XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Secuencia terapéutica en cáncer renal

¿Cómo tomar la mejor decisión?

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Fundación Biomédica Galicia Sur

INSTITUTO DE INVESTIGACIÓN SANITARIA Galicia Sur

XVII SIMPOSIUM

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MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

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COIs

Consultant or Advisory Role: BMS, MSD, Takeda, Roche, Pfizer, Ipsen, Astra-Zéneca, Merck, Boehringer, Bayer

Speaking: Roche, Ipsen, Lilly, Astellas, Janssen, Novartis, Boehringer, Eisai, Sanofi

Grant or travelsupport: MSD, Ipsen, Roche, Janssen, Pfizer, Astellas, Takeda

Participation in clinical trials: Merck, Astellas, Pfizer, Ipsen, Roche, AZ, Mirati, PharmaMar, Gilead

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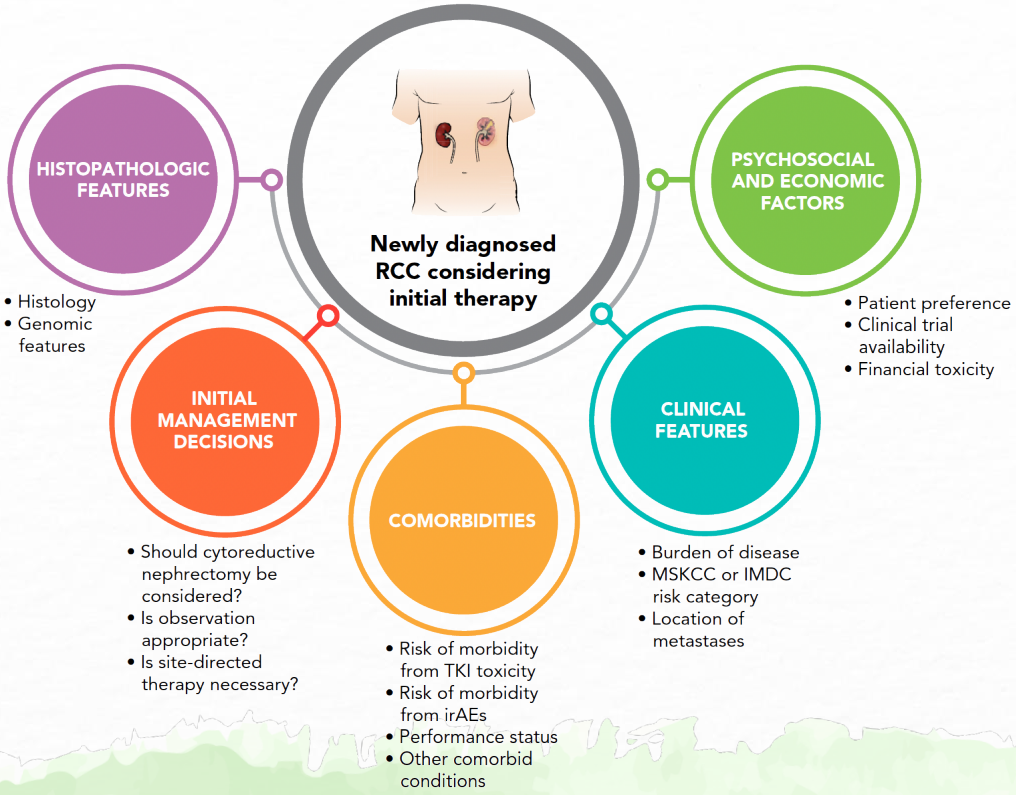
Selección de tratamiento en 1ª línea
Factores



K.N. Fitzgerald, et al. J Natl Compr Canc Netw, doi: 10.6004/jnccn.2022.7003

Criterios IMDC

Karnofsky performance score <80%

Time from initial diagnosis to targeted tx <1 yr

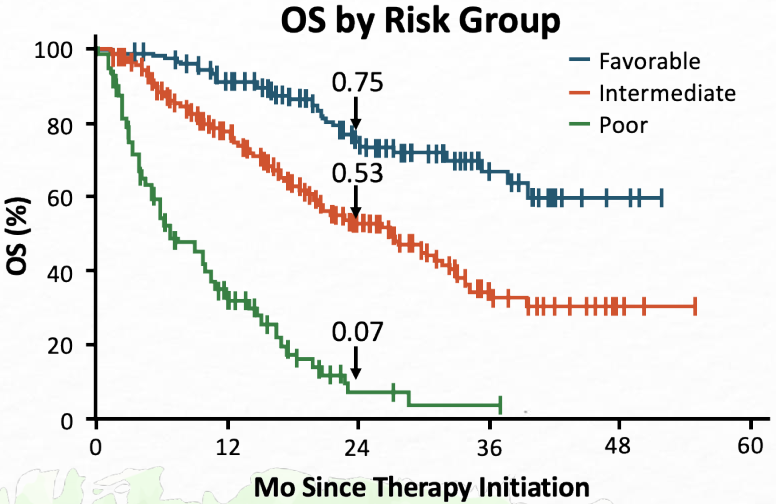
Hemoglobin < LLN

Calcium >10 mg/dL

Platelet count > ULN

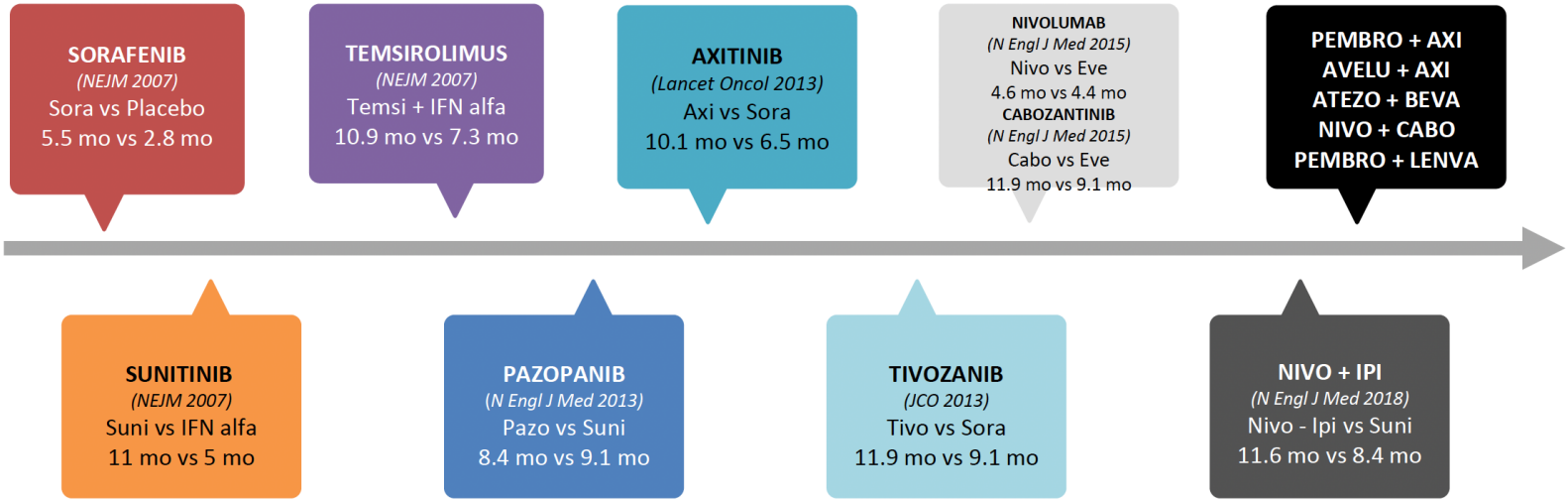
Neutrophil count > ULN

- Favorable: 0 risk factors
- Intermediate: 1-2 risk factors
- Poor: 3+ risk factors

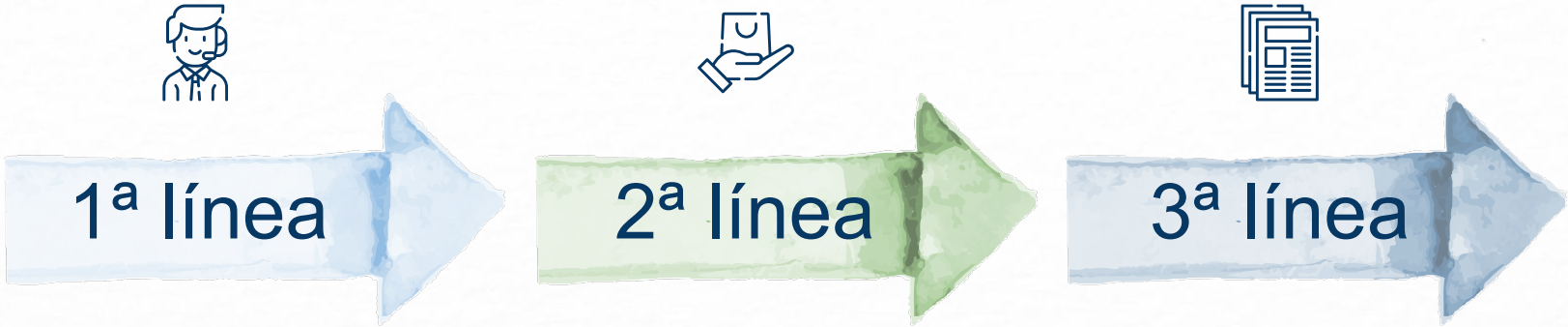


International Kidney Cancer Coalition. Heng. JCO. 2009;27:5794.

Evolución del tratº en cáncer renal



Pacientes que reciben líneas sucesivas de tratº



1ª línea	2ª línea	3ª línea
7.498 pac	3.854 pac	1.813 pac
100%	51%	24%

Stukalin. Kidney Cancer 2018;2:31.

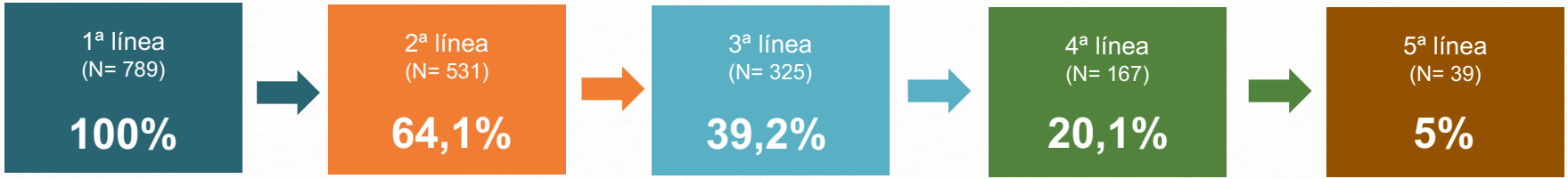
INTRODUCCIÓN

Aproximadamente la mitad de los pacientes que reciben una primera línea llegan a una 2ª línea y menos de 1/3 a la tercera.

**Según un estudio retrospectivo observacional publicado en 2024 de pacientes diagnosticados con cáncer de células renales entre abril de 2014 y diciembre de 2018. El estudio analizó a los pacientes desde el diagnóstico hasta diciembre de 2020 (o fallecimiento). De los 32.577 pacientes incluidos en el estudio, 5.657 pacientes tuvieron una 1L de tratamiento sistémico. De ellos, 2.606 pacientes recibieron una 2L sistémica y 989 recibieron una 3L.*

Das P, Booth, A Donaldson, et al. Patient Characteristics, Treatment Patterns, and Outcomes for Patients With Renal Cell Carcinoma in England: A Retrospective Cohort Study. Clin Genitourin Cancer. 2024;22(3):102081

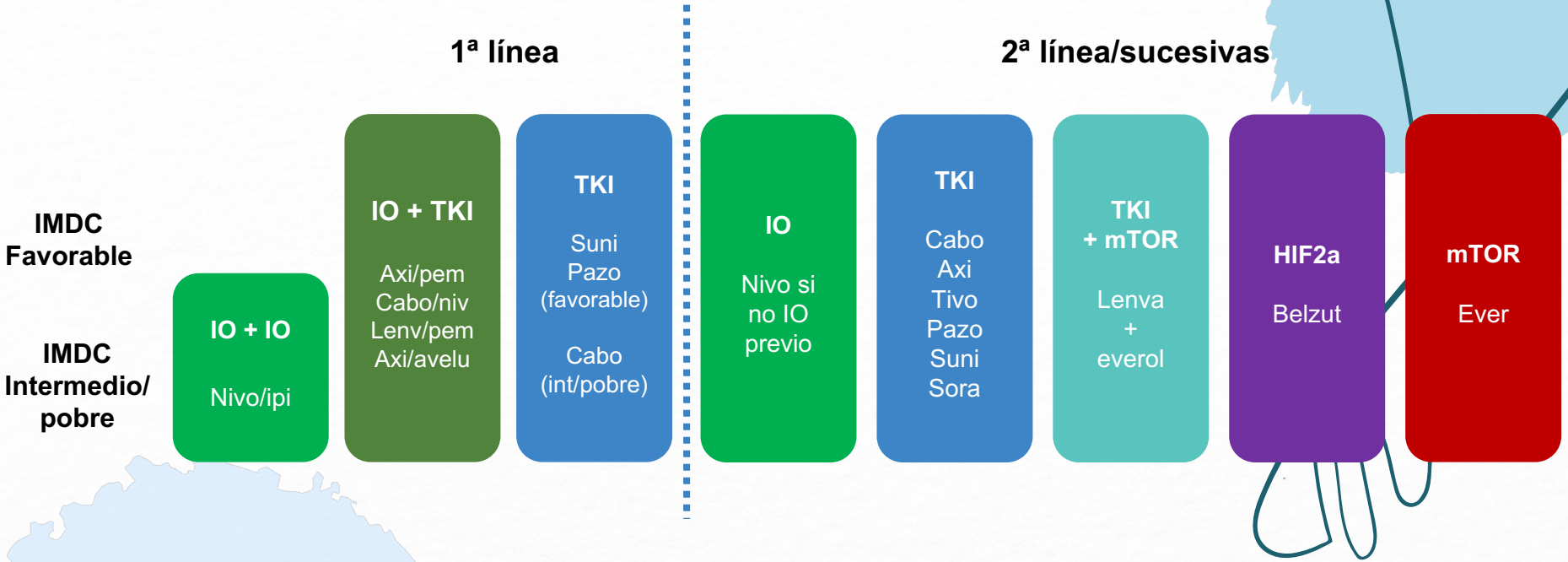
Resultados del Estudio RENO



El **39,2%** de los pacientes con RCC llegan a una tercera línea de tratamiento

Basterretxea. SEOM 2023

Tratamientos actuales



Adaptado de Braun. ASCO 24

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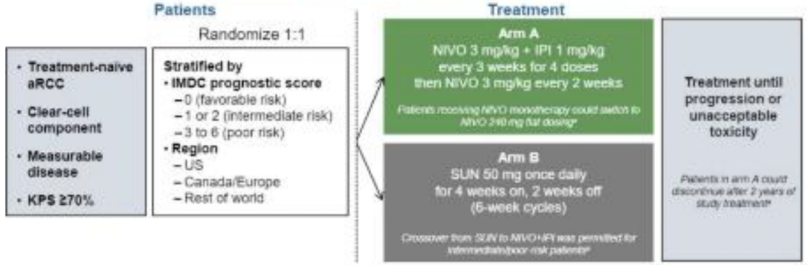
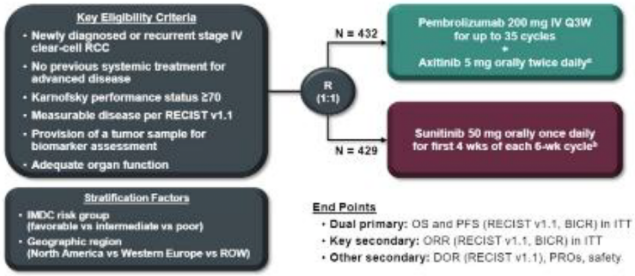
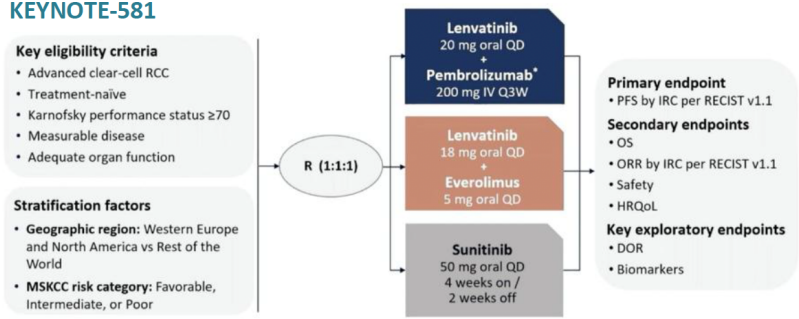
CheckMate 214: Study Design



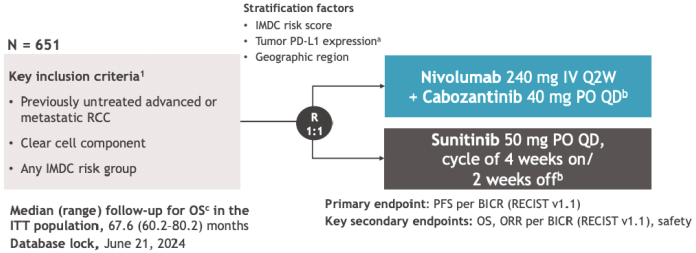
KEYNOTE-426 Study Design



KEYNOTE-581



CheckMate 9ER



ALL RISK GROUPS vs Sunitinib	CheckMate 214[1] (Ipi-nivo vs sunitinib)		KEYNOTE 426[2,3] (Pembro-axi vs sunitinib)		CheckMate 9ER[4] (Nivo-cabo vs sunitinib)		CLEAR[5] (Pembro-lenva vs sunitinib)	
Prognostic groups	Good 23%, intermediate 61%, poor 17%		Good 32%, intermediate 55%, poor 13%		Good 23%, intermediate 58%, poor 19%		Good 31%, intermediate 60%, poor 9%	
Target population	Intermediate- & poor-risk patients		All risk groups		All risk groups		All risk groups	
ORR, %	42	27	60	40	55	28	71	36
CR	10	1	9	3	9	4	16	4
PR	32	25	51	37	46	24	55	32
SD	31	44	23	35	33	42	19	38
DCR	73	70	83	75	88	70	90	74
PD	19	17	11	17	6	14	5	14

1. Motzer et al. Cancer. 2022 Jun 1;128(11):2085-2097. 2. Camilo G Porta et al. Oral Abstract 1449 ESMO 2022. 3. Motzer et al. Lancet Oncol 2022; 23: 888–98. 4. Powles et al. Lancet Oncol 2020; 21: 1563–73.

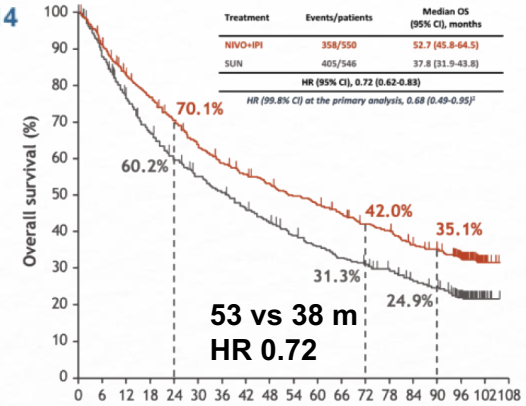
Eficacia

	CheckMate 214 (Nivo + Ipi; N = 1096)[1]	KEYNOTE-426 (Pembro + Axi; N = 861)[2]	CheckMate 9ER (Nivo + Cabo; N = 651)[3]	CLEAR (Pembro + Len; N = 712)[4]
OS, HR **mOS, mo**	0.72 52.7 vs 37.8	0.84 47.2 vs 40.8	0.77 46.5 vs 36.0	0.79 53.7 vs 54.3
Landmark OS	35% at 7.5 yr	63% at 3 yr 42% at 5 yr	49% at 4 yr	66% at 3 yr
PFS, HR **mPFS, mo**	0.88 12.4 vs 12.3	0.69 15.7 vs 11.1	0.58 16.4 vs 8.4	0.47 23.9 vs 9.2
Landmark PFS	23% at 7.5 yr (IRC) 16% at 7.5 yr (inv)	18% (5 yr)	17% (4 yr)	37% (3 yr)
ORR, %	39 vs 33	61 vs 40	56 vs 28	71 vs 37
CR, %	12 vs 3	12 vs 4	14 vs 5	18 vs 5
Med f/u, mo	96	67	56	50
Primary PD, %	18	12	7	5
mDOR (m)	**NR** vs 24.8	23.1 vs 15.1	23.6 vs 15.3.	26 vs 14.7

Tannir. ASCO GU 2024. Abstr 363. Rini. ASCO 2023. Abstr LBA4501. Bourlon. ASCO GU 2024. Abstr 362. Motzer. JCO. 2024;42:1222.

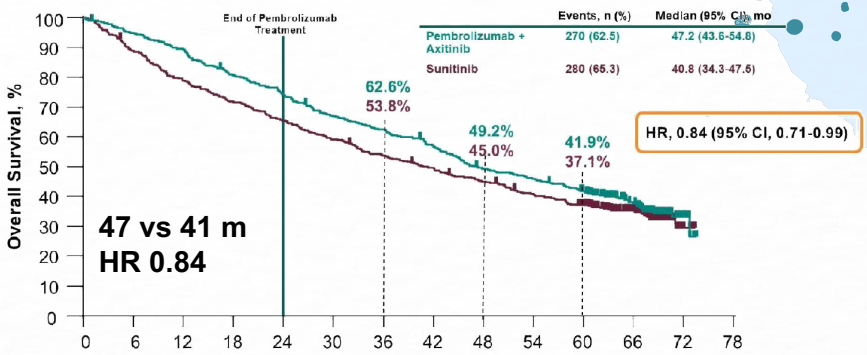
Supervivencia global

CheckMate 214



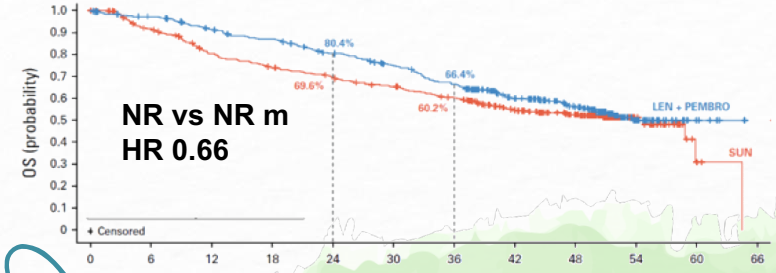
KEYNOTE-426

Median follow-up: 67.2 months

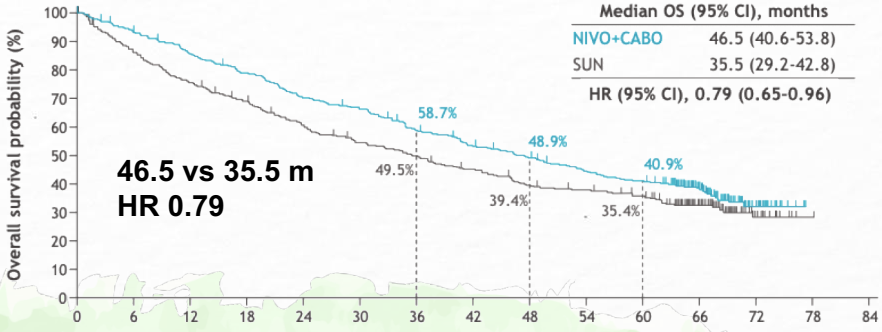


KEYNOTE-581

	Len + pembro	Sun	Len + pembro	Sun
OS HR (95% CI)	0.66 (0.49–0.88); P=0.005[c]		0.79 (0.63–0.99); P=0.0424[d]	
Median OS, mo (95% CI)	NR (33.6–NE)	NR (NE–NE)	53.7 (48.7–NE)	54.3 (40.9–NE)

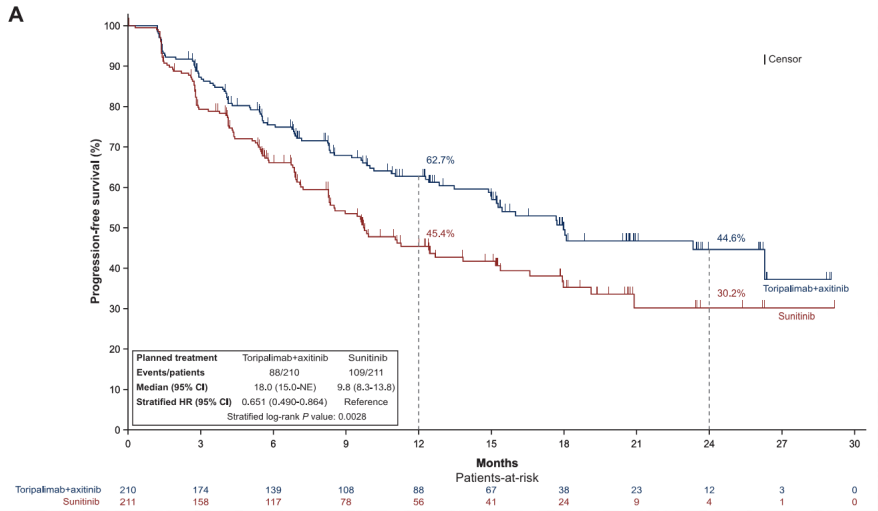


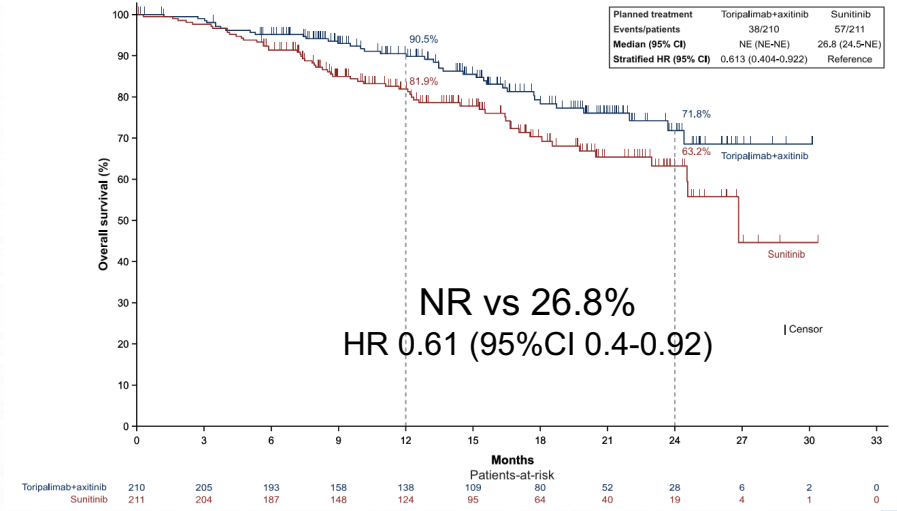
CheckMate 9ER



RENOTORCH

Axitinib/toripalimab vs sunitinib en riesgo intermedio/alto



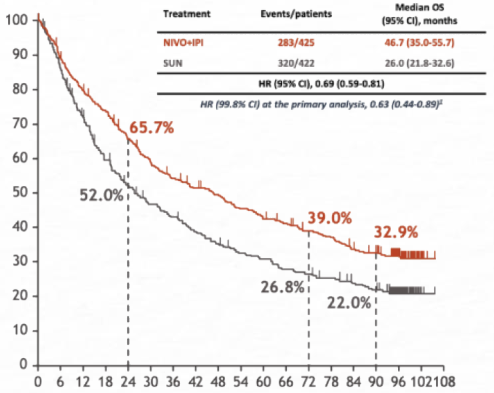


RR: 57% (5%RC) vs 31%

Yan. Ann Oncol 2024;35:190-9

OS en riesgo intermedio/pobre

CheckMate 214



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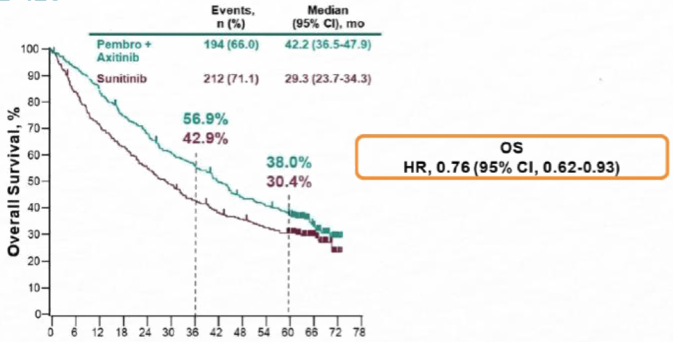

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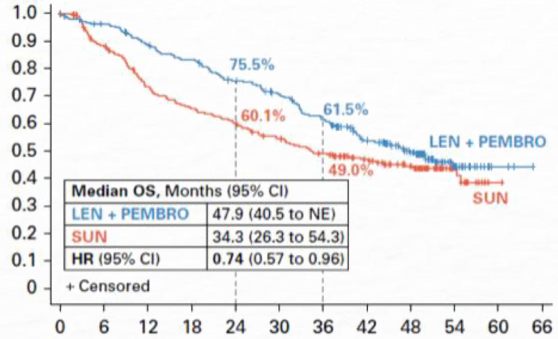
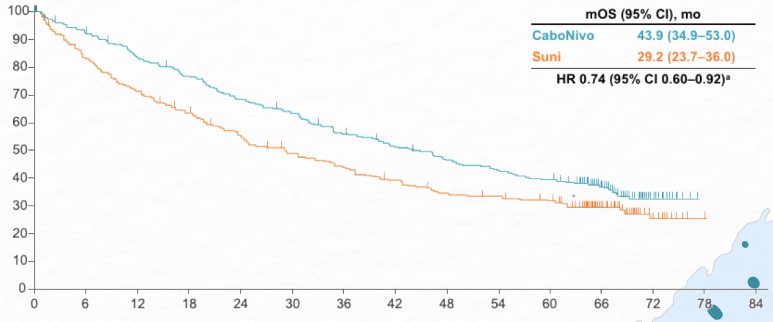
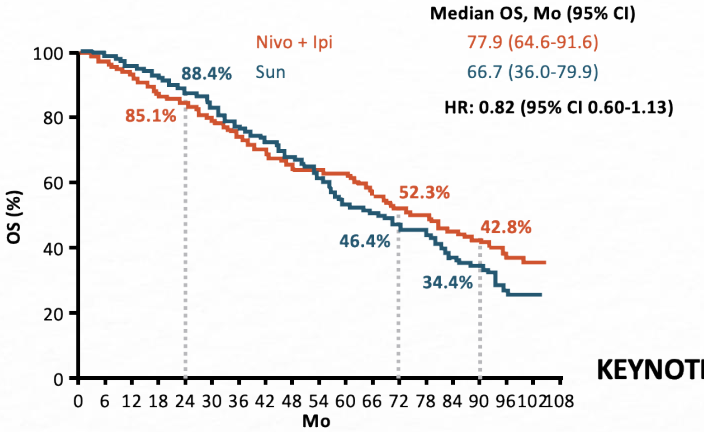


CheckMate 9ER

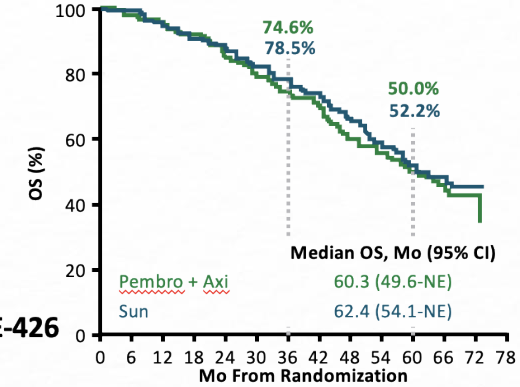


OS en pacientes de buen pronóstico

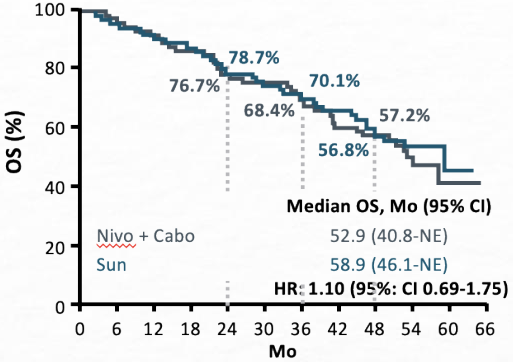
CheckMate 214



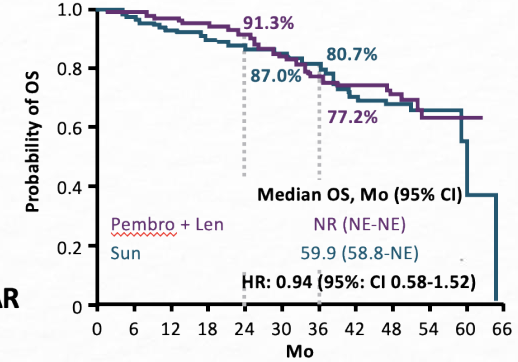
KEYNOTE-426



CheckMate 9ER



CLEAR



Tannir. ASCO GU 2024. Abstr 363. Rini. ASCO 2023. Abstract LBA4501.
Bourlon. ASCO GU 2024. Abstr 362. Motzer. JCO. 2024;42:1222.

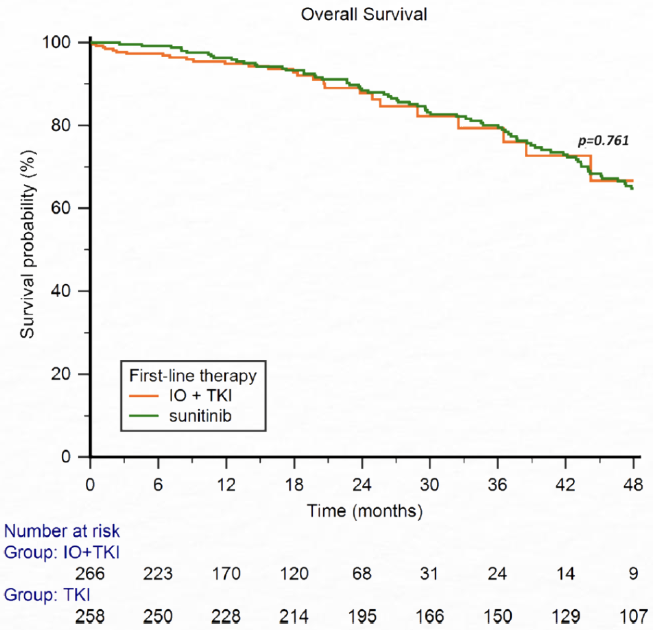
Grupos de riesgo

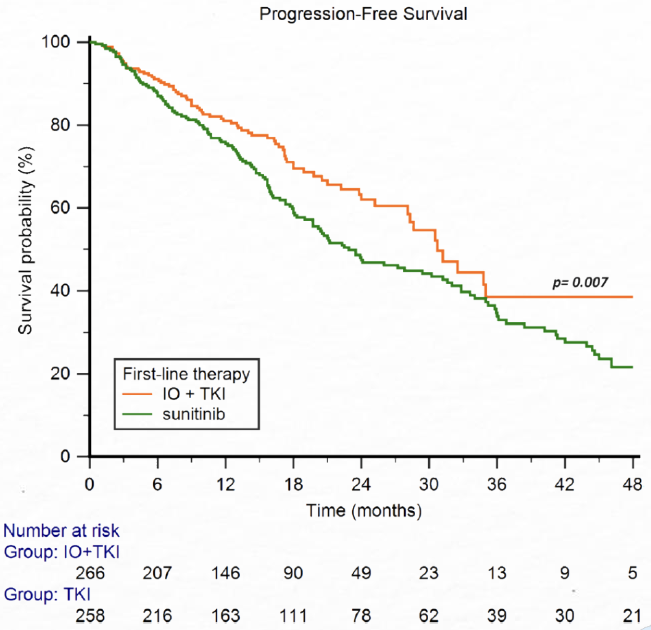
	PFS			OS		
	Favorable	**Intermedio**	**Pobre**	**Favorable**	**Intermedio**	**Pobre**
Ipi-nivo	**2.18 (1.29-3.68)**	0.82 (0.64-1.05)		**1.45 (0.51-4.12)**	0.63 (0.44-0.89)	
Pembro-axi	**0.81 (0.53-1.24)**	0.70 (0.54-0.91)	0.58 (0.35-0.94)	**0.64 (0.24-1.68)**	0.53 (0.35-0.82)	0.43 (0.23-0.81)
Cabo-nivo	**0.62 (0.38-1.01)**	0.54 (0.40-0.72)	0.37 (0.37-0.50)	**0.84 (0.35-1.97)**	0.70 (0.46-1.07)	0.37 (0.21-0.66)
Len/pemb	0.41 (0.28-0.62)			**1.15 (0.55-2.40)**	0.72 (0.5-1.05)	0.30 (0.14-0.64)

1. Motzer et al. N Engl J Med. 2018 Apr 5; 378(14): 1277–1290. ***2.*** Motzer et al. Cancer. 2022 Jun 1;128(11):2085-2097. ***3.*** Motzer et al. N Engl J Med 2021;384:1289-300. ***4.*** Camilo G Porta et al. Oral Abstract 1449 MO presented at ESMO 2022. ***5.*** Choueiri et al. N Engl J Med. 2021 Mar 4;384(9):829-841. ***6.*** Motzer et al. Lancet Oncol 2022; 23: 888–98. ***7.*** Rini et al. N Engl J Med. 2019 Mar 21;380(12):1116-1127. ***8.*** Powles et al. Lancet Oncol 2020; 21: 1563–73.

Estudio retrospectivo ARON

n=524; riesgo favorable

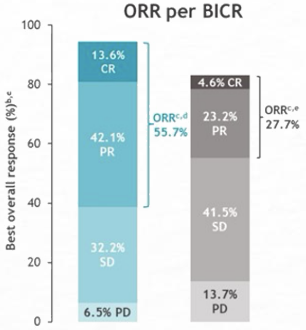




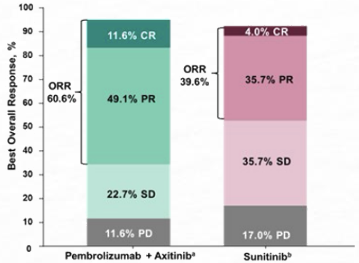
Roviello. Cancer Immunology, Immunotherapy (2025) 74:65

Selección 1ª línea

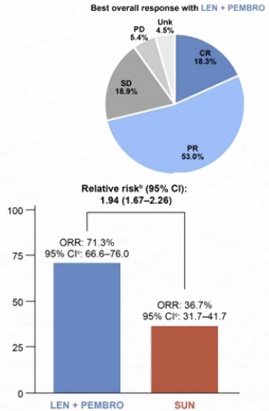
IO/TKI: alto porcentaje de respuestas



Nivo + Cabo
(CheckMate-9ER)

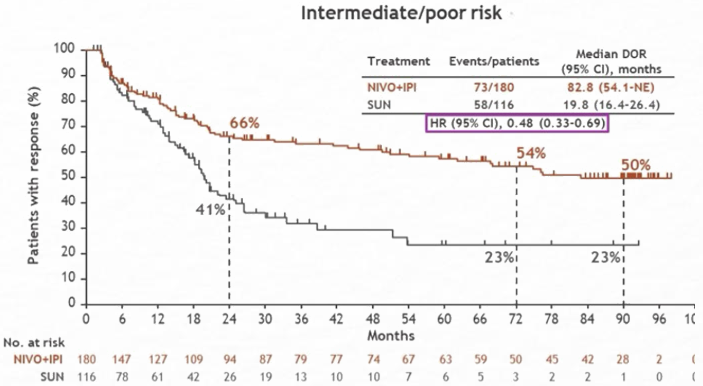


Pembro + Axi
(KEYNOTE-426)



Pembro + Lenva
(CLEAR)

IO/IO: respuestas duraderas



Nivo + Ipi
(CheckMate-214)

½ of responding patients still responding >7 years later

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501; Bourlon, ASCO GU 2024, 362; Tannir, ASCO GU 2024, 363

Adaptado de Braun. ASCO 24

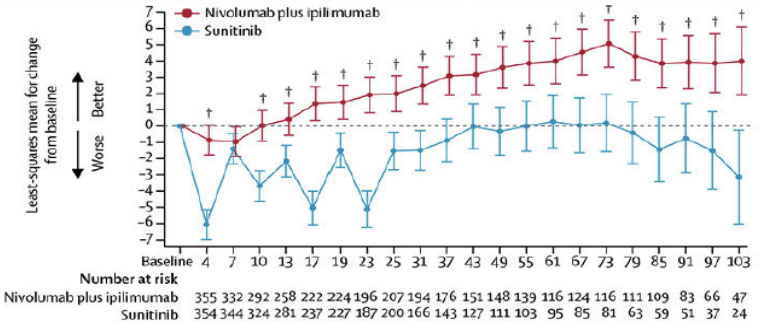
Toxicidad

Evento	CM 214	KN 426	CM 9er	CLEAR
EA G≥3 relacionados con el tratamiento	46%	62.9%	60.6%	82.4%
Muertes relacionadas con el tratamiento	1.5%	0.9%	0.3%	1.4%
Eventos que llevan a la discontinuación de los 2 fármacos	22%	11%	15%	13.4%
Mediana duración tratamiento (m)	8	8.3	14.3	17

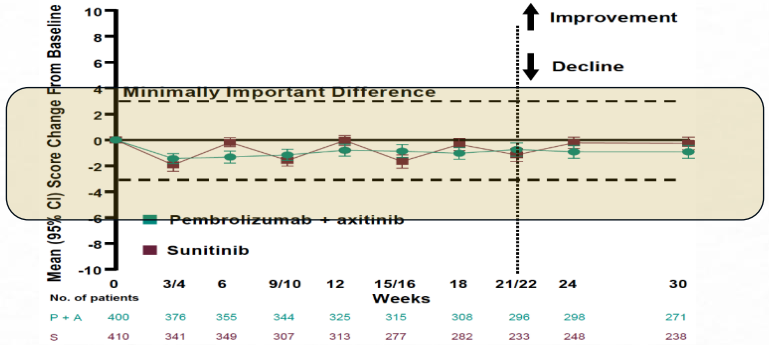
1. Motzer et al. N Engl J Med. 2018 Apr 5; 378(14): 1277–1290. ***2.*** Motzer et al. Cancer. 2022 Jun 1;128(11):2085-2097. ***3.*** Motzer et al. N Engl J Med 2021;384:1289-300. ***4.*** Camilo G Porta et al. Oral Abstract 1449 MO presented at ESMO 2022. ***5.*** Choueiri et al. N Engl J Med. 2021 Mar 4;384(9):829-841. ***6.*** Motzer et al. Lancet Oncol 2022; 23: 888–98. ***7.*** Rini et al. N Engl J Med. 2019 Mar 21;380(12):1116-1127. ***8.*** Powles et al. Lancet Oncol 2020; 21: 1563–73.

Calidad de vida

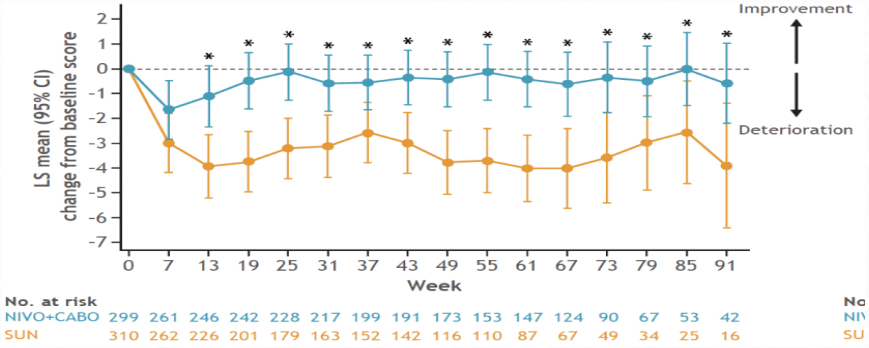
FKSI-19 total score: CheckMate-214[1]



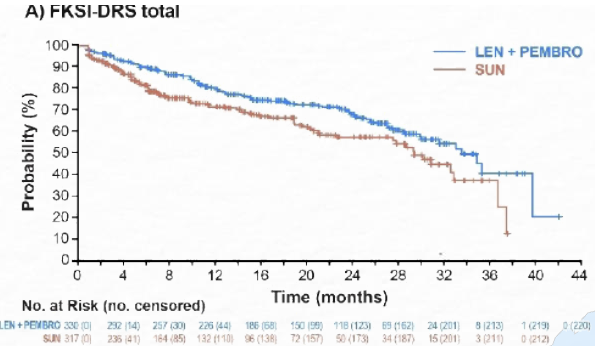
FKSI-DRS: KEYNOTE-426[3]



FKSI-19 total score: CheckMate 9ER[2]



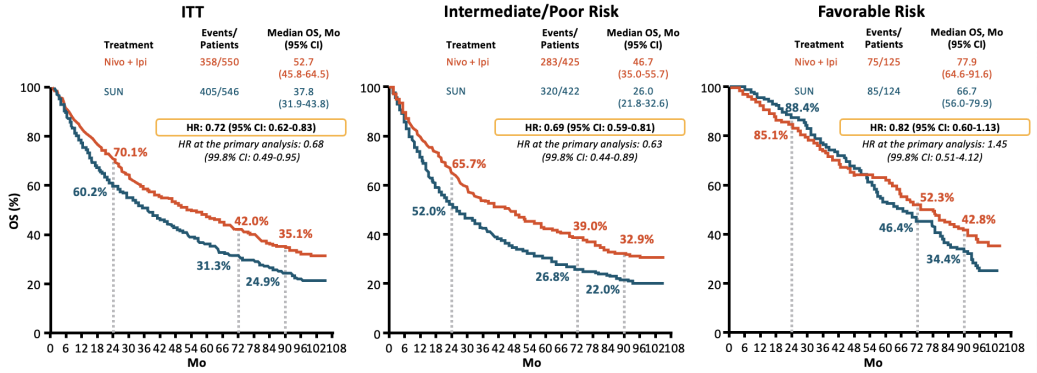
FKSI-DRS: CLEAR[4]



1. Cella D, et al. *Lancet Oncol* 2019;20:297-310; 2. Choueiri TK, et al. *Ann Oncol* 2020;31(Suppl. 4):abs. 696O; 3. Bedke J, et al. *EAU* 2020; 4. Motzer RJ, et al. *Lancet Oncol* 2022;23:768-80.

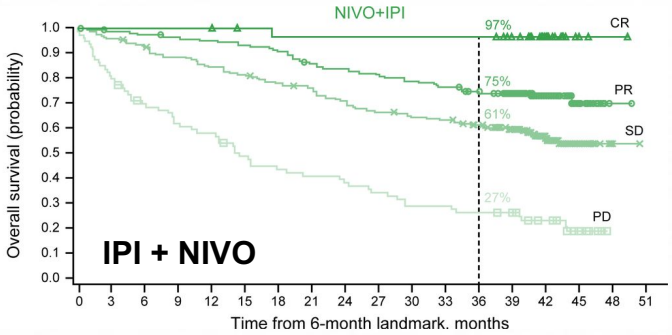
Componente sarcomatoide

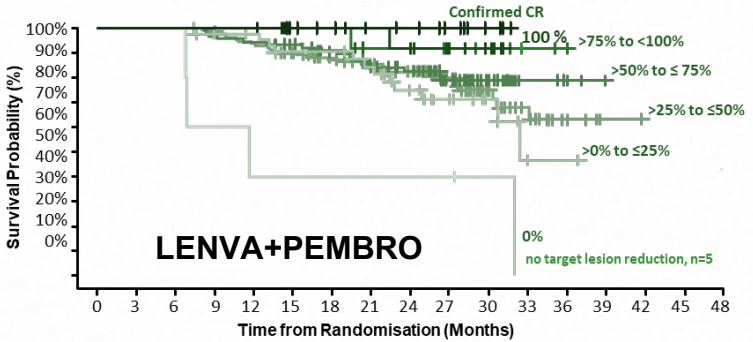
	CM 214 Nivo-ipi N=139	KN-426 Pembro-axi N=105	9er Cabo/nivo N=75	CLEAR Len/pemb N=52
OS HR	**0.45**	0.58	**0.38**	0.91
mPFS, m	8.4	NR	10.3	-
PFS HR	0.61	0.54	9.42	0.39
ORR %	60.8	58.8	56.6	60
CR %	18.9	11.8	8.8	-

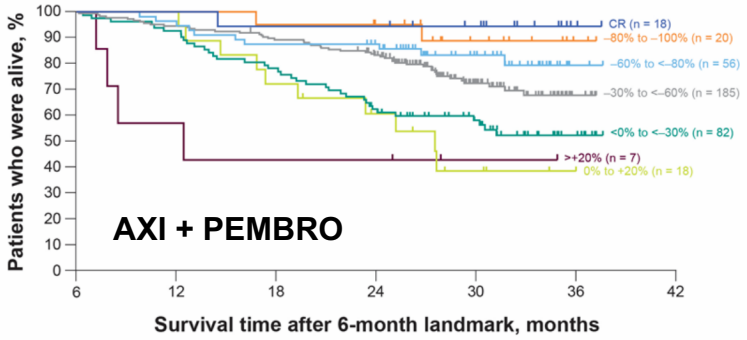


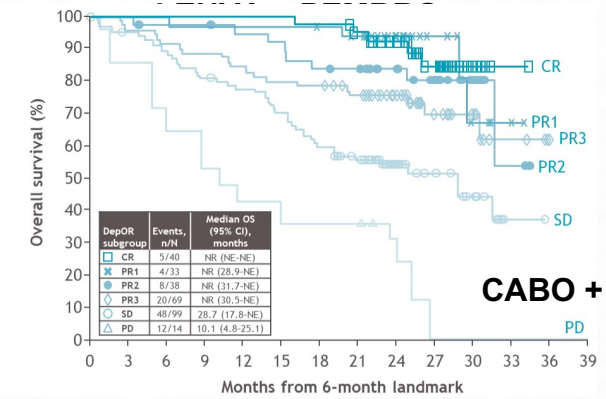
1. Rini. J ImmunoTher Cancer. 2022;10:e005445. 2. Rini. ASCO 2019. Abstr 5400. 3. Rini. NEJM. 2019;380:1116. 4. Motzer. Lancet Oncol. 2022;23:888. 5. Grunwald. Front Oncol. 2023;13:1223282.

Profundidad de la respuesta y OS





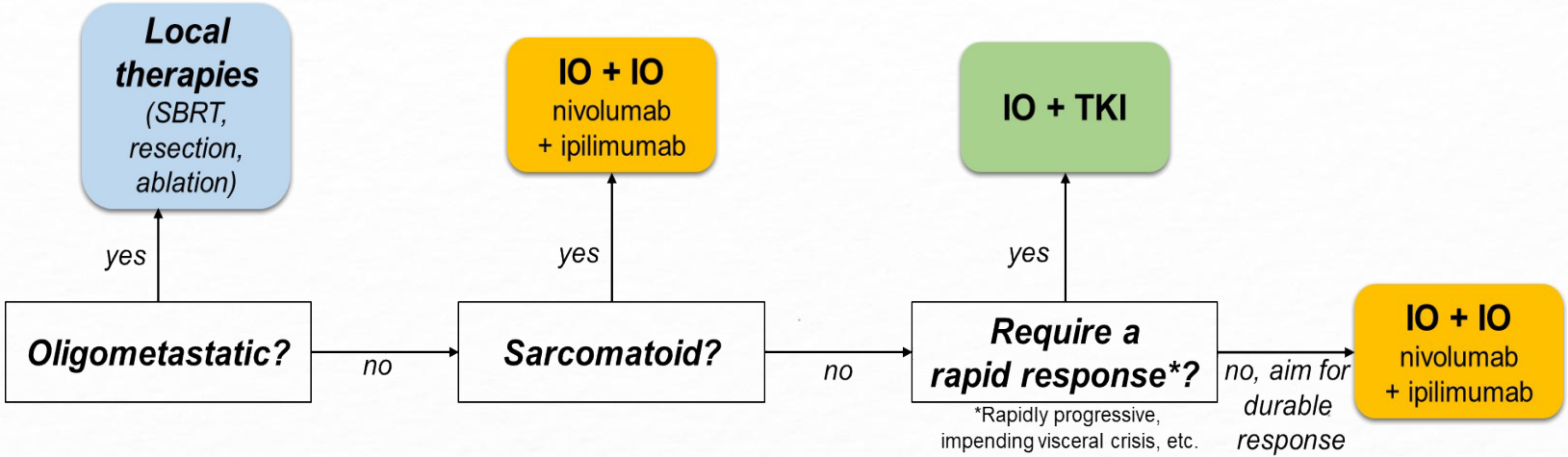




1. Motzer J et al. J Immunother Cancer 2020;8:e000891. 2. Grünwald V et al. Poster presented at the ASCO Annual Meeting; 04–08 June, 2021; Virtual Format; abstract # 4560. 3. Suárez C et al. ASCO 2022. Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 4501-4501. 4. Powles T. Lancet Oncol. 2020 Dec;21(12):1563-1573.

OPCIONES

Adyuvancia



Adaptada de Braun. ASCO 2024

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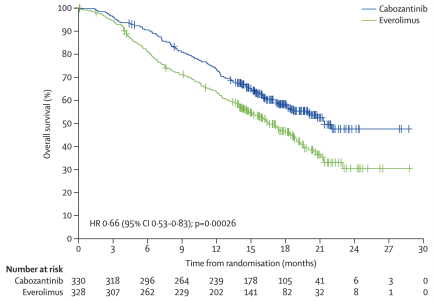
2ª línea tras TKI

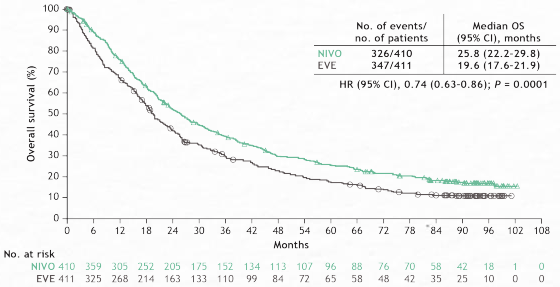
1. Buen pronóstico; baja carga, indolente
2. Donde la IO no está disponible
3. En pacientes que aún están con TKIs

METEOR



Choueiri, Lancet Oncol *2016;***17**, 917–927

CM-025



Escudier. ESMO 2022

TKIs tras IO: datos retrospectivos

Treatment	N	mPFS, mo	ORR, %
TKI[1]	70	6.4	28
TKI (Cabozantinib/Axitinib)[2]	56	8	33
TKI (sun, axi, pazo, cabo)[3]	33	8	36
TKI (sun, axi, pazo, cabo)[4]	70	13.2	41
TKI (post: CPI+VEGF vs ipi+nivo)[5]	55	3.7 vs 5.4 (mTTF)	15 vs 45
Pazopanib[6]	258	13.5	Not reported
Cabozantinib[7]	86	6.5 (mTTF)	36
Cabozantinib[8]	31	5.4 (mTTF)	22
Cabozantinib vs other TKIs[9]	247	6.2 vs 3.1 (mTTD)	54 vs 38
Cabozantinib[10]	116	7.6 (mTTF)	20
Lenvatinib +/- everolimus[11]	55	6.2	21.8
TKI vs mTOR[12]	314	6.1 vs 2.8 (mTTD)	30 vs 3.6

.Nadal R, Ann Oncol 2016; 2.Derosa L, Ann Oncol 2017; 3.Auvray M, EJC 2019; 4.Shah AT, EJC 2019; 5.Dudani, Eur Urol 2019; 6.Cao X, Clin Genitourin Cancer 2020; 7.McGregor BA, EJC 2020; 8.Gan CL, Cancer Med 2(
9.Marteau F, ASCO GU 2021; 10.Zhang H, Kidney Cancer 2021; 11.Wiele AK, Oncologist 2021; 12.Graham J, Eur Urol Oncol 2(

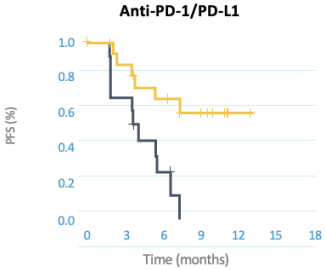
Cortesía Dra Suárez

TKIs tras IO: datos prospectivos

DRUG	STUDY	N	ORR (%)	PFS
Cabozantinib	Post-Hoc análisis Phase III **METEOR**	18	22	Not reached
Tivozanib	Post-Hoc análisis Phase III **TIVO-3**	91	Not reported	7.3
Axitinib	Phase II **CASE7815**	40	45	8.8
Sunitinib	Phase II **IMNUNOSUN**	21	19	5.6
Lenvatinib + Everolimus	Phase II **E7080-G000-218** 14mg Lenvatinib 18 mg Lenvatinib	 156 155	 30 51	 12.0 12.9
Pazopanib	Phase II **IO PAZ**	62	14.5	6.5
Cabozantinib	Phase II **BREAKPOINT***	30	37.9	8.3
Cabozantinib (±Teleglenestat)	Phase II **CANTATA**	139 65 (prior Ipi-Nivo)	- 41	9.2 -
Cabozantinib	Phase II **CABOPOINT**	85	40.5	10.9
Cabozantinib (±Atezolizumab)	Phase III **CONTACT-03**	254	41	10.8
Tivozanib (±Nivolumab)	Phase III **TINIVO-2**	343	19.8	7.4
Belzutifan	Phase III **LITESPARK-005**	374	22,7	5,6

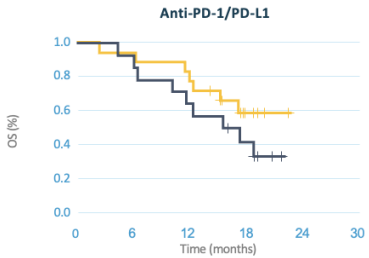
Powles T, British Journal of Cancer 2018; Rini BI, Lancet Oncol 2020; Omstein MC, Grande E, Annals Oncol 2022; Grande E, Annals Oncol 2022, Pal SK et al. Eur Urol 2022;82:283–92; Powles T et al. Presented at ESMO 2020: Lancet Oncol 2019; Procopio G, et al. *Tumori* 2023;109:129–137; Tannir N ASCO 2021 Abs 4105, Albiges et al, ESMO 2024 Poster 1693P; Choueri T, LBA4500. ASCO 2023; Albiges L, et al. Presented at ESMO 2023

Phase 3 METEOR: PFS/OS after ICI



	Median, months
Cabozantinib (n=18)	NE
Everolimus (n=14)	4.1

HR = 0.22 (95% CI 0.07–0.65)



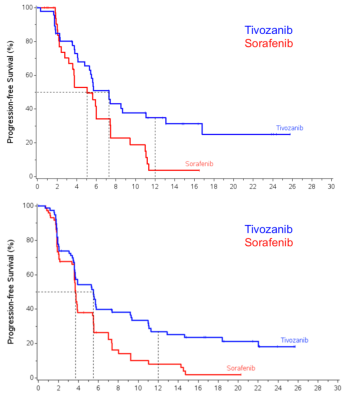
	Median, months
Cabozantinib (n=18)	NE
Everolimus (n=14)	16.3

HR = 0.56 (95% CI 0.21–1.52)

Powles T, et al. *Br J Cancer* 2018;119:663–69;
Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27.

Tivozanib tras IO

TIVO-3: PFS & ORR in Key Subgroups*



*Final analysis, as of Oct 4, 2018
Porta et al. ASCO 2019

Prior Checkpoint Inhibitor + VEGFR TKI	Tivozanib (n=47)	Sorafenib (n=44)
Median PFS, months (95% CI)	7.3 (4.8, 11.1)	5.1 (3.2, 7.4)
HR (95% CI)	0.55 (0.32, 0.94)	
P Value	0.028	
ORR	24.4%	6.8%

Two Prior VEGFR TKIs	Tivozanib (n=79)	Sorafenib (n=80)
Median PFS, months (95% CI)	5.5 (3.6, 7.4)	3.7 (3.6, 3.9)
HR (95% CI)	0.57 (0.39, 0.83)	
P Value	0.003	
ORR	15.2%	7.5%

Rini BI, et al. Lancet Oncol 2020; 21: 95-104

BREAKPOINT trial

Cabozantinib tras 1ª línea con IO; fase II

60% IO-IO
36% IO-TKI
4% IO monoterapia

Prospective, open label, single arm, multicenter, phase II study

Advanced or unresectable RCC pretreated with a P-D1/PD-L1 inhibitor as monotherapy or in combination with angiogenesis inhibitor or anti CTLA-4

Cabozantinib PO 60 mg die

(Dose reduction permitted if toxicity)

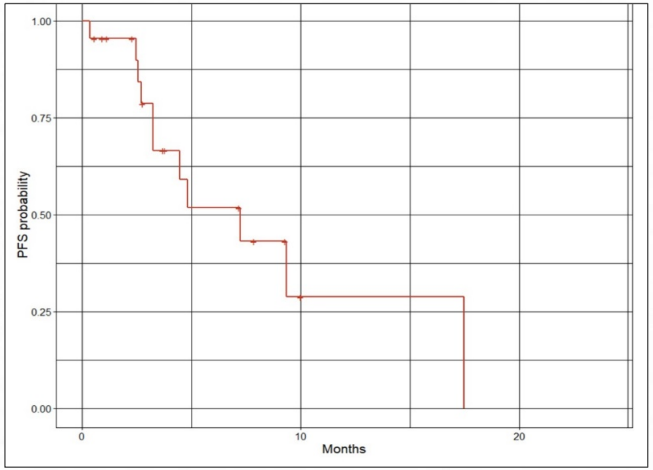
Until PD or unacceptable toxicity

Stratification criteria:
- Heng/MSKCC prognostic group
-First line duration
-Type of previous therapy received

PRIMARY ENDPOINT
- PFS

SECONDARY ENDPOINTS
- OS
- ORR
- Safety and tolerability

EXPLORATORY OBJECTIVES
- PDL1 expression by IHC
- Circulating immune cell profile
- Bone formation and bone reabsorption markers



Respuestas: 27%
Mediana duración tratº: 4.7 m
mPFS: 7.24 m

Procopio G, et al. ASCO GU 2021. Abstract 326

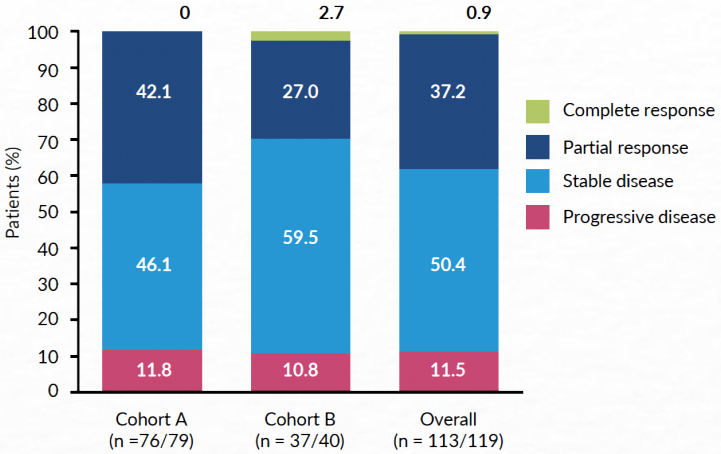
CABOPOINT

Cohorte A: tras IO/IO

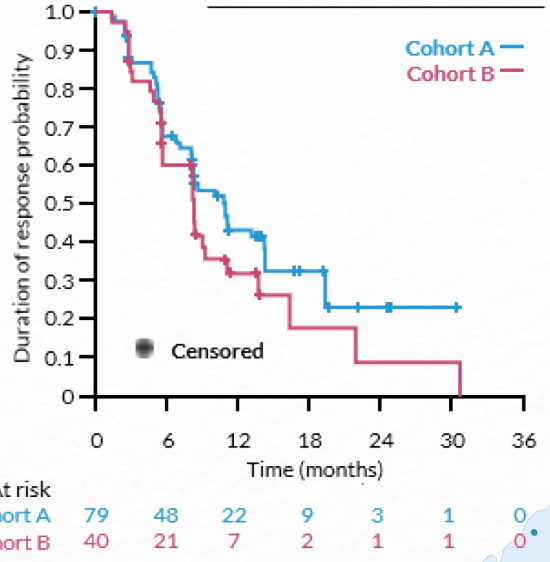
Cohorte B: tras TKI/IO

Primary endpoint: ORR and DCR by **ICR** (n=119*)

	Cohort A	Cohort B	Overall	
	79	40	119	Patients, n
p < 0.0001†	32 (40.5) 29.6–52.1	11 (27.5) 14.6–43.9	43 (36.1) 27.5–45.4	ORR, n (%) 95% CI
	67 (84.8) 75.0–91.9	33 (82.5) 67.2–92.7	100 (84.0) 76.2–90.1	DCR, n (%) 95% CI

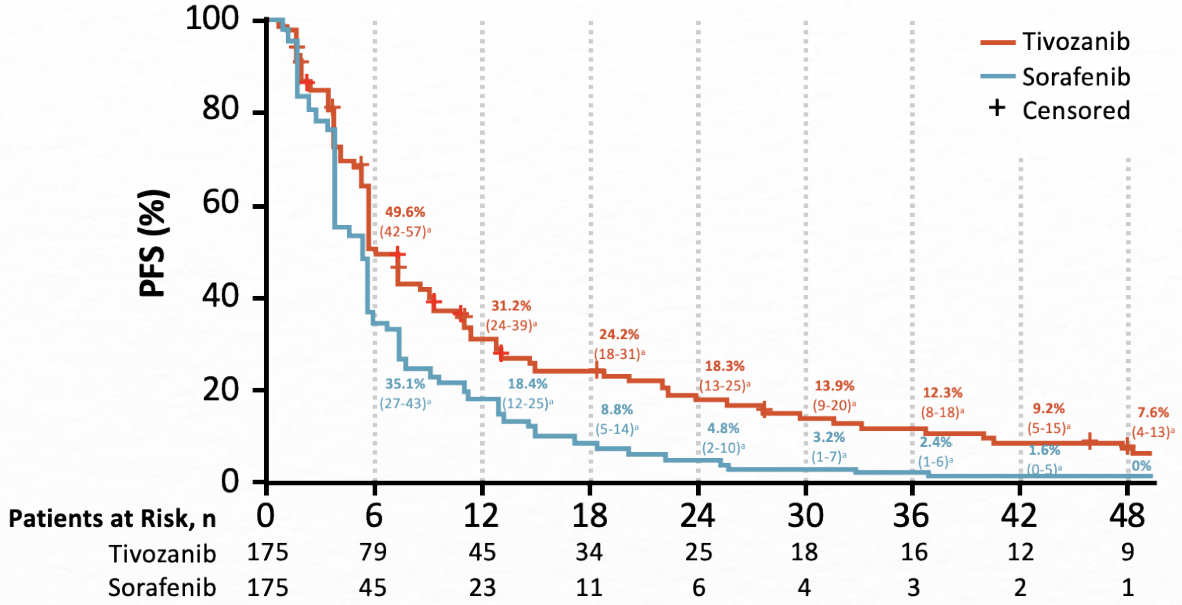


	Median PFS (IQR)
Cohort A*	10.9 (5.5–19.4)
Cohort B*	8.3 (5.4–16.4)



Albiges. ESMO 2024

TIVO-3: Tivozanib frente a sorafenib para el CCR avanzado tras terapia con TKI (se permitía IO previa)



- Overall, **26%** of patients received previous therapy with an ICI + TKI
- ORR: 18% with tivozanib vs 8% with sorafenib
- Median PFS: 5.6 vs 3.9; 0.73 (0.56-0.94)

Tivozanib is indicated for the treatment of adult patients with relapsed or refractory advanced RCC following ≥2 prior systemic therapies.

Rini. Lancet Oncol. 2020;21:95. Atkins. ASCO GU 2022. Abstr 362.

Eficacia según tratamiento recibido en 1L

	RR tras 1L IO/IO %	RR tras 1L IO/TKI m	PFS tras 1L IO/IO %	PFS tras 1L IO/TKI m
Dudani 2019	45	15	5.4	3.7
Barata 2018	33	25	7.6	6.2
Nadal 2016	36	10	8.4	5.6
McGregor 2020	42	28	8.1 (TTF)	4.7 (TTF)
Stukalin 2020	37	12	5.4 (TTF)	4.6 (TTF)

Dudani. Eur Urol 2019;76:861-7. Barata PC. British Journal of Cancer; 2018 May 21;119(2):1–4. Nadal R. Annals of Oncology. 2016 Jun 27;27(7):1304–11. McGregor A, et al. Eu J Cancer. 2020. 135, 203-210. Stukalin. Journal of Clinical Oncology 38, no. 6_suppl (February 20, 2020) 684-684.

IO post IO?

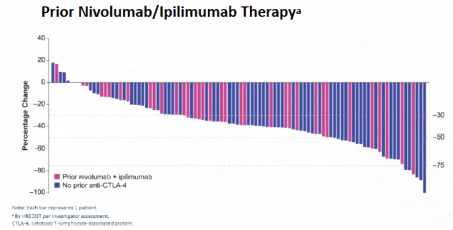
	HCRN GU 16-260	TITAN-RCC	OMNIVORE-RCC	FRACTION
n	123	207	83	46
TKI previo	No	Sí	Sí	Sí
Secuencia	Nivo -> Ipix4	Nivo -> Ipix4	Nivo-> Ipix2	Nivo+Ipix4
1ª línea; n (%)	123 (100)	109 (53%)	42 (51)	-
Tasa de respuestas *boost*	11.4%	12%	4%	15%
Respuestas completas, %	0%	6%	0%	0%

Atkins. JCO 2022; Grimm. ESMO 2022; McKay. J Clin Oncol 2020; Choueiri. ASCO 2020

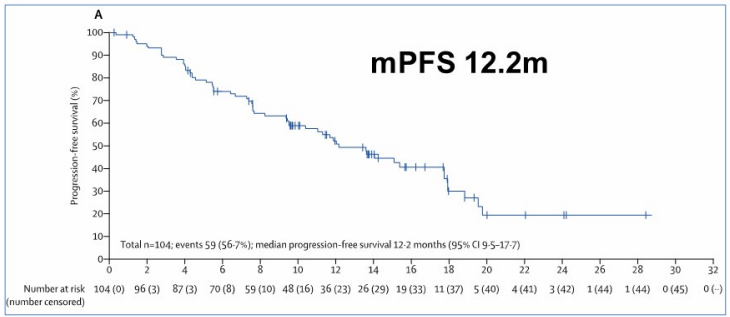
Lenvatinib/pembrolizumab (KN-146)

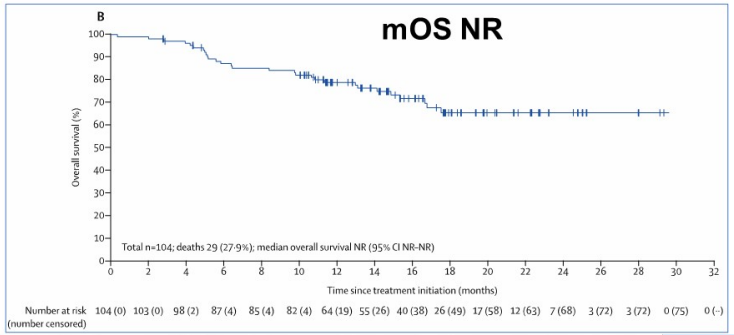
Características	N=104
Nº líneas previas	
1	39
≥2	62
Régimen previo	
Anti-PD1/PD-L1	100
Anti-PD-1/PD-L1 + antiVEGF	65
Nivo/ipi	37
Duración régimen previo (mediana)	7 m

Parámetro	IO	IO + TKI	N/I
ORR %	55	59	47
Mejor respuesta			
RP	55	59	47
SD	36	31	42
PD	5	6	8
Mediana dur resp, m	12	9	3



Lee Chung-Han et al., J Clin Oncol 38: 2020 (Abstract 5008), ASCO 2020





Lee ASCO 2021; Lee Lancet Oncol 2021

Mantener inhibición vía PD-L1

	Diseño	Tratamiento	Resultados
KN-146	Fase II ccRCC y nccRCC	Lenva/pembro	ORR 56% mDOR: 12.5 m
CONTACT-03	Fase III ccRCC y nccRCC	Atezo/cabo vs cabo	**NO** beneficio en OS, RR, PFS
TiNivo-2	Fase III ccRCC	Nivo/tizo vs tizo	Pendientes

Lee; Lancet 21. Pal; Lancet 23. Choueiri; ASCO GU 22

Vías proangiogénicas

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria
- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti−PD-1/L1 agent and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%

R (1:1)

- Belzutifan 120 mg PO QD
- Everolimus 10 mg PO QD

Safety, imaging, and survival follow-up

Stratification Factors
- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Primary End Points: PFS per RECIST v1.1 by BICR; OS
Key Secondary End Point: ORR per RECIST v1.1 by BICR
Other Secondary End Points: Safety; PROs

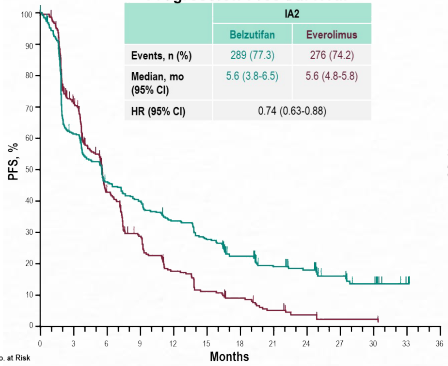
- **Median follow-up[b] at IA2: 25.7 months (range, 16.8-39.1)**

[a]Based on the number of present risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). [b]Follow-up is the time from randomization to the data cutoff date (June 13, 2023).
BICR, blinded independent central review; IA2, interim analysis 2.

Primary End Points: PFS per RECIST v1.1 by BICR and OS[1]

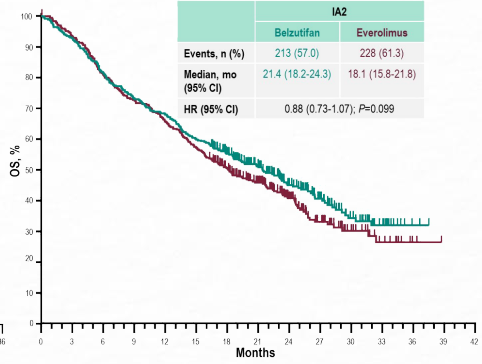
Progression-Free Survival

	IA2	
	Belzutifan	Everolimus
Events, n (%)	289 (77.3)	276 (74.2)
Median, mo (95% CI)	5.6 (3.8-6.5)	5.6 (4.8-5.8)
HR (95% CI)	0.74 (0.63-0.88)	



Overall Survival

	IA2	
	Belzutifan	Everolimus
Events, n (%)	213 (57.0)	228 (61.3)
Median, mo (95% CI)	21.4 (18.2-24.3)	18.1 (15.8-21.8)
HR (95% CI)	0.88 (0.73-1.07); *P*=0.099	



*Denotes statistical significance. Primary PFS was met at IA1 and was not formally statistically tested at IA2. 1. Albiges L et al. *Ann Oncol*. 2023;34:S1329-S1330. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

RR: 22 vs 3.5%

Powles ASCO GU 2024

Table of Contents

Trial	Treatment	Population	1° Endpoint(s)
LITESPARK-012 (NCT04736706)	Pembrolizumab + lenvatinib ± belzutifan or quavonlimab	Advanced ccRCC, no prior systemic therapy for advanced disease	PFS, OS
PROBE (NCT04510597)	Immune checkpoint inhibitor combination ± cytoreductive nephrectomy	Primary tumor + RCC metastases	OS
PDIGREE (NCT03793166)	Nivolumab + ipilimumab → nivolumab ± cabozantinib	Advanced ccRCC, no prior systemic therapy for advanced disease	OS

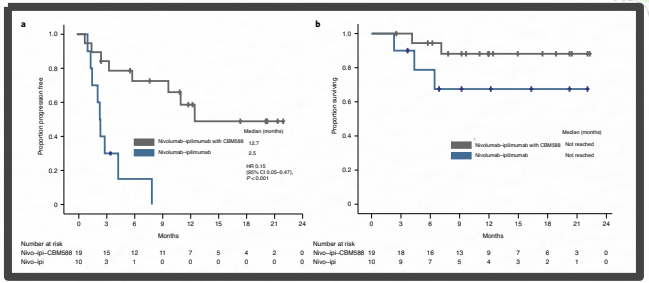
CBM-588 + nivo/ipi

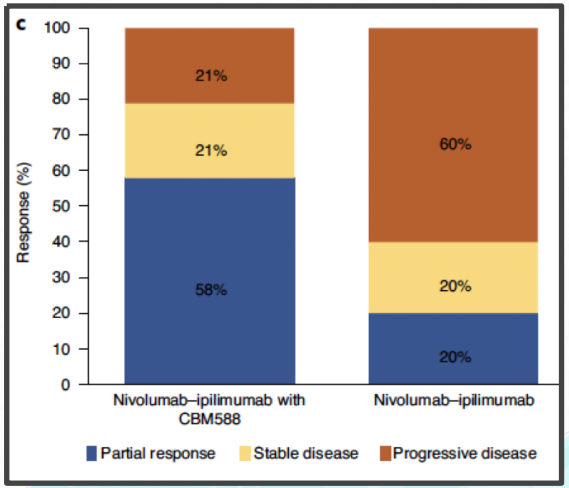
Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- Clear cell and/or sarcomatoid component
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No active autoimmune disease or receiving high dose steroids

2:1 Randomization

Nivolumab 3 mg/kg IV every 3 weeks x 4
+ Ipilimumab 1 mg/kg IV every 3 weeks x 4
→ Nivolumab 480 mg IV monthly
+
CBM-588 80 mg oral twice daily

Nivolumab 3 mg/kg IV every 3 weeks x 4
+ Ipilimumab 1 mg/kg IV every 3 weeks x 4
→ Nivolumab 480 mg IV monthly





The primary endpoint to compare the relative abundance of *Bifidobacterium* spp. at baseline and at 12 weeks was not met.

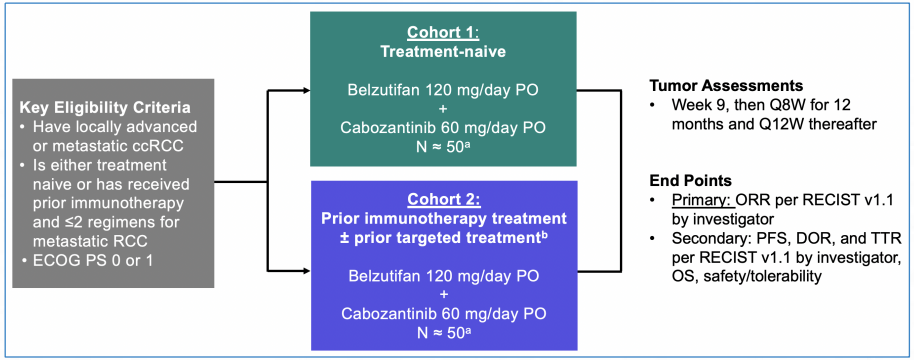
PFS 12.7 m vs 2.5 m (HR 0.15, *P* = 0.001).

RR 58% versus 20% (*P* = 0.06).

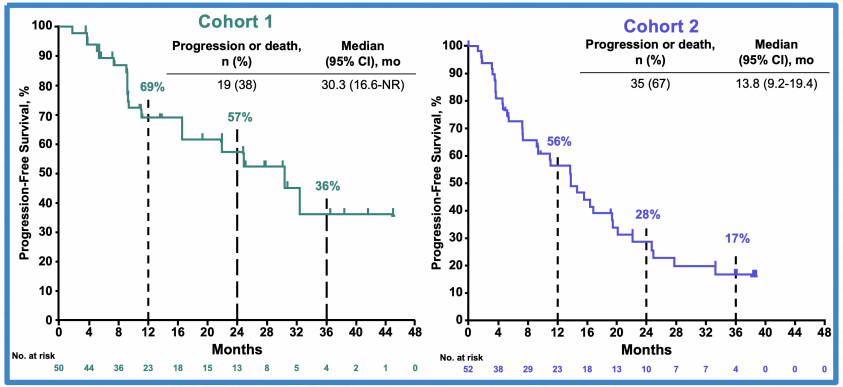
Dizman. Nat Med. 2022 Apr;28(4):704-712

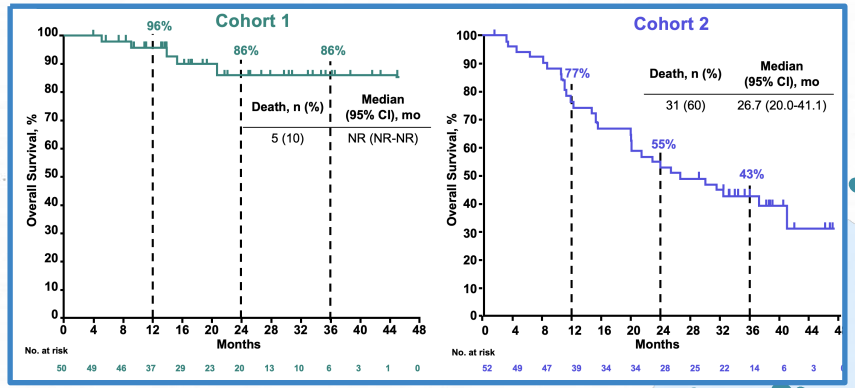
Vías proangiogénicas

Litespark-003: belzutifan+cabozantinib



	Cohort 1			Cohort 2		
	Overall N = 50	IMDC risk category		Overall N = 52	IMDC risk category	
		Favorable n = 28	Intermediate/ poor n = 22		Favorable n = 11	Intermediate/ poor n = 41
ORR (CR + PR)	**35 (70)**	22 (79)	13 (59)	**16 (31)**	3 (27)	13 (32)
DCR (CR + PR + SD)	49 (98)	28 (100)	21 (96)	48 (92)	11 (100)	37 (90)
Best response						
CR	4 (8)	3 (11)	1 (5)	2 (4)	0	2 (5)
PR	31 (62)	19 (68)	12 (55)	14 (27)	3 (27)	11 (27)
SD	14 (28)	6 (21)	8 (36)	32 (62)	8 (73)	24 (59)
PD	1 (2)	0 (0)	1 (5)	3 (6)	0 (0)	3 (7)
Not available[a]	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)

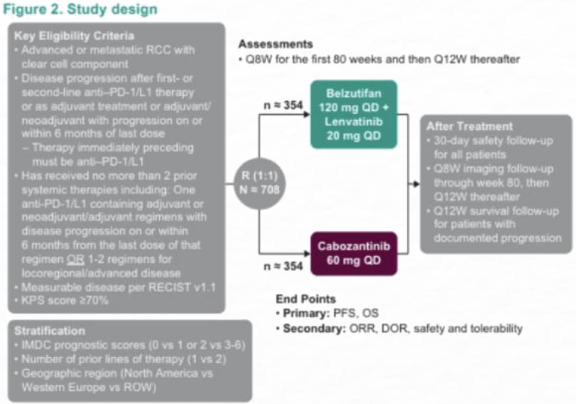




Choueiri TK, ESMO 2023

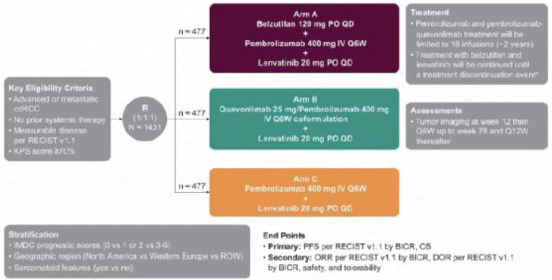
Vías proangiogénicas

LITESPARK-011 – Phase 3 Belzutifan + Lenvatinib versus Cabozantinib



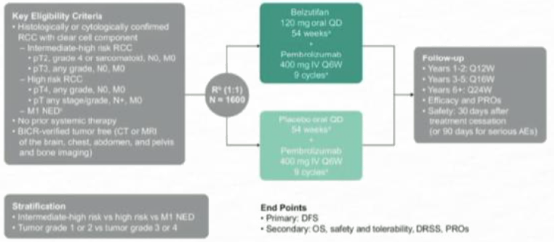
Enrollment Closed!
Primary Completion 12/23/2024

LITESPARK-012 – Phase 3 Combination Belzutifan in Front Line



Enrollment Closed!
Primary Completion 06/11/2027

LITESPARK-022 – Phase 3 Belzutifan + Pembrolizumab in Adjuvant

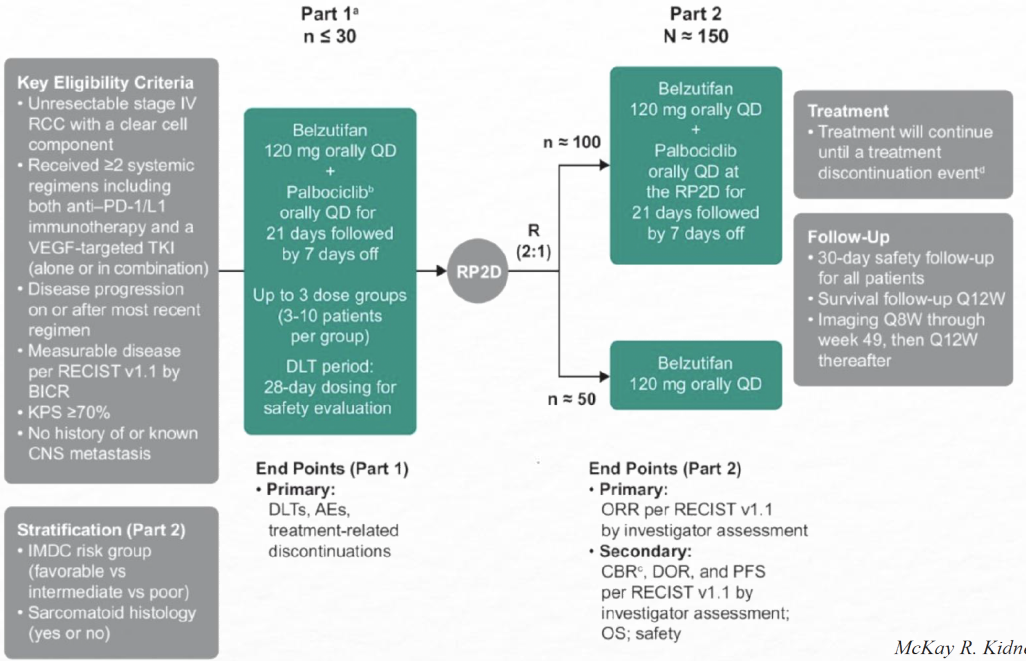


Enrollment Closed!
Primary Completion 10/28/2026

Trial in progress

Palbociclib in combination

LITESPARK-024: phase 1/2 study of belzutifan with or without palbociclib for treatment of aRCC

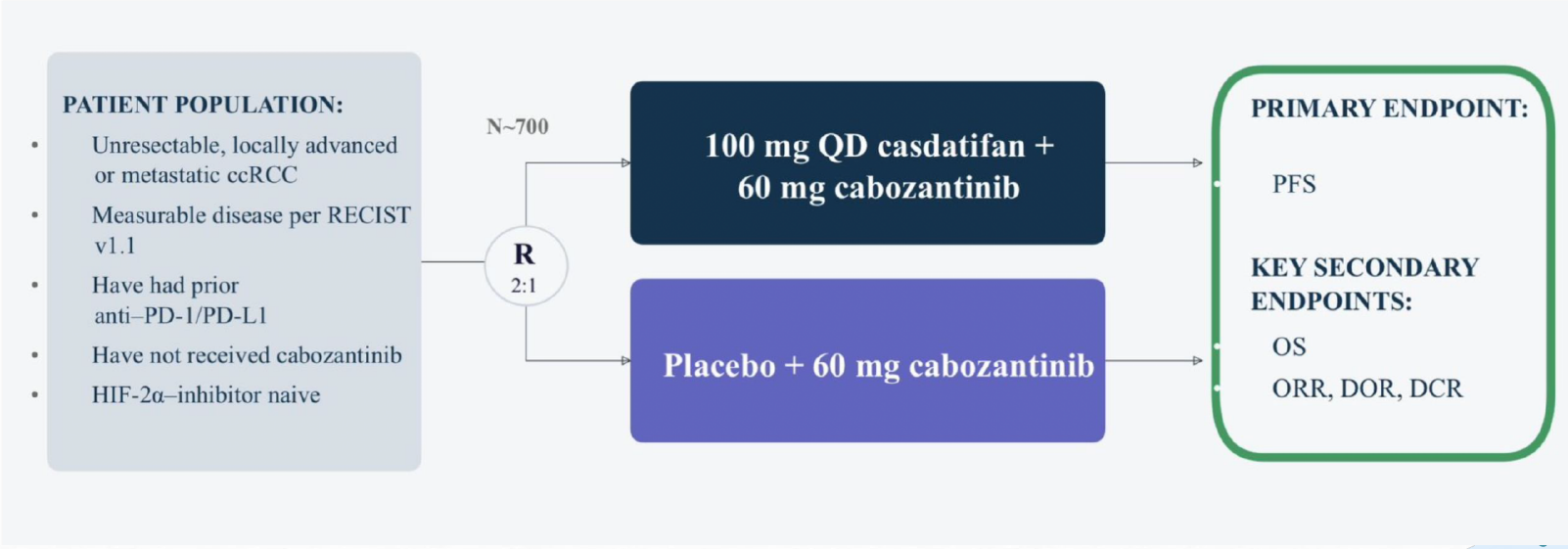


McKay R. Kidney Cancer Research Summit 2024.

Inhibidor HIF 2ª oral

PEAK-1: phase 3, casdatifan + cabozantinib

in advanced or metastatic ccRCC, following prior PD-1 therapy



Biomarcadores: KIM-1

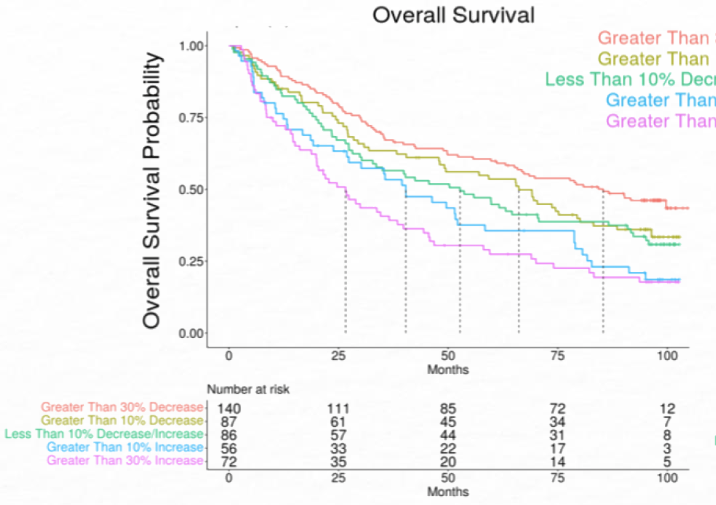
- KIM-1 es una proteína transmembrana que se sobreexpresa en el CCR de células claras. El ectodominio de KIM-1 es detectable en plasma y suero y es un biomarcador circulante emergente para el CCR de células claras.

- El KIM-1 se midió al inicio del estudio y 3 semanas después de la primera dosis de Nivo+Ipi (antes de la segunda dosis) utilizando electroquimioluminiscencia enzimática.

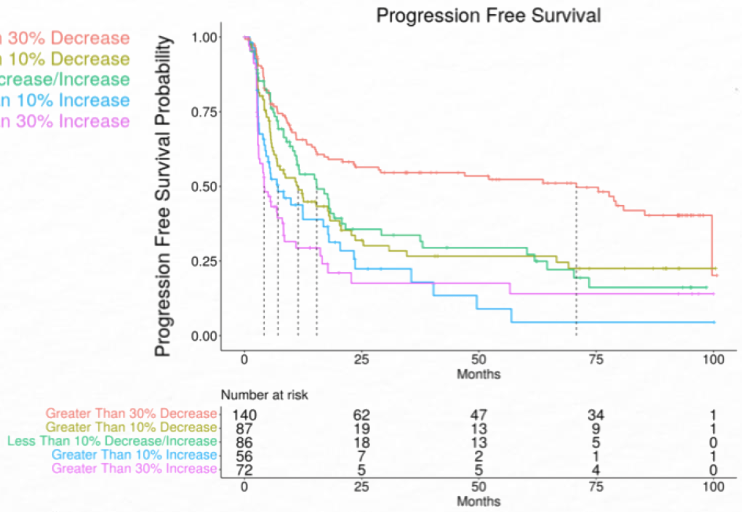
Xu et al. RCC. CM214. KIM-1 as predictive and prognostic biomarker in 1L aRCC. ASCOGU2025. Oral

Biomarcadores: KIM-1

KIM-1 en el CheckMate 214



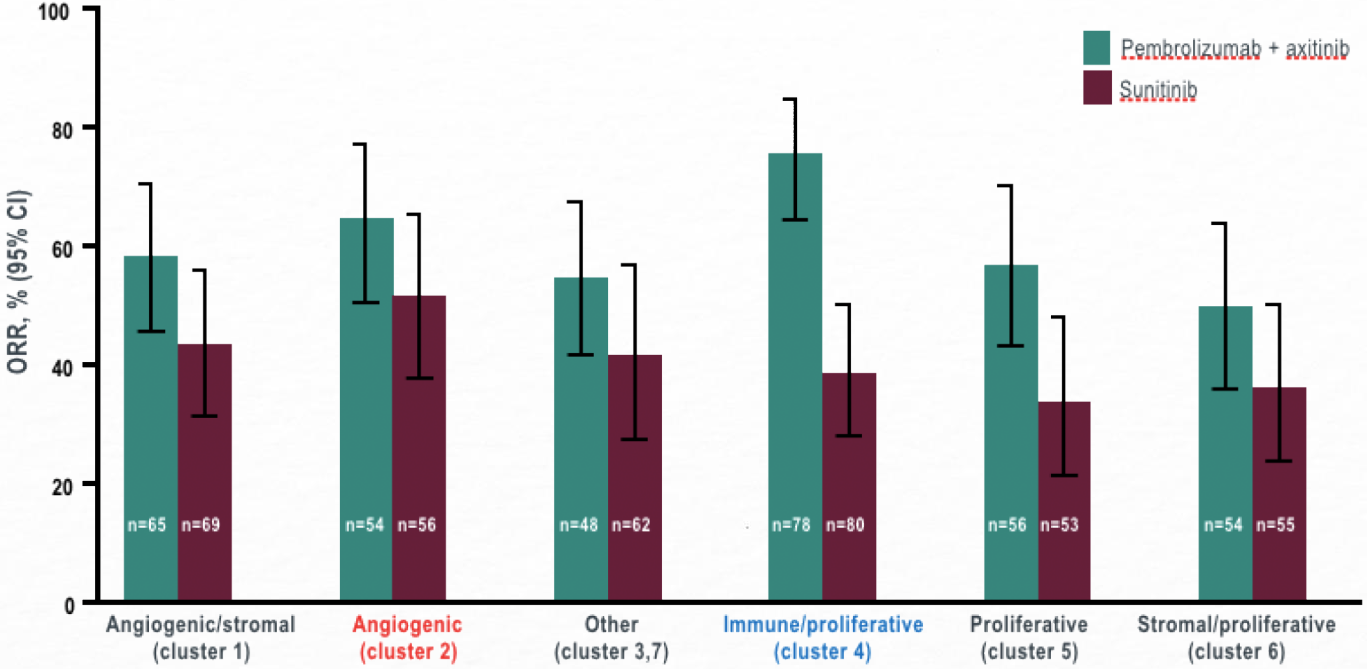
	HR (95% CI)
> 30% Decrease	1.00
> 10% Decrease	1.33 [0.93-1.88]
< 10% Change	1.48 [1.05-2.09]
> 10% Increase	1.99 [1.36-2.91]
> 30% Increase	**2.40 [1.70-3.40]**



	HR (95% CI)
> 30% Decrease	1.00
> 10% Decrease	1.81 [1.27-2.57]
< 10% Change	1.68 [1.17-2.40]
> 10% Increase	2.59 [1.75-3.82]
> 30% Increase	**3.06 [2.11-4.44]**

Xu et al. RCC. CM214. KIM-1 as predictive and prognostic biomarker in 1L aRCC. ASCOGU2025. Oral

Biomarcadores



1. *Rini B et al. Presented at ASCO 2024; abstract 4505.* ***2.*** *Motzer RJ et al. Cancer Cell. 2020;38(6):803–817.*

Girentuximab: teragnosis

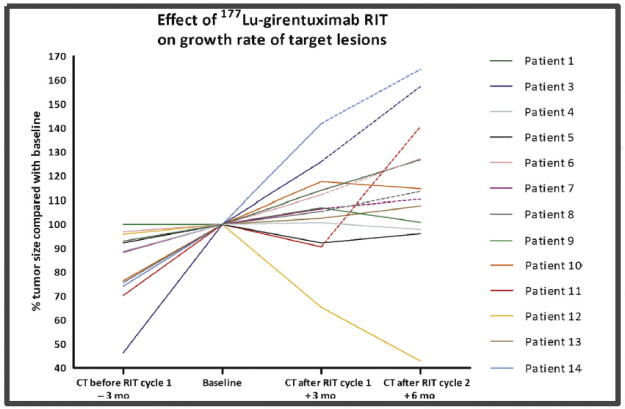
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Phase 2 Study of Lutetium 177–Labeled Anti–Carbonic Anhydrase IX Monoclonal Antibody Girentuximab in Patients with Advanced Renal Cell Carcinoma

Constantijn H.J. Muselaers [a,b,1,], Marye J. Boers-Sonderen [c,1], Tim J. van Oostenbrugge [a,b], Otto C. Boerman [b], Ingrid M.E. Desar [c], Alexander B. Stillebroer [a], Sasja F. Mulder [c], Carla M.L. van Herpen [c], Johan F. Langenhuijsen [a], Egbert Oosterwijk [a], Wim J.G. Oyen [b], Peter F.A. Mulders [a]*



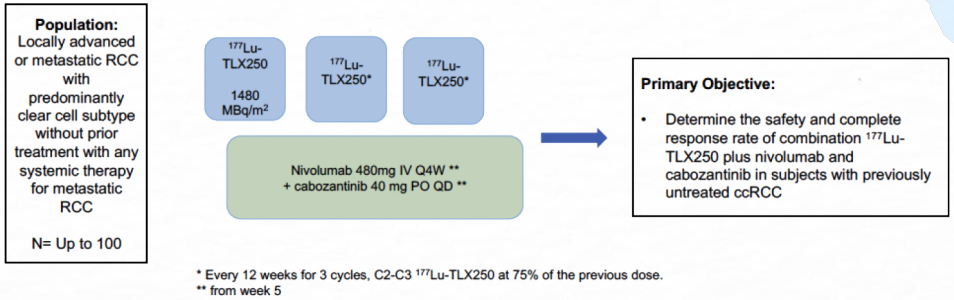
Eficacia de la radioinmunoterapia con lutecio 177-girentuximab en pacientes con cáncer renal metastásico pretratado.

El tratamiento produjo la estabilización de la enfermedad en 9 de 14 pacientes.

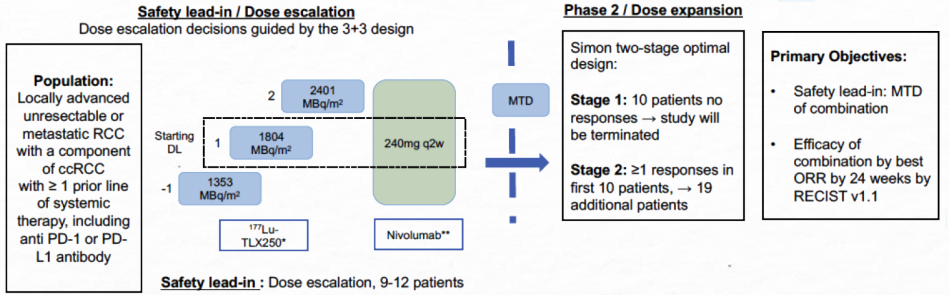
La principal toxicidad fue el recuento prolongado de células sanguíneas bajas.

177Lu-girentuximab

STARLITE 1: TLX250 + cabozantinib + nivolumab, single-arm phase 2 study



STARLITE 2: TLX250 + nivolumab, single-arm dose escalation and phase 2



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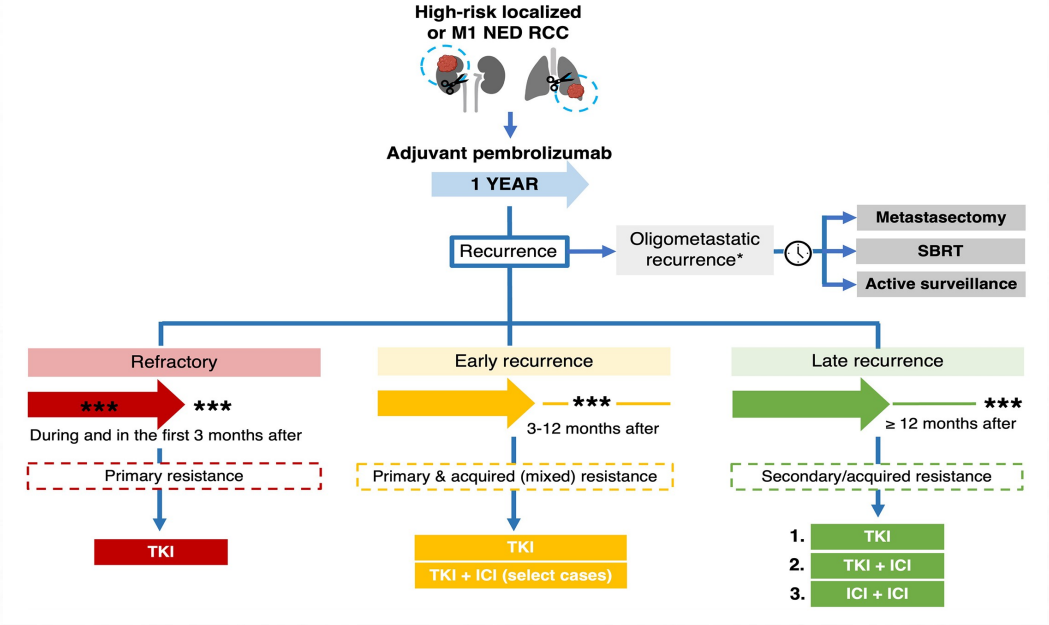
Algoritmo propuesto sobre cómo tratar el CCR recurrente tras pembrolizumab adyuvante



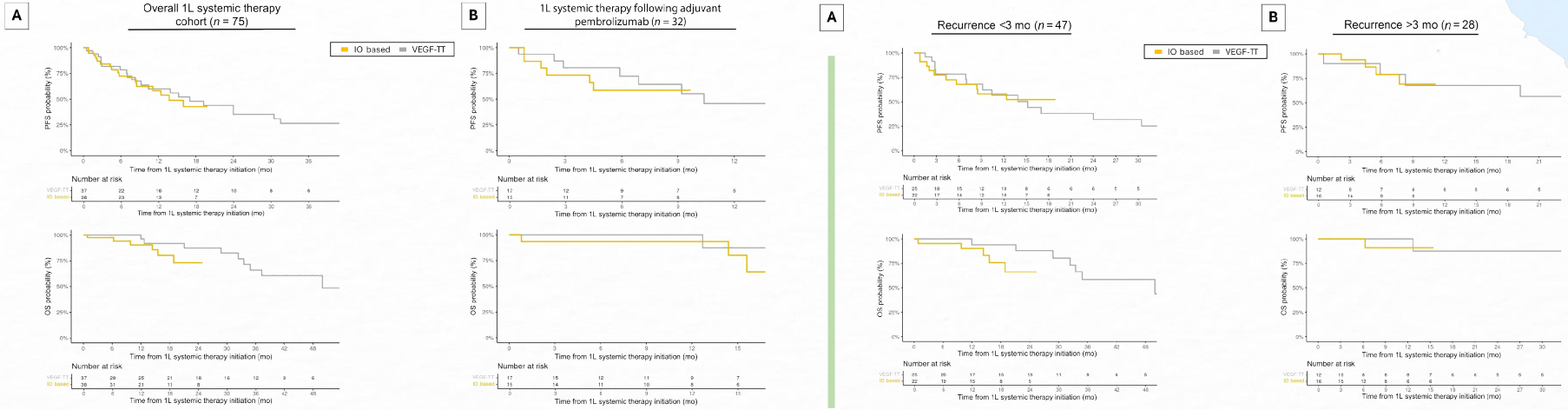
MT.Bourlon; P.Valdez; T.Choueiri and E.Lam. Using Clinical Characteristics to Guide Treatment of Recurrent RCC After Adjuvant Pembrolizumab. ASCO Daily news January 10, 2024

Society for Immunotherapy of Cancer

Table 3 Resistance definitions for the adjuvant setting

Resistance phenotype	Time from adjuvant therapy discontinuation
Primary resistance in the adjuvant setting	≤12 weeks or recurrence on therapy
Undeterminable	>12 weeks

First-line Systemic Therapy Following Adjuvant Immunotherapy in Renal Cell Carcinoma: An International Multicenter Study



El Zarif. Eur Urol 2024;86:503

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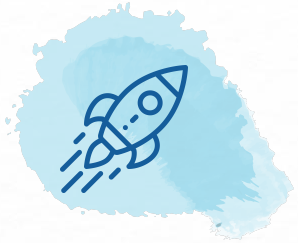
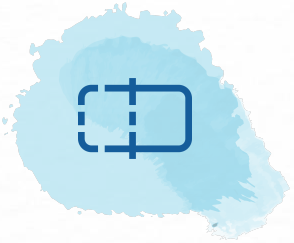
CONCLUSIONES



IO en 1ª línea

Combos IO/IO vs IO/TKI

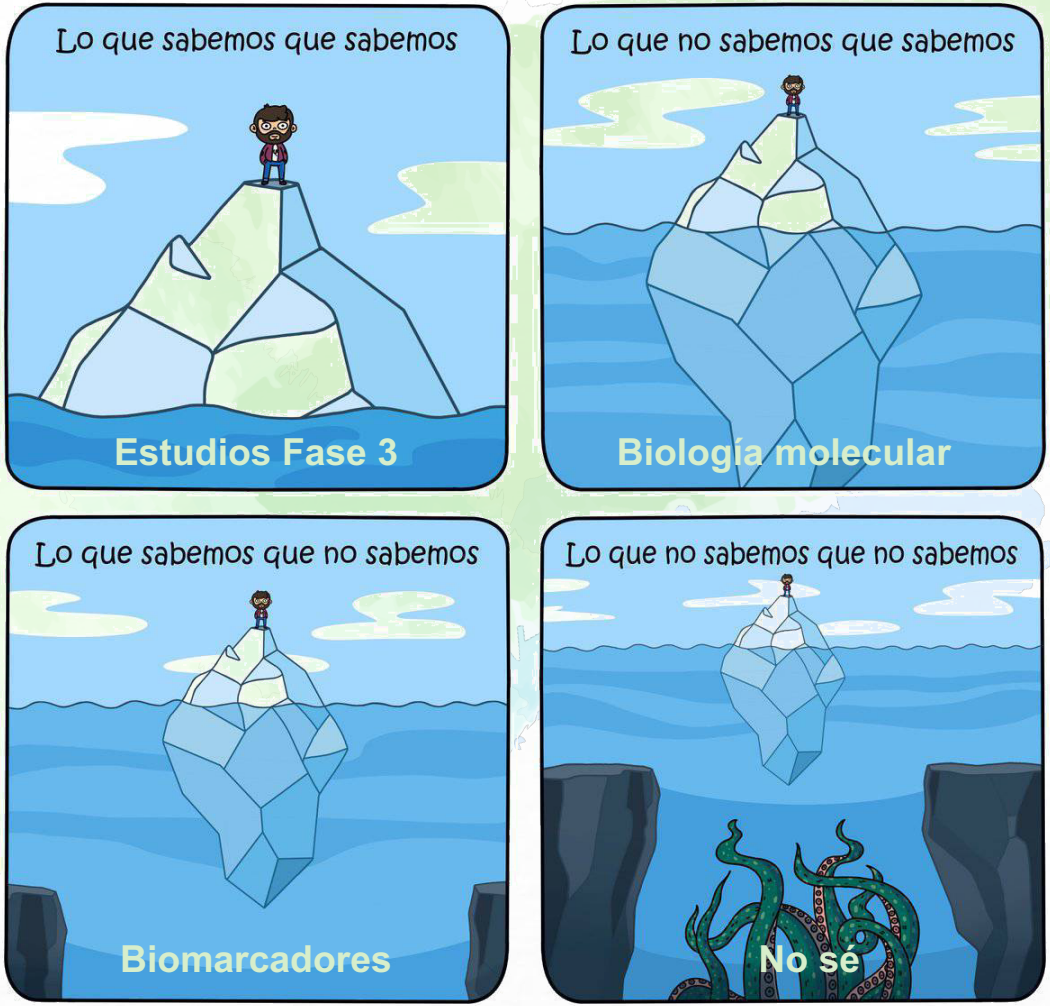


En 2ª línea

TKI no usado en 1L
Cabozantinib
ICI tras ICI: no eficaz

Lo de siempre

¡¡Necesitamos biomarcadores!!


Lo que sabemos que sabemos
Estudios Fase 3
Lo que no sabemos que sabemos
Biología molecular
Lo que sabemos que no sabemos
Biomarcadores
Lo que no sabemos que no sabemos
No sé