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Presentaciones más destacadas en cáncer renal

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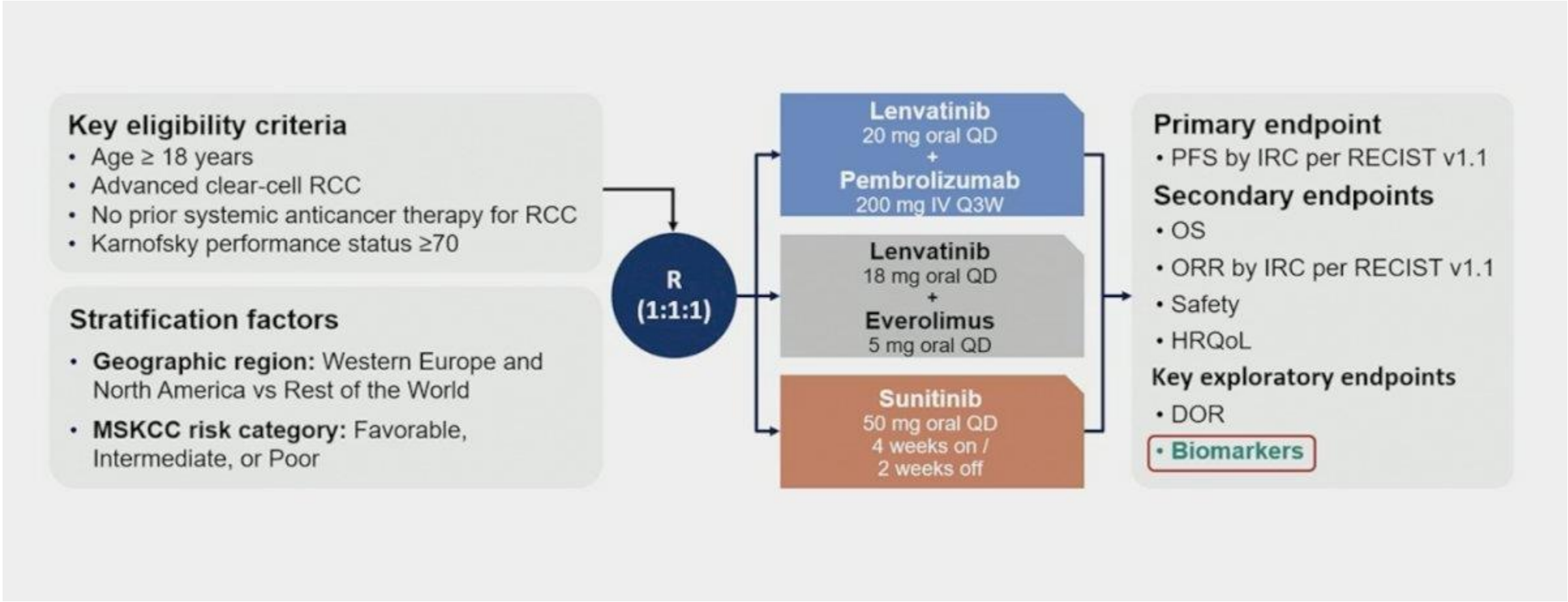
Hospital Universitario 12 de Octubre, Madrid

Temas a tratar

- Subestudios de fases 3
    - Biomarcadores de estudios pivotales
    - Partitioned Overall Survival CM9ER
    - Análisis final del JavelinRenal
    - KIM1
- RWE
    - IOIO vs IOTKI
    - 1L después de adyuvancia



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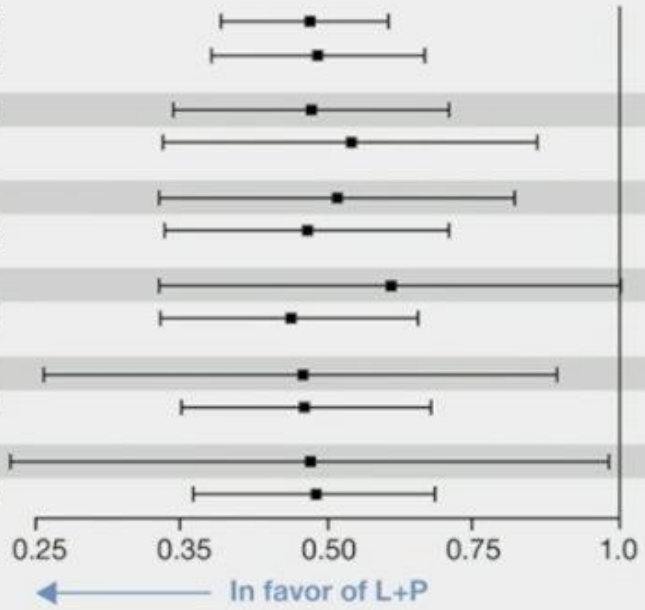
Progression-free survival was higher with lenvatinib + pembrolizumab vs sunitinib, regardless of the deleterious mutation status of BAP1, VHL, PBRM1, SETD2, and KDM5C, which are frequently mutated genes in RCC:

Subgroup		Patients L+P	Patients S	HR (95% CI) L+P vs S	Median (months) L+P	Median (months) S
Overall population		355	357	0.48 (0.39–0.58)	23.9	9.2
Gene alteration analysis set		186	194	0.49 (0.38–0.63)	25.3	9.2
VHL	Mut	122	127	0.48 (0.35–0.67)	27.6	7.5
	WT	64	67	0.53 (0.34–0.82)	20.3	9.2
PBRM1	Mut	65	64	0.51 (0.34–0.78)	18.6	7.5
	WT	121	130	0.48 (0.34–0.67)	27.7	9.2
*SETD2**	Mut	41	43	0.58 (0.34–1.01)	25.9	9.5
	WT	145	151	0.46 (0.34–0.62)	24.3	7.5
*BAP1**	Mut	34	30	0.47 (0.26–0.86)	18.6	5.6
	WT	152	164	0.48 (0.35–0.64)	27.6	9.5
*KDM5C**	Mut	21	29	0.48 (0.24–0.98)	28.6	12.8
	WT	165	165	0.49 (0.37–0.65)	24.3	9.2



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Gene signature scores were not associated with PFS outcomes for the lenvatinib + pembrolizumab arm:

Signature type	Signature	L+P n=192	S n=196
		P-value*	
T-cell inflamed	GEP	0.36	0.95
Immuno-oncology	Monocytic myeloid-derived suppressor cells	0.86	0.84
	Granulocytic myeloid-derived suppressor cells	0.81	0.31
Angiogenesis	**Angiogenesis**	0.16	**< 0.1****
	Microvessel density	0.42	**< 0.1****
	Angio36	0.81	0.31
Pan-cancer	**Proliferation**	0.42	**< 0.1****
	MYC	0.19	**< 0.1****
	RAS	0.86	0.84
	WNT	0.81	0.31
	Stroma/Epithelial-mesenchymal transition/*TGFß*	0.81	0.43
	Glycolysis	0.68	0.19
	Hypoxia	0.42	0.31

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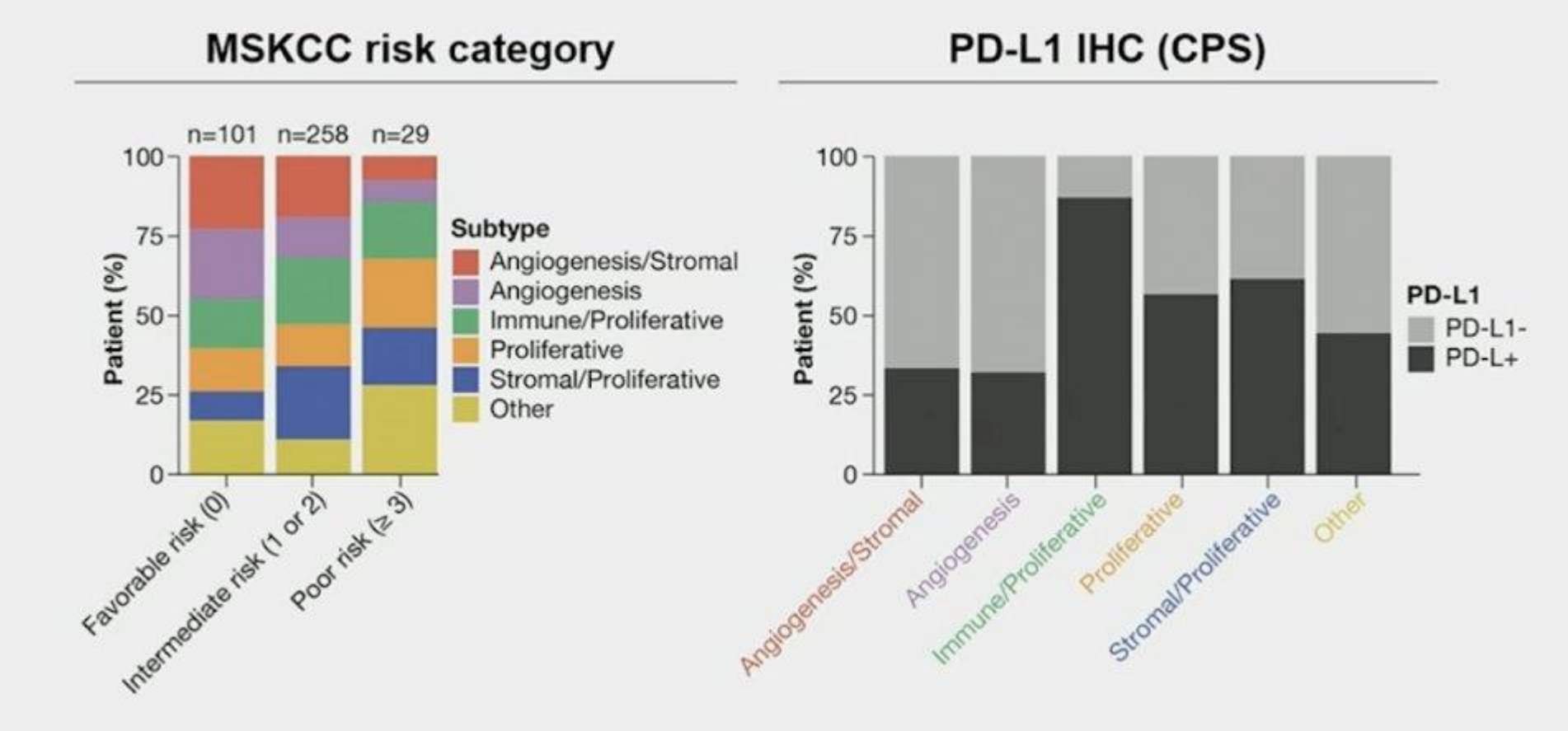

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Conclusions

- Lenvatinib + pembrolizumab showed clinical benefit over sunitinib in patients with advanced renal cell carcinoma regardless of biomarker subtypes
- The progression-free survival analysis of lenvatinib + pembrolizumab confirms the high level efficacy of the combination irrespective of PD-L1 CPS
- Lenvatinib + pembrolizumab showed longer progression-free survival and improved objective response rate versus sunitinib regardless of RCC driver gene mutation status or gene signature
- Lenvatinib + pembrolizumab demonstrated numerically higher tumor response and longer progression-free survival than sunitinib across all molecular subtypes

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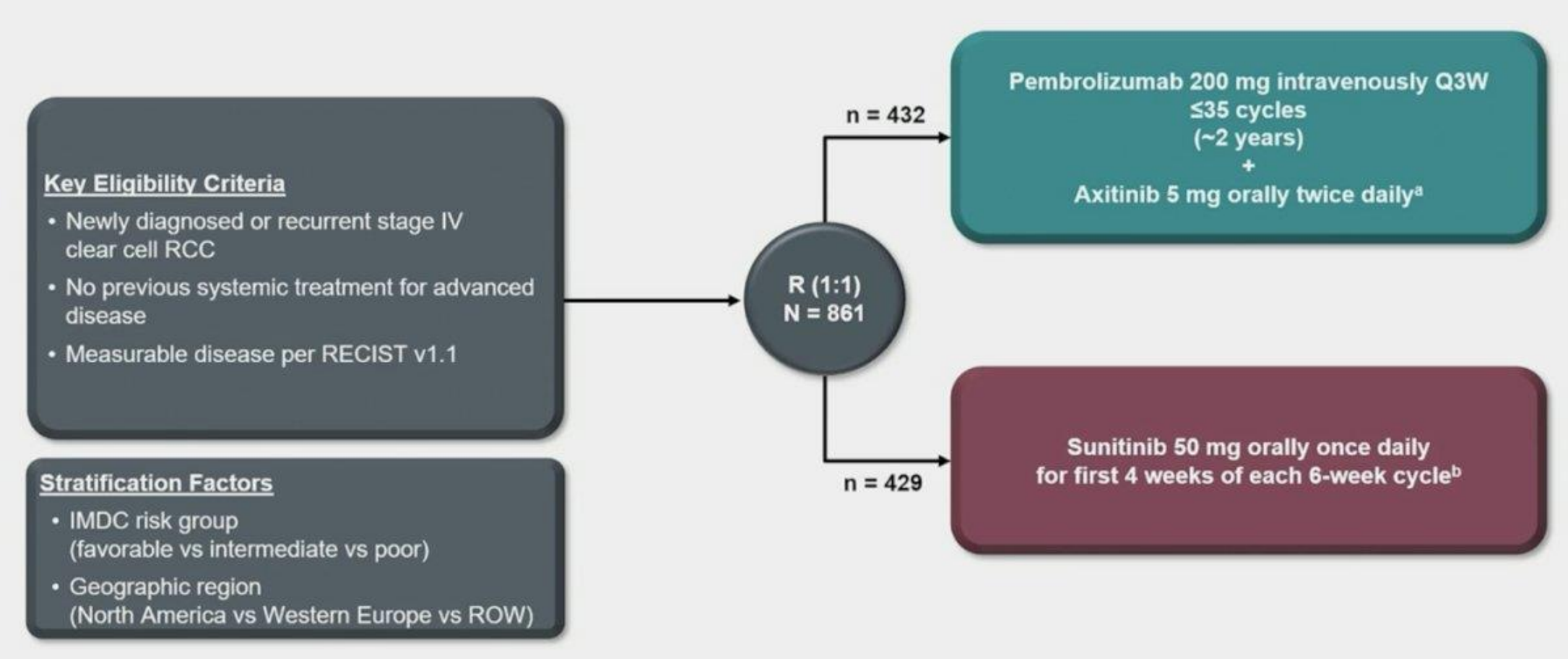
Biomarker Analysis of the Phase 3 KEYNOTE-426 Study of Pembrolizumab plus Axitinib Versus Sunitinib for Advanced Renal Cell Carcinoma



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RNA signatures: positive association with monocytic myeloid-derived suppressor cells was found for progression-free survival

	Pembrolizumab + axitinib n = 369			Sunitinib n = 361		
Signature	**ORR**	**PFS**	**OS**	**ORR**	**PFS**	**OS**
mMDSC	**0.058(+)**	**0.039(+)**	**0.057(+)**	NS	NS	NS
Hypoxia	NS	NS	NS	**0.071(+)**	NS	**0.094(+)**
MYC	NS	NS	NS	NS	**0.017(-)**	**<0.001(-)**
Proliferation	NS	NS	NS	NS	NS	**<0.001(-)**
Molecular subtype[a]	NS	NS	NS	NS	NS	**0.010**

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Conclusions

- In this exploratory analysis of KEYNOTE-426, higher T-cell inflamed gene expression profile values were positively associated with clinical outcomes for pembrolizumab + axitinib, and angiogenesis had a positive association with clinical outcomes for sunitinib
- PD-L1 CPS was not associated with clinical outcomes for pembrolizumab + axitinib
- Pembrolizumab + axitinib showed improved objective response rate versus sunitinib across molecular subtypes
  - Within the pembrolizumab + axitinib arm, the objective response rate was highest in the immune/proliferative subtype, and within the sunitinib arm, the objective response rate was highest in the angiogenic subtype
- Additional correlative data and further prospective clinical investigation are needed for biomarker-directed treatment

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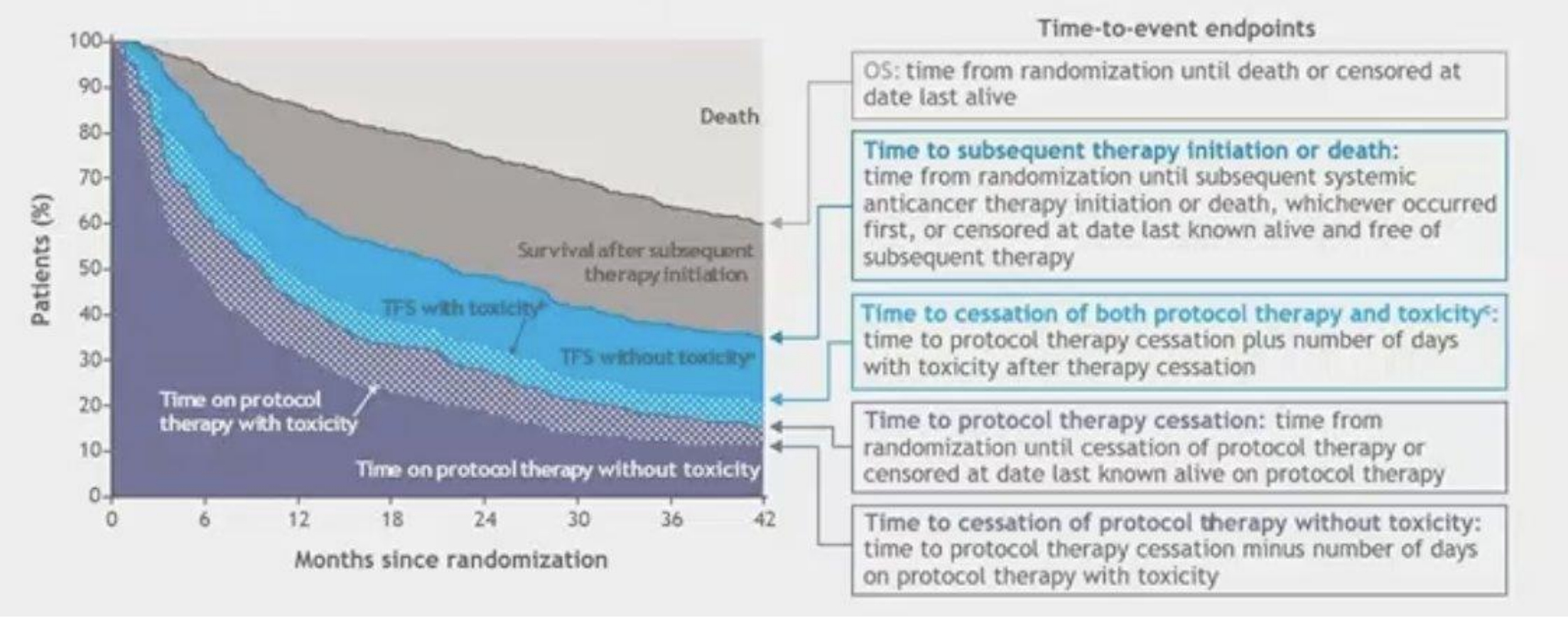
Partitioned Overall Survival: Comprehensive Analysis of Survival States over 4 Years in CheckMate 9ER



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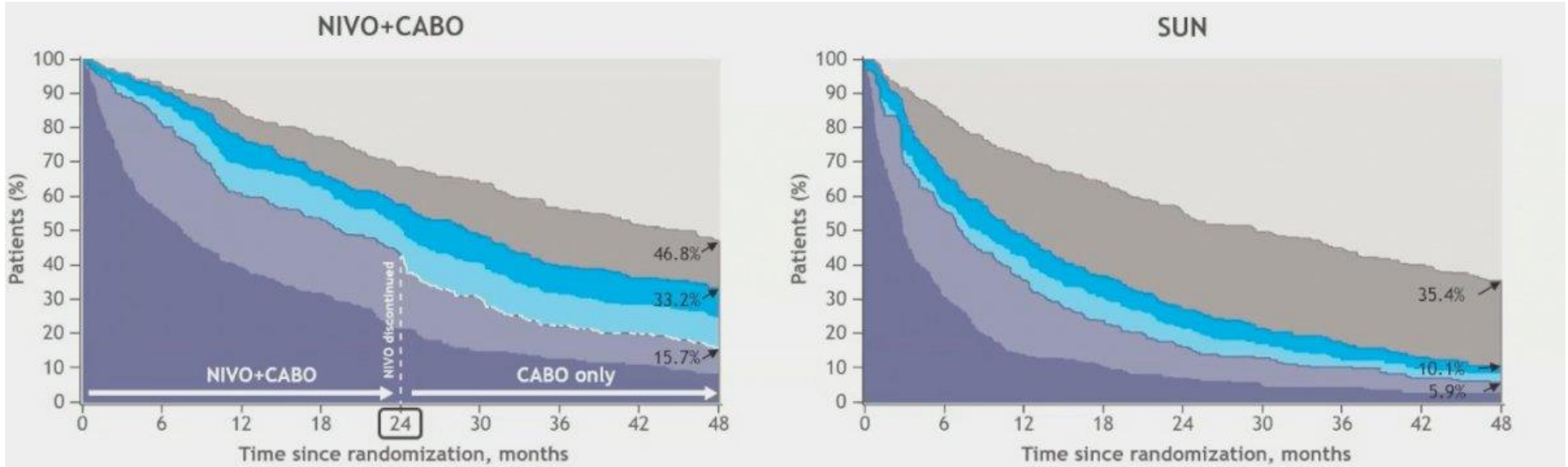
The mean TFS (95% CI) was 2.5 (0.8–4.3) months longer



Survival state 48-month mean time, months	IMDC intermediate/poor risk		
	NIVO+CABO (n = 249)	SUN (n = 256)	Difference (95% CI) NIVO+CABO vs SUN
OS	34.2	28.5	-
Survival after subsequent treatment initiation	5.1	11.3	-6.2 (-8.5 to -4.0)
TFS	7.2	4.7	2.5 (0.8-4.3)
Without grade ≥ 2 TRAE	3.2	2.5	0.6 (-0.6 to 1.9)
With grade ≥ 2 TRAE	4.1	2.1	1.9 (0.6-3.2)
Time on protocol treatment	21.8	12.5	9.4 (6.7-12.0)
With grade ≥ 2 TRAE	8.0	5.8	2.3 (0.6-4.0)
Without grade ≥ 2 TRAE	13.8	6.7	7.1 (4.8-9.3)

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Conclusions

- At four years post-randomization in the CheckMate 9ER study, there was a longer OS in patients assigned to Nivolumab + Cabozantinib compared to Sunitinib (49.2% vs. 40.2%).
- The longer OS achieved with Nivolumab + Cabozantinib was accompanied by **1.5 times longer mean time surviving treatment-free before second-line therapy compared to Sunitinib** (difference of 2.4 months).
- The mean TFS difference was similarly longer for Nivolumab + Cabozantinib versus Sunitinib across most subgroups analyzed.
- TFS was more frequently observed after patients discontinued therapy for TRAEs, toxicity, or other reasons such as completion of therapy per protocol.
- This research highlights the importance of monitoring patient status after treatment discontinuation to understand the patient survival experience.

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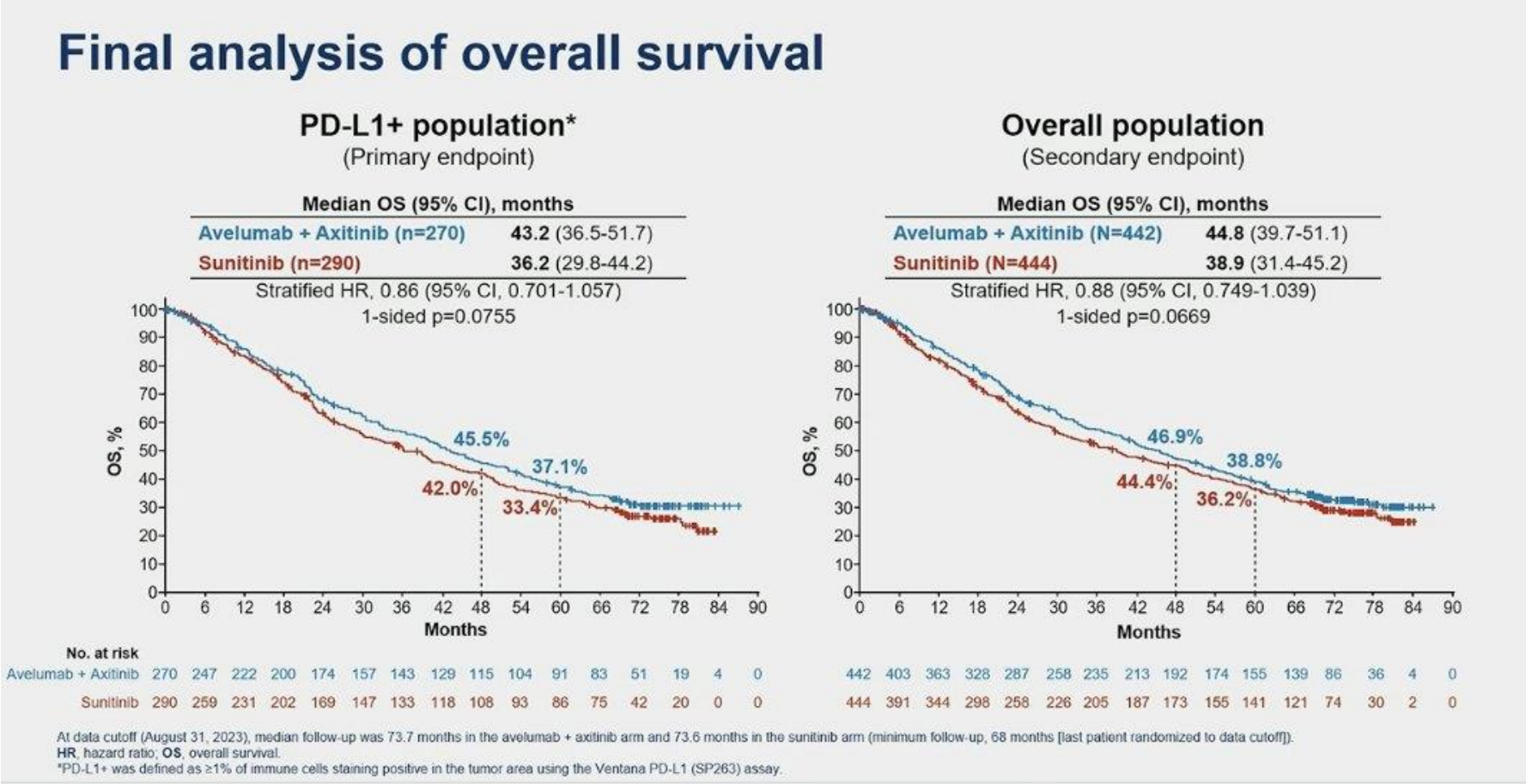
Avelumab + Axitinib vs Sunitinib in Patients with Advanced Renal Cell Carcinoma: Final Overall Survival Analysis from the JAVELIN Renal 101 Phase 3 Trial



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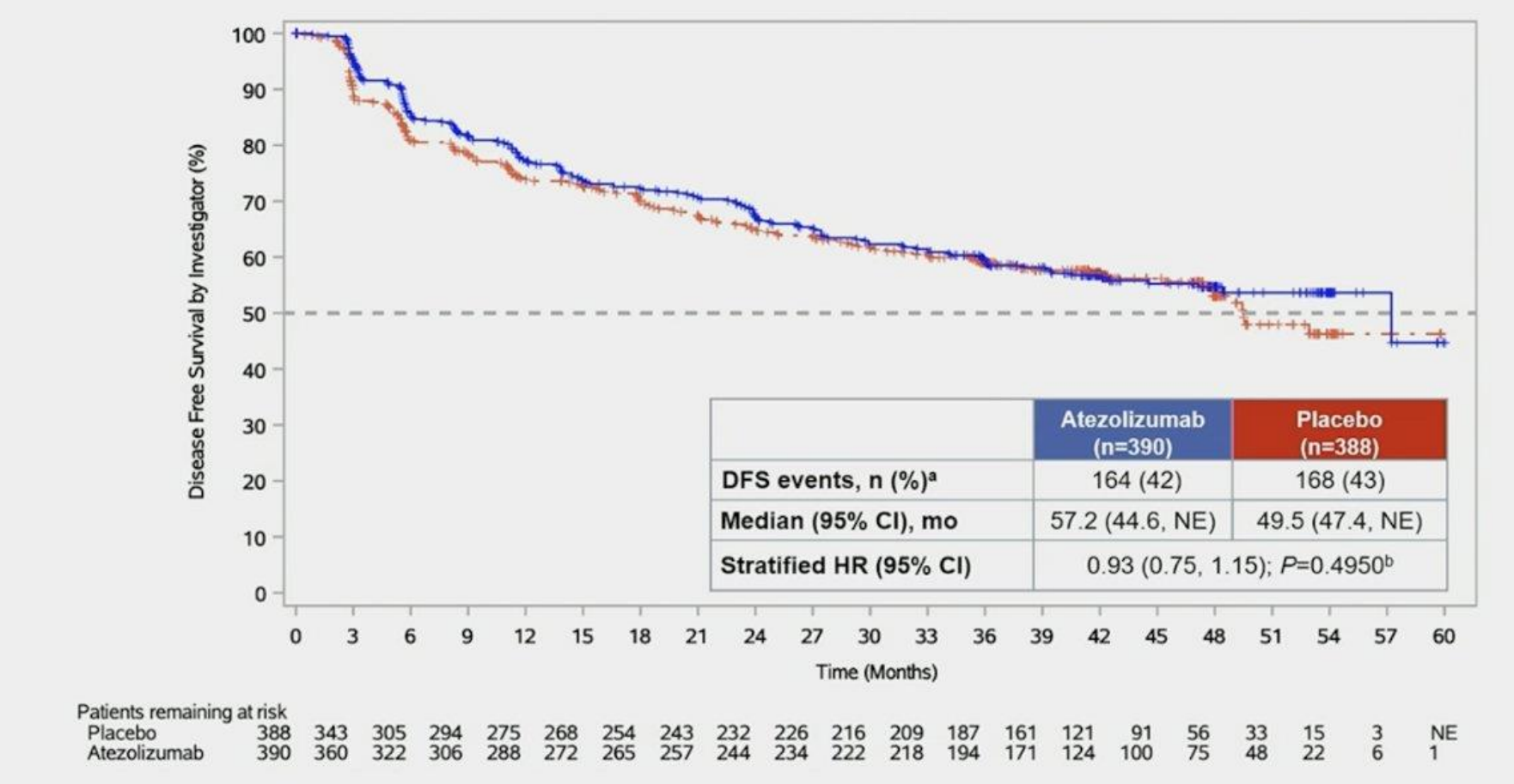
Circulating kidney injury molecule-1 biomarker analysis in IMmotion010



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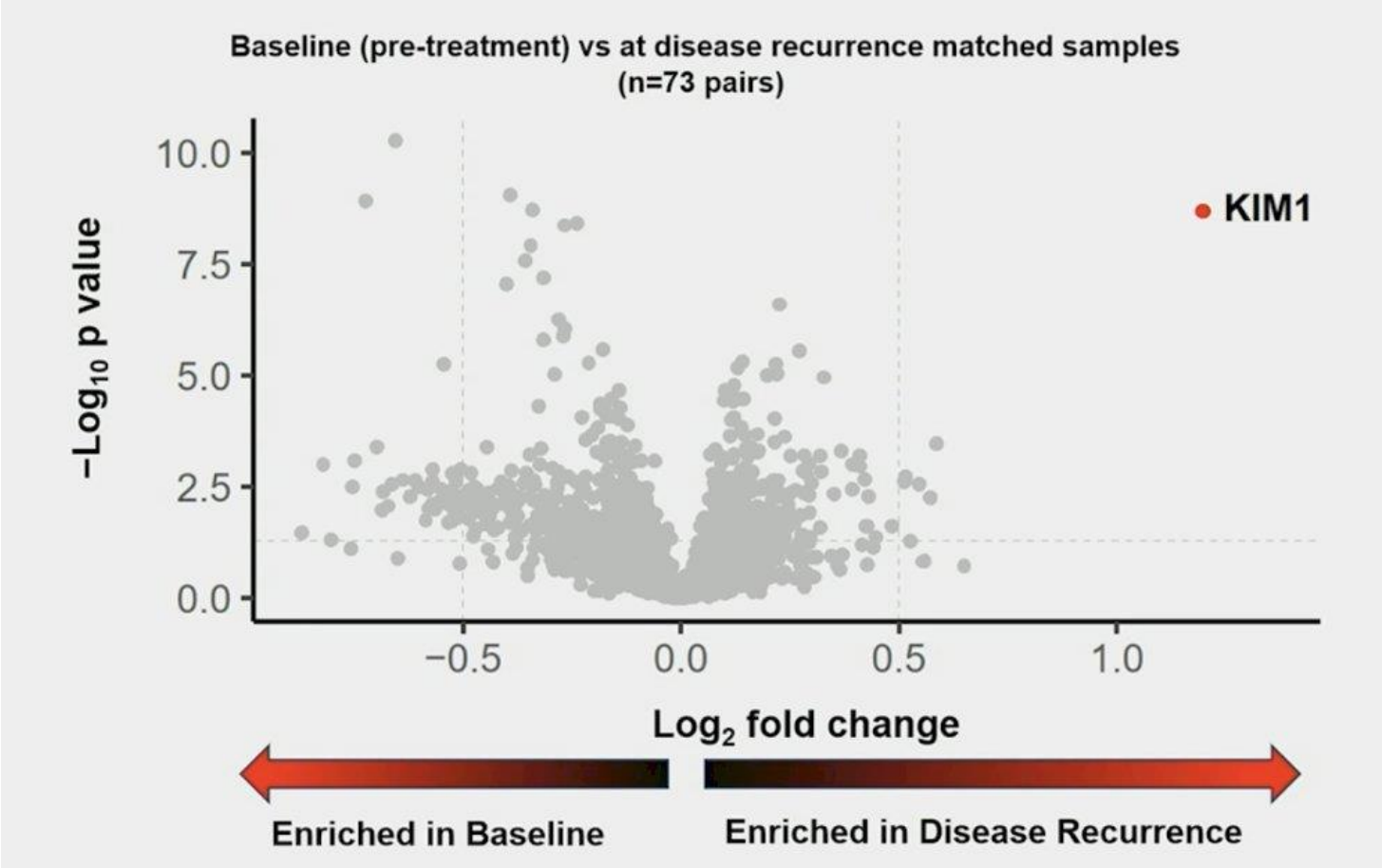
Retrospective proteomics analysis



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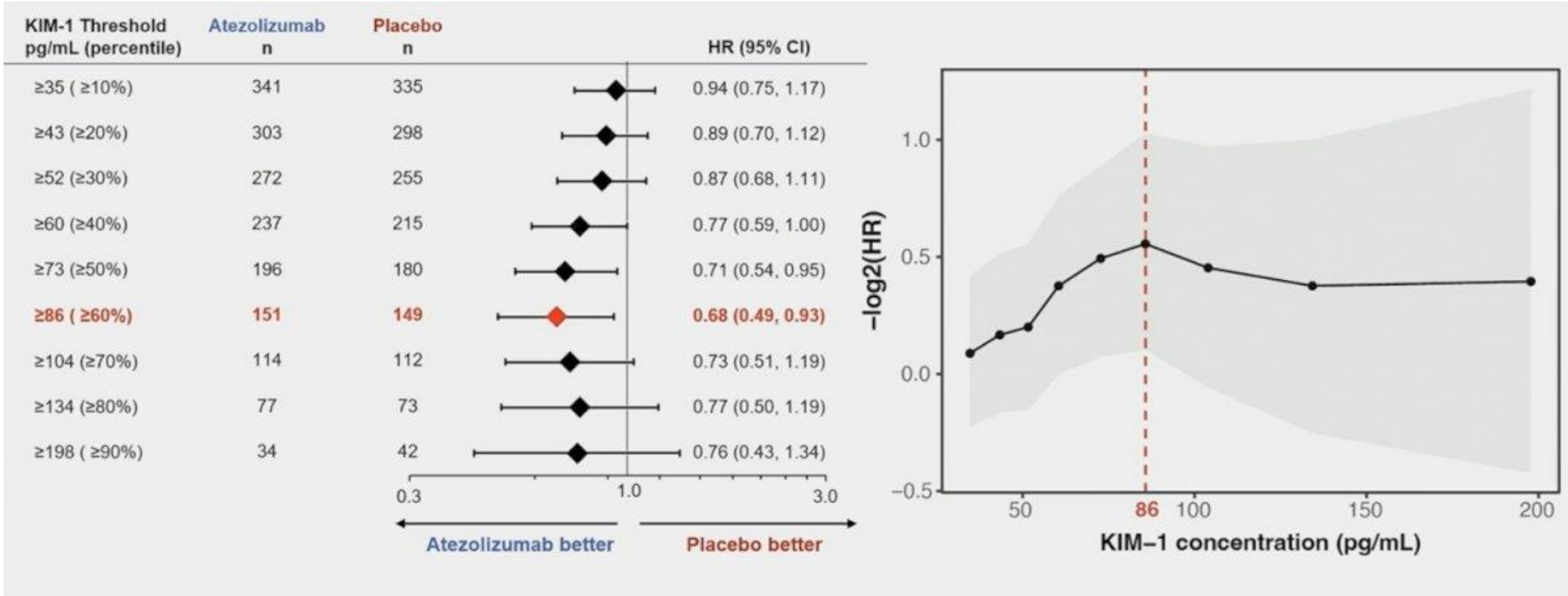

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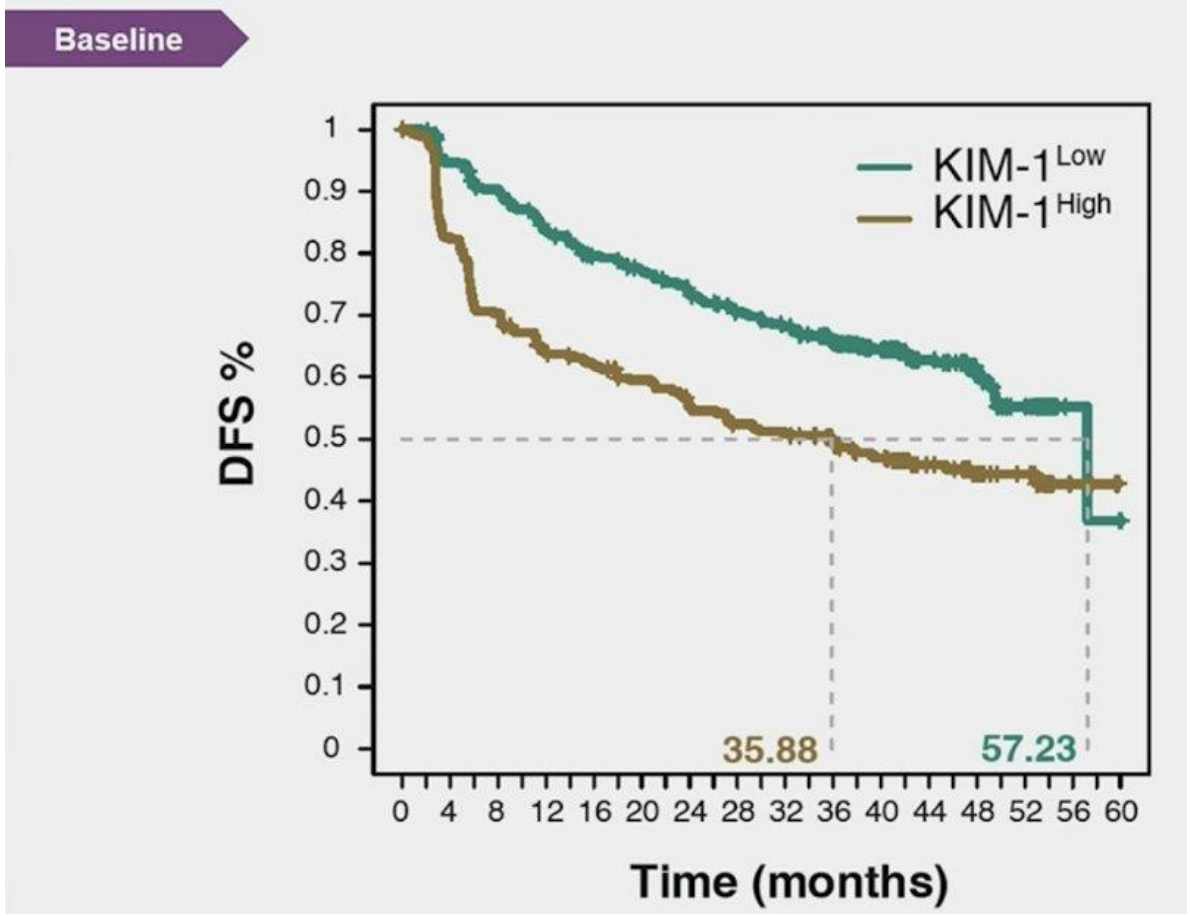
Kidney injury molecule-1–high status was associated with reduced disease-free survival

Patients with kidney injury molecule-1 high had better disease-free survival with atezolizumab versus placebo (HR 1.75, 95% CI 1.40-2.17):



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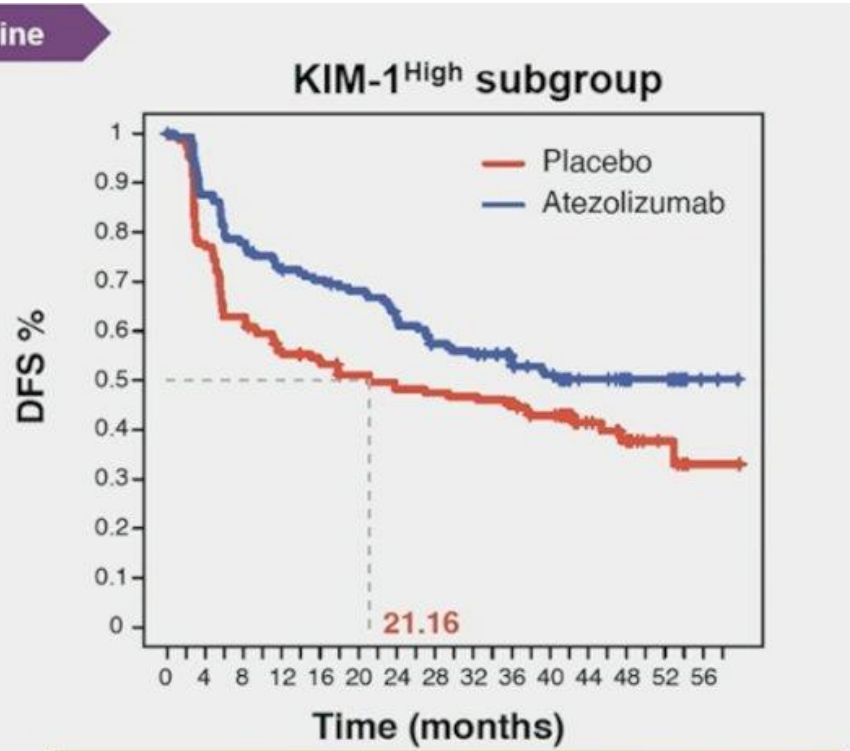
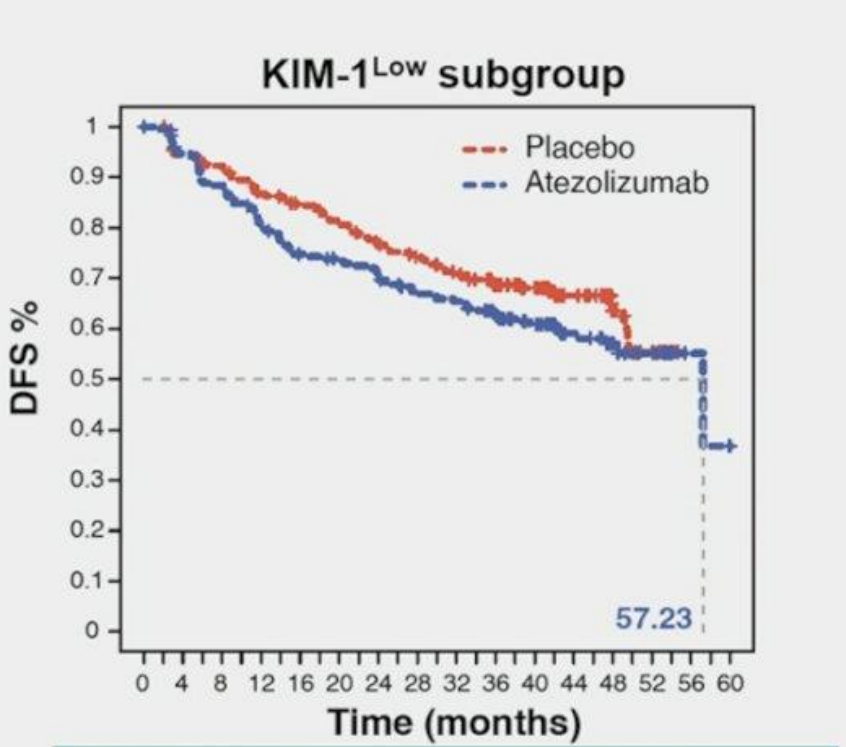
Atezolizumab improved disease free survival versus placebo in the baseline kidney injury molecule-1 high subgroup (HR 0.72, 95% CI 0.52-0.99)

Baseline



	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	



	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

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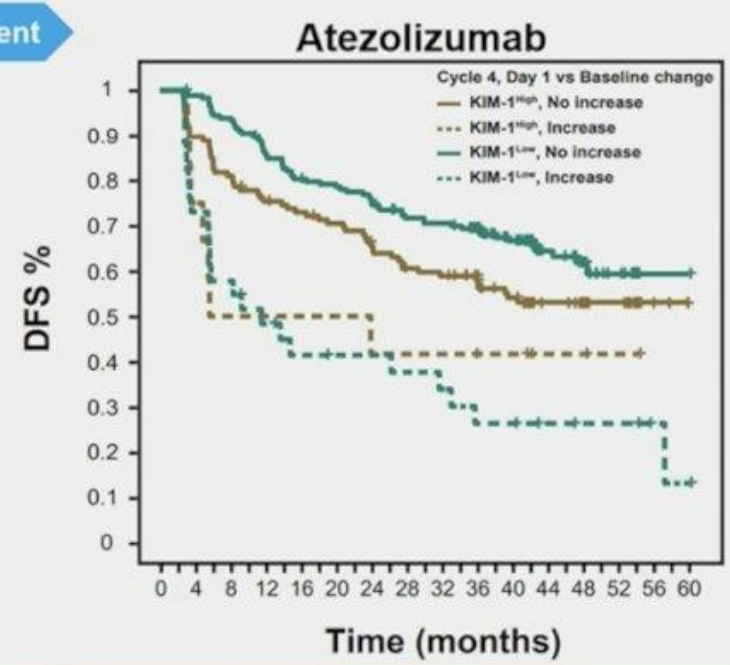
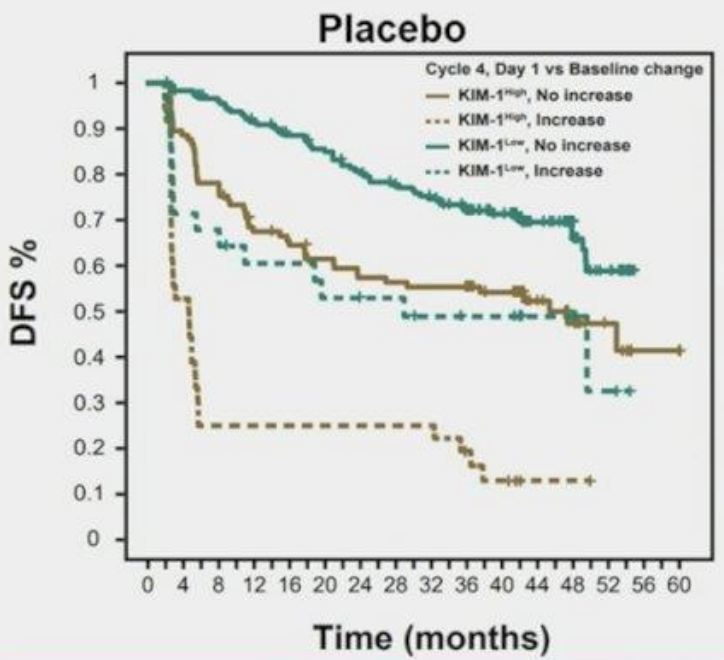
A ≥30% kidney injury molecule-1 increase was associated with worse disease-free survival

On Treatment



Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	12	14.8	1.68 (0.77, 3.69)
	No increase	126	NE	
KIM-1^{Low}	Increase[a]	34	11.5	3.56 (2.21, 5.75)
	No increase	179	NE	



Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	36	4.8	3.53 (2.24, 5.58)
	No increase	105	45.4	
KIM-1^{Low}	Increase[a]	28	29.0	2.51 (1.42, 4.44)
	No increase	179	NE	

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Conclusions

- **In IMmotion010, high baseline serum kidney injury molecule-1 levels were associated with poorer prognosis but improved clinical outcomes with atezolizumab versus placebo**
- **Increased post-treatment kidney injury molecule-1 was associated with worse disease-free survival**
- Additional validation studies are warranted to confirm the utility of circulating serum kidney injury molecule-1 in adjuvant RCC as a non-invasive biomarker for:
  - Identification of minimal residual disease
  - Predicting outcomes to checkpoint inhibitor treatment
  - Longitudinal monitoring for disease recurrence

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Comparative Effectiveness of First-Line Ipilimumab plus Nivolumab Versus Immune Checkpoint Inhibitors + Tyrosine Kinase Inhibitors

Baseline Characteristics		Ipi + Nivo (n = 779)	ICI + TKI (n = 659)	SMD
Age, mean (SD)		65.03 (10.61)	66.77 (10.32)	0.166
Race/Ethnicity, n (%)				
	White Non-Hispanic	490 (70.4)	426 (72.3)	0.072
	Black Non-Hispanic	45 (6.5)	30 (5.1)	
	Hispanic/Latino	66 (9.5)	50 (8.5)	
	Asian Non-Hispanic	16 (2.3)	13 (2.2)	
	Other	79 (11.4)	70 (11.9)	
Smoking Status, n (%)				
	No history of smoking	333 (42.9)	277 (42.1)	0.015
	History of smoking	444 (57.1)	381 (57.9)	
Practice Type, n (%)				
	Community	635 (81.5)	569 (86.3)	0.132
	Academic	144 (18.5)	90 (13.7)	
Insurance, n (%)				
	Commercial Health Plan	500 (72.8)	458 (76.3)	0.092
	Medicare/Other Government Program	103 (15.0)	81 (13.5)	
	Medicaid	18 (2.6)	16 (2.7)	
	Other	66 (9.6)	45 (7.5)	
Prior Nephrectomy				
	Yes	398 (51.2)	334 (50.8)	0.008
	No	380 (48.8)	324 (49.2)	
First-Line Start Year, mean		2019.96	2020.79	0.758

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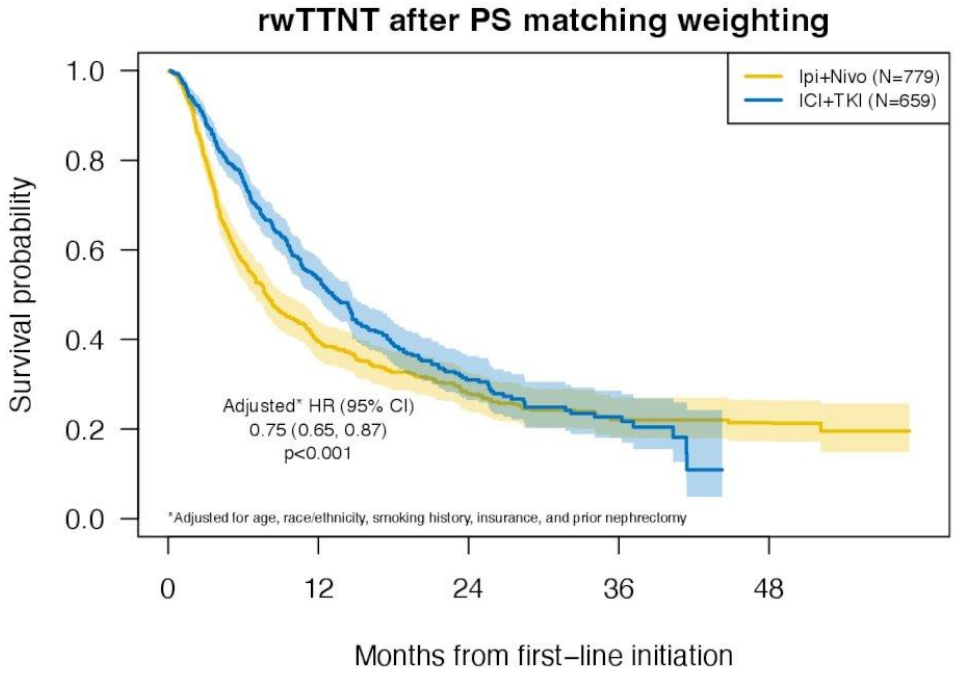
The median time-to-next therapy was 9.1 months for ipilimumab + nivolumab versus 15 months for IO + TKIs (HR: 1.29, 95% CI: 1.09 – 1.51, p=0.002).

Figure 1. Kaplan Meier Estimates of real-world time to next treatment (rwTTNT) from first-line therapy after propensity score matching weighting.



The number at risk (%)

Ipi+Nivo	531 (100)	148 (28)	59 (11)	21 (4)	1 (0)
ICI+TKI	535 (100)	203 (38)	64 (12)	23 (4)	0 (0)

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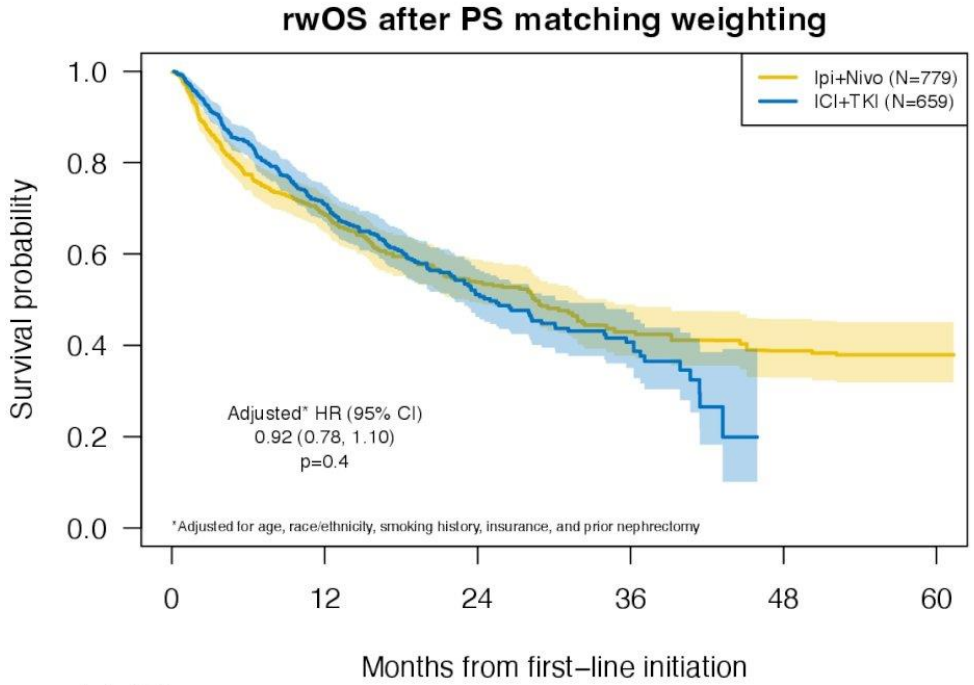
After propensity score matching, no significant difference in overall survival was noted between both groups (HR: 1.01)

Figure 2. Kaplan Meier Estimates of real-world overall survival (rwOS) from first-line therapy after propensity score matching weighting.



The number at risk (%)

Ipi+Nivo	531 (100)	253 (48)	109 (21)	37 (7)	4 (1)	0 (0)
ICI+TKI	535 (100)	270 (50)	109 (20)	44 (8)	0 (0)	0 (0)

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Comparison of TKI and CPI Strategies as First-Line Treatment of Patients with Advanced Renal Cell Carcinoma: Real-World Outcome Data from the German Research Platform CARAT

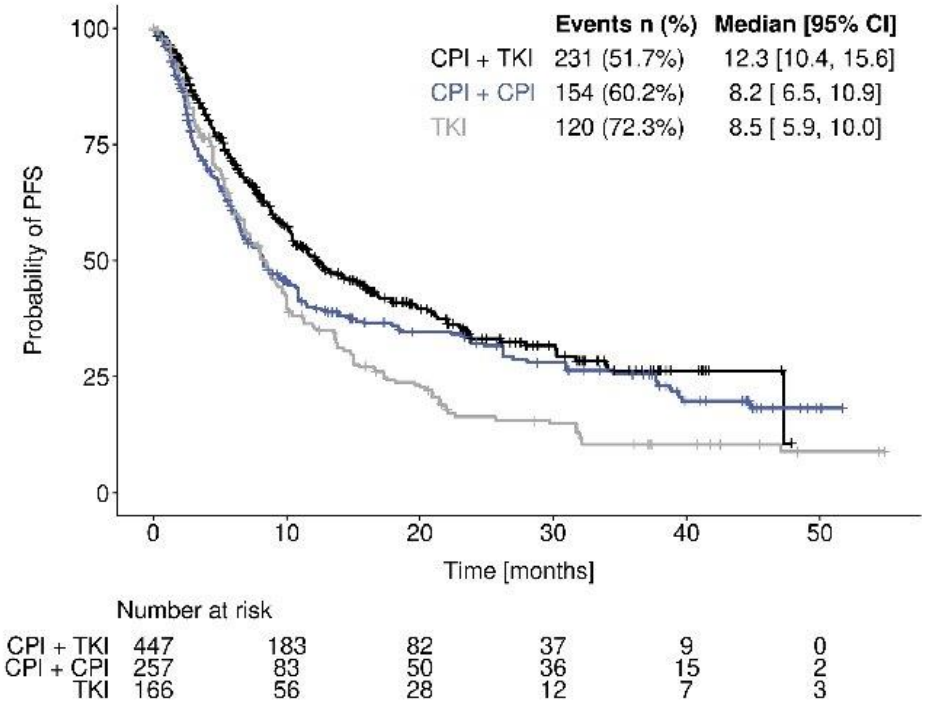
Table 1: Baseline characteristics (unadjusted, before IPTW)

Characteristic at start of first-line treatment	CPI+TKI n= 447	CPI+CPI n= 257	TKI n= 166	Other n= 66	Total n= 936
Age [y], mean (±StD)	68.1 (±10.30)	65.4 (±10.88)	72.6 (±10.73)	70.5 (±11.12)	68.3 (±10.86)
Sex					
Female	151 (33.8%)	84 (32.7%)	59 (35.5%)	19 (28.8%)	313 (33.4%)
Male	296 (66.2%)	173 (67.3%)	107 (64.5%)	47 (71.2%)	623 (66.9%)
Any comorbidity					
Yes	392 (87.7%)	220 (85.6%)	157 (94.6%)	60 (90.9%)	829 (88.6%)
No	55 (12.3%)	37 (14.4%)	9 (5.4%)	6 (9.1%)	107 (11.4%)
Histology					
Clear cell	351 (78.5%)	195 (75.9%)	127 (76.5%)	41 (62.1%)	714 (76.3%)
Non-clear cell	95 (21.3%)	62 (24.1%)	39 (23.5%)	25 (37.9%)	221 (23.6%)
Missing	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Number of metastatic sites					
0	29 (6.5%)	12 (4.7%)	11 (6.6%)	11 (16.7%)	63 (6.7%)
1	155 (34.7%)	86 (33.5%)	56 (33.7%)	22 (33.3%)	319 (34.1%)
≥2	263 (58.8%)	159 (61.9%)	99 (59.6%)	33 (50.0%)	554 (59.2%)
Keine n (%)	9 (10%)	9 (25%)	18 (14%)	9 (10%)	9 (25%)
Selected metastatic locations [b]					
Liver	70 (15.7%)	47 (18.3%)	24 (14.5%)	9 (13.6%)	150 (16.0%)
Lung	256 (57.3%)	173 (67.3%)	104 (62.7%)	37 (56.1%)	570 (60.9%)
Bones	134 (30.0%)	81 (31.5%)	52 (31.3%)	12 (18.2%)	279 (29.8%)
Brain	29 (6.5%)	10 (3.9%)	6 (3.6%)	5 (7.6%)	50 (5.3%)
Pancreas	26 (5.8%)	15 (5.8%)	16 (9.6%)	3 (4.5%)	60 (6.4%)
Clinical IMDC					
Favourable risk	77 (17.2%)	24 (9.3%)	43 (25.9%)	7 (10.6%)	151 (16.1%)
Intermediate risk	225 (50.3%)	123 (47.9%)	65 (39.2%)	27 (40.9%)	440 (47.0%)
Poor risk	95 (21.3%)	85 (33.1%)	29 (17.5%)	19 (28.8%)	228 (24.4%)
Missing	50 (11.2%)	25 (9.7%)	29 (17.5%)	13 (19.7%)	117 (12.5%)

a Charlson comorbidity index (CCI) according to Quan et al., 2011.
b multiple answers possible;
Abbreviations: ca, carcinoma; CCI, Charlson comorbidity index; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

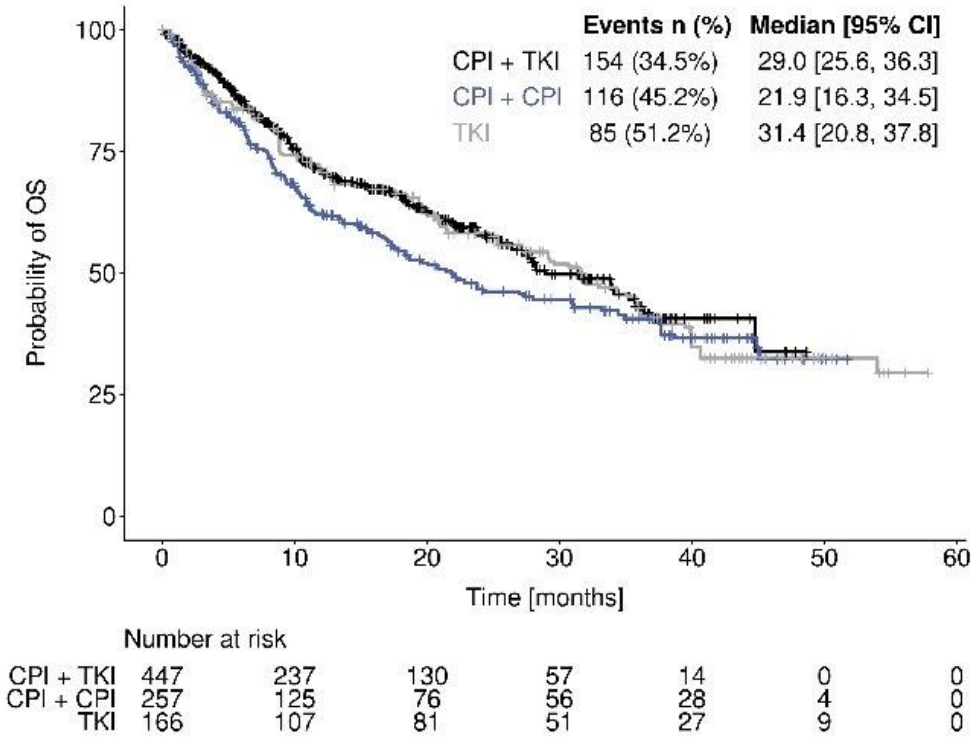
The inverse probability treatment weighting-adjusted median progression free survivals were: TKI + CPI: 12.3 months, CPI + CPI: 9.2 months, TKI: 8.5 months

Figure 3: Progression-free survival (adjusted, after IPTW)



The inverse probability treatment weighting-adjusted median overall survivals were: TKI + CPI: 29 months, CPI + CPI: 21.9 months, TKI: 31.4 months

Figure 4: Overall survival (adjusted, after IPTW)



Conclusions

- **no statistically significant differences in progression-free and overall survivals of first line CPI + CPI compared to CPI + TKI when adjusted for a wide range of potential confounding variables.**
- **However, there is a trend towards a better survival with first line CPI + TKIm compared to CPI + CPI.**
- Differences in the choice of first line TKI and subsequent treatment might explain differences in median progression free and overall survival in the present analysis, compared to recently published phase three trials.

First-Line Systemic Therapy Following Adjuvant Immunotherapy in Renal Cell Carcinoma (RCC): An International Multi-Center Study

Baseline characteristics

	Total (N=76)
	N (%)
Age at 1L initiation: Median (Q1-Q3)	58 (50-67)
Sex	
Females	16 (21%)
Males	60 (79%)
Race	
Others	8 (11%)
White	68 (89%)
Region	
United States	28 (36.8%)
Europe	30 (39.5%)
Canada	9 (11.8%)
Australia	6 (7.9%)
Others	3 (3.9%)
Disease risk category	
M0, intermediate-to-high risk	51 (67%)
M0, high risk	12 (16%)
M1, NED	13 (17%)
Histology	
Clear cell	63 (83%)
Non–clear cell	13 (17%)
Sarcomatoid features	
No	64 (84%)
Yes	12 (16%)

Adjuvant Immunotherapy	N (%)
Pembrolizumab	37 (39%)
Atezolizumab	28 (30%)
Nivolumab + Ipilimumab	15 (16%)
Nivolumab	10 (11%)
Pembrolizumab + Belzutifan	3 (2.3%)
Durvalumab	1 (1.1%)
Recurrence timing from IO completion	
< 3 months	48 (63%)
> 3 months	28 (37%)
Sites of Recurrence **	
Lung	43 (57%)
Bone	11 (15%)
Liver	7 (9.2%)
CNS	3 (3.9%)
Others	53 (70%)
Treatment received at recurrence	
IO+IO	12 (13%)
IO+VEGF-TT	26 (28%)
VEGF-TT	37 (40%)
VEGF-TT+mTORi	1 (1.1%)

**Sum of sites of recurrence is > 94 as a subset of patients have multiple sites of metastases.

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Following disease recurrence, most patients received:

- **VEGF inhibitors: 46%**
- **IO + VEGF inhibitors: 30%**
- **IO monotherapy or IO + IO: 17%**
- **The objective response rates were comparable among these three subsequent treatment groups:**
- VEGF inhibitors: 35%
- IO + VEGF inhibitors: 45%
- IO monotherapy or IO + IO: 42%

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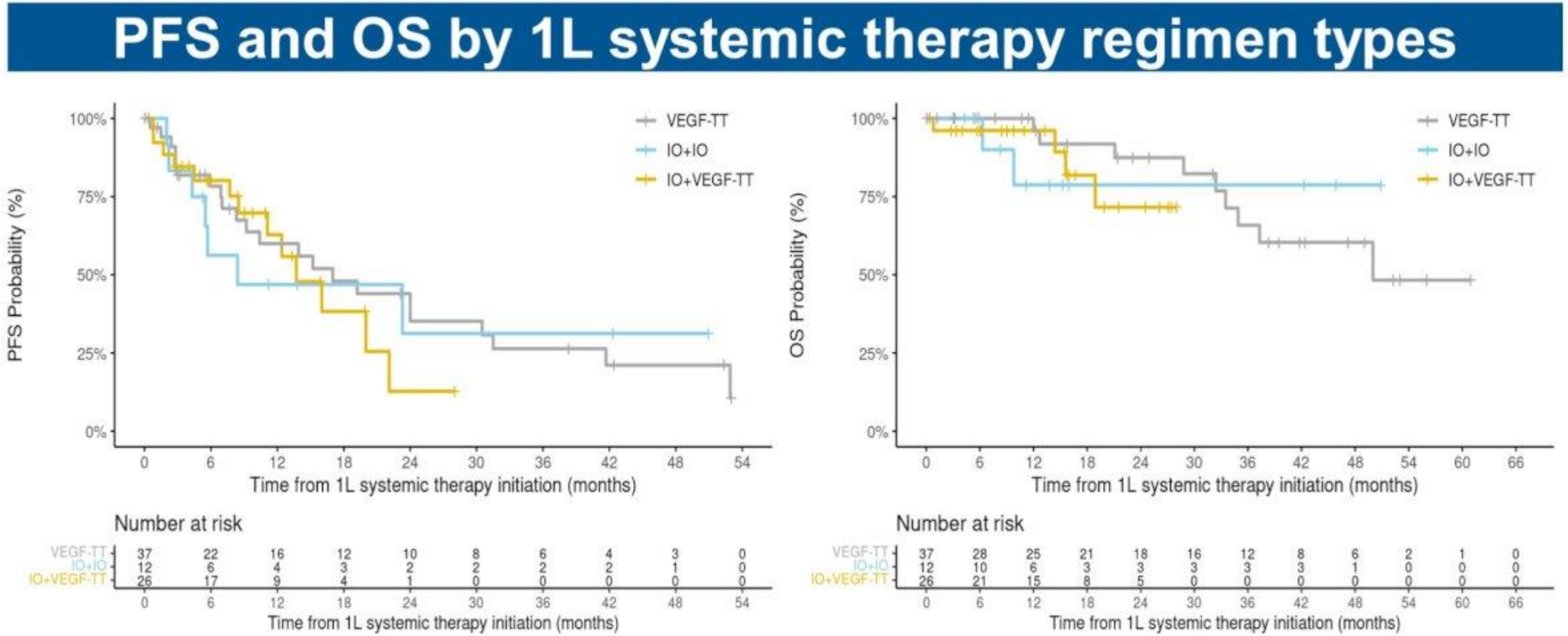
There were no significant differences in progression-free and overall survivals by 1st line systemic therapy regimen type administered:



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Changes in Treatment Patterns and Attrition Rates in Patients with Metastatic Clear Cell Renal Cell Carcinoma

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Table 1. Treatment landscape in mccRCC from first to third line before and after 4/16/2018

Rx	1L b2018 n (%)	1L a2018 n (%)	2L b2018 n (%)	2L a2018 n (%)	3L b2018 n (%)	3L a2018 n (%)
Overall	4561	3362	2639 (58)	1408 (42)	1458 (32)	551 (16)
TKI	3595 (79)	880 (26)	1029 (39)	630 (45)	688 (47)	285 (52)
PD-1+CTLA-4	26 (0.6)	1079 (32)	69 (3)	113 (8)	48 (3)	37 (7)
PD-1+TKI	23 (0.5)	862 (26)	86 (3)	356 (25)	75 (5)	123 (22)
PD-1	170 (4)	475 (14)	807 (31)	251 (18)	340 (23)	49 (9)
Others	747 (16)	66 (2)	648 (25)	58 (4)	307 (21)	57 (10)

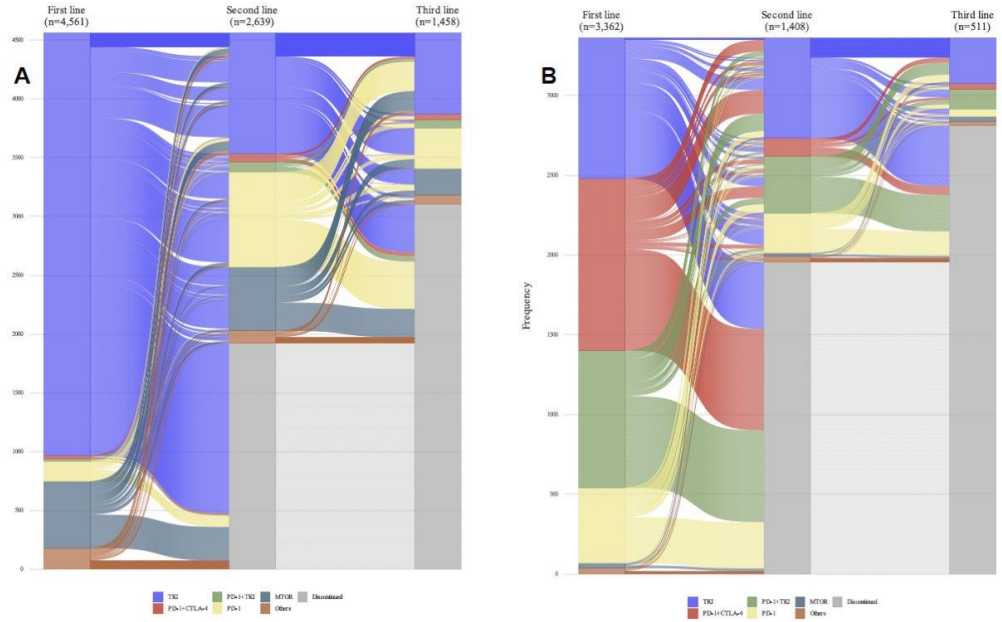

Figure 1. Treatment landscape in mccRCC from first to third line before (A) and after (B) 4/16/2018

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Status at attrition rate analysis	b2018 -1 year after Rx discontinuation n (%)	a2018-1 year after Rx discontinuation n (%)
After First line		
Received subsequent therapy [a]	2622 (59)	1120 (52)
Died without subsequent therapy [b]	1382 (31)	768 (35)
Discontinued therapy/remained alive [c]	430 (10)	280 (13)
After Second Line		
Received subsequent therapy [a]	1208 (57)	630 (56)
Died without subsequent therapy [b]	761 (36)	403 (36)
Discontinued therapy/remained alive [c]	159 (7)	100 (8)
After Third Line		
Received subsequent therapy [a]	588 (60)	372 (56)
Died without subsequent therapy [b]	332 (34)	244 (37)
Discontinued therapy/remained alive [c]	66 (6.7)	49 (7)

[a] pts with records of any subsequent Rx received within 1 year of prior Rx discontinuation. [b] pts with death recorded without documented subsequent Rx within 1 year of prior Rx discontinuation. [c] pts lost to follow-up or alive without documented subsequent Rx within 1 year of prior Rx discontinuation

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Conclusions

- **Despite the increased utilization of PD-1-based combination regimens since 2018, a significant number of patients did not receive novel combination regimens in the 1st line metastatic ccRCC setting in a real-world US population.**

- **With the uptake of PD-1-based combinations in the 1st line setting, a higher proportion of patients experienced treatment-free intervals or were alive without further therapy at 1-year attrition rate analysis after 1st line treatment discontinuation.**

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Conclusiones