

# Investigator Perspectives on Available Research Findings and Challenging Questions in Renal Cell Carcinoma

*A CME-Accredited Virtual Event Held in Conjunction  
with the 2023 ASCO® Annual Meeting*

**Tuesday, June 6, 2023**

**7:00 AM – 8:00 AM**

## **Faculty**

**David F McDermott, MD**

**Sumanta Kumar Pal, MD**

## **Moderator**

**Neil Love, MD**

# Faculty



**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



**Moderator**

**Neil Love, MD**

Research To Practice  
Miami, Florida



**Sumanta Kumar Pal, MD**

Professor, Department of Medical Oncology  
and Therapeutics Research  
City of Hope  
Duarte, California

Friday  
June 2

**Gastroesophageal Cancers**

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

**Non-Small Cell Lung Cancer**

6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)

Saturday  
June 3

**Hepatobiliary Cancers**

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

**Prostate Cancer**

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Sunday  
June 4

**Ovarian Cancer**

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

**Lymphoma, Chronic Lymphocytic  
Leukemia and Multiple Myeloma**

7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Monday  
June 5

**Urothelial Bladder Cancer**

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

**Breast Cancer**

7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Tuesday  
June 6

**Renal Cell Carcinoma (Webinar)**

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

# Exciting CME Events in Chicago You Do Not Want to Miss

*A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO Annual Meeting*

## Gastroesophageal Cancers

**Friday, June 2, 2023**

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

### Faculty

Yelena Y Janjigian, MD

Manish A Shah, MD

Harry H Yoon, MD, MHS

*Additional faculty to be announced*

## Hepatobiliary Cancers

**Saturday, June 3, 2023**

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

### Faculty

Anthony El-Khoueiry, MD

Robin K (Katie) Kelley, MD

Professor Arndt Vogel, MD

## Non-Small Cell Lung Cancer

**Friday, June 2, 2023**

6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)

### Faculty

Edward B Garon, MD, MS

John V Heymach, MD, PhD

Ticiana Leal, MD

Helena Yu, MD

*Additional faculty to be announced*

## Prostate Cancer

**Saturday, June 3, 2023**

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

### Faculty

Emmanuel S Antonarakis, MD

Prof Karim Fizazi, MD, PhD

Rana R McKay, MD

Alicia K Morgans, MD, MPH

A Oliver Sartor, MD

# Exciting CME Events in Chicago You Do Not Want to Miss

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## Ovarian Cancer

**Sunday, June 4, 2023**

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

### Faculty

Philipp Harter, MD, PhD

David M O'Malley, MD

Shannon N Westin, MD, MPH

## Urothelial Bladder Cancer

**Monday, June 5, 2023**

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

### Faculty

Matthew D Galsky, MD

Scott T Tagawa, MD, MS

Andrea Necchi, MD

## Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma

**Sunday, June 4, 2023**

7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

### Faculty

Shaji K Kumar, MD

Ann S LaCasce, MD, MMSc

Sagar Lonial, MD

Loretta J Nastoupil, MD

*Additional faculty to be announced*

## Breast Cancer

**Monday, June 5, 2023**

7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

### Faculty

Kevin Kalinsky, MD, MS

Ian E Krop, MD, PhD

Joyce O'Shaughnessy, MD

Hope S Rugo, MD

Professor Peter Schmid, FRCP, MD, PhD

*Additional faculty to be announced*

# Exciting CME Events in Chicago You Do Not Want to Miss

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## **Renal Cell Carcinoma Webinar**

**Tuesday, June 6, 2023**

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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David F McDermott, MD

Sumanta Kumar Pal, MD

# What I Tell My Patients: Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

*Part 2 of a 3-Part Complimentary NCPD Webinar Series  
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**Wednesday, June 14, 2023**

**5:00 PM – 6:00 PM ET**

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**Amanda K Wagner, APRN-CNP, AOCNP**

### **Moderator**

**Neil Love, MD**

# ***Meet The Professor***

## **The Current and Future Management of Non-Hodgkin Lymphoma**

**Thursday, June 15, 2023  
5:00 PM – 6:00 PM ET**

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**Ian W Flinn, MD, PhD**

**Moderator**

**Neil Love, MD**



# The Implications of New Research Findings for the Management of Endometrial Cancer

*A CME/MOC-Accredited Virtual Event in Partnership  
with the Society of Gynecologic Oncology*

**Wednesday, June 28, 2023**

**5:00 PM – 6:00 PM ET**

## **Faculty**

**Bradley J Monk, MD**

**Matthew A Powell, MD**

## **Moderator**

**Neil Love, MD**

## Commercial Support

This activity is supported by educational grants from Aveo Pharmaceuticals and Exelixis Inc.

## Dr Love — Disclosures

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

# Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

## Dr McDermott — Disclosures

<b>Consulting Agreements</b>	Bristol Myers Squibb, Clinigen Limited, Exelixis Inc, Iovance Biotherapeutics, Merck, Pfizer Inc
<b>Data and Safety Monitoring Board/Committee (Unpaid)</b>	RAMPART RCC trial

# Dr Pal — Disclosures

<b>Travel</b>	CRISPR Therapeutics, Ipsen Biopharmaceuticals Inc
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# Clinicians, Please Complete the Pre- and Postmeeting Surveys

**Meet The Professor**  
Optimizing the Selection and Sequencing of Therapy for Patients with Gastrointestinal Cancer

Wednesday, August 25,  
5:00 PM – 6:00 PM EST

Faculty  
Wells A Messersmith, MD

Moderator  
Neil Love, MD

**Quick Survey**

- ☐ Ceritinib +/- dexamethasone
- ☐ Pomalidomide +/- dexamethasone
- ☐ Ceritinib + pomalidomide +/- dexamethasone
- ☐ Eribulin + lenalidomide +/- dexamethasone
- ☐ Eribulin + pomalidomide +/- dexamethasone
- ☐ Daratumumab + lenalidomide +/- dexamethasone
- ☐ Daratumumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + bortezomib +/- dexamethasone
- ☐ Isosorbide + Rd
- ☐ Other

Submit

Participants (10)

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith

**Regulatory and reimbursement issues aside, which would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) if follow-up 3 years later is found to have asymptomatic (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

**Quick Poll**

- ☐ Nivolumab/ipilimumab
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- ☐ Other

Submit

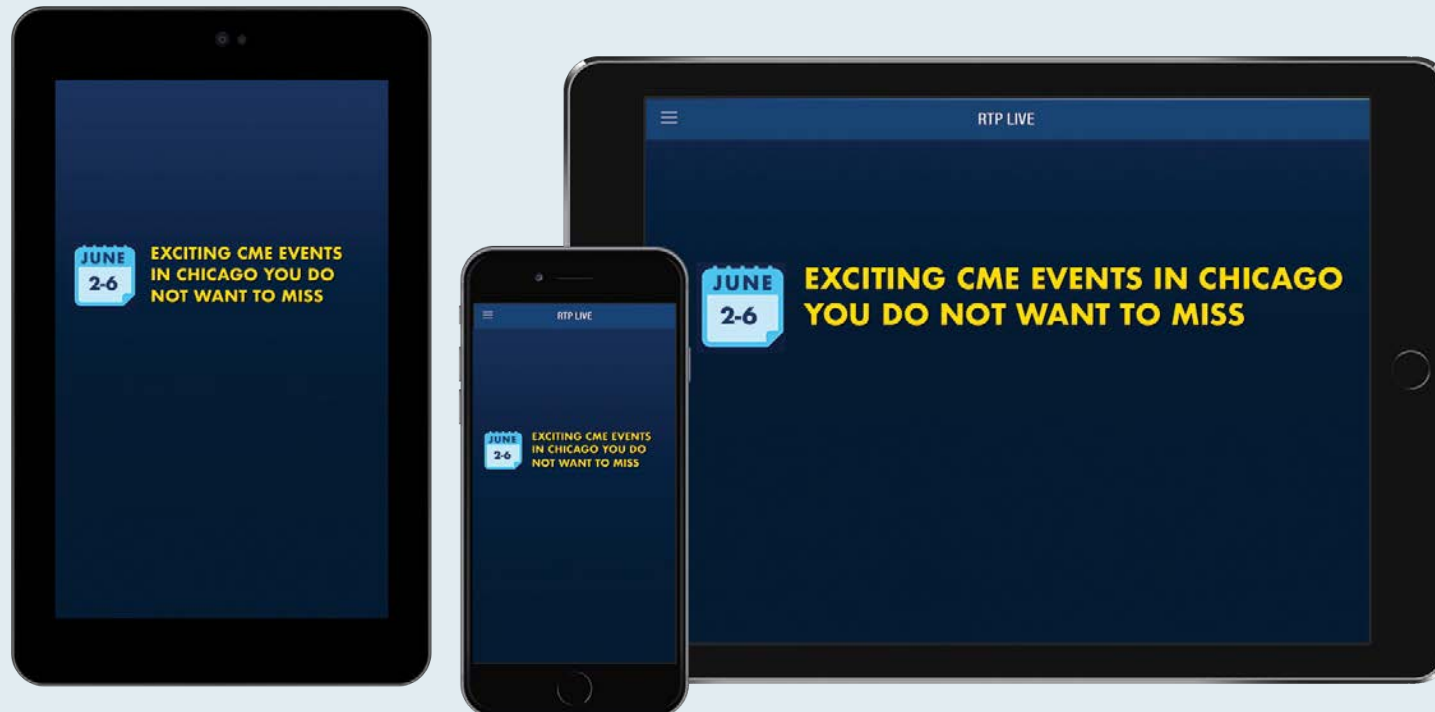
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- JS Jeremy Smith

## Make the Meeting Even More Relevant to You

**Download the RTP Live app on your smartphone or tablet to access program information, including slides being presented during the program:**

**[www.ResearchToPractice.com/RTPLiveApp](http://www.ResearchToPractice.com/RTPLiveApp)**





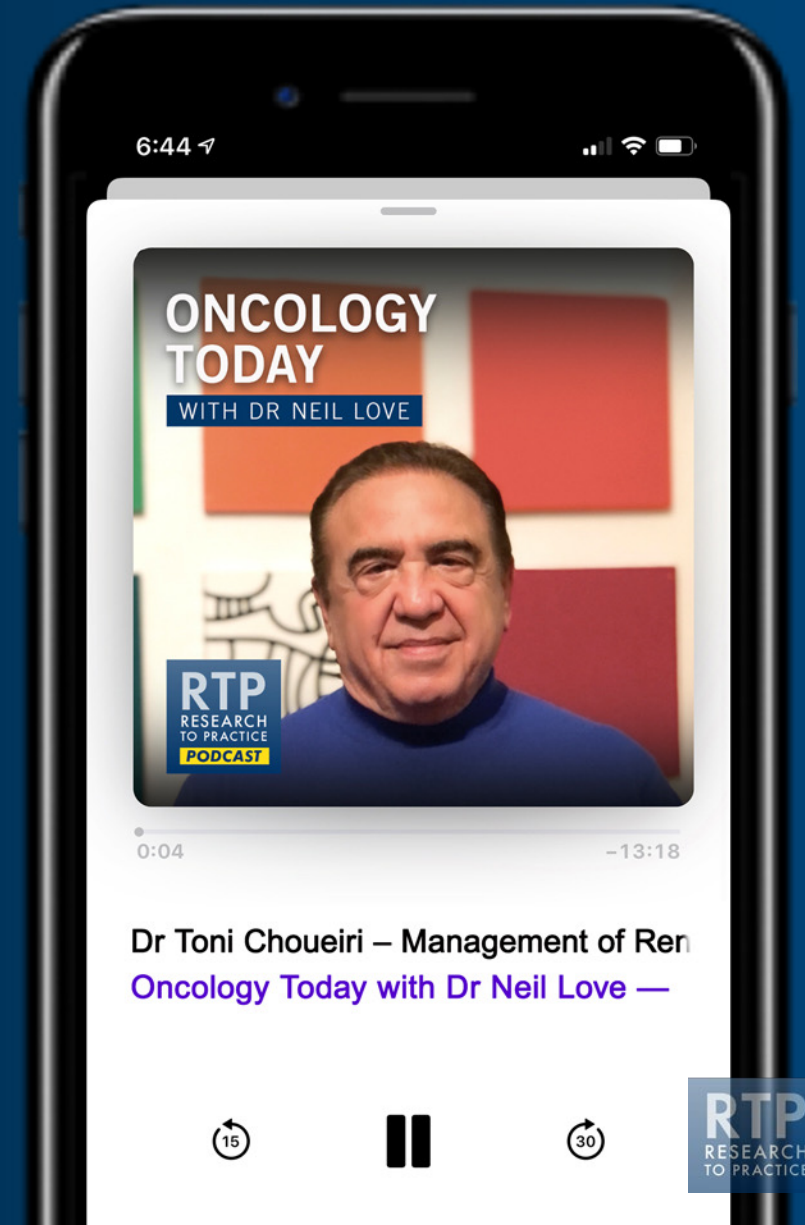
# ONCOLOGY TODAY

WITH DR NEIL LOVE

## Management of Renal Cell Carcinoma



DR TONI CHOUEIRI  
DANA-FARBER CANCER INSTITUTE



# Investigator Perspectives on Available Research Findings and Challenging Questions in Renal Cell Carcinoma

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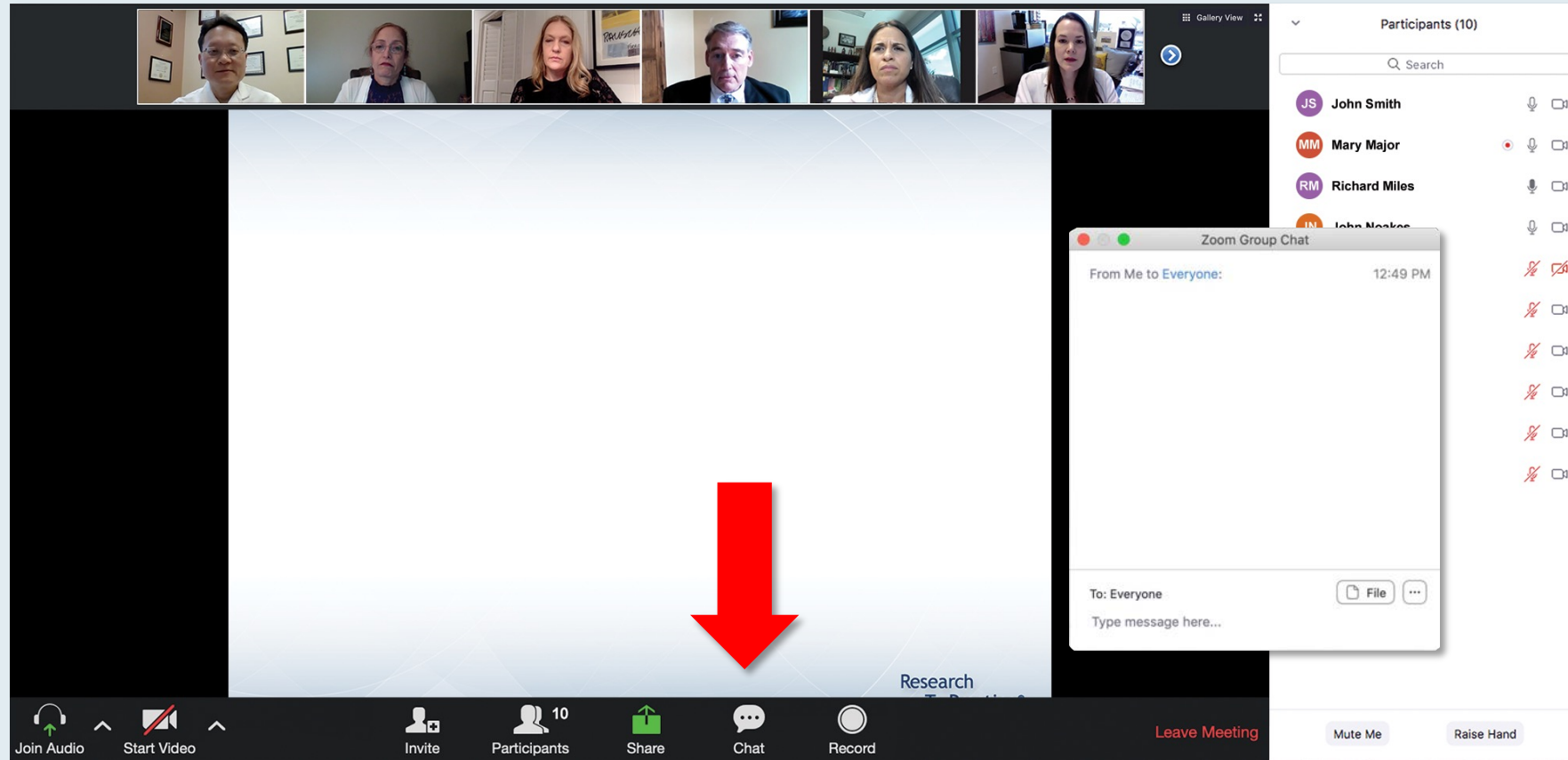
Research To Practice  
Miami, Florida



**Sumanta Kumar Pal, MD**

Professor, Department of Medical Oncology  
and Therapeutics Research  
City of Hope  
Duarte, California

# We Encourage Clinicians in Practice to Submit Questions



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

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

The screenshot shows a Zoom meeting window. At the top, a row of seven participant video thumbnails is visible. The main content area on the left displays a presentation slide with the following text:   
**Meet The Professionals**  
**Optimizing the Selection and Sequencing of Therapy for Patients with Metastatic Gastrointestinal Cancer**  
Wednesday, August 25, 2022  
5:00 PM – 6:00 PM EST  
Faculty  
Wells A Messersmith, MD  
Moderator  
Neil Love, MD  
The RTP Research to Practice logo is in the bottom right corner of the slide. A 'Quick Survey' pop-up window is centered over the slide, listing several treatment combinations with radio button options. To the right of the main window is a 'Participants (10)' sidebar showing a list of names with their respective status icons (mute, video on/off). At the bottom of the Zoom window is a toolbar with icons for Join Audio, Start Video, Invite, Participants, Share, Chat, Record, and a red 'Leave Meeting' button.

**Quick Survey**

- ☐ Ceritinib +/- dexamethasone
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- ☐ Daratumumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + bortezomib +/- dexamethasone
- ☐ Isaxozim + Rd
- ☐ Other

Submit

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**Regulatory and reimbursement issues aside, which treatment would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has been on a TKI for 3 years and follow-up 3 years later is found to have asymptomatic (PS 0)?**  
The slide lists eight options:   
1. Nivolumab/ipilimumab  
2. Avelumab/axitinib  
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**Ian W Flinn, MD, PhD**

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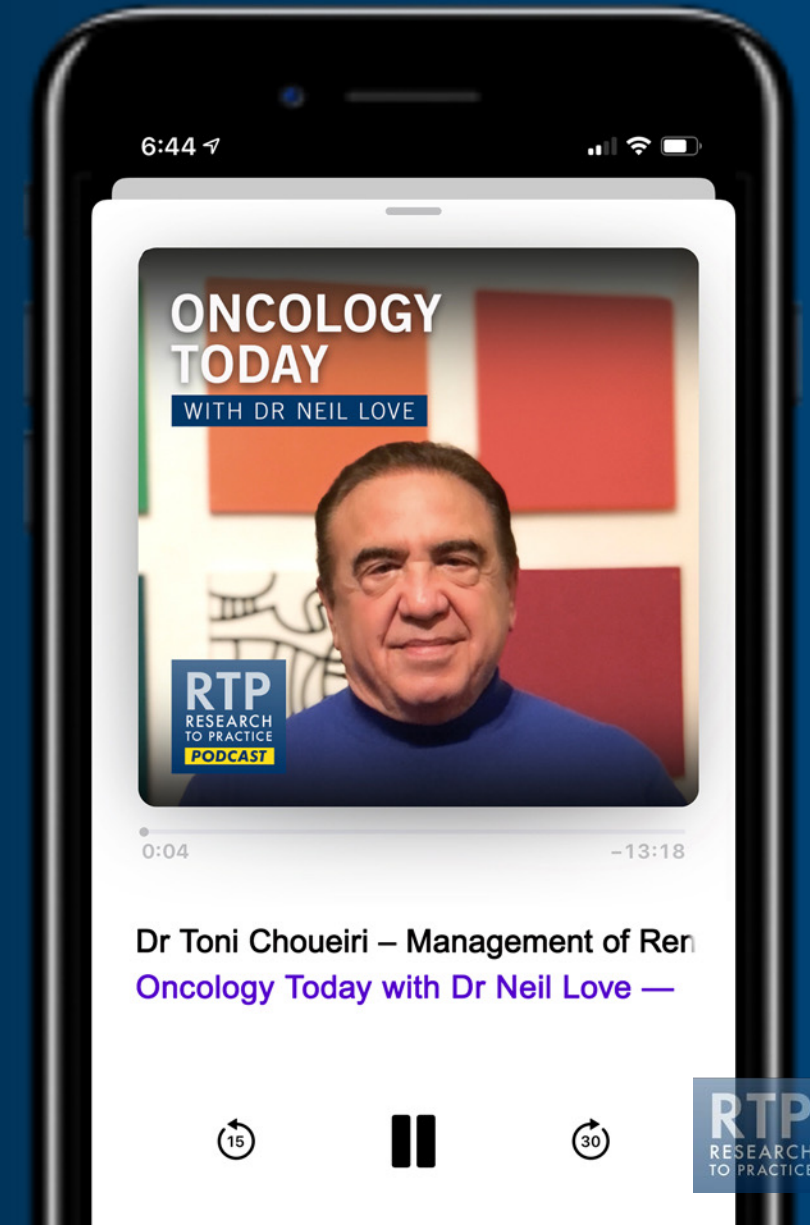
# ONCOLOGY TODAY

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## Management of Renal Cell Carcinoma



DR TONI CHOUEIRI  
DANA-FARBER CANCER INSTITUTE



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## Dr McDermott — Disclosures

<b>Consulting Agreements</b>	Bristol Myers Squibb, Clinigen Limited, Exelixis Inc, Iovance Biotherapeutics, Merck, Pfizer Inc
<b>Data and Safety Monitoring Board/Committee (Unpaid)</b>	RAMPART RCC trial

# Dr Pal — Disclosures

<b>Travel</b>	CRISPR Therapeutics, Ipsen Biopharmaceuticals Inc
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# Agenda

## **Module 1 – ASCO 2023**

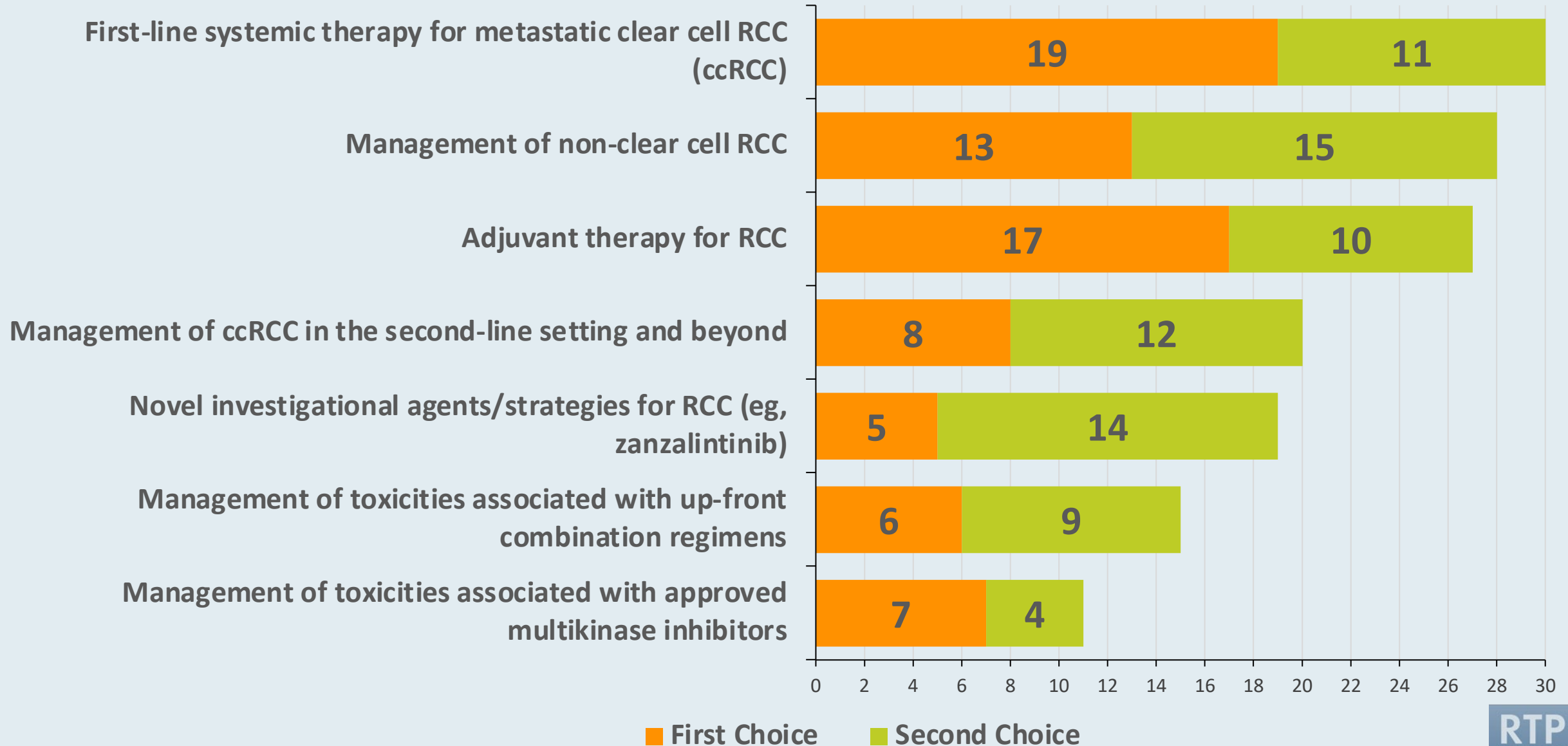
## **Module 2 – Management of Advanced Renal Cell Carcinoma (RCC)**

- First-line systemic therapy for metastatic clear cell RCC (ccRCC)
- Management of toxicities associated with up-front combination regimens
- Management of ccRCC in the second-line setting and beyond
- Management of toxicities associated with approved multikinase inhibitors

## **Module 3 – Treatment Approaches for Nonmetastatic RCC; Optimal care of Patients with Non-Clear Cell RCC**

- Adjuvant therapy for RCC
- Management of non-clear cell RCC
- Novel investigational agents/strategies for RCC (eg, zanzalintinib)

# Topics of Interest for Future CME Programs



# Agenda

## Module 1 – ASCO 2023

### Module 2 – Management of Advanced Renal Cell Carcinoma (RCC)

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# ASCO 2023 – Advanced RCC

- Choueiri TK et al. **Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study.** ASCO 2023;Abstract LBA4500
- Rini BI et al. **Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426.** ASCO 2023;Abstract LBA4501
- Hutson TE et al. **Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC).** ASCO 2023;Abstract 4502
- Cella D et al. **Health-related quality of life (HRQoL) of risk-based patient subgroups with advanced renal cell cancer (aRCC) treated with nivolumab plus cabozantinib (NIVO+CABO) vs sunitinib (SUN) in the CheckMate 9ER trial.** ASCO 2023;Abstract 4527
- Albiges L et al. **Belzutifan plus lenvatinib for patients (pts) with advanced clear cell renal cell carcinoma (ccRCC) after progression on a PD-1/L1 and VEGF inhibitor: Preliminary results of arm B5 of the phase 1/2 KEYMAKER-U03B study.** ASCO 2023;Abstract 4553

# ASCO 2023 – Adjuvant and Non-clear cell RCC

## Adjuvant Treatment

- Motzer RJ et al. **Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: Subgroup analyses from the phase 3 CheckMate 914 (part A) trial.** ASCO 2023;Abstract 4506

## Non-clear Clear Cell RCC

- Lee C-H et al. **First-line lenvatinib + pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study.** ASCO 2023; Abstract 4518
- McGregor BA et al. **Phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with variant histologies (RCCvh).** ASCO 2023;Abstract 4520
- Lee C-H et al. **Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: Updated results from a phase 2 trial.** ASCO 2023;Abstract 4537
- Labaki C et al. **Efficacy of first-line (1L) immunotherapy (IO)-based regimens in patients with sarcomatoid and/or rhabdoid (S/R) metastatic non-clear cell renal cell carcinoma (nccRCC): Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).** ASCO 2023;Abstract 4519

## ASCO 2023 – Non-clear cell RCC (con't)

- Tripathi A et al. **Pathologic concordance rate and outcomes by histologic subtype in advanced papillary renal cell (pRCC) carcinoma: An analysis from the SWOG S1500 (PAPMET) trial.** ASCO 2023;Abstract 4562
- Johns A et al. **CABOSUN II: Results from a phase 2, open-label, multi-center randomized study of cabozantinib (CABO) vs. sunitinib (SUN) for non-clear cell renal cell carcinoma (NCCRCC).** ASCO 2023;Abstract 4597

# ASCO 2023 – RCC Education Sessions

- **Oligometastatic renal Cell Carcinoma: Observe, Exercise, Ablate?**

Tuesday, June 6; 9:45 AM CT

- **Doublet and Triplet Therapy for Metastatic Renal Cell Carcinoma: The More the Merrier or Is Three a Crowd?**

Tuesday, June 6; 11:30 AM CT

# Agenda

## Module 1 – ASCO 2023

## Module 2 – Management of Advanced Renal Cell Carcinoma (RCC)

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# PRECISION MANAGEMENT OF ADVANCED KIDNEY CANCER

**David McDermott, MD**  
**Beth Israel Deaconess Medical Center**  
**Harvard Medical School**

Beth Israel Lahey Health



Beth Israel Deaconess  
Medical Center



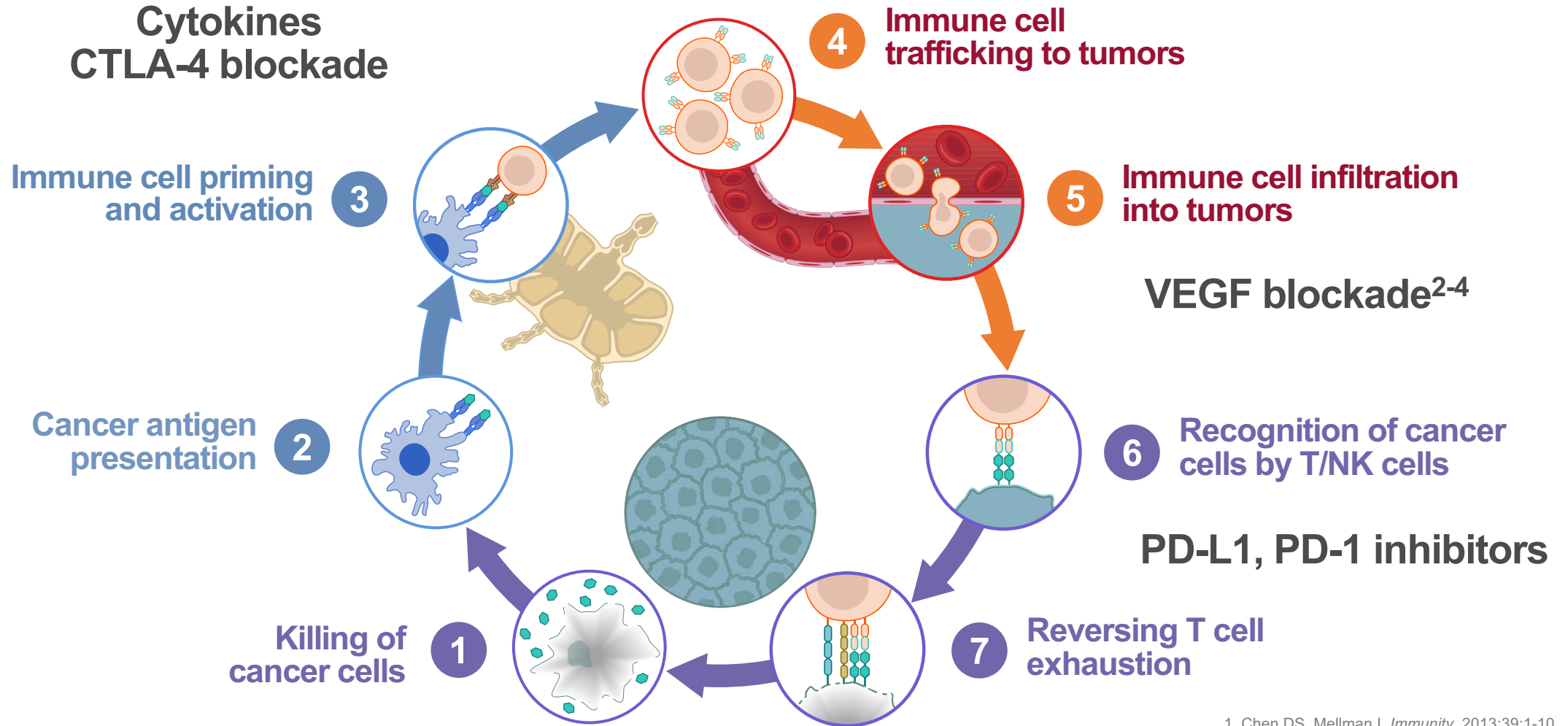
HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL

# Kidney Cancer: Most Applied Sequence 2015

Setting	NCCN	Alternative
1st-Line Therapy	VEGF Blockade	
2nd-Line Therapy	PD-1 Blockade	

# Strengthen the Anti-Kidney Cancer Immune Response<sup>1</sup>

— Immune desert  
— Immune excluded  
— Inflamed

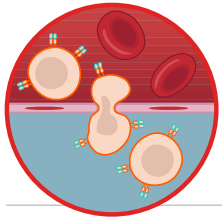


1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.  
2. Shrimali RK et al. *Can Res*. 2010;70:6171-6180.  
3. Manning EA et al. *Clin Cancer Res*. 2007;13:3951-3959.  
4. Motz GT et al. *Nat Med*. 2014;20:607-615.



# Fusion of First- and Second-line Therapy

Setting		NCCN	Alternative
Treatment Naïve	<b>PD-1 + VEGF Blockade</b>		
3rd-Line Therapy			



## 5 Immune cell infiltration into tumors

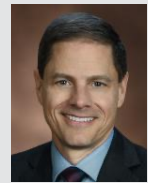
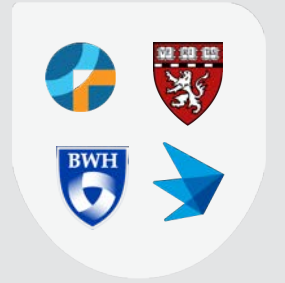
# Confirmation of combination benefit

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators\*



Rini



Atkins



Powles



Plimack

# mRCC: Superior Front-Line Combination Therapy

Setting	NCCN	Alternative
1st-Line Therapy	<b>PD-1 + CTLA-4 Blockade</b>	
2nd-Line Therapy		

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

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APRIL 5, 2018

VOL. 378 NO. 14

## Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators\*



# First-Line Phase 3 Trials in Advanced Kidney Cancer

Control	Experimental Arm
Sunitinib	Axitinib + avelumab
Sunitinib	Bevacizumab + atezolizumab
Sunitinib	<b>Nivolumab + cabozantinib</b>
Sunitinib	<b>Lenvatinib + pembrolizumab</b>
Sunitinib	<b>Axitinib + pembrolizumab</b>
Sunitinib	<b>Nivolumab + ipilimumab</b>

**Which regimen should be favored?**

Bold – met both OS and PFS endpoints

# Clinical Take-Homes

## PD-1 + VEGF

## PD-1/CTLA-1

### PROS

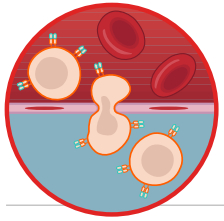
- Improved OS
- **High ORR, low PD rate**
- **Longer PFS**
- Lower irAE rate

- Improved OS
- Mature follow-up data available
- **Durable responses**
- **Potential to stop therapy**
- QOL during maintenance

### CONS

- Unclear AE attribution
- Less mature follow-up
- Chronic TKI toxicity

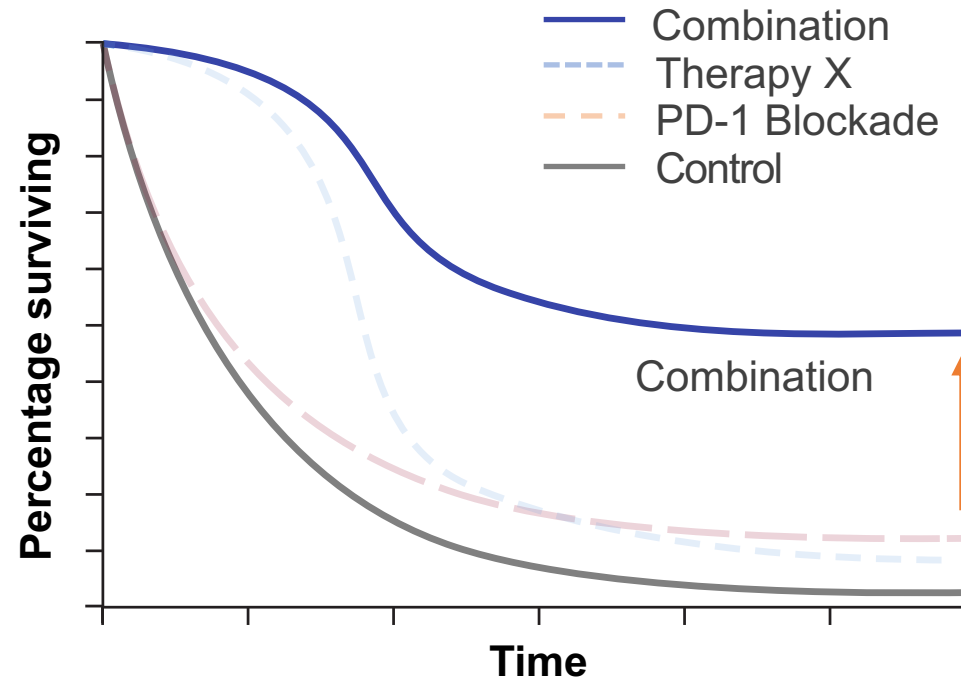
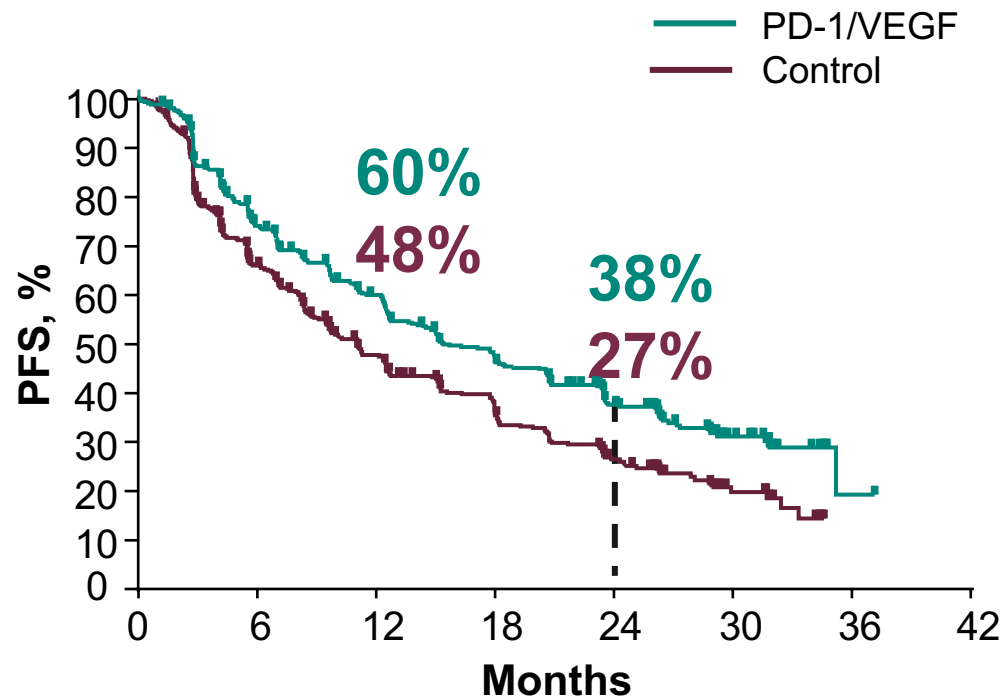
- Higher irAE rate
- Lower PFS/response rate



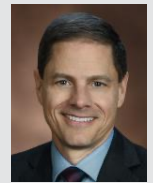
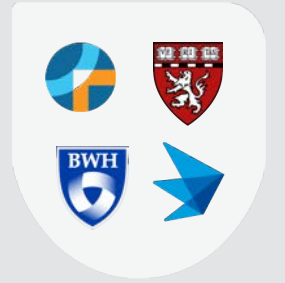
## 5 Immune cell infiltration into tumors

### Trouble with the Curves?

#### PD-1/VEGF (IO + Targeted Rx)



Rini NEJM 2019, Motzer NEJM 2021,



Rini



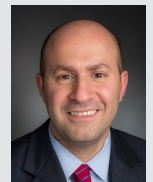
Atkins



Powles



Plimack

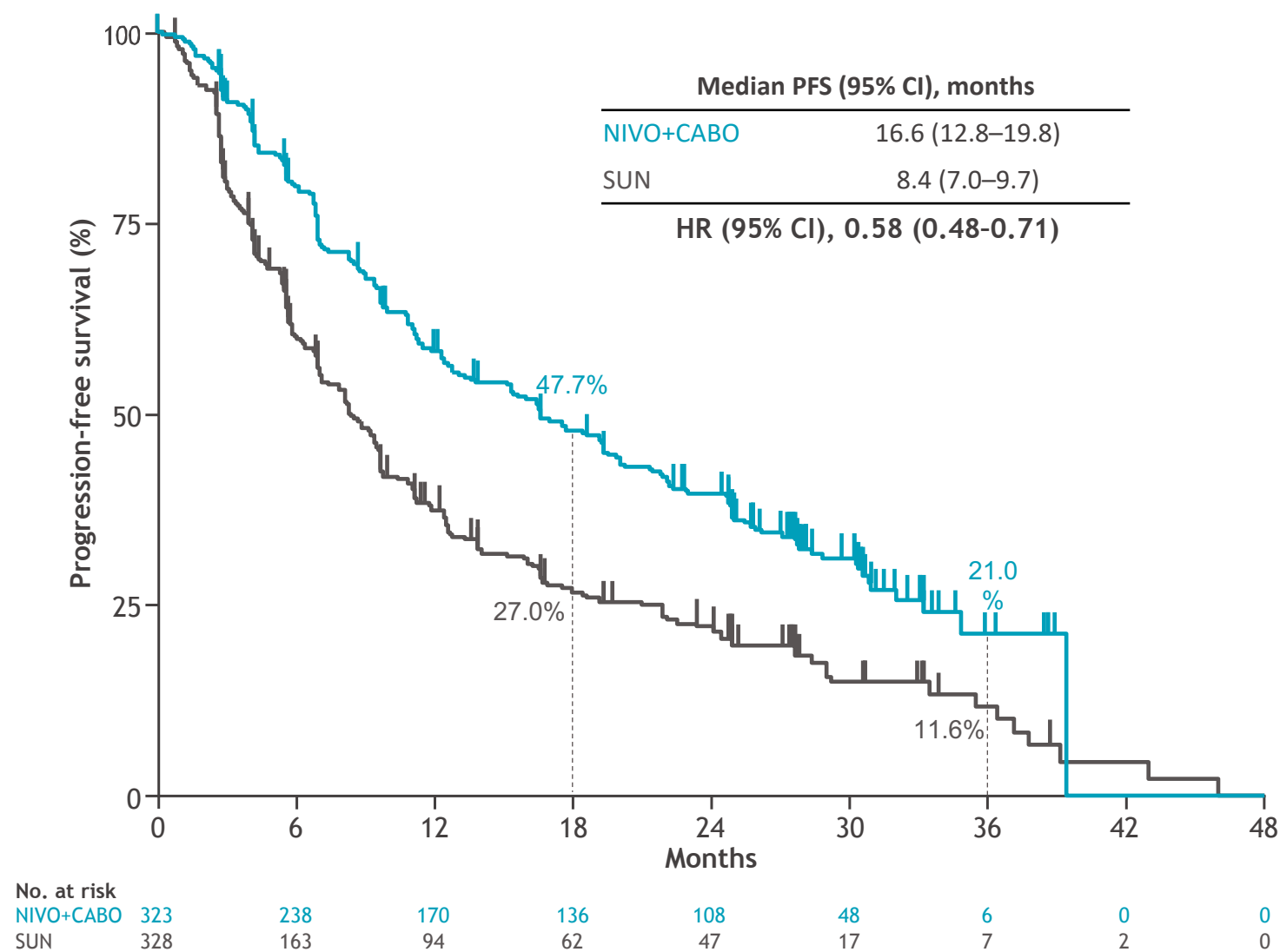


Choueiri



Motzer

# CheckMate 9ER: PFS: ITT population

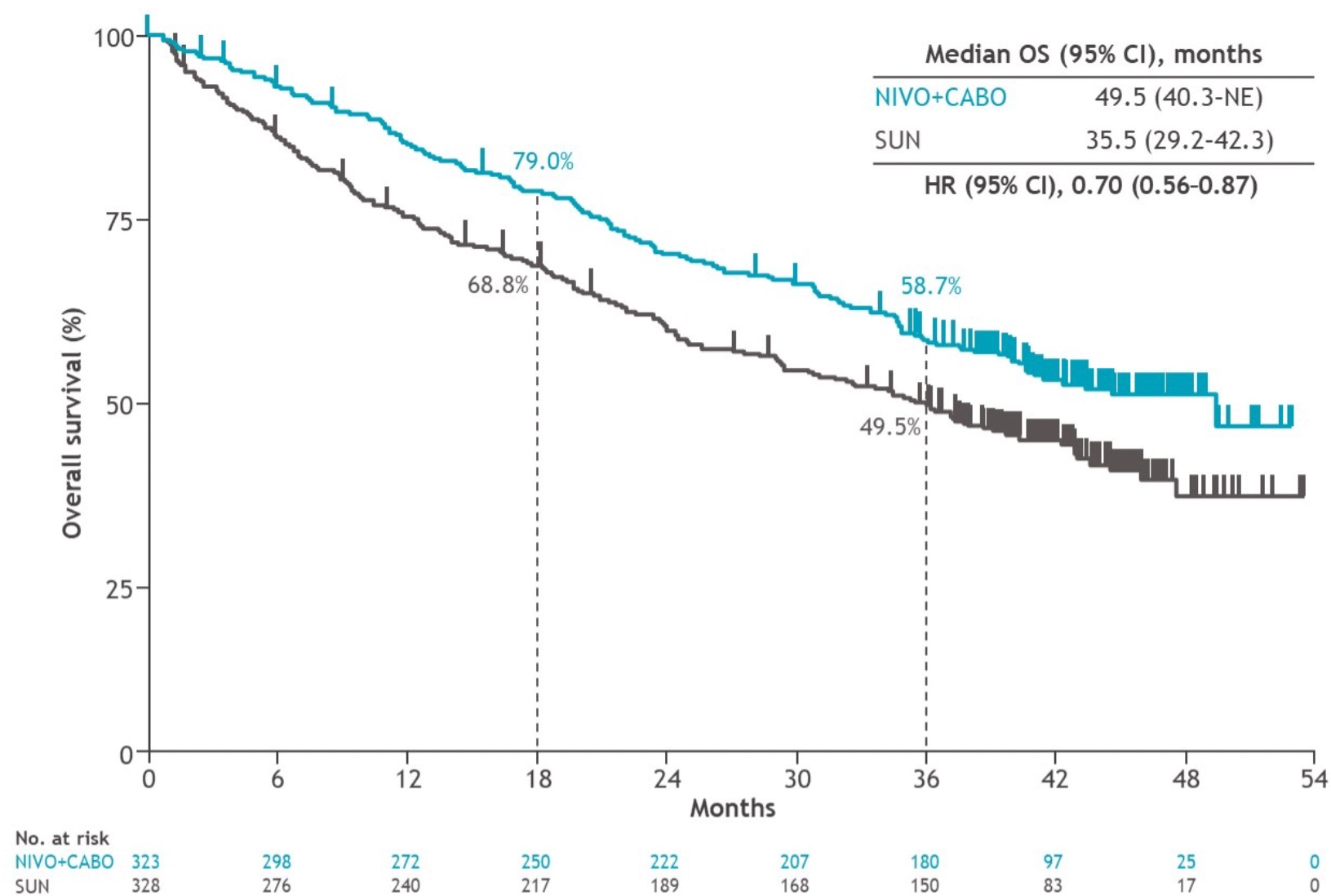


Burotto et al GU ASCO 2023

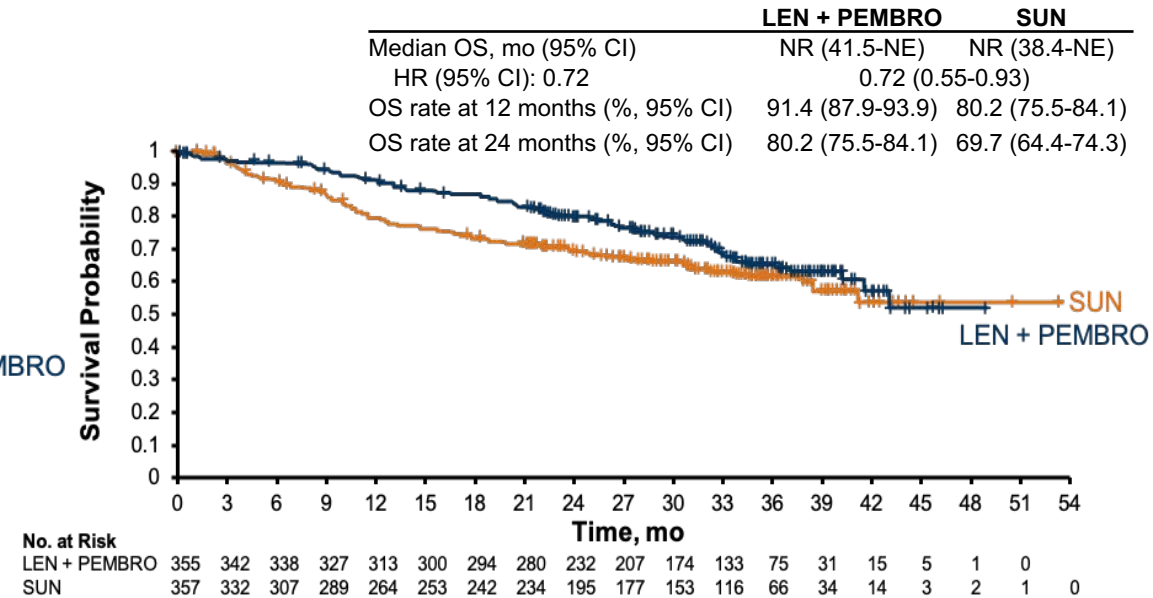
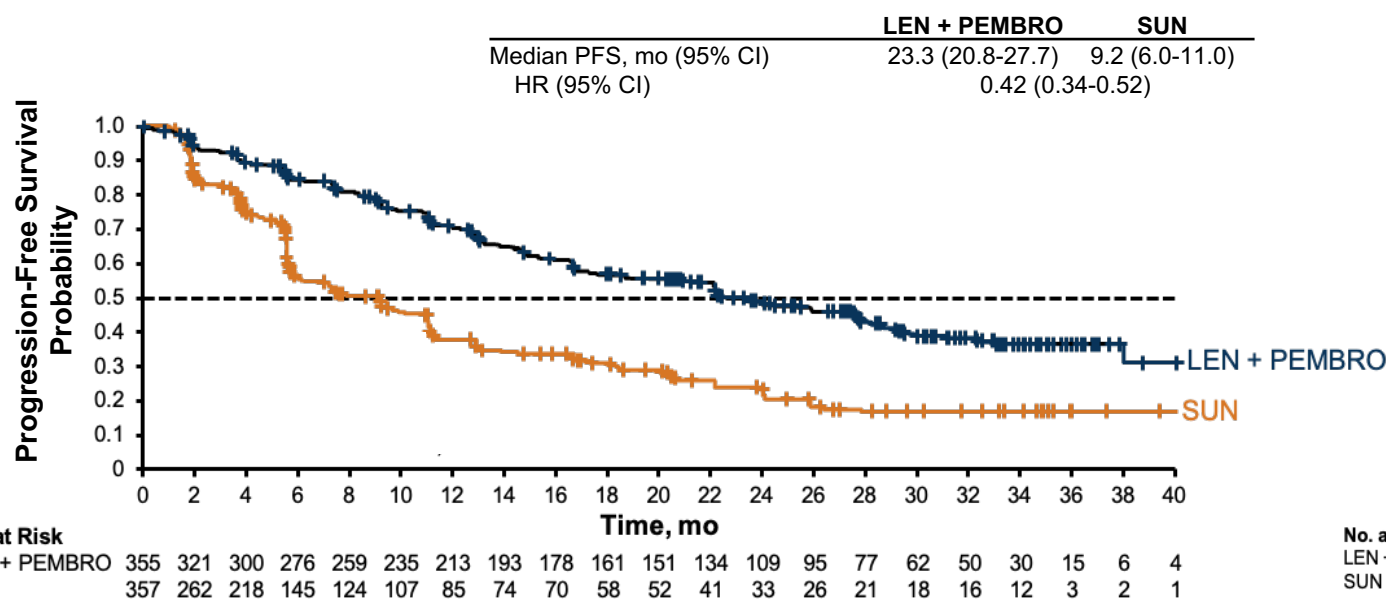
Median follow-up for OS, 44.0 months. Stratified Cox proportional hazard model used for HR.  
CI, confidence interval.



# CheckMate 9ER: OS: ITT population



# CLEAR: Pembrolizumab Plus Lenvatinib<sup>1,2</sup>



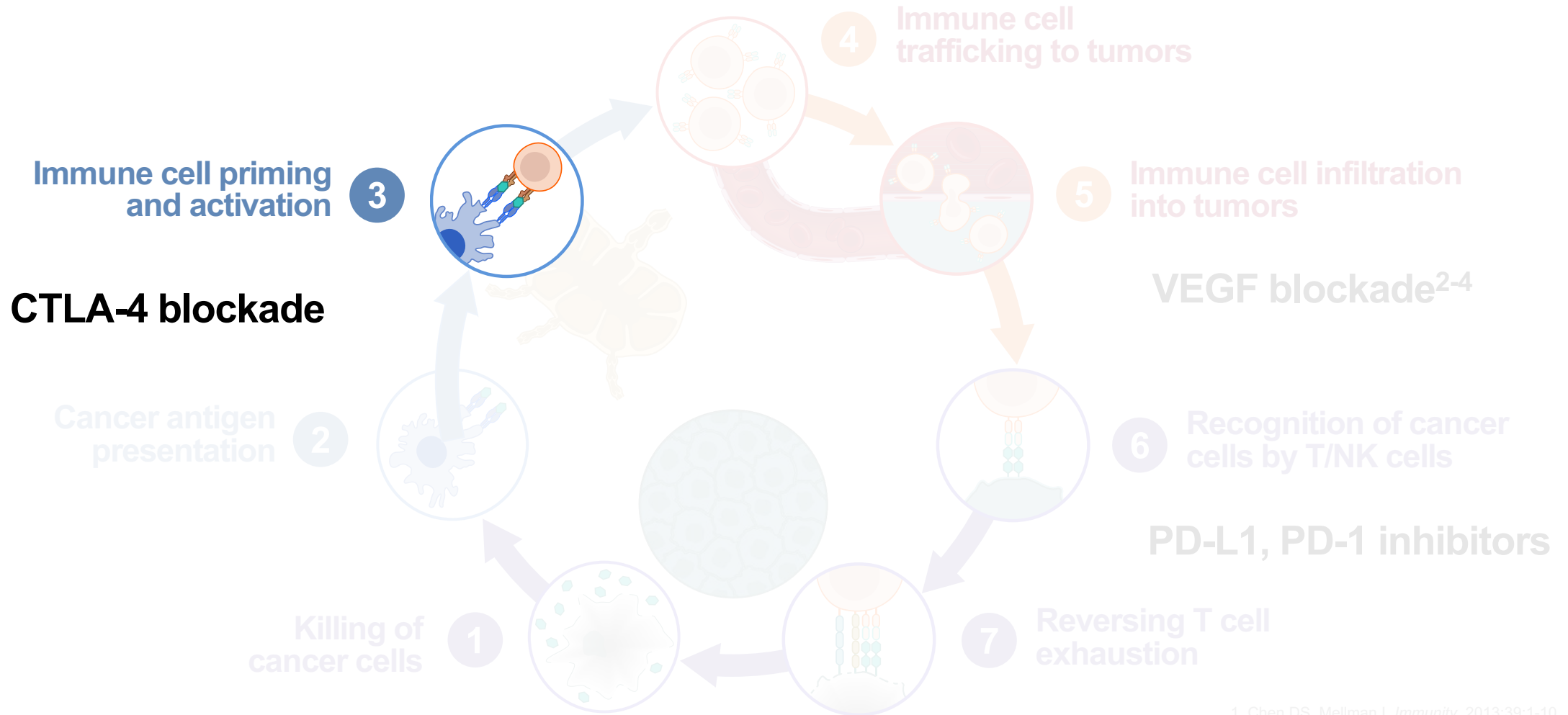
- Pembrolizumab + lenvatinib demonstrated significant improvement in PFS, OS, and ORR vs sunitinib<sup>a</sup>
- ORR: 71.0% (CR 17.2%)
- PFS across all MSKCC and IMDC risk groups and OS across poor and intermediate risk groups favored lenvatinib + pembrolizumab

<sup>a</sup> Data cutoff: March 31, 2021.

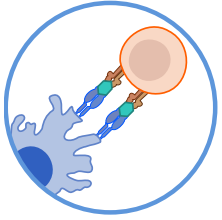
1. Motzer RJ et al. *N Engl J Med*. 2021;384:1289-1300. 2. Porta CG et al. ESMO 2022. Abstract 1449MO.

# Strengthen the Anti-Kidney Cancer Immune Response<sup>1</sup>

— Immune desert  
— Immune excluded  
— Inflamed



1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.  
2. Shrimali RK et al. *Can Res*. 2010;70:6171-6180.  
3. Manning EA et al. *Clin Cancer Res*. 2007;13:3951-3959.  
4. Motz GT et al. *Nat Med*. 2014;20:607-615.



### 3 Immune cell priming and activation

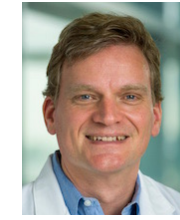
## Durable Benefit



Albiges



Escudier



Hammers

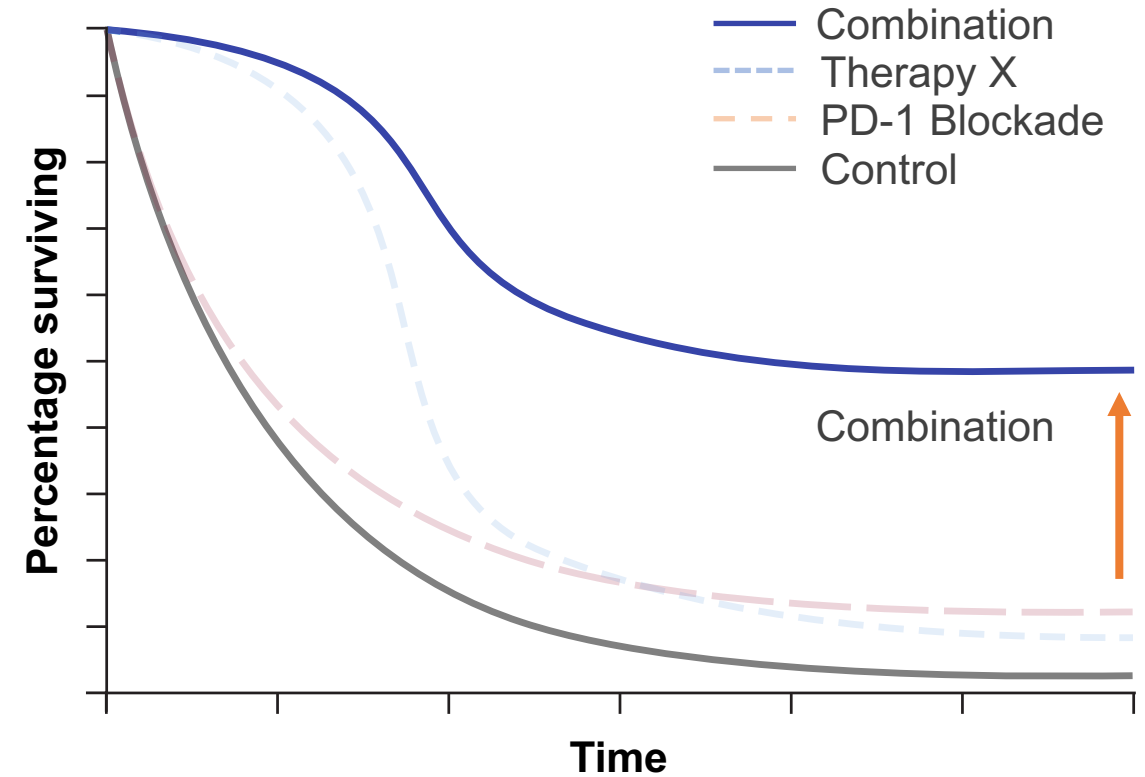
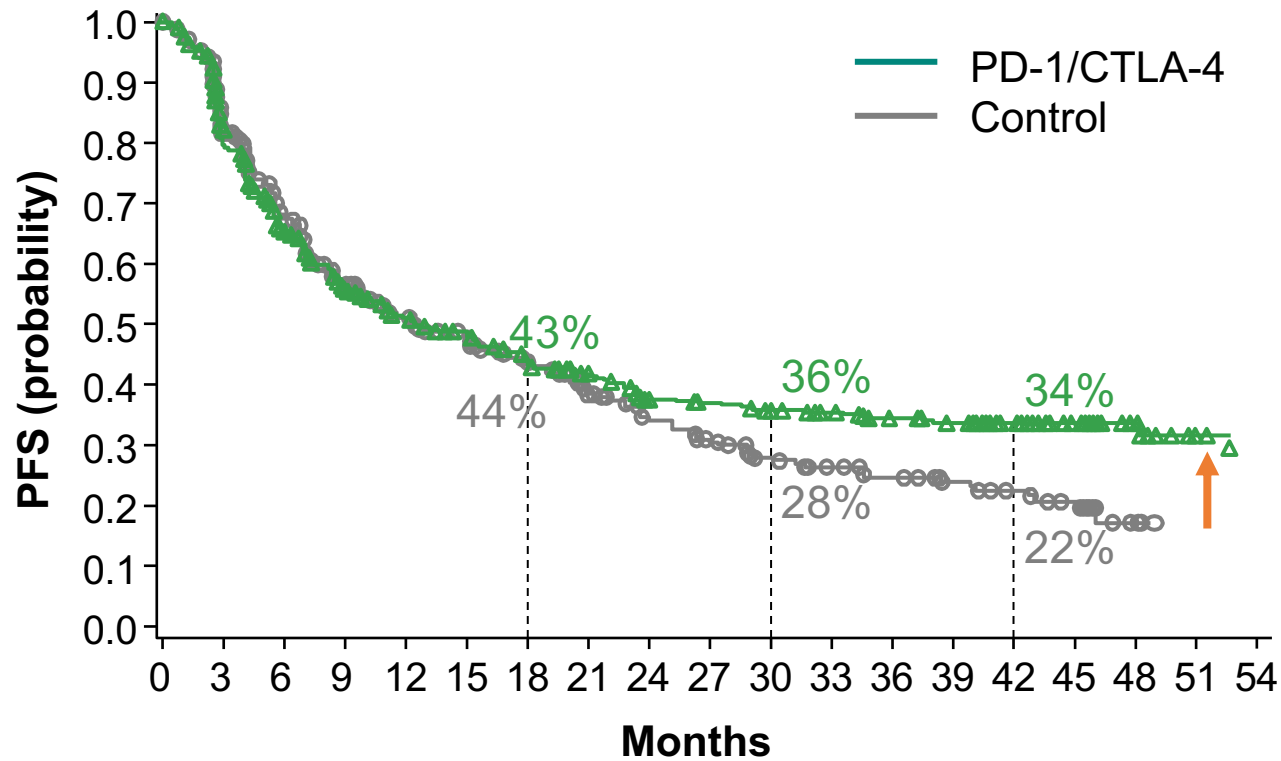


Motzer




Tannir

### PD-1/CTLA-4 (IO Combination)



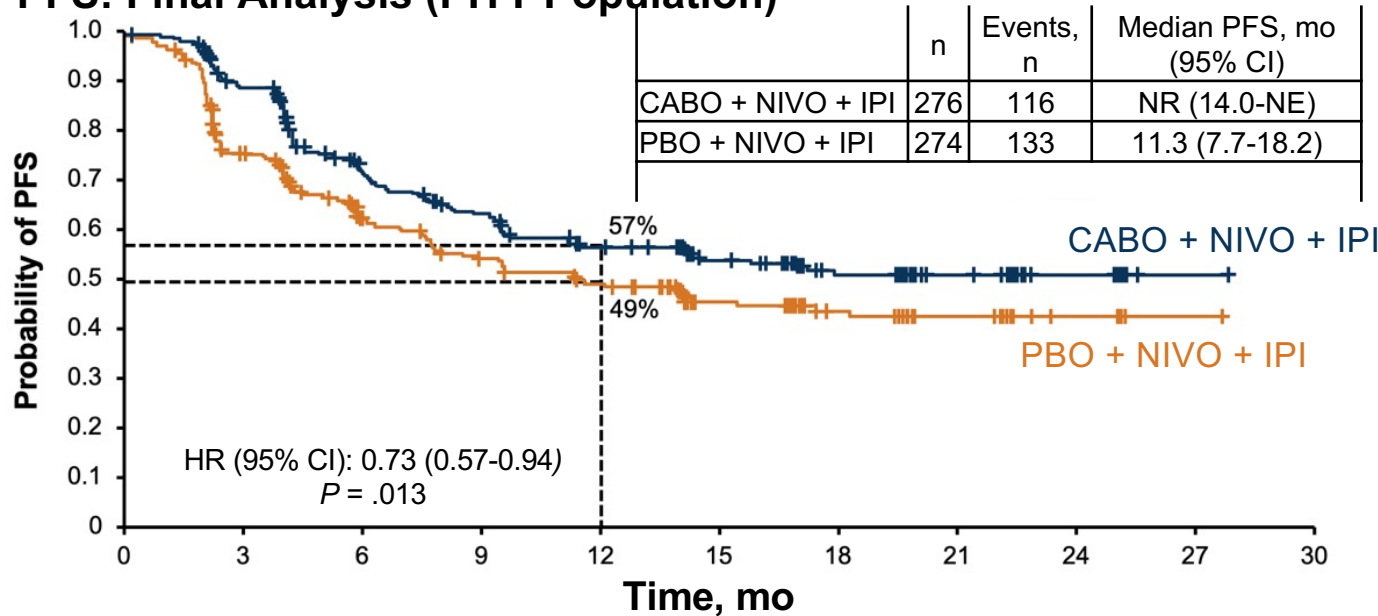
Hammers JCO 2017, Albiges ESMO Open 2020,  
Motzer, Cancer 2022; NEJM 2015, 2018

# Which PD-1 based combination is superior?

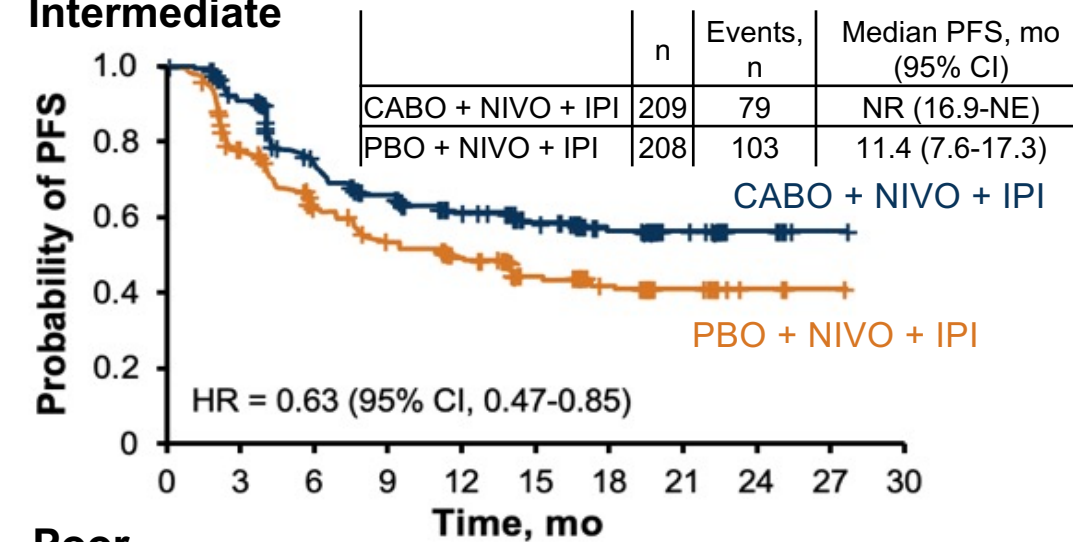
Endpoints	PD-1/VEGF	PD-1/CTLA-4
Early – first 2 years (ORR, mPFS)		
Late – after 2 years (DOR, ImPFS, ItOS)		
Durable – post treatment (TFS)		

# COSMIC-313: Triplet Therapy With Cabozantinib Plus Nivolumab Plus Ipilimumab<sup>1</sup>

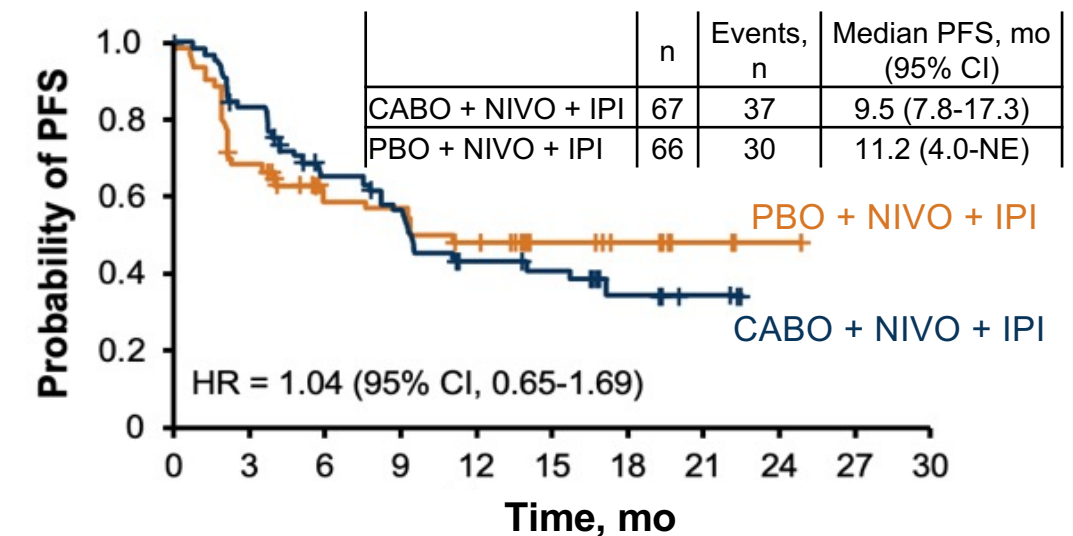
## PFS: Final Analysis (PITT Population)



## Intermediate



## Poor



- Primary endpoint (PFS in PITT) = met
- OS analysis still needed –likely negative
- Toxicity impact
  - Rate of grade 3/4 toxicities in triplet substantially higher (e.g., liver)
- Path to the clinic is bumpy

# What Emerging Data Could Impact Standards of Care?

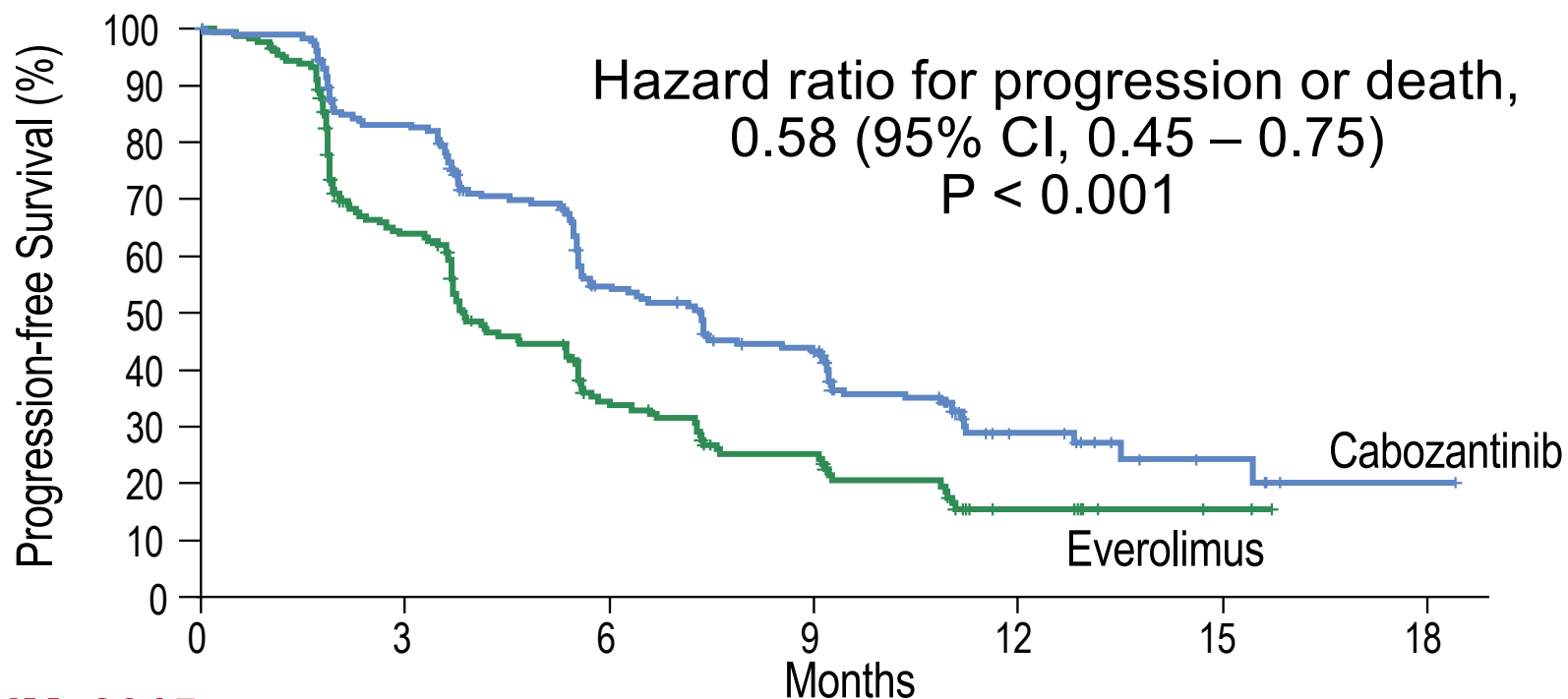
- What novel therapies and approaches are most promising?
- **What works after PD-1 failure?**

PD-1, program death receptor-1

ORIGINAL ARTICLE

## Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

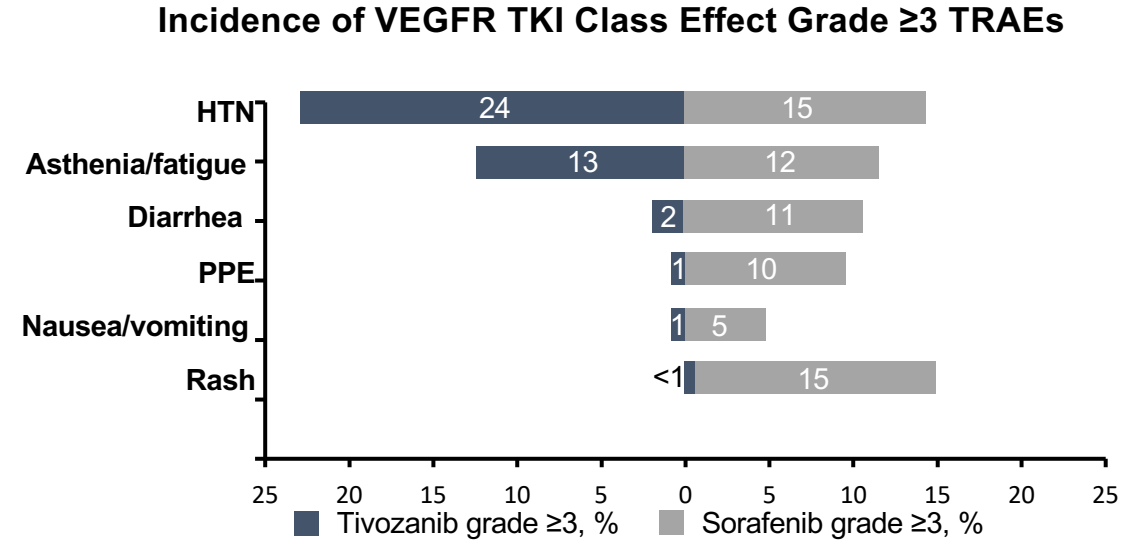
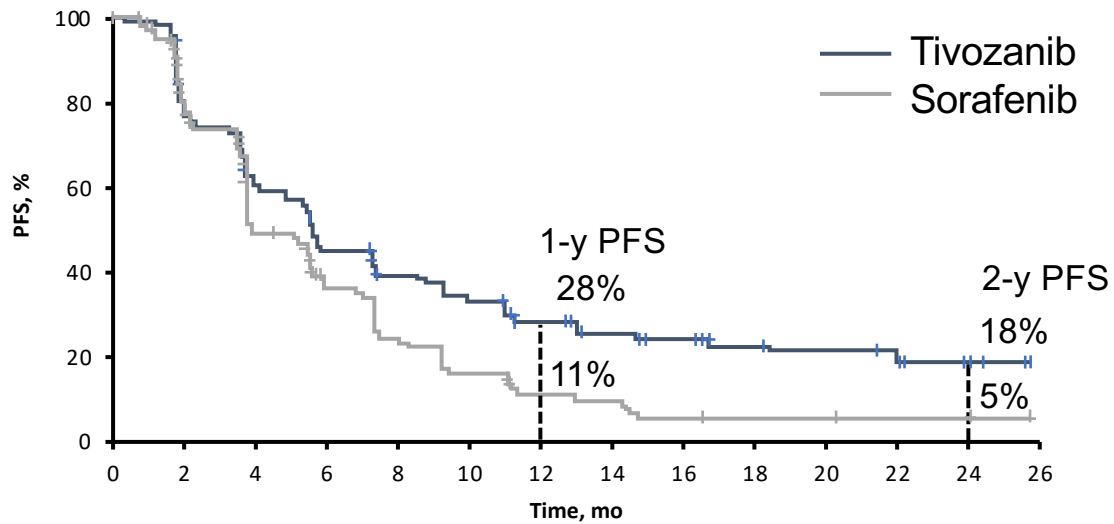
T.K. Choueiri, B. Escudier, T. Powles, Paul N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, D.O., J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators



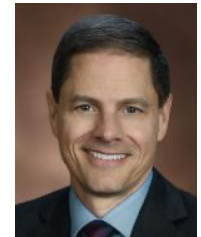
Choueiri<sup>DFCI</sup>



# Phase 3 TIVO-3: Tivozanib in RCC<sup>1-3</sup>



**FDA approved for patients with relapsed or refractory advanced RCC following ≥2 prior systemic therapies**



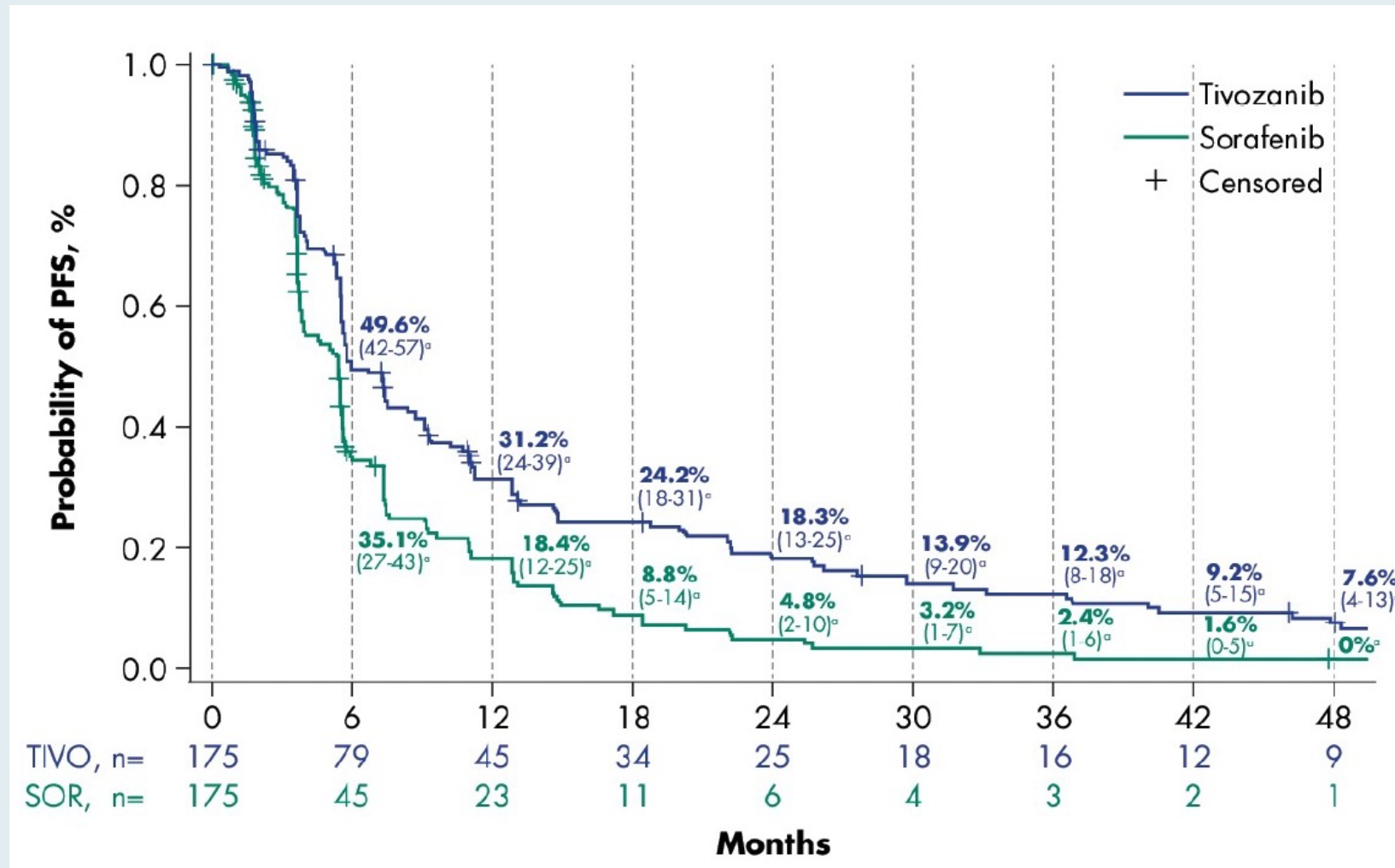
B. Rini

# Long-Term PFS from TIVO-3: Tivozanib (TIVO) versus Sorafenib (SOR) in Relapsed/Refractory (R/R) Advanced RCC

Atkins MB et al.

Genitourinary Cancers Symposium 2022;Abstract 362.

# TIVO-3: Long-Term (48-Month) Progression-Free Survival

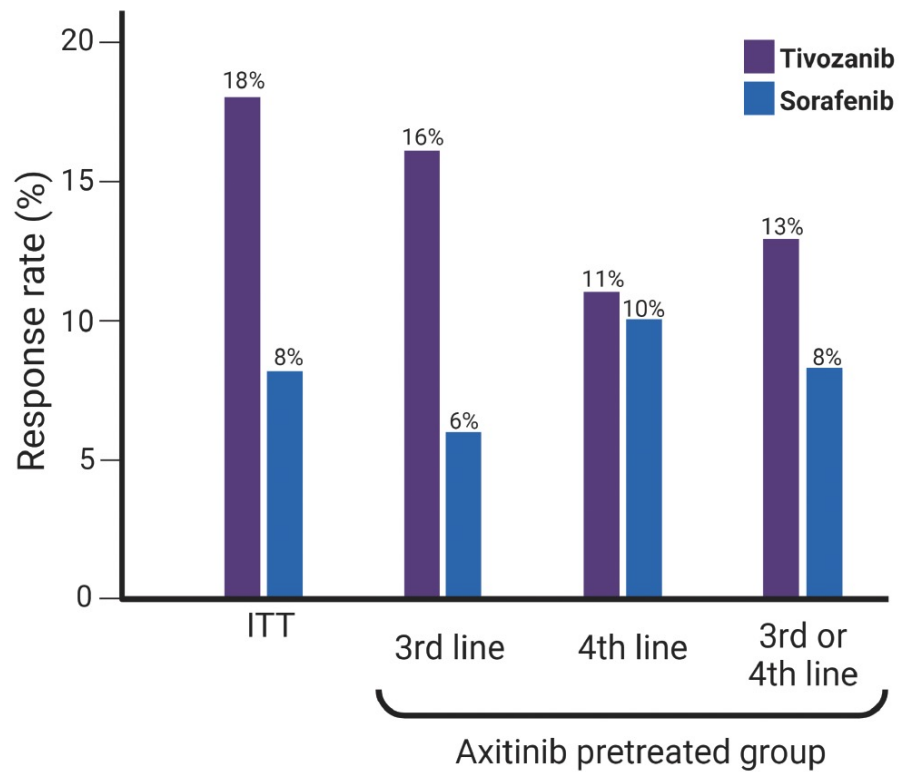


# Tivozanib in Patients with Advanced Renal Cell Carcinoma Previously Treated with Axitinib: Subgroup Analysis from TIVO-3

Luis Meza<sup>1</sup>,, David F. McDermott<sup>2</sup>, Bernard Escudier<sup>3</sup>, Thomas E. Hutson<sup>4</sup>, Camillo Porta<sup>5</sup>, Elena Verzoni<sup>6</sup>, Michael B. Atkins<sup>7</sup>, Vijay Kasturi<sup>8</sup>, Sumanta K. Pal<sup>\*,1,‡</sup>, Brian Rini<sup>\*,9,‡</sup>

*The Oncologist* 2023;28(3):e167-70.

# TIVO-3: Response Rates and Safety of Tivozanib in Patients with Prior Axitinib Treatment



AE	Prior axitinib	No prior axitinib
Treatment-related AE	84.5%	92.3%
Reduction due to AE	28.0%	29.7%
Interruption due to AE	53.5%	53.8%
Discontinuation due to AE	25.6%	19.8%

Abbreviation: AE, adverse event.

# PD-1 Blockade Salvage Therapy

Setting	NCCN
Treatment-Naïve	<b>PD-1 Blockade Based Tx</b>
Salvage Therapy	<b>VEGF Blockade</b>

NCCN, National Comprehensive Cancer Network; PD-1, program death receptor-1; tx, treatment; VEGF, vascular endothelial growth factor

Rini BI et al. *N Engl J Med*. 2019;380:1116-1127.  
Choueiri TK et al. *N Engl J Med*. 2015;373:1814-1823.

# Randomized PD-1/VEGF Blockade Salvage Trial = Negative

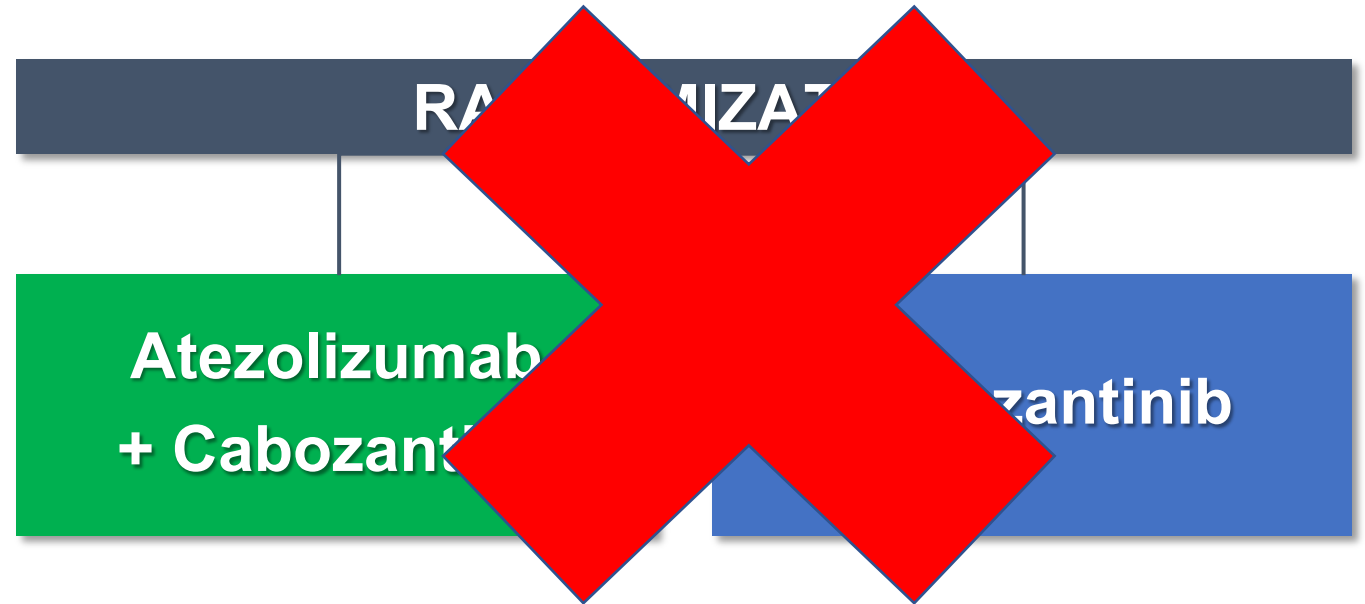
**CONTACT-03 (NCT04338269)**

**mRCC 2/3L**

**VEGFR TKI  $\pm$  PD-L1  
inhibition**

**Phase 3 (N = 500)**

**Primary endpoints: PFS, OS**



2/3L, second/third line; OS, overall survival; PD-1, program death receptor-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

CONTACT-03. NCT04338269. Updated January 22, 2021. Accessed February 7, 2021. <https://clinicaltrials.gov/ct2/show/NCT04338269>

# Standard Therapy for mRCC: 2030

Setting	NCCN	Alternative
1st-Line Therapy	Treatment based on TME Profile	
2nd-Line Therapy	Not Necessary	



# Questions from General Medical Oncologists

## Advanced RCC

- **A 72 yo male presents with metastatic renal cell cancer with severe pain from several bone metastases. You decide to use len/pembro. What advice would you give about dosing and support for the lenvatinib**
- **Role of nephrectomy for debulking in metastatic RCC**
- **What is the preferred TKI + ICI combo with bone mets?**
- **60 yo with metastatic RCC on nivo + cabozantinib presents for restaging scan, which showed one new lesion in the jejunum. He is clinically well and does not have any symptoms. What would be your recommendation in this case?**
- **What are the reasons for which IPI + NIVO + CABO clinical trial was not that impressive?**



# Questions from General Medical Oncologists Advanced RCC

- I have a patient with metastatic kidney cancer to the bones who I was never able to treat because he was too afraid to initiate therapy. I bargained with him, I tried, offering him single-agent therapy, and then transitioning to perhaps combination. He ultimately died because of a pain control issue... I was unable to find someone to help me in changing his mind to choose therapy over death and suffering. Have your specialists had difficulties such as this, and do they have any pearls of wisdom as to how to try to ease our patients into decisions that are difficult?
- Do you ever select nivo/ipi for low-risk patients with metastatic ccRCC? If so, why?
- I have a 67-year-old patient with metastatic RCC who got adjuvant TKI + PD-L1 with good response. He had brain mets that were resected. Would you consider nephrectomy in such a patient?



# Questions from General Medical Oncologists Advanced RCC

- Tivozanib, cabozantinib and lenvatinib/everolimus all generally have poor durable responses second line and are largely chosen by toxicity profile. Is there more to this decision?
- Len/everolimus benefits versus single-agent TKIs
- Given all the choices in systemic, how often is high-dose IL-2 used and when?
- How do you decide second-line lenvatinib vs tivozanib?  
Do you base the decision on type of histology?
- Cabo second line if not already used? Or would you try tivozanib?



# Questions from General Medical Oncologists Advanced RCC

- Belzutifan has a different MOA and may have better results than using other TKIs at progression. Is there an assay that can determine if HIF is a driver mutation in any given patient? Can ICIs be reintroduced in a later line of therapy?
- For a somatic VHL mutation, can we use belzutifan?
- When do we use belzutifan? Is HLA typing needed?
- With belzutifan combination clinical trials in progress, do you think there will be any role for triplets in the future for metastatic renal cell cancer?



# Questions from General Medical Oncologists

## TKI-associated Toxicity

- I have a 66-year-old on cabo. He had hand/foot syndrome. How would you manage this?
- Fatigue has been a significant issue with lenvatinib in my patients. How low could you go on the dose?
- Patient has severe diarrhea with cabozantinib even with 20 mg and on max dose of antidiarrhea meds. What would you recommend?
- Compare the toxicity profiles of tivozanib, cabozantinib and lenvatinib
- Lenvatinib dose reductions needed in almost all patients getting this in combo with pembrolizumab. Will this alter the efficacy?



# Questions from General Medical Oncologists

## TKI-associated Toxicity

- In a patient with significant thrombocytopenia on cabozantinib, how do you adjust the dosing and what do you use as a starting dose?



# Questions from General Medical Oncologists

## Immune-mediated Toxicity

- Patient develops Guillain-Barre to adjuvant immunotherapy. Now what?
- If patient has rheumatoid arthritis but under control, should we use pembro in this setting or not?
- How to manage immunotherapy-mediated skin issues
- I have a patient who achieved a response with pembrolizumab and then developed OPTIC NEURITIS! She now has relapsed. Can I re-treat her with another checkpoint inhibitor?
- Can experts take us through some real cases of pts who experienced significant toxicities and walk us through their approach?



# Agenda

## Module 1 – ASCO 2023

## Module 2 – Management of Advanced Renal Cell Carcinoma (RCC)

- First-line systemic therapy for metastatic clear cell RCC (ccRCC)
- Management of toxicities associated with up-front combination regimens
- Management of ccRCC in the second-line setting and beyond
- Management of toxicities associated with approved multikinase inhibitors

## Module 3 – Treatment Approaches for Nonmetastatic RCC; Optimal care of Patients with Non-Clear Cell RCC

- Adjuvant therapy for RCC
- Management of non-clear cell RCC
- Novel investigational agents/strategies for RCC (eg, zanzalintinib)



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

Sumanta Kumar Pal, M.D.

Clinical Professor

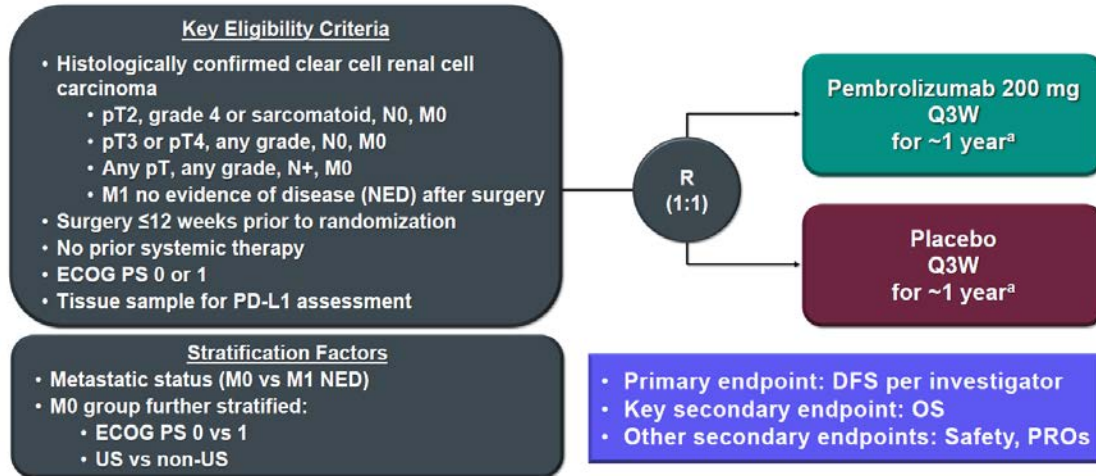
Department of Medical Oncology &  
Experimental Therapeutics

City of Hope Comprehensive Cancer  
Center

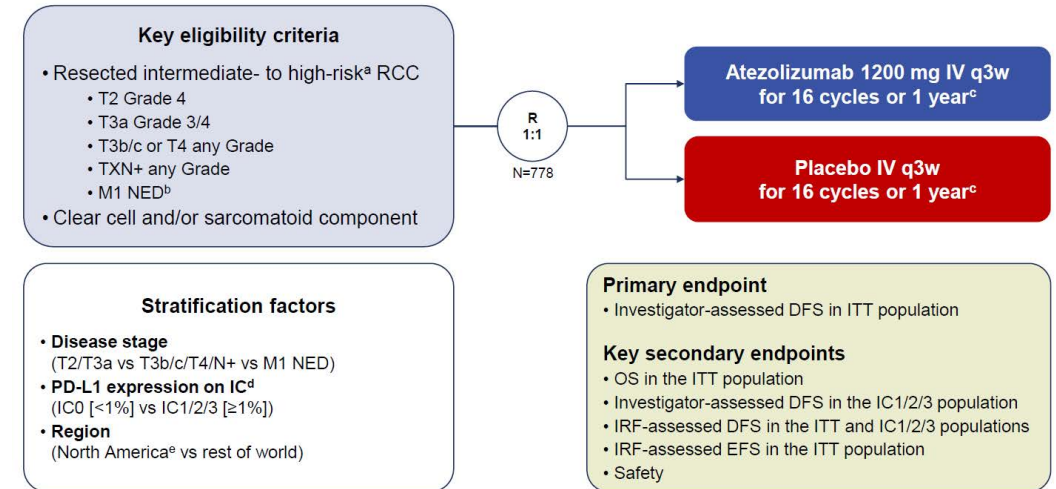


# Key Trials in the Adjuvant Space

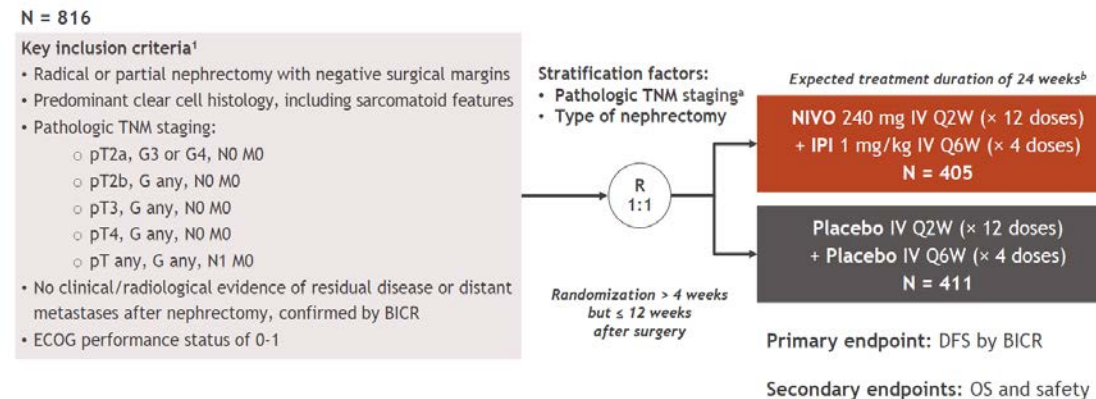
## KEYNOTE-564



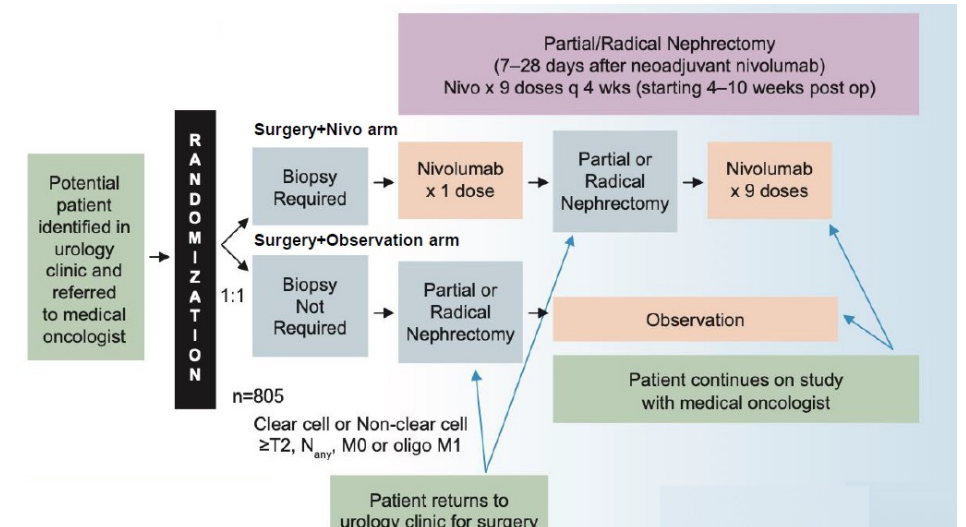
## Immotion010



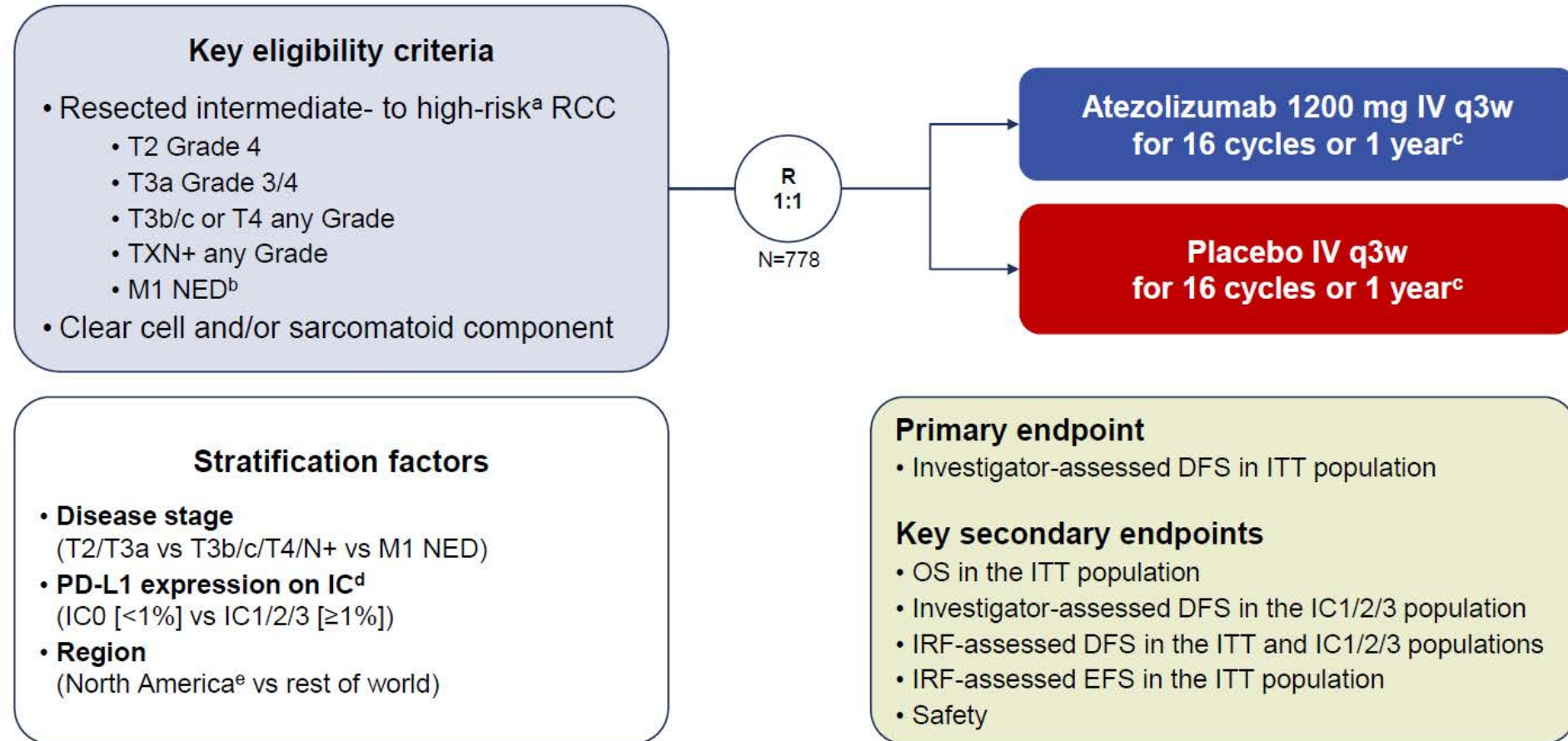
## CheckMate 914



## ECOG PROSPER

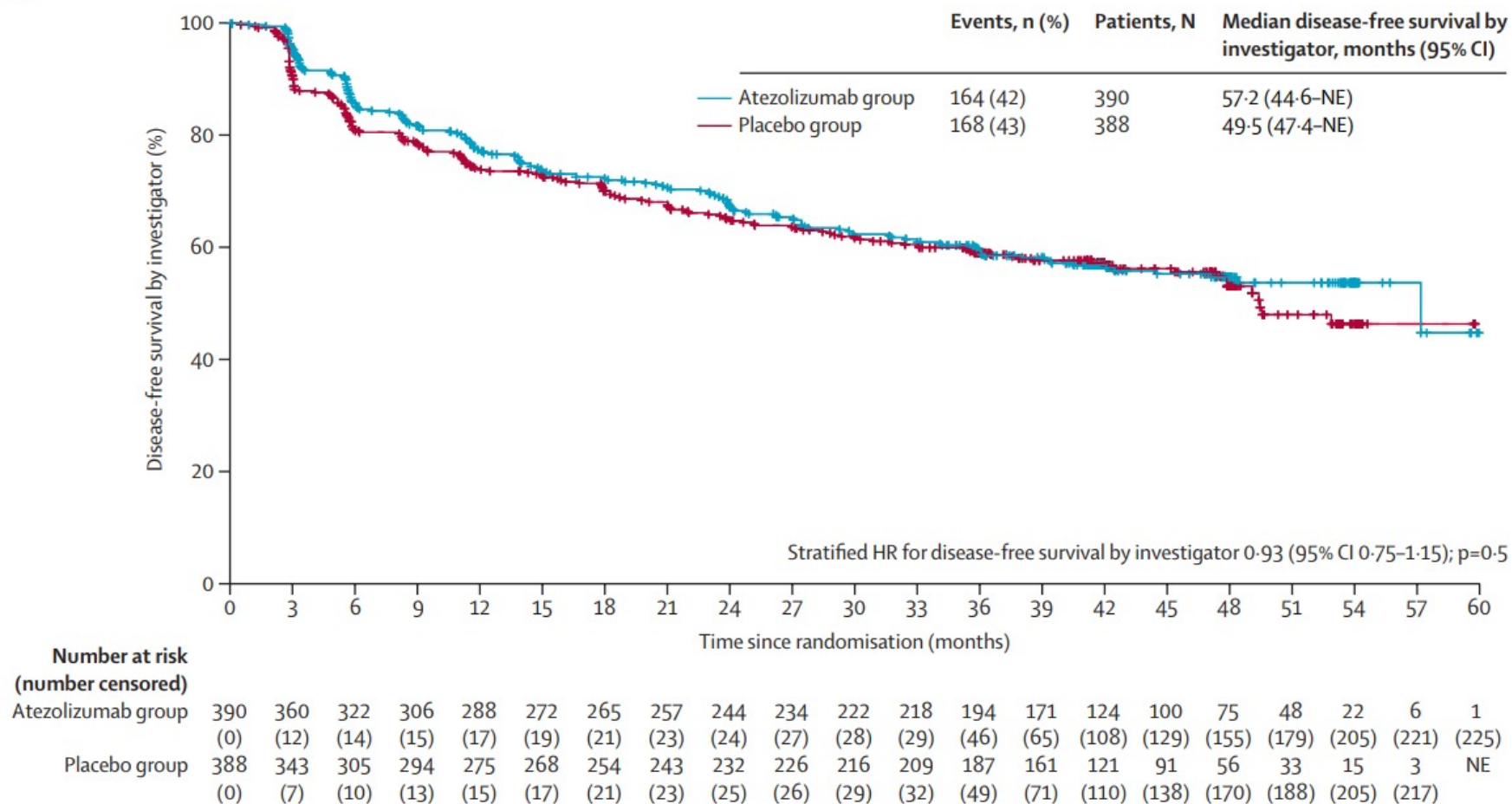


# IMmotion010 (NCT03024996)



# IMmotion010 (NCT03024996)

A





# CheckMate-914 (NCT03138512)

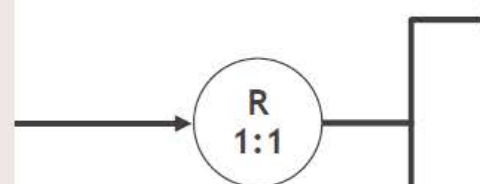
N = 816

## Key inclusion criteria<sup>1</sup>

- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1

## Stratification factors:

- Pathologic TNM staging<sup>a</sup>
- Type of nephrectomy



*Randomization > 4 weeks  
but ≤ 12 weeks  
after surgery*

*Expected treatment duration of 24 weeks<sup>b</sup>*

**NIVO 240 mg IV Q2W (× 12 doses)  
+ IPI 1 mg/kg IV Q6W (× 4 doses)  
N = 405**

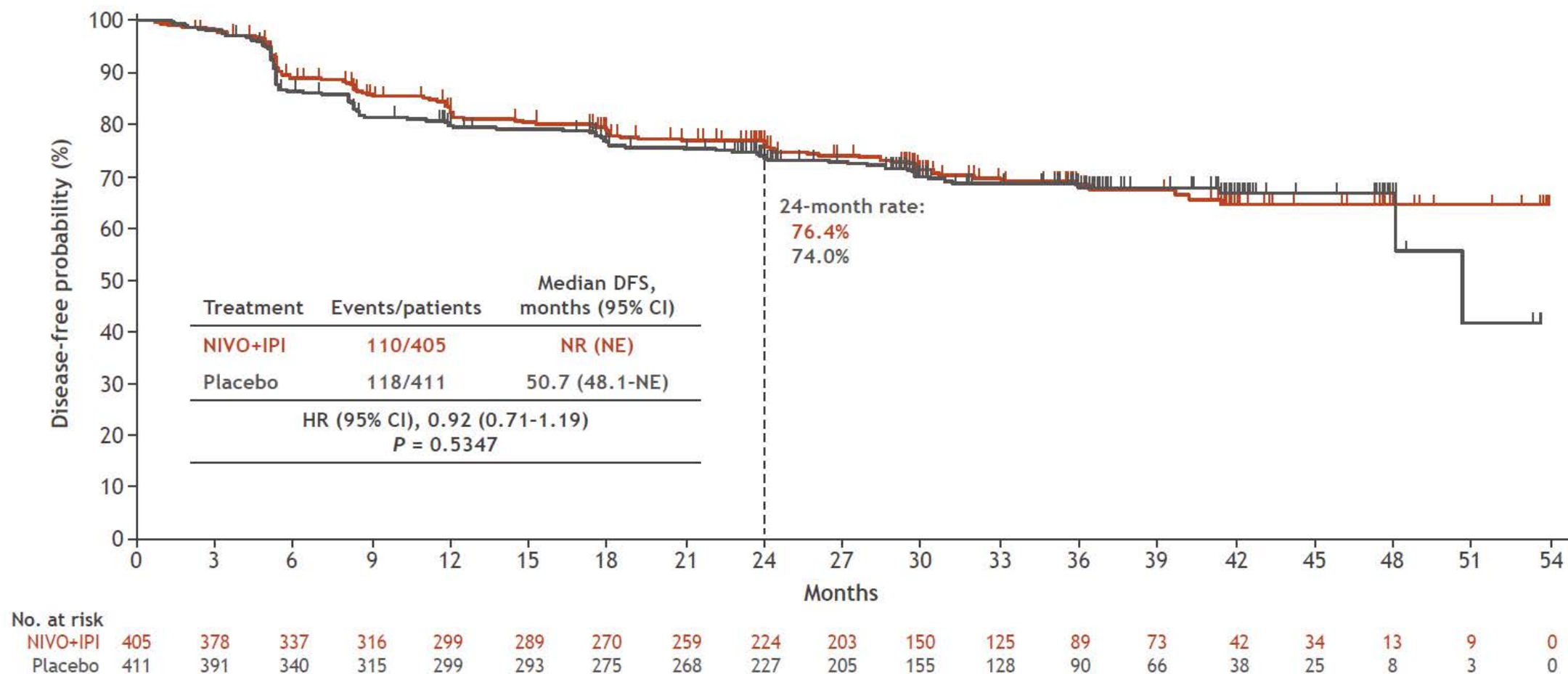
**Placebo IV Q2W (× 12 doses)  
+ Placebo IV Q6W (× 4 doses)  
N = 411**

**Primary endpoint: DFS by BICR**

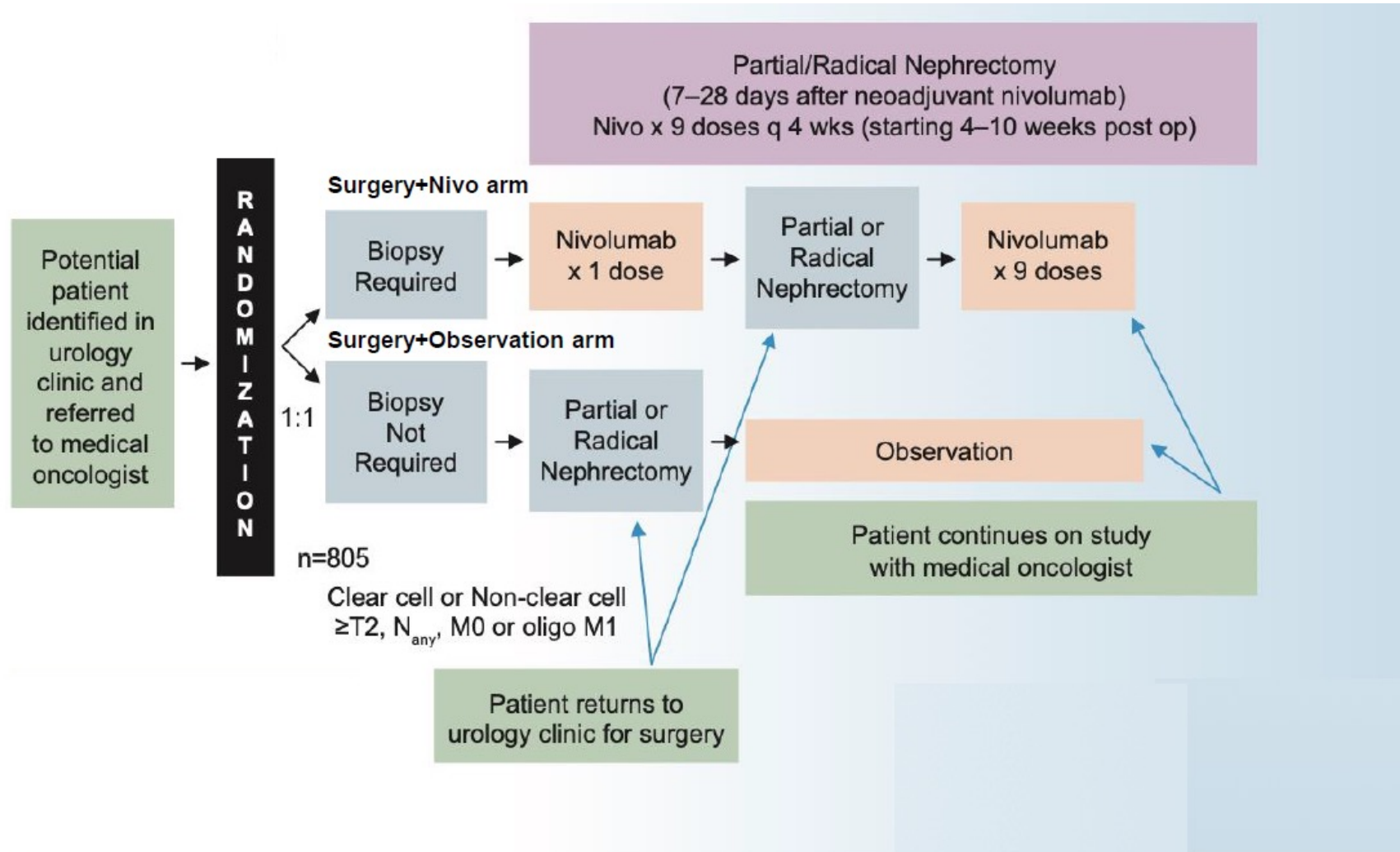
**Secondary endpoints: OS and safety**

**Median (range) study follow-up, 37.0 (15.4-58.0) months**

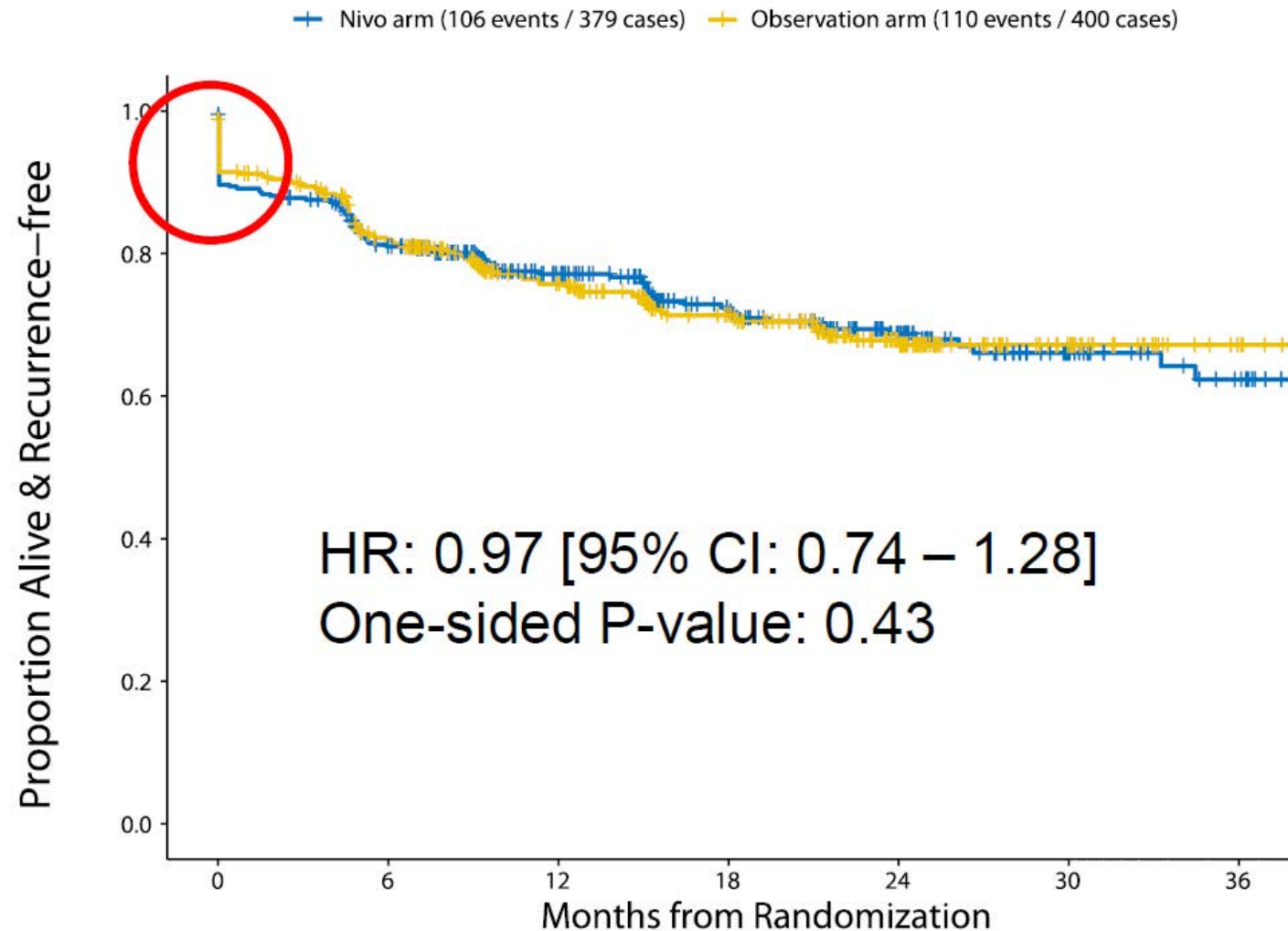
# CheckMate-914 (NCT03138512)



# ECOG-ACRIN EA8143: PROSPER



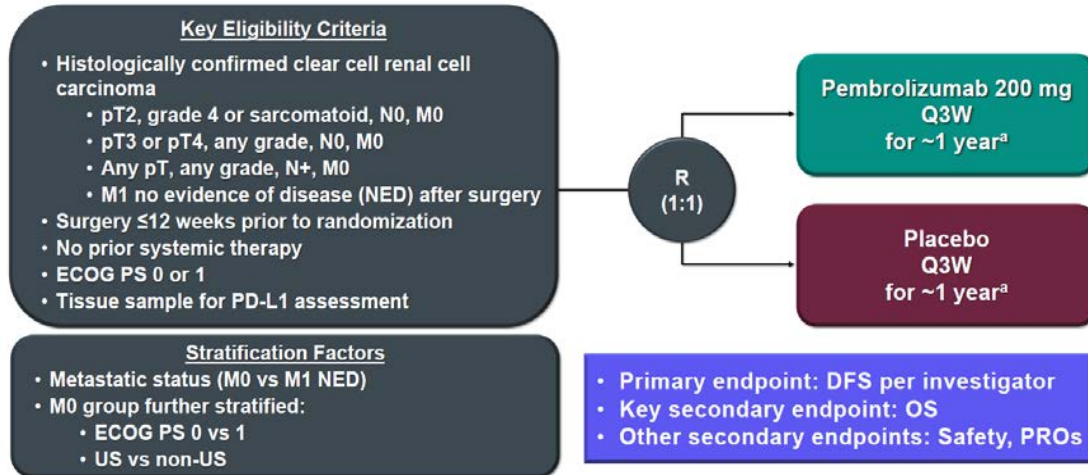
# ECOG-ACRIN EA8143: PROSPER



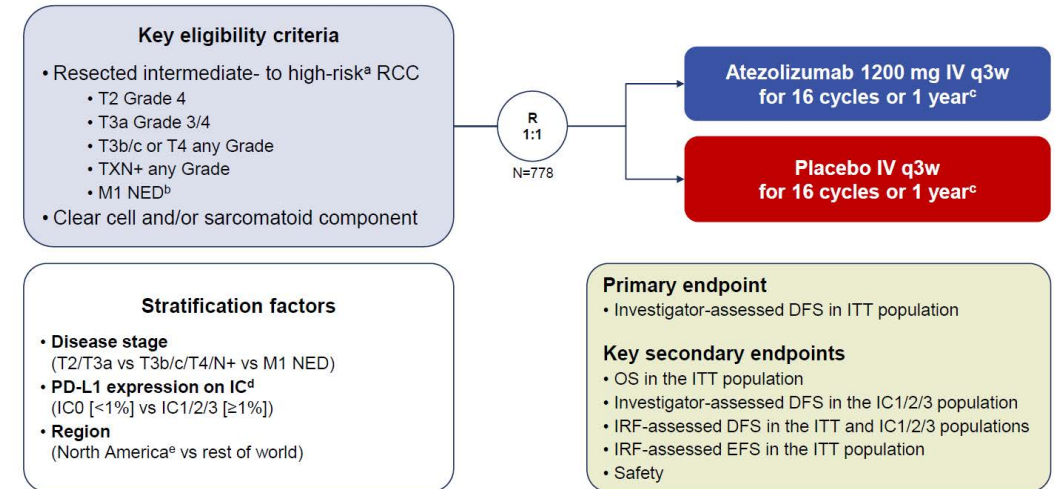


# The Bottom Line ...

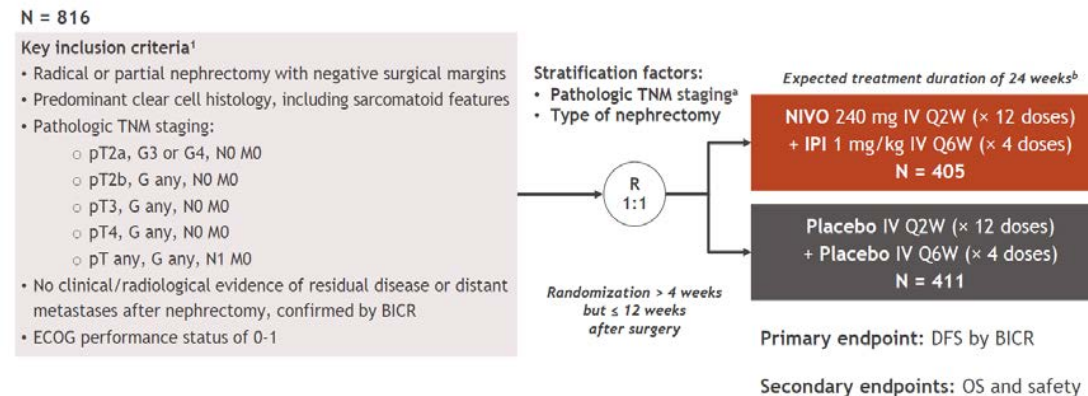
## KEYNOTE-564



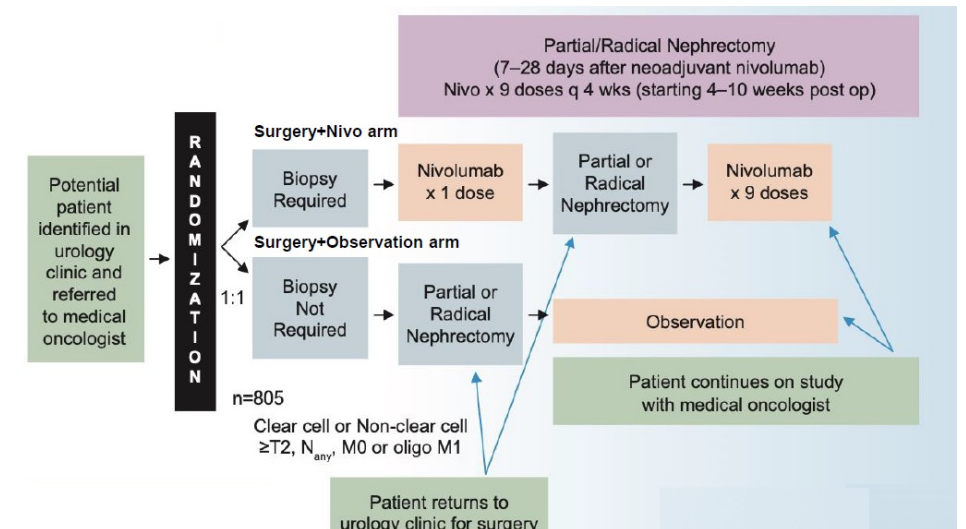
## Immotion010



## CheckMate 914



## ECOG PROSPER



## The Bottom Line ...

# KEYNOTE-564

## KEYNOTE-564

- **It's a positive study**
- **Appropriate sample size**
- **Substantial DFS benefit across subgroups**
- **OS in the right direction!**

**embrolizumab 200 mg  
Q3W  
for ~1 year<sup>a</sup>**

**Placebo  
Q3W  
for ~1 year<sup>a</sup>**

FS per investigator  
point: OS  
endpoints: Safety, PROs

# Immotion010

### Key eligibility criteria

- Resected inter
  - T2 Grad
  - T3a Gr
  - T3b/c c
  - TXN+ a
  - M1 NE
- Clear cell a

# IMmotion010

- **Smaller sample size**
- **Different definition of M1 population**
- **PD-1 versus PD-L1**

**trastuzumab 1200 mg IV q3w  
cycles or 1 year<sup>c</sup>**

bo IV q3w  
cles or 1 year<sup>c</sup>

ITT population

the IC1/2/3 population  
r and IC1/2/3 populations  
ITT population

- Safety

## CheckMate 914

N = 816

### Key inclusion

- Radical or pa
- Predominant
- Pathologic T
  - pT2a
  - pT2b
  - pT3,
  - pT4,
  - pT and
- No clinical/r
- metastases a
- ECOG perfor

## CheckMate 914

- High rates of toxicity
- Lots of drug discontinuation
- Did toxicity get in the way of treatment?

treatment duration of 24 weeks<sup>b</sup>

mg IV Q2W (× 12 doses)  
g/kg IV Q6W (× 4 doses)  
N = 405

- o IV Q2W (× 12 doses)
- o IV Q6W (× 4 doses)

**N = 411**

- **Key point: DFS by BICR**

Primary endpoints: OS and safety

**ECOG PROSPER**

# ECOG PROSPER

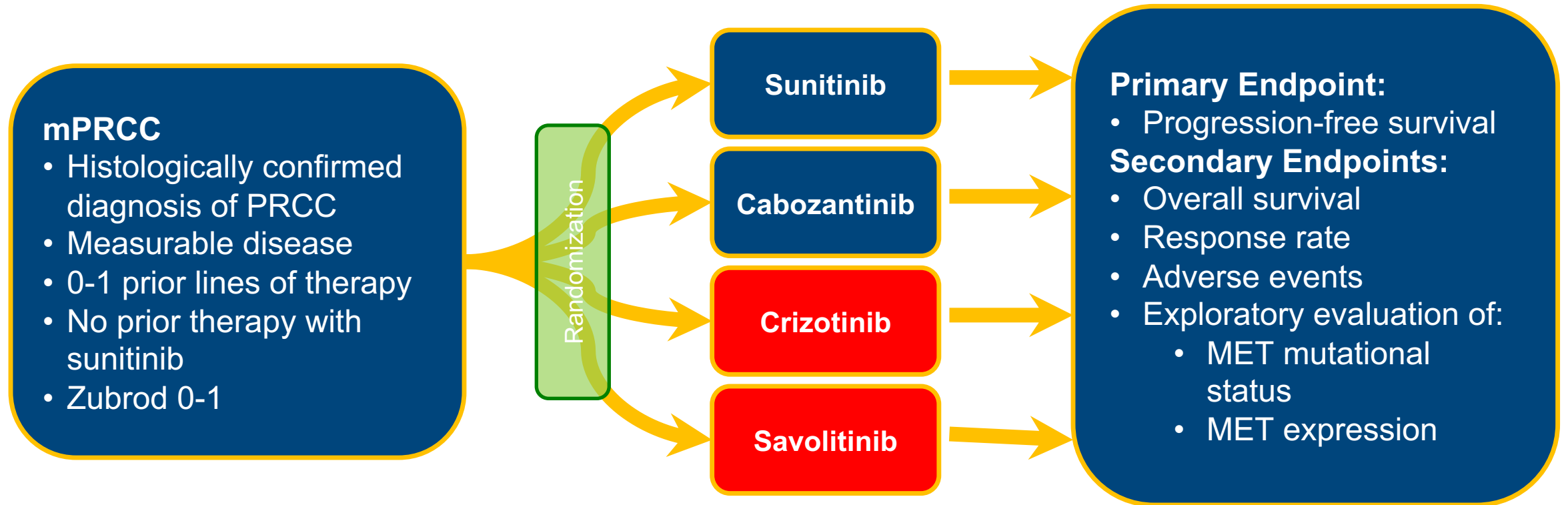
- **Neoadjuvant versus adjuvant**
- **Lower risk population (e.g., T1/T2)**

≥T2, N<sub>aux</sub>, M0 or oligo M1

Patient returns to urology clinic for surgery

# Non-Clear Cell RCC

## SWOG 1500: PAPMET



N=152 across 65 centers; Accrual: 3.6 patients/month

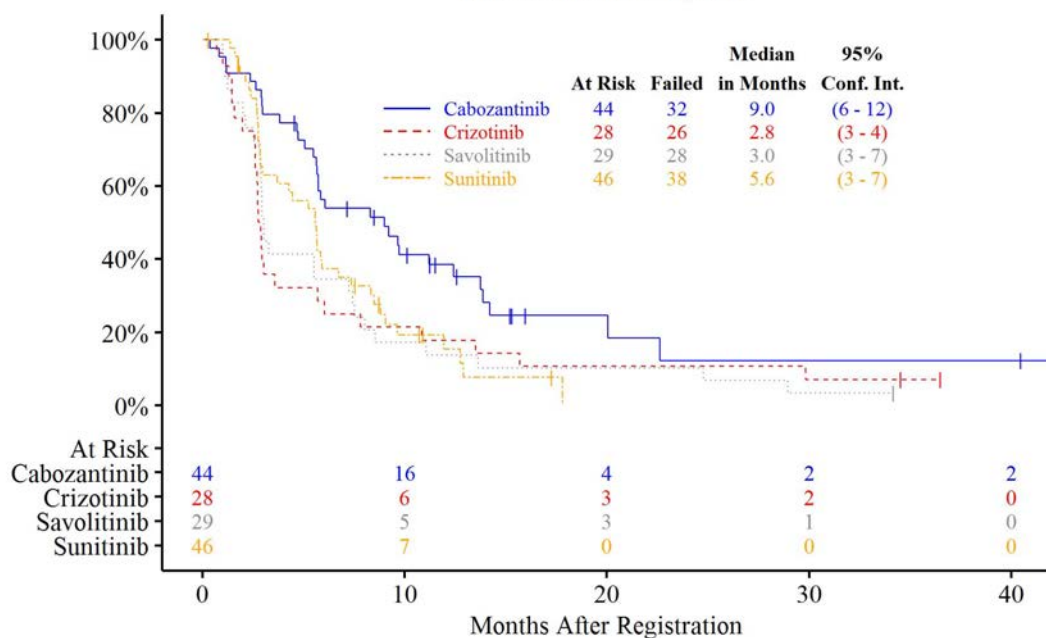
Pal et al Lancet 2021

# Non-Clear Cell RCC

## SWOG 1500: PAPMET

### Progression-Free Survival

Data as of October 14, 2020



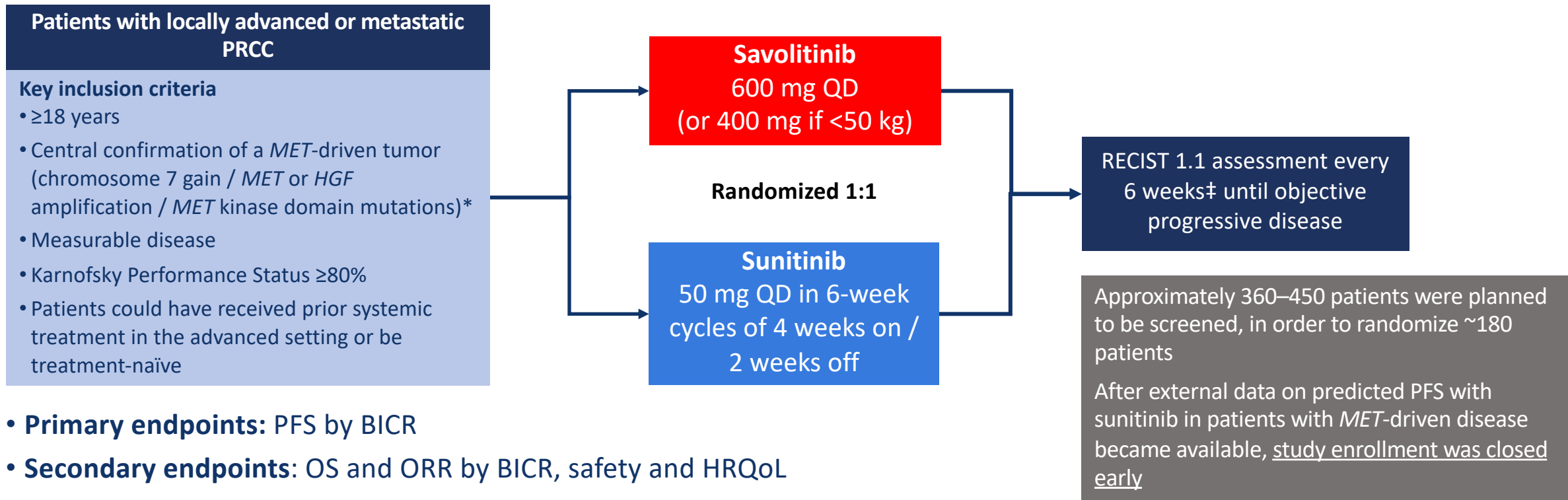
Confirmed overall response rate with cabozantinib (23%) significantly higher than with sunitinib (4%) (2-sided P-value= 0.010)

	Sunitinib [n (%)]	Cabozantinib [n (%)]	Crizotinib [n (%)]	Savolitinib [n (%)]
Complete Response	0 (0)	2 (5)	0 (0)	0 (0)
Partial Response (PR)	2 (4)	8 (18)	0 (0)	1 (3)
Unconfirmed Partial Response	1 (2)	2 (5)	1 (4)	2 (7)
Stable Disease	23 (50)	23 (51)	7 (25)	8 (28)
Increasing Disease	11 (24)	4 (9)	12 (43)	8 (28)
Symptomatic Deterioration	1 (2)	1 (2)	3 (11)	1 (3)
Early Death	1 (2)	1 (2)	0 (0)	0 (0)
Assessment Inadequate	7 (15)	3 (7)	5 (18)	9 (31)
Total	46 (100)	44 (100)	28 (100)	29 (100)

Pal et al Lancet 2021

# Non-Clear Cell RCC

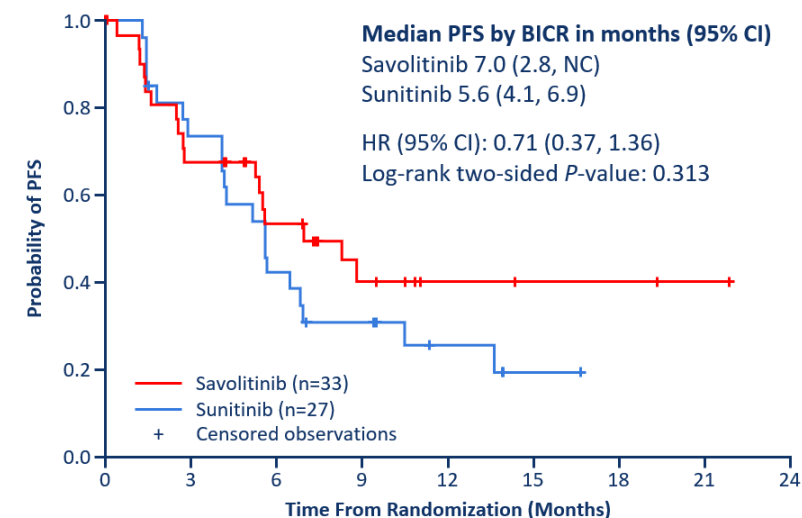
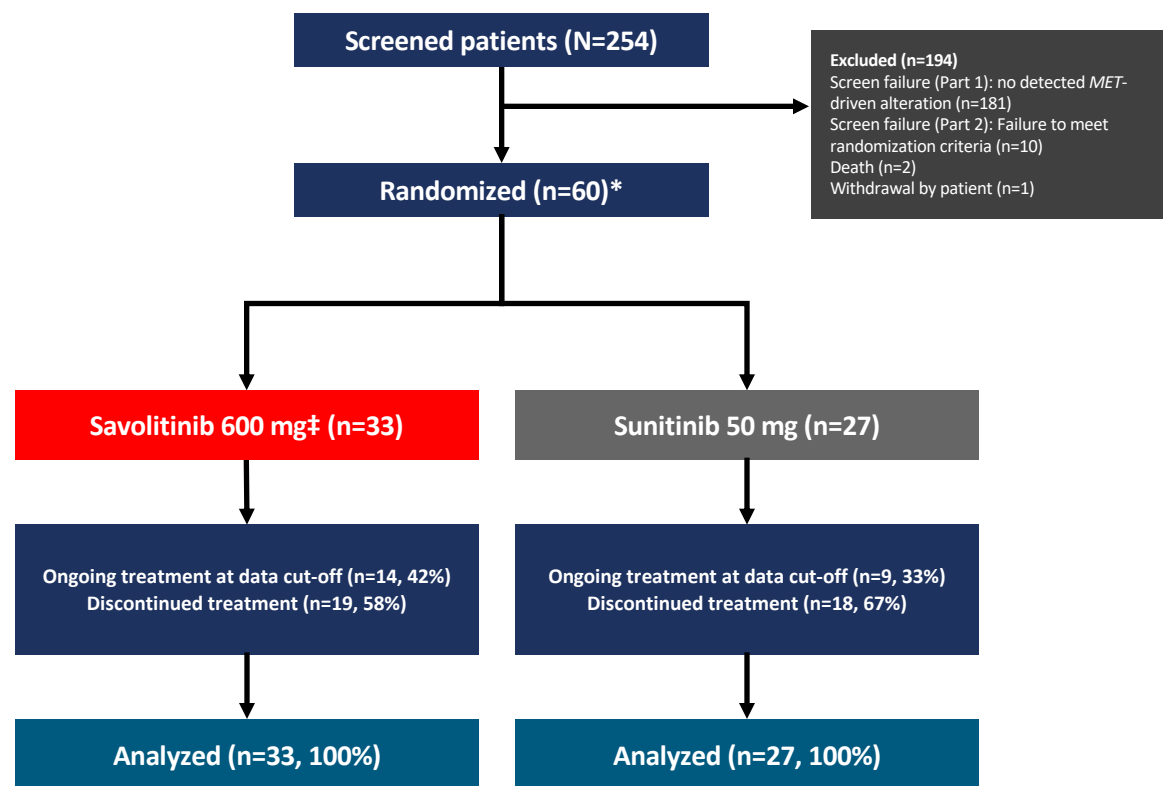
## SAVOIR



Choueiri et al JAMA Oncol 2020

# Non-Clear Cell RCC

## SAVOIR



Number of Patients at Risk									
Savolitinib	33	21	15	8	4	3	3	1	0
Sunitinib	27	19	11	7	4	1	0	0	0

Number Randomized/ Number of Events	
33/17	
27/20	

Endpoint, n (%) [95% CI]

**Savolitinib (N=33)**

**Sunitinib (N=27)**

ORR by BICR,  
*All partial responses*

9 (27) [13.3, 45.5]

2 (7) [0.9, 24.3]

Disease control rate by BICR

At 6 months  
 At 12 months

16 (48) [30.8, 66.5]  
 10 (30) [15.6, 48.7]

10 (37) [19.4, 57.6]  
 6 (22) [8.6, 42.3]

Choueiri et al JAMA Oncol 2020

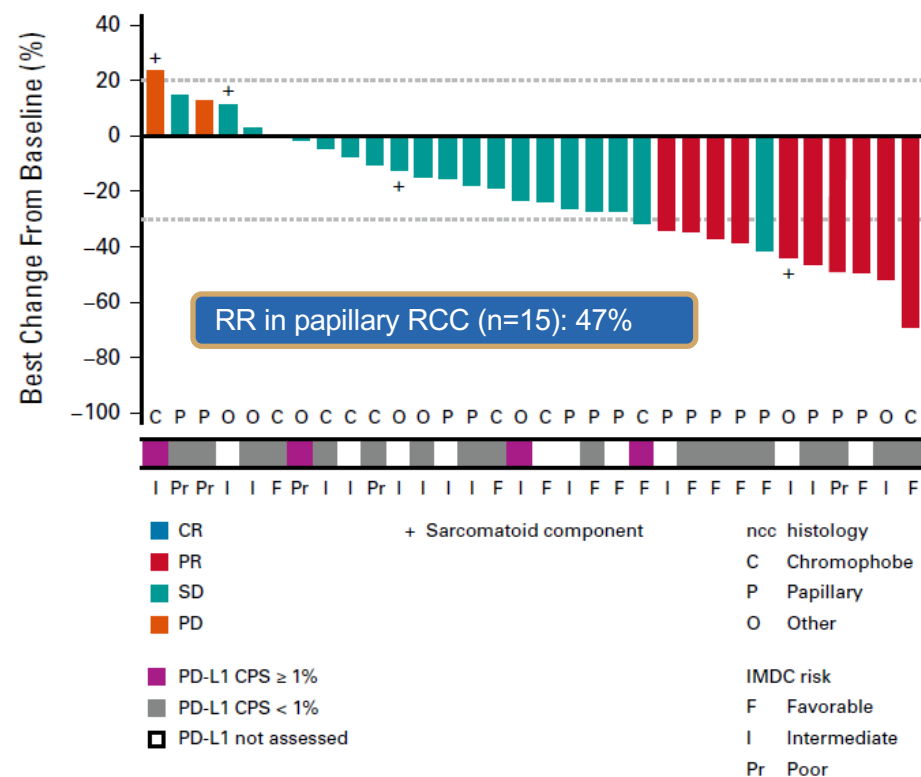




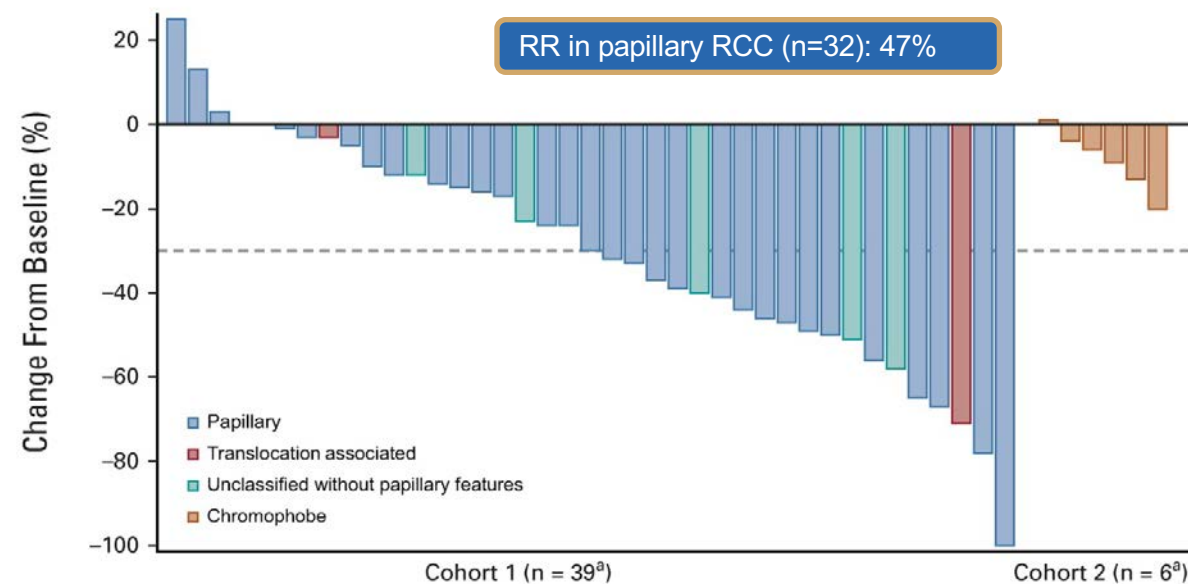
# Non-Clear Cell RCC

## What About Combination Therapy?

### Cabozantinib/Atezolizumab



### Cabozantinib/Nivolumab

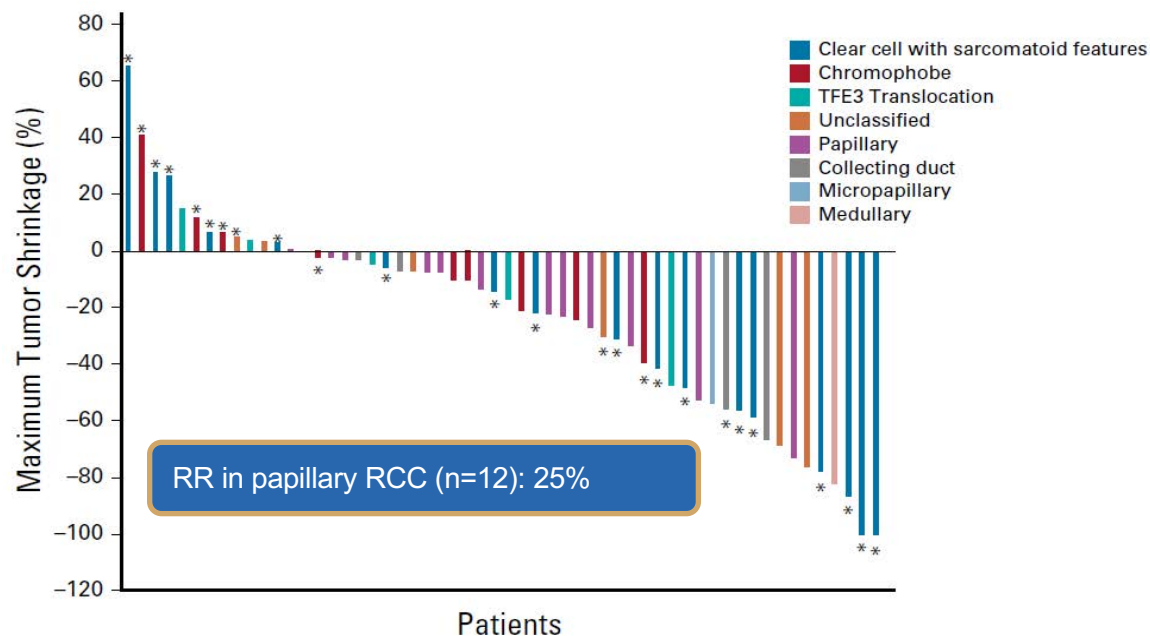


Pal et al JCO 2021; Lee CH et al JCO 2022

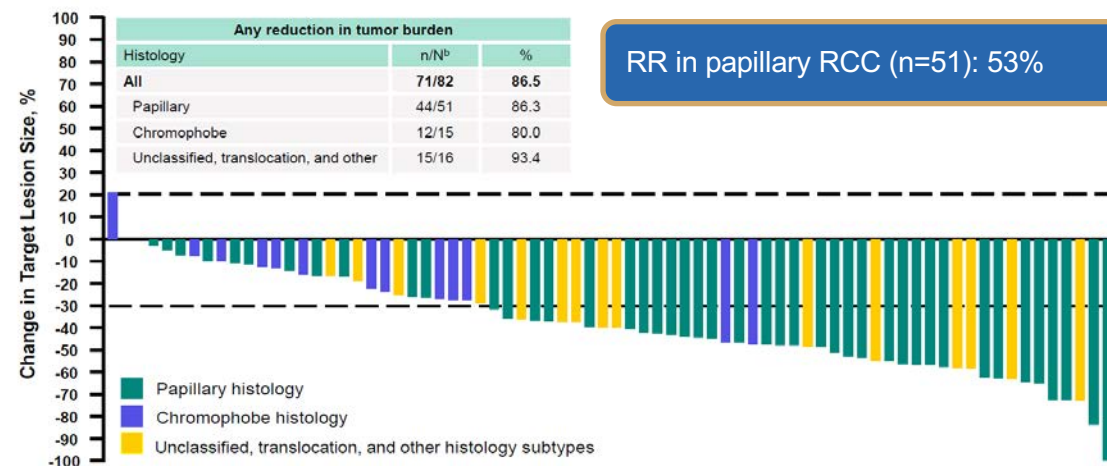
# Non-Clear Cell RCC

## What About Combination Therapy?

### Bevacizumab/Atezolizumab



### Lenvatinib/Pembrolizumab



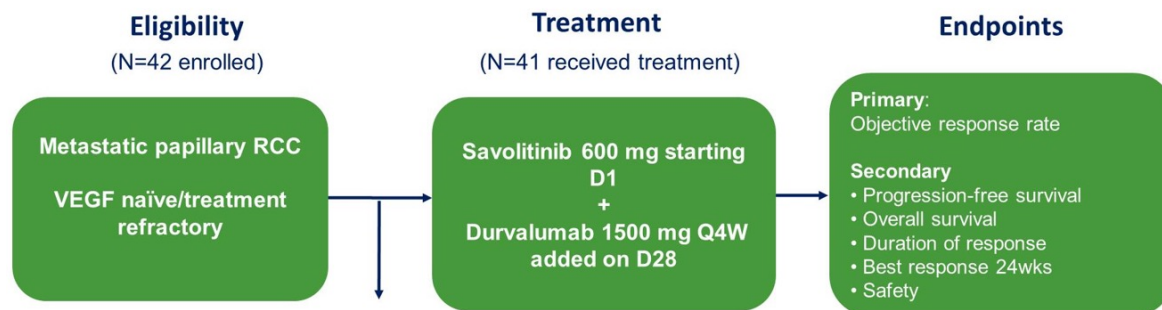
McGregor et al JCO 2019; Albiges et al ESMO 2022 (Abstr 1448O)



# Non-Clear Cell RCC

## Savolitinib with Durvalumab

### Phase II Data



1 pt progressed before

Best overall response	All patients (N=41)		Previously untreated (N=28)	
	n (%)	95% CI for %	n (%)	95% CI for %
PR	11 (27)	(14 - 43)	9 (32)	(16 - 52)
SD	16 (39)	(24 - 55)	12 (43)	(24 - 63)
PD	11 (27)	(14 - 43)	5 (18)	(6 - 37)
NA*	3 (7)	(2 - 20)	2 (7)	(1 - 24)

### Phase III SAMETA Trial

#### Key Eligibility Criteria

- Locally advanced or metastatic PRCC
- Confirmation of MET-driven PRCC without co-occurring FH mutations using central laboratory validated NGS Assay
- 1L patients (Tx naïve in metastatic setting)
- No prior METi, durvalumab or sunitinib
- Measurable disease per RECIST1.1
- Karnofsky Score >70
- Stable/asymptomatic brain mets permitted
- No history of serious liver disease, no active or recent clinically significant cardiac conditions, no active infection, autoimmune or inflammatory disorders\*

N=200  
R: 2:1:1

Arm A: Savolitinib +  
Durvalumab (N=100)

Arm B: Sunitinib  
(N=50)

Arm C: Durvalumab  
(N=50)

#### Primary Endpoint

- PFS by BICR per RECIST 1.1 (Arm A vs. B)

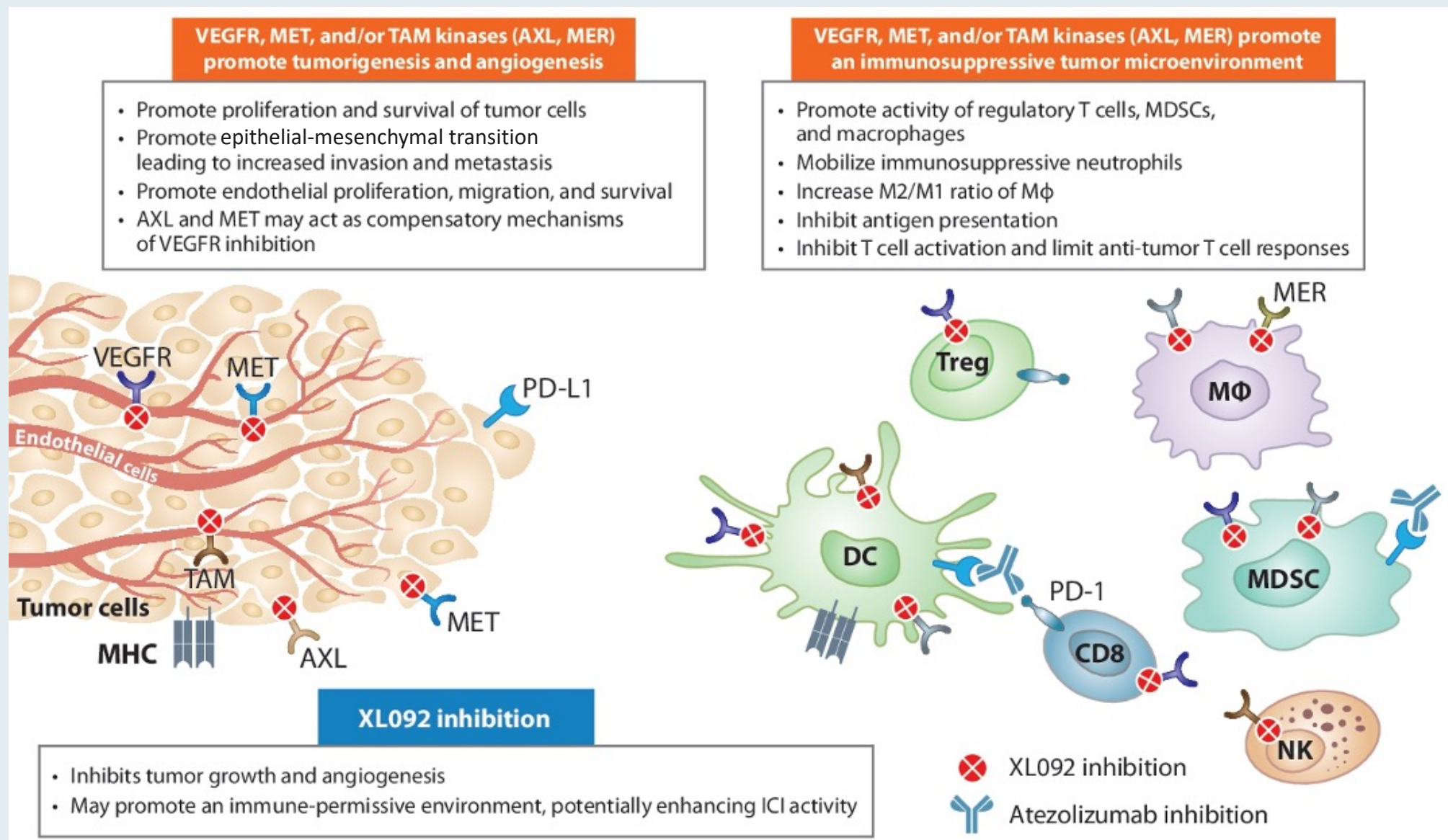
#### Main Secondary Endpoints

- OS
- ORR, DoR, DCR by BICR
- PFS2
- Safety
- PRO/HRQoL
- Pharmacokinetics

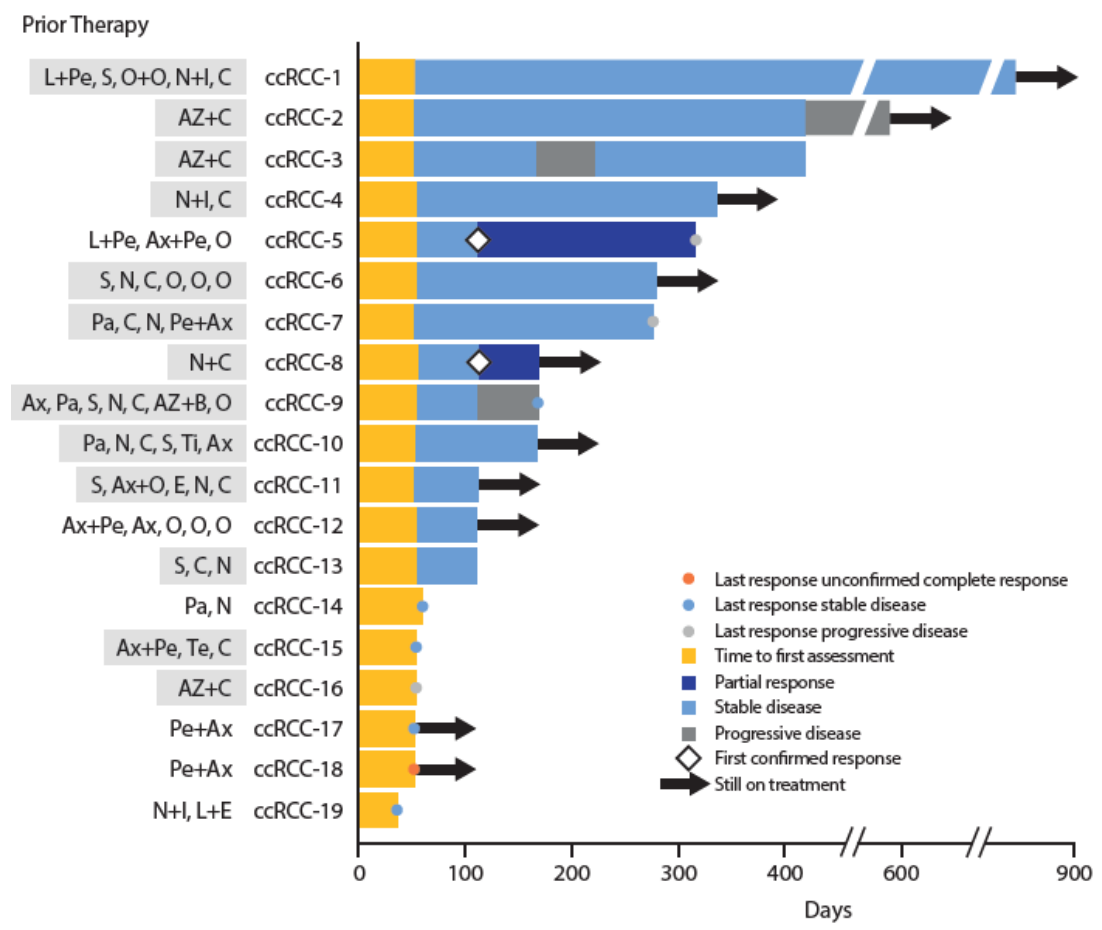
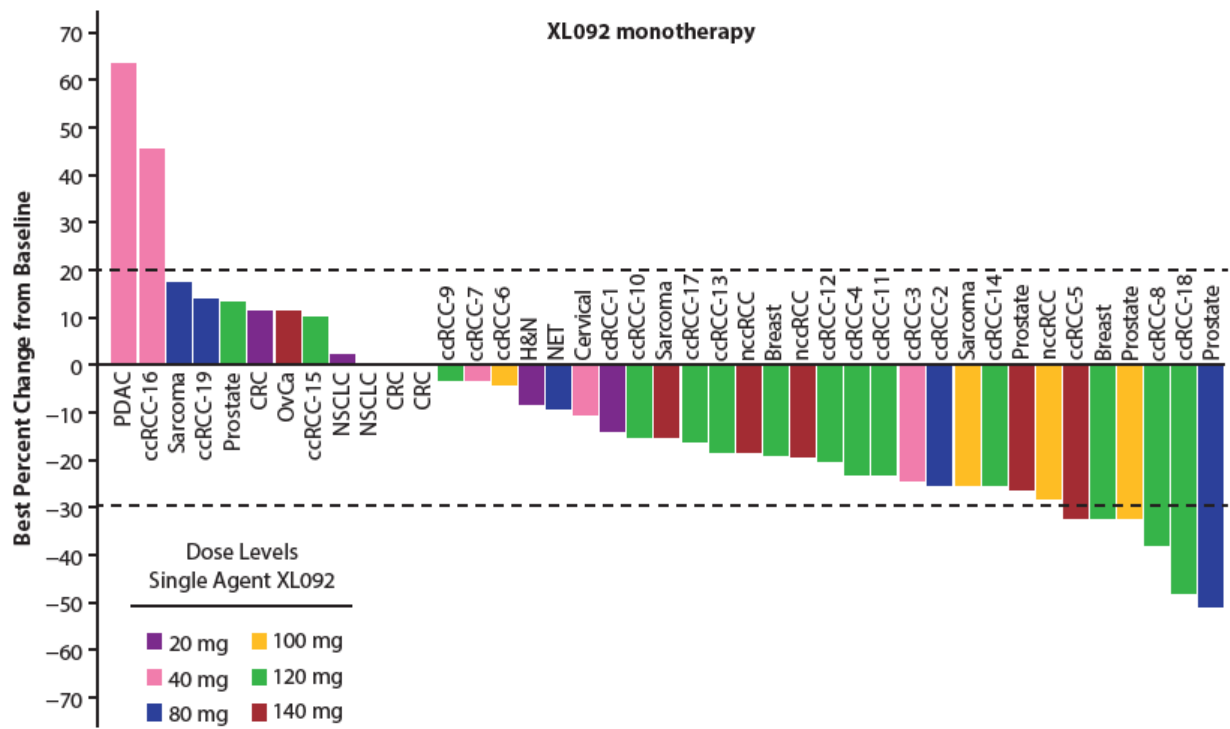
Powles et al ASCO GU 2019

Choueiri et al ASCO 2021

# Zanzalintinib (XL092): Mechanism of Action



# Zanzalintinib (XL092): Targets MET, VEGFR2 & TAM (Half-life ~21 hrs)



Sharma et al ESMO 2022



# STELLAR-304

## Patient Population

### Advanced or metastatic nccRCC (N=291)

- Unresectable, advanced or metastatic nccRCC
- Histologic subtypes: papillary, unclassified, and translocation-associated
  - Tumor tissue required
- KPS  $\geq 70\%$
- No prior treatment for nccRCC (adjuvant PD-1 allowed if >6 months ago)

2:1

### Experimental

Zanzalintinib (XL092)  
PO QD  
+  
Nivolumab  
IV Q4W

### Control

Sunitinib  
PO QD  
4 weeks on, 2 weeks off

Treatment until loss of clinical benefit, disease progression or unacceptable toxicity

## Stratification

- Histologic subtype
- IMDC Risk Group

## Study Endpoints

- **Primary:** PFS and ORR by BIRC
- **Secondary:** OS

# Questions from General Medical Oncologists Nonmetastatic RCC

- **Why is pembro a positive study when the other ICI studies are negative? Without OS data, is it advisable to use? Can ctDNA be used to determine if adjuvant therapy is necessary?**
- **Any role/recommendations for adjuvant Tx in non-clear cell RCC?**
- **Please review the role of adjuvant therapy after metastasectomy for patients with oligomets**
- **How to figure out benefit/detriment ratio for adjuvant therapy**
- **Is there a role for ctDNA in selecting patients for adjuvant RCC?**





# Questions from General Medical Oncologists Non-clear Cell RCC

- Could you elaborate on the best regimens to use in non clear cell cancer and how best to sequence them?
- Treatment of sarcomatoid RCC
- What is best therapy for cMET-mutated disease?
- I have a patient with an ALK1 mutation in the renal cancer. What should be used as therapy?
- Is there any role for adjuvant therapy in non clear cell RCC?
- This is a completely challenging area in management of RCC, and even though I do follow the limited guidelines we have, I have never seen any substantial response.



# Questions from General Medical Oncologists Non-clear Cell RCC

- What is the mechanism of action of zanzalintinib?
- How effective is zanzalintinib? How does it work?
- Will zanzalintinib work after progression on a prior multikinase inhibitor like cabozantinib?
- How do you interpret tivozanib data in papillary renal cell compared to clear cell carcinoma?



# Questions from General Medical Oncologists

## Immune-mediated Toxicity

- Patient treated with ipi + nivo developed hypoadrenalism and hypothyroidism; rx appropriately. However, the patient progressed. Are there any immune-related adverse events that would predict for positive response?
- My patient on 1st-line nivolumab/ipilimumab had Grade 4 colitis. We were able to restart nivolumab alone without recurrent colitis, but what are the data on using infliximab empirically to prevent recurrence?
- I had a 65-year-old male who got ipi/nivo and developed myocarditis. How would you manage this?





# Questions from General Medical Oncologists

## Immune-mediated Toxicity

- Of all the toxicity associated with checkpoint inhibitors, the most difficult for me to manage has been skin toxicities. I have found at least locally that dermatology consultations have been difficult to obtain and not overly useful in terms of providing effective measures.
- My biggest problem has been with itching. Do you use acetylcysteine, photodynamic therapy and naloxone in patients with refractory itching?



# Impediments you have encountered in delivering high-quality care to patients with renal cell carcinoma

- **Finding urologists competent in giving a good opinion in the community for partial nephrectomies in early RCC**
- **For early-stage RCC, in which resection or cryoablation is appropriate, there is a significant delay in referrals to academic medical centers due to insurance denials for higher levels of care. Challenging in California to access some of the immunotherapies due to managed care plans**

# What I Tell My Patients: Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

*Part 2 of a 3-Part Complimentary NCPD Webinar Series  
in Partnership with the 2023 ONS Congress*

## Colorectal and Gastroesophageal Cancers

**Wednesday, June 14, 2023**

**5:00 PM – 6:00 PM ET**

### **Faculty**

**Kristen K Ciombor, MD, MSCI**

**Amanda K Wagner, APRN-CNP, AOCNP**

### **Moderator**

**Neil Love, MD**

***Thank you for joining us!***

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

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