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Importancia de una buena secuenciación en el cáncer renal

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DISCLOSURES

Personal confilcts of interest: Scientific Consultancy Role (speaker and advisory role) and travel grant: *IPSEN, Pfizer, Roche, Bayer, Sanofi, Janssen, Astellas, Eisai, Adacap, Lilly, Novartis, BMS, MSD, Adium, Asofarma.*

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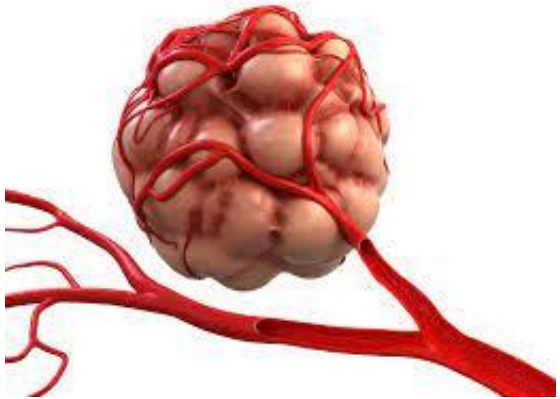
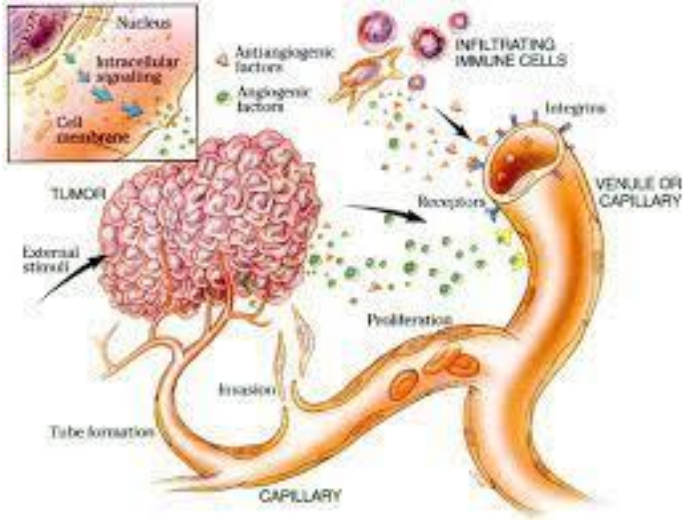
Research support: *Roche, Pfizer, IPSEN, Janssen*

Different 2L clinical scenarios according to 1L

LET´S START WITH 2L AFTER VEGFR-TKI IN 1L





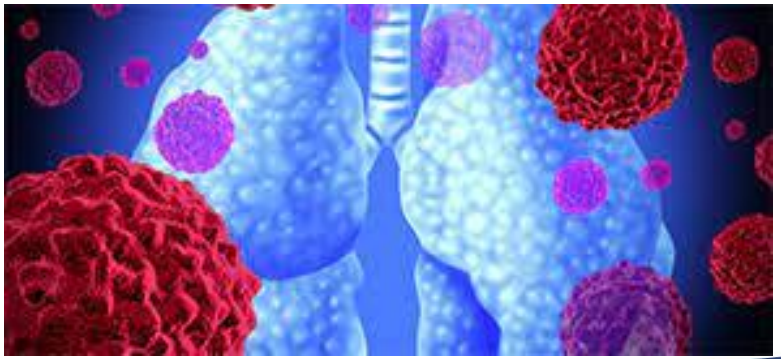
AFTER TKI MONOTHERAPY

	Study design	Treat line	Control arm	DCR (CR + PR + SD)	PD	PFS	OS
Everolimus[1]	Phase III	2nd – 5th	Placebo	0 + 1 + 63%	19%	4,9 vs 1,8 m (HR 0,33)	14,7 vs 14,3 (HR 0,87)
Axitinib[2]	Phase III	2nd	Sorafenib	0 + 19 + 50%	22%	6,7 vs 4,7 m (HR 0,66)	20,1 vs 19,2 (HR0,97)
Nivolumab[3]	Phase III	2nd – 3rd	Everolimus	1 + 24 + 34%	35%	4,6 vs 4,3m (HR0,88)	25 vs 19 m (HR0,73)
Cabozantinib[4]	Phase III	2nd – 3rd	Everolimus	0 + 17 + 65%	12%	7,4 vs 3,8m (HR0,66)	21,4 vs 16,5m (HR0,66)
Lenvatinib + Everolimus[5]	Phase II	2nd	Lenvatinib vs Everolimus	2 + 33 + 47%	4%	14,6 vs 7,4 vs 5,5 m (HR 0,66 and HR0,40)	25,5 vs 18,4 vs 17,5m (HR0,55 and HR0,74)
Tivozanib[6]	Phase III	3rd-4th	Sorafenib	0 + 18 + 55%	21%	5,6 vs 3,9 m (HR 0,73)	16,4 vs 19,7 m (HR 0,99)

[1]Motzer RJ, et al. Lancet 2008; [2]Rini BI, et al. AXIS. Lancet 2011; [3]Motzer RJ, et al. NEJM 2015; Escudier B, et al. ESMO 2022; [4]Choueiri TK, et al. NEJM 2015; [5]Motzer RJ, et al. Lancet Oncology, 2016; [6]Rini B, et al. Lancet Oncology 2020

Different 2L clinical scenarios according to 1L

LET´S CONTINUE WITH ≥2L AFTER PREVIOUS IO-BASED COMBINATIONS.
FROM RETROSPECTIVE TO PROSPECTIVE TRIALS.



Activity from MKI

If any PD1 monotherapy 1L, CTLA-4i rescue?

Any role in keeping PD1/PDL1 axis blockade?

Novel strategies?

	Study treatment	Comparator arm	N	Primary objective	NCT Identifier	Results
IMmotion 151	Atezolizumab + Bevacizumab	Sunitinib	915	PFS PDL1-ve OS ITT	NCT02420821	No impact OS
JAVELIN Renal 101	Avelumab + Axitinib	Sunitinib	886	PFS or OS PDL-1ve	NCT02684006	Final OS pending
CHECKMATE 214	Nivolumab + Ipilimumab	Sunitinib	1096	OS I/P ORR I/P PFS I/P	NCT02231749	✓
MK3475_426	Pembrolizumab + Axitinib	Sunitinib	861	OS & PFS ITT	NCT02853331	✓
CLEAR	Pembrolizumab + Lenvatinib	Sunitinib /Lenvatinib + Everolimus	1050	PFS BICR Key: OS, ORR	NCT02811861	✓
CHECKMATE 9ER	Nivolumab + Cabozantinib	Sunitinib	630	PFS BICR	NCT03141177	✓
COSMIC 313	Nivolumab + Ipilimumab + Cabozantinib	Nivolumab + Ipilimumab	855	PFS BICR First 550pts randomized	NCT03937219	✓ Pending OS

**Toripalimab+ Axitinib PFS and OS in Chinese population only
**Benmelstobart plus Anlotinib PFS in Chinese population only

VEGFR-TARGETED THERAPIES – RETROSPECTIVE STUDIES

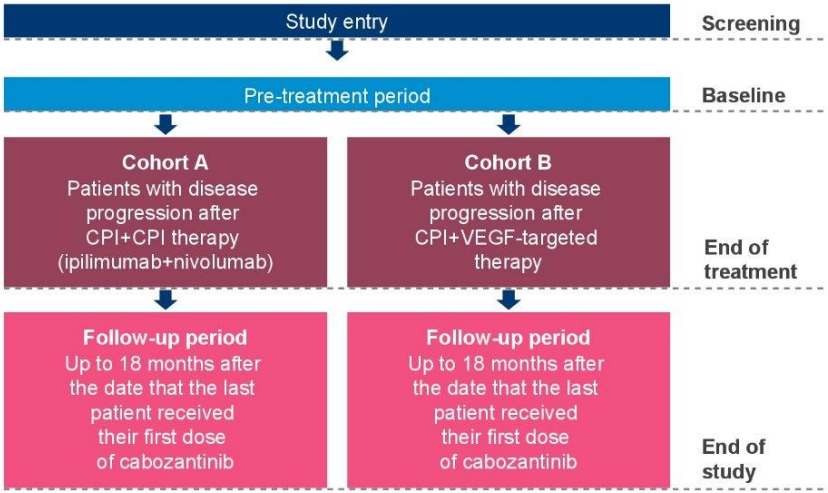
Study	Previous IO	N	Targeted therapies	N	Median TTF/PFS (95%CI), months (m)	ORR (%)	1 yr-Overall Survival/median OS (95% CI)
Derosa 2017	IOIO	56	CABO	56	8	33	12.3
Shah A EJC 2019/ 2015-2018	PD-1 PD-1/CTLA-4 PD-(L)1/VEGF	12 32 24	AXI CABO PAZO SUN	25 20 19 6	13.2 (8.6 – NR) 15.2 (7.9 – NR) 24.2 (6.1 – NR) 3.6 (0.9 – NR)	10/25: 40 8/20: 40 9/19: 47 1/6: 16	79.6% (mOS NR)
Dudani S EurUrol 2019/ 2005 - 2018	Ipilimumab/Nivo PD-(L)1/VEGF	75 113	SUN CABO PAZO AXI, NIVO, LEN EVE	24 11 11 7, 5, 2	1st: 10.2 (6.7 – 15.1) 1st: 14.3 (9.2 – 16.1) 2nd: 3.7 (2.5 – 9.6). 2nd: 5.4 (3.4 – 14.7)	9/20:45 3/20: 15 (0.04)	NA (35.1 – NR) NA (22.3 – NR)
Ged Y BMC Urol 2020/ 18m/ 2013 – 2018	IO-VEGFR TKI IO-Bev	35 24	CABO AXI PAZO/ LEN EVE	22 18 4 + 4	12.0 (8.2–24.5)	25%	24.5 (12–NE)
McGregor A/ 2012 - 2018	IO /IOIO IOVE IO + Other (N=80 prior VEGFi)	55 25 6	CABO	55 25 6	8.1 (6.4 – 14.9) 4.7 (3.3 – 5.9) 5.7 (3.2 – NR)	42 28 17	63 40 42
Wells JC/ 2014 – 2019	IO / IOIO PD-(L)1/VEGF	75 27	SUN	75 27	5.4 (3.6-14.8) 4.7 (3.4 – 9.6)	27.5 20.8 (0.55)	16.1 (8.5 - 35.2) 11.8 (9.5 – NR)
Marteau JCO Suppl, 2021	IOIO/IOVE		CABO Others	187 60	6.2 3.1	53.5 38.3	
Iacovelli R Target oncol 2020	IO (NIVO)	84	CABO	84	11.5 (8.3–14.7)	52	17.3

AFTER IO + IO OR IO + VEGFR-TKI COMBOS (antiangiogenics)

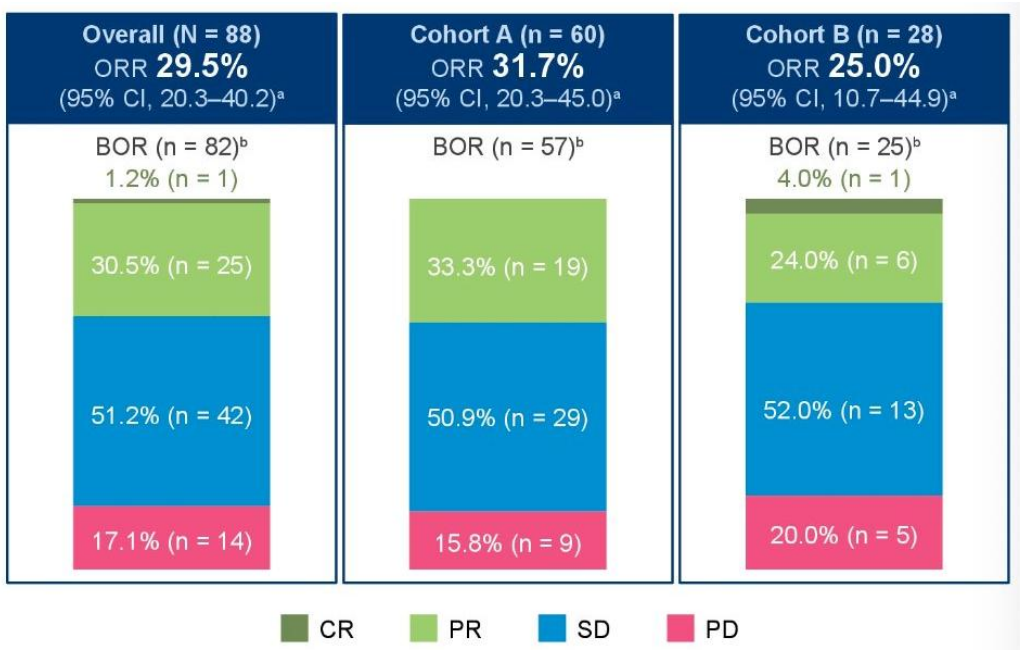
Phase II, single arm studies	N	Primary endpoint	Previous VEGFR-TKI	Previous treatment lines	ORR	PFS	OS
CABOPOINT Cabozantinib	88 (60 + 28)	ORR Cohort A BICR	31.8%	≥ 1L	29.5% (1.2% CR)	10.9 m (95% CI 5.5 – 19.4)	NR
BREAKPOINT Cabozantinib	30	SLP	26%	1L	37.9% (0% CR)	8.3 m (95%CI 3.9 - 17.4)	13.8 m (95%CI 7.7 - 29.0)
AXITINIB	40	SLP	70%	≥ 3L	45% (3%CR)	8.8 m (95% CI 5.7–16.6)	NR
INMUNOSUN Sunitinib	21	ORR RECIST 1.1 by investigator	47.7%	1L	19% (0% CR)	5.6 m (95% CI 3.1 - 8.0)	23.5 m (95% CI 6.3 - 40.7)
IO-PAZ Pazopanib	62	SLP	43.5%	1-2 L	14.5% (3.2% CR)	6.5 m (95% CI, 3.7-9.2)	21.3 m (95% CI, 14.9 - NE)
LITESPARK 003, COHORT 2 Belzutifan + Cabozantinib	52	ORR RECIST 1.1 by investigator	46%	1-2 L	31% (4% CR)	13.8 m (95% IC 9.2-19.4)	26.7 m (95%IC 20.0-41.1)

Albiges L, et al. Procopio G, et al. Tumori. 2023 Feb;109(1):129-137; Ornstein MC, et al. Lancet Oncol. 2019 Oct;20(10):1386-1394; Grande E, et al. ESMO Open. 2022 Apr;7(2):100463; Powles TB, et al. Ann Oncol 2020; 31 (4s): S564; Choueiri TK, et al. Ann Oncol. 2023; 34 (suppl_2): S1254-S1335; Albiges L, et al. ESMO 2024..

ROLE OF VEGFR TKI – CABOPOINT TRIAL



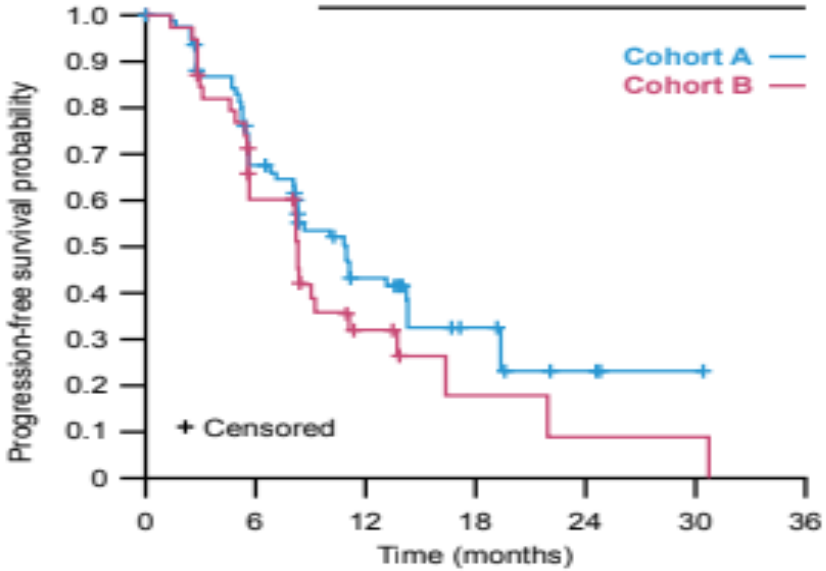
Baseline was defined as the date of cabozantinib initiation. Cabozantinib was initiated in the 15 days after the screening visit.
Figure adapted from Albiges *et al.* 2022.[6]
CPI, checkpoint inhibitor; VEGF, vascular endothelial growth factor.



Albiges L, et al. Presented at ASCO GU 2023

ROLE OF VEGFR TKI – CABOPOINT TRIAL

	Median PFS (IQR)
Cohort A[b]	10.9 (5.5–19.4)
Cohort B[b]	8.3 (5.4–16.4)

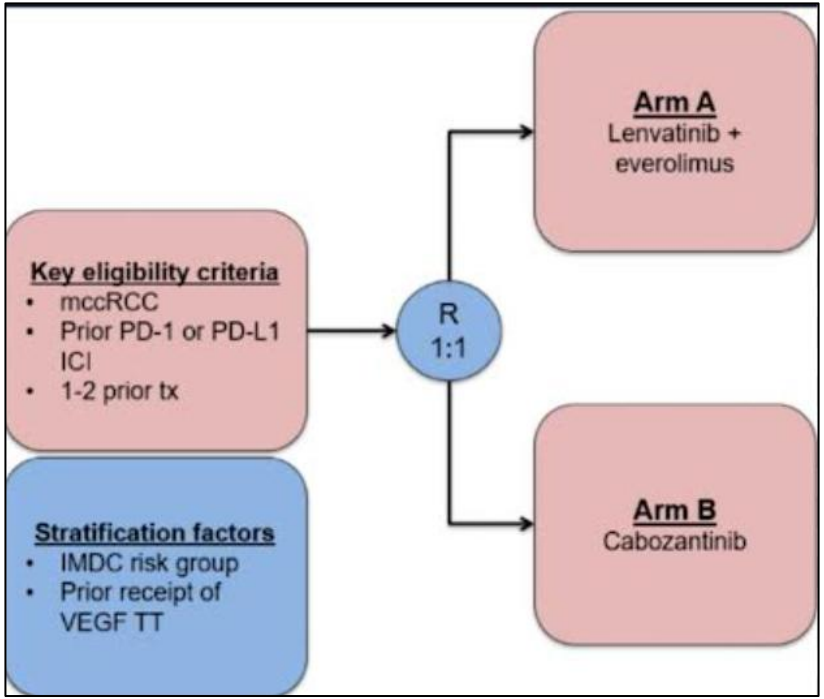


At risk							
Cohort A	79	48	22	9	3	1	0
Cohort B	40	21	7	2	1	1	0

Albiges L, et al. Presented at ESMO 2024

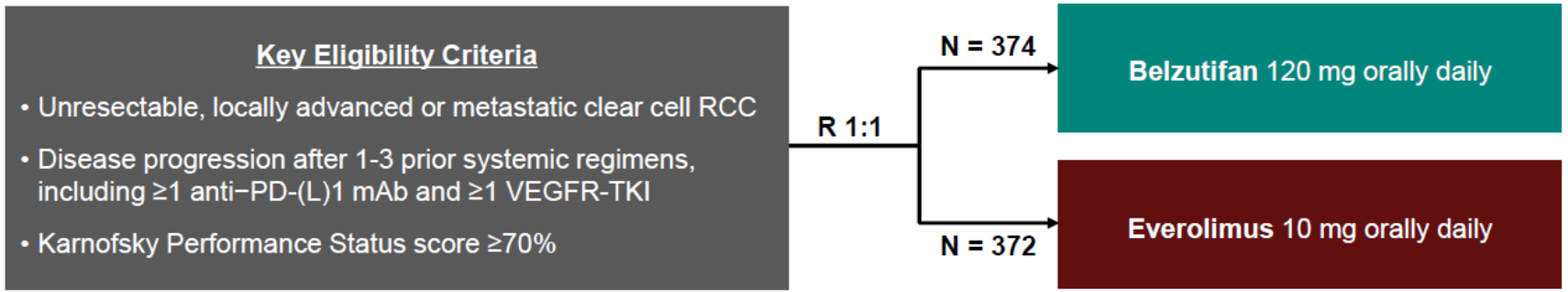
MKI AFTER IO – PROSPECTIVE STUDIES

Lenvatinib With Everolimus Versus Cabozantinib for Second-Line or Third-Line Treatment of Metastatic Renal Cell Cancer (NCT05012371). The most recent must include PD-1/PD-L1 ICI.



www.clinicaltrials.gov

LITESPARK-005 PHASE III CLINICAL TRIAL



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

Dual Primary Endpoints:
- PFS per RECIST 1.1 by BICR
- OS
- The study was considered positive if either of the dual primary endpoints was met

Key Secondary Endpoint:
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:
- DOR per RECIST 1.1 by BICR
- Safety

Rini B, et al. ESMO 2024

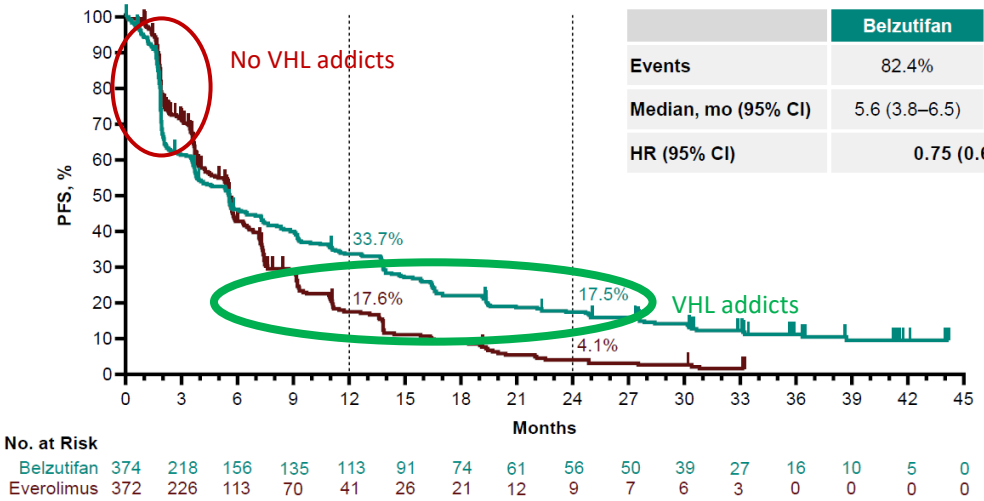
LITESPARK-005 PHASE III CLINICAL TRIAL

Characteristic	ITT		Ongoing Treatment
	Belzutifan (N = 374)	Everolimus (N = 372)	Belzutifan (n = 54)
Age, median (range), yrs	62 (22–90)	63 (33–87)	64 (44–79)
Male, %	79.4	76.3	81.5
KPS score[a], %			
90/100	63.6	64.5	81.5
70/80	36.1	35.2	18.5
IMDC risk categories, %			
Favorable	21.7	22.6	31.5
Intermediate	66.3	65.1	59.3
Poor	12.0	12.4	9.3
Sarcomatoid features present, %	11.2	8.3	11.1
Prior nephrectomy, %	69.8	69.6	83.3
No. prior VEGFR-TKIs, %			
1	49.7	51.1	46.3
2-3	50.3	48.9	53.7
No. prior lines of therapy[b], %			
1	12.0	14.0	16.7
2	42.2	44.6	44.4
3	45.2	40.3	38.9

Rini B, et al. ESMO 2024

LITESPARK-005 PHASE III CLINICAL TRIAL

Primary Endpoint: PFS per RECIST 1.1 by BICR



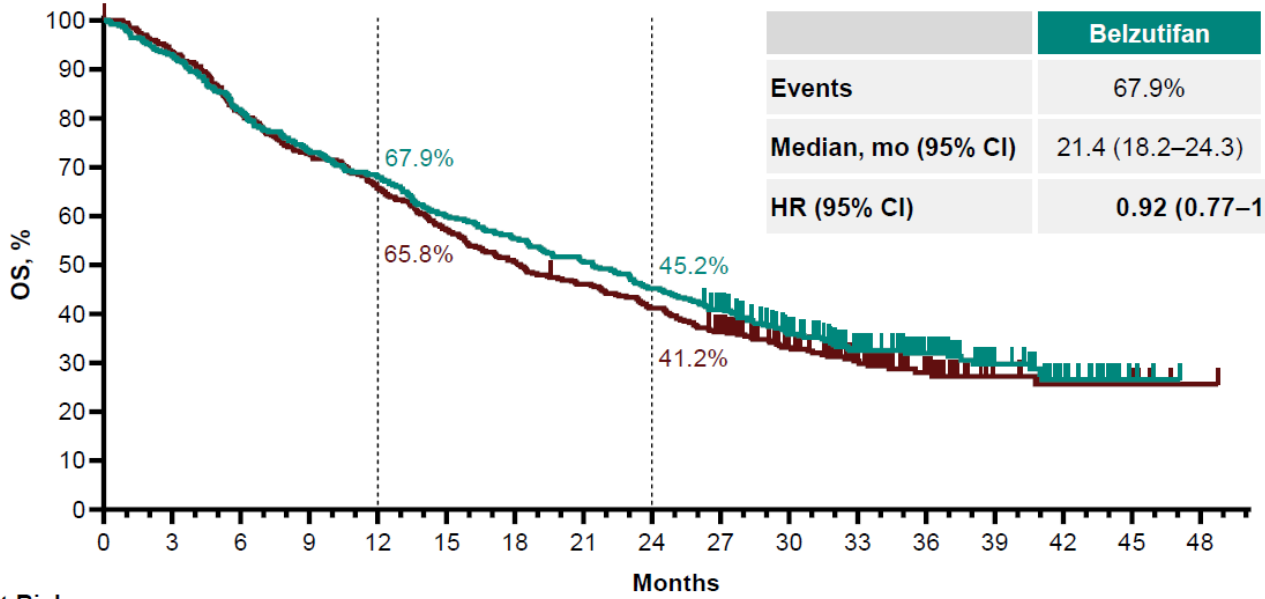
	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.88)	

	Belzutifan (N = 374)	Everolimus (N = 372)
ORR, % (95% CI)	22.7% (18.6–27.3)	3.5% (1.9–5.9)
Estimated difference in % (95% CI)	19.2 (14.8–24.1)	
Confirmed best objective response, %		
CR	3.5%	0
PR	19.3%	3.5%
SD	38.2%	65.9%
PD	34.0%	21.5%
Not evaluable[a]	1.3%	2.4%
No assessment[b]	3.7%	6.7%

Rini B, et al. ESMO 2024

LITESPARK-005 PHASE III CLINICAL TRIAL

Primary Endpoint: OS



	Belzutifan	Everolimus
Events	67.9%	69.6%
Median, mo (95% CI)	21.4 (18.2–24.3)	18.2 (15.8–21.8)
HR (95% CI)	**0.92 (0.77–1.10); *P*=0.18**	

No. at Risk

Belzutifan	374	347	305	274	254	224	207	189	169	148	111	75	54	31	18	4	0
Everolimus	372	347	301	270	244	212	188	170	152	128	92	64	38	20	12	5	1

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LITESPARK-005 PHASE III CLINICAL TRIAL

ADR	Incidence, n (%)	Time to onset, median (range), mo
Anemia	310 (83.3)	1.0 (0.03–27.4)
Hypoxia	53 (14.2)	1.0 (0.03–21.1)
Dizziness	50 (13.4)	2.3 (0.03–34.2)
Dyspnea	57 (15.3)	1.9 (0.03–25.8)
Fatigue	120 (32.3)	1.5 (0.03–29.9)
Nausea	69 (18.5)	1.4 (0.03–24.0)
Weight increased	22 (5.9)	3.3 (0.5–15.0)

ADR	Incidence, n (%)	Duration, median (range), mo
Anemia	310 (83.3)	4.6 (0.1+–47.1+)
Hypoxia	53 (14.2)	0.5 (0.03–31.9+)
Dizziness	50 (13.4)	1.1 (0.03–35.2)
Dyspnea	57 (15.3)	3.3 (0.03–39.5+)
Fatigue	120 (32.3)	NR (0.1–43.9+)
Nausea	69 (18.5)	1.2 (0.03–38.6)
Weight increased	22 (5.9)	16.6 (0.6–40.0+)

Rini B, et al. ESMO 2024

Phase II Belzutifan + Cabozantinib LITESPARK-003 (NCT03634540)

Key Eligibility Criteria
- Advanced or metastatic ccRCC
- Either treatment naive or has received prior PD-1/L1 immunotherapy and ≤2 regimens for locally advanced or metastatic RCC
- ECOG PS 0 or 1

Cohort 1:
Treatment- naive
belzutifan 120 mg/day + cabozantinib 60 mg/day
N ≈ 50

Cohort 2:
Prior immunotherapy treatment
belzutifan 120 mg/day + cabozantinib 60 mg/day
N ≈ 50

Safety and tolerability were evaluated in the first 6 participants enrolled, irrespective of cohort
- If tolerability was established, enrollment continued
- If tolerability was not established, dose was reviewed

Assessments
- Q8W after week 9 for 12 months and then Q12W thereafter

Postreatment
- 28-day safety follow-up
- Follow-up visits every 6 months

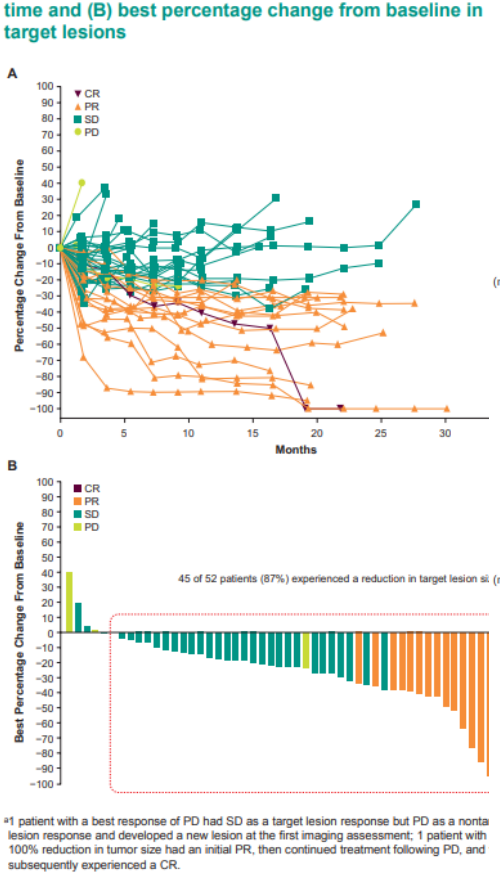
End Points
- Primary: ORR
- Secondary: PFS, TTR, DOR, OS, safety/ tolerability, PK/PD

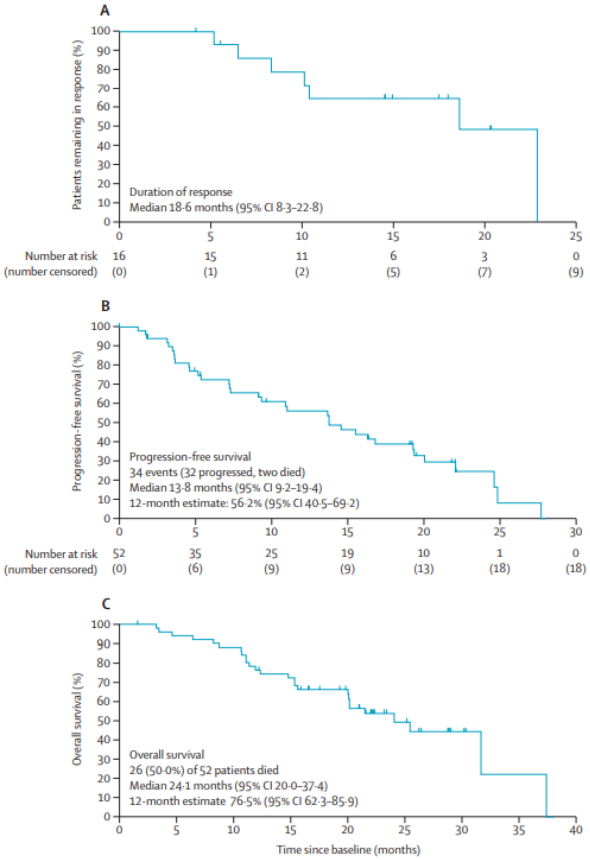
Phase II Belzutifan + Cabozantinib LITESPARK-003 (NCT03634540)

Table 3. ORR by prior anticancer therapy

	All patients N = 52	Prior anticancer therapy		Line of prior anticancer therapy	
		Immunotherapy only[a] n = 28	Immunotherapy/ anti-VEGF therapy[b] n = 24	1 line of prior therapy n = 29	2 lines of prior therapy n = 23
ORR, % (95% CI)	31 (18.7-45.1)	32 (15.9-52.4)	29 (12.6-51.1)	31 (15.3-50.8)	30 (13.2-52.9)
Best overall response					
CR	1 (2)	1 (4)	0 (0)	1 (3)	0 (0)
PR	15 (29)	8 (29)	7 (29)	8 (28)	7 (30)
SD	32 (62)	17 (61)	15 (63)	18 (62)	14 (61)
PD	3 (6)	1 (4)	2 (8)	2 (7)	1 (4)
Not available	1 (2)	1 (4)	0 (0)	0 (0)	1 (4)

Figure 2. (A) Percentage change in target lesion size over time and (B) best percentage change from baseline in target lesions

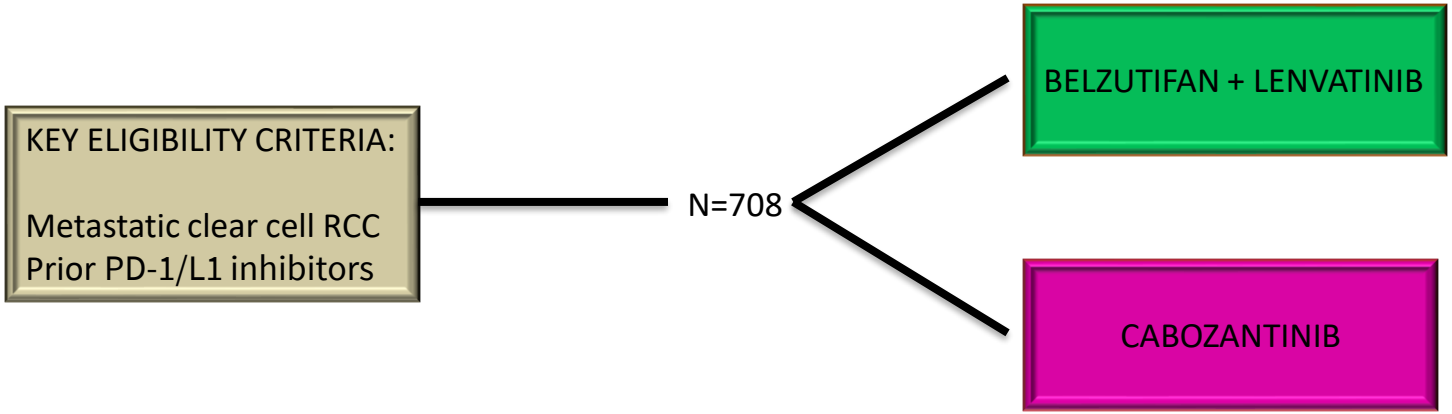




McDermott, et al. ESMO 2022
Choueiri T et al. Lancet Oncol 2023

Ongoing Clinical Trials: Belzutifan in IO-pretreated patients

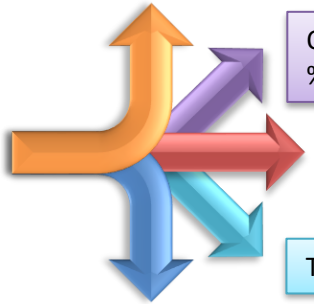
A Study of Belzutifan (MK-6482) in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011) NCT04586231



Primary endpoint: Progression-Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to approximately 34 months]

Continuing IO-Based strategies

IO response adaptive strategy (CTLA-4 addition or PD-1 inhibition rechallenge)



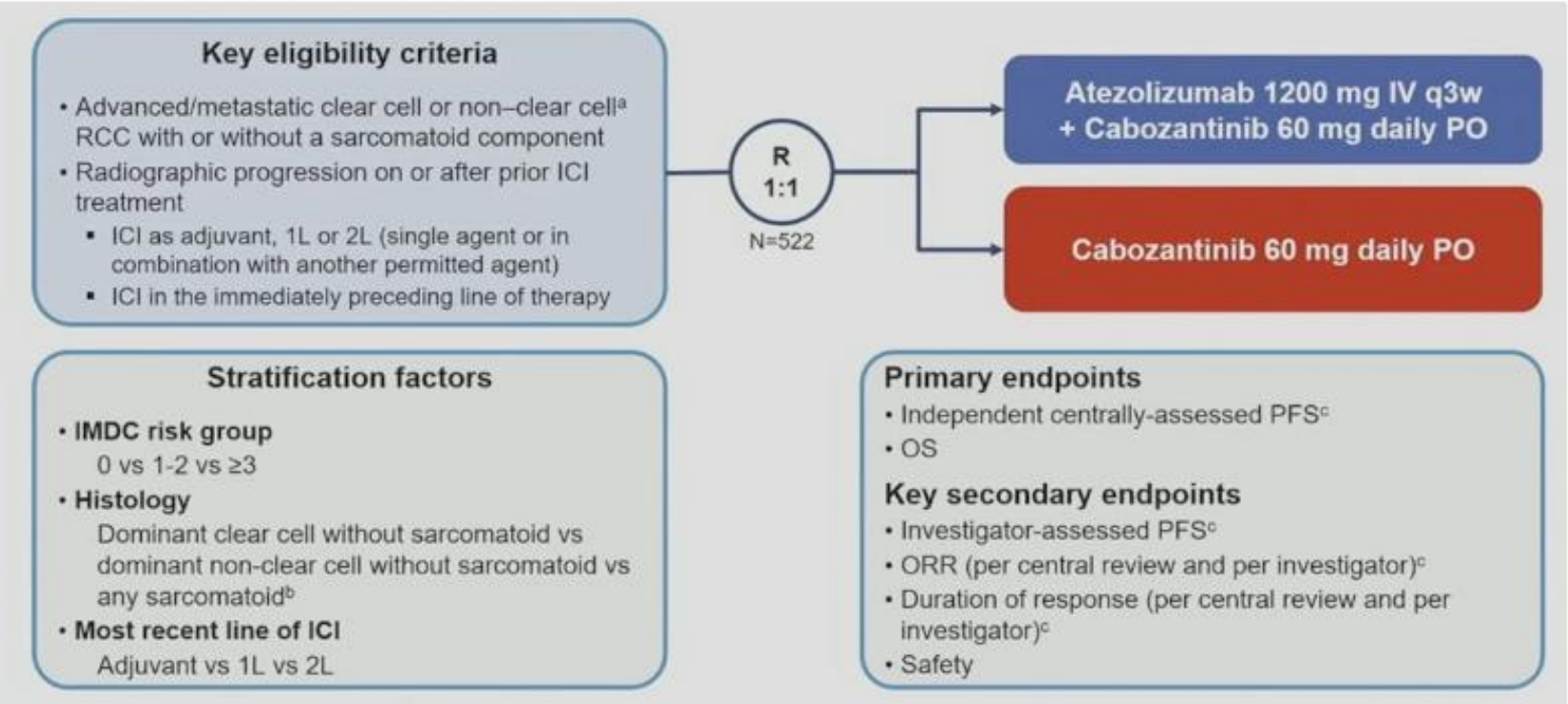
Trial & Primary Endpoint & N	ORR PD-1i	Criteria CTLA4-i addition	N; ORR to CTLA4-i
HCRN GU16-260 (A) & TFS (N=128)	34% (6.5%) Part A	SD/PD (N= 34)	11.5% (3%) Part B
OMNIVORE (A) & % PR/CR 1-year off nivolumab (N=12)	1L 17% ≥ 2L 12%	PD (N=3)	N/A (re-PD1 inh)
OMNIVORE (B) & %SD/PD with NIVO achieving PR/CR with IPI (N = 57)	1L 17% ≥ 2L 12%	SD/PD (N=57)	4% (0)
TITAN & ORR full analysis set (N= 207)	1L: 28% (CR 2%) 2L: 18% (CR 0%)	SD/PD (N=108)	1L: 36% (CR 7%) 2L: 32% (CR 6%)
FRACTION RCC & ORR, DoR, PFS at 24w (N = 46)	N/A	PD to PD-1 inh (N=46)	17.4% (0)

In the first line, adding CTLA-4 to PD-1 inhibitor upfront achieves better antitumor efficacy compared to adding CTLA-4 as a rescue agent to PD-1 progression.
In the second line, CTLA-4 inhibitor is able to rescue few patients progressing to PD-1 inhibitor (difficult to select which patients).

Alonso Gordoa T. ESMO 20204. Atkins MB, et al. J Clin Oncol 2022;40:2913–23; McKay RR, et al. J Clin Oncol. 2020 Dec 20;38(36):4240-4248; Grimm MO, et al. Lancet Oncol. 2023 Nov;24(11):1252-1265; Choueiri TK, et al. J Immunother Cancer. 2022 Nov;10(11):e005780.

CONTACT-03

CONTINUING IO-BASED STRATEGIES

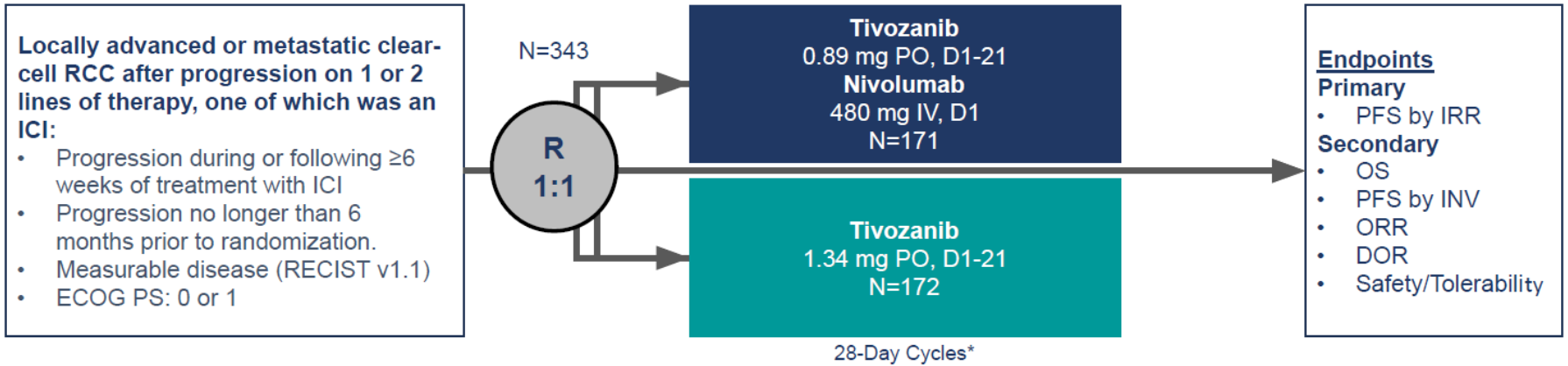


Choueiri T et al. ASCO 2023

CONTINUING IO-BASED STRATEGIES

TiNivo-2: Phase 3 Study

TiNivo: Tivozanib 1.5mg/24h (3/1) + Nivo 480 mg Q4W
TIVO-1: Tivozanib 1.5 mg/24h (3/1)
TIVO-3: Tivozanib 1.5 mg/24h (3/1)



Stratification Factors
- IMDC risk category
- Prior therapy (ICI as most recent therapy or not)

Key Considerations
- Reduced dose of tivozanib in combination arm was agreed with regulatory authorities due to potential risk of higher rate of grade 3/4 hypertension
- Prior therapy (ICI as most recent therapy or not)
  - Test if ICI break impacts outcome (reset the immune system?)

Choueiri T, et al. ESMO 2024

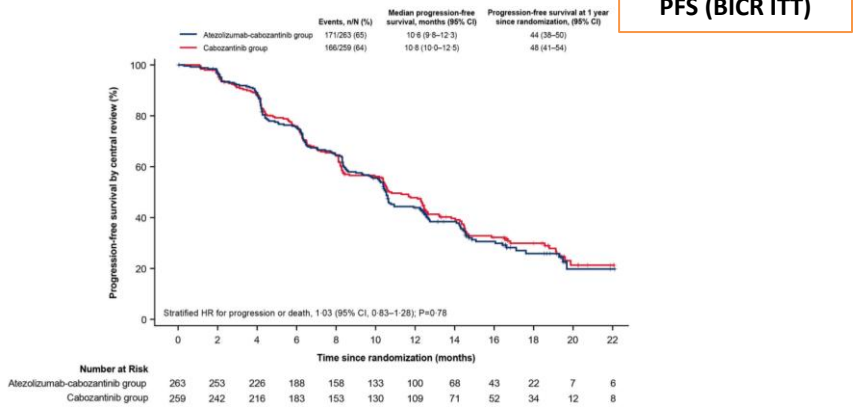
BASELINE CHARACTERISTICS		CONTACT-03 (2020-2021)	TINIVO-2 (2021 – 2023)
Number of patients		522	343
Experimental arm		Cabozantinib 60 mg/24h + Atezolizumab 1200 mg iv q3w	Tivozanib 0.89 mg/24h 3/1 + nivolumab 480mg
Control arm		Cabozantinib 60 mg/24h	Tivozanib 1.34 mg/24h
Median follow up, months		15.6	11.8
Sarcomatoid pheatures, N (%)		25 (10)	-
IMDC	Favorable, N (%) Intermediate, N (%) Poor, N (%)	49 (19) 172 (65) 41 (16)	30 (18) 114 (67) 27 (16)
Previous treatment	**Adjuvant, N (%)** 1L Metastatic, N (%) 2L Metastatic, N (%)	**1 (<1)** 144 (55) 118 (45)	**25 (15%)** 111 (65%) 60 (35%)
1L treatment		Ipilimumab + nivolumab 80 (31%) Sunitinib 77 (29%); Pazopanib 36 (14%) **Axitinib + pembrolizumab 36 (14%)**	Ipilimumab + nivolumab 63 (39%); Nivolumab 6 (4%) Sunitinib or Pazopanib 11 (6%) **TKI + IO 60 (35%)**
2 L treatment		**Nivolumab 104/119 (87%)**	Cabozantinib/Sunitinib 38/65 (22%); **Nivolumab 11/65 (6%)**
VEGFR-TKI treatment	0L, N(%) 1L, N(%) **2L, N(%)**	93 (35%) 166 (63%) **4 (2%)**	53 (31%) 96 (56%) **22 (13%)**

Most recent therapy Non ICI: 49 (29%)

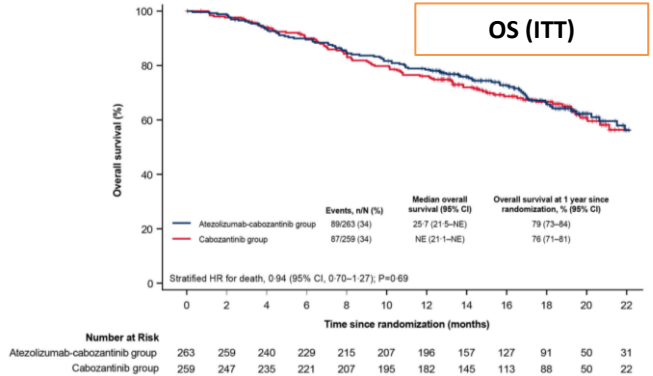
Pal SK, et al. Lancet. 2023 Jul 15;402(10397):185-195; Choueiri TK, et al. ESMO 2024; Choueiri TK, et al. Lancet. 2024; Published Online September 13, 2024.

CONTACT-03

PFS (BICR ITT)

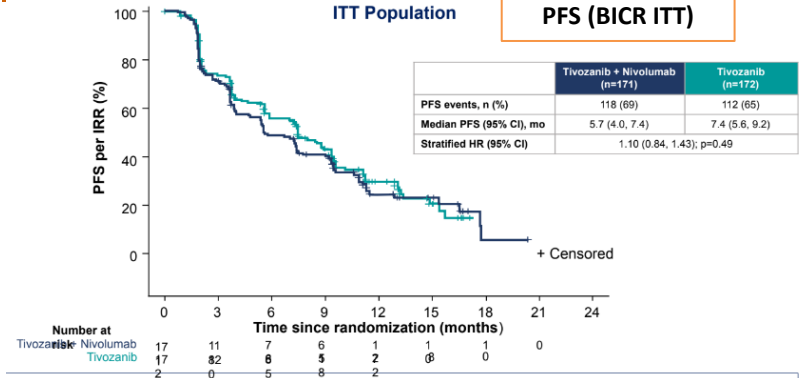


OS (ITT)



TINIVO-2

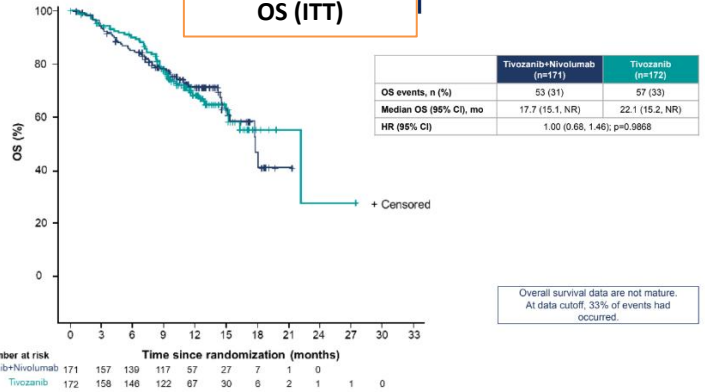
PFS (BICR ITT)



	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 for the tivozanib + nivolumab cohort and 12.5 months for tivozanib monotherapy

OS (ITT)



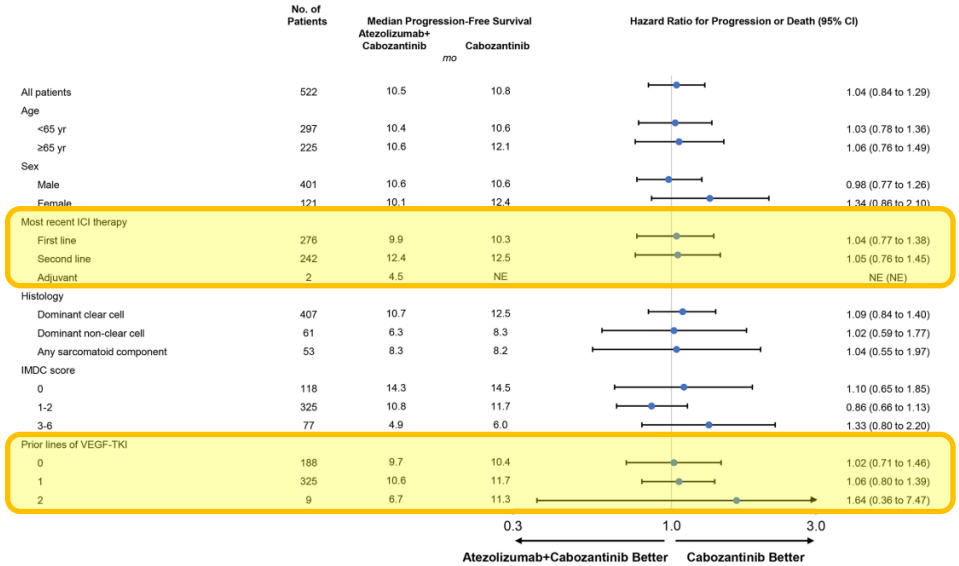
	Tivozanib+Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1, NR)	22.1 (15.2, NR)
HR (95% CI)	1.00 (0.68, 1.46); p=0.9868	

Overall survival data are not mature. At data cutoff, 33% of events had occurred.

Choueiri TK, et al. ESMO 2024; Pal SK, et al. Lancet. 2023 Jul 15;402(10397):185-195.

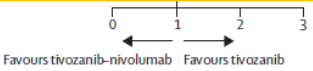
CONTACT-03

PFS subgroup analysis



TINIVO-2

	Tivozanib–nivolumab event/N	Tivozanib event/N	Tivozanib–nivolumab median progression-free survival, months (95% CI)	Tivozanib median progression-free survival, months (95% CI)	Hazard ratio for progression or death (95% CI)
Age (years)					
<65	68/89	65/97	4·8 (3·4–7·3)	7·4 (5·5–9·2)	1·25 (0·89–1·76)
≥65	50/82	47/75	9·2 (5·5–9·6)	7·6 (5·2–10·0)	0·92 (0·61–1·37)
Sex					
Male	86/125	88/134	5·6 (3·9–7·5)	7·4 (5·5–9·2)	1·01 (0·75–1·36)
Female	32/46	24/38	6·7 (3·7–10·9)	7·4 (5·6–12·9)	1·27 (0·75–2·16)
ECOG					
0	52/76	53/85	7·3 (4·0–9·4)	8·8 (7·2–11·1)	1·15 (0·78–1·69)
1	66/94	59/87	5·5 (3·7–9·0)	6·0 (3·7–8·6)	0·95 (0·67–1·36)
IMDC risk category					
Favourable	18/30	15/31	9·3 (4·0–11·4)	11·2 (9·3–13·1)	1·37 (0·69–2·73)
Intermediate	78/114	75/115	5·7 (4·0–9·4)	7·4 (4·5–8·4)	0·99 (0·72–1·36)
Poor	22/27	22/26	3·7 (2·7–7·4)	5·7 (2·3–9·2)	1·35 (0·73–2·50)
Previous nephrectomy status					
Complete	45/70	59/85	9·0 (5·5–9·6)	9·3 (5·5–11·1)	0·99 (0·65–1·49)
Partial	21/32	15/22	4·8 (2·2–10·9)	7·5 (2·1–15·2)	1·17 (0·60–2·27)
Other	4/6	11/14	5·8 (1·9–NE)	5·2 (1·5–9·2)	0·60 (0·19–1·97)
Previous systemic anticancer therapies (line of therapy)					
Second line	71/111	64/105	7·3 (5·4–9·3)	9·2 (7·4–10·0)	1·15 (0·82–1·62)
Third line	47/60	48/67	4·8 (3·2–7·5)	5·5 (2·9–7·4)	0·97 (0·65–1·45)
Use of immune checkpoint inhibitor in most recent line					
Yes	78/122	75/122	7·4 (5·6–9·6)	9·2 (7·4–10·0)	1·10 (0·80–1·52)
No	40/49	37/50	3·7 (2·7–5·4)	3·7 (1·9–7·2)	0·95 (0·61–1·50)
Use of VEGFR TKI in most recent line*					
Yes	37/45	37/50	3·4 (2·2–4·8)	3·7 (1·9–7·2)	0·96 (0·61–1·52)
No	37/66	36/65	9·6 (7·5–11·2)	9·3 (7·4–14·7)	0·95 (0·60–1·51)
Previous use of VEGFR TKI (any previous line)					
0 VEGFR TKI	29/53	28/53	9·6 (7·4–15·3)	9·4 (7·4–15·5)	1·03 (0·61–1·74)
1 VEGFR TKI	69/96	70/101	5·4 (3·7–6·7)	7·4 (5·5–8·8)	1·04 (0·74–1·45)
2 VEGFR TKI	20/22	14/18	3·1 (2·1–4·0)	3·8 (1·9–7·2)	1·33 (0·67–2·65)



Choueiri TK, et al. ESMO 2024
Pal S et al. Lancet 2023

CONTACT-03

RECIST 1.1 per central review[a]

	Atezo + Cabo (n=259)	Cabo (n=254)
Confirmed objective response, n, (%) [95% CI]	105 (40.5) [34.5, 46.8]	104 (40.9) [34.8, 47.3]
Complete response, n (%)	0	2 (0.8)
Partial response, n (%)	105 (40.5)	102 (40.2)
Stable disease, n (%)	131 (50.6)	121 (47.6)
Progressive disease, n (%)	11 (4.2)	13 (5.1)
Not evaluable or missing, n (%)	12 (4.6)	16 (6.3)
Ongoing response at data cutoff, n/N (%)[b]	53/105 (50.5)	55/104 (52.9)
Median duration of response (range), mo	12.7 (2.1+ to 22.9+)	14.8 (2.3+ to 25.6+)

TINIVO-2

	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
ORR, n (%), [95% CI]	33 (19.3) [13.7, 26.0]	34 (19.8) [14.1, 26.5]
CR, n (%)	1 (0.6)	1 (0.6)
PR, n (%)	32 (18.7)	33 (19.2)
SD, n (%)	74 (43.3)	81 (47.1)
PD, n (%)	49 (28.7)	43 (25.0)
NE, n (%)	15 (8.8)	14 (8.1)
mDOR, mo (95% CI)	15.77 (5.65-NR)	9.66 (3.71-NR)

	CONTACT-03 Cabo (60 mg QD) arm (n=259)	TiNivo-2 Tivo (1.34 mg QD*) arm (n=172)
Select Any Gr TEAEs, %		
Diarrhea	71	36
Nausea	36	27
Asthenia	29	20
Fatigue	24	40
Anemia	19	9
Hypertension	34	40

Choueiri TK, et al. ESMO 2024
Pal S et al. Lancet 2023

Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

Sumanta Kumar Pal, Laurence Albiges, Piotr Tomczak, Cristina Suárez, Martin H Voss, Guillermo de Velasco, Jad Chahoud, Anastasia Mochalova, Giuseppe Procopio, Hakim Mahammedi, Friedemann Zengerling, Chan Kim, Takahiro Osawa, Martín Angel, Suyasha Gupta, Omara Khan, Guillaume Bergthold, Bo Liu, Melania Kalaitzidou, Mahrukh Huseni, Christian Scheffold, Thomas Powles, Toni K Choueiri

Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study

Toni K Choueiri, Laurence Albiges*, Philippe Barthélémy, Roberto Iacovelli, Sheik Emambux, Javier Molina-Cerrillo, Benjamin Garmezy, Pedro Barata, Arnab Basu, Maria T Bourlon, Helen Moon, Raffaele Ratta, Rana R McKay, Alexander Chehrazi-Raffle, Hans Hammers, Daniel Y C Heng, Edgar Braendle, Kathryn E Beckermann, Bradley A McGregor, Robert J Motzer*

CONTACT 03 & TINIVO-2 limit the role for continuing/rechallenging PD-1/PD-L1 inhibition after progression in advanced RCC, but these studies highlight the role of TKI in treatment sequence according to current clinical practice.

ENTRATA Trial

Key Inclusion / Exclusion Criteria

- Advanced/metastatic RCC with clear cell component
- At least 2 prior therapies including at least 1 prior VEGFR-targeting TKI
- KPS ≥ 70%
- Treated/stable brain mets allowed
- No prior mTOR inhibitor

2:1

- Telaglenastat (800 mg BID) + Everolimus (10 mg QD)
- Placebo + Everolimus (10 mg QD)

Survival Follow-Up

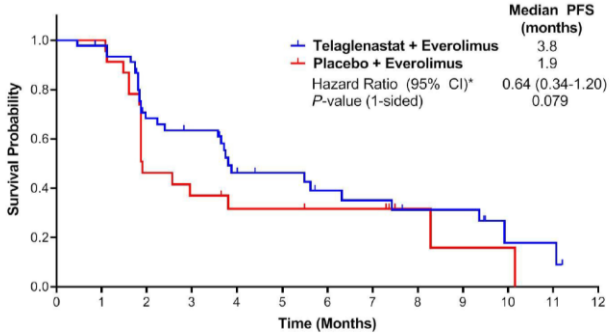
ENDPOINTS

Primary
PFS per investigator

Secondary
OS

Additional
Safety, ORR, QOL

- Stratification factors:
  - MSKCC (Intermediate/poor vs. favorable)
  - Prior TKI (1 vs. >1)



Follow-up
Minimum: 3 months
Median: 7.5 months

CANTATA Trial

Key Inclusion / Exclusion Criteria

- Clear cell RCC
- KPS ≥ 70%
- 1-2 lines of prior therapy including at least one antiangiogenic therapy **or** nivolumab + ipilimumab

1:1

- Telaglenastat (800 mg BID PO) + Cabozantinib (60 mg QD PO)
- Placebo BID + Cabozantinib (60 mg QD PO)

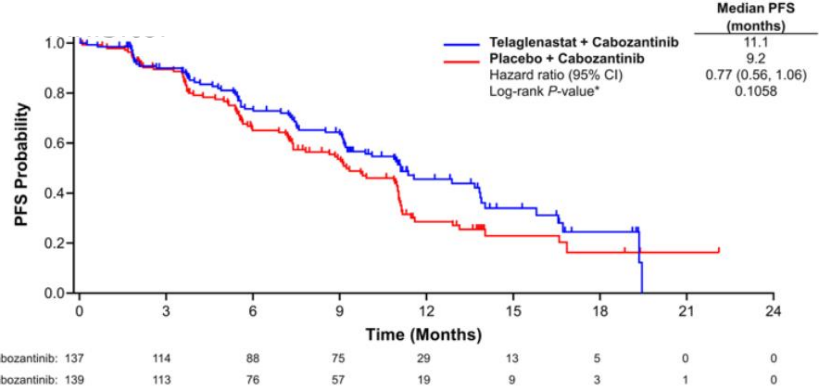
Survival Follow-Up

ENDPOINTS

Primary
IRC-adjudicated PFS per RECIST v1.1

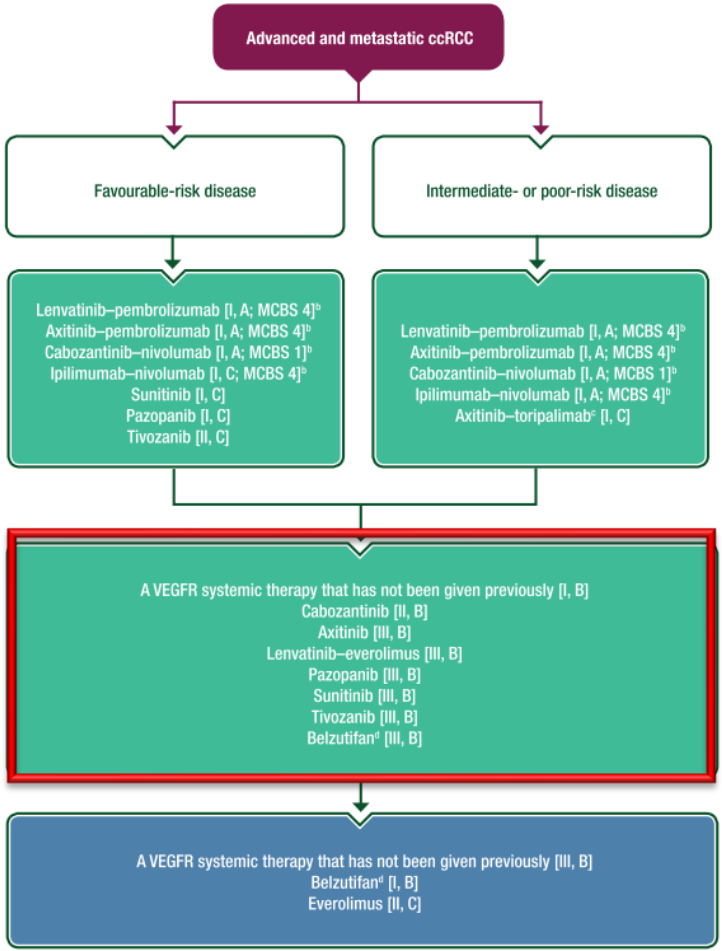
Secondary
Overall Survival
Investigator-assessed PFS

- N~416 planned
- Stratification factors:
  - Prior PD-(L)1 inhibitor therapy (yes vs. no)
  - IMDC Prognostic Risk Group (favorable vs. intermediate vs. poor)



Chung-Han L et al. ESMO 2019
Tannir NM et al. ASCO 2021

ESMO Guidelines



T. Powles, L. Albiges, A. Bex, et. al, on behalf of the ESMO Guidelines Committee eUpdate – Renal Cell Carcinoma Treatment Recommendations. Published: 28 September 2021

NCCN Guidelines

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] • Everolimus + lenvatinib • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[d] • Belzutifan (category 2B) • Bevacizumab[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[c] • Cabozantinib • Everolimus + lenvatinib • Tivozanib[d]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[e] (category 2B) • Axitinib + avelumab[b] (category 3)

Different 2L clinical scenarios according to 1L

TKI

- NIVOLUMAB**
- CABOZANTINIB*

*If not in 1st line for int/poor risk

- CABOZANTINIB
- NIVOLUMAB

- CLINICAL TRIAL
- OTHER TKI: LEN + EVE, AXI, TIVO

IO + IO

- CABOZANTINIB / TIVO/ BEL/ OTHER TKI
- CLINICAL TRIAL

- OTHER TREATMENT: BEL, LEN + EVE, AXI
- CLINICAL TRIAL

IO + TKI

- CABOZANTINIB* / TIVO/ BELZU/ TKIs/ LENVATINIB + EVEROLIMUS* / OTHER

*If not in 1st line with nivolumab o pembrolizumab

- CLINICAL TRIAL

- OTHER TKI
- CLINICAL TRIAL

IO (adj)

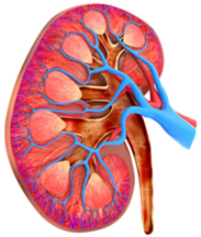
- TKI +/- IO/ According to time to relapse and type of relapse

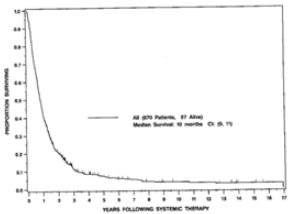
Clinical trials (evaluating triplets): IO +/- IO +/- TKI +/- HIF2a

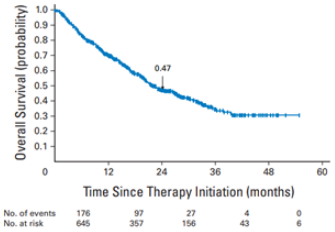
- TKI
- CLINICAL TRIAL

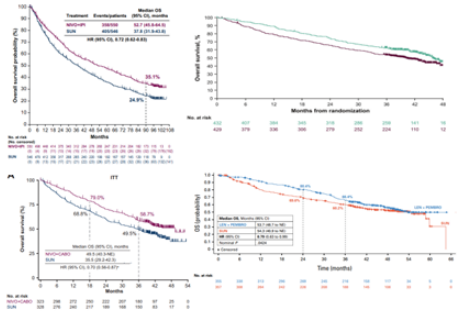
** nivolumab + ipilimumab

Novel agents, treatment sequencing, local therapies, safety management









Median Overall Survival	MSKCC (Motzer, 1999)	IMDC (Heng, 2009)		CM214	K…	CLEAR	CM9ER
All population, months	10 (95% CI 9–11)	22 (95% CI, 20.2 to 26.5)		52.7			49.5
Favorable, months	19.9 (95% CI 17.1 – 27.9)	NR	2-y OS = 75%	77.9			
Intermediate, months	10.3 (95% CI 8.9 – 11.4)	27	2-y OS = 53%	48.1			.5
Poor, months	3.9 (95% CI 3.4 – 5.0)	8.8	2-y OS = 7%				4.8

x 5 All population
x 4 Favorable
x 5 Intermediate
x 9 Poor

Courtesy of Dra Alonso. ESMO 2024

CONCLUSIONS

- Despite the improvement in oncological outcomes achieved in the first line treatment, most patients will finally progress and need further subsequent treatment.

- Time on treatment, tolerability, tumor burden at disease progression, patient comorbidities and preferences are relevant in treatment decision.

- Scientific knowledge is progressively improving with current trials including patients receiving contemporary strategies:
  - CONTACT-03/ TINIVO-2: No Benefit in IO (PD-1/PD-L1) continuation or rechallenge, but showing relevant information from control arms (cabozantinib and tivozanib).
  - Discouraging results from the CTLA-4 rechallenge to PD-1 progression.
  - Belzutifan is coming in the field of treatment sequencing.

- Novel strategies, hopefully, will show promising results in the near future. We need biomarkers!

THANK YOU FOR YOUR ATTENTION