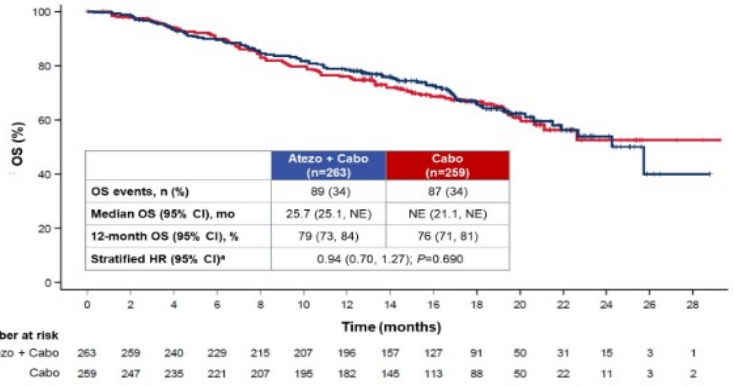
Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	



Interim analysis of OS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
OS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	



Choueiri et al ASCO 2023

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Conclusions

- Immunotherapy has become the backbone for bladder and kidney cancer treatment regimens.
- ADCs and IO combination in bladder cancer are very promising with high ORR and will change the treatment landscape.
- Multiple VEGF inhibitor + IO combinations have demonstrated superior disease control to sunitinib monotherapy in frontline advanced/metastatic RCC.
- Without direct comparisons in a clinical trial setting and positive results from each combination, differentiation among these approved VEGF + IO combinations relies on the ease of use for the regimen and selecting the appropriate regimen for each patient based on patient characteristics and risk factors.
- Biomarkers are required for better patient selection and treatment response.

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