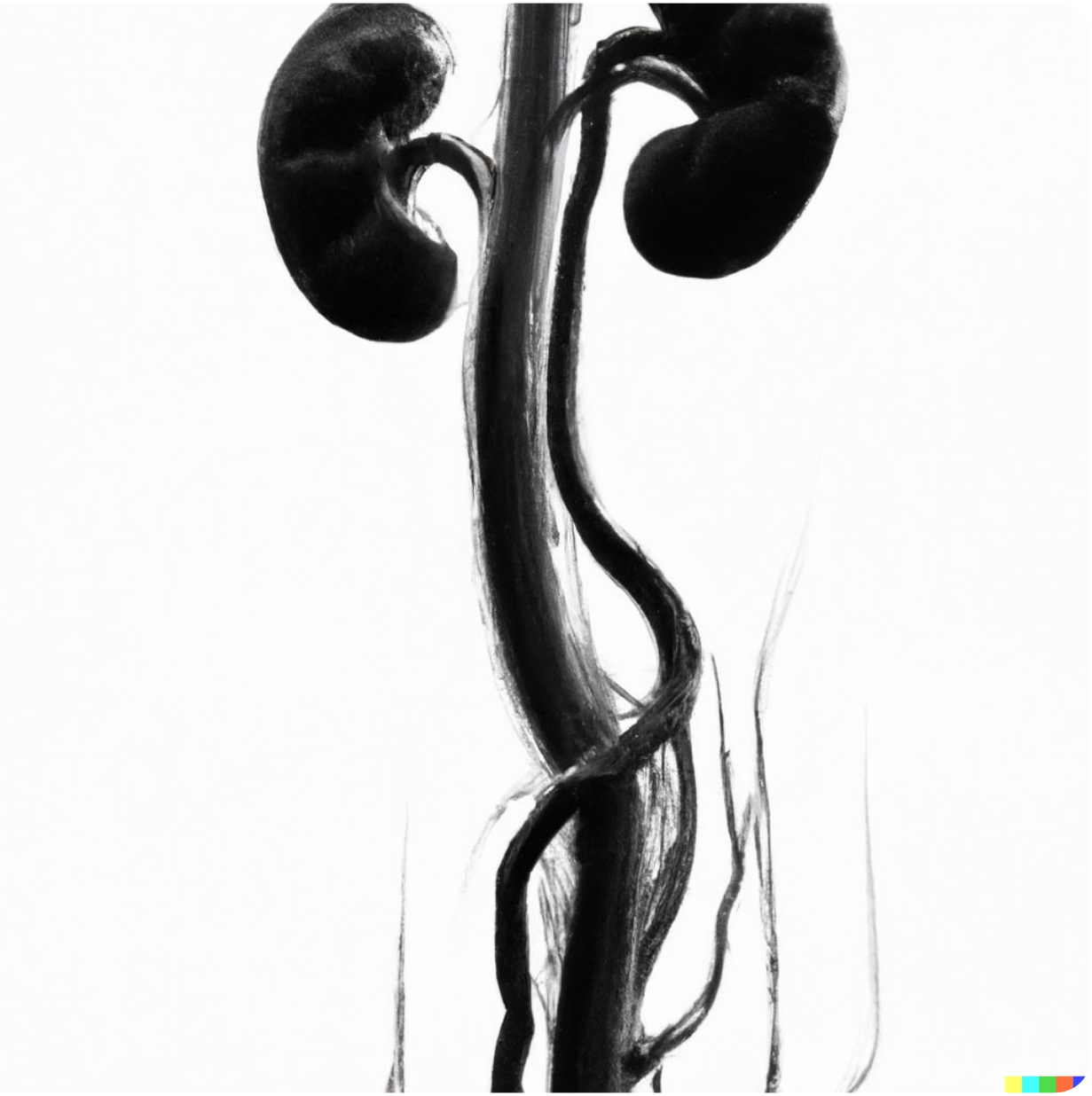


Tratamiento adyuvante con pembrolizumab en cáncer renal

¿Un nuevo estándar?

Dr. Alfonso Gómez de Liaño
CHUIMI
@Uro_Oncologist

Conflicts of Interest

Me or my institution has received honoria for speaking, advisory role, research funding, travel, accomodations and expenses from

The current knowledge

1. Perioperative systemic treatments have been successful in several other solid tumors (bladder, breast, lung, colon,…), but perioperative strategies with systemic terapy have lagged in RCC
2. Nephrectomy can potentailly cure patients with early localized disease; however risk of recurrence in stage II-III remains significant, with 20-40% experiencing local or distant relapse
3. There are no approved neoadjuvant treatments for localized RCC prior to nephrectomy
   There are 2 approved therapis for patients with high risk RCC after surgery

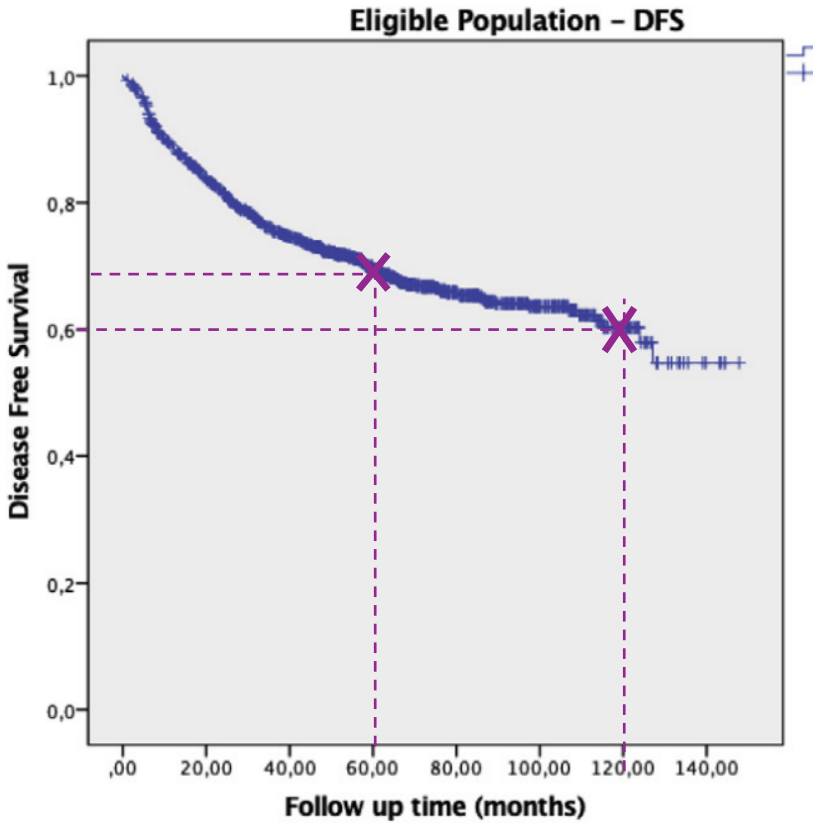
Despite surgery, risk of recurrence remains high

Prevalence, Disease-free, and Overall Survival of Contemporary Patients With Renal Cell Carcinoma Eligible for Adjuvant Checkpoint Inhibitor Trials

Lorenzo Marconi,[1] Maxine Sun,[2] Christian Beisland,[3,4] Tobias Klatte,[5,6] Boerje Ljungberg,[7] Grant D. Stewart,[8] Saeed Dabestani,[9] Toni K. Choueiri,[2] Axel Bex[10,11]

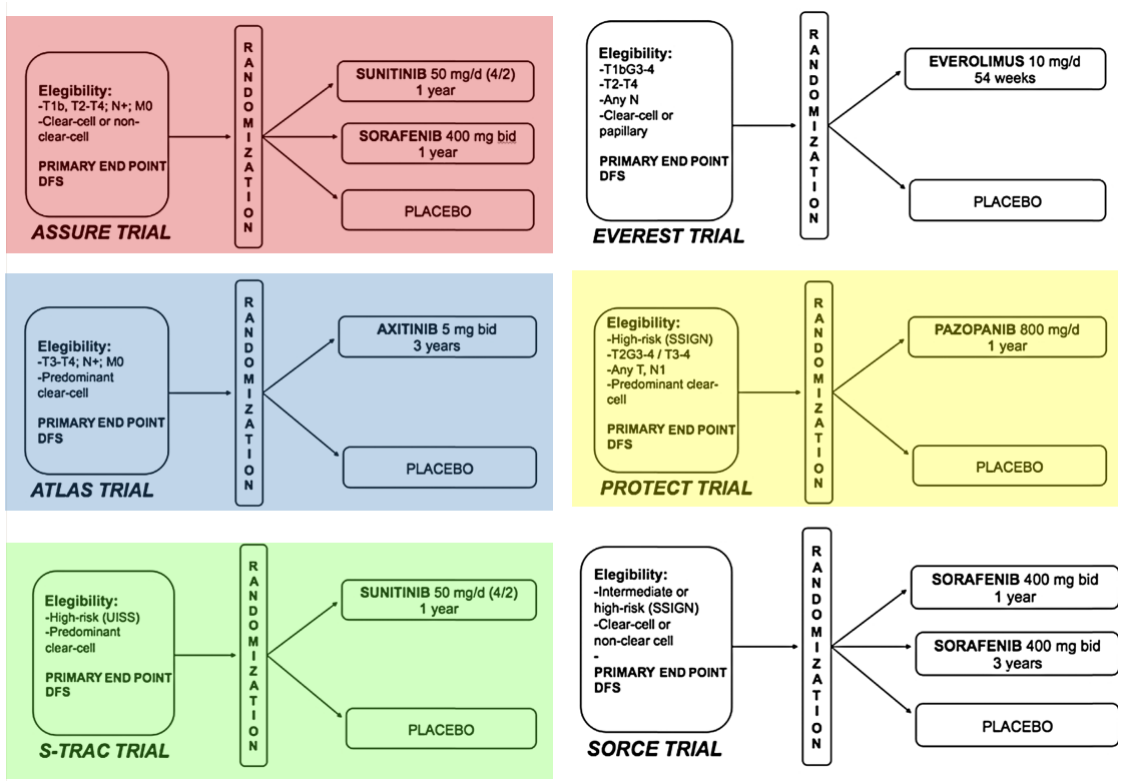
Table 3 Analysis of Survival in the RECUR Population According to the Eligibility for the Different Adjuvant Trials

RECUR Population Eligible for:	n	Progression, n	Death (RCC), n	Death (Other Causes), n	Median DFS Time Estimates, mos (95% CI)	Median OS Time Estimates, mos	DFS, %			
							1 Year	3 Years	5 Years	10 Years
IMMotion-010	408	222	140	44	43.59 (30.78-56.41)	76.5 (64.5-88.4)	76	53.5	45	38.6
CheckMate-914	725	311	187	92	109.26 (83.93-134.6)	97 (80.6-113.5)	83.1	65.3	57	46.3
Keynote-564	609	278	170	79	75.8 (52.7-98.8)	93.1 (80.7-105.6)	81.6	62.7	54.3	44
RAMPART (Model 1)	1363	415	244	173	Not reached	129.3 (110-148.5)	88.7	75.4	69.6	60.5
RAMPART (Model 2[a])	818	320	196	102	Not reached	103 (88-118)	84.3	66.6	60.4	53.1
PROSPER	1071	383	239	138	Not reached	109.5 (95.8-123.3)	86.2	71.2	64.5	55.5



1. - Stephenson AJ, et al. J Urol 2004. 2. – Marconi L, et al. Clin Genitourin Cancer. 2021

Adjuvant trials testing TKIs and mTORi in RCC



TRIAL	ENDPOINT	STATISTICALLY SIGNIFICANT?
ASSURE	DFS	NO
SORCE	DFS	NO
S-TRAC	DFS	**YES**
PROTECT	DFS	NO
ATLAS	DFS	NO
EVEREST	DFS	NO

Haas NB, Lancet 2016; Ravaud A, NEJM 2016; Motzer RJ, J Clin Oncol 2017; Gross-Goupil M, Ann Oncol 2018; Motzer RJ, Eur Urol 2018; Ryan CW, ASCO GU 2022

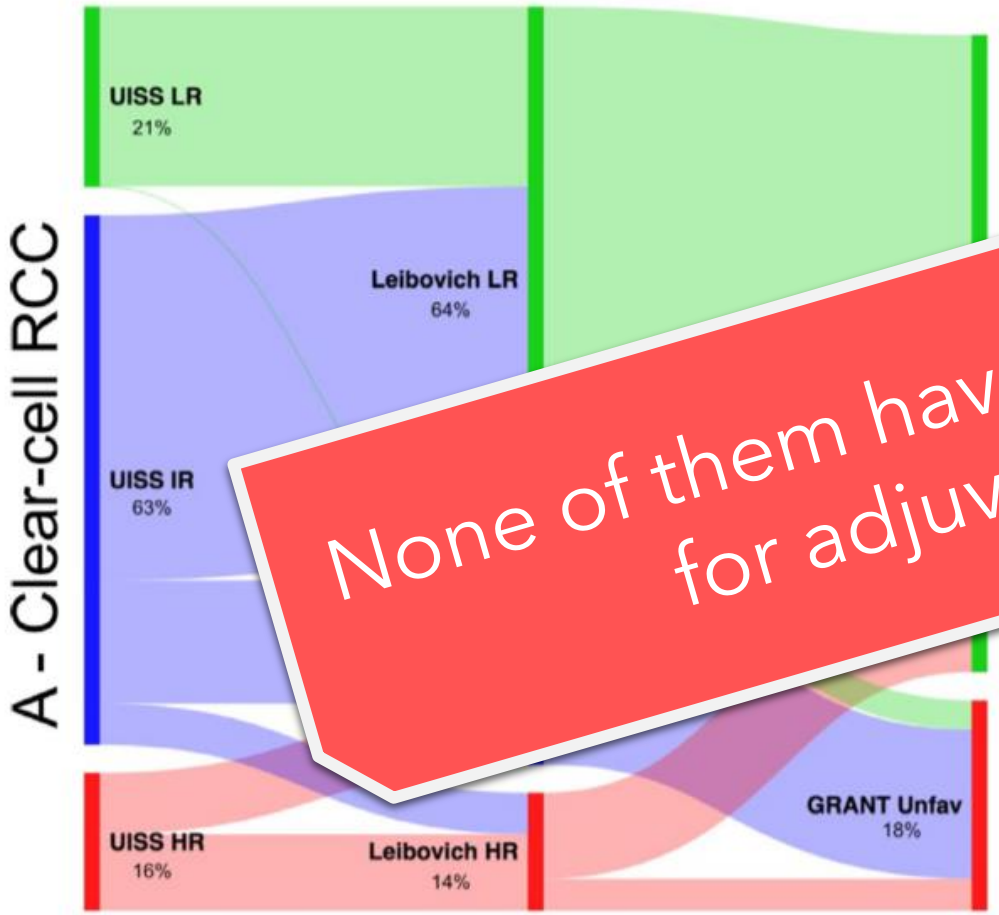
Several classifications predict risk of recurrence

Model	Parameters	Outcome	Risk groups	Type
UISS (UCLA)	TNM, grade, ECOG	OS	3	KM analysis
SSIGN	TNM, pN+, pM+, grade, tumor size, necrosis	CSS	-	Algorithm
Leibovich 2003	TNM, pN+, grade, tumor size, necrosis	MFS	3	Algorithm
Leibovich 2018	2003 +other 7	PFS, OS	-	KM analysis
GRANT	TNM, pN+, Grade, Age	DFS, OS	2	Algorithm
VENUSS	TNM, pN+, grade, tumor size, tumour thrombus	RFS	3	Algorithm
MSKCC	TNM, T size, grade, necrosis, symptoms	RFS		Nomogram
Kattan	TNM, T size, histology, symptoms	RFS		Nomogram
Yaycioglu	T size, symptoms	RFS	2	Formula
Karakiewic	TNM, age, sex, +margin, T size, symptoms	CSS		Nomogram
Cindolo	T size, symptoms	RFS	2	Formula
Rini	16 gene signature	RFS	3	Gene signature
Wei	6 SNP signature + TNM,grade, necrosis	RFS		Nomogram

Zisman et al, JCO, 2002: Frank et al, J Urol 2002: Leibovich et al, Cancer, 2003; Leibovich et al, Eur Urol, 2018; Sorbellini et al, J Urol, 2005; Kattan et al, J Urol, 2001; Yaycioglu et al, Urology, 2001; Karakiewicz et al, JCO, 2007; Cindolo et al, BJU Int, 2003; Rini et al, Lancet Oncol 2015; Wei et al, Lancet Oncol 2019

Limited interchangeability

Different prognostic performance



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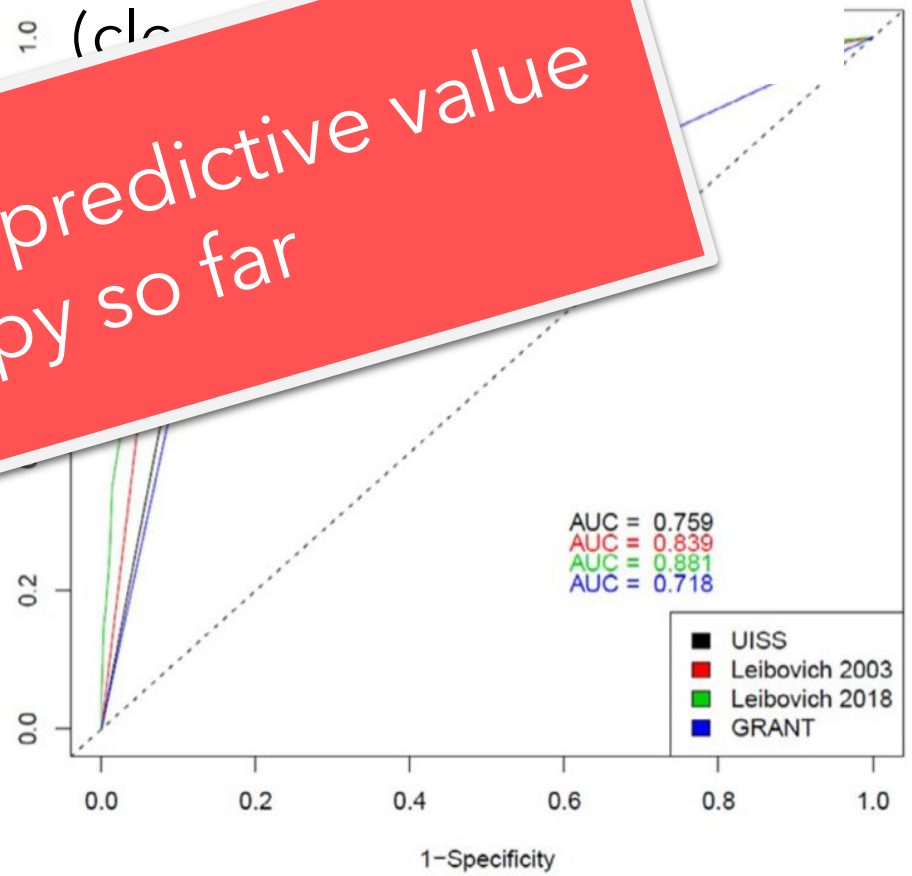
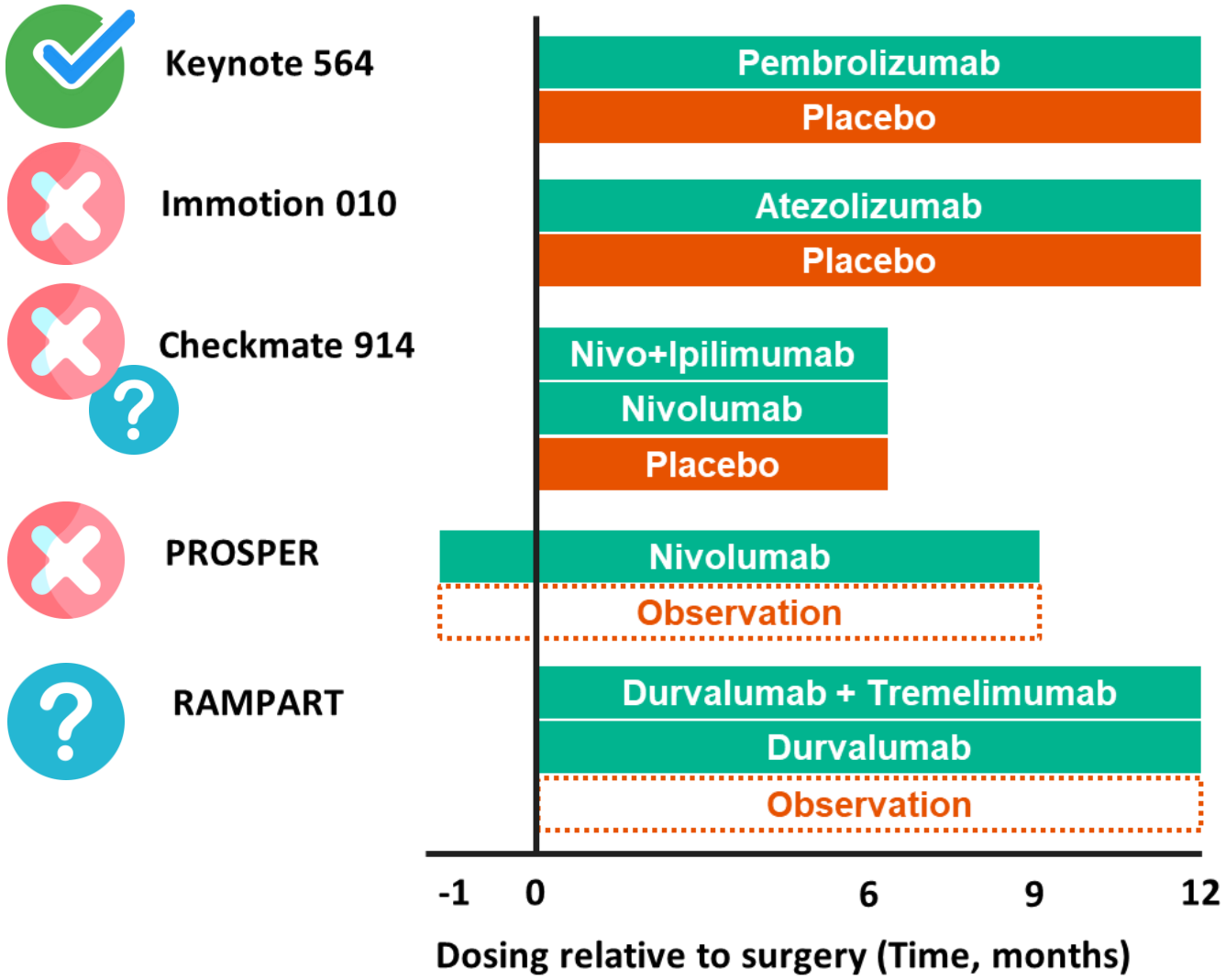
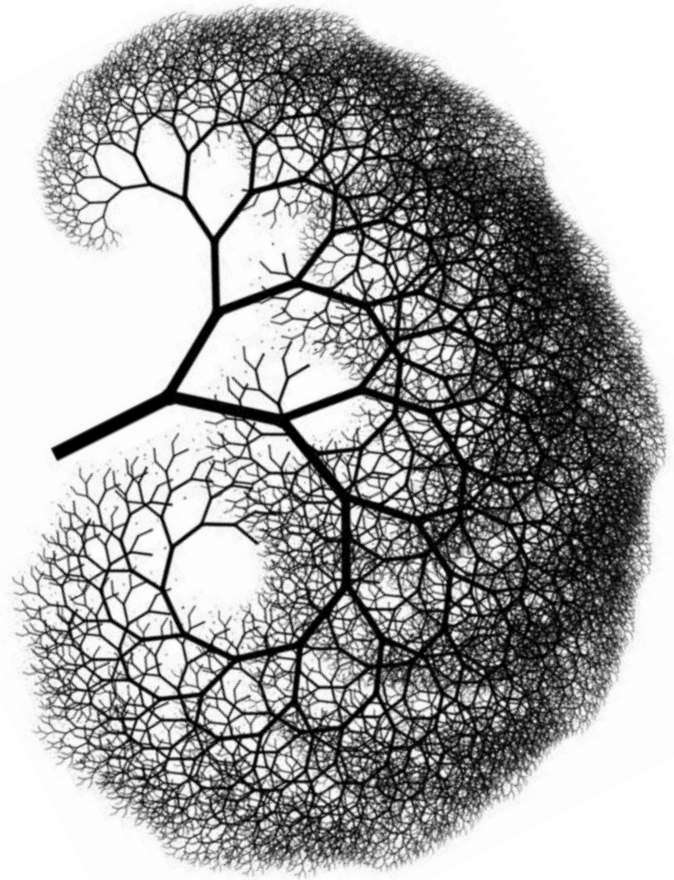


None of them have proven predictive value for adjuvant therapy so far

Rosiello G, et al, Urol. Oncol 2022

Phase III trials with adjuvant ICIs in RCC





1. –Choueiri TK et al, NEJM 2021; 2. – Pal, SK. et al, Lancet 2022; 3.- Motzer R. et al, ESMO 2022 ; 4.- Allaf M. et al, ESMO 2022

Keynote-564: Adjuvant Pembrolizumab

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

Choueiri TK et al, NEJM 2021; Powles T, et al, Lancet Oncol 2022

Keynote-564: The population

Prespecified Disease Risk Categories

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Choueiri TK et al, NEJM 2021; Powles T, et al, Lancet Oncol 2022

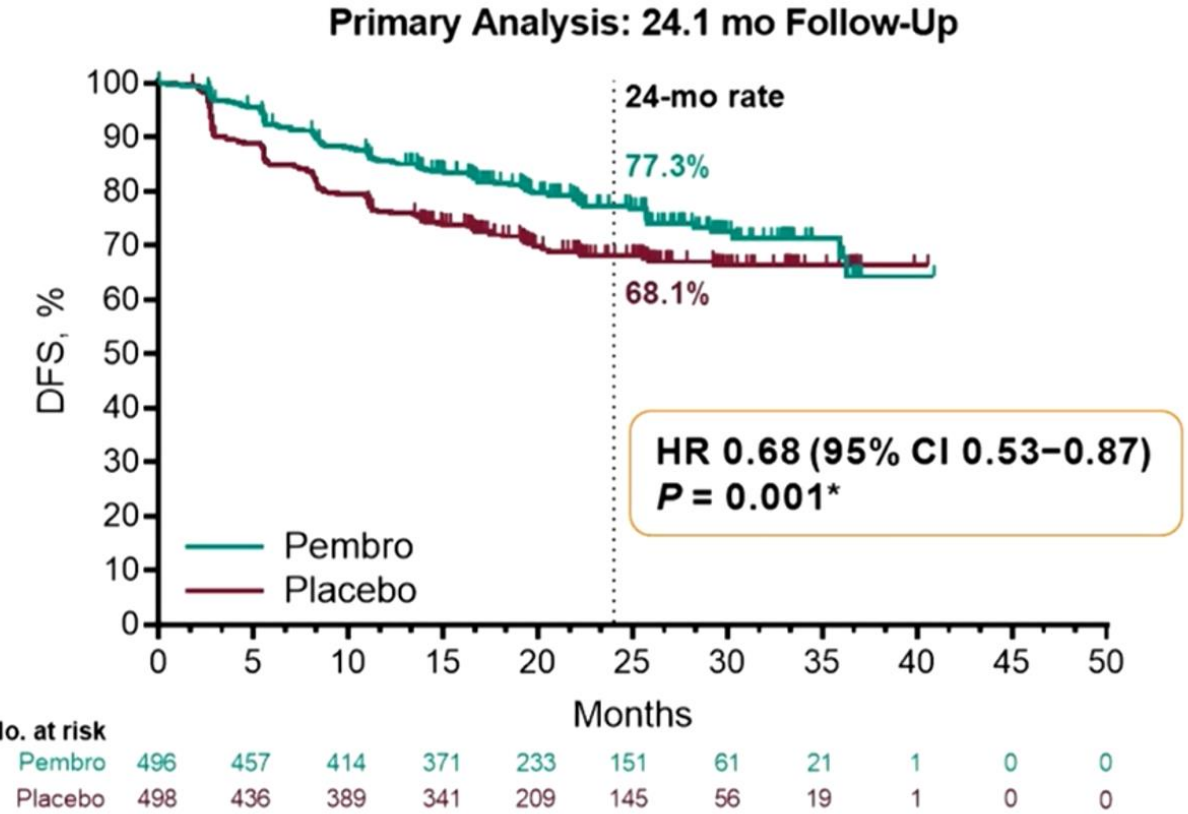
Keynote-564: Baseline characteristics

	Pembro Arm (N = 496)	Placebo Arm (N = 498)
Age, median (range)	60 (27–81)	60 (25–84)
Male	347 (70.0%)	359 (72.1%)
ECOG PS 1	75 (15.1%)	72 (14.5%)
Geographic location		
North America	133 (26.8%)	125 (25.1%)
European Union	188 (37.9%)	187 (37.6%)
Rest of world	175 (35.3%)	186 (37.3%)
Disease risk category		
M0 intermediate-high	427 (86.1%)[a]	433 (86.9%)
M0 high risk	40 (8.1%)	36 (7.2%)
M1 NED	29 (5.8%)	29 (5.8%)
Sarcomatoid features[b]		
Present	52 (10.5%)	59 (11.8%)
Absent	414 (83.5%)	415 (83.3%)
PD-L1 CPS[c,d]		
<1	124 (25.0%)	113 (22.7%)
≥1	365 (73.6%)	383 (76.9%)

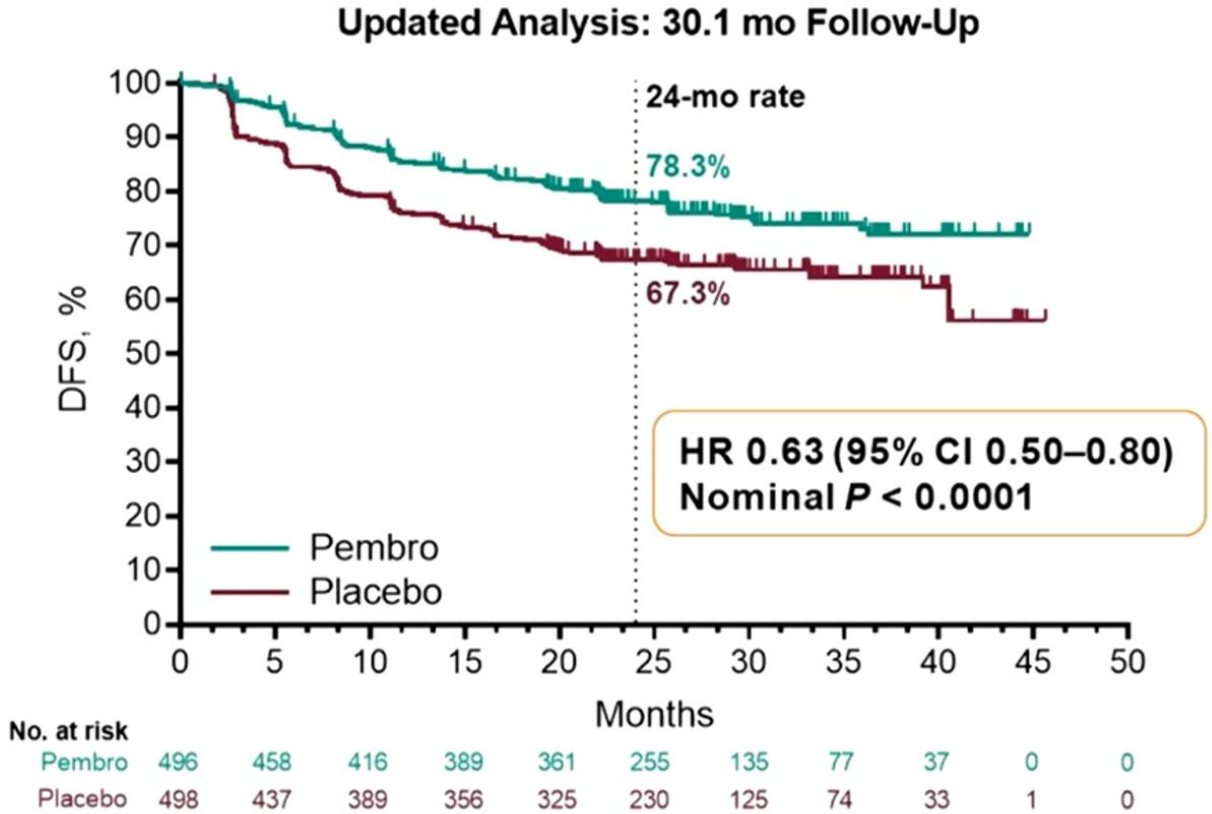
	Pembro Arm (N = 496)	Placebo Arm (N = 498)
Primary tumor stage		
T1	11 (2.2%)	15 (3.0%)
T2	27 (5.4%)	33 (6.6%)
T3	444 (89.5%)	437 (87.8%)
T4	14 (2.8%)	13 (2.6%)
Tumor nuclear grade[e]		
Grade 1	19 (3.8%)	16 (3.2%)
Grade 2	153 (30.8%)	150 (30.1%)
Grade 3	219 (44.2%)	213 (42.8%)
Grade 4	103 (20.8%)	119 (23.9%)
Lymph node stage		
N0	465 (93.8%)	467 (93.8%)
N1	31 (6.3%)	31 (6.2%)
Metastatic stage		
M0	467 (94.2%)	469 (94.2%)
M1 NED	29 (5.8%)	29 (5.8%)

Choueiri TK et al, NEJM 2021; Powles T, et al, Lancet Oncol 2022

KEYNOTE-564, DFS in ITT population



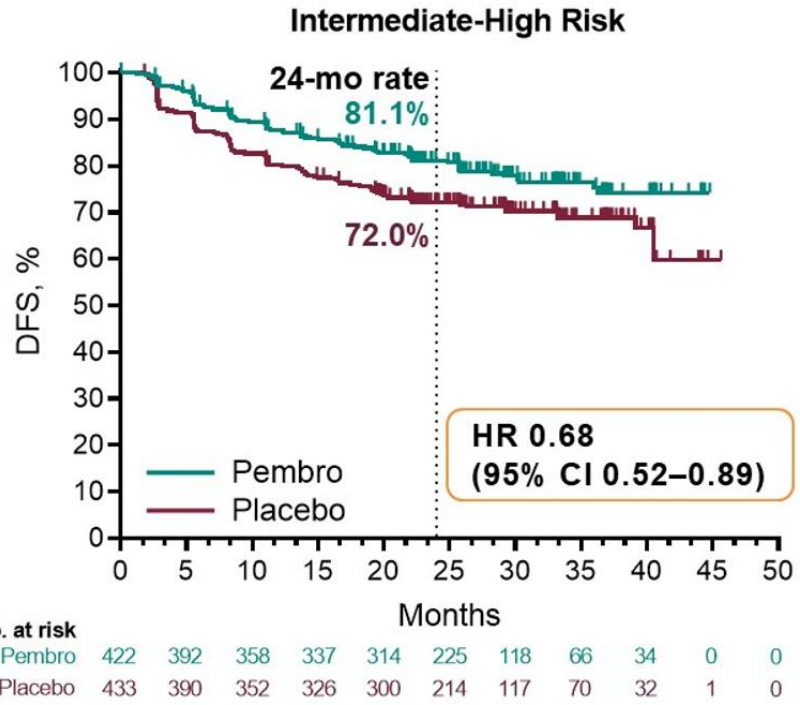
	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

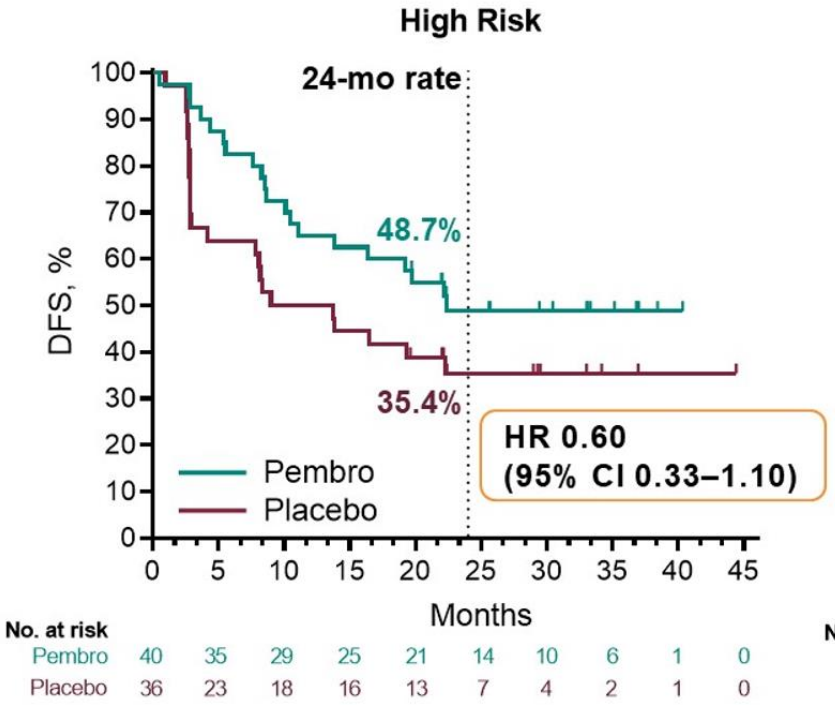


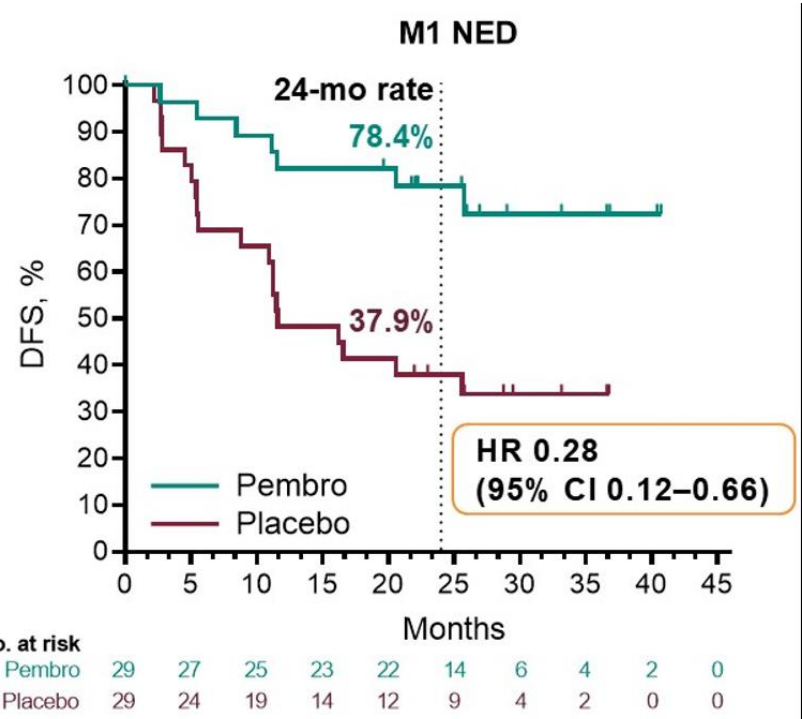
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

KEYNOTE-564, DFS in ITT population



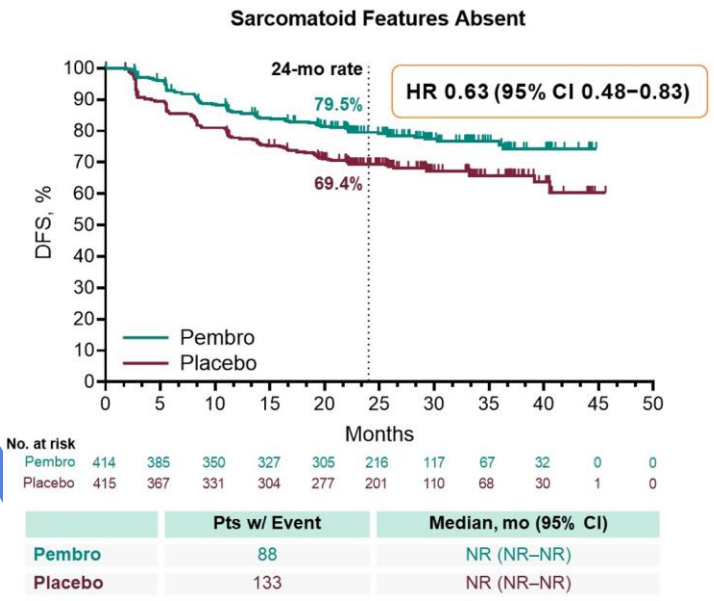




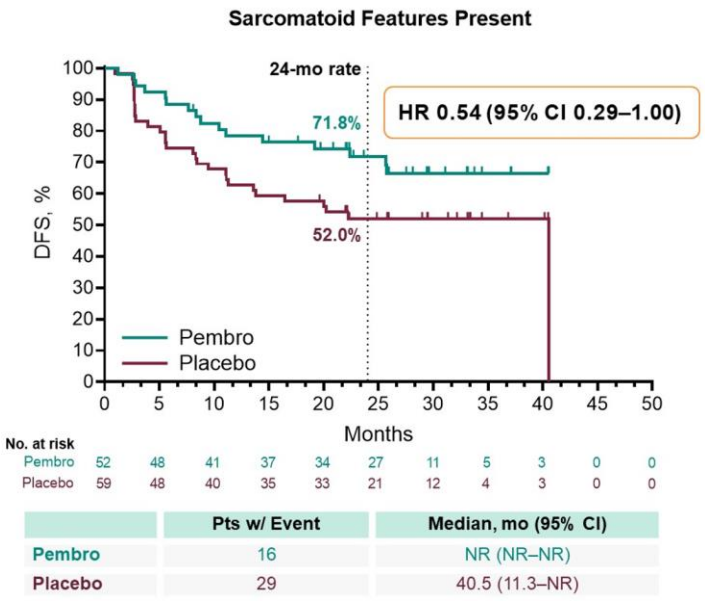
Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.

1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

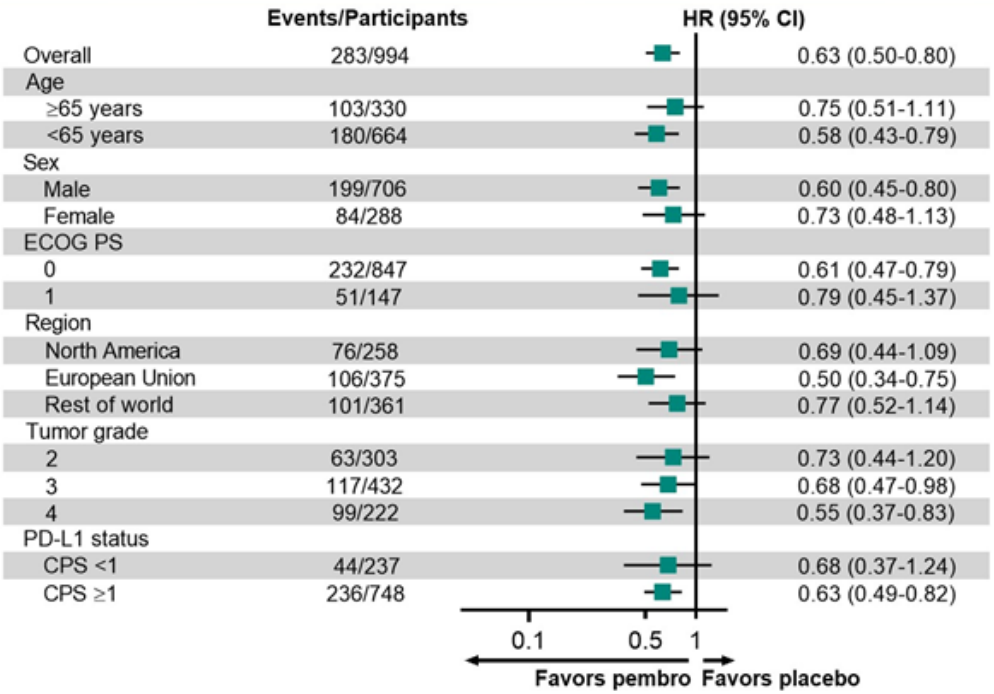
DFS in key subgroups



	Pts w/ Event	Median, mo (95% CI)
Pembro	88	NR (NR–NR)
Placebo	133	NR (NR–NR)

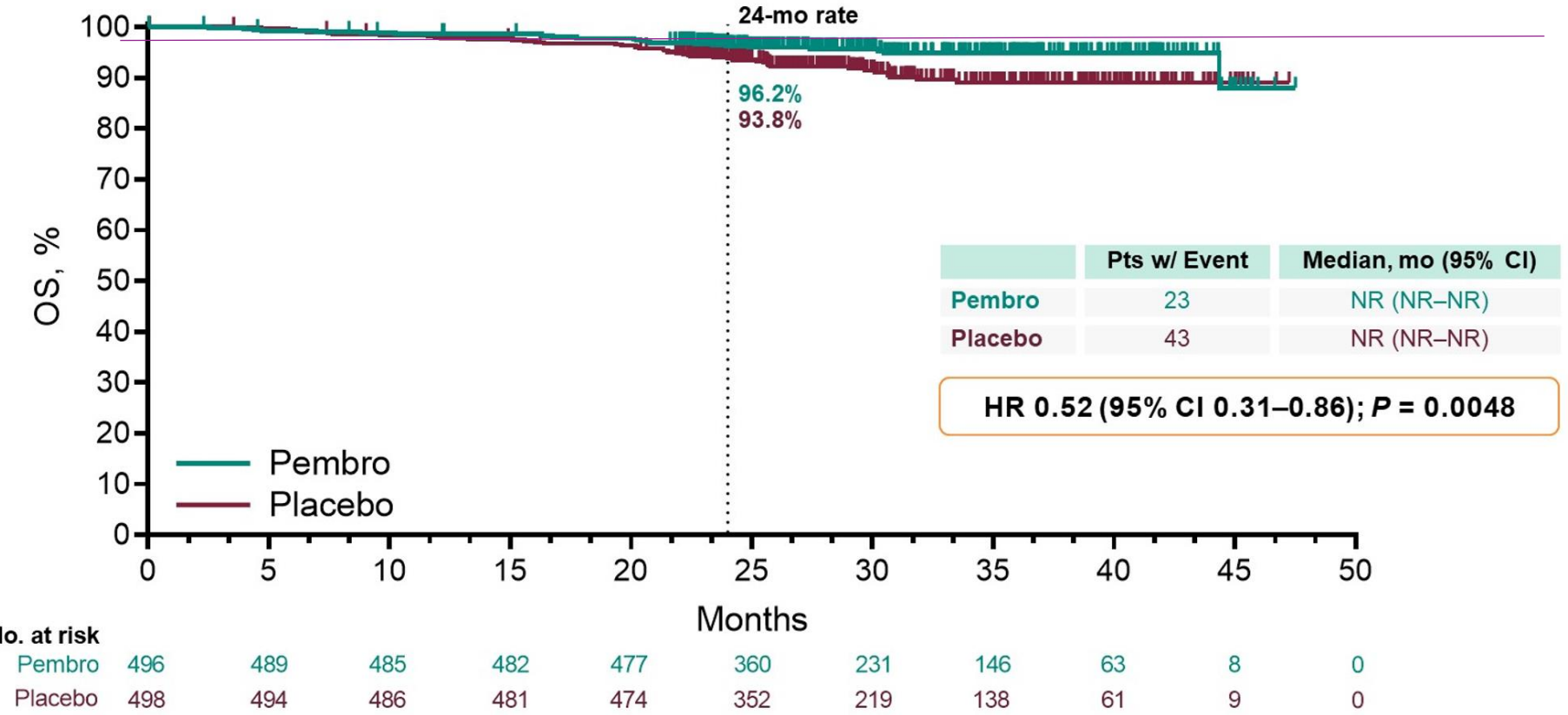


	Pts w/ Event	Median, mo (95% CI)
Pembro	16	NR (NR–NR)
Placebo	29	40.5 (11.3–NR)



1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

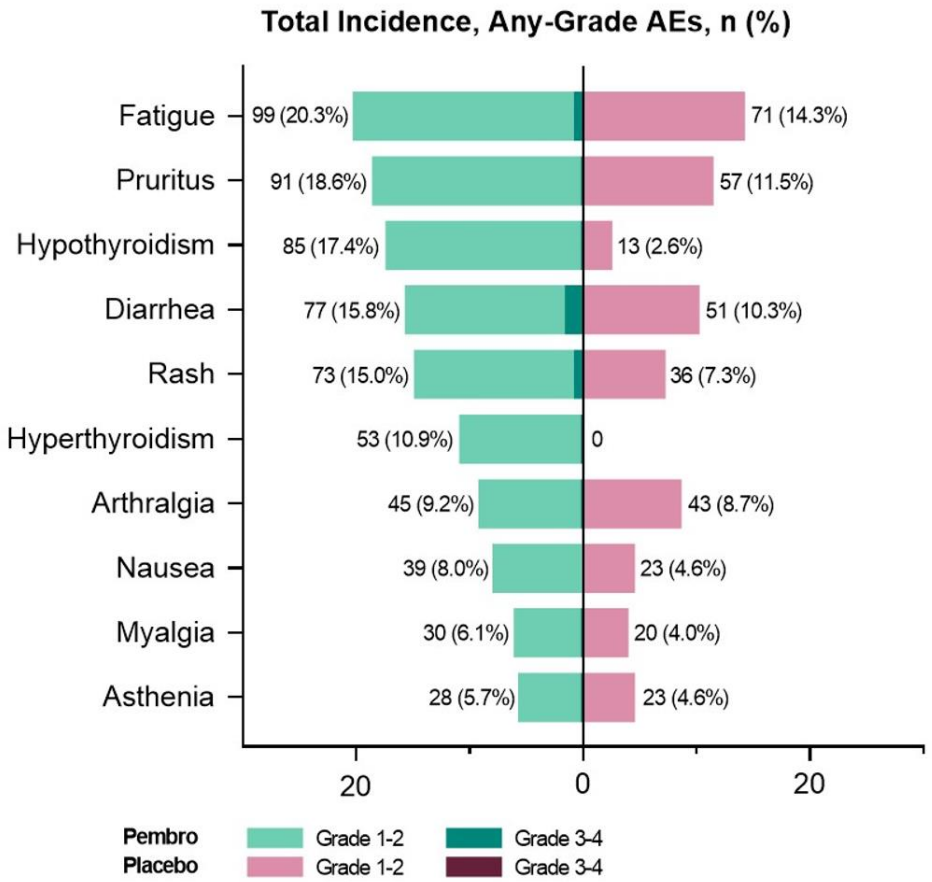
OS in ITT population

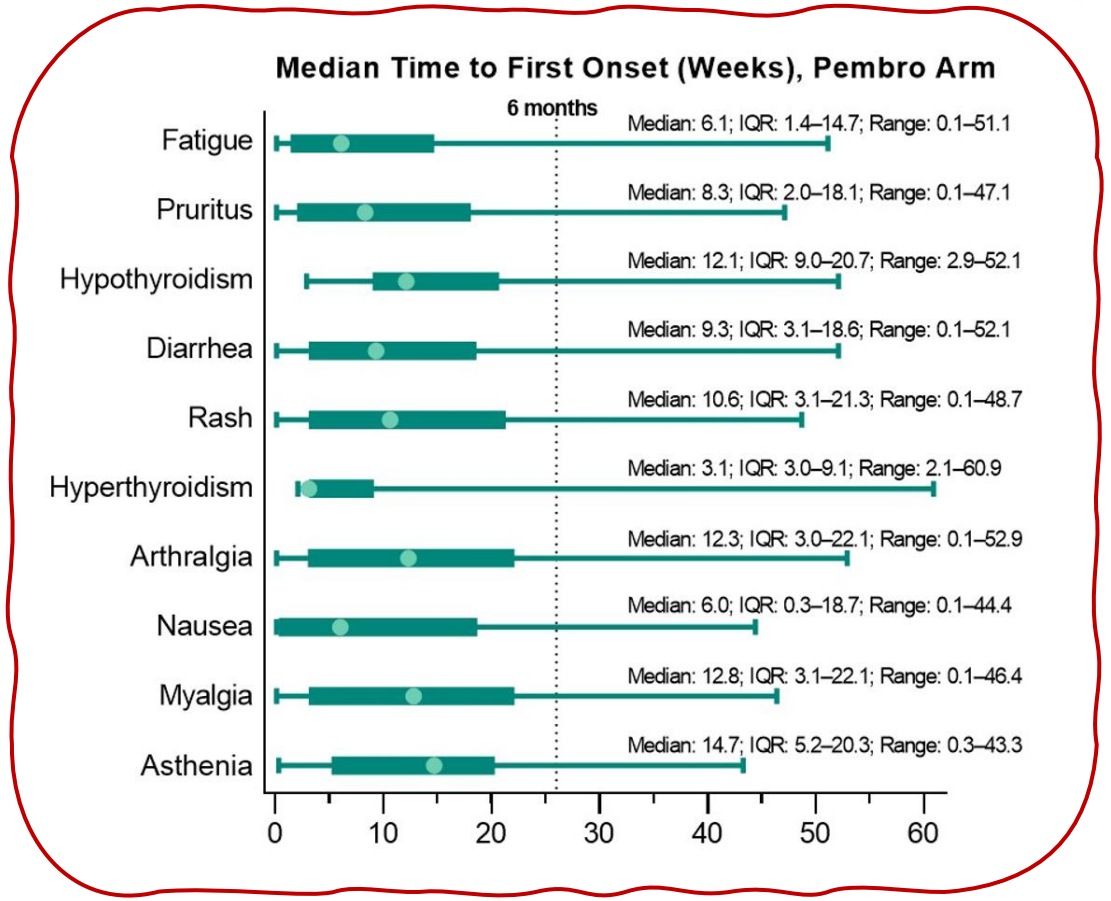


- *P*-value did not cross the prespecified boundary for statistical significance of 0.000095 (one-sided)
- Final analysis for OS to occur after approximately 200 OS events; only 66 events had accrued for this updated analysis

1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

Treatment-Related AEs with Incidence ≥5%, As-Treated Population



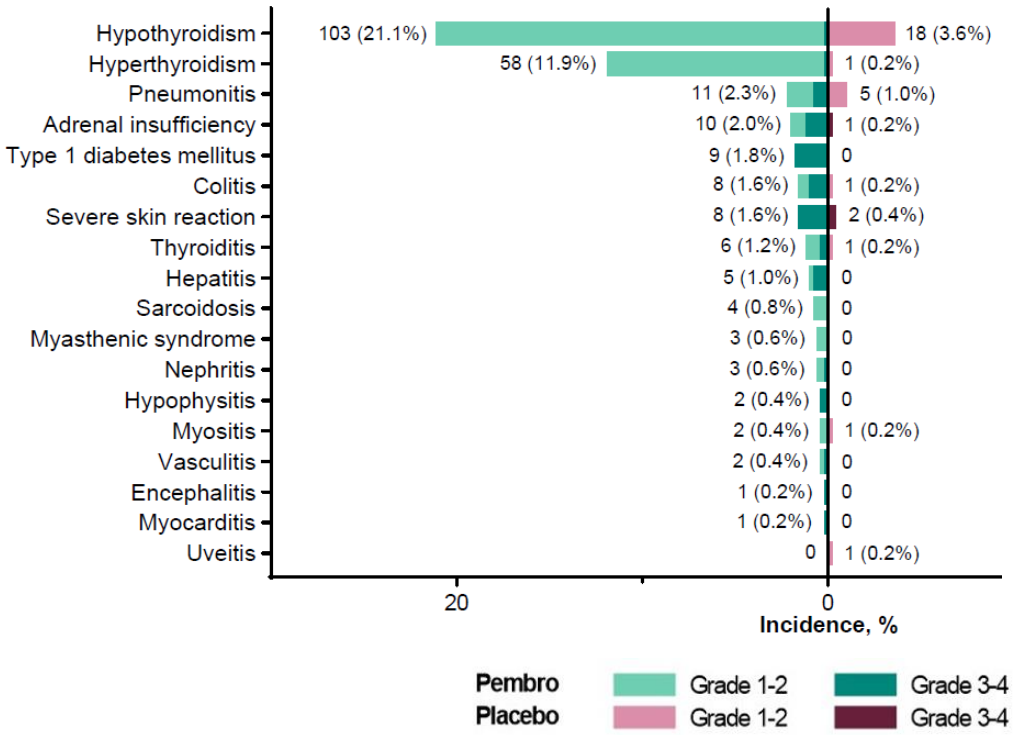


AE, adverse event.
As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: June 14, 2021.

1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

Pembro safety in KN564

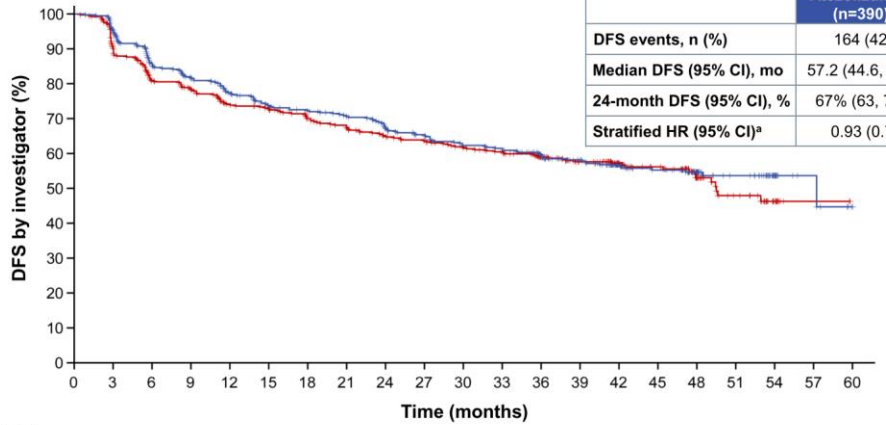
- 19% of **G3-4 AEs**
- 21% of **treatment discontinuation** due to all-cause AEs
- 36% of **IRAEs**; 9% were G3-4
- 8% of pts needed **high-dose steroids** for IRAEs



1.- Choueiri T, et al. NEJM 2021; 2- Powles T, et al. Lancet Oncol 2022

The negative phase 3 trials

Investigator-assessed DFS in the ITT population

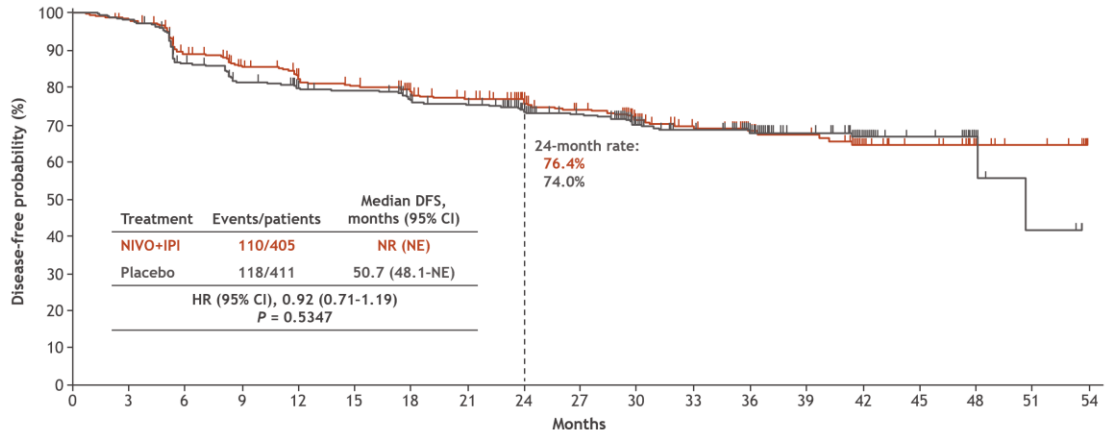


	Atezolizumab (n=390)	Placebo (n=388)
DFS events, n (%)	164 (42)	168 (43)
Median DFS (95% CI), mo	57.2 (44.6, NE)	49.5 (47.4, NE)
24-month DFS (95% CI), %	67% (63, 72)	65% (60, 70)
Stratified HR (95% CI)[a]	0.93 (0.75, 1.15); *P*=0.4950[b]	

Number at risk

Atezolizumab	390	360	322	306	288	272	265	257	244	234	222	218	194	171	124	100	75	48	22	6	1
Placebo	388	343	305	294	275	268	254	243	232	226	216	209	187	161	121	91	56	33	15	3	NE

Primary endpoint: disease-free survival per BICR

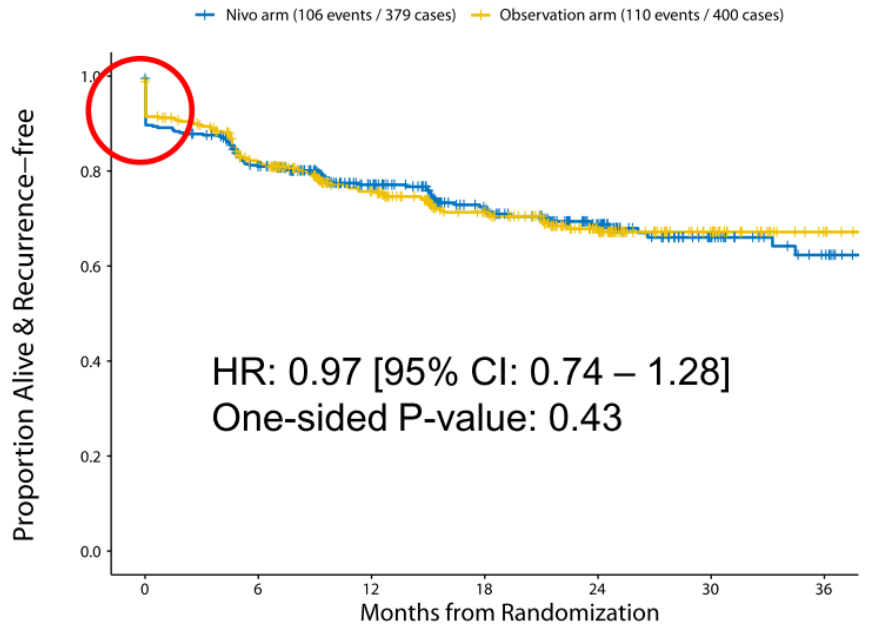


Treatment	Events/patients	Median DFS, months (95% CI)
NIVO+IPI	110/405	NR (NE)
Placebo	118/411	50.7 (48.1-NE)

HR (95% CI), 0.92 (0.71-1.19)
P = 0.5347

No. at risk

NIVO+IPI	405	378	337	316	299	289	270	259	224	203	150	125	89	73	42	34	13	9	0	
Placebo	411	391	340	315	299	293	275	268	227	205	155	128	90	66	38	25	8	3	0	

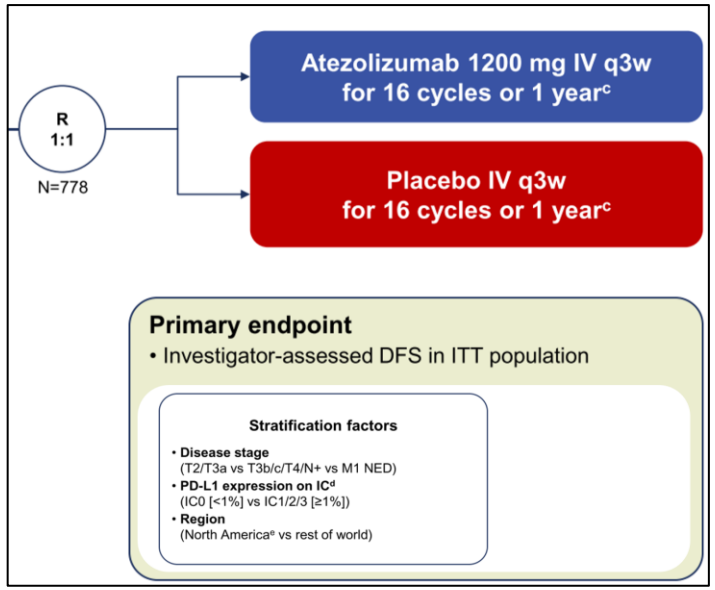


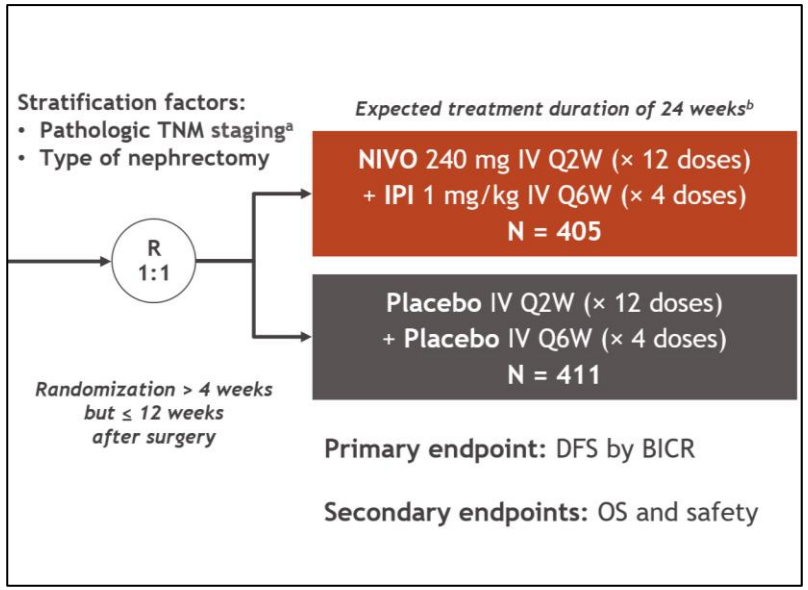
Number at risk

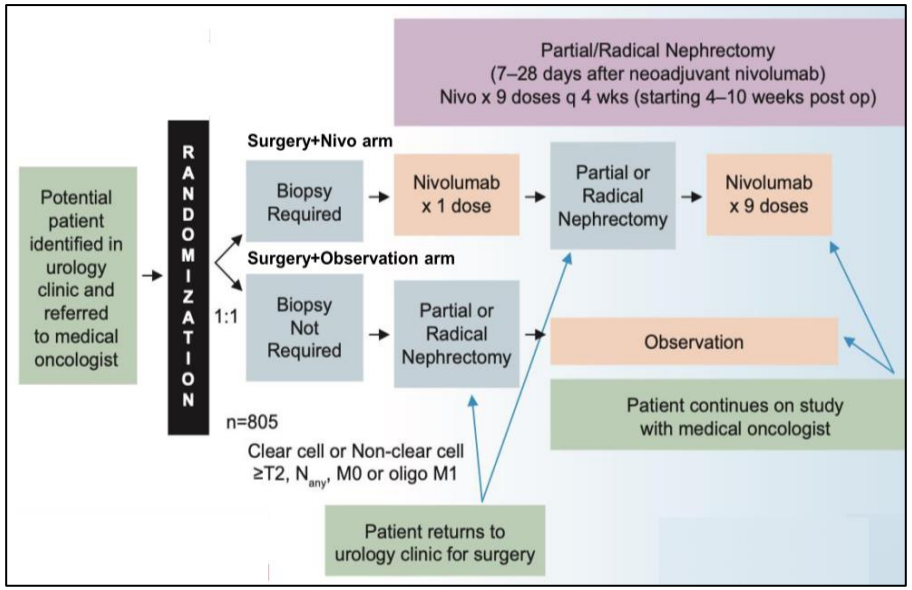
Nivo arm	379	291	208	151	99	50	30
Observation arm	400	300	214	161	100	47	22

Pal SK, et al. Lancet 2022; RJ Motzer, et al. Lancet 2023; Allaf ME, et al. ESMO 2022

Design of negative phase III studies testing ICI in RCC







	KEYNOTE-564 N=994	Immotion010 N=778	CM914 part A N=816	PROSPER N=819
Treatment arms & expected duration	Pembro x17 Q3W Vs Pbo ***51 weeks***	Atezo x 16 Q3W vs Pbo ***48 weeks***	Ipi1x4 Q6W + Nivo3 x12 Q2W Vs Pbo + Pbo ***24 weeks***	Nivox1 NA →Nephr. →Nivo x9 Q4W VS observation ***36 weeks***

1.-Bex A. et al, Immotion 010. ESMO 2022; 2.-Motzer R. Checkmate 914 (Part A). ESMO 2022; 3.-Allaf M. PROSPER. ESMO 2022;

Profile of patients included in perioperative phase 3 trials testing ICIs

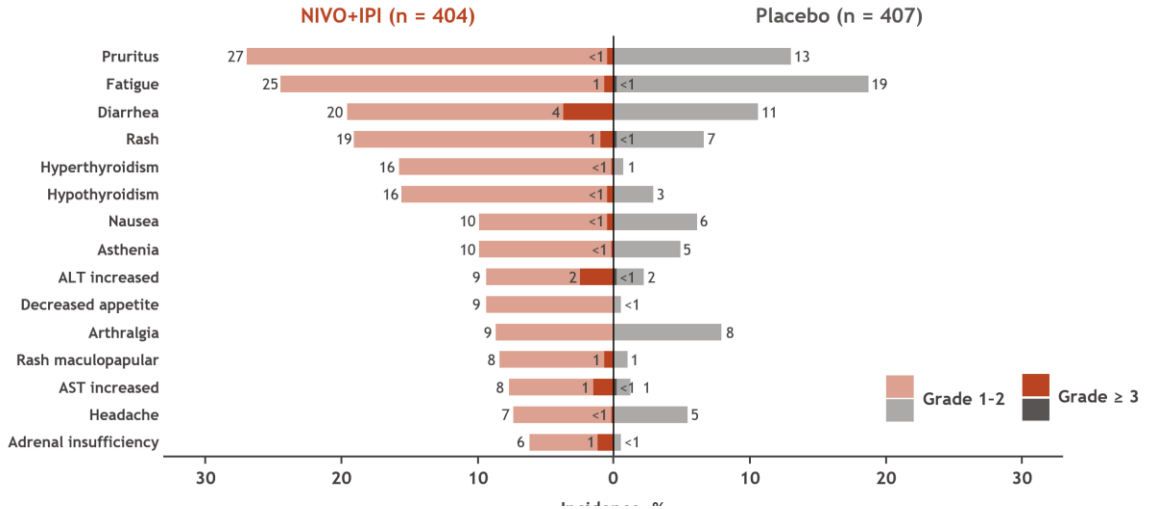
	KEYNOTE-564 N=994		Immotion010 N=778		CM914 part A N=816		PROSPER N=819	
Intermediate-High risk	pT2 G4/sarcomatoid	86%	pT2 G4	64%	pT2a G3/4	15%	cT1	3%
					pT2b any G			
	pT3 any G		pT3a G3/4		pT3 any G	78%	cT2	49%
High risk	pT4 any G	8%	pT3b/c or pT4 any G	21%	pT4 any G	7%	cT3/T4	48%
	N+		N+		N+			
M1 NED	M1 NED ≤1 year from nephrectomy	6%	M1 NED Synchronous / metachronous	14%			oligoM1	3%

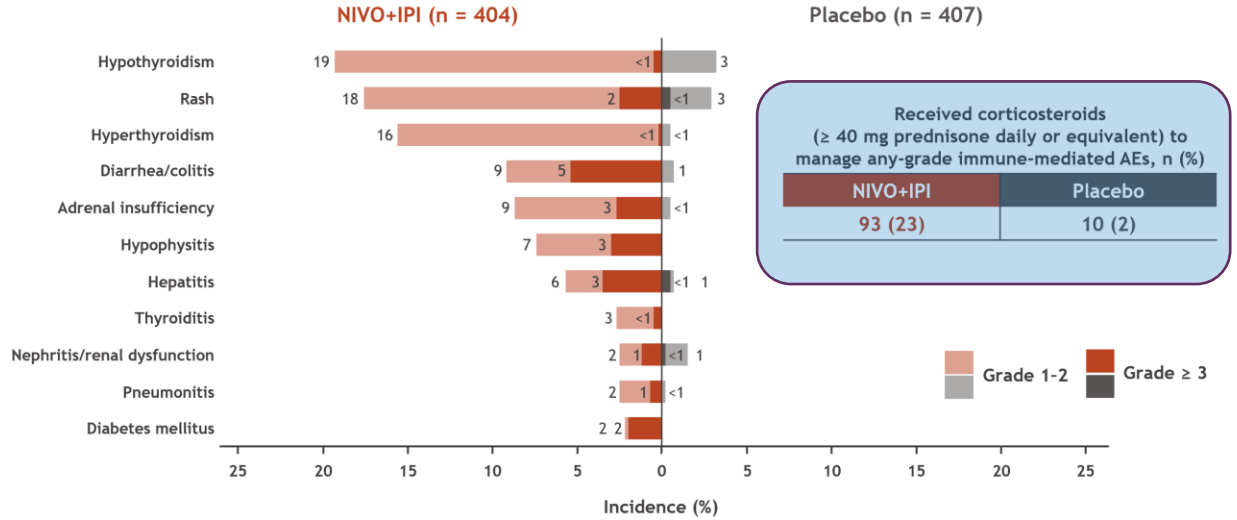
≈20% non-clear cell

1.- Choueiri T, et al. NEJM 2021; 2- Pal SK, et al. Lancet 2022; 3.- RJ Motzer, et al. Lancet 2023; 4.- Allaf ME, et al. ESMO 2022

Checkmate-914: Did toxicity impact the outcome?

	NIVO+IPI (n = 404)	Placebo (n = 407)
Median duration of therapy (range), months Q1, Q3	5.1 (< 0.1-8.3) 2.8, 5.3	5.1 (< 0.1-8.1) 5.1, 5.3
Median number of doses received (range)	NIVO, 12 (1-12) IPI, 4 (1-4)	12 (1-12)[a] 4 (1-4)[b]
Completed all 12/4 doses of NIVO/IPI, n (%)	231 (57)	361 (89)
Discontinued treatment, n (%)[c]	173 (43)	46 (11)
Discontinued due to study drug toxicity, n (%)	132 (33)	5 (1)
All-cause AEs, n (%)[d] Grade ≥ 3 Led to treatment discontinuation	392 (97) 155 (38) 129 (32)	361 (89) 42 (10) 9 (2)
Treatment-related AEs, n (%)[d] Grade ≥ 3 Led to treatment discontinuation[e]	359 (89) 115 (28) 117 (29)	231 (57) 8 (2) 4 (1)
Deaths due to study drug toxicity, n (%)	4 (1)[f]	0

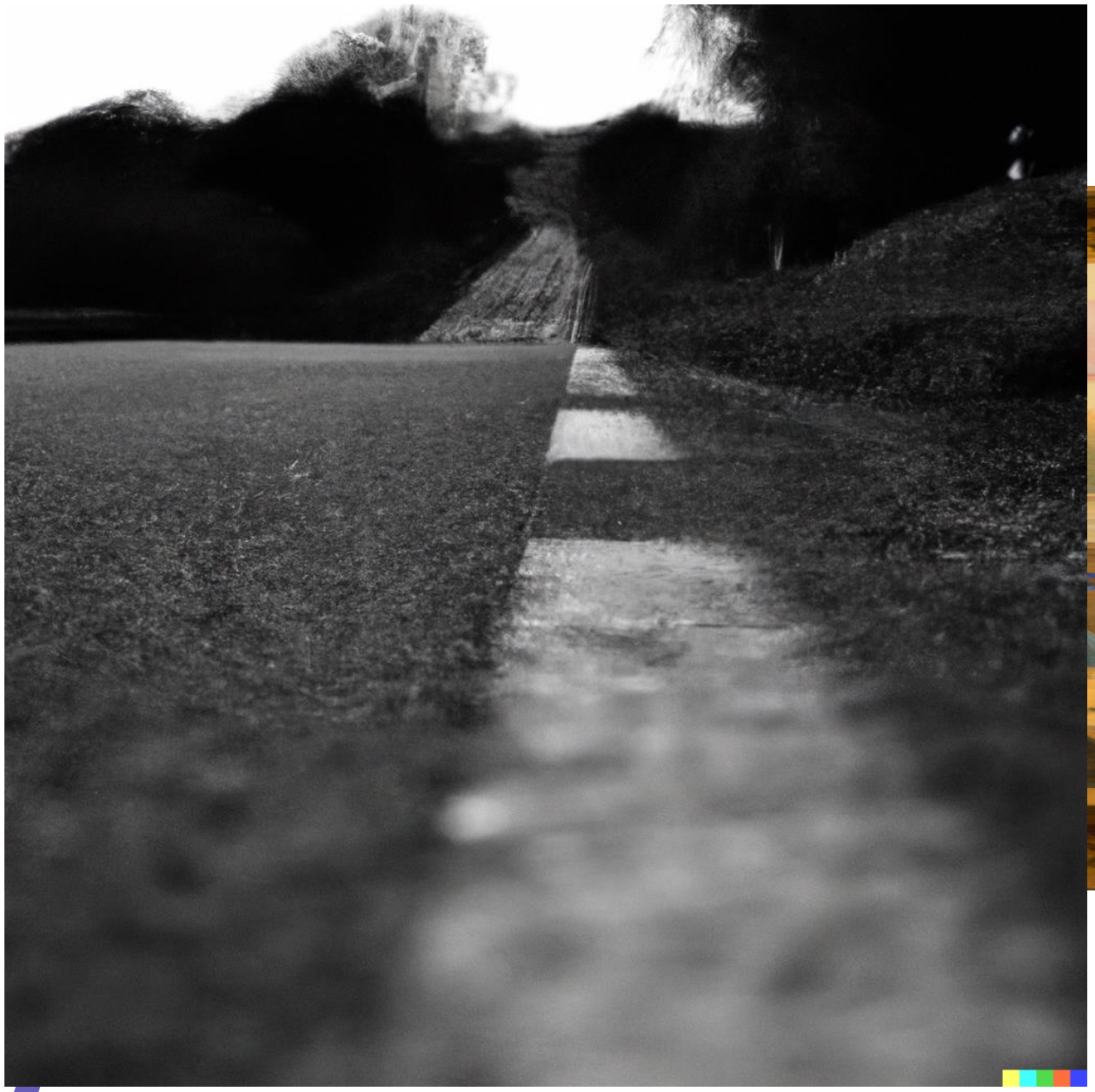




Received corticosteroids (≥ 40 mg prednisone daily or equivalent) to manage any-grade immune-mediated AEs, n (%)

NIVO+IPI	Placebo
93 (23)	10 (2)

RJ Motzer, et al. Lacner 2023



LITESPARK 022 - NCT05239728

Key Eligibility Criteria
- Histologically or cytologically confirmed RCC with clear cell component
  - Intermediate-high risk RCC
    - pT2, grade 4 or sarcomatoid, N0, M0
    - pT3, any grade, N0, M0
  - High risk RCC
    - pT4, any grade, N0, M0
    - pT any stage/grade, N+, M0
  - M1 NED[c]
- No prior systemic therapy
- BICR-verified tumor free (CT or MRI of the brain, chest, abdomen, and pelvis and bone imaging)

R[b] (1:1)
N ≈ 1600

Belzutifan
120 mg oral QD
54 weeks[a]
+
Pembrolizumab
400 mg IV Q6W
9 cycles[a]

Placebo oral QD
54 weeks[a]
+
Pembrolizumab
400 mg IV Q6W
9 cycles[a]

Follow-up
- Years 1-2: Q12W
- Years 3-5: Q16W
- Years 6+: Q24W
- Efficacy and PROs
- Safety: 30 days after treatment cessation (or 90 days for serious AEs)

Stratification
- Intermediate-high risk vs high risk vs M1 NED
- Tumor grade 1 or 2 vs tumor grade 3 or 4

End Points
- Primary: DFS
- Secondary: OS, safety and tolerability, DRSS, PROs

RAMPART multiarm adjuvant durvalumab and tremelimumab (NCT03288532)

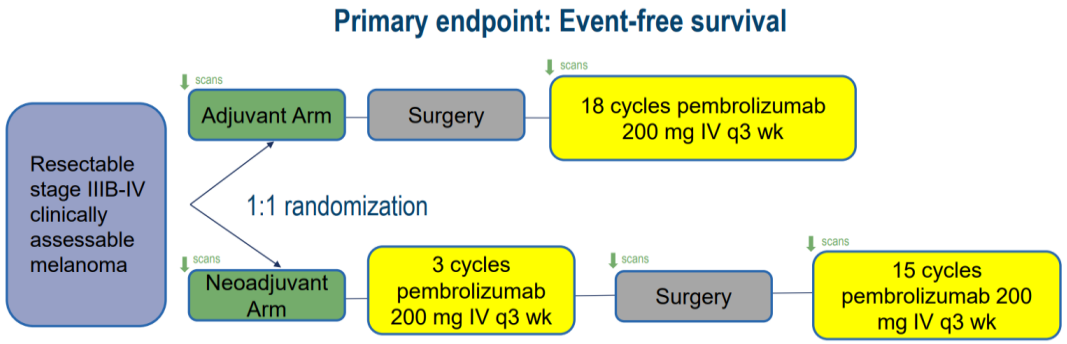
Patients with confirmed RCC, high or intermediate (up to year 3 or 25%)

Leibovich score eligible for randomisation into the study

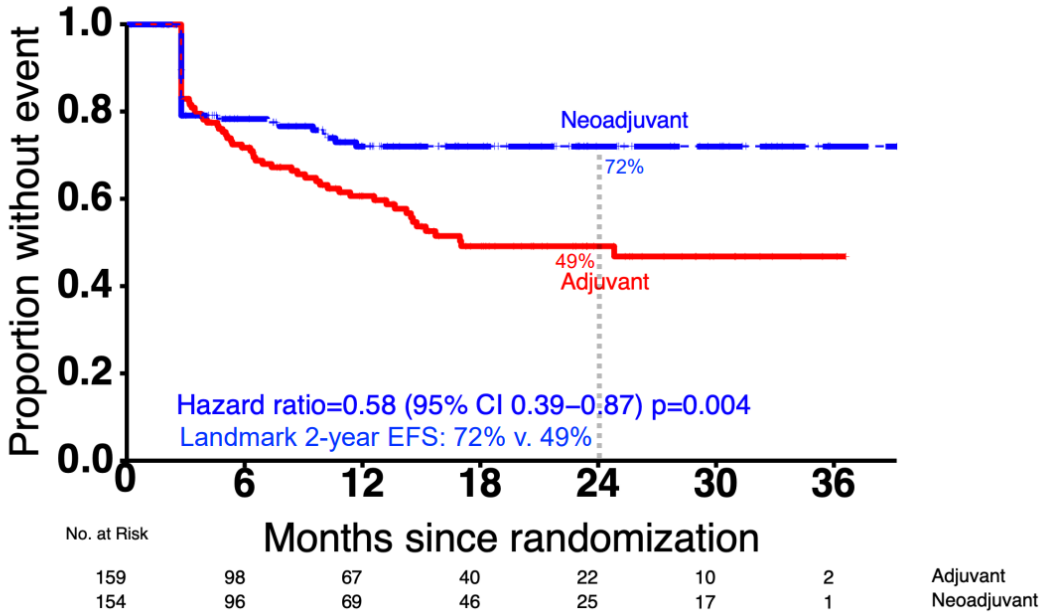
Randomisation

Arm A	Arm B	Arm C	Arm D
active monitoring for 1 year	durvalumab 1500mg q4w for 1 year	durvalumab 1500mg q4w for 1 year and tremelimumab 75mg at day 1 and	to be added at a later stage in the trial

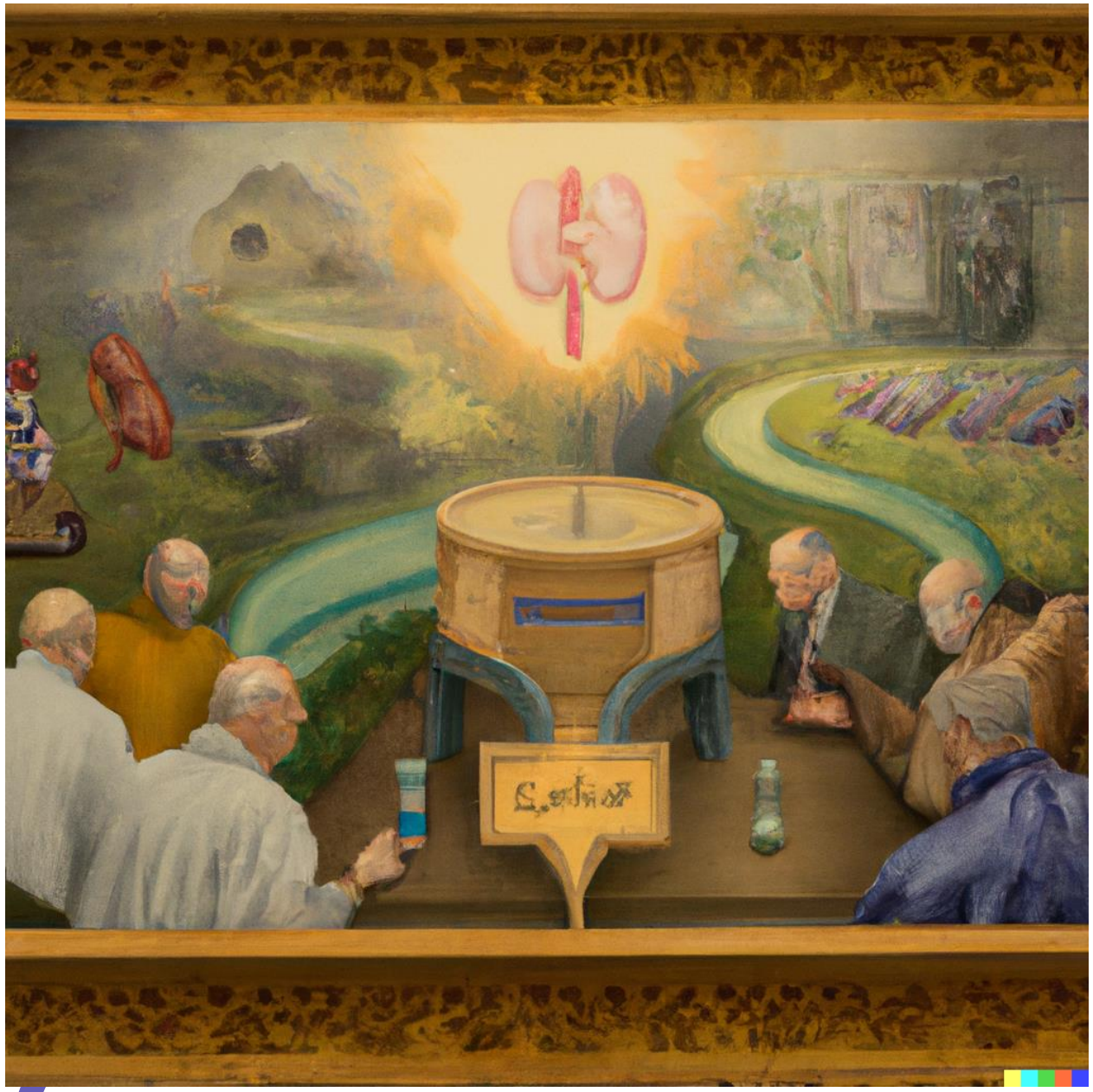
Can we extrapolate the melanoma model? From adjuvant to perioperative



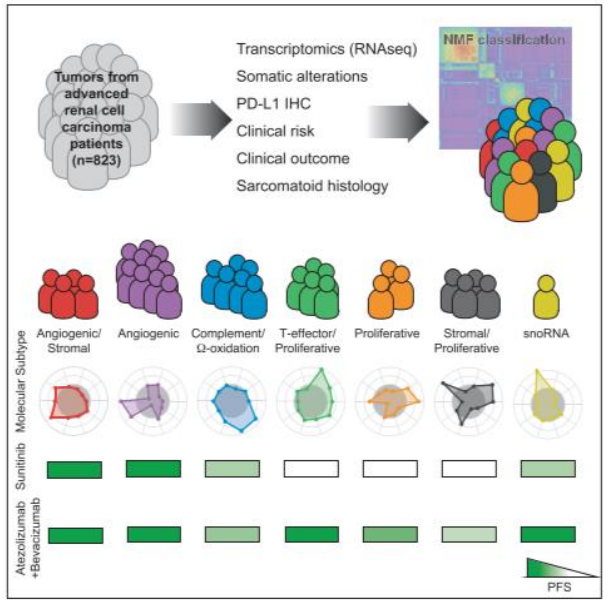
S1801 primary endpoint: Event-free survival

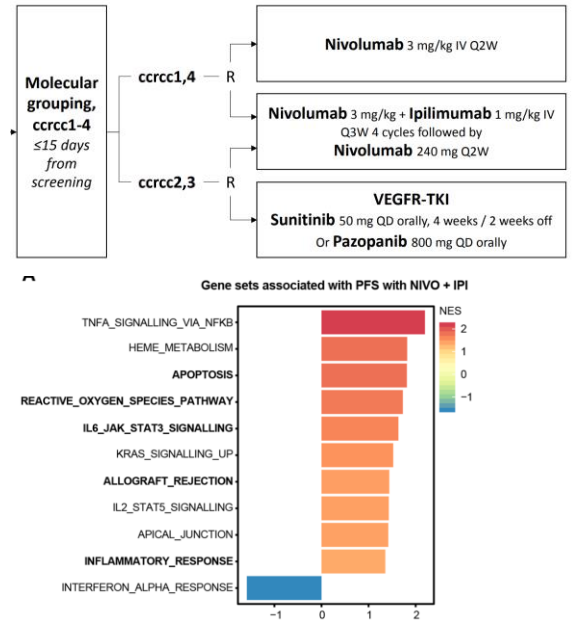


Sapna P. Patel et al, ESMO 2022



Should we focus on biomarker-driven studies rather than a prognostic selection?





Motzer RJ, et al, Cancer Cell 2020; Vano YA, et al, Lancet Oncol 2022; Motzer RJ, et al, JITC 2022

Entonces, ¿a quien ofrecer tratamiento con Pembrolizumab adyuvante?

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

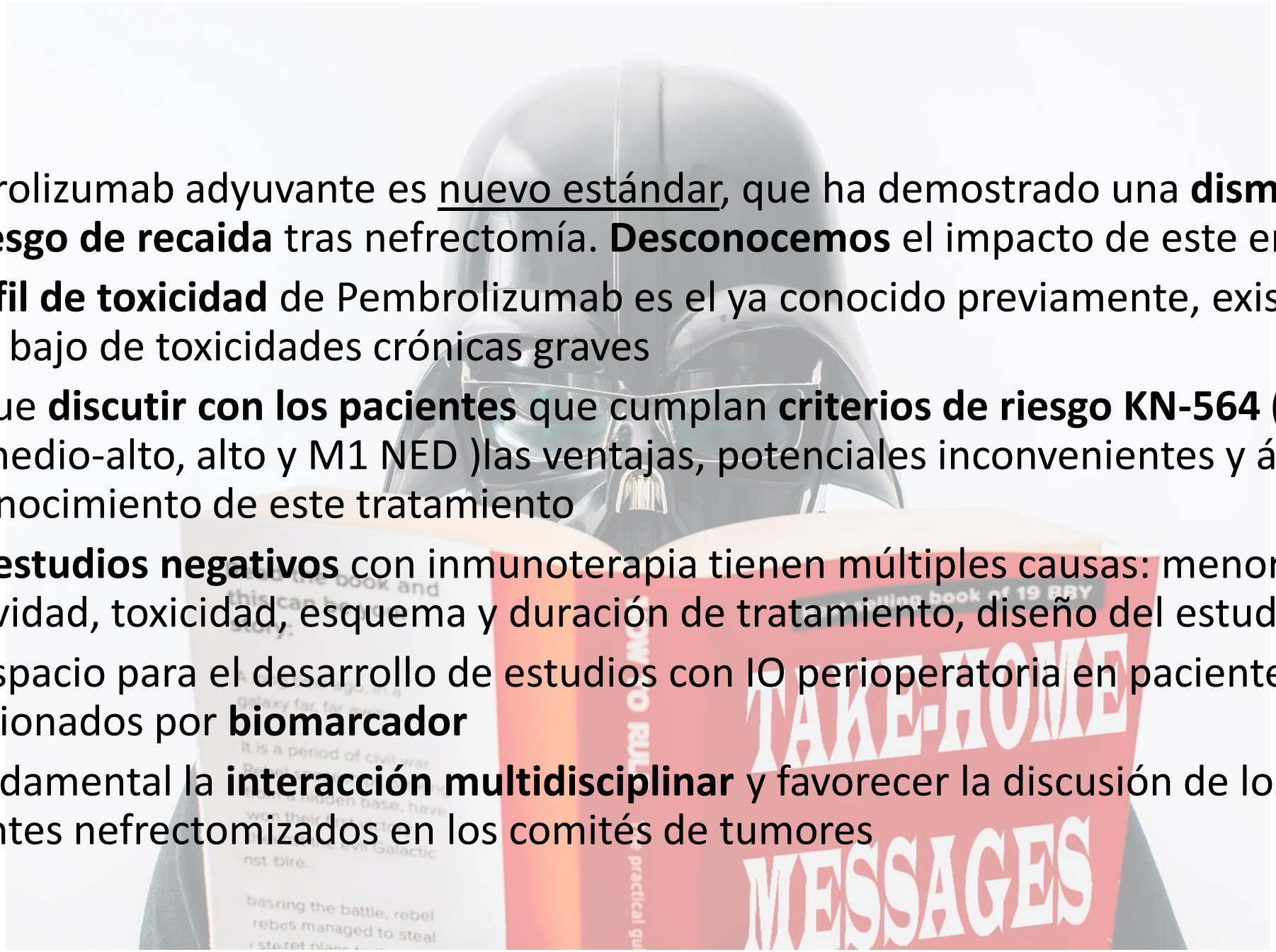
Discuss Pros & Cons with patient

The multispeciality approach to the management of localised kidney cancer

Grant D Stewart, Tobias Klatte, Laura Cosmai, Axel Bex, Benjamin W Lamb, Holger Moch, Evis Sala, Shankar Siva, Camillo Porta, Maurizio Gallieni**

Lancet 2022; 400: 523–34


Read the book and this can be your story:
A long time ago, in a galaxy far, far away...
It is a period of civil war. Rebel spaceships, striking from a hidden base, have won their first victory theainst the evil Galactic nst Dire.
HOW TO RULE
Best selling book of 19 BBY
TAKE-HOME MESSAGES



- Pembrolizumab adyuvante es nuevo estándar, que ha demostrado una **disminución del riesgo de recaida** tras nefrectomía. **Desconocemos** el impacto de este en **OS**
- El **perfil de toxicidad** de Pembrolizumab es el ya conocido previamente, existe un riesgo bajo de toxicidades crónicas graves
- Hay que **discutir con los pacientes** que cumplan **criterios de riesgo KN-564 (**riesgo intermedio-alto, alto y M1 NED)las ventajas, potenciales inconvenientes y áreas de desconocimiento de este tratamiento
- Los **3 estudios negativos** con inmunoterapia tienen múltiples causas: menor efectividad, toxicidad, esquema y duración de tratamiento, diseño del estudio, …
- Hay espacio para el desarrollo de estudios con IO perioperatoria en pacientes seleccionados por **biomarcador**
- Es fundamental la **interacción multidisciplinar** y favorecer la discusión de los pacientes nefrectomizados en los comités de tumores


GRACIAS!!