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Original Article

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Original Article

Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup 3-year follow-up analysis from the Phase III CheckMate 025 study

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Abstract

Background: Nivolumab treatment resulted in superior efficacy and safety versus everolimus treatment in the 2-year follow-up of the CheckMate 025 Phase III study, with consistent results in the global population and the Japanese population. Here, we report the 3-year follow-up in both groups.

Methods: Patients were randomized 1:1 to nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10 mg orally once daily until progression/intolerable toxicity. The primary endpoint was overall survival (OS). Key secondary endpoints included objective response rate, progression-free survival, safety and patient-reported quality of life.

Results: Of 410 and 411 patients randomized to nivolumab and everolimus, 37 and 26 were Japanese, respectively. The median OS for the global population was 25.8 months with nivolumab and 19.7 months with everolimus (hazard ratio 0.74; 95.5% confidence interval [CI]: 0.63–0.88; $P = 0.0005$); in the Japanese population, median OS was 45.9 months and not reached (hazard ratio 1.08; 95% CI: 0.50–2.34; $P = 0.85$), respectively. The investigator-assessed objective response rate was 26% versus 5% with nivolumab versus everolimus (odds ratio [OR] 6.19; 95% CI: 3.82–10.06) in the global population and 43% versus 8% in the Japanese population (OR 6.80; 95% CI: 1.60–28.91; $P = 0.0035$), respectively. The incidence of any-grade treatment-related adverse events

was lower with nivolumab versus everolimus in both the global patient population (80% versus 89%) and the Japanese population (81% versus 100%).
Conclusions: At the 3-year follow-up, the efficacy and safety results of CheckMate 025 are generally consistent in the global and the Japanese populations.

Key words: everolimus, immune checkpoint inhibitor, Japanese, nivolumab, renal cell carcinoma

Introduction

Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, disrupts PD-1 ligand 1 (PD-L1)-mediated signaling to restore the immune system's antitumor defenses (1,2). Nivolumab was approved in Japan for the treatment of patients with previously treated unresectable or metastatic renal cell carcinoma (RCC) with targeted drugs, based on results from the international Phase III CheckMate 025 study (NCT01668784) (3). Historically, there have been differences in efficacy and safety of RCC treatments in Asian patients compared with global clinical trial populations, possibly due to environmental and/or genetic differences. Hence, nivolumab treatment in this population requires specific investigation (4–7).

Recently, the results of the 2-year follow-up of Japanese patients with advanced RCC (aRCC) treated with nivolumab or everolimus in CheckMate 025 were published (8). Nivolumab treatment resulted in superior efficacy to everolimus treatment, consistent with the results of the global population. Median (95% confidence interval [CI]) overall survival (OS) in the global population was 26.0 (22.2–29.6) months for nivolumab and 19.7 (17.6–22.3) months for everolimus; median OS was not reached for both treatment arms in the Japanese population. The objective response rate (ORR) for the global population was 26% for nivolumab versus 5% for everolimus (odds ratio [OR] 6.13; 95% CI: 3.77–9.95); ORR for Japanese patients was 43% versus 8% (OR 9.14; 95% CI: 1.76–88.33). Nivolumab demonstrated a favorable safety profile compared with everolimus in both populations.

Here, we present the 3-year follow-up analysis of efficacy and safety data from the global population and the subgroup of Japanese patients treated with nivolumab or everolimus from CheckMate 025.

Patients and methods

Study design and treatment

The design methodology of CheckMate 025, a Phase III, randomized open-label study of nivolumab versus everolimus in patients with RCC, was reported previously (3). Patients were randomized 1:1 to receive nivolumab 3 mg/kg intravenously for 60 min every 2 weeks or everolimus 10-mg tablet orally once daily. Randomization was stratified 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 number of prior antiangiogenic therapies (one or two) for aRCC. Japanese patients were included as part of the 'rest of the world' stratification group.

Patients

Adult patients had histological confirmation of aRCC with a clear cell component, received one or two prior antiangiogenic therapies and had to have progression within 6 months before study enrollment with a Karnofsky performance status (KPS) ≥70.

Endpoints and assessments

The primary endpoint was OS. Key secondary endpoints were investigator-assessed ORR, progression-free survival (PFS), safety and patient-reported quality of life. Disease assessments (per Response Evaluation Criteria in Solid Tumors v1.1) (9) were performed using computed tomography or magnetic resonance imaging at baseline and every 8 weeks after randomization for the first year, then every 12 weeks until progression or treatment discontinuation. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0. Treatment-related select AEs (AEs by category that may be immune-mediated, differ from those caused by non-immunotherapies, may require immunosuppression for management and whose early recognition may mitigate severe toxicity) were reported. Quality of life was assessed using patient questionnaires, including the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) questionnaire (10). The questionnaire consists of nine symptom-specific questions, with a summary score that ranges from 0 to 36, with 36 as the best possible score. A change of at least 2 points was considered a clinically meaningful change.

Study oversight

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

Statistical analyses

OS, PFS and duration of response were estimated using Kaplan–Meier methodology. Median OS and corresponding 95% CIs for each treatment arm were determined using Brookmeyer and Crowley methodology (11) with log-log transformation. The two treatment arms were compared with stratified log-rank tests. The estimated hazard ratios (HRs) and associated 95% CIs obtained for OS and PFS of nivolumab versus everolimus were calculated using a stratified Cox proportional hazards model with the treatment as a single covariate. ORR and the corresponding 95% CIs were calculated based on the Clopper and Pearson method (12).

Results

Patients

As reported previously, 410 and 411 patients in CheckMate 025 were randomized to nivolumab and everolimus treatments, respectively. Of these, 96 patients in the nivolumab arm and 98 patients in the everolimus arm were stratified by the 'rest of the world' region, which included Japan. Thirty-seven of 410 patients (9%) and 26 of

411 patients (6%), respectively, were Japanese. All Japanese patients who were randomized received treatment (8). The demographic and baseline characteristics of the Japanese population were reported previously (8) and were generally similar to the global population of the study, except that compared with the global population, a higher proportion of Japanese patients had higher baseline KPS and favorable MSKCC risk score, while a lower proportion had a poor MSKCC risk score. Additionally, a lower proportion of Japanese patients in the everolimus than in the nivolumab arm had ≥2 sites of metastases, liver metastases and PD-L1 expression ≥1% (Supplemental Table 1). The distribution of prior regimens in the metastatic setting differed between the global and the Japanese populations (8). More patients in the Japanese population versus the global population had prior treatment with axitinib (20 of 63 patients [32%] versus 101 of 821 patients [12%]), interferon-α (17 of 63 patients [27%] versus 18 of 821 patients [2%]) and sorafenib (22 of 63 patients [35%] versus 57 of 821 patients [7%]), and fewer Japanese patients were treated with pazopanib (2 of 63 patients [3%] versus 250 of 821 patients [30%]) and sunitinib (28 of 63 patients [44%] versus 488 of 821 patients [59%]). At a median follow-up of 40 months, 7% of patients in the nivolumab arm and 1% in the everolimus arm continued to receive treatment in the global population; 14% and 4%, respectively, continued treatment in the Japanese population. The primary reason for discontinuation in both arms of both populations was disease progression (global population: 77% in the nivolumab arm and 74% in the everolimus arm; Japanese population: 65% for both treatment groups).

Efficacy

At a median follow-up of 40 months, the median OS for the global population was 25.8 months with nivolumab and 19.7 months with everolimus (HR 0.74 [95% CI: 0.63–0.88]; $P = 0.0005$; Fig. 1). The 24-month OS rates (95% CI) in the global population were 52% (47–57) with nivolumab and 42% (37–47) with everolimus; 36-month OS rates were 39% (34–44) and 30% (25–34), respectively. In the Japanese population, the median OS was 45.9 months versus not reached with nivolumab and everolimus, respectively (HR 1.1 [95% CI: 0.50–2.34]; $P = 0.85$; Fig. 1). The 24-month OS rates (95% CI) in the Japanese population were 75% (57–86) with nivolumab and 73% (52–86) with everolimus; 36-month OS rates were 58% (40–72) and 54% (33–71), respectively.

ORR (95% CI) was higher with nivolumab than with everolimus treatment in the global and the Japanese populations (global: 26% [22–30] versus 5% [3–8]; OR 6.19; 95% CI: 3.82–10.06; Japanese: 43% [27–61] versus 8% [1–25]; OR 6.80; 95% CI: 1.60–28.91; Fig. 2). In the global population, 4 (1%), 102 (25%) and 137 (33%) patients had a best response of complete response (CR), partial response (PR) and stable disease (SD) with nivolumab treatment, respectively. Two (<1%) CR, 20 (5%) PR and 229 SD (56%) best responses were observed with everolimus treatment. Best responses of progressive disease were observed in 143 (35%) and 115 (28%) of patients treated with nivolumab and everolimus, respectively. In the Japanese population, 0, 16 (43%) and 16 (43%) patients had a best response of CR, PR and SD with nivolumab treatment, respectively; 1 (4%), 1 (4%) and 20 (77%) patients had a best response of CR, PR and SD with everolimus treatment, respectively.

Best responses of progressive disease were observed in 5 (14%) and 4 (15%) patients treated with nivolumab and everolimus, respectively.

Among global population responders, the median (range) time to response (TTR) and median (95% CI) duration of response (DOR) were similar with nivolumab and everolimus treatments (TTR: 3.6 months [1.4–24.8] and 3.7 months [1.5–11.2], respectively; DOR: 12.3 months [9.1–18.2] and 12.0 months [6.4–21.7], respectively; Fig. 2). With nivolumab, 24 of 106 responders (23%) had an ongoing response and 3 of 22 everolimus responders (14%) had an ongoing response. Of the patients who responded to treatment, nine patients in the nivolumab arm and two in the everolimus arm discontinued treatment but had sustained response. Among Japanese responders, the median (range) TTR was 3.3 months (1.9–9.2) with nivolumab and 2.7 months (1.9–3.5) with everolimus (Fig. 2). The median (95% CI) DOR was 13.4 months (2.2–25.8) with nivolumab and not reached (12.0–not estimable) with everolimus (Fig. 2). Among responders, one patient in the nivolumab arm and one patient in the everolimus arm had an ongoing response (Fig. 3). Although some patients exhibited disease progression or occurrence of new lesions, response to nivolumab treatment until eventual progression was durable among Japanese patients (Fig. 4).

At a median follow-up of 40 months, the median PFS in the global population was 4.2 months with nivolumab and 4.5 months with everolimus (HR 0.85 [95% CI: 0.73–0.99]; $P = 0.0371$; Fig. 5). The proportion of patients progression-free at 36 months (95% CI) was 8% (6–11) and 2% (1–4) with nivolumab and everolimus, respectively. In the Japanese population, the median PFS was 5.6 months with nivolumab and 9.4 months with everolimus (HR 1.26 [95% CI: 0.66–2.38]; $P = 0.48$; Fig. 5). The proportion of patients progression-free at 36 months (95% CI) was 9% (2–20) and 5% (0–21) with nivolumab and everolimus, respectively.

Safety

Treatment-related AEs of any grade in the global population occurred in 325 (80%; Grade 3–4: 84, 21%) patients treated with nivolumab and 352 (89%; Grade 3–4: 147, 37%) patients treated with everolimus. The most common any-grade treatment-related AEs with nivolumab were fatigue ($n = 139$, 34%), pruritus ($n = 63$, 16%) and nausea ($n = 61$, 15%); the most common with everolimus were fatigue ($n = 135$, 34%), stomatitis ($n = 117$, 29%) and anemia ($n = 97$, 24%). The most common Grade 3–4 treatment-related AE was fatigue ($n = 11$, 3%) with nivolumab and anemia ($n = 34$, 9%) with everolimus. In the Japanese population, treatment-related AEs occurred in 30 (81%; Grade 3–4: 8, 22%) patients treated with nivolumab and 26 (100%; Grade 3–4: 15, 58%) patients treated with everolimus (Fig. 6). The most common any-grade treatment-related AEs in patients treated with nivolumab were diarrhea ($n = 7$, 19%), fatigue ($n = 6$, 16%) and anemia ($n = 6$, 16%); the most common with everolimus were stomatitis ($n = 20$, 77%), decreased platelet count ($n = 13$, 50%) and anemia ($n = 12$, 46%). The most common Grade 3–4 treatment-related AE was anemia ($n = 2$, 5%) with nivolumab and hypertriglyceridemia ($n = 3$, 12%) with everolimus. Any-grade treatment-related AEs leading to discontinuation occurred in 34 (8%) and 50 (13%) patients in the global population treated with nivolumab and everolimus, respectively, and 6 (16%) and 6 (23%) Japanese patients in the nivolumab and everolimus arms, respectively. Among patients in the global population, 271 (67%) and 293 (74%) died in the nivolumab and everolimus arms, respectively; the primary reason for death was disease progression in both arms (237 [58%] and 266 [67%] patients in the nivolumab and everolimus arms, respectively). No deaths related to study treatment were reported in the nivolumab arm, while two drug-related deaths occurred in the everolimus arm, one from acute bowel ischemia and one from septic shock. Among Japanese patients, 17 (46%) and 12 (46%) died in the nivolumab and everolimus arms, respectively; the primary reason for

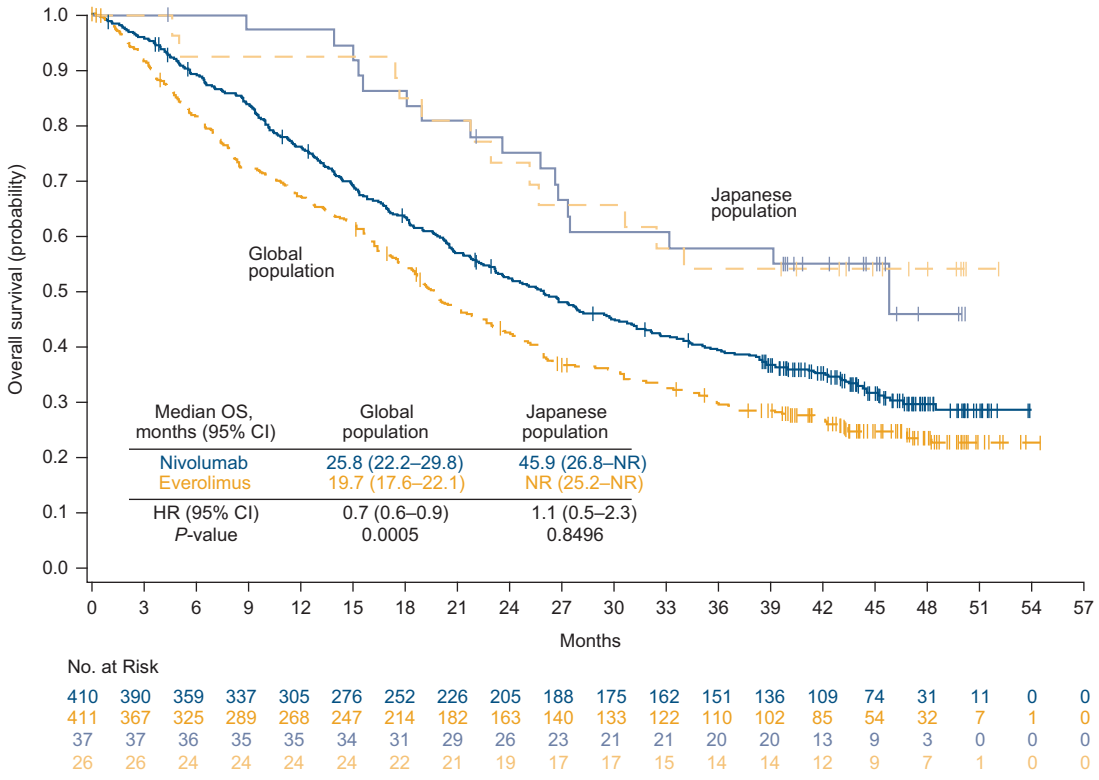

Figure 1. Kaplan–Meier curve for OS in global and Japanese patients. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

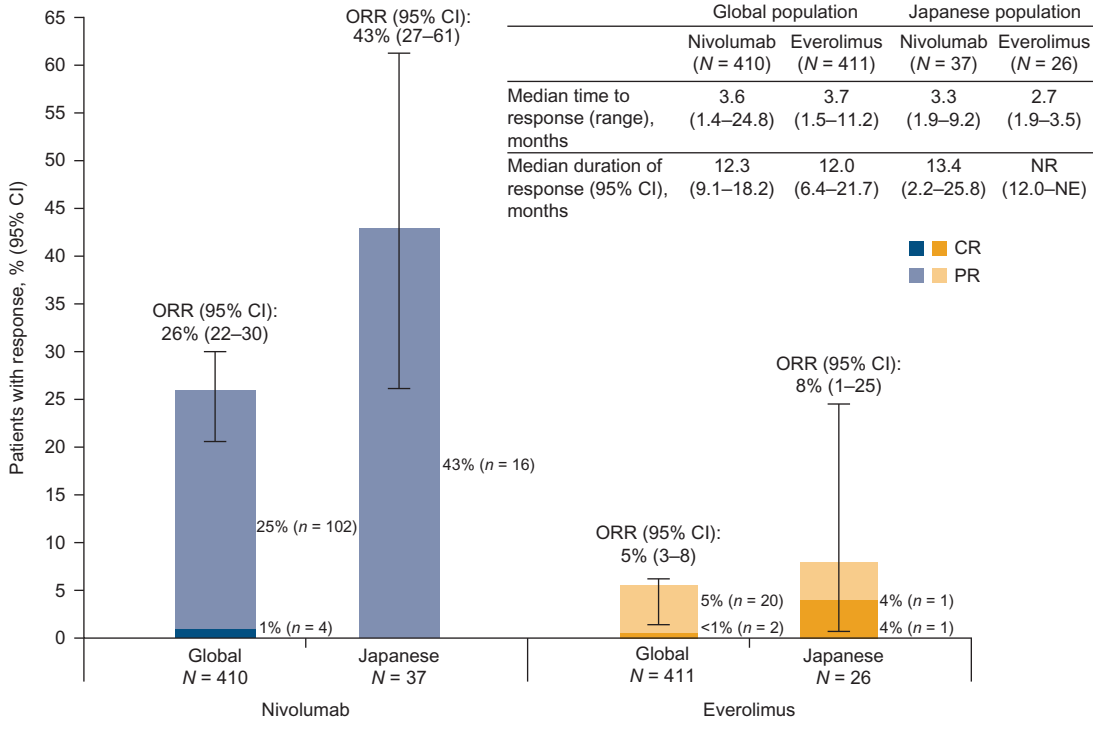

Figure 2. Antitumor activity in global and Japanese patients. CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; PR, partial response.

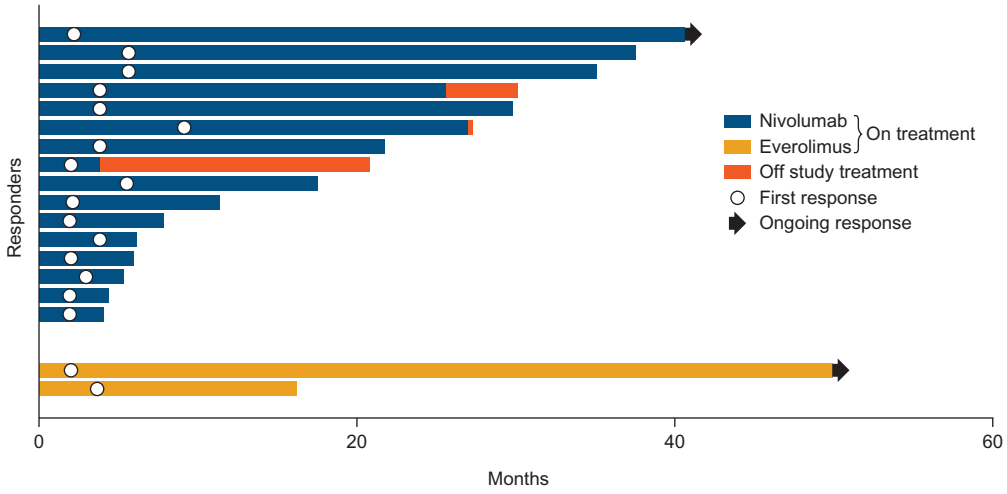

Figure 3. Response characterization in Japanese patients.

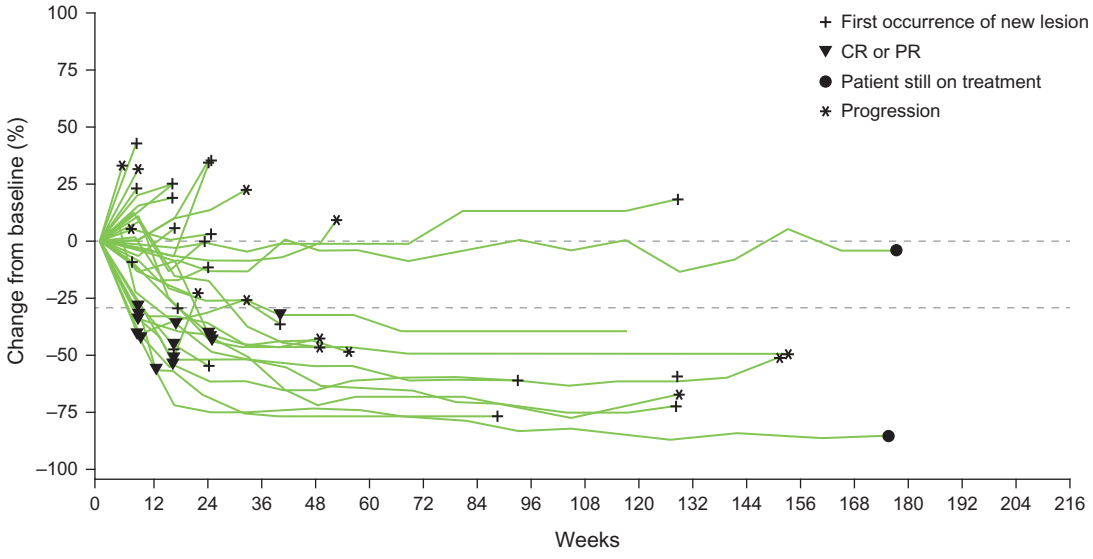

Figure 4. Change in tumor burden over time in Japanese patients treated with nivolumab. CR, complete response; PR, partial response.

death was disease progression in both arms (15 [41%] and 12 [46%] patients in the nivolumab and everolimus arms, respectively). No treatment-related deaths occurred in either arm.

The incidence of treatment-related select AEs in the Japanese population was grouped by system organ class. Treatment-related select AEs of any grade for nivolumab versus everolimus were observed as follows: endocrine (5% versus 0%), gastrointestinal (19% versus 12%), hepatic (22% versus 31%), pulmonary (5% versus 46%), renal (3% versus 15%) and skin (24% versus 69%) (Fig. 7). Grade 3–4 treatment-related select AEs for nivolumab versus everolimus treatment were observed in hepatic (5% versus 0%), gastrointestinal (3% versus 4%), pulmonary (0% versus 8%) and skin (0% versus 4%); no Grade 3–4 select AEs were observed in the endocrine or renal organ categories for either treatment arm (Fig. 7). In both treatment arms, most treatment-related select AEs occurred in the first 6 months of treatment (54% for nivolumab, 85% for everolimus). The incidence of treatment-related select AEs decreased after 6 months of treatment. After >36 months of treatment, the incidence of AEs decreased to ≤5% for both nivolumab and everolimus (Fig. 8). Among all treated Japanese patients, 51% (n = 19) and 81% (n = 21) received immune-modulating therapy for AE management while on nivolumab and everolimus, respectively.

Quality of life

The FKSI-DRS quality-of-life questionnaire completion rate was >70% in the nivolumab arm for almost 3 years (up to Week 140) in the global and the Japanese populations. In the global population, completion rates in the everolimus arm declined to <80% after Week 64, with the exception of Weeks 76, 84, 132, 136 and 140. Completion rates in the everolimus arm of the Japanese population remained >75% up to Week 120. In the Japanese population, the mean FKSI-DRS score was generally equal to or slightly exceeded baseline values at every assessment in the nivolumab arm, indicating improvement. The scores were lower than baseline in every assessment in the everolimus arm (indicating worsening), with some assessments being at least 2 points below baseline, which is

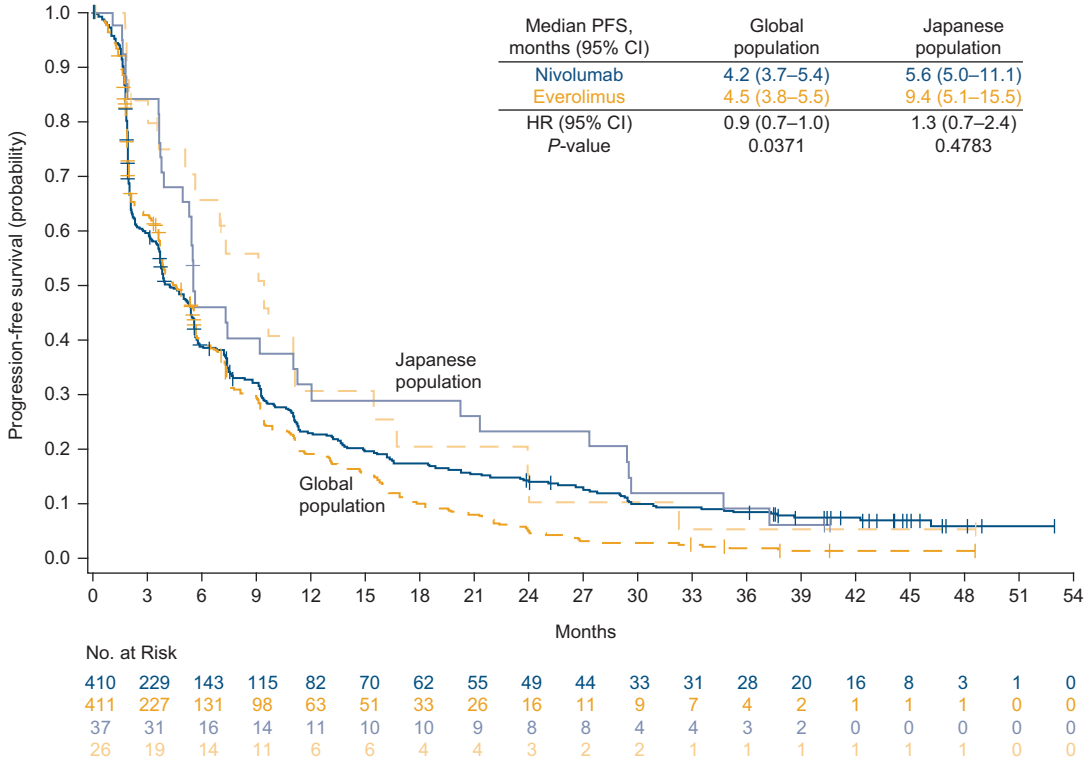

Figure 5. Kaplan–Meier curve for PFS in global and Japanese patients. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

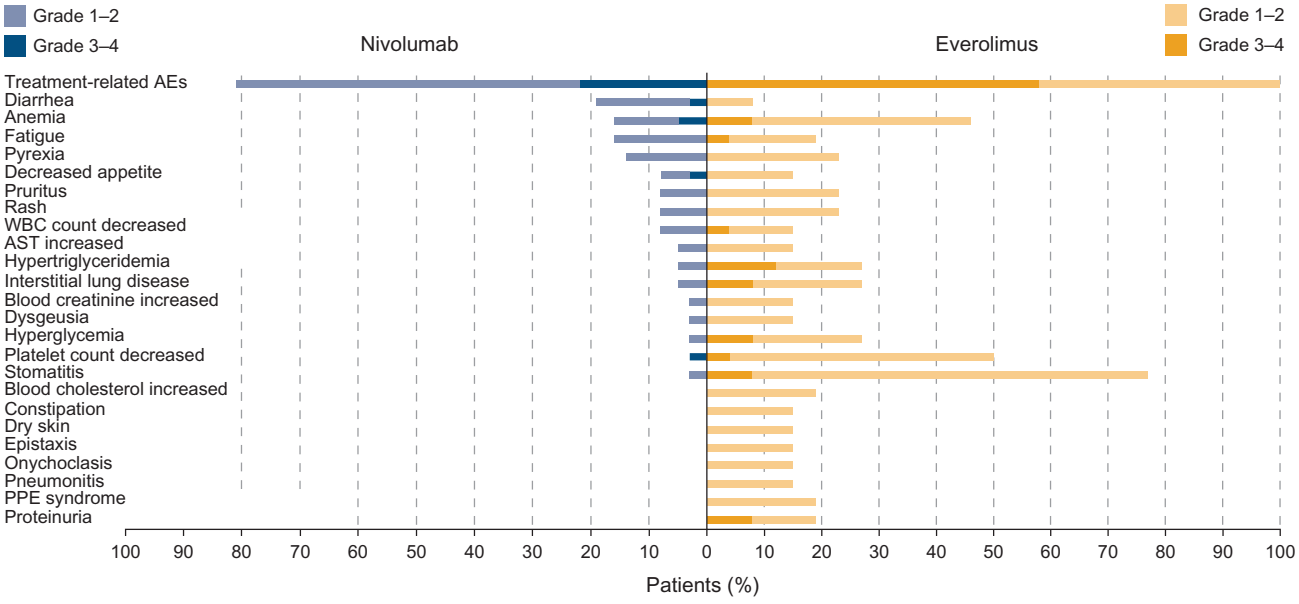

Figure 6. Treatment-related adverse events in ≥15% of Japanese patients in either arm.

considered a clinically meaningful change in score (Supplemental Fig. 1). These results are consistent with those of the global population (Supplemental Fig. 2).

Subsequent therapy

In the global population, 264 (64%) and 279 (68%) patients randomized to nivolumab and everolimus, respectively, received subsequent systemic therapy. The median (range) time from last study drug dose to subsequent systemic therapy was 1.0 month (0.1–20.9) with nivolumab and 0.9 months (<0.1–20.0) with everolimus. The most common subsequent systemic therapy used after treatment with nivolumab was everolimus (136 patients, 33%; Supplemental Table 2); the most common subsequent therapy after treatment with everolimus was axitinib (165 patients, 40%; Supplemental Table 2). In the everolimus arm, 61 patients (15%)

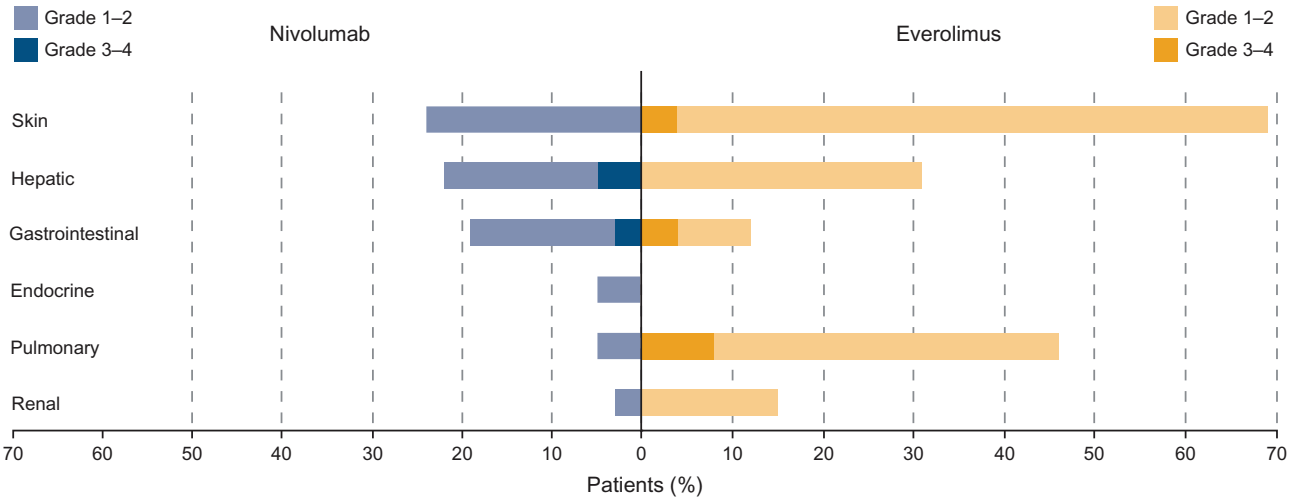

Figure 7. Treatment-related select adverse events in the Japanese population.

crossed over to the nivolumab extension phase. The most common subsequent therapies received by patients who crossed over were axitinib (32 patients, 52%), pazopanib (12 patients, 20%) and sunitinib (10 patients, 16%). Fifty-four (89%) of the patients who crossed over from everolimus to nivolumab were alive at the 3-year follow-up.

In the Japanese population, 27 of 37 (73%) and 23 of 26 (88%) patients randomized to nivolumab and everolimus, respectively, received subsequent systemic therapy. The most common subsequent systemic therapy was axitinib for both arms (46% in the nivolumab arm, 17 patients; 58% in the everolimus arm, 15 patients; Supplemental Table 2). The median (95% CI) time from last study drug dose to subsequent therapy was 1.0 months (0.7–2.1) and 1.5 months (0.7–4.0) in the nivolumab and everolimus arms, respectively.

Discussion

At a median follow-up of 40 months, nivolumab treatment in Japanese patients resulted in significantly higher ORR compared with everolimus (OR 6.80; 95% CI: 1.60–28.91), with no new safety signals identified.

In the interval since the previous update at 2 years of follow-up (8), the median OS with nivolumab treatment in Japanese patients was reached in the 3-year follow-up, while it has not yet been reached in the everolimus treatment arm. However, the OS curve with nivolumab treatment in Japanese patients appears to be notably higher than that in the corresponding 3-year update in the global population. The ORR was consistent between both treatment arms in the 3-year and 2-year follow-up analyses of the Japanese population, and superior in the nivolumab arm compared with the everolimus arm. An additional best response of SD was observed with nivolumab treatment in the 3-year follow-up compared with the 2-year follow-up. The magnitude of difference between arms in the 3-year follow-up was greater in the Japanese population versus the global population, consistent with the results of the 2-year follow-up. The median PFS was also the same in the 3-year and 2-year follow-up analyses of the Japanese population and higher in the everolimus arm compared with the nivolumab arm; in contrast, the PFS curves in the 3-year follow-up of the global population separated with longer follow-up, and now favor nivolumab over everolimus (HR 0.85; 95% CI: 0.73–0.99; $P = 0.0371$) (9). Longer follow-up is needed to see if a similar separation in the Japanese population of PFS curves may occur. Differences in prior therapy, baseline MSKCC risk factor distribution and baseline KPS could have contributed to the differences in efficacy results between the global and Japanese populations. Additionally, the lower incidence of liver metastases and ≥2 sites of metastases in Japanese patients treated with everolimus compared with nivolumab could have contributed to the higher OS and PFS observed with this treatment in this population. Differences in subsequent therapy between the global and the Japanese populations may also potentially contribute to the disparity of the OS results between the two populations. Although no differences were observed with nivolumab versus everolimus treatment in OS or PFS in Japanese patients, both OS and PFS exceeded those in the global population of CheckMate 025.

The incidence of treatment-related AEs with nivolumab was lower than with everolimus in the 3-year follow-up of the Japanese population, consistent with the 2-year (8) and the 3-year follow-up analyses of the global population. No new safety signals were observed with extended follow-up. The incidence of any-grade endocrine and renal select AEs with nivolumab treatment were lower in the Japanese population versus the global population, while hepatic select AE incidence was higher in the Japanese population versus the global population. Gastrointestinal, skin and pulmonary treatment-related select AE incidence was similar in the Japanese and global populations; Grade 3–4 treatment-related select AEs were also similar between the two populations (13). Most patients experienced treatment-related select AEs in the first 6 months of treatment. Both the global and the Japanese populations experienced an improvement in quality of life with nivolumab treatment compared with everolimus. Similar proportions of patients in the global and Japanese populations received subsequent therapy.

There are several limitations to this analysis of the Japanese population of CheckMate 025. The small sample size of Japanese patients reduced the confidence level and increased the margin of error. Additionally, the different sample size in arms due to stratification as part of a larger regional group may have affected outcomes.

In conclusion, longer follow-up of Japanese patients enrolled in CheckMate 025 confirmed the efficacy results of the 2-year follow-up, with no new safety signals identified.

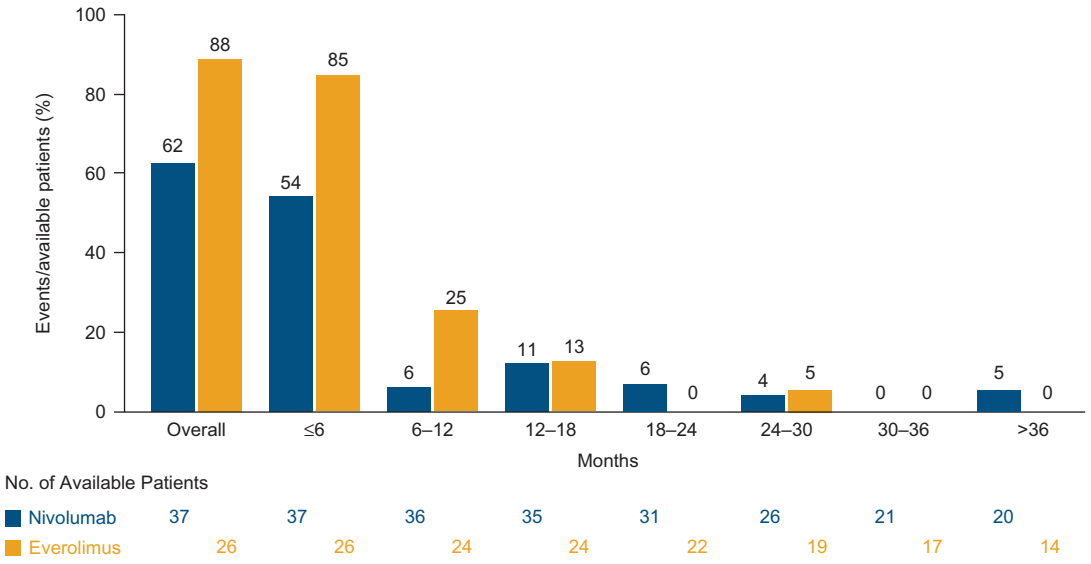

Figure 8. Treatment-related select adverse events by time in Japanese patients.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement

Yoshihiko Tomita has received consultancy/advisory fees from Novartis and ONO Pharmaceutical Company Ltd; and honoraria from Astellas, Novartis, ONO Pharmaceutical Company Ltd, Pfizer and Sanofi-Aventis.

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Burcin Simsek is an employee of Bristol-Myers Squibb.

Elmer Berghorn is an employee of and holds stock options in Bristol-Myers Squibb.

Robert J. Motzer has received consultancy/advisory fees from Eisai Pharmaceuticals, Exelixis, Genentech/Roche, Merck, Novartis, and Pfizer.

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Authors' contributions

Yoshihiko Tomita had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Yang, Berghorn.

Provision of study materials or patients: Tomita, Fukasawa, Shinohara, Kitamura, Oya, Eto, Tanabe, Saito, Kimura, Yonese, Yao, Uemura, Motzer, Ozono.

Collection and assembly of data: Yang, Berghorn.

Data analysis and interpretation: All authors.

Drafting of the manuscript: Tomita.

Critical revision of the manuscript for important intellectual content: All authors.

Final approval of manuscript: All authors.

References

1. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;28:3167–75.
2. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002;99:12293–7.
3. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–13.
4. Naito S, Tomita Y, Rha SY, et al. Kidney Cancer Working Group report. *Jpn J Clin Oncol* 2010;40:i51–6. (suppl 1).
5. Oh WK, McDermott D, Porta C, et al. Angiogenesis inhibitor therapies for advanced renal cell carcinoma: toxicity and treatment patterns in clinical practice from a global medical chart review. *Int J Oncol* 2014;44:5–16.
6. Tsuchiya N, Narita S, Inoue T, et al. Risk factors for sorafenib-induced high-grade skin rash in Japanese patients with advanced renal cell carcinoma. *Anticancer Drugs* 2013;24:310–4.
7. Ye D, Eto M, Chung JS, et al. Use of targeted therapies for advanced renal cell carcinoma in the Asia-Pacific region: opinion statement from China, Japan, Taiwan, Korea, and Australia. *Clin Genitourin Cancer* 2014;12:225–33.
8. Tomita Y, Fukasawa S, Shinohara N, et al. Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study. *Jpn J Clin Oncol* 2017;47:639–46.
9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
10. Cella D, Yount S, Brucker PS, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. *Value Health* 2007;10:285–93.
11. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982;38:29–41.
12. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–14.
13. Sharma P, Tykodi SS, Escudier B, et al. Three-year efficacy and safety update from the phase III CheckMate 025 study of nivolumab versus everolimus in patients with advanced renal cell carcinoma. Presented at: 16th International Kidney Cancer Symposium; November 3–4, 2017; Miami, FL, USA.

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