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Quality of life in patients with advanced renal cell carcinoma treated with nivolumab versus everolimus in CheckMate 025, a randomised, phase 3 clinical trial

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Summary

Background—In the phase 3 CheckMate 025 study, previously treated patients with advanced renal cell carcinoma (aRCC) randomised to nivolumab had an overall survival (OS) benefit versus everolimus. We compared health-related quality of life (HRQoL) between treatment arms and explored the relationship with OS.

Methods—In this open-label study (NCT01668784) in 146 oncology centres in 24 countries, patients with aRCC were randomised (1:1; block size of 4) to receive nivolumab 3 mg/kg by 60-minute intravenous infusion every 2 weeks or everolimus 10 mg tablet orally once daily. The study was stopped early at the planned interim analysis in July 2015 as the study met its primary endpoint. A protocol amendment permitted patients in the everolimus group to cross over to nivolumab treatment. All patients not on active study therapy are being followed for survival. At the interim analysis, HRQoL was assessed using the Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms (FKSI-DRS) and European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) questionnaires. FKSI-DRS completion rate was calculated using number of patients with at least one baseline assessment and at least one post-baseline assessment. FKSI-DRS completion was defined as completion of five or more items; otherwise data were treated as missing. FKSI-DRS symptom index score was prorated for missing items. No adjustments were made for EQ-5D missing data. Descriptive statistics and multivariate analyses, including mixed-effects model repeated-measures (MMRM) were used. Analyses were powered according to the original study protocol. A correlation between baseline HRQoL and OS was performed.

Findings—Patients were randomised from October 2012 through March 2014. HRQoL data were collected at baseline for 362 (88%) of 410 (nivolumab) and 344 (84%) of 411 (everolimus) randomised patients. The mean difference (95% CI) in FKSI-DRS score between nivolumab and everolimus arms was 1·6 (1·4–1·9, p<0·001) with descriptive statistics and 1·7 (1·2–2·1, p<0·001) with MMRM analysis. More patients experienced clinically meaningful HRQoL improvement with nivolumab versus everolimus (200 [55%] of 361 *vs* 126 [37%] of 343, respectively; p<0·001). Median (95% CI) time to improvement in HRQoL was shorter in patients treated with nivolumab (4·7 [3·7–7·5] months) versus everolimus (not reached [range not estimable]). A positive correlation between OS and FKSI-DRS (r=0·27; p≤0·001), EQ-5D utility (r=0·24, p≤0·001), and EQ-5D VAS (r=0·26, p≤0·001) baseline scores across both arms was observed.

Interpretation—Nivolumab treatment was associated with HRQoL improvement compared with everolimus in previously treated patients with aRCC.

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Keywords

Patient-reported outcome; quality of life; health-related quality of life; nivolumab; everolimus; Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms; FKSI-DRS; renal cell carcinoma; survival; CheckMate 025

Introduction

Renal cell carcinoma (RCC) is the most commonly diagnosed kidney cancer worldwide, with approximately 30% of patients presenting with advanced disease.[1,2] Anti-angiogenic and mTOR-targeted agents have changed the therapeutic landscape for advanced or metastatic RCC (aRCC), but these treatments are associated with limited overall survival (OS), toxicities related to their specific mechanisms of action, and limited improvement in health-related quality of life (HRQoL) for this patient population.[1,3–5]

Nivolumab is a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands 1 (PD-L1) and 2 (PD-L2).[2] In the phase 3 CheckMate 025 study of nivolumab versus everolimus for the treatment of aRCC, OS was longer (p=0·002) for nivolumab; median OS (95% confidence interval [CI]) was 25·0 months (21·8–not estimable [NE]) with nivolumab versus 19·6 months (17·6–23·1) with everolimus; hazard ratio (HR) for death with nivolumab versus everolimus was 0·73 (98·5% CI 0·57–0·93).[2] Grade 3 or 4 treatment-related adverse events were less frequent with nivolumab versus everolimus.[2] Furthermore, one analysis of HRQoL scores showed that median change from baseline using the Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms (FKSI-DRS) questionnaire increased over time with nivolumab treatment and differed significantly from the change from baseline scores with everolimus treatment at each assessment point through week 104, representing an improvement in HRQoL (p<0·05) with nivolumab.[2] Here, we report on the complete HRQoL analysis, including results from mixed model analyses from CheckMate 025. We evaluated changes in HRQoL over time between and within treatment arms in patients with aRCC treated with nivolumab versus everolimus using FKSI-DRS and European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) assessments. In addition, we explored the association between baseline HRQoL scores and OS for the entire study cohort.

Methods

Study design and participants

This was a phase 3, randomised, open-label study of nivolumab versus everolimus in patients with aRCC (NCT01668784). Patients were randomised from October 2012 through March 2014 (first and last dates of patient enrolment were October 22, 2012, and March 11, 2014, respectively) at 146 sites in 24 countries in North America, Europe, Australia, South America, and Asia. Full details of the study design have been previously reported.[2] After patients' initial eligibility was established and informed consent had been obtained, patients were enrolled into the study using an interactive voice response system. Nivolumab was provided by the sponsor (Bristol-Myers Squibb, Lawrenceville, NJ, USA). Everolimus was

provided by the sponsor for sites outside the United States, and by AcariaHealth (Hawthorne, NY, USA) for sites within the United States.

Adults 18 years of age or older with histological confirmation of aRCC with a clear-cell component, measurable disease (Response Evaluation Criteria in Solid Tumors [RECIST] version 1·1), Karnofsky performance status of ≥70% at the time of study entry, and patients who previously received one or two anti-angiogenic therapies for aRCC were eligible. 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 enrolment. There was a washout period for anticancer therapy or palliative, focal radiation therapy that occurred less than 14 days prior to the first dose of study drug (less than 28 days for bevacizumab). Key exclusion criteria were previous treatment with an mTOR inhibitor, a condition requiring treatment with glucocorticoids (equivalent to >10 mg of prednisone daily), or metastasis to the central nervous system.

This study was approved by the institutional review board or independent ethics committee at each centre 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.

Randomisation and masking

Patients were randomised 1:1 to either nivolumab or everolimus with a block size of 4. Patients were stratified according to region (United States or Canada, Western Europe, and the rest of the world), Memorial Sloan Kettering Cancer Center prognostic risk group, and the number of previous anti-angiogenic therapy regimens (one or two). This was an open-label study, thus, patients and investigators were not blinded to treatments.

Procedures

Previously treated patients with aRCC were randomised to receive nivolumab 3 mg/kg as a 60-minute intravenous infusion every 2 weeks or everolimus 10 mg tablet orally once daily. The primary endpoint was OS, which was defined as the time from randomisation to the date of death. Patients remained on treatment until progression or intolerable toxicity. Dose modifications were not permitted for nivolumab but were permitted for everolimus. Disease assessments were performed using 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 assessed by the investigator to determine tumour response (using RECIST version 1·1). Patients were permitted to continue study drug after initial disease progression if the investigator reported a clinical benefit and the treatment was tolerable. The study was stopped early at the planned interim analysis in July 2015 as the study met its primary endpoint. A protocol amendment permitted patients in the everolimus group to cross over to nivolumab treatment. All patients not on active study therapy are being followed for survival.

Safety assessments were conducted at each clinic visit. After treatment discontinuation, patients were followed every 3 months for assessment of survival and subsequent anticancer therapy. All adverse events based on the June 2015 data cutoff have been published.[2]

HRQoL endpoints and assessments included evaluation of HRQoL improvement and deterioration from baseline, both within and between each treatment arm as assessed by the FKSI-DRS (a disease-specific questionnaire); changes in global health outcomes from baseline within and between treatment arms as assessed by EQ-5D (a general health status questionnaire comprising a utility index and a visual analogue scale [VAS]); and the association between baseline HRQoL scores and OS.[6,7] Assessments were made before any clinical activities, after randomisation before cycle 1 dosing) and on day 1 of each cycle (starting with cycle 2), and at the first two follow-up visits. Questionnaires were completed before physician contact, treatment dosing, or any procedures. Assessments were completed every 4 weeks during the treatment phase for FKSI-DRS and EQ-5D. FKSI-DRS and EQ-5D assessments were also collected at follow-up visits occurring approximately 30 and 100 days after last dose. Only EQ-5D assessments were collected at each of 10 survival follow-up visits, occurring every 3 months (figure 1).

The FKSI-DRS questionnaire (see appendix p1) comprises nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnoea, cough, fevers, and haematuria.[6] Completion was defined as answering at least five of nine items, which is standard and recommended as part of the scoring manual. Each symptom was rated on a Likert-type scale ranging from 0 to 4, with 0 representing “not at all” and 4 representing “very much.” Each answered item in each questionnaire was reverse-scored such that higher scores corresponded to better HRQoL and fewer symptoms; the individual items were then summed to obtain a score. This score was multiplied by the number of items in the subscale (ie, nine) and divided by the number of items answered. A summary score ranging from 0 to 36 was then produced, with 36 being the best possible score (no symptoms) and 0 being the worst possible score (all worst symptoms). The FKSI-DRS completion rate was calculated using the number of patients with non-missing data at baseline and at least one post-baseline visit.

The EQ-5D utility index (see appendix p2) comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This index was computed with scores ranging from worst (ie, unconscious) to best imaginable health state.[8] EQ-5D VAS (see appendix p3) was used to record patients’ self-rated health state on a 100-point vertical VAS (0 = worst imaginable; 100 = best imaginable).[9]

A prespecified important difference (ID) for FKSI-DRS was a change of at least 2 points from baseline (3 points was used as an additional threshold). An ID increase from baseline indicated clinically meaningful improvement in HRQoL, while an ID decrease from baseline indicated HRQoL progression or clinically meaningful deterioration. For EQ-5D, a change from baseline of 0·08 points for the utility index score and of 7 points for the VAS score was considered an ID for defining a clinically meaningful change (≥0·08 indicated clinically meaningful improvement on the utility index; ≥7 indicated clinically meaningful improvement on the VAS).[6,10,11]

Outcomes

Primary endpoint (OS) was defined as the time from randomisation to the date of death, which has been previously published.[2] The main patient-reported outcome objective in the protocol was assessment of disease-related symptom progression rate in each treatment group based on the FKSI-DRS subscale of the FKSI-15. However, the observation of improvement in HRQoL in patients treated with nivolumab prompted a formal analysis of HRQoL improvement.

Statistical analyses

A sample size of 569 events (deaths) was required to compare OS (the primary endpoint) between patients randomised to receive nivolumab or everolimus. An independent data monitoring committee reviewed data for a preplanned interim analysis, conducted after 398 events (70%). This provided 90% power to detect a HR of 0·76 with an overall type 1 error of 0·05 (two-sided). The stopping boundaries at interim and final analyses were based on the number of deaths using the O'Brien and Fleming alpha spending function. The study was registered at clinicaltrials.gov (NCT01668784).

Statistical analyses of HRQoL were performed in three stages: 1) descriptive statistics at each time point and change from baseline; 2) *t*-test for differences in descriptive statistic means between and within arms; and 3) a longitudinal mixed-effects model repeated-measures (MMRM) to analyse and confirm differences between treatment arms. FKSI-DRS and EQ-5D analyses were performed on all randomised patients who had a baseline assessment and at least one post-baseline assessment. If fewer than half of the items were completed, data were treated as missing. For FKSI-DRS, the score was prorated if there were missing items; for EQ-5D, no adjustments were made for missing data. Statistical software used was SAS version 9·4.

Descriptive statistics at each time point and for change from baseline to each time point were performed. Wilcoxon–Mann–Whitney tests were used to evaluate the between-arm differences in the median change from baseline in HRQoL. Means were evaluated based on *t*-tests. Chi-square analyses were used to assess differences in the proportion of patients who experienced meaningful improvement with nivolumab versus everolimus. A Cox proportional hazard model was utilised, treating baseline HRQoL score as a covariate to test time to improvement. Univariate and mixed-effects analyses were performed on individual items from the FKSI-DRS. Longitudinal MMRM modelling with random intercepts and slopes was used to assess treatment differences in HRQoL using time-related variables.[12] Longitudinal modelling was conducted using the MMRM model, including HRQoL outcome scores at baseline and stratification factors (ie, number of prior anti-angiogenic therapy regimens, region, and Memorial Sloan Kettering Cancer Center risk group) as covariates.[13] Several variance structures were considered, and a compound symmetry covariate structure that included random statement provided the best model. Study day was treated as a random effect. Time point was treated as a repeated measure. Standardised mean difference between treatment arms was calculated using Hedges' g and a 95% CI.

A pattern mixture model sensitivity analysis was conducted to evaluate the impact of missing data on outcomes. Dropout patterns were examined by first identifying the last week on treatment where patient-reported outcomes (PROs) were observed for each patient. The median of the last week on treatment where PROs were observed across the overall sample (week 24) was used to define two dropout patterns, early and late. The early and late dropout patterns were then analysed by the pattern mixture model to test the impact of missing data on treatment results. There was no significant interaction between dropout, treatment, and time observed in the pattern mixture models (overall p value for the FKSI-DRS=0·635). Therefore, missing data for the FKSI-DRS and EQ-5D may be considered at random, indicating that the MMRM model results are not biased.

Exploratory analyses of the association between baseline HRQoL (FKSI-DRS scores) and OS were conducted using the Pearson correlation coefficient method, and change from baseline HRQoL and OS using an approach previously described.[14] Four groups of patients were evaluated (regardless of treatment) based on their FKSI-DRS scores at baseline and up to 12 weeks: high baseline, improved; high baseline, not improved; low baseline, improved; and low baseline, not improved. High and low baseline scores were determined as above or below the median baseline scores, respectively. Improvement in HRQoL was defined as a 2-point ID change from baseline in FKSI-DRS score. The Kaplan–Meier method was used to estimate median OS. Two-sided 95% CI was computed by the Brookmeyer and Crowley method (log–log transformation). Significance testing was two-sided at the 0·05 level, with no adjustment for multiplicity. Analyses were powered according to the original study protocol, although some analyses were not prespecified. In the context of the overall protocol, these were not the primary objectives but were exploratory and not intended to confirm p values based on hypotheses. However, presenting p values was useful for comparisons. Estimates of treatment effect (and their precision) were also conducted as they were considered clinically meaningful, regardless of the power for the statistical testing.

Role of the funding source

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Results

Overall HRQoL data were collected at baseline for 706 (86%) of 821 randomised patients, 362 (88%) of 410 treated with nivolumab and 344 (84%) of 411 treated with everolimus. Median (range) follow-up for OS was 18·25 (0·0–30·7) months (interquartile range [IQR] 11·6–22·8 months) in the nivolumab group and 17·22 (0·0–31·5) months (IQR 7·2–21·4 months) in the everolimus group. Dose reductions were required for 102 (25·7%) of 397 patients treated with everolimus. No dose modifications were permitted for patients treated with nivolumab. Thirty-five patients treated with nivolumab and 53 patients treated with everolimus discontinued due to drug-related toxicity. There were no treatment-related deaths

in the nivolumab arm and two treatment related deaths in the everolimus arm. Among patients with HRQoL assessments at baseline, demographics and disease characteristics were balanced between treatment arms (table 1). At baseline, mean (standard deviation [SD]) HRQoL scores were similar for nivolumab versus everolimus (FKSI-DRS 30·2 [4·4] *vs* 30·1 [4·8], EQ-5D utility index 0·78 [0·24] *vs* 0·78 [0·21], and EQ-5D VAS 73·3 [18·5] *vs* 72·5 [18·7], respectively). The FKSI-DRS completion rates at baseline in the treated population were 361 (89%) of 406 for the nivolumab arm and 343 (86%) of 397 for the everolimus arm; EQ-5D completion rates were 361 (89%) of 406 and 344 (87%) of 397, respectively. Completion rates for the entire study are provided in appendix p5. Analyses were limited to on-study assessments because fewer patients were available to complete the questionnaires at follow-up visits. At end of treatment, in both arms, the majority of patients who had discontinued treatment had done so because of disease progression.[2]

Within the nivolumab arm, patients had an improvement from baseline in HRQoL, as assessed by FKSI-DRS, starting at week 20 (mean [SD], 0·6 [3·8], p=0·031) through week 104 (3·5 [4·1], p=0·001) (figure 2).[2] Within the everolimus arm, patients had a deterioration (p<0·04) from baseline in HRQoL, starting at week 4 (–1·5 [4·5], p<0·001) through week 32 (–1·1 [4·7], p=0·019) and again from week 60 (–1·6 [4·4], p=0·016) through week 64 (–1·5 [4·8], p=0·040) (figure 2). Between arms, a difference (p<0·001) in mean change (95% CI) was observed for patients receiving nivolumab versus everolimus (1·6 [1·4–1·9]).

Using FKSI-DRS, a clinically meaningful deterioration (p<0·001) in HRQoL was observed for patients receiving everolimus from baseline to week 84 using the MMRM; least squares mean (standard error) within the everolimus arm was −1·8 (0·2). HRQoL remained stable for patients in the nivolumab arm over the same time period. Between the nivolumab and everolimus arms, differences (p<0·001) in the mean change from baseline to week 84 favouring nivolumab were also observed using MMRM analysis (1·7 [1·2–2·1]) with standardised mean difference Hedges' g (95% CI) of 0·4 (0·3–0·6) (figure 3).

In the nivolumab arm, 200 (55%) of 361 patients experienced clinically meaningful HRQoL improvement versus 126 (37%) of 343 in the everolimus arm (p<0·001), as determined by FKSI-DRS. Using a higher FKSI-DRS scoring threshold (ID of 3 points), 148 (41·0 %) of 361 nivolumab patients experienced a clinically meaningful HRQoL improvement (p<0·001) compared with 95 (27·7 %) of 343 everolimus patients. Median (95% CI) time to improvement in HRQoL (ID of 2 points using FKSI-DRS) was shorter in patients treated with nivolumab (4·7 [3·7–7·5] months) versus everolimus (not reached [NE–NE]). The HR (95% CI) was 1·66 (1·33–2·08), p<0·001, favouring nivolumab. Median (95% CI) time (months) to improvement in HRQoL (ID of 3 points) was not estimable (13·3–NE) with nivolumab and not estimable (25·0–NE) with everolimus. The HR (95% CI) was 1·61 (1·24–2·09), p<0·001, favouring nivolumab. At later time points (>1·5 years), fewer patients were available for assessment, but results between and within treatments arms at these time points were consistent with those from earlier time points.

Descriptive statistical analyses for individual FKSI-DRS items demonstrated differences (p≤0·03) favouring nivolumab in lack of energy, pain, weight loss, bone pain, fatigue, haematuria, dyspnoea, cough, and fevers (see appendix p4). MMRM analyses demonstrated

a difference (p<0·05) for all individual FKSI-DRS items observed in descriptive results, except for bone pain (p=0·678) (see appendix p4).

For EQ-5D utility index and EQ-5D VAS measures, mean scores were similar for nivolumab versus everolimus at baseline. Findings with EQ-5D utility index and EQ-5D VAS were similar to those with FKSI-DRS, although less pronounced. On both EQ-5D utility index and EQ-5D VAS, improvement occurred from baseline to week 104 with nivolumab, while deterioration occurred with everolimus; between-arm differences favoured nivolumab (see appendix p10–11). For nivolumab versus everolimus, more patients experienced a clinically meaningful HRQoL improvement (p=0·001) assessed by EQ-5D VAS (192 [53%] of 361 *vs* 134 [39%] of 344) and a shorter time (p=0·005) to improvement (6·5 months [3·9–12·2] *vs* 23·1 months [15·4–NE]; [HR=1·37 (1·10–1·71)]). There was no difference in the proportion of patients experiencing clinically meaningful HRQoL improvement (p=0·07) or time to improvement (p=0·863) when assessed by EQ-5D utility scores.

When analysed using MMRM, differences between arms were also observed. For EQ-5D utility index, differences between arms favoured nivolumab (mean change [95% CI] from baseline to endpoint, 0·04 [0·02–0·07], p<0·001) (see appendix p12). Similarly, for EQ-5D VAS, differences between arms favoured nivolumab (mean change [95% CI] from baseline to endpoint, 5·7 [3·8–7·7], p<0·001; see appendix p13). Descriptive analysis of individual EQ-5D items demonstrated differences (p<0·05) favouring nivolumab for mobility, activity, and anxiety, but not self-care or pain.

In an exploratory analysis, a positive correlation between baseline HRQoL scores and OS for the entire study population (n=705) was observed for the FKSI-DRS (correlation coefficient, 0·27; p≤0·001), EQ-5D utility (0·24, p≤0·001), and EQ-5D VAS (0·26, p≤0·001). In an exploratory analysis of the association between HRQoL (FKSI-DRS) baseline scores (high or low), change in HRQoL (improved or not improved), and OS up to 12 weeks, median OS (95% CI) was longest (not reached [28·1–NE]) in patients with high baseline HRQoL scores and HRQoL improvement from baseline (figure 4). In patients with high baseline HRQoL scores and no HRQoL improvement from baseline, median OS (95% CI) was 29·0 (27·4–NE) months (figure 4). The shortest median (95% CI) OS times were observed in patients with low baseline HRQoL scores and either HRQoL improvement from baseline (17·6 [15·2–20·3] months) or no HRQoL improvement from baseline (17·0 [14·4–18·8] months) (figure 4).

Discussion

The analyses reported here demonstrate that treatment with nivolumab, relative to everolimus, was associated with clinically meaningful HRQoL improvement in previously treated patients with aRCC. Results from the phase 3 CheckMate 025 trial demonstrated an OS benefit for nivolumab compared with everolimus in patients with aRCC.[2] Using the disease-specific FKSI-DRS, we have demonstrated that patients treated with nivolumab experienced improvement in HRQoL, whereas patients treated with everolimus experienced a deterioration in HRQoL. Furthermore, more patients receiving nivolumab experienced a clinically meaningful improvement in HRQoL, which was generally observed early on in

treatment. Results from the MMRM analysis support the findings from the descriptive analyses, showing that HRQoL was better for patients in the nivolumab arm compared with patients in the everolimus arm overall.

Conventional treatments for aRCC, such as interferon-α or interleukin-2, produce high levels of toxicity, which negatively affects HRQoL.[15,16] Newer targeted therapies like temsirolimus, sunitinib, and sorafenib have shown improved HRQoL compared with interferon-α. However, no direct comparisons between these agents have been reported that show an improvement in HRQoL.[3,17–19] In patients receiving first-line therapy with pazopanib, or second-line and subsequent therapy with axitinib, sorafenib, pazopanib, and everolimus, HRQoL was maintained but not improved when compared with placebo.[3,5,18,20] In the CheckMate 025 trial, the deterioration in HRQoL in patients treated with everolimus may reflect toxicities associated with this agent.[21] Consequently, the improvements in HRQoL with nivolumab treatment compared with everolimus treatment in the CheckMate 025 trial are particularly noteworthy.

In this study, a prespecified ID was used to define a clinically meaningful HRQoL threshold. Prespecified IDs are commonly used in HRQoL studies, however, IDs can vary by treatment population, clinical context, and methodology.[2] In this analysis, we report that patients treated with nivolumab in the CheckMate 025 trial had clinically meaningful improvements in HRQoL using a prespecified ID.

EQ-5D was developed as a HRQoL instrument for the general population[6,22] and may not capture small changes in health that are important in studies of HRQoL in patients with cancer.[23] For example, in the phase 3 randomised, placebo-controlled study of pazopanib monotherapy in patients with aRCC, there was no significant difference in EQ-5D when analysed by MMRM over the course of 48 weeks.[20] In a subsequent post hoc analysis, time to HRQoL deterioration from baseline, measured by the EQ-5D utility index, was also not significantly different between treatment groups.[11] However, in our analyses, both EQ-5D utility index and EQ-5D VAS showed significant improvement in HRQoL from baseline for patients treated with nivolumab arm and significant deterioration for patients receiving everolimus, with significant differences between arms favouring nivolumab.

Because OS was the primary endpoint of the CheckMate 025 trial, we chose to explore the relationship between HRQoL and OS. Exploration of the association between HRQoL and other outcomes (such as progression-free survival and response) are interesting to consider for future analyses. One challenge with investigating HRQoL and RECIST-related outcomes is that the relevance of such outcomes is unclear when assessing immunotherapies.[24] Additionally, patients receiving immunotherapies who initially progress by RECIST criteria may be considered for treatment beyond progression, which was the case in this trial.

Initial analysis of the association between HRQoL and OS resulted in a significant positive correlation between baseline HRQoL scores and OS. In an expanded exploratory analysis of the association between HRQoL (FKSI-DRS scores) and OS, two factors that were associated with improvement in OS outcomes were a high HRQoL baseline score (above the median) and an improvement from baseline HRQoL (a 2-point ID). These results highlight

the potential for baseline HRQoL to be considered as a prognostic indicator of clinical outcomes. Given the potential toxicities related to immunotherapy, standardised methods for assessing PRO, such as FKSI-DRS and EQ-5D, may be valuable measures of the patient's perspective during immunotherapy. Additional research will help clarify the value of baseline HRQoL as a prognostic factor in clinical practice.

A limitation to the current analyses was that they were restricted to on-treatment data. Although it would be of interest to study the longer-term HRQoL benefit after discontinuation of treatment, the small number of patients available for HRQoL assessment at follow-up visits would limit interpretation the data. In addition, analyses were powered according to the original study protocol, even though some analyses were not prespecified. Estimates of treatment effect (and their precision) were provided because they are considered clinically meaningful, regardless of the power for the statistical testing.

In summary, this analysis of HRQoL assessments from the global CheckMate 025 trial, nivolumab treatment compared with everolimus resulted in rapid and sustained HRQoL improvement in previously treated patients with aRCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

We searched PubMed using the search terms “nivolumab”, “renal cell carcinoma”, “RCC”, “kidney cancer”, “advanced and metastatic RCC”, “health-related quality of life”, “overall survival”, “FKSI-DRS”, and “EQ-5D”, with specific attention to randomised phase 3 trials of mTOR inhibitors (everolimus, temsirolimus), VEGF inhibitors (sunitinib, sorafenib, bevacizumab, axitinib, pazopanib), and immune oncology therapeutics. The search encompassed material published from 1990–2016. The only randomised, open-label, phase 3 study we found was the CheckMate 025 study, published in September 2015, which compared nivolumab with everolimus in patients with advanced or metastatic renal cell carcinoma (aRCC). The analyses reported here are based on data from this study. In CheckMate 025, overall survival (OS) was significantly longer for patients treated with nivolumab versus patients treated with everolimus with aRCC; grade 3 or 4 treatment-related adverse events were less frequent with nivolumab versus everolimus. The study reported that median changes from baseline in the FKSI-DRS score in the nivolumab group increased over time and differed significantly from median changes in the everolimus group at each assessment point through week 104 ($p<0·05$).

Added value of this study

Here, we report on the complete CheckMate 025 health-related quality of life (HRQoL) analysis using the disease-specific FKSI-DRS instrument and the general health EQ-5D, and employing both descriptive statistics and mixed model analyses. We evaluate changes in HRQoL over time between and within treatment arms, and explore the association between HRQoL baseline scores and OS in patients with aRCC treated with nivolumab or everolimus. Several key findings are of clinical importance. Within the nivolumab arm, patients experience an improvement in HRQoL, whereas within the everolimus arm, patients experienced a deterioration in HRQoL. Differences between arms demonstrated improved HRQoL for patients receiving nivolumab compared with patients receiving everolimus. More patients receiving nivolumab than everolimus experienced a clinically meaningful improvement in HRQoL, which occurred earlier with nivolumab treatment compared with everolimus treatment.

Implications of all the available evidence

Our analyses demonstrate that nivolumab treatment compared with everolimus results in rapid and sustained HRQoL improvement in previously treated patients with aRCC. Our preliminary findings also suggest that assessing baseline HRQoL scores of patients with aRCC may help to evaluate potential OS benefit.

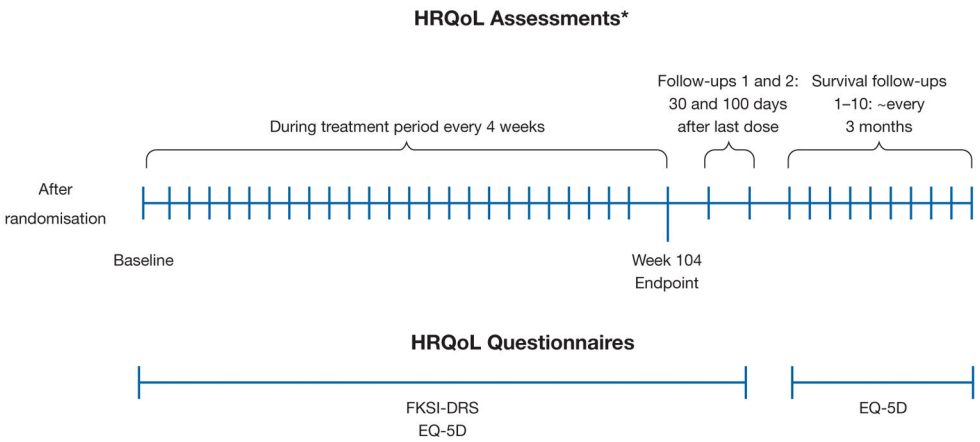

Figure 1. HRQoL assessment collections

*Assessments were done prior to dosing. EQ-5D=European Quality of Life-5 Dimensions. FKSI-DRS=Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms. HRQoL=health-related quality of life.

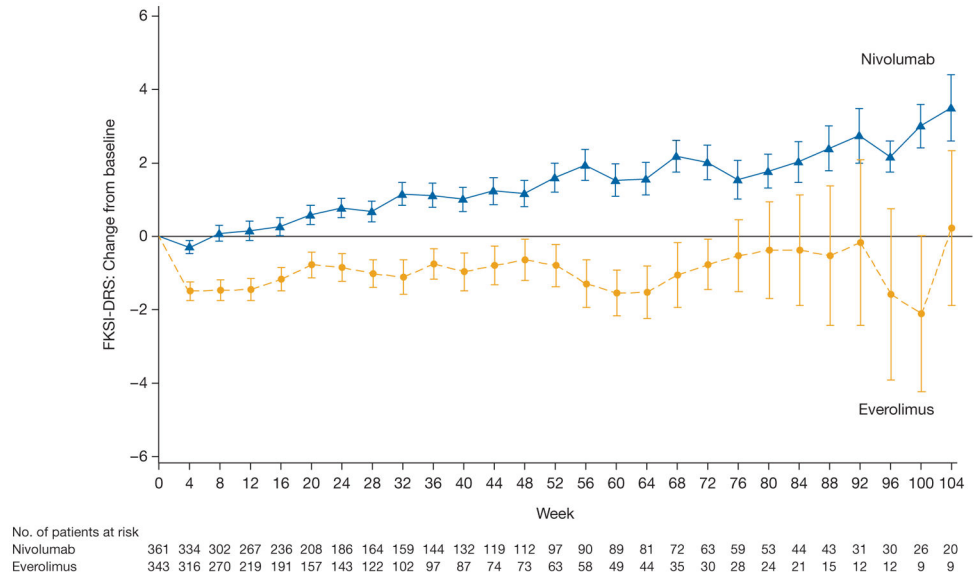

Figure 2. Change from baseline in HRQoL scores on FKSI-DRS

Note: Only time points where data were available for five or more patients are shown. Between arms, from week 4 (p<0·001) through week 76 (p=0·043), a mean difference was observed between nivolumab and everolimus. Within nivolumab, an improvement from baseline starting at week 20 (0·6 [3·8], p=0·031) through week 104 (3·5 [4·1], p=0·001); within everolimus, a deterioration from baseline starting at week 4 (–1·5 [4·5], p<0·001) through week 32 (–1·1 [4·7], p=0·019) and again from week 60 (–1·6 [4·4], p=0·016) through week 64 (–1·5 [4·8], p=0·040). FKSI-DRS=Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms. HRQoL=health-related quality of life.

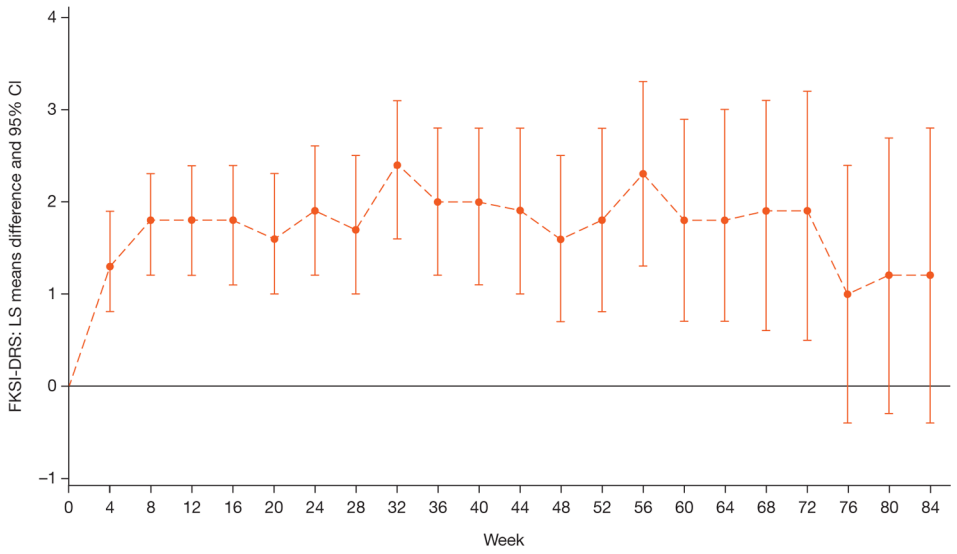

Figure 3. FKSI-DRS change from baseline least square means difference and 95% confidence interval over time between treatment arms (MMRM benefit assessment of nivolumab across time points)

FKSI-DRS=Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms. MMRM=mixed-effects model repeated-measures.

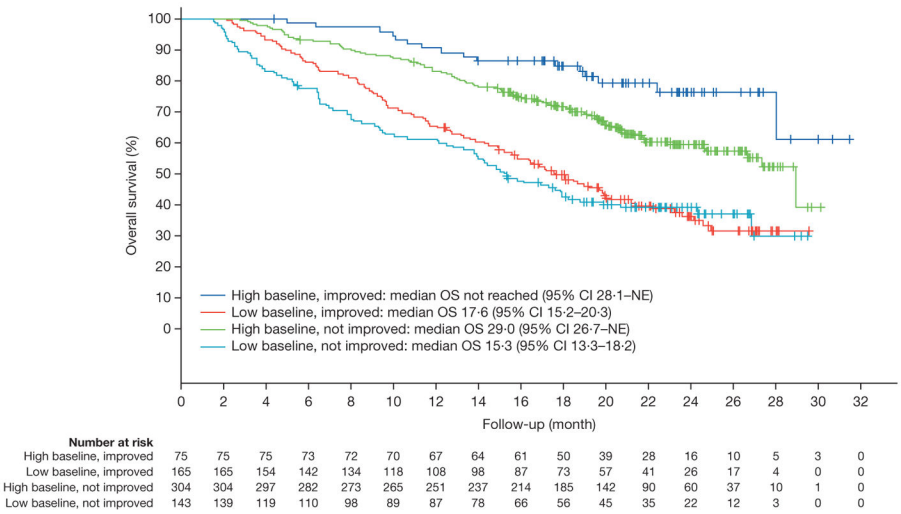

Figure 4. Association between HRQoL at baseline and improvement in HRQoL (2-point change in FKSI-DRS score from baseline) up to 12 weeks and median OS

FKSI-DRS=Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms. HRQoL=health-related quality of life. OS=overall survival.

Table 1

Patient demographics and baseline disease characteristics for patients with at least one HRQoL assessment

	Nivolumab (N=362)	Everolimus (N=344)
Median age (Q1, Q3), years	62·0 (53·0, 68·0)	62·5 (56·0, 69·0)
Age category		
<65 years	230 (63·5%)	199 (57·8%)
≥65 and <75 years	105 (29·0%)	112 (32·6%)
≥75 years	27 (7·5%)	33 (9·6%)
Sex		
Female	83 (22·9%)	90 (26·2%)
Male	279 (77·1%)	254 (73·8%)
Baseline MSKCC risk group		
Favourable	131 (36·2%)	132 (38·4%)
Intermediate	181 (50·0%)	166 (48·3%)
Poor	50 (13·8%)	46 (13·4%)
Number of prior anti-angiogenic regimens in advanced or metastatic setting		
1	256 (70·7%)	247 (71·8%)
2	106 (29·3%)	97 (28·2%)
Region		
United States/Canada	155 (42·8%)	145 (42·2%)
Western Europe	119 (32·9%)	112 (32·6%)
Rest of world	88 (24·3%)	87 (25·3%)

HRQoL=health-related quality of life. MSKCC=Memorial Sloan Kettering Cancer Center. Q=quartile. SD=standard deviation.