Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Renal Cell Carcinoma

Part 1 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Wednesday, February 15, 2023

7:15 PM – 8:45 PM PT

Faculty

Prof Laurence Albiges, MD, PhD

Thomas Powles, MBBS, MRCP, MD

Toni K Choueiri, MD

Moderator

Brian Rini, MD

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Faculty

Prof Laurence Albiges, MD, PhD
Medical Oncologist
Chair, Medical Oncology Department
Gustave Roussy Cancer Center
Villejuif, France

Thomas Powles, MBBS, MRCP, MD
Professor of Genitourinary Oncology
Barts Cancer Institute
Director of Barts Cancer Centre
Queen Mary University of London
London, United Kingdom

Toni K Choueiri, MD
Director, Lank Center for
Genitourinary Oncology
Department of Medical Oncology
Dana-Farber Cancer Institute
The Jerome and Nancy Kohlberg Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Moderator
Brian Rini, MD
Professor of Medicine
Chief of Clinical Trials
Vanderbilt-Ingram Cancer Center
Division of Hematology/Oncology
Vanderbilt University Medical Center
Nashville, Tennessee

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Commercial Support

This activity is supported by educational grants from Aveo Pharmaceuticals, Eisai Inc, Exelixis Inc, and Merck.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Prof Laurence Albiges, MD, PhD — Disclosures

Faculty

No relevant conflicts of interest to disclose

Toni K Choueiri, MD — Disclosures
Faculty

No relevant conflicts of interest to disclose

Thomas Powles, MBBS, MRCP, MD — Disclosures

Faculty

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc, Exelixis Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Merck Serono, Merck Sharp & Dohme LLC, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc, Exelixis Inc, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Merck Serono, Merck Sharp & Dohme LLC, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Travel/Accommodation/ Expenses	AstraZeneca Pharmaceuticals LP, Ipsen Biopharmaceuticals Inc, Merck Sharp & Dohme LLC, Pfizer Inc, Roche Laboratories Inc

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Brian Rini, MD — Disclosures
Moderator

Advisory Committee and Consulting Agreements	Alkermes, Allogene Therapeutics, Aravive Inc, Arrowhead Pharmaceuticals, Athenex, Aveo Pharmaceuticals, Bristol-Myers Squibb Company, Corvus Pharmaceuticals, Debiopharm, Eisai Inc, EUSA Pharma, Genentech, a member of the Roche Group, Merck, NiKang Therapeutics Inc, Pfizer Inc, Sanofi, Shionogi Inc, Surface Oncology
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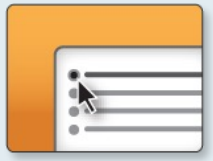
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP
Stock Options/Ownership — Public Company	PTC Therapeutics
Nonrelevant Financial Relationship	MashupMD — Podcast partnership

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. Survey results will be presented and discussed throughout the meeting.

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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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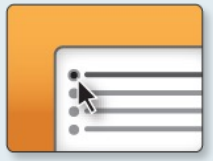
Clinicians Attending via Zoom

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. Survey results will be presented and discussed throughout the meeting.

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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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Prostate Cancer

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Thursday, February 16, 2023
7:15 PM – 9:15 PM PT

Faculty

Emmanuel S Antonarakis, MD
Prof Karim Fizazi, MD, PhD
Maha Hussain, MD, FACP, FASCO
Matthew R Smith, MD, PhD

Moderator

Alan H Bryce, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Urothelial Bladder Cancer

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Friday, February 17, 2023
6:30 PM – 8:00 PM PT

Faculty

Matthew D Galsky, MD
Arlene Siefker-Radtke, MD
Jonathan E Rosenberg, MD

Moderator

Elisabeth I Heath, MD

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Renal Cell Carcinoma

Part 1 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Wednesday, February 15, 2023

7:15 PM – 8:45 PM PT

Faculty

Prof Laurence Albiges, MD, PhD

Thomas Powles, MBBS, MRCP, MD

Toni K Choueiri, MD

Moderator

Brian Rini, MD

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Agenda

Module 1: Available Data with and Ongoing Investigation of Immune Checkpoint Inhibitors in Nonmetastatic Renal Cell Carcinoma (RCC) — Prof Powles

Module 2: Evidence-Based Selection of First-Line Therapy for Metastatic RCC — Dr Choueiri

Module 3: Treatment Options for Relapsed/Refractory RCC — Dr Rini

Module 4: Management of RCC Among Special Patient Populations — Prof Albiges

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Victoria Giffi, MD
Meritus Hematology and Oncology Specialists
Hagerstown, Maryland

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Nikesh Jasani, MD
Texas Oncology Cypress
Houston, Texas

Sunil Gandhi, MD
Florida Cancer Specialists
Lecanto, Florida

Eric H Lee, MD, PhD
Compassionate Cancer Care Medical Group
Fountain Valley, California

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Helen H Moon, MD
Kaiser Permanente Southern California
Riverside, California

Swati Vishwanathan, MD
Oncology/Hematology United Hospital Center
WVU Medicine
Bridgeport, West Virginia

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

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MODULE 1: Available Data with and Ongoing Investigation of Immune Checkpoint Inhibitors in Nonmetastatic Renal Cell Carcinoma (RCC) — Prof Powles

Case Presentation: 61-year-old woman s/p left nephrectomy (T3aN0M0 clear cell carcinoma)

Dr Swati Vishwanathan (Bridgeport, West Virginia)

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QUESTIONS FOR THE FACULTY

Swati Vishwanathan, MD

In what settings do you recommend adjuvant pembrolizumab, and how do you explain conflicting trial data to patients?

What about Stage 4 NED?

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Case Presentation: 50-year-old man s/p 2 cycles of adjuvant pembrolizumab for RCC develops renal dysfunction

Dr Justin Favaro (Charlotte, North Carolina)

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Case Presentation: 67-year-old man with Stage III ccRCC discontinues adjuvant pembrolizumab due to severe musculoskeletal pain and joint swelling

Dr Priya Rudolph (Athens, Georgia)

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QUESTIONS FOR THE FACULTY

Justin Peter Favaro, MD, PhD

What types of renal dysfunction have you seen with immunotherapy? How do you manage it, and do you restart the IO?

Priya Rudolph, MD, PhD

What about musculoskeletal disorders?

Is there a role for ctDNA assays in the localized disease setting?

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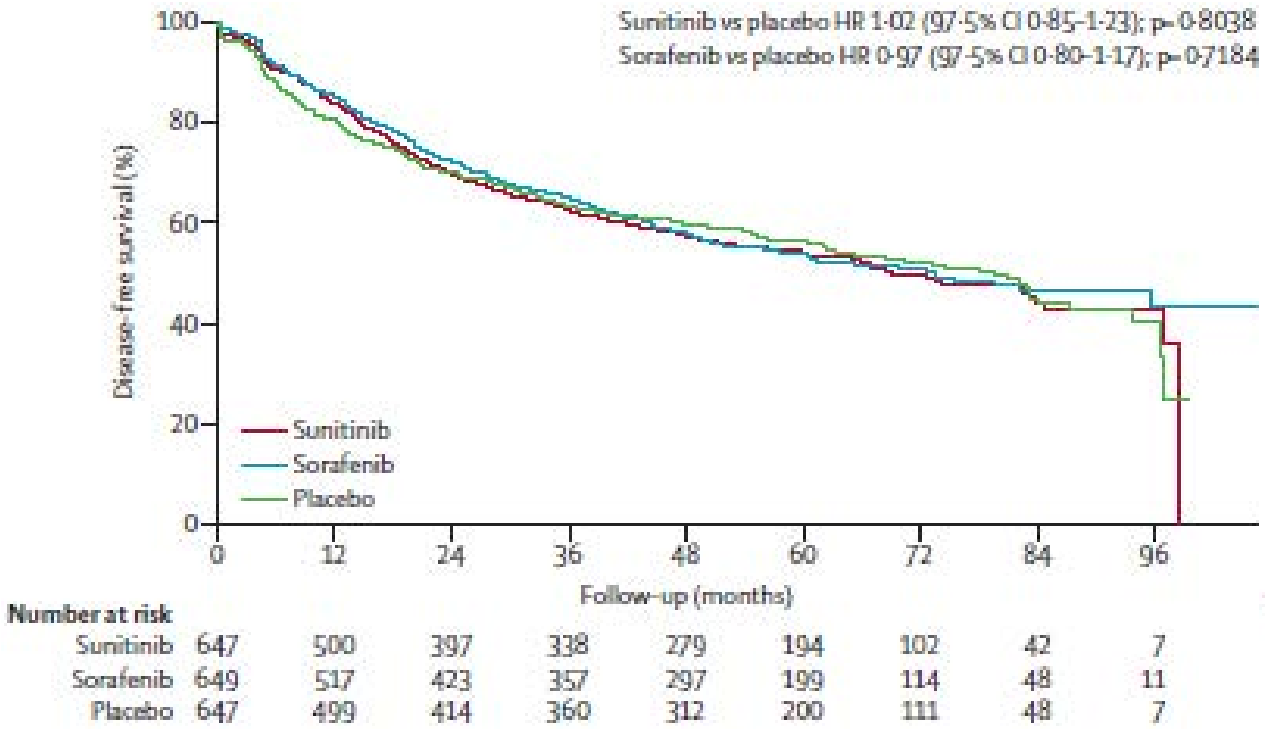
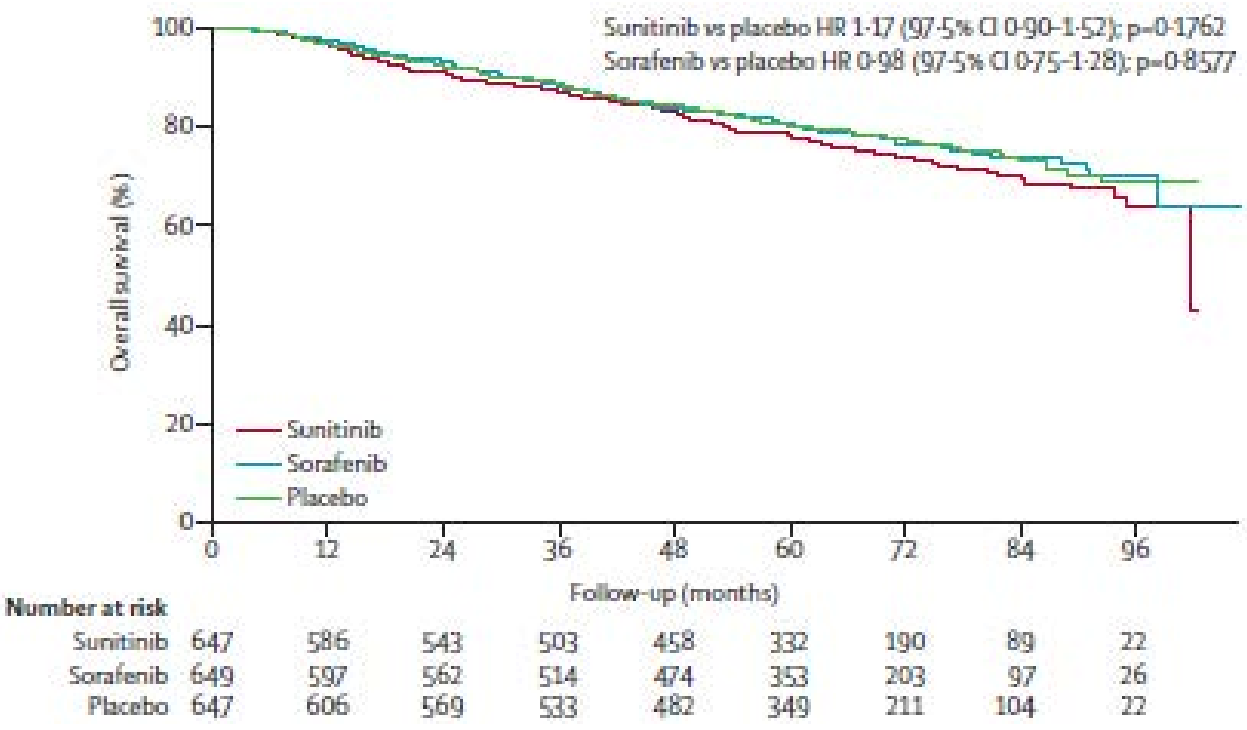
Adjuvant immune therapy in clear cell RCC

Thomas Powles
Director of Barts Cancer Center.
Professor of Urology Cancer, Barts Cancer Institute.

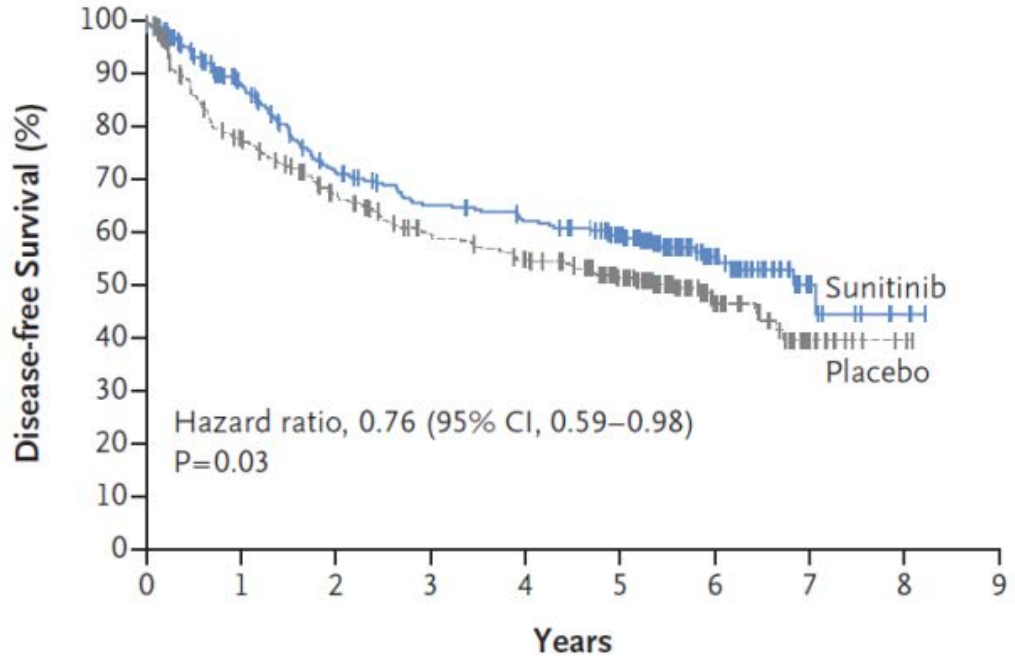
ASSURE TRIAL: summarises the adjuvant VEGF TKI story.





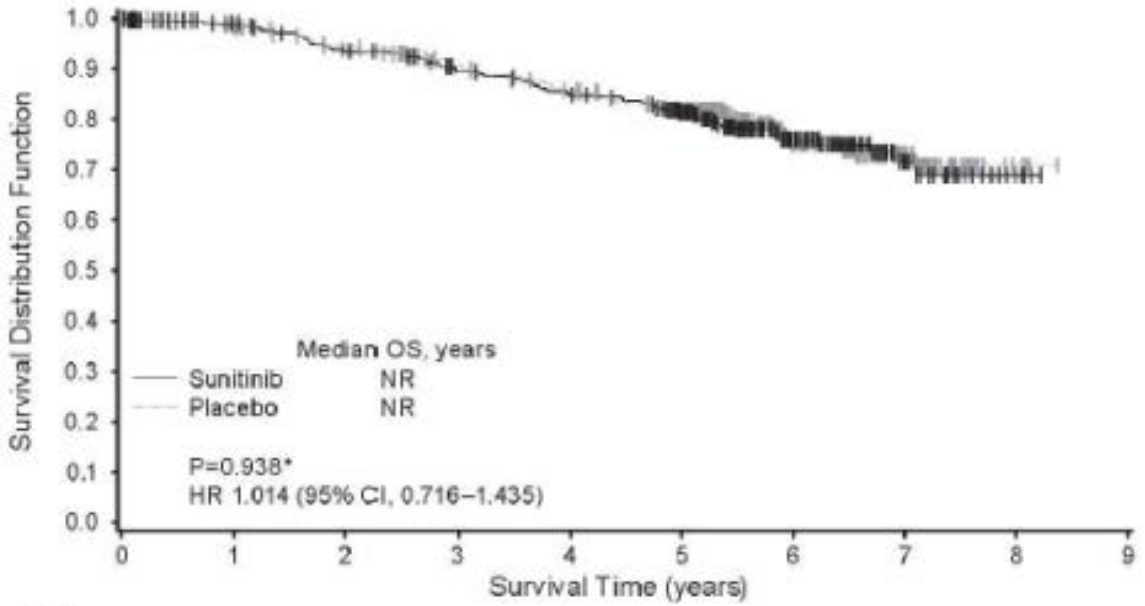
Adapted from: Haas NB et al. Lancet 2016

The STRAC trial was the exception
DFS but again no OS benefit



No. at Risk

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0



No. at risk

Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

DFS, disease-free survival.
Ravaud A et al. *N Engl J Med* 2016;375(23):2246–2254.

Adapted from: Ravaud A et al. N Engl J Med 2016

Adjuvant and 1st line immune checkpoint inhibitor studies.

Advanced disease (1st line vs sunitinib)	ICI	PFS	OS
Ipilimumab and nivolumab	PD1		
Axitinib and pembrolizumab	PD1		
Axitinib and avelumab	PDL1		
Bevacizumab and atezolizumab	PDL1		
Cabozantinib and nivolumab	PD1		
Lenvatinib and pembrolizumab	PD1		
Cabozantinib/ipi/nivolumab	combo		
PEG-IL2 and nivolumab*	PD1		

Perioperative disease	ICI	PFS	OS
Pembrolizumab	PD1		
Nivolumab (neoadjuvant)	PD1		
Atezolizumab	PDL1		
Ipilimumab and nivolumab*	combo		
Nivolumab adjuvant	PD1		

Positive
Negative
Awaited

Modified Powles ESMO 22

Adjuvant ipilimumab and nivolumab in renal cell carcinoma: more questions than answers

*Ursula Maria Vogl, David McDermott, *Thomas Powles*
thomas.powles1@nhs.net

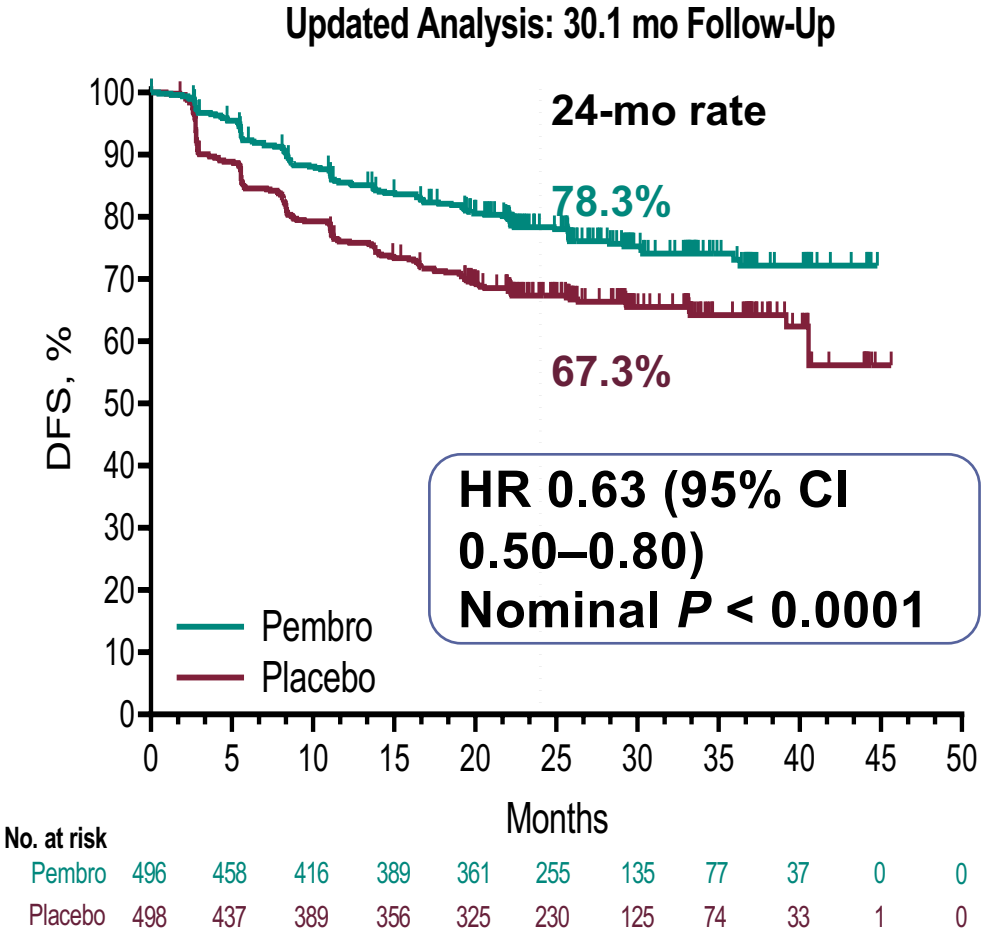
Questions:

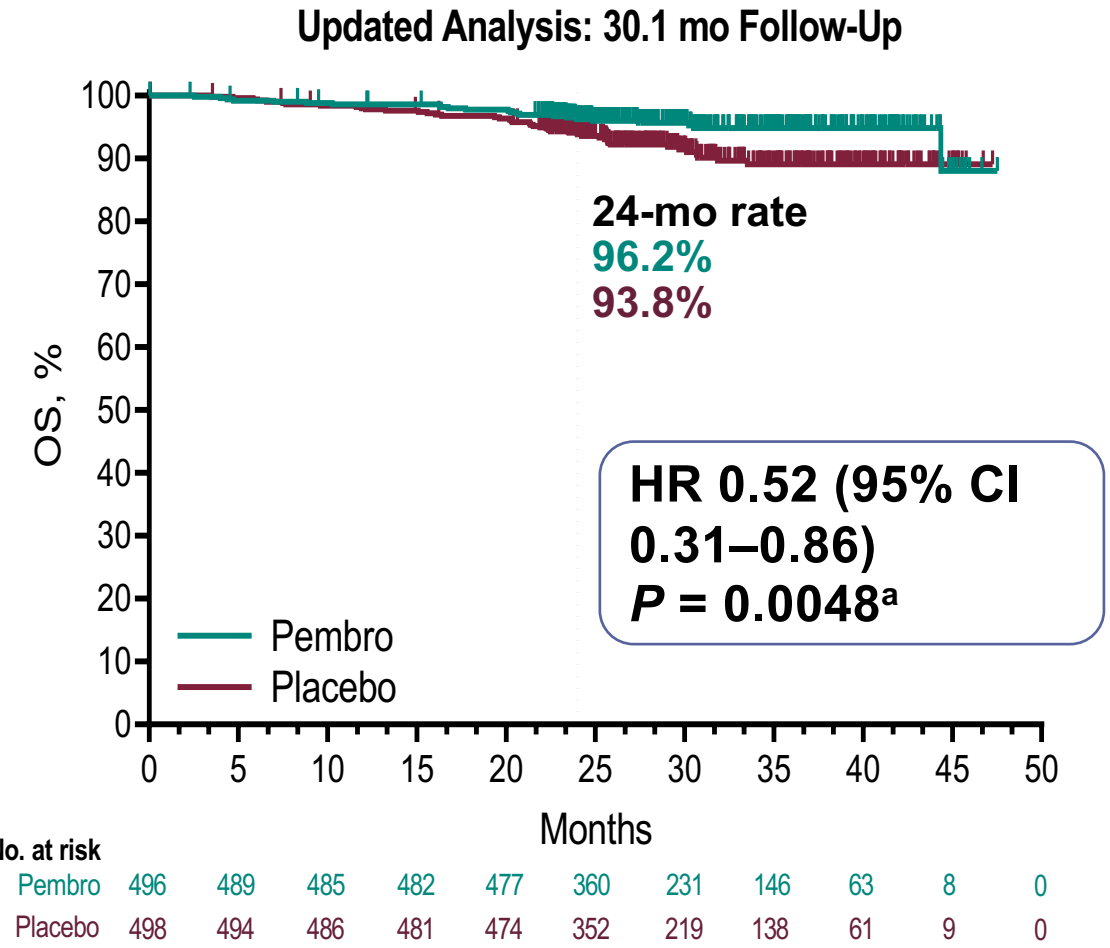
- Can trial design or imbalances explain the inconsistency?
- How much does ipilimumab add to PD-1 therapy in efficacy and toxicity?
- Does ipilimumab have to be given in a certain manner?
- Are all PD(L)1 therapies the same?
- Is there a future for neoadjuvant therapy?

Comparison of trial design.

	Pembrolizumab (564)	Atezolizumab (010)	Nivolumab (neoadjuvant)	Ipilimumab Nivolumab (914)
Stage	TNM M1 NED	By TNM M1 NED	Radiological definition	TNM
Pathology	Clear cell	Clear cell	80% clear cell 20% non-clear cell	Clear cell
Method	Double blind	Double blind	Open label	Double blind
Target and duration	PD-1 1 year	PD-L1 1 year	PD-1 1 year	PD-1+CTLA4 6 months
Assessment of DFS	Investigator assessed	Investigator assessed	Investigator assessed but it included surgery!	Central review
Median duration of follow up	30 months	44 months	16 months	37 months

KEYNOTE-564 Pembrolizumab vs placebo in intermediate and high risk renal cancer.



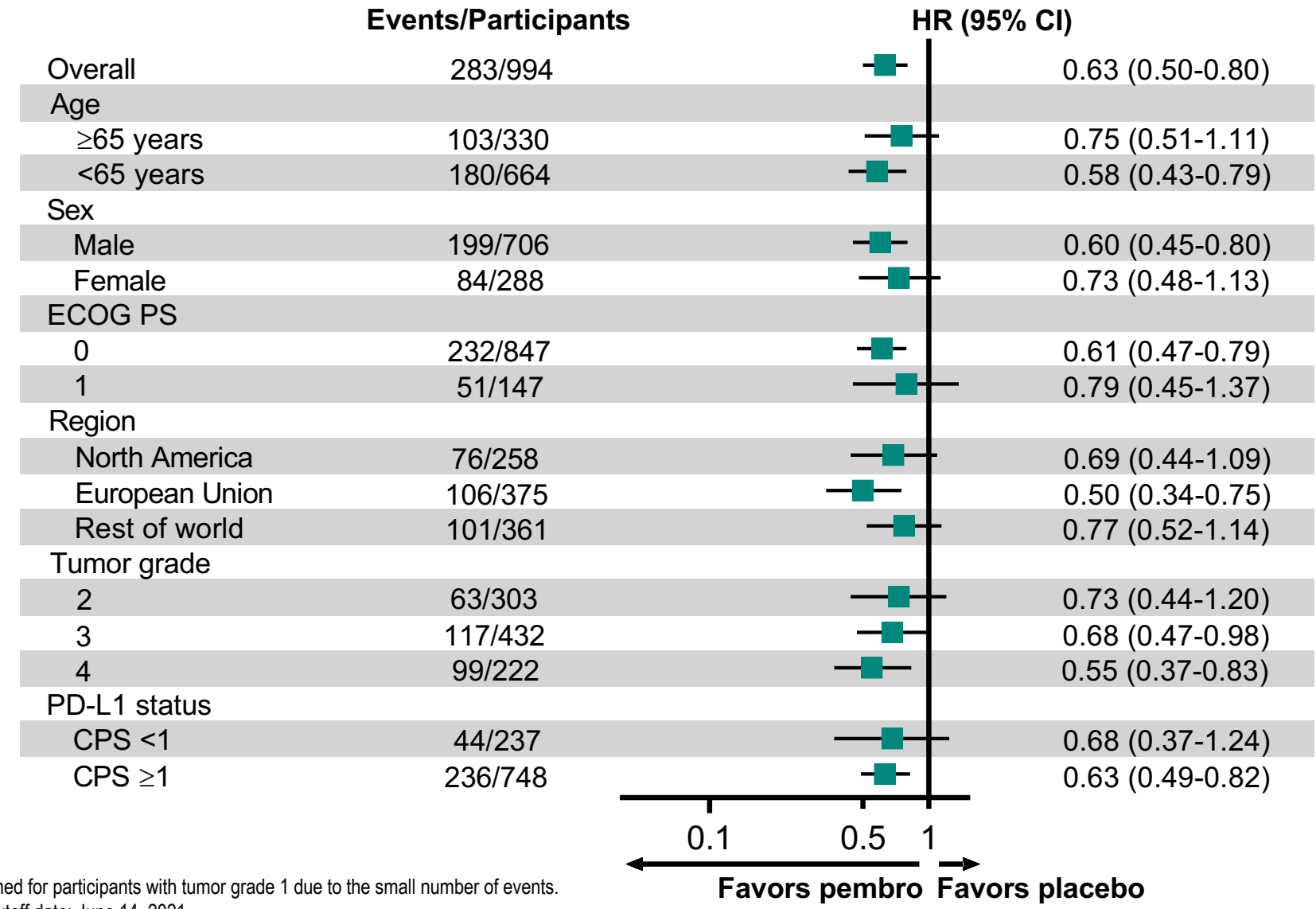


Early discontinuation: 20%

Steroid use: 10%

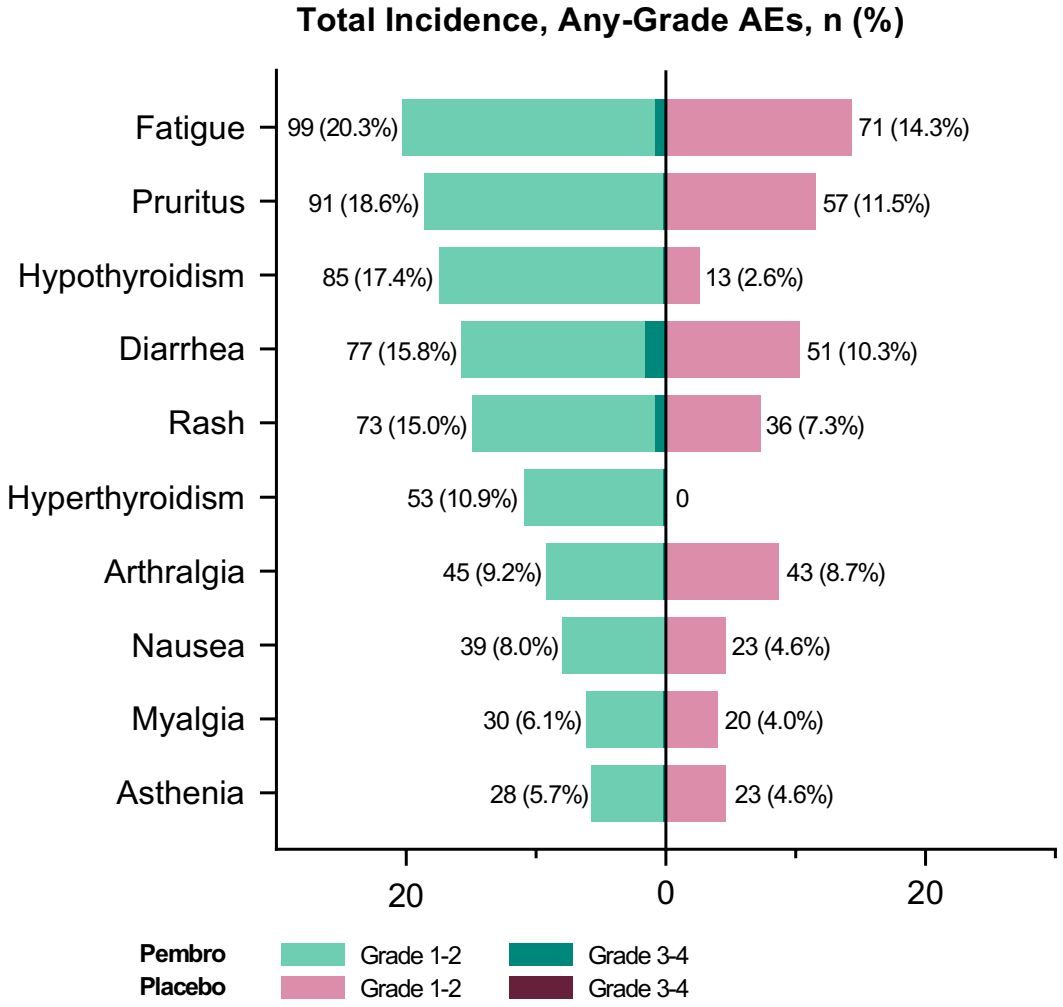
Powles T et al. Lancet Oncol 2022 Sep;23(9):1133-44.
Choueiri TK et al. Genitourinary Cancers Symposium 2022;Abstract 290.

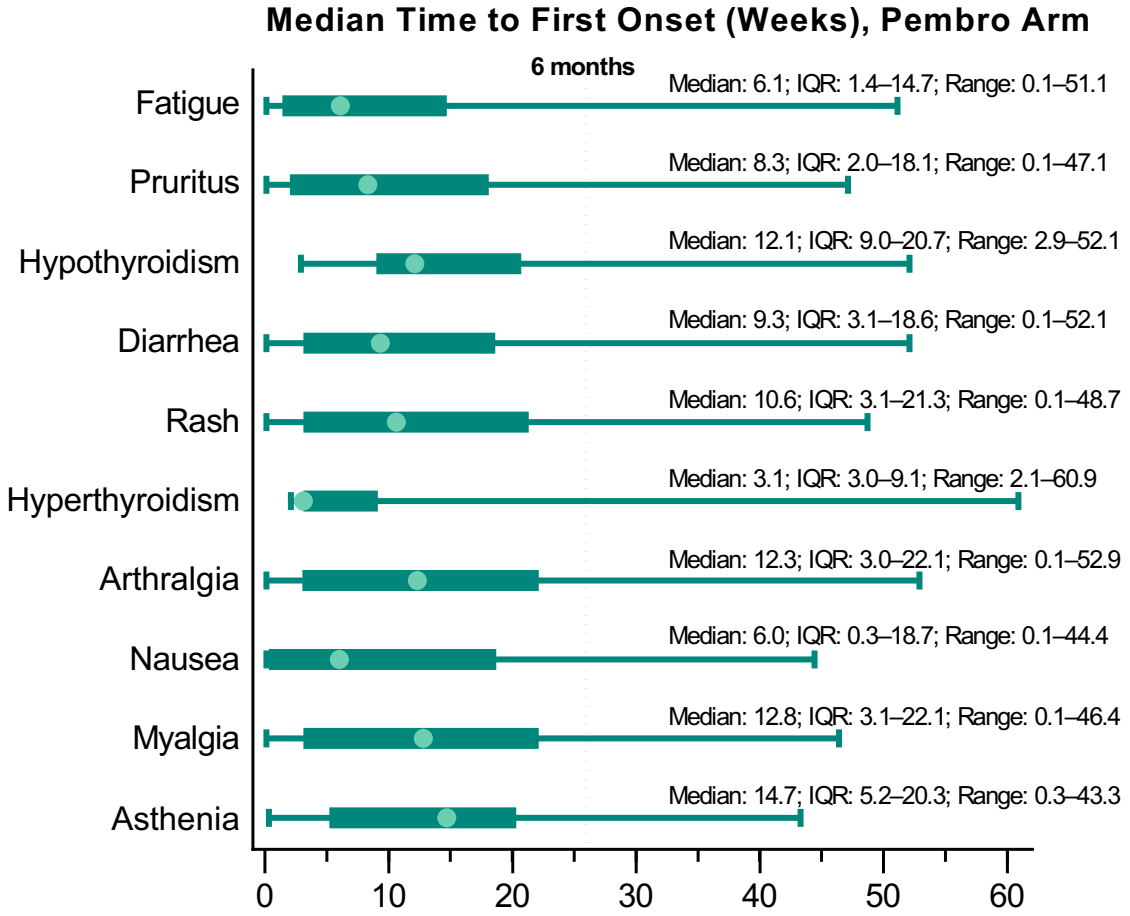
DFS in Key Subgroups



Subgroup analysis was not performed for participants with tumor grade 1 due to the small number of events.
DFS, disease-free survival. Data cutoff date: June 14, 2021.

Treatment-Related AEs with Incidence ≥5%, As-Treated Population



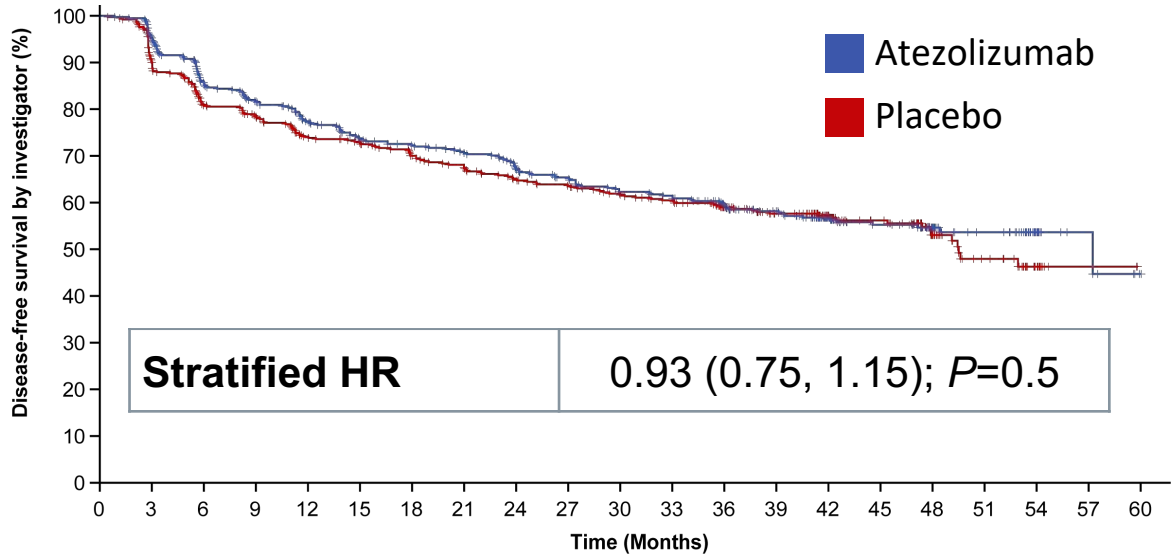


AE, adverse event.
As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: June 14, 2021.

Choueiri TK et al. Genitourinary Cancers Symposium 2022;Abstract 290.

IMmotion010: Atezolizumab vs placebo in intermediate and high risk renal cancer.

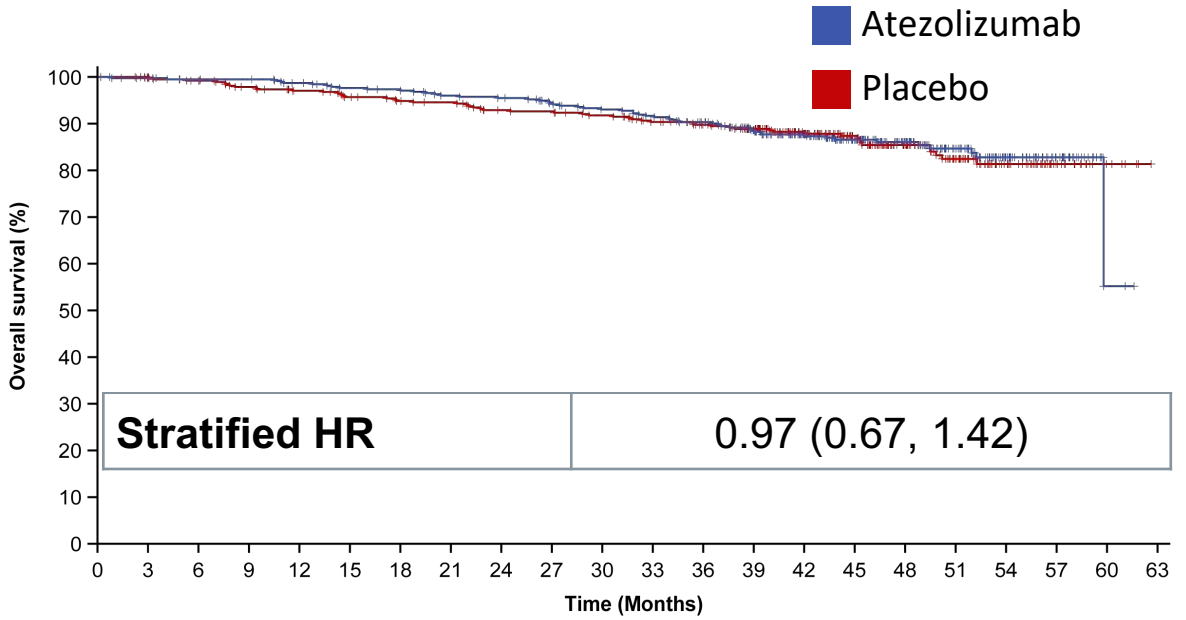
Disease free survival



Number at risk

Atezolizumab	390	360	322	306	288	272	265	257	244	234	222	218	194	171	124	100	75	48	22	6	1
Placebo	388	343	305	294	275	268	254	243	232	226	216	209	187	161	121	91	56	33	15	3	NE

Overall survival



Number at risk

Atezolizumab	390	383	379	378	371	365	363	357	355	347	341	336	326	300	250	196	144	103	58	28	2	NE
Placebo	388	379	372	363	355	349	343	340	331	330	325	314	304	287	226	181	138	92	49	20	6	NE

Bex A et al. ESMO 2022;Abstract LBA66.

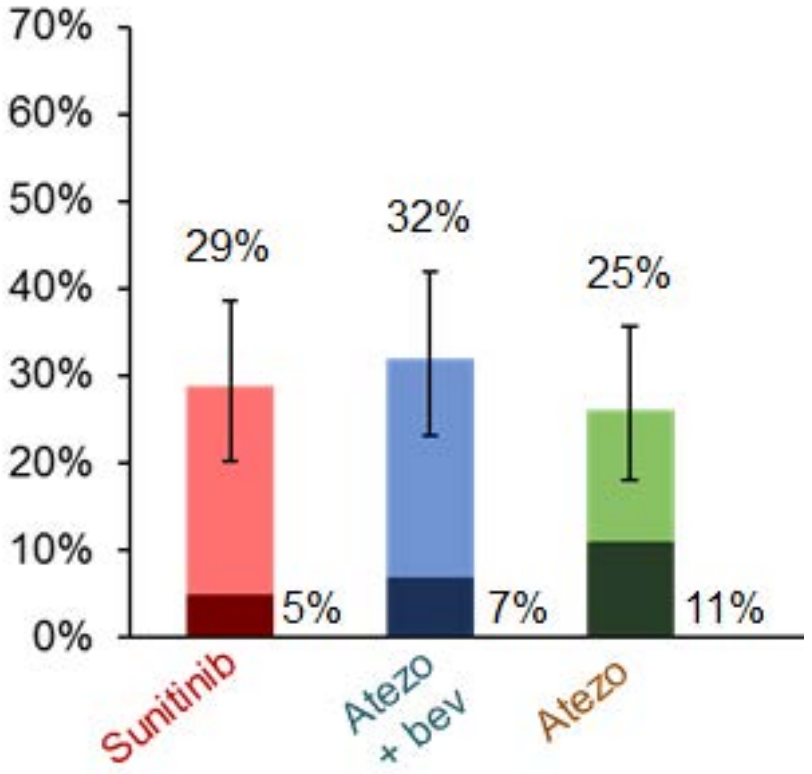
Is PD-L1 inhibition less active in clear cell RCC?

Subgroup analysis from the adjuvant studies

	Pembrolizumab	Atezo
Sarcomatoid	0.54 (0.29-1.00)	0.77 (0.44-1.36)
M1 NED	0.28 (0.12-0.66)	0.93 (0.48-0.49)

McDermott et al Nat Med 2017

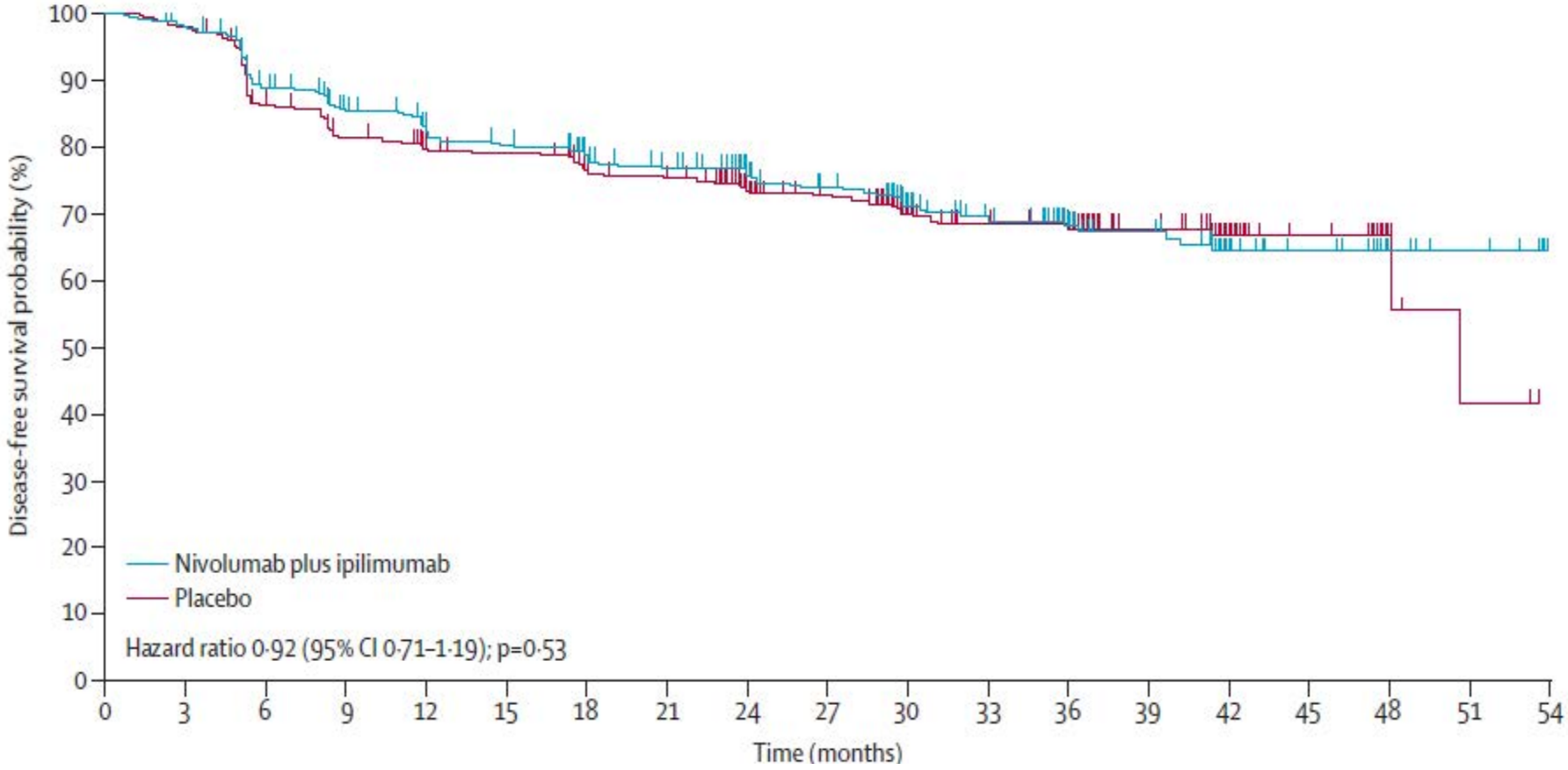
Single agent atezo in advanced RCC



Response rate for pembrolizumab =36% (n=110)

Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial

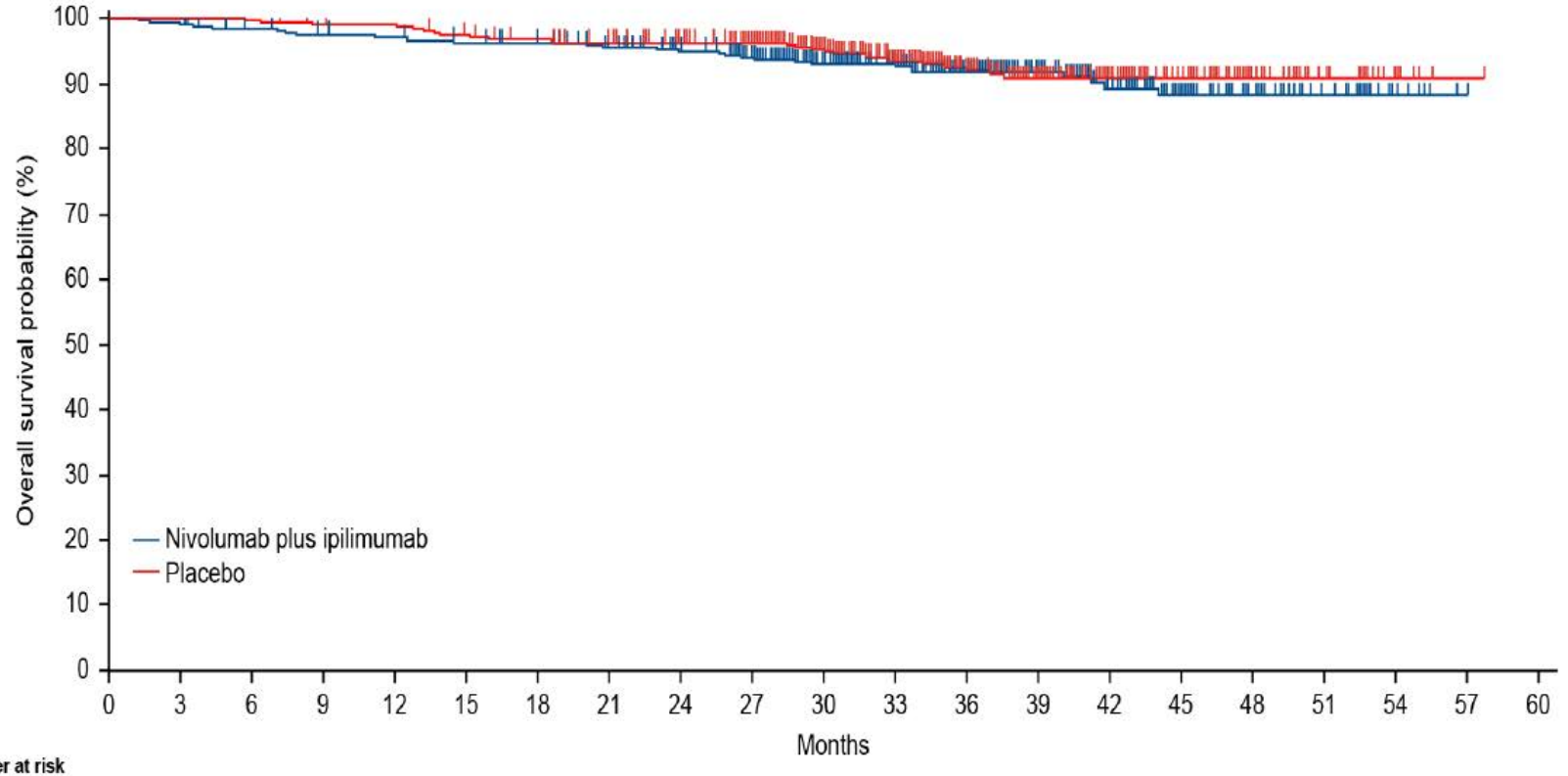
Primary endpoint
DFS



Motzer Lancet 2023

Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial

Overall survival



Number at risk (number censored)																					
Nivolumab plus ipilimumab	405 (0)	399 (3)	391 (8)	386 (10)	383 (11)	378 (13)	374 (17)	363 (25)	348 (38)	330 (52)	278 (101)	230 (149)	184 (192)	137 (239)	96 (277)	68 (304)	40 (332)	23 (349)	8 (364)	1 (371)	0 (372)
Placebo	411 (0)	403 (8)	400 (10)	396 (12)	395 (13)	386 (15)	381 (18)	372 (25)	361 (36)	343 (53)	292 (101)	237 (151)	184 (201)	138 (245)	98 (285)	66 (317)	36 (347)	22 (361)	10 (373)	1 (382)	0 (383)

Motzer lancet 2023

Drug exposure and safety

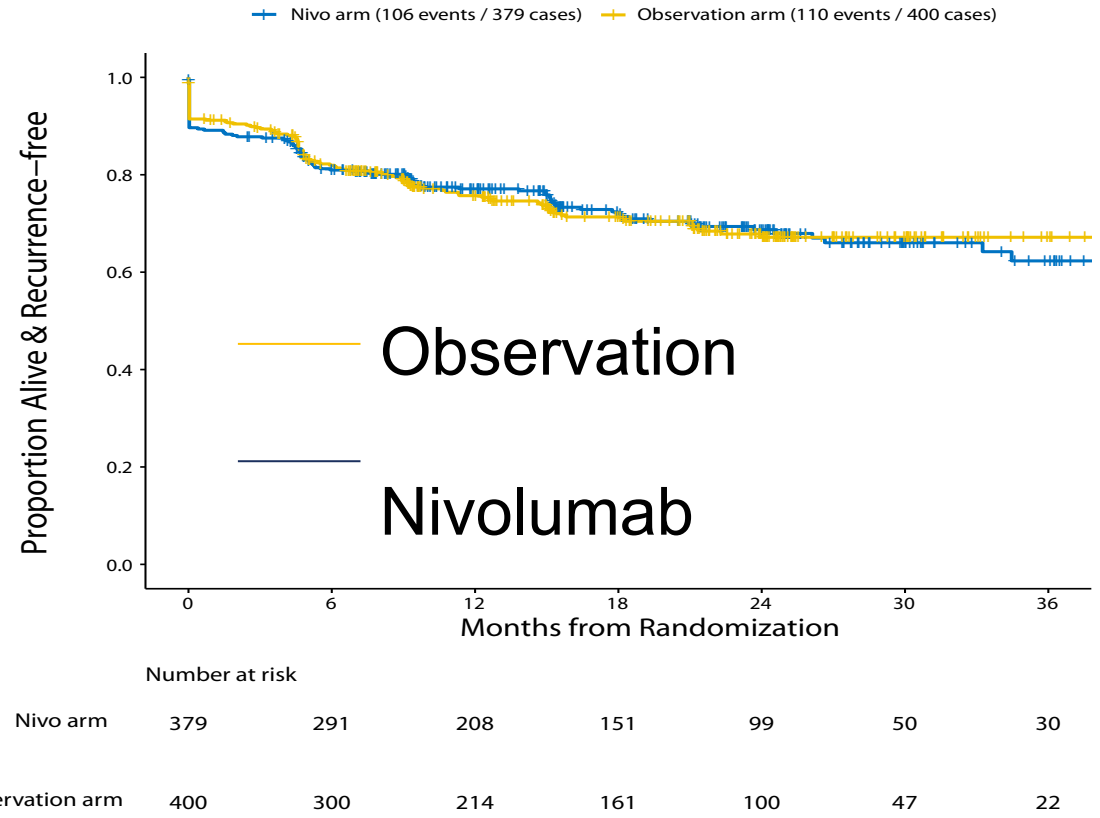
	NIVO+IPI (n = 404)	Placebo (n = 407)
Median duration of therapy (range), months	**5.1 (< 0.1-8.3)**	**5.1 (< 0.1-8.1)**
Q1, Q3	2.8, 5.3	5.1, 5.3
Median number of doses received (range)	**NIVO, 12 (1-12)** **IPI, 4 (1-4)**	**12 (1-12)[a]** **4 (1-4)[b]**
Completed all 12/4 doses of NIVO/IPI, n (%)	**231 (57)**	**361 (89)**
Discontinued treatment, n (%)[c]	**173 (43)**	**46 (11)**
Discontinued due to study drug toxicity, n (%)	132 (33)	5 (1)
All-cause AEs, n (%)[d]	**392 (97)**	**361 (89)**
Grade ≥ 3	155 (38)	42 (10)
Led to treatment discontinuation	129 (32)	9 (2)
Treatment-related AEs, n (%)[d]	**359 (89)**	**231 (57)**
Grade ≥ 3	115 (28)	8 (2)
Led to treatment discontinuation[e]	117 (29)	4 (1)
Deaths due to study drug toxicity, n (%)	4 (1)[f]	0

How much does ipilimumab add? Front-line Nivo and Ipi/Nivo in mRCC: IMDC Int/Poor risk

	HCRN (Nivo)[1] (n=88)	TITAN (Nivo)[2] (n=105)	CheckMate 214 (Ipi/Nivo)[3] (n=425 vs n=422)	PRISM (Ipi/Nivo)[4] (n=67) Standard	PRISM (Ipi/Nivo)[4] (n=70) Q12 Ipi	COSMIC control (Ipi/Nivo)[5] N=274
mPFS, mos	**5.4**	**5.5**	**11.6**	**8.6**	**10.5**	**11.3**
Landmark PFS	**30%** at 12 months	**35%** at 12 months	**50%** at 12 months **31%** at 5 years	**48%** at 12 months (est.)	**48%** at 12 months (est.)	**49%** at 12 months
ORR	**25%**	**29%**	**42%**	**41%**	**47%**	**36%**
CR	**5%**	**2%**	**11%**	**2%**	**7%**	**3%**
Primary PD	**41%**	**12%**	**19%**	**21%**	**27%**	**20%**
Med f/u, mos	**26.9**	**8.4**	**67.7**	**31**	**32**	**20.2**

Rini et al Uromigos 1. Atkins et al. JCO 2022 2. Grimm et al. ESMO 2022 3.Motzer et al. Cancer 2022 4. Vasudev et al. ESMO 2021 et al. ASCO 2021 5. Choueiri et al. ESMO 2022

Phase III Randomized Study Comparing Perioperative Nivolumab versus Observation in Patients with Renal Cell Carcinoma Undergoing Nephrectomy



HR: 0.97 [95% CI: 0.74 – 1.28]
One-sided P-value: 0.43

Uromigos @Uromigos · 27/09/2022

The #UromigosLive Poll Q4: #IMotion010 evaluated adjuvant #atezolizumab. It was the 1st study to open & the 1st to finish accrual - results just crossed the finish line & also soundly neg. Why? @MichaelStaehler @neerajaiims @montypal @ShuchiGulati @AbhiTrip87 @koshkin85 (5/6)

aPD-L1 < aPD-1	66%
Smaller study	7%
Different M1 population	27%

142 votes · Final results

5 7 6

Uromigos @Uromigos · 27/09/2022

The #UromigosLive Poll Q3: #PROSPER was a Herculean effort from @allaf_mo @LaurenCHarshman @NaomiHaas5 et al in @eaonc comparing periop nivo to observation but was soundly neg. Why is that? @ALLIANCE_org @BradMcG04 @DrChoueiri @AlbigesL @Silke_Gillessen @RCCadvocate (4/6)

Neoadj don't work in RCC	20%
Low risk pts included	69%
Observation ctrl	11%

127 votes · Final results

2 3 5

Uromigos @Uromigos · 27/09/2022

The #UromigosLive Poll Q2: Some found it quite surprising that #CM914 (adj nivo/ipi) was negative; after all, #nivolumab/ #ipilimumab RR in metastatic #kidneycancer quite high. Why did it fail? @motzermd @KidneyCancerDoc @MosheOrnsteinMD @AmandaNizamMD (3/6)

Adj ipi not active	20%
Excess toxicity	59%
Needs time to mature	21%

128 votes · Final results

2 3 5

Summary

The pembrolizumab trial is strongly positive for DFS. The OS signal is supportive but not mature.

While PD-L1 therapy has activity it has performed less well in clear cell RCC. This may in part explain the results of adjuvant atezolizumab.

The neoadjuvant nivolumab trial has a number of design and methodology issues. It is not possible to judge the comparative activity of nivolumab based on this study.

Adjuvant ipilimumab/nivolumab data showed more toxicity without activity. This is more difficult to explain. Was the ipi tox holding back nivolumab, how much is ipilimumab adding?

The nivolumab alone arm of 914 is important for nivolumab

The ipilimumab/nivolumab arm of 8Y8 study is important for ipilimumab.

The contradictory findings of these 3 adjuvant trials won't be down to luck alone.

This is not an exact replication of the VEGF TKI adjuvant trial story.

We really need to start selecting patients for therapy.

Patients should be aware that pembrolizumab delays DFS with a chance of life changing toxicity. It may improve OS in the future. They should also be aware that other ICIs have not been able to replicate the pembrolizumab data creating new uncertainty in renal cancer.

MODULE 2: Evidence-Based Selection of First-Line Therapy for Metastatic RCC — Dr Choueiri

RTP
RESEARCH
TO PRACTICE

Case Presentation: 71-year-old man with metastatic RCC enrolls on the PDIGREE trial and receives nivolumab/ ipilimumab without response followed by cabozantinib

Dr Helen Moon (Riverside, California)

QUESTIONS FOR THE FACULTY

Helen H Moon, MD

In general, how do you decide to use ipilimumab/nivolumab vs IO/TKI in metastatic RCC, and how do you select the IO/TKI combination?

This patient had no tolerability issues with ipilimumab/nivolumab but also no response: Is there a correlation?

What is the rationale for the PDIGREE study in metastatic RCC?

In what situations, if any, would you prefer a triplet approach to first-line treatment of metastatic RCC as in COSMIC-313?

Case Presentation: 70-year-old man receives ipilimumab/nivolumab for widely metastatic RCC and develops autoimmune hepatitis

Dr Victoria Giffi (Hagerstown, Maryland)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 63-year-old man with metastatic ccRCC receives ipilimumab/nivolumab → nivolumab with response but develops hypothyroidism and hypoadrenalism

Dr Philip Brooks (Brewer, Maine)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Victoria Giffi, MD

How do you approach first-line treatment of metastatic disease in patients on chronic hemodialysis?

In patients with significant autoimmune toxicity on ipilimumab/nivolumab, in what situations, if any, do you restart nivolumab alone? What about adding a TKI?

Philip L Brooks, MD

At what point, if any, do you discontinue immunotherapy in a patient with metastatic disease?

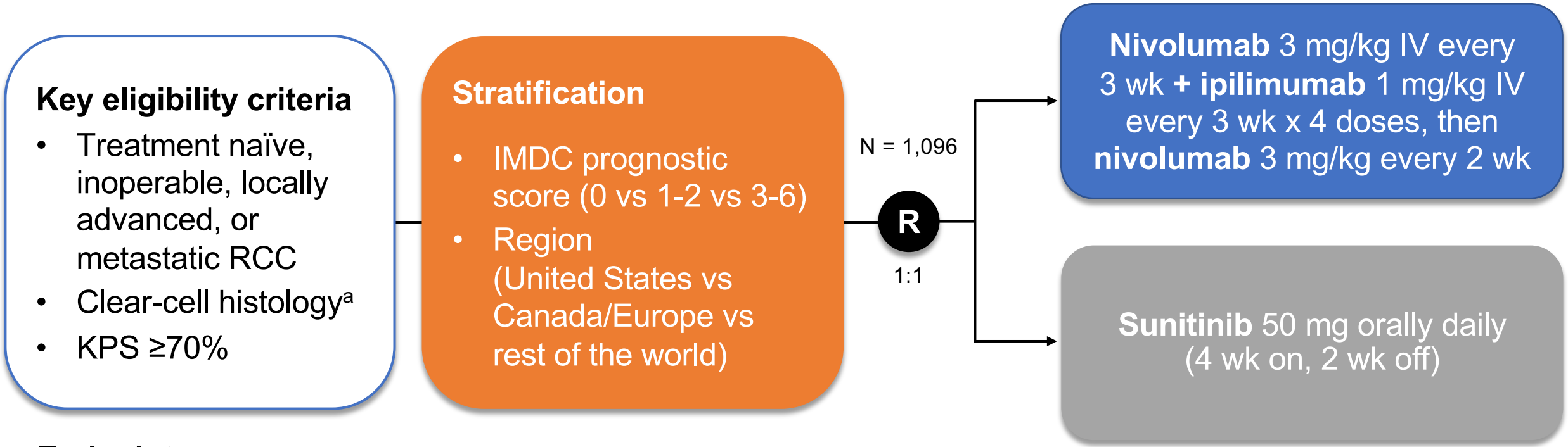
How often and for how long do you screen for thyroid abnormalities in patients on IOs? Do you continue screening after treatment is discontinued? What will lead you to check for hypoadrenalism?

RTP
RESEARCH
TO PRACTICE

Evidence-Based Selection of First-Line Therapy for Metastatic RCC

Toni K Choueiri, MD

CheckMate 214: Nivolumab Plus Ipilimumab in Newly Diagnosed Advanced Clear-Cell RCC



Endpoints

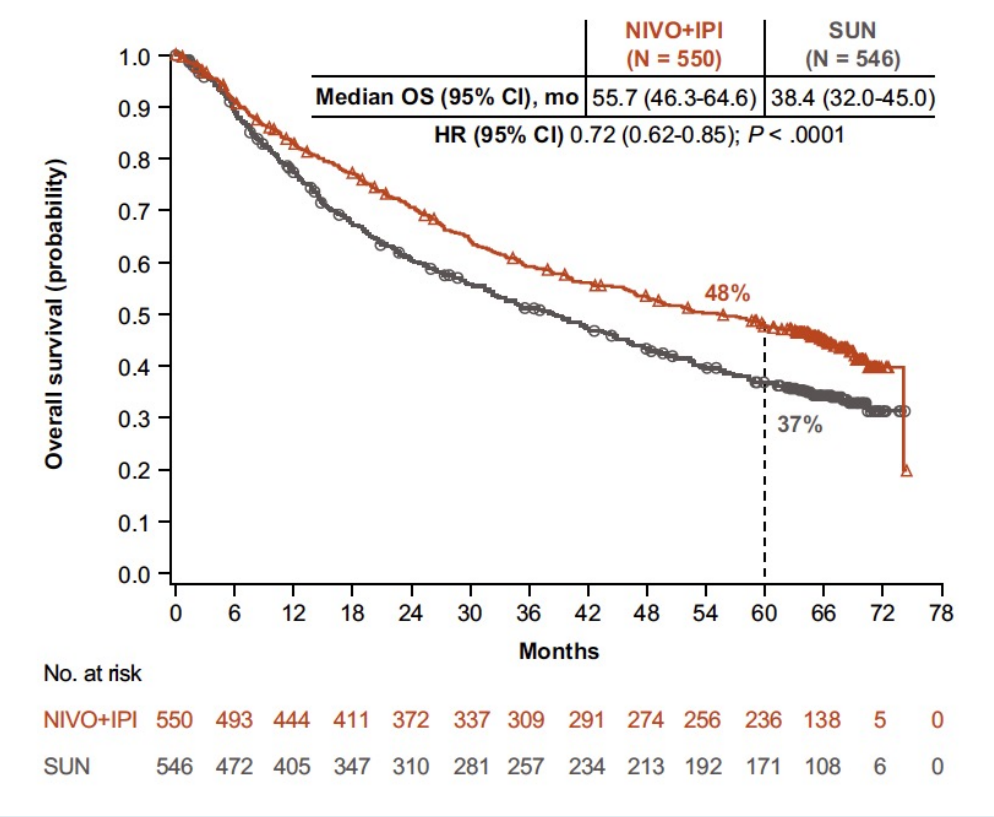
- **Coprimary:** PFS, OS, ORR (intermediate/poor risk)
- **Secondary:** PFS, OS, ORR (ITT)
- **Exploratory:** PFS, OS, ORR (favorable risk)

CheckMate 214: Intermediate-/Poor-Risk Patients

Minimum Follow-Up, mo	**Median OS, mo (95% CI)**		**Median PFS, mo (95% CI)**	
	Nivolumab + Ipilimumab (n = 425)	**Sunitinib (n = 422)**	**Nivolumab + Ipilimumab (n = 425)**	**Sunitinib (n = 422)**
17.5[1]	NR (28.2-NE)	26.0 (22.1-NE)	11.6 (8.7-15.5)	8.4 (7.0-10.8)
	HR (99.8% CI) **0.63** (0.44-0.89); *P* <.001		HR (99.1% CI) **0.82** (0.64-1.05); *P* = .03	
30[2]	NR (35.6-NE)	26.6 (22.1-33.4)	8.2 (6.9-10.0)	8.3 (7.0-8.8)
	HR (95% CI) **0.66** (0.54-0.80); *P* <.0001		HR (95% CI) **0.77** (0.65-0.90); *P* = .0014	
42[3]	47.0 (35.6-NE)	26.6 (22.1-33.5)	11.6 (8.4-15.5)	8.3 (7.0-10.8)
	HR (95% CI) **0.66** (0.55-0.80); *P* <.0001		HR (95% CI) **0.75** (0.62-0.90); *P* = .0015	
48[4]	48.1 (35.6-NE)	26.6 (22.1-33.5)	11.2 (8.4-16.1)	8.3 (7.0-10.8)
	HR (95% CI) **0.65** (0.54-0.78); *P* <.0001		HR (95% CI) **0.74** (0.62-0.88); *P* = .0015	
60[5]	47.0 (35.4-57.4)	26.6 (22.1-33.5)	11.6 (8.4-16.5)	8.3 (7.0-10.4)
	HR (95% CI) **0.68** (0.58-0.81); *P* <.0001		HR (95% CI) **0.73** (0.61-0.87); *P* = .0004	

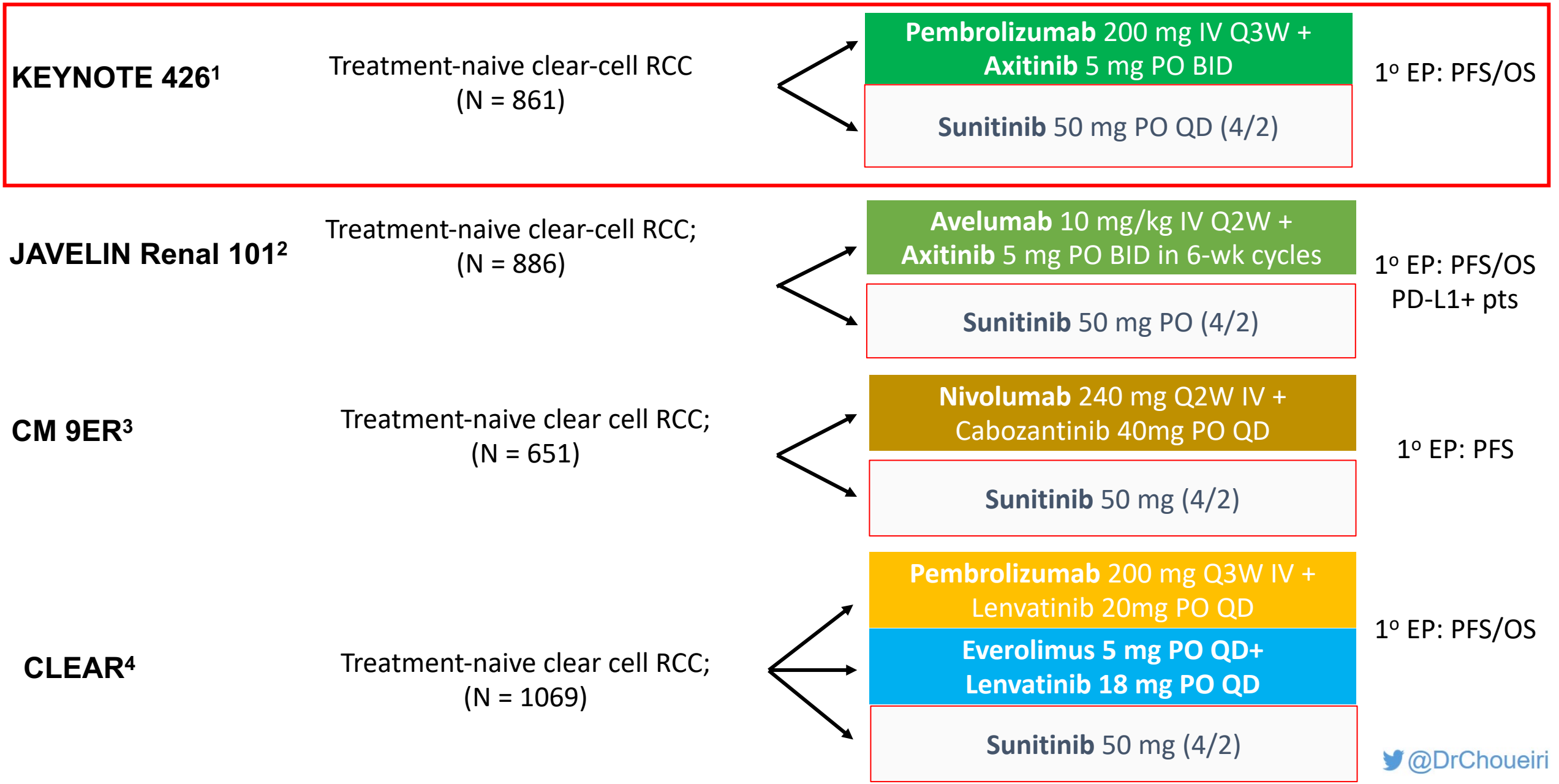
1. Motzer RJ et al. *N Engl J Med*. 2018. PMID: 29562145. 2. Motzer RJ et al. *Lancet Oncol*. 2019. PMID: 31427204. 3. Motzer RJ et al. *J Immunother Cancer*. 2020. PMID: 32661118. 4. Albiges L. et al., *ESMO Open*, 2021. PMID: 33246931. 5. Motzer R.J. et al., ESMO Annual Congress, 2021.

CheckMate 214: Efficacy Summary in Intent-to-Treat Population (Median Follow-Up 67.7 Months)



- PFS (median, 12.3 vs 12.3 months; hazard ratio, 0.86), and objective response (39.3% vs 32.4%) benefits were maintained with NIVO+IPI versus SUN, respectively, in intent-to-treat patients

Motzer RJ et al. *Cancer* 2022;128(11):2085-97.

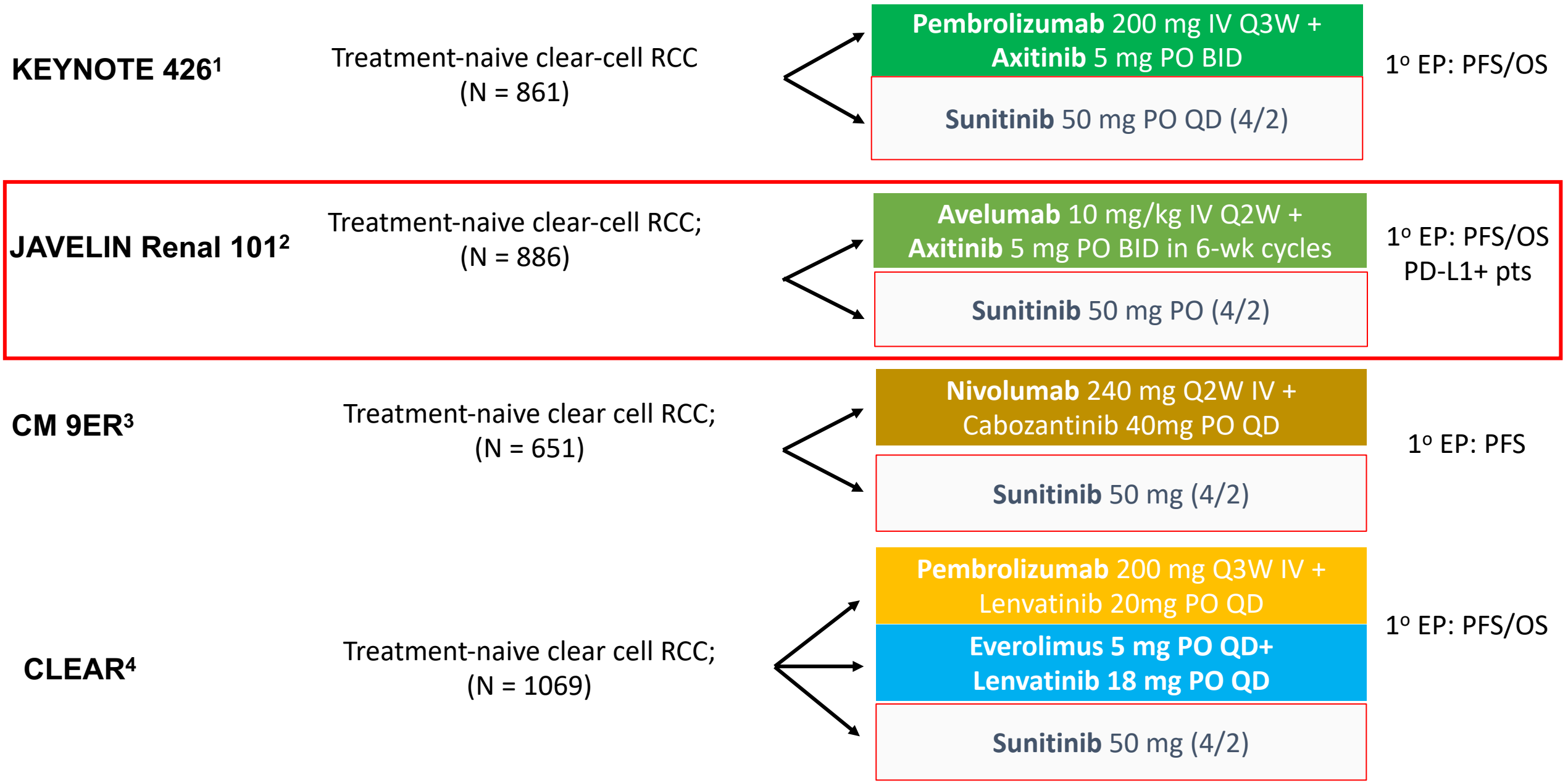


1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

KEYNOTE-426 Highlights

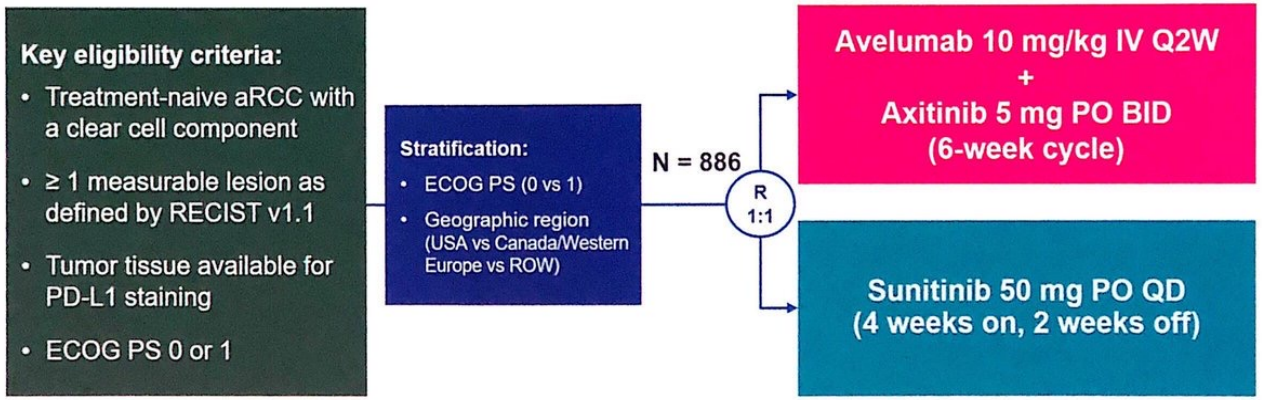
Median follow-up (months)	12.8	30.6	42.8
OS, months	NR	NR	45.7
HR (95% CI)	0.53 (0.38-0.74)	0.68 (0.55-0.85)	0.73 (0.6-0.88)
PFS, months	15.1	15.4	15.7
HR (95% CI)	0.69 (0.57-0.84)	0.71 (0.6-0.84)	0.68 (0.58-0.8)
ORR(%)/CR(%)	59/6	60/9	60/10

1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Powles et al, *Lancet Oncol.*, 2020. PMID: 33284113. 3. Rini et al, ASCO 2021.



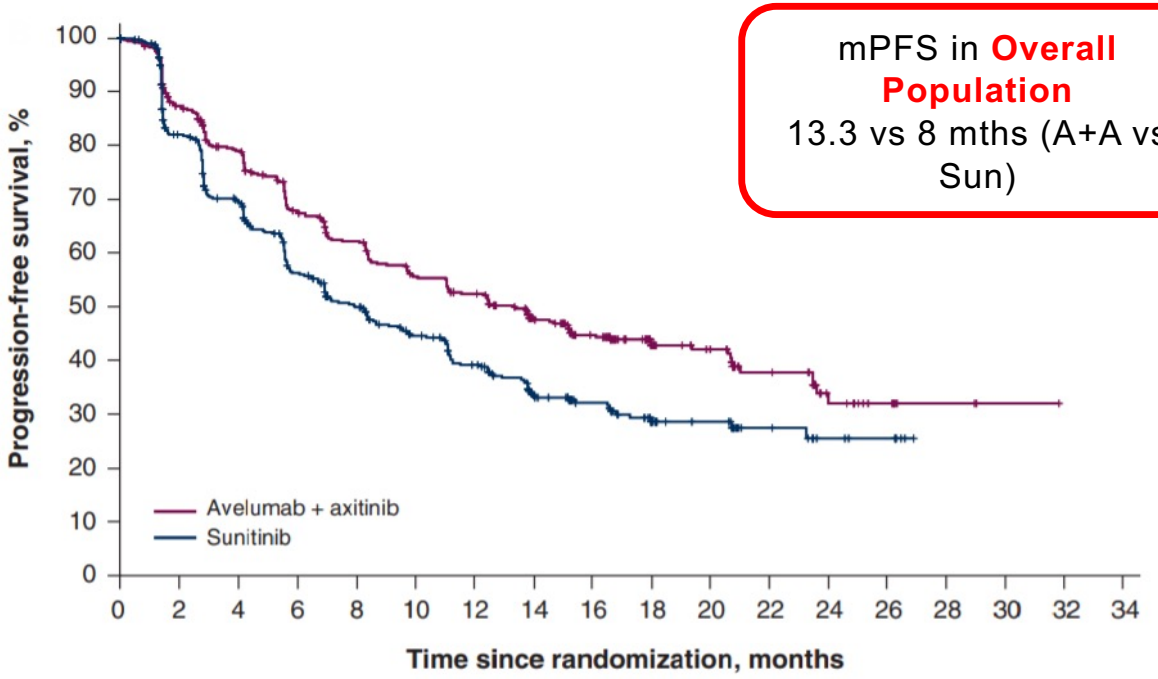
1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

JAVELIN Renal 101- Highlights

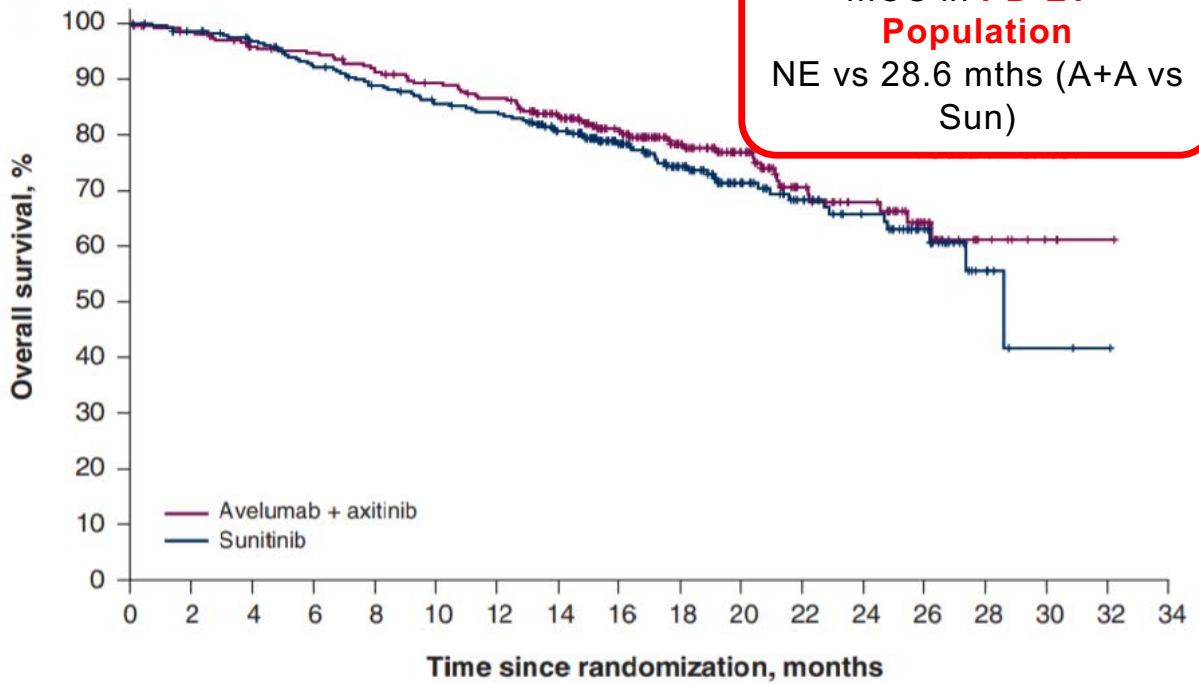


Primary Endpoint: PFS or OS in patients *with PD-L1+ tumors*

OS: Not Significant
HR: 0.828 (95% CI 0.596-1.151); one-sided P = 0.13



mPFS in **Overall Population**
13.3 vs 8 mths (A+A vs Sun)



mOS in **PD-L1+ Population**
NE vs 28.6 mths (A+A vs Sun)

1.Choueiri T.K. et al., *Ann Onc.*, 2020. PMID: 32339648

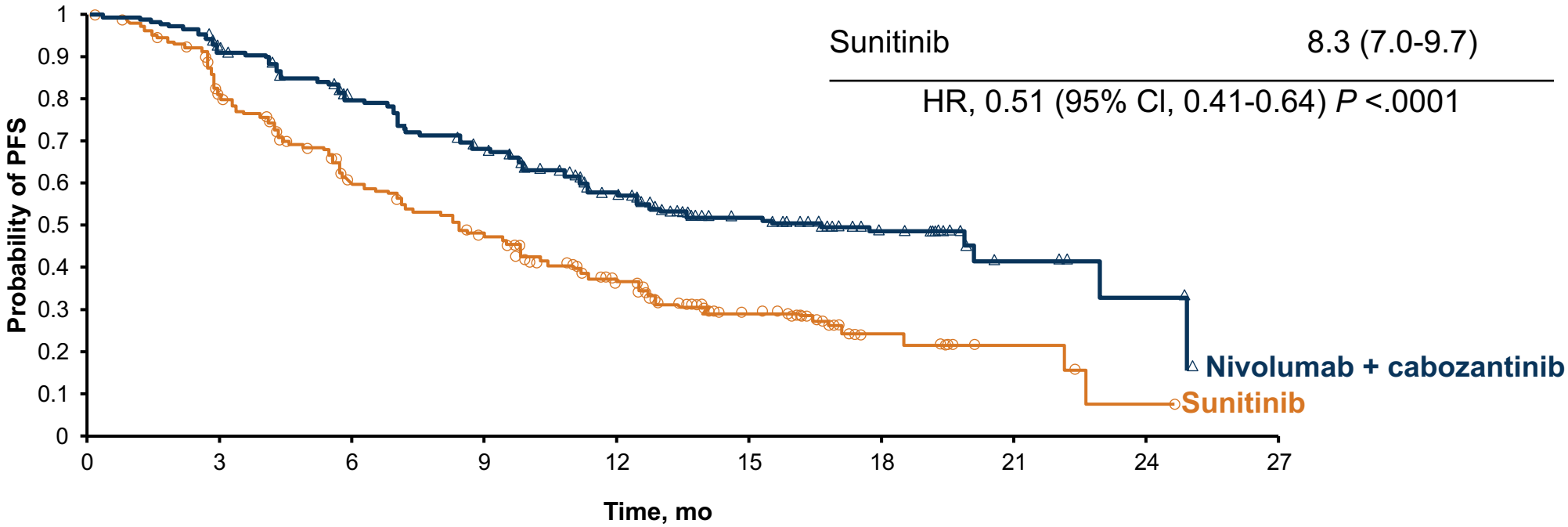
KEYNOTE 426[1]	Treatment-naive clear-cell RCC (N = 861)	**Pembrolizumab** 200 mg IV Q3W + **Axitinib** 5 mg PO BID **Sunitinib** 50 mg PO QD (4/2)	1º EP: PFS/OS
JAVELIN Renal 101[2]	Treatment-naive clear-cell RCC; (N = 886)	**Avelumab** 10 mg/kg IV Q2W + **Axitinib** 5 mg PO BID in 6-wk cycles **Sunitinib** 50 mg PO (4/2)	1º EP: PFS/OS PD-L1+ pts
CM 9ER[3]	Treatment-naive clear cell RCC; (N = 651)	**Nivolumab** 240 mg Q2W IV + Cabozantinib 40mg PO QD **Sunitinib** 50 mg (4/2)	1º EP: PFS
CLEAR[4]	Treatment-naive clear cell RCC; (N = 1069)	**Pembrolizumab** 200 mg Q3W IV + Lenvatinib 20mg PO QD **Everolimus 5 mg PO QD+ Lenvatinib 18 mg PO QD** **Sunitinib** 50 mg (4/2)	1º EP: PFS/OS

1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

CheckMate 9ER: PFS[1,2]

	Median (95% CI), mo
Nivolumab + cabozantinib	16.6 (12.5-24.9)
Sunitinib	8.3 (7.0-9.7)

HR, 0.51 (95% CI, 0.41-0.64) *P* <.0001



No. at Risk										
Nivolumab + cabozantinib	323	279	234	196	144	77	35	11	4	0
Sunitinib	328	228	159	122	79	31	10	4	1	0

Minimum study follow-up, 10.6 months.

1. Choueiri TK et al. ESMO 2020, 2. Choueiri T.K. et al., *NEJM*, 2021. PMID: 33657295.

CheckMate 9ER Highlights

Median follow-up (months)	18[1]	23.5[2]	32.9[3]
OS, months	NR	NR	37.7
HR (95% CI)	0.60 (0.40-0.89)	0.66 (0.50-0.87)	0.70 (0·55-0·90)
PFS, months	16.6	17.0	16.6
HR (95% CI)	0.51 (0.41-0.64)	0.52 (0.43-0.64)	0.56 (0·46-0·68)
ORR(%)/CR(%)	55.7/8.0	56.5/8.5	55.7/12.4

1. Choueiri et al, ESMO 2020, *NEJM*, 2021. 2. Motzer R.J. et al., ASCO GU Cancer Symposium, 2021. 3. Powles et al, ASCO GU Cancer Symposium, 2022 and Motzer et al, Lancet Oncol, 2022

First-Line Nivolumab with Cabozantinib Shows Durable Survival with More Than 3 Years of Follow-Up in the CheckMate 9ER Trial for Advanced RCC

Press Release: February 13, 2023

"[It was announced that the] three-year (36.5 months minimum; 44.0 months median) follow-up results from the Phase 3 CheckMate 9ER trial demonstrated sustained survival and response rate benefits with the combination of nivolumab and cabozantinib versus sunitinib in the first-line treatment of advanced renal cell carcinoma.

Additionally, a biomarker analysis showed that improvements in median progression-free survival (PFS) and overall survival (OS) were sustained with the combination of nivolumab and cabozantinib regardless of PD-L1 status. These updated results will be featured in one oral and one poster presentation at the American Society of Clinical Oncology (ASCO) 2023 Genitourinary Cancers Symposium from February 16-18, 2023."

https://finance.yahoo.com/news/opdivo-nivolumab-combination-cabometyx-cabozantinib-220000099.html

RTP RESEARCH TO PRACTICE

Nivolumab plus Cabozantinib vs Sunitinib for First-Line Treatment of Advanced Renal Cell Carcinoma (aRCC): 3-Year Follow-Up from the Phase 3 CheckMate 9ER Trial

Burotto M et al.

Abstract 603.

Oral Abstract Session C: Renal and Rare Tumors

February 18, 2023

2:00 PM PT (5:00 PM ET)

Biomarker Analysis from the Phase 3 CheckMate 9ER Trial of Nivolumab + Cabozantinib v Sunitinib for Advanced Renal Cell Carcinoma (aRCC)

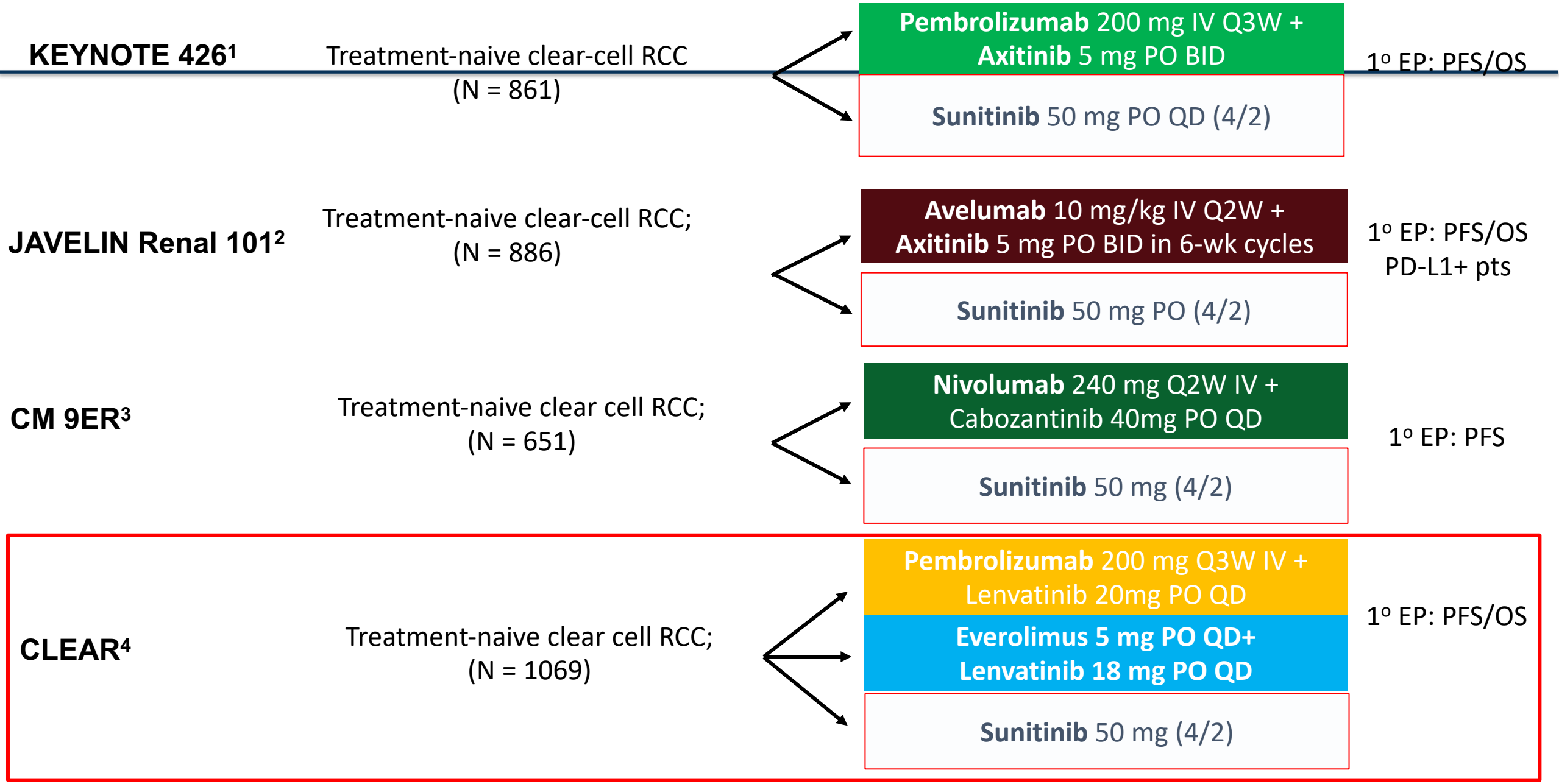
Choueiri TK et al.

Abstract 608.

Rapid Abstract Session: Biomarkers of Response and Risk Stratification in Genitourinary Cancers

February 18, 2023

7:00 AM PT (10:00 AM ET)



1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

CLEAR Highlights

Median follow-up (months)	26.6[1]	33.7[2-3]
OS, months	NR	NR
HR (95% CI)	0.66 (0.49–0.88)	0.72 (0.55-0.93)
PFS, months	23.9	23.3
HR (95% CI)	0.39 (0.32-0.49)	0.42 (0.34-0.52)
ORR(%)/CR(%)	71/16.1	71/17.2

1. Motzer et al, *NEJM*, 2021. Choueiri et al, IKCS, 2021, Porta et al, ESMO, 2022

Treatment-related AEs on Phase III

(The case of CheckMate 9ER as an example)

Treatment-Related Adverse Events in ≥ 15% of Patients in Any Treatment Group

	Cabo + Nivo N = 320		Sunitinib N = 320	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Diarrhea	56.9	5.6	42.5	4.4
PPE	38.1	7.5	40.3	7.5
Hypothyroidism	33.4	0.3	28.1	0.3
Hypertension	30.3	10.9	33.4	12.2
Fatigue	26.9	2.5	30.3	3.8
ALT increased	25.0	4.7	6.3	0.6
AST increased	23.4	3.1	8.8	0.6
Dysgeusia	21.6	0	20.3	0
Nausea	21.3	0.6	25.3	0
Decreased appetite	20.3	1.3	16.6	0.6
Rash	19.4	1.6	6.9	0
Mucosal inflammation	19.1	0.9	25.0	2.5
Asthenia	17.8	3.1	15.0	2.2
Pruritus	16.3	0.3	4.1	0
Stomatitis	15.6	2.2	23.1	2.2
Lipase increased	15.0	5.3	10.9	4.7
Vomiting	11.3	1.3	16.3	0.3
Anemia	10.0	0.9	19.1	2.5
Thrombocytopenia	5.9	0.3	19.1	4.4
Platelet count decreased	5.3	0	18.4	4.4

Choueiri TK, et al. ESMO 2020 Abs 696O Oral.

original reports

Prospective Cardiovascular Surveillance of Immune Checkpoint Inhibitor–Based Combination Therapy in Patients With Advanced Renal Cell Cancer: Data From the Phase III JAVELIN Renal 101 Trial

Brian I. Rini, MD[1]; Javid J. Moslehi, MD[2,3]; Marc Bonaca, MD, MPH[4]; Manuela Schmidinger, MD[5]; Laurence Albiges, MD, PhD[6]; Toni K. Choueiri, MD[7]; Robert J. Motzer, MD[8]; Michael B. Atkins, MD[9]; John Haanen, MD, PhD[10]; Mariangela Mariani, PhD[11]; Jing Wang, PhD[12]; Subramanian Hariharan, MD[13]; and James Larkin, MD, PhD[14]

J Clin Oncol Jun 2022;40(17):1929-38.

Summary of MACE During the On-Treatment Period (safety analysis set)

	Avelumab Plus Axitinib (n = 434)	Sunitinib (n = 439)	Avelumab Plus Axitinib *v* Sunitinib	
MACE	**No. (%)**	**No. (%)**	**Risk Difference**	**95% CI**
MACE, total	31 (7.1)	17 (3.9)	0.033	–0.034 to 0.099
Cardiac deaths	6 (1.4)	1 (0.2)	0.012	–0.055 to 0.078
Cardiopulmonary failure	0 (0)	1 (0.2)	—	—
Death	4 (0.9)	0 (0)	—	—
Myocarditis	1 (0.2)	0 (0)	—	—
Sudden death	1 (0.2)	0 (0)	—	—
Fatal stroke	1 (0.2)	1 (0.2)	0.000	–0.066 to 0.066
Cerebrovascular accident	1 (0.2)	1 (0.2)	—	—
Nonfatal arrhythmia	4 (0.9)	1 (0.2)	0.007	–0.060 to 0.073
Atrial fibrillation	4 (0.9)	0 (0)	—	—
Electrocardiogram QT prolonged	0 (0)	1 (0.2)	—	—
Nonfatal congestive heart failure	7 (1.6)	3 (0.7)	0.009	–0.057 to 0.076
Cardiac failure	1 (0.2)	0 (0)	—	—
Ejection fraction decreased	6 (1.4)	3 (0.7)	—	—
Nonfatal myocardial infarction	9 (2.1)	3 (0.7)	0.014	–0.053 to 0.080
Acute coronary syndrome	2 (0.5)	0 (0)	—	—
Acute myocardial infarction	3 (0.7)	0 (0)	—	—
Angina pectoris	0 (0)	2 (0.5)	—	—
Coronary artery disease	0 (0)	1 (0.2)	—	—
Coronary artery occlusion	1 (0.2)	0 (0)	—	—
Myocardial ischemia	0 (0)	1 (0.2)	—	—
Troponin I increased	1 (0.2)	0 (0)	—	—
Troponin T increased	1 (0.2)	0 (0)	—	—
Nonfatal myocarditis	1 (0.2)	0 (0)	0.002	–0.064 to 0.069
Myocarditis	1 (0.2)	0 (0)	—	—
Nonfatal stroke	3 (0.7)	8 (1.8)	–0.011	–0.078 to 0.055
Brain hypoxia	0 (0)	1 (0.2)	—	—
Cerebellar hemorrhage	0 (0)	1 (0.2)	—	—
Cerebrovascular accident	2 (0.5)	2 (0.5)	—	—

Summary of Patients With LVEF% Decrease of at Least 10 Points From Baseline to a Postbaseline Value Below the LLN During On-Treatment Period— Safety Analysis Set

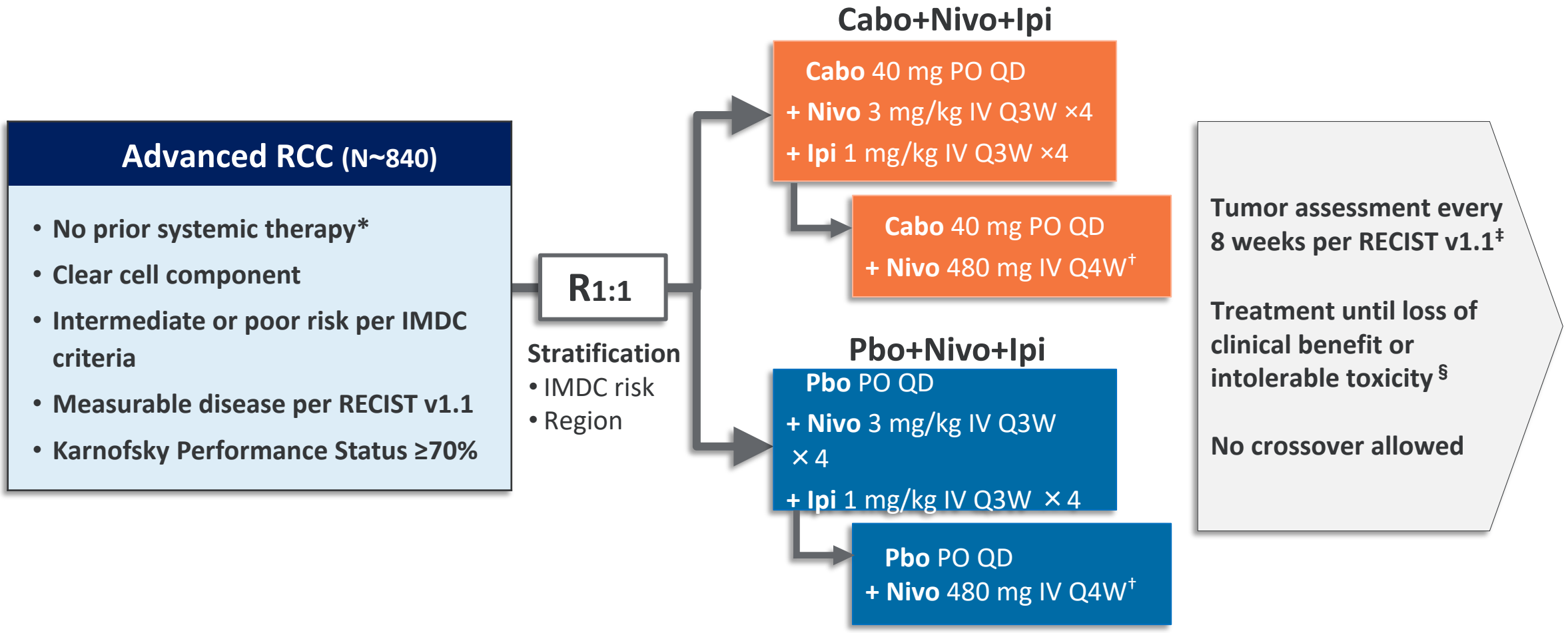
Left Ventricular Ejection Fraction Characteristic	Avelumab Plus Axitinib (n = 434)	Sunitinib (n = 439)
Patients with LVEF% ≥ 10-point decrease from baseline to a postbaseline value < LLN, No. (%)[a]	37 (8.5)	7 (1.6)
Time to onset of LVEF% ≥ 10-point decrease from baseline to postbaseline value < LLN, median, weeks[b]	18.1	7.6
Recovery		
Time to LVEF recovery, median, weeks	12.1	12.2
Recovered, No. (%)[c]	22 (59.5)	4 (57.1)
Ongoing, No. (%)[d]	15 (40.5)	3 (42.9)

Relative Risk of MACE by Serum Cardiac Biomarker Levels at Baseline

	Avelumab Plus Axitinib (n = 434)			Sunitinib (n = 439)		
Cardiac Serum Biomarker	MACE, No.	No MACE, No.	Relative Risk of MACE (95% CI)	MACE, No.	No MACE, No.	Relative Risk of MACE (95% CI)
Troponin T						
High	6	29	3.31 (1.19 to 9.22)	2	39	0.89 (0.2 to 3.98)
Not high	7	128		9	156	

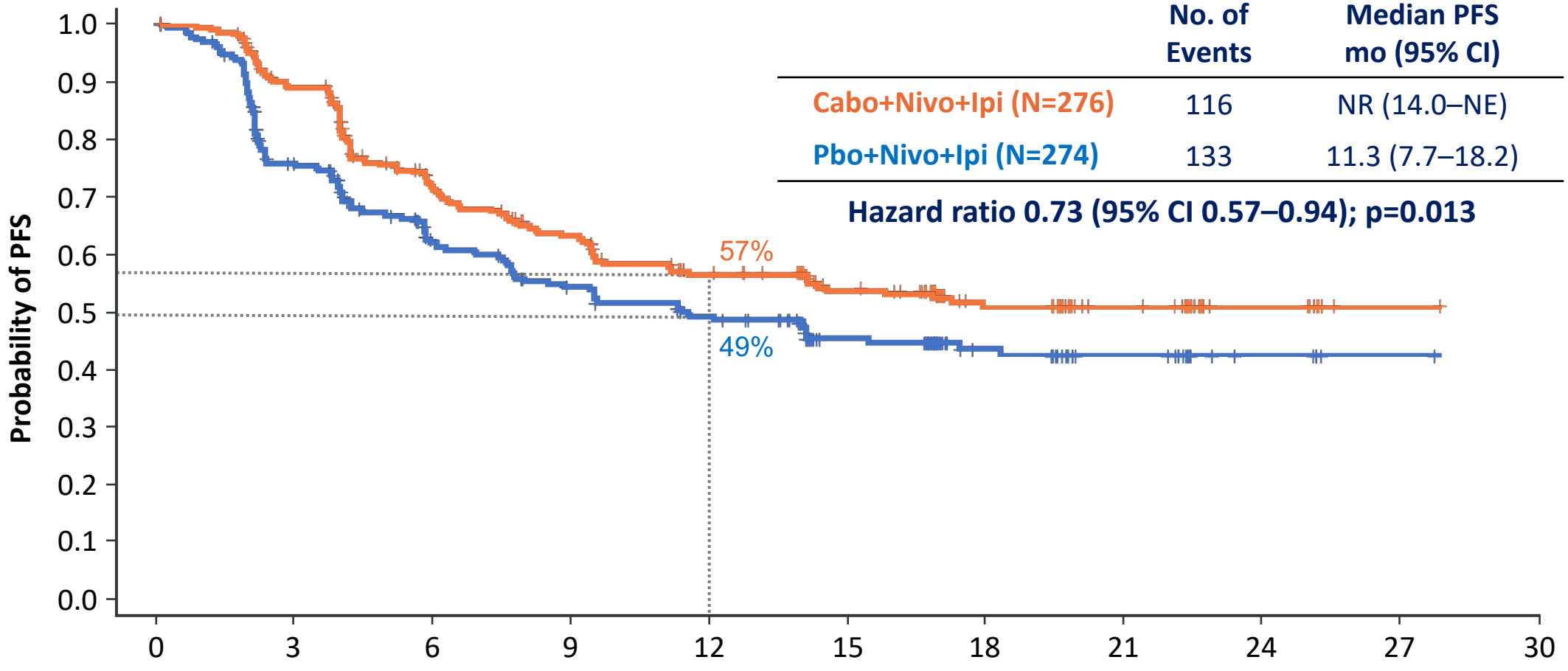
Rini B et al. *J Clin Oncol* 2022;40(17):1929-38.

COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

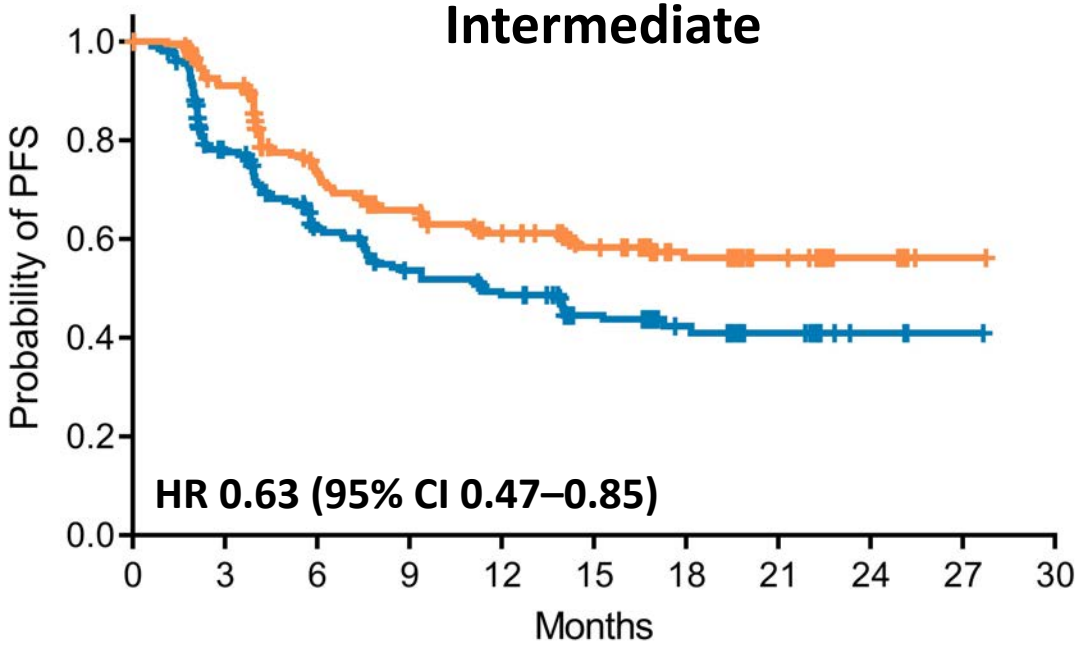
Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

PFS and ORR by IMDC Risk Group (PITT Population)

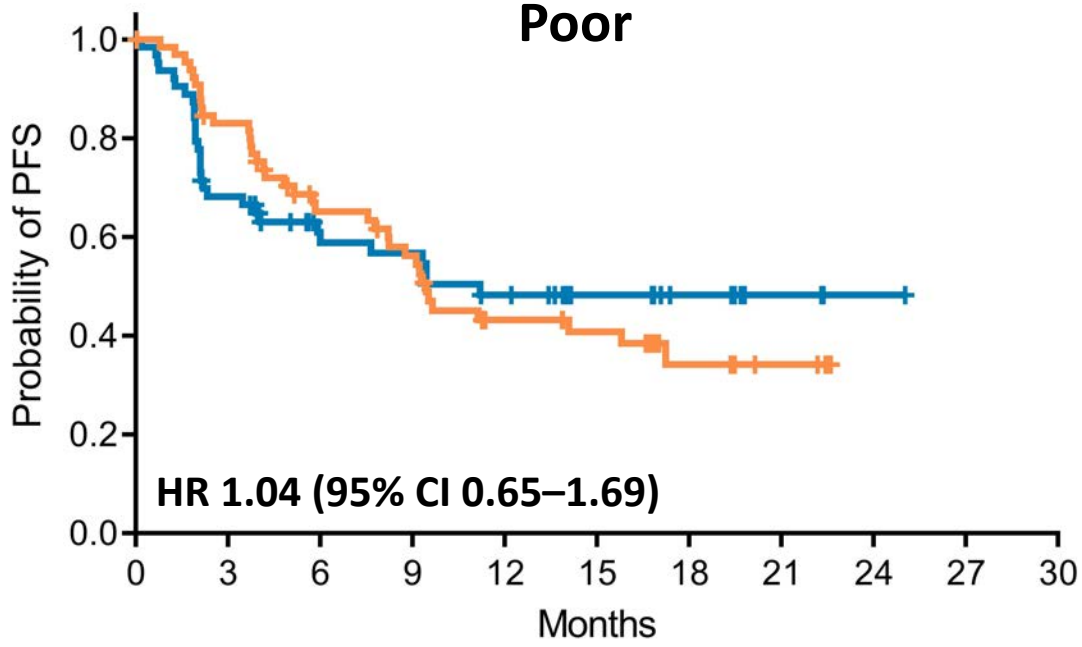
Intermediate



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs
35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi

Poor



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs
38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Summary of Adverse Events (Safety Population)

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	**99**	**73**	**91**	**41**
Alanine aminotransferase increased	**46**	**26**	**17**	**6**
Aspartate aminotransferase increased	**44**	**20**	**16**	**5**
Diarrhea	**41**	**4**	**18**	**3**
Palmar-plantar erythrodysesthesia	**28**	**3**	**4**	**0**
Hypothyroidism	**24**	**<1**	**15**	**0**
Hypertension	**23**	**8**	**5**	**2**
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

- Grade 5 TRAEs occurred in 3 patients (1%) with Cabo+Nivo+Ipi (gastrointestinal hemorrhage, hepatic failure, and respiratory failure) and 3 patients (1%) with Pbo+Nivo+Ipi (renal failure, myocarditis, and sudden death) ≤30 days after last dose; through 100 days after last dose, two additional patients had grade 5 TRAEs with Cabo+Nivo+Ipi (immune-mediated hepatitis and acute hepatic failure) and one additional patient with Pbo+Nivo+Ipi (perforated ulcer)
- Use of high-dose corticosteroids (≥40 mg of prednisone or equivalent) for AEs was 58% with Cabo+Nivo+Ipi and 35% with Pbo+Nivo+Ipi

*Occurring in ≥20% of either treatment group.

Data cut-off: Jan 31, 2022

MODULE 3: Treatment Options for Relapsed/Refractory RCC — Dr Rini

Case Presentation: 63-year-old woman with metastatic ccRCC receives lenvatinib/pembrolizumab but develops difficult-to-manage hypertension

Dr Eric Lee (Fountain Valley, California)

QUESTIONS FOR THE FACULTY

Eric H Lee, MD, PhD

How do you screen for and manage hypertension in patients on TKIs? How do you approach dosing of lenvatinib (plus pembrolizumab)?

How do you approach patients who are resistant to dose reducing a TKI because of concerns that it will decrease the antitumor benefit?

In which situations, if any, do you use tivozanib? Can it be combined with IO?

In which situations, if any, do you use everolimus, and how do you use it?

Case Presentation: 64-year-old woman with metastatic ccRCC and somatic VHL gene mutation receives ipilimumab/nivolumab and develops a solitary brain metastasis

Dr Sunil Gandhi (Lecanto, Florida)

RTP
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QUESTIONS FOR THE FACULTY

Sunil Gandhi, MD

How often are metastases to the spleen observed in RCC, and what is the clinical significance?

How would you manage a patient who developed a new symptomatic brain met on ipilimumab/nivolumab with systemic disease who was responding to treatment?

Is there any clinical significance to NGS findings of somatic VHL alterations? Is there a role for belzutifan in patients with sporadic RCC?

Treatment Options for Relapsed/Refractory RCC

Brian I. Rini, MD, FASCO

Chief of Clinical Trials

Vanderbilt-Ingram Cancer Center

Ingram Professor of Medicine

Division of Hematology/Oncology

Vanderbilt University Medical Center

The vast majority of RCC patients will receive IO-based therapy front-line

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
HR mOS, months	**0.72** 55.7 vs 38.4	**0.73** 45.7 vs 40.1	**0.70** 37.7 vs 34.3	**0.72** NR vs NR
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **70%** vs 60%	**90%** vs 79% (est.) **79%** vs. 70%
HR mPFS, months	**0.86** **12.3** vs 12.3	**0.68** **15.7** vs 11.1	**0.56** **16.6** vs 8.3	**0.39** **23.9** vs 9.2
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Med f/u, months	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Landmark PFS	30% (5 years)	29% (3 years)	39% (2 years)	

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2022; *Lancet Oncol* 2022.
4. Motzer et al. ASCO GU 2021; Porta C et. Al, ESMO 2022.

@brian_rini and @Uromigos

2nd-Line Agents: Post VEGF-TKI

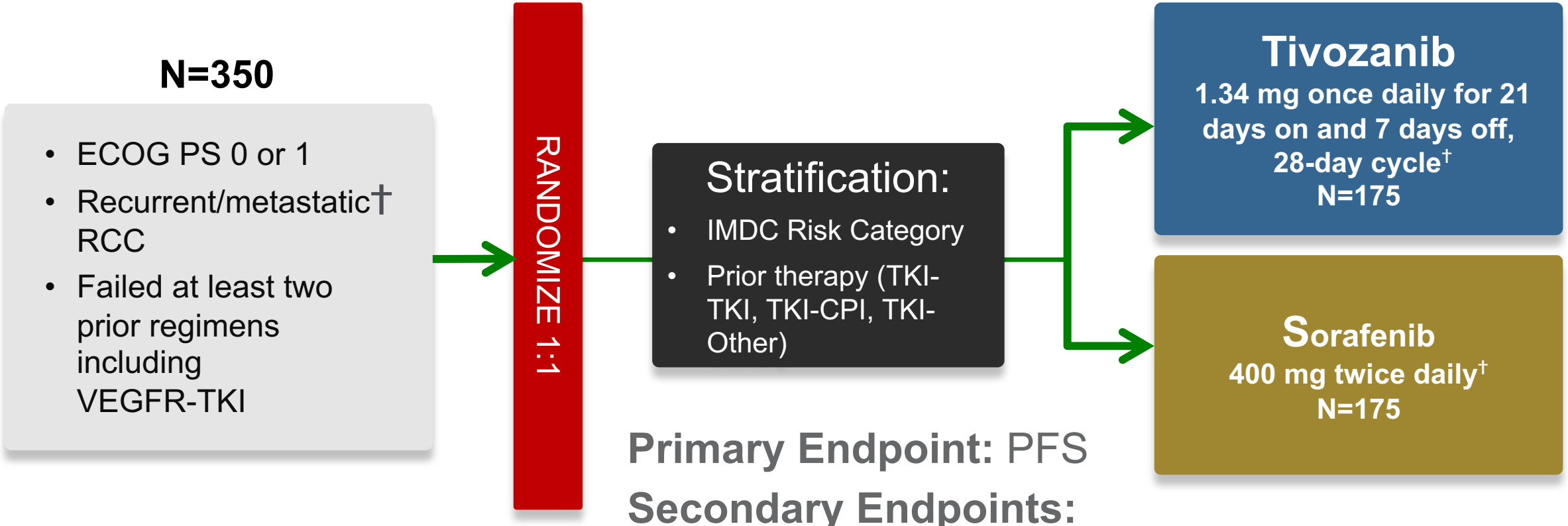
	Axitinib [1,2]	Nivolumab [3]	Cabozantinib [4]	Lenvatinib/Eve (RP2) [5,6]
Patient Population	2nd Line	TKI-refractory (72% 1 prior)	TKI-refractory (71% 1 prior)	TKI-refractory (100% 1 prior)
MSKCC risk: good/int/poor	28/37/33	35/49/16	45/42/12	24/37/39
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR, % PD, %	19% 22%	22% 35%	17% 12%	35% 4%
PFS, months	4.8	4.6	7.4	12.8
OS, months	20.1	25.0	21.4	25.5
Dose reductions	31% (37% Increase)	n/a	62%	71%
D/C due to AE	4%	8%	12%	24%
Toxicity	Grade 3: 50% Grade 4: 6%	Grade 3 or 4: 19%	Grade 3: 63%* Grade 4: 8%	Grade 3: 57% Grade 4: 14%

* All AEs regardless of attribution to the drugs

[1] Motzer, et al. *Lancet Oncol*. 2013;14:552. [2] Rini, et al. *Lancet* 2011;378:19312. [3] Motzer, et al. *N Engl J Med*. 2015;373:1803. [4] Choueiri, et al. *Lancet Oncol*. 2016.
[5] Motzer, et al. *Lancet* 2015;16:1473. [6] Motzer, et al. *Lancet* 2016;17:E4-45.

TIVO-3: Study Schema

Randomized Phase 3 Trial in Relapsed or Refractory Advanced Renal Cell Carcinoma



Primary Endpoint: PFS

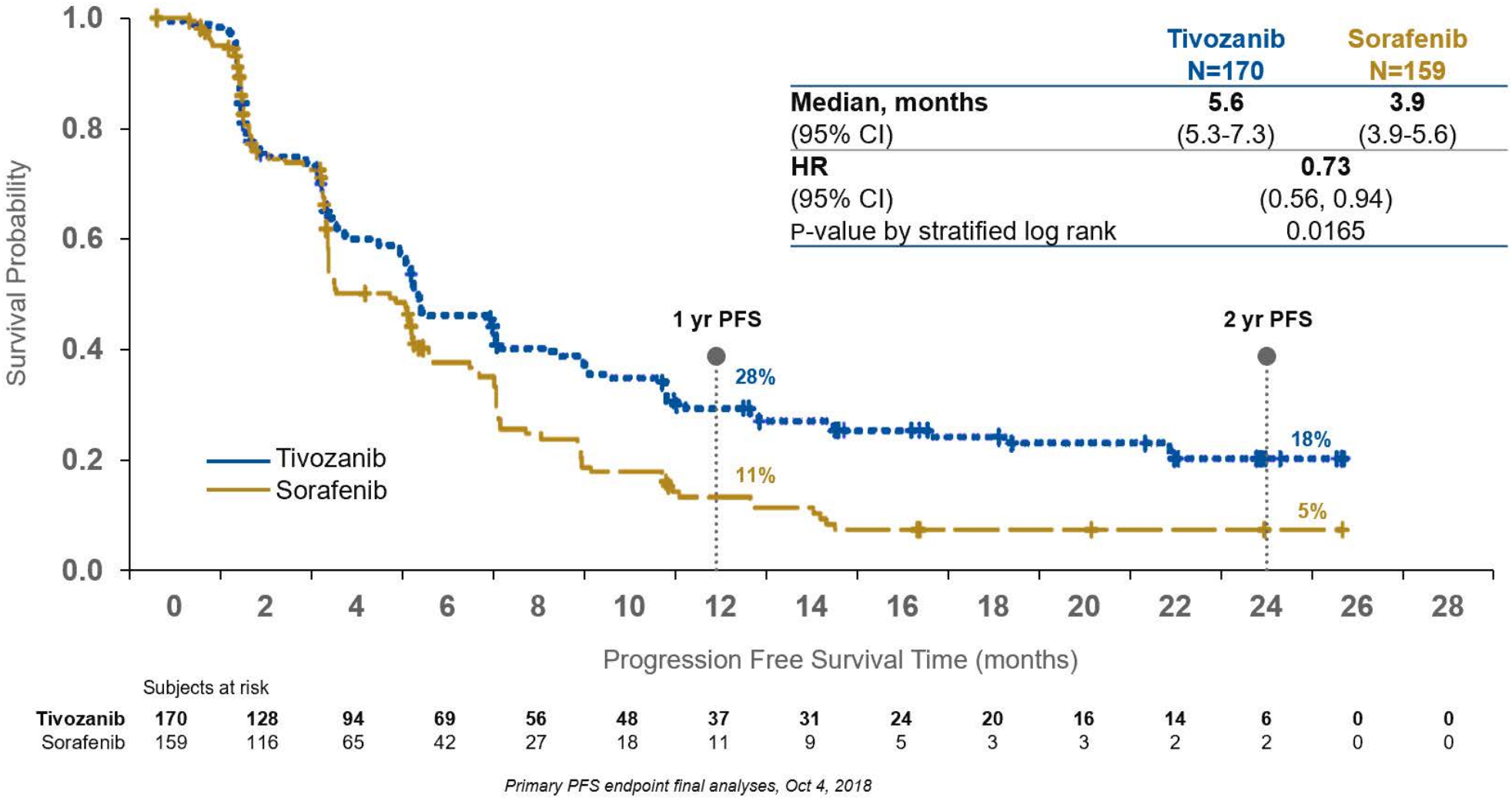
Secondary Endpoints: OS, ORR, DoR, Safety and Tolerability for ITT

† Patients were treated until disease progression or unacceptable toxicity

ECOG, Eastern Cooperative Oncology Group;
TKI, Tyrosine Kinase Inhibitor; CPI, Checkpoint Inhibitor
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

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

Primary Endpoint: PFS



	Tivozanib N=170	Sorafenib N=159
Median, months	**5.6**	**3.9**
(95% CI)	(5.3-7.3)	(3.9-5.6)
HR	**0.73**	
(95% CI)	(0.56, 0.94)	
P-value by stratified log rank	0.0165	

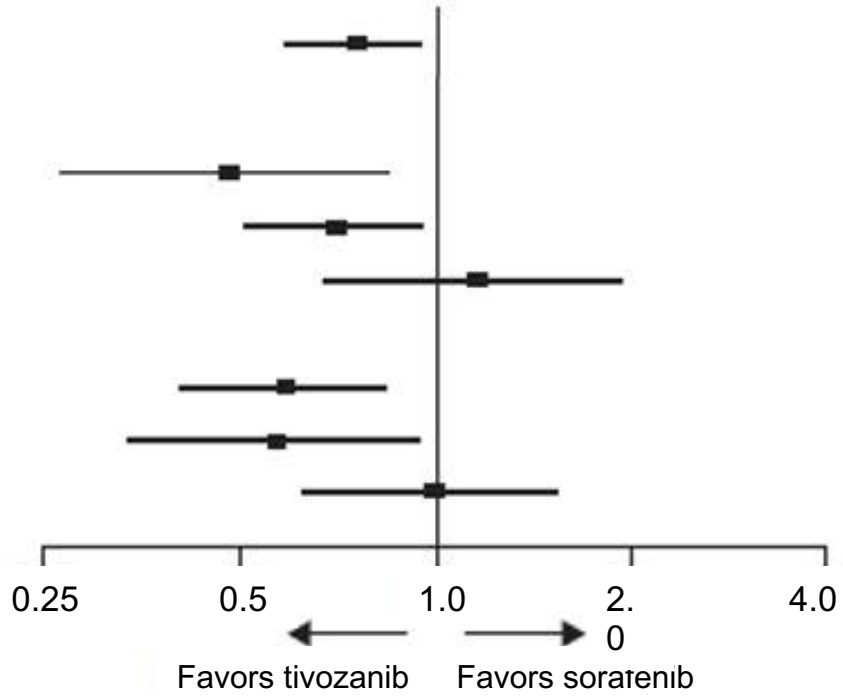
Subjects at risk

Tivozanib	**170**	**128**	**94**	**69**	**56**	**48**	**37**	**31**	**24**	**20**	**16**	**14**	**6**	**0**	**0**
Sorafenib	159	116	65	42	27	18	11	9	5	3	3	2	2	0	0

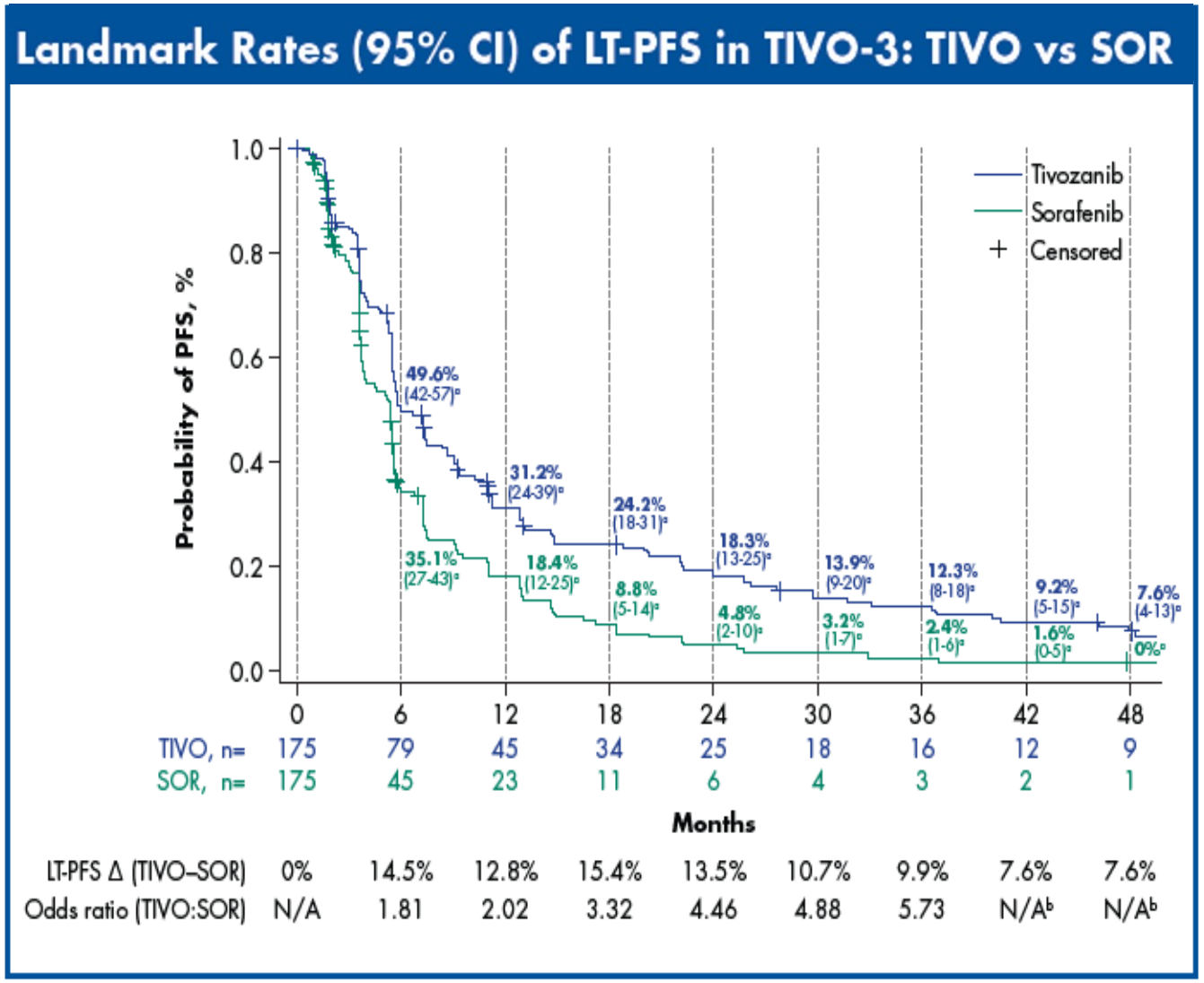
Primary PFS endpoint final analyses, Oct 4, 2018

PFS in Stratified Subgroups

	Events/Patients		Hazard Ratio (95% CI)
	Tivozanib	Sorafenib	
All patients	**123/175**	**123/175**	**0.73 (0.56-0.94)**
IMDC risk category			
Favorable	21/34	22/36	0.46 (0.25-0.85)
Intermediate	73/109	74/105	0.69 (0.49-0.95)
Poor	29/32	27/34	1.15 (0.67-2.00)
Previous therapy			
Two previous VEGFR TKIs	56/59	61/80	0.57 (0.39-0.83)
Checkpoint inhibitor plus VEGFR TKI	29/47	27/44	0.55 (0.32-0.94)
Previous VEGFR TKI plus other agents	38/49	35/51	0.98 (0.62-1.56)



Long-Term Progression Free Survival (LT-PFS) Analysis



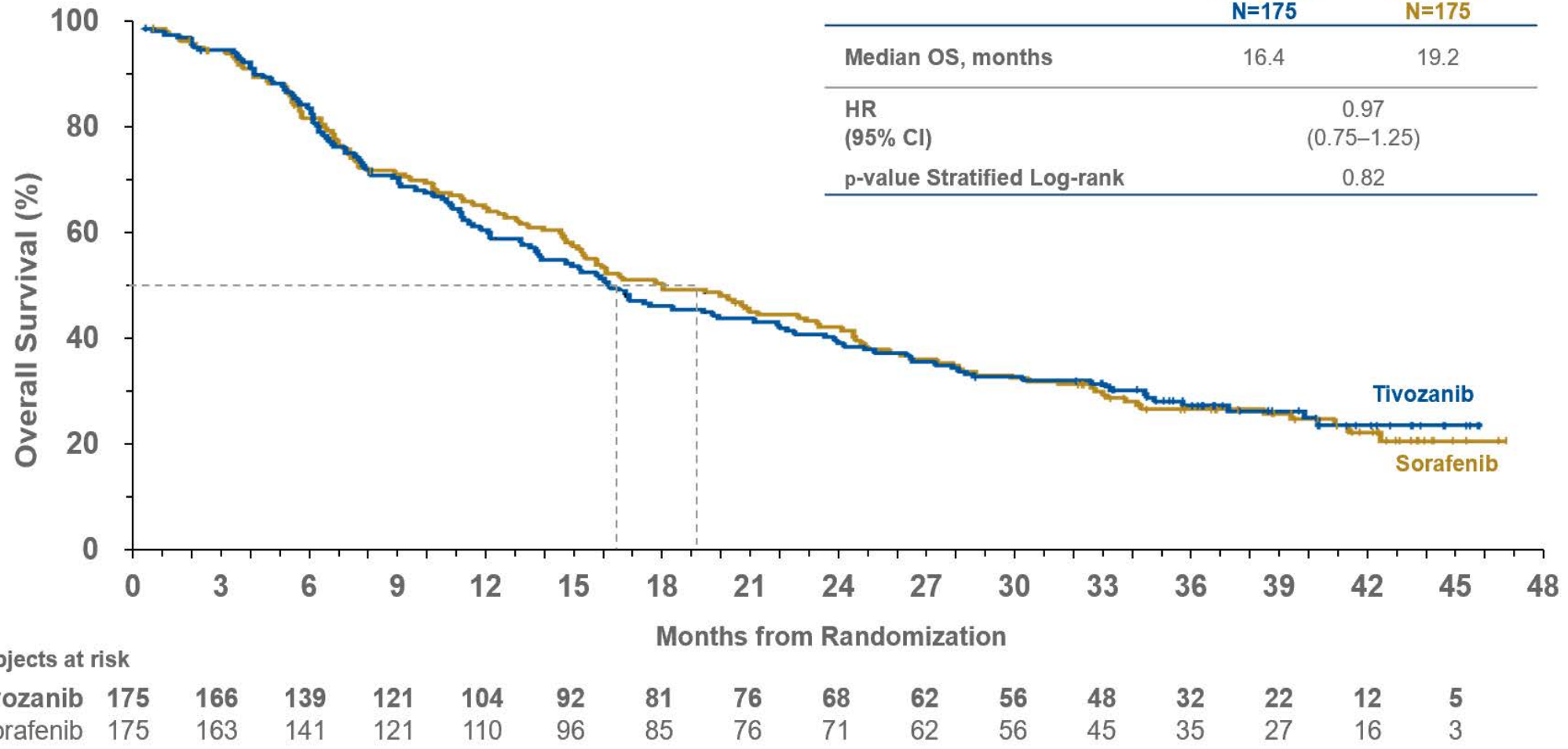
ª% (95% CI). ᵇOR not calculated at months 42 and 48 due to insufficient number at risk.

***primary IRC PFS HR (0.672; 95% CI, 0.52-0.87)**

Atkins M et al *J Cliln Oncol* 2022;40 (6) suppl_362

- LT-PFS is based on investigator-assessed (INV) PFS HR with extended follow-up (data cutoff May 2021)
- INV PFS HR (0.624; 95% CI, 0.49-0.79), which was comparable to the primary IRC PFS HR reported at the original October 2018 data cutoff (HR, 0.672; 95% CI, 0.52-0.87)
- The safety profile of tivozanib with extended analysis was consistent with the full Prescribing Information
- Higher LT-PFS rates with TIVO vs SOR were observed across subgroups, with clinically meaningful effects in the TIVO group (defined as ≥15% INV LT-PFS at 36 months) patients with:
  - favorable risk status evaluated by IMDC
  - female sex
  - ECOG PS of 0
  - age ≥65 years
  - treatment received in North America

Overall Survival



Rini BI et al *Lancet Oncol* 2020;21(1):95-104; Rini BI et al *ASCO*2022 Abstract 4557.

TABLE 2. BOR to Prior ICI and to Salvage Ipilimumab and Nivolumab

BOR to Prior ICI	No. (%)	BOR to Salvage Ipilimumab and Nivolumab	No. (%)
PR	24 (53)	PR	4 (17)
		SD	2 (8)
		PD	17 (71)
		NE	1 (4)
SD	12 (27)	PR	3 (25)
		SD	5 (42)
		PD	4 (33)
PD	9 (20)	PR	2 (22)
		PD	7 (78)

Abbreviations: BOR, best objective response; ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Published in: Anita Gul; Tyler F. Stewart; Charlene M. Mantia; Neil J. Shah; Emily Stern Gatof; Ying Long; Kimberly D. Allman; Moshe C. Ornstein; Hans J. Hammers; David F. McDermott; Michael B. Atkins; Michael Hurwitz; Brian I. Rini; *Journal of Clinical Oncology* 2020 383088-3094.
DOI: 10.1200/JCO.19.03315

The role of NIVO + IPI (salvage/rescue)

	HCRN ASCO GU 2022	OMNIVORE ASCO 2020	FRACTION J Immunother Cancer 2022	TITAN RCC ESMO 2022	Salvage Ipi/Nivo (JCO 2020)
N	35	83	46	207	45
Prior TKI	No	Yes	Yes	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo+Ipi	Nivo→Ipi	Nivo+Ipi after prior IO
Ipi doses	4	2	4	4	4
ORR	11%	4%	17%	32%	20%
CR	3%	0%	0%	6%	0%

Nivo+ipi combo untreated ccRCC ORR 39%, CR 12% (CheckMate 214)[1]

Lenvatinib + Pembrolizumab After Progression on Prior IO Therapy

Phase II KEYNOTE-146/Study 111

(N = 104)
- Metastatic clear-cell RCC with PD after anti–PD-1/ PD-L1 therapy
- ≥1 previous lines of therapy

→

Lenvatinib 20 mg QD PO

Pembrolizumab 200 mg Q3W IV

Primary Endpoint:
ORR at 24 wks

Key Secondary Endpoints:
ORR, PFS, DoR, Safety and tolerability

Baseline Characteristic	Patients (N = 104)
1/≥ 2 prior anticancer regimens, %	39/62
Prior ICI regimen, %[a]	
Anti–PD-L1/anti–PD-1 in combination or as monotherapy	100
Anti–PD-L1/anti–PD-1 and anti-VEGF in combination or sequentially	65
Ipilimumab/nivolumab	37
Median duration of prior ICI therapy, mos (IQR)	7 (3-13)

Lee. ASCO 2020. Abstr 5008.

Lenvatinib + Pembrolizumab After Progression On Prior IO Therapy

Phase II KEYNOTE-146/Study 111: Responses by Previous Therapy

Event	Anti–PD-1/PD-L1 (n = 104)	Anti–PD-1/PD-L1 and Anti-VEGF (n = 68)	Nivo + Ipi (n = 38)
ORR, % (95% CI)	**55** (45-65)	59 (46-71)	47 (31-64)
Best objective response, %			
• PR	55	59	47
• SD	36	31	42
• PD	5	6	8
• NE	5	4	3
Median DoR, mos (95% CI)	12 (9-18)	9 (7-17)	NR (7-NR)

Lee. ASCO 2020. Abstr 5008; Lee et. al, *Lancet Oncol 2021.*

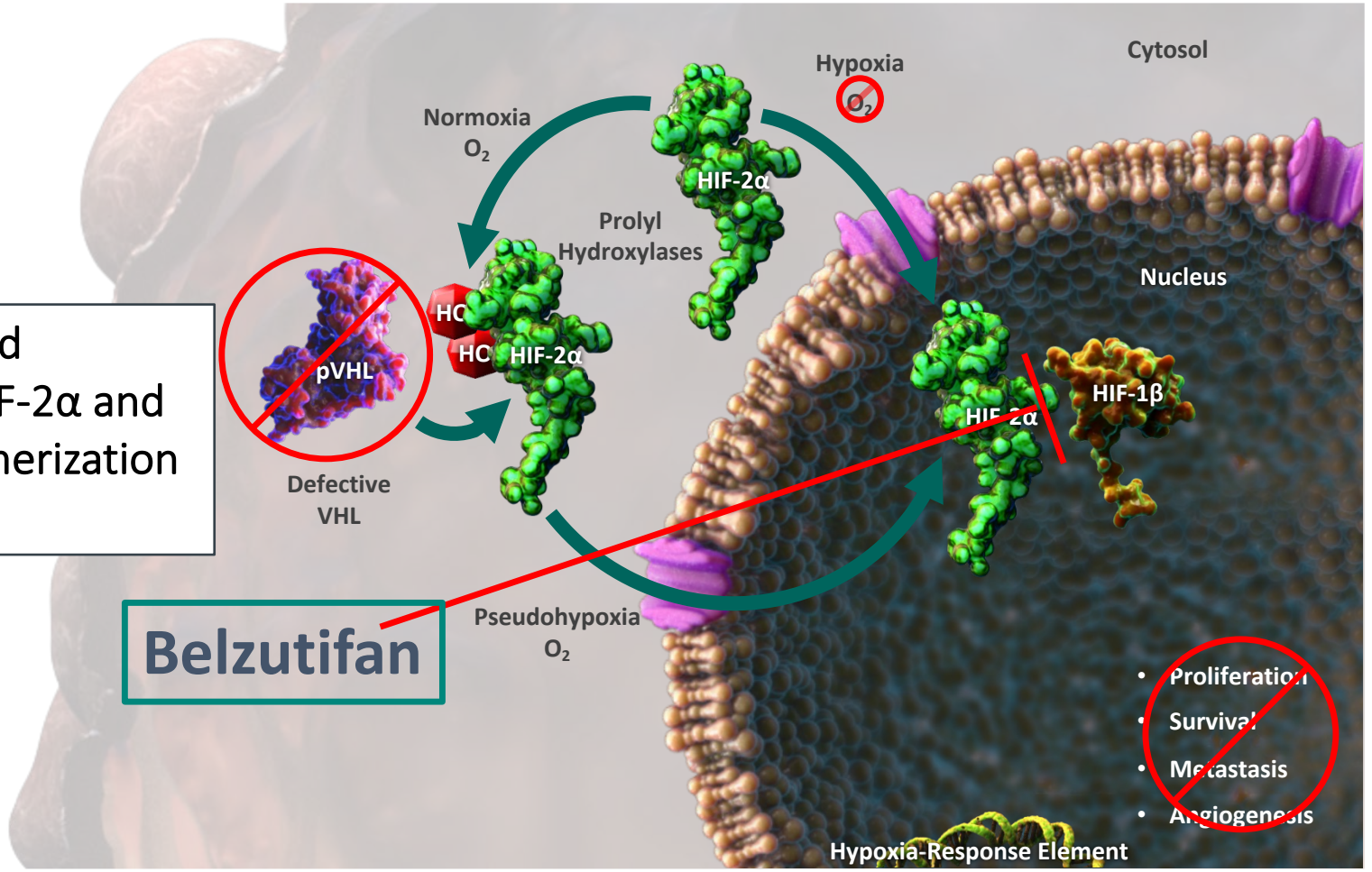
Ongoing Phase III Trials in the Post-IO Setting

Title	Inclusion	Treatment Arms
CONTACT-03: Phase III Trial of Atezo + Cabo vs Cabo in Advanced RCC After PD-1/PD-L1 Therapy (n = 500)[2]	▪ Clear-cell RCC or non–clear-cell RCC (papillary or unclassified) ▪ Prior first- or second-line therapy with PD-1/PD-L1 inhibitor as immediate preceding therapy ▪ No more than 1 previous PD-1/PD-L1 inhibitor	Atezolizumab + cabozantinib vs Cabozantinib
TiNivo-2: Phase III Trial of Tivozanib + Nivolumab vs Tivozanib in Advanced RCC After IO Therapy (n = 326)[3]	▪ Clear-cell RCC ▪ PD during or following ≥6 wk of treatment with an IO therapy ▪ ≤2 previous lines of therapy	Nivolumab + tivozanib vs Tivozanib

1. NCT04338269. 2. NCT04987203.

Belzutifan: HIF-2α Inhibitor

Belzutifan potently and selectively binds to HIF-2α and prevents its heterodimerization with HIF-1β

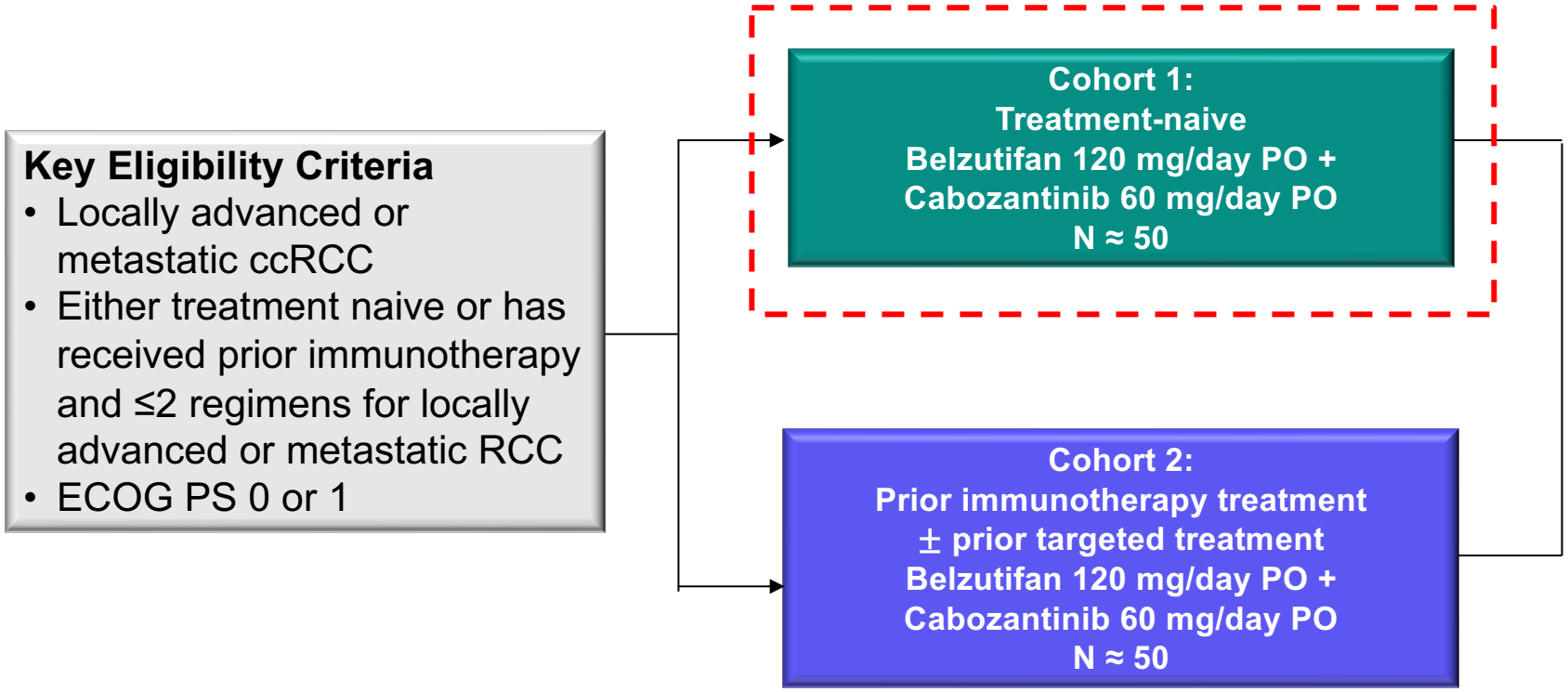


Best Confirmed Objective Response by RECIST v1.1 per Investigator Assessment (ccRCC cohort)

Efficacy Parameter, n (%) [95%CI]	All Patients N = 55	IMDC Favorable n = 13	IMDC Intermediate/Poor n = 42
Objective Response Rate	14 (25) [15-39]	4 (31) [9-61]	10 (24) [12-40]
Complete Response (CR)	0	0	0
Partial Response (PR)	14 (25)	4 (31)	10 (24)
Stable Disease (SD)	30 (54)	8 (62)	22 (52)
Disease Control Rate (CR + PR + SD)	44 (80) [67-90]	12 (92) [64-100]	32 (76) [61-88]
Progressive Disease	8 (15)	1 (8)	7 (17)
Not Evaluable	3 (5)	0	3 (7)

Jonasch E, ASCO 2022; Abstract 4509.

Study Design of LITESPARK-003 (NCT03634540)



Tumor Assessments

- Week 9, then Q8W through month 12 and Q12W thereafter

End Points

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

Choueiri et al. ESMO 2022

Primary End Point: Objective Response Rate by Investigator

n (%)	Overall N = 35	IMDC risk category	
		Favorable n = 21	Intermediate/poor n = 14
ORR (CR + PR)	**20 (57)**	**13 (62)**	**7 (50)**
DCR (CR + PR + SD)	33 (94)	19 (90)	14 (100)
Best response			
CR	2 (6)	2 (10)	0 (0)
PR	18 (51)	11 (52)	7 (50)
SD	13 (37)	6 (29)	7 (50)
PD	0 (0)	0 (0)	0 (0)
Not available[a]	2 (6)	2 (10)	0 (0)

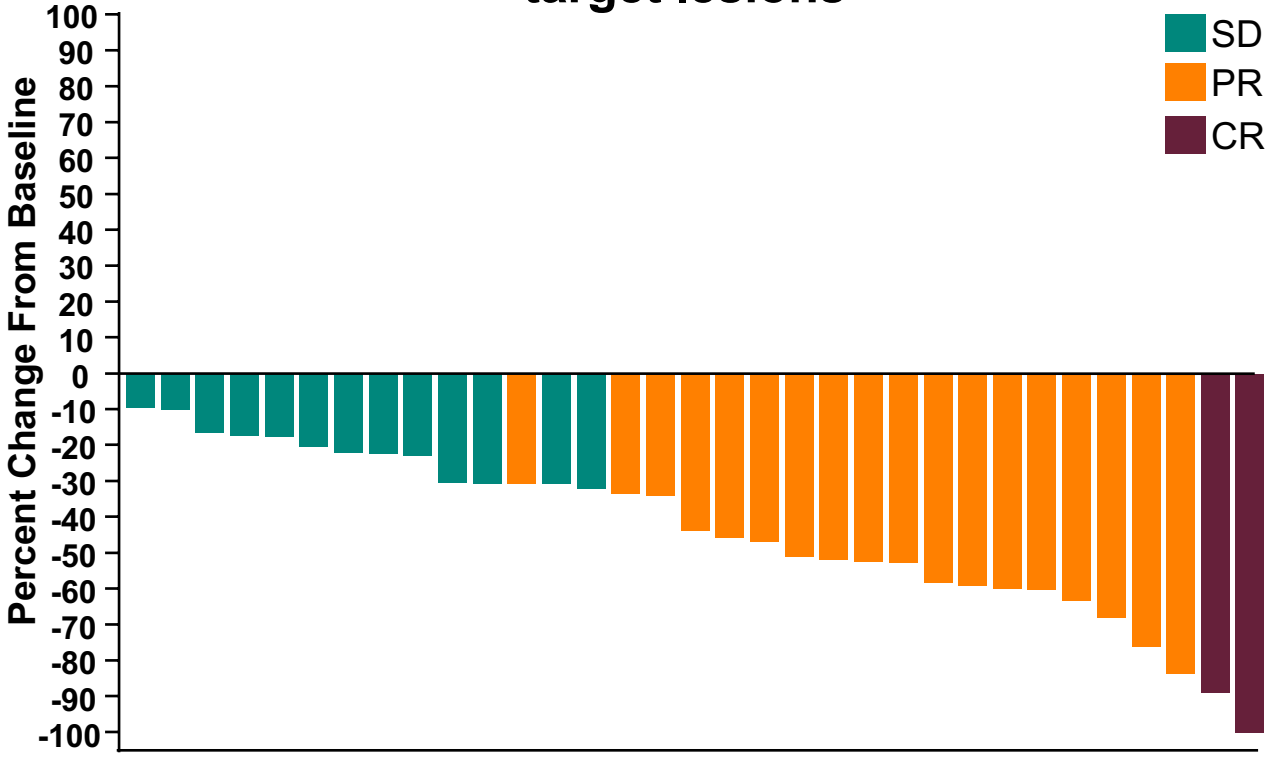
[a]Two patients did not have opportunity assessment and thus had no postbaseline available but remain on therapy.
Data cutoff date: February 1, 2022.

Choueiri et al. ESMO 2022

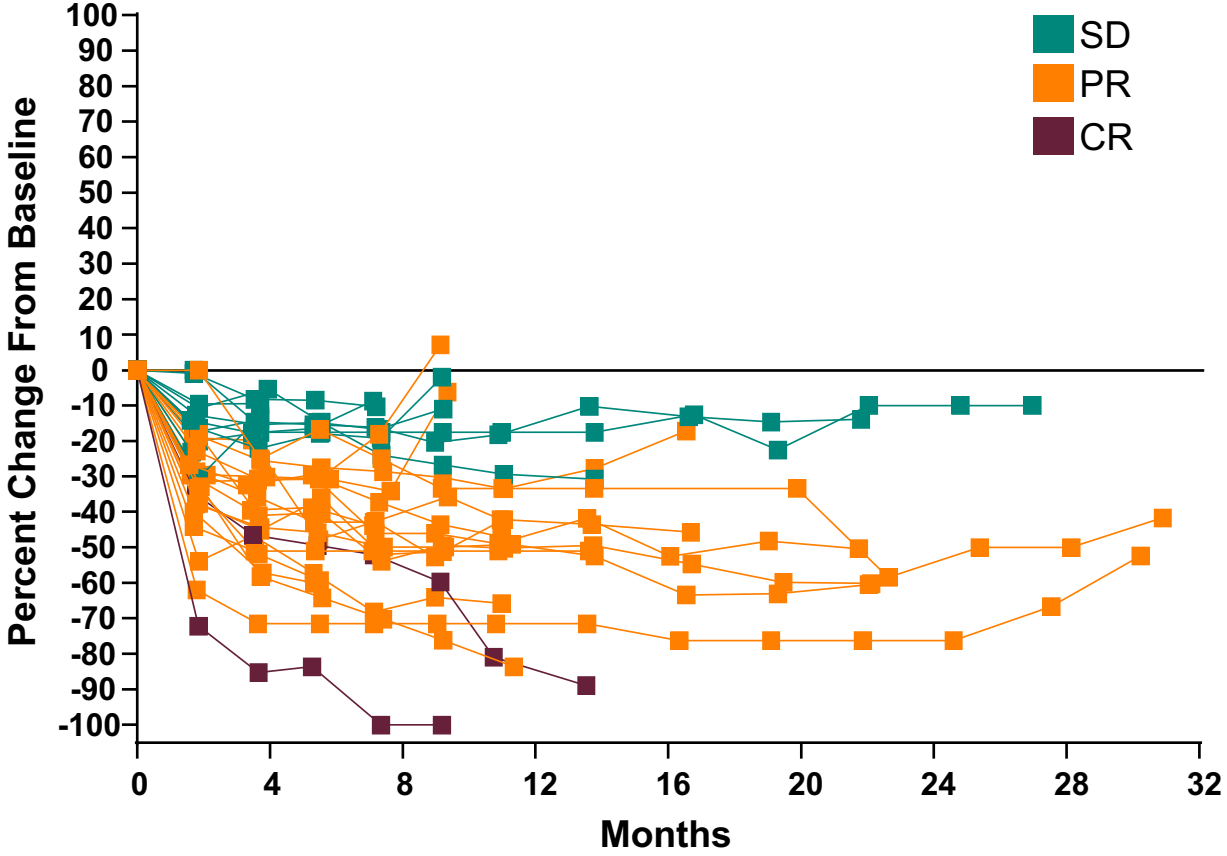
Change From Baseline in Target Lesions by Investigator

- 33 of 35 patients (94%) experienced a reduction in target lesion size[a]

Best percentage change from baseline in target lesions[b]



Percentage change from baseline in target lesions over time



[a]Two patients did not have opportunity assessment and thus had no postbaseline available but remain on therapy.
[b]One patient with a CR and 88% reduction had both nodal and non-nodal lesions. The non-nodal lesion had a 100% reduction in size and the lymph node reduced to <10 mm in diameter, which satisfied RECIST v1.1 criteria for CR.
Data cutoff date: February 1, 2022.

Choueiri et al. ESMO 2022

Cohort 2: Objective Response Rate

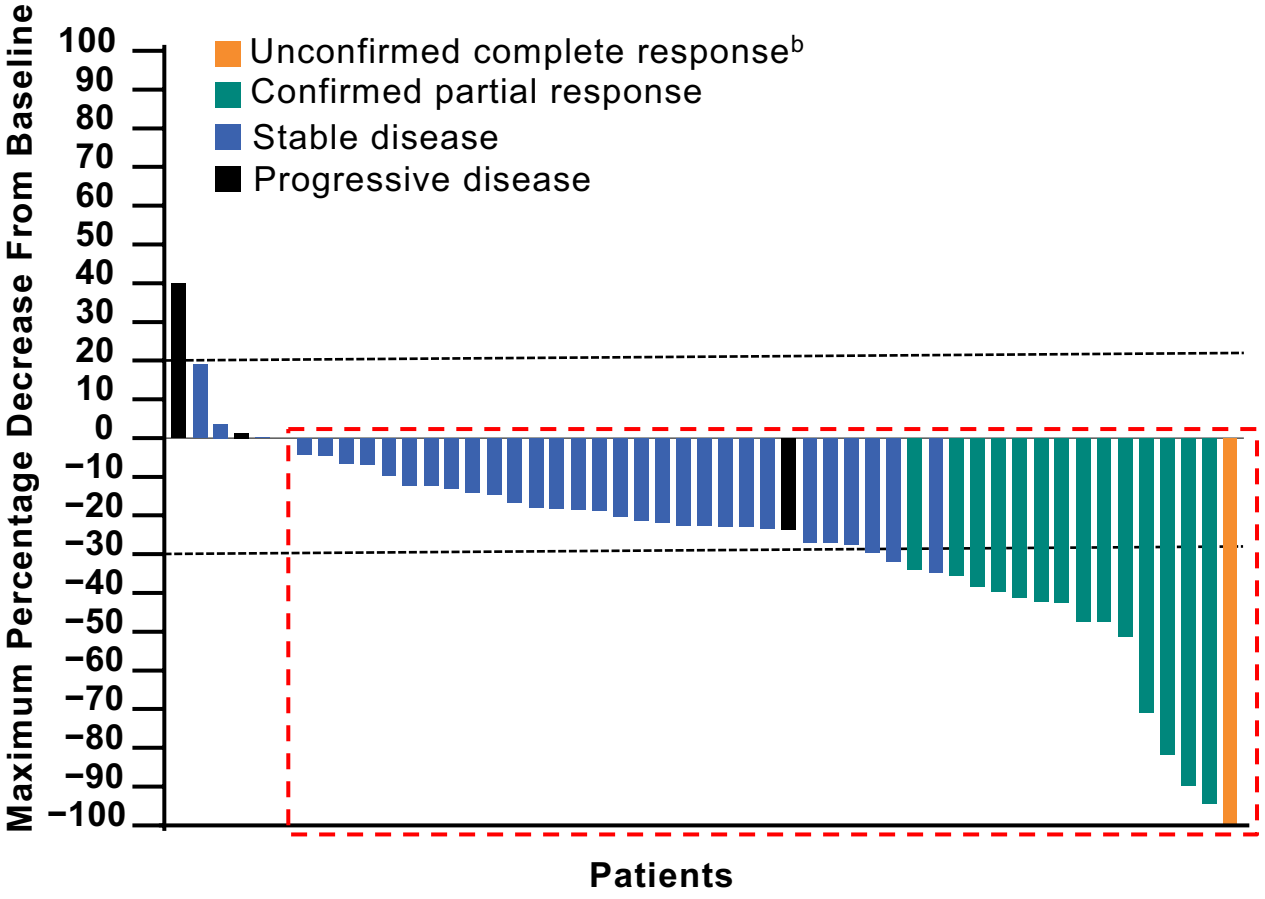
	ORR (CR + PR)		DCR (CR + PR + SD)	
Population	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
All patients	15/52	28.8 (17.1-43.1)	48/52	92.3 (81.5-97.9)
IMDC risk category				
Favorable	3/11	27.3 (6.0-61.0)	11/11	100 (71.5-100)
Intermediate/poor	12/41	29.3 (16.1-45.5)	37/41	90.2 (76.9-97.3)
Prior anticancer therapy				
IO only	8/28	28.6 (13.2-48.7)	26/28	92.9 (76.5-99.1)
IO/VEGF	7/24	29.2 (12.6-51.1)	22/24	91.7 (73.0-99.0)

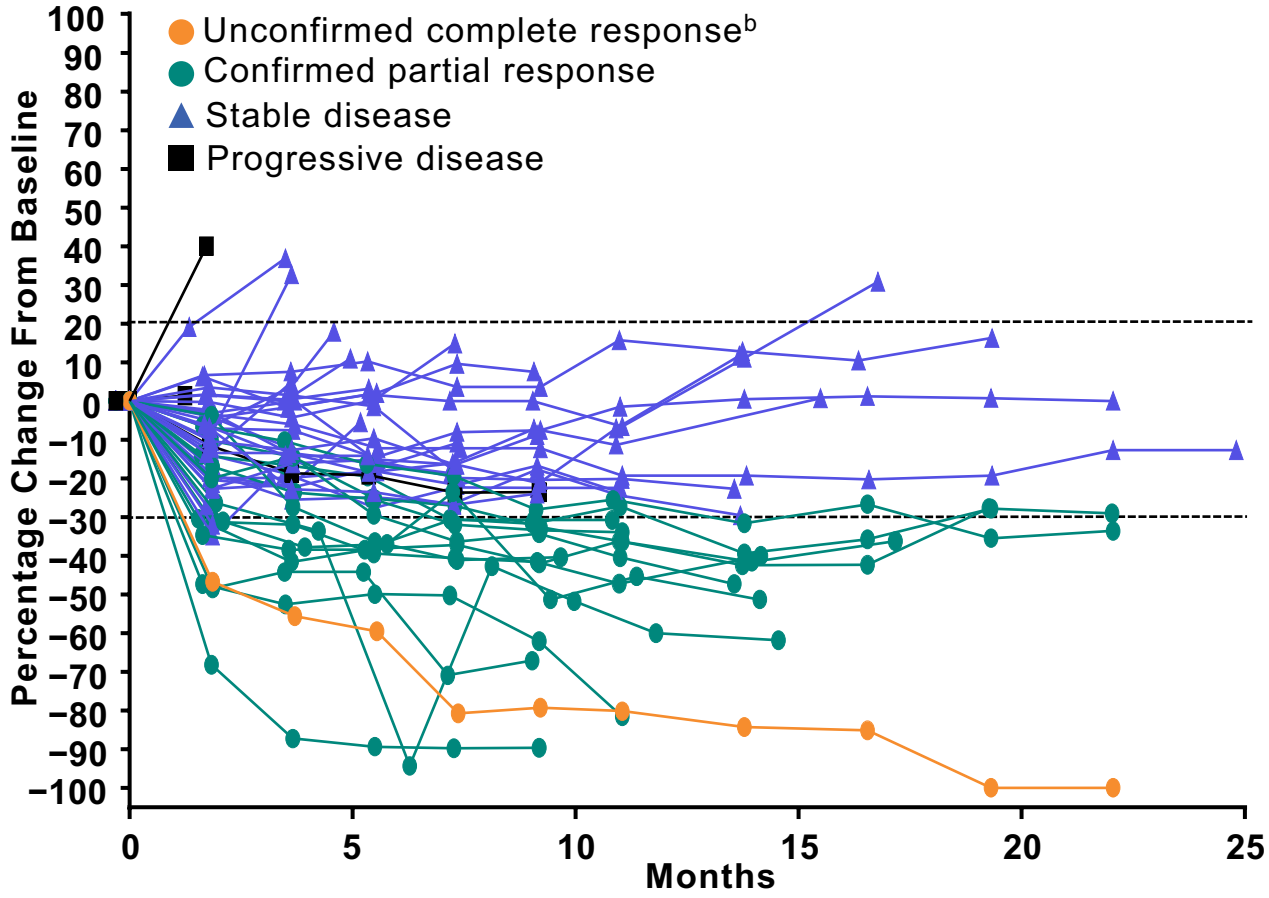
Data cutoff: May 3, 2021.

McDermott et al. ESMO 2021

Cohort 2: Best Tumor Change From Baseline

- 45 of 52 patients (86.5%) experienced a reduction in target lesion size[a]





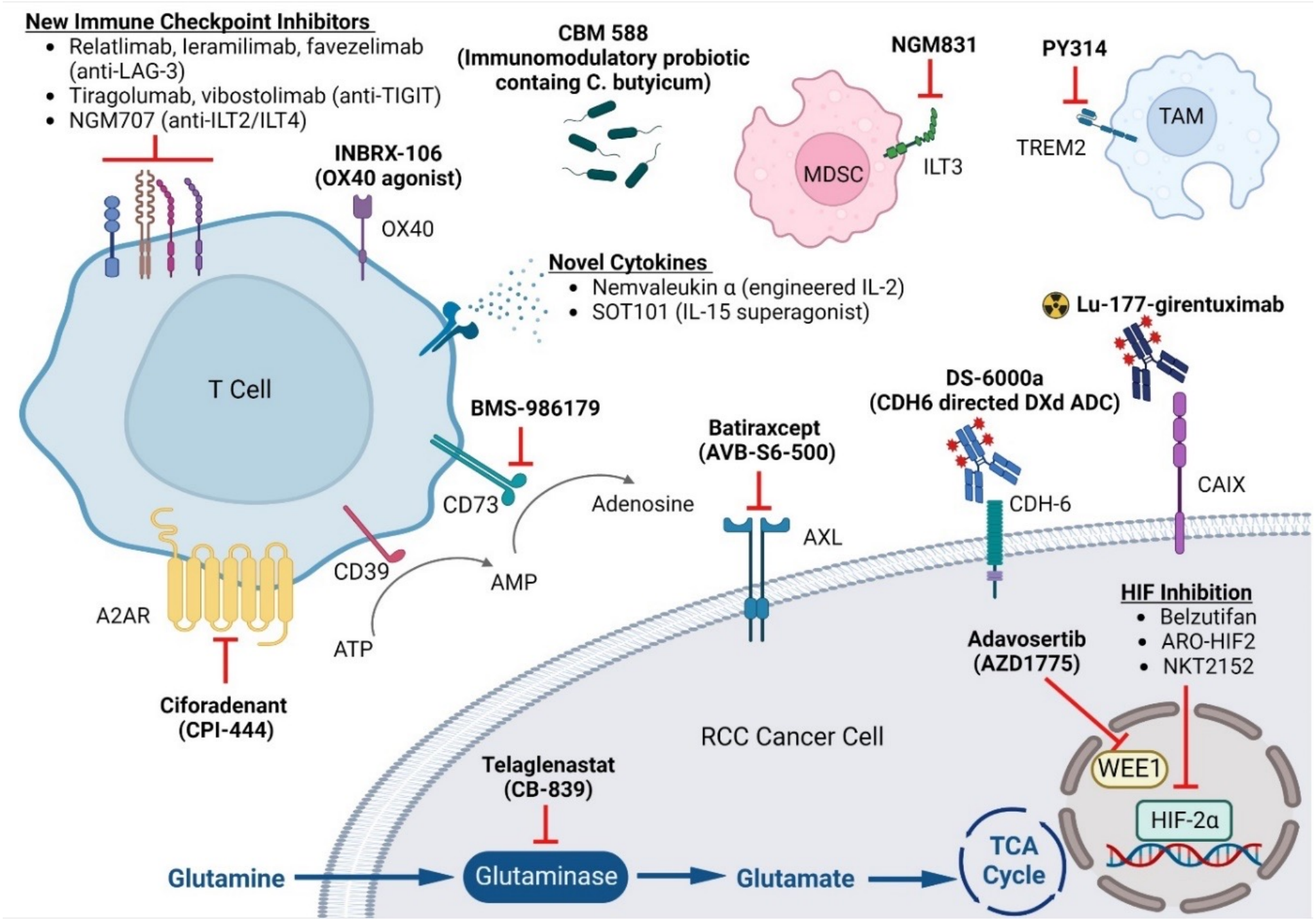
[a]1 patient had a response of "not available" and was recorded as having no change from baseline value. [b]Documented at a single time point before the data cutoff date; to be confirmed at a subsequent time point. Data cutoff: May 3, 2021.

McDermott et al. ESMO 2021

Ongoing Phase III Trials in the Post-IO Setting

Title	Inclusion	Treatment Arms
MK-6482-005: Phase III Trial of Belzutifan vs Everolimus in Advanced RCC After PD-1/PD-L1 and TKI Therapy (n = 736)[1]	▪ Clear-cell RCC ▪ Prior therapy with PD-1/PD-L1 inhibitor and VEGF TKI, as monotherapy or in combination ▪ ≤3 prior therapies	Belzutifan vs Everolimus
A Study of Belzutifan in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011)	▪ Clear-cell RCC ▪ Prior therapy with PD-1/PD-L1 inhibitor in adjuvant or 1st/2nd-line with PD within 6 months ▪ ≤2 prior therapies	Belzutifan + Lenvatinib vs Cabozantinib

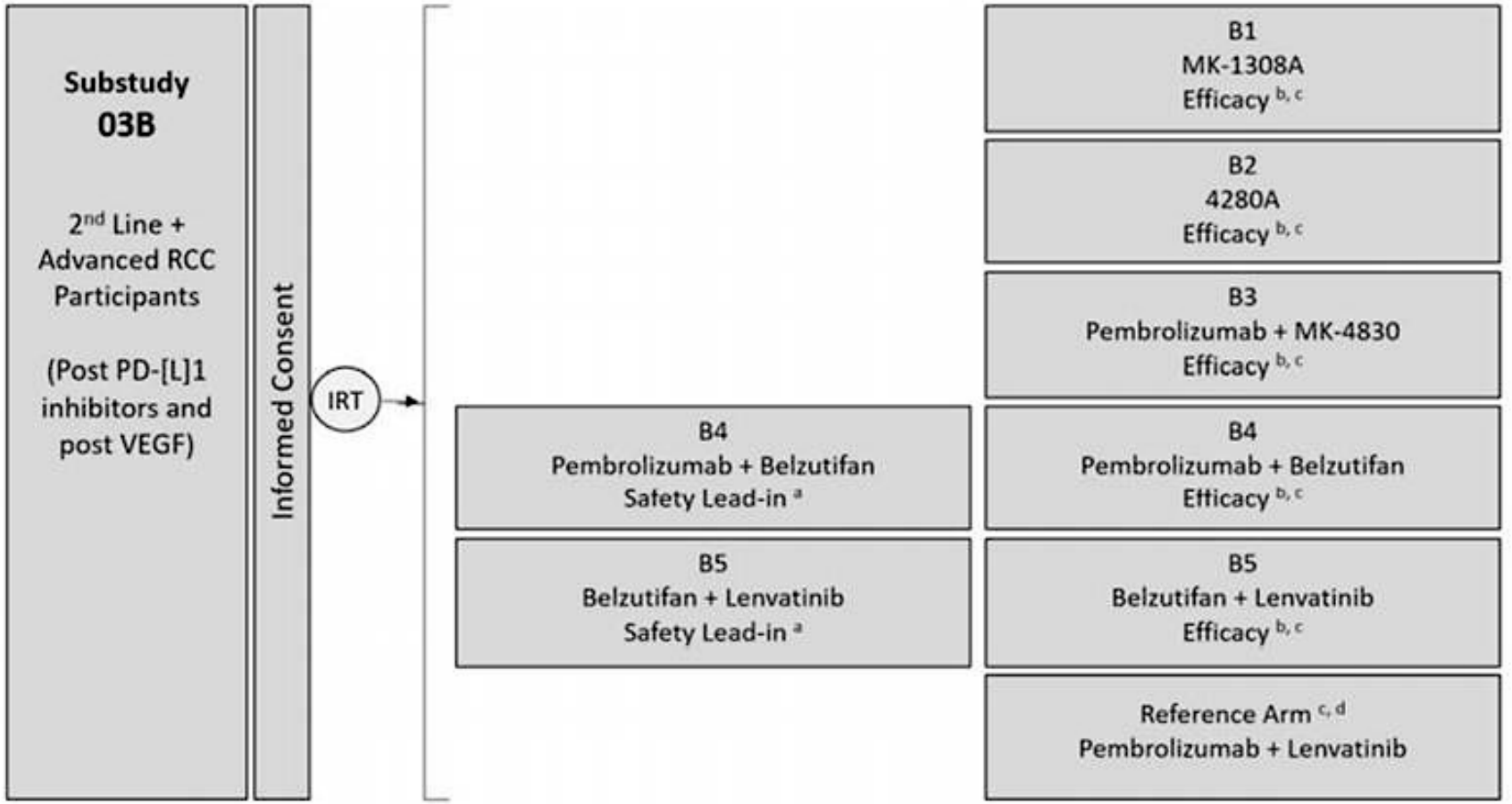
1. NCT04195750. 2. NCT04586231.



Chen, Rini, and Beckermann; 2022

Umbrella study in post-IO setting

Figure 1 Study Design



[a] Safety Lead-in: N ≥ 10 per arm. Exact N will depend on number of doses assessed. Lead-in participants are not randomized but are allocated by IRT.
[b] Efficacy Phase: N = 50 per experimental arm.
[c] Randomization Ratio: 1:1 randomization ratio. For 1 participant enrolled in efficacy arm(s), 1 is enrolled *concurrently* into reference arm.
[d] Reference Arm: N ≥ 50. Exact N will depend on enrollment period for the experimental efficacy arms.

IRT=interactive response technology; PD-[L]1=programmed cell death/ programmed cell death ligand 1; RCC=renal cell carcinoma; VEGF=vascular endothelial growth factor.

Clinical Activity of Batiraxcept (Axl Inhibitor) + Cabozantinib

Efficacy Evaluable	All P1b Patients (N=26)	P1b 15 mg/kg (n=16)	P1b 20 mg/kg (n=10)
Best Response			
Confirmed Partial Response	11 **(42%)**	8 (50%)	3 (30%)
Confirmed Stable Disease	11 (42%)	6 (38%)	5 (50%)
Progressive Disease [2]	4 (15%)	2 (12%)	2 (20%)

	Best Response		
	All P1b Patients (n=26) [1]	**P1b 15 mg/kg (n=16)**	**P1b 20 mg/kg (n=10) [1]**
PR for Patients with low sAXL/GAS6	0/5 **(0%)**	0/4 (0%)	0/1 (0%)
Confirmed PR for Patients with high sAXL/GAS6	12/20 **(60%)**	8/12 (67%) [2]	4/8 (50%)

Conclusions

- Single-agent VEGF is the (unexciting) SOC for now in refractory RCC
- IO-based combinations appear to have activity, but randomized trial data is needed for clinical adoption
- HIF inhibition, alone and in combination has activity in refractory RCC
- Several novel drugs / mechanisms are under investigation.

MODULE 4: Management of RCC Among Special Patient Populations — Prof Albiges

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Case Presentation: 69-year-old man with Waldenström macroglobulinemia and metastatic papillary RCC receives first-line ipilimumab/nivolumab → nivolumab but develops disease progression, including brain metastases

Dr Nikesh Jasani (Houston, Texas)

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QUESTIONS FOR THE FACULTY

Nikesh Jasani, MD

How do you manage patients with non-clear cell RCC, including papillary carcinoma, and how does this differ based on subtype and stage?

What's your likely second-line therapy in this patient with progression on ipilimumab/ nivolumab? Is the approach different due to the brain metastases?

What is the current role of cytoreductive nephrectomy?

RTP
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Case Presentation: 71-year-old woman with a history of psoriatic arthritis develops metastatic ccRCC, receives pembrolizumab/axitinib and develops elevated LFTs

Dr Georges Azzi (Fort Lauderdale, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Georges Azzi, MD

This patient had a history of psoriatic arthritis. How do you approach the use of IOs in patients with a history of an autoimmune disorder?

How do you approach dosing and dose reduction of axitinib?

RTP RESEARCH TO PRACTICE

Management of RCC Among Special Patient Populations

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GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Management of RCC Among Special Patient Populations

- Non-clear cell subtypes
- Papillary RCC: toward a tailored approach
- A role for combination of VEGFR TKI-CPI in non-clear cell subtypes
- VHL disease: a specific entity
- HIF inhibition in VHL disease

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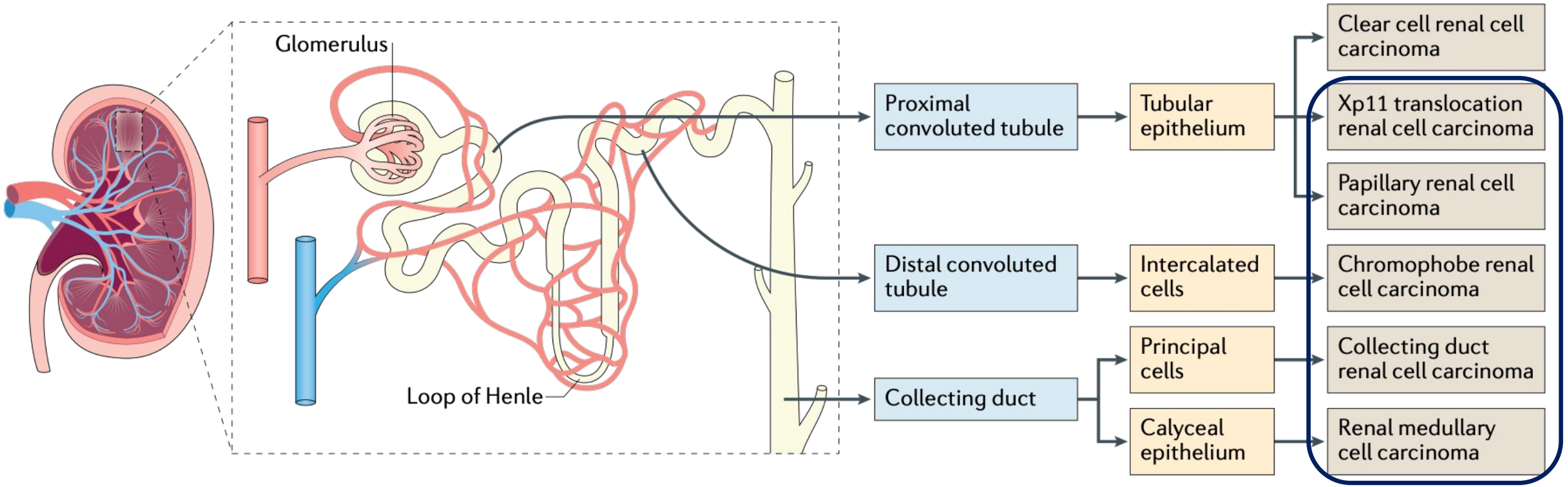
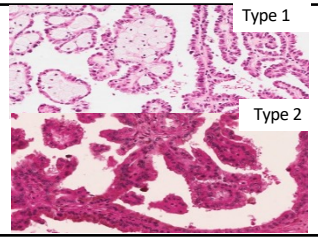
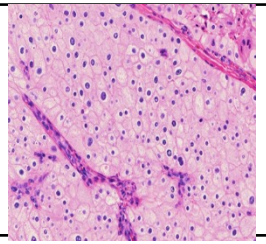
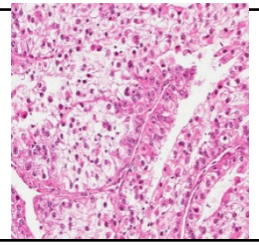
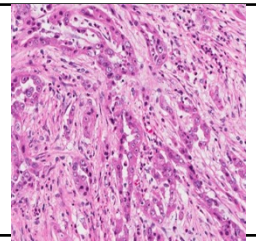
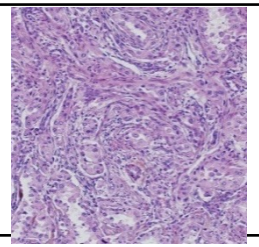
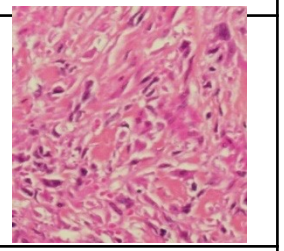
Non-clear cell RCC subtypes emerge from distinct part/cells of the kidney



Dizmanet al. Nat Rev Nephrol 2020

Non-clear cell RCC subtypes are distinct entities

Papillary		Chromophobe	Translocation	Collecting Duct	Medullary	Sarcomatoid
						
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 - TGFβ - MTOR **Downregulation** - HIF/VEGF **Deregulation** - Chromatin remodeling	**Activation** - Immune response - Cell cycle **Deregulation** - Metabolism	-	**Activation** - Cell cycle - TGFβ **Deregulation** - Chromatin remodeling

Albiges et al JCO 2018

Non-clear cell RCC subtypes: WHO New classification separates morphological and molecular-defined entities

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Renal cell tumours	
Clear cell renal tumours	
8310/3	Clear cell renal cell carcinoma
8316/1	Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours	
	Papillary adenoma
	Papillary renal cell carcinoma [a]
Oncocytic and chromophobe renal tumours	
8290/0	Oncocytoma
8317/3	Chromophobe cell renal carcinoma
	Other oncocytic tumours of the kidney
Collecting duct tumours	
8319/3	Collecting duct carcinoma
Other renal tumours	
8323/1	Clear cell papillary renal cell tumour[a]
8480/3	Mucinous tubular and spindle cell carcinoma
8316/3	Tubulocystic renal cell carcinoma
8316/3	Acquired cystic disease–associated renal cell carcinoma
8311/3	Eosinophilic solid and cystic renal cell carcinoma
8312/3	Renal cell carcinoma, NOS
Molecularly defined renal carcinomas	
	TFE3-rearranged renal cell carcinomas
	TFEB-altered renal cell carcinomas
	ELOC (formerly *TCEB1*)-mutated renal cell carcinoma
	Fumarate hydratase–deficient renal cell carcinoma
	Hereditary leiomyomatosis and renal cell carcinoma syndrome–associated renal cell carcinoma
	Succinate dehydrogenase–deficient renal cell carcinoma
	ALK-rearranged renal cell carcinomas
	Medullary carcinoma, NOS
	SMARCB1-deficient medullary-like renal cell carcinoma
	SMARCB1-deficient undifferentiated renal cell carcinoma, NOS
	SMARCB1-deficient dedifferentiated renal cell carcinomas of other specific subtypes

pRCC = a single entity

Molecular defined entities (classified independently of morphology)

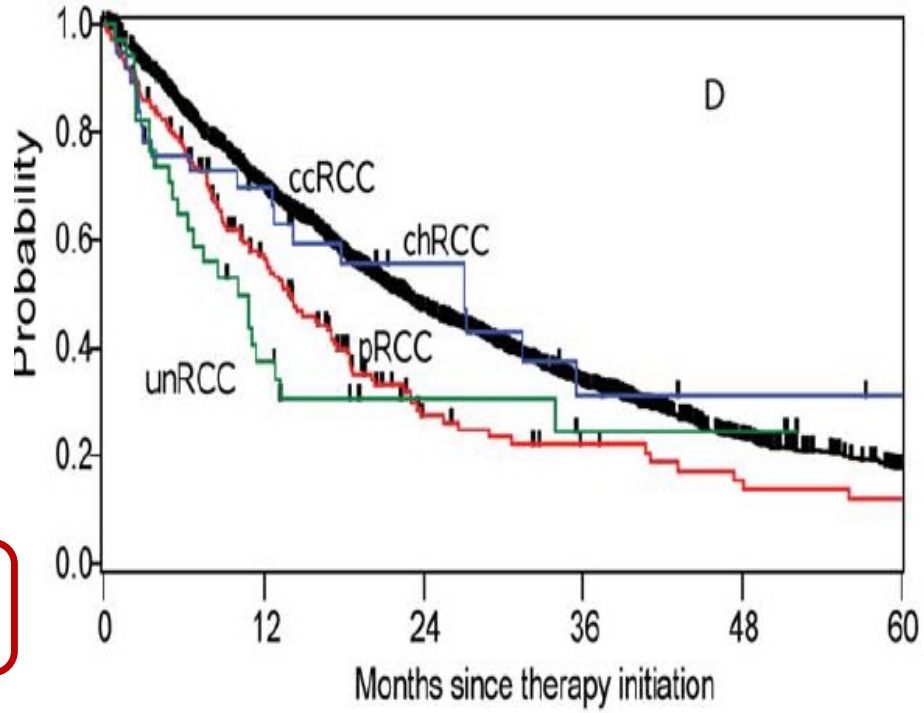
Moch, H. *et al. Eur Urol.* 2022

Non-clear cell RCC displays a dismal prognosis compared to ccRCC

The IMDC experience in the VEGFR TKI era

TABLE 3. Best Response Rates and Overall Survival (OS) Between ccRCC and nccRCC

	General Comparison		nccRCC Subtypes Compared With ccRCC			
	ccRCC	nccRCC	pRCC	chRCC	unRCC	Other/Unknown
BR first-line	17/428/803/350	2/30/101/69	0/17/63 /41	1/6/16/9	1/6/9/9	0/1/13/10
CR/PR/SD/PD (%)	(1.1/26.8/50.2/21.9)	(1.0/14.9/50.0/34.2)	(0/14.0/52.1/33.9)	(3.1/18.8/50.0/28.1)	(4.0/24.0/36.0/36.0)	(0/4.2/54.2/41.7)
BR second-line	3/76/334/261	0/7/37/38	0/2/22/20	0/2/5/7	0/1/4/5	0/2/6/6
CR/PR/SD/PD (%)	(0.4/11.3/49.6/38.7)	(0/8.5/45.1/46.3)	(0/4.5/50.0/45.5)	(0/14.3/35.7/50.0)	(0/10/40/50)	(0/14.3/42.9/42.9)
OS analyses, n	1963	252	151	37	34	30
No. of deaths	1240	177	105	21	24	27
Median (95% CI)	22.3 (20.7-23.5)	12.8 (11.0-16.1)	14.0 (10.9-17.1)	27.1 (12.6-75.3)	10.1 (5.1-13.2)	11.3 (9.6-19.4)
Unadjusted HR (95% CI)	Reference	1.44 (1.23-1.69)	1.48 (1.21-1.81)	0.98 (0.64-1.51)	1.71 (1.14-2.56)	1.67 (1.14-2.45)
Unadjusted *P*		< .0001	.0001	.923	.010	.008



Kroeger N et al, *Cancer*. 2013;119:2999-3006.

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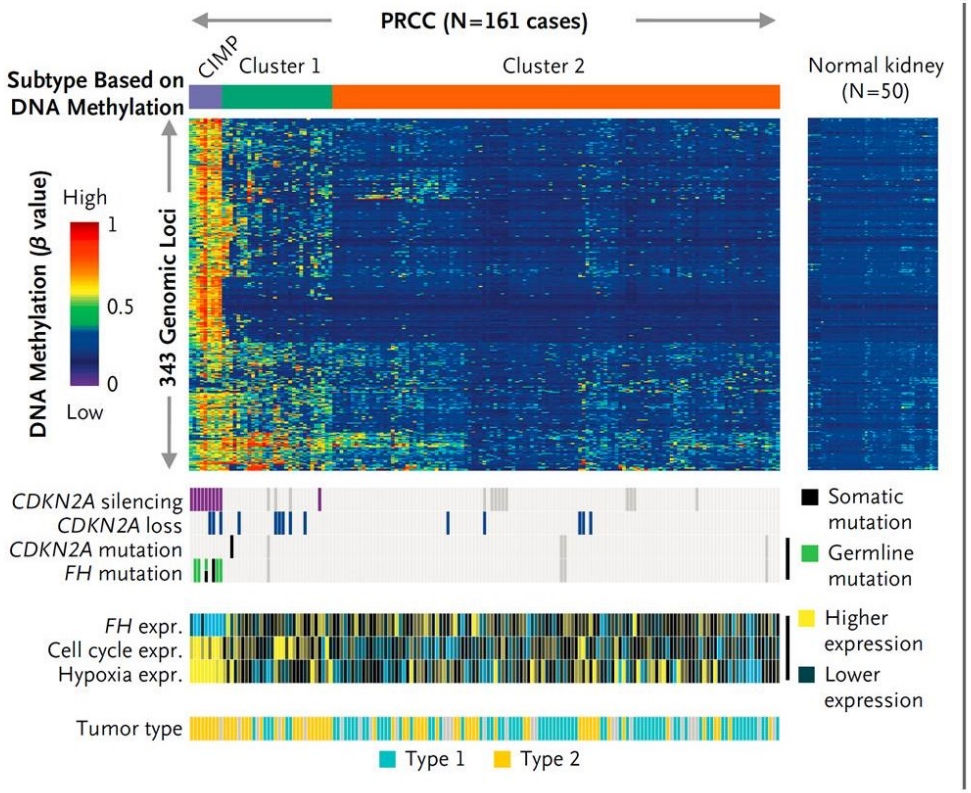
Understanding papillary RCC (pRCC)

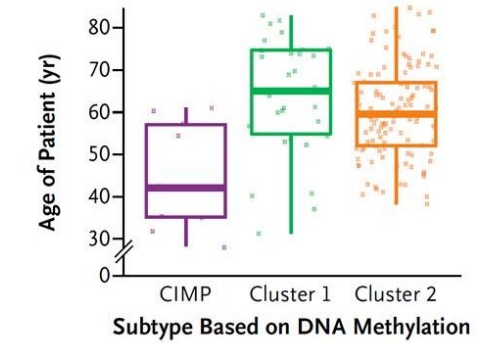
The NEW ENGLAND JOURNAL of MEDICINE

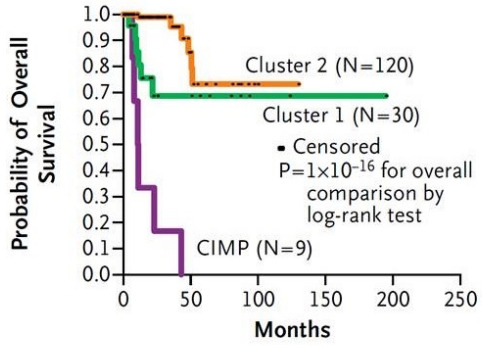
ORIGINAL ARTICLE

Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma

The Cancer Genome Atlas Research Network*







5 Subtypes

- Type I: MET alteration
- Type II includes several subtypes (3)
- CIMP subtype = FH altered RCC

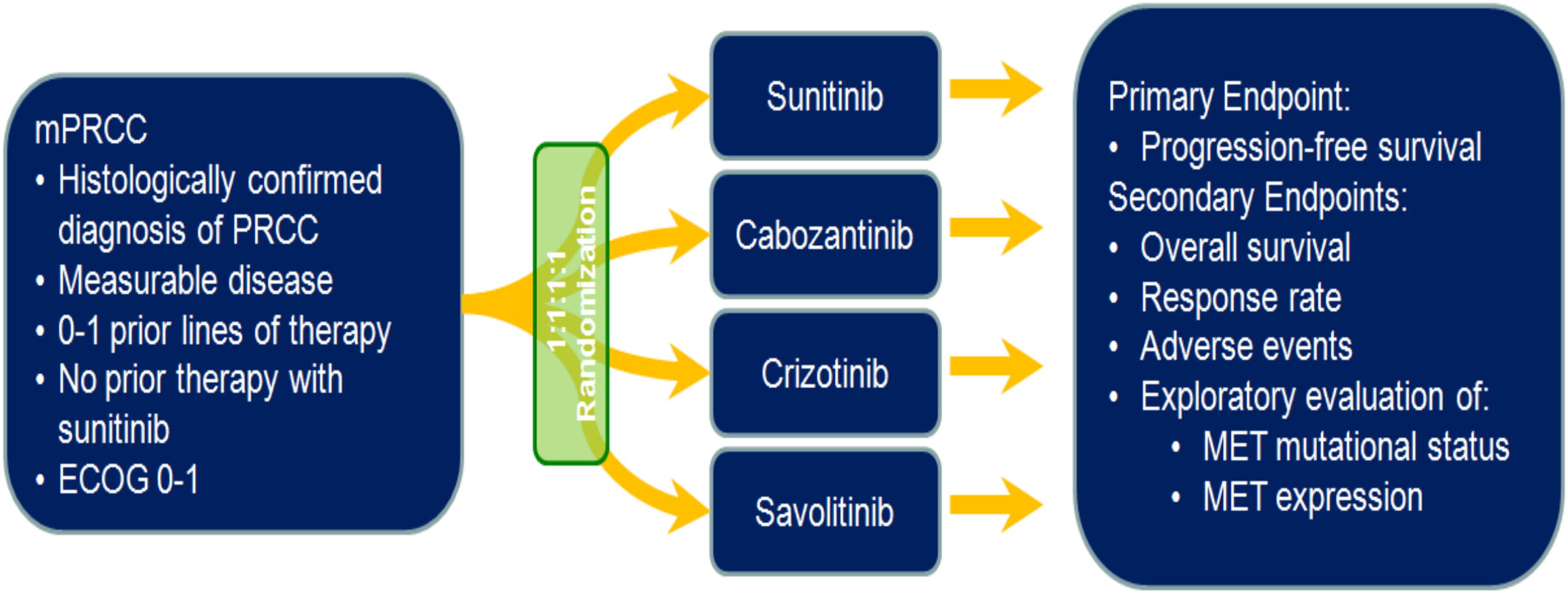
Linehan WM et al. NEJM, 2015

Papillary RCC paved the way toward tumor-specific trials

	Ravaud[1] (SUPAP)	Escudier[2] (RAPTOR)	Negrier[3] (AXIPAP)
N	60	92	44
Histology	Papillary	Papillary	Papillary
Agent	sunitinib	everolimus	axitinib
Primary endpoint	ORR	PFS	PFS
Previously treated	No	No	No
ORR (RECIST)	12%	NA	28.6%
PFS (months)	5.6	7.3 3.7 (central)	6.6
OS (months)	12.5	21 -28 (type I) -20.3 (type II)	18.9

[1]Ravaud et al. Ann Oncol, 2015; [2]Escudier et al. Eur J Cancer, 2016; [3] Negrier et al. Eur J Cancer, 2020

SWOG-1500 – PAPMET: pRCC randomised phase II Cabozantinib a new standard of care in pRCC



Pal et al. Lancet, 2021

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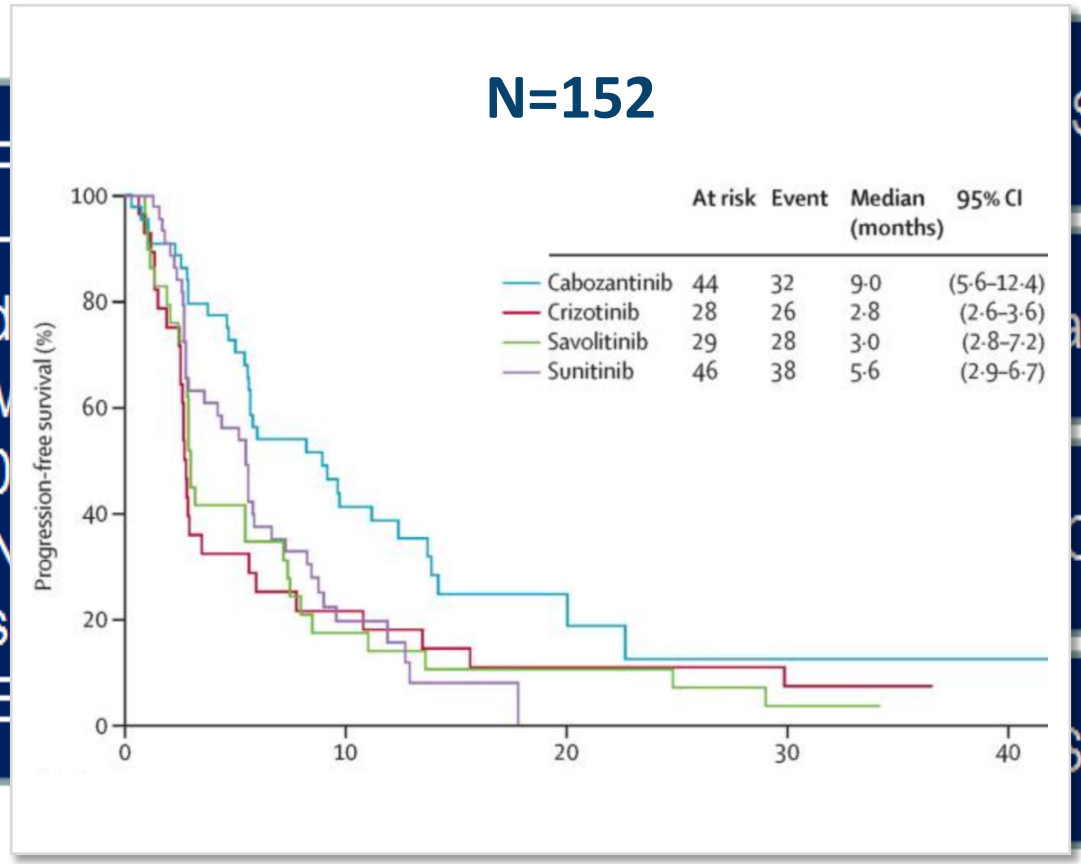
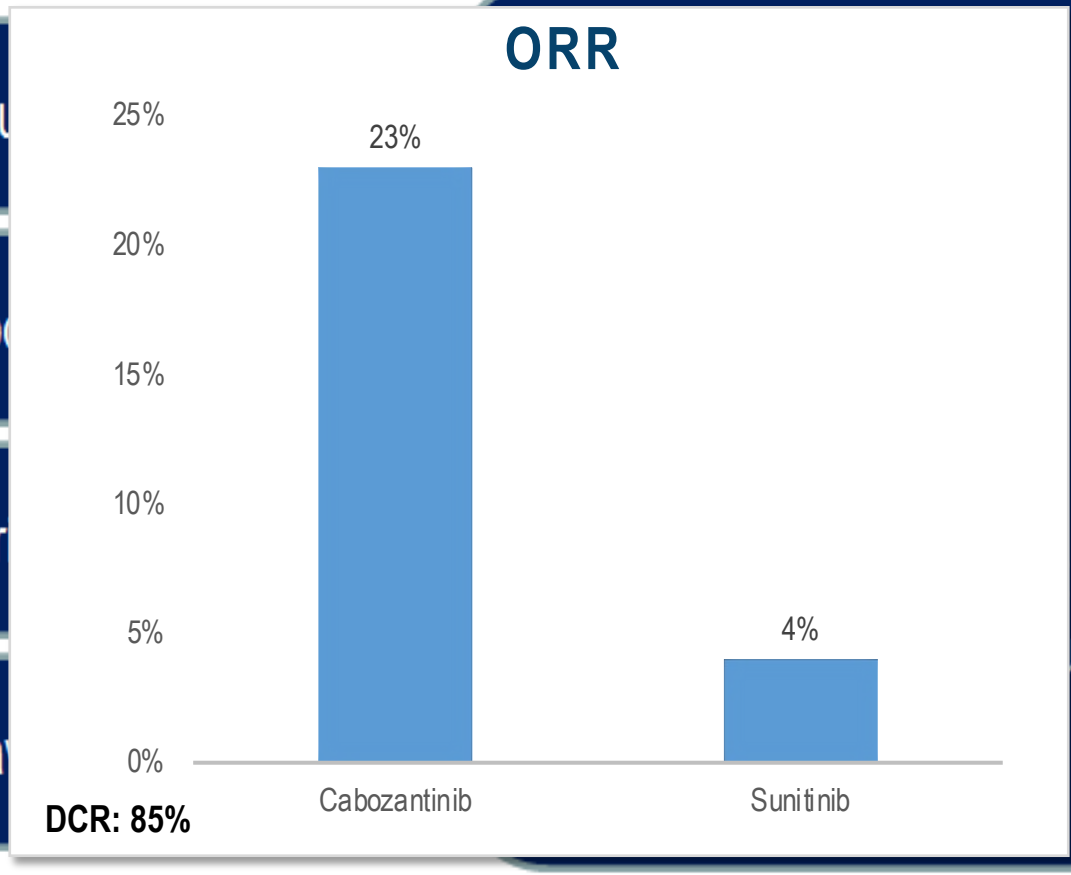




Pal et al. Lancet, 2021

Randomized phase III in a biomarker selected population: SAVOIR Study

Open-label, randomized, Phase III trial (NCT03091192)

Patients with locally advanced or metastatic PRCC

Key inclusion criteria

- ≥18 years
- Central confirmation of a *MET*-driven tumor (chromosome 7 gain / *MET* or *HGF* amplification / *MET* kinase domain mutations)*
- Measurable disease
- Karnofsky Performance Status ≥80%
- Patients could have received prior systemic treatment in the advanced setting or be treatment-naïve#

Savolitinib
600 mg QD
(or 400 mg if <50 kg)

Randomized 1:1

Sunitinib
50 mg QD in 6-week cycles of 4 weeks on / 2 weeks off

RECIST 1.1 assessment every 6 weeks‡ until objective progressive disease

Approximately 360–450 patients were planned to be screened, in order to randomize ~180 patients

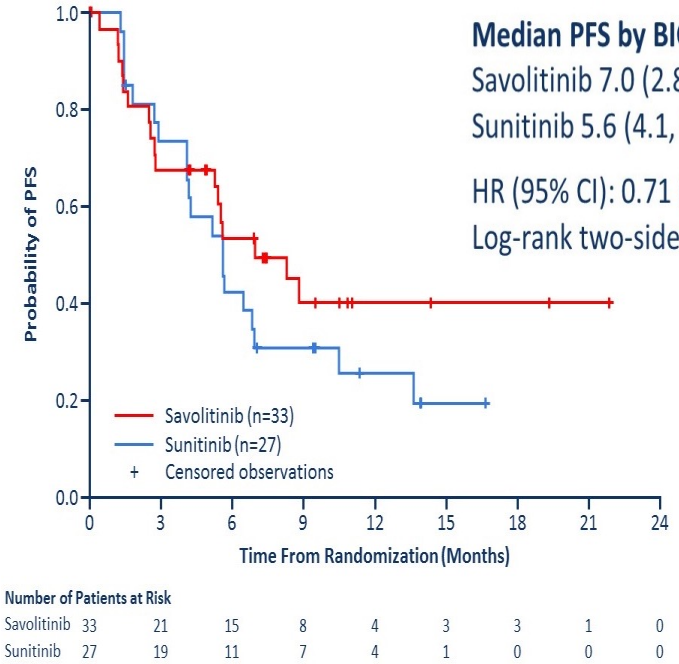
After external data on predicted PFS with sunitinib in patients with *MET*-driven disease became available, study enrollment was closed early[1]

- **Primary endpoints:** PFS by BICR
- **Secondary endpoints**: OS and ORR by BICR, safety and HRQoL

1. Albiges et al. ASCO; May 29–31, 2020; presented here: abstract e19321; 2. Frigault et al. AACR 2018;78:4541–4541.
*In the absence of co-occurring *FH* or *VHL* mutations.[2] #Patients were excluded if they had previously received sunitinib or a MET inhibitor. ‡Follow-up every 12 weeks after first year. BICR, blinded independent central review; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRCC, papillary renal cell carcinoma; QD, once daily; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors

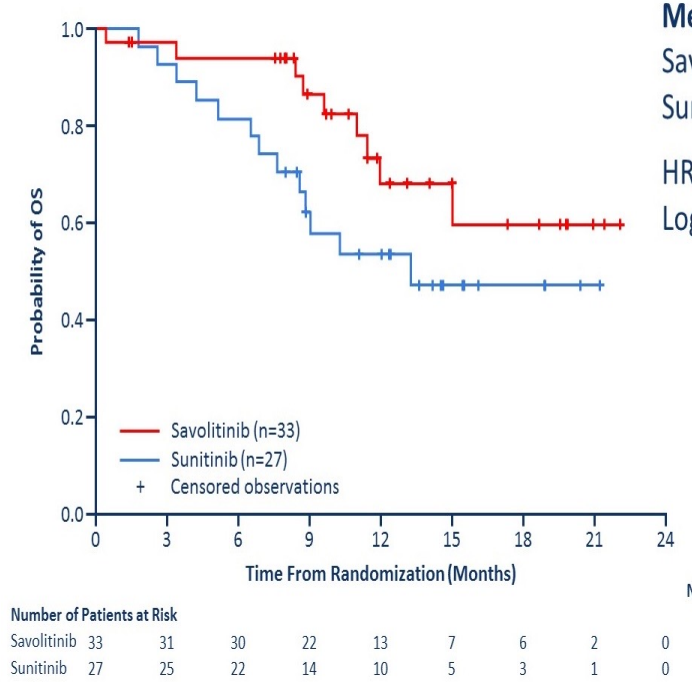
Choueiri ASCO 2020

Randomized phase III in a biomarker selected population: SAVOIR Study



Median PFS by BICR in months (95% CI)
Savolitinib 7.0 (2.8, NC)
Sunitinib 5.6 (4.1, 6.9)

HR (95% CI): 0.71 (0.37, 1.36)
Log-rank two-sided *P*-value: 0.313



Median OS by BICR in months (95% CI)
Savolitinib NC (11.9, NC)
Sunitinib 13.2 (7.6, NC)

HR (95% CI): 0.51 (0.21, 1.17)
Log-rank two-sided *P*-value: 0.110

Endpoint, n (%) [95% CI]	Savolitinib (N=33)	Sunitinib (N=27)
ORR by BICR,* *All partial responses*	9 (27) [13.3, 45.5]	2 (7) [0.9, 24.3]
Disease control rate by BICR,# At 6 months At 12 months	 16 (48) [30.8, 66.5] 10 (30) [15.6, 48.7]	 10 (37) [19.4, 57.6] 6 (22) [8.6, 42.3]

Choueiri et al. JAMA Oncol. 2020

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Is there a role for CPI in non-clear cell RCC? Overview of CPI-only prospective studies

Single agent CPI

Study	KEYNOTE-427 (cohort B)[1]	HCRN GU16-260 (cohort B)*[2]
Design	Phase II, non randomized	Phase II, non randomized
N	165	35
Agent	Pembrolizumab	Nivolumab
ORR	26.7%	14.3%
mPFS	4.5 months	4 months
DCR	43%	NR

Dual CPI-CPI

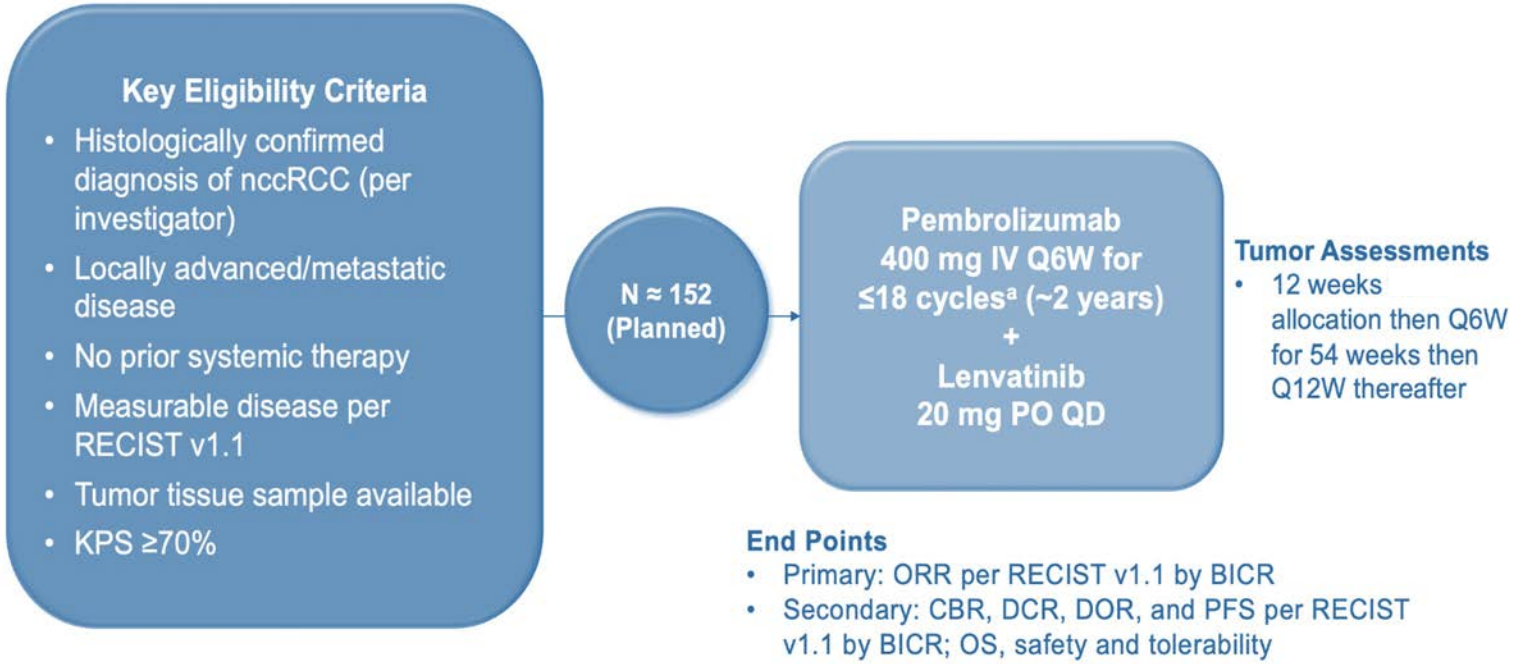
Study	CheckMate 920[3]
Design	Phase IIIb/IV, non randomized
N	52
Agent	Ipilimumab + Nivolumab
ORR	19.6%
mPFS	3.7 months
DCR	NR

SUNNIFORECAST: Randomized Phase-II Study of Nivolumab Plus Ipilimumab vs. Standard of Care in Untreated and Advanced Non-clear Cell RCC (*NCT03075423*)

[1]McDermott et al. J Clin Oncol, 2021
[2]Atkins et al. ASCO GU, 2022
[3]Tykodi et al. BMJ, 2022

Study Design of KEYNOTE-B61

NCT04704219



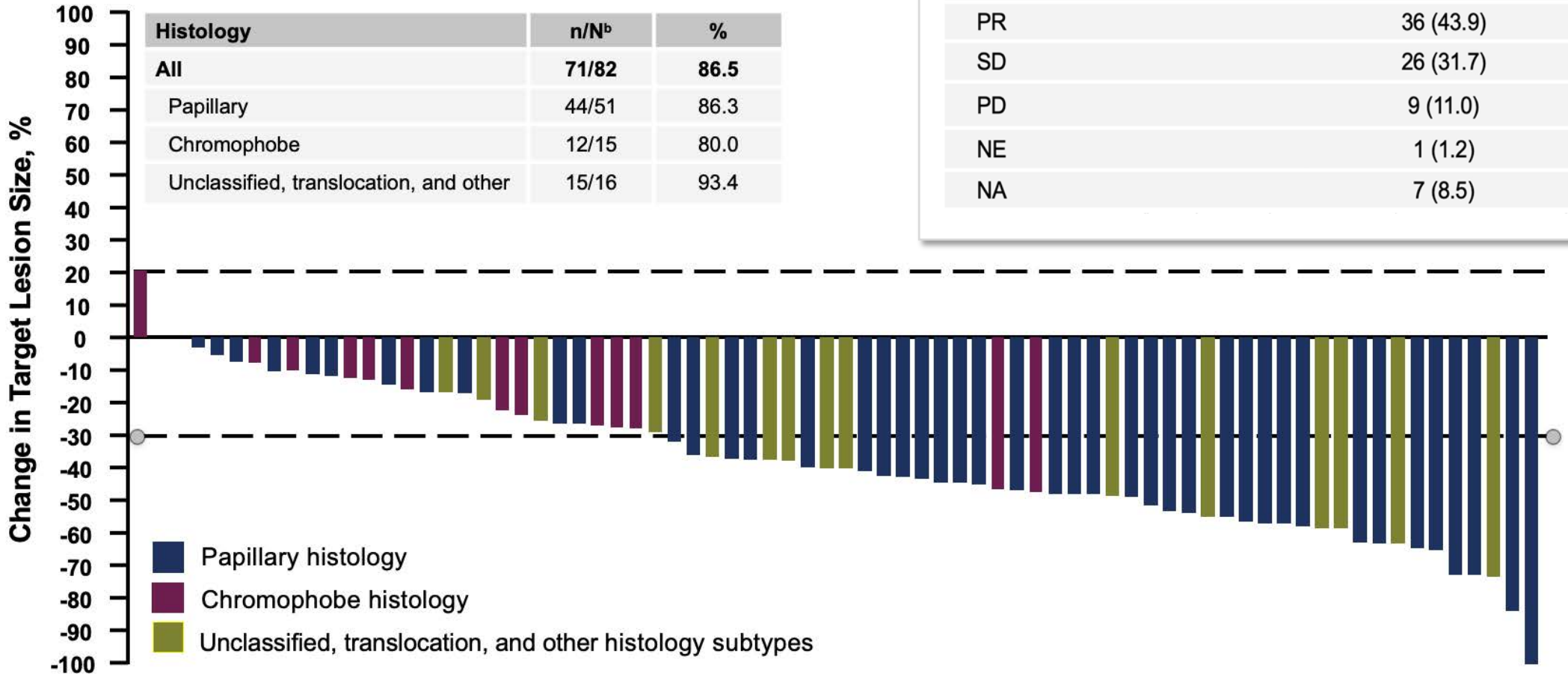
	Efficacy population n = 82
Presence of sarcomatoid features[c]	
Yes	10 (12.2)
No	52 (63.4)
RCC histology	
Papillary	51 (62.2)
Chromophobe	15 (18.3)
Unclassified	7 (8.5)
Translocation	5 (6.1)
Other	4 (4.9)
Liver metastases	14 (17.1)
Bone metastases	24 (29.3)

Albiges et al, ESMO 2022.

KEYNOTE-B61 Key results

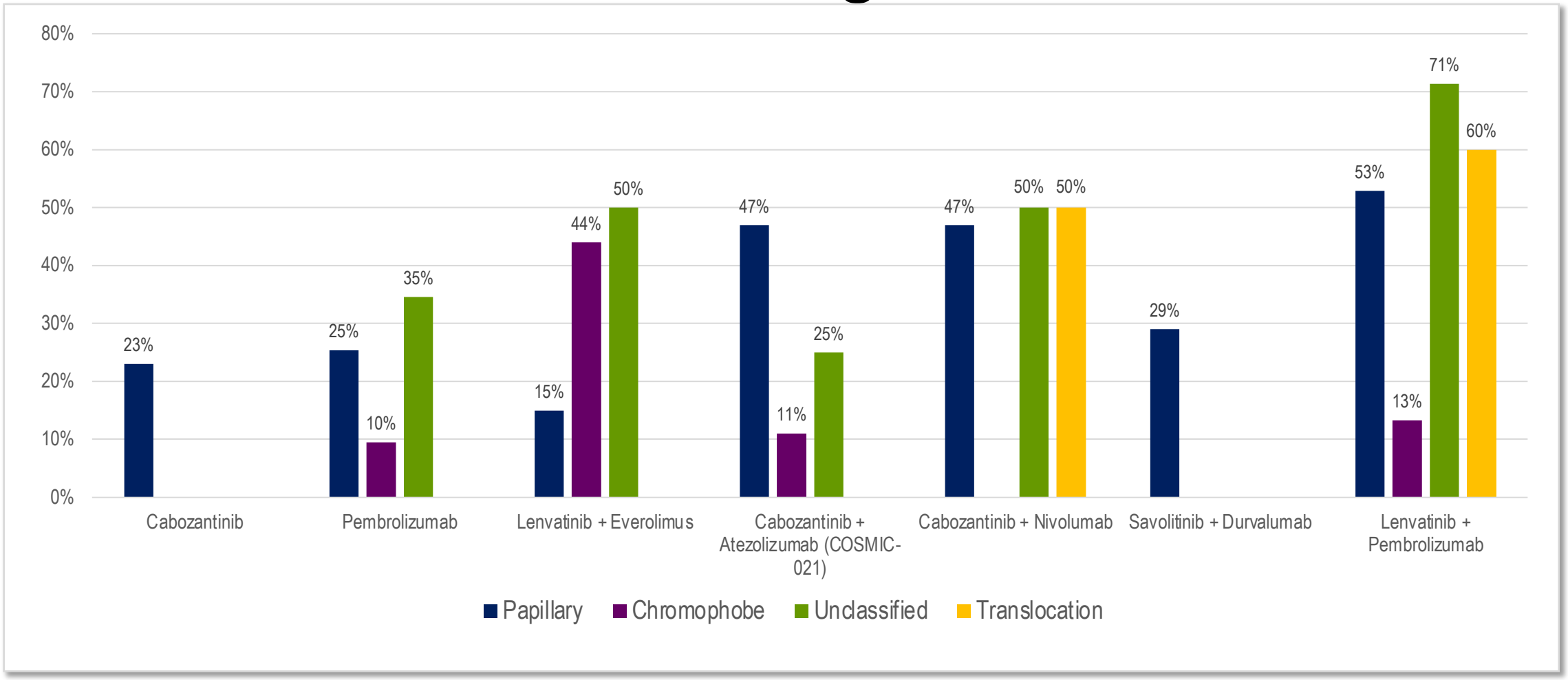
	Efficacy Population n = 82
ORR (CR + PR), % (95% CI)	**47.6 (36.4-58.9)**
DCR (CR + PR + SD), % (95% CI)	**79.3 (68.9-87.4)**
Best response, n (%)	
CR	3 (3.7)
PR	36 (43.9)
SD	26 (31.7)
PD	9 (11.0)
NE	1 (1.2)
NA	7 (8.5)

Histology	n/N[b]	%
All	**71/82**	**86.5**
Papillary	44/51	86.3
Chromophobe	12/15	80.0
Unclassified, translocation, and other	15/16	93.4



Albiges et al, ESMO 2022.

Non-clear cell: contemporary cohorts
ORR across different histologies



Courtesy of Andre P. Fay, ESMO 2022

Pal et al. Lancet, 2021
McDermott et al. J Clin Oncol, 2021
Hutson et al. Eur urol, 2021
Pal et al. J Clin Oncol, 2021
Lee et al. J Clin Oncol, 2022
Suarez-Rodriguez et al. ASCO 2021
Albiges et al, ESMO 2022.

Pivotal Phase III STELLAR-304 Trial Initiated to Evaluate Zanzalintinib for Advanced Non-Clear Cell RCC

Press Release: December 22, 2022

"Today [the initiation was announced] of STELLAR-304, a phase 3 pivotal trial evaluating zanzalintinib in combination with nivolumab versus sunitinib in patients with advanced non-clear cell renal cell carcinoma (nccRCC). Zanzalintinib, which was adopted as the generic name for XL092, is a next-generation tyrosine kinase inhibitor (TKI) in development for multiple advanced tumor types.

'In September at ESMO 2022, we presented zanzalintinib phase 1 data which demonstrated promising clinical activity across a range of tumors with a manageable safety profile. We were particularly encouraged by the activity of zanzalintinib in advanced kidney cancer patients, including patients with non-clear cell subtypes. Based on this zanzalintinib data and given that nivolumab has shown activity in non-clear cell kidney cancer, we are excited to evaluate this combination regimen in this population in STELLAR-304,' said [the company's] Chief Medical Officer. 'STELLAR-304 is the first and only randomized controlled phase 3 study to focus specifically across non-clear cell renal cell carcinoma subtypes, a patient population with limited clinical data and poorer treatment outcomes. We look forward to continuing our legacy of working towards improving care for all kidney cancer patients.'"

https://www.businesswire.com/news/home/20221221005589/en/Exelixis-Announces-Initiation-of-the-STELLAR-304-Phase-3-Pivotal-Trial-Evaluating-Zanzalintinib-in-Patients-with-Advanced-Non-Clear-Cell-Kidney-Cancer

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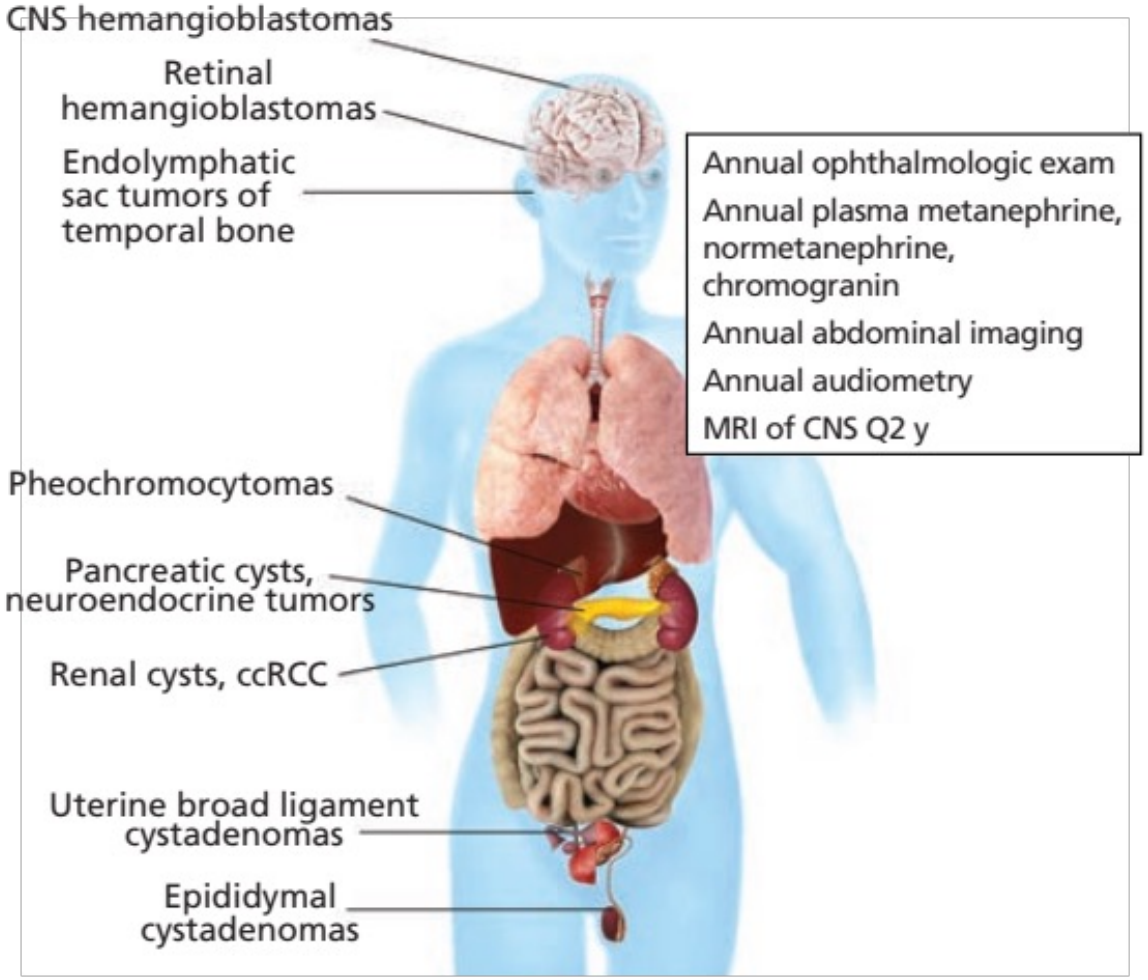
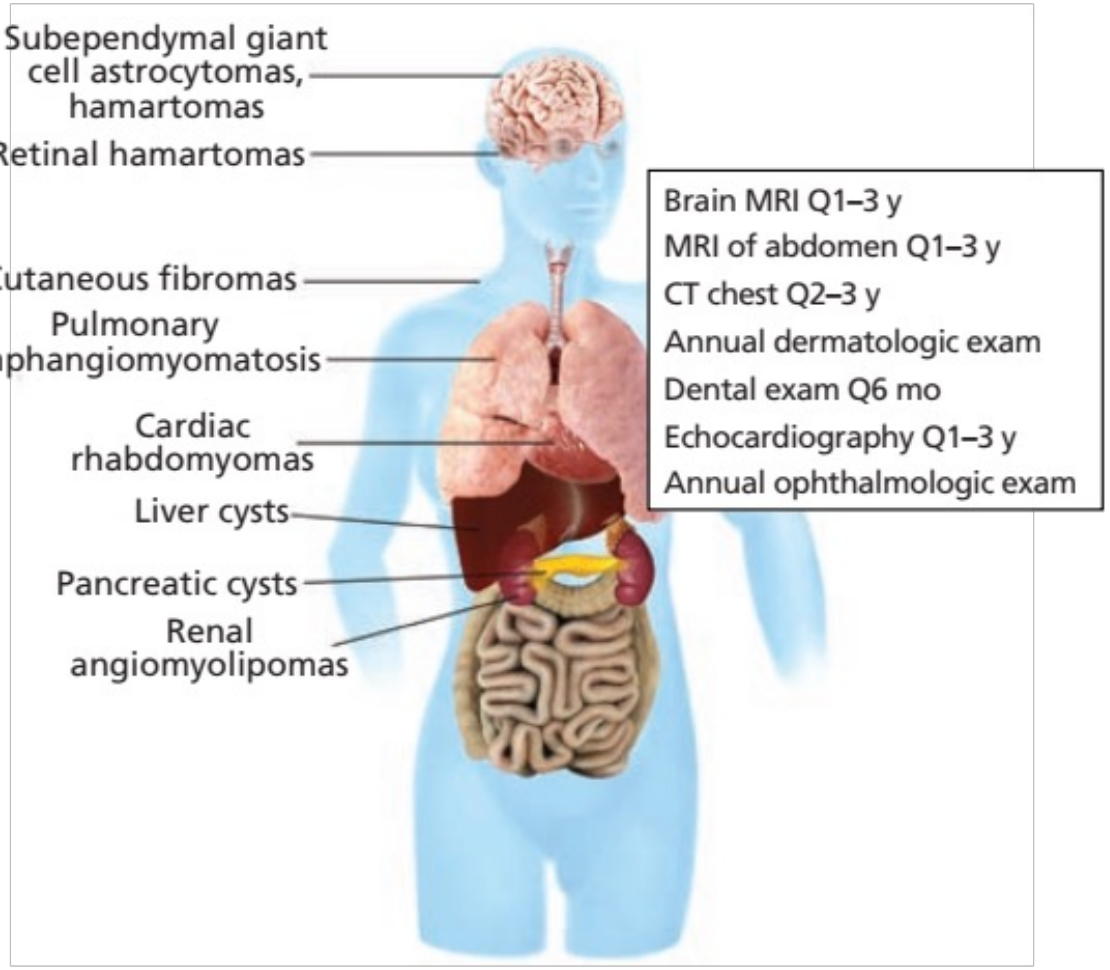
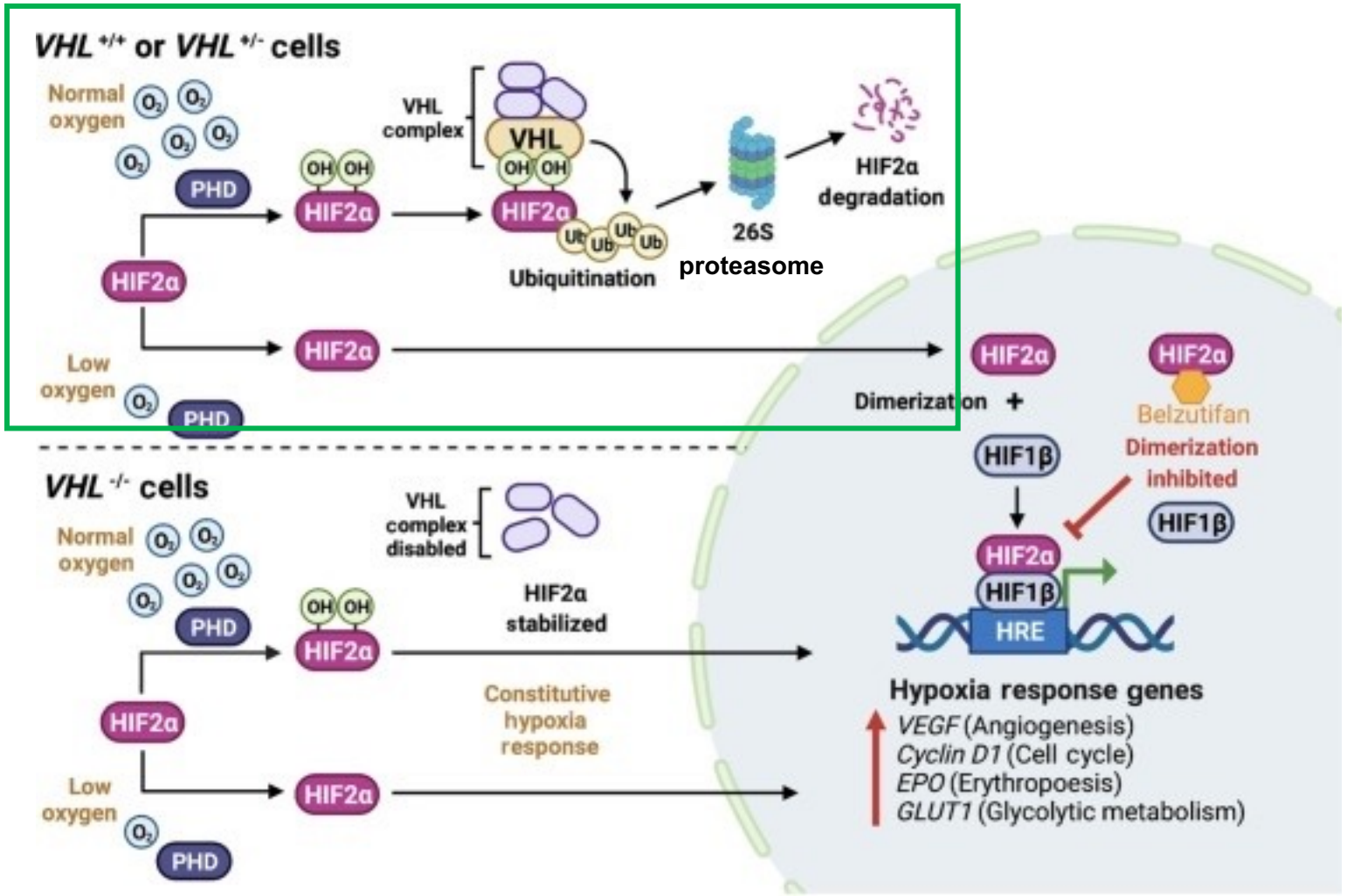
Von Hippel-Lindau (VHL)-associated RCC





Ho & Jonasch JNCCN 2014, 12 (9): 1347-55

Von Hippel-Lindau (VHL)-associated RCC
A model for HIF inhibition



McCabe , Trends in Pharmacological Science , 2022

Von Hippel-Lindau (VHL)-associated RCC
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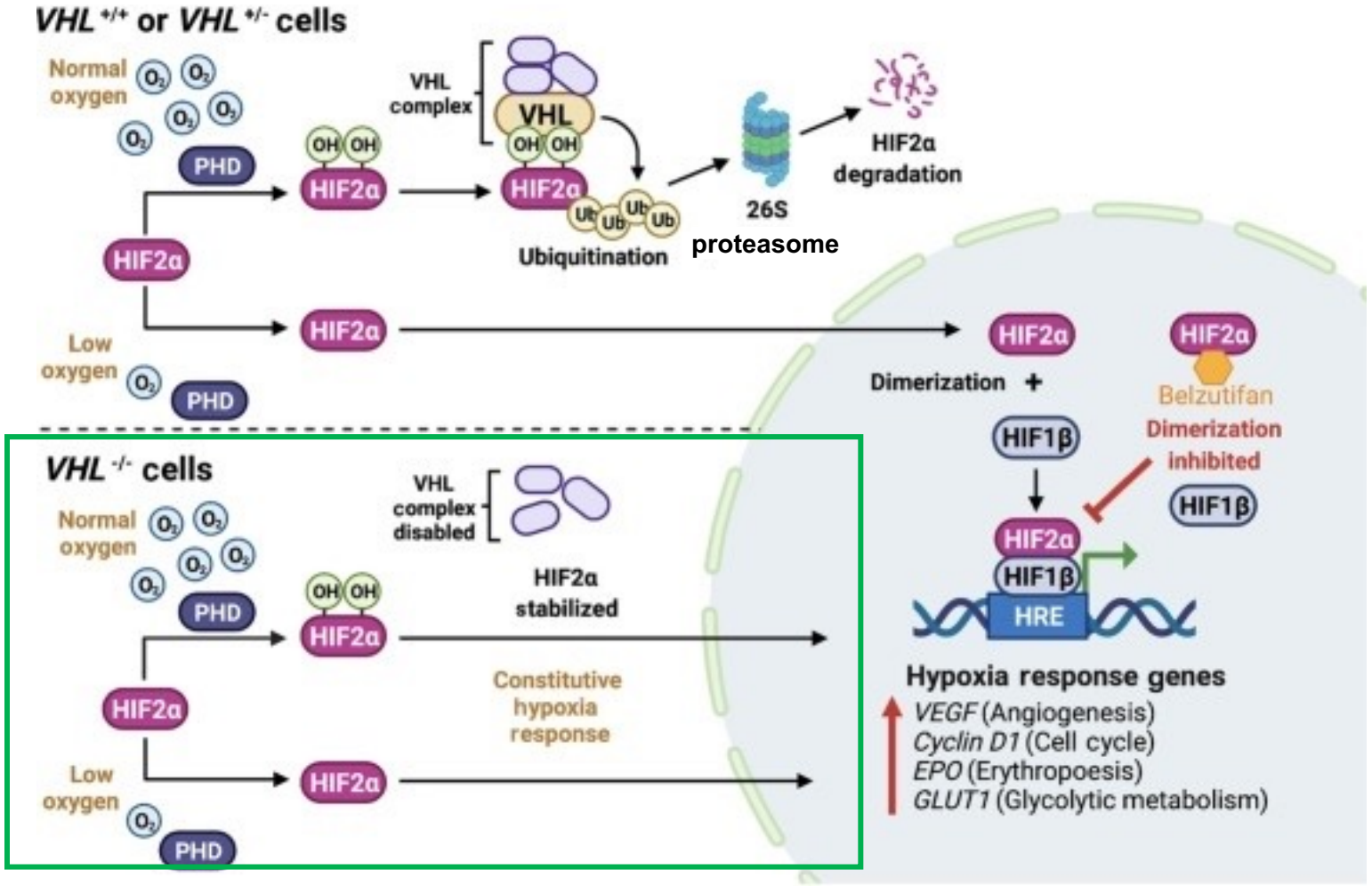

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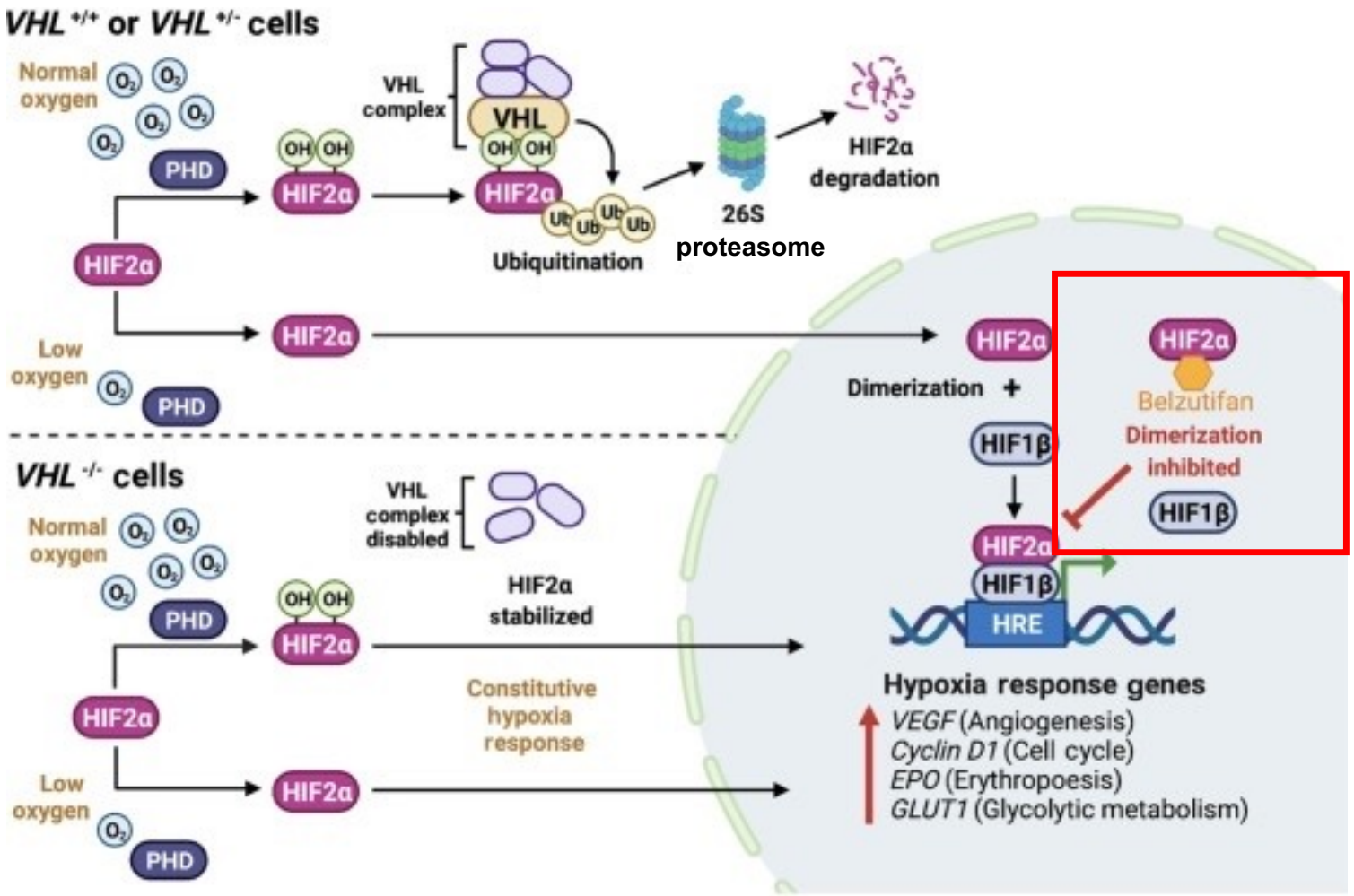

McCabe , Trends in Pharmacological Science , 2022

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HIF inhibition in VHL disease-associated RCC a proof of concept model

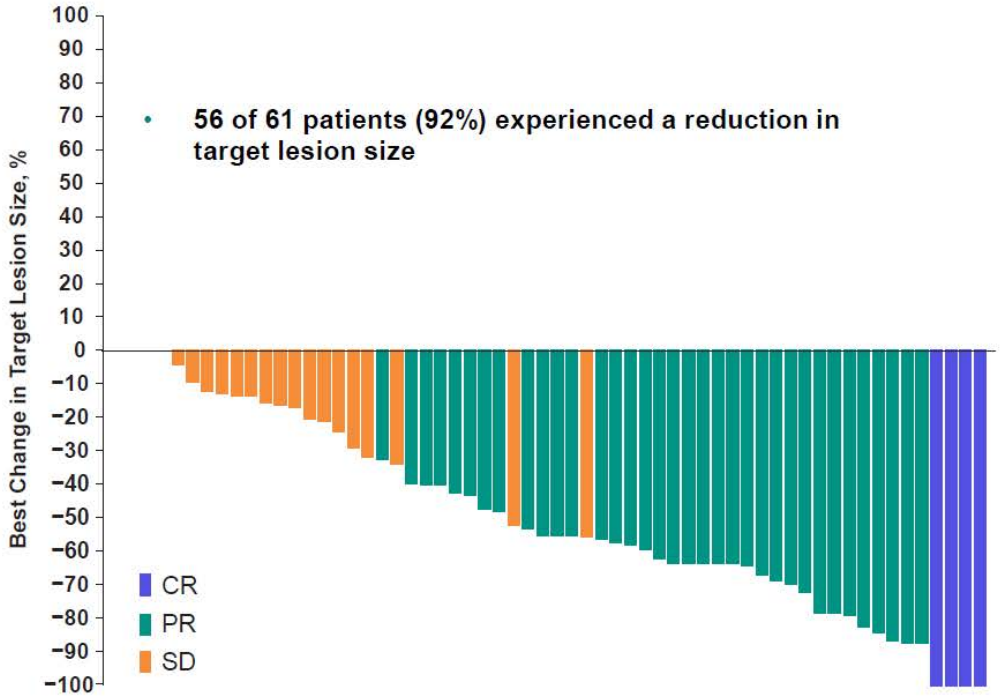
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Best Objective Response per RECIST v1.1 by IRC in VHL Disease–Associated RCC

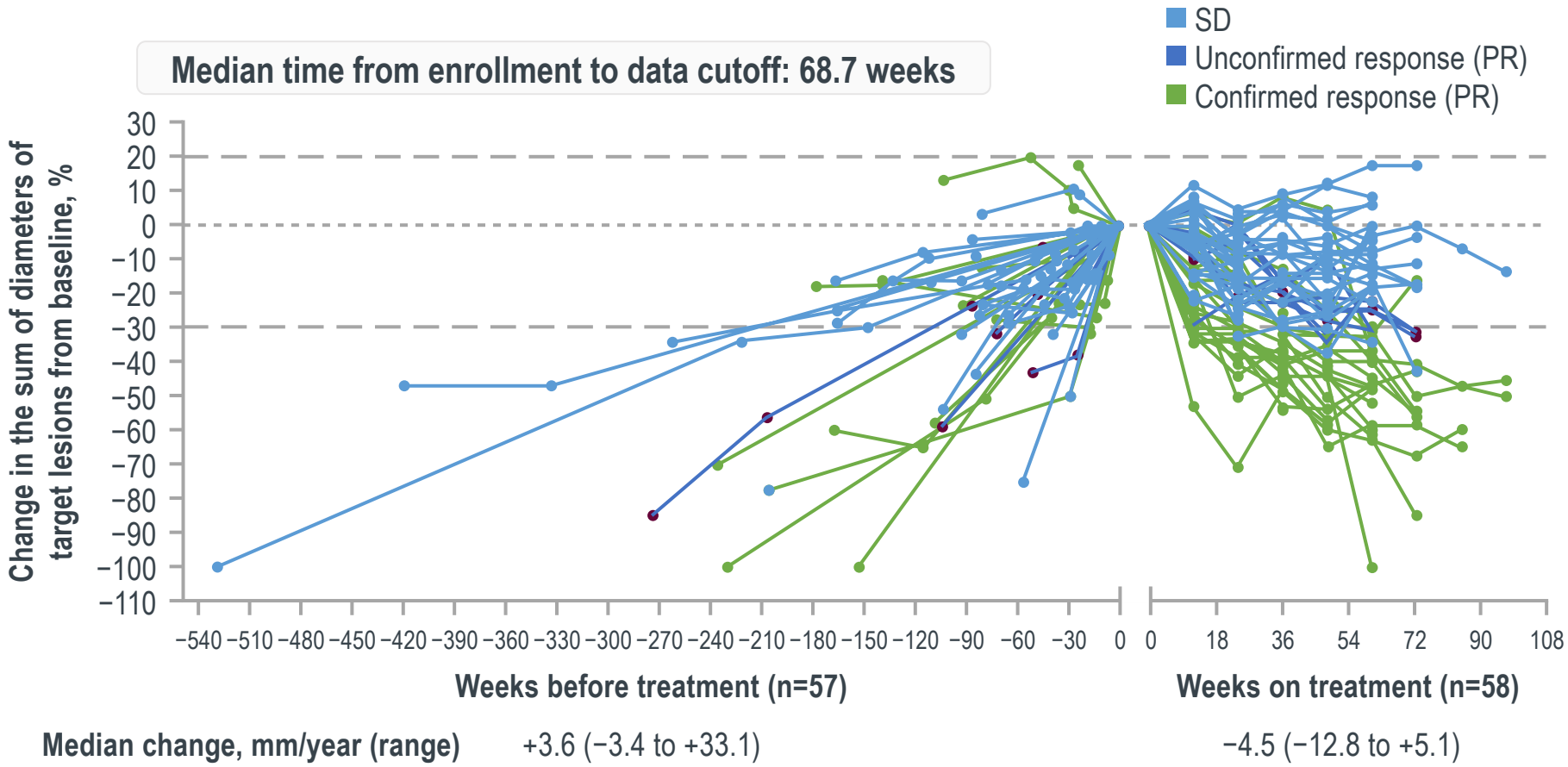
	RCC N = 61
ORR, % (95% CI)	**64 (50.6-75.8)**
Best response n (%)	
CR	4 (7)
PR	35 (57)
SD	21 (34)
PD	0
NE[a]	1 (2)



[a]1 patient discontinued the study before the first postbaseline tumor assessment. Data cutoff date: April 1, 2022.

Jonasch NEJM 2021
Srinivasan et al. ASCO 2022

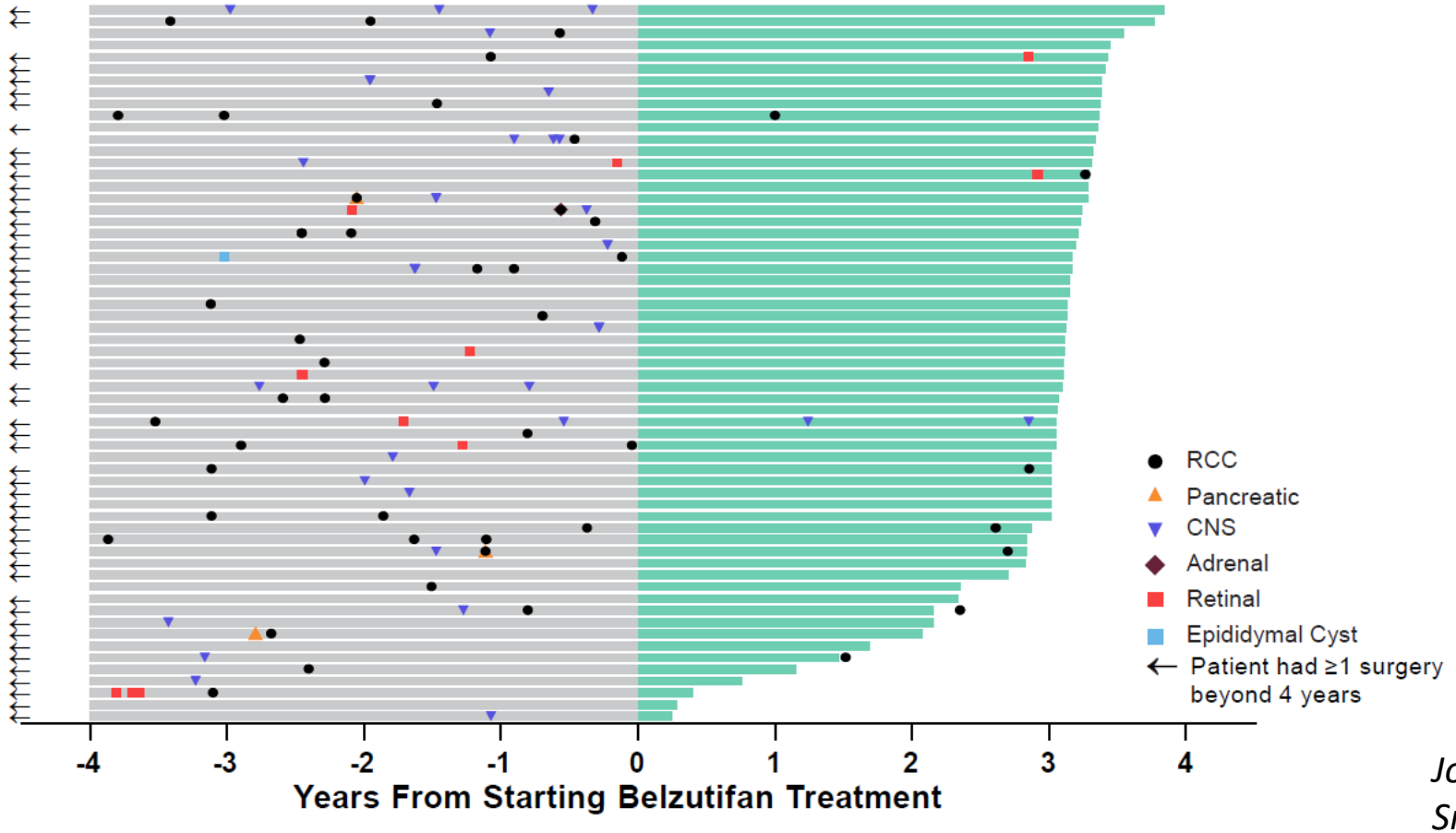
HIF inhibition in VHL disease-associated RCC a proof of concept model



Jonasch NEJM 2021

HIF inhibition in VHL disease-associated RCC a proof of concept model

Distribution of VHL Disease–Related Surgeries



a cutoff date: April 1, 2022.

Jonasch NEJM 2021
Srinivasan et al. ASCO 2022

Belzutifan safety in VHL disease

- No grade 4
- Mostly G1/2 anemia

Table 4. Adverse Events in at Least 10% of the Safety Population (61 Patients).

Event	Any Grade	Grade 1	Grade 2	Grade 3*
	number (percent)			
Anemia	55 (90)	24 (39)	26 (43)	5 (8)
Fatigue	40 (66)	29 (48)	8 (13)	3 (5)
Headache	25 (41)	20 (33)	5 (8)	0
Dizziness	24 (39)	20 (33)	4 (7)	0
Nausea	21 (34)	15 (25)	6 (10)	0
Dyspnea	14 (23)	13 (21)	0	1 (2)
Arthralgia	12 (20)	10 (16)	2 (3)	0
Constipation	12 (20)	10 (16)	2 (3)	0
Myalgia	12 (20)	9 (15)	2 (3)	1 (2)
Upper respiratory tract infection	11 (18)	4 (7)	7 (11)	0
Alanine aminotransferase level increase	10 (16)	10 (16)	0	0
Hypertension	10 (16)	3 (5)	2 (3)	5 (8)
Vision blurred	10 (16)	6 (10)	4 (7)	0
Abdominal pain	9 (15)	5 (8)	4 (7)	0
Diarrhea	8 (13)	7 (11)	0	1 (2)
Weight increase	8 (13)	5 (8)	2 (3)	1 (2)
Peripheral edema	7 (11)	6 (10)	1 (2)	0
Aspartate aminotransferase level increase	7 (11)	7 (11)	0	0
Urinary tract infection	7 (11)	1 (2)	5 (8)	1 (2)
Muscle spasms	7 (11)	5 (8)	2 (3)	0

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Take Home Messages

- Non-clear cell subtypes: **not all the same!**
- Papillary RCC: a tailored approach with **MET targeting – dedicated trials**
- A role for combination of VEGFR TKI-CPI in non-clear cell subtypes – **stay tuned for more follow up!**
- VHL disease-associated RCC: **a specific entity where HIF inhibition is the new SOC**

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Renal Cell Carcinoma

Part 1 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Wednesday, February 15, 2023

7:15 PM – 8:45 PM PT

Faculty

Prof Laurence Albiges, MD, PhD

Thomas Powles, MBBS, MRCP, MD

Toni K Choueiri, MD

Moderator

Brian Rini, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Prostate Cancer

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Thursday, February 16, 2023
7:15 PM – 9:15 PM PT

Faculty

Emmanuel S Antonarakis, MD
Prof Karim Fizazi, MD, PhD
Maha Hussain, MD, FACP, FASCO
Matthew R Smith, MD, PhD

Moderator

Alan H Bryce, MD

RTP RESEARCH TO PRACTICE

Thank you for attending!

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In-person attendees can use the networked iPads® to claim CME credit.

CME credit instructions will be emailed to all clinician attendees within 3 to 5 business days.

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