Investigator Perspectives on Available Research and Challenging Questions in Renal Cell Carcinoma: A Post-ASCO Annual Review

Wednesday, June 19, 2024
5:00 PM – 6:00 PM ET

Faculty

Rana R McKay, MD
Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Rana R McKay, MD
Associate Professor of Medicine and Urology
Associate Director, Translational Sciences
Interim Associate Director, Clinical Sciences
Co-Lead, Genitourinary Oncology Program
University of California San Diego
Moores Cancer Center
La Jolla, California

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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

RTP
RESEARCH
TO PRACTICE

Commercial Support

This activity is supported by an educational grant from Merck.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

RTP
RESEARCH
TO PRACTICE

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.

Dr McKay — Disclosures
Faculty

Consulting Agreements	Ambrx, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Neomorph, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Contracted Research (Institutional)	AstraZeneca Pharmaceuticals LP, ArteraAI, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Oncternal Therapeutics

RTP
RESEARCH
TO PRACTICE

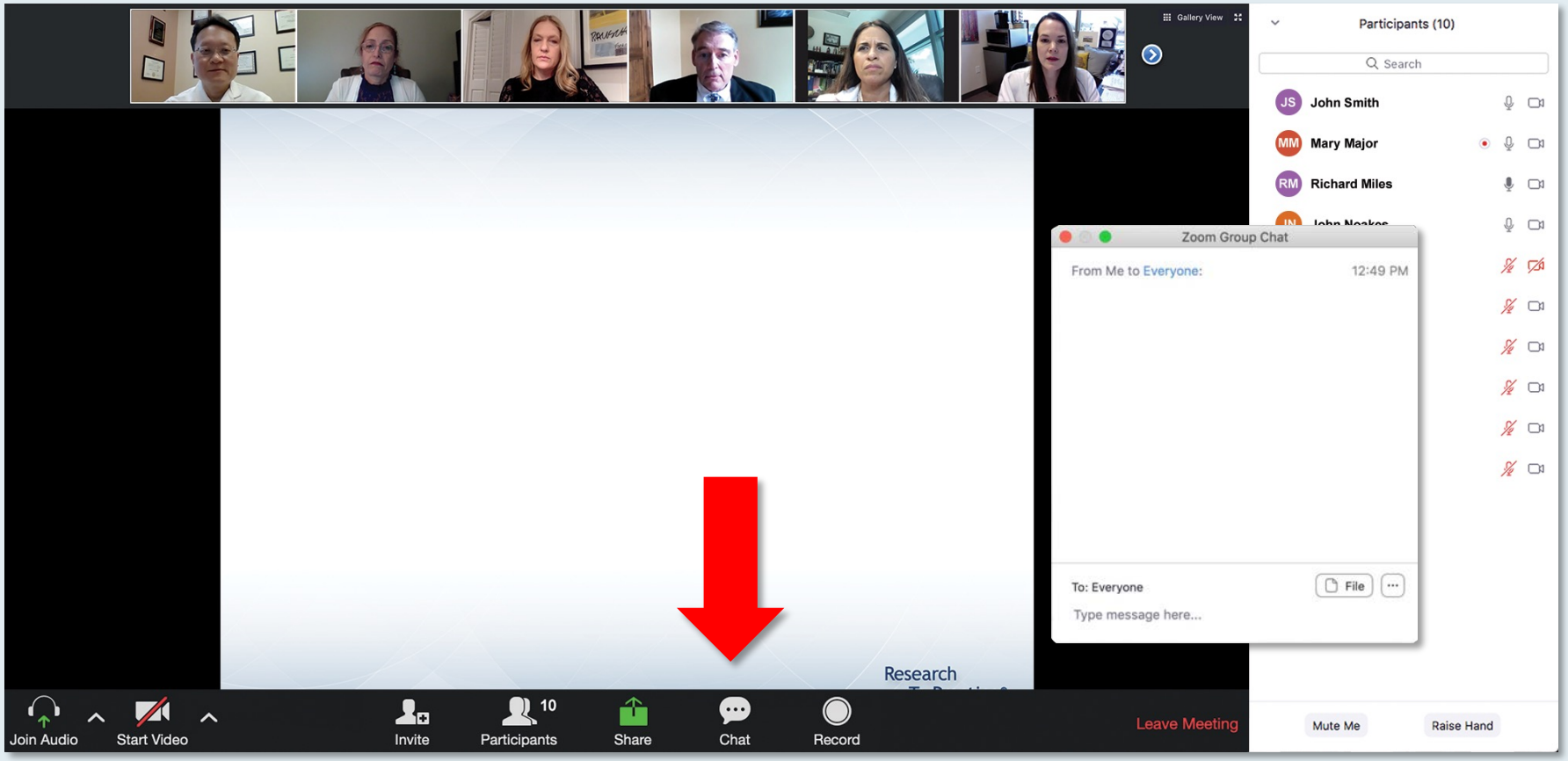
Prof Powles — Disclosures
Faculty

Advisory Committees, Grants/Funding to Organization/Institution and Strategic Advisory Roles	Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Merck Serono, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Gilead Sciences Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Mashup Media, LLC, Merck Serono, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Eisai Inc, Genentech, a member of the Roche Group, Merck, Novartis, Pfizer Inc

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.

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions

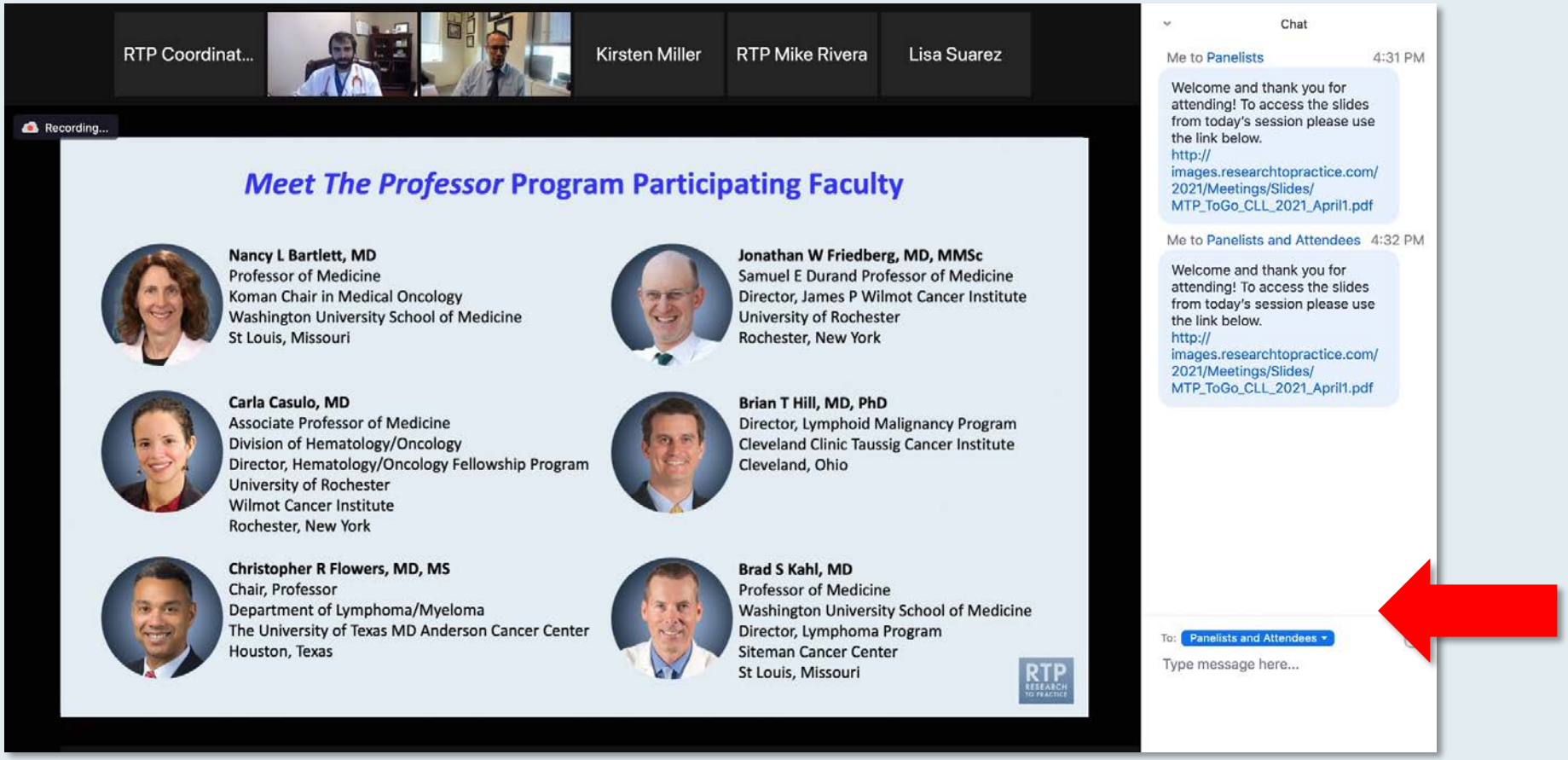


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

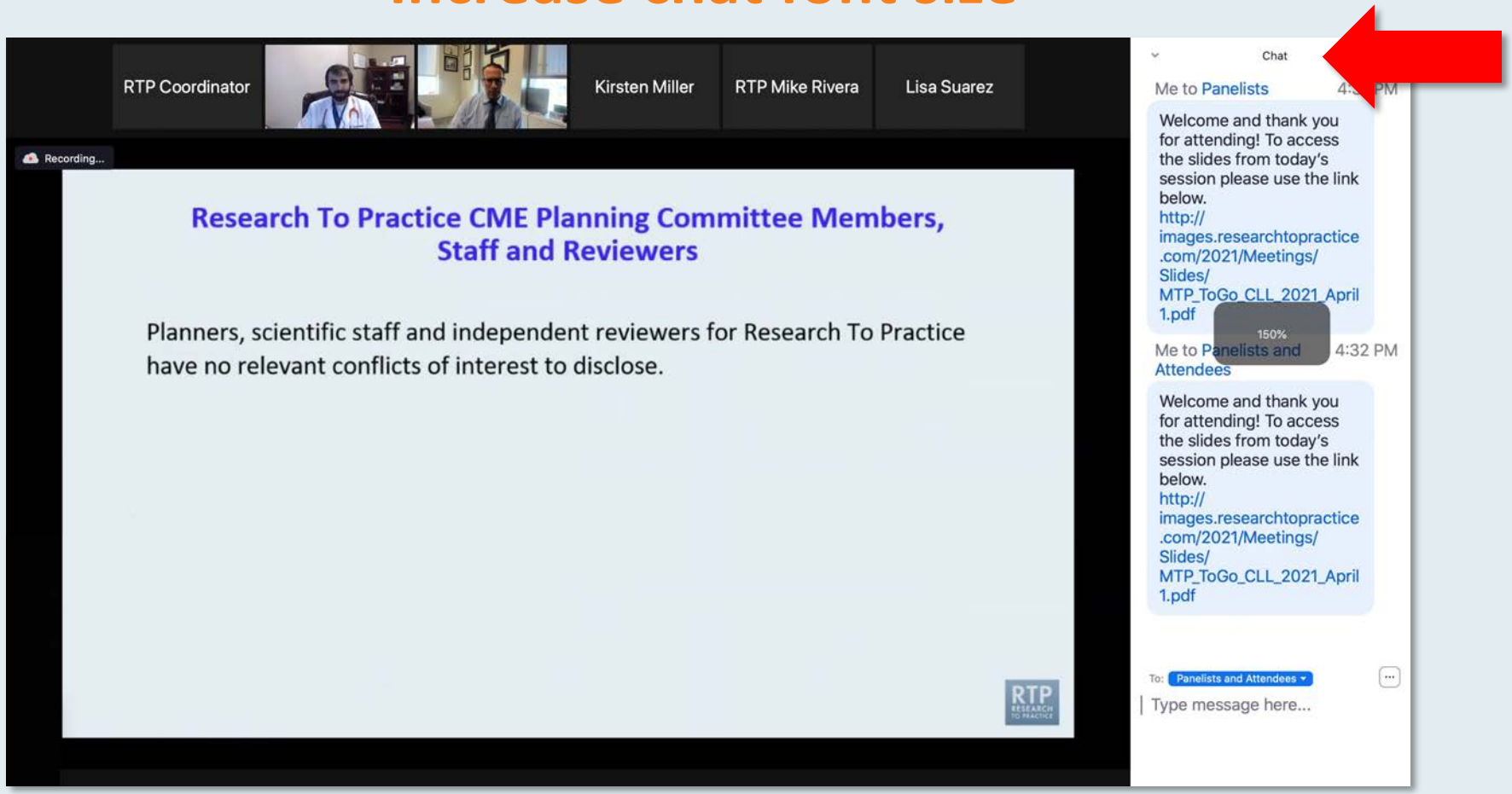


Drag the white line above the submission box up to create more space for your message.

RTP RESEARCH TO PRACTICE

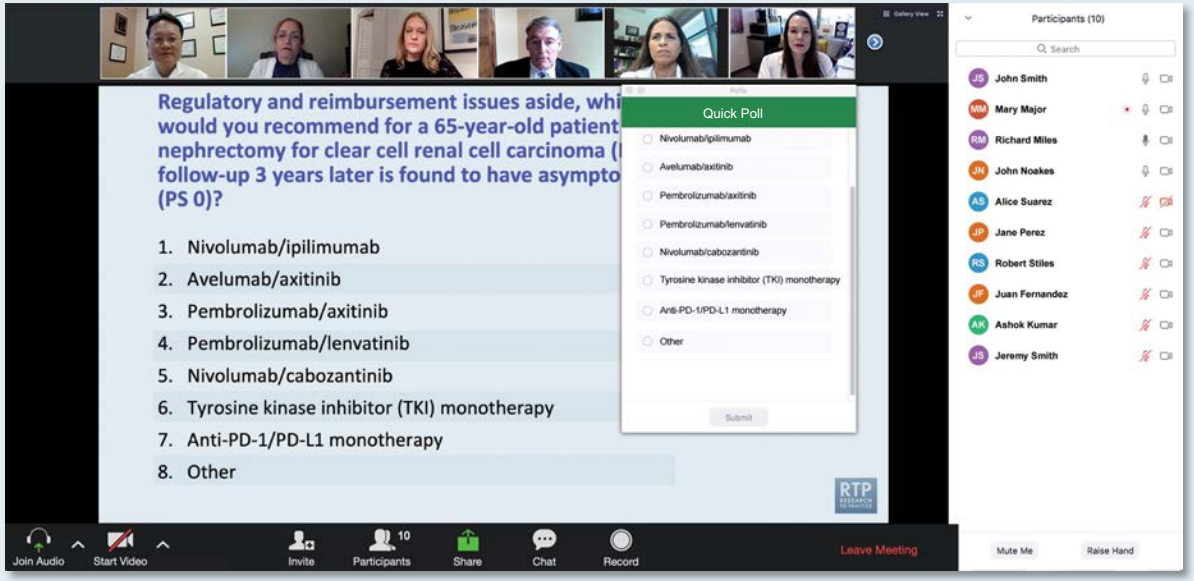
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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



RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Renal Cell Carcinoma

DR TONI CHOUEIRI
DANA-FARBER CANCER INSTITUTE

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

What Clinicians Want to Know About the Management of Triple-Negative Breast Cancer

A CME/MOC-Accredited Live Webinar

Thursday, June 20, 2024
5:00 PM – 6:00 PM ET

Faculty

Kevin Kalinsky, MD, MS
Heather McArthur, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Year in Review: Gynecologic Oncology

A CME/MOC-Accredited Live Webinar

Tuesday, June 25, 2024
5:00 PM – 6:00 PM ET

Faculty

Dana M Chase, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Year in Review: Multiple Myeloma

A CME/MOC-Accredited Live Webinar

Tuesday, July 9, 2024
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Thomas Martin, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Inside the Issue: Integrating Antibody-Drug Conjugates into the Management of HR-Positive and Triple-Negative Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, July 17, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Peter Schmid, FRCP, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Inside the Issue: Integrating ALK-Targeted Therapy into the Management of Localized Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Professor Ben Solomon, MBBS, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP
RESEARCH
TO PRACTICE

Investigator Perspectives on Available Research and Challenging Questions in Renal Cell Carcinoma: A Post-ASCO Annual Review

Wednesday, June 19, 2024
5:00 PM – 6:00 PM ET

Faculty

Rana R McKay, MD
Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

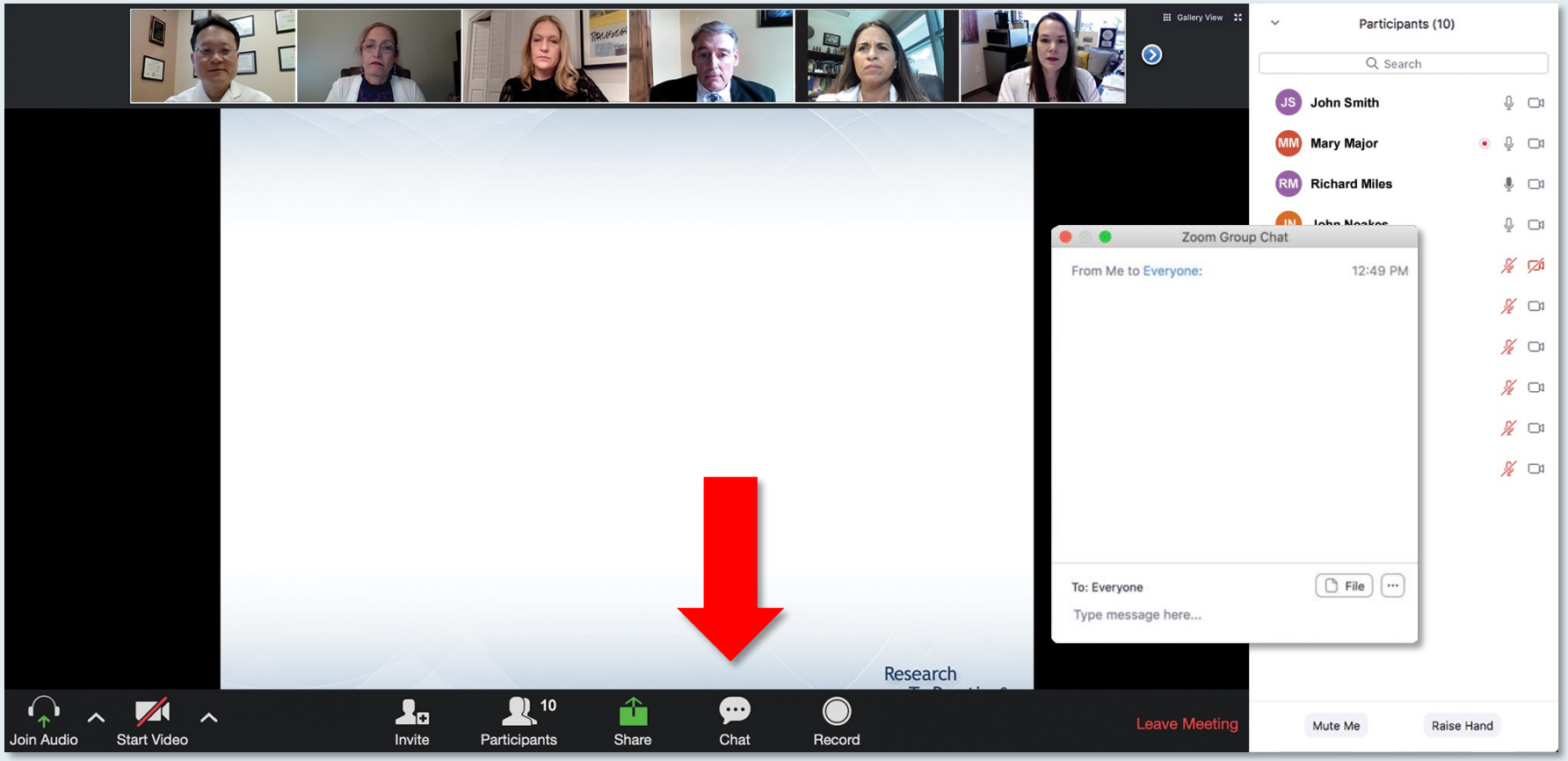
Rana R McKay, MD
Associate Professor of Medicine and Urology
Associate Director, Translational Sciences
Interim Associate Director, Clinical Sciences
Co-Lead, Genitourinary Oncology Program
University of California San Diego
Moores Cancer Center
La Jolla, California

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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

RTP
RESEARCH
TO PRACTICE

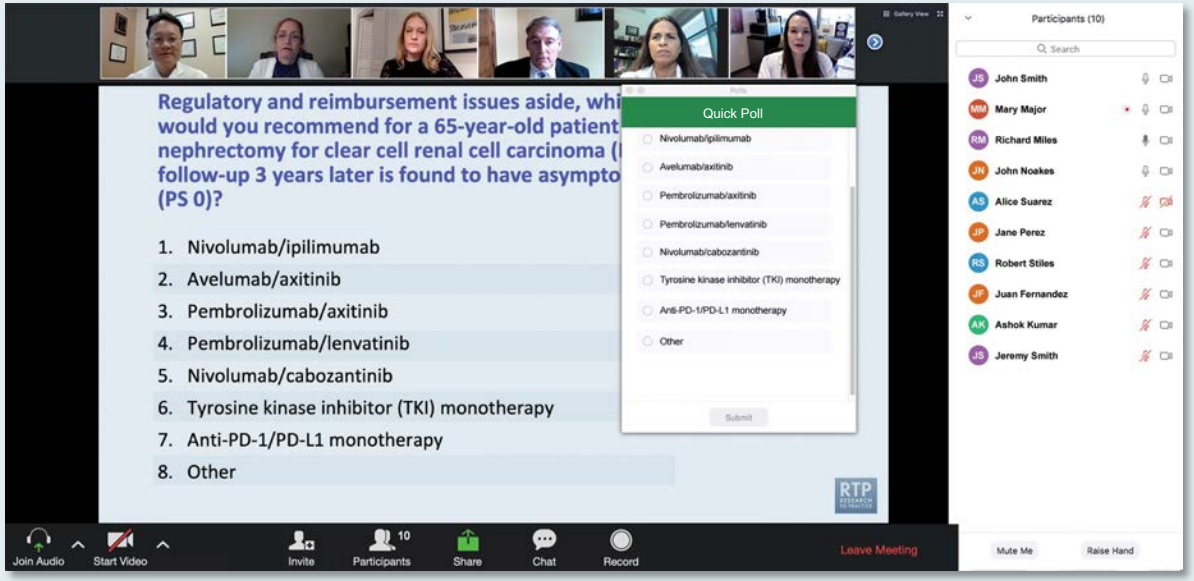
We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

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



RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Renal Cell Carcinoma

DR TONI CHOUEIRI
DANA-FARBER CANCER INSTITUTE

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

What Clinicians Want to Know About the Management of Triple-Negative Breast Cancer

A CME/MOC-Accredited Live Webinar

Thursday, June 20, 2024
5:00 PM – 6:00 PM ET

Faculty

Kevin Kalinsky, MD, MS
Heather McArthur, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Year in Review: Gynecologic Oncology

A CME/MOC-Accredited Live Webinar

Tuesday, June 25, 2024
5:00 PM – 6:00 PM ET

Faculty

Dana M Chase, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Year in Review: Multiple Myeloma

A CME/MOC-Accredited Live Webinar

Tuesday, July 9, 2024
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Thomas Martin, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Inside the Issue: Integrating Antibody-Drug Conjugates into the Management of HR-Positive and Triple-Negative Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, July 17, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Peter Schmid, FRCP, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Inside the Issue: Integrating ALK-Targeted Therapy into the Management of Localized Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Professor Ben Solomon, MBBS, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Investigator Perspectives on Available Research and Challenging Questions in Renal Cell Carcinoma: A Post-ASCO Annual Review

Wednesday, June 19, 2024
5:00 PM – 6:00 PM ET

Faculty

Rana R McKay, MD
Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Dr McKay — Disclosures
Faculty

Consulting Agreements	Ambrx, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Neomorph, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Contracted Research (Institutional)	AstraZeneca Pharmaceuticals LP, ArteraAI, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Oncternal Therapeutics

RTP
RESEARCH
TO PRACTICE

Prof Powles — Disclosures
Faculty

Advisory Committees, Grants/Funding to Organization/Institution and Strategic Advisory Roles	Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Merck Serono, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Gilead Sciences Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Mashup Media, LLC, Merck Serono, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Eisai Inc, Genentech, a member of the Roche Group, Merck, Novartis, Pfizer Inc

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

RTP
RESEARCH
TO PRACTICE

Commercial Support

This activity is supported by an educational grant from 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.

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.

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Prof Powles

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr McKay

Module 3: ASCO 2024

Agenda

Module 1: Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Prof Powles

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr McKay

Module 3: ASCO 2024

RTP RESEARCH TO PRACTICE

Where Are We Now?

First-Line Therapy for Metastatic Clear Cell RCC in 2024

RTP
RESEARCH
TO PRACTICE

Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC)

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

JAVELIN Renal 101: a multicenter, randomized, phase 3 trial

Key eligibility criteria
- Previously untreated advanced or metastatic RCC with a clear-cell component
- ≥1 measurable lesion per RECIST 1.1
- Any IMDC risk group
- ECOG PS 0 or 1

Patients enrolled from March 29, 2016, through December 19, 2017 at 144 sites in 21 countries

NCT02684006

R 1:1

N=442 → **Avelumab** 10 mg/kg IV Q2W **+ Axitinib** 5 mg PO BID 6-week cycle

N=444 → **Sunitinib** 50 mg PO QD 4 weeks on, 2 weeks off

Stratification
- ECOG PS (0 vs 1)
- Geographic region (US vs Canada/Western Europe vs ROW)

Primary endpoints
- PFS (RECIST v1.1) by BICR and OS in the PD-L1+ population

Secondary endpoints
- OS and PFS (RECIST v1.1) in the overall population
- PFS by investigator, ORR, and duration of response (RECIST v1.1)
- Safety
- Patient-reported outcomes

- The primary (final) OS analysis was planned when 368 deaths had occurred in the PD-L1+ population, which would provide 90% power to detect an HR of 0.70 using a 1-sided log-rank test at a significance level of 0.021
  - A 4-look group sequential design with a Lan–DeMets (O'Brien–Fleming) α spending function was used to determine the efficacy boundary
  - Overall type I-error was maintained at or below 1-sided 0.025 by allocating α=0.004 to the PFS comparison and α=0.021 to the OS comparison in the PD-L1+ population
  - A gatekeeping procedure was used to allow further testing of PFS and OS in the overall population

BICR, blinded independent central review; **BID**, twice daily; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HR**, hazard ratio; **IMDC,** International Metastatic RCC Database Consortium; **IV**, intravenous; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once daily; **R**, randomization; **RCC**, renal cell carcinoma; **ROW**, rest of the world.

Prior results from JAVELIN Renal 101 in the overall population

	Primary analysis of PFS 1st interim analysis of OS ≥6 months of follow-up[1]		3rd interim analysis of OS ≥28 months of follow up[2]	
	Avelumab + Axitinib (N=442)	Sunitinib (N=444)	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
PFS				
Median PFS (95% CI), months	13.8 (11.1-NE)*	8.4 (6.9-11.1)*	13.9 (11.1-16.6)†	8.5 (8.2-9.7)†
HR (95% CI) p-value	0.69 (0.563-0.838) 1-sided p<0.001		0.67 (0.568-0.785) 1-sided p<0.0001	
OS				
Median OS (95% CI), months	Not reached (NE)	Not reached (NE)	Not reached (42.2-NE)	37.8 (31.4-NE)
HR (95% CI)	0.78 (0.554-1.084)		0.79 (0.643-0.969)	
Confirmed ORR (95% CI), %	51.4 (46.6-56.1)*	25.7 (21.7-30.0)*	59.3 (54.5-63.9)†	31.8 (27.4-36.3)†

- The analysis of OS remained immature in 3 prespecified interim analyses

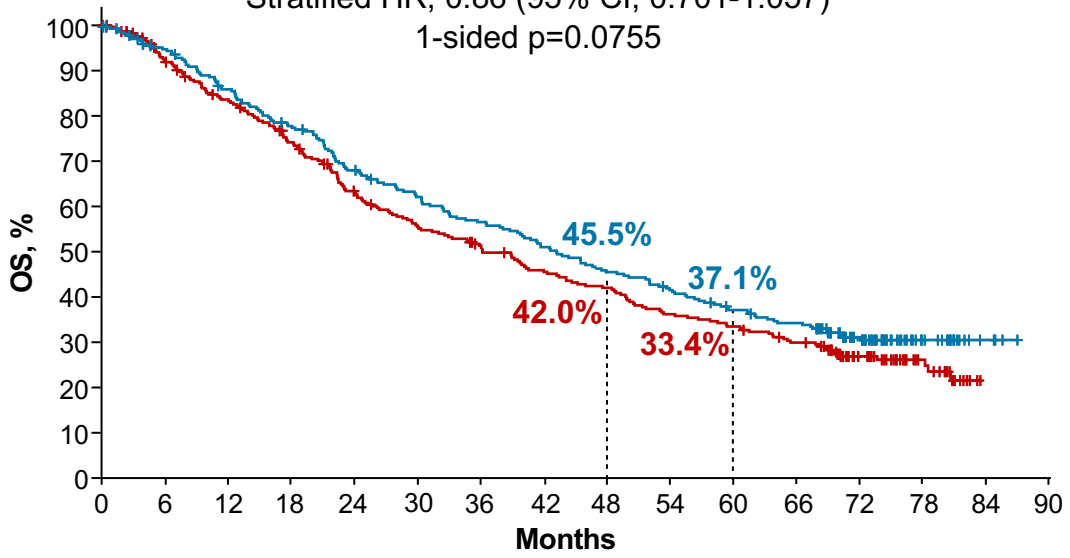
HR, hazard ratio; **NE**, not estimable; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival.
*By blinded independent central review. †By investigator assessment.
1. Motzer RJ, et al. N Engl J Med. 2019; 380:1103-15; 2. Haanen J, et al. ESMO Open 2023;8:101210.

Final analysis of overall survival

PD-L1+ population*
(Primary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (n=270)	**43.2** (36.5-51.7)
Sunitinib (n=290)	**36.2** (29.8-44.2)

Stratified HR, 0.86 (95% CI, 0.701-1.057)
1-sided p=0.0755

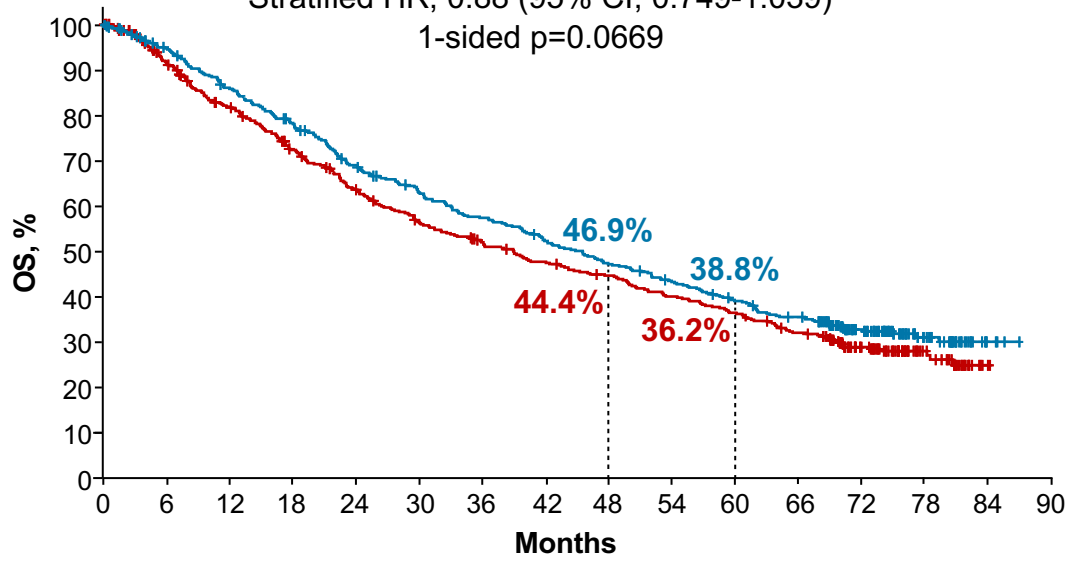


No. at risk																
Avelumab + Axitinib	270	247	222	200	174	157	143	129	115	104	91	83	51	19	4	0
Sunitinib	290	259	231	202	169	147	133	118	108	93	86	75	42	20	0	0

Overall population
(Secondary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (N=442)	**44.8** (39.7-51.1)
Sunitinib (N=444)	**38.9** (31.4-45.2)

Stratified HR, 0.88 (95% CI, 0.749-1.039)
1-sided p=0.0669



Avelumab + Axitinib	442	403	363	328	287	258	235	213	192	174	155	139	86	36	4	0
Sunitinib	444	391	344	298	258	226	205	187	173	155	141	121	74	30	2	0

At data cutoff (August 31, 2023), median follow-up was 73.7 months in the avelumab + axitinib arm and 73.6 months in the sunitinib arm (minimum follow-up, 68 months [last patient randomized to data cutoff]).
HR, hazard ratio; **OS**, overall survival.
*PD-L1+ was defined as ≥1% of immune cells staining positive in the tumor area using the Ventana PD-L1 (SP263) assay.

Final analysis of OS in IMDC risk groups in the overall population

Favorable risk

Median OS (95% CI), months	
Avelumab + Axitinib (n=94)	**79.4** (59.4-NE)
Sunitinib (n=96)	**65.5** (53.4-78.6)

Unstratified HR, 0.78 (95% CI, 0.52-1.17)
1-sided p=0.2281*

Intermediate risk

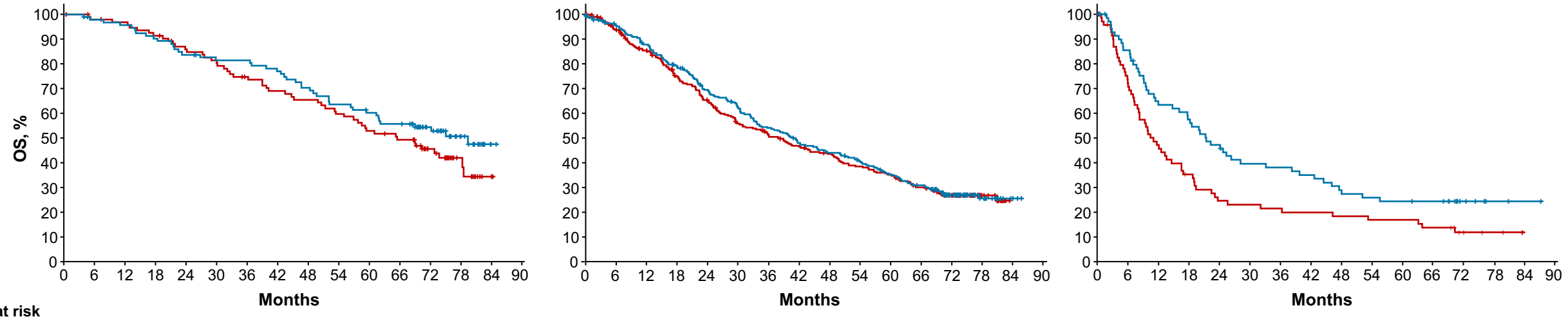
Median OS (95% CI), months	
Avelumab + Axitinib (n=270)	**41.3** (33.7-50.0)
Sunitinib (n=277)	**38.0** (29.6-47.6)

Unstratified HR, 0.95 (95% CI, 0.78-1.17)
1-sided p=0.6504†

Poor risk

Median OS (95% CI), months	
Avelumab + Axitinib (n=73)	**21.3** (14.7-33.1)
Sunitinib (n=71)	**11.0** (7.8-16.5)

Unstratified HR, 0.63 (95% CI, 0.43-0.92)
1-sided p=0.0147‡



No. at risk

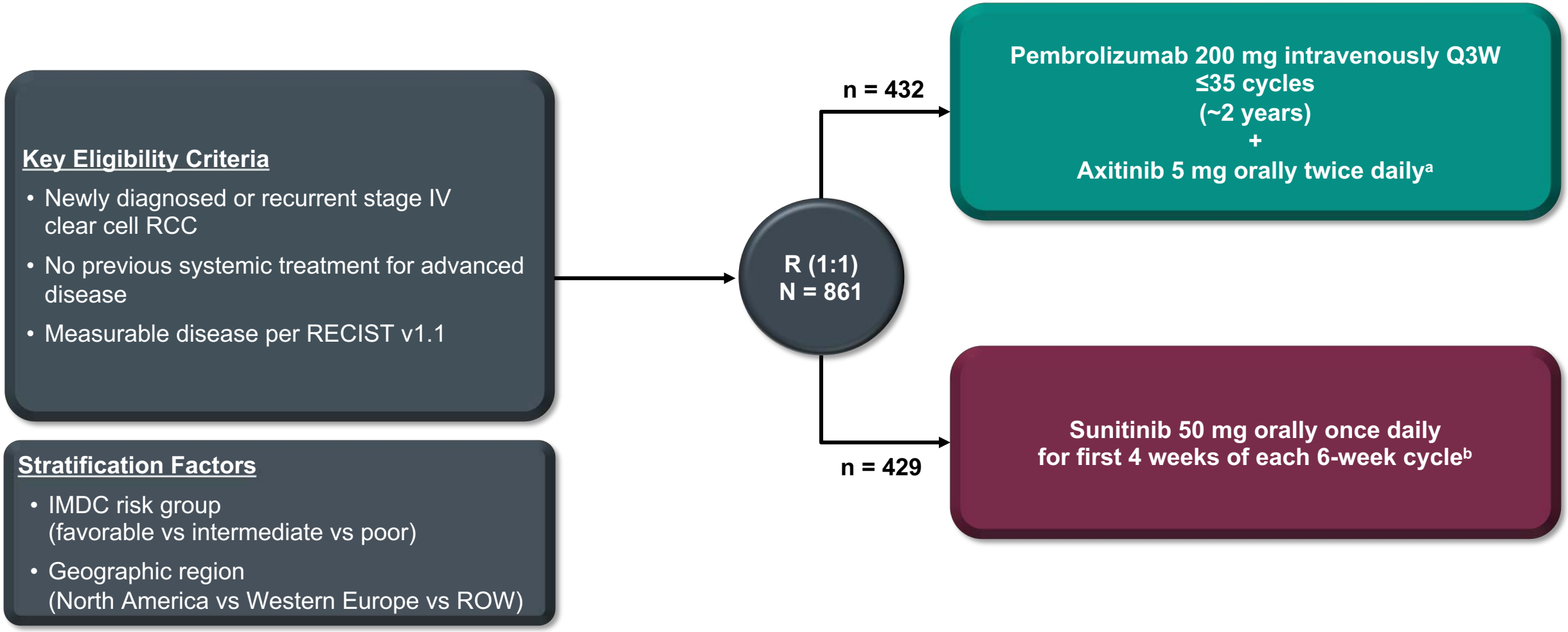
Avelumab + Axitinib	94	90	88	83	77	73	73	69	63	57	53	49	33	17	1	0
Sunitinib	96	92	90	85	77	72	65	60	57	52	46	42	26	11	2	0

Avelumab + Axitinib	270	250	228	203	176	157	136	120	110	99	85	74	46	17	2	0
Sunitinib	277	250	222	190	165	139	126	114	104	92	84	70	44	16	0	0

Avelumab + Axitinib	73	59	43	39	32	26	25	23	18	17	16	15	6	2	1	0
Sunitinib	71	49	32	23	16	15	14	13	12	11	11	9	4	3	0	0

HR, hazard ratio; **IMDC,** International Metastatic RCC Database Consortium; **NE**, not estimable; **OS**, overall survival, **RCC**, renal cell carcinoma.
*Stratified HR, 0.73 (95% CI, 0.48-1.10); 1-sided p=0.1290. †Stratified HR, 0.96 (95% CI, 0.78-1.18); 1-sided p=0.7119. ‡Stratified HR, 0.58 (95% CI, 0.39-0.87); 1-sided p=0.0076.

KEYNOTE-426 Study Design (NCT02853331)



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria are met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 23, 2023.

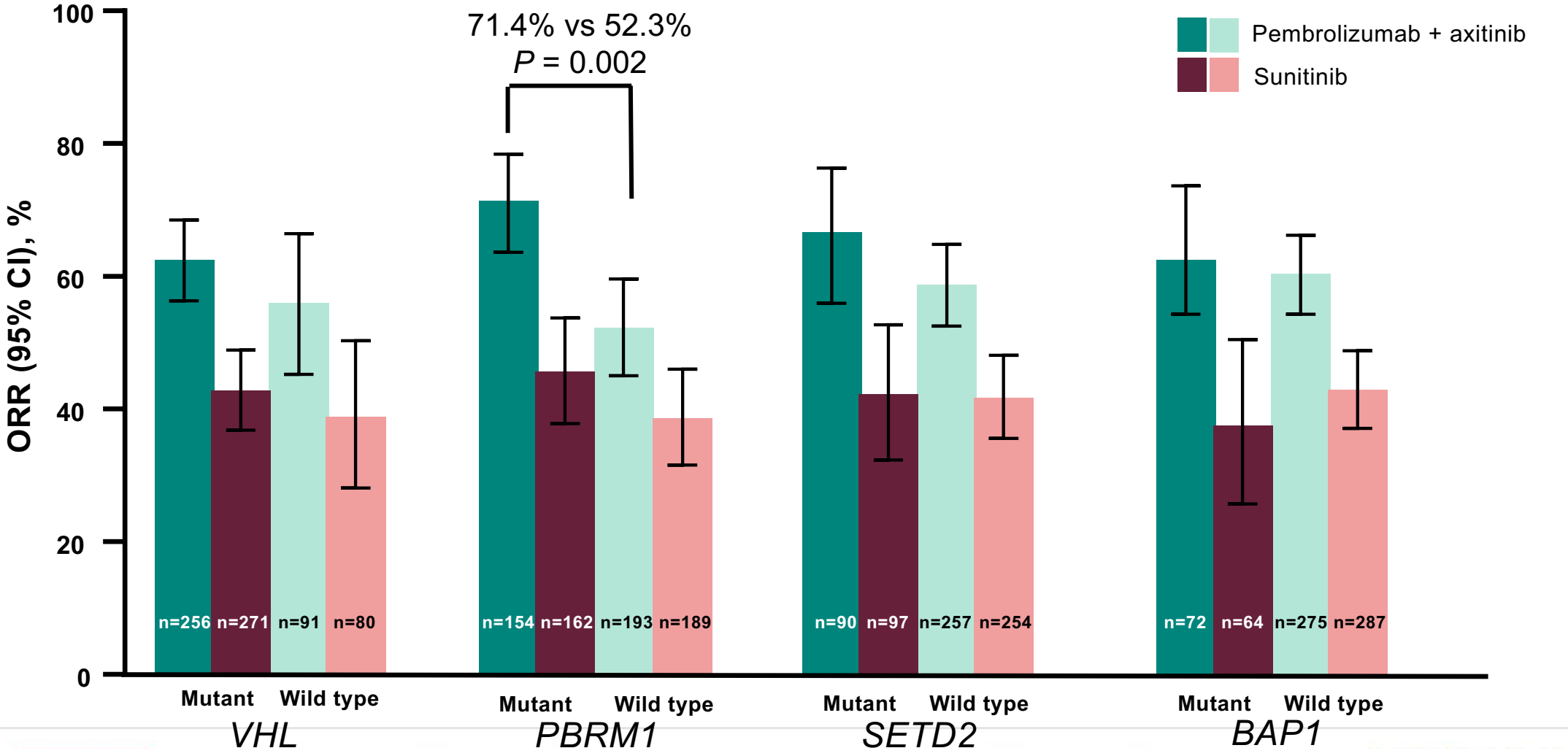
Within-Arm Association Among $Tcell_{inf}$GEP, Angiogenesis Gene Signatures, PD-L1 CPS, and Clinical Outcome

	Pembrolizumab + axitinib			Sunitinib		
Biomarker	**ORR**	**PFS**	**OS**	**ORR**	**PFS**	**OS**
$Tcell_{inf}$GEP	**<0.0001(+)**	**<0.0001(+)**	**0.002(+)**	NS	NS	NS
Angiogenesis	NS	NS	**0.004(+)**	**0.002(+)**	**<0.001(+)**	**<0.0001(+)**
PD-L1 CPS	NS	NS	NS	NS	NS	**0.025(-)**

- Higher $Tcell_{inf}$GEP was associated with improved clinical outcome within the pembrolizumab + axitinib arm
- Higher angiogenesis gene expression was associated with improved clinical outcome within the sunitinib arm
- PD-L1 CPS was negatively associated with OS within the sunitinib arm

PD-L1 CPS: pembrolizumab + axitinib, n = 407; sunitinib, n = 409. Bold indicates significance. +/– indicates the observed association is positive/negative. NS, not significant. Clinical data cutoff: January 23, 2023.

ORR by Mutational Status

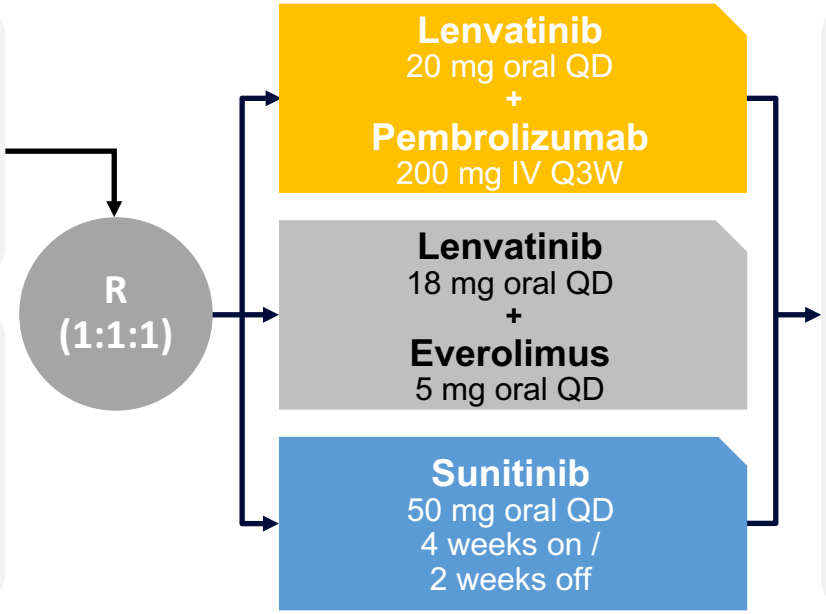


Clinical data cutoff: January 23, 2023.

Study design: CLEAR

Key eligibility criteria
- Age ≥ 18 years
- Advanced clear-cell RCC
- No prior systemic anticancer therapy for RCC
- Karnofsky performance status ≥70

Stratification factors
- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor



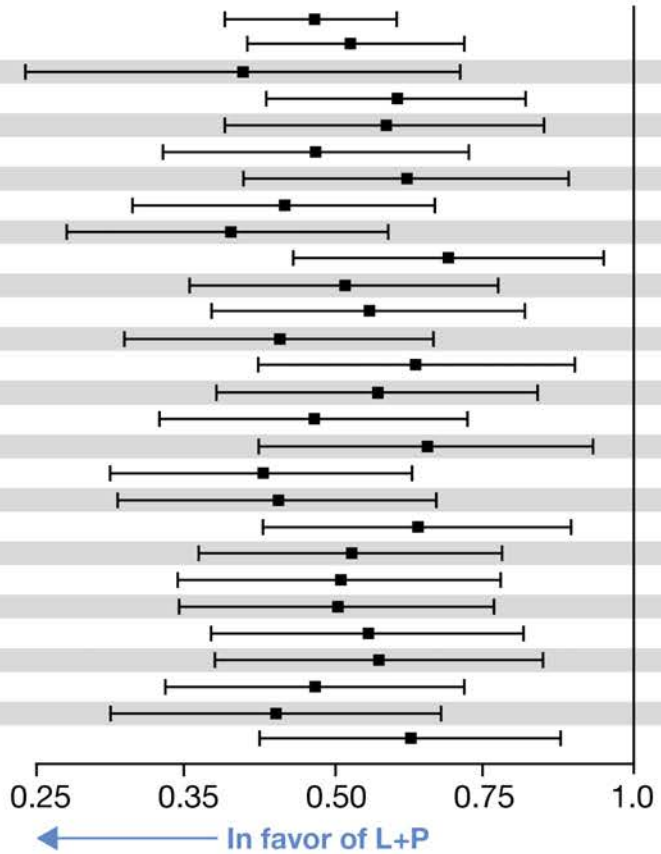
Primary endpoint
- PFS by IRC per RECIST v1.1

Secondary endpoints
- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

Key exploratory endpoints
- DOR
- **Biomarkers**

PFS by gene signature-high and -low subgroups

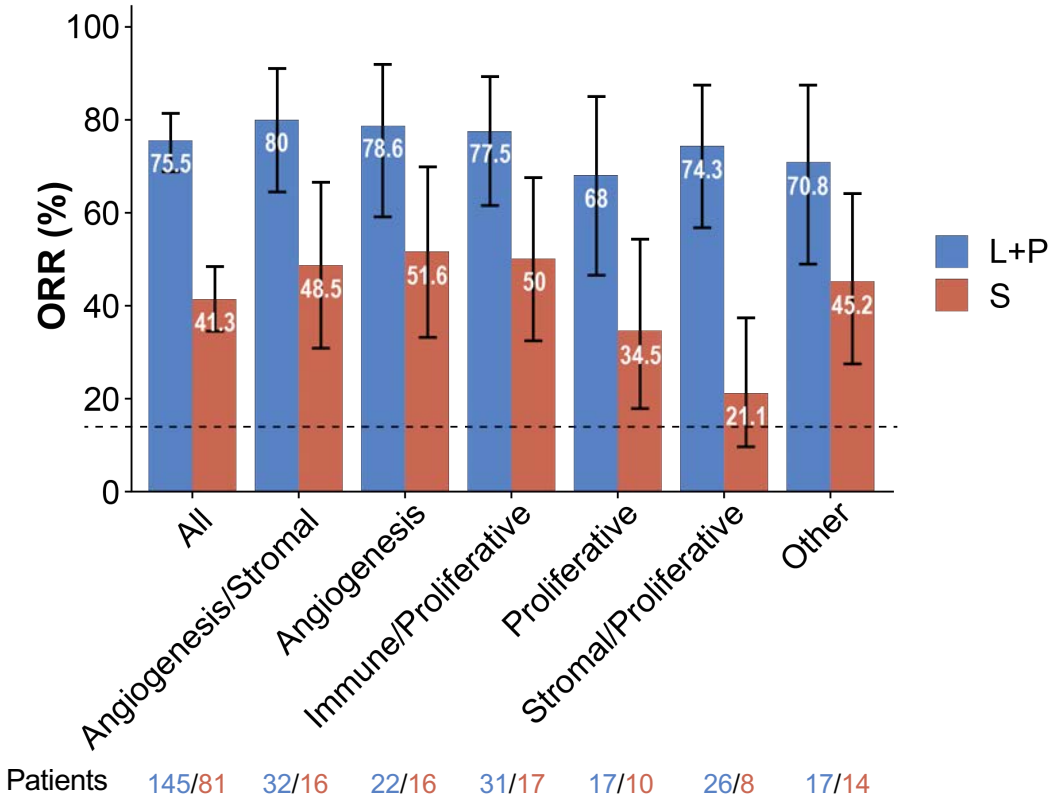
Subgroup		Patients L+P	Patients S	HR (95% CI) L+P vs S	Median (months) L+P	Median (months) S
Overall population		355	357	0.48 (0.39–0.58)	23.9	9.2
Gene alteration analysis set		192	196	0.52 (0.41–0.68)	24.3	9.4
GEP	-Low	58	60	0.41 (0.24–0.68)	27.7	6.0
	-Non-low	134	136	0.58 (0.43–0.79)	24.0	10.1
mMDSC	-Low	93	93	0.57 (0.39–0.82)	24.0	9.4
	-High	99	103	0.48 (0.34–0.69)	25.9	9.2
gMDSC	-Low	96	97	0.59 (0.41–0.87)	26.9	11.1
	-High	96	99	0.45 (0.31–0.64)	23.9	7.3
Angiogenesis	-Low	88	98	0.39 (0.27–0.57)	20.3	5.7
	-High	104	98	0.66 (0.46–0.94)	28.6	13.8
MVD	-Low	92	99	0.51 (0.36–0.74)	20.3	9.2
	-High	100	97	0.54 (0.38–0.79)	27.6	11.1
Angio36	-Low	103	88	0.44 (0.31–0.63)	24.0	9.2
	-High	89	108	0.61 (0.42–0.88)	24.3	11.0
Proliferation	-Low	93	102	0.56 (0.38–0.81)	27.6	11.1
	-High	99	94	0.48 (0.34–0.69)	22.0	7.0
MYC	-Low	91	98	0.62 (0.42–0.92)	27.7	11.2
	-High	101	98	0.42 (0.30–0.60)	16.7	5.9
RAS	-Low	95	100	0.44 (0.30–0.64)	27.6	9.5
	-High	97	96	0.61 (0.43–0.87)	22.2	9.2
WNT	-Low	104	97	0.52 (0.37–0.74)	24.0	11.0
	-High	88	99	0.51 (0.35–0.74)	24.3	9.2
Stroma/EMT/TGFβ	-Low	94	97	0.51 (0.35–0.73)	24.3	9.9
	-High	98	99	0.54 (0.38–0.78)	24.0	7.4
Glycolysis	-Low	90	104	0.56 (0.38–0.82)	26.9	11.1
	-High	102	92	0.48 (0.34–0.68)	24.0	7.4
Hypoxia	-Low	94	101	0.44 (0.30–0.65)	24.0	9.2
	-High	98	95	0.60 (0.42–0.85)	24.3	11.0



L+P arm showed longer PFS than S arm regardless of signature-high and -low subgroups

Cutoff values (1st tertile of GEP, median of non-GEP signatures) were determined based on the combined 3 arms. High/Non-low: >= cutoff; Low: <cutoff

ORR and PFS by molecular subtypes

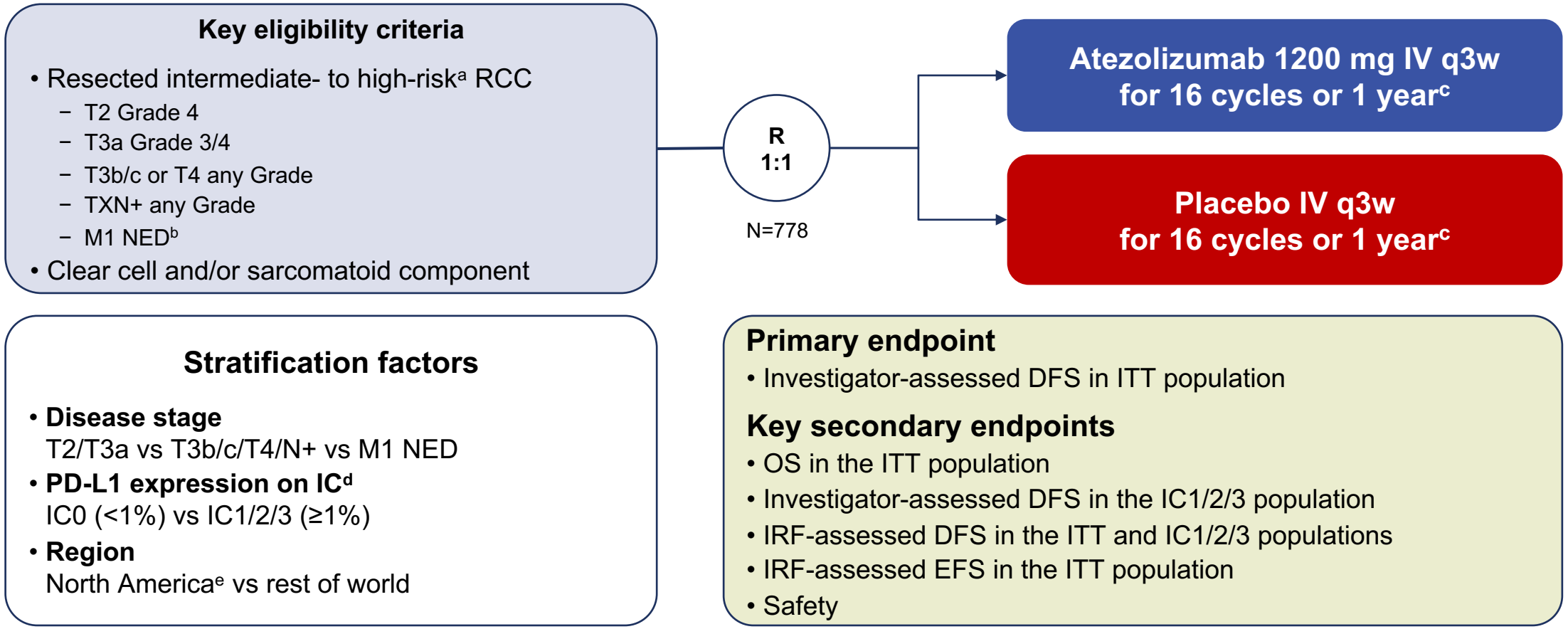


Cluster*	L+P		S	
	n	Median PFS (95% CI)	n	Median PFS (95% CI)
All	192	24.3 (18.6–28.6)	196	9.4 (6.0–11.1)
Angiogenesis/Stromal	40	28.6 (15.9–37.0)	33	13.0 (10.1–NE)
Angiogenesis	28	27.6 (16.6–42.2)	31	18.2 (5.6–26.3)
Immune/Proliferative	40	23.9 (11.1–29.1)	34	9.5 (5.6–18.4)
Proliferative	25	15.3 (7.4–26.9)	29	5.6 (3.9–9.7)
Stromal/Proliferative	35	25.3 (11.1–31.1)	38	5.6 (3.7–7.0)
Other	24	43.3 (12.7–NE)	31	11.0 (5.6–27.8)

L+P demonstrated numerically higher tumor response and longer PFS than S across all molecular subtypes

*Associations between molecular subtypes and PFS were tested by a 5-degree of freedom likelihood ratio test (while adjusting for KPS). An association between PFS and the S arm (p=0.0009) was further evaluated by adding signatures (associated significantly with KPS-adjusted PFS; such as Proliferation, MYC, Angiogenesis and MVD) as covariates to test the independent value of the molecular subtypes. Molecular subtypes were associated with PFS in the S arm but not after adjustment for KPS and gene signatures that were shown to individually associate with PFS in the S arm (Pr[>Chisq]=0.1721).

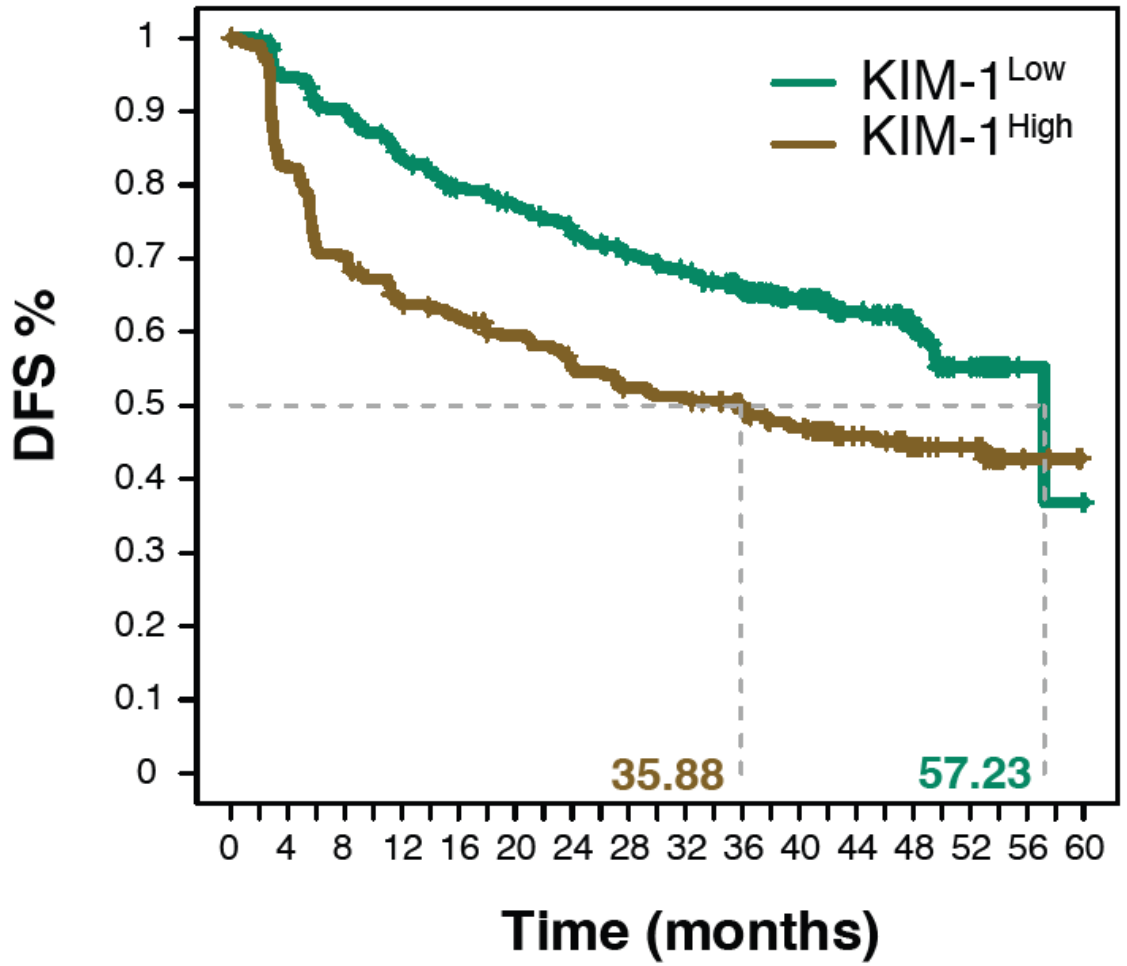
IMmotion010 Study design (NCT03024996)



EFS, event-free survival; IC, tumour-infiltrating immune cells; IRF, independent review facility; ITT, intention to treat; IV, intravenous; NED, no evidence of disease; OS, overall survival; q3w, every 3 weeks; R, randomized; TNM, tumor, node, metastasis. [a] Per TNM/grading system or status post metastasectomy. [b] Including patients with synchronous metastasectomy and patients with metachronous metastasectomy ≥12 months after primary surgery. [c] Whichever occurred first. [d] Per VENTANA SP142 immunohistochemistry assay. [e] Not including Mexico.

KIM-1^{High} status at baseline was associated with worse DFS in IMmotion010

Baseline



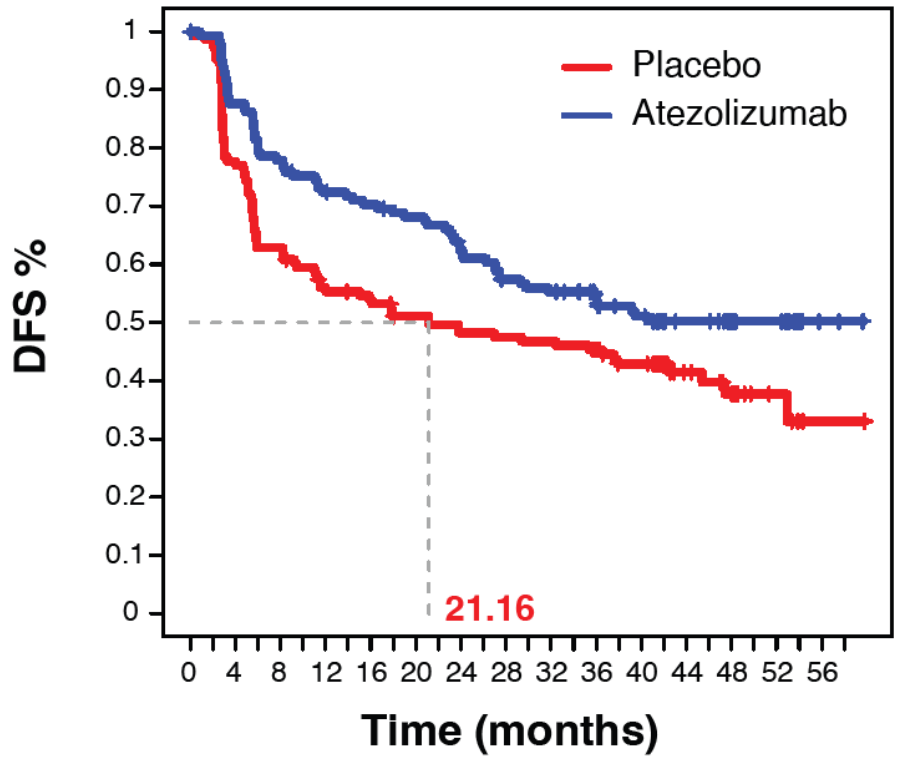
	n	Median DFS (months)	HR[a] (95% CI)
KIM-1^{High}	300	35.88	1.75 (1.40, 2.17)
KIM-1^{Low}	452	57.23	

[a] HR stratified by pathologic disease stage and geographic region.

Atezolizumab improved DFS vs Placebo in the baseline KIM-1^{High} subgroup

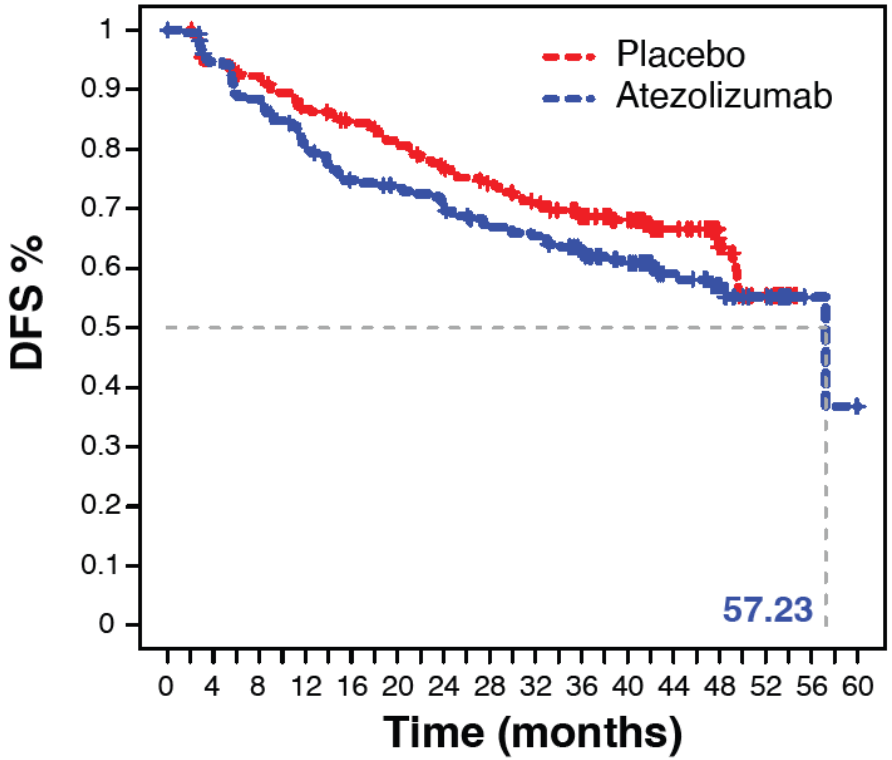
Baseline

KIM-1^{High} subgroup



	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

KIM-1^{Low} subgroup

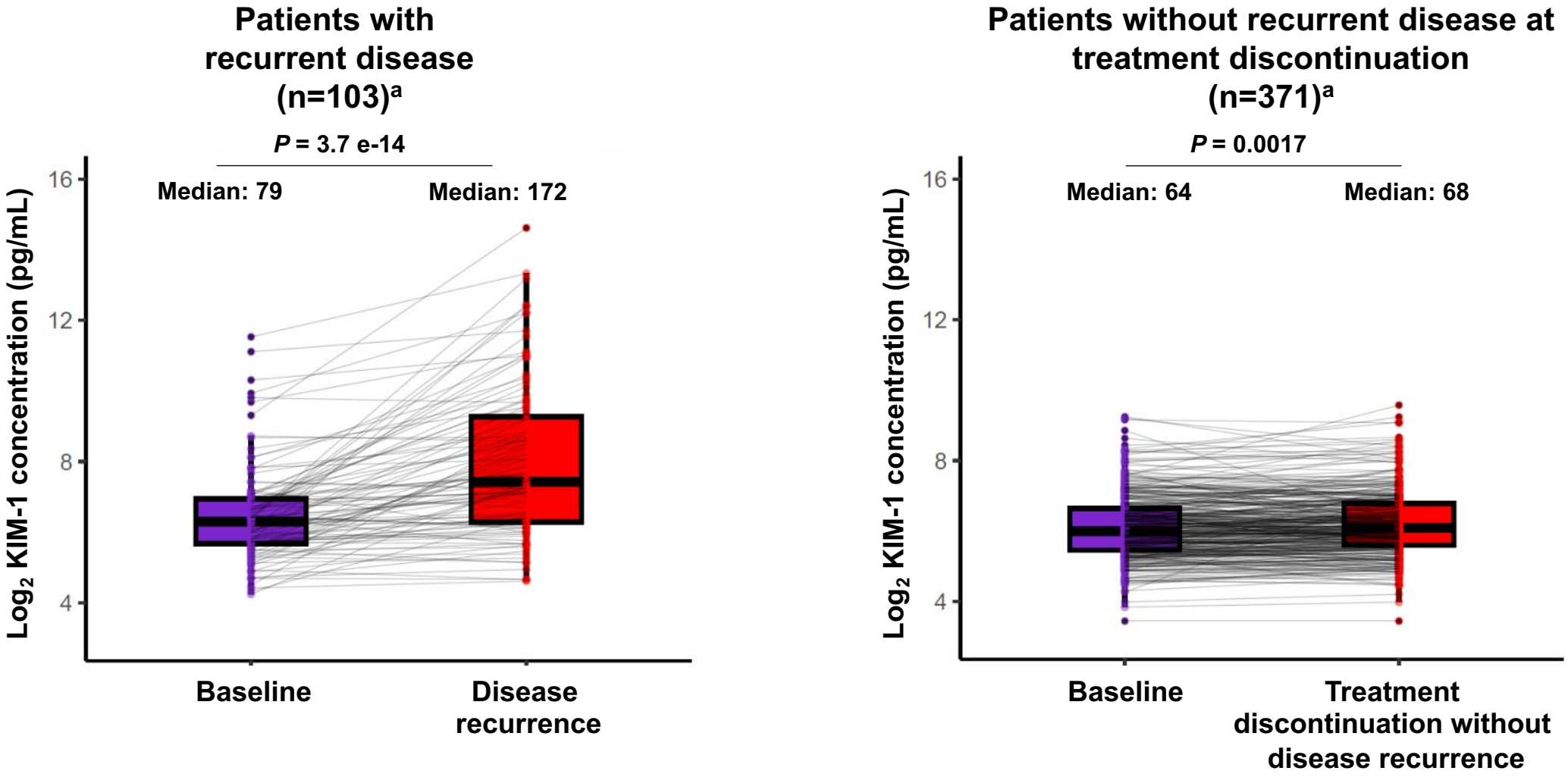


	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

[a] HR stratified by pathologic disease stage and geographic region.

Serum KIM-1 levels increased at time of disease recurrence vs baseline

Disease Recurrence/ Treatment Discontinuation



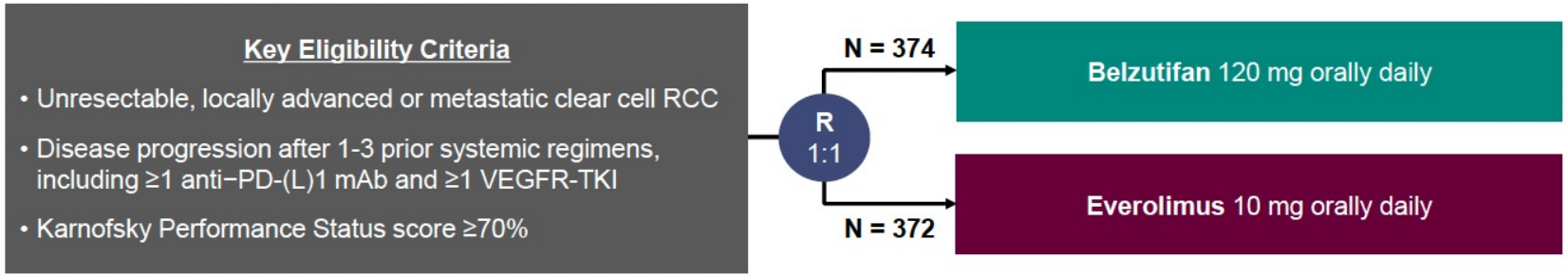
[a] Analysis conducted in patients with matched samples at baseline and at disease recurrence or at treatment discontinuation without disease recurrence (approximately 1 year or 16 treatment cycles)

Where Are We Now?

Belzutifan for RCC in 2024 and Beyond

RTP
RESEARCH
TO PRACTICE

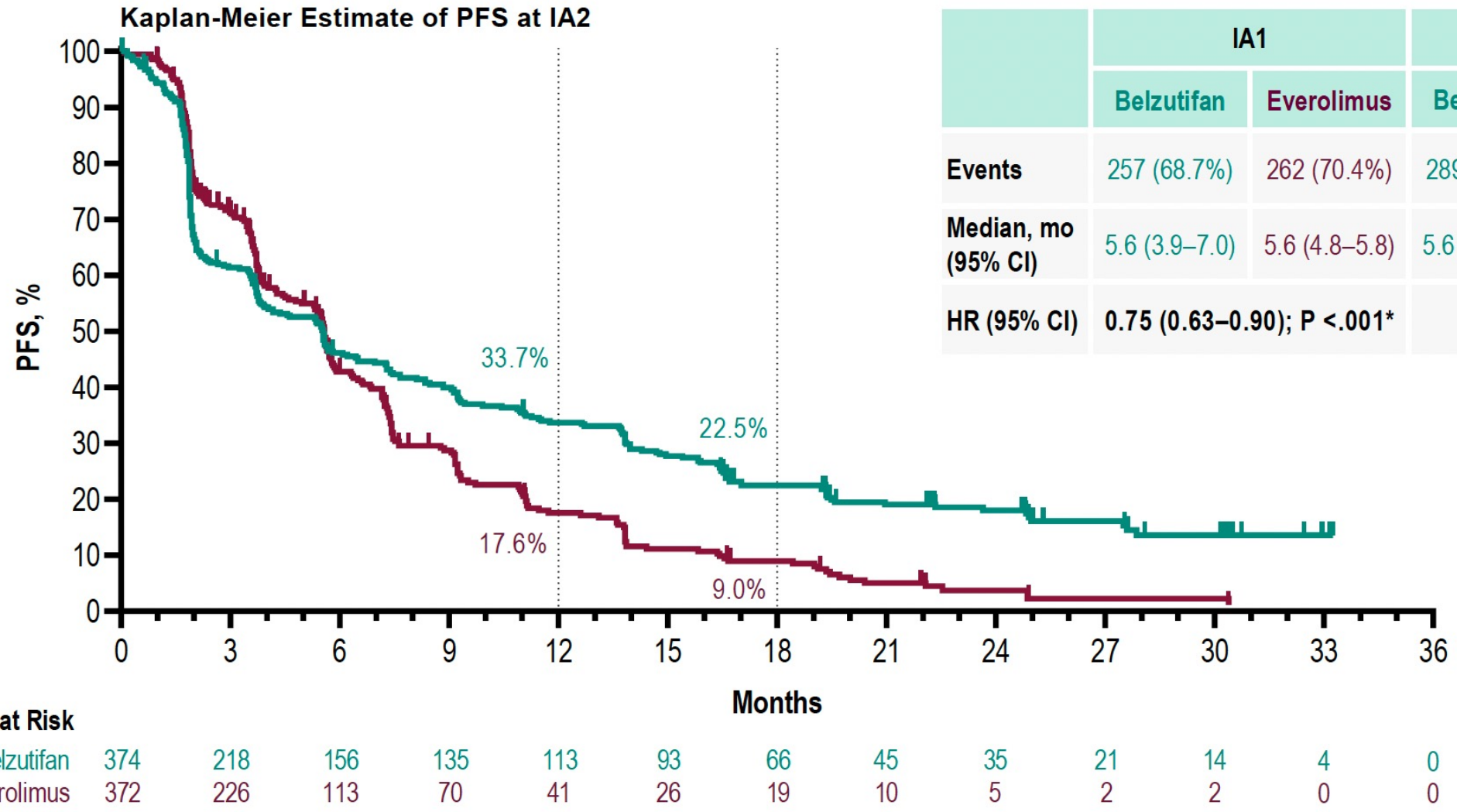
Belzutifan versus Everolimus for Previously Treated Advanced ccRCC: Randomized Open-Label Phase III LITESPARK-005 Study



	Belzutifan (N = 374)	Everolimus (N = 372)
Age, median (range), yrs	62 (22–90)	63 (33–87)
Male	79.4%	76.3%
KPS score[a]		
90/100	63.6%	64.5%
70/80	36.1%	35.2%
IMDC risk categories		
Favorable	21.1%	22.3%
Intermediate	66.6%	65.6%
Poor	12.3%	12.1%
Sarcomatoid features		
Yes	11.2%	8.3%
No/Unknown/Missing	88.8%	91.7%
Prior nephrectomy	69.8%	69.6%
# Prior VEGF/VEGFR-TKIs		
1	50.0%	51.1%
2-3	50.0%	48.9%
# Prior lines of therapy[b]		
1	12.3%	14.0%
2	42.0%	44.6%
3	45.2%	40.3%

Albiges L et al. ESMO 2023;Abstract LBA88.

LITESPARK-005: Primary Endpoint of PFS by BICR



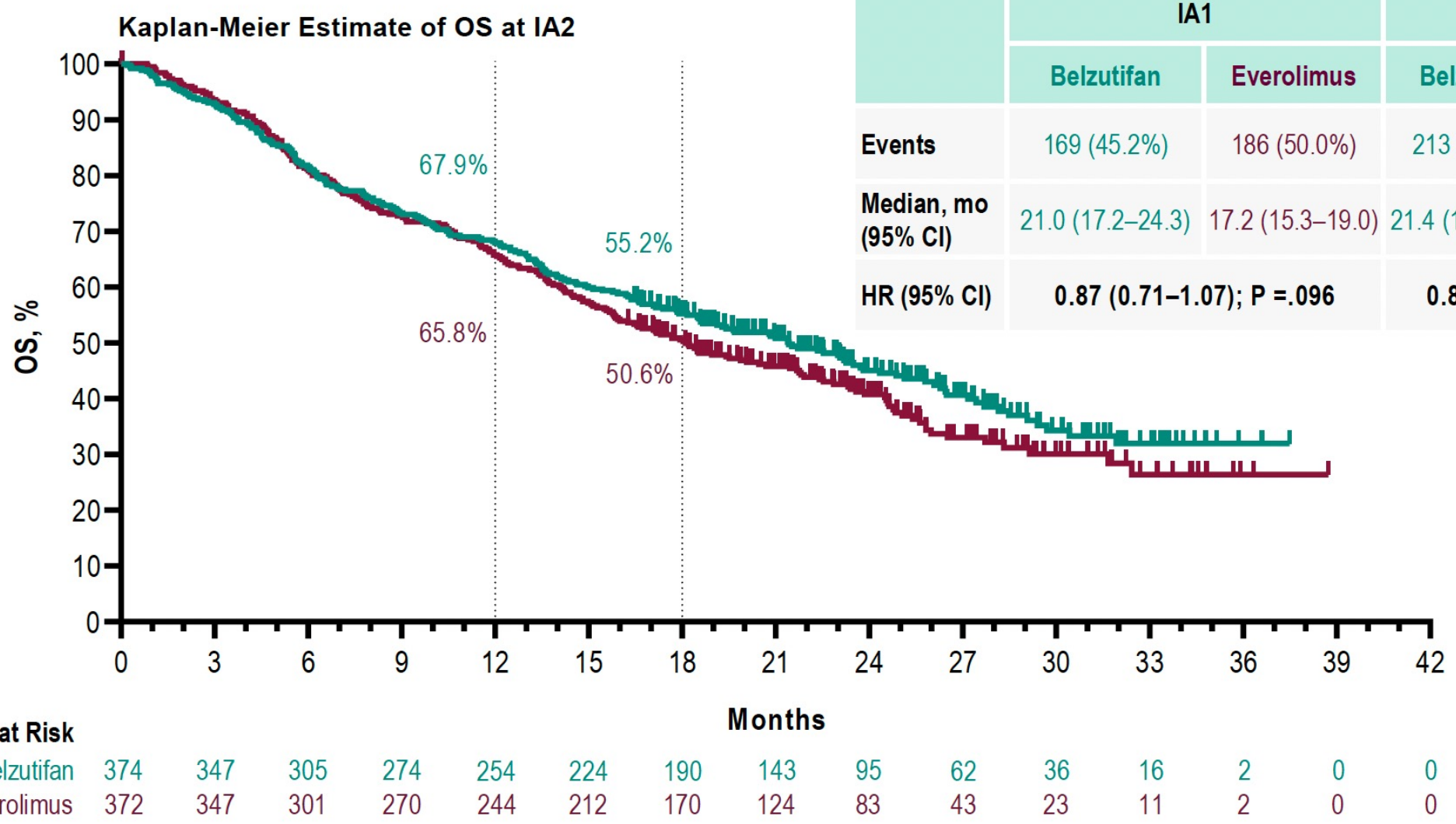
	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

PFS = progression-free survival; BICR = blinded independent central review;
IA = interim analysis

Albiges L et al. ESMO 2023;Abstract LBA88.

RTP RESEARCH TO PRACTICE

LITESPARK-005: Primary Endpoint of Overall Survival (OS)

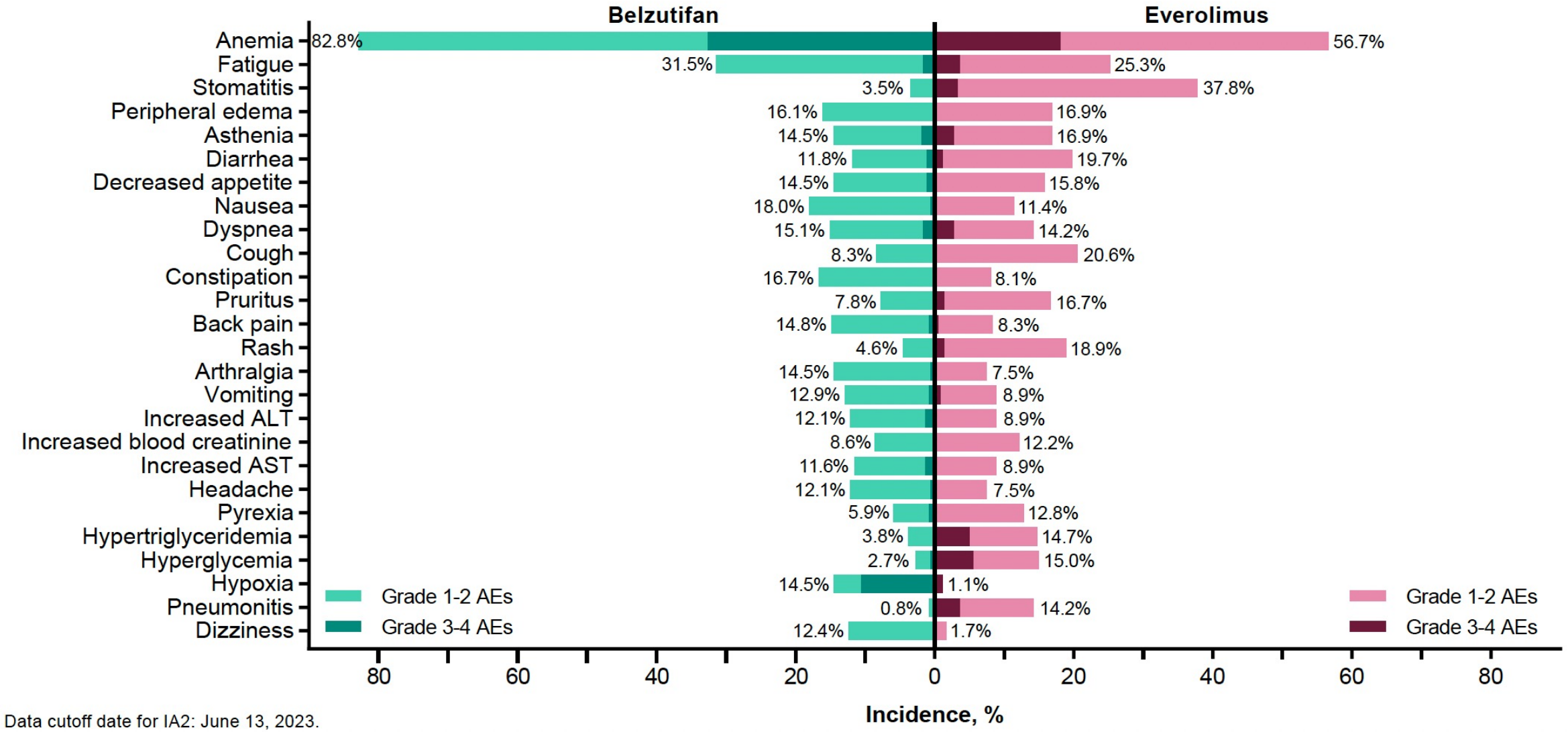


	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Albiges L et al. ESMO 2023;Abstract LBA88.

RTP RESEARCH TO PRACTICE

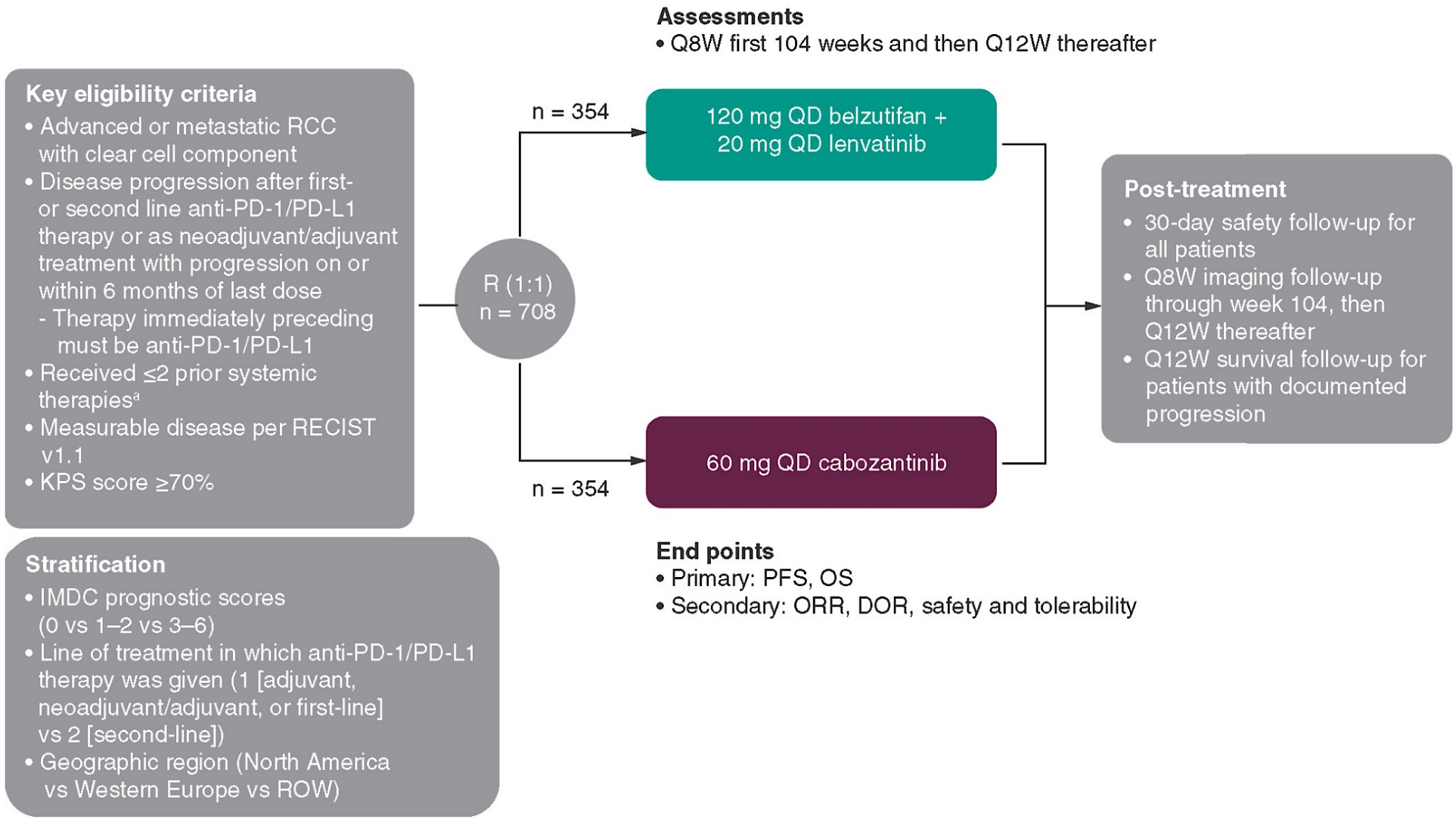
LITESPARK-005: Safety Profile



Data cutoff date for IA2: June 13, 2023.

Albiges L et al. ESMO 2023;Abstract LBA88.

LITESPARK-011: Belzutifan and Lenvatinib versus Cabozantinib for Advanced Renal Cell Carcinoma After Anti-PD-1/PD-L1 Therapy

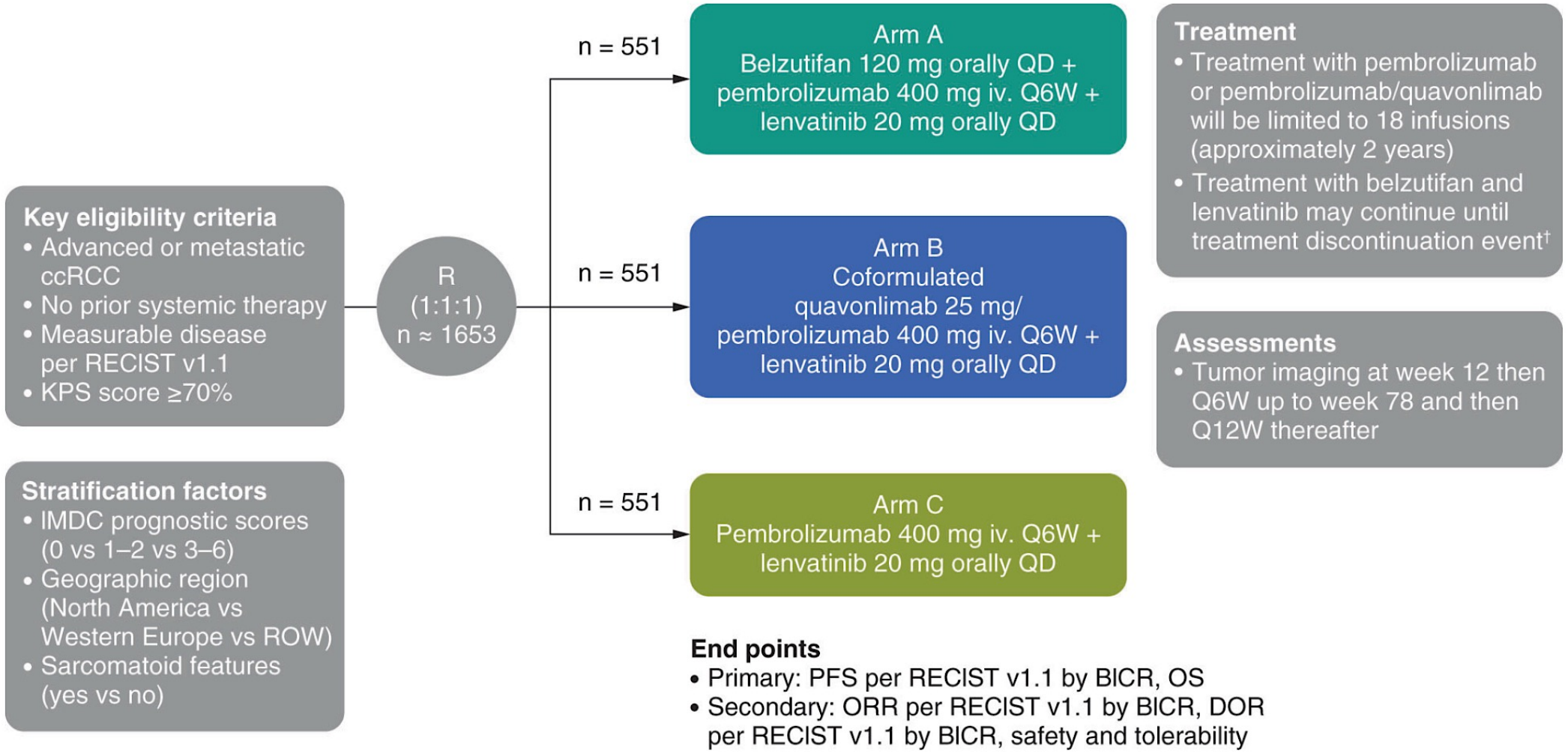


RCC = renal cell carcinoma; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; DOR = duration of response

Motzer RJ et al. *Future Oncol* 2023;19(2):113-21.

RTP RESEARCH TO PRACTICE

LITESPARK-012: Pembrolizumab and Lenvatinib with or without Belzutifan or Quavonlimab for Advanced Renal Cell Carcinoma



ccRCC = clear cell renal cell carcinoma; PFS = progression-free survival; BICR = blinded independent central review; OS = overall survival; ORR = objective response rate; DOR = duration of response

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

RTP RESEARCH TO PRACTICE

Health-related quality of life with nivolumab subcutaneous or intravenous in patients with advanced or metastatic clear cell renal cell carcinoma who have received prior therapy in the phase 3 CheckMate 67T trial

Saby George,[1] Maria T. Bourlon,[2] Matt Dixon,[3] Jennifer Lord-Bessen,[3] Gill Worthy,[4] Katie Frampton,[4] Christine Yip,[5] Rachael Lawrance,[4] Fiona Taylor,[5] Laurence Albigès[6]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [3]Bristol Myers Squibb, Princeton, NJ; [4]Adelphi Values, Bollington, Cheshire, UK; [5]Adelphi Values, Boston, MA; [6]Gustave Roussy, Villejuif, France

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

R 1:1

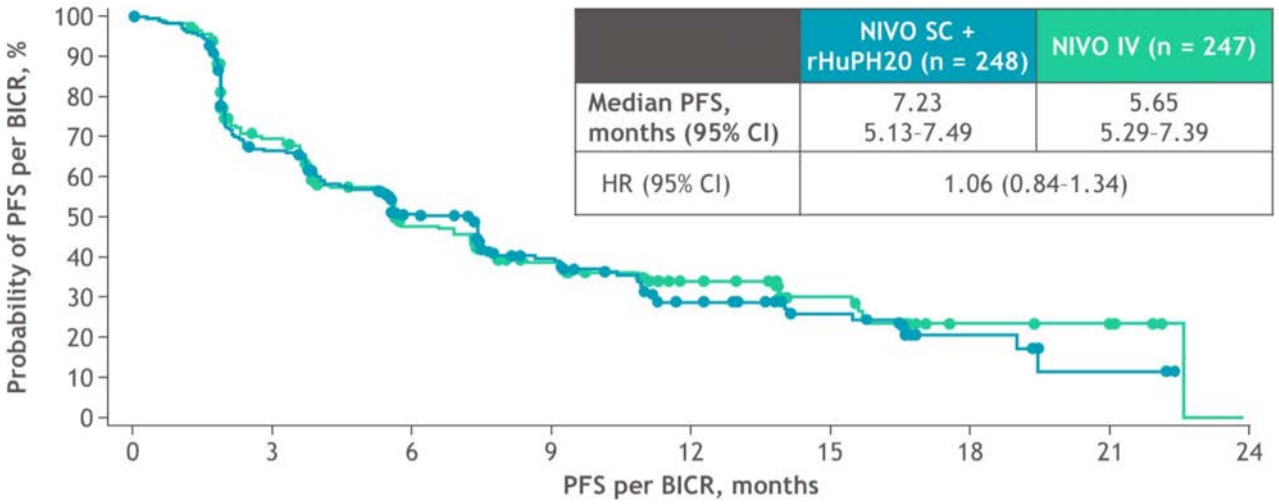
- NIVO SC 1200 mg + rHuPH20 Q4W (n = 248)
- NIVO IV 3 mg/kg Q2W (n = 247)

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

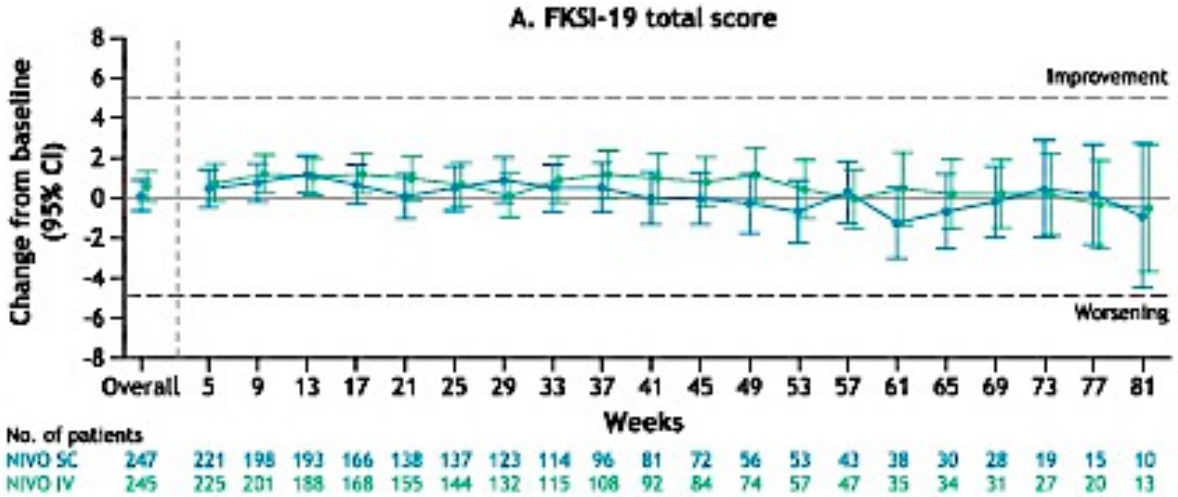
Key stratification factors
- IMDC risk group
- Baseline weight

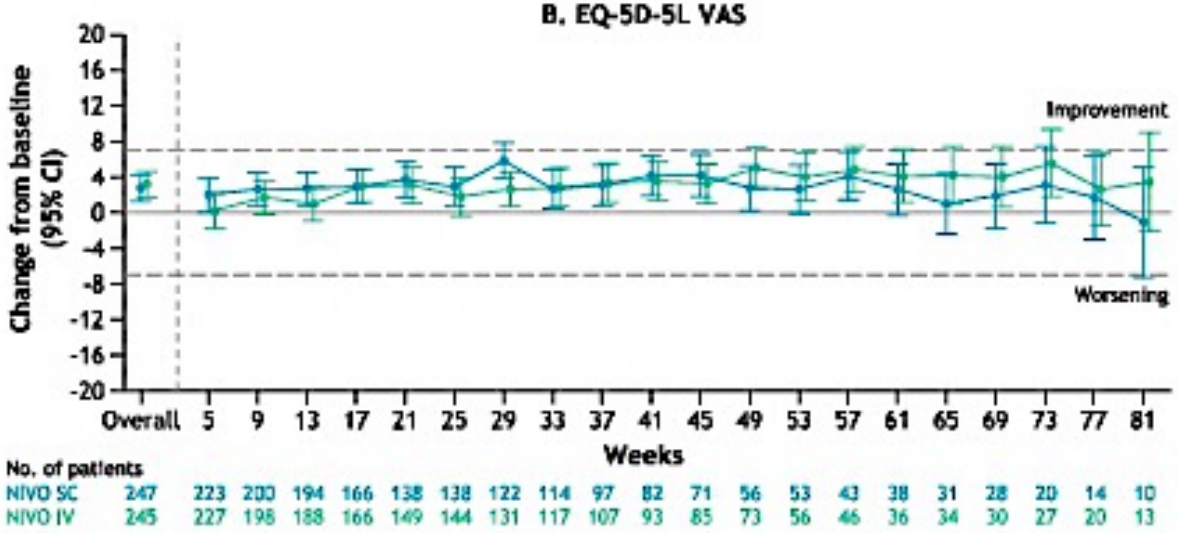
- Patients were enrolled across 73 sites in 17 countries[a]
- Minimum follow-up was 8 months

Exploratory endpoints:
- FKSI-19 to assess kidney-related HRQoL
- EQ-5D-5L to assess patients' health status



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





George S et al. ASCO 2024; Abstract 4535.
George S et al. ASCO 2024; Abstract LBA360.

Phase III CheckMate 67T Study: Safety Summary

- Safety was consistent between NIVO IV and NIVO SC
  - Rates of AEs, TRAEs, SAEs, TRSAEs, AEs leading to discontinuation, and TRAEs leading to discontinuation for SC arm were similar or lower than IV arm
  - Study drug toxicity led to 3 deaths in the NIVO SC arm and 1 death in the NIVO IV arm
  - Local site reactions in the NIVO SC arm were low grade, transient (mean duration, 3.02 days), and most resolved without treatment
  - No anaphylactic reactions were observed in either arm

n (%)	NIVO SC + rHuPH20 (n = 247)		NIVO IV (n = 245)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
AE	230 (93.1)	87 (35.2)	229 (93.5)	100 (40.8)
TRAE	146 (59.1)	24 (9.7)	158 (64.5)	36 (14.7)
AE leading to discontinuation	25 (10.1)	18 (7.3)	29 (11.8)	21 (8.6)
TRAE leading to discontinuation	10 (4.0)	6 (2.4)	12 (4.9)	9 (3.7)
SAE	69 (27.9)	52 (21.1)	71 (29.0)	56 (22.9)
TRSAE	17 (6.9)	16 (6.5)	17 (6.9)	16 (6.5)
Select AEs				
Hypersensitivity/infusion-related reactions	3 (1.2)	1 (0.4)	9 (3.7)	0
Local site reactions	20 (8.1)	0	5 (2.0)	0

AE, adverse event; IV, intravenous; NA, not applicable; NIVO, nivolumab; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious adverse event; SC, subcutaneous; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

George S et al. ASCO 2024;Abstract LBA360.

Phase III CheckMate 67T: Most Common Adverse Events (AEs)

n (%)	NIVO SC + rHuPH20 (n = 247)		NIVO IV (n = 245)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
AE	230 (93.1)	87 (35.2)	229 (93.5)	100 (40.8)
Arthralgia	29 (11.7)	1 (0.4)	39 (15.9)	1 (0.4)
Fatigue	19 (7.7)	2 (0.8)	39 (15.9)	5 (2.0)
Diarrhea	24 (9.7)	1 (0.4)	33 (13.5)	1 (0.4)
Hyperglycemia	23 (9.3)	6 (2.4)	32 (13.1)	5 (2.0)
Decreased appetite	22 (8.9)	0	28 (11.4)	2 (0.8)
Back pain	19 (7.7)	2 (0.8)	27 (11.0)	4 (1.6)
Oedema peripheral	11 (4.5)	1 (0.4)	24 (9.8)	2 (0.8)
Nausea	20 (8.1)	0	22 (9.0)	0
Hypokalemia	17 (6.9)	6 (2.4)	21 (8.6)	1 (0.4)
Abdominal pain	16 (6.5)	0	16 (6.5)	1 (0.4)

George S et al. ASCO 2024;Abstract LBA360.

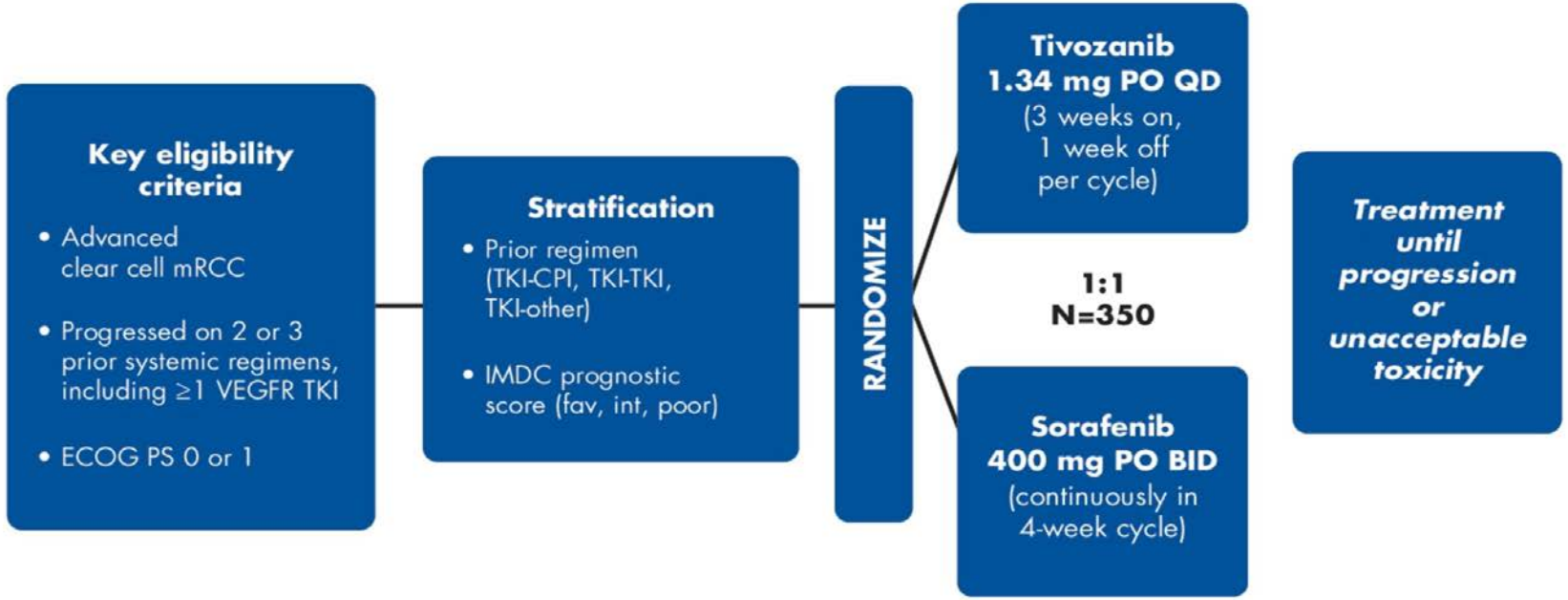
Questions?

RTP
RESEARCH
TO PRACTICE

TIVO-3 Study: Tivozanib (TIVO) versus Sorafenib for Relapsed/Refractory Advanced RCC

- TIVO-3 (NCT02627963) is a phase 3, global, open-label, parallel-arm study comparing TIVO with SOR in patients with R/R advanced mRCC (**Figure 1**)

Figure 1. TIVO-3 Study Design

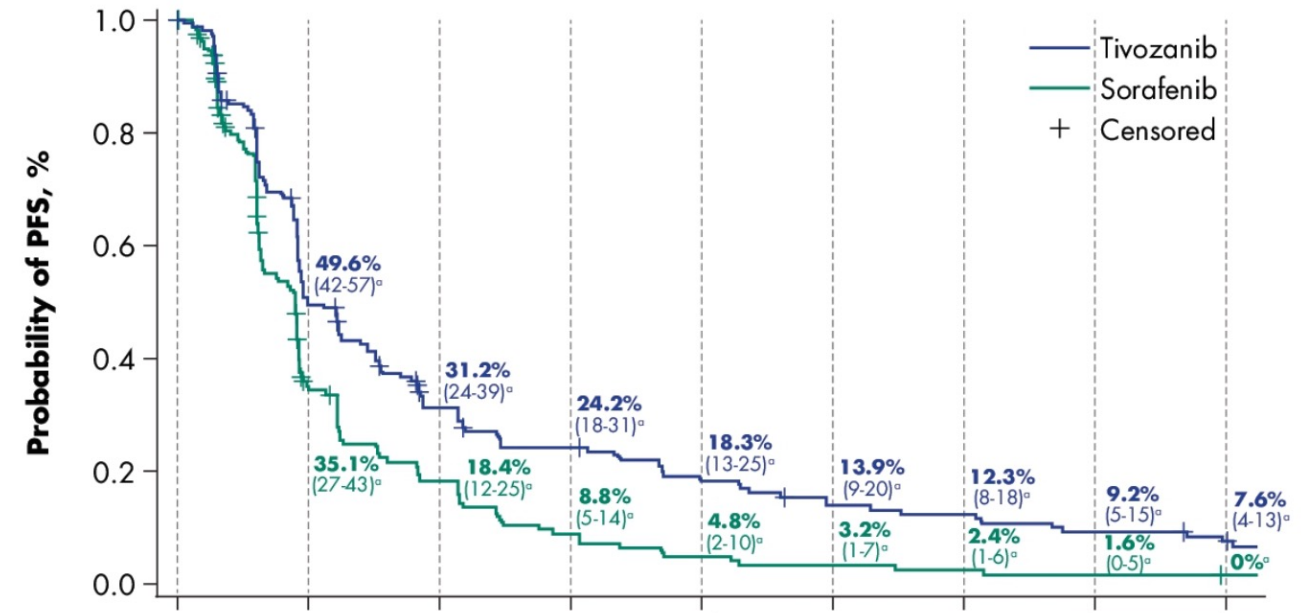


BID, twice daily; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; fav, favorable; IMDC, International Metastatic RCC Database Consortium; int, intermediate; mRCC, metastatic renal cell carcinoma; PO, oral; QD, once daily; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Atkins MB et al. Genitourinary Cancers Symposium 2022;Abstract 362.

Long-Term PFS from TIVO-3: Tivozanib (TIVO) versus Sorafenib for Relapsed/Refractory Advanced RCC

Figure 2. Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR



LT-PFS Δ (TIVO–SOR)	0%	14.5%	12.8%	15.4%	13.5%	10.7%	9.9%	7.6%	7.6%
Odds ratio (TIVO:SOR)	N/A	1.81	2.02	3.32	4.46	4.88	5.73	N/Aᵇ	N/Aᵇ

HR, 0.624 (95% CI, 0.49-0.79); log-rank *P*<.0001

Atkins MB et al. Genitourinary Cancers Symposium 2022;Abstract 362.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Prof Powles

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr McKay

Module 3: ASCO 2024

Where Are We Now?

Adjuvant Treatment of RCC in 2024

Treatment Approaches for Nonmetastatic RCC and Optimal Care of Patients with Non-Clear Cell RCC

Rana R. McKay, MD, FASCO

Associate Professor of Medicine and Urology

Associate Director, Clinical Sciences

Interim Associate Director, Translational Sciences

Co-Lead, Genitourinary Oncology Program

University of California San Diego – Moores Cancer Center

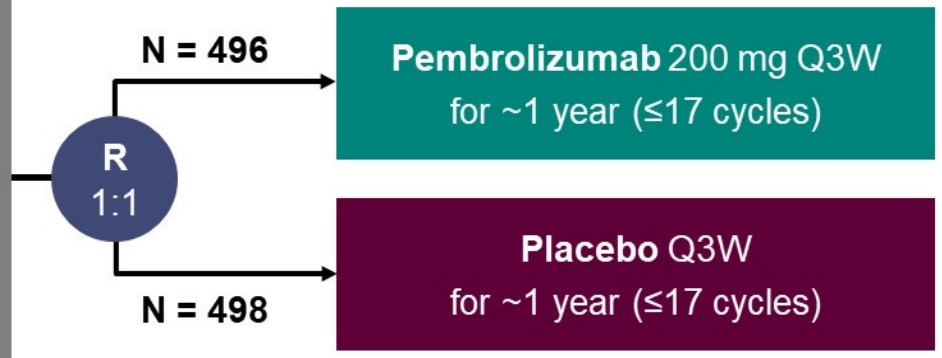
La Jolla, California

Nonmetastatic RCC

Phase III KEYNOTE-564 Trial of Adjuvant Pembrolizumab for Clear Cell RCC: Study Design

Key Eligibility Criteria

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



Stratification Factors

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

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

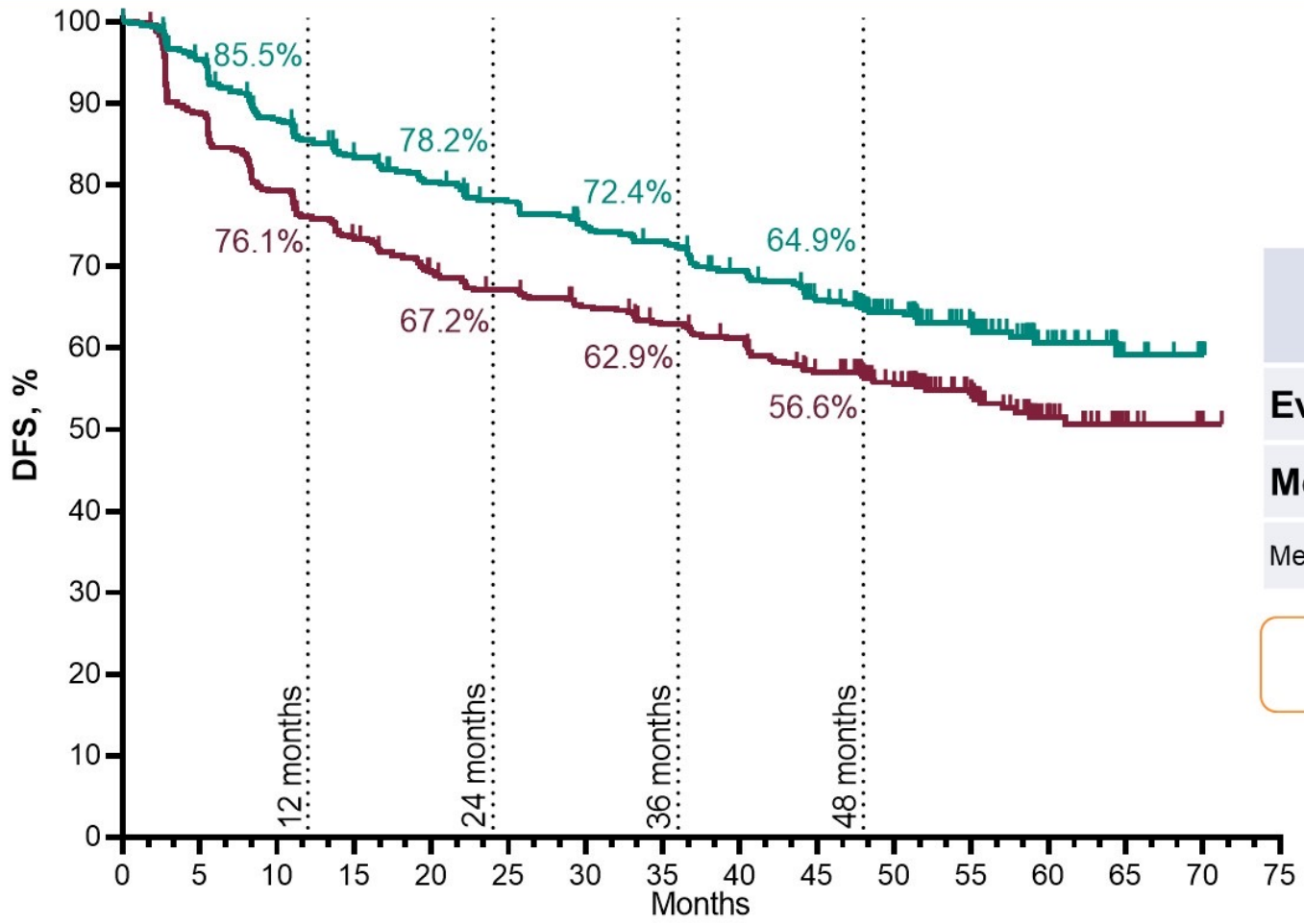
- Overall survival

Other Secondary Endpoints

- Safety

Choueiri TK et al. ASCO 2024; Abstract LBA359

KEYNOTE-564: Investigator-Assessed DFS in the ITT Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

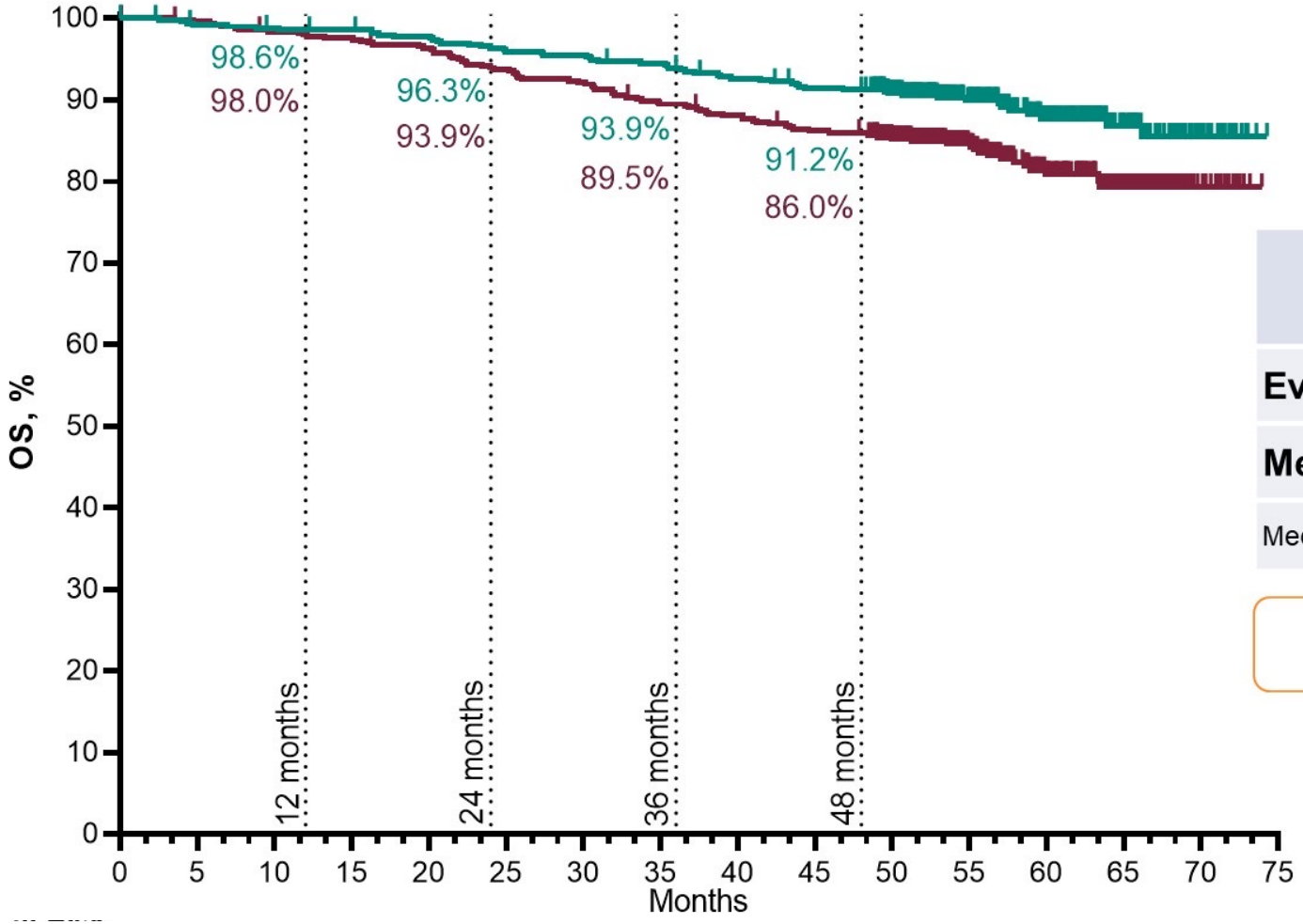
HR 0.72 (95% CI 0.59–0.87)

DFS = disease-free survival; ITT = intention to treat

Choueiri TK et al. ASCO 2024;Abstract LBA359.

RTP RESEARCH TO PRACTICE

KEYNOTE-564: OS in the ITT Population



38% reduction in risk of death with adjuvant pembrolizumab versus placebo

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

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

* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function.

OS = overall survival; ITT = intention to treat

Choueiri TK et al. ASCO 2024;Abstract LBA359.

RTP RESEARCH TO PRACTICE

KEYNOTE-564: Safety

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

Safety findings did not change substantially from last analysis

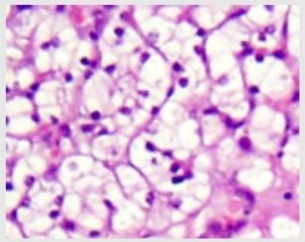
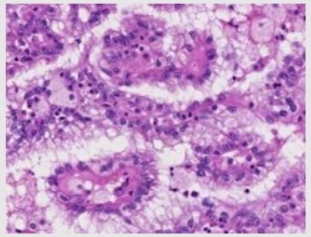
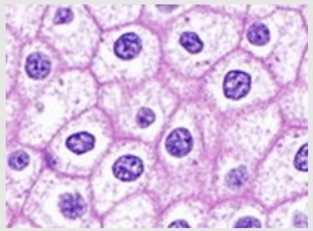
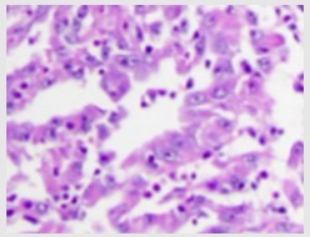
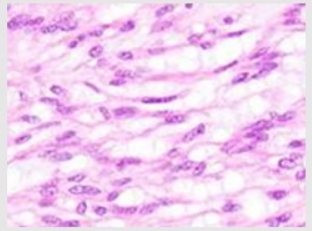
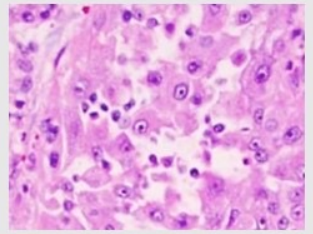
Choueiri TK et al. ASCO 2024;Abstract LBA359.

Where Are We Now?

First-Line Therapy for Advanced Non-Clear Cell RCC in 2024

Non-Clear Cell Renal Cell Carcinoma (nccRCC)

Variant Renal Cell Carcinoma Histologies

Clear Cell	Papillary	Chromophobe	Collecting Duct	Mucinous Tubular	Unclassified
					
Proximal Tubule	Proximal and Distal Tubules	Distal Tubule Intercalated Cells	Collecting Duct	Proximal Tubule	-
80%	15-20%	5%	1-2%	<1%	4-5%
VHL, chr 3p	MET, chr 7, FH	PTEN, TP53, MTOR, TSC 1/2	NF2, CDKN2A/B, SMARCB1	chr loss and gain	NF2,SETD2, BAP1
5-year OS 81%	5-year OS 82%	5-year OS 91%	5-year OS 44%	Favorable	5-year OS 60%

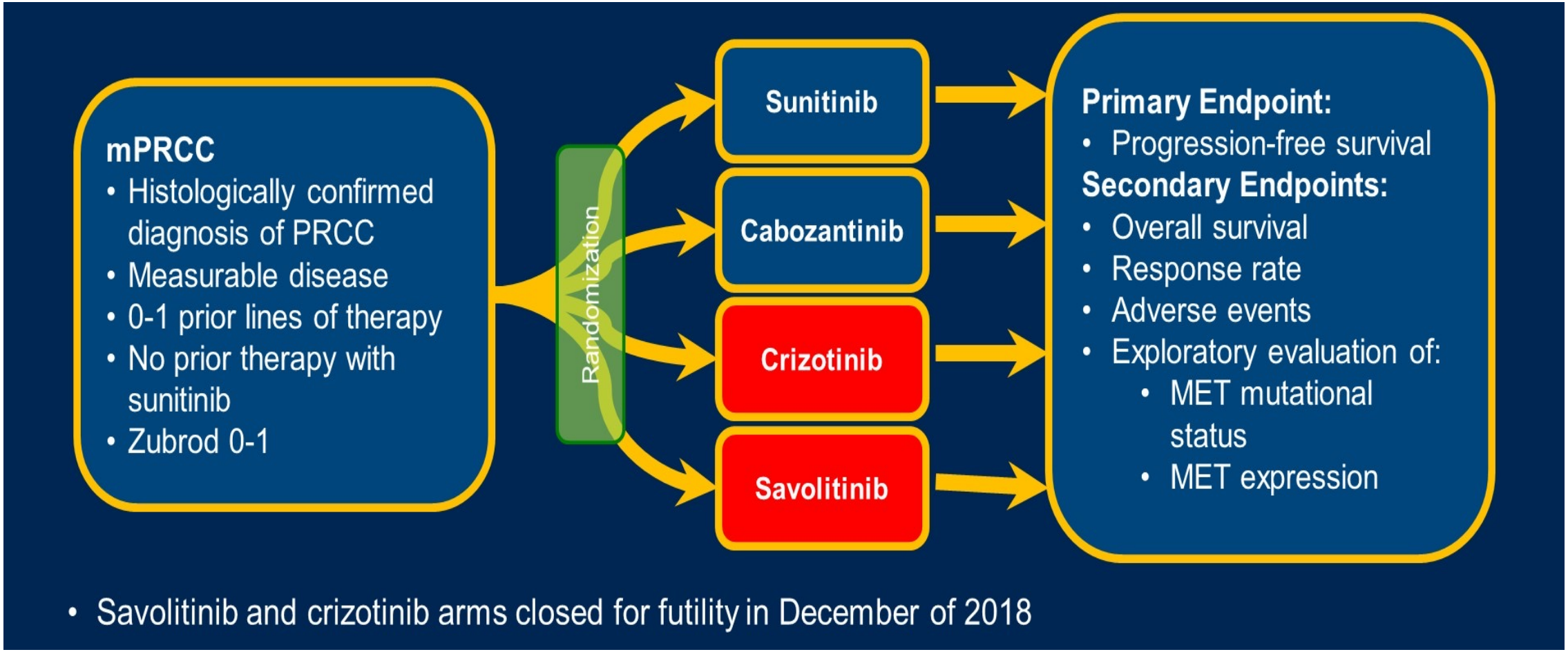
OS=Overall survival. *5-year OS for patients with localized disease.

Moch et al, Eur Urol, 2022

McKay RR et al. Genitourinary Cancers Symposium 2024.

RTP RESEARCH TO PRACTICE

Phase II SWOG-1500 Trial of Sunitinib versus Cabozantinib, Crizotinib or Savolitinib for Advanced Papillary RCC: Study Design



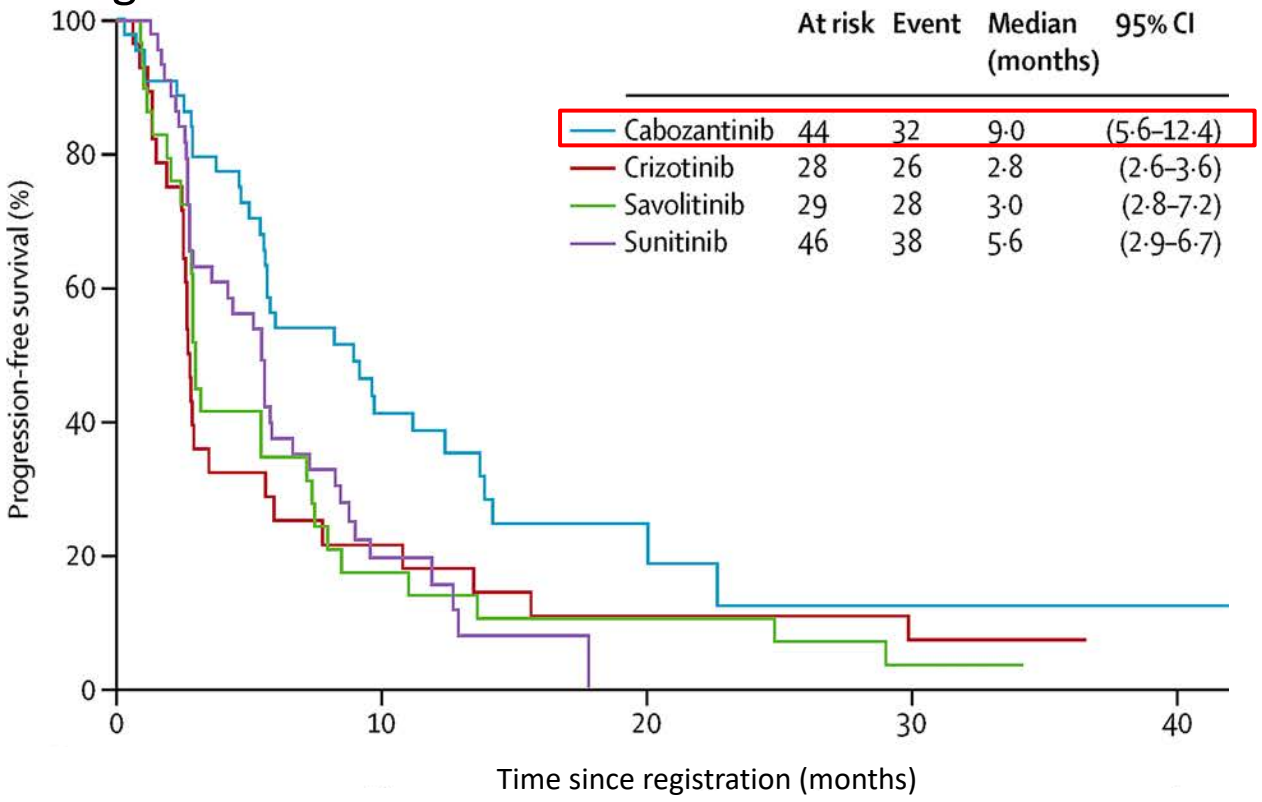
mPRCC = metastatic papillary RCC

Pal SK et al. Genitourinary Cancers Symposium 2021;Abstract 270.

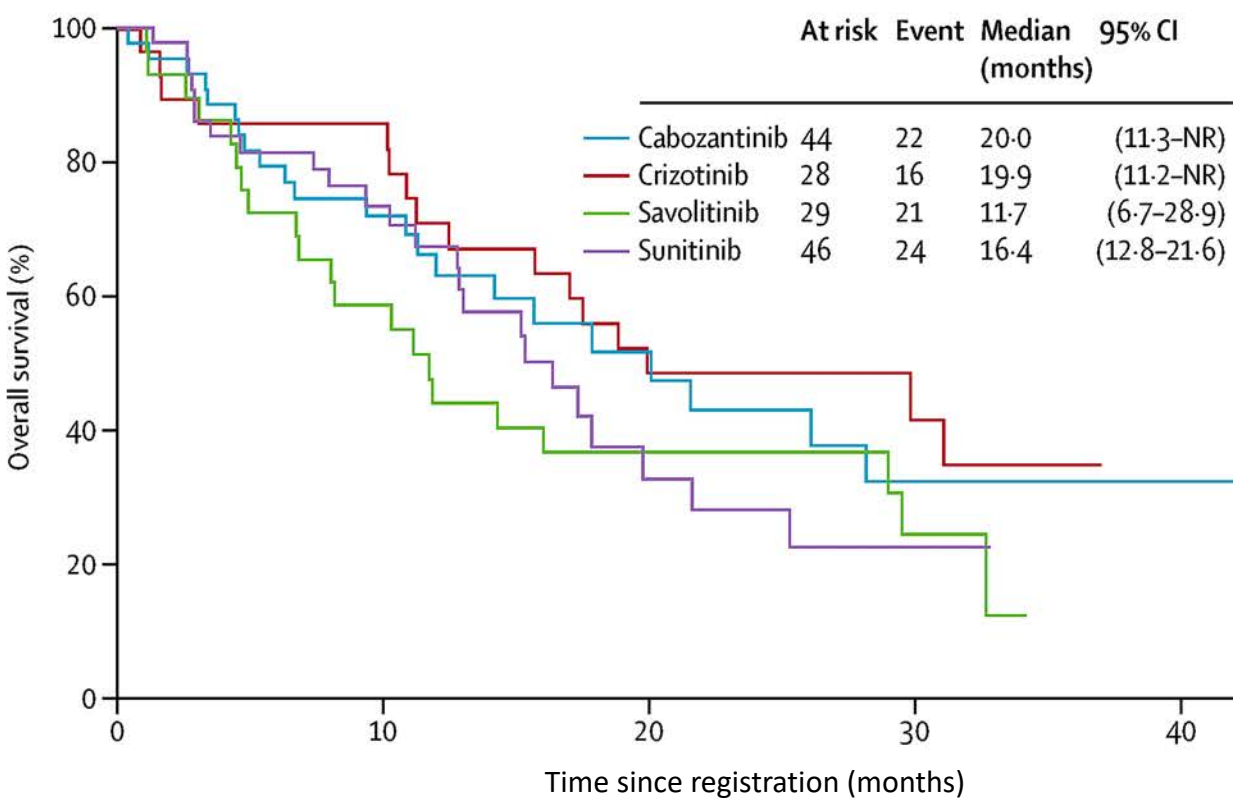
RTP RESEARCH TO PRACTICE

Phase II SWOG-1500 Study: Survival Outcomes

Progression-free survival



Overall survival

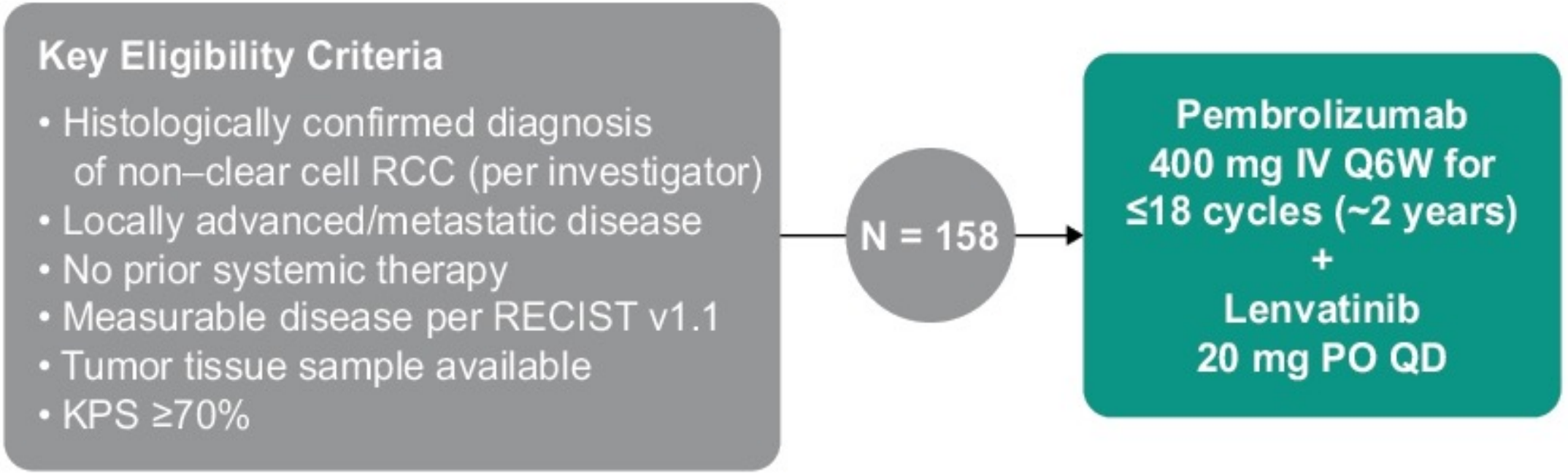


- Cabozantinib treatment resulted in significantly longer PFS compared with sunitinib for patients with metastatic PRCC. Savolitinib and crizotinib did not improve PFS compared to sunitinib. No significant differences in overall survival were observed between treatment groups.

Pal SK et al. *Lancet* 2021;397:695-703.

RTP RESEARCH TO PRACTICE

KEYNOTE-B61: A Phase II Trial of Pembrolizumab with Lenvatinib as First-Line Therapy for Advanced nccRCC



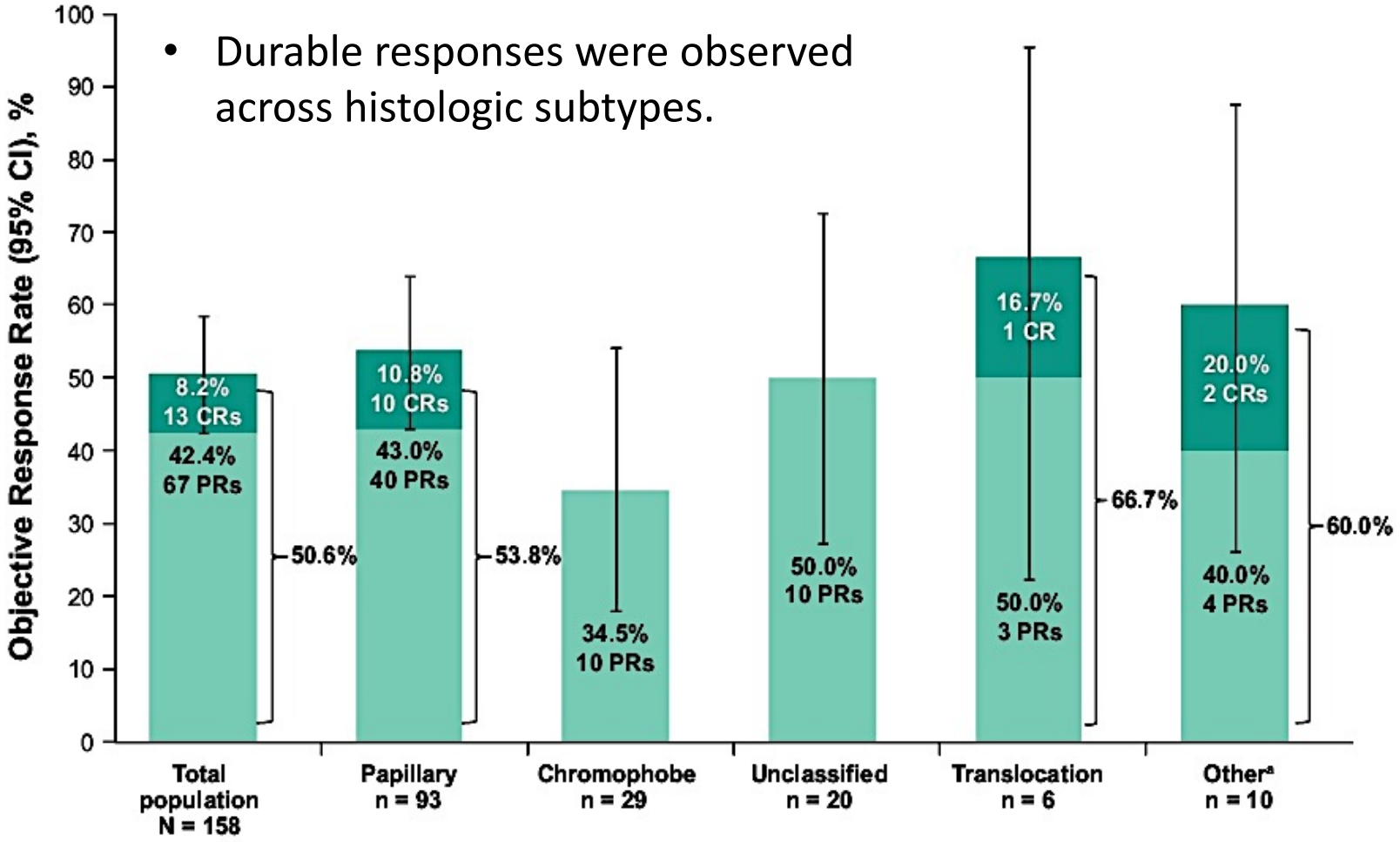
Primary endpoint: ORR per RECIST v1.1 by BICR

ORR = objective response rate

Voss MH et al. Genitourinary Cancers Symposium 2024;Abstract 2.

KEYNOTE-B61: Responses

- Durable responses were observed across histologic subtypes.



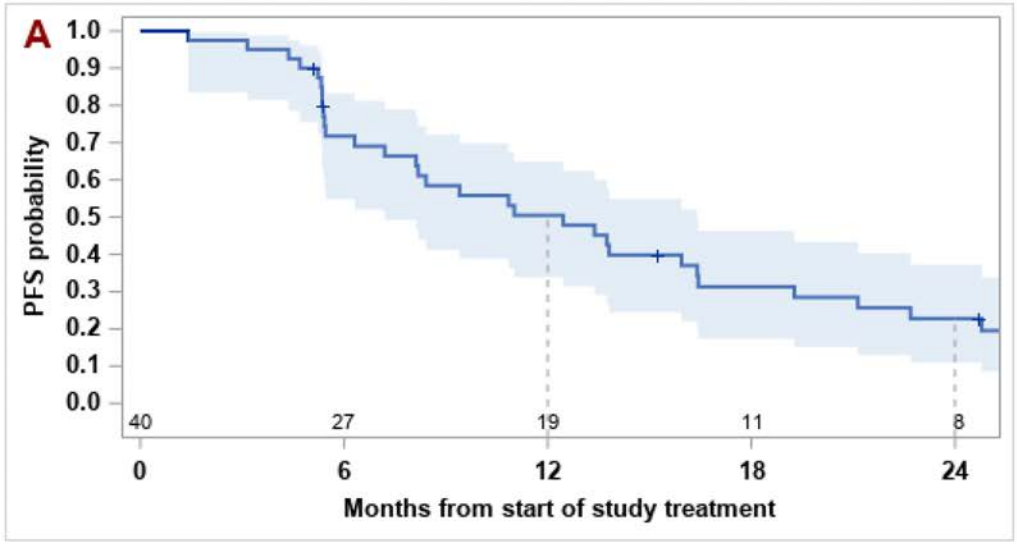
	Pembrolizumab + lenvatinib N = 158
ORR, % (95% CI)	50.6 (42.6-58.7)
DCR,[a] % (95% CI)	82.3 (75.4-87.9)
CBR,[b] % (95% CI)	71.5 (63.8-78.4)
Best overall response, n (%)	
CR	13 (8.2)
PR	67 (42.4)
SD	50 (31.6)
SD ≥6 months	33 (20.9)
PD	17 (10.8)
NE/NA[c]	11 (7.0)

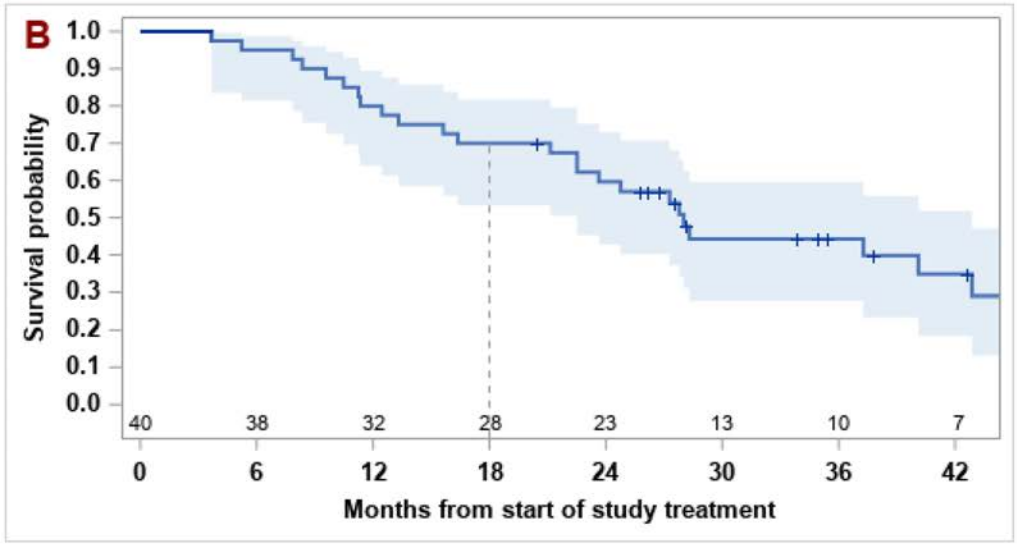
Voss MH et al. Genitourinary Cancers Symposium 2024;Abstract 2.

CA209-9KU: A Phase II Study of Cabozantinib and Nivolumab for nccRCC

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)

CI = confidence interval; ORR = objective response rate; NE = not estimable; PFS = progression-free survival; TA-RCC = translocation-associated renal cell carcinoma; UCP = unclassified without papillary features.





Fitzgerald KN et al. *Eur Urol May* 22 2024;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Phase II CA209-9KU Study: Safety

Symptomatic AEs

Adverse event	Patients, *n* (%)	
	All grades	Grade 3–4
Fatigue	28 (70)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	27 (68)	2 (5.0)
Diarrhea	25 (63)	3 (7.5)
Dry mouth	19 (48)	0 (0)
Hypertension	17 (43)	5 (13)
Mucositis oral	14 (35)	0 (0)
Nausea	14 (35)	1 (2.5)
Hoarseness	12 (30)	0 (0)
Dry skin	11 (28)	0 (0)
Dyspnea	11 (28)	0 (0)
Constipation	10 (25)	0 (0)
Gastroesophageal reflux disease	10 (25)	0 (0)
Headache	10 (25)	0 (0)
Pruritus	10 (25)	0 (0)
Back pain	9 (23)	0 (0)
Cough	9 (23)	0 (0)
Anorexia	8 (20)	0 (0)
Arthralgia	8 (20)	0 (0)
Dysgeusia	8 (20)	0 (0)
Rash maculopapular	8 (20)	0 (0)
Nasal congestion	7 (18)	0 (0)
Vomiting	7 (18)	0 (0)
Weight loss	7 (18)	0 (0)

Laboratory AEs

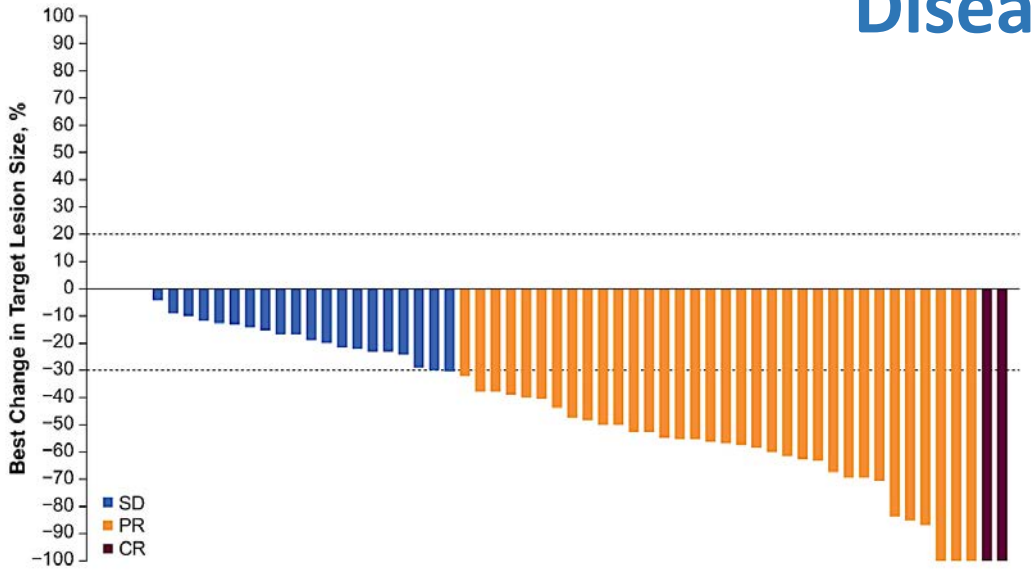
Adverse event	Patients, *n* (%)	
	All grades	Grade 3–4
Aspartate aminotransferase increased	36 (90)	5 (13)
Alanine aminotransferase increased	28 (70)	6 (15)
Hypophosphatemia	26 (65)	13 (33)
Serum amylase increased	19 (48)	7 (18)
Lipase increased	16 (40)	6 (15)
Hypomagnesemia	11 (28)	1 (2.5)
Alkaline phosphatase increased	10 (25)	0 (0)
Platelet count decreased	7 (18)	0 (0)
Lymphocyte count decreased	6 (15)	2 (5.0)

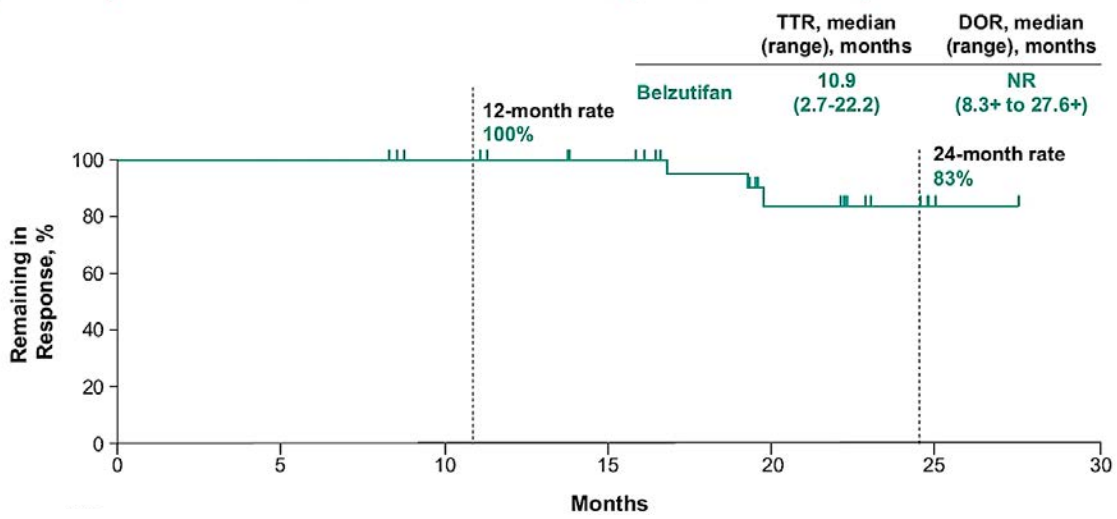
- There were no major differences observed in the known safety profile of cabozantinib with nivolumab.

Fitzgerald KN et al. *Eur Urol May* 22 2024;[Online ahead of print].

RTP RESEARCH TO PRACTICE

LITESPARK-004 Trial: Belzutifan for von Hippel-Lindau (VHL) Disease – RCC Cohort





	RCC N = 61
ORR, n (%) [95% CI]	36 (59) [45.7-71.4]
Best objective response, n (%)	
CR	2 (3)
PR	34 (56)
SD	24 (39)
PD	0 (0)
Nonevaluable	1 (2)

CR, complete response; PR, partial response; SD, stable disease.

- From the previous data cutoff date of December 12, 2020 to the current data cutoff date of July 15, 2021, the confirmed objective response rate in VHL disease-associated RCC increased from 49% to 59%, including 2 CRs

Jonasch E et al. ASCO 2022;Abstract 4546.

RTP RESEARCH TO PRACTICE

LITESPARK-004: Treatment-Related Adverse Events (TRAEs) with Incidence ≥10% Among All Patients

TRAE	Any grade	Grade 3[a,b]
Any	61 (100)	10 (16)
Anemia	54 (89)	6 (10)
Fatigue	37 (61)	3 (5)
Dizziness	15 (25)	0 (0)
Nausea	14 (23)	0 (0)
Headache	11 (18)	0 (0)
Dyspnea	10 (16)	0 (0)
Myalgia	8 (13)	0 (0)
Alanine aminotransferase increased	6 (10)	0 (0)

- No new safety signals emerged with additional follow-up.
- Anemia was the most common TRAE (primarily Grade 1-2)
- No Grade 4 or 5 TRAEs occurred.

Jonasch E et al. ASCO 2022;Abstract 4546.

RTP RESEARCH TO PRACTICE

Questions?

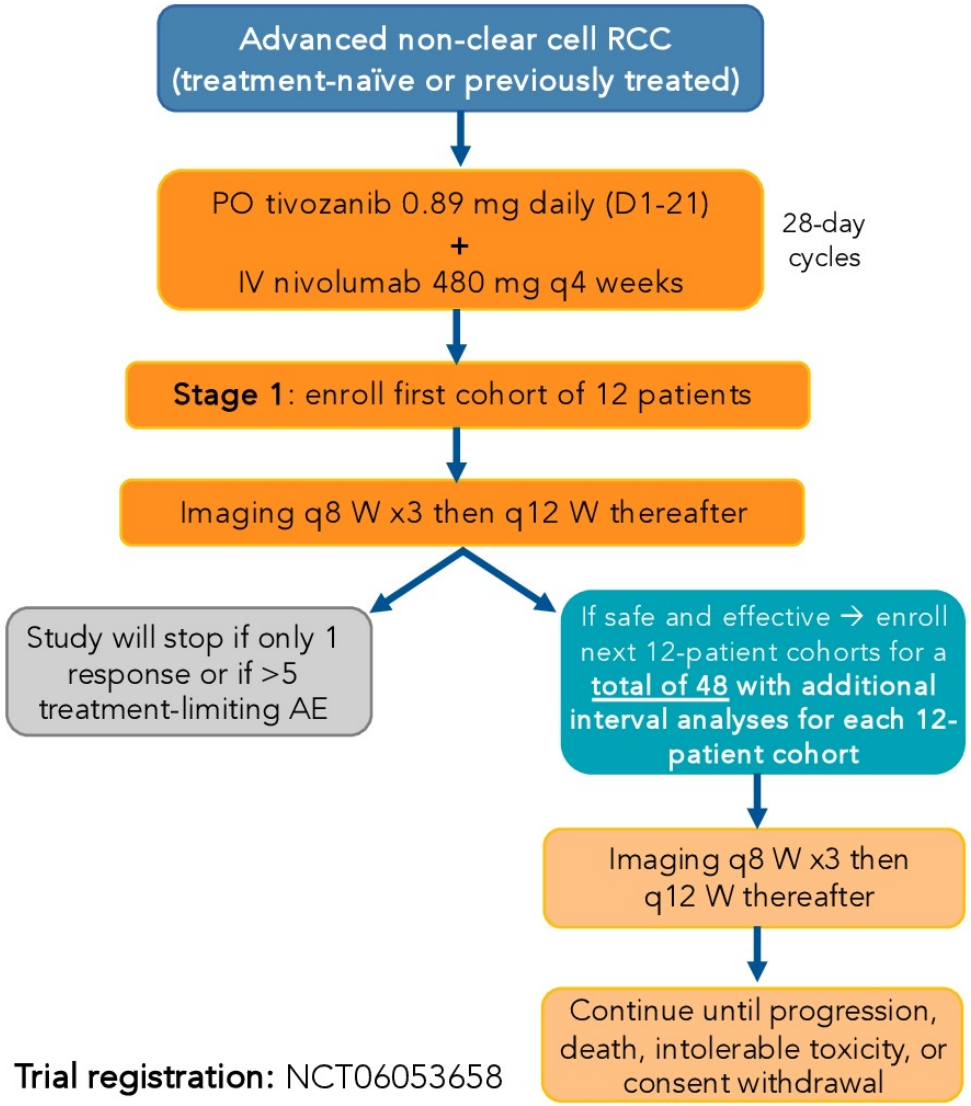
RTP
RESEARCH
TO PRACTICE

FORTUNE: A Single-Arm Phase II Study of Tivozanib and Nivolumab for Patients with Advanced nccRCC

STUDY ENDPOINTS

Primary:
- Objective response rate (ORR) per RECIST 1.1

Secondary:
- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of therapy
- Adverse events (AE) per CTCAE v5.0



Trial registration: NCT06053658

Nguyen CB et al. ASCO 2024;Abstract TPS4612.

RTP RESEARCH TO PRACTICE

Phase III STELLAR-304 Trial: Zanzalintinib with Nivolumab

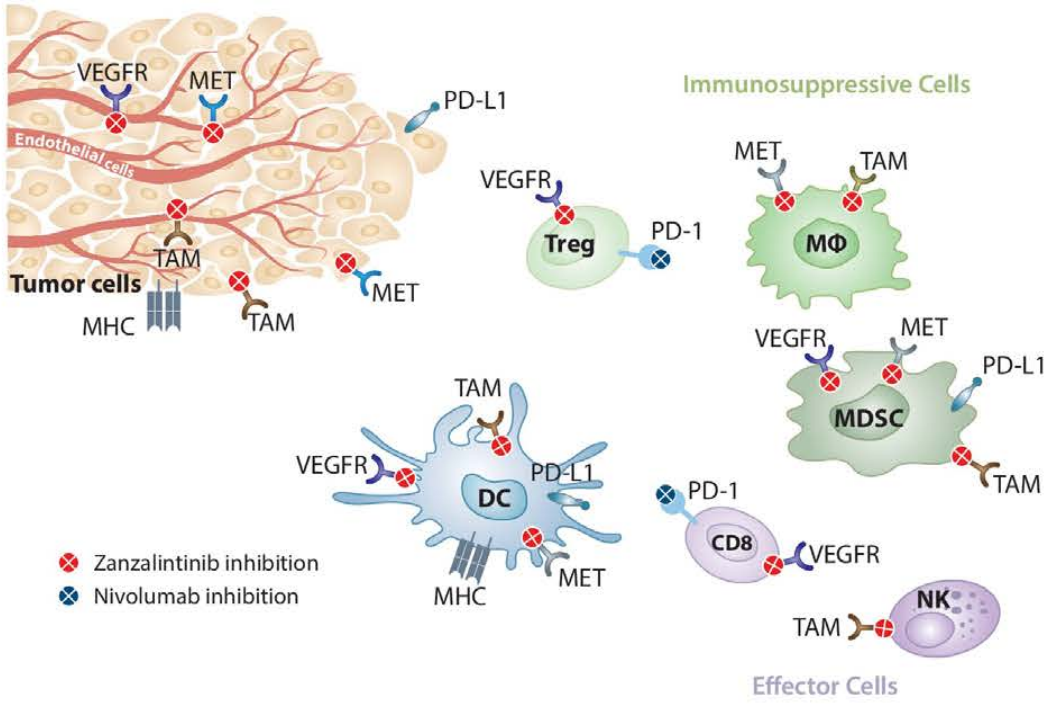
Previously untreated advanced nccRCC (papillary, unclassified, and translocation-associated)

N≈291

R2:1

- **Zanzalintinib + Nivolumab**
- **Sunitinib**

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



VEGFR, MET, and TAM kinases promote tumorigenesis and angiogenesis in tumor cells

- Promote proliferation and survival of tumor cells
- Promote epithelial–mesenchymal transition leading to increased invasion and metastasis
- Promote endothelial proliferation, migration, and survival
- TAM and MET may act as compensatory mechanisms of VEGFR inhibition

VEGFR, MET, and TAM kinases promote an immunosuppressive tumor microenvironment

- Promote activity of Tregs, MDSCs, and MΦs
- Increase M2/M1 ratio of Mϕ
- Inhibit antigen presentation
- Inhibit T cell activation and limit anti-tumor T cell responses

Zanzalintinib and nivolumab combination

- Zanzalintinib inhibits VEGFR, MET, and TAM kinases and may enhance the activity of nivolumab by promoting an immune-permissive tumor microenvironment
- Nivolumab binds to the PD-1 receptor on immune cells and blocks interactions with ligands, such as PD-L1, which restores T-cell activation and increases antitumor effects

Pal SK et al. ASCO 2024;Abstract TPS4611.

Conclusions

- Adjuvant pembrolizumab for patients with high-risk ccRCC
- First-line treatment options for advanced nccRCC
- Belzutifan for patients with VHL-associated RCC
- Novel therapies under investigation for nccRCC

Agenda

Module 1: Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Prof Powles

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr McKay

Module 3: ASCO 2024

RTP RESEARCH TO PRACTICE

Other ASCO 2024 Oral Abstracts on RCC

Doshi et al. A multi-institution analysis of outcomes with first-line systemic therapy for 99 patients with metastatic chromophobe renal cell carcinoma. ASCO 2024;Abstract 4512.

Pal et al. Preliminary safety, pharmacokinetics and clinical activity of DFF332, an oral HIF2a inhibitor, as monotherapy in a phase 1 dose escalation study in patients with advanced clear cell renal cell carcinoma. ASCO 2024;Abstract 4513.

Zarba et al. Systemic treatments in favorable and very favorable risk metastatic renal cell carcinoma (mRCC): Real world evidence from the International mRCC Database Consortium (IMDC). ASCO 2024;Abstract 4514.

Kashima et al. Investigation of T cell phenotypes associated with response or resistance to immune checkpoint inhibitors (ICI) through single-cell analysis of renal cell carcinoma (RCC). ASCO 2024;Abstract 4515.

What Clinicians Want to Know About the Management of Triple-Negative Breast Cancer

A CME/MOC-Accredited Live Webinar

Thursday, June 20, 2024
5:00 PM – 6:00 PM ET

Faculty

Kevin Kalinsky, MD, MS
Heather McArthur, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP
RESEARCH
TO PRACTICE