Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103-15. DOI: 10.1056/NEJMoa1816047

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Definitions of Selected Terms and Endpoints

Eastern Cooperative Oncology Group performance status was scored and defined as follows:

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

International Metastatic Renal Cell Carcinoma Database Consortium prognostic risk score (favorable [score of 0], intermediate [score of 1 or 2], or poor [score of 3 to 6]) was determined according to the number of the following risk factors present: a Karnofsky performance status score of 70, less than 1 year from time of initial diagnosis, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium concentration of more than 10 mg per deciliter (2.5 mmol per liter), an absolute neutrophil count above the upper limit of the normal range, and a platelet count above the upper limit of the normal range.

Memorial Sloan Kettering Cancer Center prognostic risk score (favorable [score of 0], intermediate [score of 1 or 2], or poor [score of ≥3]) was determined according to the number of the following risk factors present: Karnofsky performance status score < 80, less than 1 year from time of initial diagnosis to start of therapy, a hemoglobin level below the lower limit of the normal range, lactate dehydrogenase level more than 1.5 times above the upper limit of normal, and a corrected serum calcium concentration of more than 10 mg per deciliter (2.5 mmol per liter).

Progression-free survival was defined as the time from randomization to the first documentation of objective disease progression or death due to any cause, whichever occurred first.

Overall survival was defined as the time from randomization to death due to any cause.

The objective response rate was defined as the percentage of patients with a confirmed best response of complete response or partial response according to RECIST, version 1.1.

Duration of response was defined as the time from the first documentation of objective response to progression or death.

Sensitivity Analyses

Sensitivity analyses were performed to explore the robustness of the primary analysis results for PFS; these results were similar to those of the primary analysis methodology. The model assumption of proportional hazards was assessed and an analysis of restricted mean survival time was also performed. The model assumption of proportional hazards was assessed based on the Schoenfeld's residual test and by plotting log(-log(PFS)) versus log(time) within each randomization stratum. The results suggested that there was no evidence the proportional hazards assumption was violated and the model used to assess the treatment effect of avelumab in combination with axitinib compared to sunitinib on PFS was valid (Figures S4 and S5 in the Supplementary Appendix). Although the proportional hazards assumption does not appear to be violated, an analysis based on the restricted mean survival time for PFS was performed and the results were consistent with those based on the log-rank test ($P<0.001$) comparing the combination arm with the sunitinib arm using a truncation point equal to the minimum of the longest follow-up time of either arm, in both the PD-L1–positive group and the overall population.

Figure S1. Gatekeeping Testing Strategy.

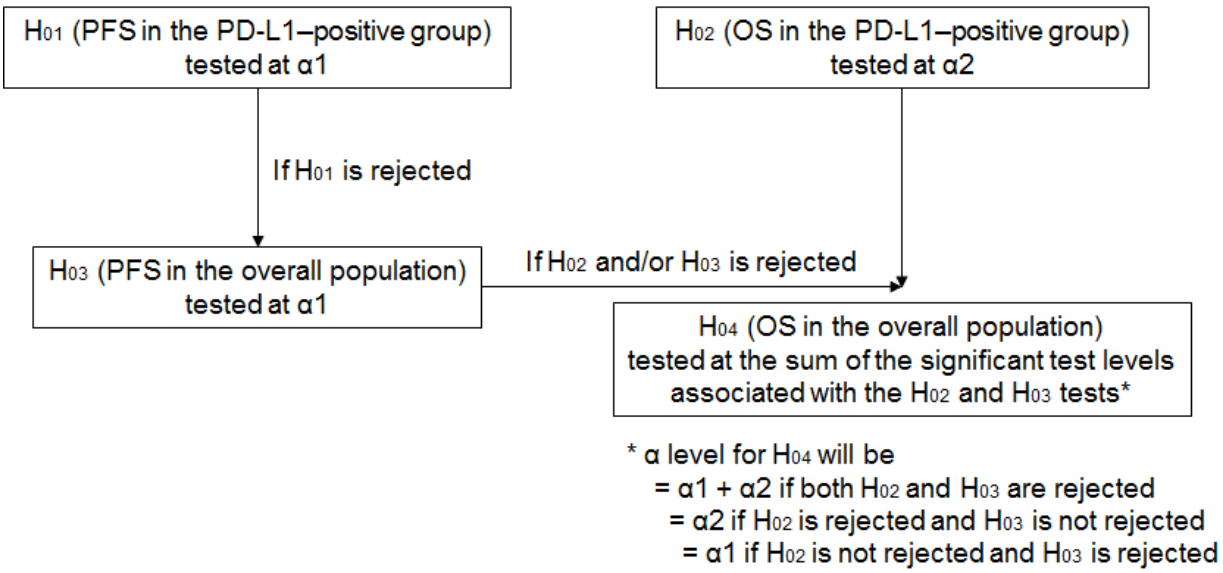
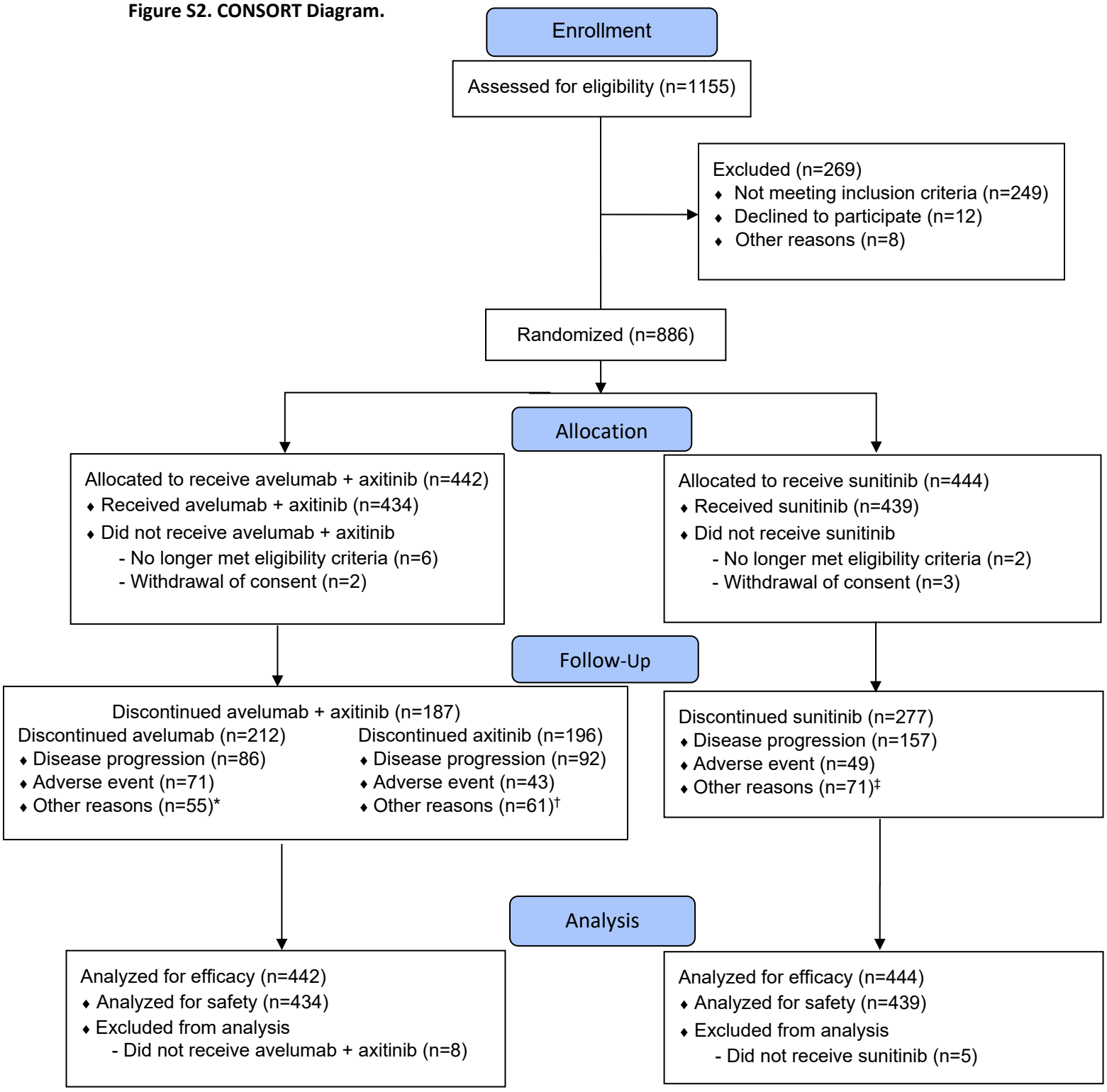


Figure S2. CONSORT Diagram.



* Reasons included global deterioration of health status (n=15), withdrawal of consent (n=12), and death (n=12).

† Reasons included global deterioration of health status (n=19), withdrawal of consent (n=14), death (n=13).

‡ Reasons included withdrawal of consent (n=25), global deterioration of health status (n=16), and death (n=14).

Figure S3. Kaplan-Meier Plot of Overall Survival in the Overall Population.

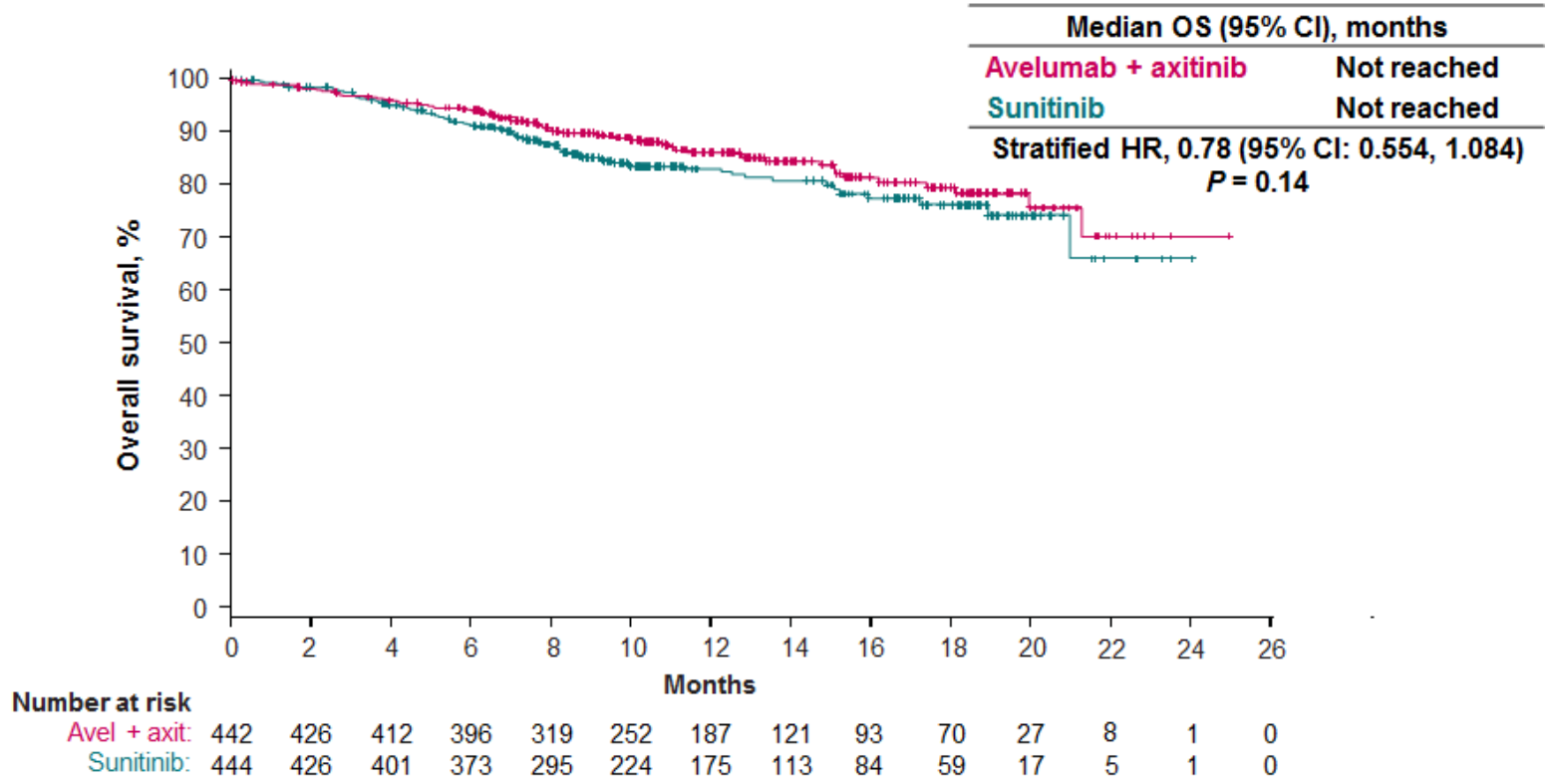


Figure S4. Plot of Schoenfeld Residuals from Stratified Cox Proportional Regression Model for Progression-Free Survival in the PD-L1–Positive group.

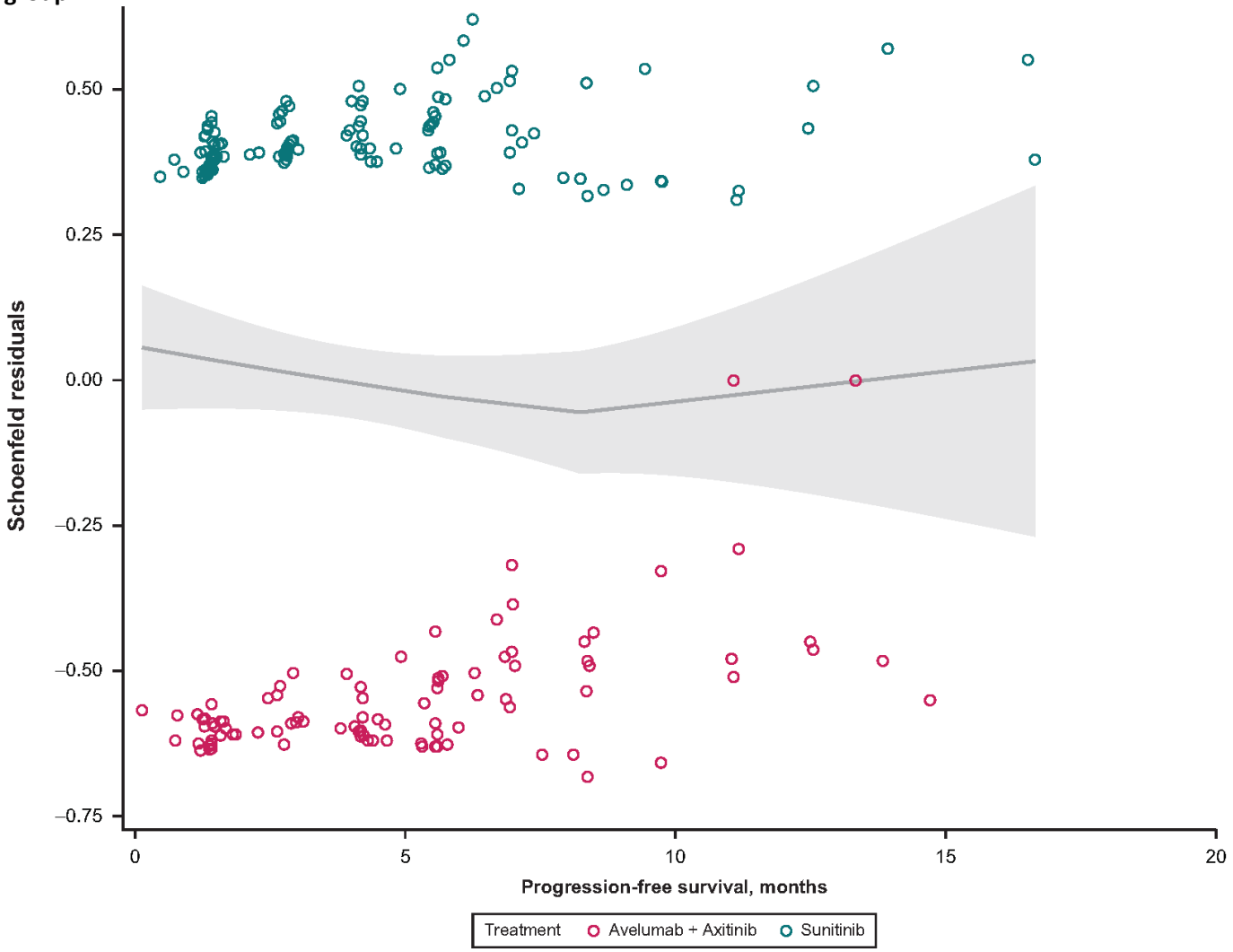


Figure S5. Plot of Schoenfeld Residuals from Stratified Cox Proportional Regression Model for Progression-Free Survival in the Overall Population.

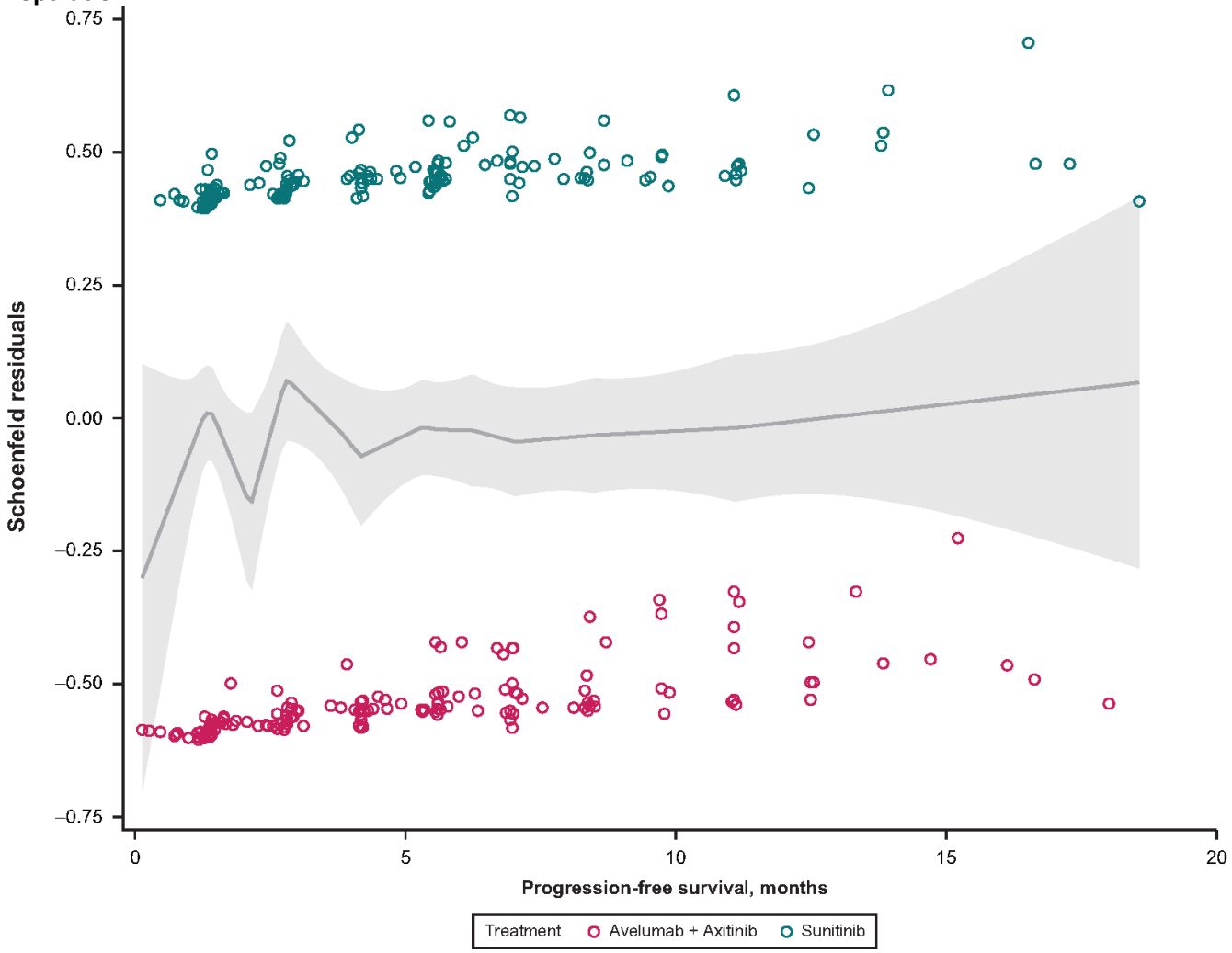


Figure S6. Time to and Duration of Response to Avelumab Plus Axitinib in the PD-L1–Positive group (N = 149).

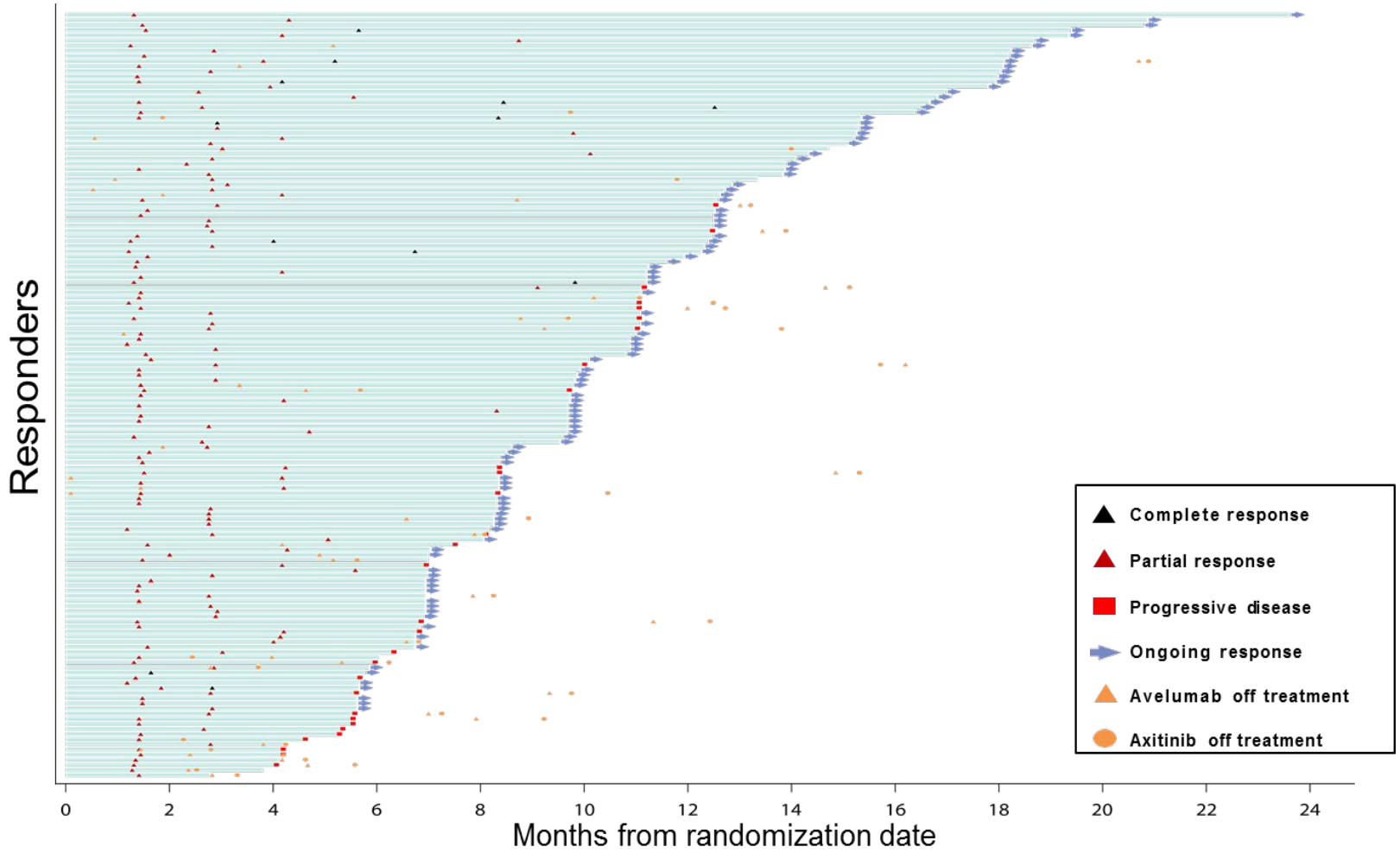


Figure S7. Subgroup Analysis of Prognostic Factors for Progression-Free Survival in the Overall Population.

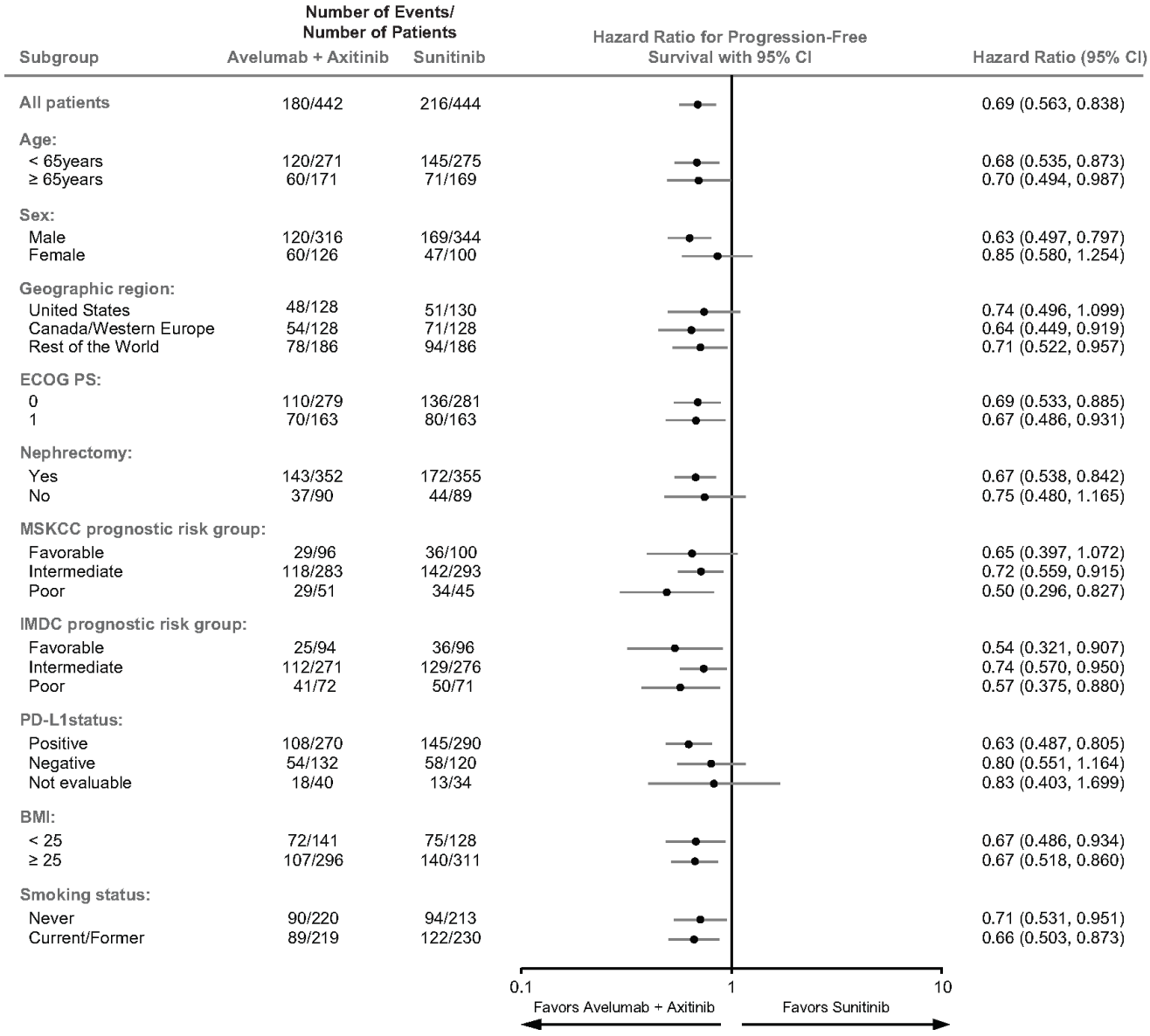


Figure S8. Subgroup Analysis of Prognostic Factors for Objective Response in the PD-L1–Positive Group.

Subgroup	Number of Responders/ Number of Patients		Obejctive Response Rate		Odds Ratio for Objective Response Rate with 95% CI	Odds Ratio (95% CI)
	Avelumab + Axitinib	Sunitinib	Avelumab + Axitinib	Sunitinib		
All patients	149/270	74/290	55.2	25.5		3.60 (2.478, 5.221)
Age:						
< 65 years	84/165	47/189	50.9	24.9		3.13 (1.952, 5.041)
≥ 65 years	65/105	27/101	61.9	26.7		4.45 (2.371, 8.414)
Sex:						
Male	115/203	57/224	56.7	25.4		3.83 (2.493, 5.891)
Female	34/67	17/66	50.7	25.8		2.97 (1.349, 6.615)
ECOG PS:						
0	96/168	55/193	57.1	28.5		3.35 (2.112, 5.307)
1	53/102	19/97	52.0	19.6		4.44 (2.259, 8.870)
Geographic region:						
United States	46/75	26/82	61.3	31.7		3.42 (1.684, 6.959)
Canada/Western Europe	43/80	19/81	53.8	23.5		3.79 (1.835, 7.927)
Rest of the World	60/115	29/127	52.2	22.8		3.69 (2.049, 6.672)
Nephrectomy:						
Yes	135/233	67/252	57.9	26.6		3.80 (2.552, 5.678)
No	14/37	7/38	37.8	18.4		2.70 (0.842, 9.132)
MSKCC prognostic risk group:						
Favorable	39/52	20/60	75.0	33.3		6.00 (2.446, 14.978)
Intermediate	94/180	51/201	52.2	25.4		3.22 (2.042, 5.072)
Poor	12/33	3/24	36.4	12.5		4.00 (0.877, 24.698)
IMDC prognostic risk group:						
Favorable	40/52	20/59	76.9	33.9		6.50 (2.608, 16.549)
Intermediate	91/173	48/191	52.6	25.1		3.31 (2.075, 5.280)
Poor	17/44	6/39	38.6	15.4		3.46 (1.092, 12.104)
BMI:						
< 25	48/93	18/81	51.6	22.2		3.73 (1.838, 7.711)
≥ 25	100/176	56/206	56.8	27.2		3.52 (2.247, 5.535)
Smoking status:						
Never	71/136	32/138	52.2	23.2		3.62 (2.089, 6.305)
Current/Former	78/133	42/152	58.6	27.6		3.71 (2.198, 6.289)

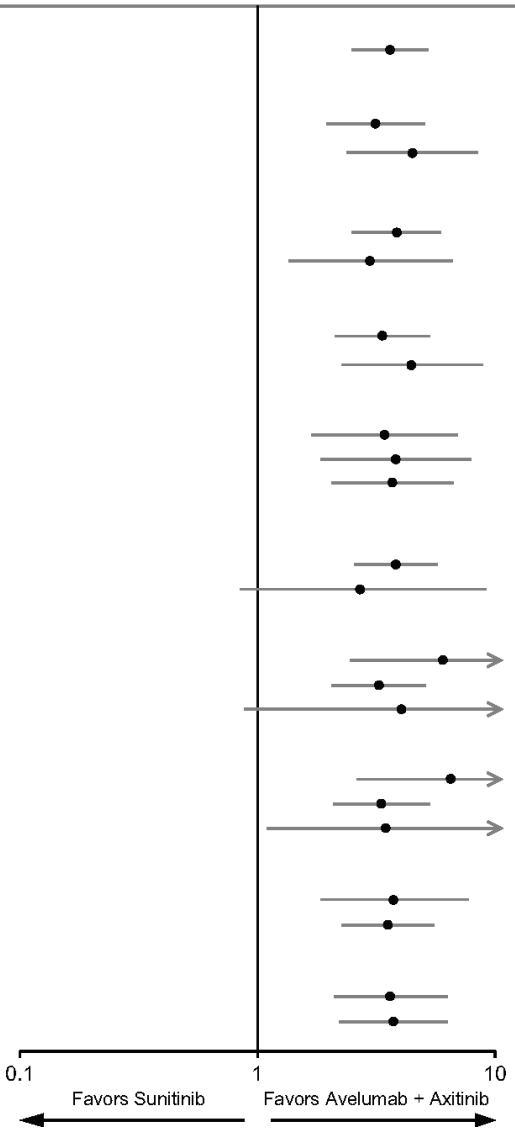


Figure S9. Subgroup Analysis of Prognostic Factors for Objective Response in the Overall Population.

Subgroup	Number of Responders/ Number of Patients: Avelumab + Axitinib	Number of Responders/ Number of Patients: Sunitinib	Objective Response Rate: Avelumab + Axitinib	Objective Response Rate: Sunitinib	Odds Ratio for Objective Response Rate with 95% CI	Odds Ratio (95%)
All patients	227/442	114/444	51.4	25.7		3.06 (2.281, 4.100)
Age:						
< 65 years	130/271	71/275	48.0	25.8		2.65 (1.820, 3.863)
≥ 65 years	97/171	43/169	56.7	25.4		3.84 (2.367, 6.254)
Sex:						
Male	164/316	87/344	51.9	25.3		3.19 (2.266, 4.489)
Female	63/126	27/100	50.0	27.0		2.70 (1.487, 4.957)
ECOG PS:						
0	151/279	84/281	54.1	29.9		2.77 (1.926, 3.977)
1	76/163	30/163	46.6	18.4		3.87 (2.284, 6.633)
Geographic region:						
United States	73/128	38/130	57.0	29.2		3.21 (1.861, 5.564)
Canada/Western Europe	59/128	34/128	46.1	26.6		2.36 (1.356, 4.139)
Rest of the World	95/186	42/186	51.1	22.6		3.58 (2.235, 5.758)
Nephrectomy:						
Yes	196/352	99/355	55.7	27.9		3.25 (2.348, 4.500)
No	31/90	15/89	34.4	16.9		2.59 (1.218, 5.653)
MSKCC prognostic risk group:						
Favorable	63/96	38/100	65.6	38.0		3.12 (1.670, 5.826)
Intermediate	140/283	71/293	49.5	24.2		3.06 (2.116, 4.438)
Poor	16/51	4/45	31.4	8.9		4.69 (1.323, 20.746)
IMDC prognostic risk group:						
Favorable	64/94	36/96	68.1	37.5		3.56 (1.874, 6.771)
Intermediate	139/271	70/276	51.3	25.4		3.10 (2.127, 4.523)
Poor	22/72	8/71	30.6	11.3		3.47 (1.334, 9.716)
PD-L1status:						
Positive	149/270	74/290	55.2	25.5		3.59 (2.478, 5.221)
Negative	62/132	34/120	47.0	28.3		2.24 (1.286, 3.923)
Unknown	16/40	6/34	40.0	17.6		3.11 (0.949, 11.154)
BMI:						
< 25	66/141	27/128	46.8	21.1		3.29 (1.864, 5.877)
≥ 25	159/296	85/311	53.7	27.3		3.09 (2.170, 4.392)
Smoking status:						
Never	114/220	47/213	51.8	22.1		3.80 (2.452, 5.910)
Current/Former	113/219	66/230	51.6	28.7		2.65 (1.762, 3.989)

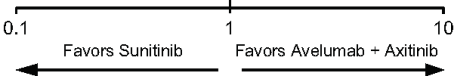


Figure S10. Best Percentage Change in Target Lesions in the Overall Population.

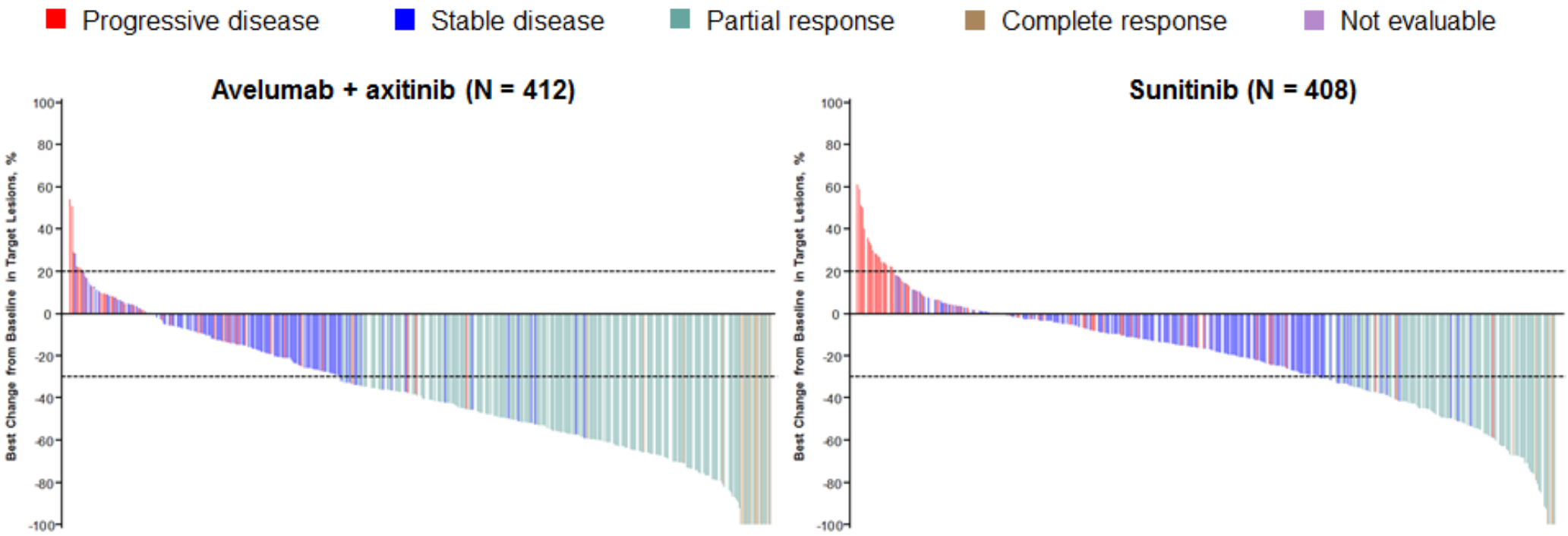
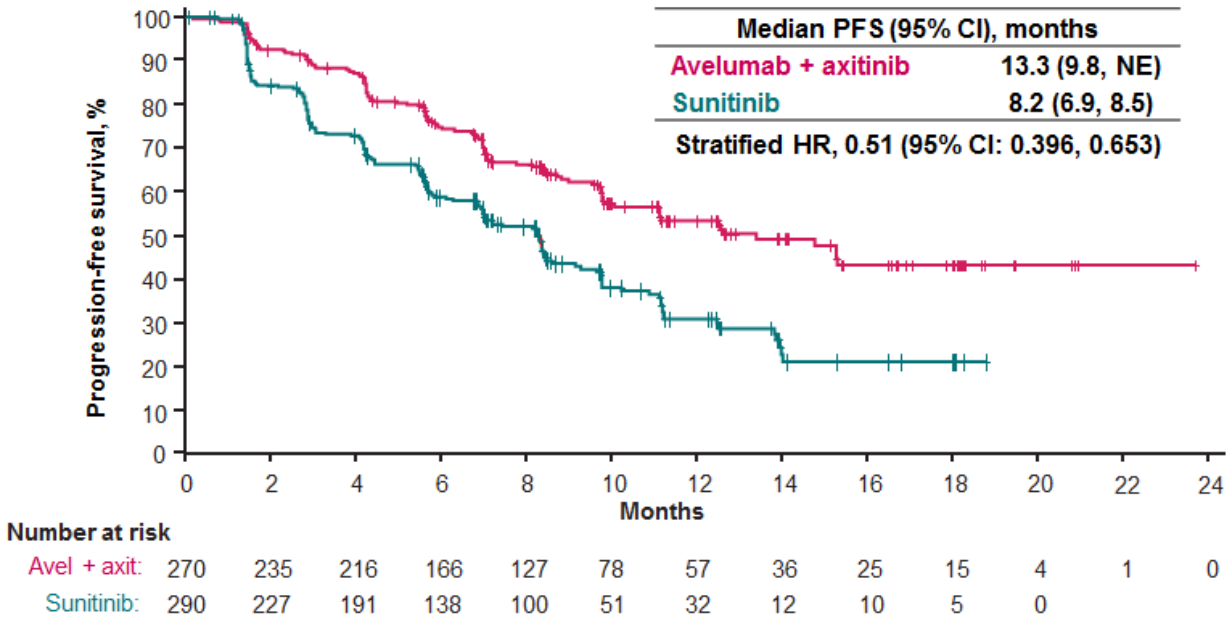
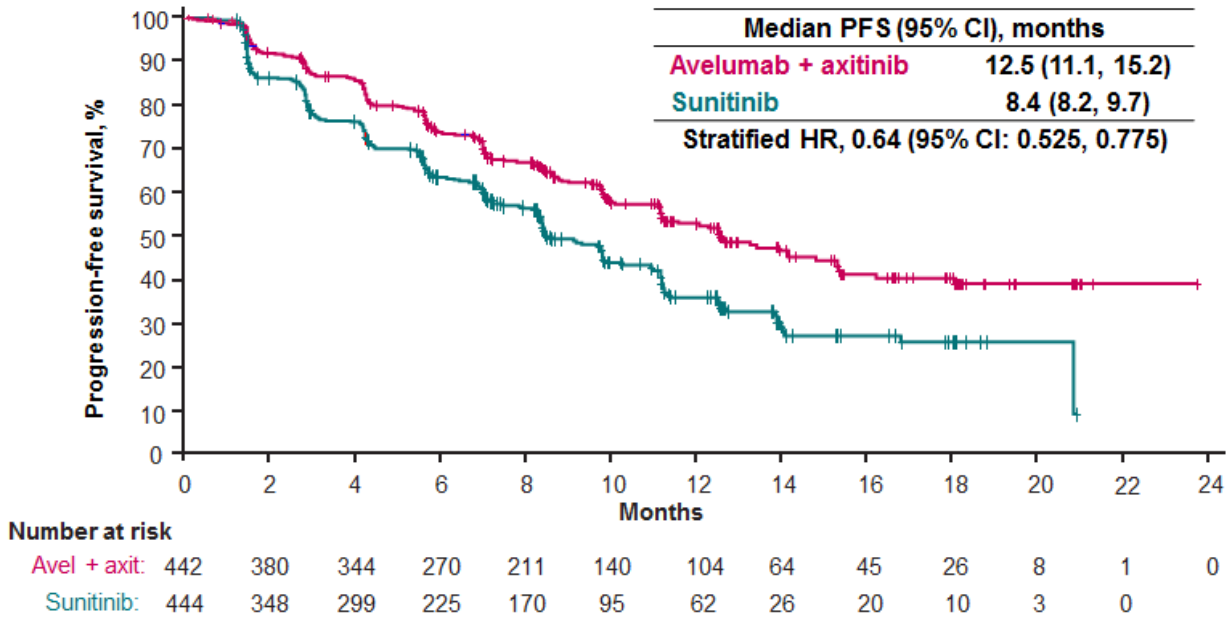


Figure S11. Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment in the PD-L1–Positive Group (A) and the Overall Population (B).

A



B



NE, not estimable.

Table S1. P-values for Interactions of Treatment per Subgroup.

Covariate	PD-L1–Positive Group	Overall Population
	P-value for Interaction*,†	
Age	0.483	0.874
Sex	0.129	0.168
Geographic region	0.192	0.792
ECOG PS	0.452	0.823
Prior nephrectomy	0.950	0.607
MSKCC prognostic risk group	0.739	0.292
IMDC prognostic risk group	0.758	0.503
PD-L1 status	–	0.411

* P-value for the interaction is based on the likelihood ratio test. The p-value is 2-sided.

† Interaction p-values for treatment by BMI and smoking status are not included because these are ad hoc exploratory subgroups.

Table S2. Investigator-Assessed Antitumor Activity in the PD-L1–Positive Group and the Overall Population.

Characteristic	PD-L1–Positive Group		Overall Population	
	Avelumab Plus Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab Plus Axitinib (N = 442)	Sunitinib (N = 444)
Confirmed objective response rate (95% CI), %	61.9 (55.8, 67.7)	29.7 (24.5, 35.3)	55.9 (51.1, 60.6)	30.2 (25.9, 34.7)
Stratified odds ratio (95% CI)	3.98 (2.721, 5.710)		2.99 (2.230, 3.970)	
Confirmed best overall response, no. (%)				
Complete response	11 (4.1)	9 (3.1)	14 (3.2)	10 (2.3)
Partial response	156 (57.8)	77 (26.6)	233 (52.7)	124 (27.9)
Stable disease	66 (24.4)	128 (44.1)	127 (28.7)	202 (45.5)
Progressive disease	20 (7.4)	51 (17.6)	38 (8.6)	68 (15.3)
Not evaluable	16 (5.9)*	24 (8.3)†	29 (6.6)‡	39 (8.8)§
Other‖	1 (0.4)	1 (0.3)	1 (0.2)	1 (0.2)
Median time to response (range), months	2.6 (1.1, 13.8)	2.8 (1.2, 12.5)	2.8 (1.1, 15.0)	2.8 (1.2, 12.5)
Median duration of response (95% CI), months	NR (11.9, NE)	8.8 (7.0, NE)	NR (11.9, NE)	12.6 (8.3, 15.3)
Patients with ongoing response, no./total no. (%)	112/167 (67.1)	49/86 (57.0)	164/247 (66.4)	82/134 (61.2)

NE, not estimable; NR, not reached.

* No postbaseline assessments due to early death or other reasons such as withdrawal of consent or start of new anti-cancer therapy (n = 10); stable disease <6 weeks after randomization (n = 4); all postbaseline assessments have overall response of not evaluable (n = 2).

† Stable disease <6 weeks after randomization (n = 11); no postbaseline assessments due to early death or other reasons such as withdrawal of consent or start of new anti-cancer therapy (n = 9); new anticancer therapy started before first postbaseline assessment (n = 2); progressive disease >12 weeks after randomization (n = 2).

‡ No postbaseline assessments due to early death or other reasons such as withdrawal of consent or start of new anti-cancer therapy (n = 18); stable disease <6 weeks after randomization (n = 7); no adequate baseline assessment (n = 2); all postbaseline assessments have overall response of not evaluable (n = 2).

§ Stable disease <6 weeks after randomization (n = 19); no postbaseline assessments due to early death or other reasons such as withdrawal of consent or start of new anti-cancer therapy (n = 13); new anticancer therapy started before first postbaseline assessment (n = 3); no adequate baseline assessment (n = 2); progressive disease >12 weeks after randomization (n = 2).

‖ Patients without target lesions at baseline per independent review who achieved non–complete response/non–progressive disease.

Table S3. Treatment-Related Adverse Events of Any Grade Occurring in ≥10% or Grade ≥3 Events Occurring in ≥5% of Treated Patients in the Overall Population.

Preferred Term	All Treated Patients (N = 873)			
	Avelumab Plus Axitinib (N = 434)		Sunitinib (N = 439)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	no. (%)			
Patients with events	414 (95.4)	246 (56.7)	423 (96.4)	243 (55.4)
Diarrhea	235 (54.1)	22 (5.1)	196 (44.6)	11 (2.5)
Hypertension	208 (47.9)	106 (24.4)	142 (32.3)	67 (15.3)
Fatigue	156 (35.9)	13 (3.0)	159 (36.2)	16 (3.6)
Palmar-plantar erythrodysesthesia syndrome	144 (33.2)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	116 (26.7)	2 (0.5)	12 (2.7)	0
Nausea	107 (24.7)	3 (0.7)	148 (33.7)	5 (1.1)
Hypothyroidism	105 (24.2)	1 (0.2)	59 (13.4)	1 (0.2)
Stomatitis	96 (22.1)	8 (1.8)	100 (22.8)	4 (0.9)
Decreased appetite	86 (19.8)	7 (1.6)	115 (26.2)	4 (0.9)
Chills	62 (14.3)	1 (0.2)	16 (3.6)	0
Mucosal inflammation	58 (13.4)	5 (1.2)	60 (13.7)	4 (0.9)
Alanine aminotransferase increased	57 (13.1)	21 (4.8)	43 (9.8)	9 (2.1)
Dysgeusia	56 (12.9)	0	141 (32.1)	0
Rash	54 (12.4)	2 (0.5)	42 (9.6)	2 (0.5)
Dyspnea	53 (12.2)	6 (1.4)	24 (5.5)	1(0.2)
Pruritus	53 (12.2)	0	19 (4.3)	0
Arthralgia	52 (12.0)	1 (0.2)	24 (5.5)	0
Infusion-related reaction	52 (12.0)	7 (1.6)	0	0
Aspartate aminotransferase increased	49 (11.3)	12 (2.8)	48 (10.9)	6 (1.4)
Weight decreased	49 (11.3)	7 (1.6)	17 (3.9)	1 (0.2)
Vomiting	42 (9.7)	1 (0.2)	68 (15.5)	7 (1.6)
Asthenia	41 (9.4)	5 (1.2)	54 (12.3)	8 (1.8)
Dyspepsia	24 (5.5)	0	74 (16.9)	0
Thrombocytopenia	12 (2.8)	1 (0.2)	78 (17.8)	24 (5.5)
Anemia	9 (2.1)	1 (0.2)	73 (16.6)	22 (5.0)
Neutropenia	6 (1.4)	1 (0.2)	79 (18.0)	34 (7.7)

Table S4. Subsequent Anticancer Therapies in the Overall Population.

Preferred Term	Overall Population	
	Avelumab Plus Axitinib (N = 442)	Sunitinib (N = 444)
Patients with any follow-up anticancer treatment, no. (%)	92 (20.8)	174 (39.2)
Cabozantinib	42 (9.5)	28 (6.3)
Everolimus	19 (4.3)	19 (4.3)
Axitinib	15 (3.4)	17 (3.8)
Sunitinib	15 (3.4)	23 (5.2)
Nivolumab	14 (3.2)	107 (24.1)
Lenvatinib	11 (2.5)	16 (3.6)
Pazopanib	7 (1.6)	12 (2.7)
Bevacizumab	3 (0.7)	1 (0.2)
Ipilimumab	3 (0.7)	7 (1.6)
Investigational drug	2 (0.5)	23 (5.2)
Blinded therapy	1 (0.2)	0
Drug, unspecified	1 (0.2)	0
Tivozanib	1 (0.2)	1 (0.2)
Atezolizumab	0	2 (0.5)
Durvalumab	0	6 (1.4)
Gemcitabine	0	2 (0.5)
Gimeracil/Oteracil/Tegafur	0	1 (0.2)
Ibrutinib	0	1 (0.2)
Interferon	0	1 (0.2)
Pembrolizumab	0	1 (0.2)
Sorafenib	0	2 (0.5)
X4P-001	0	1 (0.2)