What Clinicians Want to Know: Addressing Current Questions Related to the Management of Renal Cell Carcinoma

A CME Symposium Held in Conjunction with the 2025 ASCO® Genitourinary Cancers Symposium

Friday, February 14, 2025

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Thomas E Hutson, DO, PharmD, PhD

Rana R McKay, MD

Tian Zhang, MD, MHS

Moderator

Sumanta Kumar Pal, MD

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Dr Hutson — Disclosures
Faculty

Advisory Committees, Consulting Agreements, Contracted Research and Speakers Bureaus	Astellas, AstraZeneca Pharmaceuticals LP, EMD Serono Inc, Exelixis Inc, Merck, Pfizer Inc, Seagen Inc

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Dr McKay — Disclosures
Faculty

Advisor/Consultant	Ambrx, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Neomorph, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Institutional Research Funding	ArteraAI, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Oncternal Therapeutics, Tempus

Dr Zhang — Disclosures
Faculty

Advisory Committees	Amgen Inc, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Exelixis Inc, Gilead Sciences Inc, Janssen Biotech Inc, Lilly, Merck, Novartis, Pfizer Inc, Sanofi
Consulting Agreements	Aptitude Health, DAVA Oncology, Pfizer Inc, Vaniam Group
Contracted Research	ALX Oncology, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Exelixis Inc, Janssen Biotech Inc, Janux Therapeutics, Lilly, Merck, OncoC4, Pfizer Inc, Tempus
Nonrelevant Financial Relationships	Mashup Media LLC, MJH Life Sciences, PeerView

Dr Pal — Disclosures
Moderator

Travel Support	CRISPR Therapeutics, EverImmune, Exelixis Inc, Ipsen Biopharmaceuticals Inc

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This activity is supported by educational grants from Bristol Myers Squibb, Eisai Inc, and Exelixis Inc.

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Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

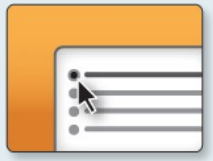
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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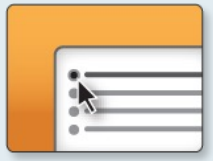
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Survey of General Medical Oncologists: January 29 – February 6, 2025

Results available on iPads and Zoom chat room

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Immunotherapeutic Strategies for Localized and Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Hutson

Module 2: Optimal Management of Relapsed/Refractory RCC — Dr Zhang

Module 3: Role of HIF-2α Inhibitors in the Treatment of Sporadic and von Hippel-Lindau-Associated RCC — Dr McKay

Module 4: Current and Future Care of Patients with Non-Clear Cell RCC — Dr Pal

Agenda

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ASCO GU 2025 RCC

Immunotherapeutic Strategies for Localized and Metastatic Clear Cell RCC

Thomas E Hutson, DO, PharmD, PhD FACP

Professor of Medicine | Division Chief Hem/Onc |UMC Cancer Center Director

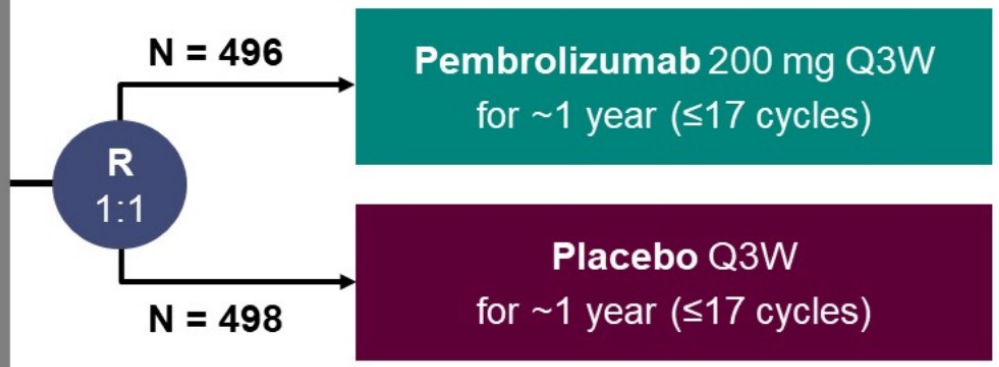
TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™

Long Term Phase 3 KEYNOTE-564

KEYNOTE-564: Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

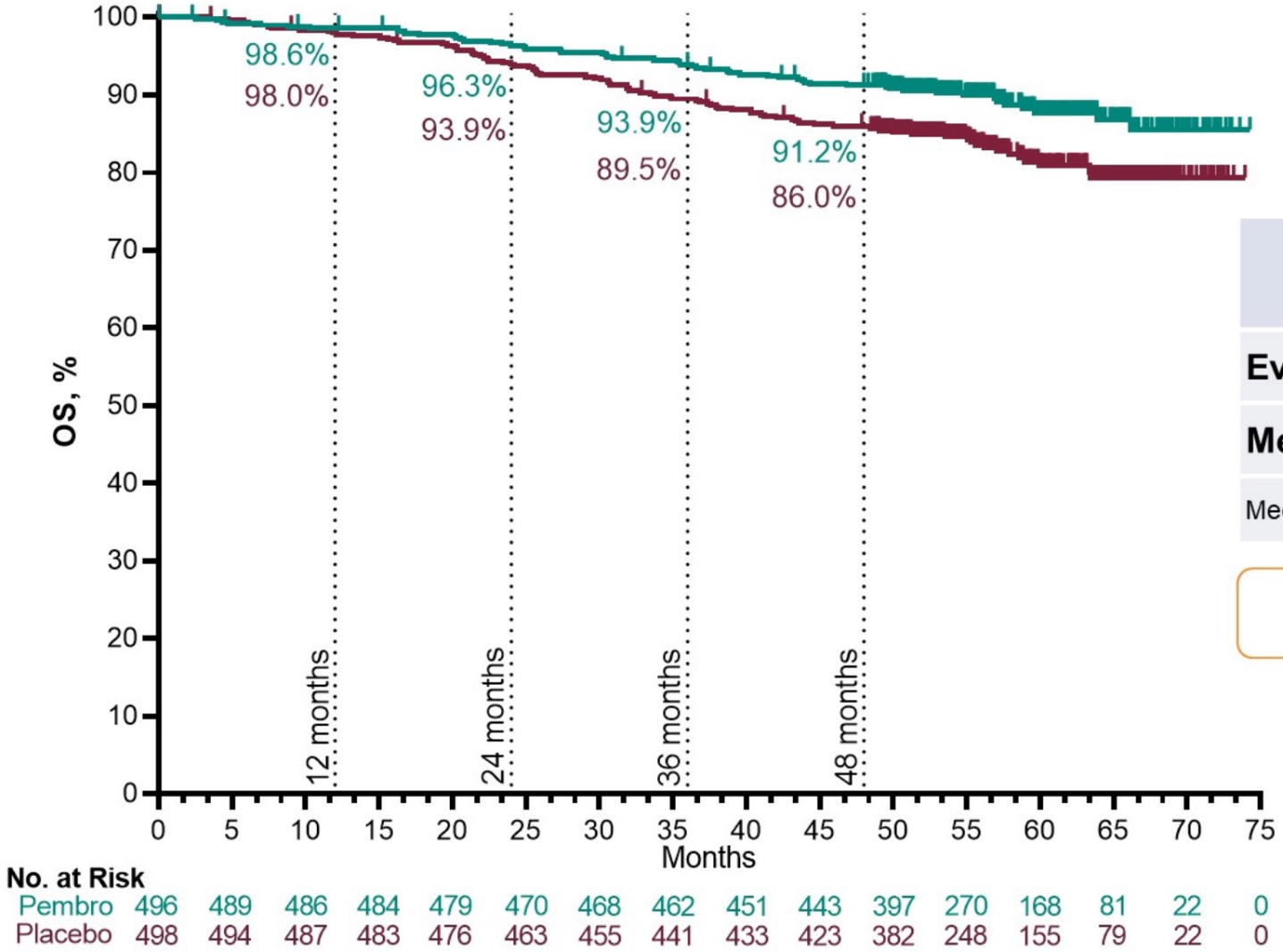
- Overall survival

Other Secondary Endpoints

- Safety

Choueiri et al, ASCO 2024; Abstract LBA359.

KEYNOTE-564: Overall Survival



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

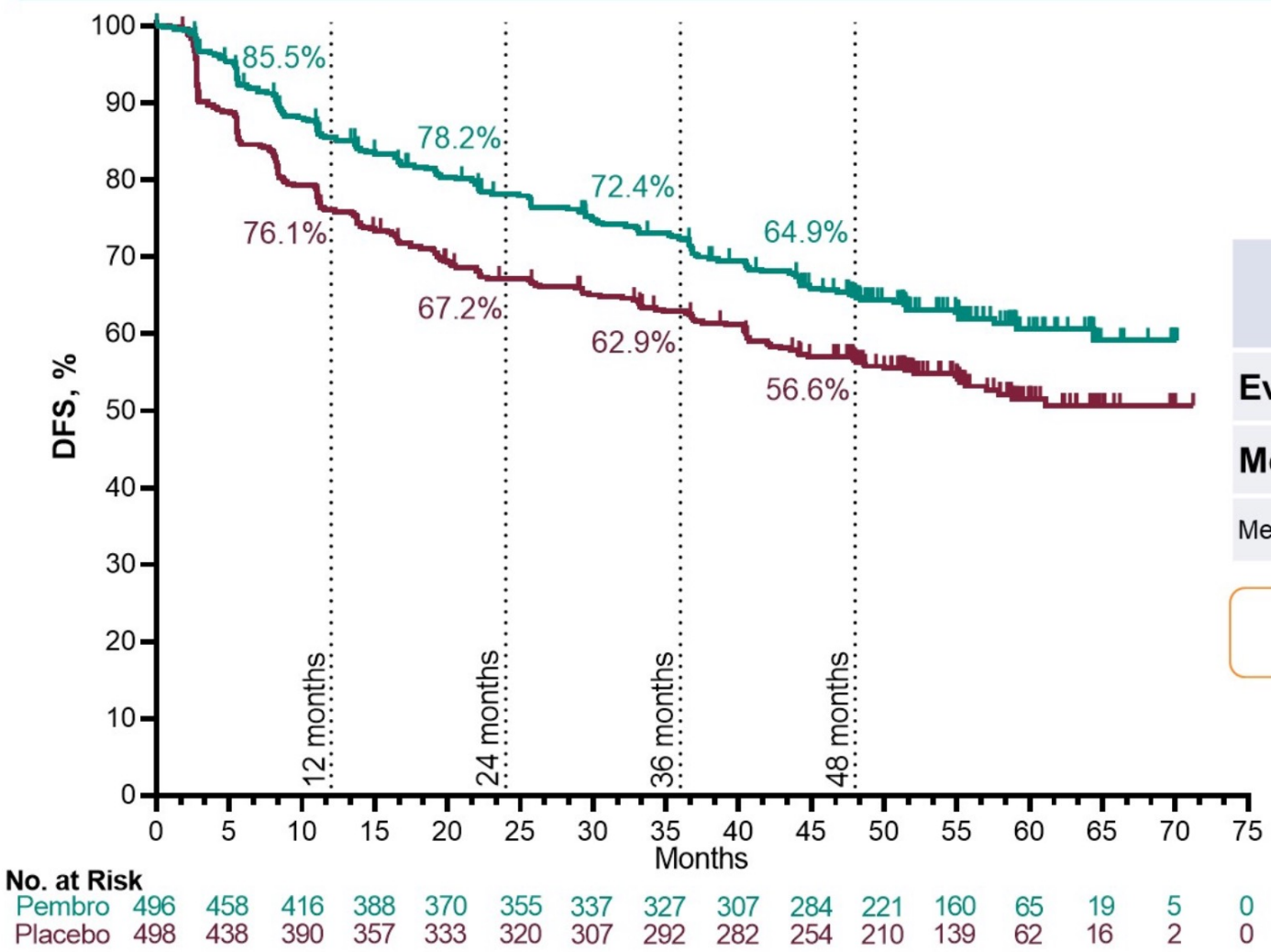
HR 0.62 (95% CI 0.44–0.87); *P* =.002*

* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

Choueiri et al, ASCO 2024; Abstract LBA359.

KEYNOTE-564: Updated Disease-Free Survival



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.

Choueiri et al, ASCO 2024; Abstract LBA359.

KEYNOTE-564: Updated Safety

	Prior Analysis (30.1 mo follow-up)		IA3 (57.2 mo follow-up)	
	Pembrolizumab (N = 488)	Placebo (N = 496)	Pembrolizumab (N = 488)	Placebo (N = 496)
Duration of therapy, median (range), months	11.1 (0.03–14.3)	11.1 (0.03–15.4)	11.1 (0.03–14.3)	11.1 (0.03–15.4)
Any-cause AEs[a]	470 (96.3%)	453 (91.3%)	470 (96.3%)	453 (91.3%)
Grade 3 to 5	157 (32.2%)	88 (17.7%)	156 (32.0%)	88 (17.7%)
Led to treatment discontinuation	103 (21.1%)	11 (2.2%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious AEs[a]	101 (20.7%)	57 (11.5%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs[a]	386 (79.1%)	265 (53.4%)	386 (79.1%)	263 (53.0%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	89 (18.2%)	4 (0.8%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs and infusion reactions[b]	174 (35.7%)	34 (6.9%)	178 (36.5%)	36 (7.3%)
Grade 3 to 4	45 (9.2%)	3 (0.6%)	46 (9.4%)	3 (0.6%)
Led to death	0	0	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

[a]AEs were graded per the NCI CTCAE v4.0 and reported from randomization to 30 days (90 days for serious AEs) after study therapy discontinuation. [b]Based on a list of preferred terms intended to capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator.
Data cutoff date: September 15, 2023.

Choueiri et al, ASCO 2024; Abstract LBA359.

STAGE	PRIMARY TREATMENT[c,d]	ADJUVANT TREATMENT	FOLLOW-UP[f] (CATEGORY 2B)
Stage II	Partial nephrectomy or Radical nephrectomy	**Clear cell histology:** Surveillance[e] or Adjuvant pembrolizumab (category 1) (Grade 4 tumors with clear cell histology ± sarcomatoid features) **Non-clear cell histology:** Surveillance[e]	Follow-up (KID-C) → Relapse or progression, (KID-4)
Stage III	Radical nephrectomy or Partial nephrectomy, if clinically indicated	**Clear cell histology:** Adjuvant pembrolizumab (category 1) or Surveillance[e] **Non-clear cell histology:** Surveillance[e] or clinical trial	

[c] General Principles of Management for Renal Cell Carcinoma (KID-A).
[d] SBRT may be considered for non-optimal surgical candidates with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See Principles of Radiation Therapy (KID-B).
[e] Follow-up (KID-C).
[f] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: All recommendations are category 2A unless otherwise indicated.

Latest Data in Treatment of First-Line Advanced Renal Cell Carcinoma

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b,d]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Ipilimumab + nivolumab[b,d] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

**The MSKCC (Motzer) criteria are also widely used in this setting [225].*

***Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three to six risk factors.*

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0)[h] OR RELAPSED DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[i]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Clinical trial • Cabozantinib • Cabozantinib + nivolumab[b,c] • Lenvatinib + pembrolizumab[b]	• Erlotinib + bevacizumab[g] + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Everolimus + lenvatinib • Nivolumab[b,c] • Pembrolizumab[b] • Sunitinib	• Axitinib • Everolimus + bevacizumab[g] • Everolimus • Ipilimumab[b] + nivolumab[b,d] (category 2B)

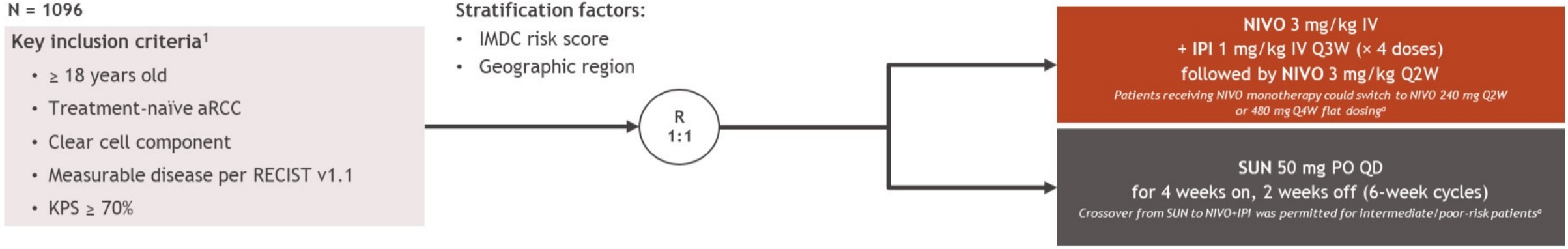
[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[d] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[h] For first-line only.
[i] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

Nivolumab + Ipilimumab

CheckMate 214, Long-term Follow-up ASCO GU 2024

CheckMate 214: Trial Design

- NIVO+IPI is approved for first-line treatment of IMDC intermediate/poor-risk aRCC, based on superior OS and ORR over SUN in the randomized, phase 3 CheckMate 214 trial[1-3]
- NIVO+IPI has demonstrated durable survival and response benefits versus SUN across a broad range of patients, providing the opportunity to conduct long-term survival analyses[4-6]
- With a median follow-up of 8 years in the CheckMate 214 trial, we present updated efficacy and safety outcomes, and exploratory subgroup analyses in patients by organ sites of metastasis at baseline

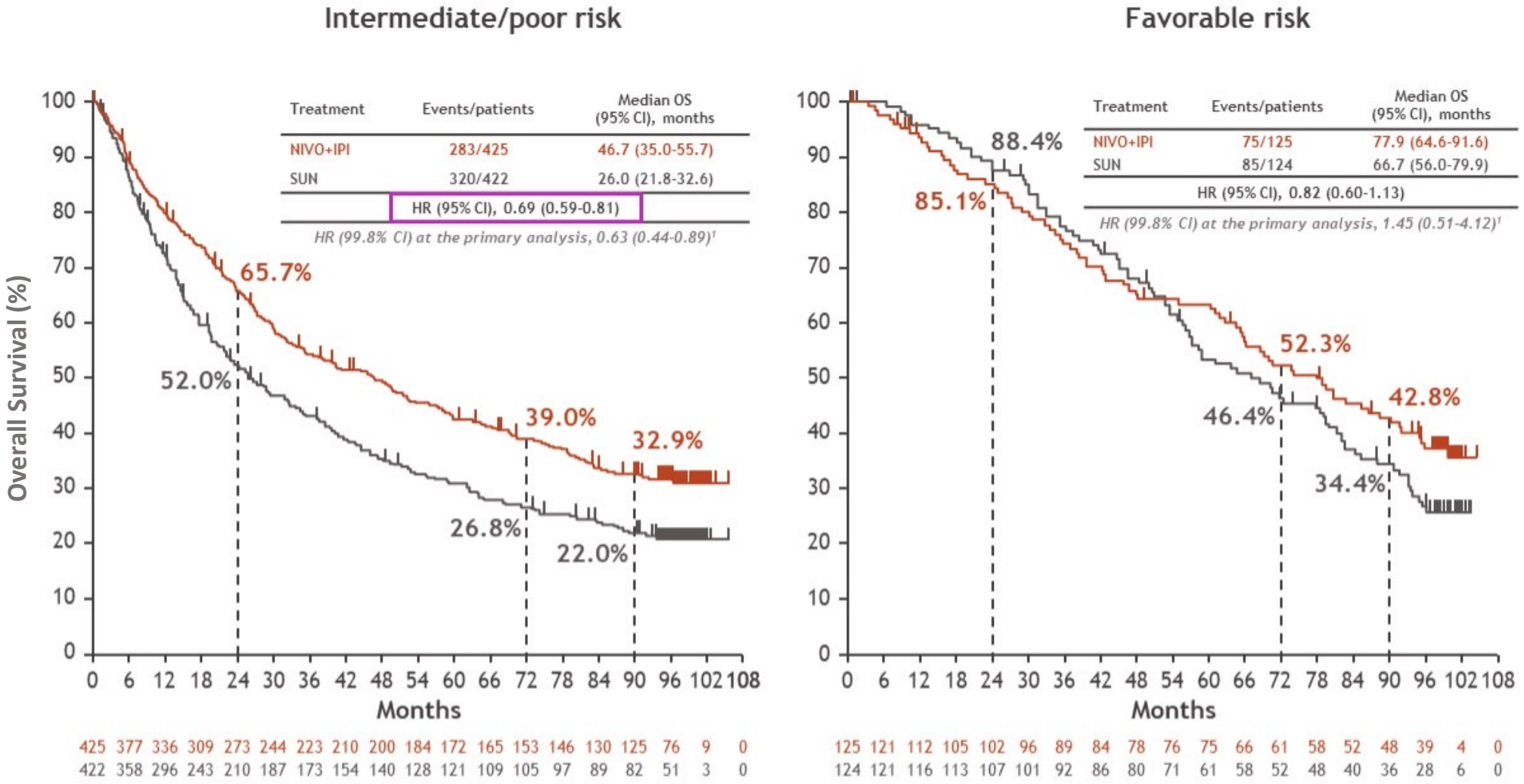


Median (range) follow-up for OS, 99.1 (91.0-107.3) months

Primary endpoints: OS, PFS and ORR (both per IRRC) in IMDC intermediate/poor-risk patients
Secondary endpoints: OS, PFS and ORR (both per IRRC) in ITT patients; safety in all treated patients
Exploratory endpoints: OS, PFS and ORR (both per IRRC) in IMDC favorable-risk patients

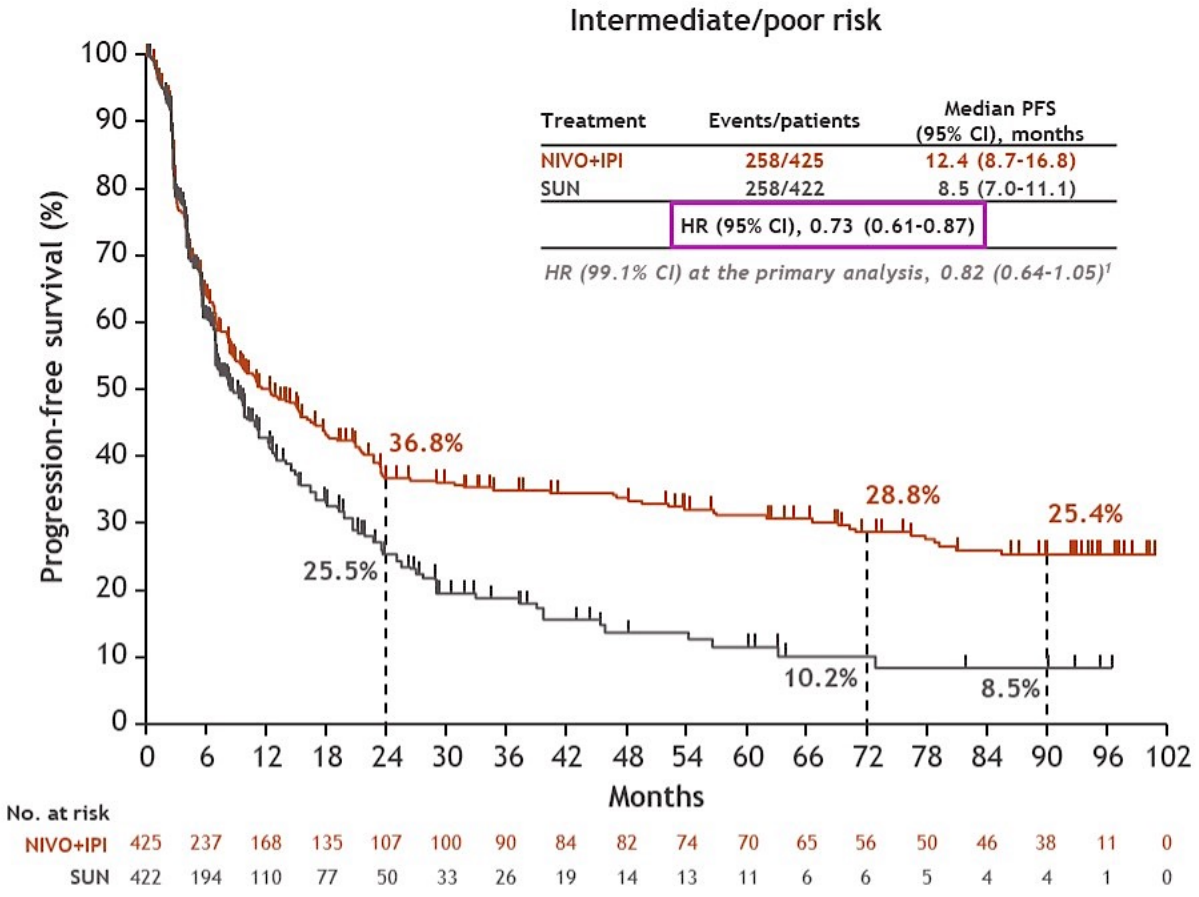
Nizar Tannir, ASCO GU 2024, #363

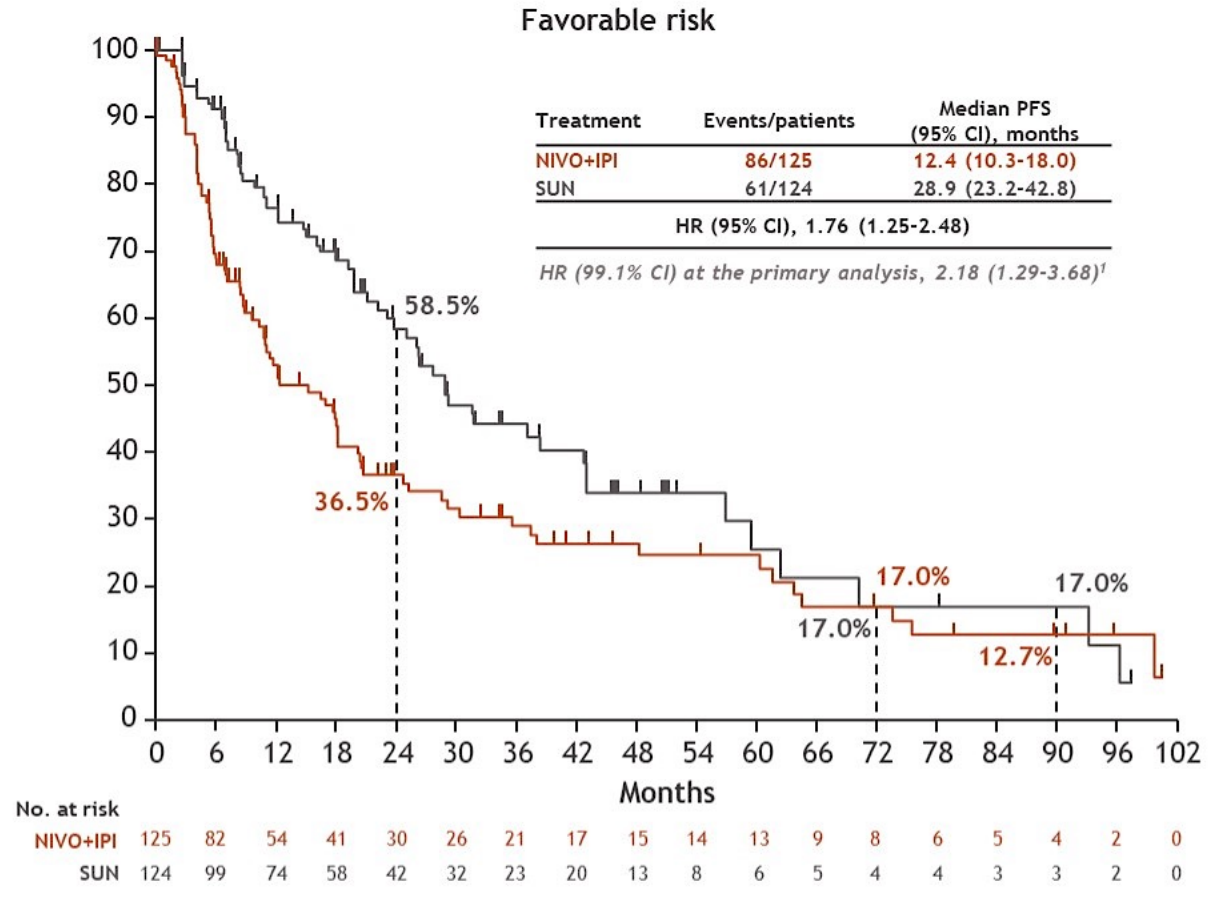
CheckMate 214: Overall Survival by IMDC Risk Subgroup



Nizar Tannir, ASCO GU 2024, #363

CheckMate 214: Progression Free Survival by IMDC Risk Subgroup



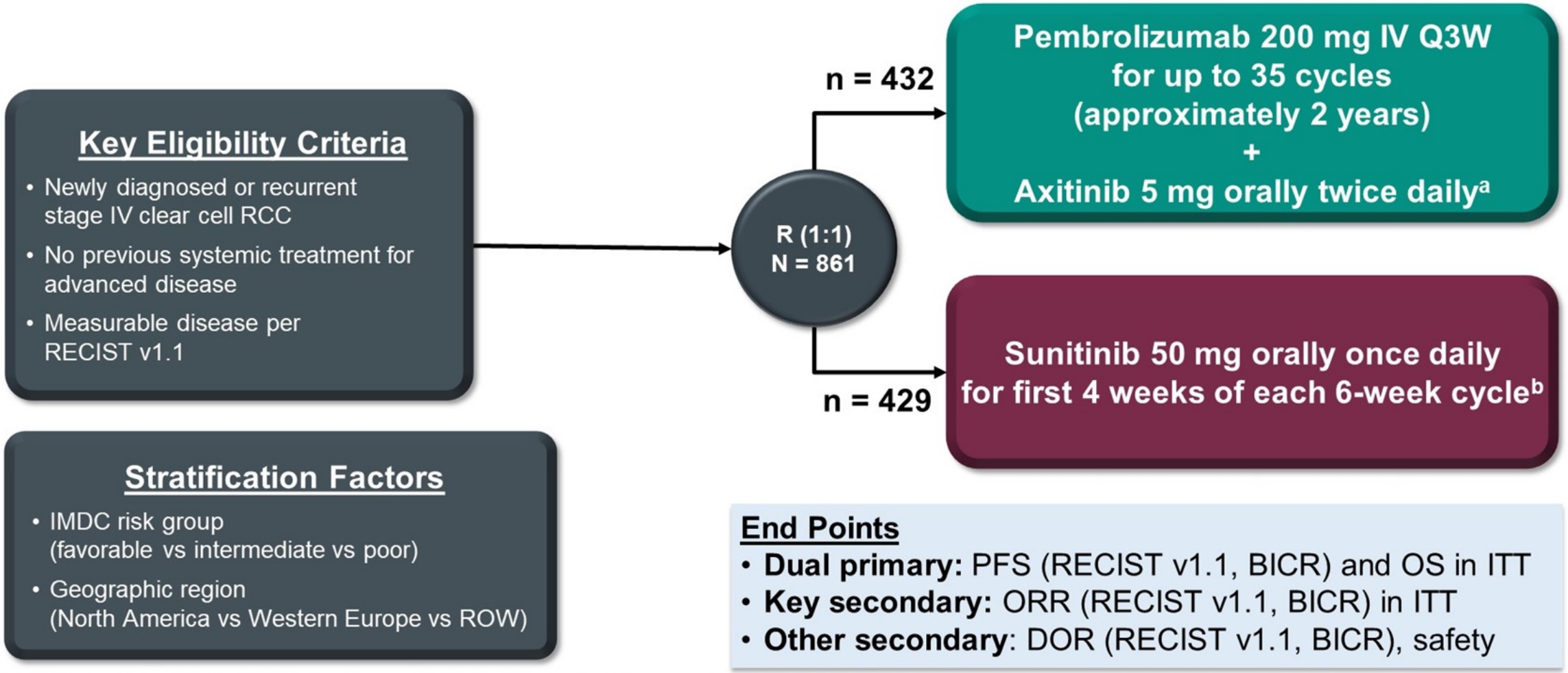


Nizar Tannir, ASCO GU 2024, #363

Axitinib + Pembrolizumab

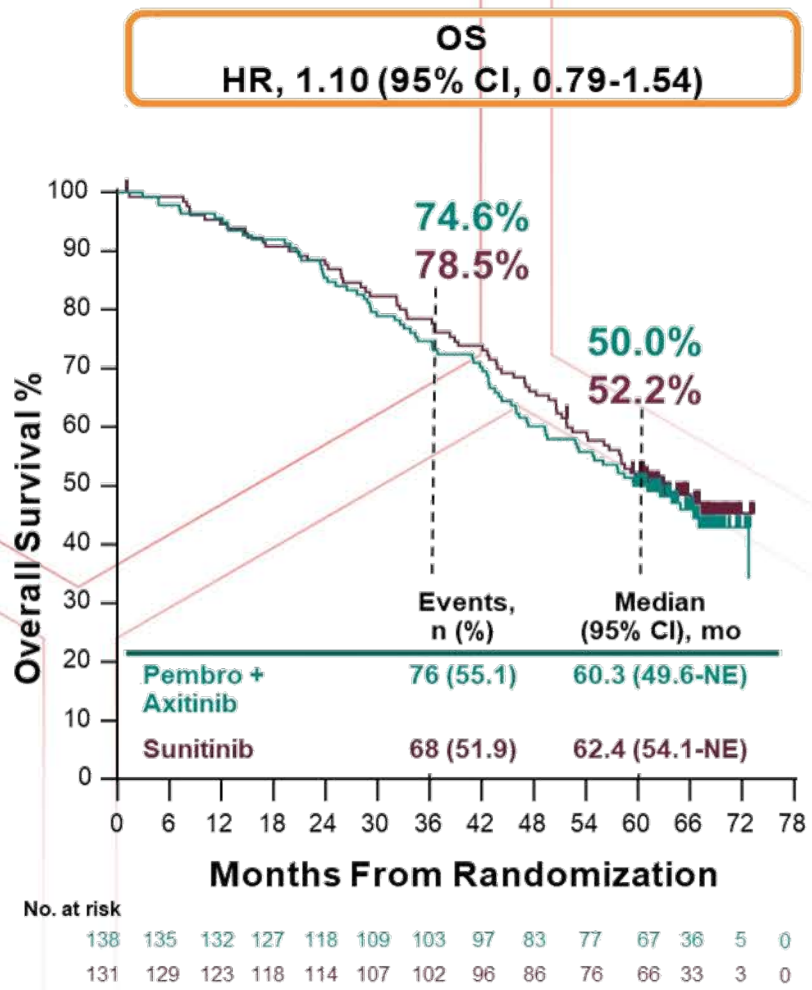
KEYNOTE-426, Long-term Follow-up ASCO 2023

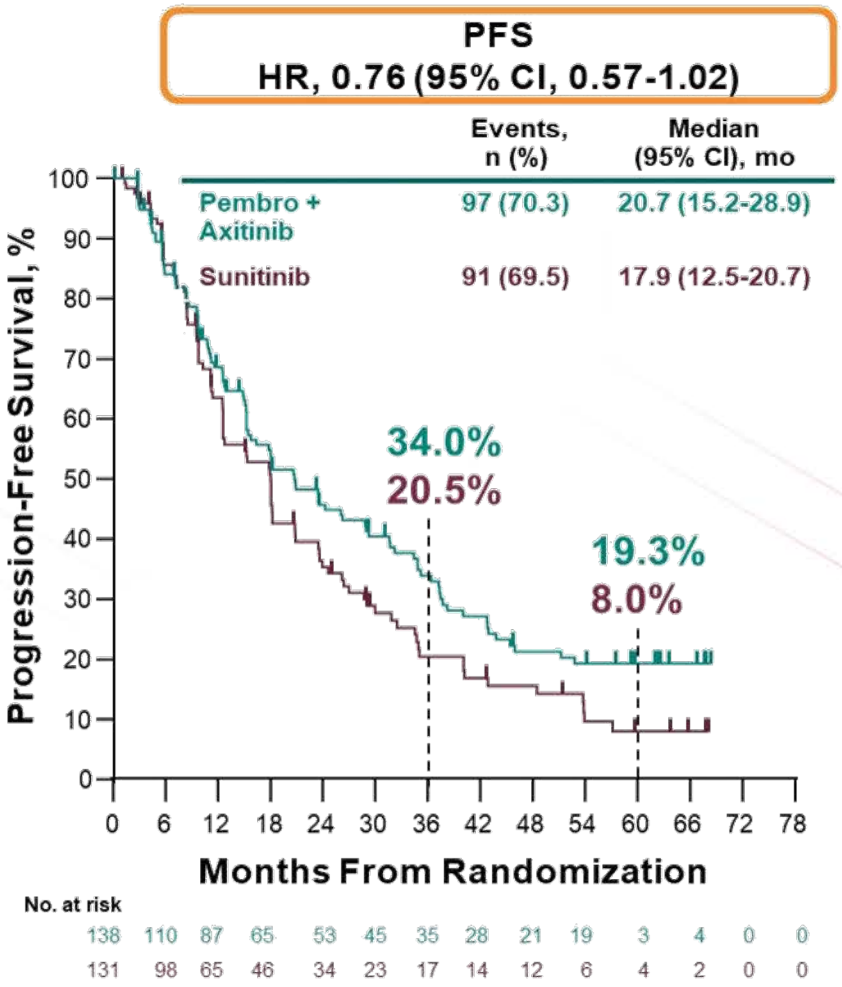
KEYNOTE-426: Trial Design

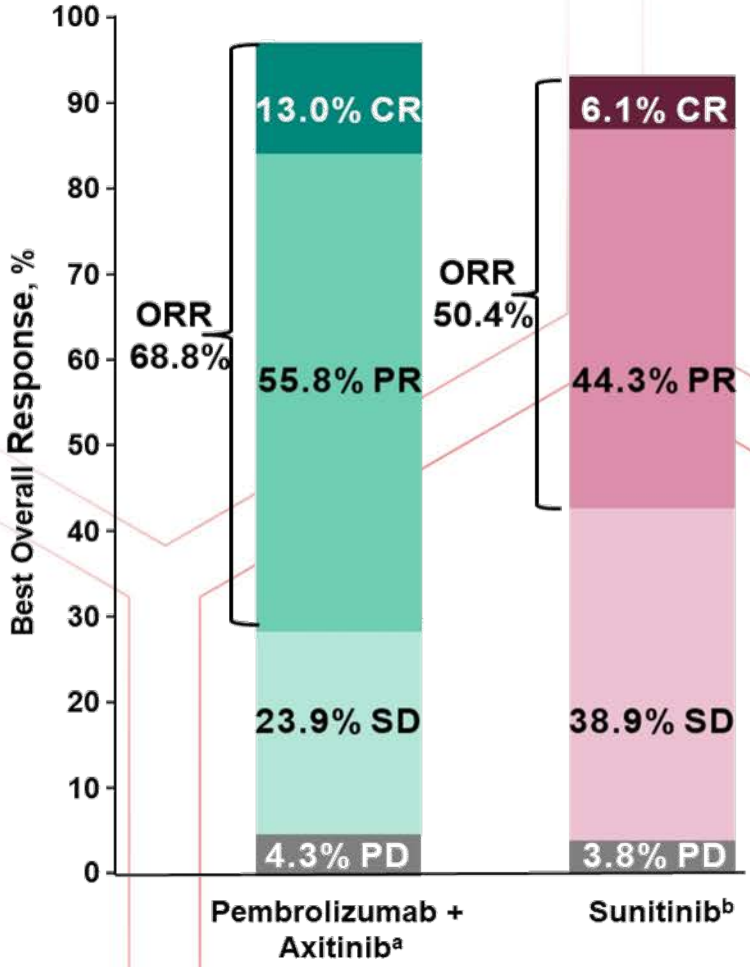


Rini et al, ASCO 2023 #LBA4501

KEYNOTE-426: Efficacy in Favorable Risk RCC



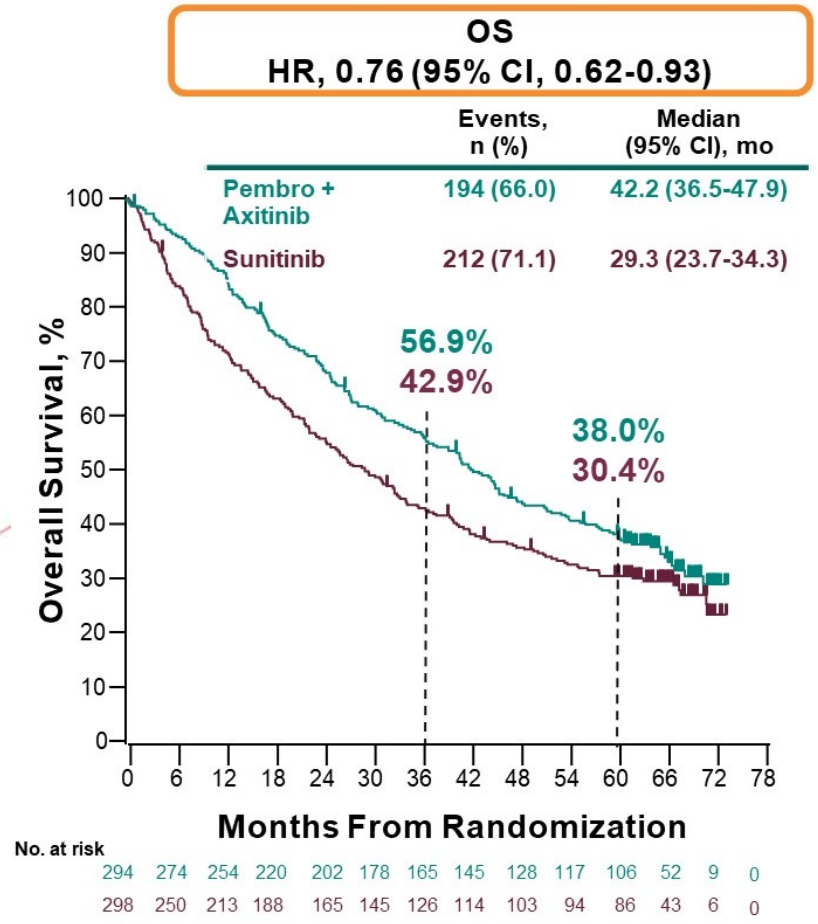


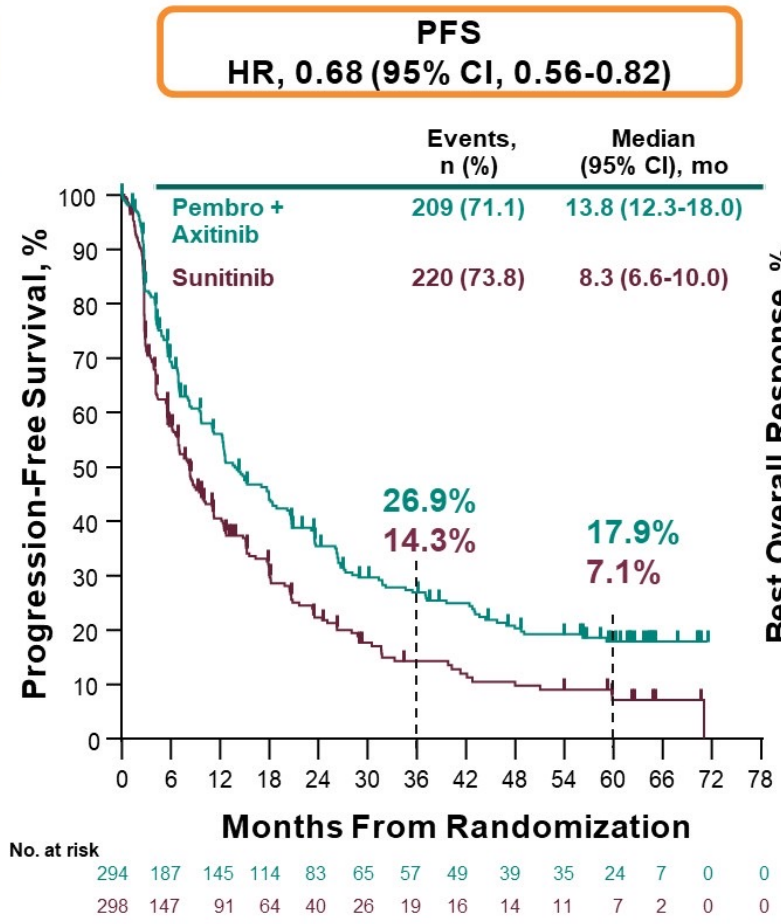


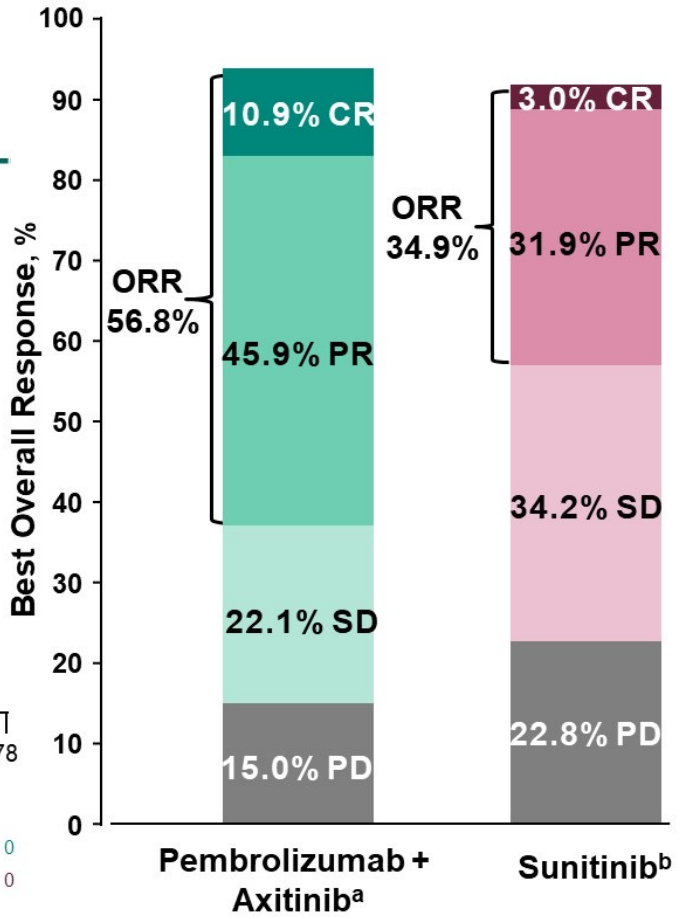
[a]Includes 0.7% NE and 2.2% NA. [b]Includes 1.5% NE and 5.3% NA. Data cutoff: January 23, 2023.

Rini et al, ASCO 2023 #LBA4501

KEYNOTE-426: Efficacy in Intermediate/Poor Risk RCC







[a]Includes 1.7% NE and 4.4% NA. [b]Includes 1.3% NE and 6.7% NA. Data cutoff: January 23, 2023.

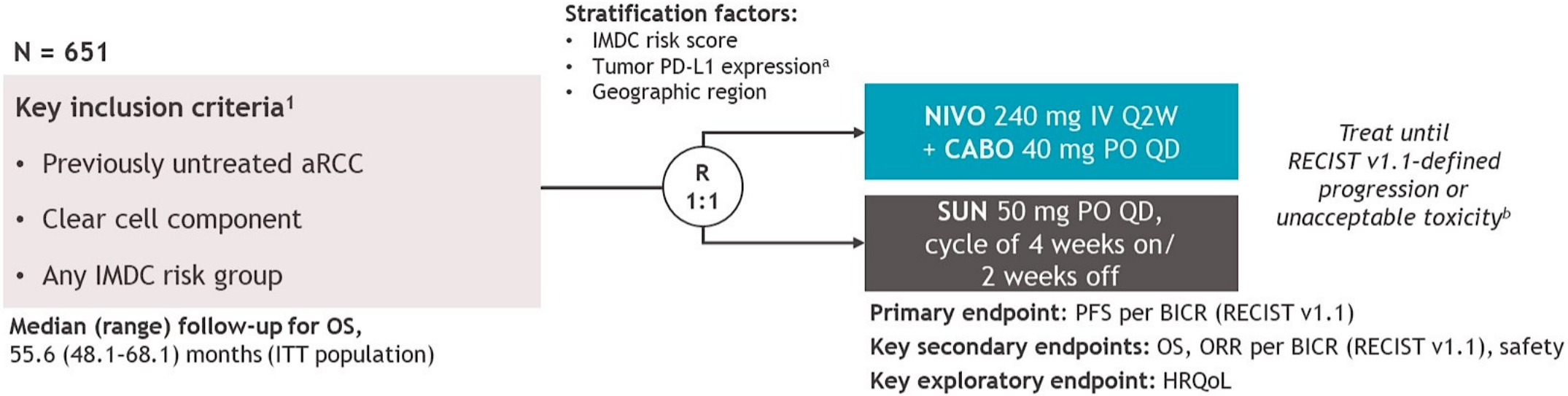
Rini et al, ASCO 2023 #LBA4501

Cabozantinib + Nivolumab

CheckMate 9ER, 55-month Follow-up ASCO GU 2024

CheckMate 9ER: Trial Design

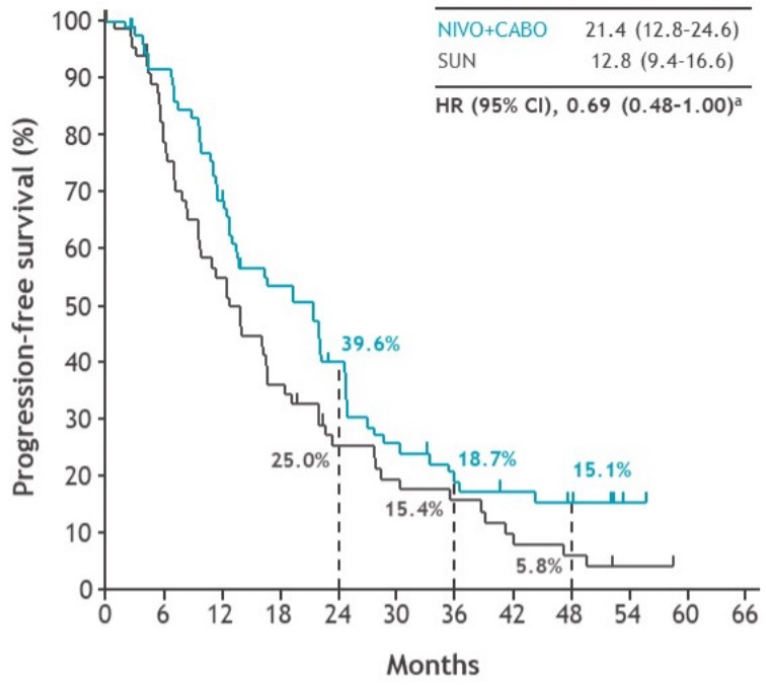
- NIVO+CABO demonstrated superior PFS, OS, and ORR and better HRQoL versus SUN in patients with previously untreated aRCC in the primary analysis (18.1 months median follow-up for OS) of the phase 3 CheckMate 9ER trial[1]
- With extended follow-up, NIVO+CABO maintained efficacy and HRQoL benefits versus SUN (44.0 months median follow-up for OS)[2,3]
- Here, we report updated efficacy in ITT patients with 55.6 months median follow-up for OS, by IMDC risk and organ sites of metastases, and HRQoL and safety



Maria Bourlon, ASCO GU 2024, Abstract #362

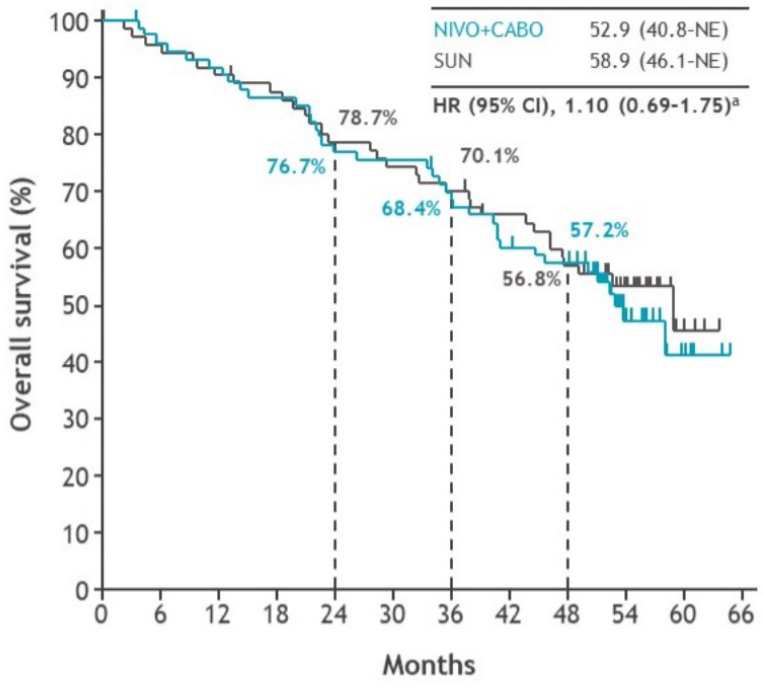
CheckMate 9ER: Efficacy in Favorable Risk RCC

PFS per BICR



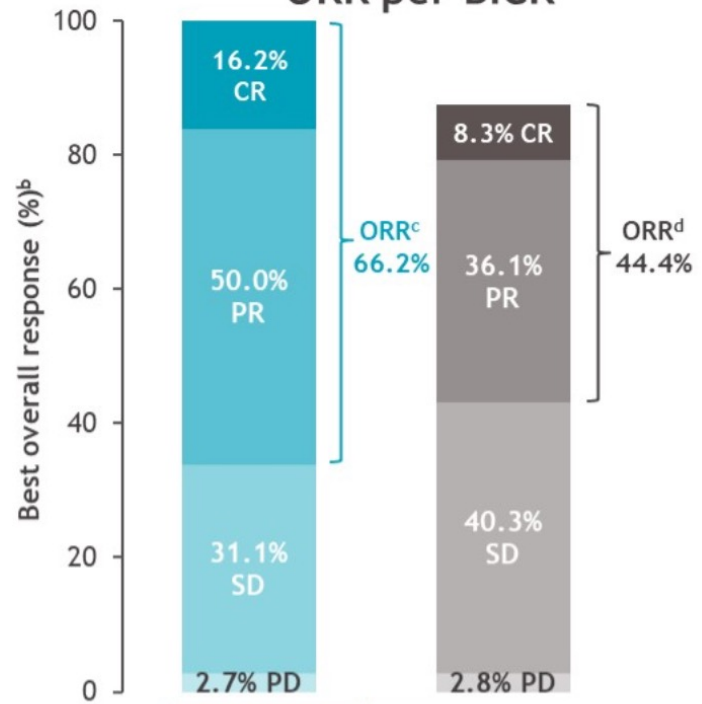
No. at risk												
NIVO+CABO	74	63	46	35	25	16	11	9	6	1	0	0
SUN	72	46	32	21	13	10	8	4	3	1	0	0

OS



No. at risk												
NIVO+CABO	74	70	67	63	56	55	49	43	40	18	5	0
SUN	72	68	64	61	55	52	49	44	38	20	3	0

ORR per BICR

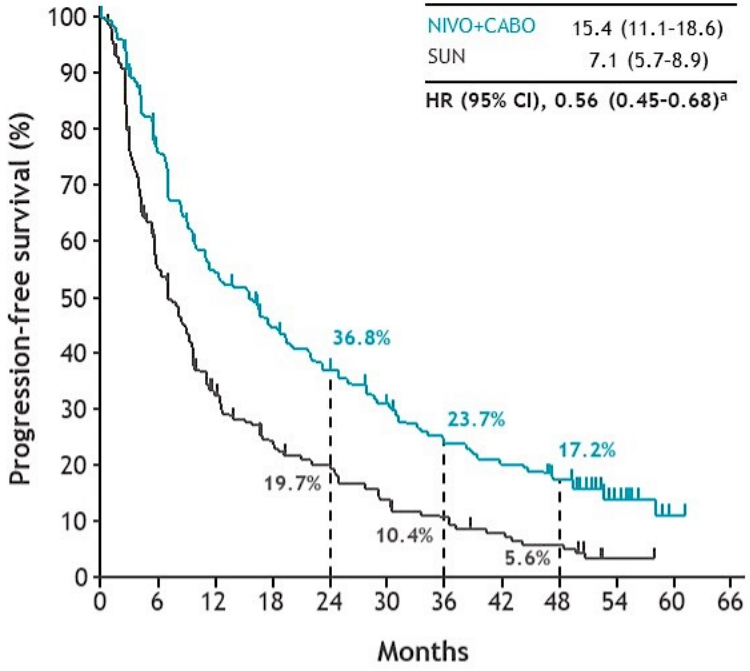


	NIVO+CABO (n = 74)	SUN (n = 72)
Median TTR (range), mo[e]	2.8 (1.5-19.8)	4.3 (1.7-30.4)
Median DOR (95% CI), mo[e]	18.7 (13.9-22.2)	17.8 (11.1-19.4)

Maria Bourlon, ASCO GU 2024, Abstract #362

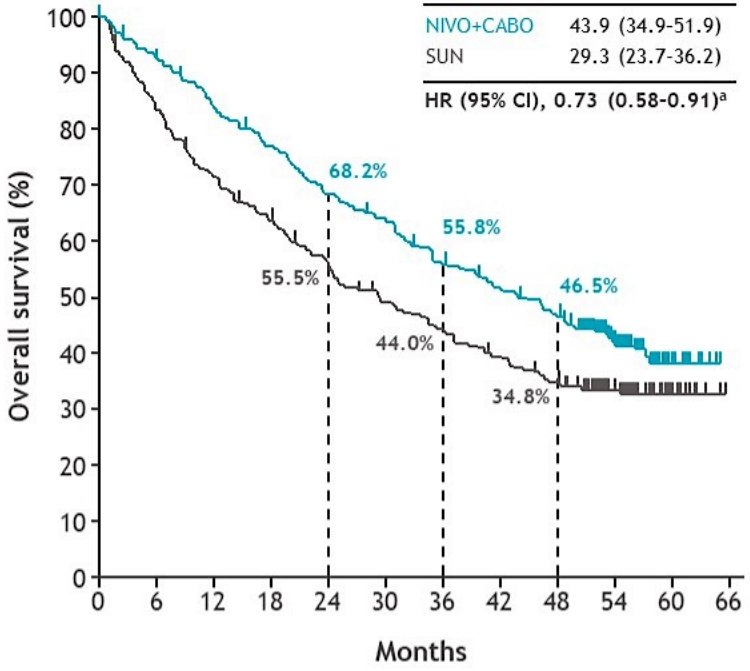
CheckMate 9ER: Efficacy in Intermediate/Poor Risk RCC

PFS per BICR



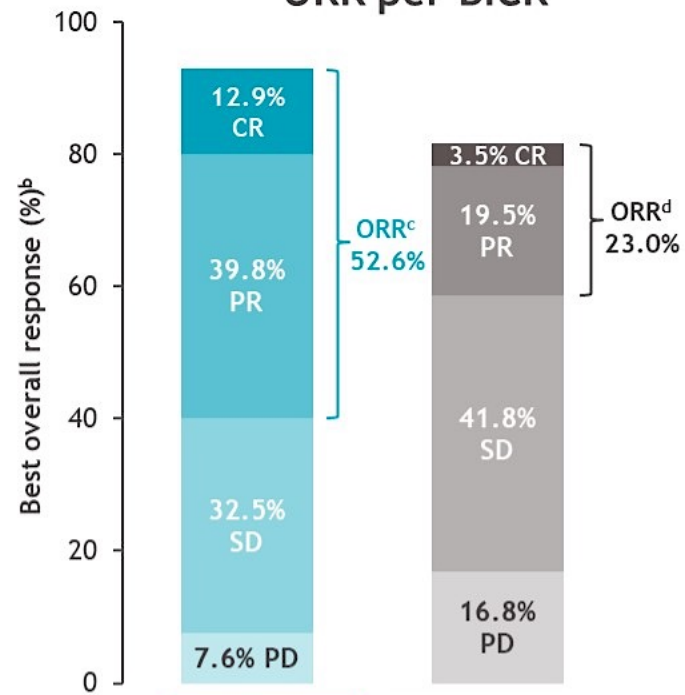
No. at risk												
NIVO+CABO	249	174	122	96	79	63	48	40	32	13	1	0
SUN	256	115	61	40	32	22	16	11	8	1	0	0

OS



No. at risk												
NIVO+CABO	249	228	205	187	166	153	134	121	109	65	13	0
SUN	256	209	178	158	136	118	106	94	82	46	11	0

ORR per BICR



	NIVO+CABO (n = 249)	SUN (n = 256)
Median TTR (range), mo[e]	2.8 (1.0-22.2)	4.4 (1.7-18.1)
Median DOR (95% CI), mo[e]	23.1 (17.3-30.5)	13.8 (7.1-23.5)

Maria Bourlon, ASCO GU 2024, Abstract #362

Nivolumab plus Cabozantinib (N+C) vs Sunitinib (S) for Previously Untreated Advanced Renal Cell Carcinoma (aRCC): Final Follow-Up Results from the CheckMate 9ER Trial

Motzer RJ et al.

Genitourinary Cancers Symposium 2025;Abstract 439.

February 15, 2025

8:25 AM – 8:35 AM PST

CheckMate 9ER: Follow-Up Efficacy Analysis

	FAV N+C; n = 74	FAV S; n = 72	INT N+C; n = 188	INT S; n = 188	Poor N+C; n = 61	Poor S; n = 68
PFS HR (95% CI)	0.67 (0.46–0.97)	-	0.63 (0.50–0.80)	-	0.36 (0.23–0.56)	-
mPFS (95% CI), mo	21.4 (12.8–24.6)	12.8 (9.4–16.6)	16.6 (11.3–21.7)	8.5 (6.9–10.4)	9.9 (5.9–17.7)	4.2 (2.9–5.7)
60-mo PFS rate, %	15.1	3.9	12.7	4.7	15.7	0
OS HR (95% CI)	1.08 (0.70–1.66)	-	0.86 (0.67–1.11)	-	0.49 (0.33–0.74)	-
mOS (95% CI), mo	53.7 (40.8–70.7)	58.9 (46.1–NE)	47.4 (38.2–55.8)	36.2 (25.7–46.3)	34.8 (21.4–53.4)	10.5 (6.8–20.7)
60-mo OS rate, %	46.3	49.4	41.2	38.2	33.1	12.9
ORR (95% CI), %	66.2 (54.3–76.8)	43.1 (31.4–55.3)	55.9 (48.4–63.1)	27.7 (21.4–34.6)	42.6 (30.0–55.9)	10.3 (4.2–20.1)
CR, %	16.2	6.9	15.4	4.8	6.6	1.5
60-mo DOR rate, %[a]	22.0	NE	19.0	13.0	37.0	0

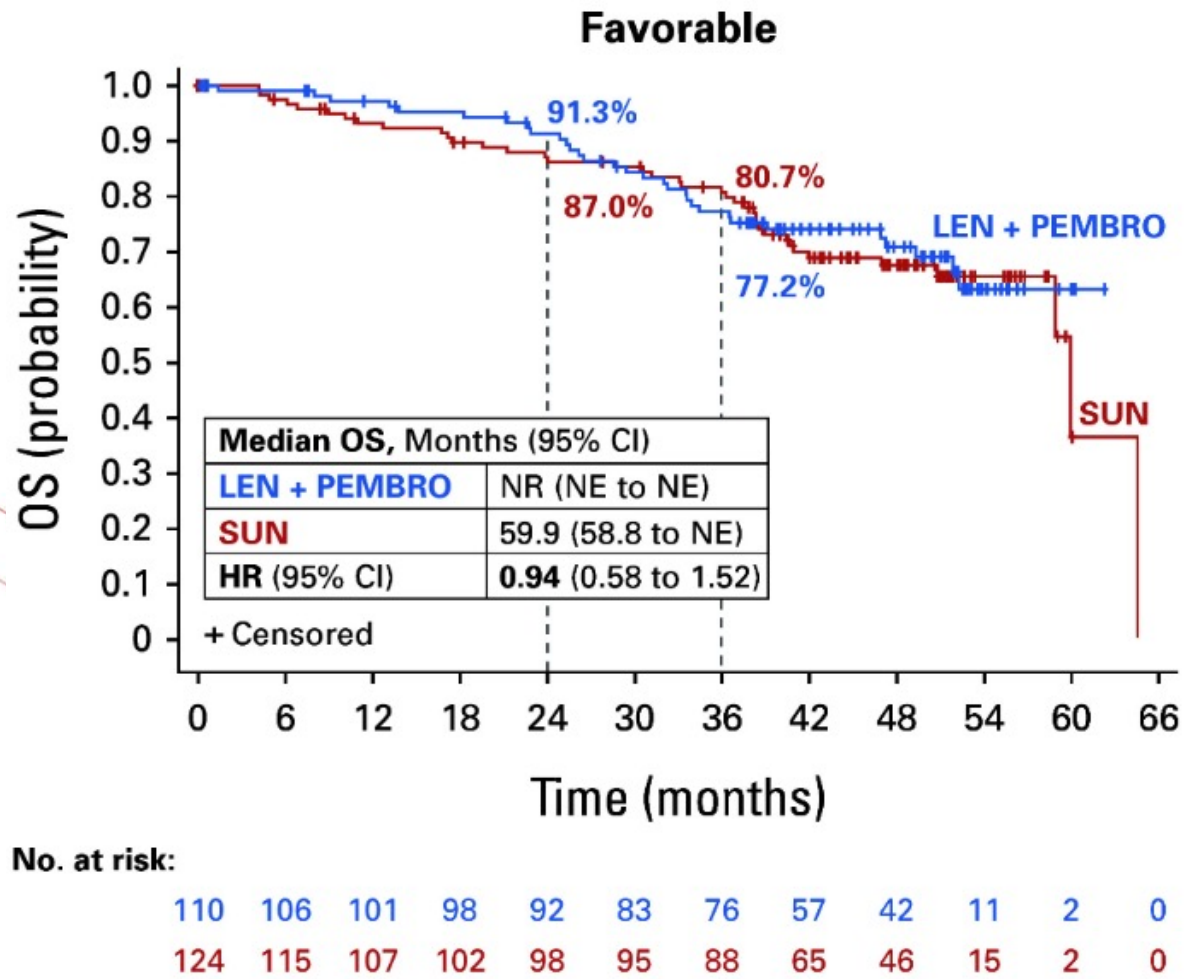
FAV, IMDC favorable; INT, IMDC intermediate; NE, not estimable; poor, IMDC poor.
[a]Based on pts with objective response.

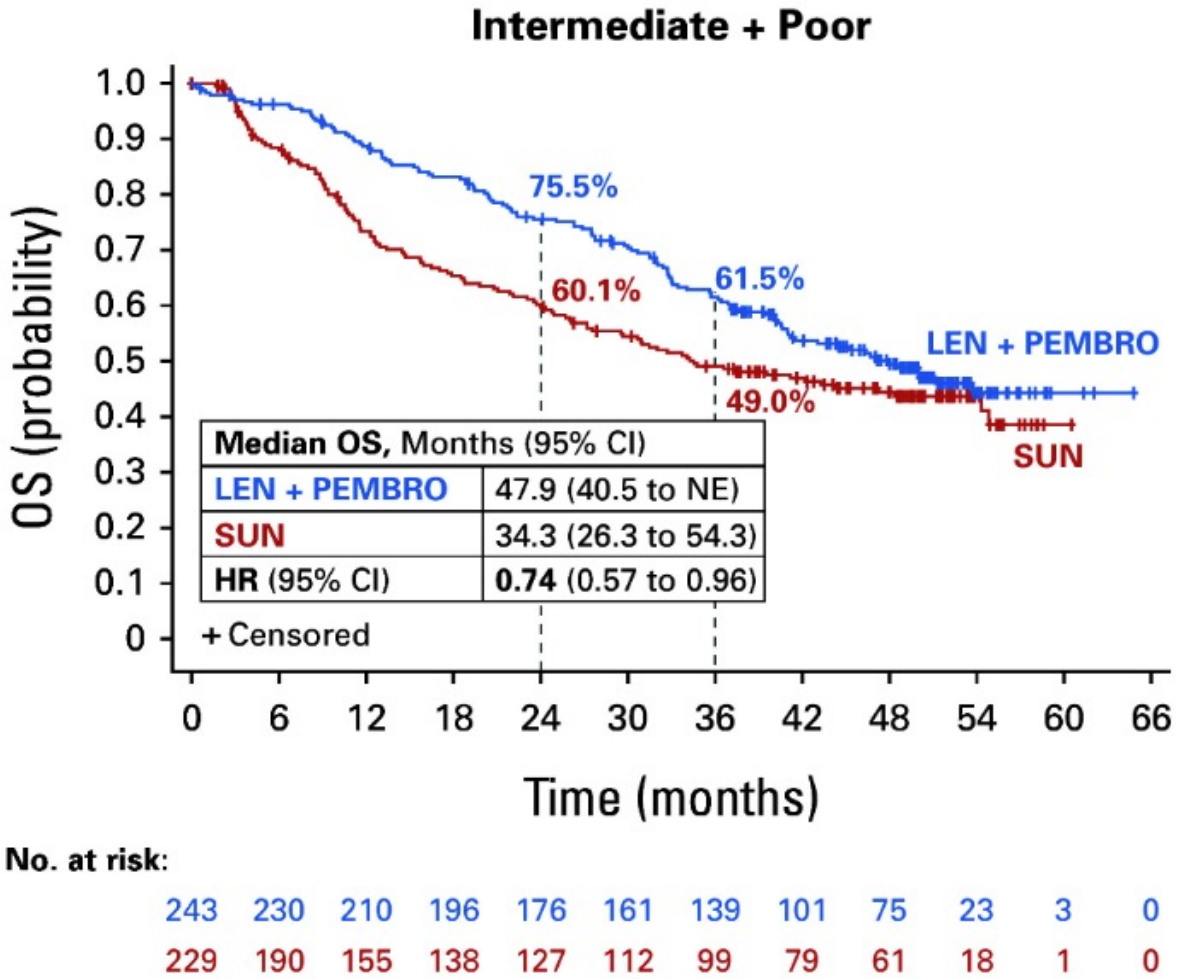
Motzer RJ et al. Genitourinary Cancers Symposium 2025;Abstract 439.

Lenvatinib + Pembrolizumab

CLEAR, Final OS JCO 2024, Patterns of Progression ASCO 2024

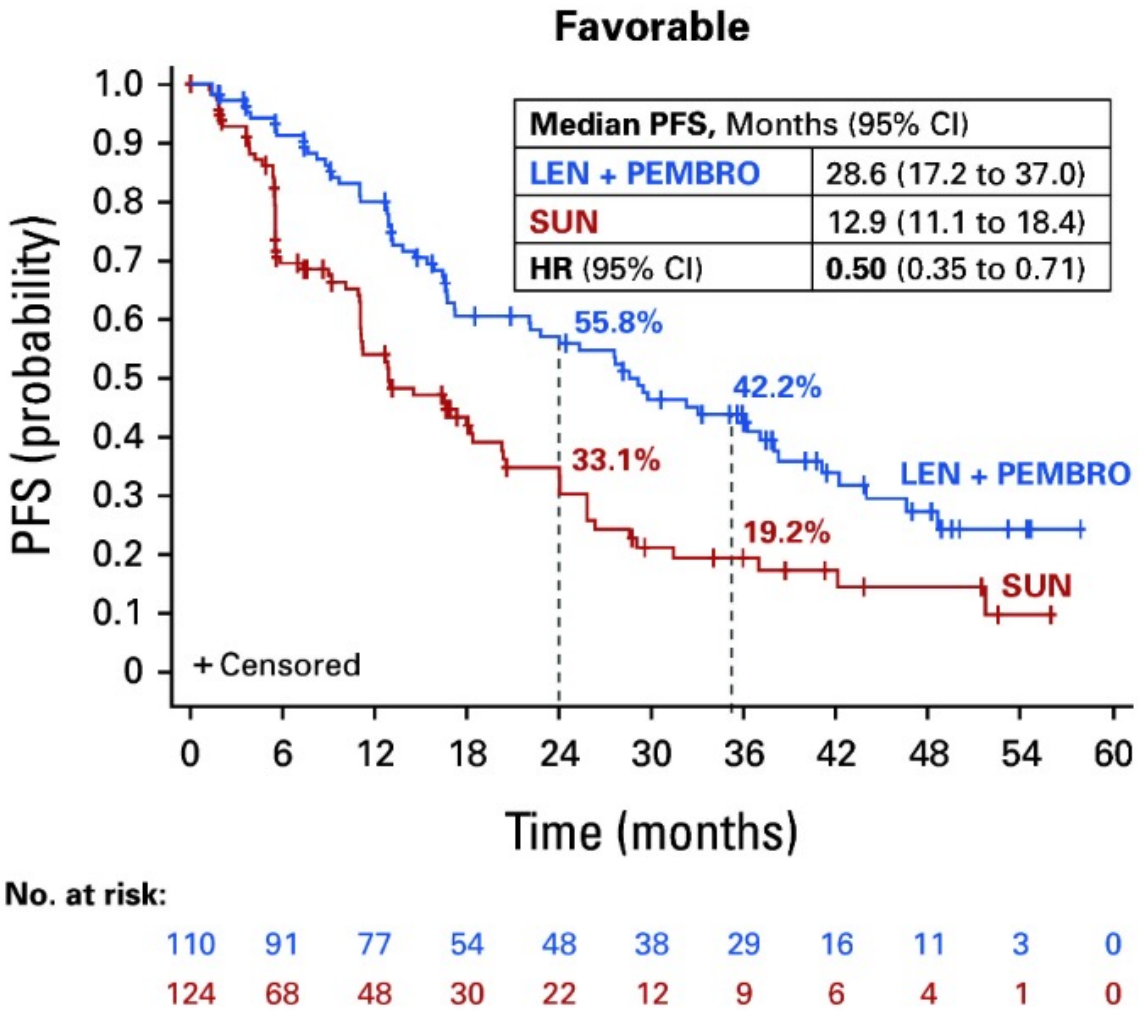
CLEAR: Overall Survival by IMDC Subgroup

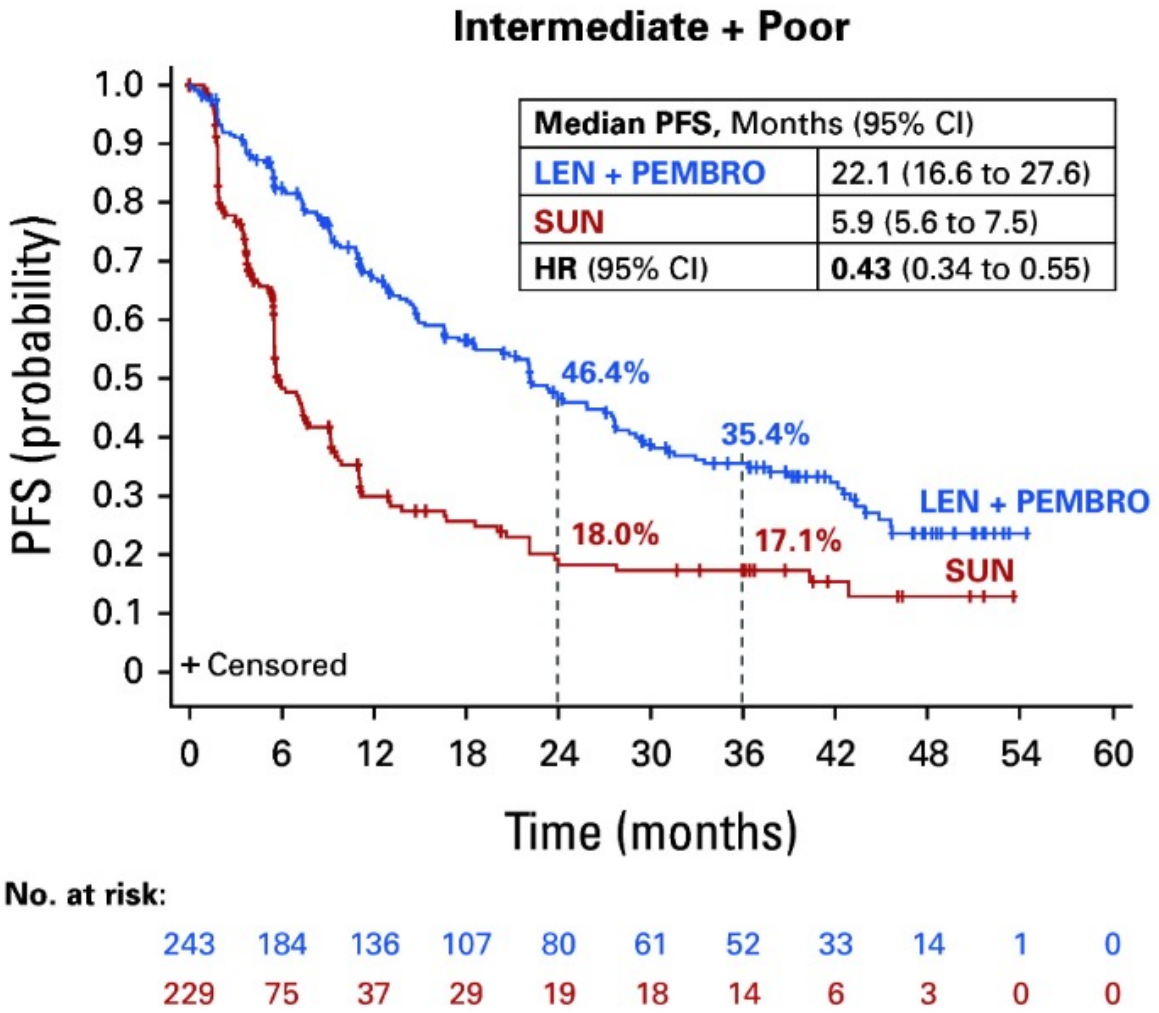




Motzer et al. *JCO*. 2024;42(11):1222-1228.

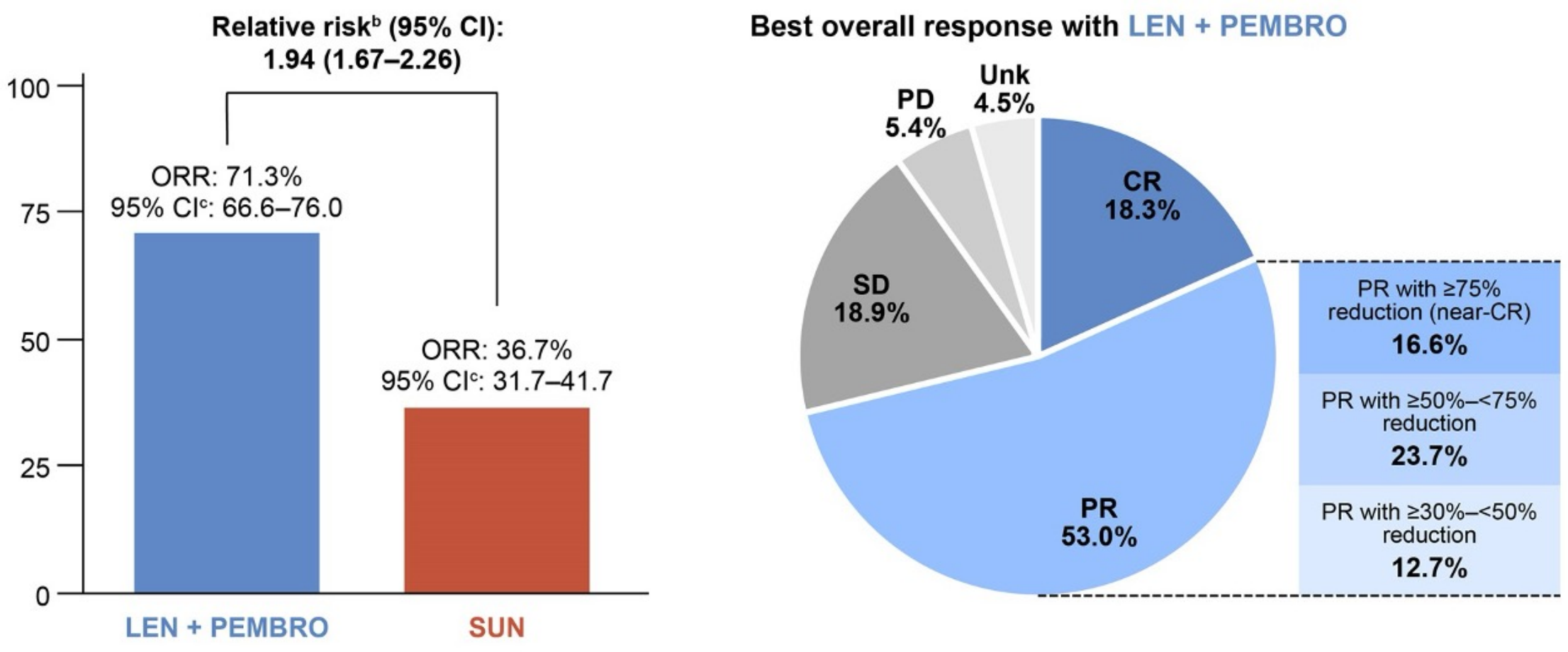
CLEAR: Progression Free Survival by IMDC Subgroup





Motzer et al. *JCO*. 2024;42(11):1222-1228.

CLEAR: Objective Response Rate (ORR) per Independent Review



LEN = lenvatinib; PEMBRO = pembrolizumab; SUN = sunitinib; SD = stable disease; PD = progressive disease; Unk - unknown; CR = complete response; PR = partial response

Hutson TE et al. ASCO 2023;Abstract 4502.

Analyses on Impact of Tumor Burden at Progression and Changes in IMDC from Baseline in Patients (pts) with Advanced Renal Cell Carcinoma (aRCC) Treated with Lenvatinib + Pembrolizumab (L+P) in the Phase 3 CLEAR Trial

Grünwald V et al.

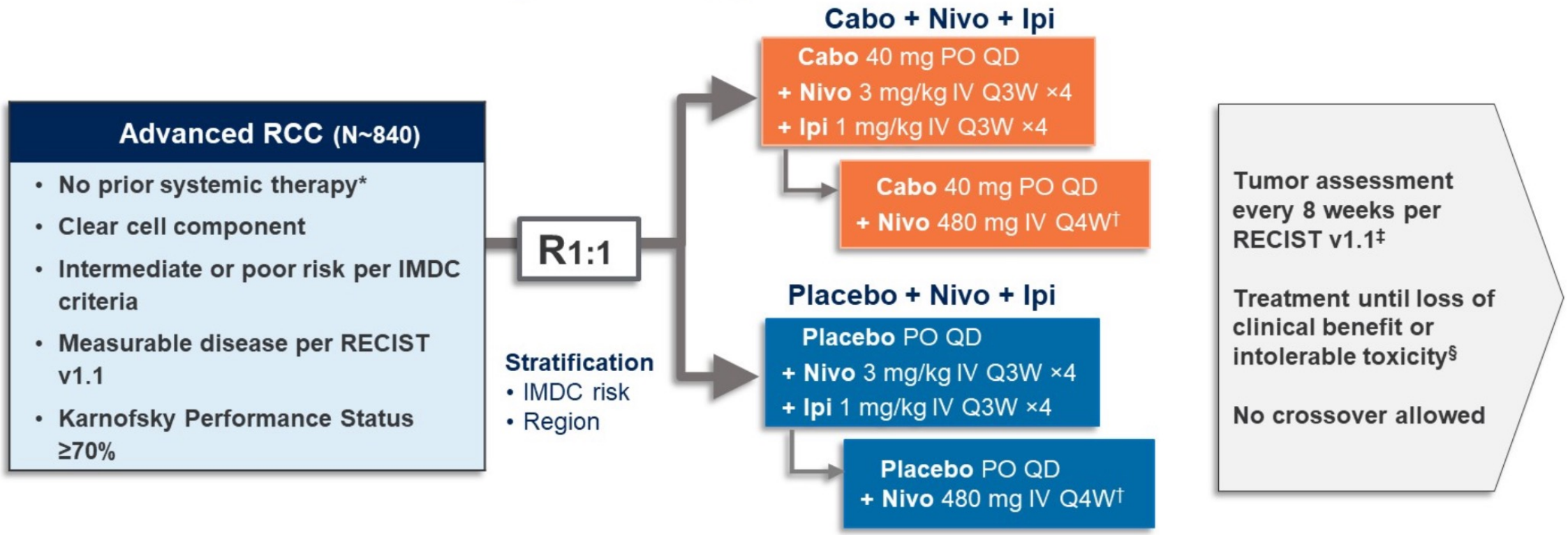
Genitourinary Cancers Symposium 2025;Abstract 531.

February 15, 2025

Poster Session

Phase III COSMIC-313 Trial

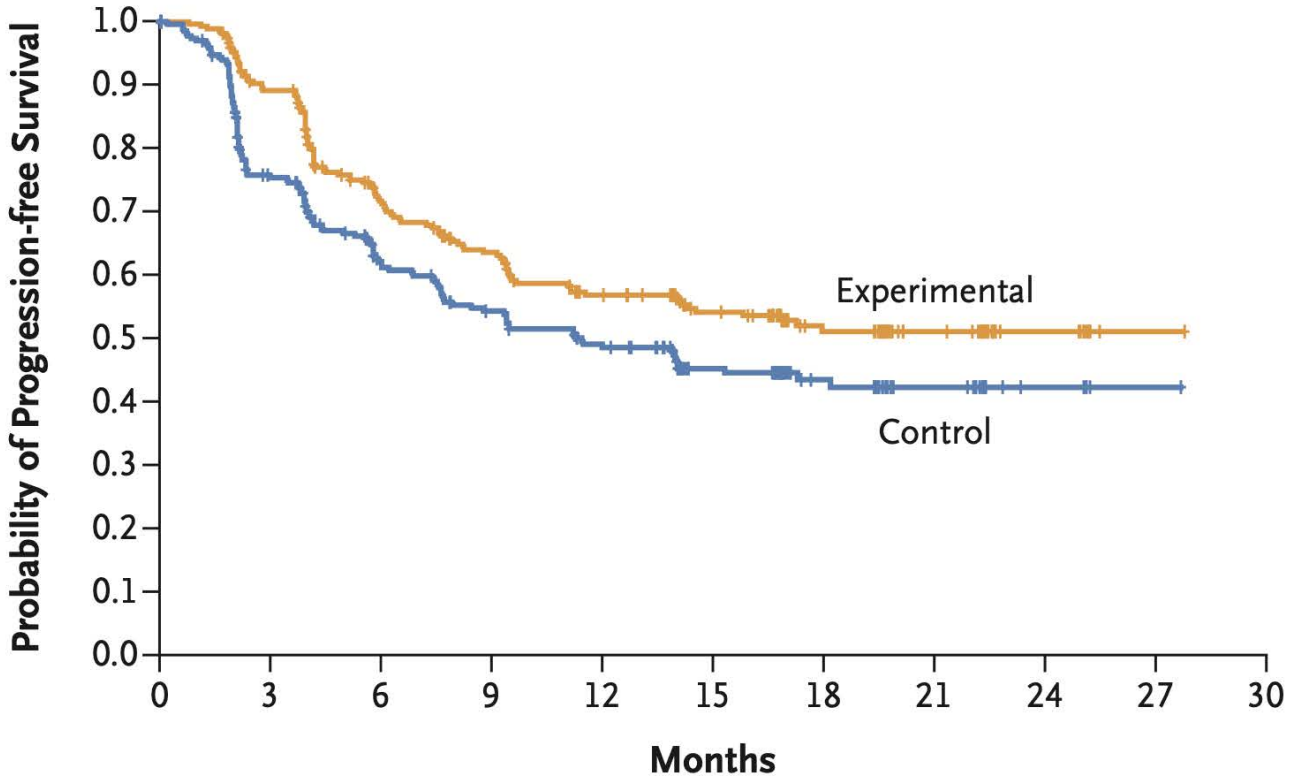
Phase III COSMIC-313 study



Primary endpoint: PFS per RECIST v1.1 by BIRC after the 249th event in the first 550 randomized patients (PITT population)
Secondary endpoint (ongoing): OS after 433 events in all randomized patients (ITT patients)
Additional endpoints: ORR, DOR, and safety

Powles et al, ASCO GU 2023

Phase III COSMIC-313: Final PFS Analysis



No. at Risk											
Experimental	276	234	170	145	119	97	56	33	10	1	0
Control	274	185	136	115	98	69	37	19	5	1	0

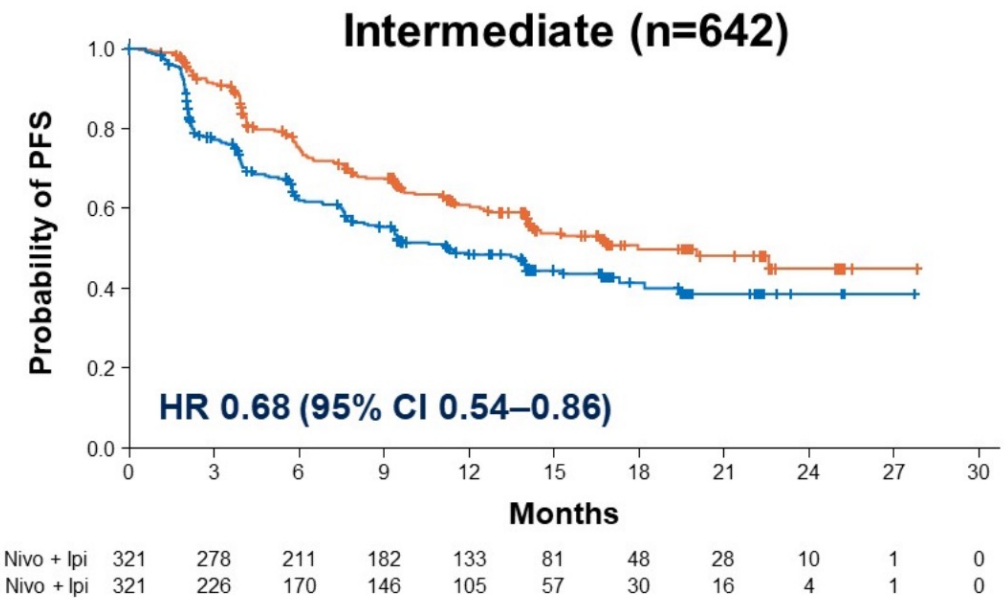
	No. of Patients	No. of Events	Median Progression-free Survival
			mo
Experimental	276	116	NR (14.0–NE)
Control	274	133	11.3 (7.7–18.2)

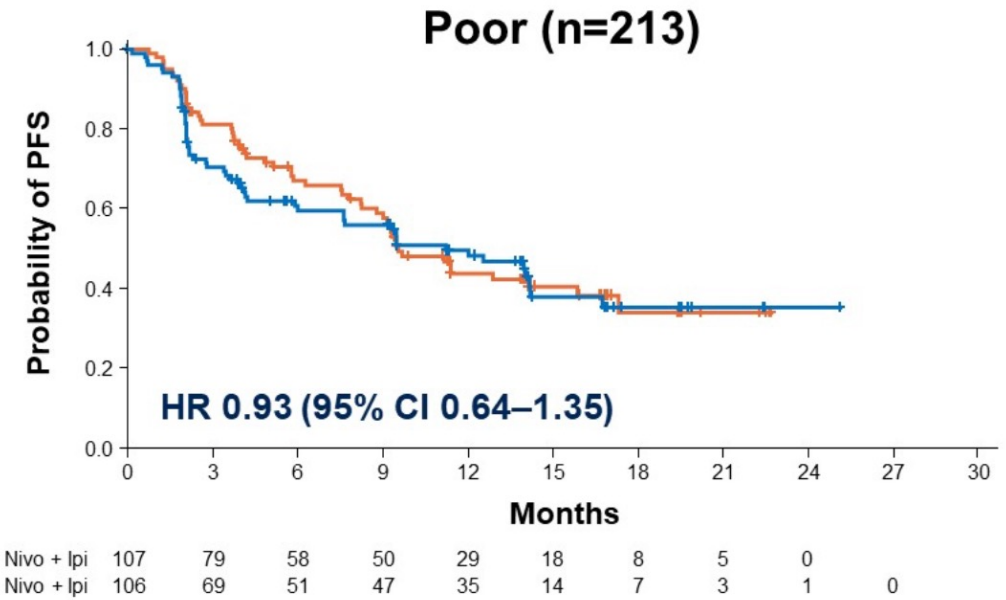
Hazard ratio for disease progression or death, 0.73 (95% CI, 0.57–0.94)
P=0.01

Choueiri et al, NEJM 2023.

Phase III COSMIC-313: PFS by IMDC Subgroup

A 32% reduction in the risk of progression or death was observed with the triplet regimen compared with the control in the intermediate risk





	n	No. of events	Median PFS, mo (95% CI)
Cabo + Nivo + Ipi	321	131	17.9 (14.1–NE)
Pbo + Nivo + Ipi	321	161	11.3 (8.4–15.3)

	n	No. of events	Median PFS, mo (95% CI)
Cabo + Nivo + Ipi	107	55	9.5 (8.3–15.8)
Pbo + Nivo + Ipi	106	55	11.2 (6.0–14.2)

Median follow-up of 17.7 mo; total of 855 patients and 402 PFS events per RECIST 1.1 by BIRC at data cutoff of January 31, 2022.

Powles et al, ASCO GU 2023

Cabozantinib (C) in Combination with Nivolumab (N) and Ipilimumab (I) in Previously Untreated Advanced Renal Cell Carcinoma (aRCC): Final Results of COSMIC-313

Albiges A et al.

Genitourinary Cancers Symposium 2025;Abstract 438.

February 15, 2025

8:15 AM – 8:25 AM PST

COSMIC-313: Final Efficacy Outcomes

	C+N+I (n=428)	P+N+I (n=427)
Median OS (95% CI), mo	41.9 (34.8–47.9)	42.0 (34.9–53.1)
HR (95% CI); *P*-value	1.02 (0.85–1.23); *P*=0.84	
Median PFS (95% CI), mo	16.6 (14.0–22.6)	11.2 (9.3–14.0)
HR (95% CI)	0.82 (0.69–0.98)	
ORR (95% CI), %	46 (41–51)	37 (32–41)
Complete response, %	4	3
Partial response, %	42	33
Stable disease, %	40	36
Progressive disease, %	8	20

Albiges A et al. Genitourinary Cancers Symposium 2025;Abstract 438.

Phase 3 CheckMate 67T

CheckMate 67T: Subcutaneous nivolumab (NIVO SC) vs intravenous nivolumab (NIVO IV) in advanced/metastatic ccRCC

Key eligibility criteria

- Advanced or metastatic ccRCC that progressed during or after receiving 1-2 prior systemic regimens
- No prior immuno-oncology therapy
- Karnofsky PS ≥ 70

R 1:1

- NIVO SC 1200 mg + rHuPH20 Q4W (n = 248)
- NIVO IV 3 mg/kg Q2W (n = 247)

Treat until disease progression, unacceptable toxicity, withdrawal of consent, completion of 2 years' treatment, or death

Key stratification factors

- IMDC risk group
- Baseline weight

Co-primary PK endpoints for noninferiority testing:

- C_{avgd28} and C_{minss}

Key powered secondary endpoint for noninferiority testing:

- ORR by BICR

- Patients were enrolled across 73 sites in 17 countries[a]
- Minimum follow-up was 8 months

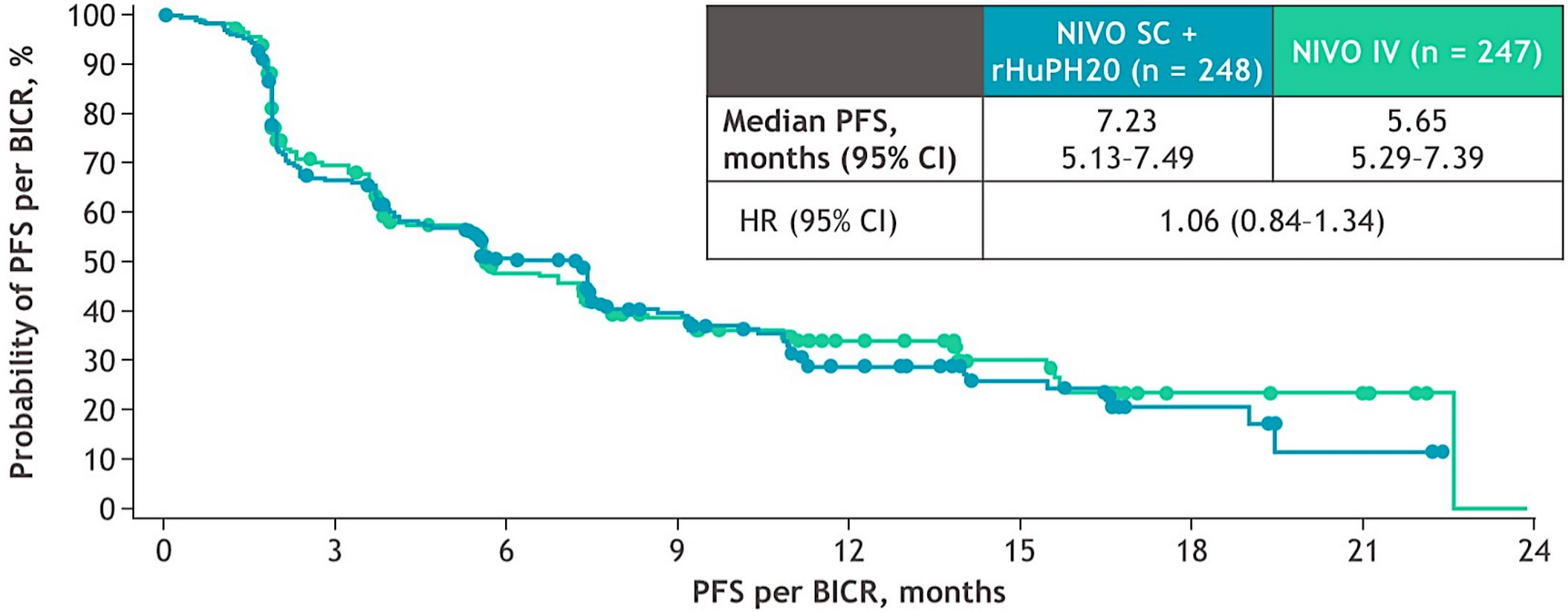
Other secondary endpoints:

- Other efficacy, safety, and PK measures
- Incidence of anti-NIVO antibodies and neutralizing antibodies

George et al, ASCO GU 2024; Abstract LBA360.

CheckMate 67T: PFS by BICR

- Progression-free survival was similar between the NIVO SC and NIVO IV arms



	NIVO SC + rHuPH20 (n = 248)	NIVO IV (n = 247)
Median PFS, months (95% CI)	7.23 5.13-7.49	5.65 5.29-7.39
HR (95% CI)	1.06 (0.84-1.34)	

Number of patients at risk

NIVO SC	248	149	103	61	28	17	6	2	0
NIVO IV	247	152	94	65	33	19	6	4	0

George et al, ASCO GU 2024; Abstract LBA360.

Questions from General Medical Oncologists

- **Man in his mid-60s with metastatic clear cell RCC with sarcomatoid features, otherwise healthy. What would you recommend as first-line treatment? Do you always prefer IO/IO for sarcomatoid?**
- **What is the optimal first-line treatment for patients with clear cell RCC who progress within 12 months of adjuvant pembrolizumab? Would you recommend ipilimumab/nivolumab, a combination of IO + TKI or a TKI alone? If so, which combination or TKI?**
- **Is COSMIC-313 practice-changing, and should triplet therapy be used in routine practice? If so, which patients should receive this regimen?**

Questions from General Medical Oncologists

- In general, which first-line therapy would you use for a patient with treatment-naïve advanced clear cell RCC with multiple painful bone metastases? What about symptomatic liver metastases? What about bilateral lung metastases? Are there clinical characteristics beyond disease burden that help guide treatment selection?
- When initiating lenvatinib/pembrolizumab for a patient with advanced RCC, what starting dose of lenvatinib do you use?
- My relatively basic understanding of the data is that len/pem seems somewhat better than the other IO + TKI combinations, but it doesn't seem that experts are that bullish on the regimen. Why?

Questions from General Medical Oncologists

- With the availability of subQ nivo, are the faculty more commonly favoring cabo/nivo to make things easier for their patients?
- Which patients with RCC should receive adjuvant pembrolizumab? What about the use adjuvant therapy in patients with intermediate-risk disease? What about patients who are immunocompromised or who have undergone renal transplant?
- Should adjuvant pembrolizumab be continued for 12 months or is a shorter duration (eg, 6 months) effective?
- Would ctDNA testing help guide the decision to use adjuvant pembrolizumab?

Agenda

Module 1: Immunotherapeutic Strategies for Localized and Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Hutson

Module 2: Optimal Management of Relapsed/Refractory RCC — Dr Zhang

Module 3: Role of HIF-2α Inhibitors in the Treatment of Sporadic and von Hippel-Lindau-Associated RCC — Dr McKay

Module 4: Current and Future Care of Patients with Non-Clear Cell RCC — Dr Pal

Research To Practice®

AN INTEGRATED APPROACH TO ONCOLOGY EDUCATION

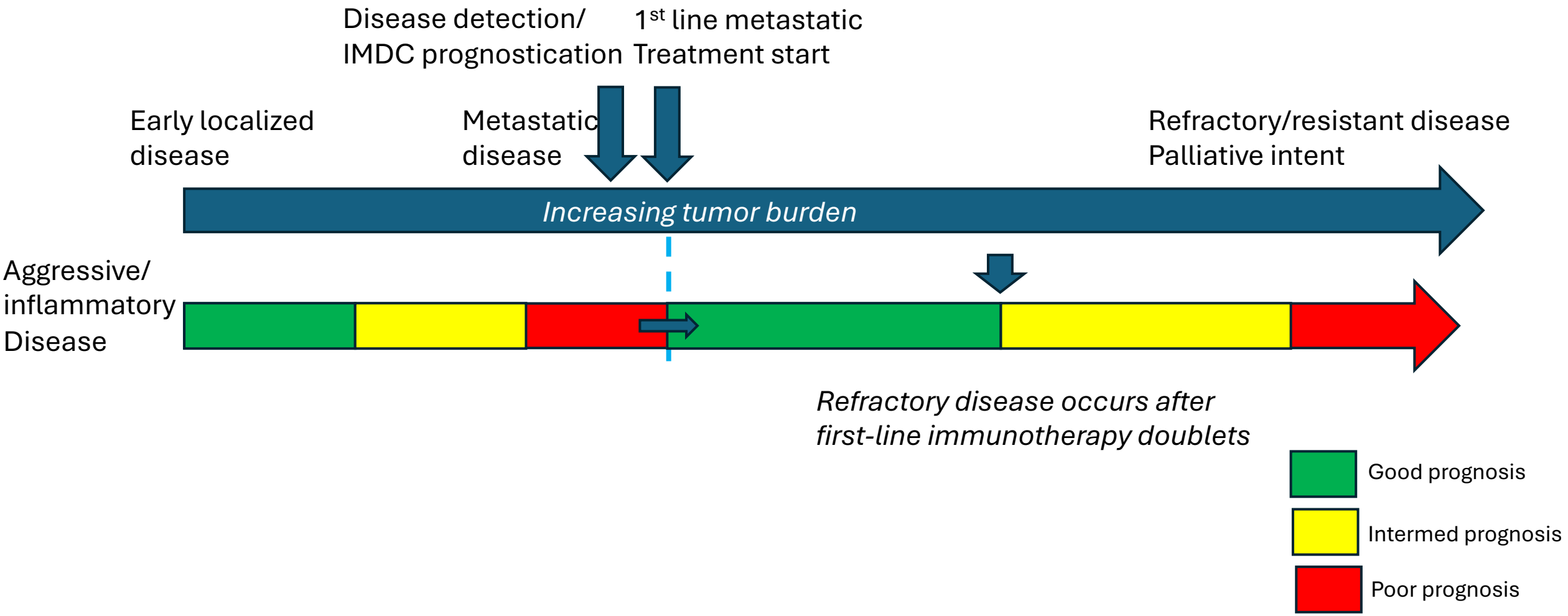
Optimal management of patients with relapsed/refractory renal cell carcinoma

Tian Zhang, MD, MHS

Associate Professor
Associate Director of Clinical Research
Simmons Comprehensive Cancer Center
UT Southwestern Medical Center

Research To Practice
What Clinicians want to know: Addressing current questions related to management of GU Cancers
February 14, 2025

Modifying disease biology after treatment



Adapted T. Powles KCRS 2023

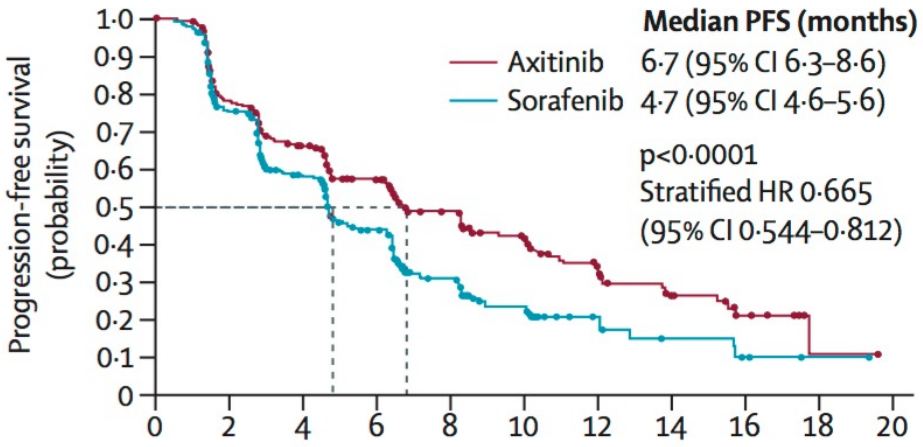
Successful registrational trials in refractory setting

	AXIS	METEOR	CheckMate 025	Study 205	TIVO-3	LITESPARK -005
Treatment Sample size	**Axitinib** vs Sorafenib N=723	**Cabozantinib** vs Everolimus N=658	**Nivolumab** vs Everolimus N=821	Lenvatinib-everolimus vs Everolimus N=153	**Tivozanib** vs Sorafenib N=350	**Belzutifan** vs Everolimus N=746
mPFS (months)	6.7	7.4	4.6	14.6	5.6	5.6
HR (95% CI)	0.66 (0.544-0.812)	0.51 (0.42-0.62)	0.88 (0.75-1.03)	0.40 (0.24-0.68)	0.73 (0.56-0.94)	0.74* (0.63-0.88)
ORR (%)	19%	17%	25%	43%	12.3%	22%
mOS HR (95% CI)	0.97 (0.80-1.17)	0.66 (0.53-0.83)	0.72 (0.57-0.93)	0.51 (0.30-0.88)	0.89 (0.70-1.14)	0.88* (0.73-1.07)

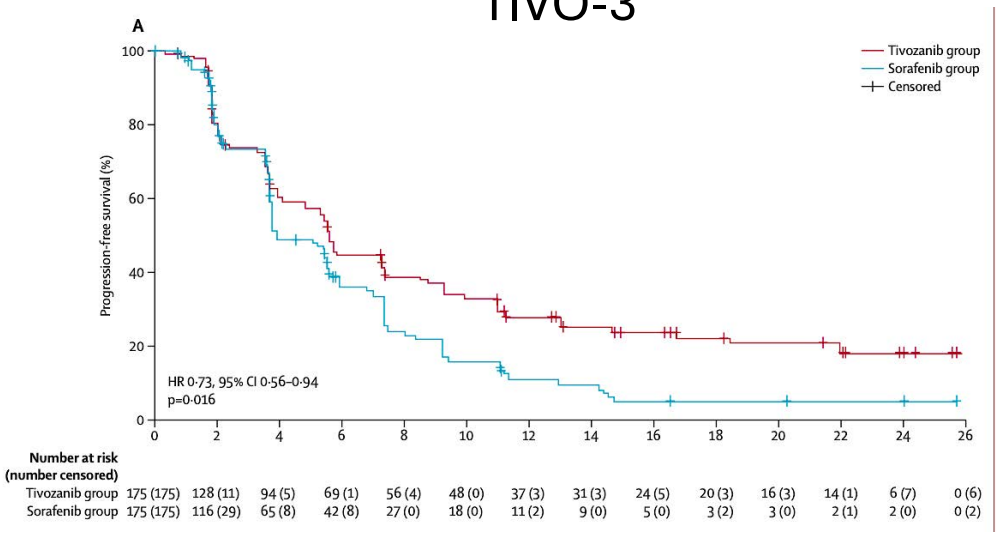
Rini BI et al, *Lancet*, 2011
Choueiri TK et al, *NEJM*, 2015
Motzer RJ et al, *NEJM*, 2015
Motzer RJ et al, *Lancet Onc*, 2015
Rini BI et al, *Lancet Onc*, 2020
Choueiri TK et al, *NEJM*, 2024

Progression free survival across trials

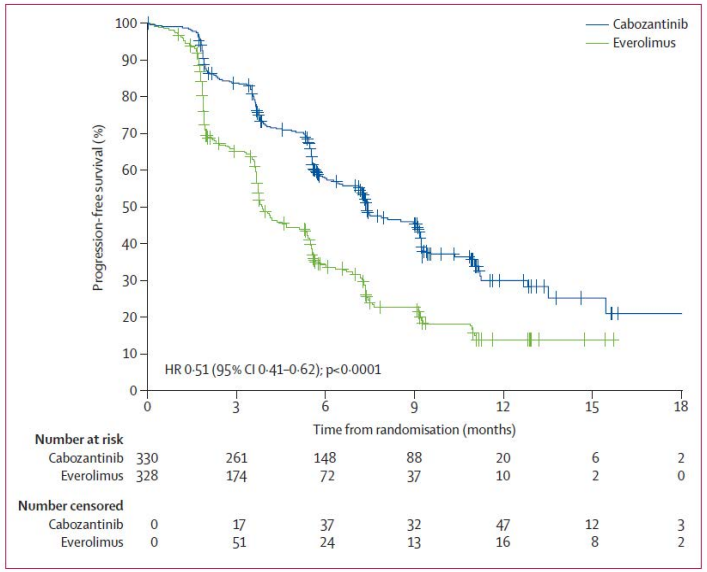
AXIS - Axitinib vs Sorafenib PFS



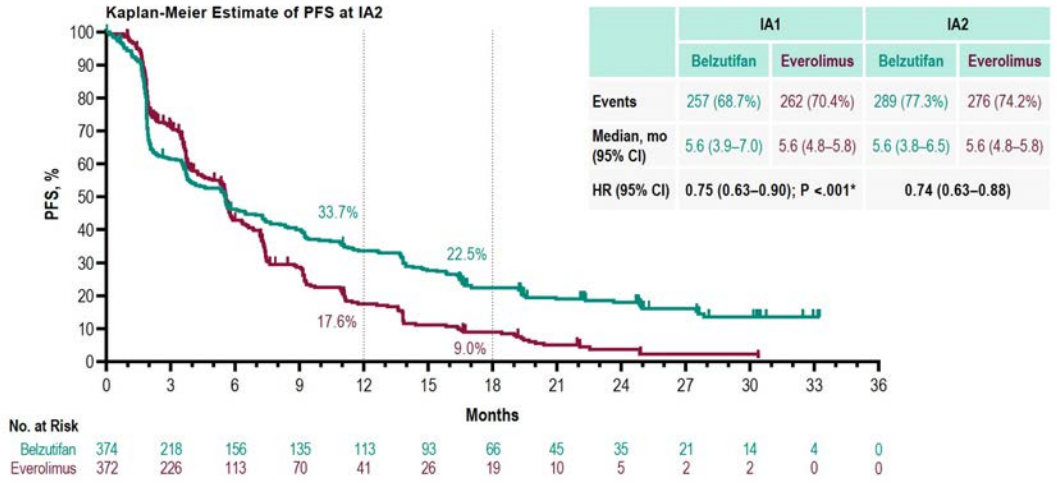
TIVO-3



METEOR



LITESPARK-005



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

Rini BI et al, *Lancet*, 2011
Choueiri TK et al, *NEJM*, 2015
Motzer RJ et al, *NEJM*, 2015
Motzer RJ et al, *Lancet Onc*, 2015
Rini BI et al, *Lancet Onc*, 2020
Choueiri TK et al, *NEJM*, 2024

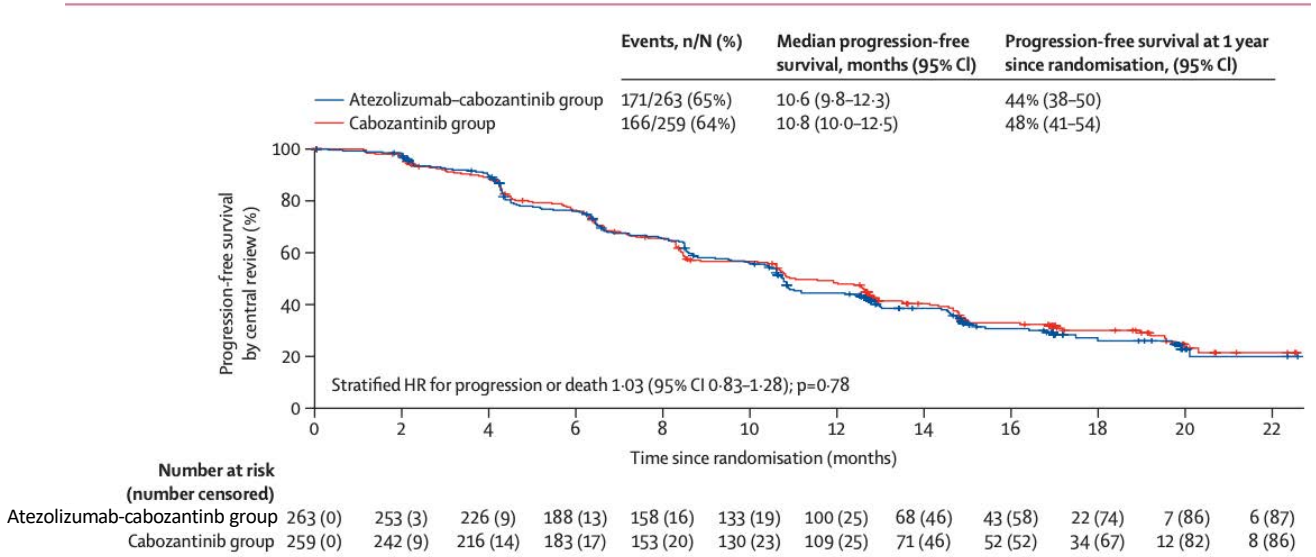
What not to do: Less successful trials in refractory disease

	CONTACT-03	TiNIVO-2	CANTATA
Treatment Sample size	**Cabozantinib-atezolizumab vs cabozantinib** N=522	**Tivozanib-nivolumab** vs tivozanib N=343	**Cabozantinib + Telaglenastat** vs Cabozantinib N=444
mPFS (months)	10.6 vs. 10.8	5.7 vs 7.4	9.2 vs 9.3
HR (95% CI)	1.03 (0.83-1.28)	1.10 (0.84-1.43)	0.94 (0.74-1.21)
ORR (%)	41% vs 40%	19% vs 20%	31%
mOS HR (95% CI)	0.94 (0.70-1.27)	1.00 (0.68-1.46)	**

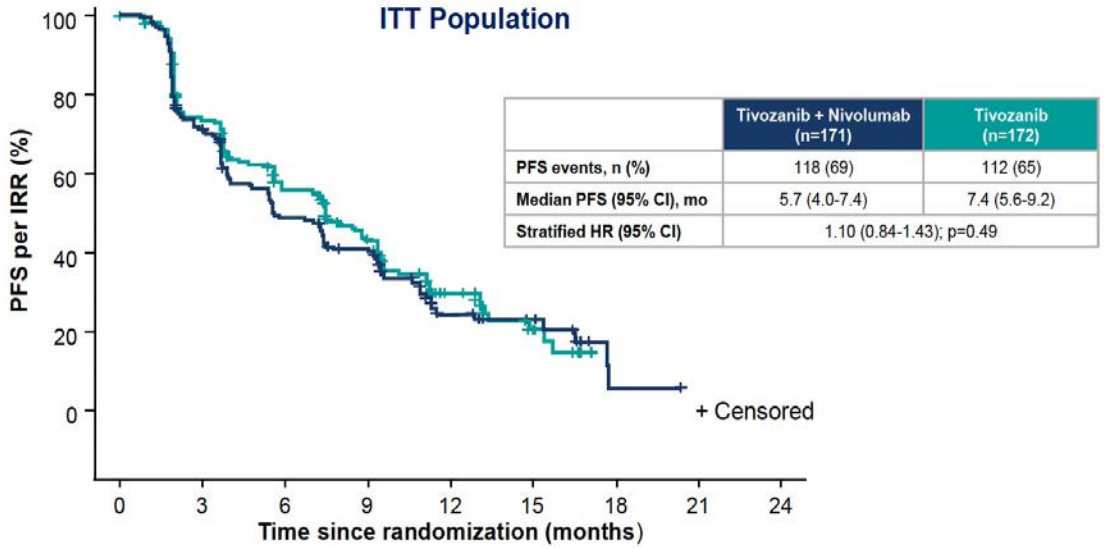
Pal SK et al, *Lancet*, 2023
Choueiri TK et al, ESMO Annual Congress, 2024
Tannir NM et al, r RJ et al, *Lancet Onc*, 2015
Rini BI et al, *Lancet Onc*, 2020
Choueiri TK et al, *NEJM*, 2024

Lesson learned from CONTACT-03 and TiNivo-2

CONTACT-03



TiNIVO-2



PD-1 or PD-L1 inhibition after prior progression on immunotherapy does not improve PFS outcomes

Novel sequencing and therapy approaches

- PDIGREE (adaptive ipi-nivo → cabo-nivo)
- Lenvatinib-belzutifan (KEYMAKER-U03 - Albiges et al GU ASCO)
- Zanzalintinib (STELLAR-001)
- Evolocumab-nivolumab (BOOST-RCC)
- CA-IX targeted girentuximab (STARLITE 1)

A031704 PDIGREE – Study design

Metastatic renal cell carcinoma
- Clear cell component
- No prior systemic therapy

(HD IL-2 and adjuvant sunitinib allowed)
- IMDC intermediate or poor risk
- Archival tissue available or fresh biopsy

N=1111

Induction therapy: Ipilimumab 1mg/kg IV every 3 weeks, Nivolumab 3mg/kg IV every 3 weeks

3-month response (investigator assessed)

CR → Nivolumab 480mg IV every 4 weeks

Non-CR, Non-PD → R

- R → Nivolumab 480mg IV every 4 weeks
- R → Nivolumab 480mg IV every 4 weeks + Cabozantinib 40mg PO daily

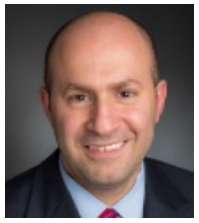
N=552

PD → Cabozantinib 60mg PO daily

Discontinue:
Progression of disease
Unacceptable toxicity
Complete response at 1 year

1º endpoint:
3-year OS
(60% nivo vs 70% nivo-cabo, HR 0.70
85% power, 2-sided α=0.05)

Key 2º endpoints:
-- 1-year CR rate
-- PFS
-- ORR by RECIST
-- Toxicity of nivo-cabo

Study chairs: Zhang & Choueiri

PDIGREE: Alliance trial A031704
Clinicaltrials.gov: NCT03793166

Study activated in NCTN May 2019 – almost 5 years!

BOOST-RCC:

Phase 2 trial of PCSK9 inhibition with nivolumab in metastatic renal cell carcinoma

Metastatic renal cell carcinoma
- Progression on or after prior PD-1 inhibitor (>6 months)
- Progression on prior VEGF inhibitor (could be in combination with PD-1 inhibitor)
- Radiographically evident disease
- Adequate organ function

→

PCSK9 inhibitor
Evolocumab
Q4 weeks
+
Nivolumab 480mg
IV
q4 weeks

→

Expand if >=1 responses

Stage 1: N=10 → Stage 2: N=19

Stage 1:
- Safety lead-in for combination treatment in first 5 patients
- Paired biopsies for up to 10 patients

Discontinue treatment:
Disease progression
or
Intolerable adverse event

Primary endpoint:
Objective response rate

Secondary endpoints:
Safety of combination
Progression free survival
Overall survival

Exploratory endpoints:

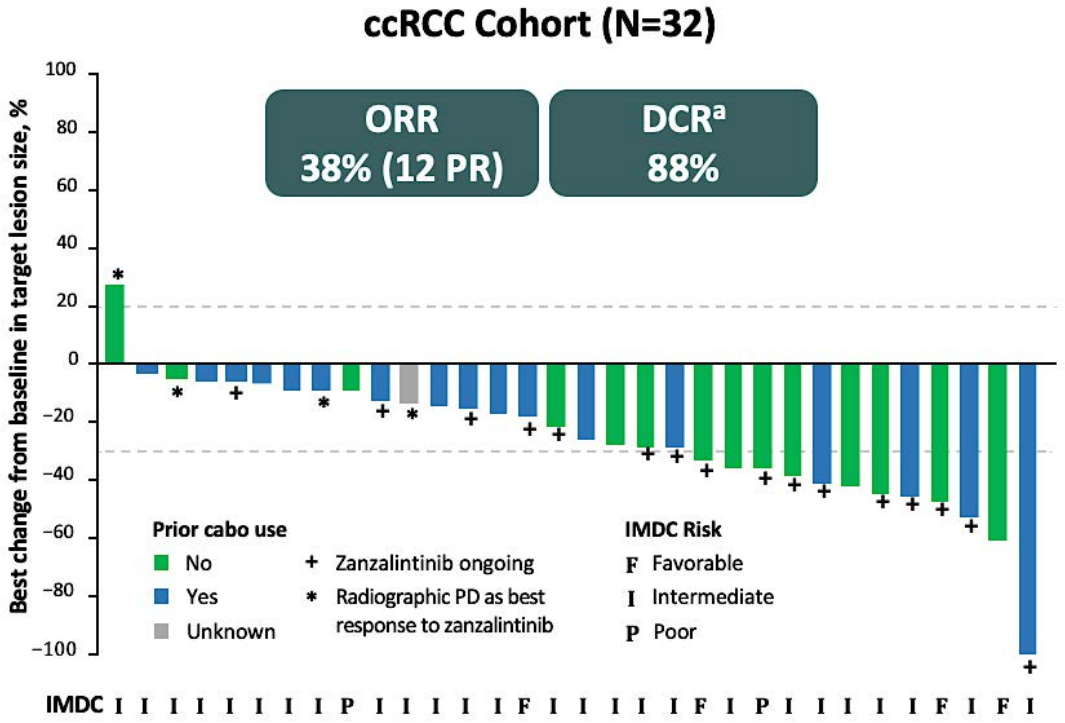
To evaluate effect of T-cell infiltration and MHC-1 expression on baseline and on-treatment biopsies

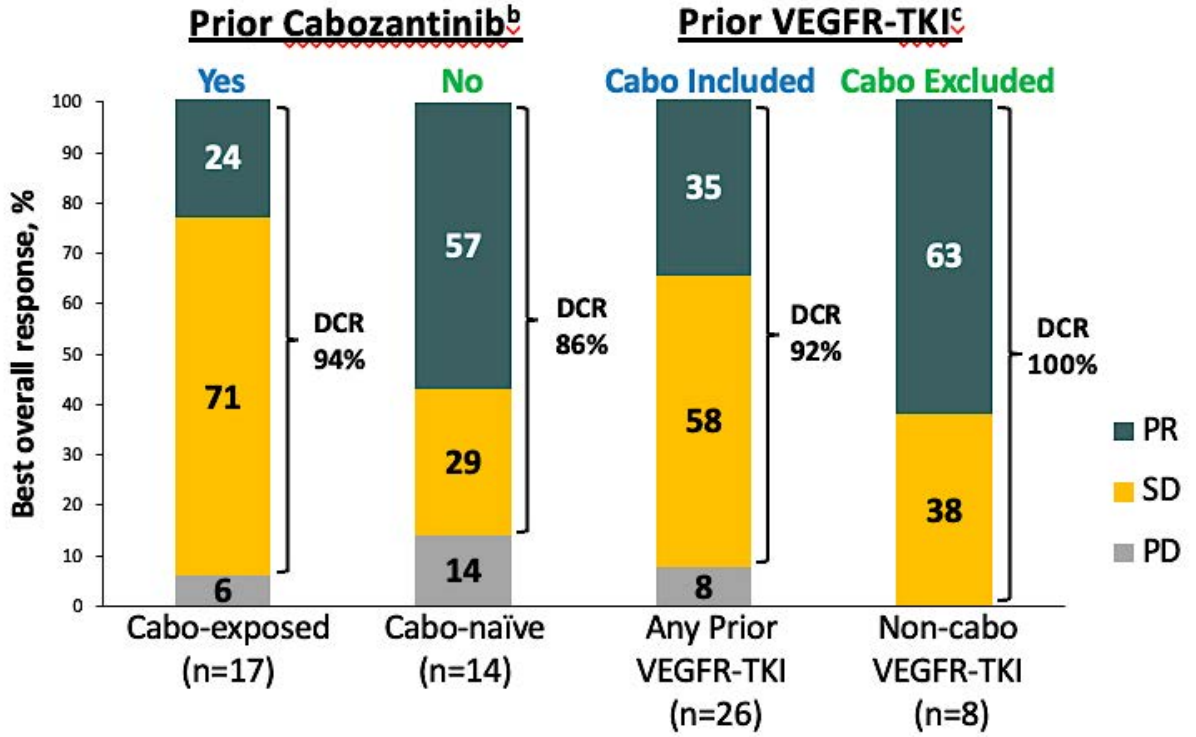
NCT06284564
UTSW and MD Anderson
CPRIT supported trial

Sample size:

H0: ORR 5%, HA: ORR 20%
Stage 1: 10 patients - if 1 or more responses, proceed to stage 2
Stage 2: 19 patients (29 total)
Reject H0 if 4 or more responses are observed in 29 patients.
Assumes one-sided alpha of 0.05 and a power of 80%.

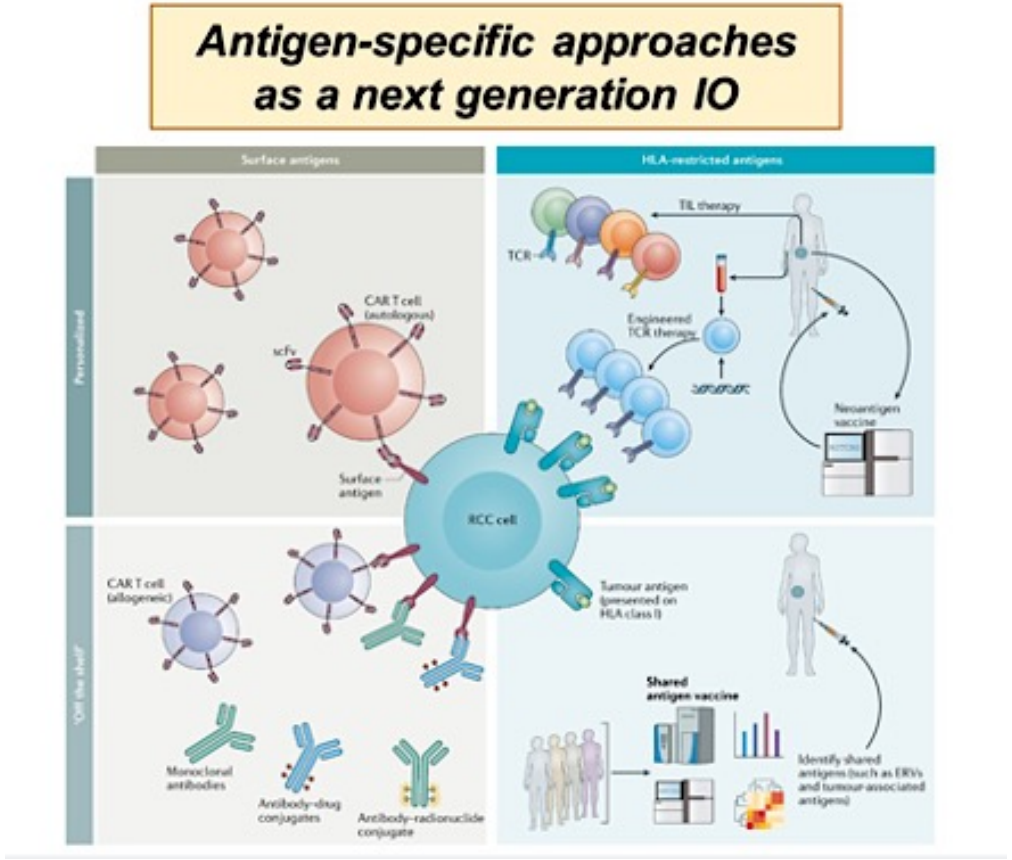
Zanzalintinib (XL-092)





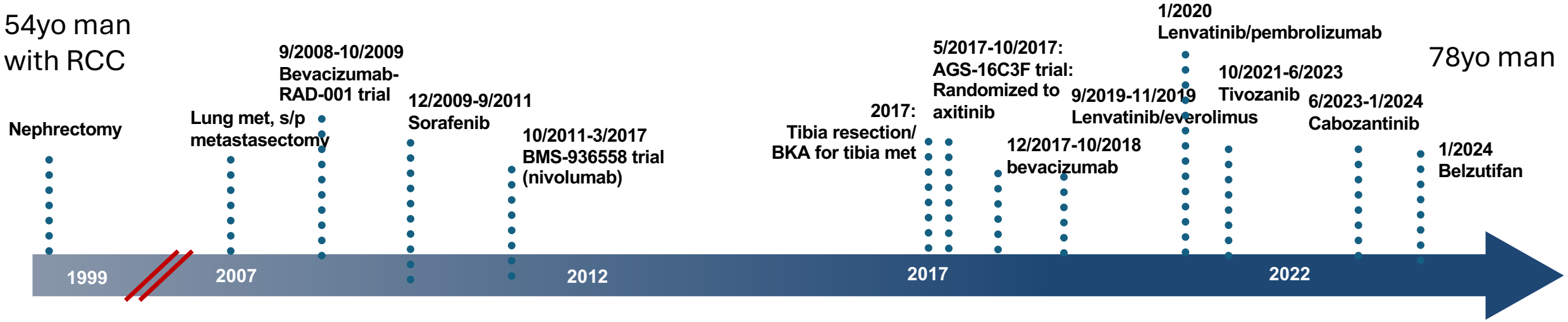
Pal SK et al, IKCS 2023

Challenge for future of refractory RCC:
Tackle mechanisms of immune checkpoint resistance



Zhu S, Zhang T, et al, *J Hematol Oncol*, 2021; 14: 156
Braun D, *Nat Rev Clin Oncol*, 2021

Ultimately our patients win



- Lived with metastatic RCC for 17 years
- 10 lines of treatment for metastatic disease
- 3 interventional trials
- 3 oncologists: Harshman, Srinivas, Zhang

Sequencing life-extending treatments in RCC

Challenge everyone to continue rational drug discovery for him and many others like him in our clinics

Outline/Takeaways

- Resistance to first-line immunotherapies occurs in many patients
- PD-1 therapy has no role for post-IO treated patients
- We should change treatment mechanism for patients with IO-refractory disease – tivozanib, belzutifan, and Lenvatinib-everolimus, cabozantinib are all approved

Questions from General Medical Oncologists

- I have a patient with advanced clear cell RCC who is doing well on a first-line IO/TKI regimen but has slight increases in the sizes of some nodules in the lung. How should I approach treatment? In your opinion, is slow progression enough to change treatment, or do you wait for the development of symptoms or other changes in clinical status before switching?
- Is there any data to support immunotherapy rechallenge after failure on first-line IO/TKI?
- What would the faculty recommend as next therapy for a patient who progresses on the COSMIC-313 regimen (ipi/nivo/cabo)?

Questions from General Medical Oncologists

- What is the panel's current go-to second-line regimen for patients who progress on ipi/nivo? For a patient who progresses after just 5 months of up-front ipi/nivo, would they continue the ipi/nivo and add cabo? Continue the nivo only and add cabo? Switch to cabo alone or to a different regimen altogether?
- How do you sequence TKIs in patients who are progressing on first-line IO + TKI? Is there any difference in your approach if they have received first-line IO/IO?
- How does the panel decide between cabozantinib and tivozanib as second-line treatment? Is one better tolerated than the other?

Questions from General Medical Oncologists

- Should sequence of therapy differ for specific patient populations, such as those with bone-only metastases? Does it matter if disease progression is asymptomatic or symptomatic? Do any of the available TKIs have better activity in the brain?
- When using lenvatinib in the relapsed setting, is it always partnered with everolimus? Where are you typically sequencing that regimen? Do you ever use either of those agents alone?
- Are there any novel agents or strategies in development that look promising and interesting? What trials would you consider for a patient who is running out of options?

Agenda

Module 1: Immunotherapeutic Strategies for Localized and Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Hutson

Module 2: Optimal Management of Relapsed/Refractory RCC — Dr Zhang

Module 3: Role of HIF-2α Inhibitors in the Treatment of Sporadic and von Hippel-Lindau-Associated RCC — Dr McKay

Module 4: Current and Future Care of Patients with Non-Clear Cell RCC — Dr Pal

UC San Diego Health | UC San Diego Moores Cancer Center

Role of HIF-2α Inhibitors in Sporadic and von Hippel-Lindau (VHL)-Associated RCC

Rana R. McKay, MD, FASCO

Professor of Medicine and Urology

Moores Cancer Center, University of California San Diego

Objectives

- Biologic rationale for targeting HIF-2α in patients with advanced RCC
- Review current efficacy and safety data of belzutifan monotherapy in RCC
- Review current efficacy and safety data of belzutifan in combination with other systemic therapies (eg, VEGFR TKIs, immune checkpoint inhibitors) for patients with RCC
- Highlight ongoing phase III trials evaluating belzutifan combinations in the adjuvant and advanced disease settings
- Review characteristics of VHL-associated RCC and activity of belzutifan in this population
- Alternate HIF-2α targeting agents

VHL Mutations Drive Pathogenesis in RCC

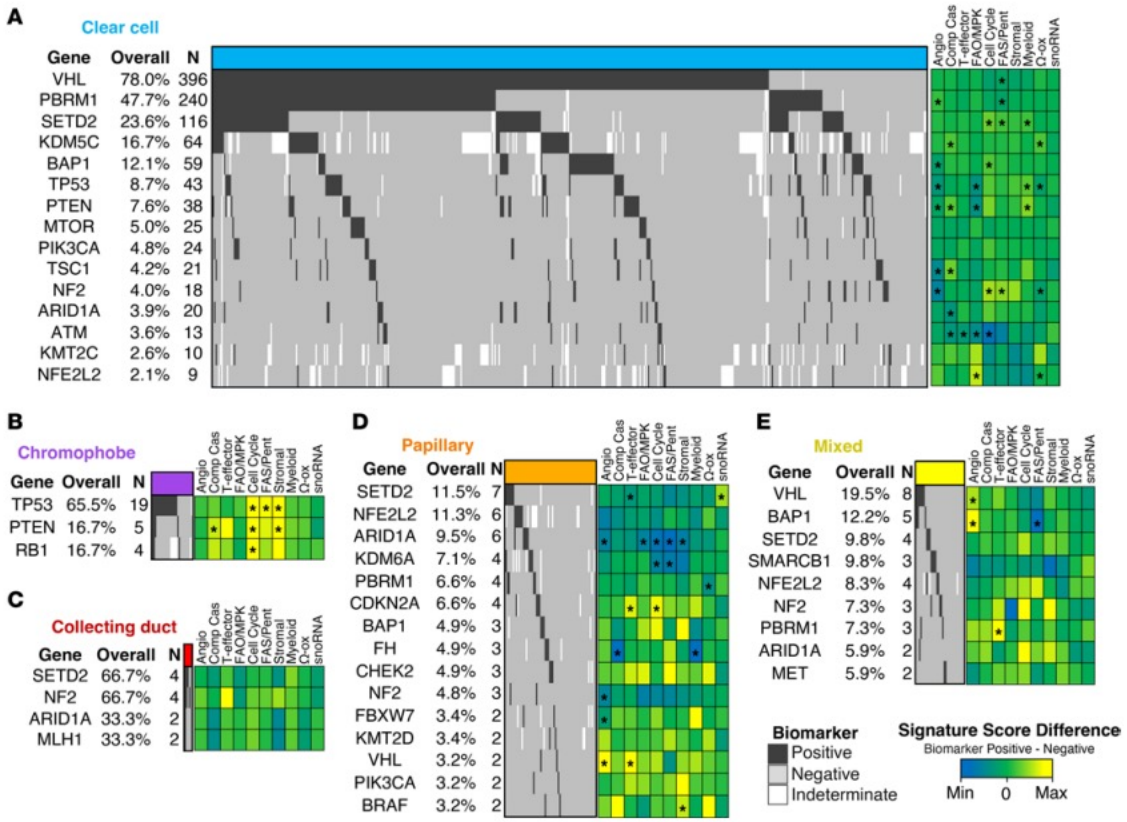
Identification of the von Hippel–Lindau Disease Tumor Suppressor Gene

Farida Latif, Kalman Tory, James Gnarra, Masahiro Yao, Fuh-Mei Duh, Mary Lou Orcutt, Thomas Stackhouse, Igor Kuzmin, William Modi, Laura Geil, Laura Schmidt, Fangwei Zhou, Hua Li, Ming Hui Wei, Fan Chen, Gladys Glenn, Peter Choyke, McClellan M. Walther, Yongkai Weng, Dah-Shuhn R. Duan, Michael Dean, Damjan Glavač, Frances M. Richards, Paul A. Crossey, Malcolm A. Ferguson-Smith, Denis Le Paslier, Ilya Chumakov, Daniel Cohen, A. Craig Chinault, Eamonn R. Maher,* W. Marston Linehan,* Berton Zbar,* Michael I. Lerman*

A gene discovered by positional cloning has been identified as the von Hippel–Lindau (VHL) disease tumor suppressor gene. A restriction fragment encompassing the gene showed rearrangements in 28 of 221 VHL kindreds. Eighteen of these rearrangements were due to deletions in the candidate gene, including three large nonoverlapping deletions. Intragenic mutations were detected in cell lines derived from VHL patients and from sporadic renal cell carcinomas. The VHL gene is evolutionarily conserved and encodes two widely expressed transcripts of approximately 6 and 6.5 kilobases. The partial sequence of the inferred gene product shows no homology to other proteins, except for an acidic repeat domain found in the procyclic surface membrane glycoprotein of *Trypanosoma brucei*.

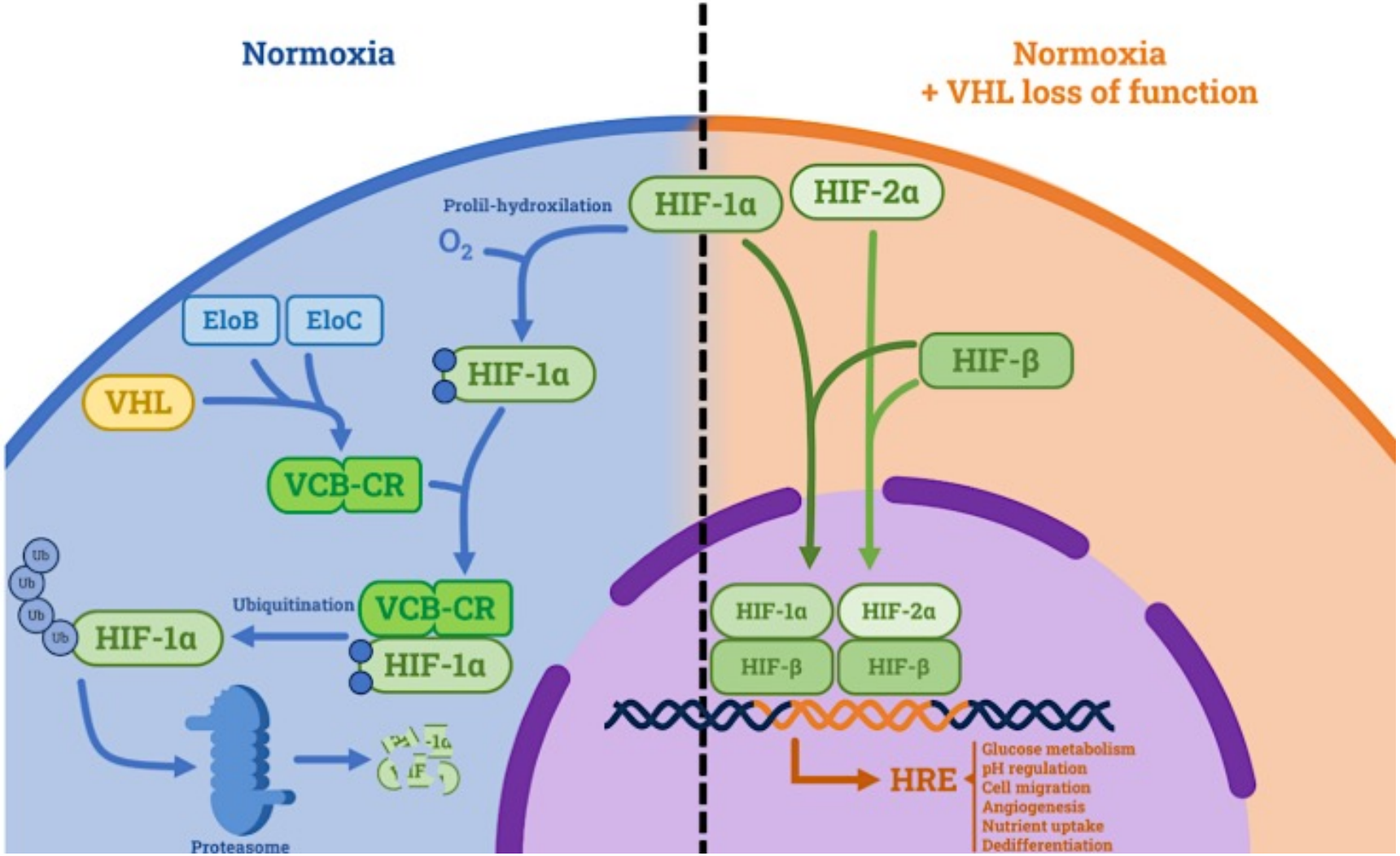
The Journal of Clinical Investigation

RESEARCH ARTICLE



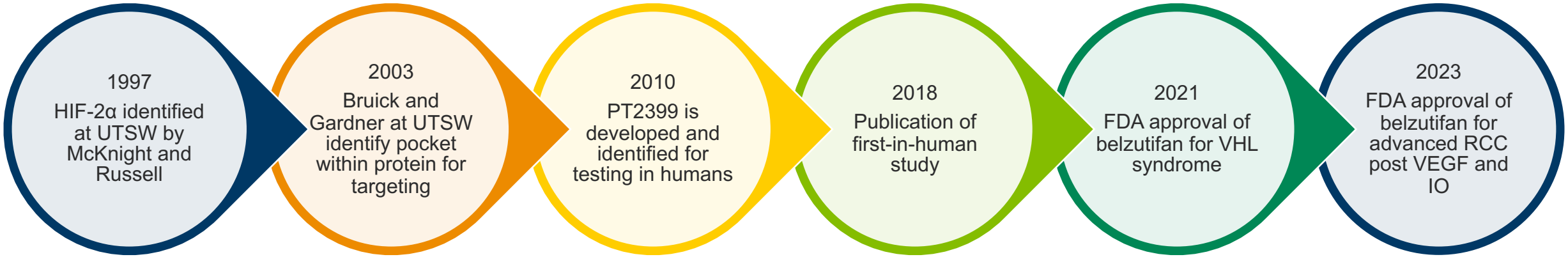
Latif et al, Science, 1993
Barata et al, JCI, 2024

HIF-VHL Pathway in RCC for Pathogenesis

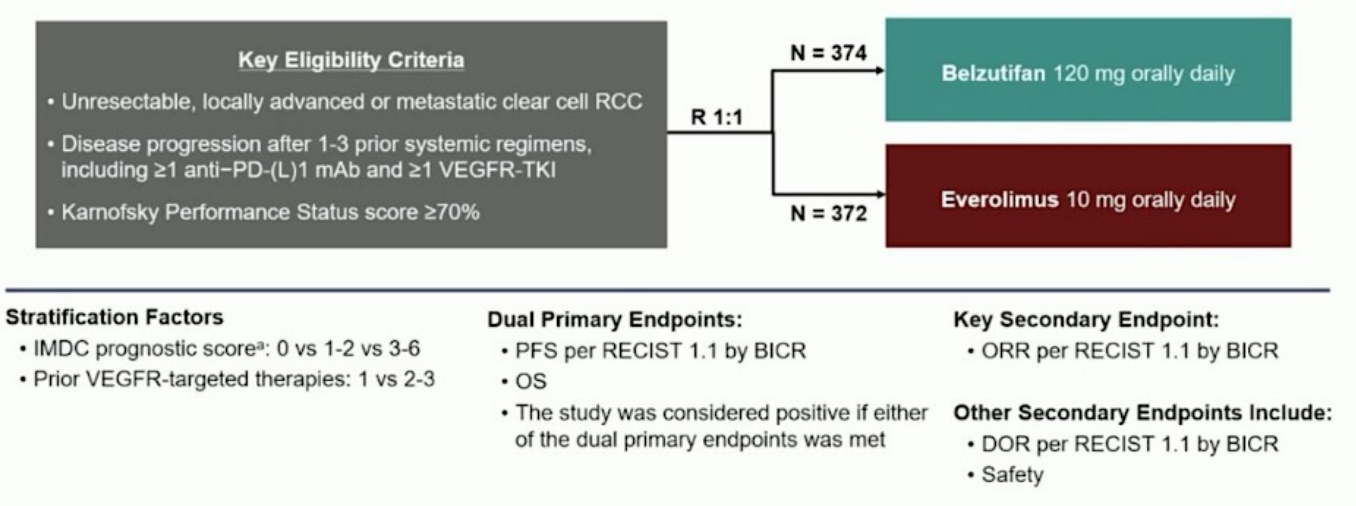


Pezzicoli et al, Current Oncology, 2023

Targeting HIF-2α and Belzutifan Drug Discovery



LITESPARK-005 – Study Design and Patients

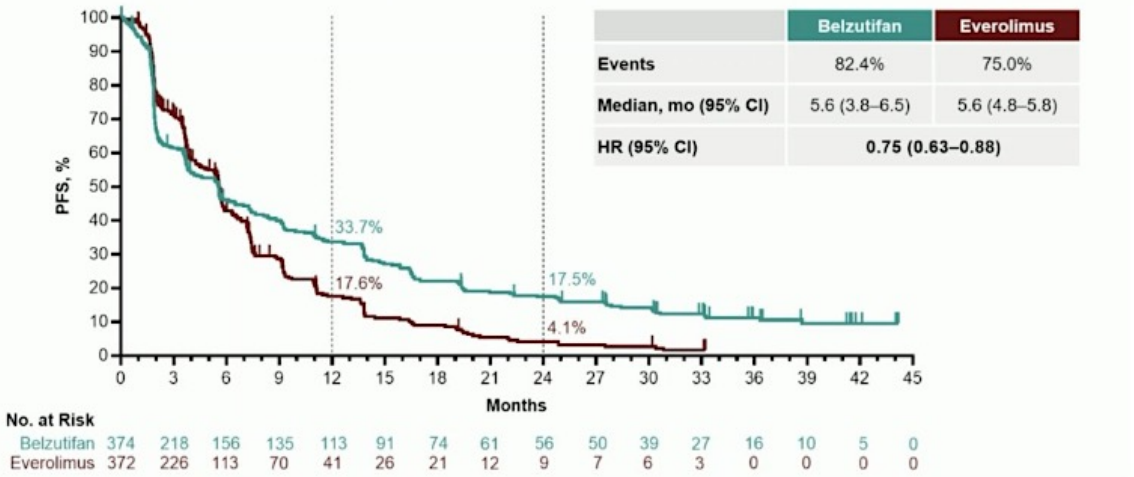


Characteristic	ITT		Ongoing Treatment
	Belzutifan (N = 374)	Everolimus (N = 372)	Belzutifan (n = 54)
Age, median (range), yrs	62 (22–90)	63 (33–87)	64 (44–79)
Male, %	79.4	76.3	81.5
KPS score[a], %			
90/100	63.6	64.5	81.5
70/80	36.1	35.2	18.5
IMDC risk categories, %			
Favorable	21.7	22.6	31.5
Intermediate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

Rini et al, ESMO, 2024

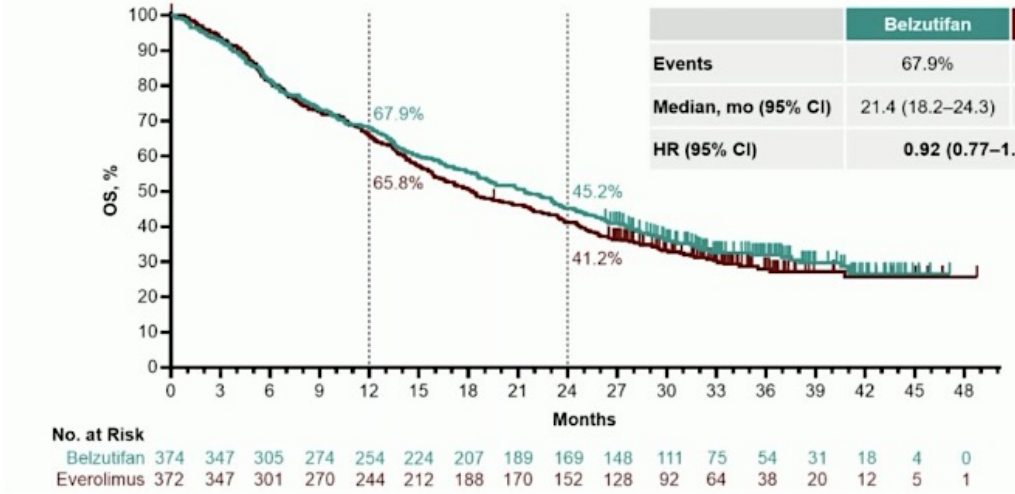
LITESPARK-005 – PFS, OS, ORR

Primary Endpoint: PFS per RECIST 1.1 by BICR



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

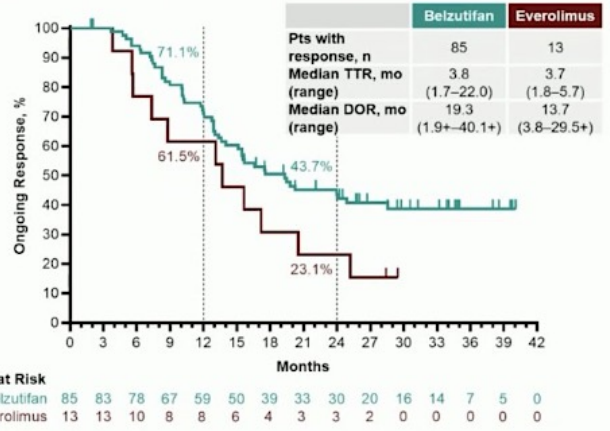
Primary Endpoint: OS



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

ORR (Key Secondary) and DOR (Secondary Endpoint) by BICR per RECIST 1.1

	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%



	Belzutifan	Everolimus
Pts with response, n	85	13
Median TTR, mo (range)	3.8 (1.7–22.0)	3.7 (1.8–5.7)
Median DOR, mo (range)	19.3 (1.9+–40.1+)	13.7 (3.8–29.5+)

Rini et al, ESMO, 2024

Efficacy Outcomes with Belzutifan versus Everolimus by Baseline Disease Characteristics and Burden Subgroups in the Phase 3 LITESPARK-005 Study

de Velasco G et al.

Genitourinary Cancers Symposium 2025;Abstract 538.

February 15, 2025

Poster Session

LITESPARK-005: Efficacy by Baseline Disease Characteristics and Tumor Burden

	Bone mets, yes		Bone mets, no		Liver mets, yes		Liver mets, no		Sum target lesion diameters, < median		Sum target lesion diameters, ≥ median	
	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve
N	187	181	187	191	89	103	285	269	174	193	198	171
PFS, median, mo	3.7	4.3	7.0	6.3	4.6	3.7	5.6	5.8	7.3	5.7	4.2	4.8
PFS HR	0.88		0.65		0.55		0.84		0.67		0.80	
(95% CI)	(0.69–1.11)		(0.51–0.82)		(0.39–0.77)		(0.69–1.02)		(0.52–0.86)		(0.63–1.01)	
OS, median, mo	15.0	15.1	26.5	23.7	19.1	12.9	21.7	21.8	26.4	26.5	17.3	12.3
OS HR	0.95		0.89		0.63		1.06		0.95		0.76	
(95% CI)	(0.75–1.20)		(0.69–1.15)		(0.45–0.88)		(0.86–1.30)		(0.73–1.24)		(0.61–0.96)	
ORR, %	17.6	2.8	27.8	4.2	24.7	3.9	22.1	3.3	28.7	4.1	17.7	2.9

Bel=belzutifan; eve=everolimus; mets=metastasis.

de Velasco G et al. Genitourinary Cancers Symposium 2025;Abstract 538.

LITESPARK-013 – Study Schema and Results

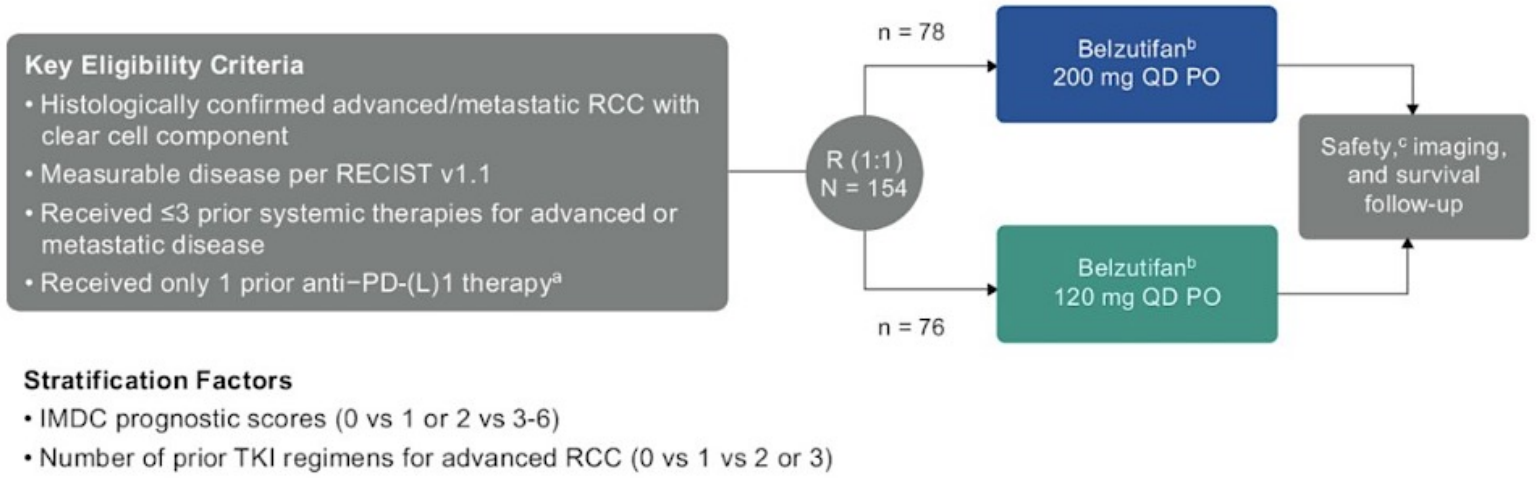


Table 2. Best objective response per RECIST version 1.1 as assessed by BICR

	Belzutifan 200 mg (*n* = 78)	Belzutifan 120 mg (*n* = 76)
ORR (CR + PR)	18 (23.1)	18 (23.7)
Estimated difference, % (95% CI)	−0.5 (−14.0 to 12.9); one-sided *P* = 0.5312	
Best response		
CR	4 (5.1)	0 (0)
PR	14 (17.9)	18 (23.7)
Stable disease	43 (55.1)	39 (51.3)
Stable disease ≥6 months	32 (41.0)	36 (47.4)
Progressive disease	12 (15.4)	15 (19.7)
No assessment[a]	5 (6.4)	4 (5.3)

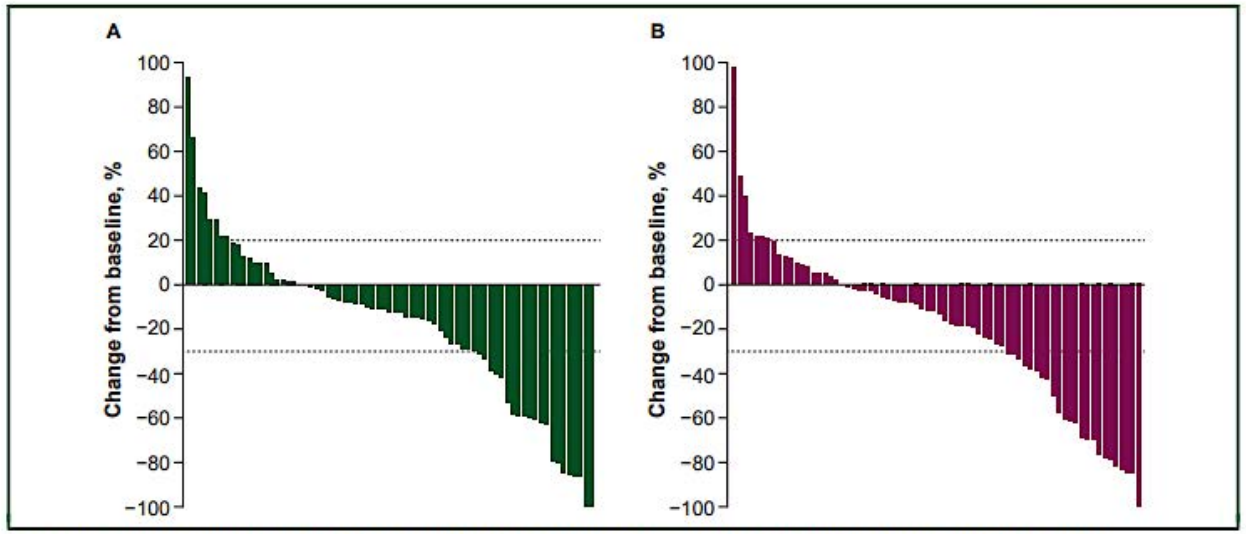
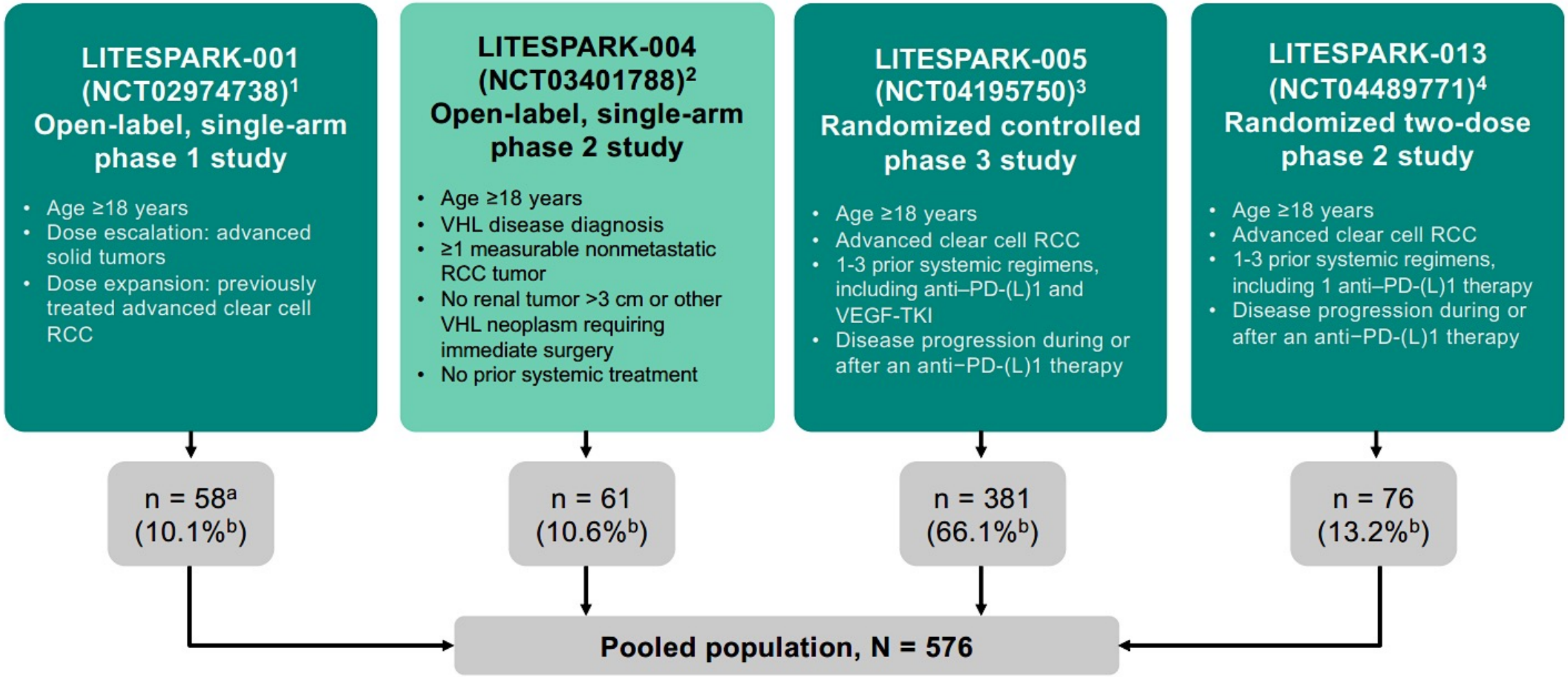


Figure 2. Best percentage change from baseline as assessed by blinded independent central review in the (A) 200 mg and (B) 120 mg groups.

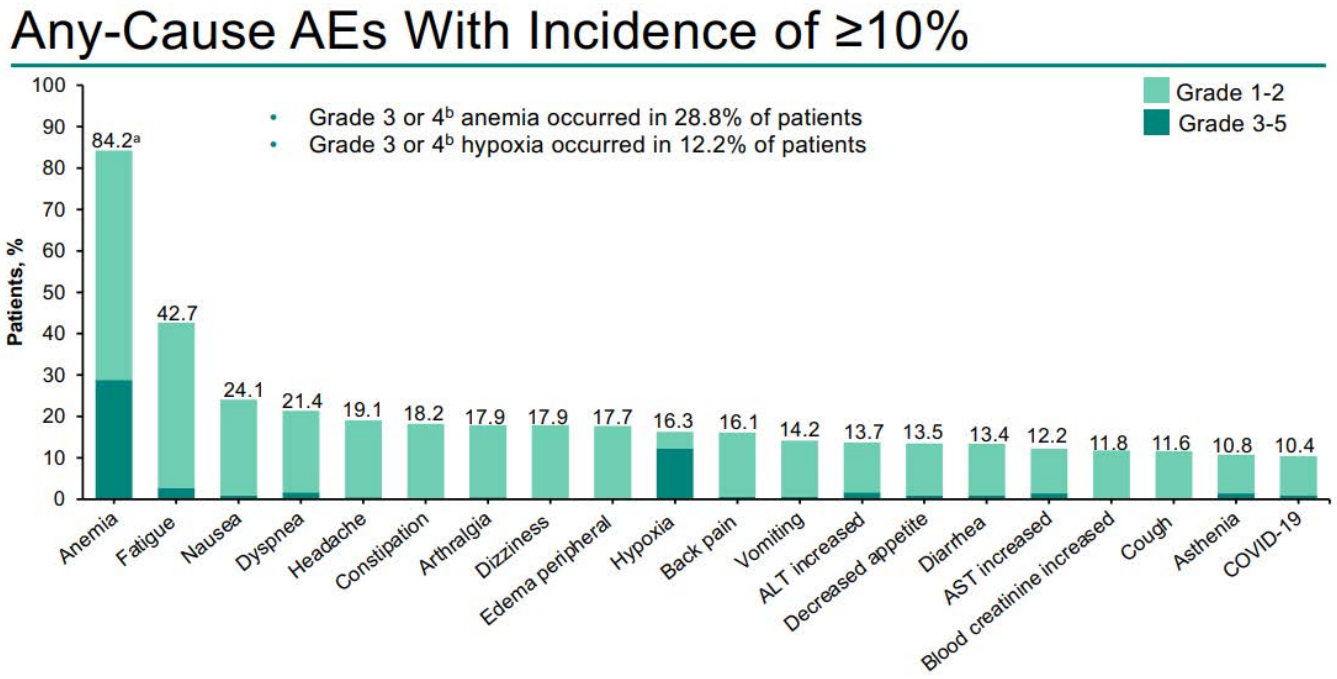
Agarwal et al, Annals of Oncology, 2024

Belzutifan Safety



Choueiri et al, KCRS, 2024

Belzutifan Adverse Events



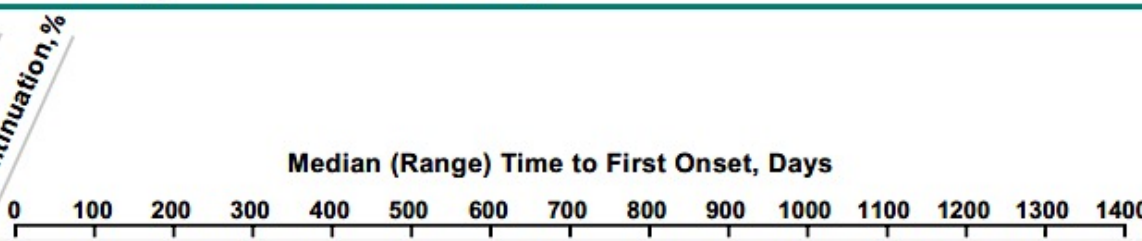
- Any cause grade 3-5 AEs – 61.6%
- Treatment related grade 3-5 AEs – 37.7%
- Treatment discontinuation – 6.4%
- Anemia management
  - ESA only 22.9%
  - Blood transfusions 17.5%
  - ESA and blood transfusions 12.8%

Choueiri et al, KCRS, 2024

Belzutifan Adverse Events Time of Onset

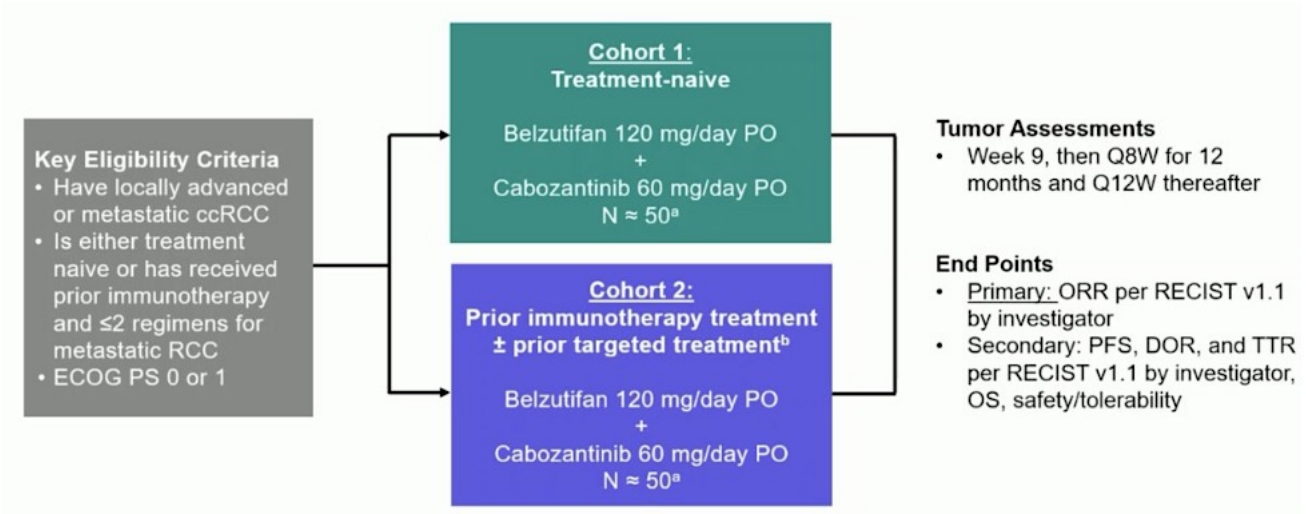
Time to First Onset of Common Any-Grade AEs Attributed to Belzutifan (Adverse Drug Reactions)

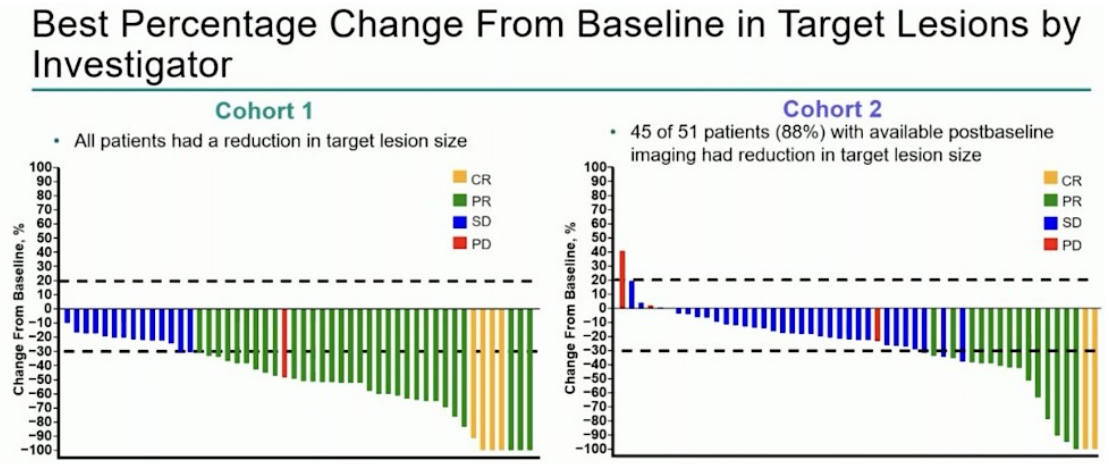
AE	Incidence n	Incidence %	Dose interruption, %	Dose reduction, %	Treatment discontinuation, %	Median (Range) Time to First Onset, Days
Anemia[a]	485	84.2	7.1	3.8	0.3	29 (Min: 1 / Max: 834)
Hypoxia	94	16.3	5.4	6.3	1.4	31 (Min: 1/ Max: 952)
Fatigue	246	42.7	2.6	1.7	0.2	42 (Min: 1 / Max: 1017)
Nausea	139	24.1	2.4	0.3	0.2	43 (Min: 1 / Max: 1346)
Dizziness	103	17.9	1.6	0	0.2	49 (Min: 1 / Max: 974)
Dyspnea	123	21.4	1.7	0.5	0.2	57 (Min: 1 / Max: 911)
Weight increased	44	7.6	0	0	0	111 (Min: 4 / Max: 671)



Choueiri et al, KCRS, 2024

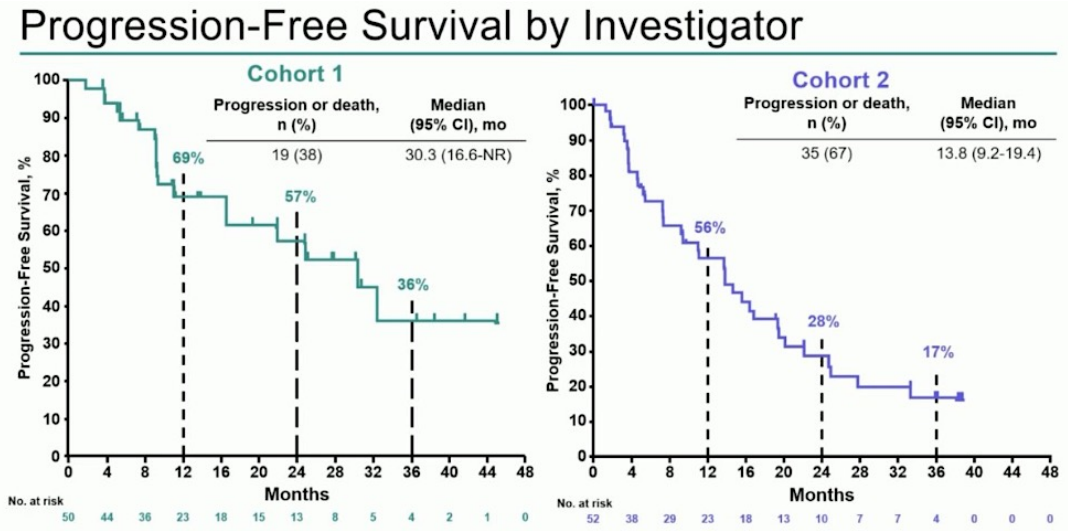
LITESPARK-003 – Belzutifan + Cabozantinib





ORR by Investigator in All Patients and by IMDC Risk

	Cohort 1			Cohort 2		
	Overall N = 50	IMDC risk category		Overall N = 52	IMDC risk category	
		Favorable n = 28	Intermediate/ poor n = 22		Favorable n = 11	Intermediate/ poor n = 41
ORR (CR + PR)	**35 (70)**	22 (79)	13 (59)	**16 (31)**	3 (27)	13 (32)
DCR (CR + PR + SD)	49 (98)	28 (100)	21 (96)	48 (92)	11 (100)	37 (90)
Best response						
CR	4 (8)	3 (11)	1 (5)	2 (4)	0	2 (5)
PR	31 (62)	19 (68)	12 (55)	14 (27)	3 (27)	11 (27)
SD	14 (28)	6 (21)	8 (36)	32 (62)	8 (73)	24 (59)
PD	1 (2)	0 (0)	1 (5)	3 (6)	0 (0)	3 (7)
Not available[a]	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)



Choueiri et al, ESMO, 2023. Choueiri et al, *Lancet Oncol* 2025;26(1):64-73.

Updated Results from the Phase 2 LITESPARK-003 Study of Belzutifan plus Cabozantinib in Patients with Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

Choueiri TK et al.

Genitourinary Cancers Symposium 2025;Abstract 549.

February 15, 2025

Poster Session

LITESPARK-003: Updated Efficacy Analysis

	Cohort 1	Cohort 2
IMDC risk category		
Favorable	n = 33 ORR, 73% (95% CI, 54-87); 5 CRs, 19 PRs	n = 9 ORR, 67% (95% CI, 30-93); 1 CR, 5 PRs
Intermediate or poor	n = 17 ORR, 65% (95% CI, 38-86); 1 CR, 10 PRs	n = 43 ORR, 23% (95% CI, 12-39); 1 CR, 9 PRs
Baseline tumor burden[a]		
Low (< median)	n = 25 ORR, 80% (95% CI, 59-93); 3 CRs, 17 PRs	n = 26 ORR, 27% (95% CI, 12-48); 2 CRs, 5 PRs
High (≥ median)	n = 25 ORR, 60% (95% CI, 39-79); 3 CRs, 12 PRs	n = 26 ORR, 35% (95% CI, 17-56); 0 CRs, 9 PRs

[a]Based on the sum of diameter of the target lesions at baseline.

Choueiri TK et al. Genitourinary Cancers Symposium 2025;Abstract 549.

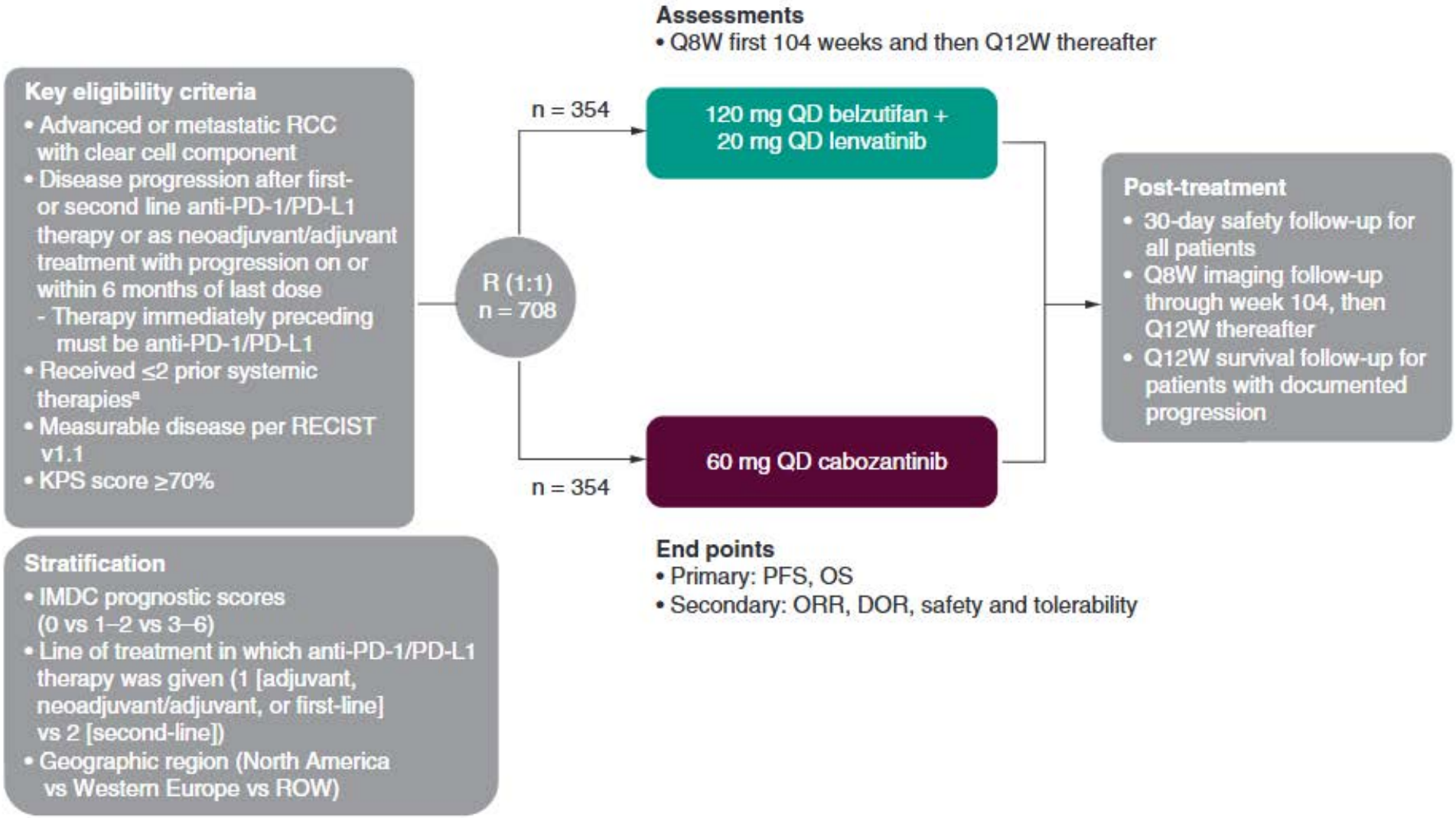
KEYMAKER-U03 Substudy 03B: Pembrolizumab (pembro) and targeted therapy combinations for advanced clear cell renal cell carcinoma (ccRCC).

Laurence Albiges, Cristina Suárez, Thomas Powles, Robert J. Motzer, Walter Michael Stadler, Wilson H. Miller Jr., Carlos Rojas, Avivit Peer, Jeffrey C. Goh, Se Hoon Park, Tom Waddell, Philippe Barthelemy, Pablo Gajate, Andrew Weickhardt, Guy Faust, Rodolfo F. Perini, Lockman Bousserouel, Ding Wang, Hans J. Hammers, Katy Beckermann; Gustave Roussy, Paris-Saclay University, Villejuif, France; Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute and Queen Mary University of London, London, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Chicago, Chicago, IL; Jewish General Hospital, Montréal, QC, Canada; Bradford Hill, Santiago, Chile; Rambam Health Care Campus, Haifa, Israel; Royal Brisbane & Women's Hospital, Herston, QLD, Australia; Sungkyunkwan University Samsung Medical Center, Seoul, Korea, Republic of; Christie Hospital, Manchester, United Kingdom; Institut de cancérologie Strasbourg Europe, Strasbourg University Hospital, Strasbourg, France; Ramón y Cajal University Hospital, Madrid, Spain; Olivia Newton John Cancer Research Institute, Heidelberg, VIC, Australia; University Hospitals of Leicester NHS Trust, Leiceste, United Kingdom; Merck & Co., Inc., Rahway, NJ; UT Southwestern Medical Center, Dallas, TX; Vanderbilt University Medical Center, Nashville, TN

	Arm B4 Pembro + belzutifan n = 62	Arm B5 Lenvatinib + belzutifan n = 64	Ref arm Pembro + lenvatinib n = 73
ORR (95% CI), %	19 (10-31)	47 (34-60)	40 (29-52)
CR, n (%)	2 (3)	1 (2)	0 (0)
PR, n (%)	10 (16)	29 (45)	29 (40)
CBR (95% CI), %	32 (21-45)	59 (46-72)	58 (45-69)
DOR, median (range), mo	Not reached (1.4+-33.0+)	22.1 (1.4+-32.8+)	8.3 (2.6+-25.6+)
PFS, median (95% CI), mo	5.4 (2.8-6.9)	12.5 (5.9-26.3)	9.4 (6.9-11.2)
6-mo PFS rate, %	42	63	67
OS, median (95% CI), mo	27.4 (12.6-not reached)	32.3 (22.4-not reached)	Not reached (21.8-not reached)
12-mo OS rate, %	68	80	82

Albiges L et al. Genitourinary Cancers Symposium 2025;Abstract 440.

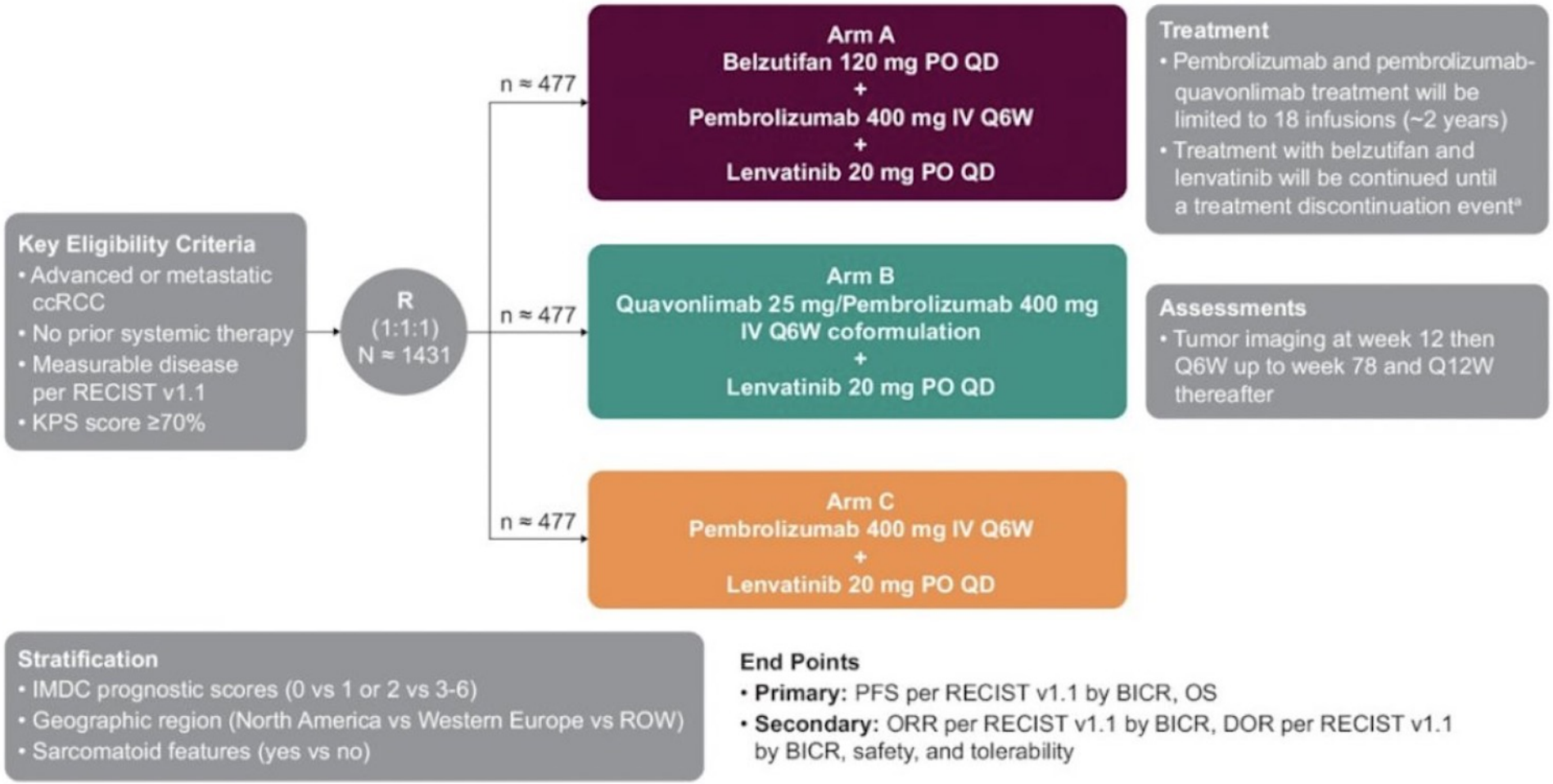
LITESPARK-011 – Belzutifan + Lenvatinib



Motzer RJ et al. *Future Oncol* 2023;19(2):113-121.

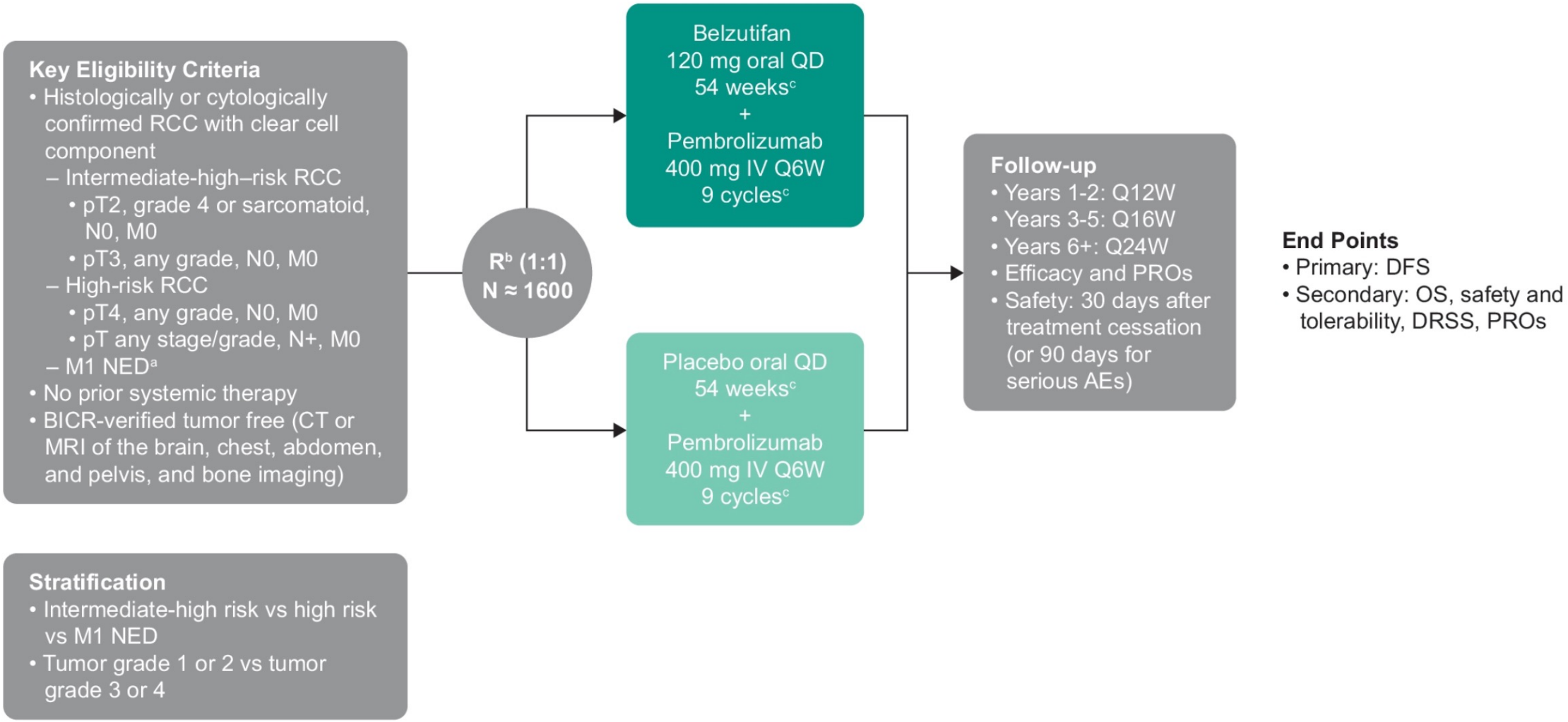
LITESPARK-012 – Belzutifan in Frontline RCC

Figure 1. Study design



Choueiri TK et al. *Future Oncol* 2023;19(40):2631-2640.

LITESPARK-022 – Adjuvant Therapy with Belzutifan + Pembrolizumab



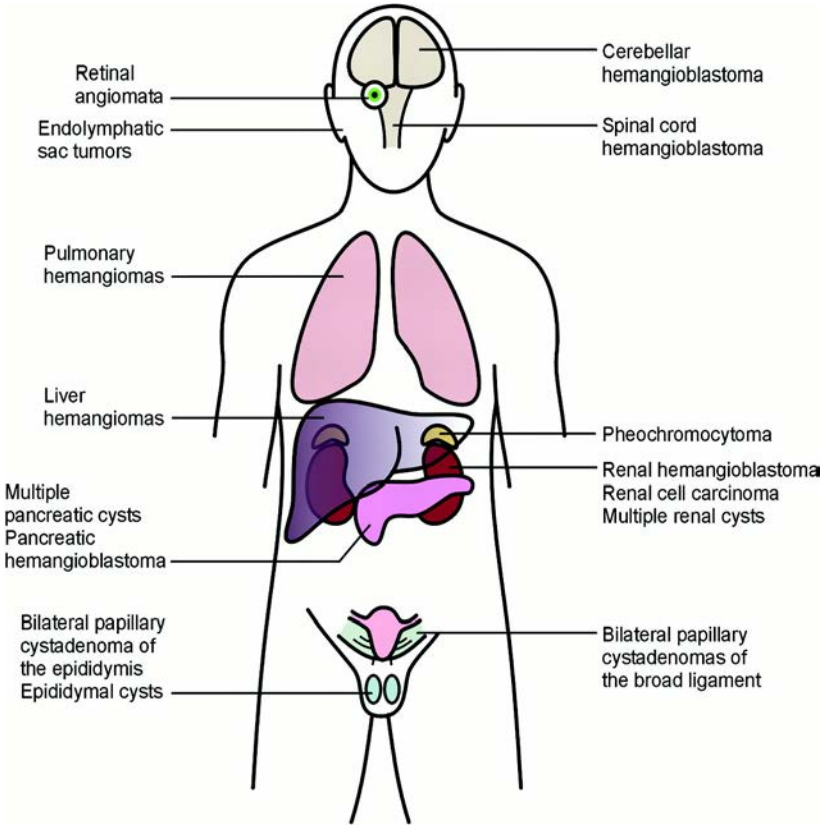
Choueiri TK et al. Genitourinary Cancers Symposium 2023;Abstract TPS748.

Von Hippel-Lindau Syndrome

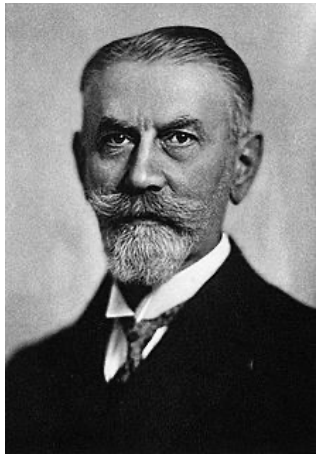
1904
von Hippel first describes angiomas in the eye

1927
Lindau first describes angiomas in the cerebellum and spine

1936
Term Von-Hippel-Lindau disease first use



Eugene von Hippel



(Aus der Universitäts-Augenklinik zu Heidelberg.)

Über eine sehr seltene Erkrankung der Netzhaut.

Klinische Beobachtungen.

Von

Prof. Eugen v. Hippel
in Heidelberg.

Mit Tafel III—VI, Fig. 1—5.

Im Jahre 1895 stellte ich in der Demonstrationssitzung des Heidelberger Kongresses einen Patienten mit einer sehr ungewöhnlichen Erkrankung der Netzhaut vor, in der Hoffnung eine Belehrung darüber zu erhalten, wie der Fall zu deuten sei. Von den zahlreichen Untersuchern schien niemand einen analogen gesehen zu haben, eine Ansicht über das Wesen der Sache wurde nur von v. Michel geäussert, der sich zuerst für die Annahme eines Tumors, dann für Tuberkulose aussprach. Der Fall wurde von mir verfolgt, bis das Auftreten von Katarakt eine weitere ophthalmoskopische Beobachtung unmöglich machte. Am 15. VIII. 1896 sah ich einen zweiten vollkommen analogen Fall; ich konnte damals nur ein paar kurze Notizen machen, da der Patient, den ich zum Zeichnen des Befundes bestellt hatte, ausblieb und erst fünf Jahre später wieder erschien.

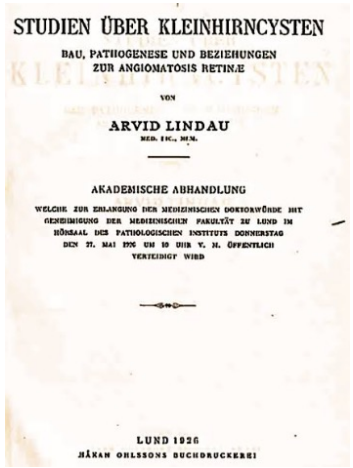
Die beiden Beobachtungen betreffen ein offenbar sehr seltenes Krankheitsbild, ich fand zunächst in der Literatur nur einen analogen Fall. Als ich beim vorjährigen Heidelberger Kongress meine Abbildungen zeigte und kurz erläuterte, wurde ich noch auf drei Veröffentlichungen [1]) aufmerksam gemacht, in welchen ähnliche Beobachtungen mitgeteilt wurden, ausserdem führten Sattler, Wagenmann und Herzog je einen derartigen Fall an, den sie zu untersuchen und behandeln Gelegenheit hatten.

[1]) Fall Leplat, v. Dzialowski und Goldzieher. (Vgl. die späteren kritischen Bemerkungen.)

64*

German Ophthalmologist

Arvid Lindau



STUDIEN ÜBER KLEINHIRNCYSTEN

BAU, PATHOGENESE UND BEZIEHUNGEN ZUR ANGIOMATOSIS RETINÆ

VON

ARVID LINDAU

MED. DR., DOCENT

AKADEMISCHE ABHANDLUNG

WELCHE ZUR ERLANGUNG DER MEDIZINISCHEN DOKTORWÜRDE MIT GENEHMIGUNG DER MEDIZINISCHEN FAKULTÄT ZU LUND IM HÖRSAAL DES PATHOLOGISCHEN INSTITUTS DONNERSTAG DEN 27. MAI 1926 UM 10 UHR V. M. ÖFFENTLICH VERTEIDIGT WIRD

LUND 1926
HÅKAN OHLSSONS BUCHDRUCKEREI

Swedish Pathologist

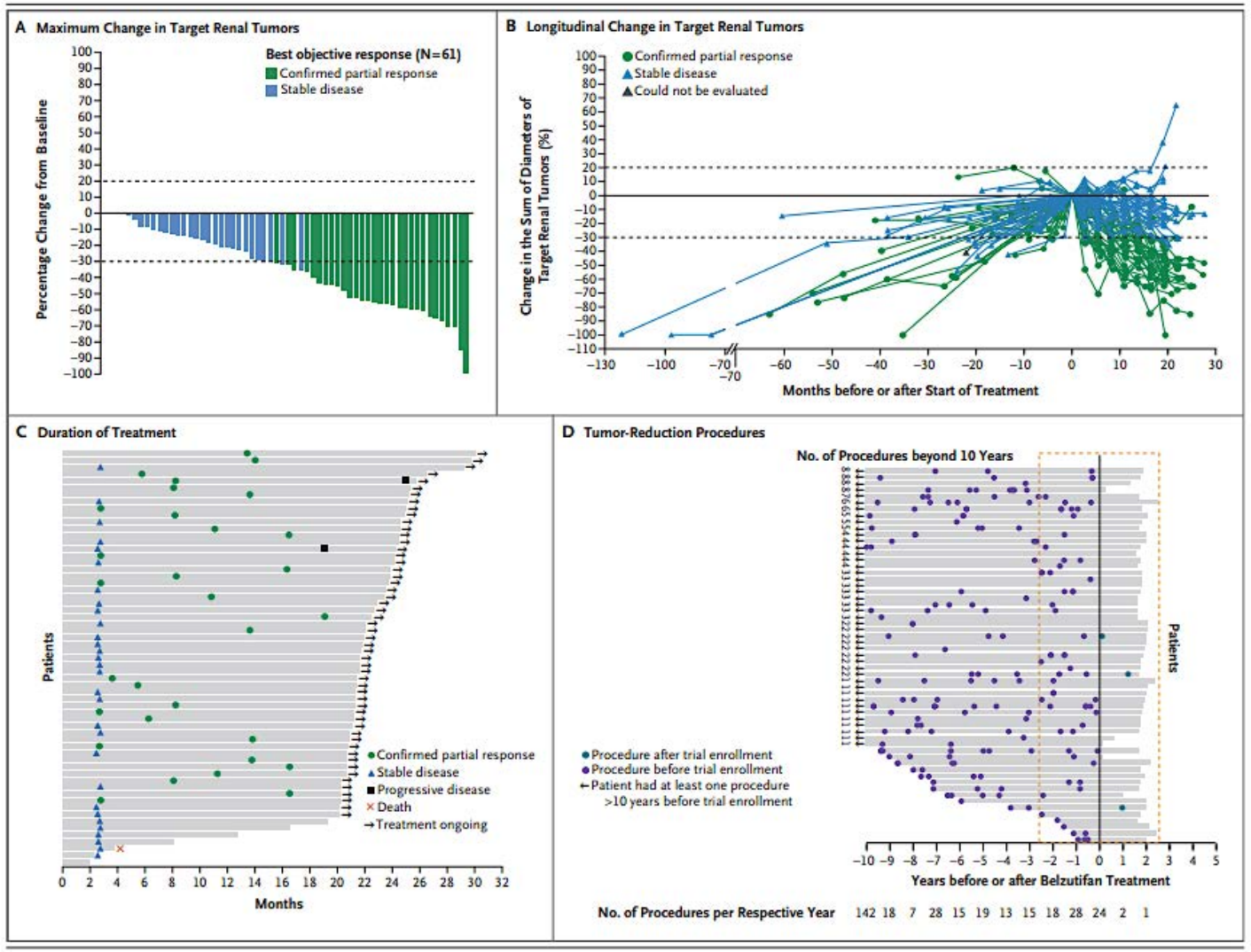
- Autosomal dominant
  - 80% have an affected parent
  - 20% are *de novo*
  - Nearly all patients will express syndrome by age 65
- Incidence of 1 in 36,000
- 2/3 will have RCC

Belzutifan for RCC Associated with VHL Disease

Table 2. Best Objective Response in Renal Cell Carcinoma Associated with VHL Disease.*

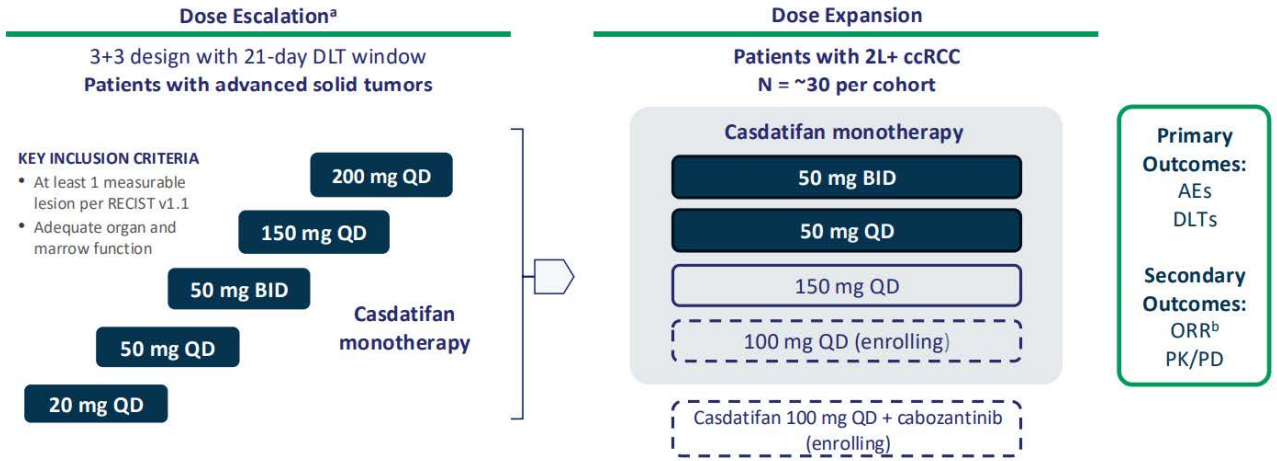
Variable	Efficacy Population (N=61)
Objective response — no. (% [95% CI])	30 (49 [36 to 62])
Best response — no. (%)	
Complete response	0
Partial response	30 (49)
Stable disease	30 (49)
Disease progression	0
Unable to be evaluated†	1 (2)
Median time to response (range) — mo	8.2 (2.7 to 19.1)
Median duration of response (range) — mo‡	NR (2.8+ to 22.3+)

Pancreatic lesions – 77%
CNS hemangioblastomas – 30%
Retinal hemangioblastomas – 100%



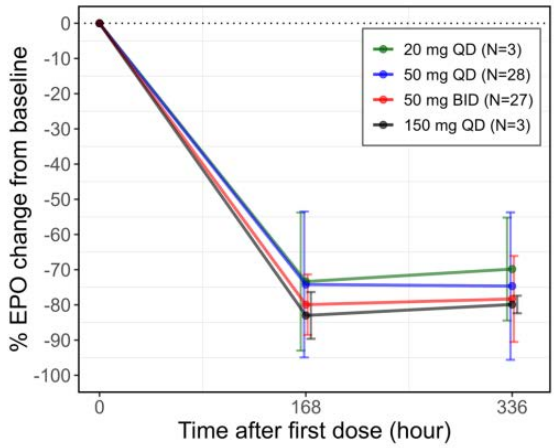
Jonasch et al, NEJM, 2021

Casdatifan Development



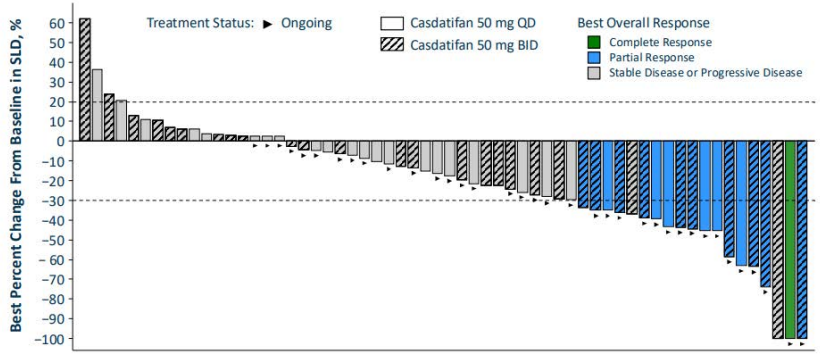
Characteristic	Dose Escalation Advanced Solid Tumors[a]	Dose Expansion 2L+ ccRCC	
	20 mg – 200 mg (n = 22)	50 mg BID (n = 33)	50 mg QD (n = 31)
Age, years, median (range)	66 (49–78)	62 (41–79)	65 (43–82)
Sex, female/male, n (%)	12 (55) / 10 (45)	8 (24) / 25 (76)	10 (32) / 21 (68)
ECOG PS 0/1, n (%)	5 (23) / 17 (77)	16 (48) / 17 (52)	18 (58) / 13 (42)
IMDC risk score, n (%)			
Favorable	NA	9 (27)	8 (26)
Intermediate		20 (61)	16 (52)
Poor		2 (6)	5 (16)
Unknown		2 (6)	2 (6)
Number of regimens, all settings, n (%) 1/2/3/4 or more	**4 (18) / 2 (9) / 6 (27) / 10 (45)**	**2 (6) / 14 (42) / 8 (24) / 9 (27)**	**5 (16) / 9 (29) / 8 (26) / 9 (29)**
Patients with both VEGFR-TKI and PD-1/PD-L1 inh, n (%)	12 (55)	33 (100)	31 (100)
Number of regimens with any VEGFR-TKI, n (%) 1/2/3/4 or more	3 (14) / 5 (23) / 3 (14) / 2 (9)	13 (39) / 12 (36) / 3 (9) / 5 (15)	15 (48) / 8 (26) / 5 (16) / 3 (10)
Number of patients with prior mTOR treatment, n (%)	NA	5 (15)	7 (23)

ARC-20 Change in EPO (Mean ± SD) vs Time in Patients With ccRCC and Other Solid Tumors[2]



Efficacy Evaluable Population	Dose Expansion 50 mg BID (n = 32)	Dose Expansion 50 mg QD (n = 28)
Median follow-up [ongoing], months (range)	**11 (3–15+)**	**8 (4–10+)**
ORR, %, n (90% CI)	**31.3%, 10[a] (16.1, 50.0)**	**25.0%, 7 (10.7, 44.9)**
Responses pending confirmation, n	1	1
Confirmed ORR, %, n (90% CI)	**25.0%, 8 (11.5, 43.4)**	**21.4%, 6 (8.3, 41.0)**
Time to response, months, median (range)	2.8 (1.2–5.5)	4 (1.3–4.1)
Patients with progressive disease, %, n	**18.8%, 6**	**14.3%, 4**
Disease control rate (90% CI)	81.3% (63.6, 92.8)	85.7% (67.3, 96.0)
Median progression-free survival	Not reached	Not reached

[a]One patient in 50 mg BID cohort had a new response (also pending confirmation) after data cutoff date; updated ORR, 34.4%



Choueiri et al, EOORTC-NCI-AACR Symposium, 2024

Casdatifan (Cas) monotherapy in patients (pts) with previously treated clear cell renal cell carcinoma (ccRCC): Safety, efficacy and subgroup analysis across multiple doses from ARC-20, a phase 1 open-label study.

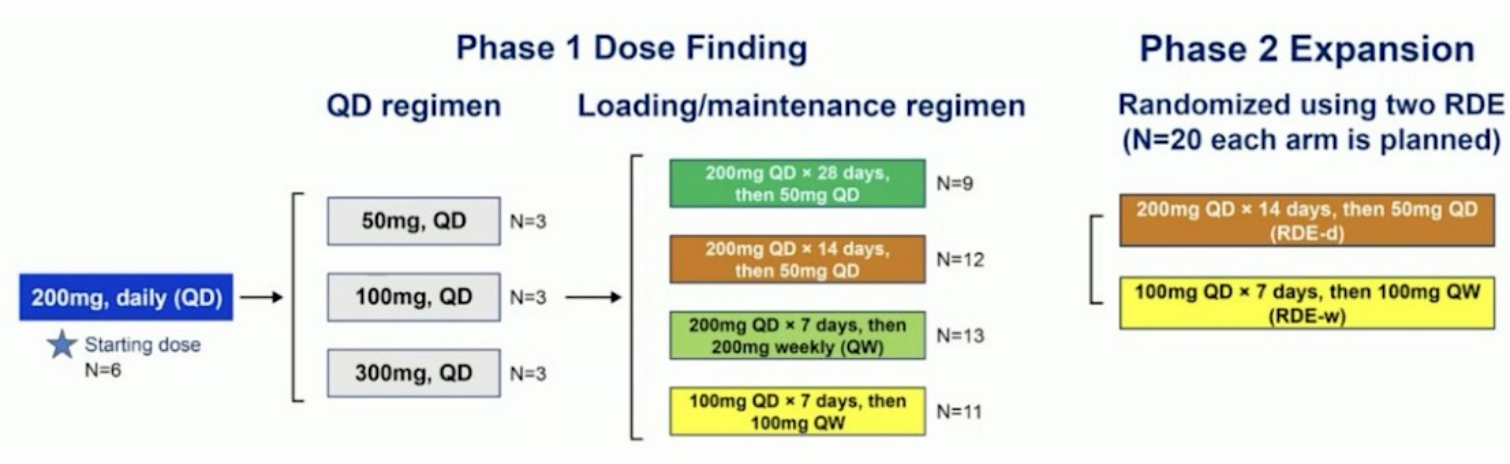
Toni K. Choueiri, Jae Lyun Lee, Jaime R. Merchan, Amita Patnaik, Benjamin Garmezy, Alexandra Drakaki, Moshe C. Ornstein, Bradley Alexander McGregor, Ralph J. Hauke, Kai Tsao, Brian I. Rini, Pedro C. Barata, Paul G. Foster, Sutapa Mukhopadhyay, Neal Gupta, Jianfen Chen, Manish Monga, Dimitry S. A. Nuyten, Sun Young Rha; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Democratic People's Republic of; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; The START Center for Cancer Research, San Antonio, TX; Sarah Cannon Research Institute, Nashville, TN; University of California, Los Angeles, Los Angeles, CA; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Dana Farber Cancer Institute, Boston, MA; Nebraska Cancer Specialists, Omaha, NE; The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Vanderbilt-Ingram Cancer Center, Nashville, TN; University Hospitals Seidman Cancer Center, Cleveland, OH; Arcus Biosciences, Hayward, CA; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Seoul, Korea, Democratic People's Republic of

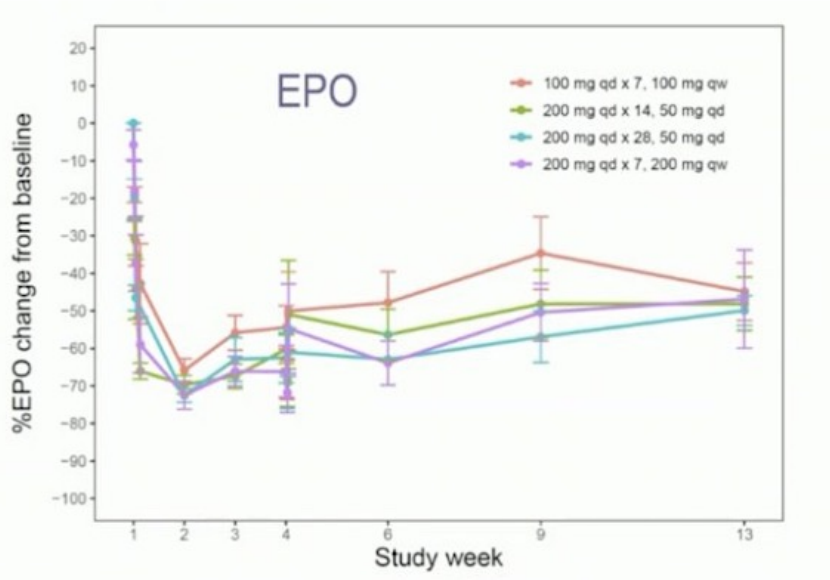
	Cas 50 mg BID (n = 32[a])	Cas 50 mg QD (n = 28[a])	IDMC Favorable (n=15)	IMDC intermediate/ poor/un-known (n=45)	Without prior mTOR inhibitor treatment (n=51)	With prior mTOR inhibitor treatment (n=9)
Unconfirmed ORR, % (n) (95% CI)	34 (11[b]) (19, 53)	25 (7) (11, 45)	40 (6) (16, 68)	27 (12) (15, 42)	31 (16) (19, 46)	22 (2) (3, 60)
Confirmed ORR, % (n) (95% CI)	25 (8) (11, 43)	21 (6) (8, 41)	33 (5) (12, 62)	20 (9) (10, 35)	26 (13) (14, 40)	1 (11) (<1, 48)
Disease control rate, % (95% CI)	81 (64, 93)	86 (67, 96)	93 (68, 100)	80 (65, 90)	82 (69, 92)	89 (52, 100)

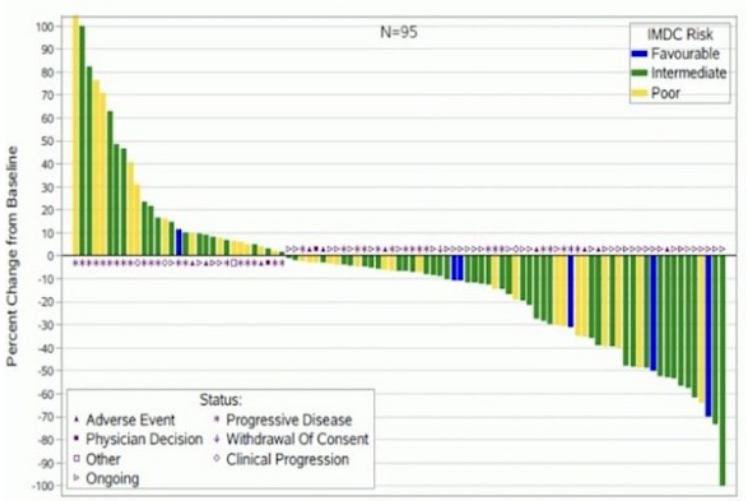
[a]Efficacy-evaluable pts: all pts who had measurable disease at BL, received ≥1 dose and had ≥1 post-BL efficacy assessment, or who discontinued study treatment due to progression or death. Disease control rate: ORR+SD.
[b]Includes 1 pt who achieved PR after data cut-off.

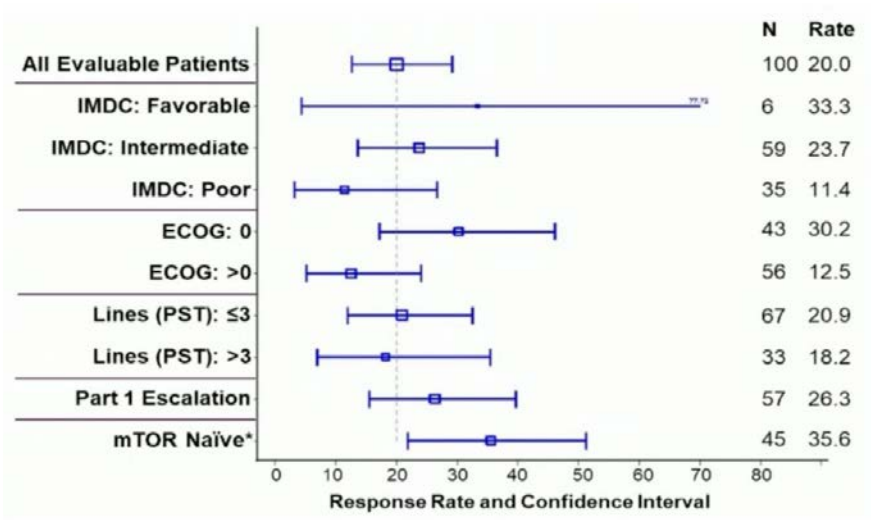
Choueiri TK et al. Genitourinary Cancers Symposium 2025;Abstract 441.

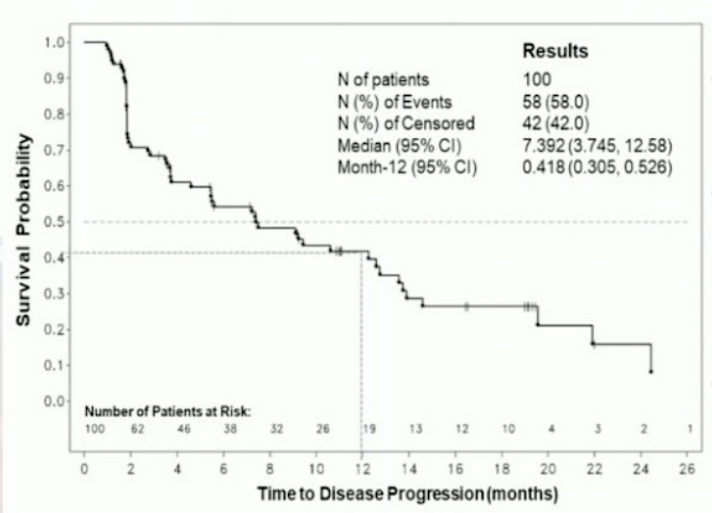
NKT2152 Development











Jonasch et al, ESMO, 2024

Pharmacological and Efficacy Characteristics of HIF-2α Inhibitors

Agent	t1/2	Dosing	Maximum EPO Suppression	Phase	N	ORR (%)	PD (%)	Median PFS (months)	Dose for Expansion
Belzutifan (MK-6482)	14 h	120 mg QD	~60% at 120 mg QD	3	746	22.7%	34%	5.6	120 mg QD
Casdatifan (AB521)	18-24 h	50 mg BID	~80% at 20 mg QD	1	33	34.4%	18.8%	Not reached	100 mg QD
NKT2152	38 d	Loading: 100-200 mg QD (7-28 days) Maintenance: 50 mg QD or 100-200 mg weekly	~72% at higher dose levels	1	100	20%	28%	7.4	Not specified
DFF332	~85 d	Not established	Variable*	1	40	5%	Not specified	Not specified	Discontinued

Rini et al, ESMO, 2024; Choueiri et al, EOORTC-NCI-AACR Symposium, 2024; Jonasch et al, ESMO, 2024

Conclusions

- VHL is mutated in nearly 80% of patients with clear cell RCC and drives RCC pathogenesis
- HIF-2α is a therapeutic target in RCC
- Belzutifan is FDA approved for the treatment of refractory RCC
- On pathway toxicity to belzutifan includes anemia and hypoxia
- Belzutifan is being evaluated in combination with immunotherapy and TKIs in RCC
- Other HIF-2α inhibitors are under development in RCC

Questions from General Medical Oncologists

- **Do you recommend routine screening of VHL alterations in all patients with RCC? Which test do you generally order in your own practice — germline-only testing or comprehensive genome testing using NGS?**
- **What is the best line of therapy for HIF-2α inhibitors (1L, 2L or 3L) for VHL-associated RCC? Should HIF-2α inhibitors be used before or after VEGF inhibitors or immunotherapy?**
- **What is your experience with the use of belzutifan for patients with advanced RCC without VHL alterations? How would you compare the efficacy of belzutifan to that of single-agent TKIs in advanced RCC?**

Questions from General Medical Oncologists

- Would you prefer belzutifan over the established single-agent TKIs (eg, cabozantinib, sunitinib, axitinib) in any circumstances for sporadic RCC?
- How do the experts decide between belzutifan and tivozanib for patients with multiply relapsed RCC and no VHL alterations?
- What is the clinical data supporting the use of HIF-2α inhibitors in combination regimens?
- What are the most common side effects associated with HIF-2α inhibitors?

Questions from General Medical Oncologists

- How should hypoxia associated with HIF-2α inhibitors be managed? Does hypoxia reverse quickly after stopping the drug?
- Is pulmonary function testing necessary before starting HIF-2α inhibitors?
- How should anemia be managed in patients receiving HIF-2α inhibitors? How often do the experts monitor blood counts with belzutifan?

Agenda

Module 1: Immunotherapeutic Strategies for Localized and Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Hutson

Module 2: Optimal Management of Relapsed/Refractory RCC — Dr Zhang

Module 3: Role of HIF-2α Inhibitors in the Treatment of Sporadic and von Hippel-Lindau-Associated RCC — Dr McKay

Module 4: Current and Future Care of Patients with Non-Clear Cell RCC — Dr Pal

Current & Future Care of Patients with Non-Clear Cell RCC

Sumanta K. Pal, MD, FASCO

Professor & Vice Chair of Academic Affairs

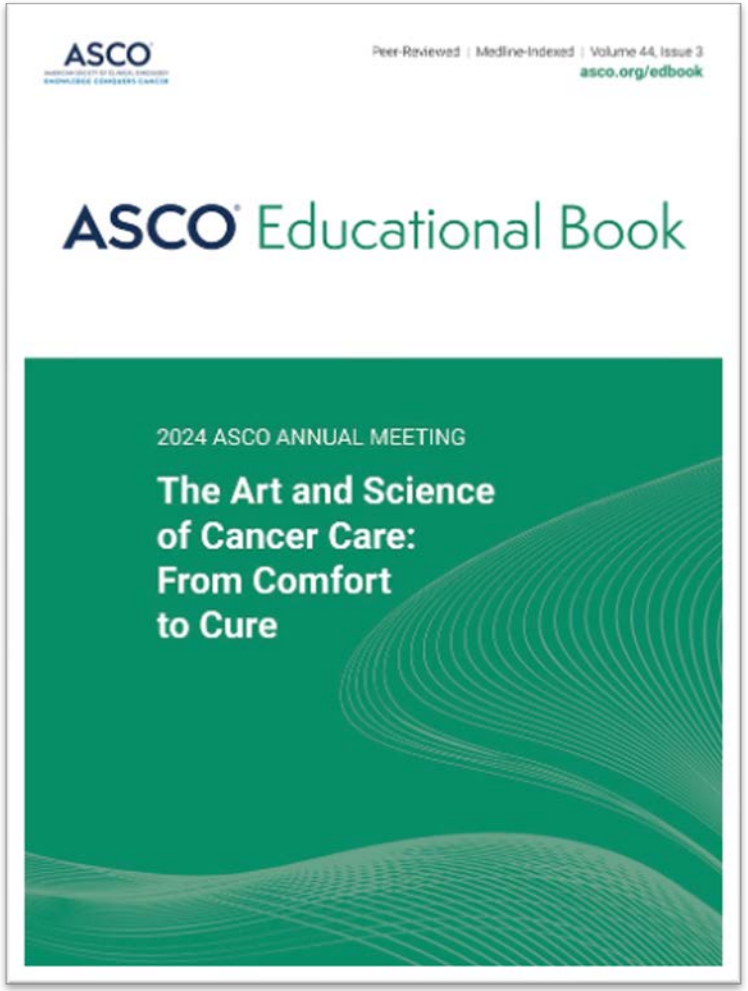
City of Hope Comprehensive Cancer Center

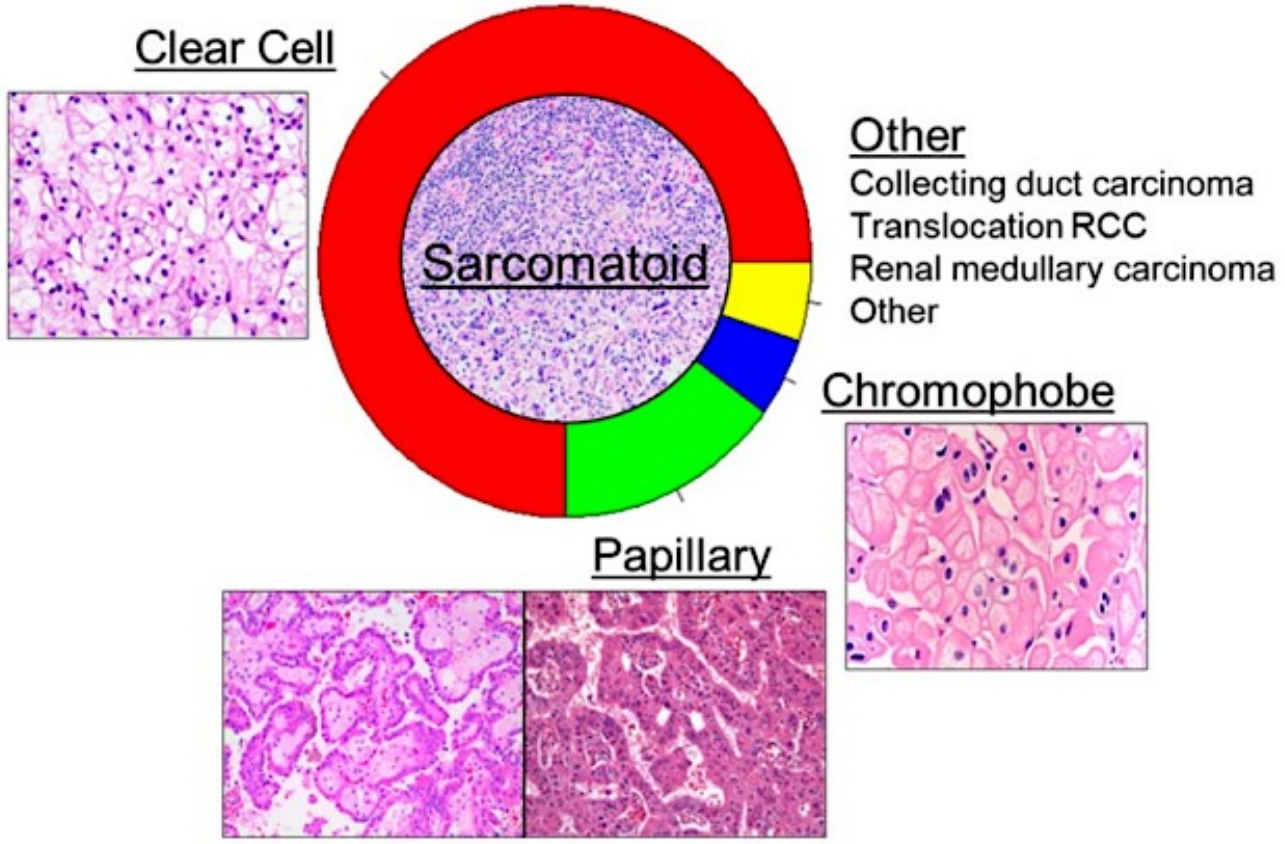
Key Takeaways

For variant histologies of renal cell carcinoma (RCC):

- There have been randomized phase II trials in papillary RCC
- Single arm studies in exquisitely rare histologies have been successfully conducted (collecting duct, renal medullary cancer) and can guide therapy
- Multiple randomized studies are ongoing and need your support!

Variant Histologies of RCC





Salgia *et al* ASCO Ed Book 2024

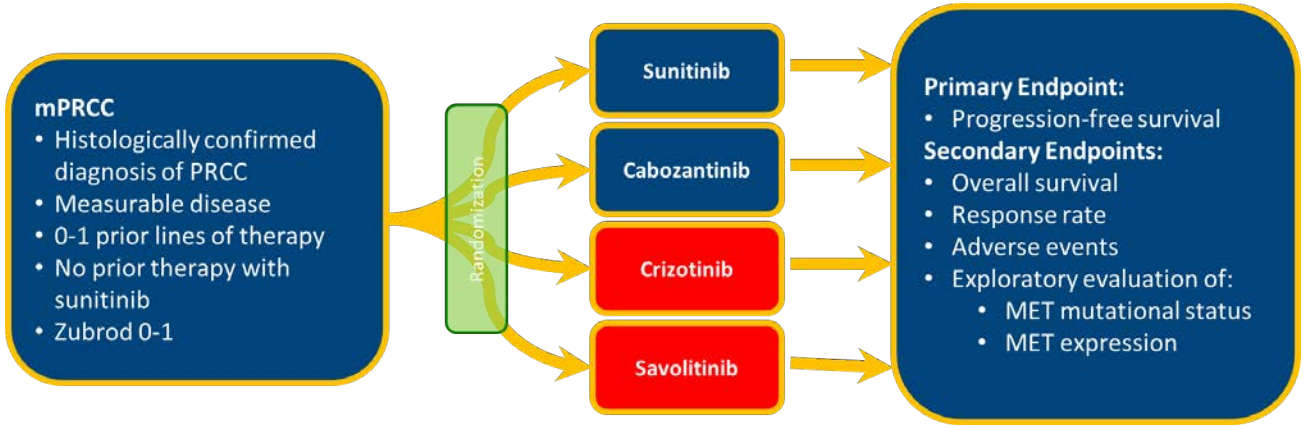
RCC: Hereditary Forms

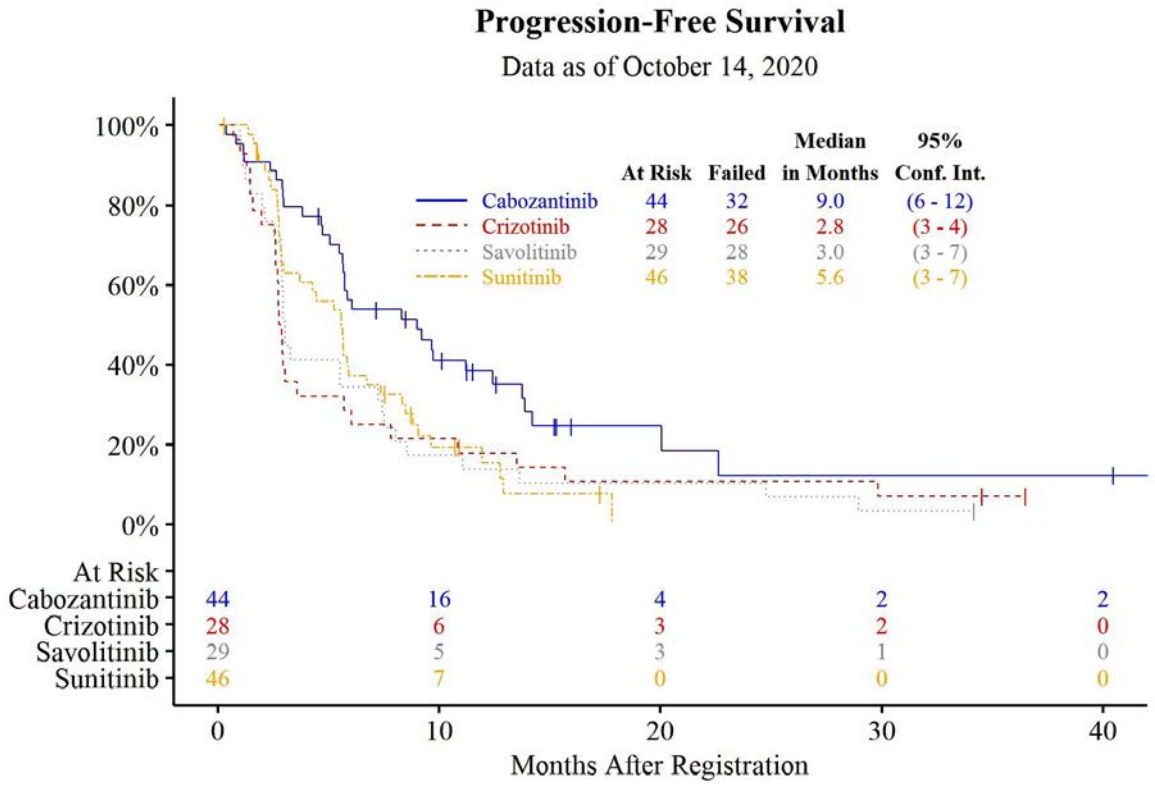
Hereditary syndrome	Gene involved	Common histologies	Inheritance pattern	Major clinical manifestations
von Hippel-Lindau (VHL)	VHL	Clear cell	Autosomal dominant	Hemangioblastomas of the brain, spinal cord, retina, renal cysts, pheochromocytoma and paraganglioma, pancreatic cysts, epididymal and broad ligament cysts
Birt-Hogg-Dubé (BHD)	FLCN	Chromophobe, papillary, clear cell, hybrid oncocytic tumors, angiomyolipomas	Autosomal dominant	Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, spontaneous pneumothorax
Formerly, hereditary leiomyomatosis and renal cell cancer (HLRCC)	FH	FH-deficient RCC	Autosomal dominant	Leiomyomas of the skin and uterus, PET-positive adrenal adenomas, aggressive RCC tumors
Hereditary paraganglioma pheochromocytoma (PGL/PCC) syndrome	SDHA, SDHB, SDHC, SDHD	SDH-deficient RCC	Autosomal dominant	Paraganglioma of head and neck, adrenal or extra-adrenal pheochromocytoma, gastrointestinal stromal tumors
Tuberous sclerosis complex (TSC)	TSC1, TSC2	Clear cell, papillary, chromophobe unclassified, benign renal oncocytoma	Autosomal dominant	Angiomyolipoma, simple and complex renal cysts, oncocytoma, eosinophilic solid and cystic RCC, RCC of fibromyomatous stroma
Hereditary papillary renal carcinoma (HPRC)	MET	Papillary	Autosomal dominant	Bilateral, multifocal renal cell tumors
BAP1 tumor predisposition syndrome (TPDS)	BAP1	Clear cell	Autosomal dominant	Kidney cancer, mesothelioma, melanoma of skin or uvea

Naik *et al* Ther Adv Urol 2024

Papillary RCC: Randomized Data

SWOG 1500: PAPMET



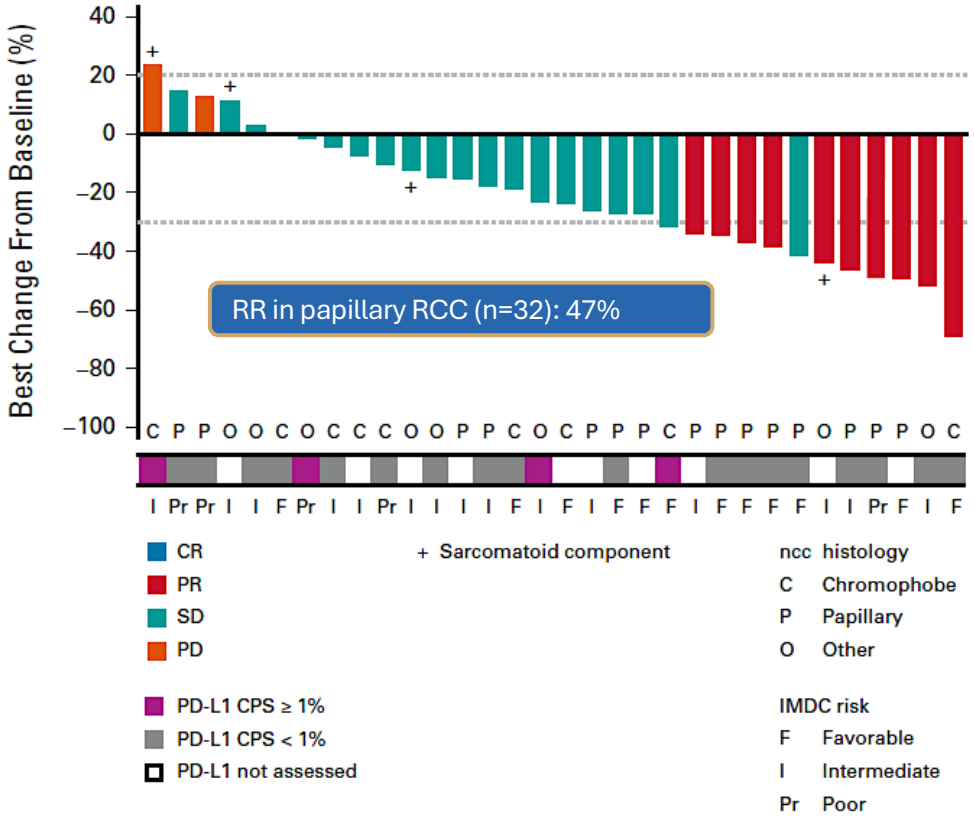


- Study showed PFS advantage with cabozantinib over sunitinib (9.0 v 5.6 mos; 1-sided P=0.019)
- No overall survival advantage
- Is cabozantinib *the* standard of care?

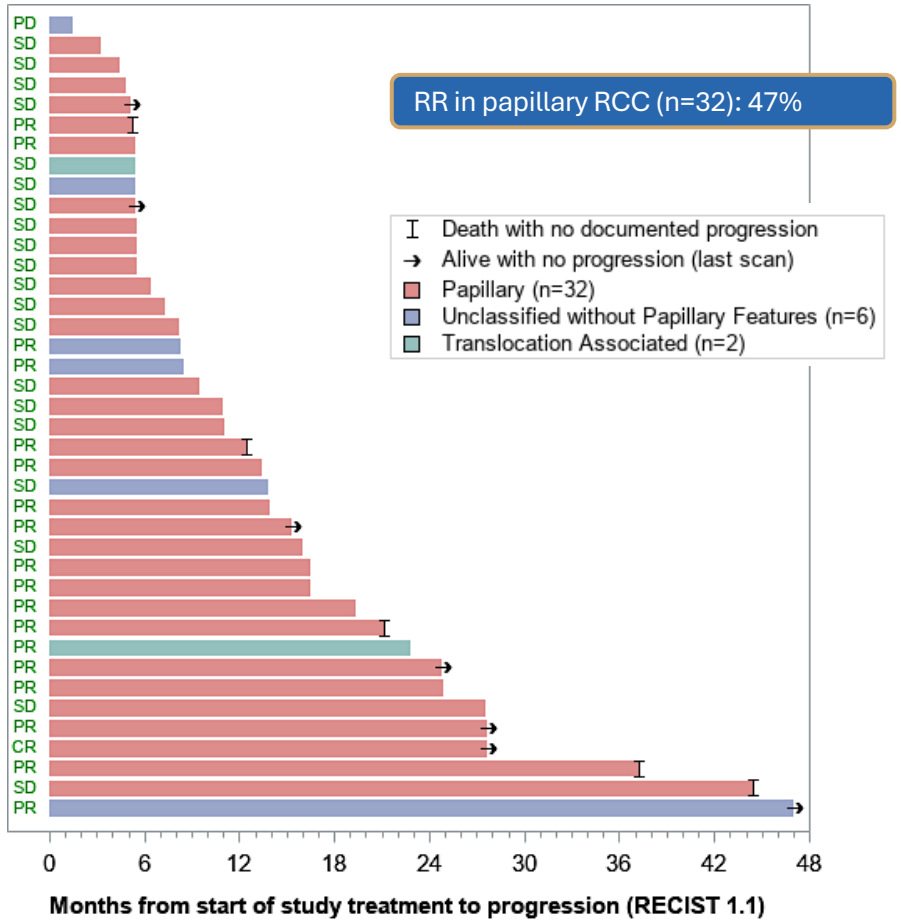
Pal *et al* Lancet 2021 (Updated by Barata *et al* JCO 2024)

Papillary RCC: Single-Arm Studies

Cabozantinib/Atezolizumab



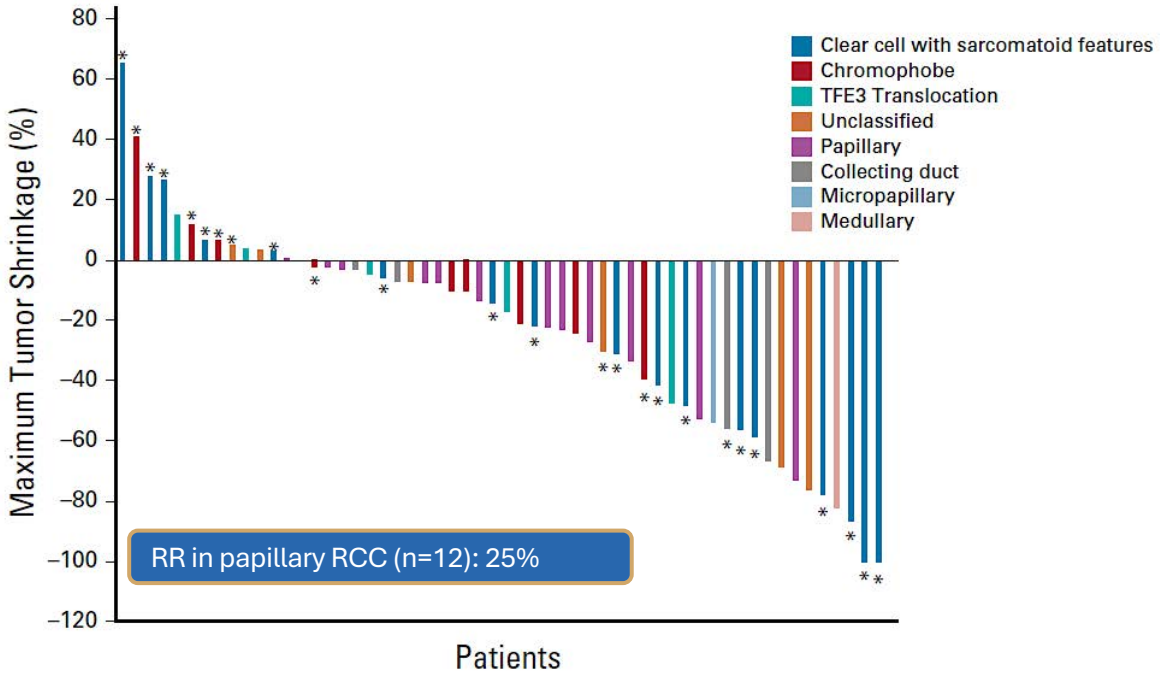
Cabozantinib/Nivolumab



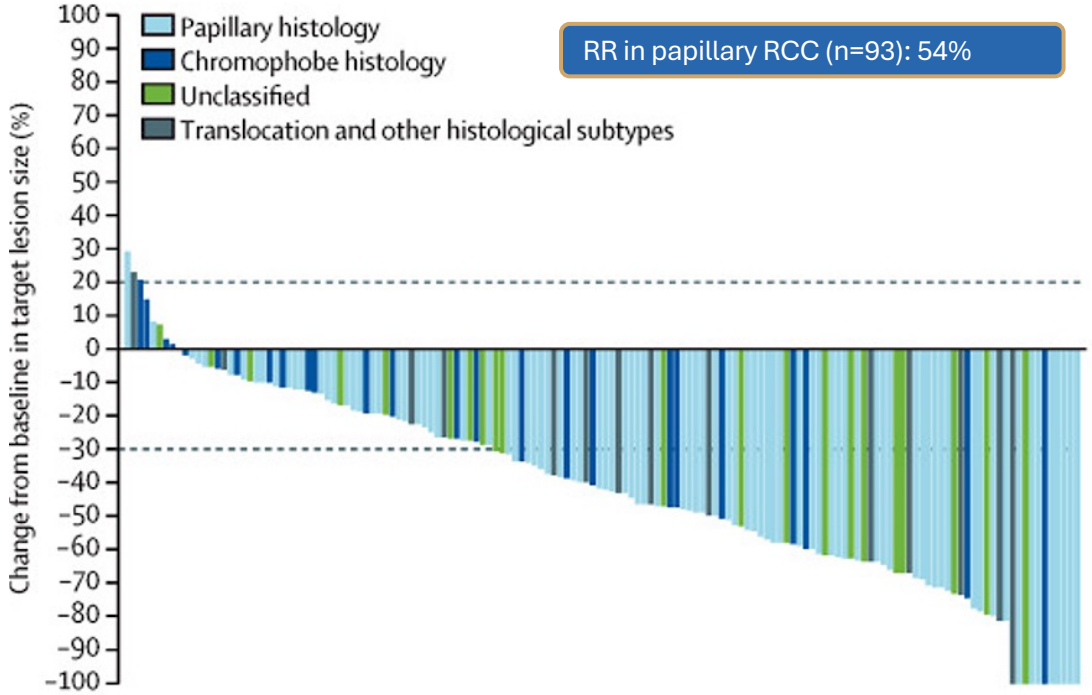
Pal *et al* JCO 2021; Fitzgerald *et al* Eur Urol 2024

Papillary RCC: Single-Arm Studies

Bevacizumab/Atezolizumab

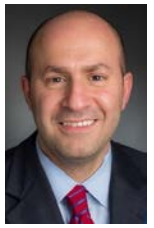


Lenvatinib/Pembrolizumab

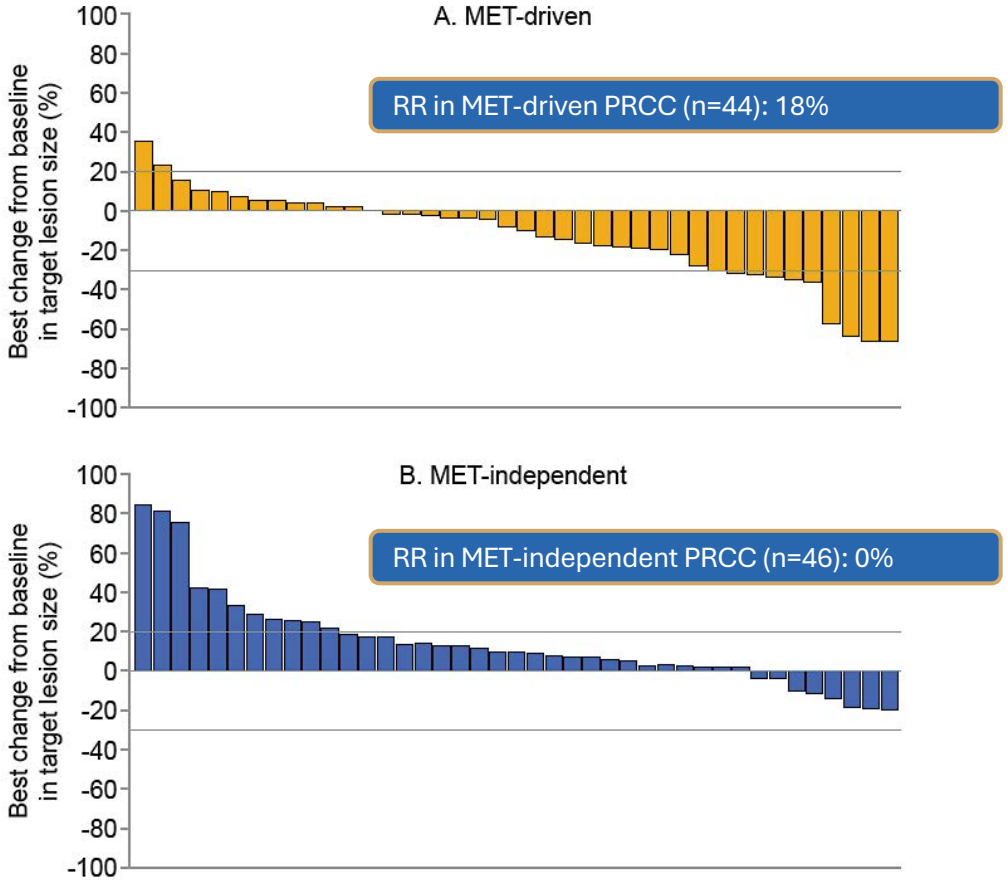


McGregor *et al* JCO 2019; Albiges *et al* Lancet Oncol 2023

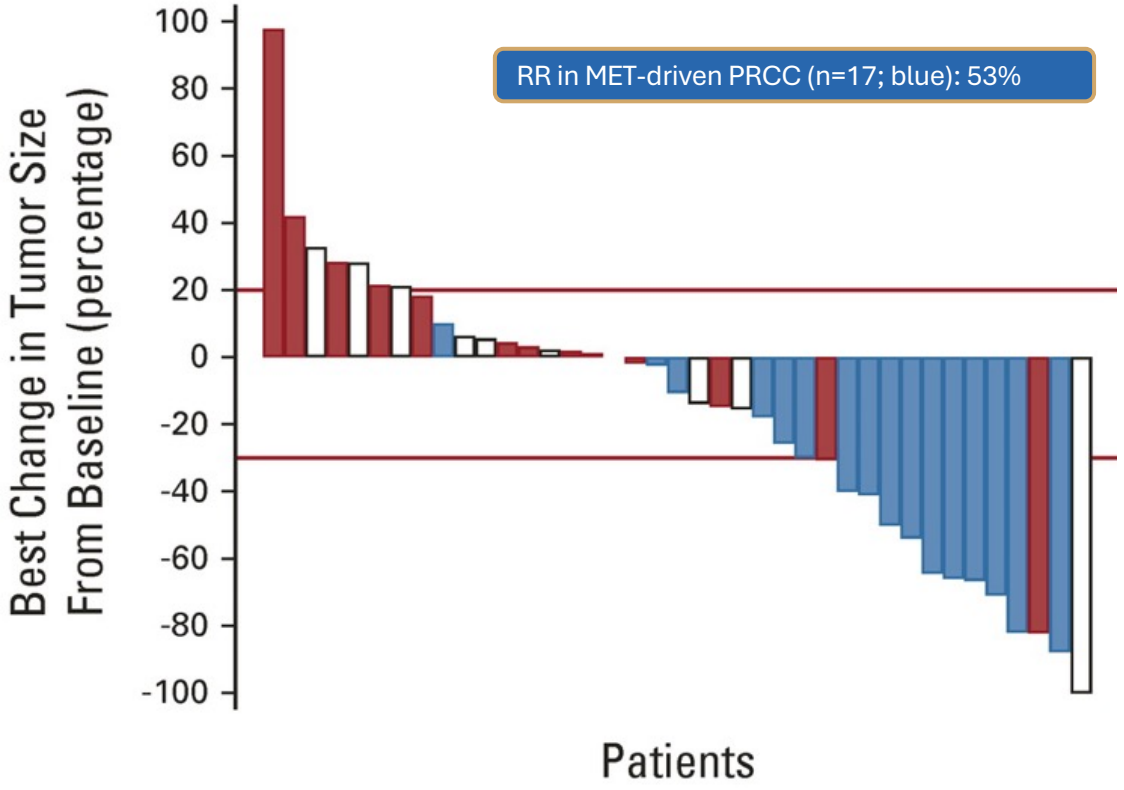
Papillary RCC: Single-Arm Studies




Savolitinib



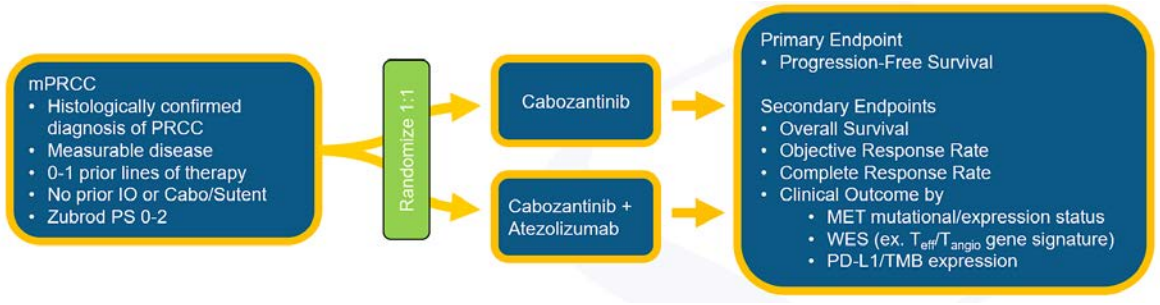
Savolitinib/Durvalumab



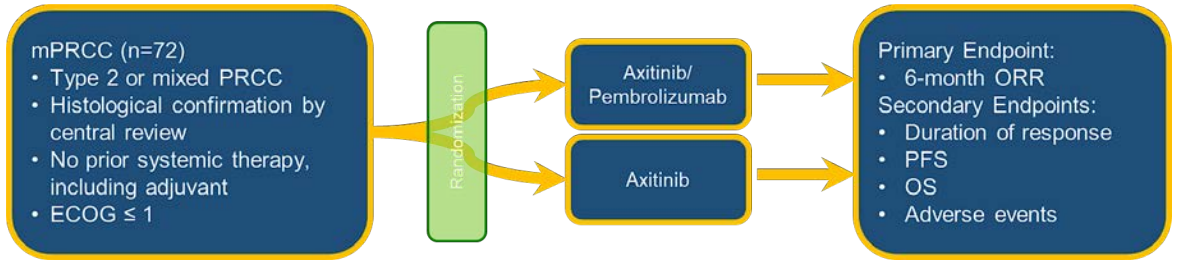
Choueiri *et al* JCO 2017; Suarez *et al* JCO 2023

Papillary RCC: Ongoing Studies

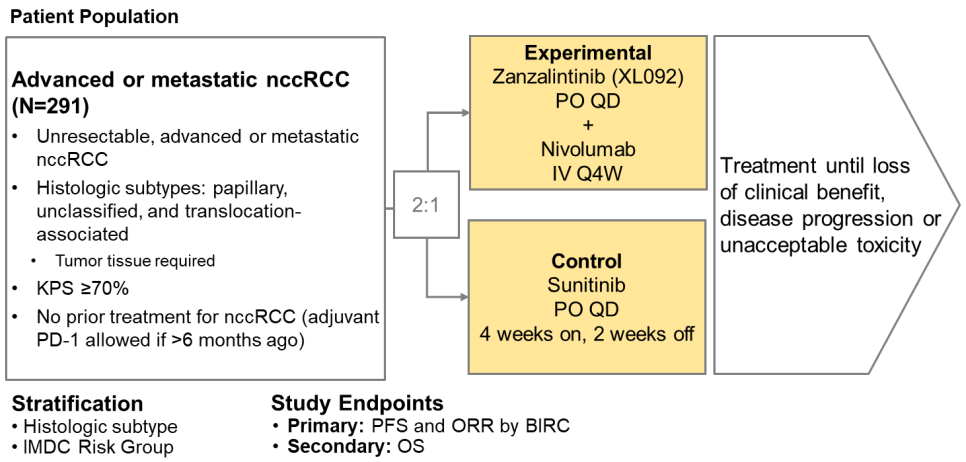
S2200/PAPMET2 (NCT05411081; PIs: Maughan/Pal)



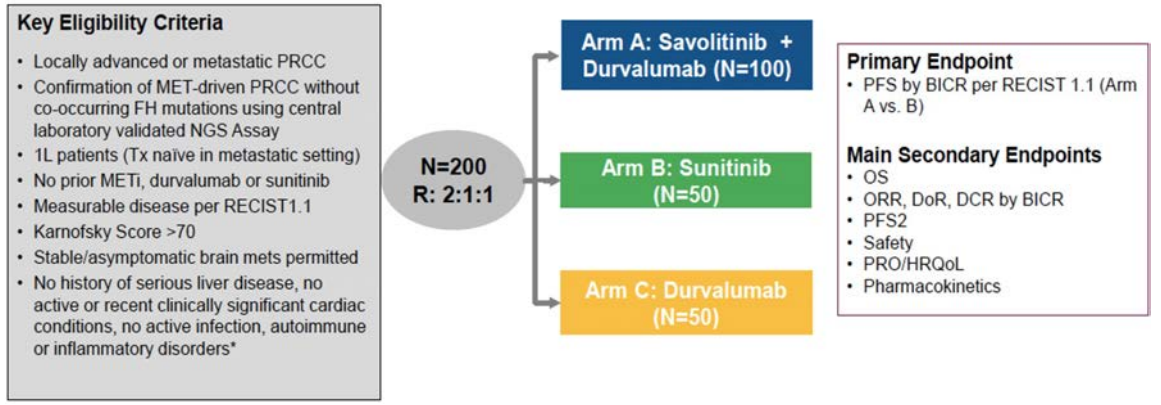
PAXIPEM (NCT05096390; PI: Negrier)



STELLAR-304 (NCT05678673; PIs: Pal/Suarez)

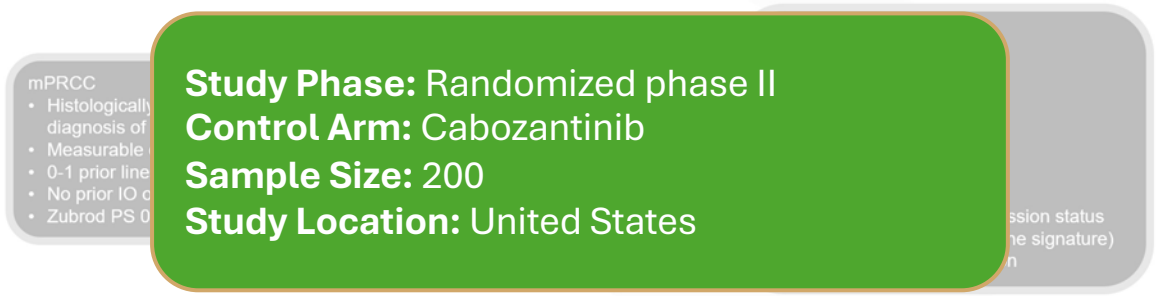


SAMETA (NCT05043090; PIs: Choueiri/Powles)



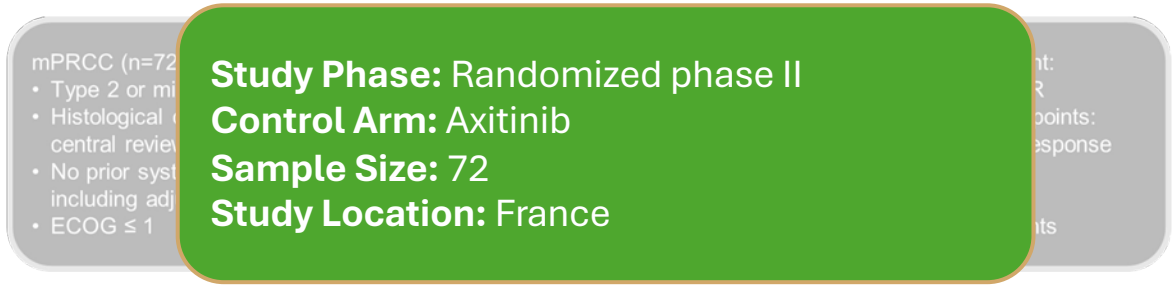
Papillary RCC: Ongoing Studies

S2200/PAPMET2 (NCT05411081; PIs: Maughan/Pal)



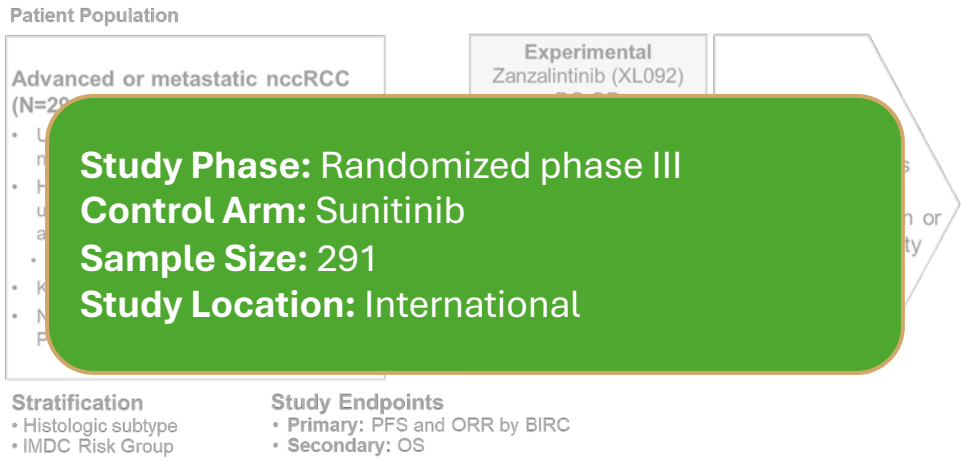
Study Phase: Randomized phase II
Control Arm: Cabozantinib
Sample Size: 200
Study Location: United States

PAXIPEM (NCT05096390; PI: Negrier)



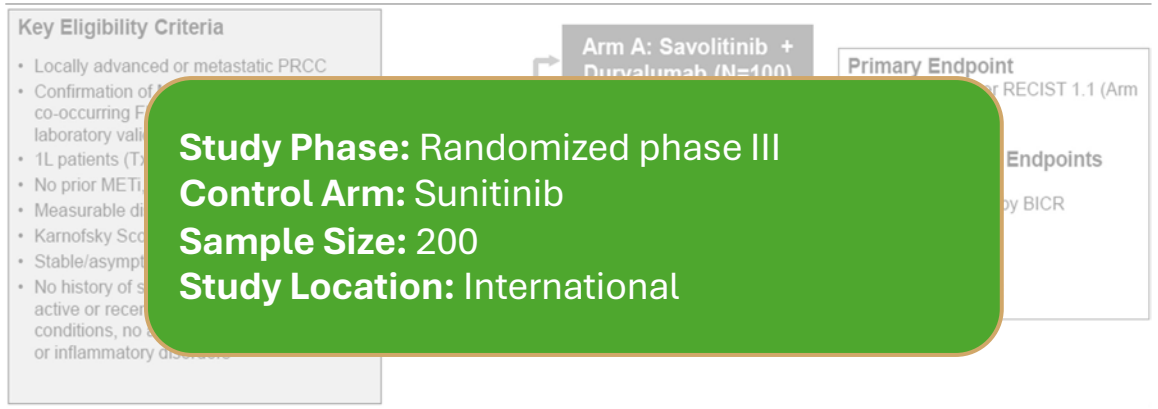
Study Phase: Randomized phase II
Control Arm: Axitinib
Sample Size: 72
Study Location: France

STELLAR-304 (NCT05678673; PIs: Pal/Suarez)



Study Phase: Randomized phase III
Control Arm: Sunitinib
Sample Size: 291
Study Location: International

SAMETA (NCT05043090; PIs: Choueiri/Powles)



Study Phase: Randomized phase III
Control Arm: Sunitinib
Sample Size: 200
Study Location: International

Zanzalintinib

Single-Agent Dose Escalation Cohorts (n=49)

- Inoperable, locally advanced, metastatic, or recurrent solid tumor treated with zanzalintinib 10–140 mg QD

Recommended Dose: Zanzalintinib 100 mg QD[1,a]

ccRCC Expansion Cohort (N=32)

- Advanced, metastatic, or recurrent RCC with a clear cell histology (sarcomatoid features permitted)
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Received 1–3 prior systemic anticancer therapies

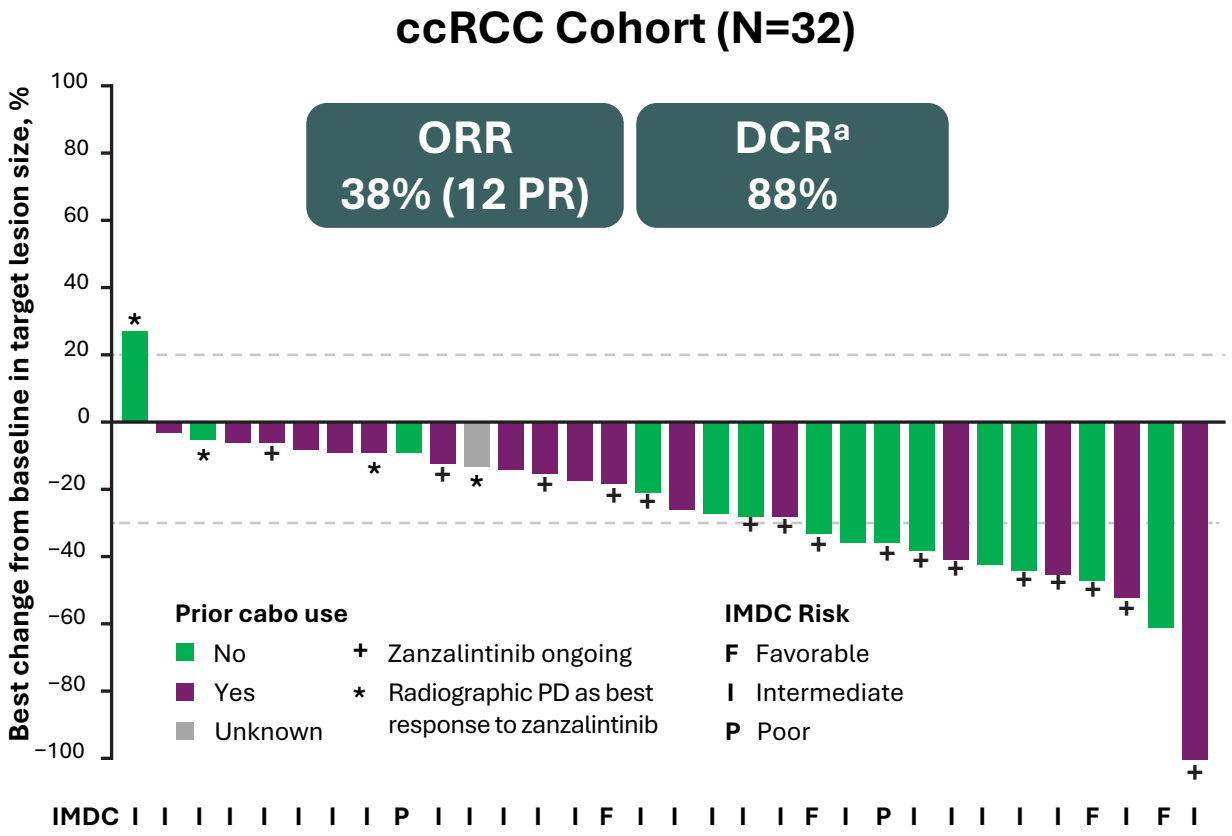
Safety Population N=81

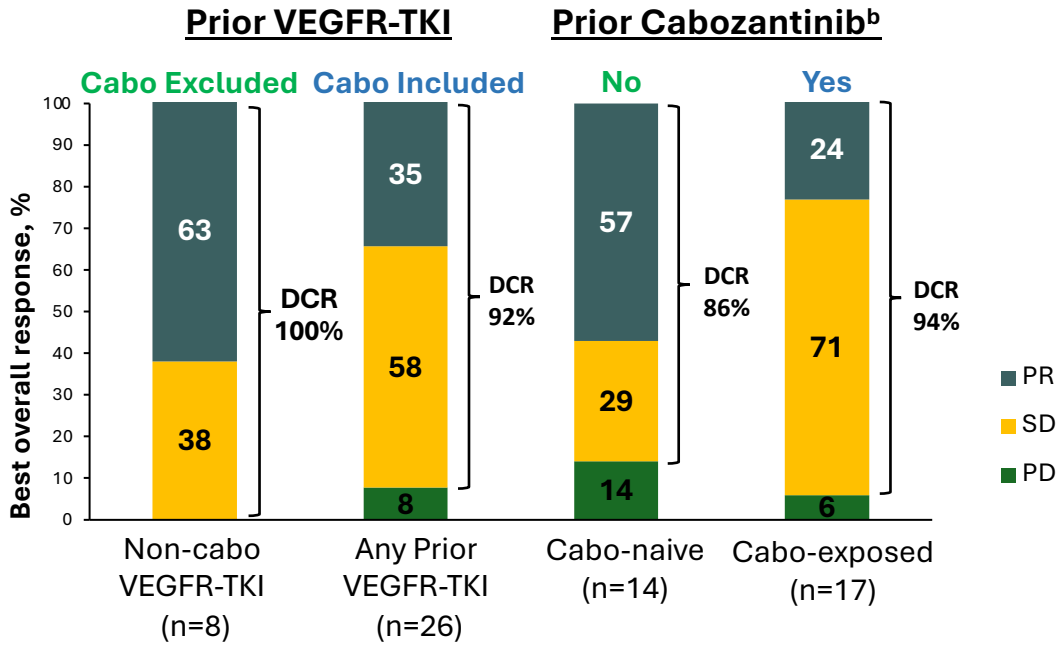
Zanzalintinib is an oral TKI targeting VEGFR, MET, and TAM kinases

- **Primary Endpoints:** ORR and PFS rate at 6 months per RECIST v1.1 by investigator
- **Secondary Endpoint:** Safety
- **Exploratory Endpoints:** PFS and DOR per RECIST v1.1 by investigator; OS

1. Sharma M, et al. *Ann Oncol.* 2022;33(7_suppl):Abstract 481P. [a]Treatment until lack of clinical benefit or unacceptable toxicity; treatment post-progression allowed if there was clinical benefit per the investigator.

Zanzalintinib



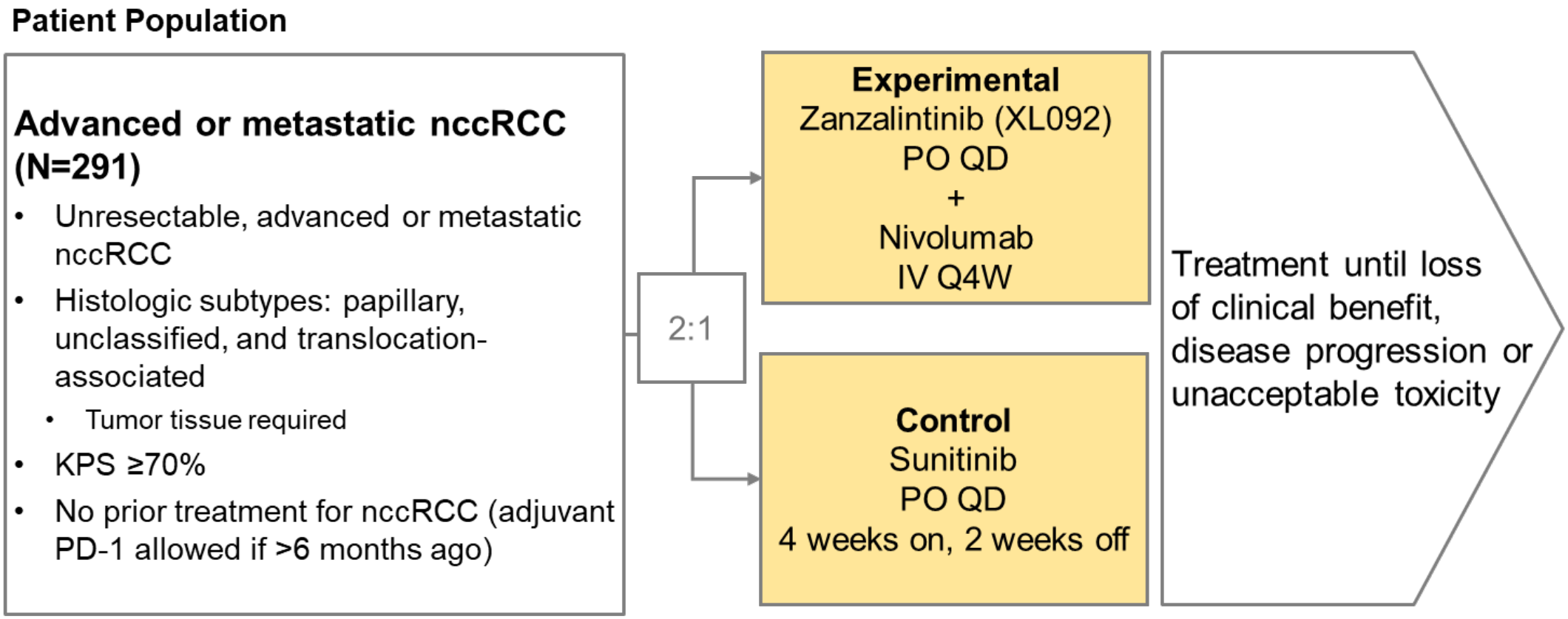


Three of the four cabo-exposed patients who responded to zanzalintinib had discontinued prior cabozantinib due to disease progression

Data cutoff: June 10, 2023.

[a]DCR is defined as proportion of patients with a best overall response of confirmed CR/PR or any single best response of SD. [b]Cabo exposure was unknown for 1 patient.

Zanzalintinib: STELLAR-304



Stratification
- Histologic subtype
- IMDC Risk Group

Study Endpoints
- **Primary:** PFS and ORR by BIRC
- **Secondary:** OS

Pal *et al* IKCS 2023

Papillary RCC: Current Standard?

01/04/2023

Dear Sumanta Pal,

The request for [redacted] 40 MG TABLET has been denied.

Per NCCN guideline, Cabozantinib and Sunitinib is mentioned as preferred regimens. Please try treatment with Sunitinib prior to Cabometyx. Sunitnib is a preferred medication in [redacted] coverage plan.

Please send a confirmation and/or begin the PA process for the recommended medication regimen before prescribing the medication(s) to your patient.

If your patient has already tried/failed, had an inadequate response, and/or has contraindications to the medication(s) listed above, please provide all pertinent records.

If you would like to appeal this determination, please write a letter of medical necessity, and submit medical records substantiating the need for the requested drug explicitly, including but not limited to failure of all recommended formulary alternatives, clinical rationale to skip step therapy, contraindications, and/or other reasons the patient cannot tolerate alternative treatment options.

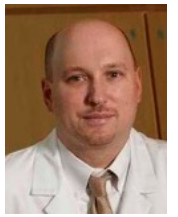
Approval will not be considered without sufficient documentation.
We greatly appreciate your cooperation in this matter.

Recommendations	Strength rating
Offer cabozantinib to patients with papillary RCC (pRCC) based on a positive randomised controlled trial.	Weak
Offer lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak

Recommendations	Strength rating
Offer sunitinib to patients with other non-clear cell renal cell carcinoma (cc-RCC) subtypes than papillary RCC.	Weak
Offer lenvatinib plus pembrolizumab to patients with non-ccRCC subtypes.	Weak
Offer cabozantinib and nivolumab to patients with non-ccRCC subtypes other than chromophobe RCC.	weak

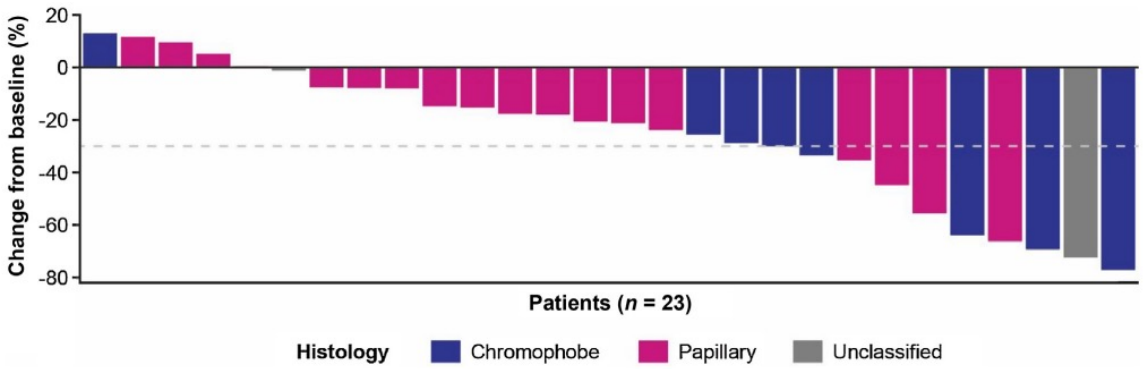
Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference

Chromophobe RCC



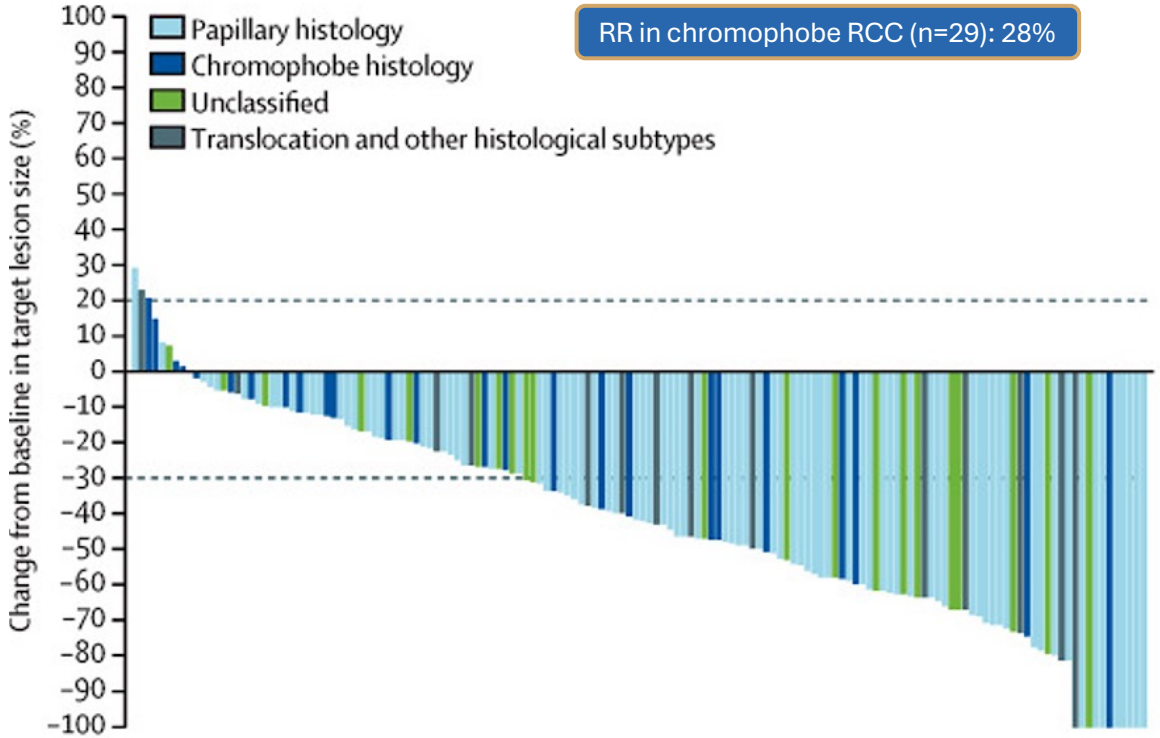
Lenvatinib/Everolimus

RR in chromophobe RCC (n=9): 44%



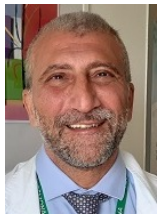
Lenvatinib/Pembrolizumab

RR in chromophobe RCC (n=29): 28%

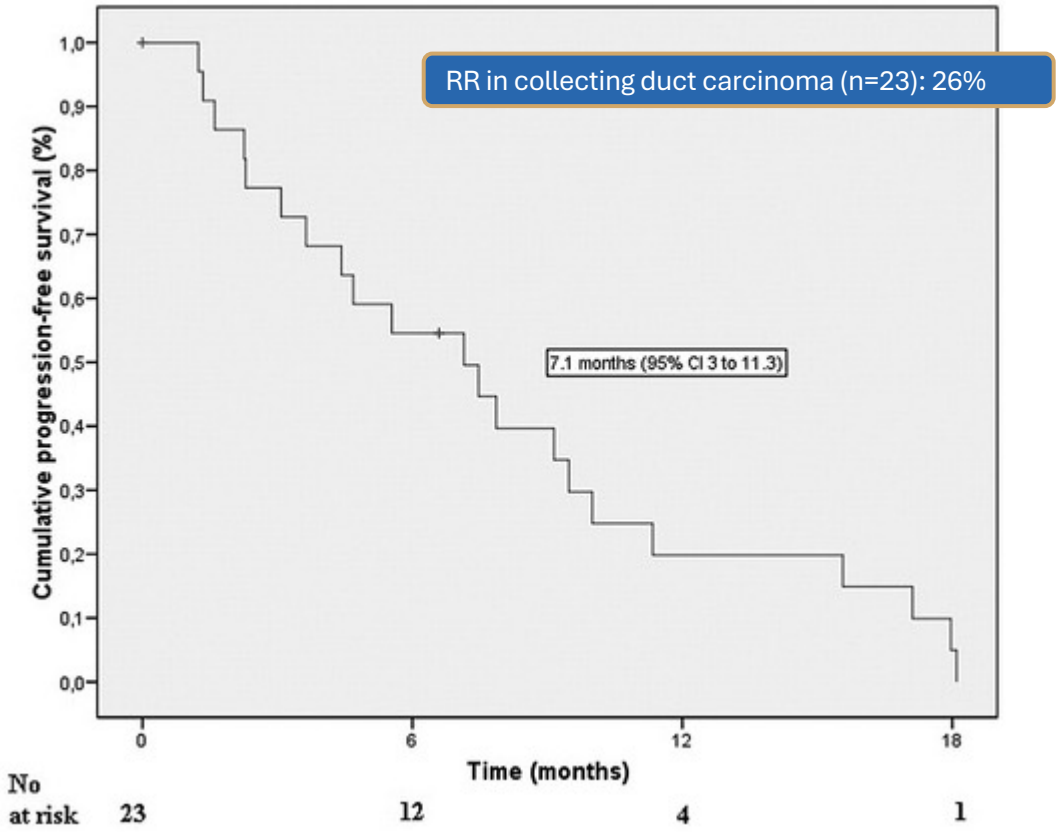


Hutson *et al* Eur Urol 2023; Albiges *et al* Lancet Oncol 2023

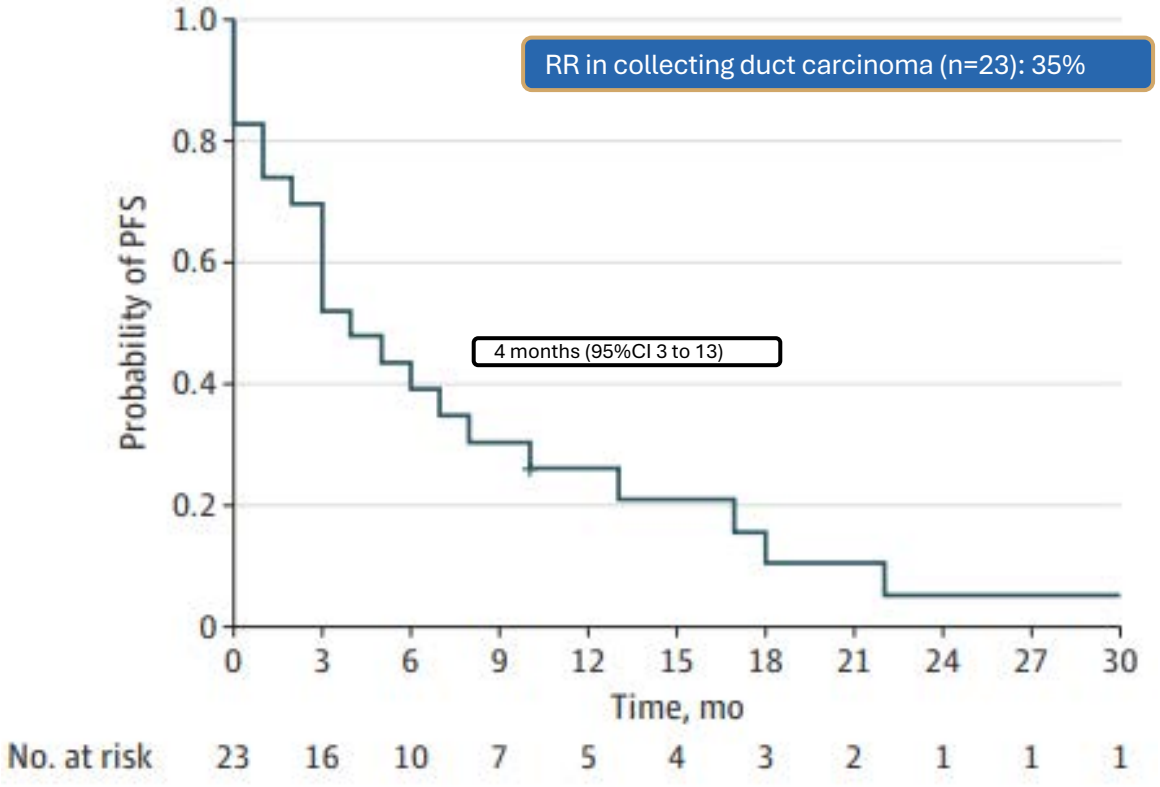
Collecting Duct Carcinoma



Cisplatin or Carboplatin with Gemcitabine



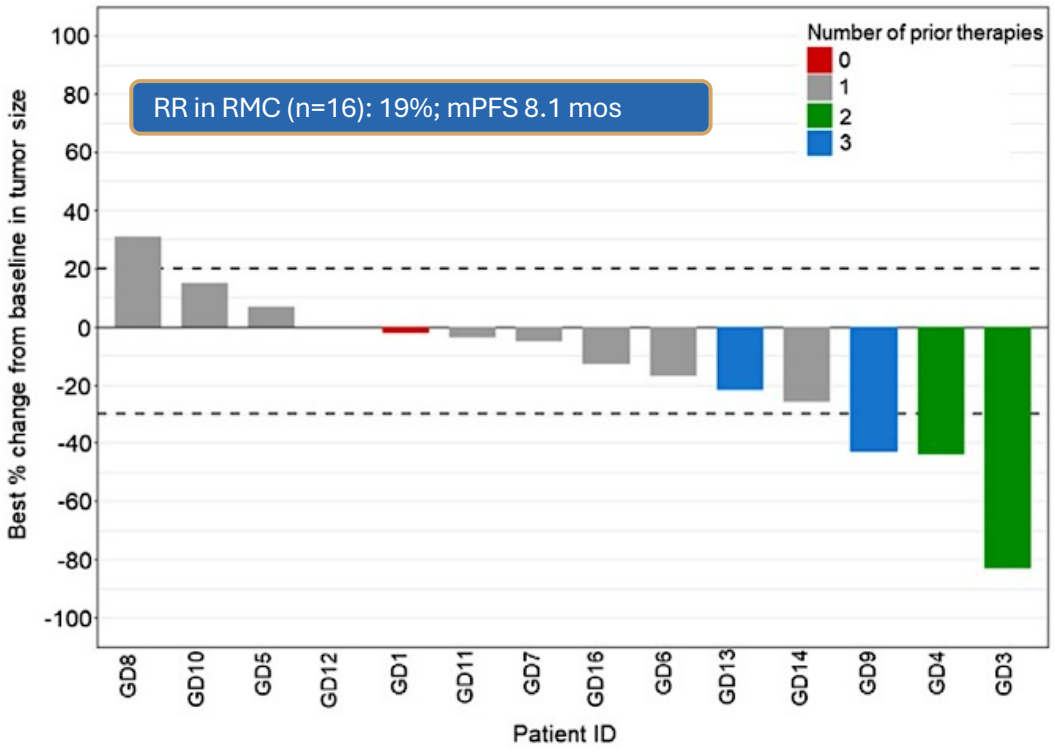
Cabozantinib



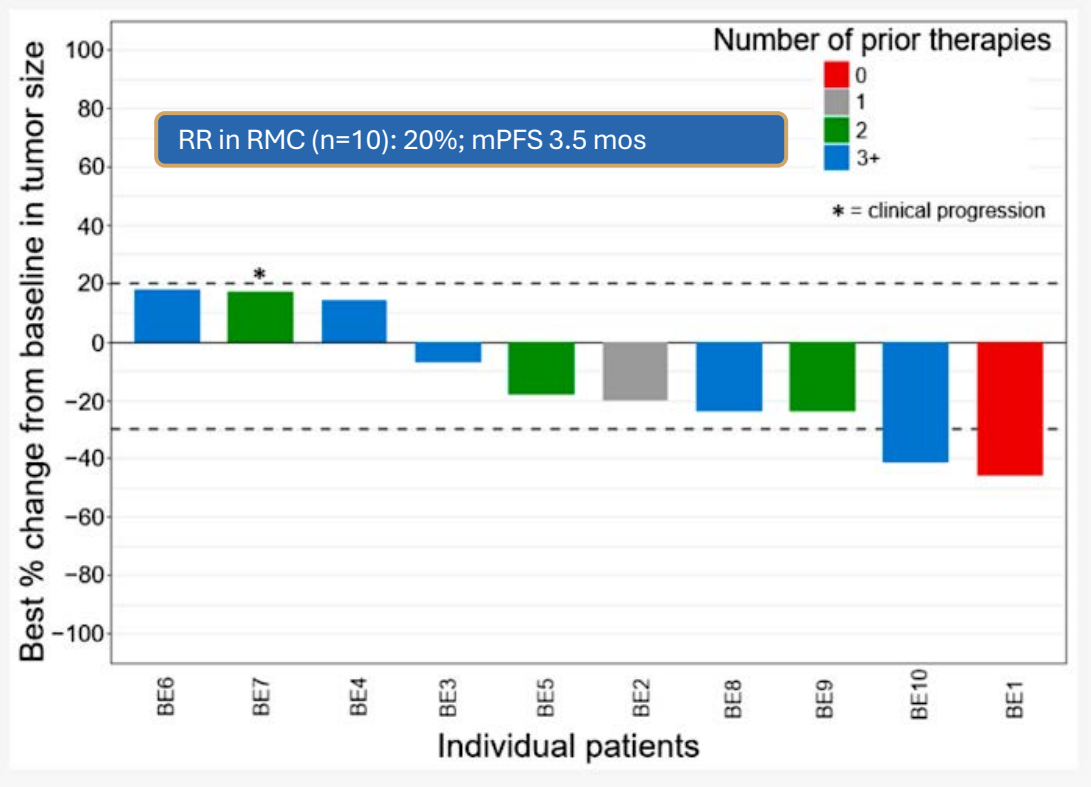
Oudard *et al* J Urol 2007; Procopio *et al* JAMA Oncol 2022

Renal Medullary Carcinoma

Doxorubicin with Gemcitabine



Bevacizumab with Erlotinib



Wilson *et al* Clin Genitourin Cancer 2021; Wiele *et al* Cancers 2021

Renal Medullary Carcinoma

Treatment Algorithm (Courtesy of Pavlos Msaouel, MD)

1st line therapy:
Platinum-based chemotherapy
(ORR 29%; durable CR in up to 5% of patients)

Msaouel *et al* GGU 2019

2nd line therapy:
Gemcitabine + doxorubicin

Wilson *et al* CGU 2021

3rd line therapy:
EGFR targeting regimens

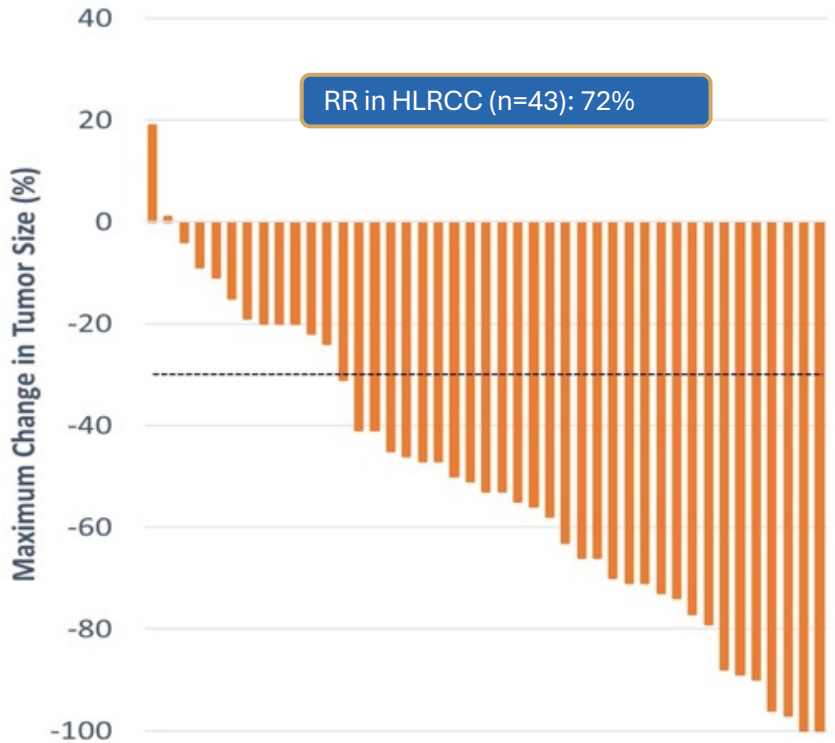
Wiele *et al* Cancers 2021

Definitive chemoradiation:
A potentially curative option in selected patients with oligoprogressive or oligometastatic RMC

Mbilinyi *et al* CGU 2024

Hereditary Leiomyomatosis & RCC (HLRCC)

Bevacizumab with Erlotinib



Bevacizumab/Erlotinib/Atezolizumab

Cohort 1 (n=21)

Adult and pediatric patients with advanced HLRCC*

Cohort 2 (n=21)

Adult and pediatric patients with advanced sporadic/non-HLRCC papillary RCC*

Safety run-in

12 adult patients from Cohort 1 and Cohort 2

If ≤ 3 DLT, then continue into Arm 1 and Arm 2

Arm 1
Adult patients from Cohort 1 and Cohort 2

Bevacizumab 15mg/kg IV Q21D
Atezolizumab 1,200mg IV Q21D
Erlotinib 150mg PO QD

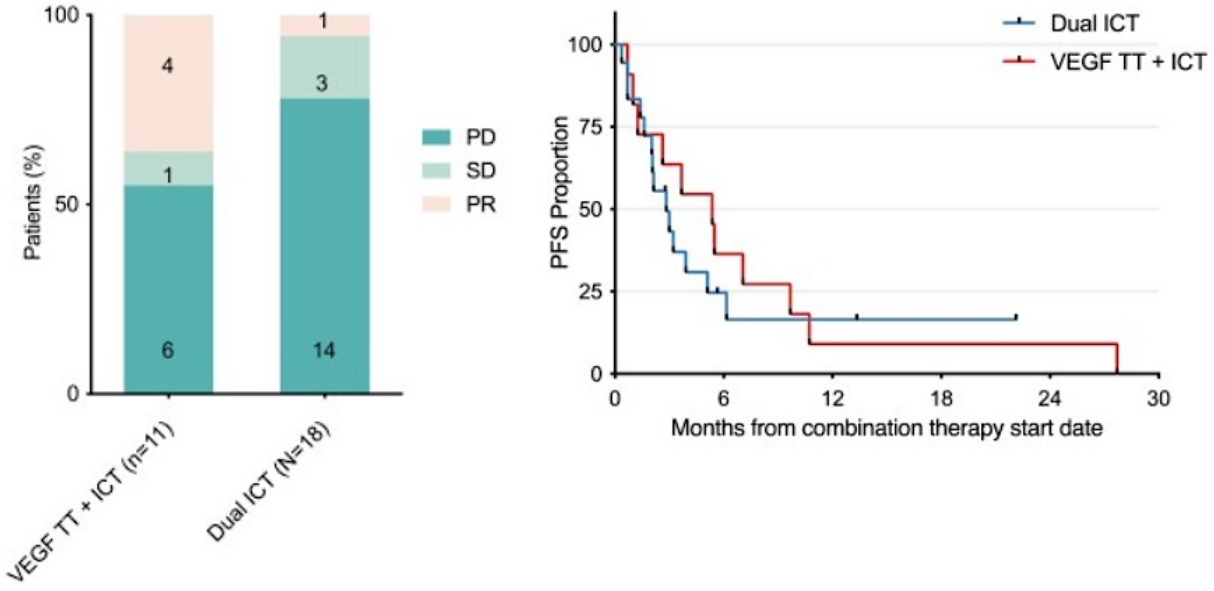
Arm 2
Pediatric patients from Cohort 1 and Cohort 2

Bevacizumab 15mg/kg IV Q21D
Atezolizumab 15mg/kg (max 1,200mg) IV Q21D
Erlotinib 85mg/m^2 (max 150mg) PO QD

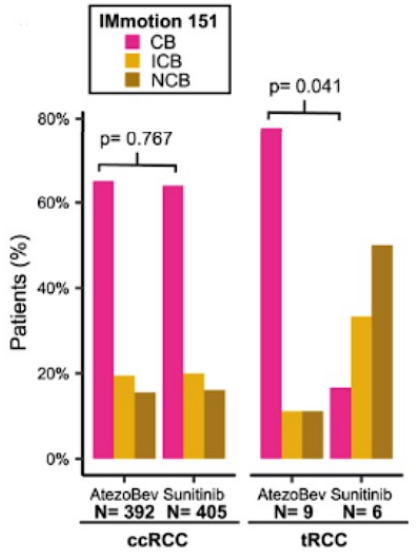
Srinivasan *et al* ASCO 2022; NCT04981509

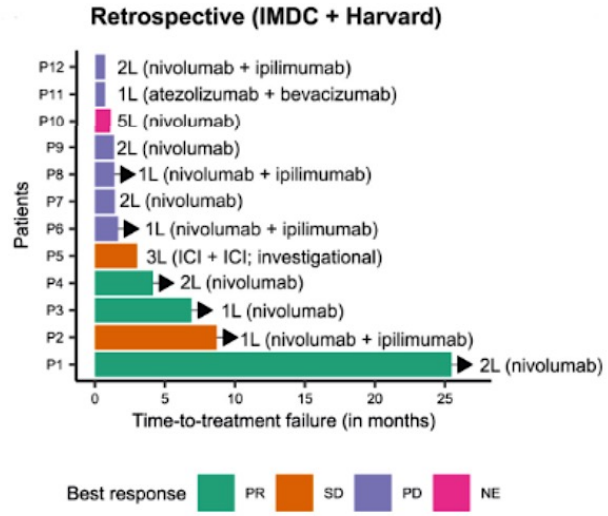
Translocation RCC

Retrospective data from 11 centers



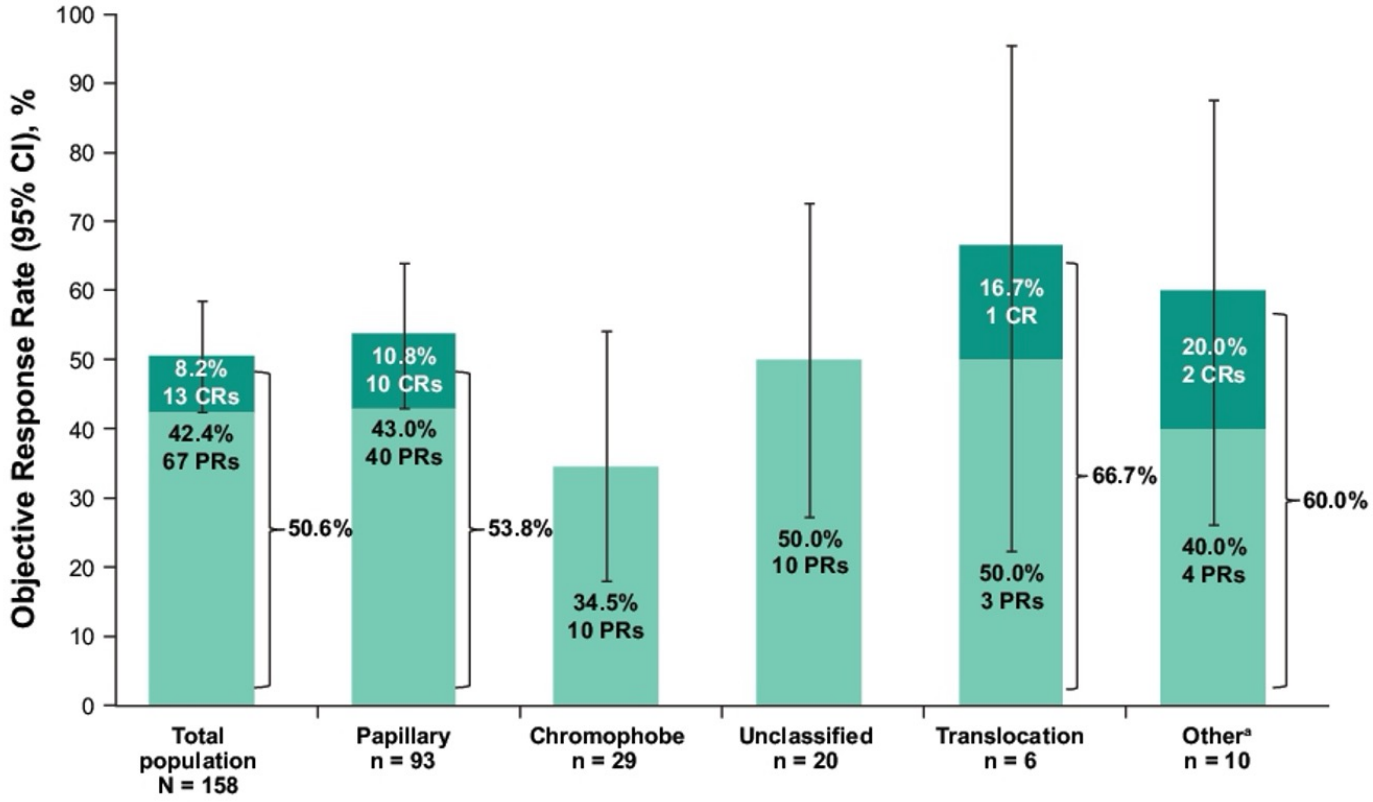
IMmotion151 & the DFCI/Harvard experience

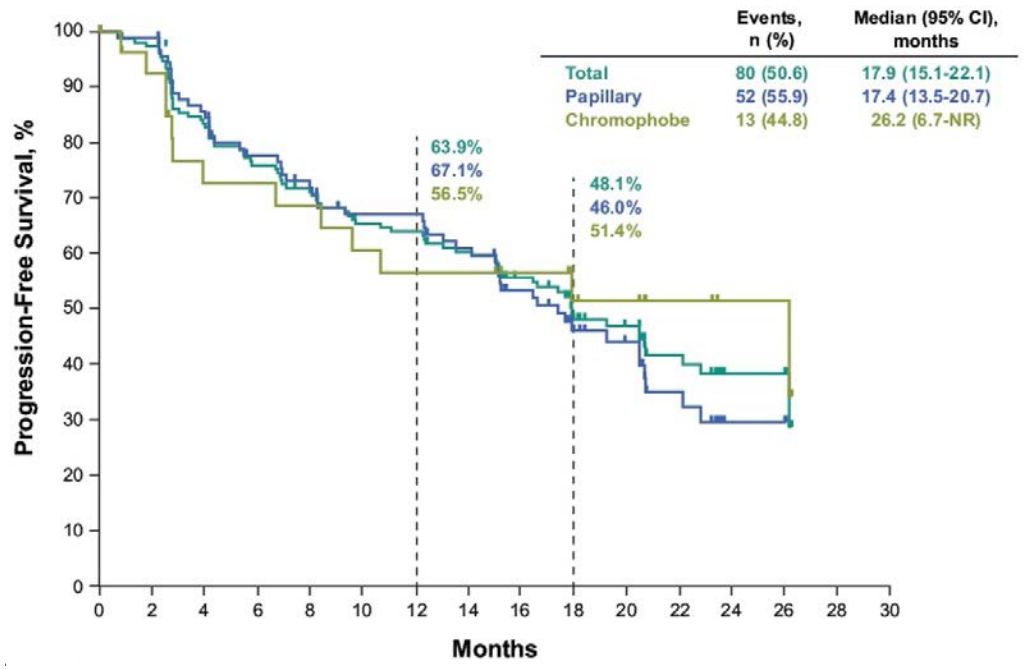


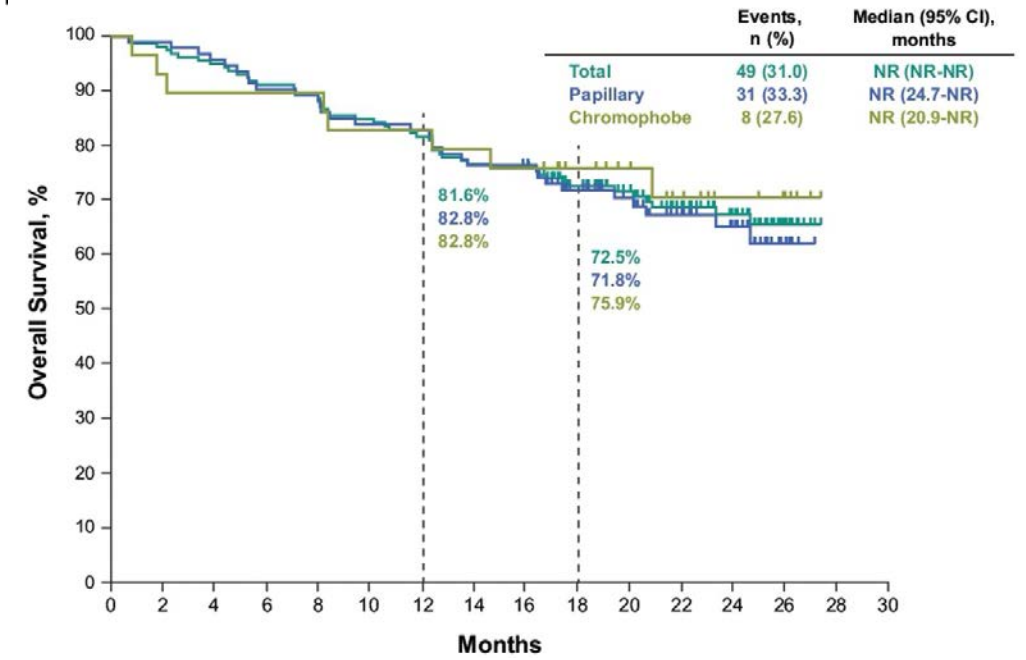


Alhalabi *et al* Oncologist 2023; Bakouny *et al* Cell Rep 2022

KEYNOTE-B61: Extended follow-up

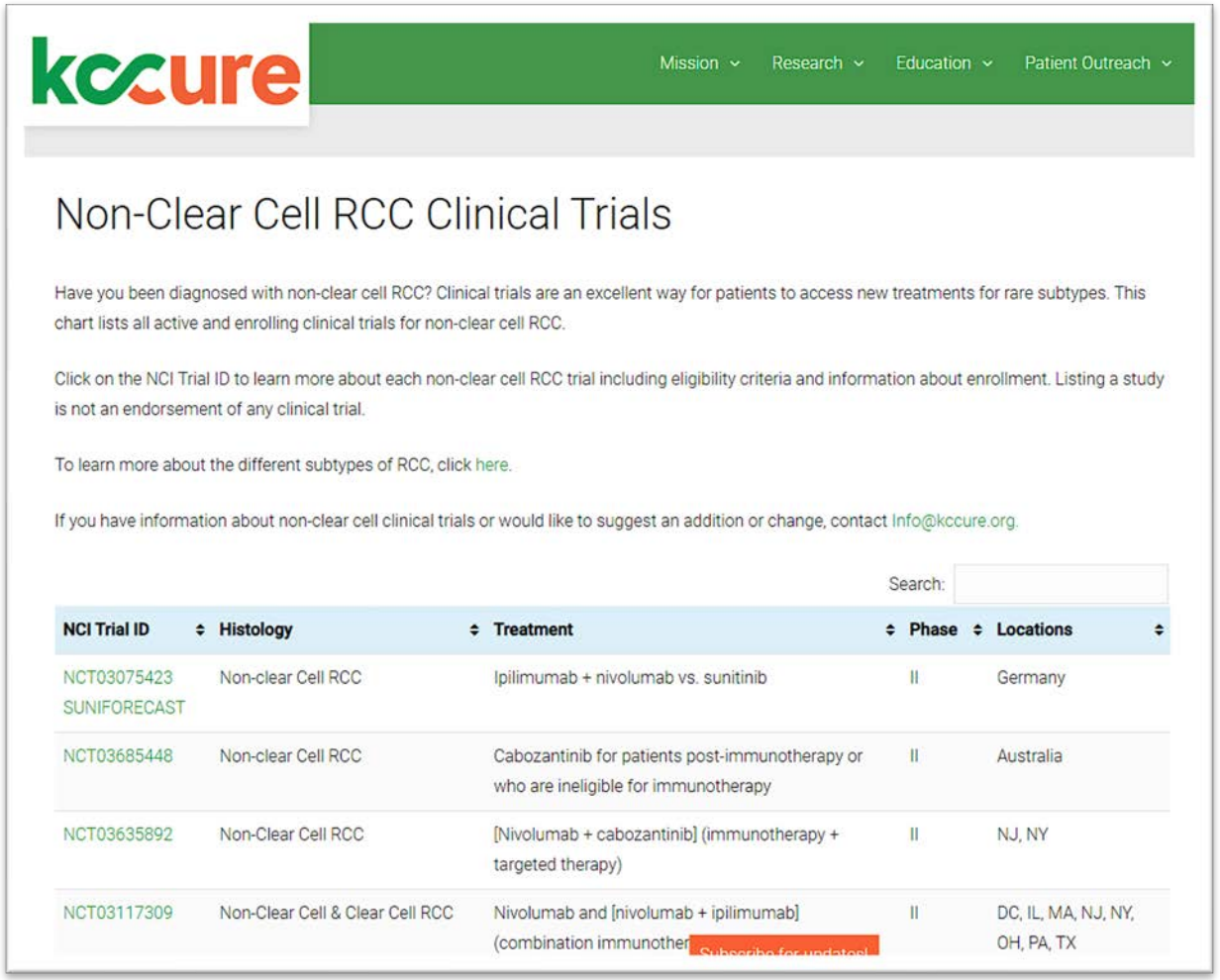


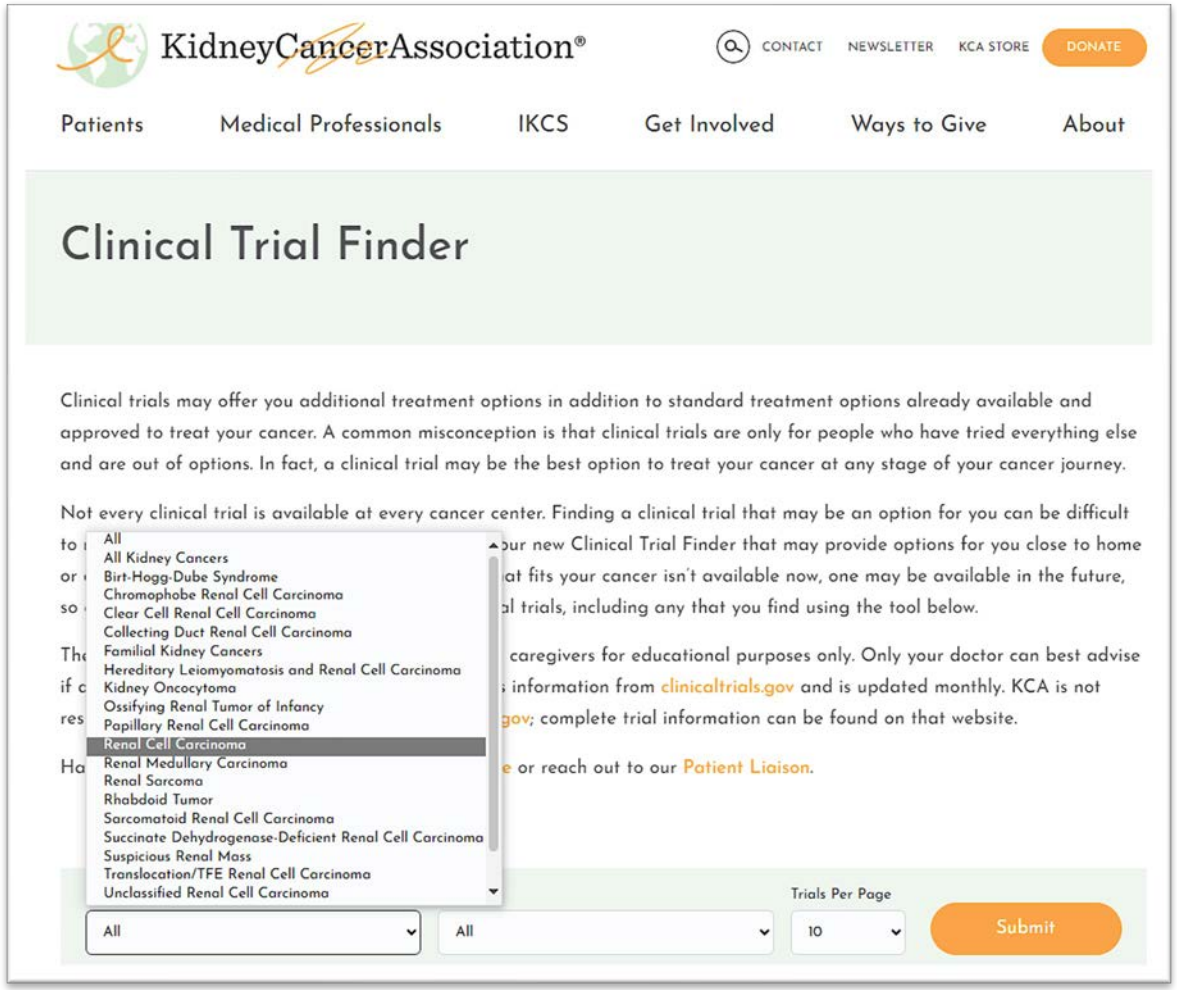




Voss M et al. ASCO 2024; Abstract 2.

How to find trials?





Key Takeaways

For variant histologies of renal cell carcinoma (RCC):

- There have been randomized phase II trials in papillary RCC
- Single arm studies in exquisitely rare histologies have been successfully conducted (collecting duct, renal medullary cancer) and can guide therapy
- Multiple randomized studies are ongoing and need your support!

Questions from General Medical Oncologists

- I would appreciate a general overview of preferred treatment approaches for non-clear cell RCC. This is such a diverse group of RCC. How does one determine optimal treatment in the metastatic setting? What other factors are key in the decision-making process other than histology, TMB/MSI, etc?
- I tend to follow guidelines for ccRCC in treating nccRCC. Is this reasonable? How does your approach to nccRCC differ from your approach to ccRCC?
- Which initial therapy would you recommend for a 64 y/o patient with metastatic papillary RCC?

Questions from General Medical Oncologists

- What treatment should we start with for some of the uncommon pathologies, like chromophobe RCC, renal medullary carcinoma or collecting duct carcinoma?
- Are IO-TKI combos just as effective in non-clear cell RCC as they are in clear cell disease? Do any of these combinations stand out?
- The lenvatinib/pembro data appear impressive. Is it the regimen investigators consider as first-line therapy in the management of metastatic non-clear cell RCC? If so, what is the best second-line therapy after lenvatinib/pembro?

Questions from General Medical Oncologists

- Where does TKI monotherapy fit into nccRCC management? How do the data with cabozantinib in papillary disease indirectly compare to the various IO combinations? Who is the ideal candidate for this approach?
- We need more trials for this group. I would love to have an overview of new drugs in the pipeline that will improve patient care.
- Does adjuvant pembrolizumab benefit patients with other types of RCC (eg, papillary, translocation-associated)?

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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