Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

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

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Commercial Support

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Dr Love — Disclosures

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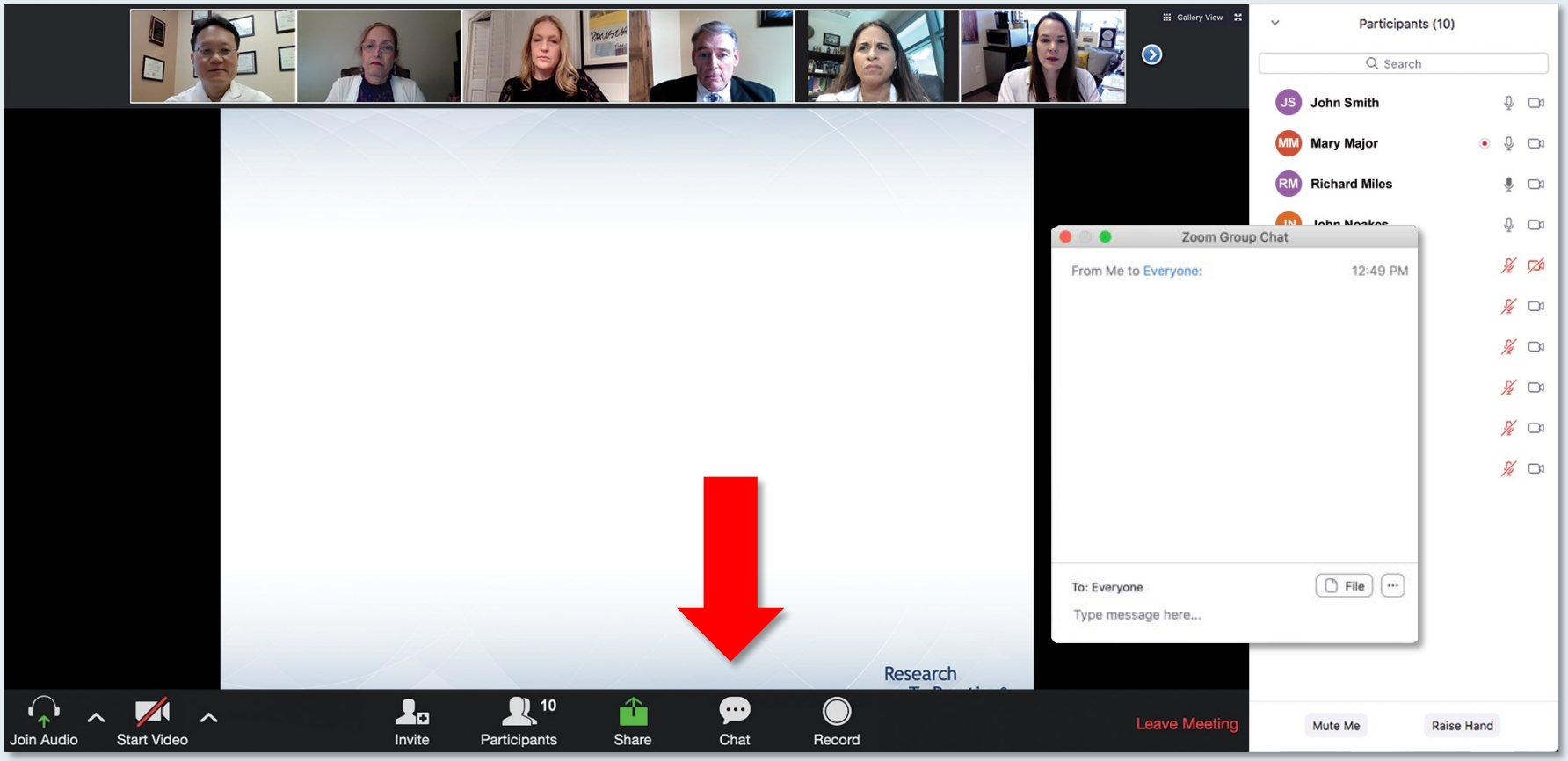
We Encourage Clinicians in Practice to Submit Questions



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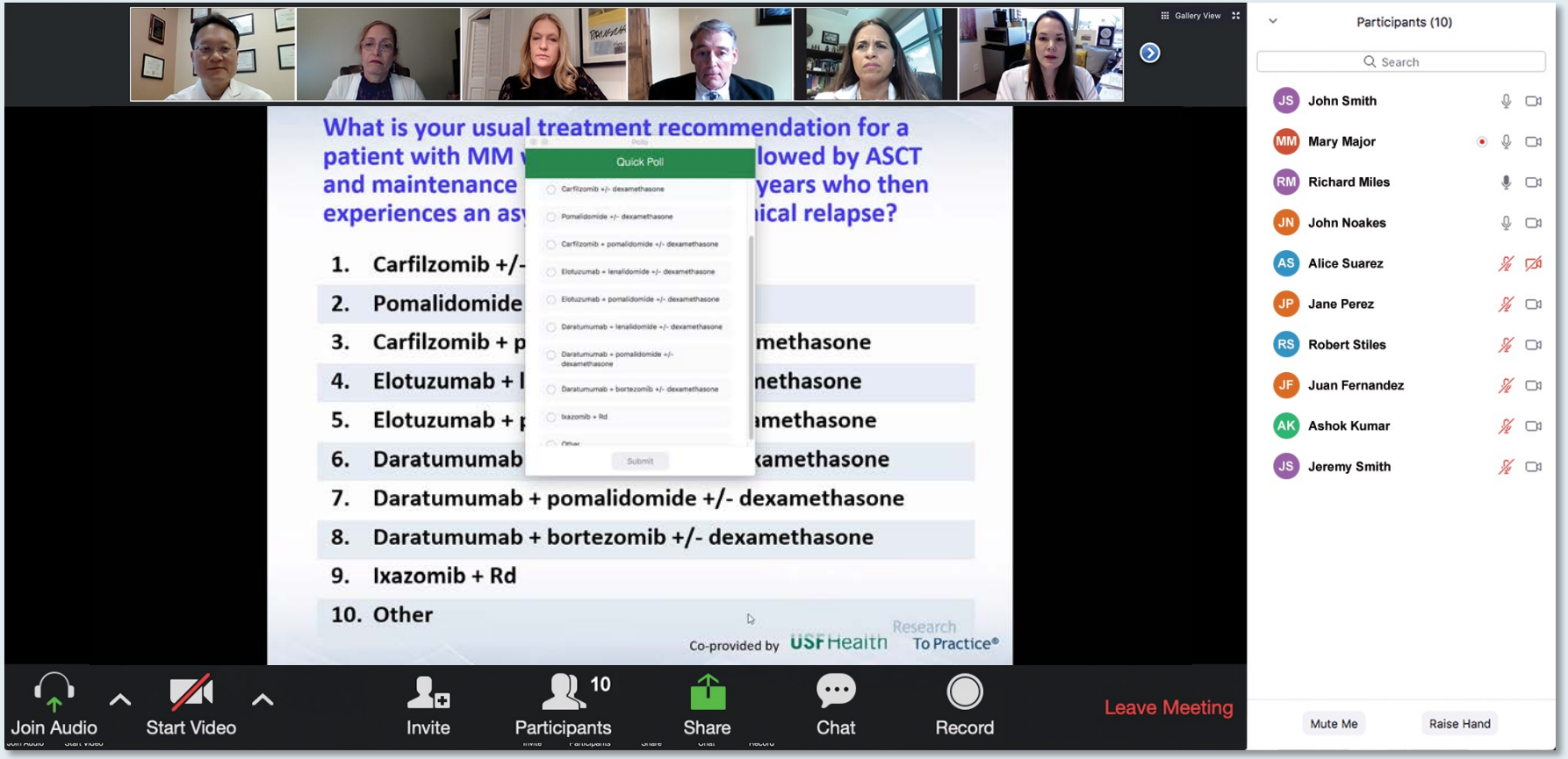

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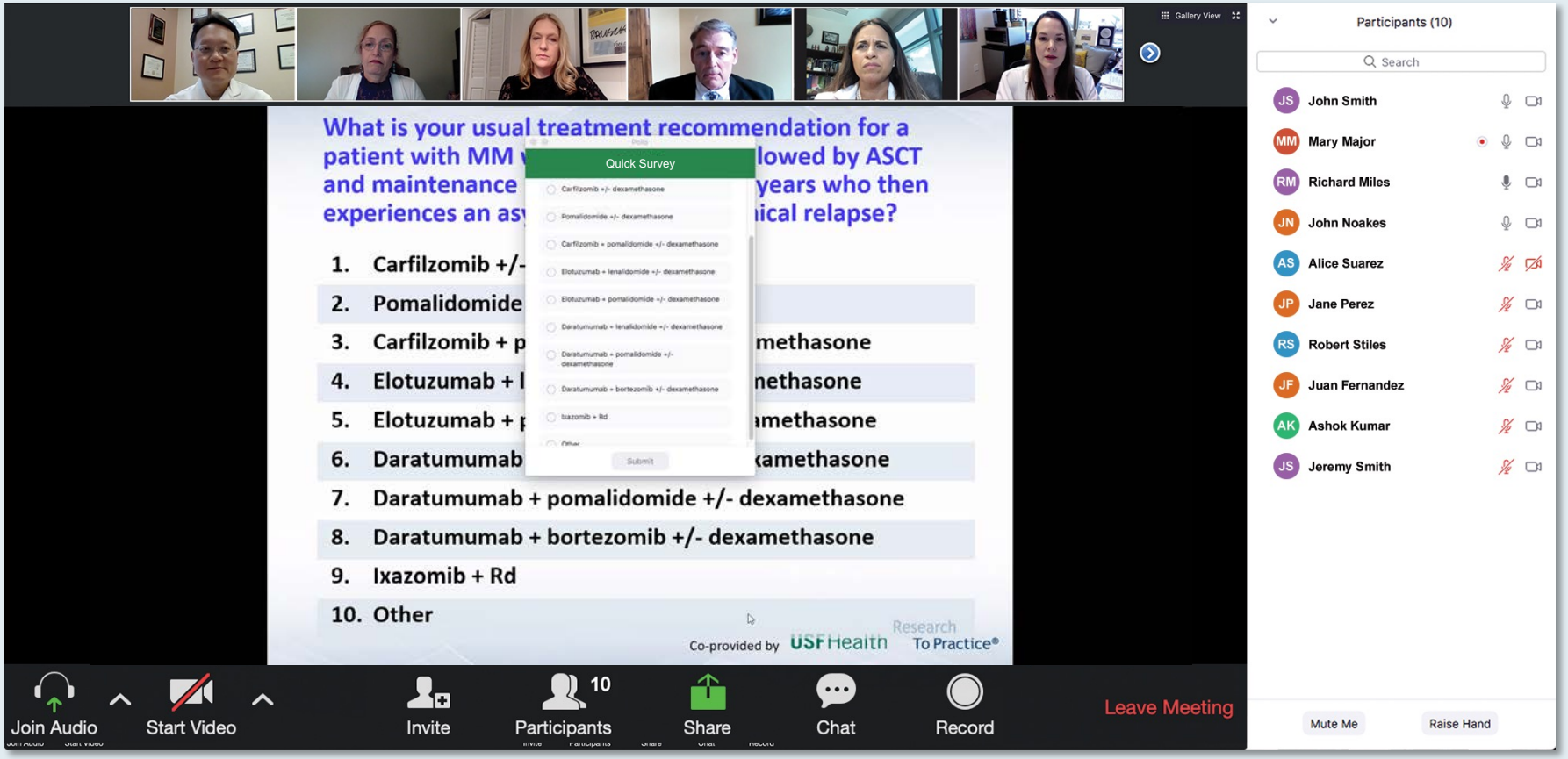

Clinicians in practice, please complete the premeeting survey.

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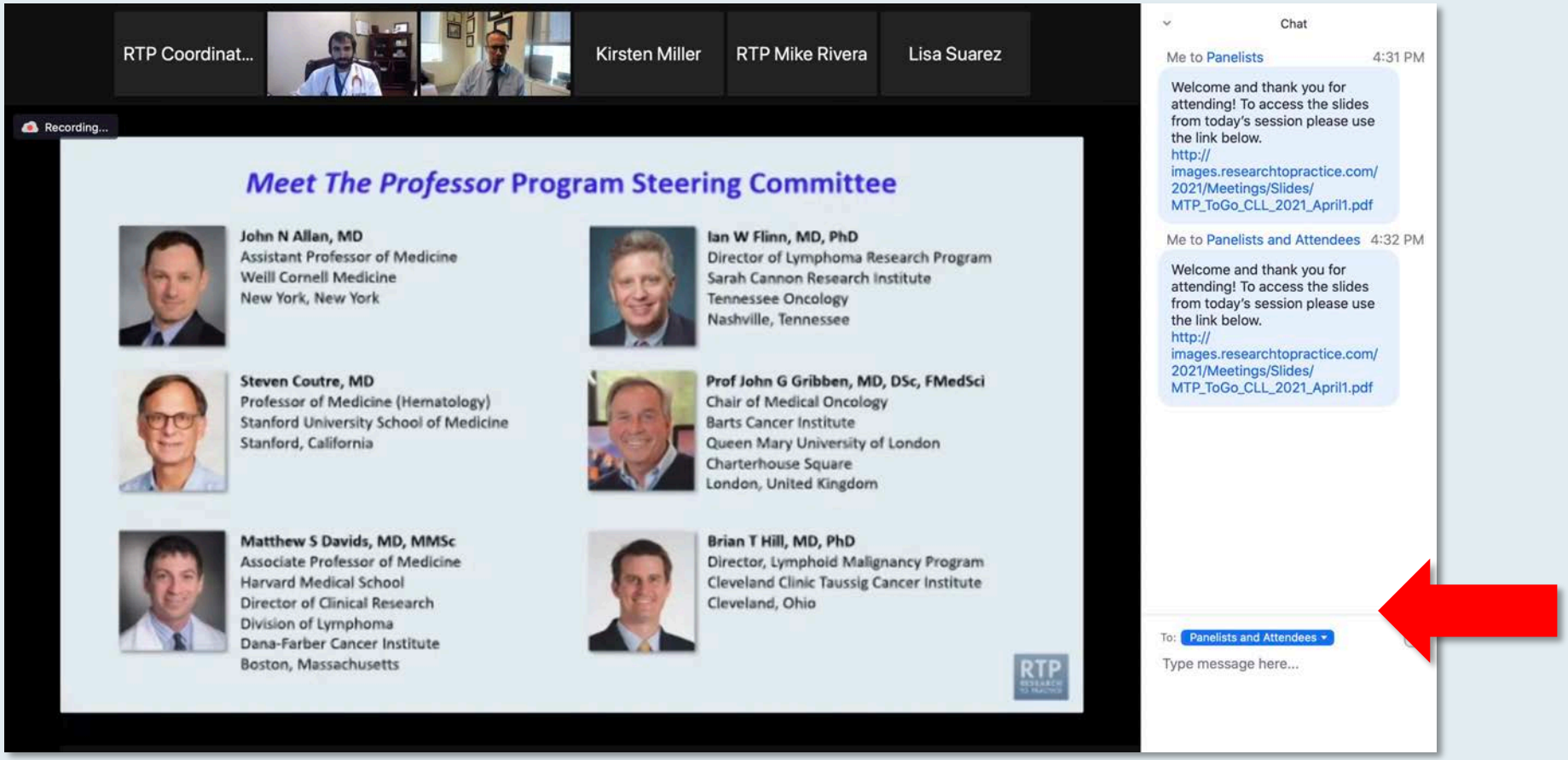

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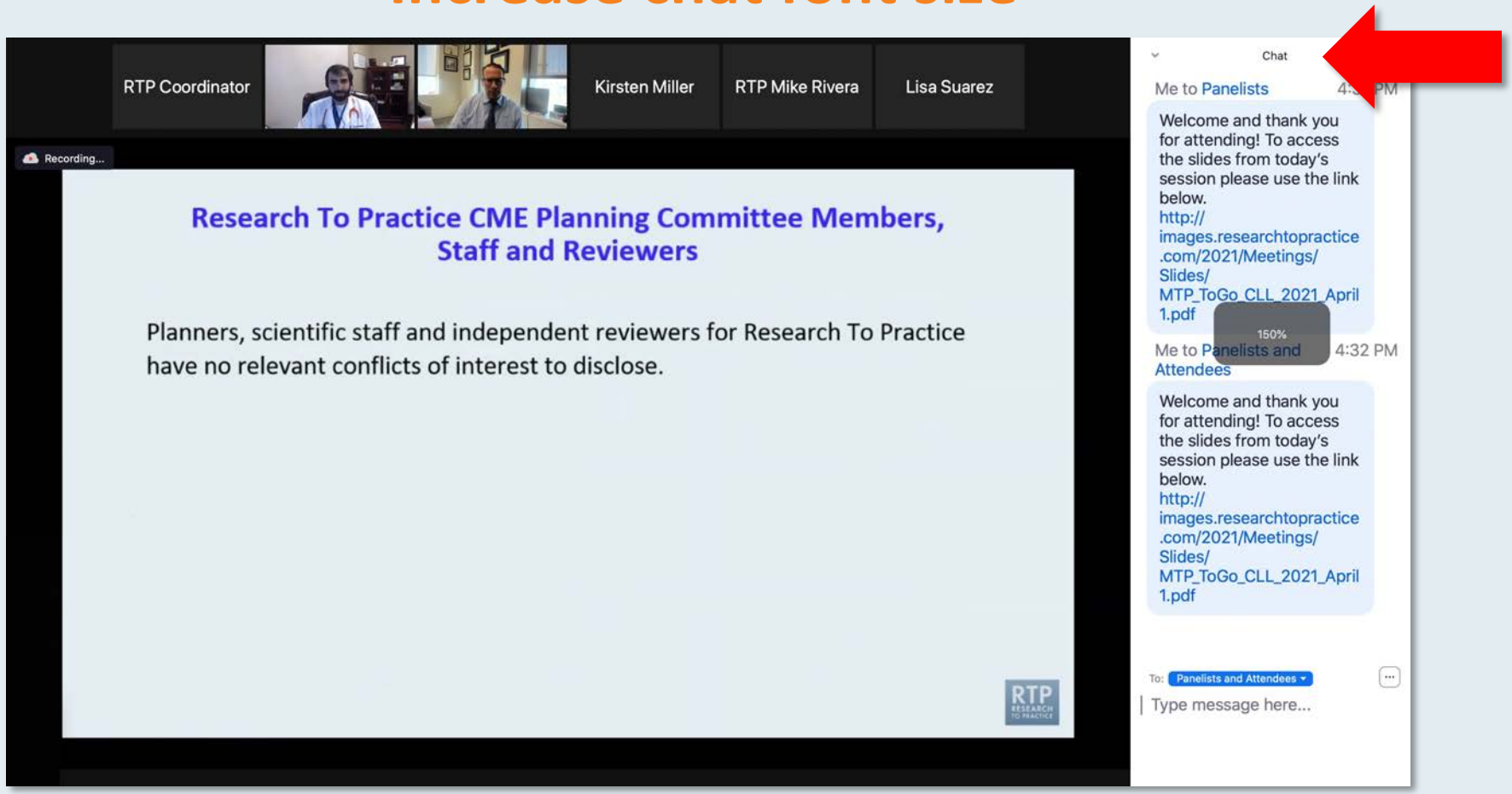

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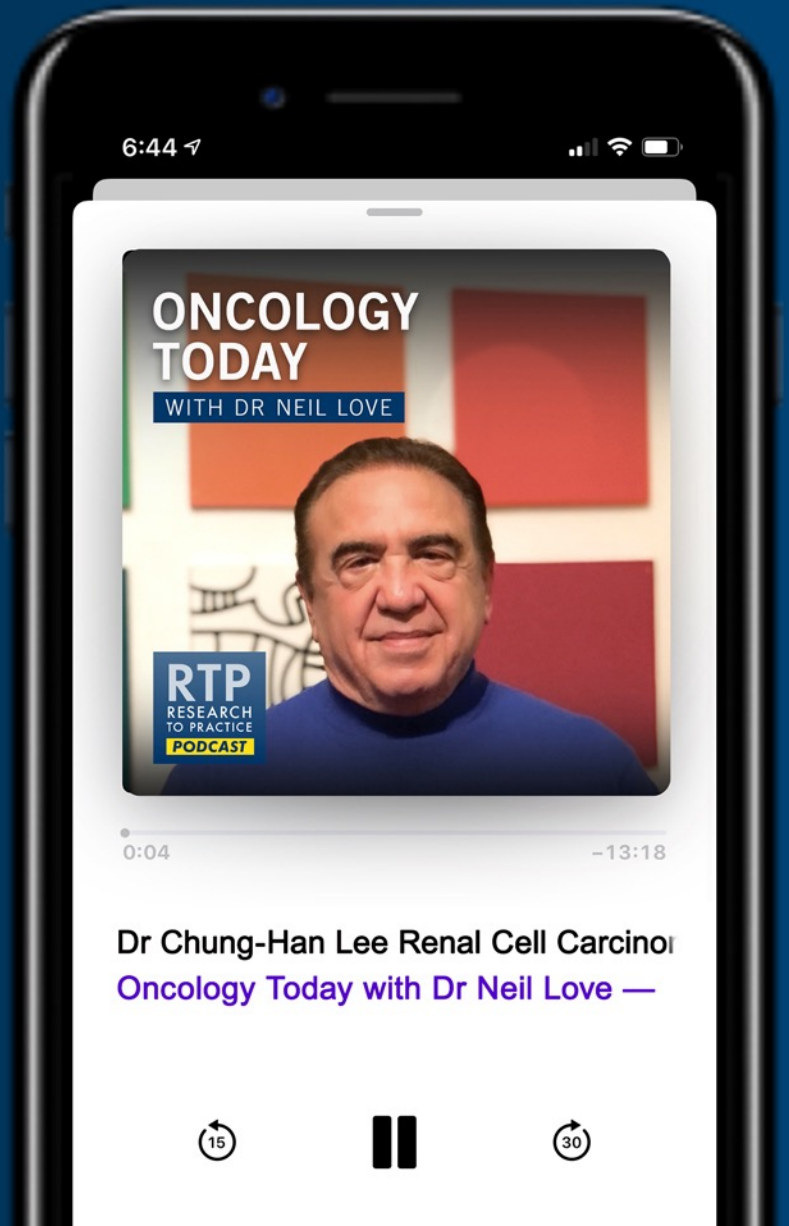

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Triple-Negative Breast Cancer

Tuesday, August 24, 2021
5:00 PM – 6:00 PM ET

Faculty

Sara Hurvitz, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Wednesday, August 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Wells A Messersmith, MD

Moderator

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Summer Oncology Nursing Series

A Complimentary NCPD-Accredited Virtual Curriculum

Gynecologic Cancers

Thursday, August 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Thomas J Herzog, MD
Kimberly A Spickes, MNSc, RN, APRN, OCN, ACNP-BC

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Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Chronic Lymphocytic Leukemia

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Philip A Thompson, MB, BS
Additional faculty to be announced.

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Immunotherapy and Novel Agents in Gynecologic Cancers

Wednesday, September 1, 2021
5:00 PM – 6:00 PM ET

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Moderator

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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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Boston, Massachusetts

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and Treatment Center
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Professor of Medicine
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Eugene P Frenkel, MD Scholar in Clinical Medicine
Co-Leader, Kidney Cancer Program
Co-Leader, Experimental Therapeutics
Associate Professor, Internal Medicine
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Eric Jonasch, MD
Professor of Medicine
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The University of Texas
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Leader, Kidney Cancer Program
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Professor of Medicine
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Boston, Massachusetts

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Professor, Department of Hematology/Oncology
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Professor of Genitourinary Oncology
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Moderator
Neil Love, MD
Research To Practice
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Ingram Professor of Medicine
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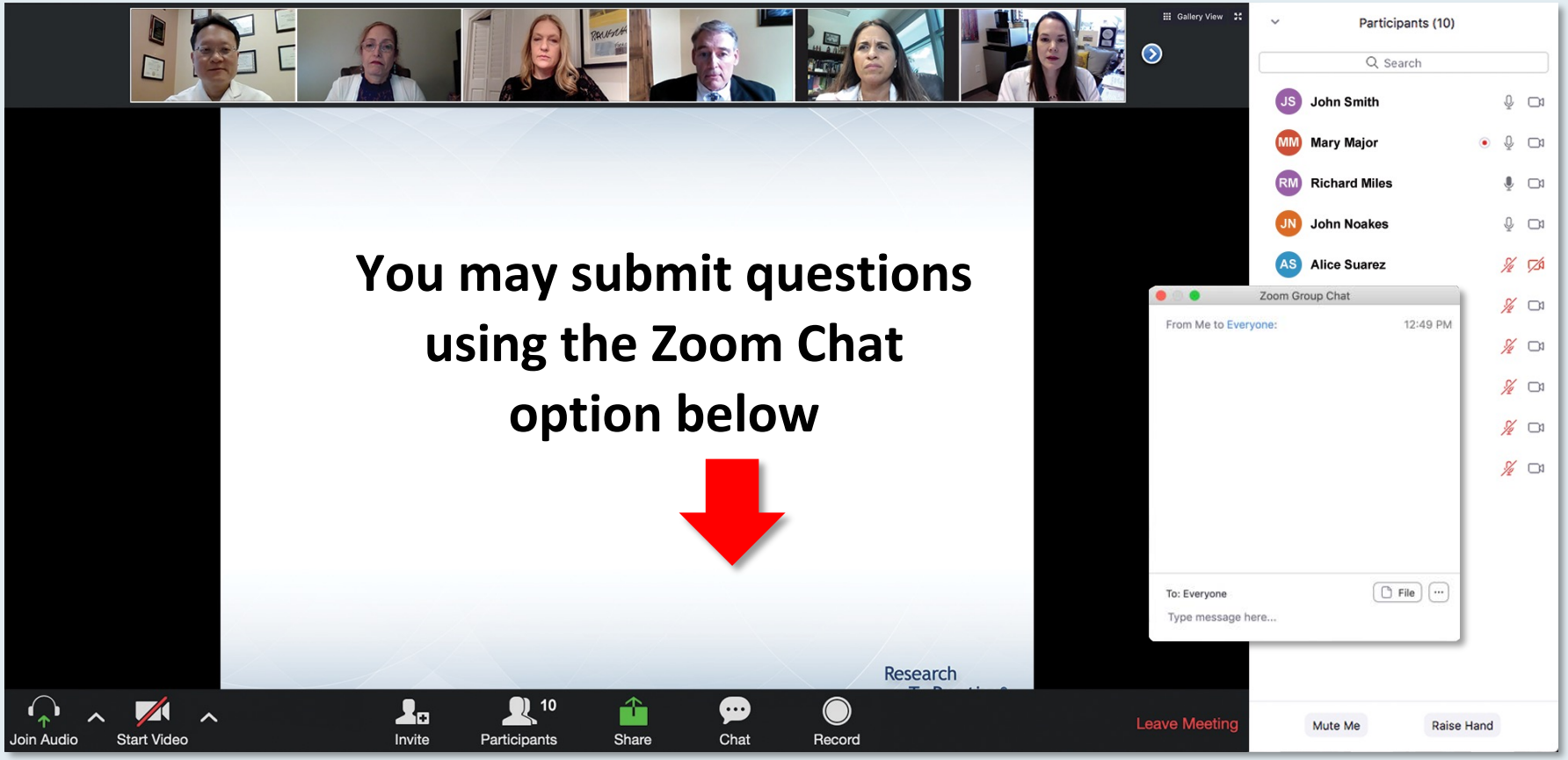

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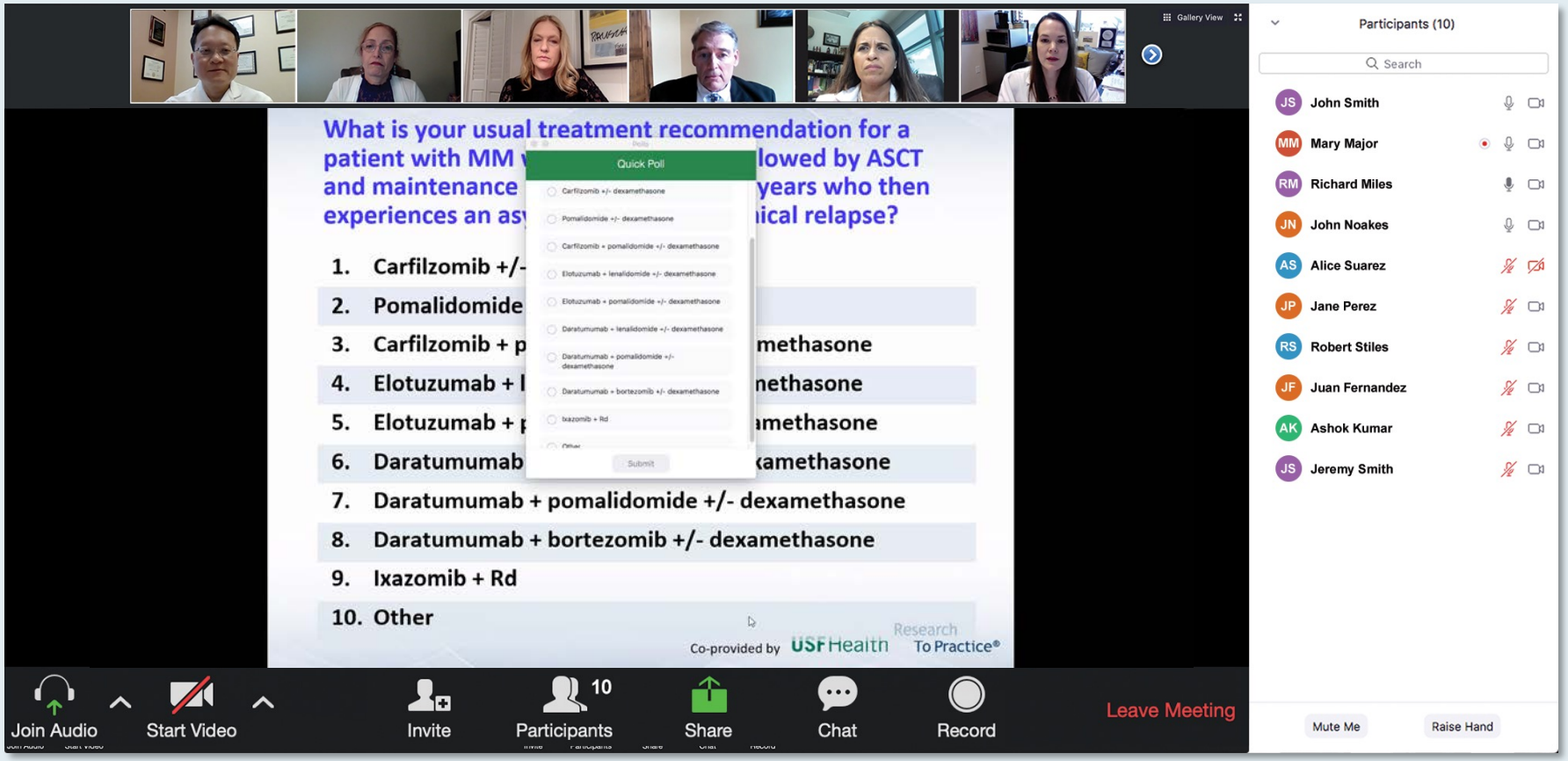

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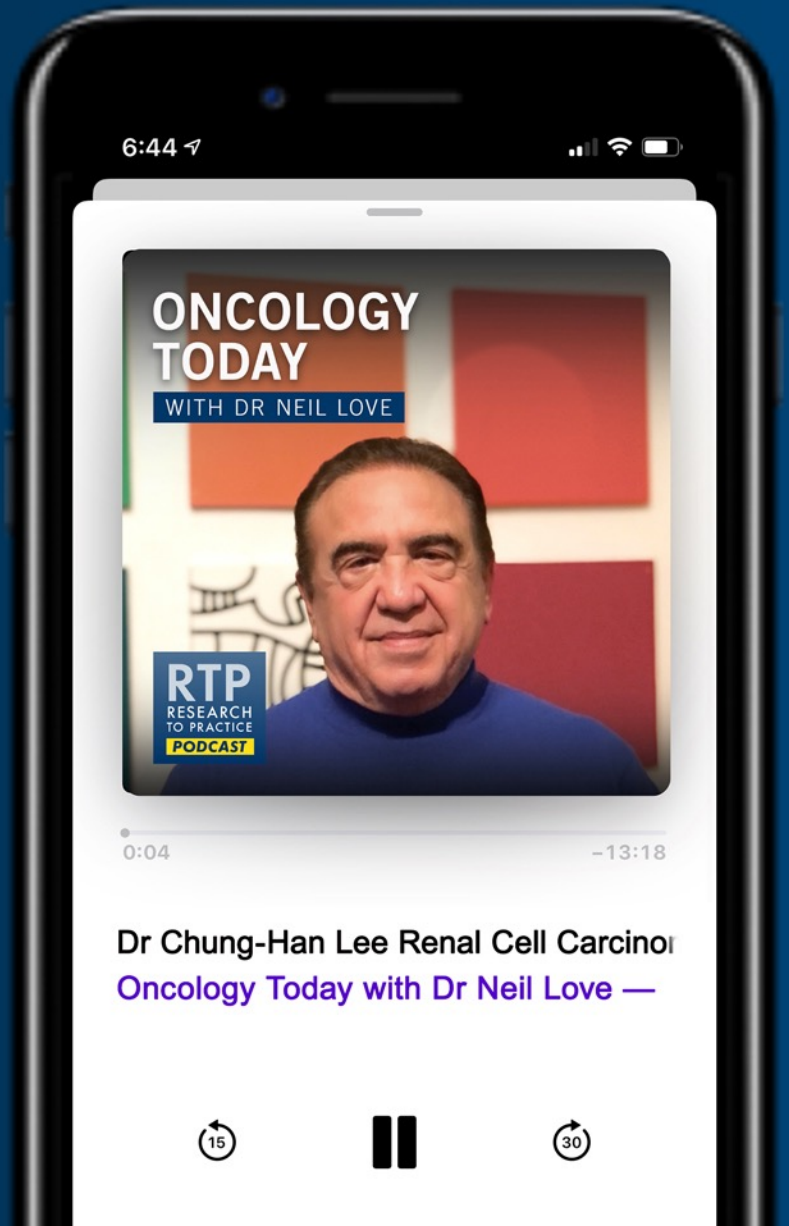

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Northern Light Eastern Maine
Medical Center
Brewer, Maine

Eric Jonasch, MD
Professor of Medicine
Department of Genitourinary Medical Oncology
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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

Meet The Professor with Dr Choueiri

MODULE 1: Case Presentations

- Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC
- Dr Jonasch: A 64-year-old man with clear cell RCC invasive into the renal vein
- Dr Brooks: A 61-year-old man with metastatic clear cell RCC
- Prof Powles: A 66-year-old man with metastatic papillary RCC
- Dr Jonasch: A 30-year-old man with von Hippel-Lindau disease

MODULE 2: Journal Club with Dr Choueiri

MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets

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Case Presentation – Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC

Prof Thomas Powles

- Marathon runner who presents with recent weight loss, pain and SOB (PS 2)
- Pleural effusion, lung metastases (1.5-cm x 10) and 9-cm renal mass

Questions

- For a patient with poor-risk metastatic RCC that is largely driven by the renal mass, would you consider a nephrectomy if the surgeons believed that it was feasible?

Case Presentation – Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC (continued)

Prof Thomas Powles

- Marathon runner who presents with recent weight loss, pain and SOB (PS 2)
- Pleural effusion, lung metastases (1.5-cm x 10) and 9-cm renal mass
- ***Ipilimumab/nivolumab, with rapid symptom and PS improvement by 3 weeks***
  - ***At week 12: CR in lungs, great response in kidney, with apparent necrotic tissue***
  - ***At 8 months: Increase in necrotic-type tissue in the kidney***

Questions

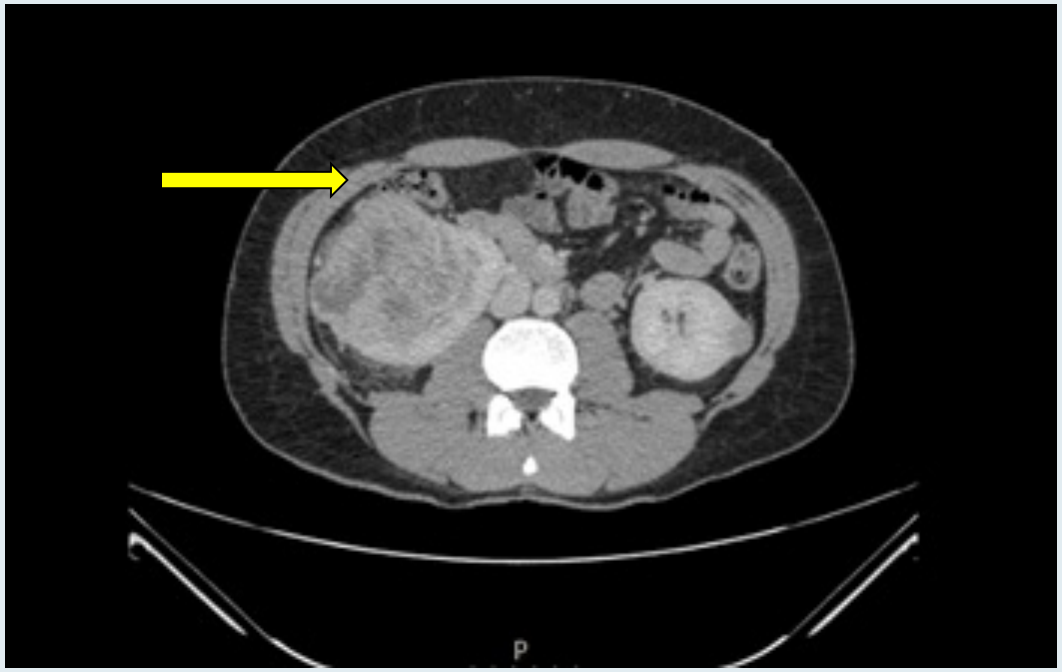
- ***What is the role of nephrectomy in a patient who has a achieved a CR to systemic therapy?***

Case Presentation – Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC (continued)

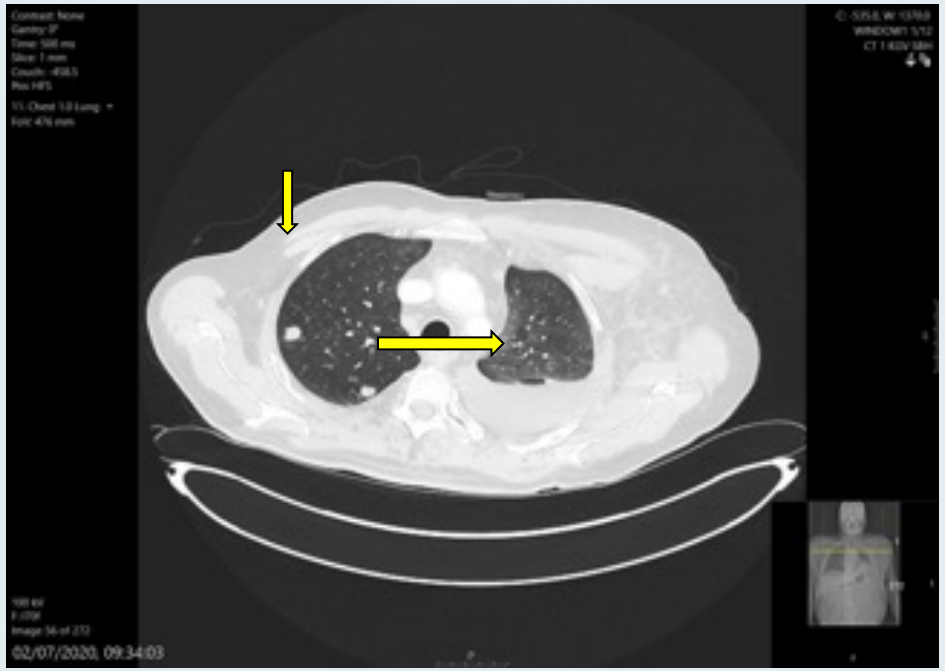
Prof Thomas Powles

Improvement with ipi/nivo at week 3

Large right kidney mass



Right lung nodule,
Left lung pleural effusion

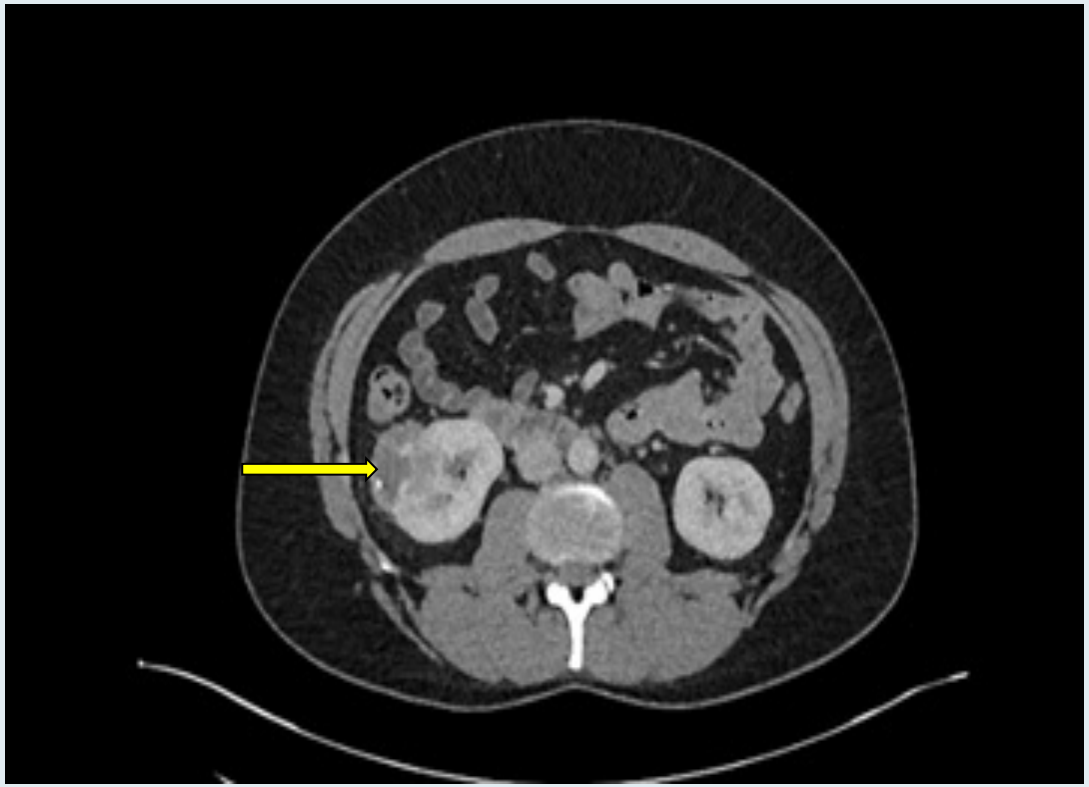


Case Presentation – Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC

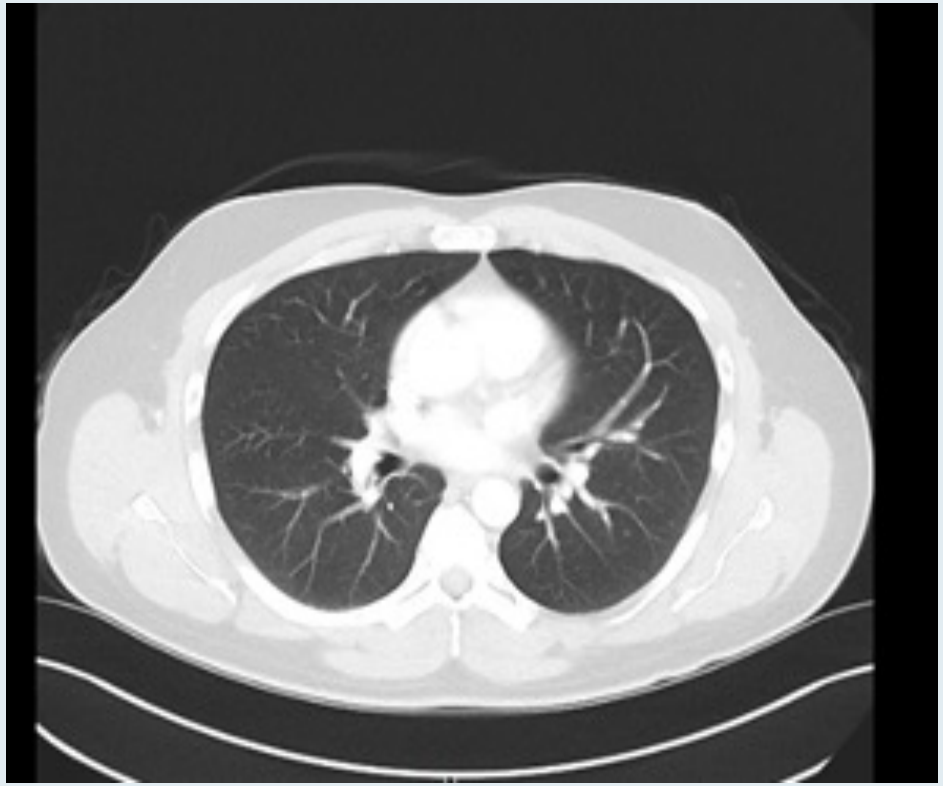
Prof Thomas Powles

Continued improvement with ipi/nivo at week 12

Right lung nodule and left pleural effusion are gone



Right kidney mass decreased markedly



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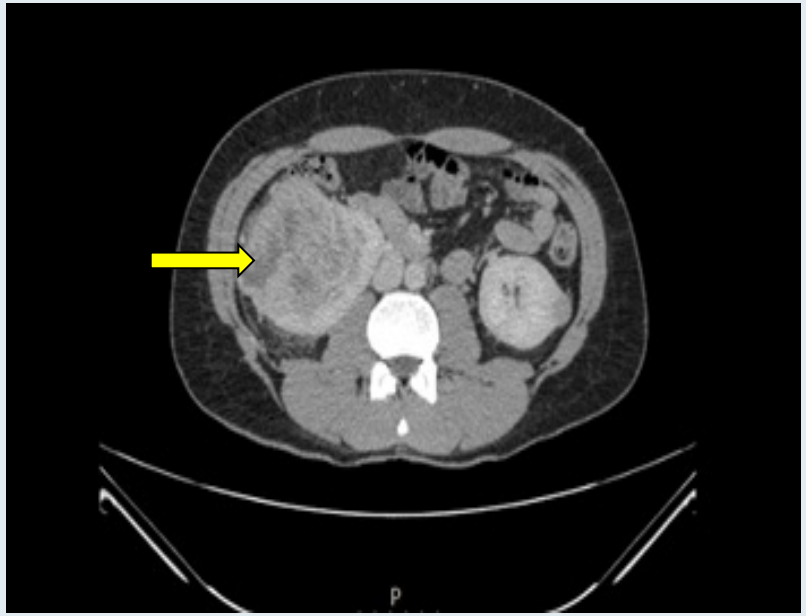
Case Presentation – Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC (continued)

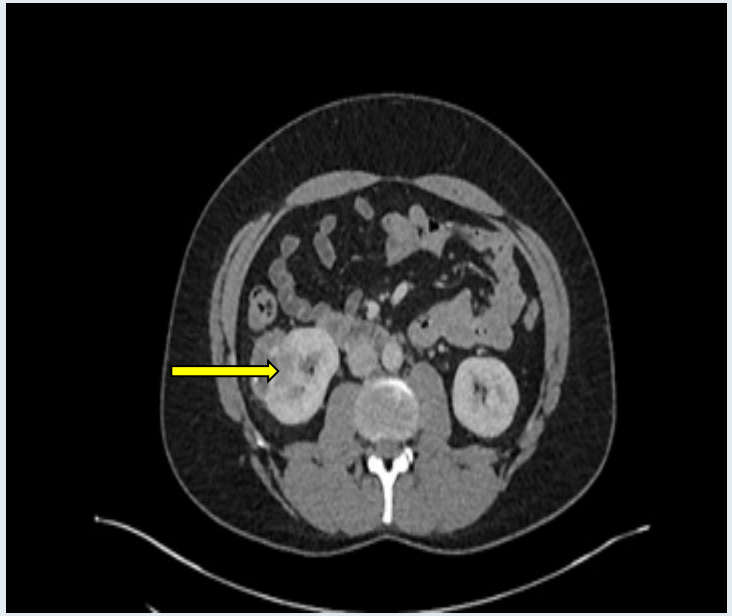
Prof Thomas Powles

Serial reduction in kidney mass over time

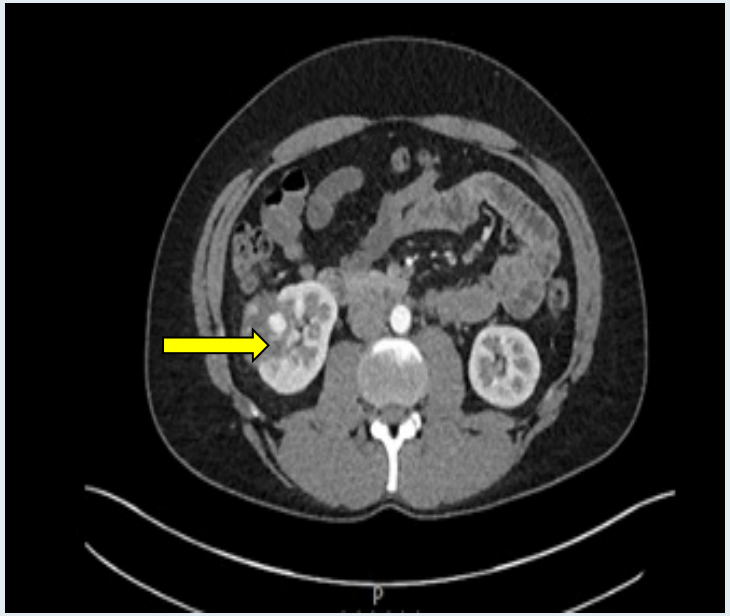
Baseline



3 months of therapy



8 months of therapy



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Case Presentation – Dr Jonasch: A 64-year-old man with clear cell RCC invasive into the renal vein

Dr Eric Jonasch

- Right renal mass found incidentally after presentation with abdominal pain and fever and diagnosis of diverticulitis
- Nephrectomy → Grade 3 clear cell RCC with renal vein invasion
- Post-operative imaging detects right parietal bone lesion

Questions

- What would you do next for this patient?

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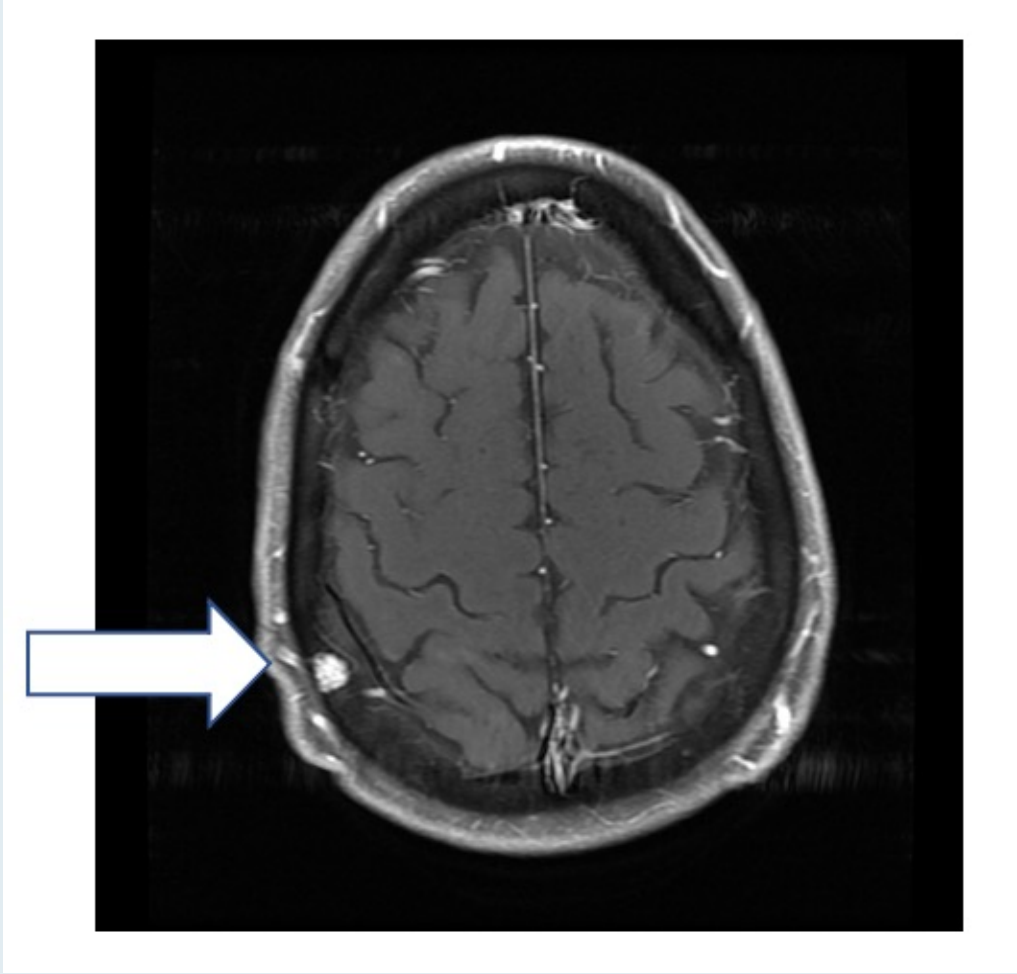
Case Presentation – Dr Jonasch: A 64-year-old man with clear cell RCC invasive into the renal vein (continued)

Dr Eric Jonasch



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Case Presentation – Dr Jonasch: A 64-year-old man with clear cell RCC invasive into the renal vein (continued)

Dr Eric Jonasch

- Right renal mass found incidentally after presentation with abdominal pain and fever and diagnosis of diverticulitis
- Nephrectomy → Grade 3 clear cell RCC with renal vein invasion
- ***Benign parietal bone lesion***
- ***Adjuvant therapy not recommended***
- ***Observation x 2 years and ongoing***

Case Presentation – Dr Brooks: A 61-year-old man with metastatic clear cell RCC

Dr Philip Brooks

- 2013: Hematuria but no follow up until 2/2018
- Right radical nephrectomy, removal of part of the IVC and thrombectomy
  - T3bN0 clear cell RCC
- Mid-2019 follow up CT: Multiple pulmonary nodules (largest 16 x 13 mm) and a soft tissue mass to the right of the IVC measuring 3 cm
  - Asymptomatic
- Followed x 3 months but clear progression of pulmonary nodules
- 10/2019: Ipilimumab/nivolumab
  - Tolerated it very well but by the 4th dose of ipilimumab he developed hypothyroidism
  - Currently, receiving replacement thyroid and cortisol

Questions

- What are the treatment options for this asymptomatic patient?
- What are your thoughts about the use of nephrectomy in patients with metastatic disease?
- Would you delay treatment in order to get a patient vaccinated against COVID-19?

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Case Presentation – Prof Powles: A 66-year-old man with metastatic papillary RCC

Prof Thomas Powles

- Initially diagnosed with Stage T3 papillary RCC → nephrectomy
- Five months later, metastases to the lung and lymph nodes detected
- Patient is also anemic

Questions

- What is the optimal treatment for patients with papillary RCC?
- Should all these patients undergo genetic testing? Is the MET biomarker relevant?
- Is VEGF-targeted therapy recommended for these patients? If so, which agent?
- Would immune checkpoint inhibitors be appropriate therapy?

Case Presentation – Dr Jonasch: A 30-year-old man with von Hippel-Lindau disease

Dr Eric Jonasch

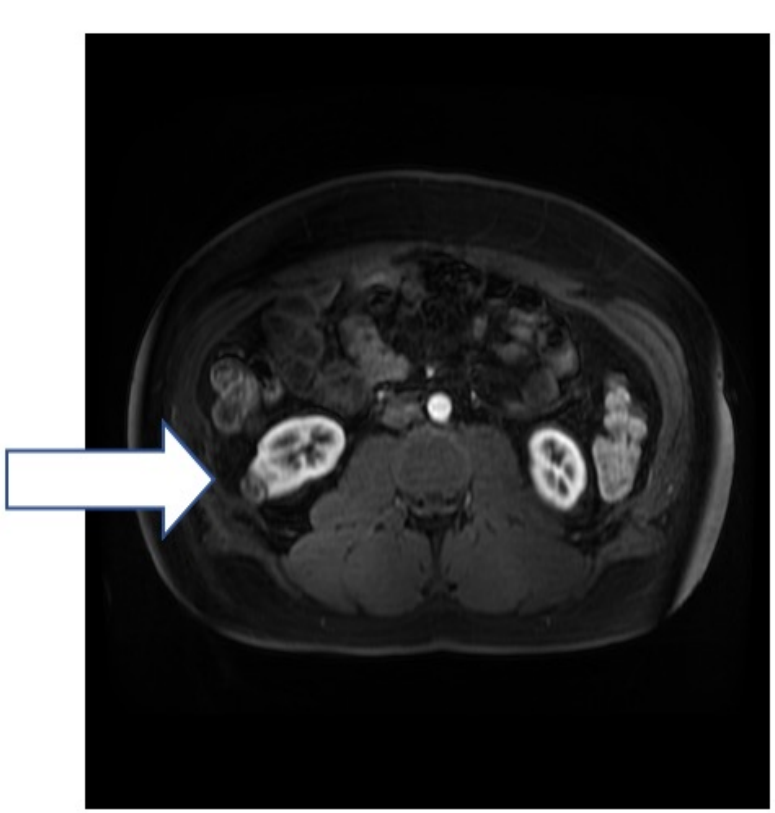
- Began surveillance in his early 20s
- PMH: hemangioblastoma, small renal cell mass

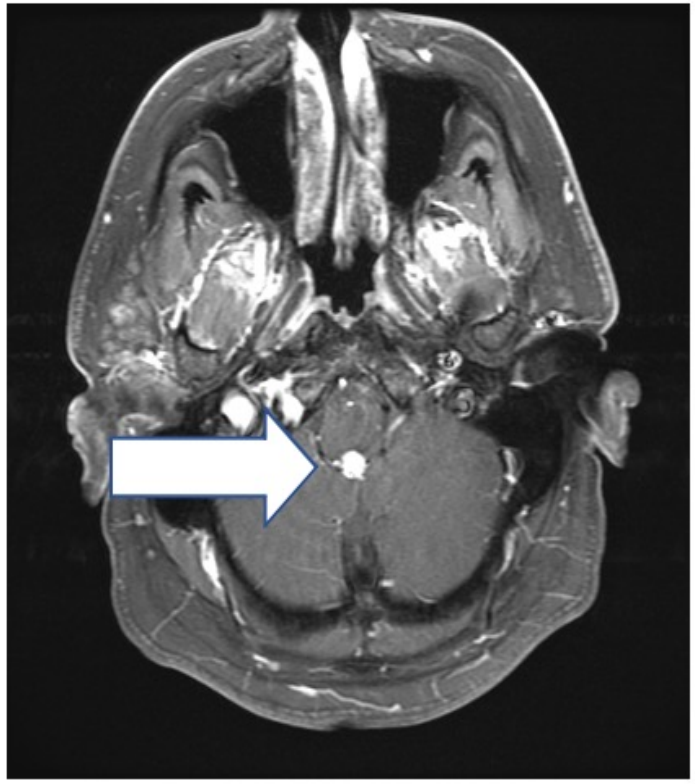
Questions

- Where should individuals with von Hippel-Lindau disease receive their care?
- If they don't have access to a VHL Alliance certified clinical care center, how do you build the teams to take care of these individuals? If they do come to a point where they require interventions, how do you manage that?

Case Presentation – Dr Jonasch: A 30-year-old man with von Hippel-Lindau disease (continued)

Dr Eric Jonasch





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Journal Club with Dr Choueiri – Part 1

- KEYNOTE-564: Pembrolizumab versus placebo as postnephrectomy adjuvant therapy
- CheckMate 214 extended 4-year follow-up of first-line nivolumab with ipilimumab versus sunitinib
- Phase II study of MK-6482 in combination with cabozantinib for advanced clear cell RCC
- CheckMate 9ER: Nivolumab with cabozantinib versus sunitinib for advanced RCC
- PROSPER: Perioperative nivolumab versus observation for patients with RCC undergoing nephrectomy
- Phase I/II study of the oral HIF-2α inhibitor MK-6482 for advanced clear cell RCC
- Next steps: Sequencing therapies for metastatic kidney cancer in the contemporary era
- Post hoc analysis of CLEAR: Effect of subsequent therapy on survival outcomes with lenvatinib + everolimus versus sunitinib
- Efficacy outcomes with nivolumab + cabozantinib versus pembrolizumab + axitinib for advanced RCC
- OMNIVORE: Optimized management of nivolumab and ipilimumab for advanced RCC

Journal Club with Dr Choueiri – Part 2

- Lenvatinib with pembrolizumab or everolimus for advanced RCC
- Time to resolution of axitinib-related adverse events after treatment interruption in advanced RCC
- Effect of high-dose corticosteroid use on efficacy of immune checkpoint inhibitors (ICIs) in RCC
- Evaluation of clear cell, papillary and chromophobe RCC metastasis sites and association with survival
- Impact of antibiotic exposure on clinical outcomes in patients with metastatic RCC treated with ICIs or VEGF-targeted therapy
- Clinical utility of cell-free and circulating tumor DNA in kidney and bladder cancer
- Progressive immune dysfunction with advancing disease stage in RCC
- Metabolic reprogramming in renal cancer: Events of a metabolic disease

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Yen-Hwa Chang[6]; Jaroslav Hajek[7]; Stefan Symeonides[8]; Jae Lyun Lee[9]; Naveed Sarwar[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Mahave[13]; Naomi Haas[14]; Piotr Sawrycki[15]; Rodolfo F. Perini[16]; Pingye Zhang[16]; Jaqueline Willemann-Rogerio[16]; Kentaro Imai[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]Fiona Stanley Hospital, Perth, Australia; [6]Taipei Veterans General Hospital, Taipei, Taiwan; [7]Fakultni Nemocnice Ostrava, Ostrava, Czech Republic; [8]Edinburgh Cancer Center and University of Edinburgh, Edinburgh, UK; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Imperial College Healthcare NHS Trust, London, UK; [11]University Hospital Jean Minjoz, Besançon, France; [12]University Hospital Bordeaux-Hôpital Saint-André, Bordeaux, France; [13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [14]Abramson Cancer Center, Philadelphia, PA, USA; [15]Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu, Torun, Poland; [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.

Presented By: **Dr. Toni K. Choueiri**

2021 ASCO ANNUAL MEETING

ASCO 2021;Abstract LBA5.

2021 ASCO ANNUAL MEETING

PEMBROLIZUMAB VS PLACEBO AS POST NEPHRECTOMY ADJUVANT THERAPY FOR PATIENTS WITH RENAL CELL CARCINOMA: RANDOMIZED, DOUBLE-BLIND, PHASE 3 KEYNOTE-564 STUDY

Toni K. Choueiri, MD

Dana-Farber Cancer Institute, Boston, MA, USA

June 6, 2021

Prespecified Disease Risk Categories

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

NED, no evidence of disease.

Summary and Conclusions

- Adjuvant pembrolizumab post nephrectomy demonstrated a statistically significant and clinically meaningful improvement in DFS vs placebo
  - Additional follow-up is planned for the key secondary endpoint of OS
- Benefit was consistent across subgroups, including the M1 NED population, potentially extending the use of pembrolizumab to these patients
- Safety results were in line with expectations and no new safety signals were observed
  - Low incidence of high-dose corticosteroid treatment for immune-mediated AEs
- KEYNOTE-564 is the first positive phase 3 study of an adjuvant immunotherapy in RCC
- Pembrolizumab is a potential new standard of care for patients with RCC in the adjuvant setting

Open access Original research

Check for updates

Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial

Laurence Albiges ,[1] Nizar M Tannir,[2] Mauricio Burotto,[3] David McDermott,[4,5] Elizabeth R Plimack,[6] Philippe Barthélémy,[7,8] Camillo Porta ,[9] Thomas Powles,[10,11] Frede Donskov,[12] Saby George,[13] Christian K Kollmannsberger,[14] Howard Gurney,[15,16] Marc-Oliver Grimm,[17] Yoshihiko Tomita,[18] Daniel Castellano,[19] Brian I Rini,[20] Toni K Choueiri,[21] Shruti Shally Saggi,[22] M Brent McHenry,[23] Robert J Motzer[24]

ESMO Open 2020;5(6):e001079

Phase 2 Study of the Oral Hypoxia-Inducible Factor 2α Inhibitor Belzutifan (MK-6482) in Combination With Cabozantinib in Patients With Advanced Clear Cell Renal Cell Carcinoma

Toni K. Choueiri[1]; Todd M. Bauer[2]; David F. McDermott[3]; Edward Arrowsmith[4]; Ananya Roy[5]; Rodolfo Perini[5]; Donna Vickery[5]; Scott S. Tykodi[6]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Tennessee Oncology, Chattanooga, TN, USA; [5]Merck & Co., Inc., Kenilworth, NJ, USA; [6]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Genitourinary Cancers Symposium 2021;Abstract 272.

N Engl J Med 2021;384(9):829-41

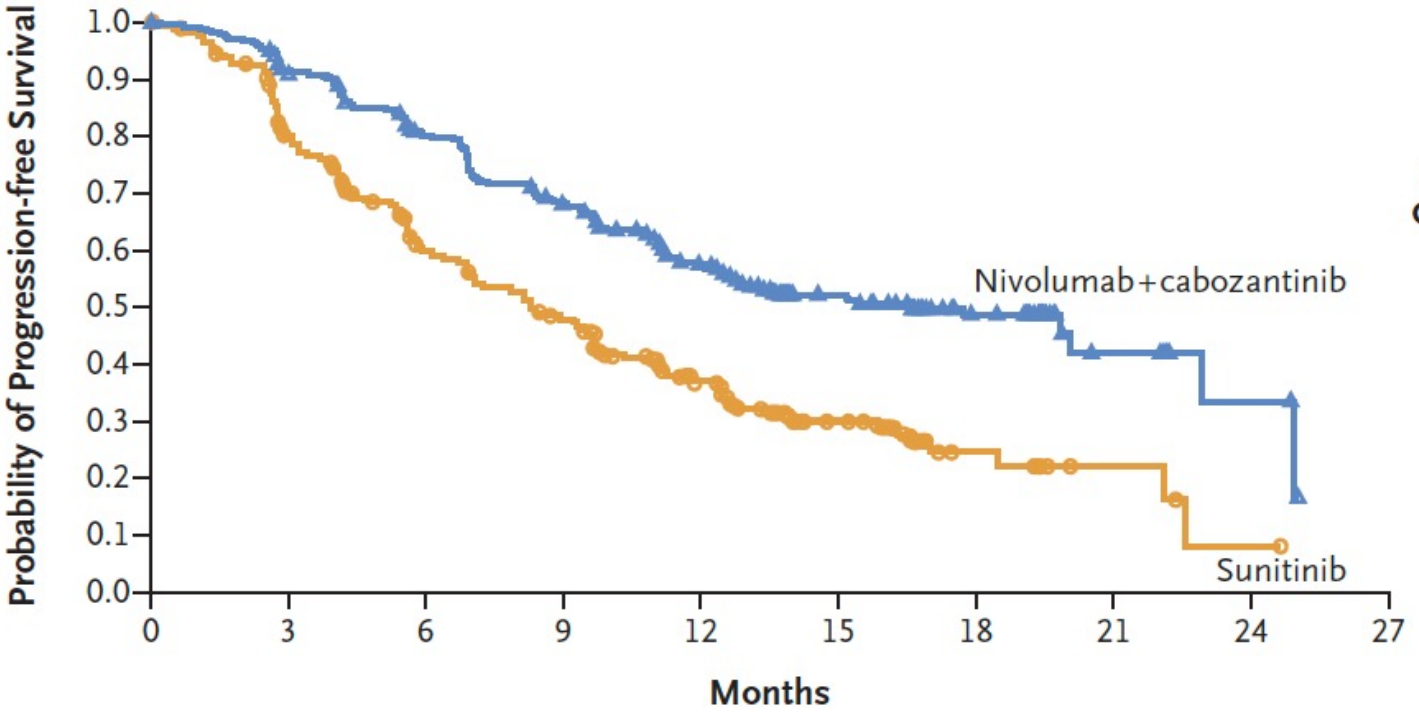
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*

CheckMate 9ER: Progression-Free Survival



	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	16.6 (12.5–24.9)
Sunitinib	328	8.3 (7.0–9.7)

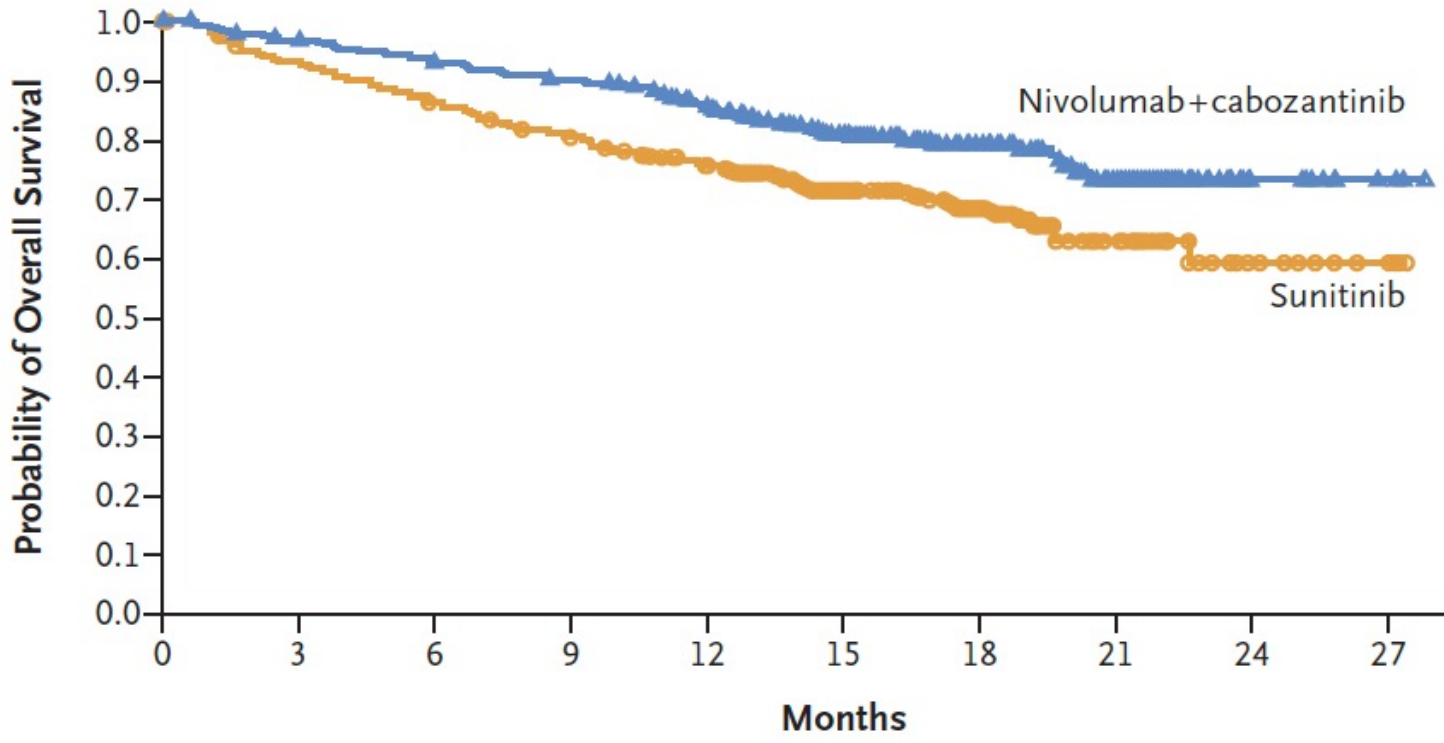
Hazard ratio for disease progression or death, 0.51 (95% CI, 0.41–0.64)
P<0.001

No. at Risk

Nivolumab+cabozantinib	323	279	234	196	144	77	35	11	4	0
Sunitinib	328	228	159	122	79	31	10	4	1	0

Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41.

CheckMate 9ER: Overall Survival



	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	NR (NE)
Sunitinib	328	NR (22.6–NE)

Hazard ratio for death, 0.60 (98.89% CI, 0.40–0.89)
P=0.001

No. at Risk

Nivolumab+cabozantinib	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

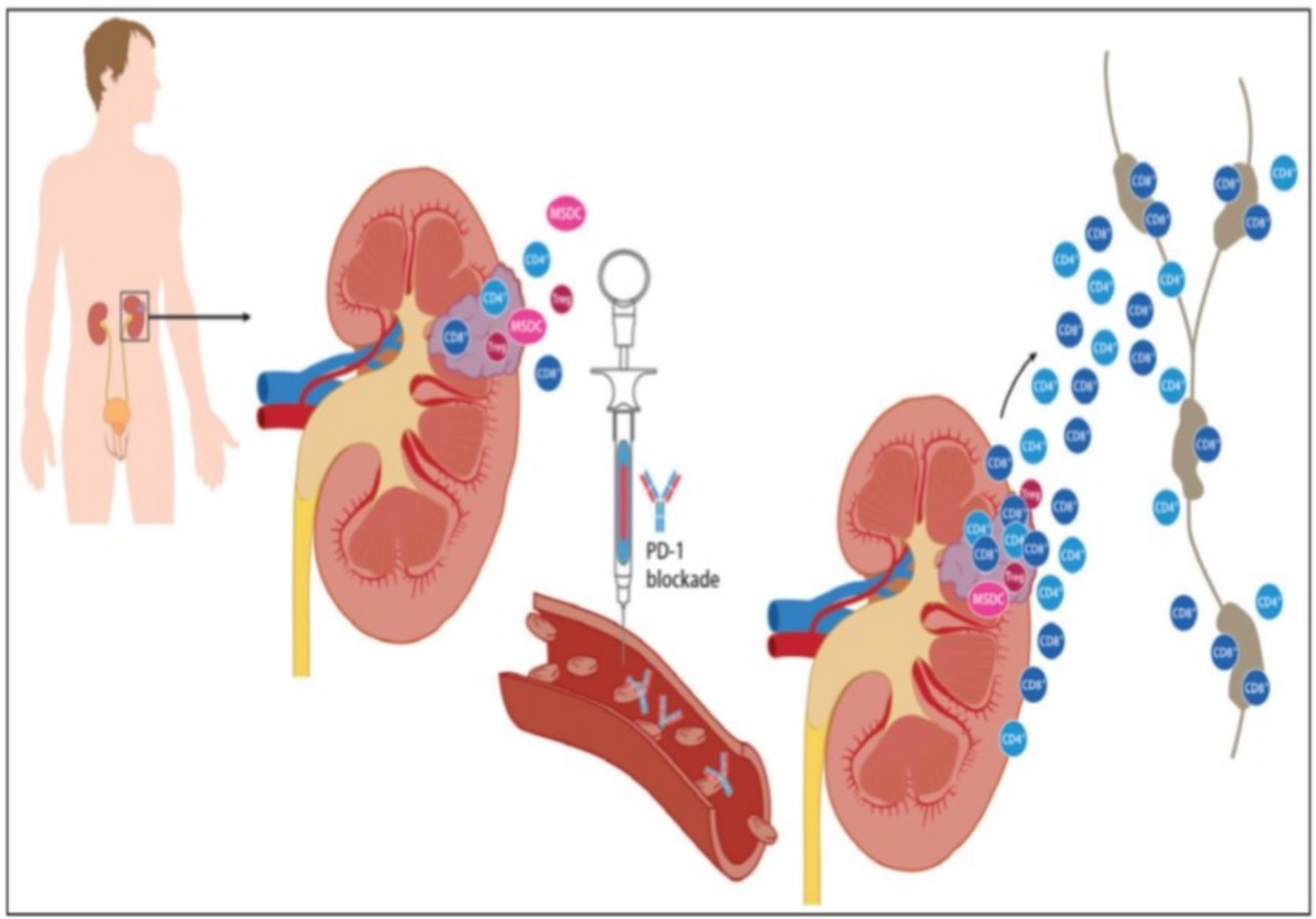
Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41.

PROSPER: Phase III Randomized Study Comparing PERioperative Nivolumab versus Observation in Patients with Renal Cell Carcinoma (RCC) Undergoing Nephrectomy (ECOG-ACRIN EA8143)

Allaf ME et al.

ASCO 2021;Abstract TPS4596.

Rationale for Priming with PD-1 Blockade



Harshman…Allaf et al Kidney Cancer 2017

Allaf ME et al. ASCO 2021;Abstract TPS4596.

The Oral HIF-2α Inhibitor Belzutifan (MK-6482) in Patients With Advanced Clear Cell Renal Cell Carcinoma: Updated Follow-up of a Phase 1/2 Study

Todd Michael Bauer,[1] Toni K. Choueiri,[2] Kyriakos P. Papadopoulos,[3] Elizabeth R. Plimack,[4] Jaime R. Merchan,[5] David F. McDermott,[6] M. Dror Michaelson,[7] Leonard Joseph Appleman,[8] Sanjay Thamake,[9] Rodolfo F. Perini,[9] Eric Kristopher Park,[9] Eric Jonasch[10]

[1]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [3]South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA; [4]Fox Chase Cancer Center, Philadelphia, PA, USA; [5]University of Miami, Miami, FL, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]University of Pittsburgh Medical Center, Pittsburgh, PA; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Genitourinary Cancers Symposium 2021;Abstract 273.

Summary of Adverse Events (ccRCC cohort)

n (%)	N = 55
Any grade AE	55 (100)
Grade 3-5 AE	39 (71)
Any grade treatment-related AEs	53 (96)
Grade 3-5 treatment-related AE	22 (40)
Discontinuation of treatment due to an AE[a]	5 (9)
Discontinuation of treatment due to a treatment-related AE[b]	2 (4)
Deaths due to an AE[c]	4 (7)
Death due to a treatment-related AE	0 (0)

- Fifty-three patients (96%) had a treatment-related AE
  - Twenty-two patients (40%) had a grade 3 treatment-related AE
  - There were no grade 4/5 treatment-related AEs
  - Two patients (4%) discontinued due to a treatment-related AE (both hypoxia)[b]

[a]5 patients experienced 7 adverse events (hypoxia [n = 2], abdominal pain [n = 1], cardiac arrest [n = 1], decreased appetite [n = 1], disease progression [n = 1], and fatigue [n = 1]). [b]One patient discontinued treatment due to grade 2 hypoxia and one patient discontinued due to grade 3 hypoxia. [c]Deaths were due to disease progression (n = 1), malignant neoplasm progression (n = 1), acute kidney injury (n = 1), and cardiac arrest (n = 1). Data cutoff: June 1, 2020.

Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

All-Cause Adverse Events ≥20% (ccRCC cohort)

All cause AEs in ≥20% of patients, n (%)	Belzutifan N = 55			
	Any Grade	Grade 3	Grade 4[a]	Grade 5[b]
Any	55 (100)	33 (60)	2 (4)	4 (7)
Anemia	42 (76)	15 (27)	0 (0)	0 (0)
Fatigue	39 (71)	3 (5)	0 (0)	0 (0)
Dyspnea	27 (49)	3 (5)	0 (0)	0 (0)
Nausea	20 (36)	1 (2)	0 (0)	0 (0)
Cough	17 (31)	0 (0)	0 (0)	0 (0)
Hypoxia	17 (31)	9 (16)	0 (0)	0 (0)
Vomiting	16 (29)	0 (0)	0 (0)	0 (0)
Edema peripheral	15 (27)	0 (0)	0 (0)	0 (0)
Arthralgia	14 (25)	0 (0)	0 (0)	0 (0)
Blood creatinine increased	14 (25)	1 (2)	0 (0)	0 (0)
Headache	14 (25)	1 (2)	0 (0)	0 (0)
Dizziness	13 (24)	0 (0)	0 (0)	0 (0)
Back pain	12 (22)	1 (2)	0 (0)	0 (0)
Diarrhea	12 (22)	0 (0)	0 (0)	0 (0)
Hyperkalemia	12 (22)	1 (2)	0 (0)	0 (0)
Constipation	12 (22)	0 (0)	0 (0)	0 (0)
Dehydration	11 (20)	1 (2)	0 (0)	0 (0)

[a]2 patients experienced 4 grade 4 adverse events (sepsis [n = 2], hypercalcemia [n = 1], respiratory failure [n = 1]). [b]4 patients experienced grade 5 adverse events (disease progression [n = 1], malignant neoplasm progression [n = 1], acute kidney injury [n = 1], cardiac arrest [n = 1]). Data cutoff: June 1, 2020.

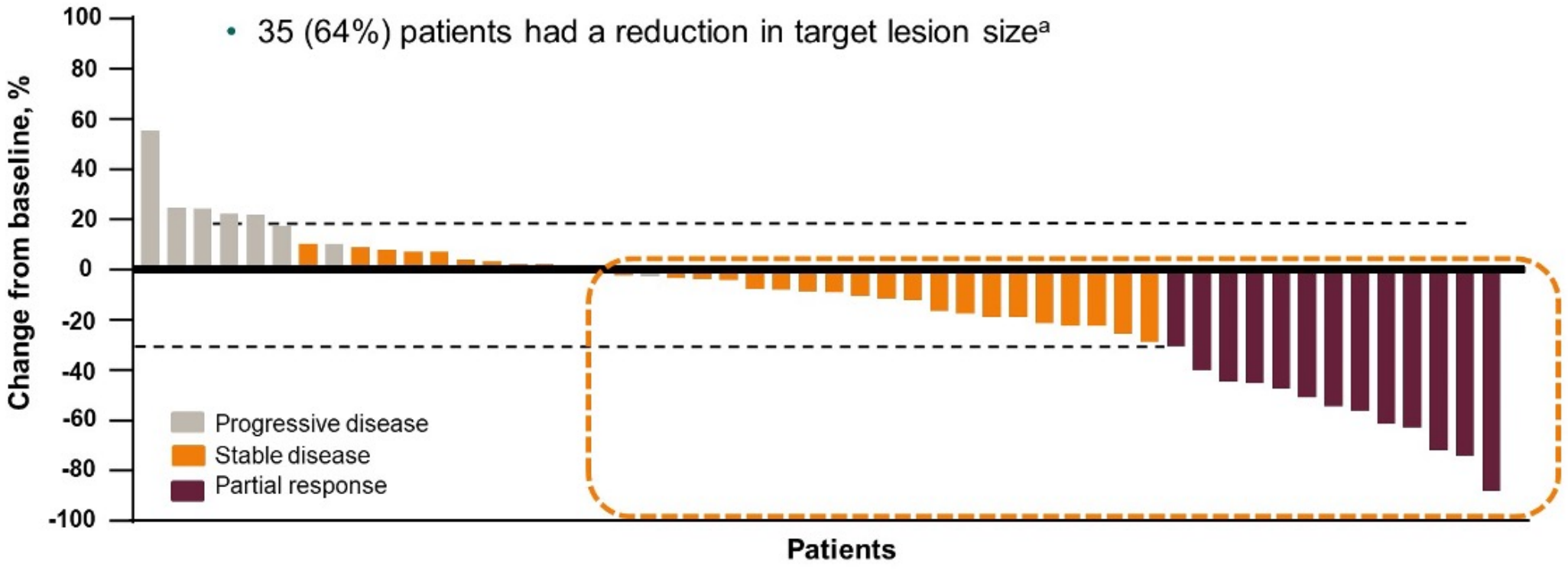
Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

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)

Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

Best Tumor Change From Baseline per Investigator Assessment (ccRCC cohort)



Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

GENITOURINARY CANCER—KIDNEY AND BLADDER

Next Steps: Sequencing Therapies in Metastatic Kidney Cancer in the Contemporary Era

Andrew L. Schmidt, MD[1]; Alexandra L. Tabakin, MD[2]; Eric A. Singer, MD, MA, MS, FACS[2]; Toni K. Choueiri, MD[1]; and Rana R. McKay, MD[3]

ASCO Education Book 2021;41:1-11

2021 ASCO ANNUAL MEETING

POST HOC ANALYSIS OF THE CLEAR STUDY IN ADVANCED RENAL CELL CARCINOMA: EFFECT OF SUBSEQUENT THERAPY ON SURVIVAL OUTCOMES IN THE LENVATINIB + EVEROLIMUS VS SUNITINIB TREATMENT ARMS

Thomas Hutson[1], Toni K. Choueiri[2], Robert Motzer[3], Sun Young Rha[4], Anna Alyasova[5], Jaime Merchan[6], Howard Gurney[7], Avivit Peer[8], Toshio Takagi[9], Camillo Porta[10], Thomas Powles[11], Viktor Grünwald[12], Ugo De Giorgi[13], Ulka Vaishampayan[14], Manuela Schmidinger[15], Hilary Glen[16], Karla Rodriguez-Lopez[17], Dongyuan Xing[18], Lea Dutta[18], Masatoshi Eto[19]

[1]Texas Oncology, Dallas, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Memorial Sloan Kettering Cancer Center; New York, NY, USA; [4]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [5]Prevoljskiy Region Medical Centre, Novgorod, Russia; [6]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [7]Macquarie University, Sydney, NSW, Australia; [8]Rambam Health Care Campus, Haifa, Israel; [9]Tokyo Women's Medical University, Tokyo, Japan; [10]San Matteo University Hospital Foundation, Pavia, Italy; [11]The Royal Free NHS trust, London, England, UK; [12]University Hospital Essen, Essen, Germany; [13]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola FC, Italy; [14]University of Michigan, Ann Arbor, MI, USA; [15]Medical University of Vienna, Vienna, Austria; [16]Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Eisai Inc., Woodcliff Lake, NJ, USA; [19]Kyushu University, Fukuoka, Japan.

June 4–8, 2021

Abstract No. 4562

Efficacy Outcomes of Nivolumab + Cabozantinib versus Pembrolizumab + Axitinib in Patients with Advanced Renal Cell Carcinoma (aRCC): Matching-Adjusted Indirect Comparison (MAIC)

McGregor BA et al.

ASCO 2021;Abstract 4578.

original reports

Optimized Management of Nivolumab and Ipilimumab in Advanced Renal Cell Carcinoma: A Response-Based Phase II Study (OMNIVORE)

Rana R. McKay, MD[1]; Bradley A. McGregor, MD[2]; Wanling Xie, MS[2]; David A. Braun, MD, PhD[2]; Xiao Wei, MD[2]; Christos E. Kyriakopoulos, MD[3]; Yousef Zakharia, MD[4]; Benjamin L. Maughan, MD, PharmD[5]; Tracy L. Rose, MD[6]; Walter M. Stadler, MD[7]; David F. McDermott, MD[8]; Lauren C. Harshman, MD[2]; and Toni K. Choueiri, MD[2]

J Clin Oncol 2020;38(36):4240-8

N Engl J Med 2021;384(14):1289-300

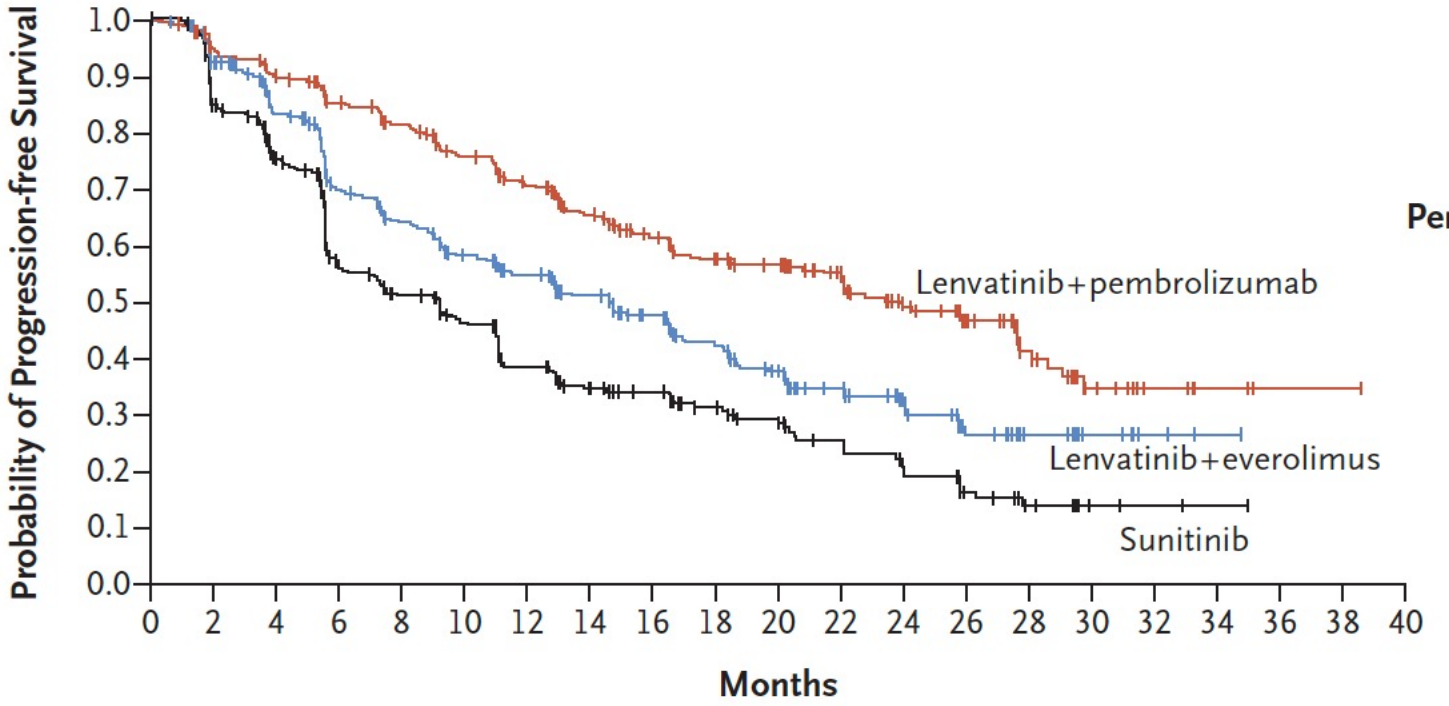
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2021 VOL. 384 NO. 14

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

CLEAR: Progression-Free Survival



No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Median Progression-free Survival (95% CI)

	mo
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

Motzer R et al. *N Engl J Med* 2021;384(14):1289-300.

Original study

Time to Resolution of Axitinib-Related Adverse Events After Treatment Interruption in Patients With Advanced Renal Cell Carcinoma

Brian I. Rini,[1] Michael B. Atkins,[2] Toni K. Choueiri,[3] Despina Thomaidou,[4] Brad Rosbrook,[5] Maghull Thakur,[6] Thomas E. Hutson[7]

Clin Genitourin Cancer 2021;[Online ahead of print].

2021 ASCO ANNUAL MEETING

CONQUER CANCER® THE ASCO FOUNDATION | MERIT AWARD RECIPIENT

Abstract 4583

Effect of high-dose corticosteroid use on efficacy of immune checkpoint inhibitors in patients with renal cell carcinoma (RCC)

Chris Labaki[1,*], Sarah Abou Alaiwi[2], Andrew L. Schmidt[1], Talal El Zarif[1], Ziad Bakouny[1], Pier V. Nuzzo[1], Wenxin Xu[1], David A. Braun[1], Bradley A. McGregor[1], Toni K. Choueiri[1]

1. Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; 2. Brigham and Women's Hospital, Boston, MA
*: Email address: chris_labaki@dfci.harvard.edu

June 4, 2021

ASCO 2021;Abstract 4583

Dana-Farber Cancer Institute

JAMA Network Open

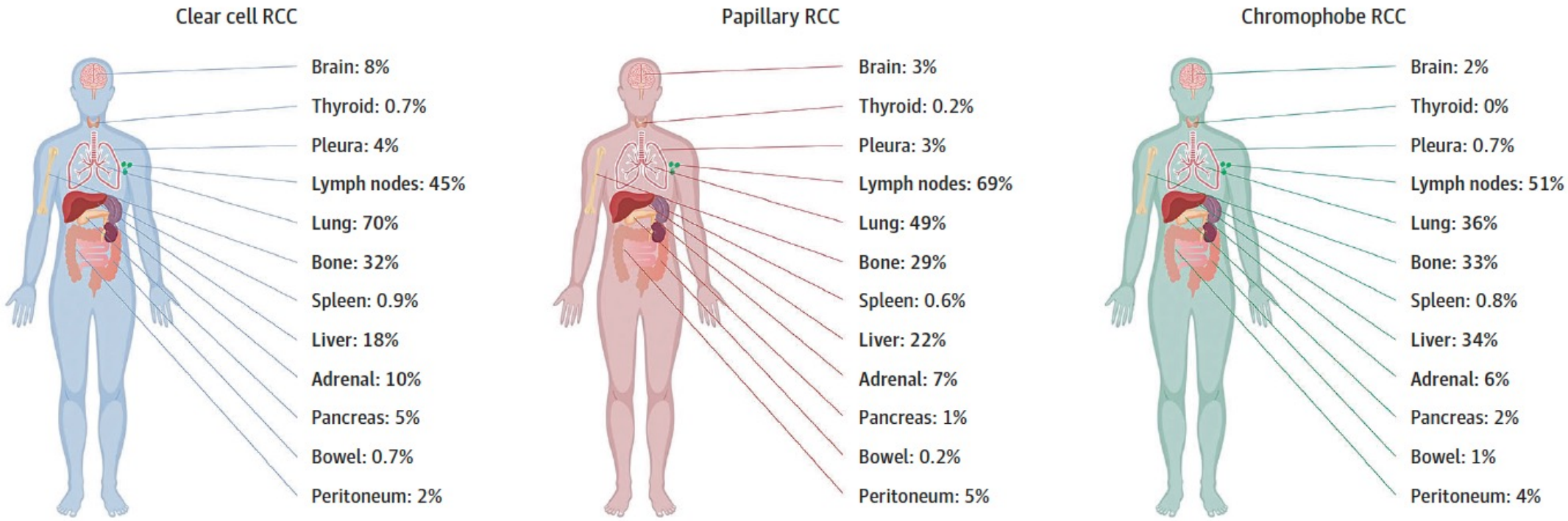
JAMA Netw Open 2021;4(1):e2021869

Original Investigation | Oncology

Evaluation of Clear Cell, Papillary, and Chromophobe Renal Cell Carcinoma Metastasis Sites and Association With Survival

Shaan Dudani, MBChB; Guillermo de Velasco, MD; J. Connor Wells, MD; Chun Loo Gan, MBBS; Frede Donskov, MD; Camillo Porta, MD; Anna Fraccon, MD; Felice Pasini, MD; Jae Lyun Lee, MD; Aaron Hansen, MBBS; Georg A. Bjarnason, MD; Benoit Beuselinck, MD; Sumanta K. Pal, MD; Takeshi Yuasa, MD; Nils Kroeger, MD; Ravindran Kanesvaran, MD; M. Neil Reaume, MD; Christina Canil, MD; Toni K. Choueiri, MD; Daniel Y. C. Heng, MD

Sites of RCC Metastasis by Histologic Subtype



The percentage of patients with involved site of metastasis at the time of first systemic therapy initiation for metastatic disease are presented. The 5 most frequent sites of metastasis across all histologic profiles are highlighted in bold type.

Dudani S et al. *JAMA Netw Open* 2021;4(1):e2021869.

The Impact of Antibiotic (Ab) Exposure on Clinical Outcomes in Patients with Metastatic Renal Cell Carcinoma (mRCC) Treated with Immune Checkpoint Inhibitors (ICI) or VEGF Targeted Therapy (VEGF-TT)

Ernst MS et al.

ASCO 2021;Abstract 4552.

EUO-445; No. of Pages 11

ARTICLE IN PRESS

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

Eur Urol Oncol 2021;[Online ahead of print].

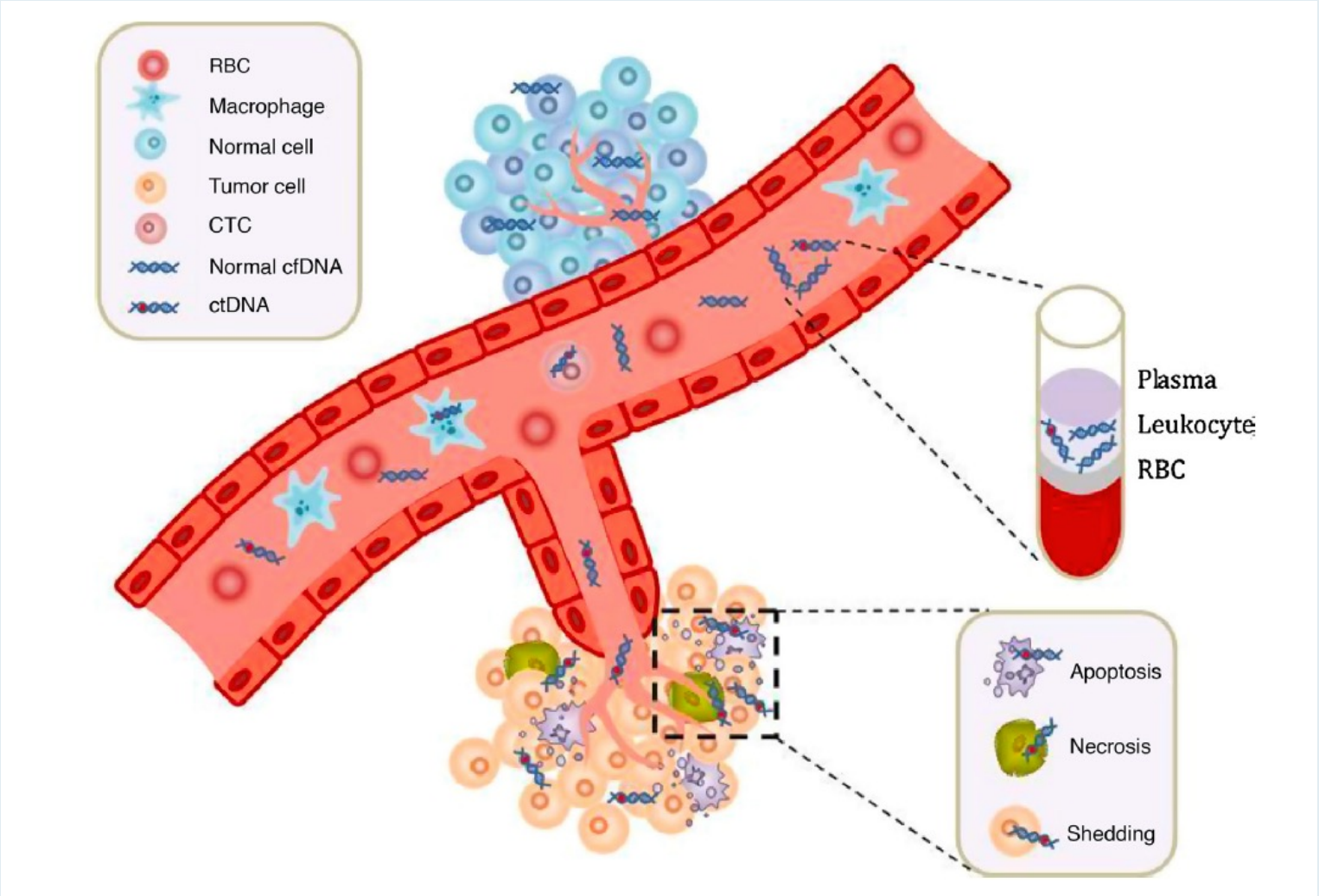
European Association of Urology

EUO Collaborative Review – Bladder Cancer

Clinical Utility of Cell-free and Circulating Tumor DNA in Kidney and Bladder Cancer: A Critical Review of Current Literature

Elizabeth A. Green[a], *Roger Li*[a,b,*], *Laurence Albiges*[c], *Toni K. Choueiri*[d], *Matthew Freedman*[d], *Sumanta Pal*[e], *Lars Dyrskjøt*[f,g], *Ashish M. Kamat*[h]

Circulating Tumor DNA Denotes the Fraction of Mutated Cell-Free DNA Originating from Cancer Cells



Green EA et al. *Eur Urol Oncol* 2021;[Online ahead of print].

***Cancer Cell* 2021;39(5):632-48.e8**

Progressive immune dysfunction with advancing disease stage in renal cell carcinoma

David A. Braun[1,2,3,17], Kelly Street[4,5,17], Kelly P. Burke[1,2,6], David L. Cookmeyer[2,6], Thomas Denize[2,7], Christina B. Pedersen[8,9], Satyen H. Gohil[1,2,3,10], Nicholas Schindler[1], Lucas Pomerance[1,2], Laure Hirsch[1,2], Ziad Bakouny[1], Yue Hou[1,11], Juliet Forman[1,3,11], Teddy Huang[1,11], Shuqiang Li[1,3,11], Ang Cui[3,12], Derin B. Keskin[1,3,11], John Steinharter[1], Gabrielle Bouchard[1], Maxine Sun[1], Erica M. Pimenta[1,2], Wenxin Xu[1,2], Kathleen M. Mahoney[1,2,13], Bradley A. McGregor[1,2], Michelle S. Hirsch[2,7], Steven L. Chang[2,14], Kenneth J. Livak[1,11], David F. McDermott[2,13], Sachet A. Shukla[3,11], Lars R. Olsen[8,9], Sabina Signoretti[2,7,15], Arlene H. Sharpe[3,6,7,16], Rafael A. Irizarry[4,5], Toni K. Choueiri[1,2,18], Catherine J. Wu[1,2,3,18,19]

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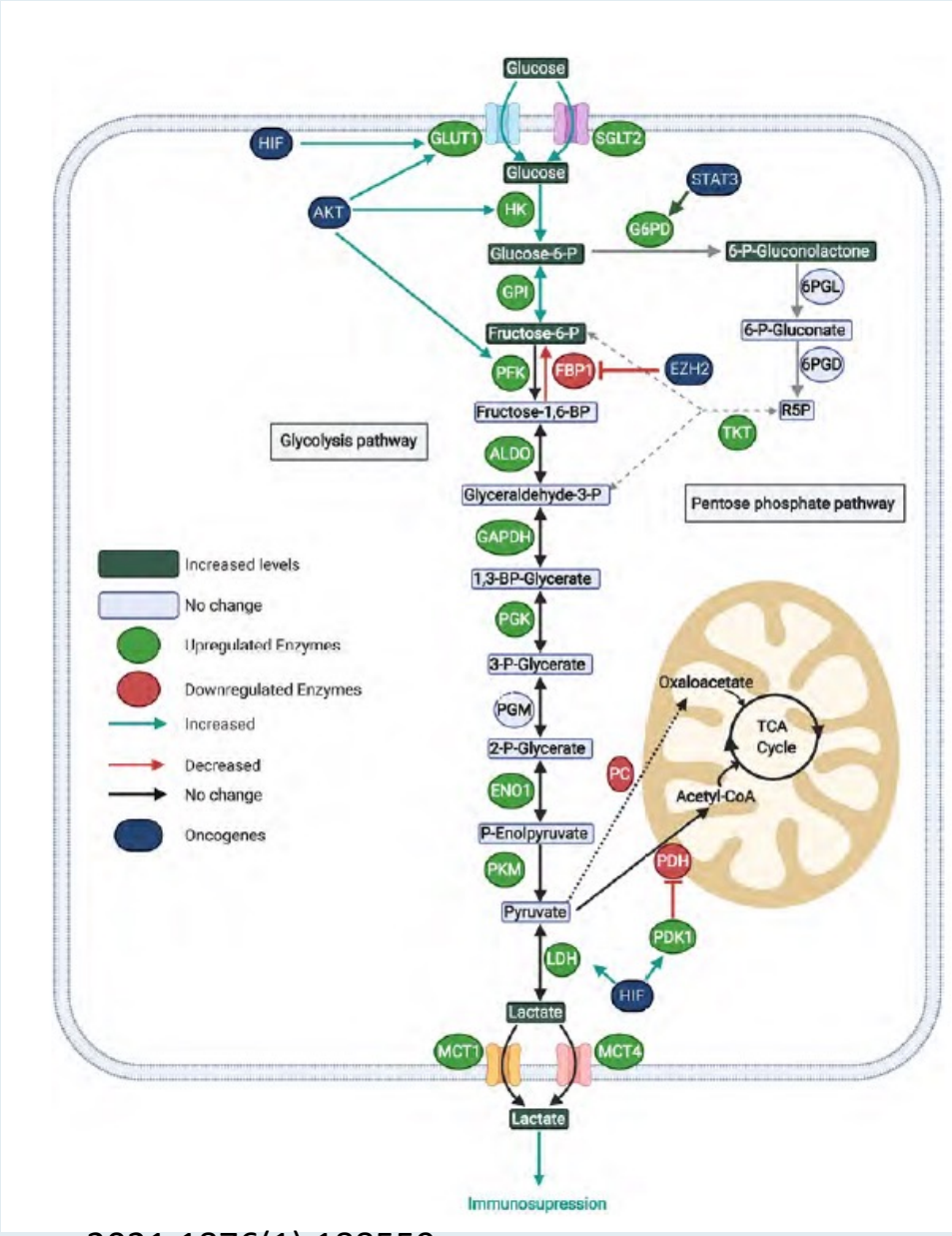
Review

Metabolic reprogramming in renal cancer: Events of a metabolic disease

Samik Chakraborty [a,c,1], Murugabaskar Balan [a,c], Akash Sabarwal [a,c], Toni K. Choueiri [b,c], Soumitro Pal [a,c,*,1]

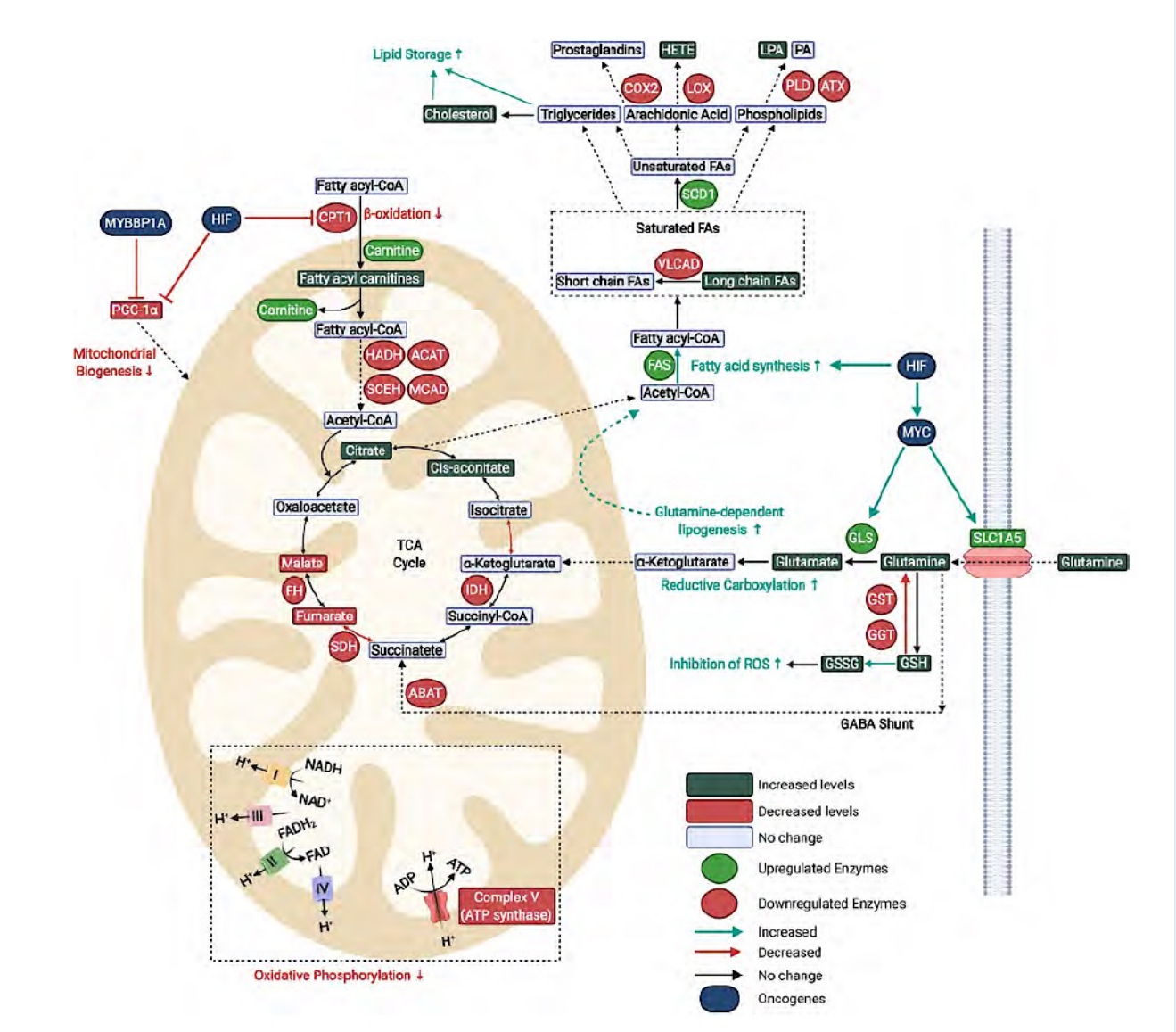
[a] Division of Nephrology, Boston Children's Hospital, MA 02115, United States of America
[b] Dana Farber Cancer Institute, Boston, MA 02115, United States of America
[c] Harvard Medical School, Boston, MA 02115, United States of America

Reprogramming of Glucose Transport and Glucose Metabolism in Renal Cancer



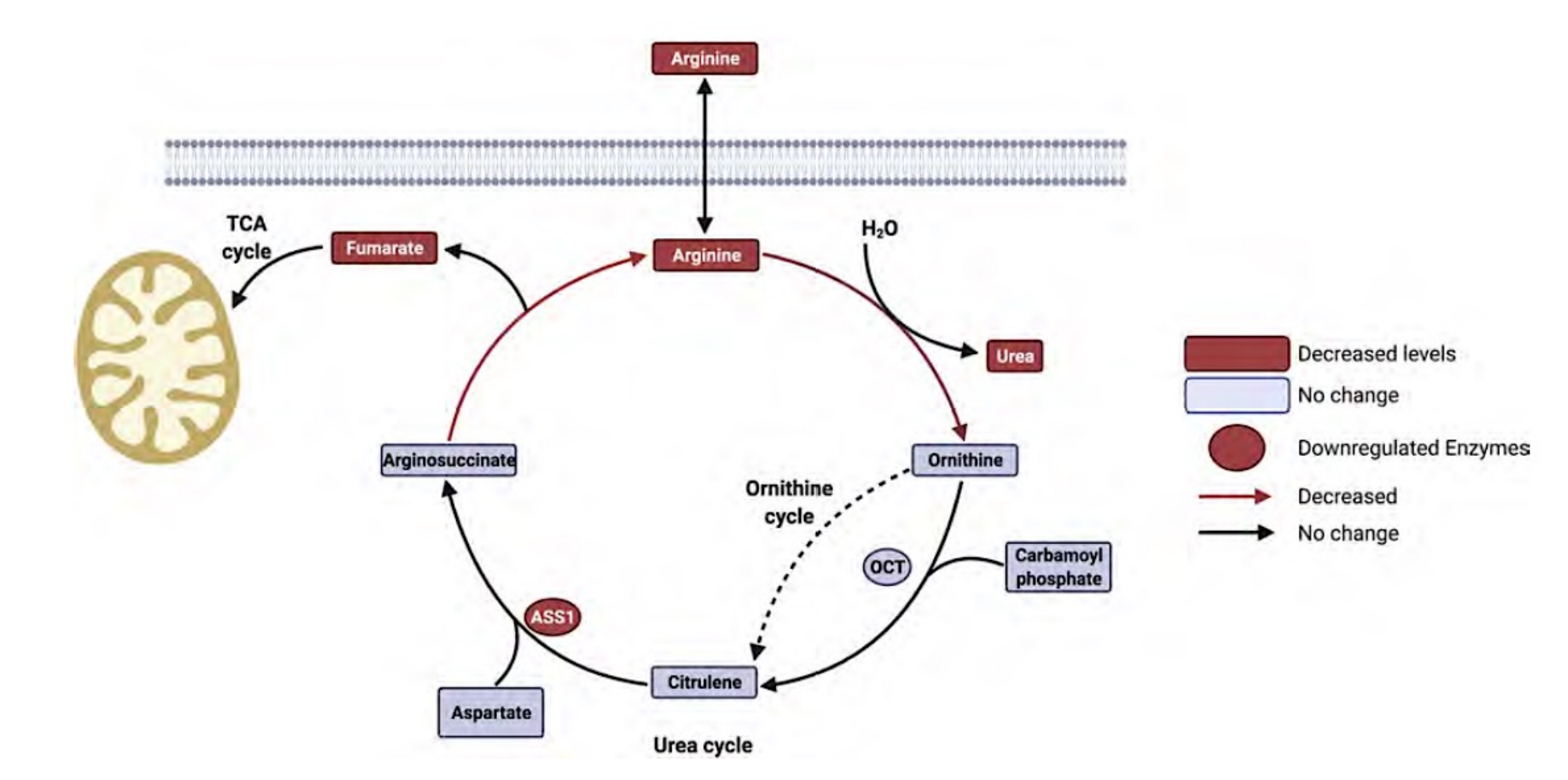
Chakraborty S et al. *Biochim Biophys Acta Rev Cancer* 2021;1876(1):188559.

Reprogramming of TCA Cycle, Fatty Acid and Glutamine Metabolism in Renal Cancer



Chakraborty S et al. *Biochim Biophys Acta Rev Cancer* 2021;1876(1):188559.

Reprogramming of Arginine Metabolism in Renal Cancer



Chakraborty S et al. *Biochim Biophys Acta Rev Cancer* 2021;1876(1):188559.

Meet The Professor with Dr Choueiri

MODULE 1: Case Presentations

- Prof Powles: A 47-year-old man with newly diagnosed metastatic clear cell RCC
- Dr Jonasch: A 64-year-old man with clear cell RCC invasive into the renal vein
- Dr Brooks: A 61-year-old man with metastatic clear cell RCC
- Prof Powles: A 66-year-old man with metastatic papillary RCC
- Dr Jonasch: A 30-year-old man with von Hippel-Lindau disease

MODULE 2: Journal Club with Dr Choueiri

MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets

RTP
RESEARCH
TO PRACTICE

Optimizing Front-Line Decision-Making for Advanced Renal Cell Carcinoma (RCC)

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient with a history of nephrectomy for clear cell renal cell carcinoma (RCC) who on routine follow-up 3 years later is found to have asymptomatic bone metastases (PS 0)?

1. Nivolumab/ipilimumab
2. Avelumab/axitinib
3. Pembrolizumab/axitinib
4. Pembrolizumab/lenvatinib
5. Nivolumab/cabozantinib
6. Tyrosine kinase inhibitor (TKI) monotherapy
7. Anti-PD-1/PD-L1 monotherapy
8. Other

Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient with a history of nephrectomy for clear cell renal cell carcinoma (RCC) who on routine follow-up 3 years later is found to have asymptomatic bone metastases (PS = 0)?

 Dr Choueiri	Nivolumab/ cabozantinib	 Dr Motzer	Nivolumab/ cabozantinib
 Dr Hutson	Nivolumab/ cabozantinib	 Dr Plimack	Pembrolizumab/ axitinib
 Dr Jonasch	Nivolumab/ cabozantinib	 Prof Powles	Pembrolizumab/ lenvatinib
 Dr McDermott	Nivolumab/ipilimumab	 Dr Rini	Pembrolizumab/ lenvatinib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient who presents with clear cell RCC with multiple painful bone metastases and hemoglobin (Hb) of 11.4 g/dL (PS 1)?

1. Nivolumab/ipilimumab
2. Avelumab/axitinib
3. Pembrolizumab/axitinib
4. Pembrolizumab/lenvatinib
5. Nivolumab/cabozantinib
6. TKI monotherapy
7. Anti-PD-1/PD-L1 monotherapy
8. Other

Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient who presents with clear cell RCC with multiple painful bone metastases and hemoglobin (Hb) of 11.4 g/dL (PS = 1)?

 Dr Choueiri	Nivolumab/ cabozantinib	 Dr Motzer	Nivolumab/ipilimumab
 Dr Hutson	Nivolumab/ cabozantinib	 Dr Plimack	Pembrolizumab/ lenvatinib
 Dr Jonasch	Nivolumab/ cabozantinib	 Prof Powles	Pembrolizumab/ axitinib
 Dr McDermott	Pembrolizumab/ lenvatinib	 Dr Rini	Pembrolizumab/ lenvatinib

RTP RESEARCH TO PRACTICE

In general, which first-line therapy would you recommend for a 65-year-old patient who presents with metastatic clear cell RCC and for whom the use of immune checkpoint inhibitors is contraindicated?

1. Sunitinib
2. Pazopanib
3. Cabozantinib
4. Axitinib
5. Other

In general, which first-line therapy would you recommend for a 65-year-old patient who presents with metastatic clear cell RCC and for whom the use of immune checkpoint inhibitors is contraindicated?

 Dr Choueiri	Cabozantinib	 Dr Motzer	Cabozantinib
 Dr Hutson	Cabozantinib	 Dr Plimack	Pazopanib
 Dr Jonasch	Sunitinib	 Prof Powles	Pazopanib
 Dr McDermott	Cabozantinib	 Dr Rini	Cabozantinib

RTP RESEARCH TO PRACTICE

In general, how would you compare the efficacy of tivozanib to that of commercially available tyrosine kinase inhibitors (TKIs; eg, axitinib, cabozantinib, lenvatinib) in patients with relapsed metastatic RCC?

 Dr Choueiri	I don't know (likely same as axitinib)	 Dr Motzer	I don't know
 Dr Hutson	Efficacy is about the same	 Dr Plimack	Efficacy is about the same
 Dr Jonasch	Efficacy is about the same	 Prof Powles	Efficacy is about the same
 Dr McDermott	Efficacy is about the same	 Dr Rini	Efficacy is about the same

RTP RESEARCH TO PRACTICE

In general, how would you compare the tolerability of tivozanib to that of commercially available TKIs (eg, axitinib, cabozantinib, lenvatinib) in patients with relapsed metastatic RCC?

 Dr Choueiri	Tivozanib is more tolerable	 Dr Motzer	Tivozanib is more tolerable
 Dr Hutson	Tivozanib is more tolerable	 Dr Plimack	Tivozanib is more tolerable
 Dr Jonasch	Tivozanib is more tolerable	 Prof Powles	Tolerability is about the same
 Dr McDermott	Tivozanib is more tolerable	 Dr Rini	Tivozanib is more tolerable

RTP RESEARCH TO PRACTICE

Sequencing of Therapy for Patients with Relapsed/Refractory RCC; Novel Approaches under Investigation

In general, what would you recommend as second-line treatment for a 65-year-old patient (PS 0) with metastatic clear-cell RCC who receives first-line ipilimumab/nivolumab and experiences disease progression after 12 months?

1. Sunitinib
2. Pazopanib
3. Cabozantinib
4. Axitinib
5. Avelumab/axitinib
6. Pembrolizumab/axitinib
7. Nivolumab/cabozantinib
8. Other

In general, what would you recommend as second-line treatment for a 65-year-old patient (PS 0) with metastatic clear cell RCC who receives first-line ipilimumab/nivolumab and experiences disease progression after 12 months?

 Dr Choueiri	Cabozantinib	 Dr Motzer	Axitinib
 Dr Hutson	Cabozantinib	 Dr Plimack	Pembrolizumab/ axitinib
 Dr Jonasch	Cabozantinib	 Prof Powles	Cabozantinib
 Dr McDermott	Cabozantinib	 Dr Rini	Axitinib

RTP RESEARCH TO PRACTICE

In general, what would you recommend as second-line treatment for a 65-year-old patient (PS 0) with metastatic clear-cell RCC who receives first-line pembrolizumab/axitinib and experiences disease progression after 12 months?

1. Sunitinib
2. Pazopanib
3. Cabozantinib
4. Sorafenib
5. Lenvatinib/everolimus
6. Nivolumab/ipilimumab
7. Nivolumab/cabozantinib
8. Other

In general, what would you recommend as second-line treatment for a 65-year-old patient (PS 0) with metastatic clear cell RCC who receives first-line pembrolizumab/axitinib and experiences disease progression after 12 months?

 Dr Choueiri	Cabozantinib	 Dr Motzer	Cabozantinib
 Dr Hutson	Cabozantinib	 Dr Plimack	Cabozantinib
 Dr Jonasch	Cabozantinib	 Prof Powles	Cabozantinib
 Dr McDermott	Cabozantinib	 Dr Rini	Cabozantinib

RTP RESEARCH TO PRACTICE

In general, what would you recommend as second-line treatment for a 65-year-old patient (PS 0) with metastatic clear cell RCC who receives first-line nivolumab/cabozantinib and experiences disease progression after 12 months?

 Dr Choueiri	Lenvatinib + everolimus	 Dr Motzer	Lenvatinib + everolimus
 Dr Hutson	Lenvatinib + everolimus	 Dr Plimack	Lenvatinib + everolimus
 Dr Jonasch	Lenvatinib + everolimus	 Prof Powles	Axitinib
 Dr McDermott	Nivolumab/ipilimumab	 Dr Rini	Axitinib

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Choueiri

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MODULE 2: Journal Club with Dr Choueiri

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RTP RESEARCH TO PRACTICE

Open access Original research

ESMO Open
Cancer Horizons

Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial

Laurence Albiges ,[1] Nizar M Tannir,[2] Mauricio Burotto,[3] David McDermott,[4,5] Elizabeth R Plimack,[6] Philippe Barthélémy,[7,8] Camillo Porta ,[9] Thomas Powles,[10,11] Frede Donskov,[12] Saby George,[13] Christian K Kollmannsberger,[14] Howard Gurney,[15,16] Marc-Oliver Grimm,[17] Yoshihiko Tomita,[18] Daniel Castellano,[19] Brian I Rini,[20] Toni K Choueiri,[21] Shruti Shally Saggi,[22] M Brent McHenry,[23] Robert J Motzer[24]

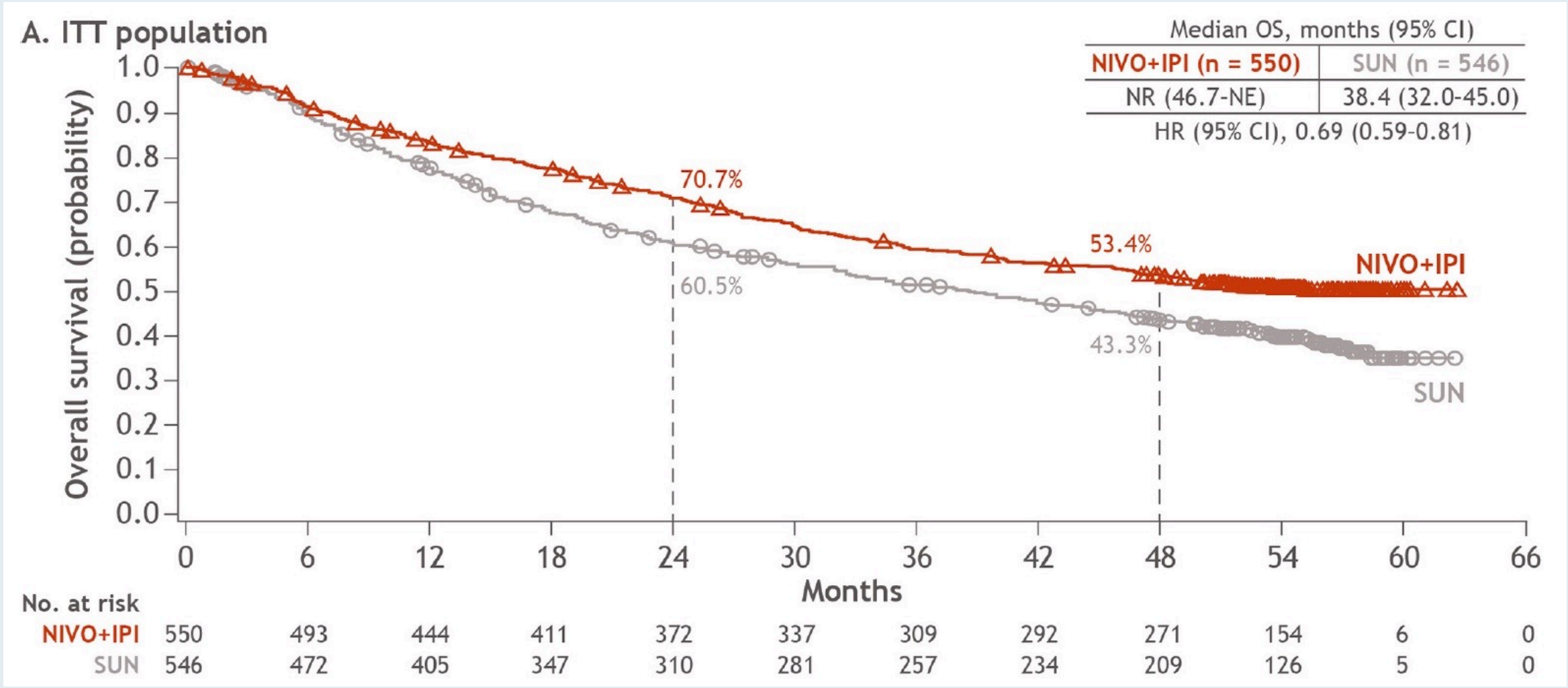
ESMO Open 2020;5(6):e001079.

CheckMate 214: Overall Response and Best Response Rate per IRRC at 4 Years Minimum Follow-Up in ITT Population

	Intent-to-Treat		Intermediate/Poor Risk		Favorable Risk	
	Nivo + Ipi (n = 550)	Sunitinib (n = 546)	Nivo + Ipi (n = 425)	Sunitinib (n = 422)	Nivo + Ipi (n = 125)	Sunitinib (n = 124)
Confirmed ORR	39.1%	32.4%	41.9%	26.8%	29.6%	51.6%
CR	10.7%	2.6%	10.4%	1.4%	12.0%	6.5%
PR	28.4%	29.9%	31.5%	25.4%	17.6%	45.2%
Stable disease	36.0%	42.1%	30.8%	44.3%	53.6%	34.7%
Progressive disease	17.6%	14.1%	19.3%	16.8%	12.0%	4.8%
Ongoing response	65.1%	52.0%	65.2%	49.6%	64.9%	56.3%

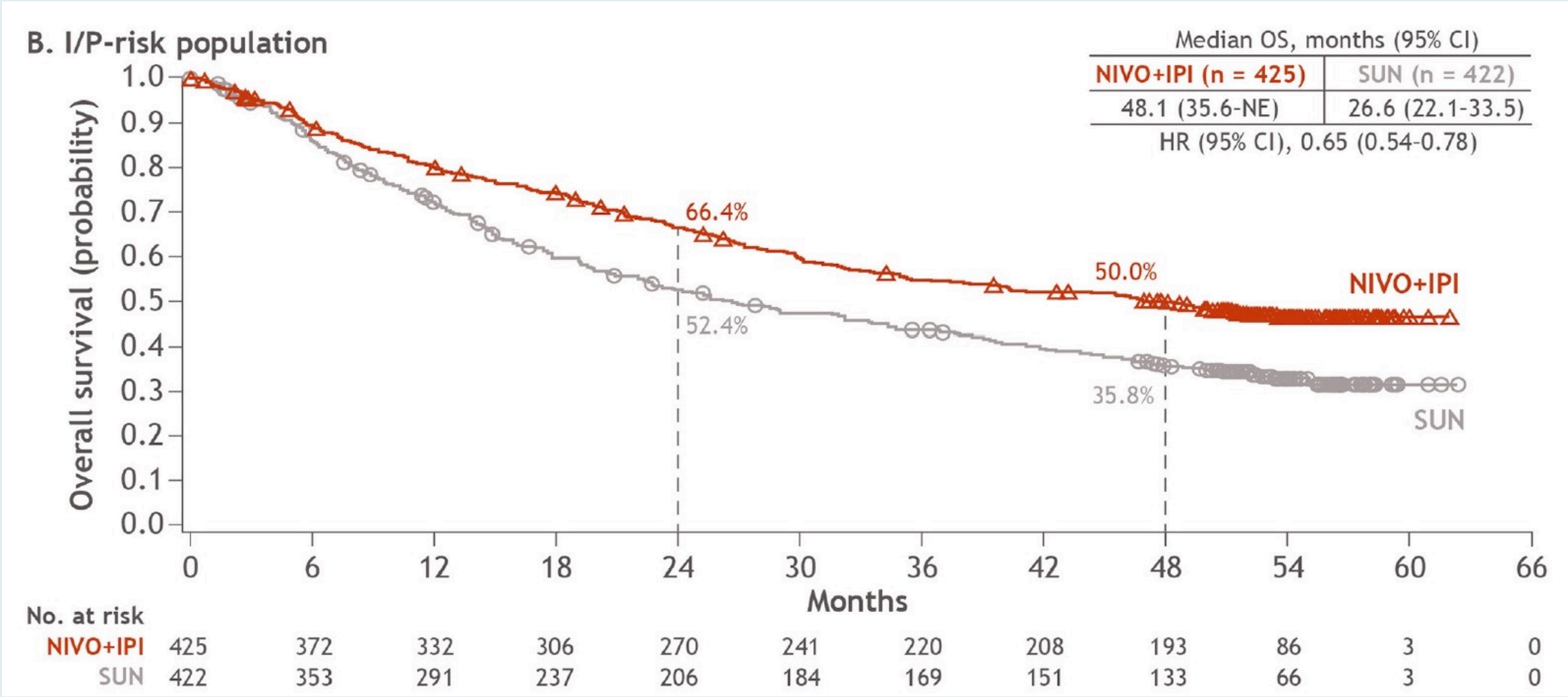
Albiges L et al. *ESMO Open* 2020;5(6):e001079.

CheckMate 214: Overall Survival (ITT)



Albiges L et al. *ESMO Open* 2020;5(6):e001079.

CheckMate 214: Overall Survival (Intermediate/Poor Risk)



Albiges L et al. *ESMO Open* 2020;5(6):e001079.

ORIGINAL ARTICLE

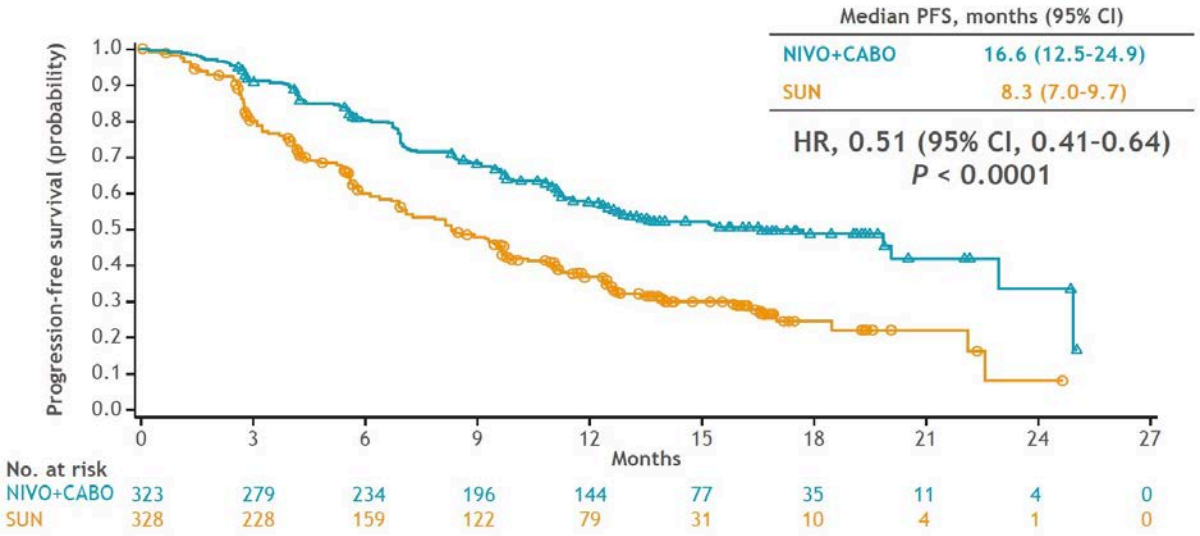
Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*

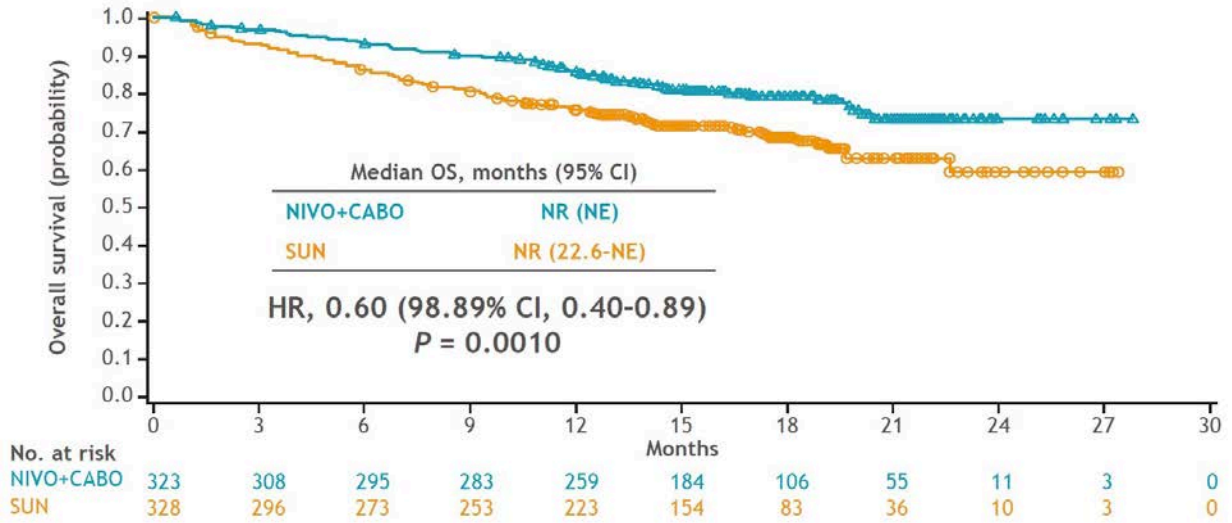
N Engl J Med 2021;384(9):829-41.

CheckMate 9ER Survival Analyses: Nivolumab/Cabozantinib for Previously Untreated Advanced RCC

Progression-free survival per BICR



Overall survival



Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41; ESMO 2020;Abstract 696O.

RTP RESEARCH TO PRACTICE

ABSTRACT 4509: NIVOLUMAB PLUS CABOZANTINIB IN PATIENTS WITH NON-CLEAR CELL RENAL CELL CARCINOMA: RESULTS OF A PHASE 2 TRIAL

Chung-Han Lee, Martin H Voss, Maria Isabel Carlo, Ying-Bei Chen, Ed Reznik, Andrea Knezevic, Robert A Lefkowitz, Natalie Shapnik, Diana Tassone, Chloe Dadoun, Mark Zucker, Neil J. Shah, Colette Ngozi Owens, Deaglan Joseph McHugh, David Henry Aggen, Andrew Leonard Laccetti, Ritesh Kotecha, Darren R. Feldman, Robert J. Motzer

June 6, 2021

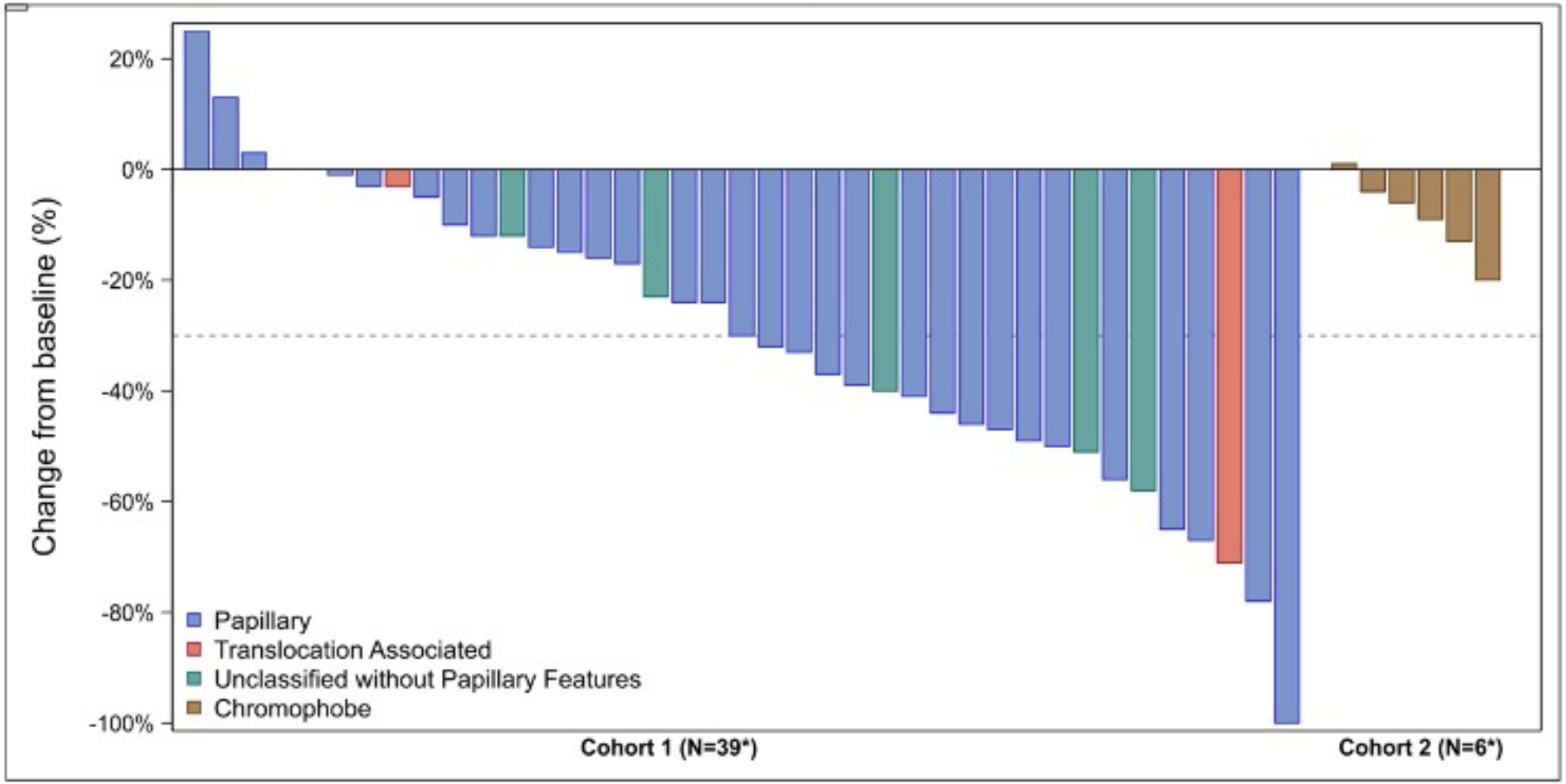
Memorial Sloan Kettering Cancer Center™

Corresponding Author Contact:
Dr. Chung-Han Lee
leec4@mskcc.org

Lee CH et al. ASCO 2021;Abstract 4509.

RTP RESEARCH TO PRACTICE

Maximum Change in Target Lesions by Histology



Lee CH et al. ASCO 2021;Abstract 4509.

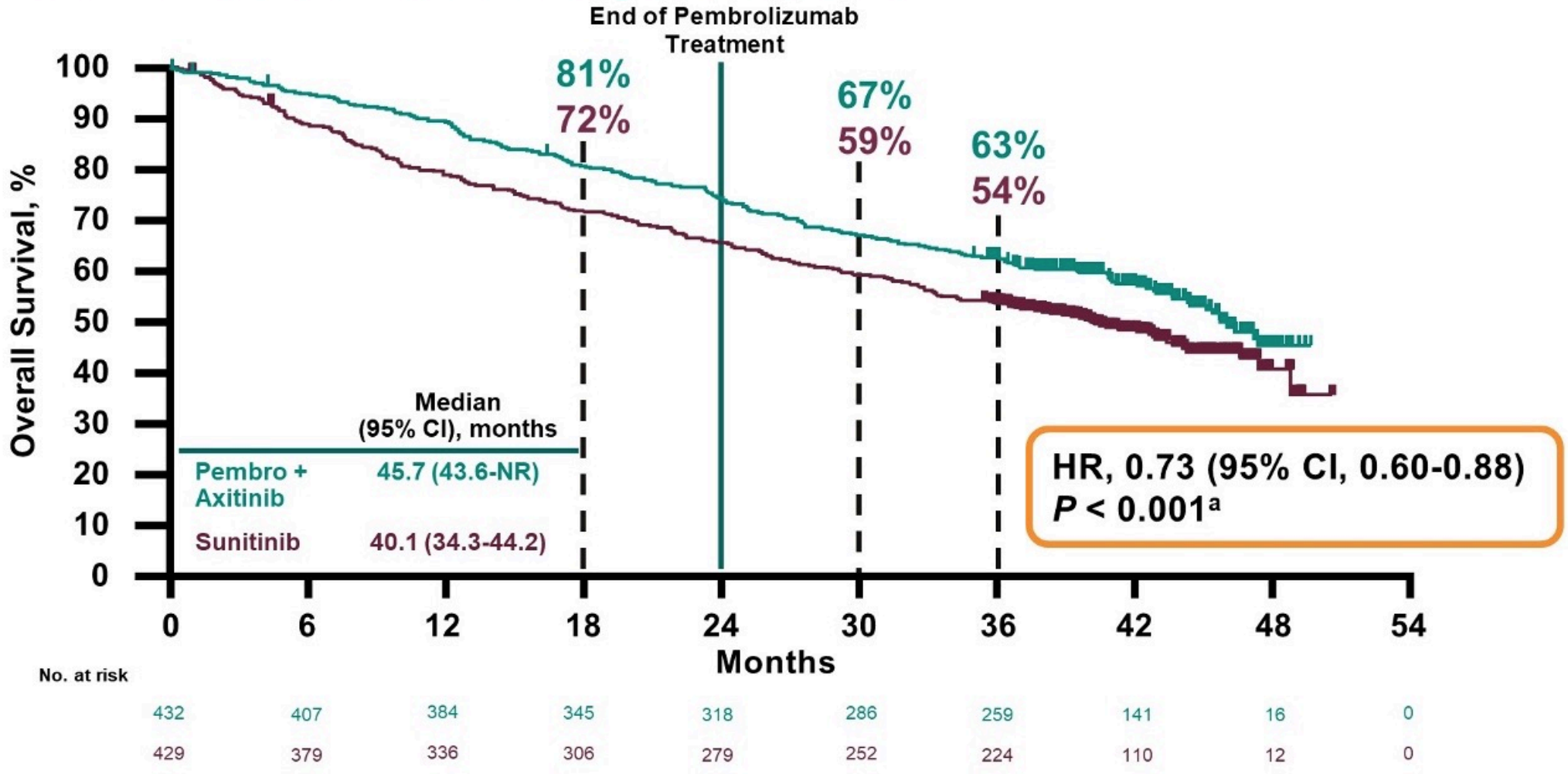
Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma: Results From 42-Month Follow-Up of KEYNOTE-426

B. I. Rini[1]; E. R. Plimack[2]; V. Stus[3]; T. Waddell[4]; R. Gafanov[5]; F. Pouliot[6]; D. Nosov[7]; B. Melichar[8]; D. Soulieres[9]; D. Borchiellini[10]; I. Vynnychenko[11]; R. S. McDermott[12]; S. J. Azevedo[13]; S. Tamada[14]; A. Kryzhanivska[15]; C. Li[16]; J. E. Burgents[16]; L. R. Molife[17]; J. Bedke[18]; T. Powles[19]

[1]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro, Ukraine; [4]The Christie NHS Foundation Trust, Manchester, United Kingdom; [5]Russian Scientific Center of Roentgenoradiology, Moscow, Russia; [6]CHU of Québec and Laval University, Québec City, QC, Canada; [7]Central Clinical Hospital With Outpatient Clinic, Moscow, Russia; [8]Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; [9]Centre Hospitalier de l'Universitaire de Montréal, Montréal, QC, Canada; [10]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [11]Sumy State University, Sumy Regional Oncology Center, Sumy, Ukraine; [12]Adelaide and Meath Hospital and University College Dublin, Dublin, Ireland; [13]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [14]Osaka City University Hospital, Osaka, Japan; [15]Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]MSD UK, London, United Kingdom; [18]Eberhard Karls Universität Tübingen, Tübingen, Germany; [19]Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, and Queen Mary University of London, London, United Kingdom

Rini BI et al. ASCO 2021;Abstract 4500.

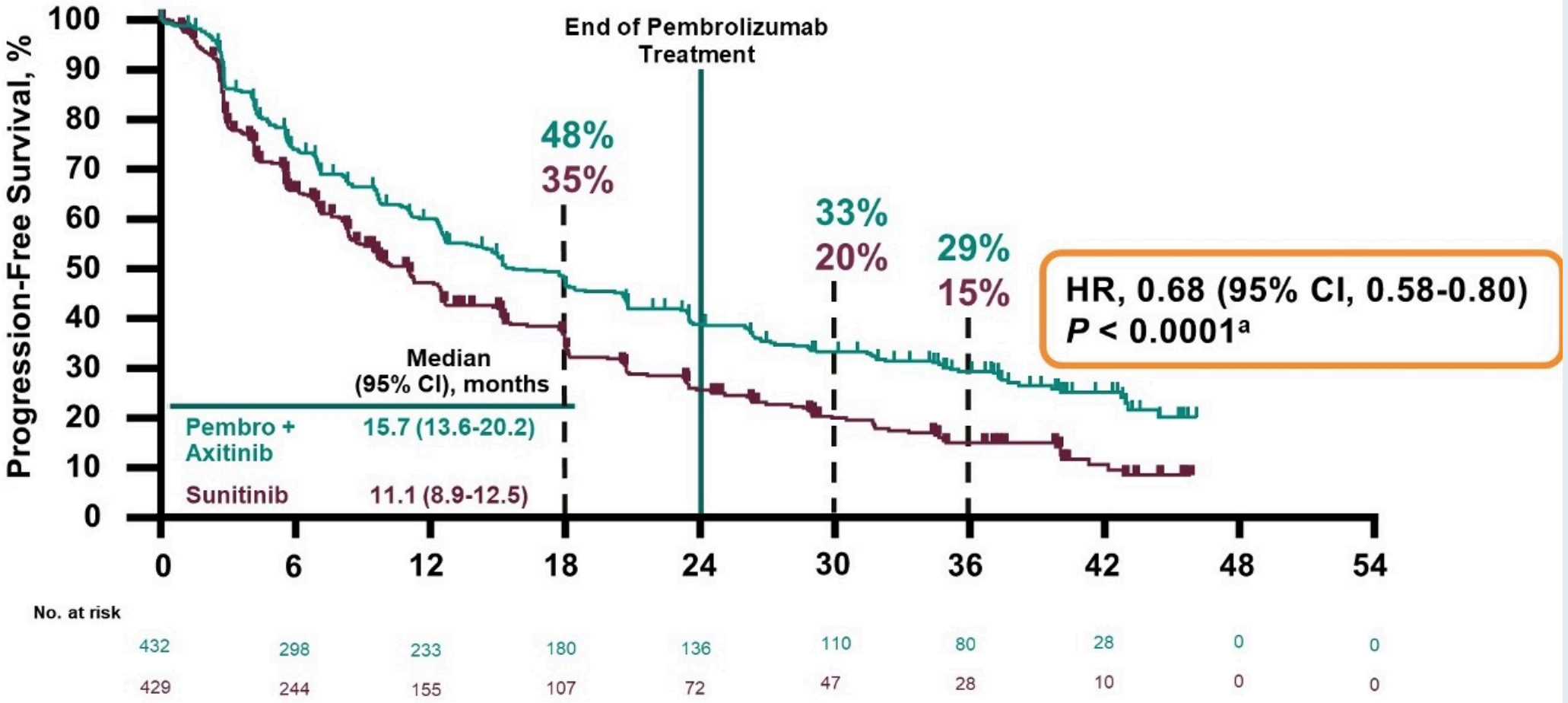
OS in the ITT Population



[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.

PFS in the ITT Population



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

Rini BI et al. ASCO 2021;Abstract 4500.

Ann Oncol 2020;31(8):1030-9

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma

T. K. Choueiri[1*], R. J. Motzer[2], B. I. Rini[3†], J. Haanen[4], M. T. Campbell[5], B. Venugopal[6], C. Kollmannsberger[7], G. Gravis-Mescam[8], M. Uemura[9], J. L. Lee[10], M.-O. Grimm[11], H. Gurney[12], M. Schmidinger[13], J. Larkin[14], M. B. Atkins[15], S. K. Pal[16], J. Wang[17], M. Mariani[18], S. Krishnaswami[19], P. Cislo[20], A. Chudnovsky[21], C. Fowst[18], B. Huang[19], A. di Pietro[22] & L. Albiges[23]

JAVELIN Renal 101: Overall Response and Best Response Rate in the PD-L1-Positive and Overall Populations

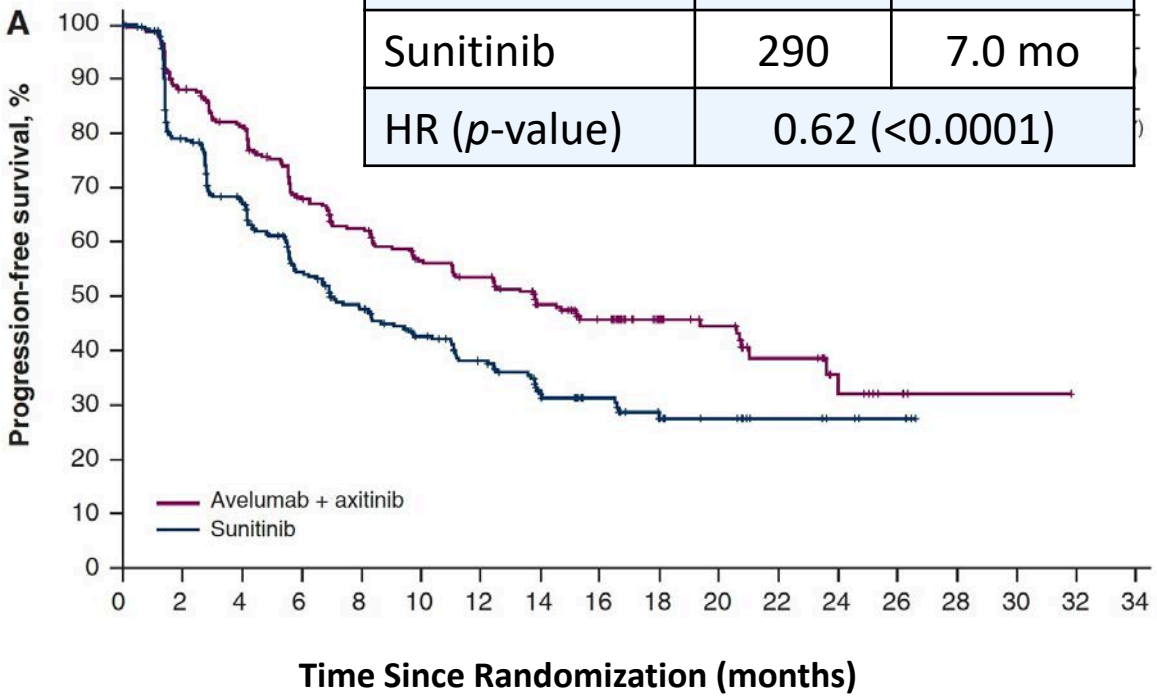
	PD-L1-positive		Overall	
	Avelumab + axitinib (n = 270)	Sunitinib (n = 290)	Avelumab + axitinib (n = 442)	Sunitinib (n = 444)
Confirmed ORR	55.9%	27.2%	52.5%	27.3%
CR	5.6%	2.4%	3.8%	2.0%
PR	50.4%	24.8%	48.6%	25.2%
Stable disease	27.0%	41.4%	28.3%	43.7%
Progressive disease	11.5%	22.4%	12.4%	19.4%
Ongoing response	55.6%	53.2%	54.3%	50.4%

Choueiri TK et al. *Ann Oncol* 2020;31(8):1030-9.

JAVELIN Renal 101: PFS in the PD-L1-Positive and Overall Populations

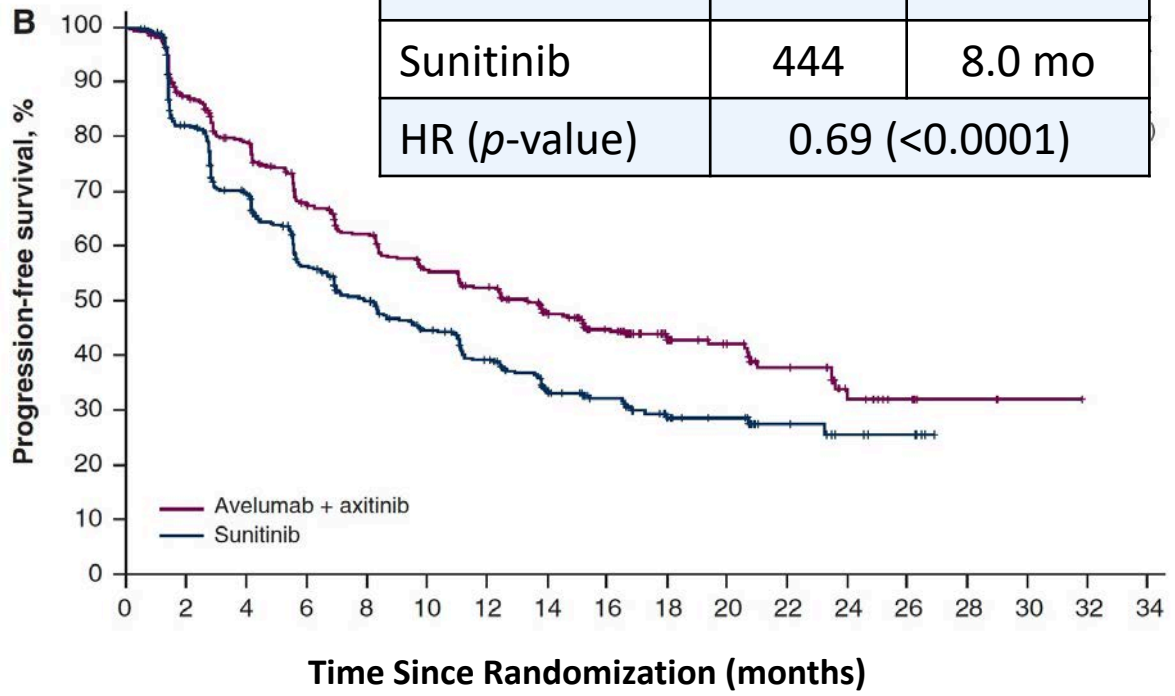
PD-L1 ≥ 1% Population

	N	mPFS
Avelumab + axitinib	270	13.8 mo
Sunitinib	290	7.0 mo
HR (*p*-value)	0.62 (<0.0001)	



Overall Population

	N	mPFS
Avelumab + axitinib	442	13.3 mo
Sunitinib	444	8.0 mo
HR (*p*-value)	0.69 (<0.0001)	



Choueiri TK et al. *Ann Oncol* 2020;31(8):1030-9.

RTP RESEARCH TO PRACTICE

FDA Approves Lenvatinib with Pembrolizumab for Advanced Renal Cell Carcinoma

Press Release – August 10, 2021

"The Food and Drug Administration approved the combination of lenvatinib plus pembrolizumab for first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

The efficacy of this combination was investigated in CLEAR (Study 307/KEYNOTE-581; NCT02811861), a multicenter, open-label, randomized phase 3 trial in patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status.

The recommended dosages for patients with advanced RCC are lenvatinib 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks up to 2 years, until disease progression or until unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

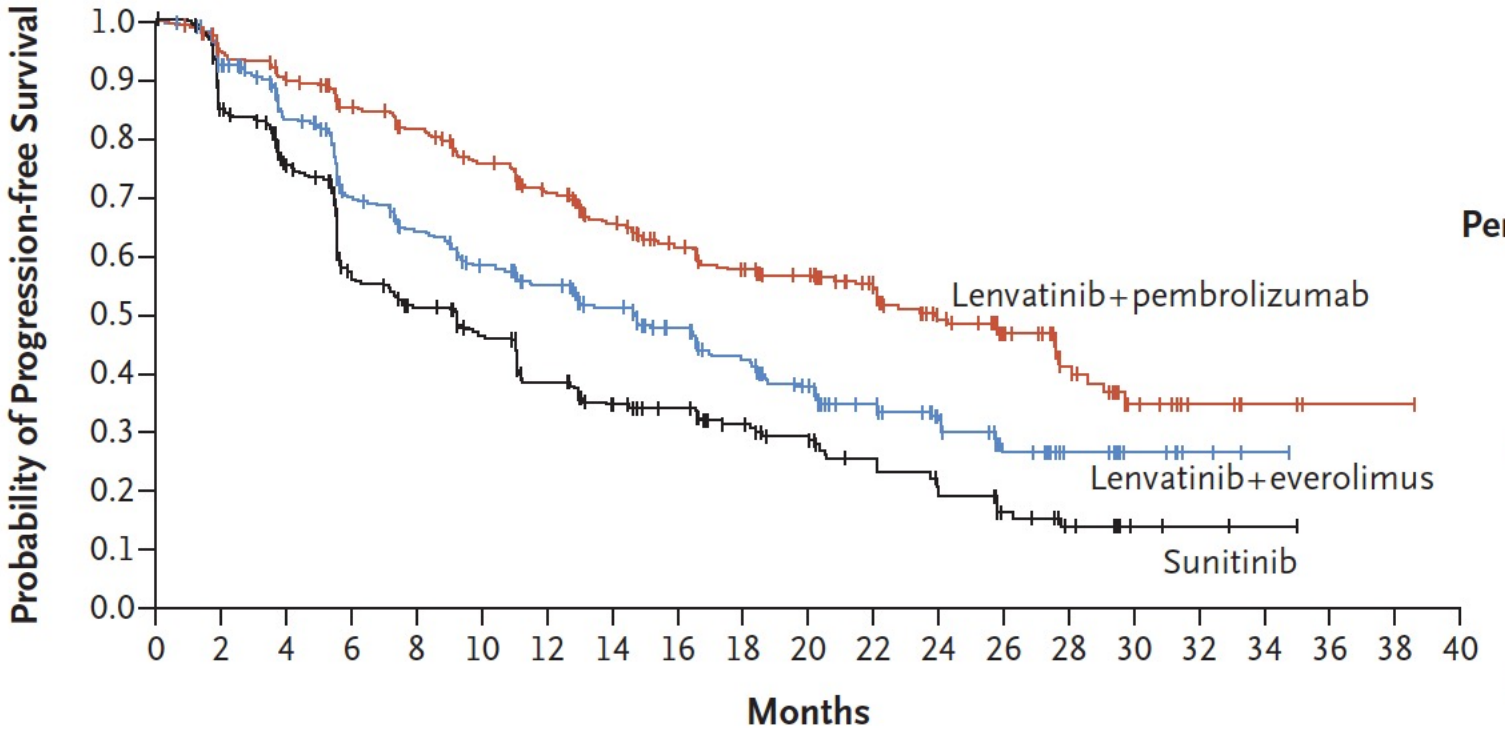
ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

N Engl J Med 2021;[Online ahead of print].

CLEAR: Progression-Free Survival



No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Median Progression-free Survival (95% CI)

	mo
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

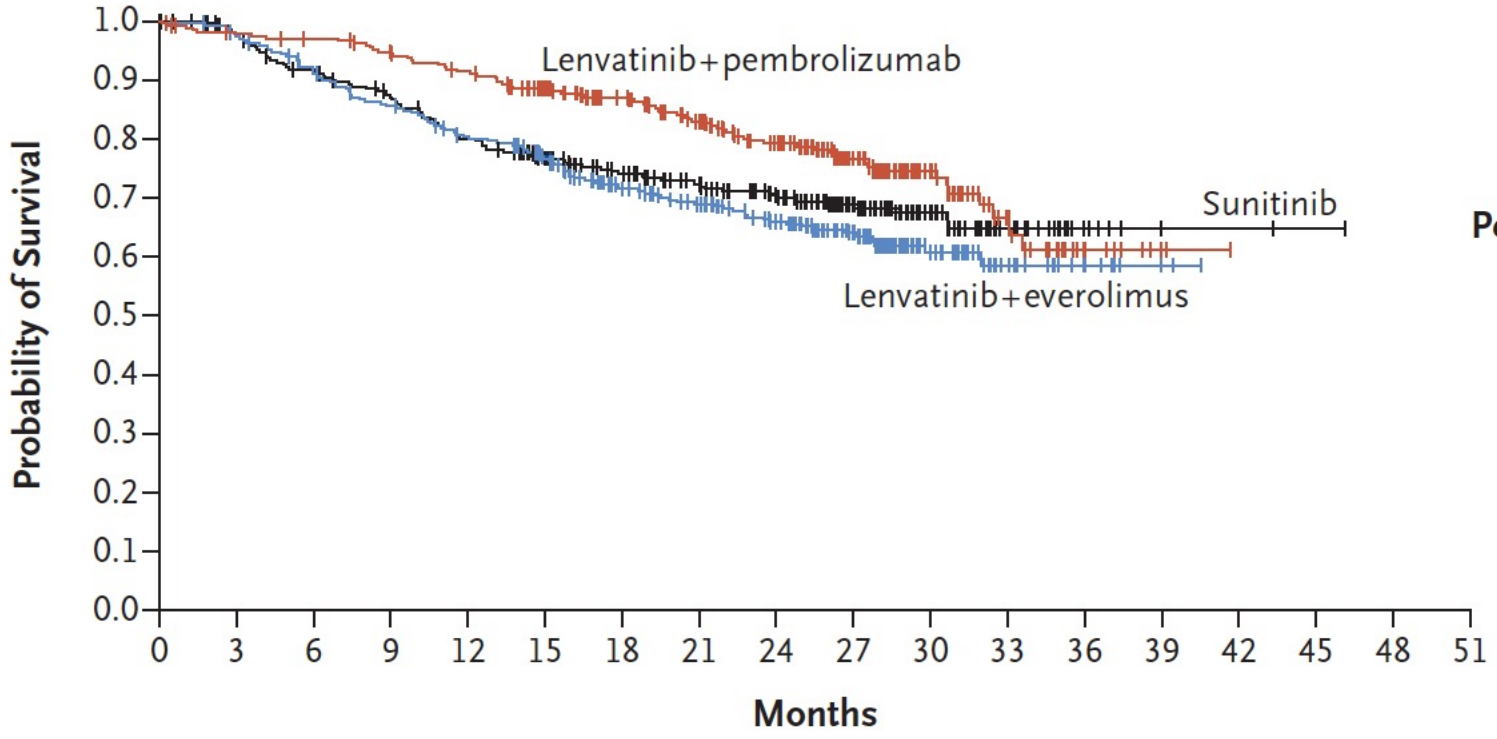
Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+ everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

Motzer R et al. *N Engl J Med* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

CLEAR: Overall Survival



	Median Overall Survival (95% CI) *mo*
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+ everolimus vs. sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

Motzer R et al. *N Engl J Med* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

ANALYSIS OF THE CLEAR STUDY IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA: DEPTH OF RESPONSE AND EFFICACY FOR SELECTED SUBGROUPS IN THE LENVATINIB-PLUS-PEMBROLIZUMAB AND SUNITINIB TREATMENT ARMS

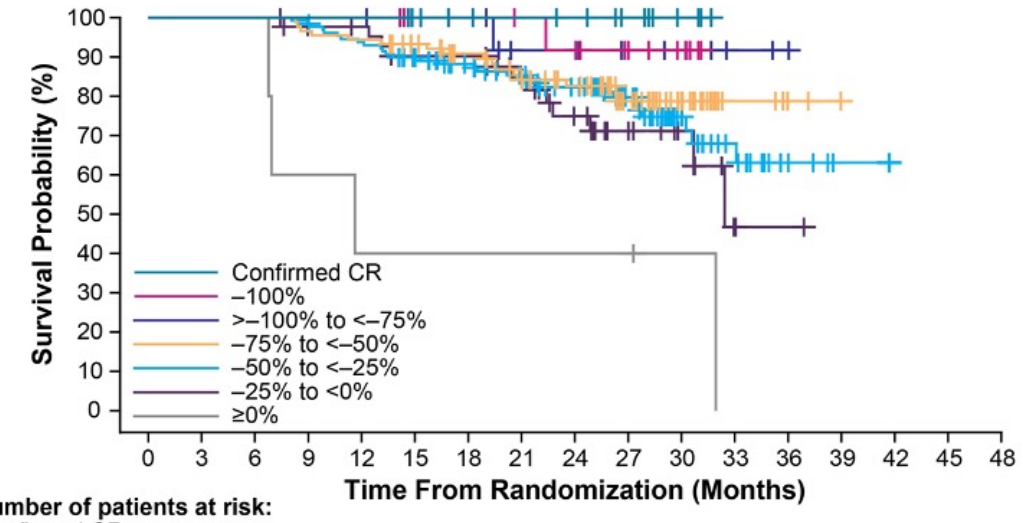
Viktor Grünwald[1], Thomas Powles[2], Evgeny Kopyltsov[3], Vadim Kozlov[4], Teresa Alonso Gordoa[5], Masatoshi Eto[6], Thomas Hutson[7], Robert Motzer[8], Eric Winquist[9], Pablo Maroto[10], Bhumsuk Keam[11], Giuseppe Procopio[12], Shirley Wong[13], Bohuslav Melichar[14], Frederic Rolland[15], Mototsugu Oya[16], Karla Rodriguez-Lopez[17], Kenichi Saito[18], Alan Smith[19], Camillo Porta[20]

[1]University Hospital Essen, Essen, Germany; [2]The Royal Free NHS Trust, London, England, UK; [3]State Institution of Healthcare "Regional Clinical Oncology Dispensary", Omsk, Russia; [4]State Budgetary Health Care Institution "Novosibirsk Regional Clinical Oncology Dispensary", Novosibirsk, Russia; [5]Hospital Universitario Ramón y Cajal, Madrid, Spain; [6]Kyushu University, Fukuoka, Japan; [7]Texas Oncology, Dallas, TX, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Western University, London, Ontario, Canada; [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [11]Seoul National University Hospital, Seoul, Korea; [12]Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [13]Western Health, VIC, Australia; [14]Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic; [15]Centre René Gauducheau Centre de Lutte Contre Le Cancer Nantes, Saint-Herblain, France; [16]Keio University School of Medicine, Tokyo, Japan; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Eisai Inc., Woodcliff Lake, NJ, USA; [19]Eisai Ltd., Hatfield, England, UK; [20]San Matteo University Hospital Foundation, Pavia, Italy.

Grunwald V et al. ASCO 2021;Abstract 4560.

CLEAR: 6-Month OS Analysis by Depth of Response

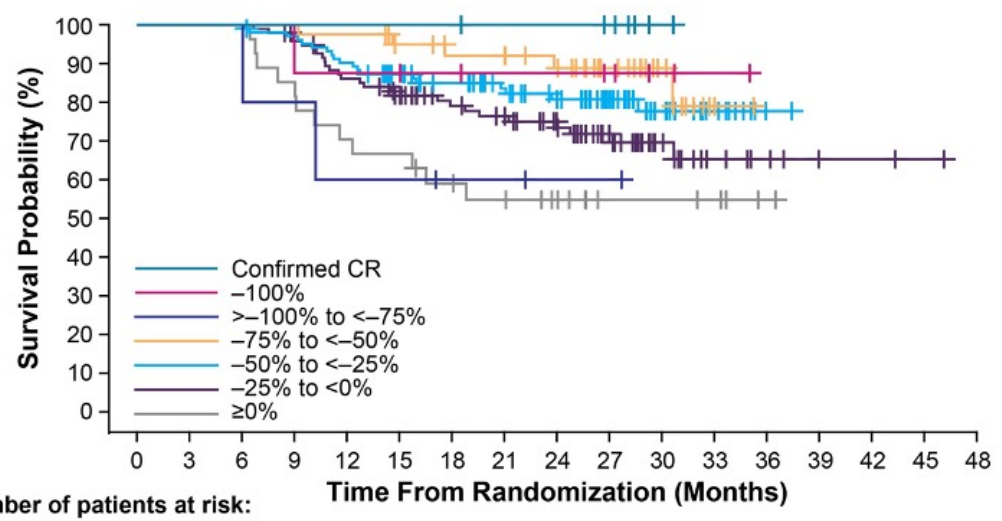
Lenvatinib plus Pembrolizumab



Number of patients at risk:

Confirmed CR	16	16	16	14	12	11	10	7	3	0	0	0	0	0	0
–100%	20	20	20	17	14	12	11	8	5	0	0	0	0	0	0
>–100% to <–75%	16	16	16	13	13	9	9	6	5	2	1	0	0	0	0
–75% to <–50%	89	86	84	78	70	61	54	37	20	5	2	0	0	0	0
–50% to <–25%	129	128	120	108	96	88	76	53	23	14	5	1	0	0	0
–25% to <0%	44	40	39	35	35	29	21	13	8	2	1	0	0	0	0
≥0%	5	3	2	2	2	2	2	2	1	0	0	0	0	0	0

Sunitinib



Number of patients at risk:

Confirmed CR	7	7	7	7	7	6	6	5	1	0	0	0	0	0	0
–100%	8	8	7	7	6	5	5	4	2	1	0	0	0	0	0
>–100% to <–75%	5	4	3	3	2	2	1	1	0	0	0	0	0	0	0
–75% to <–50%	40	40	39	35	32	32	28	19	10	2	0	0	0	0	0
–50% to <–25%	103	99	92	80	71	61	53	39	21	9	1	0	0	0	0
–25% to <0%	96	90	80	71	60	56	47	34	17	9	5	2	2	1	0
≥0%	27	23	19	18	15	13	10	5	5	4	1	0	0	0	0

Among patients treated with lenvatinib plus pembrolizumab, all those who had a complete response were alive at 2 years; survival rates were similar for patients who had more than 75% reduction in target lesions.

Tumors assessed by Independent Review Committee per RECIST v1.1

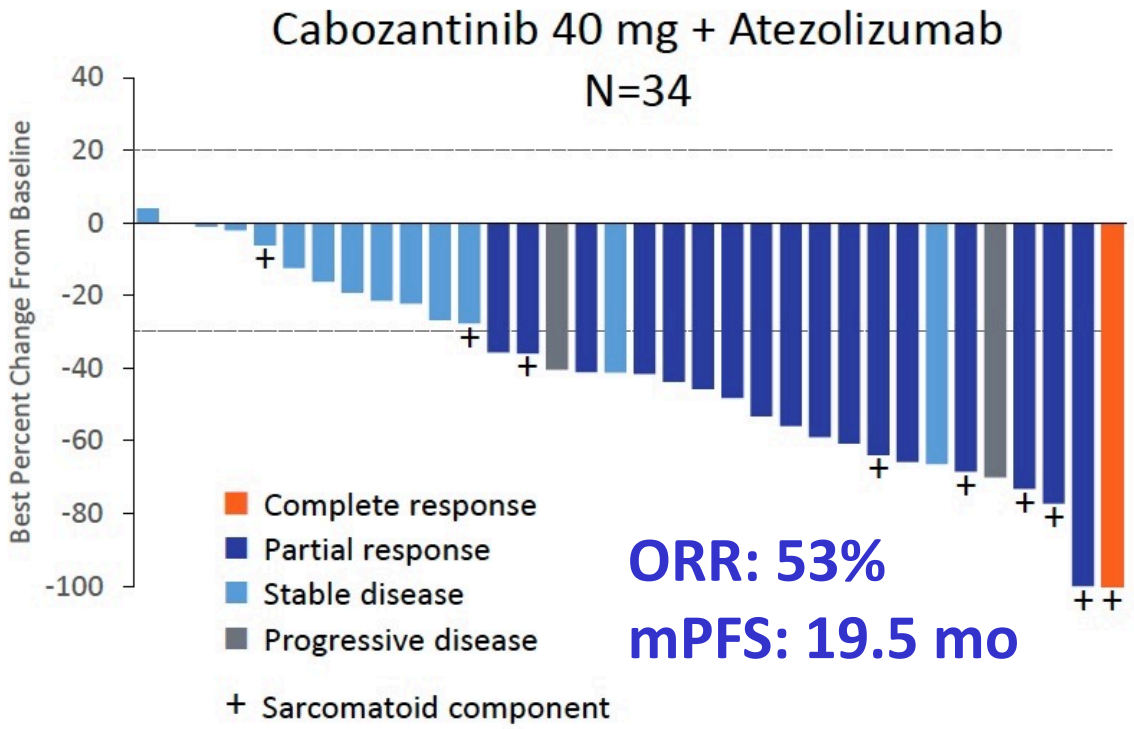
Grunwald V et al. ASCO 2021;Abstract 4560.

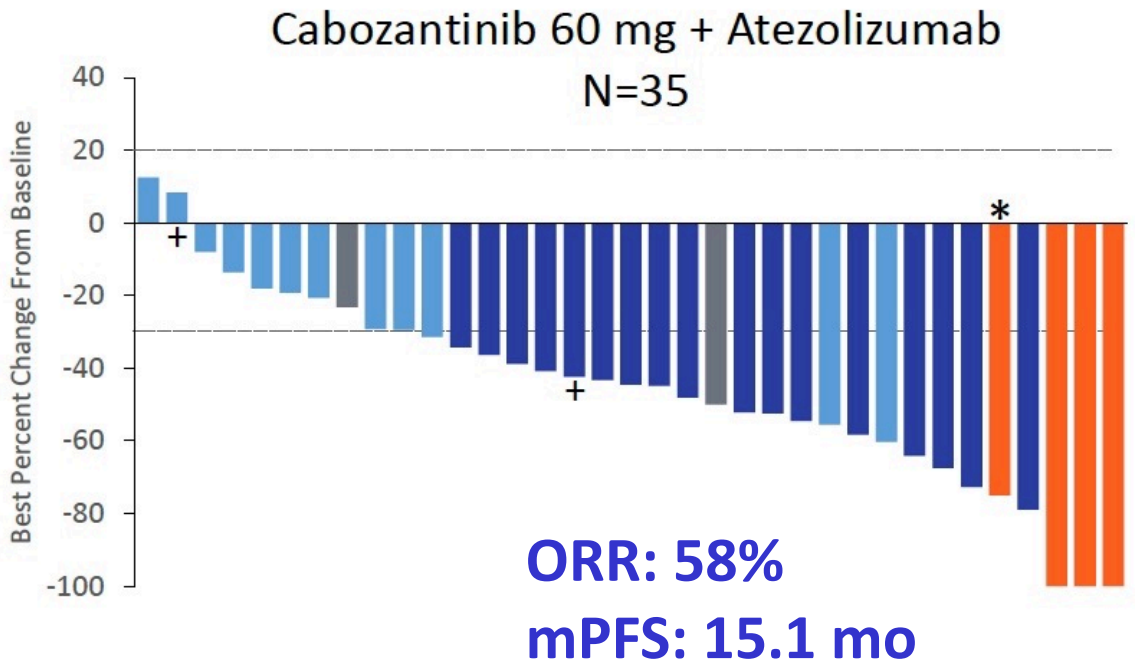
Cabozantinib (C) in Combination with Atezolizumab (A) as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from the COSMIC-021 Study

Pal S et al.

ESMO 2020;Abstract 702O.

COSMIC-021: Cabozantinib/Atezolizumab for Previously Untreated Advanced ccRCC





Pal S et al. ESMO 2020;Abstract 702O.

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Clinical Trials for Previously Untreated Metastatic RCC

Study acronym	Target accrual	Randomization	Primary endpoint	Estimated primary completion
COSMIC-313	840	• Cabozantinib + nivolumab + ipilimumab (4 doses) → cabozantinib + nivolumab • Placebo + nivolumab + ipilimumab (4 doses) → placebo + nivolumab	PFS	Nov 2021
PDIGREE	1,046	After induction nivolumab/ipilimumab • Pts with CR → Nivolumab • Pts with non-CR or non-PD, *randomized* → Nivolumab → Nivolumab + cabozantinib • Pts with PD → Cabozantinib	OS	Sept 2021

Sequencing of Therapy for Patients with Relapsed/Refractory RCC; Novel Approaches under Investigation

FDA Approves Tivozanib for Relapsed or Refractory Advanced RCC

Press Release: March 10, 2021

"On March 10, 2021, the Food and Drug Administration approved tivozanib, a kinase inhibitor, for adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

Efficacy was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open-label, multicenter trial of tivozanib versus sorafenib in patients with relapsed or refractory advanced RCC who received two or three prior systemic treatments, including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib.

The recommended tivozanib dose is 1.34 mg once daily (with or without food) for 21 consecutive days every 28 days until disease progression or unacceptable toxicity."

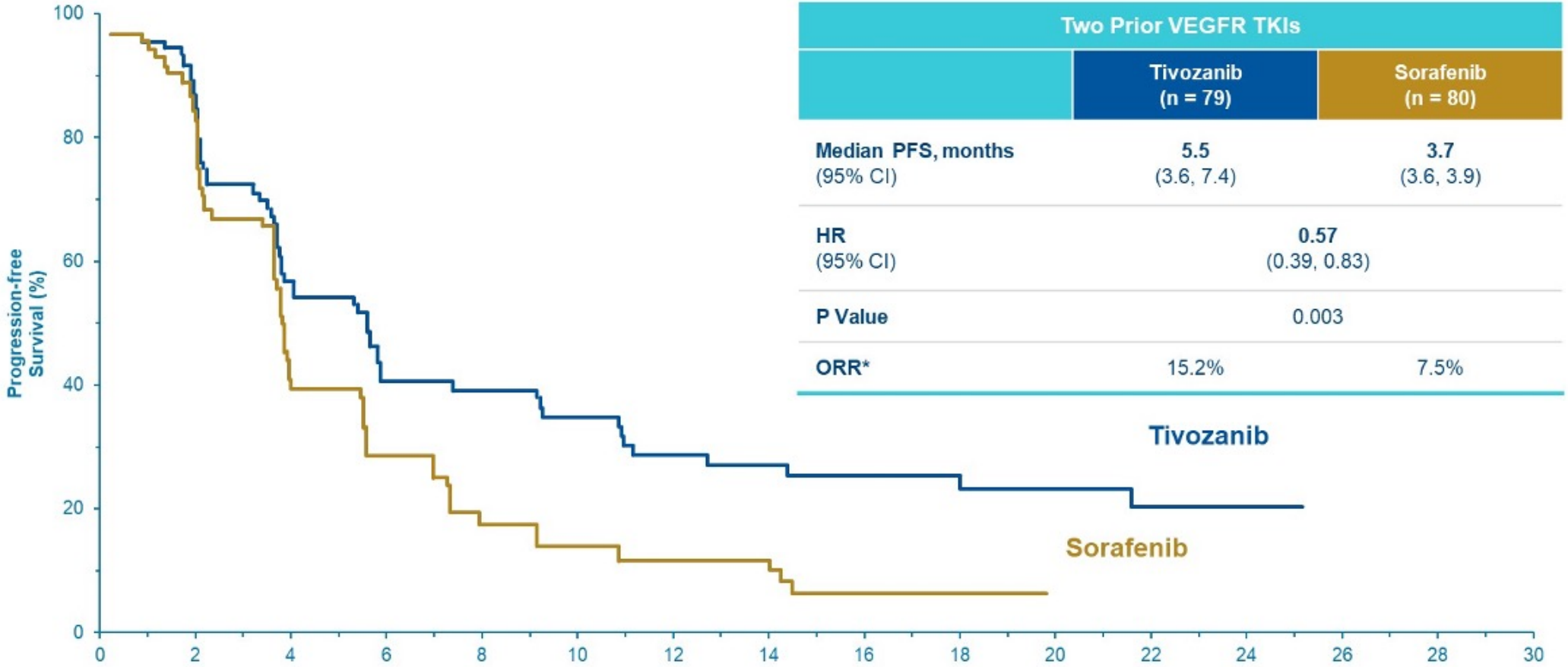
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma

Tivozanib in Patients with Advanced Renal Cell Carcinoma (aRCC) Who Have Progressed After Prior Treatment of Axitinib: Results from TIVO-3

Rini BI et al.

Genitourinary Cancers Symposium 2021;Abstract 278.

TIVO-3: Progression-Free Survival and ORR in Patient Subgroup with 2 Prior TKIs



Two Prior VEGFR TKIs		
	Tivozanib (n = 79)	Sorafenib (n = 80)
Median PFS, months (95% CI)	5.5 (3.6, 7.4)	3.7 (3.6, 3.9)
HR (95% CI)	0.57 (0.39, 0.83)	
P Value	0.003	
ORR*	15.2%	7.5%

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

TIVO-3: Tivozanib After Axitinib

RCC Population	N (subjects)		mPFS (months)		HR	ORR	
	Tivo	Sor	Tivo	Sor		Tivo	Sor
ITT	175	175	5.6	3.9	0.73	18%	8%
3rd Line Any Prior Axitinib	47	46	5.5	3.9	0.71	16%	6%
4th Line Any Prior Axitinib	36	43	5.5	3.6	0.64	11%	10%
3rd and 4th Line Any Prior Axitinib	83	89	5.5	3.7	0.68	13%	8%

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

TIVO-3: Durability of Response and Updated Overall Survival of Tivozanib versus Sorafenib in Metastatic Renal Cell Carcinoma (mRCC)

Verzoni et al.
ASCO 2021;Abstract 4546.

"Tivozanib demonstrated clinically meaningful and statistically significant improvement in ORR and DoR with similar OS to sorafenib in patients with highly relapsed or refractory mRCC"

- *Median DoR was 20.3 months with tivozanib, twice that observed with sorafenib*

FDA Approves Belzutifan for Cancers Associated with von Hippel-Lindau Disease

Press Release – August 13, 2021

"The Food and Drug Administration approved belzutifan, a hypoxia-inducible factor inhibitor for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Belzutifan was investigated in the ongoing Study 004 (NCT03401788), an open-label clinical trial in 61 patients with VHL-associated RCC (VHL-RCC) diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney. Enrolled patients had other VHL-associated tumors, including CNS hemangioblastomas and pNET. Patients received belzutifan 120 mg once daily until disease progression or unacceptable toxicity."

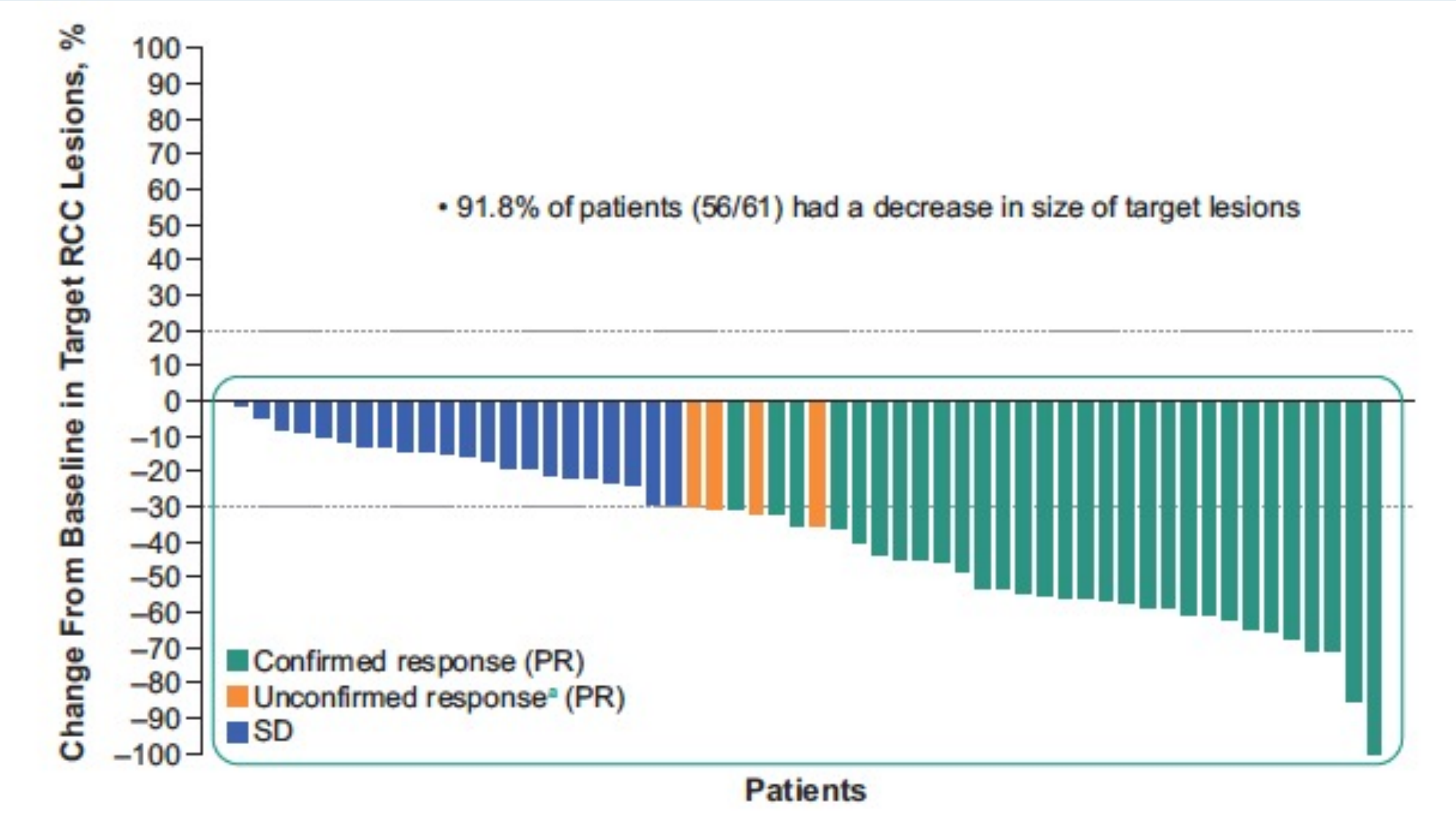
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease

Phase 2 Study of Belzutifan (MK-6482), an Oral Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitor, for Von Hippel-Lindau (VHL) Disease-Associated Clear Cell Renal Cell Carcinoma (ccRCC)

Srinivasan R et al.

ASCO 2021;Abstract 4555.

Maximum Change from Baseline in Sum of Target RCC Lesions



Srinivasan R et al. ASCO 2021;Abstract 4555.

RTP RESEARCH TO PRACTICE

Genitourinary Cancers Symposium 2021;Abstract 272.

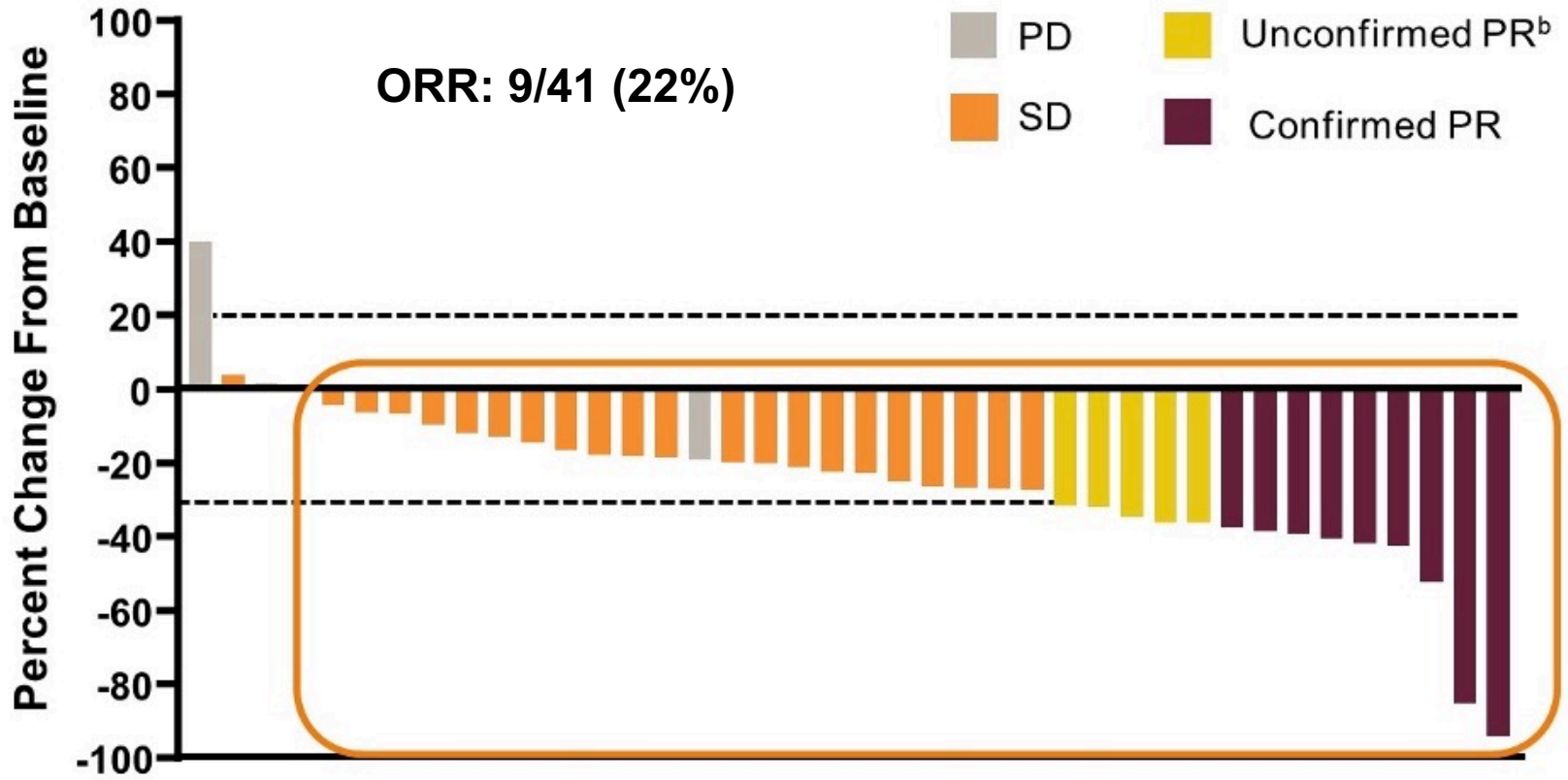
Phase 2 Study of the Oral Hypoxia-Inducible Factor 2α Inhibitor Belzutifan (MK-6482) in Combination With Cabozantinib in Patients With Advanced Clear Cell Renal Cell Carcinoma

Toni K. Choueiri[1]; Todd M. Bauer[2]; David F. McDermott[3]; Edward Arrowsmith[4]; Ananya Roy[5]; Rodolfo Perini[5]; Donna Vickery[5]; Scott S. Tykodi[6]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Tennessee Oncology, Chattanooga, TN, USA; [5]Merck & Co., Inc., Kenilworth, NJ, USA; [6]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Best Tumor Change from Baseline

- 36 of 41 patients (88%) experienced a reduction in target lesion size[a]



Choueiri TK et al. Genitourinary Cancers Symposium 2021;Abstract 272.

Summary of Adverse Events

n (%)	N = 52
Any grade treatment-emergent AE	52 (100)
Any grade treatment-related AE	51 (98)
Related to belzutifan	51 (98)
Related to cabozantinib	51 (98)
Grade 3-5 treatment-emergent AEs	35 (67)
Grade 3[b] treatment-related AEs	31 (60)
Related to belzutifan	17 (33)
Related to cabozantinib	28 (54)
Serious treatment-emergent AEs	16 (31)
Serious treatment-related AEs	7 (13)
Related to belzutifan	4 (8)
Related to cabozantinib	4 (8)

n (%)	N = 52
Deaths due to a treatment-emergent AE	1 (2)[c]
Deaths due to a treatment-related AE	0 (0)
Belzutifan dose reduced[d]	10 (19)
Cabozantinib dose reduced[e]	25 (48)
Discontinued any drug due to a treatment-emergent AE	8 (15)
Discontinued belzutifan[f]	6 (12)
Discontinued cabozantinib[g]	8 (15)

Choueiri TK et al. Genitourinary Cancers Symposium 2021;Abstract 272.

Treatment-Related Adverse Events

Treatment-Related AEs in ≥15% of Patients	Safety Analysis Set N = 52			
	Any Grade		Grade 3	
	Event, n	n (%)	Event, n	n (%)
Any	742	51 (98)	60	31 (60)
Anemia	92	40 (77)	8	6 (12)
Fatigue	67	35 (67)	10	6 (12)
Hand-foot syndrome	56	28 (54)	1	1 (2)
Diarrhea	49	23 (44)	2	2 (4)
Hypertension	52	23 (44)	15	12 (23)
Nausea	24	18 (35)	1	1 (2)
ALT increased	48	17 (33)	7	3 (6)
AST increased	34	17 (33)	2	2 (4)
Decreased appetite	22	15 (29)	1	1 (2)
Dysgeusia	19	12 (23)	1	1 (2)
Headache	12	10 (19)	0	0 (0)
Hypophosphatemia	18	9 (17)	2	2 (4)
Stomatitis	10	8 (15)	0	0 (0)

[a]All patients who received ≥1 dose of treatment. Data cutoff: October 15, 2020.

- There were no grade 4/5 treatment-related AEs
- Of all 742 AEs, 92% were grade 1 or 2 in severity
- Treatment-related hypoxia, considered an on-target AE for belzutifan, occurred in 2 patients (4%) (both were grade 3 AEs)

Choueiri TK et al. Genitourinary Cancers Symposium 2021;Abstract 272.

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Triple-Negative Breast Cancer

Tuesday, August 24, 2021
5:00 PM – 6:00 PM ET

Faculty

Sara Hurvitz, MD

Moderator

Neil Love, MD

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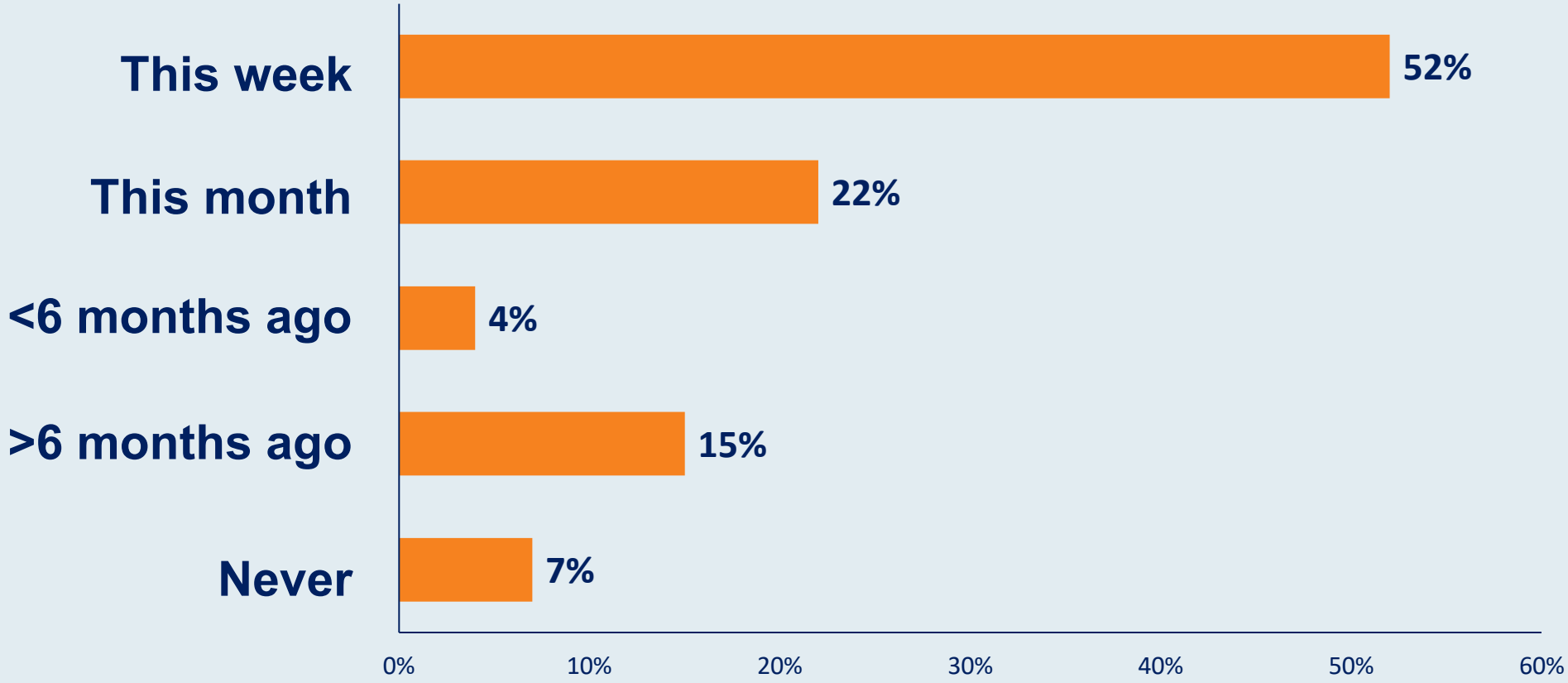
TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE

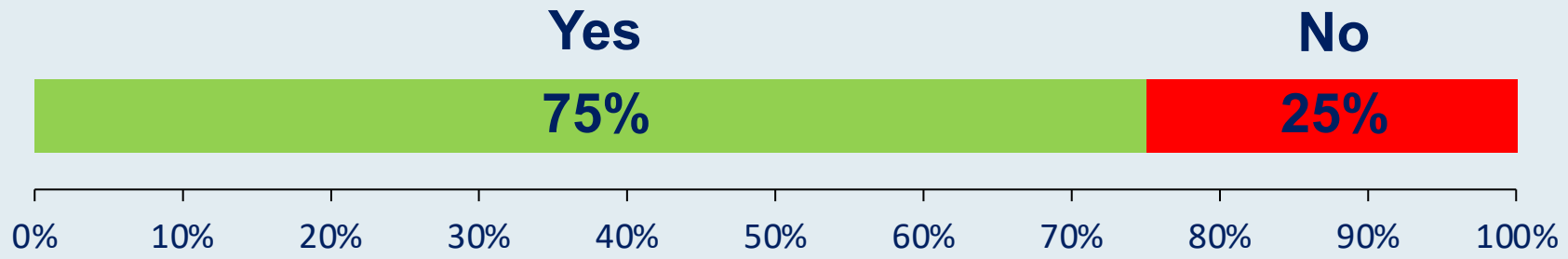
When was the last time that you presented, or had a case presented for you, at a local tumor board meeting?



Premeeting survey: July 2021

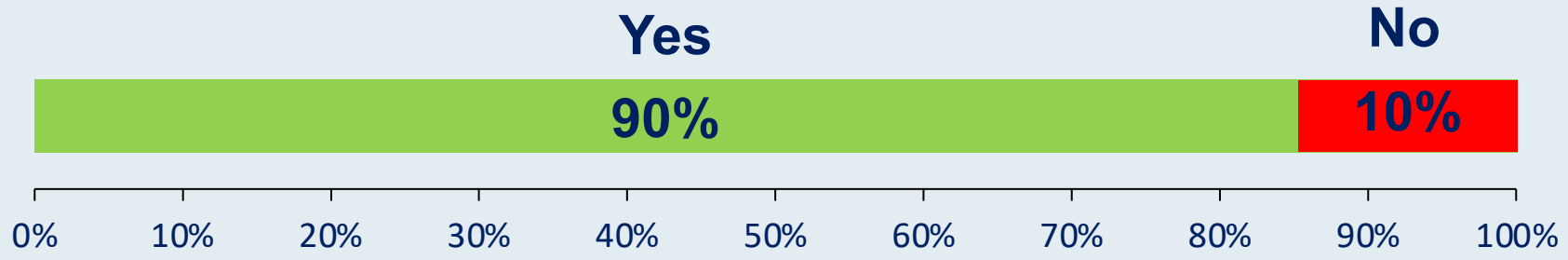
RTP RESEARCH TO PRACTICE

In the past month have you listened to audio podcasts not related to medicine?



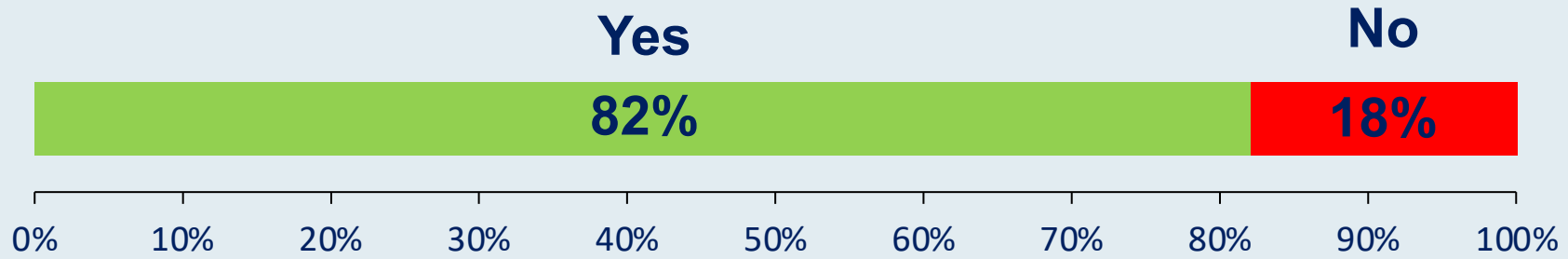
Median: 5 hours
Range: 1-60

In the past month have you listened to oncology-related audio podcasts?



Median: 5 hours
Range: 1-40

In the past month have you listened to RTP audio podcasts?



Median: 4 hours
Range: 1-66

Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE