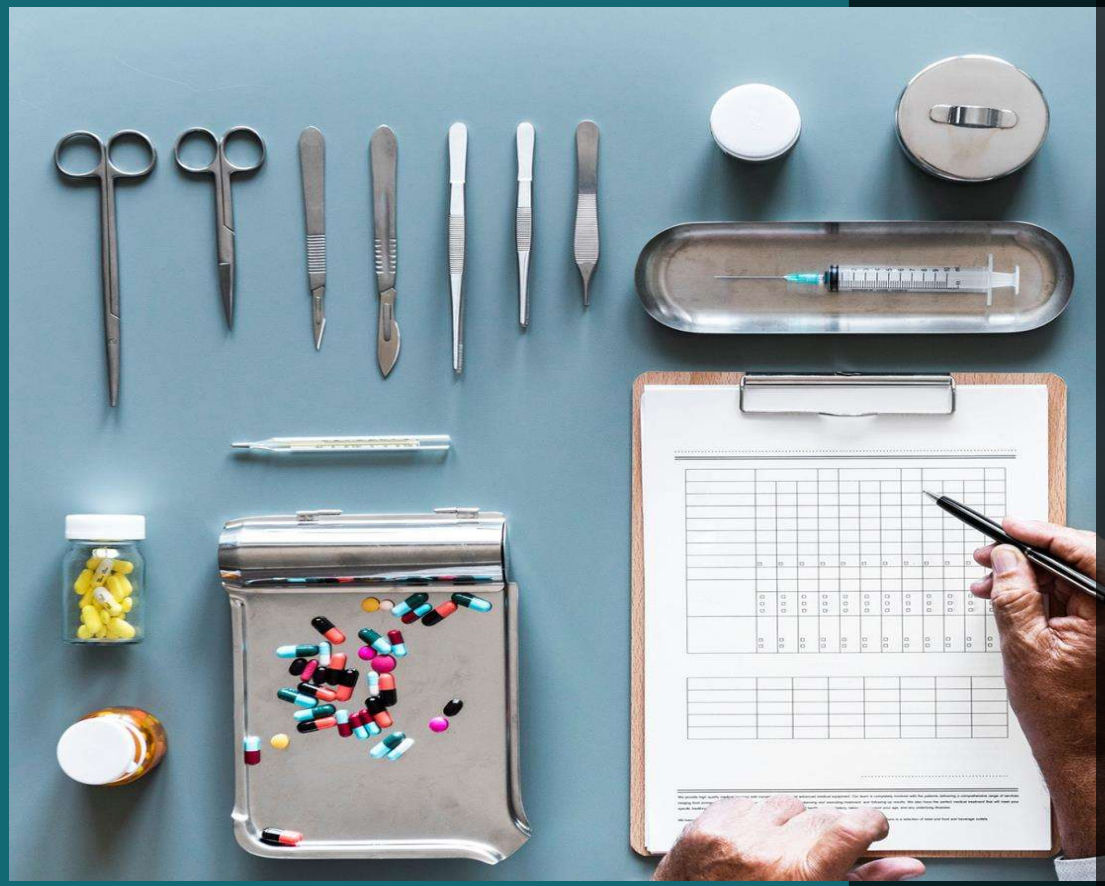
Targeted Therapies in Metastatic RCC: Monotherapy versus Combination Therapy

Primo N Lara, Jr., MD
Director, University of California Davis Comprehensive Cancer Center
Professor of Medicine and Executive Associate Dean for Cancer Programs
UC Davis School of Medicine, Sacramento, CA

UCDAVIS COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

- **Consulting**
  - Pfizer, Exelixis, Astra Zeneca, Genentech, Merck, BMS, Nektar
- **Research Support (to UC Davis)**
  - Tracon, Janssen, Merck, Incyte, Pharmacyclics
- **The field is moving too damn fast**



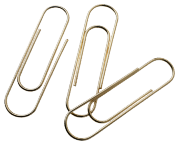
Metastatic RCC: Treatment Considerations

1. Risk stratification
2. Suitability for cytoreduction
3. Eligibility for frontline IO-based combination therapy
4. New treatment initiated at time of progression or unacceptable toxicity
5. Predictive biomarkers

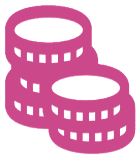
mRCC Treatment Principles

1. Goal is CURE
   - … or prolongation of life
2. Immunotherapy offers best chance for cure
   - Combination IO-based therapy now frontline standard of care for most patients
3. Angiogenesis is active throughout ccRCC natural history
   - Allows for within-class sequential therapy

Monotherapy has hypothetical advantages



Simplicity



Lower cost

Tolerability

Improved Adherence

Reduced drug-drug interactions

mRCC used to be dominated by monotherapy

Single-agent Angiogenesis Inhibitors	Single-agent mTOR Inhibitors	Single-agent Immunotherapy	Combinations
• Sunitinib • Pazopanib • Cabozantinib • Axitinib • Sorafenib • Bevacizumab	• Everolimus • Temsirolimus	• HD IL2 • Nivolumab	• Bevacizumab + IFN • Nivolumab + Ipilimumab • Lenvantinib + Everolimus

FDA-approved agents in mRCC

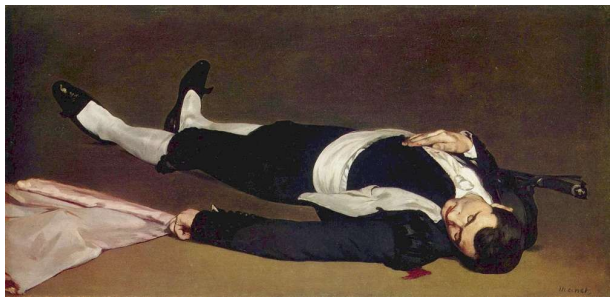
mRCC used to be dominated by monotherapy

Single-agent Angiogenesis Inhibitors	Single-agent mTOR Inhibitors	Single-agent Immunotherapy	Combinations
• Sunitinib • Pazopanib • Cabozantinib • Axitinib • Sorafenib • Bevacizumab	• Everolimus • Temsirolimus	• HD IL2 • Nivolumab	• Bevacizumab + IFN • Nivolumab + Ipilimumab • Lenvantinib + Everolimus • Pembrolizumab + Axitinib • Avelumab + Axitinib • (Bevacizumab + Atezolizumab)

… but active combinations are rapidly becoming established as SOC

Fate of mRCC Monotherapy Control Arms

Interferon



Everolimus

Sunitinib

Scorecard: Frontline RCC

Pivotal Trial	N	Response Rate (%)	Median PFS (months)	Median OS (months)
Sunitinib vs. IFN-α [1]	750	47 vs. 12	11 vs. 5	26.4 vs. 21.8
Bevacizumab + IFN-α vs. IFN-α [2]	649	31 vs. 12	10.4 vs. 5.5	23.3 vs. 21.3
	732	25.5 vs. 13.1	8.4 vs. 4.9	18.3 vs. 17.4
Pazopanib vs. placebo [3]	233	30 vs. 3	11.1 vs. 2.8	22.9 vs. 20.5
Pazopanib vs. Sunitinib [4]	1,110	31 vs. 25	8.4 vs. 9.5	28.4 vs. 29.3
Cabozantinib vs. Sunitinib (intermediate/poor risk)* [5]	157	46 vs. 18	8.2 vs. 5.6	30 vs. 21.8
Temsirolimus vs. IFN-α (poor risk) [6]	626	8.6 vs. 4.8	5.5 vs. 3.1	10.9 vs. 7.3
Nivo/Ipi vs. Sunitinib (interm./poor risk)[7]	1,070	41.6 vs. 26.5	11.5 vs. 8.4	NR vs 26
Atezo/Bev vs Sunitinib (PDL1+ group)[8]**	915 (ITT); 362(PDL1+)	43 vs 35	11.2 vs. 7.7 (Inv Review)	NR vs 23.3
Avelumab/Axitinib vs. Sunitinib[9]	886	55 vs 25.5	13.8 vs 8.4	NR
Pembrolizumab/Axitinib vs. Sunitinib[10]	840	59 vs 36	15 vs 11	NR

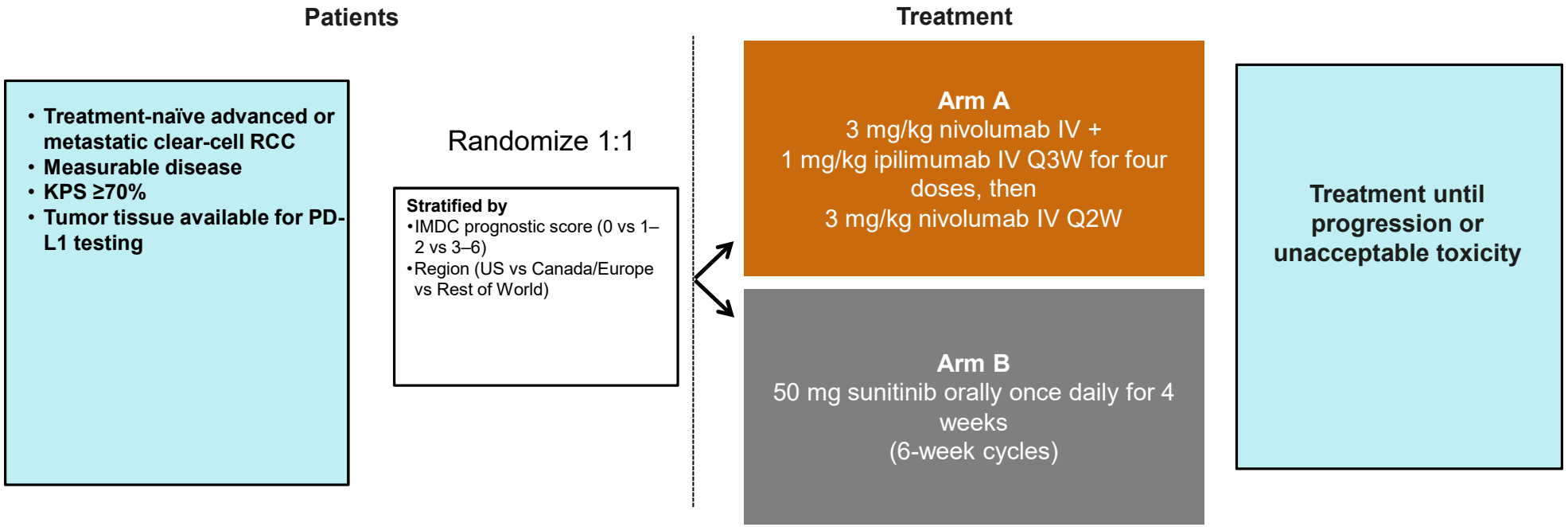
* Phase II trial

** Not yet FDA approved

Angiogenesis inhibition | mTOR inhibition | IO-based therapy

1)Motzer NEJM 2007,2)Escudier Lancet 2007, 3)Stemberg JCO 2010, 4)Motzer NEJM 2013, 5)Choueiri JCO 2017,6)Hudes NEJM 2007, 7)Motzer NEJM 2018; 8) Basappa Can Urol Assoc J. 2017; 9) NEJM 2019; 10) Rini, NEJM 2019

CheckMate 214:
Nivolumab/Ipilumumab vs. Sunitinib in mRCC



Co-primary end points: Overall survival (alpha level, 0.04), Objective Response Rate (alpha level, 0.001), Progression-free survival (alpha level, 0.009) among patients with intermediate or poor prognostic risk.

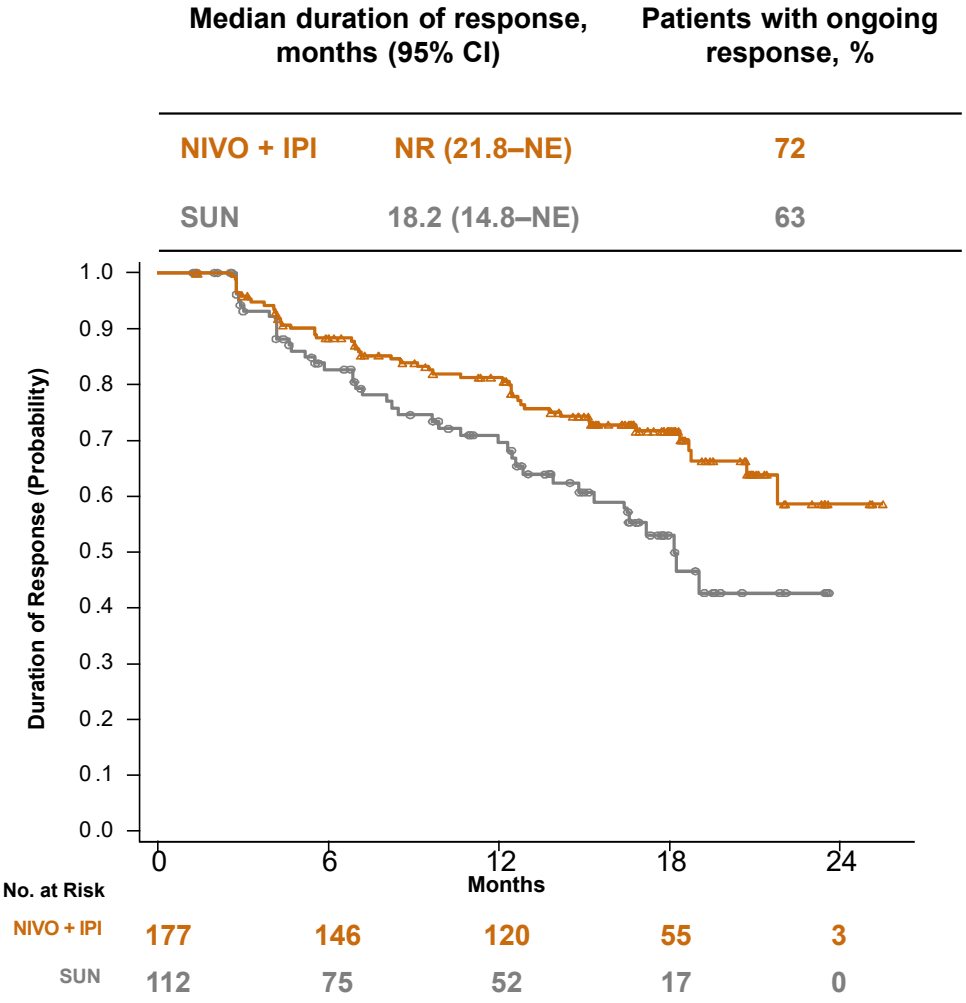
Motzer, NEJM 2018

Co-primary endpoint: ORR

ORR and DOR: IMDC intermediate/poor risk

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9[b]**	**1[b]**
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

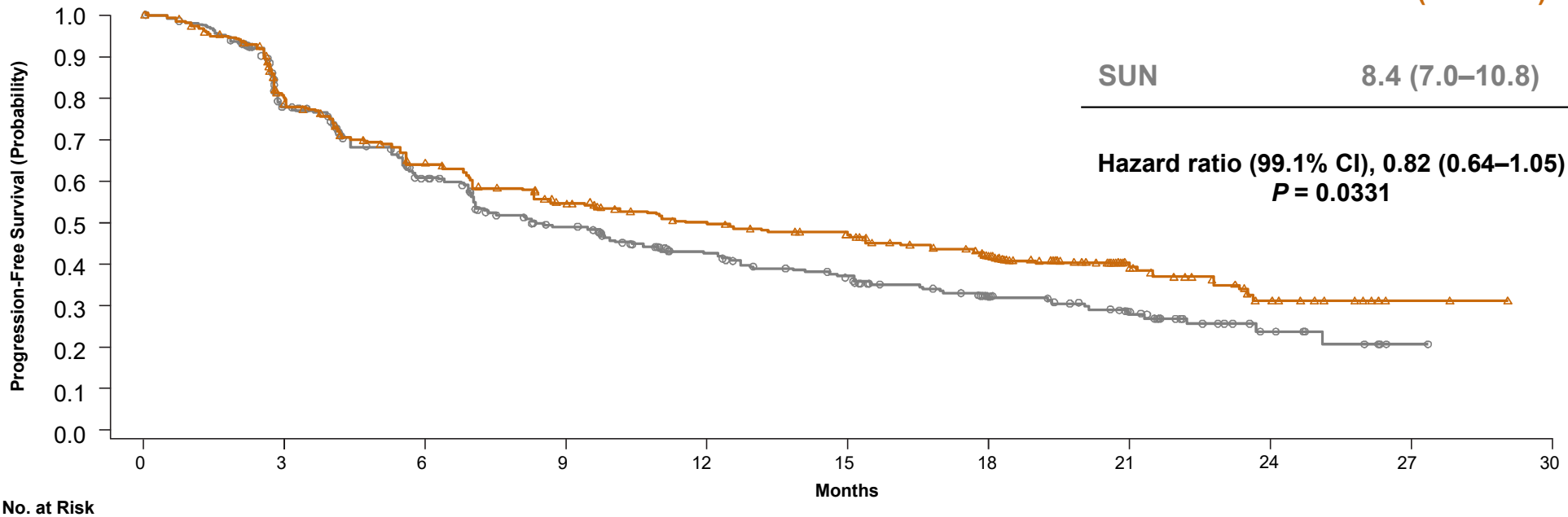


Co-primary endpoint

PFS per IRRC: IMDC intermediate/poor risk

Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

Hazard ratio (99.1% CI), 0.82 (0.64–1.05)
P = 0.0331



No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

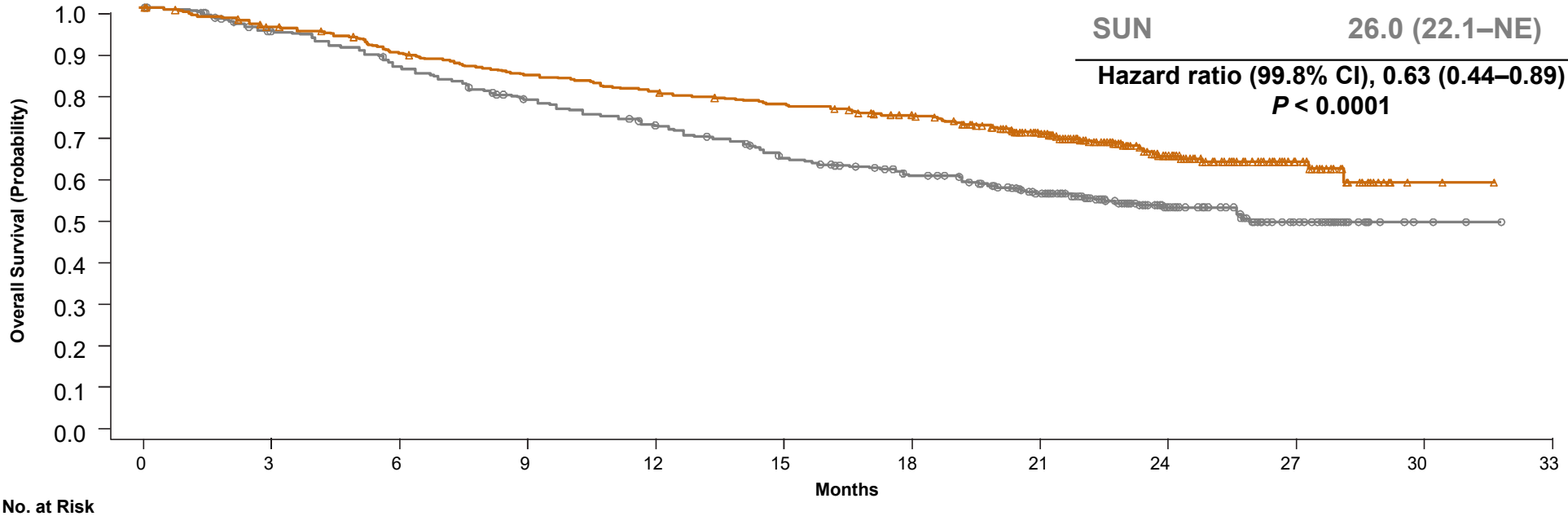
Co-primary endpoint

OS: IMDC intermediate/poor risk

Median OS, months (95% CI)

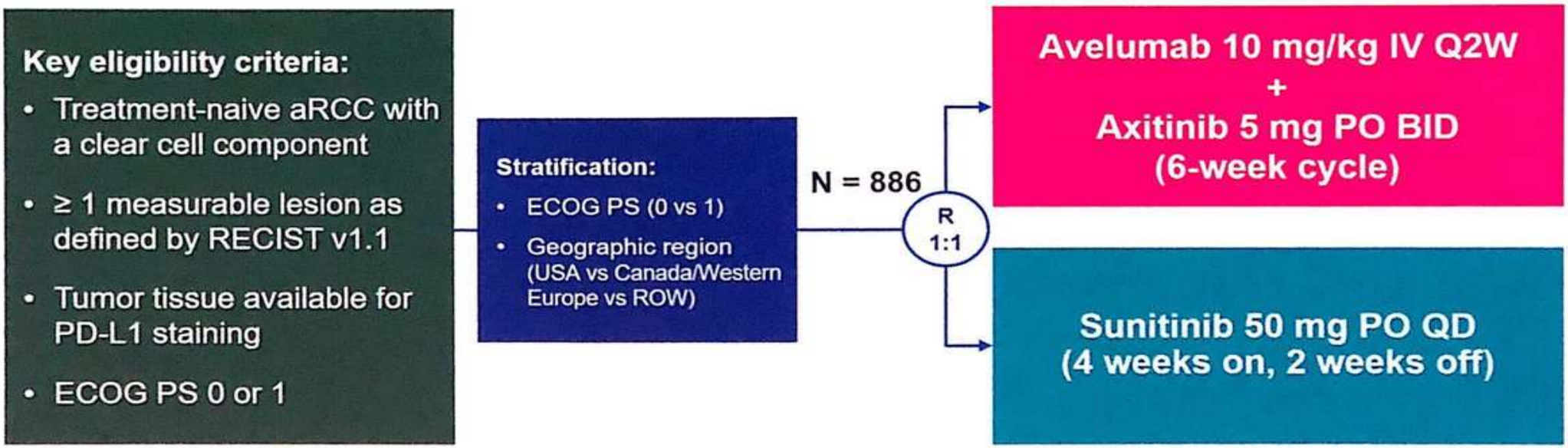
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

Hazard ratio (99.8% CI), 0.63 (0.44–0.89)
***P* < 0.0001**



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

JAVELIN Renal 101: study design

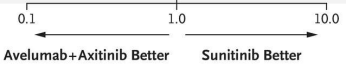


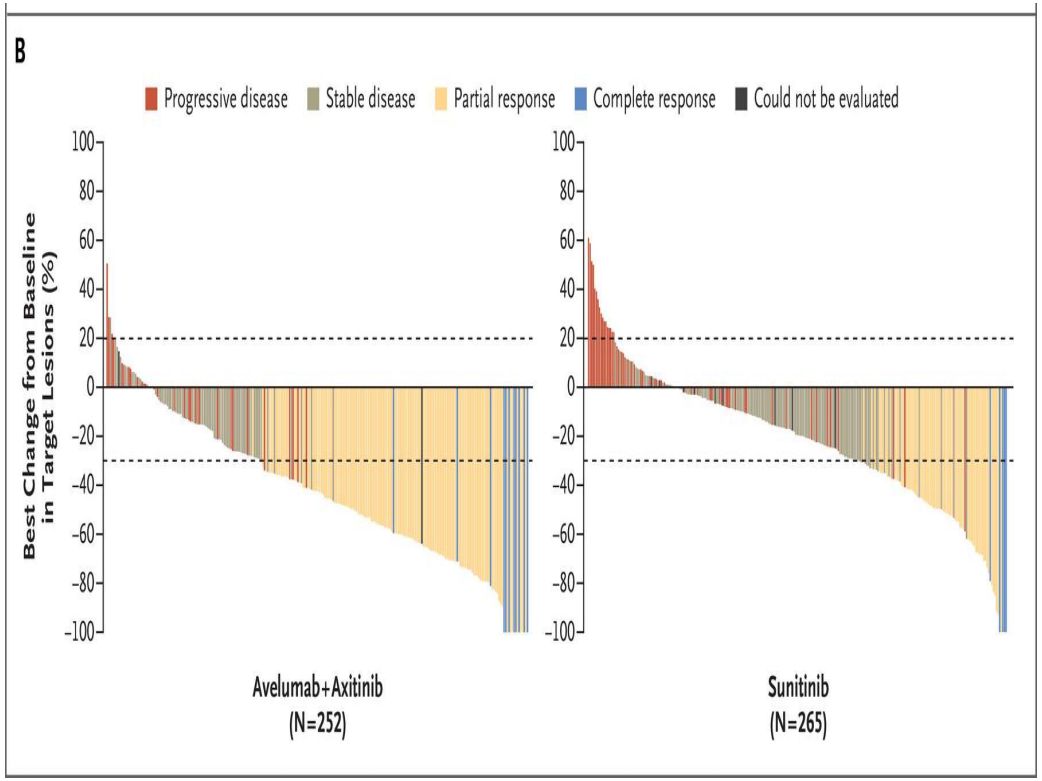
BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

Javelin 101: Avelumab*/Axitinib vs Sunitinib

A

Subgroup	Avelumab+Axitinib	Sunitinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
All patients	108/270	145/290	0.63 (0.49–0.81)
Age			
<65 yr	71/165	101/189	0.60 (0.44–0.81)
≥65 yr	37/105	44/101	0.71 (0.46–1.09)
Sex			
Male	76/203	113/224	0.56 (0.42–0.75)
Female	32/67	32/66	0.90 (0.55–1.47)
Geographic region			
United States	28/75	36/82	0.58 (0.35–0.96)
Canada and Western Europe	33/80	50/81	0.47 (0.30–0.74)
Rest of the world	47/115	59/127	0.78 (0.53–1.15)
ECOG performance-status score			
0	61/168	97/193	0.56 (0.41–0.78)
1	47/102	48/97	0.73 (0.48–1.09)
Nephrectomy			
Yes	95/233	126/252	0.63 (0.48–0.82)
No	13/37	19/38	0.63 (0.31–1.29)
MSKCC prognostic risk group			
Favorable	16/52	24/60	0.57 (0.30–1.08)
Intermediate	71/180	101/201	0.62 (0.46–0.84)
Poor	19/33	17/24	0.55 (0.28–1.08)
IMDC prognostic risk group			
Favorable	14/52	24/59	0.50 (0.26–0.97)
Intermediate	68/173	93/191	0.64 (0.47–0.88)
Poor	26/44	27/39	0.53 (0.30–0.93)
Body-mass index			
<25	45/93	51/81	0.57 (0.38–0.86)
≥25	63/176	93/206	0.63 (0.45–0.87)
Smoking status			
Never smoked	51/136	57/138	0.69 (0.47–1.01)
Current or former smoker	56/133	88/152	0.58 (0.42–0.82)

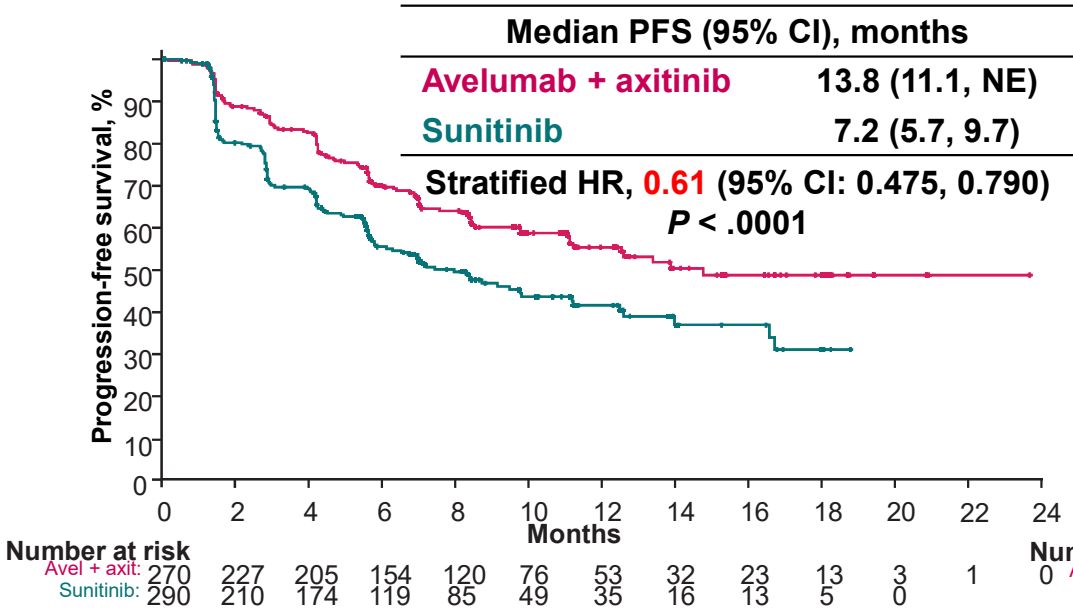




Motzer, NEJM 2019

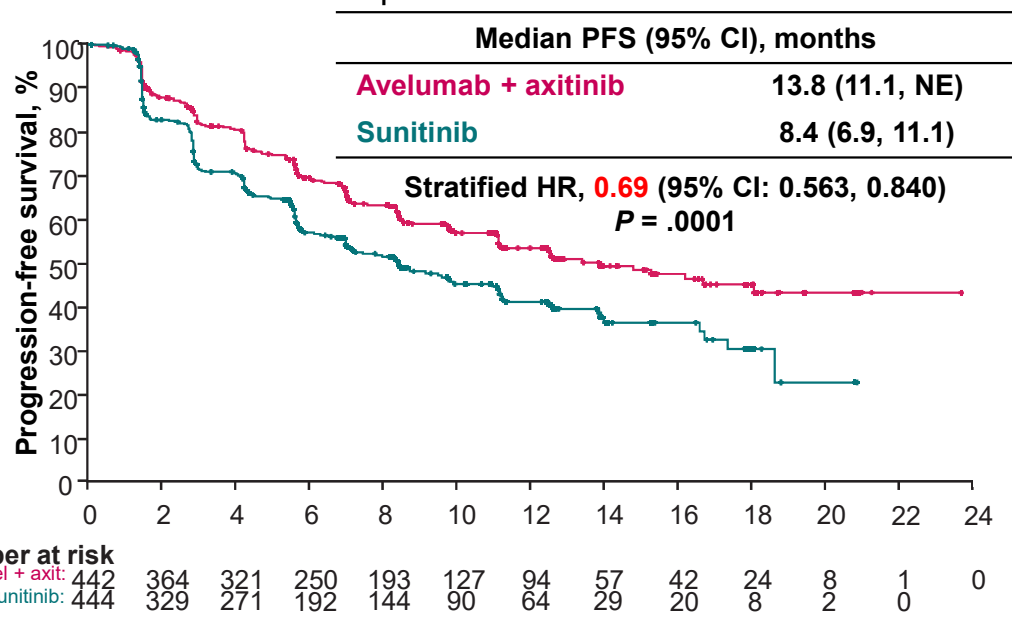
Javelin 101: Avelumab*/Axitinib vs Sunitinib

PD-L1+ (n=560)



ITT (n=886)

Motzer et al. presidential session ESMO 2018

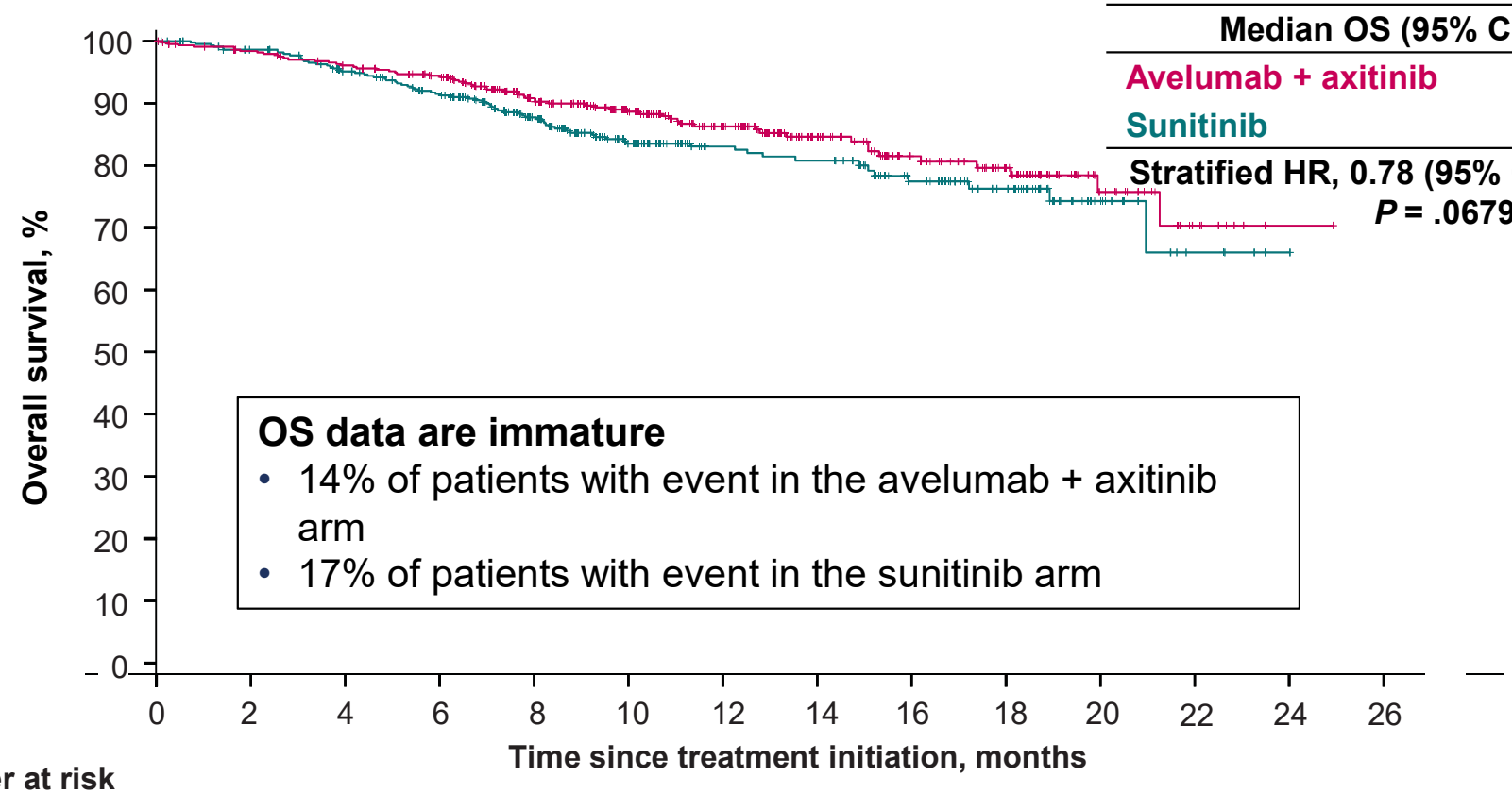


Months

*Anti-PDL1 Antibody

Motzer, NEJM 2019

Javelin 101: Avelumab*/Axitinib vs Sunitinib



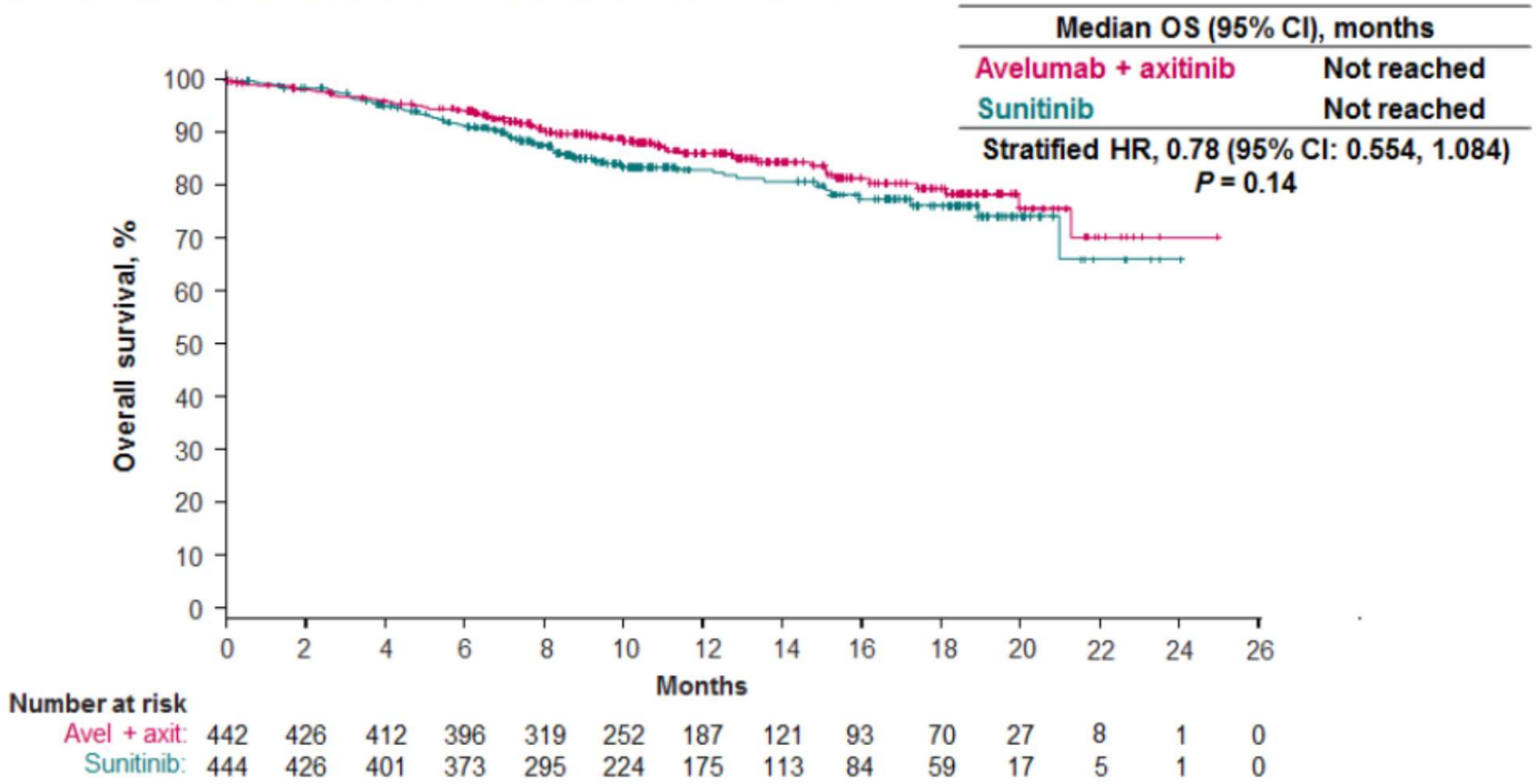
Number at risk

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

Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

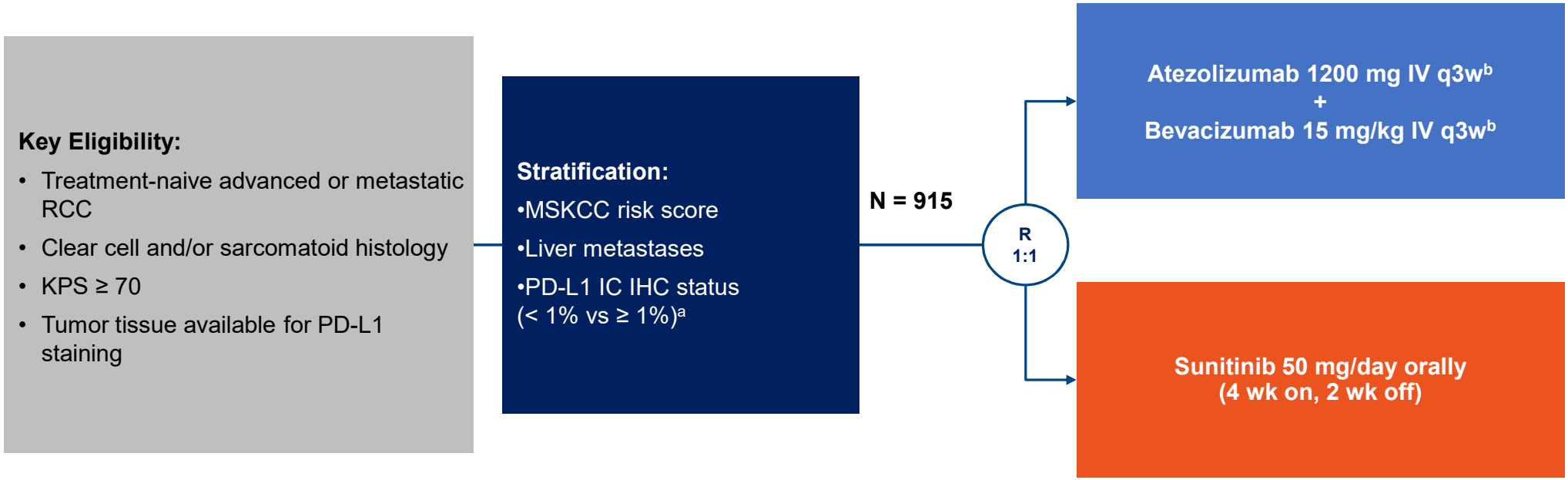
Motzer et al. ESMO 2018

Figure S3. Kaplan-Meier Plot of Overall Survival in the Overall Population.



Motzer, NEJM 2019

IMMotion 151: Atezolizumab/Bevacizumab vs. Sunitinib in mRCC



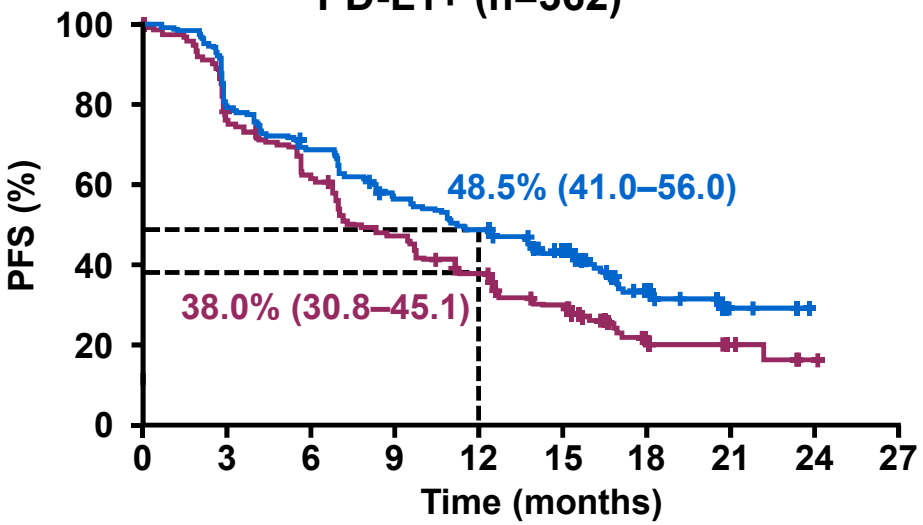
Coprimary endpoints:

- Progression-free survival (by investigator per RECIST v1.1) in PD-L1+ pts (≥ 1% IC)
- Overall survival in intent-to-treat (ITT) pts.

[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

IMMotion 151: Atezolizumab/Bevacizumab vs. Sunitinib in mRCC

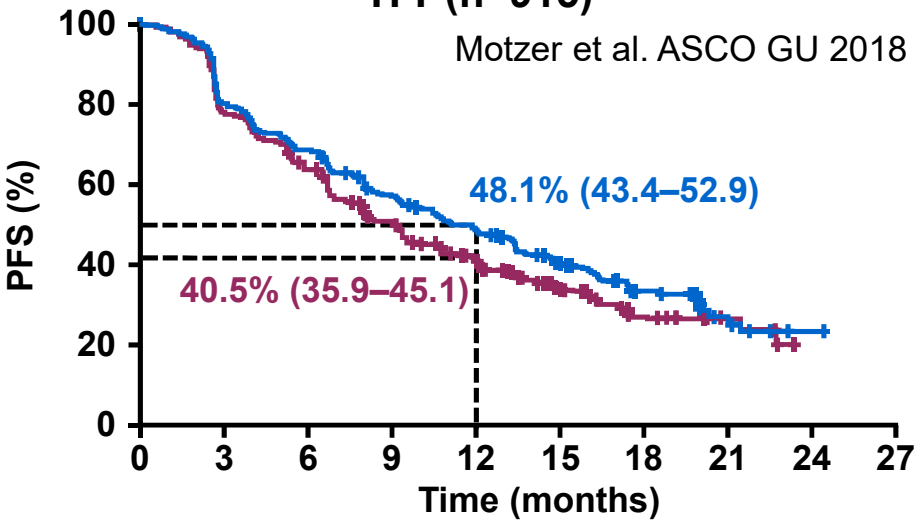
PD-L1+ (n=362)



	Median PFS, months (95% CI)
Atezolizumab + bevacizumab	11.2 (8.9–15.0)
Sunitinib	7.7 (6.8–9.7)
p=0.02	**HR=0.74** (95% CI, 0.57–0.96)

ITT (n=915)

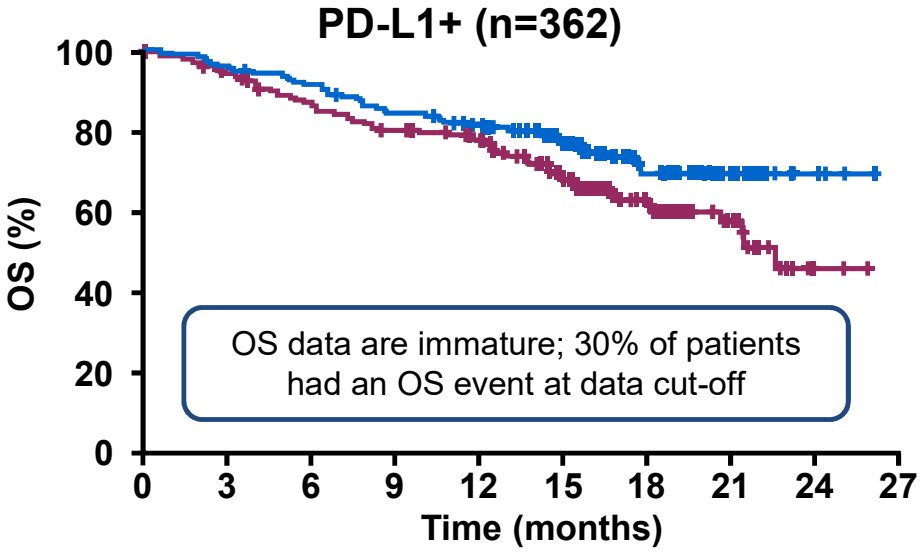
Motzer et al. ASCO GU 2018



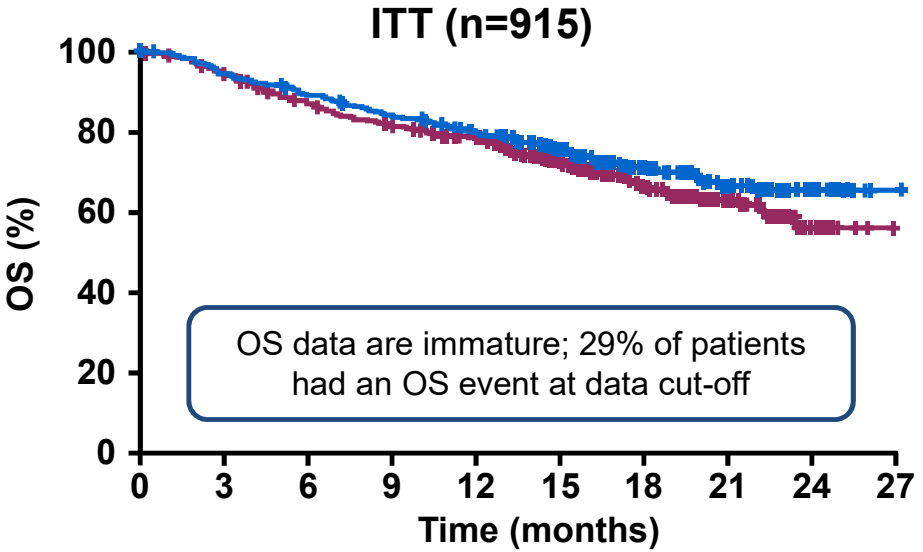
	Median PFS, months (95% CI)
Atezolizumab + bevacizumab	11.2 (9.6–13.3)
Sunitinib	8.4 (7.5–9.7)
	HR=0.83 (95% CI, 0.70–0.97)

IMMotion 151: Atezolizumab/Bevacizumab vs. Sunitinib in mRCC

- Minimum follow-up, 12 months. Median follow-up, 15 months. Event/patient ratio: 25% for atezolizumab + bevacizumab, 35% for sunitinib



	Median OS, months (95% CI)
Atezolizumab + bevacizumab	NR
Sunitinib	23.3 (23.1–NR)
	HR=0.68 (95% CI, 0.46–1.00)



	Median OS, months (95% CI)
Atezolizumab + bevacizumab	NR
Sunitinib	NR
p=0.09	**HR=0.81** (95% CI, 0.63–1.03)

Motzer et al. ASCO GU 2018

KEYNOTE-426 Study Design

Key Eligibility Criteria

- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECIST v1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

Stratification Factors

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

R (1:1)

N = 432

Pembrolizumab 200 mg IV Q3W for up to 35 cycles
+
Axitinib 5 mg orally twice daily[a]

N = 429

Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle[b]

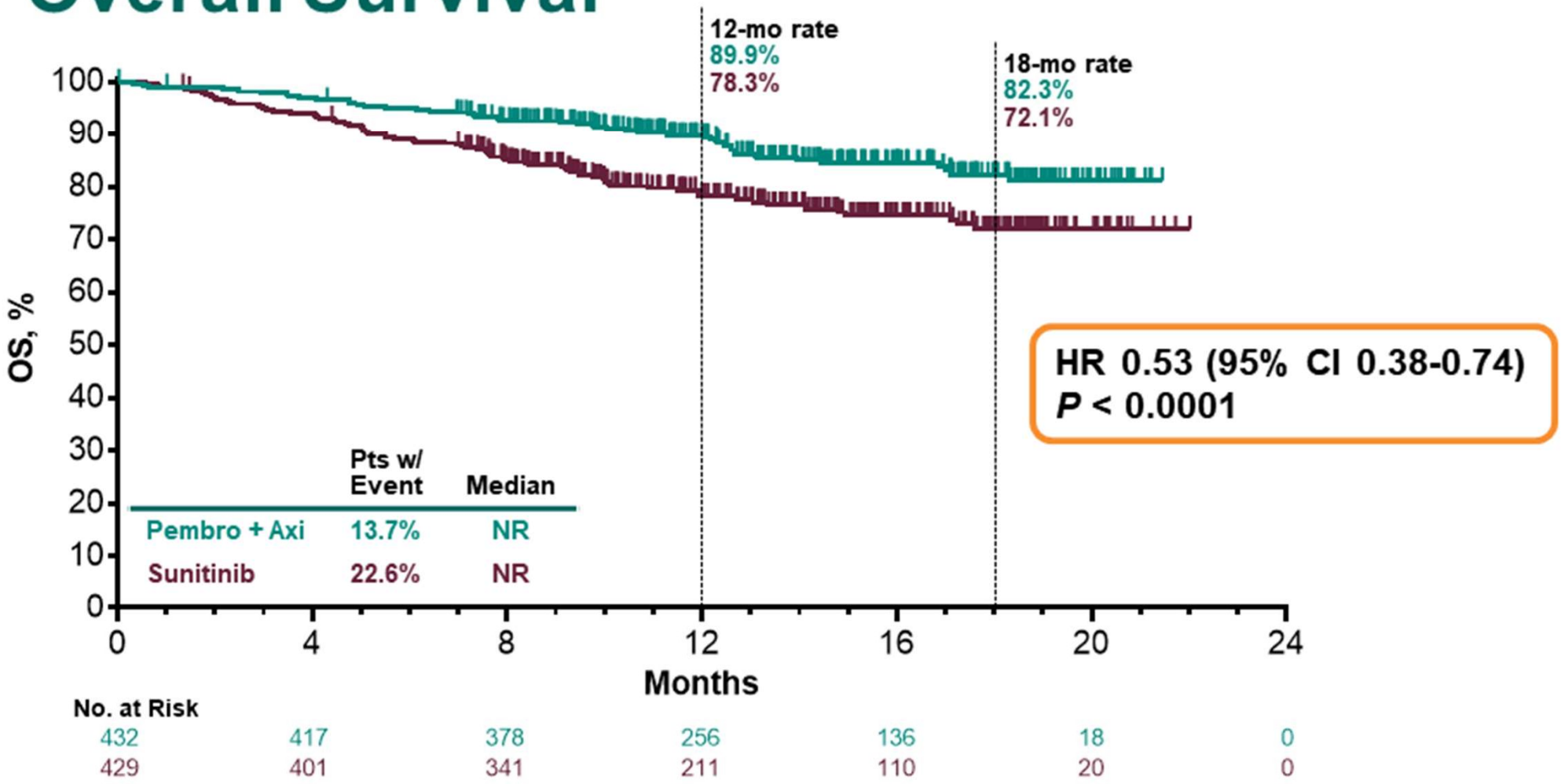
End Points

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

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Powles KN426 ASCO-GU 2019

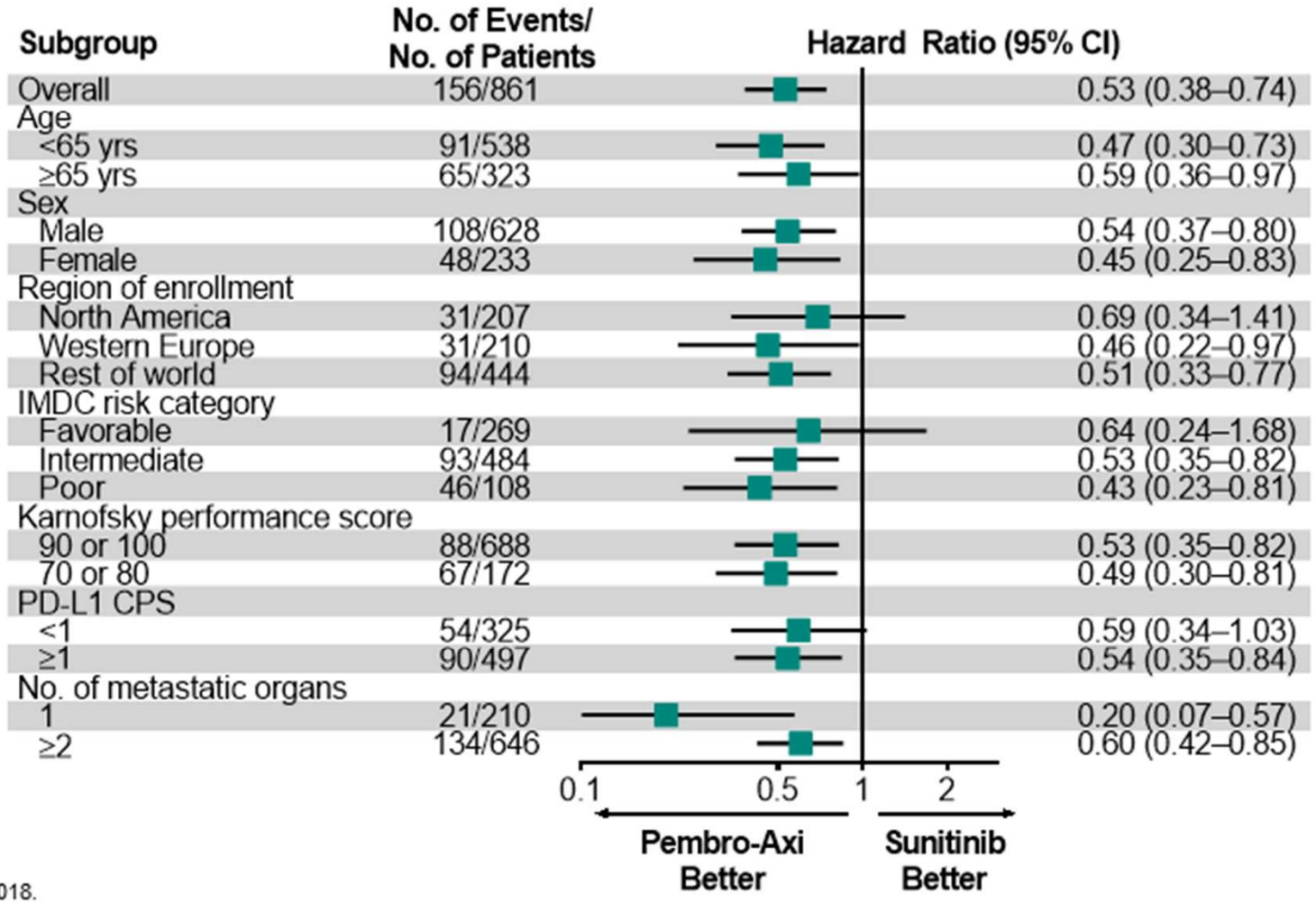
Overall Survival



HR 0.53 (95% CI 0.38-0.74)
P < 0.0001

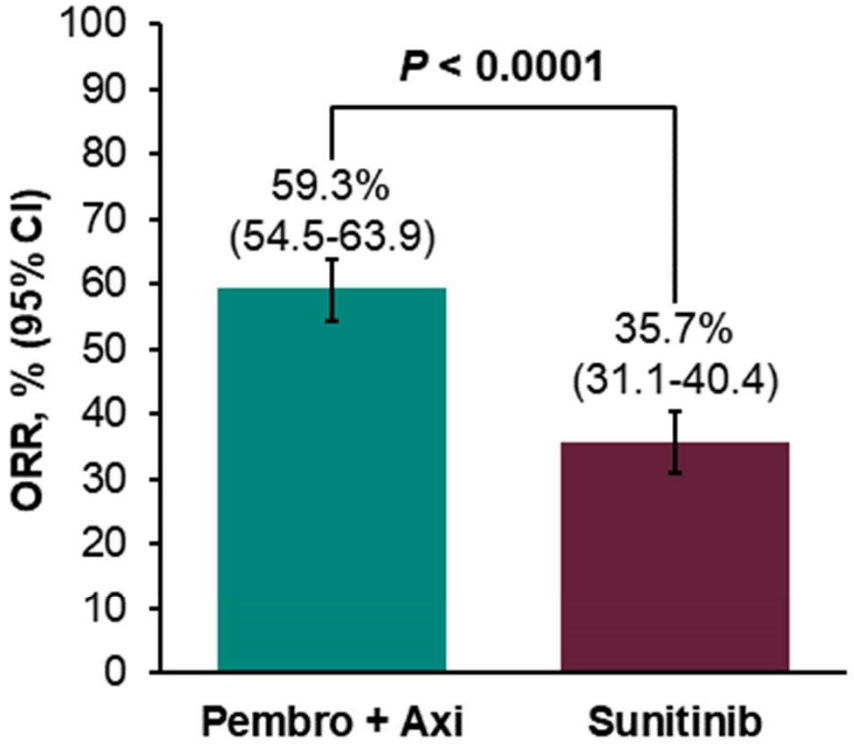
Data cutoff date: Aug 24, 2018.

Overall Survival in Key Subgroups



Data cutoff date: Aug 24, 2018.

Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib 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[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Frontline mRCC:
Who still deserves HD-IL2 monotherapy?

- HD IL2 still listed as a monotherapy option in some guidelines
  - Reserved for robust patients with excellent PS and normal end-organ function
- Subset of patients who benefit from checkpoint inhibitors likely overlaps with those who benefit from HD IL2
- HD IL2 has a rapidly diminishing role

Frontline mRCC:

Who deserves VEGFR-TKI monotherapy (circa August 2019)?

1. Ineligible for IO
   - Active autoimmune disease
   - Supra-physiologic corticosteroid therapy
2. Refuses IO
3. **Selected patient subsets**
   - Bone-only metastases???
   - Some favorable risk patients???
   - Pembrolizumab alone???
   - Non-clear cell histology

It's tough to ignore Checkmate 214

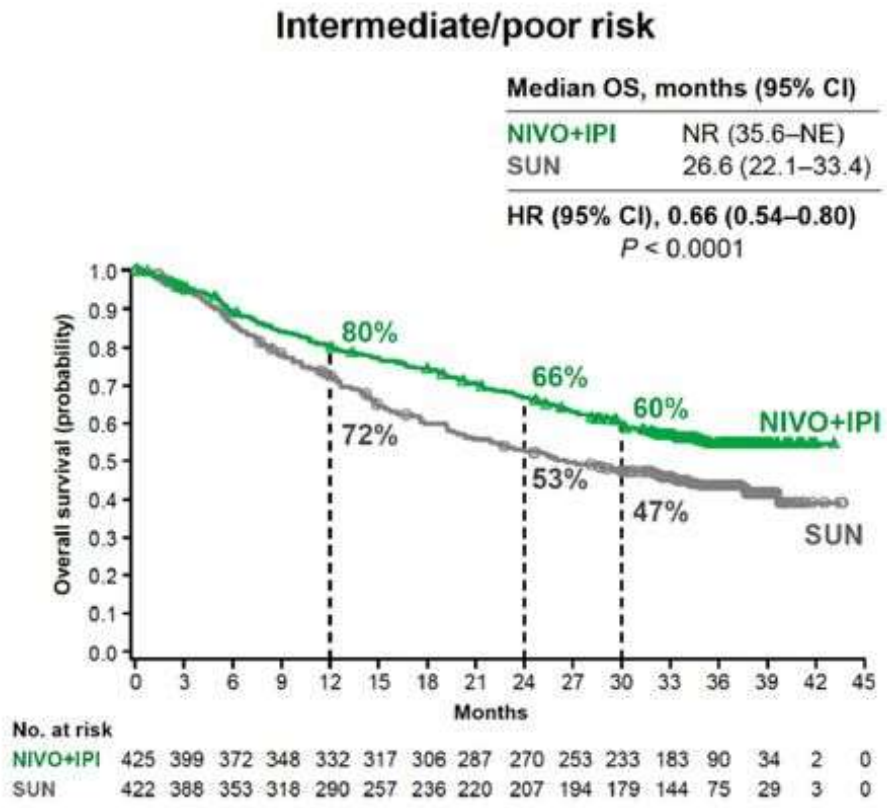
Favorable risk patients did better with sunitinib

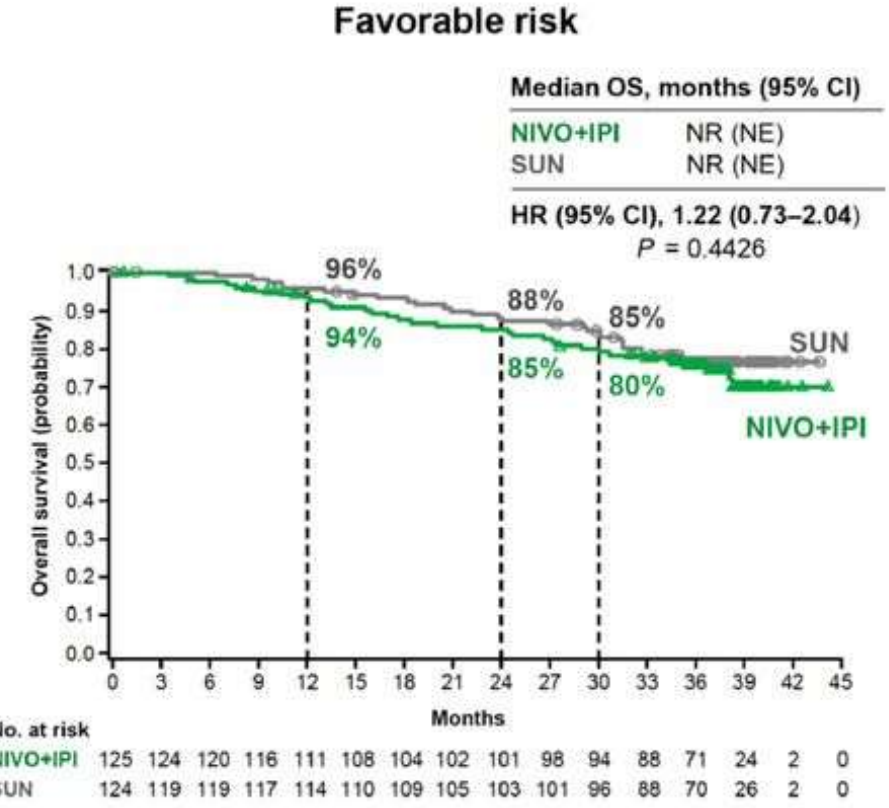
	N = 249[a]	
Outcome	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

Escudier et al ESMO 2017

It's tough to ignore Checkmate 214

Favorable risk: no OS benefit from Nivo-Ipi





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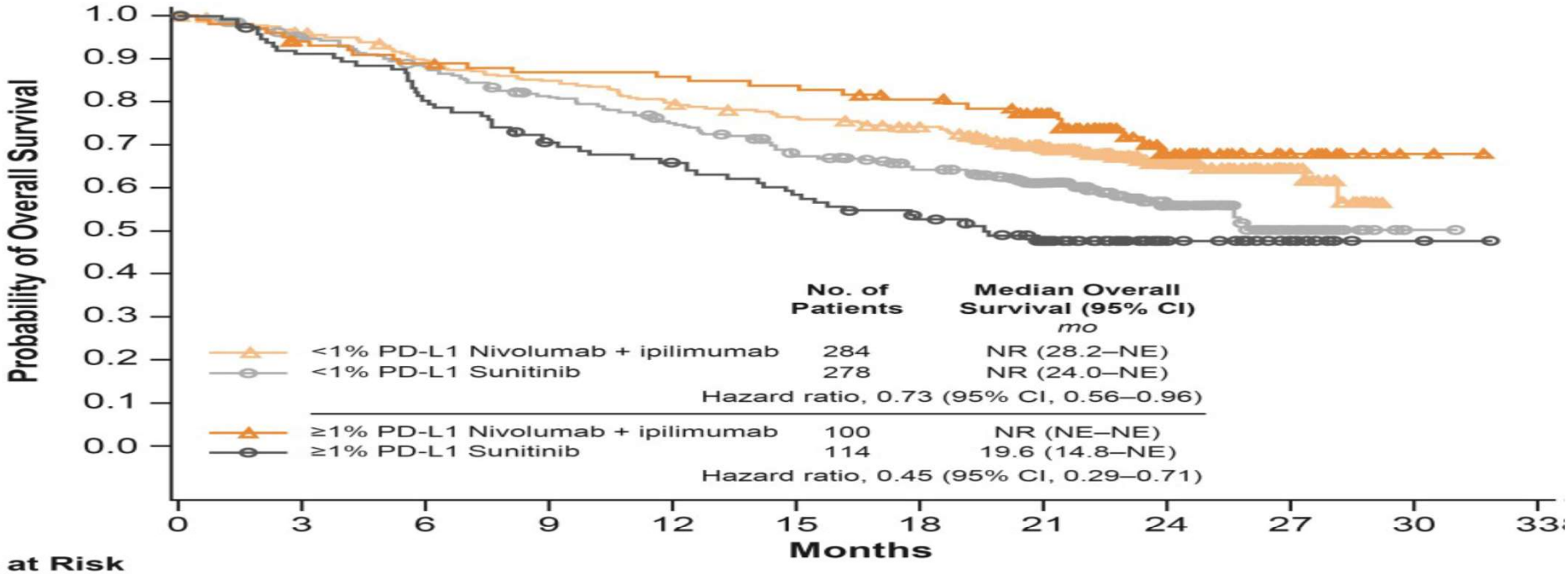
Tannir N, et al. ASCO GU 2019

Checkmate 214 - Int/Poor Risk by PDL-1 status

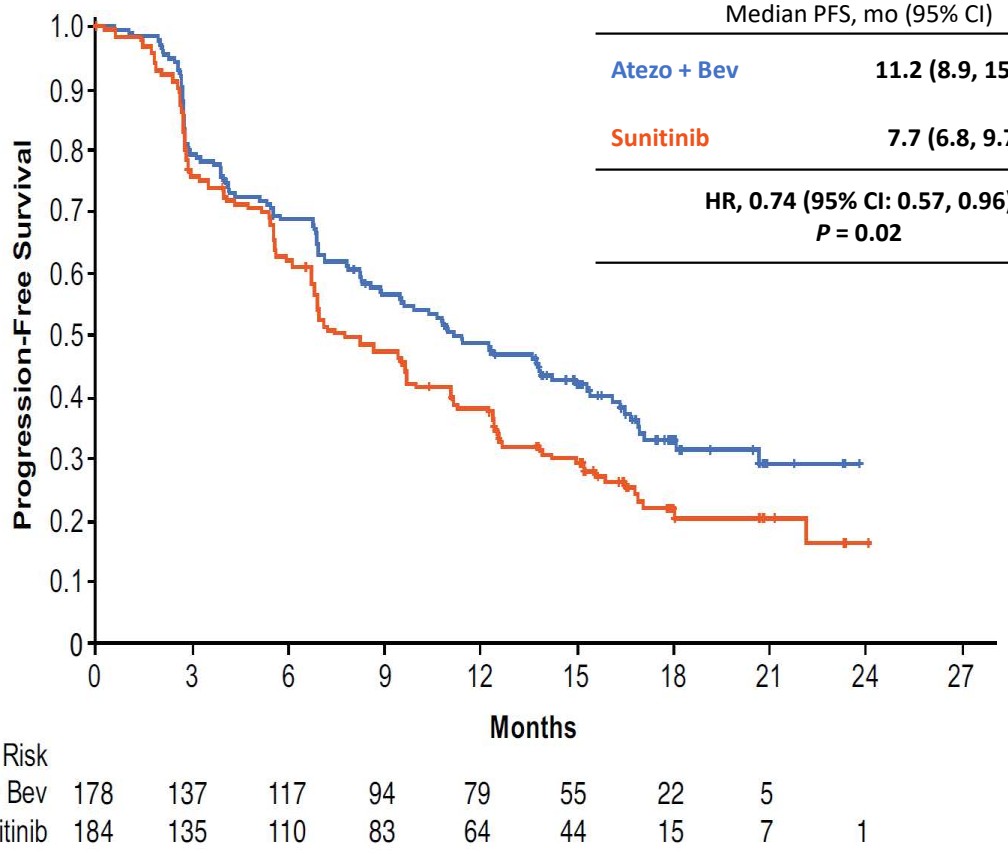
PDL1+ patients on sunitinib have worst OS



No. at Risk						
NIVO + IPI <1% PD-L1	284	251	223	200	76	0
SUN <1% PD-L1	278	239	198	157	61	1
NIVO + IPI ≥1% PD-L1	100	87	83	76	33	2
SUN ≥1% PD-L1	114	90	72	55	21	2

IMMotion 151 (all risk groups):

PDL+: worse PFS with sunitinib



Median PFS, mo (95% CI)	
Atezo + Bev	**11.2 (8.9, 15.0)**
Sunitinib	**7.7 (6.8, 9.7)**
HR, 0.74 (95% CI: 0.57, 0.96) ***P* = 0.02**	

mPFS lower than originally reported in sunitinib vs IFN trial (11 months; CI 10,12)

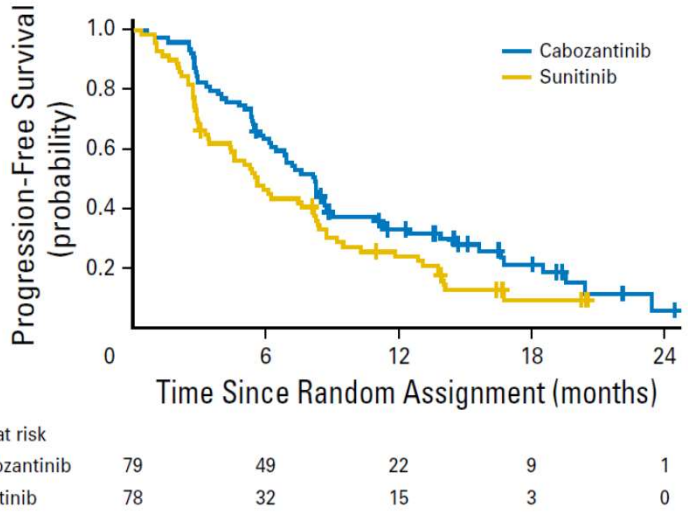
Implication:
mRCC patients with PDL+ tumors have suboptimal outcomes with single agent VEGFR TKI

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo. The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

Basappa N and Puliot F. New research in kidney cancer, ASCO-GU 2017. Can Urol Assoc J. 2017 Jun; 11(6Suppl2): S163–S165; Motzer, et al. ASCO GU 2017

Frontline VEGFR TKI Monotherapy: Phase II CABOSUN trial in Intermediate/Poor risk

Modest PFS advantage



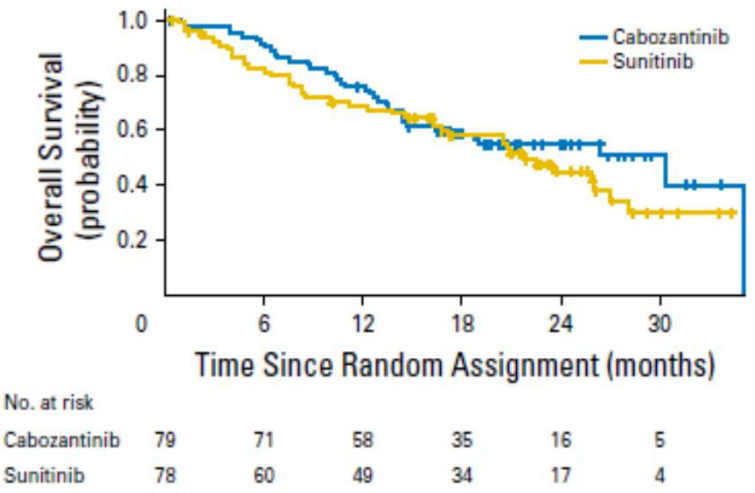


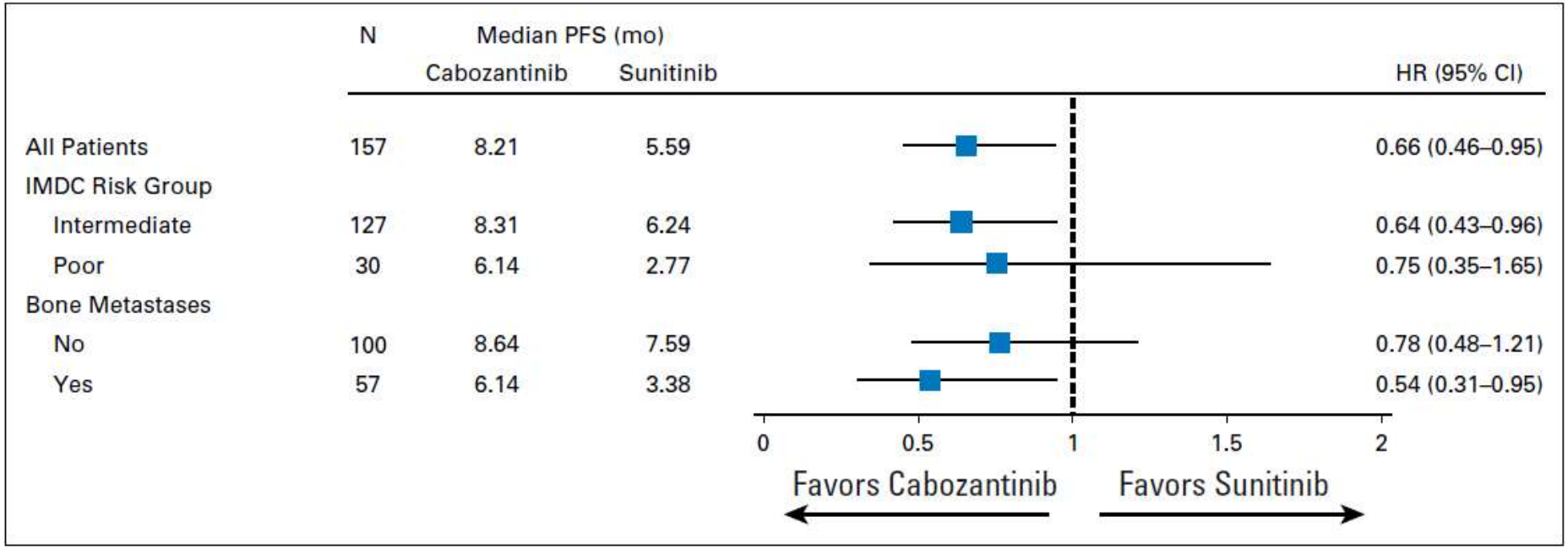
Table 2. Tumor Response

Response	Cabozantinib (n = 79)	Sunitinib (n = 78)
ORR, % (95% CI)*	33 (23 to 44)	12 (5.4 to 21)
Best overall response, No. (%)		
Confirmed CR	1 (1.3)	0
Confirmed PR	25 (31.6)	9 (11.5)
Stable disease	36 (45.6)	33 (42.3)
Progressive disease	14 (17.7)	20 (25.6)
Not evaluable or missing†	3 (3.8)	16 (20.5)

Surprisingly low response rate for sunitinib

Choueiri, JCO 2017

Frontline VEGFR TKI Monotherapy: Phase II CABOSUN trial in Intermediate/Poor risk



Patients with bone metastases preferentially benefit from cabozantinib

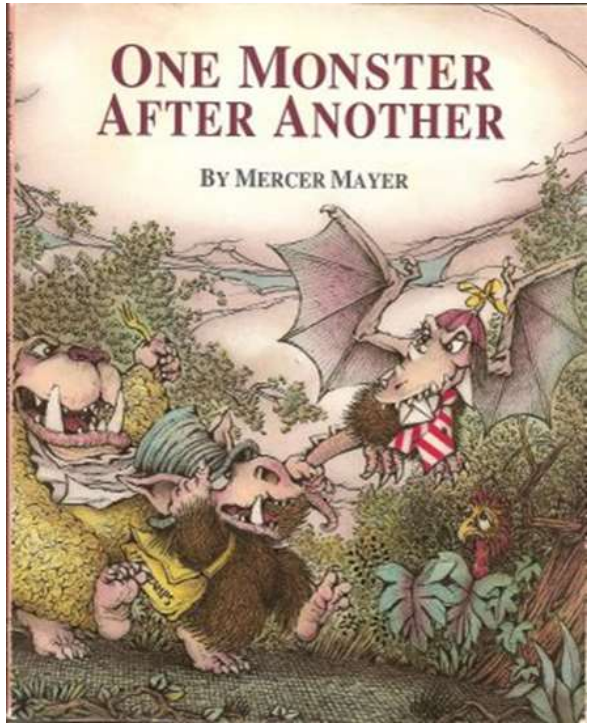
Non-Clear Cell RCC: Single-agent sunitinib is king (for now)

Trial	Treatment	Randomized?	Number Enrolled	Histology Type	Overall Response Rate	Progression-Free Survival	Overall Survival
ESPN	Sunitinib vs. everolimus	Yes	68 patients	All non-clear cell	9% vs. 3%	6.1 vs. 4.1 months	16.2 vs. 14.9 months
ASPEN	Sunitinib vs. everolimus	Yes	108 patients	All non-clear cell	18% vs. 9%	8.3 vs. 5.6 months	31.5 vs. 13.2 months
RECORD-3	Sunitinib vs. everolimus	Yes	66 patients	All non-clear cell	N/A	7.2 vs 5.1 months	N/A
SUPAP	Sunitinib	No	61 patients	Papillary	13% (type I) and 11% (type II)	6.6 months (type I) and 5.5 months (type II)	17.8 months (type I) and 12.4 months (type II)

Pal, et al. ASCO Educ Book 2017

Second-line and beyond: Who deserves monotherapy?

- Nearly all patients in the 2nd line setting are candidates for monotherapy
  - Nivolumab in VEGFR-pretreated
  - VEGFR-targeted therapy in IO-pretreated
    - Only approved combination: Lenvantinib/Everolimus
    - Sequential VEGFR-TKI therapy is reasonable
- Limited role for single-agent mTORi (everolimus)
- No justification for IFN use in modern era



Second-line options in metastatic RCC after VEGF-targeted therapy

MONOTHERAPY

Treatment option	Mode of action	Pivotal Trial	Indication
Sorafenib	VEGFR-TKI	**TARGET** (sorafenib vs placebo)	Advanced RCC in patients who have failed prior IFN-α- or IL-2-based therapy or are considered unsuitable for such therapy
Everolimus	mTOR inhibitor	**RECORD-1** (everolimus + BSC vs placebo + BSC)	Advanced RCC in patients whose disease progressed on/after VEGF-targeted therapy
Axitinib	VEGFR-TKI	**AXIS** (axitinib vs sorafenib)	Advanced RCC in adults after failure of prior treatment with sunitinib or a cytokine
Nivolumab	PD-1 inhibitor	**CheckMate-025** (nivolumab vs everolimus)	Advanced RCC after prior therapy
Cabozantinib	VEGFR, AXL and MET inhibitor	**METEOR** (cabozantinib vs everolimus)	Advanced RCC in adults following prior VEGF-targeted therapy
Lenvatinib plus everolimus	VEGFR-TKI plus mTOR inhibitor	**HOPE 205** (lenvatinib plus everolimus vs lenvatinib vs everolimus)	Advanced RCC in adults following one prior VEGF-targeted therapy

1)Escudier B, NEJM 2007, 2)Motzer RJ Lancet 2008, 3)Rini B Lancet 2011,
4)Motzer RJ NEJM 2015, 5)Motzer RJ, Lancet Oncol 2015, 6) Choueiri TK, NEJ< 2015

"Angiogenesis is active throughout mRCC natural history"

AXIS Trial: Best Response by RECIST*

Best Response (%)	Axitinib	Sorafenib
Partial response*	19.4	9.4
Stable disease	49.9	54.4
Progressive disease	21.6	21.0
Indeterminate	6.1	11.6
Risk ratio (95% CI)	2.1 (1.4–3.0)	

NOTE:
* 54% of patients received prior sunitinib

*Axitinib *vs*. sorafenib: P=0.0001

Increased frontline axitinib use in combination with Avelumab or Pembrolizumab will erode 2nd line axitinib use

Rini B, *et al.* Lancet 2011

Hypothetical Scenarios

Conclusions

- Monotherapy in frontline setting is now limited to a small and diminishing subset of patients
- Combination IO-based therapy is frontline SOC
- In 2nd line (or beyond), monotherapy remains a reasonable strategy
  - Ongoing trials are testing novel combinations in IO-refractory
- Empiric sequencing remains the standard approach
  - Biomarker enrichment is not yet in place

Kidney Cancer

Edited by: Primo N. Lara Jr. and Peter Mulders

Following on from the launch *Kidney Cancer* in summer 2017, we are now pleased to announce publication of a new issue of the journal. Click on the banner image to go straight to the issue!

Aims and Scope

Kidney Cancer is an international multidisciplinary journal to facilitate progress in understanding the epidemiology/etiology, genetics, molecular correlates, pathogenesis, pharmacology, ethics, patient advocacy and survivorship, diagnosis and treatment of tumors of the kidney. The journal publishes research reports, reviews, short communications, and letters-to-the-editor. The journal is dedicated to providing an open forum for original research in basic science, translational research and clinical medicine that will expedite our fundamental understanding and improve treatment of tumors of the kidney.

Editorial Board

Primo N. Lara Jr, MD

University of California Davis Comprehensive Cancer Center
Sacramento, CA, USA

Email: kca@iospress.com

Peter Mulders, MD, PhD

Radboud UMC Nijmegen,The Netherlands

Email: kca@iospress.com

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