RTP Live from Chicago: Investigator Perspectives on Available Research Findings and Challenging Questions in the Management of Renal Cell Carcinoma

Monday, June 2, 2025
7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Professor Laurence Albiges, MD, PhD
Tian Zhang, MD, MHS

Moderator

Neil Love, MD

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Faculty

Professor Laurence Albiges, MD, PhD
Medical Oncologist
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MODERATOR
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Dallas, Texas

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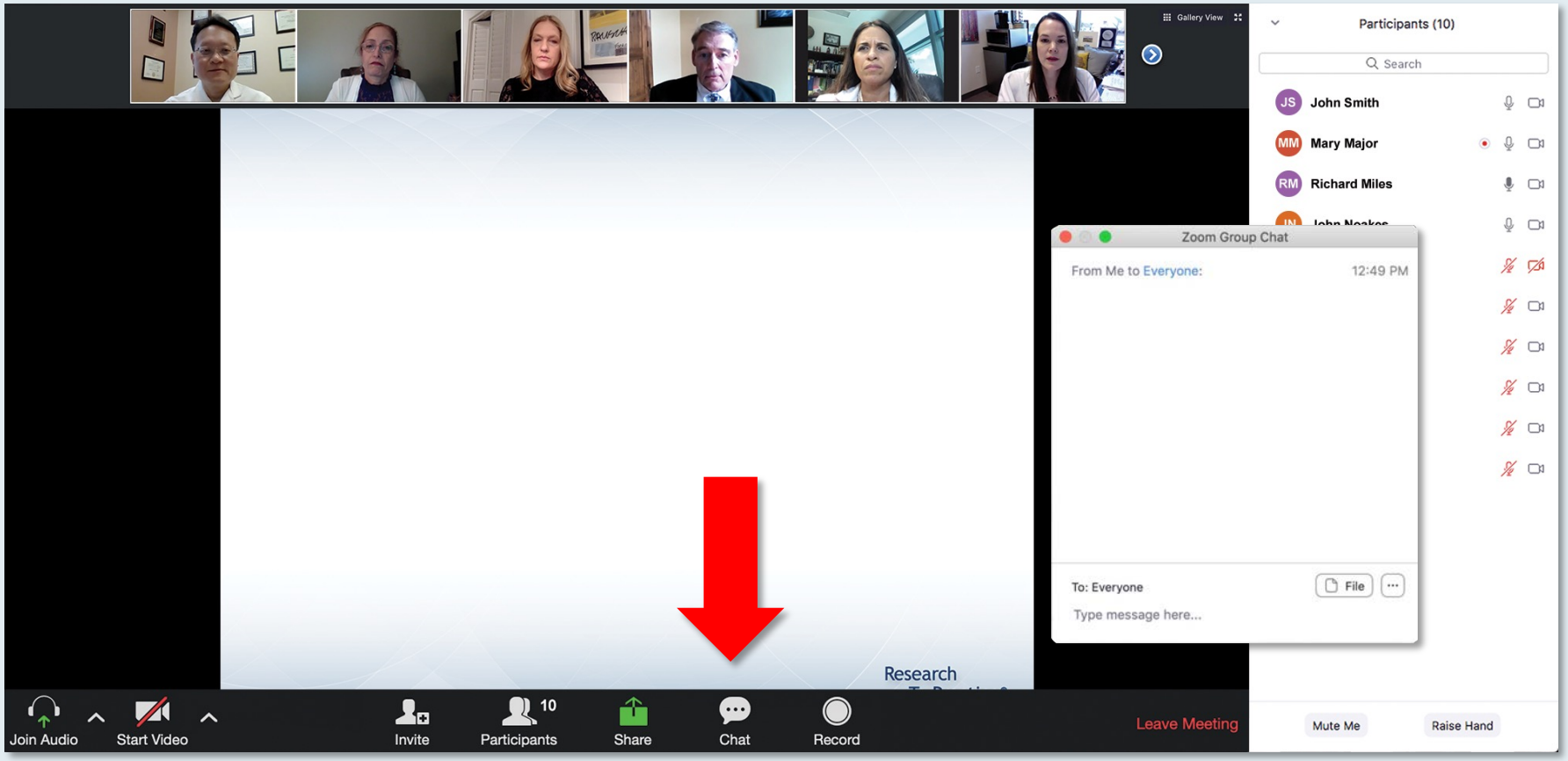
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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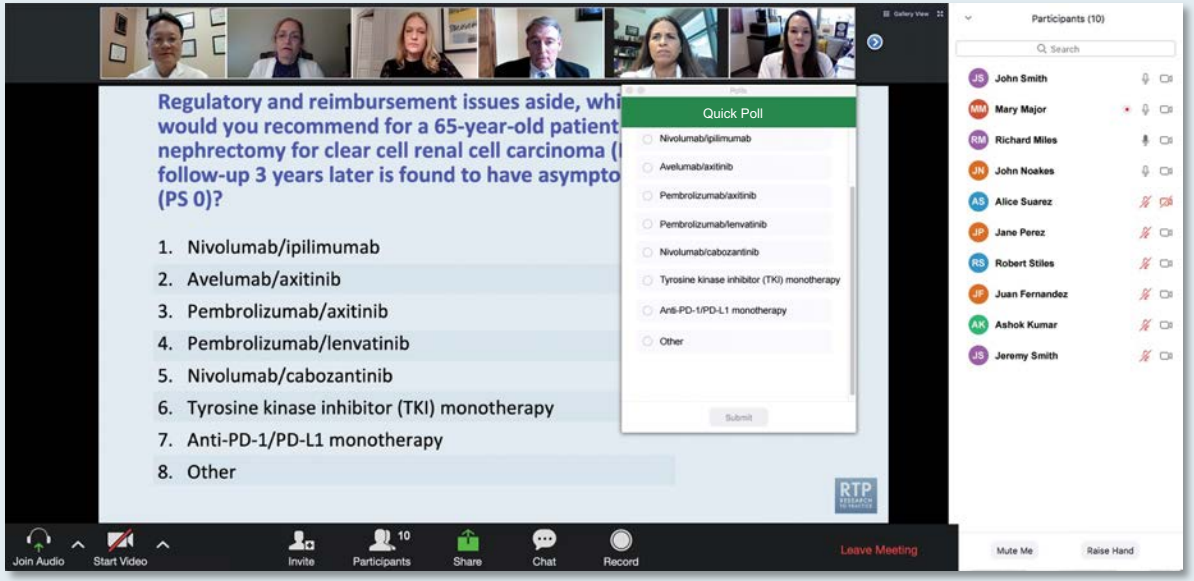
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Prof Albiges — Disclosures
Faculty

Advisory/Consulting/Honoraria (All Paid to Institution)	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, Eisai Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Merck, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Telix Pharmaceuticals Limited, Xencor.

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
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Dr Love — Disclosures

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Commercial Support

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Agenda

Introduction: Adjuvant Immunotherapy for Localized Renal Cell Carcinoma (RCC)

Module 1: Metastatic Clear Cell RCC — Faculty Presentation

Module 2: Metastatic Clear Cell RCC — Survey Questions

Module 3: Non-Clear Cell RCC — Faculty Presentation

Module 4: Non-Clear Cell RCC — Survey Questions

Module 5: ASCO 2025

Agenda

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RTP RESEARCH TO PRACTICE

Survey of 50 Community-Based General Medical Oncologists
May 14-24, 2025

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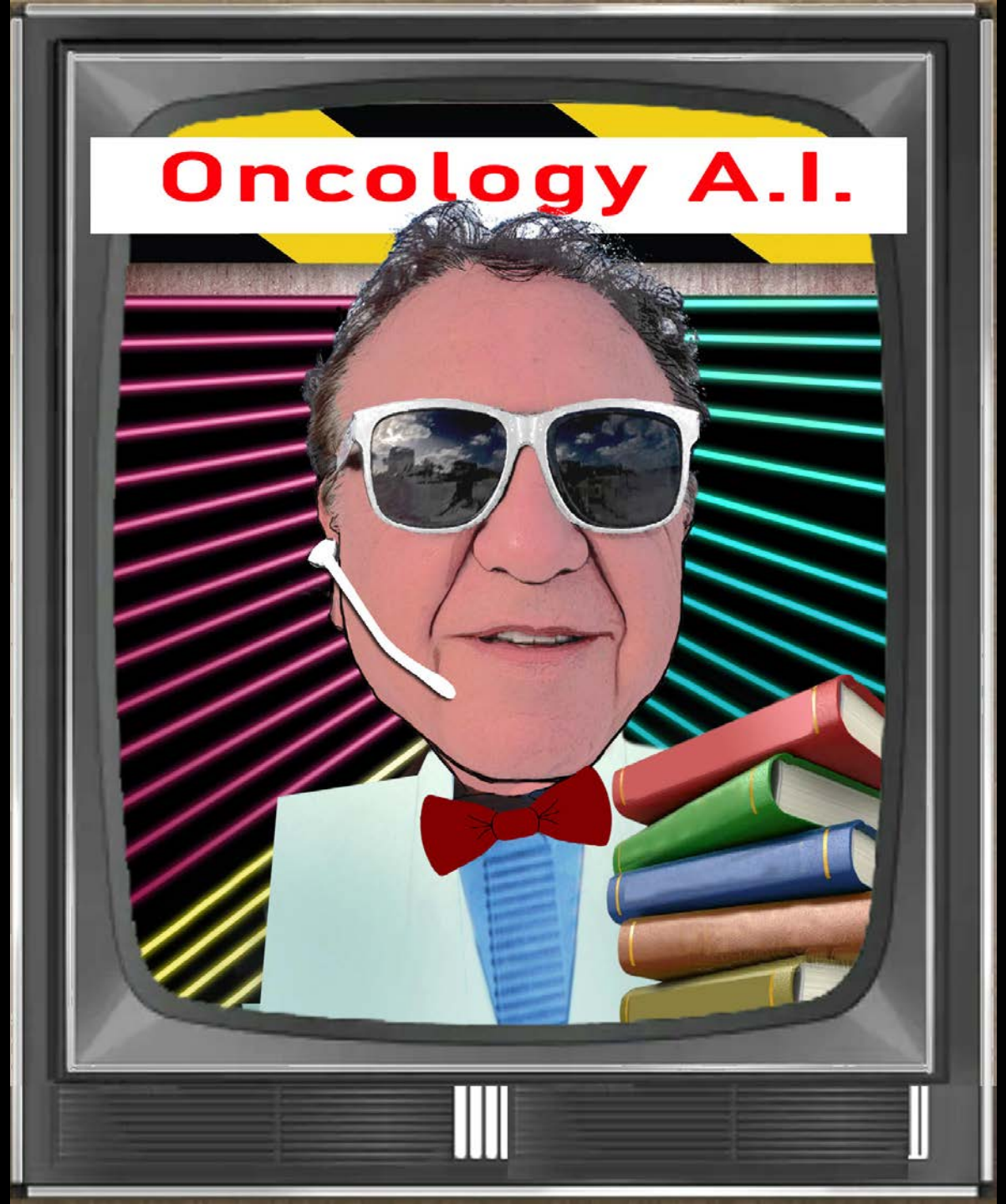
MAX HEADROOM


Oncology A.I.

Questions from General Medical Oncologists — Adjuvant Immunotherapy for Localized RCC

- **We have difficulties coordinating multidisciplinary management with urology and radiation oncology, including limited referrals from urology for patients with early-stage RCC who can qualify for adjuvant pembrolizumab.**
- **Insurance authorization is often a time-consuming hassle. Even when finally approved, there can be a delay in initiating therapy, which creates anxiety for both the patient and for the provider as well.**

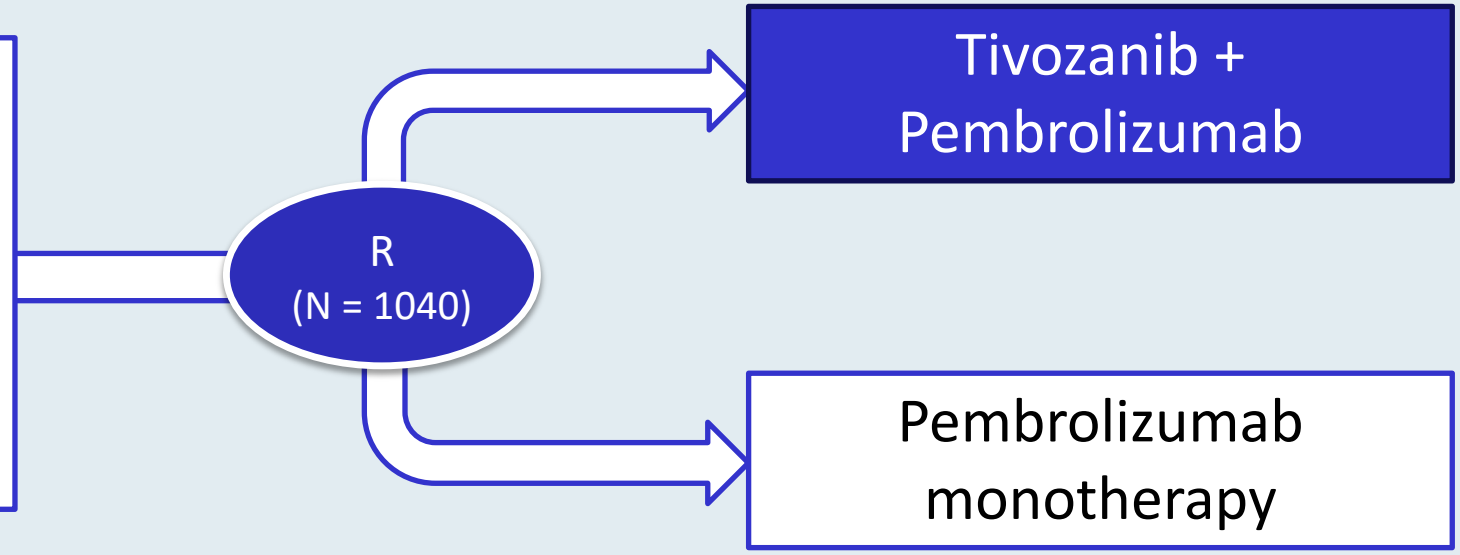
Questions from General Medical Oncologists — Adjuvant Immunotherapy for Localized RCC

- **Is there a specific online risk calculator that you recommend to assist in estimating the risk of recurrence, and if yes, what level of risk do you feel justifies adjuvant therapy?**
- **Do you recommend adjuvant pembrolizumab for patients with oligometastatic disease who have completed local therapy to all sites of disease?**
- **Any trials adding oral TKIs to IOs? CTLA-4 plus PD-1?**

Adjuvant Pembrolizumab ± Tivozanib: Phase III STRIKE Study

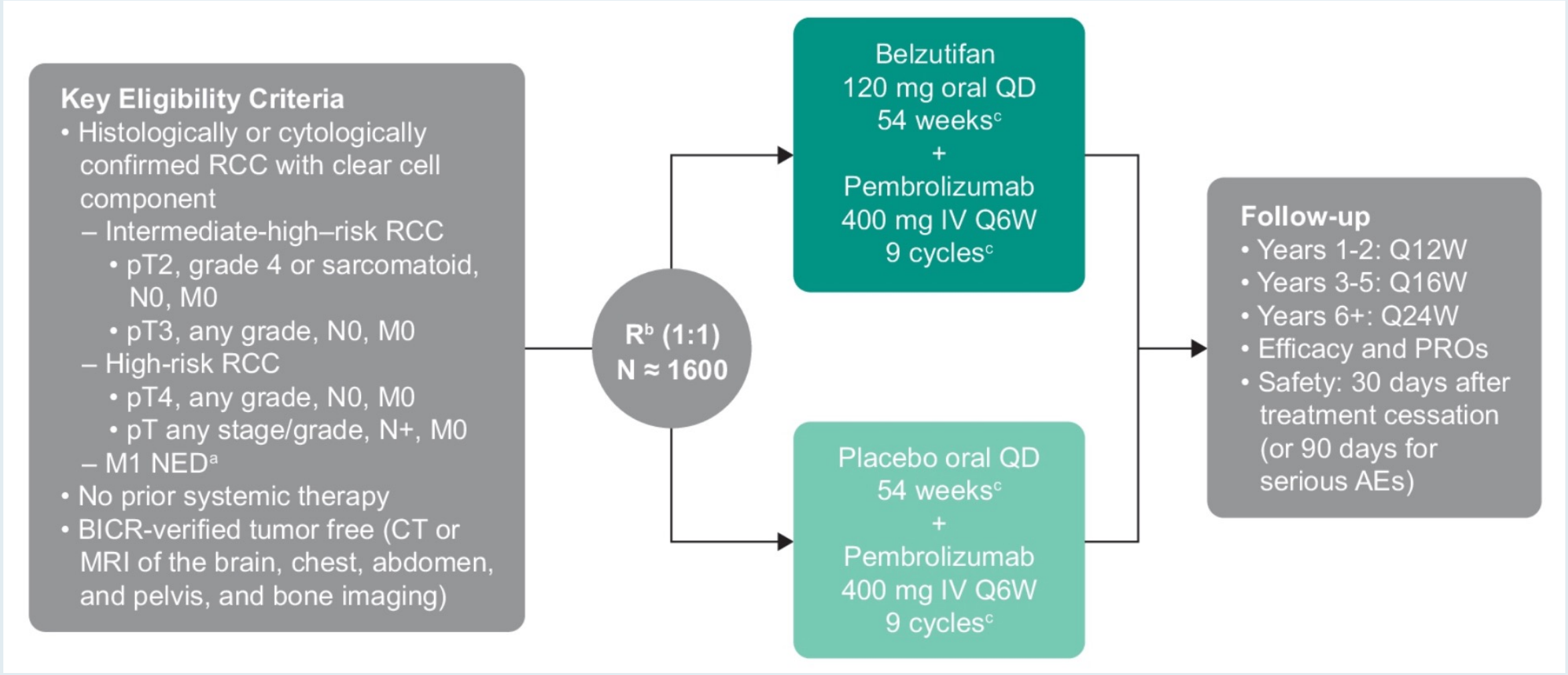
Key Inclusion Criteria:

- High-risk RCC with clear cell component with or without sarcomatoid features
- Complete resection of the primary tumor (radical or partial nephrectomy)



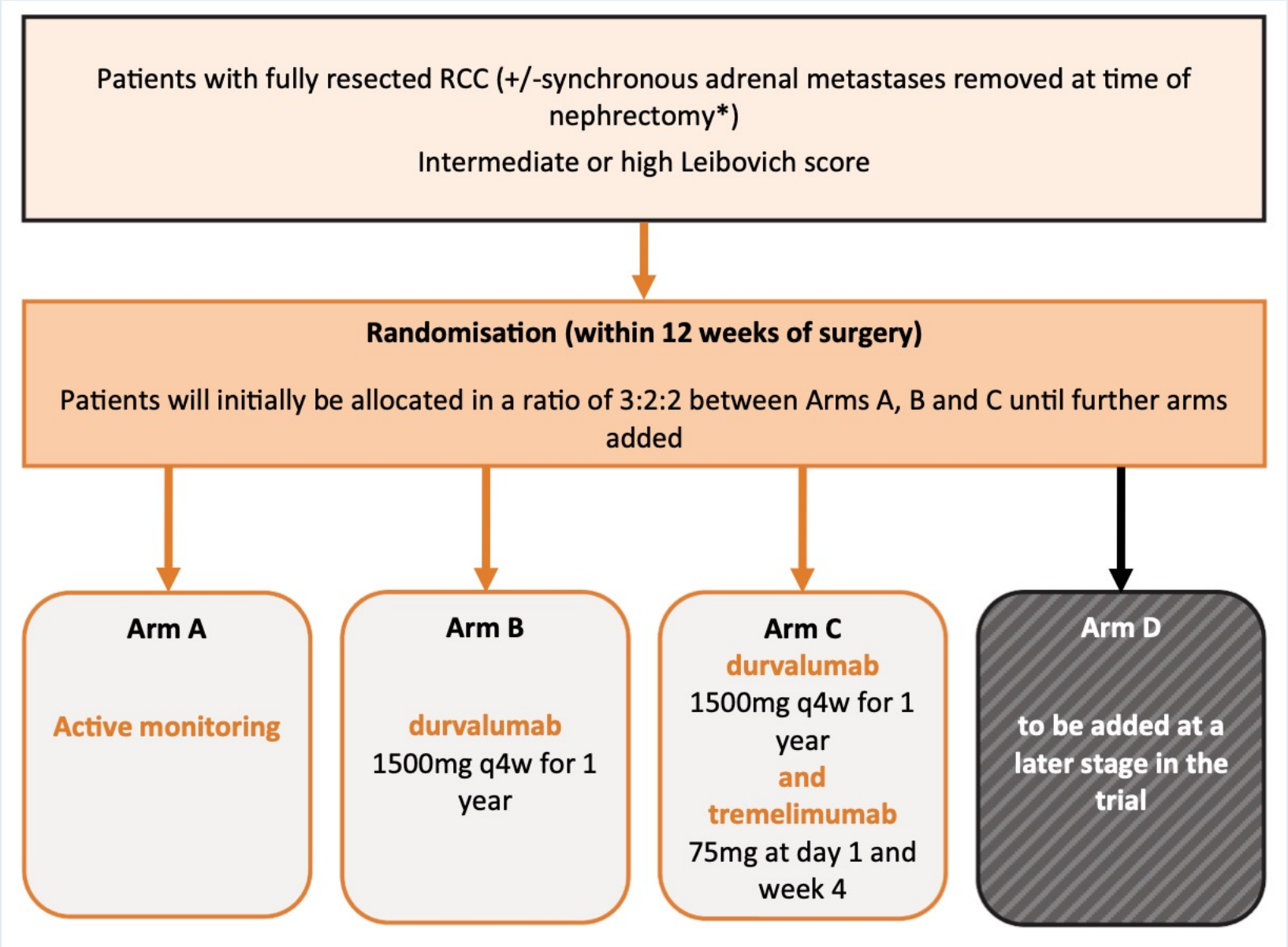
ClinicalTrials Identifier: NCT06661720. Accessed June 2025.

Adjuvant Pembrolizumab ± Belzutifan: Phase III LITESPARK-022 Study



Choueiri T et al. ASCO GU 2023;Abstract TPS748.

Adjuvant Durvalumab ± Tremelimumab: Phase III RAMPART Study



Oza B et al. *Contemp Clin Trials* 2021;108:106482.

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AN INTEGRATED APPROACH TO ONCOLOGY EDUCATION

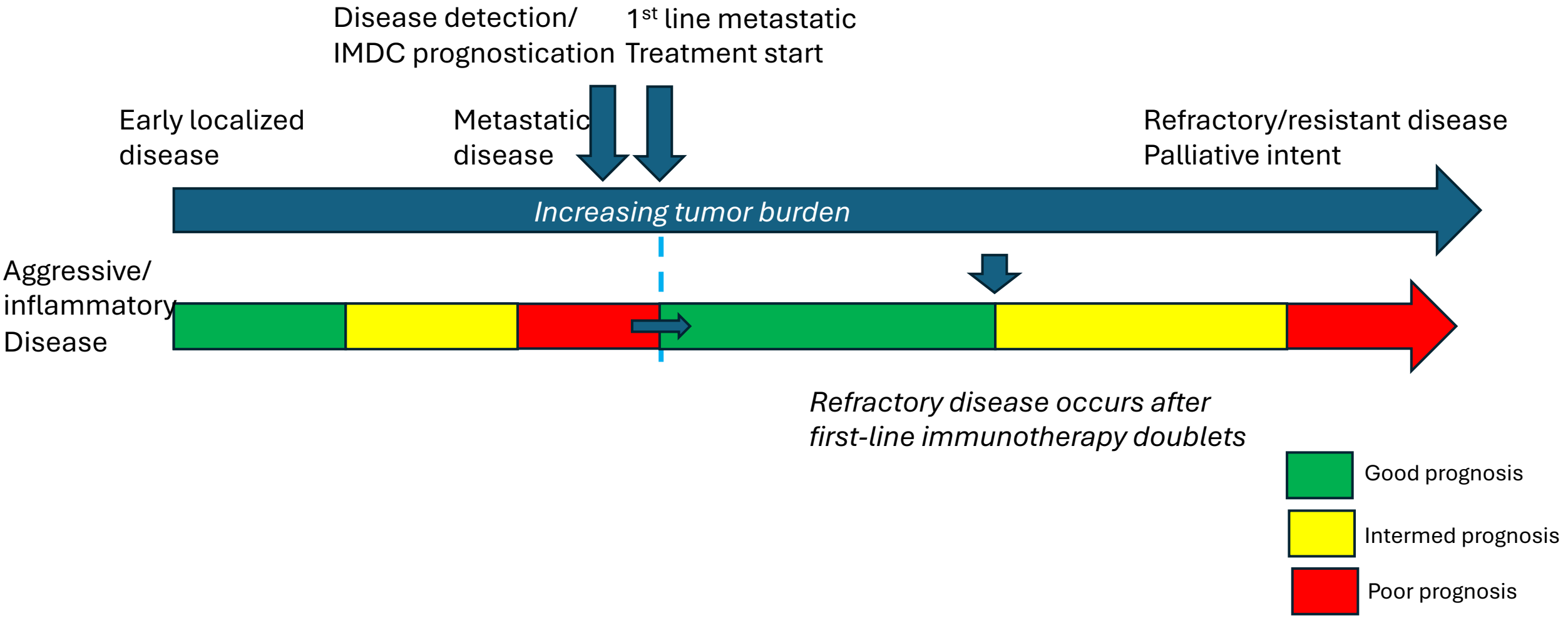
Management of metastatic renal cell carcinoma: from front line to refractory treatments

Tian Zhang, MD, MHS

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

Research To Practice
June 2, 2025

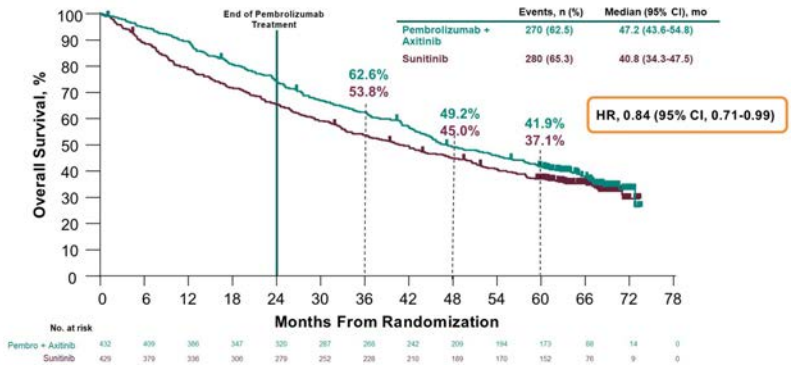
Modifying disease biology after treatment



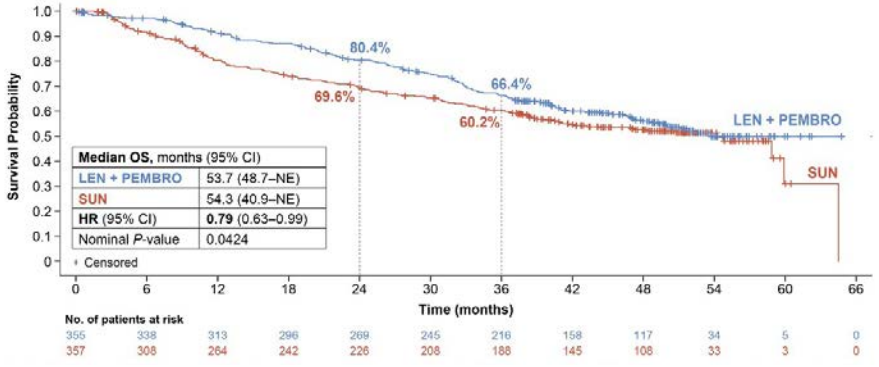
Adapted T. Powles KCRS 2023

Immune checkpoint inhibitor combinations have made a remarkable difference in ccRCC outcomes

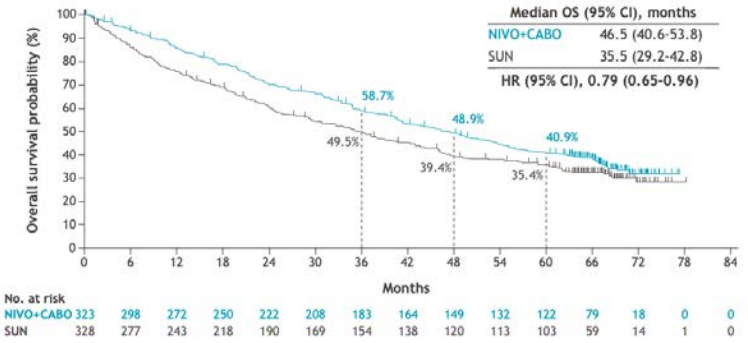
Keynote 426: OS
(5yr follow up)



CLEAR/Keynote 581: OS
(4yr follow up)

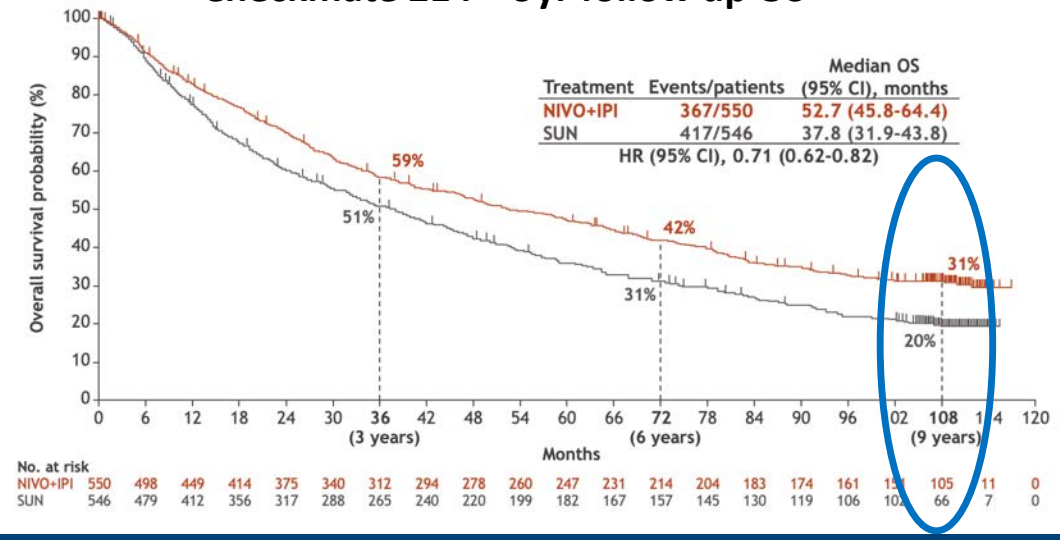


Checkmate 9ER OS
(5yr follow up)



Abstract 4505

Checkmate 214 – 9yr follow up OS

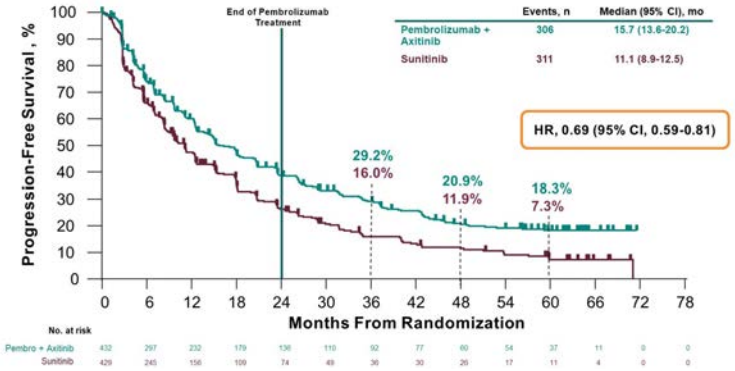


9-year survival in a *metastatic* population

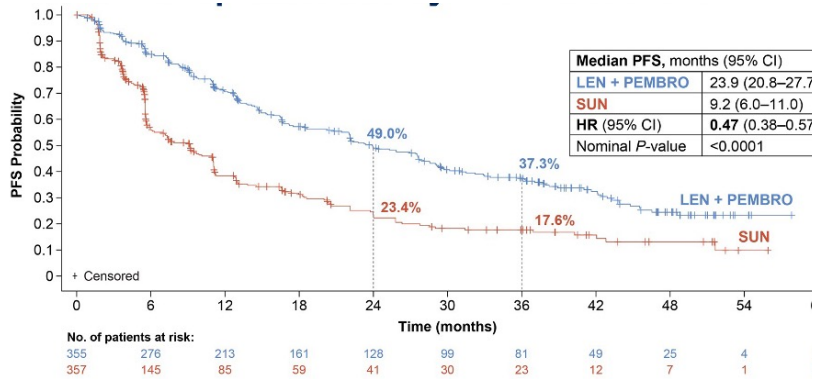
Choueiri TK et al, ASCO 2025
Rini BI et al, ASCO 2023
Motzer RJ, Porta C, Eto M, et al. *J Clin Oncol*. 2024.
Motzer RJ et al, *NEJM*, 2021
Motzer RJ et al, GU ASCO, 2025

Durability of responses across immunotherapy doublets

Keynote 426: PFS
ITT (5yr follow up)



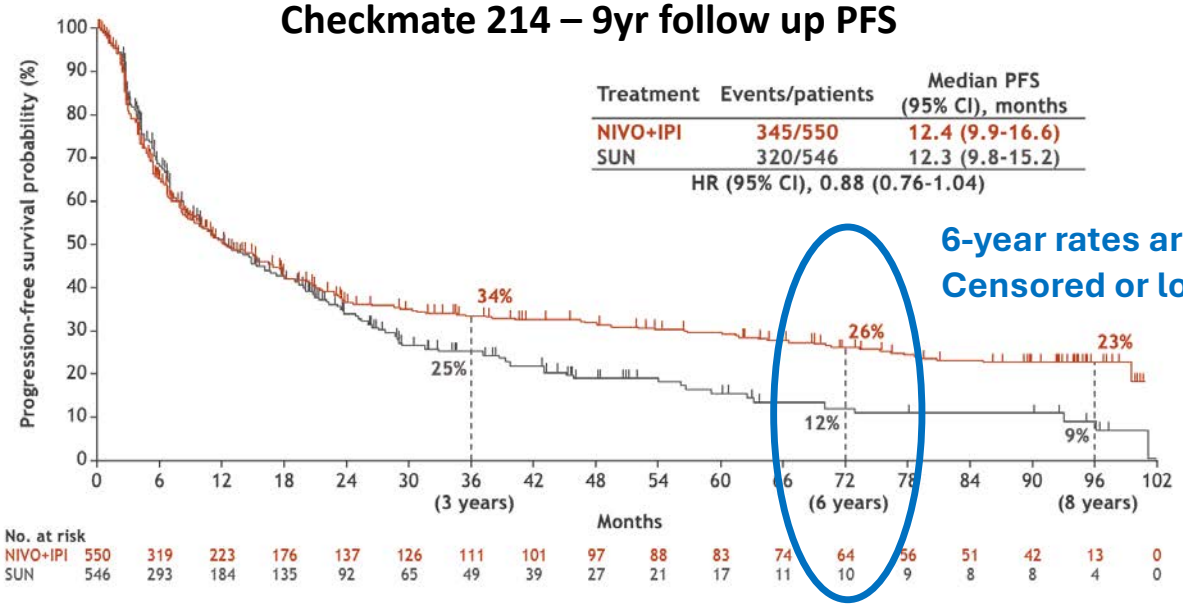
CLEAR/Keynote 581: PFS
(4yr follow up)



Checkmate 9ER PFS:
67mo follow up

Abstract 4505

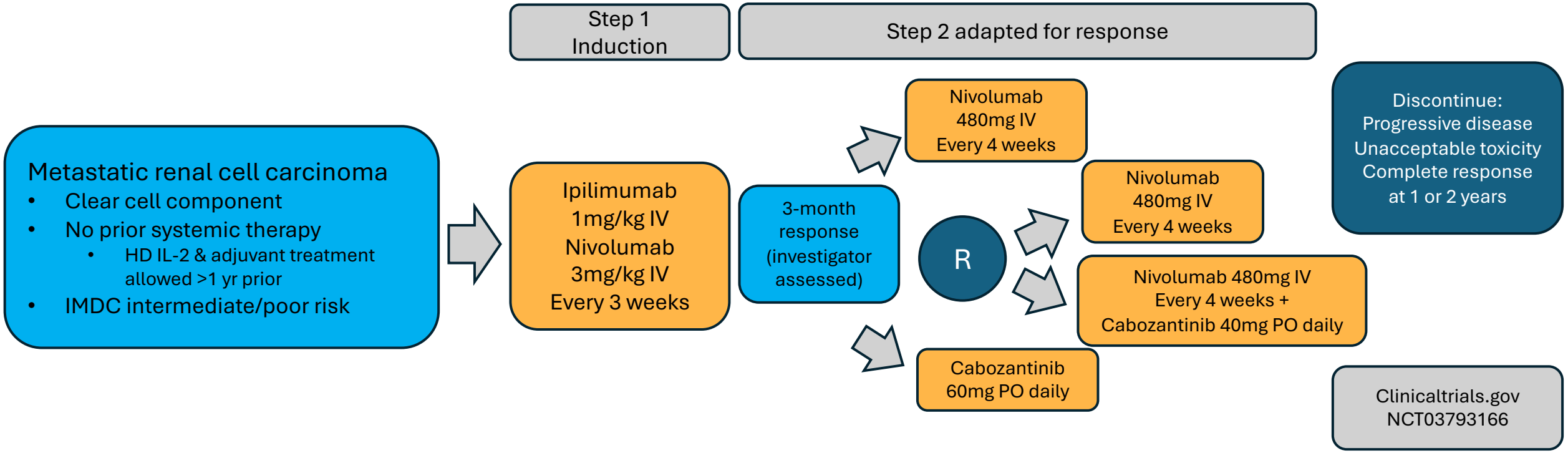
Checkmate 214 – 9yr follow up PFS



6-year rates are likely last dependable data
Censored or lost to follow up after 6 years

Choueiri TK et al, ASCO 2025
Rini BI et al, ASCO 2023
Motzer RJ et al, *NEJM*, 2021
Motzer RJ et al, GU ASCO, 2025

PDIGREE Design: Phase 3 Adaptive Trial

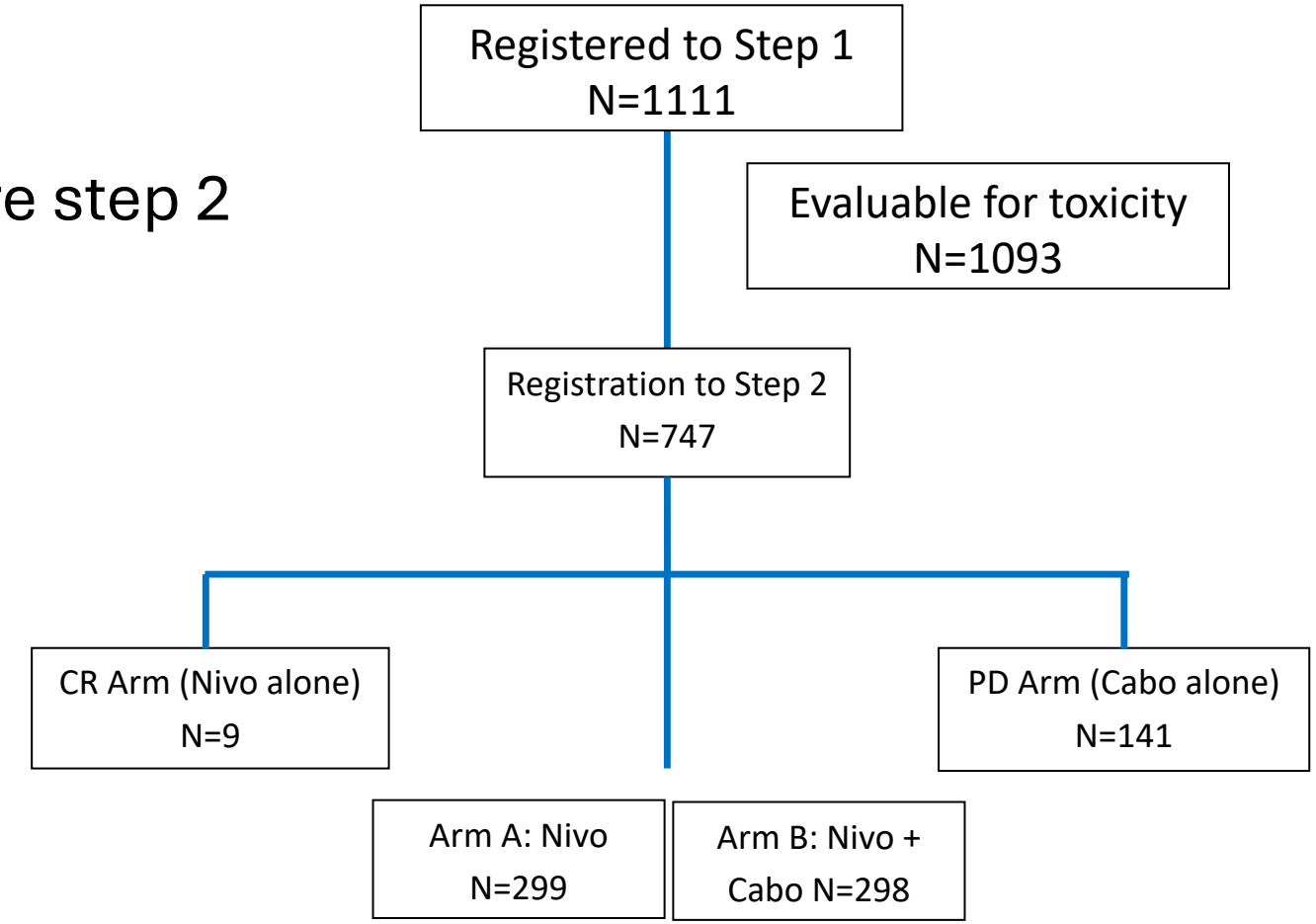


Primary endpoint: Overall Survival of randomized cohort

Zhang T et al, ASCO 2025

Step 1 Discontinuation Analysis

- 364 patients (33%) withdrew before step 2
  - 160 – AEs
  - 46 – PD
    - 5 before step 1 therapy
  - 42 – patient withdrew
    - 10 before step 1 therapy
  - 39 – alternative therapies
    - 1 before step 1 therapy
  - 37 – deaths
    - 15 from AEs; others due to disease
  - 12 – other complicating disease
  - 20 – other
    - 4 hospice; 2 screen failure before step 1 therapy
  - 8 – physician discretion



Zhang T et al, ASCO 2025

Step 1 & 2 Patient Characteristics

Patient Characteristics	ITT (Total =1111)	Step 1 Discontinued Subset (N=364)	Step 2 Subset (N=747)	P-value
Age, Median (range)	64 years (29-86)	64 years (39-86)	63 years (29-85)	0.197
Gender				
Male (%)	819 (73.7%)	255 (70.1%)	564 (75.5%)	0.053
Female (%)	292 (26.3%)	109 (29.9%)	183 (24.5%)	
Ethnicity				
Hispanic/LatinX	115 (10.4%)	27 (7.4%)	88 (11.8%)	0.068
Non-Hispanic	967 (87%)	330 (90.7%)	637 (85.3%)	
Race				
White	945 (85%)	313 (86%)	632 (84.6%)	0.772
Black	47 (4.2%)	16 (4.4%)	31 (4.1%)	
Asian	36 (3.2%)	10 (2.7%)	26 (3.5%)	
American Indian or Alaskan native	14 (1%)	3 (0.8%)	11 (1.5%)	

Zhang T et al, ASCO 2025

Step 1 & 2 Disease Characteristics

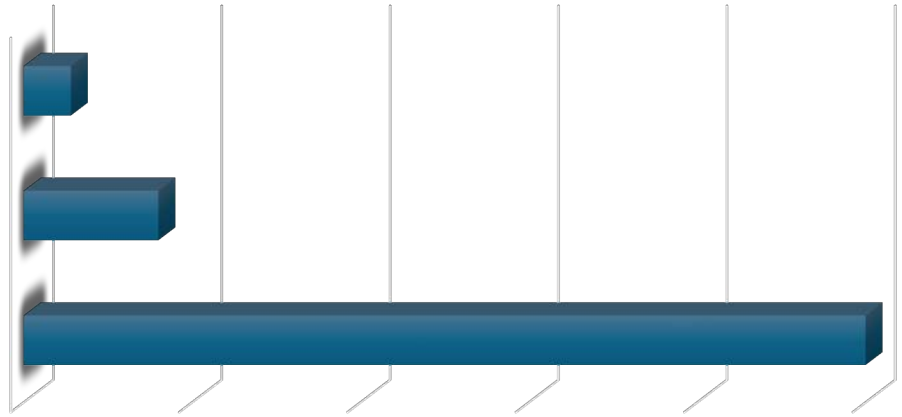
Disease Characteristics	ITT (Total =1111)	Step 1 Discontinued Subset (N=364)	Step 2 Subset (N=747)	P-value
IMDC risk				
Intermediate	849 (76.8%)	261 (72.3%)	588 (78.9%)	0.0144
Poor	257 (23.2%)	100 (27.7%)	157 (21.1%)	
Bone metastases				
Yes	307 (27.7%)	124 (34.2%)	183 (24.5%)	0.0007
No	803 (72.3%)	239 (65.8%)	564 (75.5%)	
De novo metastases				
Yes	603 (54.3%)	201 (55.2%)	402 (53.8%)	0.66
No	508 (45.7%)	163 (44.8%)	345 (46.2%)	
Enrolling site				
Academic center	458 (41.2%)	143 (39.3%)	315 (42.2%)	0.29
Community oncology	540 (48.6%)	177 (48.6%)	363 (48.6%)	
Regional center	113 (10.2%)	44 (12.1%)	69 (9.2%)	

- Of total in each group, 39% poor risk (vs 30.7% intermediate risk), 40% bone metastases (vs 30% without bone metastases), and 33% de novo metastatic disease (vs 32% without) patient cohorts did not proceed to Step 2

Zhang T et al, ASCO 2025

Step 1 Grade 3 or 4 Treatment-related toxicities

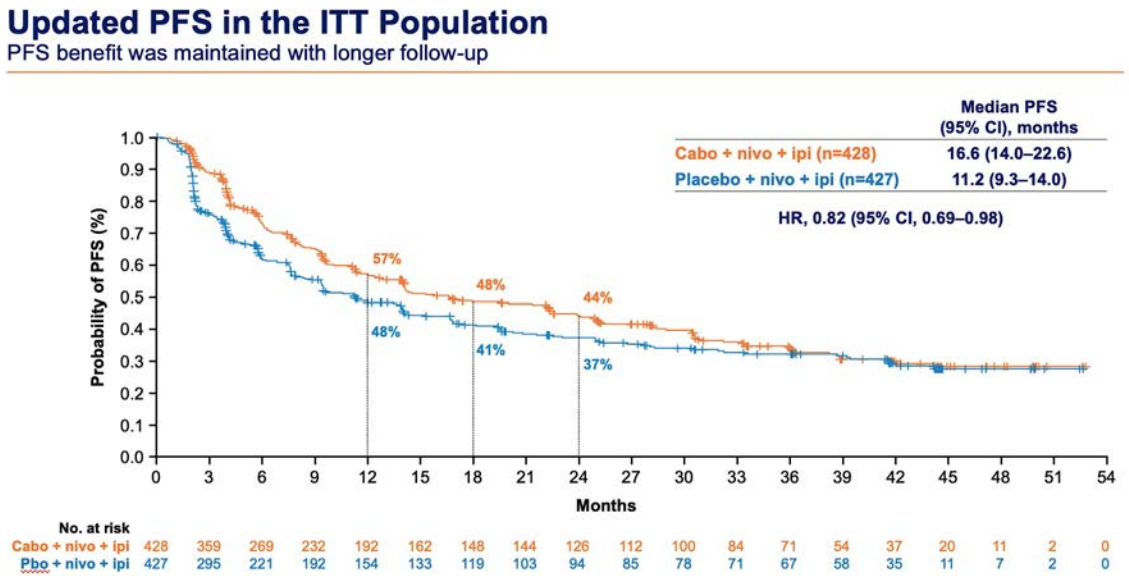
Common Adverse Events (N=1093)	Grade 3	Grade 4
Diarrhea	52 (5%)	1 (0.1%)
AST elevation	30 (3%)	4 (0.4%)
ALT elevation	30 (3%)	7 (1%)
Colitis	26 (2%)	4 (0.4%)
Maculopapular rash	26 (2%)	0
Adrenal insufficiency	19 (2%)	0
Fatigue	21 (2%)	0
Hypophysitis	16 (1%)	0

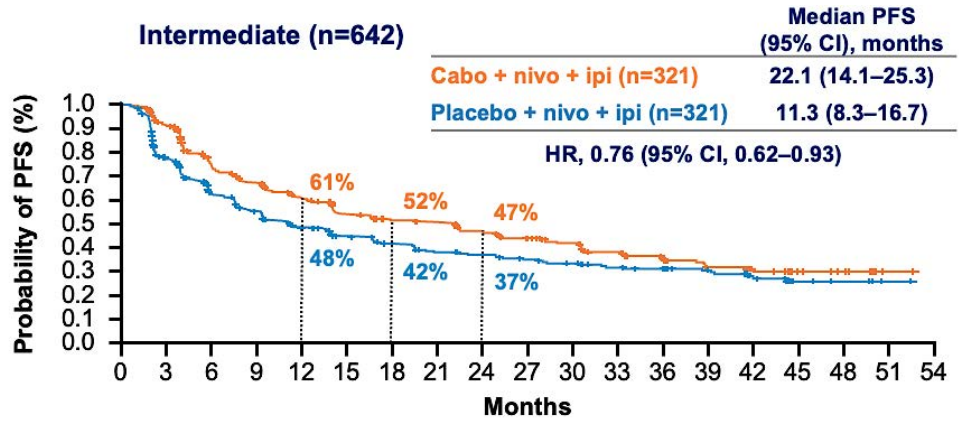


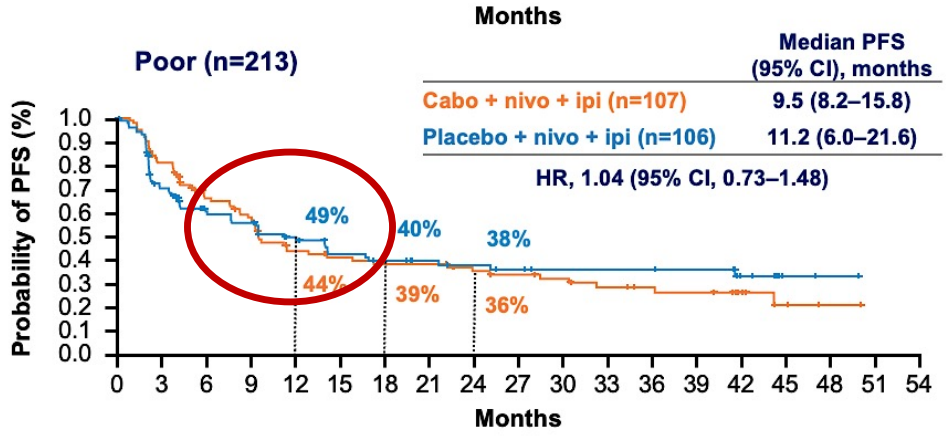
Fifteen grade 5 due to AEs: atrial fibrillation, hepatic failure, sepsis, nutritional disorder, renal disorder other, aspiration, cardiac arrest, respiratory failure x3, death or sudden death NOS x5

Zhang T et al, ASCO 2025

Frontline triplets – COSMIC 313 as a lesson







No overall survival benefit for cabo-ipi-nivo

Albiges et al, GU ASCO 2025

Triplet therapy had less dose exposure – Treatment exposure matters!

Treatment exposure and dose modifications

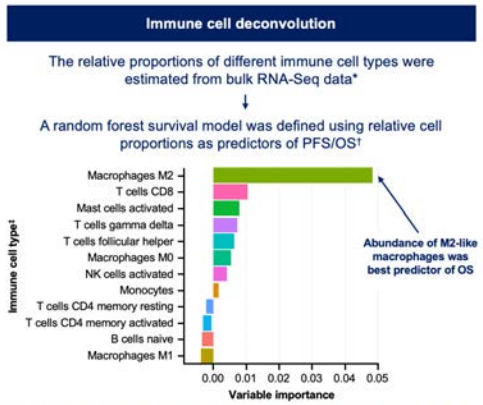
	Cabo + nivo + ipi (n=426)	Placebo + nivo + ipi (n=423)
Median duration of exposure of study treatment, months (range)	13.7 (0.2–53.4)	10.3 (0.1–55.3)
Median average daily dose of cabo/placebo, mg (range)	22.4 (3.6–40.0)	35.2 (0.8–40.0)
Median nivo infusions per patient, n (range)	11.0 (1–52)	9.0 (1–48)
1 / 2 / 3 / 4 cycles of ipi administered, %	7 / 22 / 13 / 58	6 / 7 / 13 / 74
Dose modification (any treatment component) due to AE, %	92	76
Treatment-related AE leading to discontinuation of ≥1 component, %	49	26

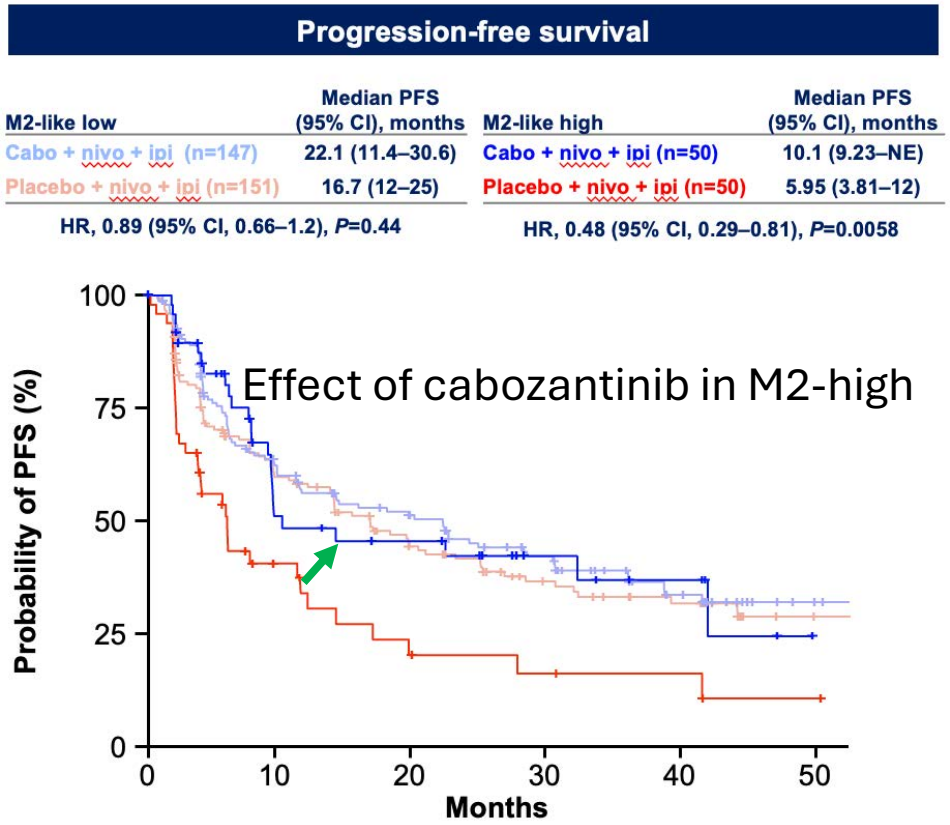
Triplet therapy:

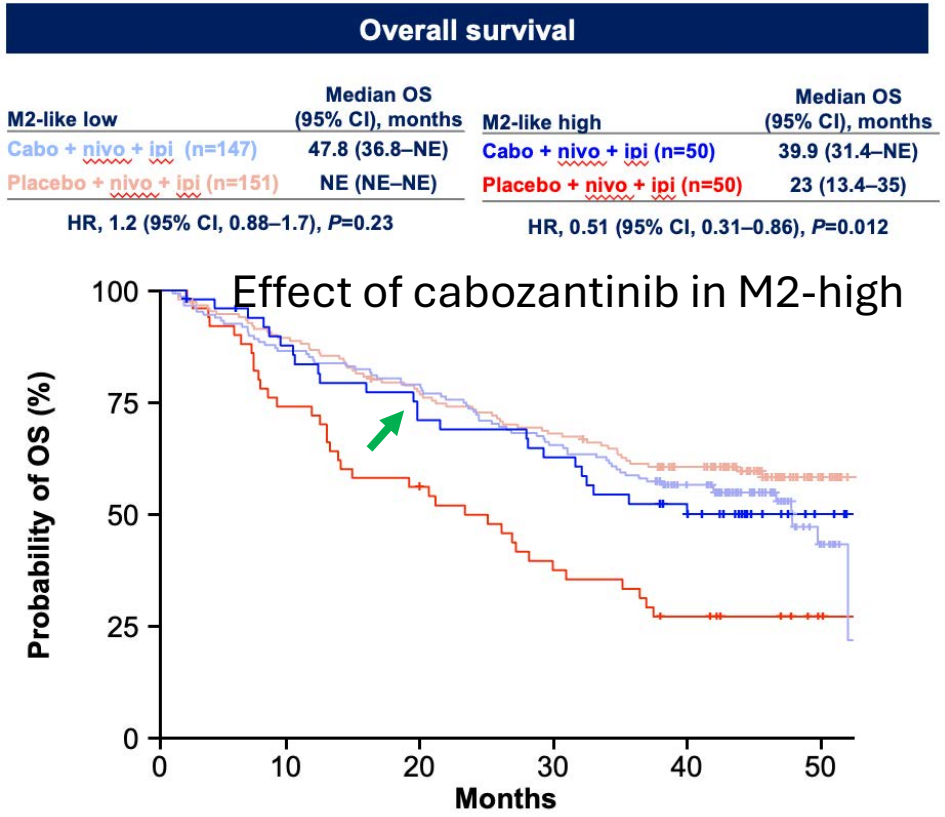
- Less average daily dose of cabozantinib
- Fewer received 4 cycles of ipilimumab
- Almost all patients had dose modification & half discontinued at least 1 study treatment

Albiges et al, GU ASCO 2025

M2-high tumors associated with poor prognosis: Improved outcomes with cabozantinib







Albiges et al, GU ASCO 2025

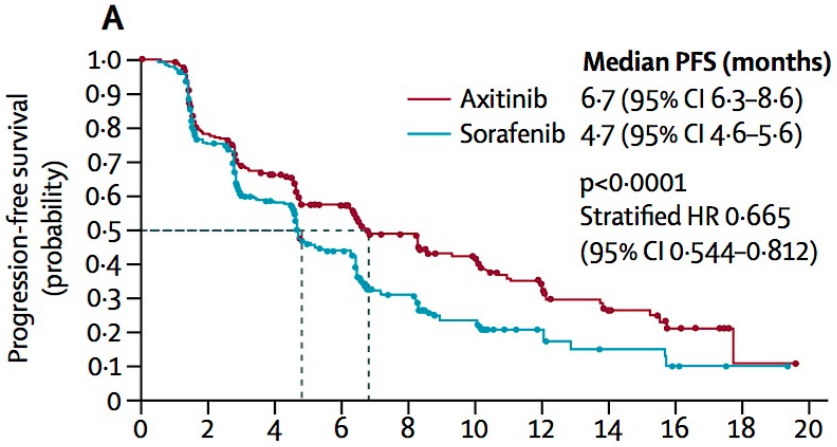
Successful registrational trials in refractory setting

	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%	23%
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)	0.91 (0.72-1.17)	0.88* (0.73-1.07)

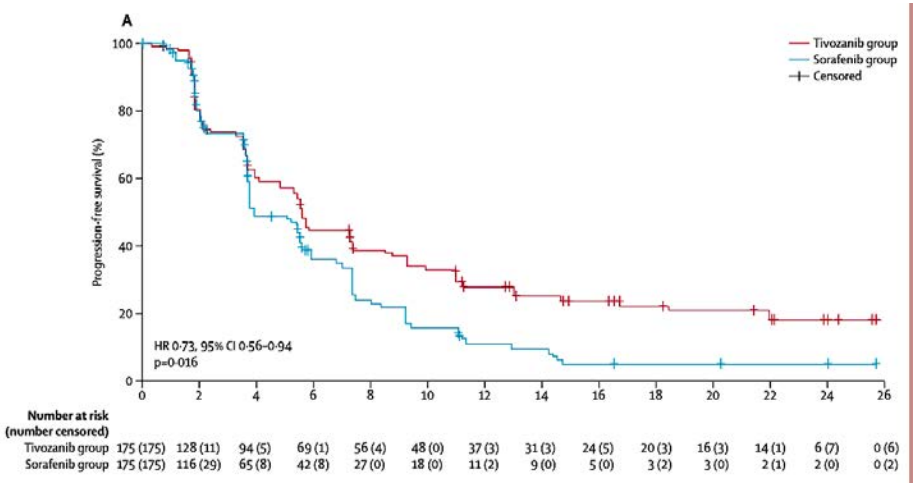
Rini BI et al, *Lancet*, 2011
Choueiri TK et al, *NEJM*, 2015
Motzer RJ et al, *NEJM*, 2015
Motzer RJ et al, *Lancet Onc*, 2015
Rini BI et al, *Lancet Onc*, 2020
Choueiri TK et al, *NEJM*, 2024

Progression free survival across trials

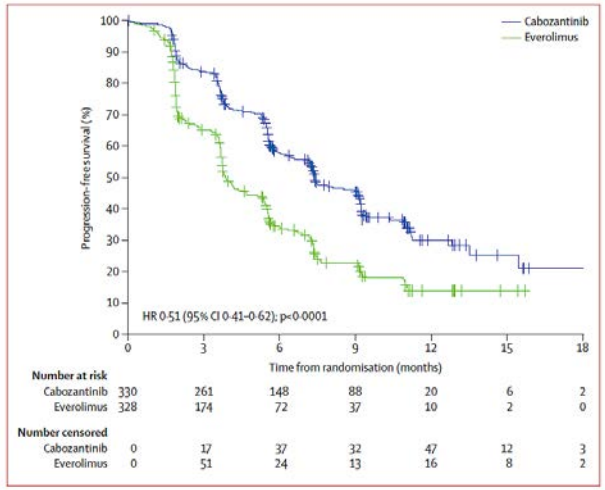
AXIS - Axitinib vs Sorafenib PFS



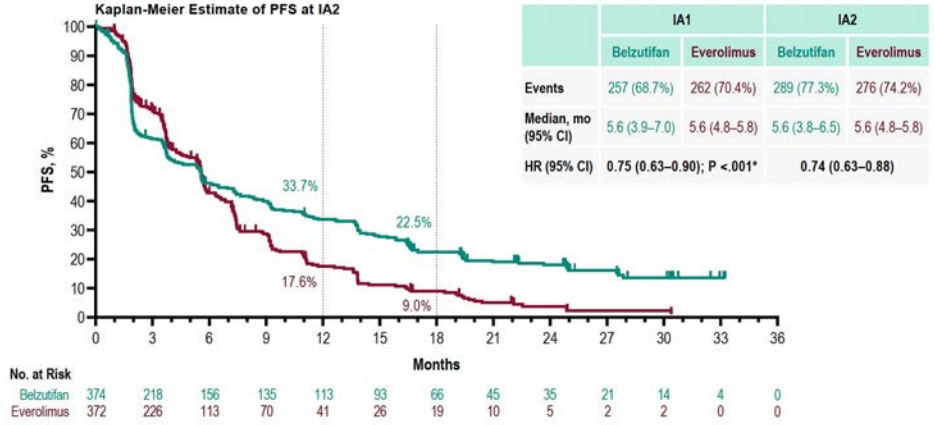
TIVO-3 – Tivozanib vs sorafenib PFS



METEOR – cabozantinib vs everolimus



LITESPARK 005 – belzutifan vs everolimus



	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

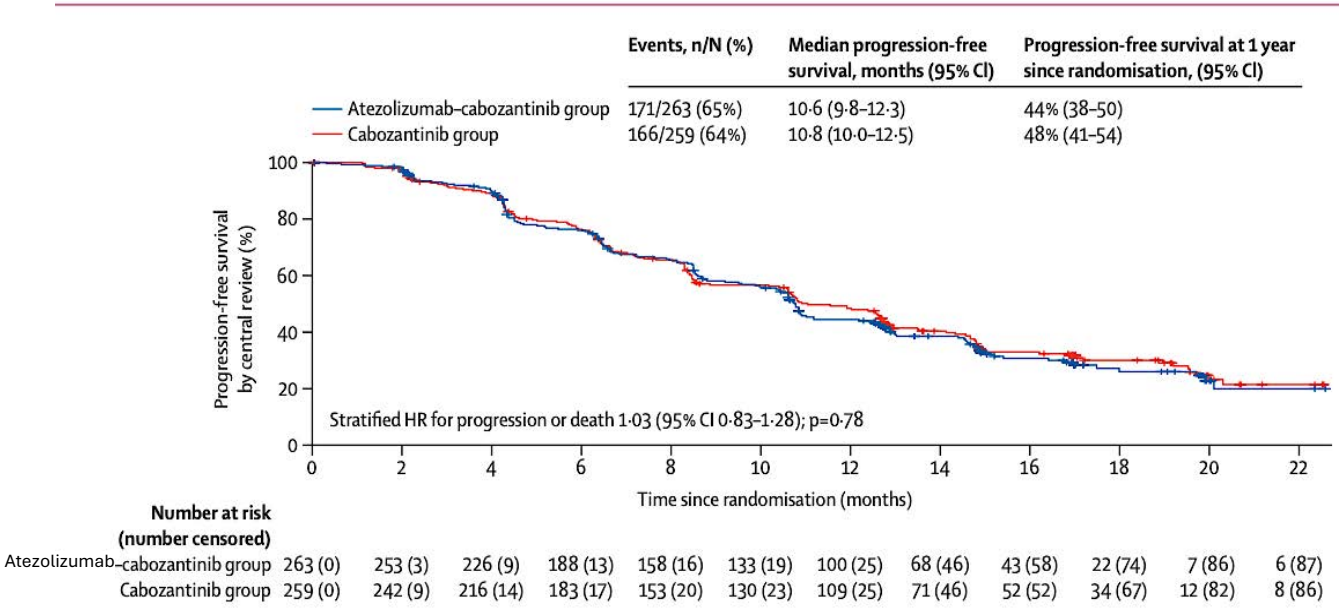
Less successful trials in refractory disease

	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)	**

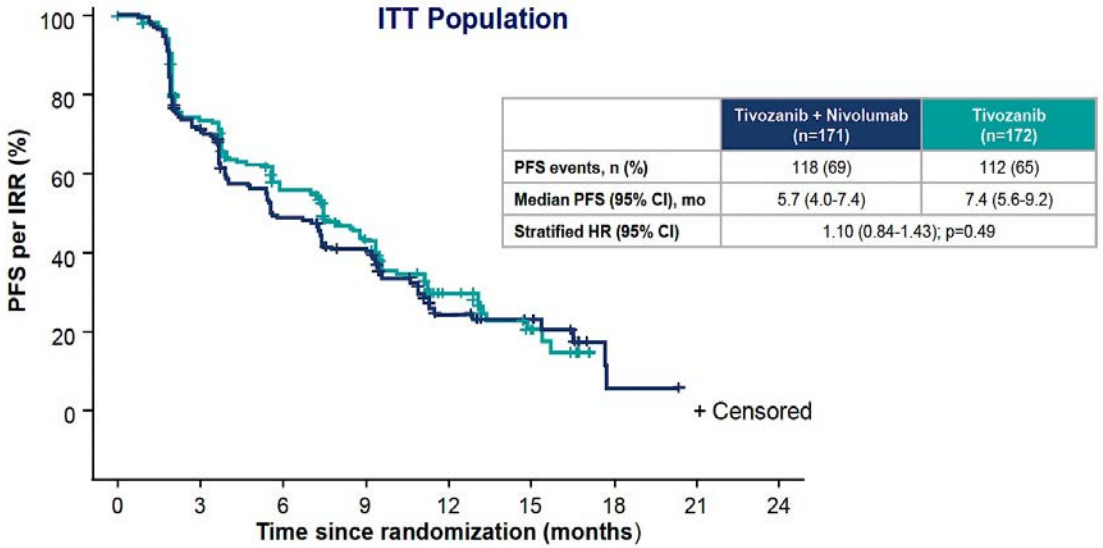
Pal SK et al, *Lancet*, 2023
Choueiri TK et al, ESMO Annual Congress, 2024
Tannir NM et al, r RJ et al, *Lancet Onc*, 2015
Rini BI et al, *Lancet Onc*, 2020
Choueiri TK et al, *NEJM*, 2024

Lessons learned from CONTACT-03 and TiNIVO2

CONTACT-02



TiNIVO-2



PD-1 or PDL1 inhibition after prior progression on immunotherapy does not improve PFS outcomes

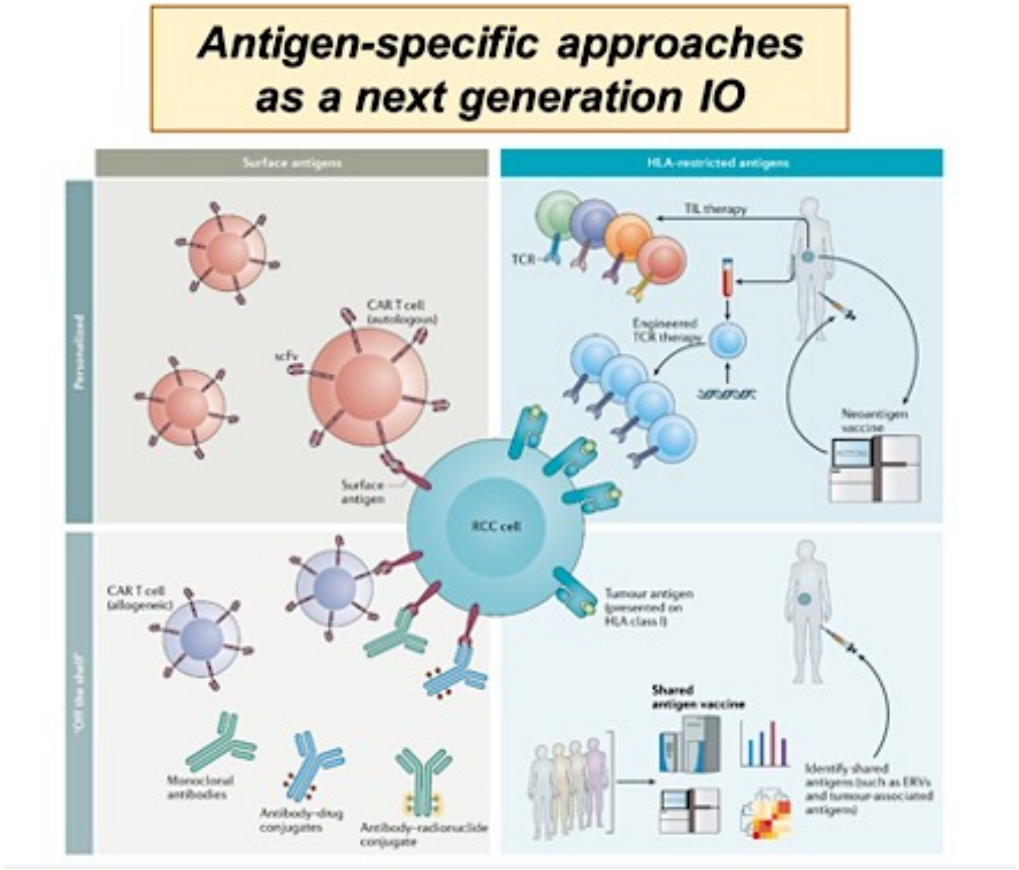
HIF2a inhibitor trials in refractory RCC

	LITESPARK 005	ARC-20	ARC-20	ARC-20	LITESPARK 003	Keymaker U03	ARC-20
Treatment Sample size	Belzutifan vs Everolimus N=746	Casdatifan 50mg BID N=32	Casdatifan 50mg daily N=28	Casdatifan 100mg daily N=27	Belzutifan 120mg daily + Cabozantinib	Belzutifan 120mg daily + Lenvatinib 20mg daily N=63	Casdatifan 100mg daily+ Cabozantinib 60mg daily N=24
ORR (%)	23%	25%	29%	33%	31%	46.9%	45.8%
mPFS (months)	5.6	NR	NR	NR	13.8	12.5	NR
HR (95% CI)	0.74 (0.63-0.88)	n/a	n/a	n/a	n/a	n/a	n/a
mOS & HR (95% CI)	0.88 (0.73-1.07)	n/a	n/a	n/a	26.7 (n/a)	n/a	n/a
Grade 3/4 anemia	32.5%	42%	32%	17%	15%	~20%	24%

ASCO Abstract 4506 – ARC-20

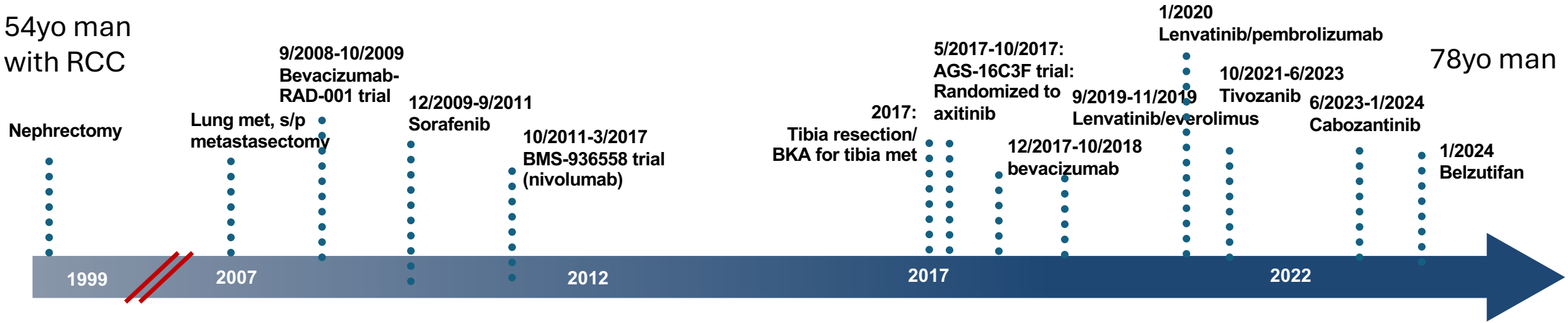
Choueiri TK et al, *NEJM*, 2024
Choueiri TK et al, ESMO 2023
Albiges L et al, GU ASCO 2025
Choueiri TK et al, GU ASCO 2025
Choueiri TK et al, ASCO 2025

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

Agenda

Introduction: Adjuvant Immunotherapy for Localized Renal Cell Carcinoma (RCC)

Module 1: Metastatic Clear Cell RCC — Faculty Presentation

Module 2: Metastatic Clear Cell RCC — Survey Questions

Module 3: Non-Clear Cell RCC — Faculty Presentation

Module 4: Non-Clear Cell RCC — Survey Questions

Module 5: ASCO 2025

Approximately how many patients with metastatic clear cell renal cell carcinoma (ccRCC) are currently in your practice?

Median: 6

Have you administered the following for metastatic ccRCC on or off protocol?

Nivolumab/Ipilimumab/cabozantinib: 14 (28%)

Tivozanib alone or in combination nivolumab: 14 (28%)

Questions from General Medical Oncologists — First-Line Treatment for mccRCC

- We have 2 main choices for therapy with either combination TKI/IO or dual checkpoint inhibitor therapy. How do we decide which option may be best for an individual patient; and are there any biomarkers that may be useful to help with this decision.
- Although I stick to the data and try to provide the most updated and data-driven treatment, I'm always plagued by the confusion of what the single “Best of the Best” is the best. As a general oncologist, renal cancer is a small part of my practice, but it provokes the same therapeutic anxieties as all the other cancers I treat. I guess that's inherent in the field of medical oncology today.

Questions from General Medical Oncologists — First-Line Treatment for mccRCC

- An 87-year-old man with metastatic RCC, intermediate-poor risk. Pt started on axi/pembro and did not tolerate axi well. Should a single-agent treatment be considered?
- A 76-year-old female with 3 sites of metastases a few years after nephrectomy. Asymptomatic. Good risk. Pt has to take care of ill husband. Poor social support. Should I provide SBRT to all 3 sites vs single-agent TKI or IO vs combination of TKI/IO vs combination of IO/IO?

Questions from General Medical Oncologists — COSMIC-313 Trial

- In light of the COSMIC-313 trial results showing improved progression-free survival but no overall survival benefit and increased toxicity with the addition of cabozantinib to nivolumab and ipilimumab, how should clinicians approach the use of this triplet?
- How does nivo/ipi/cabo compare to nivo/cabo?
- Toxicity related to this combination?

Questions from General Medical Oncologists — Subcutaneous Nivolumab

- **Are there any insurance issues in getting subcutaneous nivolumab? Any compromise in efficacy?**
- **What is the potential impact of subcutaneous nivolumab on patient adherence and clinic resource utilization compared to the IV formulation?**
- **Nivo just with cabo?**

Questions from General Medical Oncologists — Relapsed/Refractory mccRCC

- Role of immunotherapy in patients with recurrent disease who have been pretreated in the past with IO in the adjuvant setting.
- How do you sequence treatment options in the second-line setting for metastatic ccRCC? Tivozanib vs belzutifan? Does belzutifan have activity in patients without VHL mutation?
- Any clinical pearls for managing the side effects of tivozanib, belzutifan and lenvatinib/everolimus?

Questions from General Medical Oncologists — Relapsed/Refractory mccRCC

- What evidence or clinical experience supports choosing cabozantinib versus lenvatinib/everolimus in patients progressing on front-line pembrolizumab/axitinib? What is the role of tivozanib in this setting?
- Who is the ideal patient for belzutifan? Please comment on management of hypoxia.
- I typically choose cabozatinib vs lenvatinib/everolimus based on how symptomatic the patient is. I'd like to see some guidance.

Questions from General Medical Oncologists — Relapsed/Refractory mccRCC

- **Did TiNivo-2 definitively confirm that ICI rechallenge following progression on ICI therapy should be discouraged in *all* cases? Does is matter whether the patient progressed on ICI as the most recent line of therapy or after an ICI followed by non-ICI agents?**
- **Would tivozanib be a reasonable option after first-line cabo/nivo? Is it effective in the second line, or would trying another MOA be better?**
- **Which of the various TKIs do you view as most tolerable?**

Agenda

Introduction: Adjuvant Immunotherapy for Localized Renal Cell Carcinoma (RCC)

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Module 5: ASCO 2025

RTP RESEARCH TO PRACTICE

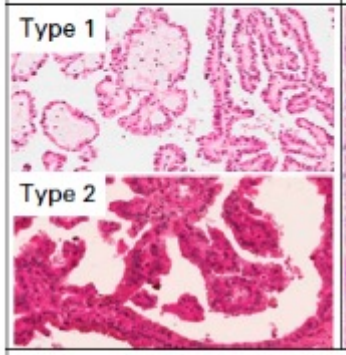
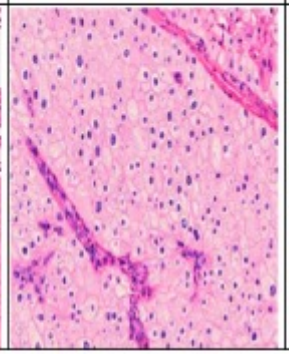
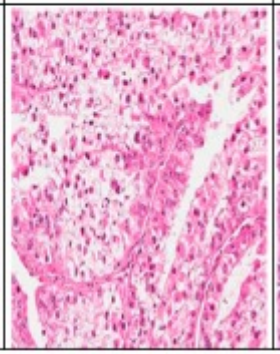
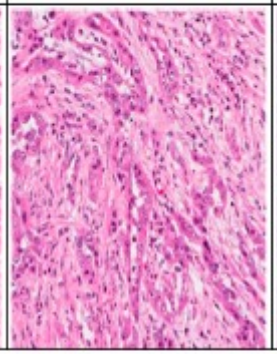
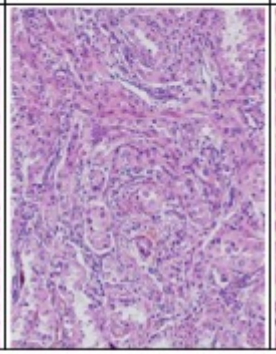
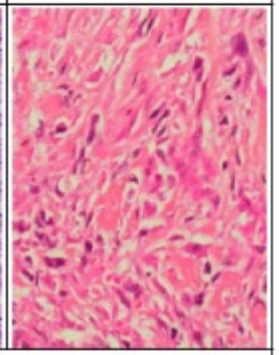
Non-Clear Cell RCC

Professor Laurence Albiges, MD, PhD

Gustave Roussy Cancer Center

Villejuif, France

NON-CLEAR CELL RENAL CELL CARCINOMA (NCCRCC) SUBTYPES HAVE DISTINCT MOLECULAR AND GENOMIC FEATURES

Papillary		Chromophobe	Translocation	Collecting Duct	Medullary	Sarcomatoid
 Type 1 / Type 2						
Cytogenetic Alterations						
Type 1 Gain Chr. 7, 17	**Type 2** Del Chr. 9p	Del Chr. 1, 2, 6, 10, 13, 17	Transloc. Xp11.2 [*TFE3*] Transloc. (6;11) [*TFEB*]	Del Chr. 8p, 16p, 1p, 9p Gain Chr. 13q	Del. 22q	-
Molecular Alterations						
Type 1 *MET* *TERT* *CDKN2A/B* *EGFR*	**Type 2** *SETD2* *CDKN2A/B* *NF2* *FH* *TERT*	*TP53* *PTEN* *TERT* fusion *MTOR, TSC1/2* *MT-ND5*	*TFE3* fusion *TFEB* fusion	*NF2* *SETD2* *SMARCB1* *CDKN2A*	*SMARCB1* rearrangements	*TP53* *CDKN2A* *NF2* *RELN* *BAP1* *ARID1A*
Pathway Deregulations						
Activation Cell cycle MAP kinases **Deregulation** Chromatin remodeling	**Activation** Cell cycle Hippo NRF2-ARE **Deregulation** Chromatin remodeling Metabolism Methylation	**Activation** MTOR APOBEC **Deregulation** Metabolism	**Activation** TNF TGF-β MTOR **Downregulation** HIF/VEGF **Deregulation** Chromatin remodeling	**Activation** Immune response Cell cycle **Deregulation** Metabolism	-	**Activation** Cell cycle TGF-β **Deregulation** Chromatin remodeling

Adapted from Albiges, et al. *J Clin Oncol* 2018 Oct 29:JCO2018792531. doi: 10.1200/JCO.2018.79.2531.

SINGLE AGENT TKI

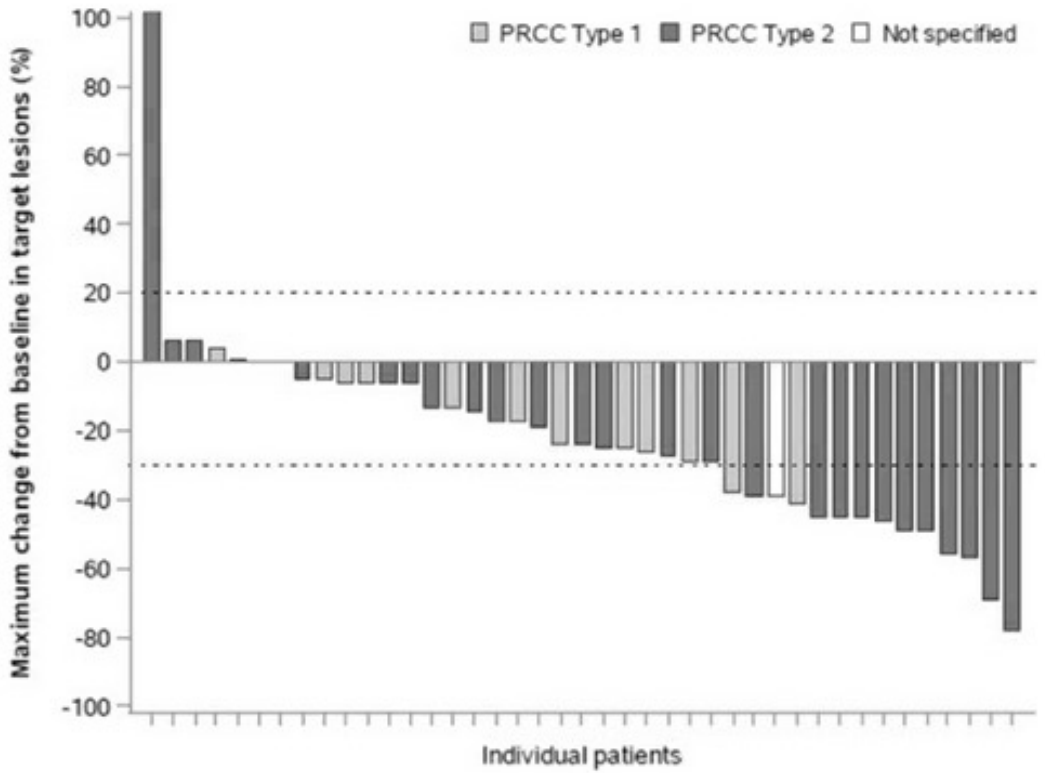
HISTORICAL STUDIES – SUNITINIB AND EVEROLIMUS

Clinical Trial	Treatment	Histology	ORR, %	PFS, mo
SUPAP [24]	Sunitinib	Metastatic pRCC	13 (type I) and 11 (type II)	6.6 (type I) and 5.5 (type II)
RAPTOR [49]	Everolimus	Metastatic pRCC		7.9 (type I) and 5.1 (type II)
ESPN [20]	Sunitinib vs everolimus	vRCC and ccRCC with >20% sarcomatoid features	9 vs 3	6.1 vs 4.1
ASPEN [19]	Sunitinib vs everolimus	vRCC	18 vs 9	8.3 vs 5.6
RECORD-3 [21]	Sunitinib-everolimus vs everolimus-sunitinib	vRCC and ccRCC	—	7.2 vs 5.1
GLOBAL ARCC [22]	Temsirolimus vs interferon-α	vRCC and ccRCC	5 vs 8	7 vs 1.8

Flippot et al. 2020

AXITINIB
PAPILLARY RCC – AXIPAP TRIAL

Endpoints	Type 1 subgroup ($N = 13$)	Type 2 subgroup ($N = 28$)
Best response		
PR	1 (7.7%)	10 (35.7%)
SD	10 (76.9%)	16 (57.1%)
PD	2 (15.4%)	2 (7.1%)
Median PFS (months)	6.7 (95% CI, 2.9–14.0)	6.2 (95% CI, 5.4–9.2)
24w-PFR	46.2 (95% CI, 23.4 to +∞)	42.9 (95% CI, 27.5 to +∞)
Median OS (months)	NR	17.4 (95% CI, 11.4–NR)



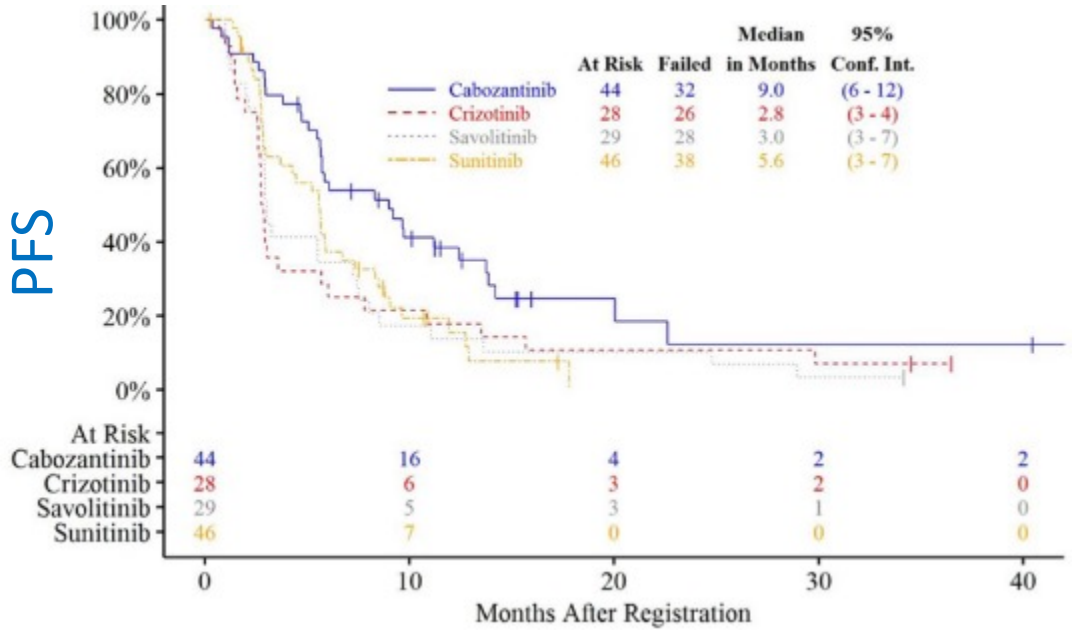
Négrier et al. EJC 2020

CABOZANTINIB
PAPILLARY RCC – PAPMET TRIAL

mPRCC
- Histologically confirmed diagnosis of type 1 PRCC
- Measurable disease
- 0-1 prior lines of therapy
- No prior therapy with sunitinib
- ECOG 0-1

1:1:1:1 RANDOMIZATION

- SUNITINIB
- CABOZANTINIB
- ~~CRIZOTINIB~~
- ~~SAVOLITINIB~~



	Sunitinib [n (%)]	Cabozantinib [n (%)]
Complete Response	0 (0)	2 (5)
Partial Response (PR)	2 (4)	8 (18)
Unconfirmed Partial Response	1 (2)	2 (5)
Stable Disease	23 (50)	23 (51)
Increasing Disease	11 (24)	4 (9)

Pal S. Presented at the 2021 Genitourinary Cancers Symposium. By permission of Prof S.K. Pal; Pal S, *et al.* Lancet 2021;397(10275):695–703.

Comprehensive Molecular Characterisation of Papillary Renal-Cell Carcinoma

The Cancer Genome Atlas Research Network. N Engl J Med 2016;374(2):135-45

Characterisation of clinical cases of advanced papillary renal cell carcinoma via comprehensive genomic profiling

Pal SK, *et al.* European Urology 2018;73:71-78

MET is a potential target across all papillary renal cell carcinomas: Result from a large molecular study of PRCC with CGH array and matching gene expression array

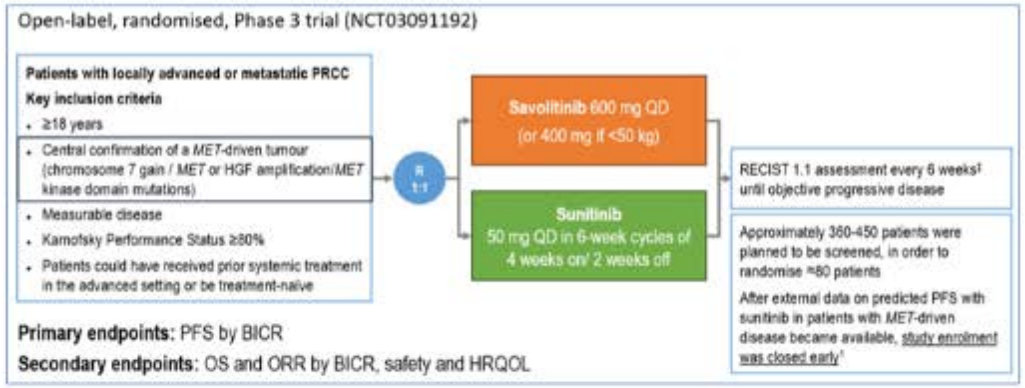
Albiges L, *et al.* Clin Cancer Res 2014;20(13):3411-21

MET INHIBITORS: PHASE 2 TRIALS

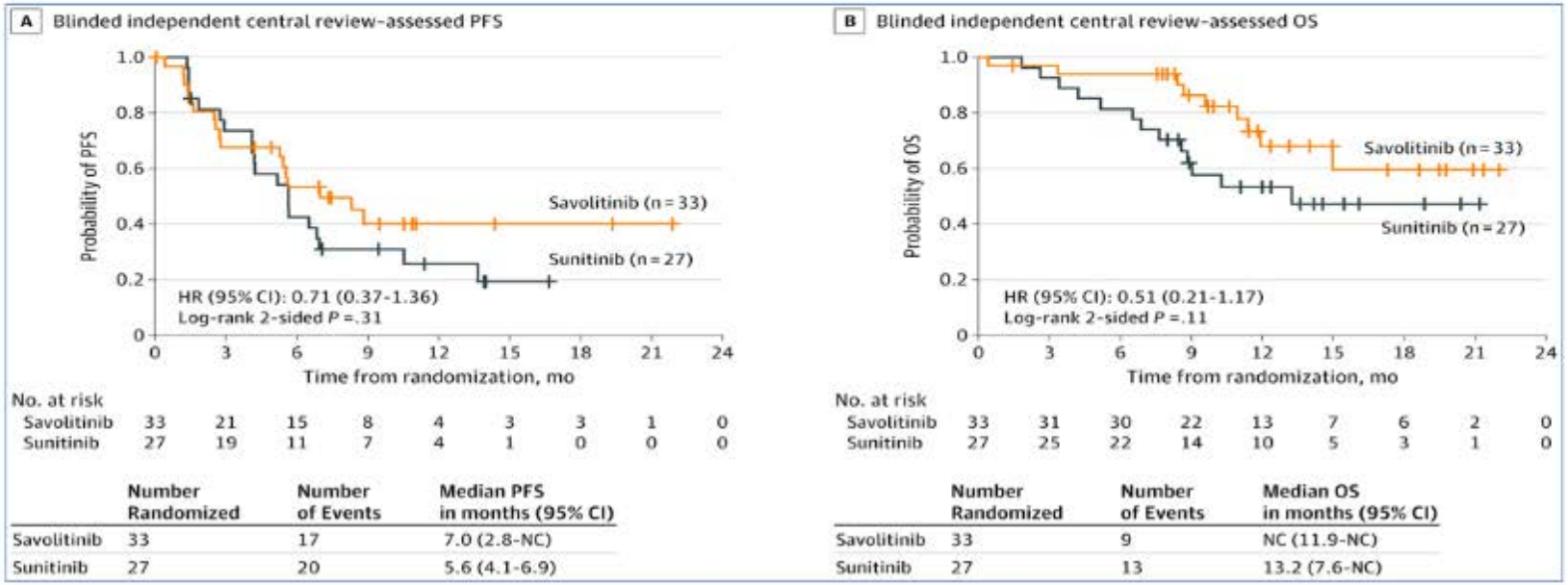
	Histology	MET Status	PFS (m)	ORR
Foretinib (N=74) 1st and 2nd line	All papillary	MET +: 10 MET −: 57 NA: 7	9.3	MET +: **50%** MET −: 9%
Savolitinib (N=109) 1st–3rd line	All papillary	MET +: 44 MET −: 46 NA: 19	MET +: 6.2 MET −: 1.4	MET +: 18% MET −: 0%
Crizotinib (N=109) 1st–3rd line	Type 1 Papillary	MET +: 4 MET −: 16 NA: 3	5.8 MET +: 30.5 MET −: 3	MET +: **50%** MET −: 25%

Choueiri TK, *et al.* J Clin Oncol 2013; Choueiri TK, *et al.* J Clin Oncol 2017; Schöffski P, *et al.* ASCO GU 2018.

MET INHIBITORS: SAVOIR



Outcome	Savolitinib (n=33)	Sunitinib (n=27)
ORR* by BICR, % (95 % CI)	27 (13.3-45.5)	7 (0.9-24.3)
DCR by BICR,% (95% CI)		
6 months	48 (30.8-66.5)	37 (19.4-57.6)
12 months	30 (15.6-48.7)	22 (8.6-42.3)
Any tumour shrinkage, %	67	71

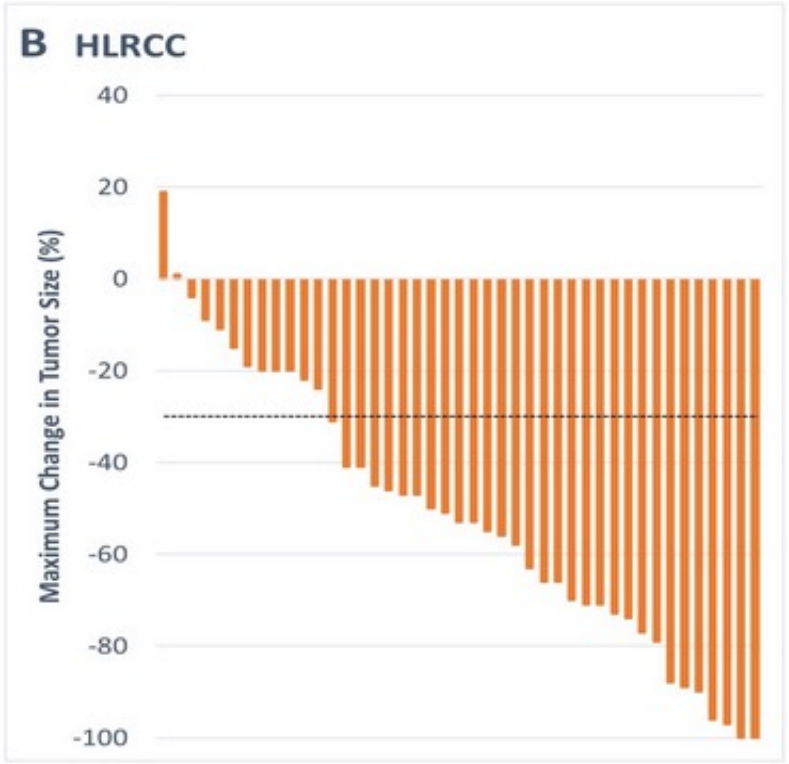


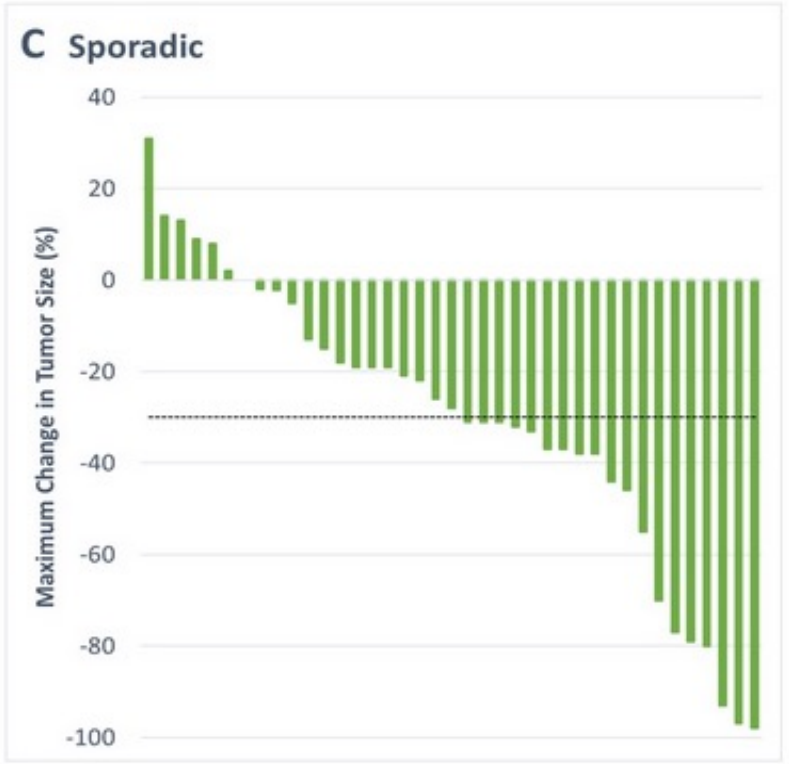
	Number Randomized	Number of Events	Median PFS in months (95% CI)
Savolitinib	33	17	7.0 (2.8-NC)
Sunitinib	27	20	5.6 (4.1-6.9)

	Number Randomized	Number of Events	Median OS in months (95% CI)
Savolitinib	33	9	NC (11.9-NC)
Sunitinib	27	13	13.2 (7.6-NC)

Choueiri TK, *et al.* Presented at ASCO 2020; Choueiri TK, *et al.* JAMA Oncol 2020;6(8):1247–55.

METABOLIC ALTERATIONS AND HLRCC
BEVACIZUMAB + ERLOTINIB





- Median time to response 1.8 months
- Median Duration of response
  - HLRCC: 19.3 months
  - Sporadic PRCC: 17.5 months

Srinivasan ASCO 2020

TARGETING MET IN MET-ALTERED PRCC – THE SAVOIR STUDY

MET-driven papillary RCC = *MET* and/or *HGF* amplification, chromosome 7 gain and/or *MET* kinase domain mutations

	Savolitinib (n = 33)	Sunitinib (n = 27)
PFS events, n (%)	17 (52)	20 (74)
Median PFS (95% CI), mo	7.0 (2.8, NR)	5.6 (4.1, 6.9)
HR (95% CI)	0.71 (0.37, 1.36); p = 0.313	
Deaths, n (%)	9 (27)	13 (48)
Median OS (95% CI), mo	NR (11.9, NR)	13.2 (7.6, NR)
HR (95% CI)	0.51 (0.21, 1.17); p = 0.110	
ORR n (%) [95% CI] *All partial responses*	9 (27) [13.3, 45.5]	2 (7) [0.9, 24.3]

Choueiri et al. JAMA Oncol 2021

A ROLE FOR IO OR IO-IO

IMMUNOTHERAPY: PEMBROLIZUMAB (KEYNOTE 427)

Open-label, single-arm, Phase 2 study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma

Key eligibility criteria
- Locally advanced or metastatic disease
- Measurable disease per RECIST v1.1 by BICR
- No prior systemic therapy for advanced RCC
- Karnofsky Performance Status score ≥70%

Screening for Eligibility

Cohort A CCRCC N=110

Cohort B nccRCC N=165

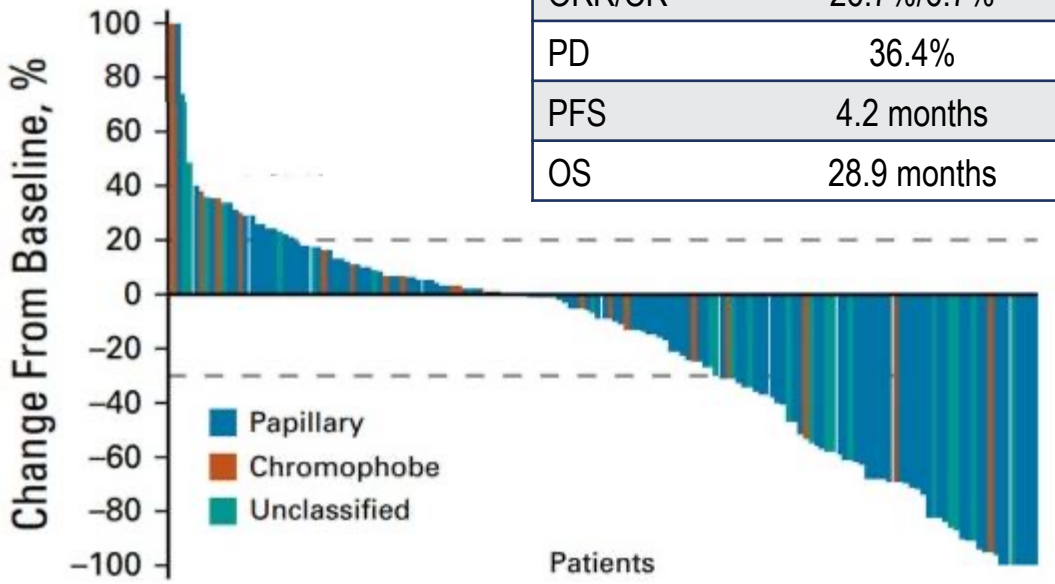
Response assessed at Week 12, Q6W until Week 54, and Q12W thereafter

Pembrolizumab 200 mg Q3W up to 35 cycles (2 years)

Endpoints
- Primary: ORR (RECIST v1.1 by BICR)
- Secondary: OS, PFS, DOR, DCR (RECIST v1.1 by BICR), safety

Characteristics	N (n=165)	ORR
Papillary	71.5%	28.8%
Chromophobe	12.7%	9.5%
Unclassified	15.8%	30.8%
Sarcomatoid	23.0%	42.1%
Prior treatment	0%	26.7%
PD-L1+	61.8%	35.3% (12.1%)

Outcome	(n=165)
ORR/CR	26.7%/6.7%
PD	36.4%
PFS	4.2 months
OS	28.9 months

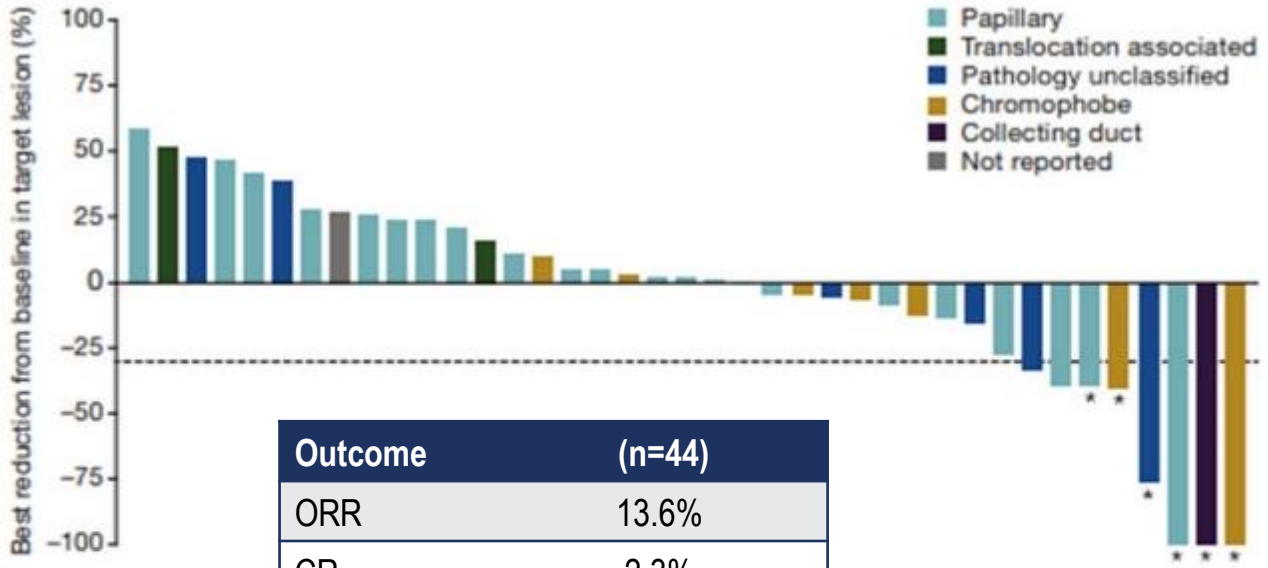


McDermott D, J Clin Onc 2020:39(9); https://doi.org/10.1200/JCO.20.02365. Lee DL, *et al.* presented at ESMO 2021

IMMUNOTHERAPY: NIVOLUMAB (CHECKMATE-374)

Safety and efficacy of nivolumab in patients with advanced non-clear cell renal cell carcinoma: Results from the Phase 3b/4 CheckMate 374 Study

Characteristics	N (n=44)	ORR
Papillary	54.5%	8.3%
Chromophobe	15.9%	28.6%
Unclassified	18.2%	12.5%
Translocation	5%	0%
Collecting duct	2%	100%
Medullary	2%	0%
Not reported	2%	-
Sarcomatoid	9.1%	50%
Prior treatment	34.1%	-



Outcome	(n=44)
ORR	13.6%
CR	2.3%
PD	40.9%
PFS	2.2 months
OS	16.3 months

Vogelzang NJ, *et al.* Clin Genitourin Cancer 2020;18(6):461-468.e3.v DOI: 10.1016/j.clgc.2020.05.006.

IMMUNOTHERAPY: NIVOLUMAB-IPILIMUMAB (CHECKMATE-920)

Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial

N=200

Key inclusion criteria

- Advanced or metastatic RCC (ccRCC and nccRCC)
- No prior systemic therapy for advanced/ metastatic RCC
- Any IMDC risk
- Brain metastases allowed if asymptomatic and not on CS or receiving radiation (enrolled to cohort 3 or 4)
- KPS 70% (cohorts 1-3) or 50-60% (cohort 4)

Cohort 1: predominantly ccRCC KPS ≥ 70% (n = 100)
NIVO 6 mg/kg + IPI 1 mg/kg Q8W alternating with NIVO 480 mg Q8W, staggered Q4W

Cohort 2: nccRCC KPS ≥ 70% (n = 50)
NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

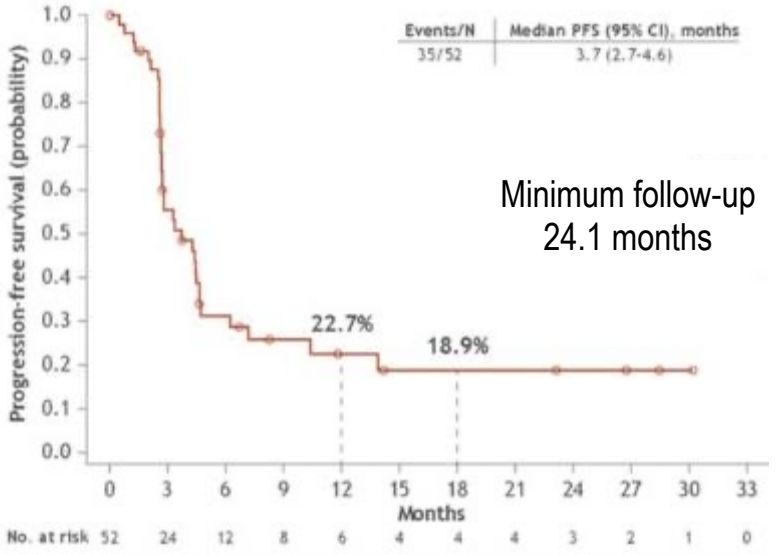
Cohort 3: cc/nccRCC with non-active brain metastases KPS > 70% (n = 25) NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

Cohort 4: cc/nccRCC KPS 50% -60% (n = 25) NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

NIVO 480 mg Q4W

Treat for ≤ 2 years or until RECIST v1.1-defined progression, unacceptable toxicity, or withdrawal of consent

Characteristics	N (n=44)	ORR
Unclassified	42.3%	-
Papillary	34.6%	-
Chromophobe	13.5%	-
Translocation	3.8%	-
Collecting duct	3.8%	-
Medullary	1.9%	-
Sarcomatoid	28.8%	35.7%
Prior treatment	0%	19.6%
PD-L1+	38.5%	30.8%

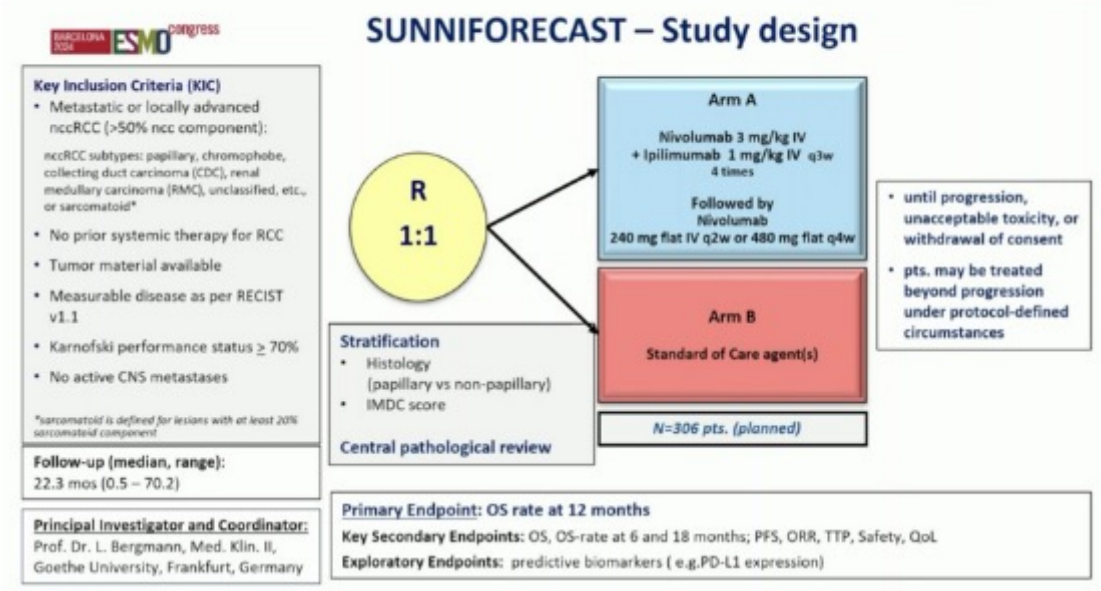


Minimum follow-up
24.1 months

Outcome	
ORR/CR	19.6%/4.3%
PD	41.3%
PFS	3.7 months
OS	21.2 months

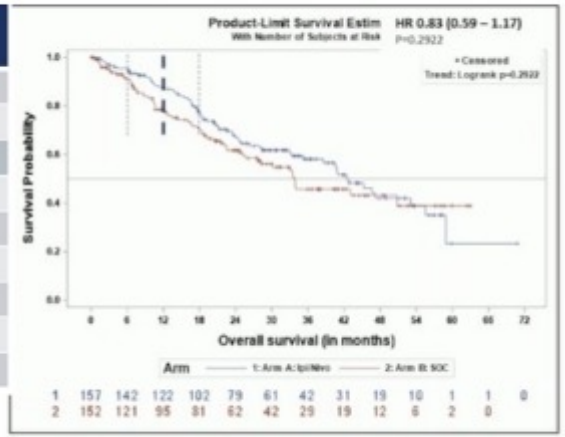
Tykodi SS, *et al.* J Immunother Cancer 2022;10:e003844. doi:10.1136/jitc-2021-003844.

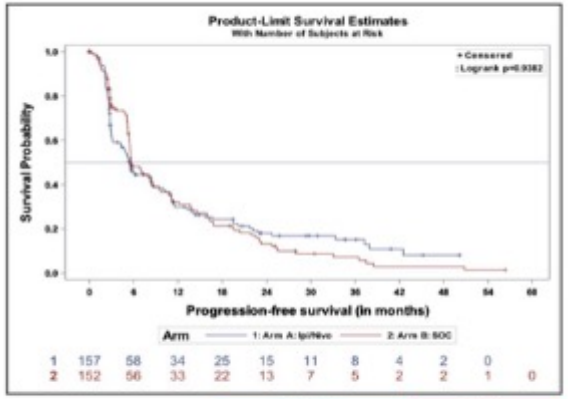
IMMUNOTHERAPY: NIVOLUMAB-IPILIMUMAB (SUNNIFORECAST)



	Total N=309	Ipilimumab/ Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
OS rate at 12 mos (95%-CI)	**82.5%** (77.46% - 86.46%)	**86.9%** (80.24% - 91.46%)	**76.8%** (68.62% - 83.09%)	***p=0.0141***
OS rate at 6 mos (95%-CI)	92.8% (95.27% - 2.83%)	94.7% (89.72% - 97.32%)	90.0% (83.75% - 93.98%)	*p=0.067*
OS rate at 18 mos (95%-CI)	73.4% (67.67% - 78.28%)	76.6% (68.69% - 82.79%)	69.1% (60.25% - 76.34%)	*p=0.084*
OS mos (median, 95%-CI)	40.8 (33.2 - 47.21)	42.4 (35.24 – 55.54)	33.9 (25.52 – *)	*p=0.292*

Histology	Treatment	CR	PR	ORR	SD	PD
all nccRCC (N=247*)	Nivo/Ipi	10 (8.0%)	31 (24.8%)	41 (32.8%)	41 (32.8%)	43 (34.4%)
	SOC	2 (1.6%)	22 (18.0%)	124 (19.6%)	75 (61.5%)	23 (18.9%)
				p=0.001		
papillary (N=148)	Nivo/Ipi	7 (9.7%)	14 (19.4%)	21 (29.2%)	27 (37.5%)	24 (33.3%)
	SOC	2 (2.6%)	14 (18.4%)	16 (21.0%)	46 (60.5%)	14 (18.4%)
non-papillary (N=97)	Nivo/Ipi	3 (5.7%)	17 (32.1%)	20 (37.7%)	14 (18.4%)	19 (27.1%)
	SOC	0 (0.0%)	8 (18.2%)	8 (18.2%)	27 (61.4%)	9 (20.5%)
chromophobe (N=54)	Nivo/Ipi	0 (0.0%)	7 (25.9%)	7 (25.9%)	12 (44.4%)	8(29.6%)
	SOC	0 (0.0%)	3 (11.1%)	3 (11.1%)	21 (77.8%)	4 (14.8%)





	IPI/Nivo	SOC
PFS mos. (median, range)	5.52 (4.30 – 8.23)	5.65 (5.49 – 8.46)
	HR 0.99 (0.76-1.18)	

Bergmann L, *et al.* Presented at ESMO 2024; abstract LBA75. By permission of Prof L. Bergmann.

Median follow-up: 24.3 mos (0.5 -70.2)

A ROLE FOR IO-TKI

NIVOLUMAB+CABOZANTINIB IN NON-CLEAR RCC

Key inclusion criteria
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0-1 prior lines of systemic therapy

→ **Cabozantinib** 40 mg PO daily
+
Nivolumab 240 mg IV every 2 weeks
(or 480 mg IV 4 weeks)

→ **Primary endpoint**
- ORR by RECIST

Secondary endpoints
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)

Cohort 2: chromophobe RCC (N=7)

Parameter	Line of treatment		Renal cell carcinoma histology		
	1st line (n=26)	2nd line (n=14)	Papillary (n=32)	UCP (n=6)	TA-RCC (n=2)
ORR,% (95% CI)	54 (33-73)	36 (13-65)	47 (30-64)	50 (12-88)	50 (1-99)
Complete response, n (%)	1 (3.8)	0 (0)	1 (3.1)	0 (0)	0 (0)
Partial response, n (%)	13 (50)	5 (36)	14 (44)	3 (50)	1 (50)
Stable disease, n (%)	12 (46)	7 (50)	16 (50)	2 (33)	1 (50)
Progressive disease, n (%)	0 (0)	2 (14)	1 (3.1)	1 (17)	0 (0)
Median PFS, mo (95% CI)	11 (7-19)	13 (5-16)	13 (7-16)	8 (1-NE)	14 (5-23)

Fitzgerald KN, *et al.* Eur Urol 2024;86(2):90-94;

NIVOLUMAB+CABOZANTINIB IN NON-CLEAR RCC

Key inclusion criteria
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0-1 prior lines of systemic therapy

Cabozantinib 40 mg PO daily
+
Nivolumab 240 mg IV every 2 weeks
(or 480 mg IV 4 weeks)

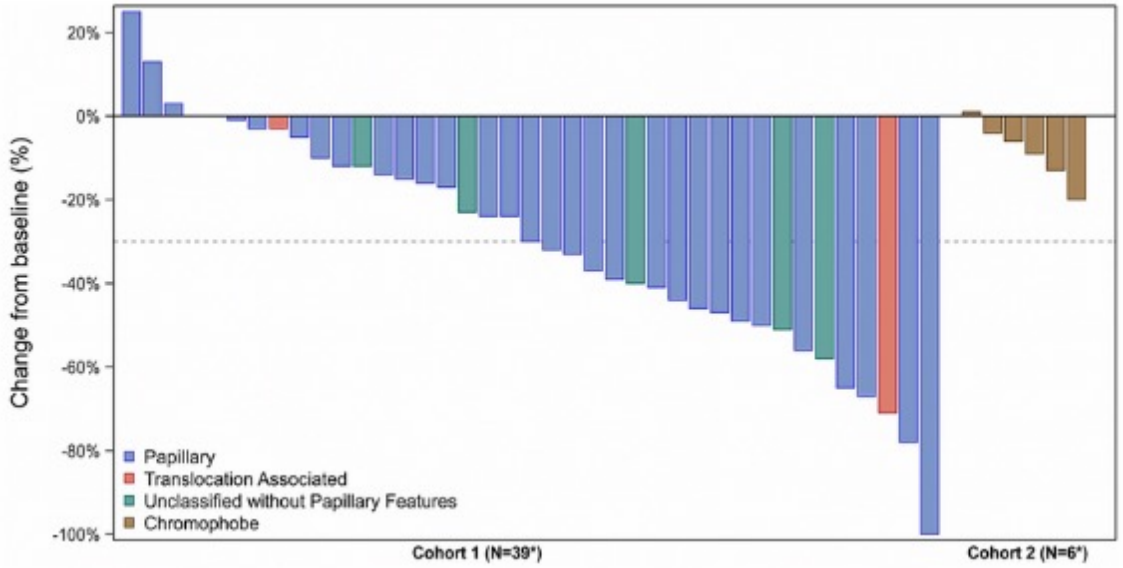
Primary endpoint
- ORR by RECIST

Secondary endpoints
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)

Cohort 2: chromophobe RCC (N=7)

	Cohort 1 (N=40)	Cohort 2 (N=7)
Objective response rate (95% CI)	47.5% (31.5, 63.9)	0% (0, 41.0)
Best response, n (%)		
Partial response	19 (47%)	0 (0%)
Stable disease	20 (50%)	5 (71%)
Progressive disease	1 (3%)	1 (14%)
Not Evaluable	0 (0%)	1 (14%)
Disease control rate (95% CI)	97.5% (86.8, 99.9)	71.4% (29.0, 96.3)
Clinical benefit rate (95% CI)	75.0% (58.8, 87.3)	57.1% (18.4, 90.1)
Median progression-free survival, months (95% CI)	12.5 (6.3, 15.9)	*
Median duration of response, months (95% CI)	13.6 (9.7, 19.8)	†



Fitzgerald KN, *et al.* Eur Urol 2024;86(2):90-94;

LENVATINIB-PEMBROLIZUMAB IN NON-CLEAR RCC (KEYNOTE-B61)

Key eligibility criteria
- Histologically confirmed diagnosis of nccRCC (per investigator)
- Locally advanced/metastatic disease
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- Tumour tissue sample available
- KPS ≥70%

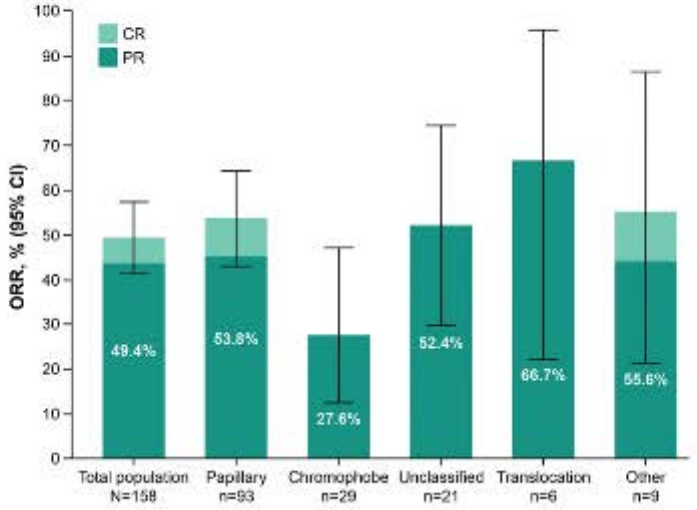
N=158

Pembrolizumab
400 mg IV Q6W for ≤18 cycles (~2 years)
+
Lenvatinib
20 mg PO QD

Tumour assessments
12 weeks from allocation then Q6W for 54 weeks then Q12W thereafter

Endpoints
- Primary: ORR per RECIST v1.1 by BICR
- Secondary: CBR, DCR, DOR, and PFS per RECIST v1.1 by BICR; OS, safety and tolerability

	Pembrolizumab + Lenvatinib N=158
ORR (CR + PR), % (95% CI)	49.4 (41.3-57.4)
DCR (CR+PR+SD), % (95% CI)	82.3 (75.4-87.9)
CBR (CR, PR, or SD for ≥6 months), % (95% CI)	71.5 (63.8-78.4)
Best response, n (%)	
CR	9 (5.7)
PR	69 (43.7)
SD	52 (32.9)
PD	17 (10.8)
NE	1 (0.6)
NA[b]	10 (6.3)



Albiges L, *et al.* Lancet Oncol 2023;24(8):881-891; Voss M.ASCO GU Meeting 2024.

DURVALUMAB+SAVOLITINIB IN PAPILLARY RCC (CALYPSO)

Phase 2 study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO)

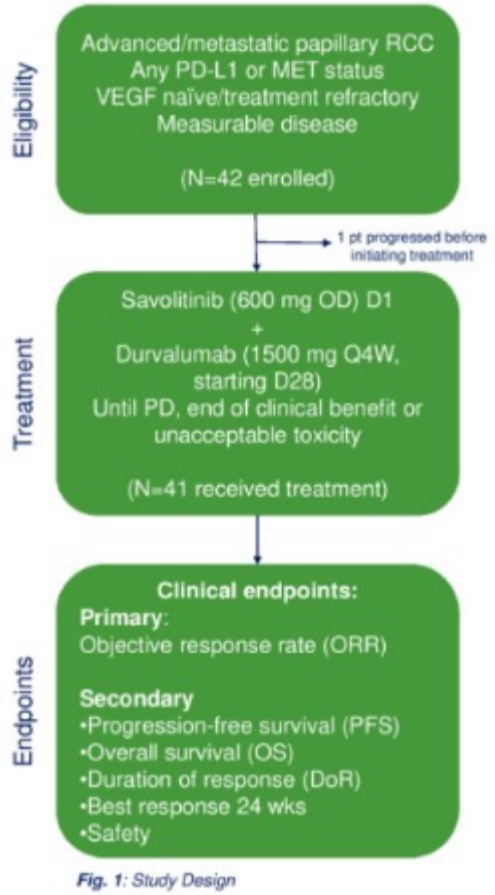


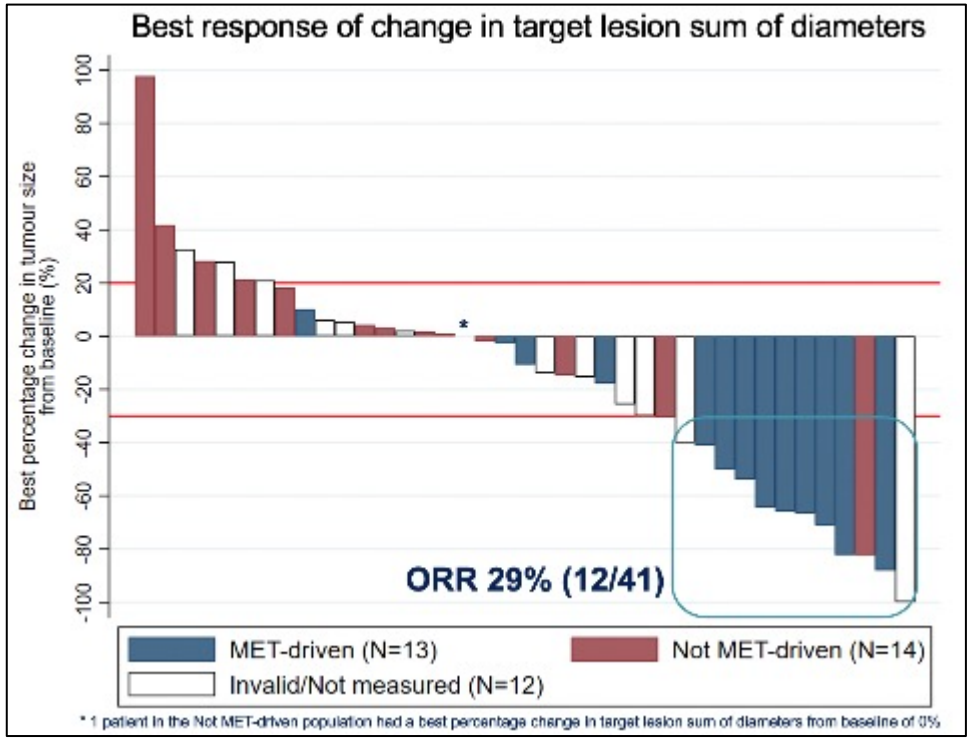
Fig. 1: Study Design

14/41 (34%) patients in the PRC cohort were MET-driven defined as:

- *MET* amplification
- MET kinase domain variations
- chromosome 7 gain
- HGF amplification

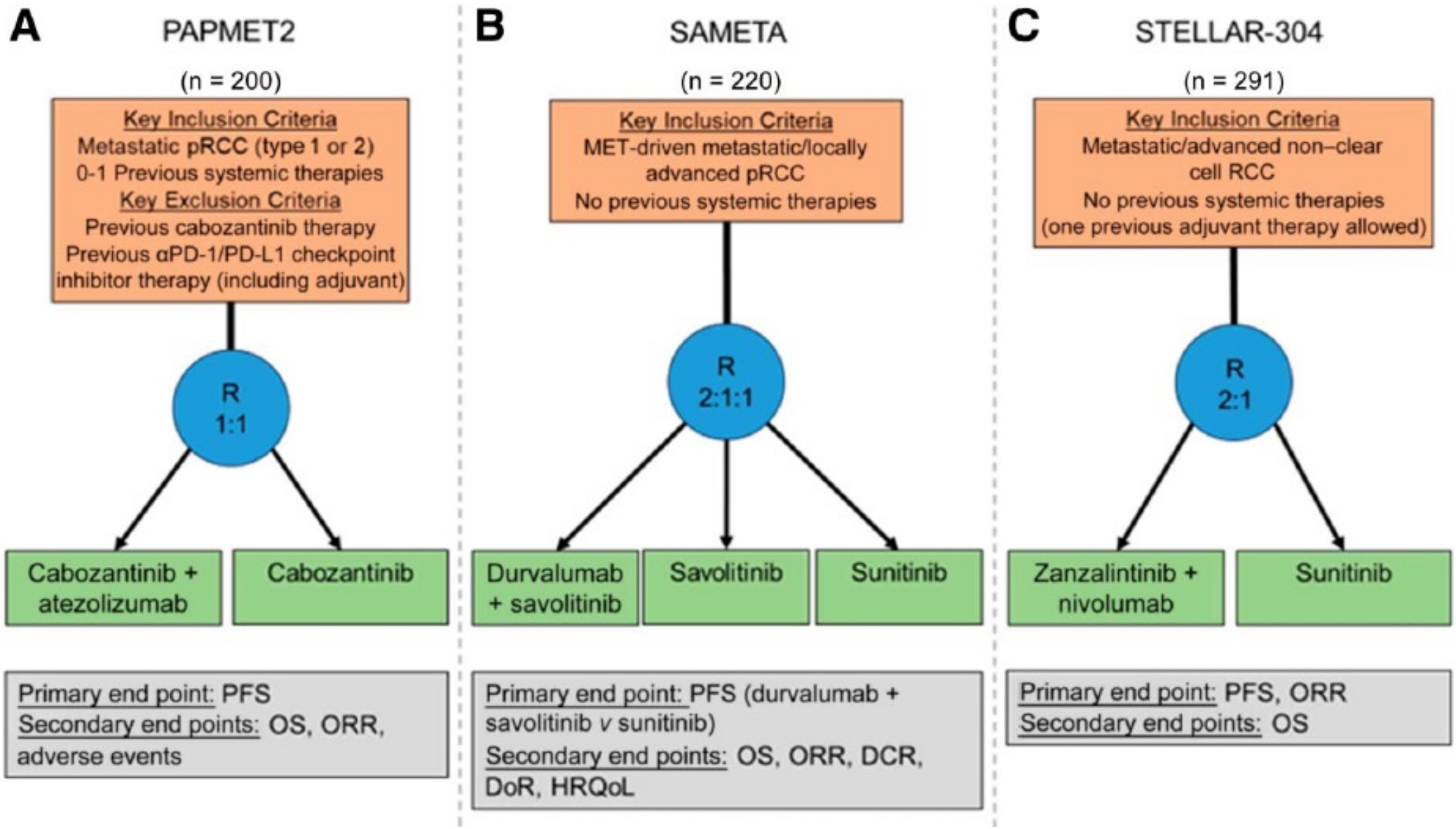
Response in MET-driven papillary RCC patients

- Confirmed response rate in MET-driven patients was 57% (8/14)
- Median duration of response was 9.4 months
- Median follow-up is 26.8 months.



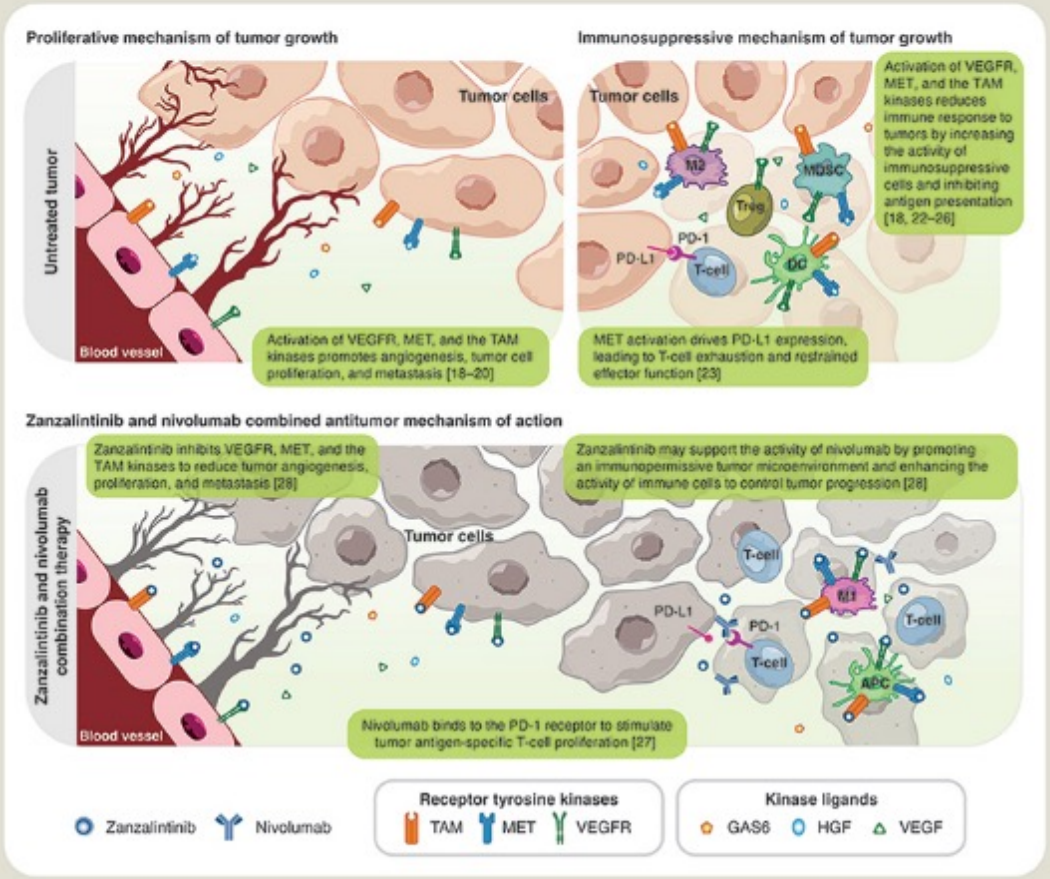
Suárez C, *et al.* Phase II Study Investigating the Safety and Efficacy of Savolitinib and Durvalumab in Metastatic Papillary Renal Cancer (CALYPSO), J Clin Oncol 41(14), 2493-2502. https://doi.org/10.1200/JCO.22.01414.

ONGOING TRIALS FOR NON-CLEAR CELL RCC



Am Soc Clin Oncol Educ Book. 2024 Jun;44(3):e438642.

Zanzalintinib (XL092) Mechanism of Action



- **Zanzalintinib:** targets VEGFR, MET, and TAM kinases
- Inhibiting these kinases reduces tumor angiogenesis, proliferation, metastasis, and immune checkpoint expression
- **Zanzalintinib + nivolumab:** inhibition of zanzalintinib targets may promote an immunopermissive tumor microenvironment that enhances response to nivolumab

STELLAR-304 Study Design: Randomized, Open-Label, Global, Phase III

Advanced nccRCC (N≈291)

- Papillary, unclassified, and translocation-associated histologies (sarcomatoid features allowed)
- Measurable disease per RECIST v1.1 by investigator
- Karnofsky Performance Status ≥70%
- No prior systemic anticancer therapy for unresectable locally advanced or metastatic nccRCC

R2:1

Zanzalintinib + nivolumab	Sunitinib

Endpoints

- **Dual primary:** PFS and ORR per RECIST v1.1 by BIRC
- **Secondary:** OS
- **Other:** Safety, including incidence and severity of AEs

Abbreviations: AE: adverse event; APC: antigen-presenting cell; BIRC: blinded independent radiology committee; DC: dendritic cell; M1: M1 macrophage; M2: M2 macrophage; MDSC: myeloid-derived suppressor cell; nccRCC: non-clear cell renal cell carcinoma; PD-1: programmed death-1; PD-L1: programmed death ligand-1; PFS: progression-free survival; ORR: objective response rate; OS: overall survival; R: randomized; RECIST: Response Evaluation Criteria in Solid Tumors; TAM: TYRO3/AXL/MER; Treg: regulatory T cell; VEGF(R): vascular endothelial growth factor (receptor).

TAKE HOME MESSAGES

- Non- clear cell RCC : heterogeneous group, only ~25% of RCC
  - Low level of evidence for systemic therapy
  - Clinical trials should be preferred

- Rare cancer networks/expert pathology review should be requested

- First-line in 2025
  - IO - TKI
  - Randomized data are pending !

Agenda

Introduction: Adjuvant Immunotherapy for Localized Renal Cell Carcinoma (RCC)

Module 1: Metastatic Clear Cell RCC — Faculty Presentation

Module 2: Metastatic Clear Cell RCC — Survey Questions

Module 3: Non-Clear Cell RCC — Faculty Presentation

Module 4: Non-Clear Cell RCC — Survey Questions

Module 5: ASCO 2025

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Metastatic Non-Clear Cell RCC

- **Is there a way of rating one TKI over another? How does front-line TKI affect choice of second line?**
- **How do you manage diabetic or hypertensive patients with proteinuria when you are trying to give TKI therapy (progressed on immunotherapy, already on ACE inhibitor)?**

Questions from General Medical Oncologists — Metastatic Non-Clear Cell RCC

- **A major barrier I encounter is the lack of clear guidance and trial data for treating non-clear cell histologies, particularly in patients who cannot tolerate immunotherapy. This makes clinical decision-making uncertain and variable across institutions.**

Questions from General Medical Oncologists — Zanzalintinib for Non-Clear Cell RCC

- I know this is a multitargeted TKI including inhibition of VEGF. Are there patients who are out two or three regimens and may have developed mutations where this drug may be of value? Is repeat NGS sequencing important?
- How is this agent different from cabozantinib? Is there any reason to believe it may be effective in patients who have previously received cabo?
- How does the tolerability of this agent compare to cabozantinib and other TKIs? What are the most common toxicities with this drug?

Agenda

Introduction: Adjuvant Immunotherapy for Localized Renal Cell Carcinoma (RCC)

Module 1: Metastatic Clear Cell RCC — Faculty Presentation

Module 2: Metastatic Clear Cell RCC — Survey Questions

Module 3: Non-Clear Cell RCC — Faculty Presentation

Module 4: Non-Clear Cell RCC — Survey Questions

Module 5: ASCO 2025

RTP RESEARCH TO PRACTICE

Efficacy of second line (2L) treatment with tivozanib (Tivo) as monotherapy or with nivolumab (Nivo) in patients (pts) with metastatic renal cell carcinoma (mRCC) previously treated with an immune checkpoint inhibitor (ICI) combination of ipilimumab (Ipi)/Nivo or vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI)/ICI in the phase 3 TiNivo-2 study.

Chehrazi-Raffle A et al.

ASCO 2025;Abstract 4540.

Efficacy of second line treatment with tivozanib +/- nivolumab in patients with mRCC in the phase 3 TiNivo-2 study.

Best percentage change in target tumor size.

		Best % Change from Baseline	
	Prior Treatment	≥30% Reduction	≥50% Reduction
Tivo	TKI/ICI	30.5%	19.4%
	Ipi/Nivo	44.4%	27.8%
Tivo+ Nivo	TKI/ICI	17.5%	2.5%
	Ipi/Nivo	33.3%	12.1%

Chehrazi-Raffle A et al. ASCO 2025; Abstract 4540.

Zanzalintinib (zanza) + nivolumab (nivo) ± relatlimab (rela) in patients (pts) with previously untreated clear cell renal cell carcinoma (ccRCC): Results from an expansion cohort of the phase 1b STELLAR-002 study.

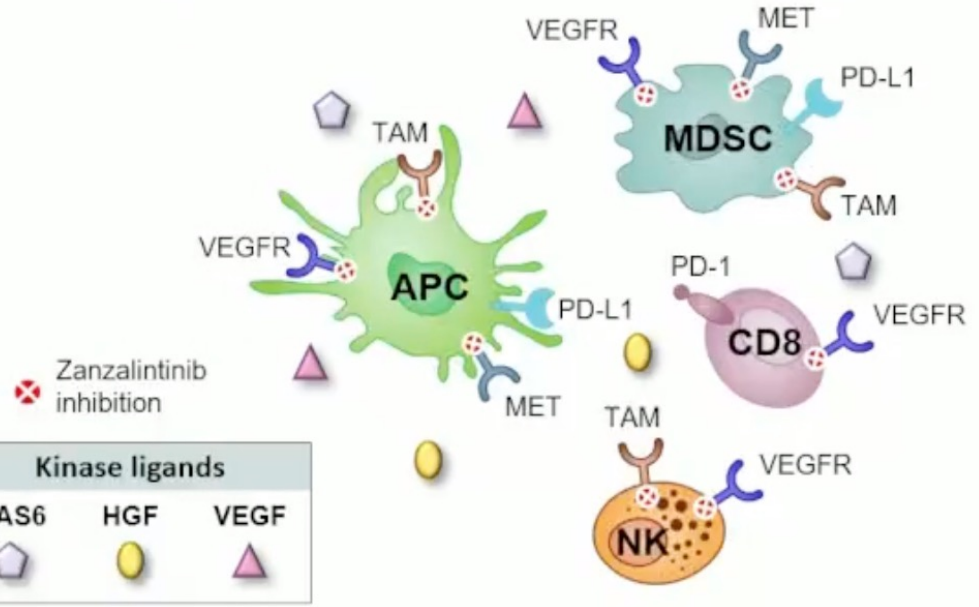
Chadoud J et al.

ASCO 2025;Abstract 4515.

Background

- Zanzalintinib (XL092) is a TKI with a short half-life that inhibits VEGFR, MET, and the TAM kinases (TYRO3, AXL, and MER), all of which are involved in immunosuppression within the tumor microenvironment[1,2]
- In the phase 1 STELLAR-001 study, single-agent zanzalintinib demonstrated tolerability and promising antitumor activity in an expansion cohort of patients with heavily pretreated advanced ccRCC[3]
- Zanzalintinib activity could potentially be augmented when combined with the PD-1 inhibitor nivolumab and the LAG-3 inhibitor relatlimab, which together restore T-cell activation and result in increased antitumor activity[4]
- Here, we report results from the non-randomized expansion cohort of patients with previously untreated advanced ccRCC who received zanzalintinib + nivolumab or zanzalintinib + nivolumab/relatlimab in the multicenter, open-label STELLAR-002 study

Zanzalintinib mechanism of action[5,a]



[a]Reproduced with permission from the author(s).

APC, antigen-presenting cell; ccRCC, clear cell renal cell carcinoma; CD8, CD8+ T cell; GAS6, growth arrest-specific 6; HGF, hepatocyte growth factor; LAG-3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cell; NK, natural killer cell; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).

1. Hsu J, et al. *Mol Cancer Ther*. 2023;22(2):179–91. 2. Chang JH, et al. *Eur J Cancer*. 2024;211(suppl_1):114638. 3. Pal S, et al. Presented at the International Kidney Cancer Symposium: North America, Nashville, TN, USA, November 9–11, 2023, Abstract 1. 4. Hofmann M, et al. *Signal Transduct Target Ther*. 2024;9(1):291. 5. Pal S, et al. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, USA, May 31–June 4, 2024, Abstract 4545.

STELLAR-002 (NCT05176483): 1L ccRCC Expansion Cohort

Patient Population

- Aged ≥18 years
- Unresectable advanced or metastatic RCC with a clear cell component (sarcomatoid features allowed)
- All IMDC risk groups
- No prior systemic anticancer therapy for RCC
  - Prior non-VEGF(R)–targeted adjuvant or neoadjuvant therapy allowed if disease recurrence occurred 6 months after the last dose

Non-randomized

Sequential assignment

Zanzalintinib 100 mg PO QD + Nivo 480 mg IV Q4W (n=40)[a]

Zanzalintinib 100 mg PO QD + Nivo/Rela 480/480 mg IV Q4W (fixed-dose combination) (n=40)[a]

Endpoints

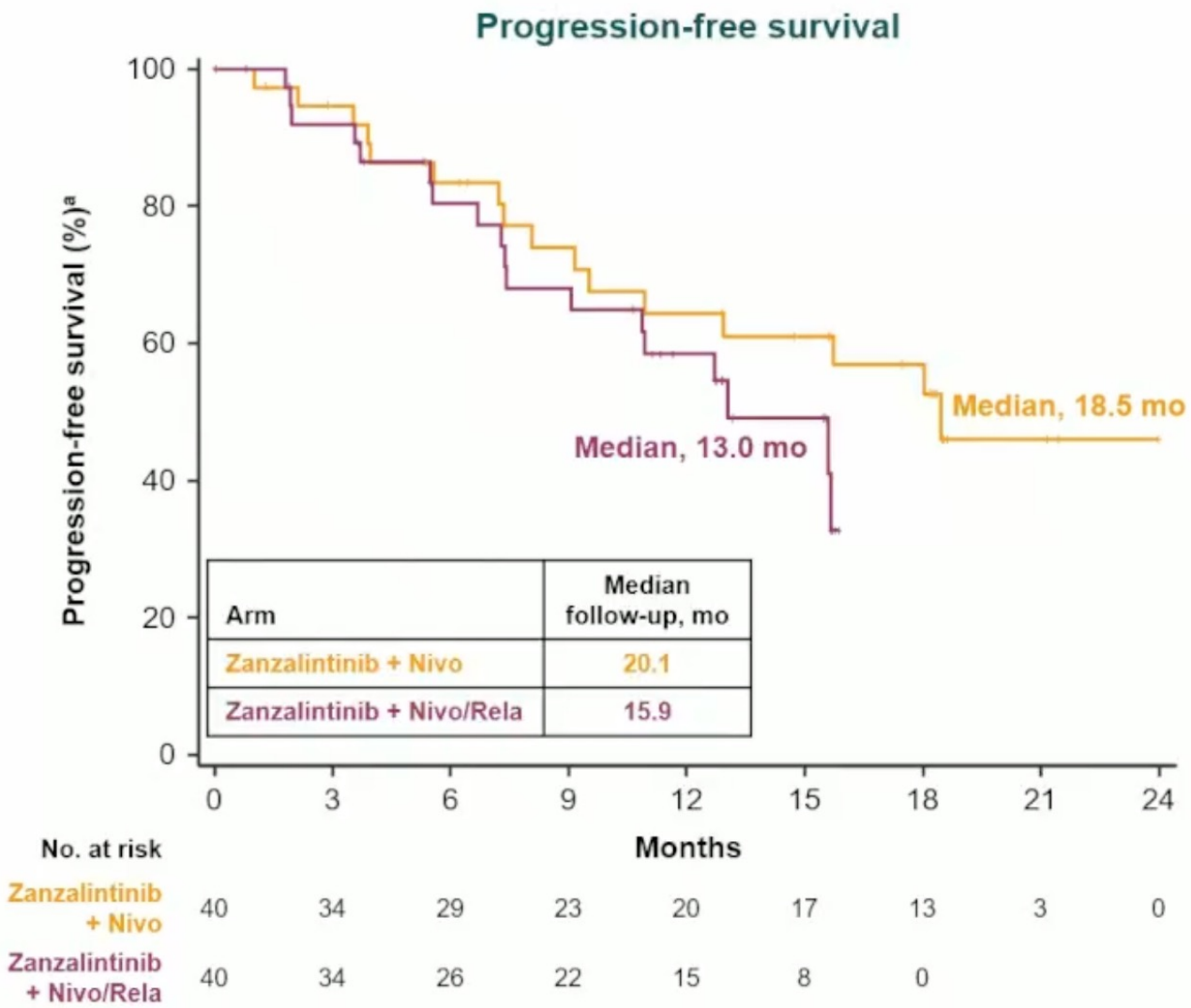
Primary:	Incidence and severity of AEs ORR per RECIST v1.1
Secondary:	PFS per RECIST v1.1

[a]Patients were allowed to receive treatment beyond radiographic progression if the investigator believed they were receiving clinical benefit.

1L, first-line; AE, adverse event; IMDC, International Metastatic RCC Database Consortium; IV, intravenously; Nivo, nivolumab; ORR, objective response rate; PFS, progression-free survival; PO, orally; Q4W, every 4 weeks; QD, once daily; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Rela, relatlimab.

Antitumor Activity Summary

	Zanzalintinib + Nivo (n=40)	Zanzalintinib + Nivo/Rela (n=40)
ORR (95% CI), %	**63 (46–77)**	**40 (25–57)**
Confirmed CR, n (%)	3 (8)	1 (3)
Confirmed PR, n (%)	22 (55)	15 (38)
SD, n (%)	11 (28)	20 (50)
PD, n (%)	2 (5)	3 (8)
DCR (95% CI), %	90 (76–97)	90 (76–97)
Median DOR (95% CI), months	NE (11.1–NE)	NE (4.0–NE)
12-month DOR (95% CI), %	73.4 (50.0–87.1)	74.1 (39.1–90.9)
Median TTR (range), months	2.1 (1.7–11.0)	3.6 (1.7–12.8)
Median PFS (95% CI), months	**18.5 (9.5–NE)**	**13.0 (7.4–NE)**
6-month PFS (95% CI), %	83.4 (66.8–92.2)	80.4 (63.1–90.2)
12-month PFS (95% CI), %	64.4 (45.7–78.1)	58.4 (39.9–73.0)



Per RECIST v1.1. [a]Kaplan-Meier estimate.
CI, confidence interval; DCR, disease control rate; DOR, duration of response; mo, months; NE, not estimable; TTR, time to objective response.

Safety Summary

Safety Overview

	Zanzalintinib + Nivo (n=40)	Zanzalintinib + Nivo/Rela (n=40)
Median exposure (range), months	16.1 (0.5–24.8)	10.9 (0.5–17.1)
Zanzalintinib	16.1 (0.5–25.1)	7.6 (0.5–18.0)
Nivo or Nivo/Rela	10.5 (0.0–24.0)	6.3 (0.0–17.1)
TEAE (any grade / grade 3/4),[a] n	40 / 33	40 / 32
Related to any study treatment	40 / 32	40 / 30
Serious TEAE, n	21	24
Related to any study treatment	10	13
Dose modification due to TEAE, n		
Zanzalintinib dose reductions	34	31
Zanzalintinib dose holds	39	39
Nivo or Nivo/Rela dose delays	30	27
irTEAE (any grade / grade 3),[b] n	32 / 12	34 / 12
AST or ALT increase[c]	23 / 7	25 / 6
Rash, maculo-papular	9 / 3	10 / 4

Grade 3/4 TEAEs[d] Occurring in >2 Patients

Zanzalintinib + Nivo (n=40)		
TEAE, n	**Any grade**	**Grade 3/4***
Hypertension	24	13
Diarrhea	31	6
AST increase	20	5
ALT increase	17	5
PPE	11	4
Decreased appetite	22	3
Fatigue	18	3
Rash, maculo-papular	11	3
Urinary tract infection	6	3

Zanzalintinib + Nivo/Rela (n=40)		
TEAE, n	**Any grade**	**Grade 3/4***
Hypertension	19	6
Rash, maculo-papular	13	6
Lipase increase	11	4
Pulmonary embolism	4	4
ALT increase	19	3
Fatigue	13	3
Hypertransaminasemia	5	3
Other AE of interest		
PPE	2	0

*Grade 4 TEAEs were reported in 2 patients in each arm:

- Zanzalintinib + Nivo: subdural hematoma and urine output decrease
- Zanzalintinib + Nivo/Rela: lipase increase and pulmonary embolism

[a]There were 2 grade 5 TEAEs in each arm; none were related to study treatment. [b]There were no grade 4 or 5 irTEAEs; the most common grade 3 events (≥2 patients) are shown; immunosuppressants were used in 16 and 17 patients in the doublet and triplet arms, respectively. [c]Includes hypertransaminasemia. [d]TEAE highest grade is reported if multiple grades present per patient per term.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; irTEAE, immune-related TEAE; PPE, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Relapsed/Refractory Multiple Myeloma

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