ORIGINAL ARTICLE

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*

ABSTRACT

BACKGROUND

The efficacy and safety of nivolumab plus cabozantinib as compared with those of sunitinib in the treatment of previously untreated advanced renal-cell carcinoma are not known.

METHODS

In this phase 3, randomized, open-label trial, we randomly assigned adults with previously untreated clear-cell, advanced renal-cell carcinoma to receive either nivolumab (240 mg every 2 weeks) plus cabozantinib (40 mg once daily) or sunitinib (50 mg once daily for 4 weeks of each 6-week cycle). The primary end point was progression-free survival, as determined by blinded independent central review. Secondary end points included overall survival, objective response as determined by independent review, and safety. Health-related quality of life was an exploratory end point.

RESULTS

Overall, 651 patients were assigned to receive nivolumab plus cabozantinib (323 patients) or sunitinib (328 patients). At a median follow-up of 18.1 months for overall survival, the median progression-free survival was 16.6 months (95% confidence interval [CI], 12.5 to 24.9) with nivolumab plus cabozantinib and 8.3 months (95% CI, 7.0 to 9.7) with sunitinib (hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.64; P<0.001). The probability of overall survival at 12 months was 85.7% (95% CI, 81.3 to 89.1) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5 to 80.0) with sunitinib (hazard ratio for death, 0.60; 98.89% CI, 0.40 to 0.89; P=0.001). An objective response occurred in 55.7% of the patients receiving nivolumab plus cabozantinib and in 27.1% of those receiving sunitinib (P<0.001). Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups. Adverse events of any cause of grade 3 or higher occurred in 75.3% of the 320 patients receiving nivolumab plus cabozantinib and in 70.6% of the 320 patients receiving sunitinib. Overall, 19.7% of the patients in the combination group discontinued at least one of the trial drugs owing to adverse events, and 5.6% discontinued both. Patients reported better health-related quality of life with nivolumab plus cabozantinib than with sunitinib.

CONCLUSIONS

Nivolumab plus cabozantinib had significant benefits over sunitinib with respect to progression-free survival, overall survival, and likelihood of response in patients with previously untreated advanced renal-cell carcinoma. (Funded by Bristol Myers Squibb and others; CheckMate 9ER ClinicalTrials.gov number, NCT03141177.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Choueiri at the Lank Center for Genitourinary Oncology, Dana–Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, 450 Brookline Ave., Boston, MA 02215, or at toni_choueiri@dfci.harvard.edu, or to Dr. Motzer at the Memorial Sloan Kettering Cancer Center, Memorial Hospital, 1275 York Ave., New York, NY 10021, or at motzerr@mskcc.org.

*A complete list of the CheckMate 9ER investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2021;384:829-41.
DOI: 10.1056/NEJMoa2026982
Copyright © 2021 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Renal-cell carcinoma is a tumor characterized by loss of the *VHL* gene, and this loss leads to increased angiogenesis.[1] Immunotherapies and antiangiogenic therapies have improved outcomes, and the treatment landscape has expanded rapidly.[1-3] Clinical benefits in patients with advanced renal-cell carcinoma have been observed with regimens that include different combinations of immune, antiangiogenic, and signal transduction–blocking agents,[4-9] and refining the individual components may further improve outcomes.

Both cabozantinib (a small-molecule inhibitor of tyrosine kinases) and nivolumab (a programmed death 1 [PD-1] immune checkpoint inhibitor antibody) are approved therapies for the treatment of advanced renal-cell carcinoma and have been shown to improve overall survival as single agents in phase 3 trials.[10-13] Cabozantinib inhibits tyrosine kinases involved in tumor-cell proliferation, neovascularization, and immune-cell regulation, including MET, vascular endothelial growth factor receptor 1 (VEGF-R1) through VEGF-R3, and the TAM family of kinases (TYRO3, AXL, and MER), and has immunomodulatory properties that counteract tumor-induced immunosuppression, which may enhance response to immune-checkpoint inhibition.[14-17] In a phase 1 dose-finding study of nivolumab plus cabozantinib involving patients with advanced genitourinary cancers, a cabozantinib dose of 40 mg per day had similar efficacy to that of 60 mg per day but had fewer toxic effects.[4] We conducted a phase 3 trial (CheckMate 9ER) to compare the efficacy and safety of the combination of nivolumab plus cabozantinib with sunitinib in the first-line treatment of patients with advanced renal-cell carcinoma with clear-cell histologic features.

Methods

Patients

Eligible patients were adults with previously untreated advanced renal-cell carcinoma with a clear-cell component. Patients had any International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic risk score[18,19] and a Karnofsky performance-status score of at least 70 (on a scale from 0 to 100, with lower scores indicating greater disability).[20] Patients had measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1, as assessed by the investigator and either advanced renal-cell carcinoma (not amenable to curative surgery or radiation therapy) or metastatic renal-cell carcinoma (American Joint Committee on Cancer stage IV). Additional enrollment criteria included no previous systemic therapy for renal-cell carcinoma (one previous adjuvant or neoadjuvant therapy for completely resectable renal-cell carcinoma was permitted) and available tumor tissue for analysis. Patients were excluded if they had active central nervous system metastases or active autoimmune disease or had received systemic treatment with either glucocorticoids (>10 mg of prednisone equivalent per day) or other immunosuppressive medications within 14 days before randomization. Full eligibility criteria are listed in the trial protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatments

CheckMate 9ER is a phase 3, randomized, open-label trial of nivolumab combined with cabozantinib as compared with sunitinib monotherapy. Patients underwent randomization in a 1:1 ratio and were stratified according to IMDC prognostic risk score (0 [favorable] vs. 1 or 2 [intermediate] vs. 3 to 6 [poor]),[18,19] geographic region (United States and Europe vs. the rest of the world), and tumor expression of the PD-1 ligand PD-L1 (≥1% vs. <1% or indeterminate). Specific risk factors that make up the IMDC score are included in the Supplementary Appendix, available at NEJM.org. Nivolumab was administered intravenously at a dose of 240 mg every 2 weeks, and cabozantinib was administered orally at a dose of 40 mg once daily. Sunitinib was administered orally at a dose of 50 mg once daily for 4 weeks, followed by 2 weeks off (6-week cycle). All trial treatment continued until disease progression or unacceptable toxic effects, with a maximum 2-year duration of nivolumab treatment. Crossover between groups was not permitted. Dose reductions were not allowed for nivolumab but were permitted for cabozantinib and sunitinib, according to the protocol. Dose delays for adverse events were permitted for all trial drugs. Discontinuation assessments for nivolumab and cabozantinib were made separately for each drug; if discontinuation criteria were met for only one drug, treatment could

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

continue with the other drug that was not related to the observed toxic effect, according to the protocol. Dose-reduction specifications and discontinuation criteria for both groups are detailed in the trial protocol.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival among all the patients who underwent randomization (intention-to-treat population). The secondary end points were overall survival and objective response (including time to and duration of response) in the intention-to-treat population and safety in patients who received at least one dose of trial treatment. Progression-free survival and objective response were assessed by blinded independent central review. Efficacy outcomes according to key disease and demographic characteristics at baseline were evaluated by means of prespecified supportive subgroup analyses. An exploratory analysis of secondary progression-free survival outcomes, including subsequent therapy (progression-free survival 2), was performed. Health-related quality of life was assessed as an exploratory end point with the use of the National Comprehensive Cancer Network 19-item Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19; scores range from 0 to 76, with higher scores indicating fewer symptoms) and the 9-item subset of disease-related symptoms (FKSI-DRS; scores range from 0 to 36, with higher scores indicating fewer symptoms).[21] Threshold values for the change in scores that was considered important to patients for the FKSI-19 instrument and subscales have been estimated (total score, 3 points; FKSI-DRS, 1 point).[22,23]

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[24] The incidences of adverse events (both of any cause and treatment-related) and of events leading to discontinuation of trial treatment or death are summarized. Immune-mediated adverse events and the use of glucocorticoids (≥40 mg prednisone daily or equivalent) to manage these events are also reported. In addition, PD-L1 expression was defined as the percent of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated by means of the validated Dako PD-L1 IHC 28-8 pharmDx assay.[25]

TRIAL OVERSIGHT

This trial was approved by the institutional review board or an ethics committee at each site and was conducted in accordance with Good Clinical Practice guidelines defined by the International Council for Harmonisation. Enrolled patients provided written informed consent according to the principles of the Declaration of Helsinki. Efficacy and safety data were reviewed by an independent data monitoring committee. The trial was designed by the authors in collaboration with the sponsor (Bristol Myers Squibb) and partner (Exelixis). The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the authors contributed to drafting and provided final approval of the manuscript. As part of the site agreement, investigators agreed to keep all aspects and outcomes of the trial confidential. A medical writer employed by the sponsor assisted with the preparation of the manuscript.

STATISTICAL ANALYSIS

It was estimated that 638 patients would undergo randomization. The overall alpha for this trial was 0.05 (two-sided) for the primary end point (progression-free survival) and secondary end points (overall survival, followed by objective response), and a hierarchical testing procedure was used.[26] Progression-free survival was to be evaluated at an alpha level of 0.05 (single final analysis). If the between-group difference in progression-free survival was significant, analysis of overall survival would be performed at an overall alpha level of 0.05, with the use of a hierarchical testing procedure. If the difference in progression-free survival (primary end point) was significant, it was specified that the trial would continue until the between-group difference in overall survival (secondary end point) was significant (0.011 at the first interim, 0.025 at the second interim, and 0.041 at the final analysis with an O'Brien and Fleming alpha spending function).[27] On rejection of the null hypothesis for overall survival, analysis of objective response would be performed at an alpha level of 0.05 (single final analysis), according to a hierarchical testing procedure. Confidence intervals were defined on the basis of the respective alpha level assigned to a given end point. All P values reported are two-sided. Further details

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

of the analysis are included in the Methods section of the Supplementary Appendix, and the full statistical analysis plan is available with the protocol.

Progression-free and overall survival were compared between the treatment groups with the use of a stratified log-rank test, and the estimate of the hazard ratio between treatment groups was calculated by means of a stratified Cox proportional-hazards model that used IMDC prognostic risk score (0 vs. 1 or 2 vs. 3 to 6), tumor PD-L1 expression (≥1% vs. <1% or indeterminate), and region (United States or Europe vs. the rest of the world) as stratification factors. Progression-free and overall survival and response duration were estimated with the use of Kaplan–Meier methods. Estimates of the percentage of patients with an objective response, along with the exact two-sided 95% confidence interval, were computed according to the Clopper–Pearson method.[28] The forest plots of the unstratified hazard ratios for progression-free and overall survival and a forest plot of unweighted differences in the percentage of patients with an objective response were produced for each prespecified subgroup, with no adjustment for multiplicity. Change from baseline in health-related quality of life was assessed with the use of descriptive statistics, and nominal P values based on a linear-regression model for repeated measures that controlled for treatment group, time point, baseline patient-reported outcomes score, and the stratification factors (IMDC prognostic risk score, tumor PD-L1 expression, and geographic region) are reported. All data reported are based on the final analysis of progression-free survival, the first interim analysis of overall survival, and the final analysis of objective response from a database lock of March 30, 2020.

RESULTS

PATIENTS AND TREATMENTS

Between September 2017 and May 2019, a total of 651 patients underwent randomization at 125 sites in 18 countries; 323 patients made up the intention-to-treat population in the nivolumab-plus-cabozantinib group, and 328 patients made up the intention-to-treat population in the sunitinib group. Among patients in the intention-to-treat population, 22.4% had IMDC favorable-risk, 57.8% had intermediate-risk, and 19.8% had poor-risk prognostic features; 25.5% had at least 1% and 74.5% had less than 1% (or indeterminate) tumor PD-L1 expression at the time of stratification. Patient characteristics at baseline were representative of a population with previously untreated advanced renal-cell carcinoma and were balanced in the two treatment groups (Table 1). The primary reason for discontinuation of trial treatment was disease progression; 55.6% of treated patients in the nivolumab-plus-cabozantinib group and 28.8% of those in the sunitinib group continued to receive treatment at the time of this analysis (Fig. S1 in the Supplementary Appendix). Details of subsequent anticancer therapy (started on or after the date of the first trial dose) are summarized in Table S1.

EFFICACY

At a median follow-up for overall survival of 18.1 months (range, 10.6 to 30.6), the median progression-free survival was 16.6 months (95% confidence interval [CI], 12.5 to 24.9) with nivolumab plus cabozantinib and 8.3 months (95% CI, 7.0 to 9.7) with sunitinib, and the probability of progression-free survival at 12 months was 57.6% (95% CI, 51.7 to 63.1) and 36.9% (95% CI, 31.1 to 42.8), respectively. Nivolumab plus cabozantinib had a superior progression-free survival benefit over sunitinib (Fig. 1A), with a hazard ratio for disease progression or death of 0.51 (95% CI, 0.41 to 0.64; P<0.001). Nivolumab plus cabozantinib also had a significant overall survival benefit over sunitinib. The probability of overall survival at 12 months was 85.7% (95% CI, 81.3 to 89.1) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5 to 80.0) with sunitinib (hazard ratio for death, 0.60; 98.89% CI, 0.40 to 0.89; P=0.001). The median overall survival was not reached in either group (Fig. 1B).

The percentage of patients who had an objective response according to independent review was 55.7% (95% CI, 50.1 to 61.2) with nivolumab plus cabozantinib and 27.1% (95% CI, 22.4 to 32.3) with sunitinib (P<0.001); a complete response occurred in 8.0% of the patients in the nivolumab-plus-cabozantinib group and in 4.6% of those in the sunitinib group (Table 2). The median time to response was 2.8 months with nivolumab plus cabozantinib and 4.2 months with sunitinib, and the median duration of response was 20.2 months and 11.5 months, respectively (Table 2). The probability of ongoing re-

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Nivolumab plus Cabozantinib (N=323)	Sunitinib (N=328)
Age		
Median (range) — yr	62 (29–90)	61 (28–86)
<65 yr — no. (%)	191 (59.1)	210 (64.0)
≥65 yr — no. (%)	132 (40.9)	118 (36.0)
Sex — no. (%)		
Male	249 (77.1)	232 (70.7)
Female	74 (22.9)	96 (29.3)
Geographic region — no. (%)		
United States or Europe	158 (48.9)	161 (49.1)
Rest of the world	165 (51.1)	167 (50.9)
Karnofsky performance-status score — no. (%)†		
90 or 100	257 (79.6)	241 (73.5)
70 or 80	66 (20.4)	85 (25.9)
Not reported	0	2 (0.6)
IMDC prognostic risk score — no. (%)		
Favorable: 0	74 (22.9)	72 (22.0)
Intermediate: 1 or 2	188 (58.2)	188 (57.3)
Poor: 3–6	61 (18.9)	68 (20.7)
Tumor PD-L1 expression — no. (%)		
≥1%	83 (25.7)	83 (25.3)
<1% or indeterminate	240 (74.3)	245 (74.7)
Sarcomatoid features — no./total no. (%)‡		
Yes	34/313 (10.9)	41/319 (12.9)
No	279/313 (89.1)	278/319 (87.1)
Previous radiotherapy — no. (%)	46 (14.2)	45 (13.7)
Previous nephrectomy — no. (%)	222 (68.7)	233 (71.0)
No. of sites with target or nontarget lesions — no. (%)§		
1	63 (19.5)	69 (21.0)
≥2	259 (80.2)	256 (78.0)
Most common sites of metastasis — no. (%)		
Lung	238 (73.7)	249 (75.9)
Lymph node	130 (40.2)	131 (39.9)
Bone	78 (24.1)	72 (22.0)
Liver	73 (22.6)	53 (16.2)
Adrenal gland	36 (11.1)	36 (11.0)

* The intention-to-treat population includes all the patients who underwent randomization. The International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic risk score, programmed death ligand 1 (PD-L1) status, and geographic region (stratification factors) were recorded at screening by means of interactive response technology.
† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.
‡ Sarcomatoid status was not reported in 10 patients in the nivolumab-plus-cabozantinib group and in 9 patients in the sunitinib group.
§ Data are for tumor sites defined at baseline by the investigators according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The number of target or nontarget lesions at baseline was not reported for one patient in the nivolumab-plus-cabozantinib group and for three patients in the sunitinib group.

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

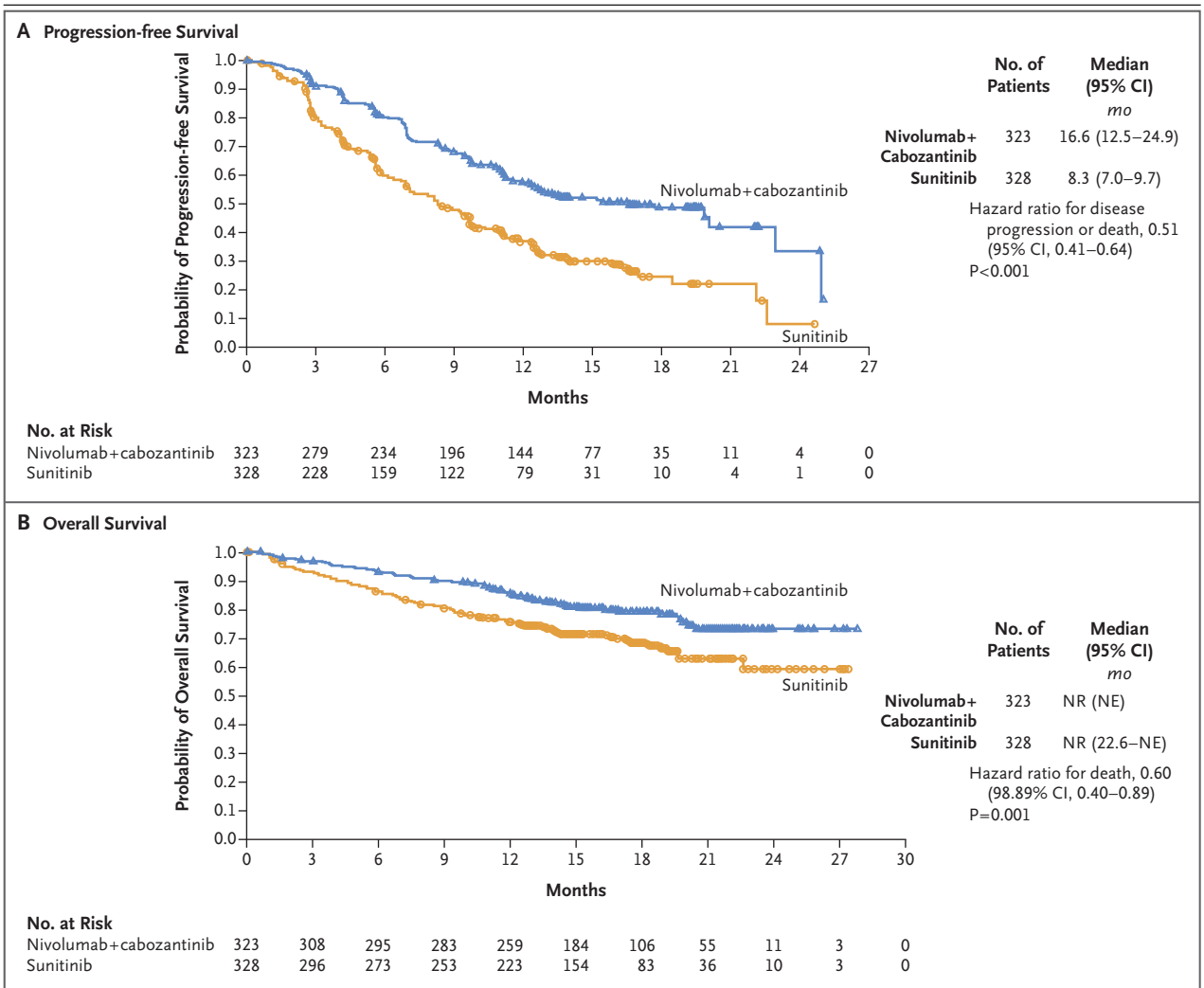


Figure 1. Progression-free and Overall Survival in the Intention-to-Treat Population.

The intention-to-treat population included all the patients who underwent randomization. Shown are Kaplan–Meier estimates of progression-free survival (Panel A) and overall survival (Panel B). Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded independent central review of radiologic imaging. NE denotes could not be estimated, and NR not reached.

sponse at 12 months was 71.1% with nivolumab plus cabozantinib and 40.9% with sunitinib (Fig. S2). Of 284 patients with data that could be evaluated in the nivolumab-plus-cabozantinib group, 94.7% had any reduction in the sum of target-lesion diameters, and 70.4% had a reduction of at least 30%; of 259 patients with data that could be evaluated in the sunitinib group, 84.9% had any reduction and 42.5% had a reduction of at least 30% (Fig. S3).

The benefits of nivolumab plus cabozantinib over sunitinib with respect to progression-free survival, overall survival, and objective response were generally consistent across subgroups, including IMDC risk status, tumor PD-L1 expression, and the presence or absence of bone metastases. (Details are provided in Fig. 2, Fig. S4, and Table S2.)

EXPOSURE AND SAFETY

A total of 320 patients in each group received at least one dose of trial treatment. The median duration of treatment was 14.3 months (range, 0.2 to 27.3) in the nivolumab-plus-cabozantinib

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Table 2. Objective Response (Intention-to-Treat Population).*

Variable	Nivolumab plus Cabozantinib (N = 323)	Sunitinib (N = 328)
Confirmed objective response — % (95% CI)†	55.7 (50.1–61.2)	27.1 (22.4–32.3)
Confirmed best overall response — no. (%)		
Complete response	26 (8.0)	15 (4.6)
Partial response	154 (47.7)	74 (22.6)
Stable disease	104 (32.2)	138 (42.1)
Progressive disease	18 (5.6)	45 (13.7)
Unable to determine or not reported	21 (6.5)	56 (17.1)
Median time to response (interquartile range) — mo‡§	2.8 (2.8–4.2)	4.2 (2.8–6.9)
Median duration of response (95% CI) — mo‡¶	20.2 (17.3–NE)	11.5 (8.3–18.4)

* Response was assessed according to RECIST, version 1.1, by blinded independent central review of radiologic imaging. Percentages may not total 100 because of rounding. NE denotes could not be estimated.
† The estimated difference in objective response between the nivolumab-plus-cabozantinib group and the sunitinib group was 28.6 percentage points (95% CI, 21.7 to 35.6), and the P value was less than 0.001.
‡ The median time to response and median duration of response were calculated only for patients who had a complete or partial response (180 patients in the nivolumab-plus-cabozantinib group and 89 patients in the sunitinib group).
§ The median time to response was 2.8 months (range, 1.0 to 19.4) with nivolumab plus cabozantinib and 4.2 months (range, 1.7 to 12.3) with sunitinib.
¶ The median duration of response was 20.2 months (range, 1.4+ to 22.2+) with nivolumab plus cabozantinib and 11.5 months (range, 1.3+ to 18.4) with sunitinib. The plus sign indicates a censored value.

group and 9.2 months (range, 0.8 to 27.6) in the sunitinib group. In the nivolumab-plus-cabozantinib group, the median duration of treatment was 13.3 months (range, 0 to 24.0) with nivolumab and 13.8 months (range, 0.2 to 27.3) with cabozantinib. Among all treated patients, 71.9% had at least one nivolumab dose delay, 68.1% had at least one cabozantinib dose delay, and 51.9% had at least one sunitinib dose delay; 56.3% of the patients had a reduction in the dose of cabozantinib, and 51.6% had a reduction in the dose of sunitinib.

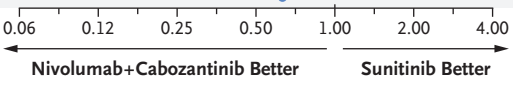
Adverse events of any cause during treatment occurred in 99.7% of the patients who received nivolumab plus cabozantinib and in 99.1% of those who received sunitinib; adverse events of any cause of grade 3 or higher occurred in 75.3% of the patients in the nivolumab-plus-cabozantinib group and in 70.6% of those in the sunitinib group (Table 3). Treatment-related adverse events occurred in 96.6% of the patients with nivolumab plus cabozantinib and in 93.1% with sunitinib; 60.6% of the patients in the nivolumab-plus-cabozantinib group and 50.9% in the sunitinib group had treatment-related adverse events of grade 3 or higher (Table S3). Among patients treated with nivolumab plus cabozantinib, 9.8% had grade 3 or 4 laboratory abnormalities in alanine aminotransferase (ALT) levels, and 7.9% had grade 3 or 4 abnormalities in aspartate aminotransferase (AST) levels; overall, resolution to grade 0 or 1 occurred in 82.9%. In the sunitinib group, 3.5% had grade 3 or 4 laboratory abnormalities in ALT levels, and 2.6% had grade 3 or 4 abnormalities in AST levels; overall, resolution to grade 0 or 1 occurred in 66.7%. Immune-mediated adverse events are summarized in Table S4. Overall, 19.1% of the patients treated with nivolumab plus cabozantinib received glucocorticoids (≥40 mg of prednisone daily or equivalent) to manage immune-mediated adverse events for any duration of time; 10.3% and 3.8% of patients received glucocorticoids continuously for at least 14 days and at least 30 days, respectively.

Adverse events of any cause led to discontinuation of a trial drug in 19.7% of the patients treated with nivolumab plus cabozantinib (6.6% discontinued nivolumab only, 7.5% discontinued cabozantinib only, and 5.6% discontinued both nivolumab and cabozantinib) and in 16.9% of the patients treated with sunitinib. Overall, one death was considered by investigators to be treatment-related with nivolumab plus cabozantinib (small-intestine perforation), and two deaths

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

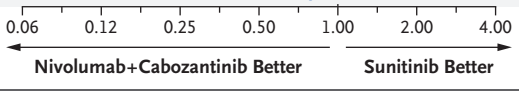
A Progression-free Survival, According to Subgroup

Subgroup	No. of Patients	Nivolumab+ Cabozantinib	Sunitinib	Hazard Ratio for Disease Progression or Death (95% CI)
		no. of events/no. of patients		
Overall	651	144/323	191/328	0.51 (0.41–0.64)
Region				
United States and Europe	319	61/158	85/161	0.46 (0.33–0.64)
Rest of the world	332	83/165	106/167	0.57 (0.42–0.76)
IMDC prognostic risk				
Favorable	146	30/74	35/72	0.62 (0.38–1.01)
Intermediate	376	82/188	108/188	0.54 (0.40–0.72)
Poor	129	32/61	48/68	0.37 (0.23–0.58)
PD-L1 expression				
≥1%	166	42/83	54/83	0.49 (0.32–0.73)
<1% or indeterminate	485	102/240	137/245	0.52 (0.40–0.67)
Age				
<65 yr	401	84/191	131/210	0.44 (0.33–0.58)
≥65 yr	250	60/132	60/118	0.68 (0.48–0.98)
Sex				
Male	481	108/249	136/232	0.48 (0.37–0.62)
Female	170	36/74	55/96	0.61 (0.40–0.94)
Karnofsky performance-status score				
90 or 100	498	109/257	129/241	0.55 (0.43–0.71)
70 or 80	151	35/66	62/85	0.44 (0.29–0.68)
Not reported	2	0	0/2	
Bone metastases				
Yes	150	33/78	45/72	0.34 (0.22–0.55)
No	501	111/245	146/256	0.57 (0.44–0.73)
Previous nephrectomy				
Yes	455	90/222	136/233	0.46 (0.35–0.60)
No	196	54/101	55/95	0.63 (0.43–0.92)



B Overall Survival, According to Subgroup

Subgroup	No. of Patients	Nivolumab+ Cabozantinib	Sunitinib	Hazard Ratio for Death (95% CI)
		no. of events/no. of patients		
Overall	651	67/323	99/328	0.60 (0.44–0.82)
Region				
United States and Europe	319	26/158	45/161	0.48 (0.30–0.79)
Rest of the world	332	41/165	54/167	0.71 (0.48–1.07)
IMDC prognostic risk				
Favorable	146	10/74	11/72	0.84 (0.35–1.97)
Intermediate	376	40/188	51/188	0.70 (0.46–1.07)
Poor	129	17/61	37/68	0.37 (0.21–0.66)
PD-L1 expression				
≥1%	166	28/83	30/83	0.80 (0.48–1.34)
<1% or indeterminate	485	39/240	69/245	0.51 (0.34–0.75)
Age				
<65 yr	401	31/191	66/210	0.44 (0.29–0.67)
≥65 yr	250	36/132	33/118	0.90 (0.56–1.44)
Sex				
Male	481	47/249	66/232	0.59 (0.40–0.85)
Female	170	20/74	33/96	0.68 (0.39–1.18)
Karnofsky performance-status score				
90 or 100	498	45/257	56/241	0.69 (0.47–1.03)
70 or 80	151	22/66	43/85	0.52 (0.31–0.86)
Not reported	2	0	0/2	
Bone metastases				
Yes	150	24/78	33/72	0.54 (0.32–0.92)
No	501	43/245	66/256	0.61 (0.41–0.89)
Previous nephrectomy				
Yes	455	36/222	66/233	0.49 (0.33–0.74)
No	196	31/101	33/95	0.79 (0.48–1.29)



The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Figure 2 (facing page). Progression-free and Overall Survival According to Subgroup.

Shown is the analysis of progression-free survival (Panel A) and overall survival (Panel B), 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. Median progression-free survival and 95% confidence intervals according to subgroup are provided in Table S2 in the Supplementary Appendix.

were considered to be treatment-related with sunitinib (pneumonia and respiratory distress in one patient each).

QUALITY OF LIFE

The mean (±SD) FKSI-19 total scores at baseline were similar in the two groups (58.7±10.6 with nivolumab plus cabozantinib and 58.4±9.9 with sunitinib); the percentage of patients who completed the FKSI-19 questionnaire was more than 90% in both groups at baseline, and the percentage was at least 80% at all subsequent assessments during treatment with sufficient data (≥10 patients) through at least week 91 in both groups. Quality of life was maintained over time with nivolumab plus cabozantinib, whereas a consistent deterioration from baseline was reported with sunitinib. When we controlled for baseline score and other relevant covariates, patients treated with nivolumab plus cabozantinib had better quality of life than those treated with sunitinib at all time points through week 91 (Fig. S5A). In addition, disease-related symptoms as measured by the FKSI-DRS subscale improved from baseline in patients in the nivolumab-plus-cabozantinib group, whereas patients in the sunitinib group had a decline from baseline after week 7 through week 91 (Fig. S5B). The between-group differences were significant ($P<0.05$) at all time points except week 7 for the FKSI-19 total score and week 79 for the FKSI-DRS score.

DISCUSSION

Progression-free survival (primary end point) was significantly longer with nivolumab plus cabozantinib than with sunitinib among patients with previously untreated advanced renal-cell carcinoma with a clear-cell component. The risk of disease progression or death was 49% lower with nivolumab plus cabozantinib than with sunitinib, and the median progression-free survival was twice as long in the combination group (16.6 months, vs. 8.3 months in the sunitinib group). Overall survival and the likelihood of objective response (secondary end points) were also better with the combination. The risk of death was 40% lower with nivolumab plus cabozantinib than with sunitinib. The percentage of patients with an objective response was twice as high with nivolumab plus cabozantinib than with sunitinib (55.7% vs. 27.1%), and complete responses were also more frequent with nivolumab plus cabozantinib (8.0%, vs. 4.6% with sunitinib). In a supportive subgroup analysis, nivolumab plus cabozantinib had consistent benefits over sunitinib with respect to progression-free survival, overall survival, and the likelihood of response, regardless of key baseline characteristics, including IMDC risk status, tumor PD-L1 expression, and the presence or absence of bone metastases. These results are consistent with previous data suggesting that cabozantinib may enhance immune-checkpoint inhibition.[4,14-17]

The adverse-event profile of nivolumab plus cabozantinib was not trivial but was consistent with previous studies of each agent as monotherapy, and no new safety signals were identified.[10,12,29] One death was considered by the investigators to be related to treatment with the combination. The incidence of the most common treatment-related adverse events of any grade or of grade 3 or higher that were observed with nivolumab plus cabozantinib was similar to those seen with sunitinib monotherapy, including palmar–plantar erythrodysesthesia syndrome, hypertension, hypothyroidism, and fatigue. Most immune-mediated adverse events that were reported in the nivolumab-plus-cabozantinib group were of low grade, and 19.1% of the patients receiving the combination received glucocorticoids (≥40 mg of prednisone daily or equivalent) for any duration of time. Nivolumab or cabozantinib or both were discontinued before progression in 19.7% of patients owing to adverse events, including 5.6% who discontinued both. Yet, the patient-reported outcome measures suggested that the toxic effects did not have a major adverse effect on quality of life.

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Table 3. Adverse Events (As-Treated Population).*

Event	Nivolumab plus Cabozantinib (N=320)		Sunitinib (N=320)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	319 (99.7)	241 (75.3)	317 (99.1)	226 (70.6)
Diarrhea	204 (63.8)	22 (6.9)	151 (47.2)	14 (4.4)
Palmar–plantar erythrodysesthesia	128 (40.0)	24 (7.5)	130 (40.6)	24 (7.5)
Hypertension	111 (34.7)	40 (12.5)	119 (37.2)	42 (13.1)
Hypothyroidism	109 (34.1)	1 (0.3)	94 (29.4)	1 (0.3)
Fatigue	103 (32.2)	11 (3.4)	111 (34.7)	15 (4.7)
Increased ALT level	90 (28.1)	17 (5.3)	27 (8.4)	7 (2.2)
Decreased appetite	90 (28.1)	6 (1.9)	65 (20.3)	4 (1.2)
Nausea	85 (26.6)	2 (0.6)	98 (30.6)	1 (0.3)
Increased AST level	81 (25.3)	11 (3.4)	35 (10.9)	4 (1.2)
Dysgeusia	76 (23.8)	0	69 (21.6)	0
Asthenia	71 (22.2)	14 (4.4)	59 (18.4)	10 (3.1)
Rash	69 (21.6)	6 (1.9)	26 (8.1)	0
Mucosal inflammation	66 (20.6)	3 (0.9)	81 (25.3)	8 (2.5)
Pruritus	60 (18.8)	1 (0.3)	14 (4.4)	0
Arthralgia	59 (18.4)	1 (0.3)	29 (9.1)	1 (0.3)
Back pain	58 (18.1)	5 (1.6)	40 (12.5)	6 (1.9)
Vomiting	55 (17.2)	6 (1.9)	66 (20.6)	1 (0.3)
Cough	55 (17.2)	0	51 (15.9)	0
Dysphonia	55 (17.2)	1 (0.3)	11 (3.4)	0
Stomatitis	54 (16.9)	8 (2.5)	79 (24.7)	7 (2.2)
Increased lipase level	53 (16.6)	20 (6.2)	38 (11.9)	15 (4.7)
Hyponatremia	51 (15.9)	30 (9.4)	28 (8.8)	19 (5.9)
Abdominal pain	50 (15.6)	5 (1.6)	27 (8.4)	1 (0.3)
Headache	50 (15.6)	0	37 (11.6)	2 (0.6)
Anemia	48 (15.0)	6 (1.9)	81 (25.3)	12 (3.8)
Increased amylase level	47 (14.7)	10 (3.1)	29 (9.1)	8 (2.5)
Hypophosphatemia	46 (14.4)	19 (5.9)	18 (5.6)	4 (1.2)
Hypomagnesemia	44 (13.8)	2 (0.6)	15 (4.7)	2 (0.6)
Increased blood creatinine level	42 (13.1)	4 (1.2)	43 (13.4)	1 (0.3)
Constipation	39 (12.2)	3 (0.9)	40 (12.5)	1 (0.3)
Pyrexia	39 (12.2)	2 (0.6)	27 (8.4)	1 (0.3)
Muscle spasms	38 (11.9)	0	5 (1.6)	0
Increased blood alkaline phosphatase level	37 (11.6)	3 (0.9)	26 (8.1)	2 (0.6)
Upper respiratory tract infection	36 (11.2)	1 (0.3)	12 (3.8)	1 (0.3)
Decreased weight	35 (10.9)	2 (0.6)	10 (3.1)	0
Peripheral edema	34 (10.6)	1 (0.3)	28 (8.8)	0
Proteinuria	33 (10.3)	9 (2.8)	25 (7.8)	7 (2.2)

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

Table 3. (Continued.)

Event	Nivolumab plus Cabozantinib (N=320)		Sunitinib (N=320)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Dizziness	33 (10.3)	1 (0.3)	19 (5.9)	0
Hyperthyroidism	32 (10.0)	2 (0.6)	9 (2.8)	0
Dyspepsia	26 (8.1)	0	39 (12.2)	1 (0.3)
Thrombocytopenia	25 (7.8)	2 (0.6)	62 (19.4)	15 (4.7)
Gastroesophageal reflux disease	25 (7.8)	0	36 (11.2)	0
Epistaxis	22 (6.9)	0	32 (10.0)	0
Decreased platelet count	18 (5.6)	0	61 (19.1)	15 (4.7)
Neutropenia	15 (4.7)	2 (0.6)	50 (15.6)	12 (3.8)

* Shown are adverse events of any cause that occurred in at least 10% of patients in either group 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 the 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. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

A limitation of this analysis is the relatively short duration of follow-up. As of the data cutoff date, the median overall survival was not reached in either group; follow-up is ongoing. In particular, few deaths have occurred in the IMDC favorable-risk group, and additional follow-up may better characterize survival with nivolumab plus cabozantinib as compared with sunitinib in these patients. Assessment of tumor response is also ongoing to determine longer-term outcomes, including depth and durability of response, especially complete responses. Another potential limitation of this trial is the lack of blinding, which could not be implemented in this trial.

First-line immunotherapy-based regimens have transformed the treatment landscape for advanced renal-cell carcinoma, providing significant improvements in clinical outcomes, including overall survival.[6,7,30,31] Dual checkpoint inhibition with nivolumab plus ipilimumab was the first to show a significant long-term survival advantage over sunitinib with a high incidence of durable and complete responses and better quality of life in the phase 3 CheckMate 214 trial; consistent outcomes were observed in intermediate- and poor-risk patients and the intention-to-treat population, which have been maintained after extended follow-up.[22,30,32,33] Regimens that combine an anti–PD-1 or anti–PD-L1 antibody with a tyrosine kinase inhibitor have also shown clinical benefits over sunitinib in phase 3 trials,[6,7] although the magnitude of benefit with respect to progression-free survival in the current trial with nivolumab plus cabozantinib as compared with sunitinib is notable in this context. Data on health-related quality of life for the new treatment combinations are limited; however, available patient-reported outcomes suggest no advantage with pembrolizumab–axitinib as compared with sunitinib through 30 weeks.[34] Patients had significantly better quality of life with nivolumab plus cabozantinib than with sunitinib at most time points through 91 weeks as measured by the FKSI-19 total scale and FKSI-DRS subscale. With improved treatment options, more patients are surviving substantially longer, and many receive treatment for an extended period of time. Therefore, overall efficacy, safety, and quality-of-life benefits as well as individual patient characteristics are important considerations when selecting appropriate therapy.[31,35]

In this trial involving patients with previously untreated advanced renal-cell carcinoma, nivolumab plus cabozantinib had significant benefits over sunitinib with respect to progression-free survival, overall survival, and the likelihood of

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

objective response. The combination was associated with substantial toxic effects; 19.7% of the patients in the combination group discontinued at least one of the trial drugs prematurely, and 5.6% discontinued both; nevertheless, quality of life was maintained at a high level. In addition, efficacy benefits with nivolumab plus cabozantinib were consistent across prespecified subgroups.

Presented, in part, at the European Society of Medical Oncology Congress, September 19–21, 2020.

Supported by Bristol Myers Squibb in collaboration with Ono Pharmaceutical and with Exelixis, Ipsen Pharma, and Takeda Pharmaceutical. The authors received no financial support or compensation for publication of this manuscript. Dr. Choueiri is supported in part by the Dana–Farber/Harvard Cancer Center Kidney Specialized Program of Research Excellence, the Kohlberg Chair at Harvard Medical School, the Trust Family, Michael Brigham, and Loker Pinard Funds for Kidney Cancer Research at Dana–Farber Cancer Institute and by various grants from the National Cancer Institute, Department of Defense, and foundations. Patients treated at the Memorial Sloan Kettering Cancer Center were supported in part by a Cancer Center Support Grant–Core Grant (P30 CA008748). The University of Texas M.D. Anderson Cancer Center is supported by a National Institutes of Health Core Grant (P30 CA016672).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families for making this trial possible; Janice Kaps-Trotter, R.N., the CheckMate 9ER protocol manager; the staff of Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay; and Jennifer Tyson, Ph.D., of Parexel for professional medical writing assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Toni K. Choueiri, M.D., Thomas Powles, M.D., Mauricio Burotto, M.D., Bernard Escudier, M.D., Maria T. Bourlon, M.D., Bogdan Zurawski, M.D., Ph.D., Victor M. Oyervides Juárez, M.D., James J. Hsieh, M.D., Ph.D., Umberto Basso, M.D., Amishi Y. Shah, M.D., Cristina Suárez, M.D., Ph.D., Alketa Hamzaj, M.D., Jeffrey C. Goh, M.B., B.S., Carlos Barrios, M.D., Martin Richardet, M.D., Ph.D., Camillo Porta, M.D., Rubén Kowalyszyn, M.D., Juan P. Feregrino, M.D., Jakub Żołnierek, M.D., Ph.D., David Pook, M.B., B.S., M.D., Elizabeth R. Kessler, M.D., Yoshihiko Tomita, M.D., Ph.D., Ryuichi Mizuno, M.D., Jens Bedke, M.D., Joshua Zhang, M.D., Matthew A. Maurer, M.D., Burcin Simsek, Ph.D., Flavia Ejzykowicz, Ph.D., Gisela M. Schwab, M.D., Andrea B. Apolo, M.D., and Robert J. Motzer, M.D.

The authors' affiliations are as follows: the Department of Medical Oncology, Lank Center for Genitourinary Oncology, Dana–Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston (T.K.C.); the Department of Genitourinary Oncology, Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London (T.P.); the Bradford Hill Clinical Research Center, Santiago, Chile (M.B.); the Department of Medical Oncology, Gustave Roussy, Villejuif, France (B.E.); the Department of Hemato-Oncology, Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City (M.T.B.), the Department of Medical Oncology, Centro Universitario contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González," Universidad Autónoma de Nuevo León, Nuevo León (V.M.O.J.), and the Department of Medical Oncology, Hospital H+ Querétaro, Querétaro (J.P.F.) — all in Mexico; the Department of Outpatient Chemotherapy, Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz (B.Z.), and the Department of Clinical Oncology and Hematology, Regional Specialist Hospital, Biała Podlaska (J. Żołnierek) — both in Poland; the Division of Oncology, Department of Medicine, Siteman Cancer Center, Washington University School of Medicine, St. Louis (J.J.H.); Oncology Unit 1, Department of Oncology, Istituto Oncologico Veneto IRCCS, Padua (U.B.), the Department of Medical Oncology, Ospedale San Donato, Istituto Toscano i, Arezzo (A.H.), the Department of Internal Medicine, University of Pavia, Pavia (C.P.), and the University of Bari "A. Moro," Bari (C.P.) — all in Italy; the Department of Genitourinary Medical Oncology, M.D. Anderson Cancer Center, Houston (A.Y.S.); the Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona (C.S.); the Department of Medical Oncology, Royal Brisbane and Women's Hospital, Herston, QLD (J.C.G.), and Cabrini Monash University Department of Medical Oncology, Cabrini Health, Malvern, VIC (D.P.) — both in Australia; the Oncology Research Center, Hospital São Lucas, Porto Alegre, Brazil (C.B.); Fundacion Richardet Longo, Instituto Oncologico de Cordoba, Cordoba (M.R.), and Instituto Multidisciplinario de Oncología, Clínica Viedma, Viedma (R.K.) — both in Argentina; the Division of Medical Oncology, Department of Internal Medicine, University of Colorado School of Medicine, Aurora (E.R.K.); the Departments of Urology and Molecular Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata (Y.T.), and the Department of Urology, Keio University School of Medicine, Tokyo (R.M.) — both in Japan; the Department of Urology, Eberhard Karls University Tübingen, Tübingen, Germany (J.B.); the Departments of Clinical Research (J. Zhang.), Clinical Oncology (M.A.M.), Biostatistics (B.S.), and Health Economics and Outcomes Research (F.E.), Bristol Myers Squibb, Princeton, NJ; the Department of Clinical Oncology, Exelixis, Alameda, CA (G.M.S.); the Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD (A.B.A.); and the Department of Medicine, Memorial Sloan Kettering Cancer Center, New York (R.J.M.)

REFERENCES

1. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354-66.
2. McKay RR, Bossé D, Choueiri TK. Evolving systemic treatment landscape for patients with advanced renal cell carcinoma. J Clin Oncol 2018 October 29 (Epub ahead of print).
3. Heidegger I, Pircher A, Pichler R. Targeting the tumor microenvironment in renal cell cancer biology and therapy. Front Oncol 2019;9:490.
4. Apolo AB, Nadal R, Girardi DM, et al. Phase I study of cabozantinib and nivolumab alone or with ipilimumab for advanced or metastatic urothelial carcinoma and other genitourinary tumors. J Clin Oncol 2020;38:3672-84.
5. Amin A, Plimack ER, Ernstoff MS, et al. Safety and efficacy of nivolumab in combination with sunitinib or pazopanib in advanced or metastatic renal cell carcinoma: the CheckMate 016 study. J Immunother Cancer 2018;6:109.

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.

6. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116-27.
7. 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.
8. Agarwal N, Vaishampayan U, Green M, et al. Phase Ib study (COSMIC-021) of cabozantinib in combination with atezolizumab: results of the dose escalation stage in patients (pts) with treatment-naïve advanced renal cell carcinoma (RCC). J Clin Oncol 2020;29:Suppl 8:872P. abstract.
9. Pal S, Tsao C-K, Suarez C, et al. Cabozantinib (C) in combination with atezolizumab (A) as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from the COSMIC-021 study. Ann Oncol 2020;31:Suppl 4:S554. abstract.
10. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803-13.
11. Schmidt E, Lister J, Neumann M, et al. Cabozantinib versus standard-of-care comparators in the treatment of advanced/metastatic renal cell carcinoma in treatment-naive patients: a systematic review and network meta-analysis. Target Oncol 2018;13:205-16.
12. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. J Clin Oncol 2017;35:591-7.
13. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27.
14. Saeed A, Phadnis M, Park R, et al. Cabozantinib (cabo) combined with durvalumab (durva) in gastroesophageal (GE) cancer and other gastrointestinal (GI) malignancies: Preliminary phase Ib CAMILLA study results. J Clin Oncol 2020;38:Suppl:4563. abstract.
15. Bergerot P, Lamb P, Wang E, Pal SK. Cabozantinib in combination with immunotherapy for advanced renal cell carcinoma and urothelial carcinoma: rationale and clinical evidence. Mol Cancer Ther 2019;18:2185-93.
16. Lu X, Horner JW, Paul E, et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. Nature 2017;543:728-32.
17. Apolo AB, Nadal R, Tomita Y, et al. Cabozantinib in patients with platinum-refractory metastatic urothelial carcinoma: an open-label, single-centre, phase 2 trial. Lancet Oncol 2020;21:1099-109.
18. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794-9.
19. Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-8.
20. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187-93.
21. Rao D, Butt Z, Rosenbloom S, et al. A comparison of the Renal Cell Carcinoma-Symptom Index (RCC-SI) and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). J Pain Symptom Manage 2009;38:291-8.
22. Cella D, Grünwald V, Escudier B, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol 2019;20:297-310.
23. Cella D, Motzer RJ, Rini BI, et al. Important group differences on the Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-Related Symptoms in patients with metastatic renal cell carcinoma. Value Health 2018;21:1413-8.
24. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).
25. Krigsfeld GS, Prince EA, Pratt J, et al. Analysis of real-world PD-L1 IHC 28-8 and 22C3 pharmDx assay utilisation, turnaround times and analytical concordance across multiple tumour types. J Clin Pathol 2020;73:656-64.
26. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29:219-28.
27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
28. Clopper CP, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-14.
29. Mennitto A, Grassi P, Ratta R, Verzoni E, Prisciandaro M, Procopio G. Nivolumab in the treatment of advanced renal cell carcinoma: clinical trial evidence and experience. Ther Adv Urol 2016;8:319-26.
30. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.
31. Grimm MO, Leucht K, Grünwald V, Foller S. New first line treatment options of clear cell renal cell cancer patients with PD-1 or PD-L1 immune-checkpoint inhibitor-based combination therapies. J Clin Med 2020;9:565.
32. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 2019;20:1370-85.
33. Motzer RJ, Escudier B, McDermott DF, et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer 2020;8:8.
34. Bedke J, Rini BI, Plimack ER, et al. Health-related quality-of-life analysis from KEYNOTE-426: pembrolizumab plus axitinib vs sunitinib for advanced renal cell carcinoma. Presented at the virtual Annual European Association of Urology Congress, July 17–19, 2020.
35. Rini BI, Battle D, Figlin RA, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC). J Immunother Cancer 2019;7:354.

Copyright © 2021 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at MONASH UNIVERSITY LIBRARY on May 3, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.