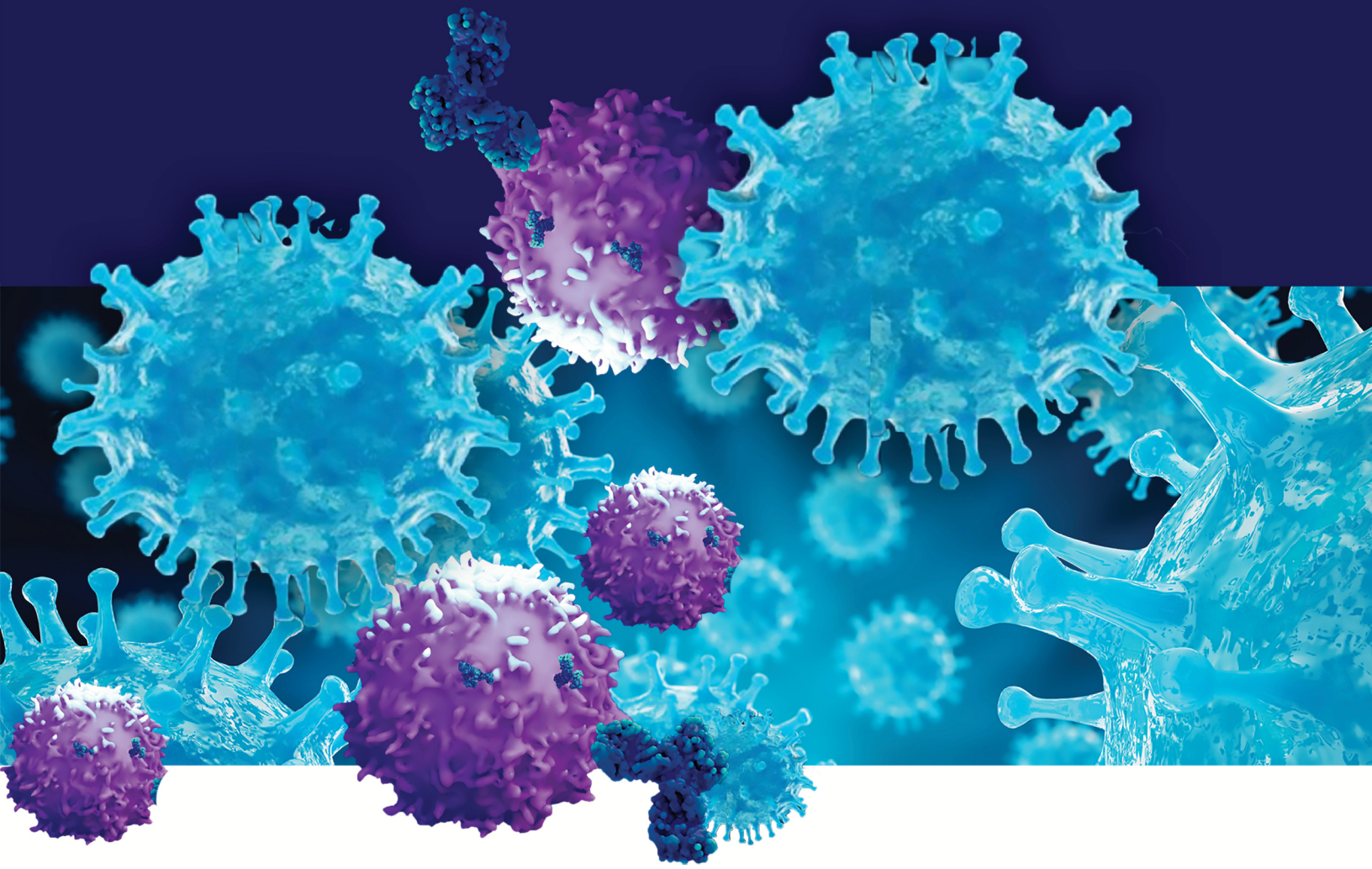
IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic:**

IMMUNO-ONCOLOGY IN ADVANCED RENAL CELL CARCINOMA



MEETING INFO

Thursday, June 10, 2021
12:00 Noon – 1:00 PM Eastern

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

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

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the COVID-19 Pandemic

Track 3: Immuno-oncology in Advanced Renal Cell Carcinoma

PROGRAM OVERVIEW

This case-based live virtual activity will cover the diagnosis, treatment, and management of patients with cancer who are treated or eligible for treatment with immunotherapy.

TARGET AUDIENCE

This initiative is designed to meet the educational needs of oncologists, oncology pharmacists, oncology nurses and other healthcare professionals and teams involved in the management of patients with cancer who are treated or eligible for treatment with immunotherapy.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

• Describe the MOAs and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of RCC

• Recognize and manage side effects and toxicities associated with available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of RCC

• Review established prognostic and potential predictive immune- and non-immune-related biomarkers for RCC

• Discuss current recommendations and emerging evidence regarding the use of immunotherapies for patients with RCC during the COVID-19 pandemic including the management of irAEs and the utility of telemedicine

• Explain patient-centered SDM approaches aimed at optimizing cancer care and survivorship for those with RCC and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies used alone or in combination

ACCREDITATION AND DESIGNATION STATEMENTS

Accreditation Statement
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Nursing Credit Information
Purpose: This program would be beneficial for nurses involved in the management of patients with cancer who are treated or eligible for treatment with immunotherapy.
Credits: 1.0 ANCC Contact Hour

Accreditation Statement
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ABIM Maintenance of Certification:
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

CONTINUING PHARMACY EDUCATION CREDIT

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

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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Amedco LLC designates this activity for a maximum of 1.0 knowledge-based CPE contact hour.
NOTE: The only official Statement of Credit is the one you pull from CPE Monitor. You must request your certificate within 30 days of your participation in the activity to meet the deadline for submission to CPE Monitor.

PROGRAM CHAIR

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

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Consulting fees/Advisory role: Genentech, Incyte, Janssen, Merck, Pfizer, AstraZeneca/Medimmune, Nektar, Seattle Genetics, and Immunomedics; **Contracted research:** Genentech, Nektar; **Contracted research (institution):** Genentech, Merck, AstraZeneca/Medimmune, Seattle Genetics, and Immunomedics; **Speaking engagements:** Genentech, Merck, and AstraZeneca/Medimmune; **Steering/Scientific Advisory Committee:** Merck; **Steering Committee Membership:** Nektar; **Equity:** EpiVax Oncology; **Scientific Advisory Board Member:** EpiVax Oncology.

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The independent reviewers, staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests:

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.

Matthew Frese, General Manager of Med Learning Group has nothing to disclose.
Christina Gallo, SVP, Educational Development for Med Learning Group has nothing to disclose.
Lauren Welch, MA, VP, Outcomes and Accreditation for Med Learning Group has nothing to disclose.
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2. Participate in the live virtual activity.
3. Complete the online post-test and evaluation.

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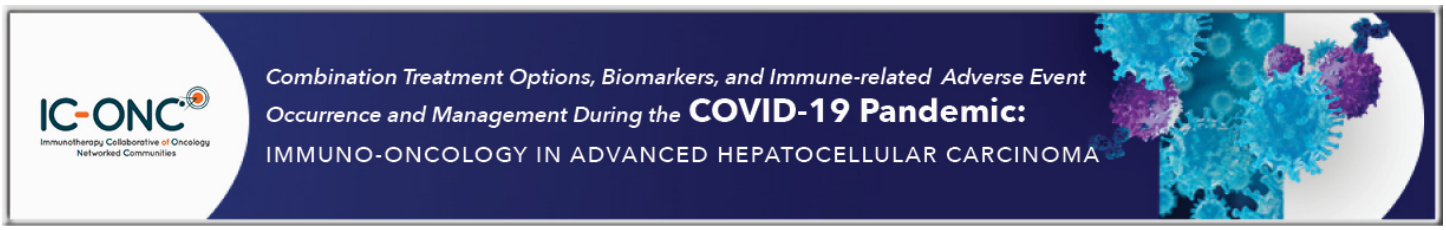
Provided by Med Learning Group

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.



Program Agenda

I. Introduction of IC-ONC Network - the Goals, Resources and Network Community Building Concept

a. Overview of IC-ONC Collaborative
b. Description of short and long-term goals and available resources that are available to the network community
c. Overview of the current scenario of new cancer immunotherapies for difficult-to-treat cancer malignancies (focus on advanced melanoma, NSCLC, RCC and HCC)
d. Rapidly changing treatment patterns and challenges in clinical practice due to the introduction of novel cancer immunotherapeutics

II. Available and Emerging Immuno-oncology Therapeutic Options for the Treatment of Advanced HCC

a. Mechanisms of action and clinical profiles of available immunotherapies used as monotherapies across lines of treatment for advanced HCC
b. Mechanisms of action and clinical profiles of available immunotherapies used as combination therapies across lines of treatment for advanced HCC
c. Mechanisms of action and clinical profiles of emerging immunotherapies alone and in combination across lines of treatment for advanced HCC

III. Immune-Related Adverse Events Secondary to ICI Therapy

a. Types of irAEs associated with immunotherapies for the treatment of advanced HCC
b. Pathophysiologic basis for irAEs
c. Surveillance and management of most common irAEs

IV. Immune- and Non-immune-related Biomarkers and Testing Methodologies

a. Prognostic and predictive biomarkers including alpha fetoprotein (Theme: MOAs biomarkers [i.e., PD-L1] on disease characteristics and response to treatment)
b. Evidence-based guidance on biomarker assessment
c. Incorporation of biomarker and genomic testing in the clinical practice setting

V. COVID-19 and Cancer

a. Malignancy as a risk factor for infection
b. Relationship between active or past cancer treatment and infection on outcomes
c. Effect of infection-risk on immunotherapy selection/initiation/continuation
d. COVID-19 vaccines and immunotherapy

VI. Multidisciplinary Oncology Team – Optimizing Patient Care and Survivorship Through Shared Decision Making

a. Educational strategies for the oncology patient
    1. Disease state, immuno-oncology medication use – dosing regimen (how and when to take, persistence/adherence, dosing options), potential adverse events and their management, review of treatment plan
b. Shared decision making in the care process – use of decision aids

c. Ongoing, routine communication between members of the multidisciplinary health care team throughout treatment
d. Team members and their respective roles

VII. Case Studies and Conclusions

VIII. Questions & Answers

WELCOME!

We will start momentarily!

Your line will automatically be muted upon entry.

Things to know…

- ✓ Please type questions in the Q&A section
- ✓ To receive credit, please visit **[insert QPro link here]**
- ✓ Please visit **www.ic-onc.org** for more information and resources
- ✓ To build a complimentary office poster, visit **immuneonc.posterprogram.com**
- ✓ ***To request a pair of glasses to view the 3D animations in this presentation, please email mjohnson@medlearninggroup.com***

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Combination Treatment Options, Biomarkers, and Immune-Related Adverse Event Occurrence and Management During the COVID-19 Pandemic

Immuno-oncology in Advanced 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
New York, NY

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Disclosures

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- During the course of this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications.

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

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- This educational activity is applicable for CME and CNE credits, in addition to ILNA recertification points. Please complete the necessary electronic evaluation to receive credits and access to the ILNA credits form.

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Learning Objectives

- Describe the mechanisms of action and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of renal cell carcinoma (RCC).
- Recognize and manage side effects and toxicities associated with available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of RCC.
- Review established prognostic and potential predictive immune- and non-immune-related biomarkers for RCC.
- Discuss current recommendations and emerging evidence regarding the use of immunotherapies for patients with RCC during the COVID-19 pandemic, including the management of immune-related adverse event (irAEs) and the utility of telemedicine.
- Explain patient-centered, shared decision-making approaches aimed at optimizing cancer care and survivorship for those with RCC and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies used alone or in combination.

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IC-ONC

- This program is part of the Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC), a global information network in which multidisciplinary healthcare providers who are responsible for treating patients with cancer are connected via education.
- **IC-ONC.org** serves as the central location for educational resources and information pertinent to patients with cancer being treated with immunotherapy.
  - It is curated by global, national, and local oncology experts.
  - It provides dates and locations of upcoming live meetings.
  - It provides access to archived and enduring activities.
  - It identifies clinical articles.
  - It is a source of downloadable content and other inter-professional resources from more than 14 collaborative educational partners.
  - It provides access to our open-source immuno-oncology registry: **The Observatory**
- Its objective is to facilitate ongoing communication and collaboration among participating healthcare providers with the aim of providing optimal care for the patient with cancer.
- For more information, please visit **www.ic-onc.org**
- Supported by an educational grant from Bristol Myers Squibb.

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IC-ONC Observatory

- Through participation in this course, you will become a member of the IC-ONC Observatory
- Your login details will be emailed to you in the coming weeks
- For immediate information, please visit www.ic-onc.org

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Renal-Cell Carcinoma
Signs and Symptoms, Paraneoplastic Syndromes

Finding	Frequency
Classic triad (ie, flank pain, hematuria, and palpable mass)	<15%
Hypertension	~ 40%
Hypercalcemia	13–20%
Erythrocytosis	8%
Polycythemia	1–8%
Anemia	>8%
Fever	20–30%
Amyloidosis	3–8%
Stauffer's syndrome*, ie, hepatic dysfunction	3–20%

*Elevations in liver enzymes and abnormal levels of hepatic synthetic products.

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

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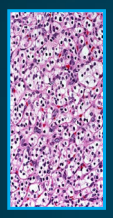
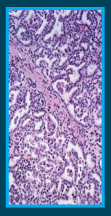
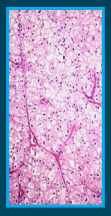
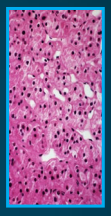
Renal-Cell Carcinoma—Pathologic Subtypes


Clear cell
75%


Papillary type 1
5%


Papillary type 2
10%


Chromophobe
5%


Oncocytoma
5%

Other malignant subtypes of RCC include medullary, small cell, lymphoma, and sarcomas of the kidney

RCC = renal-cell carcinoma.

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

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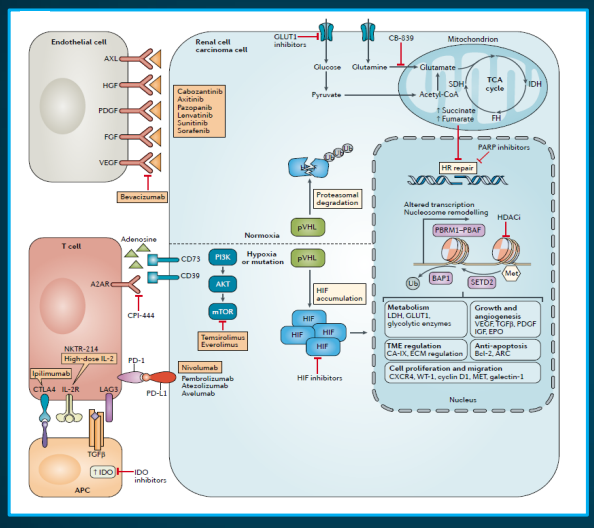
Mechanism of Action for Immuno-oncologics



HGF = hepatocyte growth factor; PDGF = platelet-derived growth factor; FGF = fibroblast growth factor; VEGF = vascular endothelial growth factor; IL = interleukin; CTLA4 = cytotoxic T-lymphocyte antigen 4; LAG3 = lymphocyte-activation gene 3; TGF = tumor growth factor; IDO = indolamine 2,3-dioxygenase; APC = antigen-presenting cell; PD-1 = programmed (cell) death 1; PD-L1 = PD-1 ligand; CD = cluster of differentiation; PI3K = phosphoinositide-3 kinase; mTOR = mechanistic target of rapamycin; pVHL = von Hippel Lindau protein; HIF = hypoxia-inducible factor; TCA = tricarboxylic acid; LDH = lactate dehydrogenase; IDH = isocitrate dehydrogenase; SDH = succinate dehydrogenase; FH = fumarate hydratase; GLUT1 = glucose transporter type 1; EPO = erythropoietin; TME = tumor microenvironment; CA-IX = carbonic anhydrase IX; ECM = extracellular matrix; MET = mesenchymal-epithelial transition (factor).

Kotecha RR, et al. *Nat Rev Clin Oncol.* 2019;16:621-633.

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Available and Emerging Immuno-oncology Therapeutic Options for Advanced RCC

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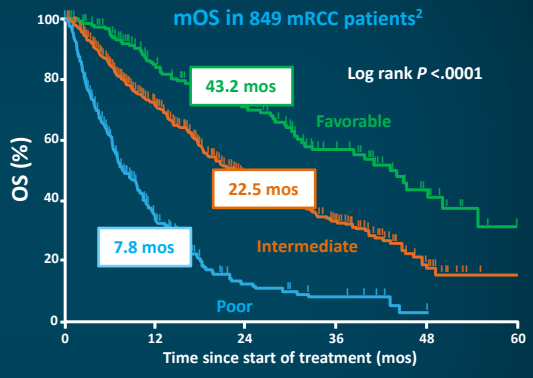
Risk Stratification for First-Line Therapy in mRCC
IMDC/Heng Criteria

IMDC Criteria Risk Factors[1]	
KPS	<80%
Time from diagnosis	<12 mos
Hemoglobin	<LLN
Neutrophil count	>ULN
Platelet count	>ULN
Corrected serum calcium	>ULN

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



645 patients with mRCC treated with VEGF-targeted therapy: sunitinib (61%); sorafenib (31%); bevacizumab (8%)[1]

mRCC = metastatic renal-cell carcinoma; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; mo(s) = month(s); LLN = lower limit of normal; ULN = upper limit of normal; OS = overall survival; mOS = median overall survival.

1. Heng DY, et al. *J Clin Oncol*. 2009;27:5794-5799. 2. Heng DY, et al. *Lancet Oncol*. 2013;14:141-148.

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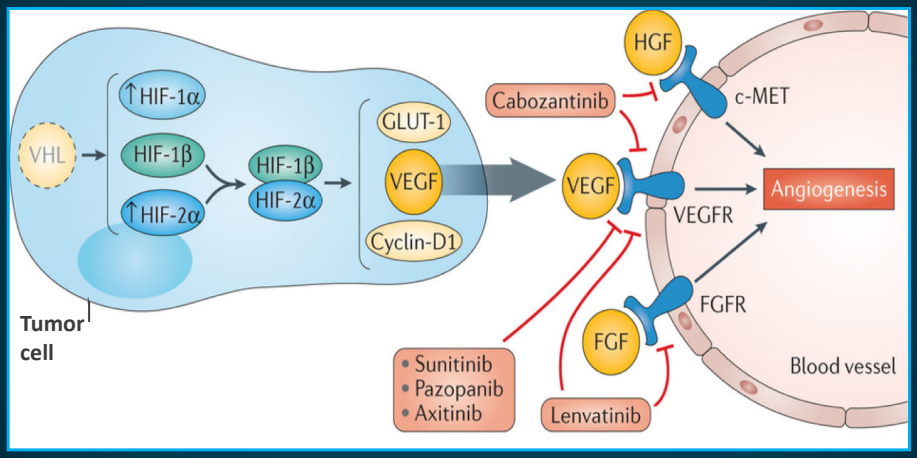
Historical Perspective in First-Line Therapy
TKI Monotherapy



TKI = tyrosine kinase inhibitor; VHL = von Hippel-Landau; c-MET = hepatocyte growth factor receptor.

Lee CH, Motzer RJ. *Nat Rev Nephrol.* 2017;13:69-70.

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Sunitinib and Pazopanib
Standards in First-Line RCC Registration Data

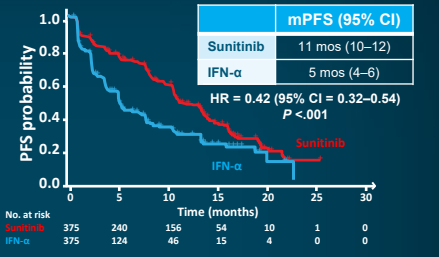
Sunitinib vs IFN-α[1]

- Untreated mRCC
- Stratified based on performance status, LDH level, prior nephrectomy

R 1:1, N = 750

- **Sunitinib** 50 mg PO QD for 4 wk; 2 wk off in 6-wk cycles (n = 375)
- **IFN-α** 9 MU SC 3x/wk (n = 375)

Primary endpoint: PFS



	mPFS (95% CI)
Sunitinib	11 mos (10–12)
IFN-α	5 mos (4–6)

HR = 0.42 (95% CI = 0.32–0.54) *P* <.001

Pazopanib vs placebo[2]

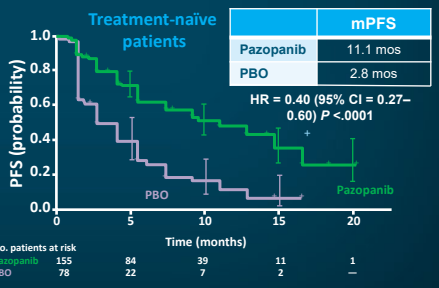
Eligibility criteria

- LA RCC or mRCC
- Predominant clear-cell histology
- Measurable disease (≥1 lesion)
- 0–1 prior systemic treatment (cytokine based) for LA or mRCC

R 2:1, N = 435

- **Pazopanib** 800 mg/day
- **Placebo**

Primary endpoint: PFS



	mPFS
Pazopanib	11.1 mos
PBO	2.8 mos

HR = 0.40 (95% CI = 0.27–0.60) *P* <.0001

PFS = progression-free survival; mPFS = median PFS; LA = locally advanced; PBO = placebo; PO = oral; QD = each day; HR = hazard ratio; CI = confidence interval; wk = week; SC = subcutaneously; R = randomization.

1. Motzer RJ, et al. *N Engl J Med.* 2007;356:115-124. 2. Sternberg CN, et al. *J Clin Oncol.* 2010;28:1061-1068.

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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	• Axi + Pemb • Pazopanib • Sunitinib • Cabo + Nivo	• Ipi/Nivo • Cabo (2B) • Axi + avelumab	• Active surveillance • High-dose IL-2 • Axi (2B)
Intermediate/ Poor	• Ipi/Nivo (1) • Axi + Pemb (1) • Cabo + Nivo • Cabo	• Pazopanib • Sunitinib • Axi + avelumab	• Axi (2B) • Temsirolimus • High-dose IL-2

Evidence category is shown in parentheses.

NCCN. Kidney cancer v2.2021 (www.nccn.org/professionals/physician_gls/default.aspx). Accessed 3/4/2021.

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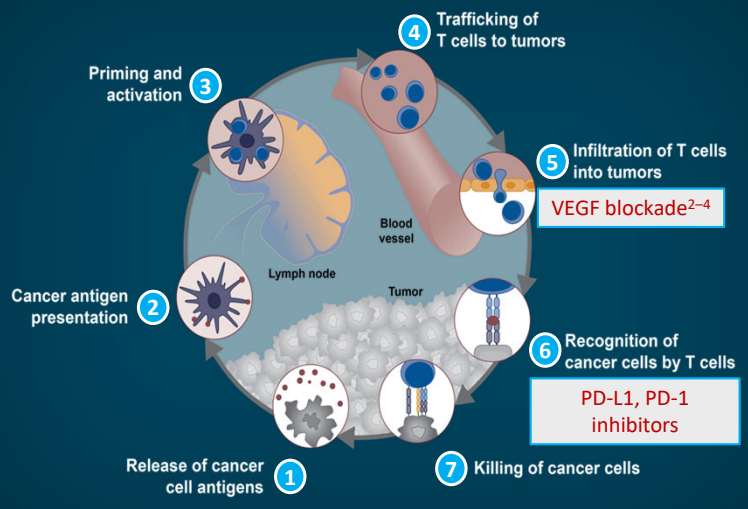
Is VEGF Inhibition Synergistic With Anti–PD-1?[1]



1. Adapted from Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Shrimali RK, et al. *Cancer 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.

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KEYNOTE-426 Study Design

Pembrolizumab (anti-PD-1) in combination with axitinib (VEGFR-TKI) in previously untreated RCC

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

R 1:1

n = 432

Pembrolizumab
200 mg IV Q3W
+ Axitinib
5 mg BID

n = 429

Sunitinib
50 mg QD x 4 wk, 2 wk off in 6-wk cycle

N = 861

- **Dual primary endpoints:** OS and PFS (RECIST v1.1, BICR)
- **Secondary endpoints:** ORR (key), DoR, PROs, safety
- **Stratification factors:** IMDC risk group (favorable vs intermediate vs poor) and geographic region (North America vs Western Europe vs ROW)

ccRCC = clear-cell RCC; BICR = blinded independent central radiologic review; DoR = duration of response; PROs = patient-reported outcomes; ROW = rest of world; RECIST = Response Evaluation Criteria in Solid Tumors; ORR = overall/objective response rate; BID = twice daily; IV = intravenous.

Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127. ClinicalTrials.gov identifier NCT02853331.

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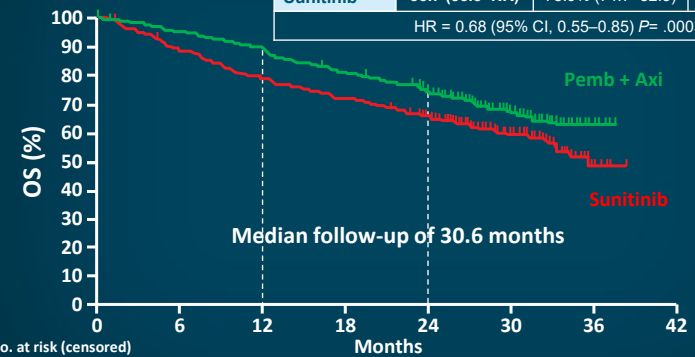
KEYNOTE-426: OS in ITT Cohort

Overall Survival (95% CI)			
	mOS (mos)	12-mo OS	24-mo OS
Pemb + Axi	NR	89.5% (86.2–92.1)	74.4% (69.9–78.2)
Sunitinib	35.7 (33.3–NR)	78.9% (74.7–82.5)	65.5% (60.8–69.8
HR = 0.68 (95% CI, 0.55–0.85) *P*= .0003			



No. at risk (censored)								
Pemb + Axi	432 (0)	408 (2)	385 (2)	346 (3)	305 (17)	163 (135)	23 (267)	0 (290)
Sunitinib	429 (0)	379 (3)	336 (3)	306 (3)	268 (14)	134 (129)	16 (235)	0 (251)

ITT = intention-to-treat; mOS = median OS; NR = not reached.

Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

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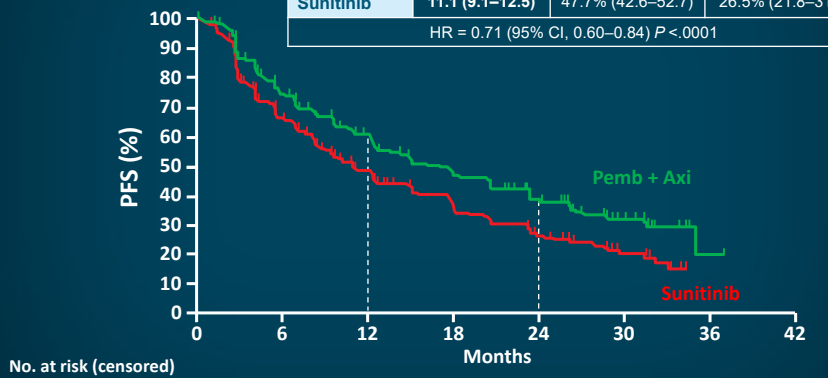
KEYNOTE-426 PFS in ITT Cohort

Progression-Free Survival (95% CI)			
	mPFS (mos)	12-mo PFS	24-mo PFS
Pemb + Axi	**15.4 (12.7–18.9**	60.0% (55.1–64.6)	37.6% (32.7–42.5)
Sunitinib	**11.1 (9.1–12.5)**	47.7% (42.6–52.7)	26.5% (21.8–31.4
HR = 0.71 (95% CI, 0.60–0.84) *P* <.0001			



No. at risk (censored)

Pemb + Axi	432 (0)	300 (24)	234 (34)	180 (40)	109 (76)	37 (134)	2 (166)	0 (168)
Sunitinib	429 (0)	248 (44)	159 (68)	112 (79)	61 (101)	19 (132)	0 (148)	0 (148)

Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

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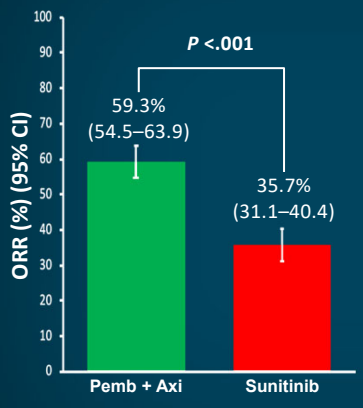
KEYNOTE-426 Confirmed Objective Responses



Best response no. (%)	Pemb + Axi n = 432	Sun n = 429
CR	**25 (5.8%)**	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	**47 (10.9%)**	**73 (17.0%)**
NE	8 (1.9%)	6 (1.4%)
NA	15 (3.5%)	28 (6.5%)

DoR	N = 256	N = 153
Median (range), mos	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

Sun = sunitinib; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable/estimable; NA = not assessed/applicable.

Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127. Powles T, et al. *J Clin Oncol.* 2019;37(suppl 7): abstract 543.

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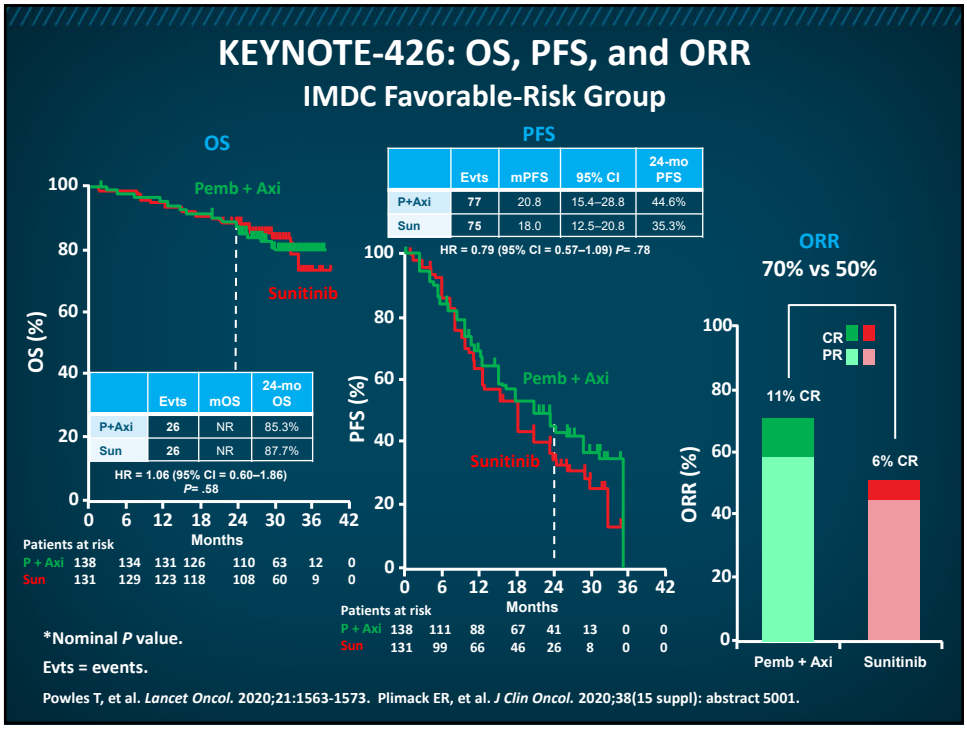
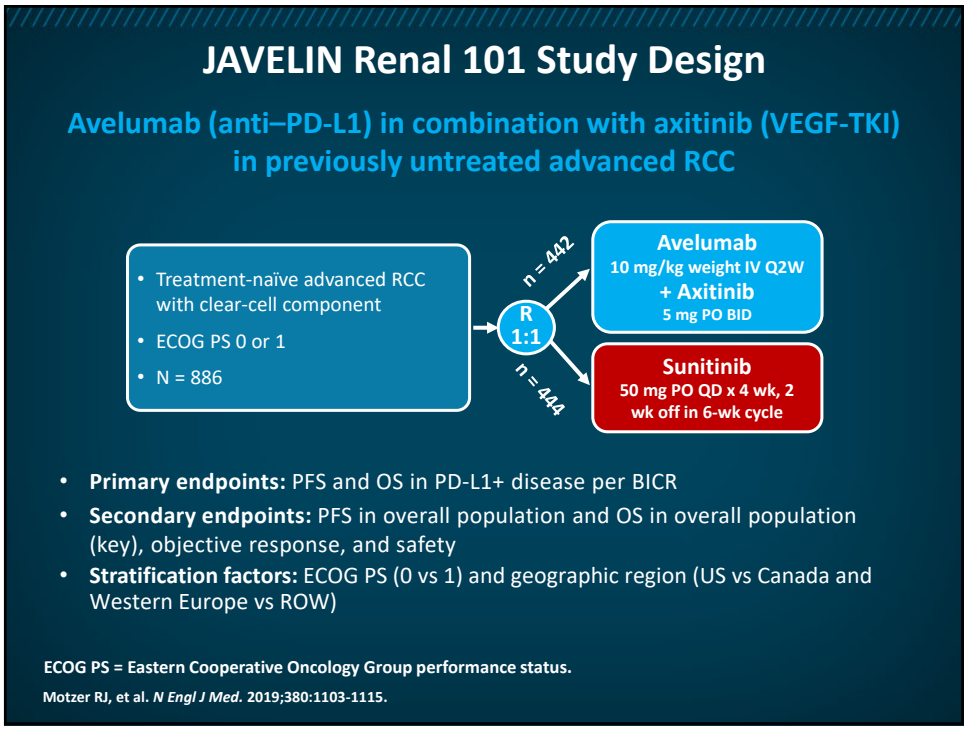
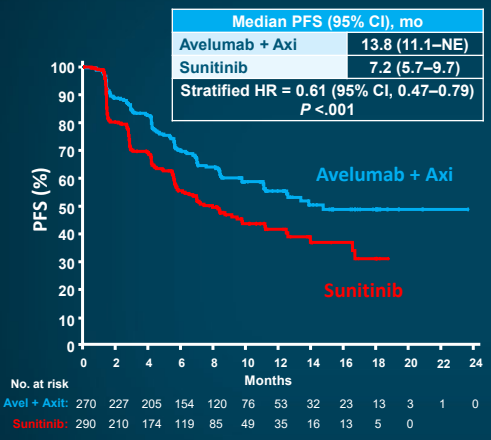

KEYNOTE-426: OS, PFS, and ORR
IMDC Favorable-Risk Group
OS
Pemb + Axi
Sunitinib
OS (%)
100
80
60
40
20
0
0 6 12 18 24 30 36 42
Months
Evts | mOS | 24-mo OS
P+Axi | 26 | NR | 85.3%
Sun | 26 | NR | 87.7%
HR = 1.06 (95% CI = 0.60–1.86)
P= .58
Patients at risk
P + Axi 138 134 131 126 110 63 12 0
Sun 131 129 123 118 108 60 9 0
PFS
Evts | mPFS | 95% CI | 24-mo PFS
P+Axi | 77 | 20.8 | 15.4–28.8 | 44.6%
Sun | 75 | 18.0 | 12.5–20.8 | 35.3%
HR = 0.79 (95% CI = 0.57–1.09) P= .78
PFS (%)
Pemb + Axi
Sunitinib
Months
Patients at risk
P + Axi 138 111 88 67 41 13 0 0
Sun 131 99 66 46 26 8 0 0
ORR
70% vs 50%
ORR (%)
CR
PR
11% CR
6% CR
Pemb + Axi
Sunitinib
*Nominal P value.
Evts = events.
Powles T, et al. Lancet Oncol. 2020;21:1563-1573. Plimack ER, et al. J Clin Oncol. 2020;38(15 suppl): abstract 5001.

21


JAVELIN Renal 101 Study Design
Avelumab (anti–PD-L1) in combination with axitinib (VEGF-TKI) in previously untreated advanced RCC
• Treatment-naïve advanced RCC with clear-cell component
• ECOG PS 0 or 1
• N = 886
R 1:1
n = 442
n = 444
Avelumab
10 mg/kg weight IV Q2W
+ Axitinib
5 mg PO BID
Sunitinib
50 mg PO QD x 4 wk, 2 wk off in 6-wk cycle
• Primary endpoints: PFS and OS in PD-L1+ disease per BICR
• Secondary endpoints: PFS in overall population and OS in overall population (key), objective response, and safety
• Stratification factors: ECOG PS (0 vs 1) and geographic region (US vs Canada and Western Europe vs ROW)
ECOG PS = Eastern Cooperative Oncology Group performance status.
Motzer RJ, et al. N Engl J Med. 2019;380:1103-1115.

22

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



Per IRC	Avelumab + Axitinib (n = 270)	Sunitinib (n = 290)
ORR, % (95% CI)	55.2 (49.0–61.2)	25.5 (20.6–30.9)
Best overall response, %*		
CR	4.4	2.1
PR	50.7	23.4
SD	26.7	43.1
PD	11.1	21.7
NE	4.4	7.2
Patients with ongoing response, %	72.5	64.9

Median follow-up = 9.9 mos (avelumab + axitinib) and 8.4 mos (sunitinib)

IRC = independent review committee.

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

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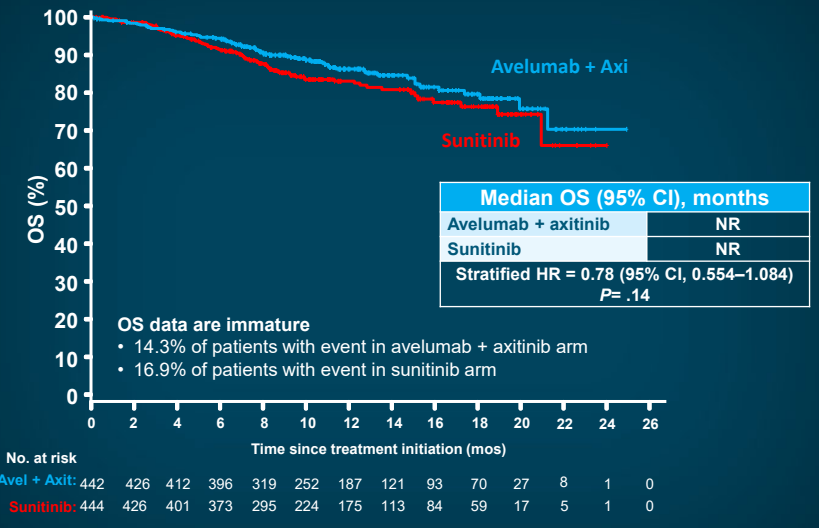
JAVELIN Renal 101: Overall Survival



Median follow-up = 12.0 mos (avelumab + axitinib) and 11.5 mos (sunitinib).

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

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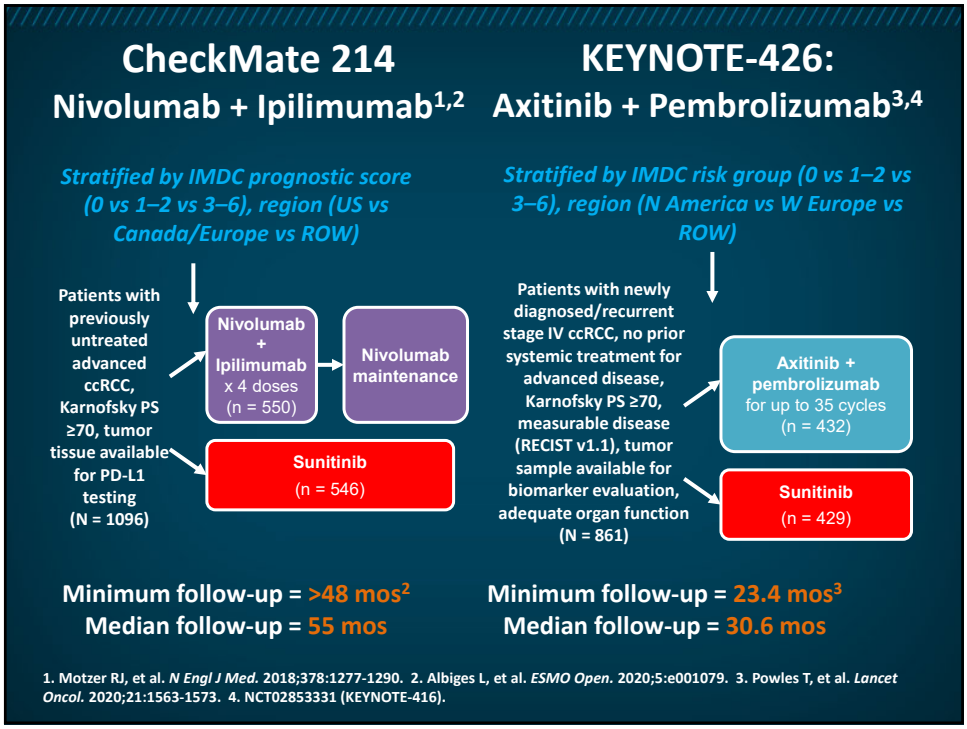

1. Motzer RJ, et al. *N Engl J Med.* 2018;378:1277-1290. 2. Albiges L, et al. *ESMO Open.* 2020;5:e001079. 3. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573. 4. NCT02853331 (KEYNOTE-416).

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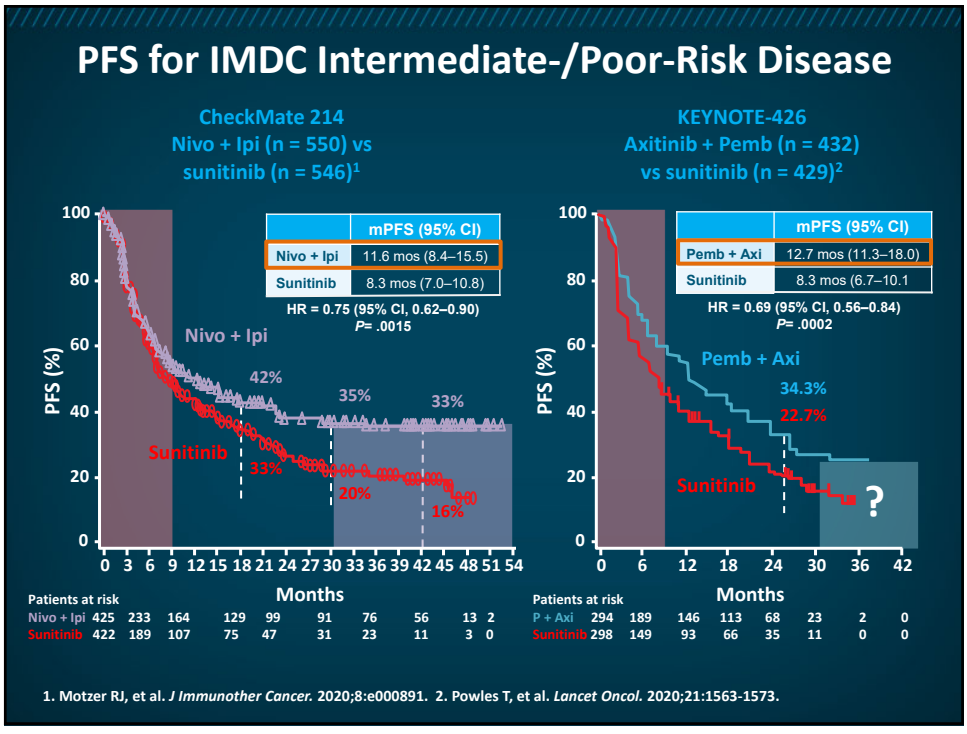

1. Motzer RJ, et al. *J Immunother Cancer.* 2020;8:e000891. 2. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

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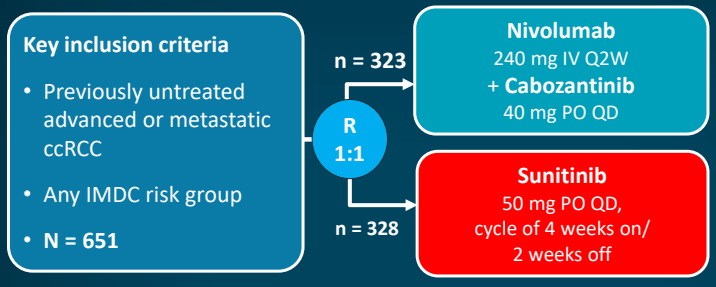
CheckMate 9ER: Study design



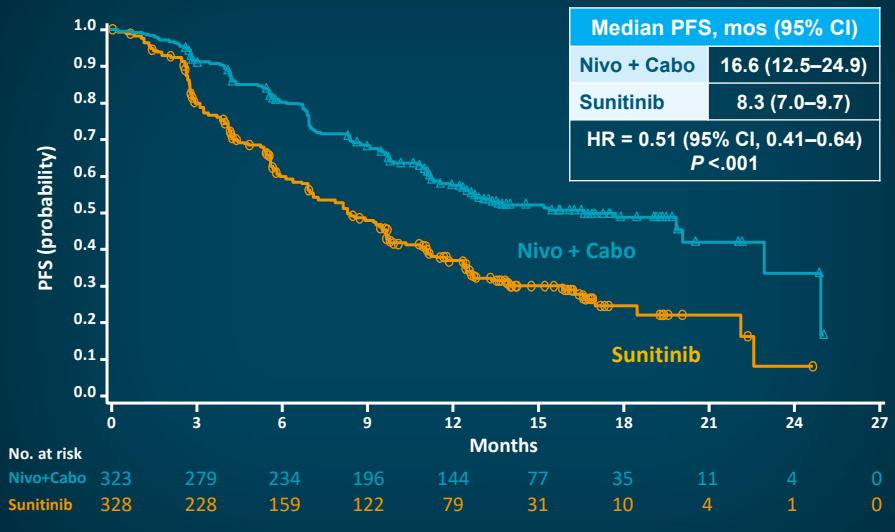
- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, and safety
- **Stratification factors:** IMDC risk score (0 vs 1–2 vs 3–6) tumor PD-L1 expression (≥1% vs <1% or indeterminate), and geographic region (US and Europe vs ROW)

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

1. NCT03141177 (CheckMate 9ER). Choueiri TK, et al. *N Engl J Med.* 2021;384:829-841.

27

CheckMate 9ER: PFS per BICR



Minimum study follow-up = 10.6 months.

Choueiri TK, et al. *N Engl J Med.* 2021;384:829-841.

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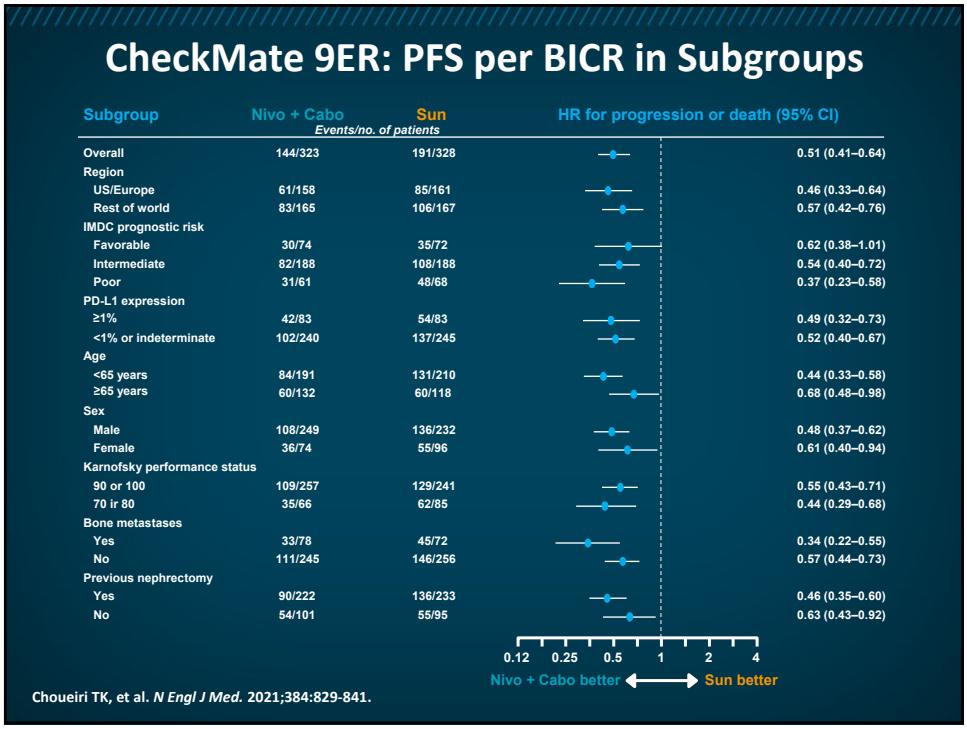
CheckMate 9ER: PFS per BICR in Subgroups
Subgroup
Nivo + Cabo
Sun
Events/no. of patients
HR for progression or death (95% CI)
Overall 144/323 191/328 0.51 (0.41–0.64)
Region
US/Europe 61/158 85/161 0.46 (0.33–0.64)
Rest of world 83/165 106/167 0.57 (0.42–0.76)
IMDC prognostic risk
Favorable 30/74 35/72 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 or 100 109/257 129/241 0.55 (0.43–0.71)
70 ir 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)
0.12 0.25 0.5 1 2 4
Nivo + Cabo better
Sun better
Choueiri TK, et al. N Engl J Med. 2021;384:829-841.

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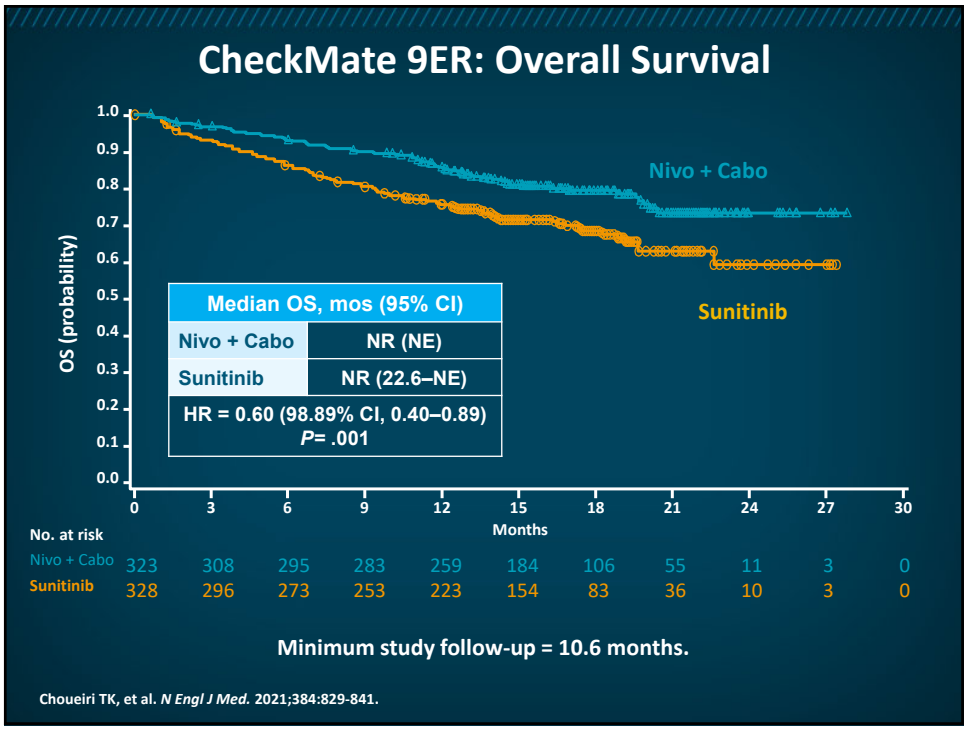
CheckMate 9ER: Overall Survival
OS (probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Nivo + Cabo
Sunitinib
Median OS, mos (95% CI)
Nivo + Cabo NR (NE)
Sunitinib NR (22.6–NE)
HR = 0.60 (98.89% CI, 0.40–0.89)
P= .001
0 3 6 9 12 15 18 21 24 27 30
Months
No. at risk
Nivo + Cabo 323 308 295 283 259 184 106 55 11 3 0
Sunitinib 328 296 273 253 223 154 83 36 10 3 0
Minimum study follow-up = 10.6 months.
Choueiri TK, et al. N Engl J Med. 2021;384:829-841.

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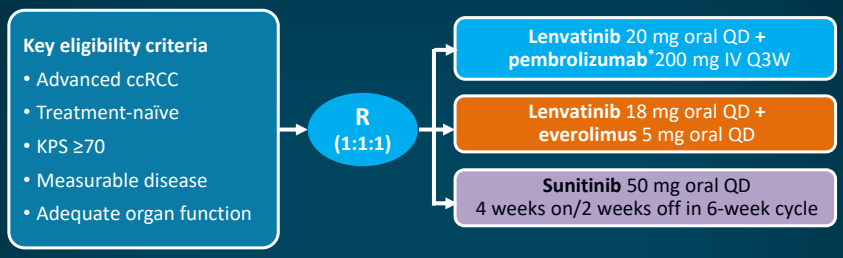
CLEAR: Study Design



- **Primary endpoint:** PFS by IRC per RECIST v1.1
- **Secondary endpoints:** OS, ORR by IRC per RECIST v1.1, safety, HRQoL
- **Key exploratory endpoints:** DoR, biomarkers
- **Stratification factors:** geographic region (W Europe and North America vs ROW) MSKCC risk category (favorable, intermediate, or poor)

*Patients could receive a maximum of 35 pembrolizumab treatments.

HRQoL = health-related quality of life; MKSCC = Memorial Sloan Kettering Cancer Center.

Grünwald V, et al. *Future Oncol.* 2019;15:929-941.

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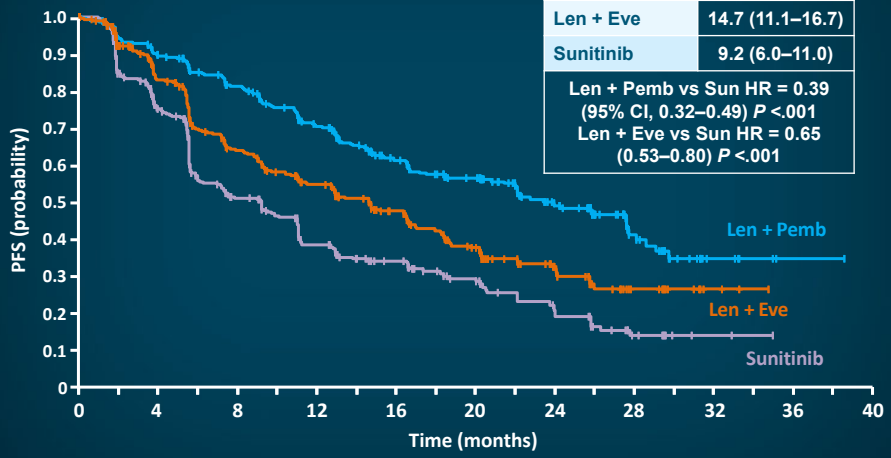
CLEAR: Progression-Free Survival

Median PFS, mos (95% CI)	
Len + Pembro	23.9 (20.8–27.7)
Len + Eve	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Len + Pemb vs Sun HR = 0.39 (95% CI, 0.32–0.49) *P* <.001
Len + Eve vs Sun HR = 0.65 (0.53–0.80) *P* <.001



Len = lenvatinib; Eve = everolimus.

Motzer R, et al. *N Engl J Med.* 2021;Feb 13: Epub ahead of print.

PRESENTED BY: Dr. Robert Motzer

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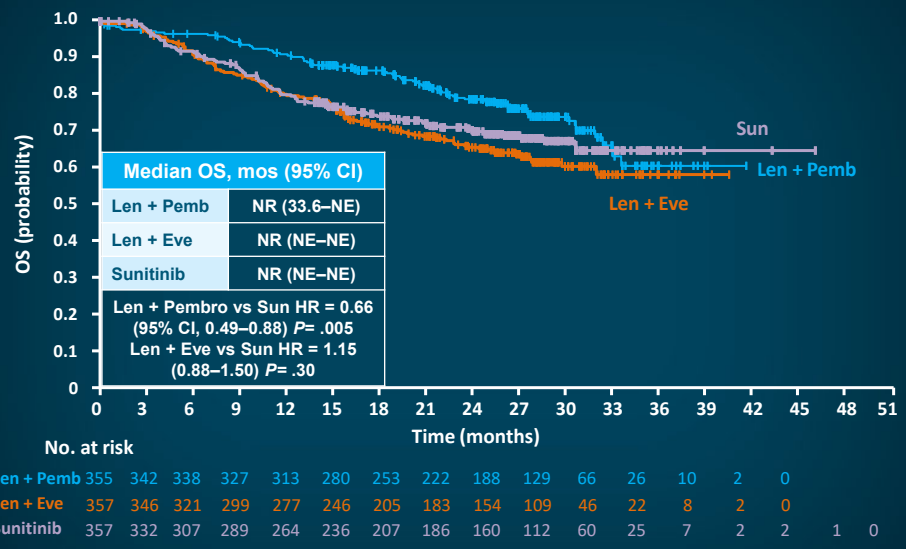
CLEAR: Overall Survival



Motzer R, et al. *N Engl J Med.* 2021;Feb 13: Epub ahead of print.

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CLEAR: Confirmed ORR

	Len + Pemb (n = 355)	Len + Eve (n = 357)	Sun (n = 357)
ORR*, % (95% CI)	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response, %			
CR	16.1	9.8	4.2
PR	54.9	43.7	31.9
SD	19.2	33.6	38.1
PD	5.4	7.3	14.0
Unknown/not evaluable	4.5	5.6	11.8
Relative risk vs Sun (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	Reference
P-value	<.001	<.001	—

*By IRC per RECIST v1.1.

Motzer R, et al. *N Engl J Med.* 2021;Feb 13: Epub ahead of print.

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Challenges in First-Line Management of Advanced RCC

- **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**
  - Can therapy not used in first-line be reserved for later lines?

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VEGF + I-O vs I-O + I-O Debate
Which Approach is Best?

Trial	KeyNote-426[1,2] (VEGF + I-O)		Checkmate-214[3,4] (I-O + I-O)	
Median follow-up	12.8 mos	30.6 mos	32.4 mos	55 mos
ITT OS HR	0.53	0.68	0.71	0.69
Fav-risk OS HR	0.64	1.06	1.22	0.93

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

I-O = immuno-oncology; Fav = favorable.

1. Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127. 2. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573. 3. Motzer RJ, et al. *Lancet Oncol.* 2019;20:1370-1385. 4. Albiges L, et al. *ESMO Open.* 2020;5:e001079.

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First-Line ccRCC ICI-TKI Combinations

	CLEAR[1]	CHECKMATE-9ER[2]	JAVELIN Renal 101[3]	KEYNOTE-426[4]
	Pembrolizumab + Lenvatinib (N = 1069)	Nivolumab + Cabozantinib (N = 651)	Avelumab + Axitinib* (PD-L1+, n = 560)	Pembrolizumab + Axitinib (N = 861)
mPFS (mos)	23.9	16.6	13.8	15.4
PFS HR (95% CI)	0.39	0.51	0.62	0.71
mOS (mos)	NR	NR	NR	NR
OS HR (95% CI)	0.66	0.60	0.83	0.68
ORR/CR (%)	71/16.1	55.7/8	55.9/5.6	60/9
Sarcomatoid features (%)	7.9	10.9	12.2	12.0
IMDC or MKSCC risk F/I/P (%)	31.0/59.2/9.3	22.9/58.2/18.9	19.3/64.1/16.3	32/55/13
Median follow-up (mos)	26.6	18.1	~19	30.6

ICI = immune checkpoint inhibitor; F/I/P = favorable/intermediate/poor.

1. Motzer R, et al. *N Engl J Med.* 2021;Feb 13: Epub ahead of print. 2. Choueiri TK, et al. *N Engl J Med.* 2021;384:829-841. 3. Choueiri TK, et al. *Ann Oncol.* 2020;31:1030-1039. 4. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

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Phase 2 KEYNOTE-146/Study 111
Len + Pemb After Progression on Previous I-O Therapy

Multicenter, open-label phase 1b/2 study, RCC cohort

Metastatic ccRCC with PD after anti-PD-1/PD-L1 therapy; ≥1 previous lines of therapy (N = 104) → **Lenvatinib** 20 mg QD PO, **Pembrolizumab** 200 mg Q3W IV

Primary endpoint: ORR at 24 weeks
Secondary endpoints: ORR, PFS, DoR, safety, and tolerability

Baseline characteristics	Patients (n = 104)
1/≥2 Prior anticancer regimens, %	39/62
Prior ICI regimen, %	
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, mos (IQR)	7 (3–13)

Lee C-H, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract 5008.

38

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)	Nivo + Ipi (n = 38)
ORR, % (95% CI)	**55 (45–65)**	**59 (46–71)**	**47 (31–64)**
Best objective response, %			
PR	55	59	47
SD	36	32	42
PD	5	6	8
NE	5	4	3
Median DoR, mos (95% CI)	12 (9–18)	9 (7–17)	NR (7–NR)

Lee C-H, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract 5008.

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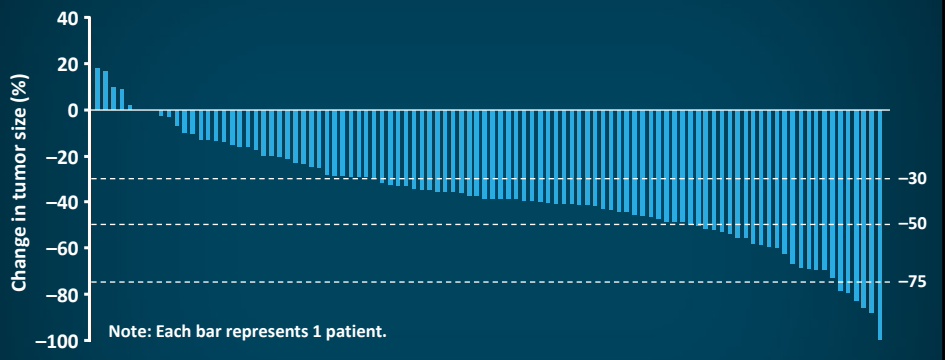
Response to Lenvatinib + Pembrolizumab
Change in Tumor Size



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

Lee C-H, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract 5008.

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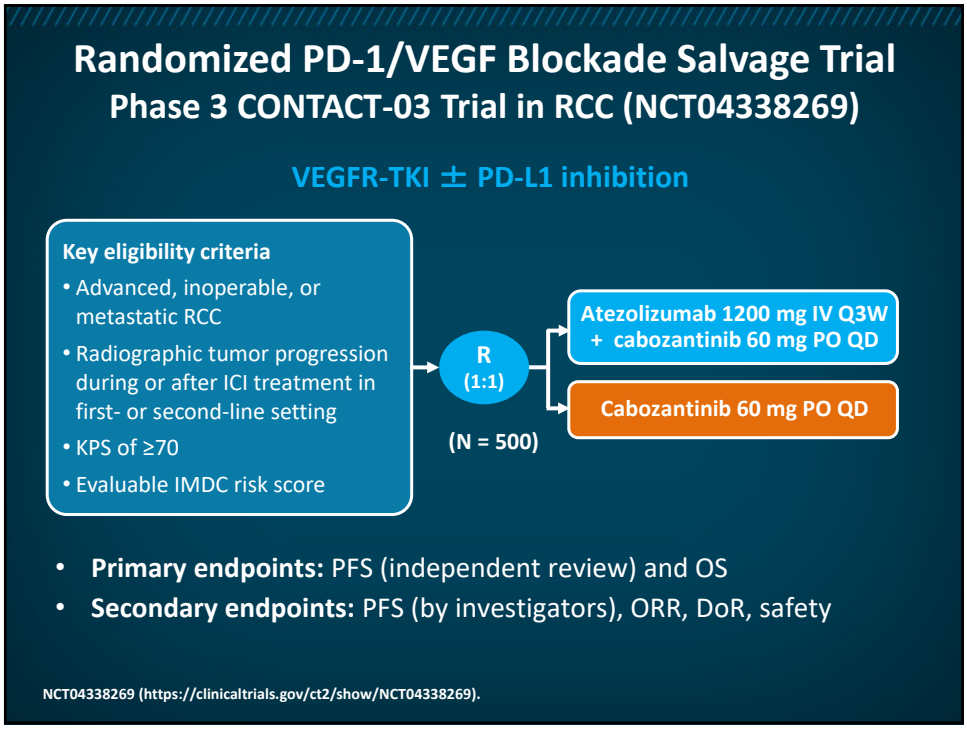
Randomized PD-1/VEGF Blockade Salvage Trial
Phase 3 CONTACT-03 Trial in RCC (NCT04338269)
VEGFR-TKI ± PD-L1 inhibition
Key eligibility criteria
• Advanced, inoperable, or metastatic RCC
• Radiographic tumor progression during or after ICI treatment in first- or second-line setting
• KPS of ≥70
• Evaluable 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
NCT04338269 (https://clinicaltrials.gov/ct2/show/NCT04338269).

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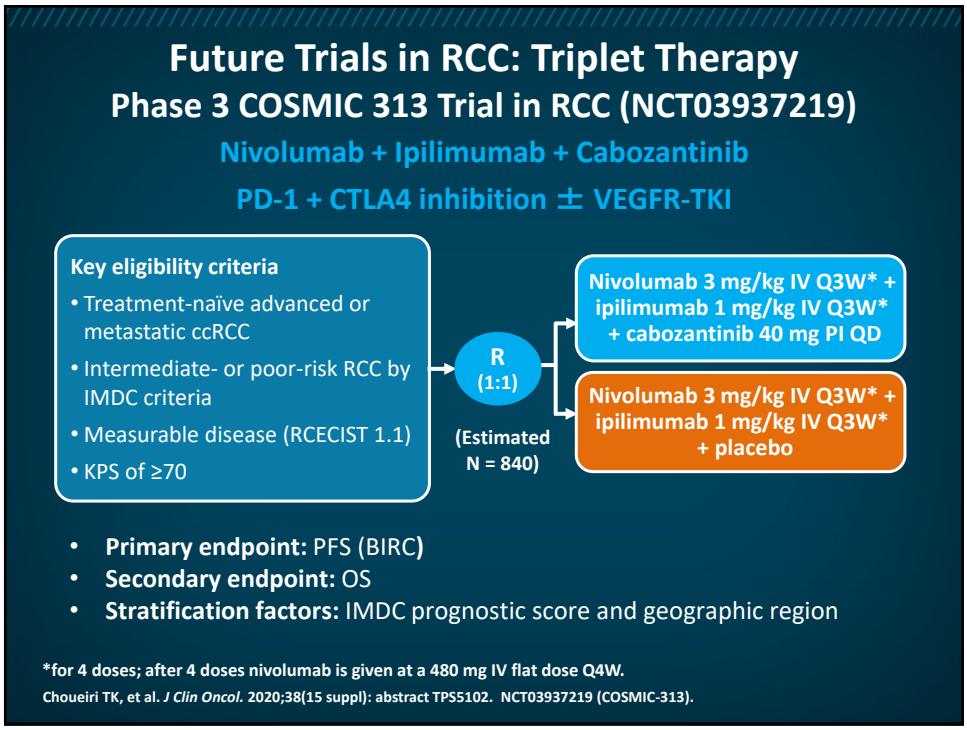
Future Trials in RCC: Triplet Therapy
Phase 3 COSMIC 313 Trial in RCC (NCT03937219)
Nivolumab + Ipilimumab + Cabozantinib
PD-1 + CTLA4 inhibition ± VEGFR-TKI
Key eligibility criteria
• Treatment-naïve advanced or metastatic ccRCC
• Intermediate- or poor-risk RCC by IMDC criteria
• Measurable disease (RCECIST 1.1)
• KPS of ≥70
R (1:1)
(Estimated N = 840)
Nivolumab 3 mg/kg IV Q3W* + ipilimumab 1 mg/kg IV Q3W* + cabozantinib 40 mg PI QD
Nivolumab 3 mg/kg IV Q3W* + ipilimumab 1 mg/kg IV Q3W* + placebo
• 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).

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Immune-Related Adverse Events Secondary to ICI Therapy

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We will now watch a brief video exploring irAEs

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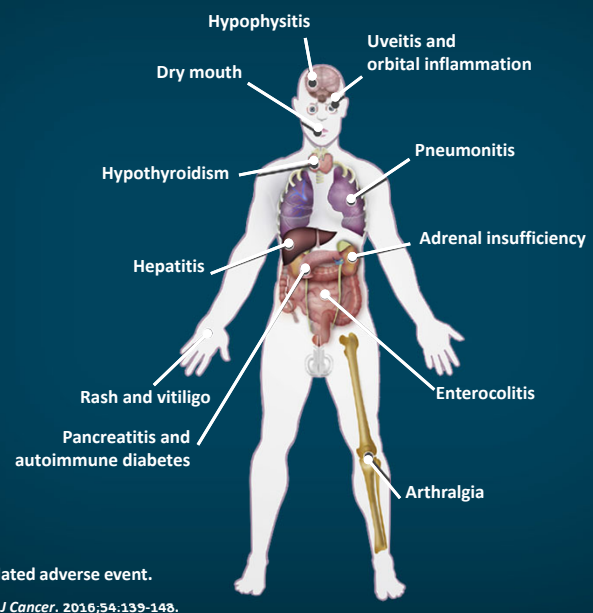
irAEs: Clinical Spectrum



irAE = immune-related adverse event.

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

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Management of irAEs
Based on CTCAE Severity Grade

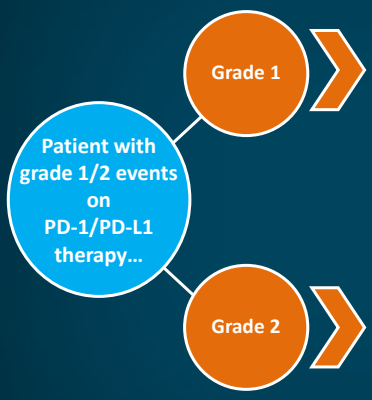
Severity CTCAE Grade	Patient Care Setting	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Not recommended up front Topical steroids or systemic steroids oral 0.5–1 mg/kg/d for persistent grade 2	Not recommended	Suspend* temporarily
3	Hospitalization	Systemic steroids oral or IV 1–2 mg/kg/d for ≥3 d then taper over 4–6 wk	Consider for patients with lack of improvement after 2–3 d 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 d with taper over 4–6 wk	Consider for patients with lack of improvement after 2–3 d 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.

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.

47

Managing Grade 1/2 irAEs



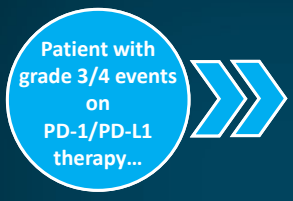
- Continue immunotherapy (or consider temporary delay)
- Symptomatic therapy

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

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. Postow MA. *UpToDate*, 2021. (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.

48

Managing Grade 3 irAEs



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

- **If no improvement or progression, consider additional immunosuppressant treatment (eg, anti-TNF therapy, infliximab, vedolizumab, or mycophenolate)**
- **If >4 wk of corticosteroids or other immunosuppressants needed, administer antimicrobial/antifungal prophylaxis to prevent opportunistic infections**
- **ASCO recommendations on managing irAEs were published in 2018***

ASCO = American Society of Clinical Oncology.

Postow MA. *Am Soc Clin Oncol Educ Book.* 2015:76-83. Postow MA. *UpToDate*, 2021. (www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy). Weber JS, et al. *J Clin Oncol.* 2015;33:2092-2099. Michot JM, et al. *Eur J Cancer.* 2016;54:139-148. *Brahmer J, et al. *J Clin Oncol.* 2018;36:1714-1768.

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Differentiating I-O vs VEGFR-TKI Toxicity

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

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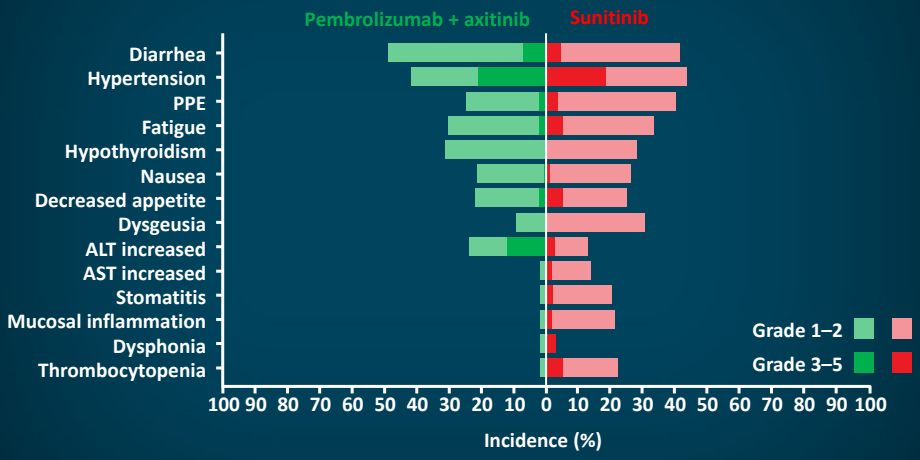
KEYNOTE-426: Toxicity

Selected treatment-related adverse events



PPE = palmar-plantar erythrodysesthesia: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573. Powles T, et al. *J Clin Oncol.* 2019;37(7 suppl): abstract 543

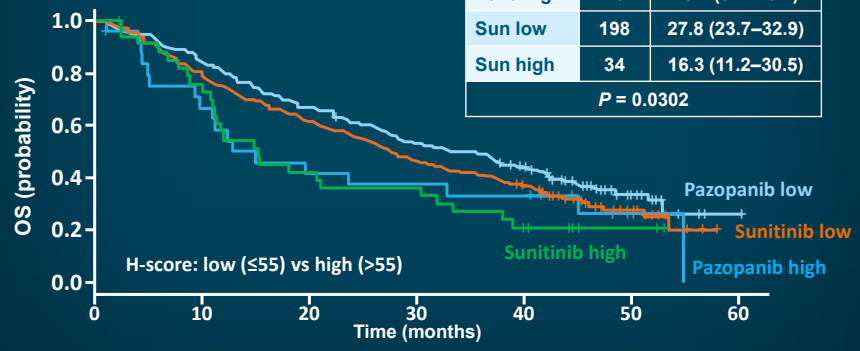
51

Immunotherapy Relevant Biomarkers in Advanced RCC

52

PD-L1 Expression Is Adverse Feature in mRCC
Pazopanib vs sunitinib (COMPARZ)

Overall Survival		
	No.	mOS 995% CI)
Pazo low	196	35.6 (27.2–40.8)
Pazo high	25	15.1 (9.4–45.1)
Sun low	198	27.8 (23.7–32.9)
Sun high	34	16.3 (11.2–30.5)
P = 0.0302		



Pazo = pazopanib.

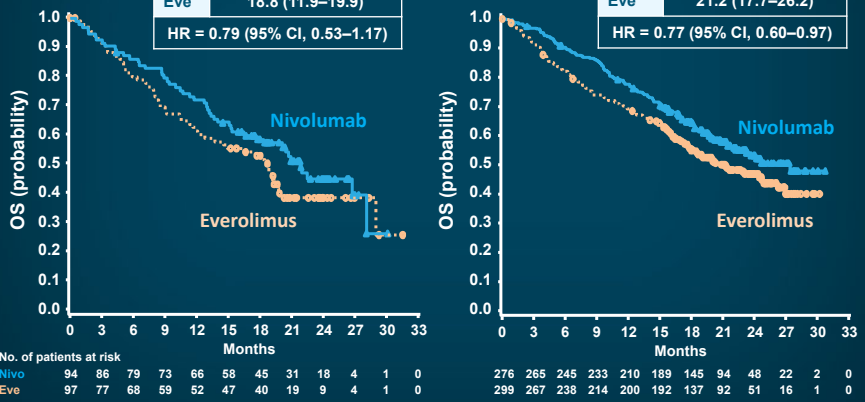
Choueiri TK, et al. *Clin Cancer Res*. 2015;21:1071-1077.

53

PD-L1 Expression Is Adverse Feature in mRCC
Nivolumab and Everolimus (CheckMate 025)

PD-L1 ≥1% (n = 24%)	
	mOS, mos (95% CI)
Nivo	21.8 (16.5–28.1)
Eve	18.8 (11.9–19.9)
HR = 0.79 (95% CI, 0.53–1.17)	

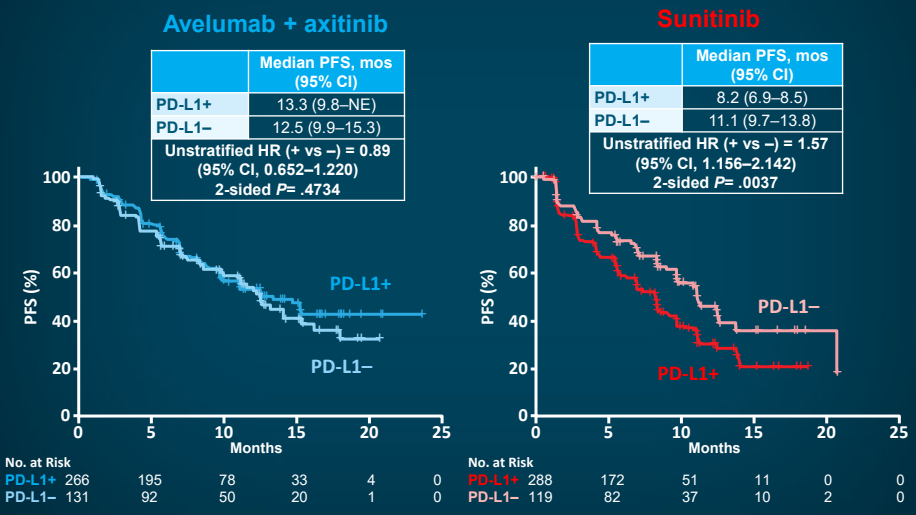
PD-L1 <1% (n = 76%)	
	mOS, mos (95% CI)
Nivo	27.4 (21.4–NE)
Eve	21.2 (17.7–26.2)
HR = 0.77 (95% CI, 0.60–0.97)	



Motzer RJ, et al. *N Engl J Med*. 2015;373:1803-1813.

54

PD-L1 Expression—Adverse Association Overcome with Combination Therapy?

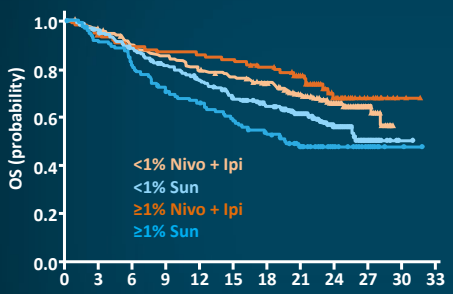


Choueiri TK, et al. *J Clin Oncol.* 2019;37(15 suppl): abstract 101.

55

PD-L1 Expression—Adverse Association Reversed with Combination Therapy?

Ipilimumab plus Nivolumab vs Sunitinib (CheckMate 214)

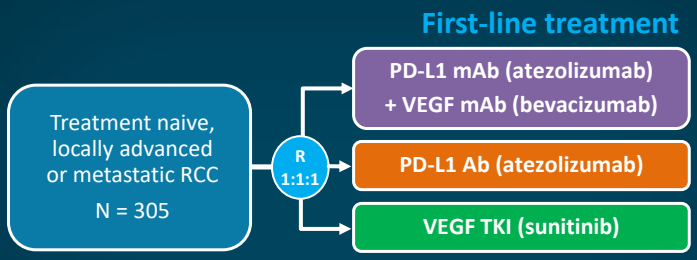


IMDC Intermediate/Poor Risk	PD-L1 <1%		PD-L1 ≥1%	
	Nivo + Ipi (n = 284)	Sun (n = 278)	Nivo + Ipi (n = 100)	Sun (n = 114)
mOS, mos (95% CI)	NR (28.2–NE)	NR (24.0–NE)	NR (NE–NE)	19.6 (14.8–NE)
	HR = 0.73 (95% CI, 0.56–0.96)		HR = 0.45 (95% CI, 0.29–0.71)	
ORR, % (95% CI)	37% (32–43)	28% (23–34)	58% (48–68)	22% (15–31)
	P= .0252		P <.001	

Motzer RJ, et al. *N Engl J Med*. 2018;378:1277-1290 plus supplement. Escudier B, et al. *Ann Oncol.* 2017:28(suppl 5):abstract LBA5.

56

IMmotion150 Trial Design: Randomized Phase 2



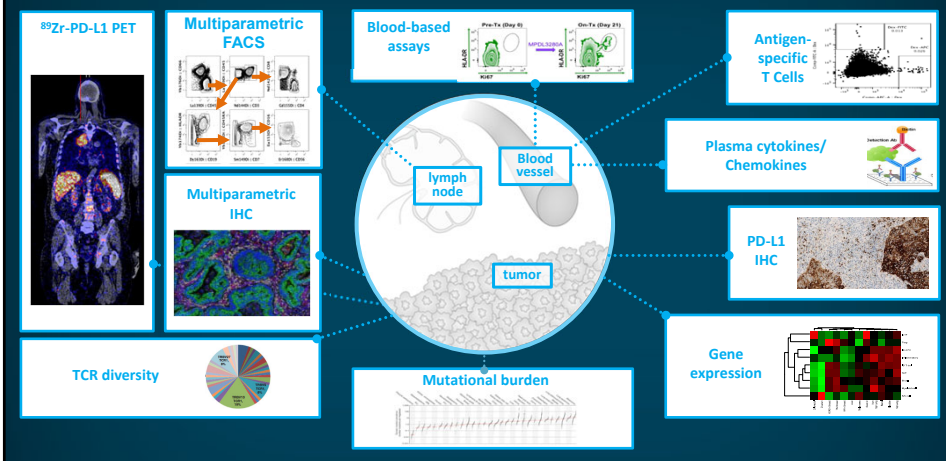
- IMmotion150 was designed to be **hypothesis generating** and to inform phase 3 study IMmotion151
- **First randomized trial to:**
  - Explore ICB (atezolizumab) + targeted therapy (bevacizumab)
  - Explore association between outcome and TME gene signatures

mAb = monoclonal antibody; ICB = immune checkpoint blockade; TME = tumor microenvironment.

McDermott DF, et al. *Nat Med*. 2018;24:749-757.

57

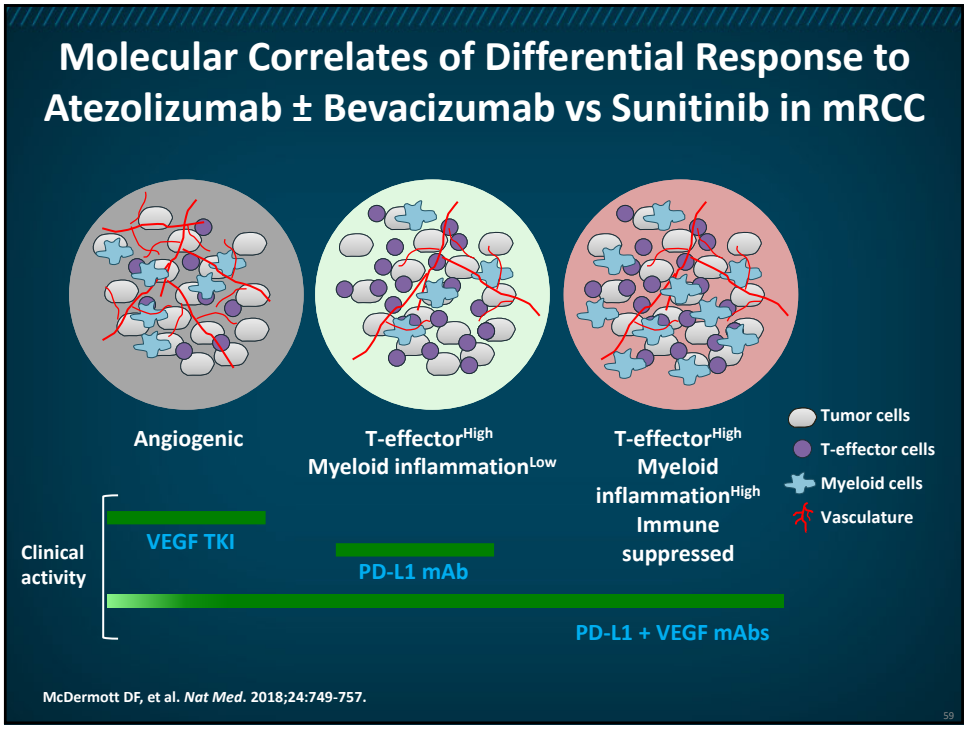
Comprehensive Biomarker Platform



FACS = fluorescence-assisted cell sorting; IHC = immunohistochemistry; TCR = T-cell receptor.

Shields AF, et al. *J Nucl Med*. 2018;59:410-417 (2016 NIH workshop). Modified from Chen DS. Society for Immunotherapy of Cancer (SITC), 2015. Chen DS. American Association for Cancer Research (AACR), 2017

58


Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC
Angiogenic
T-effector^High Myeloid inflammation^Low
T-effector^High Myeloid inflammation^High Immune suppressed
Tumor cells
T-effector cells
Myeloid cells
Vasculature
Clinical activity
VEGF TKI
PD-L1 mAb
PD-L1 + VEGF mAbs
McDermott DF, et al. Nat Med. 2018;24:749-757.
59

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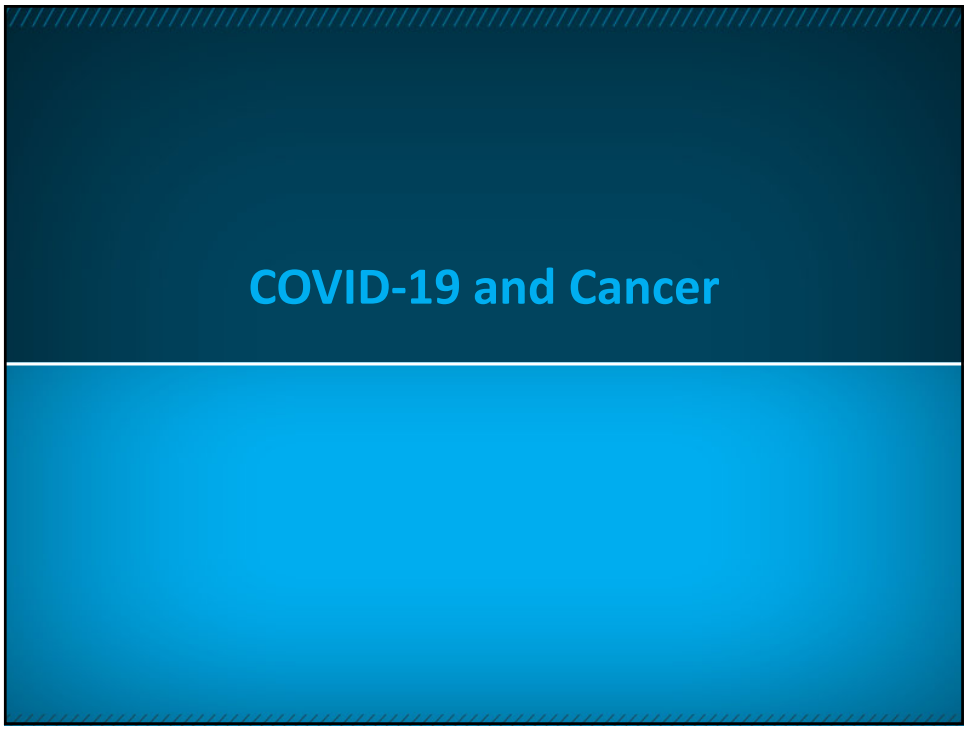
COVID-19 and Cancer

60

Treatment of Advanced RCC in Era of COVID-19
Key Questions and Considerations

1. Are patients with RCC at increased risk for infection and/or complications from COVID-19?
2. Does immunotherapy increase the risk of more severe disease or death from COVID-19?
3. What are current recommendations for use of immunotherapy in patients with RCC to mitigate risks related to COVID-19?
4. What are some additional considerations for COVID-19 risk mitigation in the care of RCC patients?
   - Risk-mitigation measures
   - Role of telemedicine
   - Impact on practice patterns

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Cancer and COVID-19 Risk

Literature review including >10 studies focused on COVID-19 in cancer patients[1]

Key findings/conclusions

- Data suggest an **increased risk of acquiring SARS-CoV-2 infection** compared with general population[1]
  - Individuals with cancer comprised a larger proportion of COVID-19 patients in both the United States (6%)[2] and China (1%)[3]
- Compared with COVID-19 patients without cancer, those with cancer appeared to have an **increased risk for severe outcomes, including intubation and death,** after adjusting for other COVID-19 risk factors[1]
- Overall case fatality rates among cancer patients range from 11% to 28%, with disproportionately higher rates in some subgroups[1]:
  - Lung cancer (18% to 55%)
  - Hematologic malignancy (33% to 41%)

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. Fung M, Babik JM. *Clin Infect Dis*. 2020; Jun 27:Epub ahead of print. 2. Miyashita H, et al. *Ann Oncol*. 2020;31:1088-1089. 3. Liang W, et al. *Lancet Oncol*. 2020;21:335-337.

62

Theoretical Concerns About ICI Use During COVID-19 Outbreak

Effects on cellular immunity or immune-related neutropenia may impair immune response to virus[1]

- Hematologic irAEs are uncommon
- Limited data on viral infections or reactivations as a complication to ICIs
  - However, few cases of infections secondary to irAE treatment have been reported

Possible negative interference of ICI in pathogenesis of COVID-19[2,3]

- Synergistic immune hyperactivation (ie, treatment-induced cytokine-release syndrome plus infection-related cytokine storm)

Potential overlap between coronavirus-related interstitial pneumonia and pulmonary toxicity from anti-PD-1/PD-L1 agents[2,3]

1. Kattan J, et al. *Immunotherapy.* 2020;12:351-354. 2. Bersanelli M. *Immunotherapy*. 2020;12:269-273. 3. Rossi E, et al. *J Immunother Cancer*. 2020;8:e000952.

63

Risk of COVID-Related Mortality in Larger Cohorts of Patients Receiving Cancer Therapy

800 patients in prospective observational UK Coronavirus Cancer Monitoring Project, who were diagnosed 3/18 to 4/26/2020[1]

- After adjusting for age, gender, and comorbidities, chemotherapy in past 4 weeks had no significant effect on mortality from COVID-19 disease, compared with cancer patients who had not received recent chemotherapy
- No significant effect on mortality for patients with cancer receiving immunotherapy (6%), hormonal therapy (8%), targeted therapy (9%), radiotherapy (10%) within 4 weeks of COVID-19 diagnosis

Observational study of 890 patients at 19 centers in UK, Italy, Spain, and Germany, who were recruited 2/26 to 4/1 (censored 5/11/2020)[2]

- Active treatment with chemotherapy (23.1%), targeted therapy (10.4%), and immunotherapy (6.3%) at time of COVID-19 diagnosis did not worsen mortality

1. Lee LY, et al. *Lancet.* 2020;395:1919-1926. 2. Pinato DJ, et al. *Cancer Discov.* 2020;10:1465-1474.

64

Guidance Regarding ICI Treatment During COVID-19

ASCO

- Consider less frequent dosing intervals
- Where possible, COVID-19 testing prior to therapy with these agents is reasonable
- Special precautions/considerations
  - Some agents are associated with a risk of inflammatory reactions and complications (eg, pneumonitis)
  - Immunosuppression for serious irAEs may not be advisable

"The potential harms and benefits of therapy should be carefully considered for each patient"

NCCN

- In all stages/settings, consider the lowest frequency dosing schedule of available regimens
- For stage IV disease, single-agent anti-PD-1 is recommended over combination ipilimumab/nivolumab due to:
  - More substantial inflammation/possible exacerbation of COVID-19
  - Need for steroids/other immunosuppressants that may adversely affect SARS-CoV-2–infected individuals
  - Increased resource utilization for visits related to toxicities/monitoring

"Decisions…should be individualized, with preference for agents with the lowest toxicity profile"

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care). NCCN (www.nccn.org/covid-19/pdf/Melanoma.pdf). Accessed 3/3/2021.

65

ASCO Guidance Regarding Initiating/Resuming Anticancer Therapy After COVID-19 Infection

After "symptoms of COVID-19 have resolved and there is some certainty the virus is no longer present (eg, a negative SARS-Cov-2 test), unless the cancer is rapidly progressing and the risk:benefit assessment favors proceeding with cancer treatment"

"…once transmission-based precautions are no longer necessary would be reasonable"

- Recommended strategy for determining duration of transmission-based precautions depends on whether patient is considered immunocompromised
- Conditions causing a high degree of immunocompromise:
  - Receipt of chemotherapy for cancer
  - Untreated HIV infection with CD4 T lymphocyte count <200/mm^3
  - Combined primary immunodeficiency disorder
  - Receipt of the equivalent of prednisone >20 mg/day for more than 14 days

HIV = human immunodeficiency virus.

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care. Centers for Disease Control and Prevention (CDC) (www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html). Accessed 3/3/2021.

66

ASCO Guidance Regarding COVID-19 Vaccines in Cancer Patients*

- The Pfizer and Moderna vaccines were shown to be safe and effective for the general population and there was no evidence that they would not be safe for most cancer patients, although it should be noted that patients receiving immunosuppressive and cytotoxic treatments were excluded from participation in the vaccine trials to date so there is little to no data on the safety and efficacy of the Pfizer and Moderna vaccines in cancer patients.
- At this time, patients with cancer may be offered vaccination against COVID-19 as long as components of that vaccine are not contraindicated.

*Statement issued prior to authorization of the J&J vaccine on 2/27/2021.

ASCO (www.asco.org/asco-coronavirusresources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer). Accessed 3/3/2021

67

Multidisciplinary Oncology Team—

Optimizing Patient Care and Survivorship Through Shared Decision-Making

68

Multidisciplinary Team

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

Multidisciplinary care improves patient outcomes!

PCP = primary care provider.

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Concepts to Consider: SDM in Oncology

Stage of cancer
Available treatments
Treatment type (chemotherapy vs immunotherapy)
Sociodemographic characteristics
Preference for involvement (high vs low input patients)
Goals of treatment(s)
Complex data delivered in a patient-centered manner
Maintain and update knowledge

SDM Goals:

- Ensure that patients understand the risks and benefits of their options
- Incorporate patient preference(s) and goals to reach clinical decisions

SDM = shared decision-making.

Hawley ST, Jagsi R. *JAMA Oncol*. 2015;1:58-59. Frerichs W, et al. *PLoS One*. 2016;11:e0149789.

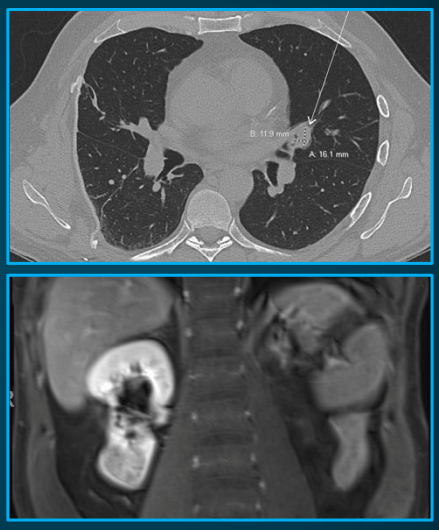
70

Case Studies

71

Case 1: Activity in Primary Tumor

- 60-year-old man with HTN and hyperlipidemia presented with gross hematuria, 2 right renal masses
- Right PN 1/16/2014 (ccRCC pT1b and pT1a Grade 3);
- Right 7th rib resection 7/23/2016 (metastatic RCC);
- 4/2019 MRI: bilateral renal masses
- Left radical nephrectomy 6/14/2019 (4 cm pT3a Grade 2 ccRCC)
- 7/2019: enlarging lingular lung mass 1.7 cm and right renal masses (1.4 cm and 3.4 cm)



HTN = hypertension; PN = partial nephrectomy; MRI = magnetic resonance imaging.

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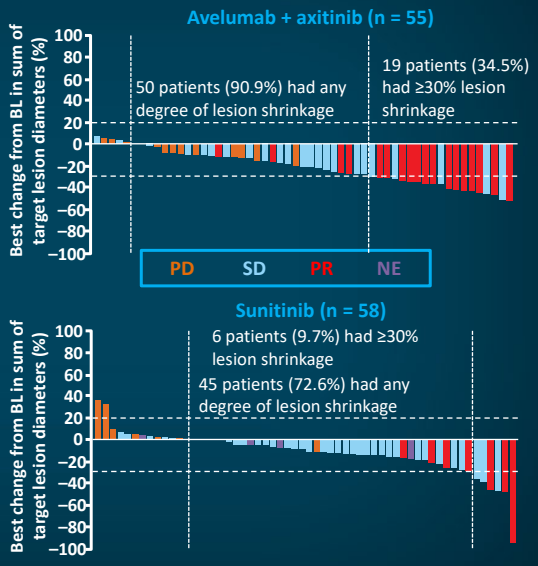
Case 1: Approach to Treatment Decision-Making

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



BL = baseline.

Albiges L, et al. *Ann Oncol.* 2019;30(suppl 5): abstract 4174.

73

How would you treat this patient?

1. Axitinib plus pembrolizumab or avelumab
2. Sunitinib
3. Ipilimumab plus nivolumab
4. IFN-alpha
5. Surgery
6. Active Surveillance

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Answer: 1

Combination PD-1/L1 antibodies with VEGFR-TKIs have shown the highest response rates in the primary kidney tumor,. Thus, in this patient where control of the primary tumor is a main concern, choice 1 is the best option.

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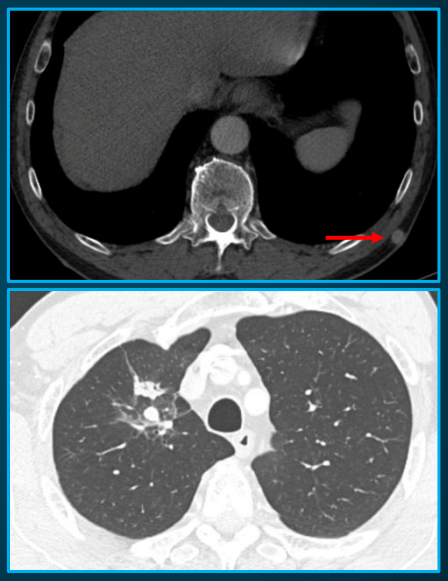
Case 2: Treatment in Later Lines

- 60-year-old doorman; PMH: HTN
- Left radical nephrectomy 9/12/2018
  - 10 cm pT3bN0 ccRCC
- April 2019: new bone and lung metastases
  - Ipilimumab/nivolumab, NKTR-214 x 11 cycles (5/22/2019–7/2020)
  - Best response was SD
- Axitinib + pembrolizumab (8/17/2020–1/2021)
  - Best response was SD; new cutaneous metastases



PMH = prior medical history.

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Case 2: Approach to Treatment Decision-Making in Later Lines

Factors in treatment decision-making

- Patient's treatment preferences, tolerance of prior therapies
- Medical contraindications (eg, refractory HTN or prior autoimmune disease)
- Differential MOA and/or off-target effects between VEGFR-TKIs
  - Subtle differences in small-molecule inhibitors contribute to differential toxicity and efficacy profiles

MOA = mechanism of action.

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What would you recommend next in treatment?

1. Cabozantinib plus nivolumab
2. Ipilimumab plus nivolumab
3. Lenvatinib plus pembrolizumab
4. 1 or 3

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Answer 4

Alternative VEGFR-TKIs have differential targets and can lead to subsequent responses, even in combination with continued PD-1 blockade. Thus, 1 or 3 are both reasonable options.

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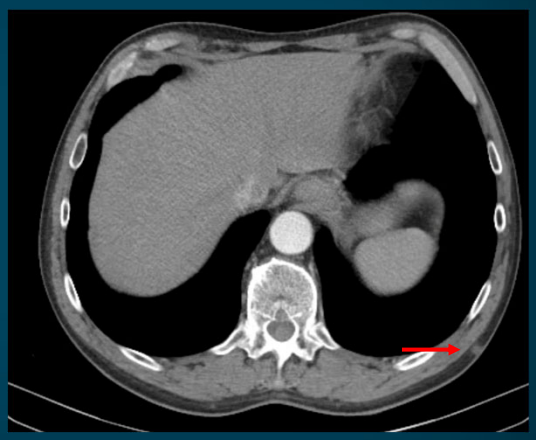
Response to Subsequent Therapy

- Cabozantinib + nivolumab (1/2021–present)
  - Clinical response to cutaneous nodules



80

Key Takeaways

- Immune-checkpoint blockade has revolutionized management of advanced RCC
- Multiple trials have proven superiority of I-O-based combination therapy over single-agent VEGFR-TKI
- Multiple I-O/VEGFR-TKI and I-O/I-O regimens have demonstrated a survival advantage
  - Responses higher and appear more rapid with VEGFR/I-O
  - Quality of life and long-term toxicity considerations
  - No single regimen clearly superior
- The optimal choice defined by individual factors:
  - IMDC risk, disease biology, patient preference, and safety profile

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Electronic Evaluation Form

- Before we move to Q&A, I want to remind you to fill out your evaluation form electronically by following the directions on the following slide
- Once you complete the evaluation form, your certificate of credit will be provided as a PDF that you can save for your records
- You will also have the opportunity to download a PDF of the program slides
- Even if you do not need credit, we appreciate you completing the evaluation form

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IC-ONC Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic:**
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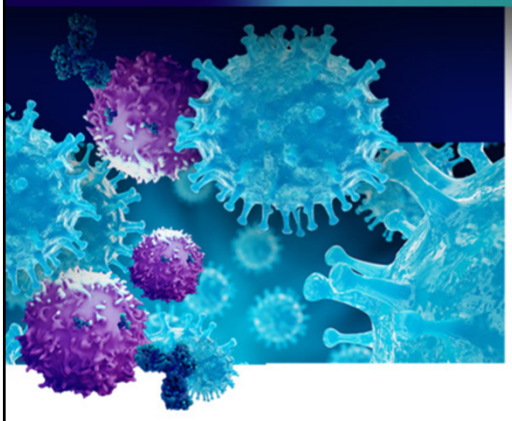

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Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic**

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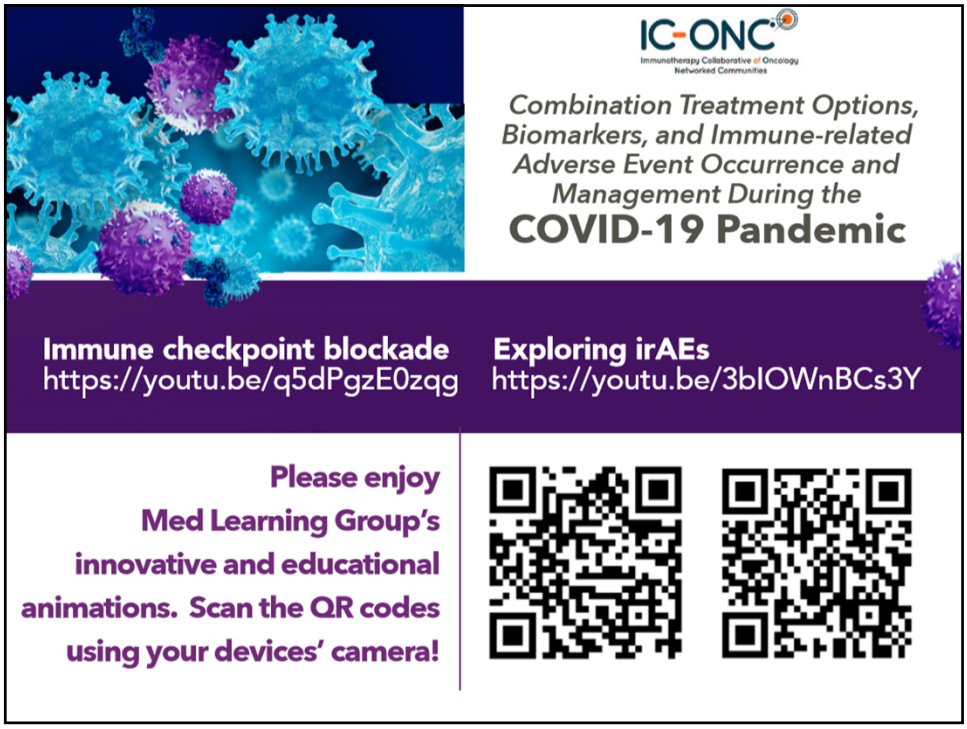
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Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the
COVID-19 Pandemic
Immune checkpoint blockade
https://youtu.be/q5dPgzE0zqg
Exploring irAEs
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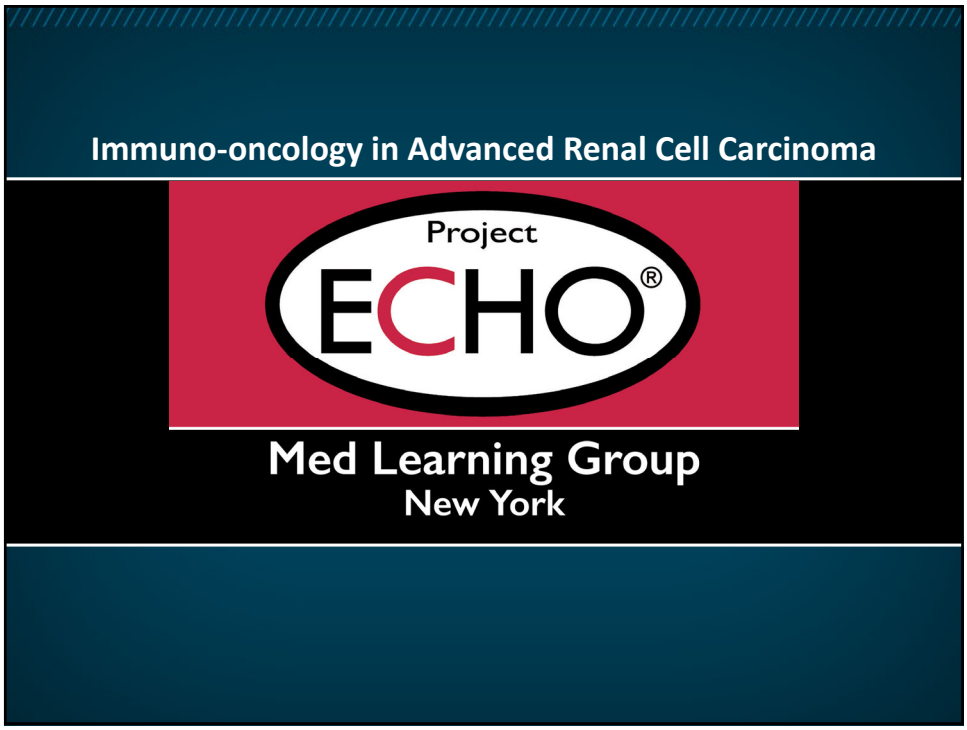
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Questions and Answers

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