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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Background and key points

- Avelumab + axitinib was approved as 1L treatment for patients with aRCC based on results from the JAVELIN Renal 101 phase 3 trial, which showed significantly prolonged PFS vs sunitinib and a manageable safety profile1
- Here, results from the final analysis of JAVELIN Renal 101 are reported, including the prespecified primary analysis of OS
- Avelumab + axitinib treatment was associated with long-term efficacy benefits vs sunitinib, and a long-term safety profile that was consistent with previous analyses
  - OS analyses favored avelumab + axitinib vs sunitinib but differences did not reach statistical significance
- JAVELIN Renal 101 provides the longest follow-up for ICI + TKI combination treatment from a phase 3 trial in aRCC reported to date (≥68 months of follow-up)

aRCC, advanced renal cell carcinoma; ORR, objective response; OS, overall survival; PFS, progression-free survival.

1. Motzer RJ, et al. N Engl J Med. 2019; 380:1103-15.

Motzer RJ, et al. Abstract number 4508 at ASCO Annual Meeting 2024 | May 31 – June 4, 2024 | Chicago, IL, USA and virtual

Prior results from JAVELIN Renal 101 in the overall population

	Primary analysis of PFS 1st interim analysis of OS ≥6 months of follow-up[1]		3rd interim analysis of OS ≥28 months of follow up[2]	
	Avelumab + Axitinib (N=442)	Sunitinib (N=444)	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
PFS				
Median PFS (95% CI), months	13.8 (11.1-NE)*	8.4 (6.9-11.1)*	13.9 (11.1-16.6)†	8.5 (8.2-9.7)†
HR (95% CI) p-value	0.69 (0.563-0.838) 1-sided p<0.001		0.67 (0.568-0.785) 1-sided p<0.0001	
OS				
Median OS (95% CI), months	Not reached (NE)	Not reached (NE)	Not reached (42.2-NE)	37.8 (31.4-NE)
HR (95% CI)	0.78 (0.554-1.084)		0.79 (0.643-0.969)	
Confirmed ORR (95% CI), %	51.4 (46.6-56.1)*	25.7 (21.7-30.0)*	59.3 (54.5-63.9)†	31.8 (27.4-36.3)†

- The analysis of OS remained immature in 3 prespecified interim analyses

HR, hazard ratio; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
*By blinded independent central review. †By investigator assessment.
1. Motzer RJ, et al. N Engl J Med. 2019; 380:1103-15; 2. Haanen J, et al. ESMO Open 2023;8:101210.

JAVELIN Renal 101: a multicenter, randomized, phase 3 trial

Key eligibility criteria
- Previously untreated advanced or metastatic RCC with a clear-cell component
- ≥1 measurable lesion per RECIST 1.1
- Any IMDC risk group
- ECOG PS 0 or 1

Patients enrolled from March 29, 2016, through December 19, 2017 at 144 sites in 21 countries

NCT02684006

R 1:1

N=442 → **Avelumab** 10 mg/kg IV Q2W **+ Axitinib** 5 mg PO BID 6-week cycle

N=444 → **Sunitinib** 50 mg PO QD 4 weeks on, 2 weeks off

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

Primary endpoints
- PFS (RECIST v1.1) by BICR and OS in the PD-L1+ population

Secondary endpoints
- OS and PFS (RECIST v1.1) in the overall population
- PFS by investigator, ORR, and duration of response (RECIST v1.1)
- Safety
- Patient-reported outcomes

- The primary (final) OS analysis was planned when 368 deaths had occurred in the PD-L1+ population, which would provide 90% power to detect an HR of 0.70 using a 1-sided log-rank test at a significance level of 0.021
  - A 4-look group sequential design with a Lan–DeMets (O'Brien–Fleming) α spending function was used to determine the efficacy boundary
  - Overall type I-error was maintained at or below 1-sided 0.025 by allocating α=0.004 to the PFS comparison and α=0.021 to the OS comparison in the PD-L1+ population
  - A gatekeeping procedure was used to allow further testing of PFS and OS in the overall population

BICR, blinded independent central review; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; R, randomization; RCC, renal cell carcinoma; ROW, rest of the world.

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Baseline characteristics in the overall population[1]

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Age, median (range), years	62.0 (29.0-83.0)	61.0 (27.0-88.0)
Sex, n (%)		
Male	316 (71.5)	344 (77.5)
Female	126 (28.5)	100 (22.5)
Prior nephrectomy, n (%)	352 (79.6)	355 (80.0)
IMDC prognostic risk group, n (%)		
Favorable	94 (21.3)	96 (21.6)
Intermediate	271 (61.3)	276 (62.2)
Poor	72 (16.3)	71 (16.0)
Not reported	5 (1.1)	1 (0.2)
PD-L1 status, n (%)*		
Positive	270 (61.1)	290 (65.3)
Negative	132 (29.9)	120 (27.0)
Not reported	40 (9.0)	34 (7.7)

IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma.
*PD-L1+ was defined as ≥1% of immune cells staining positive in the tumor area using the Ventana PD-L1 (SP263) assay.
1. Motzer RJ, et al. N Engl J Med. 2019.

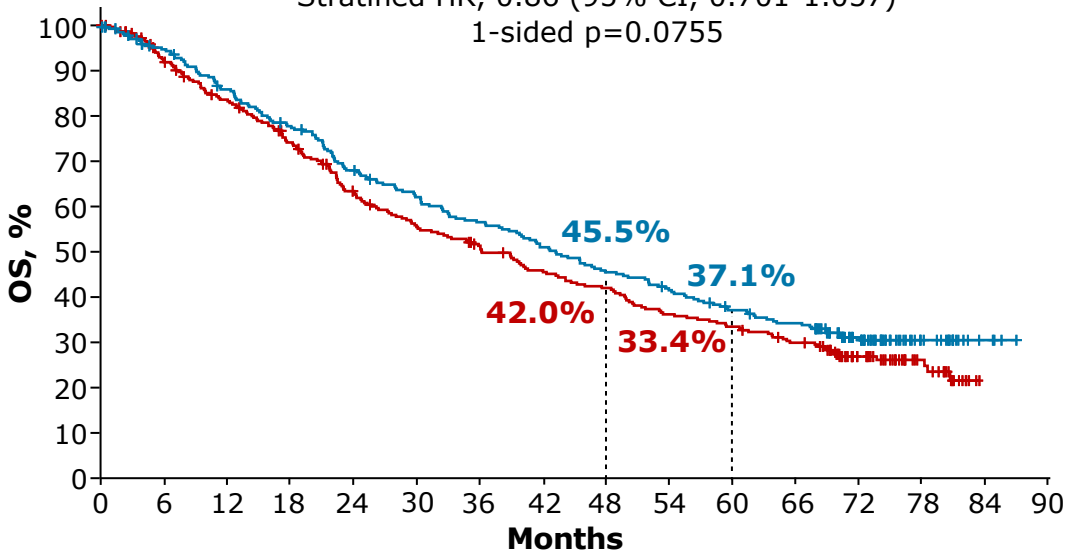
Motzer RJ, et al. Abstract number 4508 at ASCO Annual Meeting 2024 | May 31 – June 4, 2024 | Chicago, IL, USA and virtual

Final analysis of overall survival

PD-L1+ population*
(Primary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (n=270)	**43.2** (36.5-51.7)
Sunitinib (n=290)	**36.2** (29.8-44.2)

Stratified HR, 0.86 (95% CI, 0.701-1.057)
1-sided p=0.0755

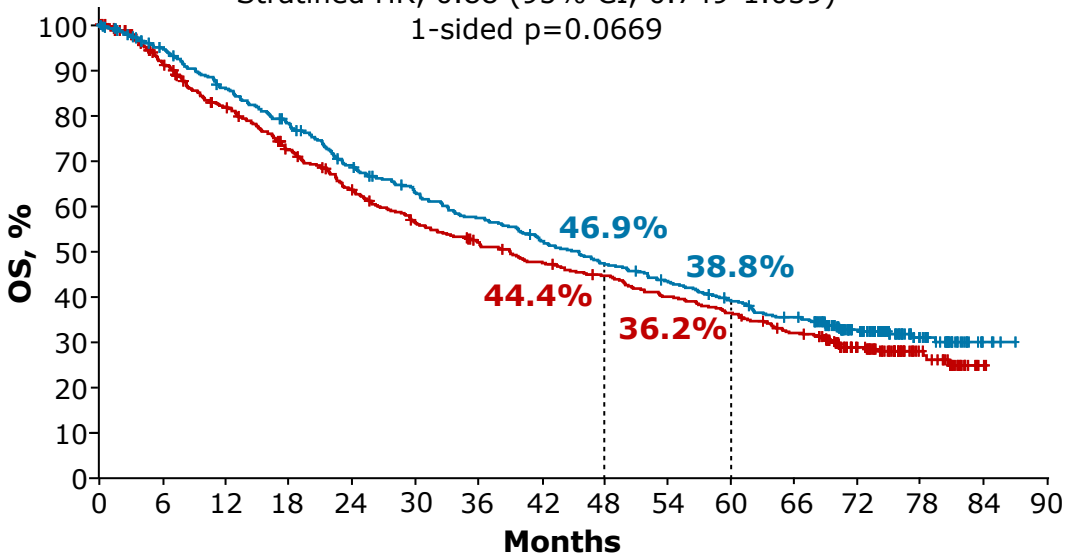


No. at risk																
Avelumab + Axitinib	270	247	222	200	174	157	143	129	115	104	91	83	51	19	4	0
Sunitinib	290	259	231	202	169	147	133	118	108	93	86	75	42	20	0	0

Overall population
(Secondary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (N=442)	**44.8** (39.7-51.1)
Sunitinib (N=444)	**38.9** (31.4-45.2)

Stratified HR, 0.88 (95% CI, 0.749-1.039)
1-sided p=0.0669



Avelumab + Axitinib	442	403	363	328	287	258	235	213	192	174	155	139	86	36	4	0
Sunitinib	444	391	344	298	258	226	205	187	173	155	141	121	74	30	2	0

At data cutoff (August 31, 2023), median follow-up was 73.7 months in the avelumab + axitinib arm and 73.6 months in the sunitinib arm (minimum follow-up, 68 months [last patient randomized to data cutoff]).
HR, hazard ratio; OS, overall survival.
*PD-L1+ was defined as ≥1% of immune cells staining positive in the tumor area using the Ventana PD-L1 (SP263) assay.

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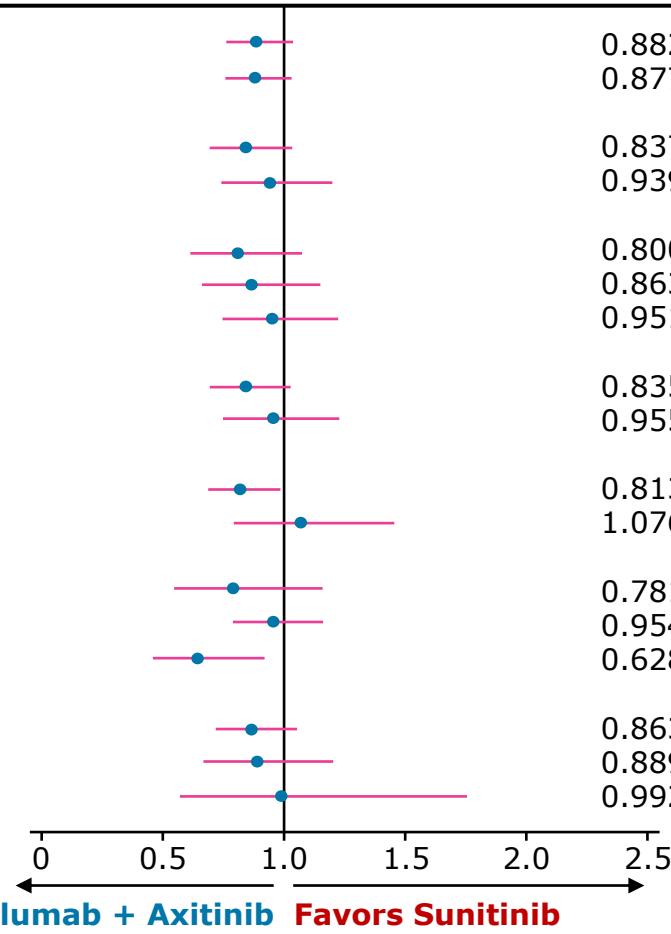
OS in prespecified subgroups in the overall population

	Subgroup	Events/patients: Avelumab + Axitinib	Events/patients: Sunitinib	HR (95% CI)
Overall	All participants (stratified)	283/442	295/444	0.882 (0.749-1.039)
	All participants (unstratified)	283/442	295/444	0.877 (0.745-1.033)
ECOG PS (per IRT)	0	164/279	175/281	0.837 (0.677-1.036)
	1	119/163	120/163	0.939 (0.728-1.210)
Geographic region (per IRT)	United States	81/128	92/130	0.800 (0.593-1.078)
	Canada/Western Europe	88/128	91/128	0.863 (0.644-1.158)
	Rest of the world	114/186	112/186	0.951 (0.733-1.235)
Age	<65 years	171/271	182/275	0.835 (0.678-1.029)
	≥65 years	112/171	113/169	0.955 (0.735-1.240)
Sex	Male	195/316	228/344	0.813 (0.671-0.984)
	Female	88/126	67/100	1.076 (0.782-1.479)
IMDC risk status	Favorable	44/94	52/96	0.781 (0.523-1.168)
	Intermediate	185/270	184/277	0.954 (0.778-1.170)
	Poor	51/73	59/71	0.628 (0.431-0.916)
PD-L1 status*	Positive	176/270	199/290	0.863 (0.704-1.057)
	Negative	81/132	77/120	0.889 (0.650-1.214)
	Unknown	26/40	19/34	0.992 (0.548-1.795)



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; IRT, interactive response technology; OS, overall survival; RCC, renal cell carcinoma.
*PD-L1+ was defined as ≥1% of immune cells staining positive within the tumor area using the Ventana PD-L1 (SP263) assay.

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Final analysis of OS in IMDC risk groups in the overall population

Favorable risk

Median OS (95% CI), months	
Avelumab + Axitinib (n=94)	**79.4** (59.4-NE)
Sunitinib (n=96)	**65.5** (53.4-78.6)

Unstratified HR, 0.78 (95% CI, 0.52-1.17)
1-sided p=0.2281*

Intermediate risk

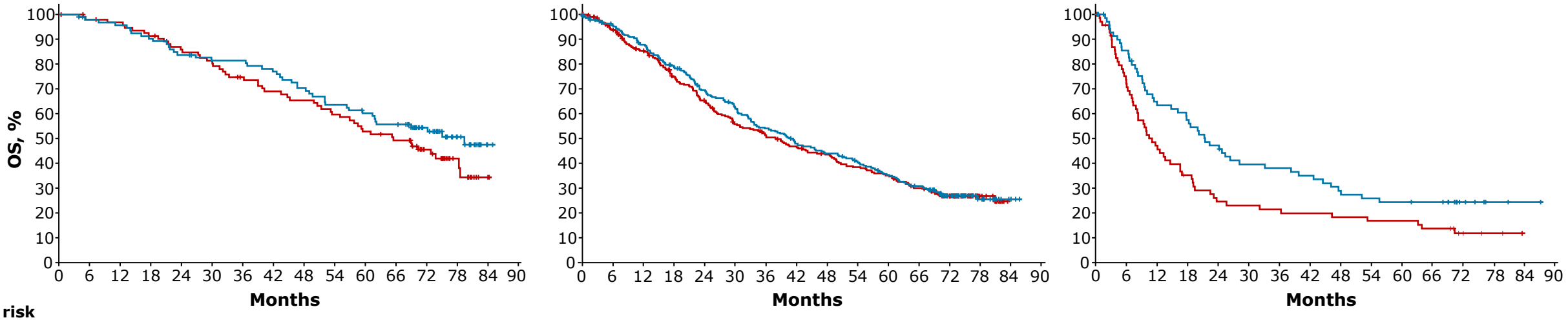
Median OS (95% CI), months	
Avelumab + Axitinib (n=270)	**41.3** (33.7-50.0)
Sunitinib (n=277)	**38.0** (29.6-47.6)

Unstratified HR, 0.95 (95% CI, 0.78-1.17)
1-sided p=0.6504†

Poor risk

Median OS (95% CI), months	
Avelumab + Axitinib (n=73)	**21.3** (14.7-33.1)
Sunitinib (n=71)	**11.0** (7.8-16.5)

Unstratified HR, 0.63 (95% CI, 0.43-0.92)
1-sided p=0.0147‡



No. at risk

Avelumab + Axitinib	94	90	88	83	77	73	73	69	63	57	53	49	33	17	1	0
Sunitinib	96	92	90	85	77	72	65	60	57	52	46	42	26	11	2	0

Avelumab + Axitinib	270	250	228	203	176	157	136	120	110	99	85	74	46	17	2	0
Sunitinib	277	250	222	190	165	139	126	114	104	92	84	70	44	16	0	0

Avelumab + Axitinib	73	59	43	39	32	26	25	23	18	17	16	15	6	2	1	0
Sunitinib	71	49	32	23	16	15	14	13	12	11	11	9	4	3	0	0

HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; NE, not estimable; OS, overall survival, RCC, renal cell carcinoma.
*Stratified HR, 0.73 (95% CI, 0.48-1.10); 1-sided p=0.1290. †Stratified HR, 0.96 (95% CI, 0.78-1.18); 1-sided p=0.7119. ‡Stratified HR, 0.58 (95% CI, 0.39-0.87); 1-sided p=0.0076.

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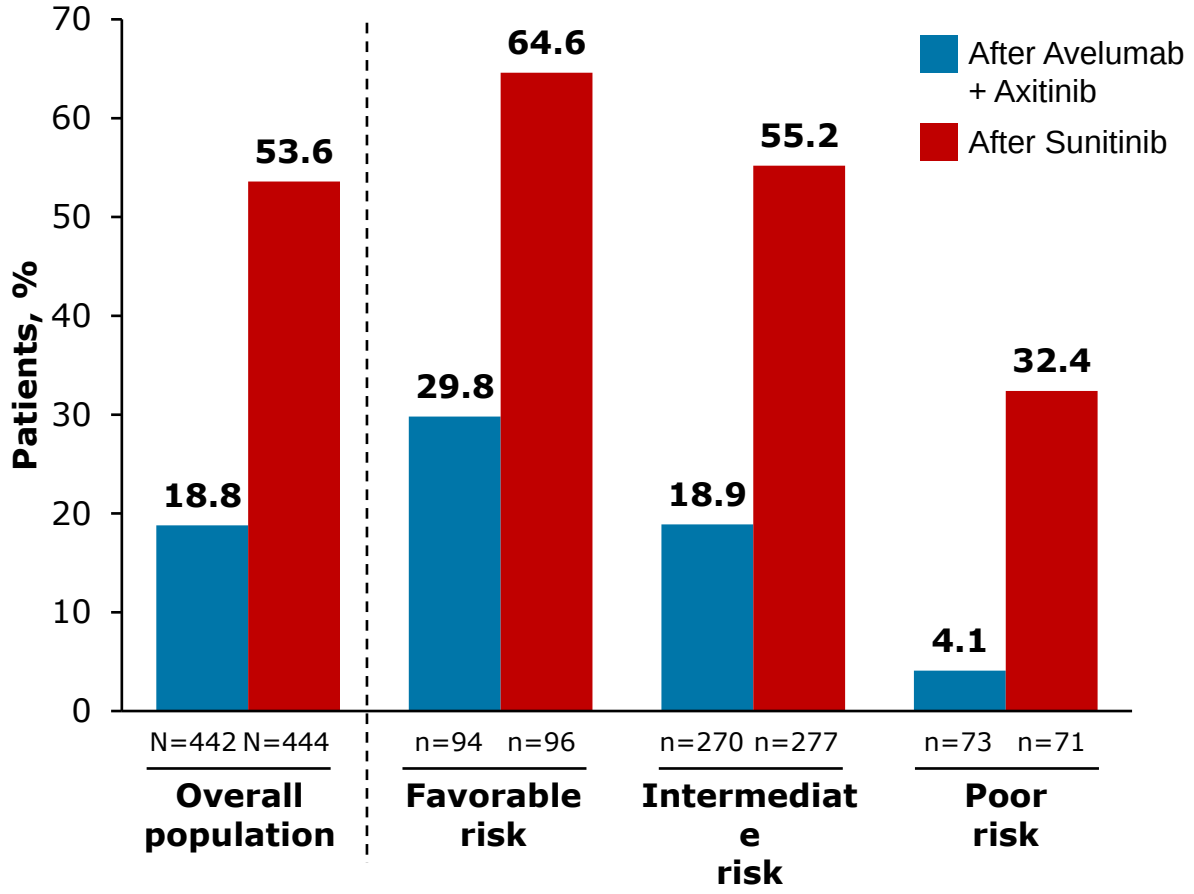
Subsequent treatment in the overall population

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Received ≥1 subsequent anticancer drug treatment, n (%)	257 (58.1)	308 (69.4)
Category of drug received, n (%)*		
PD-1 or PD-L1 inhibitor	83 (18.8)	238 (53.6)
VEGF or VEGFR inhibitor	226 (51.1)	205 (46.2)
Other drug therapy	102 (23.1)	120 (27.0)
No. of subsequent drug regimens, n (%)		
0	88 (19.9)	66 (14.9)
1	147 (33.3)	155 (34.9)
≥2	110 (24.9)	153 (34.5)
Not reported	97 (21.9)	70 (15.8)

Subsequent PD-1 or PD-L1 inhibitor treatment in the overall population and in IMDC risk groups



IMDC, International Metastatic RCC Database Consortium; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
*Patients may have received >1 category of drug.

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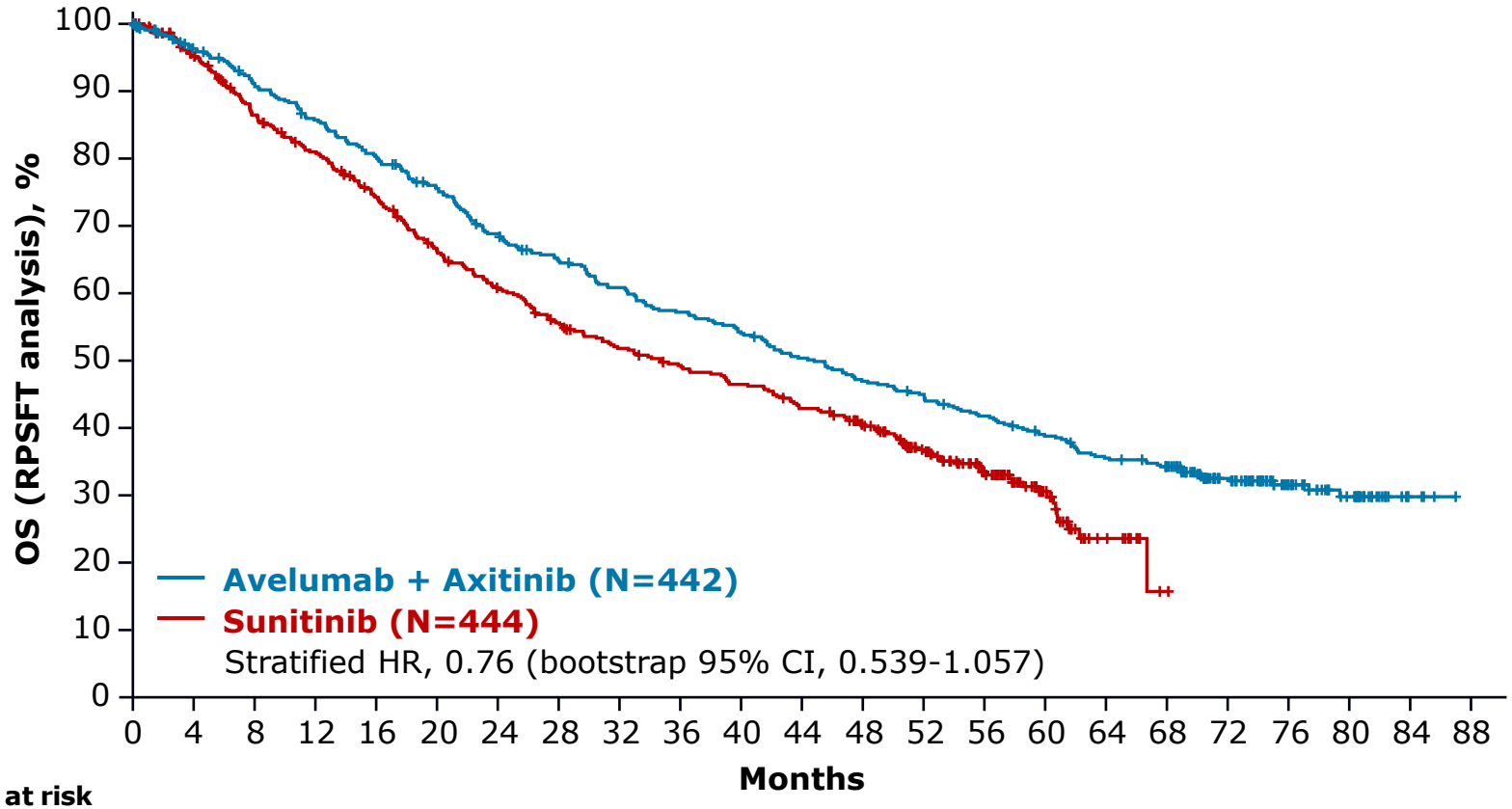
OS analyses adjusted for subsequent PD-1 or PD-L1 inhibitor treatment in the overall population



No. at risk

Avelumab + Axitinib	442	412	387	363	340	316	287	267	250	235	222	206	192	183	169	155	141	131	86	48	28	4	0
Sunitinib	444	409	366	339	306	271	246	223	205	193	182	167	148	113	75	37	12	1	0				

An exploratory, post hoc RPSFT analysis of OS adjusted for subsequent PD-(L)1 inhibitor treatment after disease progression in the sunitinib arm was conducted as described previously.1 The analysis assumes that PD-(L)1 inhibitor treatment increases OS in patients in the sunitinib arm by a common factor, irrespective of when treatment was given ("treatment effect"; untestable assumption). For the adjusted analysis, OS in the sunitinib arm was decreased based on this factor.

HR, hazard ratio; OS, overall survival; ICI, immune-checkpoint inhibitor. RPSFT, rank-preserving structural failure time.

1. Choueiri TK, et al. Ann Oncol 2020;31:1030-9.

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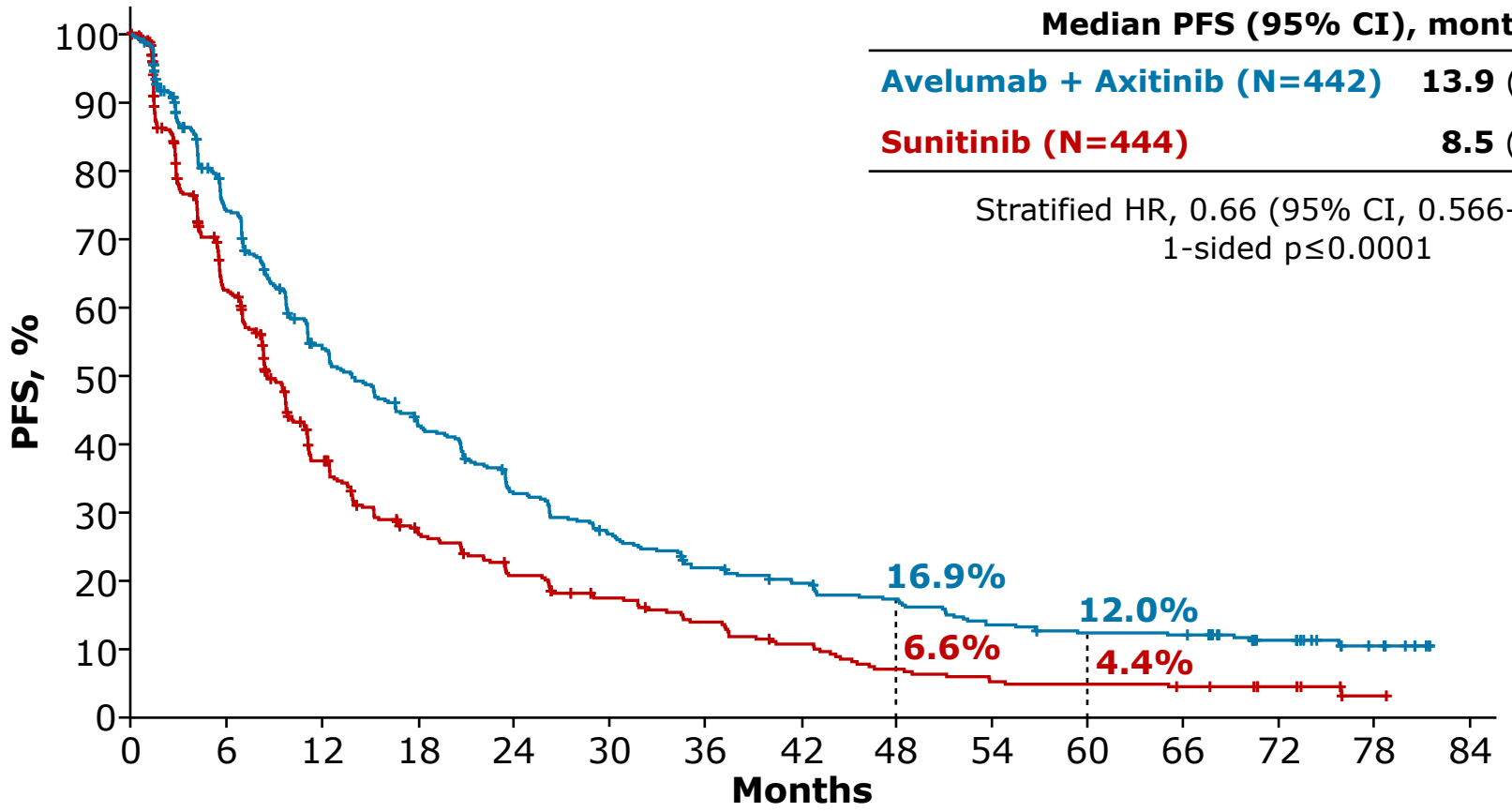
Long-term analysis of PFS by investigator assessment in the overall population



Median PFS (95% CI), months	
Avelumab + Axitinib (N=442)	**13.9** (11.1-16.6)
Sunitinib (N=444)	**8.5** (8.2-9.7)

Stratified HR, 0.66 (95% CI, 0.566-0.769)
1-sided p≤0.0001

No. at risk															
Avelumab + Axitinib	442	293	204	160	120	97	77	67	58	45	40	39	21	9	0
Sunitinib	444	240	130	86	63	49	38	28	18	13	12	10	6	1	0

HR, hazard ratio; PFS, progression-free survival.

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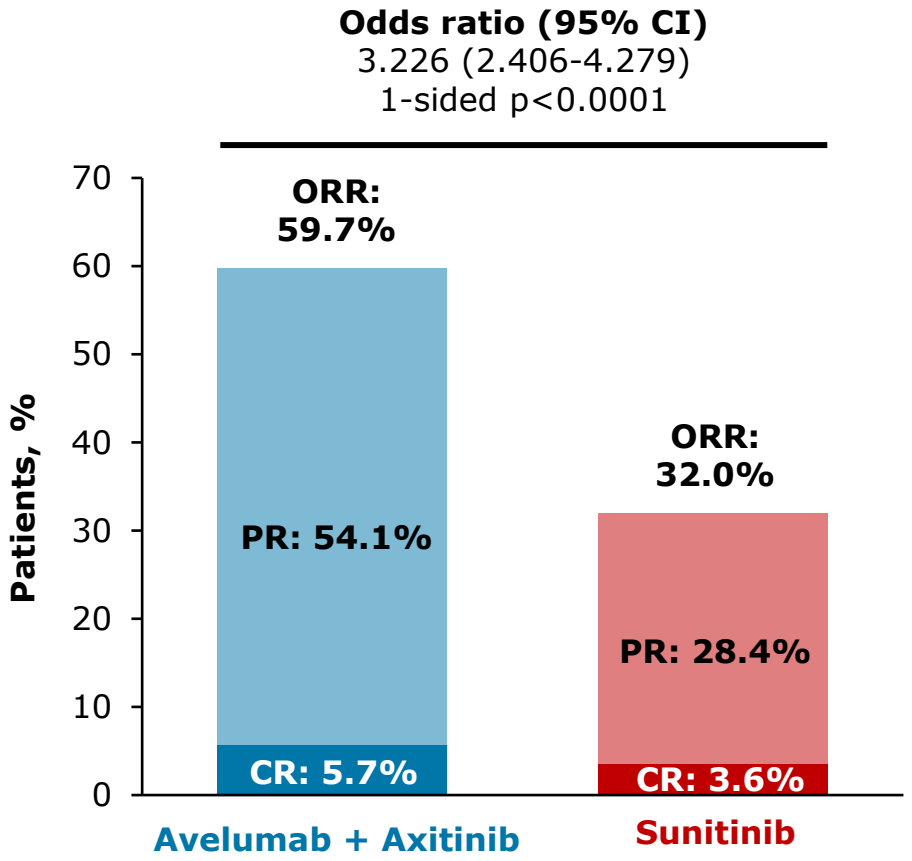
Responses by investigator assessment in the overall population

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Confirmed BOR, n (%)		
CR	25 (5.7)	16 (3.6)
PR	239 (54.1)	126 (28.4)
SD	111 (25.1)	196 (44.1)
PD	40 (9.0)	68 (15.3)
NE	26 (5.9)	37 (8.3)
Non-CR/non-PD*	1 (0.2)	1 (0.2)



BOR, best overall response; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*This category includes patients who did not have target lesions at baseline according to independent review and whose response was categorized as non-CR or non-PD.

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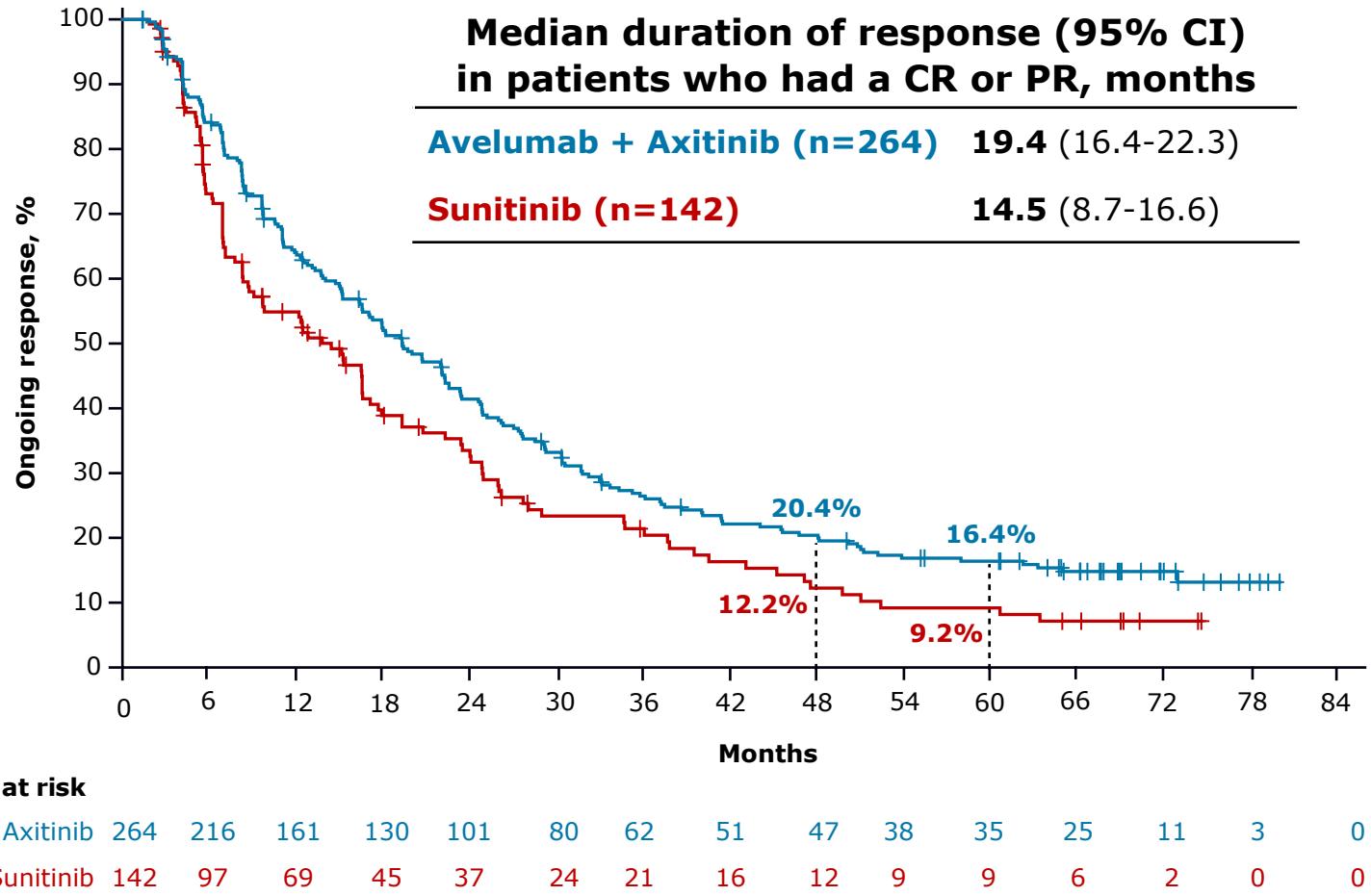
Duration of response by investigator assessment in the overall population



Median duration of response (95% CI) in patients who had a CR or PR, months

Avelumab + Axitinib (n=264)	**19.4** (16.4-22.3)
Sunitinib (n=142)	**14.5** (8.7-16.6)

No. at risk

Avelumab + Axitinib	264	216	161	130	101	80	62	51	47	38	35	25	11	3	0
Sunitinib	142	97	69	45	37	24	21	16	12	9	9	6	2	0	0

Proportion of patients in the TOTAL arm by duration of response, n (%)

Duration of response	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Any	264/442 (59.7)	142/444 (32.0)
≥6 months	216 (48.9)	97 (21.8)
≥1 years	161 (36.4)	69 (15.5)
≥2 years	101 (22.9)	37 (8.3)
≥3 years	62 (14.0)	21 (4.7)
≥4 years	47 (10.6)	12 (2.7)
≥5 years	35 (7.9)	9 (2.0)
≥6 years	11 (2.5)	2 (0.5)

CR, complete response; PR, partial response.

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Summary of long-term safety

	Avelumab + Axitinib (n=434)	Sunitinib (n=439)
Duration of treatment, median (range), months	13.8 (0.5-82.4)	8.3 (0.2-80.8)
TRAE of any grade, n (%)	420 (96.8)	425 (96.8)
Grade ≥3	290 (66.8)	270 (61.5)
Leading to discontinuation of avelumab	85 (19.6)	–
Leading to discontinuation of axitinib/sunitinib	54 (12.4)	41 (9.3)
Leading to discontinuation of all study drugs	21 (4.8)	41 (9.3)
Leading to death	6 (1.4)	1 (0.2)
irAE of any grade, n (%)	220 (50.7)	21 (4.8)
Grade ≥3	64 (14.7)	1 (0.2)
Infusion-related reaction of any grade, n (%)	127 (29.3)	0

- Overall and disease-specific health-related QOL were generally stable in both treatment arms

irAE, immune-related adverse event; QOL, quality of life; TRAE, treatment-related adverse event.

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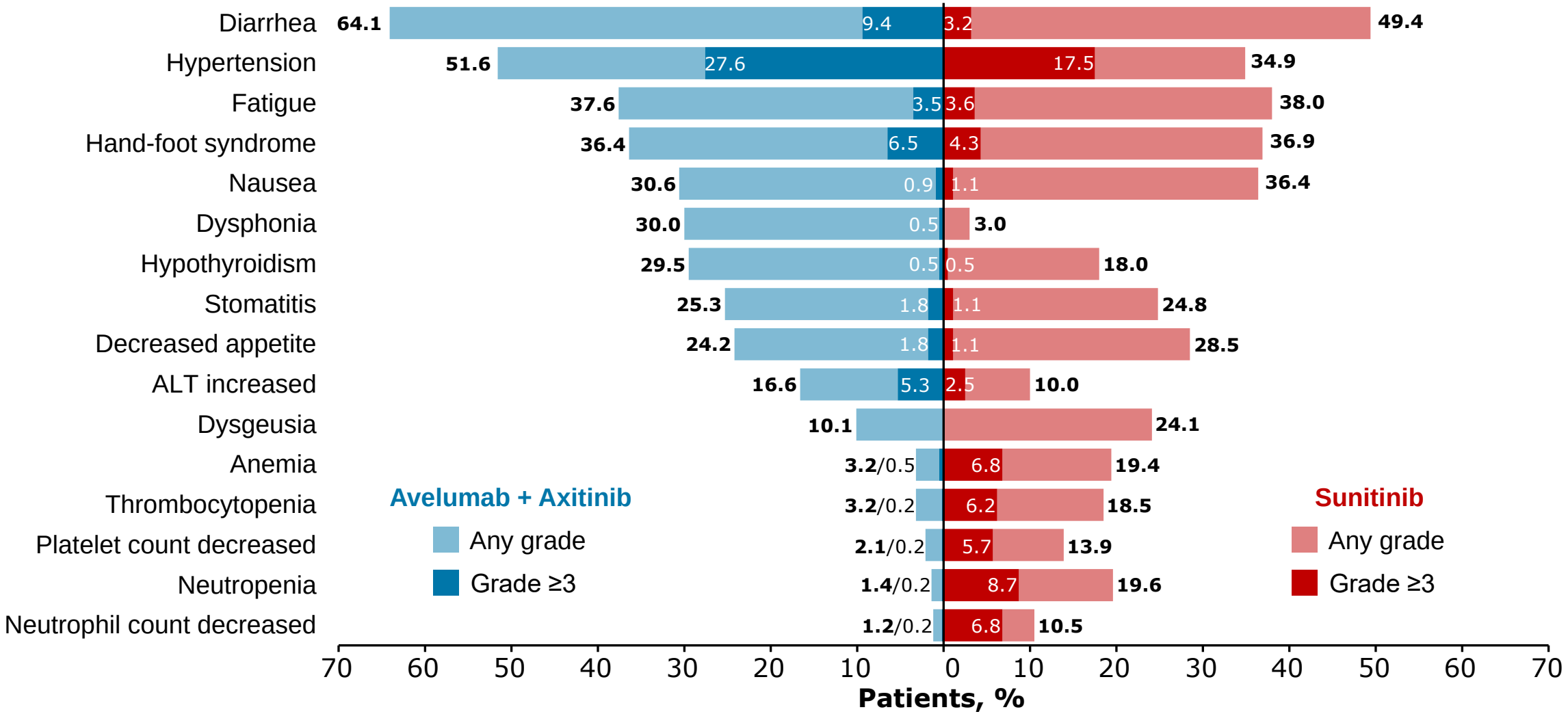
Treatment-related AEs



Any grade in ≥20% of patients or grade ≥3 in 5% in either arm.
ALT, alanine aminotransferase; AE, adverse event.

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Conclusions

- JAVELIN Renal 101 provides the longest follow-up for ICI + TKI combination treatment from a phase 3 trial in aRCC reported to date (≥68 months of follow-up)
- OS analyses favored avelumab + axitinib vs sunitinib but differences did not reach statistical significance
- Avelumab + axitinib demonstrated long-term efficacy benefits vs sunitinib, including prolonged PFS, a near-doubling in ORR, and a higher proportion of patients with durable responses
- The long-term safety profile of avelumab + axitinib was consistent with previous analyses[1-3]
- These results confirm that avelumab + axitinib treatment is associated with long-term efficacy benefits and a manageable safety profile in patients with aRCC

aRCC, advanced renal cell carcinoma; ICI, immune checkpoint inhibitor; ORR, objective response; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Motzer RJ, et al. N Engl J Med. 2019; 380:1103-15; 2. Choueiri TK, et al. Ann Oncol 2020;31:1030-9; 3. Haanen J, et al. ESMO Open 2023;8:101210.

Motzer RJ, et al. Abstract number 4508 at ASCO Annual Meeting 2024 | May 31 – June 4, 2024 | Chicago, IL, USA and virtual

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