ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE **2024**

Madrid, 28 de febrero de 2024

Secuenciación terapéutica en cáncer renal

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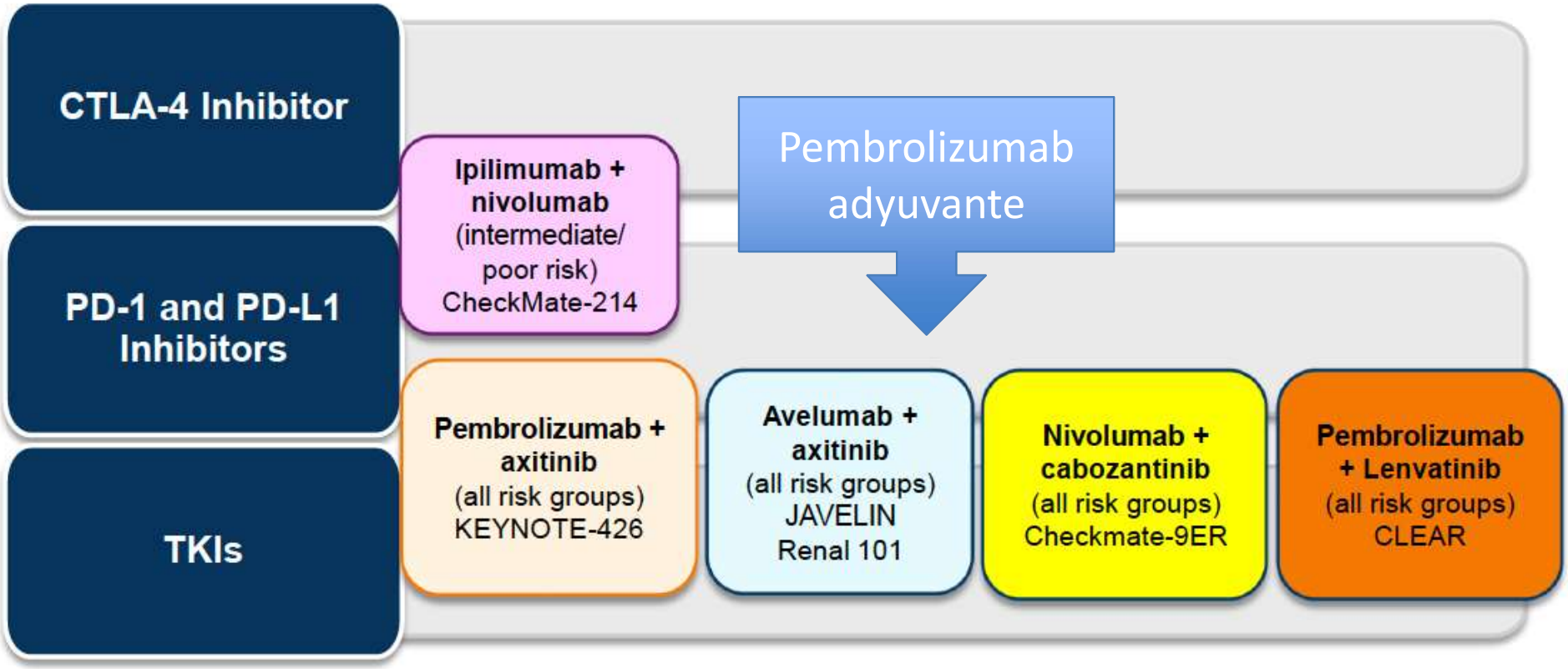
Conflictos de interés

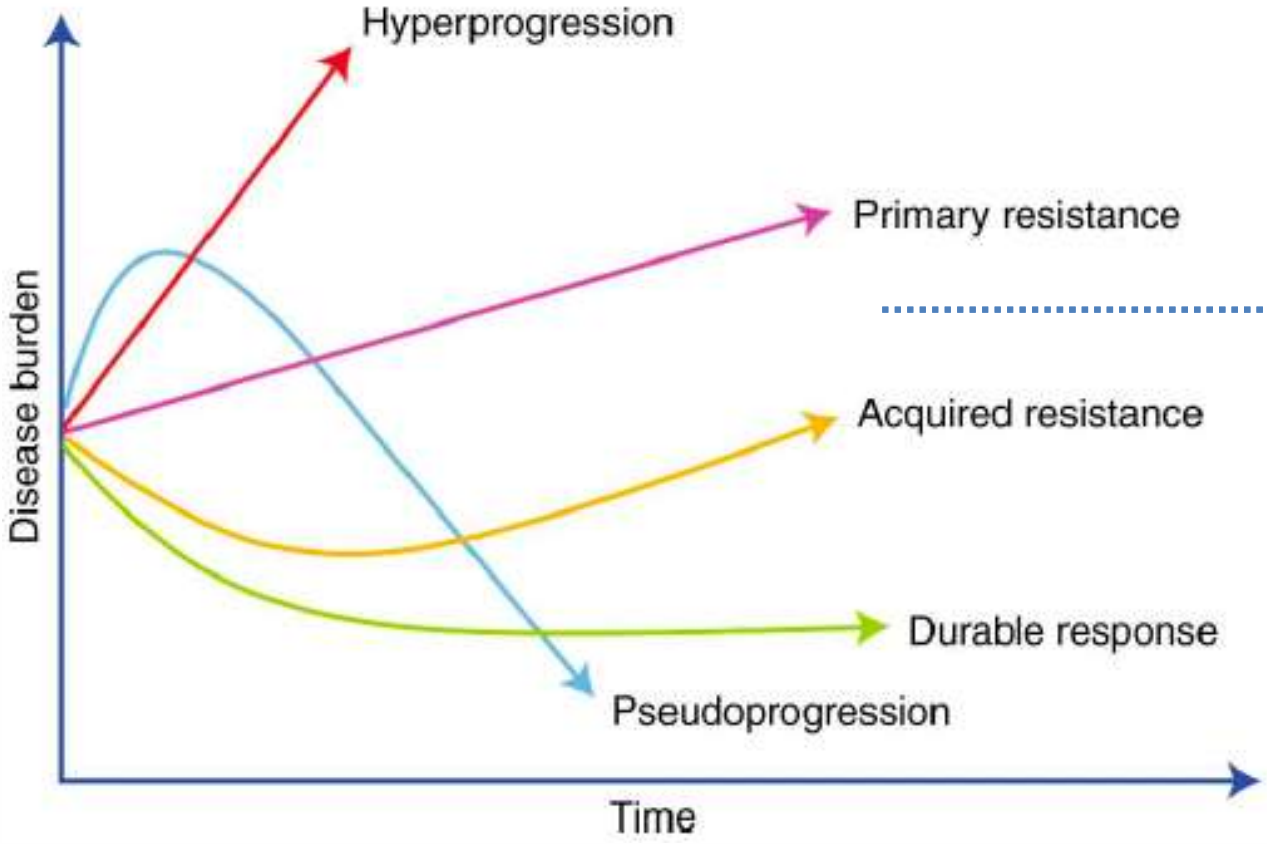
- He participado en reuniones médicas organizadas por Janssen, Pfizer, Eisai, Sanofi, AstraZeneca, Astellas, Roche, MSD.

- He participado como consultora en: Janssen y Astellas

Panorama de la primera línea



Patrones de progresión



6 meses de 1ªlínea
12 sem tras ady❓

Baxter MA, et al. Br J Cancer 2021

¿Qué hacemos después de las combinaciones?

¿Qué dicen las guías?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Kidney Cancer

NCCN Guidelines Index
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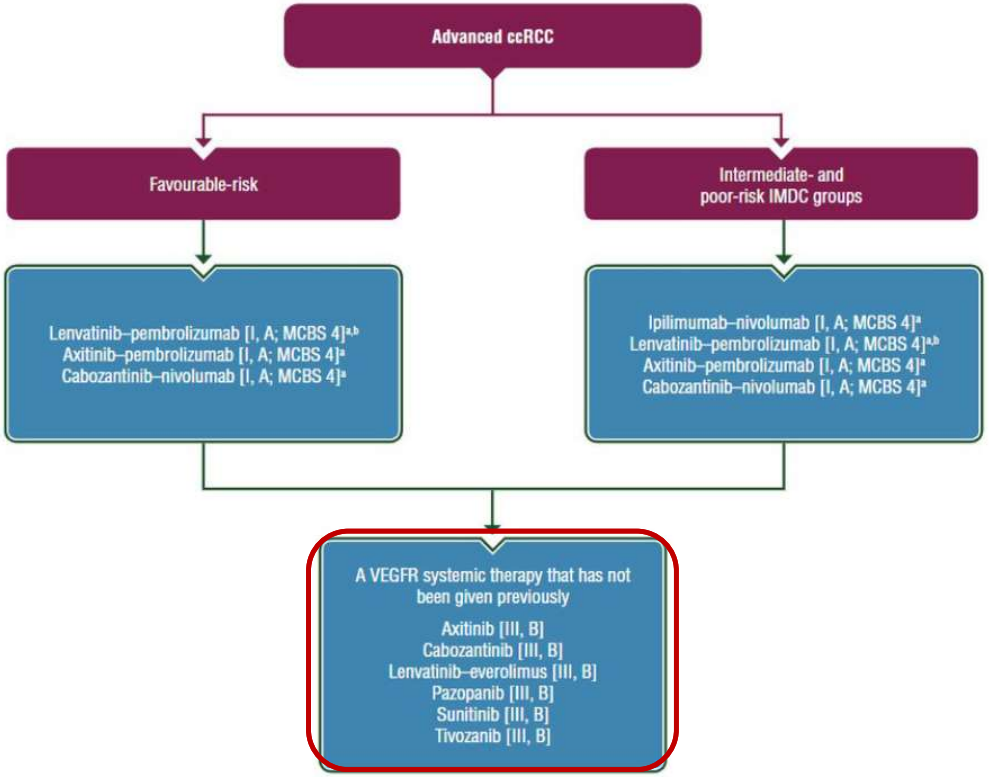
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[g] • Belzutifan (category 2B) • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[f] • Cabozantinib • Lenvatinib + everolimus • Tivozanib[g]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

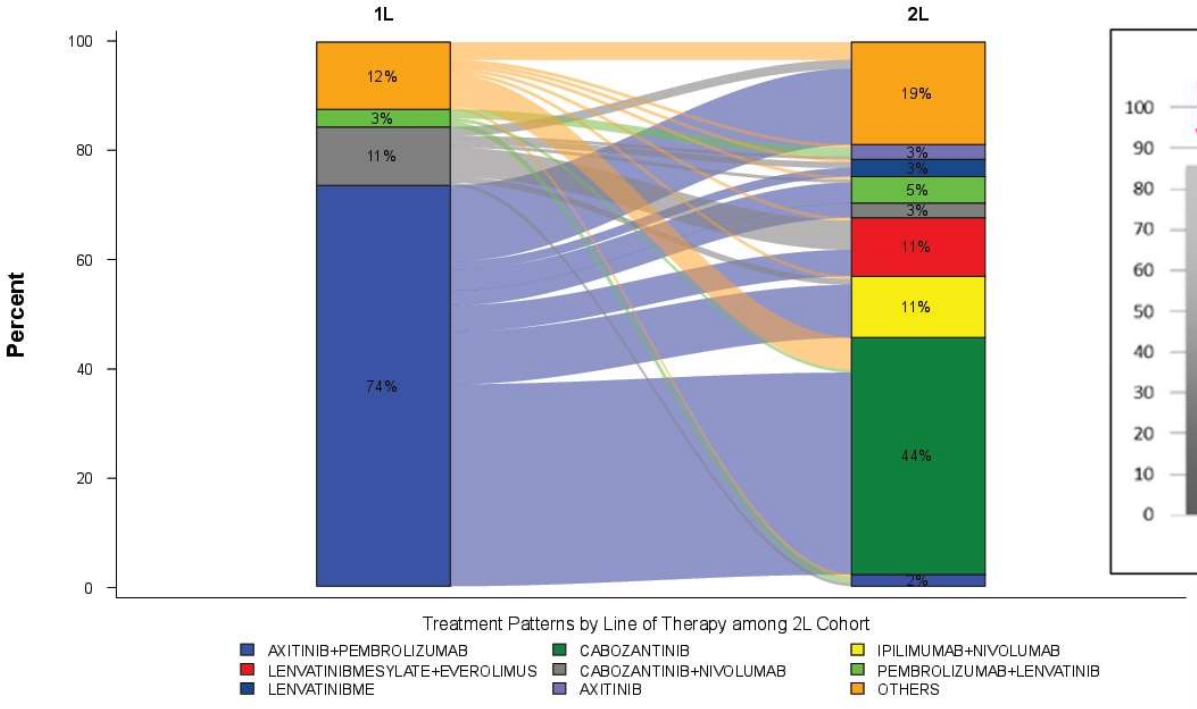
¿Qué dicen las guías?

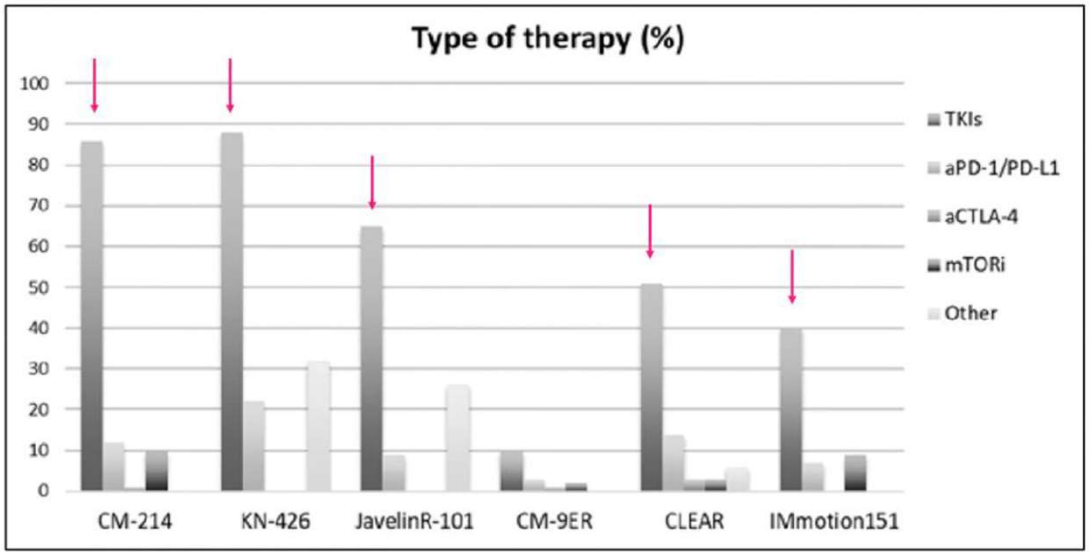


	Standard of care	Alternative
Prior IO	Any VEGF-targeted therapy that has not been used previously in combination with IO [4]	
Prior TKI	nivolumab [1b] cabozantinib [1b]	axitinib [2b]

ESMO Guidelines 2024; EAU Guidelines 2024

¿Qué hacemos en la práctica clínica?





Shah N, et al. ASCO GU 2024; Lacovelli R, et al. CancerTreatRev2022 Apr 105:102379

¿Qué evidencia tenemos de TKI tras IO?

Tras TKI e IO secuencial: ESTUDIOS RETROSPECTIVOS

Treatment	N	mPFS, mo	ORR, %
TKI[1]	70	6.4	28
TKI (Cabozantinib/Axitinib)[2]		8	33
TKI (sun, axi, pazo, ca			36
TKI (sun, axi, paz			41
TKI (post: CPI+VEG		F)	15 vs 45
Pazopa			Not reported
Cabozant			36
Cabozantini		)	22
Cabozantinib vs other		1 (mTTD)	54 vs 38
Cabozantinib[10]		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

ORR: 20-54%
PFS or TTF
6-13 months

1.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 2021; 9.Marteau F, ASCO GU; 2021 10.Zhang H, Kidney Cancer 2021; 11.Wiele AK, Oncologist 2021; 12.Graham J, Eur Urol Oncol 2021.

Tras TKI e IO secuencial: ESTUDIOS PROSPECTIVOS

DRUG	STUDY	N	ORR (%)	PFS
Cabozantinib	Post-Hoc **METEOR**	18	22	Not reached
Tivozanib	Post		ported	7.3
Axitinib				8.8
Cabozantinib				9.3
Sunitinib				5.6
Cabozantinib (Teleglenestat)				9,2
Cabozantinib	Phase II Ca		30 Prev IO-IO: 33 Prev IO-TKI: 28	Short follow-up
Cabozantinib (Atezolizumab)	Phase III **CONTACT-03**	259	41	10.8

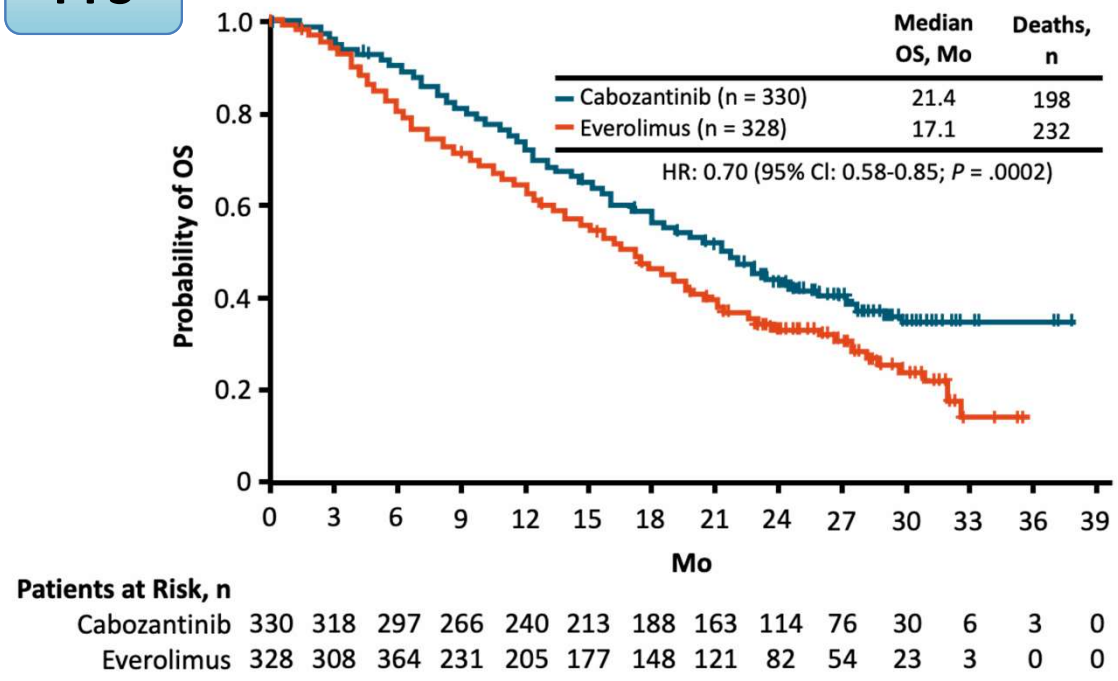
ORR: 19-45%
PFS or TTF
5.6-9.3 months

Powles T, British Journal of Cancer 2018; Rini BI, Lancet Oncol 2020; Omstein MC, Lancet Oncol 2019; Procopio G, ASCO 2022; Grande E, Annals Oncol 2022, Tannir N ASCO 2021 Abs 4105, Albiges et al, ASCOGU23, Abst 606; Choueri T, LBA4500. ASCO 2023

CABOZANTINIB

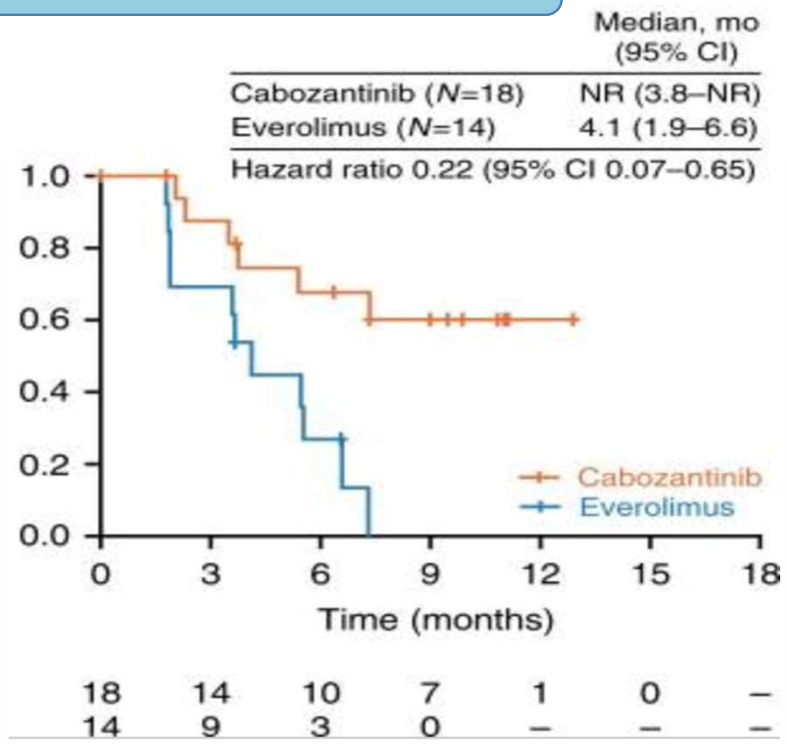
METEOR Trial: Fase III Cabozantinib vs Everolimus tras TKI

PFS



ORR global **17%** con cabo vs 3% con eve

PFS del 5% de IO previa

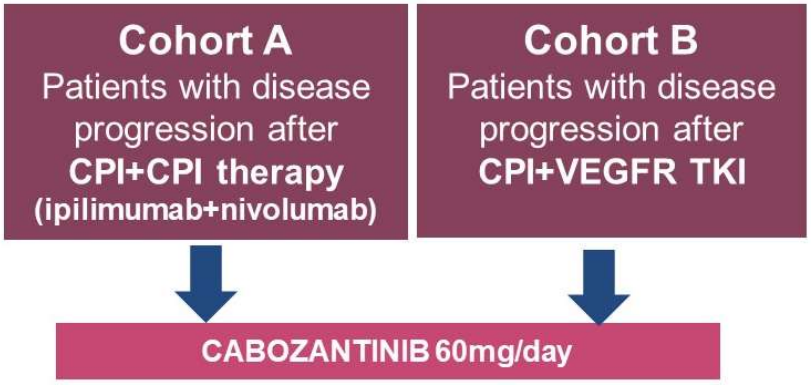


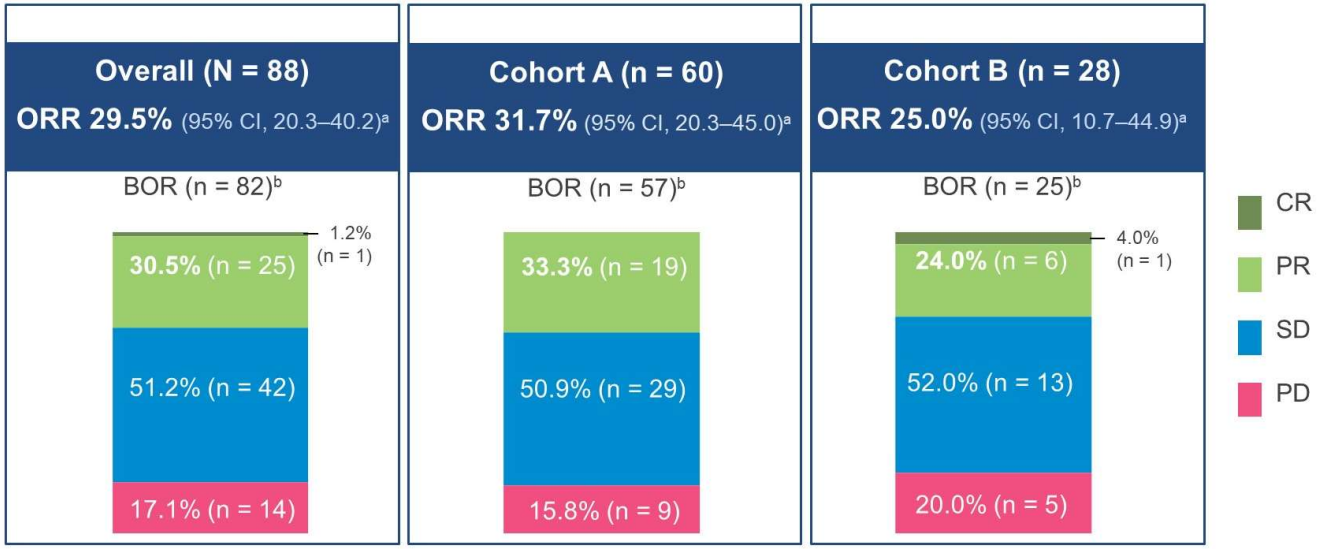
Motzer. Br J Cancer. 2018;118:1176.

CABOZANTINIB

CaboPoint: Fase II Cabozantinib tras IO (ongoing)

ORR (obj 1º)





Albiges. GU ASCO 2023. Abstr 606.

TIVOZANIB

TIVO-3: Fase III con Tivozanib vs Sorafenib tras TKI (+/-IO)

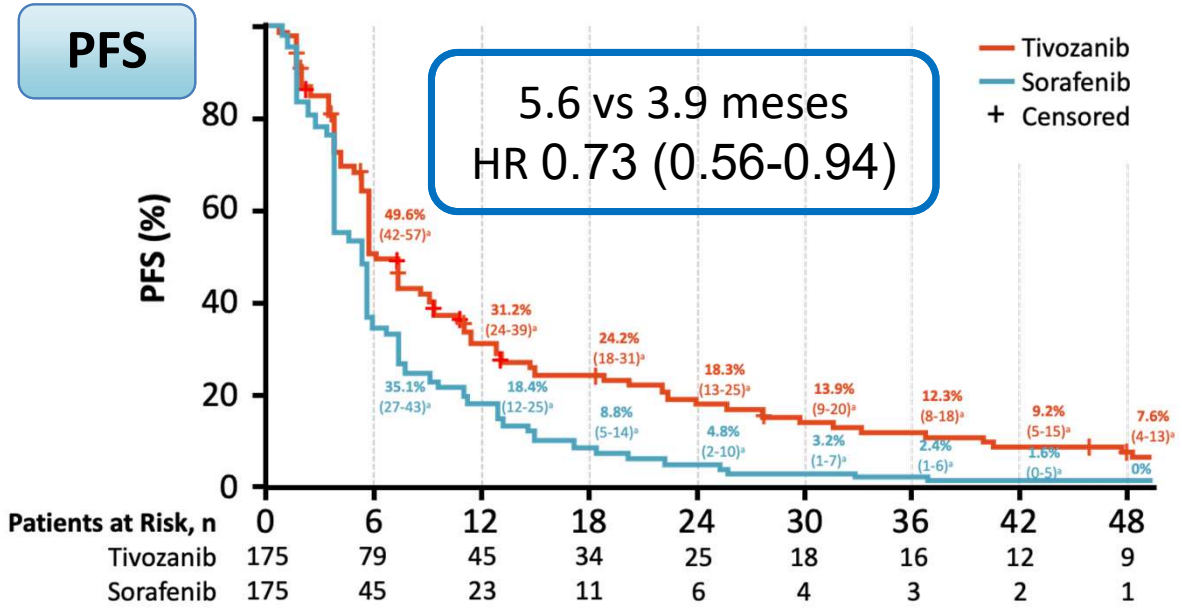
- ≥2 líneas previas (≥1 TKI)

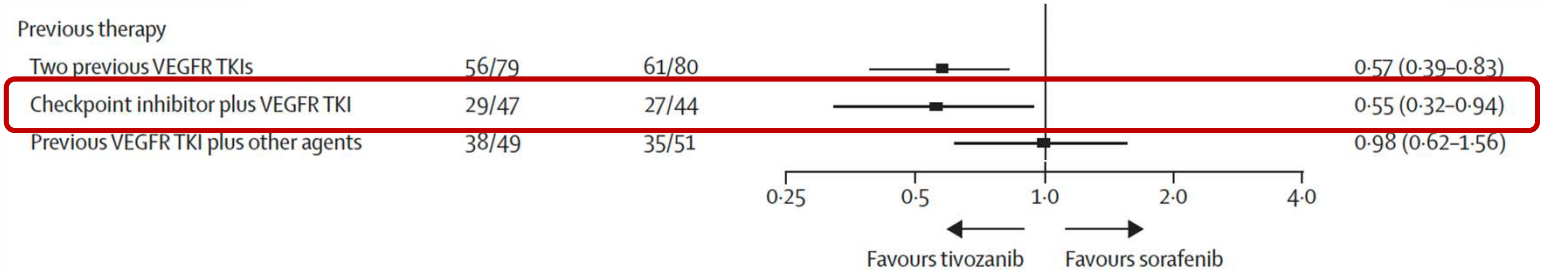
  → **26% TKI e IO previa**

- **ORR**: 18% vs 8%

PFS

5.6 vs 3.9 meses
HR 0.73 (0.56-0.94)



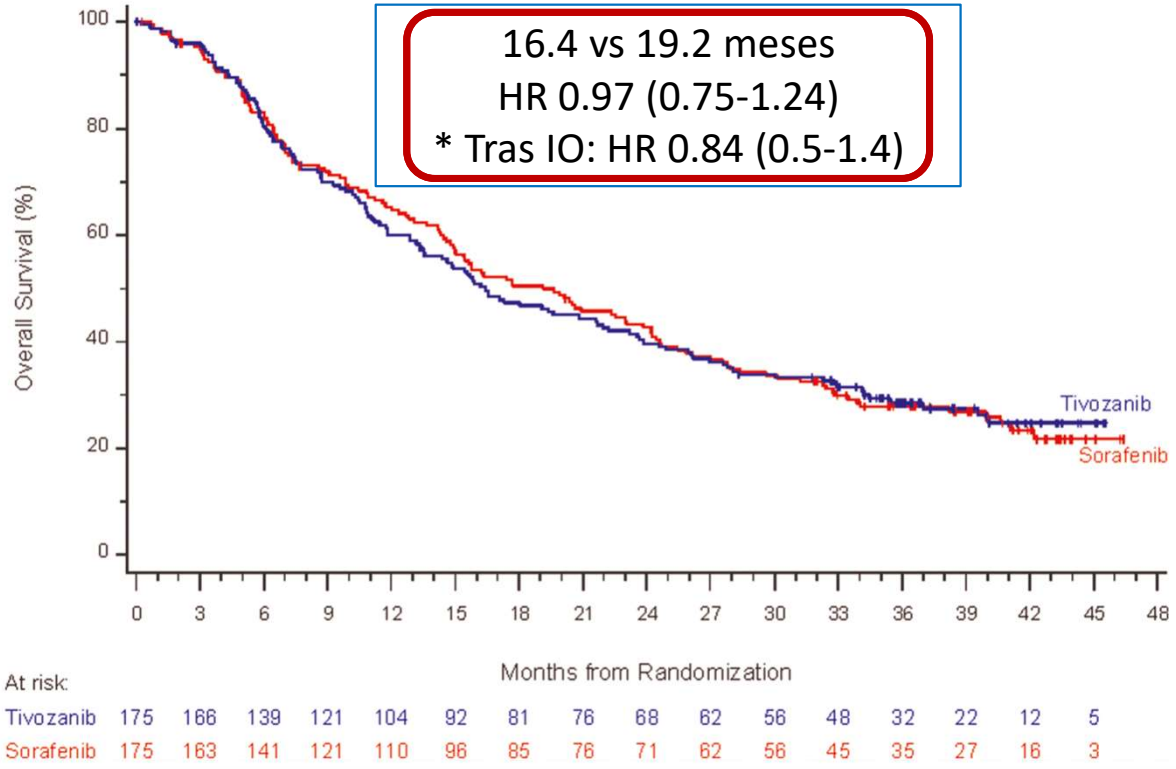


Motzer. Lancet Oncol. 2015;16:1473.

TIVOZANIB

TIVO-3: Fase III con Tivozanib vs Sorafenib tras TKI (+/-IO)

OS



16.4 vs 19.2 meses
HR 0.97 (0.75-1.24)
* Tras IO: HR 0.84 (0.5-1.4)

Crossover permitido (no cuantificado)

Menos AEs gr 3-4 con Tivozanib

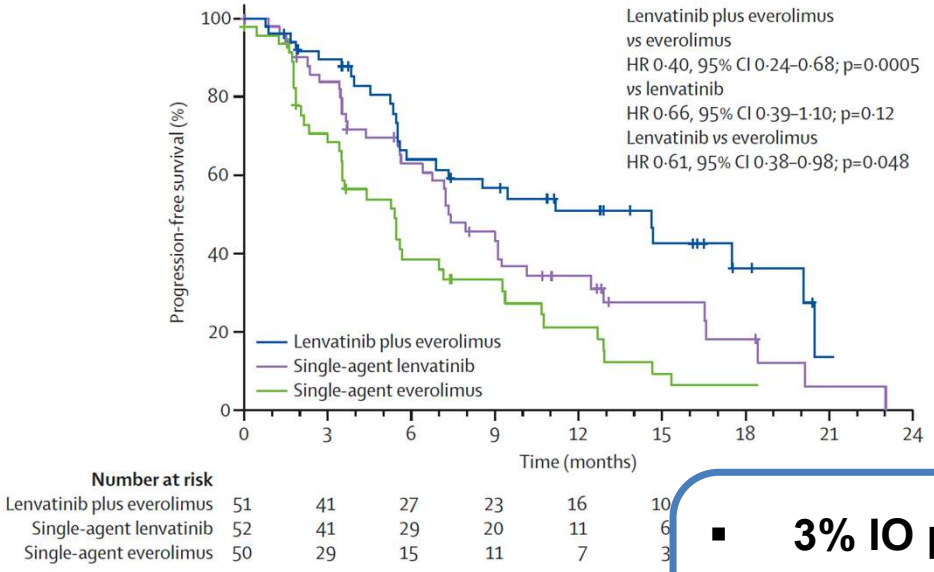
- Interrupción de tratamiento: 48% vs 63%
- Reducción de dosis por Aes: 24% vs 38%

Pal S et al. Eur Urol 2020.

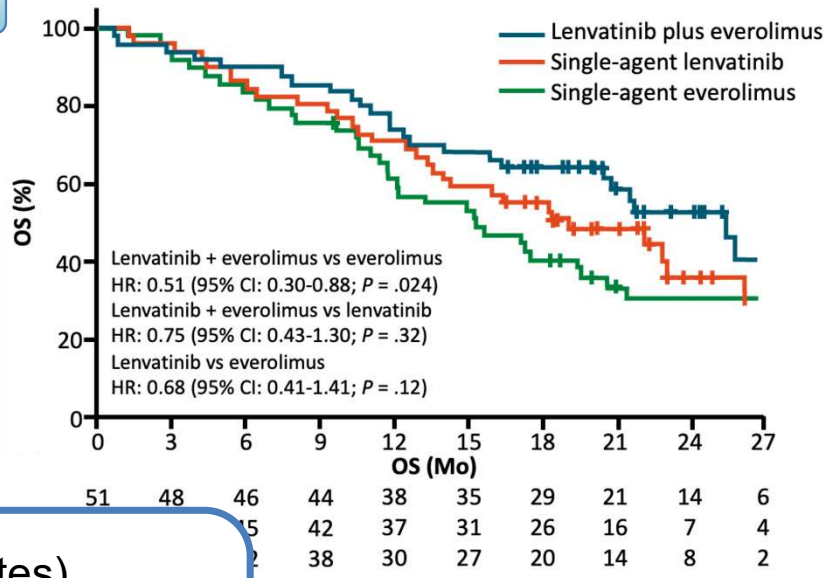
LENVATINIB + EVEROLIMUS

Fase II randomizado Lenva, Eve o Lenva/eve tras TKI

PFS



OS



- **3% IO previa** (5 pacientes)
- **ORR**: 43% con lenva/eve, 27% con lenva, 6% con everolimus

Motzer. Lancet Oncol. 2015;16:1473.

¿Tiene sentido continuar la IO a la progresión?

ACTUALIZACIÓN EN **URO-ONCOLOGÍA:**
UPDATE **2024**

¿Podemos rescatar con Ipi a la progresión a anti PD1/PDL1?

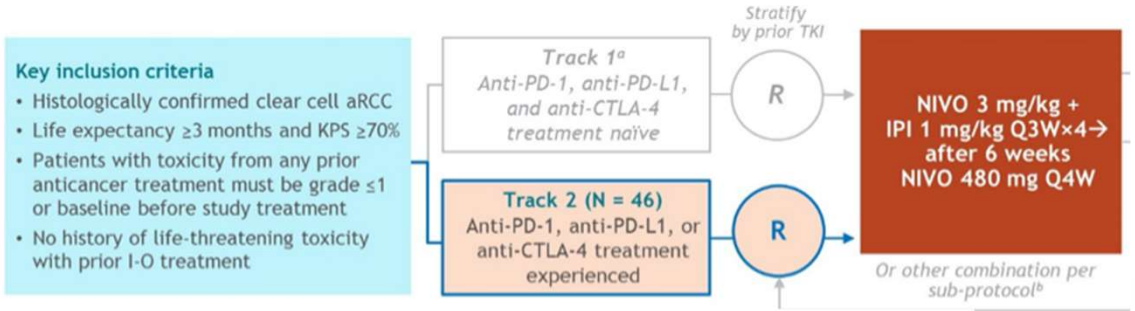
Rescate con Ipi en 1ª línea

	HCRN GU16-260[1]	TITAN-RCC[2]	OMNIVORE-RCC[3]
N	123	207	83
Previous TKI allowed	No	Yes	Yes
First line (n(%))	123 (100)	108 (52)	42 (51)
Sequence	Nivo -> IpiX4	Nivo -> IpiX4	Nivo -> IpiX2
ORR for Nivo/Ipi, %	13	18	4
CR, %	0	3	0

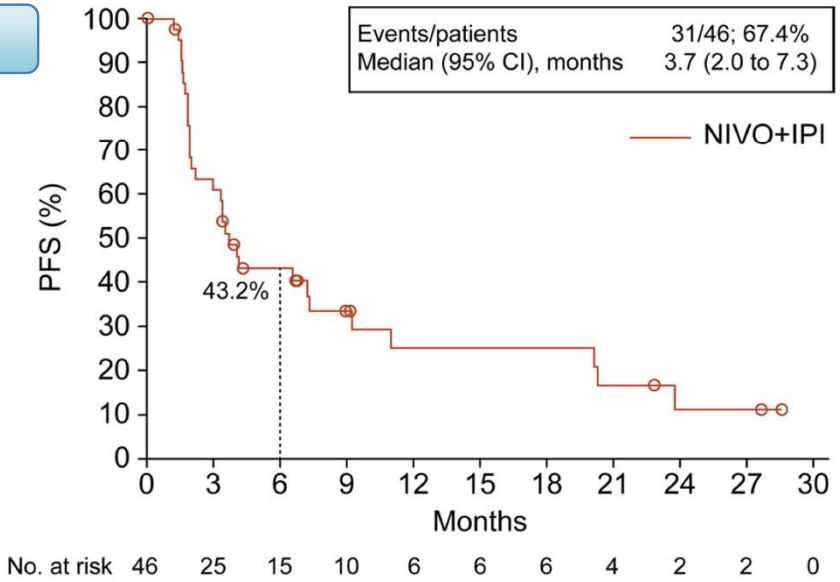
1.Atkins M, JCO 2022; 2.Grimm M.O, ASCO 2021; 3.McKay RT, JCO 2020

Evidencia en línea posteriores

FRACTION study: Fase II adaptativo



PFS



ORR

DOR 16.4 meses

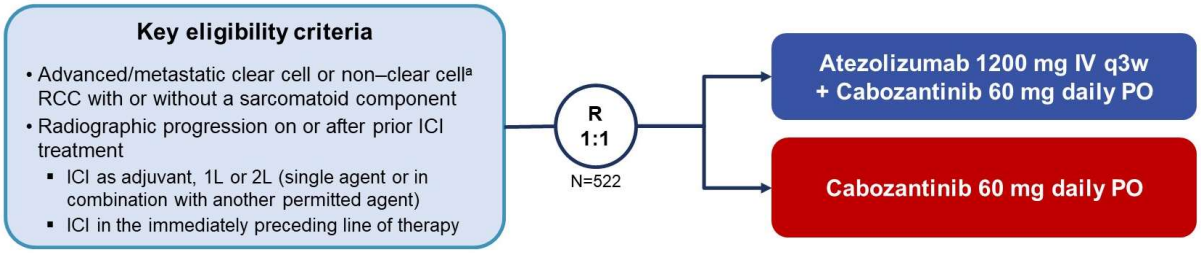
	Nivolumab plus ipilimumab (N=46)
All treated patients	
Objective response rate (95% CI), %	17.4 (7.8 to 31.4)
Disease control rate (95% CI), %*	58.7 (43.2 to 73.0)
Best overall response, n (%)	
Complete response	0
Partial response	8 (17.4)
Stable disease	19 (41.3)
Progressive disease	14 (30.4)
Not evaluable/available†	5 (10.9)
Patients with measurable tumor PD-L1 expression	
Objective response rate (95% CI), %	
PD-L1 ≥1%	12.5 (0.3 to 52.7)
PD-L1 <1%	14.3 (3.0 to 36.3)

Choueiri TK, J Immunother Cancer 2022

¿Y mantener un antiPD1/PDL-1 a la progresión?

CONTACT-03:

Fase III Cabo +-Atezo tras PD a IO



Most common prior systemic cancer treatment

	Atezo + Cabo (n=263)	Cabo (n=259)
First-line treatment, n (%)[a,b]	**262 (99.6)**	**258 (99.6)**
Ipilimumab + nivolumab	80 (30.5)	70 (27.1)
Sunitinib	77 (29.4)	72 (27.9)
Pazopanib	36 (13.7)	43 (16.6)
Axitinib + pembrolizumab	36 (13.7)	28 (10.9)
Nivolumab	6 (2.3)	10 (3.9)
Avelumab + axitinib	7 (2.7)	6 (2.3)
Bempegaldesleukin + nivolumab	3 (1.1)	9 (3.5)
Lenvatinib + pembrolizumab	6 (2.3)	3 (1.2)
Sorafenib	3 (1.1)	1 (0.4)
Second-line treatment, n (%)[a,b]	**119 (45.2)**	**125 (48.3)**
Nivolumab	104 (87.4)	116 (92.8)
Ipilimumab + nivolumab	4 (3.4)	3 (2.4)
Axitinib + pembrolizumab	2 (1.7)	3 (2.4)
Adjuvant treatment, n (%)[a,b]	**8 (3.0)**	**4 (1.5)**
Sunitinib	2 (25)	2 (50)

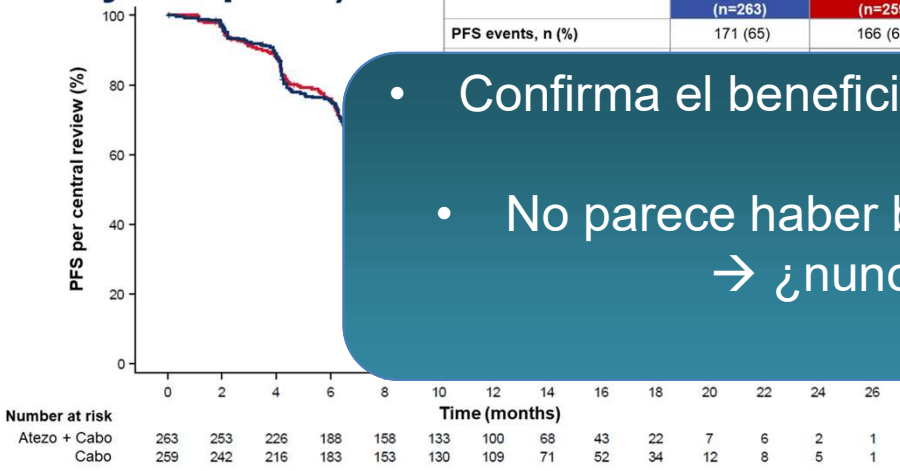
Choueiri T, et al. ASCO 2023

CONTACT-03:

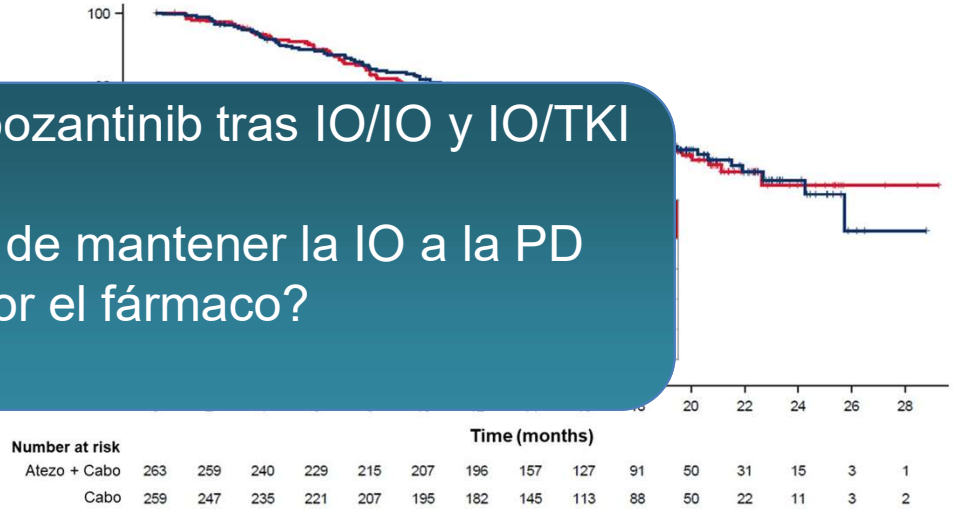
Fase III Cabo +-Atezo tras PD a IO

Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)



Interim analysis of OS (primary endpoint)



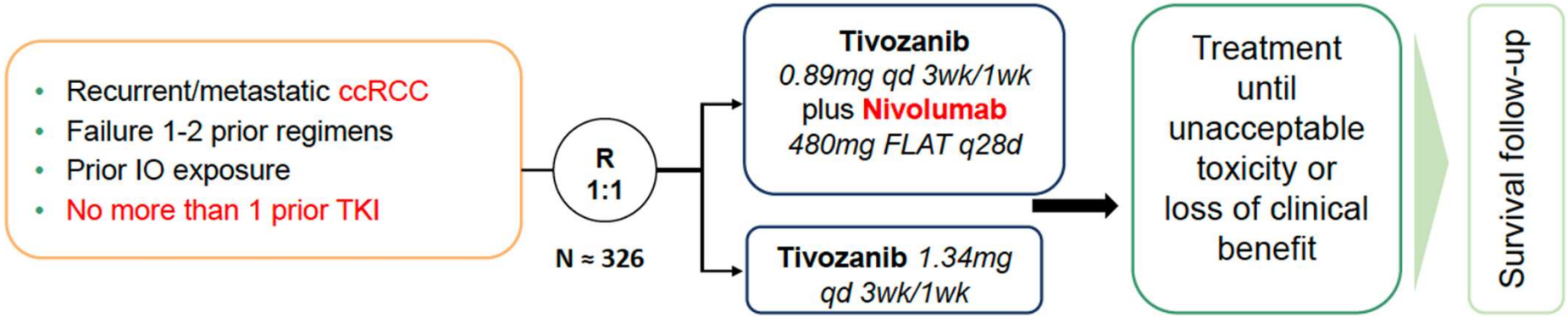
- Confirma el beneficio de Cabozantinib tras IO/IO y IO/TKI
- No parece haber beneficio de mantener la IO a la PD
  → ¿nunca o es por el fármaco?

ORR: 40,5 vs 40,9%

Choueiri T, et al. ASCO 2023

TiNivo-2

Fase III tras PD a IO: ongoing



Stratification factors
- IO given immediately prior (y/n)
- IMDC prognostic score

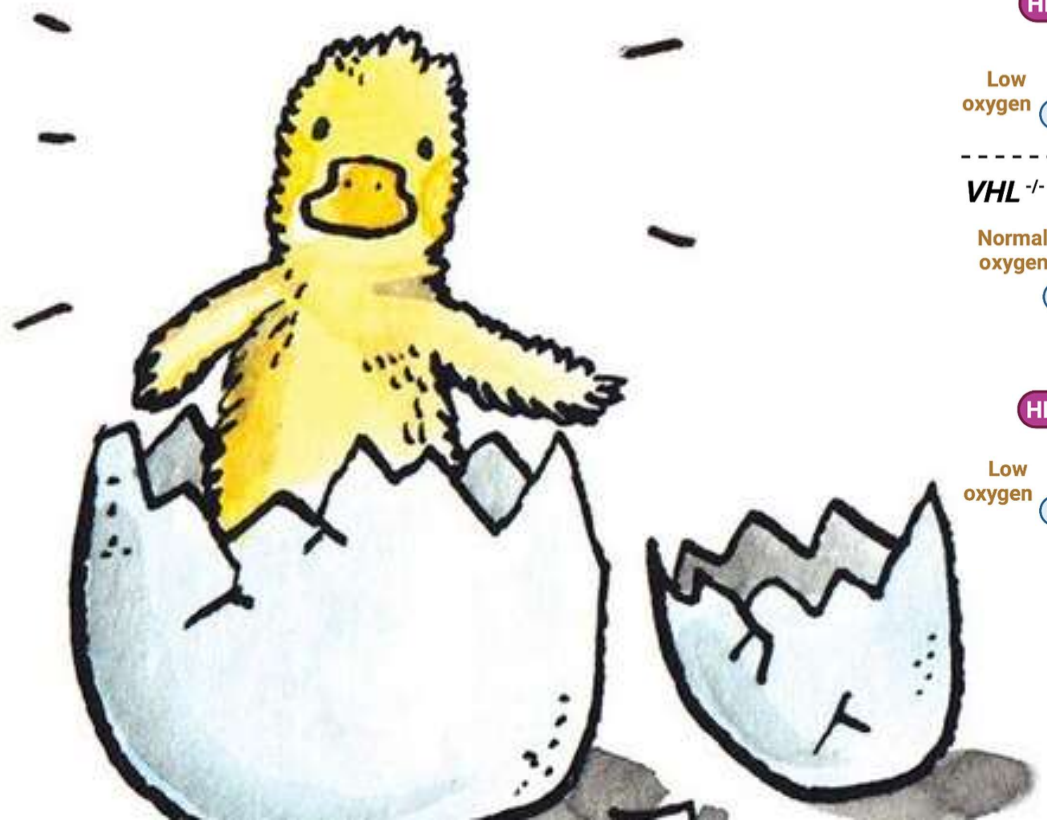
Primary endpoints
- PFS

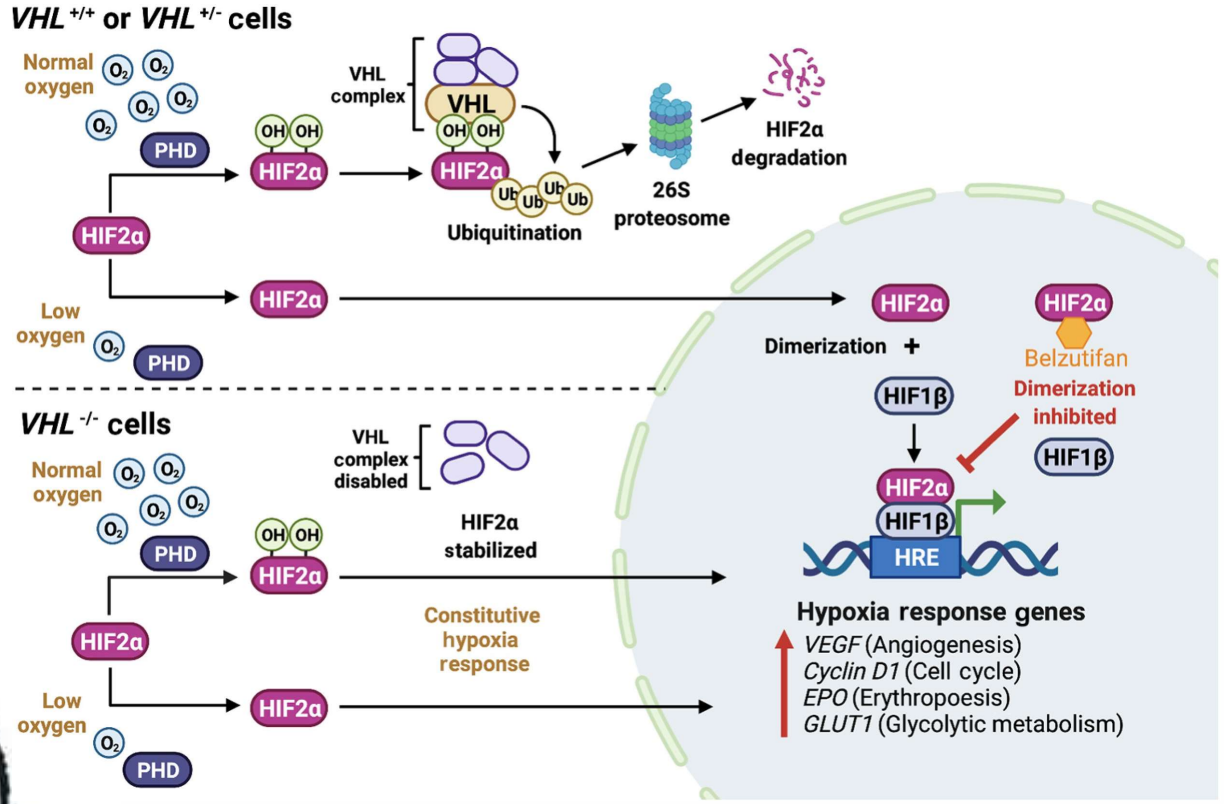
Additional endpoints
- OS, ORR, DoR, Safety

NCT04987203.


NUEVOS FÁRMACOS

BELZUTIFAN





Bauer. ASCO GU 2021. Abstr 273.

LITESPARK-001

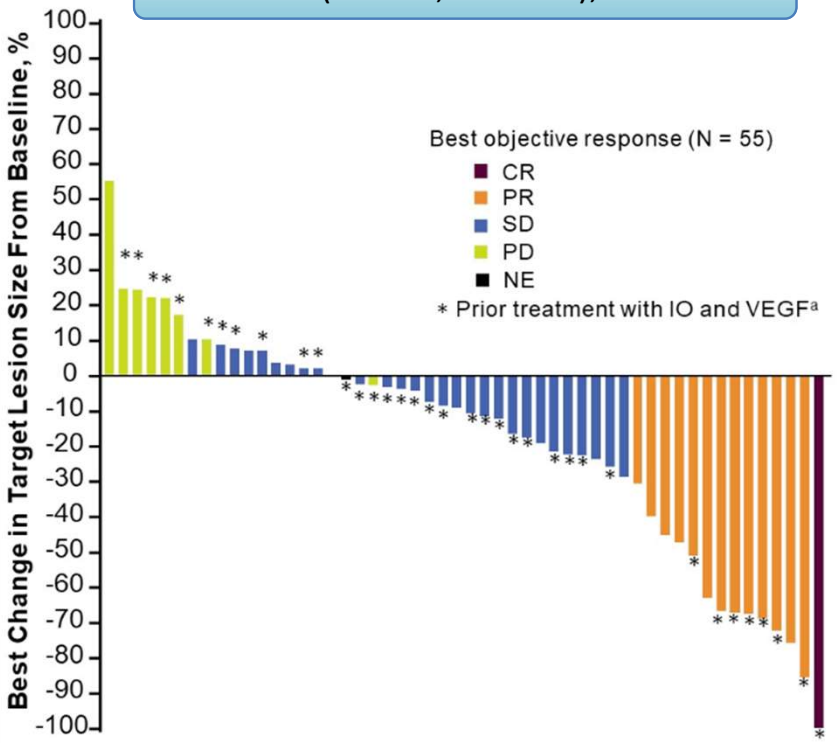
Fase I Belzutifan

Key Eligibility Criteria
- Locally advanced/metastatic solid sporadic ccRCC
- Received ≥1 prior treatment for ccRCC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

N = 55 → **Belzutifan** 120 mg orally QD Up to 1 year

All-Cause AEs in ≥20% (N = 55), n (%)	Any Grade	Grade 3	Grade 4/5
Any	55 (100)	33 (60)	6 (11)
Anemia	42 (76)	15 (27)	0 (0)
Fatigue	39 (71)	3 (5)	0 (0)
Dyspnea	27 (49)	3 (5)	0 (0)
Nausea	20 (36)	1 (2)	0 (0)
Cough	17 (31)	0 (0)	0 (0)
Hypoxia	17 (31)	9 (16)	0 (0)
Vomiting	16 (29)	0 (0)	0 (0)
Edema, peripheral	15 (27)	0 (0)	0 (0)

ORR: 25% (CR: 2%; PR: 24%); DCR: 80%



Jonasch. ASCO 2022. Abstr 4509.

LITESPARK-005

Fase III Belzutifan vs Everolimus

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%

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

R (1:1)

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

→ Safety, imaging, and survival follow-up

- **Median follow-up[b] at IA2: 25.7 months**

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

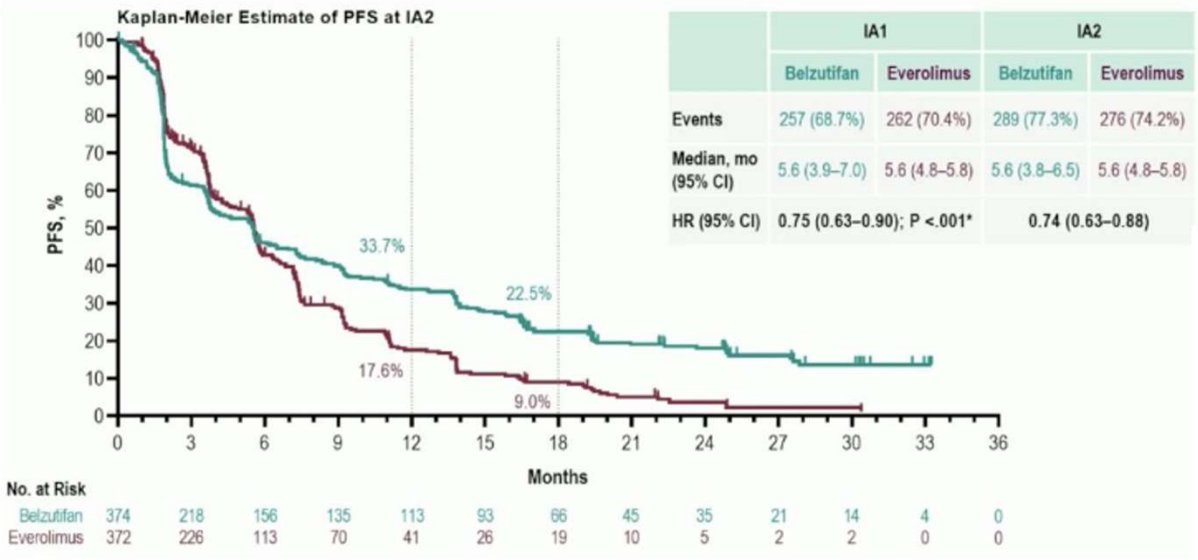
	Belzutifan (N = 374)	Everolimus (N = 372)
# Prior VEGF/VEGFR-TKIs		
1	50.0%	51.1%
2-3	50.0%	48.9%
# Prior lines of therapy[b]		
1	12.3%	14.0%
2	42.0%	44.6%
3	45.2%	40.3%

Albiges L, et al. ESMO 2023

LITESPARK-005

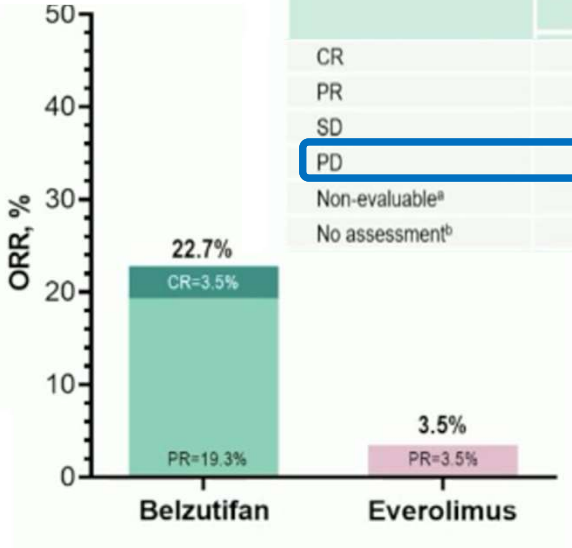
Fase III Belzutifan vs Everolimus

PFS



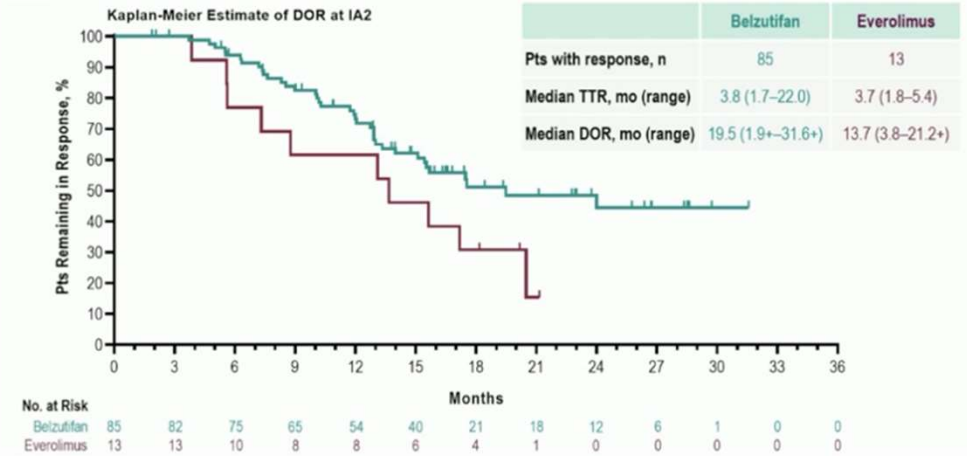
	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

ORR



	Belzutifan (N = 374)	Everolimus (N = 372)
CR	2.7%	0
PR	19.3%	3.5%
SD	39.3%	65.9%
PD	33.7%	21.5%
Non-evaluable[a]	1.3%	2.2%
No assessment[b]	3.7%	7.0%

DOR



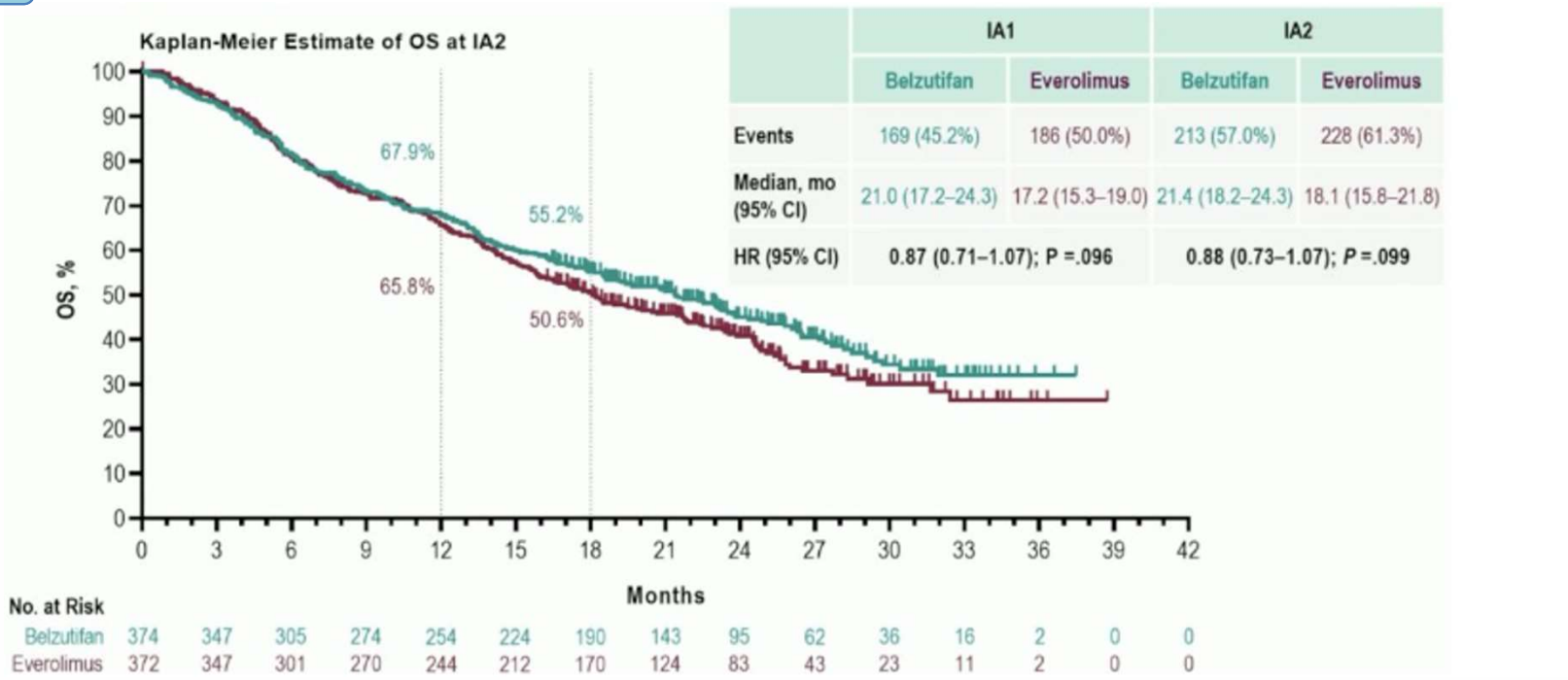
	Belzutifan	Everolimus
Pts with response, n	85	13
Median TTR, mo (range)	3.8 (1.7–22.0)	3.7 (1.8–5.4)
Median DOR, mo (range)	19.5 (1.9+–31.6+)	13.7 (3.8–21.2+)

Albiges L, et al. ESMO 2023

LITESPARK-005

Fase III Belzutifan vs Everolimus

OS



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

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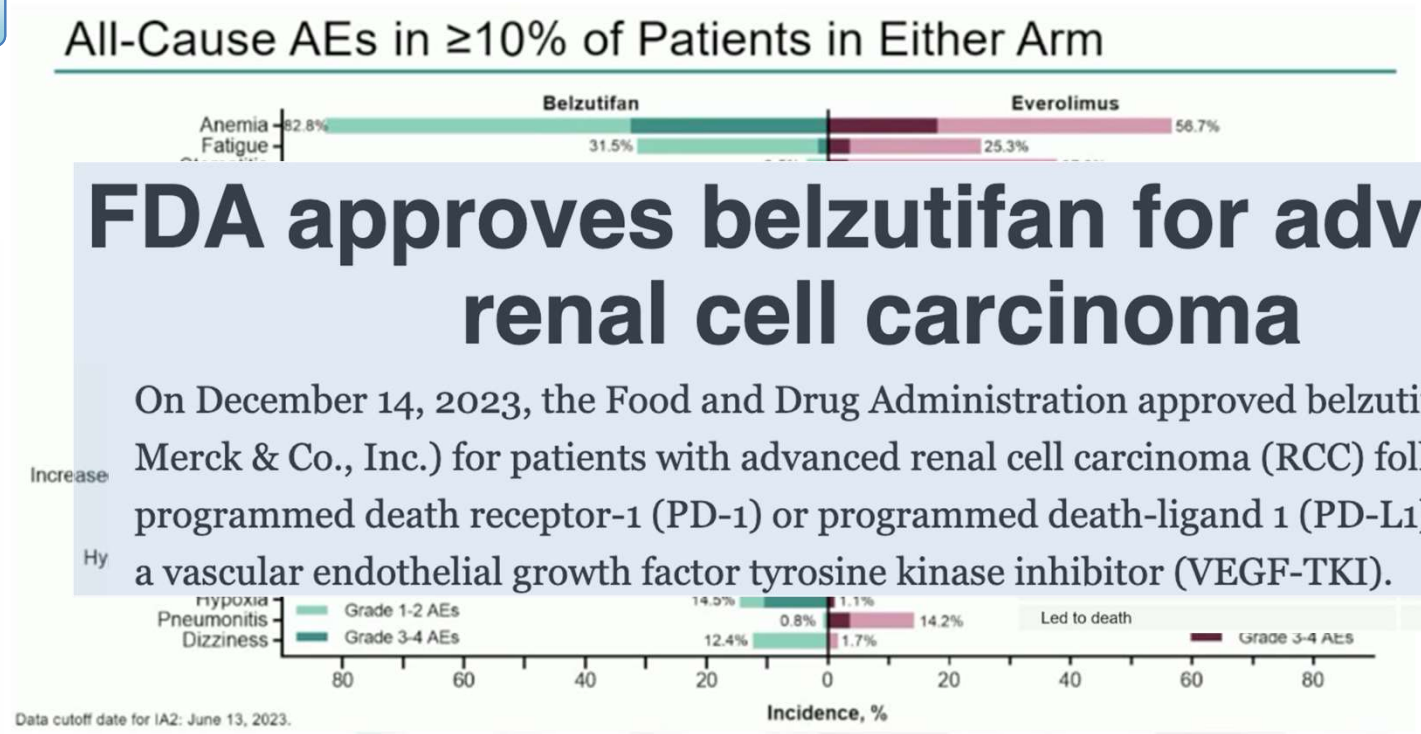
LITESPARK-005

Fase III Belzutifan vs Everolimus

AEs



FDA approves belzutifan for advanced renal cell carcinoma

On December 14, 2023, the Food and Drug Administration approved belzutifan (Welireg, Merck & Co., Inc.) for patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

	Everolimus (N = 360)
	3.9 (0.0–33.2)
	357 (99.2%)
	225 (62.5%)
	137 (38.1%)
	53 (14.7%)
	19 (5.3%)
	322 (89.4%)
	142 (39.4%)
	47 (13.1%)
Led to death	2 (0.6%)[b]
Grade 3-4 AEs	1 (0.3%)[a]

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OTROS FÁRMACOS PROMETEDORES

Trial Description	Drug
VÍA ANGIOGÉNESIS	XL-092 (Stellar-001 y 002) Sitravatinib (MGCD516) Batiraxcept (AVB-S6-500) ^{89}Zr-TLX250 (Zr-Girentuximab)
INMUNOTERAPIA	MEDI 5752 (anti-PD1/CTLA4) CBM-588 (producto bacteriano) +Nivo/Ipi
VÍAS METABÓLICAS	Ciforadenant (antagonista del receptor de adenosinaA2a)
INHIBIDORES PARP	Olaparib Talazoparib Niraparib

Adaptación de Suárez C at ESMO 2023

Combinaciones

LITESPARK-003: Fase II Belzutifan+Cabozantinib

Key Eligibility Criteria
- Have locally advanced or metastatic ccRCC
- Is either treatment naive or has received prior immunotherapy and ≤2 regimens for metastatic RCC
- ECOG PS 0 or 1

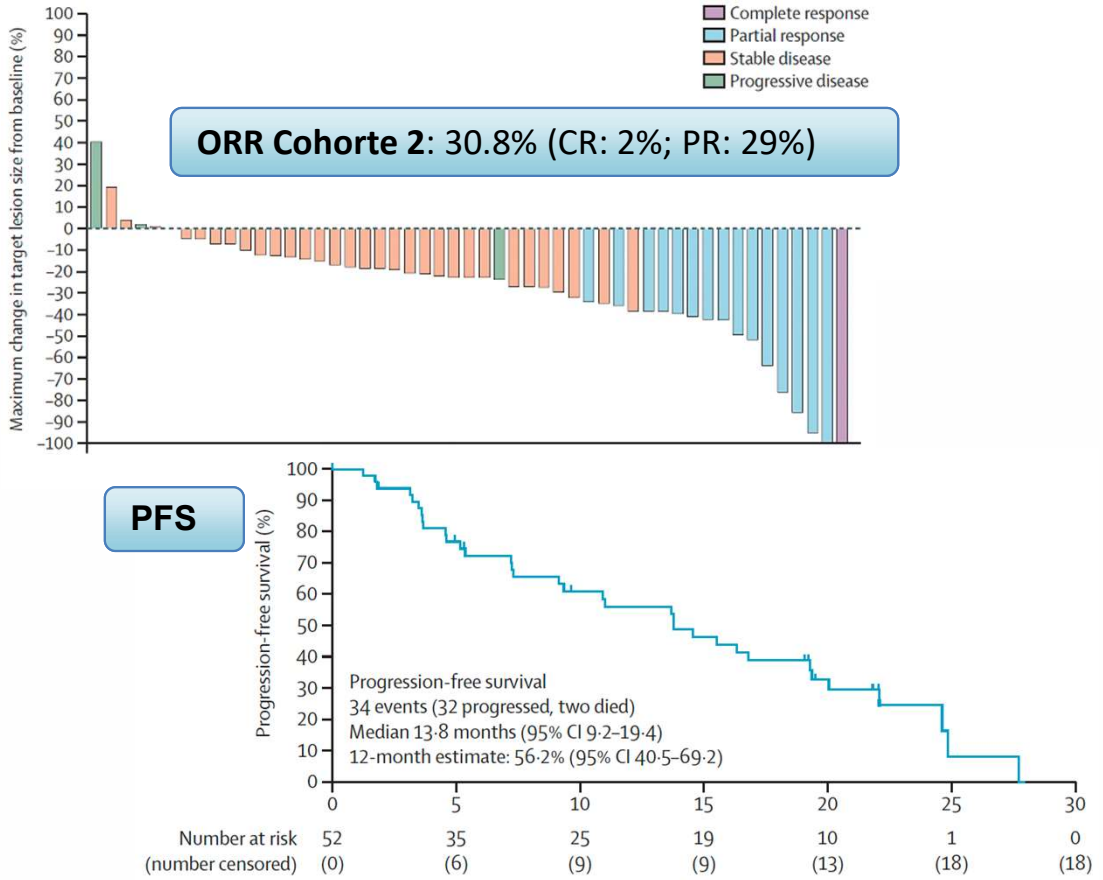
Cohort 1:
Treatment-naive

Belzutifan 120 mg/day PO
+
Cabozantinib 60 mg/day PO
N ≈ 50[a]

Cohort 2:
Prior immunotherapy treatment ± prior targeted treatment[b]

Belzutifan 120 mg/day PO
+
Cabozantinib 60 mg/day PO
N ≈ 50[a]

46% IO+TKI



ORR Cohorte 2: 30.8% (CR: 2%; PR: 29%)

PFS

Jonasch. ASCO 2022. Abstr 4509.

Combinaciones

KEYMAKER 03B: Fase IB/II

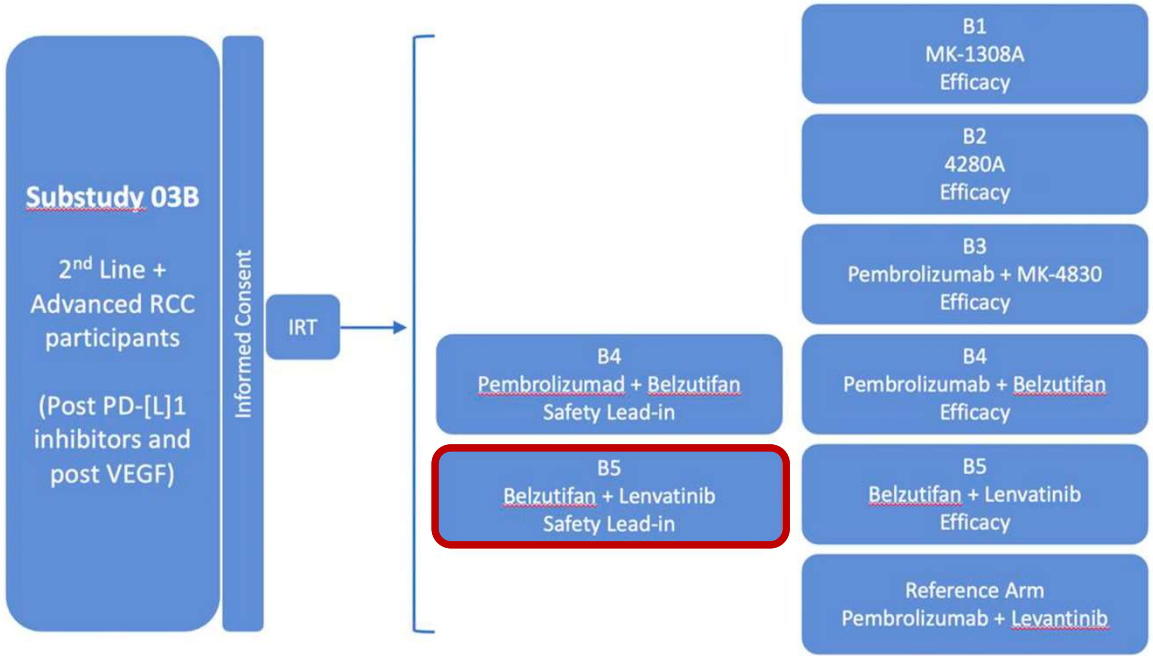
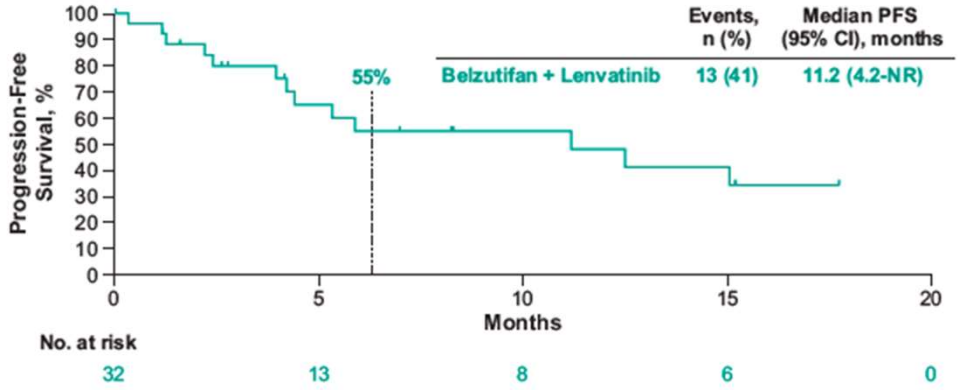


Table 2. Best overall response per RECIST v1.1 by BICR for patients who had the opportunity to receive ≥2 postbaseline scans

	Belzutifan Plus Lenvatinib n = 24
ORR, % (95% CI)	50 (29-71)
CBR[a] %, (95% CI)	54 (33-74)
Best overall response, n (%)	
CR	0
PR	12 (50)
SD	9 (38)
PD	1 (4)
Not assessed[b]	2 (8)
Duration of response, median (range), months	NR (1.4+ to 14.0+)
Response lasting ≥ 12 months, %	74

Figure 6. Kaplan-Meier estimate of progression-free survival



NR, not reached.

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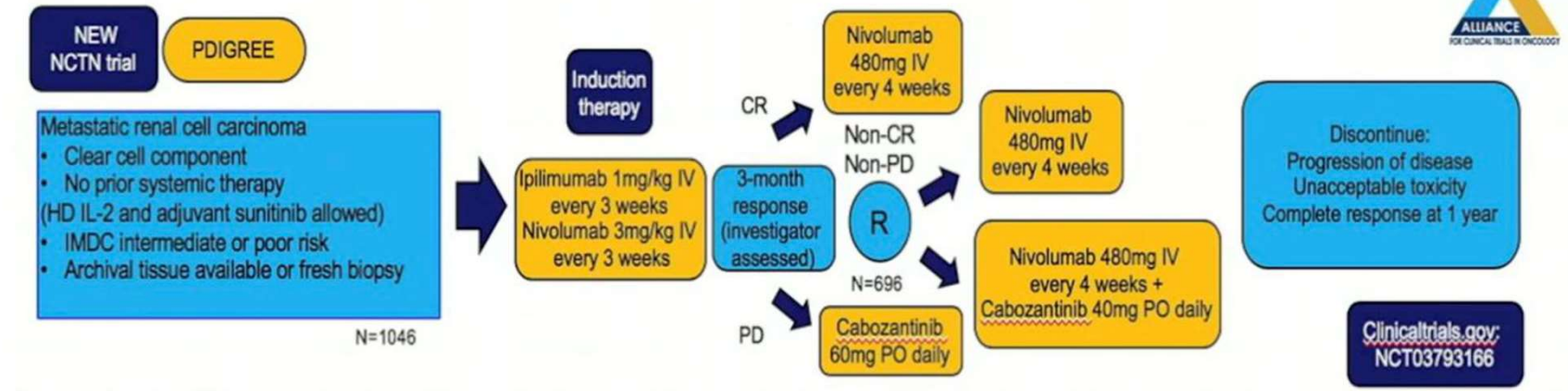
Nuevas estrategias

PD-Inhibitor nivolumab and Ipilimumab followed by nivolumab vs VEGF TKI cabozantinib with nivolumab (PDIGREE, A031704) – schema



Study chairs: Zhang & Choueiri

1° endpoint:
3-year OS
(60% nivo vs 70% nivo-cabo, HR 0.70
85% power, 2-sided α=0.05)

Key 2° endpoints:
-- 1-year CR rate
-- PFS
-- ORR by RECIST
-- Toxicity of nivo-cabo

Study activated in NCTN May 2019

PDIGREE: Alliance trial A031704
Clinicaltrials.gov: NCT03793166

Presented by Suarez C at ASCO-GU 2024

CONCLUSIONES

- **El panorama de la 2ªlínea ha cambiado** → a la espera de resultados de estudios fase 3 para identificar la mejor secuencia.

- A la hora de elegir el mejor tratamiento siempre debemos **tener en cuenta**: el tratamiento previo, el objetivo, el perfil de toxicidad, las comorbilidades y preferencias del paciente.

- Hoy por hoy, el tratamiento con mayor evidencia a la PD de las combinaciones es un **TKI que no haya recibido previamente**.

- Actualmente **no hay evidencia para poner IO a la PD de IO.**
  → ¿Posible papel en combinación con nuevos fármacos?
  → ¿Selección según el mecanismo de resistencia a IO?

- **Belzutifan** aumenta ORR y PFS a largo plazo, sin claro beneficio en OS y mayor tasa de progresiones como mejor respuesta.
  → Papel todavía no claro, ¿en combinación?¿en población seleccionada?

Gracias