Meet The Professor

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

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Chief of Clinical Trials
Vanderbilt-Ingram Cancer Center
Ingram Professor of Medicine
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Nashville, Tennessee

Commercial Support

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Dr Love — Disclosures

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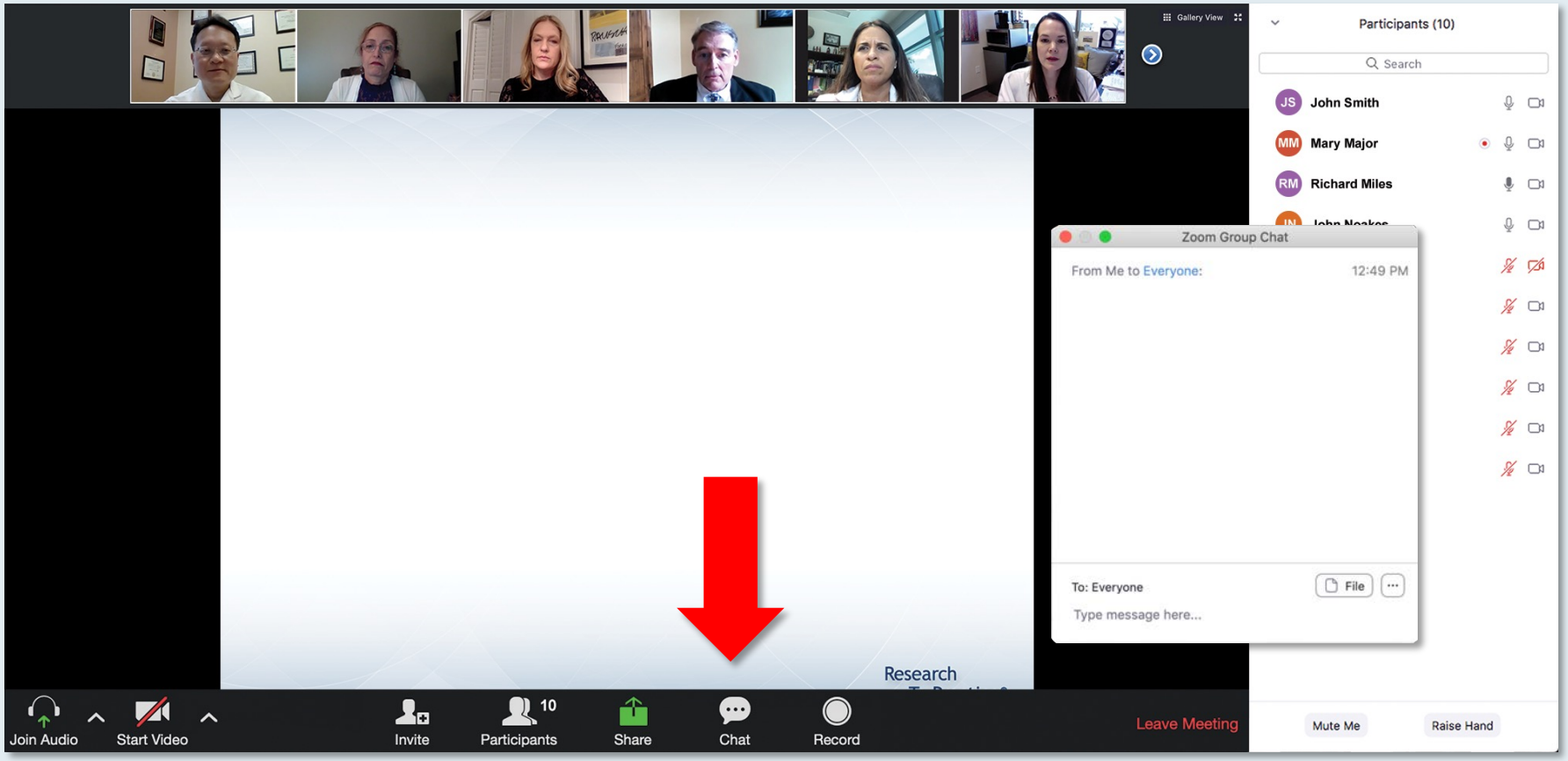
We Encourage Clinicians in Practice to Submit Questions



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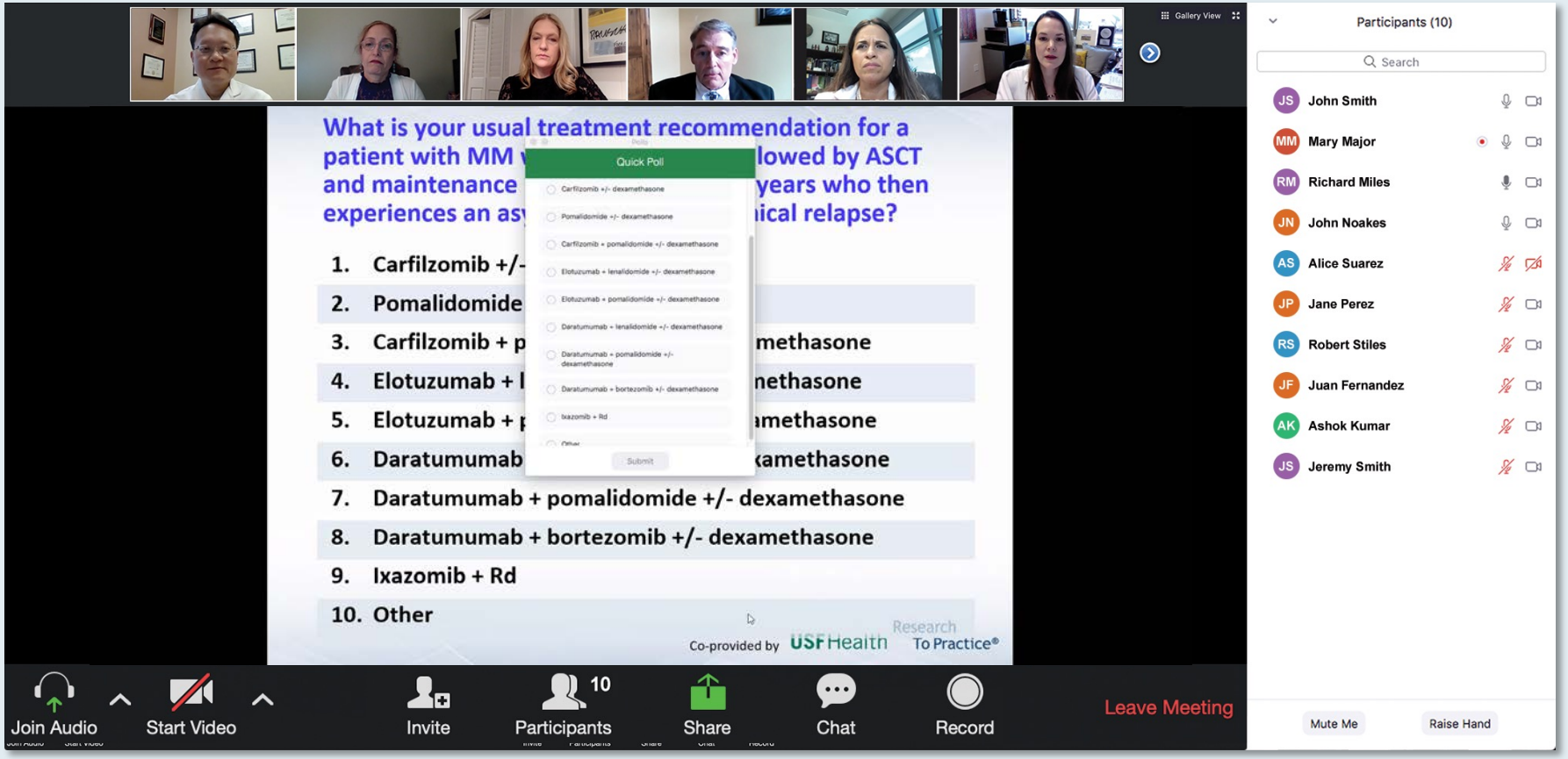

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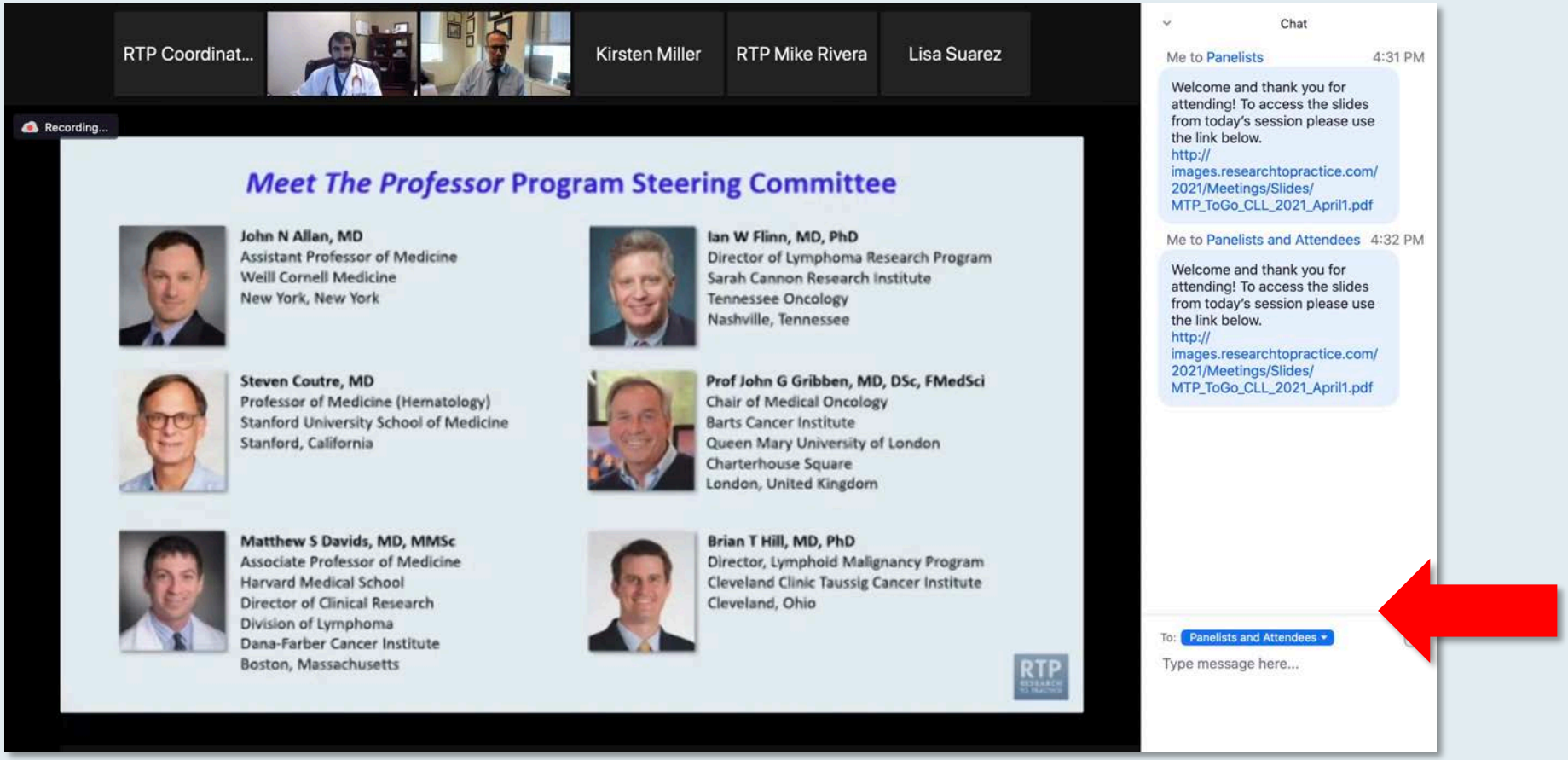

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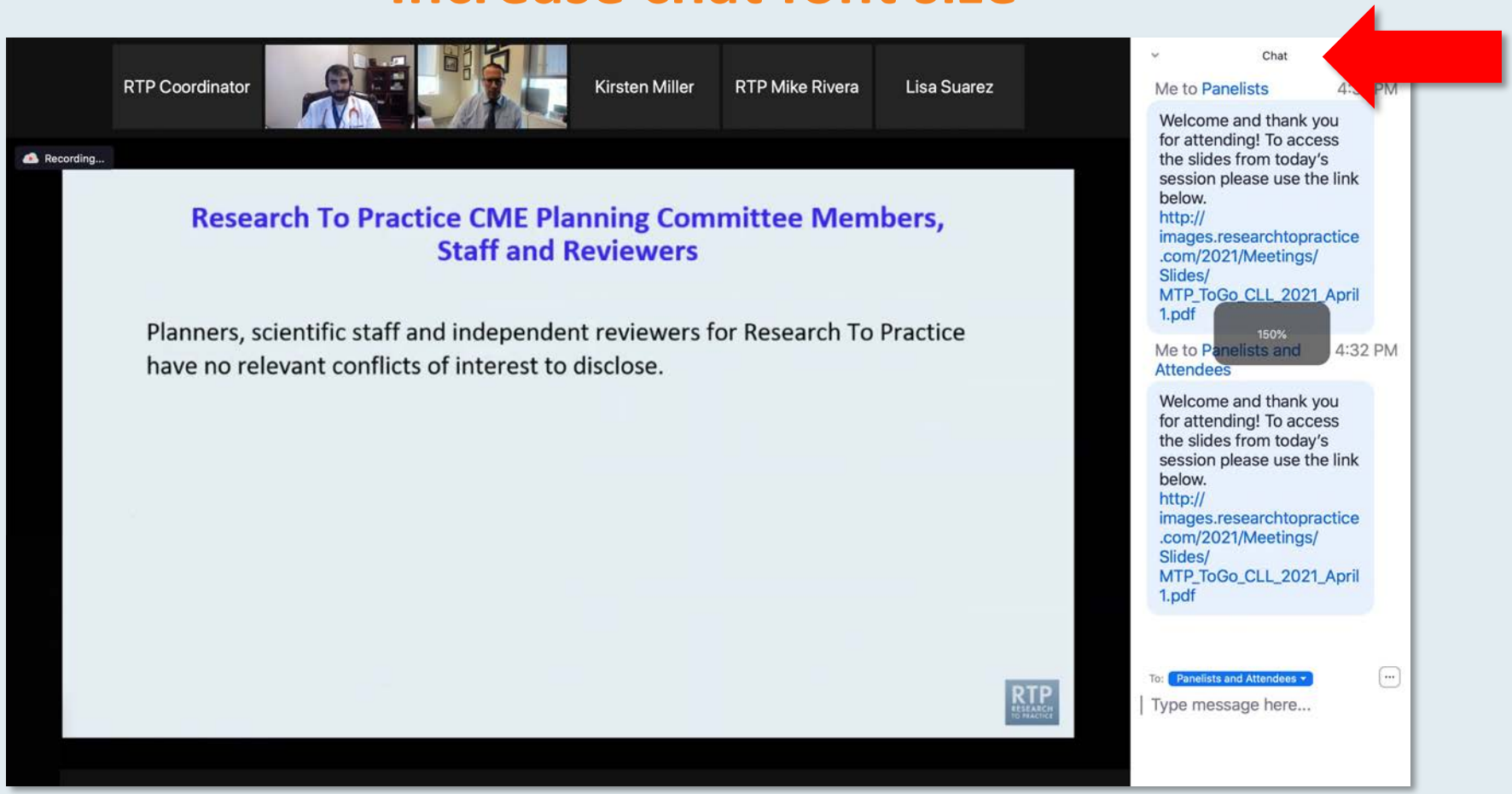

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You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Renal Cell Carcinoma

DR CHUNG-HAN LEE

MEMORIAL SLOAN KETTERING CANCER CENTER

NEW YORK, NEW YORK

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, May 20, 2021
5:00 PM – 6:00 PM ET

Faculty

Jennifer Woyach, MD

Moderator

Neil Love, MD

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Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

A Daylong Multitumor Educational Webinar
in Partnership with Florida Cancer Specialists

Saturday, May 22, 2021
10:15 AM – 4:15 PM ET

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Lymphoma and Chronic Lymphocytic Leukemia
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Additional webinars to be announced

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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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Meet The Professor Program Participating Faculty

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Dana-Farber Cancer Institute
The Jerome and Nancy Kohlberg Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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The University of Texas
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Beth Israel Deaconess Medical Center
Leader, Kidney Cancer Program
Dana-Farber/Harvard Cancer Center
Professor of Medicine
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Philadelphia, Pennsylvania

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Queen Mary University of London
London, United Kingdom

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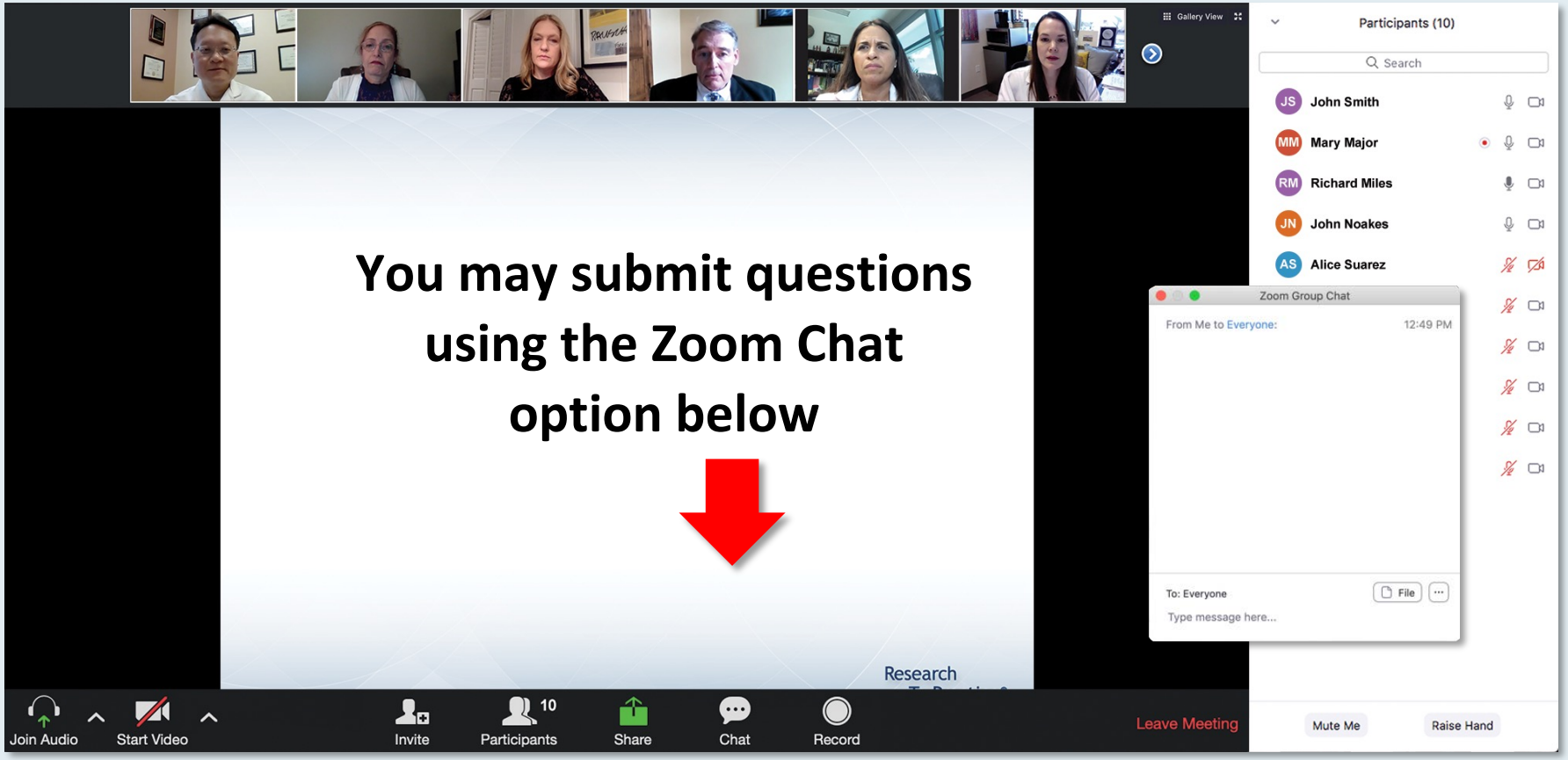

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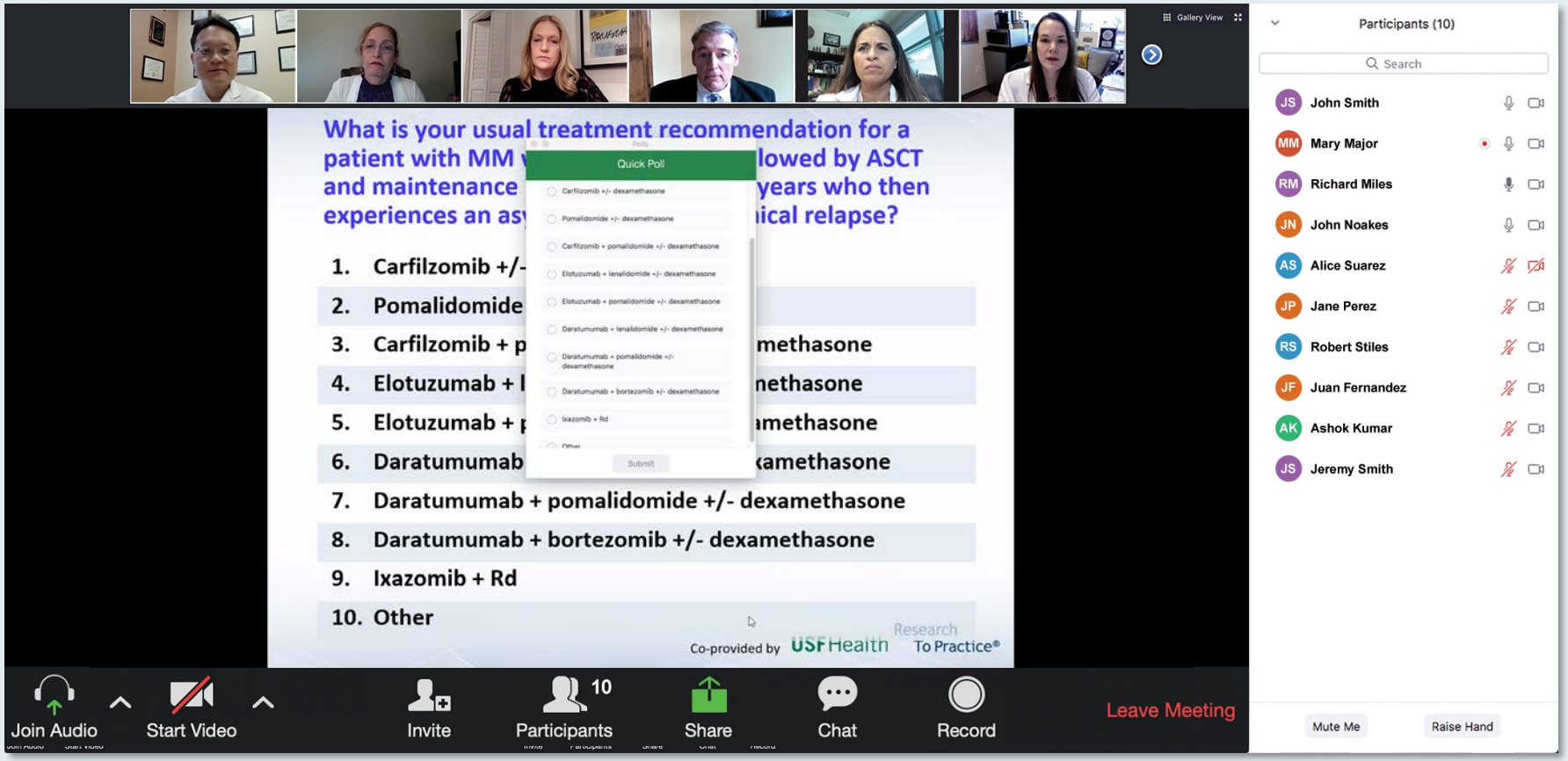

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Fox Chase Cancer Center
Temple Health
Philadelphia, Pennsylvania

William K Oh, MD
Clinical Professor of Medicine
Icahn School of Medicine at Mount Sinai
The Tisch Cancer Institute
Mount Sinai Health System
New York, New York

Meet The Professor with Dr Rini

MODULE 1: Cases from General Medical Oncology Practices

- Dr Oh: A 39-year-old man with metastatic clear cell renal cell carcinoma (ccRCC)
- Dr Plimack: A 54-year-old man with metastatic ccRCC
- Dr Oh: A 65-year-old woman with metastatic chromophobe RCC
- Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib
- Dr Oh: Management strategies for TKI-associated fatigue

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Rini

MODULE 4: Key Data Sets

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Pembrolizumab Demonstrated Superior Disease-Free Survival Compared with Placebo as Adjuvant Therapy for Patients with RCC Following Surgery

Press Release: April 8, 2021

"The pivotal Phase 3 KEYNOTE-564 trial evaluating pembrolizumab met its primary endpoint of disease-free survival (DFS) for the potential adjuvant treatment of patients with RCC following nephrectomy or following nephrectomy and resection of metastatic lesions.

Based on an interim analysis conducted by an independent Data Monitoring Committee, pembrolizumab monotherapy demonstrated a statistically significant and clinically meaningfully improvement in DFS compared with placebo. The trial will continue to evaluate overall survival (OS), a key secondary endpoint.

The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and will be submitted to regulatory authorities."

https://www.merck.com/news/mercks-keytruda-pembrolizumab-demonstrated-superior-disease-free-survival-dfs-compared-with-placebo-as-adjuvant-therapy-in-patients-with-renal-cell-carcinoma-rcc-following-surgery/

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

Choueiri TK et al.

ASCO 2021;Abstract LBA5.

Plenary Session: Sunday, June 6, 2021, 1:00-4:00 PM EDT

If a study were conducted of 100 patients who underwent nephrectomy for cure at a "typical" community hospital, approximately what proportion of those patients would experience recurrence within 5 years?

1. Less than 10%
2. 10%-20%
3. 21%-30%
4. 31%-40%
5. 41%-50%
6. 51%-60%
7. More than 60%

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Case Presentation – Dr Oh: A 39-year-old man with metastatic ccRCC (Part 1)

Dr William Oh

- Presented with cough and weight loss and workup revealed ccRCC with mediastinal lymphadenopathy and pulmonary metastases
- IDMC intermediate risk
- Genetic testing: No clinically significant findings, either germline or somatic
- Offered ipilimumab/nivolumab or axitinib/pembrolizumab

Questions

- How would factors such as the patient's age and symptomatology influence your selection of first-line therapy?
- Would you consider palliative nephrectomy for this patient? If so, at what stage in the patient's treatment course would it be performed – before or after systemic therapy?

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Case Presentation – Dr Oh: A 39-year-old man with metastatic ccRCC (Part 2)

Dr William Oh

- Presented with cough and weight loss and workup revealed clear cell RCC with mediastinal lymphadenopathy and pulmonary metastases
- IDMC intermediate risk
- Genetic testing: No clinically significant findings, either germline or somatic
- ***Ipilimumab/nivolumab x 4 cycles → nivolumab → PR***
- ***Patient elected to not undergo nephrectomy***
- ***6 months later, patient presents with worsening cough and weight loss***
- ***Restaging scans show pulmonary nodules increasing in size***

Question

- How do you know if this patient is truly progressing? What are the factors that you consider?

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Case Presentation – Dr Oh: A 39-year-old man with metastatic ccRCC (Part 3)

Dr William Oh

- Presented with cough and weight loss and workup revealed clear cell RCC with mediastinal lymphadenopathy and pulmonary metastases
- IDMC intermediate risk
- Genetic testing: No clinically significant findings, either germline or somatic
- Ipilimumab/nivolumab x 4 cycles → nivolumab → PR
- 6 months later, patient presents with worsening cough and weight loss
- Restaging scans show pulmonary nodules increasing in size
- ***Cabozantinib 40 mg/d added to nivolumab q4wks → PR***
- ***Patient remains on therapy***

Questions

- ***What treatment would you recommend as second-line therapy for this patient if he has disease progression?***

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Case Presentation – Dr Plimack: A 54-year-old man with metastatic ccRCC (Part 1)

Dr Elizabeth Plimack

- 2011: Stage III ccRCC, s/p right partial nephrectomy
- Declined enrollment on adjuvant pazopanib study → CT surveillance
- 2019: Abnormal CXR → CT, with biopsy-proven ccRCC to lung
  - IMDC Intermediate risk, serum calcium > ULN

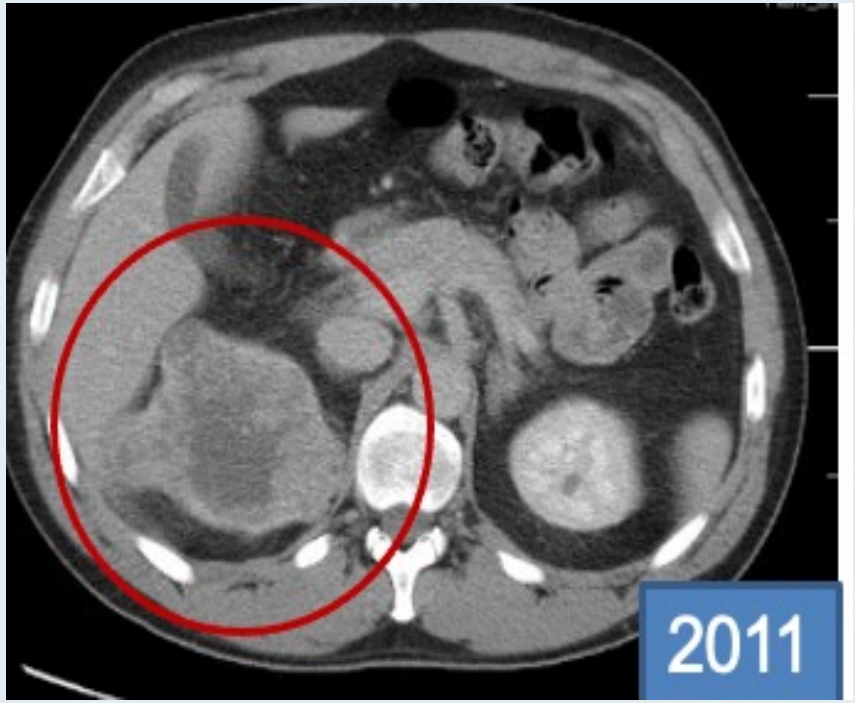
Question

- What would you recommend for this patient today?

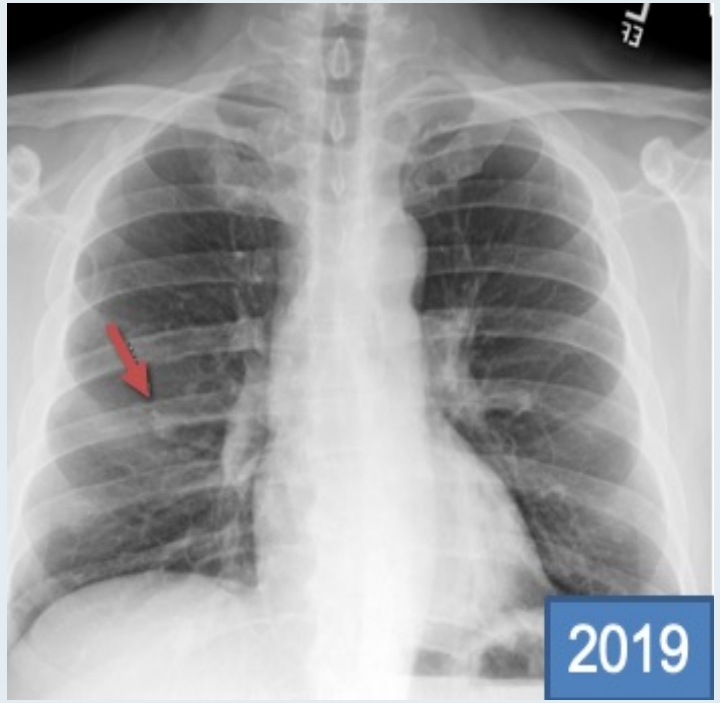
Case Presentation – Dr Plimack: A 54-year-old man with metastatic ccRCC

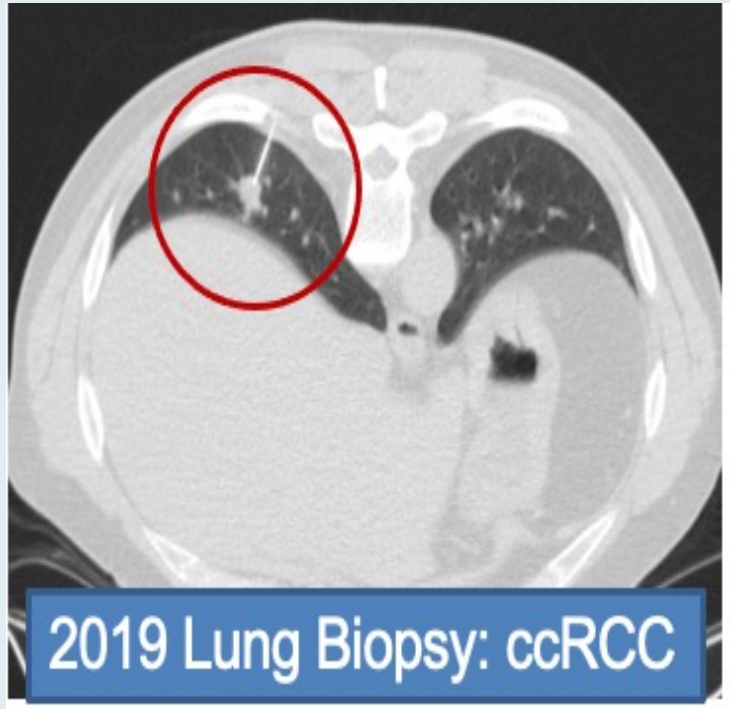
Dr Elizabeth Plimack

Diagnosis: Stage III ccRCC



Lung Nodule: Biopsy-confirmed ccRCC





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Case Presentation – Dr Plimack: A 54-year-old man with metastatic ccRCC (Part 2)

Dr Elizabeth Plimack

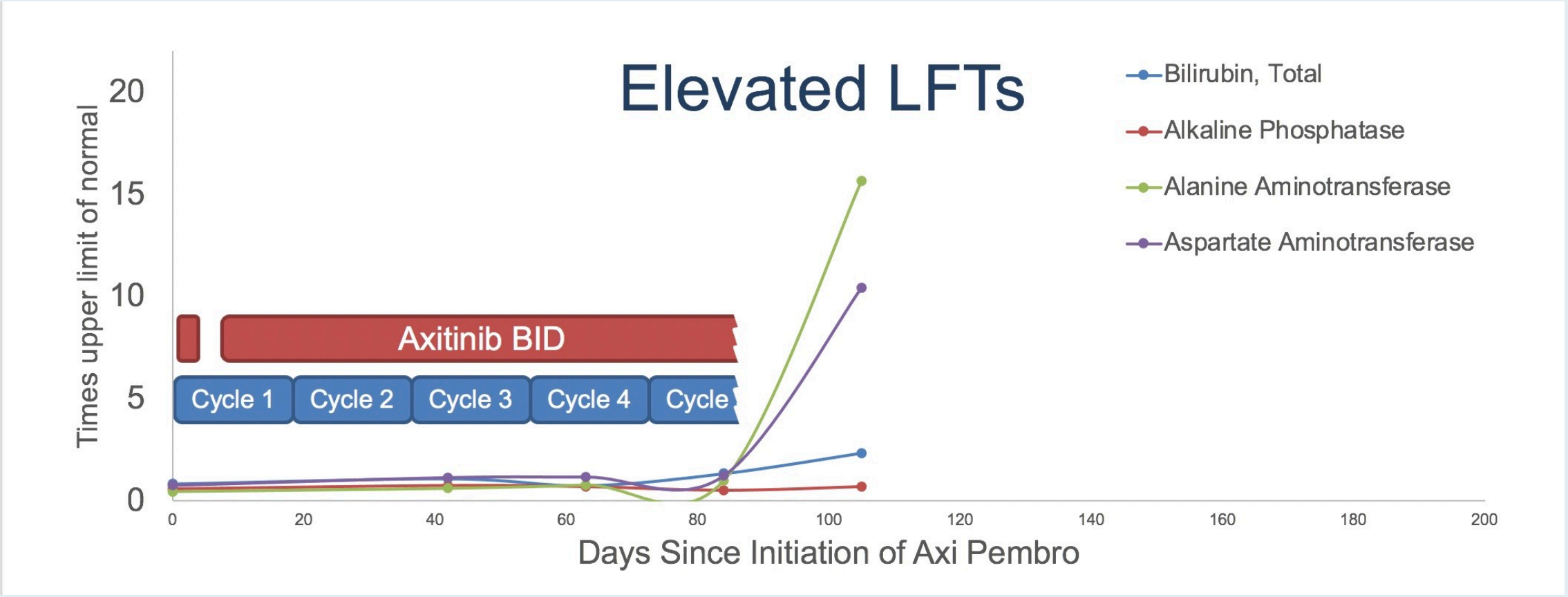
- 2011: Stage III ccRCC, s/p right partial nephrectomy
- Declined enrollment on adjuvant pazopanib study → CT surveillance
- 2019: Abnormal CXR → CT, with biopsy-proven ccRCC to lung
  - IMDC Intermediate risk, serum calcium > ULN
- ***Axitinib/pembrolizumab***
  - ***Week 1: Hypertension → Held axitinib → Antihypertensives → Resumed at 3 mg BID***
  - ***Cycle 5: Nausea/vomiting → Held axitinib → Elevated LFTs***

Question

- ***For this patient with elevated liver function tests, symptomatic with nausea on a combination of axitinib and pembro, what would your next move be?***

Case Presentation – Dr Plimack: A 54-year-old man with metastatic ccRCC

Dr Elizabeth Plimack



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  - Week 1: Hypertension → Held axitinib → Antihypertensives → Resumed at 3 mg BID
  - Cycle 5: Nausea/vomiting → Held axitinib → Elevated LFTs → ***Held axitinib/pembrolizumab***
  - ***LFTs rapidly decline, pembrolizumab continued***

Question

- ***Would you have resumed pembrolizumab, given that his LFTs improved so rapidly after just holding the axitinib?***

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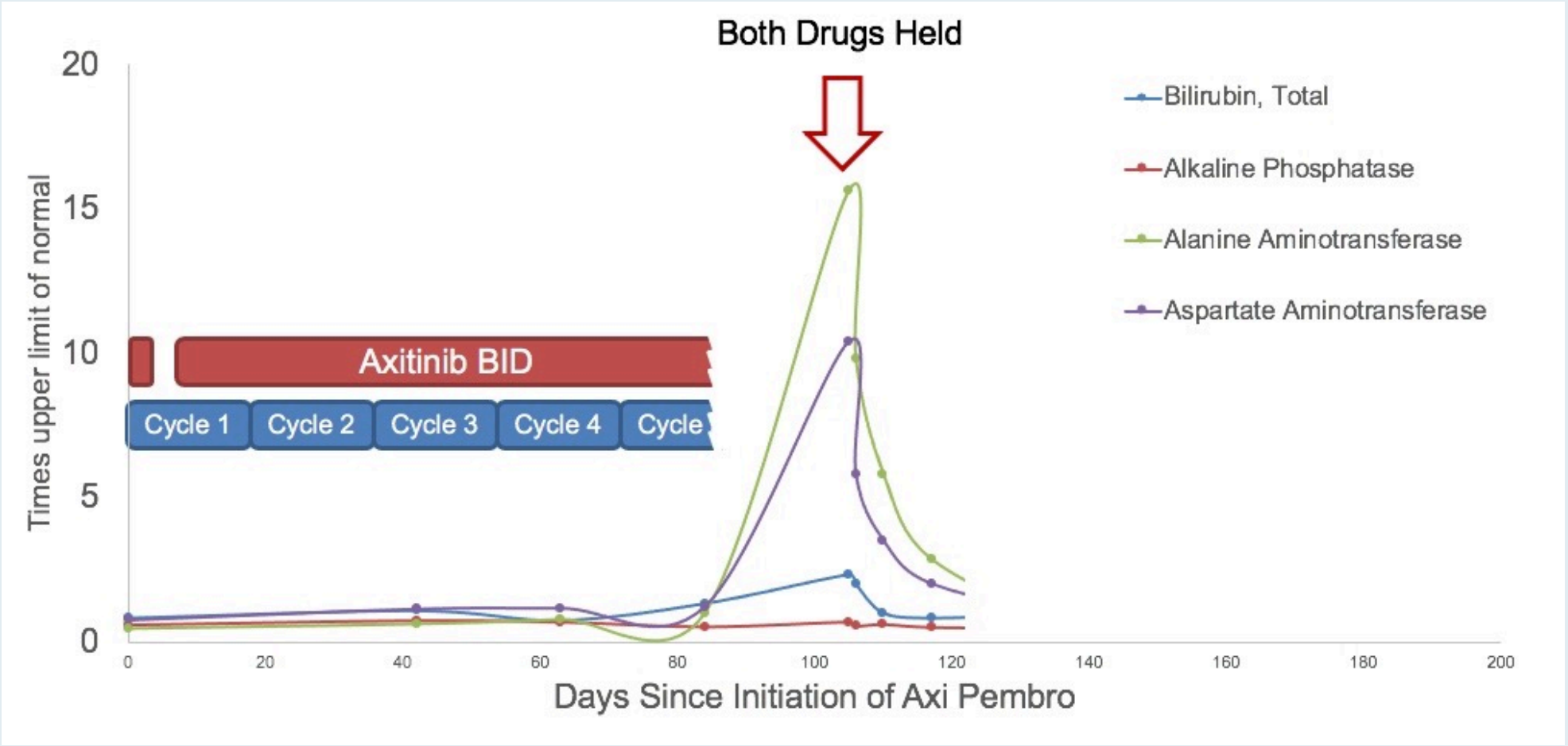
Case Presentation – Dr Plimack: A 54-year-old man with metastatic ccRCC

Dr Elizabeth Plimack

Clinical Course on Axitinib/Pembrolizumab



Case Presentation – Dr Oh: A 65-year-old woman with metastatic chromophobe RCC (Part 1)

Dr William Oh

- Early 2019: Presented with fatigue and anemia; workup revealed 7-cm renal mass
  - Nephrectomy: Chromophobe RCC, no metastatic disease
- 8 months later, patient presented with severe mid-back pain → T10 bone lesion with cord compression
  - Laminectomy confirms chromophobe RCC → Radiation
- Imaging several weeks later shows evidence of liver metastases

Question

- What first-line treatment would you recommend to this patient with chromophobe RCC?

Case Presentation – Dr Oh: A 65-year-old woman with metastatic chromophobe RCC (Part 2)

Dr William Oh

- Early 2019: Presented with fatigue and anemia; workup revealed 7-cm renal mass
  - Nephrectomy: Chromophobe RCC, no metastatic disease
- 8 months later, patient presented with severe mid-back pain → T10 bone lesion with cord compression
  - Laminectomy confirms chromophobe RCC → Radiation
- Imaging several weeks later shows evidence of liver metastases
- ***Lenvatinib/everolimus → Stable disease***

Lancet 2021;397(10275):645-7.

Cabozantinib: a new first-line option for papillary renal cell carcinoma?

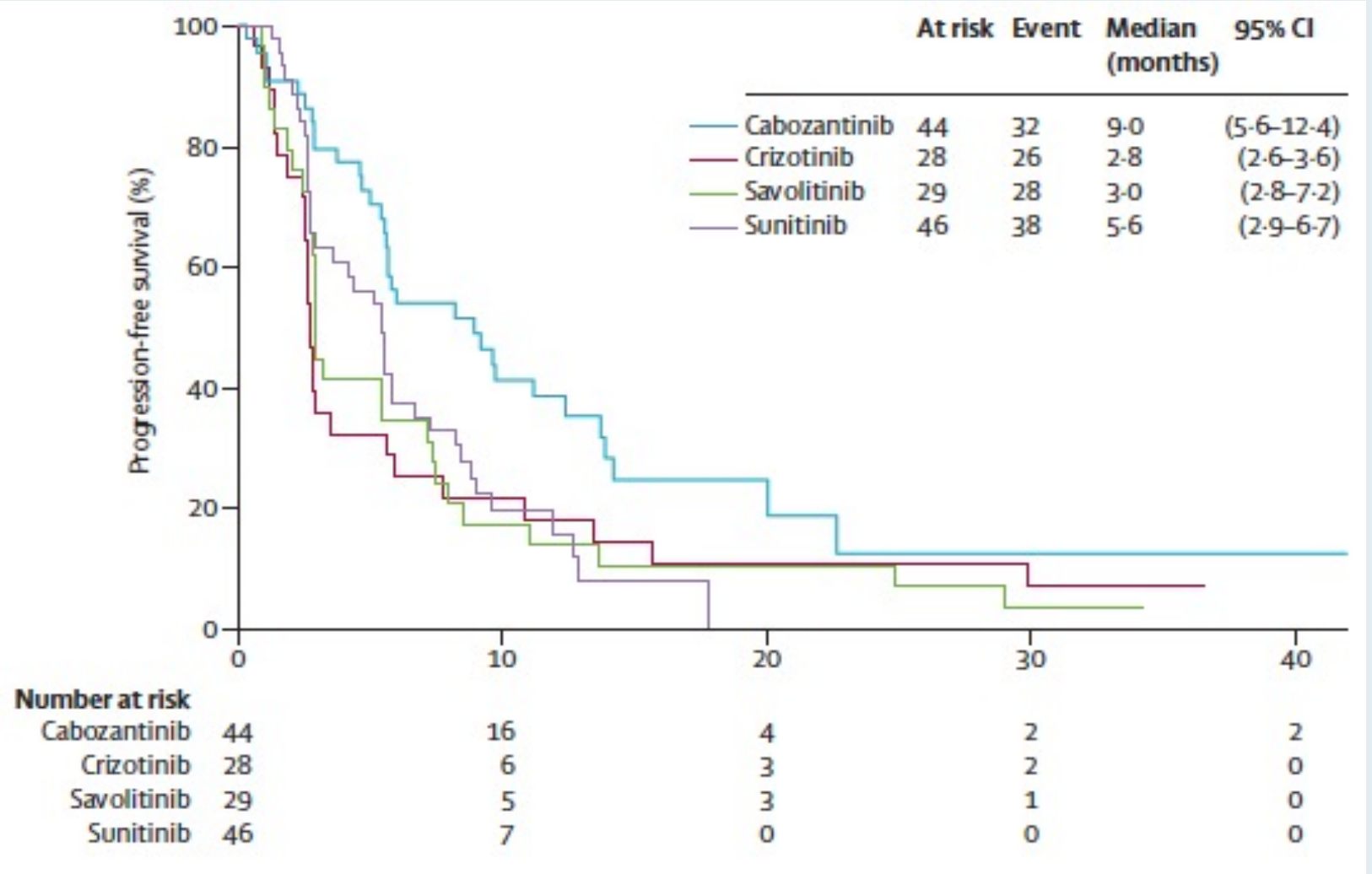
*Delphine Borchiellini, Philippe Barthélémy
delphine.borchiellini@nice.unicancer.fr

Lancet 2021;397:695-703.

A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial

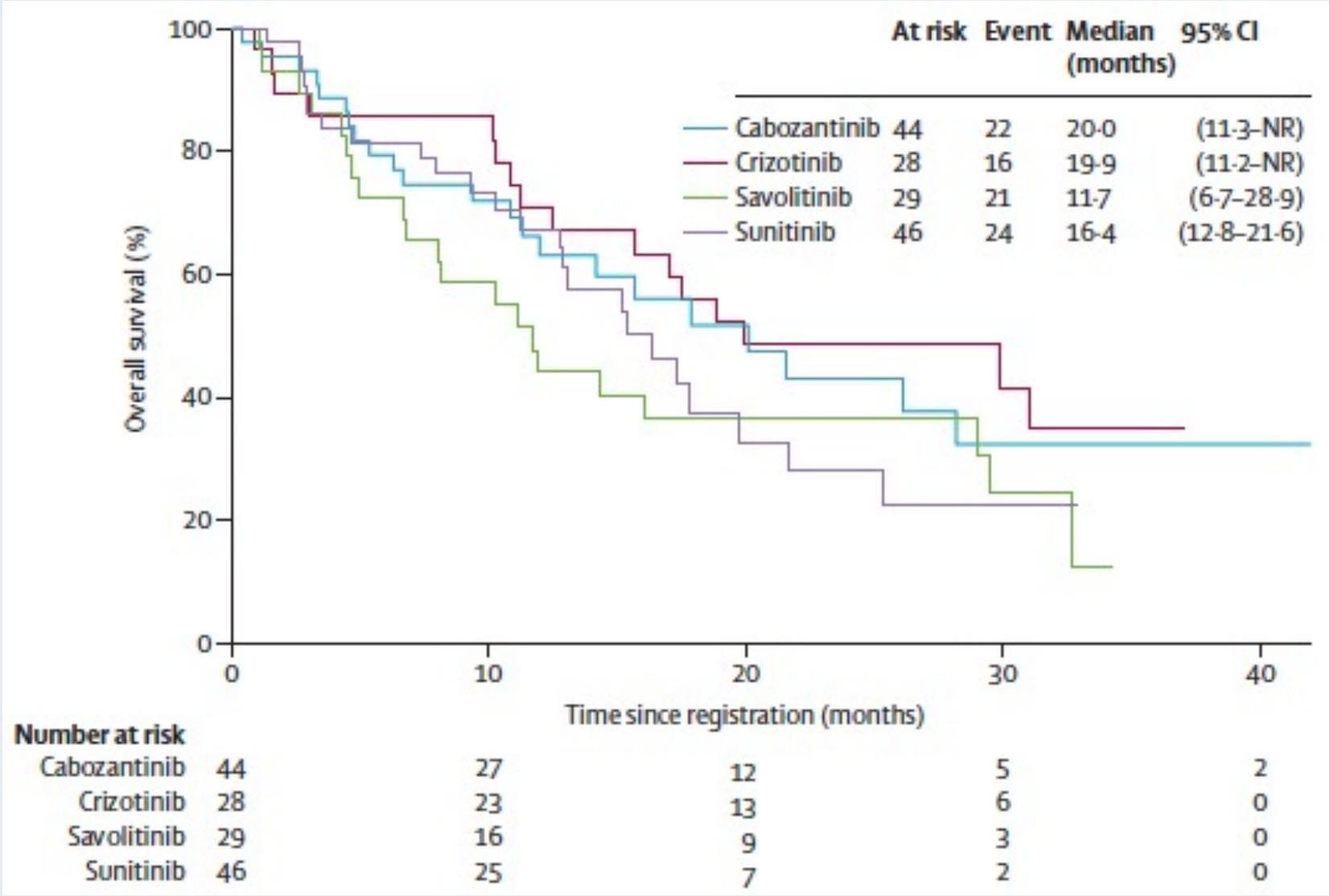
Sumanta K Pal, Catherine Tangen, Ian M Thompson Jr, Naomi Balzer-Haas, Daniel J George, Daniel Y C Heng, Brian Shuch, Mark Stein, Maria Tretiakova, Peter Humphrey, Adebowale Adeniran, Vivek Narayan, Georg A Bjarnason, Ulka Vaishampayan, Ajjai Alva, Tian Zhang, Scott Cole, Melissa Plets, John Wright, Primo N Lara Jr

Kaplan-Meier Analysis of Progression-Free Survival



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

Kaplan-Meier Analysis of Overall Survival



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

Case Presentation – Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib (Part 1)

Dr Elizabeth Plimack

- PMH: Stage II ccRCC, s/p left nephrectomy (Age 54)
- 2015 (Age 74): Presents with incidentally detected, asymptomatic metastases to pancreatic tail and body (IMDC favorable risk)

Question

- What would you select for treatment when she presents with metastatic disease?

Case Presentation – Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib (Part 2)

Dr Elizabeth Plimack

- PMH: Stage II ccRCC, s/p left nephrectomy (Age 54)
- 2015 (Age 74): Presents with incidentally detected, asymptomatic metastases to pancreatic tail and body (IMDC favorable risk)
- ***Pazopanib 800 mg daily, with response***
  - ***Held due to diarrhea (controlled with loperamide) and fatigue → Restarted at 400 mg daily***

Case Presentation – Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib (Part 3)

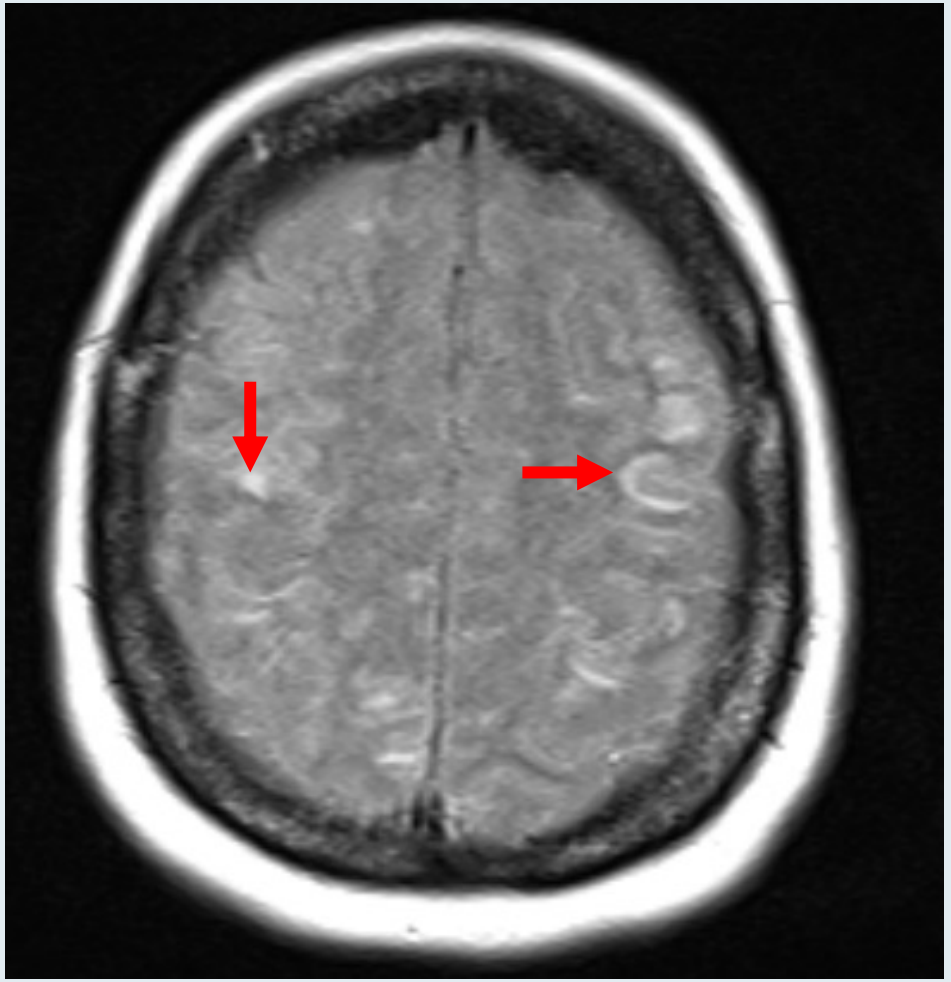
Dr Elizabeth Plimack

- PMH: Stage II ccRCC, s/p left nephrectomy (Age 54)
- 2015 (Age 74): Presents with incidentally detected, asymptomatic metastases to pancreatic tail and body (IMDC favorable risk)
- Pazopanib 800 mg daily, with response
  - Held due to diarrhea (controlled with loperamide) and fatigue → Restarted at 400 mg daily
- ***Seizure***
  - ***MRI: Posterior reversible encephalopathy syndrome (PRES), evidenced by bilateral subcortical white matter increased T2 signal on FLAIR sequence***
  - ***Pazopanib discontinued***
- ***Seven years later, patient is stable and asymptomatic without further systemic therapy***

Case Presentation – Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib

Dr Elizabeth Plimack

Bilateral Subcortical White Matter
Increased T2 Signal on FLAIR Sequence



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Management strategies for TKI-associated fatigue

Dr William K Oh

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Rini

MODULE 1: Cases from General Medical Oncology Practices

- Dr Oh: A 39-year-old man with metastatic clear cell (ccRCC)
- Dr Plimack: A 54-year-old man with metastatic ccRCC
- Dr Oh: A 65-year-old woman with metastatic chromophobe RCC
- Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib
- Dr Oh: Management strategies for TKI-associated fatigue

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Rini

MODULE 4: Key Data Sets

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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, 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 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 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

What would be your most likely third-line systemic therapy recommendation for a 65-year-old patient with metastatic RCC who experienced disease progression on first-line pembrolizumab/axitinib and second-line cabozantinib (PS 0)?

 Dr Choueiri	Tivozanib	 Dr Motzer	Lenvatinib + everolimus
 Dr Hutson	Lenvatinib + everolimus	 Dr Plimack	Lenvatinib + everolimus
 Dr Jonasch	Lenvatinib + everolimus	 Prof Powles	Lenvatinib + everolimus
 Dr McDermott	Tivozanib	 Dr Rini	Tivozanib

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

Meet The Professor with Dr Rini

MODULE 1: Cases from General Medical Oncology Practices

- Dr Oh: A 39-year-old man with metastatic clear cell (ccRCC)
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- Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib
- Dr Oh: Management strategies for TKI-associated fatigue

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Rini

MODULE 4: Key Data Sets

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Journal Club with Dr Rini (Part 1)

- Cytoreductive nephrectomy and survival in metastatic renal cell carcinoma (mRCC) receiving modern therapies
- The immunology of RCC
- Optimizing treatment of RCC with VEGFR TKIs
- RCC with non-clear cell histology or sarcomatoid differentiation: Recent insight in an unmet clinical need
- Time to resolution of axitinib-related adverse events after treatment interruption
- MK-6482, a HIF-2α inhibitor, versus everolimus in heavily pretreated, immune checkpoint inhibitor-resistant, advanced ccRCC

Journal Club with Dr Rini (Part 2)

- Effect of antibiotic use on immune checkpoint inhibitor efficacy in advanced urothelial carcinoma
- Umbrella study of investigational immune and targeted combination therapies as first-line therapy for advanced RCC
- Atezolizumab/bevacizumab after disease progression on atezolizumab or sunitinib monotherapy for mRCC in IMmotion150
- TIVO-3: Durability of response and updated overall survival with tivozanib versus sorafenib in mRCC
- Association of baseline neutrophil-to-eosinophil ratio and neutrophil-to-lymphocyte ratio with response to combination immunotherapy with ipilimumab plus nivolumab in mRCC
- Association of the neutrophil-to-eosinophil ratio with response to immunotherapy-based combinations in mRCC

Cancer Causes Control 2021;[Online ahead of print].

Cancer Causes & Control
https://doi.org/10.1007/s10552-021-01435-z

REVIEW ARTICLE

Association between cytoreductive nephrectomy and survival among patients with metastatic renal cell carcinoma receiving modern therapies: a systematic review and meta-analysis examining effect modification according to systemic therapy approach

Mary E. Hall[1] · Bimal Bhindi[2,3] · Amy N. Luckenbaugh[1] · Aaron A. Laviana[1] · Kelvin A. Moses[1] · Raj Satkunasivam[4,5] · Brian Rini[6] · Zachary Klaassen[7,8] · Christopher J. D. Wallis[1]

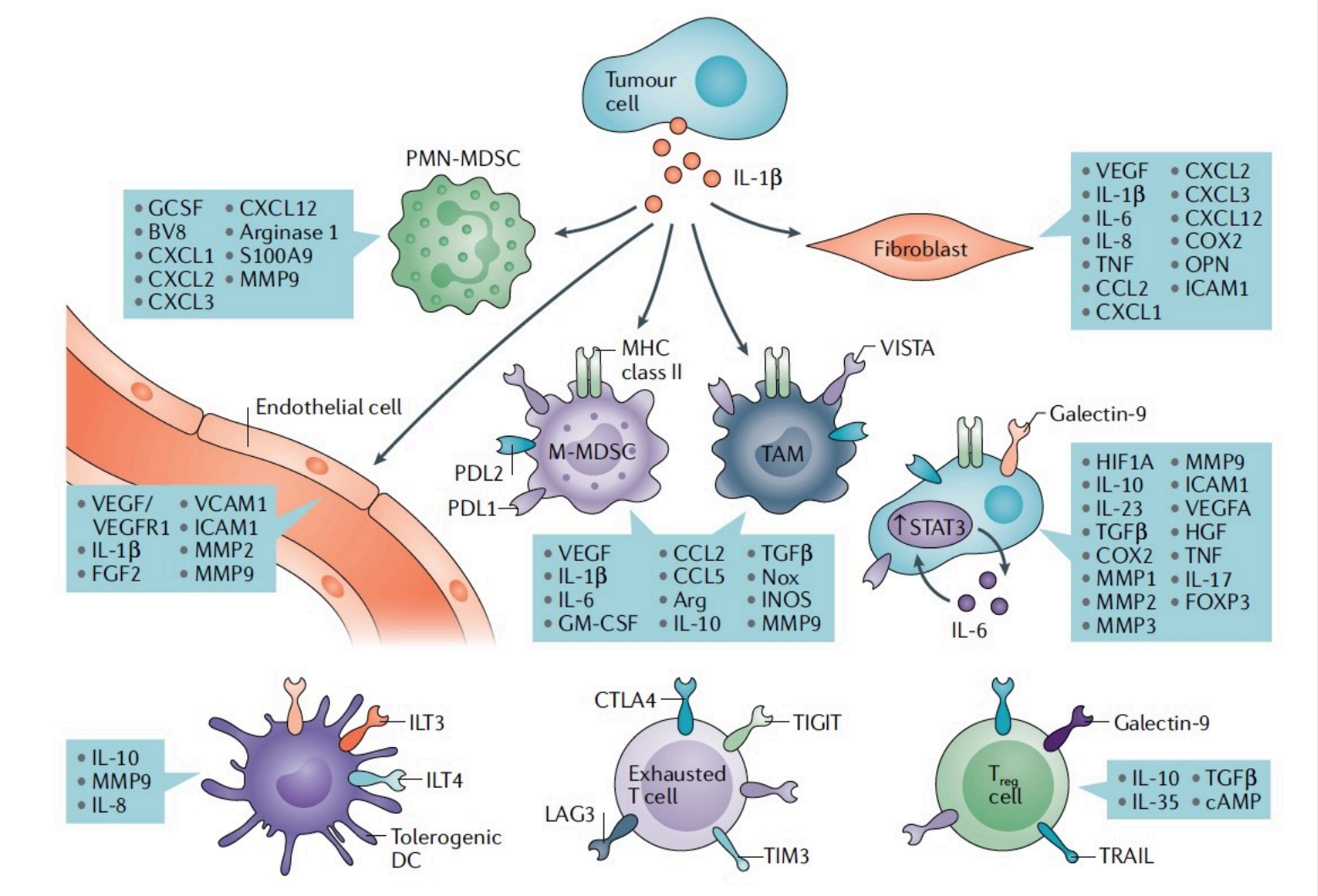
Nat Rev Nephrol 2020;16(12):721-35

REVIEWS

The immunology of renal cell carcinoma

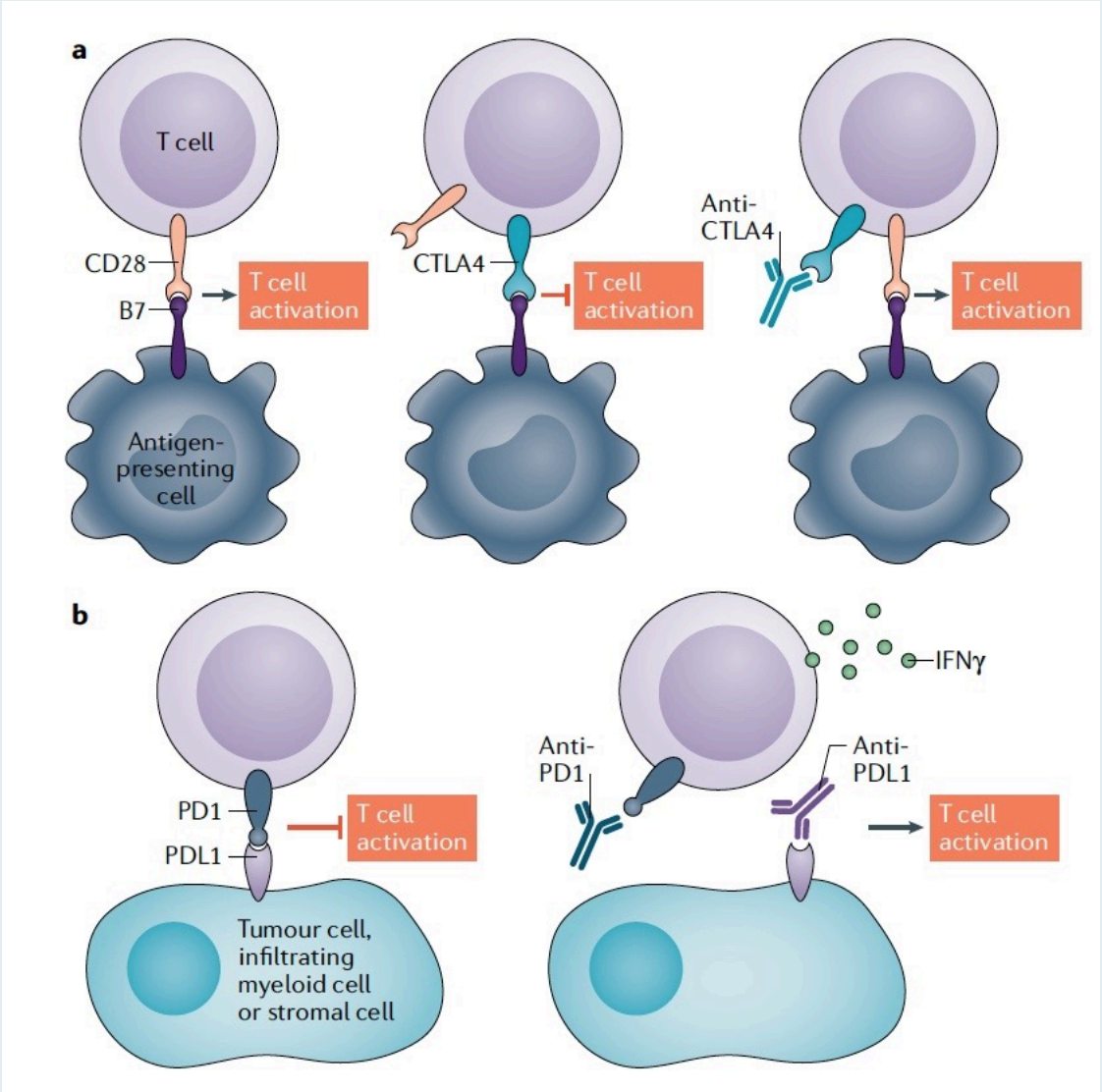
C. Marcela Díaz-Montero[1] ✉, *Brian I. Rini*[2] *and James H. Finke*[1] ✉

Inflammation and immunosuppressive networks in renal cell carcinoma



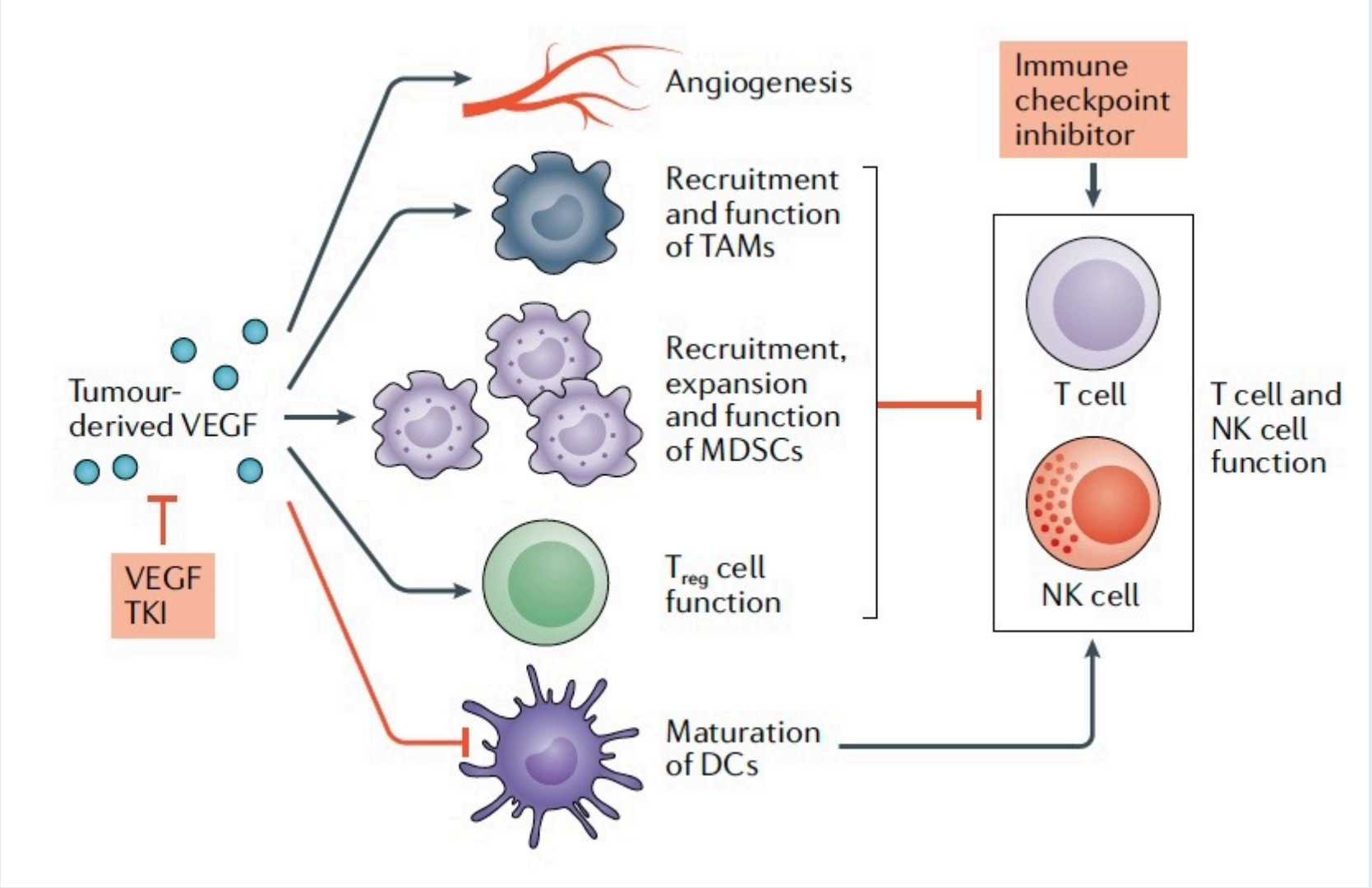
Diaz-Montero CM et al. *Nat Rev Nephrol* 2020;16(12):721-35.

Mechanisms of action of CTl4 blockade and pD1 blockade



Diaz-Montero CM et al. *Nat Rev Nephrol* 2020;16(12):721-35.

Rationale for combining anti-VegF therapy with immune checkpoint inhibition



Diaz-Montero CM et al. *Nat Rev Nephrol* 2020;16(12):721-35.

Cancer Treatment Reviews 84 (2020) 101966

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

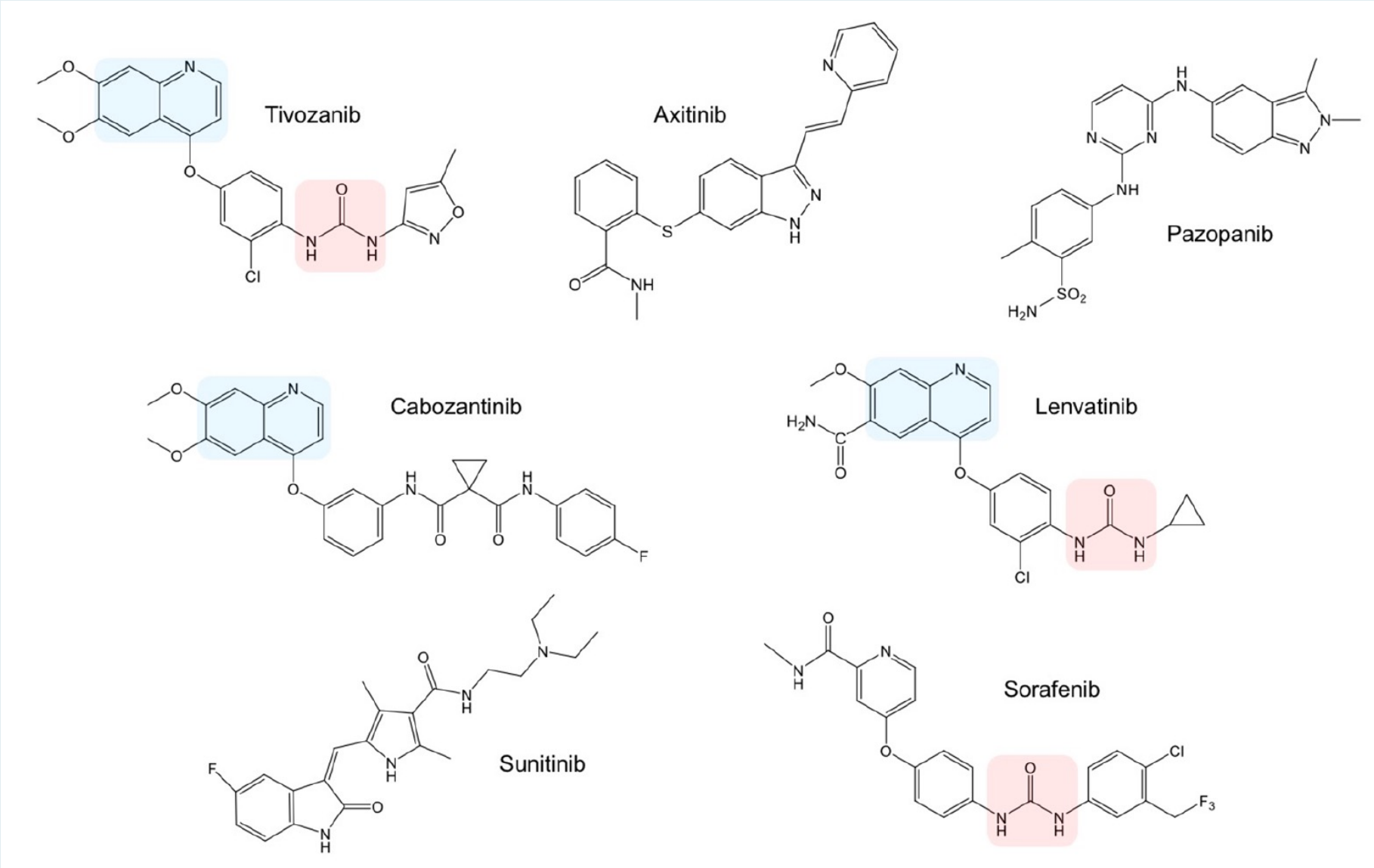
Anti-tumour Treatment

Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs

Stefano Fogli[a], Camillo Porta[b], Marzia Del Re[a], Stefania Crucitta[a], Giulia Gianfilippo[a], Romano Danesi[a,*], Brian I. Rini[c], Manuela Schmidinger[d]

[a] *Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[b] *Department of Internal Medicine, University of Pavia and Division of Translational Oncology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy*
[c] *Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA*
[d] *Clinical Division of Oncology, Department of Medicine I and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*

Chemical Structure of VEGF Tyrosine Kinase Inhibitors



Urea and quinoline moieties are highlighted in blue and red, respectively.

Fogli S et al. *Cancer Treat Rev* 2020;84:101966.

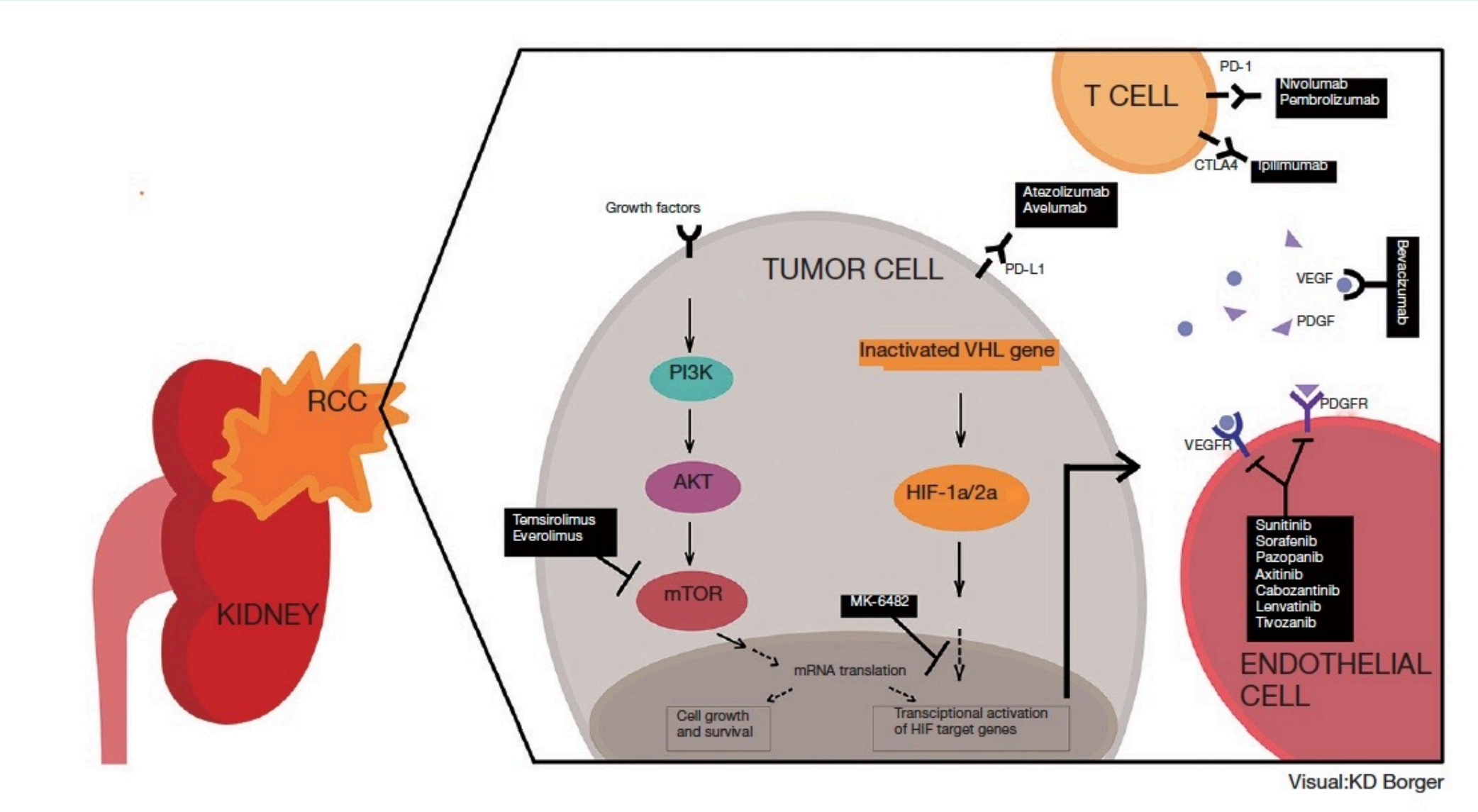
Ann Transl Med 2021;9(2):97

Editorial Commentary

Renal cell carcinoma with non-clear cell histology or sarcomatoid differentiation: recent insight in an unmet clinical need

Frede Donskov

Systemic Treatment Options in Metastatic Renal Cell Carcinoma



Donskov F. *Ann Transl Med* 2021;9(2):97.

Original study

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

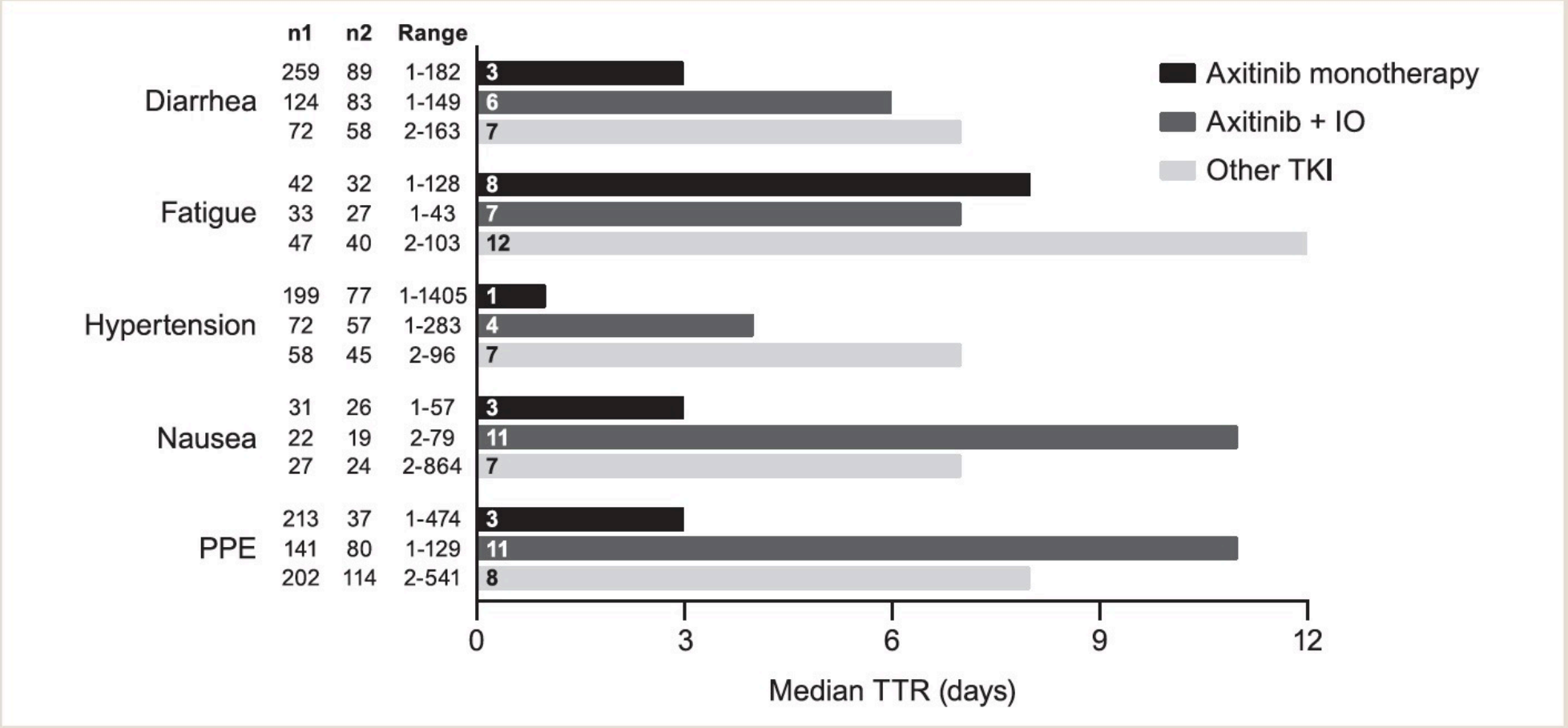
Brian I. Rini,[1] Michael B. Atkins,[2] Toni K. Choueiri,[3] Despina Thomaidou,[4] Brad Rosbrook,[5] Maghull Thakur,[6] Thomas E. Hutson[7]

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

Rini BI et al. *Clin Genitourin Cancer* 2021;[Online ahead of print].

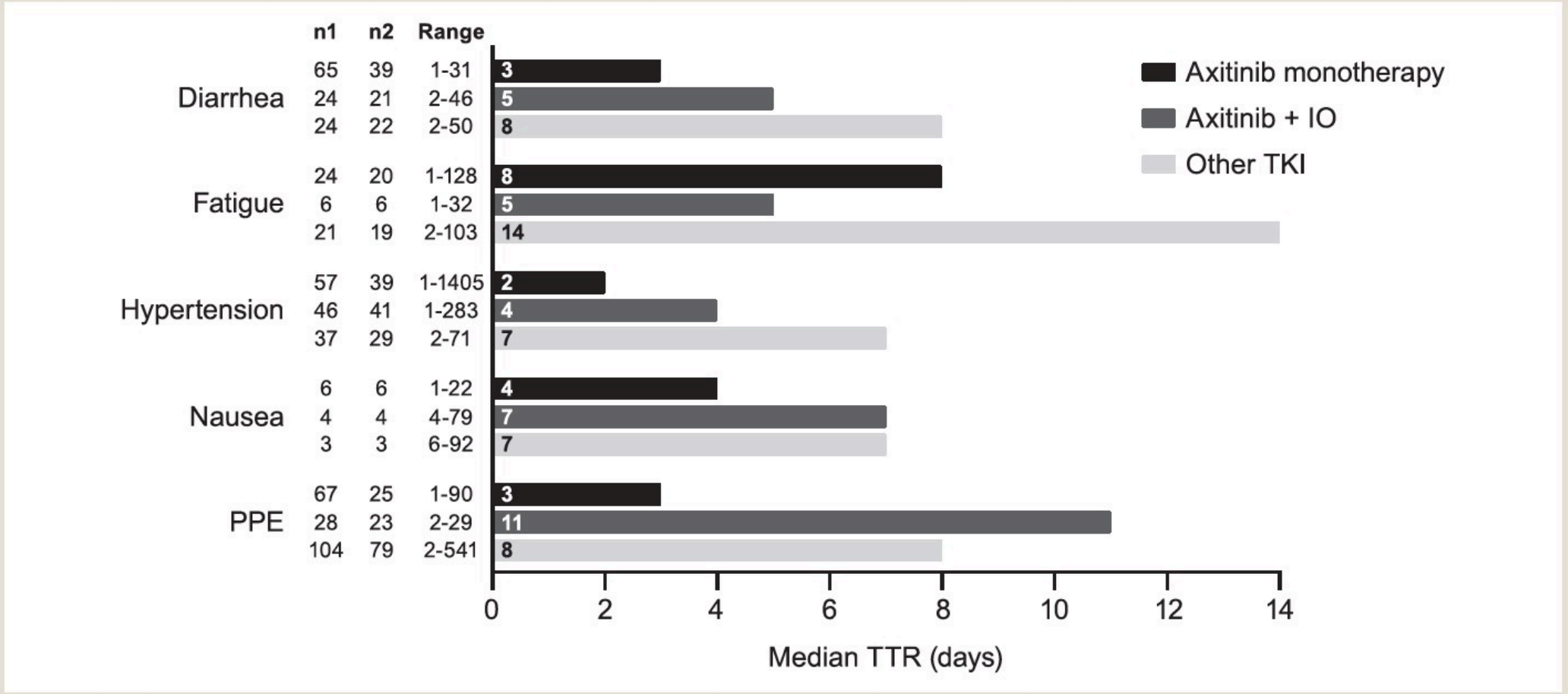
RTP RESEARCH TO PRACTICE

Figure 1 Time to resolution of any grade adverse events after temporary interruption or discontinuation of treatment by treatment cohort. Data values on the columns are the median TTR in days for each pooled treatment cohort for each AE. n1 is the number of events that resolved and n2 is the number of patients
Abbreviations: AE = adverse event; IO = immuno-oncology; PPE = palmar-plantar erythrodysesthesia syndrome; TKI = tyrosine kinase inhibitor; TTR = time to resolution



Rini BI et al. *Clin Genitourin Cancer* 2021;[Online ahead of print].

Figure 2 Time to resolution of grade ≥3 adverse events after temporary interruption or discontinuation of treatment by treatment cohort. Data values on the columns are the median TTR in days for each pooled treatment cohort for each AE. n1 is the number of events that resolved and n2 is the number of patients
Abbreviations: AE = adverse event; IO = immuno-oncology; PPE = palmar-plantar erythrodysesthesia syndrome; TKI = tyrosine kinase inhibitor; TTR = time to resolution



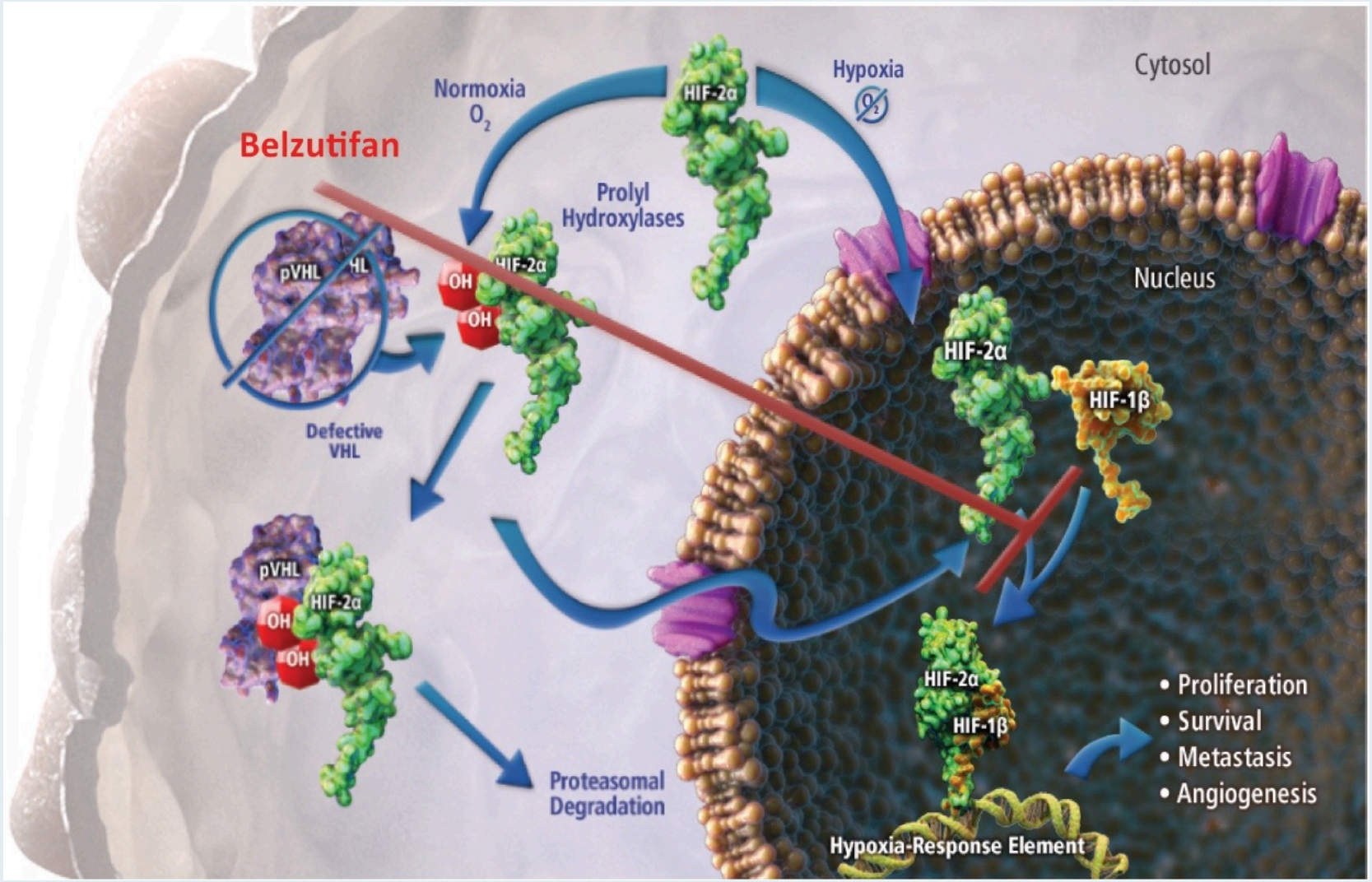
Rini BI et al. *Clin Genitourin Cancer* 2021;[Online ahead of print].

MK-6482, a Hypoxia-Inducible Factor 2α Inhibitor (HIF-2α), versus Everolimus in Heavily Pretreated, Immune Checkpoint–Inhibitor-Resistant, Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Phase III Study

Choueiri T et al.

Genitourinary Cancers Symposium 2021;Abstract TPS368.

The Role of Belzutifan in Inhibiting the HIF-2alpha Pathway



Choueiri T et al. Genitourinary Cancers Symposium 2021;Abstract TPS368.

Ged *et al. BMC Urology* (2020) 20:84
https://doi.org/10.1186/s12894-020-00647-w

BMC Urology

RESEARCH ARTICLE Open Access

Systemic therapy for advanced clear cell renal cell carcinoma after discontinuation of immune-oncology and VEGF targeted therapy combinations

Yasser Ged[1†], Ruby Gupta[2†], Cihan Duzgol[3†], Andrea Knezevic[4], Natalie Shapnik[1], Ritesh Kotecha[1], Martin H. Voss[1], Darren R. Feldman[1], Oguz Akin[1], Sujata Patil[4], Robert J. Motzer[1], Brian I. Rini[2†] and Chung-Han Lee[1*]

The Effect of Antibiotic Use on Immune-Checkpoint Inhibitor Efficacy in Patients with Advanced Urothelial Carcinoma

Khan M et al.

ASCO 2020;Abstract e17116.

A Phase 1b/2 Umbrella Study of Investigational Immune and targeted Combination Therapies as First-Line Therapy for Patients with Advanced Renal Cell Carcinoma (RCC)

Plimack E et al.

ASCO 2021;Abstract TPS4594.

Eur Urol 2021;79(5):665-73.

European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Nirmish Singla on pp. 674–675 of this issue

Efficacy and Safety of Atezolizumab Plus Bevacizumab Following Disease Progression on Atezolizumab or Sunitinib Monotherapy in Patients with Metastatic Renal Cell Carcinoma in IMmotion150: A Randomized Phase 2 Clinical Trial

Thomas Powles[a,], Michael B. Atkins[b], Bernard Escudier[c], Robert J. Motzer[d], Brian I. Rini[e], Lawrence Fong[f], Richard W. Joseph[g], Sumanta K. Pal[h], Mario Sznol[i], John Hainsworth[j], Walter M. Stadler[k], Thomas E. Hutson[l], Alain Ravaud[m], Sergio Bracarda[n], Cristina Suarez[o], Toni K. Choueiri[p], James Reeves[q], Allen Cohn[r], Beiying Ding[s], Ning Leng[s], Kenji Hashimoto[t], Mahrukh Huseni[s], Christina Schiff[s], David F. McDermott[u]*

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."

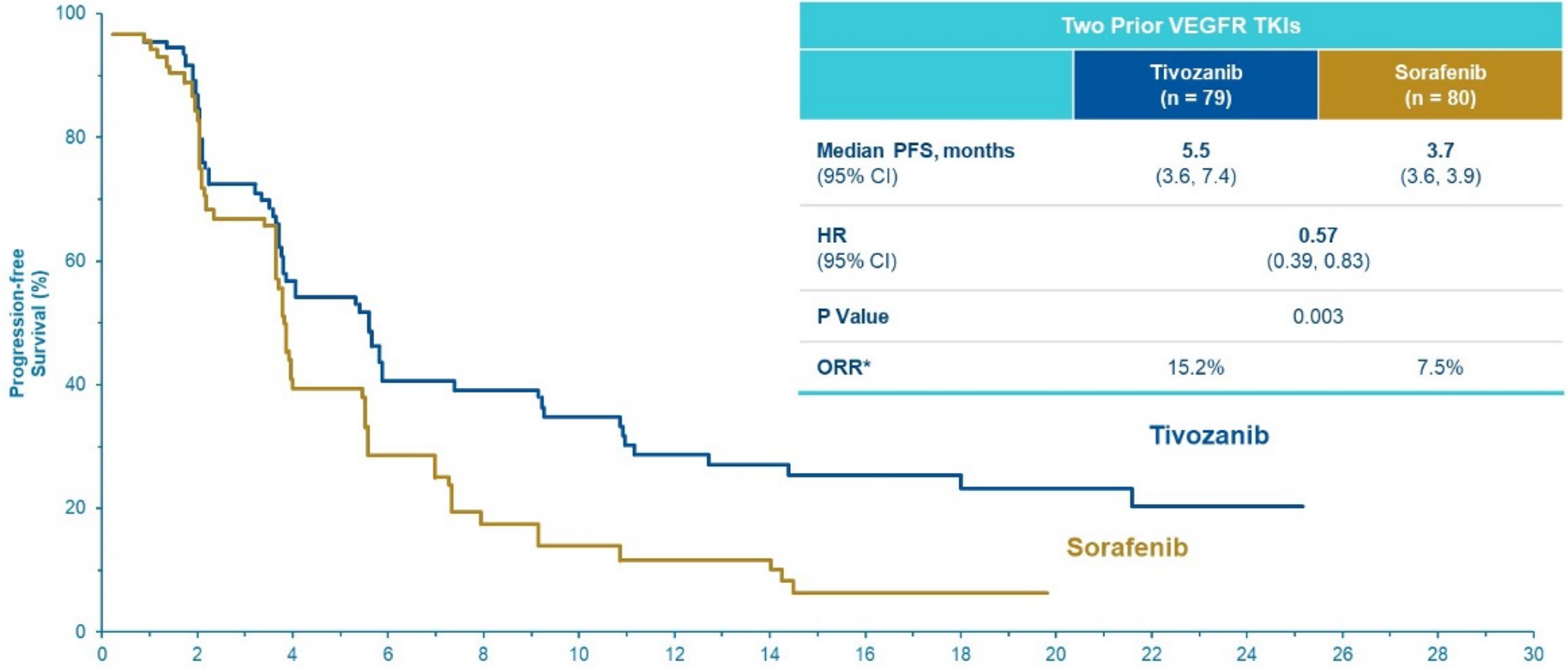
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma

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.

Association of Baseline Neutrophil-to-eosinophil Ratio (NER) and Neutrophil-to-lymphocyte Ratio (NLR) with Response to Combination Immunotherapy (IO) with Ipilimumab plus Nivolumab (ipi/nivo) in Patients with Metastatic Renal Cell Carcinoma (mRCC)

Tucker MD et al.

ASCO 2021;Abstract 4563.

Meet The Professor with Dr Rini

MODULE 1: Cases from General Medical Oncology Practices

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- Dr Oh: A 65-year-old woman with metastatic chromophobe RCC
- Dr Plimack: An 80-year-old woman with metastatic ccRCC treated with pazopanib
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Open access Original research

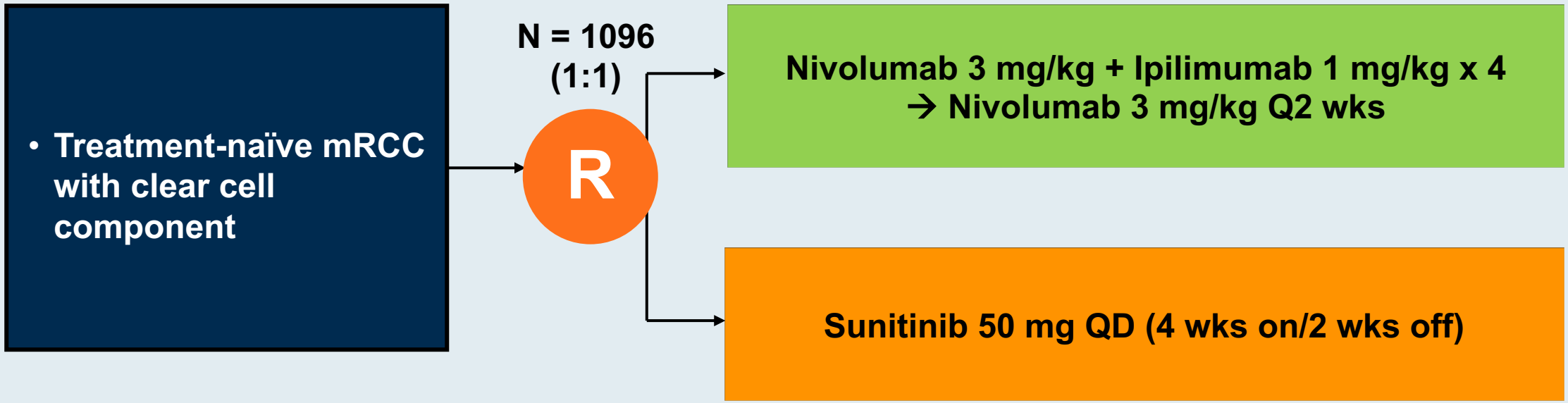
ESMO Open
Cancer Horizons

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 Phase III Schema



Co-Primary Endpoints
Objective response rate (ORR),
Progression-free survival (PFS),
Overall survival in intermediate- and poor-risk patients

Escudier B et al. ESMO 2017;Abstract LBA5; Albiges L et al. *ESMO Open* 2020;5(6):e001079.

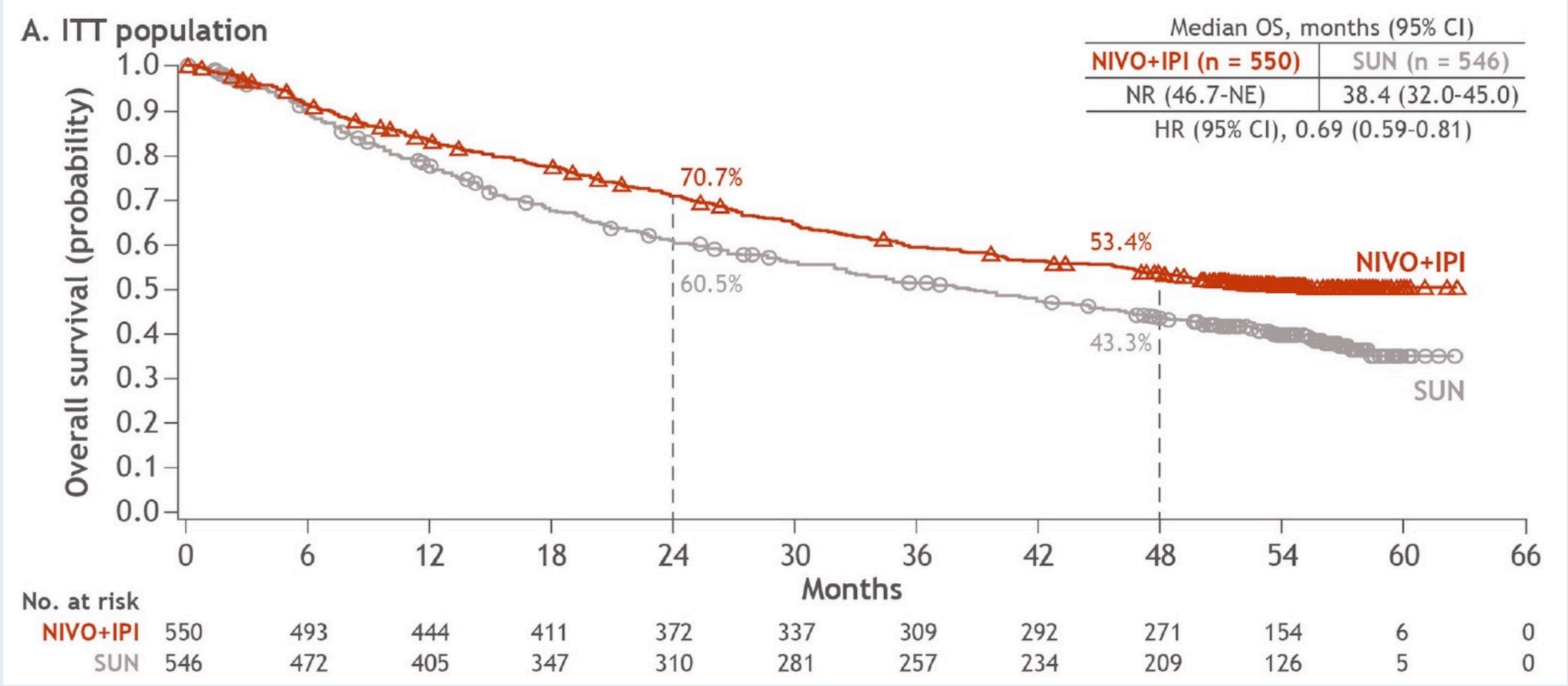
CheckMate 214: Overall Response and Best Response Rate per IRRC at 4 Years, Minimum Follow-Up in ITT

	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.

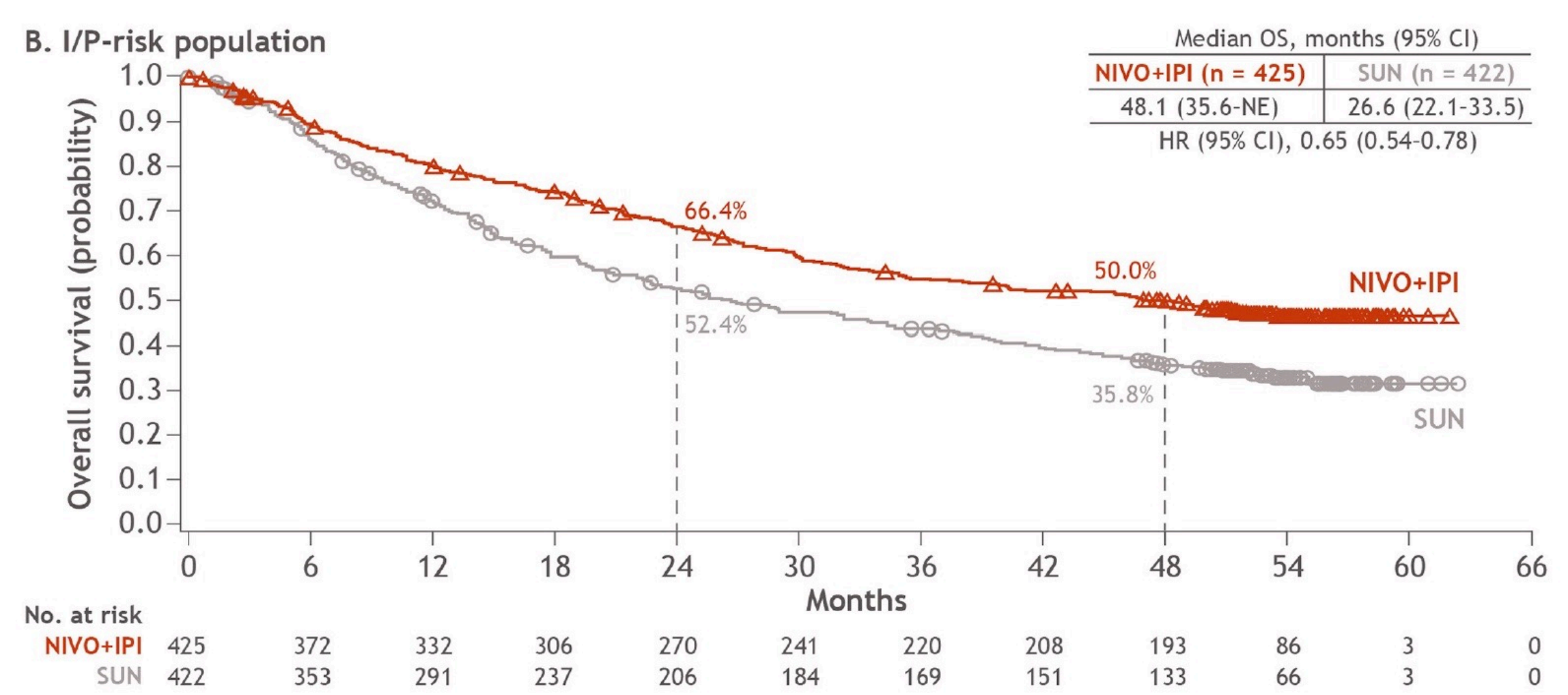
RTP RESEARCH TO PRACTICE

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.

Pembrolizumab (pembro) plus Axitinib (axi) versus Sunitinib as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from 42-Month Follow-Up of KEYNOTE-426

Rini BI et al.

ASCO 2021;Abstract 4500.

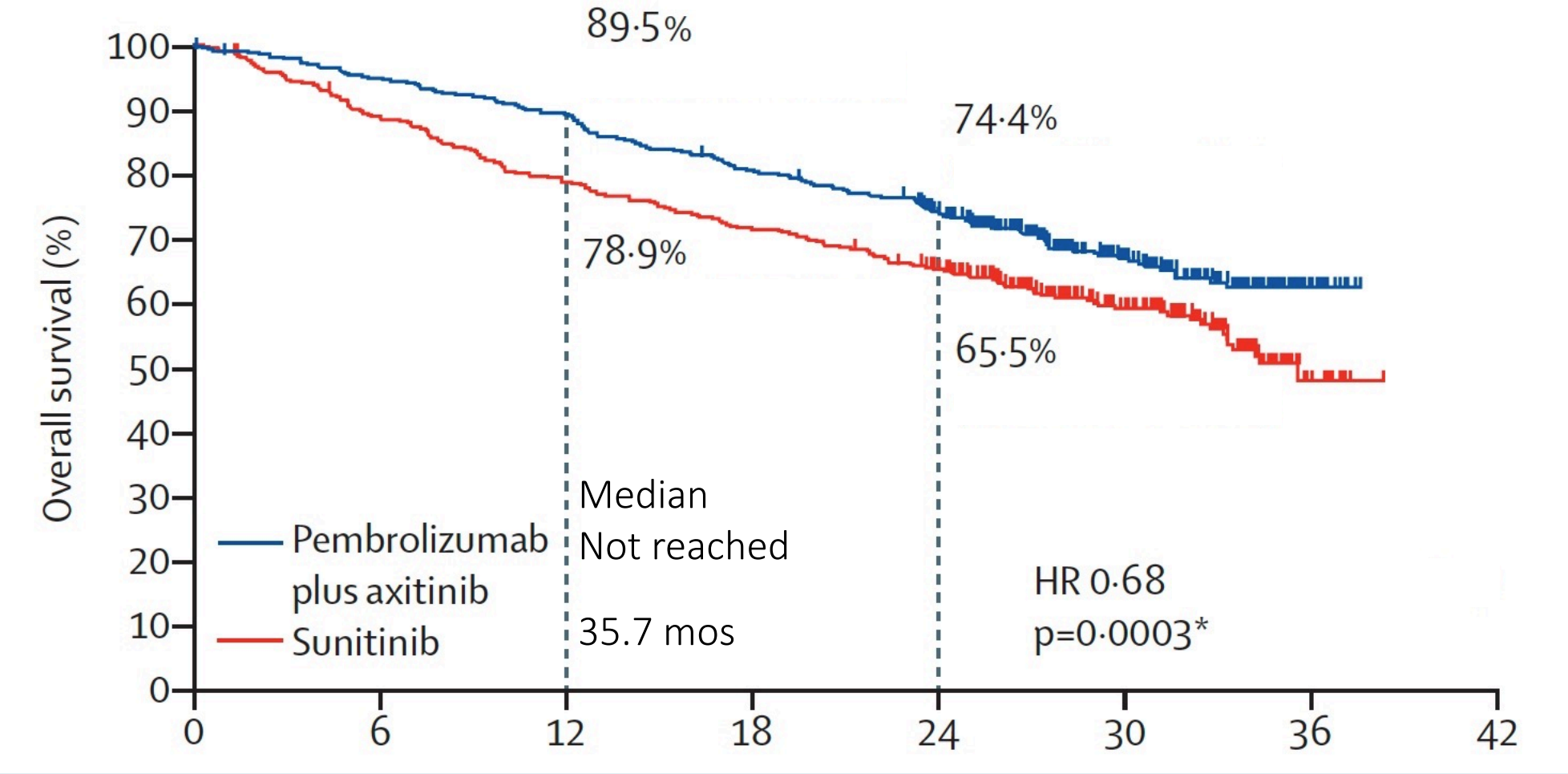
Monday, June 7, 2021, 8:00-11:00 AM EDT

Lancet Oncol 2020;21:1563-73

Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial

Thomas Powles, Elizabeth R Plimack, Denis Soulières, Tom Waddell, Viktor Stus, Rustem Gafanov, Dmitry Nosov, Frédéric Pouliot, Bohuslav Melichar, Ihor Vynnychenko, Sergio J Azevedo, Delphine Borchiellini, Raymond S McDermott, Jens Bedke, Satoshi Tamada, Lina Yin, Mei Chen, L Rhoda Molife, Michael B Atkins, Brian I Rini

KEYNOTE-426: Overall Survival with Extended Follow-Up



Powles T et al. *Lancet Oncol* 2020;21:1563-73.

RTP RESEARCH TO PRACTICE

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

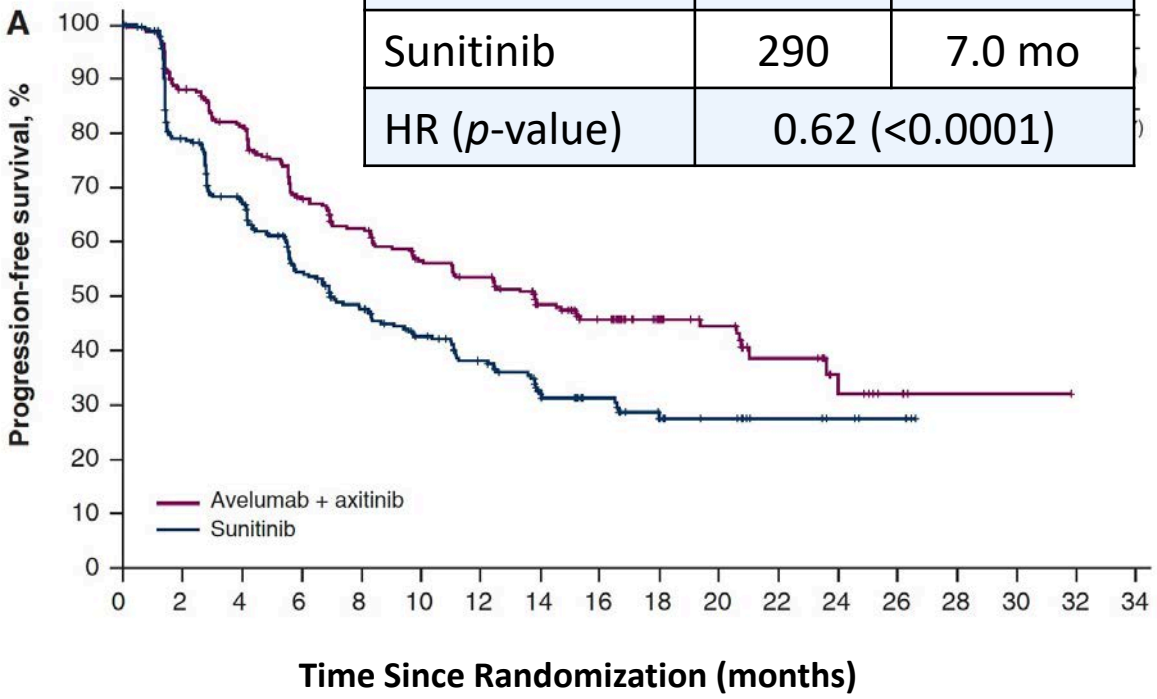
	PD-L1-Positive		Overall	
	Avelumab + Axitinib (n = 270)	Sunitinib (n = 290)	Avelumab + Axitinib (n = 442)	Sunitinib (n = 444)
Confirmed ORR	55.9%	27.2%	52.5%	27.3%
CR	5.6%	2.4%	3.8%	2.0%
PR	50.4%	24.8%	48.6%	25.2%
Stable disease	27.0%	41.4%	28.3%	43.7%
Progressive disease	11.5%	22.4%	12.4%	19.4%
Ongoing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

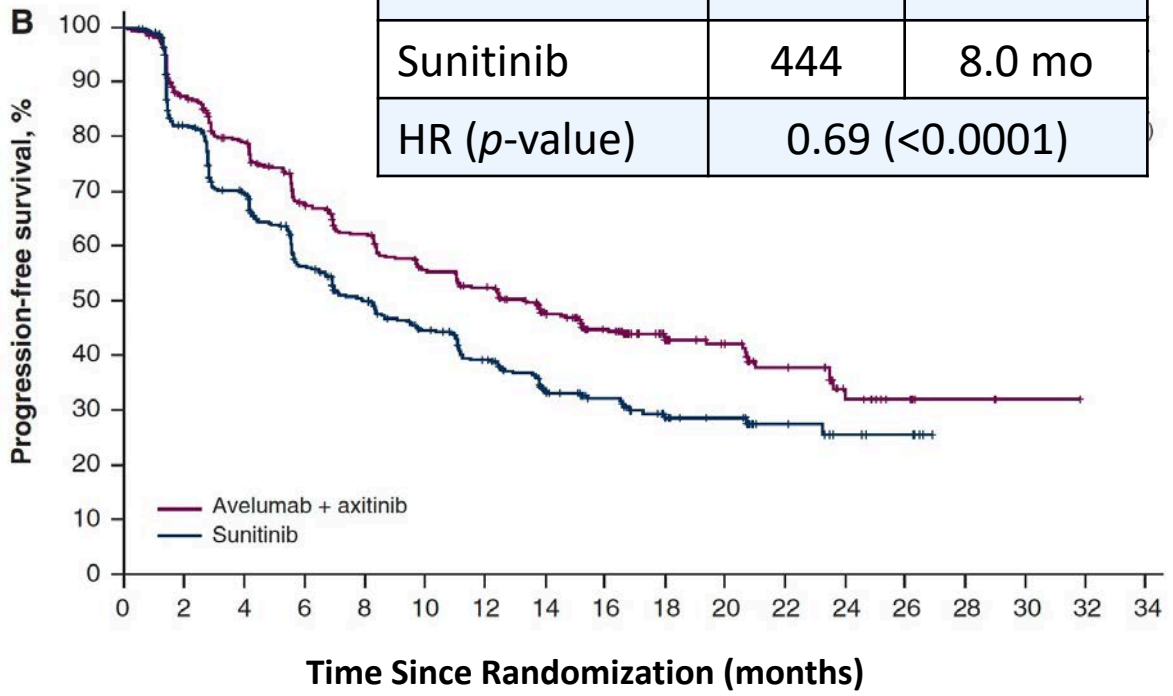
PD-L1 ≥ 1% Population

	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.

FDA Approves Nivolumab with Cabozantinib for Advanced RCC

Press Release: January 22, 2021

"On January 22, 2021, the Food and Drug Administration approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

Efficacy was evaluated in CHECKMATE-9ER (NCT03141177), a randomized, open-label trial in patients with previously untreated advanced RCC. Patients were randomized to receive either nivolumab 240 mg over 30 minutes every 2 weeks in combination with cabozantinib 40 mg orally once daily (n=323) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma

RTP RESEARCH TO PRACTICE

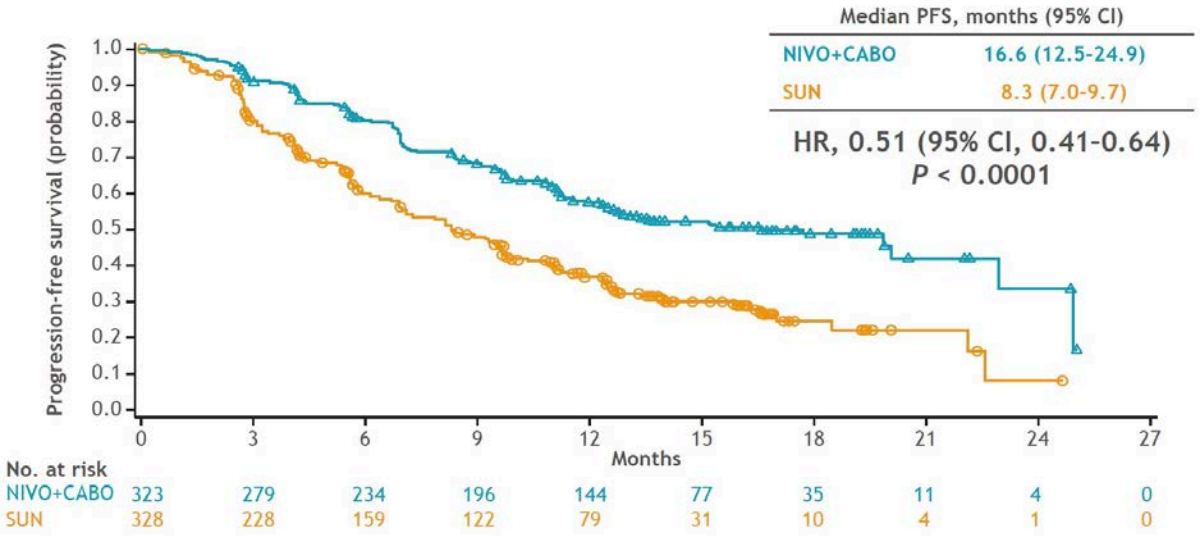
Nivolumab plus Cabozantinib versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma: First Results from the Randomized Phase 3 CheckMate 9ER Trial

Choueiri TK et al.

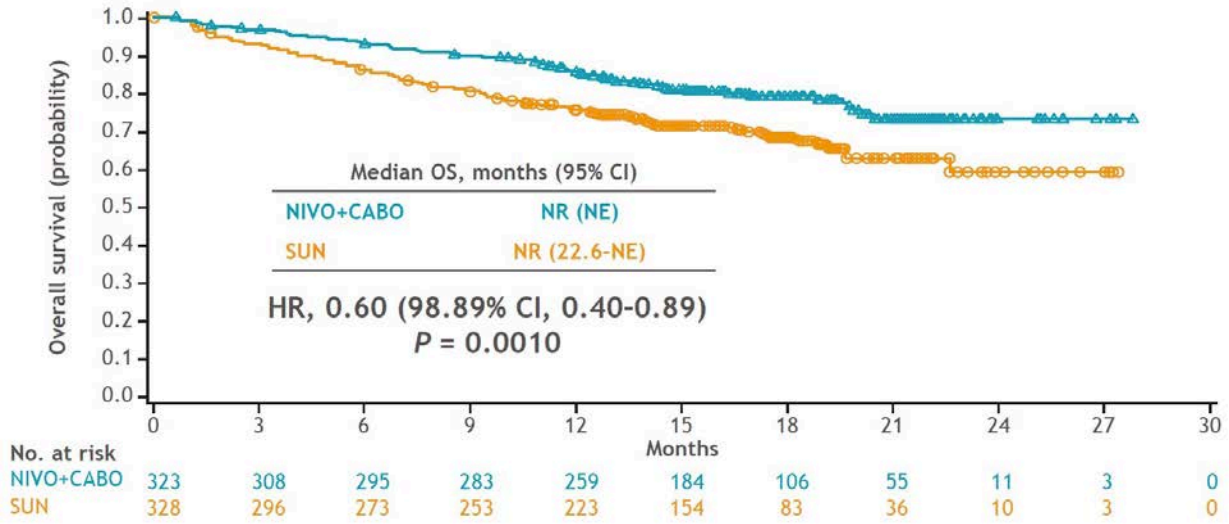
ESMO 2020;Abstract 696O.

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

Progression-free survival per BICR



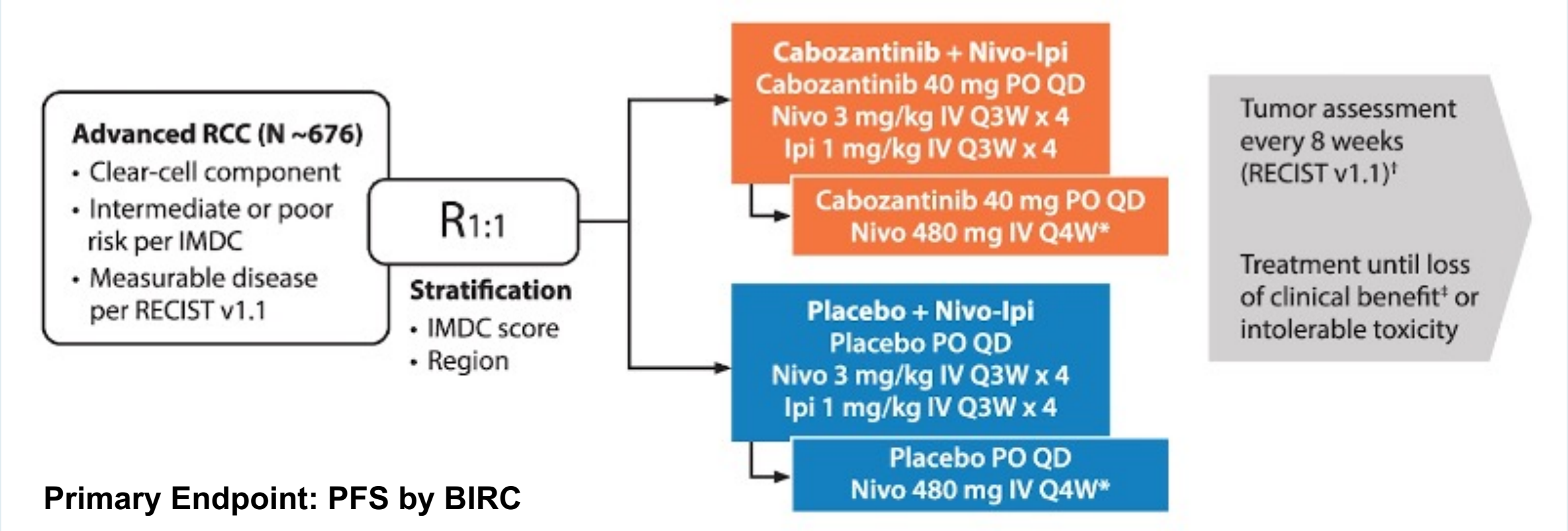
Overall survival



Choueiri TK et al. ESMO 2020;Abstract 696O.

RTP RESEARCH TO PRACTICE

COSMIC-313 Phase III Schema



Primary Endpoint: PFS by BIRC

https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-kidney-cancer/121877-asco-2020-cosmic-313-phase-iii-study-of-cabozantinib-in-combination-with-nivolumab-and-ipilimumab-in-patients-with-previously-untreated-advanced-renal-cell-carcinoma-of-intermediate-or-poor-risk.html

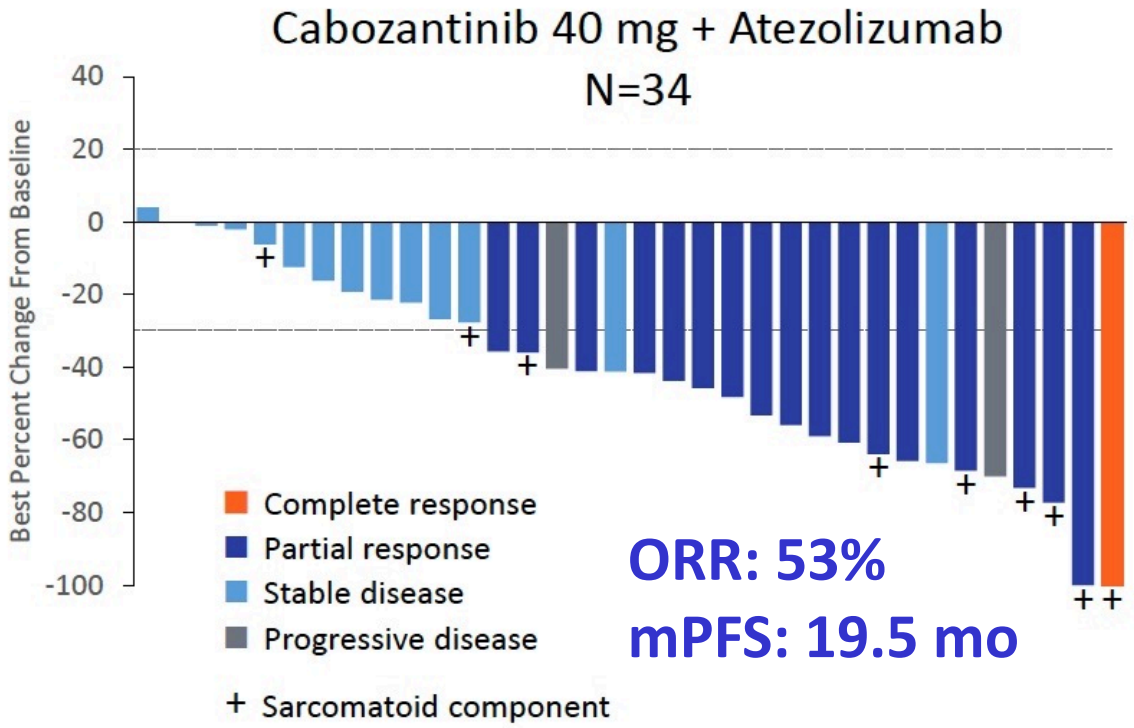
RTP RESEARCH TO PRACTICE

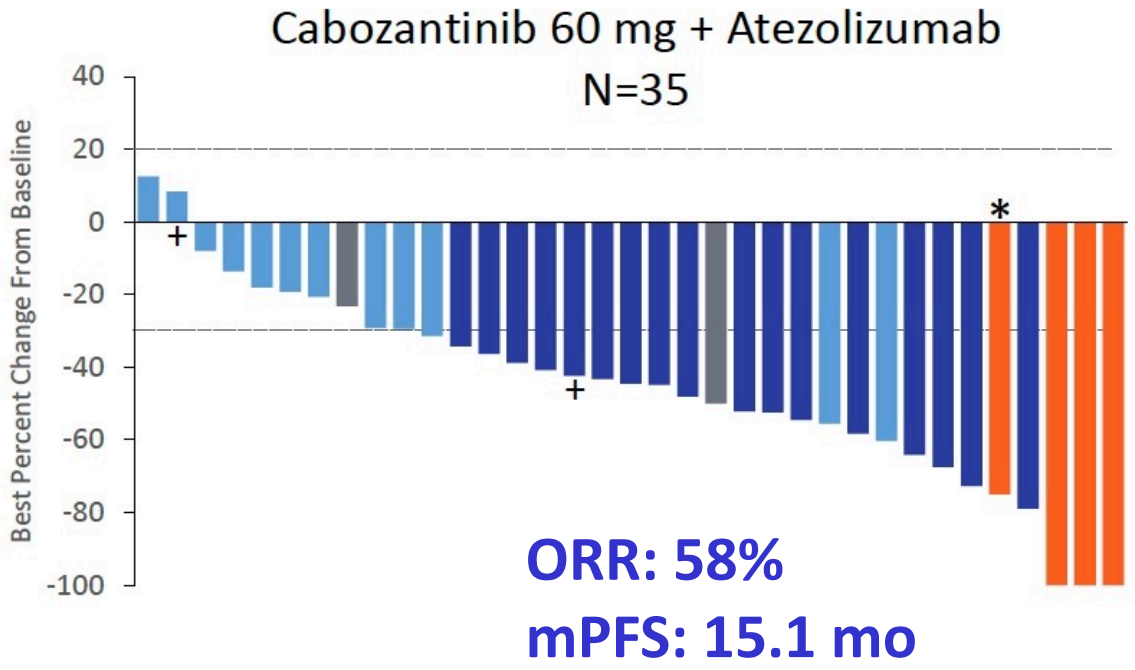
Cabozantinib (C) in Combination with Atezolizumab (A) as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from the COSMIC-021 Study

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

Health-Related Quality-of-Life (HRQoL) Analysis from the Phase 3 CLEAR Trial of Lenvatinib (LEN) plus Pembrolizumab (PEMBRO) or Everolimus (EVE) versus Sunitinib (SUN) for Patients (pts) with Advanced Renal Cell Carcinoma (aRCC)

Motzer RJ et al.

ASCO 2021;Abstract 4502.

Monday, June 7, 2021, 8:00-11:00 AM EDT

The NEW ENGLAND JOURNAL of MEDICINE

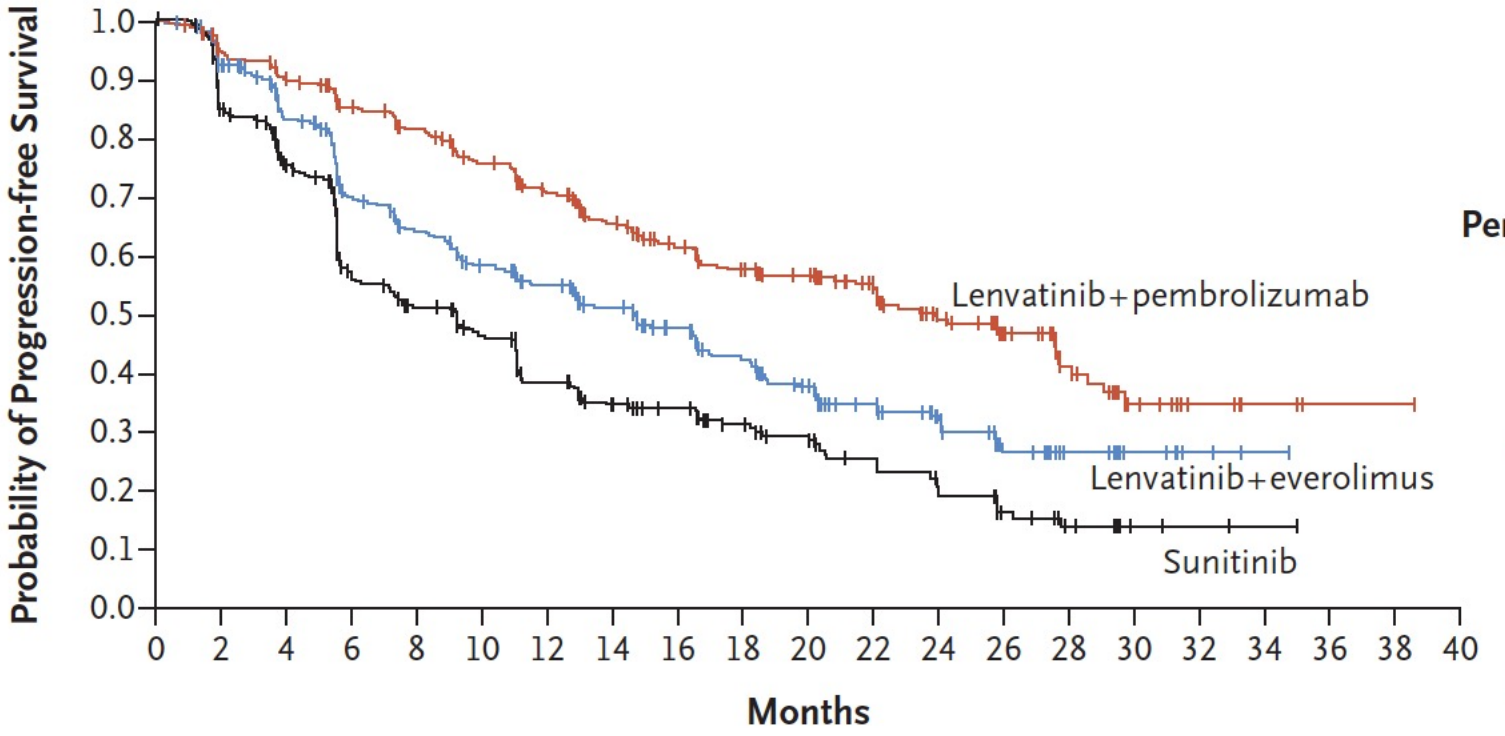
ORIGINAL ARTICLE

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)

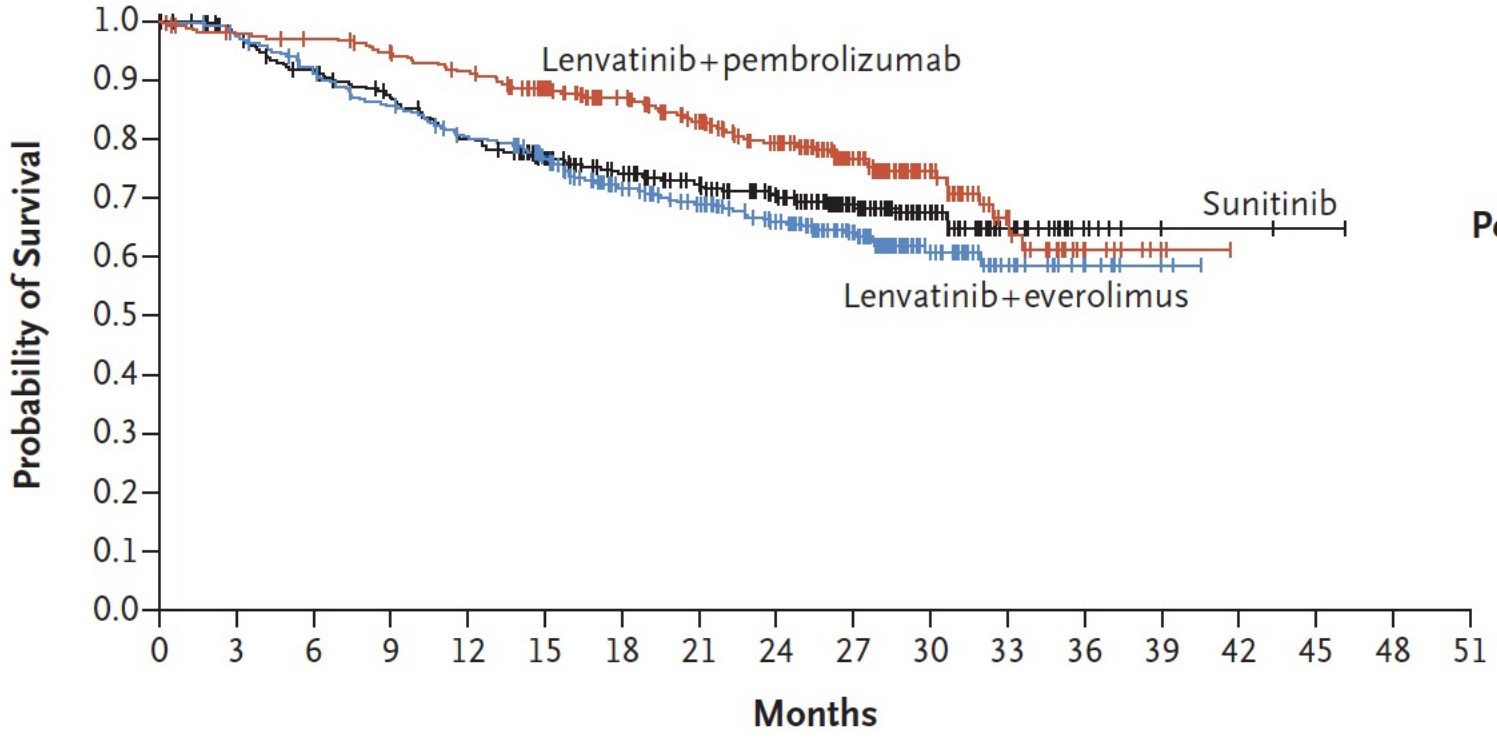
Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

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

CLEAR: Confirmed Tumor Responses

Measure	Lenvatinib plus Pembrolizumab (N = 355)	Lenvatinib plus Everolimus (N = 357)	Sunitinib (N = 357)
Objective response (95% CI) — %†	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Relative risk vs. sunitinib (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	Reference
Best overall response — no. (%)			
Complete response	57 (16.1)	35 (9.8)	15 (4.2)
Partial response	195 (54.9)	156 (43.7)	114 (31.9)
Stable disease	68 (19.2)	120 (33.6)	136 (38.1)
Progressive disease	19 (5.4)	26 (7.3)	50 (14.0)
Unknown or could not be evaluated‡	16 (4.5)	20 (5.6)	42 (11.8)
Median time to response (range) — mo	1.94 (1.41–18.50)	1.91 (1.41–14.36)	1.94 (1.61–16.62)
Median duration of response (95% CI) — mo	25.8 (22.1–27.9)	16.6 (14.6–20.6)	14.6 (9.4–16.7)

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

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

RTP RESEARCH TO PRACTICE

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

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;38:3088-94.

Salvage Ipilimumab/Nivolumab in mRCC After Prior ICI Therapy

Variable	No. (%)
No. of prior lines of systemic therapy	
1	9 (20)
2	12 (27)
3	8 (18)
4	6 (13)
> 4	10 (22)
Prior VEGF receptor inhibitor[a]	27 (60)
Prior immunotherapy	
Anti–PD-1[b]	34 (76)
Anti–PD-L1[b]	11 (24)
IL-2[c]	14 (31)
Best response to prior ICI	
PR	24 (53)
SD	12 (27)
PD	9 (20)

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

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

Gul A et al. *J Clin Oncol* 2020;38:3088-94.

RTP RESEARCH TO PRACTICE

A Pooled Analysis of the Efficacy and Safety of Cabozantinib Post Immunotherapy in Patients with Advanced Renal Cell Carcinoma

Oya M et al.

ASCO 2020;Abstract 5089.

Efficacy of Cabozantinib with or without Prior Immunotherapy

	Prior IO Group (N = 33)	No Prior IO Group (N = 332)
Objective response rate	21.2%	17.2%
Clinical benefit rate	75.8%	83.7%
Median PFS	Not reached	7.4 mo
6-months PFS	65.5%	58.3%
Median PFS	19.5 mo	21.9 mo
6-months OS	90.8%	90.6%

Oya M et al. ASCO 2020;Abstract 5089.

Phase II Trial of Lenvatinib (LEN) plus Pembrolizumab (PEMBRO) for Disease Progression After PD-1/PD-L1 Immune Checkpoint Inhibitor (ICI) in Metastatic Clear Cell Renal Cell Carcinoma (mccRCC)

Lee C-H et al.

ASCO 2020;Abstract 5008.

Efficacy of Lenvatinib/Pembrolizumab in Patients Previously Treated with Immunotherapy

	Anti-PD-1/PD-L1 (N = 104)	Anti-PD-1/PD-L1 and anti-VEGF (n = 68)	Nivolumab + Ipilimumab (n = 38)
ORR	55%	59%	47%
Median DOR	12 mo	9 mo	Not reached
Median PFS (irRECIST)	11.7 mo	Not reported	Not reported
OS at 12 months	77%	Not reported	Not reported

Lee C-H et al. ASCO 2020;Abstract 5008.

CANTATA: Primary Analysis of a Global, Randomized, Placebo (Pbo)-Controlled, Double-Blind Trial of Telaglenastat (CB-839) + Cabozantinib versus Pbo + Cabozantinib in Advanced/Metastatic Renal Cell Carcinoma (mRCC) Patients (pts) Who Progressed on Immune Checkpoint Inhibitor (ICI) or Anti-angiogenic Therapies

Tannir NM et al.

ASCO 2021;Abstract 4501.

Monday, June 7, 2021, 8:00-11:00 AM EDT

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

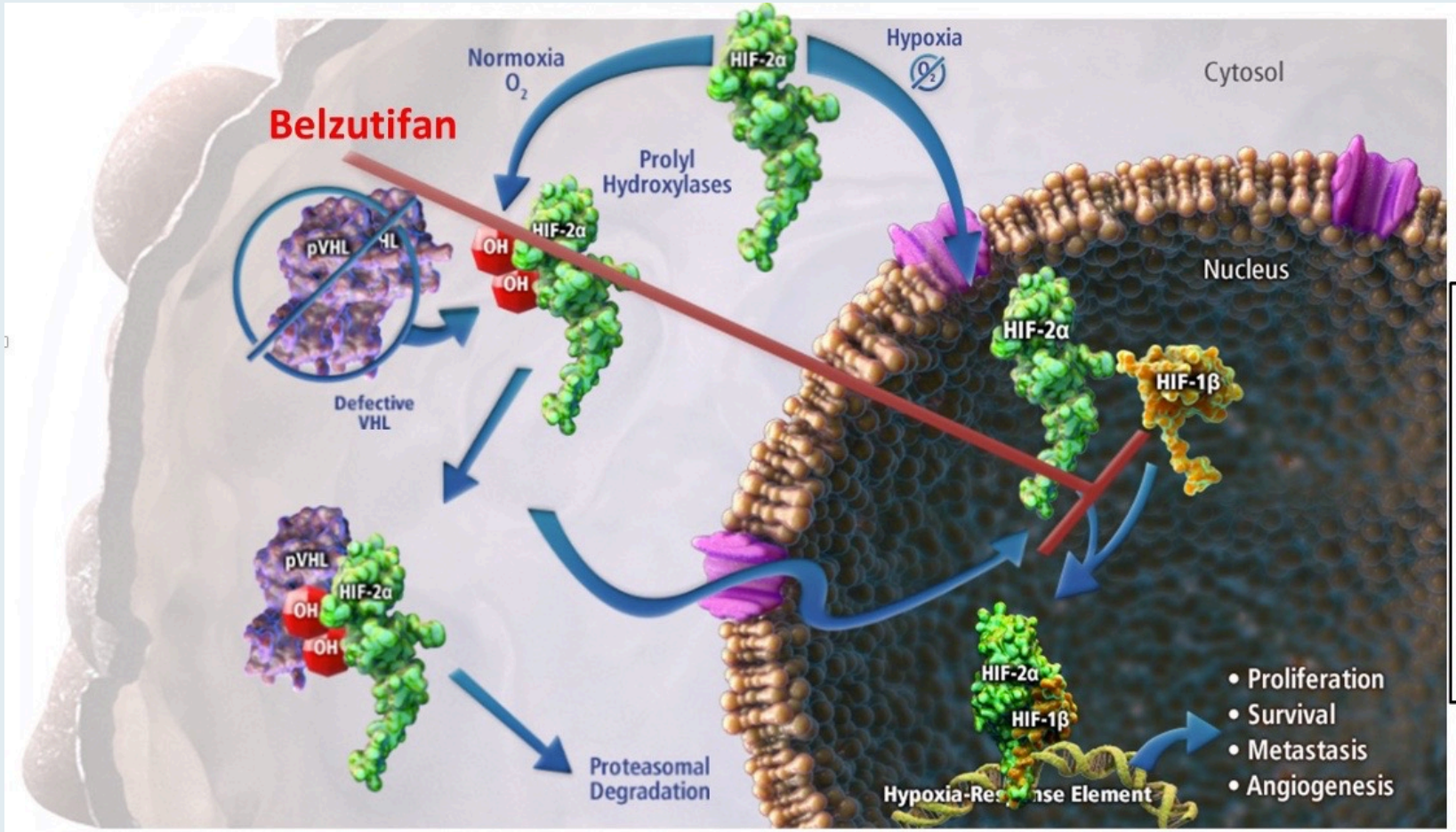
Genitourinary Cancers Symposium 2021;Abstract 273

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

pVHL Deficiency Results in HIF-2-alpha Activation

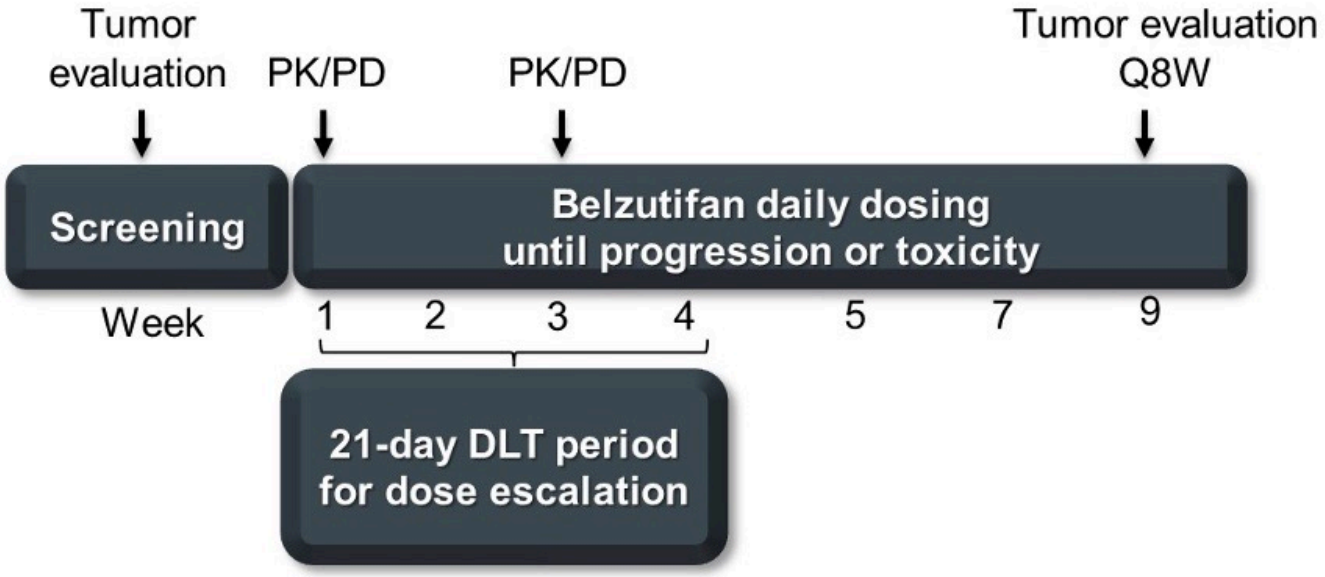


- 90% of patients with sporadic ccRCC have defective pVHL function[1]
- Loss of pVHL function results in constitutive activation of HIF-2α[2]
- Belzutifan is a potent, selective, small molecule HIF-2α inhibitor

1. Linehan WM, Rickets CJ. *Nat Rev Urol.* 2019;16:539-552. 2. Couvé S et al. *Cancer Res.* 2014;74:6554-6564.

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

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

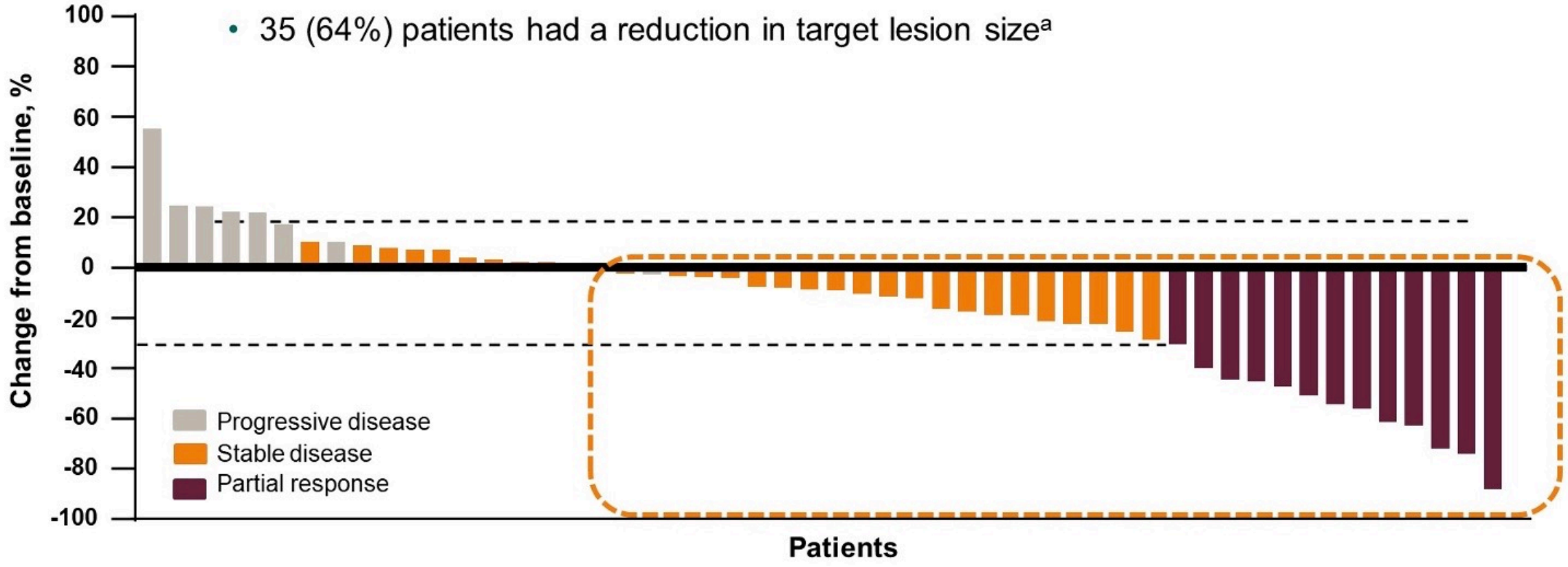
Bauer TM et al. Genitourinary Cancers Symposium 2021;Abstract 273.

Best Confirmed Objective Response (Investigator Assessment in the 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)



[a]3 patients were nonevaluable. Data cutoff: June 1, 2020.

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

Summary of Adverse Events

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.

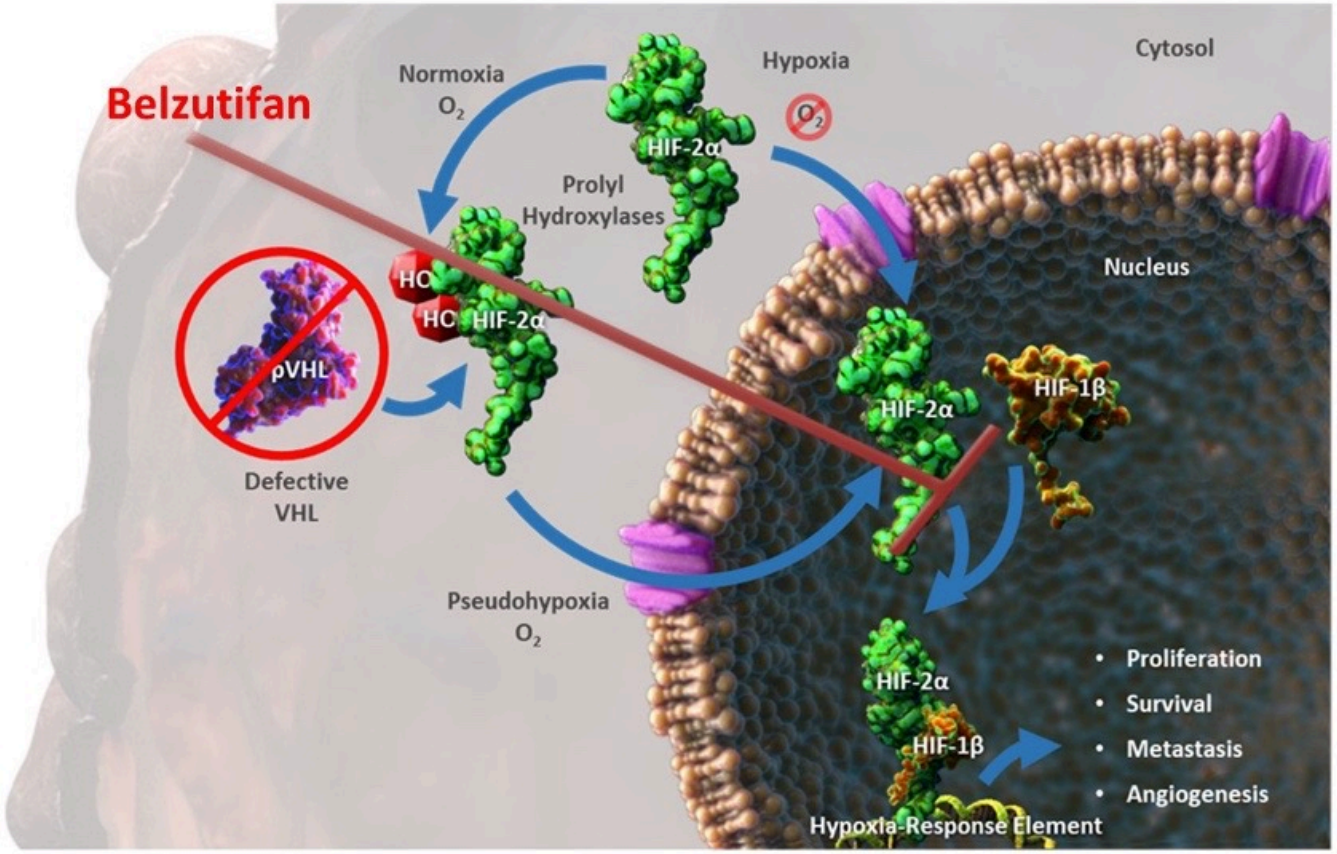
Genitourinary Cancers Symposium 2021;Abstract 272.

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

Role of HIF-2-VEGF Axis in RCC

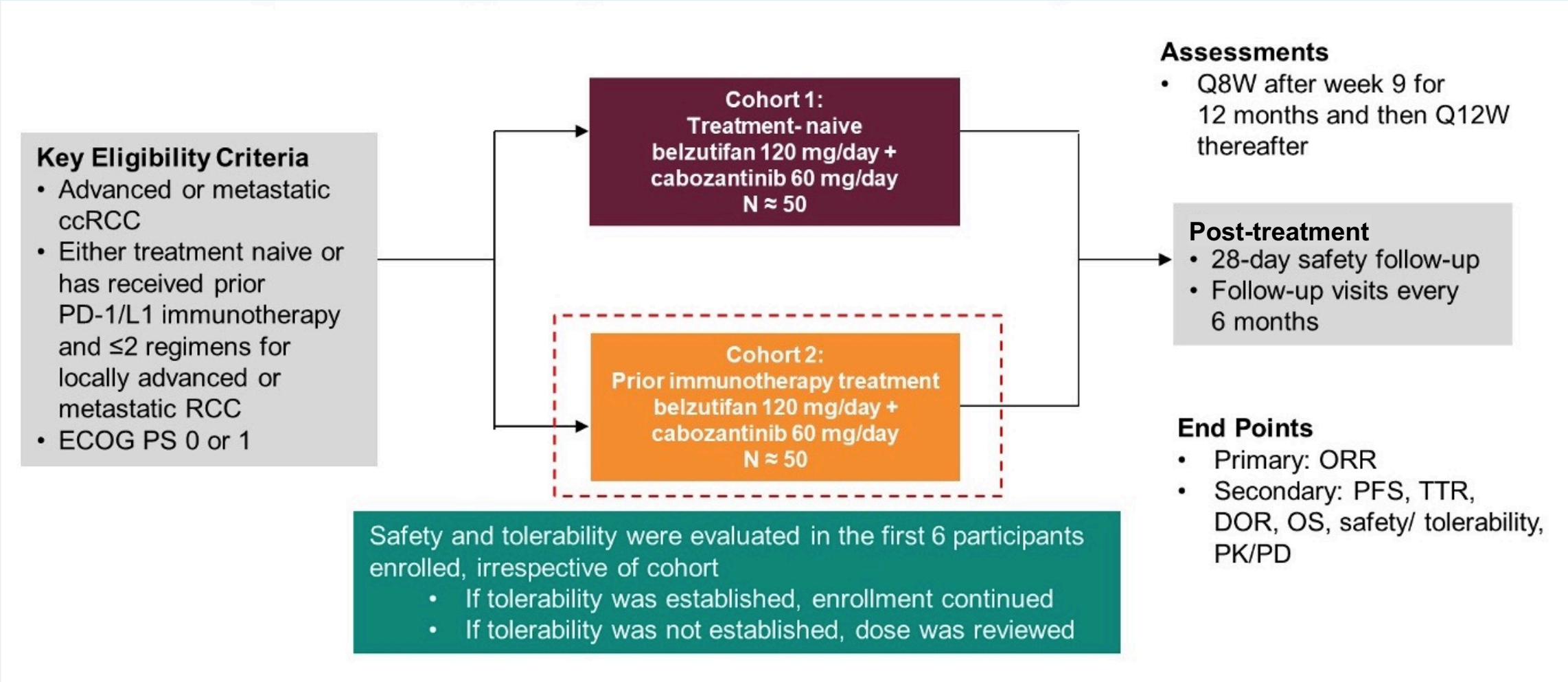


- 90% of patients with sporadic ccRCC have defective pVHL[1,2]
- HIF-2α is involved in the activation of genes associated with angiogenesis (*VEGFA, PDGFB*), proliferation (*CDK*), metabolism (*GLUT1*), and growth (*TGFα*)[3]
- Belzutifan is a potent, selective, small molecule HIF-2α inhibitor
- Cabozantinib, a VEGF, AXL, and MET5 inhibitor, is approved as monotherapy for advanced ccRCC[4-6]
- Targeting both the HIF-2α and the VEGFA pathways may improve outcomes for patients with advanced ccRCC

1. Shen C, Kaelin WG Jr. *Semin Cancer Biol*. 2013;23:18-25. 2. Sato Y et al. *Nat Genet*. 2013;45:860-867. 3. Choueiri TK, Kaelin WG Jr. *Nat Med*. 2020;26:1519-1530.
4. Choueiri TK et al. *N Engl J Med*. 2015;373:1814-1823. 5. Choueiri TK et al. *Eur J Cancer*. 2018;94:115-125. 6. Choueiri TK et al. *Lancet Oncol*. 2016;17:917-927.

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

Study Design



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Best Confirmed Objective Response

Efficacy Parameter, n (%) [95%CI]	Efficacy Analysis Set N = 41
Objective response rate (CR + PR)	9 (22) [11-38]
Disease control rate (CR + PR + SD)	37 (90) [77-97]
Best response	
Complete response	0 (0)
Partial response	9 (22)
Stable disease	28 (68)
Unconfirmed partial response[a]	5 (12)
Progressive disease	3 (7)
Not available	1 (2)

[a]Documented at one time point and to be confirmed at a subsequent time point.
Data cutoff: October 15, 2020.

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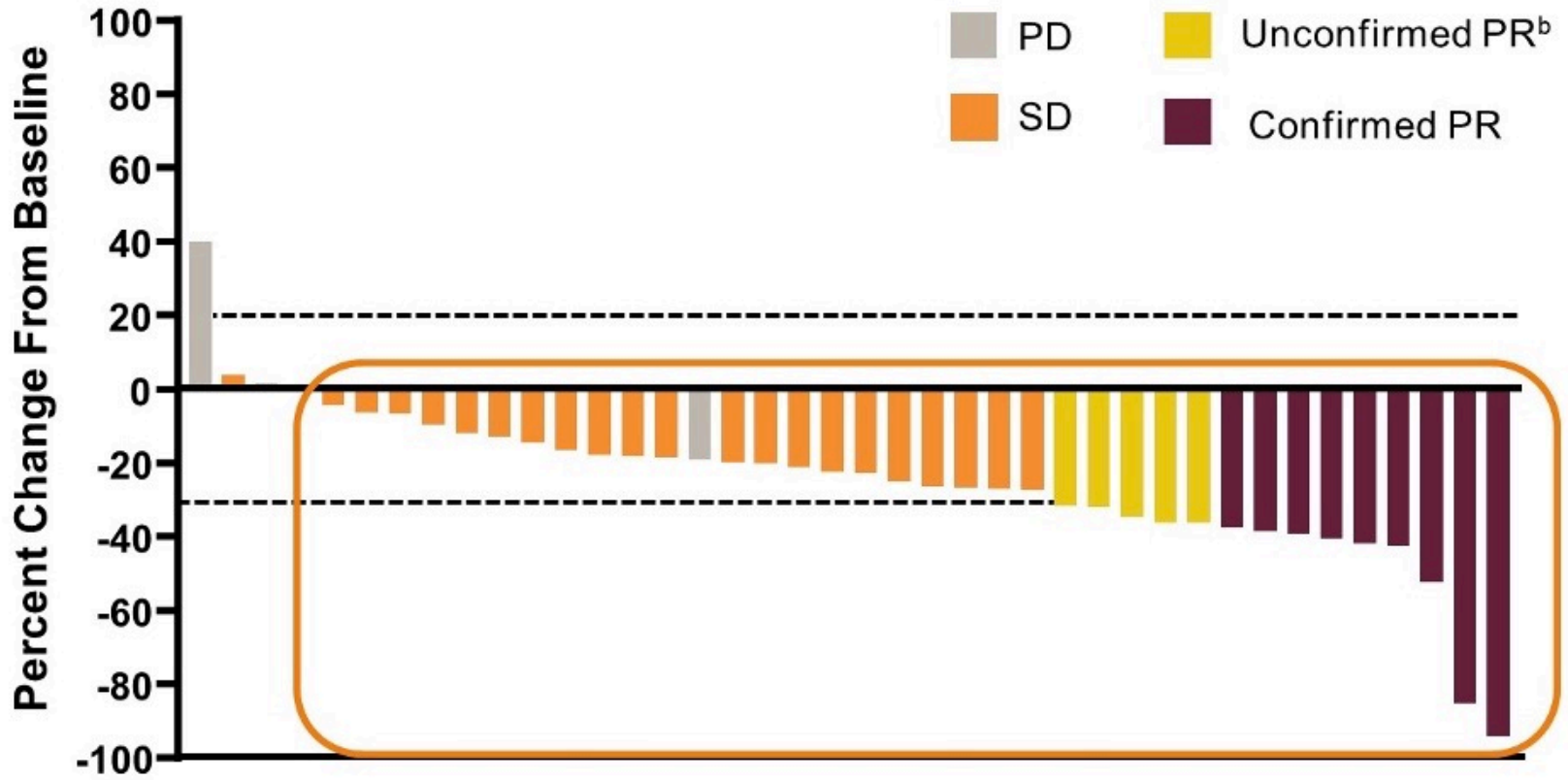
Best Tumor Change from Baseline

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



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

RTP RESEARCH TO PRACTICE

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)

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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)

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, May 20, 2021
5:00 PM – 6:00 PM ET

Faculty

Jennifer Woyach, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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