RCC in 2025: What's New for the Practicing Oncologist?

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Honolulu, Hawaii
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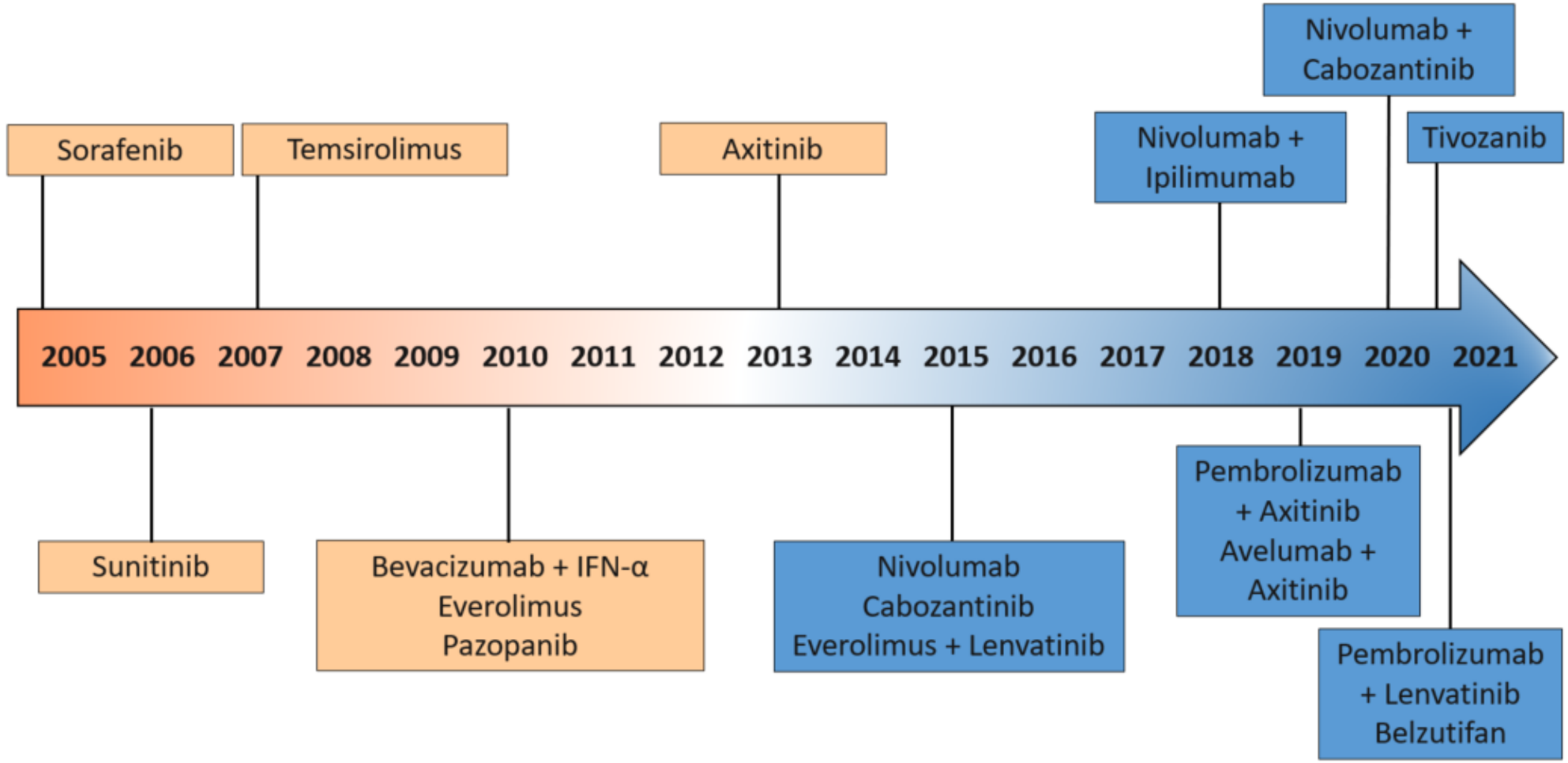
Treatment Landscape of Metastatic RCC



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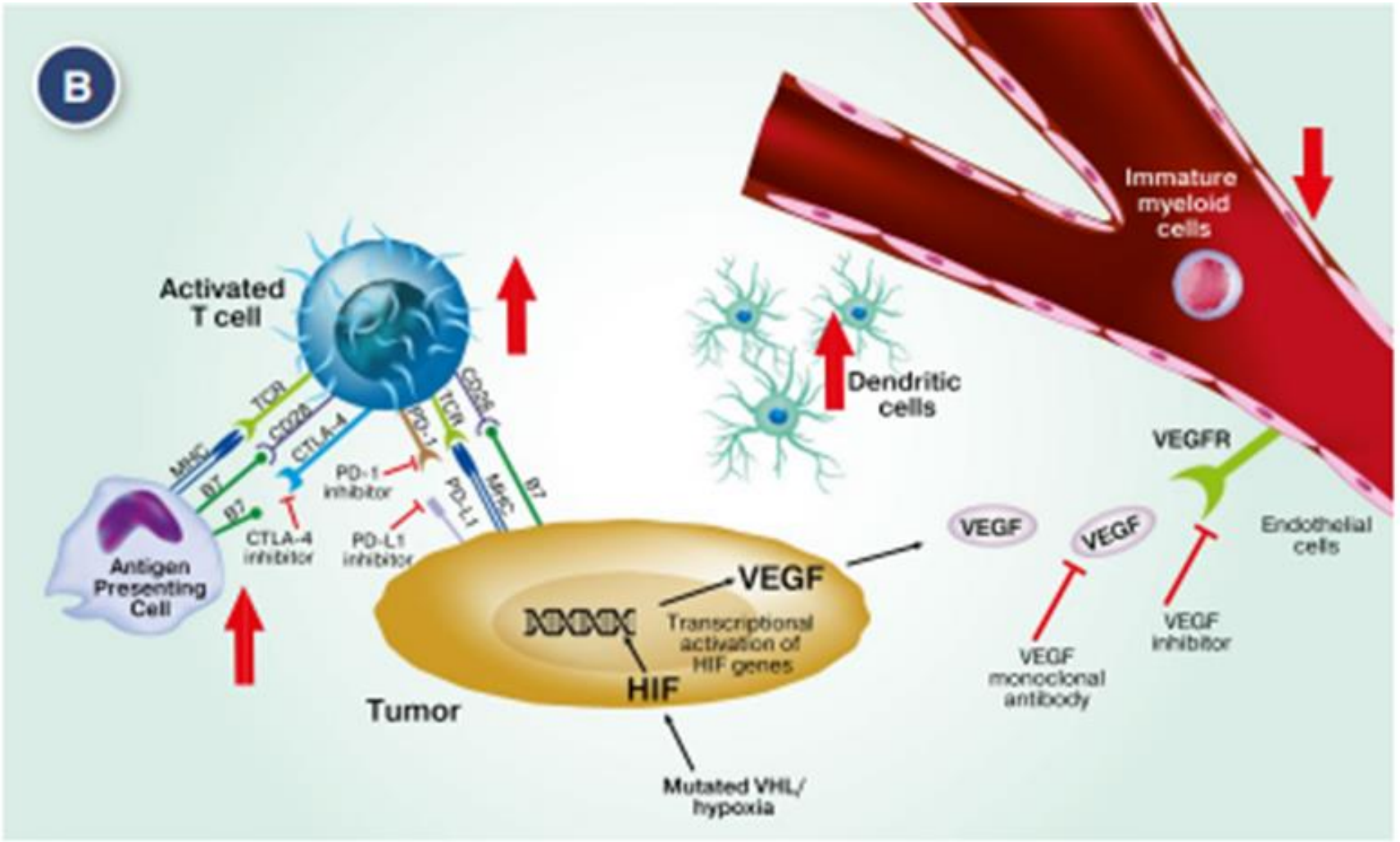
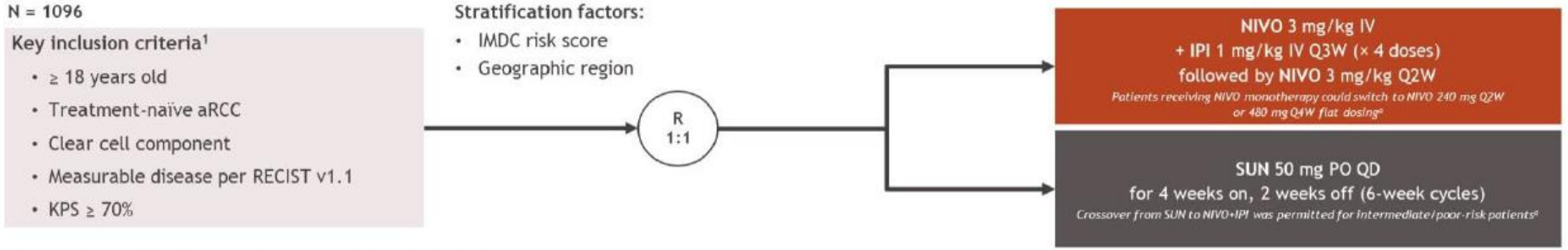


Mantia, CM, McDermott, DF. *Cancer.* 2019. 125:4148-4157

CheckMate 214: Trial Design

- NIVO+IPI is approved for first-line treatment of IMDC intermediate/poor-risk aRCC, based on superior OS and ORR over SUN in the randomized, phase 3 CheckMate 214 trial[1-3]
- NIVO+IPI has demonstrated durable survival and response benefits versus SUN across a broad range of patients, providing the opportunity to conduct long-term survival analyses[4-6]
- With a median follow-up of 8 years in the CheckMate 214 trial, we present updated efficacy and safety outcomes, and exploratory subgroup analyses in patients by organ sites of metastasis at baseline



Median (range) follow-up for OS, 99.1 (91.0-107.3) months

Primary endpoints: OS, PFS and ORR (both per IRRC) in IMDC intermediate/poor-risk patients
Secondary endpoints: OS, PFS and ORR (both per IRRC) in ITT patients; safety in all treated patients
Exploratory endpoints: OS, PFS and ORR (both per IRRC) in IMDC favorable-risk patients

CheckMate 214: Overall Survival by IMDC Risk Subgroup

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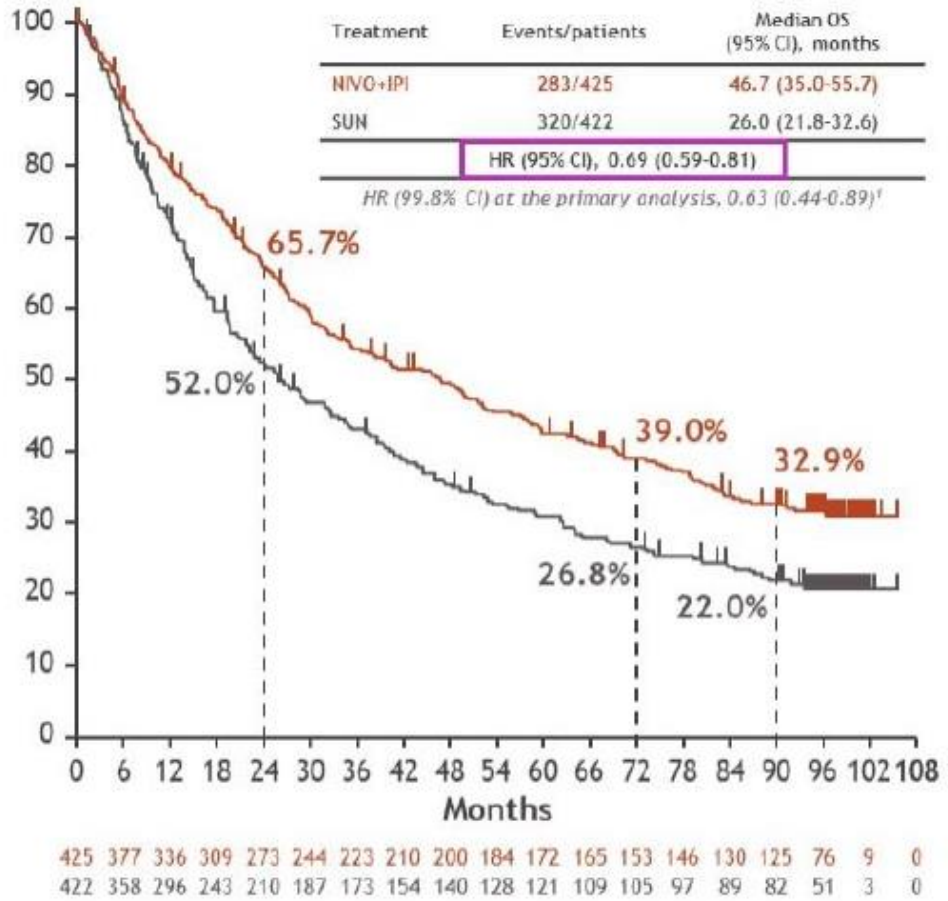
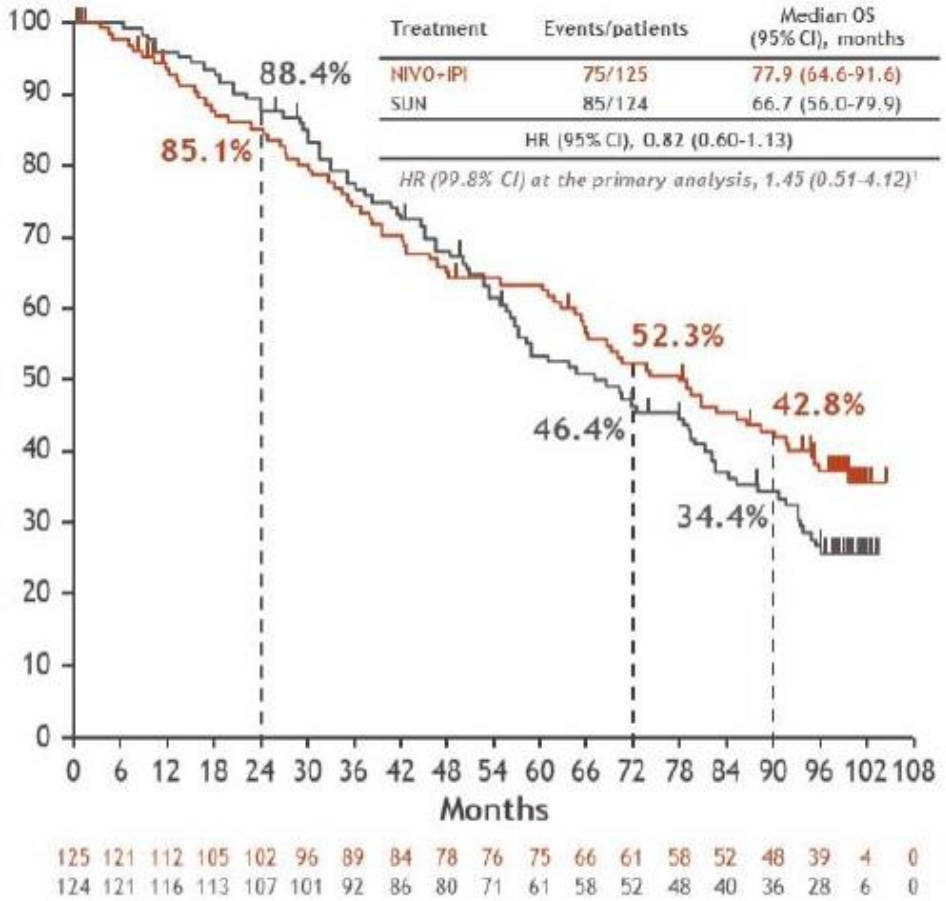
Intermediate/poor risk



Favorable risk



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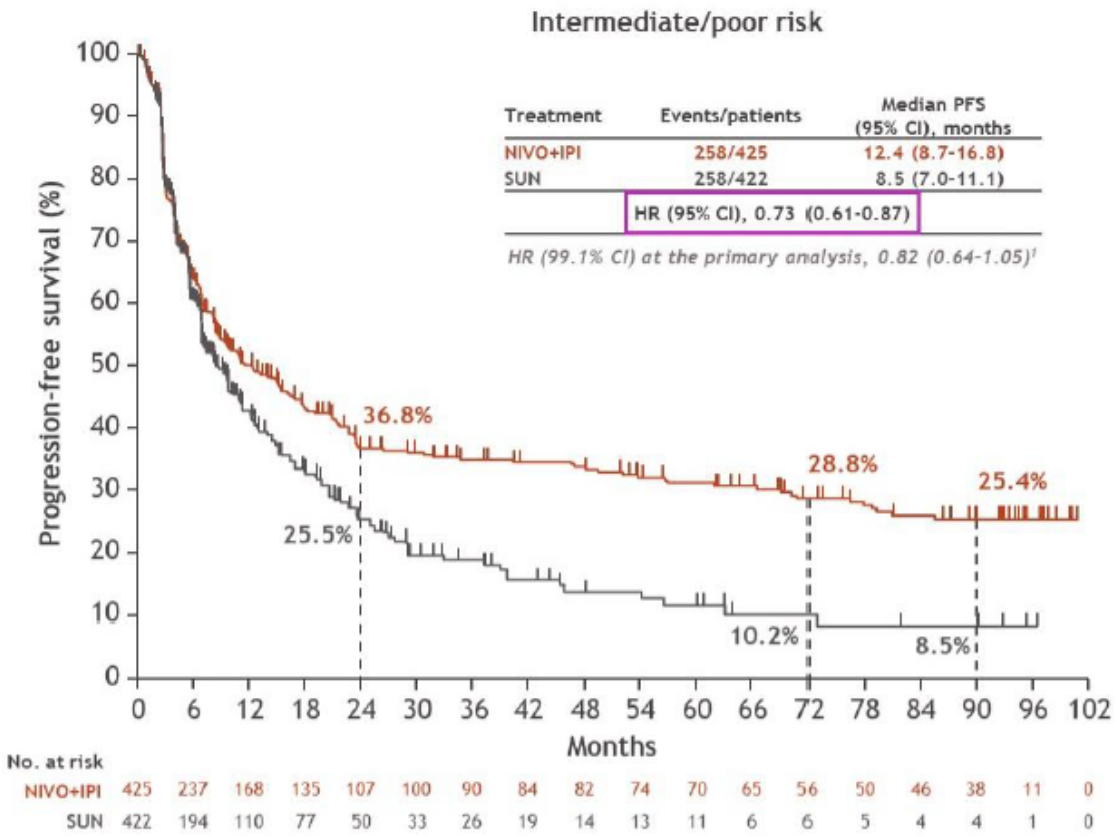
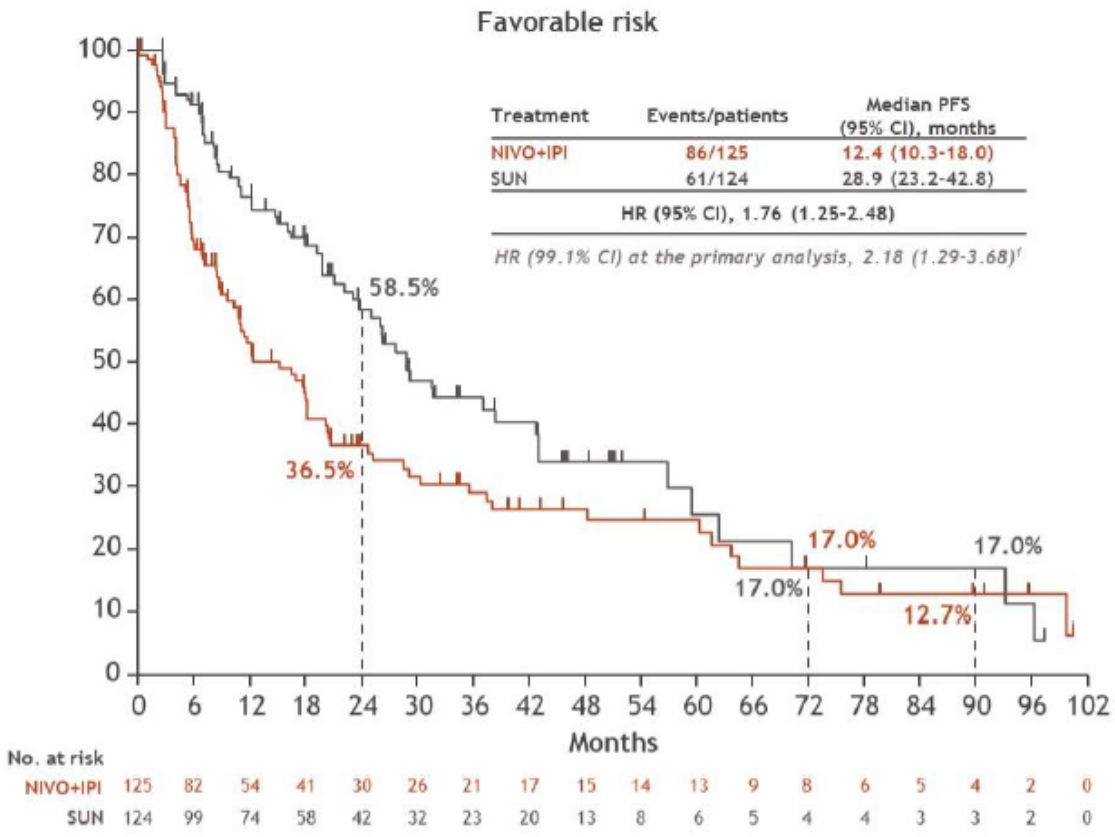
CheckMate 214: Progression Free Survival by IMDC Risk Subgroup





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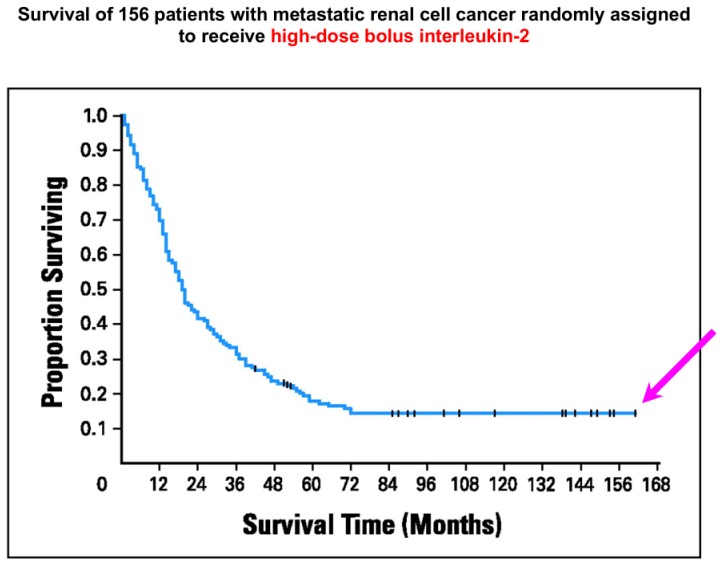
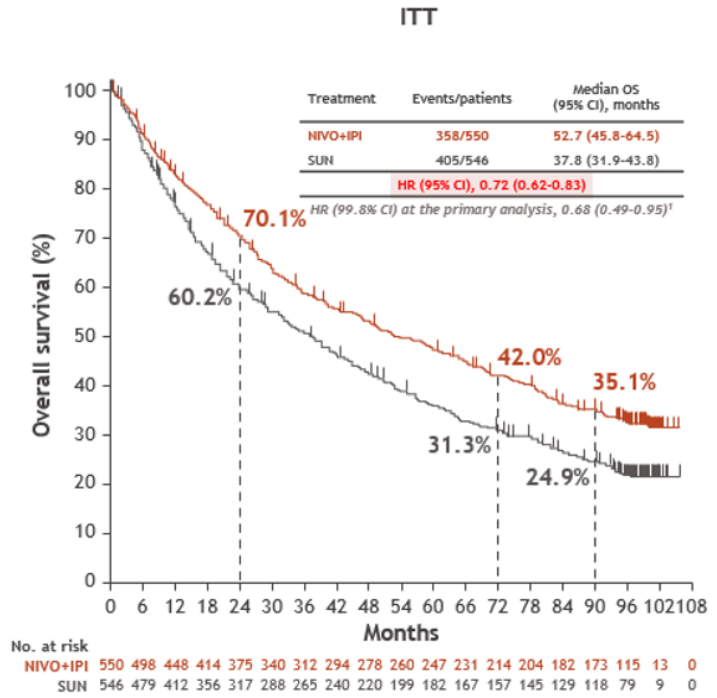
We made some progress over the years!

IL-2



Yang, J. C. et al. J Clin Oncol; 24:5576-5583 2006

Ipilimumab + Nivolumab



Tannir NM, et al. ASCO GU 2024. Abstract 363.

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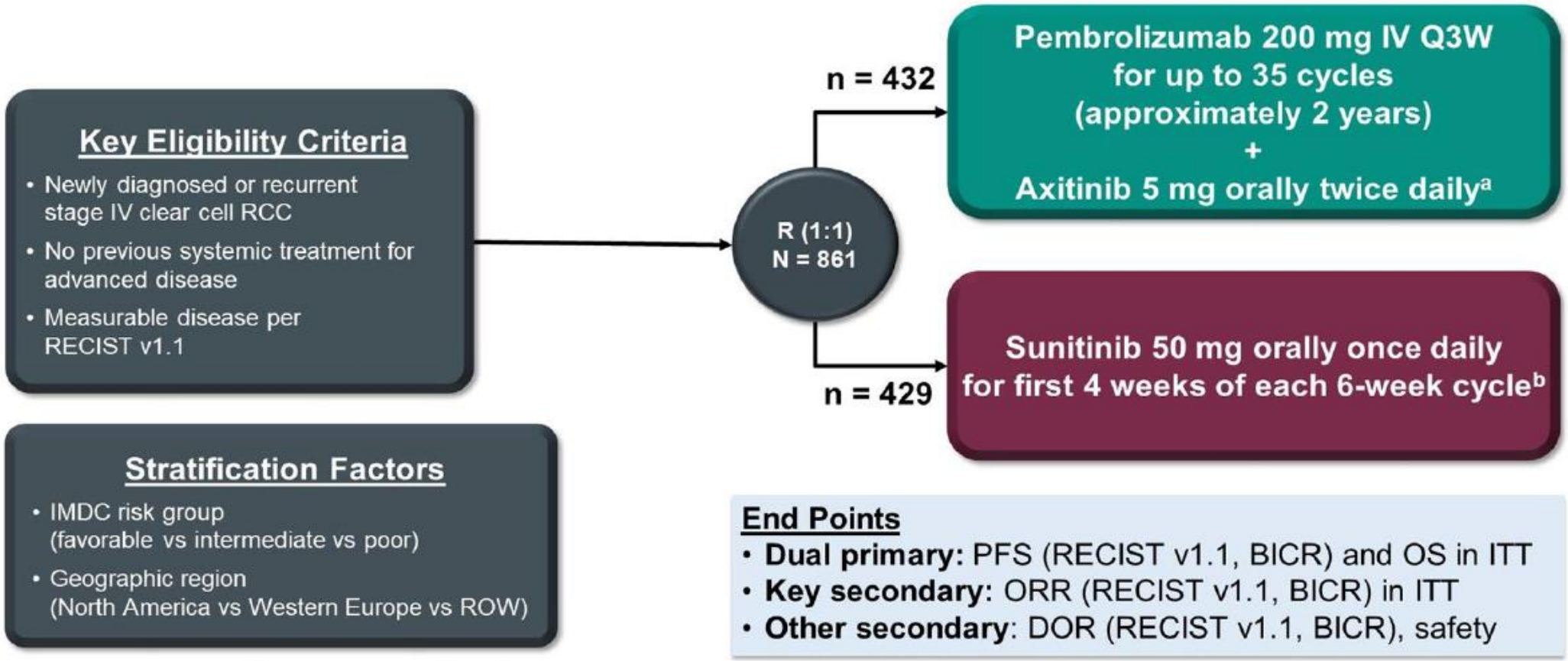
KEYNOTE-426: Trial Design



Rini et al, ASCO 2023 #LBA4501

KEYNOTE-426: Efficacy in Favorable Risk RCC

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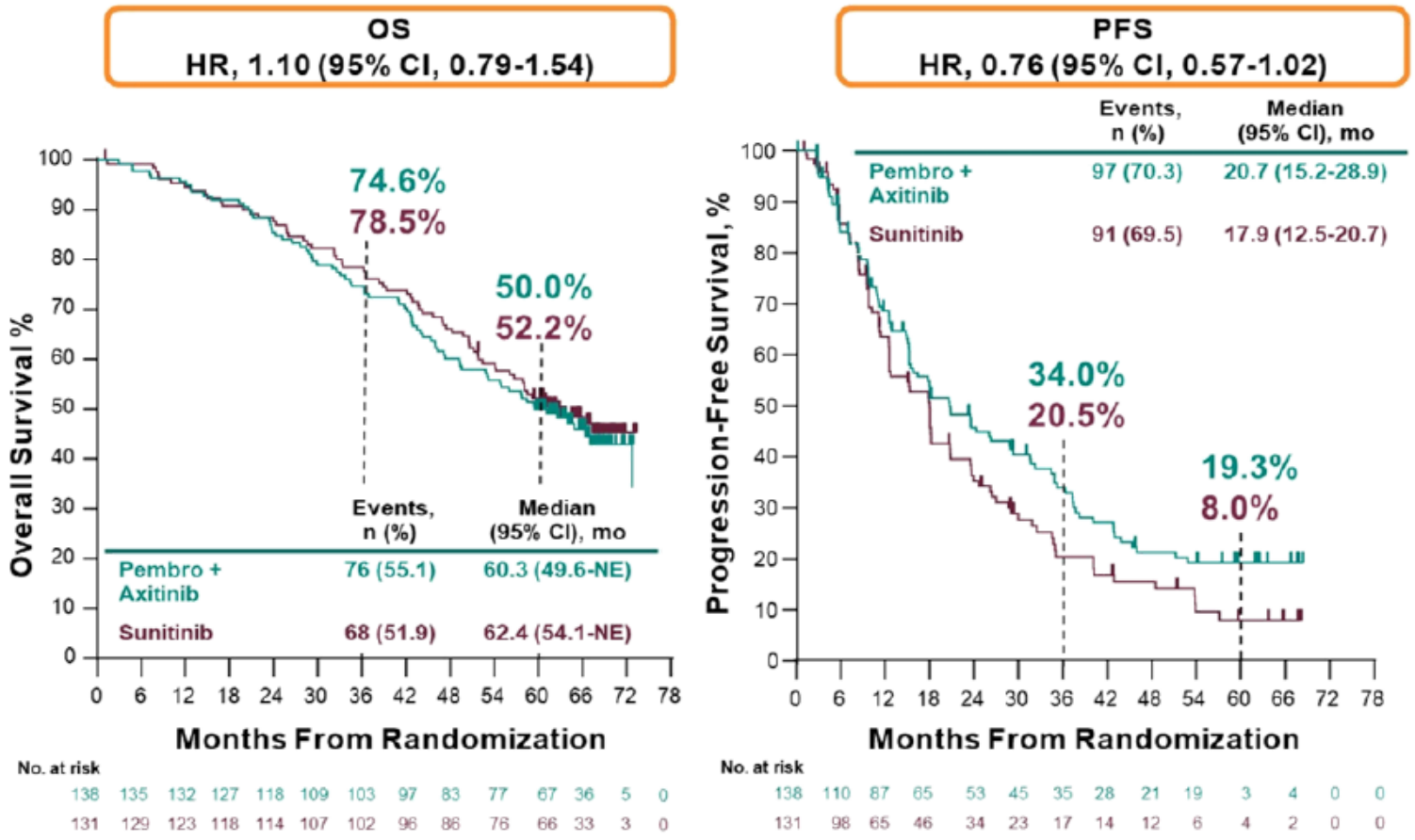

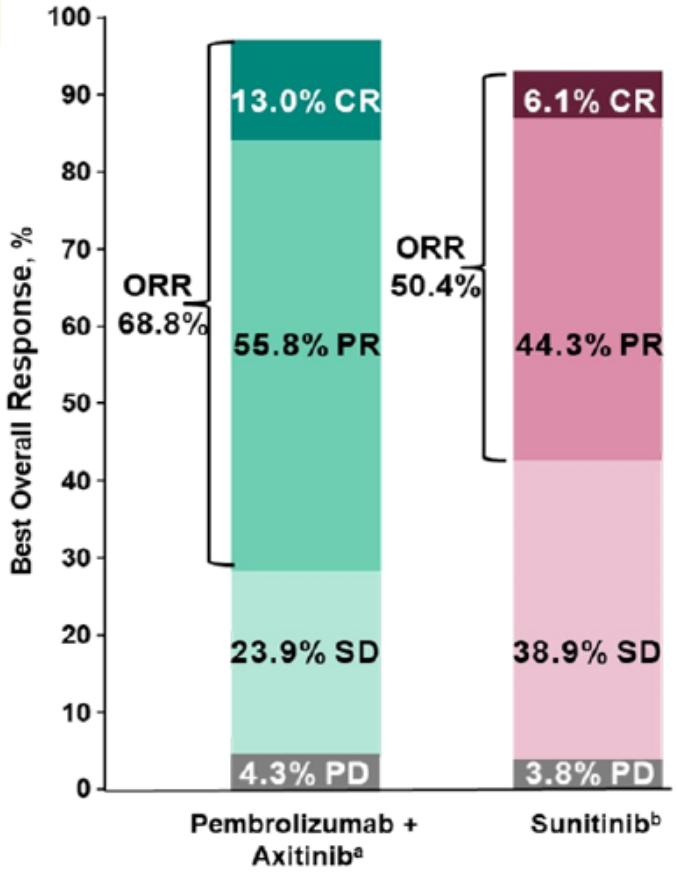

Rini et al, ASCO 2023 #LBA4501

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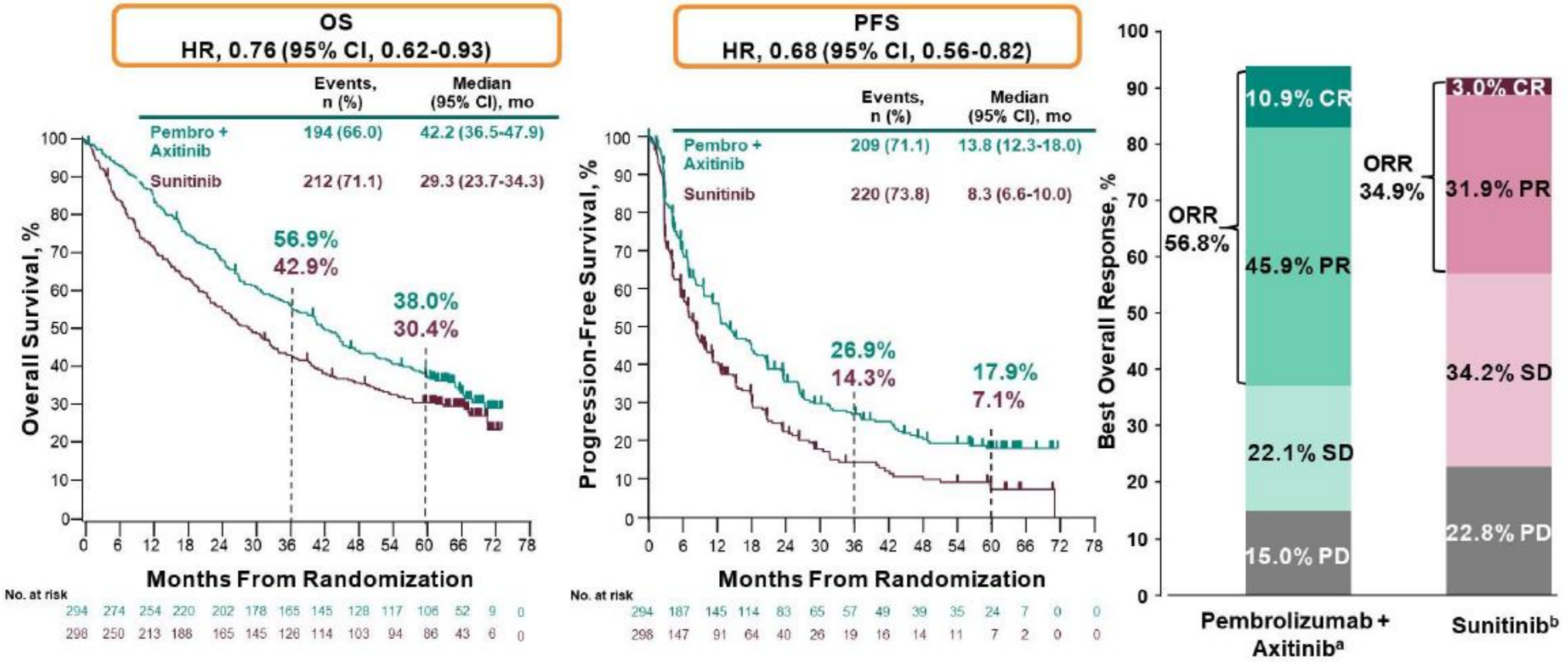
KEYNOTE-426: Efficacy in Intermediate/Poor Risk RCC



[a]Includes 1.7% NE and 4.4% NA. [b]Includes 1.3% NE and 6.7% NA. Data cutoff: January 23, 2023.

Rini et al, ASCO 2023 #LBA4501

KEYNOTE-426: $Tcell_{inf}$GEP, Angiogenesis, PD-L1

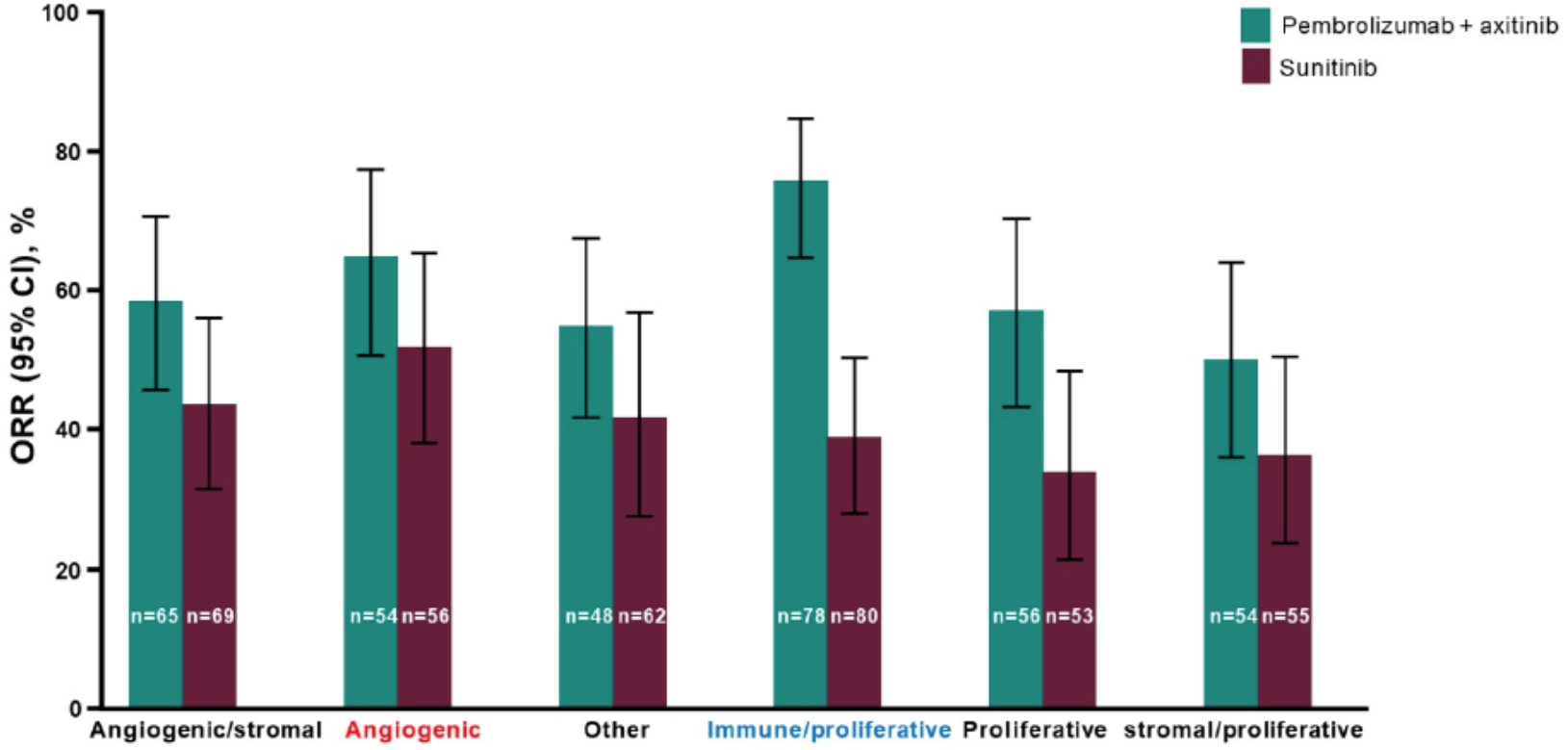
	Pembrolizumab + axitinib			Sunitinib		
Biomarker	**ORR**	**PFS**	**OS**	**ORR**	**PFS**	**OS**
$Tcell_{inf}$GEP	**<0.0001(+)**	**<0.0001(+)**	**0.002(+)**	NS	NS	NS
Angiogenesis	NS	NS	**0.004(+)**	**0.002(+)**	**<0.001(+)**	**<0.0001(+)**
PD-L1 CPS	NS	NS	NS	NS	NS	**0.025(-)**

- Higher $Tcell_{inf}$GEP was associated with improved clinical outcome within the pembrolizumab + axitinib arm
- Higher angiogenesis gene expression was associated with improved clinical outcome within the sunitinib arm
- PD-L1 CPS was negatively associated with OS within the sunitinib arm

Rini et al, ASCO 2024 #4505

KEYNOTE-426: ORR by Molecular Subtype

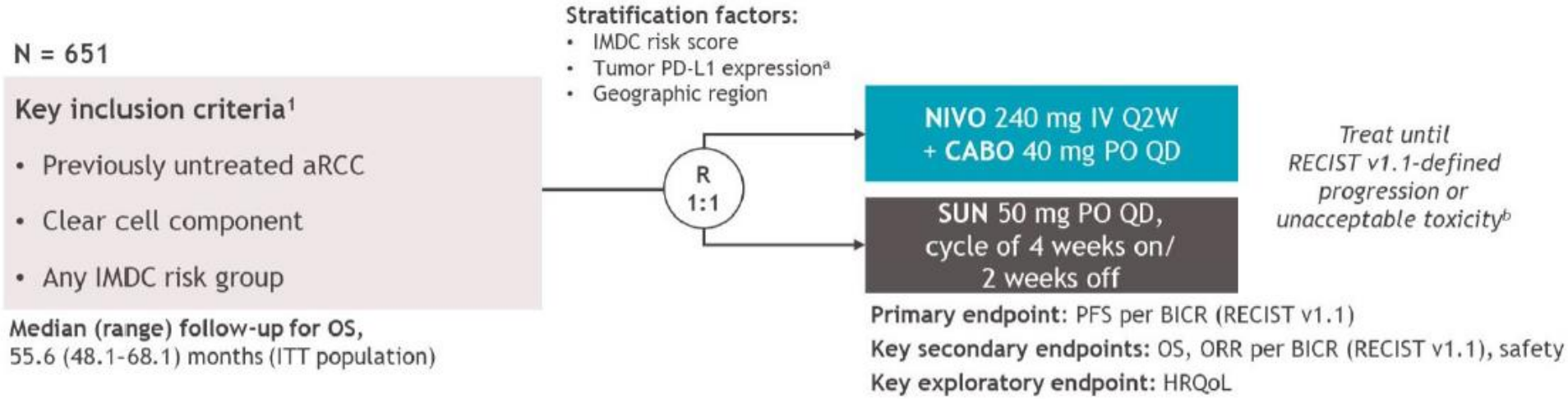
- Pembro + axitinib showed improved ORR across molecular subtypes
- Within pembro + axitinib arm, ORR highest in immune/proliferative subtype
- Within sunitinib arm, ORR highest in angiogenic subtype



Rini et al, ASCO 2024 #4505

CheckMate 9ER: Trial Design

- NIVO+CABO demonstrated superior PFS, OS, and ORR and better HRQoL versus SUN in patients with previously untreated aRCC in the primary analysis (18.1 months median follow-up for OS) of the phase 3 CheckMate 9ER trial[1]
- With extended follow-up, NIVO+CABO maintained efficacy and HRQoL benefits versus SUN (44.0 months median follow-up for OS)[2,3]
- Here, we report updated efficacy in ITT patients with 55.6 months median follow-up for OS, by IMDC risk and organ sites of metastases, and HRQoL and safety



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CheckMate 9ER: Efficacy in Favorable Risk RCC

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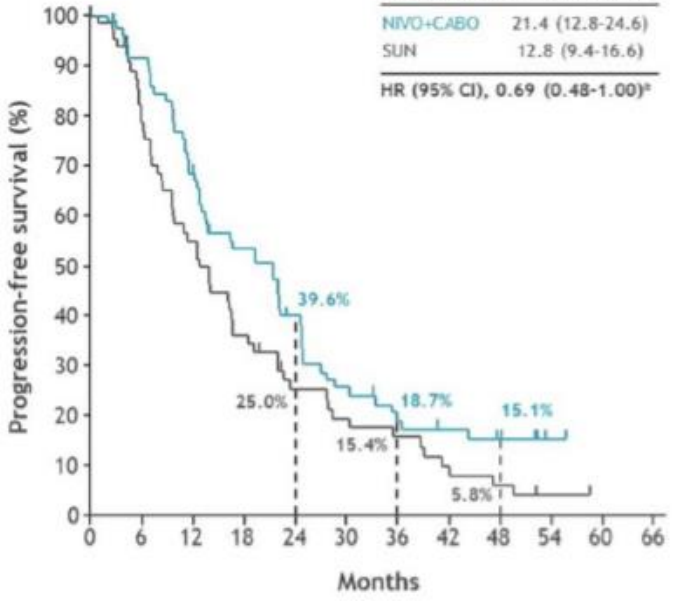
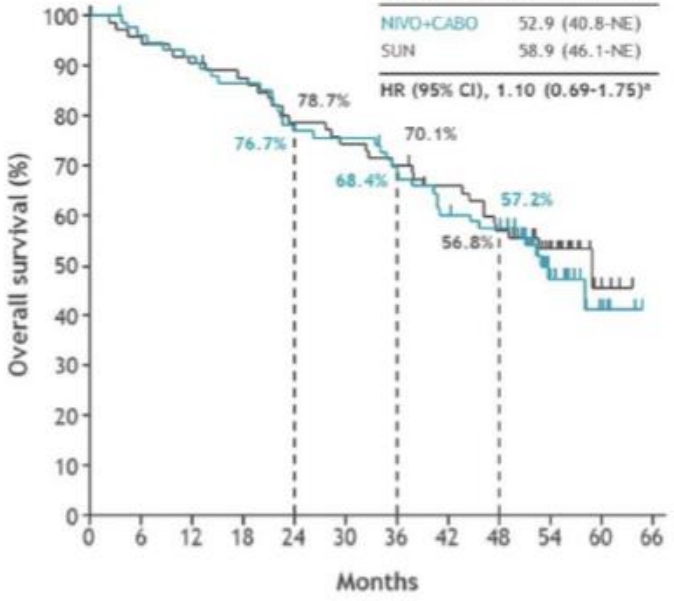
PFS per BICR



No. at risk

NIVO+CABO	74	63	46	35	25	16	11	9	6	1	0	0
SUN	72	46	32	21	13	10	8	4	3	1	0	0

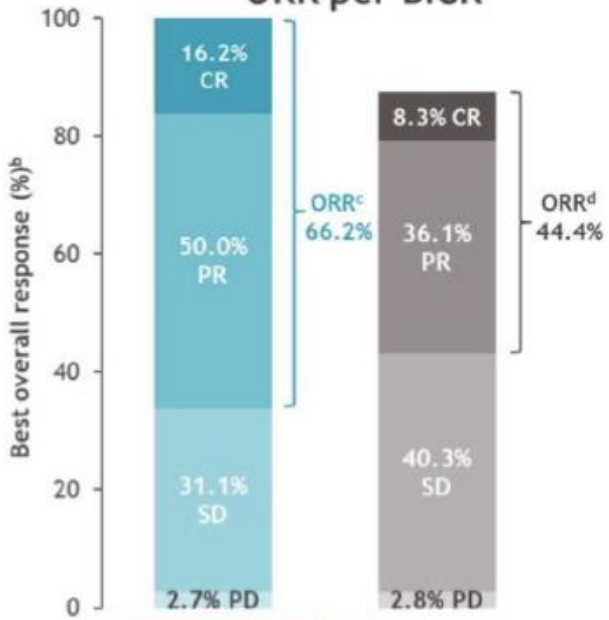
OS



No. at risk

NIVO+CABO	74	70	67	63	56	55	49	43	40	18	5	0
SUN	72	68	64	61	55	52	49	44	38	20	3	0

ORR per BICR



	NIVO+CABO (n = 74)	SUN (n = 72)
Median TTR (range), mo[e]	2.8 (1.5-19.8)	4.3 (1.7-30.4)
Median DOR (95% CI), mo[e]	18.7 (13.9-22.2)	17.8 (11.1-19.4)

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CheckMate 9ER: Efficacy in Intermediate/Poor Risk RCC

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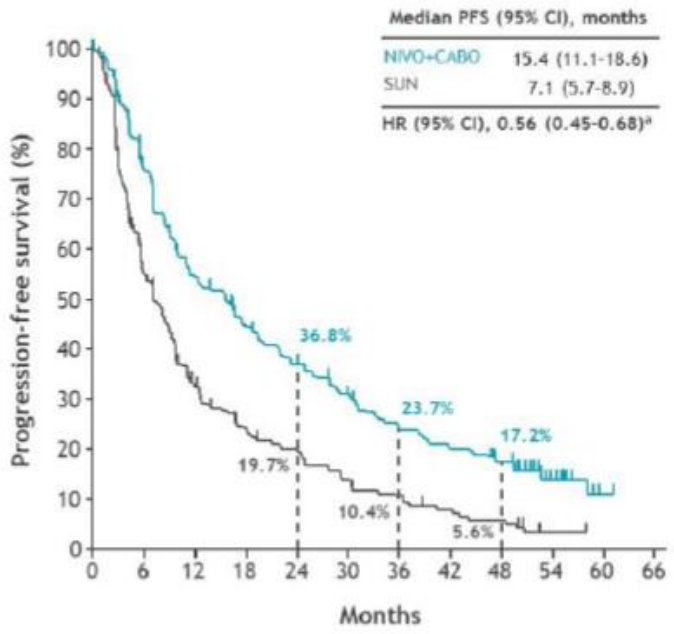
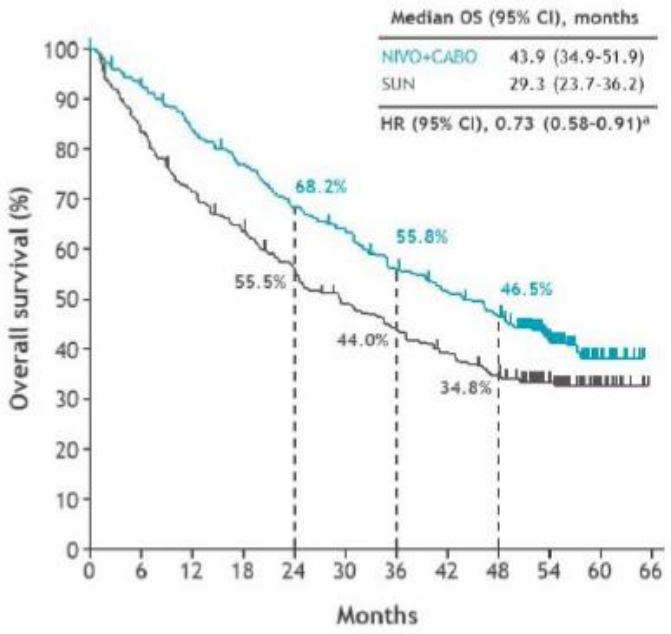
PFS per BICR



No. at risk

NIVO+CABO	249	174	122	96	79	63	48	40	32	13	1	0
SUN	256	115	61	40	32	22	16	11	8	1	0	0

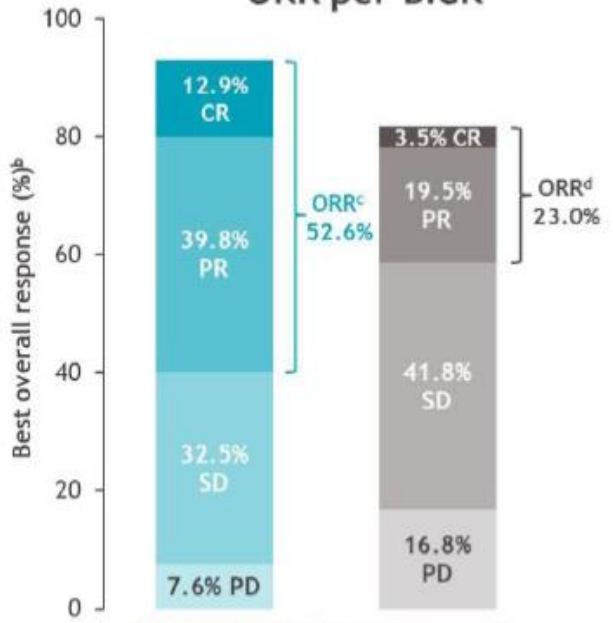
OS



No. at risk

NIVO+CABO	249	228	205	187	166	153	134	121	109	65	13	0
SUN	256	209	178	158	136	118	106	94	82	46	11	0

ORR per BICR



	NIVO+CABO (n = 249)	SUN (n = 256)
Median TTR (range), mo[e]	2.8 (1.0-22.2)	4.4 (1.7-18.1)
Median DOR (95% CI), mo[e]	23.1 (17.3-30.5)	13.8 (7.1-23.5)

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CheckMate 9ER: Efficacy by Baseline Organ Metastases

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- PFS, OS, and ORR favored NIVO+CABO versus SUN in subgroups by baseline organ sites of metastases shown here

Outcome	Liver[a,b]		Bone[a,b]		Lung[a,b]	
	NIVO+CABO (n = 73)	SUN (n = 55)	NIVO+CABO (n = 79)	SUN (n = 73)	NIVO+CABO (n = 241)	SUN (n = 251)
Median PFS (95% CI), mo	10.9 (7.0-15.2)	6.2 (2.9-8.3)	13.8 (8.3-20.1)	4.4 (3.8-8.2)	16.4 (12.3-21.4)	8.3 (6.9-9.7)
HR (95% CI)[c]	0.54 (0.36-0.81)		0.45 (0.30-0.66)		0.56 (0.46-0.69)	
Median OS (95% CI), mo	37.6 (23.5-49.9)	22.1 (9.8-29.3)	34.8 (21.4-NE)	20.7 (12.5-25.7)	47.5 (40.6-56.1)	32.6 (24.9-39.7)
HR (95% CI)[c]	0.62 (0.41-0.95)		0.57 (0.38-0.84)		0.73 (0.58-0.92)	
ORR (95% CI), %	52.1 (40.0-63.9)	21.8 (11.8-35.0)	49.4 (37.9-60.9)	9.6 (3.9-18.8)	57.3 (50.8-63.6)	28.3 (22.8-34.3)

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CLEAR: Trial Design

Key eligibility criteria
- Advanced clear cell RCC
- Treatment-naïve
- KPS ≥ 70
- Measurable disease
- Adequate organ function

Stratification factors
- Region
- MSKCC risk groups

Randomization 1:1:1

Median OS follow-up: approximately 4 years	Lenvatinib 20 mg oral QD + pembrolizumab[a] 200 mg IV Q3W	Lenvatinib 18 mg oral QD + everolimus 5 mg oral QD	Sunitinib 50 mg oral QD 4 weeks on / 2 weeks off
PFS,[b] median (95% CI), months HR (95% CI) vs sunitinib; *P*-value[c]	23.9 (20.8–27.7) **0.47** (0.38–0.57); < 0.0001	Not reported	9.2 (6.0–11.0)
OS, median (95% CI), months HR (95% CI) vs sunitinib; *P*-value[c]	53.7 (48.7–NE) **0.79** (0.63–0.99); 0.0424		54.3 (40.9–NE)
ORR[b] (95% CI), % Complete response, %	**71.3** (66.6–76.0) **18.3**		36.7 (31.7–41.7) 4.8

[a]Patients could receive a maximum of 35 pembrolizumab treatments. [b]Per independent imaging review by RECIST v1.1. [c]Nominal *P*-value

Viktor Grunwald, ASCO 2024, Abstract #4524

CLEAR: Overall Survival by IMDC Subgroup

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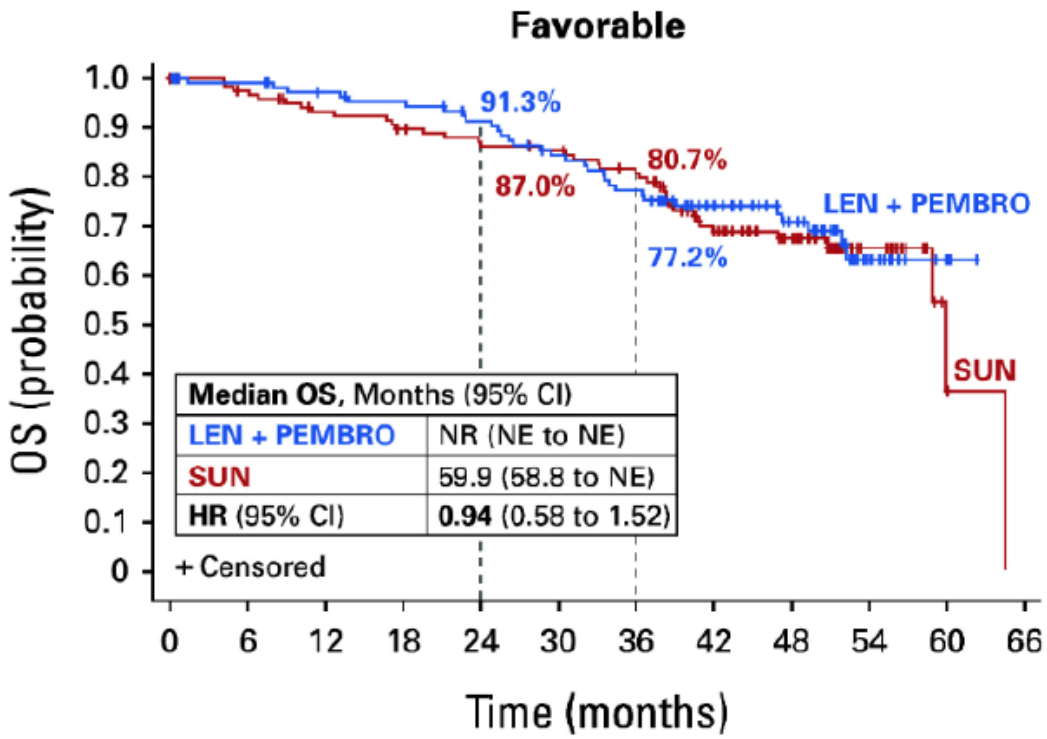
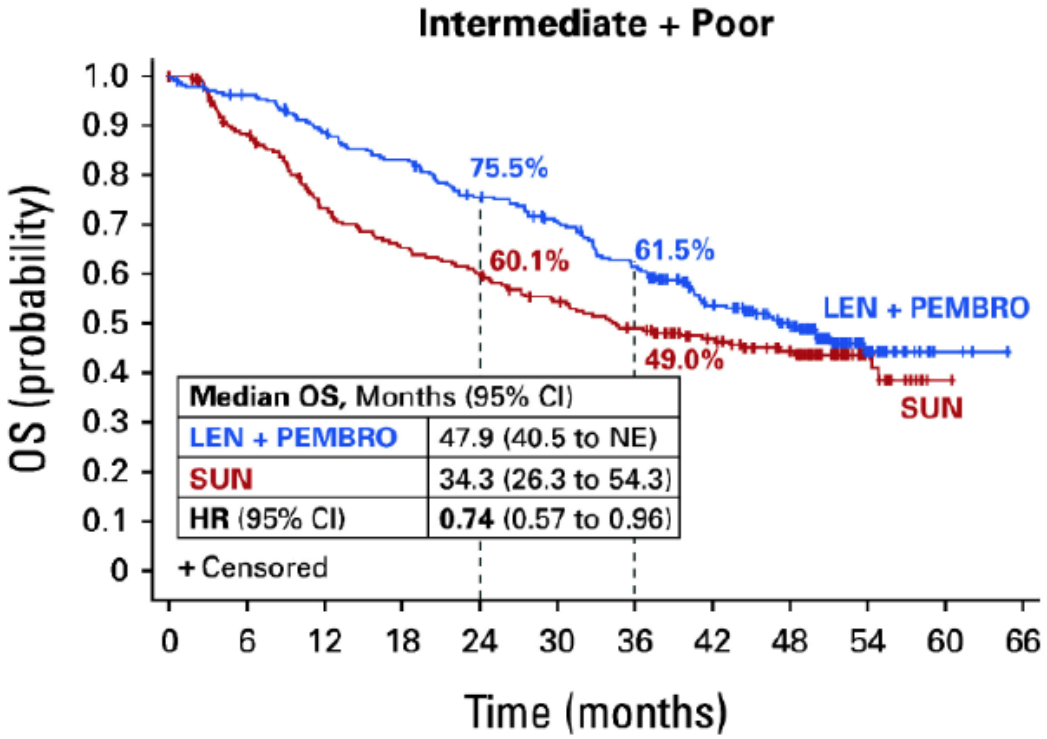


No. at risk:

LEN + PEMBRO	110	106	101	98	92	83	76	57	42	11	2	0
SUN	124	115	107	102	98	95	88	65	46	15	2	0



No. at risk:

LEN + PEMBRO	243	230	210	196	176	161	139	101	75	23	3	0
SUN	229	190	155	138	127	112	99	79	61	18	1	0

Motzer et al. *JCO*. 2024

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CLEAR: Progression Free Survival by IMDC Subgroup

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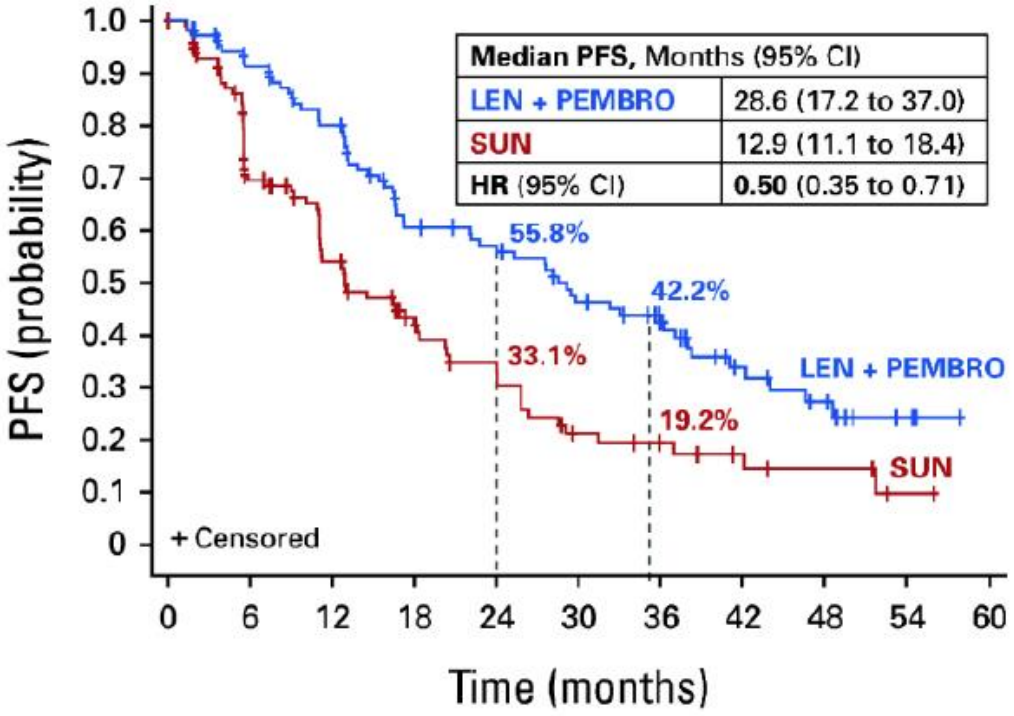
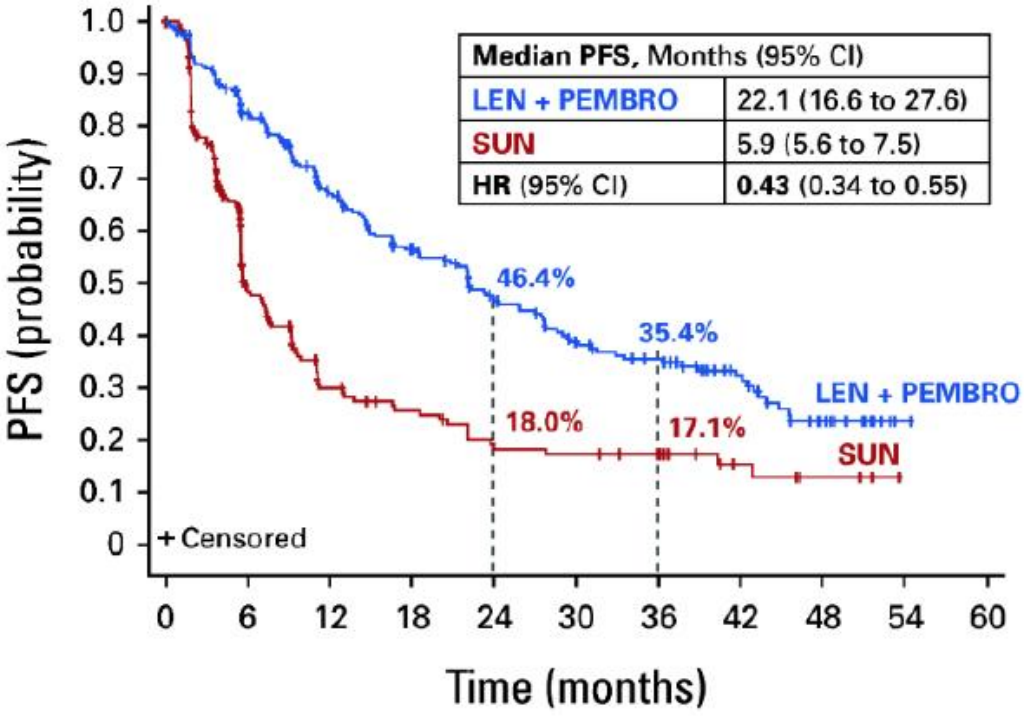
Favorable



No. at risk:

110	91	77	54	48	38	29	16	11	3	0
124	68	48	30	22	12	9	6	4	1	0

Intermediate + Poor



No. at risk:

243	184	136	107	80	61	52	33	14	1	0
229	75	37	29	19	18	14	6	3	0	0

Motzer et al. *JCO*. 2024

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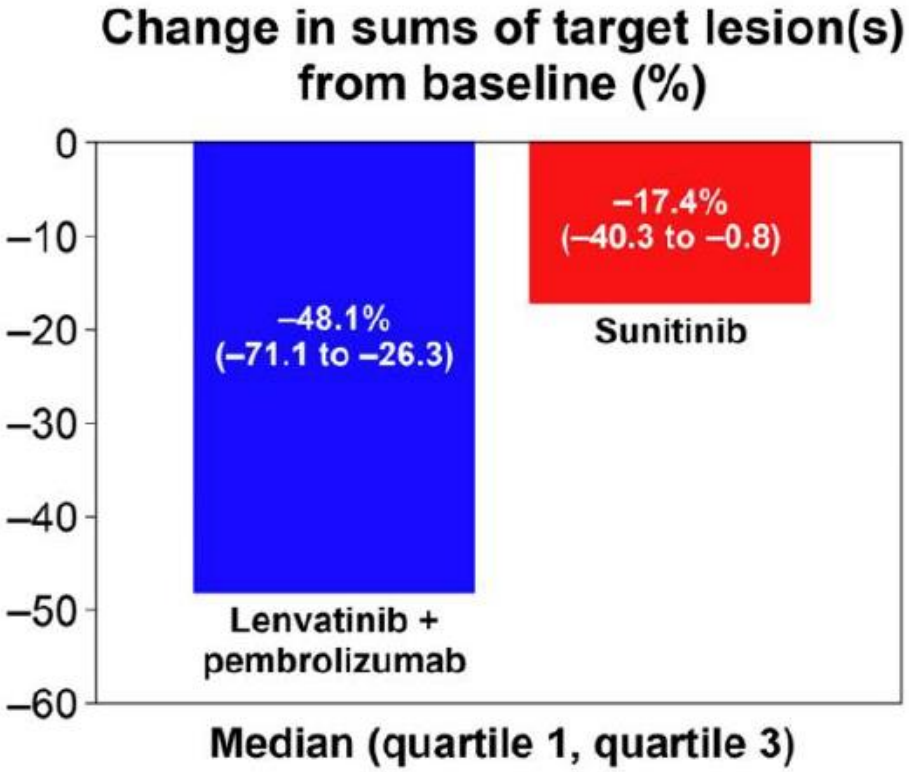
CLEAR: Change in Tumor Bulk at Baseline to Progression



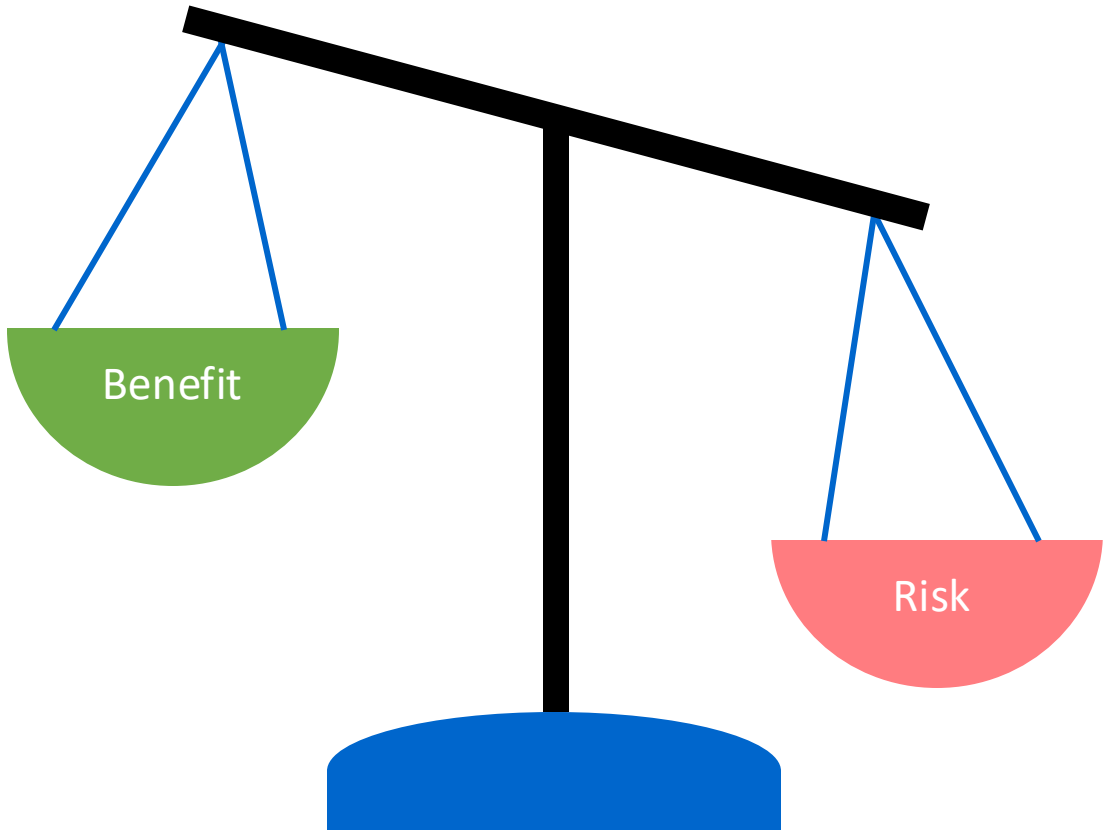
	Lenvatinib + pembrolizumab (n = 355)	Sunitinib (n = 357)
Baseline sum of target lesions (mm)		
n	176	195
Median	56.7	56.7
Quartile 1, quartile 3	32.8, 117.0	38.2, 97.6
Minimum, maximum	10.0, 348.3	10.6, 357.9
Sum of target lesions (mm) at progression		
n	176	195
Median	29.8	42.8
Quartile 1, quartile 3	12.2, 66.1	24.6, 84.3
Minimum, maximum	0.0, 301.9	0.0, 313.4

The median decreases in percent changes in sums of diameters of target lesions were greater with lenvatinib-plus-pembrolizumab versus sunitinib treatment.

Viktor Grunwald, ASCO 2024, Abstract #4524

Balancing Endpoints for Selection of Frontline Therapy

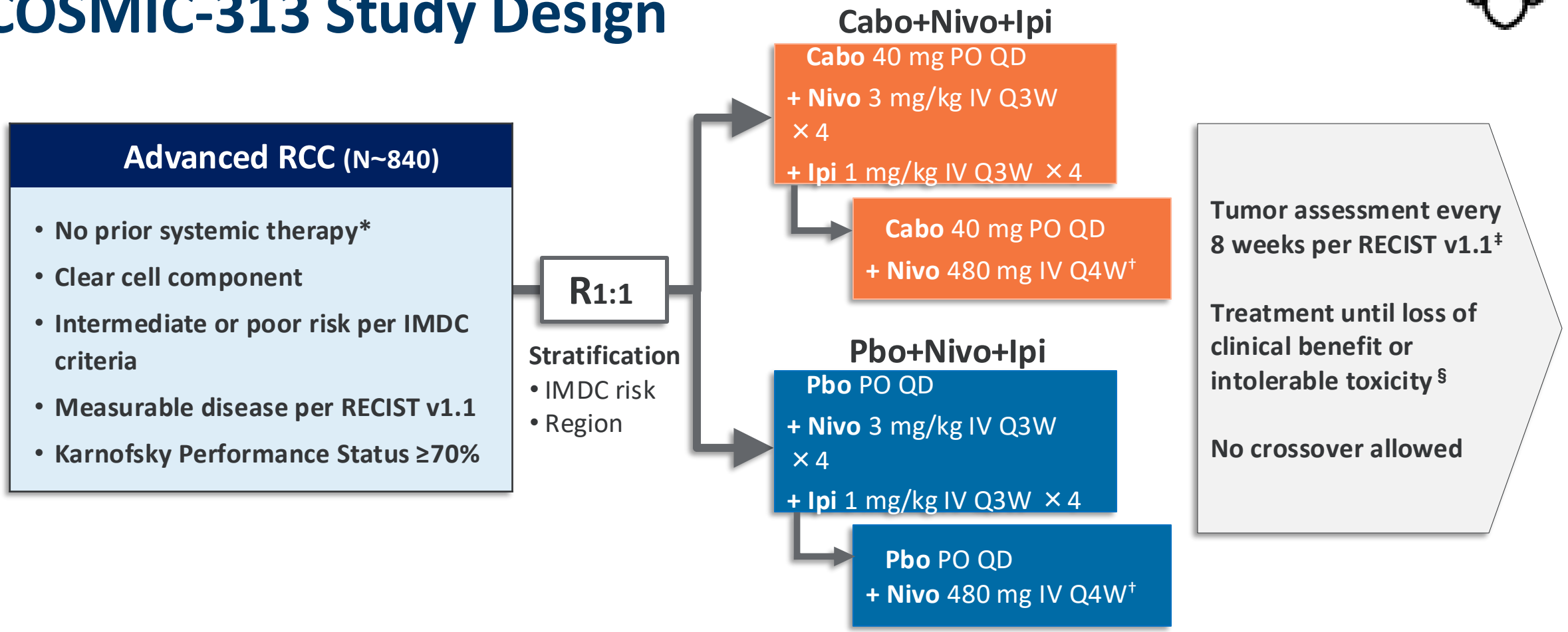
Improved OS
Improved PFS
Improved response rate
Limited PD rate
Durability of response
Depth of response
Complete response
Treatment-free survival
Improved QOL



Immune-mediated AE
Chronic TKI toxicity
Limited durability of response
Primary PD rate
No benefit in QOL

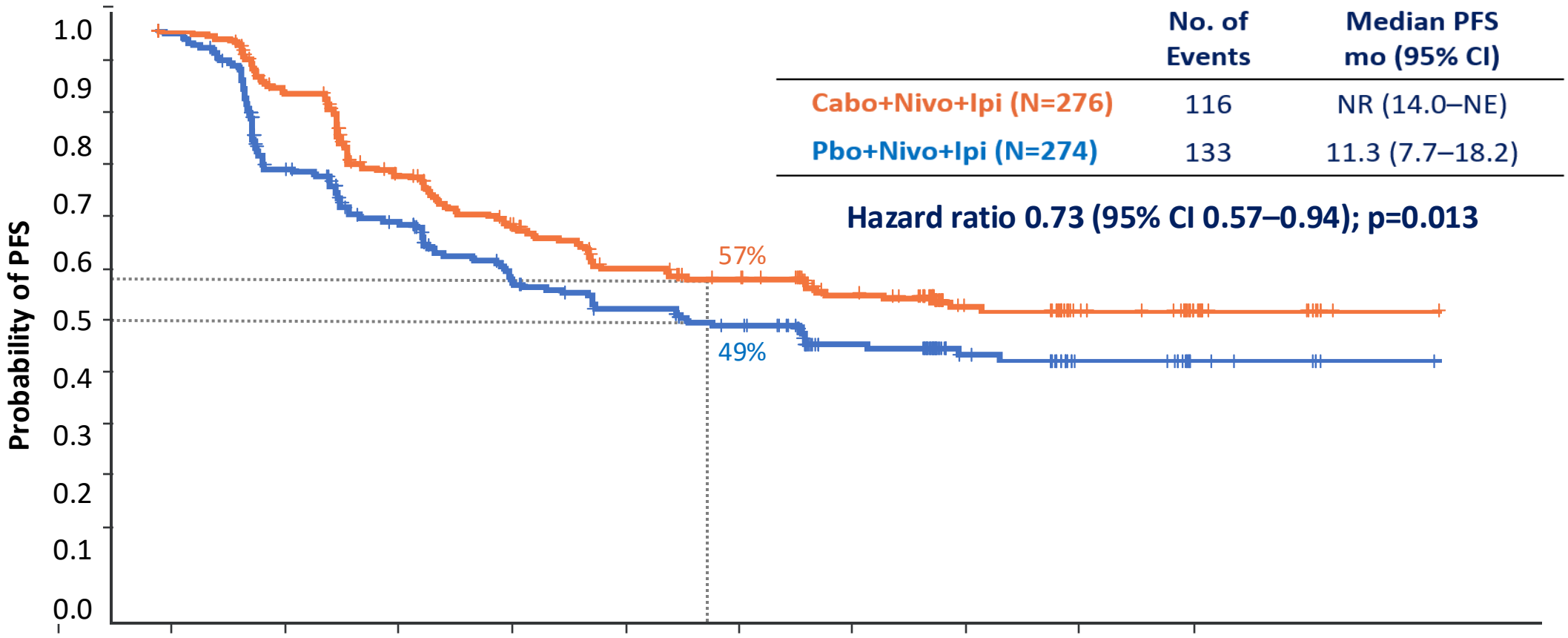
What about triple therapy?

COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter.
§ Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Tumor response per RECIST v1.1 by BIRC

Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

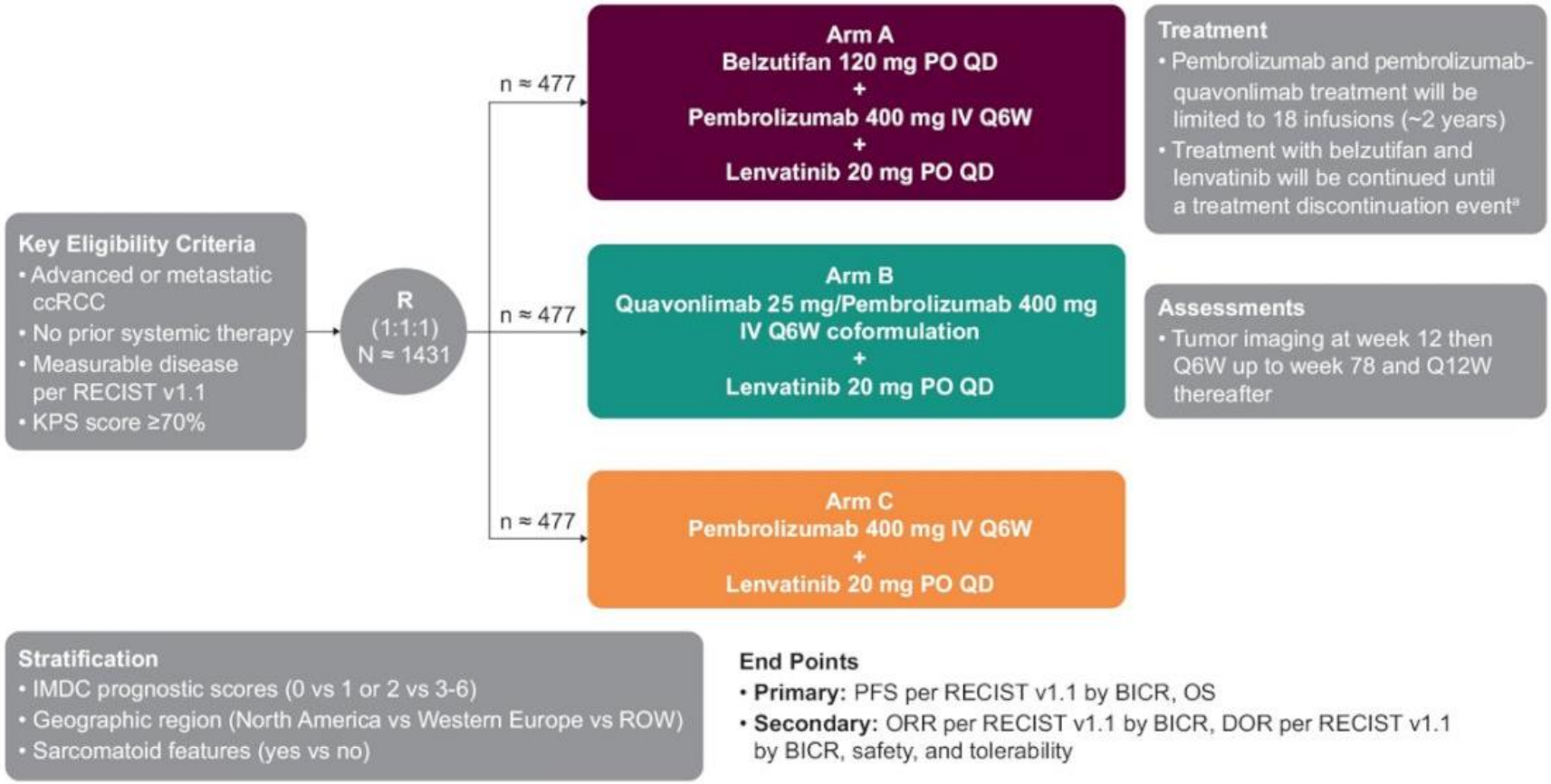
Treatment Exposure and Discontinuation

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

Data cut-off: Jan 31, 2022

Ongoing Clinical Trials

NCT04736706



Second Lone and Beyond

VEGF TKI in Refractory mRCC

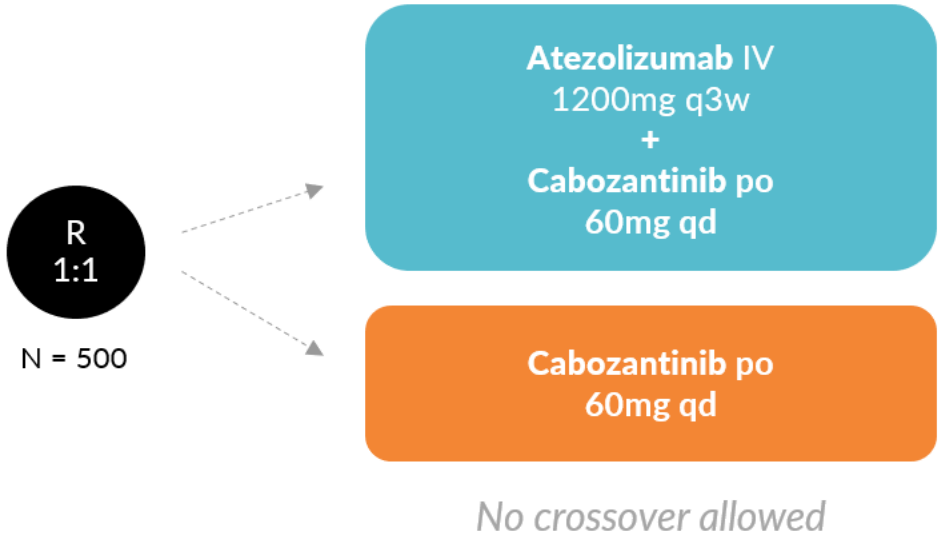
Treatment	Study/Trial Design	N	Prior Therapies	Overall Survival	Objective Response Rate	Progression Free Survival or TTF*	Grade 3 or 4 Toxicity
Cabozantinib	Phase III vs. everolimus, METEOR	658 (330 vs. 328)	1+TKI (5% prior ICI)	21.4 vs. 16.5 months (HR 0.66)	17% vs. .3%	7.4 vs. 3.9 months (HR 0.51)	71% vs 60%
	Phase II control arm, CANTATA	223	TKI or dual ICI		28%	9.2 months	79%
	Phase II, BREAKPOINT NCT03744585	48	Adjuvant or first line ICI		43%	9.3 months	34%
Lenvatinib + Everolimus	Phase II vs. everolimus, NCT01136733	91 (51 vs. 50)	TKI	25.5 vs. 15.4 months (HR 0.51)	43% vs. 6% (RR 7.2)	14.6 vs. 5.5 months (HR 0.40)	71% vs. 50%
Tivozanib	Phase III vs. Sorafenib, TIVO-3	350 (175 vs. 175)	2+ systemic therapies	At 22.8 months, HR 0.89, (CI 0.70-1.14)	18% vs. 8%	5.6 vs. 3.9 months (HR 0.73)	11% vs. 10%
Axitinib	Phase III vs. Sorafenib, AXIS	723 (361 vs. 362)	Sunitinib or other *	20.1 vs. 19.2 months (HR 0.969)	8.3 vs. 5.7 months (HR 0.66)	23% vs. 12%	17% vs. 12% HTN*
Belzutifan	Phase III vs. everolimus, Litespark-005	746 (374 vs 372)	1-3 prior, 1 TKI + 1 PD(L)1	21 vs. 21.4 months (HR 0.87)	21.9% vs 3.5%	5.6 vs 5.6 months (0.75)	

*TTF—time to treatment failure; D/C—discontinue; SD—stable disease; HTN—hypertension.**Cytokines, bevacizumab with interferon, or temsirolimus.

Salvage PD-L1 Inhibitor is not superior to TKI alone

CONTACT-03

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment



No crossover allowed

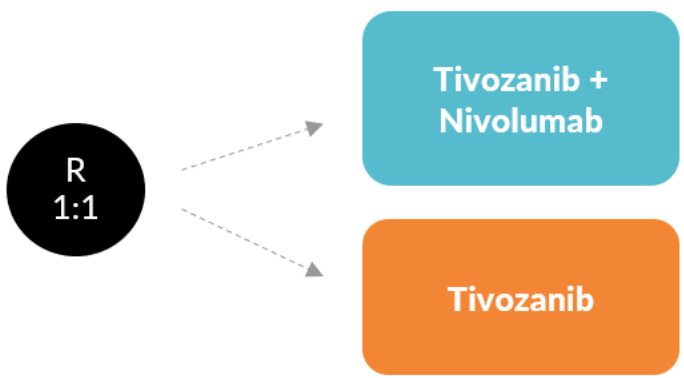
Negative Trial

Treatment until progression

- Primary endpoint: PFS, OS
- Secondary endpoint: PFS, ORR, DoR, Safety and Tolerability

TINIVO-2

- Histologically/cytologically confirmed recurrent/ metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI



Negative Trial: ESMO 2024

Treatment until progression

- Primary endpoint: PFS
- Secondary endpoint: OS, ORR, DoR, Safety and Tolerability

Moving systemic therapy earlier in the course..

Trial	Arms	Years	N	Primary Endpoint	Clear Cell Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE (Hass, *Lancet* 2016)	Sunitinib vs Sorafenib vs Placebo*	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN+	Sunitinib: 1.02 (97.5% CI, 0.85-1.23) Sorafenib: 0.97 (97.5% CI, 0.80-1.17)
STRAC (Ravaud, *N Engl J Med* 2016)	Sunitinib vs Placebo	1	615	DFS	Yes	pT3-4GxN0-x TxGxN1-2	0.76 (95% CI, 0.59-0.98)
PROTECT (Motzer, *J Clin Oncol* 2017)	Pazopanib vs. Placebo*	1	1538	DFS	Yes	pT2G3-4N0 pT3-4N0 pTxN1	0.86 (95% CI, 0.70-1.06)
ATLAS (Gross-Goupil, *Ann Oncol* 2018)	Axitinib vs Placebo	1-3	724	DFS	Yes	pT2-4GxN0 pTxN1	0.87 (95% CI, 0.66-1.147)
SOURCE (Eisen, *J Clin Oncol* 2020)	Sorafenib vs Placebo*	1-3	1711	DFS	No	Leibovich Score: 3-11	1.01 (95% CI, 0.83-1.23)
EVEREST (Ryan C, *J Clin Oncol* 2022)	Everolimus vs Placebo	1	1545	RFS	No	pT1bG3-4N0 pT2-4N1	HR, 0.85 (95% CI, 0.72-1.00)

Haas NB et al. *Lancet.* 2016;387(10032):2008-2016; Ravaud A et al. *N Engl J Med.* 2016; 375(23):2246-2254;
Motzer RJ et al. *J Clin Oncol*. 2017;35(35):3916-3923; Gross-Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378;
Tacconi EMC, et al. *Onco Targets Ther*. 2020;13:12301-12316; Ryan C, et al. *J Clin Oncol. 2022;*40(17_suppl): Abstract LBA4500.

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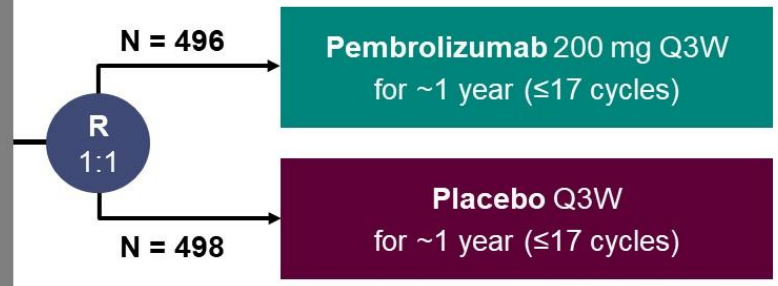
Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO GU 2022** **HR 0.63; p < 0.0001**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	**ESMO 2022** **NS DFS** **HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**ESMO 2022** ***Part A (Nivo+Ipi)*** **NS DFS** **HR, 0.92; P=0.5347**
PROSPER RCC[4]	766	cT2Nx, cTxN1, cTxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	**ESMO 2022** **NS DFS** **HR, 0.97; P=0.43** **Trial stopped for futility**

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.
Powles T, et al. *Lancet Oncol.* 2022;23;1133-1144.; Choueiri TK, et al. ASCO GU 2022. Abstract 290.; 2. NCT03024996. 3. NCT03138512. 4. NCT03055013.

KEYNOTE-564 Study (NCT03142334)

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

- Overall survival

Other Secondary Endpoints

- Safety

NED, no evidence of disease.

Choueiri *et al*. GU ASCO 2024

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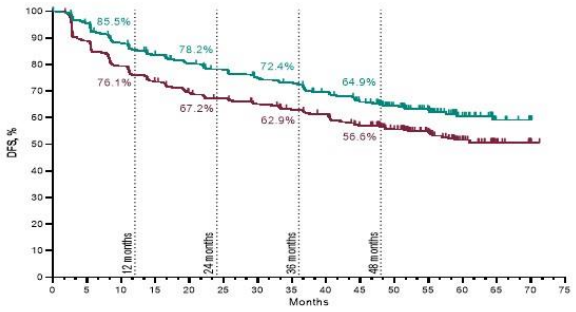
KEYNOTE-564 DFS & OS benefit Not By Chance!

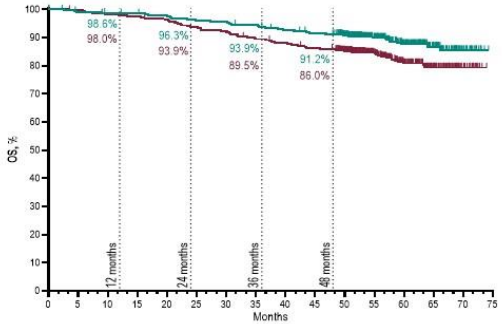
	June 2021	Sep 2022	Jan 2024
Analysis	1st	2nd	3rd
Median follow up, months	24.1	30	57.2
Disease free survival (HR, CI 95%), p-value	0.68 *P=0.0010*	0.63 *P<0.0001*	0.72 NE
DFS events	109 vs 151	114 vs 169	174 vs 224
Overall survival (HR, CI 95%)	0.54 *P=0.0164 (int)*	0.52 *P=0.0048 (int)*	0.62 ***P=0.002****
OS events	18 vs 33	23 vs 43	55 vs 86

- 1st ICI to improve DFS in RCC
  1st ICI to improve OS in any GU tumor

Disease-free survival



Overall survival



Up to 0.2% chance of **Being Struck by Lightning in a Lifetime in certain regions**

Source: ChatGPT

ASCO Genitourinary Cancers Symposium #GU24

PRESENTED BY: Pedro C. Barata, MD MSc, FACP

@PBarataMD

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NCI Designated Comprehensive Cancer Center

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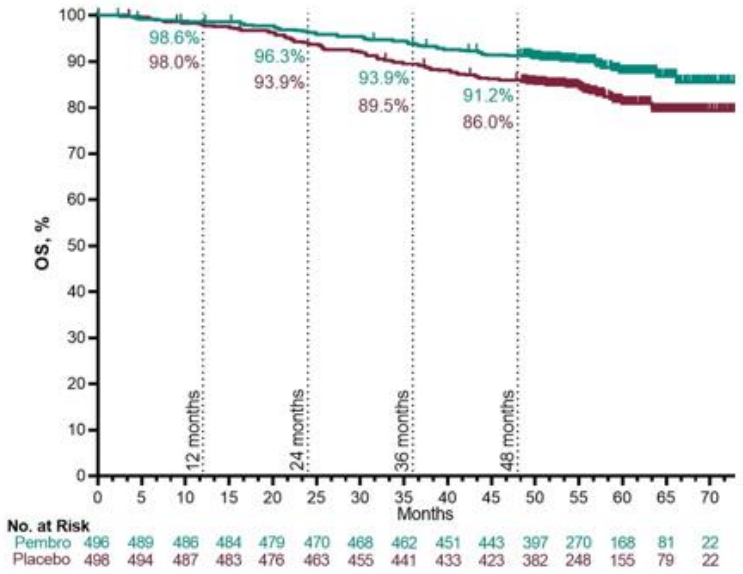
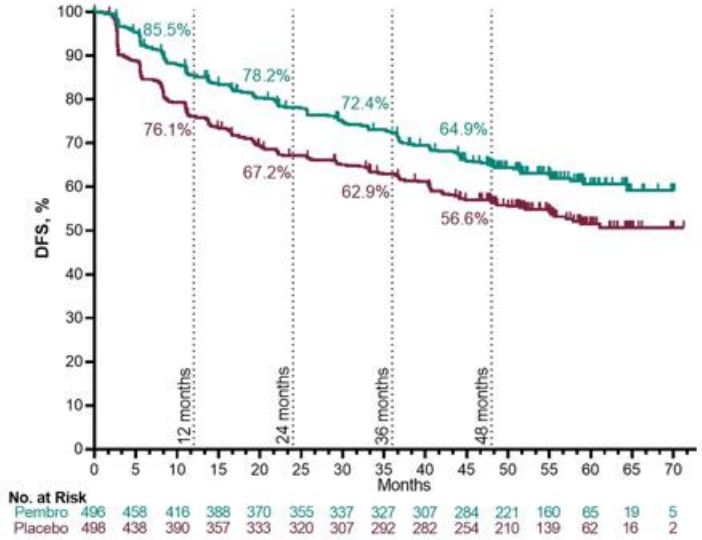
- OS



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.62 (95% CI 0.44–0.87); *P* =.002*

- DFS



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.72 (95% CI 0.59–0.87)

Choueiri *et al*. GU ASCO 2024

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Closing Remarks

- The treatment landscape for advanced renal cell carcinoma has been rapidly evolving and patients are living longer and better;
- Both IO/IO and IO/VEGF are suitable frontline treatments for patients;
- Treatment options in the subsequent line space are expanding with the introduction of novel targets in development;
- We’re seeing progress in the non-metastatic setting with impact in the management of advanced disease

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My take on adjuvant pembro

- It is positive trial, encouraging to see OS data.
- I discuss it with all my eligible clear cell patients.
- But might not push it stage T2 G4, especially older with comorbidities.
- Higher risk III, sarcomatoid.
- Rarely do metastectomy in my practice.
- Not for Non- clear cell RCC.