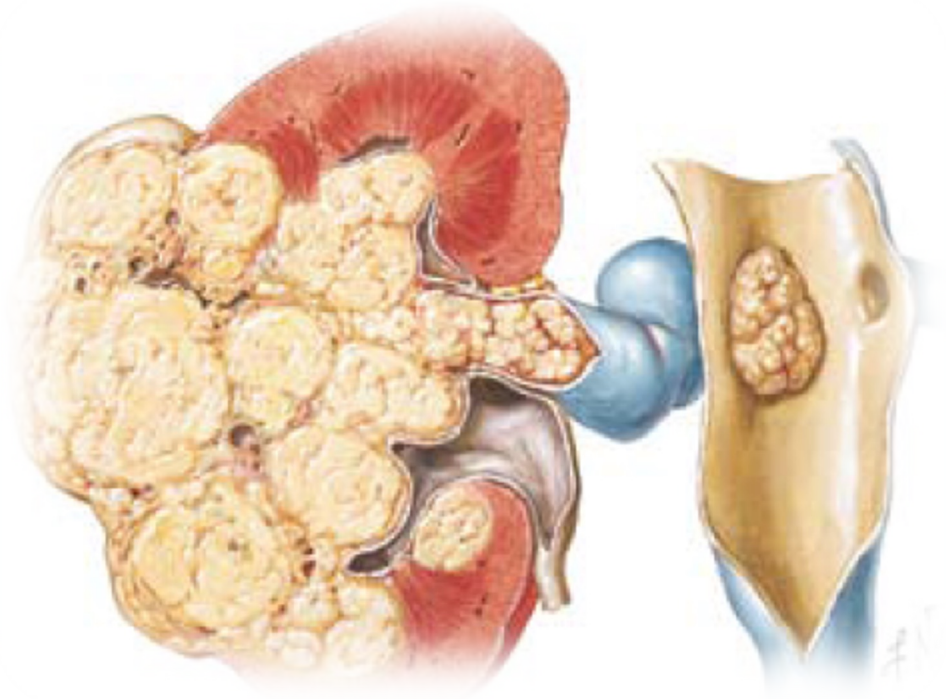
Systemisk behandling av avansert og metastatisk nyrecancer

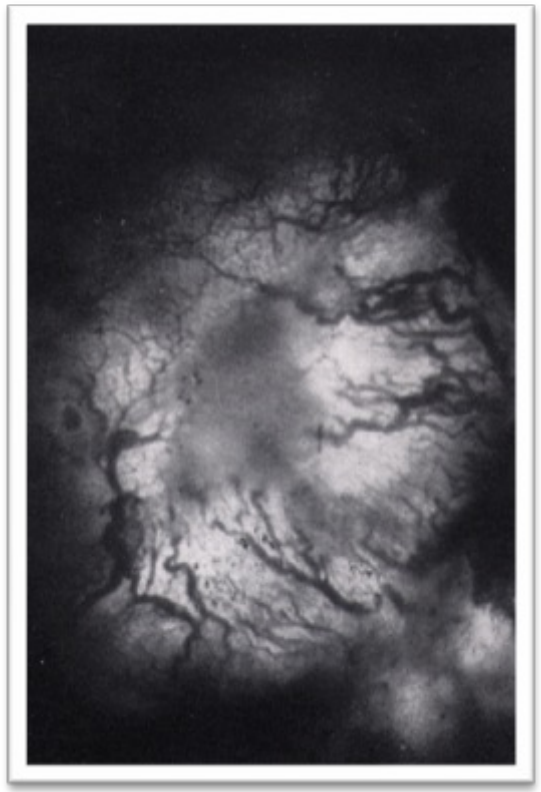


Daniel Heinrich
Onkologisk avdeling
Sykehuset Innlandet

Potensielle interessekonflikter

- Deltakelse i AdBoard: Astellas, AstraZeneca, Bayer, EISAI, IPSEN, Janssen-Cilaq, Organon, Roche
- Honorert Foredragsholder: AAA, a Novartis company, Astellas, Bayer, Bristol-Myers Squibb, Dagens Medisin, EUSA Pharma, IPSEN, Janssen-Cilaq, Novartis, PROFO, Statens Legemiddelverk
- Forskningsstøtte: (sykehus, ikke personlig) AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen-Cilaq, Merck Sharp & Dome, Pfizer, Roche

The advent of the angiogenesis hypothesis



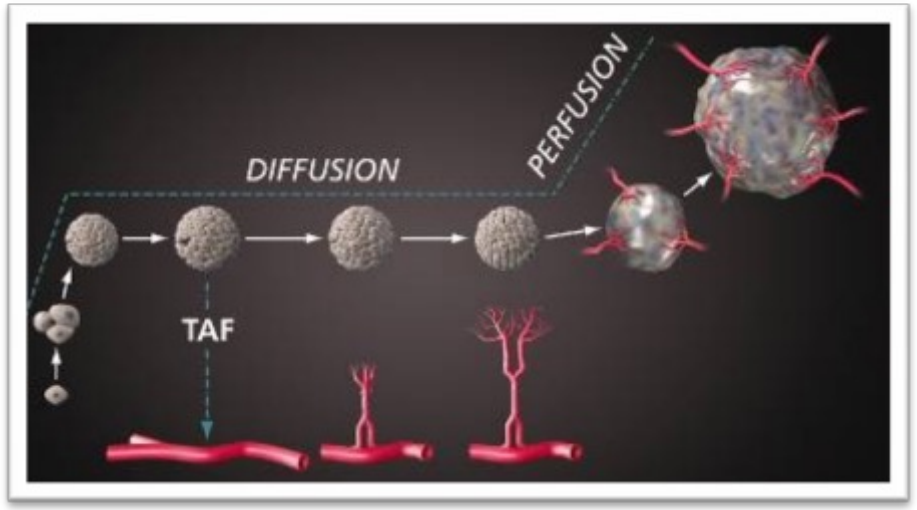
'One is almost forced to the conclusion that there is, associated with the viable growing tumour, some blood vessel growth stimulating factor'

- Gordon Ide, 1939

1939

Ide, et al. Am J Roentgenol 1939

The anti-angiogenesis theory, a new way of thinking

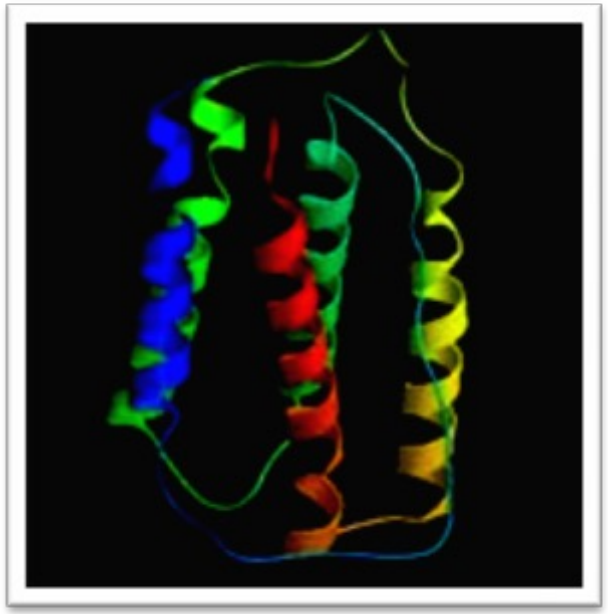


Judah Folkman

- **Isolates *'a tumour factor responsible for angiogenesis'*[1]**
- **Controversial hypothesis *'tumours are dependent on angiogenesis'*[2]**

1. Folkman, J Exp Med 1971; **2.** Folkman, NEJM 1971

The excitement of the cytokine era



1950s: IFN discovered

1980s: clinical trials using IFN

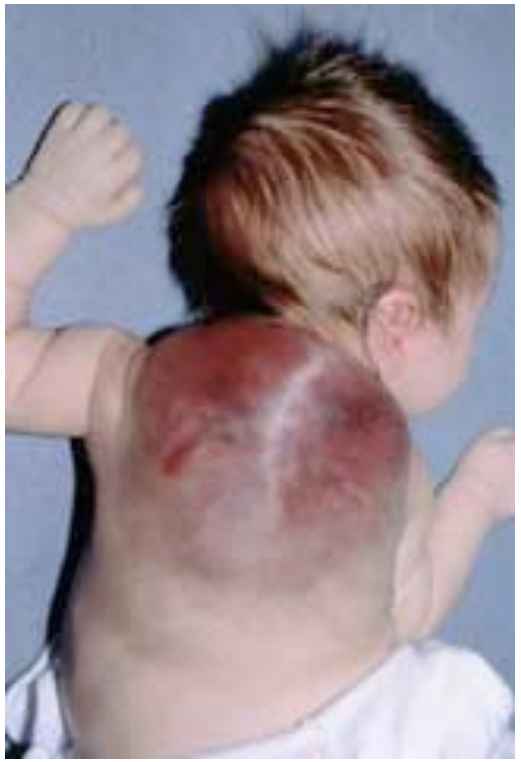
IFN in kidney cancer: proven efficacy, increased OS

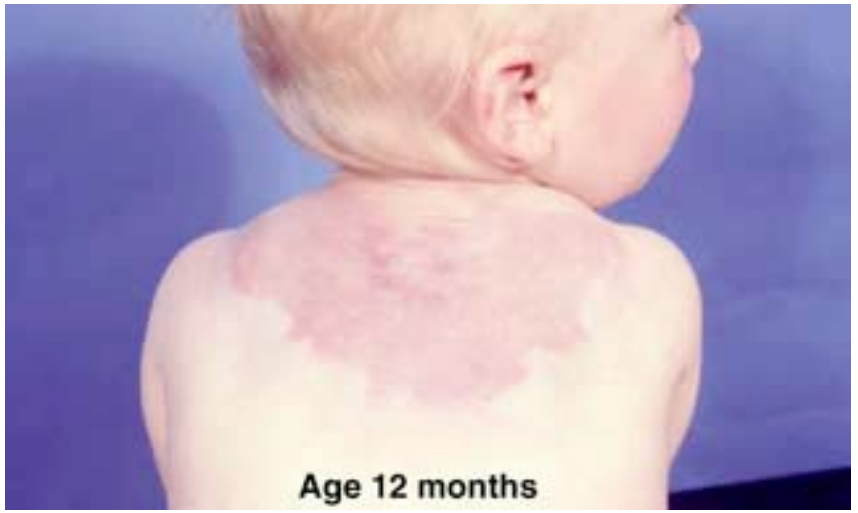
Therapy of choice in Europe early 2000s

Isaacs & Lindenmann; Proc R Soc Lond B Biol Sci. 1957

Haemangiomas

Some therapy resistant and life threatening

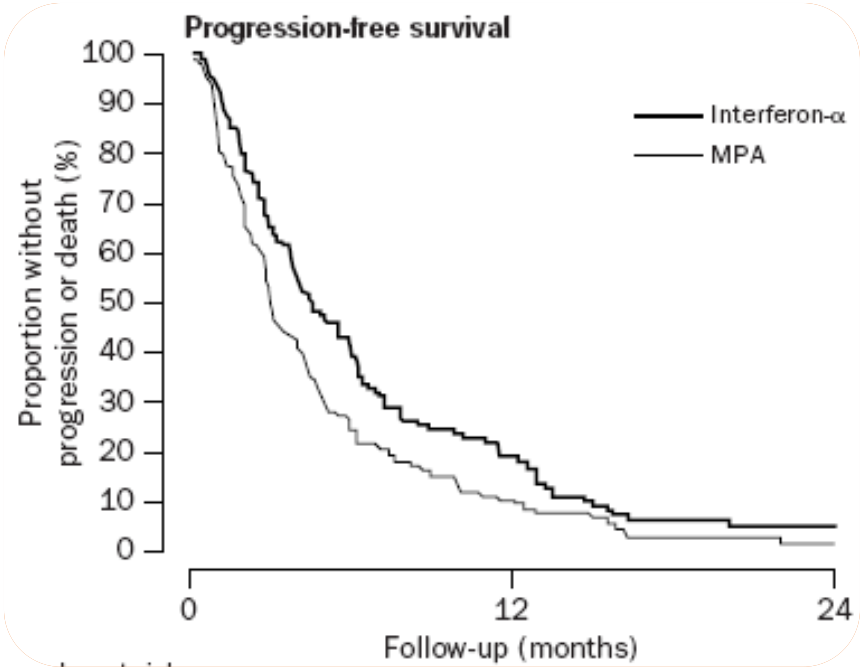




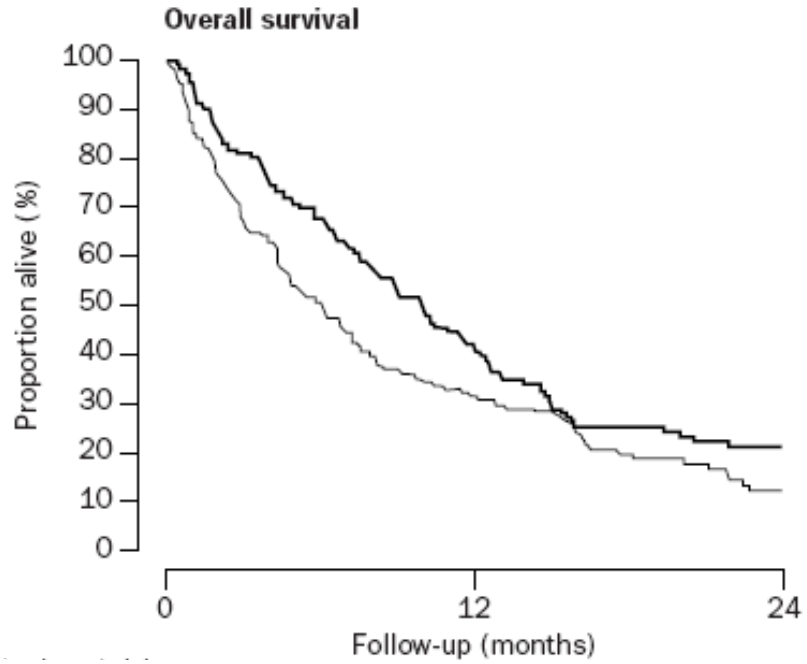
After 11 months of IFN treatment

Folkman; N Engl J Med; 1989

Interferon

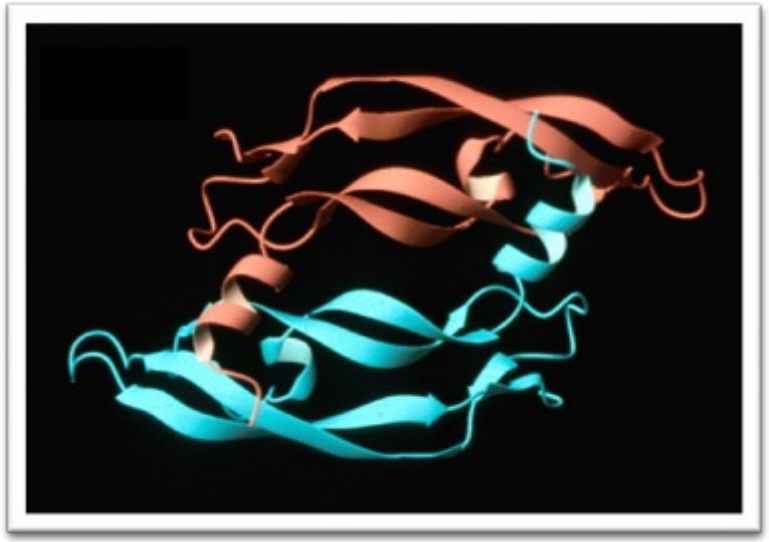


PFS 5,0 months
OS 11,4 months



MRCRCC, Lancet 1999

VEGF, the key mediator of angiogenesis

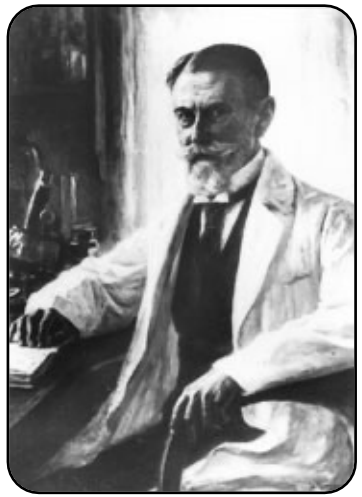


- Senger - vascular permeability factor (VPF) identified as important to tumour growth[1]
- Ferrara - discovers vascular endothelial growth factor (VEGF)[2]
- VEGF and VPF shown to be identical

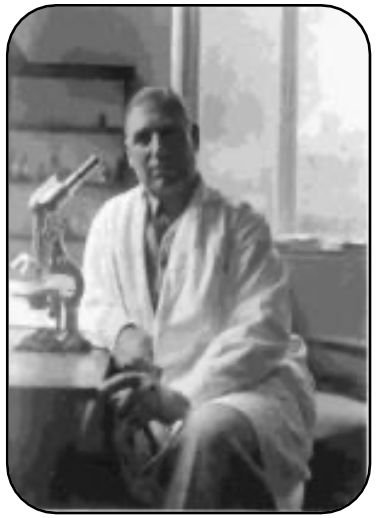
1980s

1. Senger, et al. Science 1983; **2.** Ferrara, Henzel. Biochem Biophys Res Commun 1989

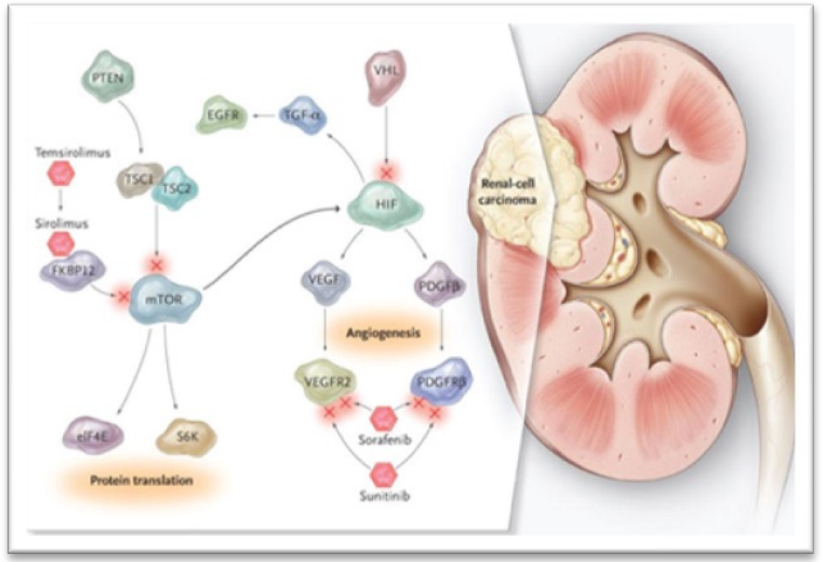
Identification of VHL



Eugen von Hippel: ”Ueber eine sehr seltene Erkrankung der Netzhaut“ 1904



Arvid Lindau: "Studien über Kleinhirncysten, Bau, Pathenogenese und Beziehungen zur Angiomatosis retinae.„ 1926

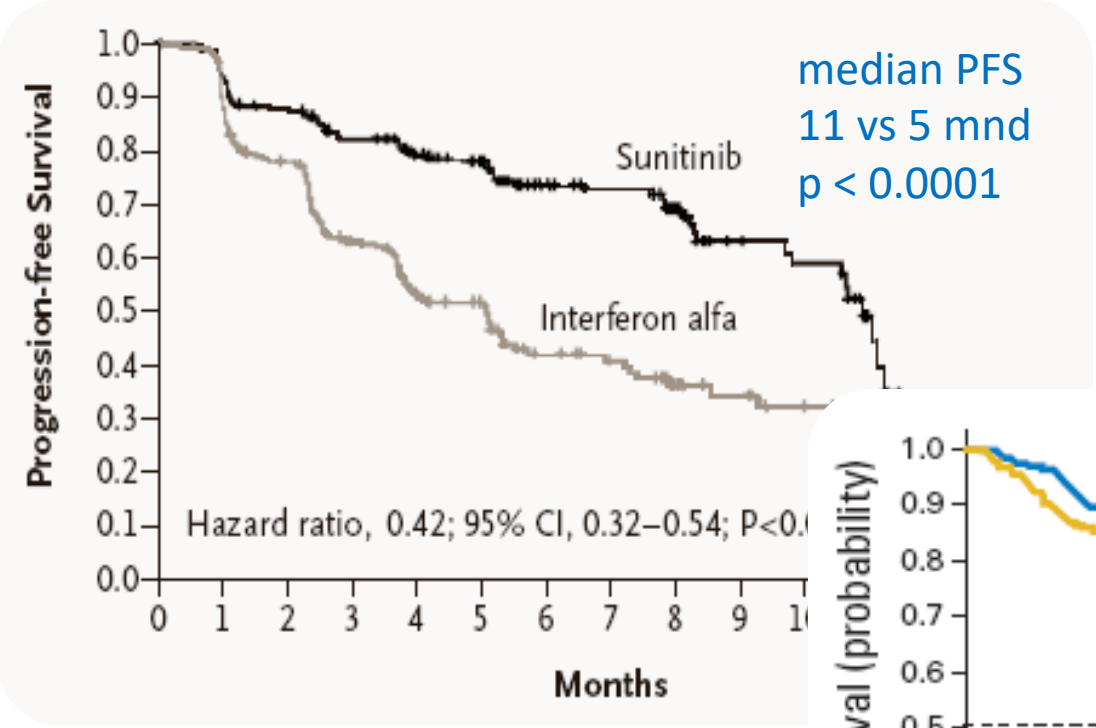


Latif et al (1993) identify VHL gene mutation and link to clear-cell RCC

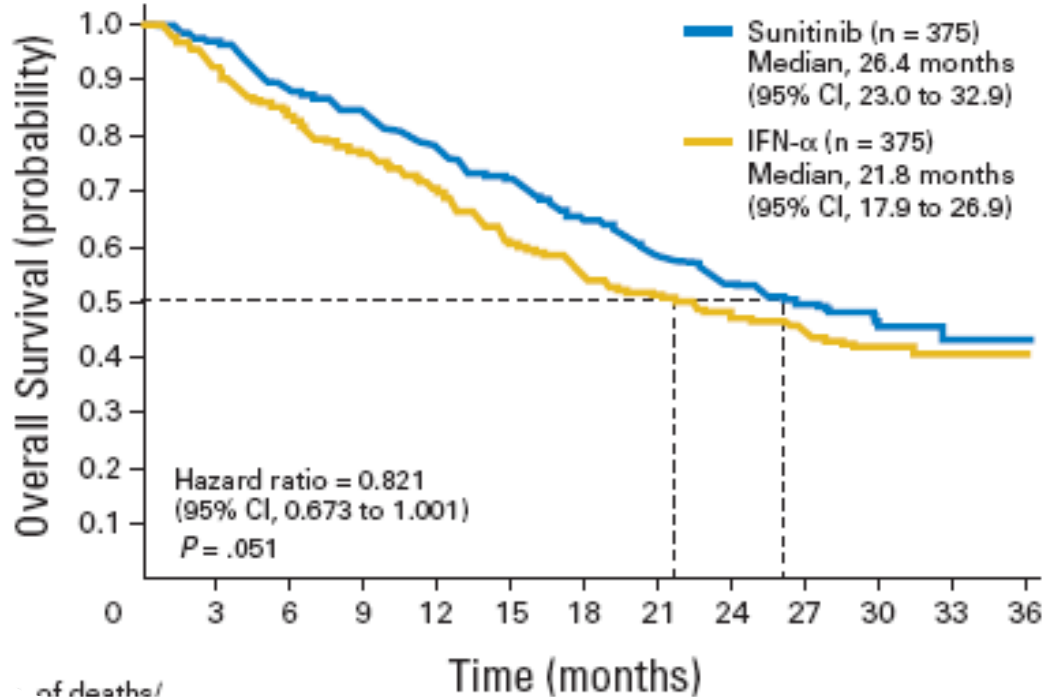
1993

Latif et al. Science 1993; v. Hippel, Albrecht von Graefes Archiv für Ophtalmologie, 1904; Lindau, Acta Ophtalmologica, 1926

1. line - Sunitinib



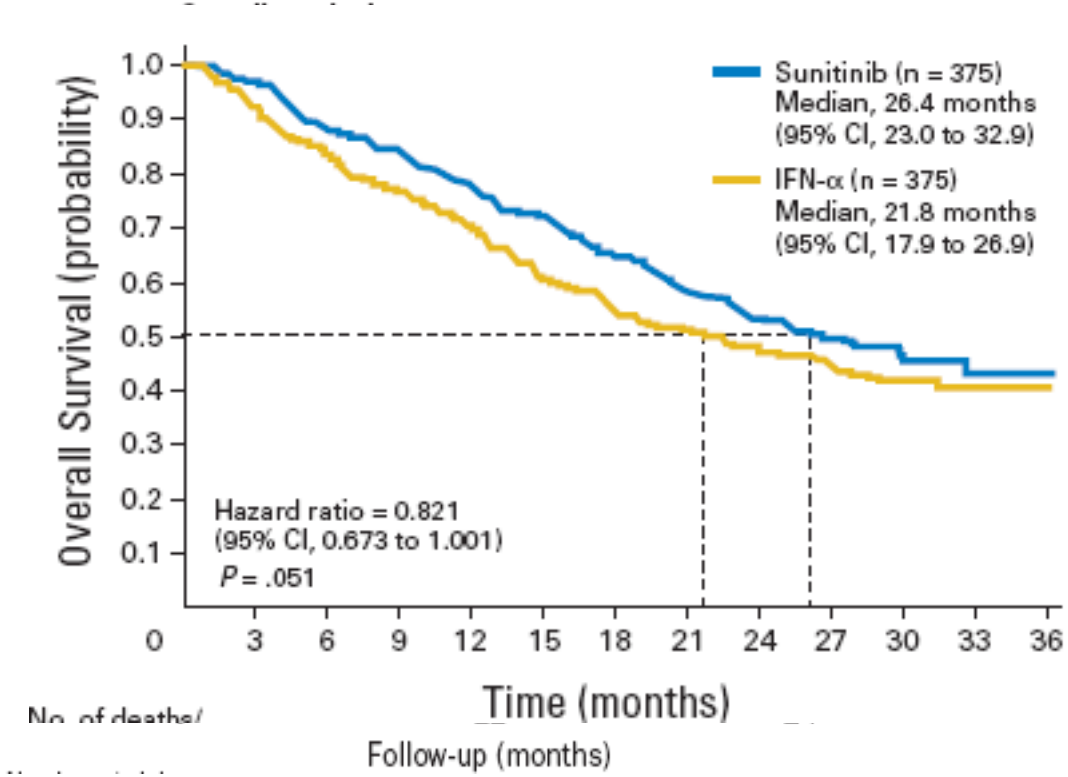
median PFS
11 vs 5 mnd
p < 0.0001



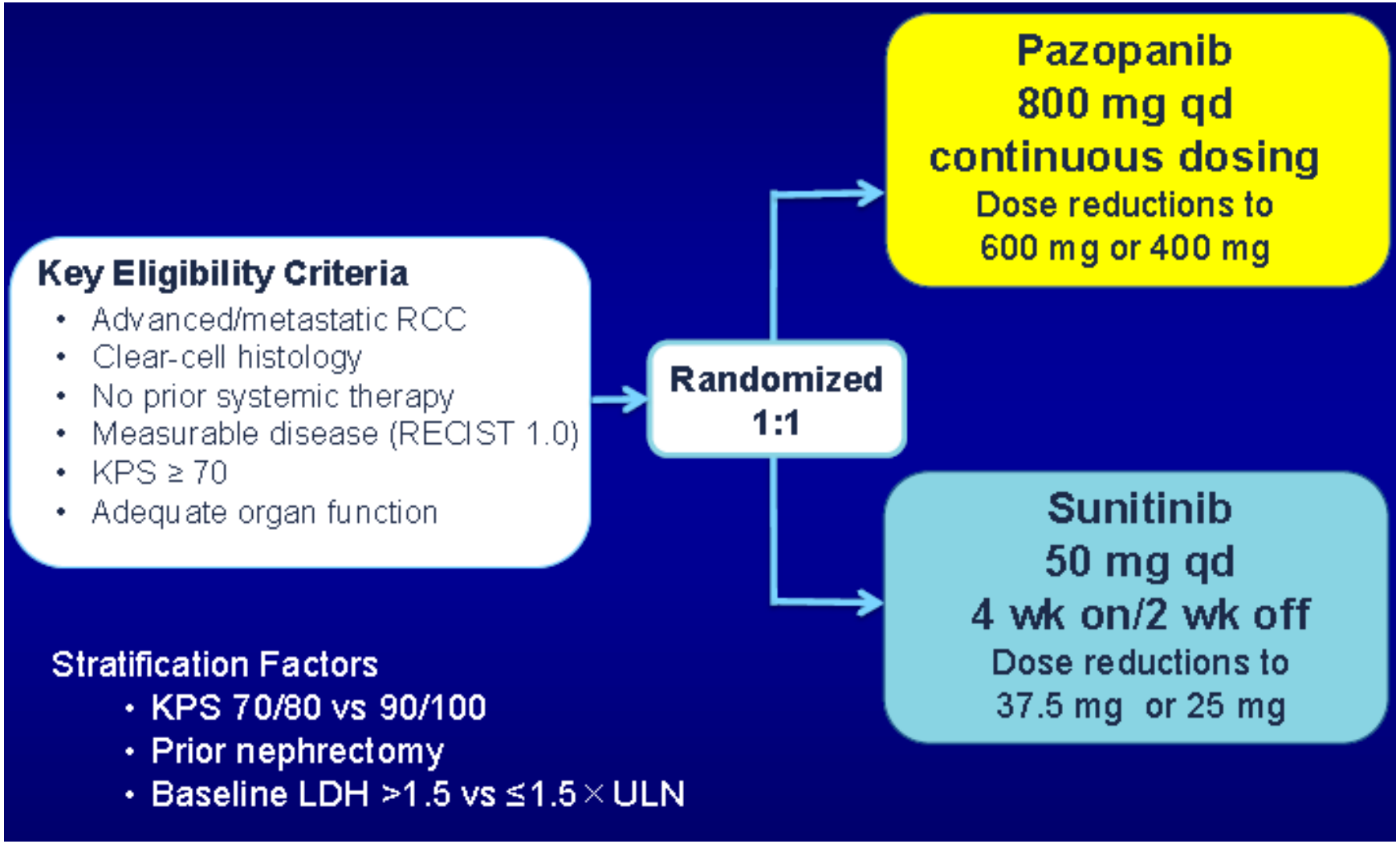
Motzer et al., N Engl J Med 2007

Motzer et al., J Clin Oncol 2009

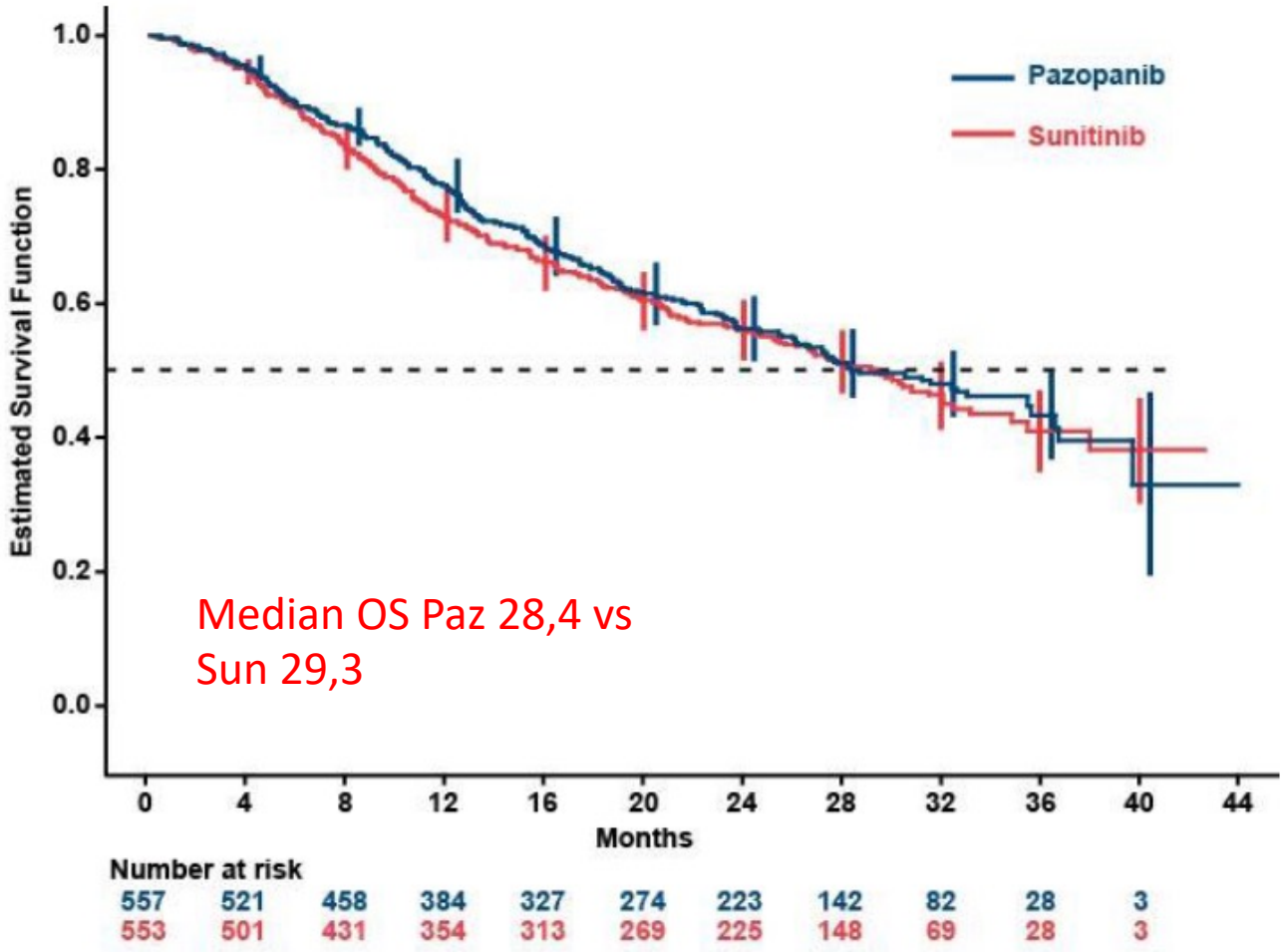
Improvement?



Sunitinib vs Pazopanib - COMPARZ



1. line - Pazopanib vs Sunitinib

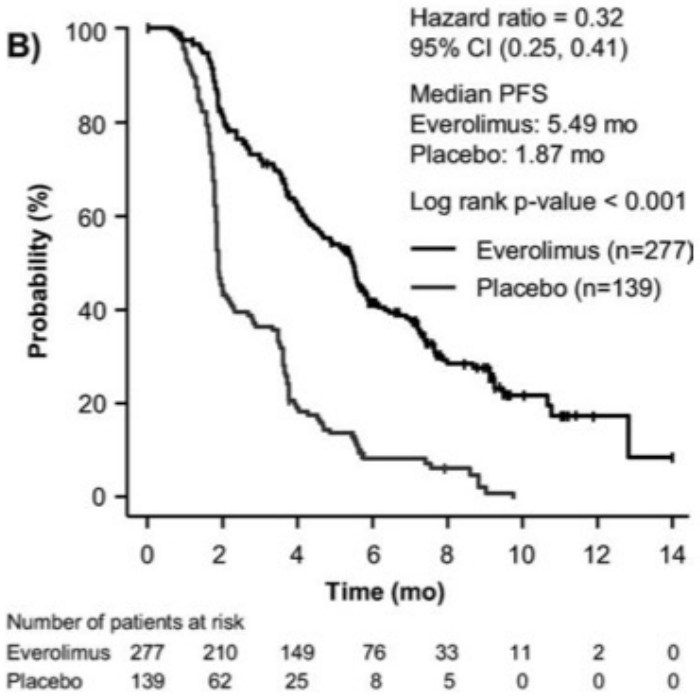


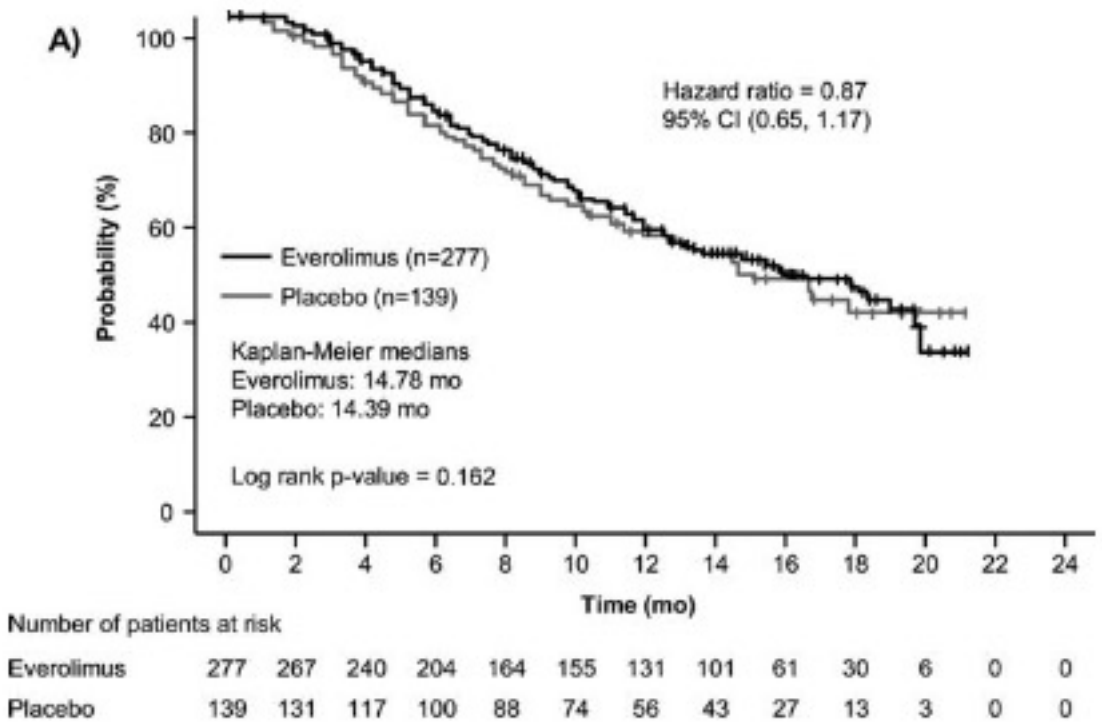
Median OS Paz 28,4 vs
Sun 29,3

Motzer et al.; N Engl J Med, 2013 supplementary appendix

2. line therapy after 1. line TKI

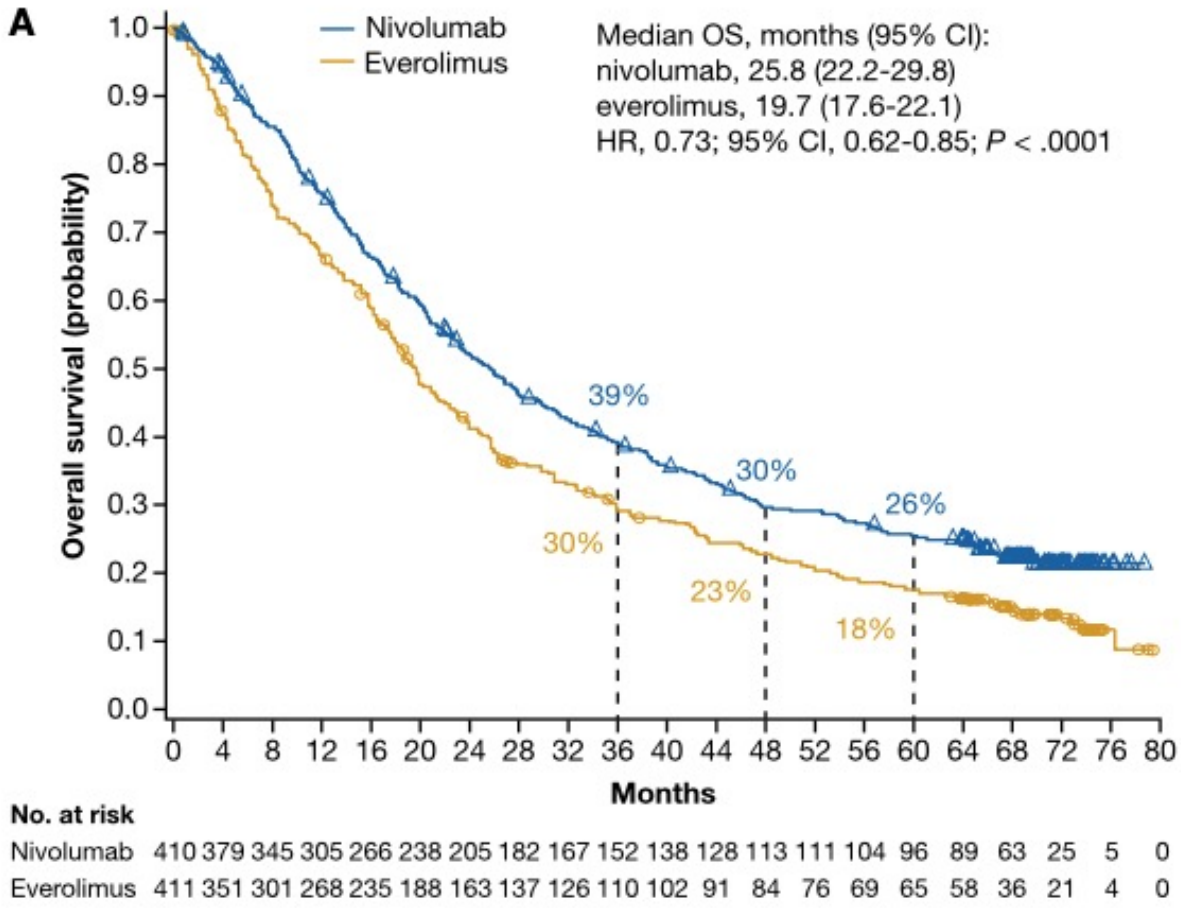
- Everolimus established 2008





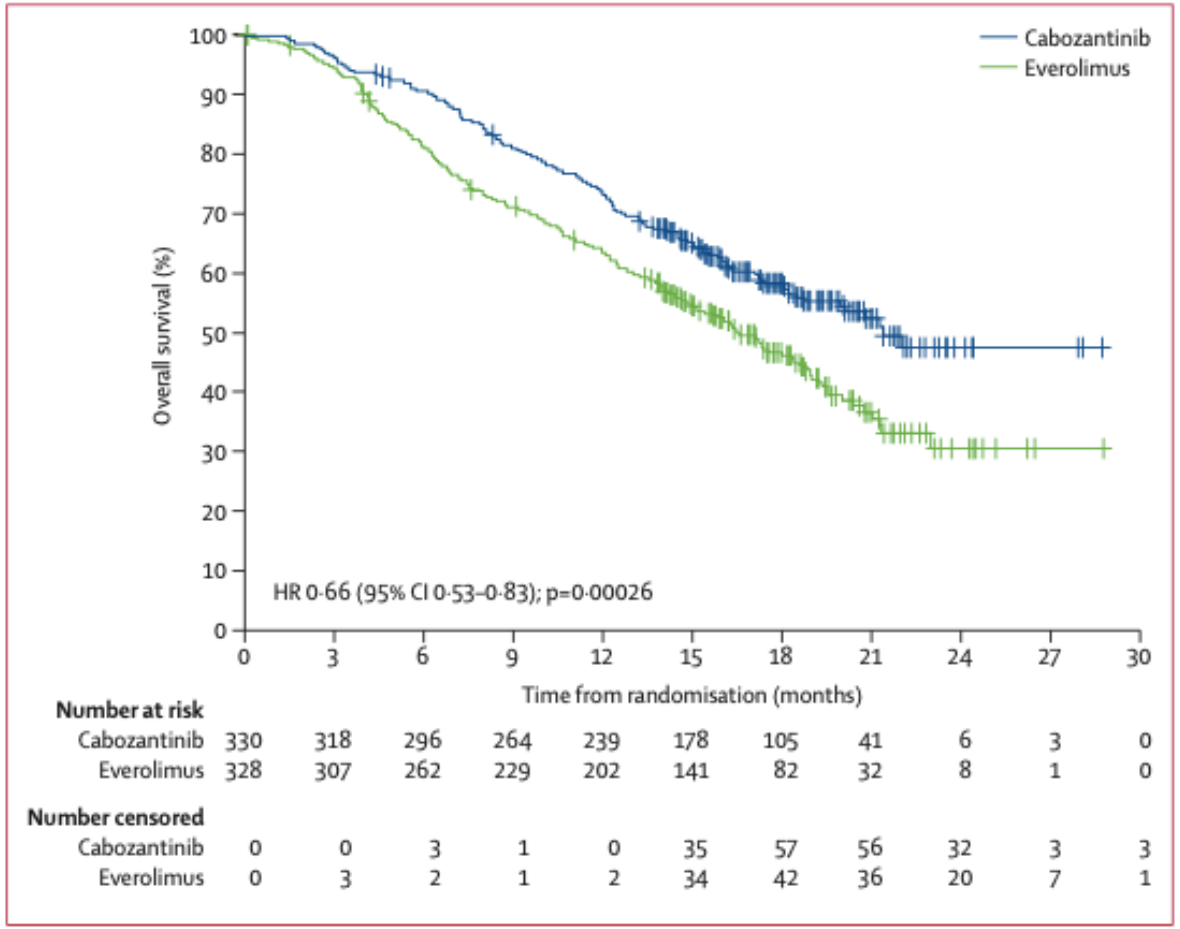
Motzer et al.; Cancer 2010

Nivolumab vs Everolimus (CheckMate 025)



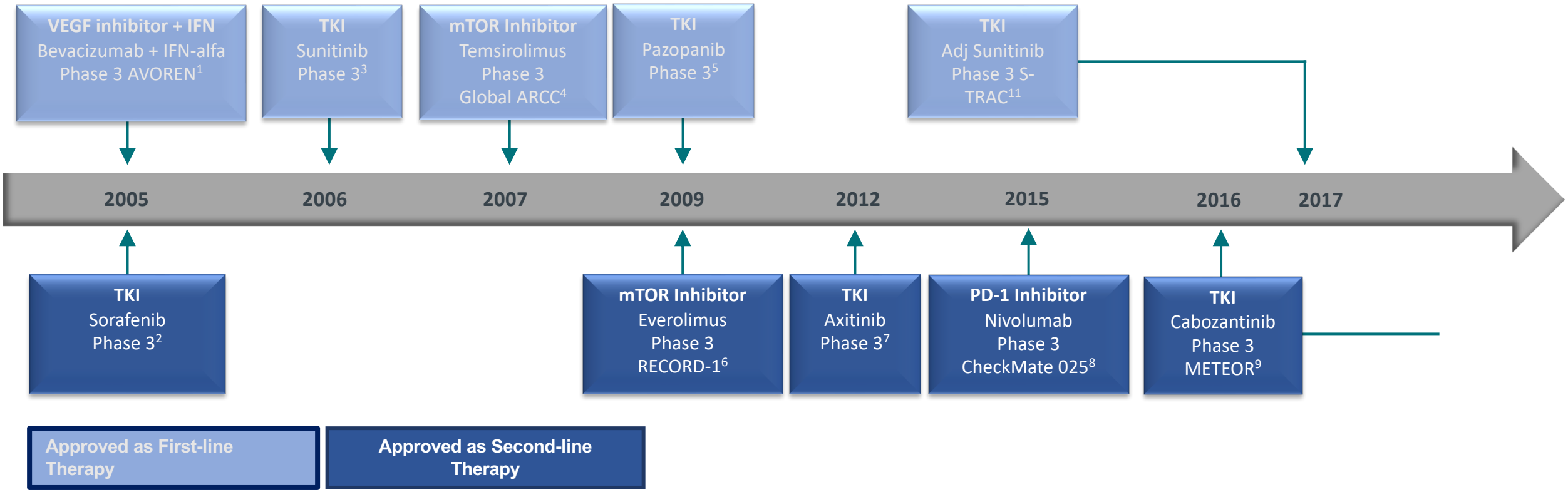
Motzer et al.; Cancer 2020

Cabozantinib vs Everolimus (METEOR)

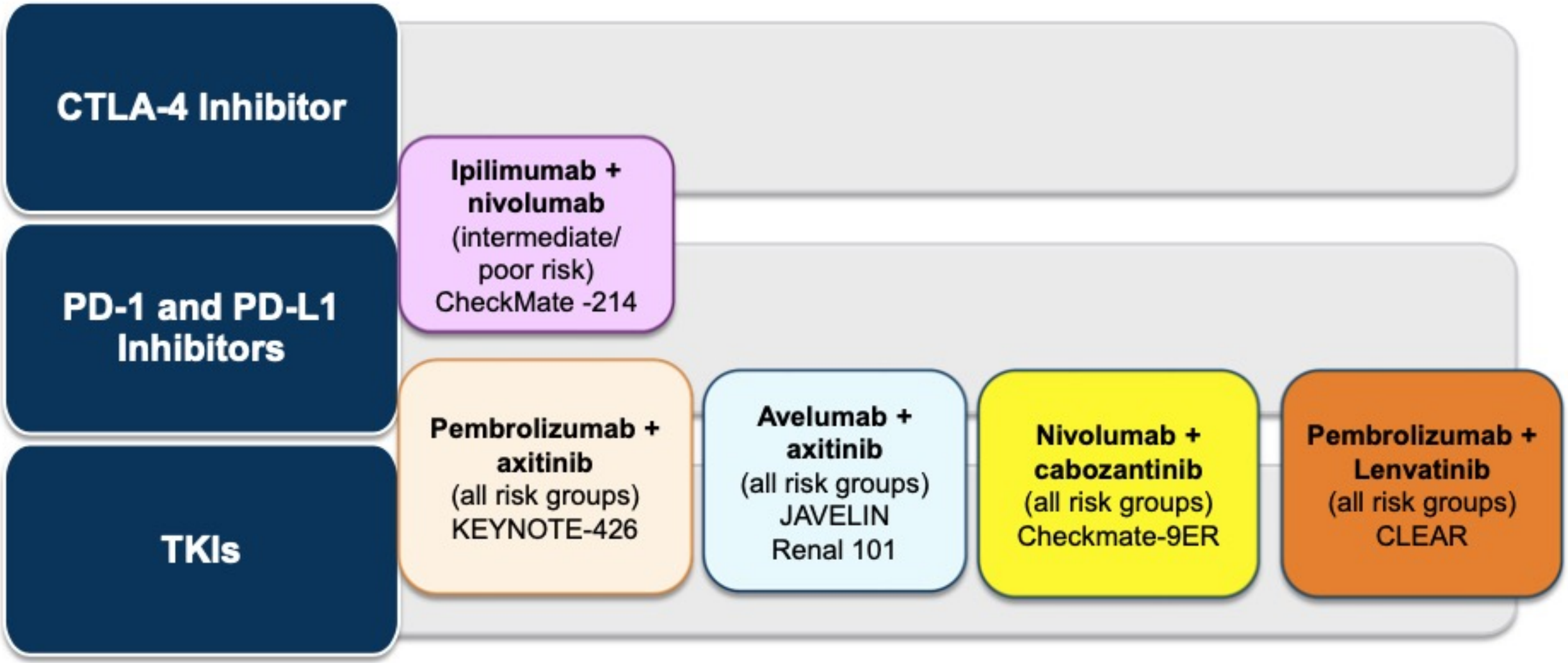


Choueiri et al.; Lancet Oncol 2018

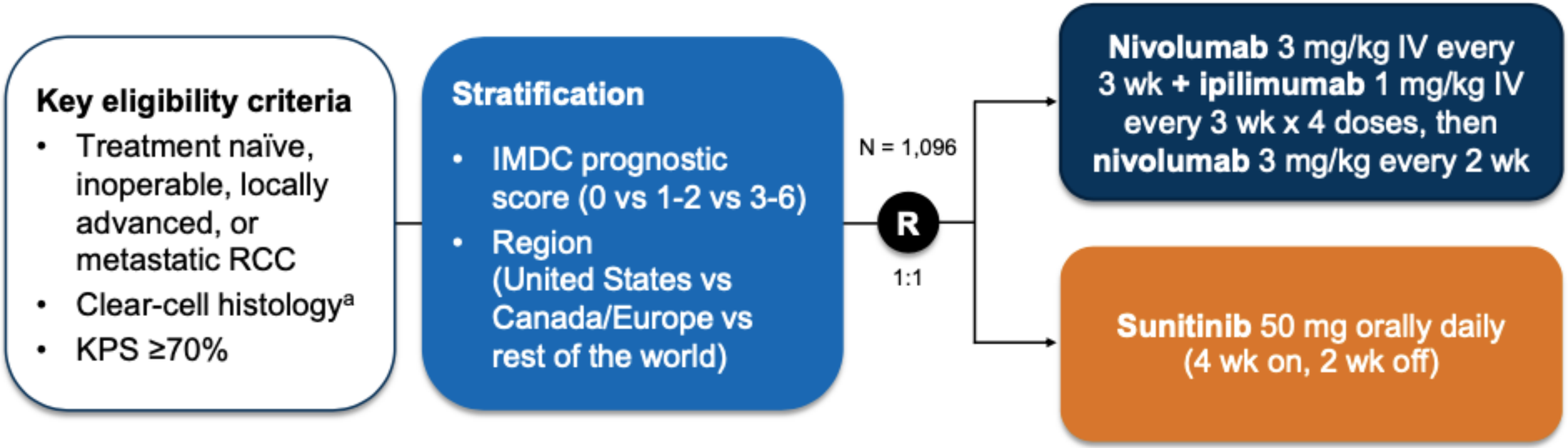
(R)Evolution of treament opportunities for mRCC 2005–2017



What has happened since then?



CheckMate 214



Endpoints

- **Coprimary:** PFS, OS, ORR (intermediate/poor risk)
- **Secondary:** PFS, OS, ORR (ITT)
- **Exploratory:** PFS, OS, ORR (favorable risk)

Motzer RJ et al. *Lancet Oncol.* 2019;20:1370-1385.

Overall and Progression Free Survival

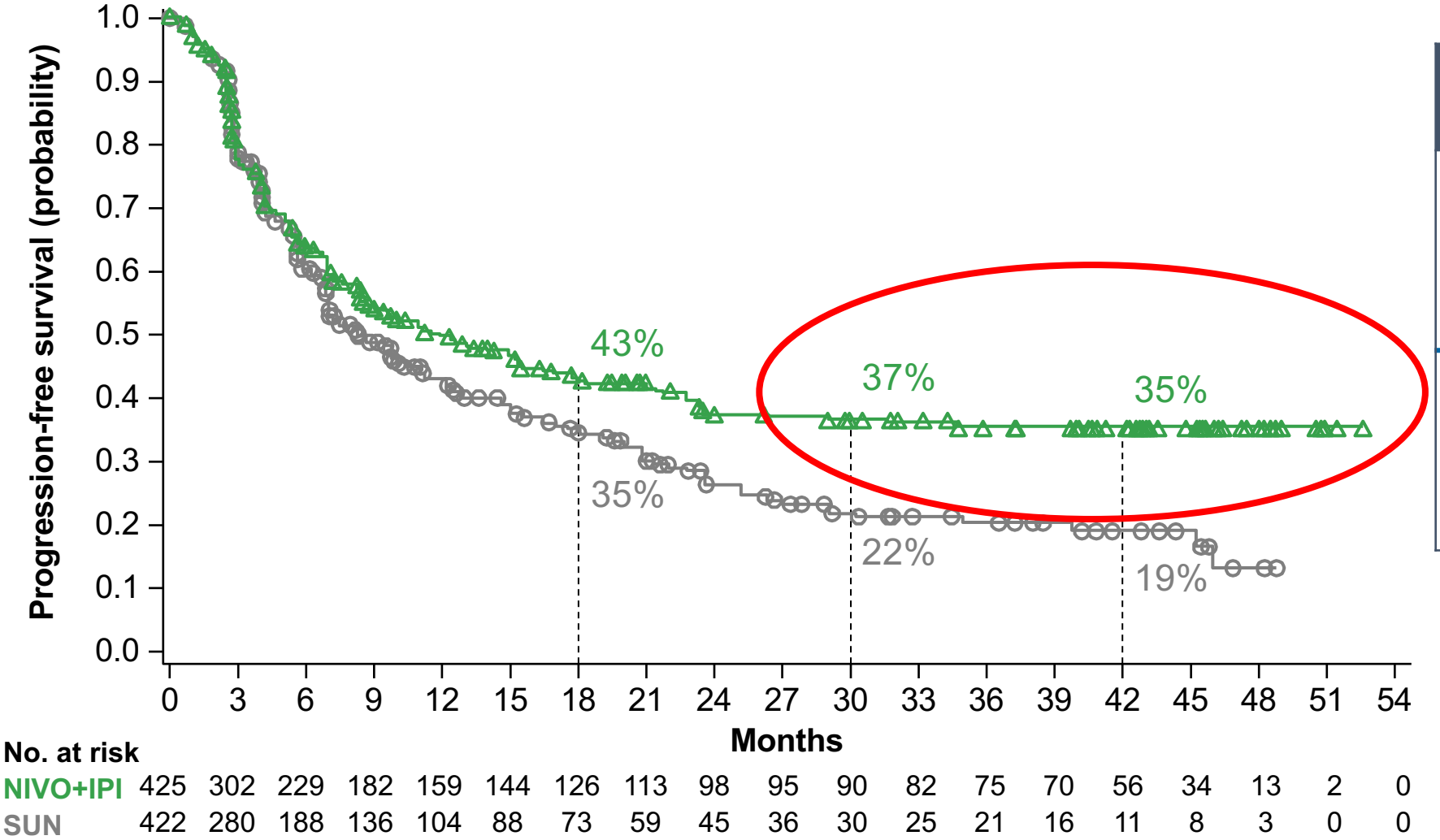
Primary efficacy population: Intermediate/poor-risk patients

Minimum Follow-Up, mo	Median OS, mo (95% CI)		Median PFS, mo (95% CI)	
	Nivolumab + Ipilimumab (n = 425)	Sunitinib (n = 422)	Nivolumab + Ipilimumab (n = 425)	Sunitinib (n = 422)
17.5[1]	NR (28.2-NE)	26.0 (22.1-NE)	11.6 (8.7-15.5)	8.4 (7.0-10.8)
	HR (99.8% CI) **0.63** (0.44-0.89); *P* <.001		HR (99.1% CI) **0.82** (0.64-1.05); *P* = .03	
30[2]	NR (35.6-NE)	26.6 (22.1-33.4)	8.2 (6.9-10.0)	8.3 (7.0-8.8)
	HR (95% CI) **0.66** (0.54-0.80); *P* <.0001		HR (95% CI) **0.77** (0.65-0.90); *P* = .0014	
42[3]	47.0 (35.6-NE)	26.6 (22.1-33.5)	11.6 (8.4-15.5)	8.3 (7.0-10.8)
	HR (95% CI) **0.66** (0.55-0.80); *P* <.0001		HR (95% CI) **0.75** (0.62-0.90); *P* = .0015	
48[4]	48.1 (35.6-NE)	26.6 (22.1-33.5)	11.2 (8.4-16.1)	8.3 (7.0-10.8)
	HR (95% CI) **0.65** (0.54-0.78); *P* <.0001		HR (95% CI) **0.74** (0.62-0.88); *P* = .0015	
60[5]	47.0 (35.4-57.4)	26.6 (22.1-33.5)	11.6 (8.4-16.5)	8.3 (7.0-10.4)
	HR (95% CI) **0.68** (0.58-0.81); *P* <.0001		HR (95% CI) **0.73** (0.61-0.87); *P* = .0004	

1. Motzer RJ et al. *N Engl J Med*. 2018. PMID: 29562145. 2. Motzer RJ et al. *Lancet Oncol*. 2019. PMID: 31427204. 3. Motzer RJ et al. *J Immunother Cancer*. 2020. PMID: 32661118. 4. Albiges L. et al., *ESMO Open*, 2021. PMID: 33246931. 5. Motzer R.J. et al., ESMO Annual Congress, 2021.

PFS per IRRC

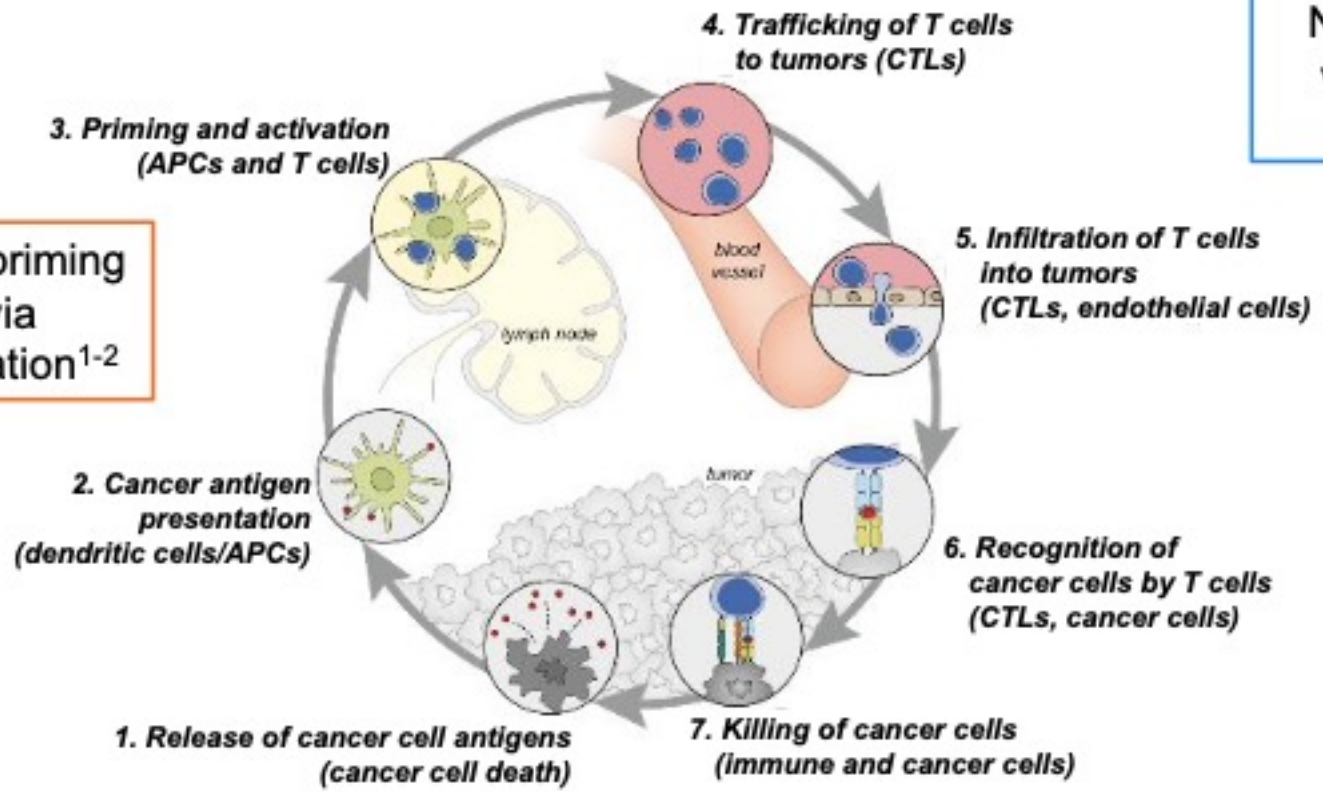
Primary efficacy population: Intermediate/poor-risk patients



Minimum follow-up	PFS	NIVO+IPI N = 425	SUN N = 422
17.5 mo[1]	Median, mo (95% CI)	11.6 (8.7–15.5)	8.4 (7.0–10.8)
	HR (99.1% CI)	0.82 (0.64–1.05) *P* = 0.03	
42 mo	Median, mo (95% CI)	12.0 (8.7–15.5)	8.3 (7.0–11.1)
	HR (95% CI)	0.76 (0.63–0.91) *P* < 0.01	

1. Albiges L. et al., ESMO 2020. Abstract 711P.

Rationale for Combining Immunotherapy with VEGF-targeted Therapy



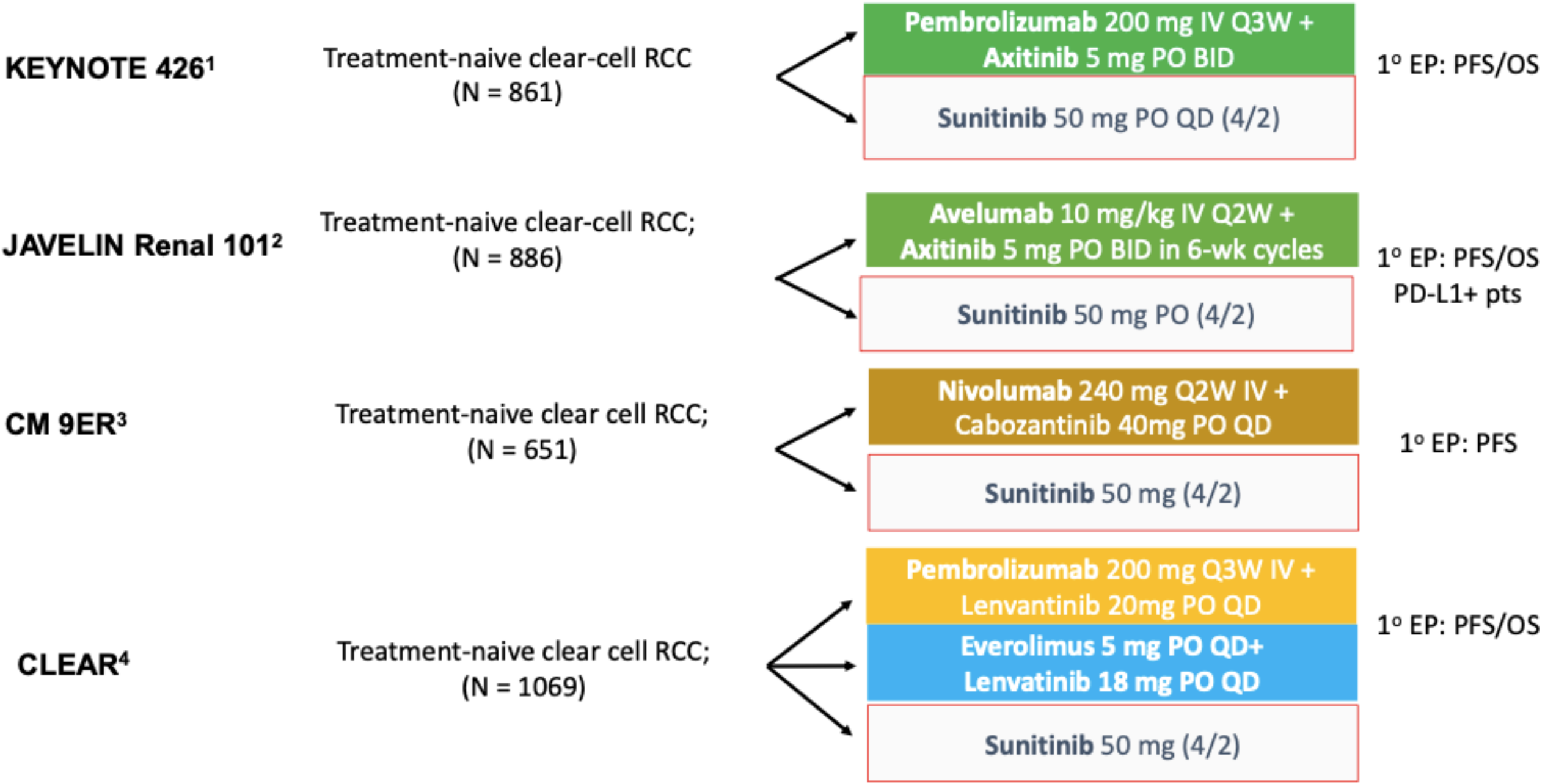
Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]

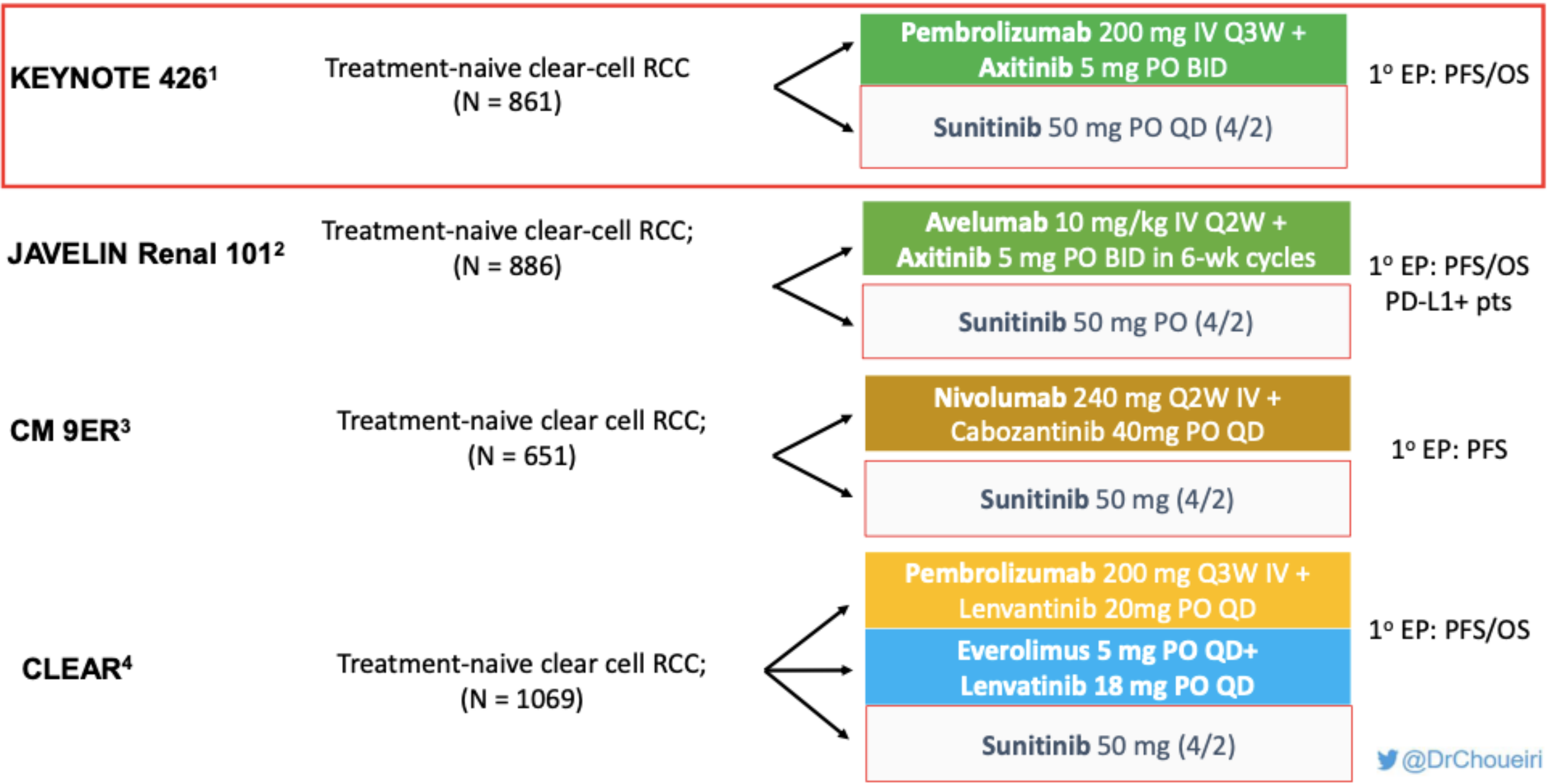
Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

➔ T-cell mediated cancer cell killing may be enhanced through reversal of VEGF-mediated immunosuppression

1. Gabrilovich DI, et al. Nat Med, 1996. PMID: 8837607. 2. Oyama T, et al. J Immunol, 1998. PMID: 9570538. 3. Goel S, et al. Physiol Rev, 2011. PMID: 21742796. 4. Motz GT, et al. Nat Med, 2014. PMID: 24793239. 5. Hodi FS, et al. Cancer Immunol Res, 2014. PMID: 24838938. 6. Wallin JJ, et al. Nat Commun, 2016. PMID: 27571927. 7. Gabrilovich DI, Nagaraj S. Nat Rev Immunol, 2009. PMID: 19197294. 8. Roland CL, et al. PLoS One, 2009. PMID: 19888452. 9. Facciabene A, et al. Nature, 2011. PMID: 21753853. 10. Voron T, et al. J Exp Med, 2015. PMID: 25601652. Figure adapted from Chen DS, Mellman I. Immunity, 2013. PMID: 23890059.

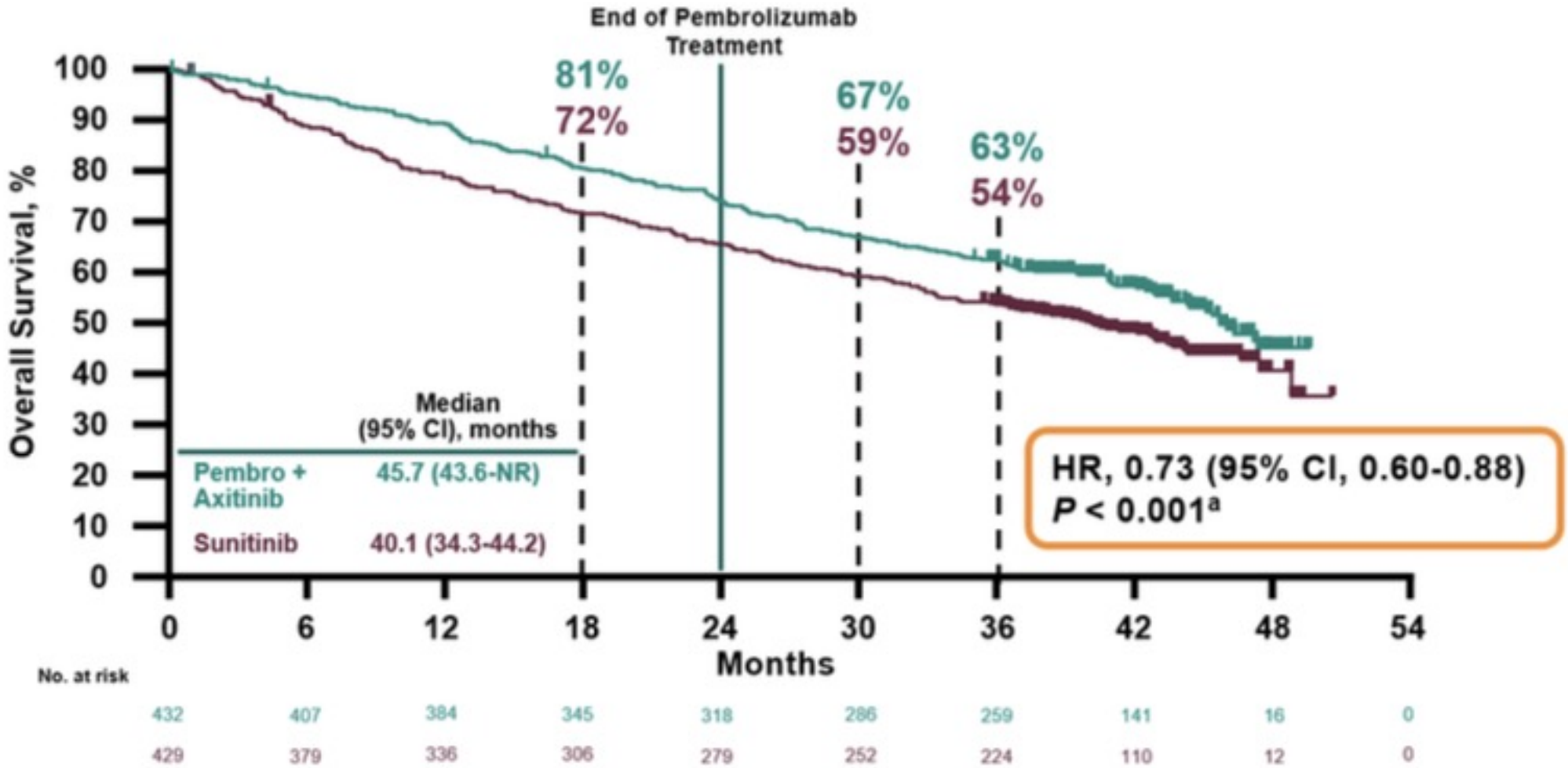


1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM,* 2021. PMID: 33657295. 4. Motzer et al, *NEJM,* 2021. PMID: 33616314.



1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

OS in the ITT Population (co-primary endpoint)

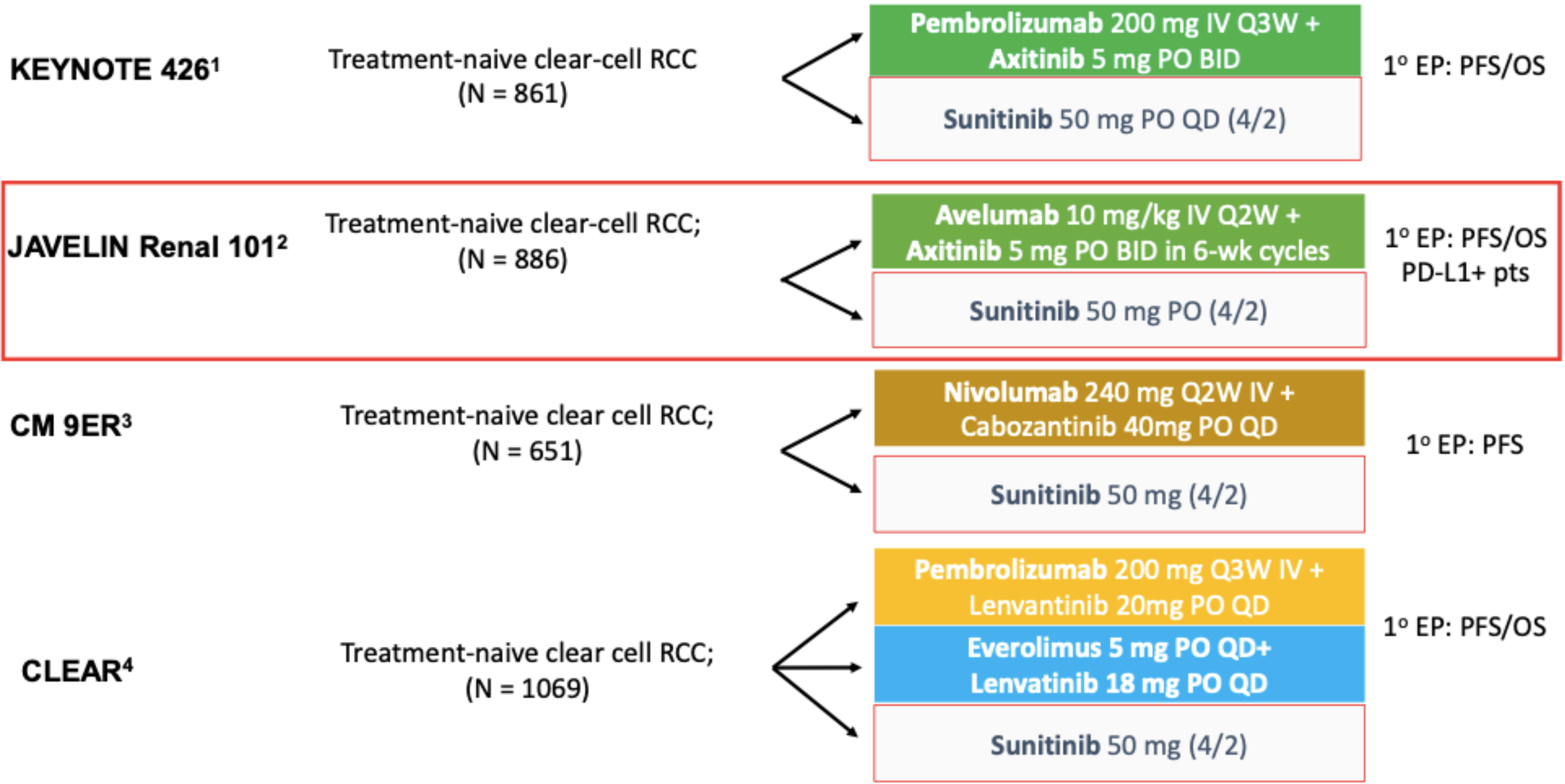


Adapted from Rini B. et al.; ASCO 2021

KEYNOTE-426 Highlights

Median follow-up (months)	12.8	30.6	42.8
OS, months	NR	NR	45.7
HR (95% CI)	0.53 (0.38-0.74)	0.68 (0.55-0.85)	0.73 (0.6-0.88)
PFS, months	15.1	15.4	15.7
HR (95% CI)	0.69 (0.57-0.84)	0.71 (0.6-0.84)	0.68 (0.58-0.8)
ORR(%)/CR(%)	59/6	60/9	60/10

1. Rini et al. *NEJM*, 2019. PMID: 30779529. 2. Powles et al, *Lancet Oncol.*, 2020. PMID: 33284113. 3. Rini et al, ASCO 2021.



1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

Javelin Renal 101- Highlights

Key eligibility criteria:

- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:

- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

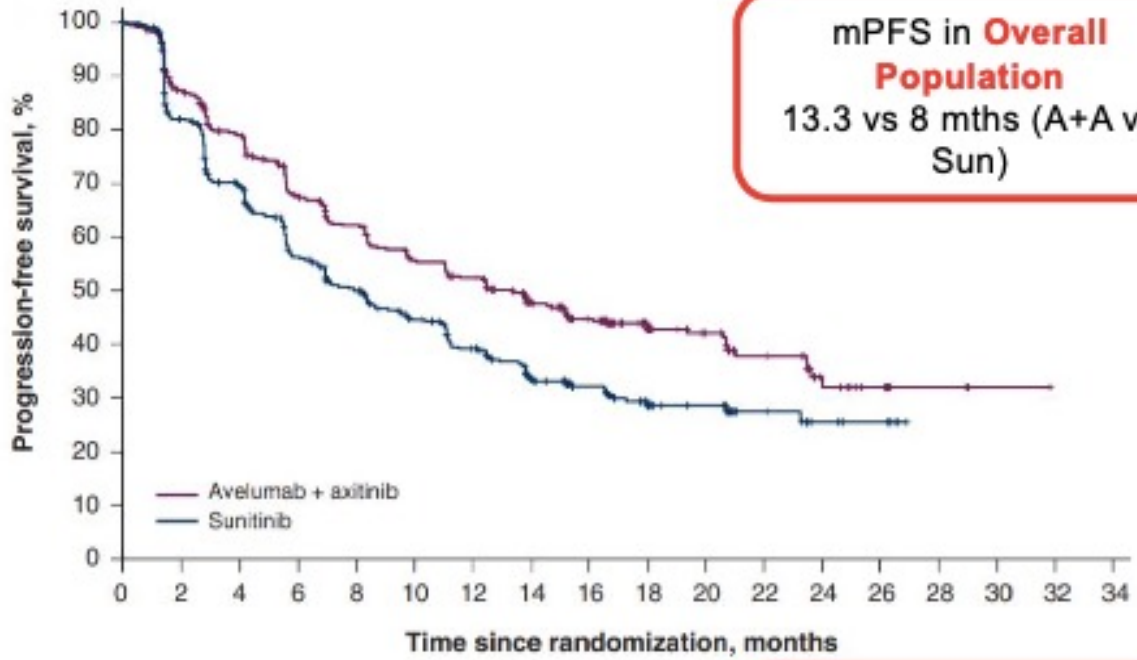
R 1:1

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

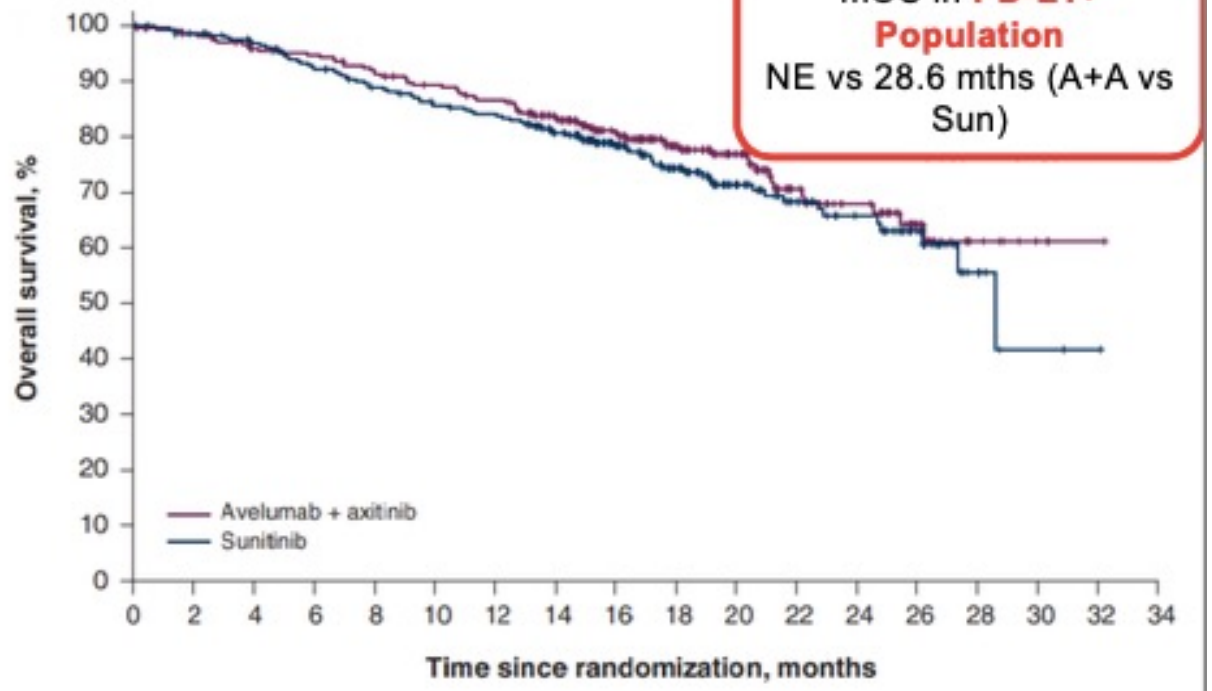
Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

Primary Endpoint: PFS or OS in patients *with PD-L1+ tumors*

OS: Not Significant
HR: 0.828 (95% CI 0.596-1.151); one-sided P = 0.13

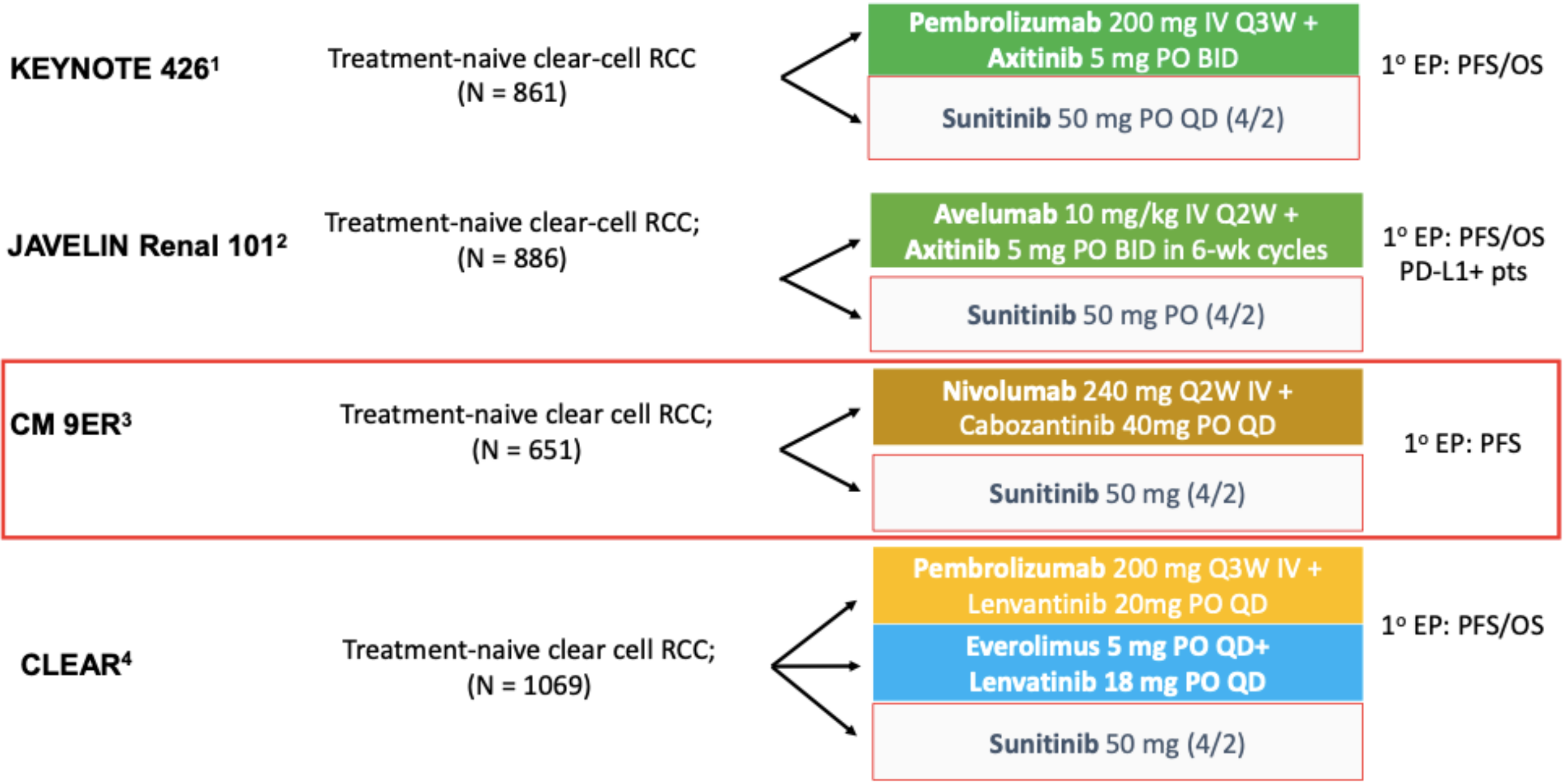


mPFS in **Overall Population**
13.3 vs 8 mths (A+A vs Sun)



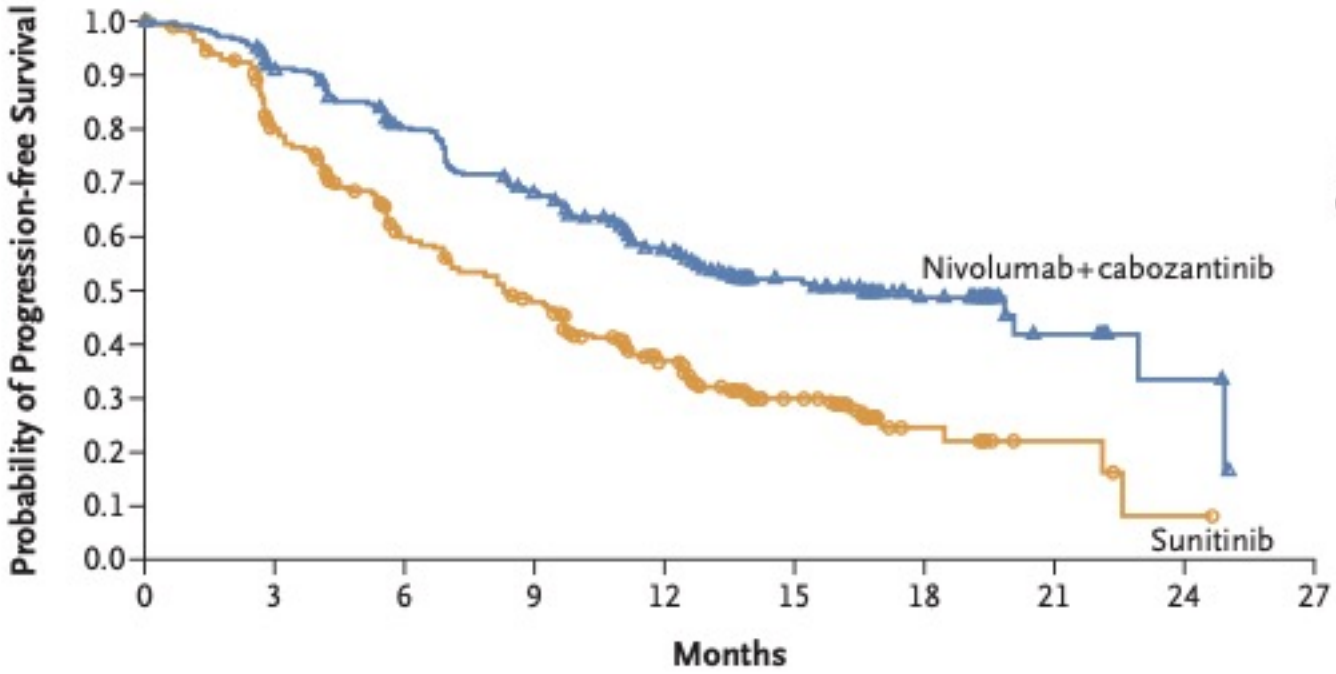
mOS in **PD-L1+ Population**
NE vs 28.6 mths (A+A vs Sun)

1.Choueiri T.K. et al., *Ann Onc.*, 2020. PMID: 32339648



1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM,* 2021. PMID: 33657295. 4. Motzer et al, *NEJM,* 2021. PMID: 33616314.

Progression free survival



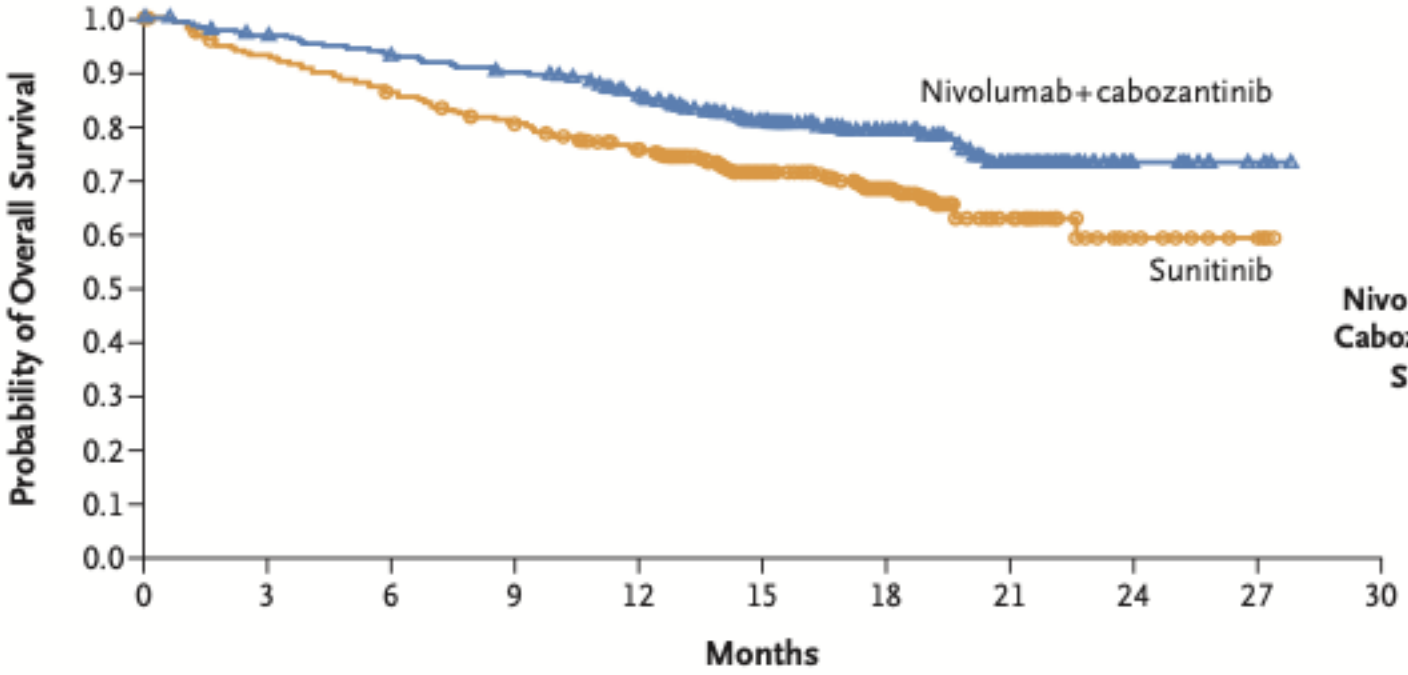
No. at Risk										
Nivolumab+cabozantinib	323	279	234	196	144	77	35	11	4	0
Sunitinib	328	228	159	122	79	31	10	4	1	0

	No. of Patients	Median (95% CI)
		mo
Nivolumab+ Cabozantinib	323	16.6 (12.5–24.9)
Sunitinib	328	8.3 (7.0–9.7)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.41–0.64)
P<0.001

Choueiri et al.; N Engl J Med 2021

Overall survival



	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	NR (NE)
Sunitinib	328	NR (22.6–NE)

Hazard ratio for death, 0.60
(98.89% CI, 0.40–0.89)
P=0.001

No. at Risk

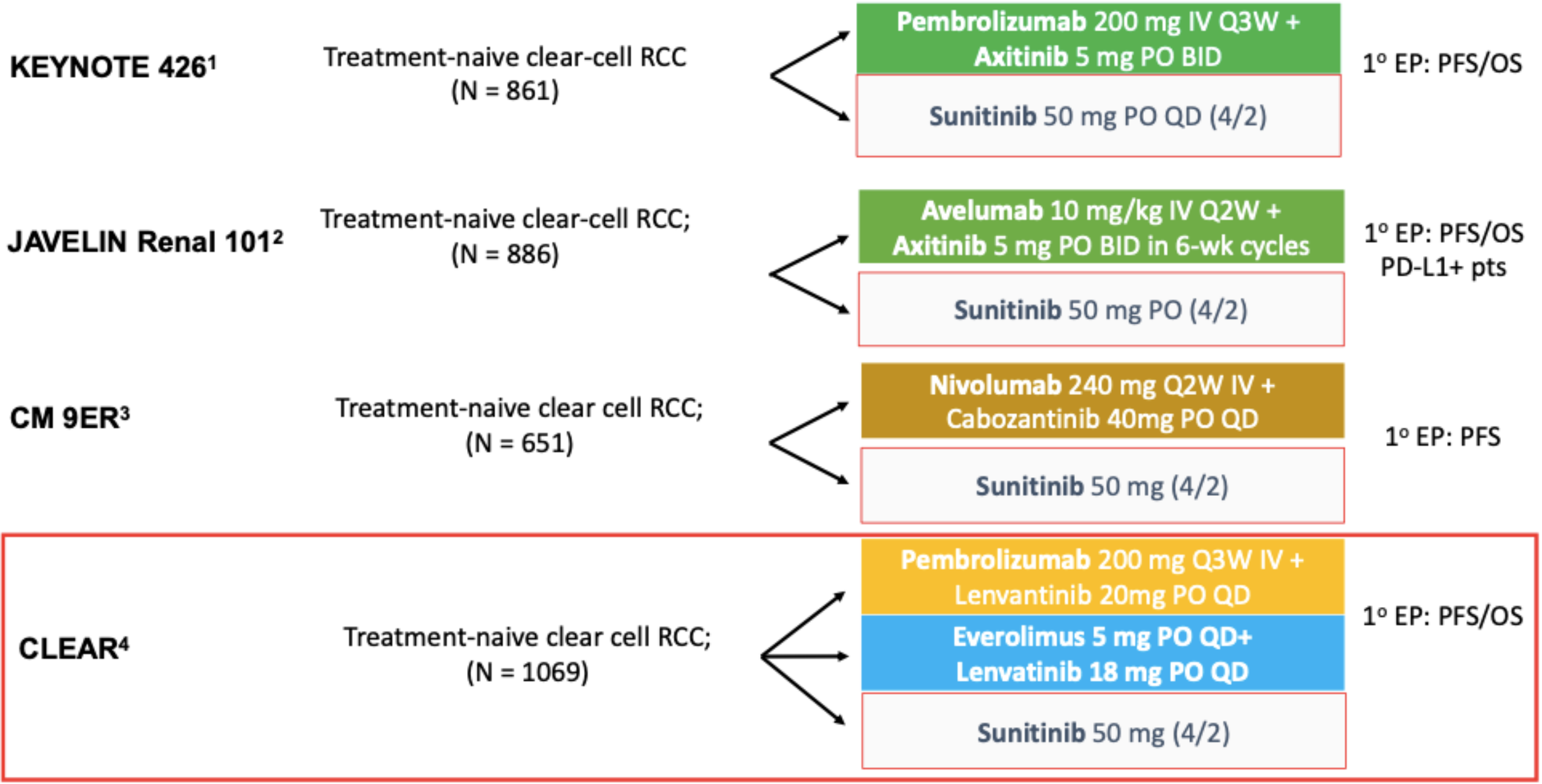
Nivolumab+cabozantinib	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

Choueiri et al.; N Engl J Med 2021

Checkmate-9ER Highlights

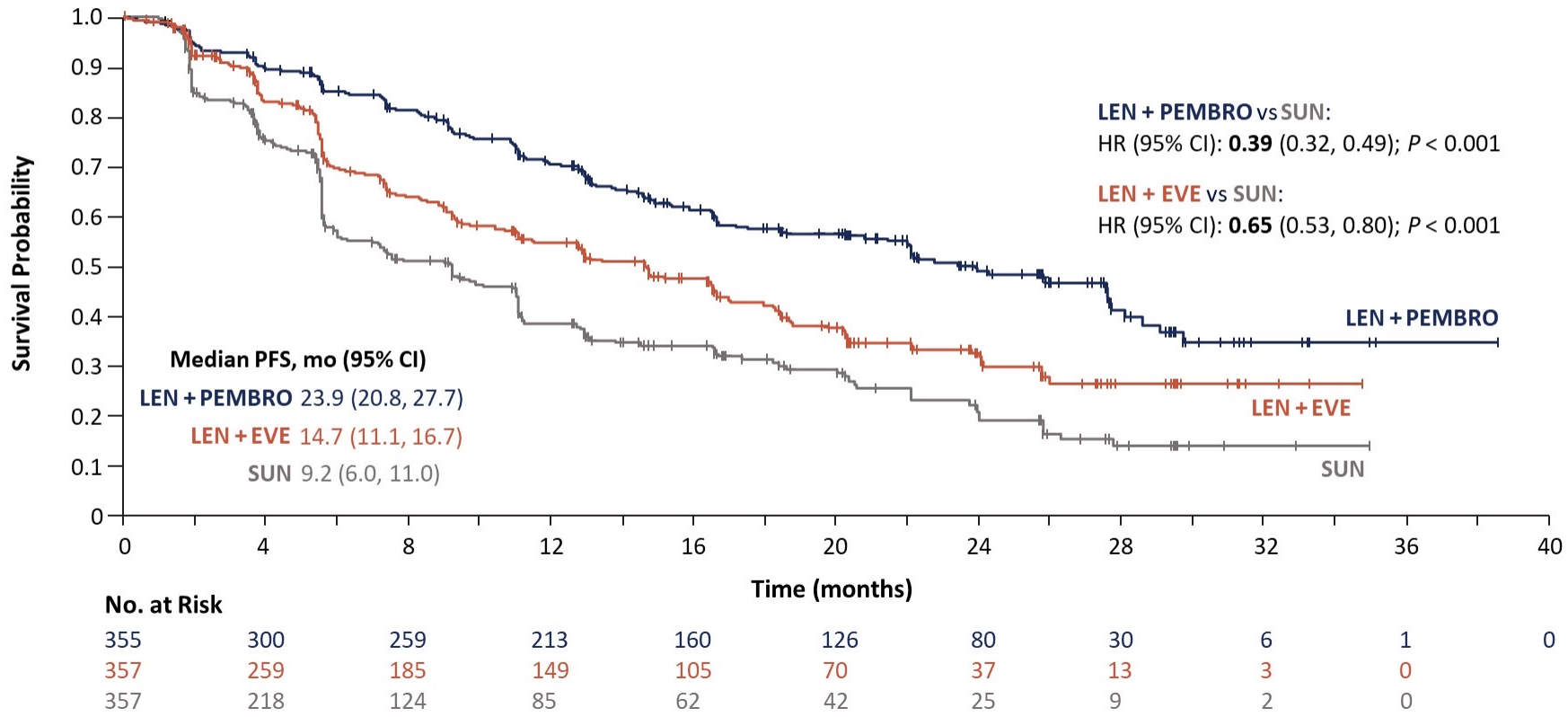
Median follow-up (months)	18[1]	23.5[2]
OS, months	NR	NR
HR (95% CI)	0.60 (0.40-0.89)	0.66 (0.50-0.87)
PFS, months	16.6	17.0
HR (95% CI)	0.51 (0.41-0.64)	0.52 (0.43-0.64)
ORR(%)/CR(%)	55.7/8.0	56.5/8.5

1. Choueiri et al, ESMO 2020, *NEJM*, 2021. 2. Motzer R.J. et al., ASCO GU Cancer Symposium, 2021.



1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM,* 2021. PMID: 33657295. 4. Motzer et al, *NEJM,* 2021. PMID: 33616314.

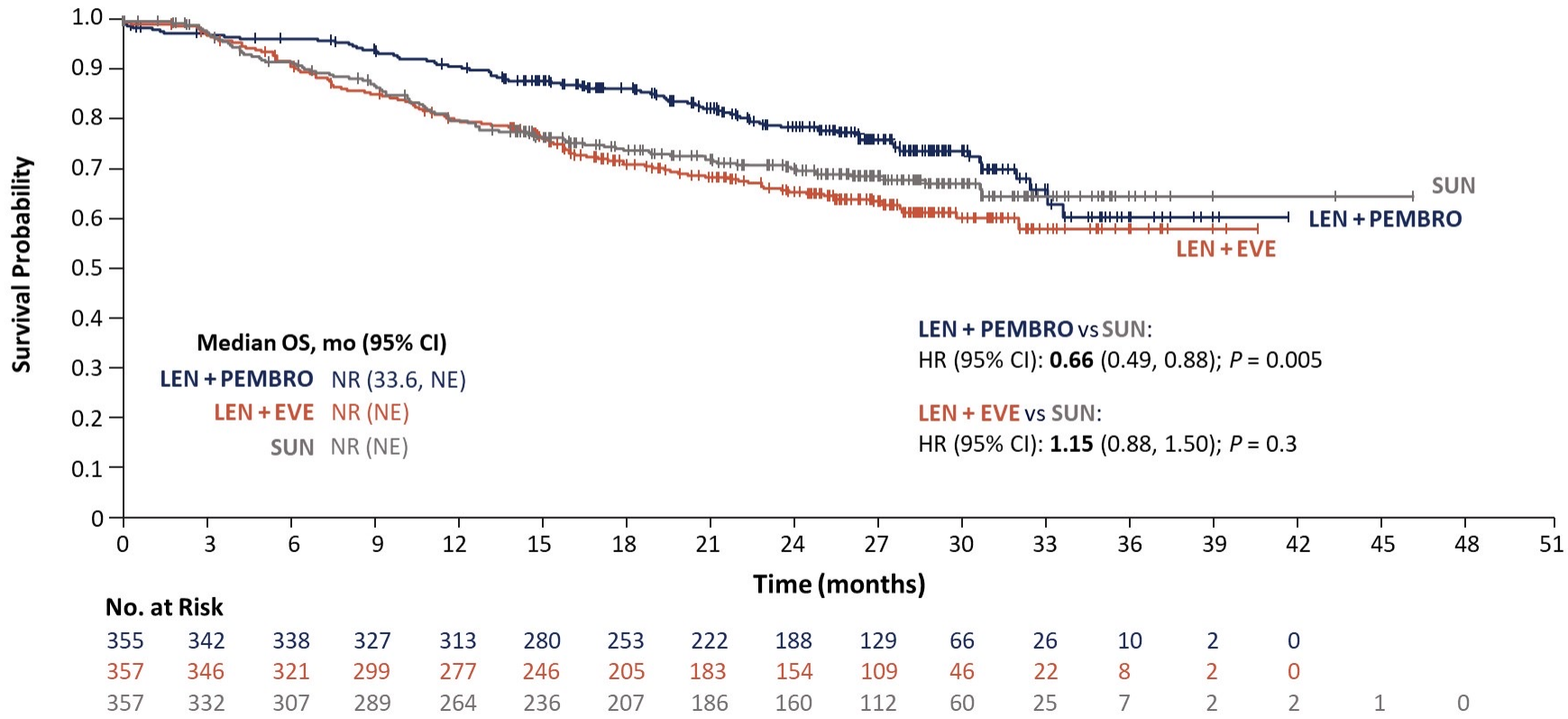
Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

Motzer R. J. et al.; N Engl J Med 2021

Overall Survival



No. at Risk

355	342	338	327	313	280	253	222	188	129	66	26	10	2	0	
357	346	321	299	277	246	205	183	154	109	46	22	8	2	0	
357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

NE, not estimable; NR, not reached.

Motzer R. J. et al.; N Engl J Med 2021

CLEAR Study Highlights

	LEN + PEMBRO	LEN + EVE	SUN
	n = 355	n = 357	n = 357
Median PFS, mo (95% CI)	23.9 (20.8–27.7)	14.7 (11.1–16.7)	9.2 (6.0–11.0)
Stratified HR (95% CI) vs SUN	**0.39 (0.32–0.49)**	**0.65 (0.53–0.80)**	--
P-value	< 0.001	< 0.001	--
Median OS, mo (95% CI)	NR (33.6–NE)	NR (NE)	NR (NE)
Stratified HR (95% CI) vs SUN	**0.66 (0.49–0.88)**	1.15 (0.88–1.50)	--
P-value	0.005	0.3	--
Objective response rate, %	71.0	**53.5**	**36.1**
Complete response, %	16.1	9.8	4.2

How to choose?

IO+IO	IO+TKI
PROS	
• Improved OS • Mature follow-up data • Durable responses • Potential to stop therapy	• Improved OS • High ORR • Longer PFS • Lower irAE rate
CONS	
• Higher irAE rate • Lower PFS/response rate	• Unclear AE attribution • Less mature follow-up • Chronic TKI toxicity

	KEYNOTE-426[1]	CheckMate 9ER[3]	CLEAR[4]
	Axi + Pembro N=432	Cabo + Nivo N=323	Len + Pembro N=355
IMDC Risk Group, %			
Favorable	32	23	31
Intermediate	55	58	59
Poor	13	19	9
Sarcomatoid features, %	18	11	8
Prior Nephrectomy, %	83	69	74
≥ 2 organs with metastasis, %	73	80	72
Liver Metastasis, %	15	23	17
Bone Metastasis, %	24	24	24

1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri T.K. et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer R.J. et al, *NEJM*, 2021. PMID: 33616314.

Summary of Immunotherapy Combination Trials with OS benefit

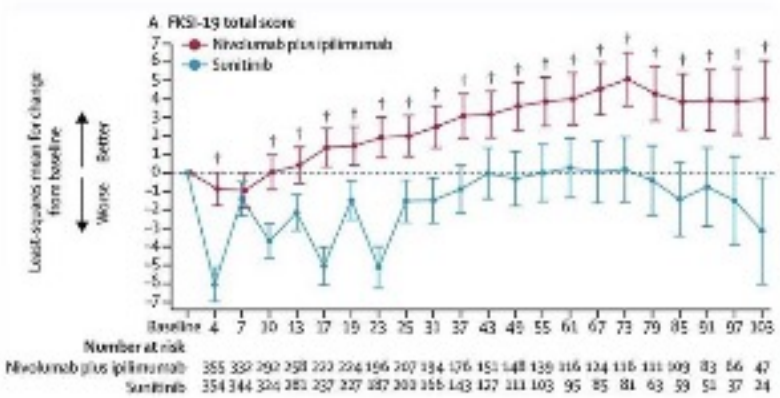
	Nivolumab + Ipilimumab CheckMate-214 n=1096[1]	Pembrolizumab + Axitinib Keynote 426 n=861[2]	Nivolumab + Cabozantinib CheckMate-9ER n=651[3]	Pembrolizumab + Lenvatinib CLEAR n=1096[4]
Follow-up, mo	60 (minimum)	42 (median)	23.5 (median)	26.6 (median)
Median PFS, mo	12.3	15.7	17	23.9
PFS HR	0.86	0.68	0.52	0.39
Median OS, mo	55.7	45.7	NR	NR
OS HR	0.72	0.73	0.66	0.66
ORR, %	39	60.4	54.8	71.0
CR, %	12	10.0	9.3	16.1
PD, %	17.6	11.3	6.2	5.4
QOL vs sunitinib	*Improved*	*Similar*	*Improved*	*Similar to Improved*

Mo=months; PFS=Progression-free survival; HR=Hazard ratio; ORR=Objective response rate; CR=Complete response rate; PD=Progressive disease rate; TTR=Time to response; DOR=Duration of response; NR=Not reached. QOL=Quality of Life

1. Motzer R. et al., ESMO 2021. PMID: 33246931. 2. Choueiri et al., Ann Oncol., 2020. PMID: 32339648. 3. Choueiri et al. NEJM, 2021. PMID: 33657295. 4. Motzer et al, NEJM, 2021. PMID: 33616314.

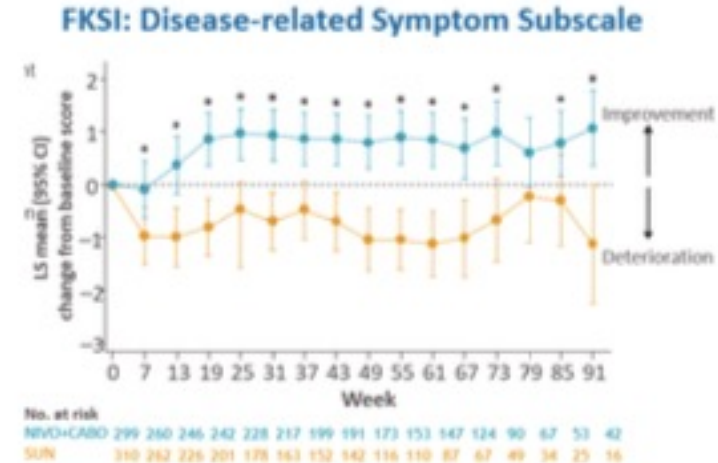
Quality of Life Data from Phase 3 Studies (vs. Sunitinib)

CheckMate-214
Nivolumab + Ipilimumab



Keynote-426
Pembrolizumab + Axitinib

CheckMate-9ER
Nivolumab + Cabozantinib



Improved QOL* (FKSI-19)

Similar QOL* (QLQ-C30)

Improved QOL* (FKSI-19/DRSS)

Caveats

- Different instruments across studies
- Different time points
- Compliance rate varies

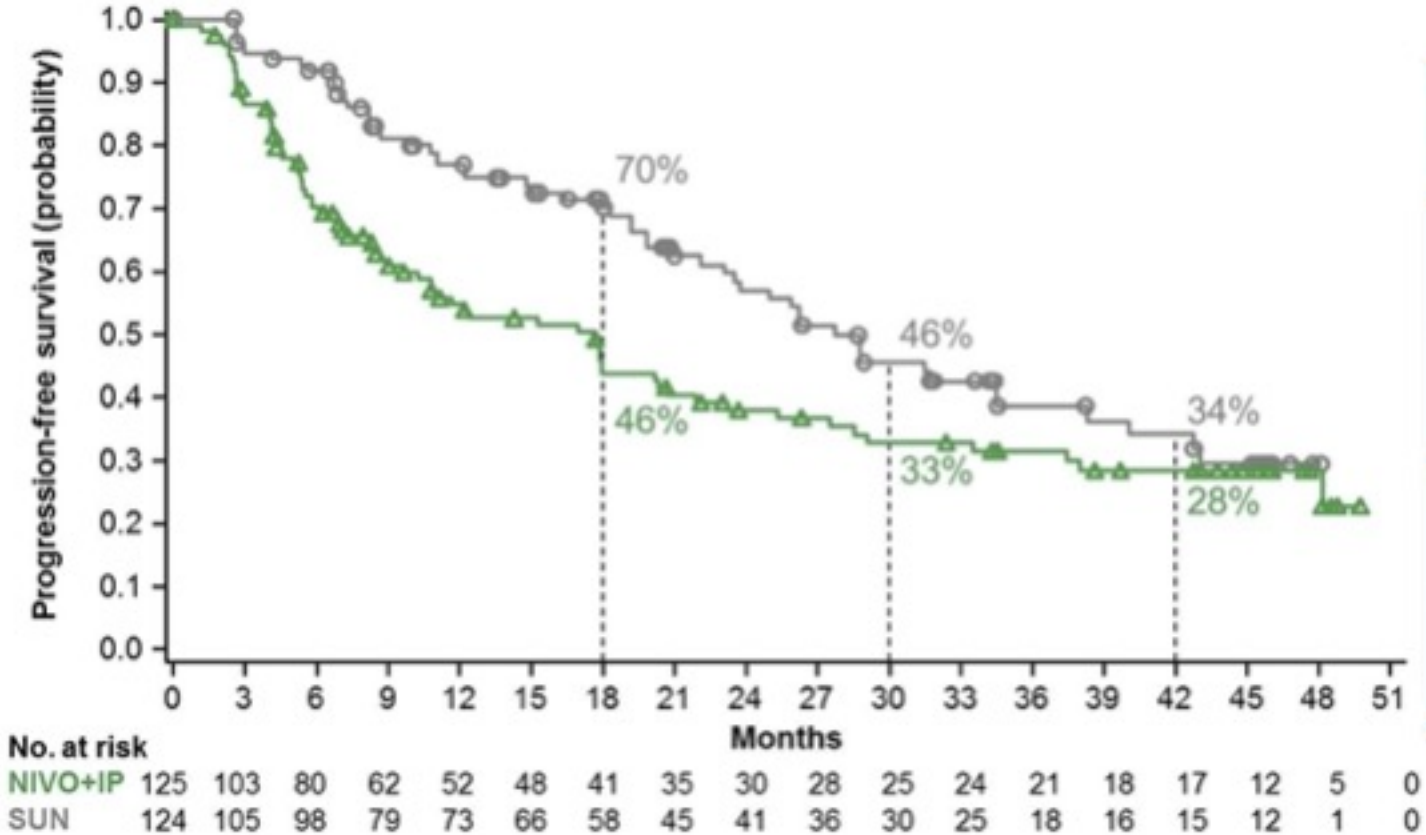
==> Comparisons between studies challenging

QOL=Quality of life.

1. Cella D. et al., *Lancet Oncol.*, 2019. PMID: 30658932. 2. Bedke et al, EAU Meeting, 2020. 3. Choueiri T.K. et al. *NEJM*, 2021. PMID: 33657295

CheckMate214: Favorable risk patients

Exploratory efficacy population: Favorable-risk patients



Minimum follow-up	PFS	NIVO+IPI N = 125	SUN N = 124
17.5 mo[1]	Median, mo (95% CI)	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI)	2.18 (1.29–3.68) $P < 0.0001$	
42 mo	Median, mo (95% CI)	17.8 (10.3–20.7)	27.7 (23.2–34.5)
	HR (95% CI)	1.62 (1.14–2.32) $P < 0.01$	

BUT: 60 months OS HR: 0.94[3]

1. Motzer R.J., et al. *N Engl J Med.* 2018. PMID: Motzer RJ et al. N Engl J Med. 2018. PMID: 29562145. 2. Tannir N, et al. ASCO GU 2020. Abstract 609. 3. Motzer R.J. et al, ESMO 2021.

Favorable risk-patients in IO+TKI combinations: PFS benefit, no OS benefit

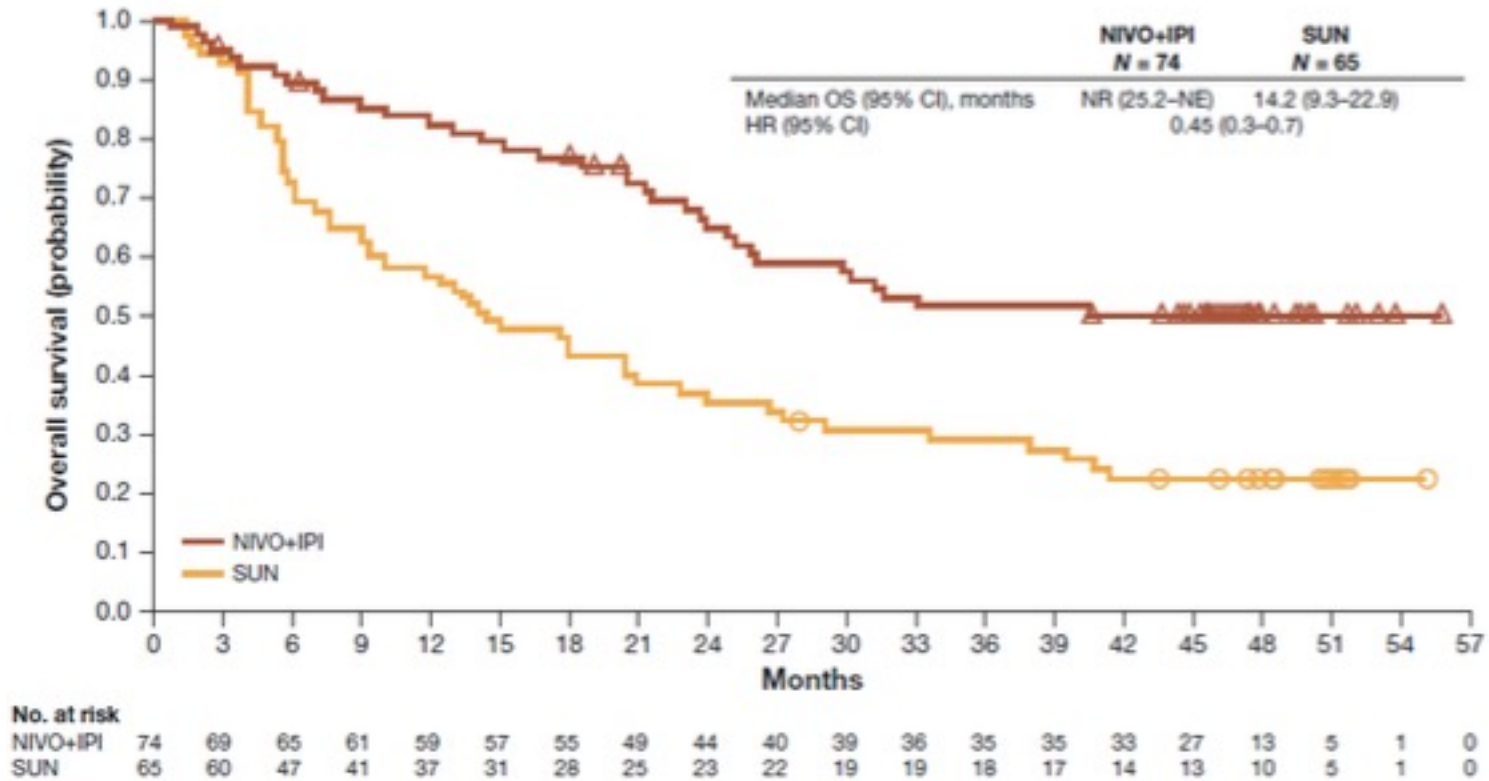
Favorable Risk	Checkmate-9ER[1]	Keynote-426[2]	CLEAR[3]
PFS HR (95% CI)	0.62 (0.38-1.01)	0.81 (0.53-1.24)	0.41 (0.28-0.62)
OS HR (95% CI)	0.84 (0.35-1.97)	0.64 (0.24-1.68)	1.15 (0.55-2.40)

OS benefit in Favorable risk patients may be elusive:

- Limited Nb. of patients
- Limited Nb. of events
- Indolent disease with available 2nd line options

1. Choueiri T.K. et al. *NEJM*, 2021. PMID: 33657295. 2. Rini B.I. et al. *NEJM*, 2019. PMID: 30779529. 3. Motzer R.J. et al, *NEJM*, 2021. PMID: 33616314.

IO + IO in mRCC with Sarcomatoid Features (CheckMate-214)



I/P mRCC	Nivo/Ipi (n=74)	Sunitinib (N=65)	HR
mOS (mo)	NR	14.2	0.45
mPFS (mo)	26.5	5.1	0.56
CR (%)	19	3	

Sarcomatoid RCC tumors are characterized by an *immune-inflamed phenotype*[2]:

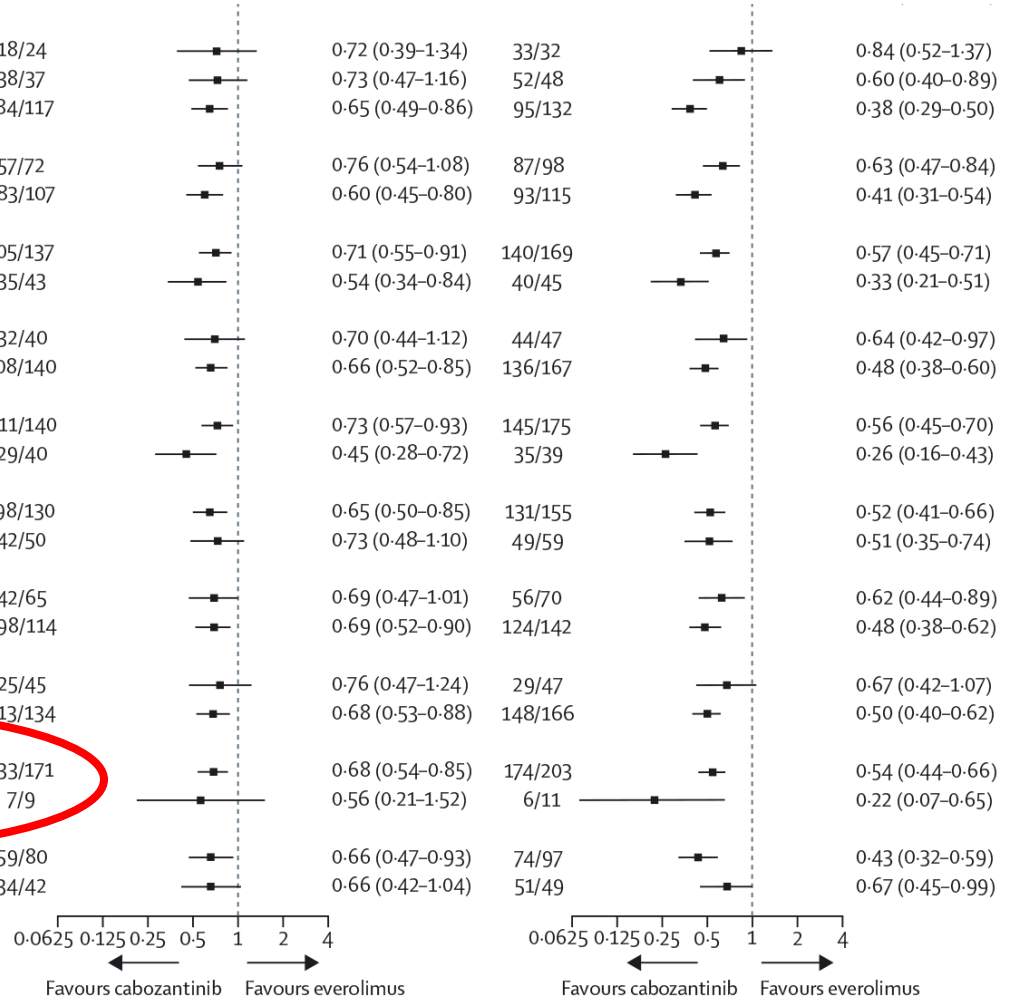
1) Activation of immune pathways
2) Increased expression of APM genes
3) Increased cytotoxic immune infiltration
4) High PD-L1 on tumor cells

1. Tannir N. et al., *Clin Cancer Res.*, 2021. PMID: 32873572. 2. Bakouny Z. et al, *Nat Commun.*, 2021. PMID: 33547292.

What to choose in 2. and later lines?

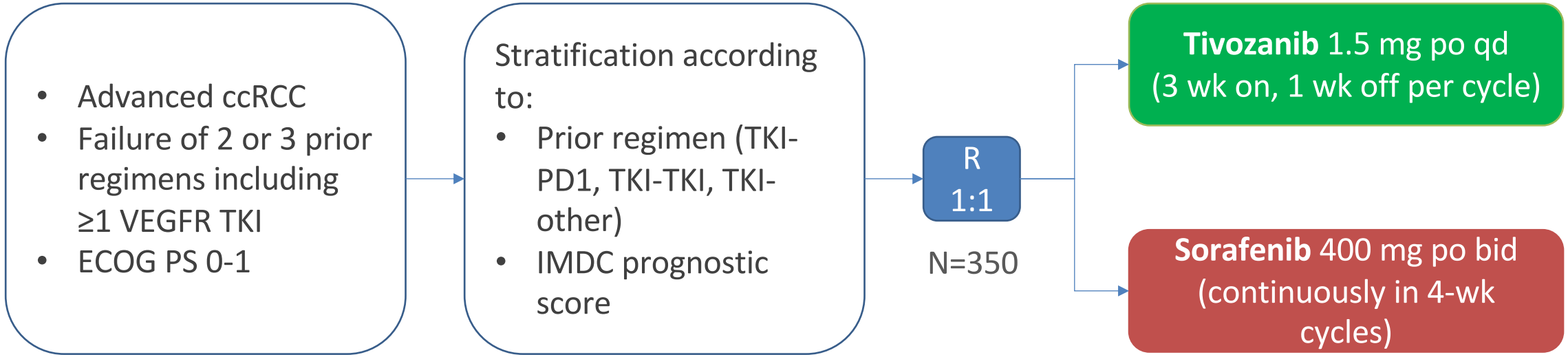
Cabozantinib post IO?

	Patients cabozantinib/ everolimus	Overall survival		Progression-free survival	
		Events cabozantinib/everolimus	HR (95% CI)	Events cabozantinib/everolimus	HR (95% CI)
Number of organs with metastases					
1	59/56	18/24	0·72 (0·39–1·34)	33/32	0·84 (0·52–1·37)
2	101/77	38/37	0·73 (0·47–1·16)	52/48	0·60 (0·40–0·89)
≥3	168/190	84/117	0·65 (0·49–0·86)	95/132	0·38 (0·29–0·50)
SoD					
<median	165/163	57/72	0·76 (0·54–1·08)	87/98	0·63 (0·47–0·84)
≥median	165/164	83/107	0·60 (0·45–0·80)	93/115	0·41 (0·31–0·54)
Bone metastases					
No	253/263	105/137	0·71 (0·55–0·91)	140/169	0·57 (0·45–0·71)
Yes	77/65	35/43	0·54 (0·34–0·84)	40/45	0·33 (0·21–0·51)
Visceral metastases					
No	89/83	32/40	0·70 (0·44–1·12)	44/47	0·64 (0·42–0·97)
Yes	241/245	108/140	0·66 (0·52–0·85)	136/167	0·48 (0·38–0·60)
Visceral and bone metastases					
No	270/276	111/140	0·73 (0·57–0·93)	145/175	0·56 (0·45–0·70)
Yes	60/52	29/40	0·45 (0·28–0·72)	35/39	0·26 (0·16–0·43)
Number of previous VEGFR TKIs					
1	235/229	98/130	0·65 (0·50–0·85)	131/155	0·52 (0·41–0·66)
≥2	95/99	42/50	0·73 (0·48–1·10)	49/59	0·51 (0·35–0·74)
Duration of first VEGFR TKI					
≤6 months	88/102	42/65	0·69 (0·47–1·01)	56/70	0·62 (0·44–0·89)
>6 months	242/224	98/114	0·69 (0·52–0·90)	124/142	0·48 (0·38–0·62)
Progression after start of most recent VEGFR TKI					
<3 months	44/68	25/45	0·76 (0·47–1·24)	29/47	0·67 (0·42–1·07)
≥3 months	283/259	113/134	0·68 (0·53–0·88)	148/166	0·50 (0·40–0·62)
Previous PD-1 or PD-L1 treatment					
No	312/314	133/171	0·68 (0·54–0·85)	174/203	0·54 (0·44–0·66)
Yes	18/14	7/9	0·56 (0·21–1·52)	6/11	0·22 (0·07–0·65)
Only previous VEGFR TKI					
Sunitinib	135/132	59/80	0·66 (0·47–0·93)	74/97	0·43 (0·32–0·59)
Pazopanib	88/83	34/42	0·66 (0·42–1·04)	51/49	0·67 (0·45–0·99)



1. 1.CABOMETYX SmPC, 2016-o9-09 2.Choueiri TK, et al. Lancet Oncol 2016;17:917-27

TIVO-3: a multi-centre, open-label, phase III study

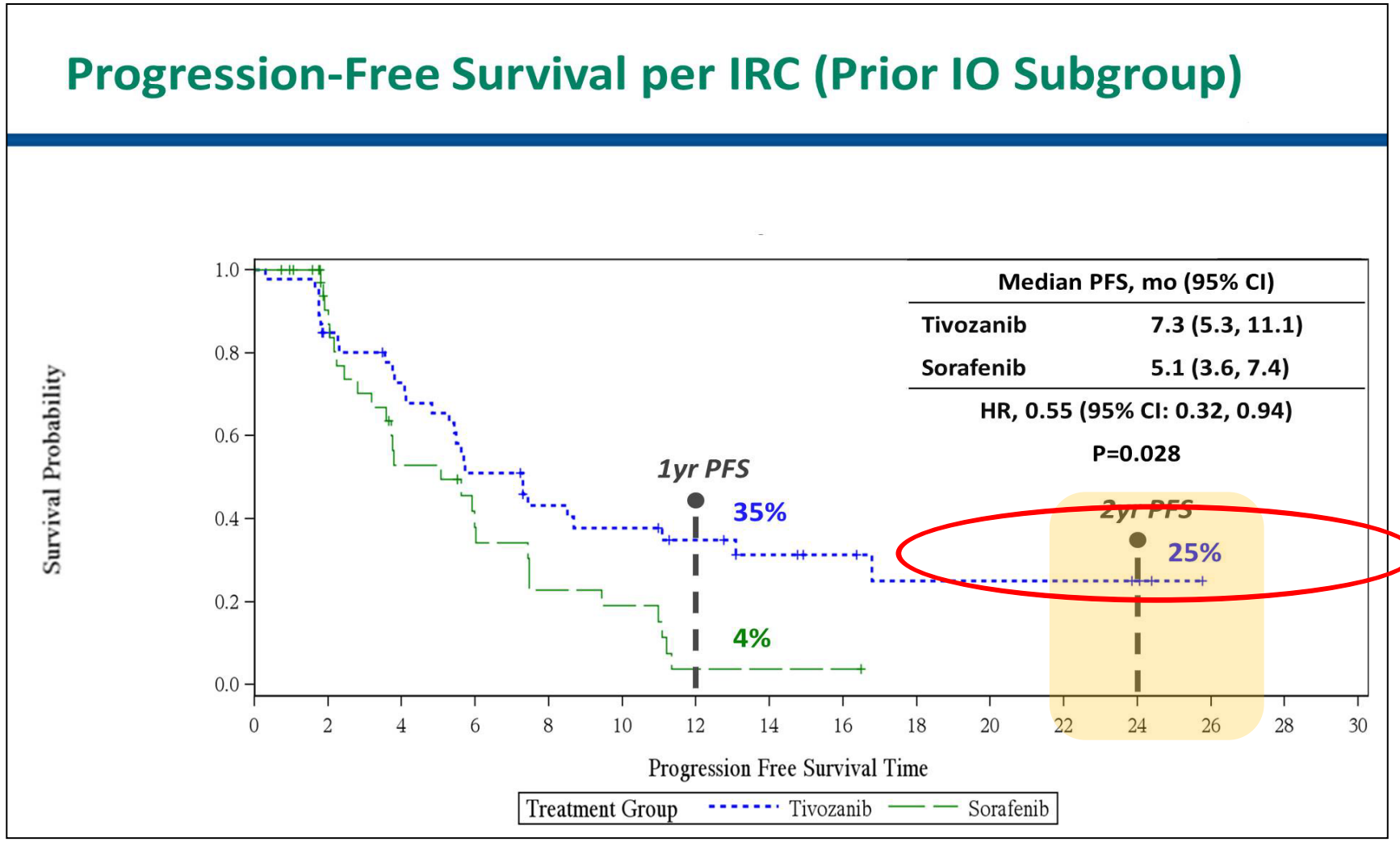


Tx until progression or unacceptable toxicity

Primary endpoint: PFS by IRC (90% power to detect PFS improvement of 4 vs 6 mo)

Rini B. ASCO GU 2019, abs.541

TIVO-3: a multi-centre, open-label, phase III study



Rini B. ASCO GU 2019, abs.541

Axitinib post IO

- Median PFS 8.8 months
- ORR 45 %

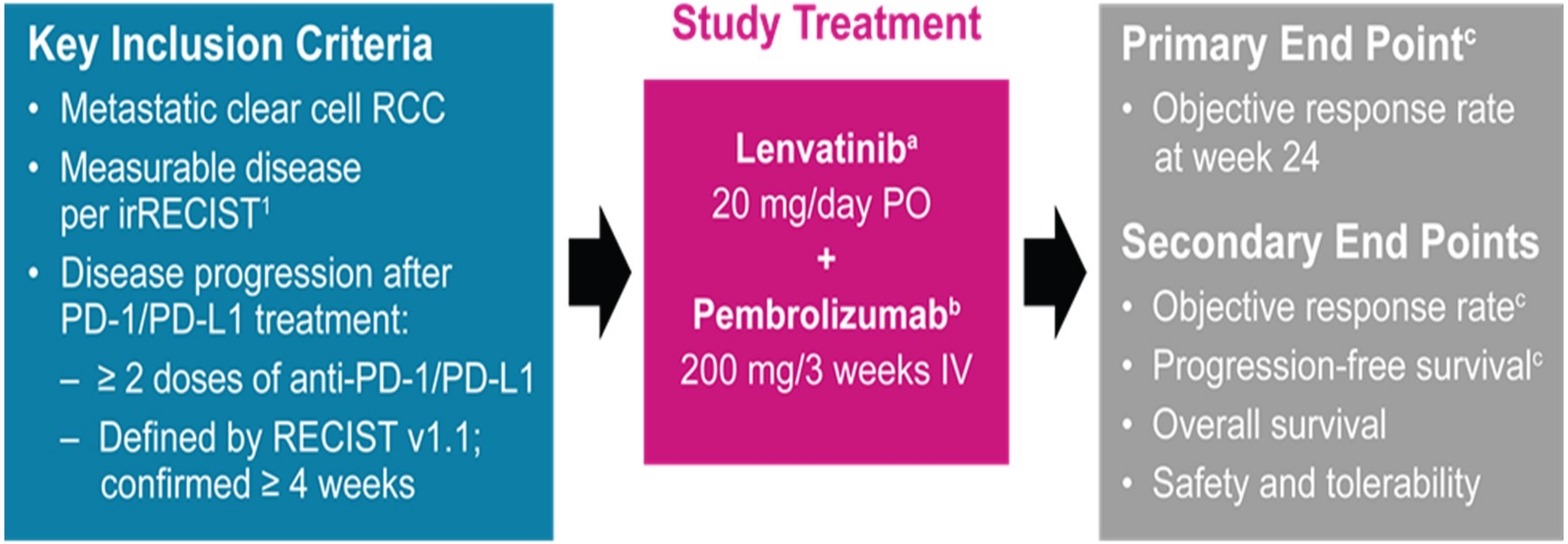
	Participants, n=40
Number of previous therapies*	
1	11 (28%)
2	19 (48%)
3	9 (23%)
4	1 (3%)
Most recent therapy	
Nivolumab	25 (63%)
Ipilimumab plus nivolumab	6 (15%)
Nivolumab plus hypoxia-inducible factor inhibitor	3 (8%)
Atezolizumab	2 (5%)
Bevacizumab plus atezolizumab	2 (5%)
Durvalumab plus tremelimumab	1 (3%)
Durvalumab	1 (3%)
Best response to checkpoint inhibitor therapy†	
Partial response	8 (20%)
Stable disease	21 (53%)
Progressive disease	10 (25%)
Duration on previous checkpoint inhibitor	
<6 months	25 (63%)
≥6 months	15 (38%)
Median duration, months	4·8 (2·0–8·7)
Reason for checkpoint inhibitor discontinuation	
Disease progression	37 (93%)
Toxicity‡	3 (8%)
Time from checkpoint inhibitor discontinuation to axitinib initiation, months	1·1 (0·7–1·7)

Values are n (%) or median (IQR). *The majority of patients (28 [70%]) received previous VEGF-directed therapy. †Unknown for one patient. ‡One patient each: fatigue, pneumonitis, and colitis.

***Table 2*: Previous therapies and response to immune checkpoint inhibitor**

Ornstein et al., Lancet Oncol 2019

Study Design for the Phase 2 RCC Cohort

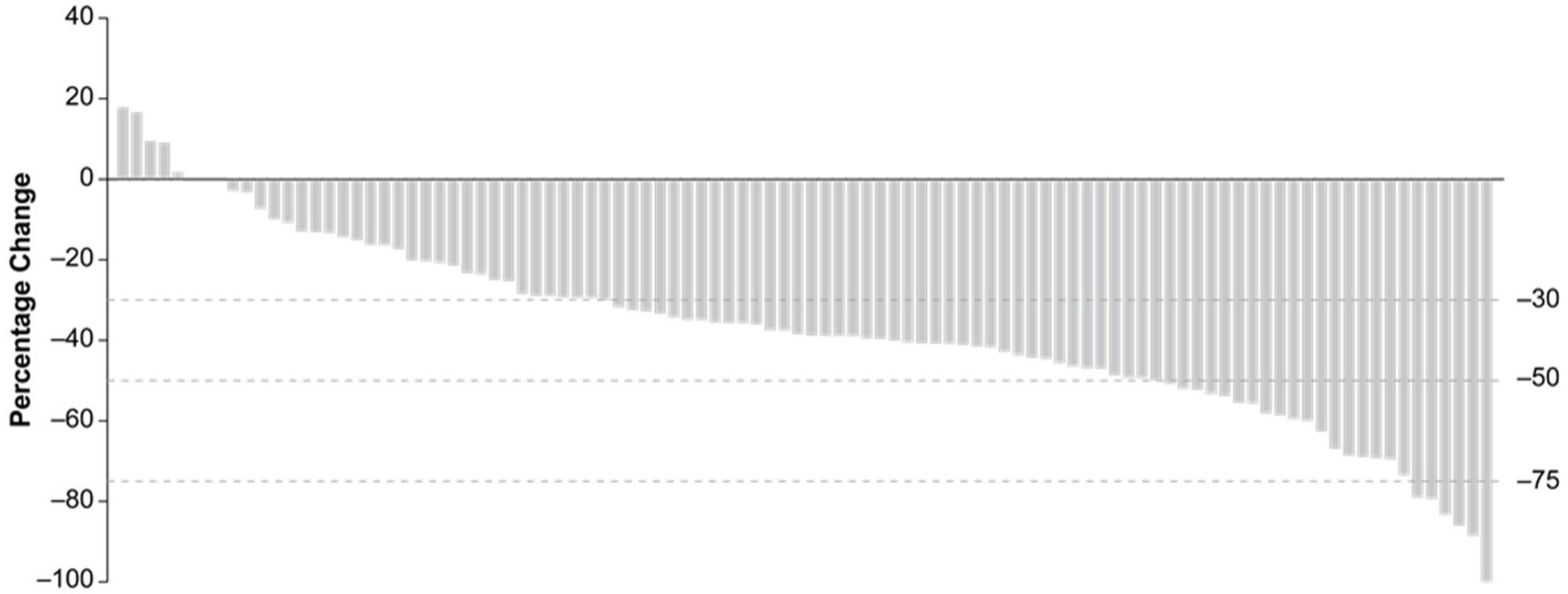


[a] Dose reductions to lenvatinib 14 mg/day, 10 mg/day, 8 mg/day and 4 mg/day were allowed to manage toxicities; dose reductions below 4 mg/day were discussed with the sponsor; [b] maximum of 35 treatments (approximately 2 years); [c] per irRECIST, by investigator assessment.

1. Perrone A. Immuno-Oncology 360° conference. New York, NY. 2016.
IV, intravenously; PO, by mouth; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Presented By Chung-Han Lee at TBD

Percentage Change in Sum of Diameters of Target Lesions From Baseline to Nadir[a]

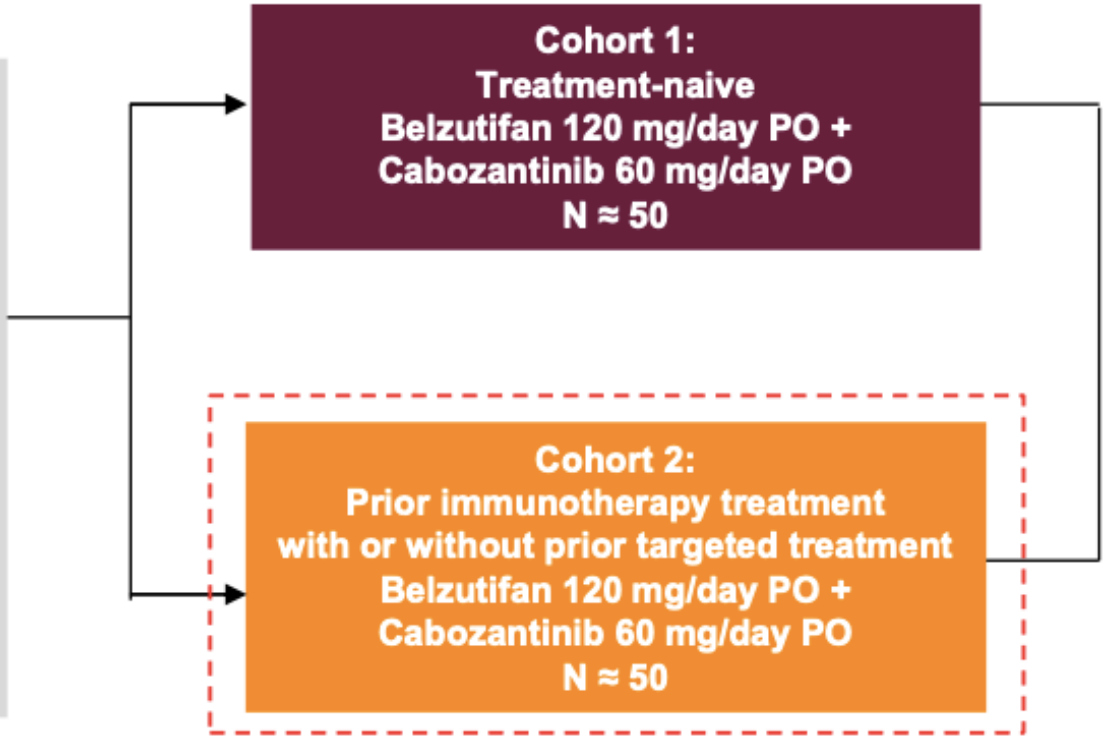


Note: Each bar represents 1 patient.
[a] By irRECIST per investigator assessment.

Presented By Chung-Han Lee at TBD

Study Design (NCT03634540)

Key Eligibility Criteria
- Advanced or metastatic ccRCC
- Being treatment naive or having previously received immunotherapy and ≤2 regimens for locally advanced or metastatic RCC
- ECOG PS 0 or 1
- All IMDC risk categories (favorable/intermediate/poor) allowed



Safety and tolerability were evaluated in the first 6 participants enrolled, irrespective of cohort
- If tolerability was established, enrollment continued
- If tolerability was not established, dose was reviewed

Tumor Assessments
- Q8W after week 9 for 12 months and then Q12W thereafter

End Points
- Primary: ORR
- Secondary: PFS, TTR, DOR, OS, safety/tolerability, PK/PD

Median follow-up[a]
- 15.4 months (range, 8.7-30.6)

Objective Response Rate and Disease Control Rate

	ORR (CR + PR)		DCR (CR + PR + SD)	
Population	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
All patients	15/52	28.8 (17.1-43.1)	48/52	92.3 (81.5-97.9)
IMDC risk category				
Favorable	3/11	27.3 (6.0-61.0)	11/11	100 (71.5-100)
Intermediate/poor	12/41	29.3 (16.1-45.5)	37/41	90.2 (76.9-97.3)
Prior anticancer therapy				
IO only	8/28	28.6 (13.2-48.7)	26/28	92.9 (76.5-99.1)
IO/VEGF	7/24	29.2 (12.6-51.1)	22/24	91.7 (73.0-99.0)

Personal preference?

- Therapy management (dose reduction, supportive measures) is easiest for the drug you know best

Takk for oppmerksomheten!