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FACE-TO-FACE AND LIVE STREAMING

26-27 JUNIO 2025

Espacio Maldonado, Madrid

GUARD CONSORTIUM

How to treat patients in 2nd line after progression to TKI+IO?

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Disclosures

I have the following potential conflict(s) of interest to report

Advisory board: Astellas, BMS, Ipsen, Genenta, J&J, Merk, MSD, Pfizer, Sanofi, Bayer, EISAI.
Consultant: Astellas, Ipsen, Merk, MSD, Pfizer, EISAI.
Research support (inst): BMS, Merck, MSD, Pfizer.
PI clinical trial: BMS, Exelixis, Ipsen, Lilly, MSD, Seagen.

Guideline member: AIOM (prostate and renal cancer)

Scientific associations member: ESMO, AIOM, SIURO

Patients' advocacy association member: EuropaUomo (scientific committee); IKCS-EU (scientific committee 2024-2027)

Agenda

- What we know about subsequent therapies in KN264, CLEAR and CM-9ER
- What the guidelines suggest?
- What about the alternative TKI and what is the most used?
- How to do better and what are the alternative strategies?
- Where are we going?
- Limits of the available and future data.

What happened in 1L TKI-IO RCT?

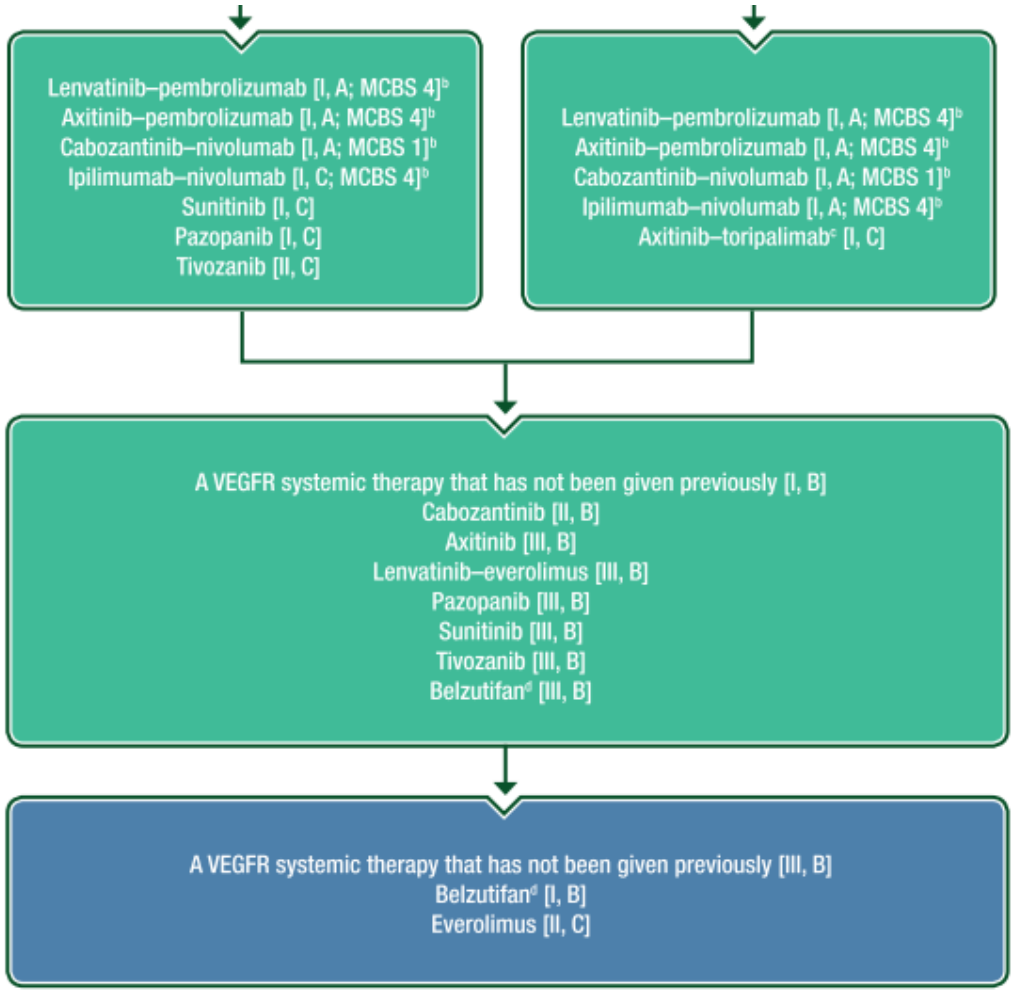
	KN 426[1] Axitinib+Pembro	CM9ER[2] Cabozantinib-Nivo	CLEAR[3] Lenva+Pembro
Patients	432	323	355
Follow up median (mos)	43.0	67.6	49.8
Discontinued TX	349/429 (81%)	299/320 (93%)	297/352 (84%)
Received Subsequent Tx	58%	43%	51%
Anti-PD(L)1	22%	36%	16%
VEGF(R) inhibitors	88%	79%	46%
Anti-CTLA4	2%	10%	3%
Other	32%	37%	6%
Number of lines*			
≥1	-	40%	34%
≥2	-	11%	9%
≥3	-	4%	6%

*Among all treated pts

1. Plimack ER, et al. Eur Urol. 2023;84(5):449-454.
2. Motzer RJ, ASCO-GU2025; abstract number 439.
3. Motzer RJ, et al. J Clin Oncol. 2024;42:1222-1228.

Suggestions from guidelines

ESMO guidelines



Powles T, Albiges L, Bex A, et al. *Ann Oncol*. 2024;35(8):692-706

Suggestions from guidelines

NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Kidney Cancer

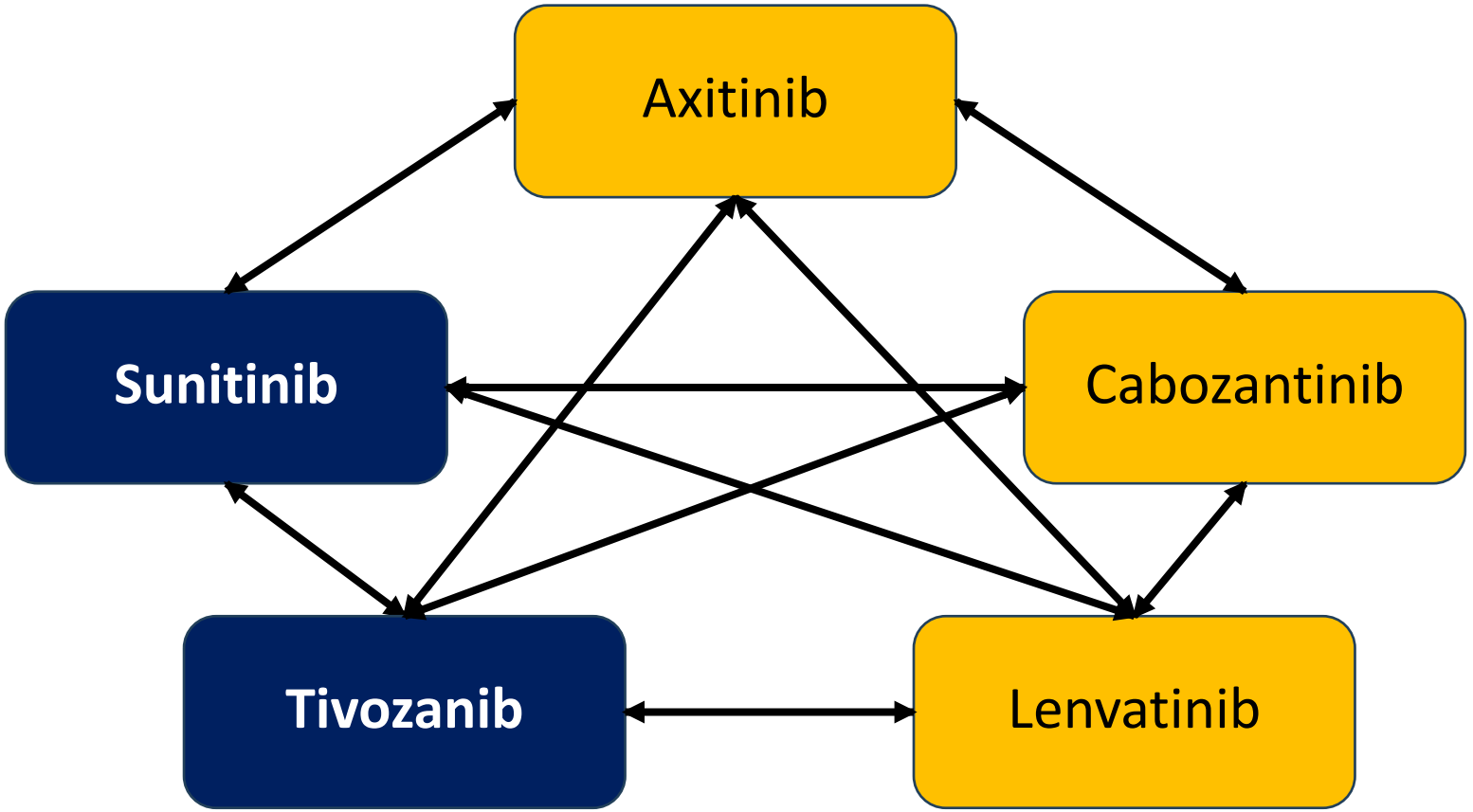
NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV OR RELAPSED 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,c] • Everolimus + lenvatinib • Ipilimumab + nivolumab[b,d] • Lenvatinib + pembrolizumab[b] • Nivolumab[b,c]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[e] • Cabozantinib • Everolimus + lenvatinib • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b,c] • Everolimus • Ipilimumab + nivolumab[b,d] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[g] (category 2B) • Axitinib + avelumab[b] (category 3)

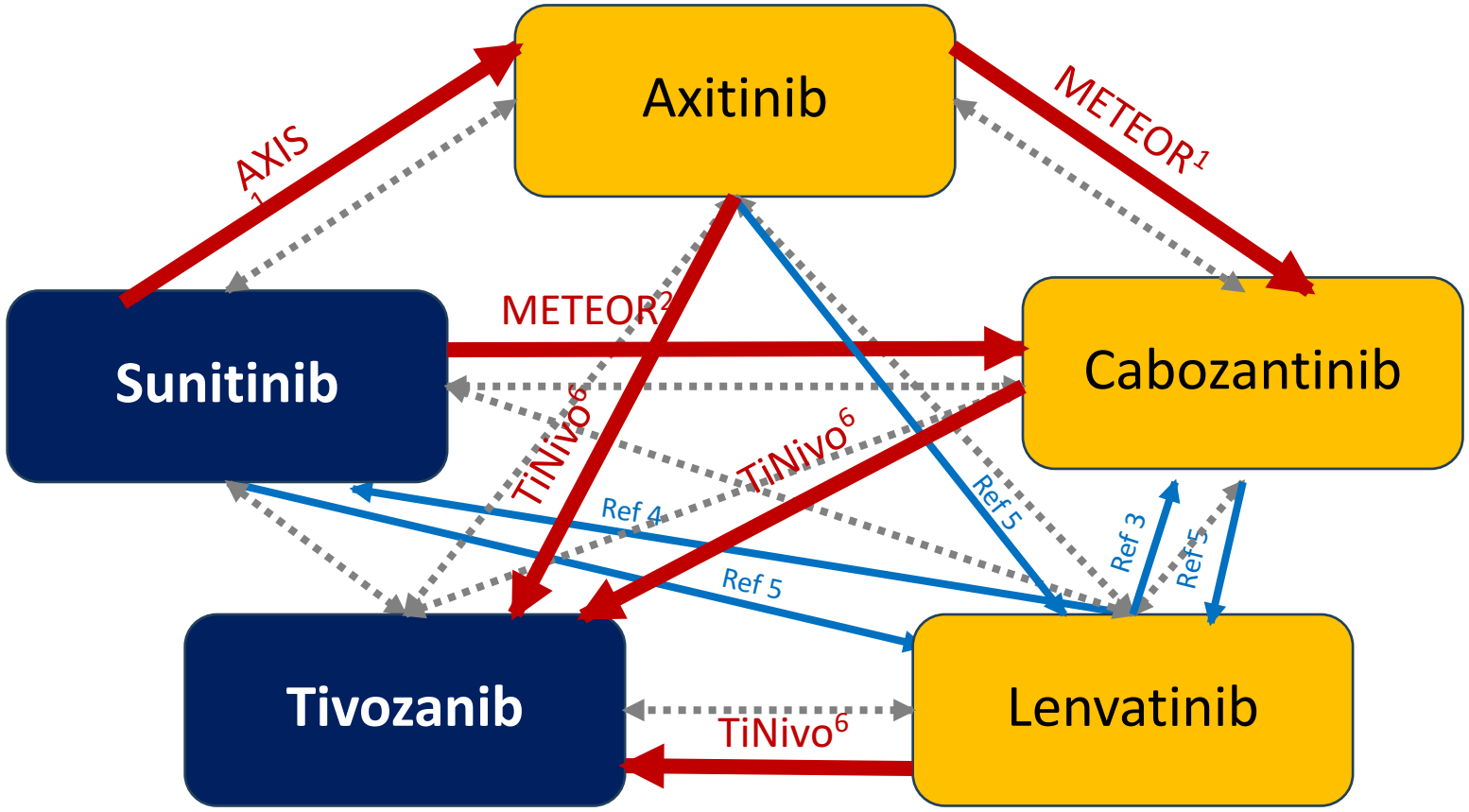
Possibilities in clinical practice



IO-based combo when 1st line

TKI single agent when 1st line

Evidence supported possibilities



Evidence from RCT

Evidence from prospective studies

Evidence from retrospective studies

1. Rini B, et al. Lancet. 2011;378:1931-9.
2. Choueiri TK, et al. N Engl J Med 2015;373:1814-182.
3. Procopio G, et al. Tumori. 2023;109:129-137.
4. Grande E, et al. ESMO Open. 2022;7:100463.
5. Lee CH, et al. Lancet Oncol. 2021;22:946-958.
6. Choueiri TK, et al. Lancet. 2024;404:1309-1320.
7. Rini B, et al. Lancet Oncol. 2020;21:95-104.

Some other retrospective studies:

1. Auvray M, et al. Eur J Cancer 2019;108:33–40;
2. Shah AY, et al. Eur J Cancer 2019;114:67–75;
3. Wiele AJ, et al. The Oncologist 2021;26:1–7;
4. Cerbone L, et al. Clin Genitourin Cancer. 2022;20:80-87.

Studies supporting cabo as “standard” 2nd line:

	BREAKPOINT[1]	CANTATA[2]	CONTACT-03[3]
Phase	2	3	3
Patients	31	221 vs. 223	263 vs. 259
Study arms	cabo	Cabo+CB839 vs. cabo+P	Cabo+Atezo vs. cabo
IMDC*(%)	17 / 53 / 30	17 / 67 / 16	19 / 65 / 16
Prior IO (%) *experimental arm only *IO-IO* *IO-TKI*	100 *63* *26§*	62 vs. 62 *29 vs. 29* *NA vs. NA*	100 vs. 100 *31 vs. 27* *14 vs. 11**
PFS median (mos) HR (95%CI)	8.3	9.2 vs. 9.3 HR: 0.94 (0.74 – 1.21)	10.6 vs. 10.8 HR: 1.03 (0.83 – 1.28)
OS median (mos) HR (95%CI)	13.8	22.2 vs. 24.8 HR: NA	25.7 vs. NE HR: 0.94 (0.70 – 1.27)
ORR (%)	38	31 vs. 28	41 vs. 41

Cabozantinib achieved a median PFS of 9-10 months and ORR of 30-40%

§Axi-avelumab 3%; Lenva-pembro 23%; * Only Axi-pembro.

1. Procopio G, et al. Tumori. 2023;109:129-137.
2. Tannir NM, et al. JAMA Oncol. 2022;8:1411-1418.
3. Pal S, et al. Lancet. 2023;402(10397):185-195.

Why cabozantinib is so active?

IC50 on VEGFR can explain main activity of TKIs:

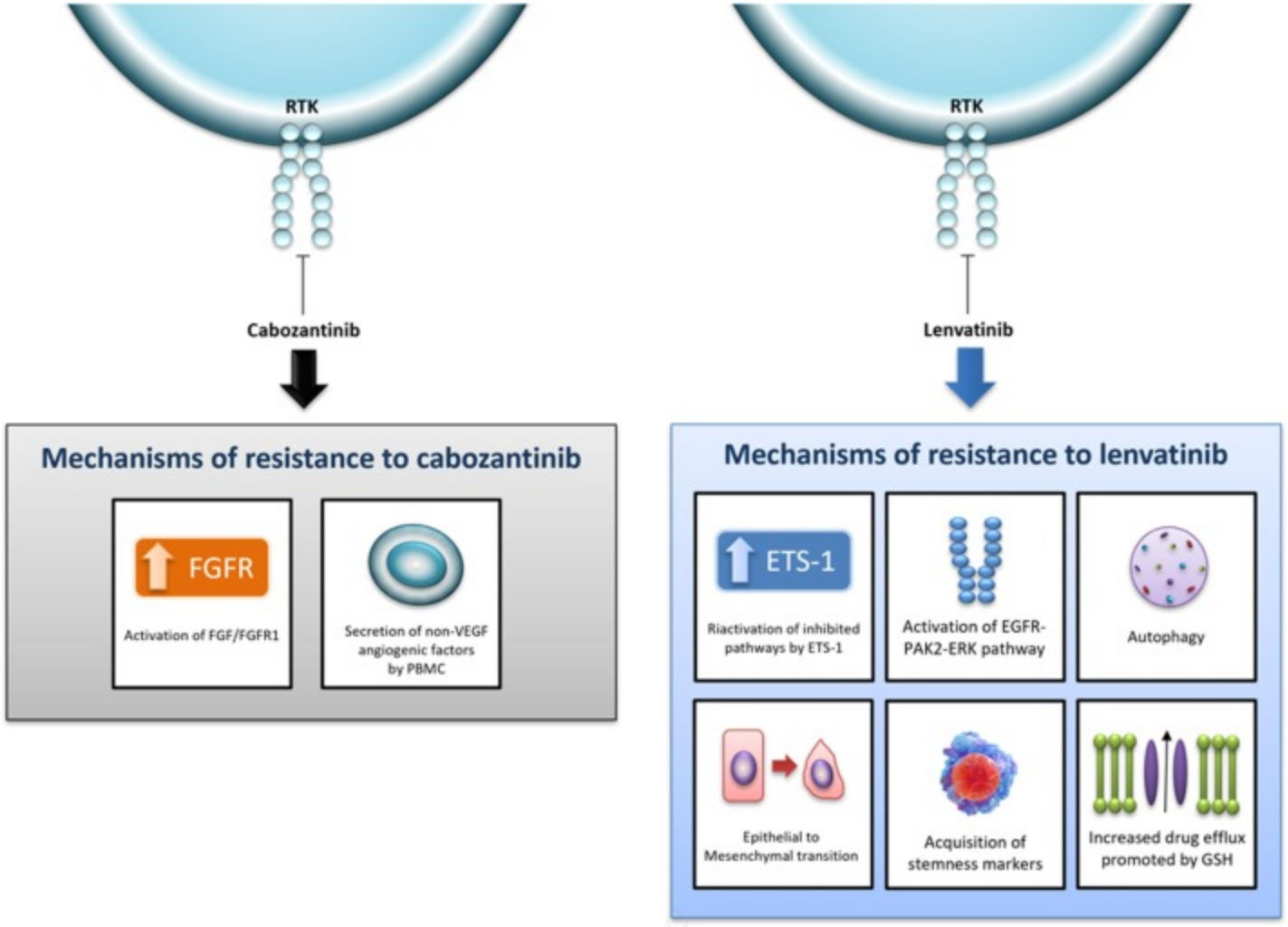
	Sorafenib	Sunitinib	Pazopanib	Axitinib	Tivozanib	Cabozantinib	Lenvatinib	Zanzalintinib
VEGFR2 IC50 (nM)[1]	90	80	30	0.20	6.5	0.035	4.0	1.6
Initial dose (mg)	800	50	800	10	1.5	60/40	20	100

There is evidence in clinical practice supporting sequencing of TKIs by IC50:

- Axitinib works well after sunitinib (AXIS[2])
- Cabozantinib works well after sunitinib (METEOR[3]), and better to sunitinib (CABOSUN[4])

1. https://www.selleckchem.com/
2. Rini B, et al. Lancet. 2011;378:1931-9.
3. Choueiri TK, et al. N Engl J Med 2015;373:1814-182
4. Choueiri TK, et al. Eur J Cancer. 2018:94:115-125.

Mechanism of resistance after lenv *vs.* cabo:



Santoni M, et al. Cancer Treat Rev. 2025 Feb:133:102881.

Can cabo works after len?

67 yo female; ECOG=0, IMDC=1

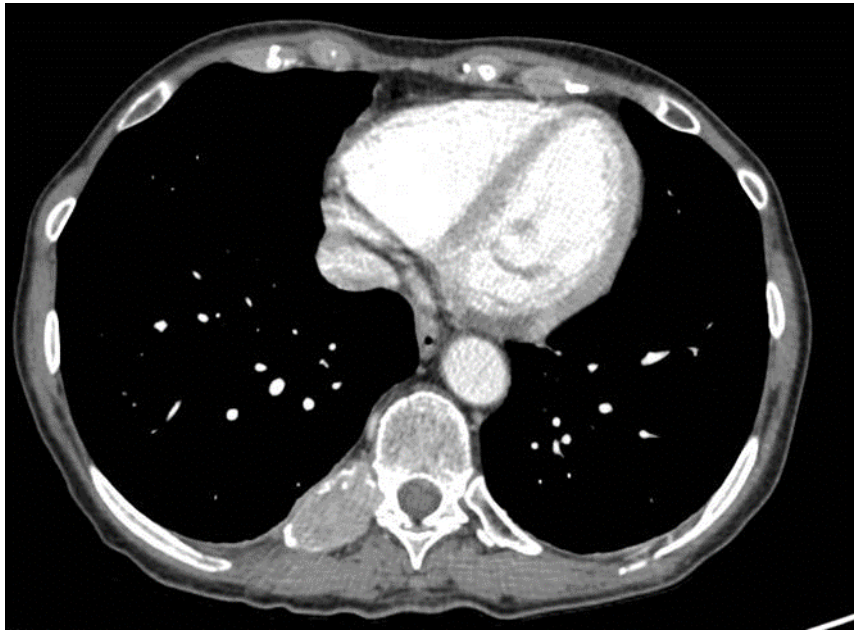
22-JAN-2024 CT: see image on T10 + adrenal gland (13 mm)

12-FEB-2024 Starts **Lenvatinib + Pembrolizumab** x 4

27-MAY-2024 CT: increase of the adrenal lesion (30 mm) + new pancreatic lesion (5 mm). Stable the bone lesion.

27-MAY-2024 Starts **Cabozantinib** 60 mg…

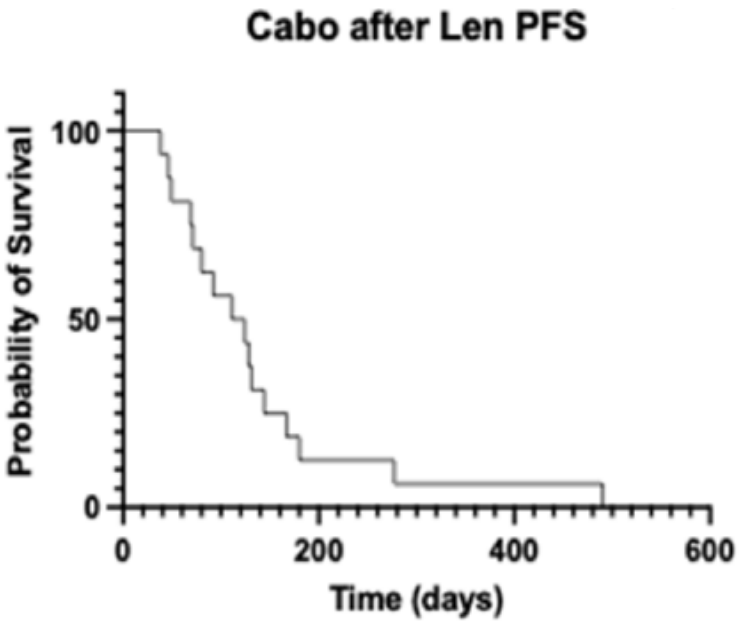
11-JUN-2025 CT: CR on pancreas; PR on adrenal gland (8mm); SD on T10.

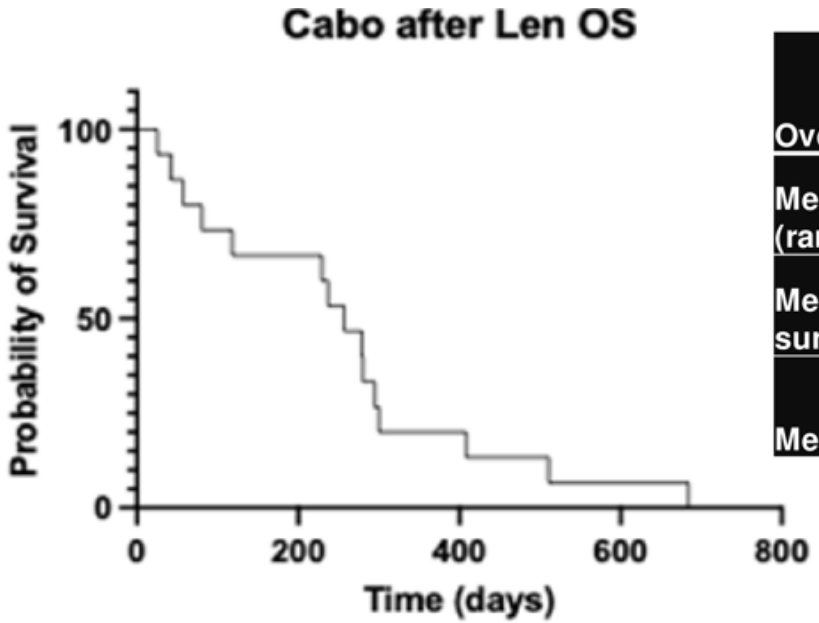


YES, Cabo worked well!

Santoni M, et al. Cancer Treat Rev. 2025 Feb:133:102881.

What happened after PD to leva when treated with cabo?





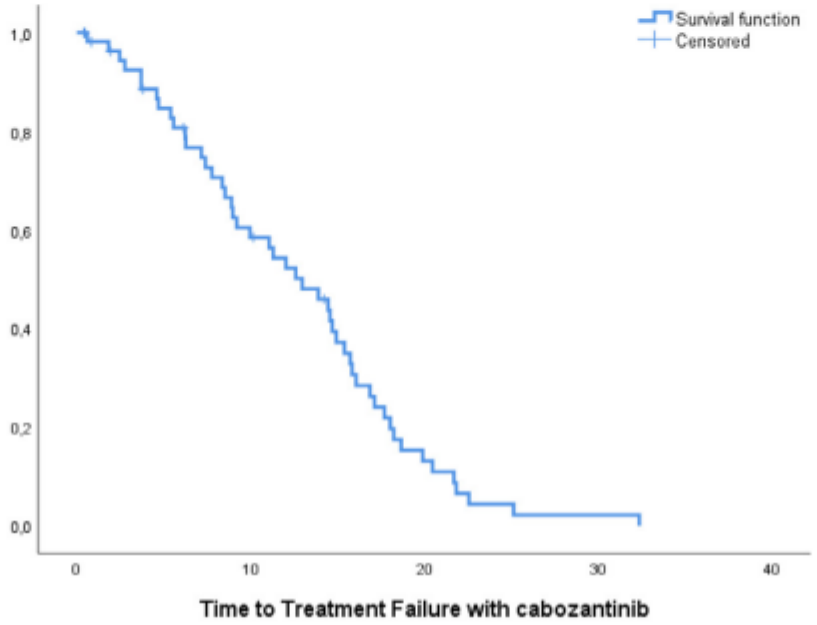
Efficacy

Overall Response Rate (%)	5.3%
Median time on treatment (range)	4.3 months (0.17-18.47)
Median Progression free survival (range)	4.1 months (1.2-16.1)
Median Overall Survival (range)	8.1 months (0.8-22.5)

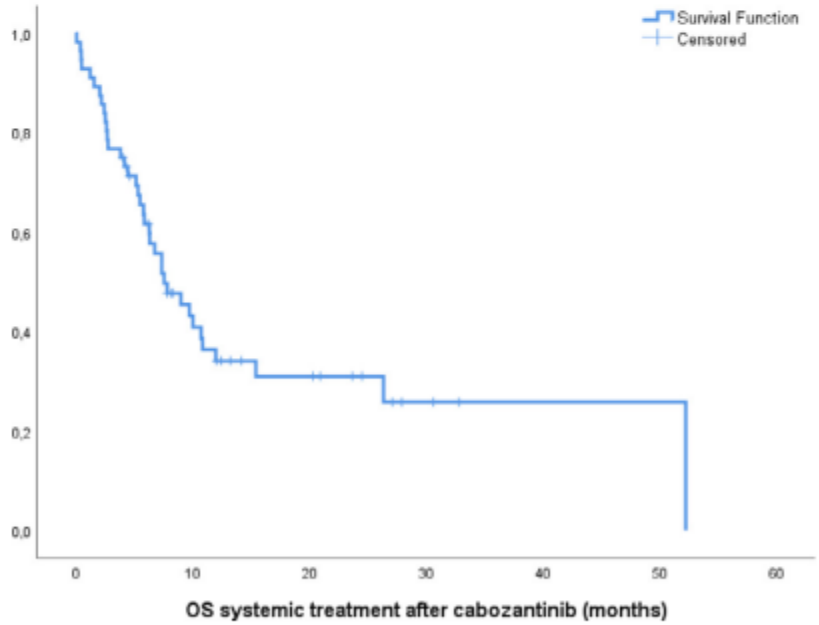
Single center retrospective study of 22 pts with aRCC who received CABO after LEN+PEM

Jaime Ivan Haro-Silerio et al. JCO 42, 433-433(2024).

What happened after PD to cabo?



Time to Treatment Failure with cabozantinib



OS systemic treatment after cabozantinib (months)

Failure and OS were 2.8 months and 7.7 months, respectively. No difference in either TTF or OS among patients treated with cabozantinib for less than 6 months versus more than 6 months

	Overall (n = 56)	Axitinib (n = 18)	ICI (n = 18)	Everolimus (n = 16)	Others (n = 4)
TTF	2.8 mo (95% CI 1.9-3.7)	5.7 mo (95% CI 0.4-11.0)	2.5 mo (95% CI 1.6-3-3)	2.3 mo (95% CI 2.1-2.4)	
OS	7,7 mo (95%CI 4,4–10.8)	9.7 mo (95% CI: 2.1-17.9)	6.3 mo (95%CI: 1.9-10.8)	7.4 mo (95% CI: 6.2-8.5)	4 mo (95%CI: 1.5-6.5)
PR=ORR	4 (7.1%)	2 (11.1%)	2 (11.1%)	0 (0%)	0 (0%)
SD	18 (32.1%)	6 (33.3%)	4 (22.2%)	4 (25%)	1 (25.0%)
PD	24(42.9%)	4 (22.2 %)	10 (55.5%)	10 (62.5%)	3 (75%)
Not Assessed	10 (17.9.2%)	6 (33.3%)	2 (11.1%)	2 (12.5%)	0 (0%)

Cerbone L, et al. Clin Genitourin Cancer. 2022;20:80-87..

How to do better?

- Looking at new TKIs
- Increasing 2L TKI efficacy by IO continuation
- Looking at new mechanisms of action (HIF2α inhibitors)

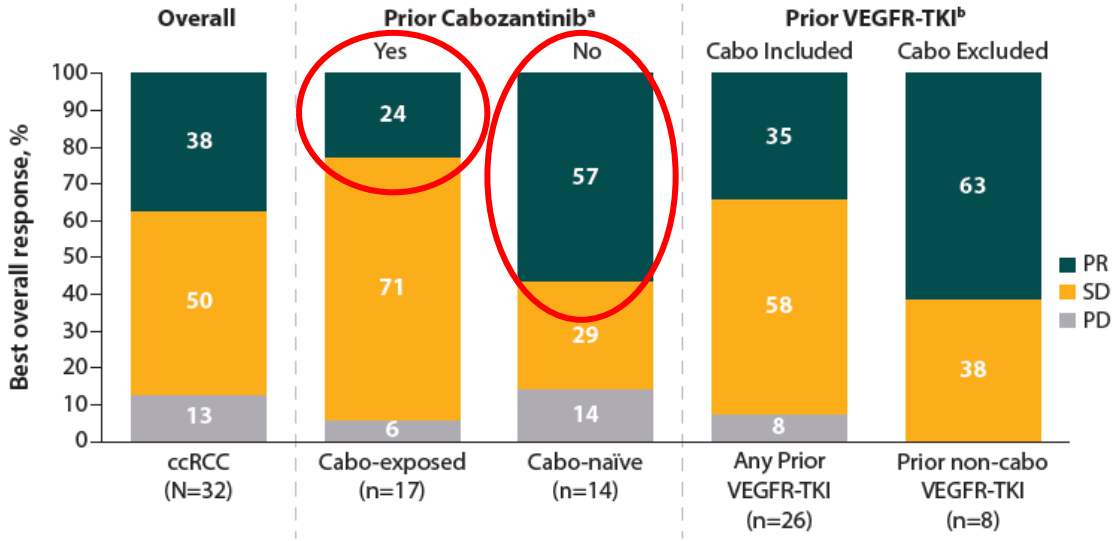
Santoni M, et al. Cancer Treat Rev. 2025 Feb:133:102881.

Can we improve TKIs and response after cabo?

ZANZALINTINIB post TKI in STELLAR-01 study[1]:

Zanzalintinib (XL092) is an orally active, ATP-competitive inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGFR2, AXL and MER.

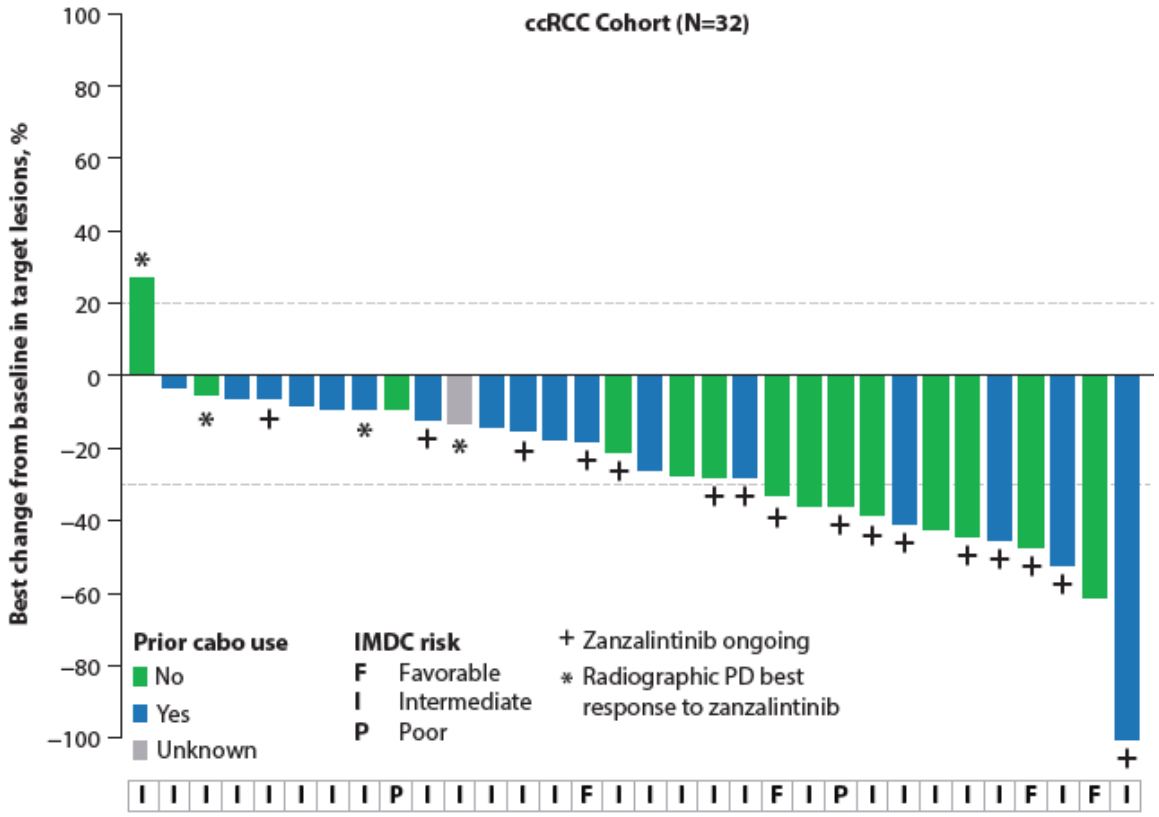
A. Tumor Response per RECIST v1.1 by Investigator



	ccRCC (N=32)	Cabo-exposed (n=17)	Cabo-naïve (n=14)	Any Prior VEGFR-TKI (n=26)	Prior non-cabo VEGFR-TKI (n=8)
ORR, % (95% CI)	38 (21–56)	24 (7–50)	57 (29–82)	35 (17–56)	63 (25–92)
DCR[c], % (95% CI)	88 (71–97)	94 (71–100)	86 (57–98)	92 (75–99)	100 (63–100)
mTTR (range), mo	1.9 (1.8–9.3)	1.8 (1.8–2.1)	1.9 (1.9–9.3)	1.9 (1.8–9.3)	1.9 (1.9–9.3)
mDOR (95% CI), mo	7.4 (3.3–NE)	NE (3.7–NE)	7.4 (3.3–NE)	NE (3.3–NE)	NE (3.3–NE)

[a]Prior cabozantinib exposure was unknown for one patient. [b]These subgroups are not mutually exclusive. [c]DCR is defined as proportion of patients with a best overall response of confirmed CR/PR or any single best response of SD.

B. Best Percent Change From Baseline in Target Lesions per RECIST v1.1 by Investigator

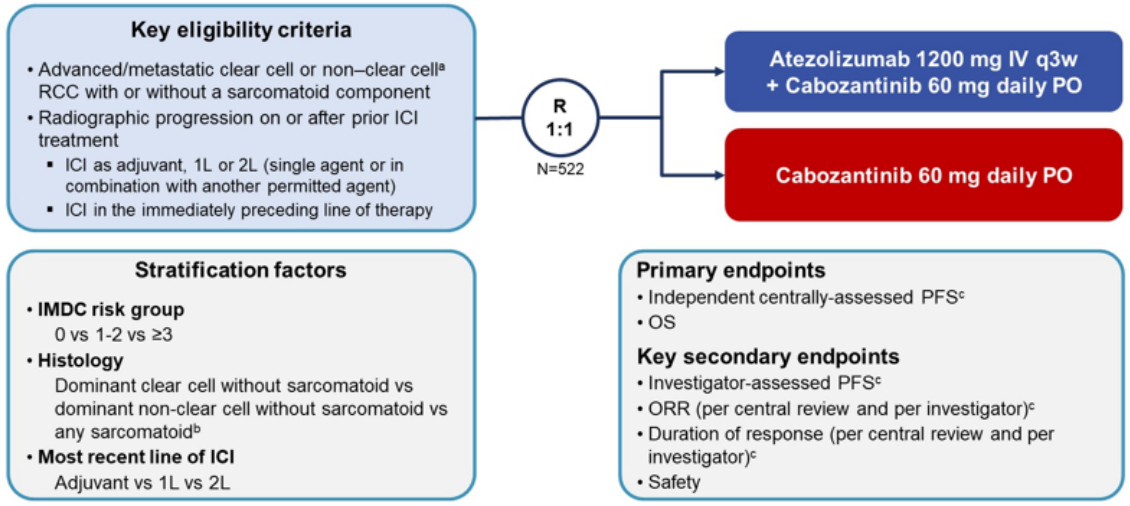


1. Pal S, IKCS North America 2023.

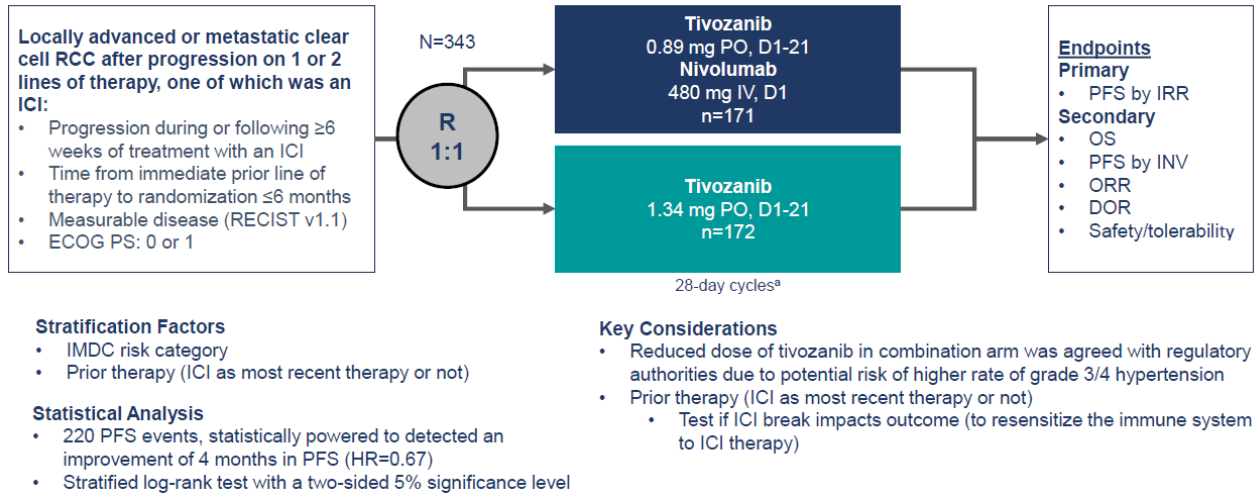
What we know about IO-continuation?

CONTACT-03 & TiNIVO-2:

Phase III CONTACT-03 study



TiNivo-2: Phase 3 Study Design



50% progressed while on first line IO

71% progressed while on IO
65% had just 1 previous Tx

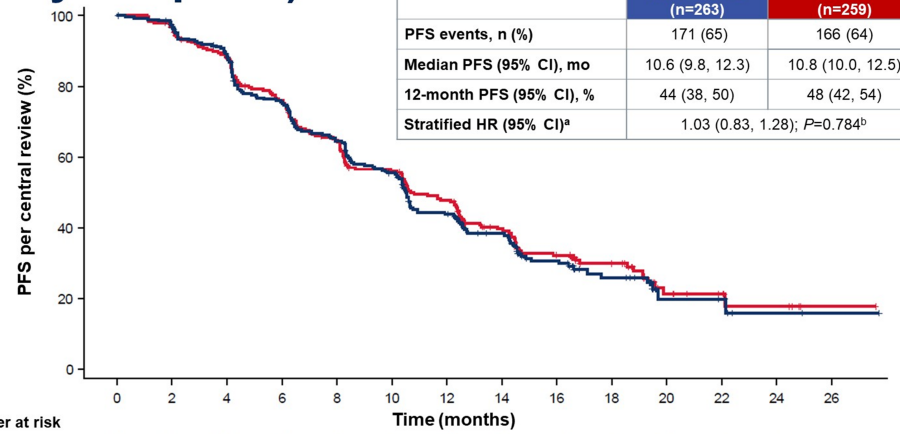
1. Pal S, et al. Lancet. 2023;402:185-195.
2. Choueiri TK, et al. Lancet. 2024;404:1309-1320.

What we know about IO-continuation?

CONTACT-03 & TiNIVO-2:

Primary analysis of centrally reviewed PFS (primary endpoint)

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



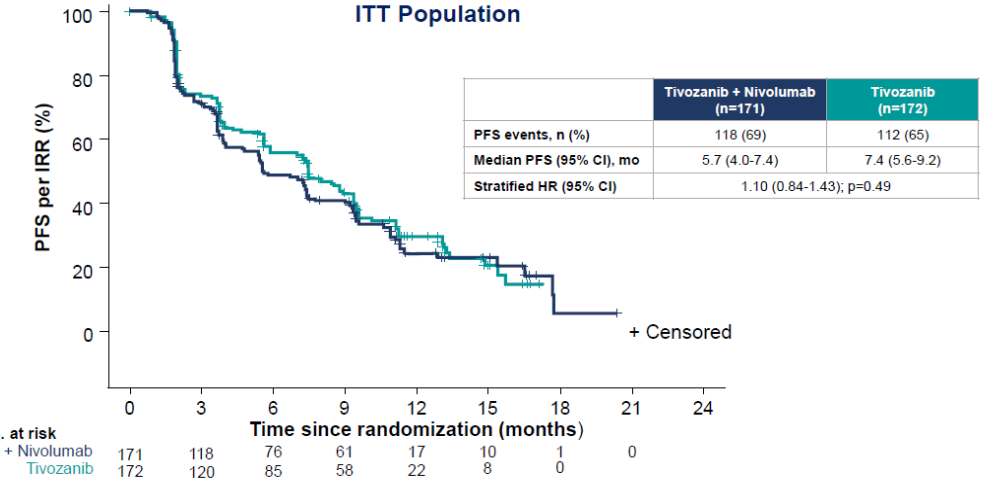
[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Toni K. Choueiri, MD

Choueiri, et al. CONTACT-03 (LBA4500) @DrChoueiri

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Primary Analysis of Centrally Reviewed PFS (primary endpoint)



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

BARCELONA 2024 ESMO congress

HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival.

Both studies reported **no benefit for continuing IO** after progression to previous IO-combo

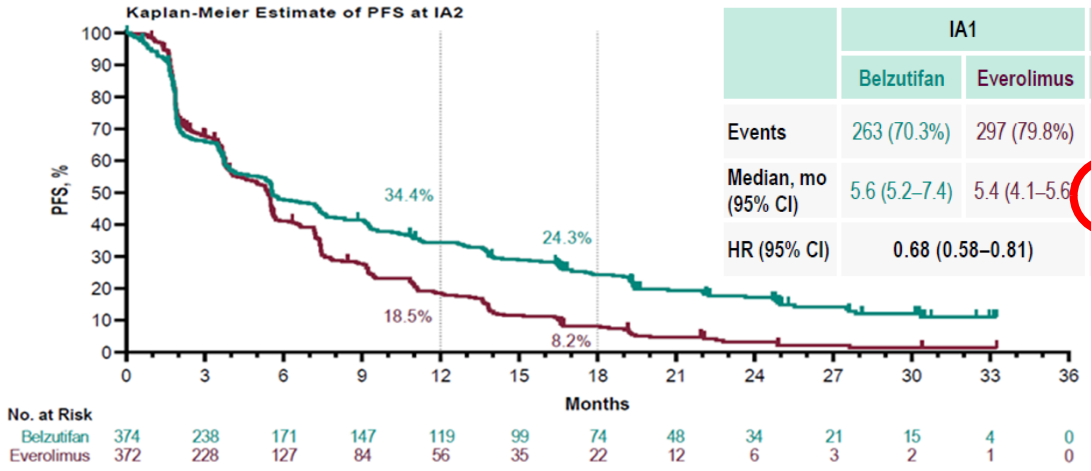
1. Pal S, et al. Lancet. 2023;402:185-195.
2. Choueiri TK, et al. Lancet. 2024;404:1309-1320.

GUARD CONSORTIUM

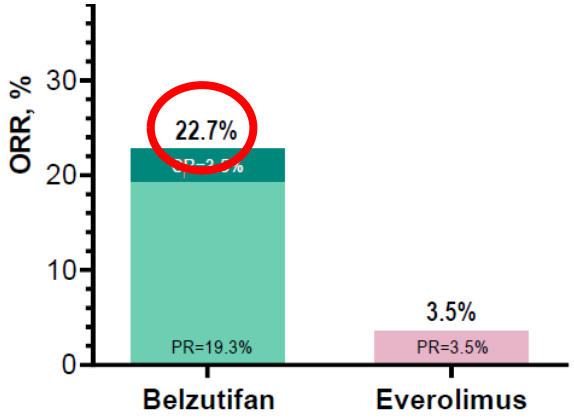
Belzutifan and other HIF2α inhibitors

LITESPARK-005 study:

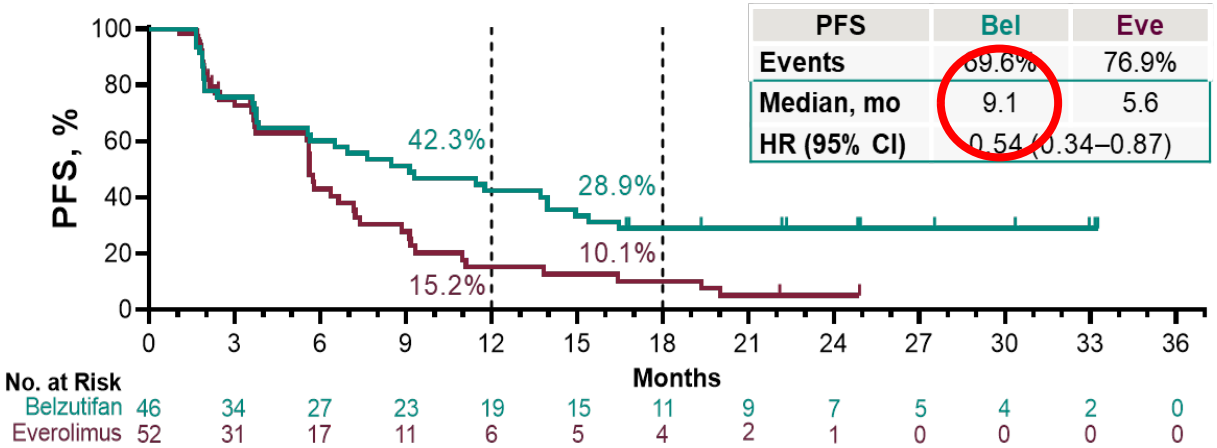
Overall population



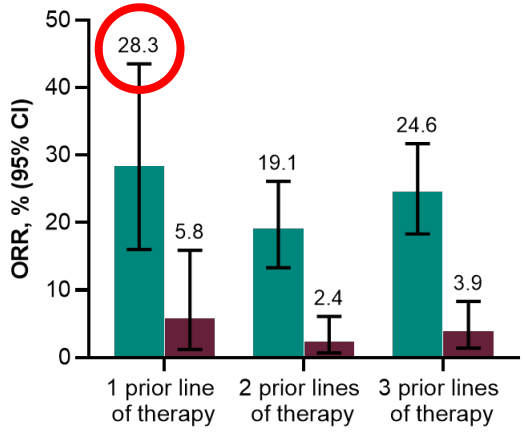
	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	263 (70.3%)	297 (79.8%)	299 (79.9%)	313 (84.1%)
Median, mo (95% CI)	5.6 (5.2–7.4)	5.4 (4.1–5.6)	5.6 (4.7–7.4)	5.4 (4.1–5.6)
HR (95% CI)	0.68 (0.58–0.81)		0.67 (0.57–0.79)	



1st Line TKI-IO



PFS	Bel	Eve
Events	69.6%	76.9%
Median, mo	9.1	5.6
HR (95% CI)	0.54 (0.34–0.87)	



Choueiri TK, et al. N Engl J Med. 2024;391:710-721
Albiges L, ESMO 2023.
Albiges L, IKCS-EU 2024.

Belzutifan and other HIF2α inhibitors

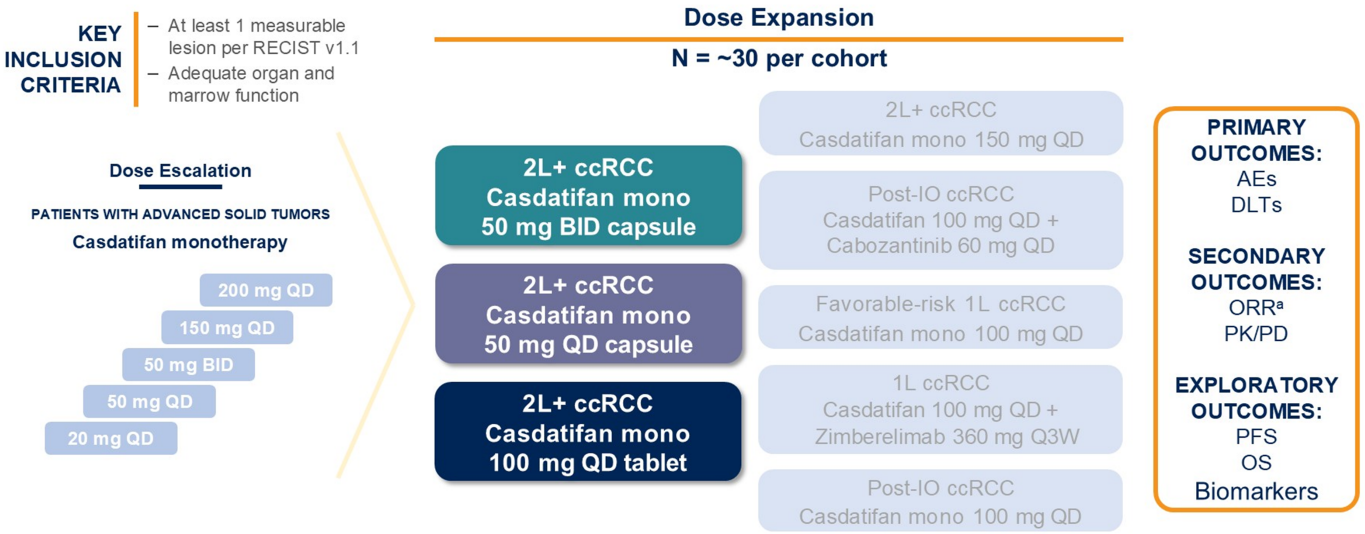
- Despite the better outcome when used as second line, I am not sure belzutifan can work better than cabozantinib in 2 line *(personal view).*

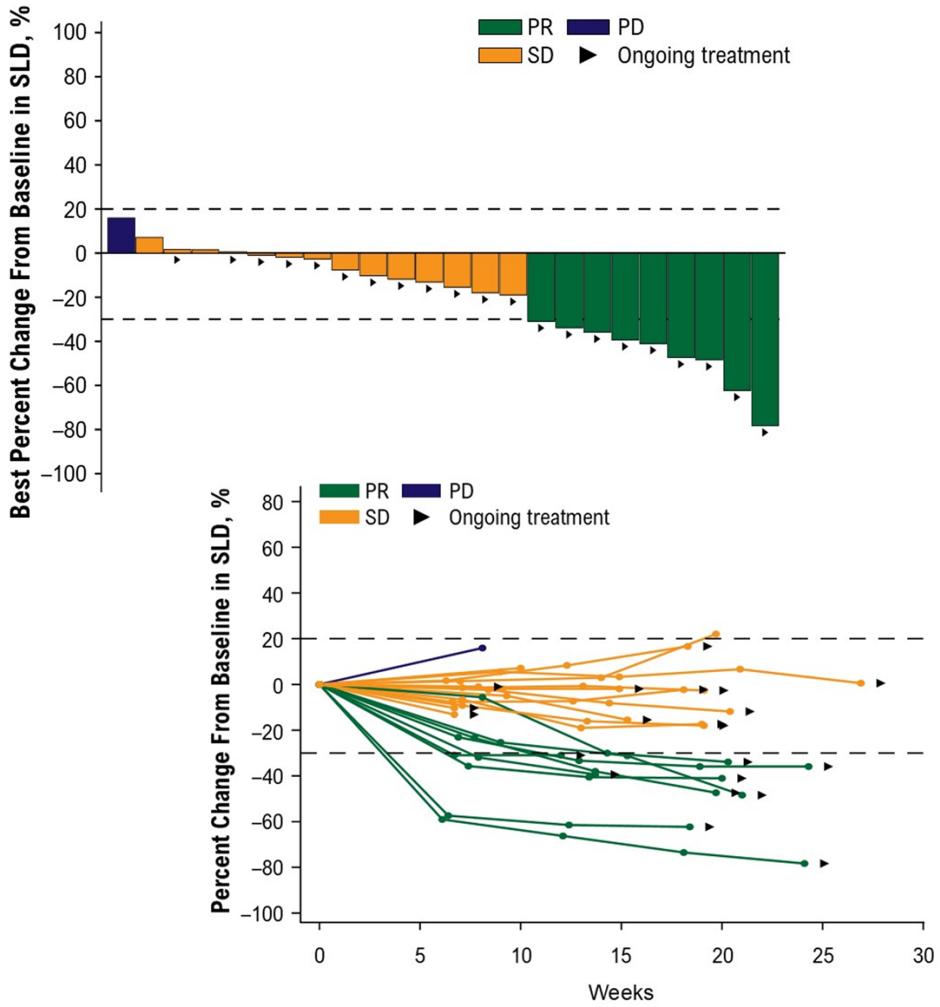
- Belzutifan can be a good choice after cabo-nivo.

- *Is the sequence of* ***len-pemb → cabo*** *better than* ***cabo-nivo → belzutifan****?*
  NO DATA!

Belzutifan and other HIF2α inhibitors

Casdatifan the newest among the HIF inhibitors:





Choueiri TK, ASCO-GU 2025

Belzutifan and other HIF2α inhibitors

Pharmacological and Efficacy Characteristics of HIF-2α Inhibitors

Agent	t1/2	Maximum EPO Suppression	Phase	Dosing	N	ORR (%)	PD (%)	Median PFS (months)	Dose for Expansion
Belzutifan (MK-6482)[1,2]	14 h	~60% at 120 mg	3	120 mg QD	746	23%	34%	5.6	120 mg QD
Casdatifan (AB521)[3]	24 h	~82% at 100 mg	1	100 mg QD	27	33%	15%	Not reached	100 mg QD
NKT2152[4]	38 d	~72% at higher dose levels	1	Variable	100	20%	28%	7.4	Not specified
DFF332[5]	~85 d	Variable*	1	Not established	40	5%	Not specified	Not specified	Discontinued

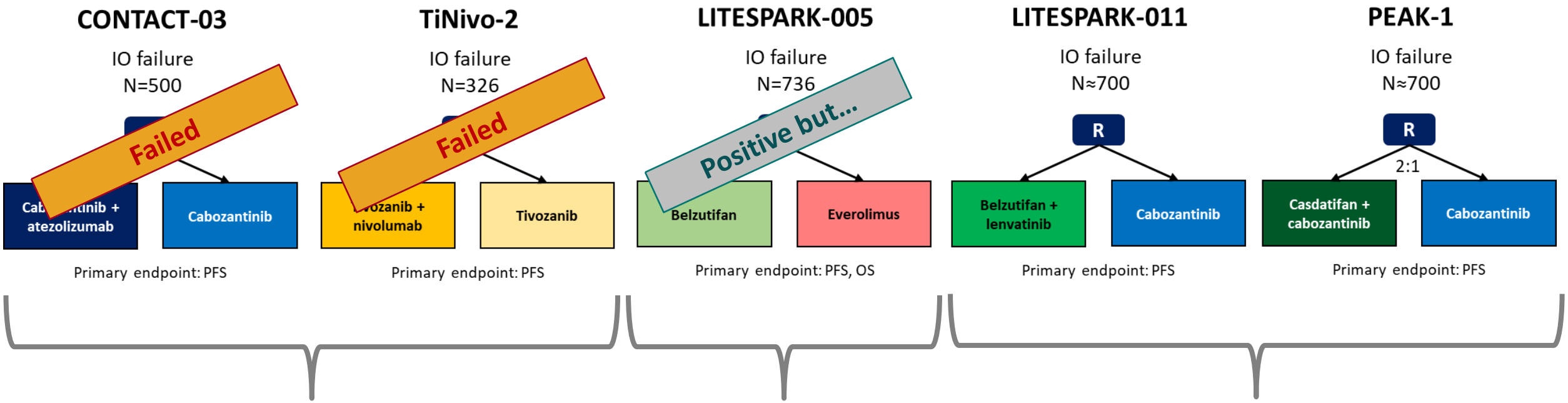
EPO=Erythropoietin; ORR=Objective response rate; PD=Progressive disease; PFS=Progression-free survival; h=Hours; D=Days; QD=Once daily.

[1]Choueiri et al, Nat Med, 2021; [2]Choueiri et al, NEJM, 2024; [3]Choueiri et al, ASCO GU, 2025; [4]Jonasch et al, ESMO, 2024; [5]Pal et al, Clin Cancer Res, 2025.

PRESENTED BY: Rana R. McKay, MD, FASCO

Where we are, where are we going…

What we learnt and what is the future for second line treatment.



No way for IO-continuation

Belzutifan has activity but less than expected

The new strategy is TKI intensification by HIF2α inhibitor *(in cabo naive!).*

Limits of the available & future data

- **Cabozantinib** was the **most used & recommended** second line, but no evidence exists about second line TKI after cabozantinib-nivolumab in 1L.
- Lenvatinib was included lately in the clinical armamentarium and there are few evidence for **cabozantinib activity after lenvatinib**.
- LITESPARK-011 wont show what is the 2L outcome to the currently most used TKI-IO combos (i.e.: cabo-nivo & len-pem).
- PEAK-1 will probably support the role of cabo in 2L (alone or in combination).
- If cabozantinib can be highly recommended as second line, there are **not algorithms to predict the possibility to receive 2L** (50-60%).

Conclusions

- A **new TKI is the most reasonable option** for patients progressed after TKI-IO.
- **Cabozantinib has the strongest data** (PFS 9-10 months; ORR 30-40%).
- Two trials suggested **no efficacy for IO continuation** with TKI, but IO can be considered for patients who interrupt treatment for toxicity (better than a TKI?)
- **New mechanism of action** are urgently **required**, and HIF2α-inhibitors partially respond to this need.
- Ongoing trials are evaluating the efficacy of TKI+HIF2α inhibitor compared to TKI alone.
- New TKI are really welcomed but **major "limit"** seems to be the **greatest activity of cabozantinib and lenvatinib** in first line.

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¡Gracias!

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