Supplementary Appendix

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

Supplement to: Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2021;384:829-41. DOI: 10.1056/NEJMoa2026982

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Presented, in part, at the European Society of Medical Oncology Congress, September 19 to 21, 2020.

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*Site enrolled patients, but did not have any patients randomized to study treatment.

ADDITIONAL METHODS

END POINT DEFINITIONS

The primary end point of progression-free survival per blinded independent central review was defined as the time between the date of randomization and the first date of the documented progression, or death due to any cause, whichever occurred first. Patients who died without a reported progression (and without start of subsequent anticancer therapy) were considered to have progressed on the date of their death. Patients who did not progress or die were censored on the date of their last evaluable tumor assessment on or before initiation of subsequent anticancer therapy. Patients who had no on-study tumor assessments and did not die were censored on their date of randomization. Patients who started anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment on or before the initiation of first subsequent anticancer therapy.

The first secondary end point was overall survival, defined as the time between the date of randomization and the date of death due to any cause. Patients who had not died were censored at the last known alive date.

The second secondary end point of objective response rate per blinded independent central review was defined as the proportion of randomized participants who achieve a best response of complete response (CR) or partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Best overall response was defined as the best response designation recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations contributed to the best overall response assessment. Duration of response was defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented tumor progression (per RECIST v1.1) or death due to any cause, whichever occurred first. Patients who neither progressed nor died were censored on the date of their last tumor assessment. Responders who started anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anticancer therapy. Time to response

was defined as the time from randomization to the date of the first confirmed documented response (CR or PR) as assessed by blinded independent central review. Duration of response and time to response were evaluated for responders (CR or PR) only.

The exploratory end point of secondary progression-free survival including subsequent therapy was defined as time from randomization to objectively documented investigator-assessed progression, after the next line of therapy or death, whichever occurred first.

DISEASE ASSESSMENTS

Disease assessments were performed by computed tomography or magnetic resonance imaging at baseline, 12 weeks (±7 days) from randomization, and continuing every 6 weeks (±7 days) until week 60, then every 12 weeks (±14 days) until progression or treatment discontinuation. All patients were permitted to continue therapy after initial investigator-assessed RECIST v1.1–defined progression if the patient had clinical benefit and was tolerating therapy. Patients were followed for survival status after discontinuation of therapy.

HEALTH-RELATED QUALITY OF LIFE ASSESSMENTS

Patient-reported outcomes (PROs) for the nivolumab-plus-cabozantinib group were collected every 2 weeks after baseline compared with every 6 weeks after baseline for the sunitinib group. However, the analysis included patients with a baseline and at least one post-baseline assessment for the corresponding PRO score, and only the common time points in the schedules of treatment arms (baseline, week 7, week 13, etc.) were included, excluding follow-up visits (1 and 2) and unscheduled visits.

PRO	Cycle 1 (Baseline)	Cycle 2 and Subsequent Visits* (Cycle = 2 Weeks for Nivolumab plus Cabozantinib and 6 Weeks for Sunitinib)	Safety Follow-up (Follow-up Visit 1 and Follow-up Visit 2)†
FKSI-19	X‡	X‡	X

* If a dose was delayed, the procedures scheduled for that same time point were also delayed to coincide with when the dosing for that time point actually occurred.
† Patients were followed for at least 100 days after last dose of study treatment. Follow-up visit 1 occurred 30 days from the last dose (±7) days or on the date of discontinuation if that date was greater than 42 days from the last dose. Follow-up visit 2 occurred approximately 100 days (±7 days) from last dose of study drug. Both follow-up visits were conducted in person.
‡ Was completed on day 1 of each treatment cycle before any study-related procedures.

To estimate longitudinal changes in PRO scores from baseline at each scheduled visit while on study drug, common to both arms, a linear-regression model for repeated measures analysis was used. The dependent variable was change in PRO score from baseline, and the fixed effects were treatment, study visit, stratification factors (International Metastatic Renal-Cell Carcinoma Database Consortium [IMDC] prognostic score, programmed death ligand 1 [PD-L1] tumor expression, and region) as categorical parameters, baseline PRO score as a continuous parameter, and the interactions between visit and treatment and between baseline PRO score and visit. A heterogeneous Toeplitz variance–covariance matrix was used to model the covariance structure among each patient's repeated measures. The prespecified linear-regression model for repeated measures analysis was limited to the first 91 weeks (time frame determined post hoc) after baseline because of the small sample size (<10 patients) in the sunitinib group beyond this point.

IMDC RISK FACTORS

The IMDC prognostic model was derived and validated in previously untreated patients with metastatic RCC who received anti–vascular endothelial growth factor receptor (VEGF) therapy.[1,2] This model is composed of six clinical parameters that are used to categorize patients into favorable (zero risk factors), intermediate (1 or 2 risk factors), and poor (3 to 6 risk factors) prognosis groups. The individual risk factors are a Karnofsky performance status score of <80%, a time from initial diagnosis to treatment of less than 1 year, a hemoglobin level below the lower limit of normal, a corrected calcium concentration above the upper limit of normal, a neutrophil count above the upper limit of normal, and a platelet count above the upper limit of normal.

PD-L1 EXPRESSION ASSESSMENT

PD-L1 expression was defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells by means of the validated Dako PD-L1 IHC 28-8 pharmDx assay. Eligible patients must have had available tumor tissue, preferably obtained within 3 months but no more than 12 months before enrollment, with an associated pathology report, which must have been received by the central laboratory during screening for determination of PD-L1 expression. In order to be randomized, a

patient must have been classified as PD-L1 expression ≥1%, PD-L1 expression <1%, or PD-L1 expression indeterminate (tumor cell membrane staining hampered for reasons attributed to the biology of the tissue sample not because of improper sample preparation or handling). PD-L1 expression was collected at randomization per interactive response technology as well as in the clinical database.

STATISTICAL ANALYSIS

The formal analysis of progression-free survival was evaluated at an alpha level of 0.05 (final analysis). It was estimated that approximately 350 progression or death events would result at least 95% power to detect a hazard ratio of 0.68 with a critical hazard ratio of 0.811. The formal analysis of progression-free survival was planned to occur after approximately 9 to 10 months minimum follow-up in intention-to-treat patients. If the formal progression-free survival analysis was statistically significant, the formal interim or final analysis of overall survival would be tested. Overall survival was evaluated at an overall alpha level of 0.05 (0.011 at the first interim and 0.025 at the second interim; 0.041 at final) with 80% power, accounting for two formal interim analyses (performed after approximately 65% and 83% of targeted deaths for each interim analysis, respectively) to assess efficacy. The boundaries for declaring superiority of the formal comparisons of overall survival were derived based on the actual number of deaths using the Lan–DeMets spending function with O'Brien and Fleming type of boundary in EAST v6.[3,4] It was specified that approximately 254 deaths would result at least 80% power to detect a hazard ratio of 0.70 for overall survival with a critical hazard ratio of 0.774. The first interim analysis of overall survival was planned to occur at the time of formal progression-free survival analysis with approximately 65% of the targeted deaths and a critical hazard ratio of 0.673. If the formal analysis of overall survival (interim or final, whichever occurs first) was statistically significant, then formal analysis of response rate would be tested. Response rate was evaluated at an alpha level of 0.05 (final analysis). At the time of database lock (March 30, 2020), overall 335 patients had disease progression or had died and 166 deaths had occurred.

ADDITIONAL RESULTS

SUBSEQUENT THERAPY

At the time of this analysis in the nivolumab plus cabozantinib group, 36 (11.1%) intention-to-treat patients received any subsequent systemic anticancer therapy (25.4% of 142 patients who discontinued study treatment), and the most common was a VEGF receptor inhibitor (n=31, 86.1% of 36 patients who received subsequent systemic therapy). In the sunitinib group, 91 (27.7%) intention-to-treat patients received any subsequent systemic therapy (39.9% of the 228 patients who discontinued study treatment), and the most common was a PD-(L)1 inhibitor (n=67, 73.6% of 91 patients who received subsequent systemic therapy). Subsequent therapy details are summarized in Table S1 in the Supplementary Appendix. Progression-free survival 2 outcomes also favored nivolumab plus cabozantinib over sunitinib (HR 0.52, 95% CI, 0.39-0.70; Fig. S6 in the Supplementary Appendix).

Figure S1. Trial Profile CONSORT Diagram.

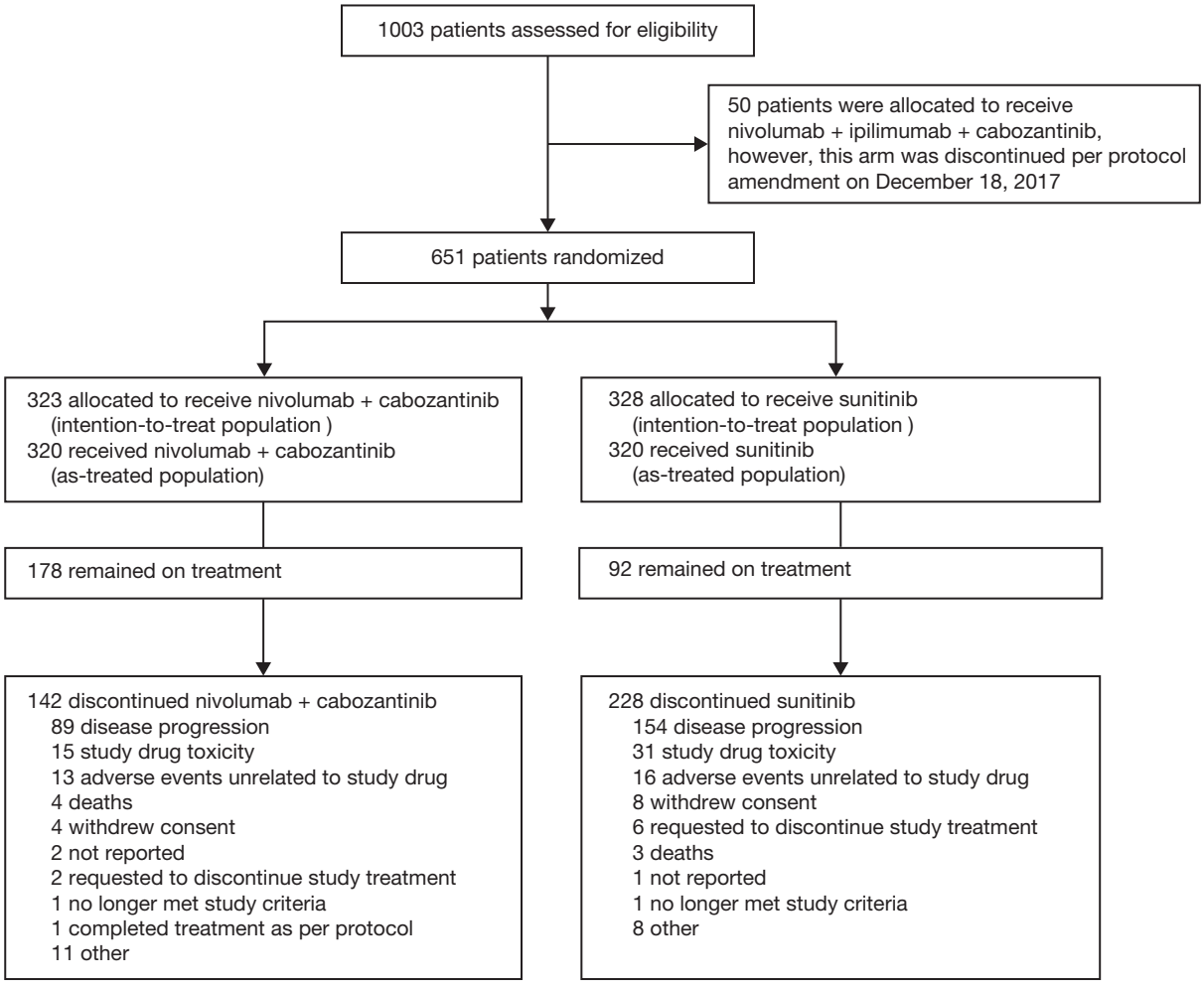


Figure S2. Duration of Response in Patients with a Best Overall Response of Complete or Partial Response per Blinded Independent Central Review.

NE denotes could not be estimated.

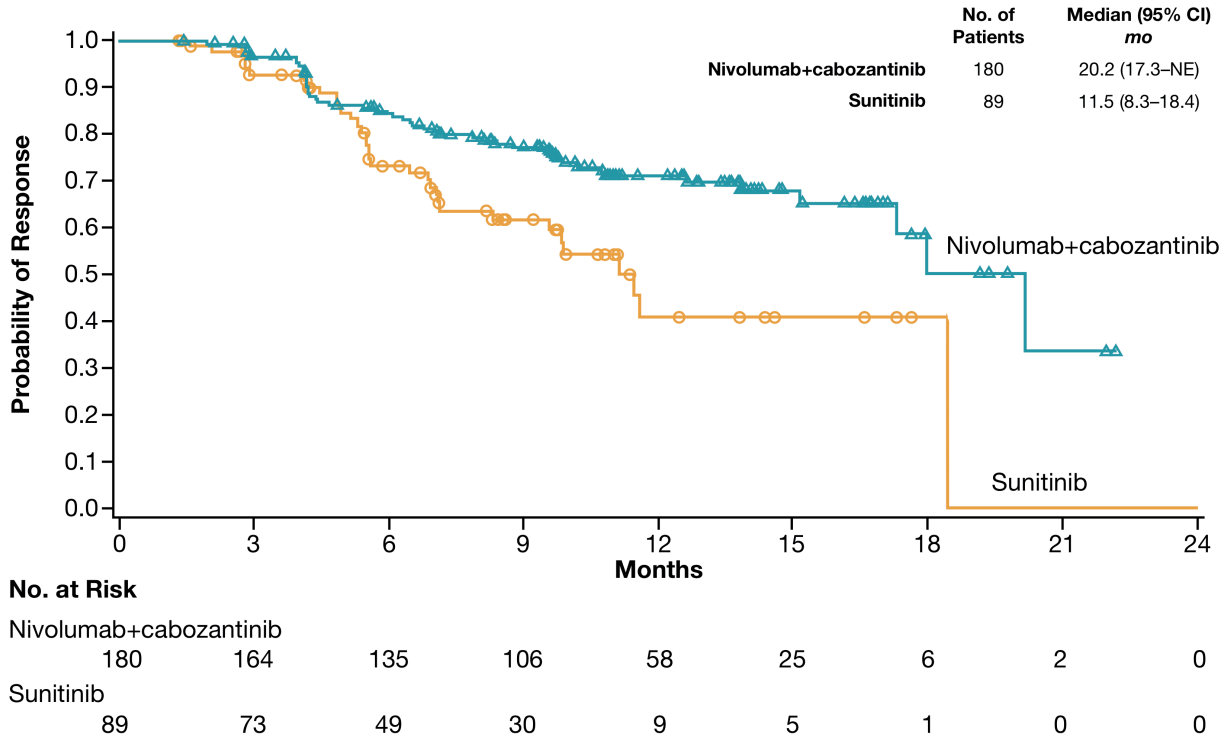


Figure S3. Depth of Response in Patients with One Baseline and at Least One Post-Baseline Measurement.

Panel A shows the nivolumab plus cabozantinib group. Panel B shows sunitinib group. Includes patients with target lesion at baseline and ≥1 on-treatment tumor assessment. Graph indicates best reduction defined as the maximum reduction in sum of diameters of target lesions (negative value means true reduction; positive value means increase only observed over time). Horizontal reference line indicates a 30% reduction consistent with a response according to Response Evaluation Criteria in Solid Tumors, version 1.1. Teal and gold colored lines represent confirmed responders per blinded independent central review.

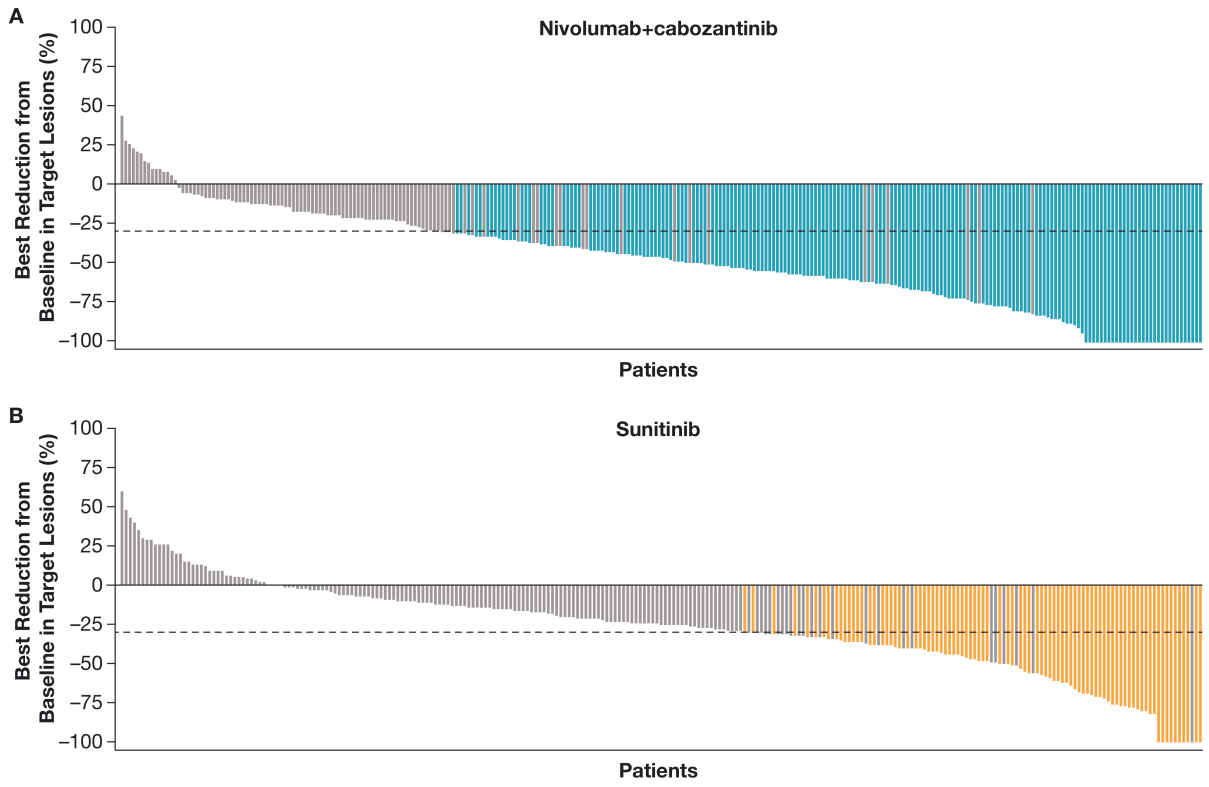


Figure S4. Objective Response per Blinded Independent Central Review According to Subgroup.

Shown is the analysis of objective response according to subgroup. The International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic risk, programmed death ligand 1 (PD-L1) status, and geographic region (stratification factors) were recorded at screening by means of interactive response technology among all the patients who underwent randomization. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.

ORR denotes objective response rate.

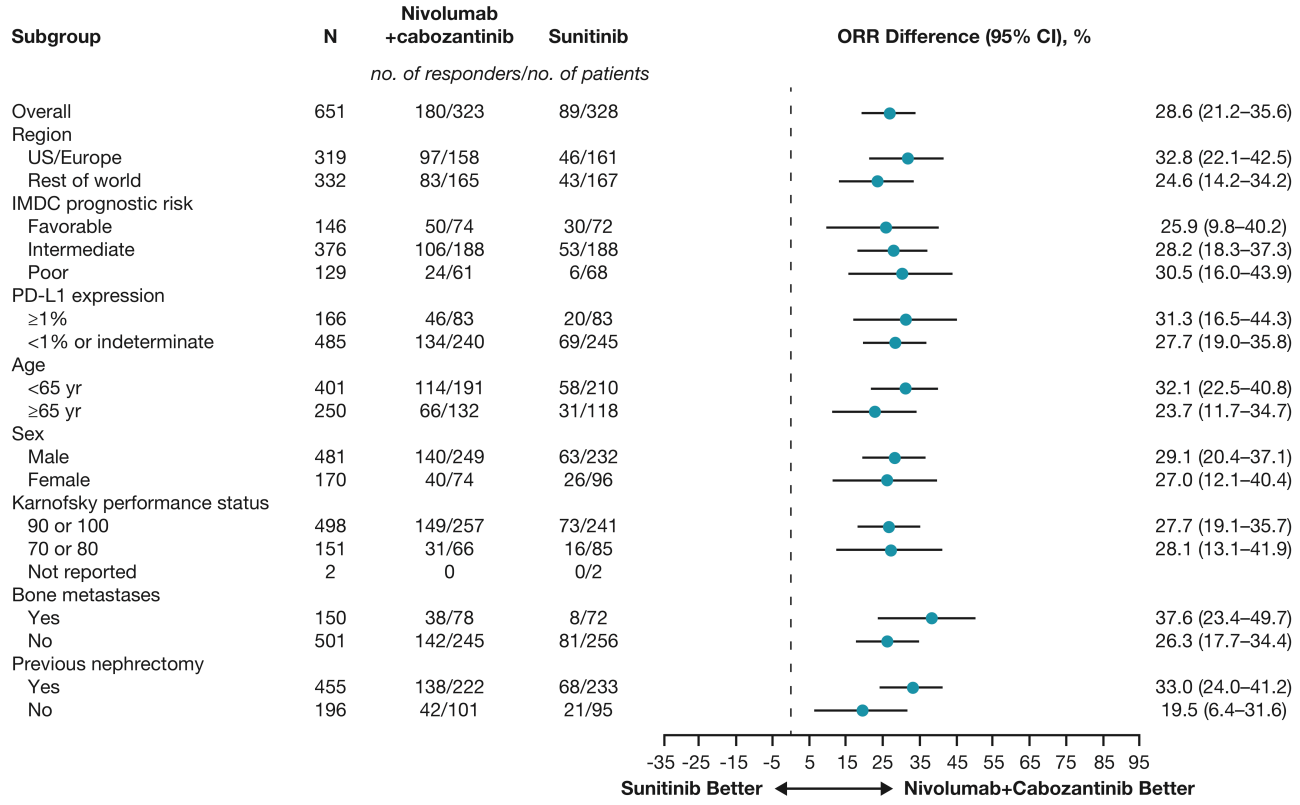


Figure S5. Health-related Quality of Life in Evaluable Patients.

Panel A shows the least squares (LS) mean change from baseline in National Comprehensive Cancer Network 19-item Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19) total scores. Panel B shows the LS mean change from baseline in the 9-item subset of disease-related symptoms (FKSI-DRS) scores. Number at risk reflects intention-to-treat patients with baseline plus at least one post-baseline assessment of health-related quality of life with non-missing patient-reported outcome data. Time 0 indicates baseline. The FKSI-19 is a validated 19-item instrument that measures kidney cancer–specific patient reported outcomes. Patients rate their symptoms on a 5-point scale, with responses ranging from "not at all" to "very much." The FKSI-19 contains the following domains: disease-related symptoms (shown separately in panel B), together with disease-related symptoms physical, disease-related symptoms emotional, treatment side effects, and functional wellbeing (not shown separately).[5] Asterisks represent time points where the between-arm difference was statistically significant (P<0.05). SE denotes robust standard error.

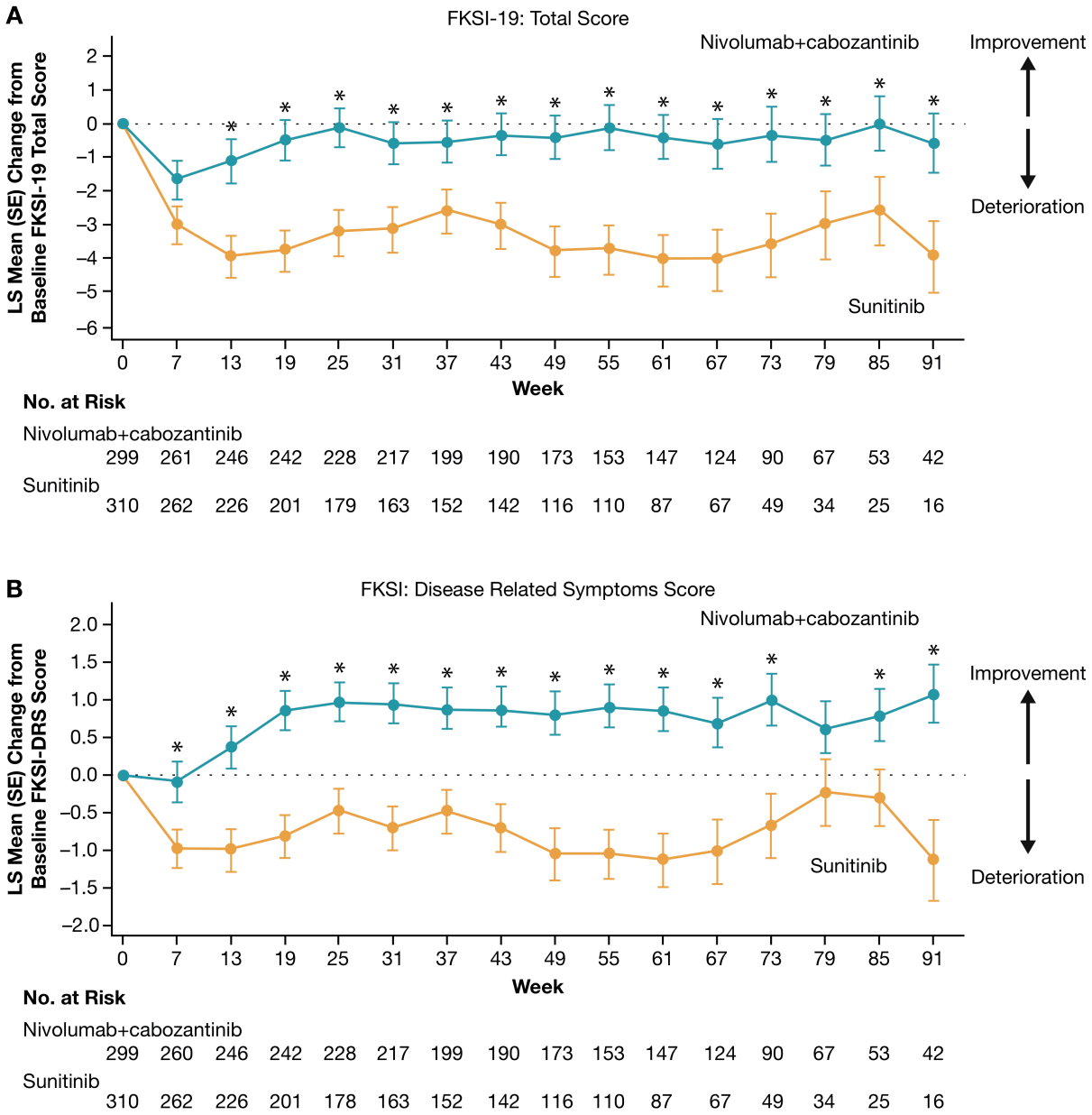
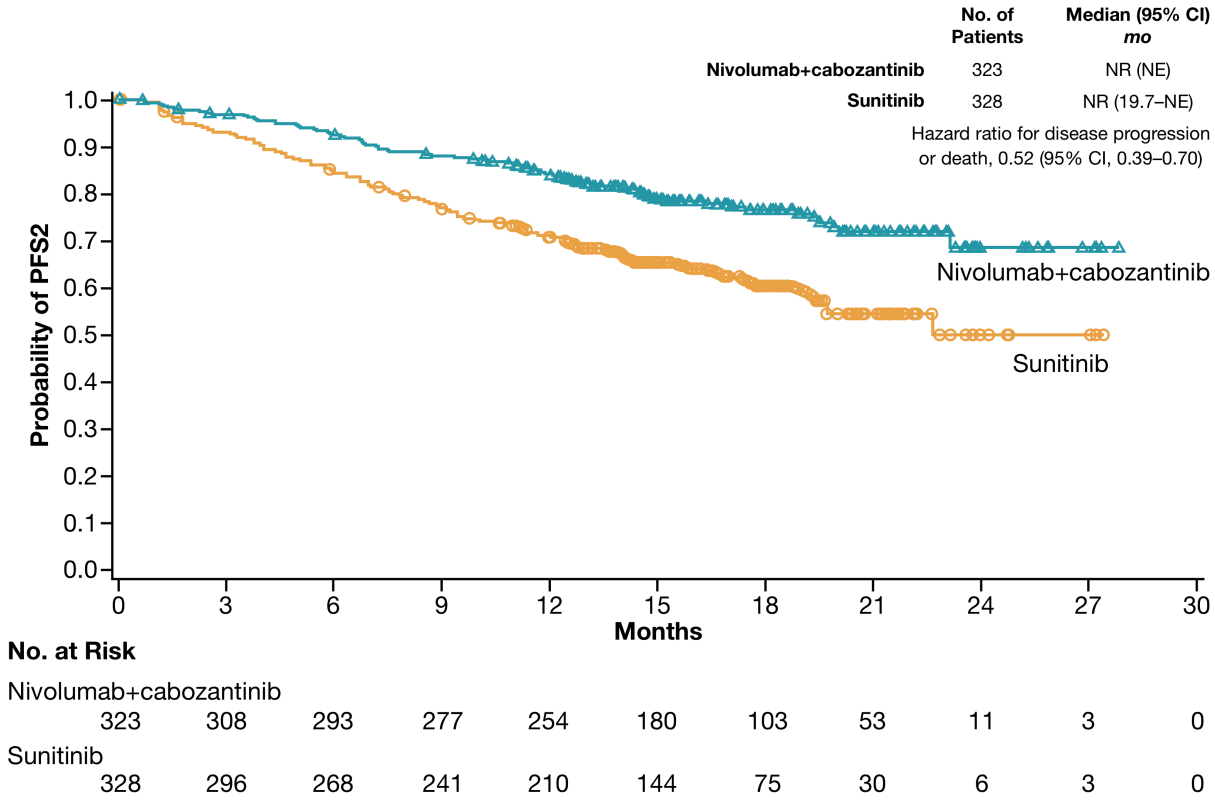


Figure S6. Progression-free Survival Including Second-line Therapy in the Intention-to-Treat Population.

NE denotes could not be estimated; NR, not reached; and PFS2, progression-free survival including second-line therapy.



No. at Risk

Nivolumab+cabozantinib	323	308	293	277	254	180	103	53	11	3	0
Sunitinib	328	296	268	241	210	144	75	30	6	3	0

Table S1. Summary of Subsequent Anticancer Therapy.

	Intention-to-Treat Population		Patients Who Discontinued Study Treatment	
Therapy*	**Nivolumab plus Cabozantinib (N=323)**	**Sunitinib (N=328)**	**Nivolumab plus Cabozantinib (N=142)**	**Sunitinib (N= 228)**
	No. of Patients (%)			
Any subsequent therapy†	61 (18.9)	108 (32.9)	61 (43.0)	108 (47.4)
Any subsequent systemic therapy	36 (11.1)	91 (27.7)	36 (25.4)	91 (39.9)
Any PD-(L)1 inhibitor	9 (2.8)	67 (20.4)	9 (6.3)	67 (29.4)
Nivolumab	7 (2.2)	60 (18.3)	7 (4.9)	60 (26.3)
Pembrolizumab	4 (1.2)	4 (1.2)	4 (2.8)	4 (1.8)
Durvalumab	0	4 (1.2)	0	4 (1.8)
Any CTLA-4 inhibitor	4 (1.2)	12 (3.7)	4 (2.8)	12 (5.3)
Ipilimumab	4 (1.2)	11 (3.4)	4 (2.8)	11 (4.8)
Tremelimumab	0	1 (0.3)	0	1 (0.4)
Nivolumab plus ipilimumab combination	1 (0.3)	2 (0.6)	1 (0.7)	2 (0.9)
Any VEGF(R) inhibitor	31 (9.6)	35 (10.7)	31 (21.8)	35 (15.4)
Axitinib	11 (3.4)	9 (2.7)	11 (7.7)	9 (3.9)
Sunitinib	9 (2.8)	3 (0.9)	9 (6.3)	3 (1.3)
Lenvatinib	5 (1.5)	0	5 (3.5)	0
Pazopanib	4 (1.2)	4 (1.2)	4 (2.8)	4 (1.8)
Lenvatinib mesylate	2 (0.6)	2 (0.6)	2 (1.4)	2 (0.9)
Pazopanib hydrochloride	2 (0.6)	0	2 (1.4)	0
Sorafenib	1 (0.3)	4 (1.2)	1 (0.7)	4 (1.8)
Sunitinib malate	1 (0.3)	0	1 (0.7)	0
Cabozantinib	0	15 (4.6)	0	15 (6.6)
Other	7 (2.2)	10 (3.0)	7 (4.9)	10 (4.4)
Everolimus	6 (1.9)	4 (1.2)	6 (4.2)	4 (1.8)
Investigational antineoplastic drugs	1 (0.3)	2 (0.6)	1 (0.7)	2 (0.9)
Investigational drug	0	2 (0.6)	0	2 (0.9)
Savolitinib	0	2 (0.6)	0	2 (0.9)

* Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after the date of first study dose (date of randomization if patient was never treated).
† Includes patients who received subsequent radiotherapy, surgery, or systemic therapy.
CTLA-4 denotes cytotoxic T-lymphocyte–associated protein 4; PD-(L)1, programmed death 1/programmed death ligand 1; VEGF(R), vascular endothelial growth factor (receptor).

Table S2. Progression-free Survival per Blinded Independent Central Review According to Subgroup.

Subgroup	Nivolumab plus Cabozantinib		Sunitinib	
	N	Median Progression-free Survival (95% CI), months	N	Median Progression-free Survival (95% CI), months
Overall	323	16.6 (12.5–24.9)	328	8.3 (7.0–9.7)
Region				
US/Europe	158	20.1 (13.6–NE)	161	9.6 (7.9–11.8)
Rest of World	165	12.3 (9.1–24.9)	167	7.0 (5.7–9.5)
IMDC risk group				
Favorable	74	NR (12.8–NE)	72	12.8 (9.6–17.0)
Intermediate	188	17.7 (11.2–24.9)	188	8.5 (7.0–10.4)
Poor	61	12.3 (6.9–20.1)	68	4.2 (2.9–5.6)
PD-L1 expression				
≥1%	83	11.9 (7.1–22.9)	83	4.7 (3.2–9.7)
<1% or indeterminate	240	17.7 (12.8–NE)	245	9.3 (7.9–10.9)
Age				
<65 year	191	16.6 (12.6–24.9)	210	7.9 (5.6–9.3)
≥65 year	132	19.8 (11.2–22.9)	118	9.7 (7.1–13.4)
Sex				
Male	249	17.7 (12.8–NE)	232	8.4 (7.0–9.7)
Female	74	12.5 (9.0–24.9)	96	7.1 (5.9–11.2)
Karnofsky performance score				
90 or 100	257	17.7 (12.8–NE)	241	9.7 (8.2–11.2)
70 or 80	66	11.1 (6.9–20.1)	85	5.6 (4.1–7.9)
Not reported	0	–	2	NR (NE)
Bone metastases				
Yes	78	20.1 (8.7–24.9)	72	4.4 (3.7–7.0)
No	245	16.6 (12.3–NE)	256	9.6 (8.1–11.1)
Previous nephrectomy				
Yes	222	20.1 (15.2–NE)	233	9.2 (7.0–10.4)
No	101	11.2 (8.8–15.3)	95	7.1 (5.3–9.4)

International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) risk, programmed death ligand 1 (PD-L1) status, and region (stratification factors) were recorded at screening per interactive response technology among all randomized patients.
NE denotes not estimable; NR, not reached.

Table S3. Any-Grade Adverse Events Attributed to Study Treatment by the Investigator that Occurred in 10% or More of Patients in the As-Treated Population in Either Group.

Event	Nivolumab plus Cabozantinib (N=320)		Sunitinib (N=320)	
	No. of Patients (%)			
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any event*	309 (96.6)	194 (60.6)	298 (93.1)	163 (50.9)
Diarrhea	182 (56.9)	18 (5.6)	136 (42.5)	14 (4.4)
Palmar-plantar erythrodysesthesia syndrome	122 (38.1)	24 (7.5)	129 (40.3)	24 (7.5)
Hypothyroidism	107 (33.4)	1 (0.3)	90 (28.1)	1 (0.3)
Hypertension	97 (30.3)	35 (10.9)	107 (33.4)	39 (12.2)
Fatigue	86 (26.9)	8 (2.5)	97 (30.3)	12 (3.8)
ALT increased	80 (25.0)	15 (4.7)	20 (6.3)	2 (0.6)
AST increased	75 (23.4)	10 (3.1)	28 (8.8)	2 (0.6)
Dysgeusia	69 (21.6)	0	65 (20.3)	0
Nausea	68 (21.3)	2 (0.6)	81 (25.3)	0
Decreased appetite	65 (20.3)	4 (1.3)	53 (16.6)	2 (0.6)
Rash	62 (19.4)	5 (1.6)	22 (6.9)	0
Mucosal inflammation	61 (19.1)	3 (0.9)	80 (25.0)	8 (2.5)
Asthenia	57 (17.8)	10 (3.1)	48 (15.0)	7 (2.2)
Pruritus	52 (16.3)	1 (0.3)	13 (4.1)	0
Stomatitis	50 (15.6)	7 (2.2)	74 (23.1)	7 (2.2)
Lipase increased	48 (15.0)	17 (5.3)	35 (10.9)	15 (4.7)
Amylase increased	39 (12.2)	8 (2.5)	25 (7.8)	7 (2.2)
Hyponatremia	38 (11.9)	22 (6.9)	19 (5.9)	14 (4.4)
Hypophosphatemia	38 (11.9)	17 (5.3)	15 (4.7)	3 (0.9)
Dysphonia	37 (11.6)	1 (0.3)	8 (2.5)	0
Vomiting	36 (11.3)	4 (1.3)	52 (16.3)	1 (0.3)
Anemia	32 (10.0)	3 (0.9)	61 (19.1)	8 (2.5)
Hypomagnesaemia	32 (10.0)	1 (0.3)	9 (2.8)	0
Thrombocytopenia	19 (5.9)	1 (0.3)	61 (19.1)	14 (4.4)
Dyspepsia	18 (5.6)	0	32 (10.0)	1 (0.3)
Platelet count decreased	17 (5.3)	0	59 (18.4)	14 (4.4)
Neutropenia	14 (4.4)	2 (0.6)	47 (14.7)	11 (3.4)

* Shown are treatment-related adverse events that occurred while patients were receiving the assigned treatment or within 30 days after the end of the trial treatment period. The as-treated population included all patients who underwent randomization and received at least one dose of trial treatment. Events are listed in descending order of frequency in the nivolumab plus cabozantinib group. Adverse events are classified according to the *Medical Dictionary for Regulatory Activities*, version 22.1.

Any-grade treatment-related adverse events led to discontinuation of either therapy in 15.3% of patients treated with nivolumab plus cabozantinib (5.6% discontinued nivolumab only; 6.6% discontinued cabozantinib only; 3.1% discontinued both nivolumab and cabozantinib) and in 8.8% of patients treated with sunitinib.

ALT denotes alanine aminotransferase; AST, aspartate aminotransferase.

Table S4. Immune-Mediated Adverse Events in the As-Treated Population.

Event*	Nivolumab plus Cabozantinib (N=320)		Sunitinib (N=320)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	No. of Patients (%)			
Hypothyroidism	79 (24.7)	1 (0.3)	31 (9.7)	1 (0.3)
Hyperthyroidism	30 (9.4)	2 (0.6)	1 (0.3)	0
Rash	19 (5.9)	3 (0.9)	1 (0.3)	0
Diarrhea	16 (5.0)	5 (1.6)	0	0
Hepatotoxicity	13 (4.1)	8 (2.5)	6 (1.9)	1 (0.3)
Pneumonitis	10 (3.1)	3 (0.9)	0	0
Increased ALT	10 (3.1)	7 (2.2)	0	0
Adrenal insufficiency	10 (3.1)	6 (1.9)	0	0
Maculo-papular rash	9 (2.8)	1 (0.3)	0	0
Increased AST	7 (2.2)	3 (0.9)	0	0
Hepatitis	4 (1.3)	2 (0.6)	0	0
Autoimmune hepatitis	3 (0.9)	3 (0.9)	0	0
Increased blood bilirubin	2 (0.6)	0	1 (0.3)	0
Increased transaminases	2 (0.6)	1 (0.3)	0	0
Increased blood creatinine	2 (0.6)	1 (0.3)	1 (0.3)	0
Hypophysitis	2 (0.6)	1 (0.3)	0	0
Hepatic failure	1 (0.3)	1 (0.3)	0	0
Acute thyroiditis	1 (0.3)	1 (0.3)	0	0
Renal failure	1 (0.3)	1 (0.3)	1 (0.3)	0
Dermatitis	1 (0.3)	1 (0.3)	0	0
Immune-mediated dermatitis	1 (0.3)	1 (0.3)	0	0
Hyperbilirubinemia	1 (0.3)	0	2 (0.6)	1 (0.3)
Dermatitis acneiform	1 (0.3)	0	1 (0.3)	0
Secondary adrenocortical insufficiency	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Acute kidney injury	1 (0.3)	0	0	0
Nephritis	1 (0.3)	0	0	0
Pemphigoid	1 (0.3)	0	0	0
Rash pruritic	1 (0.3)	0	0	0
Scrotal rash	1 (0.3)	0	0	0
Hypersensitivity	1 (0.3)	0	0	0
Infusion related reaction	1 (0.3)	0	0	0
Colitis	1 (0.3)	0	0	0
Colitis ulcerative	0	0	1 (0.3)	0

* Specific events (or groups of preferred terms describing specific events) including pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine, and others, considered by investigators to be potentially immune-mediated, that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component. Adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis were considered immune-mediated adverse events regardless of immune-modulating medication use, as these endocrine events were often managed without immune-modulating medication.
ALT denotes alanine aminotransferase; AST, aspartate aminotransferase.

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