Meet The Professor

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

David F McDermott, MD
Chief, Medical Oncology
Beth Israel Deaconess Medical Center
Leader, Kidney Cancer Program
Dana-Farber/Harvard Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Commercial Support

This activity is supported by educational grants from Aveo Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc and Exelixis Inc.

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Dr Love — Disclosures

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Consulting Agreements	Alkermes, Bristol-Myers Squibb Company, Calithera Biosciences, Eisai Inc, EMD Serono Inc, Iovance Biotherapeutics, Lilly, Merck, Pfizer Inc, Werewolf Therapeutics
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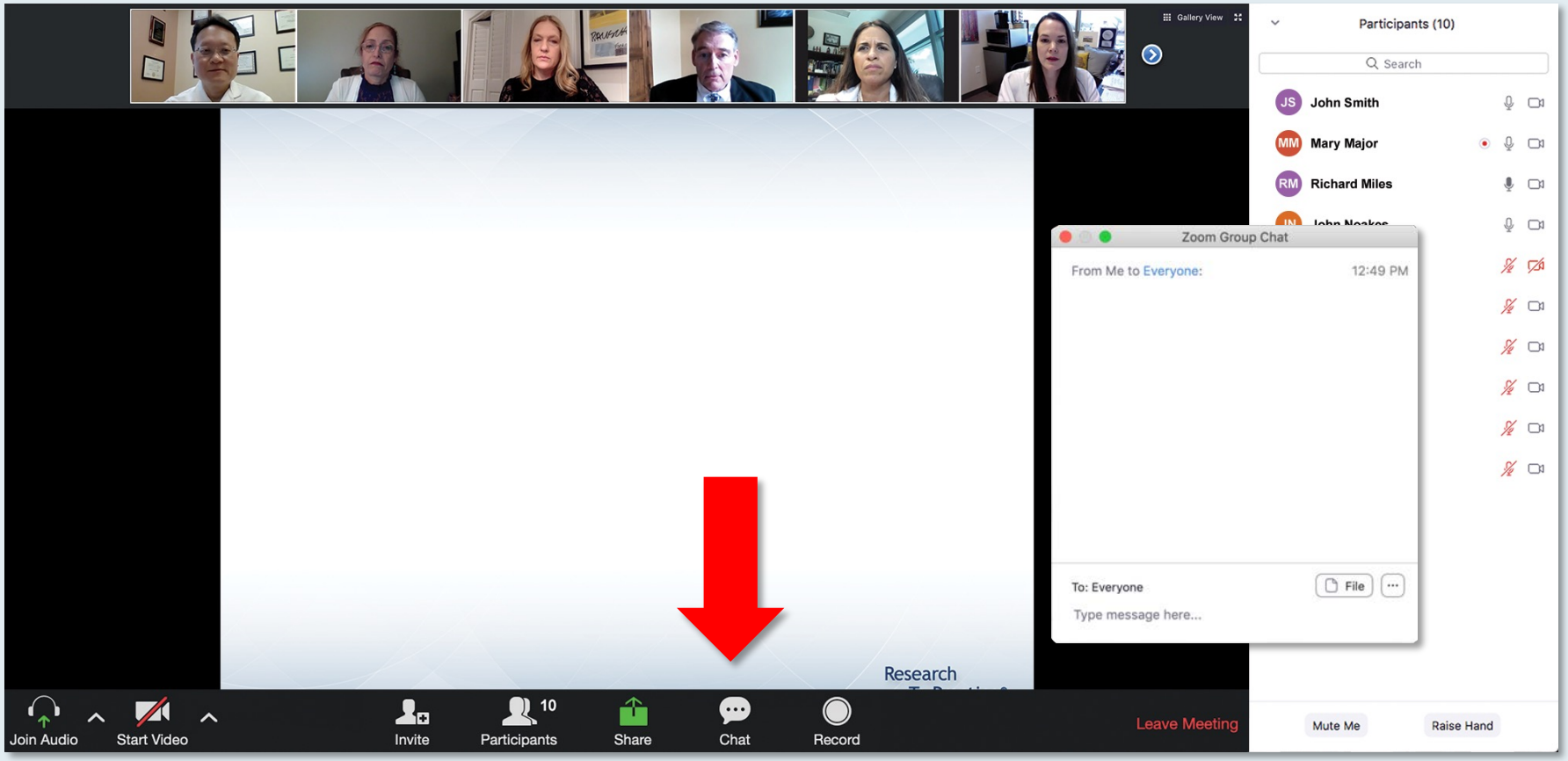
We Encourage Clinicians in Practice to Submit Questions



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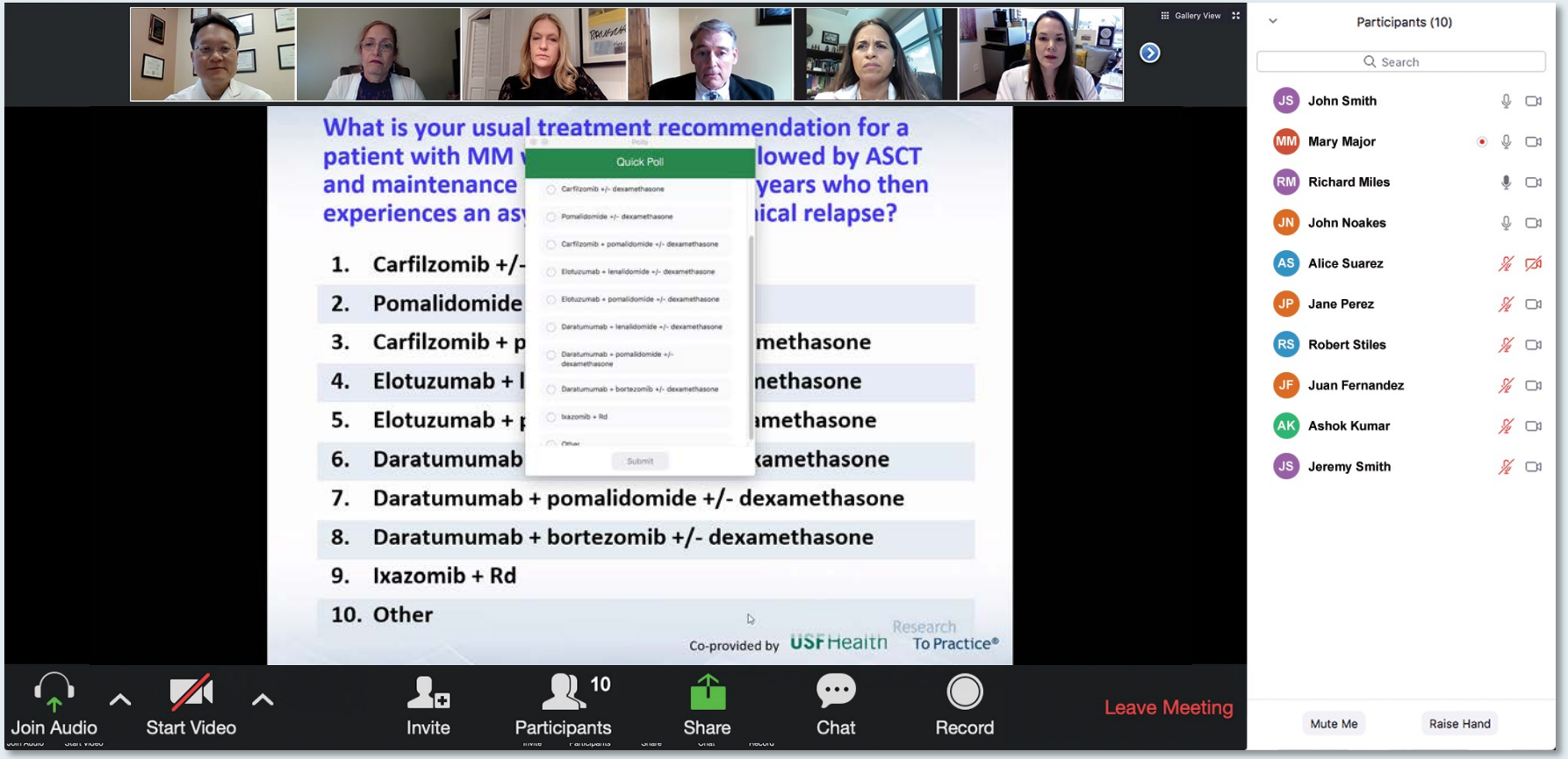

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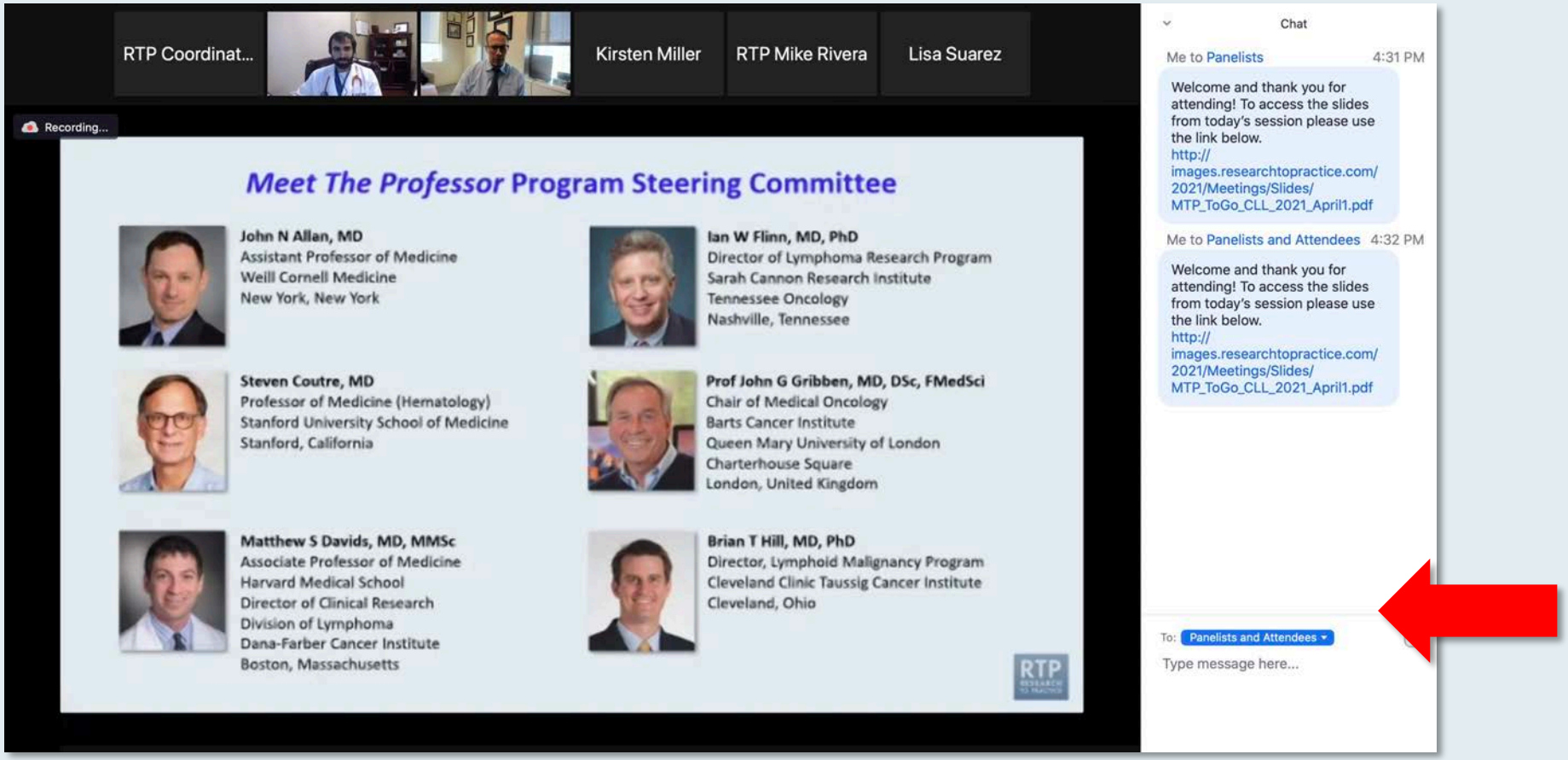
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



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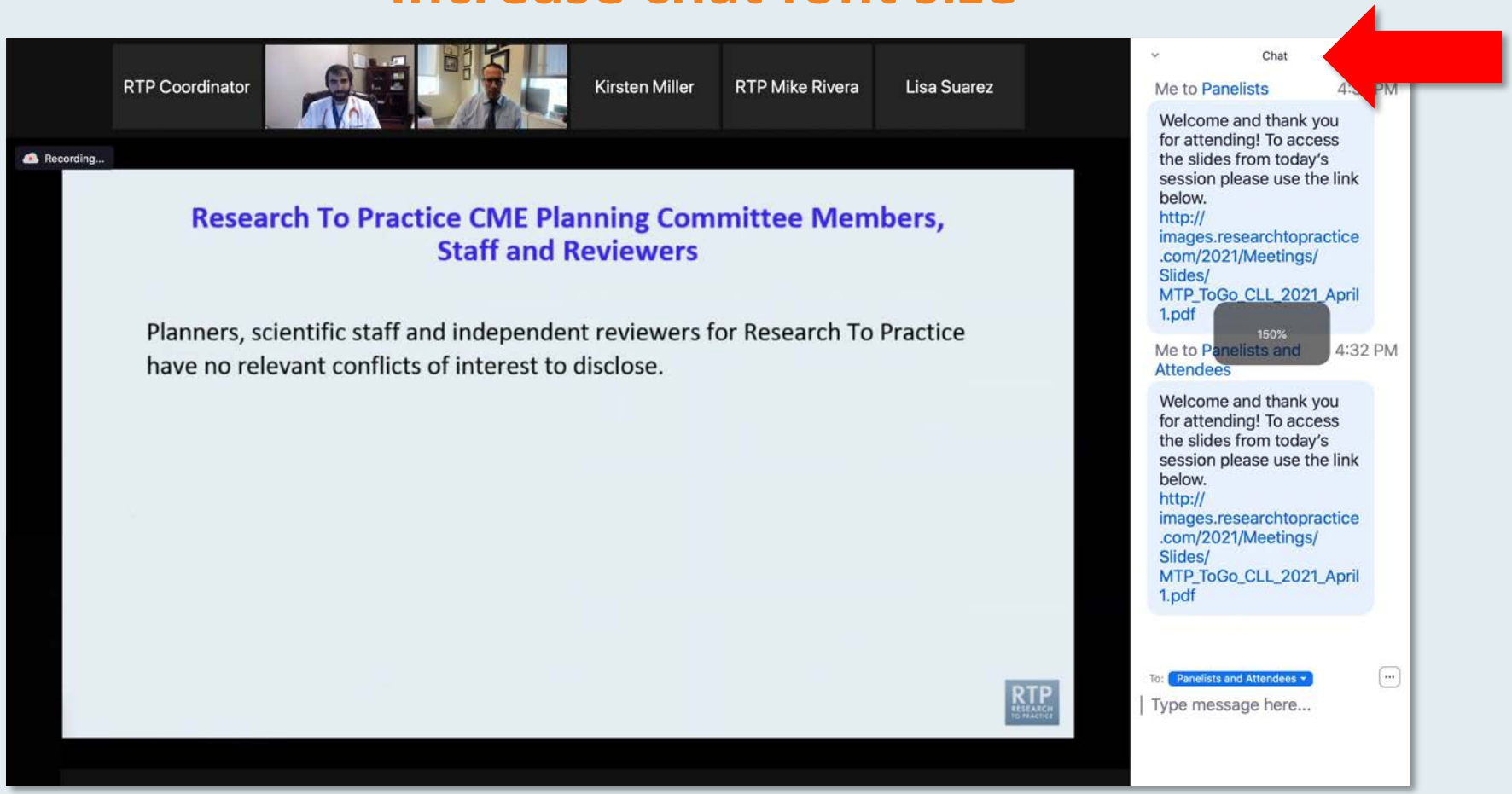
Increase chat font size



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

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MEMORIAL SLOAN KETTERING CANCER CENTER

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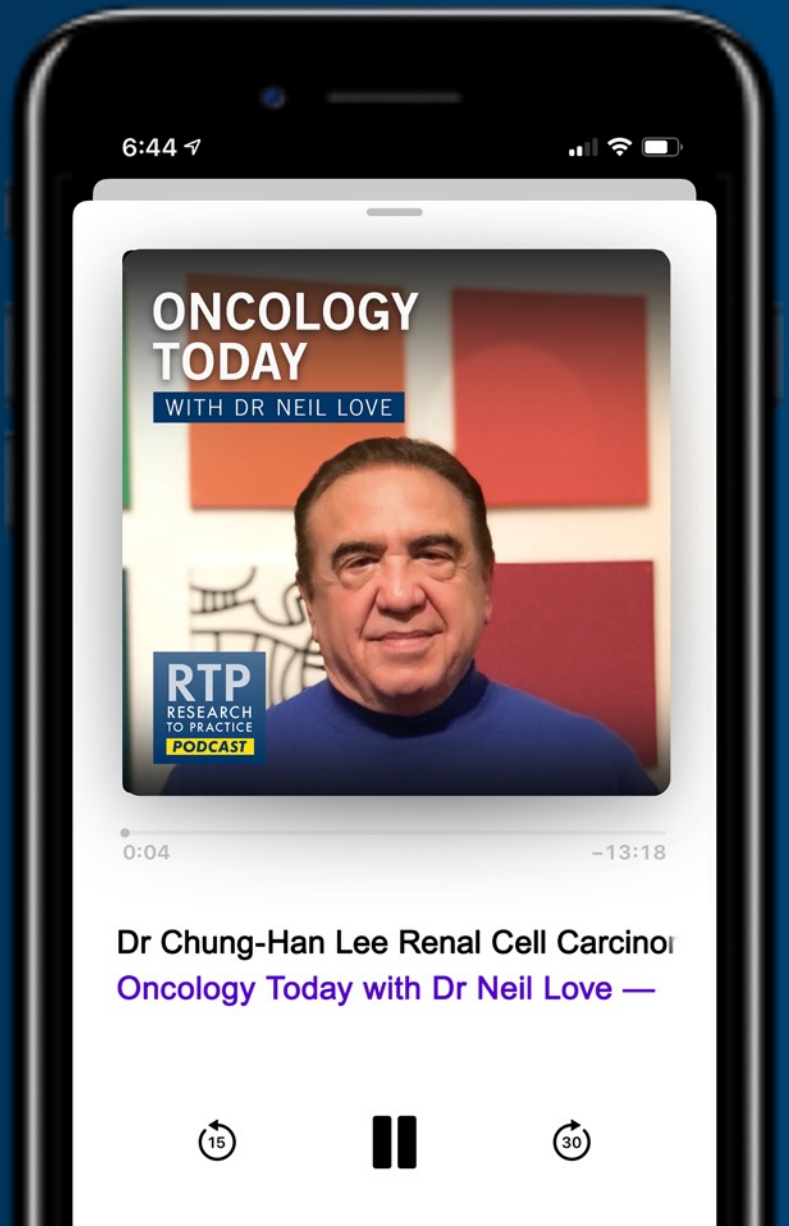

7 Exciting CME/MOC Events You Do Not Want to Miss

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Monday, July 26
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Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma
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Faculty

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David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

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What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

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Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma

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Craig Moskowitz, MD
Laurie H Sehn, MD, MPH

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Faculty

Chloe E Atreya, MD, PhD
Dustin Deming, MD
Eric Van Cutsem, MD, PhD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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Kim A Reiss Binder, MD
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP

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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Department of Medical Oncology
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The Jerome and Nancy Kohlberg Professor of Medicine
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Director, Genitourinary Clinical Research
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Fox Chase Cancer Center, Temple Health
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Director of Barts Cancer Centre
Queen Mary University of London
London, United Kingdom

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Brian I Rini, MD
Chief of Clinical Trials
Vanderbilt-Ingram Cancer Center
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Vanderbilt University Medical Center
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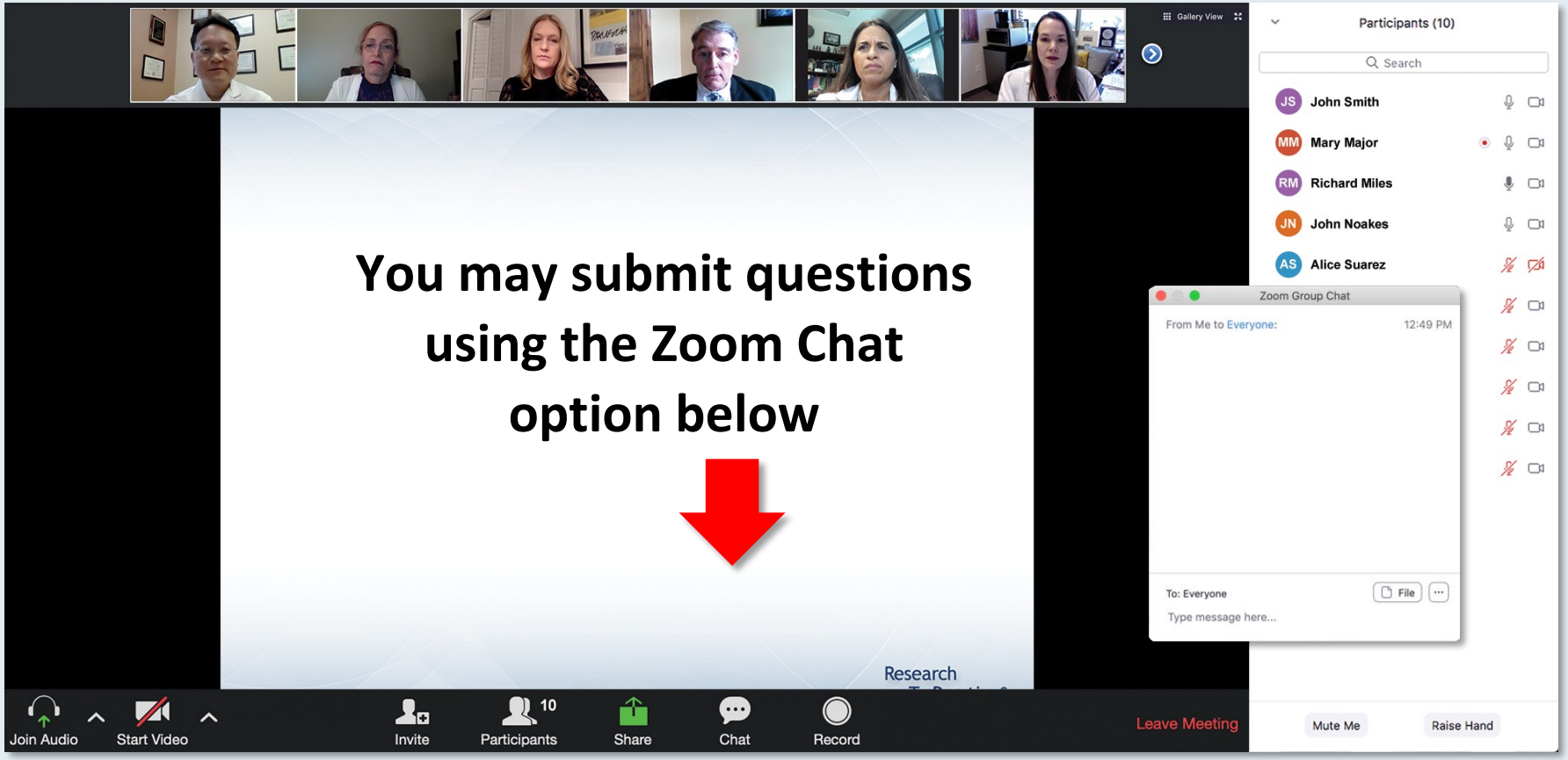

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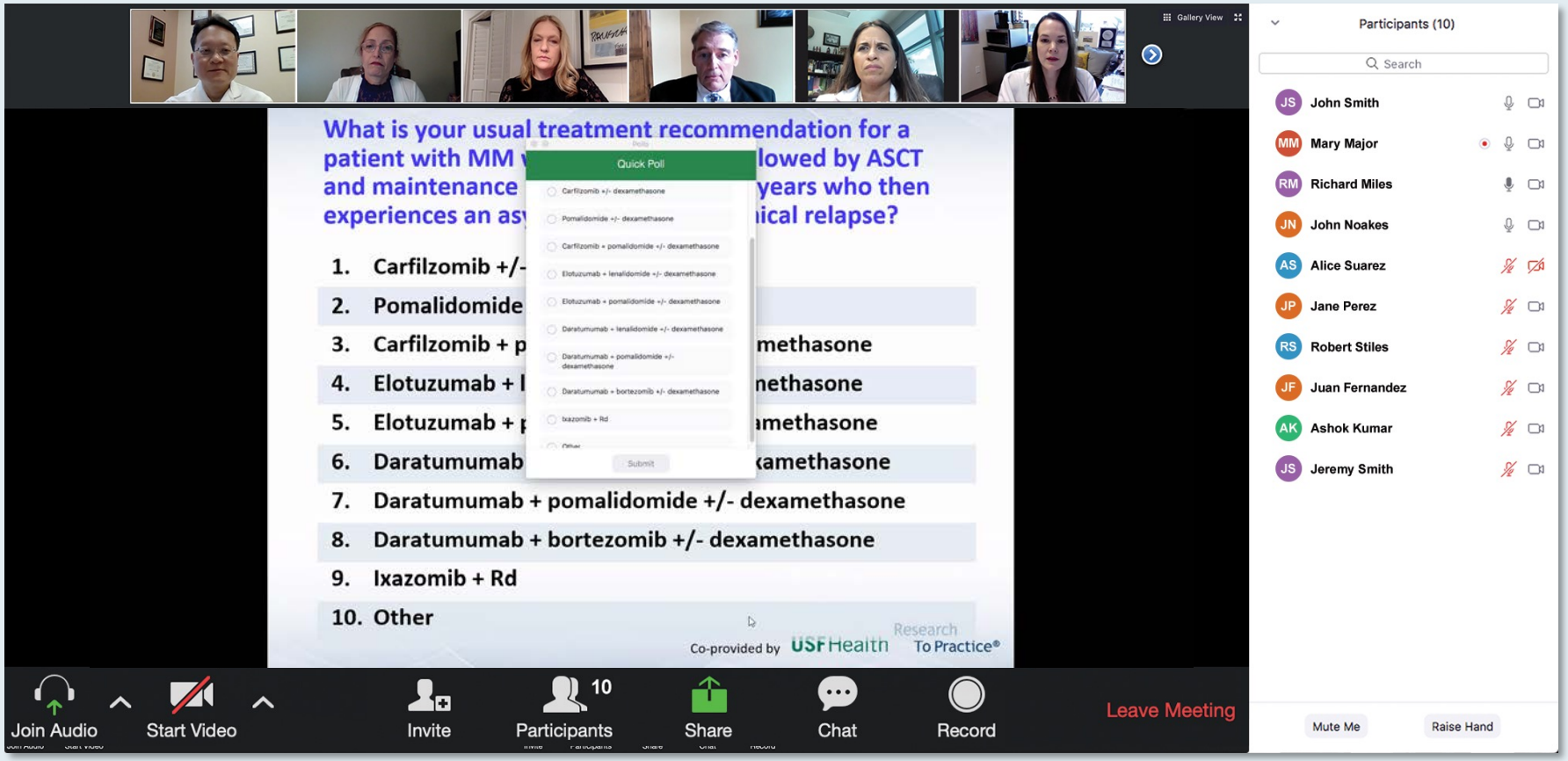

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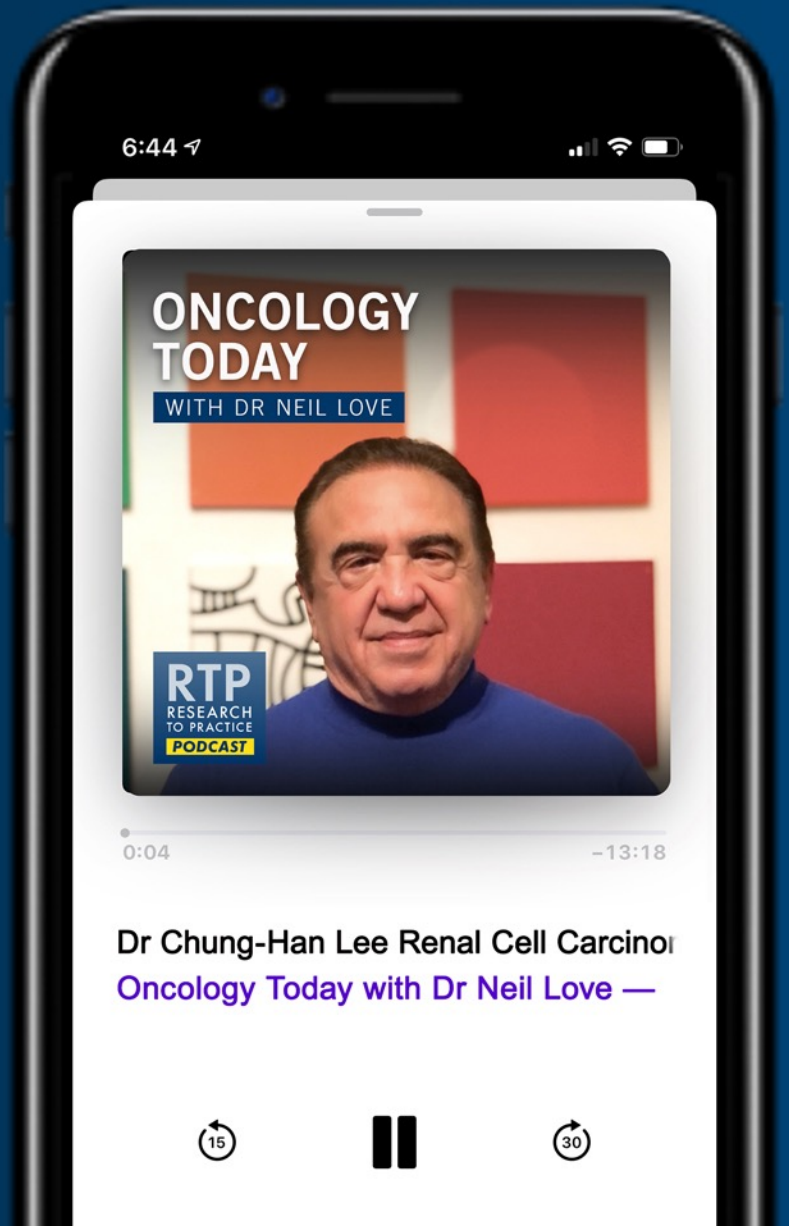

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Co-Director, Cardio-Oncology program
LVPG Hematology Oncology Associates
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Thomas Powles, MBBS, MRCP, MD
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Barts Cancer Institute
Director of Barts Cancer Centre
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London, United Kingdom

Laurie Matt-Amaral, MD, MPH
Attending Physician
Cleveland Clinic Akron General Medical Center
Akron, Ohio

Kelly Yap, MD
Assistant Clinical Professor
City of Hope
Arcadia, California

Meet The Professor with Dr McDermott

MODULE 1: Case Presentations

- Dr Gupta: A 70-year-old woman with metastatic clear cell RCC (ccRCC) and a severe psychiatric history
- Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features
- Dr Yap: A 60-year-old man with metastatic ccRCC
- Dr Powles: A 72-year-old man and former heavy smoker with metastatic ccRCC
- Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC
- Dr Powles: A 66-year-old man with metastatic papillary RCC

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr McDermott

MODULE 4: Key Data Sets

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

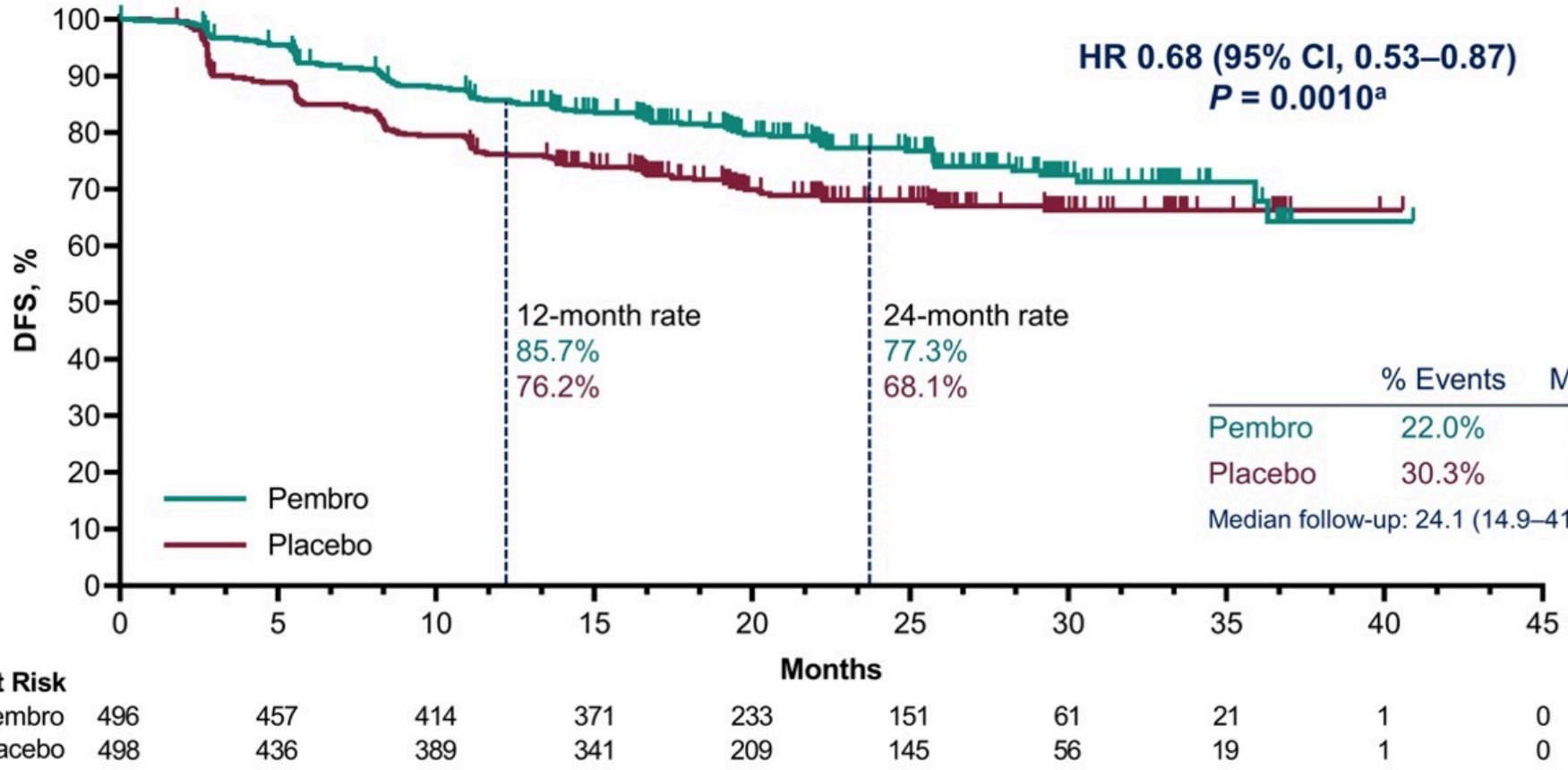
Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Yen-Hwa Chang[6]; Jaroslav Hajek[7]; Stefan Symeonides[8]; Jae Lyun Lee[9]; Naveed Sarwar[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Mahave[13]; Naomi Haas[14]; Piotr Sawrycki[15]; 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**

Choueiri TK et al. ASCO 2021;Abstract LBA5.

DFS by Investigator, ITT Population



	% Events	Median (95% CI)
Pembro	22.0%	NR (NR–NR)
Placebo	30.3%	NR (NR–NR)

Median follow-up: 24.1 (14.9–41.5) months.

No. at Risk

Pembro	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

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

Choueiri TK et al. ASCO 2021;Abstract LBA5.

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Case Presentation – Dr Gupta: A 70-year-old woman with metastatic clear-cell RCC (ccRCC) and a severe psychiatric history

Dr Ranju Gupta

- Diagnosed with poor-risk ccRCC with metastases to the bone and lungs
- ECOG PS 2-3, poor nutritional status, severe psychiatric issues
- Pembrolizumab/axitinib
  - Due to low body weight, initiated axitinib at 2 mg and then increased to 3 mg
- No autoimmune toxicities to date

Questions

- How do you select between an immunotherapy/TKI regimen and nivolumab/ipilimumab as first-line therapy for patients with ccRCC? How do you sequence these 2 regimens?

Case Presentation – Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features

Dr Laurie Matt-Amaral

- Presented to the ER with hematuria and pain, initial work-up revealed large 10-cm mass in the left kidney
- Nephrectomy → ccRCC with sarcamatoid features, grade 4, stage T3a
- Developed coughing and shortness of breath
- CT scan showed lung nodules

Case Presentation – Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features (continued)

Dr Laurie Matt-Amaral

- Presented to the ER with hematuria and pain, initial work-up revealed large mass in the left kidney
- Nephrectomy → ccRCC with sarcamatoid features, grade 4, stage T3a
- Developed coughing and shortness of breath – lung nodules detected
- ***Pembrolizumab/axitinib x 24 cycles***
  - ***Severe joint pain after first cycle that was relieved by steroids***
- ***Stable disease, but recently a small increase in chest lymphadenopathy has been detected***

Question

- ***Do you feel it would be reasonable to administer radiation therapy to target the lung nodules?***

Case Presentation – Dr Yap: A 60-year-old man with metastatic ccRCC

Dr Kelly Yap

- Presented with significant weight loss and some flank pain
- Diagnosed with Stage IV ccRCC with thoracic metastases
- Cytoreductive nephrectomy
- Ipilimumab/nivolumab x 4 cycles
  - Developed pneumonitis managed with high-dose steroids
  - Around this time, he experienced disease progression
- Lenvatinib/everolimus → PD → currently on axitinib

Questions

- What is the role of cytoreductive nephrectomy in the era of immunotherapy and VEGF TKIs?
- How would you approach this case if the patient had an absolute contraindication to immunotherapy?

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Case Presentation – Dr Powles: A 72-year-old man and former heavy smoker with metastatic ccRCC

Dr Thomas Powles

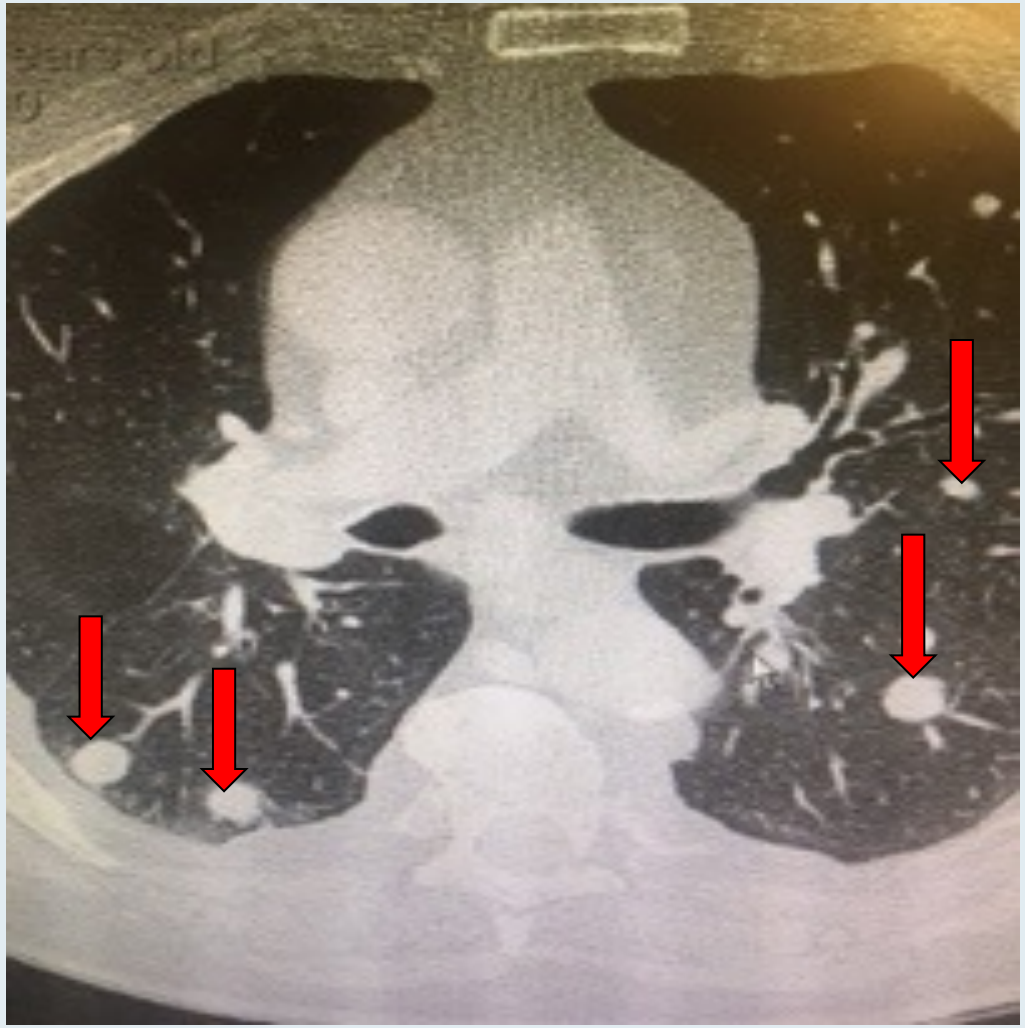
- PMH: history of heavy smoking, osteoarthritis and well-controlled hypertension
- Diagnosed initially with Grade 2, Stage T2 ccRCC → nephrectomy
- New lung metastases detected in both lungs 18 months later
- Observed for 3 months → 2 mm increase in size of lesions
- Anxious to start therapy
- Pembrolizumab/axitinib x 1 year → CR
- Experienced Grade 2-3 diarrhea with axitinib 5 mg

Question

- How long would you continue treatment with immunotherapy in a patient who has achieved a CR?

Case Presentation – Dr Powles: A 72-year-old man and former heavy smoker with metastatic ccRCC (continued)

Dr Thomas Powles



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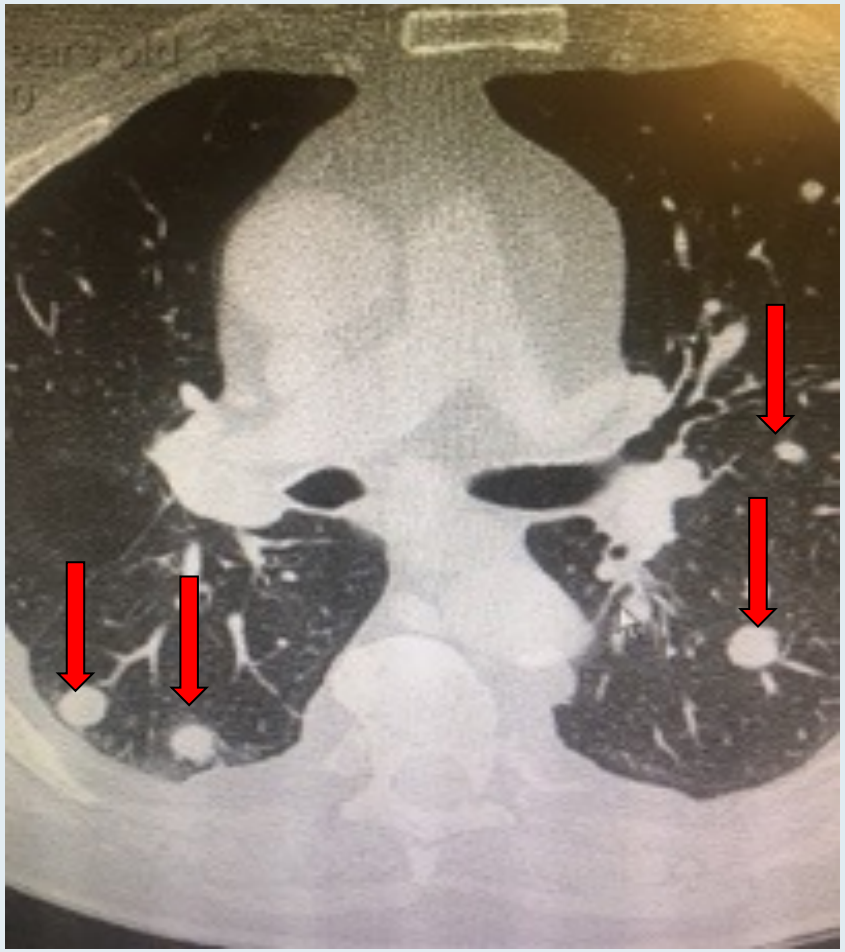

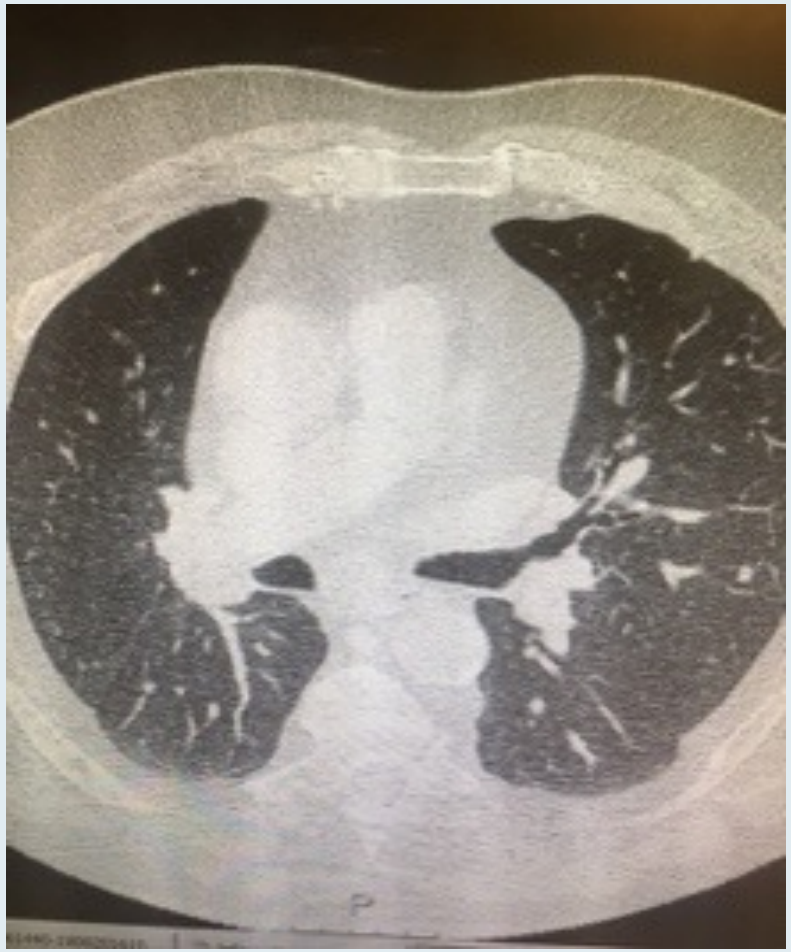

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Case Presentation – Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC

Dr Thomas Powles

- PMH: irritable bowel disease, mild psoriasis in the past
- Diagnosed with Grade 3, T2N0M1 ccRCC (biopsy proven), intermediate risk, with metastases to liver, bone and lungs
- Recently underwent childbirth – psoriasis worsened during pregnancy and controlled with medication

Questions

- What treatment would you recommend for this patient?
- How safe is it to administer immunotherapy to this patient with her history of psoriasis?
- How would you distinguish between irritable bowel disease and colitis?

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Case Presentation – Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC (continued)

Dr Thomas Powles

- PMH: irritable bowel disease, mild psoriasis in the past
- Diagnosed with Grade 3, T2N0M1 ccRCC (biopsy proven), intermediate-risk, with metastases to liver, bone and lungs
- Recently had children – psoriasis worsened during pregnancy and controlled with medication
- ***Ipilimumab/nivolumab initiated***
- ***Grade 3 transaminitis, adrenal insufficiency and grade 2 rash at week 6 → steroids x 3 weeks***
- ***Resumed ipilimumab/nivolumab → Grade 2 transaminitis reoccurred → continued with nivolumab single agent***
- ***Stable disease with nivolumab for 6 months; disease progression in bone***
- ***Axitinib initiated***

Question

- ***Would you have re-challenged with ipilimumab/nivolumab or continued only the nivolumab as a single agent?***

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

Dr 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?

Meet The Professor with Dr McDermott

MODULE 1: Case Presentations

- Dr Gupta: A 70-year-old woman with metastatic clear cell RCC (ccRCC) and a severe psychiatric history
- Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features
- Dr Yap: A 60-year-old man with metastatic ccRCC
- Dr Powles: A 72-year-old man and former heavy smoker with metastatic ccRCC
- Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC
- Dr Powles: A 66-year-old man with metastatic papillary RCC

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr McDermott

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 (R/R) 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 McDermott

MODULE 1: Case Presentations

- Dr Gupta: A 70-year-old woman with metastatic clear cell RCC (ccRCC) and a severe psychiatric history
- Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features
- Dr Yap: A 60-year-old man with metastatic ccRCC
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- Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC
- Dr Powles: A 66-year-old man with metastatic papillary RCC

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr McDermott

MODULE 4: Key Data Sets

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TO PRACTICE

Journal Club with Dr McDermott

- Safety and efficacy of immunotherapy rechallenge in RCC
- PROSPER RCC: Phase III study of perioperative nivolumab versus observation in patients with renal cell carcinoma (RCC) undergoing nephrectomy
- HCRN GU16-260 Cohort B: Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients with advanced non-clear cell RCC
- Integrative molecular characterization of sarcomatoid and rhabdoid RCC
- Salvage ipilimumab and nivolumab in metastatic RCC after prior immune checkpoint inhibitors
- Cabozantinib/nivolumab/ipilimumab for advanced RCC with variant histology
- OMNIVORE: Optimized management of nivolumab and ipilimumab in advanced RCC

Journal Club with Dr McDermott (continued)

- Oral HIF2α inhibitor MK-6482 in advanced clear cell RCC
- Phase II study of MK-6482 in combination with cabozantinib in advanced clear cell RCC
- Inhibition of hypoxia-inducible factor 2α in RCC with belzutifan
- TIVO-3: Temporal characteristics of treatment-emergent adverse events and dose modifications with tivozanib and sorafenib in relapsed or refractory mRCC
- Nivolumab plus ipilimumab versus sunitinib as first-line treatment in sarcomatoid RCC
- Progressive immune dysfunction with advancing disease stage in RCC

Research

JAMA Oncology | Brief Report

Evaluation of the Safety and Efficacy of Immunotherapy Rechallenge in Patients With Renal Cell Carcinoma

Praful Ravi, MBBChir; Charlene Mantia, MD; Christopher Su, MD; Karl Sorenson, MD; Dean Elhag, MD; Nityam Rathi, BS; Ziad Bakouny, MD; Neeraj Agarwal, MD; Yousef Zakharia, MD; Brian A. Costello, MD; Rana R. McKay, MD; Vivek Narayan, MD; Ajjai Alva, MBBS; Bradley A. McGregor, MD; Xin Gao, MD; David F. McDermott, MD; Toni K. Choueiri, MD

JAMA Oncol 2020;6(10):1606-10.

ASCO 2021;Abstract TPS4596

ECOG-ACRIN cancer research group
Reshaping the future of patient care

A Phase III RandOmized Study Comparing PERioperative Nivolumab vs. Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)

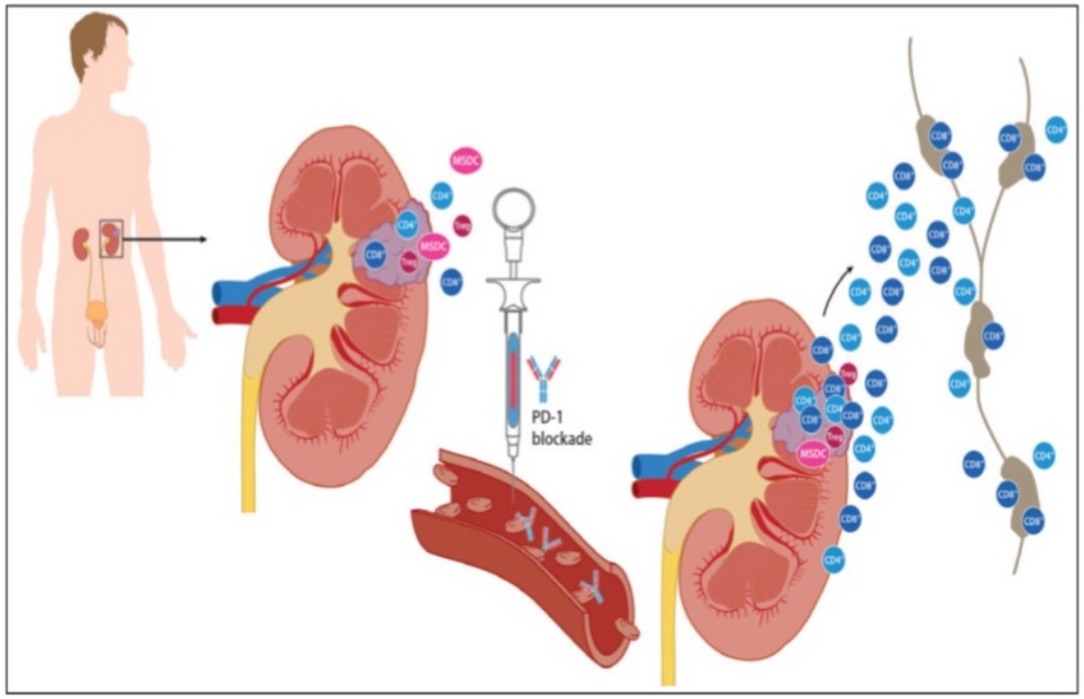
Allaf M, Kim SE, Master V, McDermott DF, Drake CJ, Signoretti S, Cella D, Gupta RT, Cole S, Shuch BM, Lara P,
Kapoor A, Heng DYC, Leibovich BC, Michaelson M D, Choueiri TK, Jewett MA , Maskens DA, Harshman LC, Carducci MA, Haas NB On Behalf of the PROSPER RCC Investigators.

NCI National Clinical Trials Network
a National Cancer Institute program

Bristol-Myers Squibb

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Rationale for Priming with PD-1 Blockade



Harshman…Allaf et al Kidney Cancer 2017

- There is an ongoing but unsuccessful anti-tumor T cell response in the primary tumor, tumor microenvironment, and tumor draining lymph nodes. **(Figure 1)**
- Post-PD-1 blockade, anti-tumor CD8 T cells may preferentially expand in these areas and traffic to distant sites and eradicate micrometastases. (Woo Cancer Res 2012)
- Nephrectomy removes the majority of these effector cells and cytokines, which could result in a less potent immune response.

Allaf ME et al. ASCO 2021;Abstract TPS4506.

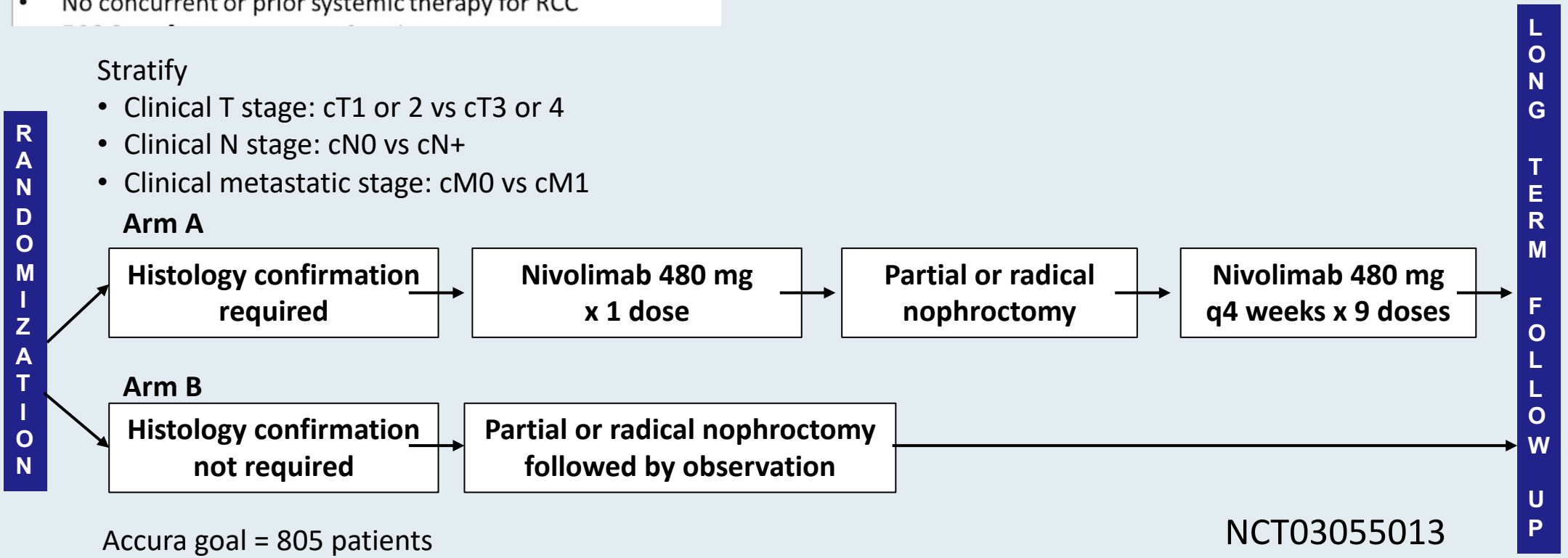
PROSPER RCC: Revised Phase III Trial Schema

Current Key Eligibility Criteria:

- Clinical T2 or any node positive RCC
- M0 or oligometastatic disease that can be rendered NED
- Clear cell or non-clear cell histology including sarcomatoid
- Planned for nephrectomy
- No concurrent or prior systemic therapy for RCC

Stratify

- Clinical T stage: cT1 or 2 vs cT3 or 4
- Clinical N stage: cN0 vs cN+
- Clinical metastatic stage: cM0 vs cM1



NCT03055013

Accura goal = 805 patients
Cycle length = 28 days

Allaf ME et al. ASCO 2021;Abstract TPS4506.

ASCO 2021;Abstract 4510

Phase II Study of Nivolumab and Salvage Nivolumab + Ipilimumab in Treatment-Naïve Patients with Advanced Non-Clear Cell Renal Cell Carcinoma (ncc-RCC) (HCRN GU16-260-Cohort B)- Poster 4510

Michael B. Atkins[1], Opeyemi A. Jegede[2], Naomi B. Haas[3], David F. McDermott[4], Mehmet A. Bilen[5],Jessica E Hawley, Jeffrey A. Sosman[7], Robert Alter[8], Elizabeth R. Plimack[9], Moshe Ornstein[10], Michael Hurwitz[11], David Peace[12], Sabina Signoretti[13], Catherine J. Wu[2], Paul J. Catalano[2], Hans Hammers[14]

[1]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; [2]Dana Farber Cancer Institute, Boston, MA; [3]University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Winship Cancer Institute of Emory University, Atlanta GA; [6]Columbia Herbert Irving Comprehensive Cancer Center, New York, NY; [7]Northwestern Lurie Comprehensive Cancer Center, Chicago, IL; [8]John Theurer Cancer Center, Hackensack, NJ; [9]Fox Chase Cancer Center, Philadelphia, PA; [10]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [11]Yale-Smilow Comprehensive Cancer Center, New Haven, CT; [12]University of Illinois Chicago, Chicago, IL; [13]Brigham and Women's Hospital Boston, MA, [14]University of Texas Southwestern Sammons Cancer Center, Dallas, TX.

Presented By: Michael B. Atkins

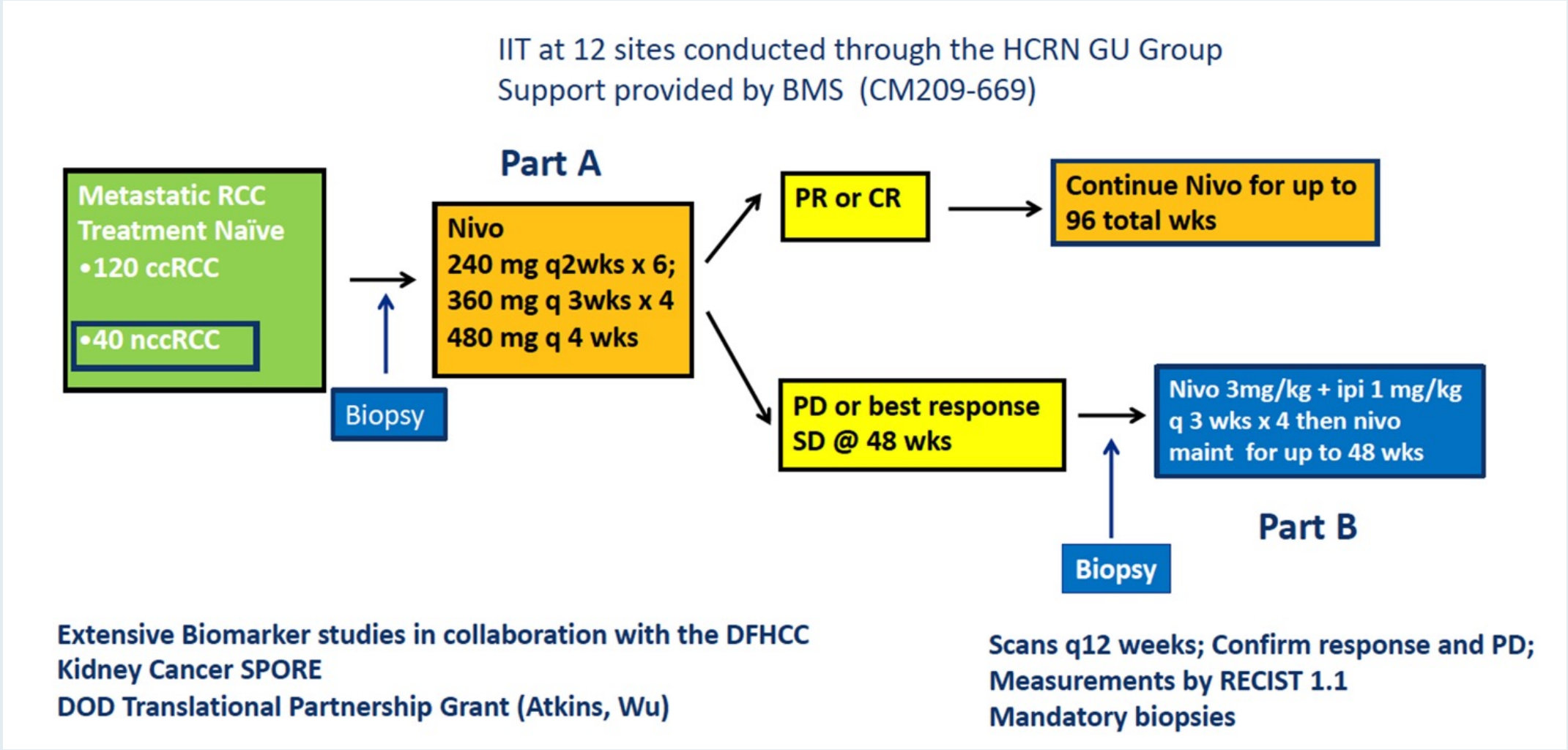
2021 ASCO ANNUAL MEETING

HCRN GU16-260-Cohort B: Background

- **Nivolumab monotherapy (nivo) is approved for VEGFR TKI resistant ccRCC based on the CM 025 Study.**
- **Combination nivolumab + ipilimumab (Nivo/ipi) is approved for treatment-naïve IMDC intermediate and poor risk ccRCC based on the CM 214 Study.**
- **HCRN GU16-260 Cohort A explored the efficacy and toxicity of Nivo monotherapy with Nivo/ipi boost in pts with ccRCC (Atkins at al JCO 2020.38.15_suppl.5006)**
- **Little information was available on the efficacy and toxicity of:**
  - Nivo monotherapy in patients with treatment naïve nccRCC
  - Nivo/ipi salvage in patients with nccRCC without response to Nivo monotherapy

Atkins MB et al. ASCO 2021;Abstract 4510.

HCRN GU16-260-Cohort B: Trial Schema



Atkins MB et al. ASCO 2021;Abstract 4510.

HCRN GU16-260-Cohort B: Results Part B

Enrollment: 13/30 (43%) pts with PD/SD x 1 yr in Part A did not enroll due to irAE /SAE (3), symptomatic PD (6) and other (4)

Efficacy: ORR 1/17 (6%): 1 PR in pt with unclassified/non-sarcomatoid RCC, PD-L1 (1-5%); Median PFS 2.8 mos (2.7-NA)

Toxicity: Grade $\geq$ 3 Treatment Related AES: 7/17 = 41%
Skin (1) Hepatic (1), GI (1), Pulm (1), Endocrine (1), Thrombosis (1)
Sudden Death (1)

Atkins MB et al. ASCO 2021;Abstract 4510.

nature COMMUNICATIONS

Nat Commun 2021;12(1):808

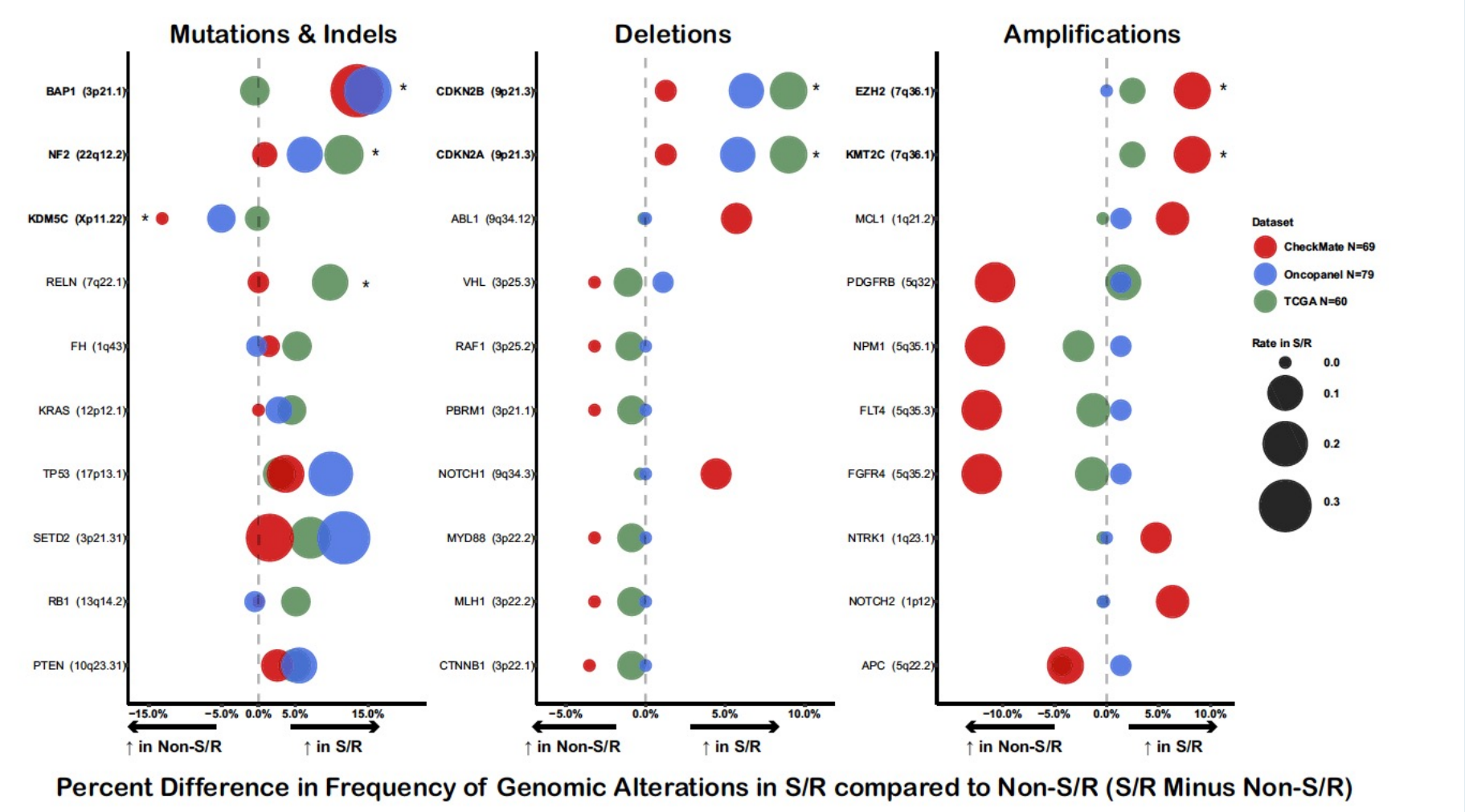
ARTICLE

https://doi.org/10.1038/s41467-021-21068-9 OPEN

Integrative molecular characterization of sarcomatoid and rhabdoid renal cell carcinoma

Ziad Bakouny[1], David A. Braun[1], Sachet A. Shukla[2], Wenting Pan[1], Xin Gao[3], Yue Hou[2], Abdallah Flaifel[4], Stephen Tang[1], Alice Bosma-Moody[1], Meng Xiao He[1], Natalie Vokes[1], Jackson Nyman[1], Wanling Xie[5], Amin H. Nassar[1], Sarah Abou Alaiwi[1], Ronan Flippot[1], Gabrielle Bouchard[1], John A. Steinharter[1], Pier Vitale Nuzzo[1], Miriam Ficial[4], Miriam Sant'Angelo[4], Juliet Forman[1,2,6], Jacob E. Berchuck[1], Shaan Dudani[7], Kevin Bi[1], Jihye Park[1], Sabrina Camp[1], Maura Sticco-Ivins[4], Laure Hirsch[1], Sylvan C. Baca[1], Megan Wind-Rotolo[8], Petra Ross-Macdonald[8], Maxine Sun[1], Gwo-Shu Mary Lee[1], Steven L. Chang[1], Xiao X. Wei[1], Bradley A. McGregor[1], Lauren C. Harshman[1], Giannicola Genovese[9], Leigh Ellis[4,10], Mark Pomerantz[1], Michelle S. Hirsch[4], Matthew L. Freedman[1], Michael B. Atkins[11], Catherine J. Wu[1,6], Thai H. Ho[12], W. Marston Linehan[13], David F. McDermott[14], Daniel Y. C. Heng[7], Srinivas R. Viswanathan[1], Sabina Signoretti[4,10], Eliezer M. Van Allen[1,15]✉ & Toni K. Choueiri[1,15]✉

Comparision of Mutation Frequencies in Sarcomatoid/Rhabdoid (S/R) RCC versus Non-S/R RCC



Bakouny Z et al. *Nat Commun* 2021;12(1):808.

rapid communications

Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

Anita Gul, MD[1]; Tyler F. Stewart, MD[2,3]; Charlene M. Mantia, MD[4]; Neil J. Shah, MD[5]; Emily Stern Gatof, MD[4]; Ying Long, PharmD[2]; Kimberly D. Allman, MSN, CNP[1]; Moshe C. Ornstein, MD, MA[1]; Hans J. Hammers, MD, PhD[6]; David F. McDermott, MD[4]; Michael B. Atkins, MD[5]; Michael Hurwitz, MD, PhD[2]; and Brian I. Rini, MD[1]

J Clin Oncol 2020;38(27):3088-94.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Cabozantinib (C) in Combination with Nivolumab (N) and Ipilimumab (I) (CaNI) for Advanced Renal Cell Carcinoma with Variant Histology (aRCCVH)

McGregor BA et al.

ASCO 2021;Abstract TPS4592.

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.

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

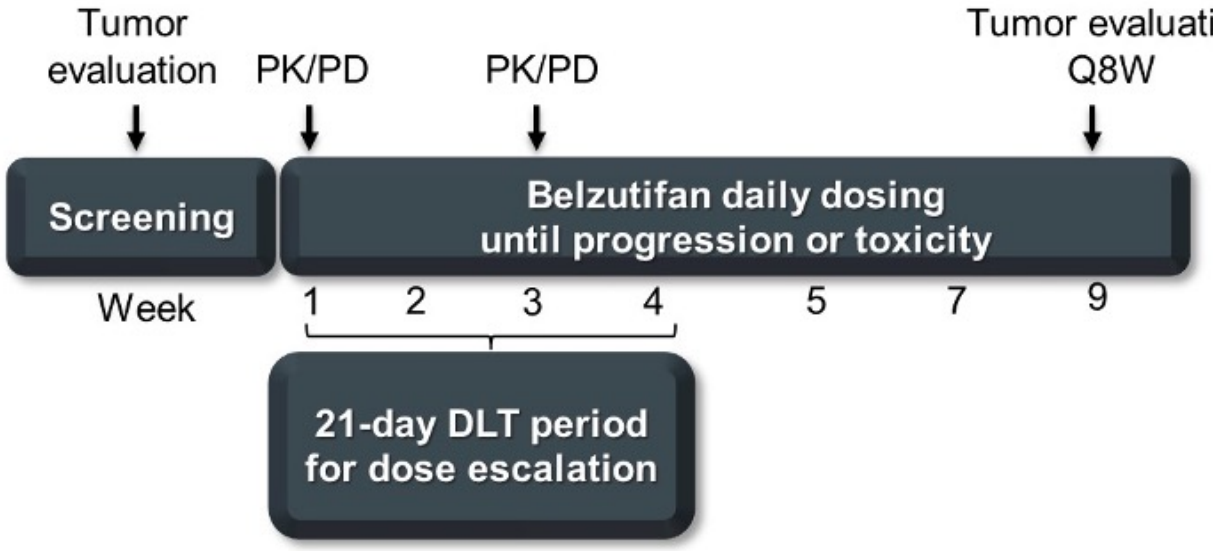
Todd Michael Bauer,[1] Toni K. Choueiri,[2] Kyriakos P. Papadopoulos,[3] Elizabeth R. Plimack,[4] Jaime R. Merchan,[5] David F. McDermott,[6] M. Dror Michaelson,[7] Leonard Joseph Appleman,[8] Sanjay Thamake,[9] Rodolfo F. Perini,[9] Eric Kristopher Park,[9] Eric Jonasch[10]

[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

2021 Genitourinary Cancers Symposium;Abstract 273.

Presented By Todd Bauer at 2021 Genitourinary Cancers Symposium

Phase I/II Study Design



- Dose-escalation cohort for patients with advanced solid tumors
- Dose-expansion cohort for patients with advanced ccRCC who previously received ≥1 therapy
  - Key end points: Safety, objective response rate, duration of response

- Dose of 120 mg once daily selected for further clinical development from the dose-escalation cohort
- **55 patients with previously treated advanced ccRCC enrolled at 120 mg orally once daily in the dose-expansion cohort**
  - 44 (80%) discontinued
    - Most common reason was disease progression: 60%
  - 11 (20%) have treatment ongoing
- Median (range) follow-up:
  - 27.7 (24.8-34.3) months

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

Best Confirmed Objective Response by RECIST v1.1 per Investigator Assessment (Dose-Escalation Cohorts)

Efficacy Parameter, n (%) [95%CI]	20 mg QD N = 6	40 mg QD N = 6	80 mg QD N = 6	120 mg QD N = 6	160 mg QD N = 6	240 mg QD N = 7	120 mg BID N = 6
Objective Response Rate	0	0	0	1 (17) [0.4-64]	2 (33) [4-78]	2 (29) [4-71]	1 (17) [0.4-64]
Complete Response (CR)	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	1 (17)[a]	2 (33)[b]	2 (29)[a]	1 (17)[a]
Stable Disease (SD)	2 (33)	2 (33)	2 (33)	3 (50)	3 (50)	1 (14)	2 (33)
Disease Control Rate (CR + PR + SD)	2 (33) [4-78]	2 (33) [4-78]	2 (33) [4-78]	4 (67) [22-96]	5 (83) [36-100]	3 (43) [10-82]	3 (50) [12-88]
Progressive Disease	3 (50)	2 (33)	3 (50)	2 (33)	1 (17)	2 (29)	3 (50)
Not Evaluable	1 (17)	2 (33)	1 (17)	0	0	2 (29)	0

[a]All responses in ccRCC; [b]Responses observed in ccRCC (n = 1) and anaplastic ependymoma (n=1). Data cutoff: June 1, 2020.

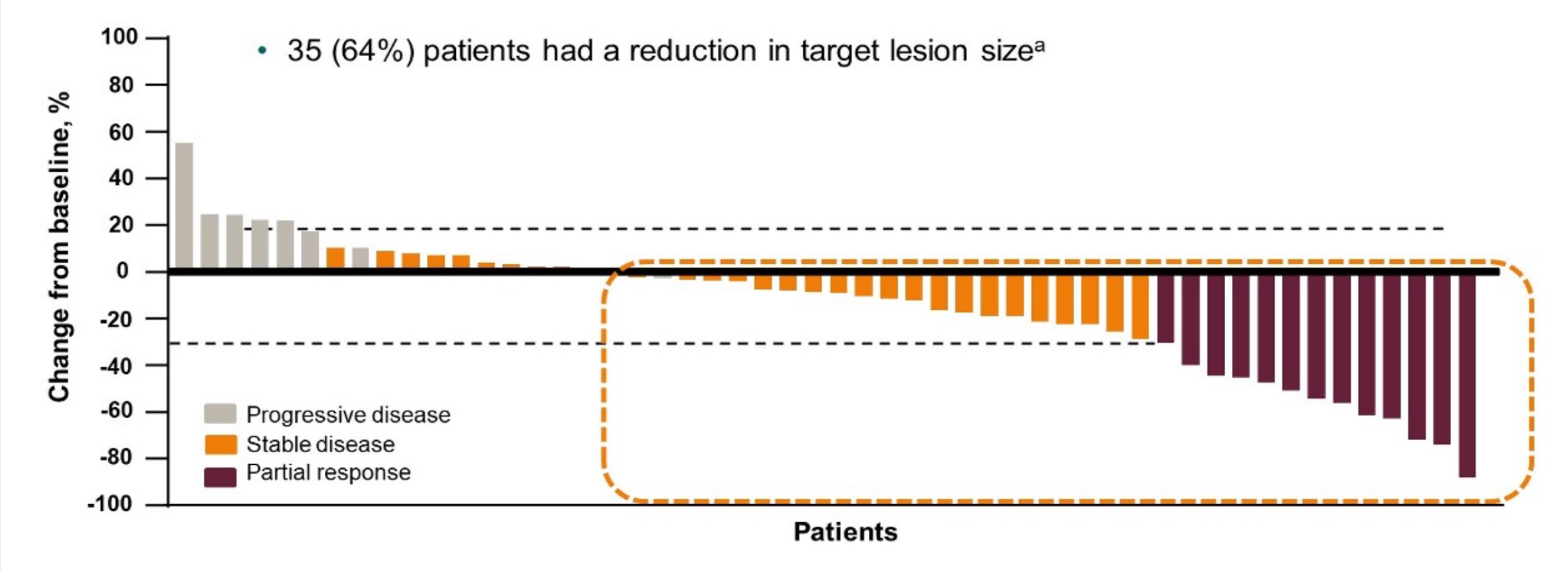
Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

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 (Investigator Assessment in the ccRCC Cohort)



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

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

2021 Genitourinary Cancers Symposium;Abstract 272.

Presented By Toni Choueiri at 2021 Genitourinary Cancers Symposium

LETTERS

Nat Med 2021;27(5):802-5.

https://doi.org/10.1038/s41591-021-01324-7

nature medicine

Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis

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

Temporal Characteristics of Treatment-Emergent Adverse Events and Dose Modifications with Tivozanib and Sorafenib in the Phase 3 TIVO-3 Study of Relapsed or Refractory mRCC

Pal SK et al.

ASCO 2021;Abstract 4567.

Clin Cancer Res 2021;27(1):78-86.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Efficacy and Safety of Nivolumab Plus Ipilimumab versus Sunitinib in First-line Treatment of Patients with Advanced Sarcomatoid Renal Cell Carcinoma

Nizar M. Tannir[1], Sabina Signoretti[2,3], Toni K. Choueiri[4], David F. McDermott[5], Robert J. Motzer[6], Abdallah Flaifel[2], Jean-Christophe Pignon[2], Miriam Ficial[2], Osvaldo Arén Frontera[7], Saby George[8], Thomas Powles[9], Frede Donskov[10], Michael R. Harrison[11], Philippe Barthélémy[12], Scott S. Tykodi[13], Judit Kocsis[14,15], Alain Ravaud[16], Jeronimo R. Rodriguez-Cid[17], Sumanta K. Pal[18], Andre M. Murad[19], Yuko Ishii[20], Shruti Shally Saggi[20], M. Brent McHenry[21], and Brian I. Rini[22]

Cancer Cell. 2021 May 10; 39(5): 632–648.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]

Meet The Professor with Dr McDermott

MODULE 1: Case Presentations

- Dr Gupta: A 70-year-old woman with metastatic clear cell RCC (ccRCC) and a severe psychiatric history
- Dr Matt-Amaral: A 49-year-old man with metastatic ccRCC with sarcomatoid features
- Dr Yap: A 60-year-old man with metastatic ccRCC
- Dr Powles: A 72-year-old man and former heavy smoker with metastatic ccRCC
- Dr Powles: A 32-year-old woman with metastatic intermediate-risk ccRCC
- Dr Powles: A 66-year-old man with metastatic papillary RCC

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr McDermott

MODULE 4: Key Data Sets

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]

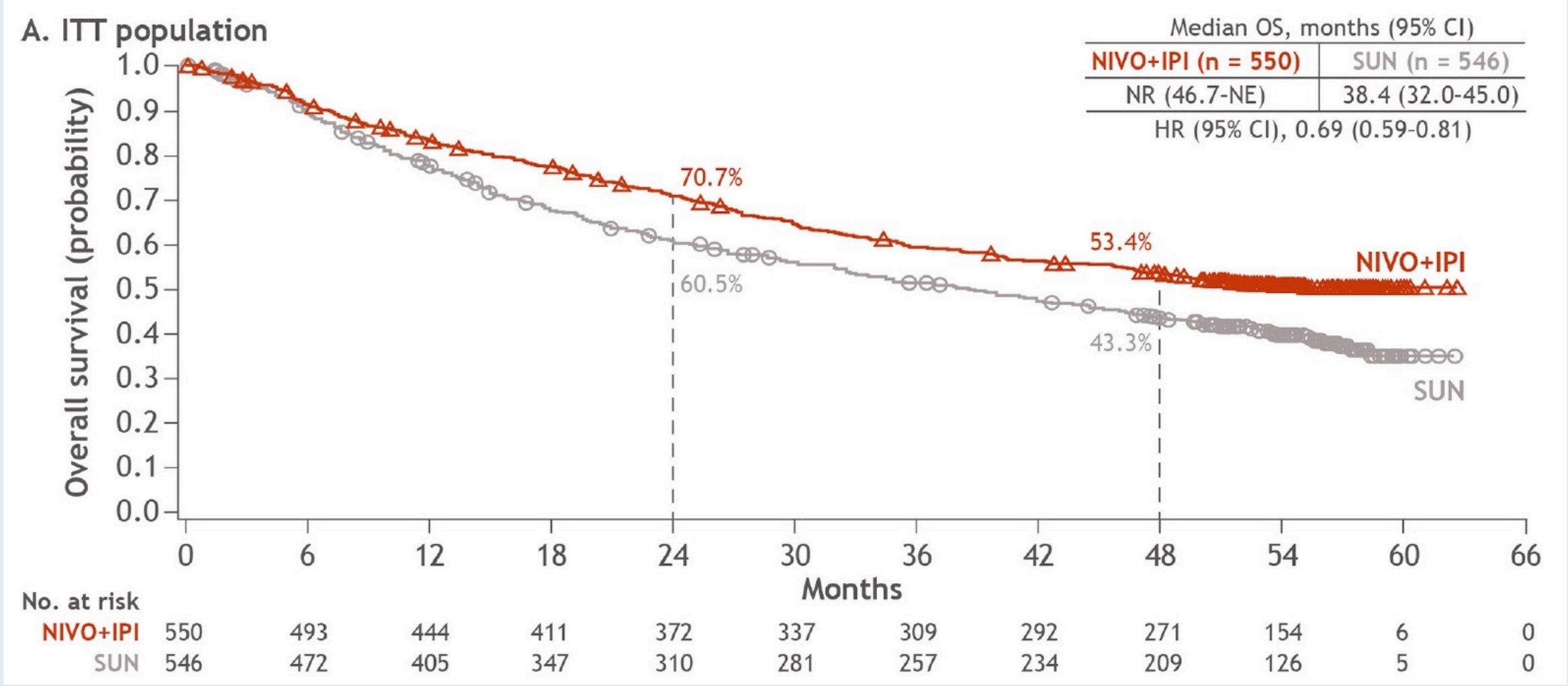
ESMO Open 2020;5(6):e001079.

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

	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%

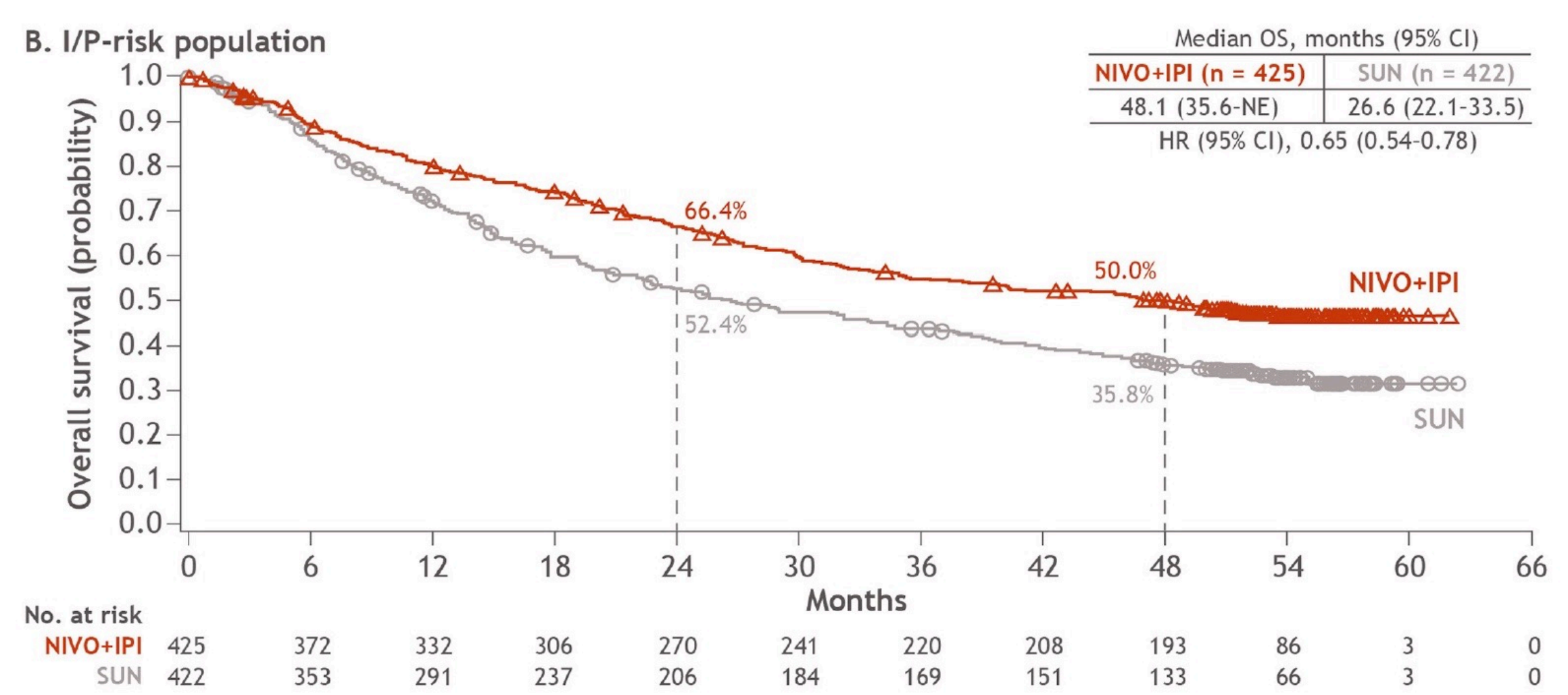
Albiges L et al. *ESMO Open* 2020;5(6):e001079.

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

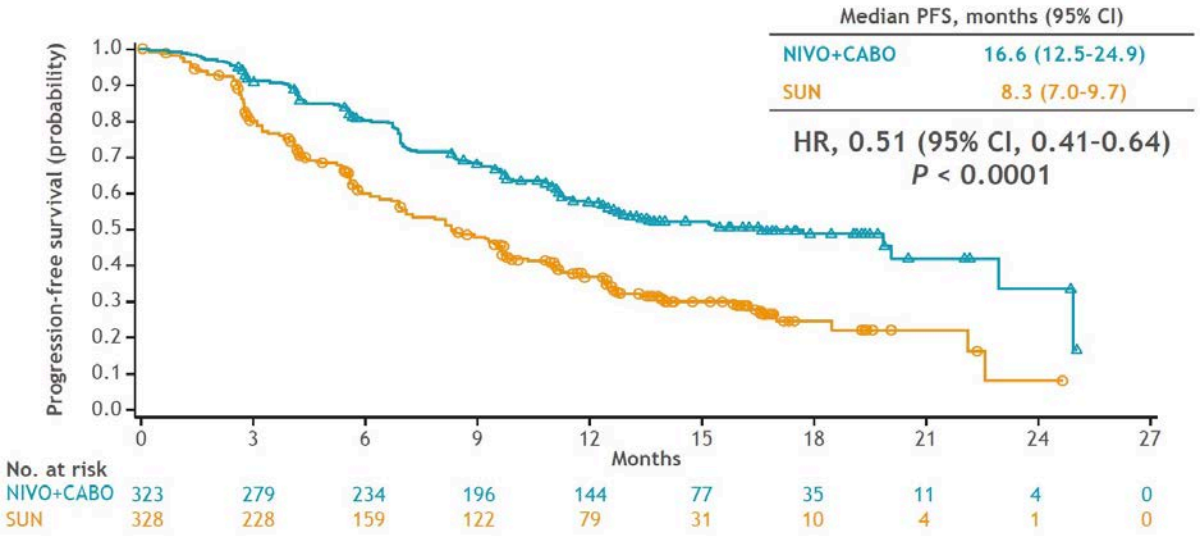
Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

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*

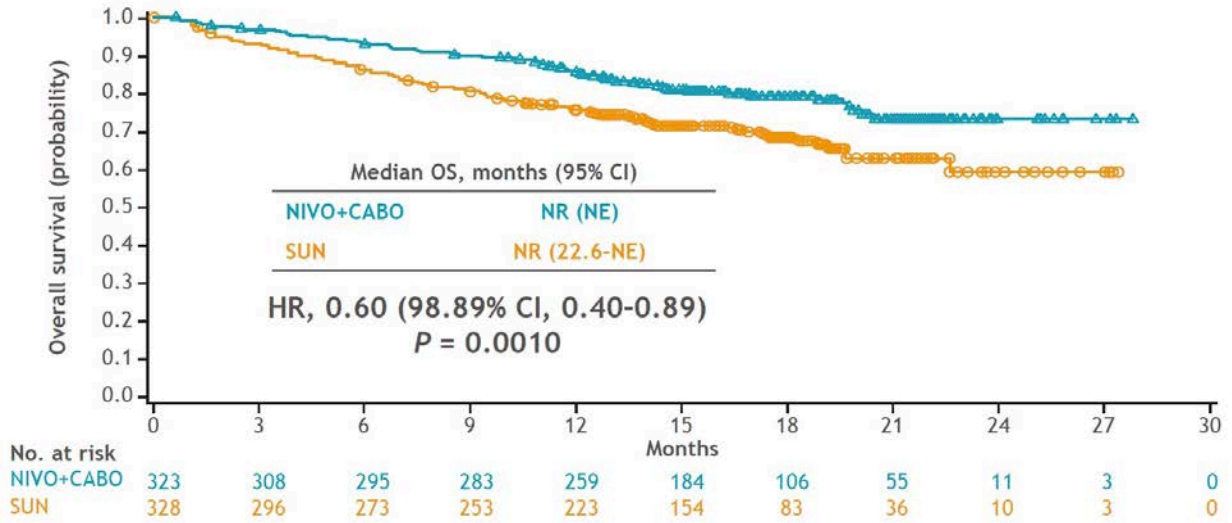
N Engl J Med 2021;384(9):829-41.

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:
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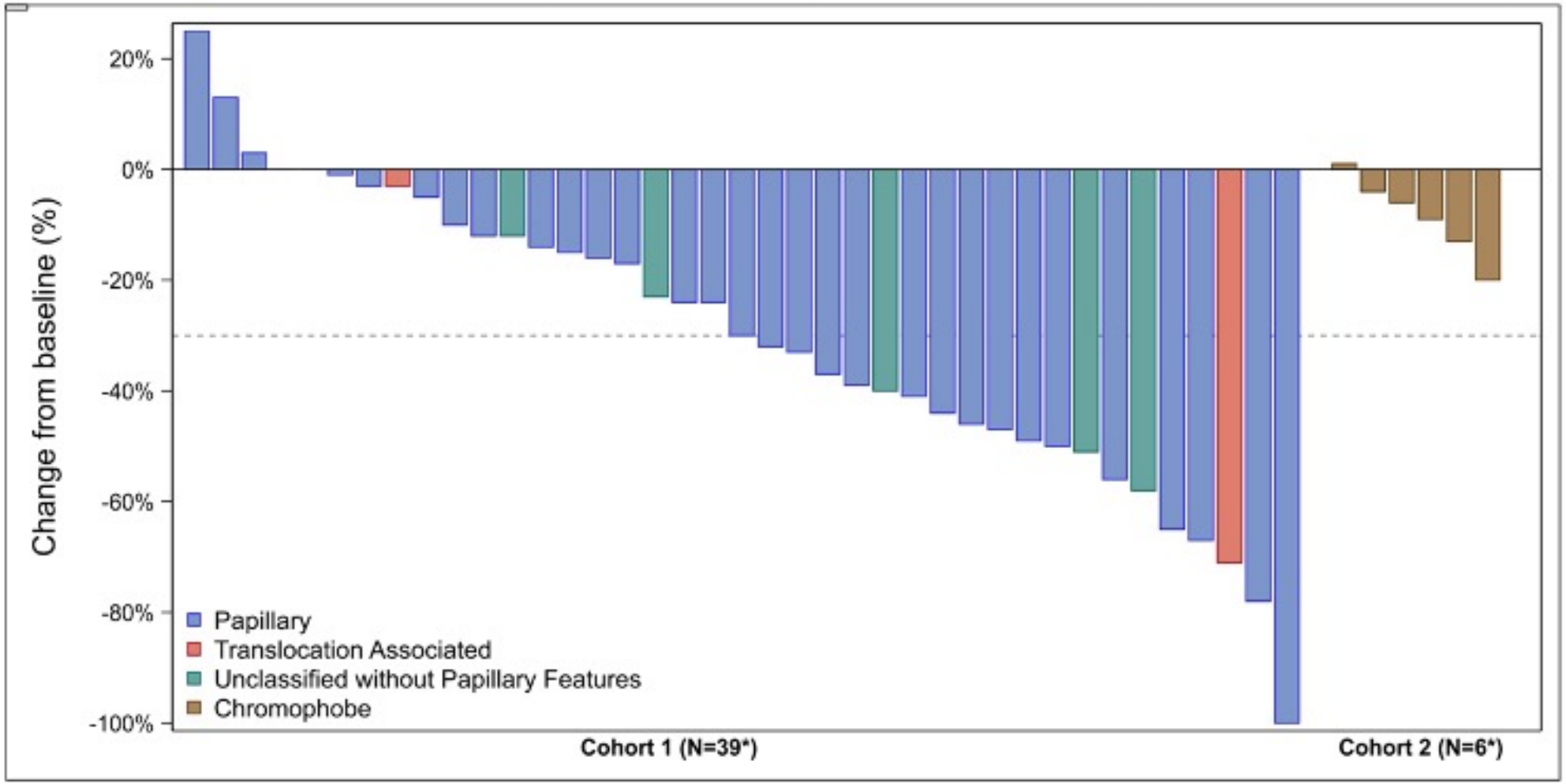
Lee CH et al. ASCO 2021;Abstract 4509.

RTP RESEARCH TO PRACTICE

Maximum Change in Target Lesions by Histology



Lee CH et al. ASCO 2021;Abstract 4509.

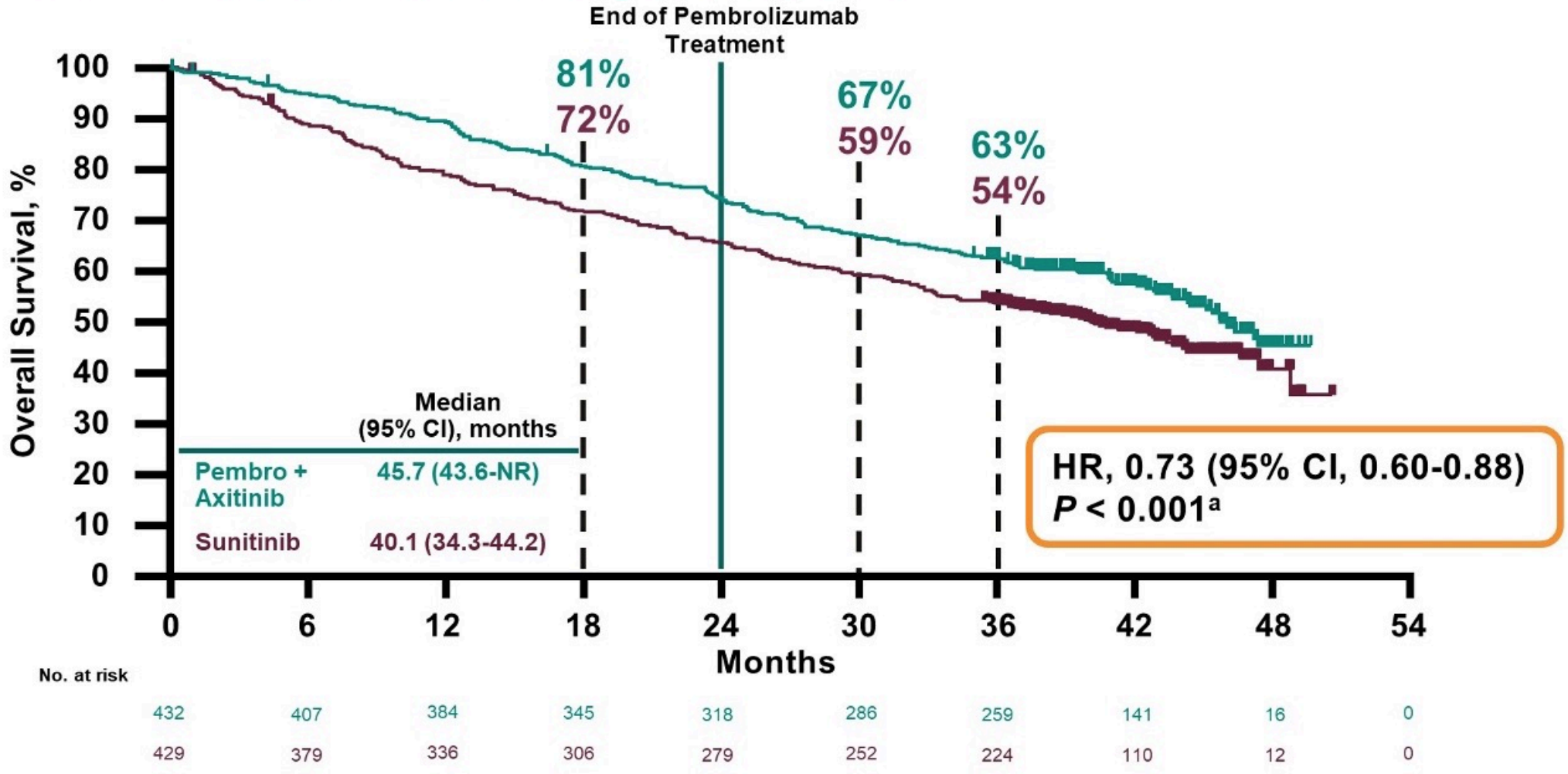
Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma: Results From 42-Month Follow-Up of KEYNOTE-426

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.

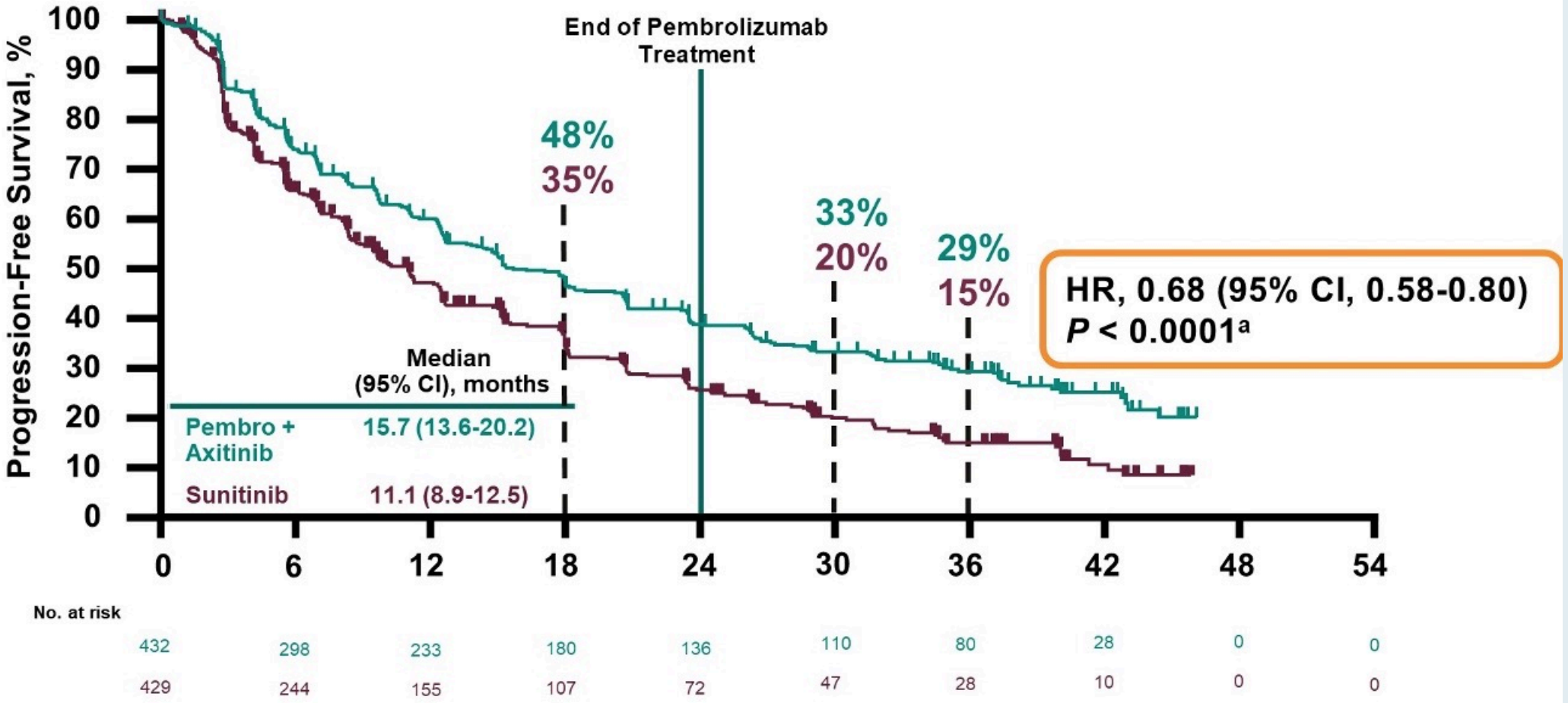
OS in the ITT Population



[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

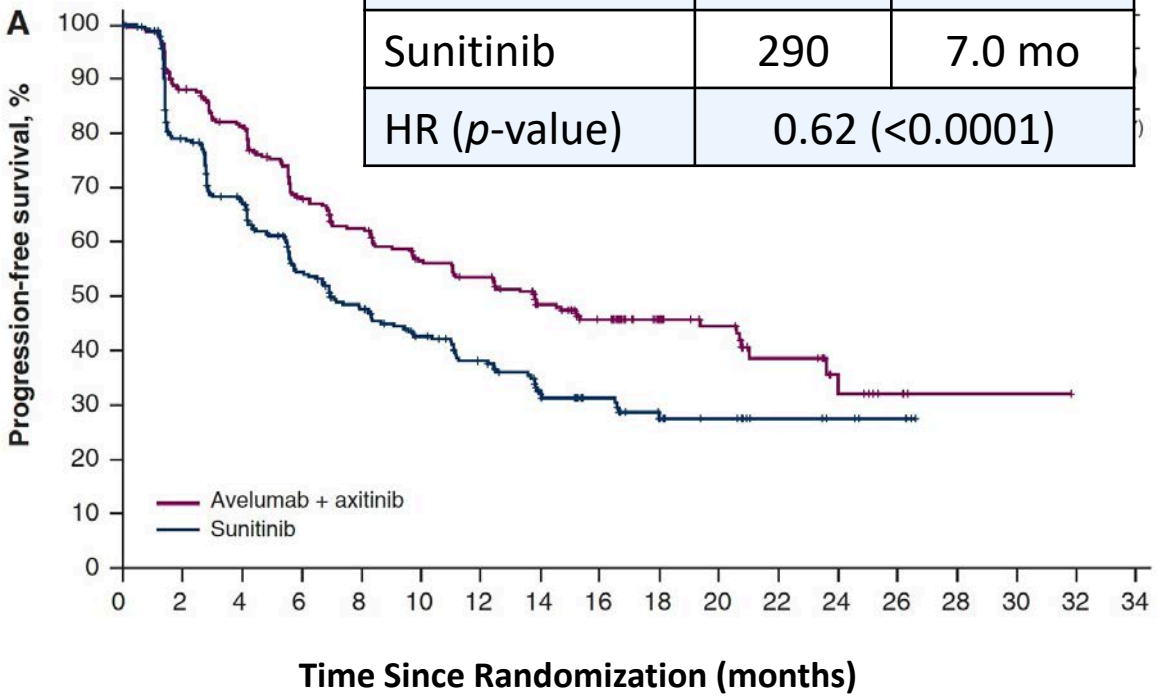
	PD-L1-positive		Overall	
	Avelumab + axitinib (n = 270)	Sunitinib (n = 290)	Avelumab + axitinib (n = 442)	Sunitinib (n = 444)
Confirmed ORR	55.9%	27.2%	52.5%	27.3%
CR	5.6%	2.4%	3.8%	2.0%
PR	50.4%	24.8%	48.6%	25.2%
Stable disease	27.0%	41.4%	28.3%	43.7%
Progressive disease	11.5%	22.4%	12.4%	19.4%
Ongoing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

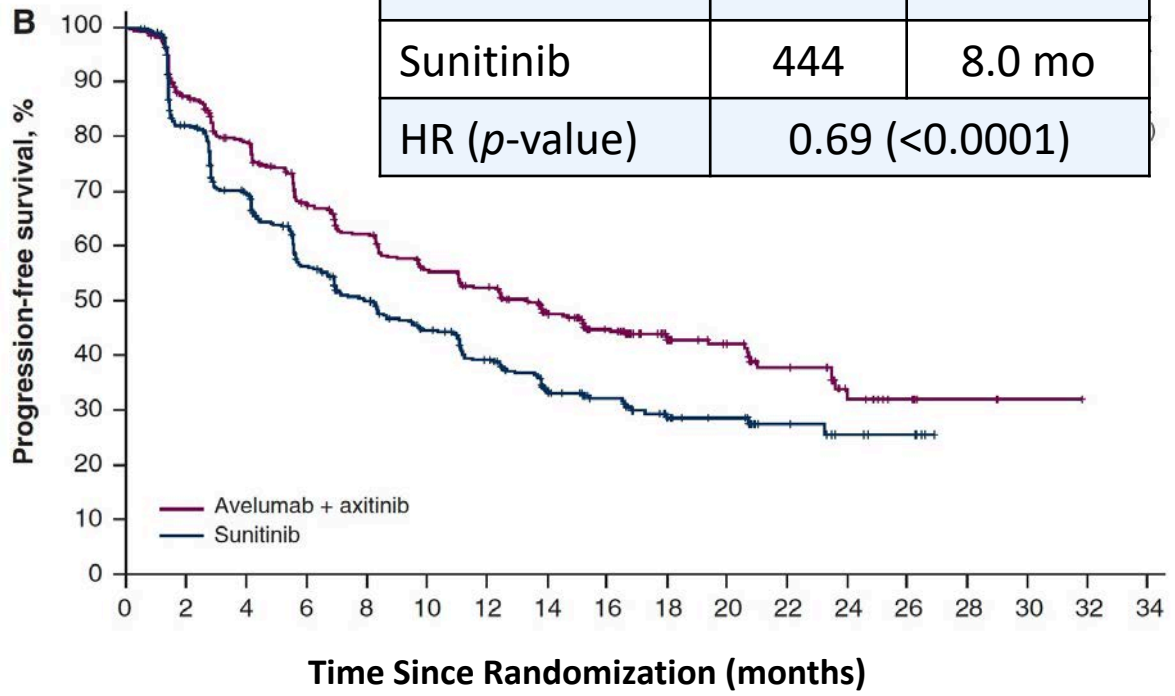
PD-L1 ≥ 1% Population

	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

The NEW ENGLAND JOURNAL of MEDICINE

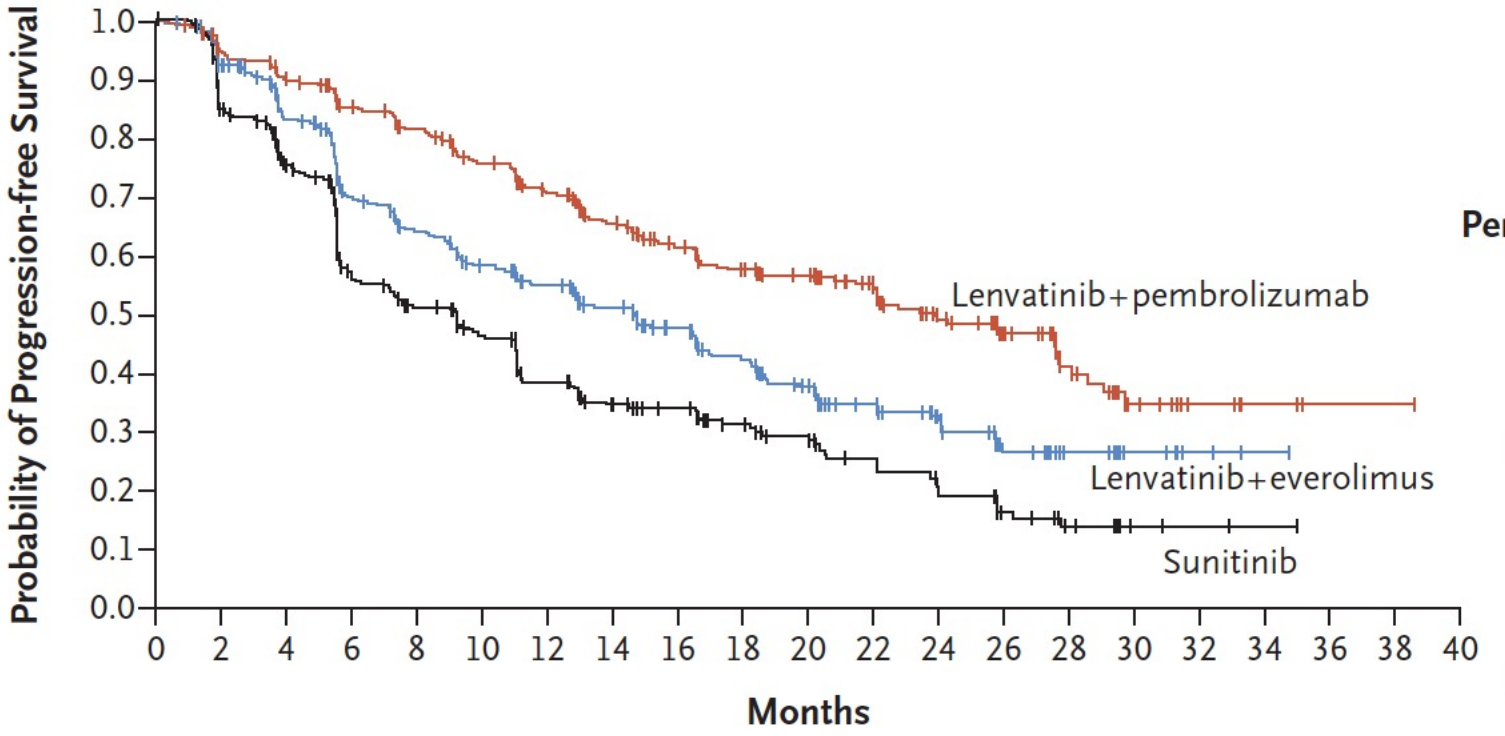
ORIGINAL ARTICLE

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)

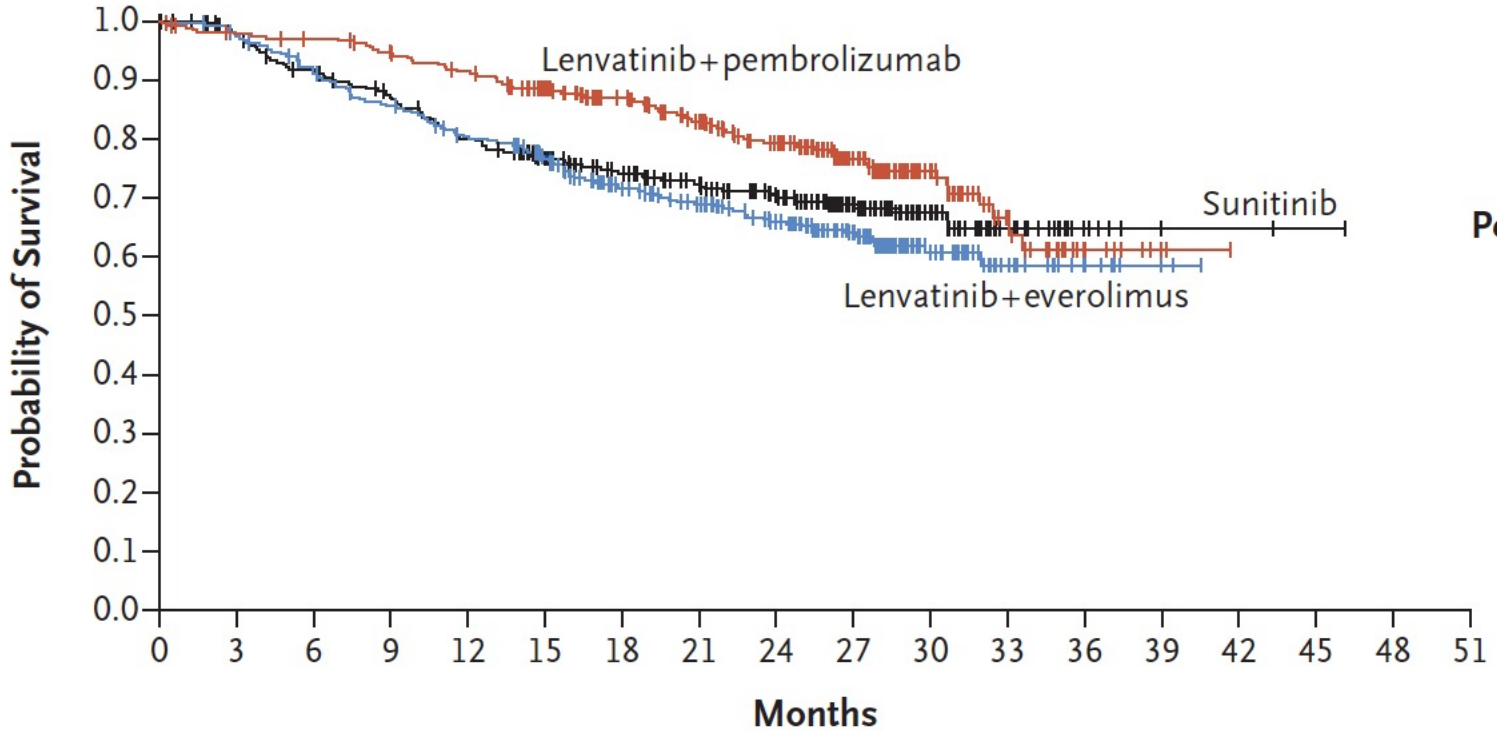
Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

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

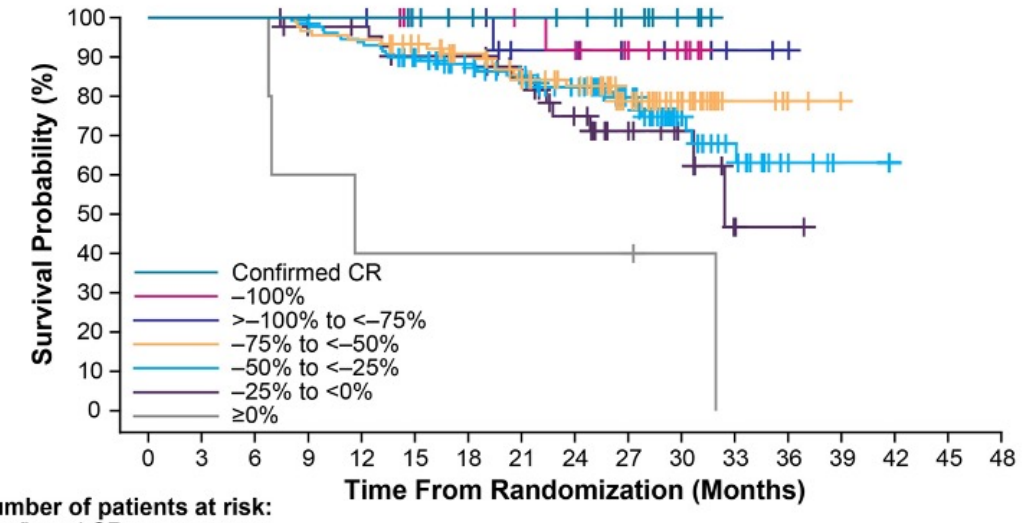
Viktor Grünwald[1], Thomas Powles[2], Evgeny Kopyltsov[3], Vadim Kozlov[4], Teresa Alonso Gordoa[5], Masatoshi Eto[6], Thomas Hutson[7], Robert Motzer[8], Eric Winquist[9], Pablo Maroto[10], Bhumsuk Keam[11], Giuseppe Procopio[12], Shirley Wong[13], Bohuslav Melichar[14], Frederic Rolland[15], Mototsugu 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

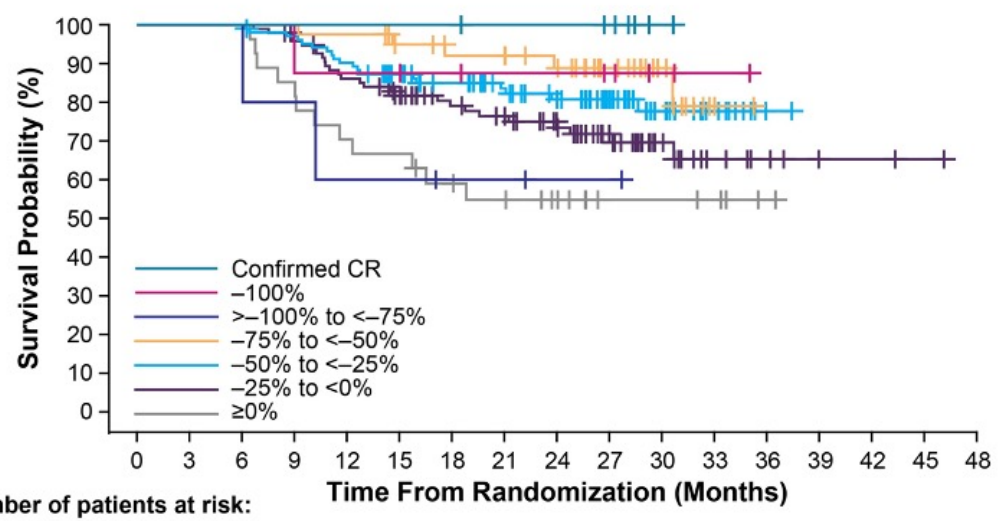
Lenvatinib plus Pembrolizumab



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

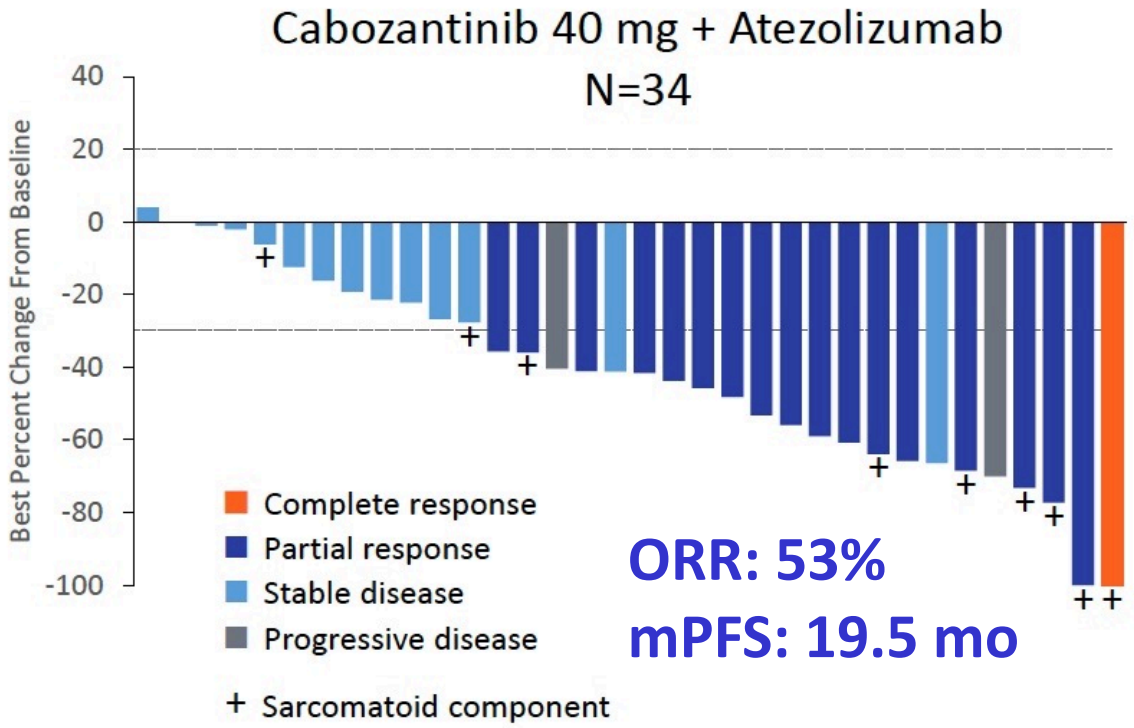
Grunwald V et al. ASCO 2021;Abstract 4560.

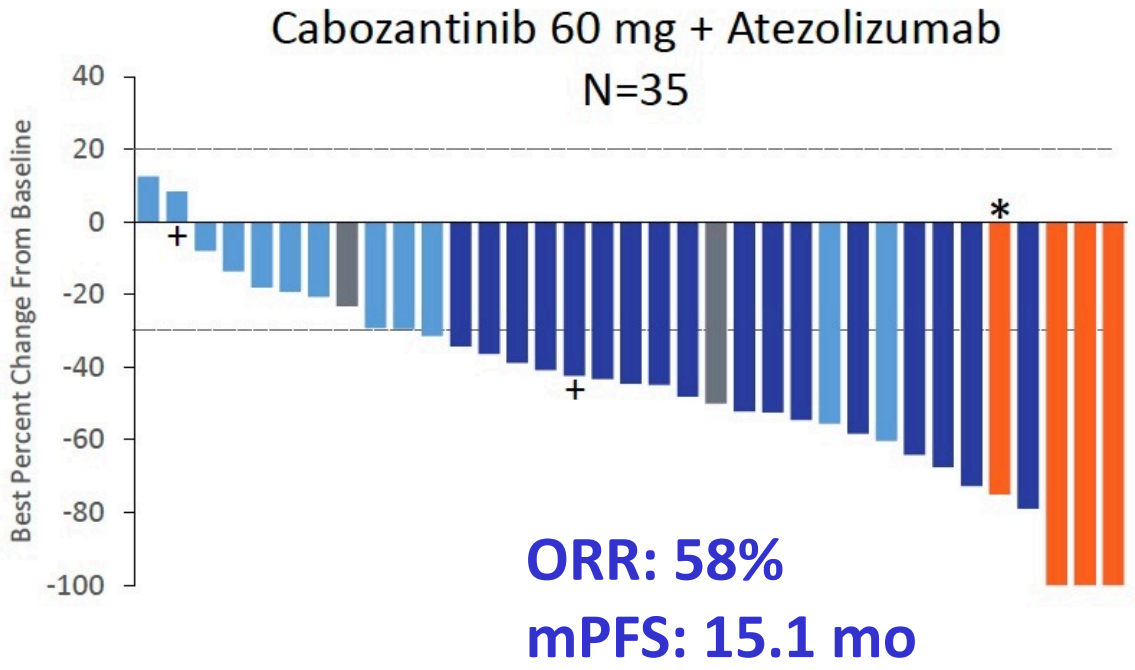
Cabozantinib (C) in Combination with Atezolizumab (A) as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from the COSMIC-021 Study

Pal S et al.

ESMO 2020;Abstract 702O.

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





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

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Clinical Trials in Previously Untreated, Metastatic Renal Cell Carcinoma

Study acronym	Target accrual	Randomization	Primary endpoint(s)	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 (R/R) 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."

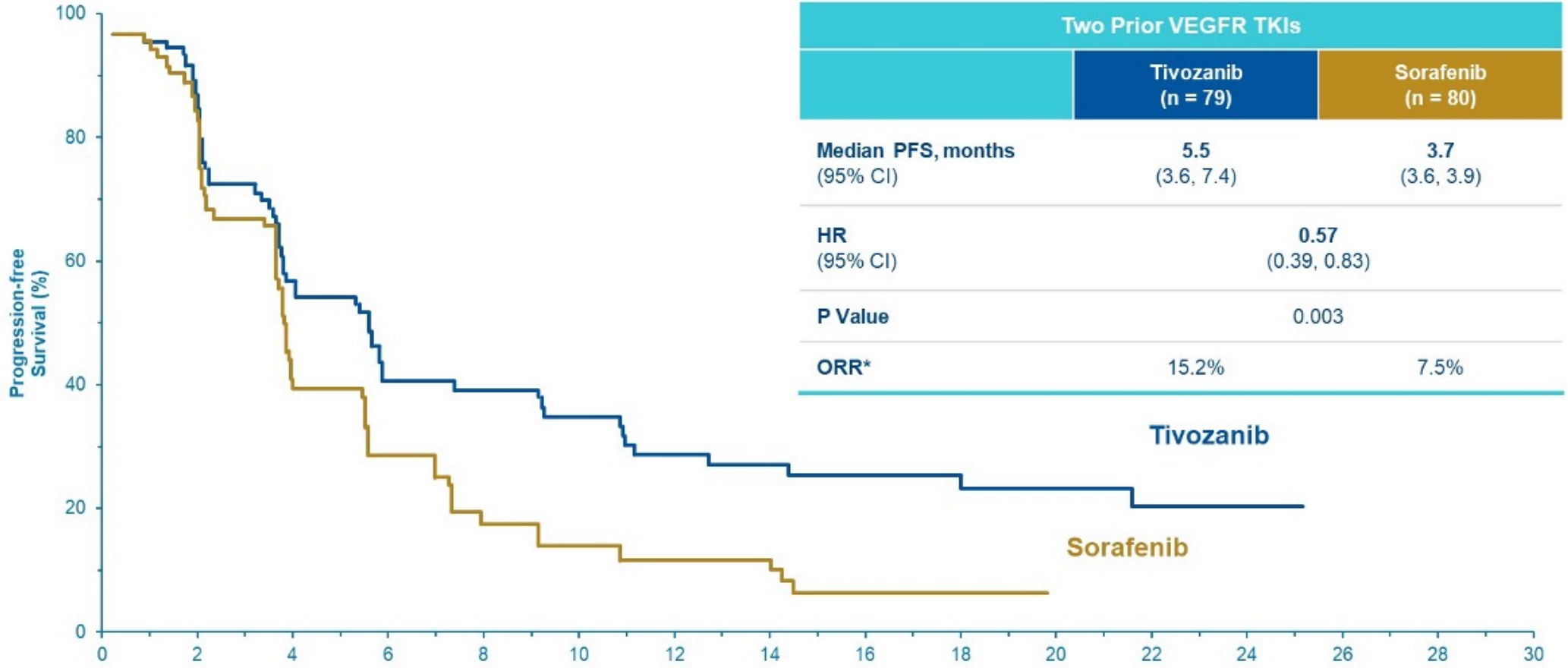
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma

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 2 Prior TKIs Patient Subgroup



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 Grants Priority Review to Belzutifan for von Hippel-Lindau Disease-Associated RCC

Press Release – March 16, 2021

"The FDA accepted a new drug application for belzutifan to treat von Hippel-Lindau disease-associated renal cell carcinoma and granted it priority review based on response rate results from a phase 2 trial.

A new drug application for belzutifan was accepted by the FDA and granted priority review for the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery…

The application is based on results of a phase 2 trial, Study-004 (NCT03401788), of belzutifan in the treatment of VHL disease-associated RCC, with a primary end point of objective response rate and secondary measures of disease control rate, duration of response, time to response, progression-free survival, time to surgery, and safety. Patients treated on the trial must have had at least 1 measurable solid tumor localized to the kidneys and were not in need of immediate surgical intervention."

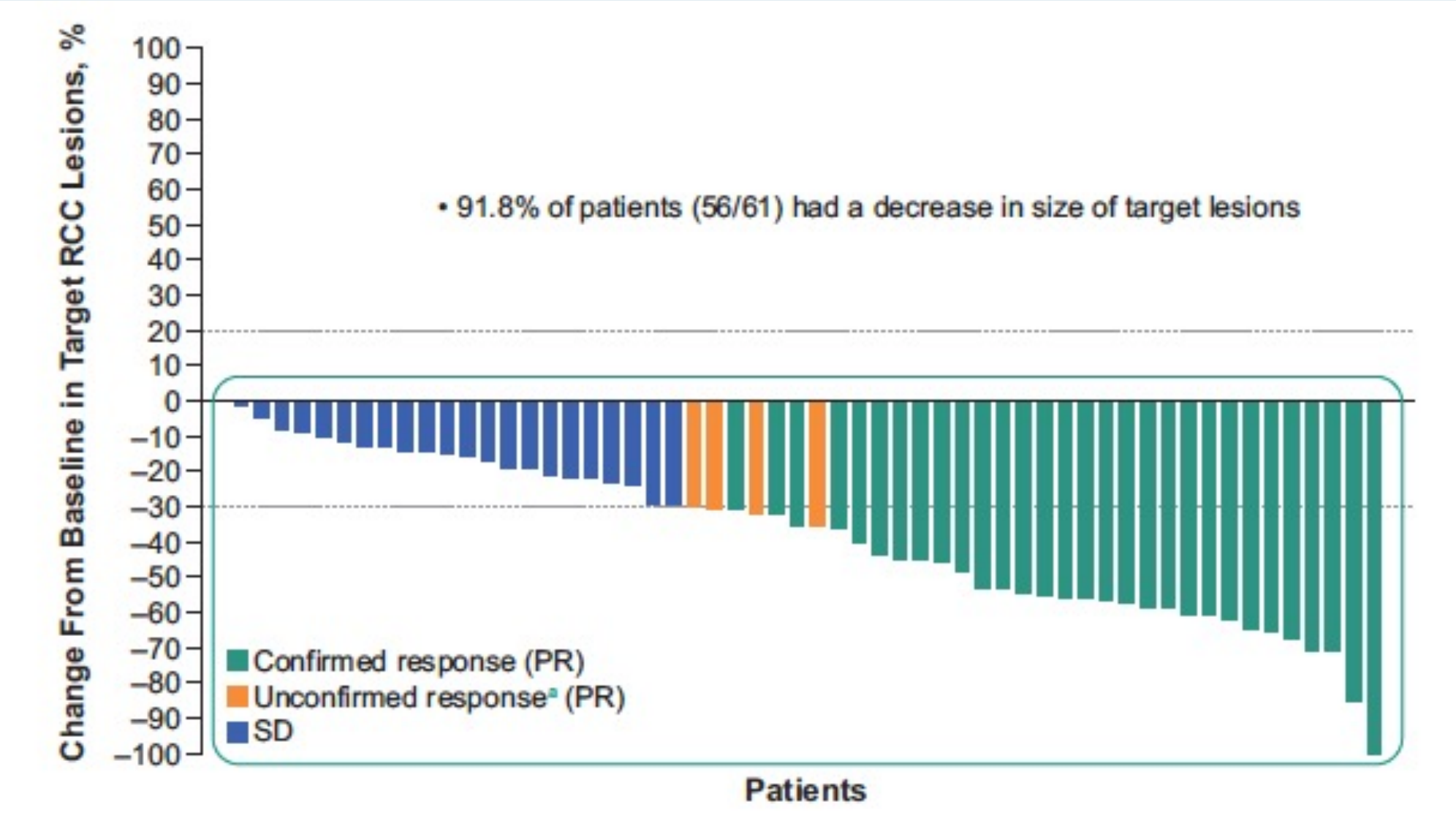
https://www.cancernetwork.com/view/fda-grants-priority-review-to-belzutifan-for-von-hippel-lindau-disease-associated-rcc

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.

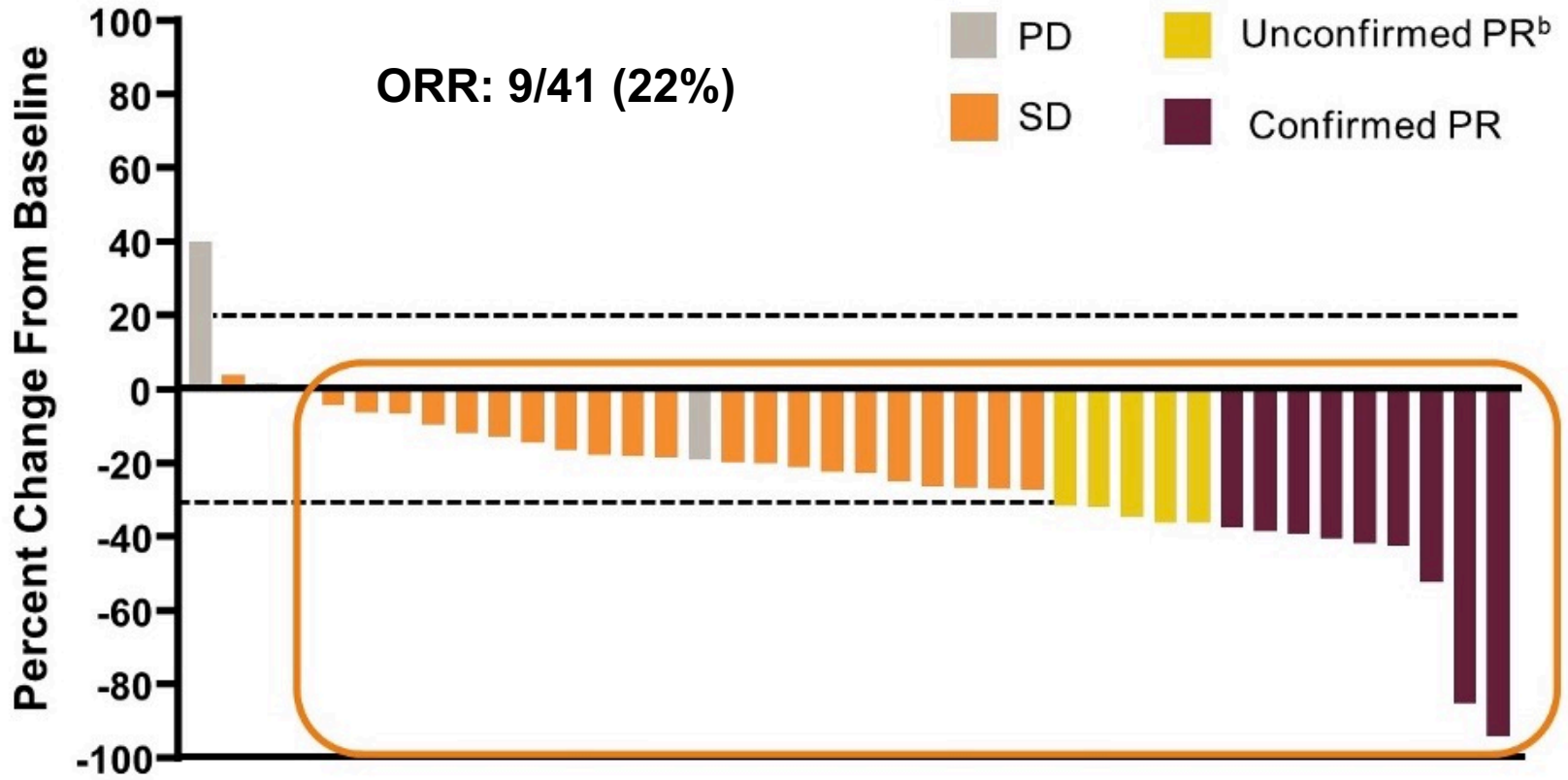
Phase 2 Study of the Oral Hypoxia-Inducible Factor 2α Inhibitor Belzutifan (MK-6482) in Combination With Cabozantinib in Patients With Advanced Clear Cell Renal Cell Carcinoma

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.

A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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

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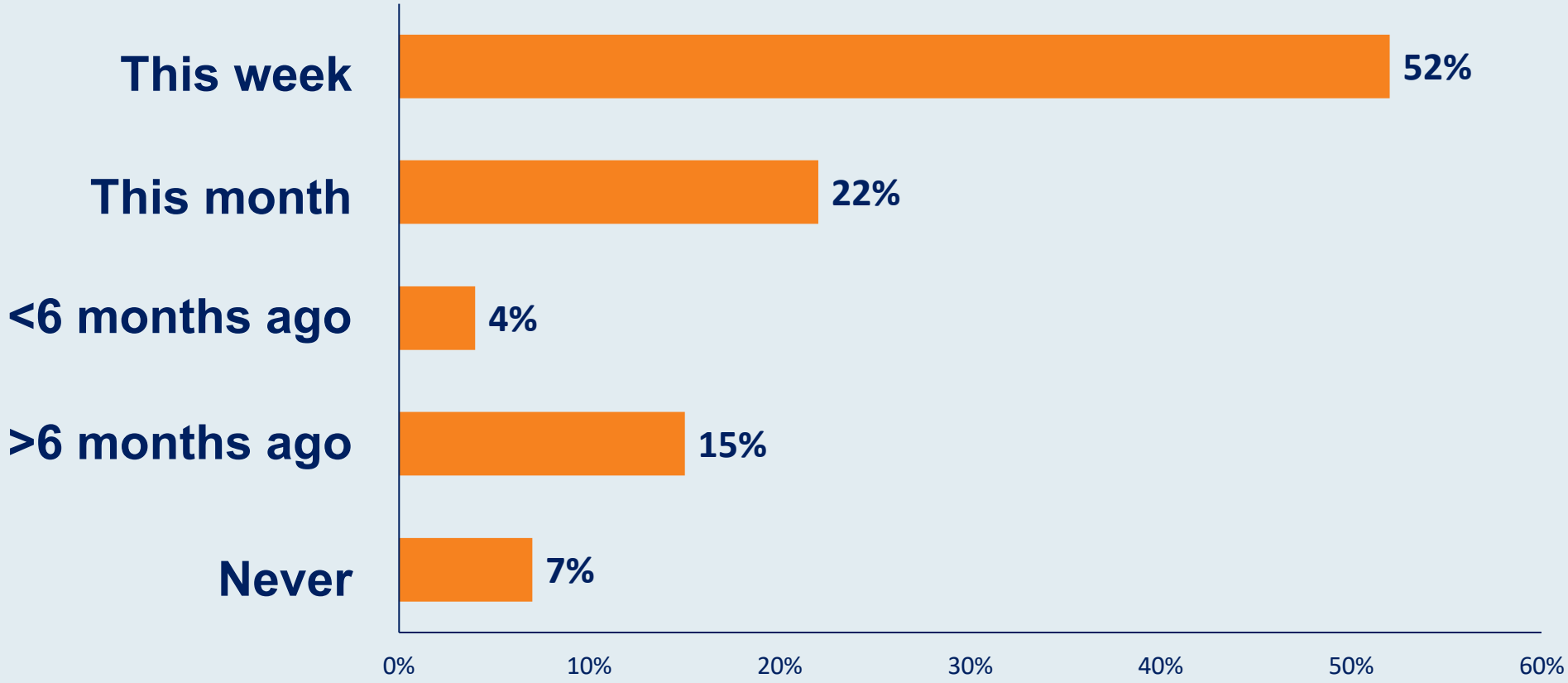
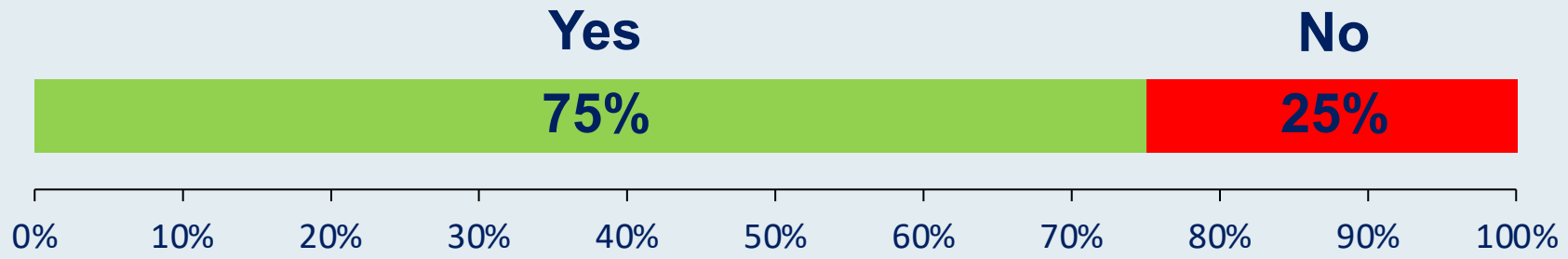
When was the last time that you presented, or had a case presented for you, at a local tumor board meeting?



Premeeting survey: July 2021

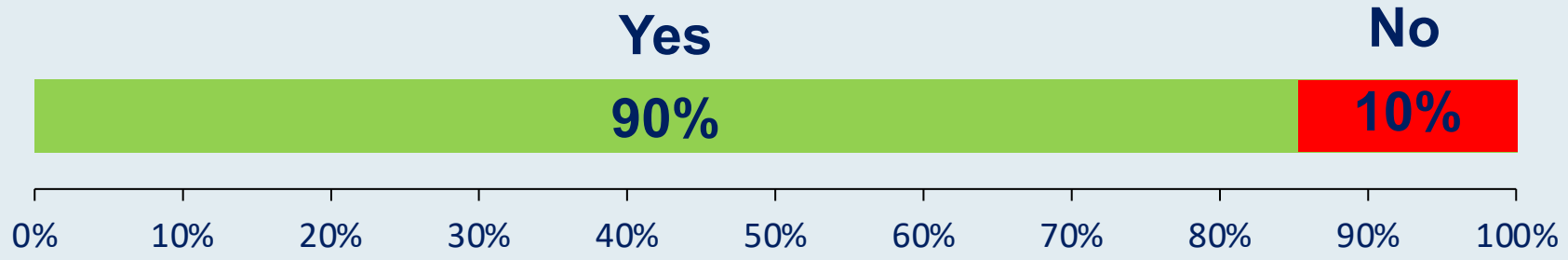
RTP RESEARCH TO PRACTICE

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



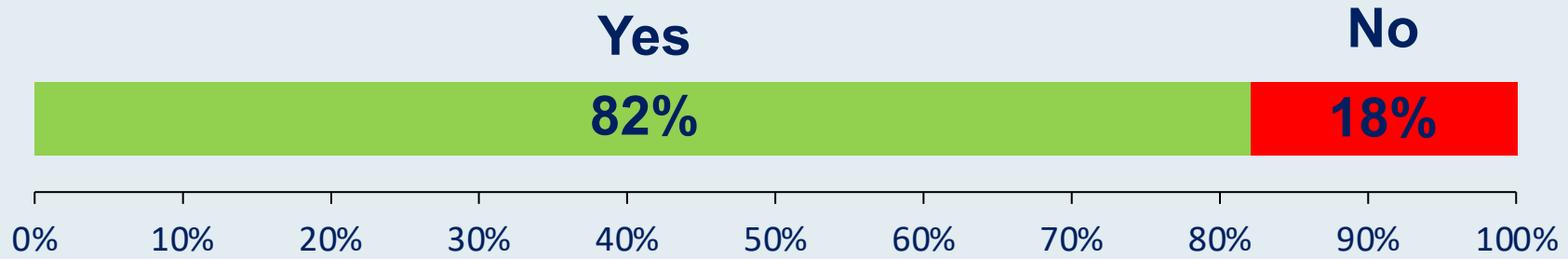
Median: 5 hours
Range: 1-60

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