2021 ESMO congress

Is there an optimal first-line combination approach for metastatic RCC?

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DECLARATION OF POTENTIAL INTERESTS

Toni K. Choueiri (financial and non-financial):

- Consultancy fees, advisory boards, manuscript preparation, travel/lodging, honoraria, grants for clinical trials:
  - AstraZeneca
  - Bristol Myers Squibb
  - Eisai
  - Eli Lilly
  - EMD Serono.
  - Exelixis/Ipsen
  - GlaxoSmithKline
  - Merck Novartis
  - Pfizer
  - Roche
  - Up-To-Date royalties and CME events (Peerview, OncLive, others)
  - ASCO and ESMO organizing committees, KidneyCan Board, NCCN (all unpaid)

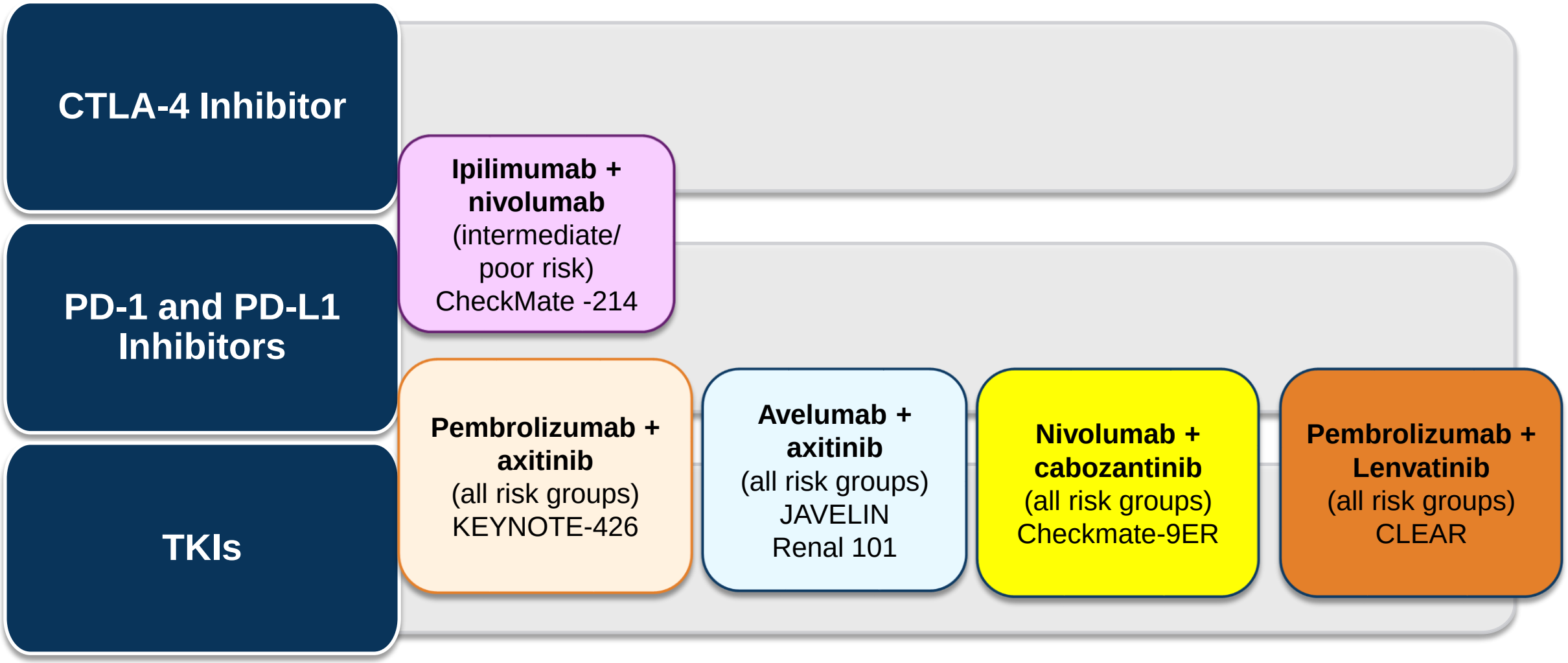
Outline

- Key combination trials for the treatment of mRCC in the **1st line setting**
- Comparison of combination trials
- Special populations (in the 1st line treatment of mRCC):
  - Favorable IMDC risk (20%)
  - Sarcomatoid features (5-15%)
- Key takeaways

Outline

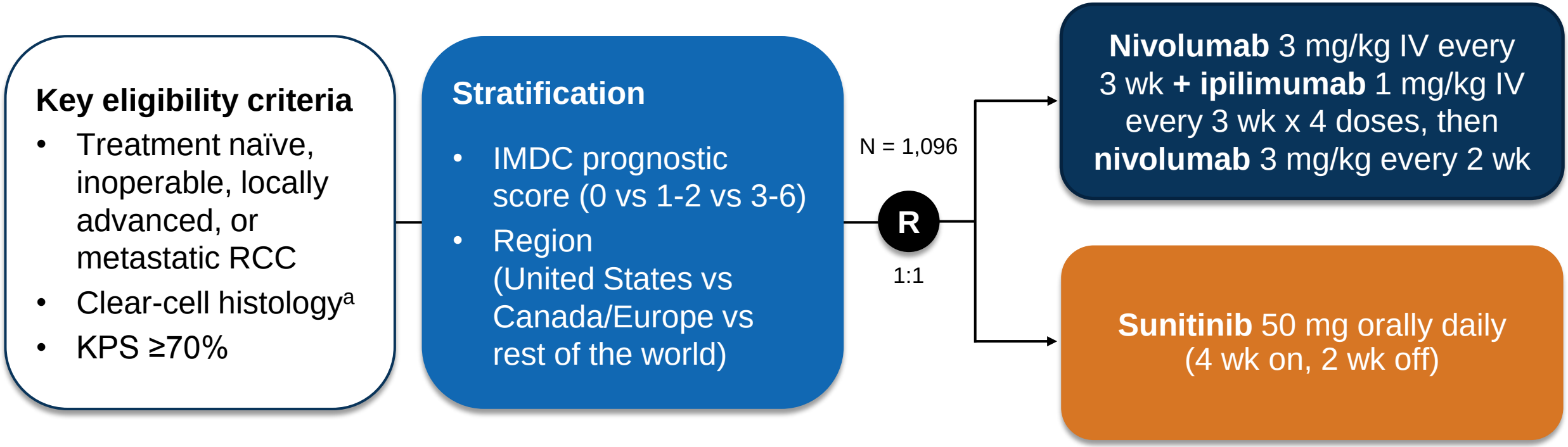
- Key combination trials for the treatment of mRCC in the **1st line setting**
- Comparison of combination trials
- Special populations (in the 1st line treatment of mRCC):
  - Favorable IMDC risk (20%)
  - Sarcomatoid features (5-15%)
- Key takeaways

First-Line Combination Therapies in Advanced RCC (FDA approved as of today)



IO+IO COMBINATION
(PD-1+CTLA4 INHIBITORS)

CheckMate -214: Nivolumab Plus Ipilimumab in Newly Diagnosed Advanced Clear-Cell RCC



Endpoints

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

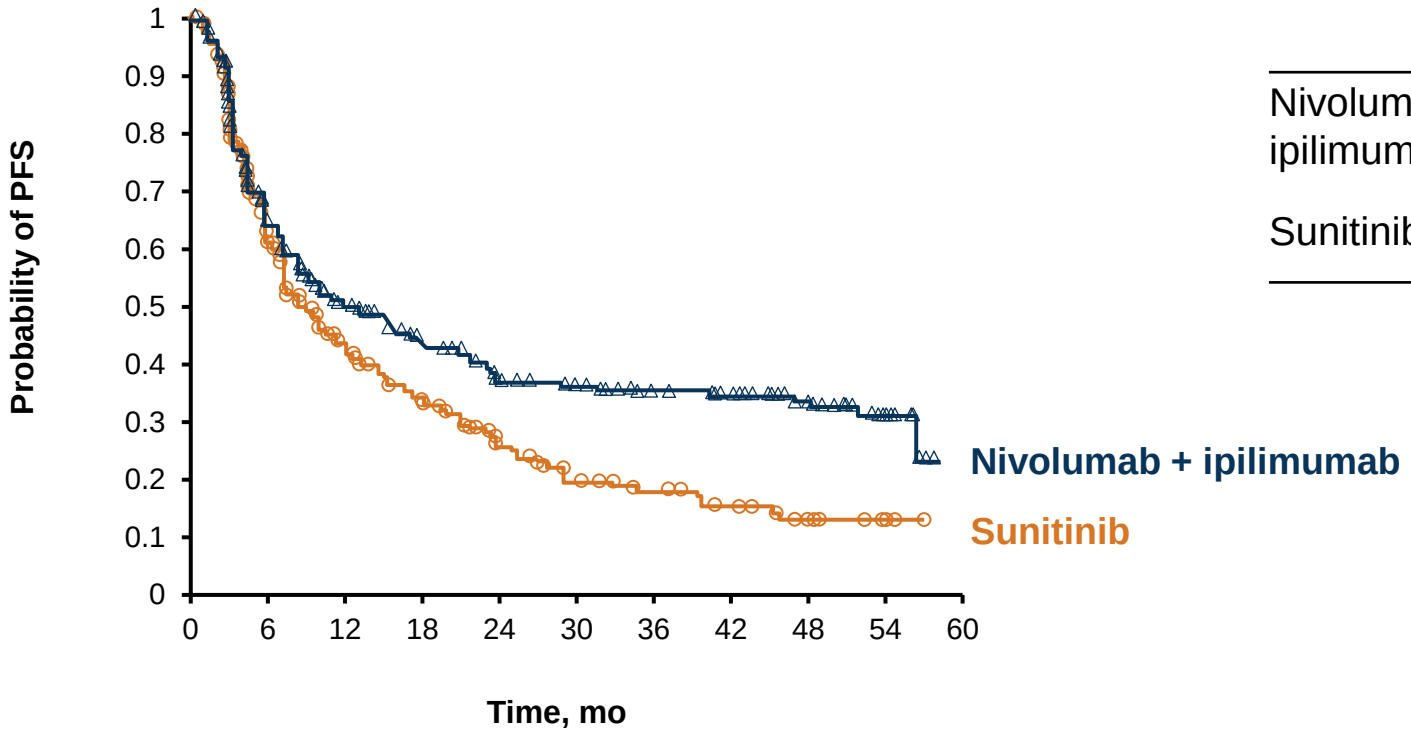
Motzer RJ et al. *Lancet Oncol*. 2019;20:1370-1385.

CheckMate -214: 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.

CheckMate -214: PFS at 48 Months (Intermediate-/Poor-Risk Patients)[1]



No. at Risk											
NIVO + IPI	425	232	163	130	101	94	80	70	50	13	0
SUN	422	189	107	75	47	30	22	16	9	3	0

	N	Median (95% CI), mo
Nivolumab + ipilimumab	425	11.2 (8.4-16.1)
Sunitinib	422	8.3 (7.0-10.8)

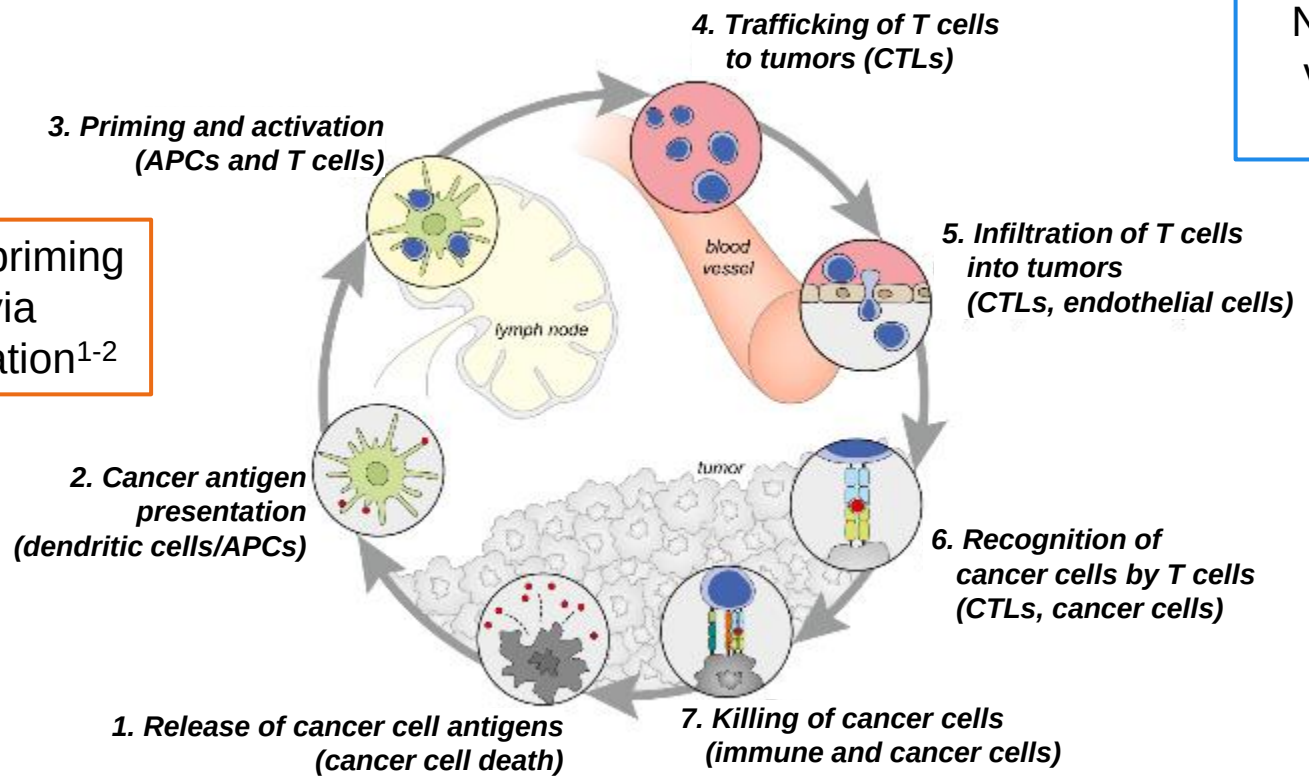
HR (95% CI), 0.74 (0.62-0.88)

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

IO + VEGF COMBINATION (S)

Rationale for Combining Immunotherapy with VEGF-targeted Therapy

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

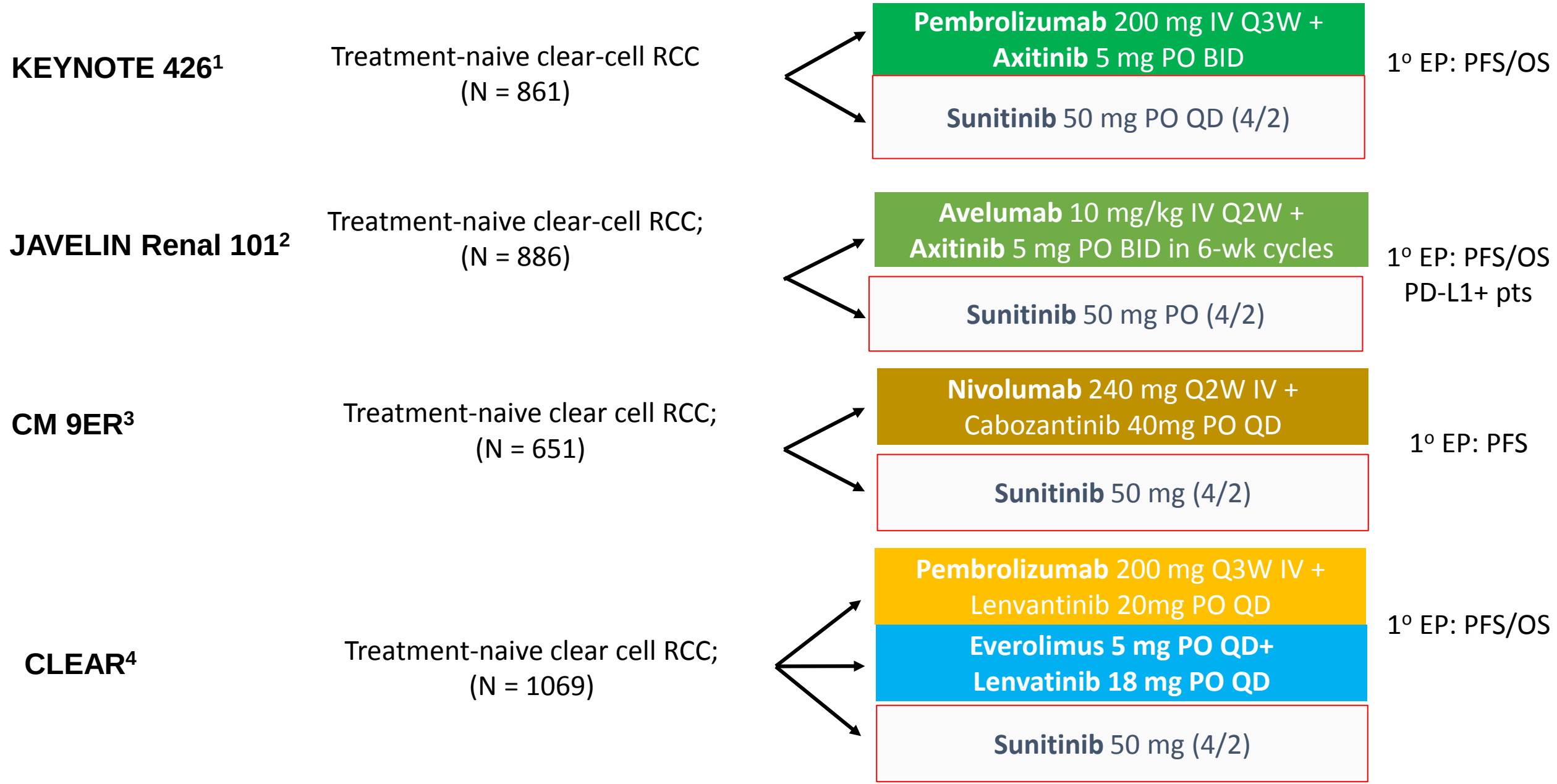


Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

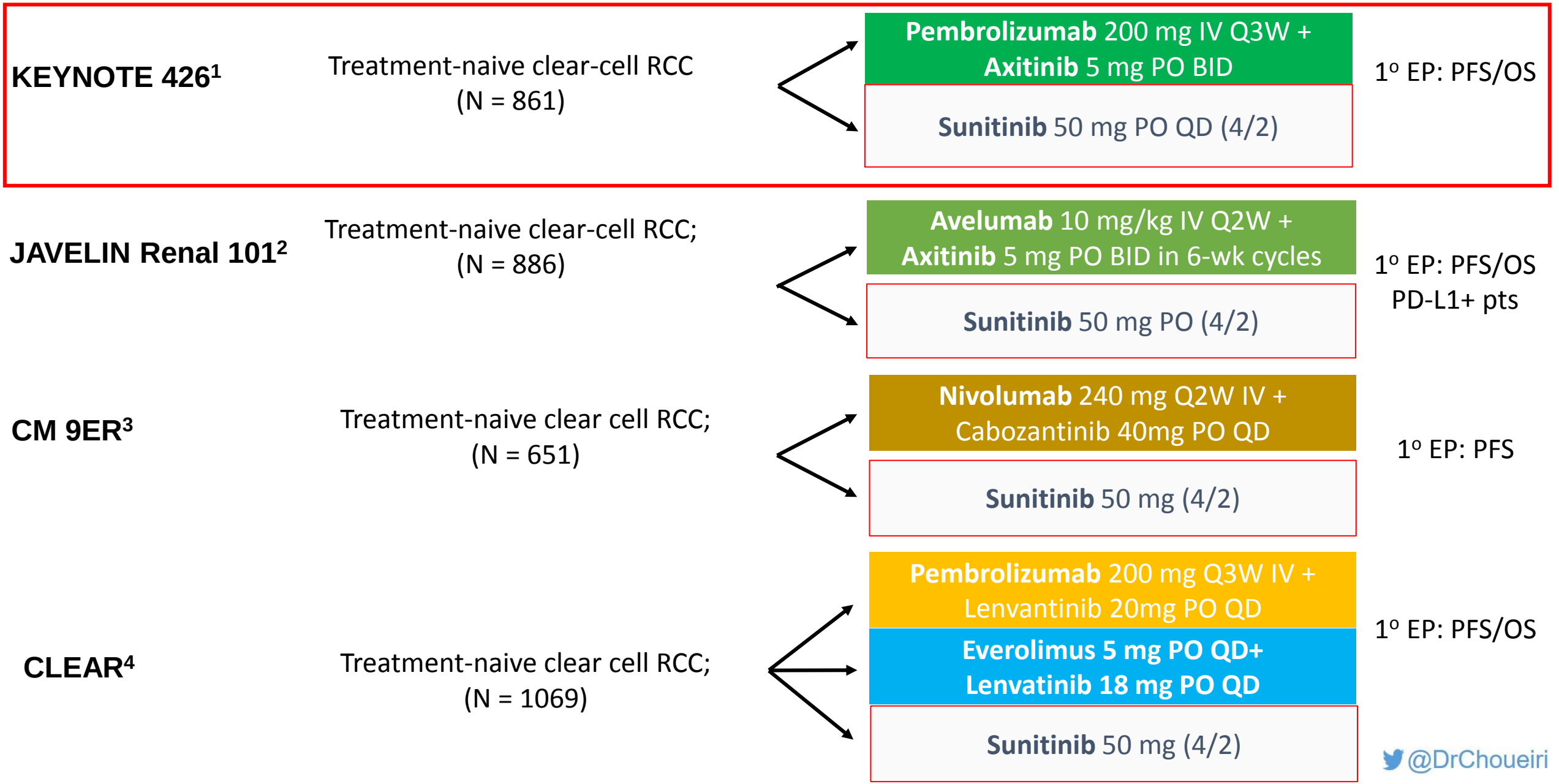
Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

➔ 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.

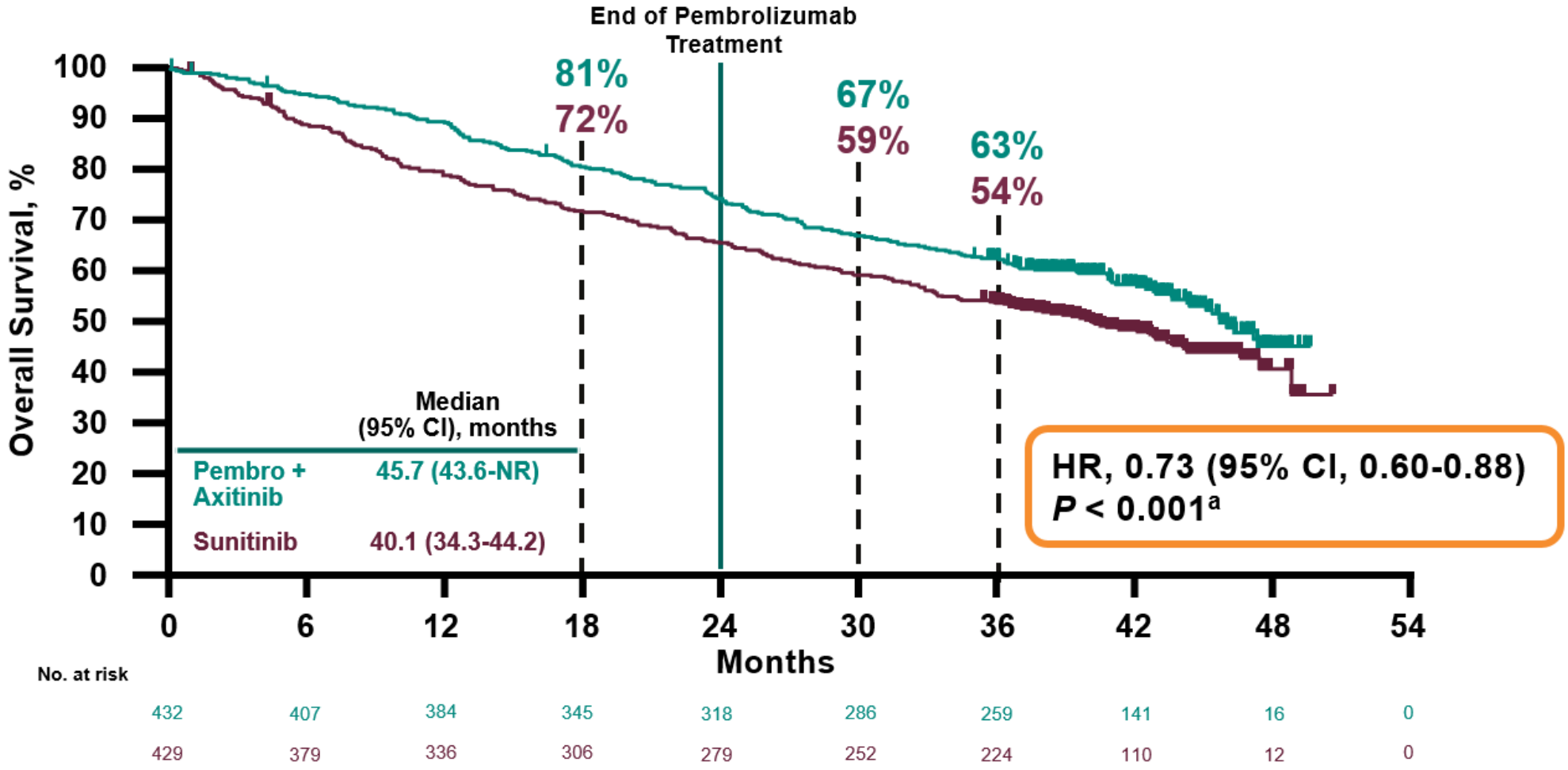


1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.



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)



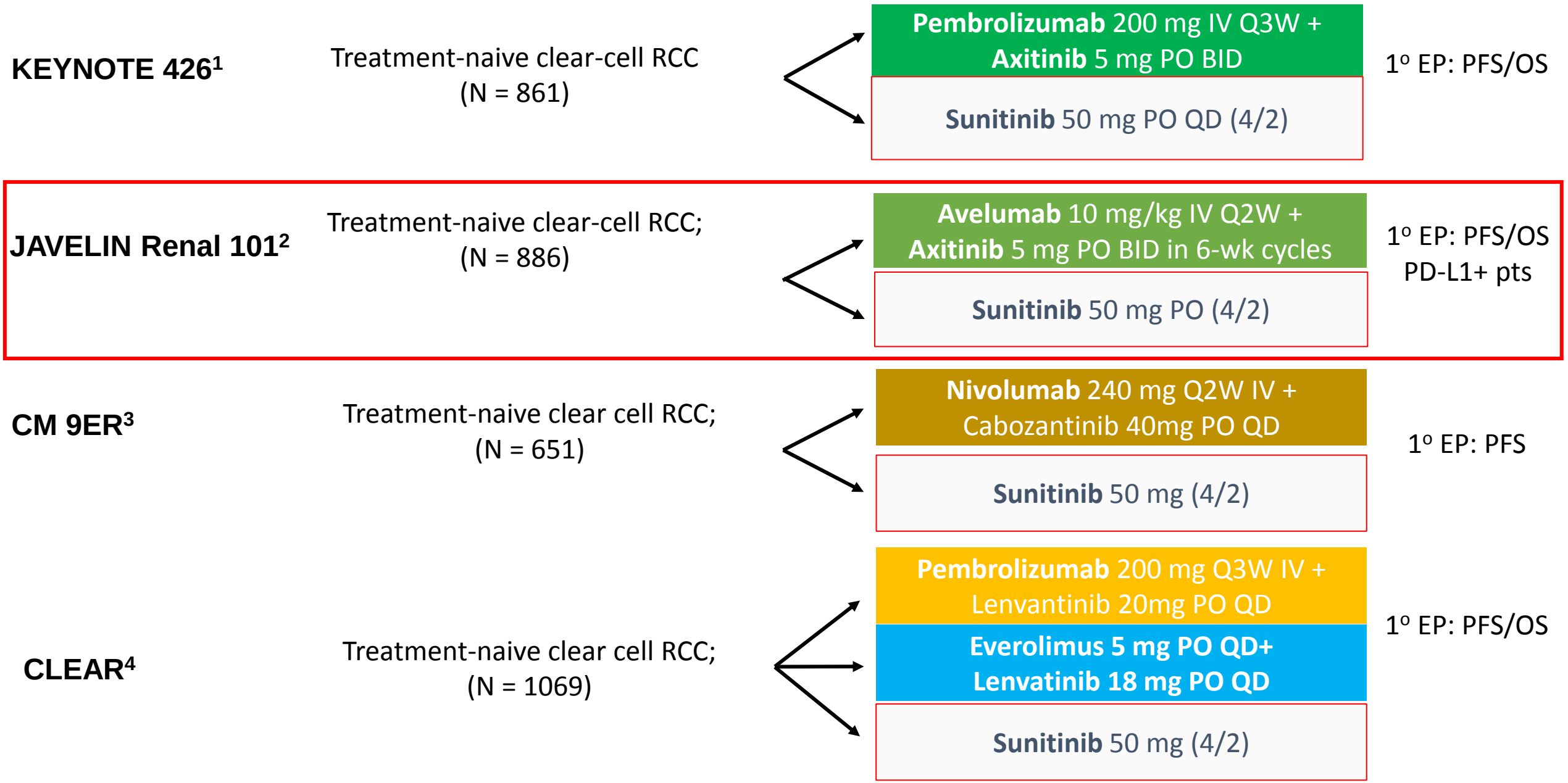
Toni K Choueiri

Adapted from Rini et al, ASCO 2021

KEYNOTE-426 Highlights

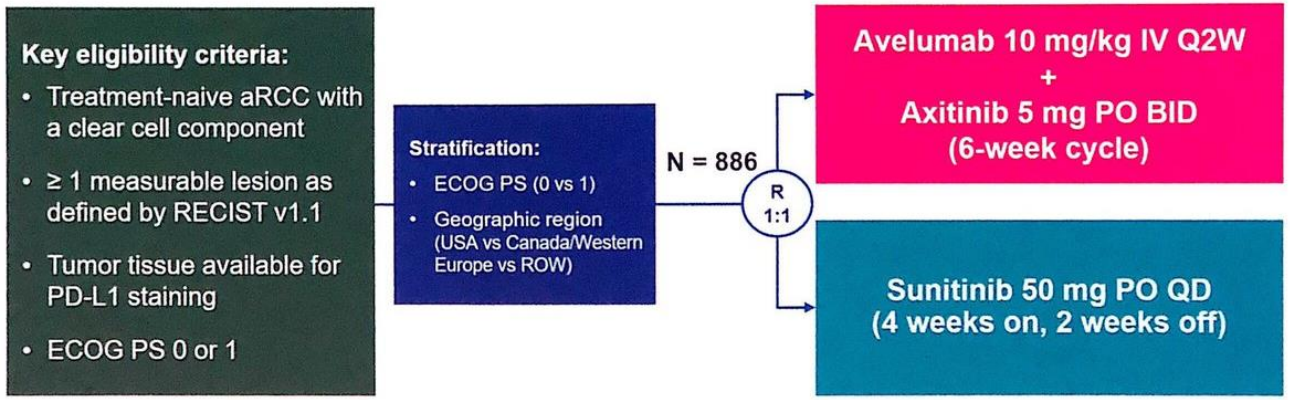
Median follow-up (months)	12.8	30.6	42.8
OS, months	NR	NR	45.7
HR (95% CI)	0.53 (0.38-0.74)	0.68 (0.55-0.85)	0.73 (0.6-0.88)
PFS, months	15.1	15.4	15.7
HR (95% CI)	0.69 (0.57-0.84)	0.71 (0.6-0.84)	0.68 (0.58-0.8)
ORR(%)/CR(%)	59/6	60/9	60/10

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



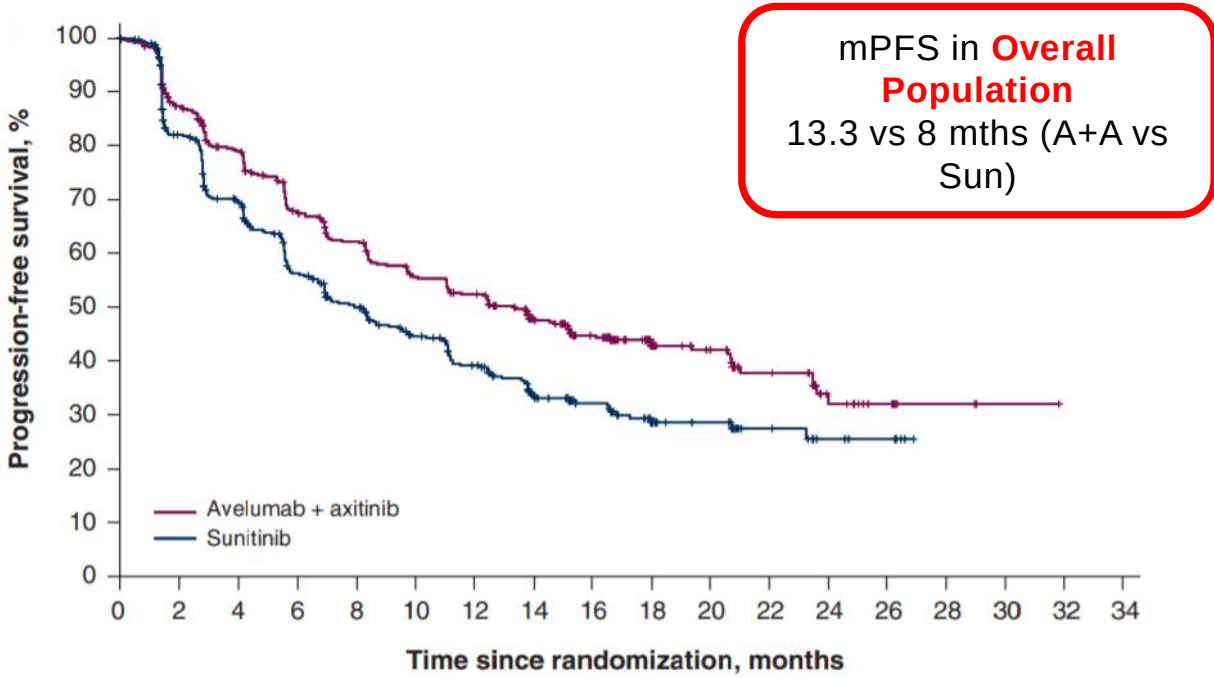
1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

Javelin Renal 101- Highlights

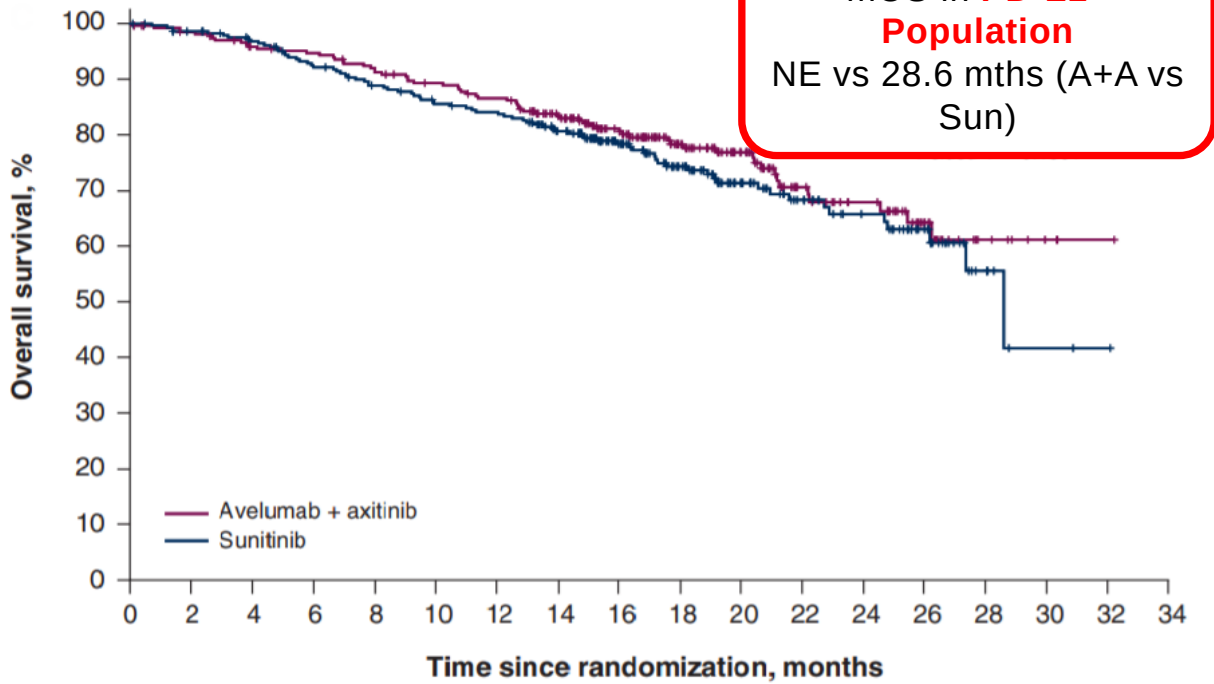


Primary Endpoint: PFS or OS in patients *with PD-L1+ tumors*

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

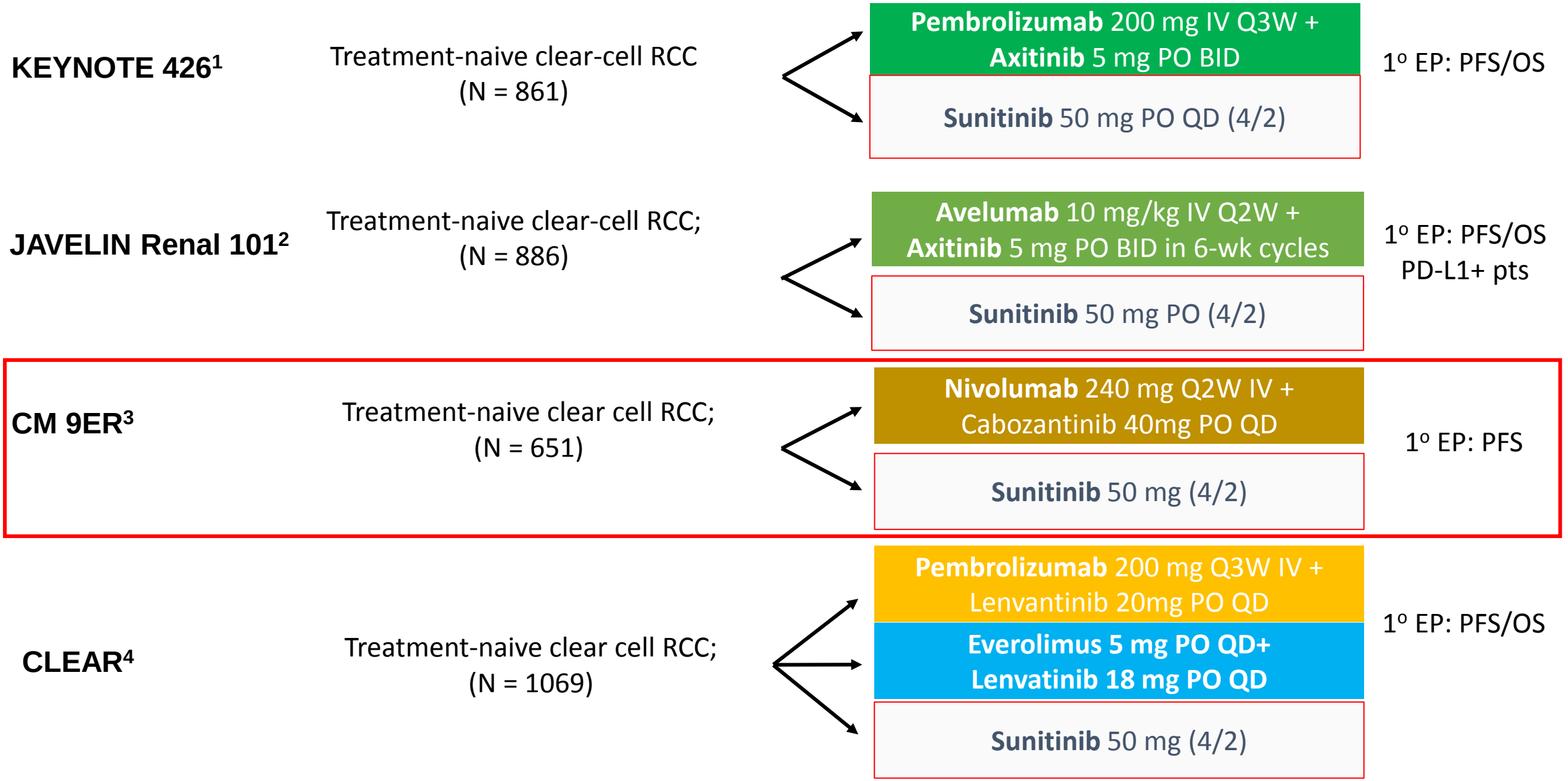


mPFS in **Overall Population**
13.3 vs 8 mths (A+A vs Sun)



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

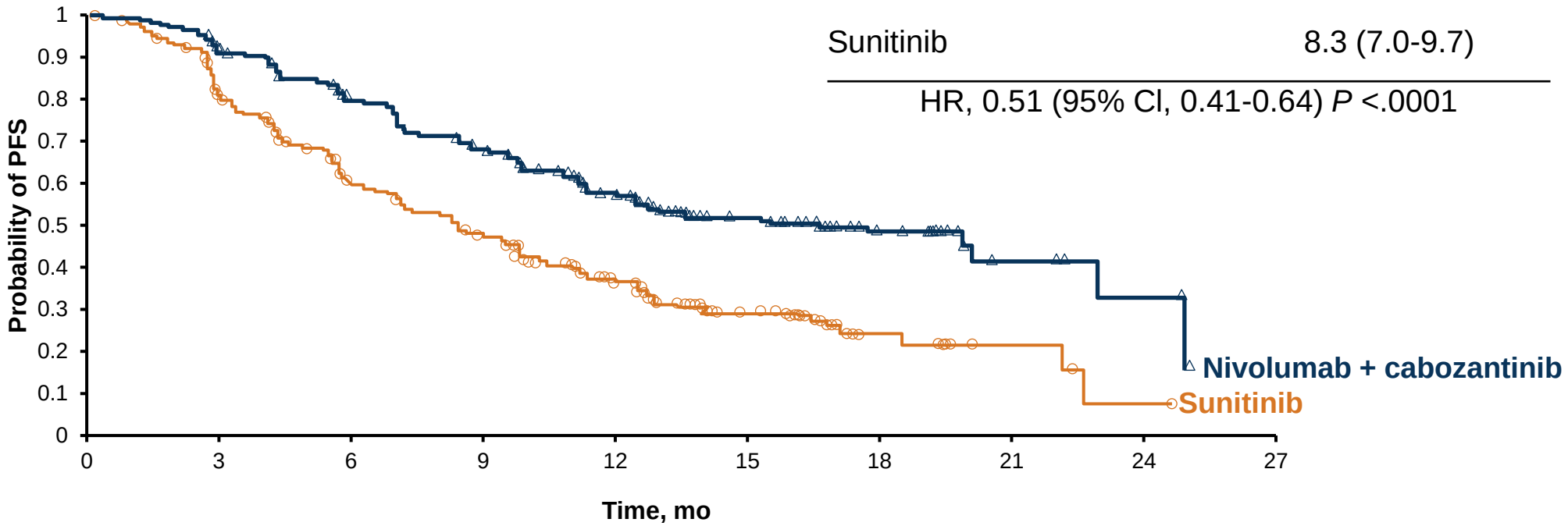


1. Rini et al. *NEJM,* 2019. PMID: 30779529. 2. Motzer et al. *NEJM,* 2019. PMID: 30779531. 3. Choueiri et al. *NEJM*, 2021. PMID: 33657295. 4. Motzer et al, *NEJM*, 2021. PMID: 33616314.

CheckMate -9ER: PFS[1,2]

	Median (95% CI), mo
Nivolumab + cabozantinib	16.6 (12.5-24.9)
Sunitinib	8.3 (7.0-9.7)

HR, 0.51 (95% CI, 0.41-0.64) *P* <.0001



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

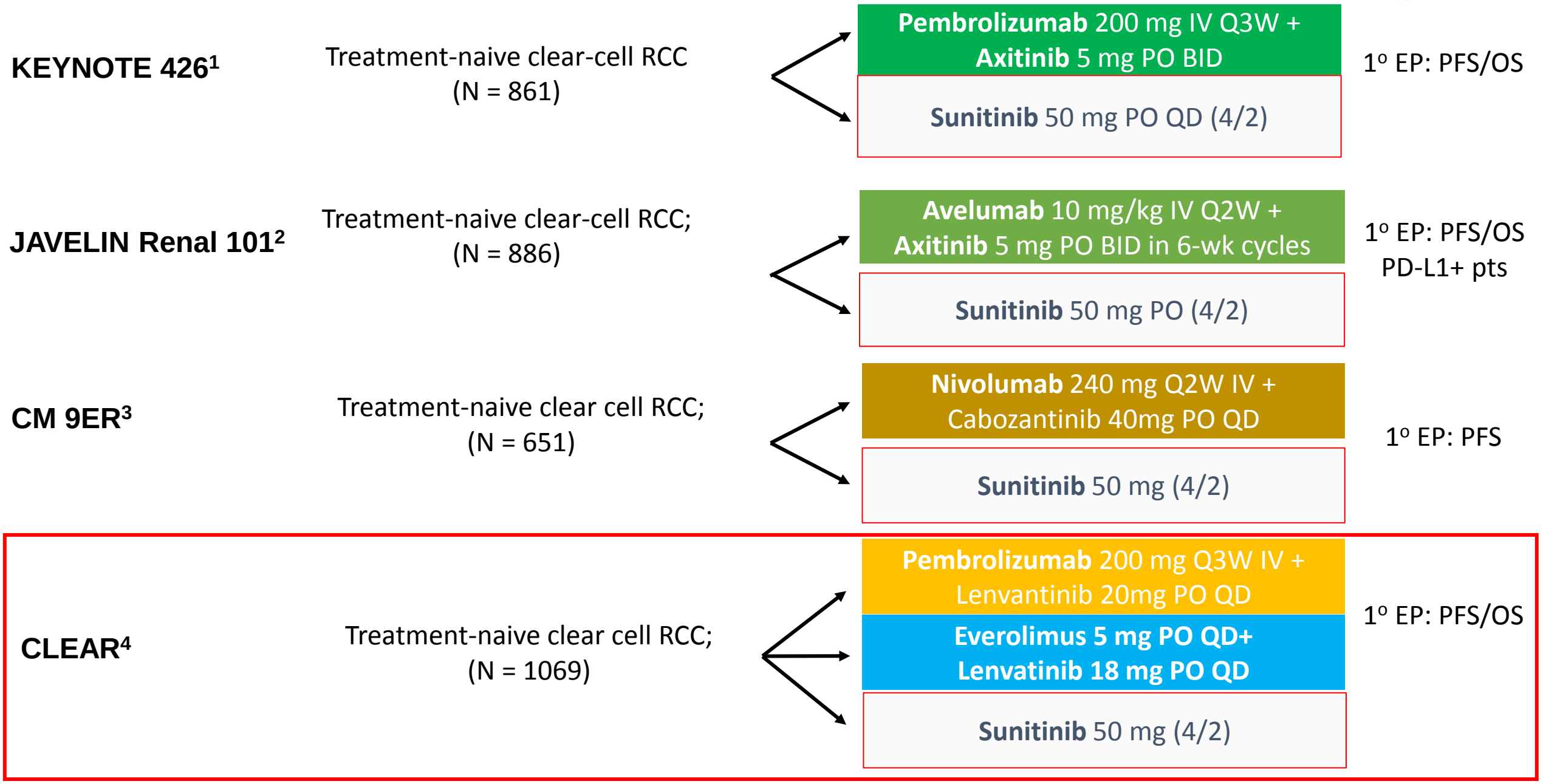
Minimum study follow-up, 10.6 months.

1. Choueiri TK et al. ESMO 2020, 2. Choueiri T.K. et al., *NEJM*, 2021. PMID: 33657295.

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.

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

1. Motzer R.J. et al, *NEJM*, 2021. PMID: 33616314.

Outline

- Key combination trials for the treatment of mRCC in the **1st line setting**
- Comparison of combination trials
- Special populations (in the 1st line treatment of mRCC):
  - Favorable IMDC risk (20%)
  - Sarcomatoid features (5-15%)
- Key takeaways

Take-Homes from the trials (IO/IO or IO/TKI)

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

Baseline Characteristics in 1L TKI + ICI RCC Phase 3 Trials

	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

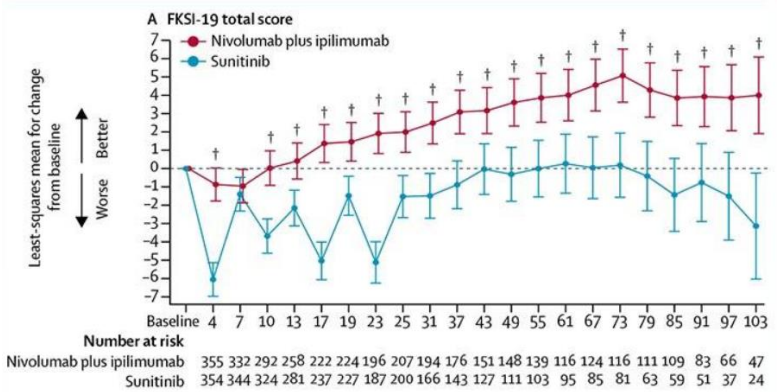
	Nivolumab + Ipilimumab CheckMate-214 n=1096[1]	Pembrolizumab + Axitinib Keynote 426 n=861[2]	Nivolumab + Cabozantinib CheckMate-9ER n=651[3]	Pembrolizumab + Lenvatinib CLEAR n=1096[4]
Follow-up, mo	60 (minimum)	42 (median)	23.5 (median)	26.6 (median)
Median PFS, mo	12.3	15.7	17	23.9
PFS HR	0.86	0.68	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.

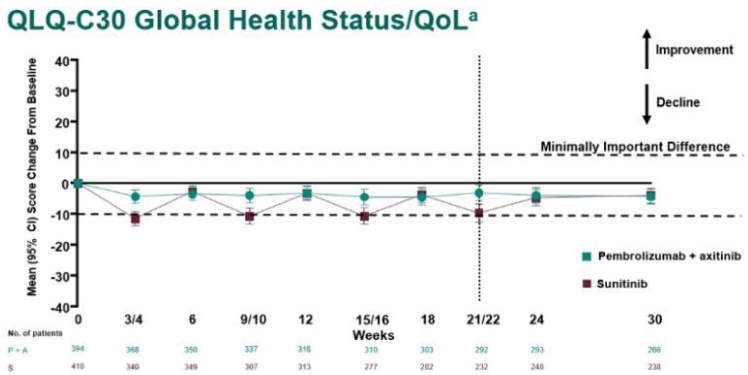
Quality of Life Data from Phase 3 Studies (vs. Sunitinib)

CheckMate-214
Nivolumab + Ipilimumab



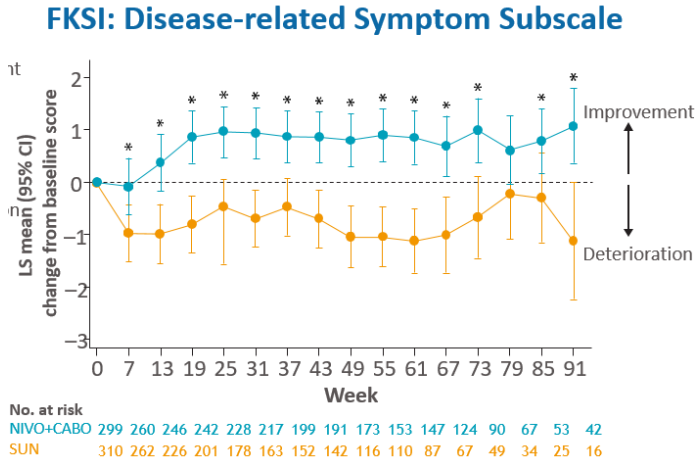
Improved QOL* (FKSI-19)

Keynote-426
Pembrolizumab + Axitinib



Similar QOL* (QLQ-C30)

CheckMate-9ER
Nivolumab + Cabozantinib



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.

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  - Sarcomatoid features (5-15%)
- Key takeaways

IMDC Favorable risk
Nivo/Ipi vs IO/TKI

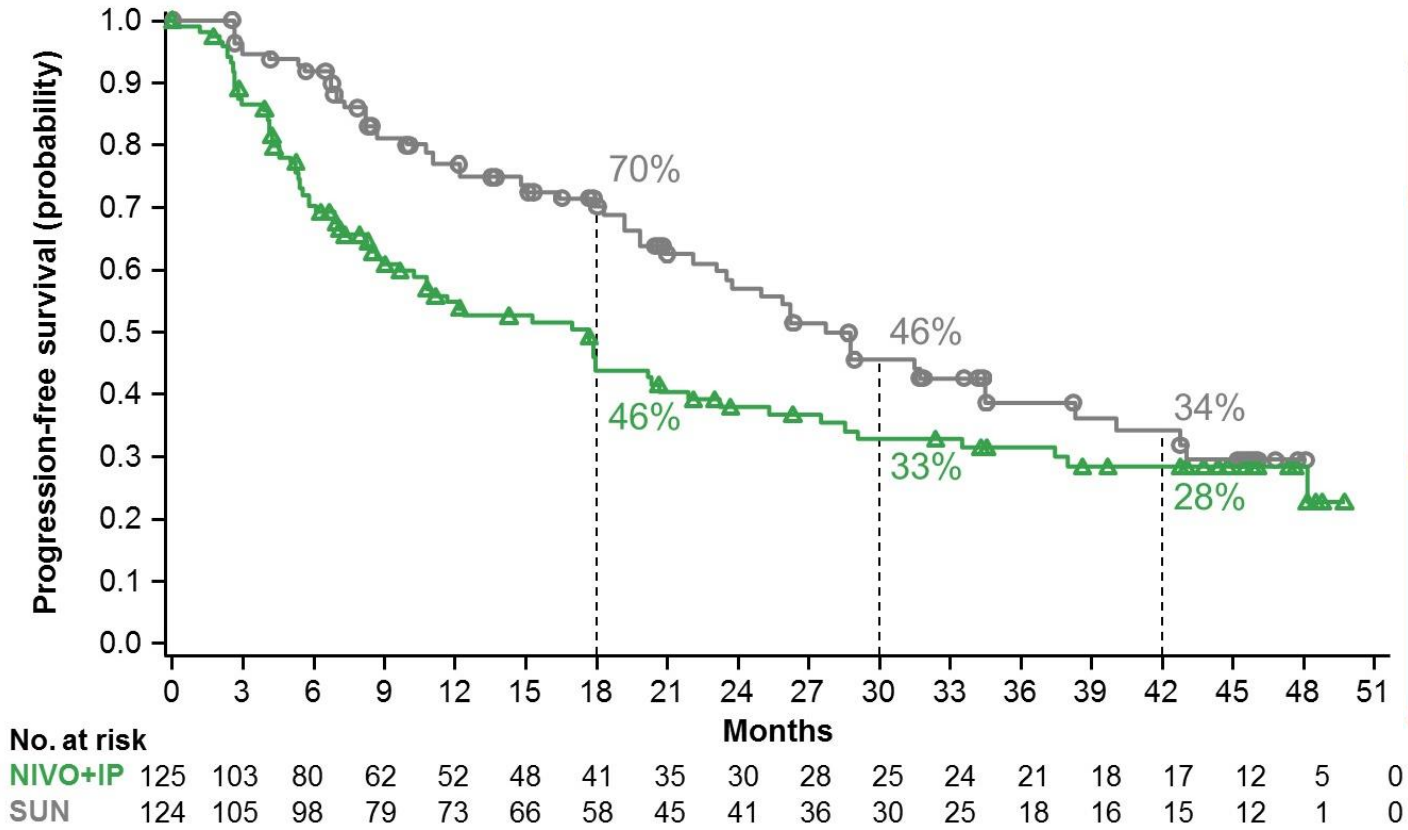
CheckMate-214: 48-Month Response

	Intermediate-/Poor-Risk		ITT		Favorable-Risk	
	NIVO + IPI (n = 425)	SUN (n = 422)	NIVO + IPI (n = 550)	SUN (n = 546)	NIVO + IPI (n = 125)	SUN (n = 124)
Confirmed ORR (95% CI), %	41.9 (37-47)	26.8 (23-31)	39.1 (35-43)	32.4 (29-37)	29.6 (22-38)	51.6 (43-61)
P	<.0001		.0134		.0005	
Best overall response, n (%)						
CR	44 (10.4)	6 (1.4)	59 (10.7)	14 (2.6)	15 (12.0)	8 (6.5)
PR	134 (31.5)	107 (25.4)	156 (28.4)	163 (29.9)	22 (17.6)	56 (45.2)
SD	131 (30.8)	187 (44.3)	198 (36.0)	230 (42.1)	67 (53.6)	43 (34.7)
PD	82 (19.3)	71 (16.8)	97 (17.6)	77 (14.1)	15 (12.0)	6 (4.8)
NE	32 (7.5)	48 (11.4)	38 (6.9)	57 (10.4)	6 (4.8)	9 (7.3)
NR	2 (0.5)	3 (0.7)	2 (0.4)	5 (0.9)	0	2 (1.6)
Ongoing response, n (%)	n = 178 116 (65.2)	n = 113 56 (49.6)	n = 215 140 (65.1)	n = 177 92 (52.0)	n = 37 24 (64.9)	n = 64 34 (56.3)

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

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

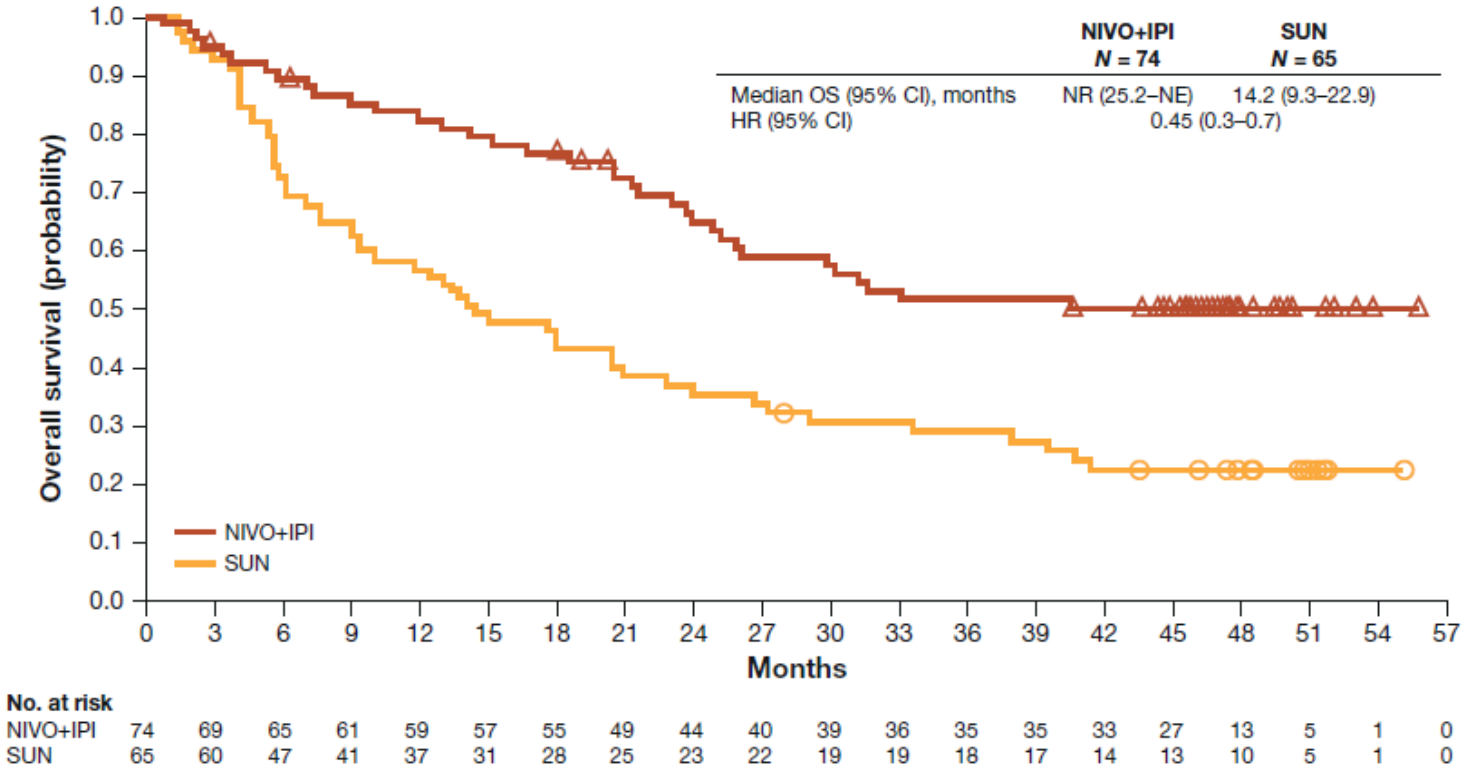
Favorable Risk	Checkmate-9ER[1]	Keynote-426[2]	CLEAR[3]
PFS HR (95% CI)	0.62 (0.38-1.01)	0.81 (0.53-1.24)	0.41 (0.28-0.62)
OS HR (95% CI)	0.84 (0.35-1.97)	0.64 (0.24-1.68)	1.15 (0.55-2.40)

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	

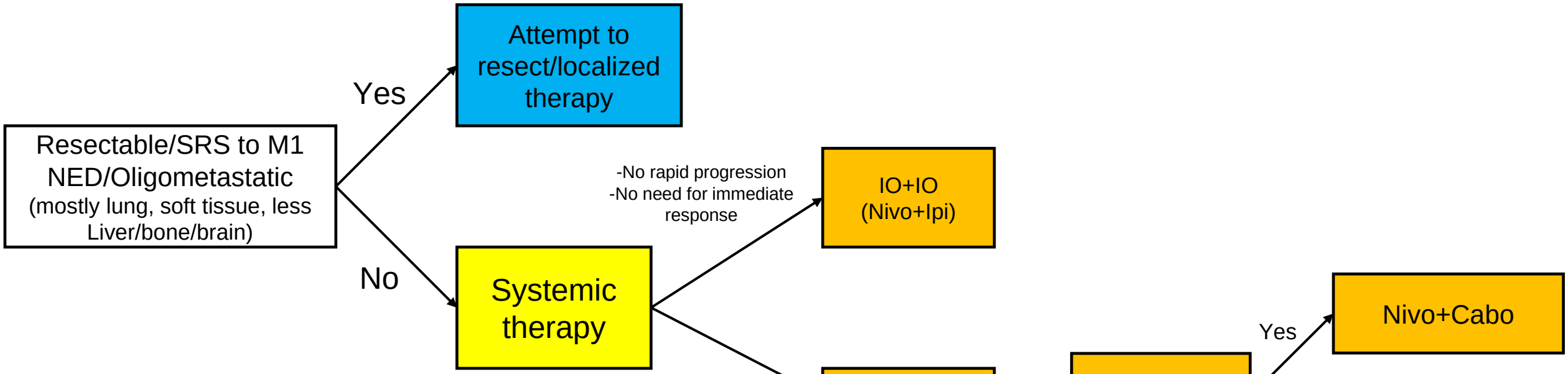
Sarcomatoid RCC tumors are characterized by an *immune-inflamed phenotype*[2]*:*

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.

My own "evolving" approach of 1st line treatment for mRCC, circa #ESMO21

@DrChoueiri



Outline

- Key combination trials for the treatment of mRCC in the **1st line setting**
- Comparison of combination trials
- Special populations (in the 1st line treatment of mRCC):
  - Favorable IMDC risk (20%)
  - Sarcomatoid features (5-15%)
- Key takeaways

Key Takeaways

- There is a wealth of evidence of different combinations for the 1L treatment of mRCC including the CheckMate 214, KEYNOTE-426, JAVELIN Renal 101, Checkmate 9ER and CLEAR studies, all were > to VEGF TKI sunitinib.
- Patients in your clinic do not always reflect the trial population and RWD collection is important.
- MANY factors may influence a physicians' choice of sequential treatment and personalization of care, including – amongst others – availability, efficacy, safety, QOLs, Prior TX, comorbidities (cardiovascular, autoimmune diseases) and costs.
- Favorable-risk population therapy remains undefined: a case can be made for IO+IO, IO+VEGF or even VEGF monotherapy.
- Sarcomatoid features: Nivo/ipi should be the standard.
- Biomarkers today remain all experimental in mRCC (sorry, I had to mention "biomarkers")
- **Finally, if adjuvant IO becomes a reality (it will be) ; 1L choice in mRCC will become more complicated!** Let us leave to that to #ESMO22!

Until we meet again in a year: ESMO 2022, also in Paris!

ESMO > Meetings

ESMO CONGRESS 2022

PARIS 2022 ESMO congress

PARIS FRANCE
9-13 SEPTEMBER 2022

Start date	09 Sep 2022
End date	13 Sep 2022
Location	Paris, France

2021 ESMO congres