VGO NORTE INTERNATIONAL GU DEBATES

Sequencing treatments in the advanced setting: Is it clear in 2026?

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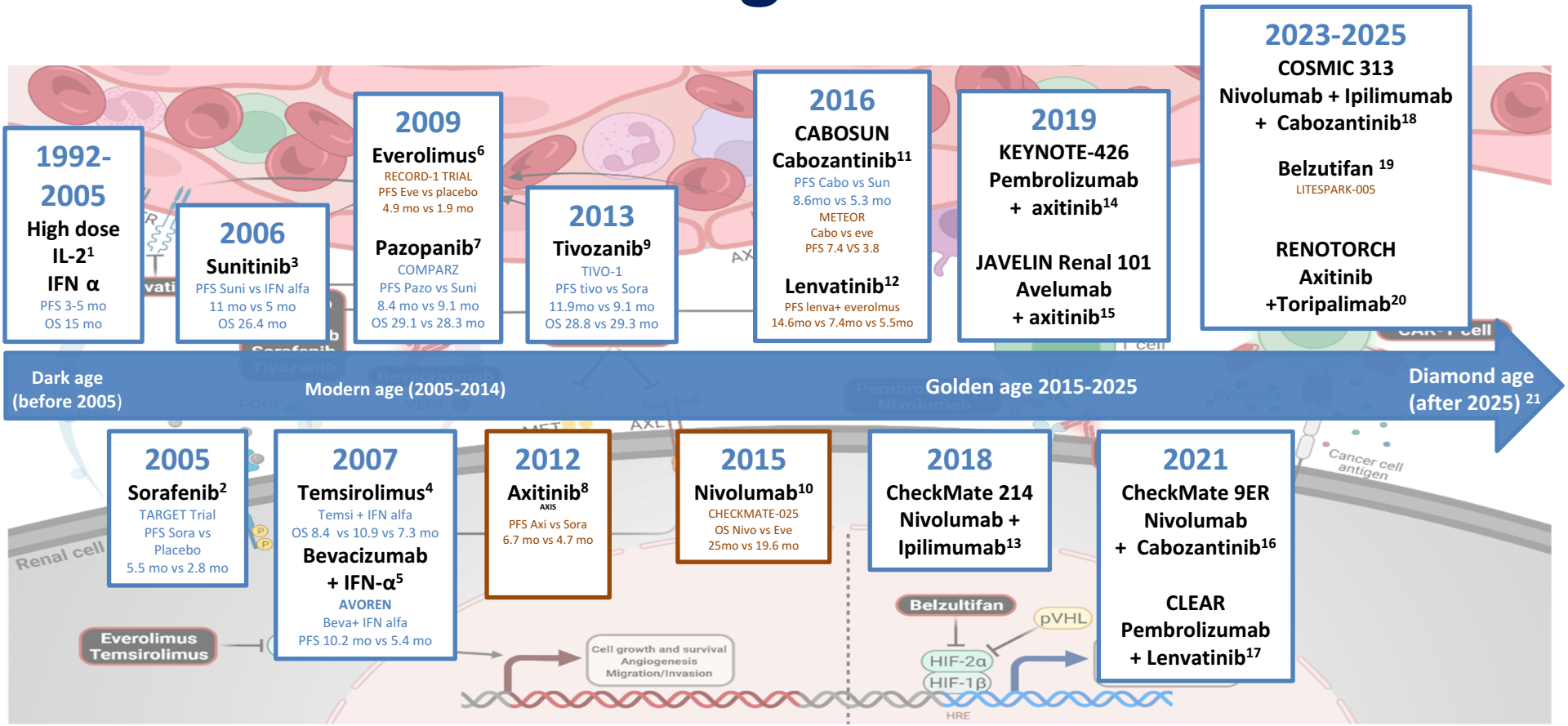
VHIO VALL D'HEBRON Institute of Oncology

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Disclosure Information

- Employment: None
- Consultant or Advisory Role: BMS, Pfizer, IPSEN, MSD, EUSA Pharma, EISAI, Tellix
- Stock Ownership: None
- Research Funding: IPSEN. BMS, Pfizer
- Speaking: Ipsen, EISAI, MSD
- Travel/acommodation expenses: Ipsen, MSD, Bayer

Background



1. Fyfe G, *et al.* J Clin Oncol 1995; 2. Escudier B, *et al.* N Engl J Med 2007; 3. Motzer RJ, *et al.* N Engl J Med 2007; 4. Hudes G, *et al.* N Engl J Med 2007; 5. Escudier B, *et al.* Lancet 2007; 6. Motzer RJ, *et al.* Lancet 2008; 7. Sternberg CN, *et al.* J Clin Oncol 2010; 8. Rini BI, *et al.* Lancet 2011; 9. Motzer RJ, *et al.* J Clin Oncol 2013; 10. Motzer RJ, *et al.* N Engl J Med 2015; 11. Choueiri TK, *et al.* N Engl J Med 2015; 12. Motzer RJ, *et al.* Lancet Oncol 2015; 13. Motzer RJ, et al. N Engl J Med 2018; 14 Rini, B. et al. N Engl J Med 2019; 15 Motzer, R. et al. N Engl J Med 2019. 16 Choueiri, TK, et al. N Engl J Med 2021; 17 Motzer RJ, et al. N Engl J Med 2021; 18 Choueiri TK, et al. N Engl J Med 2023; 19 Choueiri TK, et al.NEJM. 2024; Yan XQ, et al, Annals of Oncology 2024; 21 Hsieh JJ, et al. Nat Rev Dis Prim 2017;3:17009 Figure 1; **Figure 2.** Mechanism of action of experimental and Food and Drug Administration-approved drugs from Govindarajan A, et al. Cancers 2022.

Background

Limited use of subsequent lines of therapy in mRCC

Kidney Cancer

Real-world Treatment Patterns and Clinical Outcomes for Metastatic Renal Cell Carcinoma in the Current Treatment Era

Neil J. Shah [a,e,], Sneha D. Sura [b], Reshma Shinde [c], Junxin Shi [b], Puneet K. Singhal [c], Nicholas J. Robert [b], Nicholas J. Vogelzang [d], Rodolfo F. Perini [c], Robert J. Motzer [a,e]*

[a] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [b] Ontada LLC, The Woodlands, TX, USA; [c] Merck & Co., Inc., Rahway, NJ, United States of America; [d] Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [e] Department of Medicine, Weill Cornell Medical Center, New York, NY

2L therapies: 40%
3L therapies: 5.8%

Check for updates

Real-World Treatment Patterns and Clinical Outcomes Among Patients With Advanced Renal Cell Carcinoma

Elizabeth Esterberg,[1] Shrividya Iyer,[2] Saurabh P. Nagar,[1] Keith L. Davis,[1] Nizar M. Tannir[3]

2L therapies: 35%
3L therapies: 13%

ORIGINAL ARTICLE

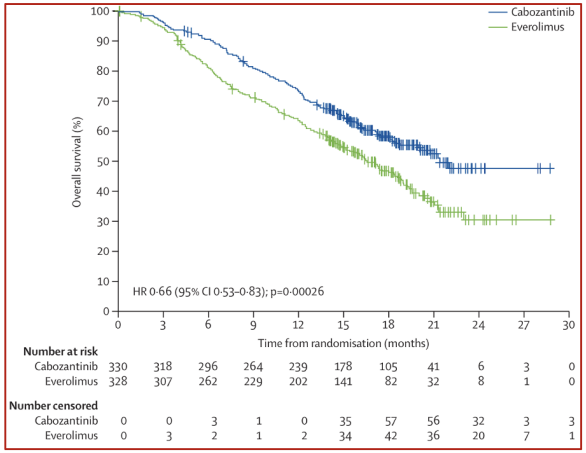
Real-world patterns of treatment and response in metastatic renal cell carcinoma: a multicentre UK-wide review with UK Renal Oncology Collaborative (UK ROC)

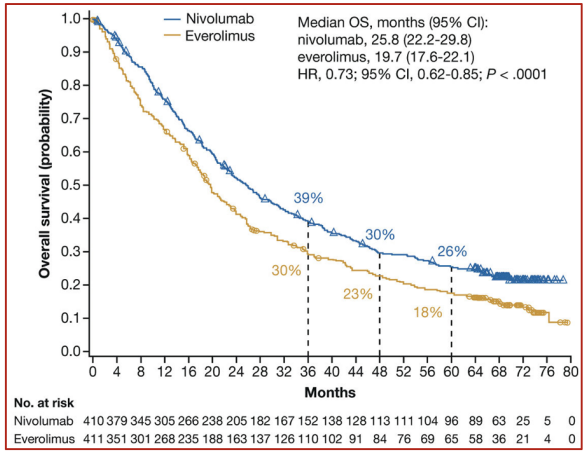
R. Frazer[1*], J. M. McGrane[2], A. Challapalli[3], G. Ratnayake[4], J. Malik[5], C. Forde[6], S. Alam[7], E. Jones[8], A. Shaheen[9], A. Ferrara[10], S. Gupta[1], S. Y. Moorcraft[11], N. Moon[2], D. Parslow[12], Y. Wang[13], S. Walters[1], J. Liu[14], T. Geldart[15], C. Dyke[16], A. Reni[17], G. J. Melendez-Torres[18] & A. Bahl[3]

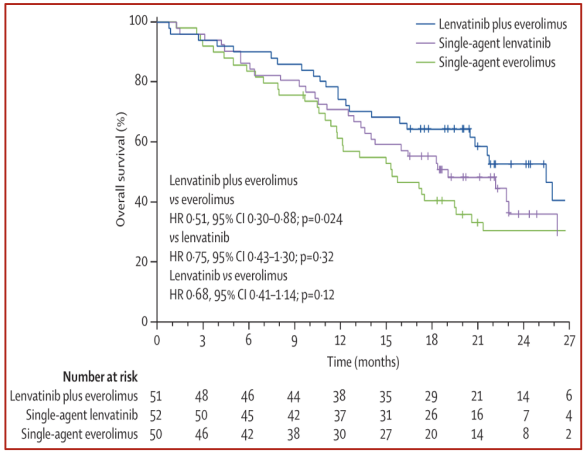
2L therapies: 59%
3L therapies: 23.5%
4L therapies: 6.3%

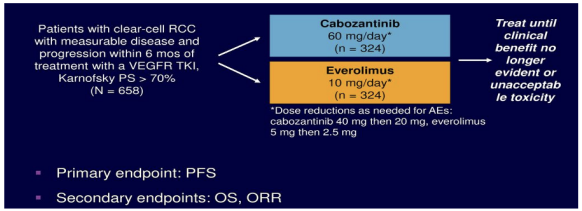
1Shah N, et al. Eur Urol Open SCI 2023; 2Esterberg E, et al. Clin Genitourin Cancer 2024; 3Frazer R, et al. ESMO RWD 2024

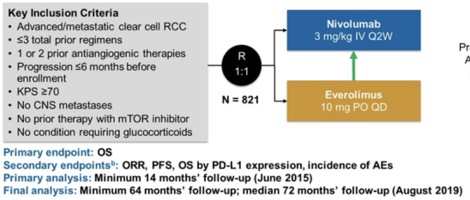
After TKI monotherapy pre-IO era

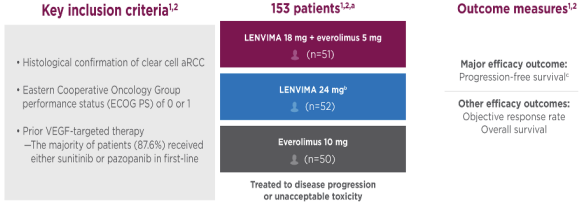












METEOR | **CheckMate-025** | **Lenv+Eve (*ph2*)**

3Choueiri TK, et al. NEJM 2015; 4Motzer RJ, et al. NEJM 2015; Escudier B, et al. ESMO 2022; 5Motzer RJ, et al. Lancet Oncology, 2016;

After TKI monotherapy pre-IO era

	Study design	Line	Control arm	DCR (CR + PR + SD)	PD	PFS	OS
EVEROLIMUS[1]	Ph **III**	2nd – 5th	Placebo	0 + 1 + 63%	19%	4.9 vs 1.8m (HR 0.33)	14.7 vs 14.3m (HR 0.87)
AXIS[2] *AXITINIB*	Ph **III**	2nd	Sorafenib	0 + 19 + 50%	22%	8.3 vs 5.7m (HR 0.66)	20.1 vs 19.2m (HR 0.97)
METEOR[3] *CABOZANTINIB*	Ph **III**	2nd – 3rd	Everolimus	0 + 17 + 65%	12%	7.4 vs 3.8m (HR 0.66)	21.4 vs 16.5m (HR 0.66)
CheckMate-025[4] *NIVOLUMAB*	Ph **III**	2nd – 3rd	Everolimus	1 + 24 + 34%	35%	4.6 vs 4.3m (HR 0.88)	25 vs 19.7m (HR 0.73)
LENVATINIB + EVEROLIMUS[5]	Ph II	2nd	Lenvatinib vs Everolimus	2 + 33 + 47%	4%	14.6 vs 7.4 vs 5.5m (HR 0.40 & HR 0.61)	25.5 vs 18.4 vs 15.4m (HR 0.51 & HR 0.68)
TIVO-3[6] *TIVOZANIB*	Ph **III**	3rd – 4th	Sorafenib	0 + 18 + 55%	21%	5.6 vs 3.9m (HR 0.73)	16.4 vs 19.2m (HR 0.97)

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

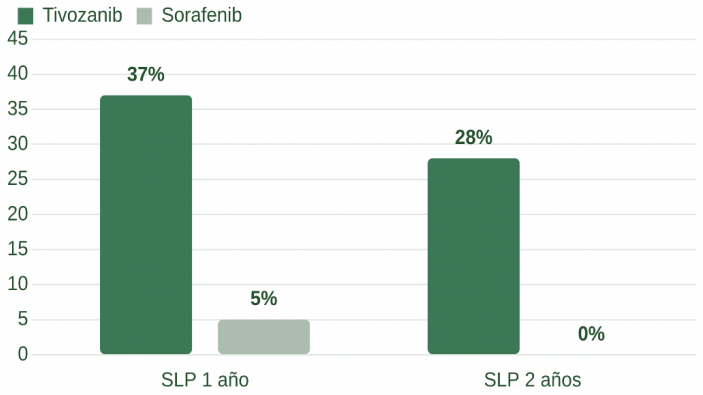
Updated Overall Survival in Patients with Prior Checkpoint Inhibition (CPI) in the phase III TIVO-3 study

Miguel Zugman, MD[1]; David F. McDermott, MD[2]; Bernard Escudier, MD[3]; Thomas E. Hutson, DO, PharmD[4]; Camillo Porta, MD[5]; Elena Verzoni, MD[6]; Michael B. Atkins, MD[7]; Brian Rini, MD[8]; Sumanta K. Pal, MD, FASCO[1]

[1]Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; [2]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; [3]Gustave Roussy, Villejuif, France; [4]Texas A&M University College of Medicine, Bryan, TX; [5]University of Bari Aldo Moro and Policlinico Consorziale di Bari, Bari, Italy; [6]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [7]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [8]Vanderbilt-Ingram Cancer Center, Nashville, TN

Table 2. Efficacy endpoints by trial arm and prior-CPI exposure

Patient trial population	Tivozanib				Sorafenib	
	ITT (N=175)		Prior-CPI (N=47)		ITT (N=175)	Prior-CPI (N=44)
Median PFS, months; HR (95% CI), P-value	5.6	0.73 (0.56-0.95), P=0.02	7.3	0.55 (0.32-0.94)	3.9	5.1
Landmark 1-year PFS Rate	28%		37%		11%	5%
Median OS, months; HR (95% CI), P-value	16.4	0.89 (0.70-1.14), P=0.35	18.1	0.69 (0.43-1.11)	19.2	20.9
ORR %	18%		24%		8%	7%
Median DOR, months	22.0		20.3		5.7	5.7



Zugman M, et al. Oncologist 2025;30(2):oyae369.
Rini BI, et al. Lancet Oncol 2020;21(1):95-104.

Data after adjuvant treatment

	Study	Drug	L	Number of patients	Adj ICI	ORR	mPFS	mOS
TKIs after ICI progression	INMUNOSUN-SOGUG[14] Phase 2	Sunitinib	2L	21	0%	19%	5.6 m	23.5 m
	Ornstein et al[15] Phase 2	Axitinib	> 2L	40	0%	45%	8.8 m	NR
	CANTATA[16] Phase 2	Cabozantinib + telaglenastat	2-3L	137	NR	31%	9.2 m	22.2 m
		Cabozantinib		139		28%	9.3 m	24.8 m
	BREAKPOINT[17] Phase 2	Cabozantinib	2L	30	10%*	37.9%	8.3 m	13.8 m
	CaboPoint[18] Phase 2	Cabozantinib	2L	88	0%	29.5%	NR	NR
Adding ipilimumab after SD or PD with nivolumab monotherapy	OMNIVORE[19] Phase 2	Nivolumab and ipilimumab x2 + nivolumab	≥ 1L	83	0%	4%	NR	NR
	TITAN-RCC[20] Phase 2	Nivolumab and ipilimumab x4 + nivolumab	≥ 1l	207	0%	18%	NR	NR
	HCRN GU16-260 (cohort A)[21] Phase 2	Nivolumab and ipilimumab x1 + nivolumab	1L	123	0%	13%	NR	NR
	FRACTION-RCC (track 2)[22] Phase 2	Nivolumab + ipilimumab	> 2L	46	NR	17.4%	3.7 m	23.8 m
ICI + TKI combo after ICI progression	KEYNOTE-146[23] Phase 1b/2	Nivolumab + lenvatinib	≥ 2L	104	0%	62.5%	12.2 m	NR
	CONTACT-03[24] Phase 3	Atezolizumab + cabozantinib	≥ 2L	263	< 1%**	41%	10.6 m	25.7 m
		Cabozantinib		259		41%	10.8 m	NS
	TiNivo 2[25] Phase 3	Nivolumab + tivozanib	≥ 2L			Ongoing		
Belzutifan as ≥ 2L after ICI progression	LITESPARK-003 (cohort 2)[26] Phase 2	Belzutifan + cabozantinib	≥ 2L	52	NR	31%	13.8 m	26.7 m
	LITESPARK-005[27] Phase 3	Belzutifan	≥ 2L	374	NR	22%	5.6 m	21.4 m
		Everolimus		372		3.5%	5.6 m	18.1 m
	LITESPARK-011[28] Phase 3	Belzutifan + lenvatinib	> 2L			Ongoing		

Abbreviations: 1L, first line; 2L, second line; 3L; third line; adj, adjuvant; ICI, immune checkpoint inhibitor; L, line; m, months; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; NS, not reached; ORR, overall response rate; PD, progressive disease; SD, stable disease; TKI, tyrosine kinase inhibitor.
*Adjuvant atezolizumab, progression during or within the first 6 months of adjuvant ICI.
**Adjuvant atezolizumab and pembrolizumab, progression during or within the first 6 months of adjuvant IC

1Bourlon MT, et al. ASCO Daily news 2024

TKI after IO treatment

	Study design	Prev. Line	Primary endpoint	Prev. therapies	ORR	PFS	OS
CASE7815[1] *AXITINIB*	Ph II	≥3L	PFS	IO: 78% TKI: 70%	45% (3% CR)	8.8m (95CI 5.7 – 16.6)	NR
INMUNOSUN[2] *SUNITINIB*	Ph II	1L	ORR RECIST	IO: all TKI: 47.7%	19% (0% CR)	5.6m (95CI 3.1 – 8.0)	23.5m (95CI 6.3 – 40.7)
IO-PAZ[3] *PAZOPANIB*	Ph II	1-2L	PFS	IO: all TKI: 43.5%	14.5% (3.2% CR)	6.5m (95CI 3.7 – 9.2)	21.3m (95CI 14.9 - NE)
TIVO-3[4] *TIVOZANIB*	Ph **III**	3rd – 4th	PFS	IO: 28% TKI: 45%	18 vs 8%	7.3 vs 5.1m (HR 0.55, 95CI 0.32 – 0.94)	NR (HR 0.84, 95CI 0.5 – 1.4)

1Ornstein MC, et al. Lancet Oncol. 2019 Oct;20(10):1386-1394; 2Grande E, et al. ESMO Open. 2022 Apr;7(2):100463; 3Powles TB, et al. Ann Oncol 2020; 31 (4s): S564; 4Rini B, et al. Lancet Oncology 2020

Cabozantinib after IO combos

	Study desing	Prev. Line	Primary endopoint	Prev. therapies	ORR	PFS	OS
CABOPOINT[1]	Ph II	≥1L	ORR in Cohort A	IO: all TKI: 31.8%	Cohort A: 41% Cohort B: 28%	Cohort A: 10.9m Cohort B: 8.3m	Cohort A: 24.3m Cohort B: 24.1m
BREAKPOINT[2]	Ph II	1L	PFS	IO: all TKI: 26%	37.9%	8.3m	13.8m
CANTATA[3] (Control arm)	Ph II	1-2L	PFS	IO: 62% TKI: 79%	31 vs 28%	9.2 vs 9.3m	22.2 vs 24.8m
CONTACT-03[4] (Control arm)	Ph III	1-2L	PFS / OS	IO: all TKI: 63%	41%	10.8m	NR

1Albiges L, et al. ESMO 2024; 2Procopio G, et al. Tumori. 2023; 3Tannir NM, et al. JAMA Oncol. 2022; 4Pal SK, et al. Lancet. 2023

Cabozantinib after IO treatment

CABOPOINT

PATIENTS
- Unresectable, locally advanced or metastatic RCC with a clear-cell component
- PD on 1L CPI ± VEGF-targeted tx

Cabo 60 mg QD PO

Cohort A: Pts who progressed after CPI+CPI (IpiNivo)

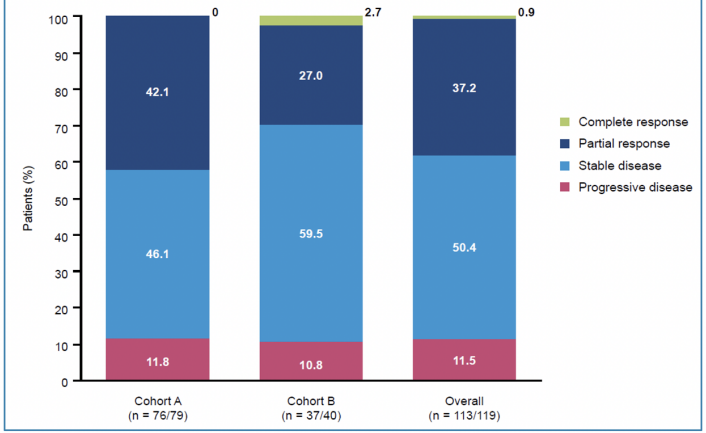
Cohort B: Pts who progressed after CPI + VEGF-targeted tx

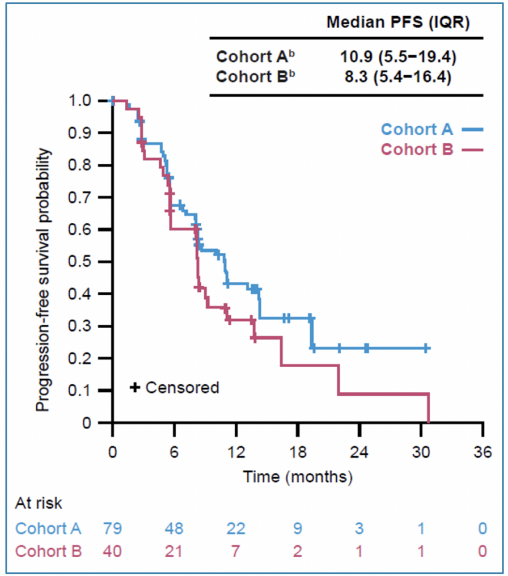
1º Endpoint: ORR per RECIST v1.1 in cohort A (independent central review)

2º Endpoints: ORR in cohort B by independent central review; ORR for both cohorts by local investigator review; TTR*; DOR*; disease control rate*; progression-free survival*; OS; change in disease-related symptoms; safety and tolerability

A

	Cohort A	Cohort B	Overall	
	79	40	119	Patients, n
$p < 0.0001^b$	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



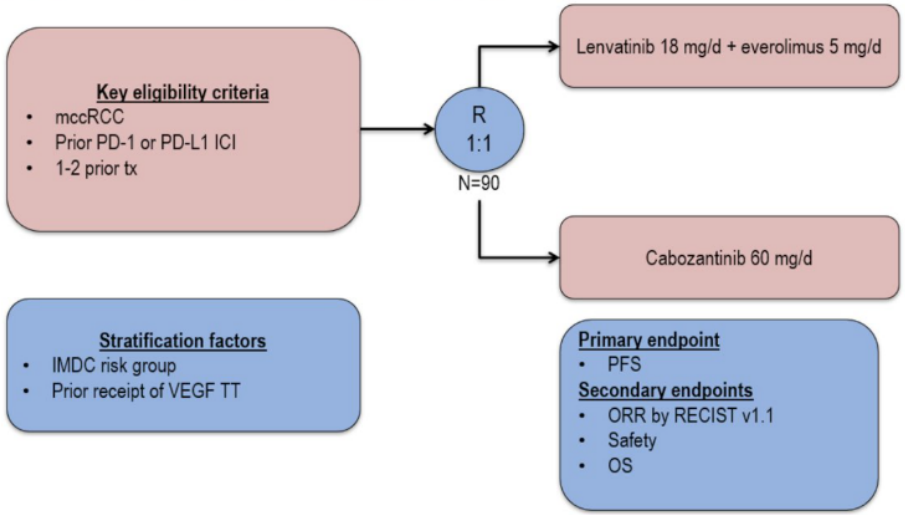


Albiges L et al. Eur Urol 2026

TKI after IO treatment: LenCabo

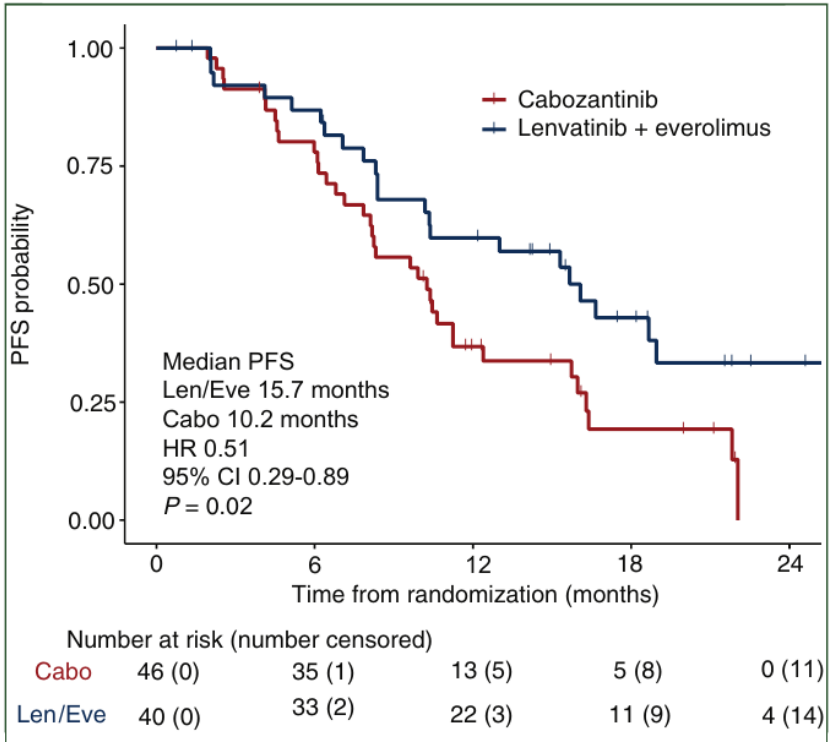
A multicenter randomized phase II trial of lenvatinib plus everolimus versus cabozantinib in patients with metastatic clear-cell RCC that progressed on PD-1 immune checkpoint inhibition (LenCabo)☆

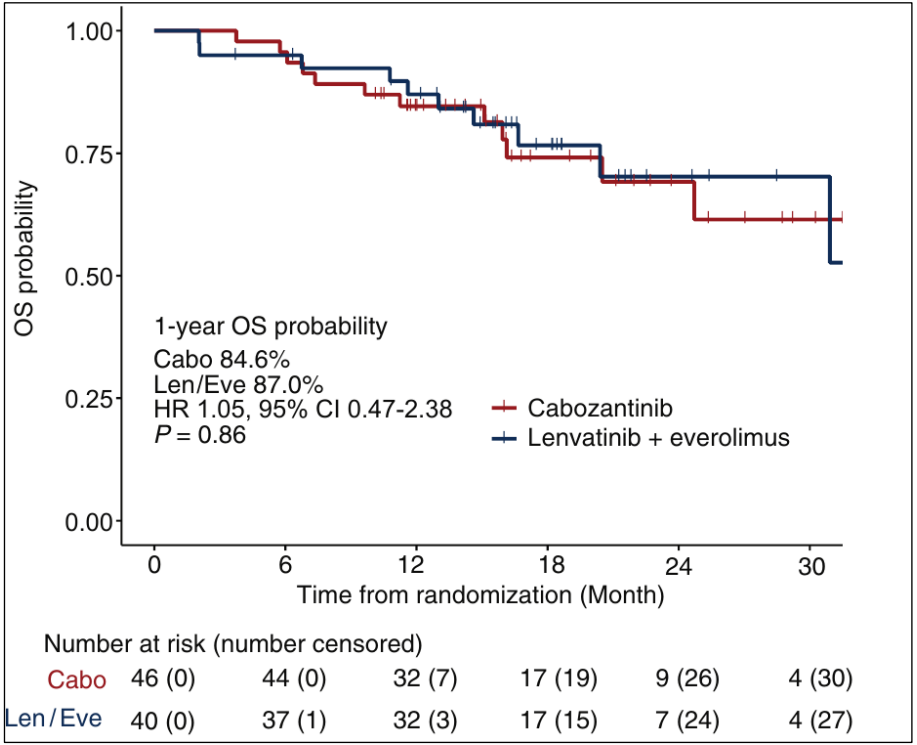
Phase II LenCabo study design



Hahn AW, et al. Ann Oncol. 2026;37(2):241-249. doi:10.1016/j.annonc.2025.10.009 · NCT05012371 · ESMO 2025

TKI after IO treatment: LenCabo

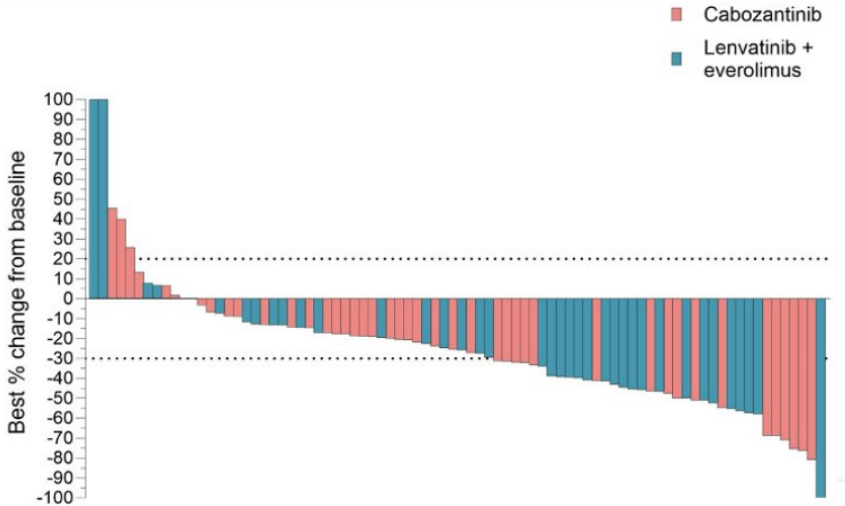




Hahn AW, et al. Ann Oncol. 2026;37(2):241-249. doi:10.1016/j.annonc.2025.10.009 · NCT05012371 · ESMO 2025

TKI after IO treatment: LenCabo

	Lenvatinib + everolimus (n=40)	Cabozantinib (n=46)
Objective response	20 (52.6%)	17 (38.6%)
Complete response	0 (0%)	0 (0%)
Partial response	20 (52.6%)	17 (38.6%)
Stable disease	15 (39.5%)	24 (54.5%)
Progressive disease	3 (7.9%)	3 (6.8%)
Not evaluable	2	2

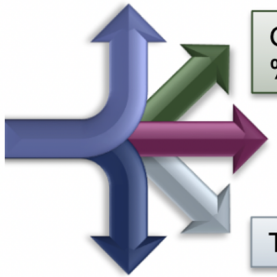


	Len/eve (n=40)	Cabo (n=46)	Odds ratio (95% CI)	P value
Serious adverse events – n (%)	11 (27.5%)	9 (19.6%)	1.55 (0.51-4.87)	0.45
Grade 3/4 adverse events – n (%)	27 (67.5%)	23 (50%)	2.06 (0.79-5.51)	0.13
Dose interruptions – n (%)	28 (70%)	36 (78.3%)	0.87 (0.34-2.25)	0.83
Dose reductions – n (%)	23 (57%)	28 (60.9%)	0.46 (0.23-1.92)	0.46
Treatment discontinuation – n (%)	8 (20%)	5 (10.9%)	2.03 (0.53-8.7)	0.37

Hahn AW, et al. Ann Oncol. 2026;37(2):241-249. doi:10.1016/j.annonc.2025.10.009 · NCT05012371 · ESMO 2025

Continuing IO after IO

HCRN GU16-260 (A) & TFS (N=128)



OMNIVORE (A) &
% PR/CR 1-year off nivolumab (N=12)

OMNIVORE (B) & %SD/PD with NIVO achieving PR/CR with IPI (N = 57)

TITAN & ORR full analysis set (N= 207)

FRACTION RCC & ORR, DoR, PFS at 24w (N = 46)

ORR PD-1i	Criteria CTLA4-i addition	N; ORR to CTLA4-i
34% (6.5%) Part A	SD/PD (N= 34)	11.5% (3%) Part B
1L 17% ≥ 2L 12%	PD (N=3)	N/A (re-PD1 inh)
1L 17% ≥ 2L 12%	SD/PD (N=57)	4% (0)
1L: 28% (CR 2%) 2L: 18% (CR 0%)	SD/PD (N=108)	1L: 36% (CR 7%) 2L: 32% (CR 6%)
N/A	PD to PD-1 inh (N=46)	17.4% (0)

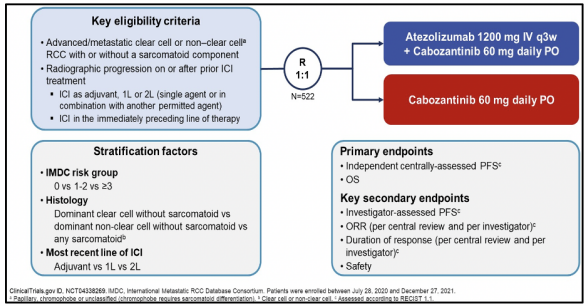
	HCRN GU16-260[1]	TITAN-RCC[2]	OMNIVORE-RCC[3]	FRACTION[4]
N	123	207	83	46
Previous TKI allowed	No	Yes	Yes	Yes
First line (n(%))	123 (100)	108 (52)	42 (51)	44 (96)
Sequence	Nivo -> IpiX4	Nivo -> IpiX4	Nivo -> IpiX2	Nivo/IpiX4

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).

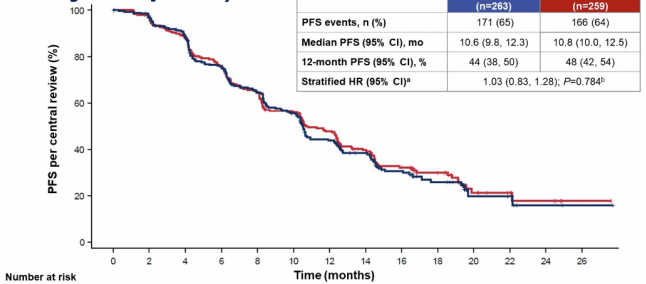
1Atkins M, et al. JCO 2022; 2Grimm M.O, et al. Lancet Oncol 2023; 3McKay RT, et al. JCO 2020; 4Choueiri TK, et al. J Immuno Cancer 2022

Continuing IO after IO

Contact-03



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.

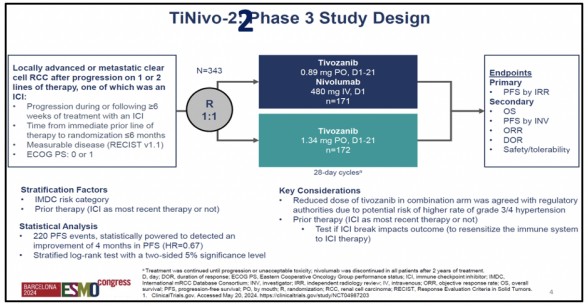
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Toni K. Choueiri, MD

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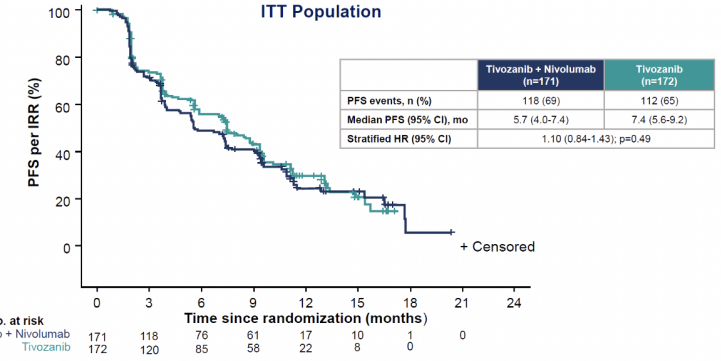
Choueiri, et al. CONTACT-03 (LBA4500)
@DrChoueiri

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Tinivo-2



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

1Pal SK, et al. Lancet 2023; Choueiri TK, et al. ASCO 2023; 2Choueiri TK, et al. ESMO 2024; Choueiri TK, et al. Lancet 2024

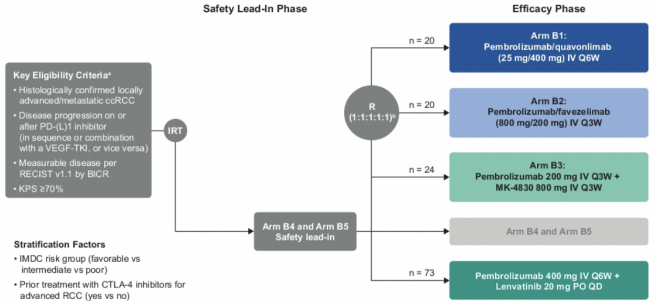
Continuing IO after IO

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%) **Most recent therapy Non ICI: 49 (29%)**
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%)**

1Pal SK, et al. Lancet 2023; 2Choueiri TK, et al. ESMO 2024; Choueiri TK, et al. Lancet 2024

Continuing IO after IO

Keymaker-U03 Substudy 3B



BICR, blinded independent central review; IMDC, International Metastatic RCC Database Consortium; IRT, interactive response technology; IV, intravenously; KPS, Karnofsky Performance Status; PO, orally; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, every day; R, randomized.

[a]Participants in arm B1 could not have received prior anti–CTLA-4 inhibitors.

[b]Participants were randomly assigned to arms open for enrollment.

End points and statistical analysis

- Primary end points were objective response rate (ORR) per RECIST v1.1 by BICR, and safety
- Secondary end points were
  - Duration of response (DOR)
  - Clinical benefit rate (CBR; defined as the percentage of participants who have complete response [CR], partial response [PR], or stable disease [SD] lasting ≥6 months)
  - Progression-free survival (PFS) per RECIST v1.1 by BICR
  - Overall survival (OS)
- End points were evaluated in each arm separately; no formal statistical comparisons were made across arms

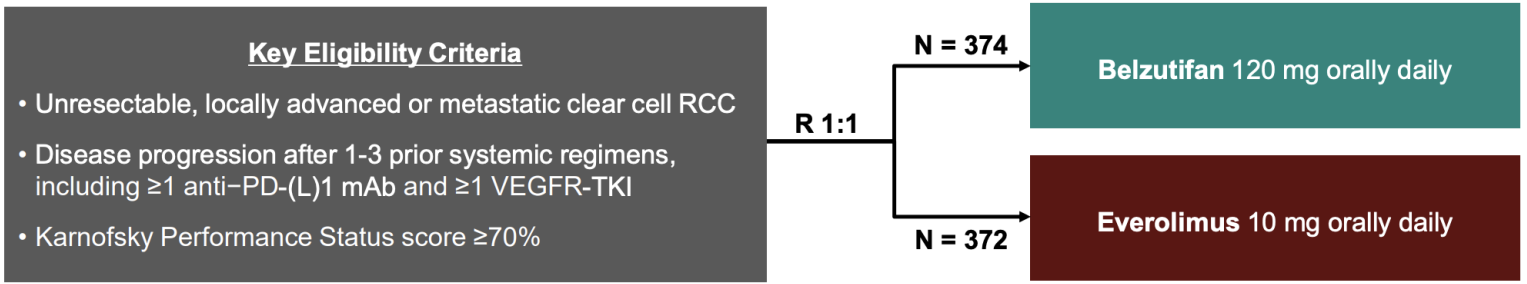
Prior first-line CTLA-4 inhibitor use	0	7 (35.0)	8 (33.3)	26 (35.6)
Number of prior lines of therapy				
1	3 (15.0)	3 (15.0)	4 (16.7)	10 (13.7)
2	6 (30.0)	8 (40.0)	10 (41.7)	27 (37.0)
≥3	11 (55.0)	9 (45.0)	10 (41.7)	36 (49.3)

	Pembrolizumab/ quavonlimab n = 20	Pembrolizumab/ favezelimab n = 20	Pembrolizumab + MK-4830 n = 24	Pembrolizumab + lenvatinib n = 73
ORR (95% CI), %	30.0 (11.9-54.3)	0 (0.0-16.8)	0 (0.0-14.2)	39.7 (28.5-51.9)
CBR (95% CI), %	35.0 (15.4-59.2)	5.0 (0.1-24.9)	0 (0.0-14.2)	57.5 (45.4-69.0)
Best response, n (%)				
CR	0	0	0	0
PR	6 (30.0)	0	0	29 (39.7)
SD	7 (35.0)	9 (45.0)	5 (20.8)	32 (43.8)
SD ≥6 months	1 (5.0)	1 (5.0)	0	13 (17.8)
PD	7 (35.0)	10 (50.0)	18 (75.0)	12 (16.4)
Not available	0	1 (5.0)	1 (4.2)	0
DOR, median (range), months	NR (5.6+ to 19.4+)	—	—	8.3 (2.6+ to 25.6+)
Participants with response duration ≥18 months, n (%)	1 (100)	—	—	2 (27.4)

"+" indicates ongoing response at the last assessment. NR, not reached.

Suarez C, et al. Annals Oncol 2025

HIF-2a inhibitor: LITESPARK-005



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

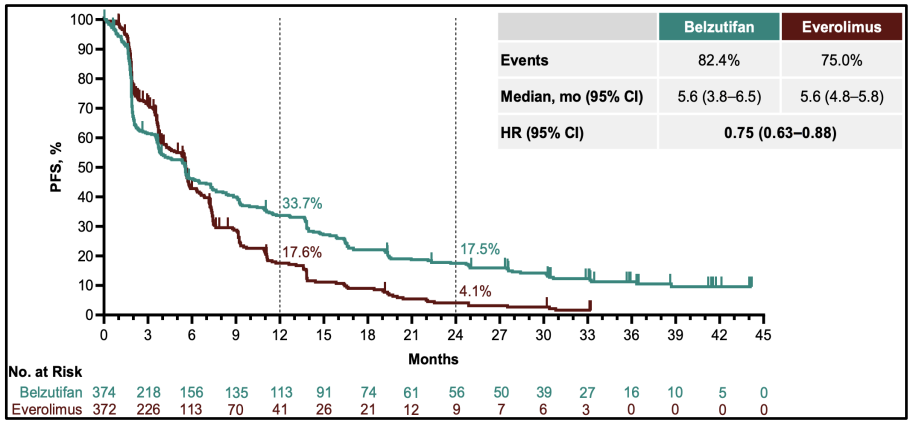
Dual Primary Endpoints:
- PFS per RECIST 1.1 by BICR
- OS
- The study was considered positive if either of the dual primary endpoints was met

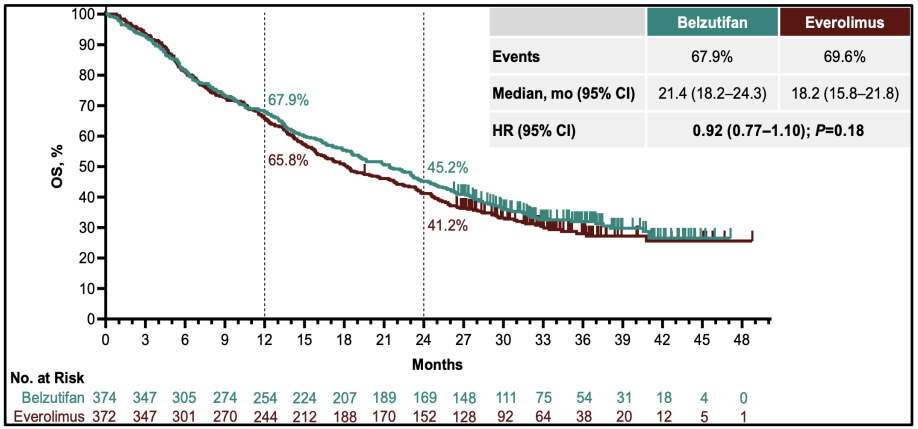
Key Secondary Endpoint:
- ORR per RECIST 1.1 by BICR

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

Choueri TK, NEJM 2024; RINI BI ESMO 2024

HIF-2a inhibitor: LITESPARK-005

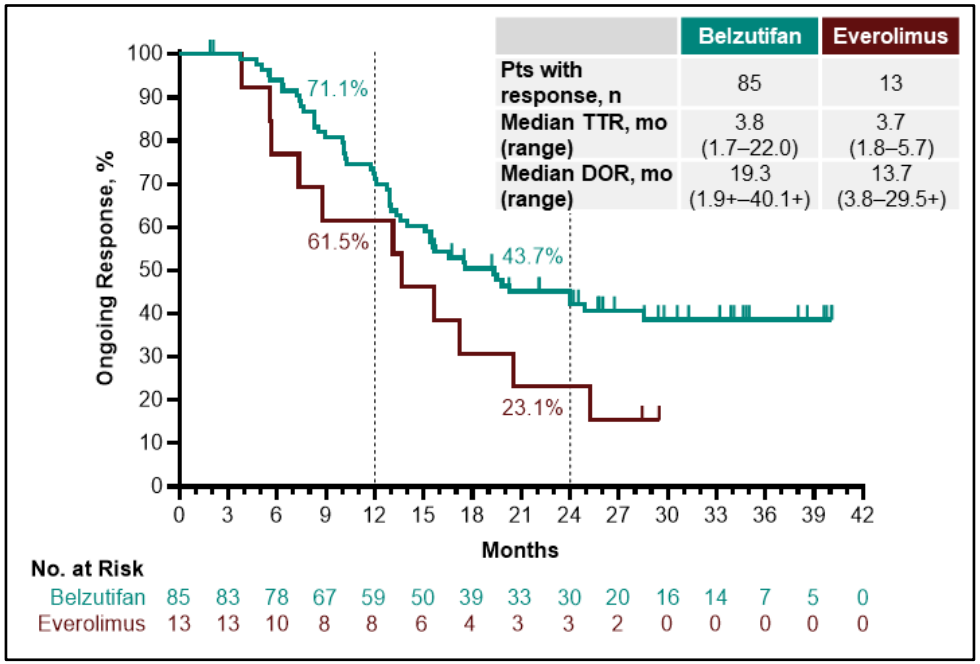




Choueri TK, NEJM 2024; RINI BI ESMO 2024

HIF-2a inhibitor: LITESPARK-005

	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%



Choueri TK, NEJM 2024; Rini BI ESMO 2024

Welireg

belzutifan

Medicine Human

Share RSS

Authorised

This medicine is authorised for use in the European Union

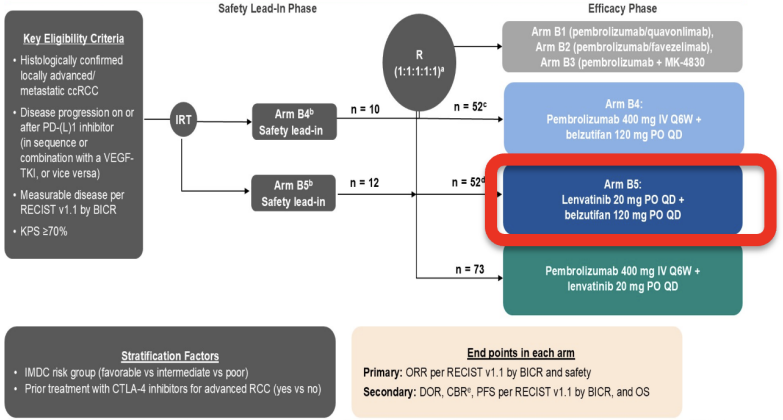
Welireg is a cancer medicine used to treat:

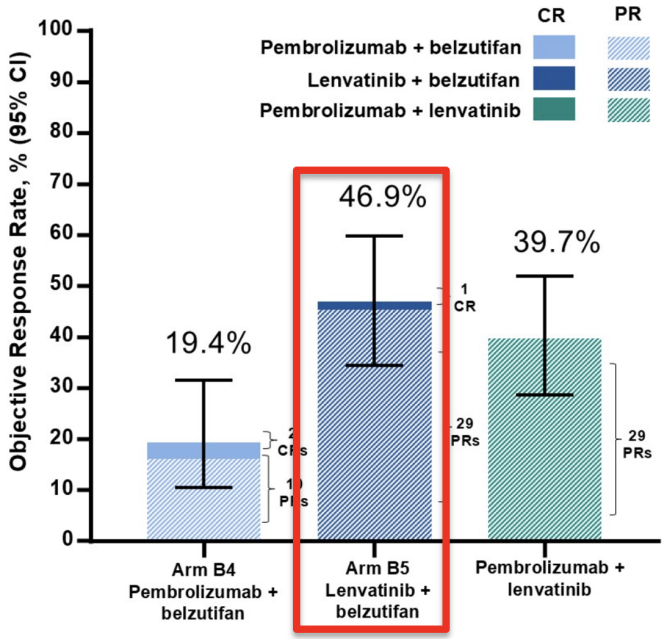
- adults with advanced clear cell renal cell carcinoma (a type of kidney cancer) that has worsened despite two or more previous treatments, including a PD-(L)1 inhibitor and at least two types of VEGF-targeted medicines. 'Advanced' means that the cancer has started to spread;
- adults with von Hippel-Lindau (VHL) disease who need treatment for associated, localised (confined to one area of the body) renal cell carcinoma, central nervous system haemangioblastomas (a type of brain cancer) or pancreatic neuroendocrine tumours (a type of pancreatic cancer), and who cannot have surgery or other local treatments. VHL disease is a genetic condition that causes tumours and cysts to grow in certain parts of the body.

TKI and HIF-2a inhibitor: KEYMAKER-U03 (3B)

Prior first-line CTLA-4 inhibitor use, n (%)	23 (37.1)	23 (35.9)	26 (35.6)
Number of prior lines of therapy, n (%)			
1	5 (8.1)	14 (21.9)	10 (13.7)
2	22 (35.5)	23 (35.9)	27 (37.0)
≥3	35 (56.5)	27 (42.2)	36 (49.3)

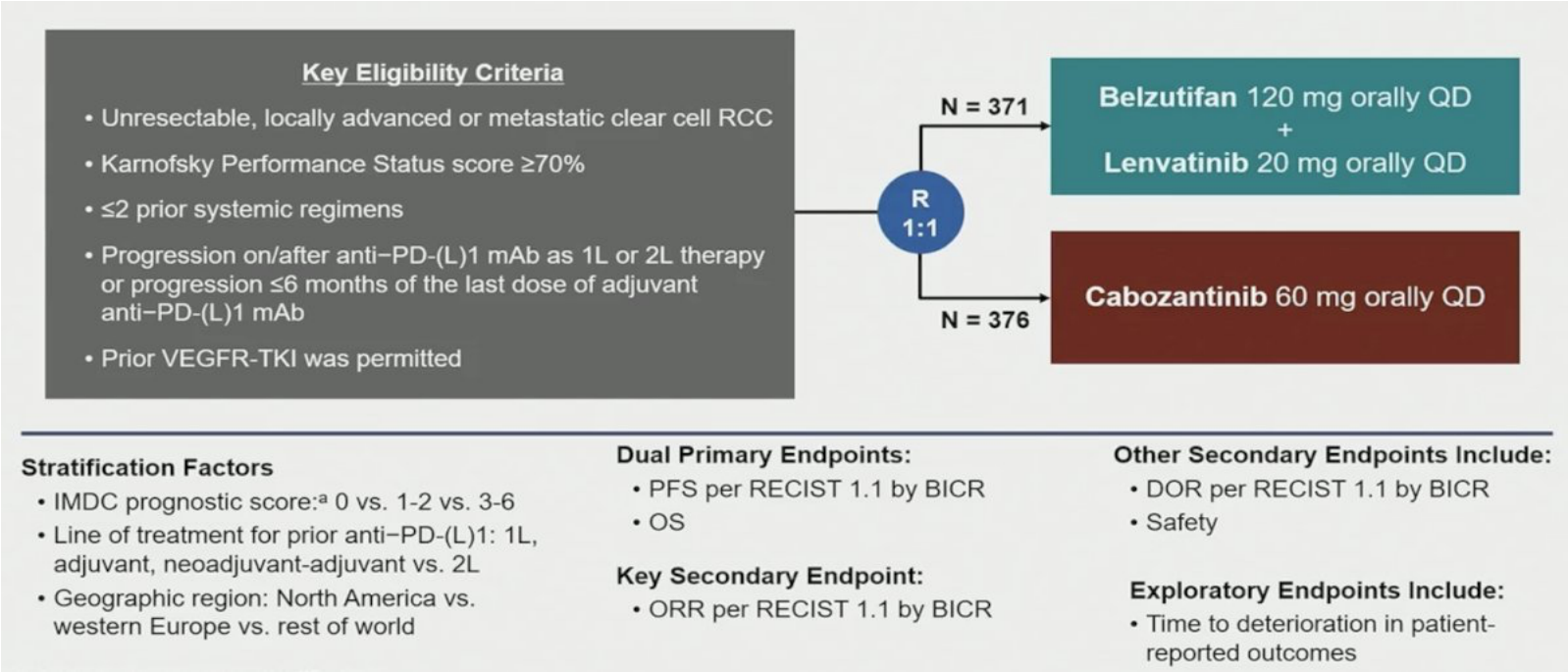
Keymaker-U03
Substudy 3B





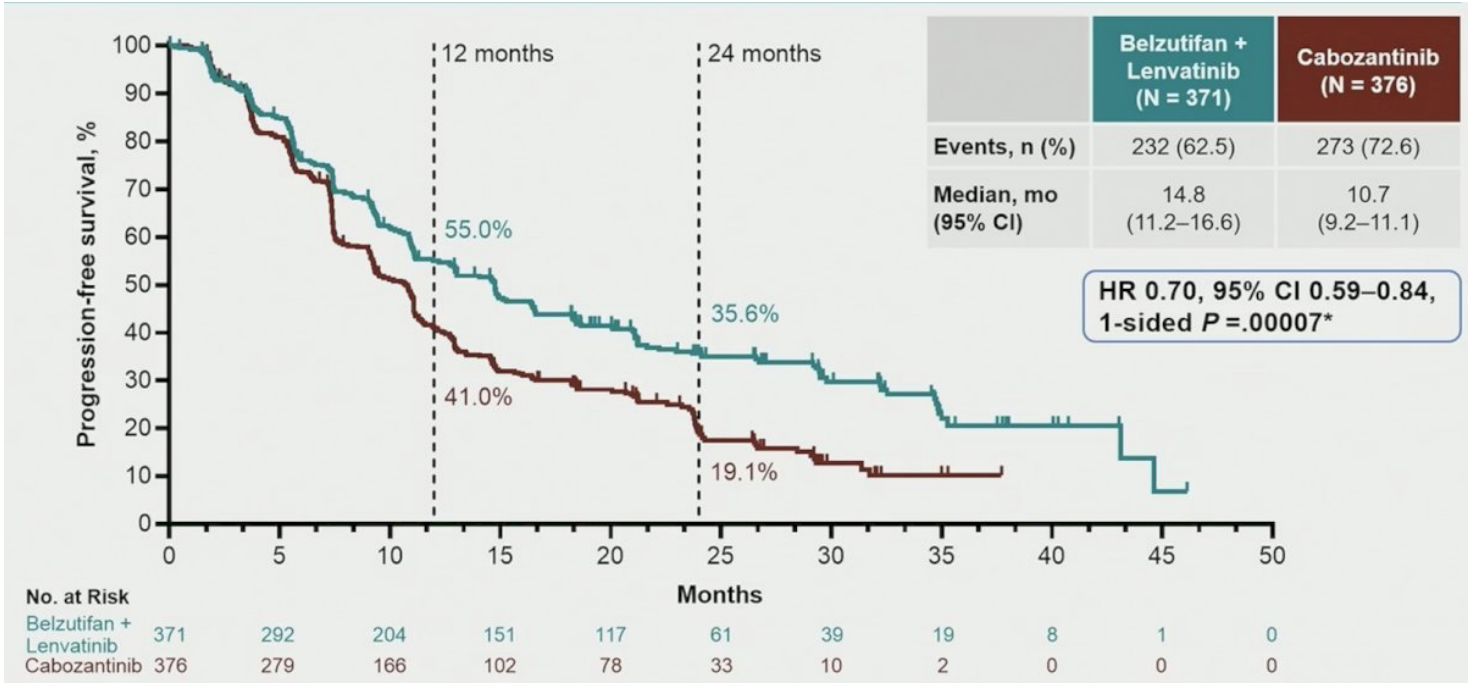
1Beckermann K, et al. ASCO GU 2025

TKI and HIF-2a inhibitor: LITESPARK-011



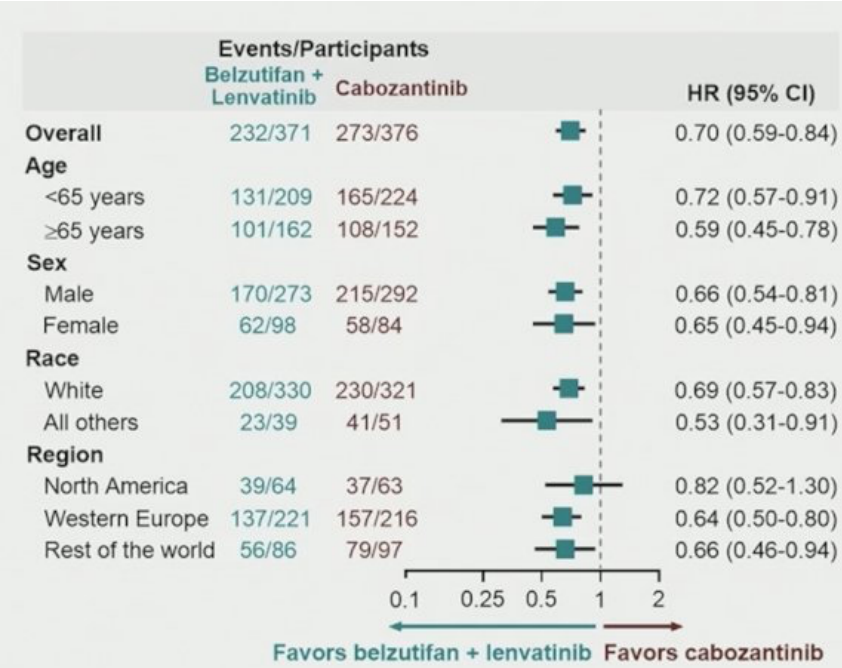
Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

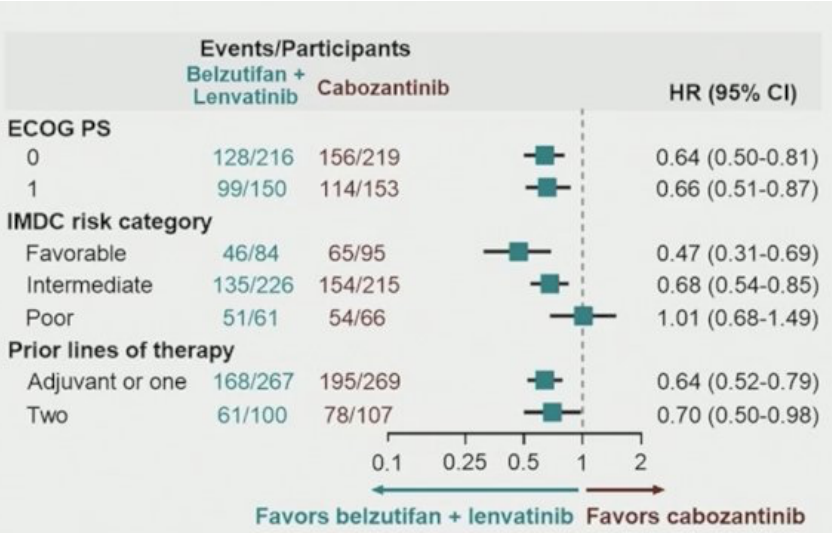
TKI and HIF-2a inhibitor: LITESPARK-011



Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

TKI and HIF-2a inhibitor: LITESPARK-011

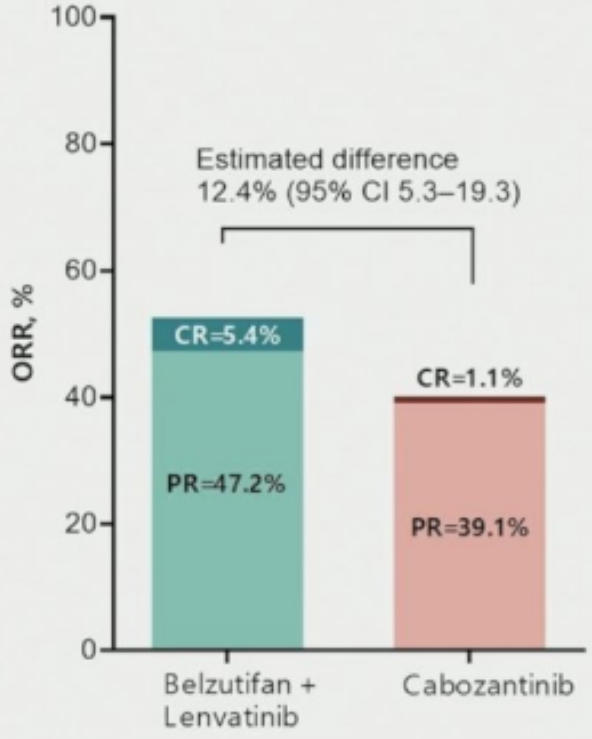




Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

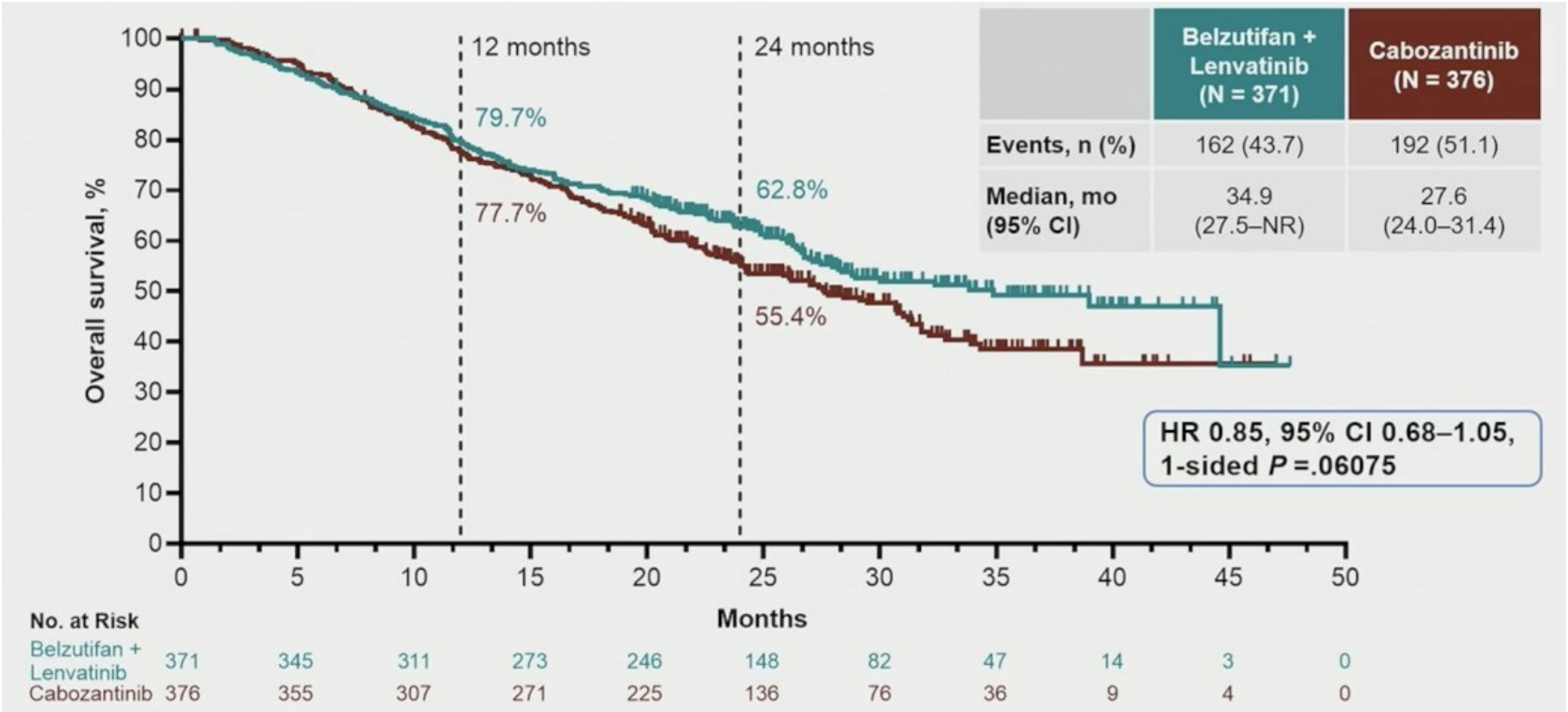
TKI and HIF-2a inhibitor: LITESPARK-011

	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
ORR, % (95% CI)	52.6 (47.3–57.7)	40.2 (35.2–45.3)
Estimated difference, % (95% CI)	12.4 (5.3–19.3)[a]	
Best overall response		
CR	20 (5.4)	4 (1.1)
PR	175 (47.2)	147 (39.1)
SD	143 (38.5)	186 (49.5)
PD	21 (5.7)	22 (5.9)
Not evaluable[b]	4 (1.1)	7 (1.9)
No assessment[c]	8 (2.2)	10 (2.7)



Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

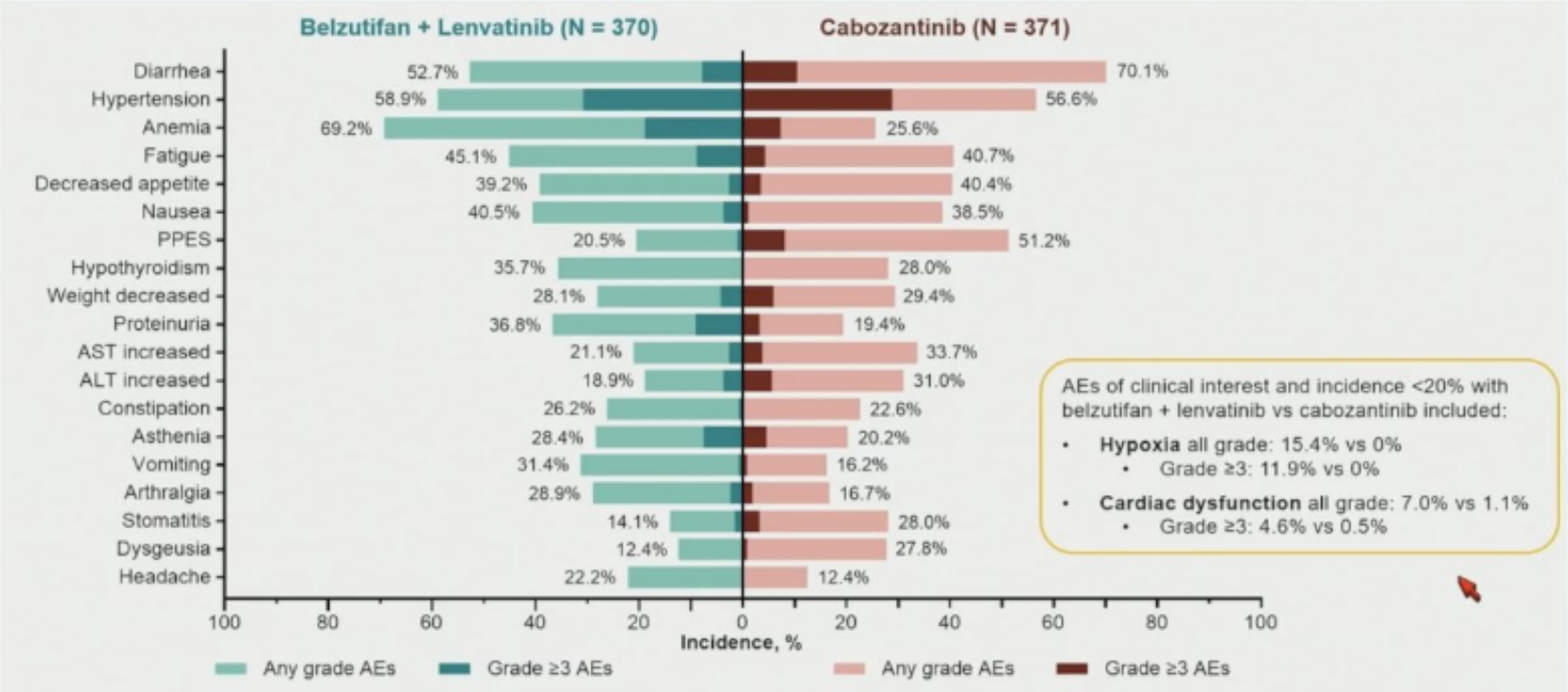
TKI and HIF-2a inhibitor: LITESPARK-011



	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Events, n (%)	162 (43.7)	192 (51.1)
Median, mo (95% CI)	34.9 (27.5–NR)	27.6 (24.0–31.4)

Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

TKI and HIF-2a inhibitor: LITESPARK-011



Motzer RJ, et al. Lancet 2026;408:808-20 (LITESPARK-011) · Motzer RJ. LITESPARK-011. ASCO GU 2026,

Final Analysis of the Phase 3 LITESPARK-011 Study: Belzutifan Plus Lenvatinib Versus Cabozantinib for Advanced Renal Cell Carcinoma After Anti–PD-(L)1 Therapy

Heng D et al

TKI and HIF-2a inhibitor: LITESPARK-003

Litespark-003

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]

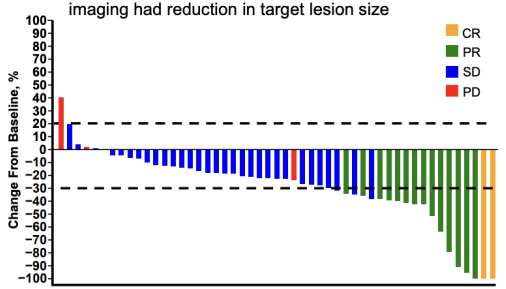
Belzutifan 120 mg/day PO
+
Cabozantinib 60 mg/day PO
N ≈ 50[a]

Tumor Assessments
- Week 9, then Q8W for 12 months and Q12W thereafter

End Points
- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

Cohort 2

- 45 of 51 patients (88%) with available postbaseline imaging had reduction in target lesion size



- Treatment was ongoing for 6 patients (12%) as of the database cutoff date
- Median TTR was 3.2 months (range, 1.5-16.6)
- Median DOR was 31.5 months (range, 4.2+ to 36.8) and 51% of patients remained in response ≥24 months by KM estimate

	Overall 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 (CR + PR)	**16 (31)**	9 (32)	7 (29)	9 (31)	7 (30)
DCR (CR + PR + SD)	48 (92)	26 (93)	22 (92)	27 (93)	21 (91)
Best response					
CR	2 (4)	1 (4)	1 (4)	1 (3)	1 (4)
PR	14 (27)	8 (29)	6 (25)	8 (28)	6 (26)
SD	32 (62)	17 (61)	15 (63)	18 (62)	14 (61)
PD	3 (6)	1 (4)	2 (8)	2 (7)	1 (4)
Not available[c]	1 (2)	1 (4)	0 (0)	0 (0)	1 (4)

1Choueiri, et al. ESMO 2023

Guidelines

National Comprehensive Cancer Network®

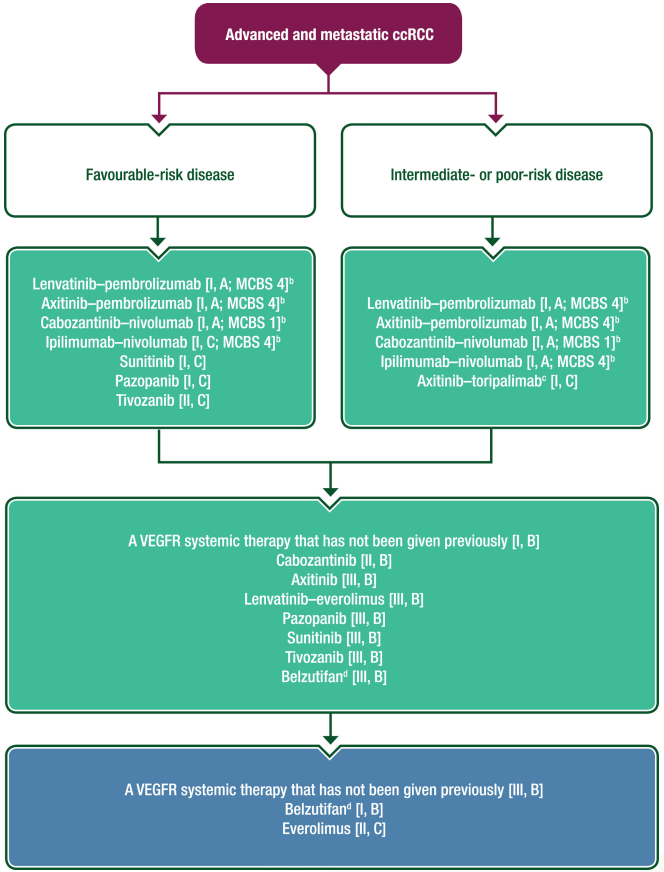
NCCN Guidelines Version 1.2027
Kidney Cancer

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	Other Recommended	Useful in Certain Circumstances
Prior IO Therapy	• Axitinib • Belzutifan[f] • Cabozantinib • Everolimus/Lenvatinib • Tivozanib	• Everolimus • Ipilimumab + Nivolumab[a,d] • Lenvatinib • Pazopanib • Sunitinib • Axitinib + Pembrolizumab[a,b] (category 2B) • Bevacizumab[g] (category 2B) • Cabozantinib + Nivolumab[a,c] (category 2B) • Lenvatinib + Pembrolizumab[a,b] (category 2B)
IO Therapy Naïve	• Axitinib + Pembrolizumab[a,b] • Cabozantinib • Cabozantinib + Nivolumab[a,c] • Everolimus/Lenvatinib • Ipilimumab + Nivolumab[a,d] • Lenvatinib + Pembrolizumab[a,b] • Nivolumab[a,c]	• Axitinib • Everolimus • Lenvatinib • Pazopanib • Sunitinib • Tivozanib • Belzutifan (category 2B) • Bevacizumab[g] (category 2B)



TREATMENT BEYOND PROGRESSION

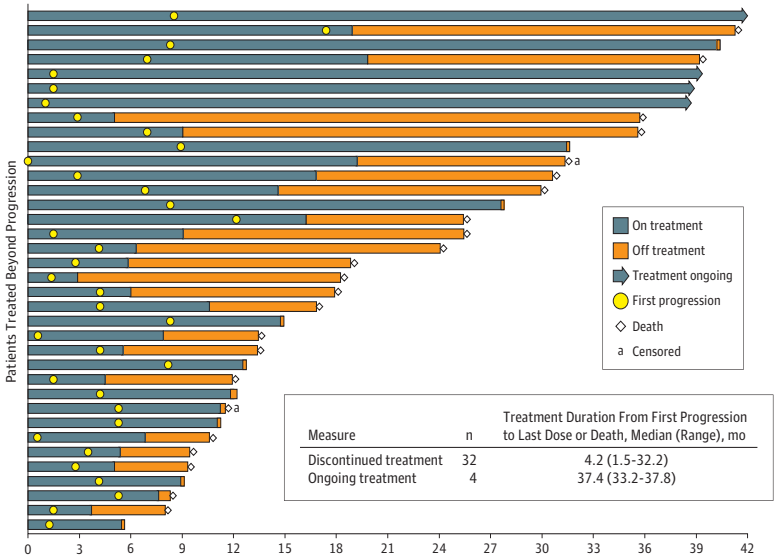
JAMA Oncology | Original Investigation

Safety and Efficacy of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Treated Beyond Progression

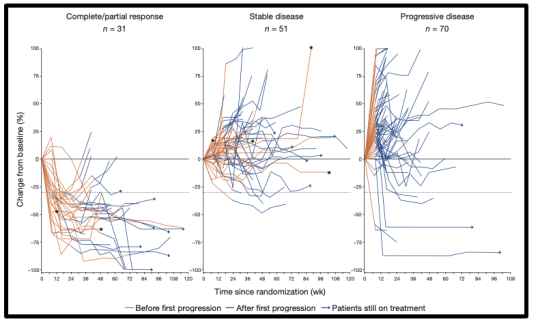
A Subgroup Analysis of a Randomized Clinical Trial

Saby George, MD; Robert J. Motzer, MD; Hans J. Hammers, MD, PhD; Bruce G. Redman, DO; Timothy M. Kuzel, MD; Scott S. Tykodi, MD, PhD; Elizabeth R. Plimack, MD, MS; Joel Jiang, PhD; Ian M. Waxman, MD; Brian I. Rini, MD

- ❑168 patients/26 were treated beyond first progression for ≤6 weeks
- ❑Following initial progression 69% patients treated beyond progression experienced subsequent tumor reduction or stabilization in target lesion size.



TREATMENT BEYOND PROGRESSION



In the CHECKMATE 025, 48% were treated beyond progression (vs 52% not treated)

Postprogression:

- ❑ Median duration of nivolumab treatment: 3.4 months
- ❑ Median OS 20.4 months
- ❑ 48% tumor burden reduction
- ❑ 13% of all patients TBP (20/153) had 30% tumor burden reduction

Differences in clinical characteristics between patients TBP versus NTBP

- ❑ Better Karnofsky performance status
- ❑ Less deterioration in Karnofsky performance status
- ❑ Shorter time to response
- ❑ Lower incidence of new bone lesions
- ❑ Improved quality of life

Escudier B, et al, Eur Urol Oncol. 2017

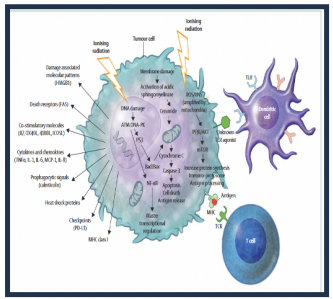
TREATMENT BEYOND PROGRESSION

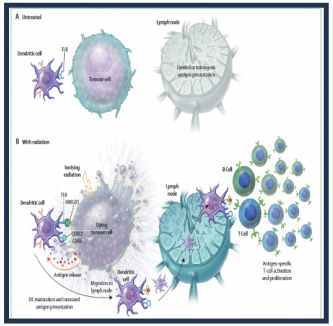
MDTs and systemic treatment do not have to be mutually exclusive

SABR immune positive effects on tumor

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake





- ❑ Radiation enhances **MHC class I surface exp**. alreticulin expression, and release of HMGB1
- ❑ Radiation enhances **FAS** surface expression
- ❑ Radiation activates **dendritic cells** and enhances cross-presentation of tumour antigens
- ❑ Radiation increases the **density of tumour-infiltrating lymphocytes**
- ❑ Radiation **modulates Treg** populations

TREATMENT BEYOND PROGRESSION

MDTs and systemic treatment do not have to be mutually exclusive

Platinum Priority – Kidney Cancer
Editorial by Shankar Siva, Piet Ost, Nicholas Zaorsky and Michael Staehler on pp. 701–702 of this issue

Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study

Patrick Cheung[a], Samir Patel[b], Scott A. North[c], Arjun Sahgal[a], William Chu[a], Hany Soliman[a], Belal Ahmad[d], Eric Winquist[e], Tamim Niazi[f], Francois Patenaude[g], Gerald Lim[h], Daniel Yick Chin Heng[i], Arbind Dubey[j], Piotr Czaykowski[k], Rebecca K.S. Wong[l], Anand Swaminath[m], Scott C. Morgan[n], Rupi Mangat[o], Sareh Keshavarzi[p], Georg A. Bjarnason[q,]*

RCC patients **(≤5 lesions)** *who had previous stability or response after ≥3 months of TKI (N=37)*

- One-year local control of irradiated lesions: 93%
- Median time to change in systemic therapy of 12.6 months

The use of SABR in mRCC, who develop growth of a few tumors while on oral targeted therapy, can significantly delay the need to change to the next line of drug therapy

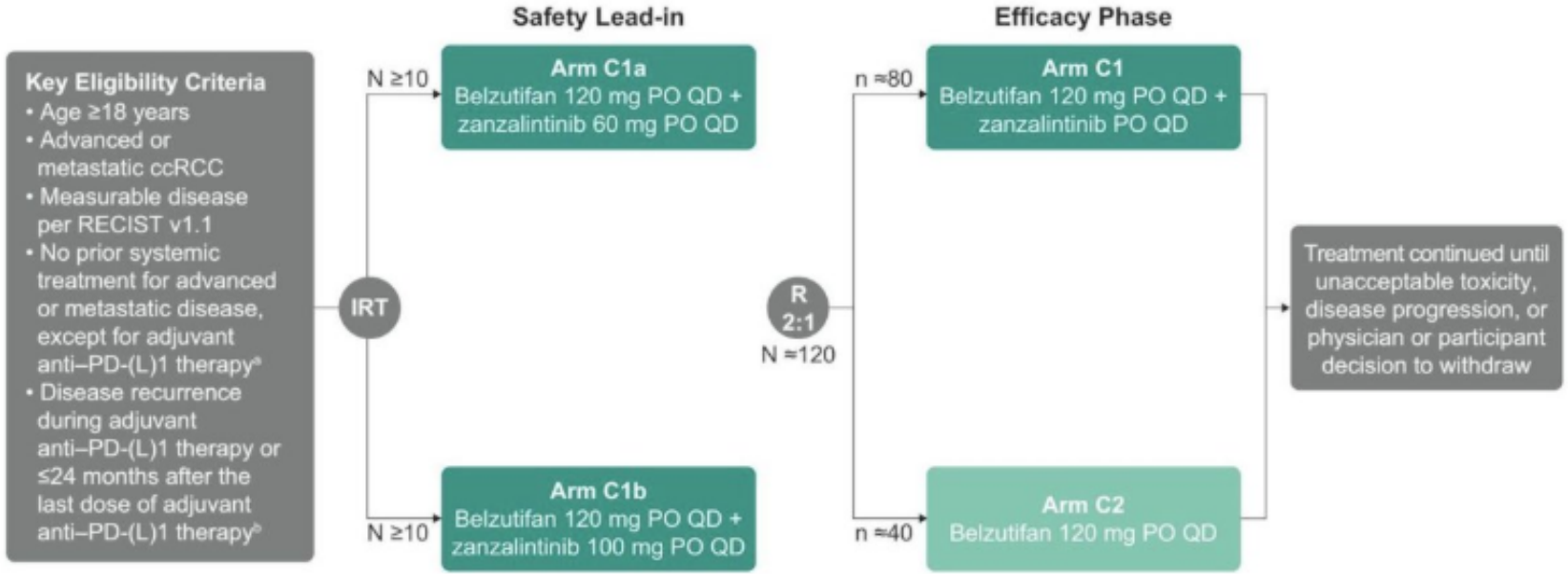
FUTURE



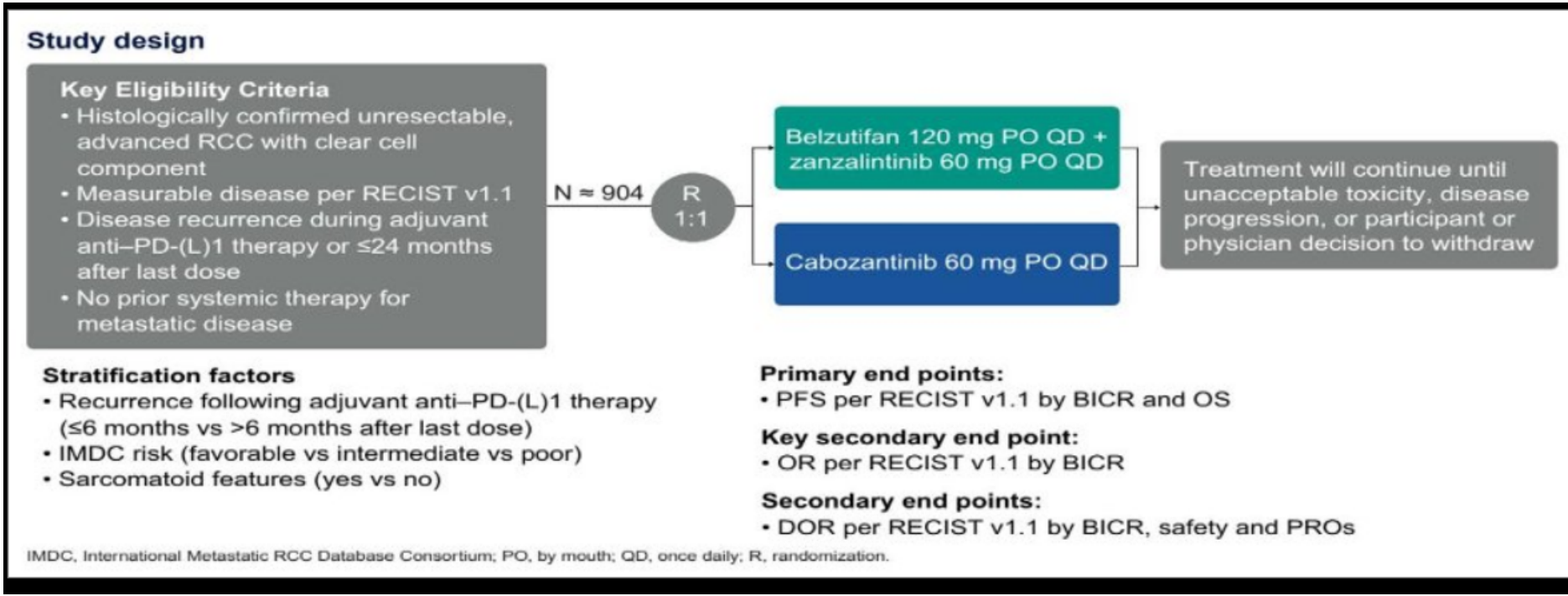
Phase 1b/2 KEYMAKER-U03 Substudy 03C

Belzutifan + Zanzalintinib or Belzutifan Monotherapy for Recurrent Clear Cell RCC During or After Anti-PD-(L)1 Therapy

Study design and participants



LITESPARK-033

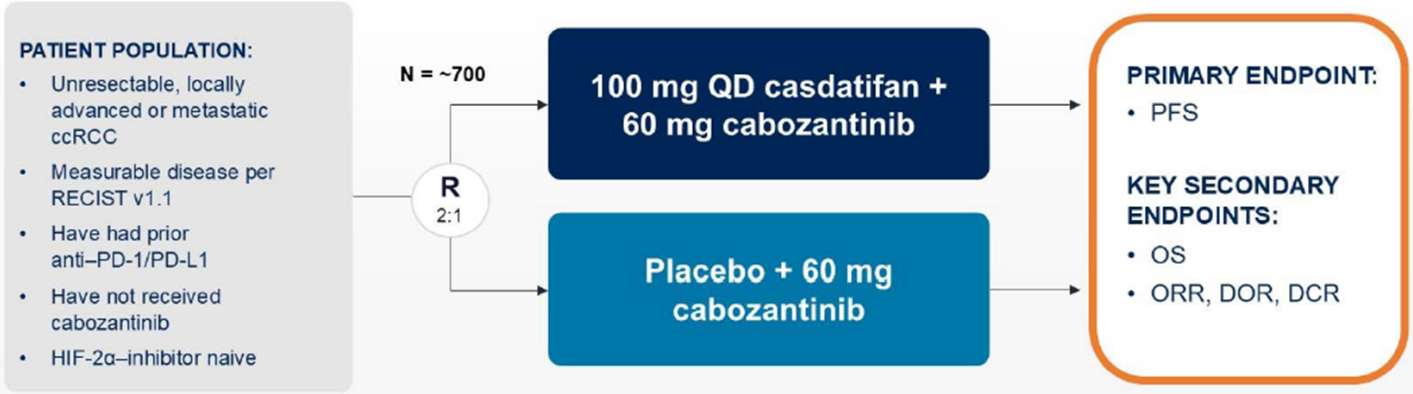


PEAK-1

Phase 3 Study Evaluating Cas + Cabo in Advanced or Metastatic ccRCC, Following Prior PD-1 Therapy

Anticipated first half 2025

PEAK–1



Cabo, cabozantinib; cas, casdatifan; HIF, hypoxia-inducible factor; R, randomized.

LITESPARK-034 — Phase 3 RCC Trial

A randomized, double-blind, phase 3 trial of belzutifan plus zanzalintinib in advanced renal cell carcinoma

Phase 3 | **Randomized** | **Double-blind**

Eligible Population

- Advanced clear-cell renal cell carcinoma (RCC)
- Measurable disease (per RECIST v1.1)
- Progression after prior anti-PD-1/L1 therapy and prior VEGF-TKI therapy
- No more than 3 prior systemic regimens

N = 758
Randomized 1:1

- **Belzutifan + Zanzalintinib**
- **Belzutifan + Placebo**

Dual Primary Endpoints

- Progression-free survival (PFS)
- Overall survival (OS)

Secondary Endpoints

- Objective response rate (ORR)
- Duration of response (DOR)
- Quality of life

Take home message: more questions than answers

- What to do after adjuvant pembrolizumab?
- What patients should we treat at oligoprogression with MTD and in what patients should we move to the next line of therapy?
- **Belzutifan** is new player in the sequencing of treatment for RCC, but…
  - When?
  - Monotherapy or in combination?
- Ongoing trials may provide more information about the role of new targets
- **Urgent need of biomarkers**: Molecular biology to guide clinical decisions and clinical trials´ design.

MUCHAS GRACIAS POR VUESTRA ATENCIÓN