Insights to Manage Renal Cell Carcinoma with First-line Immuno-oncology/Tyrosine Kinase Inhibitor Combination Therapies:

WHICH OF YOUR PATIENTS CAN BENEFIT?

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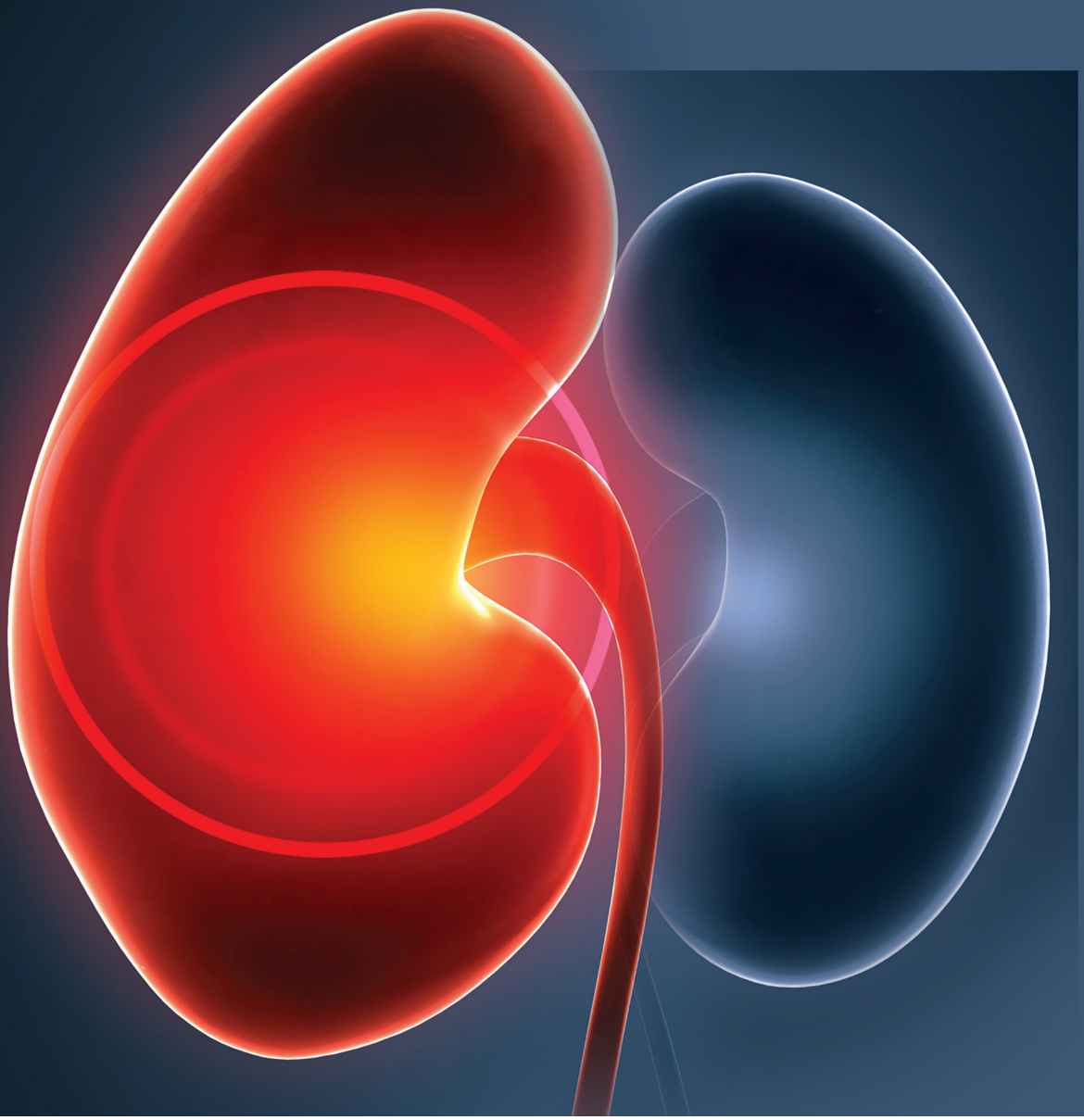

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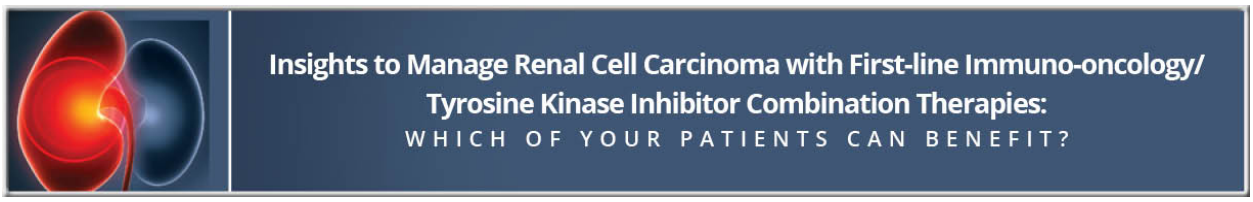

AGENDA

I. RCC: A Brief Overview

a. Clinical presentation
b. Disease pathophysiology
c. Risk stratification
d. Therapeutic targets

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

a. Historical perspective: TKI monotherapy
b. NCCN recommendations for RCC
c. Introduction to VEGF and immune checkpoint inhibition
d. MOAs and clinical trials of IO/TKI combination therapies
    a. KEYNOTE-426, JAVELIN 101, CHECKMATE 214, CHECKMATE 9ER, KEYNOTE 146/Study 111, and others
e. Challenges in first-line management
f. Future trials

III. Adverse Events

a. Recognizing the various types of AEs associated with the use of combination IO/TKI therapeutic options
b. Management strategies for irAEs/trAEs associated with the use of combination IO/TKI therapeutic options
c. Multidisciplinary irAE/trAE management team members and their respective roles

IV. Case studies

V. Conclusions and Q & A

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FACULTY

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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 educational activity is intended for US-based community oncologists and the multidisciplinary care team involved in the management of patients with RCC.

LEARNING OBJECTIVES

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

- Interpret evidence from clinical trials assessing first-line combination IO/TKI therapies for the treatment of patients with advanced and/or mRCC
- Differentiate patients with advanced and/or mRCC in your care that could benefit from first-line IO/TKI combination therapies
- Formulate management strategies that account for irAEs and trAEs associated with first-line combination IO/TKI therapies for the treatment of patients with advanced and/or mRCC

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

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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.

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Learning Objectives

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- Differentiate patients with advanced and/or mRCC in your care that could benefit from first-line IO/TKI combination therapies
- Formulate management strategies that account for irAEs and trAEs associated with first-line combination IO/TKI therapies for the treatment of patients with advanced and/or mRCC

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

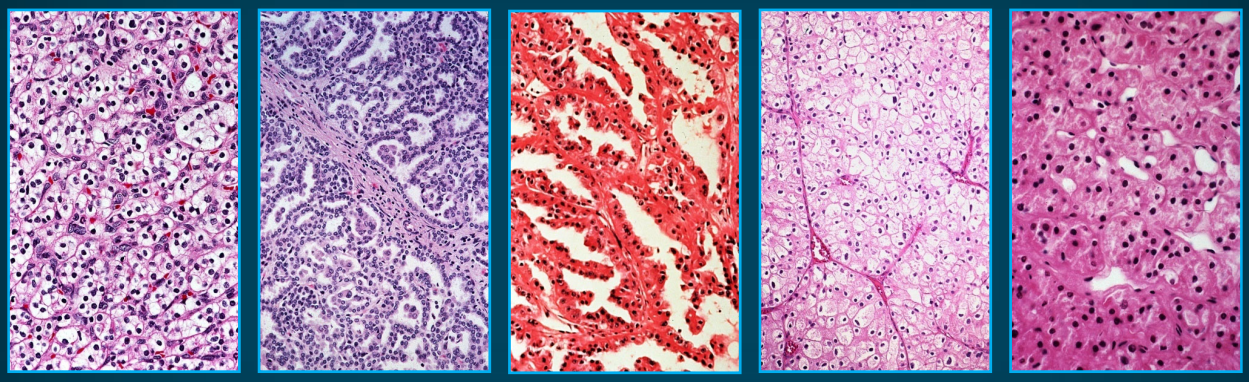
RCC: Clinical Presentation and Pathology

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

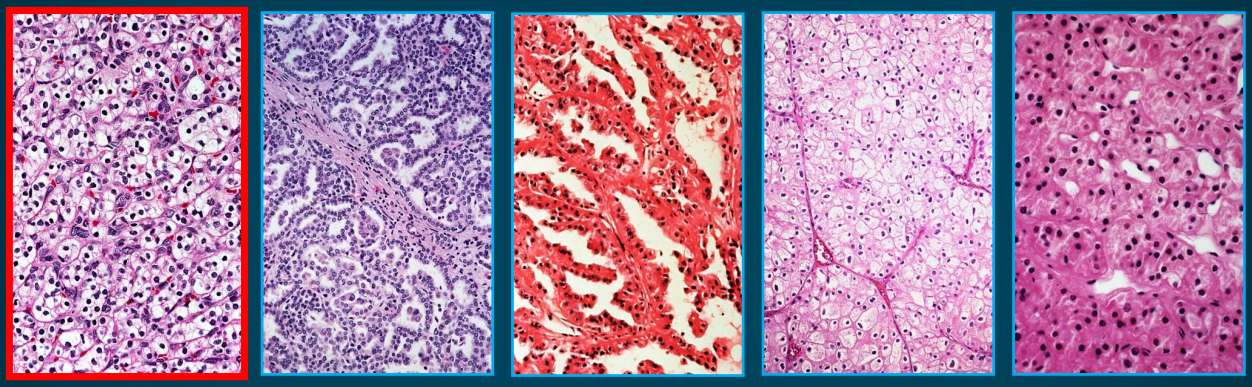


Clear Cell 75% | Papillary Type 1 5% | Papillary Type 2 10% | Chromophobe 5% | Oncocytoma 5%

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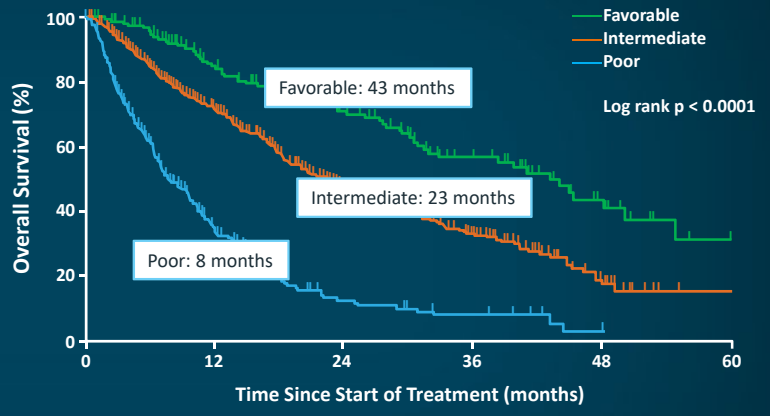
Risk Stratification for 1st-Line Therapy in mRCC: IMDC/Heng Criteria

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

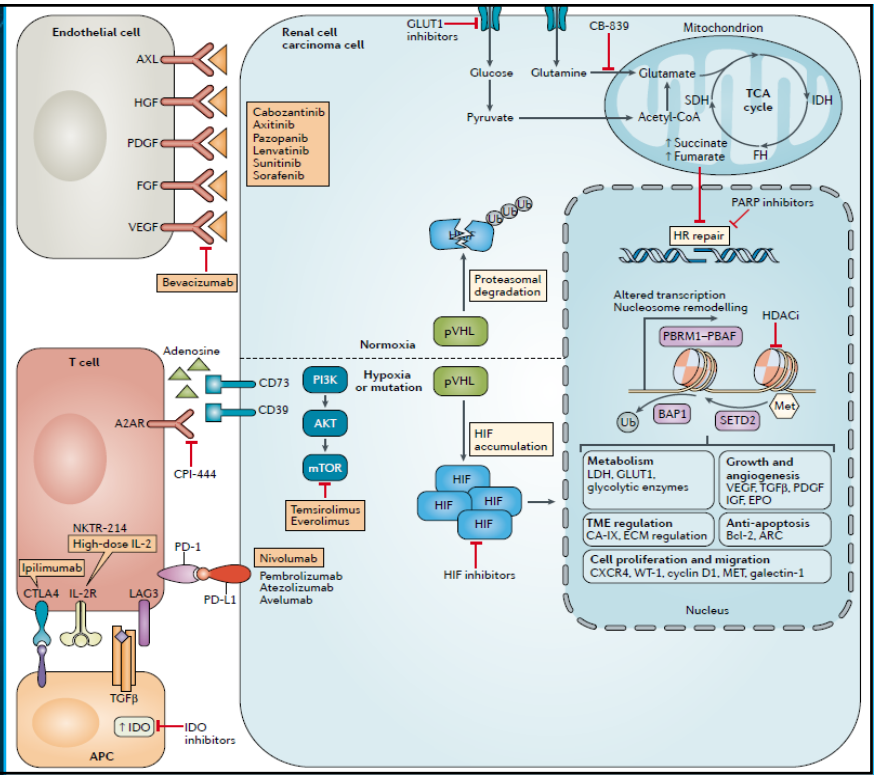


>500 patients with mRCC treated with VEGF-targeted therapy: sunitinib (61%), sorafenib (31%), bevacizumab (8%)

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.

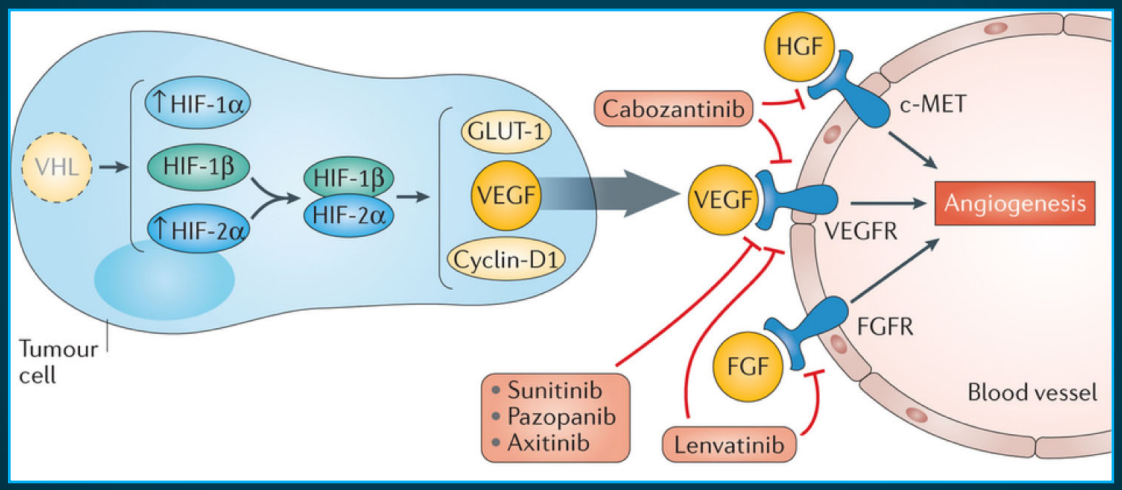
RCC: Therapeutic Targets



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

Systemic Therapy in the Metastatic Setting

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.

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

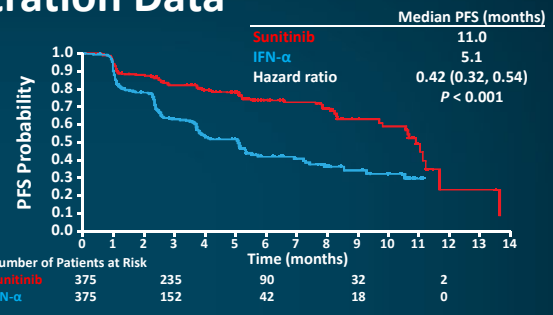
- Patients with untreated metastatic RCC
- Stratified based on performance status, LDH level, prior nephrectomy

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



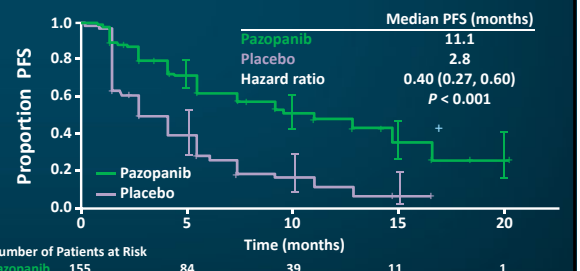
Eligibility criteria
- Locally advanced RCC or mRCC
- Predominant clear cell histology
- Measurable disease (≥ 1 lesion)
- 0 to 1 prior systemic treatment (cytokine based) for locally advanced or mRCC

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
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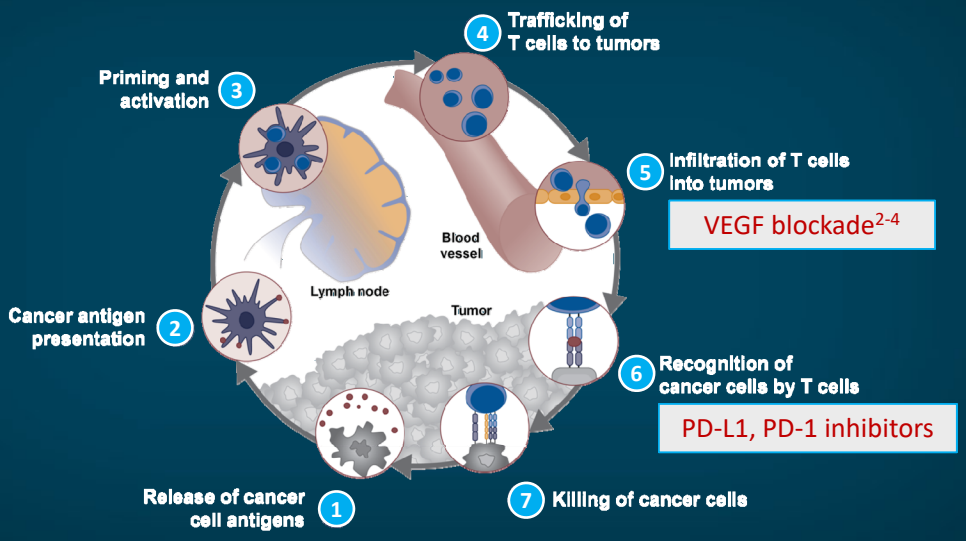
See guidelines for additional notes and information on these recommendations.

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.

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)

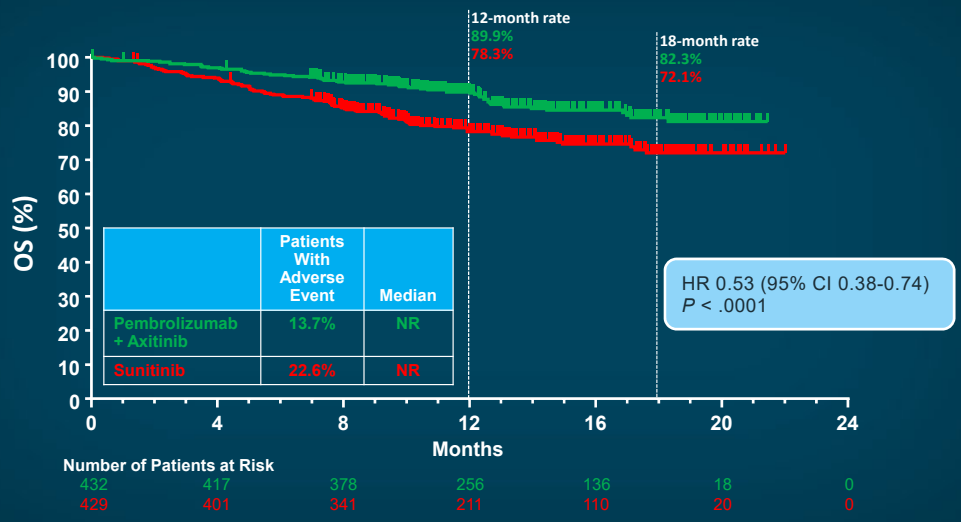
Randomized 1:1

- **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

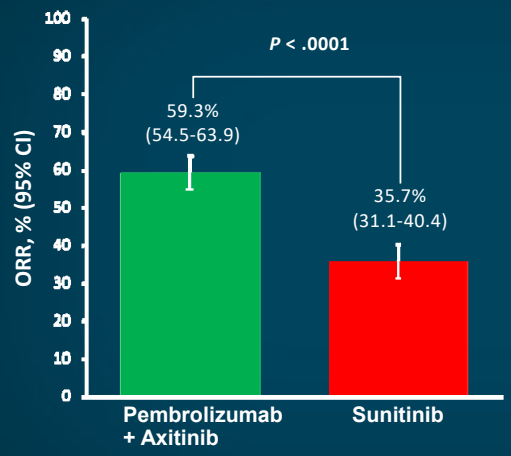


Data cutoff date: 8.24.2018. NR = not reached.
Powles T, et al. GU ASCO 2019; Abstract 543. Rini BI, et al. *N Engl J Med*. 2019;380:1116-1127.

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

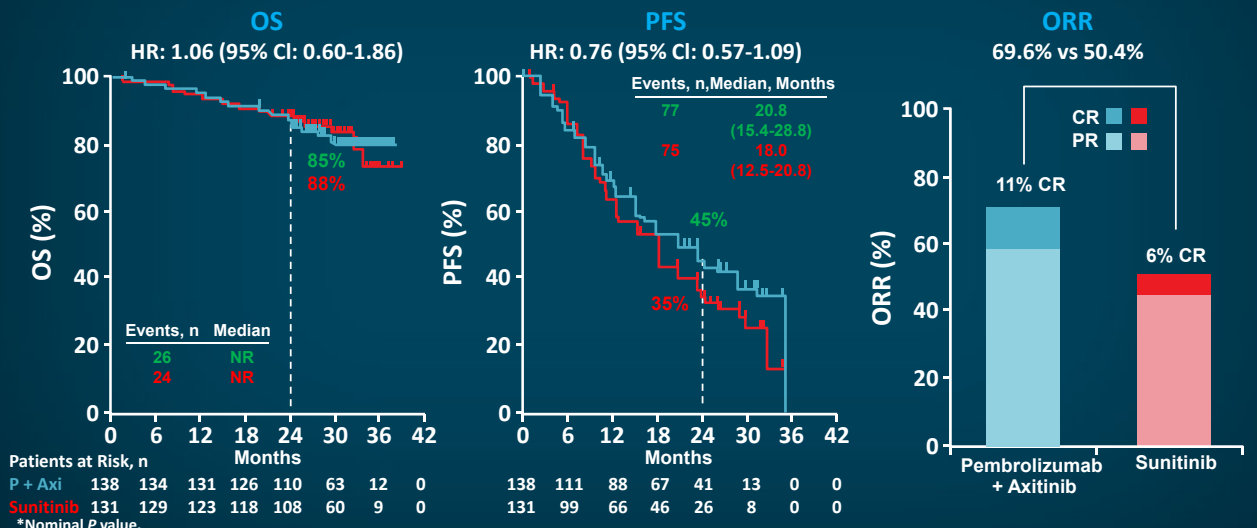


Best Response	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Complete response	25 (5.8%)	8 (1.9%)
Partial response	231 (53.5%)	145 (33.8%)
Stable disease	106 (24.5%)	169 (39.4%)
Progressive disease	47 (10.9%)	73 (17.0%)
Not evaluable[a]	8 (1.9%)	6 (1.4%)
Not assessed[b]	15 (3.5%)	28 (6.5%)

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

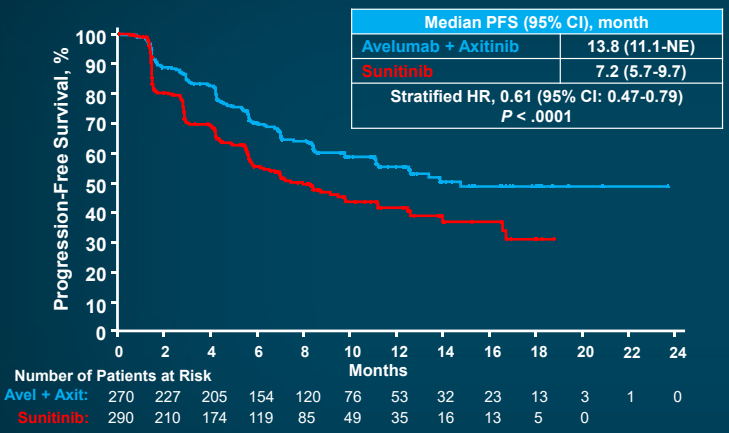
- **PFS and OS in PD-L1+ disease per BICR***
- Key secondary endpoint: PFS in overall population
- Other endpoints: objective response and safety

*≥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

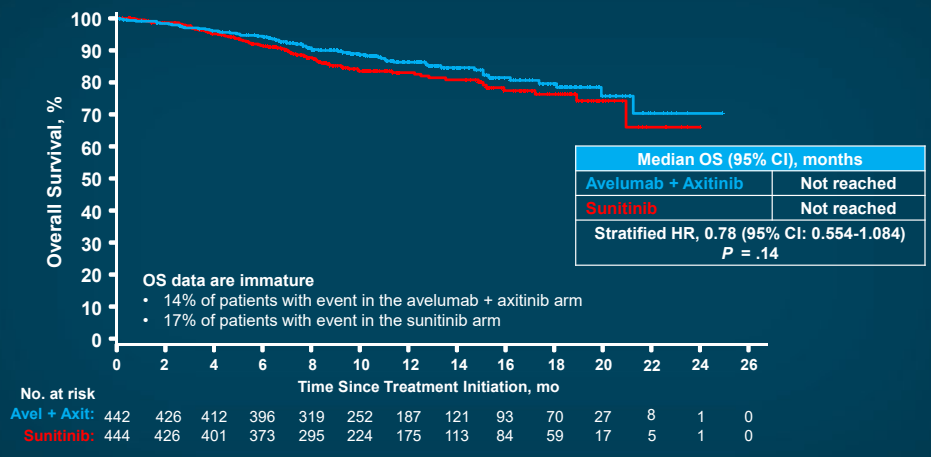


Median PFS (95% CI), month	
Avelumab + Axitinib	13.8 (11.1-NE)
Sunitinib	7.2 (5.7-9.7)
Stratified HR, 0.61 (95% CI: 0.47-0.79) *P* < .0001	

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 OS (95% CI), months	
Avelumab + Axitinib	Not reached
Sunitinib	Not reached
Stratified HR, 0.78 (95% CI: 0.554-1.084) *P* = .14	

OS data are immature
- 14% of patients with event in the avelumab + axitinib arm
- 17% of patients with event in the sunitinib arm

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.

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(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.

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)

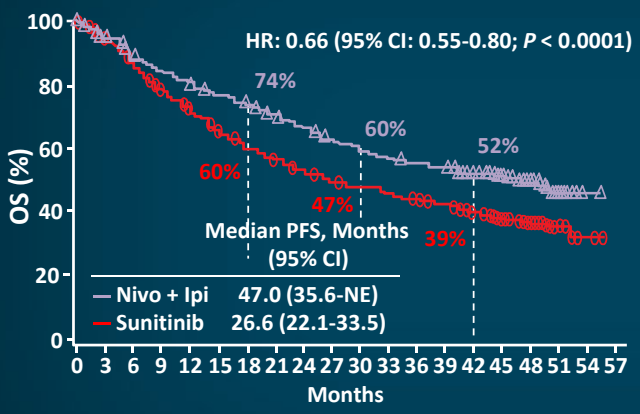
Minimum follow-up of 23 months

CCRCC = clear cell renal cell carcinoma.

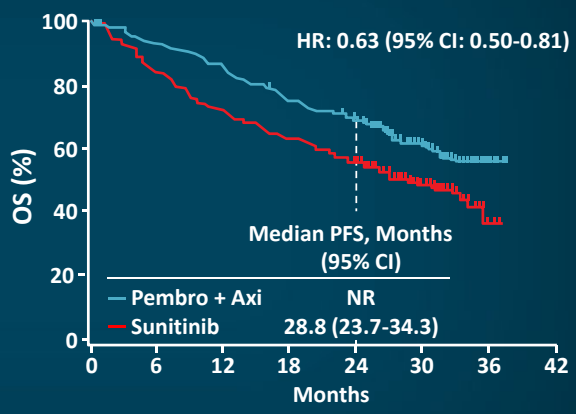
1. Tannir NM, et al. ASCO GU 2020; Abstract 609. 2. Powles T, et al. GU ASCO 2019; Abstract 543.

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]



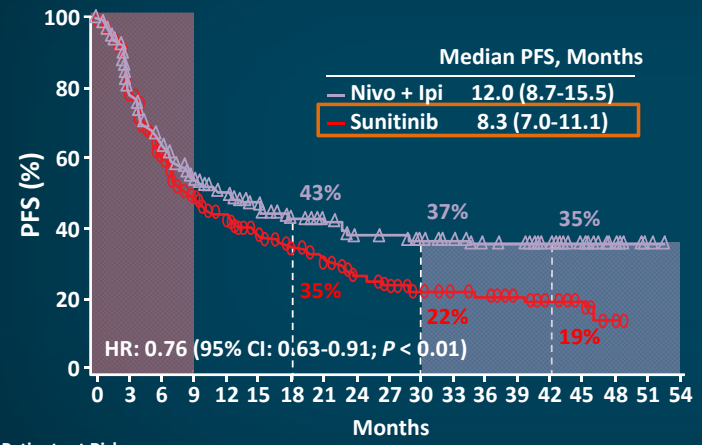
- Similar outcome on same comparator arm
- Early separation of curves for both
- Longer follow-up for CheckMate 214

*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

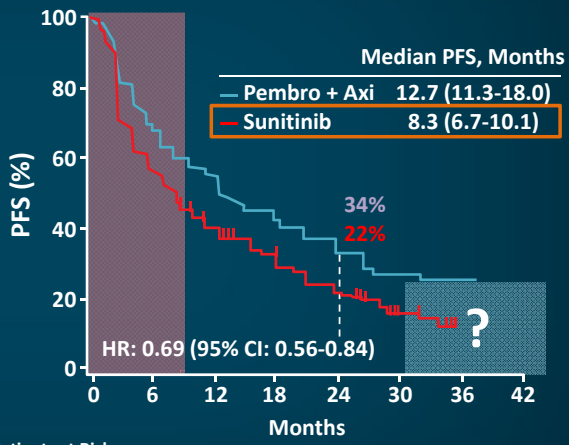
CheckMate 214: Nivo + Ipi vs Sunitinib (n = 847)[1]



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)

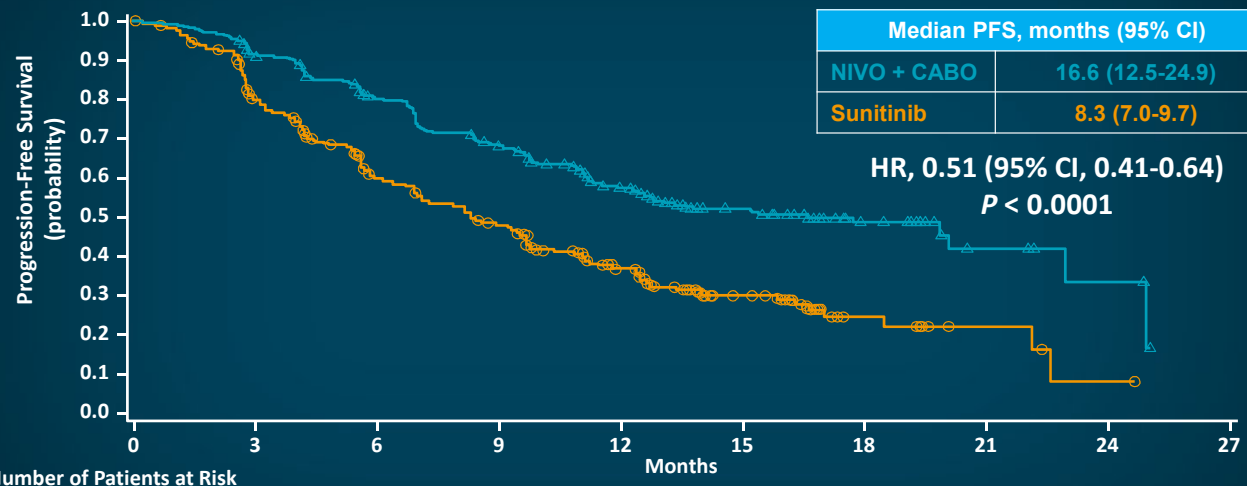
[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.

[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.

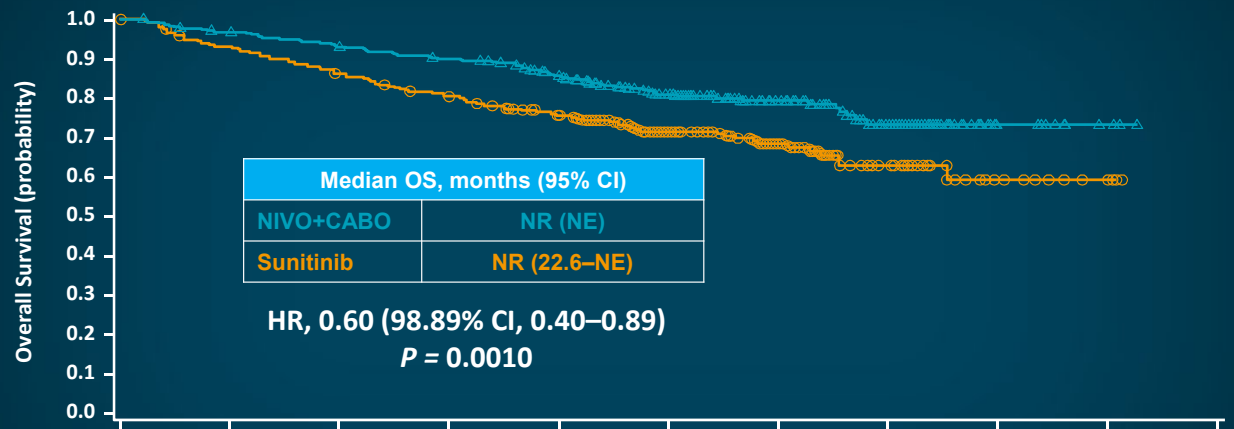
Choueiri T, et al. *NEJM*. 2021;384:829-41.

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)

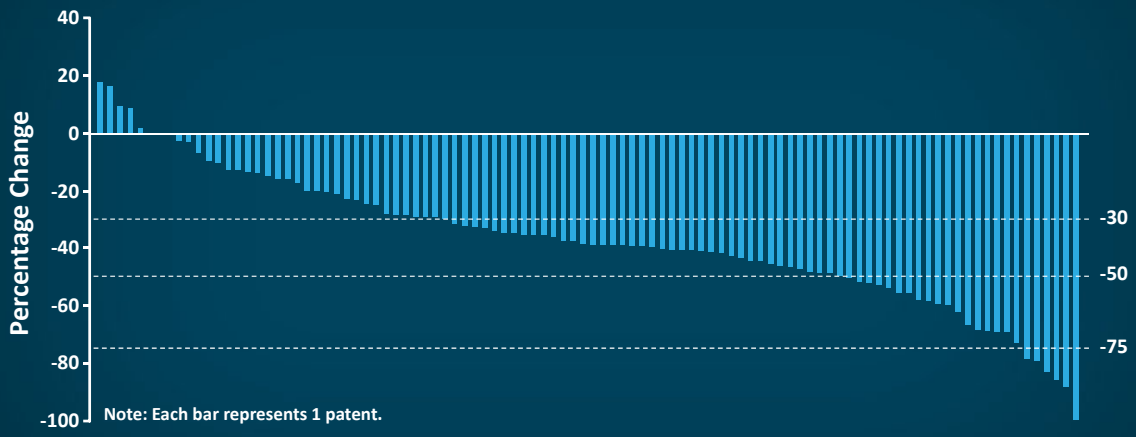
Lee C-H, et al. ASCO 2020; Abstract 5008. Not yet FDA approved for RCC.

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.

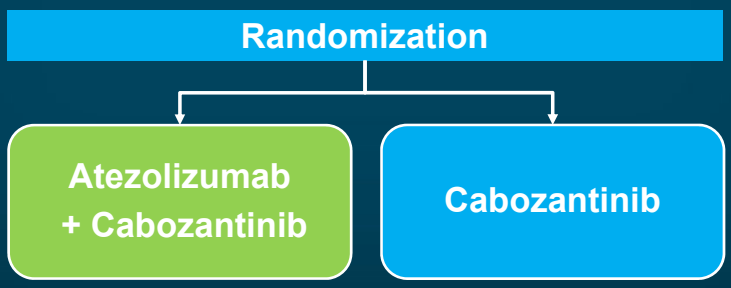
Randomized PD-1/VEGF Blockade Salvage Trial

CONTACT-03 (NCT04338269)

mRCC 2/3L

VEGFR-TKI ± PD-L1 inhibition

Phase 3 (N = 500)
Primary endpoint: PFS, OS



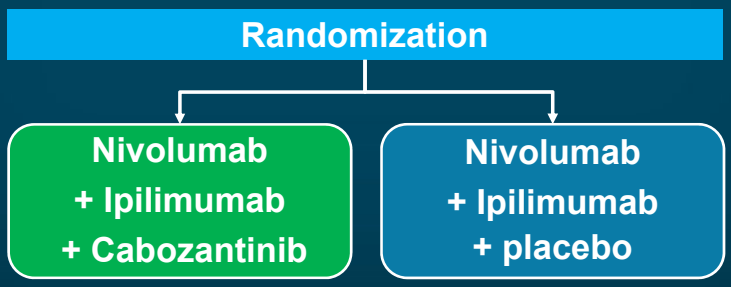
ClinicalTrials.gov. NCT04338269. https://clinicaltrials.gov/ct2/show/NCT04338269. Not yet FDA approved for RCC.

Future Trials: Triplet Therapy

COSMIC 313 - Cabozantinib + Nivolumab + Ipilimumab (NCT03937219)

PD-1 +CTLA-4 inhibition ± VEGFR-TKI

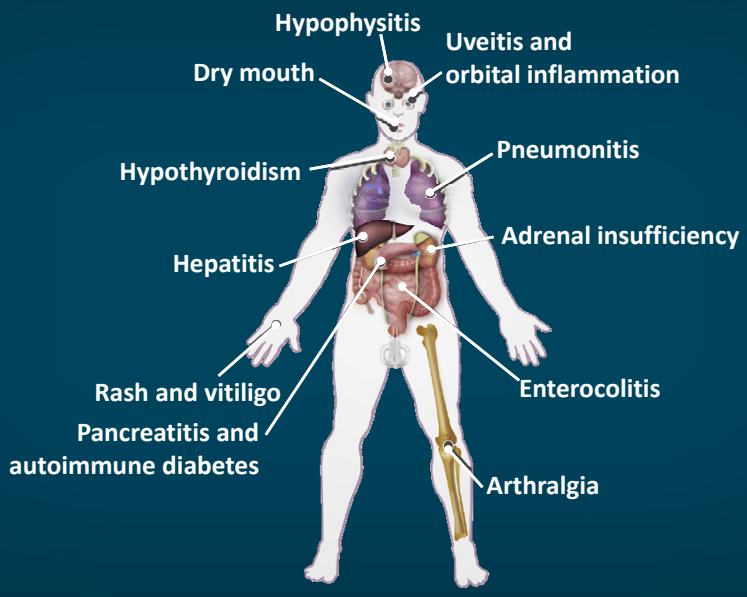
Phase 3 (N = 676)
Primary endpoint: PFS (BIRC)



Presented by Toni Choueiri at ASCO 2020. Not yet FDA approved for RCC.

Adverse Events

Immune-Related Adverse Events: Clinical Spectrum



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

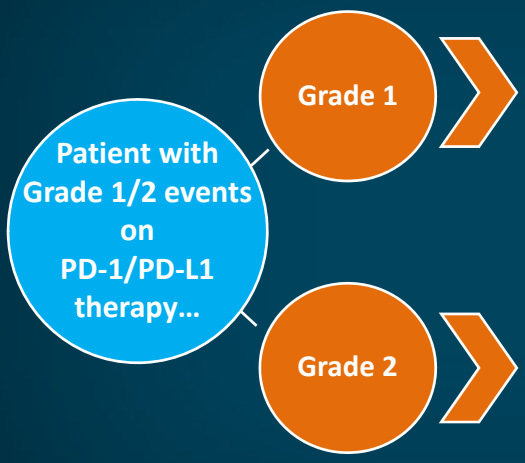
Management of Immune-Related Adverse Events

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]

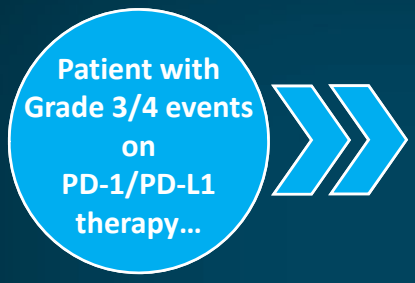


- Continue immunotherapy (or consider temporary delay)
- Symptomatic therapy

- 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)

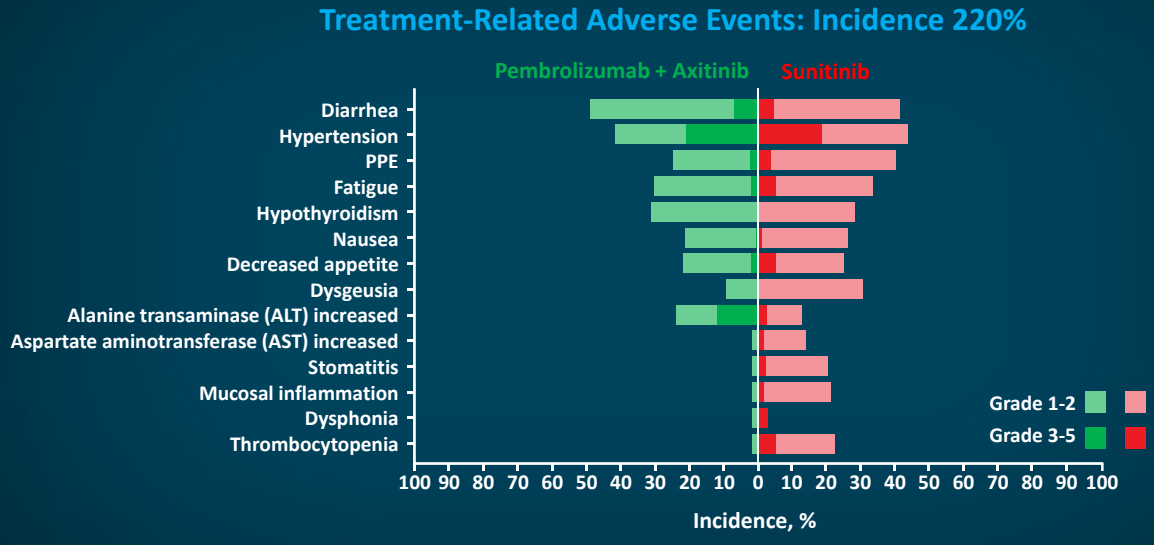
- **If no improvement or progression, consider additional immunosuppressant treatment (eg, anti-tumor necrosis factor therapy, infliximab, vedolizumab, or mycophenolate)**
- **If > 4 weeks of corticosteroids or other immunosuppressants needed, administer antimicrobial/ antifungal prophylaxis to prevent 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!

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 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

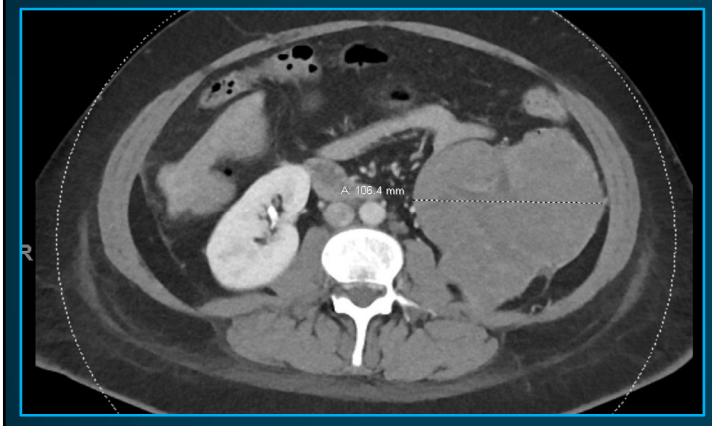
ALKALINE PHOSPHATASE	30 - 101 U/L	508 High
AST	9 - 40 U/L	112 High
ALT	5 - 40 U/L	105 High
BILIRUBIN TOTAL	< 1.3 mg/dL	1.4 High

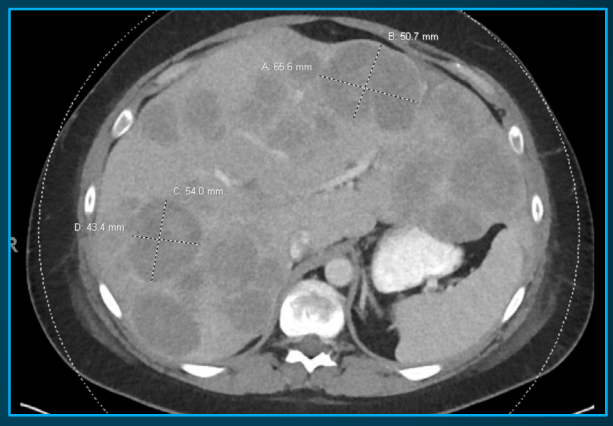
- Calcium: normal, hemoglobin: 11.6 (LLN 11.9); absolute neutrophil count: 8.76; platelets: 408
- ECOG PS 2

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?

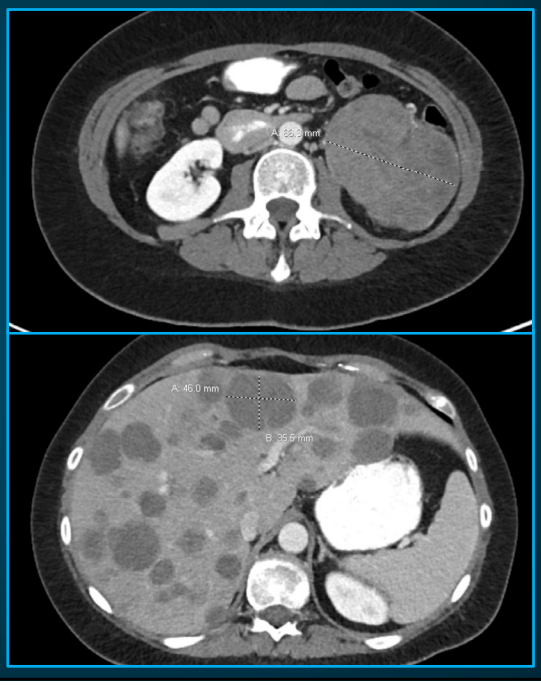
A. Sunitinib
B. Cabozantinib
C. Axitinib + pembrolizumab
D. Axitinib + avelumab
E. Nivolumab + ipilimumab
F. Active surveillance

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)

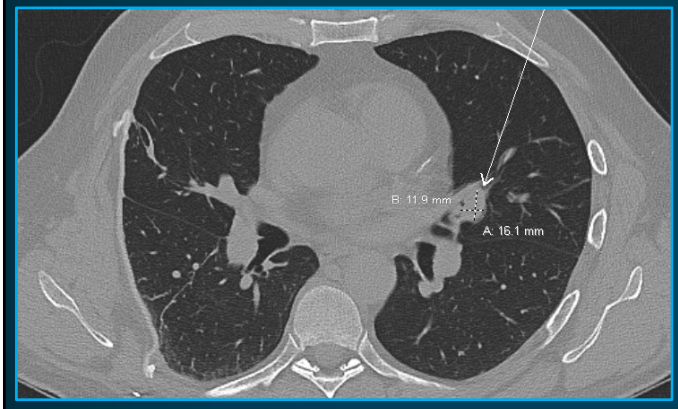


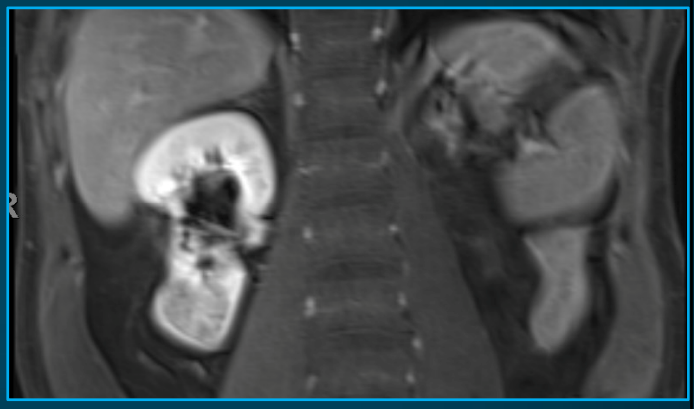
Case Study

Case Study: Activity in the Primary Cancer

- 60-year-old man, hypertension, hyperlipidemia, presented with gross hematuria, 2 right renal masses
- Right peripheral neuropathy 1/16/2014 (CCRCC pT1b and pT1a Grade 3)
- Right seventh rib resection 7/23/2016 (metastatic RCC)
- Apr 2019 MRI: bilateral renal masses
- 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

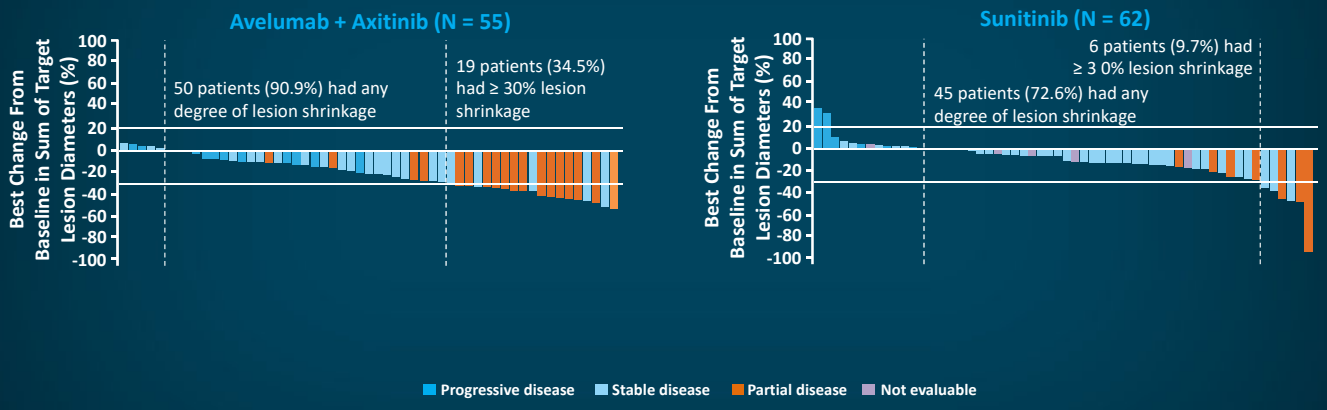
- Factors in treatment decision-making
  - IMDC risk
  - Disease extent/symptoms
  - Disease pace/kinetics
  - Time to response
  - Activity in the kidney primary
- IMDC risk: Good risk
- ECOG PS 0

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
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