THE IMMUNO-ONCOLOGY REVOLUTION:

A Guide for Health-System Pharmacists in

Renal Cell Carcinoma

Jointly provided by

Impact Education LLC

PIM Postgraduate Institute for Medicine

Supported by independent educational grants from Eisai, Inc. and Merck & Co., Inc.

Welcome and Opening Comments

Christopher A. Fausel, PharmD, MHA, BCOP
Clinical Manager, Oncology Pharmacy
Indiana University Simon Cancer Center

Agenda

Examining the Clinical Benefits of Immuno-Oncology Agents for Renal Cell Carcinoma **Sumanta Kumar Pal, MD**
Care Management Strategies to Enhance Overall Outcomes for Patients Requiring Immuno-Oncology Agents for RCC **Christopher A. Fausel, PharmD, MHA, BCOP, APRN, FNP-BC**
Case Studies **Faculty Panel**
Moderated Faculty Panel Discussion and Audience Q&A **Faculty Panel**
Adjournment

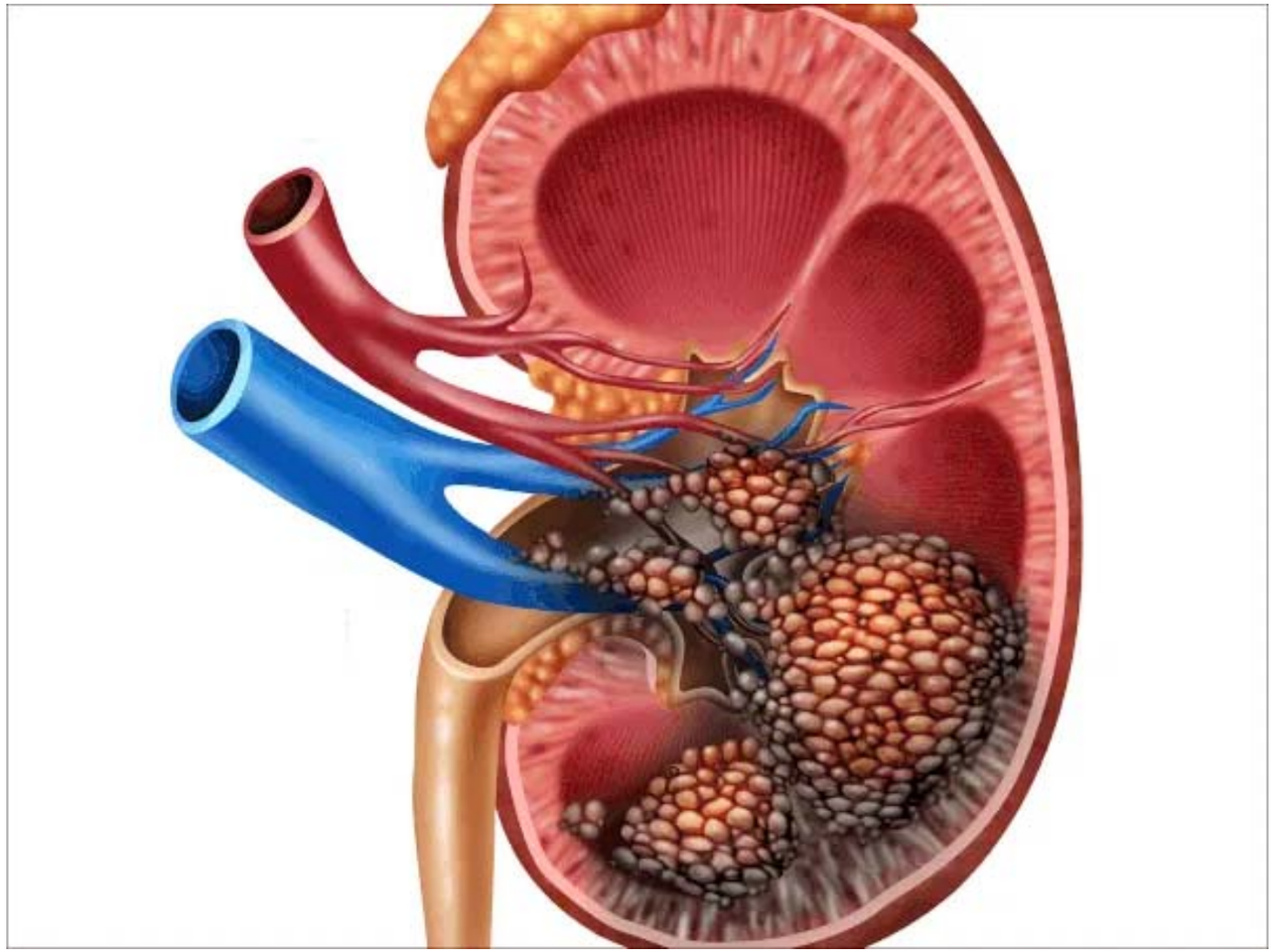
Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate improved ability to:

- Review current and emerging treatments for advanced RCC
- Discuss the rationale for consideration of IO combination therapies in the treatment of advanced RCC
- Identify when immunotherapy should be considered as a treatment option for patients with advanced RCC including patient selection, optimal drug combinations, and sequencing
- Employ early detection and management strategies for treatment-emergent adverse events in patients with advanced RCC

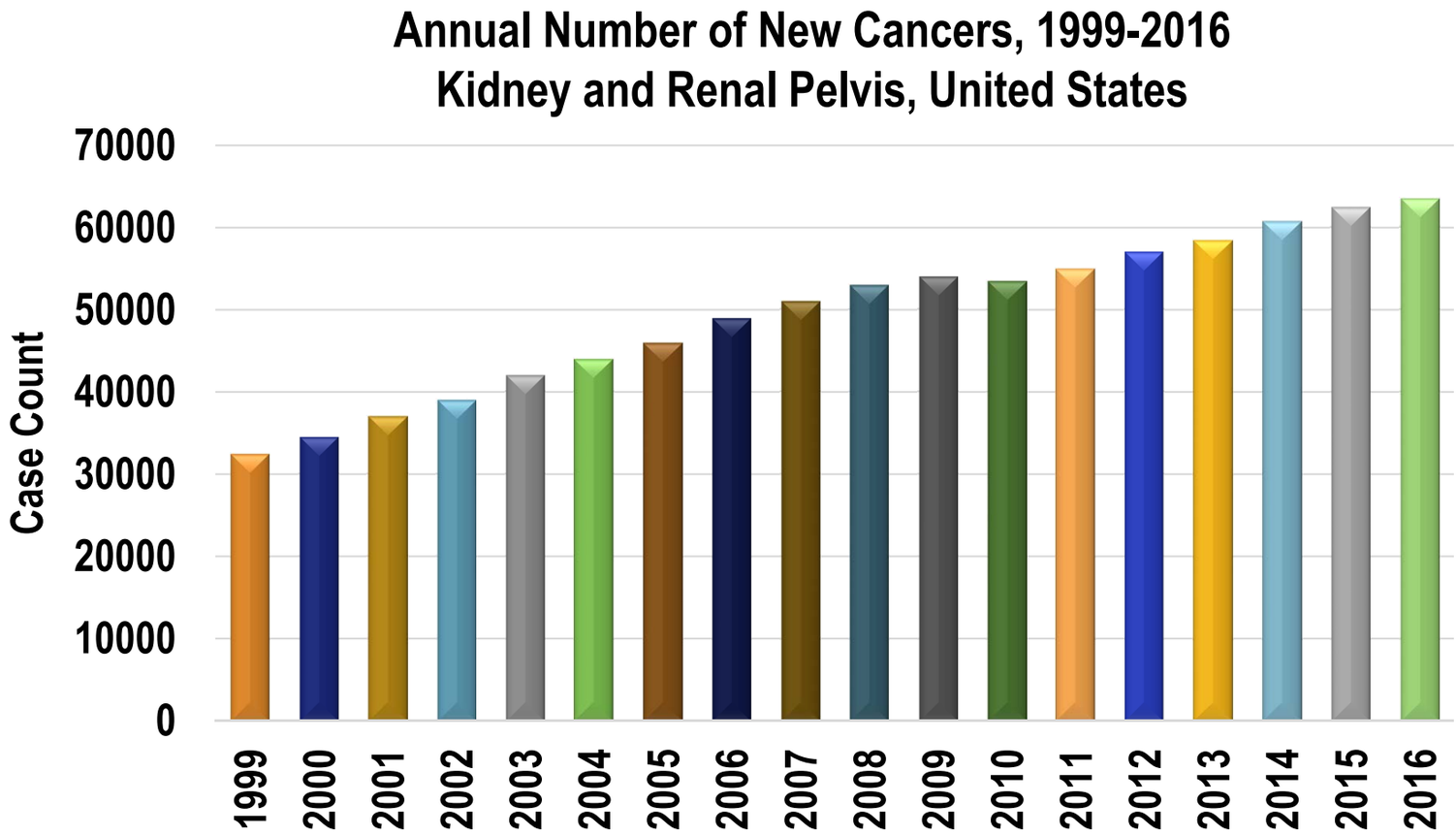
Pathophysiology

- Arises in proximal renal tubular epithelium
- Hereditary and sporadic forms, both related to chromosome 3 alterations
- Affected genes include *VHL*, *TSC* and *MET*



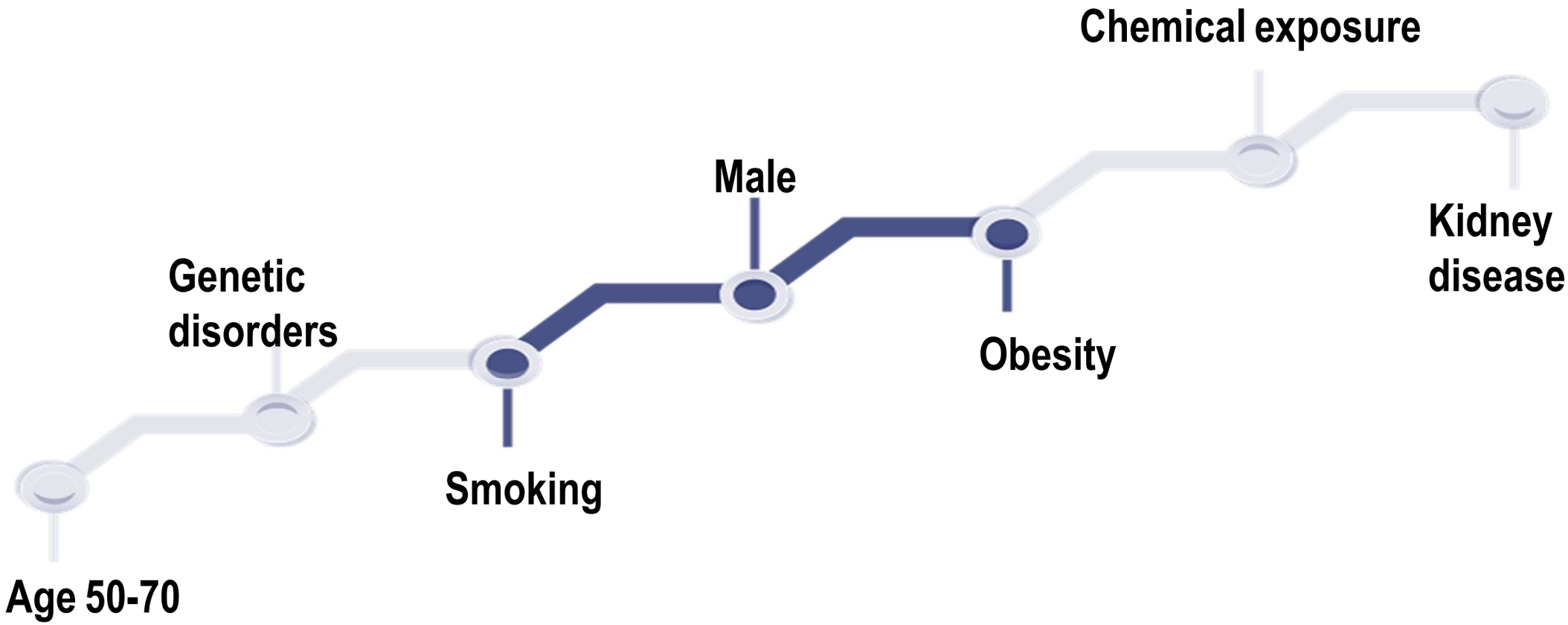
Kidney Cancer Epidemiology

- New diagnoses: 44,120 men and 29,700 women
- 14,770 deaths
- 59,000 will have RCC, primarily clear cell RCC
- Incidence rates climbed from 12.2/100,000 in 1999 to 16.8/100,000 in 2016



Kidney Cancer: Statistics. Cancer.Net website: https://www.cancer.net/cancer-types/kidney-cancer/statistics. Accessed November 2019.

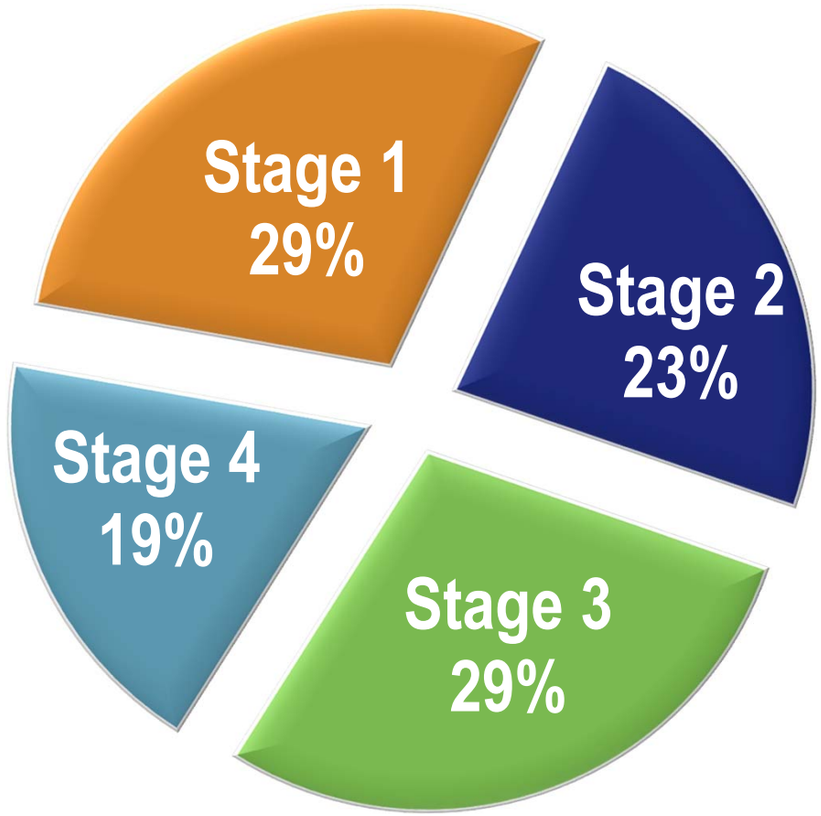
Risk Factors



Stage and Prognosis

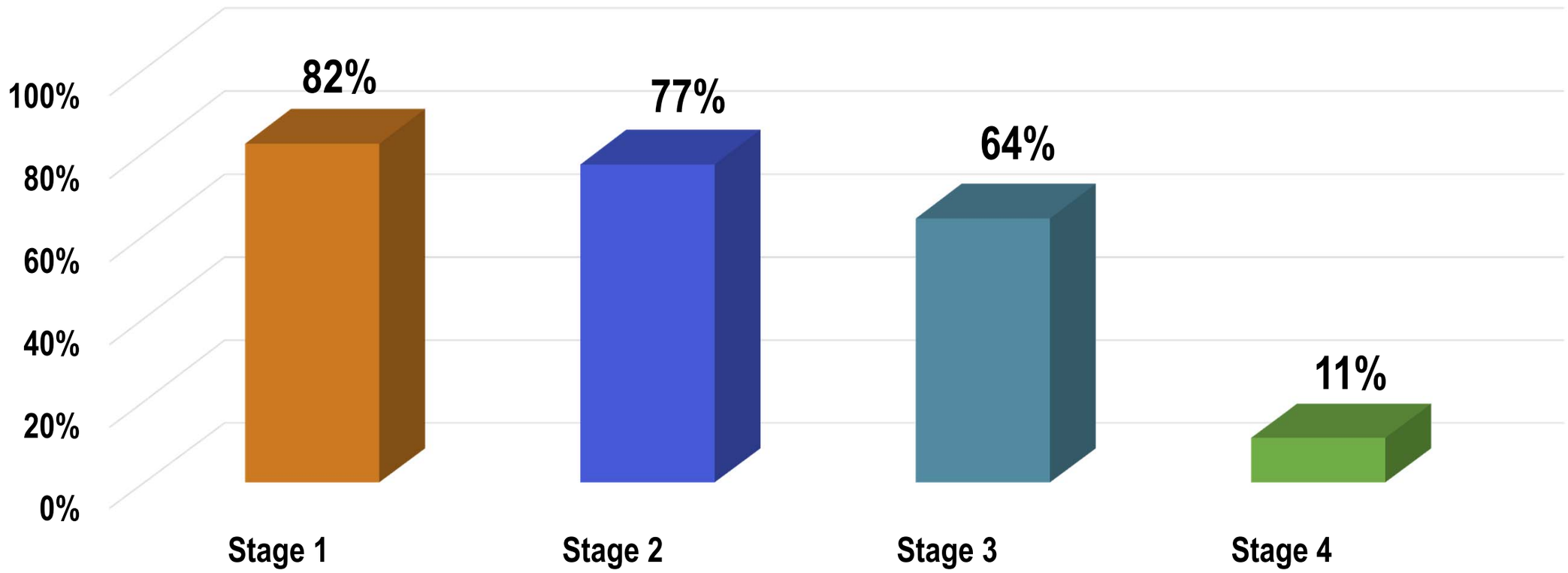
- In US, nearly 1 in 5 has metastatic disease at presentation

Stage at Diagnosis[1]



1. Datamonitor 2018 (US); American Cancer Society.

Five-year Survival Rates by Stage at Diagnosis



Source: Goodman M. Cancer: The team that's doubling survival rates. University of Texas southwestern Medical Center website. https://utswmed.org/medblog/team-s-doubling-cancer-survival-rates. Nov 9, 2018. Accessed November 2019.

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Examining the Clinical Benefits of Immuno-oncology Agents for RCC

Sumanta Kumar Pal, MD

Associate Clinical Professor

Department of Medical Oncology & Therapeutics Research

Co-director, Kidney Cancer Program

City of Hope Comprehensive Cancer Center

Conventional Treatment

Surgery

- Potentially curative
- Used for palliation

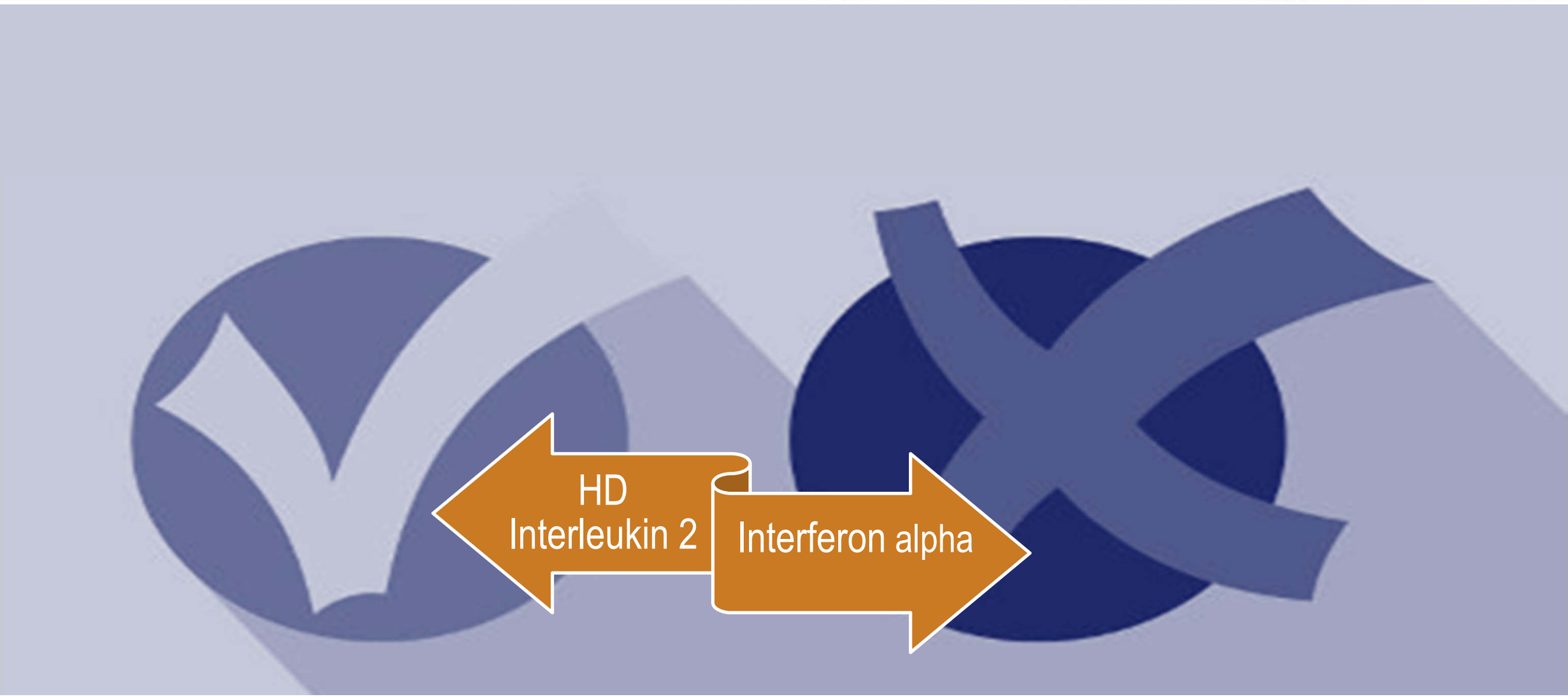
Radiofrequency Ablation

- Nonresectable patients
- Smaller lesions

Chemotherapy

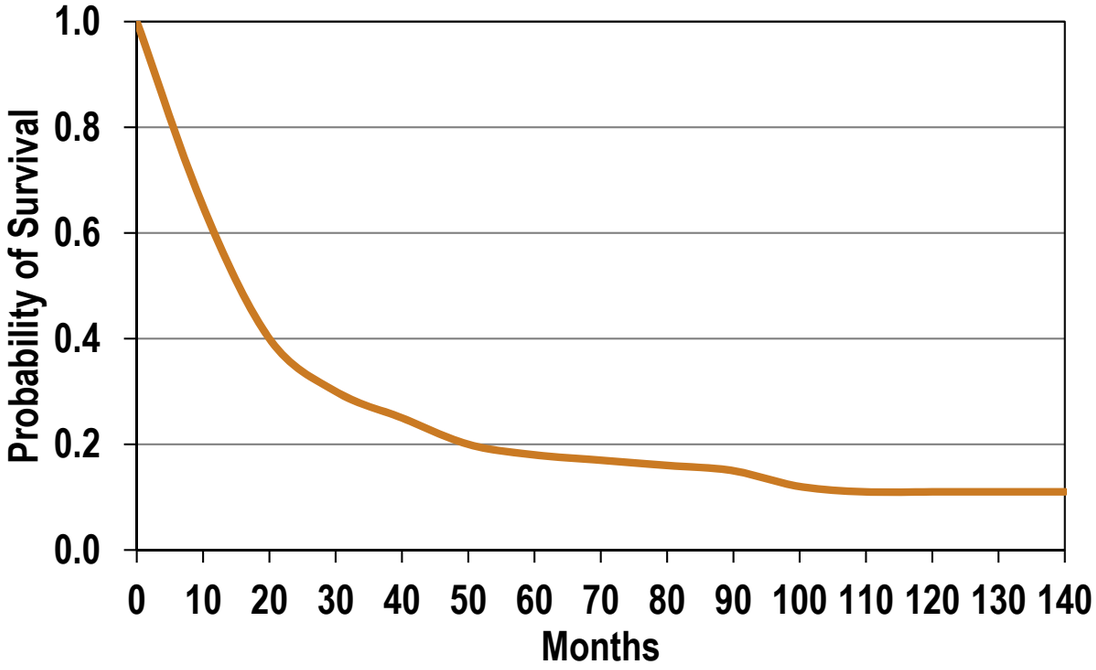
- Chemo and endocrine therapies not standard of care
- ORR<15%, not durable

First I-O Therapies: Cytokines—a Hit and a Miss



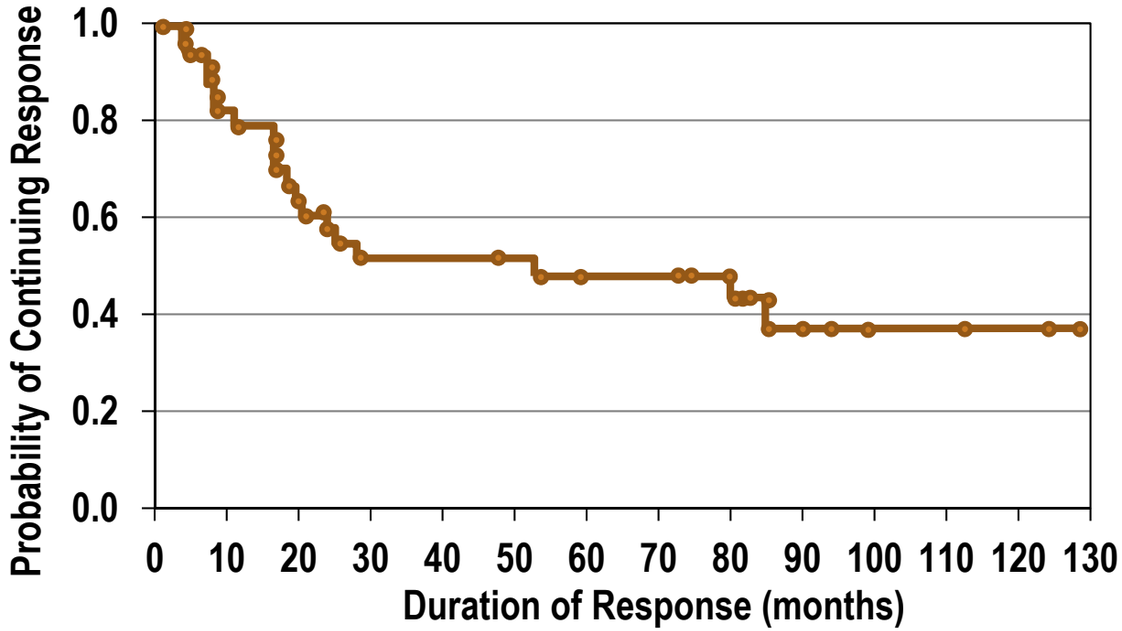
High Dose Interleukin 2 Offers Very Durable Response or Cure for Some Patients

15% of All Patients Treated with HD IL-2 Survive More than 10 Years



Survival of 255 Patients Treated With High Dose IL-2

Nearly 40% of HD IL-2 Responders Continue to Respond for More Than 10 Years



For all 37 responders out of 255 patients treated with high dose IL-2

Source: Fisher RI, Rosenberg SA, Fyfe G. *Cancer J Sci Am*. 2000;6 Suppl 1:S55-7.

Targeted Therapy Approvals

VEGFR inhibitors and multi-kinase TKIs

- Sorafenib (2005)
- Sunitinib (2006)
- Pazopanib (2009)
- Axitinib (2012)
- Lenvatinib mesylate + everolimus (2016)
- Cabozantinib (2017)

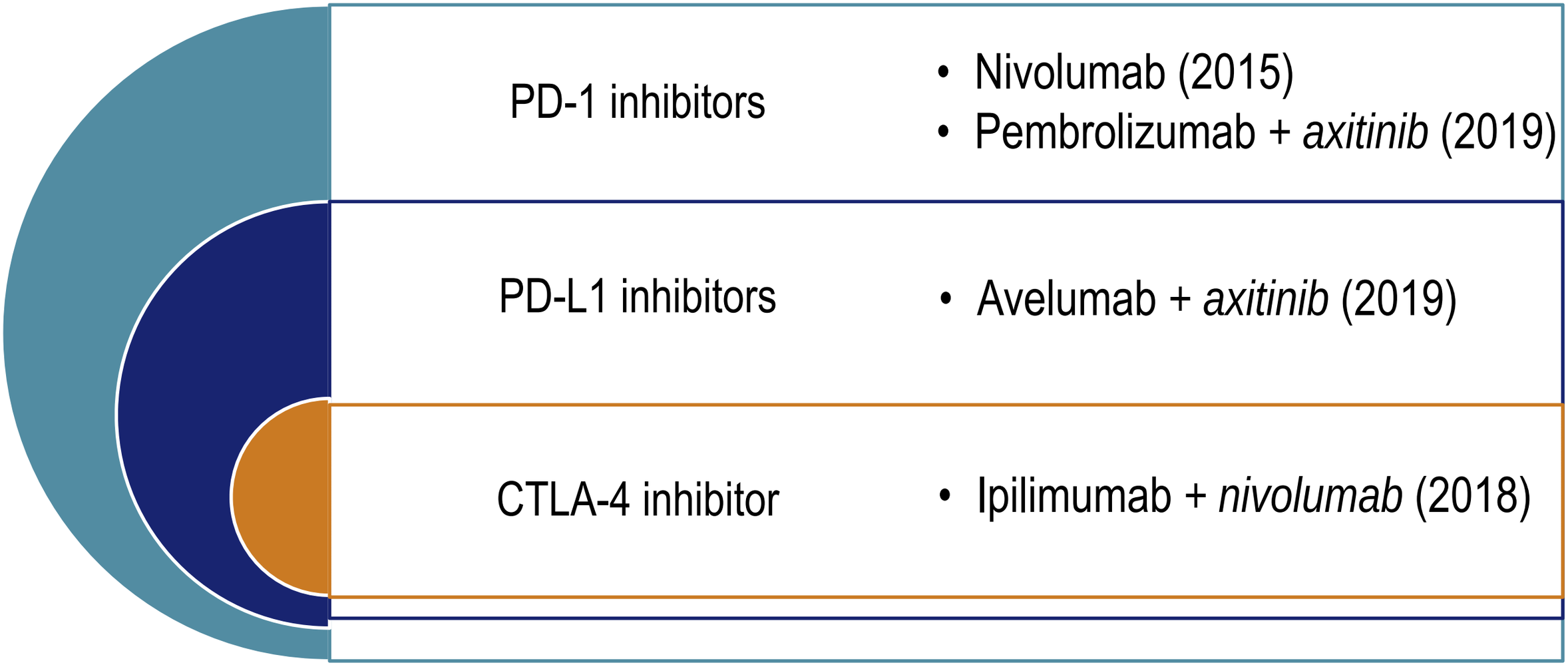
mTOR inhibitors

- Temsirolimus (2007)
- Everolimus (2009)

Monoclonal antibody targeting VEGF

- Bevacizumab + interferon alfa-2b (2010)

Immune Checkpoint Inhibitors Revolutionize Treatment



IMDC/Heng Risk Score (www.mdcalc.com)

Less than one year from time of diagnosis to systemic therapy	**No 0**	Yes +1
Performance status <80% (Karnofsky)	**No 0**	Yes +1
Hemoglobin < lower limit of normal Normal: 120 g/L or 12 g/dL	**No 0**	Yes +1
Calcium > upper limit of normal Normal: 8.5-10.2 mg/dL	**No 0**	Yes +1
Neutrophil > upper limit of normal Normal: 2.0–7.0×10³/L	**No 0**	Yes +1
Platelets > upper limit of normal Normal: 150,000 to 400,000	**No 0**	Yes +1

0 points

Favorable prognosis

Median survival: 43.2 months

Copy Results | Next Steps

Less than one year from time of diagnosis to systemic therapy	No 0	**Yes +1**
Performance status <80% (Karnofsky)	No 0	**Yes +1**
Hemoglobin < lower limit of normal Normal: 120 g/L or 12 g/dL	**No 0**	Yes +1
Calcium > upper limit of normal Normal: 8.5-10.2 mg/dL	**No 0**	Yes +1
Neutrophil > upper limit of normal Normal: 2.0–7.0×10³/L	**No 0**	Yes +1
Platelets > upper limit of normal Normal: 150,000 to 400,000	**No 0**	Yes +1

2 points

Intermediate prognosis

Median survival: 22.5 months

Copy Results | Next Steps

Less than one year from time of diagnosis to systemic therapy	No 0	**Yes +1**
Performance status <80% (Karnofsky)	No 0	**Yes +1**
Hemoglobin < lower limit of normal Normal: 120 g/L or 12 g/dL	No 0	**Yes +1**
Calcium > upper limit of normal Normal: 8.5-10.2 mg/dL	**No 0**	Yes +1
Neutrophil > upper limit of normal Normal: 2.0–7.0×10³/L	**No 0**	Yes +1
Platelets > upper limit of normal Normal: 150,000 to 400,000	**No 0**	Yes +1

3 points

Poor prognosis

Median survival: 7.8 months

Copy Results | Next Steps

International Metastatic RCC Database Consortium/Heng Risk Score for RCC calculates overall survival risk, validated in mRCC patients treated with VEGF-TKIs.

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib

959 Patients

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

Stratified by
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

Treatment

Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

Treatment until progression or unacceptable toxicity

Cella D, Grünwald V, Escudier B, et al. *Lancet Oncol*. 2019;20(2):297-310.

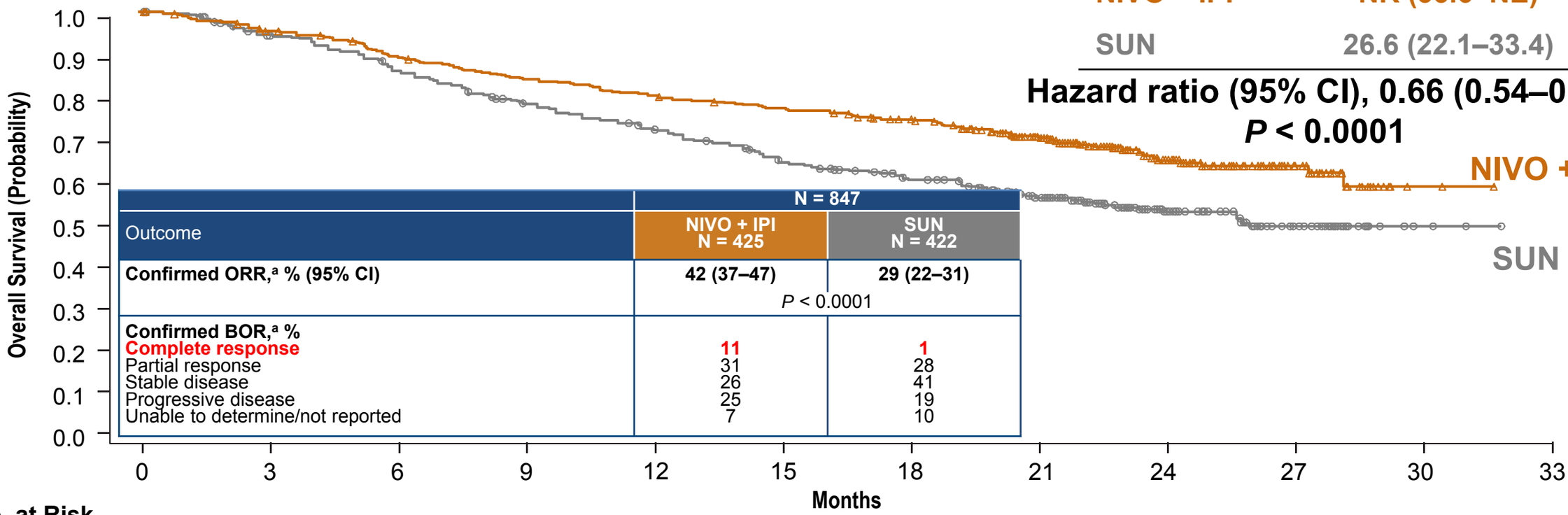
Checkmate 214
OS: IMDC Intermediate/Poor Risk

Co-primary endpoint

Median OS, months (95% CI) at median follow up of 32.4 months

NIVO + IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

Hazard ratio (95% CI), 0.66 (0.54–0.80)
***P* < 0.0001**



Outcome	N = 847 NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**29 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**11**	**1**
Partial response	31	28
Stable disease	26	41
Progressive disease	25	19
Unable to determine/not reported	7	10

No. at Risk

NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

Tannir NM, Frontera OA, Hammers HJ, Carducci MA, et al. *J Clin Oncol*. 2019;37 (Suppl; abstr 547).

Checkmate 214
ORR and PFS: IMDC Favorable Risk

Exploratory endpoint

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68)	
	***P* < 0.0001**	

Motzer R. Presentation November 6, 2019 at 37th Annual Chemotherapy Foundation Symposium

Checkmate 214 Patient Disposition: All Treated Patients

	NIVO + IPI N = 547	SUN N = 535
Treatment discontinuation, %	77	82
Reasons for treatment discontinuation, %		
Disease progression	42	55
Study drug toxicity	**24**	**12**
Adverse event unrelated to study drug	6	6
Other	4	9
Median duration of therapy (95% CI), months	7.9 (6.5–8.4)	7.8 (6.4–8.5)
Median doses received (range), no.		
Nivolumab	14 (1–63)	NA
Ipilimumab	4 (1–4)	NA
Median daily dose (range), mg/day	NA	31 (14–50)

- In the NIVO + IPI arm, 79% of patients received all four doses of IPI
- Median follow-up was 25.2 months

Escudier B, Tannir N, McDermott DF, Frontera OA, Melichar B, Plimack ER, et al Abstract presented September September 10, 2017 at ESMO. *Annals of Oncology* (2017) 28 (suppl_5): v605-v649. 10.1093/annonc/mdx440

Checkmate 214
Treatment-related AEs: All Treated Patients

Secondary endpoint

	NIVO + IPI N = 547		SUN N = 535	
Event, %	Any grade	Grade 3–5	Any grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	93	46	97	63
Fatigue	37	4	49	9
Pr				
Di				
Na				
Hy				
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 7[b]**		**n = 4[c]**	

60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

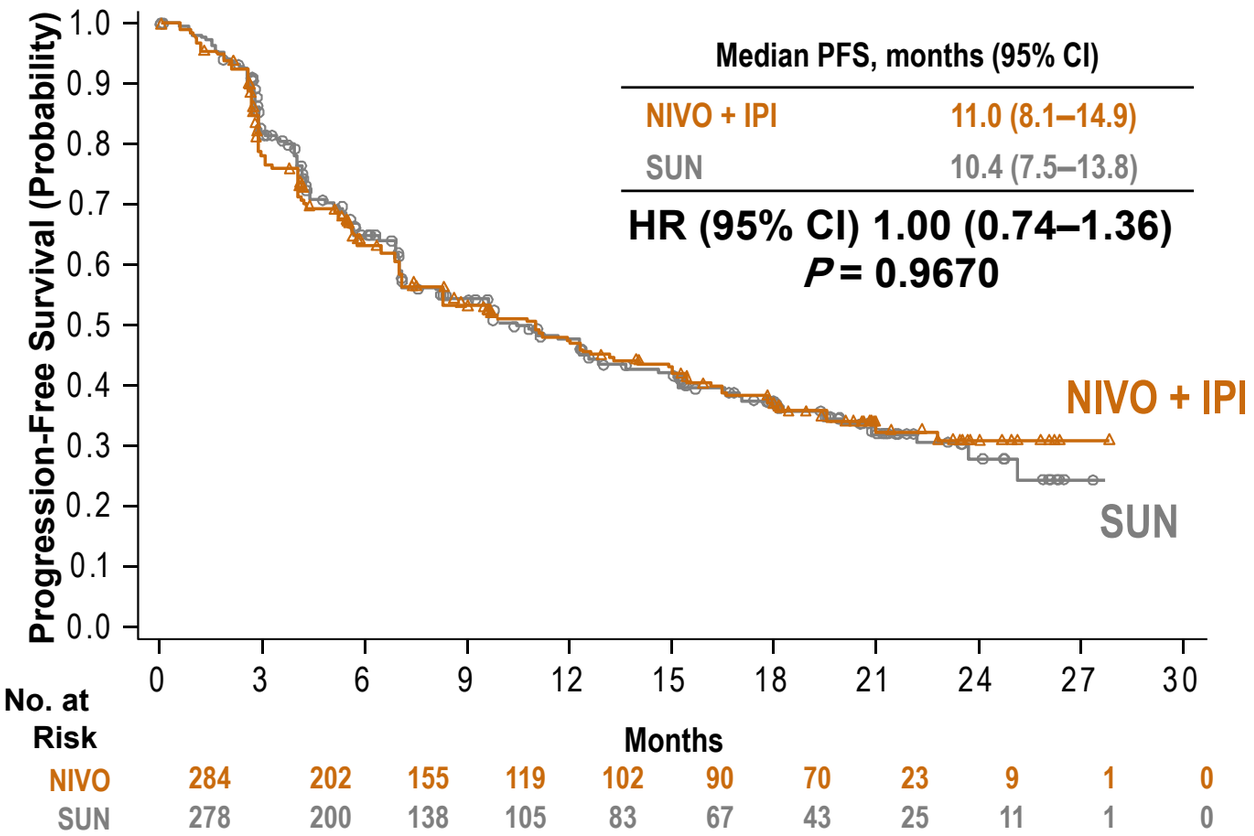
[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

Escudier B, Tannir N, McDermott DF, Frontera OA, Melichar B, Plimack ER, et al Abstract presented September September 10, 2017 at ESMO. *Annals of Oncology* (2017) 28 (suppl_5): v605-v649. 10.1093/annonc/mdx440

Checkmate 214 PFS by PD-L1 Expression: Intermediate/Poor Risk

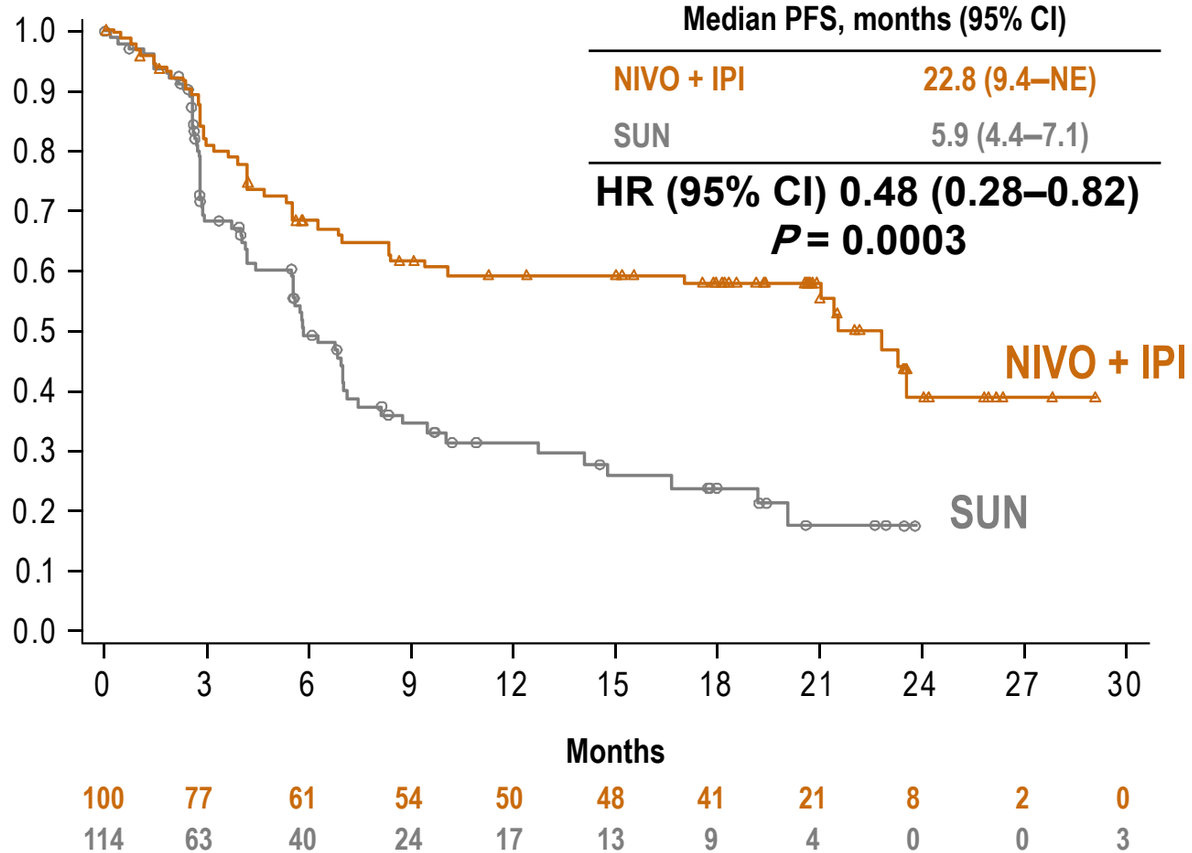
Exploratory endpoint

PD-L1 <1% (n = 562)



No. at Risk											
NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	0

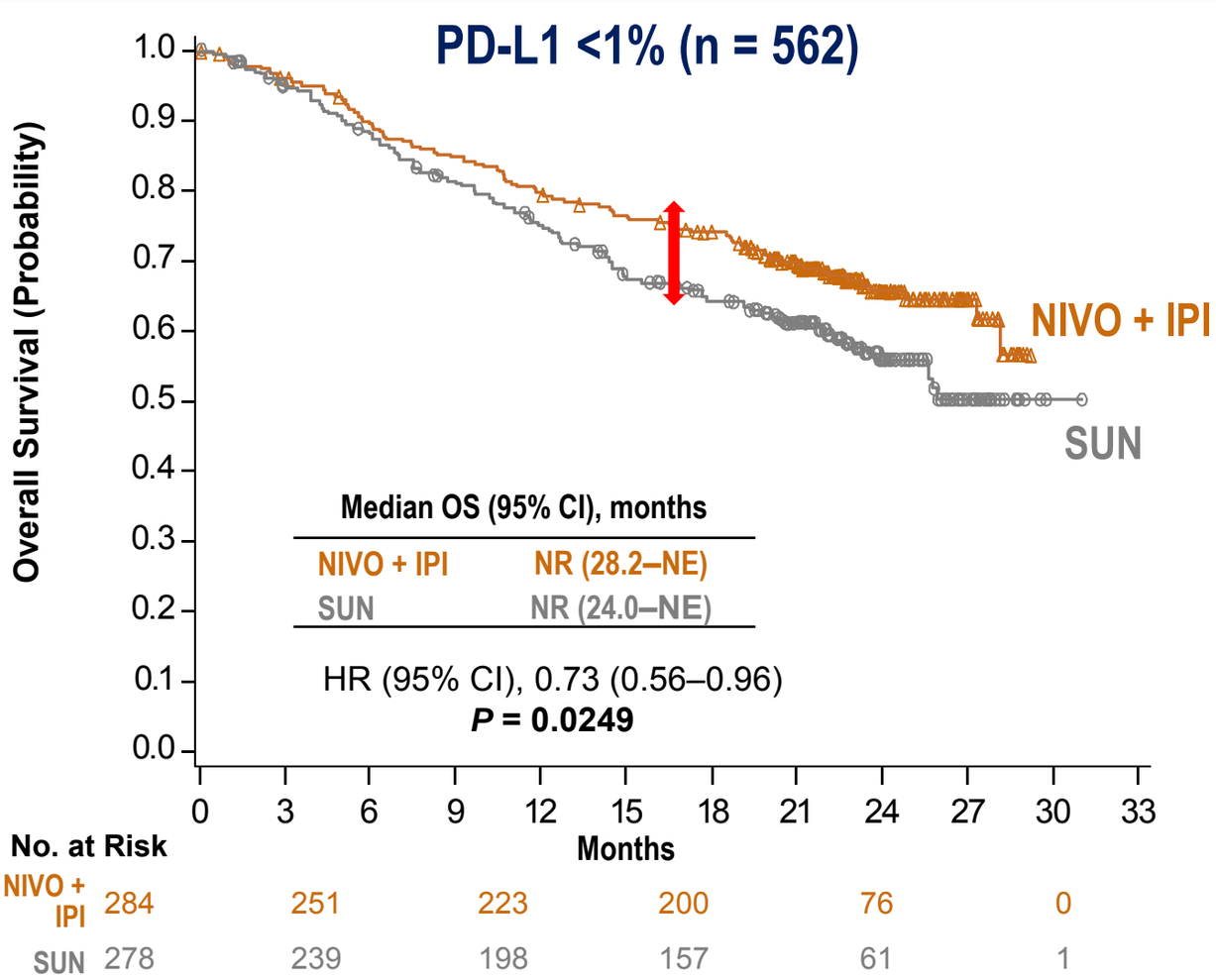
PD-L1 ≥1% (n = 214)

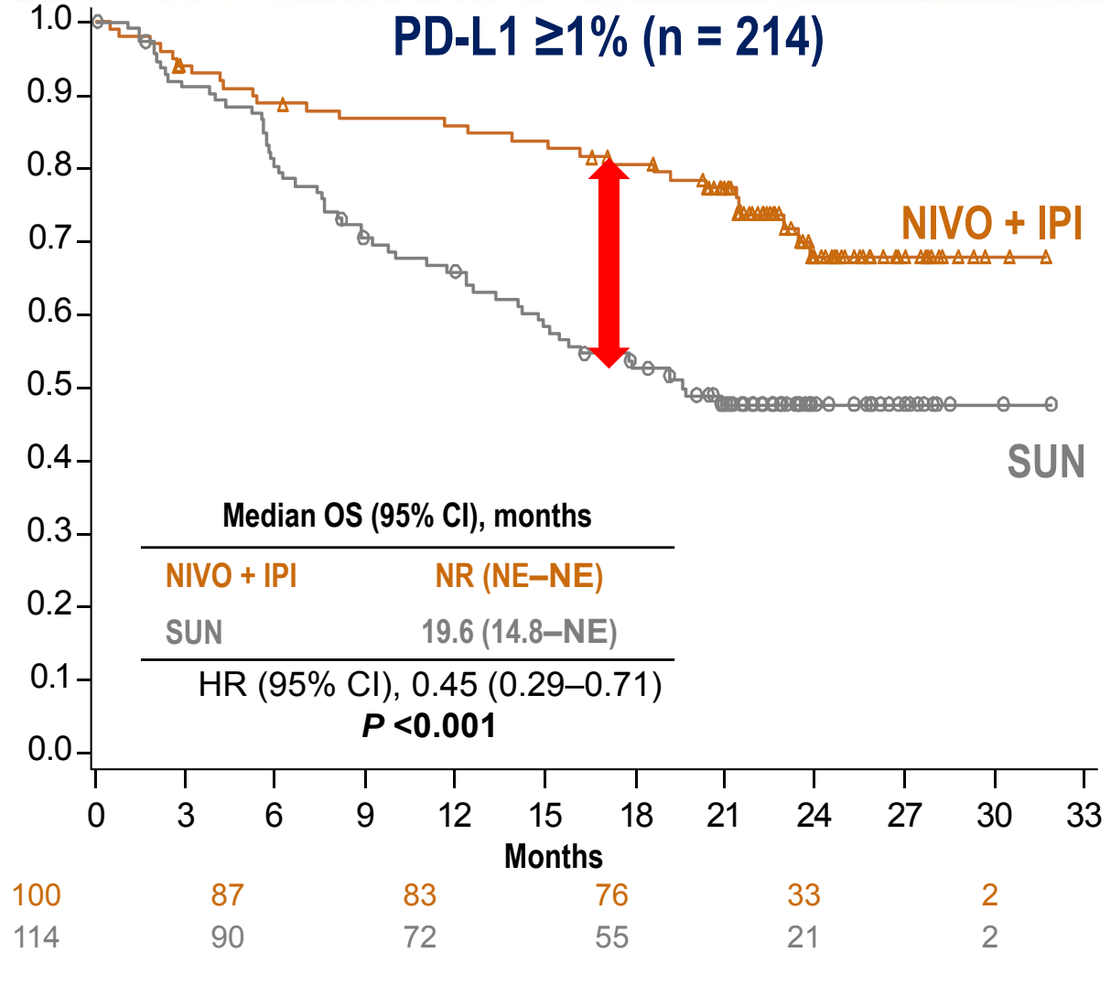


	100	77	61	54	50	48	41	21	8	2	0
	114	63	40	24	17	13	9	4	0	0	3

Motzer RJ, Tannir NM, Mcdermott DF, et al. *N Engl J Med*. 2018;378(14):1277-1290.

OS by Tumor PD-L1 Expression: IMDC Intermediate/Poor Risk





Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Plimack ER, et al. Abstract 038 presented at SITC 2017. https://jitc.biomedcentral.com/articles/10.1186/s40425-017-0297-3. Accessed November 2019.

New Standard of Care Combo: Nivolumab + Ipilimumab for Intermediate/Poor-risk

Nivolumab +Ipilimumab approved by FDA for first-line treatment of *intermediate/poor-risk* treatment-naïve patients with advanced RCC in April 2018.

KEYNOTE-426: Pembrolizumab + Axitinib vs Sunitinib

861 Patients

- **Stage 4 ccRCC**
- **Systemic treatment naïve**
- **Karnofsky performance status >70**
- **Measurable disease per RECIST v1.1**
- **Tumor sample**
- **Adequate organ function**

Randomize 1:1

Stratified by
- IMDC prognostic score (favorable vs intermediate/poor)
- Region (North America vs Europe vs Rest of World)

Treatment

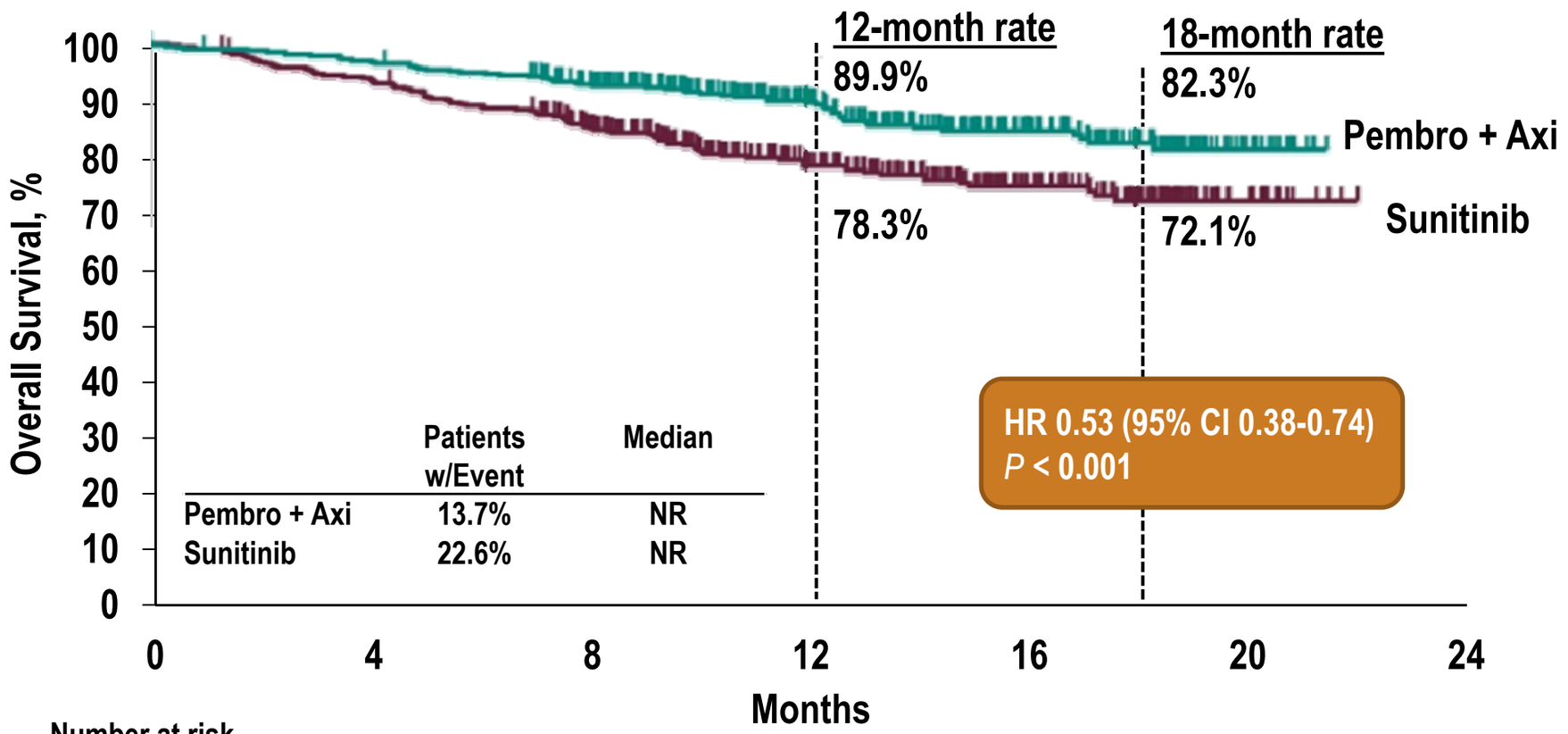
Arm A
200 mg pembrolizumab IV Q3W up to 35 cycles + axitinib 5 mg orally twice daily

Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

Treatment until progression or unacceptable toxicity

Powles T, Plimack ER, Stus V, Gafanov RA, Hawkins RE, Nosov D, et al. Abstract presented February 16, 2019 at ASCO. https://meetinglibrary.asco.org/record/170343/abstract. Accessed November 2019.

KEYNOTE-426: Pembrolizumab + Axitinib Superior to Sunitinib



Number at risk

432	417	378	256	136	18	0
429	401	341	211	110	20	0

Powles T, Plimack ER, Stus V, Gafanov RA, Hawkins RE, Nosov D, et al. Abstract presented February 16, 2019 at ASCO. https://meetinglibrary.asco.org/record/170343/abstract. Accessed November 2019.

New Standard of Care Combo: Pembrolizumab + Axitinib

FDA approved pembrolizumab + axitinib for first-line treatment of patients with advanced RCC in March 2019.

JAVELIN Renal 101: Avelumab + Axitinib vs Sunitinib

Patients

- **Advanced ccRCC**
- **Systemic treatment naïve**
- **ECOG PS 0 or 1**
- **Measurable disease per RECIST v1.1**
- **Tumor sample**
- **Adequate organ function**

Randomize 1:1

Stratified by
- ECOG PS 0 vs 1
- Region (North America vs Europe vs Rest of World)

Treatment

Arm A
Avelumab 10 mg/kg IV Q2W +
Axitinib 5 mg PO BID
(6-week cycles)

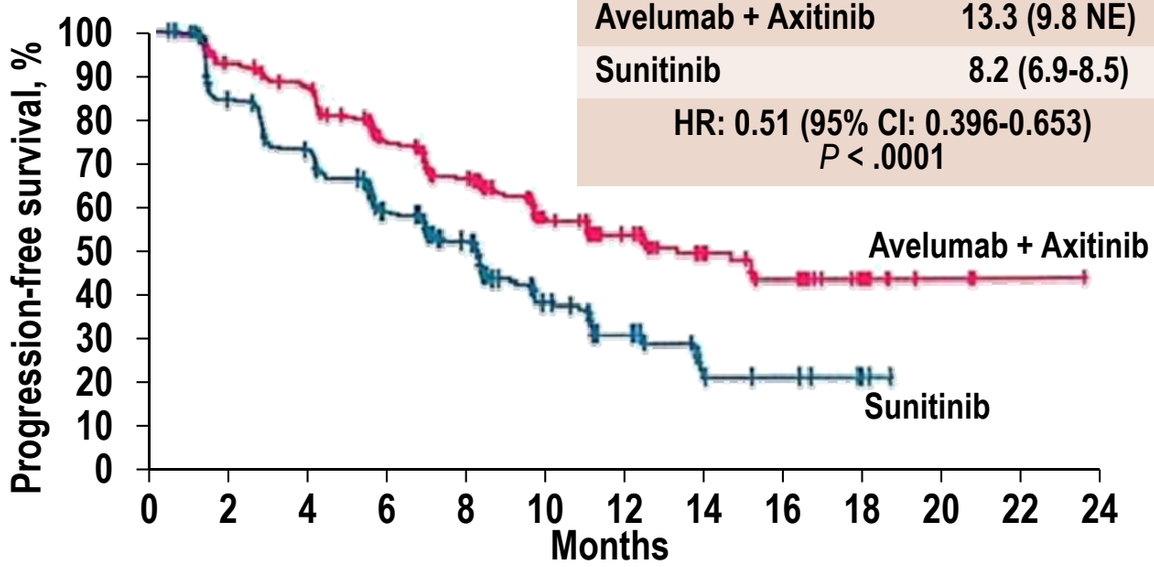
Arm B
50 mg sunitinib orally once daily for 4 weeks
(6-week cycles)

Treatment until progression or unacceptable toxicity

Choueiri TK, Motzer RJ, Campbell MT, Alekseev BY, Uemura M, et al. Abstract presented February 16, 2019 at ASCO. https://meetinglibrary.asco.org/record/169448/abstract. Accessed November 2019.

JAVELIN Renal 101: Avelumab +Axitinib

PFS in PD-L1 positive Patients

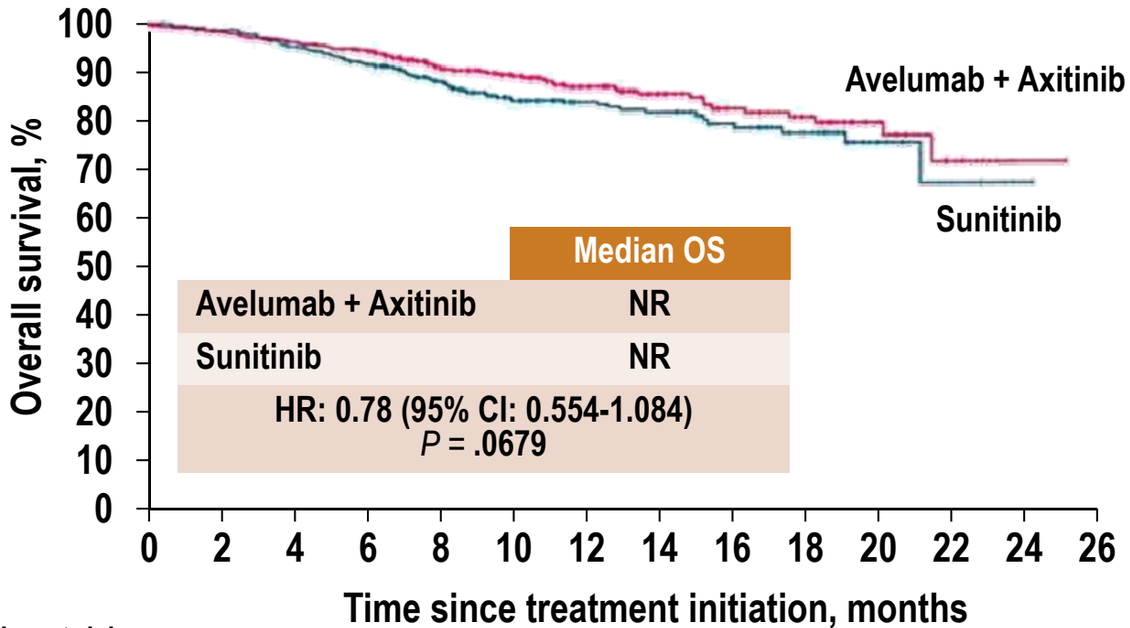


	Median PFS, mo (95% CI)
Avelumab + Axitinib	13.3 (9.8 NE)
Sunitinib	8.2 (6.9-8.5)
HR: 0.51 (95% CI: 0.396-0.653) *P* < .0001	

Number at risk

Avel+Axit:	270	235	216	166	127	78	57	36	25	15	4	1	0
Sunitinib:	290	227	191	138	100	51	32	12	10	5	0		

OS in Intent-to-Treat Cohort (Results pending)



	Median OS
Avelumab + Axitinib	NR
Sunitinib	NR
HR: 0.78 (95% CI: 0.554-1.084) *P* = .0679	

Number at risk

Avel+Axit:	442	426	412	396	319	252	187	121	93	70	27	8	1	0
Sunitinib:	444	426	401	373	295	224	175	113	84	59	17	5	1	0

Motzer R. Penkov K, Haanen JBAG, Rini BI, Albiges L, Campbell MT, et al. Abstract presented October 21, 2018 at ESMO 2018. https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/JAVELIN-Renal-101-a-randomized-phase-3-study-of-avelumab-axitinib-vs-sunitinib-as-first-line-treatment-of-advanced-renal-cell-carcinoma-aRCC

New Standard of Care Combo: Pembrolizumab + Axitinib

FDA approved avelumab + axitinib for first-line treatment of patients with advanced RCC in May 2019.

Other Phase 3 IO Combination Clinical Trials

Trial Name	Drugs	Interim Results
Immotion 151 [1] 915 patients	Atezolizumab + Bevacizumab vs Sunitinib	ITT pop PFS: A+B 11.2 vs 8.4 Sun mos OS: A+B 33.6 vs 34.9 Sun mos, HR 0.93 (95%:0.76, 1.14) PD-L1+ pop PFS: A+B 11.2 vs 7.7 mos Sun OS: A+B 34 vs 32.7 mos Sun HR 0.84 (95%: 0.6,-1.15)
CLEAR [2] 735 patients	Lenvatinib + Everolimus/ Lenvatinib + Pembrolizumab vs Sunitinib	Lenvatinib + everolimus approved for mRCC Lenvatinib + pembrolizumab promising in Phase 2 Results not yet reported

1. Rini BI, Powles T, Atkins MB, et al. Lancet. 2019; Jun 15;393(10189):2404-2415.
2. Grunwald V, Powles T, Choueiri TK, et al. Future Oncology 15(9). https://www.futuremedicine.com/doi/10.2217/fon-2018-0745 Published January 28 2019.

Other Notable Phase 3 IO Combination Clinical Trials

Trial Name	Drugs	Interim Results
PIVOT-09 600 patients	Bempegaldesleukin + nivolumab vs cabozantinib or sunitinib	Now enrolling
Cosmic-313 676 patients	Cabozantinib + nivolumab + ipilimumab vs nivolumab + ipilimumab	Intermediate/poor-risk only Launched May 2019.

George DJ, Alter RS, Chung-Han L, Tannir NM. NKTR-214 and COSMIC-313 for Previously Untreated RCC. OncLive website: https://www.onclive.com/peer-exchange/metastatic-rcc-contemporary-management/nktr214-and-cosmic313-for-previously-untreated-rcc. Published September 6, 2019.

2020 NCCN First-line ccRCC Recommendations

Risk	Preferred	Alternate	Useful in Some Circumstances
Favorable	Axitinib + Pembrolizumab Pazopanib Sunitinib	Axitinib + avelumab Ipilimumab + nivolumab, followed by nivolumab Cabozantinib (cat 2b)	Active surveillance Axitinib (cat 2b) High dose IL-2
Poor/Intermediate	Axitinib + Pembrolizumab (cat 1) Ipilimumab + nivolumab (cat 1), followed by nivolumab Cabozantinib	Axitinib + avelumab Pazopanib Sunitinib	Axitinib (cat 2b) High dose IL-2 Temsirolimus

Motzer RJ, Jonasch E, Michaelson MD, et al. *J Natl Compr Canc Netw.* 2019;17(11):1278-1285.

2020 NCCN Recommendations for Subsequent Therapy for ccRCC

Preferred	Alternate	Useful in Some Circumstances
Cabozantinib (cat 1) Nivolumab (cat 1) Ipilimumab + nivolumab	Axitinib (cat 1) Lenvatinib + everolimus (cat 1) Axitinib + pembrolizumab Everolimus Pazopanib Sunitinib Axitinib + avelumab (cat 3)	Bevacizumab or biosimilars (cat 2b) High dose IL-2 (cat 2b) Sorafenib (cat 2b) Temsirolimus (cat 2b)

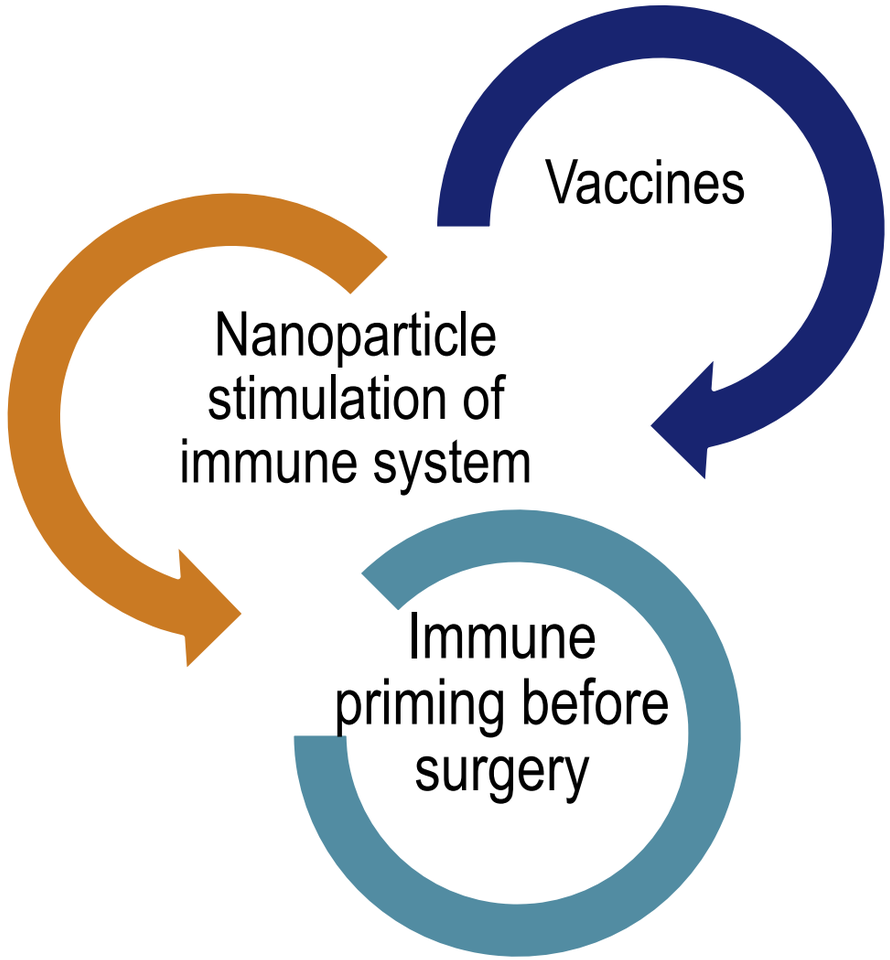
Motzer RJ, Jonasch E, Michaelson MD, et al. *J Natl Compr Canc Netw.* 2019;17(11):1278-1285.

2020 NCCN Recommendations for Advanced Non-ccRCC

Preferred	Other Options	Options in Some Cases
Clinical Trial (preferred) Sunitinib *Pembrolizumab (may become an option)*	Cabozantinib Everolimus	Axitinib Bevacizumab or biosimilar Bevacizumab + everolimus (advanced papillary RCC and HLRCC) Bevacizumab or biosimilar + everolimus Erlotinib Gemcitabine + carboplatin (only for collecting duct or medullary subtypes) Gemcitabine + cisplatin (only for collecting duct or medullary subtypes) Lenvatinib + everolimus Nivolumab Paclitaxel + carboplatin Pazopainb Temsirolimus (cat 1 for poor risk, 2A otherwise)

Motzer RJ, Jonasch E, Michaelson MD, et al. *J Natl Compr Canc Netw.* 2019;17(11):1278-1285.

New Applications of Immune-oncology in RCC



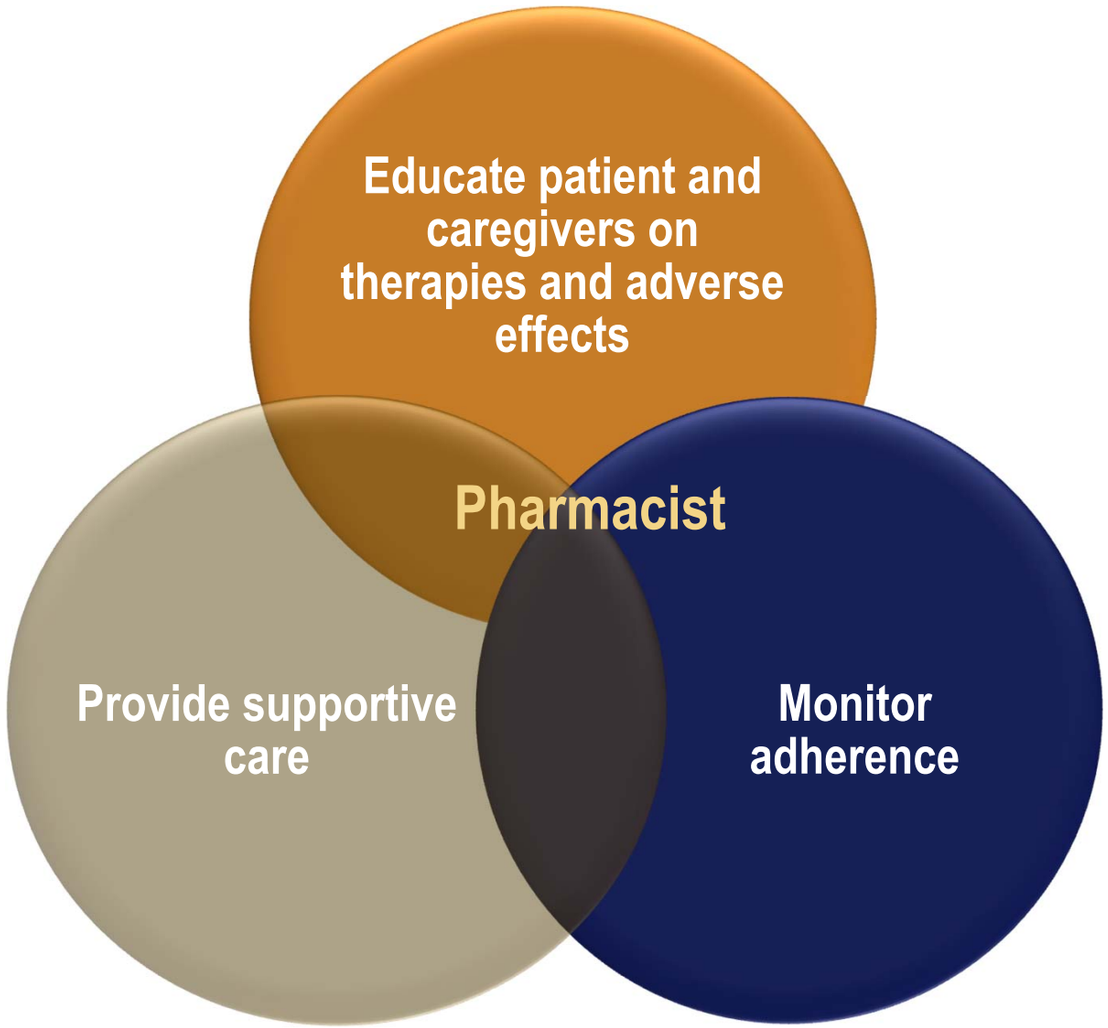
Care Management Strategies to Enhance Overall Outcomes for Patients Requiring Immuno-oncology Agents for RCC

Christopher A. Fausel, PharmD, MHA, BCOP

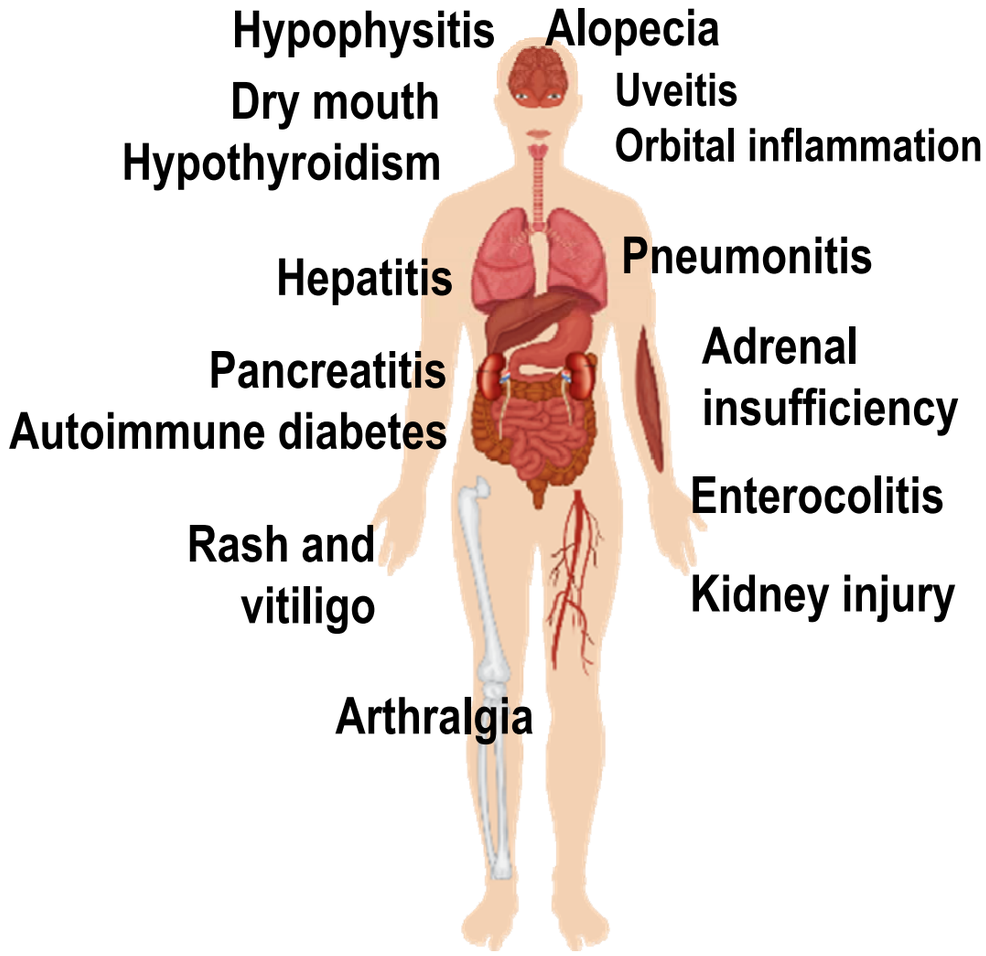
Clinical Manager, Oncology Pharmacy

Indiana University Simon Cancer Center

Care Management Strategies



Immune-related Adverse Events Common with Immune Checkpoint Inhibitors (ICIs)



Michot JM, Bigenwald C, Champiat S, et al. Eur J Cancer. 2016;54:139-148.

Frequency of Common Adverse Events for TKIs

Selected treatment-related adverse nonhematologic and nonlaboratory events reported in at least 10% of patients treated with sunitinib in the 3 mRCC studies.

	% of patients from pooled phase 2 second-line studies		% of patients from randomized phase 3 first-line study	
Adverse event	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Gastrointestinal disorders				
Constipation	20.1	0.0	NS	NS
Diarrhea	49.1	3.0	53	5
Dyspepsia	40.8	0.6	NS	NS
Nausea	49.7	1.2	44	3*
Stomatitis	41.4	3.6	25	1*
Vomiting	30.8	1.2	24	1*
General disorders				
Fatigue	50.4	10.7	51	7*
Mucosal inflammation	17.8	0.6	20	2*
Infections and infestations	12.4	2.4	NS	NS
Cardiac Disorder				
Ejection fraction decreased	14.2	2.4	10	2*
Metabolism				
Anorexia	27.8	0.6	NS	NS*
Musculoskeletal				
Pain in extremity	12.4	0.6	11	1*
Nervous system disorders				
Dysgeusia	42	0.0	NS	NS
Headache	14.8	0.6	11	1*
Skin disorders				
Dry skin	13.0	0.0	15	1*
Erythema	11.8	0.0	NS	NS
Hair color changes	14.2	0.0	14	0
Palmar-plantar erythrodysesthesia syndrome	12.4	3.6	20	5*
Rash	26.0	0.6	19	2
Skin discoloration	32.0	0.0	16	0
Vascular disorders				
Hypertension	16.6	4.1	24	8*

Kollmannsberger C, Soulieres D, Wong R, Scalera A, Gaspo R, Bjarnason G. *Can Urol Assoc J*. 2007;1(2 Suppl):S41-54.

Common Toxicities by Drug

Drug/Regimen	Type Agent	Initial Dose/Schedule	Toxicity Profile (>20% of patients)
Sunitinib	Tyrosine kinase inhibitor	50 mg PO daily 4 weeks/2 weeks off every 6 weeks	Diarrhea, fatigue, hypertension, H/F syndrome, neutropenia, thrombopenia, ↑ hepatic function tests
Sorafenib	Multikinase inhibitor	400 mg PO twice daily	Fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain
Pazopanib	Tyrosine kinase inhibitor	800 mg PO daily	Diarrhea, hypertension, nausea, hair color change, ↑ hepatic function tests, neutropenia, thrombopenia
Axitinib	Tyrosine kinase inhibitor	5 mg PO twice daily with dose escalation	Diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot skin reaction, weight loss, stomatitis
Cabozantinib	Tyrosine kinase inhibitor (MET, AXL, VEGF)	60 mg PO daily	Diarrhea, hypertension, fatigue, H/F syndrome, nausea/vomiting, weight loss, stomatitis
Lenvatinib + Everolimus	Tyrosine kinase and mTOR inhibitors	Everolimus 5 mg PO daily + Lenvatinib 18 mg PO daily	Everolimus: stomatitis, infections, asthenia, fatigue, cough, diarrhea, and non-infections pneumonitis (11-14%) Lenvatinib: hypothyroidism, fatigue, diarrhea, HTN, proteinurea

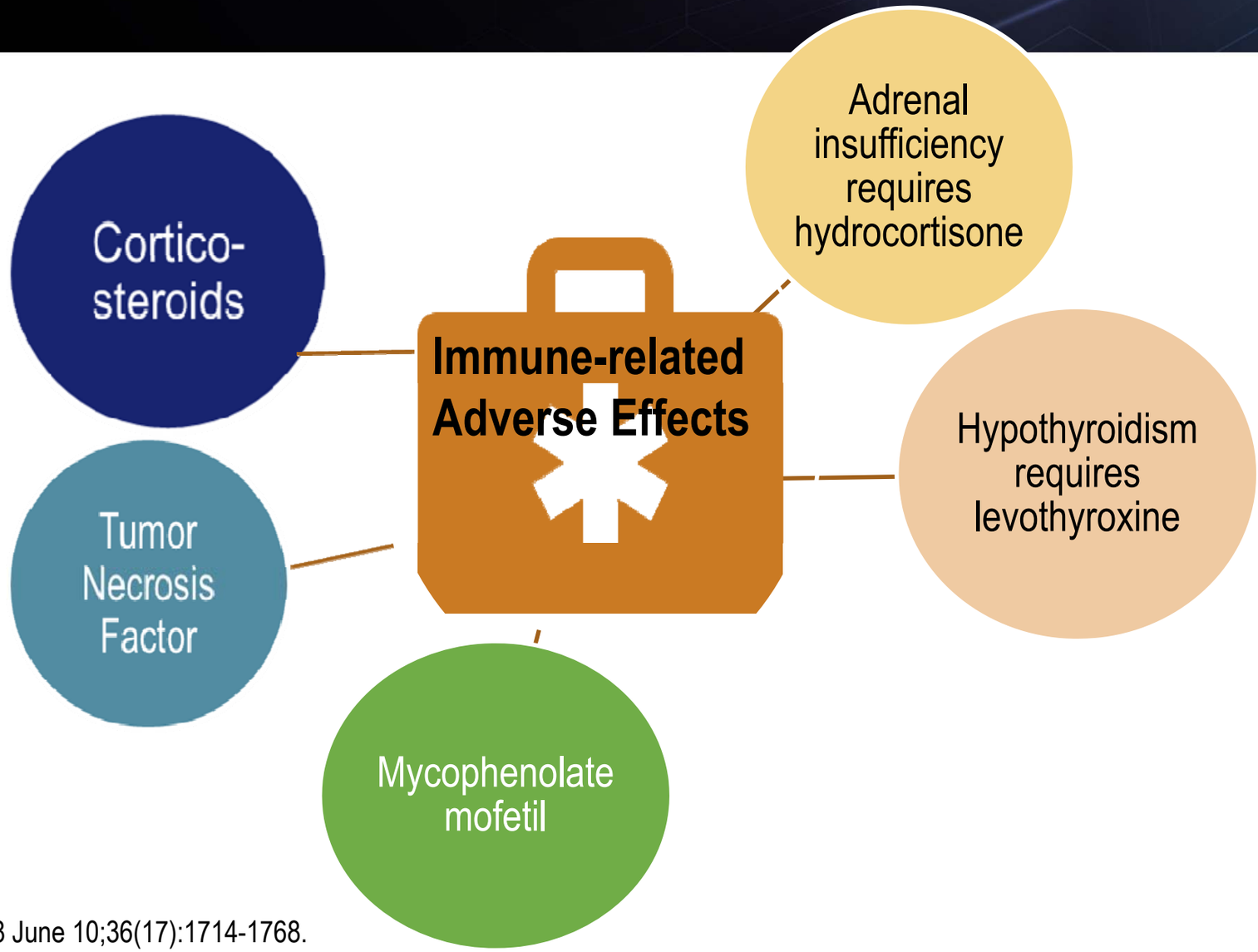
Gerber D., Bowman IA. Renal Cell Carcinoma. Cancer Therapy Advisor. https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/imaging/renal-cell-carcinoma/. Accessed November 2019.

Common Toxicities by Drug

Drug/Regimen	Type Agent	Initial Dose/Schedule	Toxicity Profile (>20% of patients)
Temsirolimus	mTOR inhibitor	25 mg IV weekly	Rash, asthenia, mucositis, nausea, edema, and anorexia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, elevated serum creatinine, thrombocytopenia, elevated AST
Everolimus	mTOR inhibitor	10 mg PO twice daily	Stomatitis, infections, asthenia, fatigue, cough, diarrhea Non-infectious pneumonitis (11-14%)
Bevacizumab + IFNα	VEGF monoclonal antibody + cytokine	Bevacizumab 10 mg/kg IV every 2 weeks	Fatigue, hemorrhage, hypertension, fever, flu-like syndrome Additional adverse events: gastrointestinal perforations, surgical and would healing complications, hemorrhage
Nivolumab	Immune Checkpoint Inhibitor	Nivolumab 240 mg IV every 2 weeks	Fatigue, nausea, pruritus, autoimmune events (e.g., colitis, pneumonitis, hepatitis; <5%)

Gerber D., Bowman IA. Renal Cell Carcinoma. Cancer Therapy Advisor. https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/imaging/renal-cell-carcinoma/. Accessed November 2019.

Adverse Effects: Immunosuppression



Brahmer JR, et al. J Clin Oncol. 2018 June 10;36(17):1714-1768.

Adverse Events: ASCO General Recommendations

Toxicity Grade	Recommendation
All	Assume high level of suspicion that all adverse events are treatment related
Grade 1	Continue therapy with close monitoring, with some exceptions
Grade 2	Hold ICPi therapy. Consider 0.5-1.0 mg/kg/d of corticosteroids. Consider resuming therapy when symptoms or lab values revert to grade 1 or lower.
Grade 3	Initiate 1-2 mg/kg/d prednisone of methylprednisolone IV 1-2 mg/kg/d. If symptoms do not improve in 48-72 hours, consider adding infliximab. Taper steroids over 4-6 weeks. When symptoms or lab values revert to grade 1 or less, consider rechallenge with ICPi therapy. Proceed with caution.
Grade 4	Permanently discontinue therapy, unless toxicity is endocrinopathy that has been controlled by hormone replacement.

Brahmer JR, Lacchetti C, Schneider BJ, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

Minimizing Drug-Drug Interactions

- **Medication Therapy Review:** Prescription, OTC, herbal products and dietary supplements
- Monitor and evaluate response to therapy and labs
- Communicate with patient and other providers
- Utilize EMR drug-drug interaction tools
- Regularly review and discuss all medications and supplements with patient

Drug-drug interactions the checkpoint inhibitors. ACCC website: https://www.accc-cancer.org/home/learn/resource-detail/Drug-Drug-Interactions-and-the-Checkpoint-Inhibitors. Published June 28, 2016. Accessed November 2019.

Potential Interactions for TKIs

Drug	Interaction Drug Class	Potential Drug Interactions
Axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib	CYP3A4 inducers	Efavirenz, dexamethasone, phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, rifapentine, St. John's wort
	CYP3A4 inhibitors	Aprepitant, ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice
	P-glycoprotein inhibitors	Omeprazole and other proton pump inhibitors, amiodarone, cyclosporine, colchicine, diltiazem, quinidine

Sunitinib (Sutent) Basics for GIST. Gist Support International website: https://www.gistsupport.org/treatments/sutent/sunitinib-sutent-basics-for-gist/#6. Accessed November 2019.

Potential Interactions for TKIs

Drug	Class	Potential Danger
Lenvatinib, pazopanib, sunitinib	Anticoagulants Antiarrhythmics Antipsychotics Antidepressants Opioids Macrolide antibiotics Quinolone antibiotics 5HT3 antagonists Domperidone	May prolong QT or QTc interval

Kollmannsberger C, Soulieres D, Wong R, Scalera A, Gaspo R, Bjarnason G. *Can Urol Assoc J*. 2007;1(2 Suppl):S41-54.

THE IMMUNO-ONCOLOGY REVOLUTION:

A Guide for Health-System Pharmacists in

Renal Cell Carcinoma

Jointly provided by

Impact Education LLC

PIM Postgraduate Institute for Medicine

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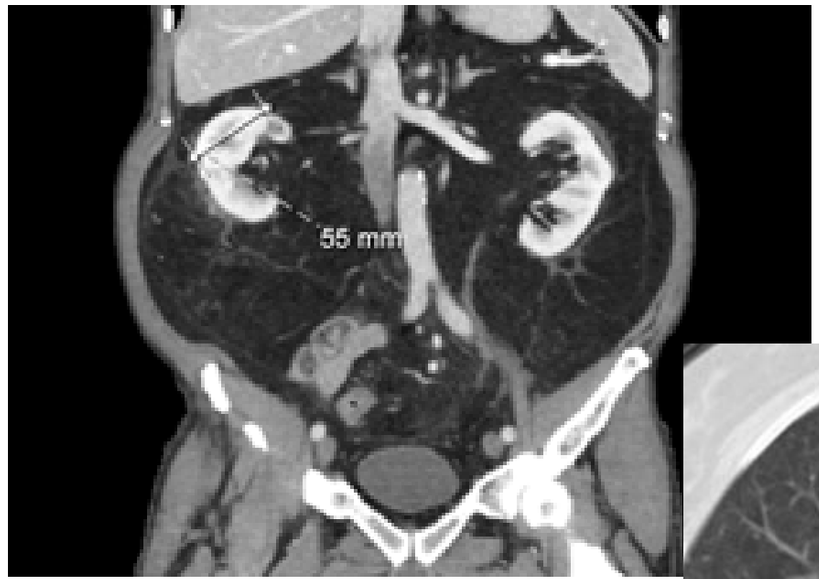
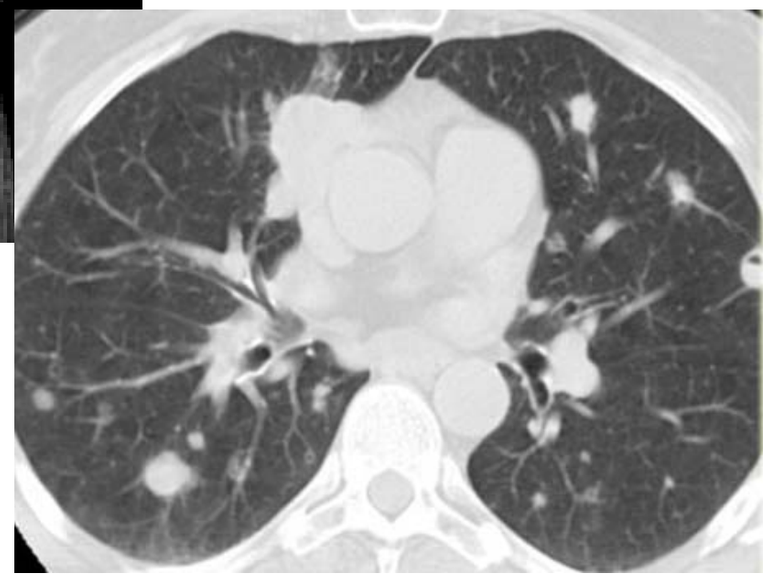
Case Studies

Christopher A. Fausel, PharmD, MHA, BCOP
and
Sumanta Kumar Pal, MD

Case 1: To Cut or Not to Cut

- 70-year-old male
- Limited past medical history
- Pt has a CT abdomen following car accident
- Imaging shows large, 6 cm renal mass
- Imaging also shows multiple pulmonary nodules up to 3 cm





Case 1: What would be your next step?

- Biopsy
- Cytoreductive nephrectomy
- Cytoreductive nephrectomy with initiation of systemic therapy
- Systemic therapy alone

Case 1: First Step

Biopsy

We can clarify the pathology and then decide what systemic therapy to offer.

Image credit: Kidneycare.com

Case 1: It's clear cell RCC. What systemic therapy would you offer?

- Cabozantinib
- Axitinib with Avelumab
- Axitinib with Pembrolizumab
- Nivolumab with Ipilimumab

Case 1: Systemic Therapy for ccRCC

Nivolumab + ipilimumab

Irrespective of labs, he inherently has *intermediate or poor risk* disease. The patient has documented clear cell pathology and is a candidate for CN. Both Nivo+Ipi and Ax+Pembro are NCCN category 1 recommendations in this population. I'd prefer to save a VEGF inhibitor for a potential second line.

Case 1: SWOG PROBE Trial: Arm A or B?

- Treatment-naïve metastatic RCC
- Zubron score 0-1
- Biopsy proven RCC

Stratified by
- IMDC prognostic score (inter vs high)
- Zubron score (0 vs 1)

Arm A

3mg/kg nivo + 1mg/kg ipi q3w for 4 doses → Nephrectomy* → 480mg q4w until progression or unacceptable toxicity

Arm B

3mg/kg nivo + 1mg/kg ipi q3w for 4 doses → 480mg q4w until progression or unacceptable toxicity

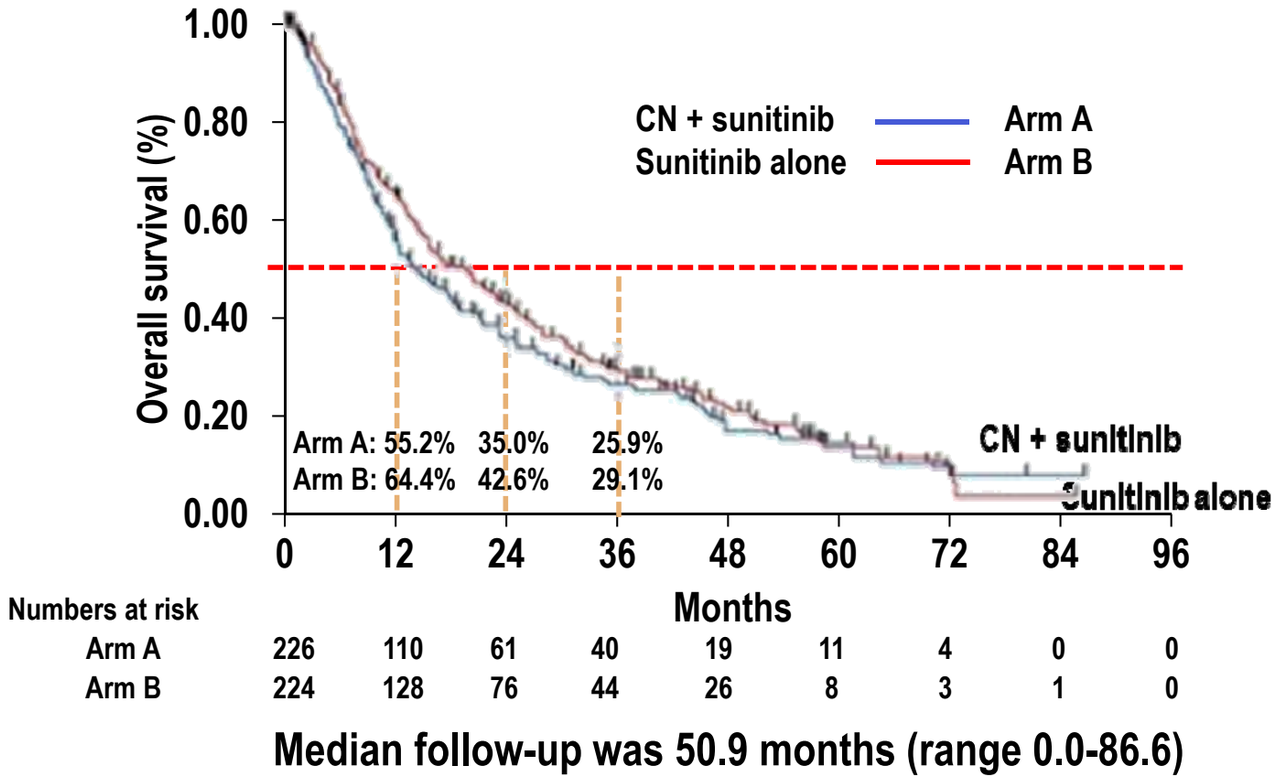
Randomize1:1
Primary endpoint: OS

*Cytoreductive nephrectomy can be deferred for disease progression or performance score >1 during immune therapy.

Courtesy of Ulka Vaishampayan, MD, and Hyung L. Kim, MD

Case 1: CARMENA Challenges Nephrectomy by Default

Sunitinib Alone is Non-inferior to Nephrectomy Followed by Sunitinib for OS



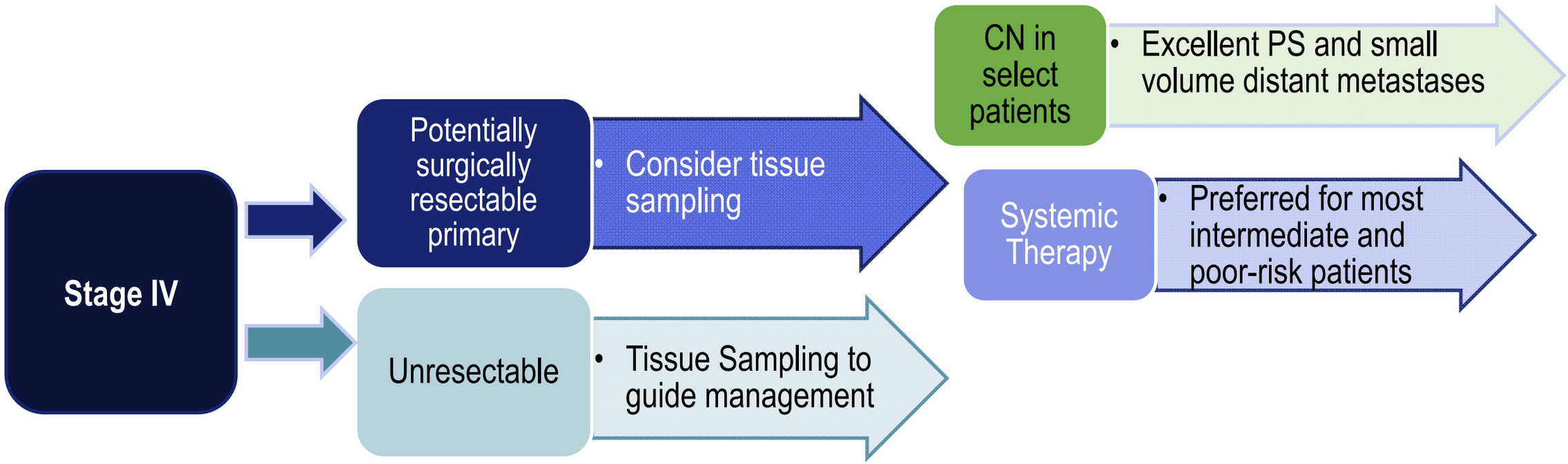
Median follow-up was 50.9 months (range 0.0-86.6)

Median OS, months (95% CI)	Arm A: CN + Sunitinib (n=226)	Arm B: Sunitinib alone (n=224)	HR (95%)
Overall	13.9 (11.8-18.3)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
MSKCC intermediate risk	19.0 (12.0-28.0)	23.4 (17.0-32.0)	0.92 (0.6-1.24)
MSKCC poor risk	10.2 (9.0-14.0)	13.3 (9.0—17.0)	0.86 (0.62-1.17)

CN, cytoreductive nephrectomy; OS, overall survival

Méjean A. Abstract LBA3. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Sunday June 3, 2018. https://meetinglibrary.asco.org/record/161512/abstract. Accessed November 2019.

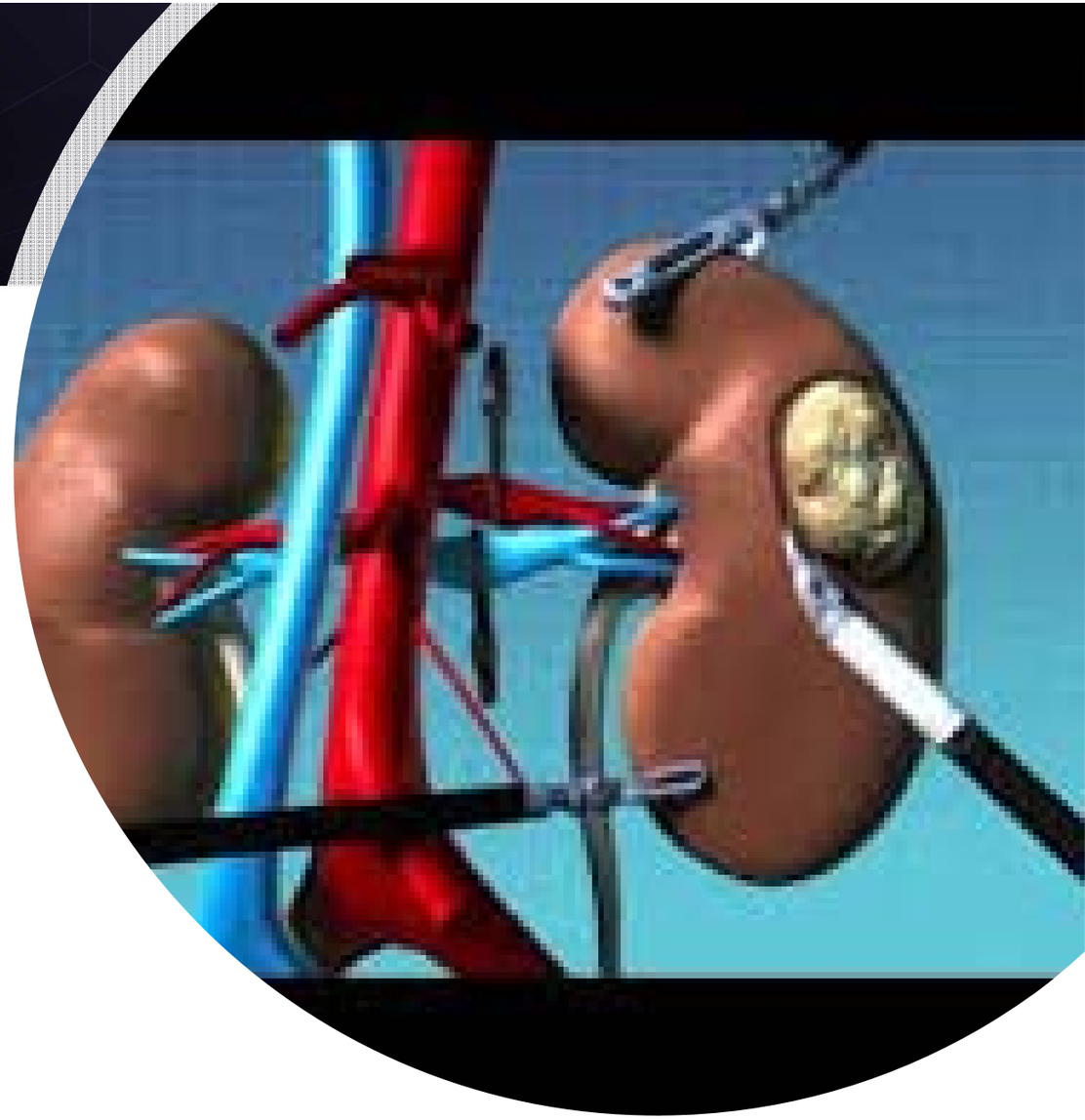
NCCN Guidelines on Nephrectomy



"New for the 2020 guidelines, systemic therapy is the preferred initial treatment option for patients with stage IV disease who have any poor-risk features, clear cell histology, and high-volume distant metastases, instead of cytoreductive nephrectomy followed by systemic treatment."

~ NCCN Guidelines Insights: Kidney Cancer, Version 2.2020

Case 1: To Cut or Not?



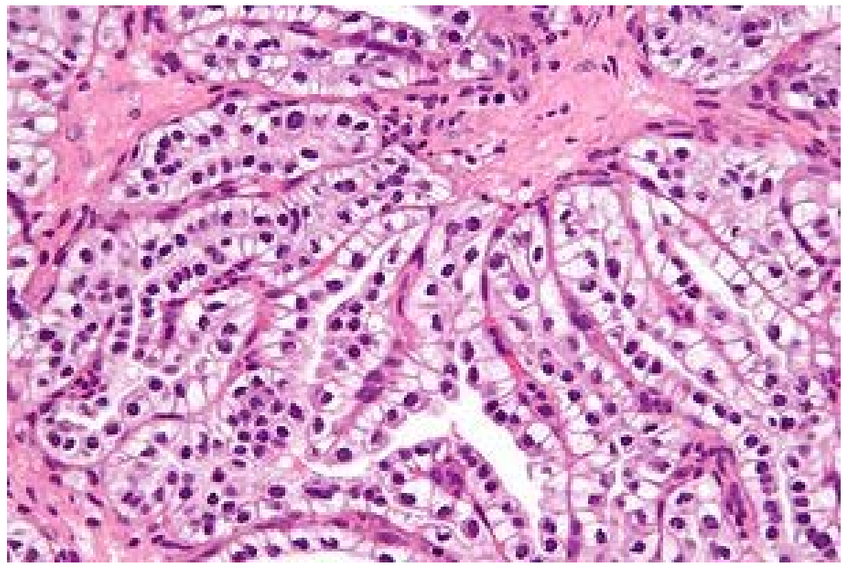
Arm?

Based on CARMENA trial, cytoreductive nephrectomy no longer standard of care for mRCC—*except* in patients with excellent PS or intermediate-risk patients with only one IMDC risk factor.

Case 2: Wait no – it's papillary. What systemic therapy would you offer?

- Cabozantinib
- Pembrolizumab
- Nivolumab with Ipilimumab
- Clinical Trial

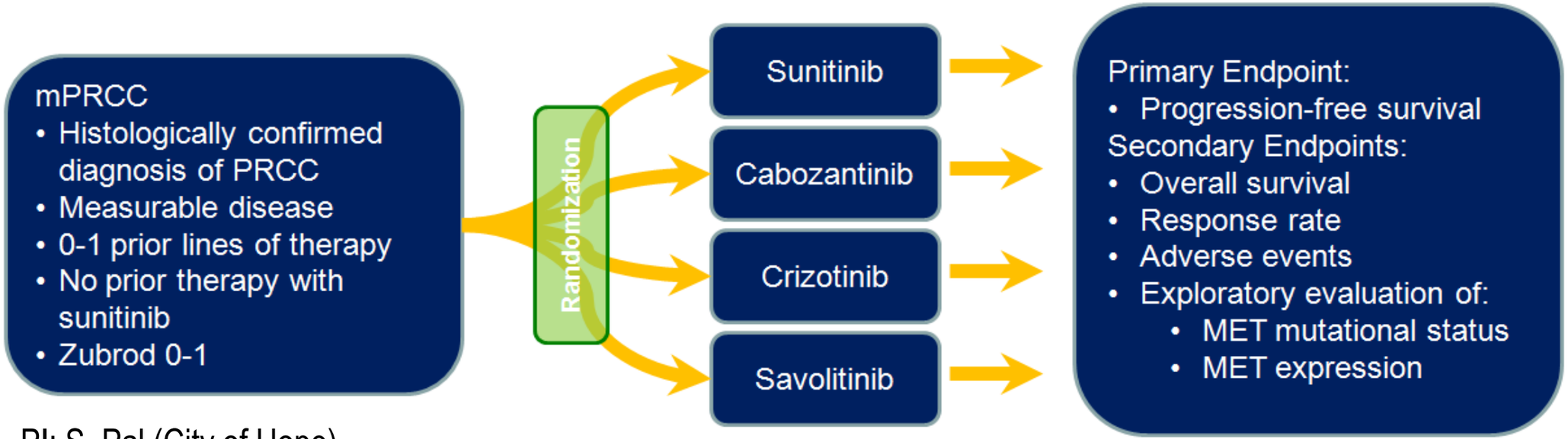
Case 2: Systemic Therapy for Papillary RCC?



Clinical trial.

No standard of care exists for PRCC. The PAPMET study compares sunitinib to cabozantinib – the original study design included two additional MET inhibitors.

Clinical Trial: SWOG 1500 for mPRCC



- PI: S. Pal (City of Hope)
- Translational PI: B. Shuch (Yale)
  - BISQFP funding for genomic characterization

- Requires 41 pts/arm → 164 pts total
- Assuming 10% ineligibility → 180 pts total

119 patients accrued!

NCT02761057: A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib [NSC #761968], Crizotinib [NSC #749005], Savolitinib [NSC #785348], and Sunitinib [NSC #736511]) in Metastatic Papillary Renal Carcinoma (PAPMET)

Case 3: Clear cell RCC patient has autoimmune disease. Which do you choose?

- Cabozantinib
- Pembrolizumab
- Nivolumab with Ipilimumab
- Clinical Trial

DFCI Experience (ASCO GU 2019)

	RCC			UC		
	AD	No AD	P	AD	No AD	P
N	25	246		27	193	
Ad Exacerbation, N(%)						
• **Overall**	8(32)			12(44)		
• **Grade 3/4**	1(4)			4(15)		
New irAE, N (%)						
• **Overall**	12(48)	107(44)		9(33)	66(34)	
• **Grade 3/4**	2(8)	30(12)		3(11)	20(10)	
Cumulative incidence at 6mos, % (95%CI)						
• **New irAE**	50(28-69)	37(31-43)	0.69	27(11-45)	33(26-40)	0.64
CPI Discontinuation						
• **For toxicity**	12(3-29)	8(5-12)	0.84	16(5-32)	6(3-10)	0.48
• **For progression**	40(21-59)	39(32-45)	0.72	47(27-65)	56(48-63)	0.17
ORR, %(95%CI)	44(24-65)	31(25-37)	0.18	42(22-63)	32(24-39)	0.35
2yr OS, %(95%CI)	54(31-72)	55(47-63)	0.79	52(24-74)	35(26-44)	0.11

Case 3: Systemic Therapy for ccRCC with Autoimmune Disease

Cabozantinib

The patient has autoimmune disease. Worried about exacerbation of AD if I were to use immunotherapy.