Updates in RCC: What Have We Learned from GU ASCO 2024?

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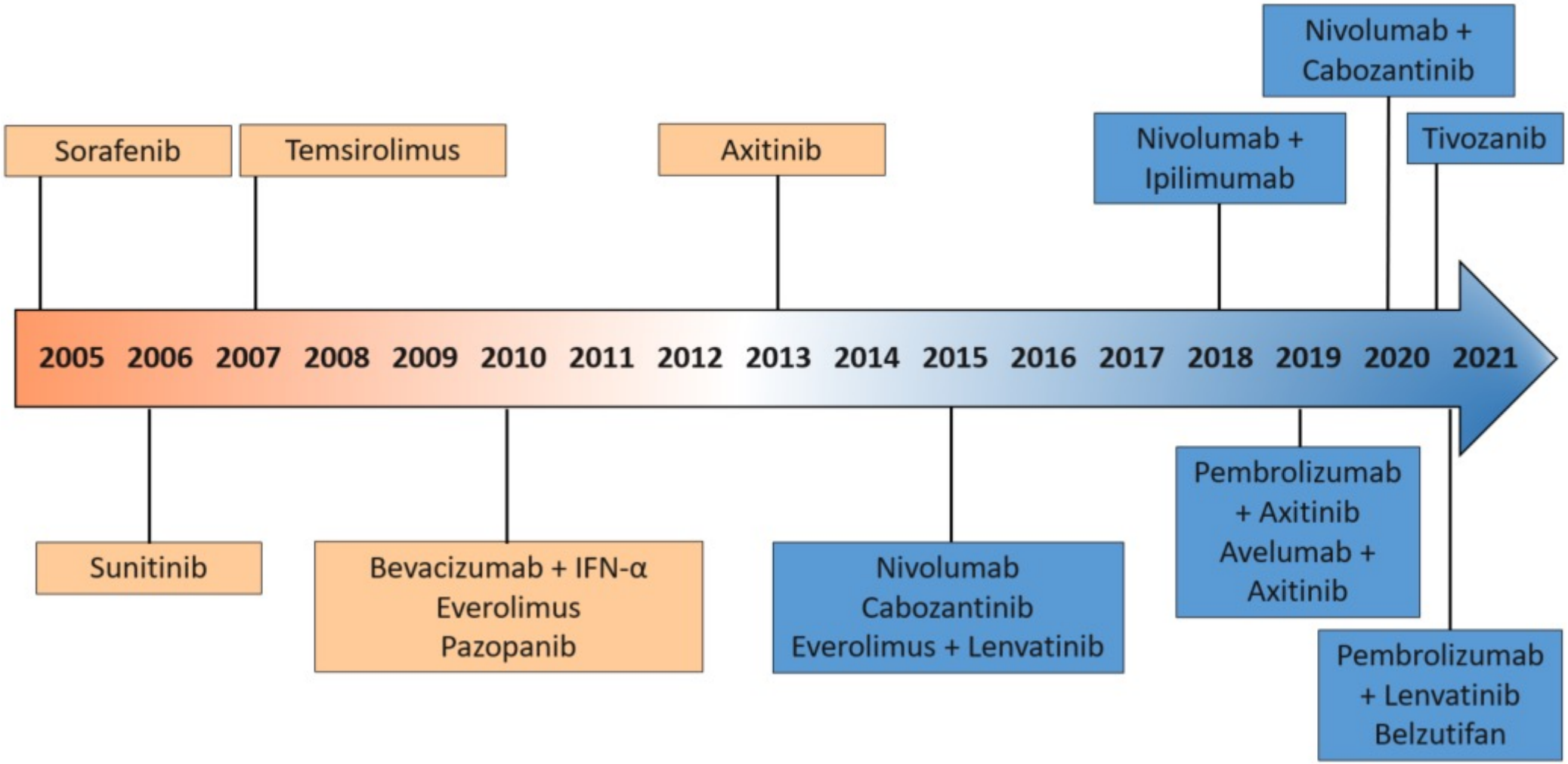
Treatment Landscape of Metastatic RCC



Courtesy Slide: P Barata

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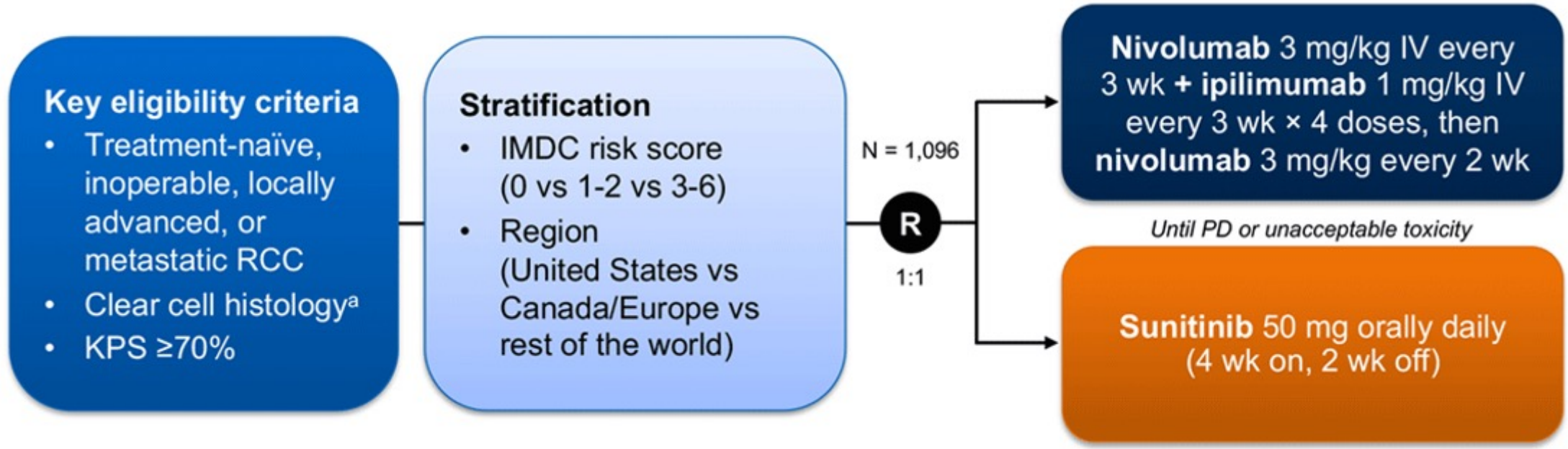
First-line IO Combination Trials in mRCC (ITT)

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.72** 52.7 vs 37.8	**0.84** 47.2 vs 40.8	**0.77** 46.5 vs 36.0	**0.79** 53.7 v. 54.3
Landmark OS	**35%** at 7.5 years	**63%** at 3 years **42%** at 5 years	**49%** at 4 years	**66%** at 3 years
PFS HR mPFS, months	**0.88** **12.4** vs 12.3	**0.69** **15.7** vs 11.1	**0.58** **16.4** vs 8.4	**0.47** **23.9** vs 9.2
Landmark PFS	**23%** at 7.5 years (IRC) **16%** at 7.5 years (investigator)	**18%** (5 years)	**17%** (4 years)	**37%** (3 years)
ORR, %	**39** vs 33	**61** vs 40	**56** vs 28	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**14** vs 5	**18** vs 4
Med f/u, months	**96**	**67**	**56**	**48**
Primary PD, %	**18**	**12**	**7**	**5**

1. Tannir et al. ASCO GU 2024
2. Rini et al. ASCO 2023
3. Bourlon et al. ASO GU 2024
4. Motzer et al. ASCO 2023

@brian_rini and @Uromigos (podcasts: https://podcasters.spotify.com/pod/show/the-uromigos)

Checkmate 214 Long Term Follow-up

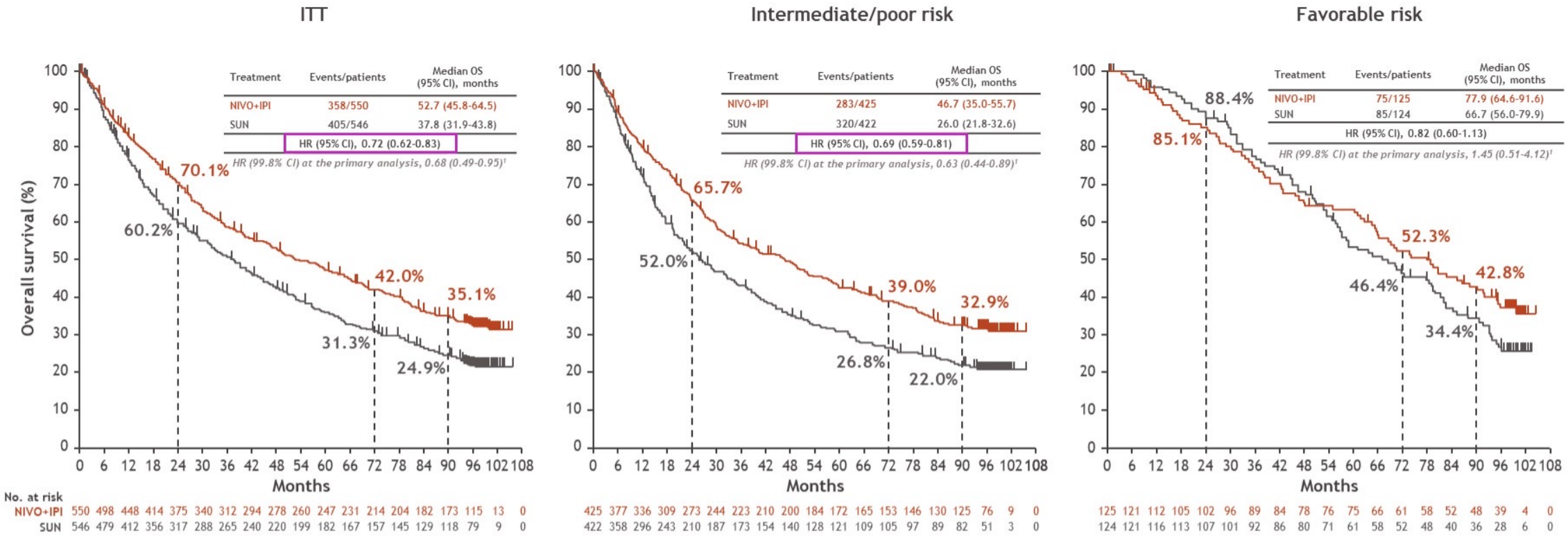


Primary Endpoints OS, PFS, ORR in IMDC intermediate/ poor- risk patients.
Secondary: PFS, OS, ORR in ITT patients.

Motzer RJ, *et al*. NEJM 2018

Overall survival

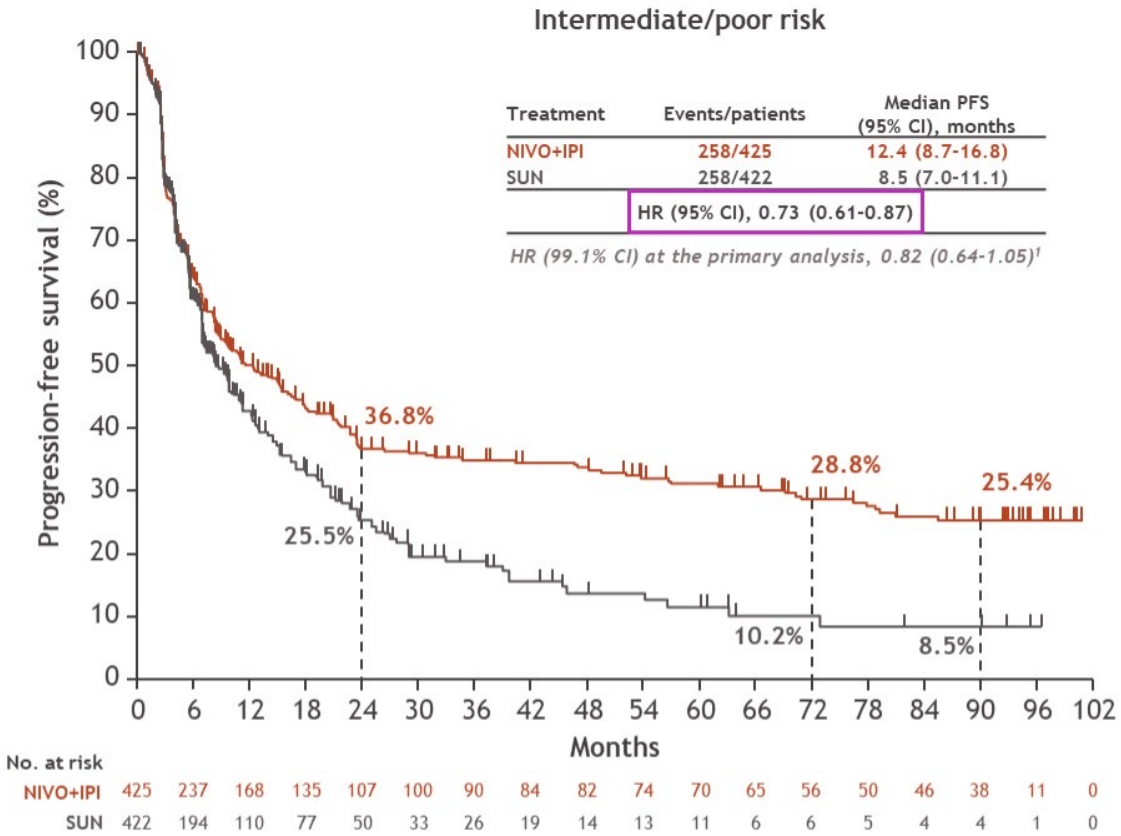
- The HR for OS has been stable over 8 years of median follow-up in ITT and intermediate/poor-risk patients and has improved over time in favorable risk patients

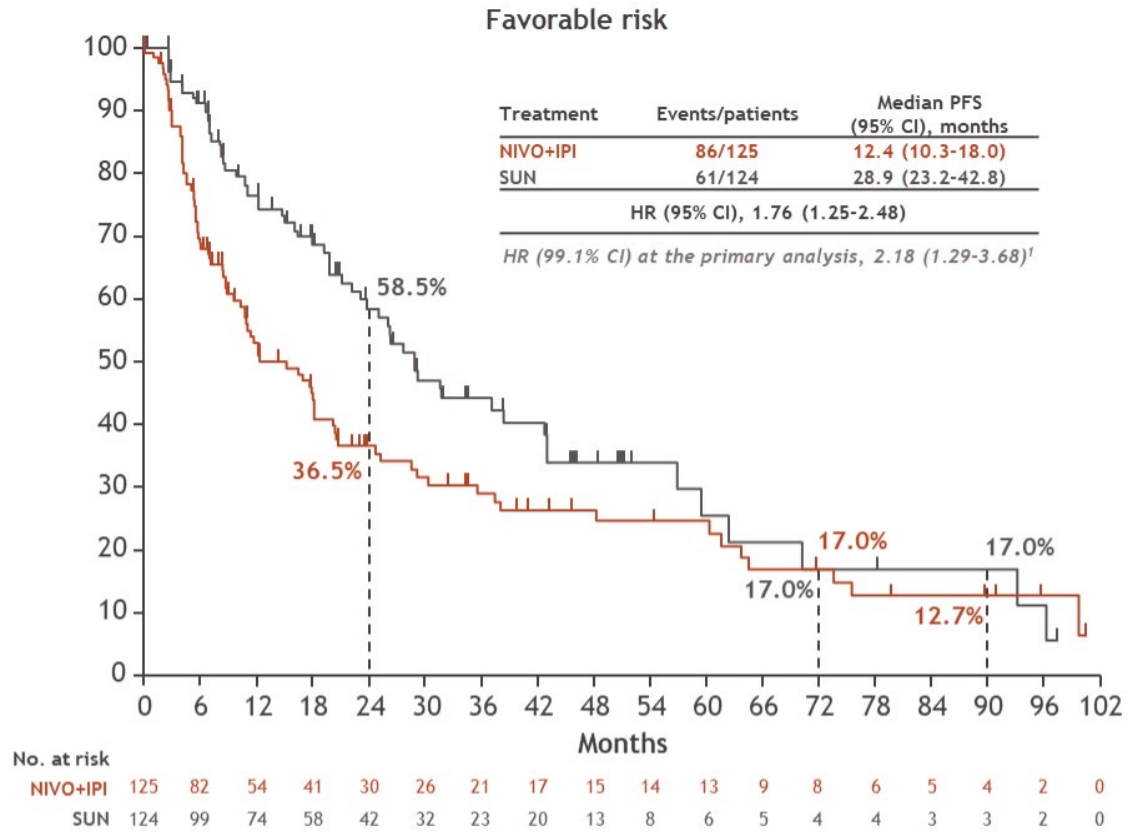


Stratified Cox proportional hazards model.

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.

PFS per IRRC by IMDC risk

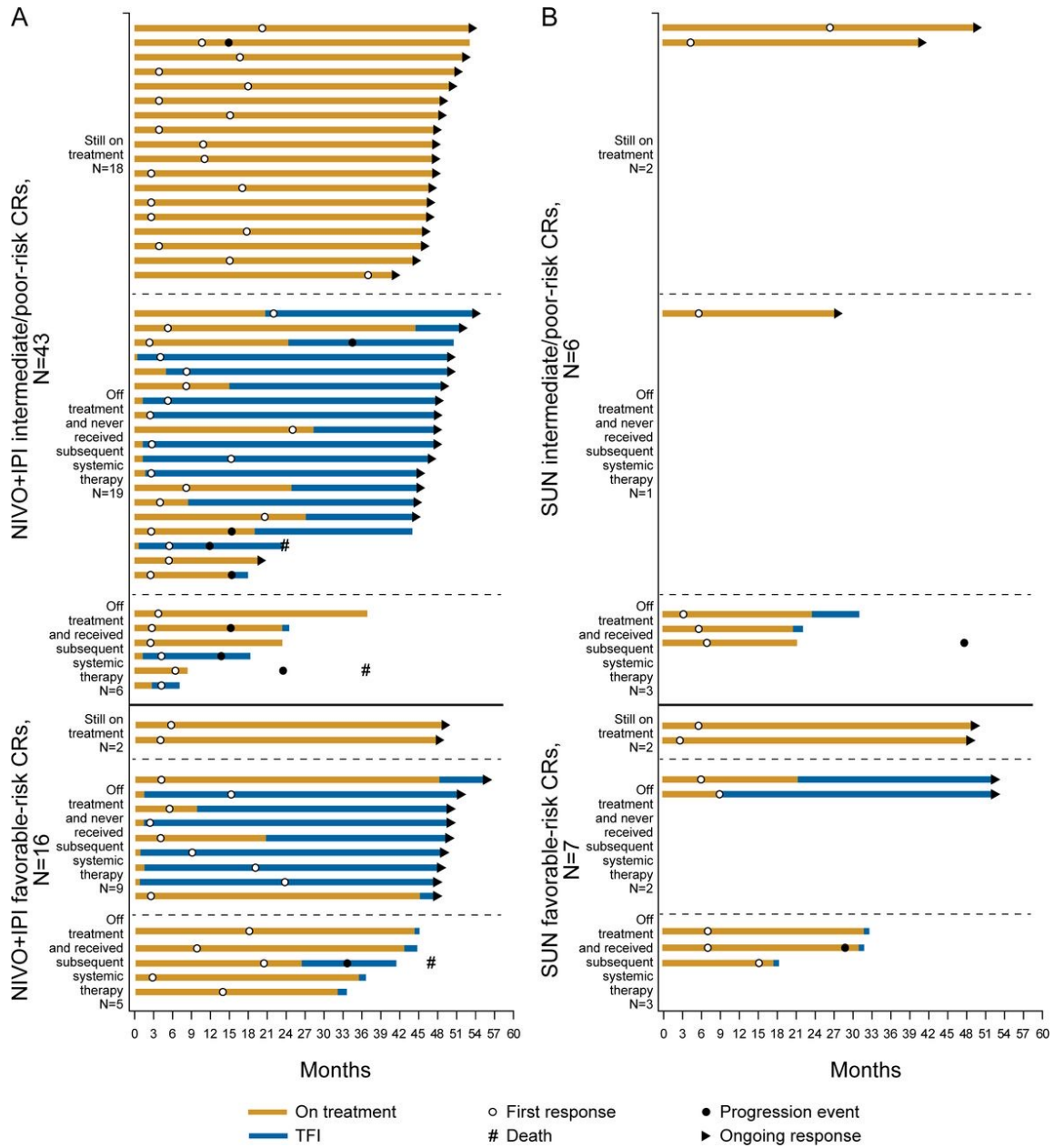




Stratified Cox proportional hazards model.

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.

Treatment-free interval and response outcomes in complete responders.



Motzer *et al*. J Immunother Cancer 2020

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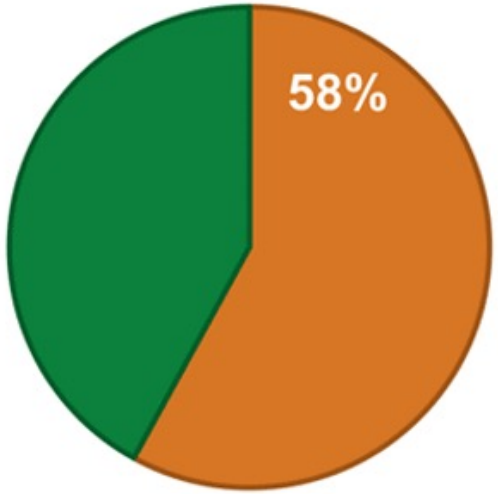
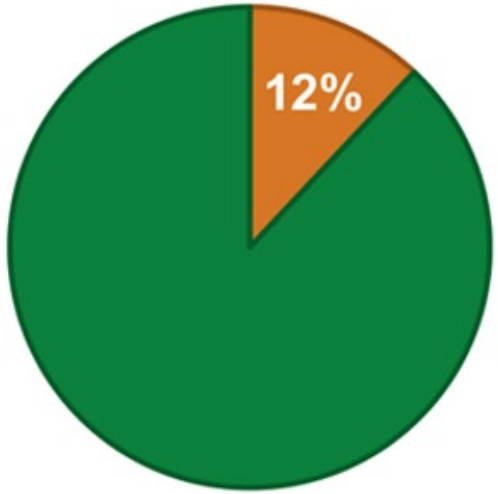
Patient Perspectives: Treatment Discontinuation

Q. Current treatments for RCC require continuous therapy. However, research suggests that patients might be able to safely discontinue therapy after a period of time and maintain efficacy. If your doctor suggested stopping your therapy because your disease was well controlled, how would you feel?[1,a]



I would be anxious about my cancer progressing



I would feel safer being able to avoid future side effects

Patients are often anxious when stopping therapy, even if data supports it, so they may need further reassurance for why it may be an optimal choice for them

Battle D *et al*. ASCO 2020

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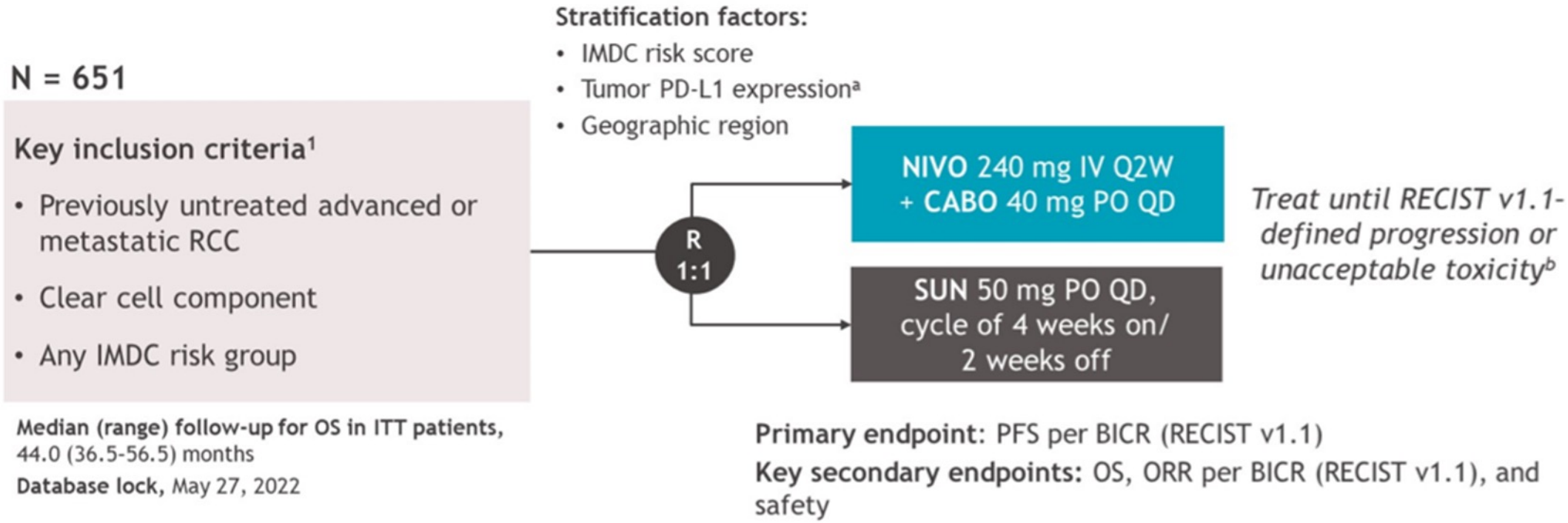
Checkmate 9ER Long Term Follow-up



Burotto *et al*. ASCO 2023

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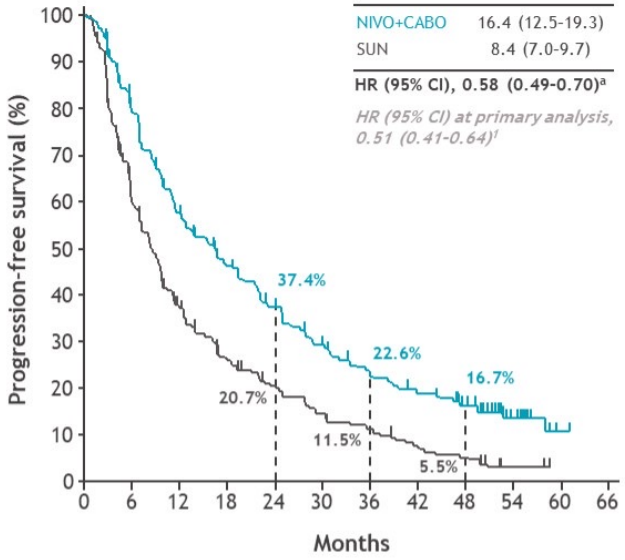
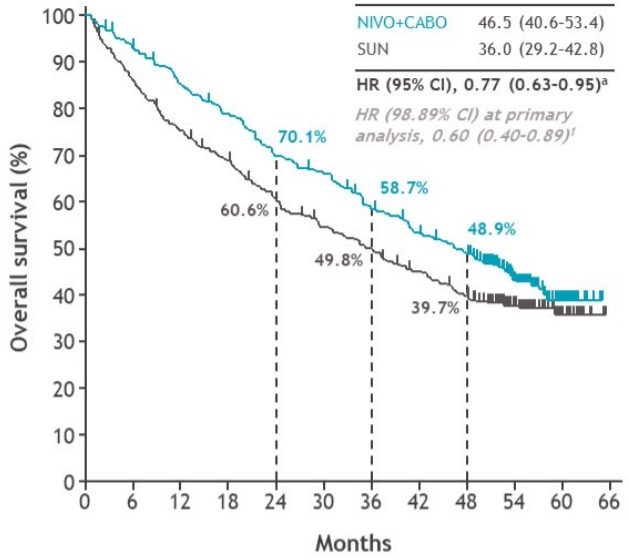
PFS per BICR, OS, ORR per BICR in *ITT population*

PFS per BICR



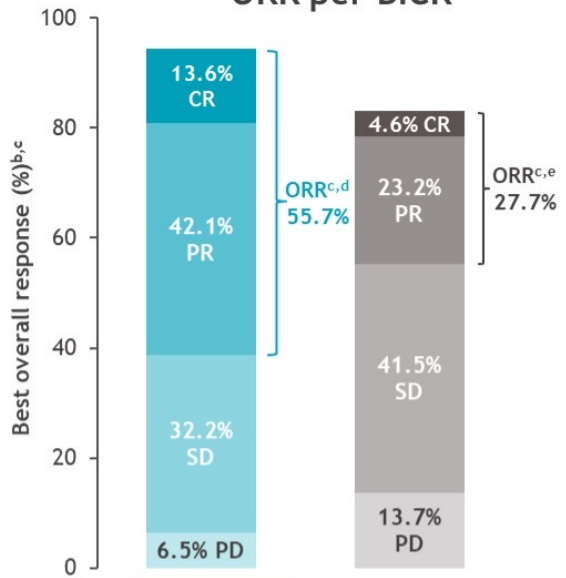
No. at risk												
NIVO+CABO	323	237	168	131	104	79	59	49	38	14	1	0
SUN	328	161	93	61	45	32	24	15	11	2	0	0

OS



No. at risk												
NIVO+CABO	323	298	272	250	222	208	183	164	149	83	18	0
SUN	328	277	242	219	191	170	155	138	120	66	14	0

ORR per BICR



	NIVO+CABO (n = 323)	SUN (n = 328)
Median TTR (range), mo[f]	2.8 (1.0-22.2)	4.3 (1.7-30.4)
Median DOR (95% CI), mo[f]	22.0 (18.0-25.2)	15.2 (10.9-19.3)

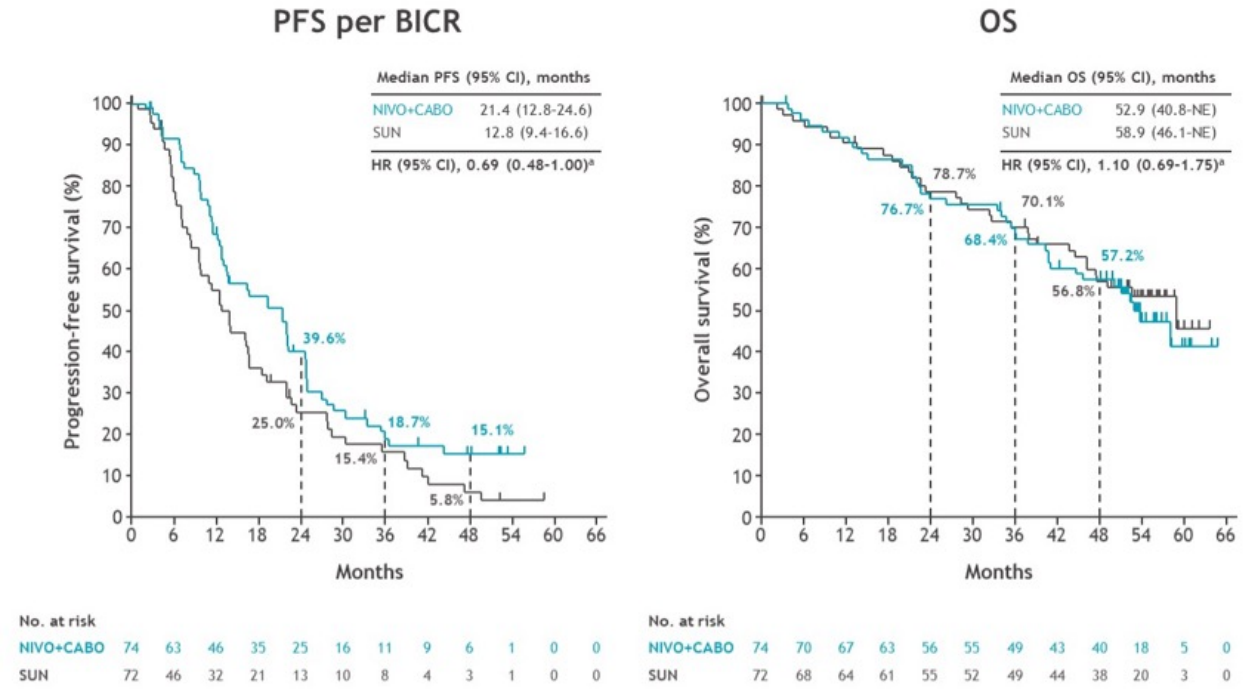
Median (range) follow-up for OS, 55.6 (48.1-68.1) months (ITT population).

[a]Stratified Cox proportional hazards model used for HR. [b]Unable to determine/not reported: 5.6% for NIVO+CABO; 17.1% for SUN. [c]No. of patients with ORR and BOR in NIVO+CABO arm: ORR, n = 180; CR, n = 44; PR, n = 136; SD, n = 104; PD, n = 21. No. of patients with ORR and BOR in SUN arm: ORR, n = 91; CR, n = 15; PR, n = 76; SD, n = 136; PD, n = 45. [d]95% CI, 50.1-61.2. [e]95% CI, 23.0-32.9. [f]TTR and DOR were calculated only for patients who had a CR or PR.

1. Choueiri TK, et al. *N Engl J Med* 2021;384:829-841.

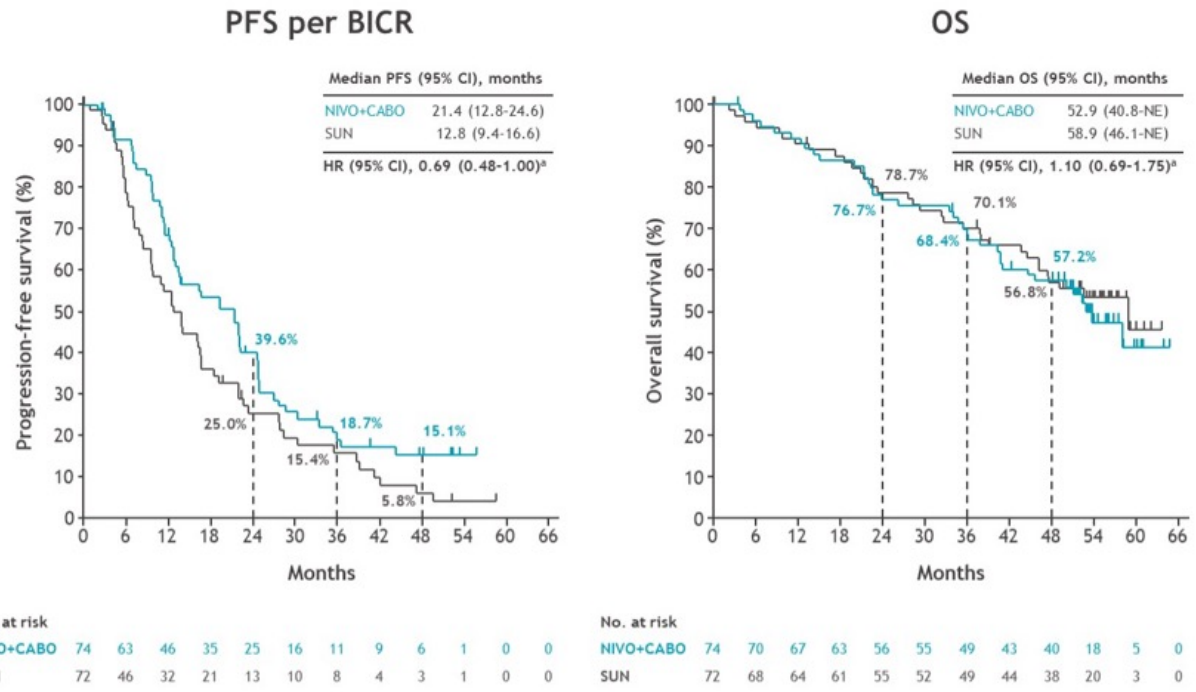
Bourlon *et al*. GU ASCO 2024

- Favorable Risk

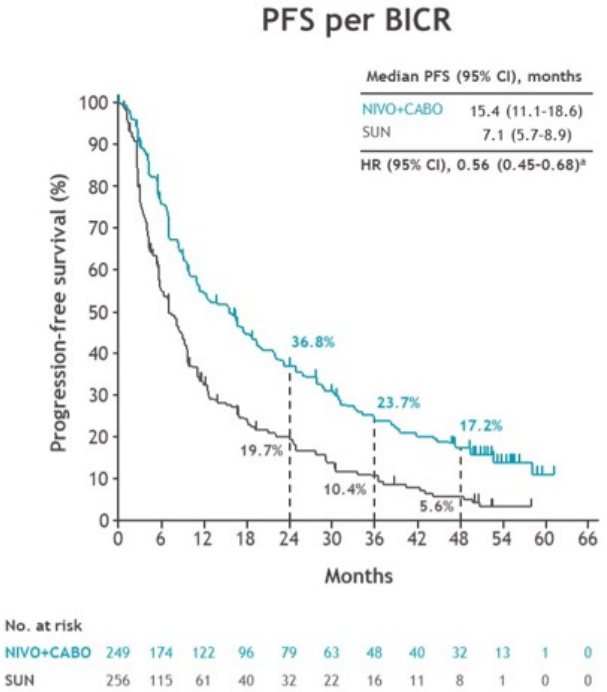


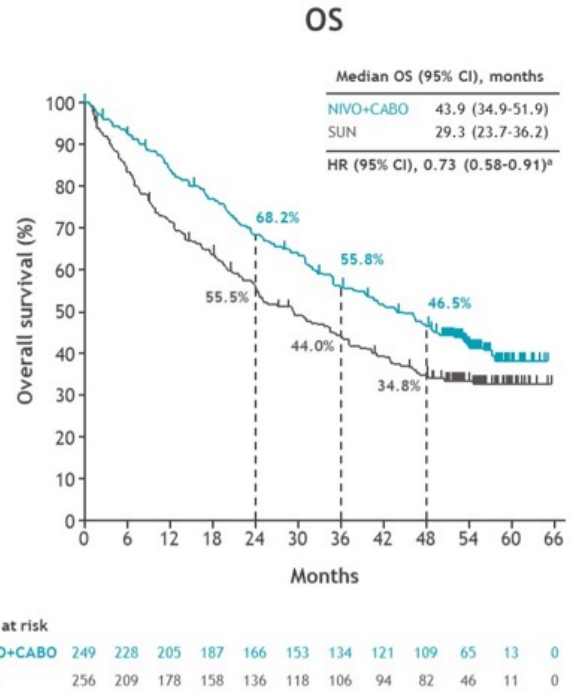
Bourlon *et al*. GU ASCO 2024

- Favorable Risk



- Intermediate/ Poor





Bourlon *et al*. GU ASCO 2024

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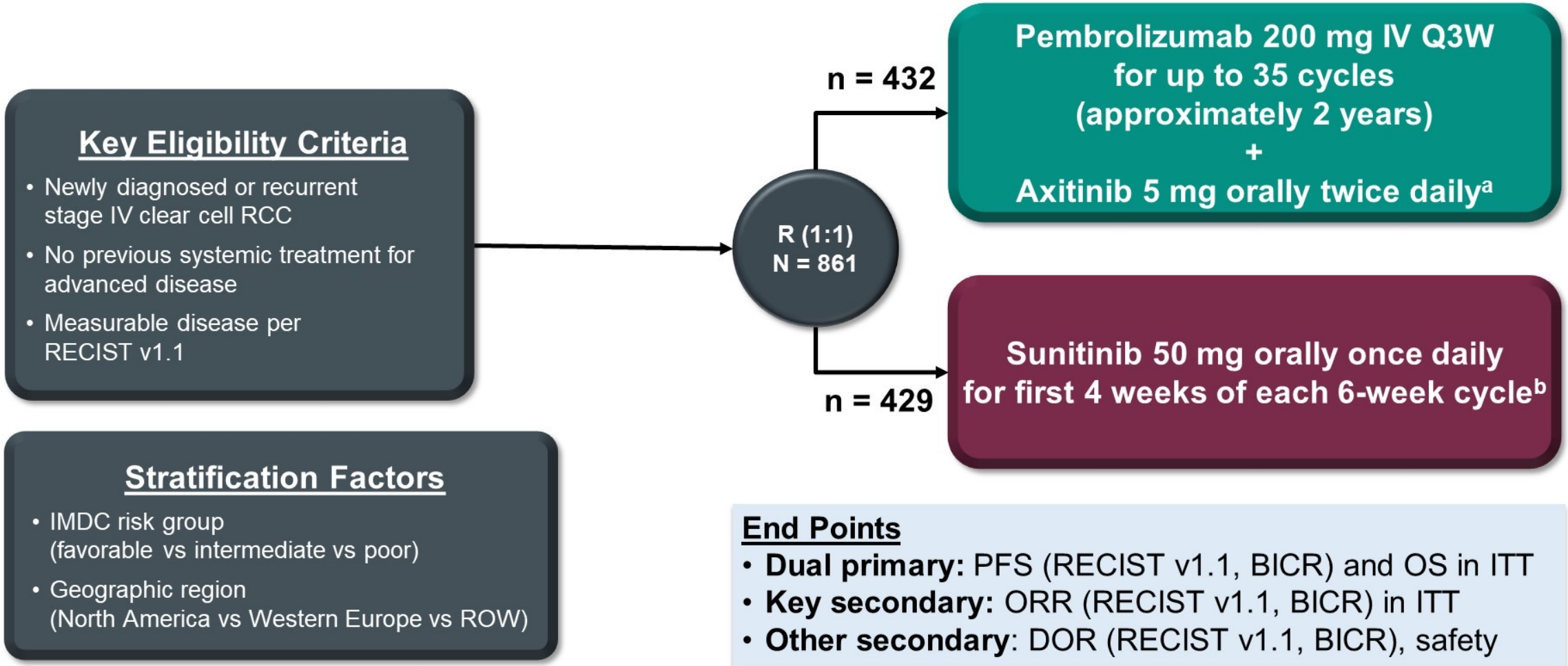
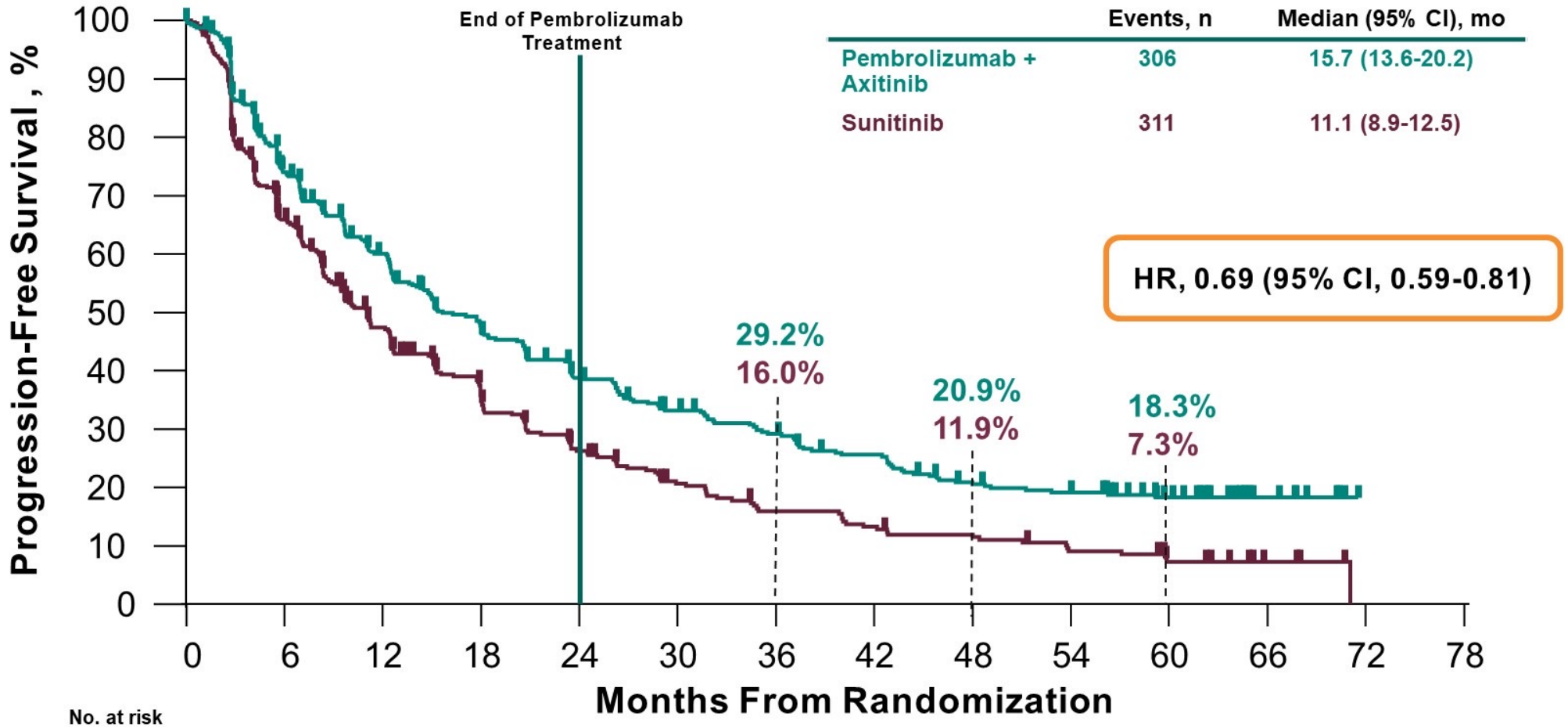
KEYNOTE-426 Study Design (NCT02853331)



BICR, blinded independent central review; DOR, duration of response; IMDC, International Metastatic RCC Database Consortium; ITT, intention-to-treat; IV, intravenously; Q3W, every 3 weeks; R, randomized; ROW, rest of world.
[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 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 23, 2023.

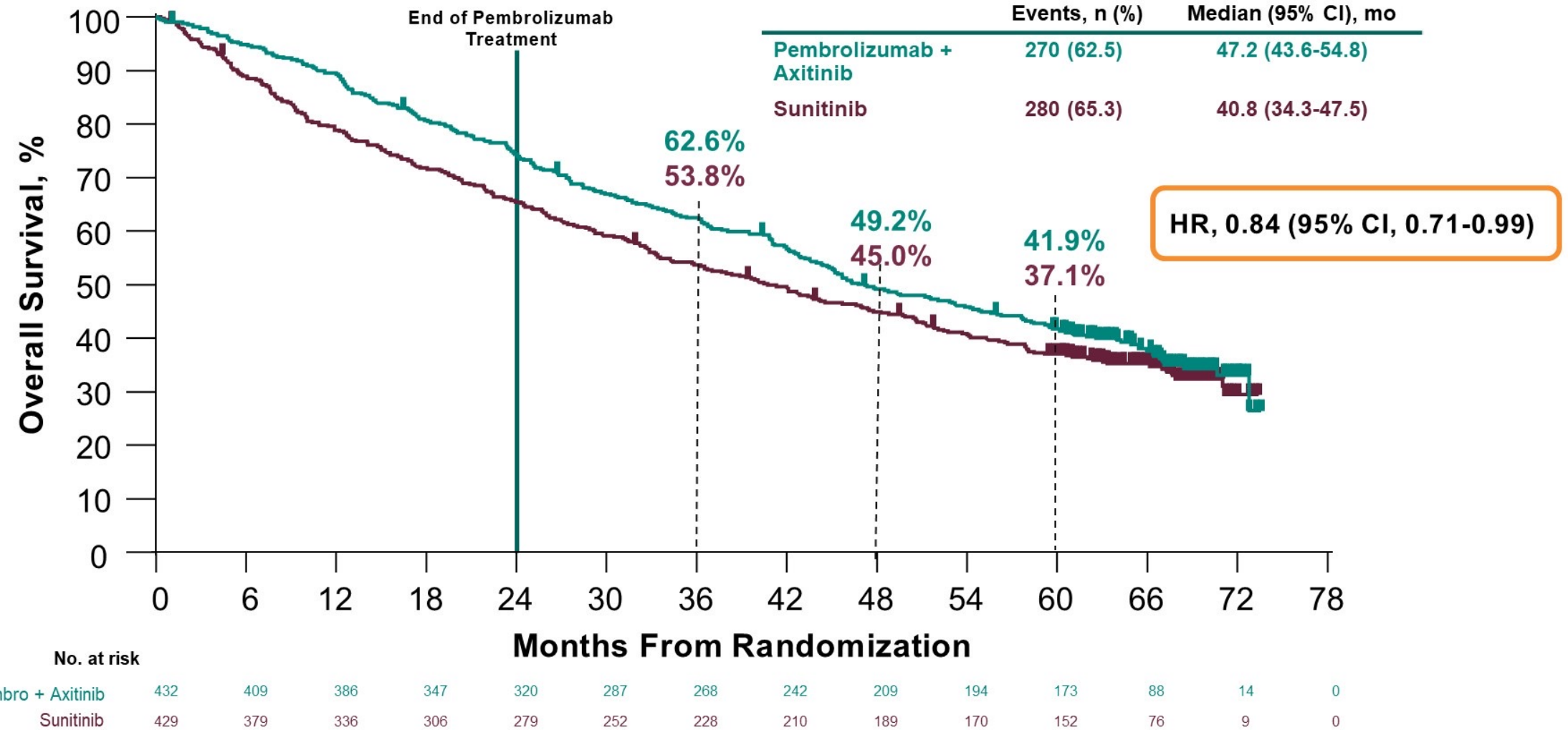
Progression-Free Survival in the ITT Population



Data cutoff: January 23, 2023.

Rini *et al*. ASCO 2023

Overall Survival in the ITT Population



Data cutoff: January 23, 2023.

Rini *et al*. ASCO 2023

Phase 3 CLEAR Study: First-line Lenvatinib + Pembrolizumab or Everolimus Versus Sunitinib

Key eligibility criteria

- Advanced clear-cell RCC
- Treatment-naïve
- Karnofsky PS ≥70
- Measurable disease
- Adequate organ function

Stratification factors

- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor

R

(1:1:1)

Lenvatinib
20 mg oral QD
+
Pembrolizumab*
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

Primary endpoint
- PFS by IRC per RECIST v1.1

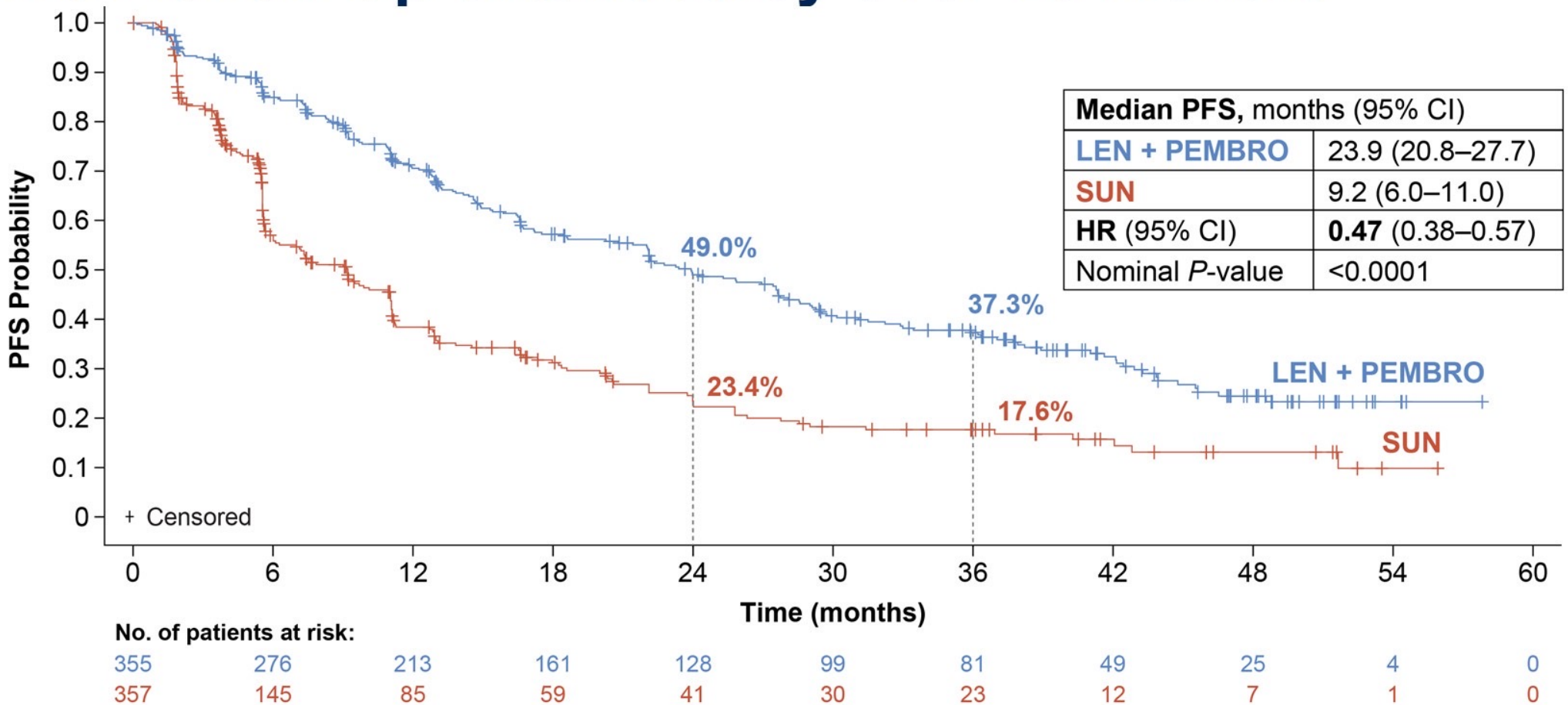
Secondary endpoints
- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

Key exploratory endpoints
- DOR
- Biomarkers

*Patients could receive a maximum of 35 pembrolizumab treatments.
DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

Motzer R, *et al*. *N Engl J Med*. 2021;384(14):1289-1300.

Continued PFS benefit of LEN+PEMBRO vs SUN with follow up extended by over 23 months



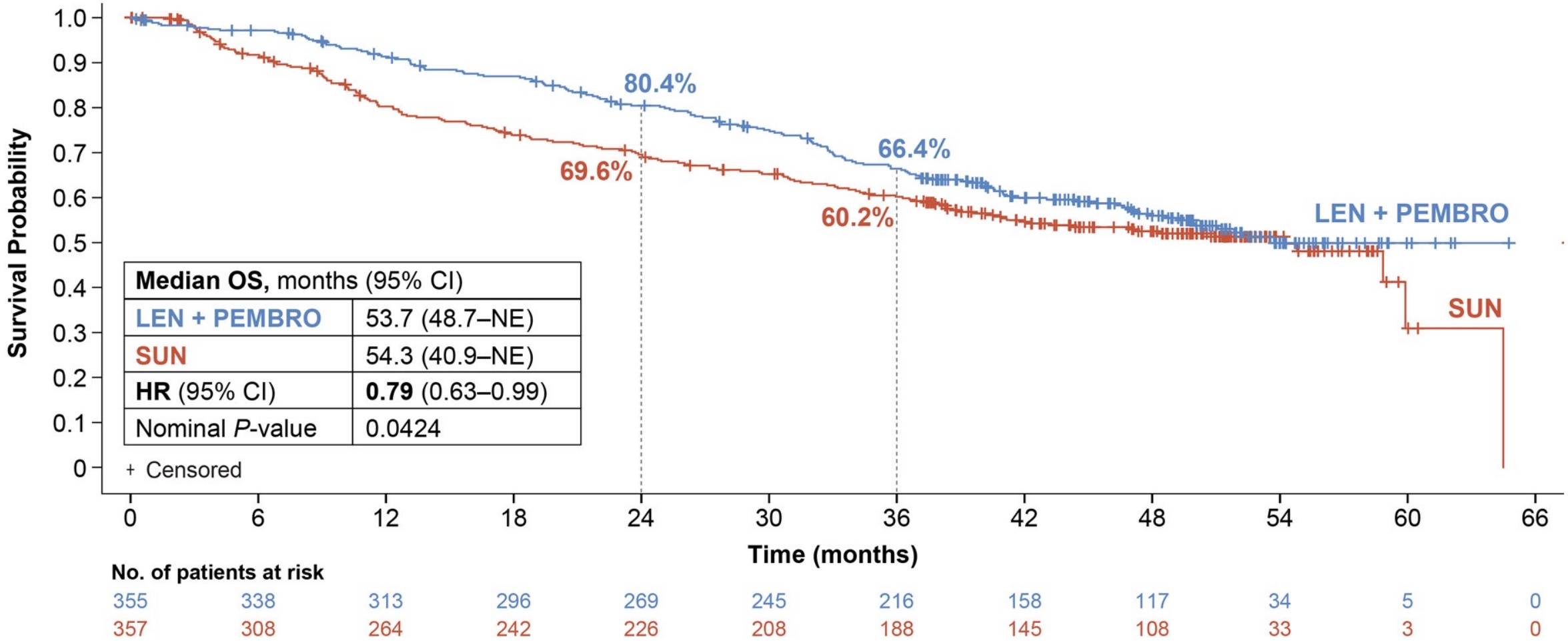
Median PFS, months (95% CI)	
LEN + PEMBRO	23.9 (20.8–27.7)
SUN	9.2 (6.0–11.0)
HR (95% CI)	**0.47** (0.38–0.57)
Nominal *P*-value	<0.0001

No. of patients at risk:

355	276	213	161	128	99	81	49	25	4	0
357	145	85	59	41	30	23	12	7	1	0

Median follow-up time (IQR) for PFS was 39.2 months (22.1–48.5) in the lenvatinib plus pembrolizumab group and 20.6 months (5.5–41.2) in the sunitinib group. PFS was determined by independent imaging review per RECIST v1.1. The 95% CIs were estimated with a generalized Brookmeyer and Crowley method. Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method was used for ties and stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS.

Final OS analysis



Median OS, months (95% CI)	
LEN + PEMBRO	53.7 (48.7–NE)
SUN	54.3 (40.9–NE)
HR (95% CI)	**0.79** (0.63–0.99)
Nominal *P*-value	0.0424

No. of patients at risk

355	338	313	296	269	245	216	158	117	34	5	0
357	308	264	242	226	208	188	145	108	33	3	0

At median OS follow-up time (IQR) of **49.8 months** (41.4–53.1) in the lenvatinib plus pembrolizumab group and **49.4 months** (41.6–52.8) in the sunitinib group, 308 target OS events had occurred (lenvatinib plus pembrolizumab, 149 events; sunitinib, 159 events). The HR and 2-sided 95% CI for lenvatinib plus pembrolizumab vs sunitinib were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by geographic region and MSKCC prognostic groups.

	Pros	Cons
IO/ TKI	• Consistent efficacy data. • High ORR, rapid shrinkage. • Manageable toxicities*	• Durability not as attractive as IO/IO • Unclear if we can stop TKI. • Hence more chronic TKI tox.
IO/ IO	• Durability of response • Long OS data • Treatment free survival • QOL might be better than TKI.	• Acute tox at the combo phase. • On cruise control once passed induction but delayed IO tox could be issue. • Higher PD rate, lower ORR. • I haven't used it in favorable risk.

Zakharia *et al*. Clinical Genitourinary cancer 2023
Zakharia *et al*. Frontier Oncology 2022

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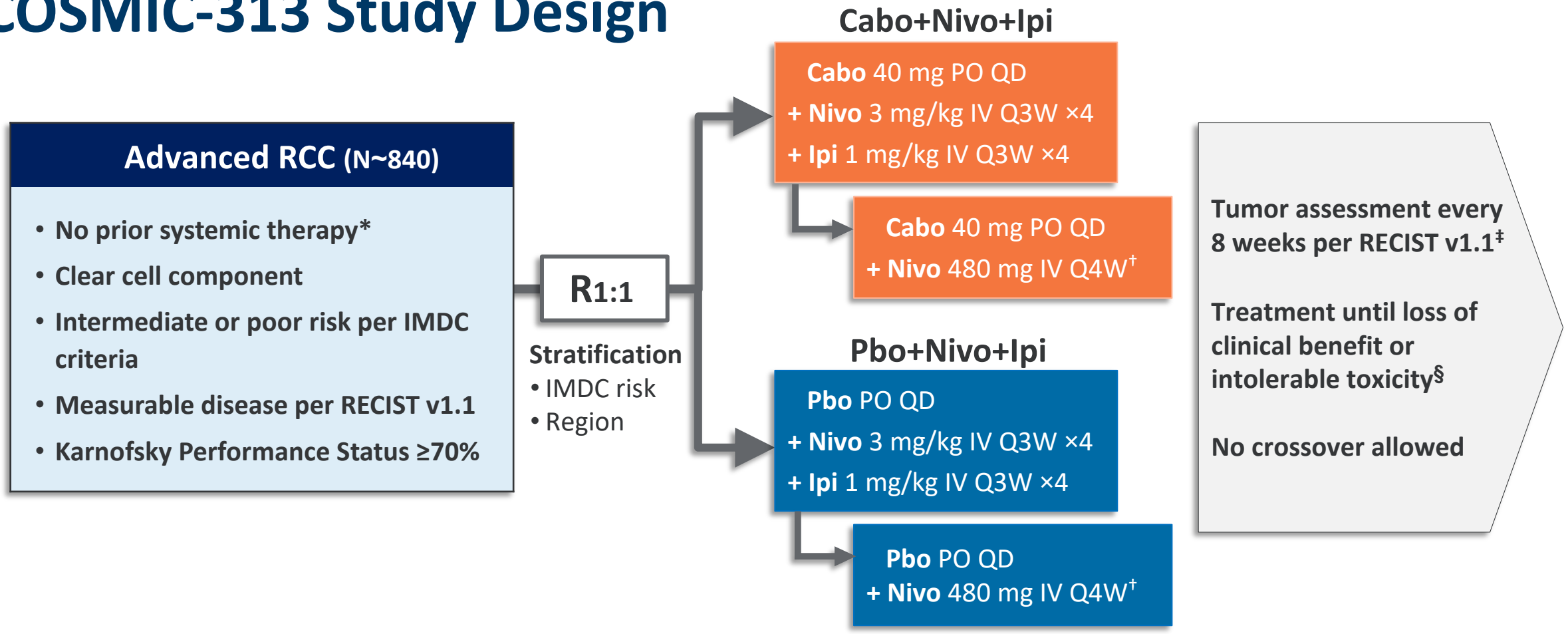
What about triple therapy?

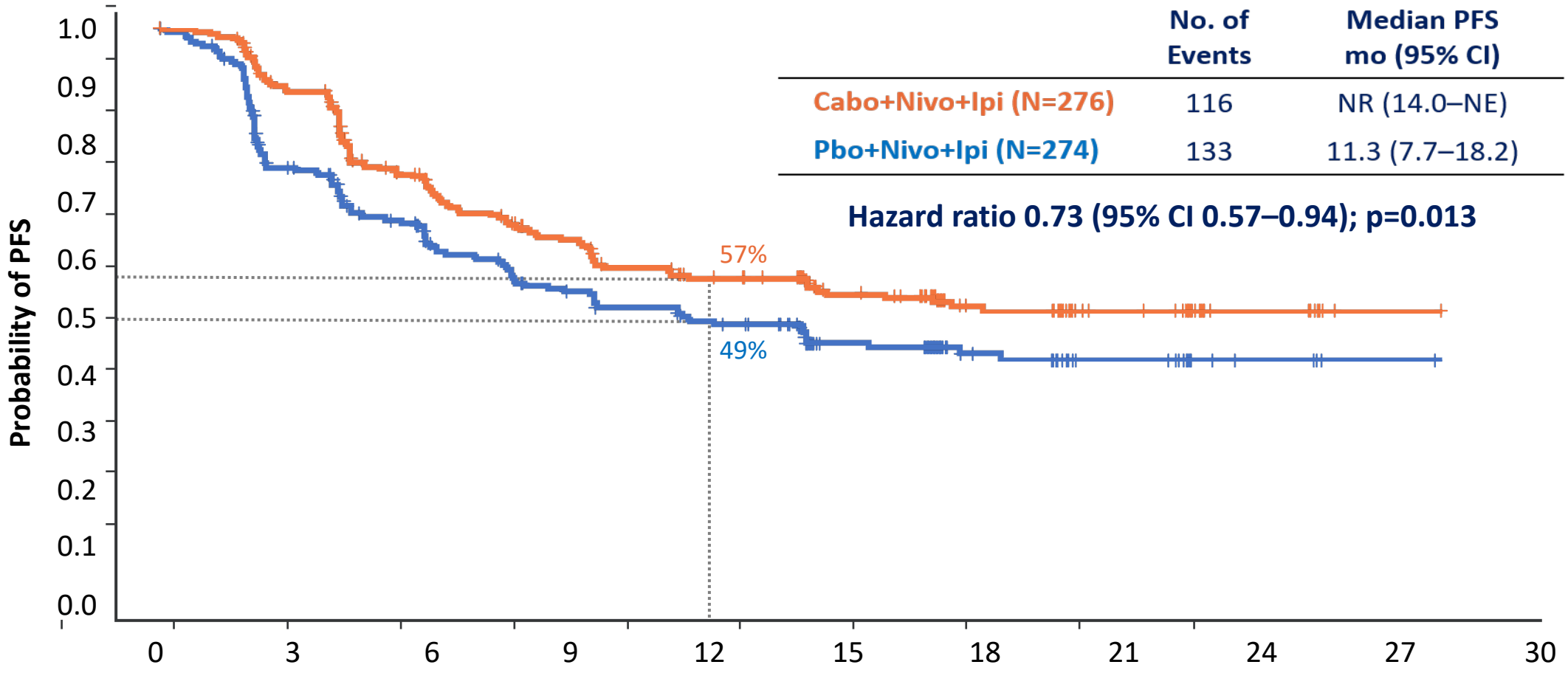
COSMIC-313 Study Design



*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.

Choueiri *et al*. ESMO 2022

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

Choueiri *et al*. ESMO 2022

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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

Choueiri *et al*. ESMO 2022

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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

Choueiri *et al*. ESMO 2022

My approach:

- Does patient need urgent reduction or can afford potential progression.
- What comorbidities, contraindication to either IO or TKI.
- What IMDC risk stratification.
- Patient long term goals of treatment.
- How much copay.
- Long acting vs. short acting TKI.
- No one size fits all.

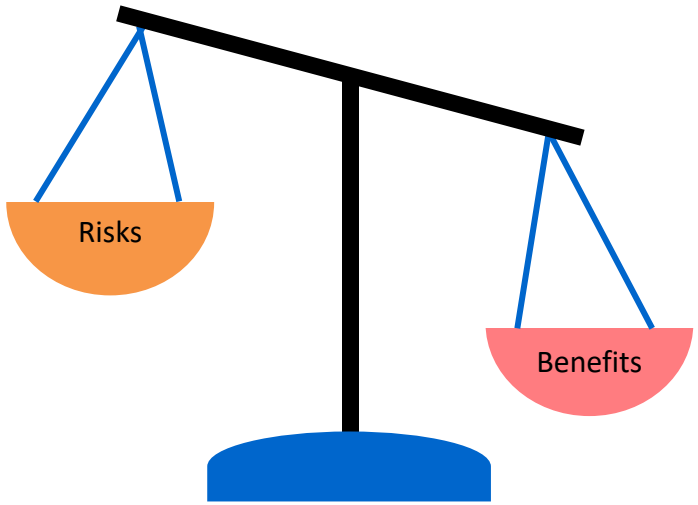
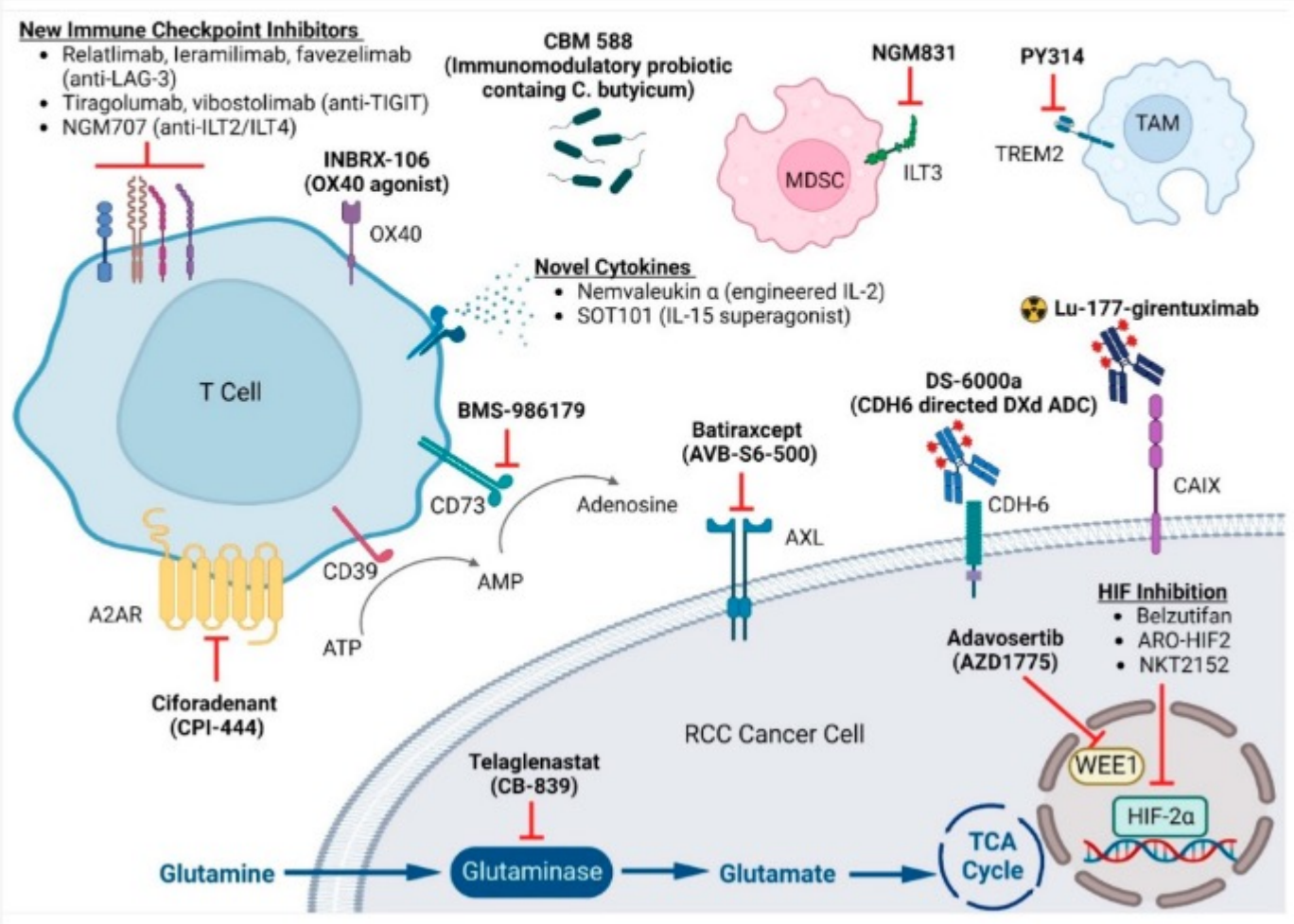


Figure 1. Emerging Targets in Clear Cell Renal Cell Carcinoma. This figure is created with BioRender.com. LAG-3: Lymphocyte-activation gene 3; TIGIT: T cell immunoreceptor with Ig and ITIM domains; ILT: Ig-like transcript; MDSC: Myeloid-derived suppressor cell; TAM: tumor-associated macrophage; A2AR: adenosine 2A receptors; ATP: adenosine triphosphate; AMP: adenosine monophosphate; CDH6: human cadherin 6; CAIX: carbonic anhydrase IX; TCA: tricarboxylic acid; HIF: hypoxia-inducible factor.



How about adjuvant therapy

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;
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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**

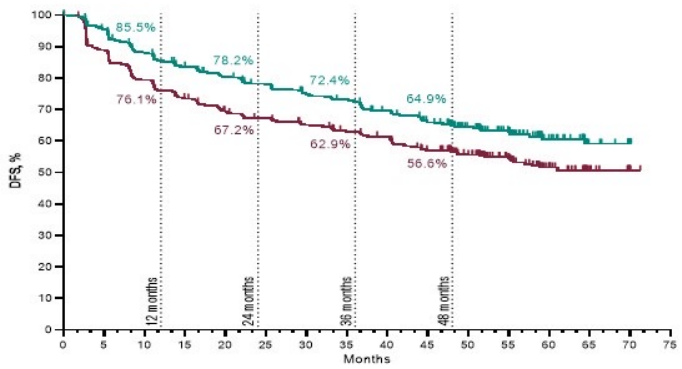
*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.
Powles T, et al. *Lancet Oncol*. 2022;23;1133-1144.; Choueiri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

KEYNOTE-564 DFS & OS benefit Not By Chance!

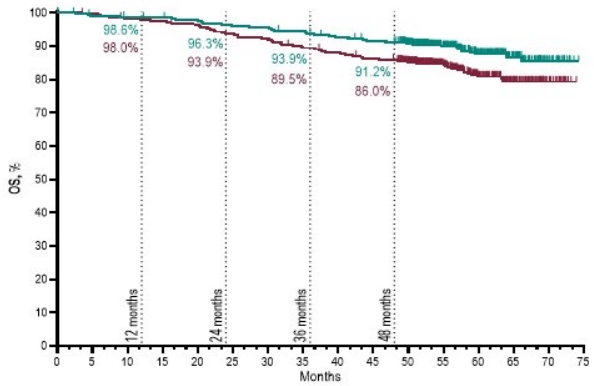
	June 2021	Sep 2022	Jan 2024
Analysis	1st	2nd	3rd
Median follow up, months	24.1	30	57.2
Disease free survival (HR, CI 95%), p-value	0.68 *P=0.0010*	0.63 *P<0.0001*	0.72 NE
DFS events	109 vs 151	114 vs 169	174 vs 224
Overall survival (HR, CI 95%)	0.54 *P=0.0164 (int)*	0.52 *P=0.0048 (int)*	0.62 ***P=0.002****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

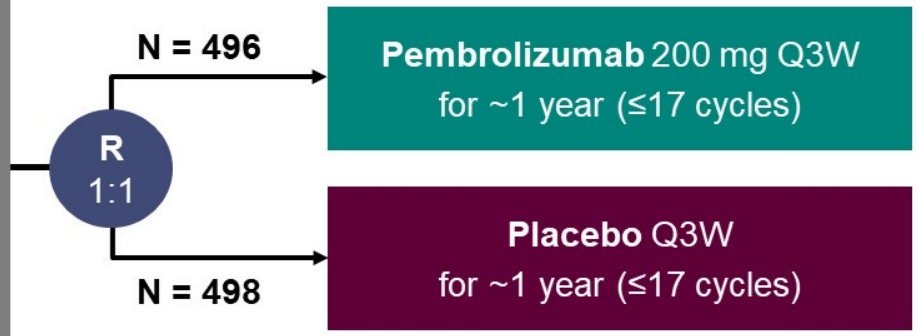
PRESENTED BY: Pedro C. Barata, MD MSc, FACP

@PBarataMD

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.

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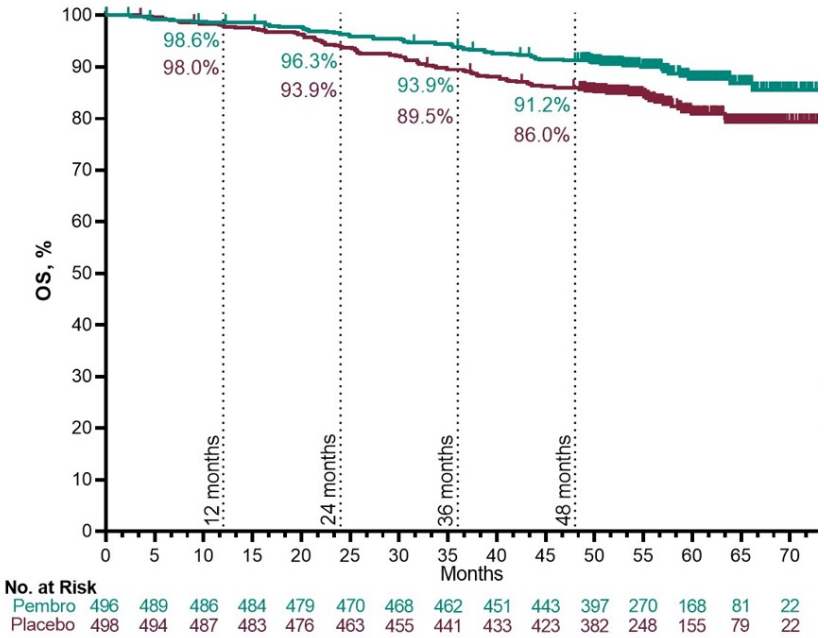
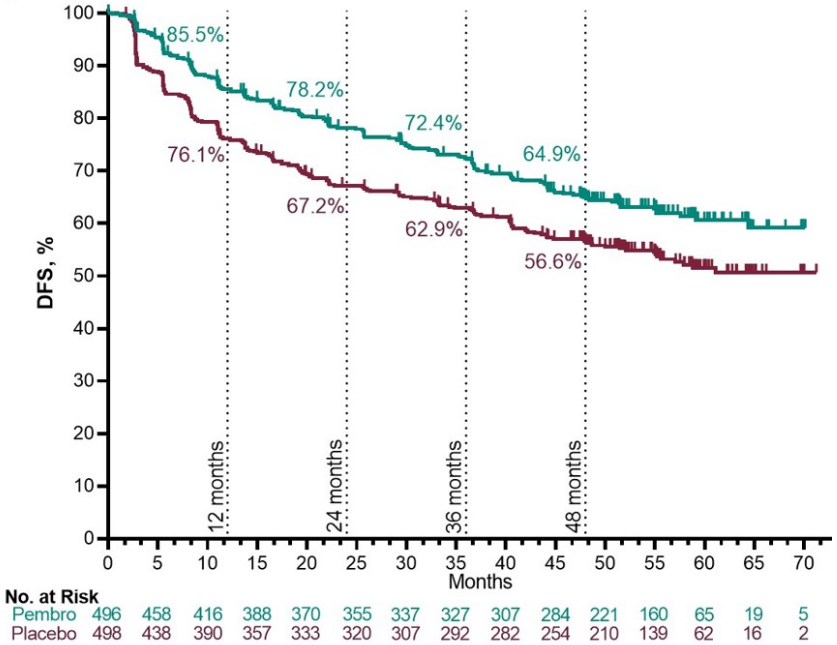
- OS



	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)

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@ZakhariaYousef

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 II G3, especially older with comorbidities.
- Higher risk III, sarcomatoid.
- Rarely do metastectomy in my practice.
- Not for Non- clear cell RCC.

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.
- No one size fits all.

@ZakhariaYousef

- Thank you

@ZakhariaYousef