# Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial

*Robert J Motzer, Thomas Powles, Mauricio Burotto, Bernard Escudier, Maria T Bourlon, Amishi Y Shah, Cristina Suárez, Alketa Hamzaj, Camillo Porta, Christopher M Hocking, Elizabeth R Kessler, Howard Gurney, Yoshihiko Tomita, Jens Bedke, Joshua Zhang, Burcin Simsek, Christian Scheffold, Andrea B Apolo, Toni K Choueiri*

*Lancet Oncol* 2022; 23: 888–98

Published Online June 7, 2022 https://doi.org/10.1016/S1470-2045(22)00290-X

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on June 27, 2022, and a further correction was made on August 30, 2022

Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA (Prof R J Motzer MD); 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, UK (T Powles MD); Bradford Hill Clinical Research Center, Santiago, Chile (M Burotto MD); Department of Medical Oncology, Gustave Roussy, Villejuif, France (B Escudier MD); Department of Hemato-Oncology, Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (M T Bourlon MD); Department of Genitourinary Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA (A Y Shah MD); Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain (C Suárez MD); Department of Medical Oncology, Ospedale San Donato, Istituto Toscano Tumori, Arezzo, Italy (A Hamzaj MD); Department of Internal Medicine, University of Pavia, Pavia, Italy (C Porta MD); Department of

## Summary

**Background** In the primary analysis of CheckMate 9ER, nivolumab plus cabozantinib showed superior progression-free survival, overall survival, and objective response over sunitinib in patients with previously untreated advanced renal cell carcinoma (median follow-up of 18·1 months). Here, we report extended follow-up of overall survival and updated efficacy and safety.

**Methods** This open-label, randomised, phase 3 trial was done in 125 hospitals and cancer centres across 18 countries. We included patients aged 18 years or older with previously untreated advanced or metastatic clear-cell renal cell carcinoma, a Karnofsky performance status of 70% or higher, measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 assessed by the investigator, any International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk category, and available tumour tissue for PD-L1 testing. Patients were randomly assigned (1:1) to nivolumab (240 mg) intravenously every 2 weeks plus cabozantinib (40 mg) orally once daily or sunitinib (50 mg orally) once daily (4 weeks per 6-week cycle). Randomisation, stratified by IMDC risk status, tumour PD-L1 expression, and geographical region, was done by permuted block within each stratum using a block size of four, via an interactive response system. The primary endpoint was progression-free survival by blinded independent central review. Overall survival was a secondary endpoint (reported here as the preplanned final analysis according to the protocol). Efficacy was assessed in all randomly assigned patients; safety was assessed in all patients who received at least one dose of any study drug. This ongoing study, closed to recruitment, is registered with ClinicalTrials.gov, NCT03141177.

**Findings** Between Sept 11, 2017, and May 14, 2019, 323 patients were randomly assigned to the nivolumab plus cabozantinib group and 328 to the sunitinib group. With an extended follow-up (data cutoff of June 24, 2021; median 32·9 months [IQR 30·4–35·9]), median overall survival was 37·7 months (95% CI 35·5–not estimable) in the nivolumab plus cabozantinib group and 34·3 months (29·0–not estimable) in the sunitinib group (hazard ratio [HR] 0·70 [95% CI 0·55–0·90], p=0·0043) and updated median progression-free survival was 16·6 months (12·8–19·8) versus 8·3 months (7·0–9·7; HR 0·56 [95% CI 0·46–0·68], p<0·0001). Grade 3–4 treatment-related adverse events occurred in 208 (65%) of 320 patients with nivolumab plus cabozantinib versus 172 (54%) of 320 with sunitinib. The most common grade 3–4 treatment-related adverse events were hypertension (40 [13%] of 320 patients in the nivolumab plus cabozantinib group *vs* 39 [12%] of 320 in the sunitinib group), palmar–plantar erythrodysaesthesia (25 [8%] *vs* 26 [8%]), and diarrhoea (22 [7%] *vs* 15 [5%]). Grade 3–4 treatment-related serious adverse events occurred in 70 (22%) of 320 patients in the nivolumab plus cabozantinib group and 31 (10%) of 320 in the sunitinib group. One additional treatment-related death occurred with sunitinib (sudden death).

**Interpretation** With extended follow-up and preplanned final overall survival analysis per protocol, nivolumab plus cabozantinib demonstrated improved efficacy versus sunitinib, further supporting the combination in the first-line treatment of advanced renal cell carcinoma.

**Funding** Bristol Myers Squibb and Ono Pharmaceutical.



## Introduction

In the phase 3 CheckMate 9ER trial of first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced or metastatic renal cell carcinoma, nivolumab plus cabozantinib showed superiority over sunitinib after a median follow-up for overall survival of 18·1 months (minimum 10·6 months; primary database lock on March 30, 2020).[1] In the primary analysis, data were

## Research in context

### Evidence before this study

We searched PubMed for published clinical trial reports, with no restrictions on language, from database inception until Jan 29, 2022, using the terms "nivolumab", "advanced renal cell carcinoma", and "renal cell carcinoma", filtered by clinical trial article type. Our search found several published randomised, phase 3 trials in patients with previously untreated advanced renal cell carcinoma that were done to evaluate anti-PD-1 or anti-PD-L1 agents combined with a VEGF or VEGFR tyrosine kinase inhibitor. Dual checkpoint inhibition with nivolumab plus ipilimumab, with its long-term efficacy and safety demonstrated in the CheckMate 214 trial, led to a change in the treatment of advanced renal cell carcinoma. The combination of an immune checkpoint inhibitor with a VEGF or VEGFR tyrosine kinase inhibitor has added to the treatment options for renal cell carcinoma. The combinations of pembrolizumab plus lenvatinib, pembrolizumab plus axitinib, and avelumab plus axitinib have each demonstrated superior efficacy over sunitinib in previously untreated advanced clear-cell renal cell carcinoma. In addition to these, the primary analysis of the randomised phase 3 CheckMate 9ER trial showed significant progression-free survival, overall survival, and objective response benefit with nivolumab plus cabozantinib versus sunitinib in the first-line treatment of patients with advanced renal cell carcinoma with a clear-cell component. On this basis of these results, nivolumab plus cabozantinib was approved in the USA and Europe as a first-line treatment option in this setting.

### Added value of this study

In this preplanned final analysis of overall survival according to the protocol from CheckMate 9ER with an extended median follow-up of 32·9 months, we report that nivolumab plus cabozantinib improved overall survival, progression-free survival, and objective response versus sunitinib among all randomised patients with advanced renal cell carcinoma, and among patient subgroups of clinical interest at baseline. We also report that tumour responses were deeper with nivolumab plus cabozantinib versus sunitinib in all target lesion organ sites assessed. No new safety signals were identified with nivolumab plus cabozantinib treatment.

### Implications of all the available evidence

These data show improved efficacy with nivolumab plus cabozantinib versus sunitinib with extended follow-up in the overall population and among multiple baseline subgroups of clinical interest, including patients with sarcomatoid features, previous nephrectomy, and different sites of metastases. Overall, these data further support nivolumab plus cabozantinib as an efficacious first-line treatment option for advanced renal cell carcinoma among a broad range of patients.

reported on the basis of the final analysis of progression-free survival (primary endpoint), the first interim analysis of overall survival, and the final analysis of objective response. Compared with sunitinib, nivolumab plus cabozantinib significantly improved progression-free survival per blinded independent central review (BICR; hazard ratio [HR] 0·51 [95% CI 0·41–0·64]; p<0·001), overall survival (HR 0·60 [98·89% CI 0·40–0·89]; p=0·001), and objective response by BICR (55·7% [95% CI 50·1–61·2] *vs* 27·1% [22·4–32·3]; p<0·001) in the intention-to-treat population.[1] On the basis of the CheckMate 9ER trial, nivolumab plus cabozantinib is recommended as a new standard of care for first-line treatment of advanced renal cell carcinoma.[2,3]

Here, we report updated results, including the preplanned final analysis of overall survival according to the protocol, together with updated progression-free survival, objective response, and safety outcomes with nivolumab plus cabozantinib versus sunitinib from the phase 3 CheckMate 9ER trial with an extended median follow-up for overall survival of 32·9 months. Additionally, we report an assessment of efficacy in prespecified and post-hoc patient subgroups of clinical interest at baseline (sarcomatoid features, previous nephrectomy status, and organ sites of metastasis), and a post-hoc exploratory assessment of maximal reduction from baseline of target lesions by organ site (kidney, liver, lung, lymph node, and bone).

## Methods

### Study design and participants

CheckMate 9ER was an open-label, randomised, phase 3 trial done in 125 hospitals and cancer centres across 18 countries (appendix p 2). The trial design and methods have been reported previously.[1] Briefly, we recruited adult patients (aged 18 years or older) who had histologically confirmed advanced or metastatic renal cell carcinoma with a clear-cell component (including sarcomatoid features), no previous systemic therapy, a Karnofsky performance status of 70% or higher, measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) assessed by the investigator, any International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk category, and available tumour tissue for PD-L1 testing. Patients were excluded if they had active CNS metastases (patients with treated, stable metastases for ≥1 month were eligible), active or suspected autoimmune disease, or a condition requiring treatment with corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before randomisation. Patients must have had adequate organ function based on laboratory testing requirements. Full details on inclusion and exclusion criteria are in the protocol (appendix).

CheckMate 9ER was approved by an institutional review board or ethics committee before initiation at each site and was done in accordance with Good Clinical

**Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy** (C Porta); **Cancer Clinical Research Unit, Lyell McEwin Hospital, Elizabeth Vale, SA, Australia** (C M Hocking MBBS); **Division of Medical Oncology, Department of Internal Medicine, University of Colorado School of Medicine, Aurora, CO, USA** (E R Kessler MD); **Department of Clinical Medicine, Macquarie University, Sydney, NSW, Australia** (H Gurney MBBS); **Departments of Urology and Molecular Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan** (Prof Y Tomita MD); **Department of Urology, Eberhard Karls University Tübingen, Tübingen, Germany** (Prof J Bedke MD); **Department of Clinical Research** (J Zhang MD) **and Department of Global Biometrics and Data Science** (B Simsek PhD), **Bristol Myers Squibb, Princeton, NJ, USA; Department of Clinical Development, Exelixis, Alameda, CA, USA** (C Scheffold MD); **Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA** (A B Apolo MD); **Department of Medical Oncology, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA** (Prof T K Choueiri MD)

Correspondence to:
Prof Robert J Motzer, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA
**motzerr@mskcc.org**

See Online for appendix

Practice guidelines, as defined by the International Conference for Harmonisation and European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). All enrolled patients provided written, informed consent. During the study, protocol amendments on Dec 18, 2017, and May 3, 2019, were made that affected the design of the study and recruitment (these included the termination of enrolment into the nivolumab plus ipilimumab plus cabozantinib triplet group, the inclusion of patients with IMDC favourable-risk disease in the primary data analysis, adjustment to interim analyses and the overall α level of endpoints, and an increase in the number of randomly assigned patients). Full details of revisions are available in the protocol (appendix).

### Randomisation and masking

Patients were randomly assigned (1:1) to the nivolumab plus cabozantinib group or the sunitinib group through an interactive response technology system. The allocation sequence was generated by the Bristol Myers Squibb (Princeton, NJ, USA) interactive response technology team. This allocation sequence was transferred to a third-party vendor for enrolment of patients and assignment to trial groups in collaboration with the investigators at the study sites. Patients were stratified according to IMDC prognostic risk score (0 [favourable] *vs* 1 or 2 [intermediate] *vs* 3 to 6 [poor]), geographical region (Canada, Europe, and the USA *vs* the rest of the world), and tumour PD-L1 expression (≥1% *vs* <1% or indeterminate). Randomisation was carried out via permuted blocks within each stratum using a block size of four. Patients and investigators were not masked to study treatment in this open-label trial.

### Procedures

Patients received either nivolumab 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally once daily, or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off in each 6-week cycle. Patients received nivolumab treatment up to a maximum of 2 years or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurred first. Crossover between treatment groups was not permitted. Dose delays for the management of adverse events were allowed for nivolumab, cabozantinib, and sunitinib; dose reductions were only allowed for cabozantinib and sunitinib. Assessments for discontinuation were done separately for nivolumab and cabozantinib; if discontinuation criteria were met for one drug but not the other, treatment might have been continued with the drug believed to be unrelated to the reported toxicity. Tumour assessments were done with CT or MRI of the chest, abdomen, pelvis, brain (baseline only), and all known sites of disease at baseline (within 28 days before randomisation), at 12 weeks (±7 days) after randomisation, then every 6 weeks (±7 days) until week 60, then every 12 weeks (±14 days) until disease progression according to RECIST 1.1 (as assessed by the investigator and confirmed by BICR). PD-L1 expression status was evaluated using the validated PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, an Agilent Technologies company, Santa Clara, CA, USA).

Adverse events were reported at each study visit for a minimum of 100 days after the last dose according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Immune-mediated adverse events were also monitored, as was the use of glucocorticoids (≥40 mg prednisone daily or equivalent) to manage these events. Immune-mediated adverse events were defined as events occurring within 100 days of the last dose, regardless of causality, treated with immune-modulating medication, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism or thyroiditis, hyperthyroidism, and diabetes), which were included regardless of treatment and no clear alternative cause based on investigator assessment or with an immune-mediated component.

### Outcomes

The primary endpoint of CheckMate 9ER was RECIST 1.1-defined progression-free survival by BICR. Overall survival was a secondary endpoint. Other secondary endpoints were objective response by BICR (including time to and duration of response), and safety and tolerability (including treatment-related adverse events and adverse events leading to discontinuation). Exploratory endpoints included health-related quality of life, predictive biomarkers, pharmacokinetics of nivolumab and cabozantinib and exposure–response relationships, immunogenicity of nivolumab, and progression-free survival after a subsequent line of treatment (progression-free survival 2). Health-related quality of life and progression-free survival 2 have been reported previously.[1,4,5]

Overall survival was defined as the time between the date of randomisation and the date of death due to any cause. Progression-free survival was defined as the time between the date of randomisation and the first date of documented progression, or death due to any cause, whichever occurred first. Patients who died without a reported progression (and died without starting subsequent anticancer therapy) were considered to have progressed on the date of death. Patients who received subsequent anticancer therapy were censored at the date of last evaluable tumour assessment on or before the date of initiation of the subsequent anticancer therapy. Objective response was defined as the proportion of randomised patients who had a best response of complete response or partial response according to RECIST 1.1.

### Statistical analysis

Details of the statistical analyses have been reported previously.[1] Overall, 638 patients were to be randomised. This study used an overall α level of 0·05 (two-sided) using a hierarchical testing procedure for progression-free survival by BICR, overall survival, and objective

response by BICR. Progression-free survival by BICR (primary endpoint; single final analysis) was evaluated at an α level of 0·05 with at least 95% power. Since the between-group difference in progression-free survival by BICR was significant, the evaluation of overall survival (secondary endpoint; planned at an overall α level of 0·05 with 80% power in two interim analyses and a final analysis with 254 events [α levels of 0·011 for the first interim analysis, 0·025 for the second, and 0·041 for the final analysis, all two-sided, using the O'Brien and Fleming α spending function[6]]) was planned. Because the first interim analysis of overall survival crossed the prespecified boundary for significance and showed a between-group difference (significance level p<0·0111), further formal analysis of overall survival was not required. Objective response (secondary endpoint) was then tested hierarchically at an overall α level of 0·05. After hierarchical testing was complete, we did the preplanned final analysis of overall survival according to the protocol that was set to occur after 254 events.

We assessed between-group comparisons of overall survival and progression-free survival using a stratified log-rank test, with HRs calculated using a stratified Cox proportional-hazards model for the intention-to-treat population. The same stratification factors used in randomisation were used for all stratified analyses. For subgroups, unstratified models were used. We examined the assumption of proportional hazards in the Cox regression model at the primary analysis by adding into the model a time-dependent variable defined by a treatment-by-time interaction. The two-sided Wald $\chi^2$ p value was 0·1408 at the primary analysis, confirming that the proportional-hazards assumption was met before this long-term follow-up. We used the Kaplan-Meier method to estimate overall survival, progression-free survival, and duration of response. Progression-free survival and overall survival rates at fixed timepoints (dependent on the minimum follow-up) are presented with their associated 95% CIs. The estimates were derived from the Kaplan-Meier method, and 95% CIs were derived based on Greenwood formula for variance derivation and on log–log transformation applied on the survivor function. We calculated the proportion of patients achieving an objective response by BICR and exact two-sided 95% CIs using the Clopper-Pearson method.[7] p values were descriptive and a significance threshold of less than 0·05 was used.

We analysed efficacy endpoints using data from the intention-to-treat population (ie, all randomly assigned patients). Additional analyses of efficacy endpoints were done in patient subgroups at baseline, based on disease and demographic characteristics, either prespecified (age, sex, geographical region, race, Karnofsky performance status, IMDC prognostic score, previous nephrectomy, previous radiotherapy, tumour PD-L1 expression, sarcomatoid features, disease stage at initial diagnosis, and bone metastasis) or post-hoc (liver metastasis and lung metastasis) and evaluated according to RECIST 1.1 by BICR. We analysed exposure, safety, and tolerability using data from all treated patients (patients who received at least one dose of any study drug).

The time to complete response by BICR was evaluated post-hoc for all patients with a confirmed complete response. We did a post-hoc analysis of depth of response in target lesions by organ site, whereby maximum

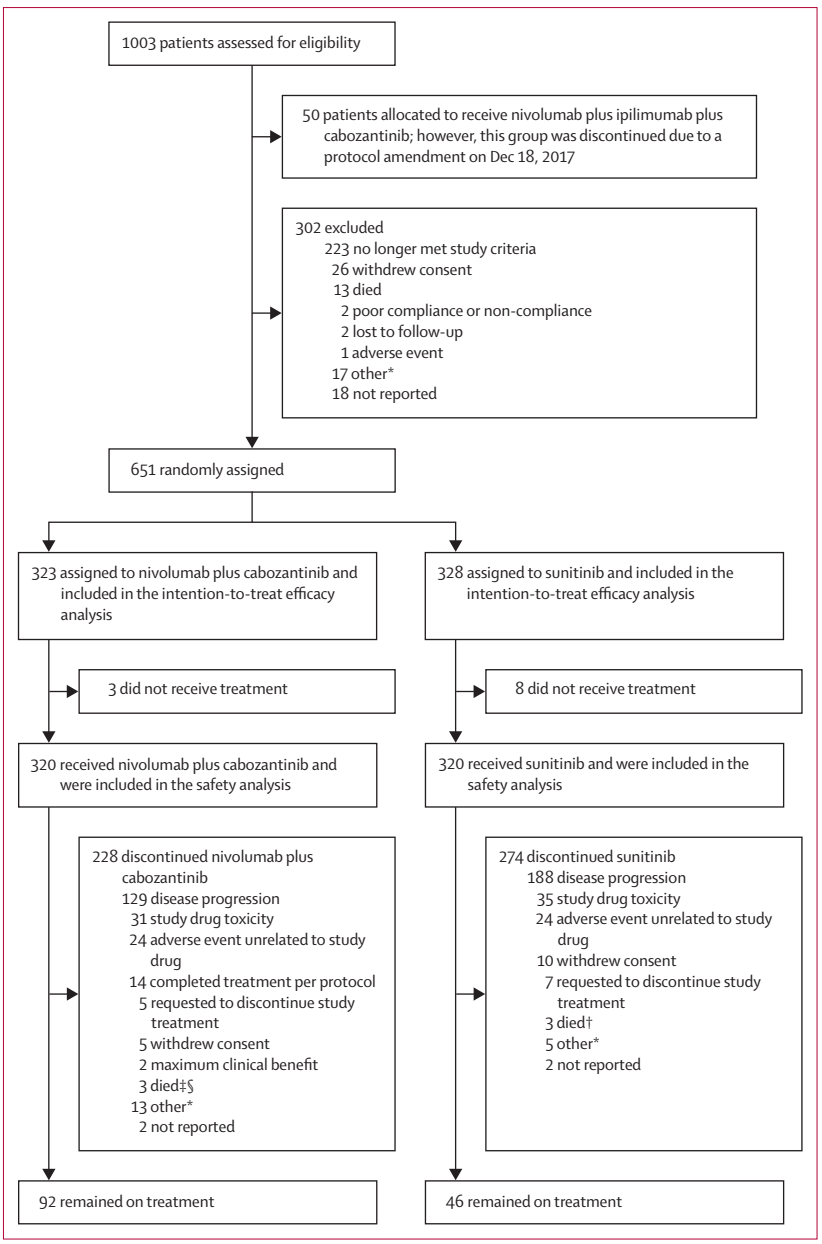


***Figure 1:*** **Trial profile**
*Other reasons are specified in the appendix (p 6). †Reasons for death were sudden death (two patients) and unknown (one patient). ‡Reasons for death were sudden death (two patients) and cardiac arrest (one patient). §At the primary database lock (March 30, 2020), four deaths were reported as the reason for discontinuation of nivolumab plus cabozantinib. At the current database lock (June 24, 2021), the reasons for discontinuation of nivolumab plus cabozantinib for three patients were reclassified from death to disease progression, adverse event unrelated to study drug, and study drug toxicity, and an additional two patients discontinued nivolumab plus cabozantinib due to death.

| | Nivolumab plus cabozantinib group (n=323) | Sunitinib group (n=328) |
|---|---|---|
| Age, years | 62 (55–69) | 61 (53–67) |
| Sex | | |
| Male | 249 (77%) | 232 (71%) |
| Female | 74 (23%) | 96 (29%) |
| Race | | |
| White | 267 (83%) | 266 (81%) |
| Black or African American | 1 (<1%) | 4 (1%) |
| Asian | 26 (8%) | 25 (8%) |
| Other or not reported* | 29 (9%) | 33 (10%) |
| Ethnicity | | |
| Hispanic or Latino | 38 (12%) | 39 (12%) |
| Not Hispanic or Latino | 149 (46%) | 151 (46%) |
| Not reported | 136 (42%) | 138 (42%) |
| Karnofsky performance status† | | |
| <90% | 66 (20%) | 85 (26%) |
| 90–100% | 257 (80%) | 241 (73%) |
| Not reported | 0 | 2 (<1%) |
| IMDC prognostic score | | |
| Favourable (0) | 74 (23%) | 72 (22%) |
| Intermediate (1–2) | 188 (58%) | 188 (57%) |
| Poor (3–6) | 61 (19%) | 68 (21%) |
| Geographical region | | |
| Europe or USA | 158 (49%) | 161 (49%) |
| Rest of the world | 165 (51%) | 167 (51%) |
| Tumour PD-L1 expression | | |
| ≥1% | 83 (26%) | 83 (25%) |
| <1% or indeterminate | 240 (74%) | 245 (75%) |
| Not reported | 0 | 0 |
| Number of organ sites with target or non-target lesions‡ | | |
| 1 | 63 (20%) | 69 (21%) |
| ≥2 | 259 (80%) | 256 (78%) |
| Not reported | 1 (<1%) | 3 (<1%) |

Data are median (IQR) or n (%). The intention-to-treat population included all patients who underwent randomisation. The IMDC prognostic risk score, PD-L1 status, and geographical region (stratification factors) were recorded at screening by means of interactive response technology for the intention-to-treat population, whereas PD-L1 status was reported on the case report form in subgroups. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. *Other race category included American Indian and Alaska Native, and answers such as Hispanic, Latino, unknown, and not specified. †Karnofsky performance status scores range from 0–100%, with lower scores indicating greater disability. ‡Data are for tumour sites defined at baseline by the investigators according to Response Evaluation Criteria in Solid Tumors version 1.1.

***Table 1:*** **Demographic and clinical characteristics at baseline in the intention-to-treat population**

reduction from baseline in the sum of diameters of target lesions was evaluated according to RECIST 1.1 by BICR (kidney, liver, lung, and lymph nodes), or by investigator (bone) in patients with a target lesion at baseline and at least one on-treatment tumour assessment and analysed descriptively. The prevalence of grade 3–4 treatment-related adverse events over time by most common system organ classes of clinical relevance was evaluated post-hoc for all treated patients in each treatment group and summarised using vector density plots.

A data monitoring committee provided oversight of efficacy, safety, and study conduct. All statistical analyses were done with SAS (version 9.2). This study is registered with ClinicalTrials.gov, NCT03141177.

### Role of the funding source

The funders contributed to the study design, data analysis, and data interpretation in collaboration with the authors. The funders did not have a role in data collection. Financial support for editorial and writing assistance was provided by the funders.

## Results

Between Sept 11, 2017, and May 14, 2019, 323 patients were randomly assigned to receive nivolumab plus cabozantinib and 328 to receive sunitinib (the intention-to-treat population; figure 1). 320 patients in the nivolumab plus cabozantinib group and 320 patients in the sunitinib group received the assigned treatment and were included in the safety analysis (all treated patients). Baseline demographic and clinical characteristics are shown in table 1.

The data cutoff for this analysis with extended follow-up was June 24, 2021. 228 (71%) of 320 patients in the nivolumab plus cabozantinib group and 274 (86%) of 320 patients in the sunitinib group had discontinued treatment; the most common reason for discontinuation was disease progression in both treatment groups (figure 1). In patients who discontinued, 70 (31%) of 228 patients in the nivolumab plus cabozantinib group and 122 (45%) of 274 patients in the sunitinib group received subsequent systemic therapy; most commonly a VEGF-targeted or VEGFR-targeted agent was used in the nivolumab plus cabozantinib group (61 [27%]) and a nivolumab-based or other PD-1 or PD-L1 inhibitor-based therapy was used in the sunitinib group (92 [34%]; appendix p 10).

At a median follow-up for overall survival of 32·9 months (IQR 30·4–35·9; minimum 25·4 months), 271 events occurred (121 events in the nivolumab plus cabozantinib group, and 150 events in the sunitinib group). Median overall survival was 37·7 months (95% CI 35·5–not estimable) with nivolumab plus cabozantinib versus 34·3 months (29·0–not estimable) with sunitinib (HR 0·70 [95% CI 0·55–0·90], p=0·0043); 24-month overall survival was 70% (95% CI 65–75) with nivolumab plus cabozantinib and 60% (55–66) with sunitinib (figure 2A). Prespecified and post-hoc subgroup analysis of overall survival are shown in the appendix (pp 23, 27–28).

207 (64%) of 323 patients in the nivolumab plus cabozantinib group and 223 (68%) of 328 patients in the sunitinib group had a progression event. Median progression-free survival was 16·6 months (95% CI 12·8–19·8) with nivolumab plus cabozantinib versus 8·3 months (7·0–9·7) with sunitinib (HR 0·56 [95% CI

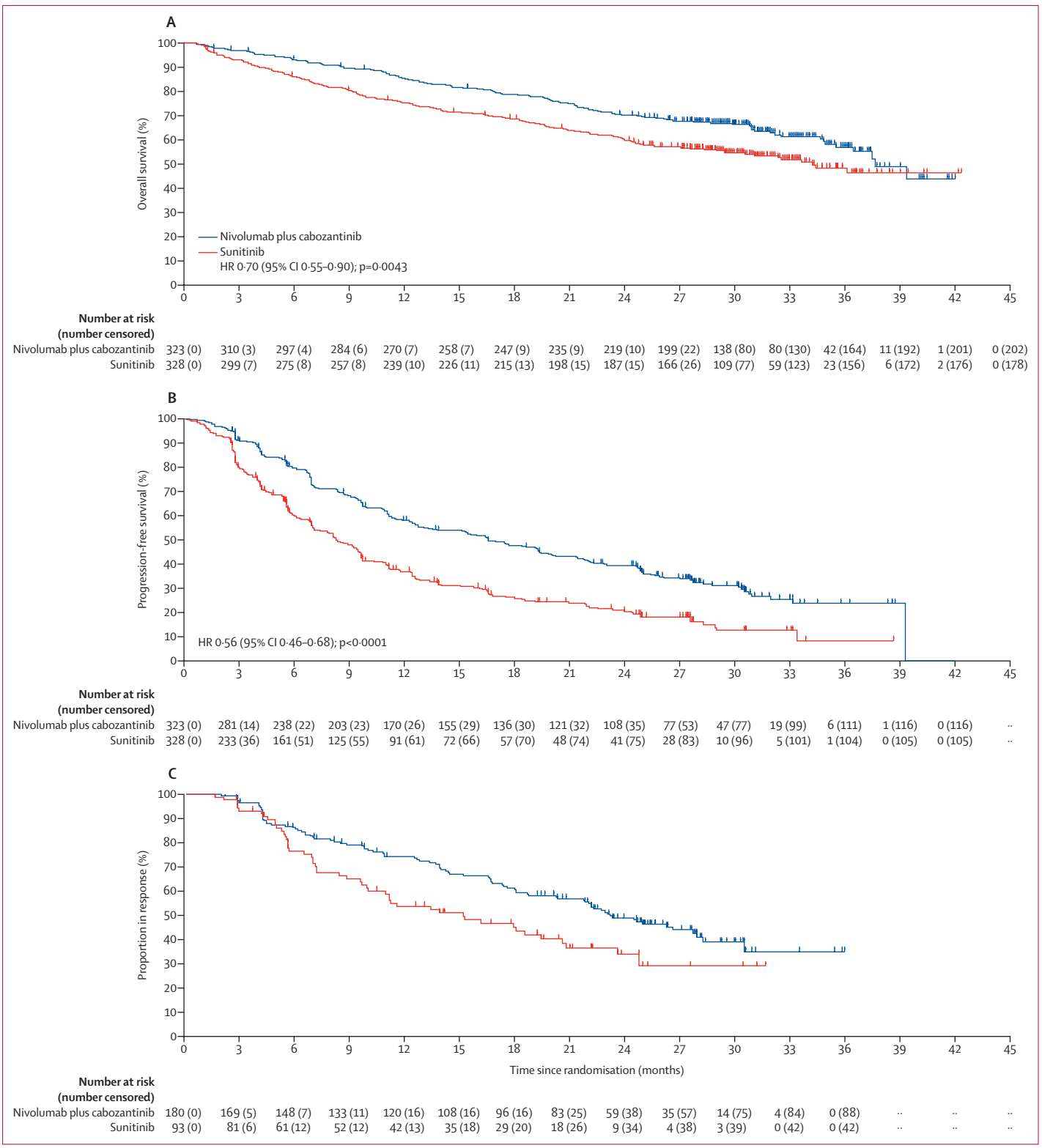


***Figure 2:*** **Overall survival (A), progression-free survival (B), and duration of response (C) in the intention-to-treat population**
Vertical lines denote censored patients. HR=hazard ratio.

| | Nivolumab plus cabozantinib group (n=323) | Sunitinib group (n=328) |
|---|---|---|
| Confirmed objective response (n [%; 95% CI]) | 180 (56%; 50–61) | 93 (28%; 24–34) |
| Confirmed best overall response | | |
| Complete response | 40 (12%) | 17 (5%) |
| Partial response | 140 (43%) | 76 (23%) |
| Stable disease | 105 (33%) | 134 (41%) |
| Progressive disease | 20 (6%) | 45 (14%) |
| Unable to determine | 18 (6%) | 55 (17%) |
| Not reported | 0 | 1 (<1%) |
| Median time to response (IQR), months | 2·8 (2·8–4·2) | 4·2 (2·8–7·1) |
| Median duration of response (95% CI), months | 23·1 (20·2–27·9) | 15·1 (9·9–20·5) |

Data are n (%), unless otherwise specified. Response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review.

***Table 2:*** **Summary of confirmed objective response by blinded independent central review in the intention-to-treat population**

0·46–0·68], p<0·0001); 24-month progression-free survival was 39·5% (95% CI 33·9–45·1) versus 20·9% (16·0–26·3; figure 2B). Prespecified and post-hoc subgroup analysis of progression-free survival are shown in the appendix (pp 24, 28–29).

The proportion of patients with a confirmed objective response was higher in the nivolumab plus cabozantinib group than in the sunitinib group (180 [56%; 95% CI 50–61] of 323 *vs* 93 [28%; 24–34] of 328; table 2). More patients had a complete response with nivolumab plus cabozantinib than with sunitinib (40 [12%] *vs* 17 [5%]), and median time to response was 2·8 months (IQR 2·8–4·2) versus 4·2 months (2·8–7·1; table 2). Median duration of response was 23·1 months (95% CI 20·2–27·9) with nivolumab plus cabozantinib versus 15·1 months (9·9–20·5) with sunitinib (table 2, figure 2C), and 88 (49%) of 180 versus 42 (45%) of 93 responses were ongoing at database lock. Median time to complete response (post-hoc analysis) was 11·5 months (IQR 5·6–19·2) with nivolumab plus cabozantinib versus 7·1 months (4·2–19·2) with sunitinib; 26 (65%) of 40 versus ten (59%) of 17 complete responses were ongoing at database lock. Prespecified and post-hoc subgroup analyses of objective response are shown in the appendix (pp 12, 25).

Prespecified and post-hoc analyses in subgroups of clinical interest at baseline included patients with sarcomatoid features, previous nephrectomy, liver metastasis, bone metastasis, and lung metastasis. Baseline characteristics for these subgroups are shown in the appendix (p 7). Superior overall survival was observed with nivolumab plus cabozantinib over sunitinib among patients with sarcomatoid features, with previous nephrectomy, with liver metastasis, with bone metastasis, or with lung metastasis at baseline (appendix pp 23, 30–31, 34). Progression-free survival and objective response benefits were also generally observed with nivolumab plus cabozantinib over sunitinib among patient subgroups of clinical interest at baseline (appendix pp 13, 24–25, 32–33, 34).

In the post-hoc exploratory analysis of depth of response in target lesions by organ site, a higher proportion of patients had target lesion shrinkage with nivolumab plus cabozantinib than with sunitinib, regardless of target lesion organ site (appendix p 35). A higher proportion of patients had a 30% or higher reduction from baseline with nivolumab plus cabozantinib versus sunitinib in kidney, liver, lung, and lymph node target lesions assessed by BICR, and bone metastases with measurable target lesions assessed by the investigator (appendix p 35). Three patients in the nivolumab plus cabozantinib group and four patients in the sunitinib group underwent post-baseline delayed nephrectomy.

Treatment exposure is summarised in the appendix (p 15). Median duration of treatment was 21·8 months (IQR 8·8–29·5) in the nivolumab plus cabozantinib group (overall), and 8·9 months (2·9–20·7) in the sunitinib group. Treated patients in the nivolumab plus cabozantinib group received a median of 35·0 (IQR 14·0–50·0) nivolumab doses and a median average daily dose of cabozantinib of 27·8 mg (20·7–38·6). The median average daily dose of sunitinib was 27·5 mg (IQR 22·5–32·1) during the 6-week cycle. Dose delays occurred in 238 (74%) of 320 patients treated with nivolumab, 270 (84%) of 320 patients treated with cabozantinib, and in 239 (75%) of 320 patients treated with sunitinib. The most common reason for dose delay in each case was for the management of adverse events (appendix p 15). Dose reductions occurred in 196 (61%) patients treated with cabozantinib and in 172 (54%) patients treated with sunitinib. The most common reason for dose reduction for cabozantinib or sunitinib was for the management of adverse events (appendix p 15). The median time to first dose level reduction due to adverse events was 108·5 days (IQR 64·5–206·0) with cabozantinib and 61·0 days (42·0–168·0) with sunitinib.

Consistent with the primary analysis,[1] all-cause adverse events of any grade (319 [100%] of 320 *vs* 317 [99%] of 320; appendix p 17) and treatment-related adverse events of any grade (311 [97%] of 320 *vs* 298 [93%] of 320) occurred at similar frequencies in the nivolumab plus cabozantinib and sunitinib groups with extended follow-up (table 3). Treatment-related adverse events of any grade led to discontinuation of either study drug in 87 (27%) of 320 patients in the nivolumab plus cabozantinib group (34 [11%] discontinued nivolumab only; 29 [9%] discontinued cabozantinib only; 20 [6%] discontinued both nivolumab and cabozantinib simultaneously; and four [1%] discontinued both nivolumab and cabozantinib sequentially) and 33 (10%) of 320 in the sunitinib group (appendix p 15). Grade 3–4 treatment-related adverse events occurred in 208 (65%) of 320 patients with nivolumab plus cabozantinib versus 172 (54%) of 320 patients with sunitinib, a nominal respective increase from the primary analysis (table 3; appendix p 37). The

| | Nivolumab plus cabozantinib group (n=320) | | | Sunitinib group (n=320) | | |
|---|---|---|---|---|---|---|
| | Grades 1–2 | Grade 3 | Grade 4 | Grades 1–2 | Grade 3 | Grade 4 |
| Any | 103 (32%) | 186 (58%) | 22 (7%) | 125 (39%) | 152 (48%) | 20 (6%) |
| Diarrhoea | 168 (53%) | 20 (6%) | 2 (<1%) | 132 (41%) | 15 (5%) | 0 |
| Hypothyroidism | 115 (36%) | 1 (<1%) | 0 | 95 (30%) | 1 (<1%) | 0 |
| Palmar–plantar erythrodysaesthesia | 98 (31%) | 25 (8%) | 0 | 108 (34%) | 26 (8%) | 0 |
| Fatigue | 79 (25%) | 8 (3%) | 0 | 86 (27%) | 15 (5%) | 0 |
| Nausea | 73 (23%) | 1 (<1%) | 0 | 87 (27%) | 0 | 0 |
| Alanine aminotransferase increased | 71 (22%) | 18 (6%) | 0 | 19 (6%) | 3 (<1%) | 0 |
| Aspartate aminotransferase increased | 71 (22%) | 12 (4%) | 0 | 33 (10%) | 2 (<1%) | 0 |
| Dysgeusia | 69 (22%) | 0 | 0 | 67 (21%) | 0 | 0 |
| Hypertension | 65 (20%) | 39 (12%) | 1 (<1%) | 68 (21%) | 39 (12%) | 0 |
| Decreased appetite | 65 (20%) | 4 (1%) | 0 | 53 (17%) | 2 (<1%) | 0 |
| Mucosal inflammation | 62 (19%) | 3 (<1%) | 0 | 75 (23%) | 7 (2%) | 1 (<1%) |
| Rash | 60 (19%) | 6 (2%) | 0 | 21 (7%) | 0 | 0 |
| Pruritus | 57 (18%) | 2 (<1%) | 0 | 14 (4%) | 0 | 0 |
| Asthenia | 48 (15%) | 11 (3%) | 0 | 41 (13%) | 8 (3%) | 0 |
| Stomatitis | 47 (15%) | 7 (2%) | 0 | 69 (22%) | 8 (3%) | 0 |
| Vomiting | 37 (12%) | 4 (1%) | 0 | 50 (16%) | 2 (<1%) | 0 |
| Dysphonia | 37 (12%) | 1 (<1%) | 0 | 8 (3%) | 0 | 0 |
| Hypomagnesaemia | 35 (11%) | 0 | 1 (<1%) | 10 (3%) | 0 | 0 |
| Lipase increased | 34 (11%) | 15 (5%) | 5 (2%) | 24 (8%) | 11 (3%) | 5 (2%) |
| Anaemia | 33 (10%) | 2 (<1%) | 0 | 55 (17%) | 11 (3%) | 1 (<1%) |
| Amylase increased | 32 (10%) | 14 (4%) | 0 | 23 (7%) | 7 (2%) | 0 |
| Arthralgia | 31 (10%) | 0 | 0 | 16 (5%) | 0 | 0 |
| Dyspepsia | 21 (7%) | 0 | 0 | 32 (10%) | 1 (<1%) | 0 |
| Thrombocytopenia | 20 (6%) | 1 (<1%) | 0 | 49 (15%) | 11 (3%) | 4 (1%) |
| Platelet count decreased | 18 (6%) | 0 | 0 | 45 (14%) | 12 (4%) | 2 (<1%) |
| Gastro-oesophageal reflux disease | 16 (5%) | 0 | 0 | 33 (10%) | 0 | 0 |
| Neutropenia | 13 (4%) | 2 (<1%) | 1 (<1%) | 39 (12%) | 13 (4%) | 1 (<1%) |

Data are n (%). Shown are grade 1–2 treatment-related adverse events 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. Events are listed in descending order of frequency in the nivolumab plus cabozantinib group. Four patients had treatment-related adverse events leading to death: one in the nivolumab plus cabozantinib group (small-intestine perforation), and three in the sunitinib group (pneumonia, respiratory distress, sudden death [one patient each]). Of these deaths, only sudden death has occurred since the primary analysis (database lock March 30, 2020).

***Table 3:*** **Treatment-related adverse events in either treatment group**

most common grade 3–4 treatment-related adverse events were hypertension (40 [13%] of 320 patients in the nivolumab plus cabozantinib group *vs* 39 [12%] of 320 in the sunitinib group), palmar–plantar erythrodysaesthesia (25 [8%] *vs* 26 [8%]), and diarrhoea (22 [7%] *vs* 15 [5%]). The prevalence of the most common organ classes of grade 3–4 treatment-related adverse events over time in each treatment group (post-hoc analysis) is shown in the appendix (p 38).

Treatment-related serious adverse events of any grade occurred in 83 (26%) of 320 treated patients in the nivolumab plus cabozantinib group (grade 3–4: 70 [22%]) and 42 (13%) of 320 treated patients in the sunitinib group (grade 3–4: 31 [10%]). The most common any-grade treatment-related serious adverse events were diarrhoea (11 [3%]), pneumonitis (nine [3%]), and adrenal insufficiency (six [2%]) in the nivolumab plus cabozantinib group, and anaemia (four [1%]), hyponatraemia (three [<1%]), and thrombocytopenia (three [<1%]) in the sunitinib group (appendix p 19).

Grade 3 or worse immune-mediated adverse events were uncommon in all patients treated with nivolumab plus cabozantinib (appendix p 22); the most common were increased alanine aminotransferase (nine [3%] of 320), diarrhoea (eight [3%]), and hepatotoxicity (seven [2%]). In the sunitinib group, grade 3 or worse immune-mediated adverse events were reported for hypothyroidism, hepatotoxicity, and hyperbilirubinaemia (each, one [<1%] of 320). 70 (22%) of 320 patients treated with nivolumab plus cabozantinib received corticosteroids (≥40 mg of prednisone daily or equivalent) for any duration of time to manage immune-mediated adverse events (occurring on therapy or ≤100 days after the end of the trial treatment period); 40 (13%) patients received corticosteroids (≥40 mg of prednisone daily or equivalent) continuously for at least 14 days and

16 (5%) patients continuously for at least 30 days. Since the primary analysis (database lock on March 30, 2020), no new deaths that investigators considered to be related to treatment occurred with nivolumab plus cabozantinib; one additional death that was considered to be related to treatment occurred with sunitinib (sudden death).

## Discussion

Results from this longer-term follow-up (median follow-up for overall survival of 32·9 months) of the phase 3 CheckMate 9ER trial in patients with previously untreated advanced renal cell carcinoma demonstrated superior efficacy with nivolumab plus cabozantinib versus sunitinib. In the preplanned final analysis of overall survival according to the protocol, median overall survival was longer with nivolumab plus cabozantinib versus sunitinib (37·7 months *vs* 34·3 months; HR 0·70 [95% CI 0·55–0·90]). Median progression-free survival was twice as long with nivolumab plus cabozantinib than sunitinib. Objective response rate was higher, and durability of response was better with nivolumab plus cabozantinib versus sunitinib. Most efficacy benefits favoured nivolumab plus cabozantinib versus sunitinib regardless of the stratification categories of geographical region, tumour PD-L1 expression, and IMDC prognostic risk category. The IMDC favourable-risk patient subset had relatively few patients, and few deaths were recorded in that subset. The evaluation of overall survival in the IMDC favourable-risk patient subset was, therefore, challenging due to the low number of death events. Furthermore, this trial was not powered to detect differences in subsets of patients stratified by IMDC risk. The safety profile of nivolumab plus cabozantinib remained consistent with the primary analysis and with previous reports for each agent as monotherapy.[1,8,9] No new safety signals emerged, and no further treatment-related deaths occurred in the nivolumab plus cabozantinib group. Some treatment-related adverse events occurred more frequently with nivolumab plus cabozantinib, including diarrhoea, increased aspartate aminotransferase, increased alanine aminotransferase, rash, and pruritus, whereas anaemia, thrombocytopenia, decreased platelet count, and neutropenia were more frequent with sunitinib. Nevertheless, it has been documented elsewhere that patients continued to report improved health-related quality of life with nivolumab plus cabozantinib versus sunitinib with extended follow-up from CheckMate 9ER.[5] Treatment with the combination reduced the risk of meaningful deterioration in health-related quality of life scores and showed a decreased risk of being bothered by treatment side-effects.[5] Taken together, these results continue to support nivolumab plus cabozantinib as an effective first-line treatment option for patients with advanced renal cell carcinoma.

Other treatment regimens combining immunotherapy with a tyrosine kinase inhibitor for the first-line treatment of advanced renal cell carcinoma have also shown clinical benefits in phase 3 trials versus sunitinib, including the combinations of pembrolizumab plus lenvatinib, pembrolizumab plus axitinib, and avelumab plus axitinib.[10–13] However, differences between trials in baseline disease characteristics (ie, IMDC prognostic risk category, previous nephrectomy, and sarcomatoid features), differences in efficacy benefits with sunitinib, and differences in duration of follow-up make cross-trial comparisons difficult. Durability of response with nivolumab plus cabozantinib was consistent with an immunotherapy–tyrosine kinase inhibitor combination in this setting, based on evidence from other phase 3 trials.[10–12]

In prespecified and post-hoc analyses of patient subgroups of clinical interest at baseline, improved progression-free survival and higher objective response rates with nivolumab plus cabozantinib versus sunitinib were generally observed. Improvements with nivolumab plus cabozantinib versus sunitinib tended to be higher in patients with sarcomatoid features versus those without, and in patients with previous nephrectomy versus those without. Indeed, efficacy outcomes favouring immunotherapy combined with a tyrosine kinase inhibitor versus sunitinib in subgroup analyses of advanced renal cell carcinoma with sarcomatoid features or previous nephrectomy status at baseline have been reported previously.[11,14–17] Nivolumab in dual checkpoint inhibition with ipilimumab has shown substantial long-term efficacy benefits in patients with sarcomatoid features.[18] Our data show improved survival and objective response with nivolumab plus cabozantinib in patients with sarcomatoid features.

Efficacy benefit with nivolumab and cabozantinib in subgroups according to organ site of metastasis at baseline (liver, bone, and lung) is consistent with results previously recorded in bone and visceral sites with nivolumab and cabozantinib in combination versus sunitinib, and both agents as monotherapies versus everolimus.[1,19–21] Bone metastasis occurs in 35–40% of advanced renal cell carcinoma cases, often leading to skeletal-related events, impaired quality of life, and poor survival outcomes.[22,23] In our study, nivolumab plus cabozantinib improved survival outcomes and objective responses compared with sunitinib in this patient subgroup.

In the post-hoc exploratory assessment of the depth of response in target lesion organ sites, a higher proportion of patients had tumour shrinkage with nivolumab plus cabozantinib versus sunitinib, regardless of organ site.

A limitation of this trial is the absence of masking, due to its open-label nature. This bias was mitigated in part through the use of BICR for radiographical assessments. In the subgroup analysis of efficacy by organ site of metastasis, most patients had additional organ sites of target or non-target lesions. The depth of response analysis is limited by its post-hoc exploratory nature and by the relatively small number of patients analysed with target kidney, liver, and bone lesions. Additionally,

radiographical assessments of target bone lesions were only available through the investigator.

Ongoing and future investigations of interest with nivolumab plus cabozantinib might include characterisation of response and safety after additional study follow-up and also take into consideration the unmet needs identified in renal cell carcinoma.[24–26] For example, a role for nivolumab plus cabozantinib in patients with advanced non-clear-cell renal cell carcinoma who have not received previous PD-1 or PD-L1-directed therapy is being explored in the phase 2, open-label CA209-9KU trial (NCT03635892). Promising efficacy with nivolumab plus cabozantinib has been observed in papillary, unclassified, or translocation-associated histologies (median progression-free survival by RECIST 1.1 12·5 months [95% CI 6·3–15·9]; median overall survival 28 months [95% CI 16·3–not estimable]; objective response 47·5% [95% CI 31·5–63·9]).[27] A role for nivolumab plus cabozantinib in patients with clear-cell renal cell carcinoma and IMDC intermediate-risk or poor-risk disease without a complete response or progressive disease after first-line nivolumab plus ipilimumab treatment is being assessed in the phase 3 PDIGREE trial (NCT03793166). Additionally, the efficacy of nivolumab plus cabozantinib in triplet combination with ipilimumab is being explored in patients with previously untreated advanced clear-cell renal cell carcinoma and IMDC intermediate-risk or poor-risk disease (COSMIC-313, NCT03937219), in which the correlation of biomarkers with clinical outcomes will also be assessed.[28]

In summary, nivolumab plus cabozantinib demonstrated improved efficacy versus sunitinib in the extended overall survival analysis of CheckMate 9ER, further supporting the combination in first-line treatment of advanced renal cell carcinoma.

#### Contributors

RJM, TP, MB, BE, AYS, CSu, JB, CSc, ABA, and TKC were involved in conceptualisation of the study. RJM, TP, MB, BE, MTB, AYS, CSu, AH, CP, CMH, ERK, HG, YT, JB, ABA, and TKC contributed to investigation. JZ and BS were involved in data curation. BS was responsible for formal analysis. All authors had full access to all the data in the study. RJM, TKC, JZ, and BS verified all data in the study. All authors wrote, reviewed, and edited the final draft, and had final responsibility for the decision to submit for publication.

#### Declaration of interests

RJM reports advisory board fees from AstraZeneca, AVEO Pharmaceuticals, Eisai, EMD Serono, Exelixis, Genentech/Roche, Incyte, Lilly Oncology, Merck, Novartis, and Pfizer; and institutional funding from Bristol Myers Squibb (BMS), Eisai, Exelixis, Genentech/Roche, Merck, and Pfizer. TP reports grants from AstraZeneca, Roche, BMS, Exelixis, Ipsen, Merck, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; consulting fees from BMS, Merck, AstraZeneca, Ipsen, Pfizer, Novartis, Incyte, Seattle Genetics, Roche, Exelixis, MSD, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; and travel support from Pfizer, MSD, AstraZeneca, Roche, and Ipsen. MB reports consulting fees from Roche/Genentech, BMS, MSD Oncology, Novartis, AstraZeneca; and speakers' bureau fees from Roche/Genentech, MSD Oncology, BMS, and AstraZeneca. BE reports an institutional research grant from BMS; consulting fees from Pfizer, BMS, Ipsen, AVEO, Oncorena, and Eisai; honoraria from Pfizer, BMS, Ipsen, Oncorena, and Eisai; and travel support from BMS, Ipsen, and MSD. MTB reports consulting fees from BMS, Asofarma, Eisai, MSD Oncology, Janssen Oncology, Novartis, Bayer, and Ferring; speakers' bureau fees from Asofarma, MSD Oncology, BMS, Bayer, Eisai, Janssen Oncology, Ipsen, Pfizer, Merck, Ferring, Tecnofarma, Medicamenta, AstraZeneca, and Astellas Pharma; honoraria from BMS and Tecnofarma; payment for expert testimony from Asofarma; travel support from Asofarma, Janssen-Cilag, MSD Oncology, BMS Mexico, Pfizer, Ipsen, and Sanofi; and steering committee honoraria from BMS. AYS reports research grants from BMS, Eisai, 4D Pharma, and EMD Serono; consulting fees from Exelixis, BMS, Pfizer, and EMD Serono; and honoraria from Eisai and Oncology Information Group. CSu reports research grants from AB Science, Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim España, BMS, Clovis Oncology, Exelixis, Genentech, GlaxoSmithKline, Hoffman-La Roche, Novartis Farmaceutica, Pfizer, and Sanofi-Aventis; speakers' bureau fees from Astellas Pharma, Bayer, BMS, EUSA Pharma, Hoffmann-La Roche, Ipsen, and Pfizer; and advisory board fees from Astellas Pharma, Bayer, BMS, EUSA Pharma, Hoffman-La Roche, Ipsen, MSD, Novartis, Pfizer, and Sanofi-Aventis. AH reports advisory board fees from MSD and Janssen. CP reports consulting fees from Angelini Pharma, AstraZeneca, BMS, Eisai, EUSA Pharma, Ipsen, Merck Serono, and MSD; speakers' bureau fees from BMS, EUSA Pharma, General Electric, Ipsen, and MSD; payment for expert testimony from EUSA Pharma and Pfizer; and travel support from Roche. CMH reports institutional research grant from BMS, and stock options from Telix Pharmaceuticals, Volpara Health Technologies, Alcidon, and Nanosonics. ERK reports a personal research grant from Medivation/Astellas; institutional research grant from BMS, Genentech/Roche, Pfizer, and Merck Serono; and stock options from Johnson & Johnson. HG reports advisory board fees from BMS, Ipsen, MSD, AstraZeneca, Janssen-Cilag, Pfizer, Roche, and Merck Serono; speakers' bureau fees from Merck Serono; and travel support from AstraZeneca. YT reports institutional research grants from Ono Pharmaceutical, Takeda, and Astellas; and honoraria from BMS, Pfizer, Ono Pharmaceutical, and Astellas. JB reports institutional research grants from BMS, Astellas Pharma, Ipsen, MSD Oncology, Novartis, Roche, Exelixis, Pfizer, and Seagen; consulting fees from BMS, Eisai, EUSA Pharma, Ipsen, MSD Oncology, AstraZeneca, Roche, Pfizer, and Merck; and speakers' bureau fees from MSD Oncology, BMS, Merck, Pfizer, Ipsen, and Roche. JZ and BS are employed by and have stock ownership in BMS. CSc is employed by and has stock ownership in Exelixis. TKC reports research grants, consulting fees, honoraria, and advisory board fees from AstraZeneca, Aravive, AVEO, Bayer, BMS, Calithera, Circle Pharma, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, IQVIA, Infinity, Ipsen, Janssen, Kanaph, Lilly, Merck, NiKang, Nuscan, Novartis, Pfizer, Roche, Sanofi-Aventis, Surface Oncology, Takeda, Tempest, UpToDate, and continuing medical education events (Peerview, OncLive, MJH, and others), outside the submitted work; institutional patents filed on molecular mutations and immunotherapy response, and circulating tumour DNA; leadership fees from the National Comprehensive Cancer Network, US NCI Genitourinary Steering Committee, American Society of Clinical Oncology, and European Society for Medical Oncology; stock ownership in Pionyr, Tempest, Osel, and NuscanDx; other financial or non-financial interests include medical writing and editorial assistance support that might in part have been funded by communications companies; potential funding (in part) from non-US sources or foreign institutions for mentoring of several non-US citizens on research projects; independent funding by drug companies or royalties potentially involved in research around the subject matter (institutional); and support in part by the Dana-Farber/Harvard Cancer Center Kidney SPORE (2P50CA101942-16) and Program 5P30CA006516-56, the Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, and Loker Pinard Funds for Kidney Cancer Research at the Dana-Farber Cancer Institute. ABA declares no competing interests.

#### Data sharing

Bristol Myers Squibb's policy on data sharing can be found online. De-identified and anonymised datasets of clinical trial information, including patient-level data, will be shared with external researchers for proposals that are complete and for which the scientific request is valid and the data are available, consistent with safeguarding patient privacy

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and informed consent. Upon execution of an agreement, the de-identified and anonymised datasets can be accessed via a secured portal that provides an environment for statistical programming with R as the programming language. The protocol and statistical analysis plan will also be available. Data will be available for 2 years from the study completion or termination of the programme (May, 2024).

**Acknowledgments**

This study was funded by Bristol Myers Squibb in collaboration with Ono Pharmaceutical. Exelixis, Ipsen Pharma, and Takeda Pharmaceutical provided indirect funding. We thank the patients who participated in this study, the clinical study teams, and the representatives of the sponsor who were involved in data collection and analyses. We acknowledge Tanvi Gangal (Bristol Myers Squibb, Princeton, NJ, USA) for serving as protocol manager. Medical writing support was provided by Tom Vizard of Parexel (London, UK), and was funded by Bristol Myers Squibb. Patients treated at Memorial Sloan Kettering Cancer Center (New York, NY, USA) were supported in part by Memorial Sloan Kettering Cancer Center Support Grant (Core Grant, number P30 CA008748).

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