Clinical Investigator Perspectives on the Management of Renal Cell Carcinoma

Thursday, May 19, 2022

5:00 PM – 6:00 PM ET

Faculty

Thomas E Hutson, DO, PharmD
Brian I Rini, MD

Moderator

Neil Love, MD

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Commercial Support

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Dr Love — Disclosures

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Dr Hutson — Disclosures

No relevant conflicts of interest to disclose.

Dr Rini — Disclosures

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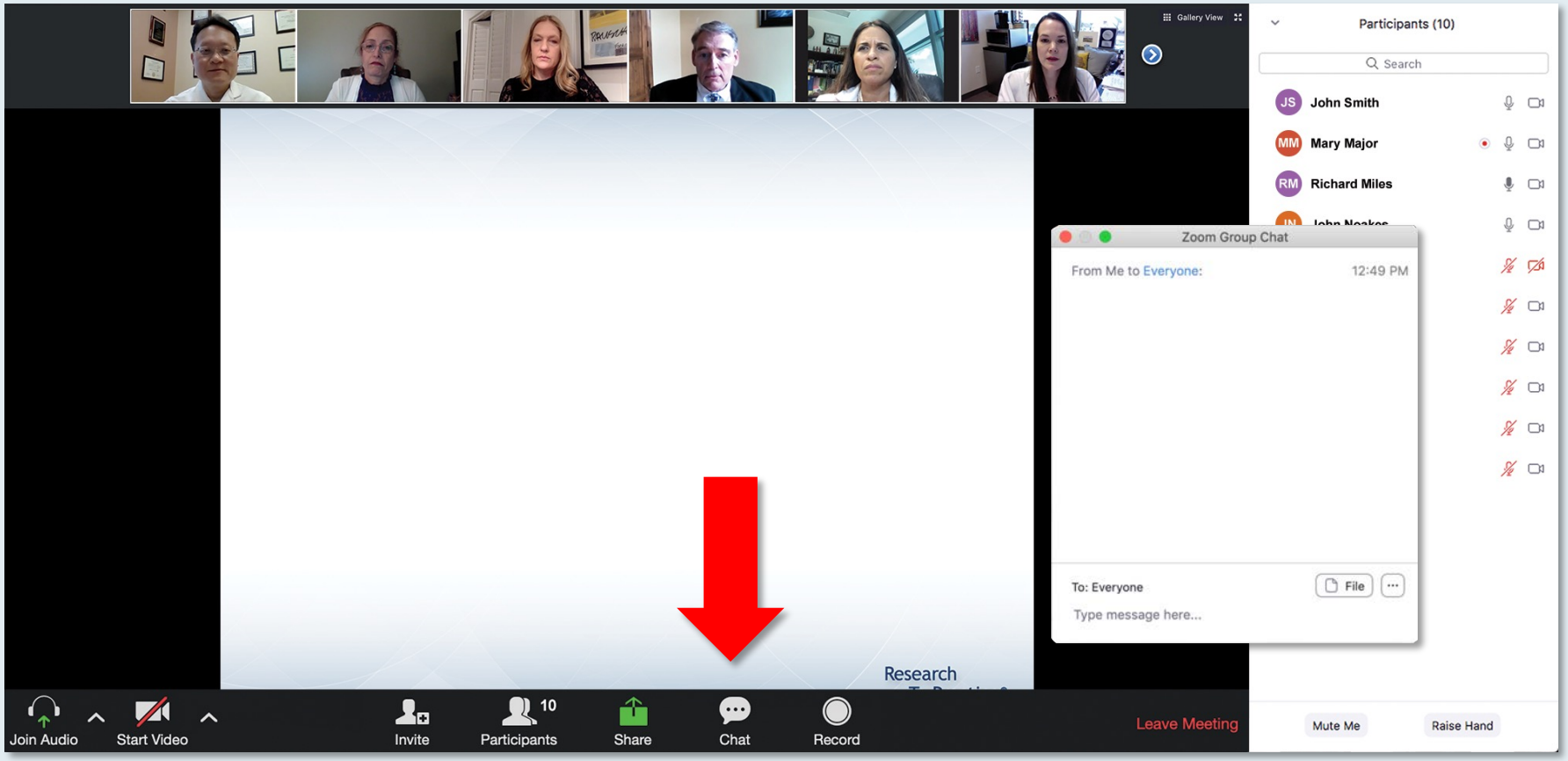
Contracted Research	Aravive Inc, Arrowhead Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Exelixis Inc, F Hoffmann-La Roche Ltd, Immunomedics Inc, Incyte Corporation, Janssen Biotech Inc, Merck, Mirati Therapeutics, Pfizer Inc, Pionyr Immunotherapeutics, Seagen Inc, Surface Oncology
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

We Encourage Clinicians in Practice to Submit Questions



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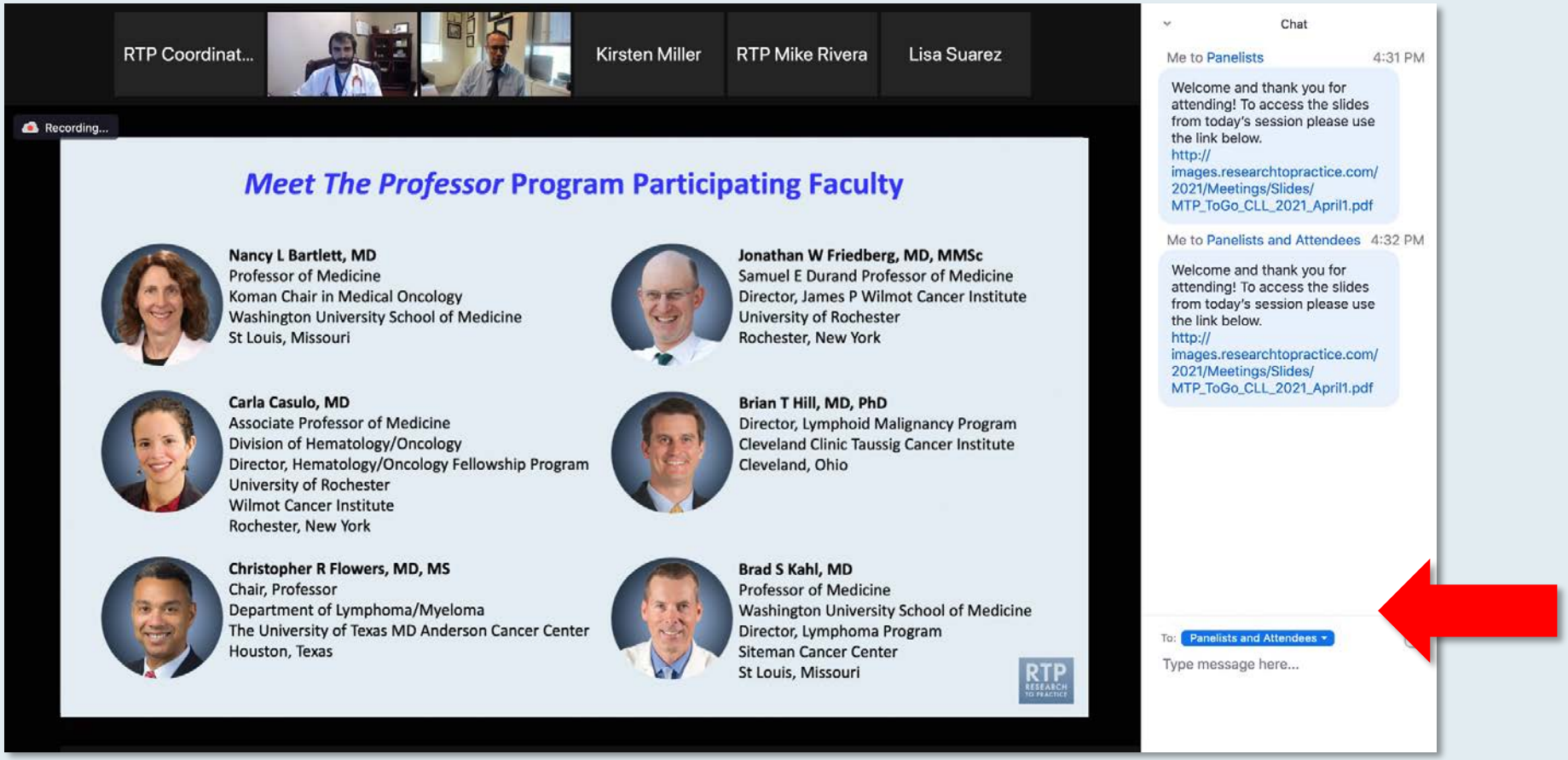

Drag the white line above the submission box up to create more space for your message.

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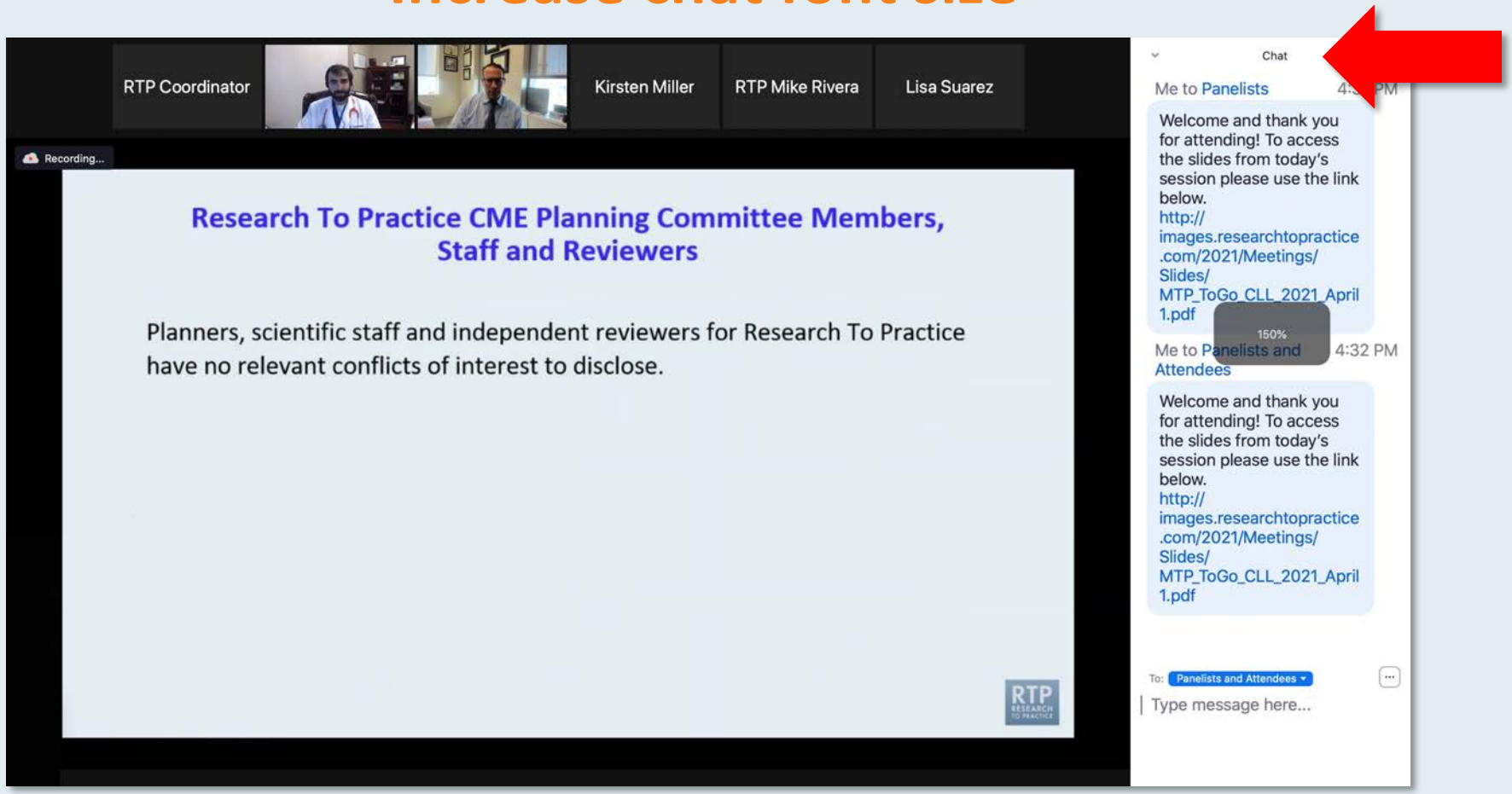

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Renal Cell Carcinoma

DR SUMANTA PAL

CITY OF HOPE COMPREHENSIVE CANCER CENTER

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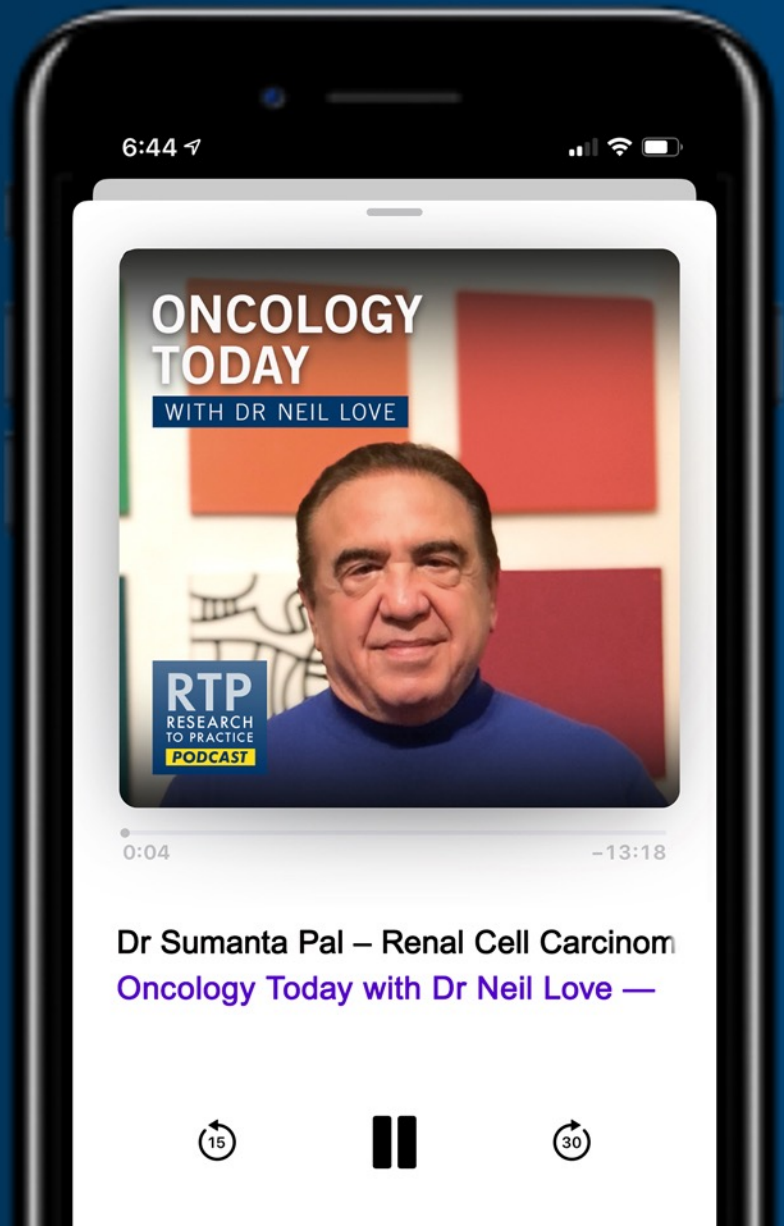

Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Tuesday, May 24, 2022
5:00 PM – 6:00 PM ET

Faculty

Susan O'Brien, MD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Myelofibrosis

Wednesday, May 25, 2022
5:00 PM – 6:00 PM ET

Faculty

John Mascarenhas, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Thursday, May 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Harry H Yoon, MD

Moderator

Neil Love, MD

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, June 3, 2022
11:45 AM – 12:45 PM CT (12:45 PM – 1:45 AM ET)

Faculty
Courtney D DiNardo, MD, MSCE
Michael R Savona, MD
Eunice S Wang, MD

Prostate Cancer

Saturday, June 4, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Andrew J Armstrong, MD, ScM
Alan H Bryce, MD
Alicia K Morgans, MD, MPH

Lung Cancer

Friday, June 3, 2022
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Faculty
Justin F Gainor, MD
Corey J Langer, MD
Luis Paz-Ares, MD, PhD
Heather Wakelee, MD
Jared Weiss, MD
Helena Yu, MD

Gastrointestinal Cancers

Saturday, June 4, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

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Ovarian Cancer

Sunday, June 5, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Antonio González-Martín, MD, PhD
Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

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6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

Thank you for joining us!

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

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Meet The Professor Program Participating Faculty

Thomas E Hutson, DO, PharmD
Director, GU Oncology Program
Co-Director, Urologic Cancer Research and Treatment Center
Texas Oncology
Charles A Sammons Cancer Center
Baylor University Medical Center
Professor of Medicine
Texas A&M HSC College of Medicine
Dallas, Texas

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

MODERATOR
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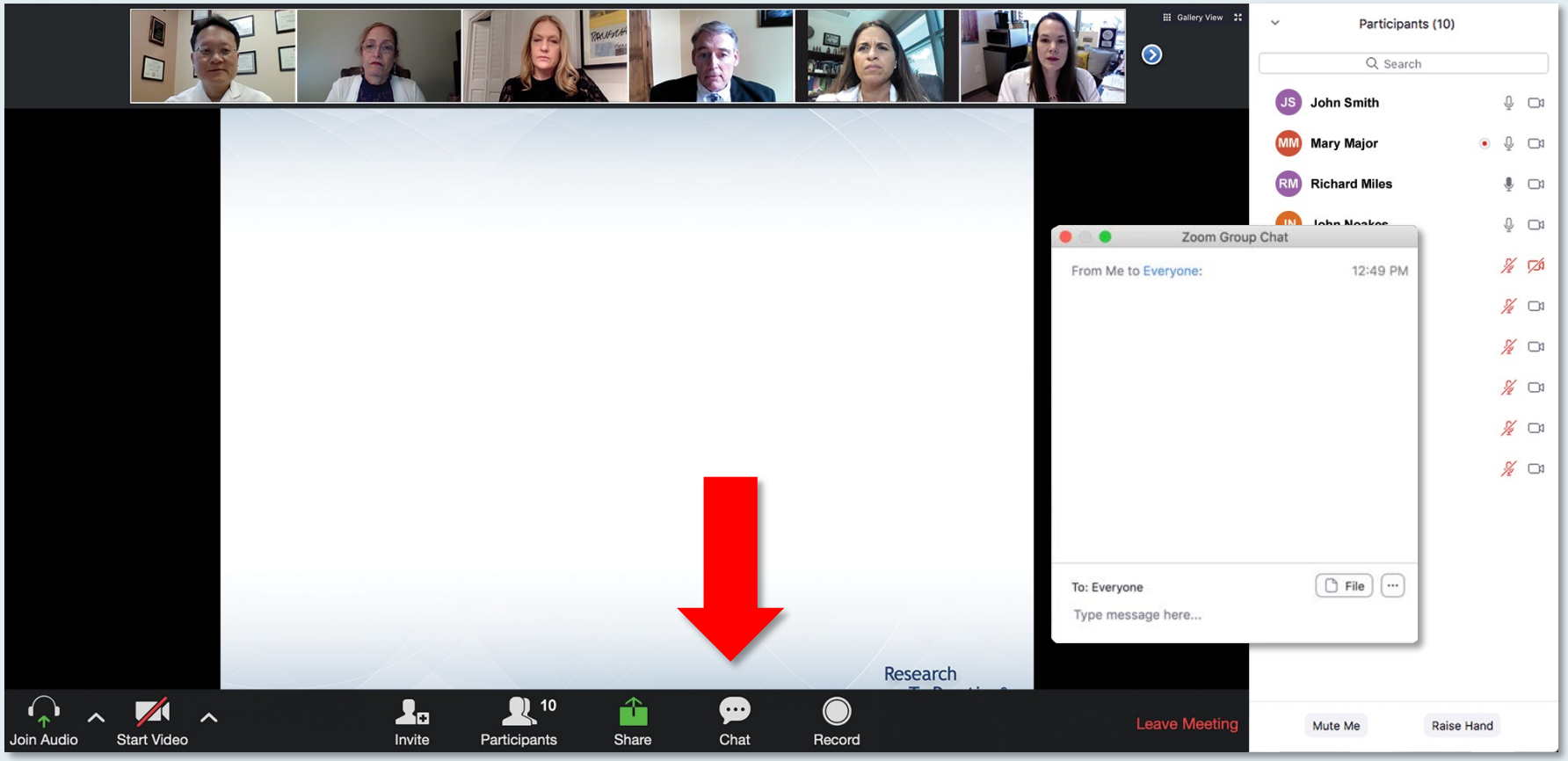

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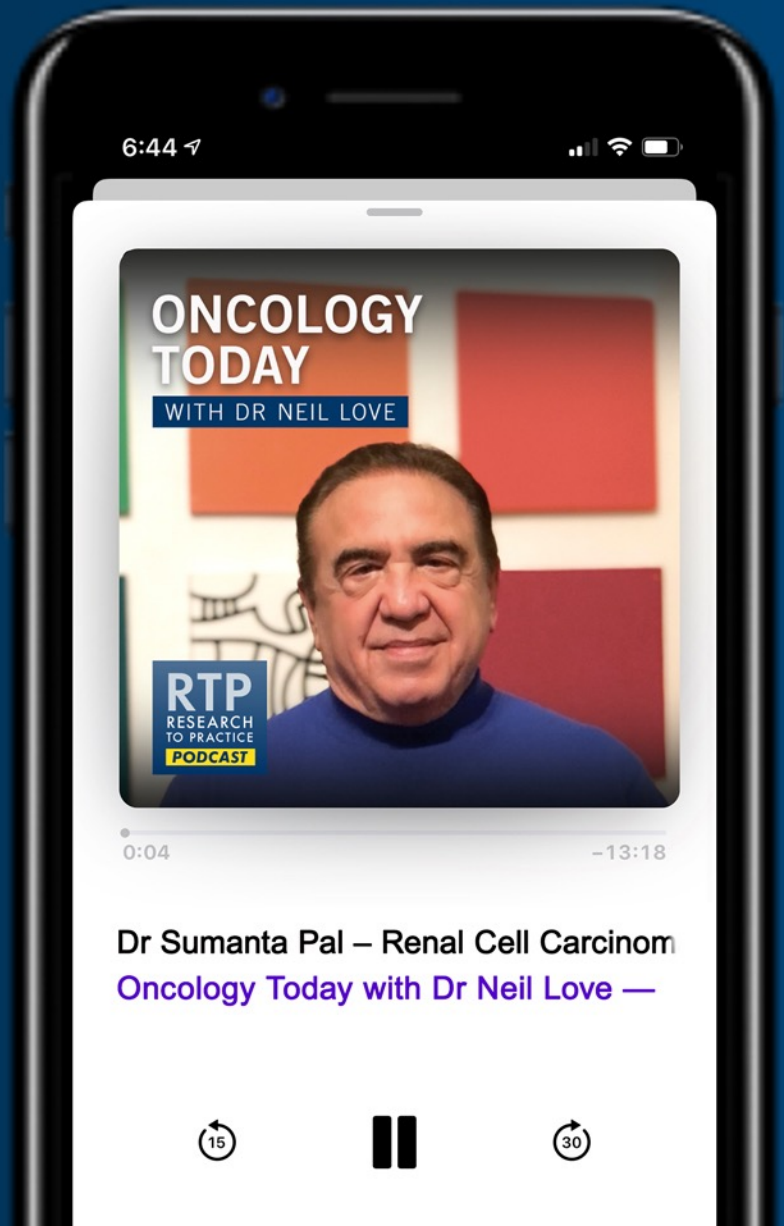

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Dr Hutson — Disclosures

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Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

Agenda

Introduction – Common Questions in the Management of Renal Cell Carcinoma

Module 1 – Adjuvant Immunotherapy

Module 2 – First-Line Treatment of Metastatic Disease

Module 3 – Management of Relapsed/Refractory Disease

Module 4 – Belzutifan

Agenda

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Module 4 – Belzutifan

Common Questions in the Management of Renal Cell Carcinoma

- What is the current role of cytoreductive nephrectomy in the modern era?
- What is the optimal approach to oligometastatic disease/oligoprogression?
- What are the current and future roles of neoadjuvant treatment?

Agenda

Introduction – Common Questions in the Management of Renal Cell Carcinoma

Module 1 – Adjuvant Immunotherapy

Module 2 – First-Line Treatment of Metastatic Disease

Module 3 – Management of Relapsed/Refractory Disease

Module 4 – Belzutifan

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The Great Adjuvant Debate — Important New Data Sets in Melanoma, Breast Cancer and Non-Small Cell Lung Cancer

Monday, February 28, 2022

5:00 PM – 6:00 PM ET

Faculty

Roy S Herbst, MD, PhD
Sara M Tolaney, MD, MPH
Jeffrey S Weber, MD, PhD

Moderator

Neil Love, MD

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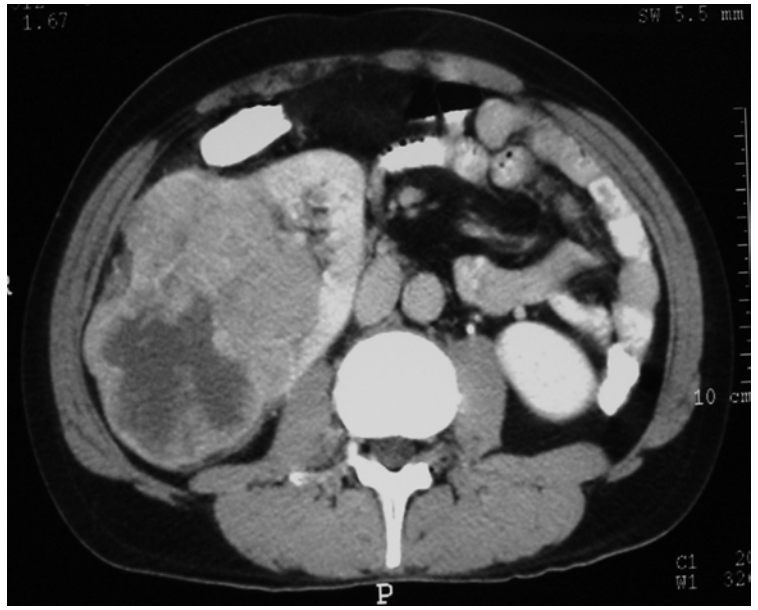
Case Presentation – Dr Rini: A 76-year-old woman with Grade III clear cell RCC

- 76-year-old female presents with right flank pain, no hematuria
- PMH: mild HTN (140/85 mm Hg not on medication); hypercholesterolemia; no other cardiac history; diabetes on metformin
- 20 pack-year smoker; FH: negative for cancer
- PE: right flank fullness, otherwise normal exam
- Labs: HgB 11.0 g/dL; ANC and Plt normal; creatinine 1.2; LDH 287, calcium normal
- CTs: no distant mets



Case Presentation – Dr Rini: A 76-year-old woman with Grade III clear cell RCC (continued)

- Patient undergoes R radical nephrectomy
- Pathology: Grade 3 clear cell RCC, margins negative; $T_{3a}N_0$

- Returns 6 weeks after nephrectomy; fully recovered
  - ECOG 0; creatinine 1.5; all other labs normal

- Patient receives adjuvant pembrolizumab
  - Develops grade 2 rash and grade 1 diarrhea 3 doses in…

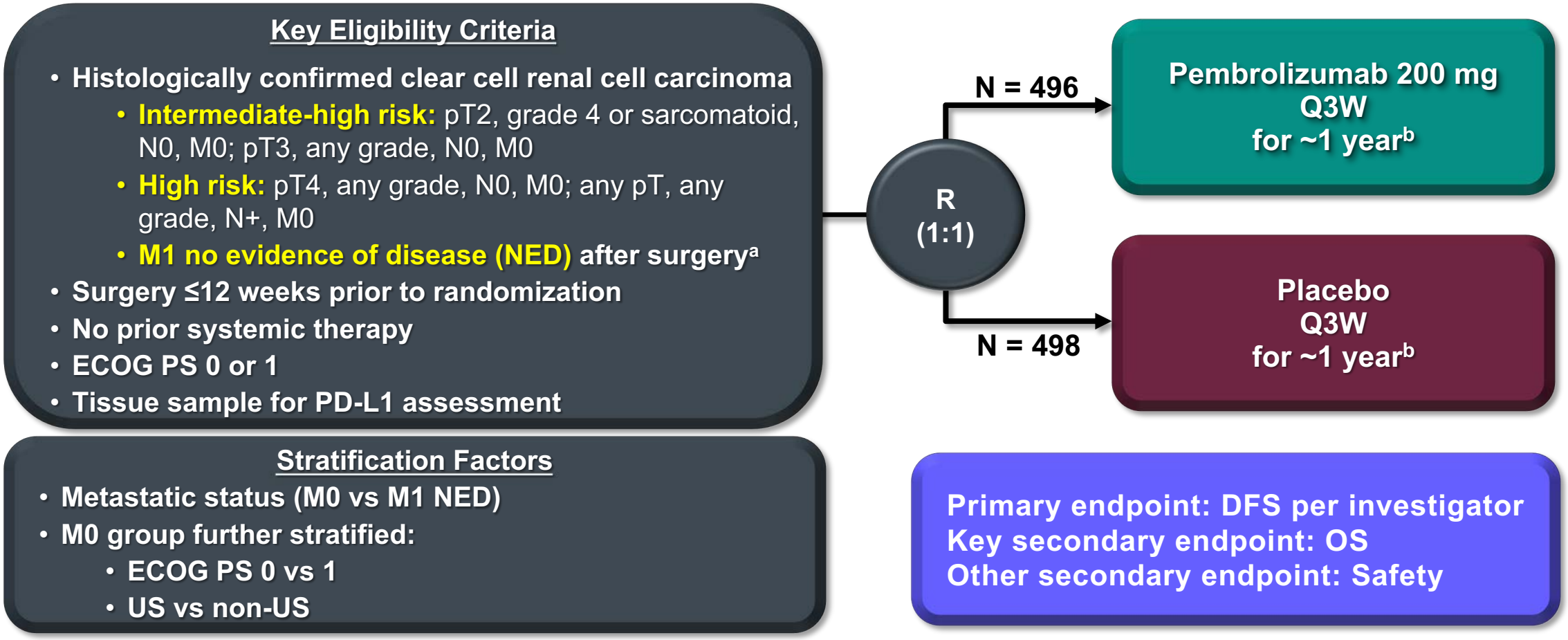
Pembrolizumab vs Placebo as Adjuvant Therapy for Patients with Renal Cell Carcinoma: Patient-Reported Outcomes in KEYNOTE-564

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Stefan Symeonides[5]; Jaroslav Hajek[6]; Thomas Ferguson[7]; Yen-Hwa Chang[8]; Jae Lyun Lee[9]; Naomi Haas[10]; Piotr Sawrycki[11]; Naveed Sarwar[12]; Marine Gross-Goupil[13]; Antoine Thiery-Vuillemin[14]; Mauricio Mahave[15]; Rodolfo F. Perini[16]; Todd L. Saretsky[16]; Pingye Zhang[16]; Jaqueline Willemann-Rogerio[16]; David Quinn[17]; Thomas Powles[18]; on behalf of the KEYNOTE-564 investigators.

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Poznań University of Medical Sciences, Poznań, Poland; [3]Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; [4]Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, UK; [5]Edinburgh Cancer Centre and University of Edinburgh, UK; [6]Fakultni Nemocnice Ostrava, Ostrava, Czech Republic; [7]Fiona Stanley Hospital, Perth, Australia; [8]Taipei Veterans General Hospital, Taipei, Taiwan; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Abramson Cancer Center, Philadelphia, PA, USA; [11]Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu, Torun, Poland; [12]Imperial College Healthcare NHS Trust, London, UK; [13]University Hospital Bordeaux-Hôpital Saint-André, Bordeaux, France; [14]University Hospital Jean Minjoz, Besançon, France; [15]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [18]Royal Free Hospital NHS Trust, University College London, London, UK.

ESMO 2021;Abstract 653O

KEYNOTE-564 (NCT03142334) Study Design

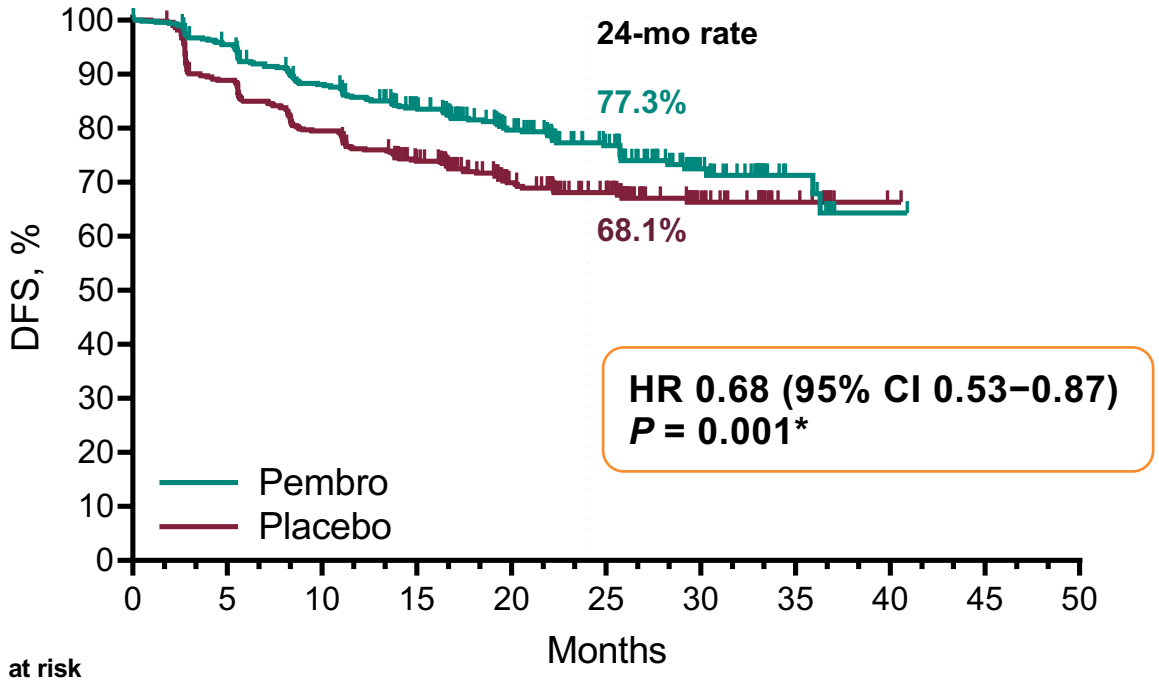


- Median (range) time from randomization to cutoff: 30.1 (20.8−47.5) months

Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

KEYNOTE-564 Primary Endpoint: Disease-Free Survival (DFS), ITT Population

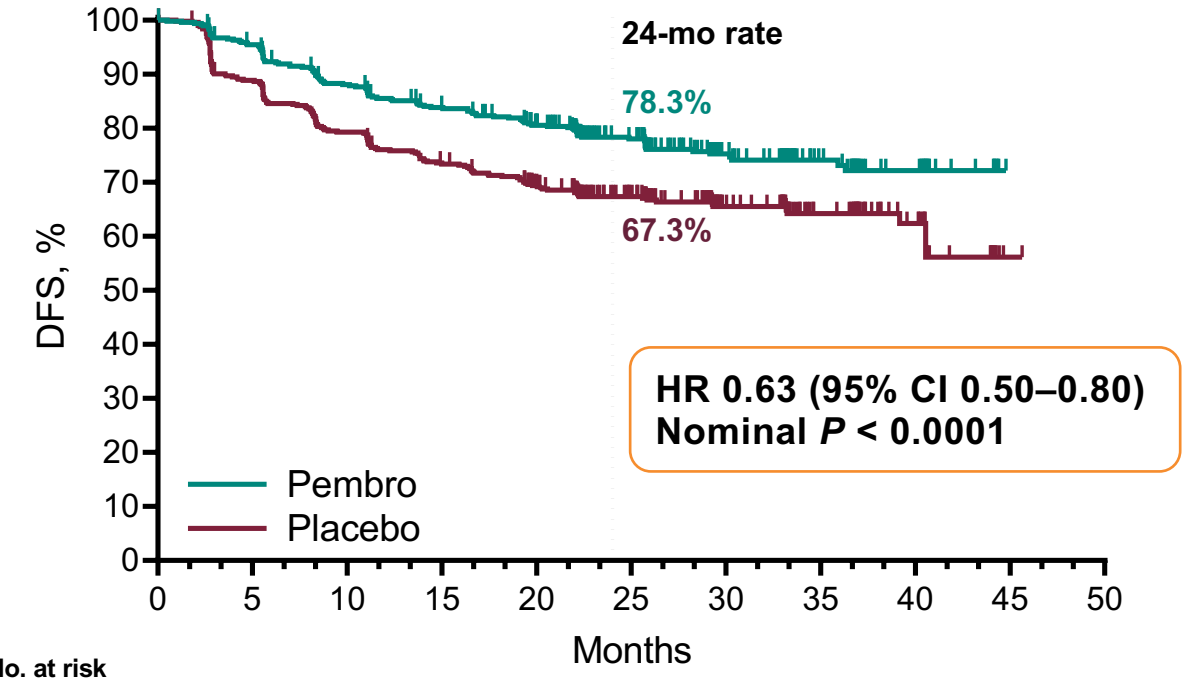
Primary Analysis: 24.1 mo Follow-Up



No. at risk											
Pembro	496	457	414	371	233	151	61	21	1	0	0
Placebo	498	436	389	341	209	145	56	19	1	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



No. at risk											
Pembro	496	458	416	389	361	255	135	77	37	0	0
Placebo	498	437	389	356	325	230	125	74	33	1	0

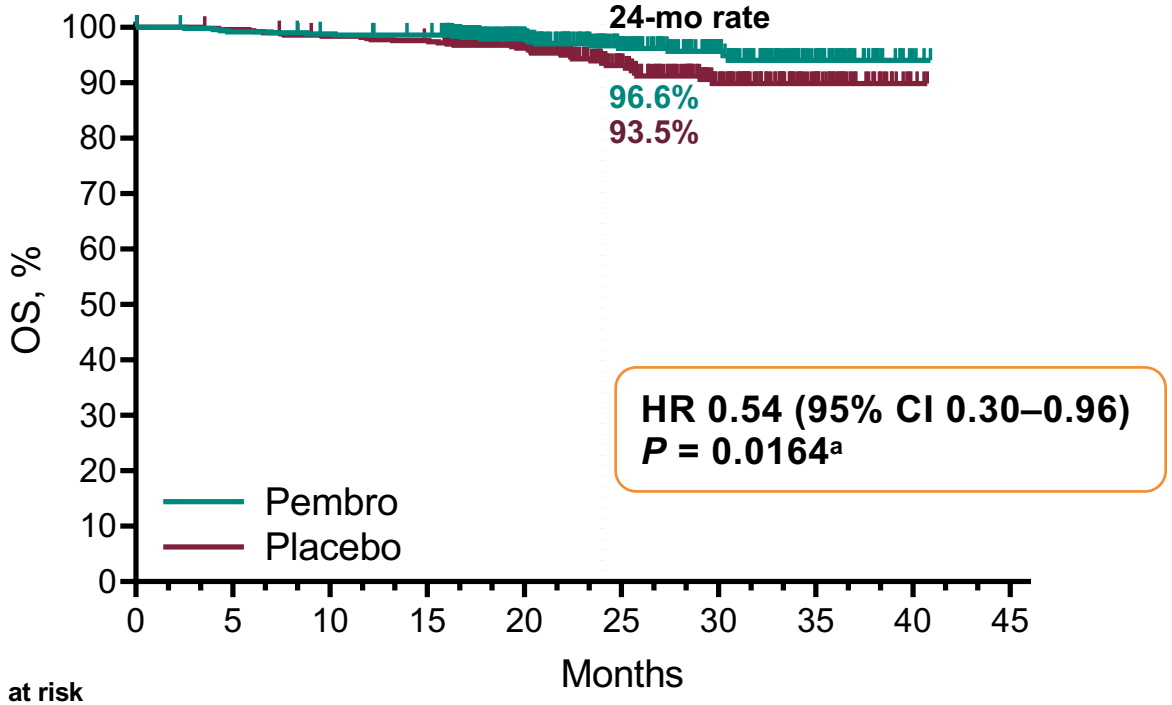
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

KEYNOTE-564 Key Secondary Endpoint: Overall Survival (OS), ITT Population

Primary Analysis: 24.1 mo Follow-Up

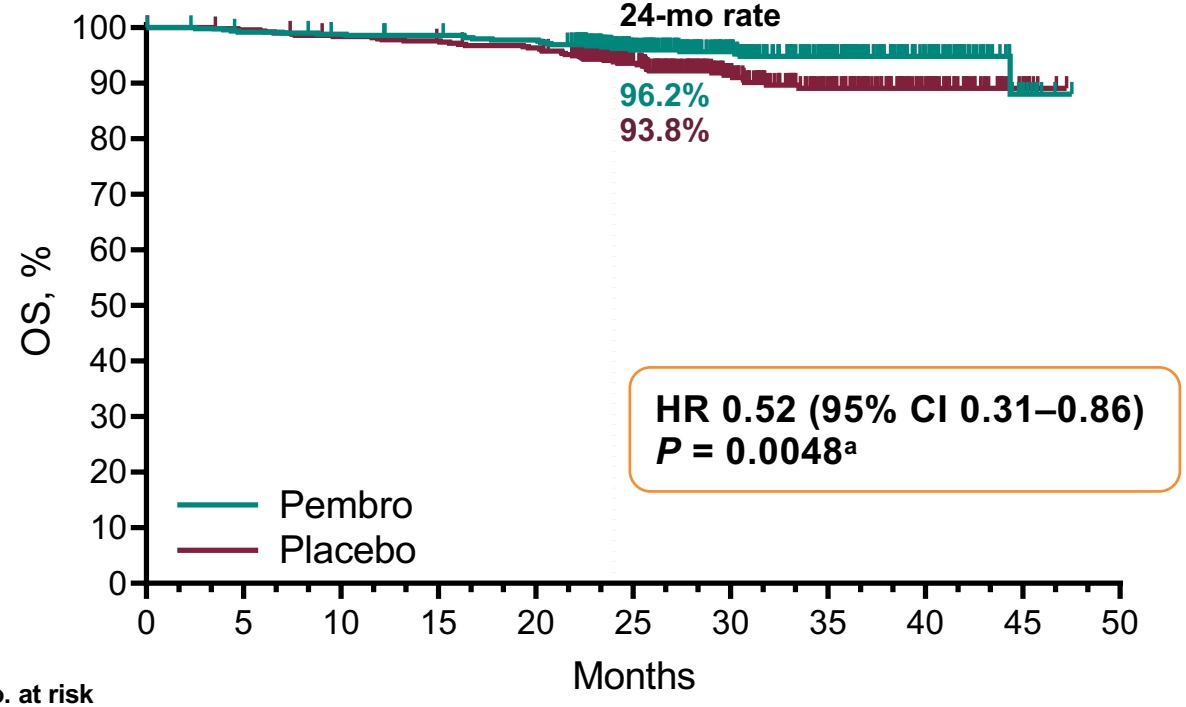


No. at risk

Pembro	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	18	NR (NR–NR)
Placebo	33	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



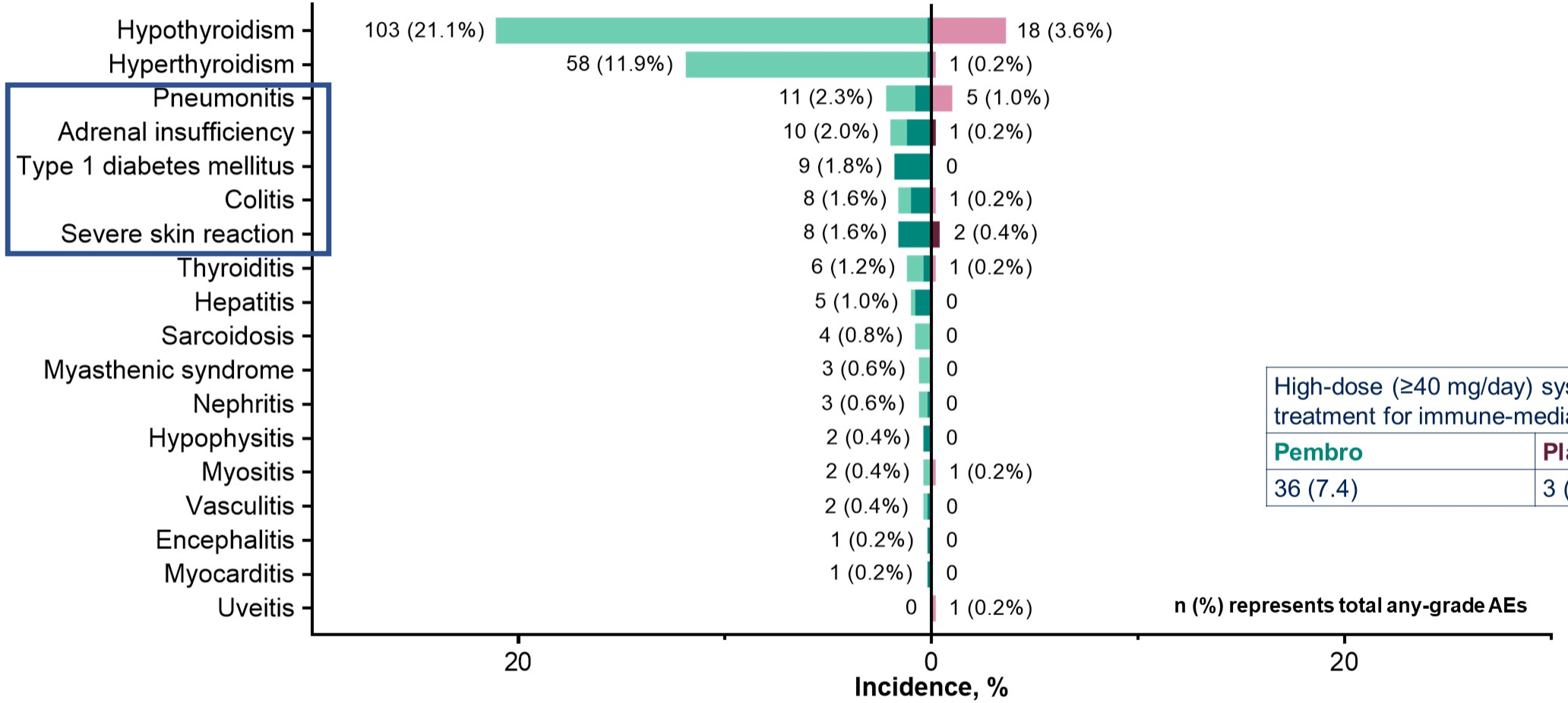
No. at risk

Pembro	496	489	485	482	477	360	231	146	63	8	0
Placebo	498	494	486	481	474	352	219	138	61	9	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

KEYNOTE-564:
Immune-Mediated AEs[a], As-Treated Population



High-dose (≥40 mg/day) systemic corticosteroid treatment for immune-mediated AEs, n (%)	
Pembro	**Placebo**
36 (7.4)	3 (0.6)

[a]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator.
Infusion reactions, pembro: any grade in 7 participants (1.4%), grade 3 in 2 participants (0.4%). Infusion reactions, placebo: any grade in 5 participants (1.0%), grade 3-4 in no participants. No deaths due to immune-mediated events occurred. As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: December 14, 2020.

Key Ongoing Studies of Adjuvant Immunotherapy in RCC

Trial	Sample size	Inclusion criteria	Treatment	Primary endpoint	Expected results
IMmotion010[1]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	1/2022
CheckMate 914[2]	1,600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs nivolumab + placebo vs placebo *(6 months)*	DFS	1/2023
PROSPER RCC[3]	766	T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	11/2023
RAMPART[4]	1,750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node or soft tissue recurrence >12 months from nephrectomy
NED = no evidence of disease; DFS = disease-free survival; EFS = event-free survival; OS = overall survival

1. NCT03024996. 2. NCT03138512. 3. NCT03055013. 4. NCT03288532.

EVEREST: Everolimus for Renal Cancer Ensuing Surgical Therapy — A Phase III Study (SWOG S0931, NCT01120249)

Ryan CW et al.

ASCO 2022;Abstract LBA4500.

Friday, June 3, 2022 – 3:45 PM EDT

RTP
RESEARCH
TO PRACTICE

Agenda

Introduction – Common Questions in the Management of Renal Cell Carcinoma

Module 1 – Adjuvant Immunotherapy

Module 2 – First-Line Treatment of Metastatic Disease

Module 3 – Management of Relapsed/Refractory Disease

Module 4 – Belzutifan

Case Presentation – Dr Rini: A 60-year-old man with advanced RCC

60M, DM and Htn

11/2018

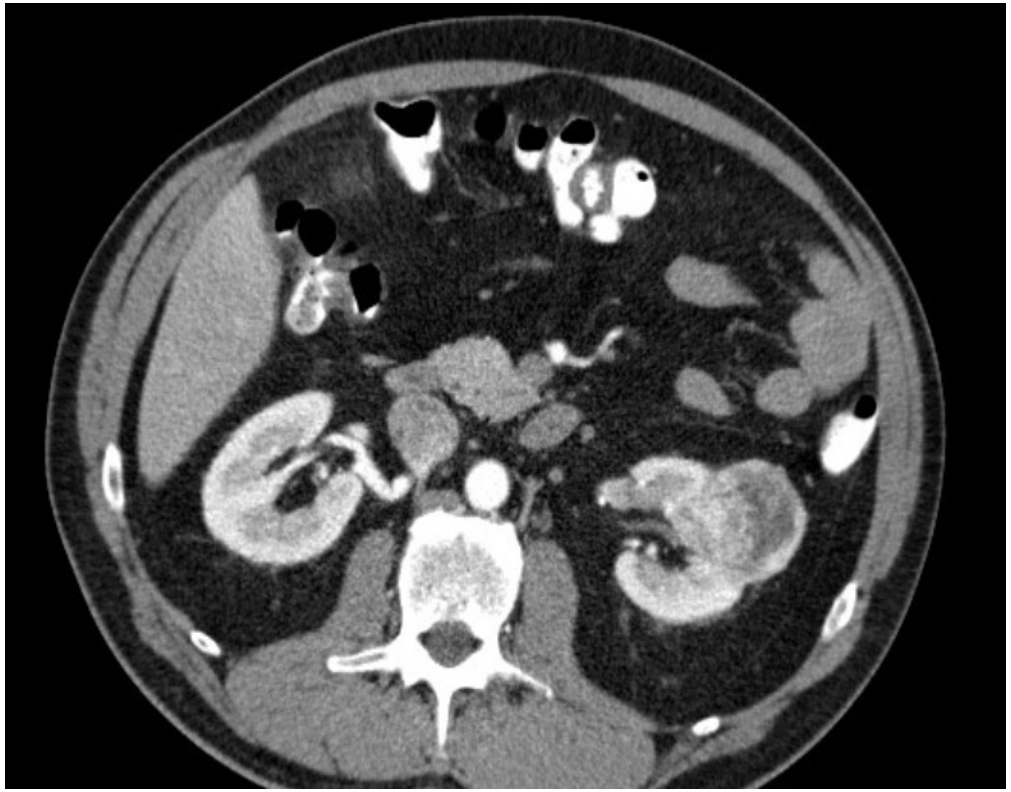
Diagnosis

Kidney mass on an abdominal CT
Size: 6 cm
ECOG PS = 0

Labs:
eGFR > 60cc/min
Hemoglobin = 14 g/dL

CT: NED except kidney mass

PMH: Htn on amlodipine besylate



Case Presentation – Dr Rini: A 60-year-old man with advanced RCC (continued)

60M, DM and Htn

11/2018 — **Diagnosis**

12/2018 — **Nephrectomy**

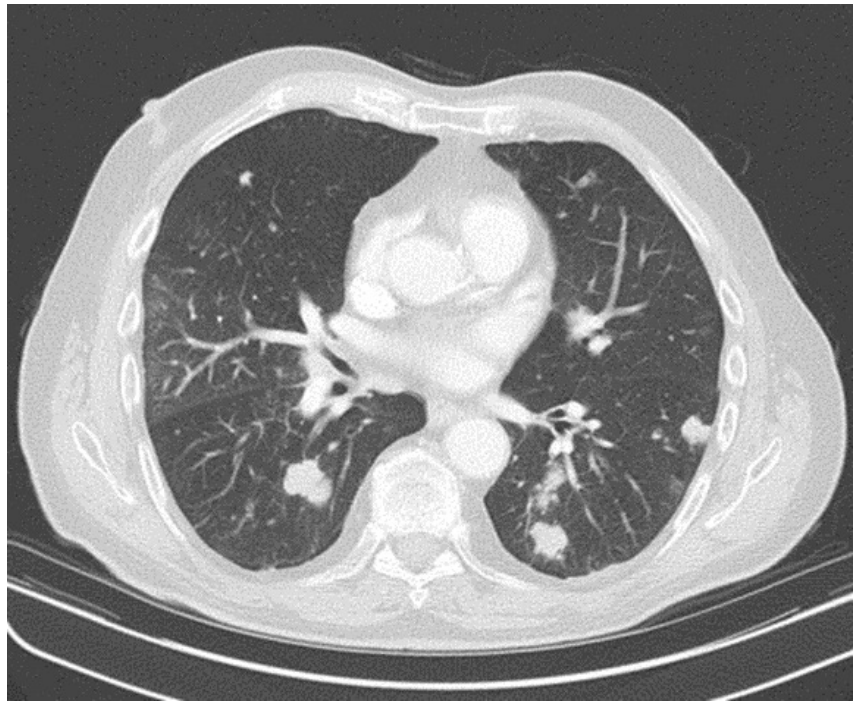
05/2019 — **PD of lung nodules**
New SC and other bulky LN, 2 liver mets

ECOG PS=1

Labs: wnl except for mild anemia

IMDC: 1 risk factor

Lung bx c/w ccRCC; no sarcomatoid elements



Case Presentation – Dr Rini: A 60-year-old man with advanced RCC (continued)

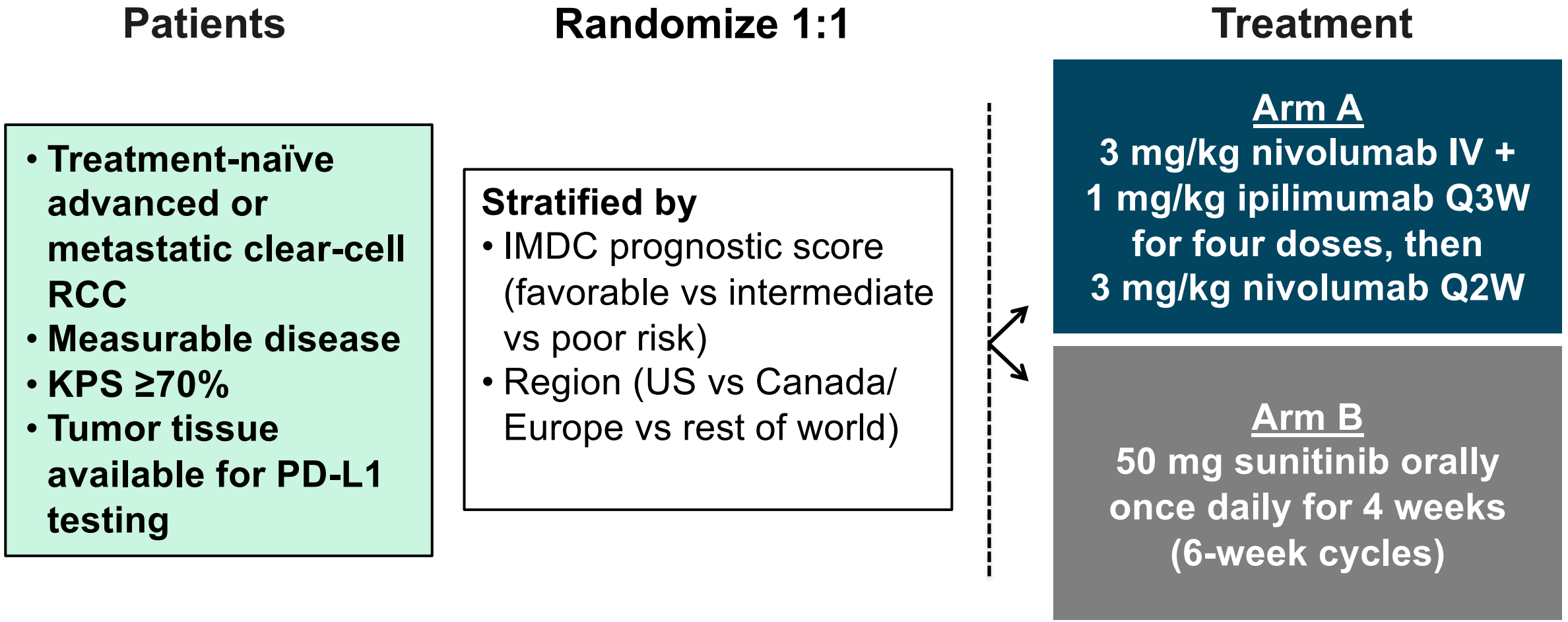
- Patient treated on CLEAR trial with lenvatinib/pembrolizumab
- Presents at week 3 with BPs running 170/100s at home, grade 3 fatigue and anorexia
- Lenvatinib held till recovery of symptoms, restarted at 14 mg and 2nd BP med added
- First scan with 32% tumor burden reduction per RECIST
- Patient tolerating therapy on 2 BP meds with grade 1-2 fatigue and grade 1 diarrhea

FDA-Approved First-Line Immunotherapy Combination Options for Advanced RCC

Randomization	FDA approval	Pivotal study	HR (PFS)	HR (OS)
Nivolumab/ipilimumab vs sunitinib[1]	4/16/18	CheckMate 214	0.89	0.69
Pembrolizumab/axitinib vs sunitinib[2]	4/19/19	KEYNOTE-426	0.71	0.68
Avelumab/axitinib vs sunitinib[3]	5/14/19	JAVELIN Renal 101	0.69	0.80
Nivolumab/cabozantinib vs sunitinib[4]	1/22/21	CheckMate 9ER	0.51	0.60
Pembrolizumab/lenvatinib vs sunitinib[5]	8/10/21	CLEAR (KEYNOTE-581)	0.39	0.66

[1] Albiges L et al. ESMO Open 2020;5(6):e001079; [2] Powles T et al. *Lancet Oncol* 2020;21:1563-73; [3] Choueiri TK et al. *Ann Oncol* 2020;31(8):1030-9; [4] Motzer R et al. *N Engl J Med* 2021;384(14):1289-300; [5] Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41.

IO + IO: CheckMate 214[1,2]

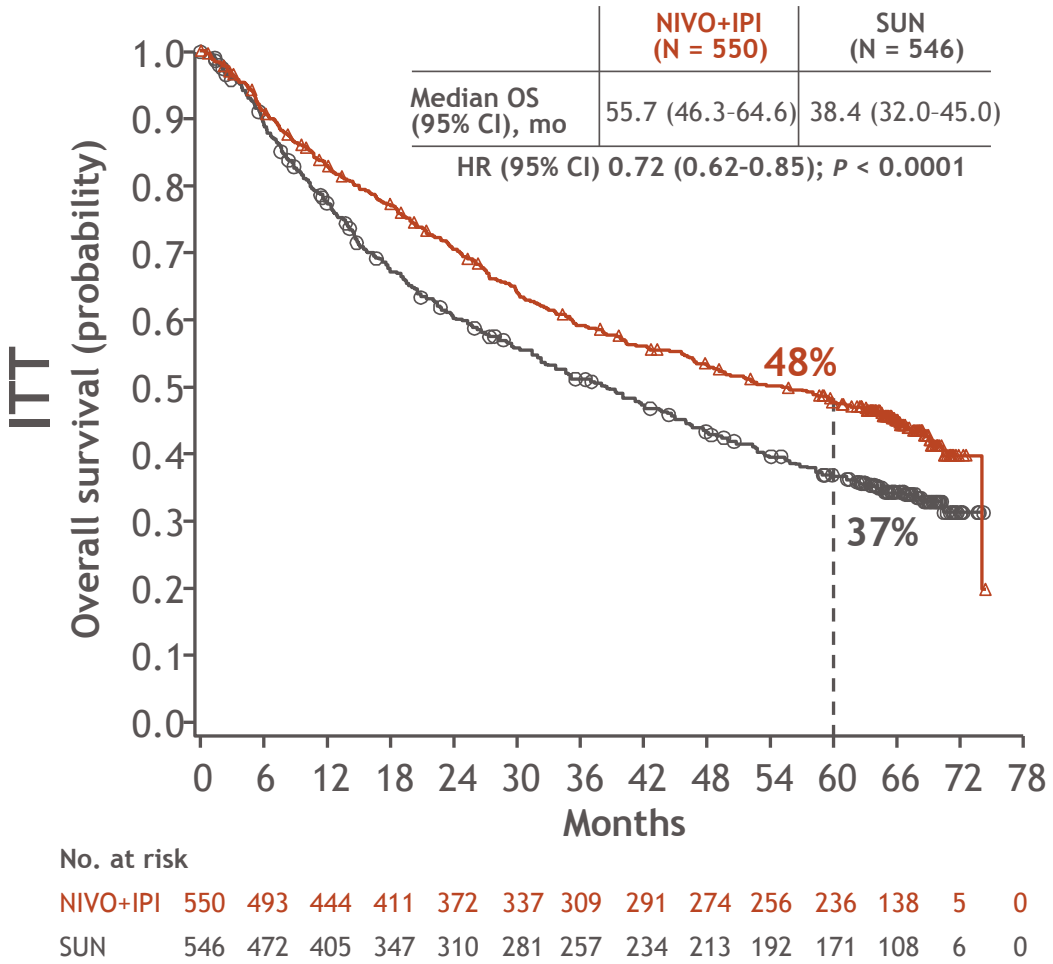


IO = immunotherapy; KPS = Karnofsky performance status; IMDC = International Metastatic RCC Database Consortium

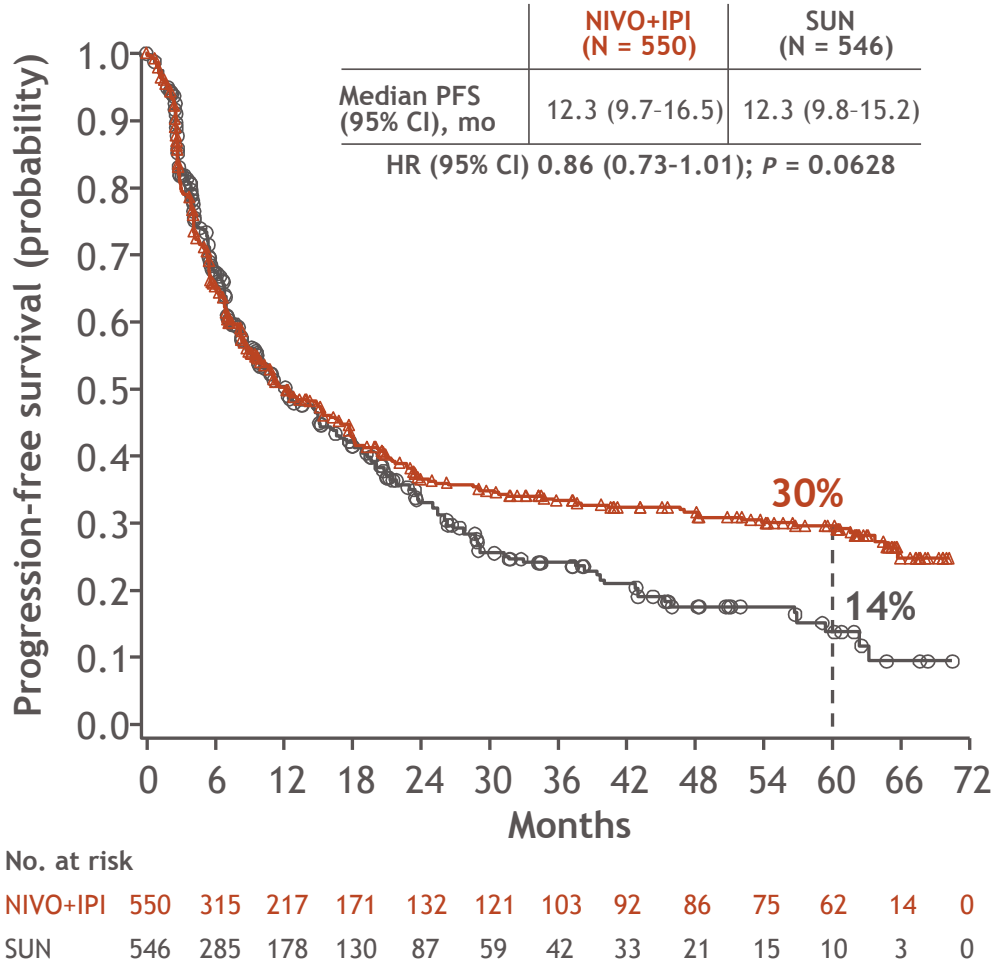
1. Motzer et al. *Lancet Oncology* 2019. **2.** Motzer RJ et al. *N Engl J Med* 2018;378:1277-90.

CheckMate 214: OS and PFS in ITT — 5-year Update

Overall survival



Progression-free survival



Motzer RJ et al. ESMO 2021;Abstract 661P.

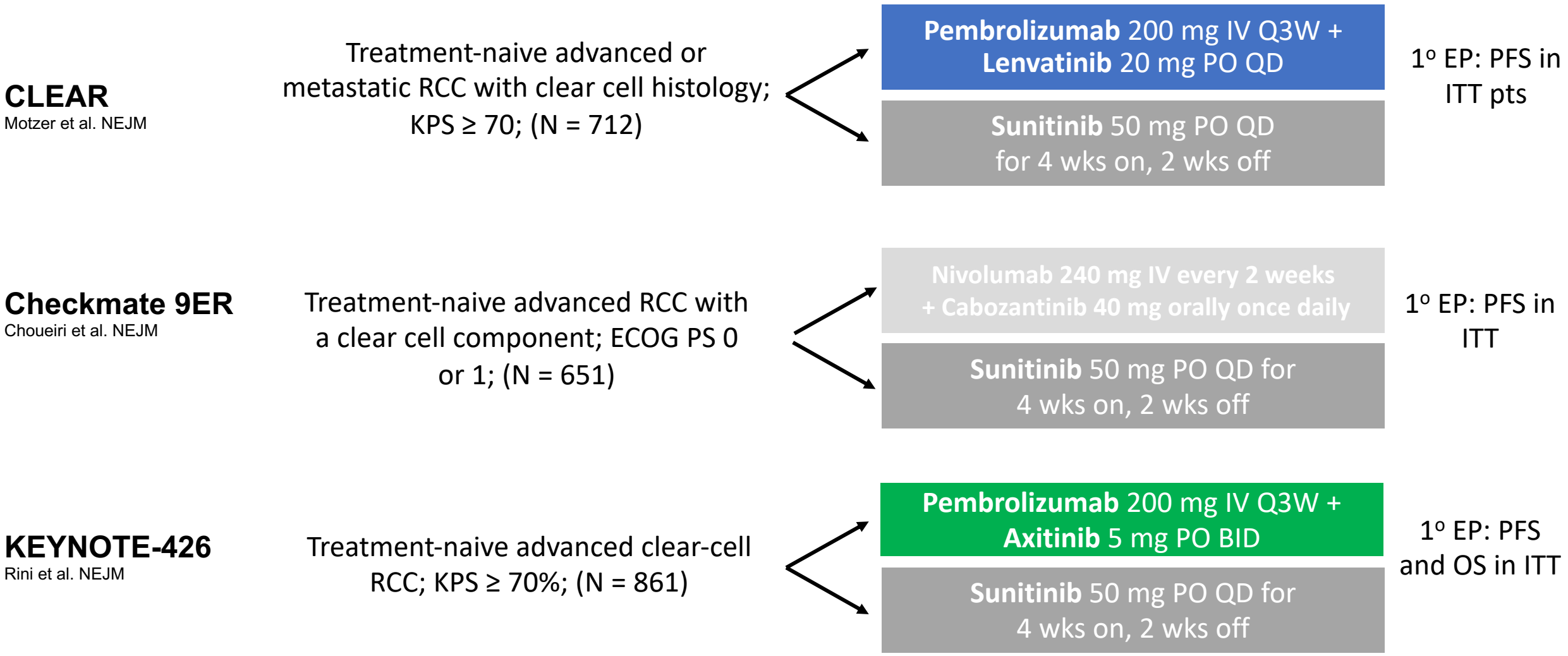
The Relationship between Health-Related Quality of Life (HRQoL) and Clinical Outcomes in Patients with Advanced Renal Cell Carcinoma (aRCC) in CheckMate (CM) 214

Cella D et al.

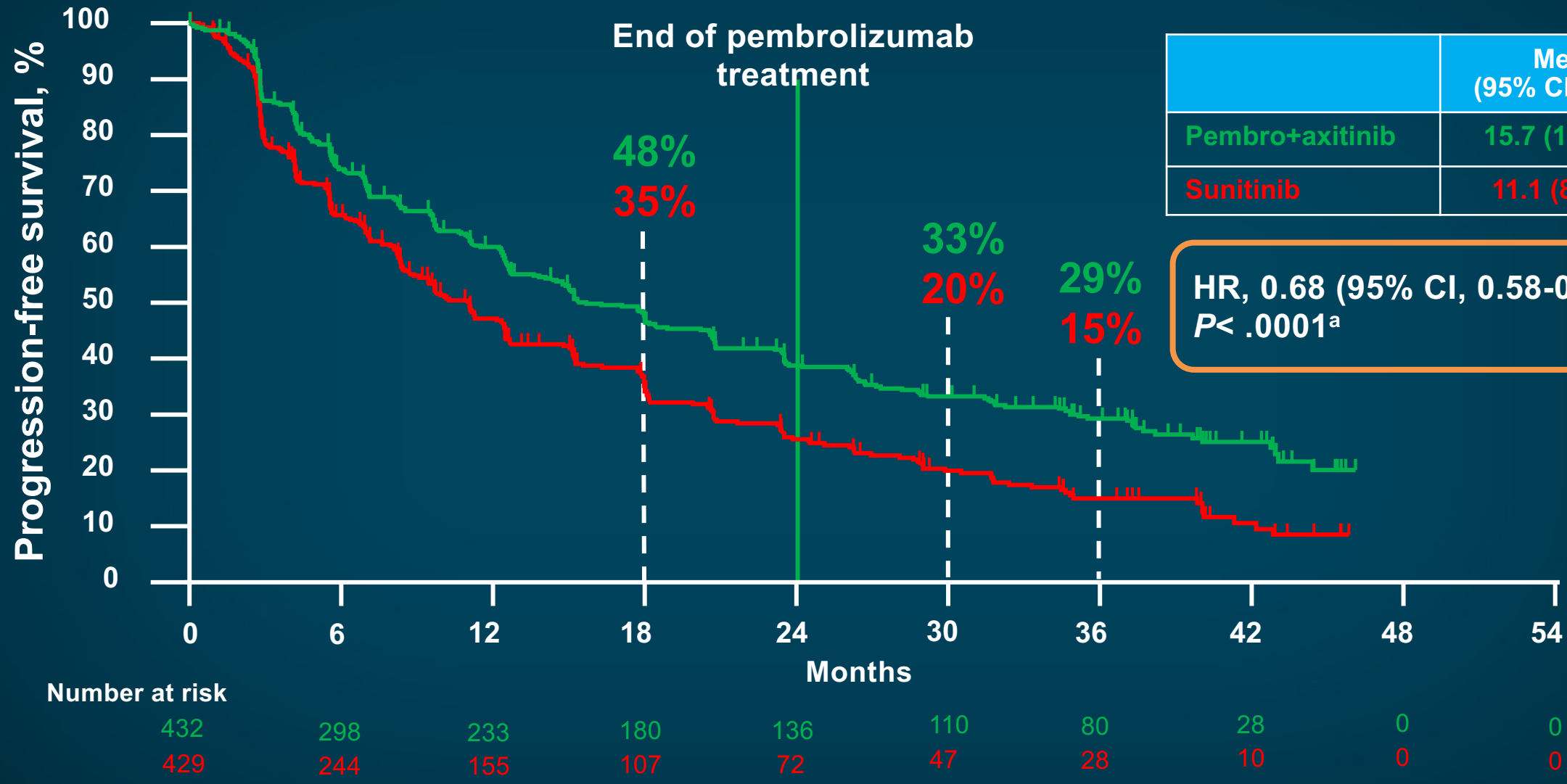
ASCO 2022;Abstract 4502.

Friday, June 3, 2022 – 4:09 PM EDT

Randomized Phase III Study Designs for IO + VEGF TKI



KEYNOTE-426: PFS in the ITT Population



	Median (95% CI), months
Pembro+axitinib	15.7 (13.6-20.2)
Sunitinib	11.1 (8.9-12.5)

HR, 0.68 (95% CI, 0.58-0.80)
P< .0001[a]

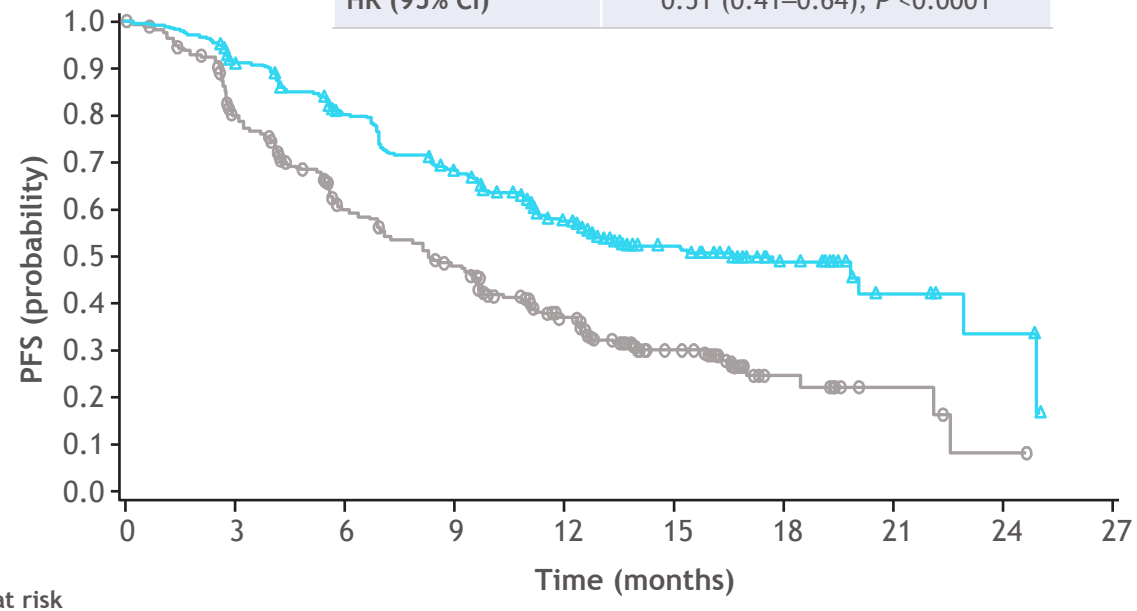
[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

Rini BI, et al. ASCO 2021; Abstract 4500. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

CheckMate 9ER: Progression-free and overall survival

Progression-free survival by BICR

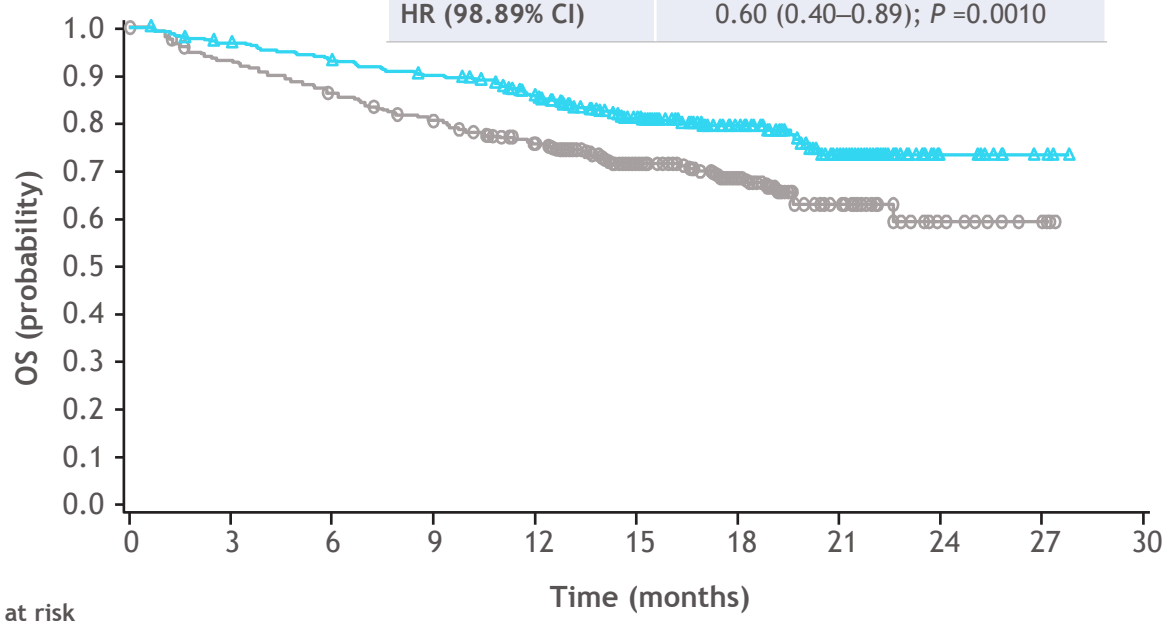
	NIVO + CABO n=323	SUN n=328
mPFS, mo (95% CI)	16.6 (12.5–24.9)	8.3 (7.0–9.7)
HR (95% CI)	0.51 (0.41–0.64); *P* <0.0001	



No. at risk										
NIVO + CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Overall survival

	NIVO + CABO n=323	SUN n=328
mOS, mo (95% CI)	NR (NE)	NR (22.6–NE)
HR (98.89% CI)	0.60 (0.40–0.89); *P* =0.0010	



No. at risk												
NIVO + CABO	323	308	295	283	259	184	106	55	11	3	0
SUN	328	296	273	253	223	154	83	36	10	3	0

BICR=blinded independent central review; CABO=cabozantinib; CI=confidence interval; HR=hazard ratio; mo=month; mOS=median OS; mPFS=median PFS; NIVO=nivolumab; OS=overall survival; PFS=progression-free survival; SUN=sunitinib.

Choueiri TK et al. Oral presentation at ESMO 2020. Abstract 696O.

Association between Depth of Response (DepOR) and Clinical Outcomes: Exploratory Analysis in Patients with Previously Untreated Advanced Renal Cell Carcinoma (aRCC) in CheckMate 9ER

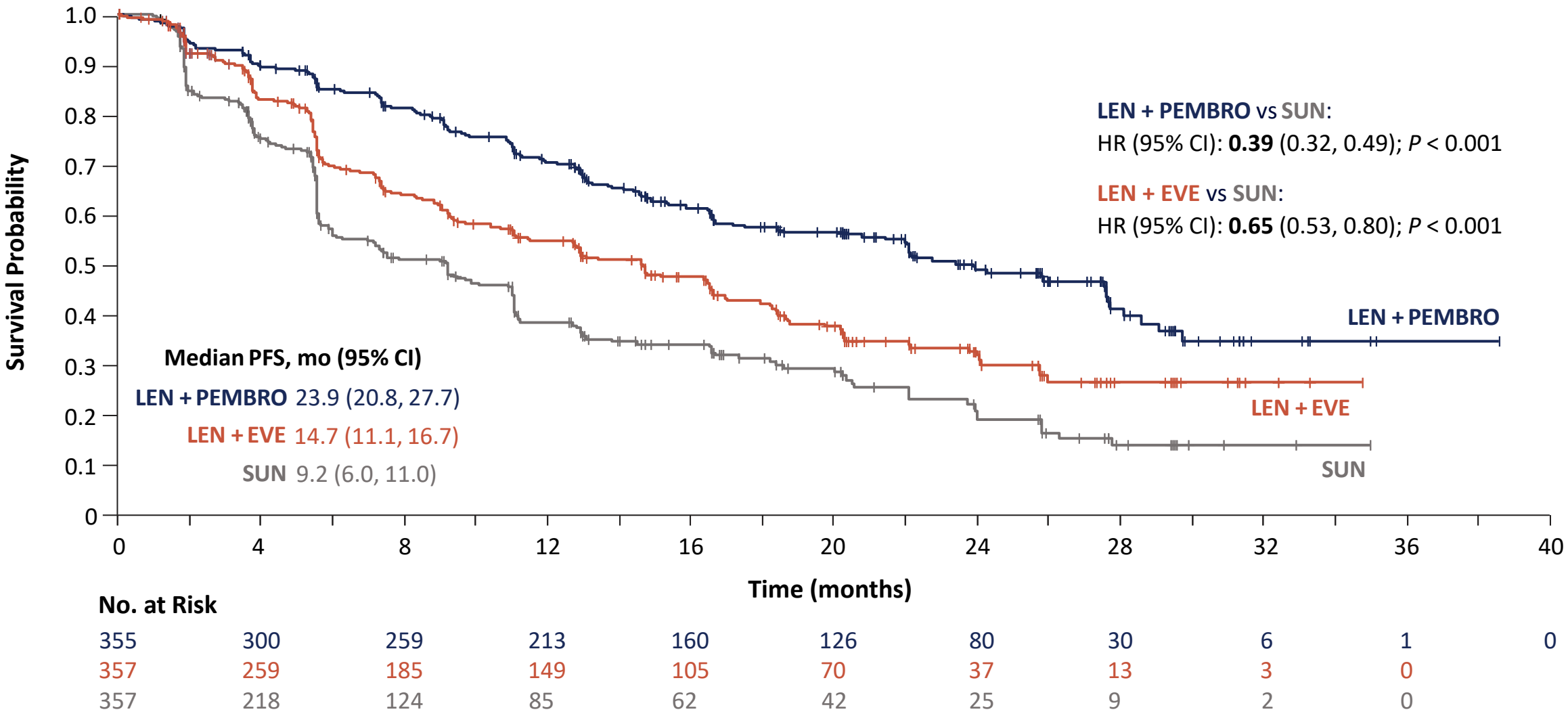
Suárez C et al.

ASCO 2022;Abstract 4501.

Friday, June 3, 2022 – 3:57 PM EDT

Motzer RJ et al. GU Cancers Symposium 2021;Abstract 269.

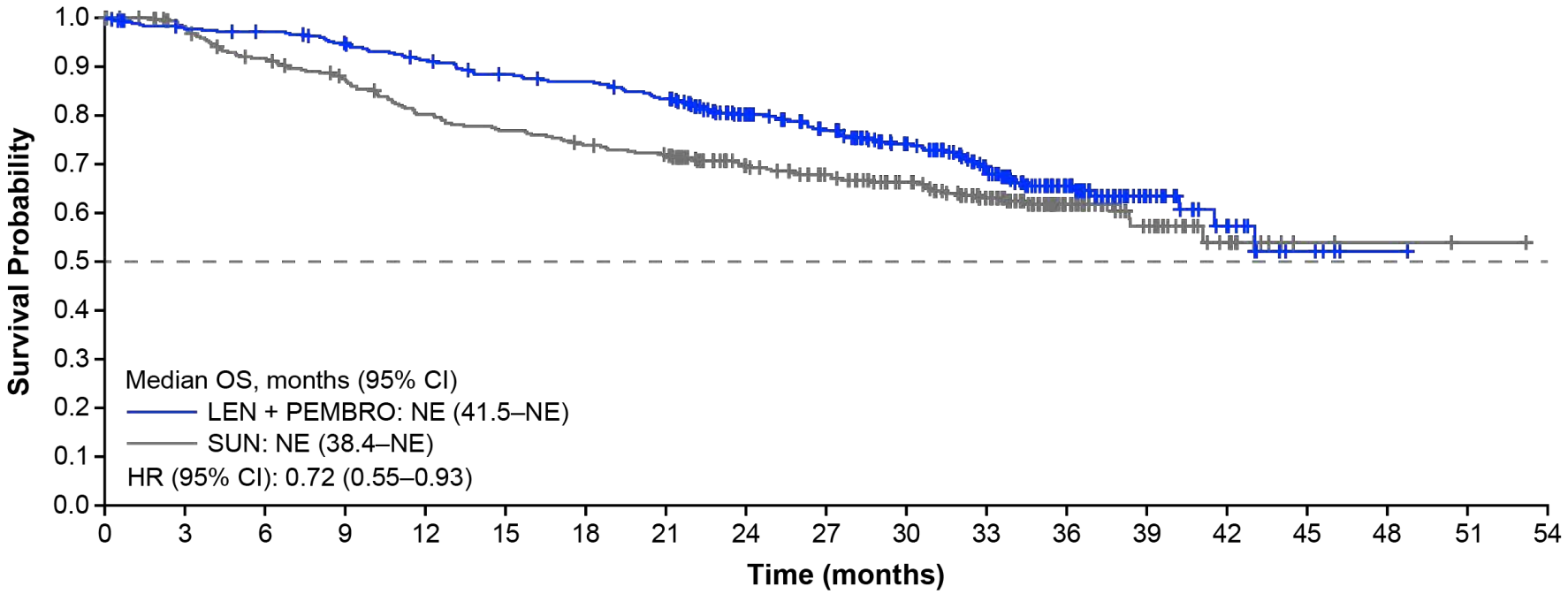
Len/Pembro CLEAR trial: Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

PRESENTED BY: Dr. Robert Motzer

Len/Pembro CLEAR trial: Overall Survival[a]



Number of patients at risk:

LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

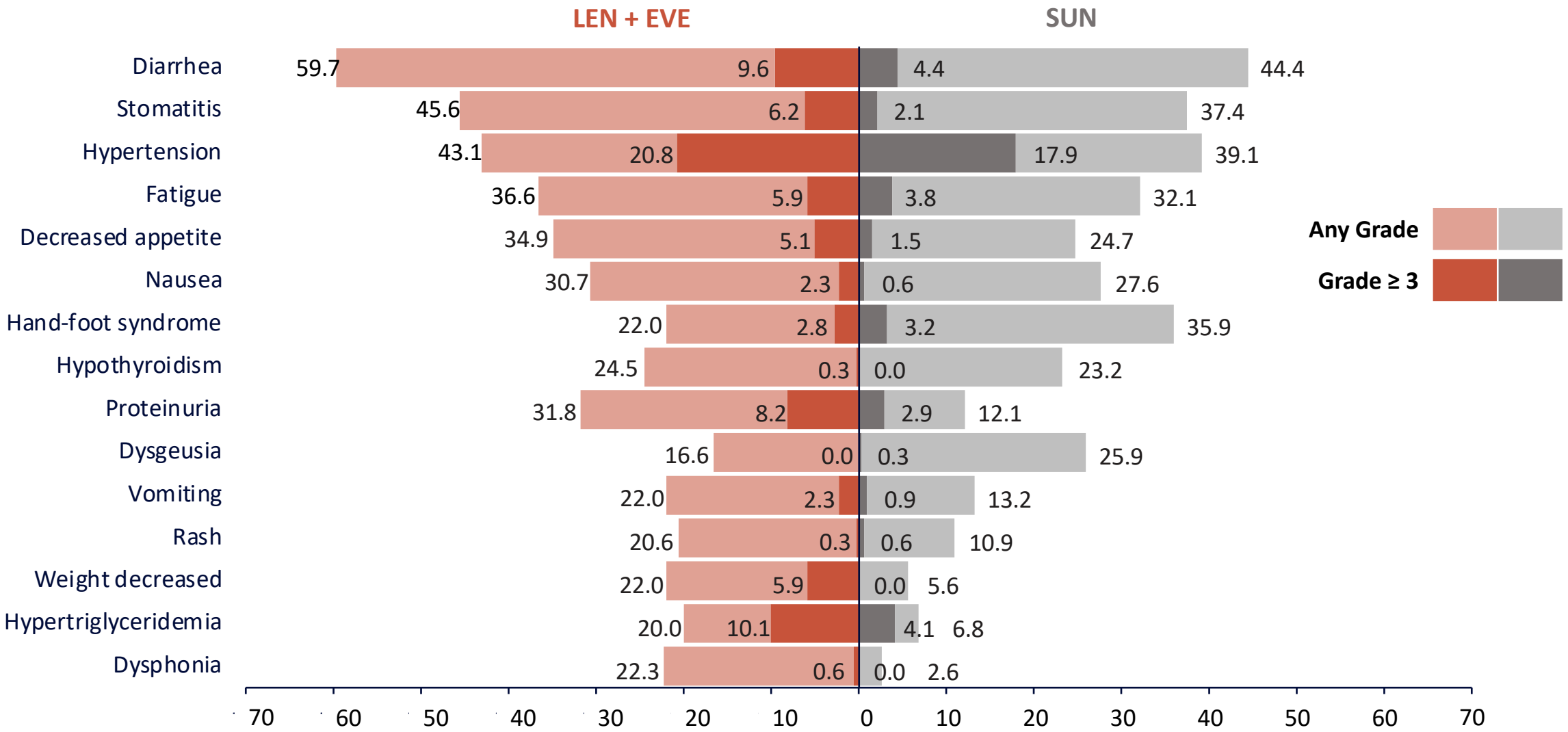
- Median duration of follow-up for OS was 33.7 months (95% CI, 32.8–34.4) in the LEN + PEMBRO arm and 33.4 months (95% CI, 32.5–34.1) in the SUN arm
- 250 (70.4%) and 235 (65.8%) patients in the LEN + PEMBRO and SUN arms were censored, respectively

[a]Data cutoff occurred on March 31, 2021.

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Motzer RJ et al. ASCO GU 2021;Abstract 269.

Len/Pembro CLEAR trial: TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 10.4/11.5% (grade 3: 2.0/1.4%) of patients in the LEN + EVE arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.

First-line IO Combination Trials in mRCC

	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
4. Motzer et al. ASCO GU 2021.

First-line IO Combination Trials in mRCC

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HR mOS, months	**0.72** 55.7 v	**0.73** Consistent OS benefit vs VEGF TKI	**0.70**	**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%
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1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.

First-line IO Combination Trials in mRCC

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Landmark PFS	30% (5 years)	29% (3 years)	39% (2 years)	

Consistent OS benefit vs VEGF TKI

More tumor shrinkage with TKI-containing regimens

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.


@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

First-line IO Combination Trials in mRCC

	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)
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Landmark PFS	30% (5 years)			

Consistent OS benefit vs VEGF TKI

More tumor shrinkage with TKI-containing regimens

Less early PD with TKI-containing regimens

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.

First-line IO Combination Trials in mRCC

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Consistent OS benefit vs VEGF TKI

More tumor shrinkage with TKI-containing regimens

Less early PD with TKI-containing regimens

CTLA-4 containing regimen perhaps with higher tail of the curve

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.

@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

Agenda

Introduction – Common Questions in the Management of Renal Cell Carcinoma

Module 1 – Adjuvant Immunotherapy

Module 2 – First-Line Treatment of Metastatic Disease

Module 3 – Management of Relapsed/Refractory Disease

Module 4 – Belzutifan

Case Presentation – Dr Rini: A 65-year-old woman who has been on axitinib + pembrolizumab for the past four years

- Originally presented with pulmonary and lymph node metastases nine months after nephrectomy for a T3a clear cell RCC.
- Pt had PR after 6 cycles. Tolerated treatment well with mild fatigue and diarrhea, hoarseness.
- Now shows new liver lesions and new pulmonary and mediastinal lesions.
- KPS 80, Hb 10.8, and other labs within normal range.

Case Presentation – Dr Rini: 65-year-old woman (continued); Patient started on cabozantinib

- She demonstrates an objective response and remains on therapy for 8 months.
  - Dose reduced ultimately to 20 mg QD for HFS, diarrhea and fatigue
- Her disease begins to progress, with increase in number of her pulmonary nodules, and regrowth of some of hepatic lesions.
- Her KPS is 80%, and she has mild anemia (hgb 10.3 g/dL).

Case Presentation – Dr Rini: 65-year-old woman (continued); 3rd line therapy choice….

- Patient is concerned about quality of life and toxicity of therapy
- Ultimately enrolled on belzutifan monotherapy trial
- Tolerates well with some worsening of anemia and mild edema
- First re-staging scans with 10% tumor burden reduction

Lenvatinib + Pembro in IO-refractory RCC

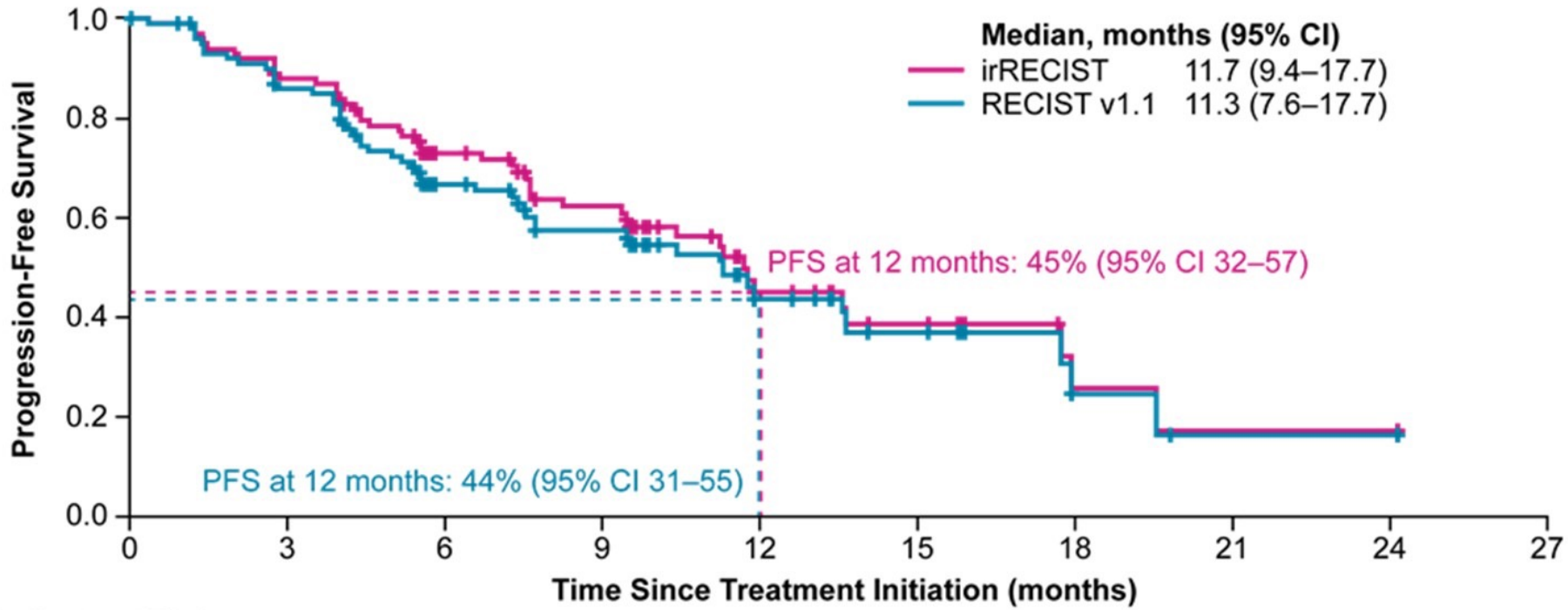
Tumor Response by Investigator Assessment

Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

[a] Up to 10 target lesions could be selected (up to 5 per organ).

DOR, duration of response.

PFS Kaplan–Meier Curves by irRECIST[a] and RECIST v1.1[a,b]



Number of Patients at Risk:

irRECIST	104	86	58	45	18	11	3	1	1	0
RECIST v1.1	104	84	53	41	17	10	3	1	1	0

[a] Per investigator assessment; [b] up to 10 target lesions could be selected (up to 5 per organ).

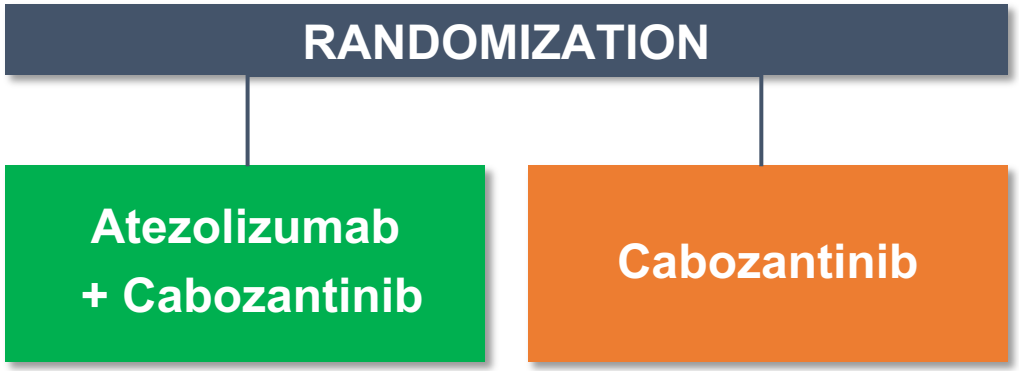
Randomized PD-1/VEGF Blockade Salvage Trial

CONTACT-03 (NCT04338269)

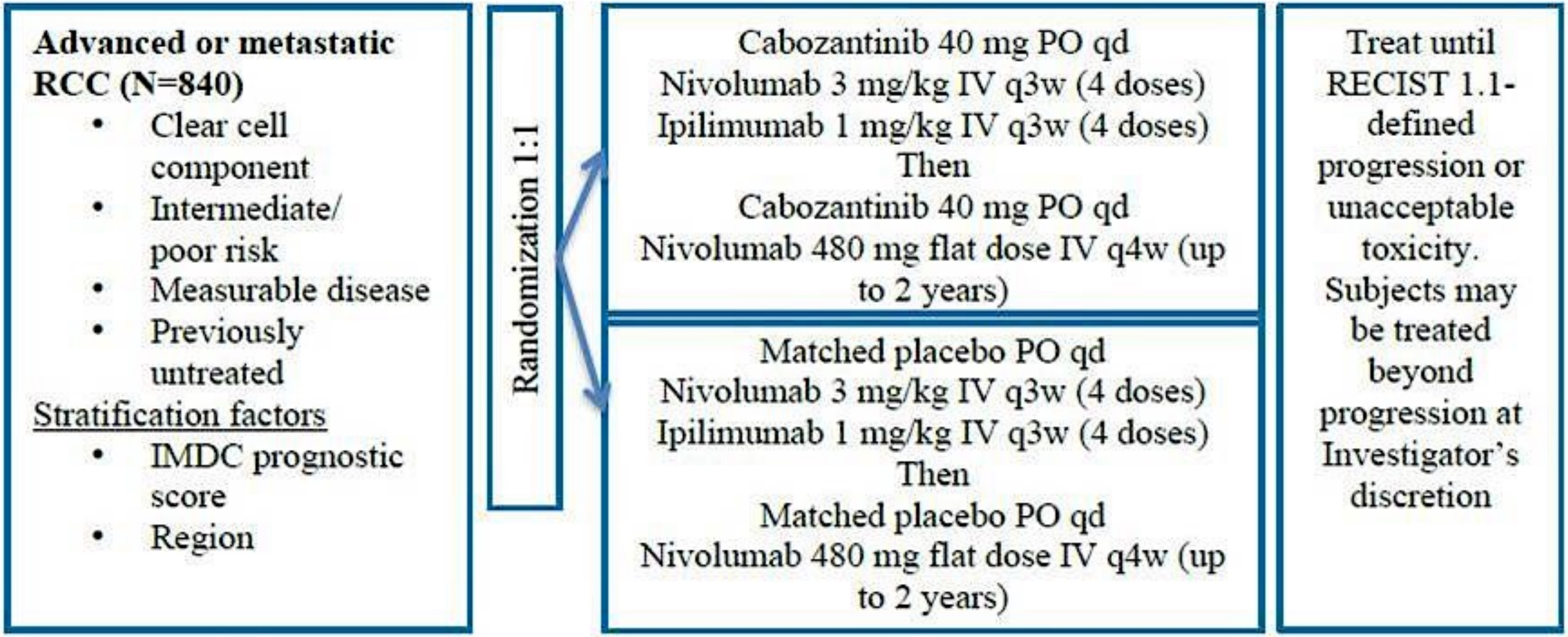
mRCC 2/3L (clear cell, papillary, unclassified)

VEGFRTKI ± PD-L1 inhibition

Phase 3 (N = 500)
Primary endpoint: PFS, OS



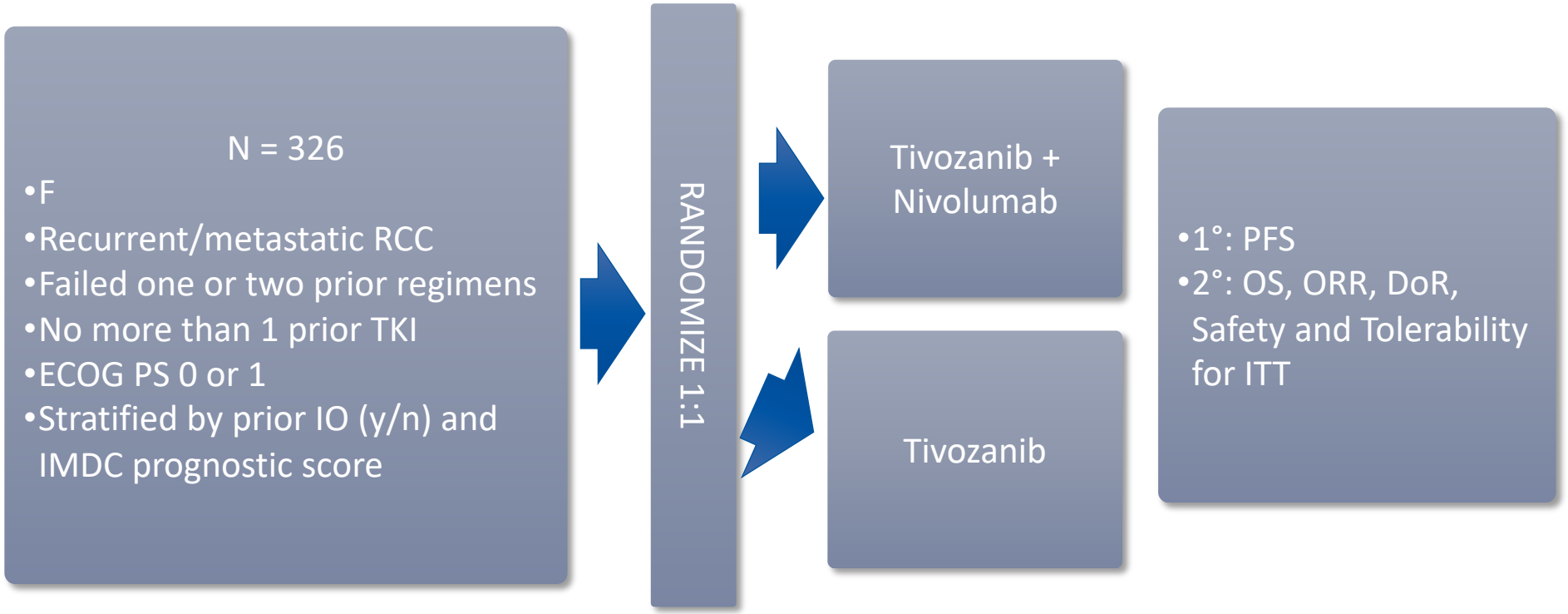
COSMIC-313



IMDC, international metastatic renal cell carcinoma database consortium; IV, intravenous; PO, oral administration; qd, once daily; q3(4)w once every 3(4) weeks; RECIST, response evaluation criteria in solid tumors; RCC, renal cell carcinoma

TiNivo-2: Tivozanib + Nivolumab Combination in RCC – Ph3

Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib + Nivolumab to Tivozanib in Subjects With 2nd and 3rd Line Advanced RCC



N = 326 (Assumes 15 vs 10 months PFS)
Data mid 2024

CALYPSO: A Three-Arm Randomized Phase II Study of Durvalumab Alone or with Savolitinib or Tremelimumab in Previously Treated Advanced Clear Cell Renal Cancer

Powles T et al.

ASCO 2022;Abstract LBA4503.

Friday, June 3, 2022 – 4:33 PM EDT

Agenda

Introduction – Common Questions in the Management of Renal Cell Carcinoma

Module 1 – Adjuvant Immunotherapy

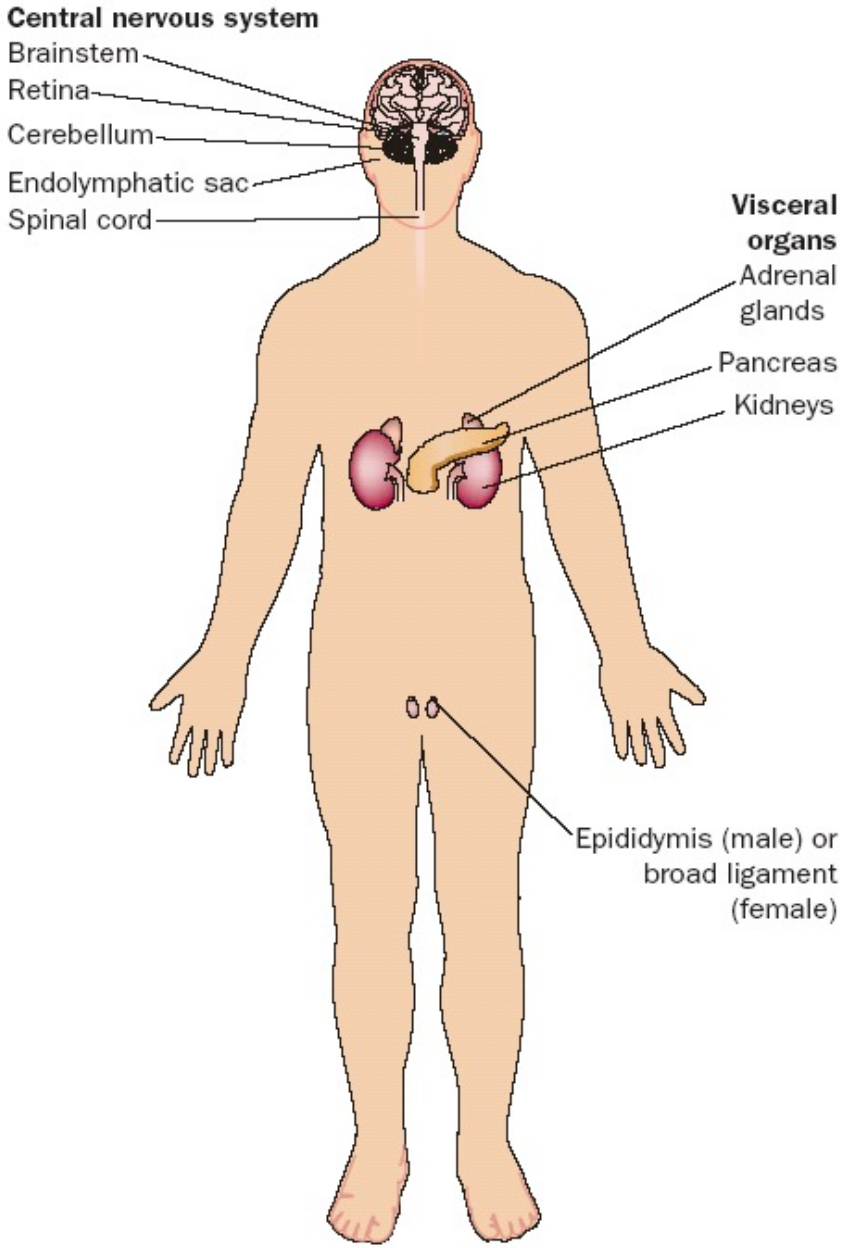
Module 2 – First-Line Treatment of Metastatic Disease

Module 3 – Management of Relapsed/Refractory Disease

Module 4 – Belzutifan

VHL disease manifestations

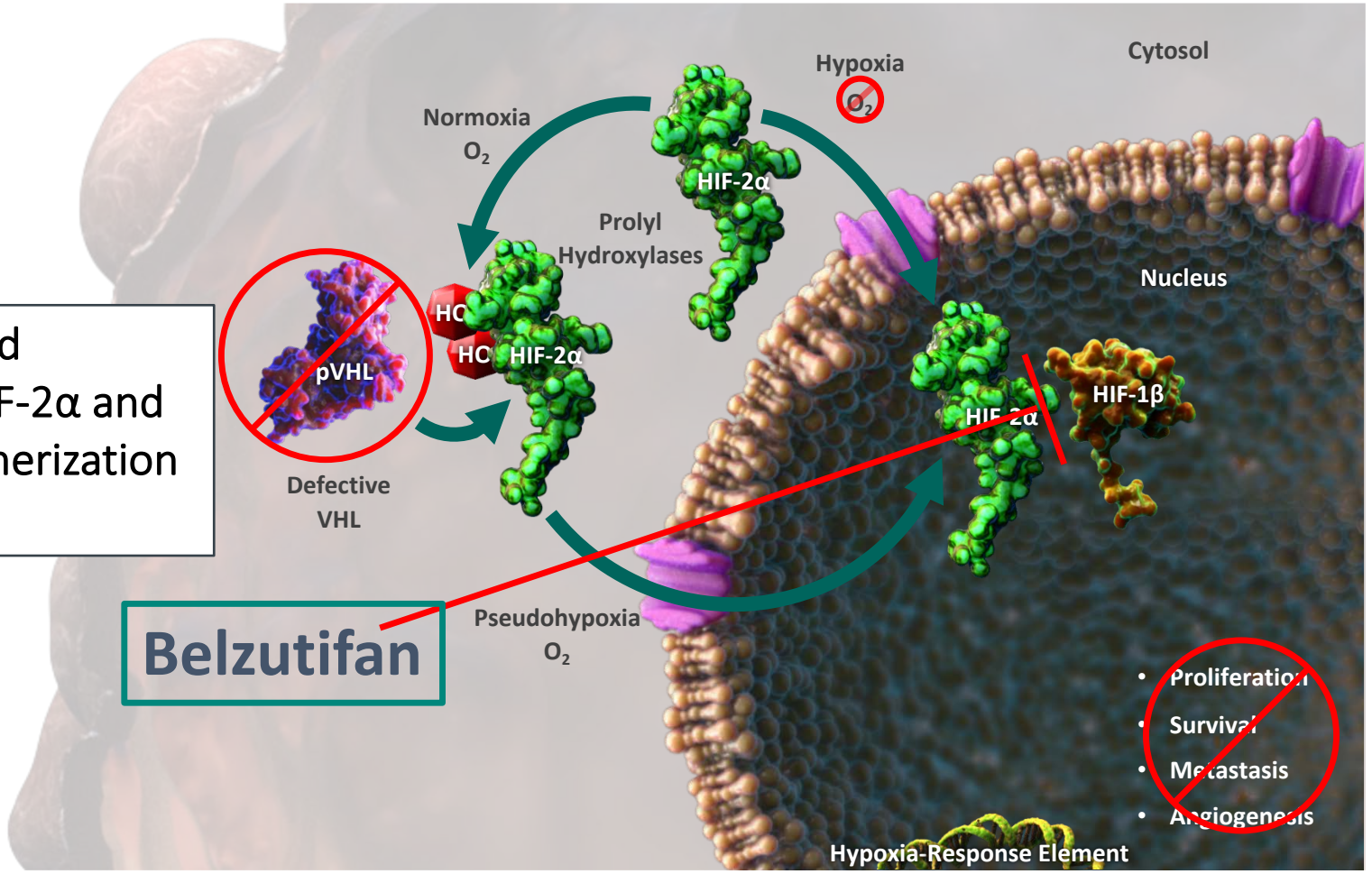
1. Endolymphatic sac tumors
2. Retinal hemangioblastomas
3. Cerebellar and spinal hemangioblastomas
4. Pancreatic cyst and neuroendocrine tumors
5. Kidney cysts and clear cell carcinomas
6. Pheochromocytomas
7. Epididymis/round ligament cysts



Lonser *Lancet* 2003

Belzutifan: HIF-2α Inhibitor

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



Kaelin WG Jr. *Trans Am Clin Climatol Assoc*. 2017;128:298-307. Kondo K et al. *Cancer Cell.* 2002;1:237-246. Xu R et al. *J Med Chem.* 2019;62:6876-6893.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., Rodolfo F. Perini, M.D., W. Marston Linehan, M.D., and Ramaprasad Srinivasan, M.D., Ph.D., for the MK-6482-004 Investigators*

N Engl J Med 2021;385:2036-46.

Belzutifan for VHL-associated RCC (NCT03401788)

- Diagnosis of VHL disease, based on germline mutation
- ≥1 measurable RCC tumor
- No prior systemic anticancer therapy
- No metastatic disease
- ECOG PS 0 or 1

N = 61

MK-6482
120 mg orally once daily

Tumor evaluation performed at screening and every 12 weeks thereafter

Primary End Point
- ORR in VHL-associated RCC tumors per RECIST v1.1 by independent central review

Secondary End Points
- ORR in non-RCC lesions
- DOR **in RCC and non-RCC lesions**
- Safety

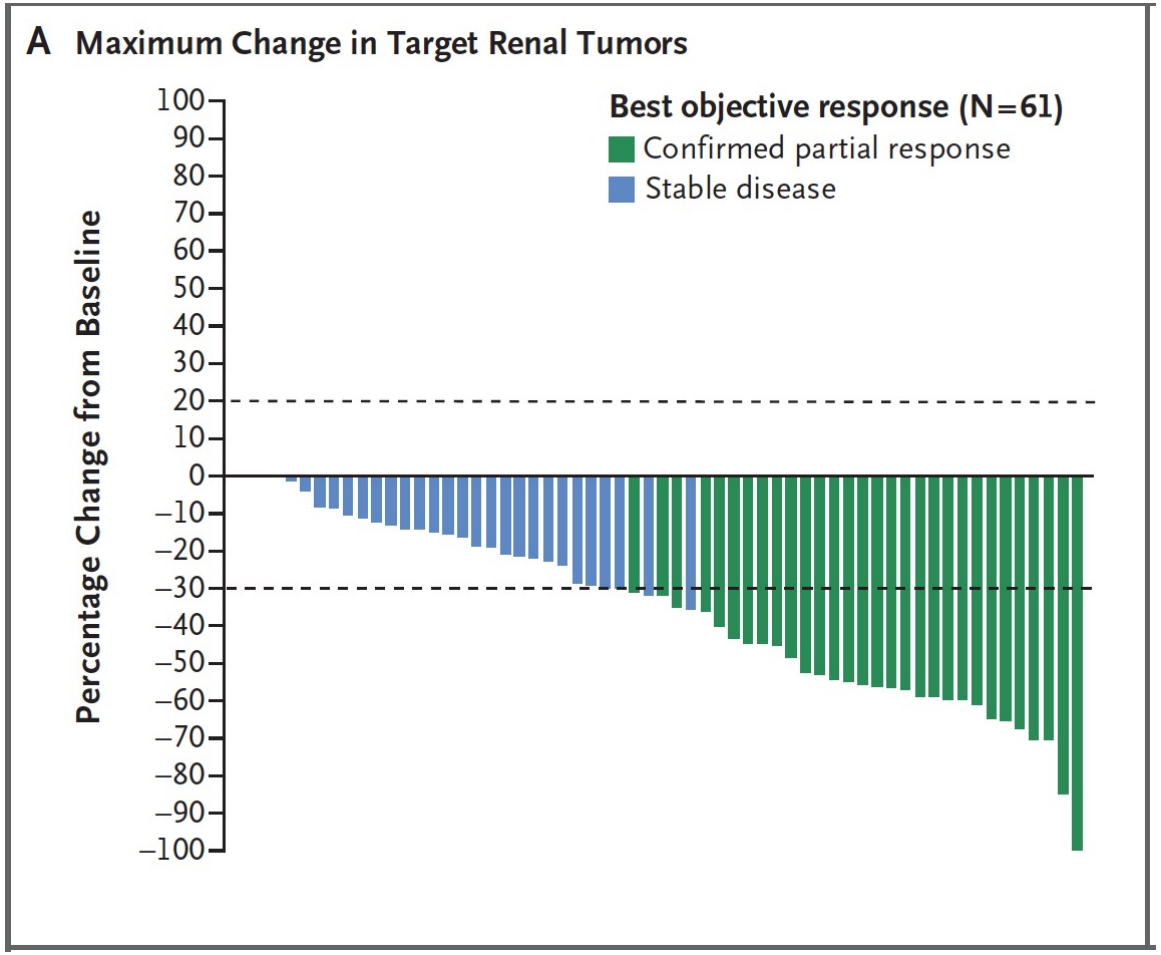
Primary Objective

- To evaluate efficacy of MK-6482 for the treatment of VHL disease–associated RCC

Response in target RCC lesions by independent central review

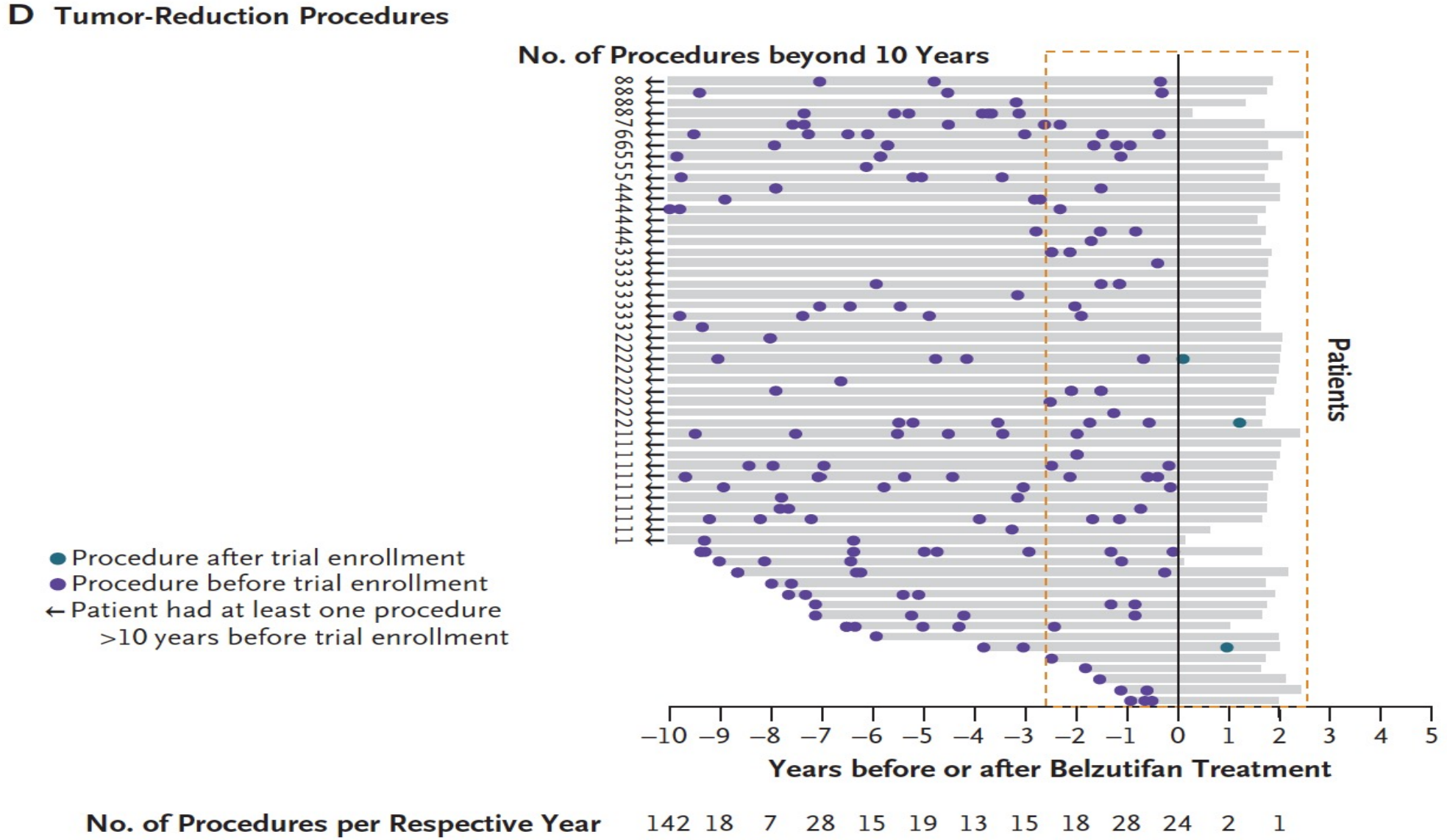
Table 2. Best Objective Response in Renal Cell Carcinoma Associated with VHL Disease.*

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



Jonasch and Srinivasan *NEJM* 2021

Distribution of all tumor reduction procedures before and after treatment initiation for individual patients



Jonasch and Srinivasan *NEJM* 2021

Confirmed ORR in pancreatic lesions and CNS hemangioblastomas by independent central review

	Pancreatic Lesions[a] N = 61	Pancreatic Neuroendocrine Tumors N = 22	CNS Hemangioblastoma N = 50
ORR, % (95% CI)	77.0 (64.5-86.8)	90.9 (70.8-98.9)	30.0 (17.9-44.6)
Best response, n (%)			
CR	6 (9.8)	3 (13.6)	3 (6.0)
PR	41 (67.2)	17 (77.3)	12 (24.0)
SD	13 (21.3)	2 (9.1)	31 (62.0)
PD	0	0	2 (4.0)
Not evaluable	1 (1.6)	0	2 (4.0)

[a]Includes pancreatic neuroendocrine tumors and serous cystadenomas.

Jonasch and Srinivasan *NEJM* 2021

Sporadic RCC: 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)

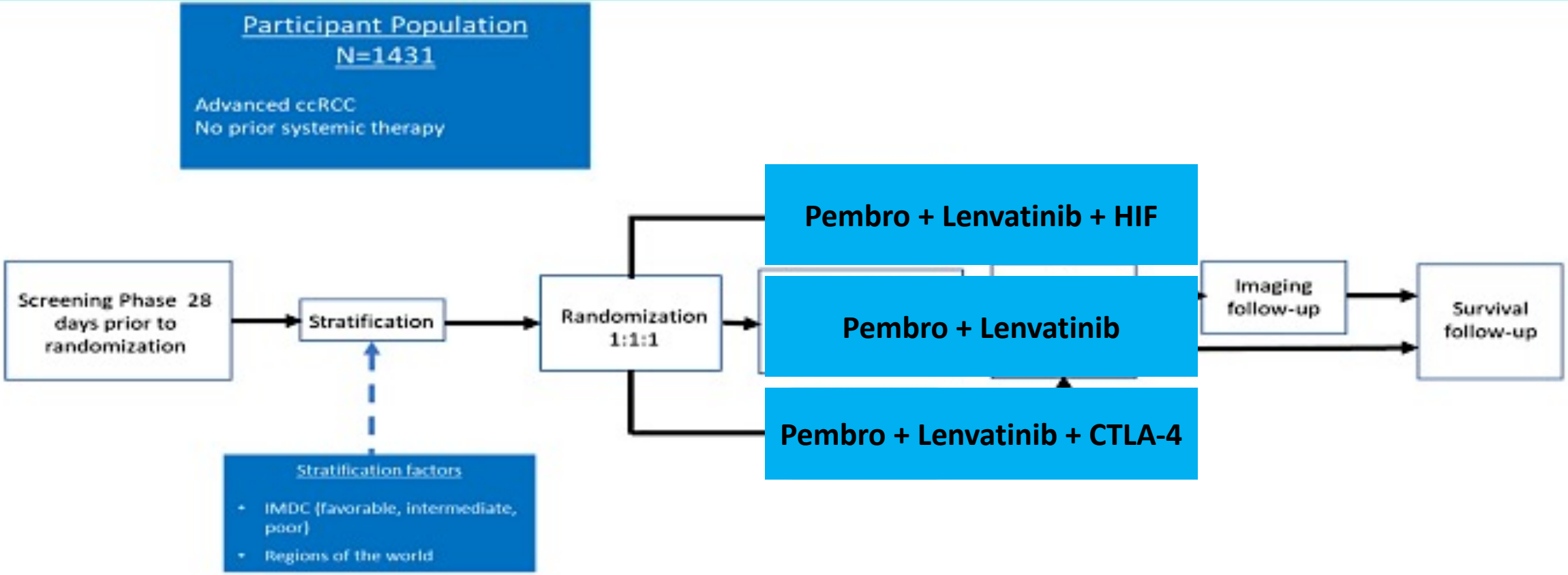
Choueiri TK et al. *Nat Med.* 2021;27:802-805.

Phase II Trial of Belzutifan: Select Adverse Events

Adverse event (n = 61)	Any grade	Grade 3
Anemia	55 (90%)	5 (8%)
Fatigue	40 (66%)	3 (5%)
Dyspnea	14 (23%)	1 (2%)
Myalgia	12 (20%)	1 (2%)
Hypertension	10 (16%)	5 (8%)
Diarrhea	8 (13%)	1 (2%)

Jonasch E et al. *N Engl J Med* 2021;385:2036-46.

MK-6482-012 Study Design



- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). Note: MK-1308A is a coformulation of pembrolizumab and MK-1308
- Global Study- ~225 sites, 33 countries

MSD

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Appendix of Recent Data Sets

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 2022;[Online ahead of print].

JAVELIN Renal 101: Relative Risk (RR) of Major Adverse Cardiovascular Event (MACE) by Baseline Serum Cardiac Biomarker Level

Cardiac serum biomarker	Avelumab + axitinib (n = 434)		Sunitinib (n = 439)	
	MACE/no MACE	RR of MACE	MACE/no MACE	RR of MACE
Troponin T				
High	6/29	3.31	2/39	0.89
Not high	7/128		9/156	

- Other cardiovascular baseline risk factors and serum cardiac biomarkers were not significantly predictive for MACE, although a trend toward an association with dyslipidemia was seen in the combination arm
- No clinical value of on-treatment routine monitoring of LVEF in relation to MACE was observed

Rini BI et al. *J Clin Oncol* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Research

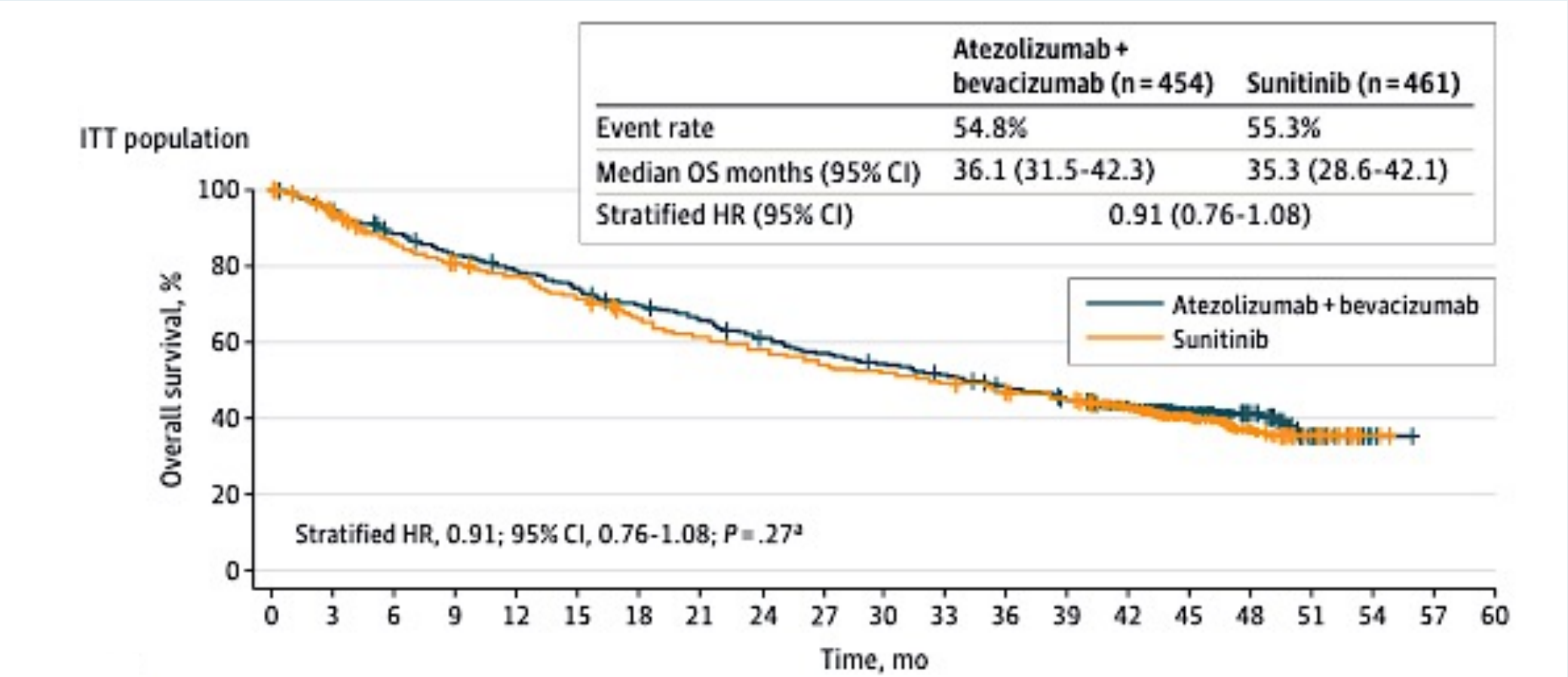
JAMA Oncology | Brief Report

Final Overall Survival and Molecular Analysis in IMmotion151, a Phase 3 Trial Comparing Atezolizumab Plus Bevacizumab vs Sunitinib in Patients With Previously Untreated Metastatic Renal Cell Carcinoma

Robert J. Motzer, MD; Thomas Powles, MD; Michael B. Atkins, MD; Bernard Escudier, MD; David F. McDermott, MD; Boris Y. Alekseev, MD; Jae-Lyun Lee, MD, PhD; Cristina Suarez, MD; Daniil Stroyakovskiy, MD; Ugo De Giorgi, MD, PhD; Frede Donskov, MD; Begoña Mellado, MD, PhD; Romain Banchereau, PhD; Habib Hamidi, PhD; Omara Khan, MSc; Veronica Craine, MS; Mahrukh Huseni, MS; Nick Flinn, PhD; Sarita Dubey, MD; Brian I. Rini, MD

JAMA Oncol 2022;8(2):275-80.

IMmotion151: Final Analysis of Overall Survival



	Atezolizumab + bevacizumab (n = 454)	Sunitinib (n = 461)
Event rate	54.8%	55.3%
Median OS months (95% CI)	36.1 (31.5-42.3)	35.3 (28.6-42.1)
Stratified HR (95% CI)	0.91 (0.76-1.08)	

- For the PD-L1-positive population, median OS was 38.7 months on the atezolizumab/bevacizumab arm and 31.6 months on the sunitinib arm (HR 0.85)

Motzer RJ et al. *JAMA Oncol* 2022;8(2):275-80.

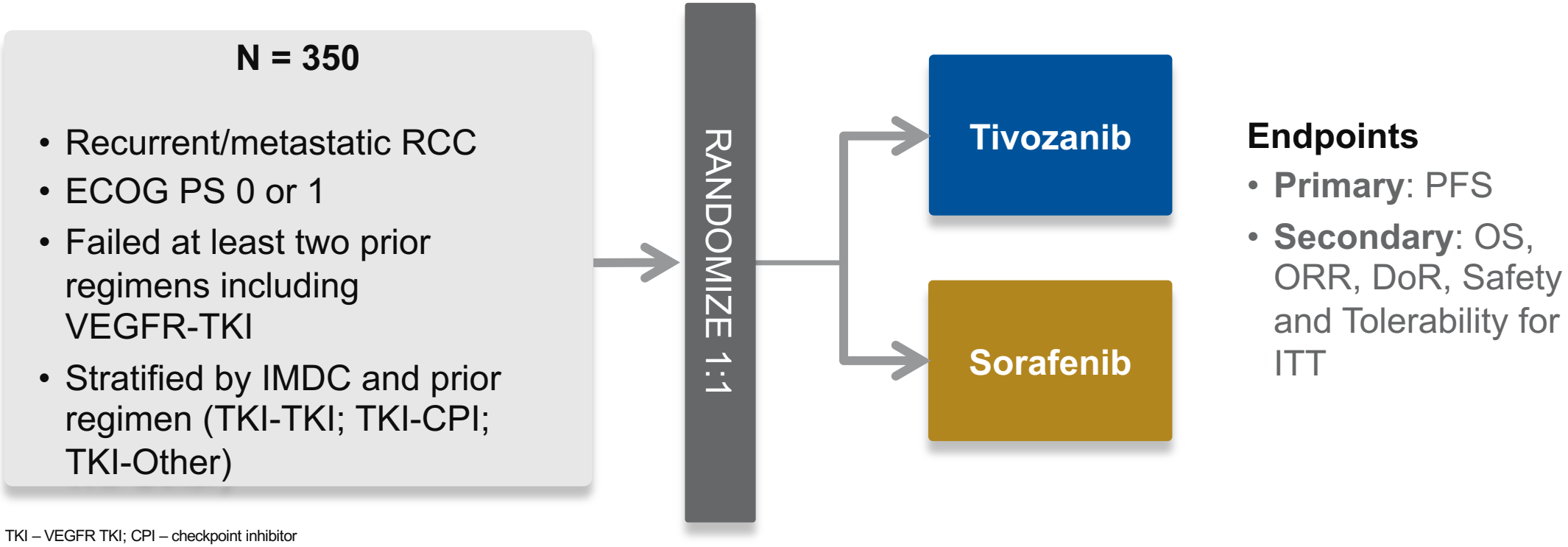
The role of NIVO + IPI (salvage/rescue)

	HCRN ASCO GU 2022	OMNIVORE ASCO 2020	FRACTION ASCO 2020	TITAN RCC ESMO 2019	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%	14%	15%	33%	20%
CR	3%	0%	0%	3%	0%

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

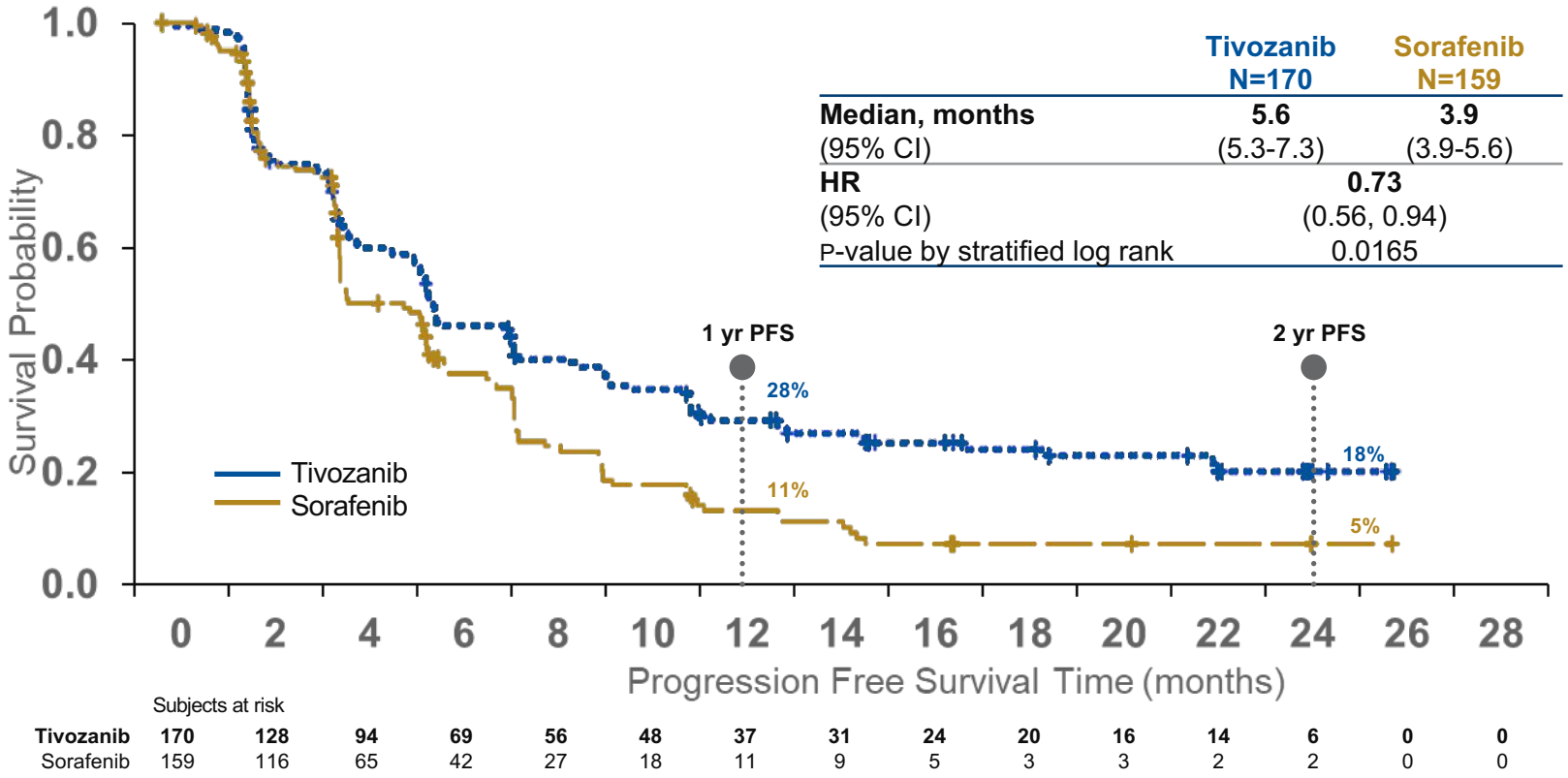
Refractory RCC: TIVO-3 Study Schema

Randomized Trial in Relapsed or Refractory Advanced Renal Cell Carcinoma



TKI – VEGFR TKI; CPI – checkpoint inhibitor

TIVO-3: Primary Endpoint of 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	

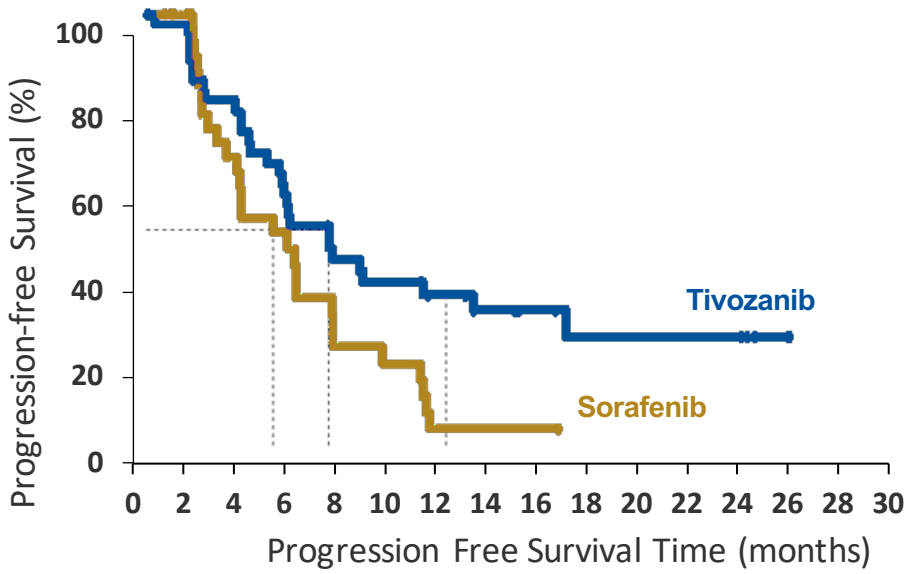
Subjects at risk

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

Rini B et al. Genitourinary Cancers Symposium 2021;Abstract 278

TIVO-3: PFS & ORR in Prior IO Subgroup



Porta et al. ASCO 2019

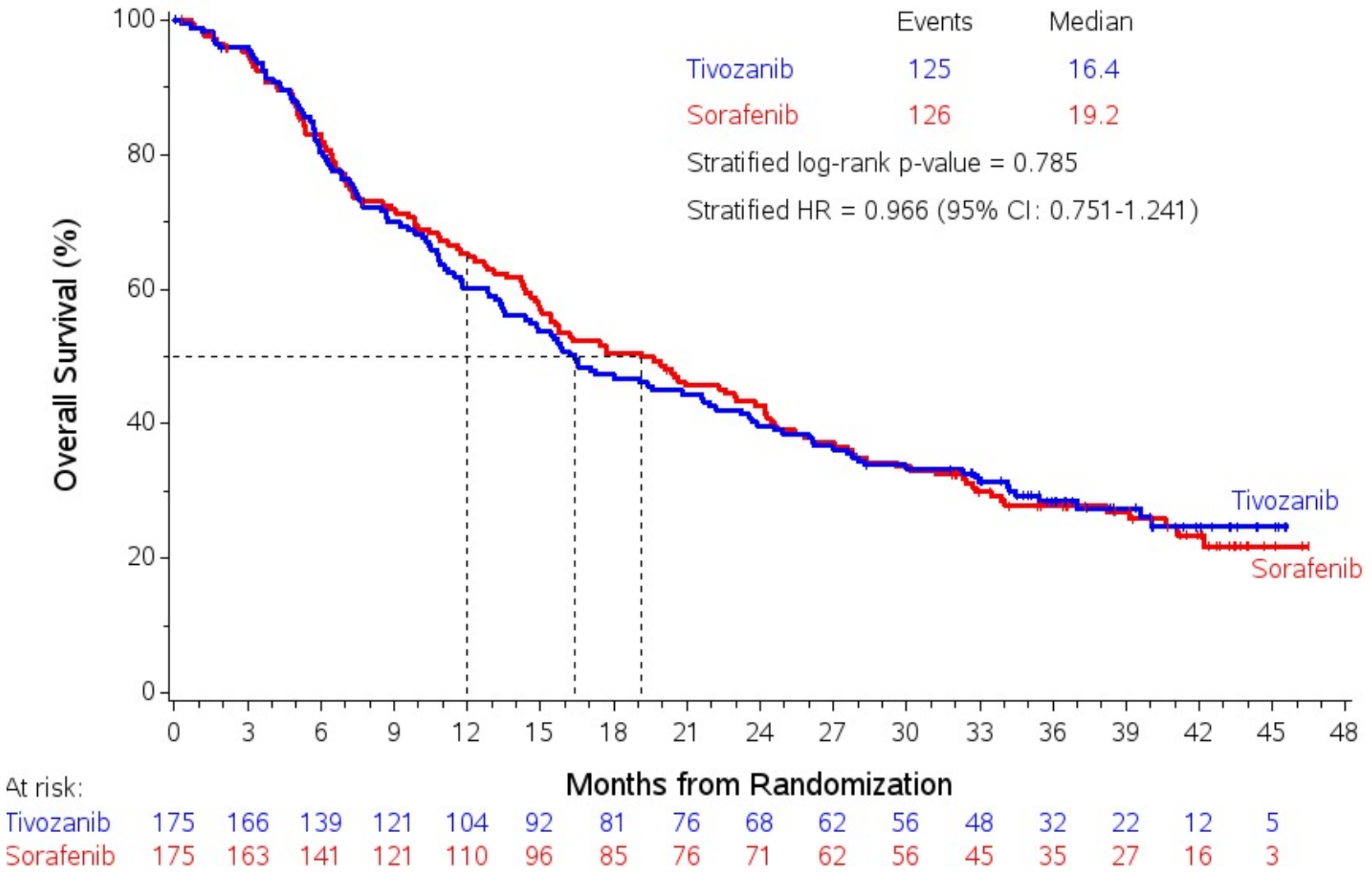
Prior Checkpoint Inhibitor (CPI) + VEGFR TKI

	Tivozanib (n=47)	Sorafenib (n=44)
Median PFS months (95% CI)	**7.3** (4.8, 11.1)	**5.1** (3.2, 7.4)
HR (95% CI)	**0.55** (0.32, 0.94)	
P-value	0.028	
ORR	24.4%	6.8%

Final analyses, Oct 4, 2018

Rini B et al. Genitourinary Cancers Symposium 2021;Abstract 278

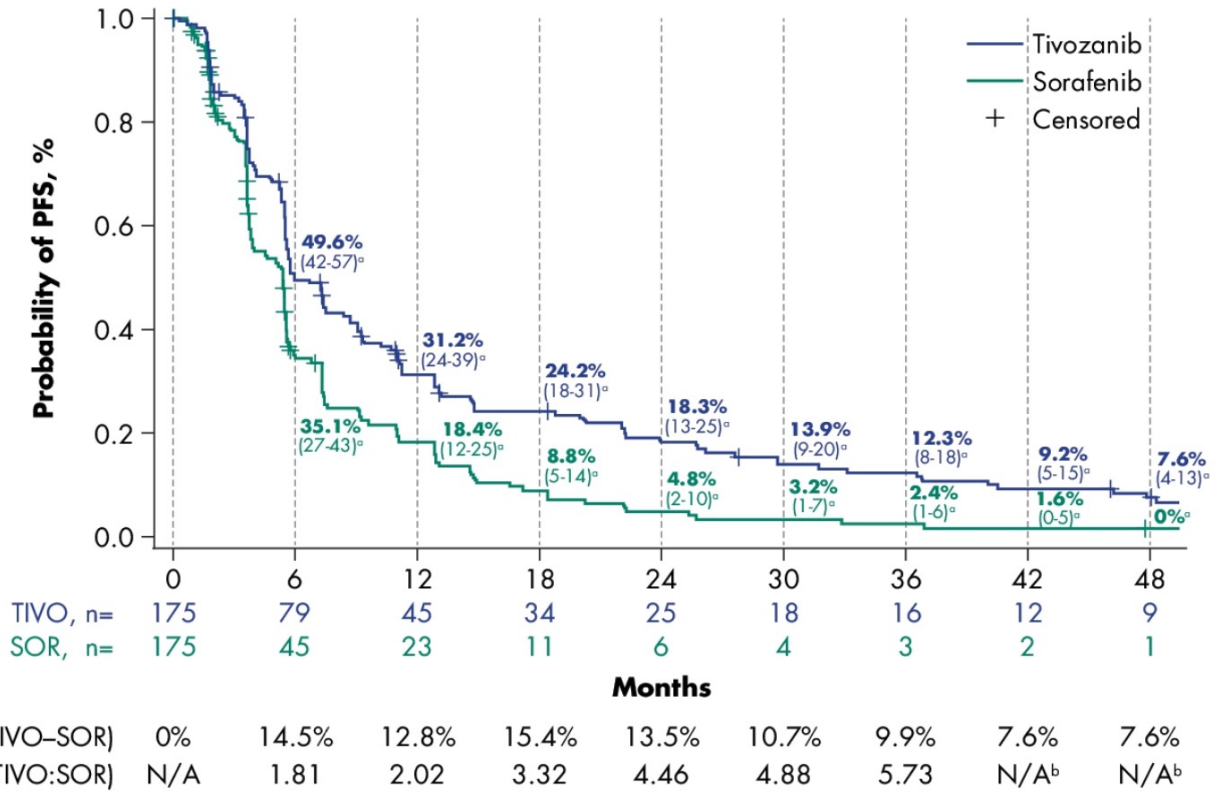
TIVO-3: Final OS



Pal. Eur Urol 2020;78(6):P783-5

Long-term PFS from TIVO-3

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/A[b]	N/A[b]

[a]% (95% CI). [b]OR not calculated at months 42 and 48 due to insufficient number at risk.
HR, 0.624 (95% CI, 0.49-0.79); log-rank *P*<.0001

- Mature OS was also analyzed, and a nonsignificant trend favoring TIVO continued to emerge with accumulation of events (HR, 0.89; 95% CI, 0.70-1.14)

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

Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Tuesday, May 24, 2022
5:00 PM – 6:00 PM ET

Faculty

Susan O'Brien, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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