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## Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

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### ABSTRACT

#### BACKGROUND

Nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, was associated with encouraging overall survival in uncontrolled studies involving previously treated patients with advanced renal-cell carcinoma. This randomized, open-label, phase 3 study compared nivolumab with everolimus in patients with renal-cell carcinoma who had received previous treatment.

#### METHODS

A total of 821 patients with advanced clear-cell renal-cell carcinoma for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned (in a 1:1 ratio) to receive 3 mg of nivolumab per kilogram of body weight intravenously every 2 weeks or a 10-mg everolimus tablet orally once daily. The primary end point was overall survival. The secondary end points included the objective response rate and safety.

#### RESULTS

The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93;  $P=0.002$ ), which met the prespecified criterion for superiority ( $P\leq 0.0148$ ). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; odds ratio, 5.98 [95% CI, 3.68 to 9.72];  $P<0.001$ ). The median progression-free survival was 4.6 months (95% CI, 3.7 to 5.4) with nivolumab and 4.4 months (95% CI, 3.7 to 5.5) with everolimus (hazard ratio, 0.88; 95% CI, 0.75 to 1.03;  $P=0.11$ ). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anemia (in 8%).

#### CONCLUSIONS

Among patients with previously treated advanced renal-cell carcinoma, overall survival was longer and fewer grade 3 or 4 adverse events occurred with nivolumab than with everolimus. (Funded by Bristol-Myers Squibb; CheckMate 025 ClinicalTrials.gov number, NCT01668784.)

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\*A complete list of investigators in the CheckMate 025 study is provided in the Supplementary Appendix, available at NEJM.org

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EACH YEAR, AN ESTIMATED 338,000 NEW cases of renal-cell carcinoma are diagnosed worldwide,<sup>1</sup> and approximately 30% of patients present with metastatic disease at the time of diagnosis.<sup>2</sup> A number of targeted therapies have been approved for the treatment of advanced or metastatic renal-cell carcinoma. These agents include vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target of rapamycin (mTOR) inhibitors.<sup>3,4</sup> Everolimus is an mTOR inhibitor that is recommended for the treatment of advanced renal-cell carcinoma after treatment with sorafenib or sunitinib has failed.<sup>3-6</sup> Although everolimus and other agents have changed the therapeutic landscape for this disease, these treatments are associated with limited overall survival after a given agent is no longer effective.

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of the cellular immune response.<sup>7-9</sup> Previous studies have shown that PD-L1 expression is associated with a poor prognosis in renal-cell carcinoma, presumably because of its immunosuppressive function.<sup>10-12</sup> It has been postulated that PD-L1 expression would be associated with improved overall survival in response to nivolumab therapy, because disruption of PD-1–PD-L1 signaling mediated by nivolumab leads to restored antitumor immunity.<sup>13,14</sup>

In a phase 2 dose-ranging trial involving previously treated patients with metastatic renal-cell carcinoma, nivolumab was found to produce objective responses in 20 to 22% of the patients and overall survival ranging from 18.2 to 25.5 months.<sup>15</sup> Here, we report results from a phase 3 study comparing nivolumab with everolimus in the treatment of patients with previously treated advanced renal-cell carcinoma.

## METHODS

### PATIENTS

Eligible patients were 18 years of age or older, had histologic confirmation of advanced or metastatic renal-cell carcinoma with a clear-cell component and measurable disease according to

the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1),<sup>16</sup> and had received one or two previous regimens of antiangiogenic therapy. Additional inclusion criteria were no more than three total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy drugs, and disease progression during or after the last treatment regimen and within 6 months before study enrollment. All patients had a Karnofsky performance status of at least 70 at the time of study entry (Karnofsky performance status scores range from 0 to 100, with higher scores indicating better functioning).<sup>17</sup> Key exclusion criteria were metastasis to the central nervous system, previous treatment with an mTOR inhibitor, or a condition requiring treatment with glucocorticoids (equivalent to >10 mg of prednisone daily).

### STUDY DESIGN

This was a randomized, open-label, phase 3 study of nivolumab in comparison with everolimus. Randomization (in a 1:1 ratio) was performed with a block size of 4, with stratification according to region (United States or Canada, Western Europe, and the rest of the world), Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group, and the number of previous antiangiogenic therapy regimens (one or two) for advanced renal-cell carcinoma. The MSKCC prognostic risk is based on the presence of zero (favorable risk), one (intermediate risk), or two or three (poor risk) of the following prognostic factors: anemia, hypercalcemia, and poor performance status.<sup>18</sup>

Nivolumab and everolimus were provided by the sponsor, except in cases in which everolimus was procured as a local commercial product in certain countries. Nivolumab was administered at a dose of 3 mg per kilogram of body weight as a 60-minute intravenous infusion every 2 weeks. Everolimus was administered orally as a daily dose of 10 mg. Dose modifications were not permitted for nivolumab but were permitted for everolimus.

### STUDY OVERSIGHT

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

monitoring committee reviewed efficacy and safety during the study.

The study was designed by the authors in collaboration with the sponsor (Bristol-Myers Squibb). The authors vouch for the accuracy and completeness of the analyses reported and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org. The development of the first draft of the manuscript was led by the first author. All the authors contributed to the drafting of the manuscript and provided final approval to submit the manuscript for publication. Medical-writing support, funded by the sponsor, was provided by PPSI.

#### END POINTS AND ASSESSMENTS

The primary end point was overall survival, which was defined as the time from randomization to the date of death. Secondary end points included the objective response rate, progression-free survival, the association between overall survival and tumor expression of PD-L1, and the incidence of adverse events. Disease assessments were performed with the use of computed tomography or magnetic resonance imaging at baseline, every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment. Imaging data were evaluated by the investigator to assess tumor response (according to RECIST version 1.1). Patients were allowed to continue the study therapy after initial disease progression if a clinical benefit as assessed by the investigator was noted and the study drug had an acceptable side-effect profile. Safety assessments were conducted at each clinic visit. After discontinuation of treatment, patients were followed every 3 months for assessment of survival and subsequent anticancer therapy.

The objective response rate (investigator-assessed) was defined as the number of patients with a complete response or a partial response divided by the number of patients who underwent randomization. The best overall response was defined as the investigator-assessed best response (complete response, partial response, stable disease, or progressive disease) from the time of randomization to objectively documented disease progression or subsequent therapy, whichever occurred first. Progression-free survival was defined as the time from randomization to first documented RECIST-defined tumor progression

or death from any cause. Tumor PD-L1 membrane expression ( $\geq 1\%$  vs.  $< 1\%$  and  $\geq 5\%$  vs.  $< 5\%$ ) was assessed at a central laboratory in sections that had at least 100 tumor cells that could be evaluated and were positive for PD-L1 expression, as assessed with Dako PD-L1 immunohistochemical staining in accordance with the manufacturer's instructions.<sup>19</sup>

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.<sup>20</sup> Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) scoring algorithm.<sup>21</sup> The FKSI-DRS questionnaire consists of nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fevers, and hematuria. A summary score ranges from 0 to 36, with 36 as the best possible score (no symptoms) and 0 as the worst possible score (all the worst symptoms).<sup>21</sup> Additional details are provided in the Supplementary Appendix, available at NEJM.org.

#### STATISTICAL ANALYSIS

This planned interim analysis was conducted after 398 of the 569 deaths (70%) required for the final analysis had occurred; the stopping boundary was derived on the basis of the number of deaths with the use of an O'Brien–Fleming alpha-spending function that provided 90% power to detect a hazard ratio of 0.76 with an overall type I error rate of 0.05 (two-sided).<sup>22</sup> Interim overall survival was projected at a 0.0148 nominal significance level; if the results for overall survival were significant at that level, the study could be stopped at the recommendation of the data monitoring committee and declared to be positive for efficacy. The interim analysis would then be considered the final analysis. In July 2015, the study was stopped early because an assessment conducted by the independent data monitoring committee concluded that the study had met its end point with regard to significant results for overall survival.

All patients who underwent randomization were included in the efficacy analyses; patients who received one or more doses of study drug were included in the safety analyses. Overall survival, progression-free survival, and the duration of response were estimated with the use of Kaplan–Meier methods.<sup>16</sup> Medians and corre-

Characteristic	Nivolumab Group (N=410)	Everolimus Group (N=411)	Total (N=821)
Median age (range) — yr	62 (23–88)	62 (18–86)	62 (18–88)
Sex — no. (%)			
Male	315 (77)	304 (74)	619 (75)
Female	95 (23)	107 (26)	202 (25)
Race — no. (%) <sup>*</sup>			
White	353 (86)	367 (89)	720 (88)
Asian	42 (10)	32 (8)	74 (9)
Black	1 (<1)	4 (1)	5 (1)
Other	14 (3)	8 (2)	22 (3)
MSKCC risk group — no. (%) <sup>†</sup>			
Favorable	145 (35)	148 (36)	293 (36)
Intermediate	201 (49)	203 (49)	404 (49)
Poor	64 (16)	60 (15)	124 (15)
Karnofsky performance status — no. (%) <sup>‡</sup>			
<70	2 (<1)	1 (<1)	3 (<1)
70	22 (5)	30 (7)	52 (6)
80	110 (27)	116 (28)	226 (28)
90	150 (37)	130 (32)	280 (34)
100	126 (31)	134 (33)	260 (32)
Disease sites that could be evaluated — no. (%)			
1	68 (17)	71 (17)	139 (17)
≥2	341 (83)	338 (82)	679 (83)
Site of metastasis — no. (%)			
Lung	278 (68)	273 (66)	551 (67)
Liver	100 (24)	87 (21)	187 (23)
Bone	76 (19)	70 (17)	146 (18)
Previous nephrectomy — no. (%)			
Yes	364 (89)	359 (87)	723 (88)
No	46 (11)	52 (13)	98 (12)
Median time from initial diagnosis to randomization (range) — mo	31 (1–392)	31 (2–372)	31 (1–392)
Previous antiangiogenic regimens for treatment of advanced renal-cell carcinoma — no. (%)			
1	294 (72)	297 (72)	591 (72)
2	116 (28)	114 (28)	230 (28)
Previous systemic cancer therapy for metastatic renal-cell carcinoma — no. (%) <sup>§</sup>			
Sunitinib	246 (60)	242 (59)	488 (59)
Pazopanib	119 (29)	131 (32)	250 (30)
Axitinib	51 (12)	50 (12)	101 (12)

**Table 1. (Continued.)**

Characteristic	Nivolumab Group (N=410)	Everolimus Group (N=411)	Total (N=821)
Patients with quantifiable PD-L1 expression — no. (%)	370 (90)	386 (94)	756 (92)
PD-L1 expression level¶			
≥1%	94 (25)	87 (23)	181 (24)
<1%	276 (75)	299 (77)	575 (76)
≥5%	44 (12)	41 (11)	85 (11)
<5%	326 (88)	345 (89)	671 (89)
Patients without quantifiable PD-L1 expression — no. (%)	40 (10)	25 (6)	65 (8)

\* Race was self-reported.

† The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups are based on the presence of 0 (favorable), 1 (intermediate), or 2 or 3 (poor) of the following prognostic factors: anemia, hypercalcemia, and poor performance status.

‡ Karnofsky performance status scores range from 0 to 100, with higher scores indicating better functioning. All patients had a Karnofsky performance status of 70 or higher at time of study entry, which may have decreased at randomization.

§ Therapeutic agents that were received by more than 10% of all patients who underwent randomization are included.

¶ The expression level is expressed as the percentage of membrane immunohistochemical staining in 100 or more tumor cells.

sponding 95% confidence intervals were determined with Brookmeyer and Crowley methods<sup>23</sup>; 95% confidence intervals were constructed by means of a log–log transformation. A stratified log-rank test was performed to compare the nivolumab group with the everolimus group with respect to overall survival and progression-free survival. We obtained a stratified hazard ratio and confidence interval for nivolumab versus everolimus by fitting a stratified Cox model with the group variable as a single covariate. The difference in response rates between the nivolumab group and the everolimus group along with the two-sided 95% confidence interval were estimated with the Cochran–Mantel–Haenszel method of weighting, with adjustment for the stratification factors.<sup>24</sup> Survival was compared between the treatment groups with the use of the interim analysis monitoring feature of East software, version 5.4 (Cytel), which is based on the Lan–DeMets error-spending-function approach, with an O’Brien–Fleming stopping boundary used to reject the null hypothesis (i.e., that there is no treatment difference), while maintaining a two-sided overall alpha level of 0.05.<sup>22</sup> If superiority with regard to the primary end point was demonstrated, a hierarchical statistical testing procedure was followed for the objective response rate (estimated along with the exact 95% confidence interval with the use of the Clopper–Pearson method<sup>25</sup>) and progression-free survival at an alpha level of 0.05. For quality-of-life assessments, descriptive statistics were used to assess completion rates

and changes in quality of life. Wilcoxon–Mann–Whitney tests were used to evaluate the between-group differences in the median change from baseline in quality-of-life scores.

## RESULTS

### PATIENTS

From October 2012 through March 2014, a total of 821 patients were randomly assigned to a treatment group at 146 sites in 24 countries in North America, Europe, Australia, South America, and Asia; 803 of the 821 patients who underwent randomization were treated — 406 in the nivolumab group and 397 in the everolimus group. At data cutoff (June 2015), 67 of the 406 patients (17%) in the nivolumab group and 28 of the 397 patients (7%) in the everolimus group continued to receive treatment (Fig. S1 in Supplementary Appendix). The minimum follow-up period was 14 months. The primary reason for discontinuation of treatment was disease progression (285 of 406 patients [70%] in the nivolumab group and 273 of 397 patients [69%] in the everolimus group) (Fig. S1 in Supplementary Appendix). The demographic and clinical characteristics of the patients were balanced between the treatment groups; the majority of patients (72%) had received one previous regimen of antiangiogenic therapy for advanced renal-cell carcinoma (Table 1).

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