Original Article

# Nivolumab Versus Everolimus in Patients With Advanced Renal Cell Carcinoma: Updated Results With Long-Term Follow-Up of the Randomized, Open-Label, Phase 3 CheckMate 025 Trial

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**BACKGROUND:** CheckMate 025 has shown superior efficacy for nivolumab over everolimus in patients with advanced renal cell carcinoma (aRCC) along with improved safety and tolerability. This analysis assesses the long-term clinical benefits of nivolumab versus everolimus. **METHODS:** The randomized, open-label, phase 3 CheckMate 025 trial (NCT01668784) included patients with clear cell aRCC previously treated with 1 or 2 antiangiogenic regimens. Patients were randomized to nivolumab (3 mg/kg every 2 weeks) or everolimus (10 mg once a day) until progression or unacceptable toxicity. The primary endpoint was overall survival (OS). The secondary endpoints were the confirmed objective response rate (ORR), progression-free survival (PFS), safety, and health-related quality of life (HRQOL). **RESULTS:** Eight hundred twenty-one patients were randomized to nivolumab (n = 410) or everolimus (n = 411); 803 patients were treated (406 with nivolumab and 397 with everolimus). With a minimum follow-up of 64 months (median, 72 months), nivolumab maintained an OS benefit in comparison with everolimus (median, 25.8 months [95% CI, 22.2-29.8 months] vs 19.7 months [95% CI, 17.6-22.1 months]; hazard ratio [HR], 0.73; 95% CI, 0.62-0.85) with 5-year OS probabilities of 26% and 18%, respectively. ORR was higher with nivolumab (94 of 410 [23%] vs 17 of 411 [4%]; $P < .001$). PFS also favored nivolumab (HR, 0.84; 95% CI, 0.72-0.99; $P = .0331$). The most common treatment-related adverse events of any grade were fatigue (34.7%) and pruritus (15.5%) with nivolumab and fatigue (34.5%) and stomatitis (29.5%) with everolimus. HRQOL improved from baseline with nivolumab but remained the same or deteriorated with everolimus. **CONCLUSIONS:** The superior efficacy of nivolumab over everolimus is maintained after extended follow-up with no new safety signals, and this supports the long-term benefits of nivolumab monotherapy in patients with previously treated aRCC. ***Cancer* 2020;126:4156-4167**. © *2020 American Cancer Society*.

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**LAY SUMMARY:**
• CheckMate 025 compared the effects of nivolumab (a novel immunotherapy) with those of everolimus (an older standard-of-care therapy) for the treatment of advanced kidney cancer in patients who had progressed on antiangiogenic therapy.
• After 5 years of study, nivolumab continues to be better than everolimus in extending the lives of patients, providing a long-lasting response to treatment, and improving quality of life with a manageable safety profile. The results demonstrate that the clinical benefits of nivolumab versus everolimus in previously treated patients with advanced kidney cancer continue in the long term.

**KEYWORDS:** advanced renal cell carcinoma (aRCC), CheckMate 025, everolimus, immune checkpoint inhibitor, nivolumab, previously treated.

## INTRODUCTION

Nivolumab, a fully human immunoglobulin G4 PD-1 immune checkpoint inhibitor, disrupts PD-L1–mediated signaling to restore the immune system's antitumor defenses.[1-3] Nivolumab monotherapy has previously demonstrated antitumor activity associated with improved overall survival (OS) in multiple malignancies, including advanced renal cell carcinoma (aRCC).[1]

The phase 3 CheckMate 025 trial compared nivolumab with everolimus, a mammalian target of rapamycin inhibitor, in patients who had aRCC with a clear cell component and had previously been treated with antiangiogenic therapy (NCT01668784). After an interim analysis performed with a minimum follow-up of 14 months, the trial was stopped early because of a demonstrated OS benefit with nivolumab over everolimus (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.57-0.93; $P = .002$]); a survival benefit was observed with nivolumab, regardless of the tumor PD-L1 expression level.[4] The objective response rate (ORR) per investigator was significantly improved with nivolumab versus everolimus ($P < .001$), and although median progression-free survival (PFS) was similar between treatment arms, a delayed benefit with nivolumab was observed after 6 months of treatment.[4] The confirmed investigator-assessed ORR was 21.5% (95% CI, 17.6%-25.8%) with nivolumab and 3.9% (95% CI, 2.2%-6.2%) with everolimus.[1] Beyond the observed clinical benefits, nivolumab was associated with improvements in patient-reported health-related quality of life (HRQOL) outcomes in comparison with everolimus.[5] Long-term updates critically inform the benefit/risk ratio of immunotherapeutic regimens. Here, we report an updated and expanded analysis with an extended minimum follow-up of 64 months for patients treated with nivolumab or everolimus in CheckMate 025.

## MATERIALS AND METHODS

### *Study Design and Participants*

The study methodology was previously reported in detail.[4] Briefly, CheckMate 025 was a randomized, open-label, phase 3 trial conducted across 146 university- or hospital-based sites in 24 countries globally. Patients were 18 years old or older, had histologically confirmed advanced or metastatic renal cell carcinoma (RCC) with a predominantly clear cell component, and had measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Eligible patients had previously received 1 or 2 antiangiogenic therapies and had a Karnofsky performance status $\geq 70$.

### *Randomization and Masking*

Patients were randomly assigned (1:1) to nivolumab or everolimus through an interactive voice response system. Randomization was performed via permuted blocks within each stratum, and stratified by Memorial Sloan Kettering Cancer Center risk group (favorable vs intermediate vs poor), number of prior antiangiogenic therapies in the advanced or metastatic setting (1 vs 2), and geographical region (United States/Canada vs Western Europe vs rest of the world). Patients and investigators were not masked to the treatment assignment because this was an open-label trial.

### *Study Oversight*

The study was approved by an institutional review board or independent ethics committee at each center and was conducted in accordance with Good Clinical Practice guidelines, as defined by the International Conference for Harmonisation. All patients provided written informed consent based on the principles of the Declaration of Helsinki.

### *Procedures*

Patients were randomized 1:1 to receive nivolumab (3 mg/kg intravenously every 2 weeks) or everolimus (10 mg/d orally) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were permitted to continue treatment beyond progression if a clinical benefit was identified by the investigator and the adverse event (AE) profile was acceptable. Dose reductions and escalations were permitted for everolimus but not for nivolumab, whereas dose delays were permitted for both treatments. Tumor assessments were performed at the baseline, every 8 weeks for

the first year, and then every 12 weeks until disease progression or discontinuation of treatment and were evaluated by the investigator per RECIST v1.1. Crossover from everolimus to a nivolumab extension phase was allowed per a protocol amendment implemented after OS superiority for patients receiving nivolumab was demonstrated in the primary analysis (July 2015). Patients treated with everolimus could be assessed for crossover to nivolumab if they met criteria for laboratory values and if all toxicities attributed to prior anticancer therapy, except for alopecia and fatigue, had resolved to grade 1 or the baseline before the initiation of nivolumab. A 14-day washout period for prior systemic anticancer therapy was required before the first nivolumab crossover dose.

AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.[6] Select AEs were defined as AEs of special clinical interest that may differ in type, frequency, or severity from AEs associated with nonimmunotherapies; these may require immunosuppression for their management, and early recognition may mitigate severe toxicity. HRQOL was assessed with the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) scoring algorithm.[7]

### Outcomes

This prespecified follow-up analysis included the original primary endpoint of OS together with the following secondary endpoints: confirmed ORR per investigator according to RECIST v1.1, PFS per investigator according to RECIST v1.1, safety, and patient-reported HRQOL.[4] The effects of various baseline clinical features on OS were assessed post hoc by univariable and multivariable models in an exploratory analysis of both arms.

The treatment-free interval was defined as the time between protocol therapy discontinuation and subsequent systemic anticancer treatment initiation or the time between protocol therapy discontinuation and the date on which a patient was last known to be alive among patients who never received subsequent systemic anticancer treatment.

Treatment-related AEs were reported between the first dose and 30 days after the last dose of study therapy or at the beginning of the nivolumab extension phase, whichever came first. Treatment-related AEs that continued beyond this time point were followed to resolution or until they were deemed irreversible by the investigator. Treatment-related select AEs were reported between the first dose and 30 days after the last dose of study therapy for patients in the nivolumab arm and included events occurring in skin, gastrointestinal, endocrine, hepatic, pulmonary, or renal systems. Median times to the onset and resolution of treatment-related select AEs were reported for patients in the nivolumab and everolimus arms.

### Statistical Analysis

The Kaplan-Meier method was used to estimate the OS, PFS, duration of response, and time to resolution of select AEs.[8] OS and PFS HRs for nivolumab versus everolimus were estimated with the Cox proportional hazards model[9] with the treatment group as a single covariate. ORRs and corresponding 95% CIs were calculated on the basis of the Clopper and Pearson method.[10] A post hoc analysis of the effects of clinically relevant baseline features—tumor PD-L1 expression, neutrophil-to-lymphocyte ratio, median sum of reference diameters of target lesions, prior nephrectomy, and individual International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk factors—on OS was performed with univariable and multivariable models sequentially for each intent-to-treat treatment arm separately to differentiate between factors relevant to nivolumab and everolimus. Each factor was first analyzed individually in the univariable analysis. Baseline factors associated with OS at $P < .1$ in the univariable model were entered into a full Cox proportional hazards multivariable regression model. Backward regression was used to build a parsimonious (reduced) multivariable model that included all baseline factors associated with OS at $P < .1$. Descriptive statistics were used to assess treatment-related AEs, the onset of select AEs, and changes from the baseline in HRQOL.

## RESULTS

### Patients

Between October 9, 2012, and March 14, 2014, 821 patients were randomized (410 into the nivolumab arm and 411 into the everolimus arm), and 803 were treated (406 in the nivolumab arm and 397 in the everolimus arm). Baseline characteristics have been previously reported and were balanced between arms (Supporting Table 1). The minimum follow-up was 64 months (median, 72 months). As of the August 2019 database lock, 100 patients (24.6%) randomized to the nivolumab arm were still alive, whereas 65 patients (16.4%) initially randomized to everolimus were. Ten patients (2.5%) in the nivolumab arm and 2 (0.5%) in the everolimus arm continued to receive treatment. The primary reason for discontinuation in both arms was disease progression (78.1% in the nivolumab arm and 74.1% in the everolimus arm; Supporting Fig. 1).

Sixty-five patients (16.4%) in the everolimus arm crossed over to the nivolumab extension. Patients who were eligible to cross over to the nivolumab extension phase were a highly select group of patients who progressed on everolimus therapy and were healthy enough to begin nivolumab treatment.

### *Efficacy*

In all randomized patients, an OS benefit was maintained with nivolumab versus everolimus (HR, 0.73; 95% CI, 0.62-0.85; $P < .0001$; Fig. 1A). The 36-, 48-, and 60-month OS probabilities with nivolumab and everolimus were 39% (95% CI, 34%-44%) and 30% (95% CI, 25%-34%), 30% (95% CI, 25%-34%) and 23% (95% CI, 19%-27%), and 26% (95% CI, 21%-30%) and 18% (95% CI, 14%-22%), respectively.

PFS with nivolumab and everolimus was similar through 6 months, after which the Kaplan-Meier curves separated; nivolumab was favored with extended follow-up (HR, 0.84; 95% CI, 0.72-0.99; $P = .0331$; Fig. 1B). The 36-, 48-, and 60-month PFS probabilities with nivolumab and everolimus were 9% (95% CI, 6%-12%) and 2% (95% CI, 1%-4%), 6% (95% CI, 4%-9%) and 1% (95% CI, 0%-3%), and 5% (95% CI, 3%-8%) and 1% (95% CI, 0%-3%), respectively.

ORR was 22.9% (95% CI, 18.9%-27.3%) with nivolumab and 4.1% (95% CI, 2.4%-6.5%) with everolimus (odds ratio, 6.86; 95% CI, 4.01-11.74; $P < .0001$; Table 1). A complete response was observed in 1.0% of the patients (n = 4) in the nivolumab group and in 0.5% of the patients (n = 2) in the everolimus group, whereas a partial response was seen in 22.0% of the nivolumab-treated patients (n = 90) and in 3.6% of the everolimus-treated patients (n = 15).

The median time to a response was 3.5 months for nivolumab and 3.7 months for everolimus. The median duration of response was 18.2 months (95% CI, 12.9-25.8 months) with nivolumab and 14.0 months (95% CI, 8.3-19.2 months) with everolimus (Fig. 2), with ongoing responses at the time of the database lock in 26 of 94 nivolumab responders (27.7%) and in 3 of 17 everolimus responders (17.6%). For patients who had a complete response with nivolumab (n = 4), the median time to a confirmed response for the complete responders was 2.2 months, and the duration of response ranged from 4.5 to 65.1+ months. Two of the 4 patients with complete responses in the nivolumab arm had an ongoing response. Both patients were off treatment and did not receive subsequent therapy. For patients who had a complete response with everolimus (n = 2), the median time to a confirmed response for the complete responders was 4.6 months with durations of 8.3 and 13.7 months. For patients in the nivolumab arm with a partial response (n = 90), the median time to a confirmed response for the partial responders was 4.8 months with a median duration of 18 months (95% CI, 12.9-25.1 months). For patients in the everolimus arm with a partial response (n = 15), the median time to a confirmed response for the partial responders was 3.5 months with a median duration of 17.9 months (95% CI, 6.4-24.0 months).

In the nivolumab arm, 59 responders (63%) received subsequent therapy, and 15 (88%) did in the everolimus arm; 8 responders (9%) in the nivolumab arm and 1 responder (6%) in the everolimus arm remained on therapy at the time of the database lock (Fig. 3). For all responders, the median duration of treatment was 23.6 months for nivolumab and 24.4 months for everolimus. For patients who responded and were off treatment without any subsequent systemic therapy, the median duration of the treatment-free interval was 12.7 months (interquartile range, 2.8-28.9 months) for nivolumab and 4.1 months (interquartile range, 4.1-4.1 months) for everolimus.

### *Patients Who Crossed Over to Nivolumab*

As expected, more patients who crossed over had Memorial Sloan Kettering Cancer Center and IMDC favorable-risk disease and only 1 site of metastasis, and a lower proportion had prior radiotherapy, prior pazopanib treatment, liver and bone baseline tumor sites, and tumor PD-L1 expression ≥ 1% (Supporting Table 1).[4] Seven patients (10.8%) who crossed over from everolimus to nivolumab continued to receive treatment at the time of the 5-year analysis. The primary reasons for discontinuation in patients who crossed over from everolimus to nivolumab were disease progression (69.2%) and toxicity with nivolumab (10.8%).

Among the 65 patients who crossed over to nivolumab, the 36-, 48-, and 60-month OS probabilities from initial study randomization were 89%, 71%, and 59%, respectively (Supporting Fig. 2A). The PFS probability was 13% (95% CI, 6.0%-25.0%) at both 24 and 36 months after crossover in this population (Supporting Fig. 2B). The ORR after crossover was 7.7% (95% CI, 2.5%-17.0%), with 1.5% of patients (n = 1) achieving a complete response and 6.2% (n = 4) achieving a partial response (Table 1). For patients who crossed over to nivolumab and had a confirmed response (n = 5), the median time to a response after crossover was 1.9 months with a median duration of 16.5 months (range, 7.4-35.5+ months), and 2 of the 5 responders (40%) had an ongoing response at the time of the database lock.

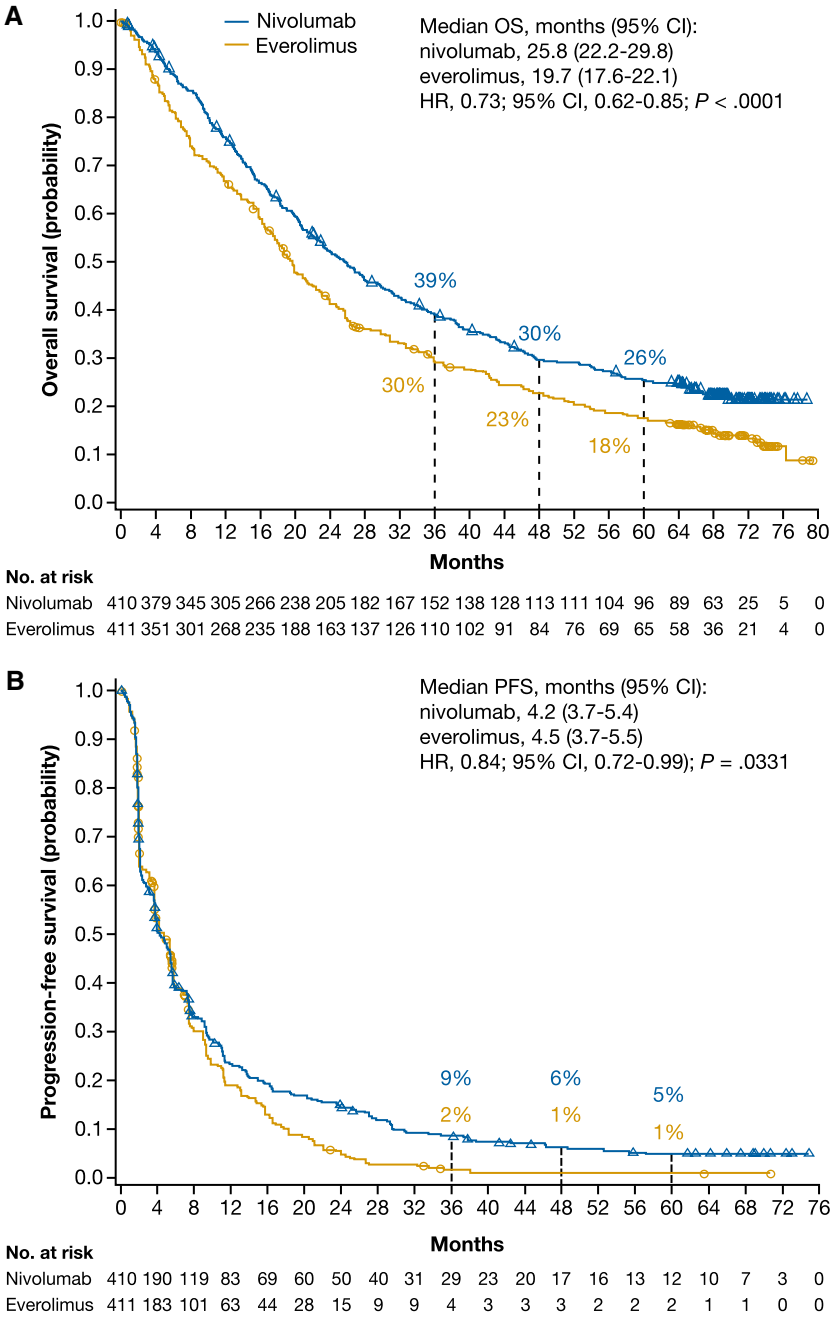


**FIGURE 1.** (A) OS and (B) PFS for patients treated with nivolumab and everolimus. CI indicates confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

### *Impact of Baseline Clinical Features on OS: A Multivariable Model*

A multivariable model was used to assess the impact of baseline clinical features on OS. Baseline factors were first analyzed individually in a univariable analysis to preclude introducing collinearity into the model (Supporting Table 2). The exploratory univariable analysis did not show baseline tumor PD-L1 expression ≥ 1% to be an independent prognostic factor for OS with either nivolumab or everolimus. Significant negative prognostic effects of lower hemoglobin levels and a higher tumor burden (sum of the reference diameters of target lesions) on OS were observed in the final reduced multivariable models in both the nivolumab and

**TABLE 1.** Best Overall Responses and Objective Response Rates

| | Nivolumab (n = 410) | Everolimus (n = 411) | Crossover to Nivolumab (n = 65) |
|---|---|---|---|
| Objective response rate, No. (%) | 94 (22.9) | 17 (4.1) | 5 (7.7) |
| 95% CI | 18.9-27.3 | 2.4-6.5 | 2.5-17.0 |
| Odds ratio (95% CI) | | 6.86 (4.0-11.7) | — |
| Best overall response, No. (%) | | | |
| Complete response | 4 (1.0) | 2 (0.5) | 1 (1.5) |
| Partial response | 90 (22.0) | 15 (3.6) | 4 (6.2) |
| Stable disease | 140 (34.1) | 224 (54.5) | 3 (4.6) |
| Progressive disease | 142 (34.6) | 106 (25.8) | 49 (75.4) |
| Unable to determine | 34 (8.3) | 64 (15.6) | 8 (12.3) |
| Ongoing response, n/N (%) | 26/94 (27.7) | 3/17 (17.6) | 2/5 (40.0) |

Abbreviation: CI, confidence interval.

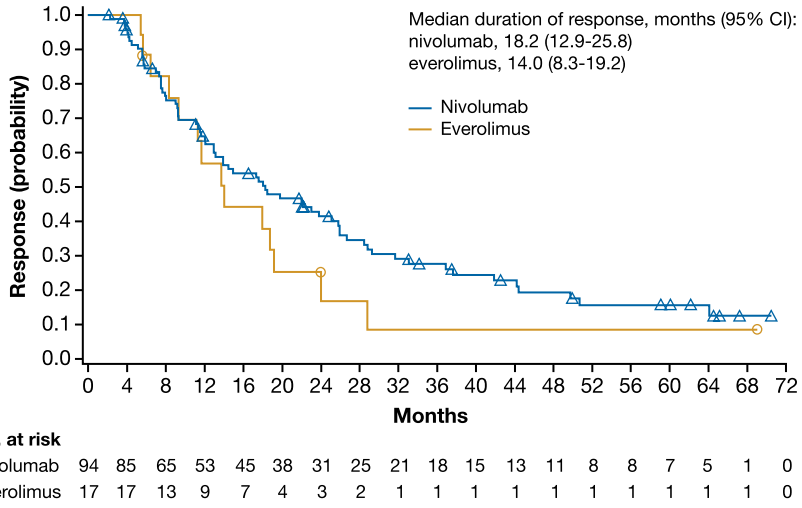


**FIGURE 2.** Duration of response in all randomized patients. CI indicates confidence interval.

everolimus arms (Supporting Table 3). A shorter time from the diagnosis of metastatic disease to the initiation of therapy was uniquely prognostic for shorter OS in the nivolumab arm. A higher corrected calcium level, a higher neutrophil-to-lymphocyte ratio, and the presence of bone metastases (with or without a soft-tissue component) were uniquely prognostic for shorter OS in the everolimus arm alone (Supporting Table 3).

### *Treatment Administration and Safety*

In all treated patients, the overall incidence of treatment-related AEs was 80.5% (grade 3 or 4, 21.4%) in the nivolumab group and 88.9% (grade 3 or 4, 36.8%) in the everolimus group. The most common treatment-related AEs of any grade with nivolumab were fatigue (34.7%), pruritus (15.5%), nausea (15.0%), and diarrhea (13.8%; Fig. 4A). The most common treatment-related AEs of any grade with everolimus were fatigue (34.5%), stomatitis (29.5%), and anemia (24.4%; Fig. 4A). The most common grade 3 or 4 treatment-related AEs with nivolumab were fatigue (2.7%), anemia (2.0%), increased alanine aminotransferase (1.7%), and increased aspartate aminotransferase (1.7%). The most common grade 3 or 4 treatment-related AEs with everolimus were anemia (8.6%), hypertriglyceridemia (4.5%), stomatitis (4.3%), and hyperglycemia (3.8%). Treatment-related AEs of any grade leading to discontinuation occurred in 39 patients (9.6%) in the nivolumab arm and in 50 patients (12.6%) in the everolimus arm. No additional treatment-related deaths were reported since the primary analysis in either arm (none in the nivolumab arm and 2 in the everolimus arm[4]). Among patients who crossed over from everolimus to nivolumab, the median duration of nivolumab treatment was 8.8 months (95% CI, 6.5-11.4 months). Treatment-related AEs of any grade occurred in 83.1%

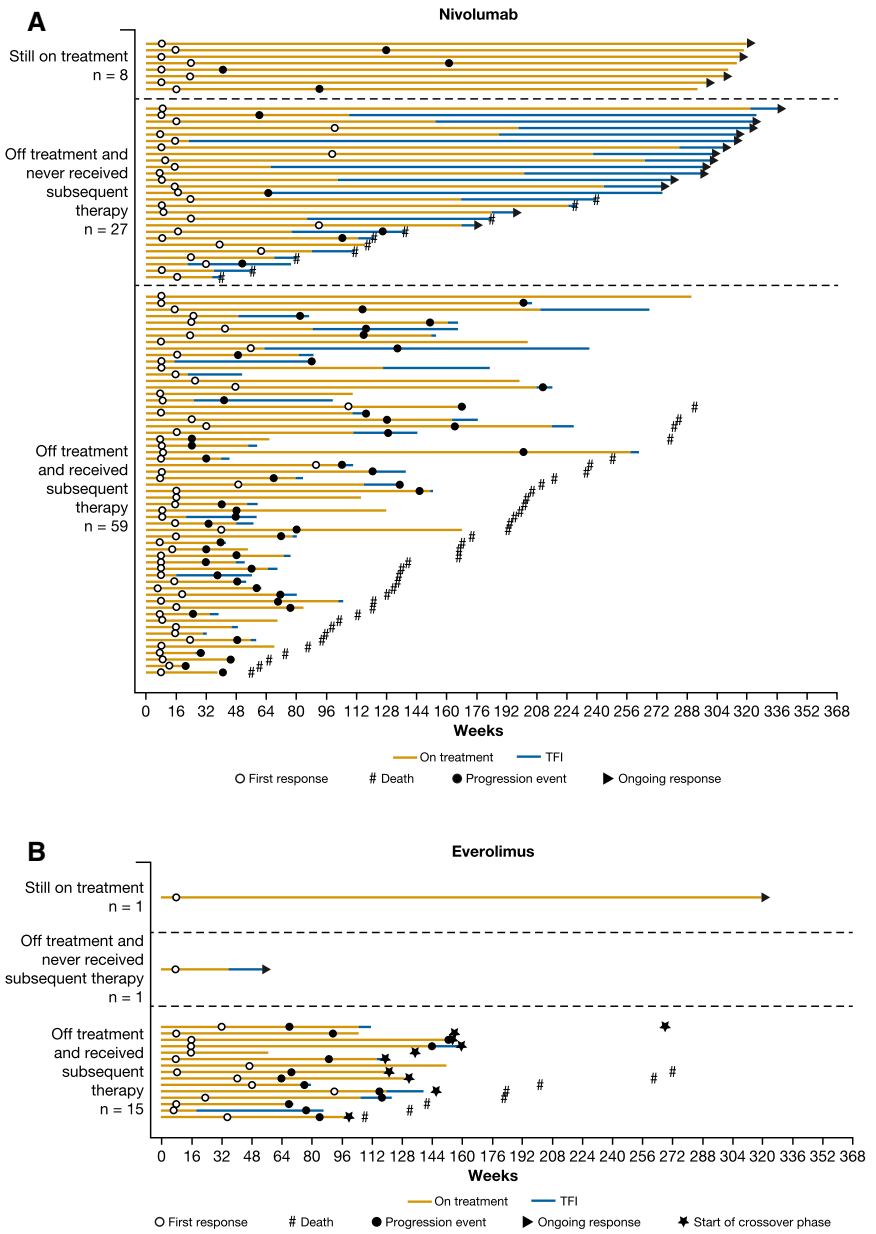


**FIGURE 3.** TFI, duration of therapy, duration of response, and subsequent therapy for all patients with confirmed responses to (A) nivolumab or (B) everolimus. TFI indicates treatment-free interval.

of patients (grade 3 or 4, 13.8%) after the crossover from everolimus to nivolumab.

Throughout the study, treatment-related select AEs of any grade occurred among patients in the nivolumab arm as follows: skin, 27.8% (grade 3 or 4, 1.2%); gastrointestinal, 14.0% (grade 3 or 4, 2.2%); endocrine, 11.1% (grade 3 or 4, 1.0%); hepatic, 11.3% (grade 3 or 4, 3.0%); renal, 6.9% (grade 3 or 4, 1.0%); and pulmonary, 5.2% (grade 3 or 4, 1.5%; see Supporting Table 4; data for everolimus are shown in Supporting Table 5). Tracking the most common organ classes of treatment-related select AEs over time, we found that the incidence of most events peaked during the initial 7 months of therapy, after which the incidence declined (Fig. 4B). Some select endocrine treatment–related AEs required management with permanent hormone replacement therapy (Fig. 4B). In the nivolumab arm, 47 of the 406 treated patients (11.6%) required ≥40 mg of prednisone per day (or equivalent) for a median duration of 3.14 weeks for the management of treatment-related select AEs.

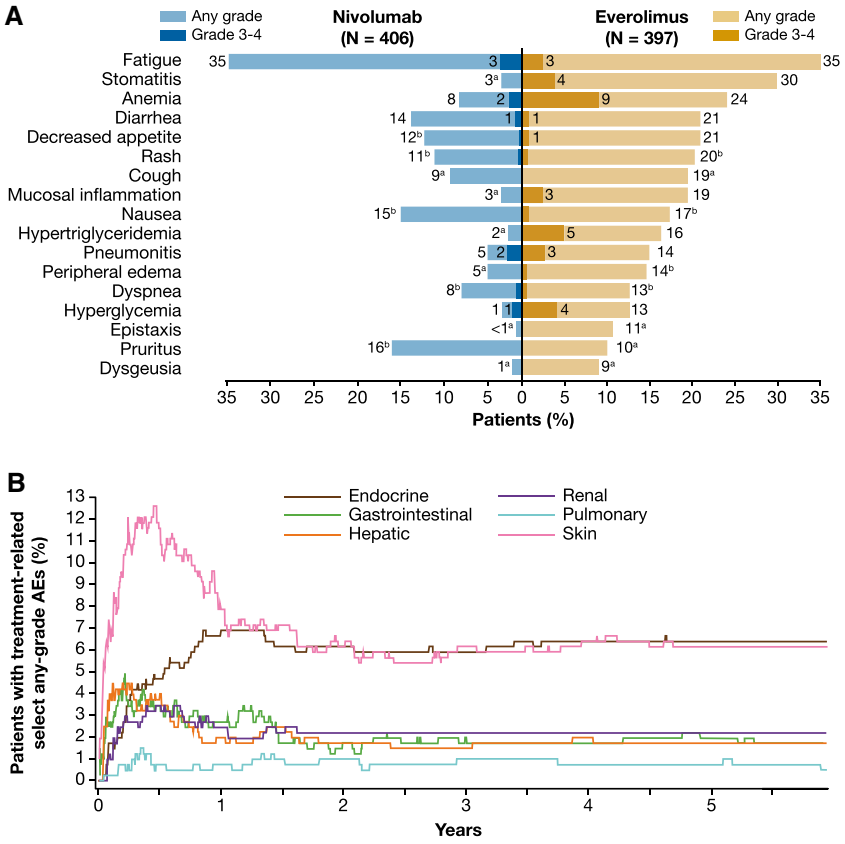


**FIGURE 4.** (A) Treatment-related AEs reported in ≥10% of treated patients in either arm and (B) median time to onset and resolution of nivolumab-related select (immune-related) AEs of any grade. [a]No patient reported a grade 3 or 4 treatment-related AE. [b]Less than 1% of patients experienced a grade 3 or 4 treatment-related AE. AE indicates adverse event.

### *Quality of Life*

Treatment with nivolumab was associated with rapid and sustained improvement in HRQOL from the baseline at each assessment point through week 104 per FKSI-DRS based on the primary analysis of CheckMate 025.[5] More than 10 randomized patients with a baseline HRQOL assessment plus 1 or more postbaseline HRQOL assessments had nonmissing patient-reported outcome data from weeks 4 through 228 and week 236 for nivolumab and from weeks 4 through 120 and week 132 for everolimus. The average change from the baseline (defined as a mean change in the FKSI-DRS score ≥ 2) was improved at weeks 56, 68, 104, 112, 116, 124, 144, 164, and 176 for patients in the nivolumab arm. The mean change from the baseline remained the same or deteriorated for patients in the everolimus arm (Fig. 5).

### *Subsequent Therapy*

In total, 276 patients (67.3%) in the nivolumab arm and 296 patients (72.0%) in the everolimus arm (including those in the everolimus arm who crossed over to the nivolumab extension phase) received subsequent systemic anticancer therapy. The median time from the last study drug dose to subsequent systemic therapy was 7.9 weeks (95% CI, 6.1-9.0 weeks) with nivolumab and 5.1 weeks (95% CI, 4.3-6.0 weeks) with everolimus. The most common subsequent systemic therapies in the nivolumab arm were everolimus (143 patients [34.9%]), axitinib (137 [33.4%]), cabozantinib (58 [14.1%]), and pazopanib (50 [12.2%]). In the everolimus arm, the most common subsequent therapies were axitinib (169 patients [41.1%]), nivolumab (107 [26.0%], including patients who had crossed over to nivolumab), pazopanib (78 [19.0%]), sorafenib (45 [10.9%]), and sunitinib (46 [11.2%]).

Among patients who crossed over to nivolumab and received subsequent systemic therapy, the most common subsequent therapies received were axitinib (37 patients [56.9%]), pazopanib (16 [24.6%]), cabozantinib (12 [18.5%]), and sunitinib (14 [21.5%]).

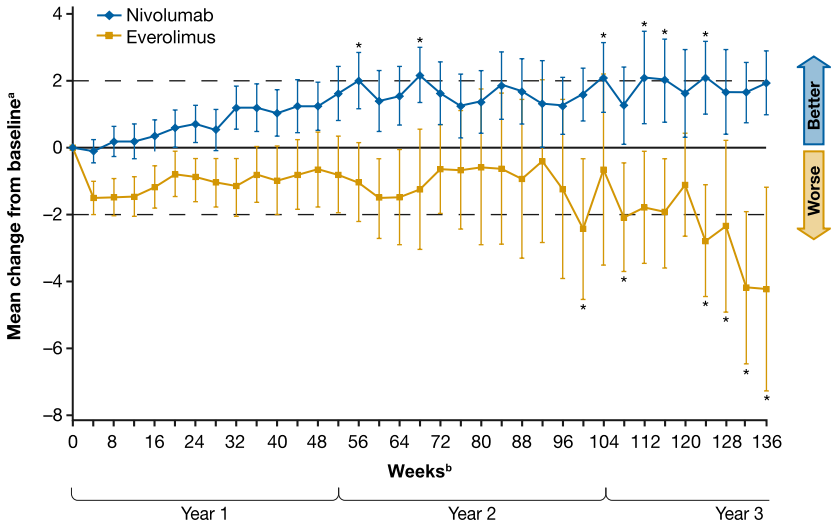


**FIGURE 5.** Mean changes from baseline Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) scores. Only time points for which data were available for 10 or more randomized patients with a baseline HRQOL assessment plus 1 or more postbaseline HRQOL assessments with nonmissing patient-reported outcome data per arm were included. Time 0 indicates the baseline. Bars show 95% confidence intervals. [a]The mean change from the baseline was also clinically meaningful at weeks 144, 164, and 176 in the nivolumab arm. [b]n = 8 for week 232 and n < 10 after week 236 in the nivolumab arm; n = 9 for weeks 124, 128, and 136 in the everolimus arm and n < 10 otherwise after week 132. *This denotes a clinically meaningful improvement with nivolumab (+2) or deterioration with everolimus (−2) from the baseline (dashed lines). HRQOL indicates health-related quality of life.

## DISCUSSION

The clinical benefit of nivolumab in the treatment of patients with aRCC after antiangiogenic therapy in CheckMate 025 was demonstrated with long-term follow-up. The significant OS benefit with nivolumab over everolimus was maintained with 64 months of minimum follow-up, with 60-month OS probabilities for nivolumab and everolimus of 26% and 18%, respectively. In the primary analysis, median PFS was similar between arms[4]; however, the PFS curves separated with longer follow-up and favored nivolumab over everolimus. The confirmed ORR was higher, and more patients demonstrated an ongoing response at long-term follow-up with nivolumab versus everolimus. The proportion of responders who experienced a treatment-free interval was higher with nivolumab than everolimus, and a lower proportion of responders treated with nivolumab required subsequent anticancer therapy in comparison with everolimus-treated patients; this suggests that antitumor effects persist after the discontinuation of nivolumab. This pattern of long-standing response appears to be characteristic of immunotherapy-based treatment in RCC and has been previously observed with interleukin 2 therapy and more recently in a long-term follow-up of the combination of nivolumab plus ipilimumab for previously untreated patients with aRCC in CheckMate 214.[11-14]

Few additional treatment-related AEs (including those leading to discontinuation) and no additional deaths were observed with longer follow-up in either arm in comparison with the primary disclosure of results from this trial.[15] There was a lower incidence of any-grade and high-grade treatment-related AEs with nivolumab versus everolimus, and this was consistent with the primary analysis. Similarly to previous reports of phase 1 or 2 trials of nivolumab monotherapy,[15-17] the most common treatment-related select AEs were fatigue, pruritus, nausea, and diarrhea in this phase 3 trial. Treatment-related select AEs of high grade or any grade were uncommon with nivolumab, and most select AEs were resolved and were manageable with established algorithms. For the first time, we report data on the use of corticosteroids (≥40 mg of prednisone daily or the equivalent) to manage treatment-related select AEs occurring within 30 days of the last dose. Relatively few patients required immune-modulating therapy in this setting of nivolumab monotherapy for the treatment of RCC. No new safety signals were apparent with extended follow-up in comparison with the primary analysis of this phase 3 trial or previous reports of the early-phase studies of nivolumab monotherapy in aRCC.[4,15-17] This study included patient-reported outcomes for patients treated with nivolumab versus

everolimus and showed that nivolumab treatment resulted in a sustained HRQOL benefit in comparison with everolimus; this highlights the favorable risk/benefit profile of nivolumab over everolimus with extended follow-up.

Patients who crossed over from everolimus to nivolumab during the study were a highly select subgroup of previously treated patients with a favorable prognosis in comparison with the overall trial population. This subgroup of crossover patients achieved a higher ORR with nivolumab and longer OS and PFS than patients treated with everolimus who did not cross over to nivolumab. No new safety signals were observed in patients who crossed over to nivolumab in comparison with patients originally randomized to nivolumab treatment. These data suggest that patients with aRCC can derive clinically meaningful benefits from nivolumab treatment in the setting of a later line of treatment after antiangiogenic therapy.

Although the association of baseline risk factors with poor OS outcomes trended as expected in the univariable and multivariable analysis, many did not reach statistical significance for nivolumab in the limited sample size with which this analysis was performed. The exploratory multivariable analysis showed that the association of individual risk factors with OS differed between treatment arms, and baseline tumor PD-L1 expression and most IMDC baseline risk factors were not associated with worse OS outcomes with nivolumab. Yet, lower hemoglobin levels, a higher tumor burden (sum of the reference diameters of target lesions), and a shorter time from the diagnosis of metastatic disease to the initiation of treatment were negatively prognostic for OS with nivolumab. These results suggest that predictive or prognostic factors for OS differ for patients treated with immunotherapy versus targeted therapies, and improved prognostic models based on the underlying tumor biology dictating the response to immunotherapy are needed for previously treated patients with aRCC.

The safety and efficacy of nivolumab monotherapy have been explored in metastatic RCC patient populations that were excluded from eligibility in our study, including patients with non–clear cell histology[18,19] and asymptomatic brain metastases.[20] These studies support the clinical benefit of nivolumab treatment in these 2 specific patient populations, which are not represented in CheckMate 025.[4] The immunotherapeutic landscape of aRCC is evolving with the first approval of the combination of nivolumab plus ipilimumab in the first-line setting for patients with aRCC and intermediate or poor risk factors followed by other immunotherapy combinations.[1,21-25]

In summary, this extended follow-up analysis (64-month minimum follow-up) reports the durability of responses and survival benefits and the greater probability of remaining progression-free with nivolumab versus everolimus. No new safety signals were detected with nivolumab or everolimus, and the previously observed improvement in quality of life with nivolumab was sustained. To our knowledge, this 5-year analysis of the CheckMate 025 trial is the longest follow-up of a phase 3 trial of immune checkpoint inhibitor therapy reported to date in previously treated patients with aRCC.

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## DATA AVAILABILITY

Bristol-Myers Squibb's policy on data sharing can be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. Deidentified and anonymized data sets 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 in a fashion consistent with safeguarding patient privacy and informed consent. Upon execution of an agreement, the deidentified and anonymized data sets can be accessed via a secured portal that provides an environment for statistical programming with R. The trial protocol and statistical analysis plan will also be available. Data will be available for 2 years from the study's completion or termination of the program (November 2022).

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