UCDAVIS
COMPREHENSIVE
CANCER CENTER

Management of Renal Cell Carcinoma

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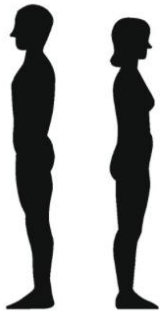
UC Davis Comprehensive Cancer Center

RCC Disease Burden and Mortality

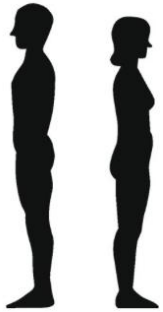
Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	



Estimated Deaths

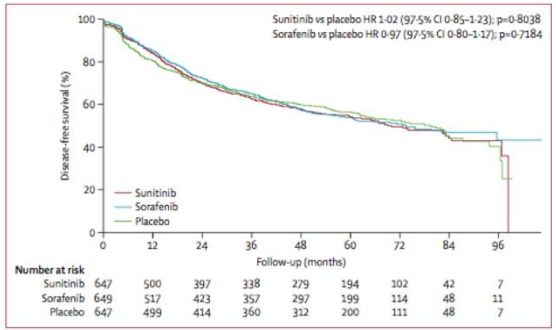
Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	
Kidney & renal pelvis	**9,450**		**Kidney & renal pelvis**	**4,940**	



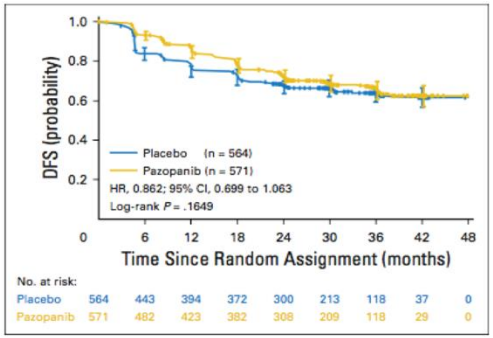
ACS Cancer Facts & Figures 2023.

Perioperative Management: VEGFi/ TKIs

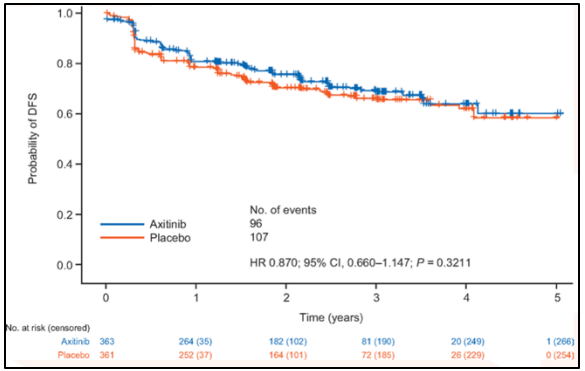
ASSURE DFS



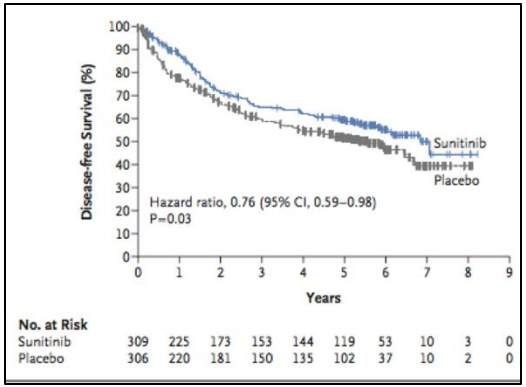
PROTECT DFS



ATLAS DFS



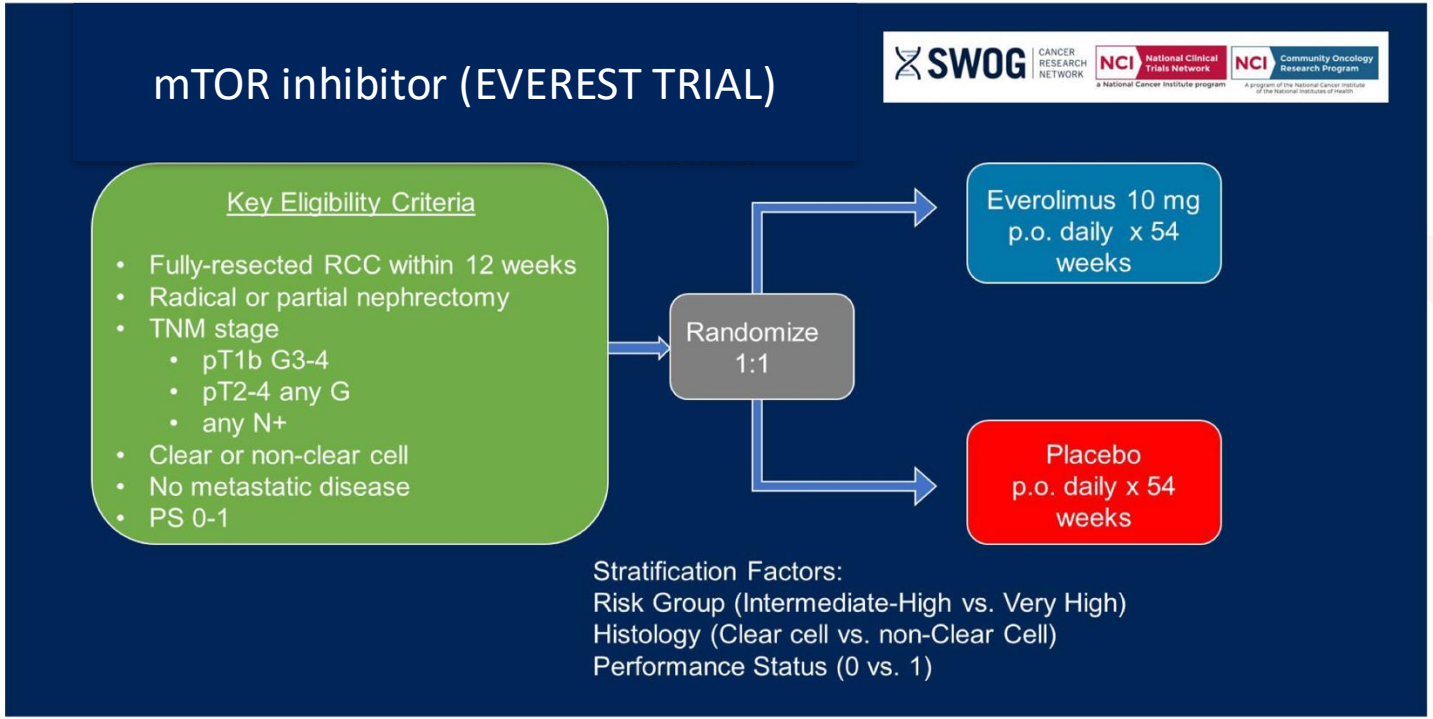
S-TRAC DFS



- Heterogeneity
- ASSURE- lower T stage, clear and non clear
- PROTECT/ S-TRAC- pT3, higher grade and higher risk tumors
- S-TRAC the only positive trial for DFS (HR 0.76)
- Sunitinib approved by the FDA but not the EMA
- OS benefit not seen in any

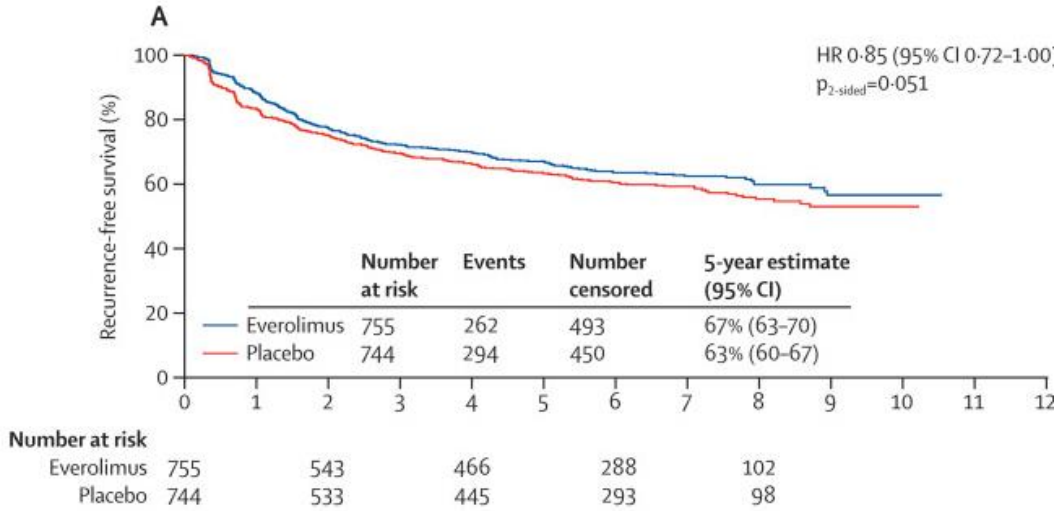
Haas NB, et al. *Lancet*. 2016;387(10032):2008-16. Motzer RJ, et al. *J Clin Oncol*. 2017;35(35):3916-3923. Ravaud A, et al. *N Engl J Med*. 2016;375(23):2246-2254. Gross- Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378.

Perioperative Management (Everolimus)



Ryan CW, et al. *J Clin Oncol*. 2022;40(17_suppl):LBA4500. Presented at: ASCO 2022.

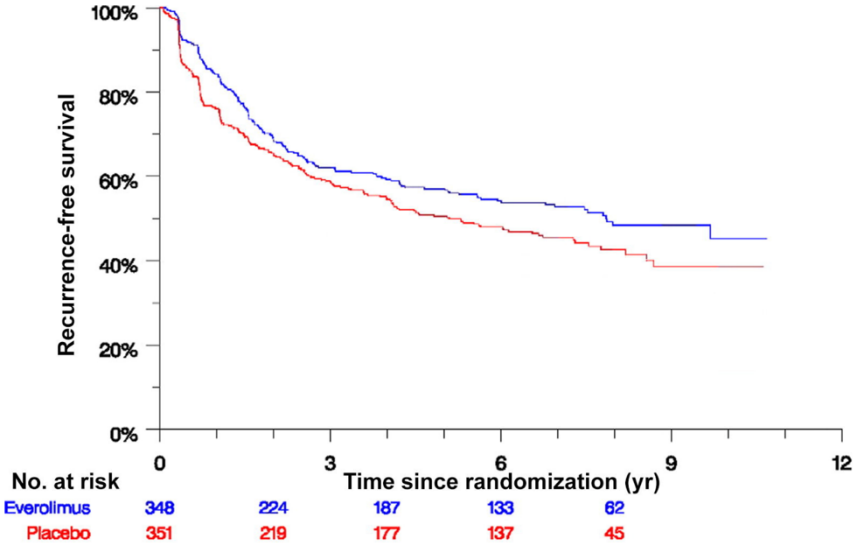
EVEREST TRIAL



- *p-value did not cross the prespecified boundary for statistical significance (p=0.044)
- DID NOT reach its primary RFS endpoint

Ryan CW, et al. *The Lancet*. 2023

EVEREST TRIAL: Subgroup analyses in very-high risk patients



- In the very-high-risk population:
- Significant improvement in RFS (HR 0.80, 95% CI 0.65–0.99; p = 0.041)
- There was no statistically significant difference in OS

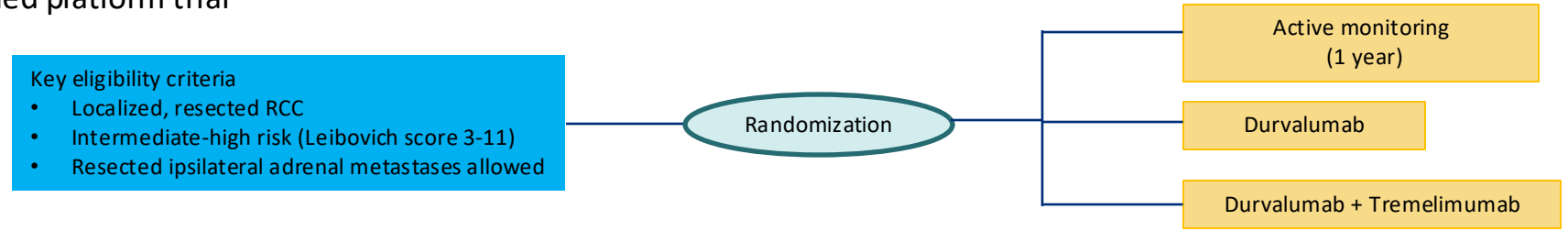
Lara PN, et al. *European Urology*. 2024

	KEYNOTE - 564 PEMBROLIZUMAB	PROSPER (EA8143) NIVOLUMAB	IMMotion 010 ATEZOLIZUMAB	CHECKMATE-914 NIVO/ IPI
RANDOMIZATION	Adjuvant Pembrolizumab Vs. Placebo	Neoadjuvant and adjuvant Nivolumab vs. surgical SOC	Adjuvant Atezolizumab Vs. Placebo	Adj Nivolumab + Ipilimumab vs Placebo (nivolumab alone added)
HISTOLOGY	cRCC with a component of clear cell histology w or w/out sarcomatoid histology	Clear and nonclear cell	Component of either ccRCC histology or sarcomatoid histology	ccRCC predominant with or without sarcomatoid histology
SACRCOMATOID?	YES	YES	YES	YES
T/N	pT2, grade 4 and higher Any N	cT2 and higher Any N	pT2, grade 4 and higher Any N	pT2 grade3-4 and higher Any N
OLIGOMETS	M1 resected within 12 months of primary tumor	Oligomets ablated or resected within 12 weeks of primary	Lung or soft tissue oligomets >12 months	NO
PFS HR P-value	**0.63 p<0.0001**	0.97 p= 0.43	0.93 p= 0.49	0.92 P= 0.53
OS HR P-value	**0.62; (95% CI, 0.44 to 0.87) P=0.005**	NS	NS	NS

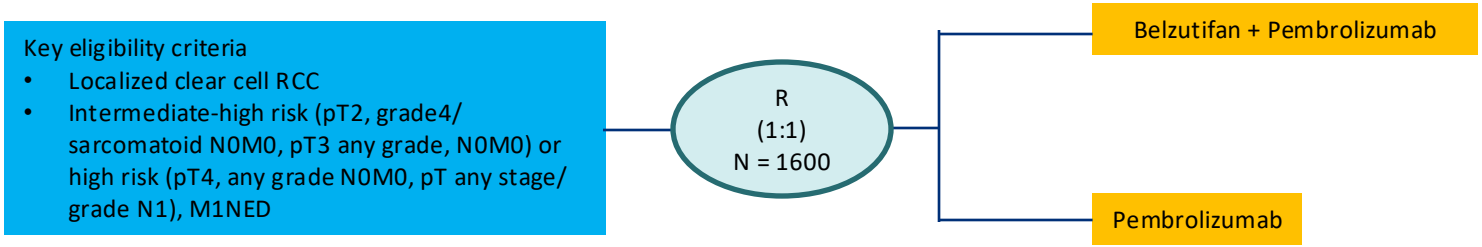
Choueiri et al. NEJM 2021, 2023; Allaf M, et al. Presented at: ESMO;2022; Pal M, Lancet 9-11-22. Bex A, et al. Presented at: ESMO 2022; Motzer RJ, et al. Presented at: ESMO;2022; Choueiri et al. NEJM 2024

Perioperative Management "Trials on Horizon"

1. RAMPART (**R**enal **A**djuvant **M**ulti**P**le **A**rm **Randomized T**rial): A Phase III multi-arm multi-stage randomized controlled platform trial



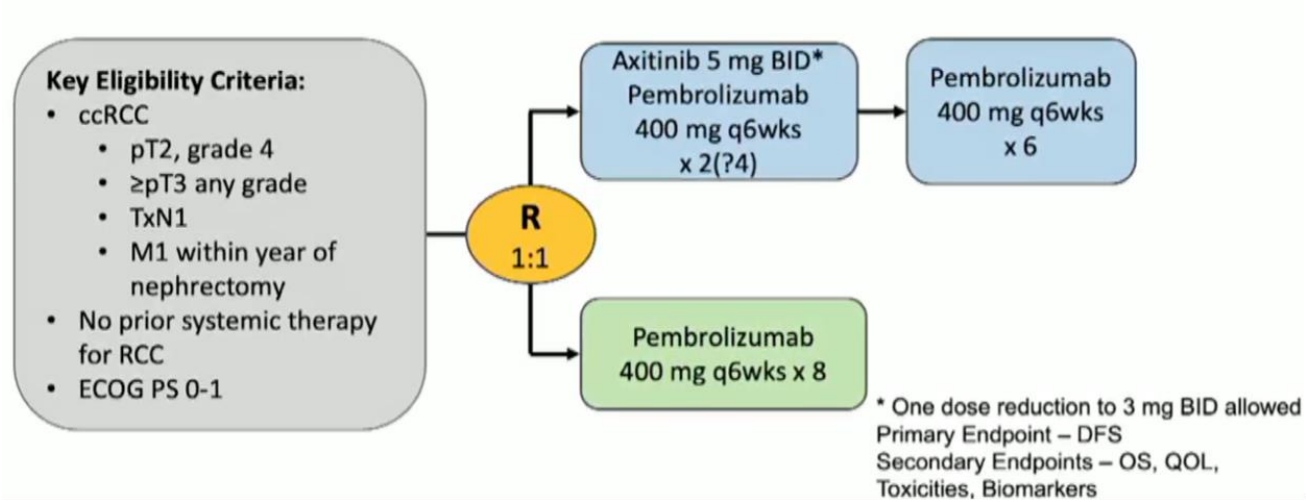
2. LITESPARK-022 (Phase-III trial comparing pembrolizumab+ belzutifan vs. pembrolizumab



Oza *et al.* Contem Clin Trials. 2021

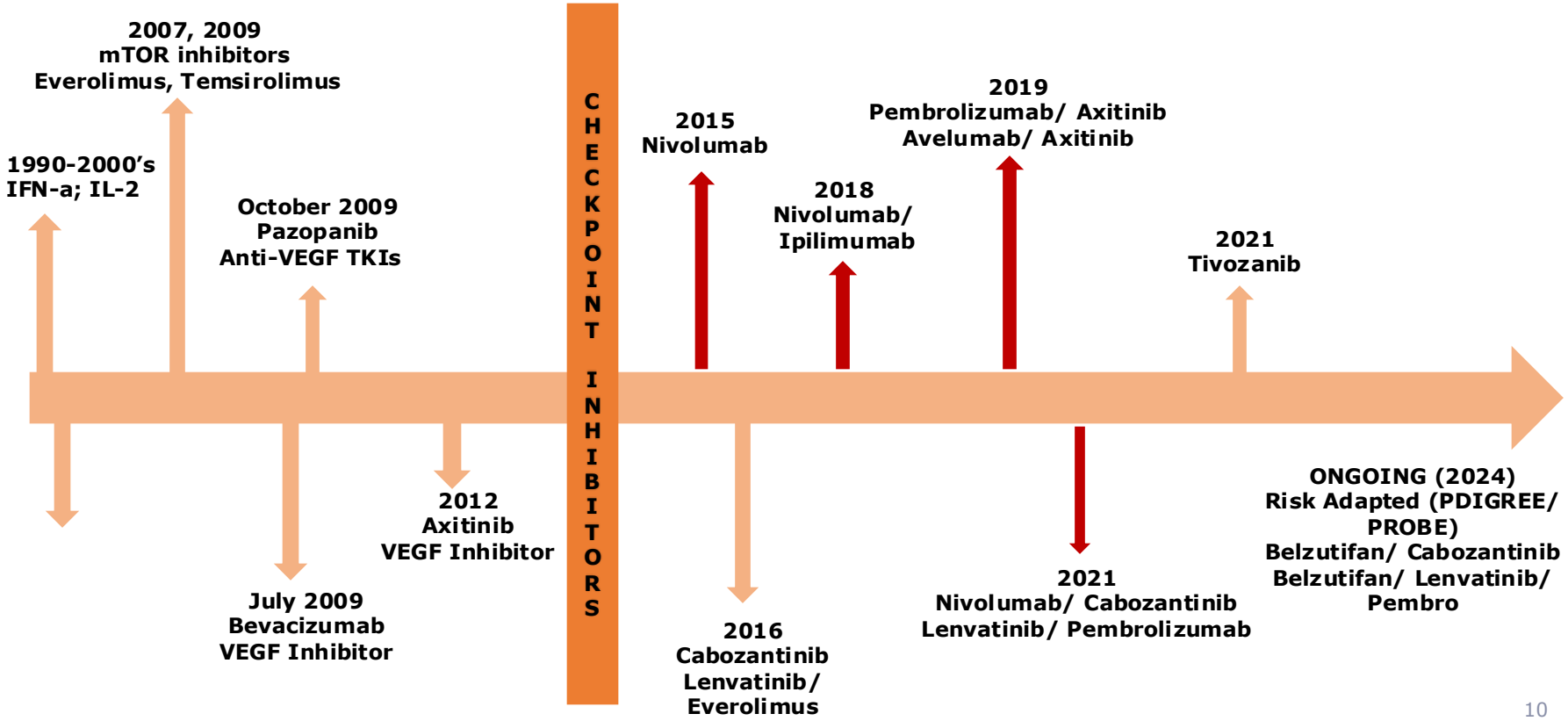
Perioperative Management "Trials on Horizon"

3. STRIKE (Phase-III trial comparing a combination of pembrolizumab+ axitinib vs. pembrolizumab



McGregor. IKCS 2022

Systemic Therapies for Advanced/ Metastatic RCC in 2023



Approved Front-Line Systemic Therapies from Phase-3 Trials (ITT)

	CHECKMATE- 214[1]	KEYNOTE-426[2]	CLEAR[3]	CHECKMATE- 9ER[4]
DRUGS	**Nivolumab + ipilimumab (N = 1096)**	**Pembrolizumab + Axitinib (N = 861)**	**Pembrolizumab + Lenvatinib (N = 1069)**	**Nivolumab + Cabozantinib (N = 651)**
Median follow-up (months)	99 months	67 months	49 months	44 months
mPFS (months)	12.2 vs. 12.3	15.7 vs. 11.1	23.9 vs. 9.2 months	16.6 vs. 8.4
HR (95% CI)	0.88 (0.75-1.03)	0.69 (0.59-0.81)	0.47 (0.38 to 0.57)	0.59 (0.49-0.71)
Landmark PFS	23% at 7.5 years	18% at 5 years	37% at 3 years	17% at 4 years
Median OS (months)	52.7 vs. 37.8	47.2 vs. 40.8	53.7 vs. 54.3	46.5 vs. 36
HR (95% CI)	0.72 (0.62-0.83)	0.84 (0.71-0.99)	0.79 (0.63-0.99)	0.75 (0.56-1.00)
Landmark OS	35% at 7.5 years	63% at 3 years 42% at 5 years	66% at 3 years	49% at 4 years
ORR	39 vs. 33%	61% vs. 40%	71% vs. 37%	56% vs. 28%
CR	12% vs. 3%	12% vs. 4%	18% vs. 5%	13% vs. 5%
Primary PD	18%	12%	7%	11.5

1. Tannir *et al*. Annals of Oncology. 2024
2. Rini *et al*. LBA4501. Presented at ASCO 2023
3. Motzer *et al*. JCO. 2024
4. Powels *et al*. Annals of Oncology. 2024

COSMIC-313: TRIPLET Therapy in mRCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, L. Albiges, M. Burotto, C. Szczylik, B. Zurawski, E. Yanez Ruiz, M. Maruzzo, A. Suarez Zaizar, L.E. Fein, F.A. Schutz, D.Y.C. Heng, F. Wang, F. Mataveli, Y.-L. Chang, M. van Kooten Losio, C. Suarez, and R.J. Motzer, for the COSMIC-313 Investigators*

FIRST trial to compare a triplet to a doublet
FIRST trial with ipilimumab/ nivolumab as the comparator

Choueiri *et al.* NEJM 2023

COSMIC 313 vs. previously published doublet trials

	CHECKMATE- 214[1]	KEYNOTE-426[2]	CLEAR[3]	CHECKMATE- 9ER[4]	COSMIC-313
DRUGS	**Nivolumab + ipilimumab (N = 1096)**	**Pembrolizumab + Axitinib (N = 861)**	**Pembrolizumab + Lenvatinib (N = 1069)**	**Nivolumab + Cabozantinib (N = 651)**	**Nivo + Ipi +Cabozantinib (N=428)**
Median follow-up (months)	**68 months**	**67 months**	**48 months**	**44 months**	**14.9 months**
mPFS (mo)	12.2 vs. 12.3	15.7 vs. 11.1	**23.9 vs. 9.2**	16.6 vs. 8.4	**15.3 vs. 11.3**
HR (95% CI)	0.86 (0.73-1.01) (0.73 for Int/Poor)	0.69 (0.59-0.81)	0.47 (0.38-0.57)	0.59 (0.49-0.71)	**0.74 (0.61-0.90)**
Median OS (mo)	55.7 vs. 38.4	47.2 vs. 40.8	53.7 vs. 54.3	49.5 vs. 35.5	Not reported
HR (95% CI)	0.72 (0.62-0.85) (0.68 for Int/Poor)	0.84 (0.71-0.99)	0.79 (0.63-0.99) (0.74 for Int/Poor)	0.70 (0.56-0.87)	
ORR	39 vs. 32%	61% vs. 40%	**71% vs. 37%**	56% vs. 28%	43% vs. 36%
CR	12% vs. 3%	12% vs. 3%	**18% vs. 5%**	13% vs. 5%	**3% vs. 3%**
Sarcomatoid features (%)	16	12	8	11.5	
% pts discontinuation of both drugs	22% vs. 12%	7% vs. 12%	**37% vs. 14%**	20% vs. 17%	**45% vs. 24%**
QOL (vs. Sunitinib)	Improved	Similar	Similar to improved	Improved	

Pal. Presented at ESMO, September 2022

COSMIC-313: Adverse Event Data

Treatment Exposure and Discontinuation (Safety Population)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

Data cut-off: Jan 31, 2022

Choueiri *et al.* NEJM 2023

COSMIC 313: CONCLUSIONS

- Positive trial for PFS (HR 0.74) to support the triplet regimen
- However, looking at the HR in the FORREST PLOT: poor risk patients DO NOT benefit
- Low response rates and equal complete response rate
- Use of high dose corticosteroids ($\geq$ 40mg/day) in experimental arm 58% vs. 35%
- High rate of discontinuation due to AEs (45% vs. 24%)

Front-line mRCC Trials on the "Horizon"

1. Trials evaluating other Triplets

Key inclusion criteria
- Advanced or metastatic RCC
- No prior systemic therapy

R
1:1:1
N=1431

- Quanvonlimab Pembrolizumab Lenvatinib
- Belzutifan Pembrolizumab Lenvatinib
- Pembrolizumab Lenvatinib

2. Adaptive designs: PDIGREE (Alliance A031704)

Key inclusion criteria
- Advanced or metastatic RCC
- No prior systemic therapy

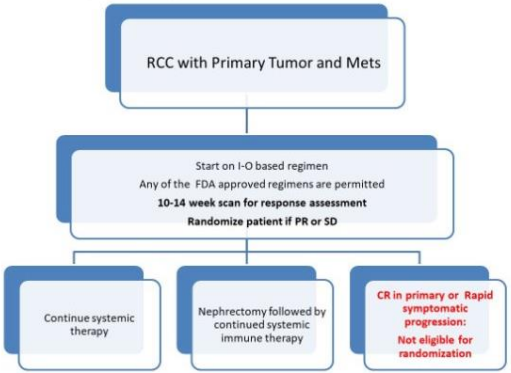
N=1046

INDUCTION

Nivolumab Ipilimumab

- **CR** → Nivolumab
- **Non-CR Non-PD** → R
  - Nivolumab
  - Nivolumab Cabozantinib
- **PD** → Cabozantinib

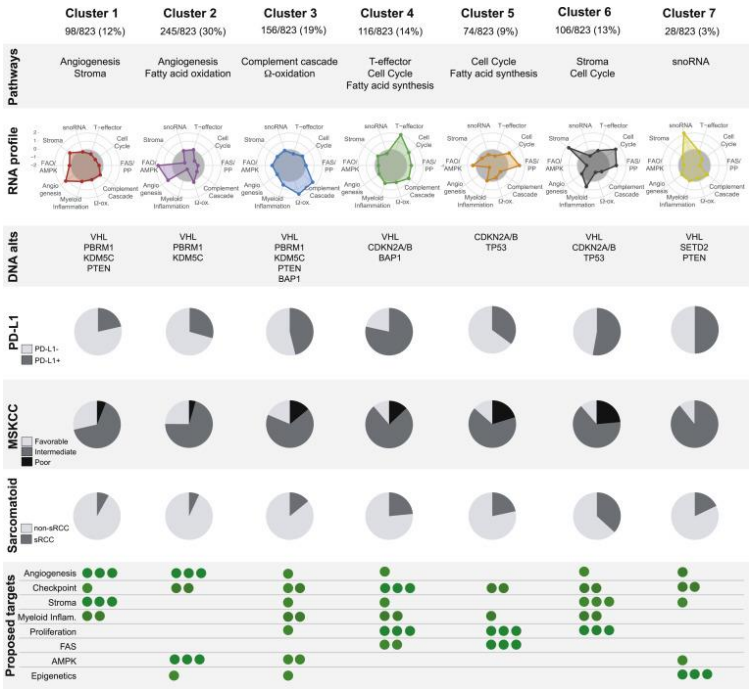
3. Trials evaluating the role of nephrectomy in mRCC: PROBE



1. Choueiri TK et al. ASCO GU 2022. Abstract TPS399; 2. Zhang T et al. ASCO GU 2021. Abstract TPS366; 3. Vaishampayan UN et al. ASCO GU 2022. Abstract TPS402.

Front-line mRCC Trials on the "Horizon"

4. Trials Utilizing Biomarkers: OPTIC Trial



Phase II, open-label, parallel single-arm study using tumor RNAseq cluster to assign protocol treatment

PI: Brian Rini, MD

Eligibility
- ECOG 0 or 1
- Newly diagnosed metastatic clear-cell renal cell carcinoma
- No prior systemic therapy
- Available tumor tissue for RNA-sequencing/cluster prediction
- Patients with clusters 3/6 will be excluded

Primary Endpoint:
-ORR per RECIST
Secondary Endpoints:
-PFS
-Depth of response >80% at 6 months.

Clusters 1/2 — Simon's MinMax Two-Stage Design — **Clusters 4/5/7**

Nivolumab/Cabozantinib (N=26)
- H_0: ORR ≤ 55%
- H_A: ORR > 75%

Stage I (N=12) ≥7/12 responders → Stage II (N=14) ≥18/26 responders

Ipilimumab/Nivolumab (N=28)
- H_0: ORR ≤ 40%
- H_A: ORR > 60%

Stage I (N=16) ≥7/16 responders → Stage II (N=12) ≥15/28 responders

1. Motzer *et al*. Cell. 2020; 2. Rini et al. IKCS 2022

Front-Line Preferred/Recommended Systemic Therapy for mccRCC

Favorable Risk

Preferred regimens:

- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Lenvatinib + pembrolizumab
- Ipilimumab+ nivolumab

Other recommended regimens:

- Axitinib + avelumab
- Cabozantinib (category 2B)
- Pazopanib
- Sunitinib

Useful in certain circumstances

- Active surveillance
- Axitinib

Intermediate/ poor risk

Preferred regimens:

- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Ipilimumab + nivolumab
- Lenvatinib + pembrolizumab
- Cabozantinib

Other recommended regimens:

- Axitinib + avelumab
- Pazopanib
- Sunitinib

Useful in certain circumstances

- Axitinib

NCCN Guidelines. Kidney Cancer. Version 1.2025.

Relapsed/ Metastatic ccRCC: Subsequent Lines Systemic Therapy

Immunotherapy Naïve

Preferred regimen: None

Other recommended regimens:

- Axitinib + pembrolizumab
- Cabozantinib
- Cabozantinib + nivolumab
- Everolimus + lenvatinib
- Ipilimumab + nivolumab
- Lenvatinib + pembrolizumab
- Nivolumab

Useful in certain circumstances

- Axitinib
- Everolimus
- Pazopanib
- Sunitinib
- Tivozanib
- Belzutifan (category 2B)
- Bevacizumab (category 2B)
- Axitinib + avelumab (category 3)

NCCN Guidelines. Kidney Cancer. Version 1.2024.

Relapsed/ Metastatic ccRCC: Subsequent Lines Systemic Therapy

Previously Treated with Immunotherapy

Preferred regimen: None

Other recommended regimens:

- Axitinib
- Belzutifan
- Cabozantinib
- Lenvatinib + everolimus
- Tivozanib

Useful in certain circumstances

- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Everolimus
- Ipilimumab + nivolumab
- Lenvatinib + pembrolizumab
- Pazopanib
- Sunitinib
- Bevacizumab
- Axitinib + avelumab

NCCN Guidelines. Kidney Cancer. Version 1.2024.

Subsequent Lines of Therapy for mccRCC

Study	Treatment evaluated	Prior treatment	Number of patients	PFS (months)	ORR (%)
METEOR (post-hoc)[6]	Cabozantinib (vs. everolimus)	Anti-PD-1/PD-L1 subgroup	32	Not reached vs. 4.1 mos (HR 0.22)	22% vs. 0%
Phase II study[3]	Axitinib	IO alone: 71% IO-TKI or IO/IO: 31%	40	8.8 months	38%
BREAKPOINT (Phase II)[1]	Cabozantinib	74%: IO/IO 17%: IO-TKI 9%: adjuvant IO	48	9.3 months	43%
INMUNOSUN-SOGUG (Phase II)[2]	Sunitinib	IO combinations and monotherapy	21	5.6 months	19%
CANTATA (Phase III)[4]	Cabozantinib vs. Cabozantinib+ Telaglenastat	IO alone or IO combinations	91	9.2 months vs. 9.3 months	31% vs. 28%
TIVO-3 (Phase III)[5]	Tivozanib vs. Sorafenib	≥3rd line, IO in 27%	350	7.3 months vs. 5.1 months	NR
Phase II[8]	Cabozantinib+ Belzutifan	65%: IO/IO 35%: IO-TKI 14%: IO after TKI or vice versa	52	I year PFS: 65%	22%

BELZUTIFAN: LITESPARK 005

The NEW ENGLAND JOURNAL of MEDICINE

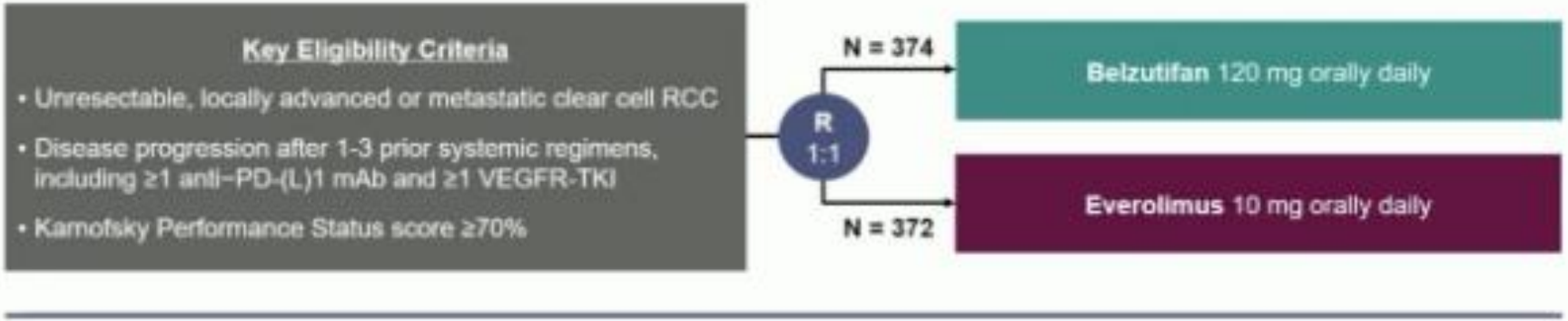
ORIGINAL ARTICLE

Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, K. Peltola, G. de Velasco, M. Burotto, C. Suarez, P. Ghatalia, R. Iacovelli, E.T. Lam, E. Verzoni, M. Gümüş, W.M. Stadler, C. Kollmannsberger, B. Melichar, B. Venugopal, M. Gross-Goupil, A. Poprach, M. De Santis, F.A. Schutz, S.H. Park, D.A. Nosov, C. Porta, J.L. Lee, X. Garcia-del-Muro, E. Biscaldi, R. Manneh Kopp, M. Oya, L. He, A. Wang, R.F. Perini, D. Vickery, L. Albiges, and B. Rini, for the LITESPARK-005 Investigators*

Choueiri *et al*. NEJM. Aug 2024

BELZUTIFAN: LITESPARK 005



Stratification Factors

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

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

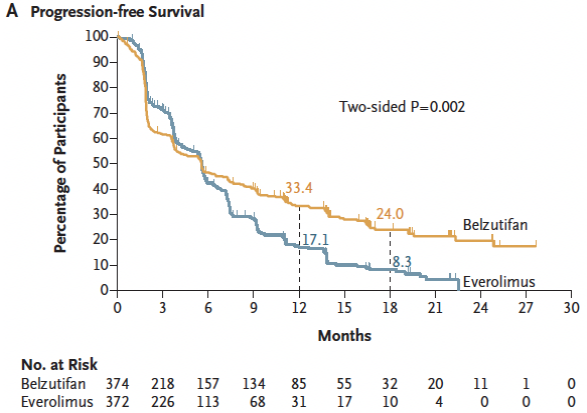
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

1. Albiges et al. Presented at ESMO 2023

BELZUTIFAN: LITESPARK 005



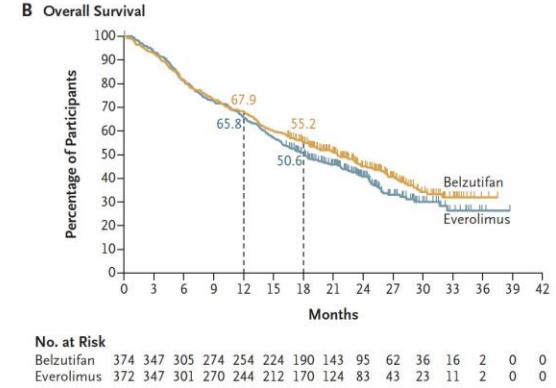


Table 2. Best Response in the Intention-to-Treat Population.[a]

Response	First Interim Analysis			Second Interim Analysis		
	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference
Objective response — % (95% CI)	21.9 (17.8–26.5)	3.5 (1.9–5.9)	18.4 (14.0–23.2)†	22.7 (18.6–27.3)	3.5 (1.9–5.9)	19.2 (14.8–24.0)
Confirmed best overall response — no. (%)						
Complete response	10 (2.7)	0		13 (3.5)	0	
Partial response	72 (19.3)	13 (3.5)		72 (19.3)	13 (3.5)	
Stable disease‡	147 (39.3)	245 (65.9)		143 (38.2)	245 (65.9)	
Progressive disease	126 (33.7)	80 (21.5)		127 (34.0)	80 (21.5)	
Not evaluable§	5 (1.3)	8 (2.2)		5 (1.3)	8 (2.2)	
No assessment¶	14 (3.7)	26 (7.0)		14 (3.7)	26 (7.0)	

ADVERSE EVENTS:

- Grade 3+ adverse events were ~62% in both treatment arms
- Most common AEs with belzutifan were anemia and hypoxia
- AEs led to discontinuation of treatment in 5.9% and 14.7% of pts on BEL and EVE, respectively

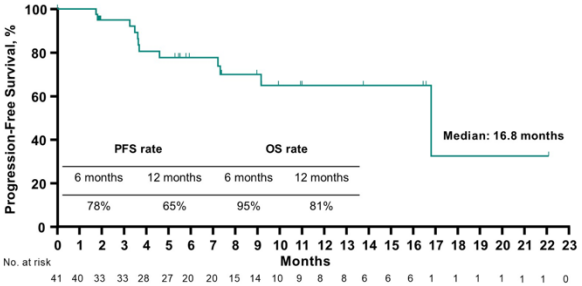
Choueiri *et al*. NEJM. Aug 2024

Other trials on the "horizon" using BELZUTIFAN

1. Phase-II trial combining Belzutifan + Cabozantinib

Key eligibility criteria
- Advanced/metastatic cc-RCC
- ECOG PS 0 or 1

COHORT 2: TREATED WITH PRIOR IO (n = 52)



Outcome, n (%)	Patients Evaluated for Efficacy (n = 41)
ORR	9 (22)
DCR	37 (90)

2. Phase-III trial comparing Belzutifan + Lenvatinib vs. Cabozantinib (LITESPARK-011)

Key eligibility criteria
- Advanced/metastatic cc-RCC
- Disease progression after 1st/ 2nd line of anti-PD-1 or anti-PD-L1 therapy (including perioperative)
- ≤ 2 prior lines of therapy
- KPS≥ 70%

R
(1:1)
N = 708

Belzutifan +Lenvatinib

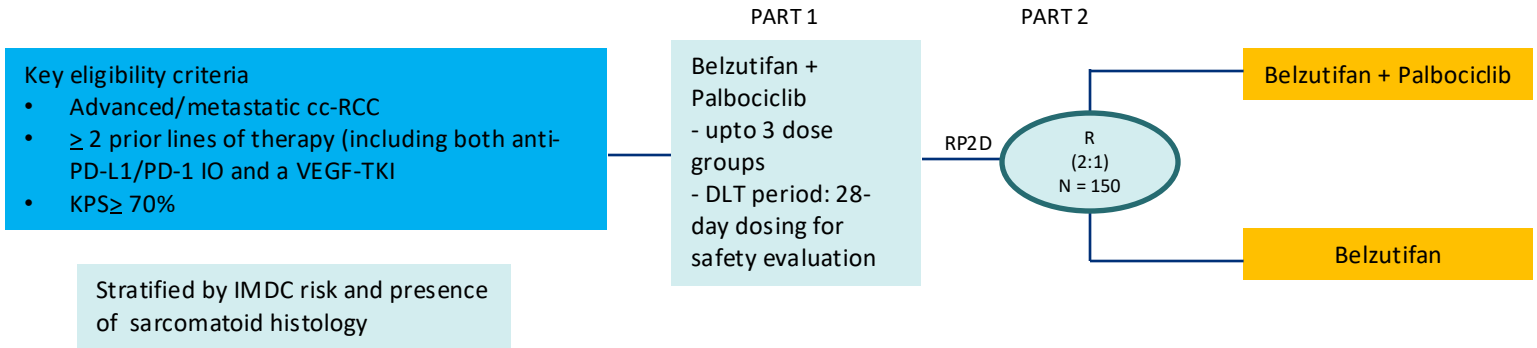
Cabozantinib

Stratified by IMDC risk, line of treatment and geographic location

1. Choueiri TK *et al.* ASCO GU 2021. Abstract 272. 2. Motzer *et al*. Future Oncology. 2023

Other trials on the “horizon” using BELZUTIFAN

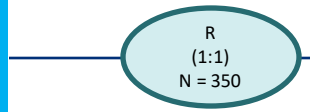
3. Randomized phase-1/2 trial evaluating Belzutifan+ CDK4/6 inhibitor palbociclib (LITESPARK-024)



1. McDermott *et al*. ASCO 2023

TIVOZANIB: TIVO-3

Key eligibility criteria
- Metastatic clear cell RCC
- Received at least 2 lines of prior systemic therapy (including 1 VEGFRi/ TKI
- Measurable disease per RECIST
- ECOG PS 0 or 1



Tivozanib 1.34 mg PO daily
21 days on and 7 days off

Sorafenib 400mg PO BID
(I cycle = 28 days)

Stratification Factors
- IMDC Risk
- Previous therapy

Primary endpoint: PFS
Secondary endpoint: OS, ORR, duration of response and safety

Rini BI et al. *Lancet Oncol.* 2020;21(1):95-104.

TIVO-3: Baseline Patient Characteristics

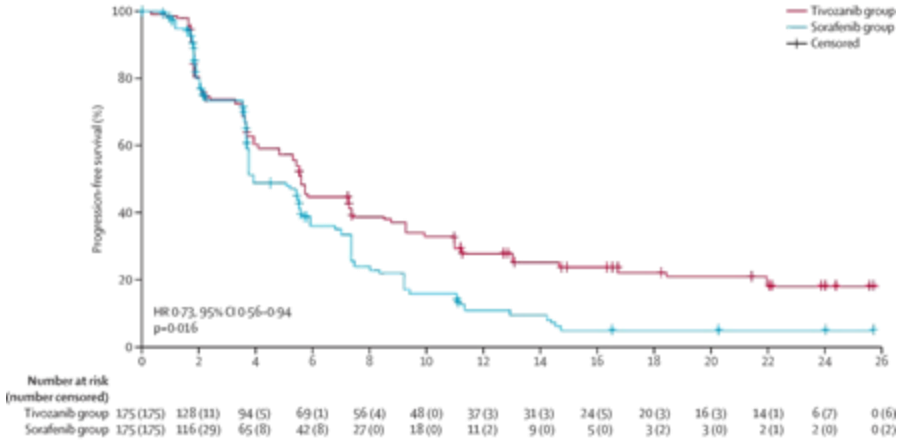
Number of previous systemic therapies		
Two	108 (62%)	104 (59%)
Three	67 (38%)	71 (41%)

Previous therapies		
Two VEGFR TKIs	79 (45%)	80 (46%)
Checkpoint inhibitor plus VEGFR TKI	47 (27%)	44 (25%)
VEGFR TKI plus other systemic agent†	49 (28%)	51 (29%)

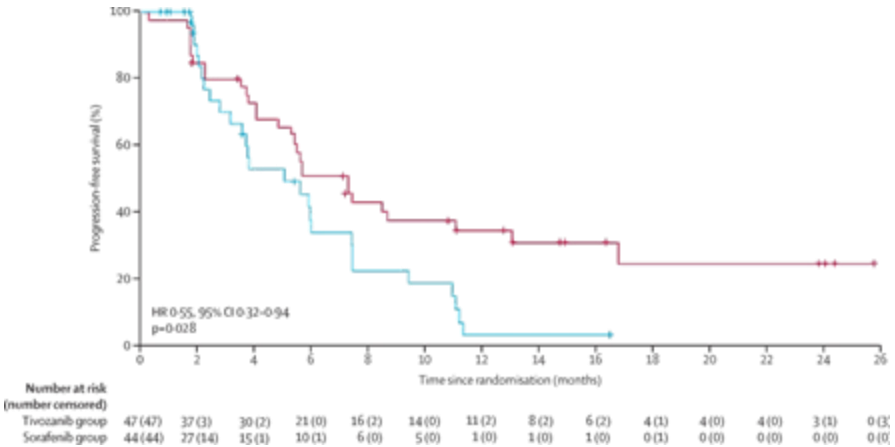
	Tivozanib group (n=175)	Sorafenib group (n=175)
Age (years)	62 (34–88)	63 (30–90)
Sex		
Male	126 (72%)	128 (73%)
Female	49 (28%)	47 (27%)
Race		
White	165 (94%)	167 (95%)
Non-white	10 (6%)	8 (5%)
Pathological diagnosis		
Clear cell	165 (94%)	160 (91%)
Clear cell component	9 (5%)	9 (5%)
Other*	1 (1%)	5 (3%)
IMDC risk category		
Favourable	34 (19%)	36 (21%)
Intermediate	109 (62%)	105 (60%)
Poor	32 (18%)	34 (19%)
Number of previous systemic therapies		
Two	108 (62%)	104 (59%)
Three	67 (38%)	71 (41%)
Previous therapies		
Two VEGFR TKIs	79 (45%)	80 (46%)
Checkpoint inhibitor plus VEGFR TKI	47 (27%)	44 (25%)
VEGFR TKI plus other systemic agent††	49 (28%)	51 (29%)
Time from initial diagnosis (months)	50 (10–347)	50 (9–224)
Time from most recent relapse (months)	1 (<1–121)	1 (<1–87)

Rini BI et al. *Lancet Oncol.* 2020;21(1):95-104.

TIVO-3: Results



PFS in ITT population:
mPFS 5.6 months with tivozanib vs. 3.9 months



PFS after an ICI and TKI combination:
mPFS 7.3 months for tivozanib vs. 5.1 months

Rini BI et al. *Lancet Oncol.* 2020;21(1):95-104.

TIVO-3: Cox Proportional Hazards Analysis

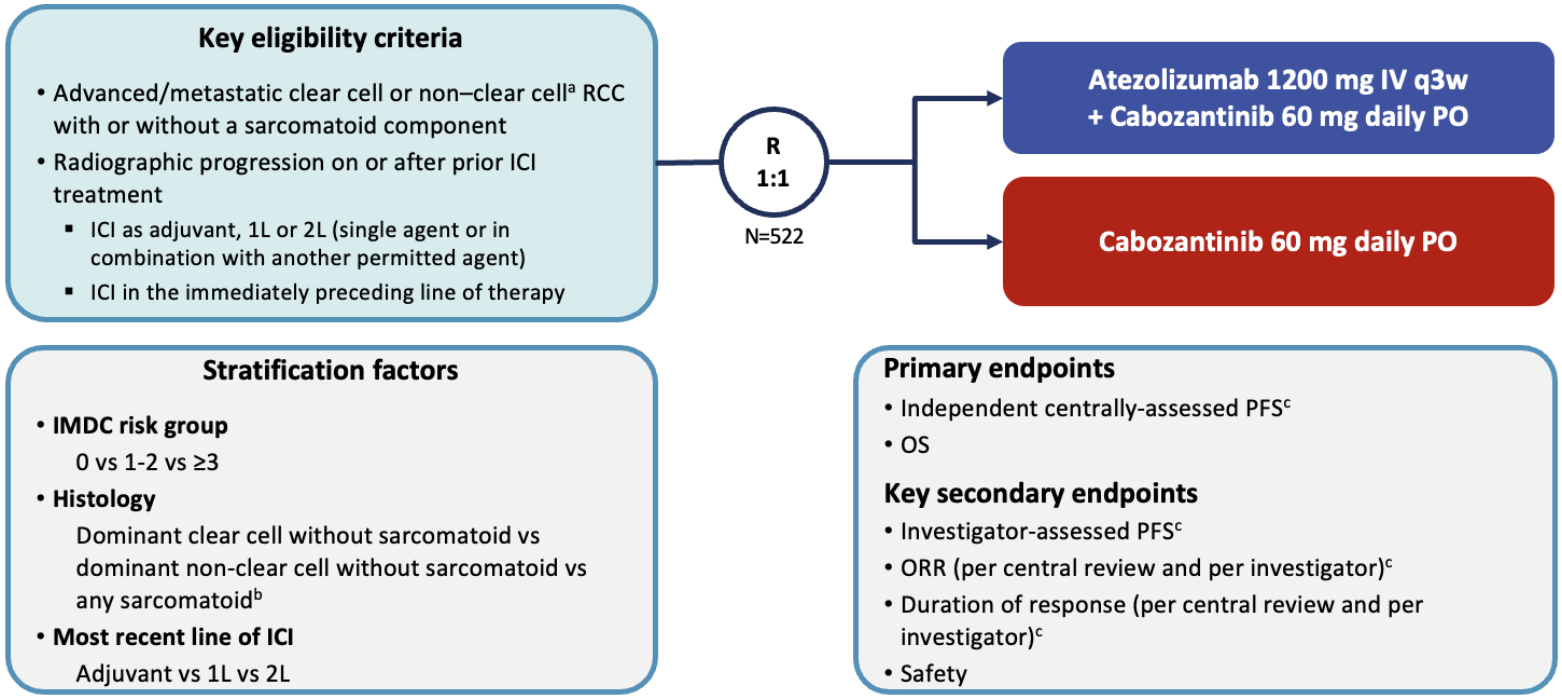
	Events/patients		Hazard ratio (95% CI)*
	Tivozanib	Sorafenib	
Age (years)			
<65	69/98	68/95	0·74 (0·53–1·04)
≥65	54/77	55/80	0·59 (0·40–0·87)
Sex			
Women	36/49	30/47	0·72 (0·44–1·18)
Men	87/126	93/128	0·64 (0·47–0·86)
Race			
White	116/165	118/167	0·66 (0·51–0·86)
Non-white	7/10	5/8	0·75 (0·23–2·48)
Baseline ECOG PS			
0	55/86	60/85	0·54 (0·37–0·78)
1	68/89	63/90	0·86 (0·60–1·21)
Geographical region			
North America	17/31	9/27	0·71 (0·31–1·60)
EU	106/144	114/148	0·69 (0·52–0·90)
IMDC risk category			
Favourable	21/34	22/36	0·46 (0·25–0·85)
Intermediate	73/109	74/105	0·69 (0·49–0·95)
Poor	29/32	27/34	1·15 (0·67–2·00)
Previous therapy			
Two previous VEGFR TKIs	56/79	61/80	0·57 (0·39–0·83)
Checkpoint inhibitor plus VEGFR TKI	29/47	27/44	0·55 (0·32–0·94)
Previous VEGFR TKI plus other agents	38/49	35/51	0·98 (0·62–1·56)
Number of metastatic sites			
1	10/12	17/23	0·96 (0·43–2·11)
≥2	113/163	106/152	0·67 (0·51–0·88)
Baseline systolic blood pressure (mm Hg)			
≤140	93/134	90/131	0·68 (0·50–0·91)
>140	30/41	33/44	0·66 (0·40–1·09)
Baseline diastolic blood pressure (mm Hg)			
≤90	112/159	111/158	0·67 (0·51–0·88)
>90	11/16	12/17	0·69 (0·30–1·58)
All patients	**123/175**	**123/175**	**0·73 (0·56–0·94)**

Rini BI et al. *Lancet Oncol.* 2020;21(1):95-104.

Subsequent Lines of Therapy for mccRCC: Role of "Salvage" with an ICI?

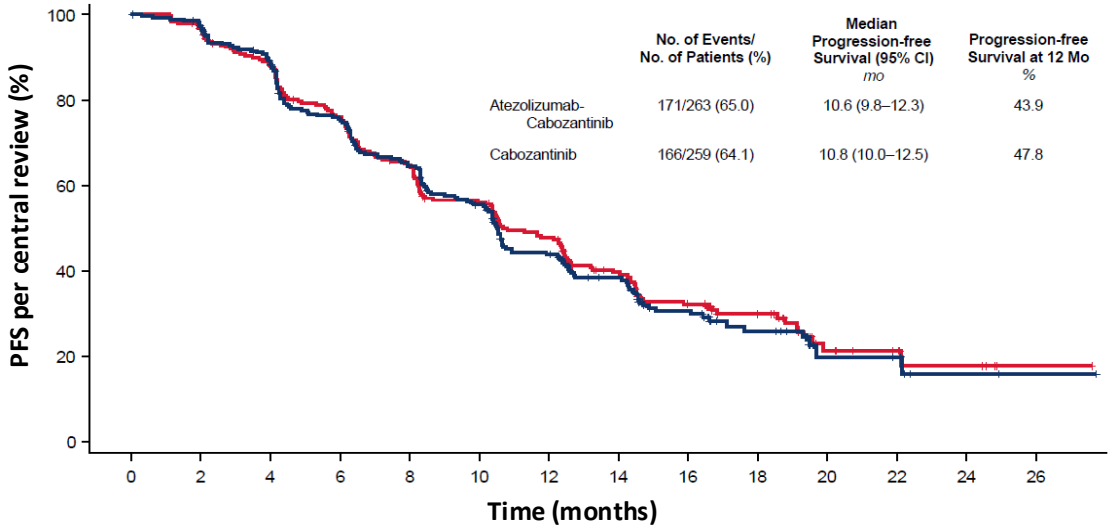
Study	Treatment evaluated	Number of patients	PFS (months)	ORR (%)
TITAN-RCC (Phase 2)[1]	Adaptive design to add ipi "boost"	1st line: 109 2nd line: 98	1st Line: 6.0 mos 2nd line: 3.7 mos	1st line: 28% N alone vs. 36% with I/N 2nd line: 18% N alone vs. 32% with I/N
OMNIVORE (Phase 2)[2]	Salvage Ipilimumab	83 (all IO naïve)	4.7	4%
HCRN GU16-260 (Phase 2)[3]	Salvage Nivolumab/ Ipilimumab	123 (35 pts went on ipi/nivo)	8.3	34% (6.5% CRs) ORR to nivo/ipi salvage 11.4% (1CR)
FRACTION-RCC (Phase 2)[4]	SalvageNivo/ Ipi in pts progressed on PD-1/PDL1	Track 2 (prior IO treated; no CTLA4i); N=46	3.7	17%

Rechallenge with an IO-based Regimen: CONTACT-03



Choueiri et al. ASCO 2023

CONTACT-03: Primary analysis of centrally reviewed PFS (primary endpoint)



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CONTACT-03: Safety Summary

Adverse event, n (%)	Atezo + Cabo (n=262)	Cabo (n=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

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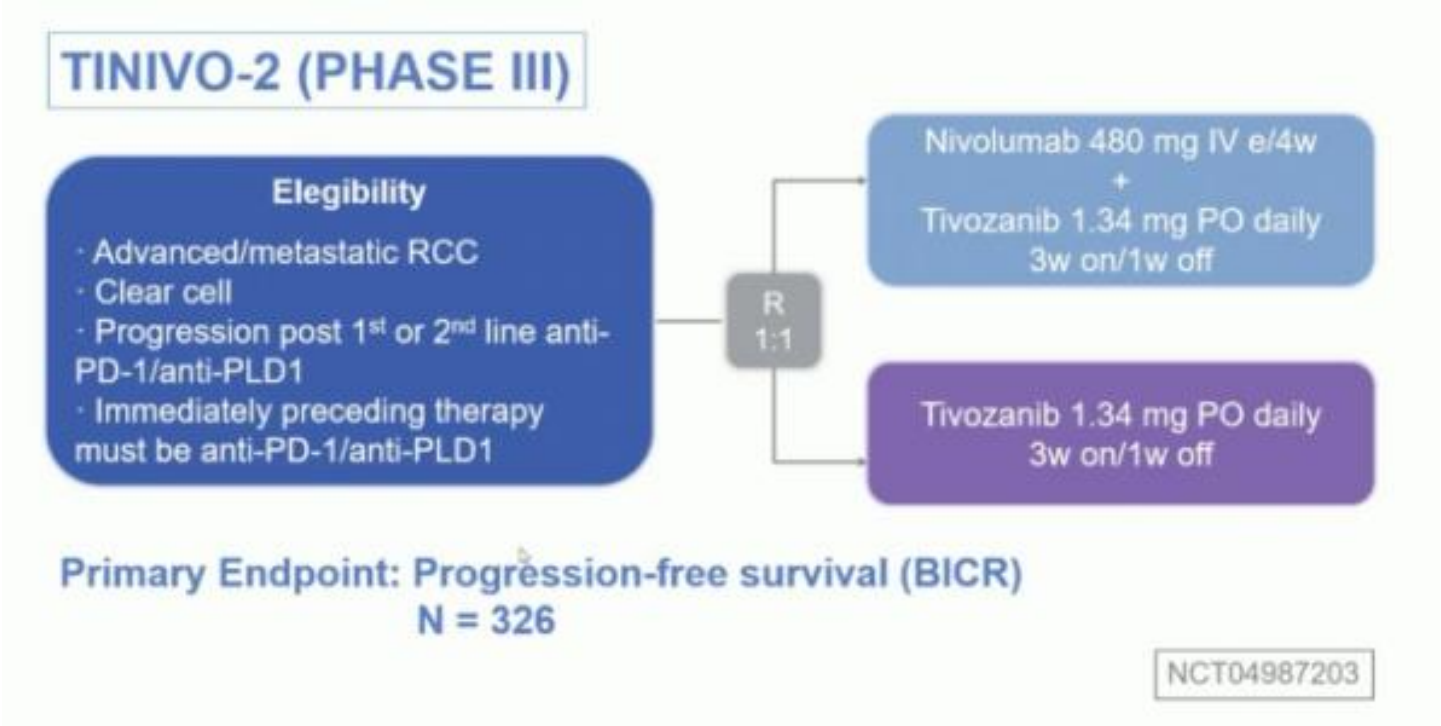
CONTACT-03: Conclusion

- CONTACT-03 was the first randomized, Phase III trial to examine the efficacy and safety of a PD-L1 inhibitor following progression on or after prior treatment with PD-L1/PD-1 therapy
- The addition of atezolizumab to cabozantinib **did not result in improved clinical outcomes**
- Increased toxicity was observed with the combination, although no specific safety signal was identified

Rechallenge with an IO-based Regimen: TiNivo-2



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Rechallenge with an IO-based Regimen: TiNivo-2

- "TiNivo-2 Phase 3 clinical trial in patients with advanced metastatic renal cell carcinoma whose tumors had progressed following prior immune checkpoint inhibitor (ICI) treatment did not meet the primary endpoint of increasing progression free survival (PFS) when nivolumab was added to low dose (0.89 mg) tivozanib."

https://www.aveooncology.com/aveo-oncology-an-lg-chem-company-announces-phase-3-renal-cell-carcinoma-clinical-trial-tinivo-2-results/#:~:text=BOSTON%2C%20July%2018%2C%202024%20(,did%20not%20meet%20the%20primary

Management of RCC in 2024: CONCLUSIONS

- Perioperative treatment of RCC has evolved to adjuvant pembrolizumab with OS benefit reported
- Doublet regimens remain standard of care in the front-line setting (no triplets)
- We do not have biomarkers to select for specific regimens
- CONTACT3 and TiNivo-2 data DO NOT support re-challenge with an ICI after progression (and there is no data to address the same question after adjuvant pembrolizumab)