



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE 2023

Madrid, 22 y 23 de noviembre de 2023

Tratamiento adyuvante en cáncer renal

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Problema clínico

- Incidencia en aumento: 431.288 casos nuevos en 2020
- A pesar del tratamiento local, 1 de cada 4 pacientes no estarán vivos a los 5 años de su diagnóstico



SEER Statistics. <https://seer.cancer.gov/statfacts/html/kidrp.html>
The Global Cancer Observatory. <https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-fact-sheet.pdf>

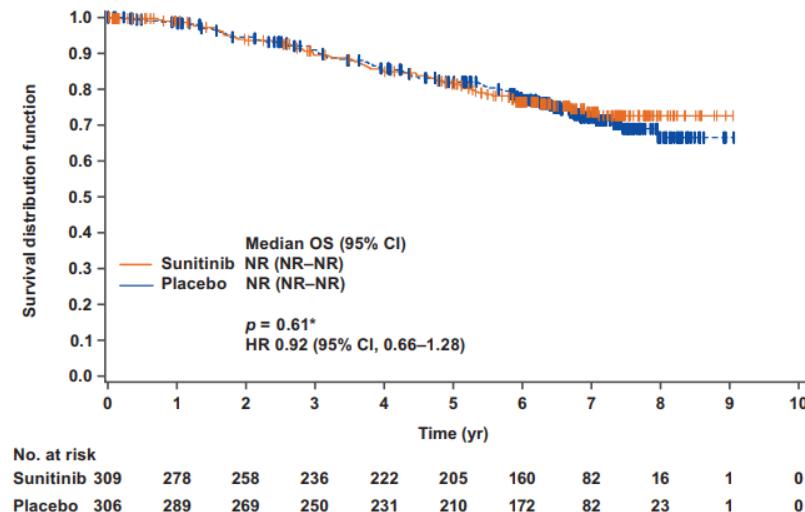
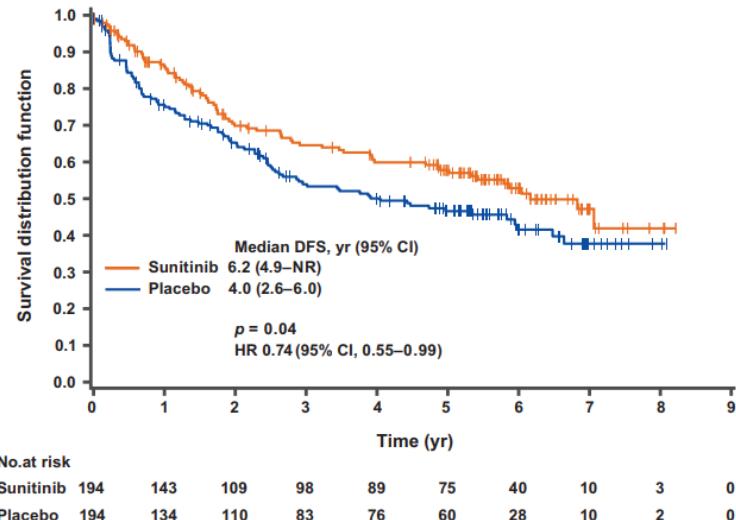
Ensayos de adyuvancia en cáncer renal con TKIs

Ensayo	Brazo experimental	N	Duración tto	Histología	Elegibilidad	End-point	Resultado
ASSURE (2016)	Sunitinib o sorafenib	1943	1	Cualquiera	≥T1b	DFS	NS
S-TRAC (2016)	Sunitinib	615	1	Células claras	≥ Stage III Alto riesgo UISS	DFS	HR 0.74
PROTECT (2017)	Pazopanib	1538	1	Células claras	pT2, pT3-4N0, N+	DFS	NS
ATLAS (2018)	Axitinib	724	1-3	Células claras	pT2, pT3-4N0, N+	DFS	NS
SORCE (2020)	Sorafenib	1711	1-3	Cualquiera	Leibovich 3-11	DFS	NS

Haas NB et al. Lancet. 2016 May 14;387(10032):2008-16. Eisen T et al. J Clin Oncol. 2020 Dec 1;38(34):4064-4075. Ravaud A et al. N Engl J Med. 2016 Dec 8;375(23):2246-2254. Motzer RJ et al. J Clin Oncol. 2017 Dec 10;35(35):3916-3923. Gross-Gouipil, M. et al Ann Oncol. 2018 Dec 1;29(12):2371-2378.



S-TRAC: El único estudio con TKIs que demostró una mejora significativa en DFS No se identificaron diferencias en supervivencia global



Motzer RJ et al. Eur Urol. 2018 Jan;73(1):62-68.

El 16 de noviembre de 2013, la FDA aprobó la indicación de 1 año de sunitinib en el contexto adyuvante.

Sin embargo, dado el beneficio limitado y las toxicidades asociadas al tratamiento, el uso en la vida real fue limitado



Toxicidad relevante

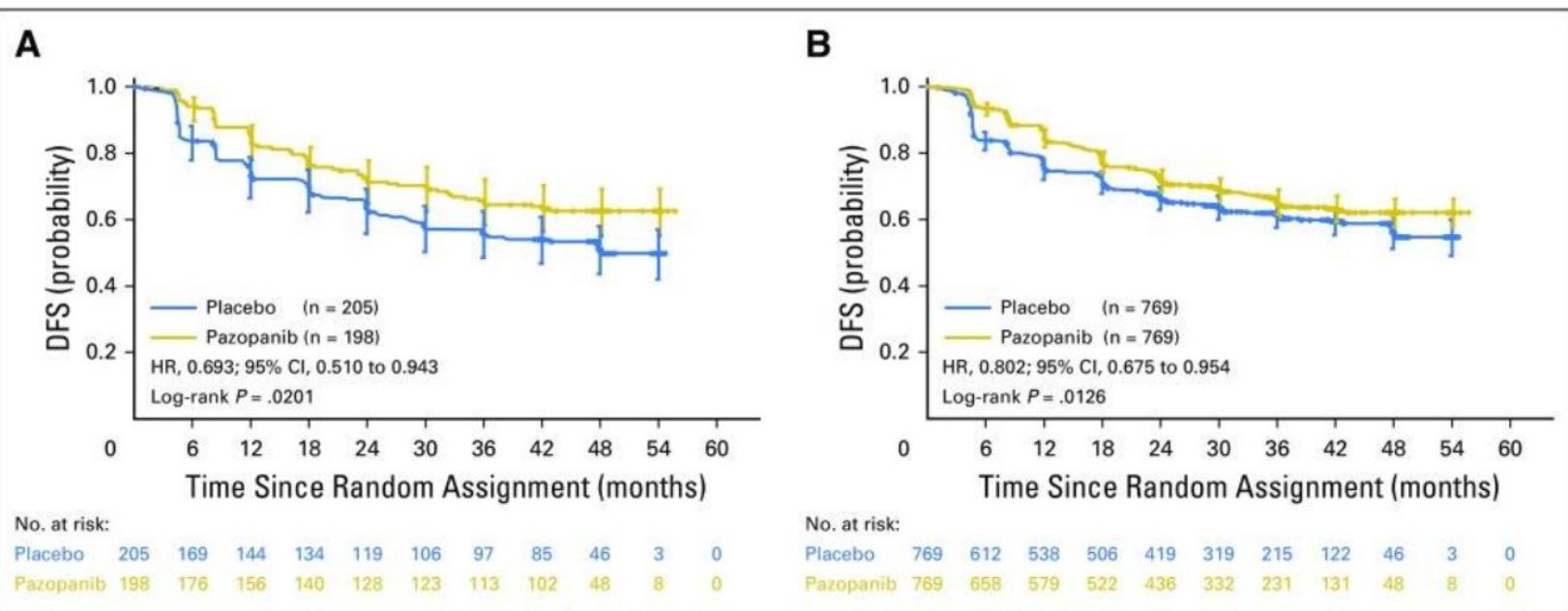
- Eventos adversos grado ≥ 3 ocurrieron en el 60% de los pacientes que recibieron sunitinib
- Sólo el 56% de los pacientes en el ensayo S-TRAC pudieron completar el año de tratamiento

Table 3. Adverse Events (Safety Population).*

Event	Sunitinib (N=306)			Placebo (N=304)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar-plantar erythrodysesthesia	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Dyspepsia	82 (26.8)	4 (1.3)	0	19 (6.3)	0	0
Stomatitis	81 (26.5)	5 (1.6)	2 (0.7)	13 (4.3)	0	0
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Hair-color change	68 (22.2)	0	0	7 (2.3)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0



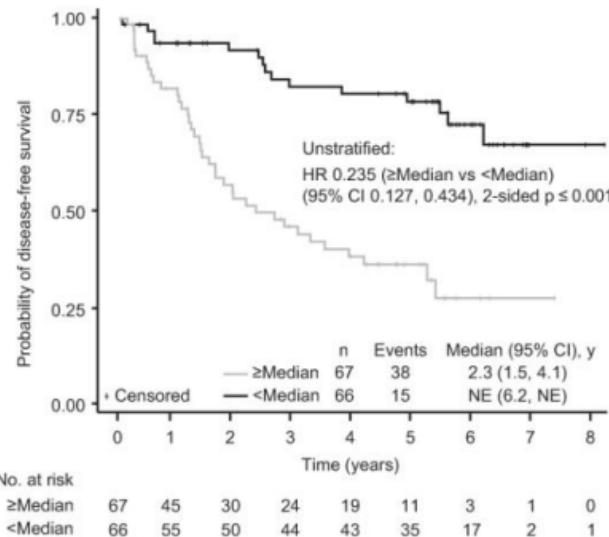
La dosis es importante



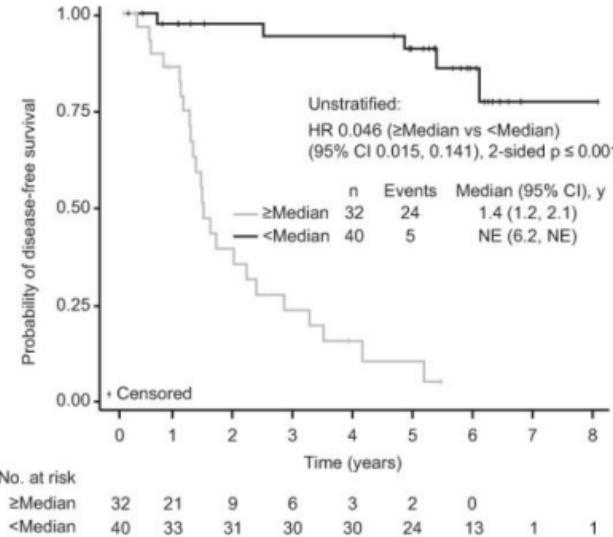


Existen importantes diferencias en pronóstico

b STRAC11 S-TRAC overall population



c STRAC11 S-TRAC sunitinib cohort



Motzer RJ et al. Nat Commun. 2022 Oct 10;13(1):5959.

Modelos pronósticos en cáncer renal localizado

Modelo	Parámetros	Outcome	Tipo
UISS	TNM, grado, ECOG PS	OS	Análisis KM
SSIGN	TNM, pN+, pM+, tamaño tumoral, grado, necrosis	CSS	Algoritmo
Leibovich	TNM, pN+, tamaño tumoral, grado, necrosis	MFS	Algoritmo
MSKCC	TNM, tamaño tumoral, grado, necrosis, síntomas	RFS	Nomograma
Kattan	TNM, tamaño tumoral, histología, síntomas	RFS	Nomograma
Yaycioglu	Tamaño tumoral, síntomas	RFS	Fórmula
Karakiewic	TNM, edad, sexo, margen+, tamaño tumoral, síntomas	CSS	Nomograma
Cindolo	Tamaño tumoral, síntomas	RFS	Fórmula

UCLA Integrated Staging System (UISS) for Renal Cell Carcinoma (RCC)

Provides 5-year disease-free prognosis for localized and metastatic RCC.

INSTRUCTIONS

- Localized: Any T; N0; M0
- Metastatic: T>0; N>1; M>1
- For accurate staging, see the [TNM Staging for RCC calculator](#)

When to Use ▾

Pearls/Pitfalls ▾

Why Use ▾

Type of disease present

Metastatic

Localized

[Fuhrman nuclear grade](#)

I

II

III

IV

[ECOG Performance Status](#)

0

≥1

Localized disease - T stage



[Fuhrman nuclear grade](#)



[ECOG Performance Status](#)



High Risk

54.7% Five Year survival

[Copy Results](#) 

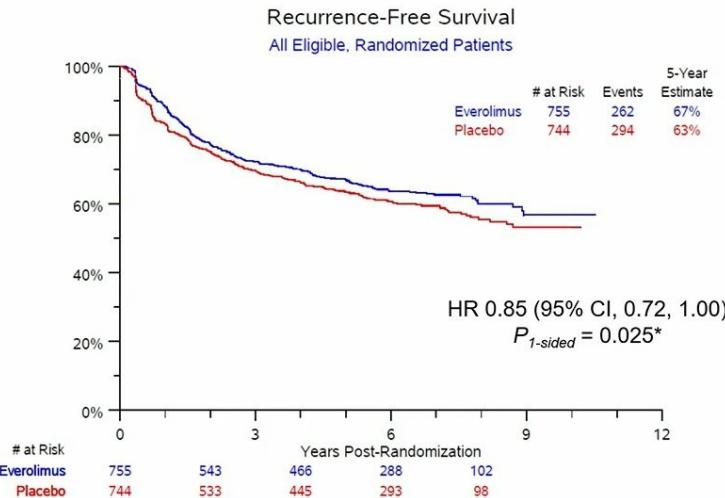
[Next Steps >>>](#)

Se necesitan más
opciones terapéuticas

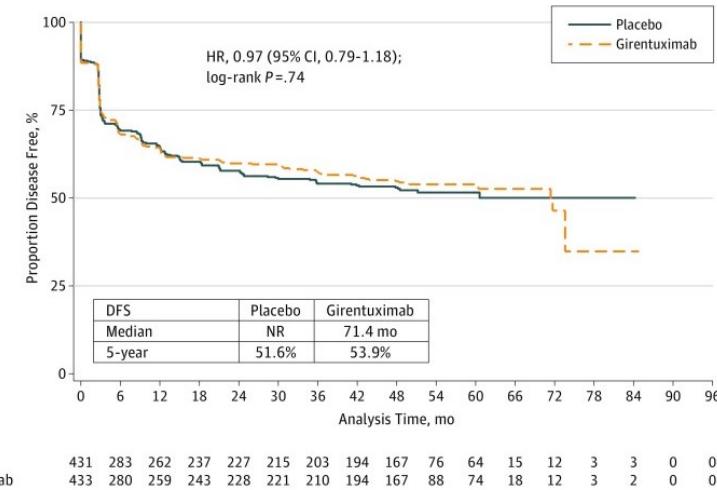


Más allá de los TKIs

Estudio EVEREST Everolimus



Estudio ARISER Girentuximab



Ensayos con anti PD-1/anti PD-L1 en la adyuvancia del cáncer renal

Ensayo	Tto experimental	n	Duración	Histología	Criterio de inclusión	Endpoint	Resultados
CM914 (2022)	Ipilimumab + Nivolumab	816	6m	Células claras	≥pT2aG3 N+	DFS	NS
IMmotion010 (2022)	Atezolizumab	778	12m	Células claras	≥pT2aG4 M1NED	DFS	NS
PROSPER (2022)	Nivolumab	819	9m	Cualquiera	cT1 OligoM1	DFS	NS
KN 564 (2021)	Pembrolizumab	984	12m	Células claras	≥pT2 G4 M1NED	DFS	HR 0.63

Motzer, R. J. et al. Lancet 401, 821–832 (2023); 2. Pal, S. K. et al. The Lancet 400, 1103–1116 (2022); 3. Allaf, M. et al. Annals of Oncology 33, S1432–S1433 (2022); 4. Choueiri, T. K. et al. NEJM 385, 683–694 (2021); 5. Powles, T. et al. Lancet Oncol 23, 1133–1144 (2022); 6. Oza, B. et al. Contemp Clin Trials 108, 106482 (2021).

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KEYNOTE-564 and IMmotion010 include patients at highest risk of recurrence, including those with M1 NED^{1,2}

CheckMate-914 includes patients with T2 Grade 3 or higher ccRCC³

RAMPART and PROSPER include patients with lower T category and nuclear grade T category vs other adjuvant studies^{4–6}

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Diseño del estudio: KEYNOTE-564

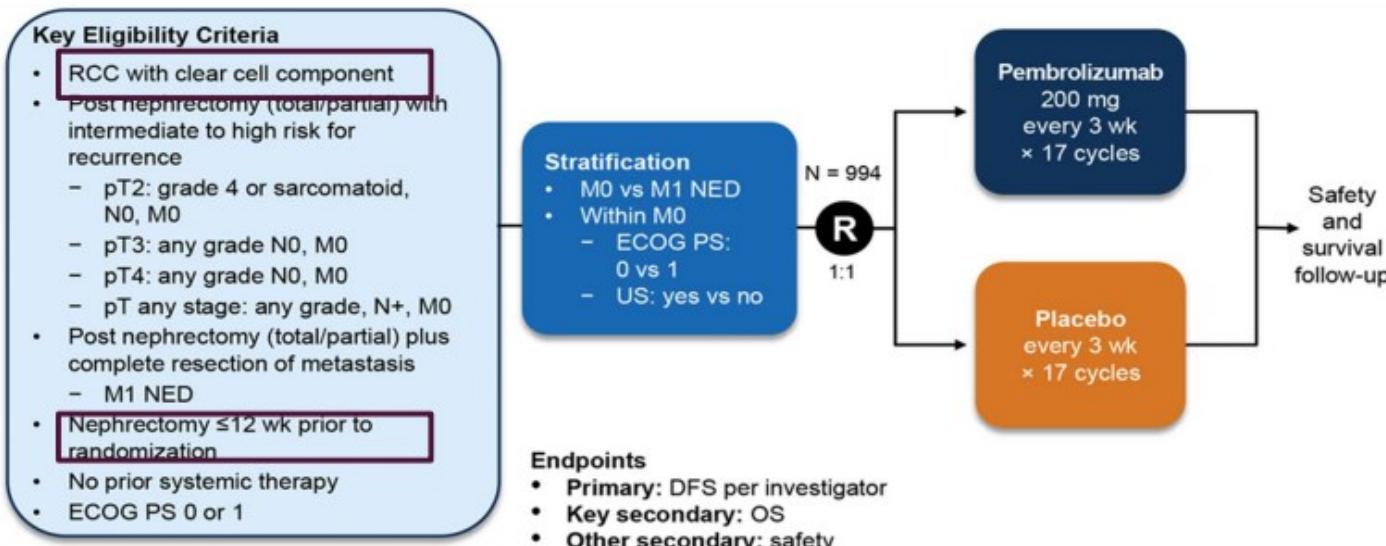


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab (N=496)	Placebo (N=498)
Age		
Median (range) — yr	60.0 (27-81)	60.0 (25-84)
≥65 yr — no. (%)	158 (31.9)	172 (34.5)
Male sex — no. (%)	347 (70.0)	359 (72.1)
ECOG performance-status score of 1 — no. (%)†	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 the world	175 (35.3)	186 (37.3)
Radical nephrectomy — no. (%)	459 (92.5)	460 (92.4)
Sarcomatoid features — no. (%)		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)
Disease risk category — no. (%)§		
M0, intermediate-to-high risk	427 (86.1)	433 (86.9)
M0, high risk	40 (8.1)	36 (7.2)
M1 NED¶	29 (5.8)	29 (5.8)
PD-L1 combined positive score — no. (%)		
<1	124 (25.0)	113 (22.7)
≥1	365 (73.6)	383 (76.9)
Missing data	7 (1.4)	2 (0.4)

Riesgo intermedio-alto

pT2 con Grado 4 o sarcomatoide, N0, M0

Riesgo alto

pT4, N0, M0, cualquier grado

M1 NED

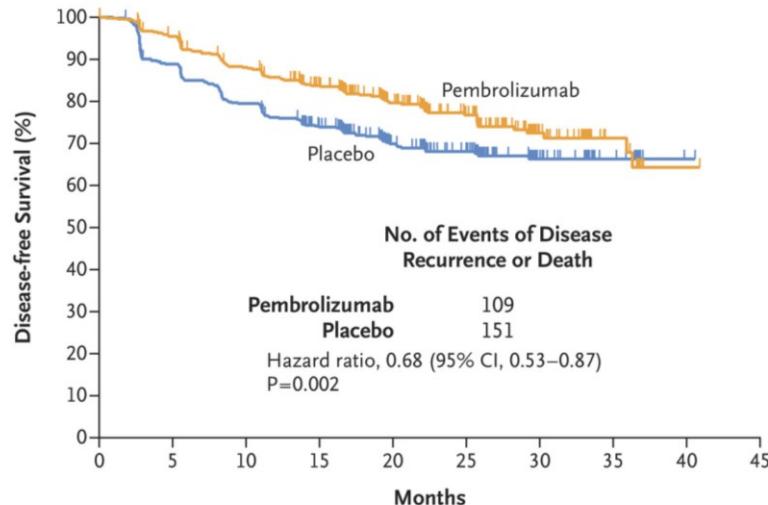
M1
Sin evidencia de enfermedad

86.1%

8.1%

5.8%

KEYNOTE-564: Objetivo principal

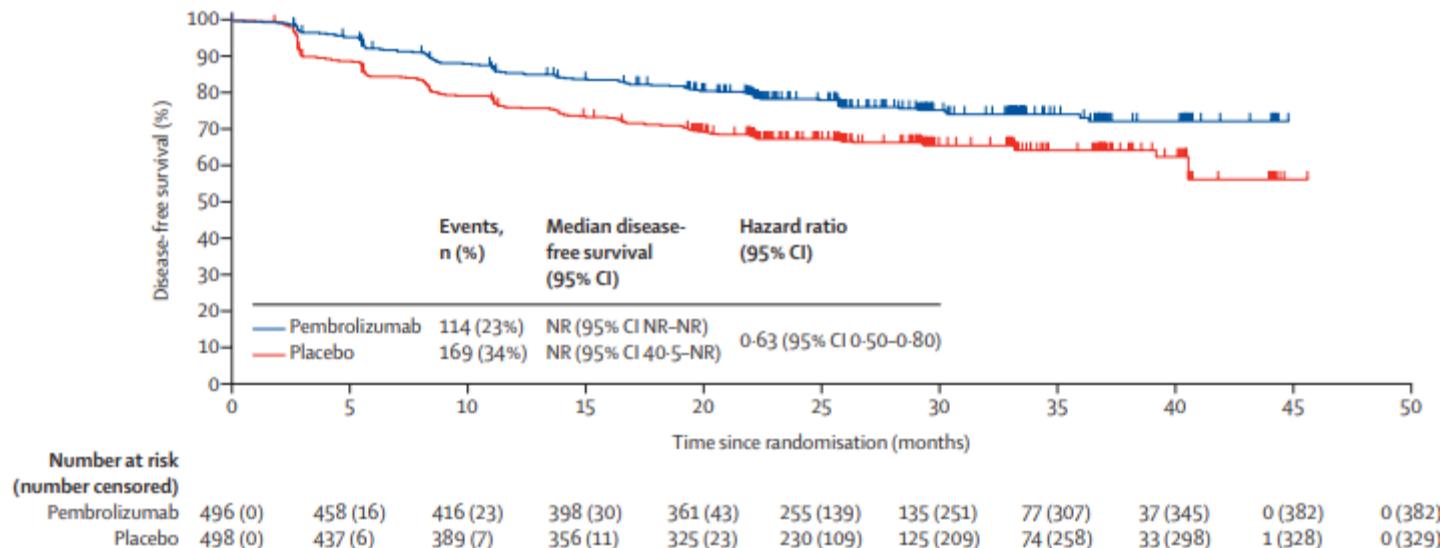


No. at Risk										
Pembrolizumab	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

A los 24 meses un 77.3% de los pacientes tratados con pembrolizumab estaban libres de enfermedad vs 68.1% en el brazo control

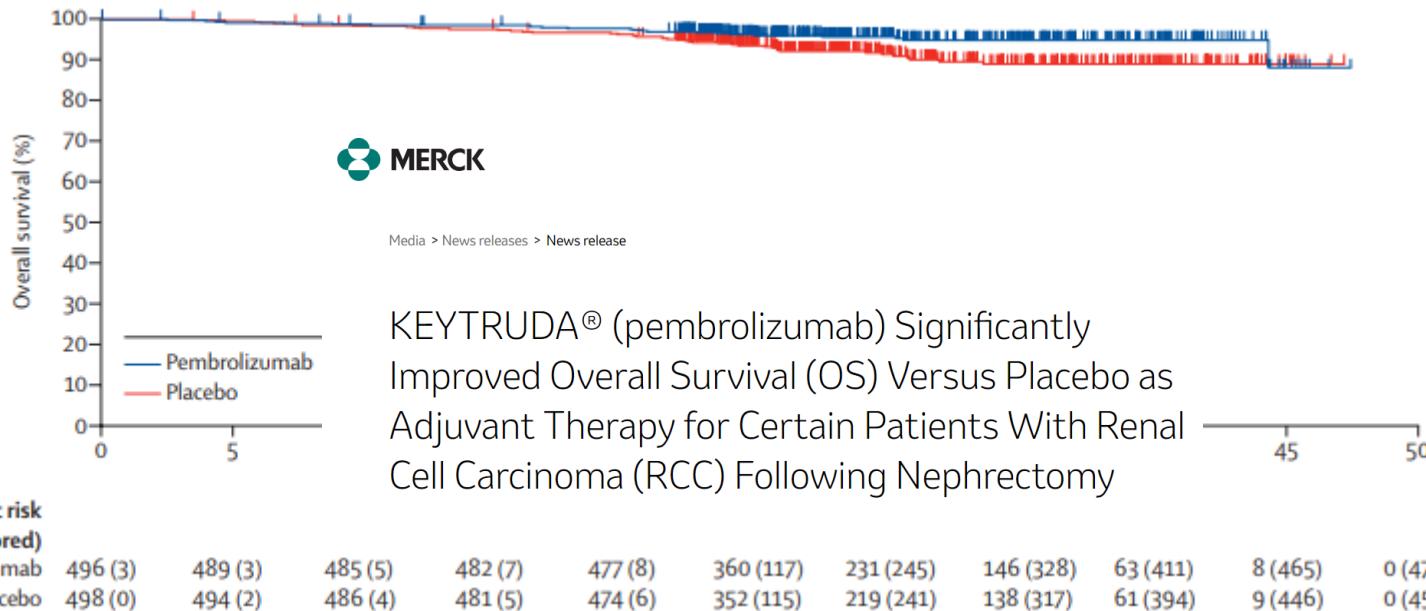
KEYNOTE-564: A 30 meses de seguimiento

A





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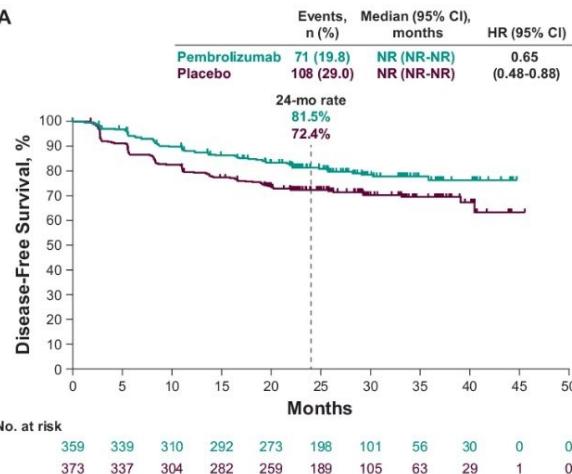


Powles, T. et al. Lancet Oncol. 2022 Sep;23(9):1133-1144

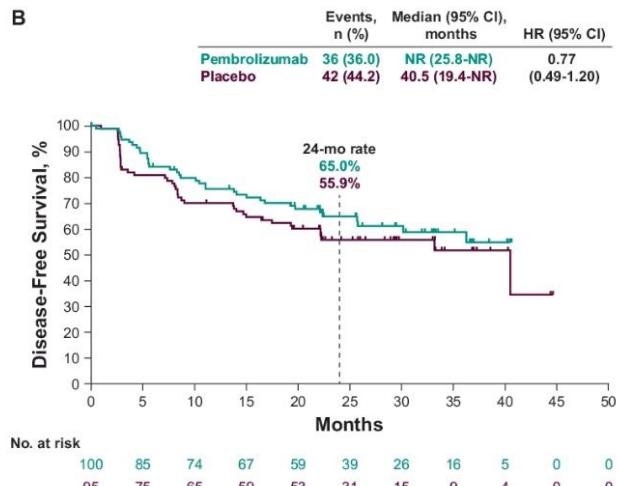


KEYNOTE-564: Análisis por subgrupos

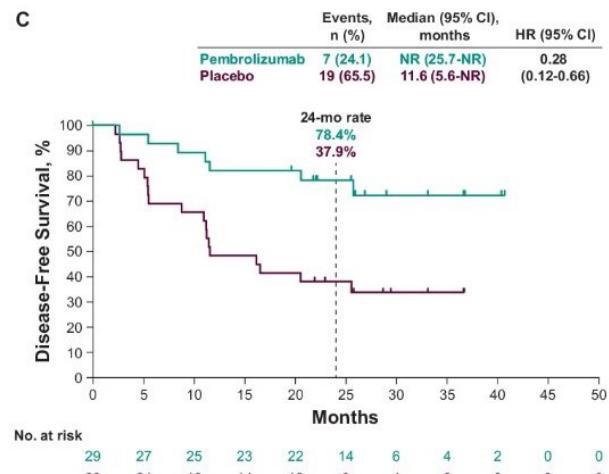
Riesgo intermedio



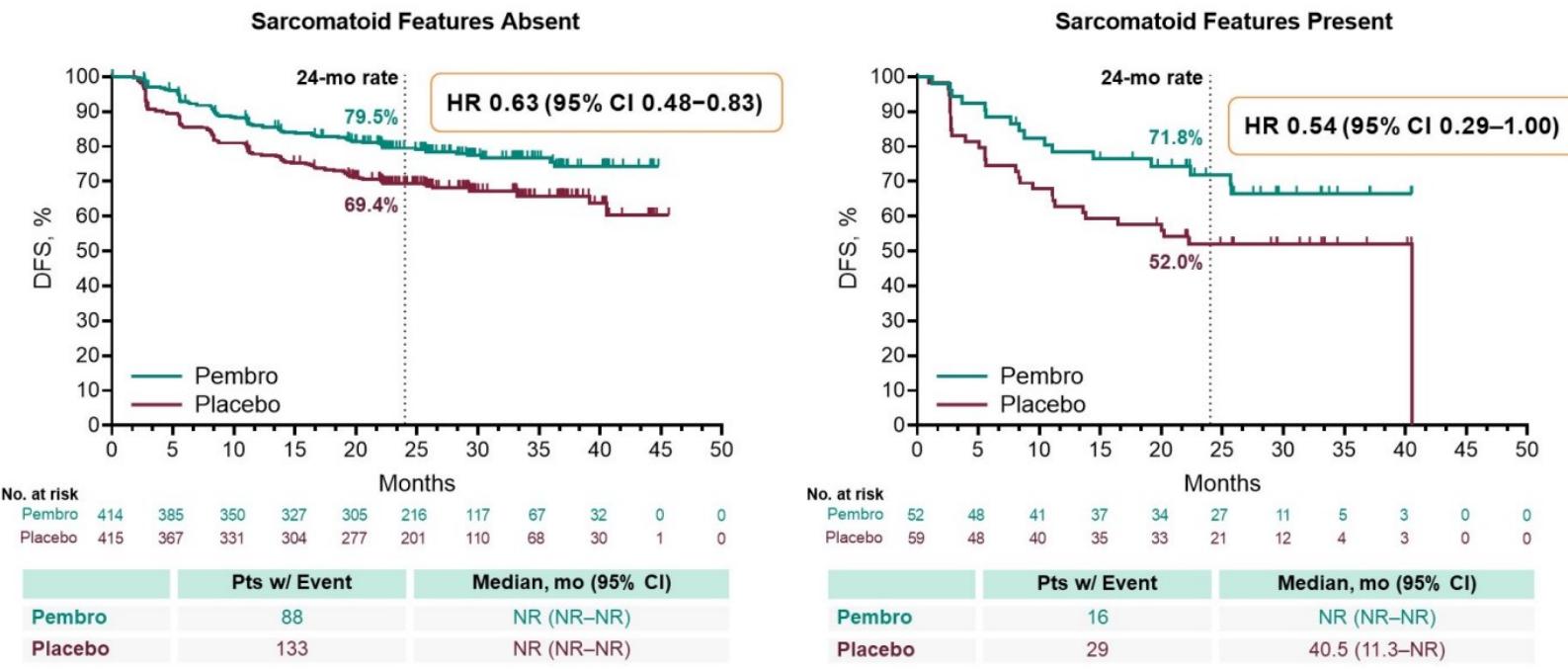
Riesgo alto



M1 NED



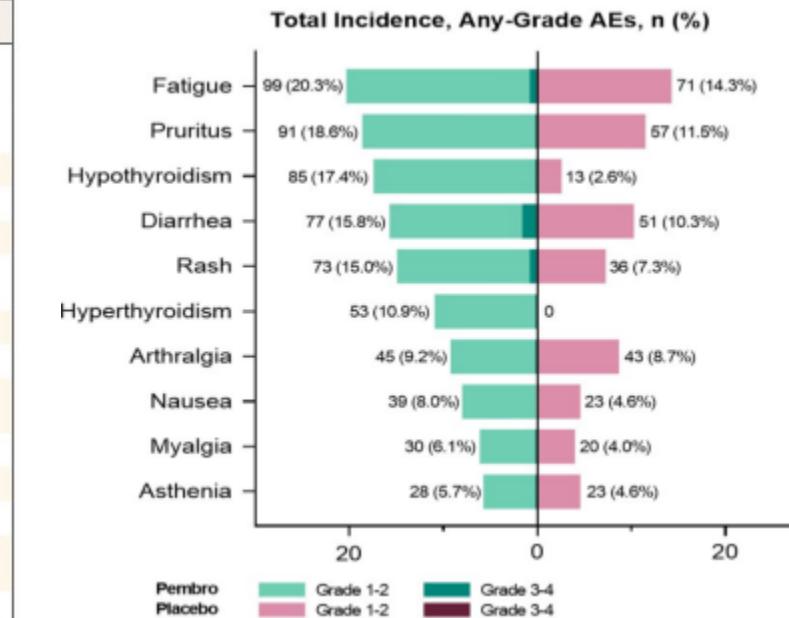
KEYNOTE-564: Análisis por subgrupos



KEYNOTE-564

Table 2. Any-Cause and Treatment-Related Adverse Events (As-Treated Population).*

Event	Pembrolizumab (N = 488)	Placebo (N = 496)
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	470 (96.3)	452 (91.1)
Adverse event of grade 3 to 5	158 (32.4)	88 (17.7)
Discontinuation of pembrolizumab or placebo due to adverse event	101 (20.7)	10 (2.0)
Death due to adverse event	2 (0.4)	1 (0.2)
Serious adverse event	100 (20.5)	56 (11.3)
Discontinuation of pembrolizumab or placebo due to serious adverse event	49 (10.0)	5 (1.0)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	386 (79.1)	265 (53.4)
Adverse event of grade 3 to 5	92 (18.9)	6 (1.2)
Discontinuation of pembrolizumab or placebo due to adverse event	86 (17.6)	3 (0.6)
Death due to adverse event	0	0
Serious adverse event	59 (12.1)	1 (0.2)
Discontinuation of pembrolizumab or placebo due to serious adverse event	37 (7.6)	0



KEYNOTE-564

Participants with ≥ 1 AE, n (%)	Primary Analysis (24.1 mo)		Updated Analysis (30.1 mo)	
	Pembro Arm (N = 488)	Placebo Arm (N = 496)	Pembro Arm (N = 488)	Placebo Arm (N = 496)
All-cause AEs	470 (96.3%)	452 (91.1%)	470 (96.3%)	453 (91.3%)
Grade 3–5	158 (32.4%)	88 (17.7%)	157 (32.2%)	88 (17.7%)
Led to treatment discontinuation	101 (20.7%)	10 (2.0%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious all-cause AEs^a	100 (20.5%)	56 (11.3%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs	386 (79.1%)	265 (53.4%)	386 (79.1%)	265 (53.4%)
Grade 3–4	92 (18.9%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	86 (17.6%)	3 (0.6%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs^b	169 (34.6%)	29 (5.8%)	170 (34.8%)	29 (5.8%)
Grade 3–4	42 (8.6%)	3 (0.6%)	43 (8.8%)	3 (0.6%)
High-dose (≥ 40 mg/day) systemic corticosteroid treatment for AEs prespecified to be immune-mediated, n (%)	36 (7.4%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

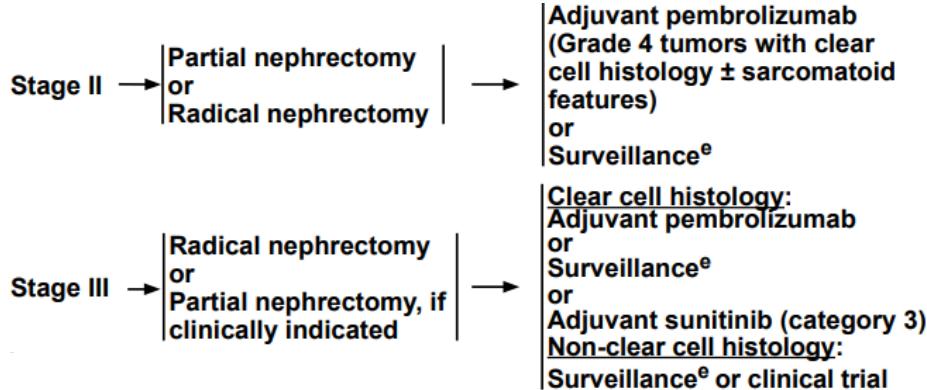


Nuevo estándar



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Cancer
Network®

NCCN Guidelines Version 1.2024 Kidney Cancer



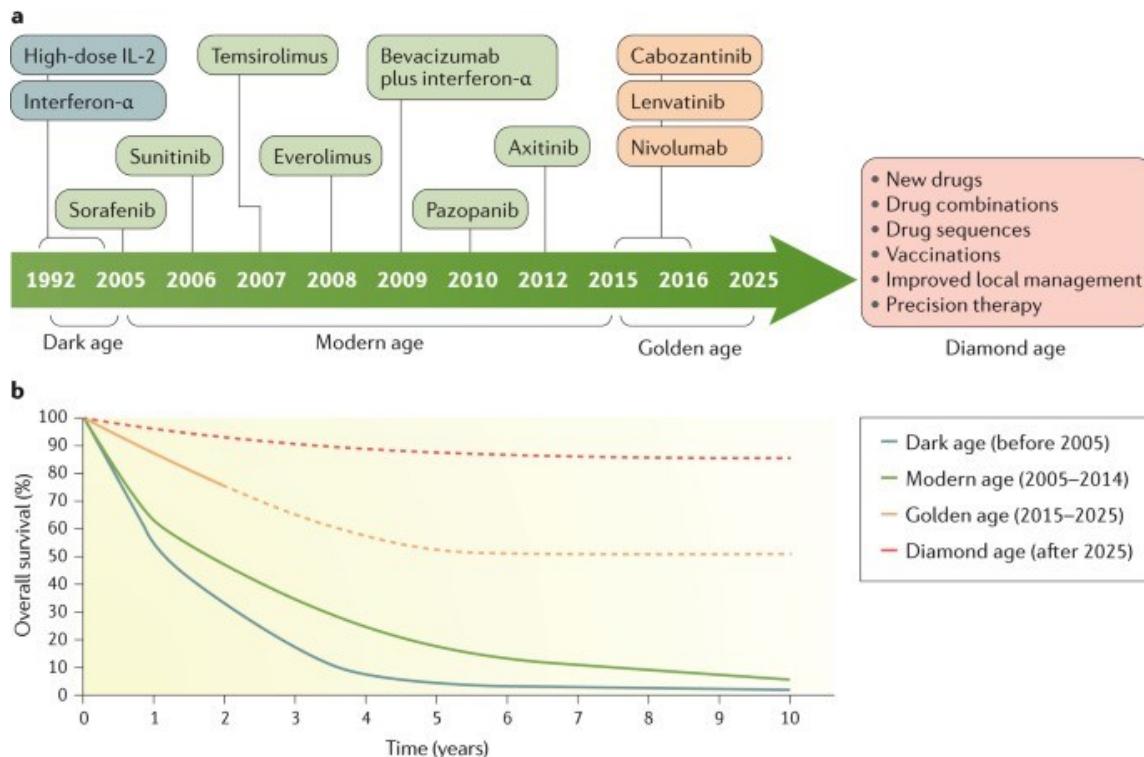
SPECIAL ARTICLE

ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma



Recommendations

- Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC (as defined by the study) after careful patient counselling regarding immature OS and potential long-term adverse events [I, C]. Further data are required in the future including positive OS data. Treatment should start within 12 weeks of surgery and continue for up to 1 year.





Gracias