Canadian Urological Association

*The **Voice** of **Urology** in Canada*

UPDATE ON THE MANAGEMENT OF RENAL CELL CARCINOMA

Accreditation

This activity is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by the Canadian Urological Association. You may claim a maximum of 1 hour (credits are automatically calculated).

Learning Objectives

At the end of this session, participants will be able to:

- Discuss first-line therapies for metastatic renal cell cancer, incorporating clinical and real-world data into current treatment algorithms
- Review the concept of dose/schedule individualization
- Explore the current landscape of first-line RCC trials

The scientific content of this program was developed by the

Canadian Urological Association

The Voice of Urology in Canada

Disclosure of Commercial Support

- This initiative was made possible through an Educational Grant by Pfizer Canada Inc.
- This program has received in-kind support from Pfizer Canada Inc. in the form of logistical support.

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All Faculty Have Adhered To the:

- CMA Code of Ethics (Update 2004)
- CMA Guidelines for Physician Interactions with Industry (2007)
- Innovative Medicines Canada (2016)

Disclosure of Commercial Support

- Potential for conflict(s) of interest:
- Pfizer developed/licenses/distributes a product which may benefit from the sale of a product that will be discussed in this program: [Avelumab, Axitinib, Sunitinib].

Faculty/Presenter Disclosures

- **This presentation discusses the off-label use of avelumab, atezolizumab, axitinib, bevacizumab, pazopanib, pembrolizumab, and sunitinib in the clinical context of treating patients with renal cell carcinoma.**

Canadian Urological Association
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Association des urologues du Canada
La voix de l'urologie au Canada.

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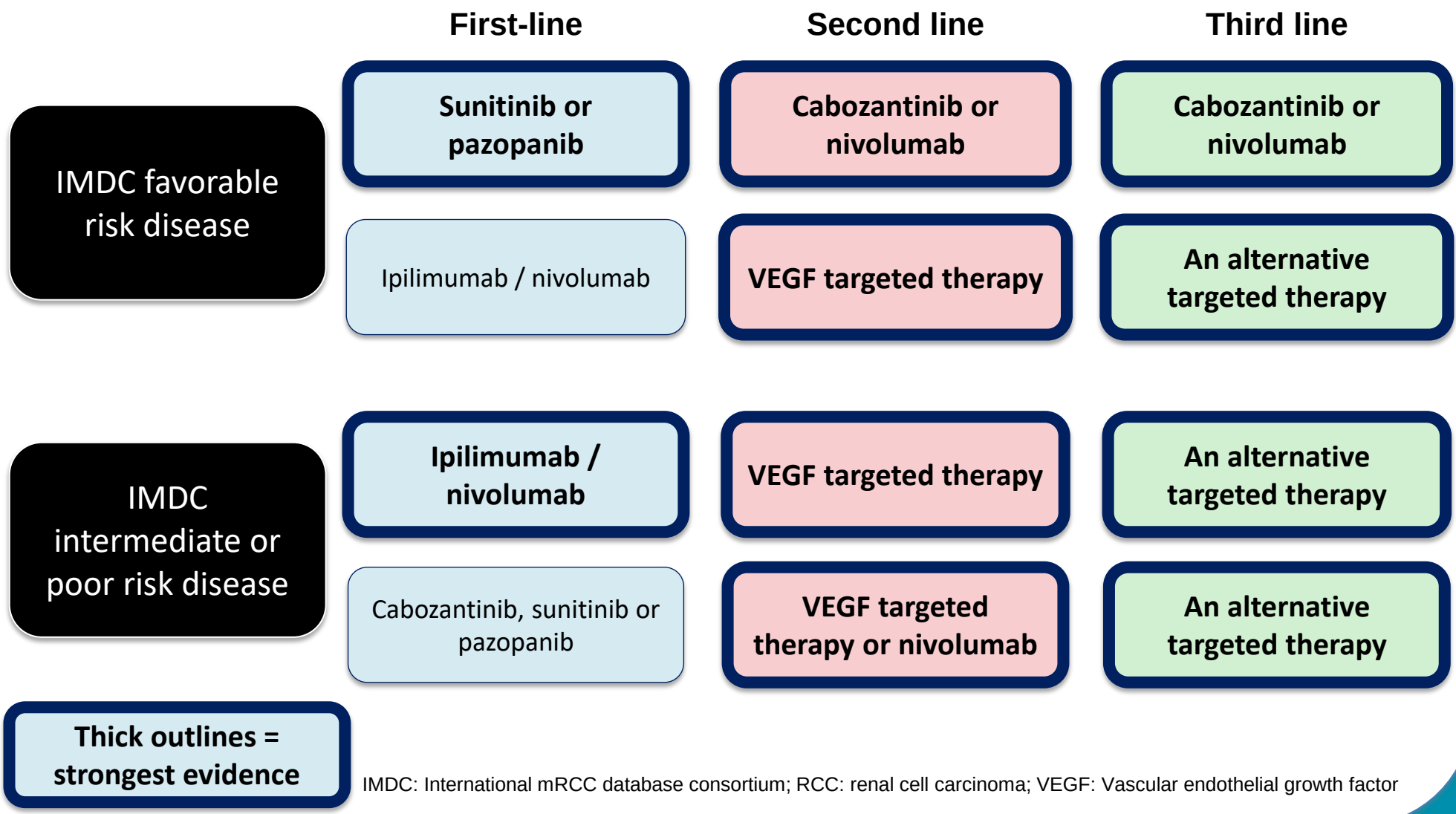
Front-Line Therapy for mRCC

European Association of Urology: 2018 Algorithm for the Management of Metastatic, Clear-cell RCC



IMDC: International mRCC database consortium; RCC: renal cell carcinoma; VEGF: Vascular endothelial growth factor

Powles T, et al. *Eur Urol* 2018; 73:311-5.

European Association of Urology: 2018 Recommendations for the Management of Metastatic, Clear-cell RCC

Recommendation	Strength of Recommendation
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic ccRCC	Strong
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-risk metastatic ccRCC	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC favourable-risk metastatic ccRCC	Weak
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic ccRCC	Weak
Do not offer tivozanib to patients with treatment-naïve metastatic ccRCC	Weak
Offer a VEGF-TKI as second-line therapy to IN-refractory patients	Weak

cc: clear cell; IMDC: International mRCC database consortium; IN: Ipilimumab and nivolumab; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor

Powles T, et al. *Eur Urol* 2018; 73:311-5.

Canadian Consensus Guidelines 2017

NB: These guidelines pre-date the CheckMate 214 Study and are being updated for 2019

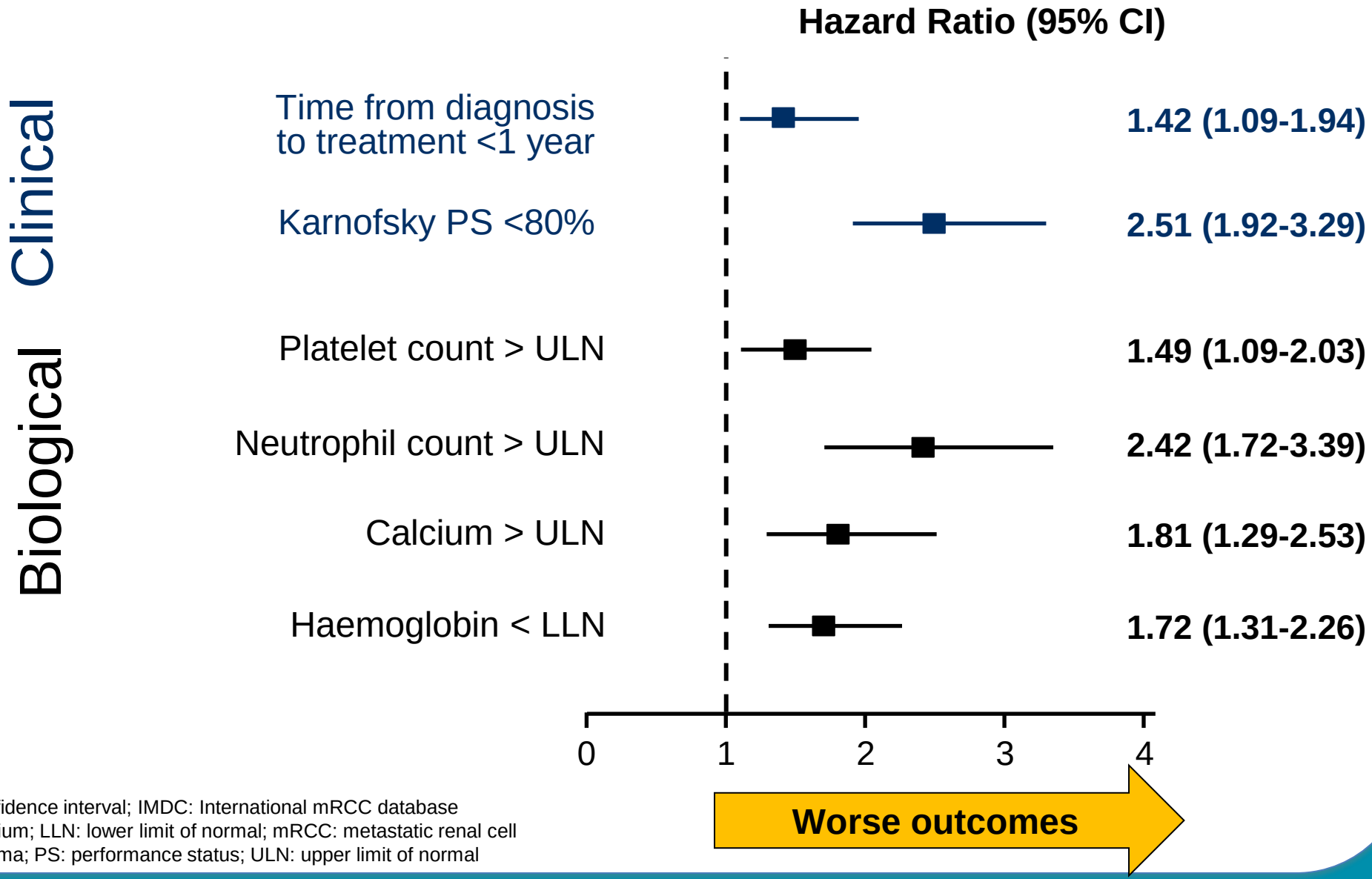
Setting	Patients	Therapy (Level 1 evidence)	Other options (<Level 1 evidence)
Untreated	Good/intermediate-risk	Sunitinib Pazopanib Bevacizumab[a] + IFN	High-dose IL-2 Sorafenib Cabozantinib[a/b] Observation
	Poor-risk	Sunitinib Temsirolimus	Pazopanib
Second-line	Cytokine refractory	Sorafenib Pazopanib Axitinib	Sunitinib, Bevacizumab[a] + IFN
	Prior VEGF targeted therapy or prior mTOR	Nivolumab Axitinib Cabozantinib[a] Everolimus[c]	Targeted therapy not previously used (Lenvatinib[a] + everolimus)[b/c]
Third-line[d]	Any	Nivolumab Cabozantinib[a] Everolimus	Axitinib chemotherapy

[a]Not approved in Canada for RCC, but is approved in the U.S.; [b]phase 2 data only; [c]if prior mTOR not used in first-line; [d]no drug has Health Canada approval for third-line.

IFN: interferon; IL: interleukin; mTOR mammalian target of rapamycin; VEGF: Vascular endothelial growth factor

Reaume MN, et al. *Can Urol Assoc J* 2017; 11(10):310-20.

Risk Stratification for Treatment Selection in mRCC: 6 Elements of The Heng (IMDC) Model



CI: confidence interval; IMDC: International mRCC database consortium; LLN: lower limit of normal; mRCC: metastatic renal cell carcinoma; PS: performance status; ULN: upper limit of normal

Heng DY, et al. *J Clin Oncol* 2009; 27:5794-9.

Scoring and Interpretation of The Heng (IMDC) Model for Risk Stratification in mRCC

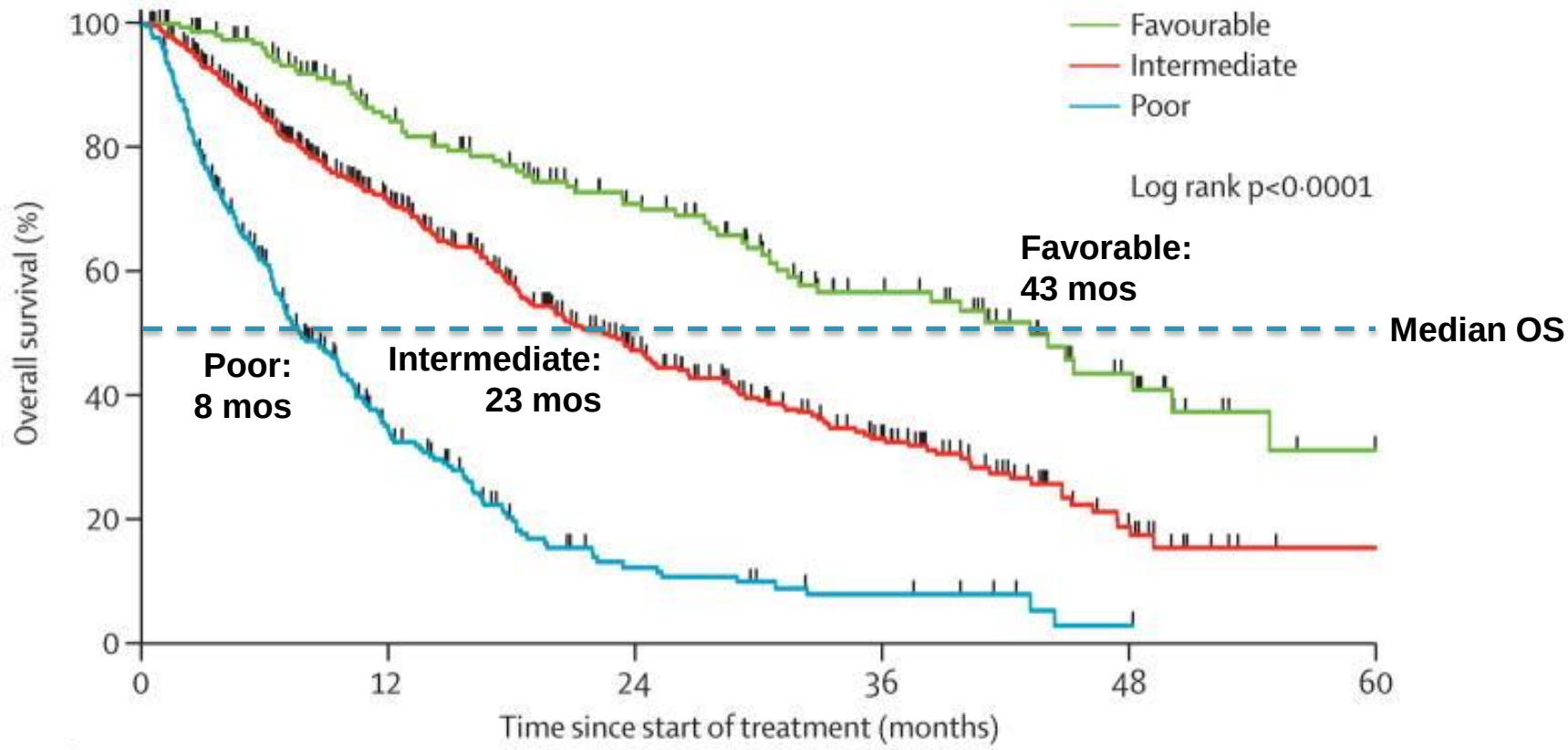
Scoring	Score	
	No	Yes
Time from diagnosis to treatment <1 year	0	+1
Karnofsky performance status <80%	0	+1
Hemoglobin < LLN	0	+1
Calcium > ULN	0	+1
Neutrophils > ULN	0	+1
Platelets > ULN	0	+1

Interpretation	Total Score	Prognosis
	0	Favorable
	1-2	Intermediate
	≥3	Poor

IMDC: International mRCC database consortium; LLN: lower limit of normal; mRCC: metastatic renal cell carcinoma; ULN: upper limit of normal

Adapted from Heng DY, et al. J Clin Oncol 2009; 27:5794-9.

Overall Survival by Risk Group: Heng (IMDC) Model



Number at risk

Favourable	157	109	74	40	17	3
Intermediate	440	247	122	59	15	1
Poor	252	65	15	7	1	0

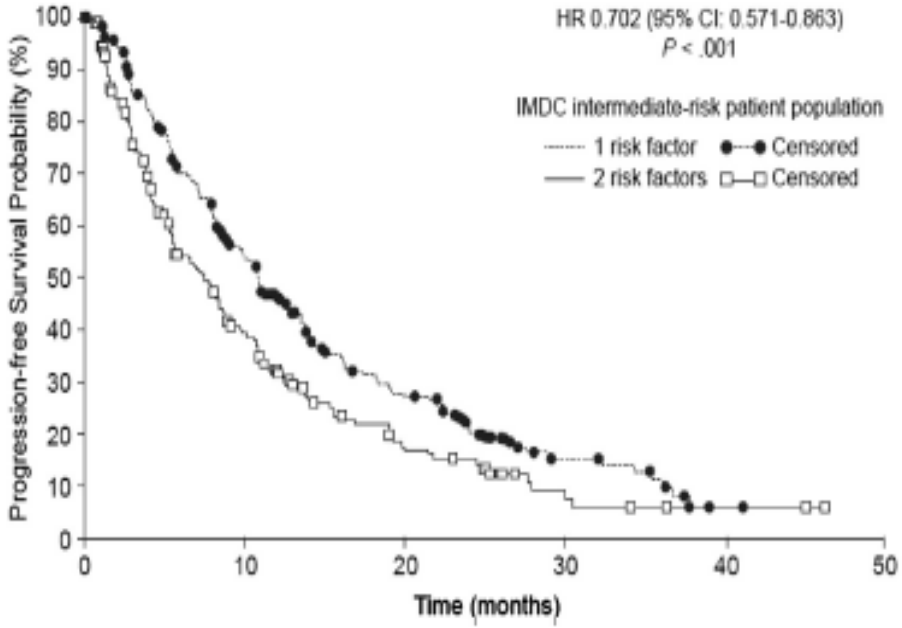
IMDC: International mRCC database consortium; OS: overall survival

Heng DY, et al. *Lancet Oncol* 2013; 14:141-8.

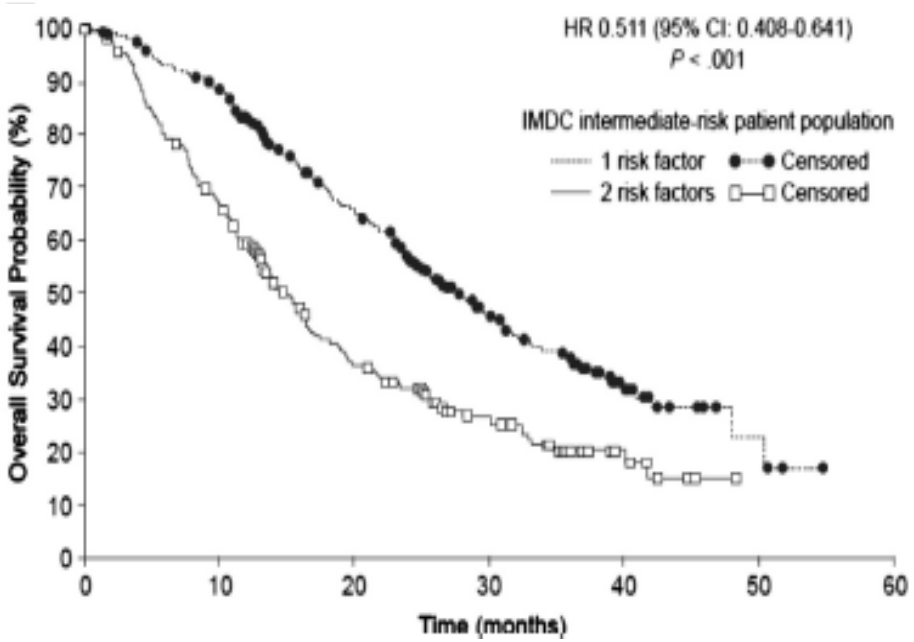
Intermediate-1 and Intermediate-2 IMDC Risk Scores May Have Different Prognoses

Retrospective Analysis of Data from 6 Sunitinib Clinical Trials

Progression-free Survival



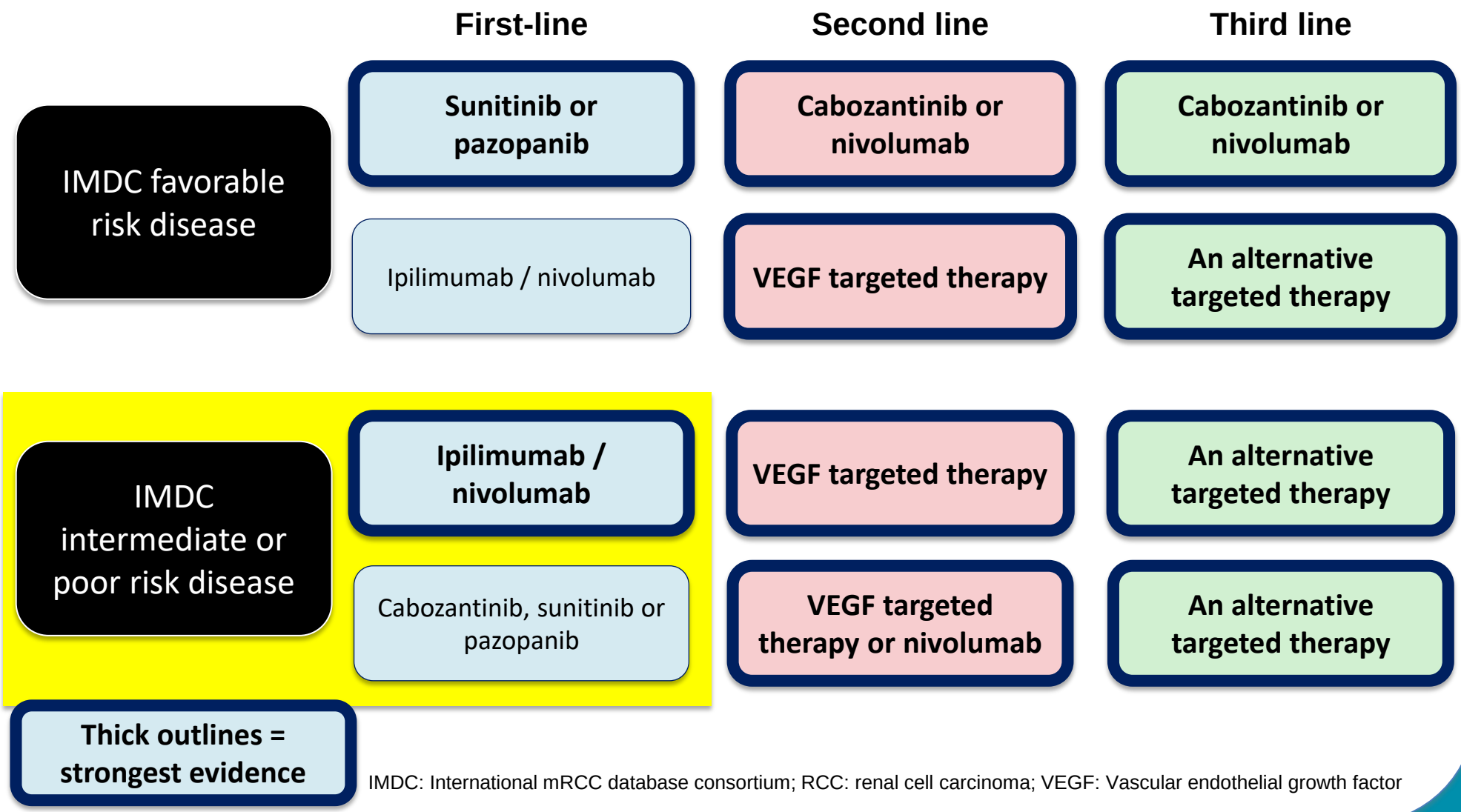
Overall Survival



CI: confidence interval; HR: hazard ratio; IMDC: International mRCC database consortium;

Sella A, et al. *Clin Genitourin Cancer* 2017; 15(2):291-9.

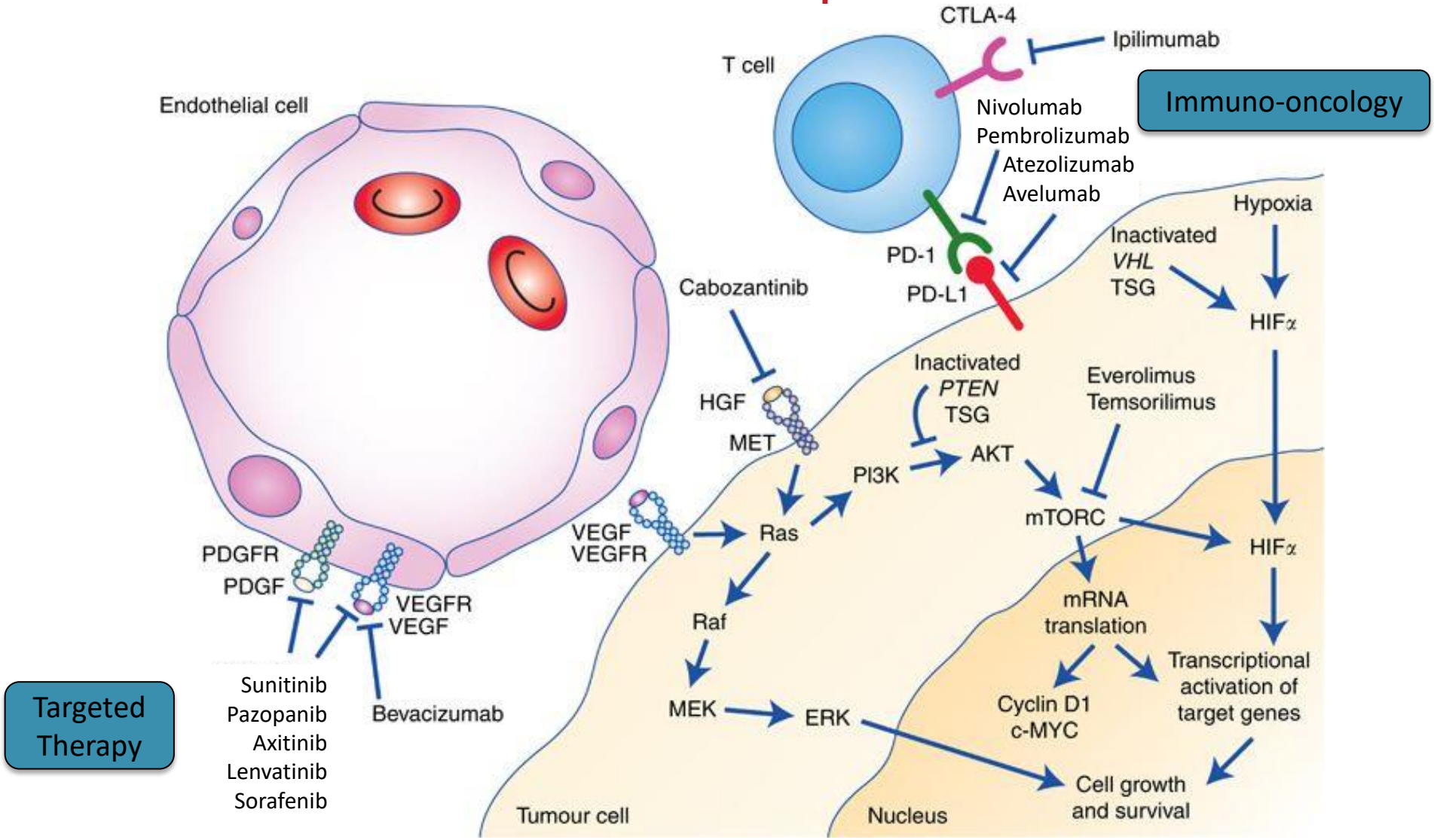
European Association of Urology: 2018 Algorithm for the Management of Metastatic, Clear-cell RCC



IMDC: International mRCC database consortium; RCC: renal cell carcinoma; VEGF: Vascular endothelial growth factor

Powles T, et al. *Eur Urol* 2018; 73:311-5.

Mechanisms of Action of Therapies for mRCC

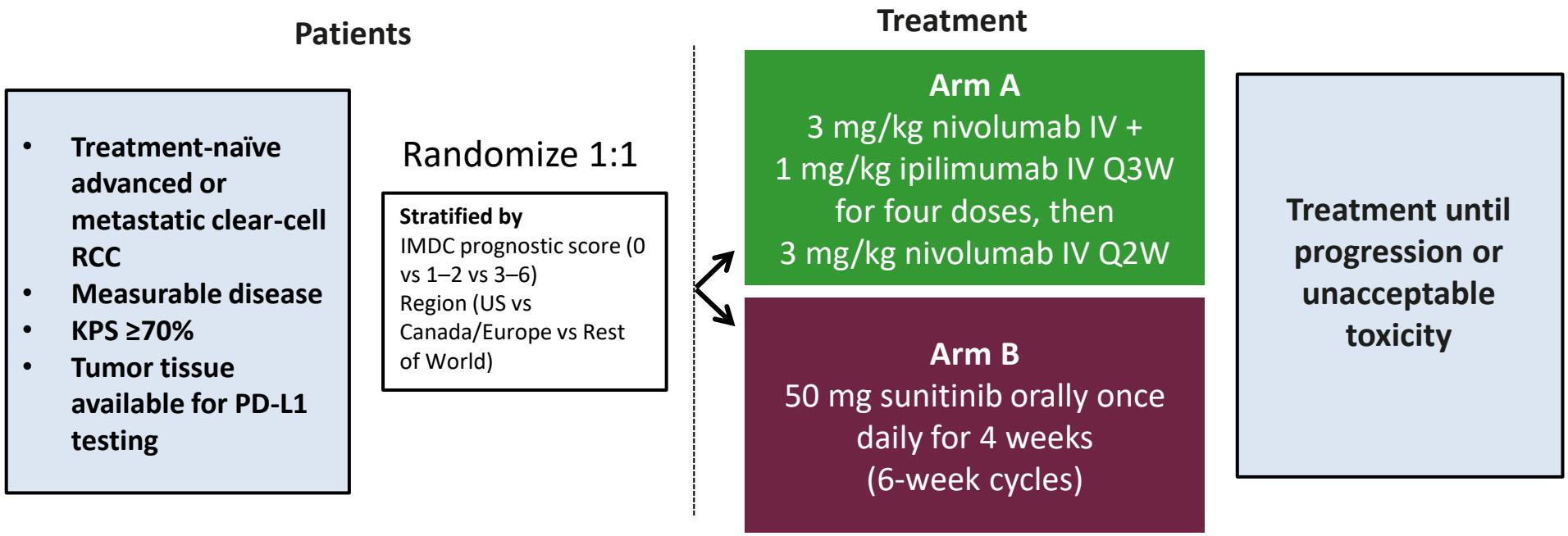


AKT: protein kinase B; CTLA-4: cytotoxic T-lymphocyte–associated antigen 4; ERK: **extracellular** signal regulated kinase; HGF: hepatocyte growth factor; HIF: hypoxia-inducible factor; MEK: mitogen-activated protein kinase kinase; MET: mesenchymal epithelial transition; mRNA: messenger ribonucleic acid; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PDGF(R): platelet-derived growth factor receptor; PI3K: phosphatidylinositol 3-kinase; PTEN: phosphatase and tensin homolog; TSG: TNF-α-stimulated gene; VEGF(R): VEGF: vascular endothelial growth factor (receptor); VHL: von Hippel-Lindau gene

Adapted from Greef B, et al. *Br J Cancer* 2016; 115:505-16.

Evidence for Ipilimumab / Nivolumab for First-line Treatment of Intermediate-Poor Risk mRCC

CheckMate 214 Study Design



Three co-primary endpoints—in IMDC intermediate- and poor-risk patients:

- Overall survival
- Objective response rate (per independent radiology review committee, IRRC)
- Progression-free survival (per IRRC)

IMDC, International Metastatic RCC Database Consortium; IV: intravenously; KPS, Karnofsky performance status; PD-L1: programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC: renal cell carcinoma

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

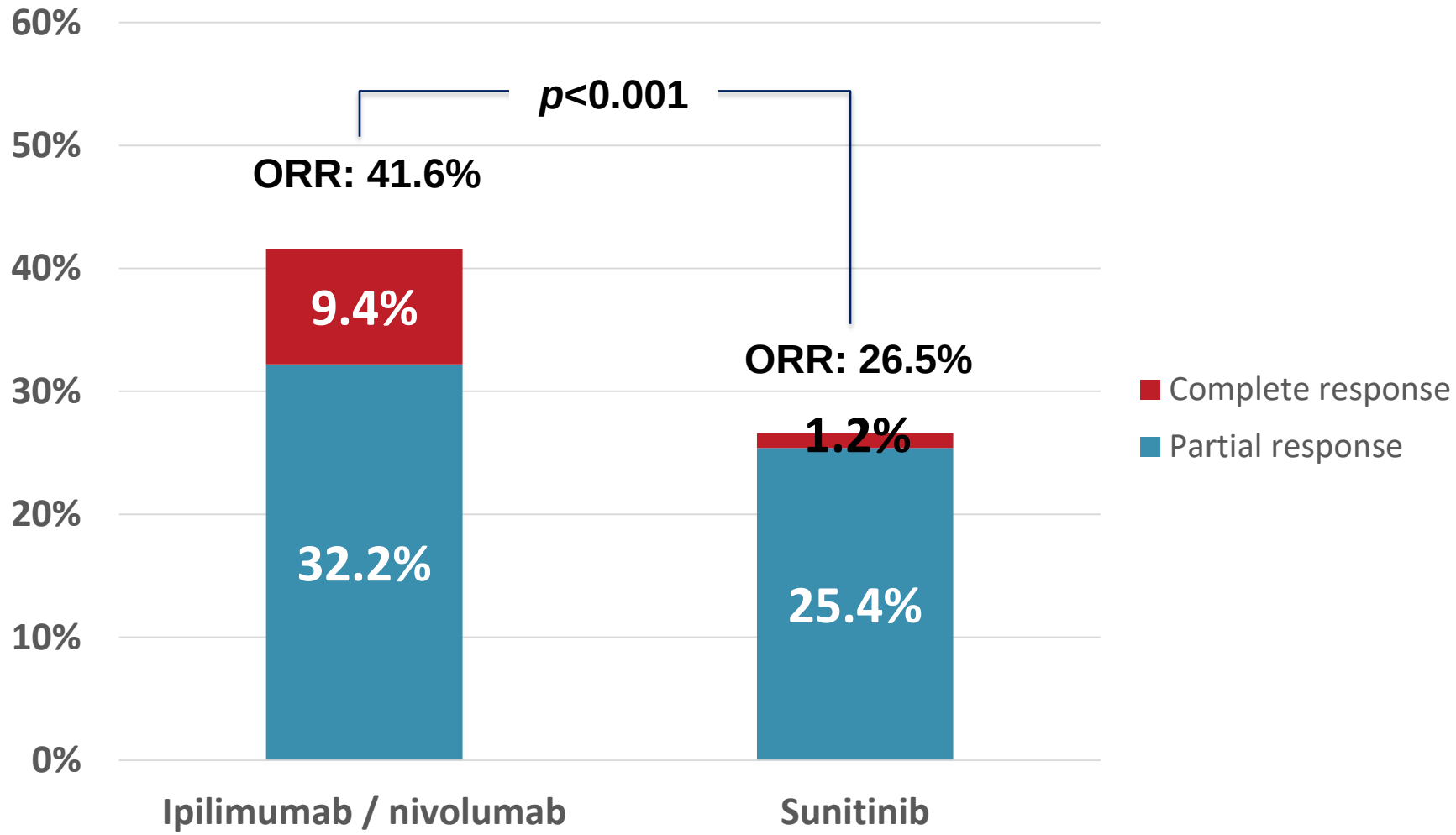
CheckMate 214: Baseline Characteristics

Characteristics	IMDC intermediate/ poor risk		Intention to treat	
	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 550	SUN N = 546
Median age, years	62	61	62	62
Male, %	74	71	75	72
IMDC prognostic score, %				
Favorable (0)	0	0	23	23
Intermediate (1–2)	79	79	61	61
Poor (3–6)	21	21	17	16
Region, %				
USA	26	26	28	28
Canada/Europe	35	35	37	36
Rest of the world	39	39	35	36
Quantifiable tumor PD-L1 expression, %	n = 384	n = 392	n = 499	n = 503
<1%	74	71	77	75
≥1%	26	29	23	25

IMDC, International Metastatic RCC Database Consortium; IPI: ipilimumab; IV: intravenously; KPS, Karnofsky performance status; NIVO: nivolumab; PD-L1: programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC: renal cell carcinoma; SUN: sunitinib

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

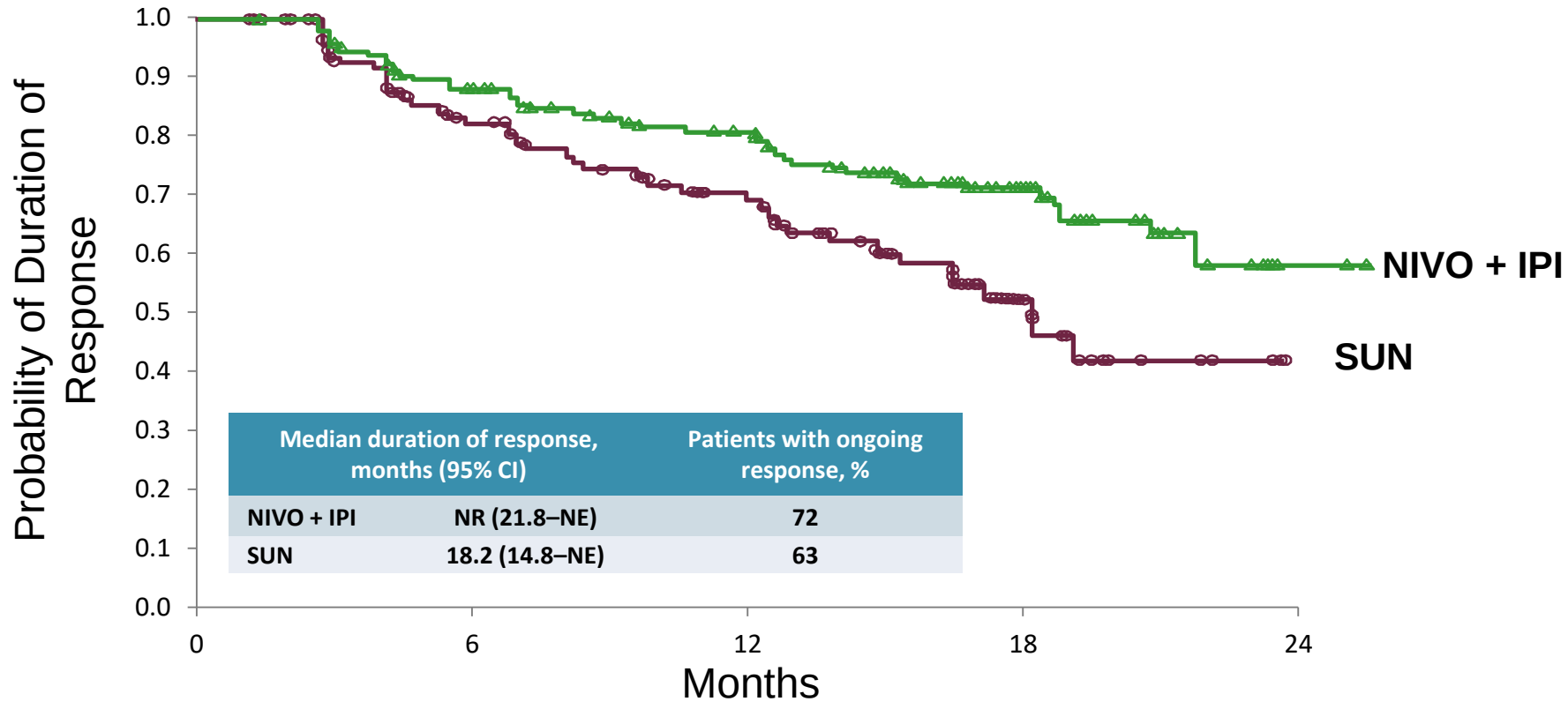
CheckMate 214: Objective Response Rates in IMDC Intermediate/Poor Risk (Co-primary Endpoint)



IMDC, International Metastatic RCC Database Consortium; ORR: objective response rate

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

CheckMate 214: Duration of Response in IMDC Intermediate/Poor Risk



Median duration of response, months (95% CI)		Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63

No. at Risk

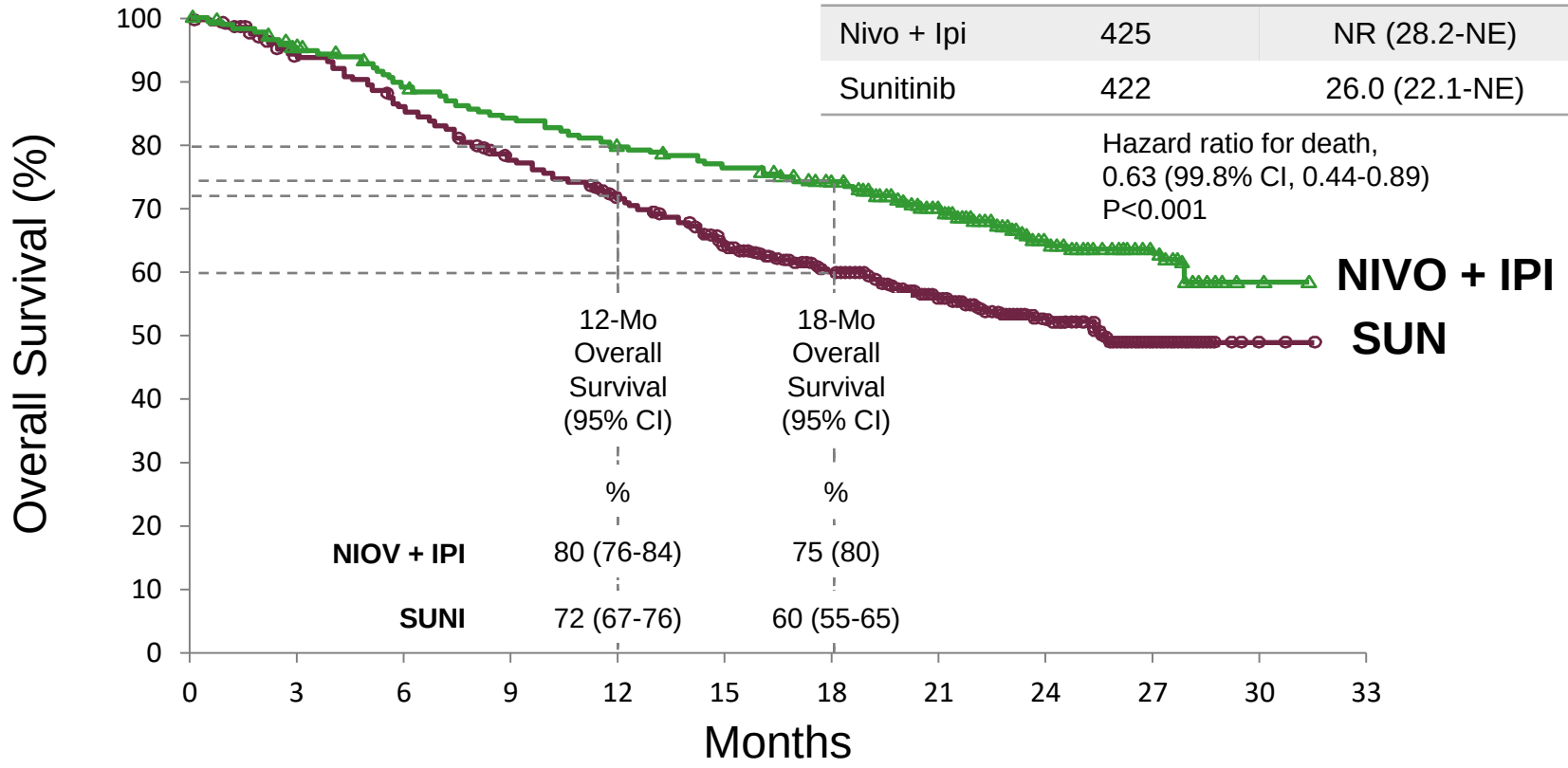
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

IMDC, International Metastatic RCC Database Consortium; IPI: ipilimumab; NE: not estimable; NR: not reached; NIVO: nivolumab; SUN: sunitinib

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90 (supplementary appendix).

CheckMate 214: Overall Survival in IMDC Intermediate/Poor Risk (Co-primary Endpoint)

	No. of patients	Median (95% CI) mo
Nivo + Ipi	425	NR (28.2-NE)
Sunitinib	422	26.0 (22.1-NE)



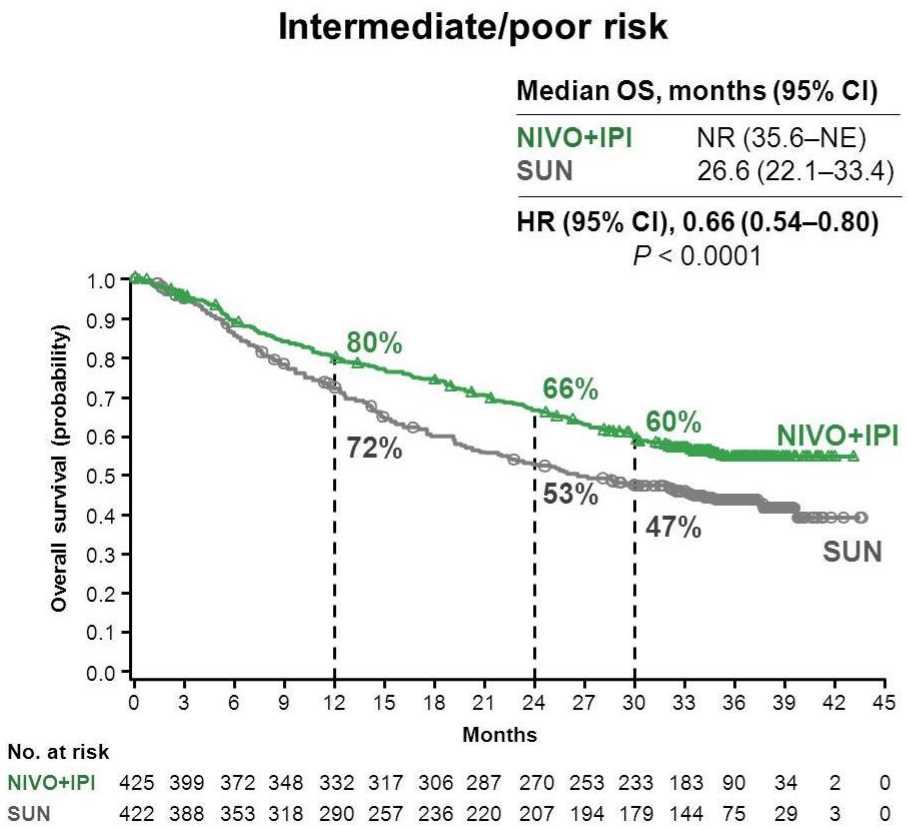
No. at Risk

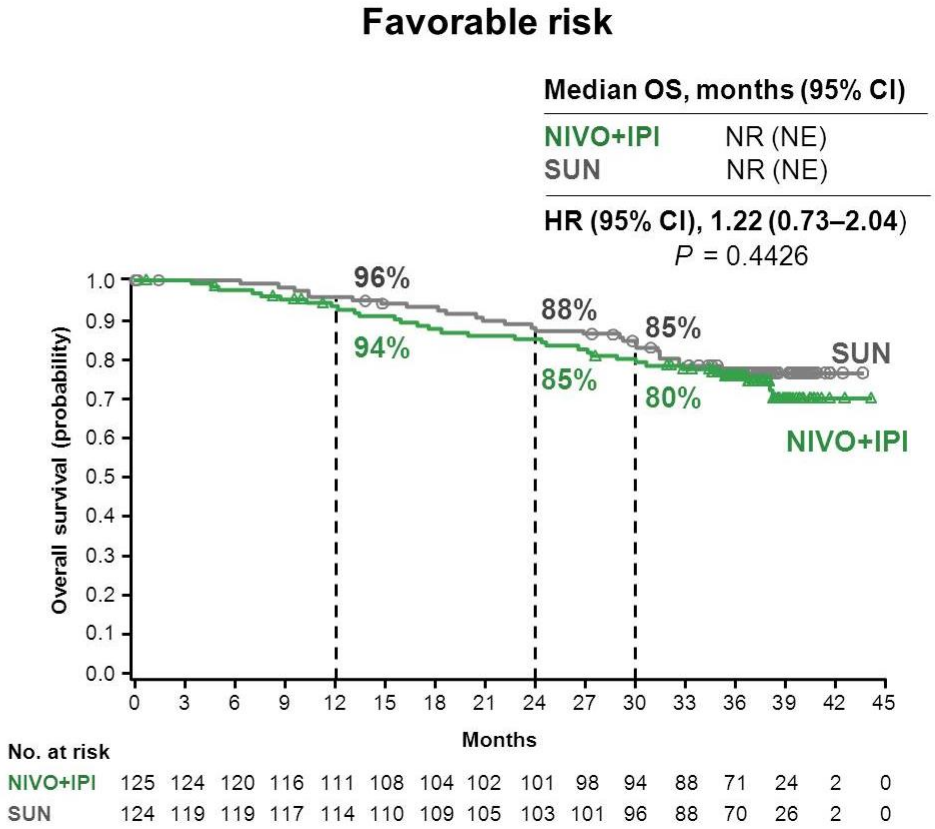
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

CI: confidence interval; IMDC, International Metastatic RCC Database Consortium; NE: not estimable; NR: not reached

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

CheckMate 214: 30-month Update on Overall Survival

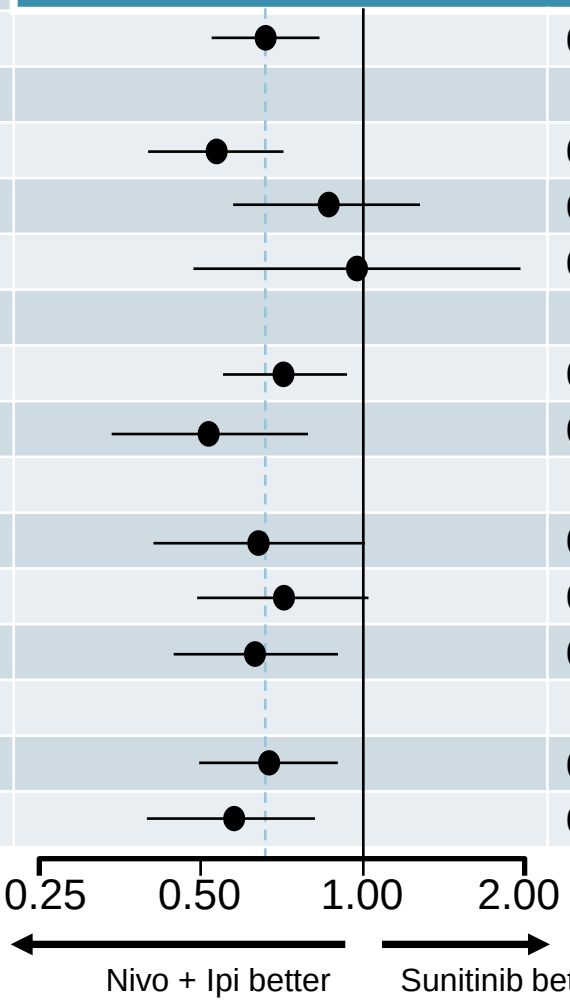




Tannir NM, et al. Presented at GU-ASCO 2019; Abstract #547.

CheckMate 214: Overall Survival in Subgroups of IMDC Intermediate/Poor Risk Patients (1 of 2)

Subgroup	Nivo + Ipi	Sunitinib	Hazard Ratio for Death (95% CI)
	No. of deaths / no. of patients		
Overall	140/425	188/422	0.66 (0.53-0.82)
Age			
<65	77/265	118/259	0.53 (0.40-0.71)
≥65 and <75 yr	46/125	55/133	0.86 (0.58-1.27)
≥75 yr	17/35	15/30	0.97 (0.48-1.95)
Sex			
Male	104/314	130/301	0.71 (0.55-0.92)
Female	36/111	58/121	0.52 (0.34-0.78)
Region			
United States	33/112	43/110	0.64 (0.40-1.00)
Canada and Europe	51/148	68/147	0.70 (0.49-1.01)
Rest of the world	56/165	77/165	0.63 (0.45-0.89)
Baseline IMDC prognostic risk			
Intermediate	87/314	121/319	0.66 (0.50-0.87)
Poor	52/102	66/97	0.57 (0.39-0.82)

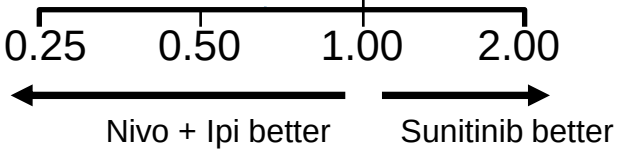


CI: confidence interval; IMDC, International Metastatic RCC Database Consortium

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

CheckMate 214: Overall Survival in Subgroups of IMDC Intermediate/Poor Risk Patients (2 of 2)

Previous nephrectomy				
Yes	103/341	127/319		0.69 (0.53-0.89)
No	37/84	61/103		0.63 (0.42-0.94)
Baseline PD-L1 expression				
≤1%	93/284	114/278		0.73 (0.56-0.96)
≥1%	28/100	57/114		0.45 (0.29-0.71)
Not reported	19/41	17/30		0.75 (0.39-1.45)
Bone metastases				
Yes	40/84	50/89		0.71 (0.47-1.08)
No	100/341	138/333		0.64 (0.49-0.82)
Liver metastases				
Yes	40/88	54/89		0.64 (0.42-0.96)
No	100/337	134/333		0.66 (0.51-0.85)
Lung metastases				
Yes	98/294	141/296		0.61 (0.47-0.78)
No	42/131	47/126		0.81 (0.53-1.22)
Lymph-node metastates				
Yes	75/190	99/216		0.79 (0.59-1.07)
No	65/235	89/206		0.55 (0.40-0.76)



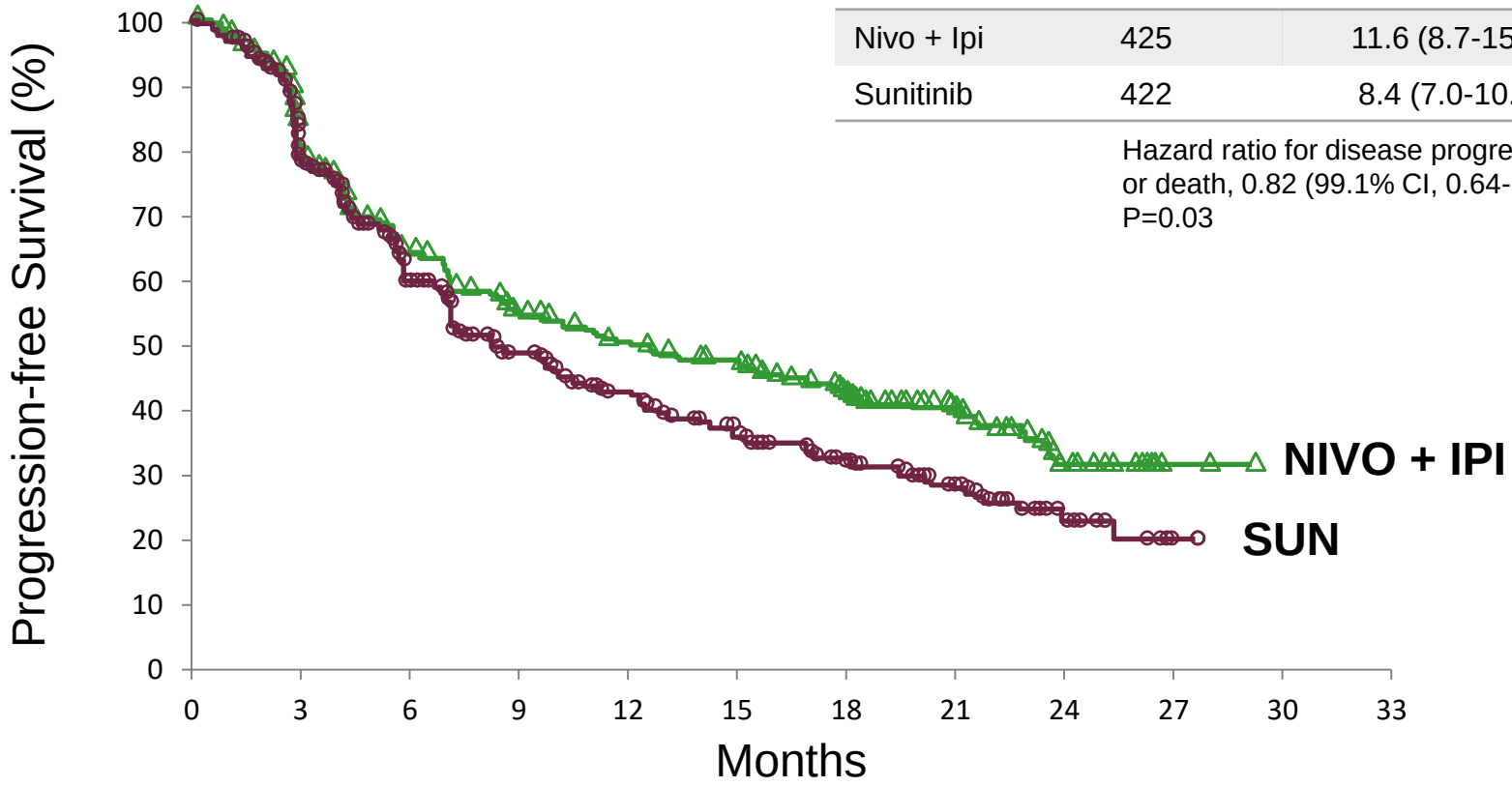
CI: confidence interval; IMDC, International Metastatic RCC Database Consortium; PD-L1: programmed death-ligand 1

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

CheckMate 214: Progression-free Survival in IMDC Intermediate/Poor Risk (Co-primary Endpoint)

	No. of patients	Median (95% CI) mo
Nivo + Ipi	425	11.6 (8.7-15.5)
Sunitinib	422	8.4 (7.0-10.8)

Hazard ratio for disease progression or death, 0.82 (99.1% CI, 0.64-1.05)
P=0.03

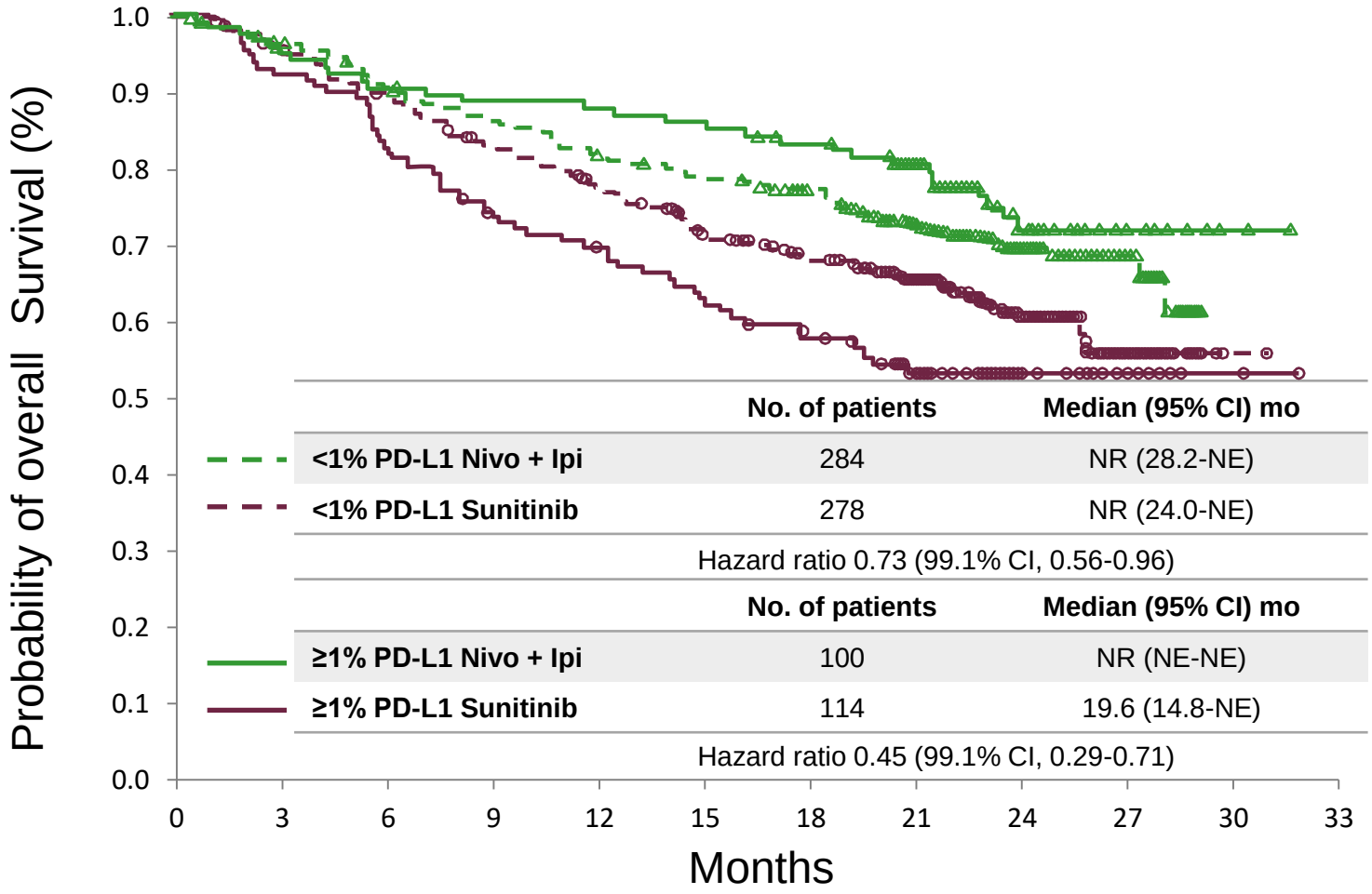


No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

CI: confidence interval; IMDC, International Metastatic RCC Database Consortium

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

CheckMate 214: OS by PD-L1 expression in IMDC Intermediate/Poor Risk (Exploratory Endpoint)

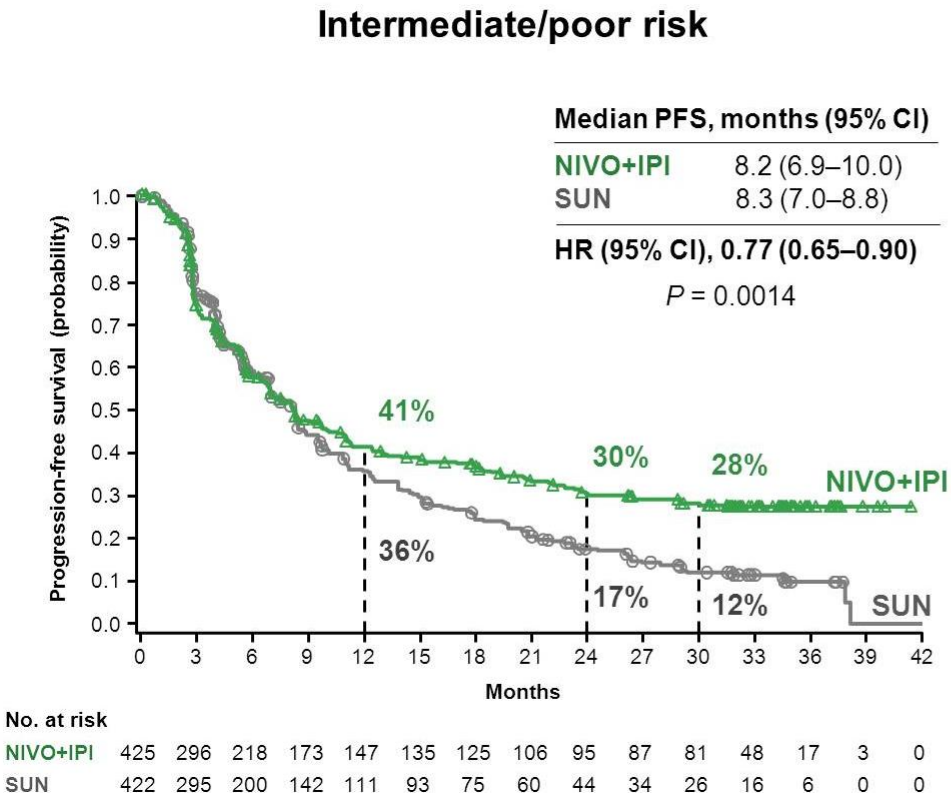


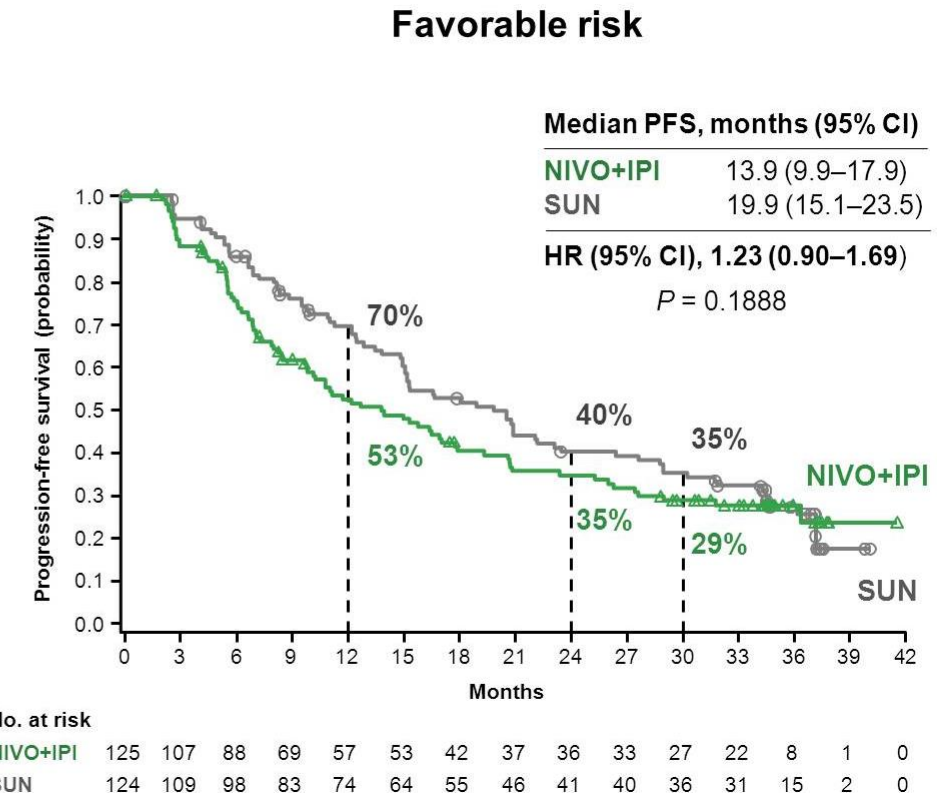
	No. of patients	Median (95% CI) mo
<1% PD-L1 Nivo + Ipi	284	NR (28.2-NE)
<1% PD-L1 Sunitinib	278	NR (24.0-NE)
Hazard ratio 0.73 (99.1% CI, 0.56-0.96)		
	No. of patients	**Median (95% CI) mo**
≥1% PD-L1 Nivo + Ipi	100	NR (NE-NE)
≥1% PD-L1 Sunitinib	114	19.6 (14.8-NE)
Hazard ratio 0.45 (99.1% CI, 0.29-0.71)		

CI: confidence interval; IMDC, International Metastatic RCC Database Consortium; NE: not estimable; NR: not reached; PD-L1: programmed death-ligand ; PFS: progression-free survival1

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90 (supplementary appendix).

CheckMate 214: 30-month Update on Progression-free Survival





Tannir NM, et al. Presented at GU-ASCO 2019; Abstract #547.

Treatment-related Adverse Events: All Treated patients

	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
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	<1	25	<1
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]**	

[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

AE: adverse event; IPI: ipilimumab; NIVO: nivolumab; SUN: sunitinib

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

Immune-mediated Adverse Events: All Treated Patients

	NIVO + IPI N = 547	
Category, %	**Any grade**	**Grade 3–4**
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

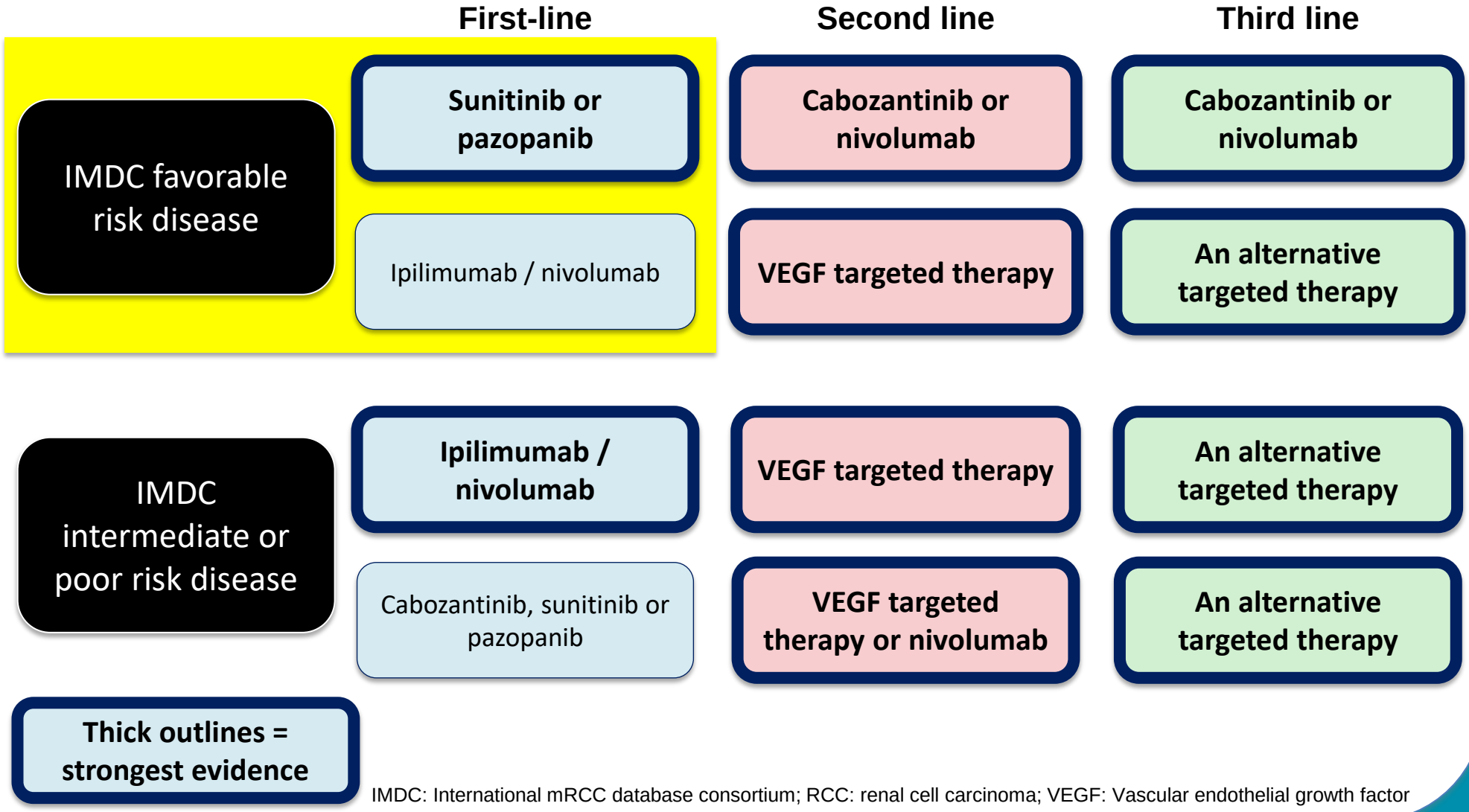
- 60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event
- Secondary immunosuppression with infliximab (3%) and mycophenolic acid (1%) was reported

Immune-mediated AE analyses included events, regardless of causality, occurring <100 days of the last dose. These analyses were limited to patients who received immune modulating medication for treatment of the event, except endocrine events that were included in the analysis regardless of treatment since these events are often managed without immunosuppression

AE: adverse event; IPI: ipilimumab; NIVO: nivolumab

Escudier B, et al. Presented at ESMO 2017; Abstract #LBA5.

European Association of Urology: 2018 Algorithm for the Management of Metastatic, Clear-cell RCC



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Powles T, et al. *Eur Urol* 2018; 73:311-5.

CheckMate 214: Results in IMDC Favorable Risk Patients (Exploratory Endpoints)

Endpoint	Ipilimumab + nivolumab (n=125)	Sunitinib (n=124)	*p* value
12-month OS	94%	96%	0.27
18-month OS	88%	93%	
Median OS	Not reached	32.9 months	Not reported
Median PFS	15.3 months	25.1 months	<0.001
ORR	29%	52%	<0.001
CR	11%	6%	Not reported

CR: complete response; IMDC, International Metastatic RCC Database Consort; NE: not estimable; NR: not reached; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

Key Learnings from CheckMate 214

- In intermediate/poor risk patients:
  - ORR and OS were significantly improved with ipilimumab + nivolumab compared to standard sunitinib
  - No significant difference between groups for PFS
- In exploratory analyses:
  - ORR and PFS results are improved with ipilimumab + nivolumab in patients with >1% tumor PD-L1 expression
  - Favorable-risk patients achieved higher response rates and longer PFS with sunitinib versus ipilimumab + nivolumab

ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand; PFS: progression-free survival

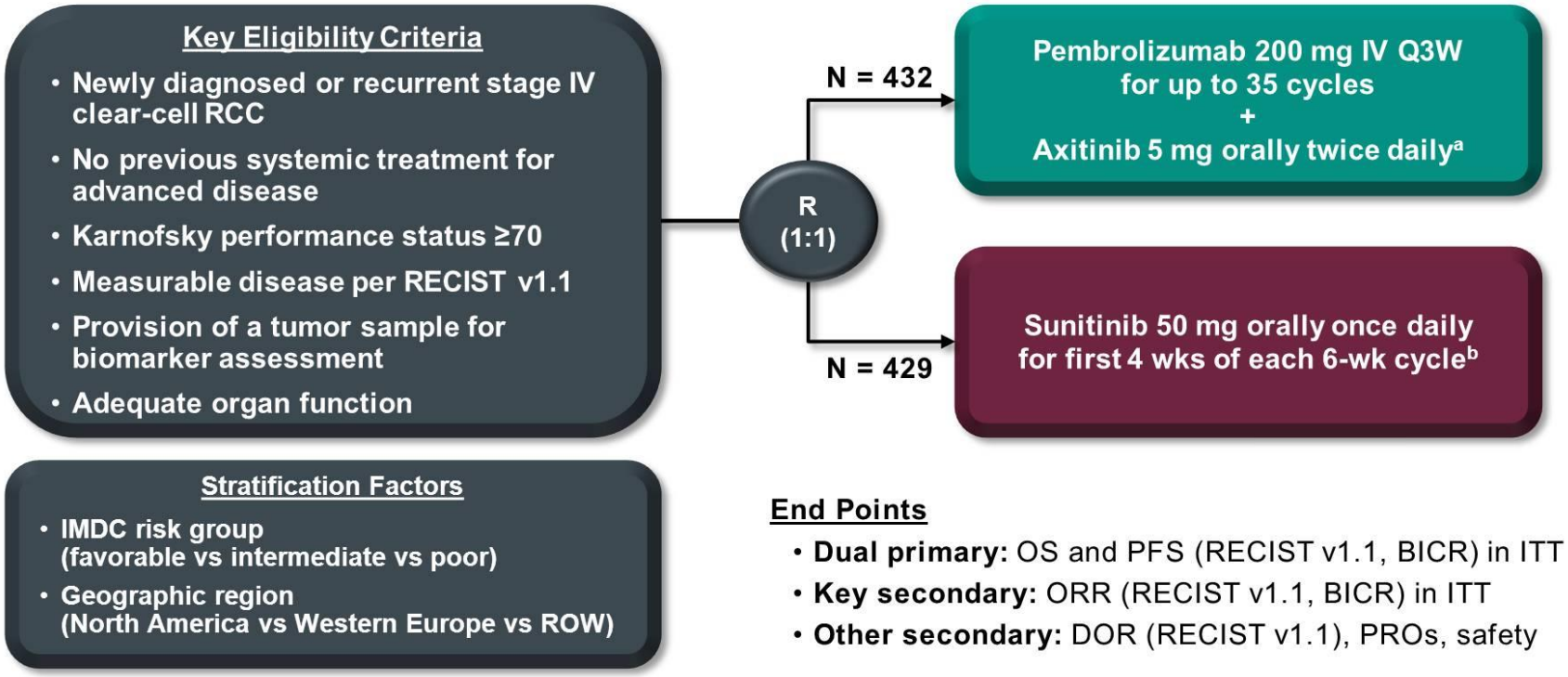
Motzer RJ, et al. *N Engl J Med* 2018; 378(14):1277-90.

What About Combining Immuno-oncology with Targeted Therapy?

Results from KEYNOTE-426, JAVELIN RENAL 101 and IMmotion151

Evidence for Pembrolizumab + Axitinib vs. Sunitinib Monotherapy in mRCC

KEYNOTE-426 Study Design



[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).

IMDC, International Metastatic RCC Database Consortium; mRCC: metastatic renal cell carcinoma; Q3W, every 3 weeks; RECIST: response evaluation criteria in solid tumours

Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

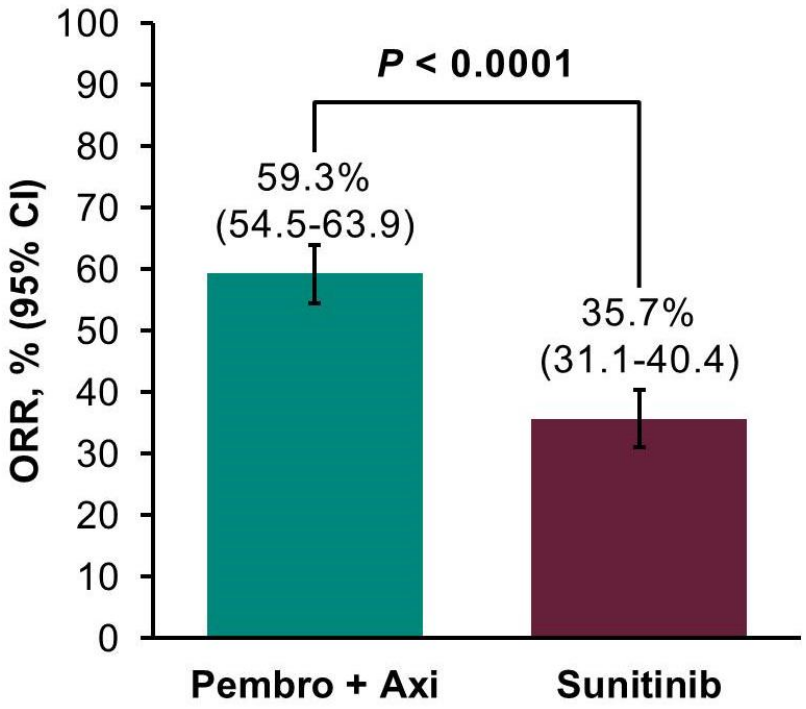
KEYNOTE-426: Baseline Characteristics

	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	315 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	358 (83.4%)

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay; CPS = combined positive score = number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells x 100.

Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

KEYNOTE-426: Confirmed Objective Response Rate (Secondary Endpoint)

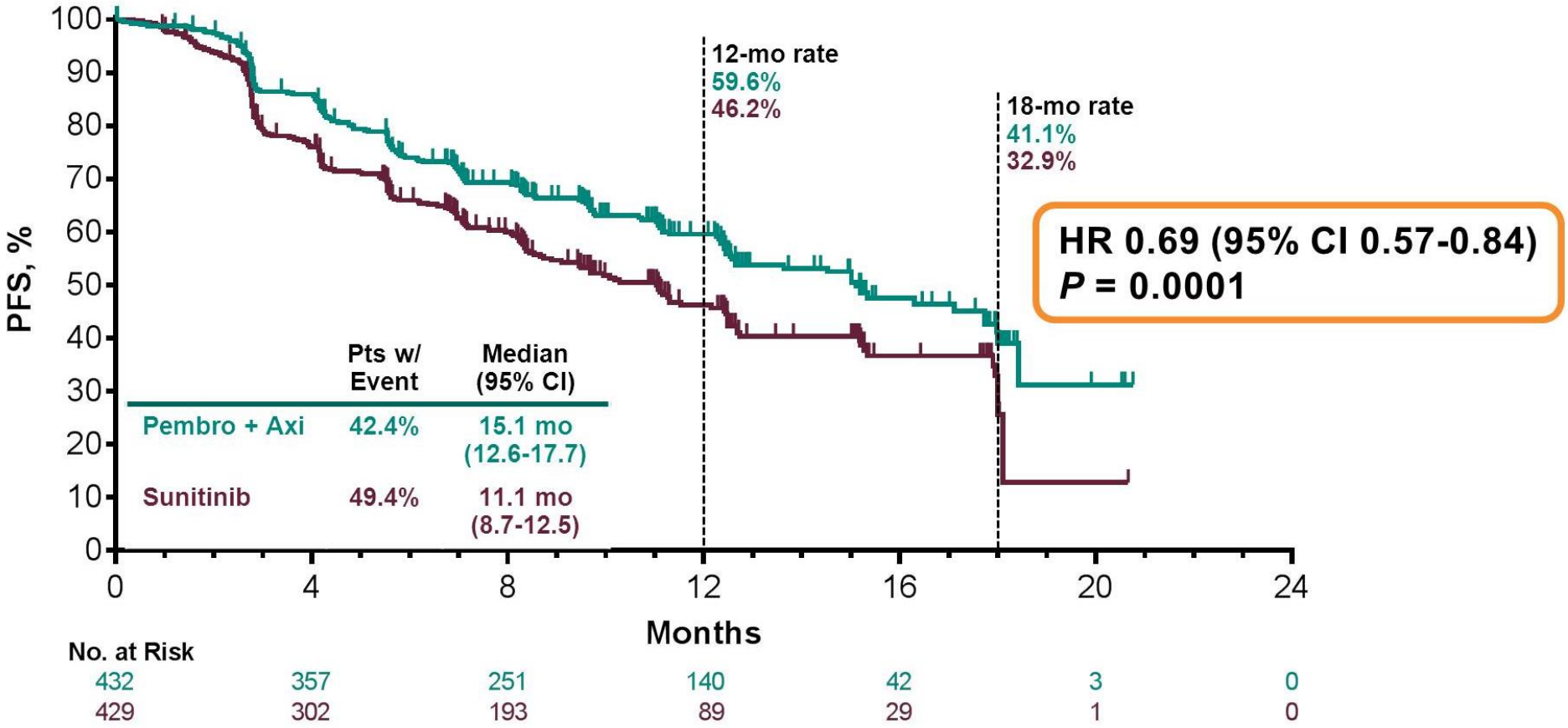


Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[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.

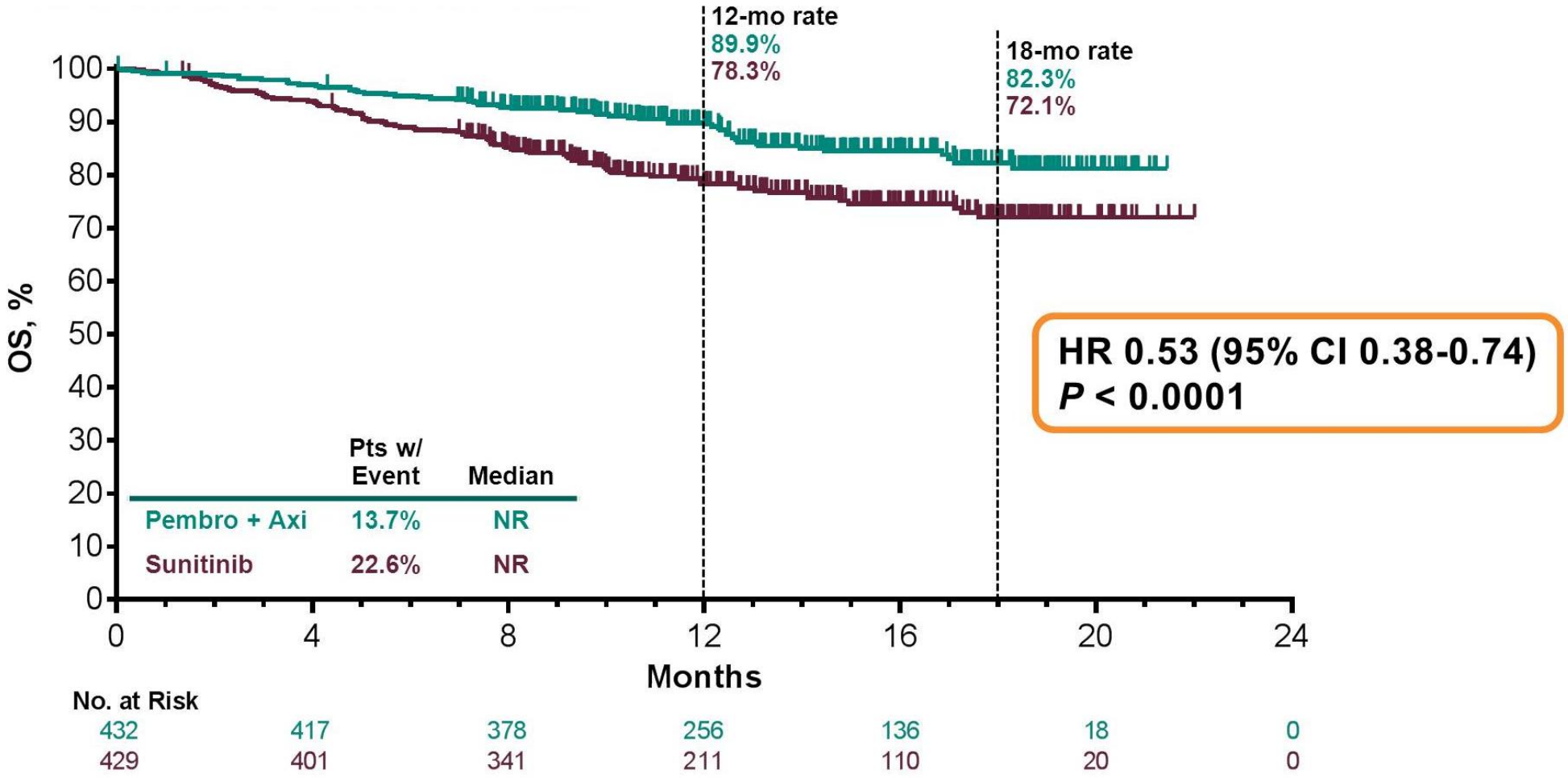
Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

KEYNOTE-426: Progression-free Survival, Overall Population (Co-primary Endpoint)



Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

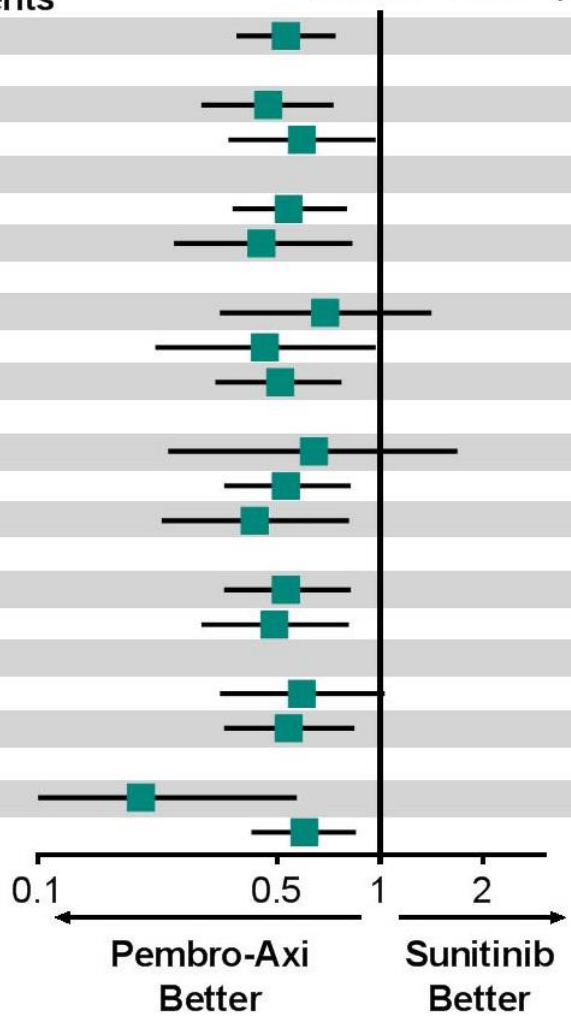
KEYNOTE-426: Overall Survival, Overall Population (Co-primary Endpoint)



Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

KEYNOTE-426: Overall Survival in Key Subgroups

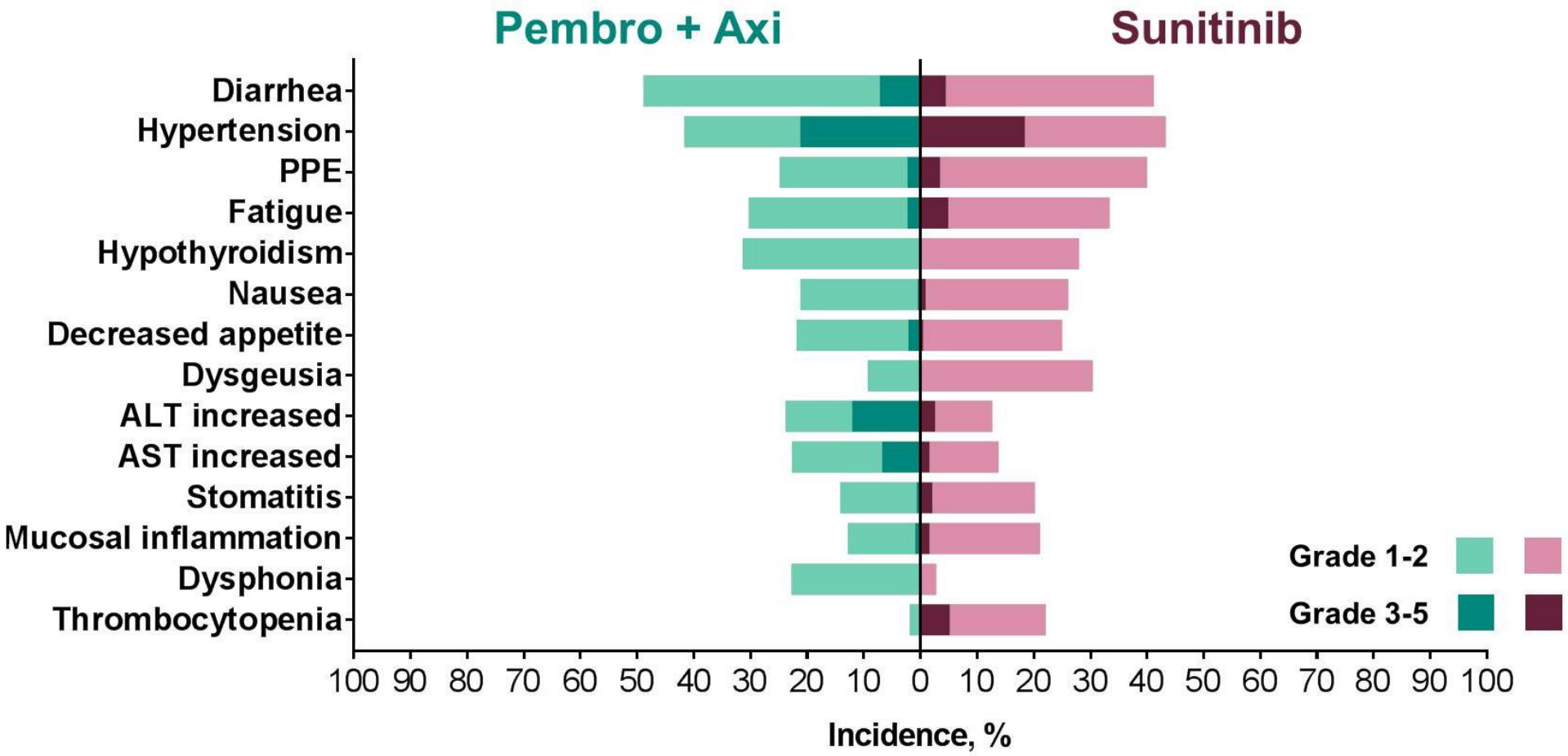
Subgroup	No. of Events/ No. of Patients	Hazard Ratio (95% CI)
Overall	156/861	0.53 (0.38–0.74)
Age		
<65 yrs	91/538	0.47 (0.30–0.73)
≥65 yrs	65/323	0.59 (0.36–0.97)
Sex		
Male	108/628	0.54 (0.37–0.80)
Female	48/233	0.45 (0.25–0.83)
Region of enrollment		
North America	31/207	0.69 (0.34–1.41)
Western Europe	31/210	0.46 (0.22–0.97)
Rest of world	94/444	0.51 (0.33–0.77)
IMDC risk category		
Favorable	17/269	0.64 (0.24–1.68)
Intermediate	93/484	0.53 (0.35–0.82)
Poor	46/108	0.43 (0.23–0.81)
Karnofsky performance score		
90 or 100	88/688	0.53 (0.35–0.82)
70 or 80	67/172	0.49 (0.30–0.81)
PD-L1 CPS		
<1	54/325	0.59 (0.34–1.03)
≥1	90/497	0.54 (0.35–0.84)
No. of metastatic organs		
1	21/210	0.20 (0.07–0.57)
≥2	134/646	0.60 (0.42–0.85)



IMDC, International Metastatic RCC Database Consortium

Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

KEYNOTE-426: Treatment-related Adverse Events With Frequency ≥20% in Either Arm



PPE: Palmar Plantar Erythrdysesthesia; ALT: Alanine Aminotransferase; AST; Aspartate Aminotransferase

Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

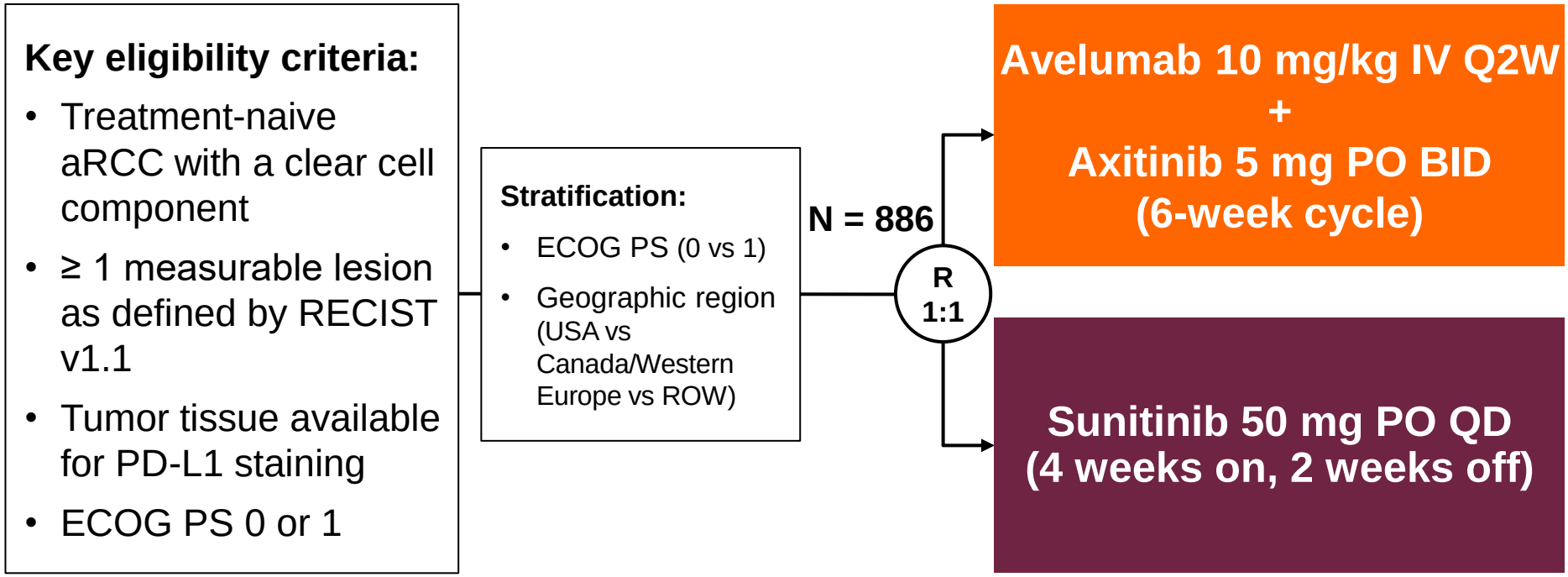
KEYNOTE-426: Adverse Events of Interest With Frequency ≥1% in Either Arm

	Pembrolizumab + Axitinib (N=429)		Sunitinib (N=425)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any	51.3%	10.7%	36.2%	1.9%
Hypothyroidism	35.4%	0.2%	31.5%	0.2%
Hyperthyroidism	12.8%	1.2%	3.8%	0
Adrenal insufficiency	3.0%	0.7%	0.2%	0
Hepatitis	2.8%	2.3%	0.5%	0.2%
Pneumonitis	2.8%	0.5%	0.2%	0
Thyroiditis	2.8%	0.2%	0.5%	0
Colitis	2.6%	1.9%	0.7%	0
Severe skin reactions	1.9%	1.2%	1.4%	0.7%
Infusion reactions	1.6%	0.2%	0.9%	0.2%
Nephritis	1.4%	0.2%	0.2%	0
Hypophysitis	1.2%	0.9%	0	0

Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

Evidence for Avelumab + Axitinib vs. Sunitinib in Advanced RCC

JAVELIN Renal 101 Study Design



Two co-primary endpoints (in patients with PD-L1+ tumours):
- Progression-free survival (assessed by blinded independent central imaging review)
- Overall survival

aRCC: advanced renal cell carcinoma; ECOG: Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium; IV: intravenously; PD-L1: programmed death-ligand; PO: orally; Q3W, every 3 weeks; RCC: renal cell carcinoma; RECIST: response evaluation criteria in solid tumours; ROW: rest of world

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.
Choueiri, T. et al. Presented at ASCO-GU 2019; Abstract #544.

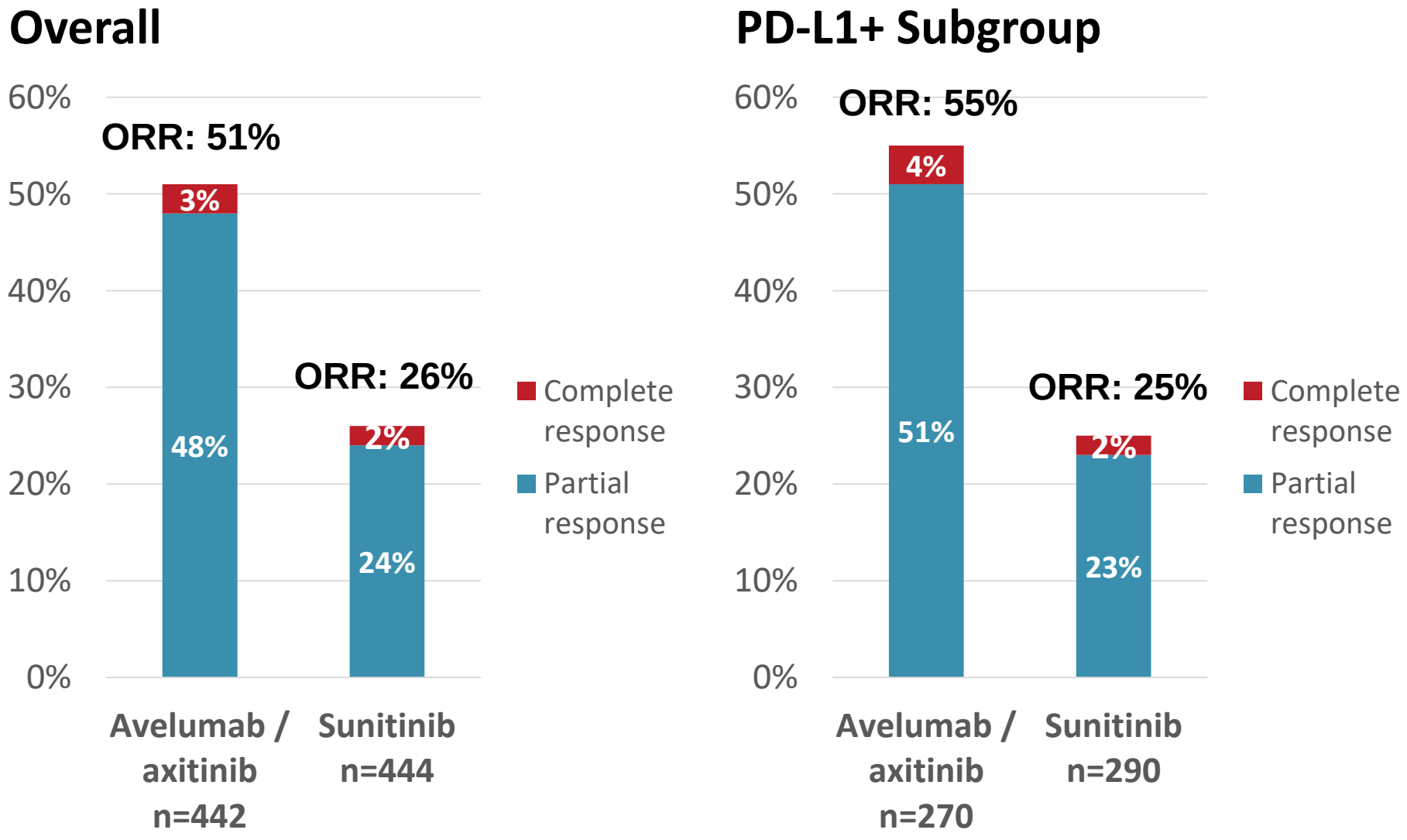
JAVELIN Renal 101: Key Baseline Characteristics

Characteristic	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
Median age, years	62	61	62	61
Male, %	75	77	72	78
Prior nephrectomy, %	86	87	80	80
ECOG performance status, %				
0/1	62/38	67/33	63/37	63/37
IMDC prognostic risk, %*				
Favorable	19	20	21	22
Intermediate/poor	64/16	66/13	61/16	62/16
MSKCC prognostic risk, %†				
Favorable	19	21	22	23
Intermediate/poor	67/12	69/8	64/12	66/10
Geographic region, %				
United States	28	28	29	30
Canada/Western Europe	30	28	29	29
Rest of the World	43	44	42	42

Values may not sum to 100% due to rounding. * Not reported in < 1% of patients. † Not reported in < 3% of patients.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; **MSKCC**, Memorial Sloan Kettering Cancer Center.

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.

JAVELIN Renal 101: Objective Response Rates (Secondary Endpoint)



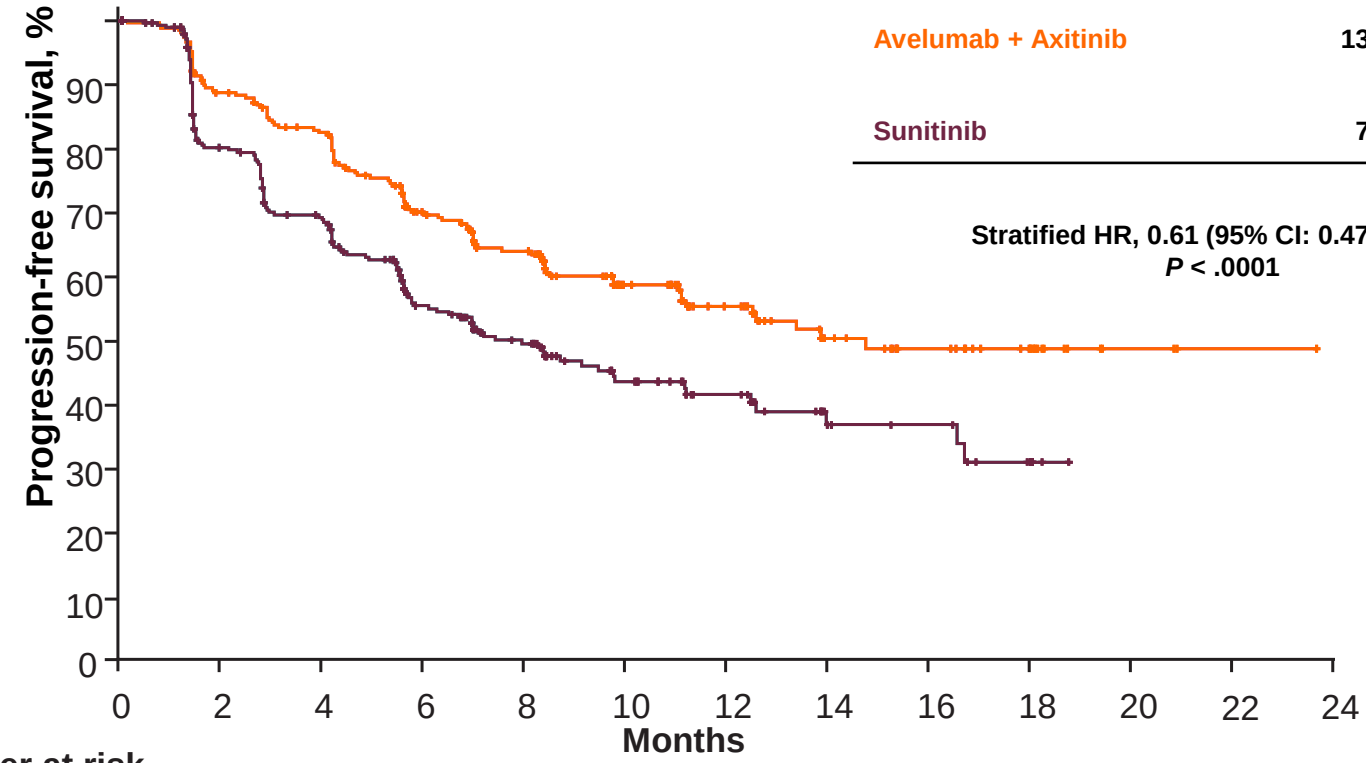
ORR: objective response rate; PD-L1: programmed death-ligand

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.

JAVELIN Renal 101: Progression-free Survival in PD-L1+ Patients (Co-primary Endpoint)

	Median PFS (95% CI), months
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	7.2 (5.7, 9.7)

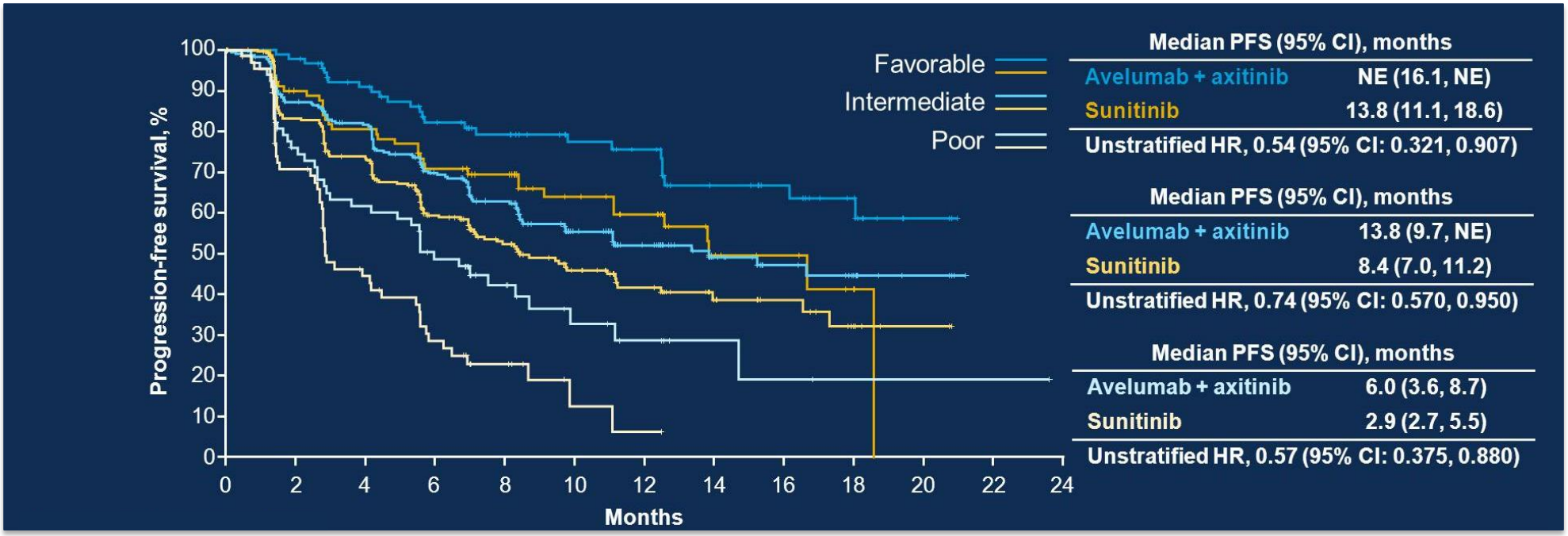
Stratified HR, 0.61 (95% CI: 0.475, 0.790)
P < .0001



CI: confidence interval; HR: hazard ratio; NE: not estimable; PD-L1: programmed death-ligand; PFS: progression-free survival

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.

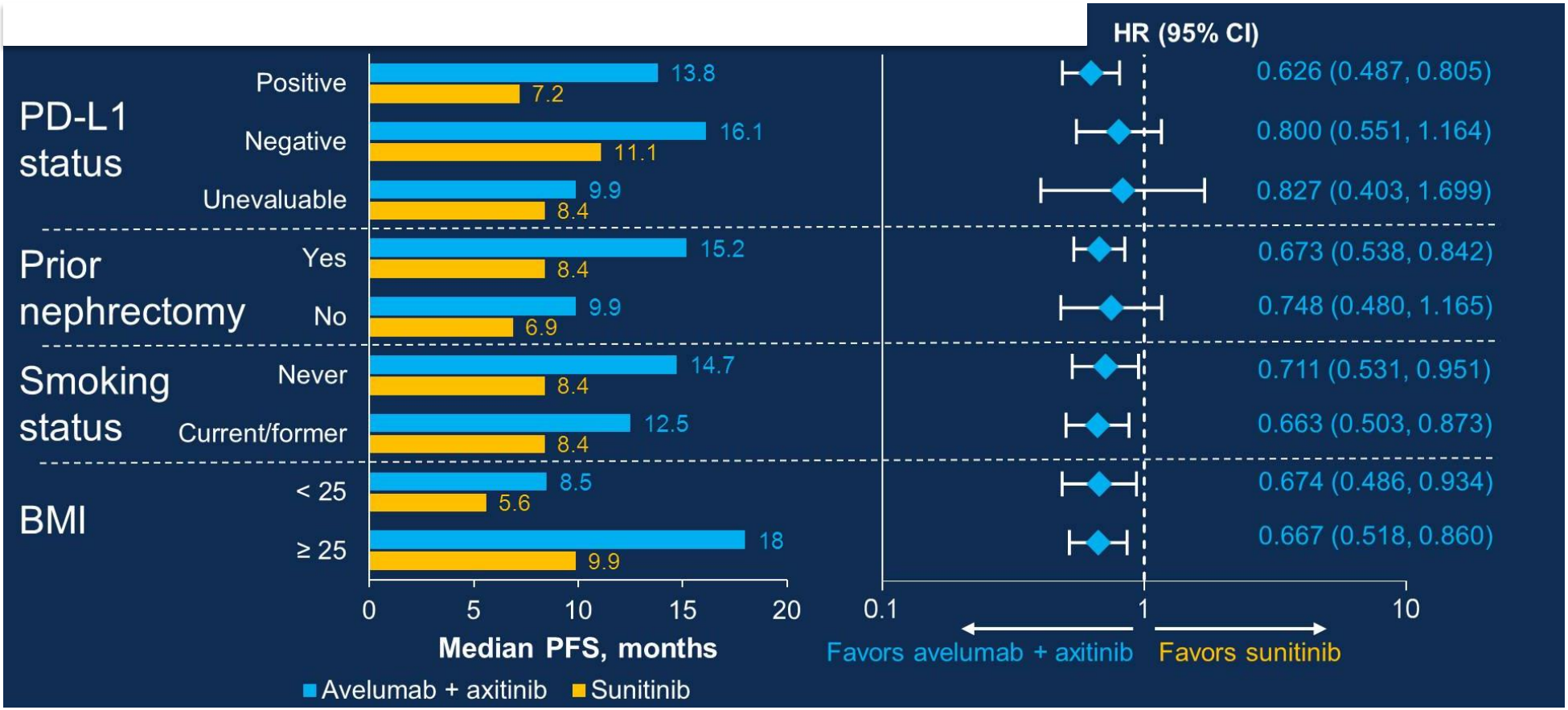
JAVELIN Renal 101 Subgroup Analysis: Progression-free Survival by IMDC Risk Group



CI: confidence interval; HR: hazard ratio; NE: not estimable; PFS: progression-free survival

Choueiri, T. et al. Presented at ASCO-GU 2019; Abstract #544.

JAVELIN Renal 101 Subgroup Analysis: Progression-free Survival in Other Key Subgroups in the Overall Population

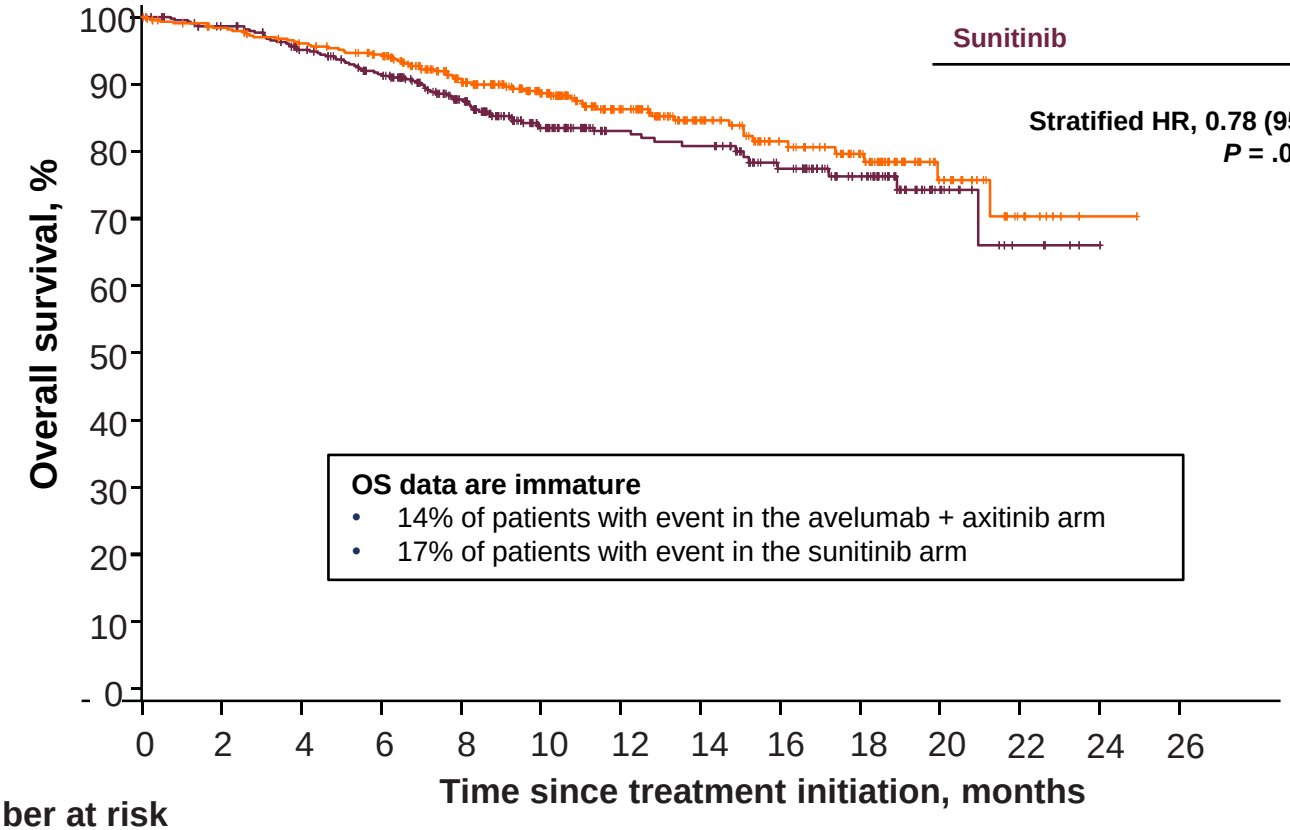


BMI: body mass index; PD-L1: programmed death-ligand; PFS: progression-free survival

Choueiri, T. et al. Presented at ASCO-GU 2019; Abstract #544.

JAVELIN Renal 101: Overall Survival in the Overall Population (Secondary Endpoint)

	Median OS (95% CI), months
Avelumab + Axitinib	Not reached
Sunitinib	Not reached



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).

Avel: avelumab; Axit: axitinib; CI: confidence interval; HR: hazard ratio; OS: overall survival

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.

JAVELIN Renal 101: Adverse Events of Interest

	Avelumab + Axitinib (N = 434)	
	All grades	**Grade 3 (4)**
All immune-related AEs, %	**38**	**8 (1)**
Hypothyroidism	21	< 1 (0)
Liver function test abnormalities	5	4 (< 1)
Adrenal insufficiency	2	1 (0)
Diarrhea	2	1 (0)
Acute kidney injury	1	1 (0)
Colitis	1	1 (0)
Hepatotoxicity	1	1 (0)
Infusion-related reaction, %	**12**	**1 (0)**

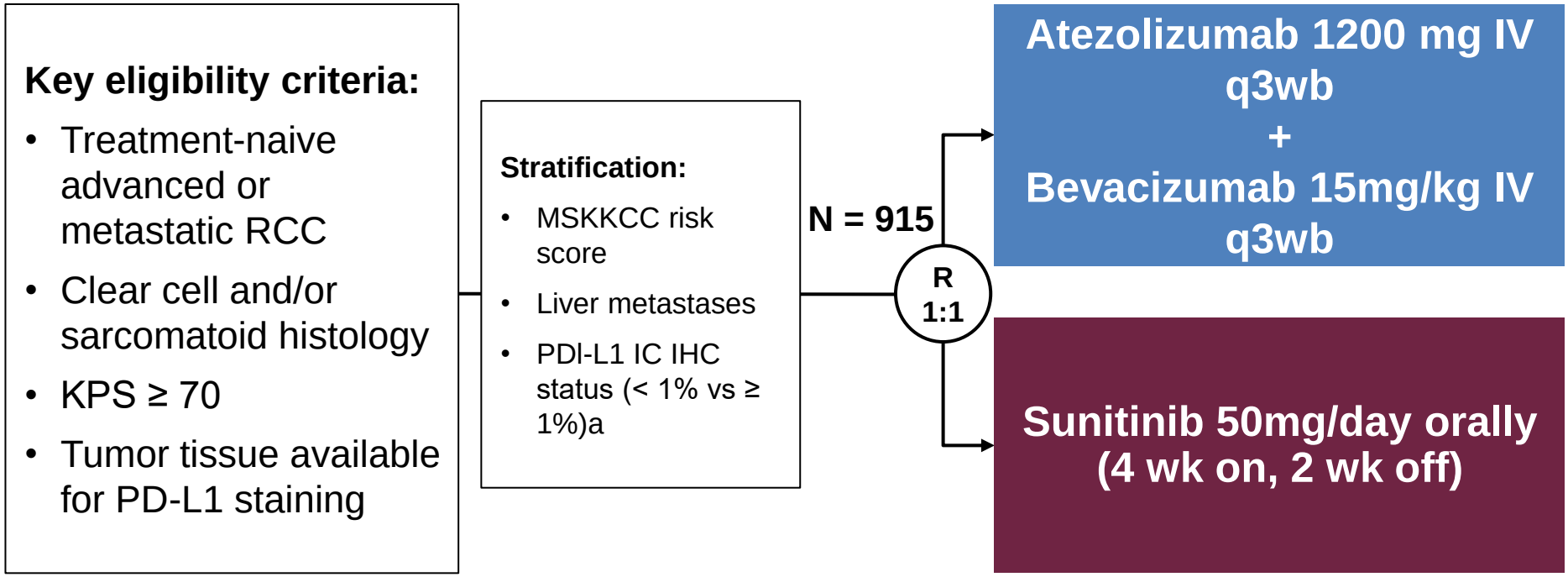
High-dose corticosteroids* were administered to 11% of patients who experienced an immune-related AE.

AE: adverse event

Motzer RJ, et al. Presented at ESMO 2018; Abstract #LAB6_PR.

Atezolizumab + Bevacizumab vs. Sunitinib for First-line Treatment of mRCC

IMmotion151 Study Design



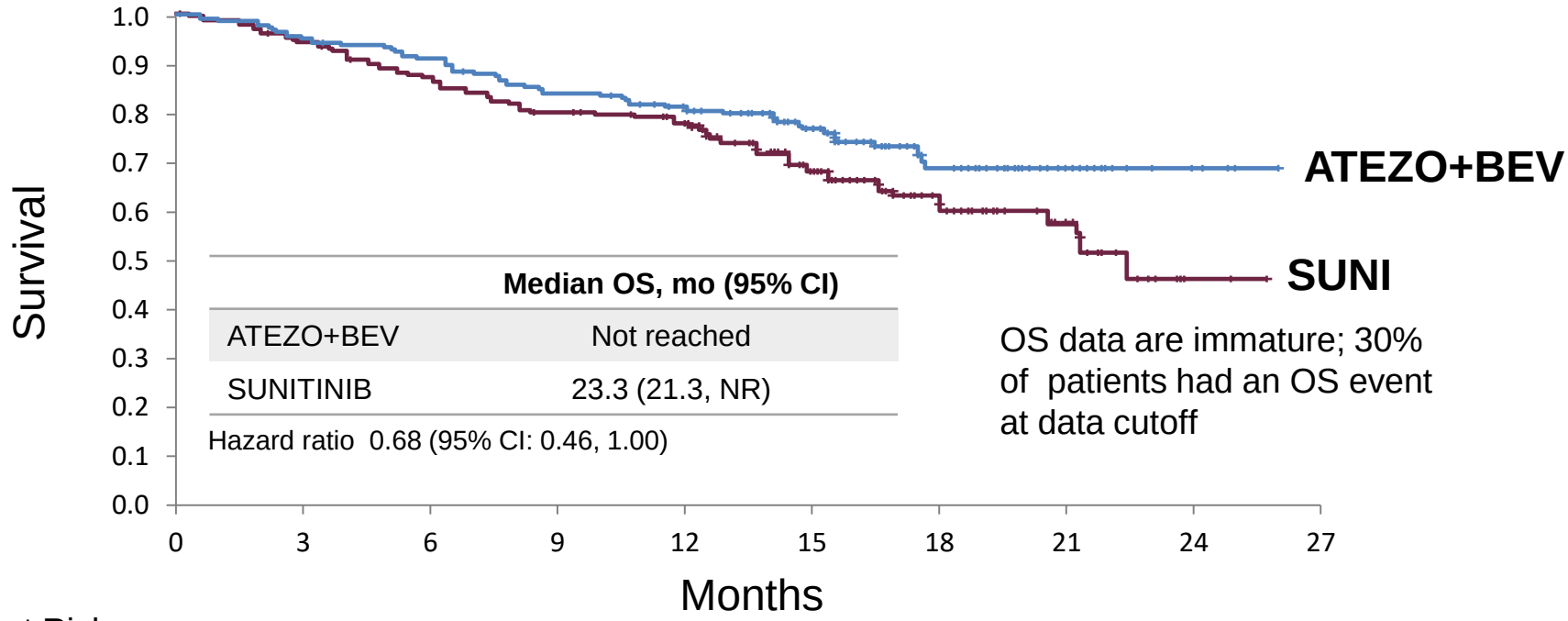
Two co-primary endpoints:

- Progression-free survival (assessed by investigator) in PD-L1+ patients
- Overall survival in ITT population

IC IHC: immune cells by immunohistochemistry; ITT: intent to treat; IV: intravenously; KPS, Karnofsky performance status; mRCC: metastatic RCC; MSKCC: Memorial Sloan Kettering Cancer Center; PD-L1: programmed death-ligand 1; Q3W, every 3 weeks; R: randomization; RCC: renal cell carcinoma

Motzer RJ, et al. Presented at GU-ASCO 2018; Abstract #578.

IMmotion 151: Overall Survival in PD-L1 + population

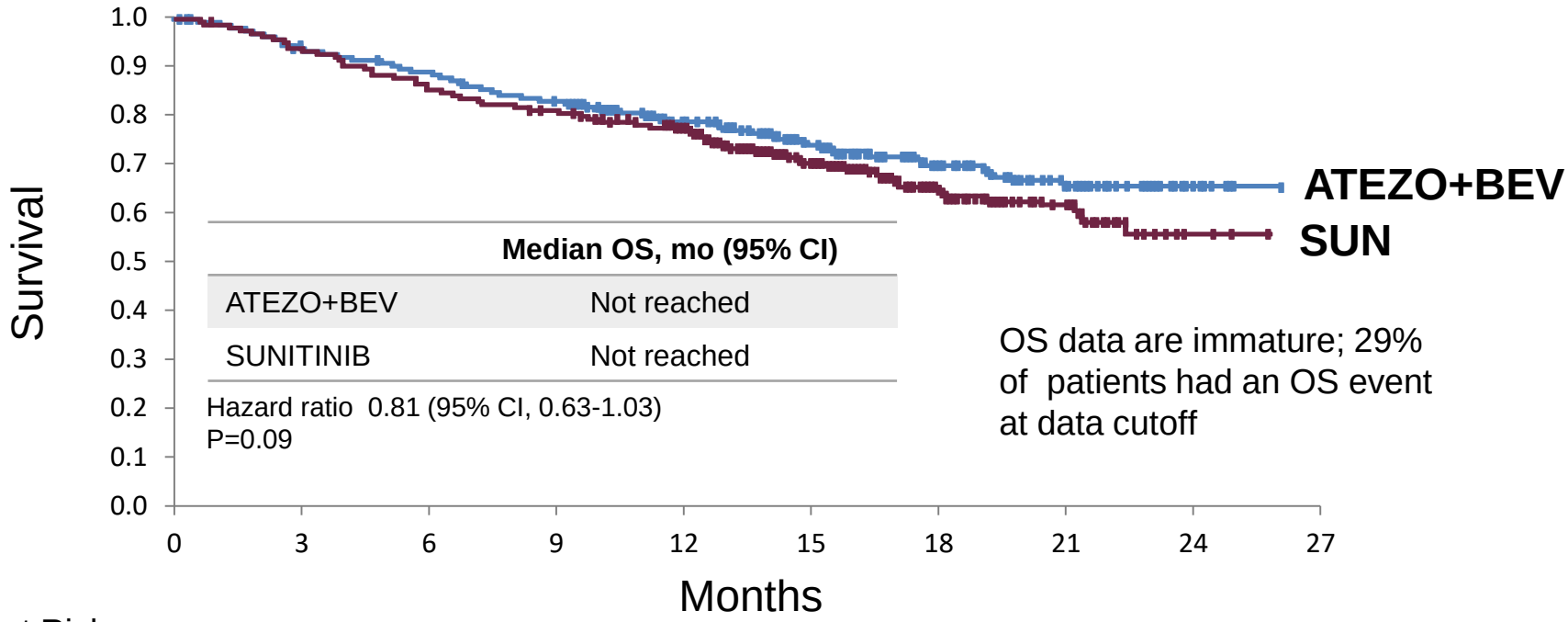


No. at Risk										
ATEZO+BEV	178	169	160	147	139	109	55	26	6	
SUNI	184	169	154	141	134	96	51	27	6	

- NR, not reached. Minimum follow-up, 12 mo. Median follow-up, 15 mo. Event/patient ratio: 25% for atezo + bev, 35% for sunitinib.

Motzer RJ, et al. Presented at GU-ASCO 2018; Abstract #578.

IMmotion 151: Overall Survival in ITT population



No. at Risk

ATEZO+BEV	454	428	398	371	341	246	141	69	18	
SUN	461	422	384	357	331	227	126	65	15	

Atezo: atezolizumab; Bev: bevacizumab; CI: confidence interval; HR: hazard ratio; mRCC: metastatic renal cell carcinoma; OS: overall survival; PD-L1: programmed death-ligand 1

Motzer RJ, et al. Presented at GU-ASCO 2018; Abstract #578.

Key Learnings from Keynote-426, JAVELIN and IMmotion151

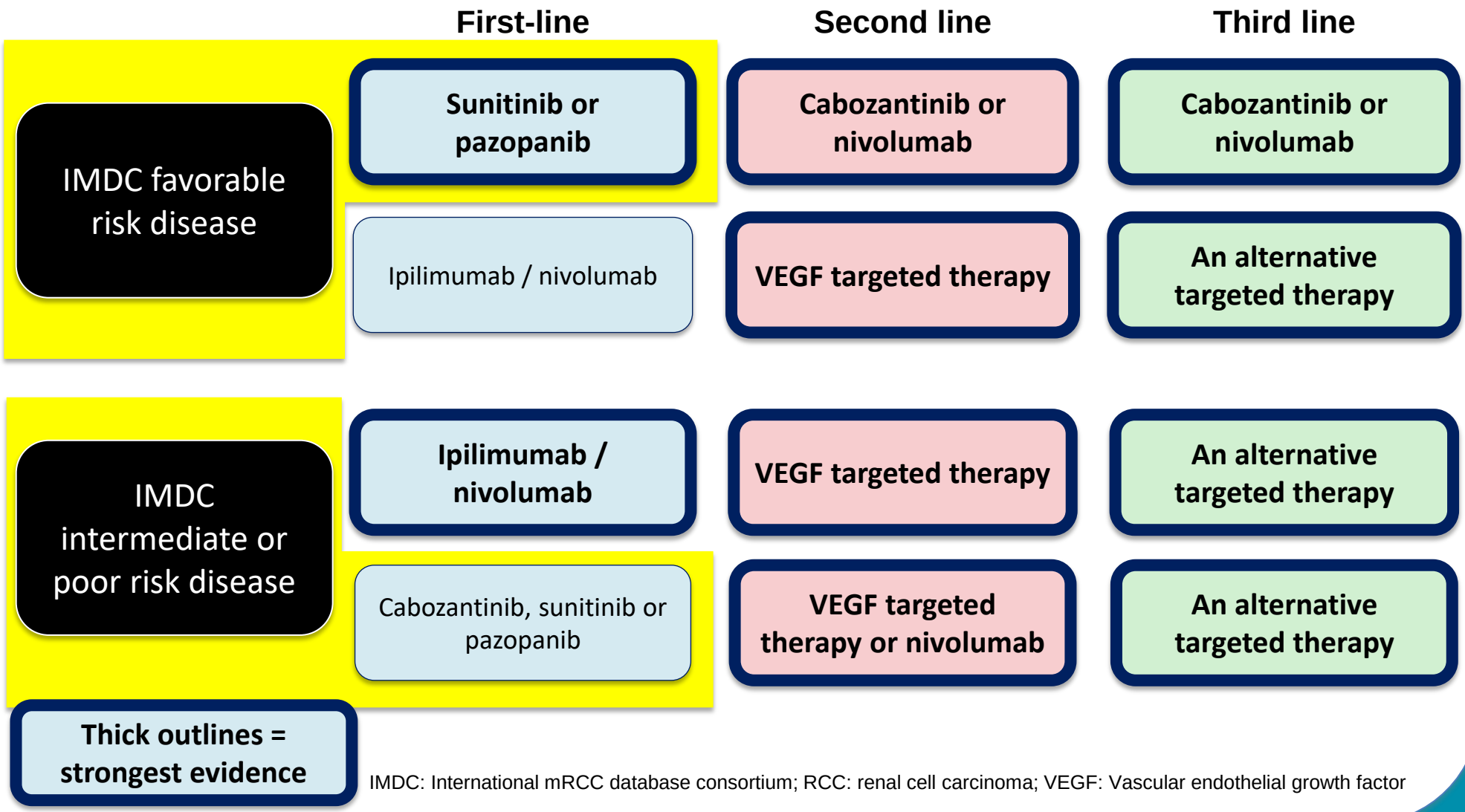
- In the KEYNOTE-426 study, Pembrolizumab plus axitinib demonstrated superior efficacy (OS, PFS, ORR) compared with sunitinib in patients with previously untreated, locally advanced or metastatic clear-cell RCC.
- JAVELIN Renal 101 demonstrated longer PFS and higher ORR with avelumab + axitinib compared to sunitinib for treatment-naive patients with advanced RCC. Study continues to follow up for OS.
- IMmotion151 met its co-primary PFS endpoint, demonstrating improved PFS for atezolizumab + bevacizumab over sunitinib in patients with PD-L1+ disease. OS data is pending, but presumed negative.

1. Powles T, et al. Presented at GU-ASCO 2019; Abstract #543.

Targeted Therapy in 1st-line

Still a Viable Option in the Immuno-oncologic Era

European Association of Urology: 2018 Algorithm for the Management of Metastatic, Clear-cell RCC

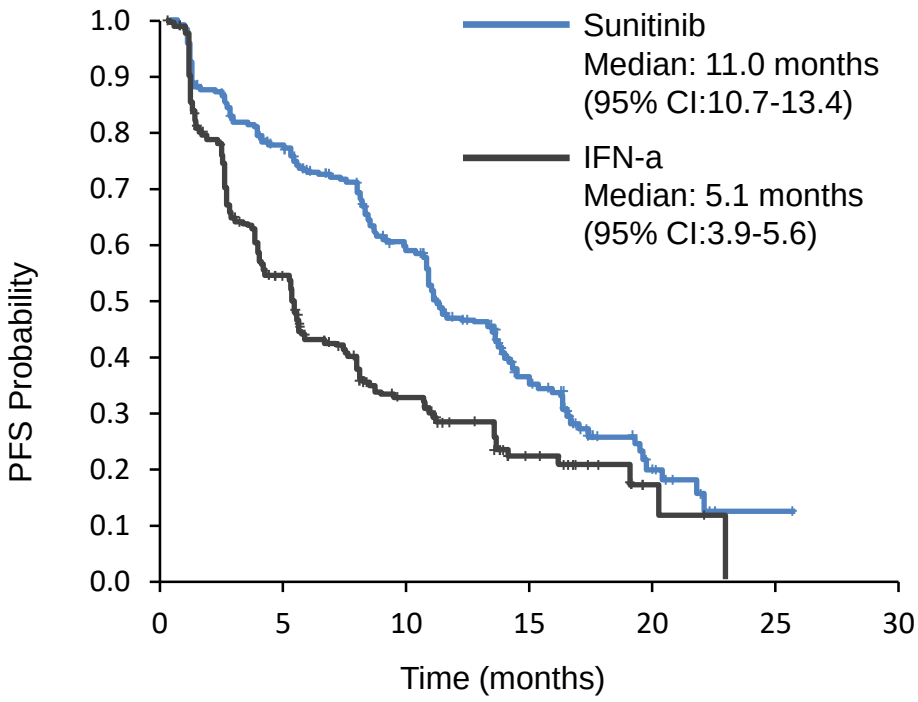


IMDC: International mRCC database consortium; RCC: renal cell carcinoma; VEGF: Vascular endothelial growth factor

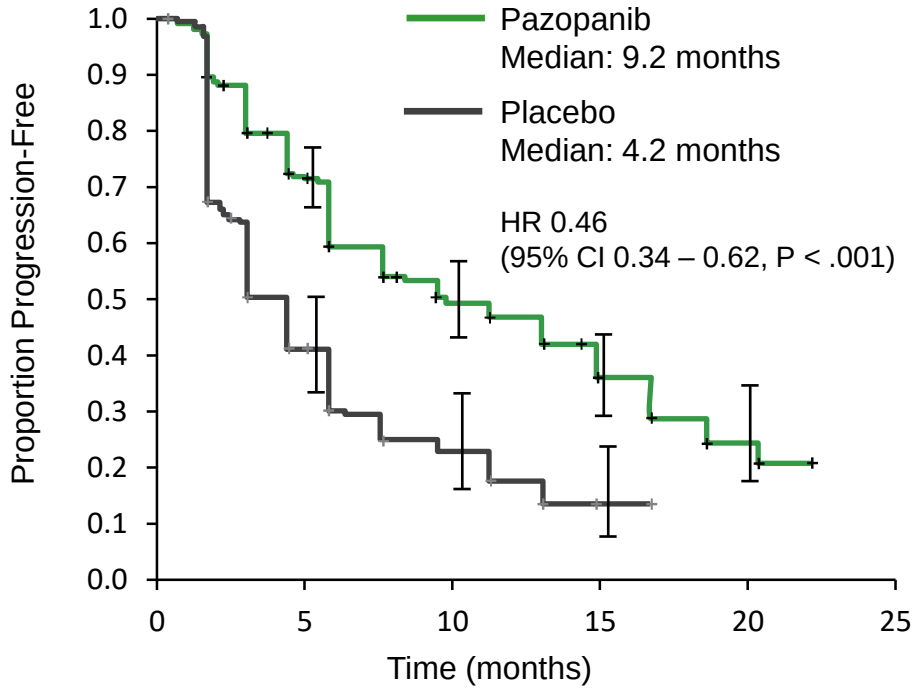
Powles T, et al. Eur Urol 2018; 73:311-5.

Evidence for First-line Targeted Treatment in mRCC: Progression-free Survival in Pivotal Trials

Sunitinib *vs.* IFN-a[1]



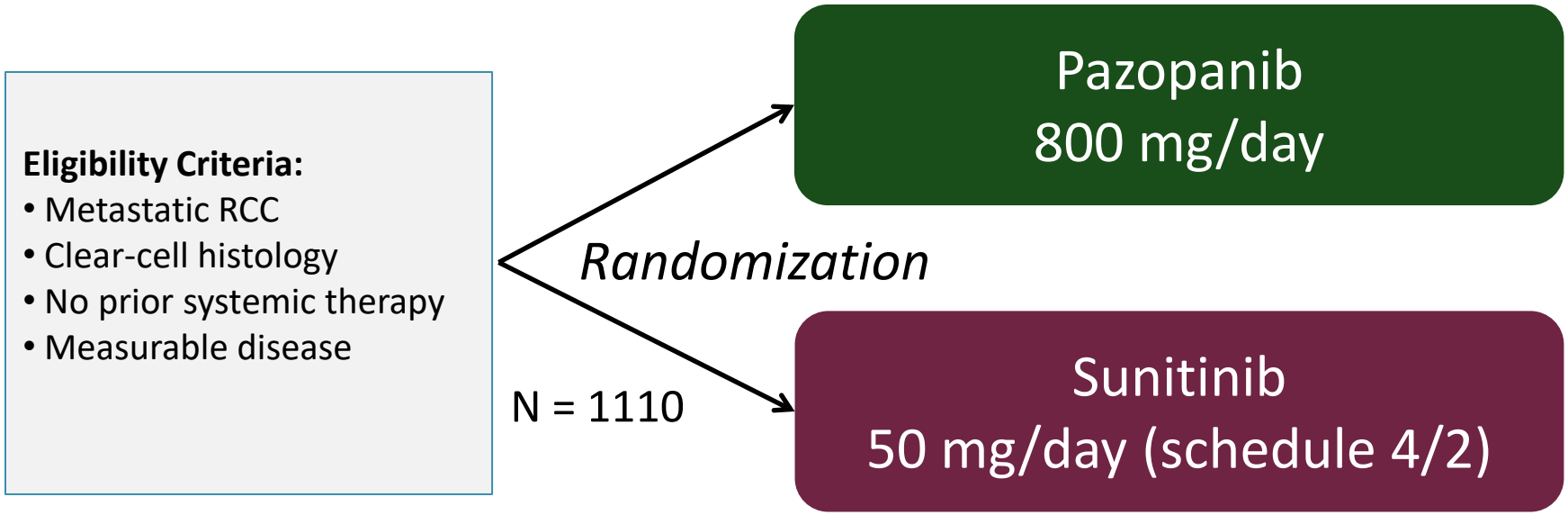
Pazopanib *vs.* Placebo[2]



CI: confidence interval; HR: hazard ratio; mRCC: metastatic renal cell carcinoma; PFS: progression-free survival

1. Motzer RJ, et al. *N Engl J Med* 2007; 356:115-24.
2. Sternberg CN, et al. *J Clin Oncol* 2010; 28:1061-8.

Pazopanib vs Sunitinib in 1st-line mRCC (COMPARZ)



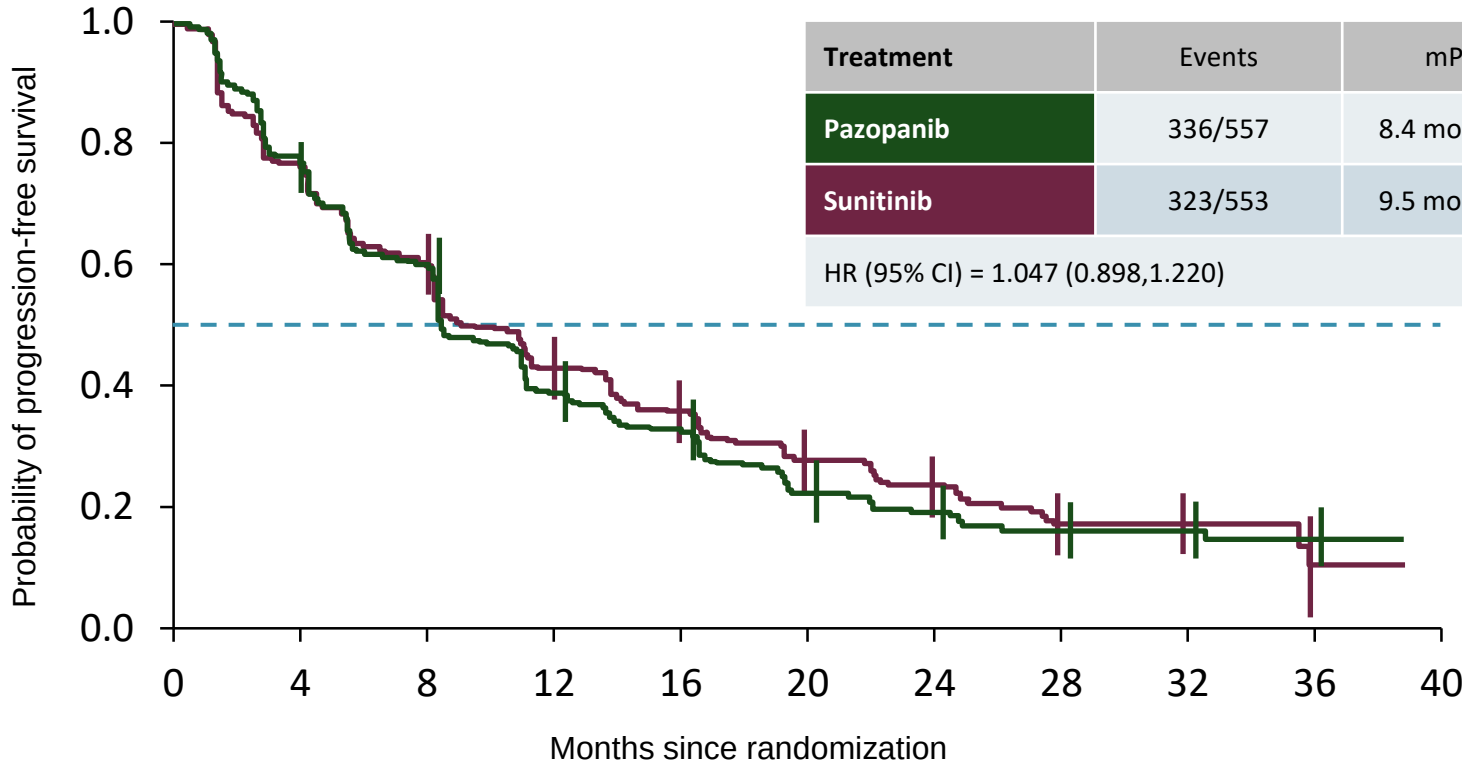
Primary endpoint: PFS (non-inferiority – HR<1.25)
Secondary endpoints: OS, ORR, safety, QoL

- Randomized 1:1
- Dose reduction(s) were allowed but schedule changes were not

HR: hazard ratio; mRCC: metastatic renal cell carcinoma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; QoL: quality of life

Motzer RJ, et al. *N Engl J Med* 2013; 369:722-31.

COMPARZ: Pazopanib is Noninferior to Sunitinib—PFS by Independent Review (Primary Endpoint)



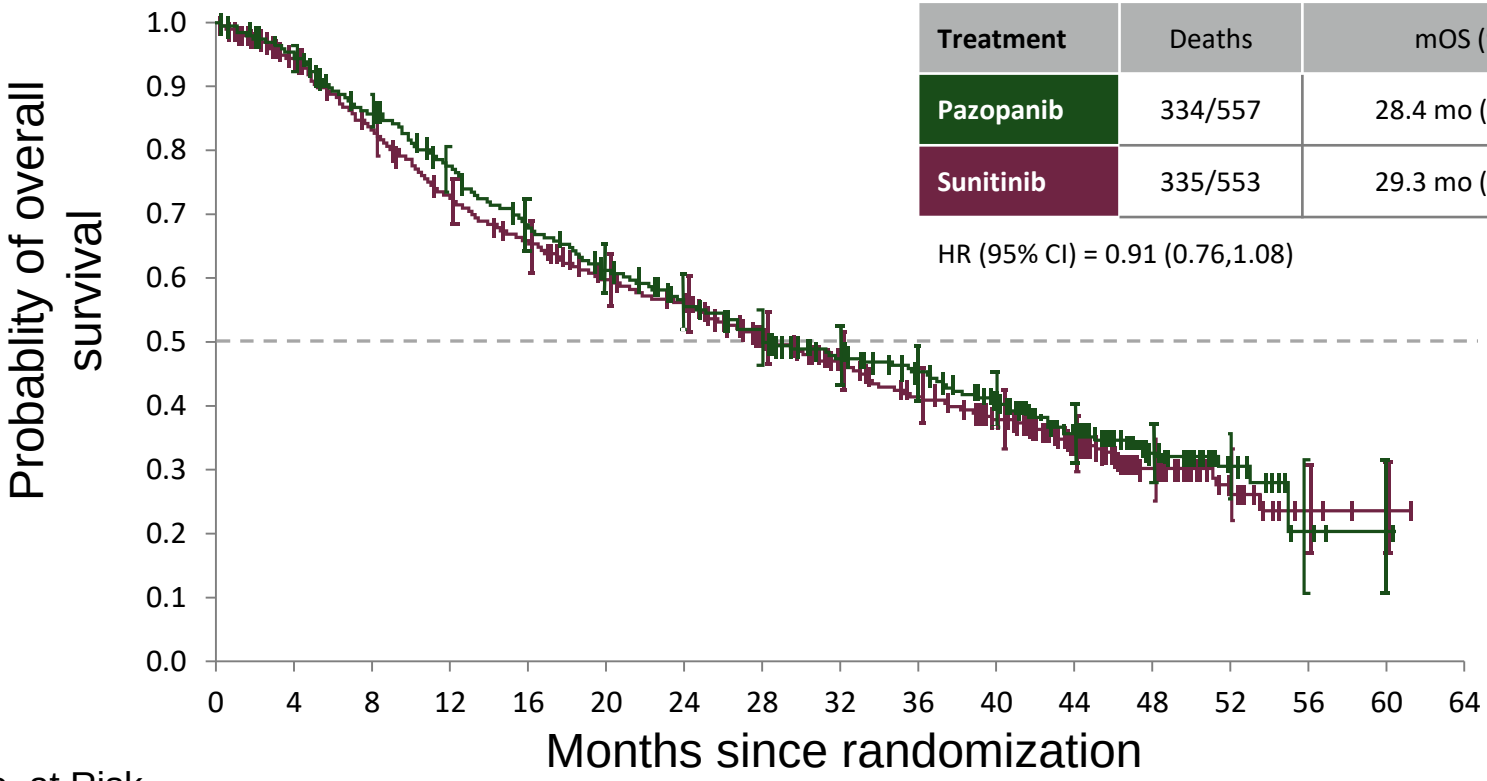
Treatment	Events	mPFS (95% CI)
Pazopanib	336/557	8.4 months (8.3, 10.9)
Sunitinib	323/553	9.5 months (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		

No. at Risk										
Pazopanib	557	361	245	136	105	61	46	19	13	1
Sunitinib	553	351	249	147	111	69	48	18	10	3

CI: confidence interval; HR: hazard ratio; mPFS: median PFS; PFS: progression-free survival

Motzer RJ, et al. *N Engl J Med* 2013; 369:722-31.

COMPARZ: No Significant Difference in Overall Survival (Secondary Endpoint)



Treatment	Deaths	mOS (95% CI)
Pazopanib	334/557	28.4 mo (26.2, 35.6)
Sunitinib	335/553	29.3 mo (25.3, 32.5)

HR (95% CI) = 0.91 (0.76,1.08)

No. at Risk

PAZO	557	521	462	409	360	320	284	243	221	197	169	99	51	21	4	1	0
SUNI	553	501	435	377	339	304	281	237	211	180	153	100	45	20	4	1	0

CI: confidence interval; HR: hazard ratio; mOS: median overall survival

Motzer RJ, et al. *N Engl J Med* 2014; 370(18):1769-70.

First-line Sunitinib vs Pazopanib: Data from the Canadian Kidney Cancer information system (CKCis)

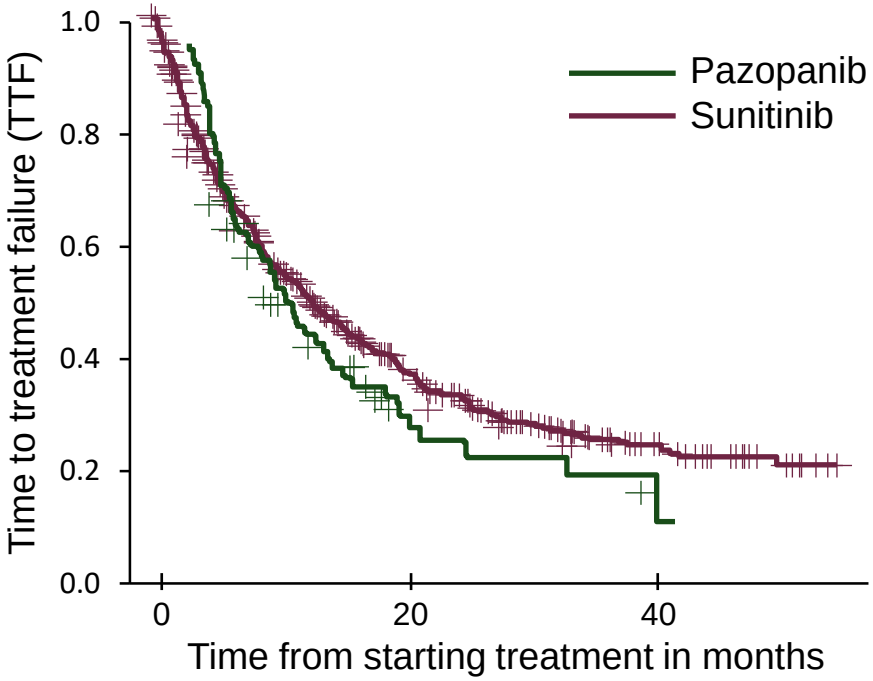
	Pazopanib (N=93)	Sunitinib (N=577)	*P* value
Age (median)	65 (43-82)	64 (32-83)	0.065
Gender: Male Female	 64/93 (69%) 29/93 (31%)	 429/577 (74%) 148/577 (26%)	0.257
KPS <80%	22/85 (26%)	84/494 (17%)	0.067
Diagnosis to treatment <1 year	44/93 (47%)	321/573 (56%)	0.144
Calcium – high	8/68 (12%)	68/398 (17%)	0.374
Hemoglobin – low	40/82 (49%)	238/487 (49%)	1.000
Neutrophils – high	10/80 (12%)	42/504 (8%)	0.211
Platelets – high	10/83 (12%)	40/515 (8%)	0.200
IMDC risk group: Favourable Intermediate Poor	 15/60 (25%) 33/60 (55%) 12/60 (20%)	 68/313 (22%) 183/313 (58%) 62/313 (20%)	0.807

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status

Lalani AA, et al. *Can Urol Assoc J* 2017; 11(3-4):112-7.

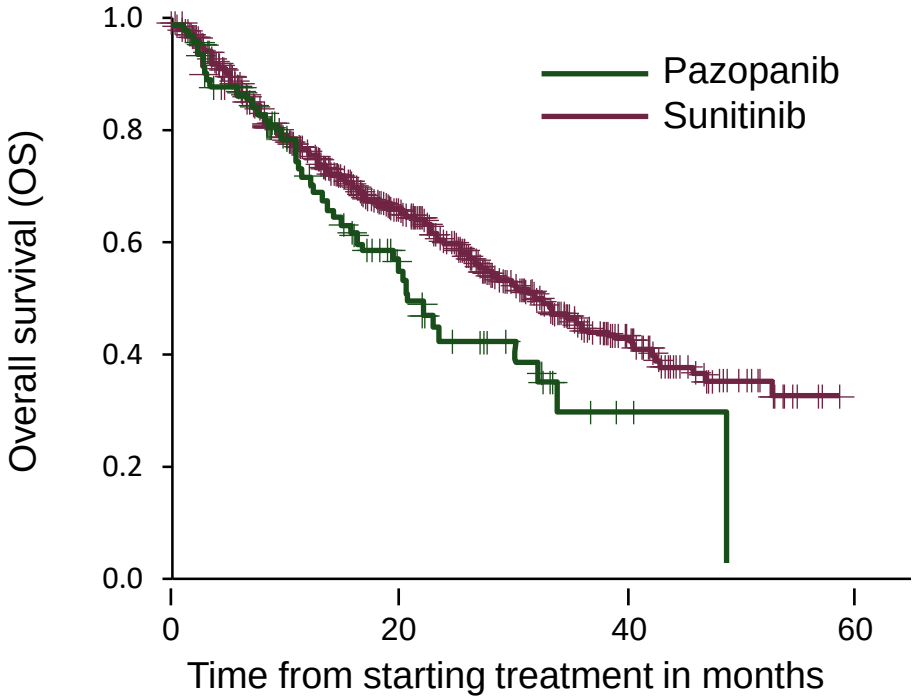
CKCis 1st Line Sunitinib vs Pazopanib: Efficacy Endpoints

Time-to-Treatment Failure



Median TTF (months)
Sunitinib 11.0 vs Pazopanib 8.4 (p=0.13)
Adjusted HR 0.87 (95% CI 0.59 – 1.28)

Overall Survival

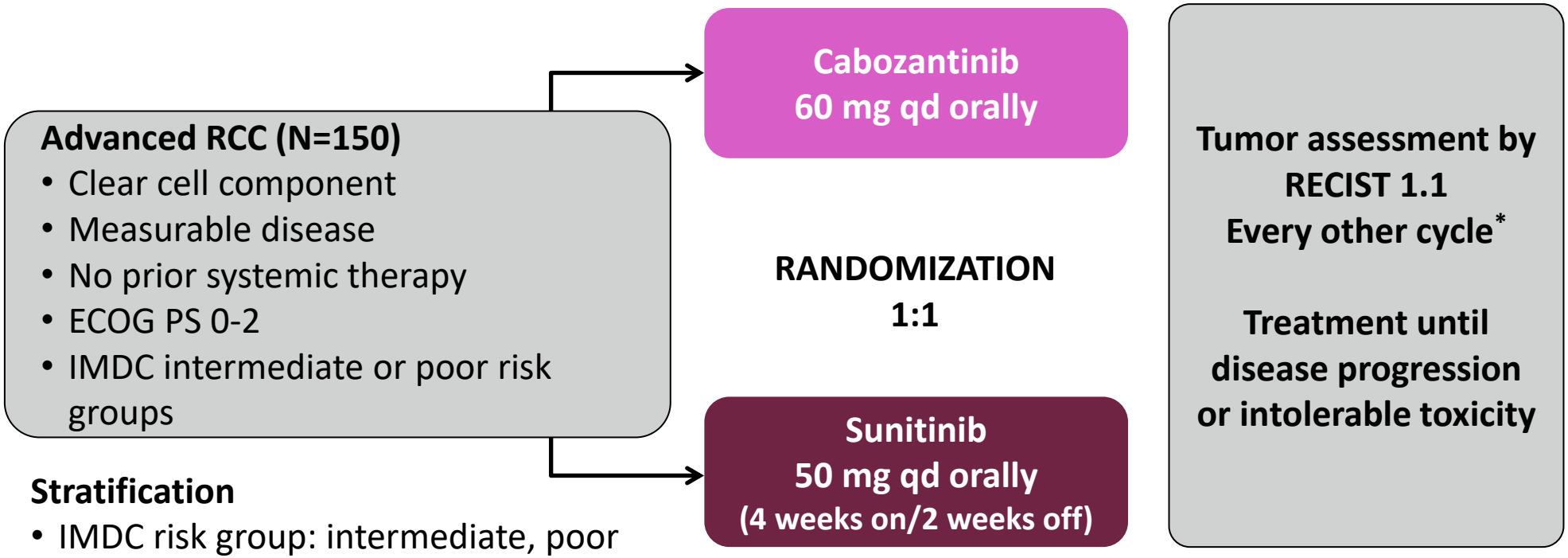


Median OS (months)
Sunitinib 31.7 vs Pazopanib 20.6 (p=0.028)
Adjusted HR 0.60 (95% CI 0.38 – 0.94)

CI: confidence interval; HR: hazard ratio

Lalani AA, et al. *Can Urol Assoc J* 2017; 11(3-4):112-7.

Cabozantinib as an Alternative to Sunitinib or Pazopanib: Phase 2 CABOSUN Study Design



*One treatment cycle was defined as 6 weeks.

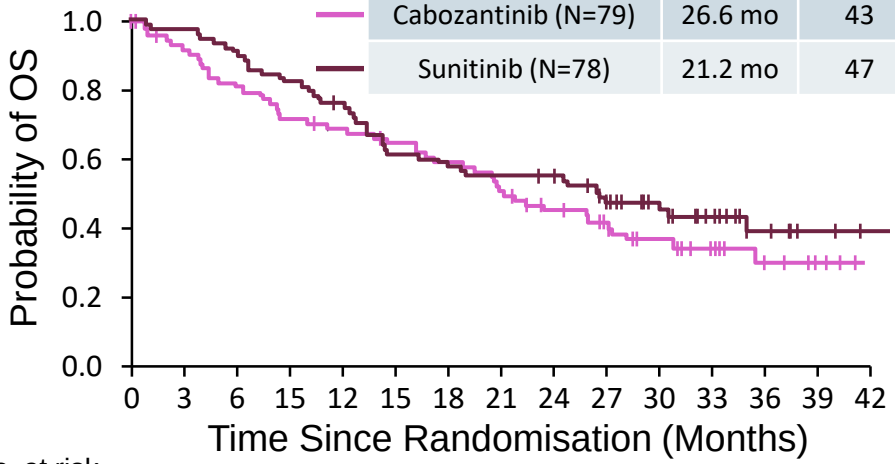
ECOG: Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium; RCC: renal cell carcinoma; RECIST: response evaluation criteria in solid tumors

Choueiri TK, et al. *J Clin Oncol* 2017; 35(6):591-7.

Phase 2 CABOSUN Study: Overall and Progression-free Survival

Overall Survival: Trend in Favor of Cabozantinib

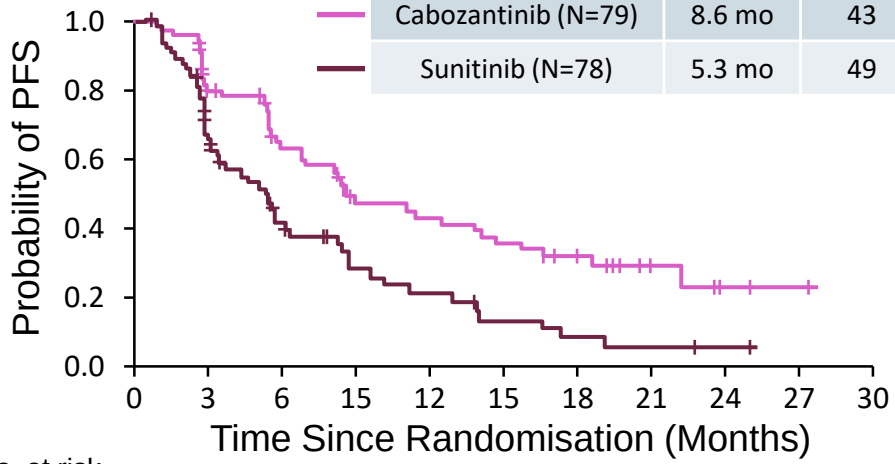
	Median OS	No. of Deaths
Cabozantinib (N=79)	26.6 mo	43
Sunitinib (N=78)	21.2 mo	47



No. at risk															
CABO	79	76	71	64	58	47	45	42	41	31	23	15	8	4	2
SUNI	78	69	61	53	50	46	42	36	29	24	17	12	6	3	0

PFS: Cabozantinib Significantly Longer than Sunitinib

	Median PFS	No. of Events
Cabozantinib (N=79)	8.6 mo	43
Sunitinib (N=78)	5.3 mo	49



No. at risk															
CABO	79	51	37	24	22	18	12	5	2	1	0	79	51	37	24
SUNI	78	36	21	12	9	5	3	2	1	0	0	78	36	21	12

Key caveats about CABOSUN:

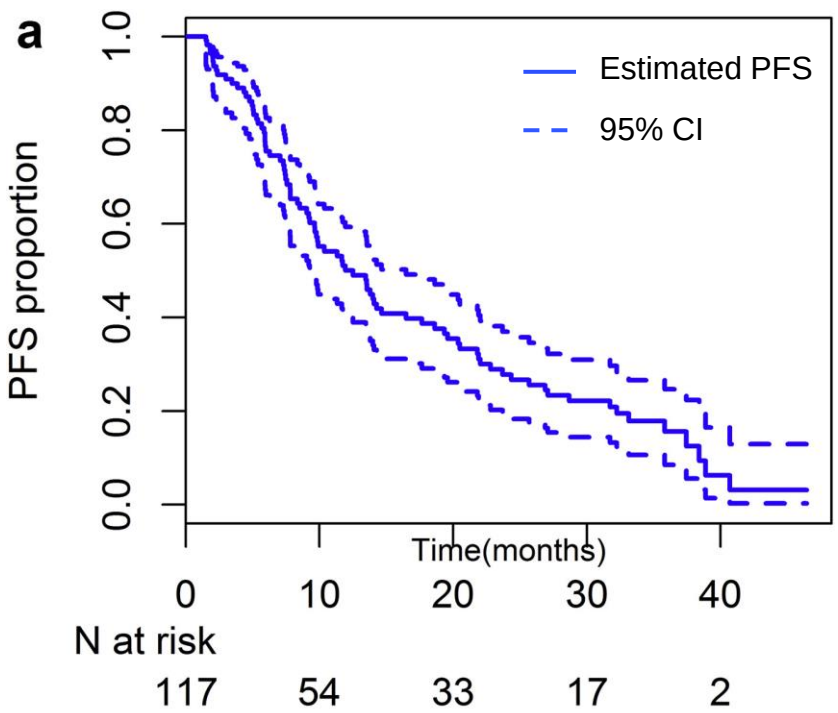
- Phase 2 trial: validation from a prospective phase 3 study required to be practice-changing
- Limited sample size, relies on investigator reports for PFS

CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival

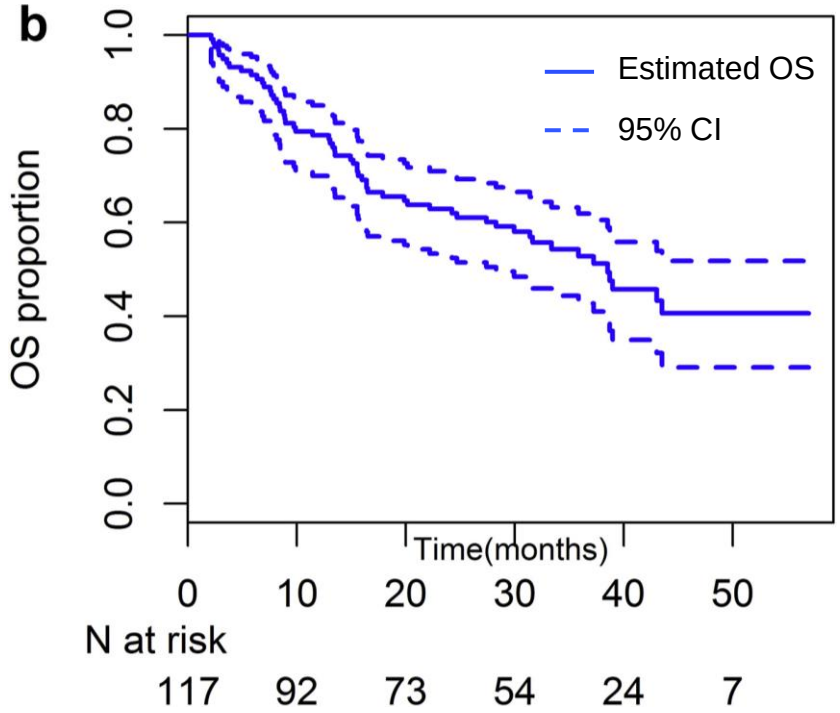
Choueiri TK, et al. *Eur J Cancer* 2018; 94:115-25.

The efficacy and safety of sunitinib given on an individualized schedule as first-line therapy for mRCC

Progression – Free Survival



Overall Survival



OS: overall survival; PFS: Progression-Free Survival

Bjarnason GA et al. Eur J Cancer. 2019 Feb;108:69-77.

Targeted Therapy in First-line Treatment of mRCC: Summary

- Targeted therapy is a recommended approach for patients with favorable IMDC risk
  - Both sunitinib and pazopanib are reasonable choices
  - Phase 2 data with cabozantinib suggest that it may be another good option, but need more robust data
  - Recent data suggests ipilimumab + nivolumab as an alternative in this setting
- For patients with intermediate or poor risk, nivolumab + ipilimumab is the recommended approach
  - Targeted therapy can be used for patients who are not good candidates for immuno-oncology treatment
- Dose individualization is important to optimize outcomes with targeted agents

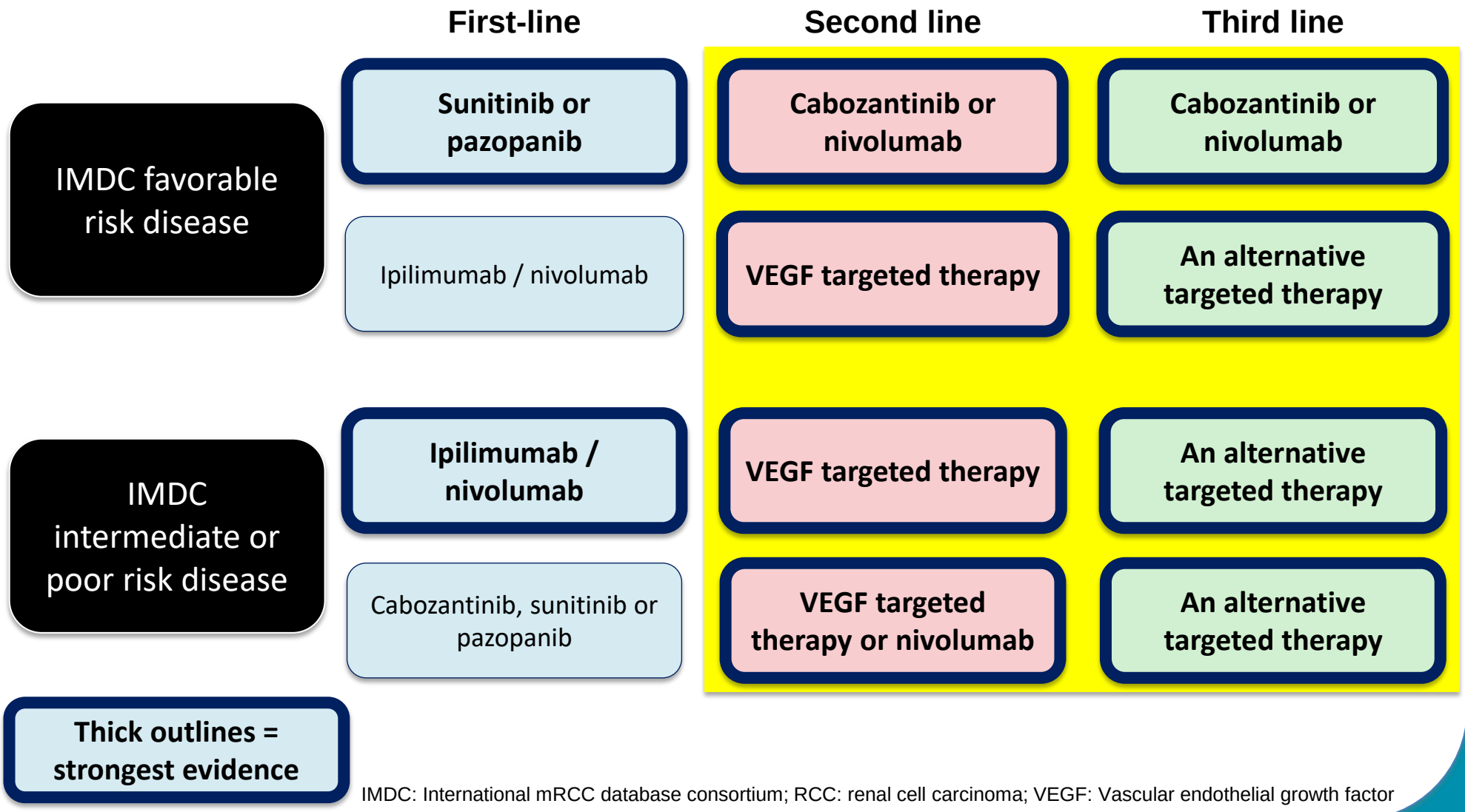
IMDC, International Metastatic RCC Database Consortium; mRCC: metastatic renal cell carcinoma

Powles T, et al. Eur Urol 2018; 73:311-5.

What About 2nd and 3rd-line Therapy for mRCC?

A few slides of guidance from the NCCN and EAU Guidelines

European Association of Urology: 2018 Algorithm for the Management of Metastatic, Clear-cell RCC



IMDC: International mRCC database consortium; RCC: renal cell carcinoma; VEGF: Vascular endothelial growth factor

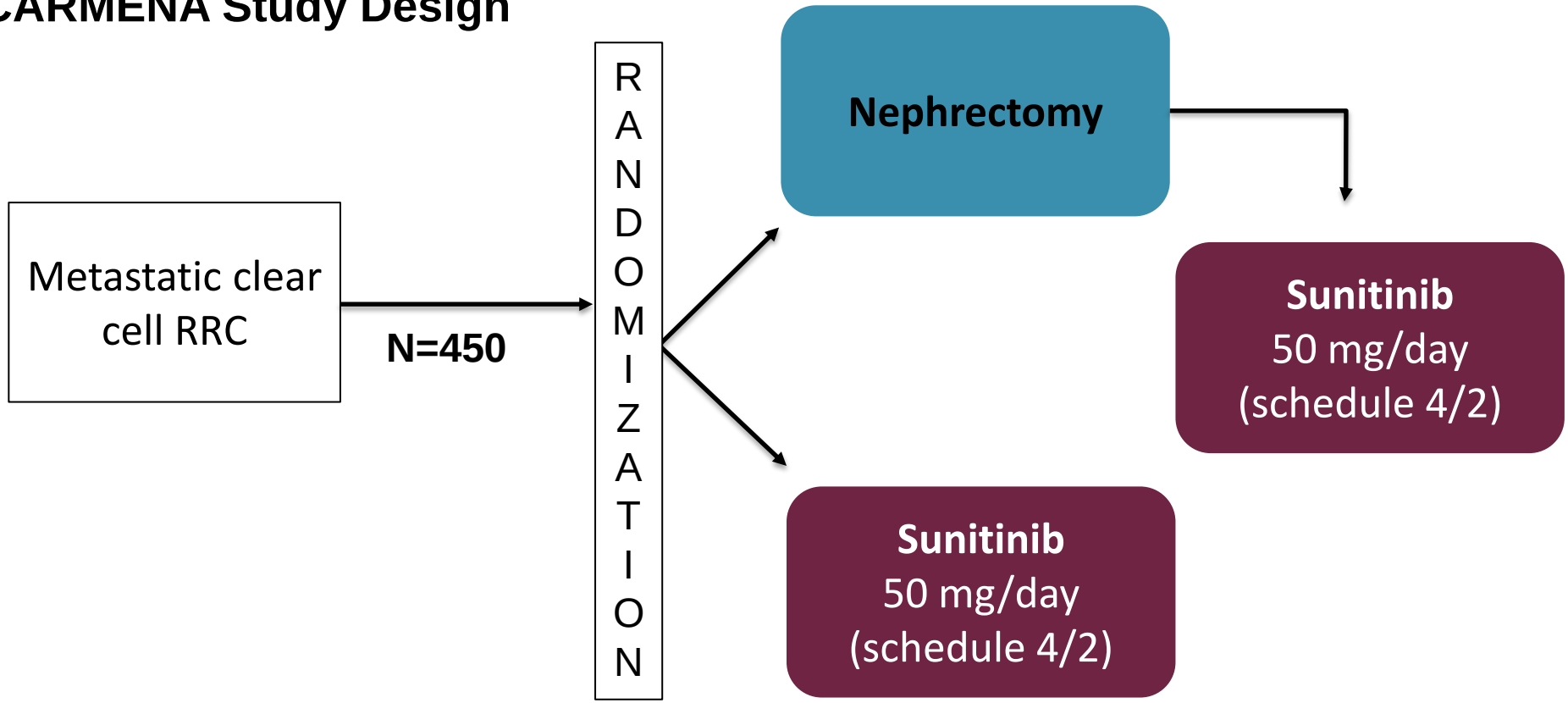
Powles T, et al. *Eur Urol* 2018; 73:311-5.

What is the Role of Cytoreductive Nephrectomy in mRCC?

Important Information from the CARMENA Study

Sunitinib ± Cytoreductive Nephrectomy in Intermediate / Poor Risk mRCC

CARMENA Study Design

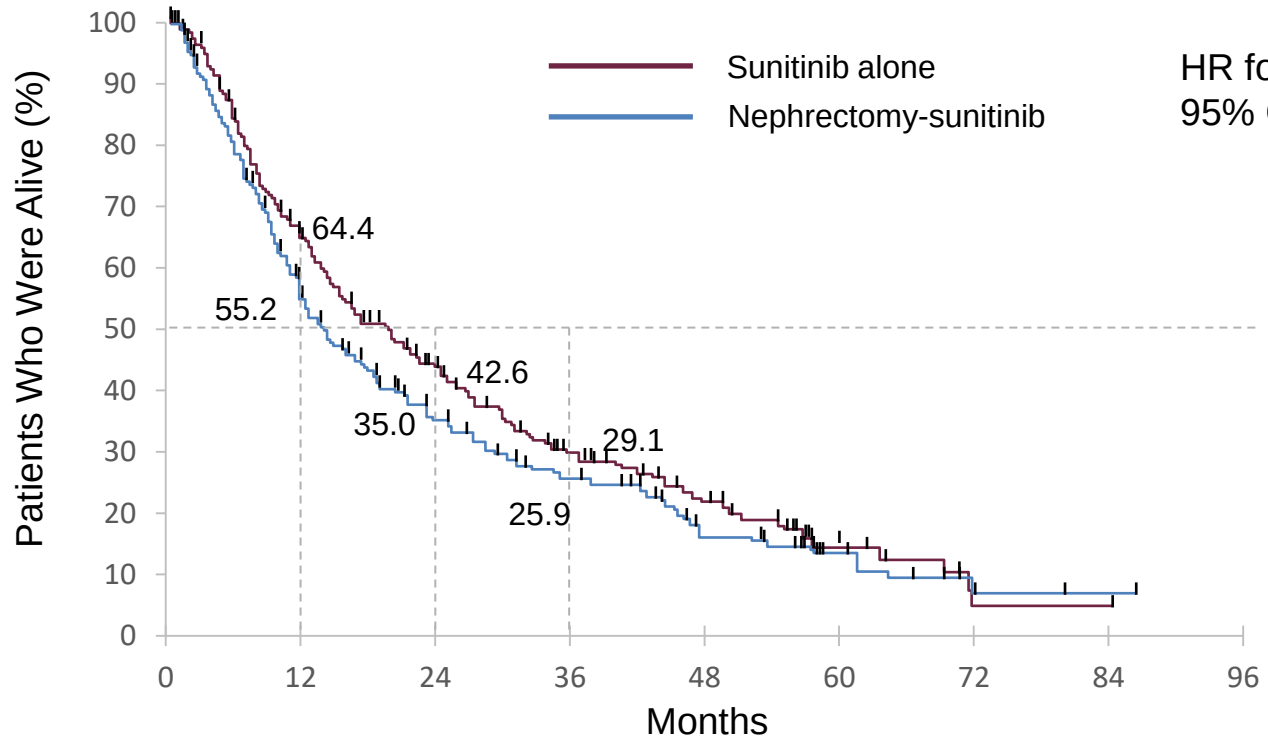


Primary endpoint: Overall survival

mRCC: metastatic renal cell carcinoma

Méjean A, et al. *N Engl J Med* 2018; 379(5):417-27.

CARMENA Study: Sunitinib Alone is Noninferior to Nephrectomy Followed by Sunitinib in Intermediate- or Poor-risk mRCC



HR for death: 0.89;
95% CI 0.71 to 1.10

No. at Risk

Nephrectomy-sunI	226	110	61	40	19	11	4	1	0
Sunitinib alone	224	128	76	44	26	8	3	1	0

NB: Sunitinib alone was also non-inferior for the PFS analysis.

CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

Méjean A, et al. *N Engl J Med* 2018; 379(5):417-27.

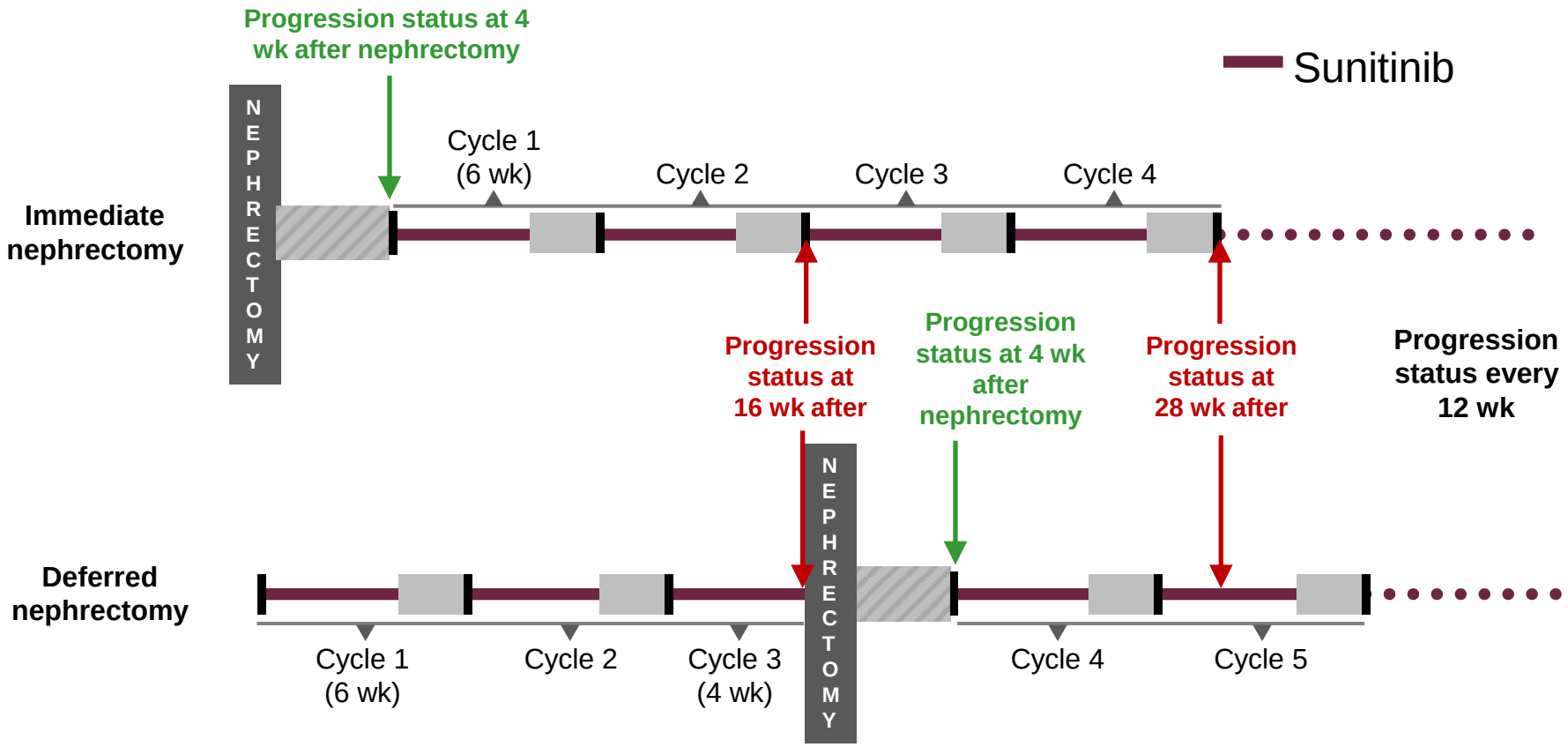
Implications of CARMENA on Treatment Selection and Sequence

- CARMENA trial showed that sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who had been classified as having MSKCC intermediate-risk or poor-risk disease.
- Immunotherapy (nivolumab and ipilimumab) is now considered first-line therapy for most patients fitting these criteria (intermediate/poor risk mRCC)
- The role and sequence of cytoreductive nephrectomy in the era of immunotherapy needs to be reinvestigated

mRCC: metastatic renal cell carcinoma

Bex A, et al. *Eur Urol* 2018; 74(6):805-9.
Méjean A, et al. N Engl J Med 2018; 379(5):417-27.

Immediate vs. Deferred Cytoreductive Nephrectomy for Clear Cell mRCC (SURTIME): Study Design



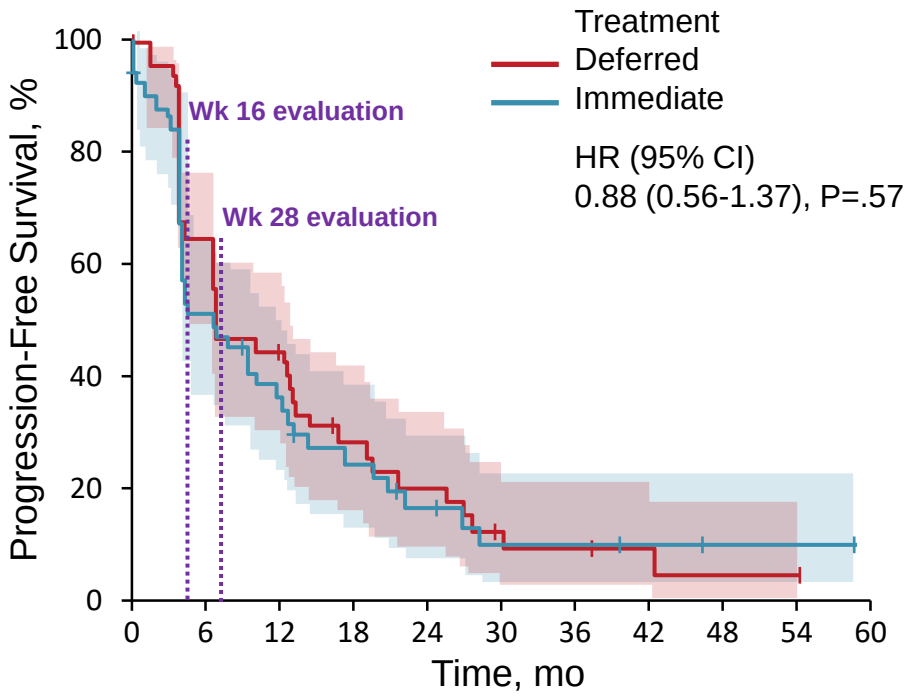
Primary endpoint: ITT 28-week progression-free rate.
Secondary endpoints: Overall survival, adverse events, post-operative progression.

mRCC: metastatic renal cell carcinoma

Bex A, *et al. JAMA Oncol* 2018; Dec. 18 [epub ahead of print].

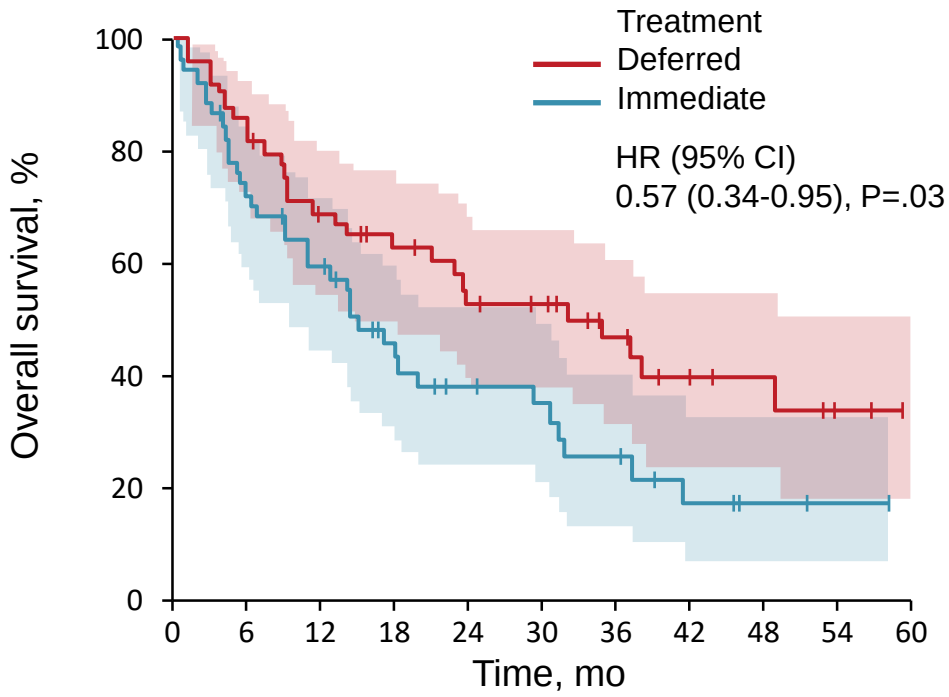
Immediate vs. Deferred Cytoreductive Nephrectomy for Clear Cell mRCC (SURTIME): Results

Progression-free Survival



Deferred	49	30	19	11	8	3	3	2	1	1	0
Immediate	50	25	16	10	6	3	3	2	1	1	0

Overall Survival



Deferred	49	42	32	27	23	20	14	10	7	5	2
Immediate	50	35	28	18	13	11	8	4	2	1	0

mRCC: metastatic renal cell carcinoma

Bex A, *et al. JAMA Oncol* 2018; Dec. 18 [epub ahead of print].

What Does the Future Hold?

Ongoing Studies in mRCC

Ongoing Phase 3 Studies with Immuno-oncology Therapies in Advanced RCC

Study name	Interventions	N	Primary endpoint(s)	Projected primary completion date
KEYNOTE-679[1] (NCT03631784)	Pembrolizumab + epacadostat vs. sunitinib or pazopanib	129	ORR	Aug. 2018
Checkmate-9ER[2] (NCT03141177)	Nivolumab + cabozantinib vs. sunitinib	630	PFS	Sept. 2019
CLEAR[3] (NCT02811861)	Lenvatinib + everolimus vs. lenvatinib + pembrolizumab vs. sunitinib	1,050	PFS	Apr. 2020
CA045002[4] (NCT03729245)	Nivolumab + NKTR-214 vs. sunitinib or cabozantinib	600	ORR, OS	Dec. 2021

ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma

1. https://clinicaltrials.gov/ct2/show/NCT03631784. Accessed March 3, 2019.
2. https://clinicaltrials.gov/ct2/show/NCT03141177. Accessed March 3, 2019.
3. https://clinicaltrials.gov/ct2/show/NCT02811861. Accessed March 3, 2019.
4. https://clinicaltrials.gov/ct2/show/NCT03729245. Accessed March 3, 2019.

Ongoing Phase 3 Study with Targeted Therapies in Advanced RCC

Study name	Interventions	N	Primary endpoint(s)	Projected primary completion date
RENAVIV[1] (NCT03592472)	Pazopanib + abexinostat vs. pazopanib	413	PFS	Jan. 2022

PFS: progression-free survival; RCC: renal cell carcinoma

1. https://clinicaltrials.gov/ct2/show/NCT03592472. Accessed March 3, 2019.

What About Neoadjuvant / Adjuvant Therapy for RCC?

List of Ongoing Studies

Ongoing Studies with Immuno-Oncology Therapy in the Adjuvant / Neo-adjuvant Setting

Study name	Interventions	N	Primary endpoint(s)	Projected primary completion date
IMmotion010[1]	Atezolizumab vs. placebo	664	DFS	May 2022
CheckMate 914[2]	Nivolumab + ipilimumab vs. placebo	800	DFS	Sept. 2022
KEYNOTE-564[3]	Pembrolizumab vs. placebo	950	DFS	Nov. 2022
PROSPER-RCC[4]	Nivolumab + nephrectomy vs. nephrectomy alone	805	RFS	Nov. 2023
RAMPART[5]	Durvalumab vs. Durvalumab + tremelimumab vs. active monitoring	1,750	DFS, OS	Dec. 2023

DFS: disease-free survival; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; RFS: recurrence-free survival

1. https://clinicaltrials.gov/ct2/show/NCT03024996. Accessed March 3, 2019.
2. https://clinicaltrials.gov/ct2/show/NCT03138512. Accessed March 3, 2019.
3. https://clinicaltrials.gov/ct2/show/NCT03142334. Accessed March 3, 2019.
4. https://clinicaltrials.gov/ct2/show/NCT03055013. Accessed March 3, 2019.
5. https://clinicaltrials.gov/ct2/show/NCT03288532. Accessed March 3, 2019.

Supplemental slides

Typical Patient Profiles Based on IMDC risk Group

Favorable (IMDC score = 0)	
Age	55 years
Sex	Male
Time from diagnosis to treatment	2.5 years
Karnofsky performance status	90
Hemoglobin	157 g/L
Serum calcium	2.4 mmol/L
Neutrophils	4,600 x 10^6/L
Platelets	310 x 10^9/L

Intermediate-1 (IMDC score = 1)	
Age	67 years
Sex	Male
Time from diagnosis to treatment	18 months
Karnofsky performance status	80
Hemoglobin	115 g/L
Serum calcium	2.6 mmol/L
Neutrophils	4,800 x 10^6/L
Platelets	325 x 10^9/L

Typical Patient Profiles Based on IMDC risk Group

Intermediate-2 (IMDC score = 2)	
Age	72 years
Sex	Female
Time from diagnosis to treatment	15 months
Karnofsky performance status	70
Hemoglobin	115 g/L
Serum calcium	2.45 mmol/L
Neutrophils	5,100 x 10^6/L
Platelets	390 x 10^9/L

Poor (IMDC score ≥3)	
Age	77 years
Sex	Male
Time from diagnosis to treatment	10 months
Karnofsky performance status	70
Hemoglobin	124 g/L
Serum calcium	2.85 mmol/L
Neutrophils	6,200 x 10^6/L
Platelets	325 x 10^9/L