UCDAVIS
COMPREHENSIVE
CANCER CENTER

Renal Cell Cancer: Recent Advances

Shuchi Gulati, MD MSc

Assistant Professor

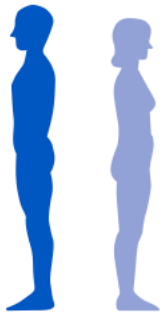
Division of Hematology and Oncology

UC Davis Comprehensive Cancer Center

RCC Disease Burden and Mortality

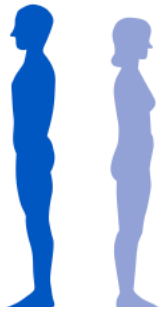
Estimated New Cases

Male			Female		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All sites	**1,010,310**		**All sites**	**948,000**	



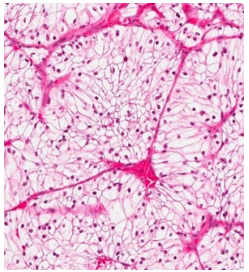
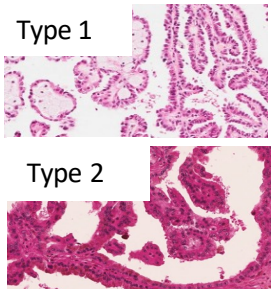
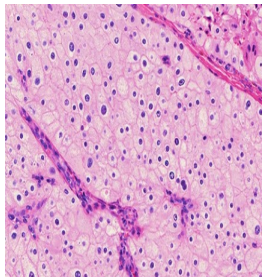
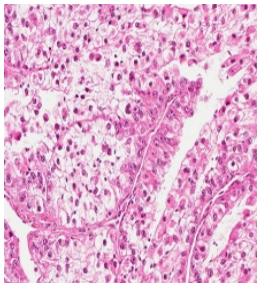
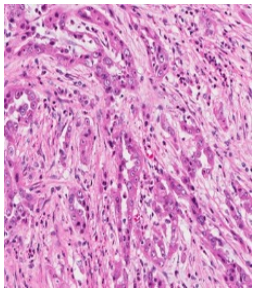
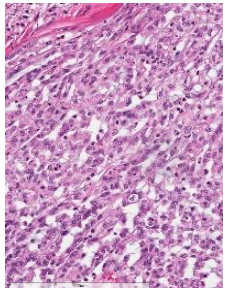
Estimated Deaths

Male			Female		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All sites	**322,080**		**All sites**	**287,740**	
Kidney & renal pelvis	**9,920**		**Kidney & renal pelvis**	**4,970**	



ACS Cancer Facts & Figures 2023.

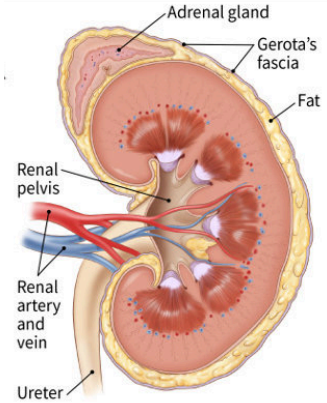
Histologic Classification of RCC

Clear Cell	Papillary		Chromophobe	Translocation	Collecting Duct	Unclassified
						
Cytogenetic Alterations						
Del Chr. 3p	**Type 1** Trisomy 7, 17	**Type 2** Del Chr. 9p	Del Chr. 1, 2, 6, 10, 13, 17, 21	Transloc. Xp11.2 [TFE3] Transloc (6;11) [TFEB]	Del Chr. 8p, 16p, 1p, 9p Gain Chr. 13q	Del Chr. 22q
Molecular Alterations						
- VHL - PBRM1 - SETD2 - PTEN - KDM5C - PI3K-MTOR-TSC1/2 - BAP1 - TP53	**Type 1** - MET - TERT - CDKN2A/B - EGFR	**Type 2** - SETD2 - CDKN2A/B - PBRM1 - NF2 - FH - TERT	- TP53 - PTEN - TERT fusion - MT-ND5 - MTOR-TSC1/2 - NRAS - FAAH2, PDHB, PDXDC1,ZNF765	- TFE3 fusion - TFEB fusion - TERT - SETD2 - NOTCH1 - BIRC7	- NF2 - SETD2 - SMARCB1 - CDKN2A	- NF2 - SETD2 - BAP1 - KMT2C - PI3K-MTOR-TSC1/2

Slide courtesy: Dr. Choueri (PER Symposium)

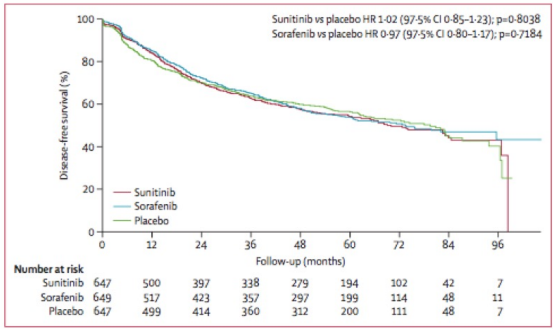
Perioperative Management of RCC

- Remains controversial in 2023!
- Identification of patients most likely to benefit remains a challenge (no biomarkers)

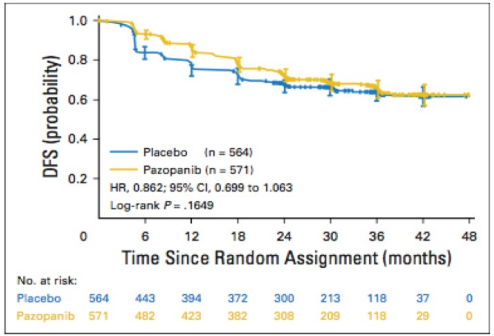


Perioperative Management: VEGFi/ TKIs

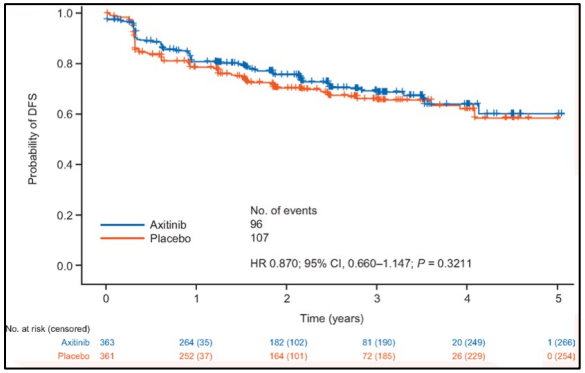
ASSURE DFS



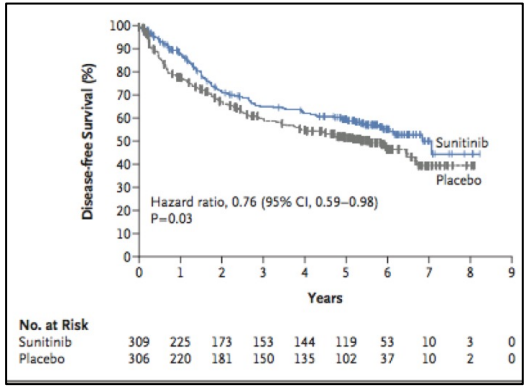
PROTECT DFS



ATLAS DFS



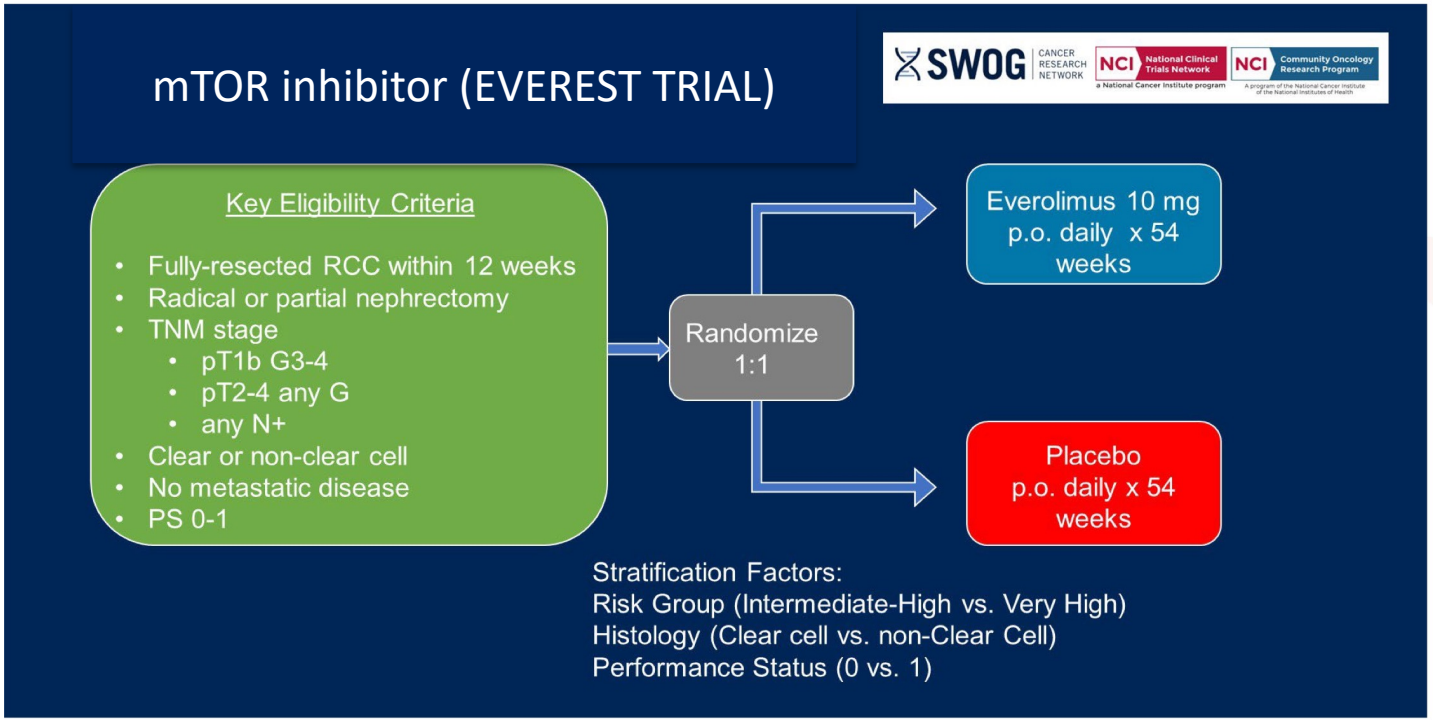
S-TRAC DFS



- 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

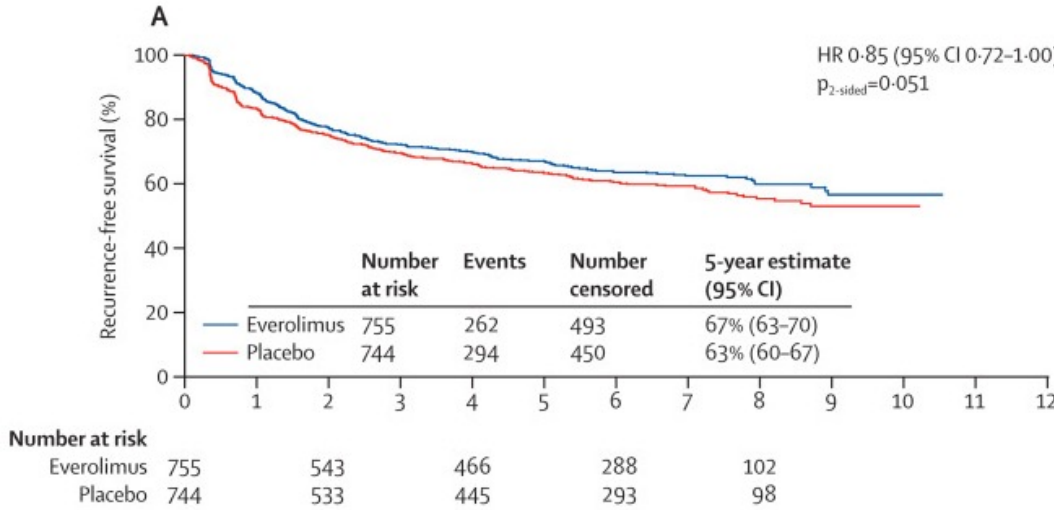
Haas NB, et al. *Lancet.* 2016;387(10032):2008-16. Motzer RJ, et al. *J Clin Oncol*. 2017;35(35):3916-3923. Ravaud A, et al. *N Engl J Med*. 2016;375(23):2246-2254. Gross- Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378.

Perioperative Management (EVEREST TRIAL)



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

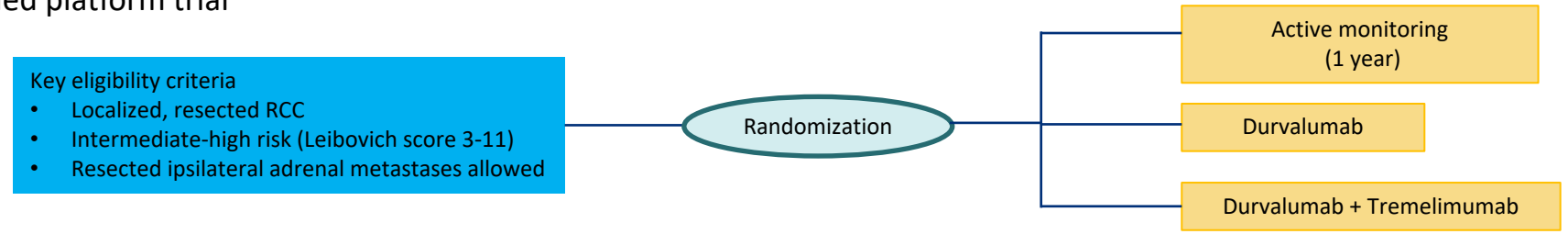
Perioperative Management: Immune Checkpoint Inhibitor Trials

	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

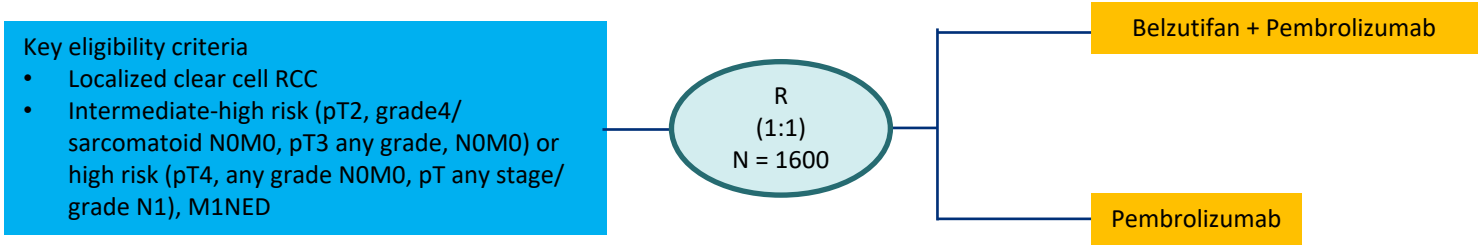
Choueiri et al. Presented at ASCO GU 2022; Allaf M, et al. Presented at: ESMO;2022; Pal M, Lancet 9-11-22. Bex A, et al. Presented at: ESMO 2022; Motzer RJ, et al. Presented at: ESMO;2022

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



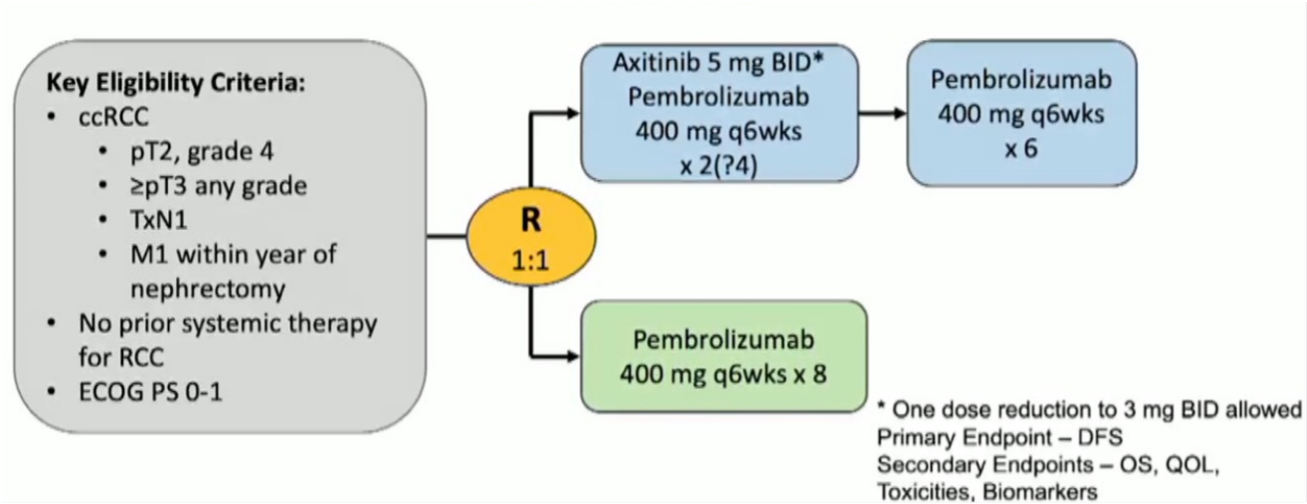
2. LITESPARK-022 (Phase-III trial comparing pembrolizumab+ belzutifan vs. pembrolizumab



Oza *et al.* Contem Clin Trials. 2021

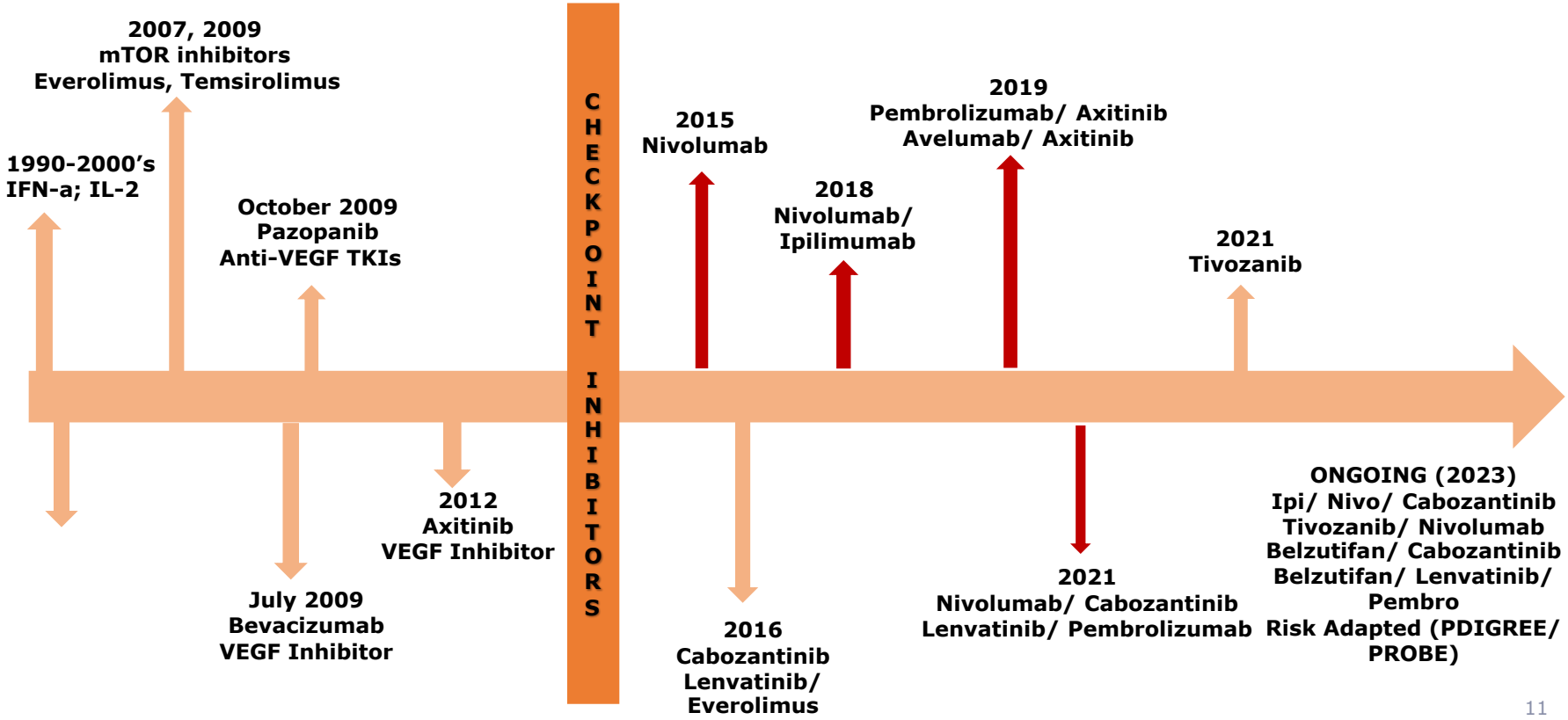
Perioperative Management "Trials on Horizon"

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)	**68 months**	**67 months**	**48 months**	**44 months**
mPFS (mo)	12.2 vs. 12.3	15.7 vs. 11.1	**23.9 vs. 9.2**	16.6 vs. 8.4
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)
Median OS (mo)	55.7 vs. 38.4	47.2 vs. 40.8	53.7 vs. 54.3	49.5 vs. 35.5
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%
CR	12% vs. 3%	12% vs. 3%	**18% vs. 5%**	13% vs. 5%
Sarcomatoid features (%)	16	12	8	11.5
% pts discontinuation of both drugs	22% vs. 12%	7% vs. 12%	**37% vs. 14%**	20% vs. 17%
QOL (vs. Sunitinib)	Improved	Similar	Similar to improved	Improved

#GU23: 3-year Follow-up data for CM-9ER
#ASCO23: 5-year Analysis for KN-426 and final analysis of CLEAR

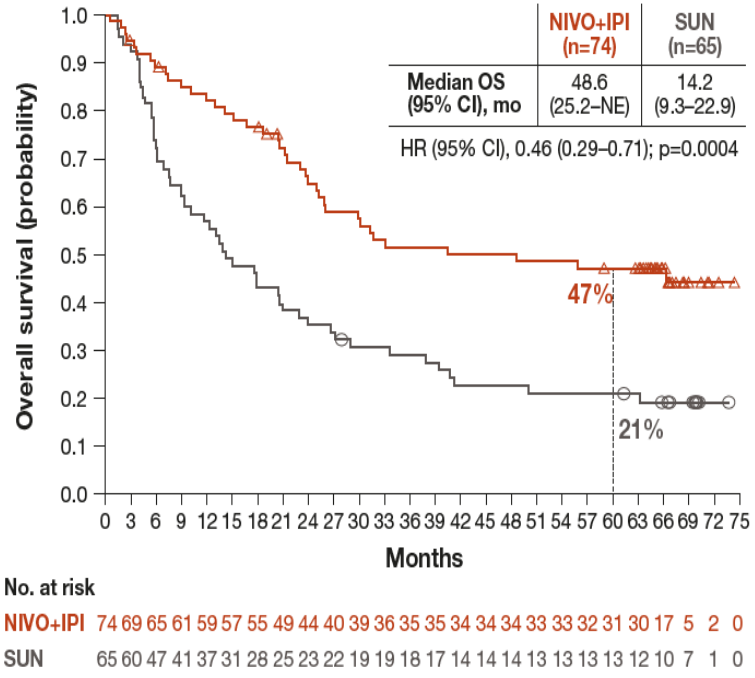
1.
3.

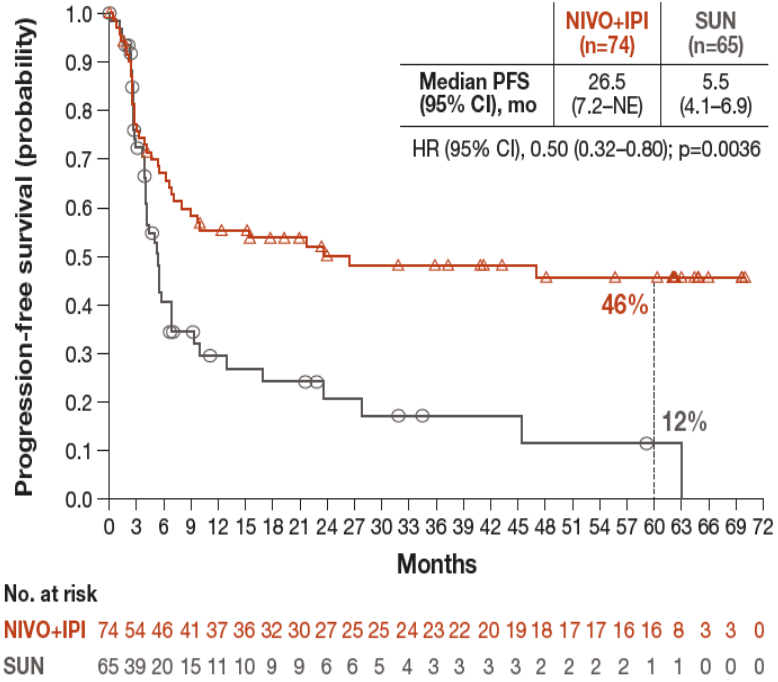
Systemic Therapies from Phase-3 Trials (favorable risk population)

	CHECKMATE- 214[1]	KEYNOTE-426[2]	CLEAR[3]	CHECKMATE- 9ER[4]
DRUGS	Nivolumab + ipilimumab (N = 125 vs. 124)	Pembrolizumab + Axitinib (N = 138 vs. 131)	Pembrolizumab + Lenvatinib (N = 110 vs. 124)	Nivolumab + Cabozantinib (N = 74 vs. 72)
Median follow-up (months)	68 months	67 months	48 months	44 months
PFS HR	1.60	0.76	**0.50**	0.72
Median PFS (months)	12.4 vs. 28.9	**20.7** vs. 17.9	**28.6** vs. 12.9	**21.4** vs. 13.9
Landmark PFS (3 years)	43%	34%	45%	21%
OS HR	**0.94**	**1.10**	**0.94**	**1.07**
Landmark OS (3 years)	**78%**	**75%**	**75%**	**68%**
ORR	30% vs. 52%	69% vs. 50%	68% vs. 51%	68% vs. 46%
CR	13% vs. 7%	13% vs. 6%	**21% vs. 5%**	16% vs. 10%

1. Motzer RJ et al. Cancer 2022; 2. Rini B et al. ASCO 2023. Abstract LBA4501;
3. Motzer RJ et al. ASCO 2023. Abstract 4502, Grunwald et al ASCO 2021; 4. Burotto M et al. ASCO GU 2023. Abstract 603.

Sarcomatoid Histology Guides Treatment





Rini BI et al. *J Immunother Cancer.* 2022;10(12):e005445.

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: Tumor Response (Progression-free Survival Population)

Variable	Experimental (N=276)	Control (N=274)
Objective response (95% CI) — %	43 (37–49)	36 (30–42)
Best overall response — no. (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Could not be evaluated or data were missing	15 (5)	21 (8)
Disease control — no. (%)†	238 (86)	198 (72)
Median time to response (range) — mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI) — mo	NR (20.2–NR)	NR (NE–NE)

Low ORR, Low CR, no OS data available yet

Choueiri et al. 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 Preferred/Recommended Systemic Therapy for mccRCC

Favorable Risk

Preferred regimens:

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

Other recommended regimens:

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

Useful in certain circumstances

- Active surveillance
- Axitinib
- High dose IL2

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
- High-dose IL-2
- Temsirolimus

NCCN Guidelines. Kidney Cancer. Version 1.2024.

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

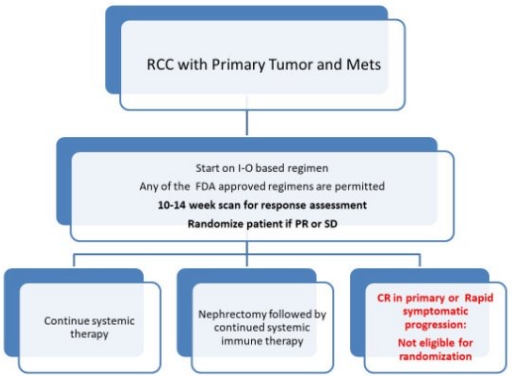
N=1046

INDUCTION

Nivolumab Ipilimumab

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

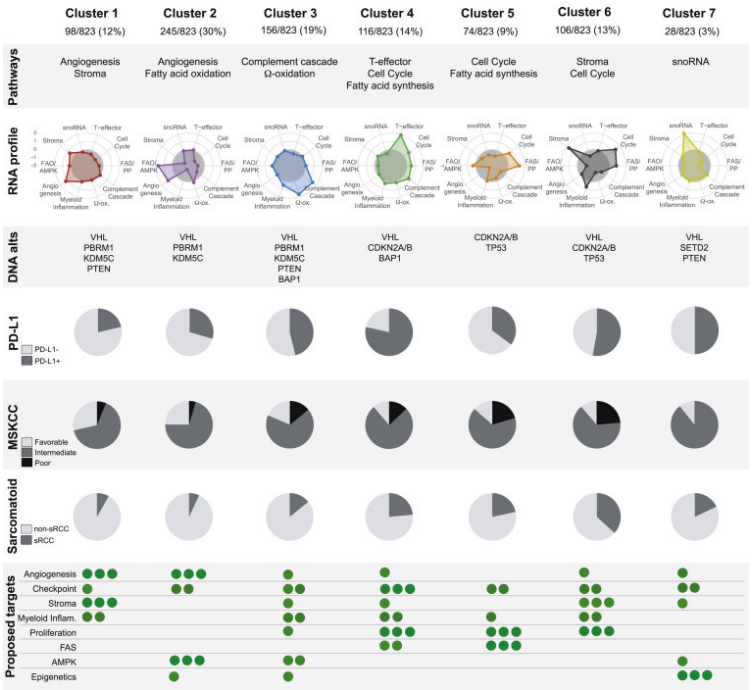
3. Trials evaluating the role of nephrectomy in mRCC: PROBE



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

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

Clusters 4/5/7

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

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%

 # GU23: CABOPOINT: Interim results from a phase-II trial sharing outcomes of patients with advanced RCC treated with cabozantinib who have progressed on IO/IO or IO/TKI showed promising results

Management of mRCC in Subsequent Lines: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

R
(1:1)
N = 350

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

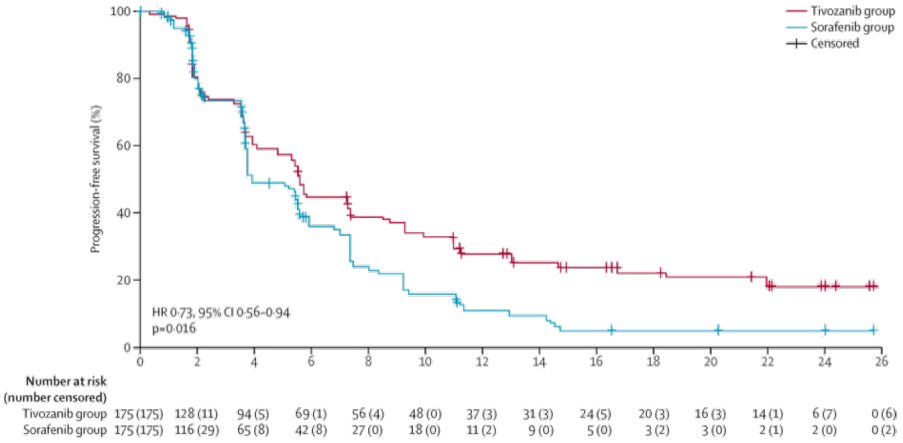
Number of previous systemic therapies		
Two	108 (62%)	104 (59%)
Three	67 (38%)	71 (41%)

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%)

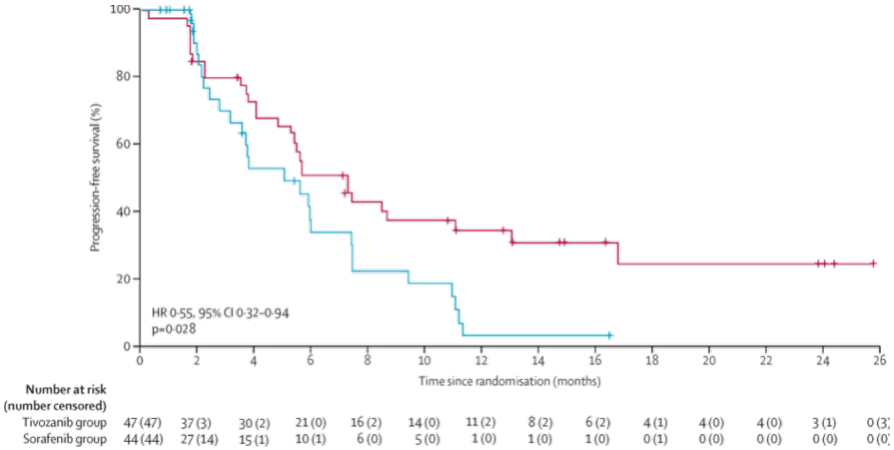
	Tivozanib group (n=175)	Sorafenib group (n=175)
Age (years)	62 (34–88)	63 (30–90)
Sex		
Male	126 (72%)	128 (73%)
Female	49 (28%)	47 (27%)
Race		
White	165 (94%)	167 (95%)
Non-white	10 (6%)	8 (5%)
Pathological diagnosis		
Clear cell	165 (94%)	160 (91%)
Clear cell component	9 (5%)	9 (5%)
Other*	1 (1%)	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

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)

	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?

2023 ASCO ANNUAL MEETING

Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor treatment in metastatic renal cell carcinoma: Phase III CONTACT-03 study

Toni K. Choueiri,[1] Laurence Albiges,[2] Piotr Tomczak,[3] Cristina Suárez,[4] Martin H. Voss,[5] Guillermo de Velasco,[6] Jad Chahoud,[7] Giuseppe Procopio,[8] Hakim Mahammedi,[9] Friedemann Zengerling,[10] Chan Kim,[11] Suyasha Gupta,[12] Guillaume Bergthold,[13] Bo Liu,[12] Melania Kalaitzidou,[14] Mahrukh Huseni,[12] Christian Scheffold,[15] Thomas Powles,[16] Sumanta Kumar Pal[17]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France; [3]Poznan University of Medical Sciences, Poznan, Poland; [4]Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [5]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [6]Medical Oncology Department, University Hospital '12 de Octubre,' Madrid, Spain; [7]Department of Genitourinary Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; [8]Department of Medical Oncology, Fondazione Istituto Nazionale dei Tumori di Milano, Milan, Italy; [9]Department of Medical Oncology, Jean Perrin Cancer Center, Clermont-Ferrand, France; [10]Department of Urology and Paediatric Urology, University Hospital Ulm, Ulm, Germany; [11]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [12]Genentech, South San Francisco, CA; [13]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [14]Roche Product Ltd, Welwyn Garden City, UK; [15]Exelixis, Inc, Alameda, CA; [16]Barts Cancer Institute, ECMC, QMUL, London, United Kingdom; [17]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA

CONTACT-03

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R
1:1
N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

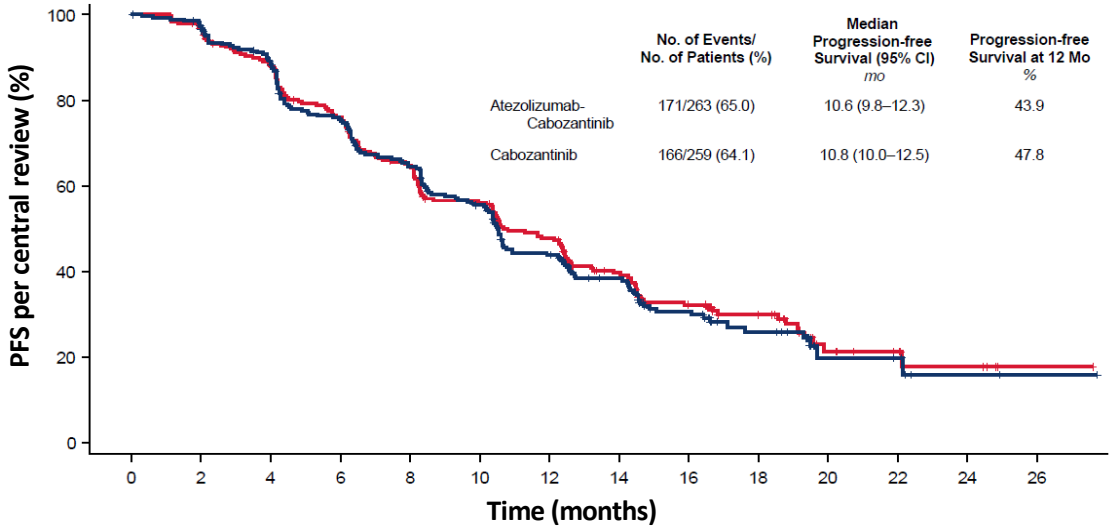
- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

Choueiri et al. ASCO 2023

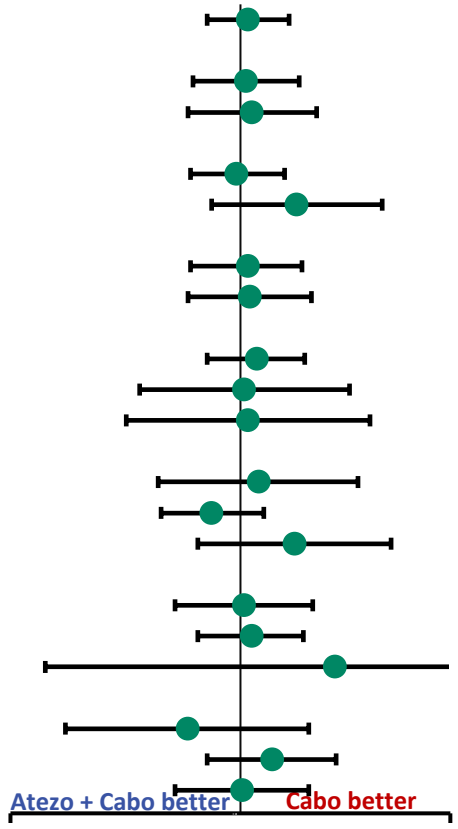
CONTACT-03: Primary analysis of centrally reviewed PFS (primary endpoint)



Choueiri et al. ASCO 2023

CONTACT-03: Centrally reviewed PFS by subgroup

Characteristic[a]	Atezo + Cabo: No. of PFS events/pts	Atezo + Cabo: Median PFS, mo	Cabo: No. of PFS events/pts	Cabo: Median PFS, mo	PFS HR (95% CI)[b]
All patients	171/263	10.5	166/259	10.8	1.04 (0.84, 1.29)
Age					
<65 y	104/153	10.4	96/144	10.6	1.03 (0.78, 1.36)
≥65 y	67/110	10.6	115/225	12.1	1.06 (0.76, 1.49)
Sex					
Male	130/204	10.6	197/401	10.6	0.98 (0.77, 1.26)
Female	41/59	10.1	62/121	12.4	1.34 (0.86, 2.10)
Most recent ICI therapy					
First line	98/144	9.9	87/132	10.3	1.04 (0.77, 1.38)
Second line	72/118	12.4	77/124	12.5	1.05 (0.76, 1.45)
Histology					
Dominant clear cell	128/207	10.7	117/200	12.5	1.09 (0.84, 1.40)
Dominant non-clear cell	25/30	6.3	27/31	8.3	1.02 (0.59, 1.77)
Any sarcomatoid	18/25	8.3	22/28	8.2	1.04 (0.55, 1.97)
IMDC score					
0	25/49	14.3	34/69	14.5	1.10 (0.65, 1.85)
1-2	109/172	10.8	104/153	11.7	0.86 (0.66, 1.13)
3-6	36/41	4.9	28/36	6.0	1.33 (0.80, 2.20)
Prior lines of VEGFR-TKI					
0	61/93	9.7	60/95	10.4	1.02 (0.71, 1.46)
1	107/166	10.6	102/159	11.7	1.06 (0.80, 1.39)
2	3/4	6.7	4/5	11.3	1.64 (0.36, 7.47)
Best response to most recent ICI					
CR/PR	25/47	11.9	16/30	10.4	0.76 (0.40, 1.43)
SD	70/104	10.5	65/97	10.5	1.18 (0.84, 1.65)
PD	63/92	10.4	63/95	10.6	1.01 (0.71, 1.43)



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)

Choueiri et al. ASCO 2023

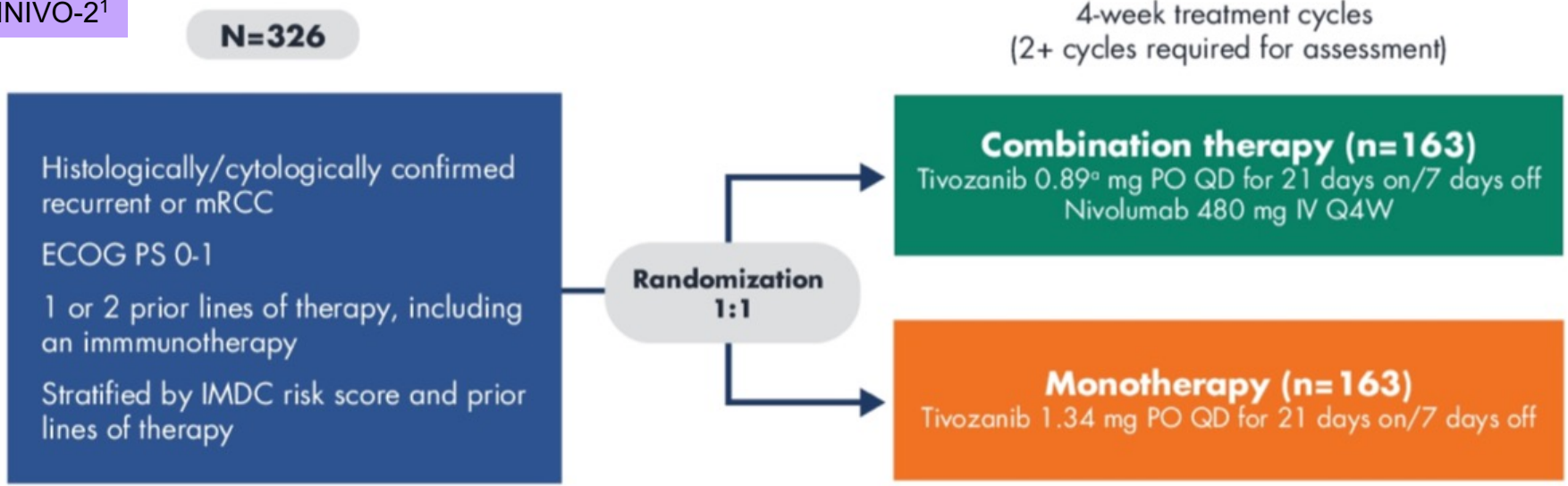
CONTACT-03: Conclusion

- 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

#ASCO23: Following progression on or after prior PD-1/L1 inhibitor, addition of atezolizumab and cabozantinib is ineffective and may infact harm the patients

Management of mRCC in Subsequent Lines: Trials on the "Horizon"

TINIVO-2[1]

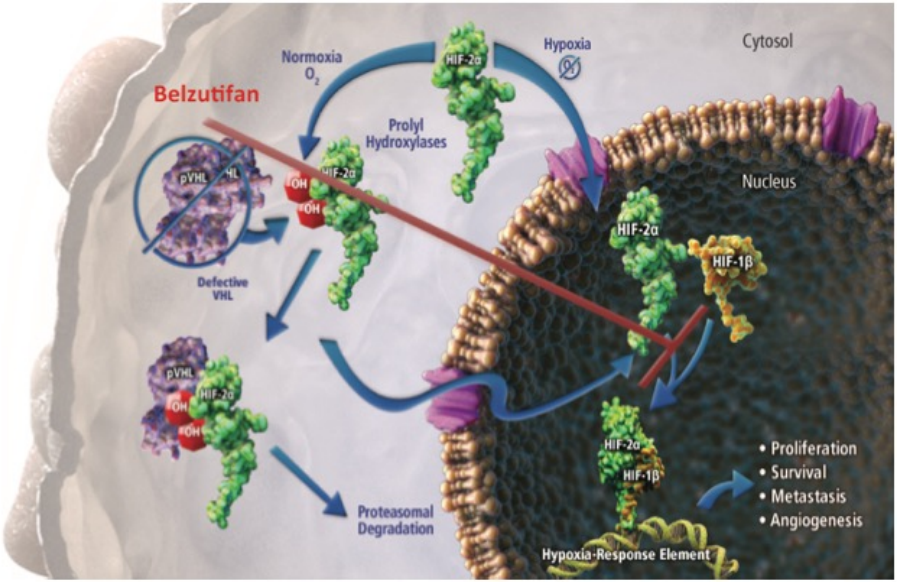


1. Pal SK et al. ASCO GU 2021. Abstract TPS370;

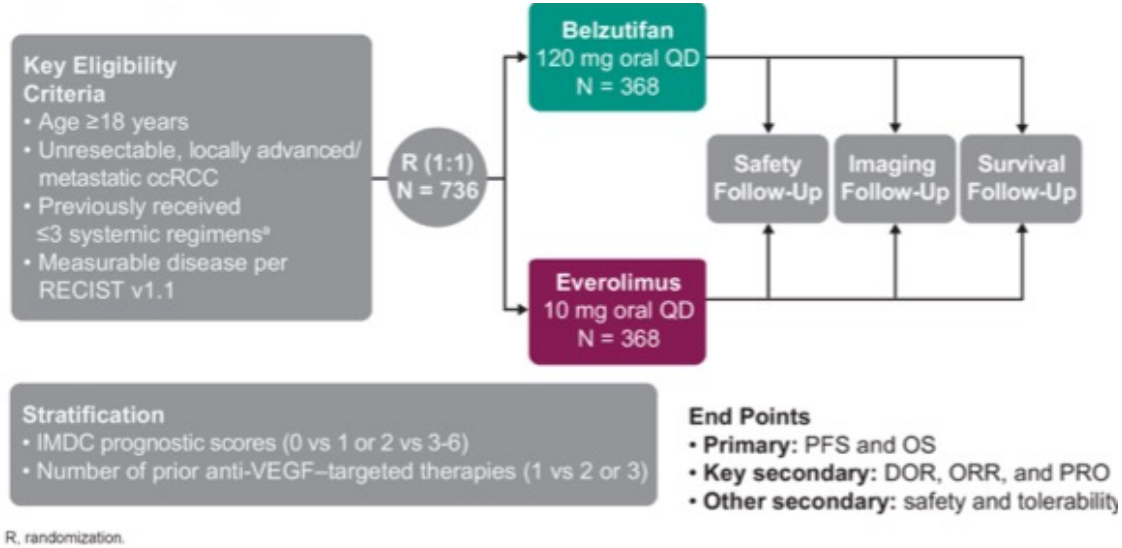
Subsequent Lines of Therapy for mccRCC: BELZUTIFAN

- HIF-2a is involved in the activation of genes associated with angiogenesis (VEGFA, PDGFB), proliferation (CDK), metabolism (GLUT1) and growth (TGFa)

- Belzutifan is an oral potent, selective small molecule HIF-2a inhibitor



BELZUTIFAN: LITESPARK 005



Merck press release 8/18/23: Litespark-005 trial has met its primary endpoint of PFS and also improved objective response rate in a statistically significant manner [2]

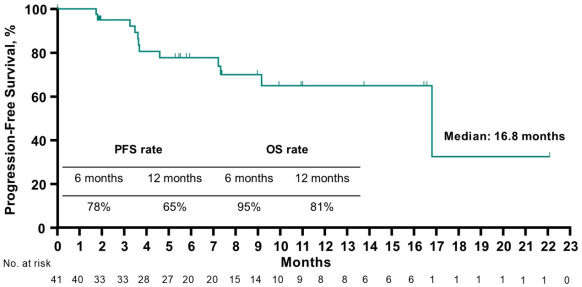
1. Choueri et al. GU ASCO 2021
2. https://www.businesswire.com/news/home/20230818906049

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

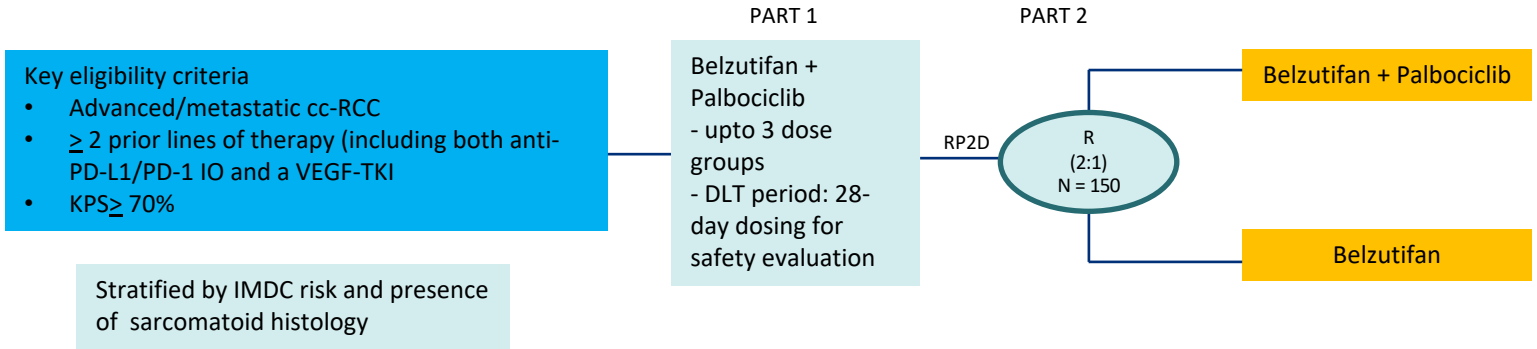
Cabozantinib

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

Relapsed/ Metastatic ccRCC: Subsequent Lines Systemic Therapy

Immunotherapy Naïve

Preferred regimen: None

Other recommended regimens:

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

Useful in certain circumstances

- Axitinib
- Everolimus
- Pazopanib
- Sunitinib
- Tivozanib
- Belzutifan
- Bevacizumab
- High-dose IL-2 for select
- Temsirolimus
- Axitinib + avelumabb

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
- Cabozantinib
- Lenvatinib + everolimus
- Tivozanib

Useful in certain circumstances

- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Everolimus
- Ipilimumab + nivolumab
- Lenvatinib + pembrolizumab
- Pazopanib
- Sunitinib
- Belzutifan
- Bevacizumab
- High-dose IL-2 for select
- Temsirolimus
- Axitinib + avelumab

NCCN Guidelines. Kidney Cancer. Version 1.2024.

Management of RCC in 2023: CONCLUSIONS

- Perioperative treatment of RCC remains controversial
- Doublet regimens remain standard of care in the front-line setting
- Patients who progress on an immune checkpoint inhibitor should NOT be rechallenged with another one (TINIVO data awaited)
- New trials incorporating drugs with novel mechanisms (HIF2A inhibitor, CDK4/6 inhibitors etc.) are being developed
- Dearth of biomarkers to effectively select patients in 2023 !