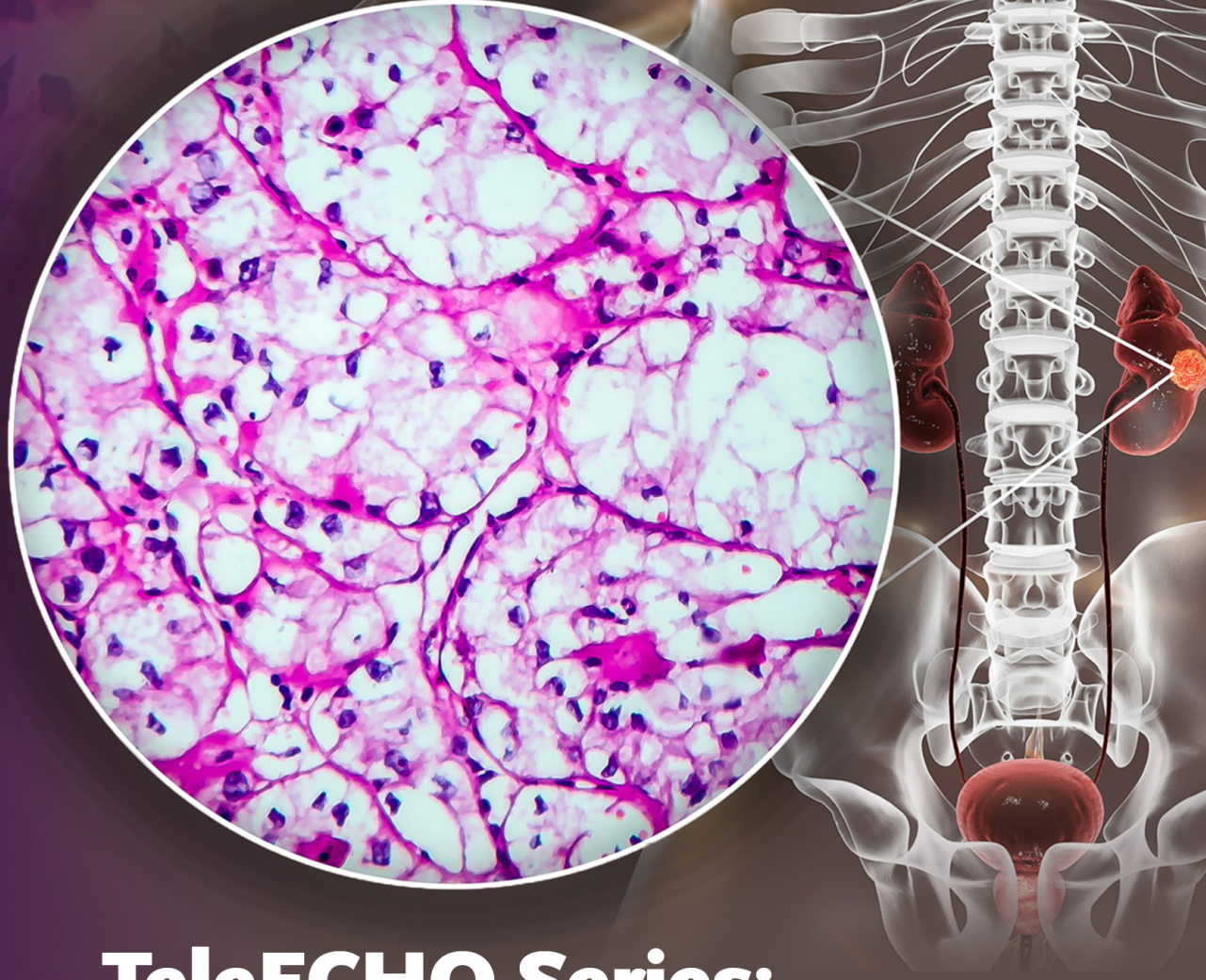

TeleECHO Series:

A Practice-Focused View for Utilizing Combinations of Immune Checkpoint and Tyrosine Kinase Inhibitors for the Treatment of Patients with **Advanced/Metastatic Renal Cell Carcinoma**

Arjun V. Balar, MD
Associate Professor of Medicine
Director, Genitourinary Medical Oncology Program Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, NY

Monday, June 7, 2021

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) and AMEDCO.
This activity is supported by an educational grant from Bristol Myers Squibb.

AGENDA

I. RCC: A Brief Overview

1. Presentation
2. Pathologic subtypes
3. Risk stratification
4. NCCN recommendations

II. IO/TKI Combination Therapeutic Options for the Treatment of Advanced and/or mRCC in the First-line Setting

1. First-line therapies
2. MOAs of IO/TKI combination therapies used for the treatment of mRCC in the first-line setting
3. Clinical trial efficacy and safety results for IO/TKI combination therapies for advanced and/or mRCC in the first-line setting

III. Individualizing the Care of Patients with Advanced and/or mRCC

1. Challenges in first-line management
2. Putting overall survival data into context
3. Recognizing the various types of AEs associated with the use of combination IO/TKI therapeutic options
4. Management strategies for irAEs/trAEs associated with the use of combination IO/TKI therapeutic options
5. Multidisciplinary irAE/trAE management team members and their respective roles
6. Involving a multidisciplinary team

V. Case studies

VI. Conclusions and Q & A

TeleECHO Series: A Practice-Focused View for Utilizing Combinations of Immune Checkpoint and TKIs for the Treatment of Patients with Advanced/Metastatic Renal Cell Carcinoma

FACULTY

Arjun V. Balar, MD
Associate Professor of Medicine
Director, Genitourinary Medical Oncology Program
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, NY

PROGRAM OVERVIEW

These live virtual TeleECHO® sessions will be a faculty-led didactic and case-based lecture focusing on treatment and management of patients with renal cell carcinoma.

TARGET AUDIENCE

This activity is intended for community and academic oncologists and other healthcare providers involved in the treatment of RCC.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Identify the MOAs and clinical profiles of ICI/ICI and ICI/TKI combination therapies for the first-line treatment of patients with advanced and/or mRCC
- Individualize management plans for patients with advanced and/or metastatic RCC in the first-line setting based on available therapeutic regimens, patient preferences, and other relevant factors
- Use recommended strategies to identify, manage, and mitigate irAEs and trAEs associated with first-line combination ICI/ICI and ICI/TKI therapies for the treatment of patients with advanced and/or mRCC
- Recognize the roles of multidisciplinary team members in the diagnosis and management of irAEs/trAEs associated with ICI/ICI and ICI/TKI combination therapies and utilize SDM approaches to patient management

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NURSING CREDIT INFORMATION

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Purpose: This program would be beneficial for nurses involved in the care of patients with renal carcinoma cancer. Credits: 1.0 ANCC Contact Hour.

Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Med Learning Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Speaking Engagements	Genentech, Merck, and AstraZeneca/Medimmune
Steering Committees/Scientific Advisory Committees	Merck and Nektar
Equity and serves as a Scientific Advisory Board Member	EpiVax Oncology

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures.

2. Participate in the live virtual activity.
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Live Learner Notification

Med Learning Group
TeleECHO Series: A Practice-Focused View for Utilizing Combinations of Immune Checkpoint and TKIs for the Treatment of Patients with Advanced/Metastatic Renal Cell Carcinoma
June 7, 2021
Online

Acknowledgement of Financial Commercial Support
Bristol Myers Squibb

Acknowledgement of In-Kind Commercial Support
No in-kind commercial support was received for this educational activity.

Satisfactory Completion
Learners must complete an evaluation form to receive a certificate of completion. You must attend the entire webinar as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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Objectives - After Attending This Program You Should Be Able To
1. Identify the MOAs and clinical profiles of ICI/ICI and ICI/TKI combination therapies for the first-line treatment of patients with advanced and/or mRCC.
2. Individualize management plans for patients with advanced and/or metastatic RCC in the first-line setting based on available therapeutic regimens, patient preferences, and other relevant factors.
3. Use recommended strategies to identify, manage, and mitigate irAEs and trAEs associated with first-line combination ICI/ICI and ICI/TKI therapies for the treatment of patients with advanced and/or mRCC.
4. Recognize the roles of multidisciplinary team members in the diagnosis and management of irAEs/trAEs associated with ICI/ICI and ICI/TKI combination therapies and utilize SDM approaches to patient management.

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Felecia Beachum	NA
Matthew Frese	NA
Christina Gallo	NA
Daniel Dasilva	NA

Scott McGee-Plys	NA
Chris Drury	NA
Lauren Welch	NA

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1. Go to http://mlg.cmecertificateonline.com
2. Click on **"6.7.21 A Practice-Focused View for Utilizing Combinations of Immune Checkpoint and TKIs for the Treatment of Patients with Advanced/Metastatic Renal Cell Carcinoma**" link.
3. Evaluate the meeting, click the provided link to open your credit certificate.
4. Print/save all pages of your certificate for your records.

Questions? Email Certificate@AmedcoEmail.com

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- If you would like to post a question or answer during the presentation, please submit your question or response in the chat feature.
- Remember to direct all questions to the "co-host." There is a toggle button above the typing space that allows you to specify the location of your message delivery.

TeleECHO Series: A Practice-Focused View for Utilizing Combinations of Immune Checkpoint and Tyrosine Kinase Inhibitors for the Treatment of Patients with Advanced/Metastatic Renal Cell Carcinoma

Arjun Balar, MD

Associate Professor of Medicine
Director, Genitourinary Medical Oncology Program
Medical Director, Clinical Trials Office
Laura and Isaac Perlmutter Cancer Center
NYC Langone Medical Center
New York, NY

Disclosures

- **Arjun Balar, MD** reports the following disclosures:

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Speaking Engagements	Genentech, Merck, and AstraZeneca/Medimmune
Steering Committees/Scientific Advisory Committees	Merck and Nektar
Equity and serves as a Scientific Advisory Board Member	EpiVax Oncology

- During the course of this lecture, the presenter will discuss the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grant from Bristol Myers Squibb.

Learning Objectives

- Identify the MOAs and clinical profiles of ICI/ICI and ICI/TKI combination therapies for the first-line treatment of patients with advanced and/or mRCC
- Individualize management plans for advanced and/or metastatic RCC in the first-line setting based on therapeutic regimens, patient preferences, and other factors
- Use recommended strategies to identify, manage, and mitigate irAEs and trAEs associated with first-line combination ICI/ICI and ICI/TKI therapies
- Recognize the roles of multidisciplinary team members in the diagnosis and management of irAEs/trAEs and utilize SDM approaches to patient management

IO = immuno-oncology; TKI = tyrosine kinase inhibitor; IRAE = immune-related adverse event; trAE = treatment-related adverse event

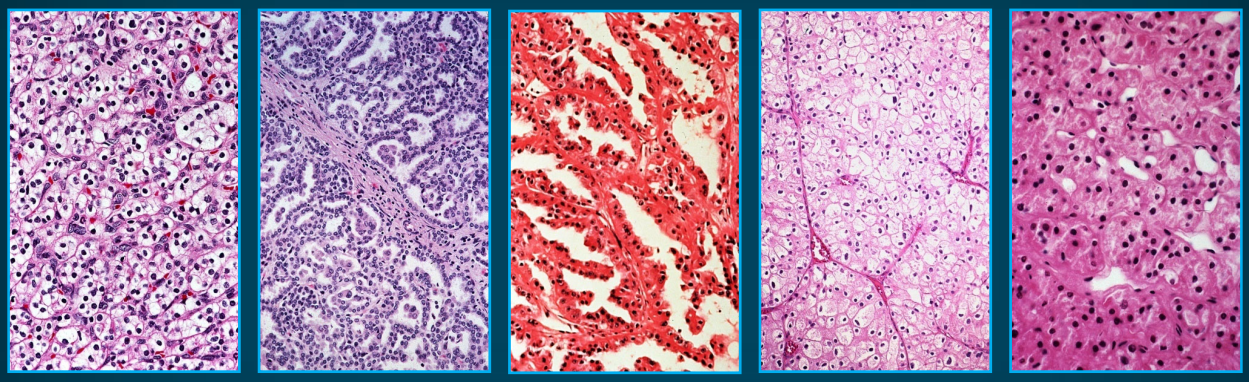
RCC: Clinical Presentation and Pathology

Clinical Presentation: Signs and Symptoms, Paraneoplastic Syndromes

	Finding	Frequency, %
Classic Triad	Flank pain	40
	Hematuria	40
	Palpable mass	35
	Hypertension	33
	Hypercalcemia	10
	Erythrocytosis	4
	Gynecomastia	Rare
	Sedimentation rate elevation	50
	Anemia	33
	Fever	18
	Amyloidosis	3
	Hepatic dysfunction	Uncommon

Palapattu GS, et al. *Rev Urol*. 2002;4(4):163-170.

Renal Cell Carcinoma: Pathologic Subtypes

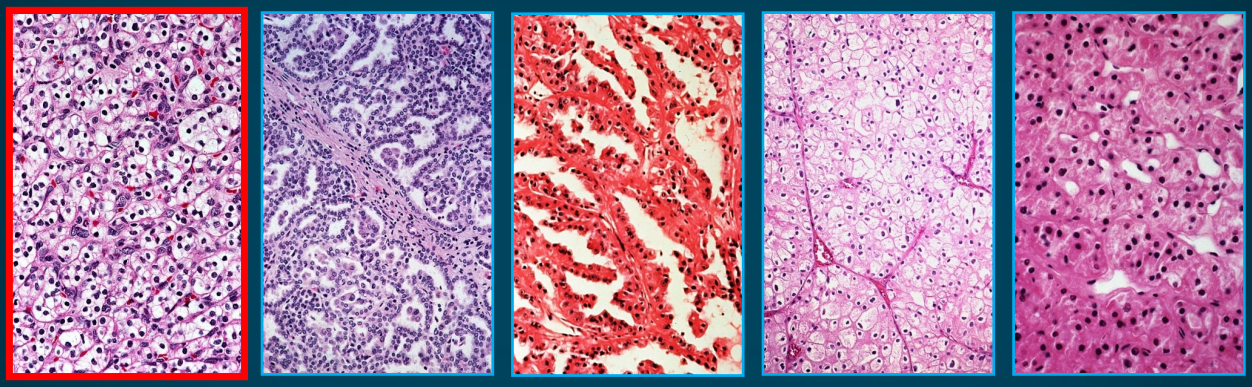


Clear Cell 75% | Papillary Type 1 5% | Papillary Type 2 10% | Chromophobe 5% | Oncocytoma 5%

Other malignant subtypes: medullary, small cell, lymphoma, sarcomas of the kidney

Adapted from Linehan WM, et al. *Clin Cancer Res*. 2004;10:6282S-6289S.

Renal Cell Carcinoma: Pathologic Subtypes



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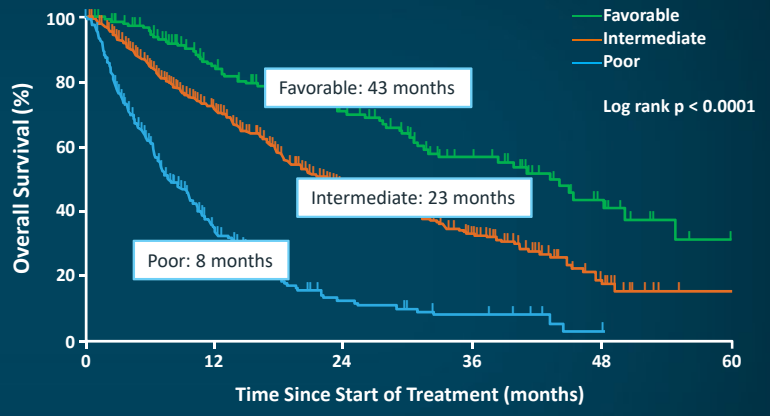
Other malignant subtypes: medullary, small cell, lymphoma, sarcomas of the kidney

Adapted from Linehan WM, et al. *Clin Cancer Res*. 2004;10:6282S-6289S.

Risk Stratification for 1st-Line Therapy in mRCC: IMDC/Heng Criteria

IMDC Criteria Risk Factors	
KPS	< 80%
Time from diagnosis	< 12 months
Hemoglobin	< LLN
Neutrophil count	> ULN
Platelet count	> ULN
Corrected serum calcium	> ULN

Risk Group by Number of Risk Factors	
Favorable (n = 133)	0
Intermediate (n = 301)	1-2
Poor (n = 152)	3-6

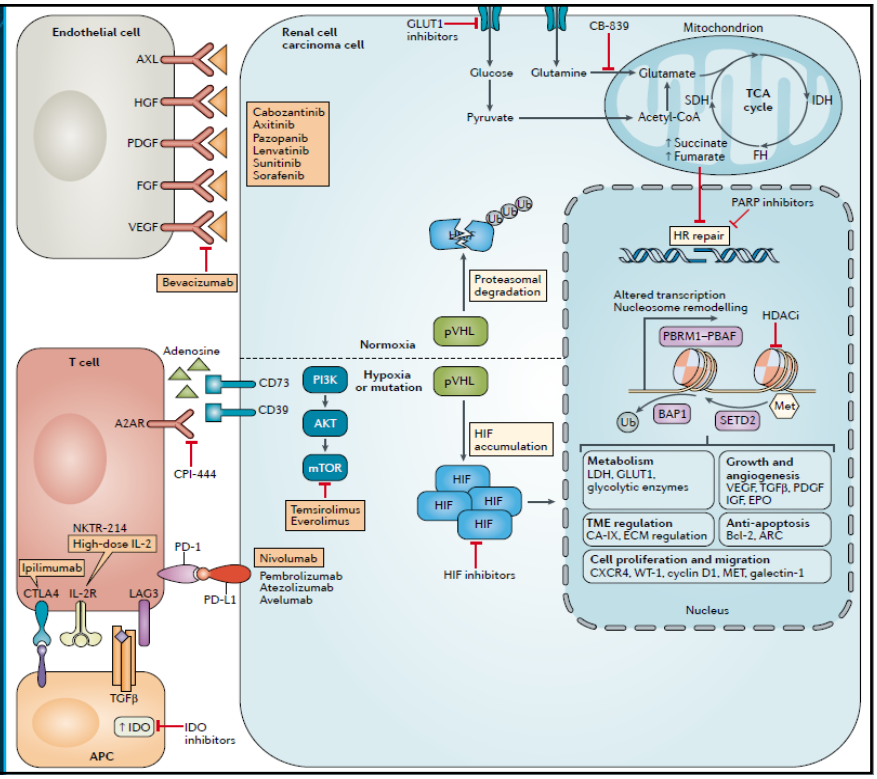


>500 patients with mRCC treated with VEGF-targeted therapy: sunitinib (61%), sorafenib (31%), bevacizumab (8%)

mRCC = metastatic renal cell carcinoma; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; ULN = upper limit of normal; LLN = lower limit of normal; VEGF = vascular endothelial growth factor.

Heng DY, et al. *J Clin Oncol*. 2009;27:5794-5799. Heng DY, et al. *Lancet Oncol*. 2013;14:141-148.

RCC: Therapeutic Targets



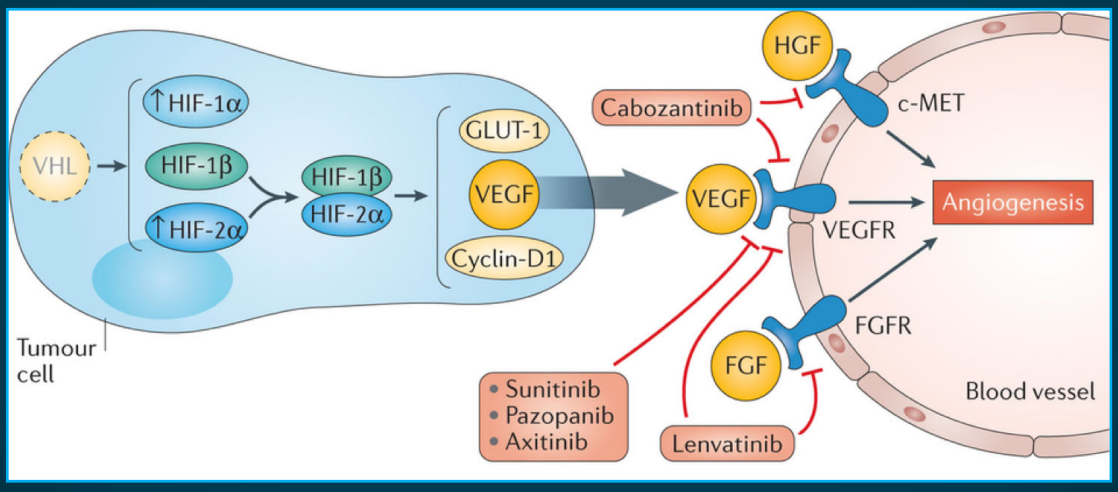
Kotecha R. *Nat Rev Clin Oncol*. 2019;16:621-33.

Systemic Therapy in the Metastatic Setting

Whiteboard Video 1
https://youtu.be/6PO3xVabiwc

TKIs for RCC Treatment

Historical Perspective on First-Line Therapy: Tyrosine Kinase Inhibitor (TKI) Monotherapy



HIF = hypoxia inducible factor; HGH = hepatocyte growth factor; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; c-MET = hepatocyte growth factor receptor; VEGFR = VEGF receptor.

Lee C-H, et al. *Nat Rev Nephrology.* 2017;13(2):69-70.

NCCN Recommendations for Stage IV Kidney Cancer (First-Line, Predominant Clear Cell Histology)

IMDC risk category	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable	• Axitinib + pembrolizumab • Cabozantinib + nivolumab • Lenvatinib + pembrolizumab (cat 1)* • Pazopanib • Sunitinib	• Axitinib + avelumab • Cabozantinib (cat 2B) • Ipilimumab + nivolumab	• Active surveillance • Axitinib (cat 2B) • High-dose IL-2
Intermediate/ Poor	• Axitinib + pembrolizumab (cat 1) • Cabozantinib + nivolumab • Ipilimumab + nivolumab (cat 1) • Lenvatinib + pembrolizumab* • Cabozantinib	• Axitinib + avelumab • Pazopanib • Sunitinib	• Axitinib (cat 2B) • High-dose Il-2 • Temsirolimus

See guidelines for additional notes and information on these recommendations.

**Not yet FDA approved for RCC*

NCCN = National Comprehensive Cancer Network.

Adapted from *NCCN clinical practice guidelines in oncology for kidney cancer (Version 3.2021)*. (https://www.nccn.org/professionals/physician_gls/default.aspx). Accessed 4/7/21.

Sunitinib and Pazopanib Are Standards in First-Line RCC Registration Data

- Patients with untreated metastatic RCC
- Stratified based on performance status, LDH level, prior nephrectomy

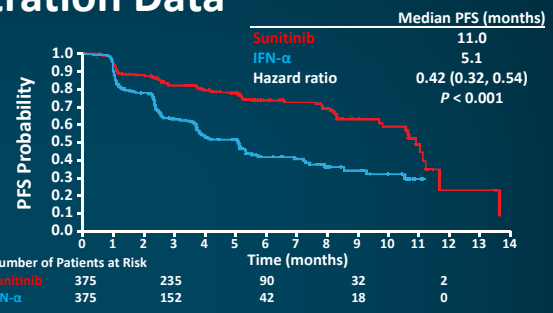
R 1:1

N = 750

Sunitinib
50 mg orally for 4 weeks, then 2 weeks off for repeated 6-week cycles (n = 375)

IFN-α
9 MU subcutaneously 3x/week (n = 375)

Primary Endpoint: Progression-Free Survival
Stratified based on performance status, LDH level, prior nephrectomy



Eligibility criteria
- Locally advanced RCC or mRCC
- Predominant clear cell histology
- Measurable disease (≥ 1 lesion)
- 0 to 1 prior systemic treatment (cytokine based) for locally advanced or mRCC

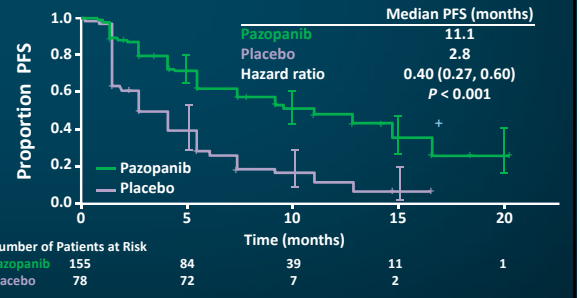
R 2:1

N = 400

Pazopanib
800 mg/day

Placebo

Primary Endpoint: Progression-Free Survival



R = randomized; IFN-α = interferon alpha group; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.

. Sternberg CN, et al. *J Clin Oncol.* 2010;28:1061-1068.

NCCN Recommendations for Stage IV Kidney Cancer
(First-Line, Predominant Clear Cell Histology)

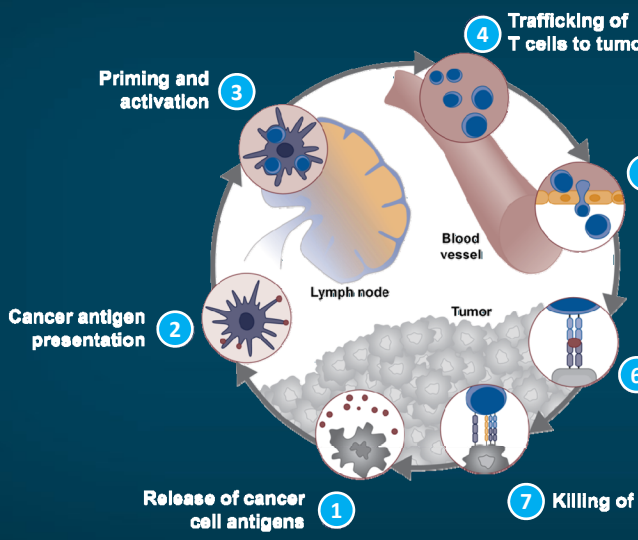
IMDC risk category	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable	• Axitinib + pembrolizumab • Cabozantinib + nivolumab • Lenvatinib + pembrolizumab (cat 1)* • Pazopanib • Sunitinib	• Axitinib + avelumab • Cabozantinib (cat 2B) • Ipilimumab + nivolumab	• Active surveillance • Axitinib (cat 2B) • High-dose IL-2
Intermediate/ Poor	• Axitinib + pembrolizumab (cat 1) • Cabozantinib + nivolumab • Lenvatinib + pembrolizumab* • Ipilimumab + nivolumab (cat 1) • Cabozantinib	• Axitinib + avelumab • Pazopanib • Sunitinib	• Axitinib (cat 2B) • High-dose Il-2 • Temsirolimus

See guidelines for additional notes and information on these recommendations.

**Not yet FDA approved for RCC*

Adapted from *NCCN clinical practice guidelines in oncology for kidney cancer (Version 3.2021)*. (https://www.nccn.org/professionals/physician_gls/default.aspx). Accessed 4/7/21.

Is VEGF Inhibition Synergistic With Anti–PD-1?[1]



PD-L1 = programmed cell death protein ligand 1; PD-1 = programmed cell death protein 1.

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.

Whiteboard Video 2

https://youtu.be/9LLec-DOxxU

Immunotherapy

KEYNOTE-426 Study Design

Pembrolizumab (anti-PD-1) in Combination With Axitinib (VEGFR-TKI) in Previously Untreated RCC

- Stage IV or recurrent clear cell RCC
- No previous systemic treatment for advanced disease
- KPS ≥ 70
- Measurable disease per RECIST v1.1
- Tumor sample for biomarker assessment

Stratification Factors
- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

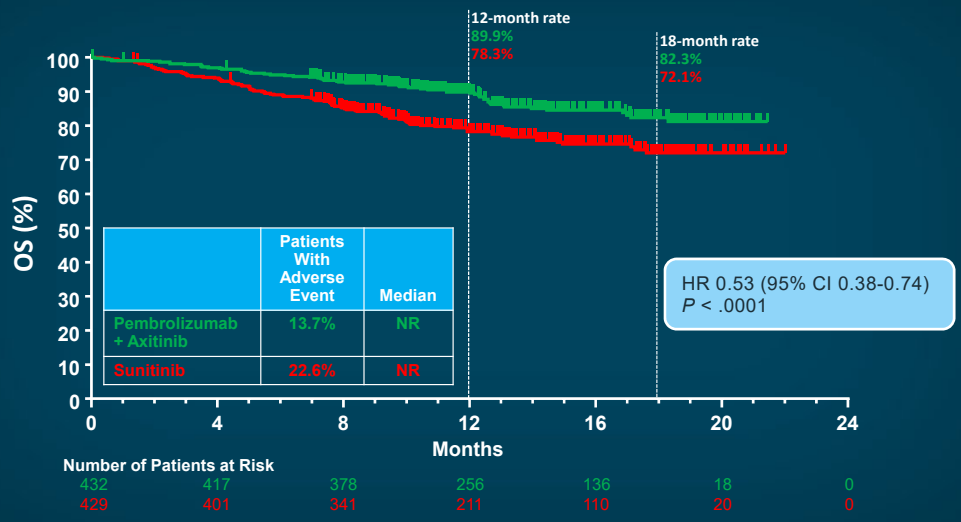
Randomized 1:1

- **Pembrolizumab + Axitinib**
- **Sunitinib**

- **Dual primary endpoint: OS and PFS (RECIST v1.1, BICR)**
- Key secondary endpoint: ORR (RECIST v1.1, BICR)
- Other secondary endpoints: DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose 5 mg twice daily; could be increased to 7 mg, then 10 mg twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg twice daily to manage toxicity.
[b]Sunitinib dose 50 mg daily, 4 weeks on/2 weeks off; could be decreased to 37.5 mg, then 25 mg once daily for the first 4 weeks of each 6-week cycle to manage toxicity.
BICR = blinded independent central radiologic review; DOR = duration of response; KPS = Karnofsky performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PROs = patient-reported outcomes; RECIST = Response Evaluation Criteria in Sold Tumors; ROW = rest of world.
NCT02853331. (https://clinicaltrials.gov/ct2/show/study/NCT02853331).

KEYNOTE-426 Overall Survival

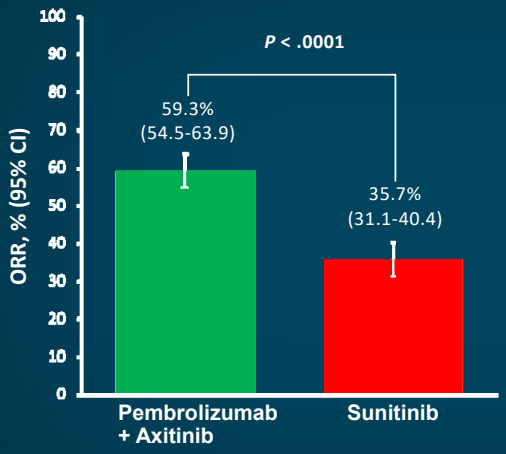


Data cutoff date: 8.24.2018. NR = not reached.
Powles T, et al. GU ASCO 2019; Abstract 543. Rini BI, et al. *N Engl J Med*. 2019;380:1116-1127.

KEYNOTE-426 Progression-Free Survival

Data cutoff date: 8.24.2018.
Powles T, et al. GU ASCO 2019; Abstract 543. Rini BI, et al. *N Engl J Med*. 2019;380:1116-1127.

KEYNOTE-426 Confirmed Objective Responses

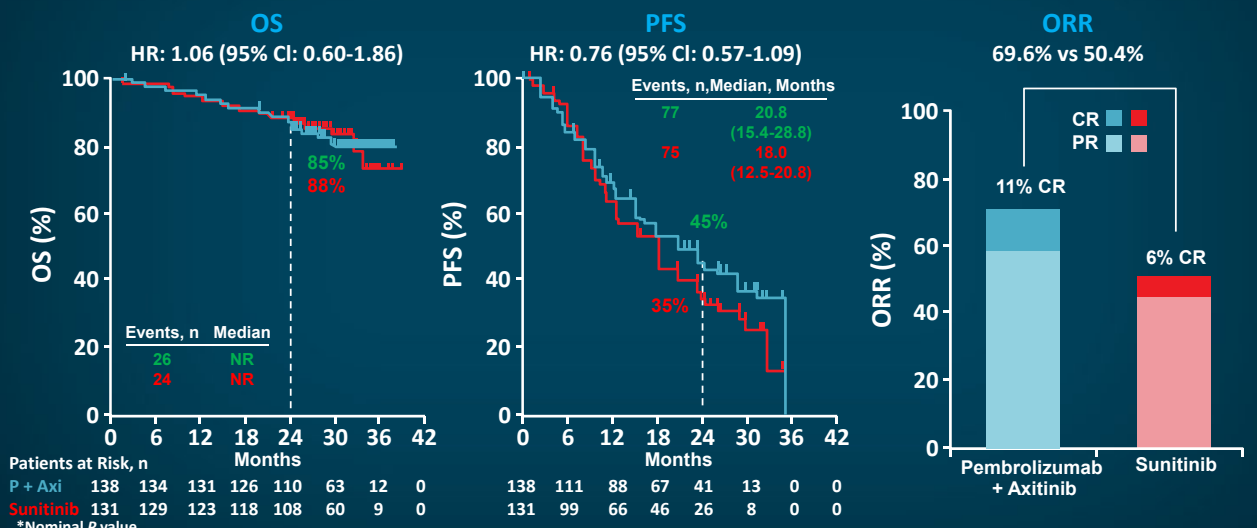


Best Response	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Complete response	25 (5.8%)	8 (1.9%)
Partial response	231 (53.5%)	145 (33.8%)
Stable disease	106 (24.5%)	169 (39.4%)
Progressive disease	47 (10.9%)	73 (17.0%)
Not evaluable[a]	8 (1.9%)	6 (1.4%)
Not assessed[b]	15 (3.5%)	28 (6.5%)

Response Duration	N = 256	N = 153
Median (range), month	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[a]Patients who had ≥1 postbaseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR.
[b]Patients who did not have ≥1 postbaseline imaging assessment.
Data cutoff date: 8.24.2018. ORR = overall response rate.
Powles T, et al. GU ASCO 2019; Abstract 543. Rini BI, et al. *N Engl J Med*. 2019;380:1116-1127.

KEYNOTE-426: OS, PFS, and ORR in IMDC Favorable-Risk Group



*Nominal *P* value.

P = pembrolizumab; Axi = axitinib; CR = complete response; PR = partial response.

Plimack ER, et al. ASCO 2020; Abstract 5001.

JAVELIN Renal 101 Study Design

Avelumab (anti–PD-L1) in Combination With Axitinib (VEGFR-TKI) in Previously Untreated RCC

- Treatment-naïve advanced RCC with a clear cell component
- ECOG PS 0 or 1
- N = 886

Stratification Factors
- ECOG PS (0 vs 1)
- Geographic region (US vs Canada and Western Europe vs ROW)

Randomized 1:1

Avelumab + Axitinib

Sunitinib

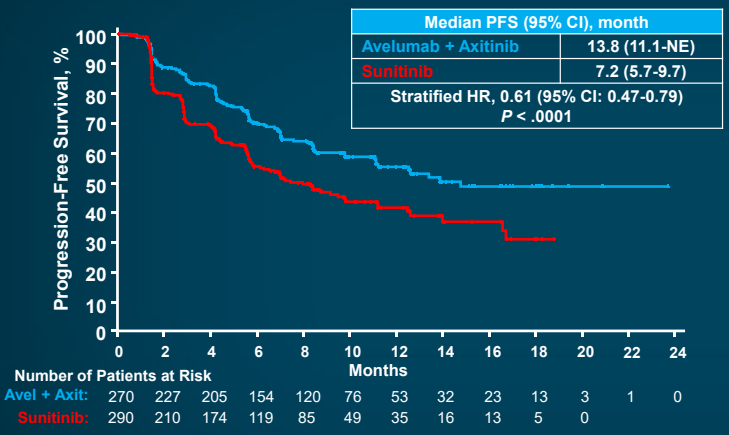
Primary endpoints
- **PFS and OS in PD-L1+ disease per BICR***
- Key secondary endpoint: PFS in overall population
- Other endpoints: objective response and safety

*≥1% of immune cells staining positive within the tumor area of the tested tissue sample. PD-L1 expression was assessed at a central laboratory with the use of the Ventana PD-L1 (SP263) assay (Ventana Medical Systems).

BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; OS = overall survival; PD-L1 = programmed cell death protein ligand 1; PFS = progression-free survival; RCC = renal cell carcinoma; ROW = rest of world.

Motzer RJ, et al. *N Engl J Med.* 2019:380:1103-1115.

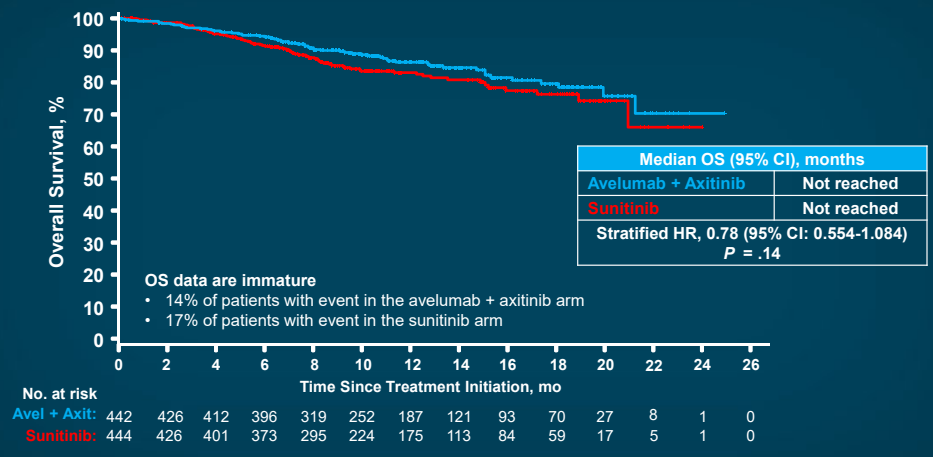
JAVELIN Renal 101: PFS and ORR per IRC in PD-L1+ Patients



Per IRC	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)
Objective response rate (95% CI), %	55 (49.0-61.2)	26 (20.6-30.9)
Best overall response, %*		
Complete response	4	2
Partial response	51	23
Stable disease	27	43
Progressive disease	11	22
Not evaluable†	4	7
Patients with ongoing response, %‡	73	65

Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib). The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).
IRC = independent review committee; NE = not estimable; PD-L1 = programmed cell death protein ligand 1; PFS = progression-free survival.
Motzer RJ, et al. *N Engl J Med*. 2019;380:1103-1115.

JAVELIN Renal 101: Overall Survival



Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).
OS = overall survival.
Motzer RJ, et al. *N Engl J Med*. 2019;380:1103-1115.

NCCN Recommendations for Stage IV Kidney Cancer
(First-Line, Predominant Clear Cell Histology)

IMDC risk category	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable	• **Axitinib + pembrolizumab** • **Cabozantinib + nivolumab** • **Lenvatinib + pembrolizumab (cat 1)*** • Pazopanib • Sunitinib	• **Axitinib + avelumab** • Cabozantinib (cat 2B) • **Ipilimumab + nivolumab**	• Active surveillance • Axitinib (cat 2B) • High-dose IL-2
Intermediate/ Poor	• **Axitinib + pembrolizumab (cat 1)** • **Cabozantinib + nivolumab** • **Ipilimumab + nivolumab (cat 1)** • **Lenvatinib + pembrolizumab*** • Cabozantinib	• **Axitinib + avelumab** • Pazopanib • Sunitinib	• Axitinib (cat 2B) • High-dose Il-2 • Temsirolimus

See guidelines for additional notes and information on these recommendations.
**Not yet FDA approved for RCC*

Adapted from *NCCN clinical practice guidelines in oncology for kidney cancer (Version 3.2021)*. (https://www.nccn.org/professionals/physician_gls/default.aspx). Accessed 4/7/21.

CheckMate 214
Nivolumab + Ipilimumab[1]

Stratified by MDC prognostic score (0 vs 1-2 vs 3-6), region (United States vs Canada/Western Europe/Northern Europe vs rest of world)

Patients with previously untreated advanced CCRCC, Karnofsky PS ≥ 70, tumor tissue available for PD-L1 testing (N = 1096)

→ **Nivolumab + Ipilimumab** x 4 doses (n = 550) → **Nivolumab maintenance**

→ **Sunitinib** (n = 546)

Minimum follow-up of 42 months

KEYNOTE-426
Axitinib + Pembrolizumab[2]

Stratified by IMDC risk group (0 vs 1-2 vs 3-6), region (North America vs Western Europe vs rest of world)

Patients with newly diagnosed/recurrent stage IV CCRCC, no prior systemic treatment for advanced disease, Karnofsky PS 2 70, measurable disease (RECIST v1.1), tumor sample available for biomarker evaluation, adequate organ function (N = 861)

→ **Axitinib + Pembrolizumab** for up to 35 cycles (n = 432)

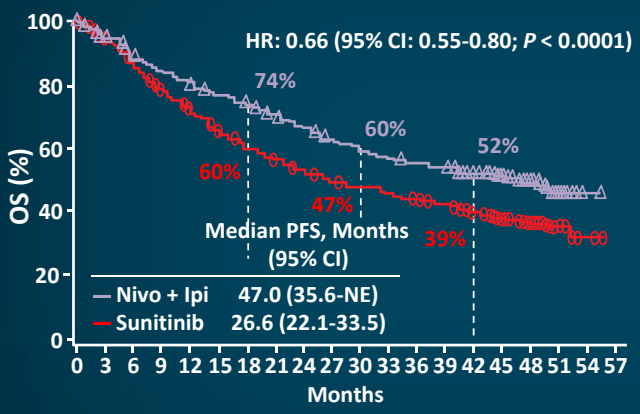
→ **Sunitinib** (n = 429)

Minimum follow-up of 23 months

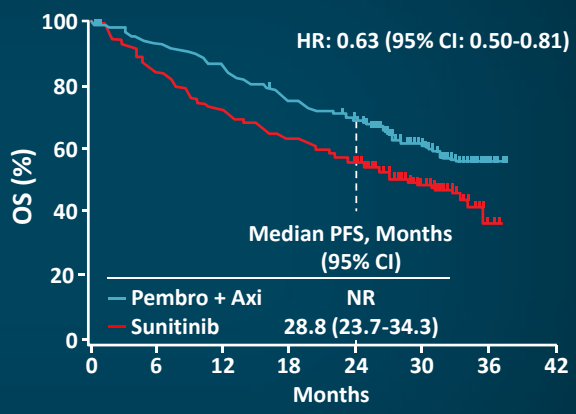
CCRCC = clear cell renal cell carcinoma.
1. Tannir NM, et al. ASCO GU 2020; Abstract 609. 2. Powles T, et al. GU ASCO 2019; Abstract 543.

OS for Intermediate-/Poor-Risk Disease

CheckMate 214: Nivo + Ipi vs Sunitinib Intermediate/Poor-Risk Disease (n = 847)[1]



KEYNOTE-426: Axi + Pembro vs Sunitinib Intermediate/Poor-Risk Disease (n = 592)[2]



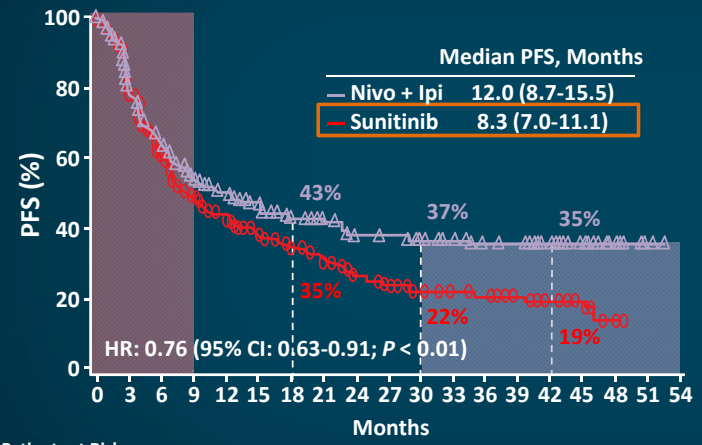
- Similar outcome on same comparator arm
- Early separation of curves for both
- Longer follow-up for CheckMate 214

*Nivolumab + Ipilimumab 47 months median OS may be unstable due to censoring.

1. Tannir NM, et al. ASCO GU 2020; Abstract 609. 2. Plimack ER, et al. ASCO 2020; Abstract 5001.

PFS for IMDC Intermediate-/Poor-Risk Disease

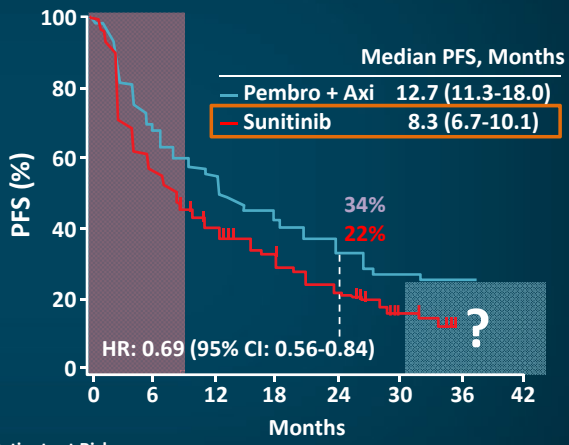
CheckMate 214: Nivo + Ipi vs Sunitinib (n = 847)[1]



Patients at Risk, n

Nivo + Ipi	425	302	229	182	159	144	126	113	98	95	90	82	75	70	56	34	13	2	0
Sunitinib	422	280	188	136	104	88	73	59	45	36	30	25	21	16	11	8	3	0	0

KEYNOTE-426: Axi + Pembro vs Sunitinib (n = 592)[2]



Patients at Risk, n

P + Axi	294	189	146	113	68	23	2	0
Sunitinib	298	149	93	66	35	11	0	0

1. Tannir NM, et al. ASCO GU 2020; Abstract 609. 2. Plimack ER, et al. ASCO 2020; Abstract 5001.

CheckMate 9ER: Study Design

Stratification factors
- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region

N = 651

Key inclusion criteria[1,2]
- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

R 1:1

Nivolumab 240 mg IV every 2 weeks + Carbozantinib 40 mg orally once daily

Sunitinib 50 mg orally once daily, cycle of 4 weeks on/ 2 weeks off

Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

Primary endpoint: PFS

Secondary endpoints: OS, ORR, and safety

Median study follow-up, 18.1 months (range, 10.6–30.6 months)

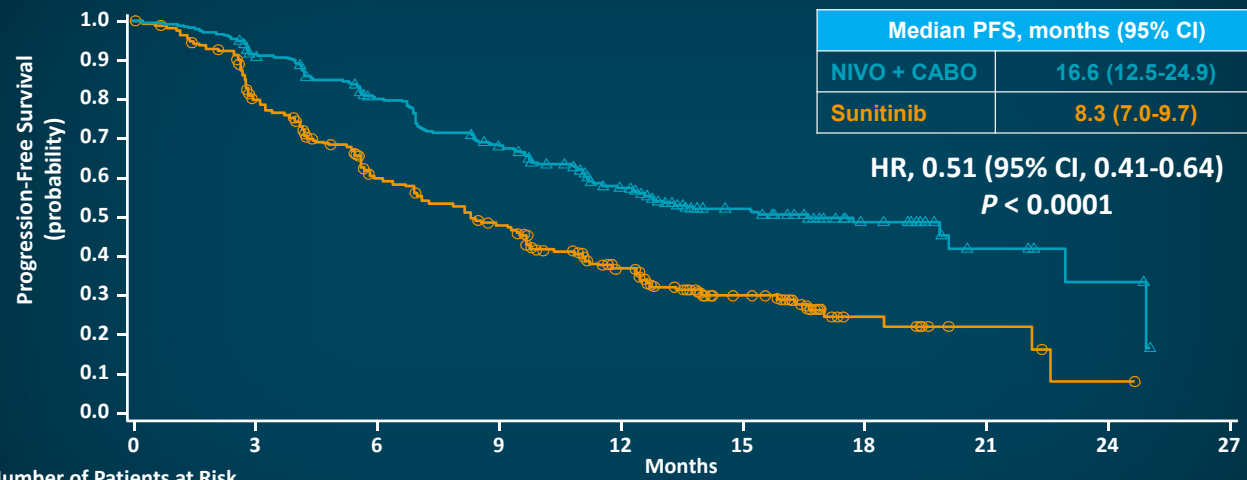
[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.

[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); carbozantinib and sunitinib treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenously; ORR = objective response rate; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Choueiri T, et al. *NEJM*. 2021;384:829-41.

CheckMate 9ER
Progression-Free Survival per BICR



Median PFS, months (95% CI)	
NIVO + CABO	16.6 (12.5-24.9)
Sunitinib	8.3 (7.0-9.7)

HR, 0.51 (95% CI, 0.41-0.64)
***P* < 0.0001**

Number of Patients at Risk

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

Minimum study follow-up, 10.6 months.

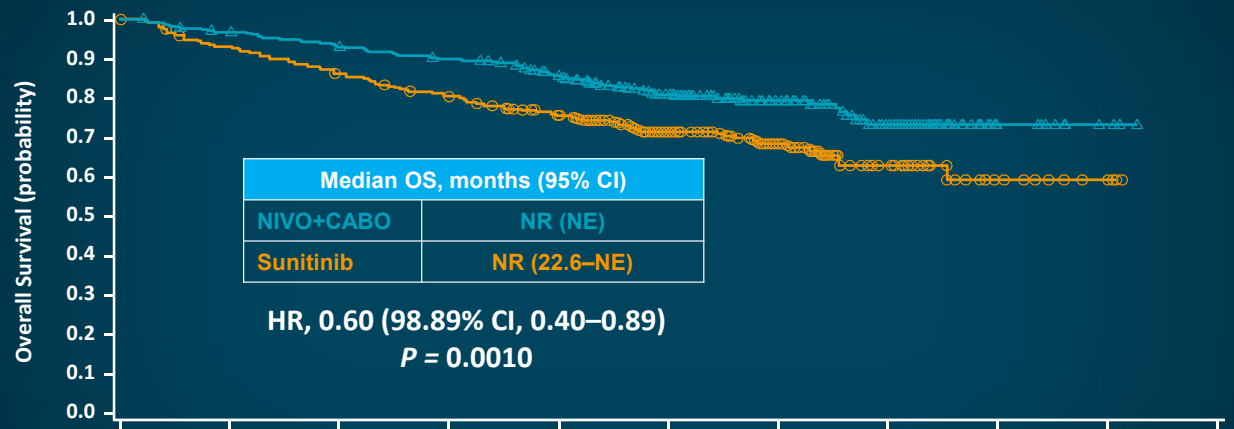
Choueiri T, et al. *NEJM*. 2021;384:829-41.

CheckMate 9ER: Progression-Free Survival per BICR in Subgroups

Subgroup	NIVO + CABO	Sunitinib	HR for progression or death (95% CI)
	Events/no. of patients		
Overall	144/323	191/328	0.51 (0.41–0.64)
Region			
US/Europe	61/158	85/161	0.46 (0.33–0.64)
Rest of world	83/165	106/167	0.57 (0.42–0.76)
IMDC prognostic risk			
Favorable	30/74	35/72	0.62 (0.38–1.01)
Intermediate	82/188	108/188	0.54 (0.40–0.72)
Poor	31/61	48/68	0.37 (0.23–0.58)
PD-L1 expression			
≥ 1%	42/83	54/83	0.49 (0.32–0.73)
< 1% or indeterminate	102/240	137/245	0.52 (0.40–0.67)
Age			
< 65 years	84/191	131/210	0.44 (0.33–0.58)
≥ 65 years	60/132	60/118	0.68 (0.48–0.98)
Sex			
Male	108/249	136/232	0.48 (0.37–0.62)
Female	36/74	55/96	0.61 (0.40–0.94)
Karnofsky performance status			
90–100	109/257	129/241	0.55 (0.43–0.71)
≤ 80	35/66	62/85	0.44 (0.29–0.68)
Bone metastases			
Yes	33/78	45/72	0.34 (0.22–0.55)
No	111/245	146/256	0.57 (0.44–0.73)
Previous nephrectomy			
Yes	90/222	136/233	0.46 (0.35–0.60)
No	54/101	55/95	0.63 (0.43–0.92)

Choueiri T, et al. *NEJM*. 2021;384:829-41.

CheckMate 9ER
Overall Survival



Median OS, months (95% CI)	
NIVO+CABO	NR (NE)
Sunitinib	NR (22.6–NE)

HR, 0.60 (98.89% CI, 0.40–0.89)
P = 0.0010

Number of Patients at Risk											
NIVO+CABO	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

Minimum study follow-up, 10.6 months. NE = not estimable; NR = not reached.

Choueiri T, et al. *NEJM*. 2021;384:829-41.

Challenges in First-Line Management

- **How should we choose first-line therapy in advanced RCC?**
  - Clinical trial design and endpoints
  - IMDC risk criteria
  - Disease and symptom burden
- **Planning for second-line therapy?**
  - Therapy not used in the first-line reserved for later lines?

Putting the First-Line Overall Survival Data Into Context: KEYNOTE-426 and CheckMate 214

Trial	KEYNOTE-426[1,2] (VEGF+IO)		CheckMate 214[3,4] (IO+IO)	
Follow-up	7 months	23 months	30 months	42 months
Intent-to-treat OS HR	0.53	0.68	0.71	0.72
Favorable-risk OS HR	0.64	1.06	1.22	1.19

- Should we look at landmark endpoints more?
- Treatment-free survival?
- Long-term toxicities (2 drugs vs 1 drug)?

1. Rini BI, et al. *N Engl J Med*. 2019;380:1116-1127. 2. Plimack E, et al. ASCO 2020; Abstract 5001. 3. Motzer R, et al. *Lancet Oncol*. 2019;20(10):1370-1385. 4. Tannir N, et al. ASCO GU 2020.
Presented by Toni Choueiri at ASCO 2020.

Phase II KEYNOTE-146/Study 111 of Lenvatinib + Pembrolizumab After Progression on Previous IO Therapy

A multicenter, open-label phase Ib/II study, RCC cohort (N = 104)

Patients metastatic CCRCC with PD after anti-PD-1/PD-L1 therapy; ≥1 previous lines of therapy (N = 104)

→ **Lenvatinib** 20 mg orally once daily
Pembrolizumab 200 mg IV every 3 weeks

Primary Endpoint
- ORR at 24 weeks

Key Secondary Endpoints
- ORR, PFS, DOR
- Safety and tolerability

Baseline Characteristics	Patients (n = 104)
1/ ≥2 Prior anticancer regimens, %	39/62
Prior ICI regimen, %[a]	
Anti-PD-L1/anti-PD-1 in combination or as monotherapy	100
Anti-PD-L1/anti-PD-1 and anti-VEGF in combination or sequentially	65
Ipilimumab/nivolumab	37
Median duration of prior ICI therapy, months (interquartile range)	7 (3-13)

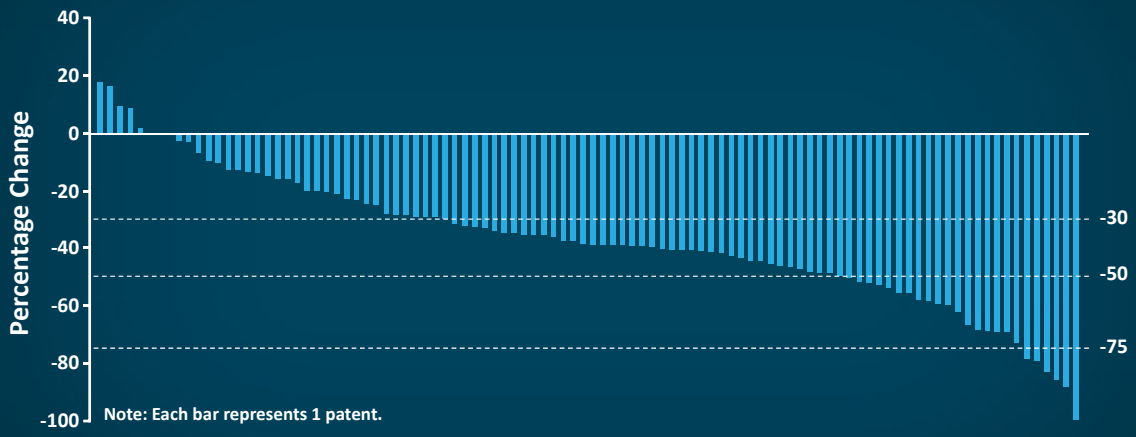
Lee C-H, et al. ASCO 2020; Abstract 5008. Not yet FDA approved for RCC.

Response to Lenvatinib + Pembrolizumab: Best Response by Previous Therapy

Event	Anti–PD-1/PD-L1 (n = 104)	Anti–PD-1/PD-L1 and Anti-VEGF (n = 68)	Nivolumab + Ipilimumab (n = 38)
ORR, % (95% CI)	55 (45-65)	59 (46-71)	47 (31-64)
Best objective response, %			
Partial response	55	59	47
Stable disease	36	32	42
Progressive disease	5	6	8
Not evaluable	5	4	3
Median duration of response, months (95% CI)			

Lee C-H, et al. ASCO 2020; Abstract 5008. Not yet FDA approved for RCC.

Response to Lenvatinib + Pembrolizumab: Change in Tumor Size



- Similar responses in subgroups with prior anti-VEGF therapy or prior IO-based therapy

Lee C-H, et al. ASCO 2020; Abstract 5008. Not yet FDA approved for RCC.

Randomized PD-1/VEGF Blockade Salvage Trial

Phase 3 CONTACT-03 Trial in RCC (NCT04338269)

VEGFR-TKI ± PD-L1 inhibition

Key eligibility criteria

- Advanced, inoperable, or metastatic RCC
- Radiographic tumor progression during or after ICI treatment in first- or second-line setting
- KPS of ≥70
- Evaluable IMDC risk score

R (1:1)

(N = 500)

- **Atezolizumab 1200 mg IV Q3W + cabozantinib 60 mg PO QD**
- **Cabozantinib 60 mg PO QD**

- **Primary endpoints:** PFS (independent review) and OS
- **Secondary endpoints:** PFS (by investigators), ORR, DoR, safety

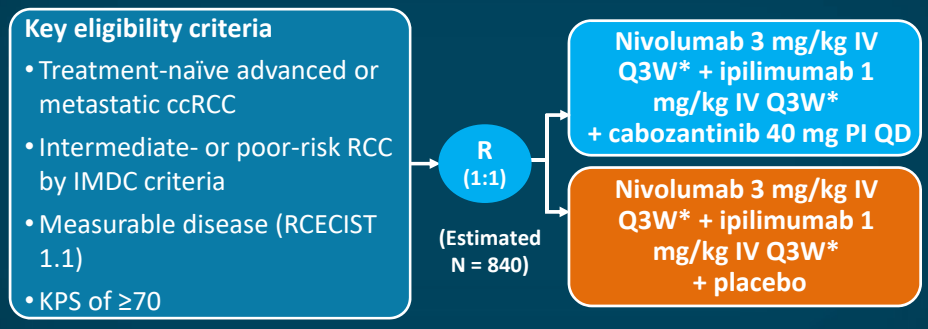
Clinicaltrials.gov. NCT04338269. Available at: (https://clinicaltrials.gov/ct2/show/NCT04338269).

Future Trials in RCC: Triplet Therapy

Phase 3 COSMIC 313 Trial in RCC (NCT03937219)

Nivolumab + Ipilimumab + Cabozantinib

PD-1 + CTLA4 inhibition ± VEGFR-TKI



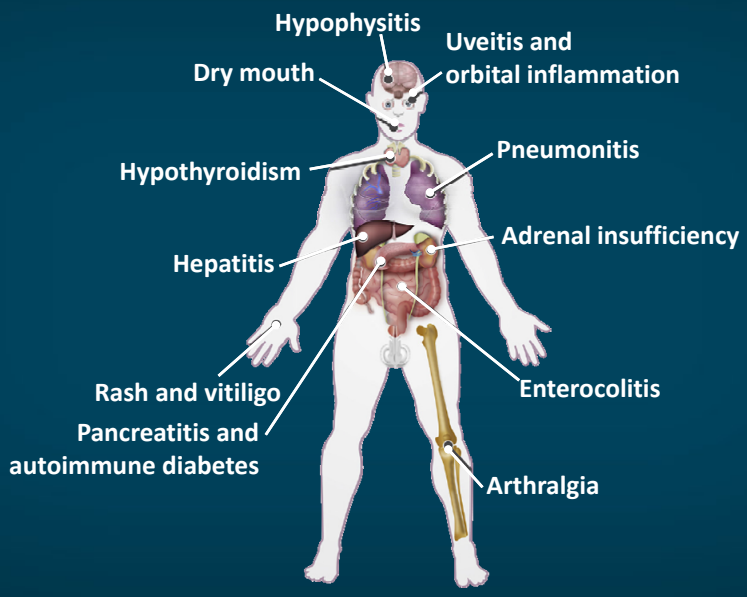
- **Primary endpoint:** PFS (BIRC)
- **Secondary endpoint:** OS
- **Stratification factors:** IMDC prognostic score and geographic region

*for 4 doses; after 4 doses nivolumab is given at a 480 mg IV flat dose Q4W.

Choueiri TK, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract TPS5102. NCT03937219 (COSMIC-313).

Adverse Events

Immune-Related Adverse Events: Clinical Spectrum



Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

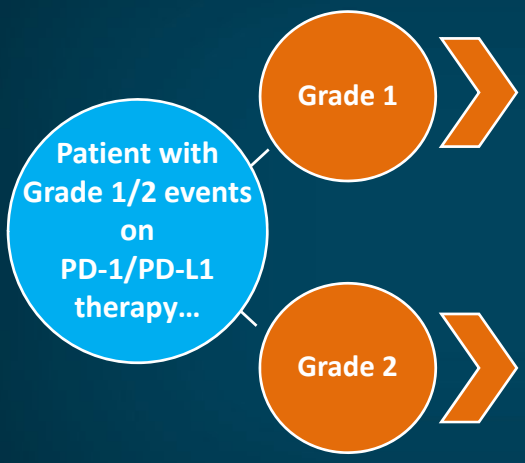
Management of Immune-Related Adverse Events

Based on CTCAE Severity Grade

Severity CTCAE Grade	Patient Care Setting	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Not recommended up front Topical steroids or systemic steroids oral 0.5–1 mg/kg/d for persistent grade 2	Not recommended	Suspend* temporarily
3	Hospitalization	Systemic steroids oral or IV 1–2 mg/kg/d for ≥3 d then taper over 4-6 weeks	Consider for patients with lack of improvement after 2-3 days of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization; consider intensive care unit	Systemic steroids IV methylprednisolone 1-2 mg/kg/d and switch to oral prednisone for ≥3 days with taper over 4-6 weeks	Consider for patients with lack of improvement after 2-3 days of steroid course Organ specialist advised	Discontinue permanently

***Outside of skin or endocrine disorders, where immunotherapy can be maintained.**
CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous.
Michot JM, et al. *Eur J Cancer*. 2016;54:139-148. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768.

Managing Grade 1/2 Immune-Related Adverse Events[1-4]

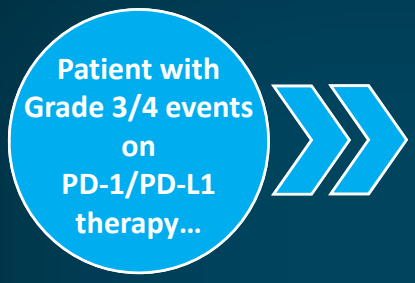


- Continue immunotherapy (or consider temporary delay)
- Symptomatic therapy

- Withhold immunotherapy
- Corticosteroids if symptoms do not resolve in 1 week (prednisone 0.5 to 1 mg/kg/d or equivalent)
- Taper corticosteroids over ≥ 1 month to reduce recurrence
- Redose if toxicity resolves to Grade ≤1

1. Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. 2. Postow MA, et al. *UpToDate* 2021. (http://www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy). 3. Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099. 4. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768.

Managing Grade 3 Immune-Related Adverse Events



- Discontinue immunotherapy; hospitalization, multidisciplinary evaluation indicated
- High-dose corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent)
- Taper high-dose corticosteroids over ≥ 1 month until toxicity resolves to grade ≤ 1 (prednisone 1 to 2 mg/kg/day or equivalent)

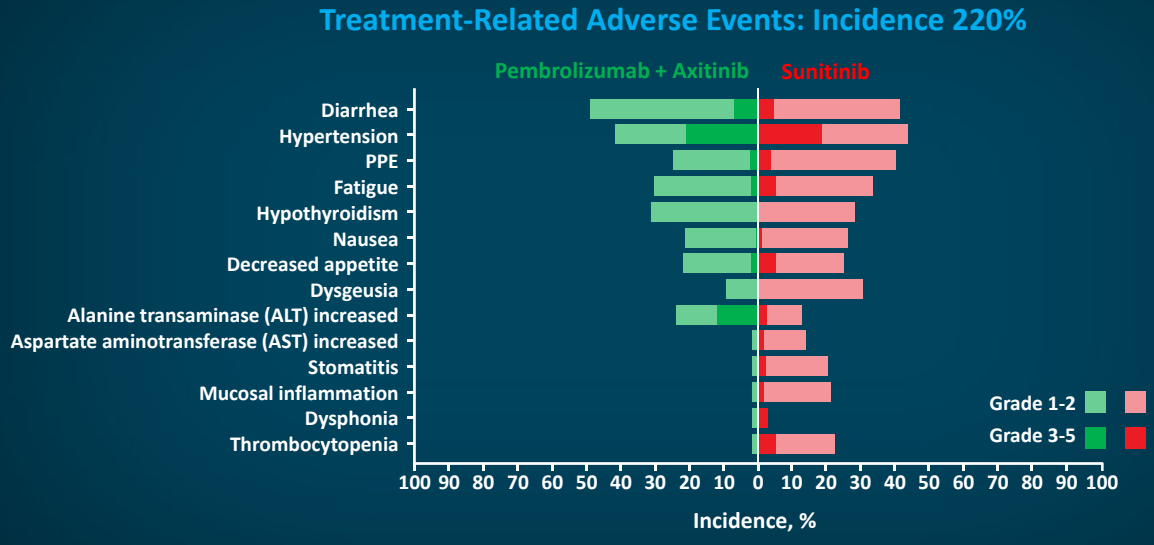
- **If no improvement or progression, consider additional immunosuppressant treatment (eg, anti-tumor necrosis factor therapy, infliximab, vedolizumab, or mycophenolate)**
- **If > 4 weeks of corticosteroids or other immunosuppressants needed, administer antimicrobial/ antifungal prophylaxis to prevent opportunistic infections**
- **ASCO recommendations on managing immune-related adverse events now published**

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. Postow MA, et al. *UpToDate*. 2021. (http://www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy). Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768.

Differentiating Immuno-Oncology vs VEGFR-TKI Toxicity

- Key VEGFR-TKI toxicities that can mimic/overlap with immuno-oncology
  - Cutaneous
  - Gastrointestinal/diarrhea
  - Liver
  - Cardiopulmonary
- Toxicity management
  - VEGFR-TKI: dose hold/interruption and supportive care
  - Immuno-oncology: dose hold and corticosteroids
- Complicating factors
  - Symptom presentation
  - Drug half-life (axitinib half-life: ~4 to 5 hours vs cabozantinib half-life: ~99 hours)

KEYNOTE-426: Toxicity



Events are shown in order of decreasing incidence in the total population.
PPE = palmar-plantar erythrodysesthesia.
Rini BI, et al. NEJM. 2019;380(12):1116-27.

Multidisciplinary Team

- Multidisciplinary consultation is recommended for optimal management
- Multidisciplinary team may include
  - Urology
  - Medical/radiation oncology
  - Internal medicine/hospital medicine
  - Primary care providers (PCPs)
  - Nursing
  - Social work

Multidisciplinary care improves patient outcomes!

Shared Decision-Making (SDM) in Oncology

Collaborative Care

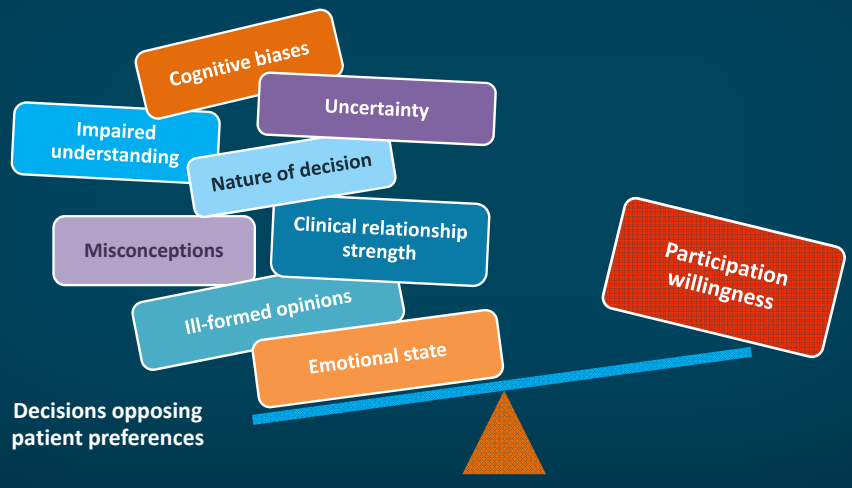
- Interconnection of essential players
- Patient-centered
- Communication is **KEY**

Adapted from: NQP Playbook: Shared Decision Making in Healthcare, 2018.

5 Essential Steps of SDM
SHARE Approach

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf).

Patient Barriers
Factors that can influence the patient's preference and participation in SDM overall



Fisher KA et al. *Patient Educ Couns.* 2018;101:2195-2201.

Benefits to the SDM Approach

Both providers and patients benefit

- Greater quality of delivered care
- Enhanced patient experience and satisfaction
- Heightened patient adherence to treatment recommendations
- Enriched provider/patient relationships

Conclusions

- A variety of studies have assessed first-line combination regimens for the treatment of patients with advanced and/or mRCC
- Many patients with RCC can now benefit from first-line immunotherapy/TKI combination therapies
- Management strategies need to anticipate treatment-related adverse events, particularly with multiple agents
- A multi-disciplinary approach with shared decision-making for RCC management is critical

Case Studies

Case Study

Case Study

- 37-year-old woman, no past medical history
- January 2020 presents with upper respiratory tract infection symptoms, then progressive nausea/vomiting and abdominal pain

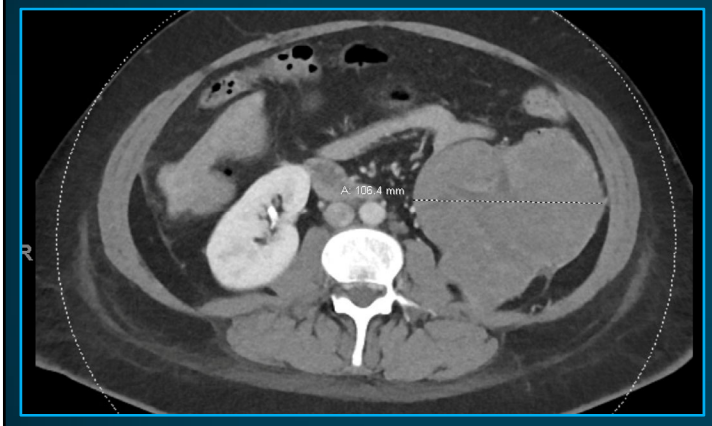
ALKALINE PHOSPHATASE	30 - 101 U/L	508 High
AST	9 - 40 U/L	112 High
ALT	5 - 40 U/L	105 High
BILIRUBIN TOTAL	< 1.3 mg/dL	1.4 High

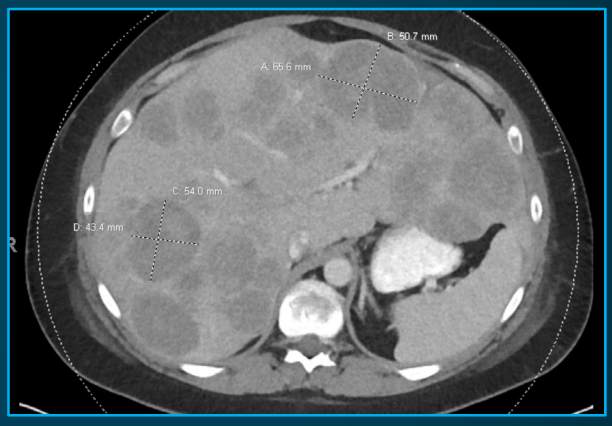
- Calcium: normal, hemoglobin: 11.6 (LLN 11.9); absolute neutrophil count: 8.76; platelets: 408
- ECOG PS 2

Liver biopsy: CCRCC

- IMDC risk: Poor risk

Case Study





What are some of the factors to consider for treatment?

Approach to Treatment Decision-Making

- Factors to guide treatment decision-making
  - IMDC risk
  - Disease extent/symptoms
  - Disease pace/kinetics
  - Time to response

Polling Question

Which therapy would you choose at this time?

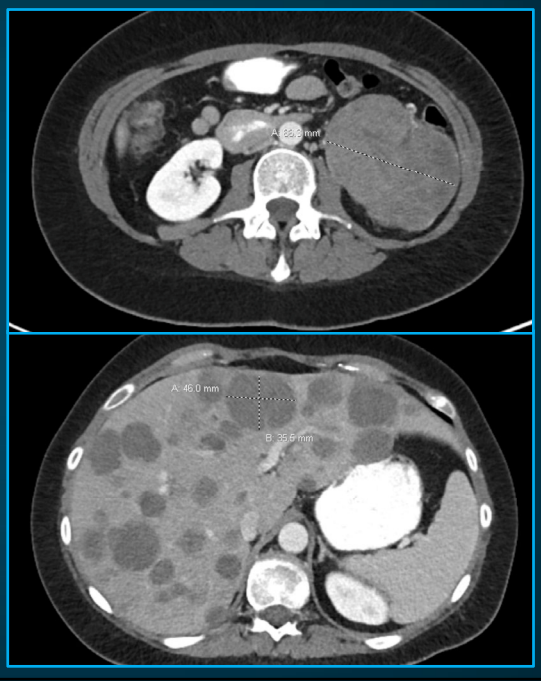
A. Sunitinib
B. Cabozantinib
C. Axitinib + pembrolizumab
D. Axitinib + avelumab
E. Nivolumab + ipilimumab
F. Active surveillance

Approach to Treatment

- Treatment: axitinib plus pembrolizumab
- Imaging after 3 cycles
- Marked improvement in symptoms

Liver function tests

Component (*latest reference range and units*)	4/15/2020
PROTEIN, TOTAL (*6.3-8.2 g/dL*)	9.5 (H)
ALBUMIN (*3.5-5.0 g/dL*)	4.2
AST (*14-36 U/L*)	168 (H)
ALKALINE PHOSPHATASE (*39-117 U/L*)	494 (H)
BILIRUBIN TOTAL *0.2-1.3 mg/dL*	1.1
ALT < *38 U/L*	129 (H)

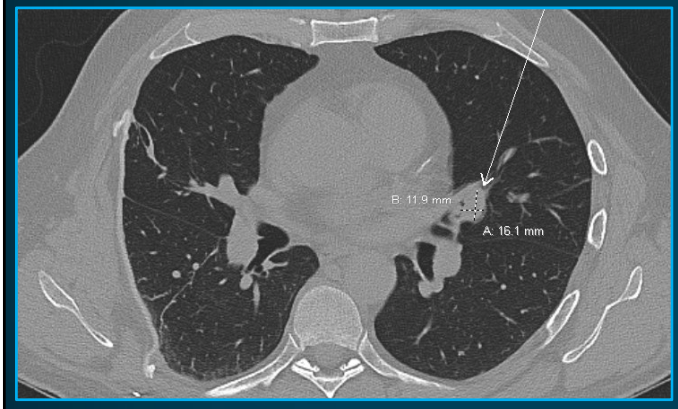


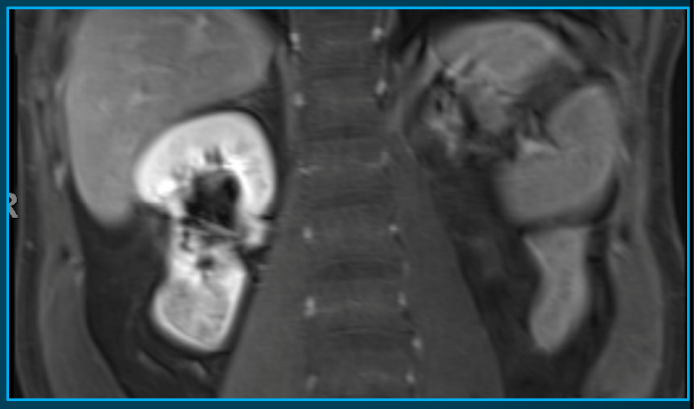
Case Study

Case Study: Activity in the Primary Cancer

- 60-year-old man, hypertension, hyperlipidemia, presented with gross hematuria, 2 right renal masses
- Right partial nephrectomy 1/16/2014 (CCRCC pT1b and pT1a Grade 3)
- Right seventh rib resection 7/23/2016 (metastatic RCC)
- Apr 2019 MRI: bilateral renal masses
- Attempted Partial -> Left radical nephrectomy 6/14/2019 (4 cm pT3a Grade 2 CCRCC)
- Jul 2019: enlarging lingular lung mass 1.7 cm and right renal masses (1.4 cm and 3.4 cm)

Case Study: Imaging





How would you characterize this patient's IMDC risk?

Approach to Treatment Decision-Making

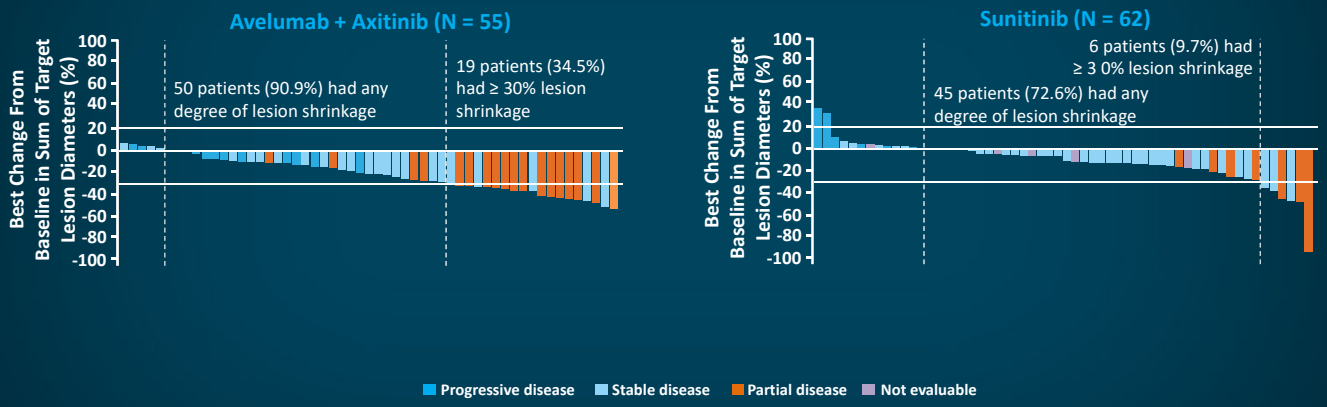
- Factors in treatment decision-making
  - IMDC risk
  - Disease extent/symptoms
  - Disease pace/kinetics
  - Time to response
  - Activity in the kidney primary
- IMDC risk: Good risk
- ECOG PS 0

Polling Question

Which therapy would you choose at this time?

A. Sunitinib
B. Pazopanib
C. Axitinib + pembrolizumab
D. Axitinib + avelumab
E. Nivolumab + ipilimumab
F. Active surveillance

Approach to Treatment



Albiges, L. European Society for Medical Oncology (ESMO) 2019; Abstract 4174.

Thank You

Project ECHO®

Med Learning Group - Renal Cell Carcinoma

Renal Cell Carcinoma: Identification and Management

Resource	Address
Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36:1714-1768.	https://pubmed.ncbi.nlm.nih.gov/29442540/
Cao G, et al. What is the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favourable, intermediate and poor risk, respectively? A systematic review and network meta-analysis. *BMJ Open*. 2020;10(8):e034626.	https://pubmed.ncbi.nlm.nih.gov/32859659/
Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1-10.	https://pubmed.ncbi.nlm.nih.gov/23890059/
Choueiri T, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *NEJM*. 2021;384:829-41.	https://pubmed.ncbi.nlm.nih.gov/33657295/
Heng DY, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141-148.	https://pubmed.ncbi.nlm.nih.gov/23312463/
Kotecha R. Towards individualized therapy for metastatic renal cell carcinoma. *Nat Rev Clin Oncol*. 2019;16:621-33.	https://pubmed.ncbi.nlm.nih.gov/30992569/
Michot JM, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139-148.	https://pubmed.ncbi.nlm.nih.gov/26765102/
Osawa T, et al. Overview of current and future systemic therapy for metastatic renal cell carcinoma. *Jpn J Clin Oncol*. 2019;49(5):395-403.	https://pubmed.ncbi.nlm.nih.gov/30722031/

Motzer RJ, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019:380:1103-1115.	https://pubmed.ncbi.nlm.nih.gov/30779531/
Palapattu GS, et al. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. *Rev Urol*. 2002;4(4):163-170.	https://pubmed.ncbi.nlm.nih.gov/16985675/
Puzanov I, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95.	https://pubmed.ncbi.nlm.nih.gov/29162153/
Rini BI, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116-1127.	https://www.nejm.org/doi/full/10.1056/NEJMoa1816714
Sanchez-Gastaldo A, et al. Systemic treatment of renal cell cancer: A comprehensive review. *Cancer Treat Rev*. 2017;60:77-89.	https://pubmed.ncbi.nlm.nih.gov/28898679/
Weber JS, et al. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33:2092-2099.	https://pubmed.ncbi.nlm.nih.gov/25918278/
Zerdes I, et al. Systemic therapy of metastatic renal cell carcinoma: Review of the current literature. *Urologia*. 2019;86(1):3-8.	https://pubmed.ncbi.nlm.nih.gov/30270773/

Resources and Societies

Resource	Address
American Association for Cancer Research	https://www.aacr.org/
American Cancer Society	https://www.cancer.org/cancer/kidney-cancer.html
American Society of Clinical Oncology	https://www.asco.org/
European Society for Medical Oncology	https://www.esmo.org/
Kidney Cancer Association	https://www.kidneycancer.org/
National Comprehensive Cancer Network Guidelines	https://www.nccn.org/professionals/physician_gls/default.aspx