# Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial

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## Summary

**Background** In the phase 3 CheckMate 025 study, previously treated patients with advanced renal cell carcinoma who were randomly assigned to nivolumab had an overall survival benefit compared with those assigned to everolimus. We aimed to compare health-related quality of life (HRQoL) between treatment groups in this trial.

**Methods** CheckMate 025 was an open-label study done at 146 oncology centres in 24 countries. Patients were randomly assigned to treatment between Oct 22, 2012, and March 11, 2014. Patients with advanced renal cell carcinoma were randomly assigned (1:1, block size of four) to receive nivolumab every 2 weeks or everolimus once per day. The study was stopped early at the planned interim analysis in July, 2015, because 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 up for survival. At the interim analysis, HRQoL was assessed with 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. Prespecified endpoints were to assess, in each treatment group, disease-related symptom progression rate based on the FKSI-DRS and changes in reported global health outcomes based on the EQ-5D. Other endpoints were post hoc. We calculated the proportion of FKSI-DRS questionnaires completed using the number of patients with non-missing data at baseline and at least one post-baseline visit. We defined FKSI-DRS completion as completion of five or more of the nine items in the questionnaire; otherwise data were treated as missing. FKSI-DRS symptom index score was prorated for missing items. We made no adjustments for missing EQ-5D data. We used descriptive statistics and multivariate analyses, including mixed-effects model repeated-measures, for between group comparisons. Analyses were powered according to the original study protocol, and we analysed FKSI-DRS and EQ-5D data for all patients who underwent randomisation and had a baseline assessment and at least one post-baseline assessment. CheckMate 025 is registered with ClinicalTrials.gov, number NCT01668784.

**Findings** HRQoL data were collected at baseline for 362 (88%) of 410 patients in the nivolumab group and 344 (84%) of 411 patients in the everolimus group. The mean difference in FKSI-DRS scores between the nivolumab and everolimus groups was 1·6 (95% CI 1·4–1·9; p<0·0001) with descriptive statistics and 1·7 (1·2–2·1; p<0·0001) with mixed-effects model repeated-measures analysis. In terms of FKSI-DRS score, more patients had a clinically meaningful (ie, an increase of at least 2 points from baseline) HRQoL improvement with nivolumab (200 [55%] of 361 patients) versus everolimus (126 [37%] of 343 patients; p<0·0001). Median time to HRQoL improvement was shorter in patients given nivolumab (4·7 months, 95% CI 3·7–7·5) than in patients given everolimus (median not reached, NE–NE).

**Interpretation** Nivolumab was associated with HRQoL improvement compared with everolimus in previously treated patients with advanced renal cell carcinoma.

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## Introduction

Renal cell carcinoma is the most commonly diagnosed kidney cancer worldwide, with about 30% of patients presenting with advanced disease.[1,2] Anti-angiogenic and mTOR-targeted agents have changed the therapeutic landscape for advanced or metastatic renal cell carcinoma, but these treatments achieve long-term survival only in a few patients, have toxic effects related to their specific mechanisms of action, and are associated with insufficient improvement in health-related quality of life (HRQoL) for this population of patients.[1,3–5]

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2.[2] In the phase 3 CheckMate 025 study of nivolumab versus everolimus for the treatment of advanced renal cell carcinoma,[2] overall survival was longer for nivolumab compared with everolimus; the median overall survival was 25·0 months (95% CI 21·8–not estimable [NE]) with nivolumab versus 19·6 months (17·6–23·1) with everolimus (p=0·002; hazard ratio [HR] 0·73, 98·5% CI 0·57–0·93 for nivolumab versus everolimus).[2] Grade 3 or 4

## 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 included articles published from Jan 1, 1990, to March 30, 2016. The only randomised, open-label, phase 3 study we found was the CheckMate 025 study, which compared nivolumab with everolimus in patients with advanced or metastatic renal cell carcinoma. The analyses reported here are based on data from this study. In CheckMate 025, overall survival was significantly longer for patients treated with nivolumab than for patients treated with everolimus, and grade 3 or 4 treatment-related adverse events were less frequent with nivolumab than with 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 up to week 104 ($p<0·05$).

### Added value of this study

Our study reports the complete CheckMate 025 health-related quality of life (HRQoL) analysis using the disease-specific FKSI-DRS instrument and the general health EQ-5D questionnaire. Several of our findings have clinical importance. HRQoL improved from baseline in patients who received nivolumab, whereas HRQoL decreased from baseline in the everolimus group, and there was a significant difference between the two treatment groups. More patients who received nivolumab had a clinically meaningful improvement in HRQoL than did those who received everolimus and such improvements occurred earlier with nivolumab than with everolimus.

### Implications of all the available evidence

Our results show that nivolumab treatment results in rapid and sustained HRQoL improvement compared with everolimus in previously treated patients with advanced renal cell carcinoma. Our preliminary findings also suggest that baseline HRQoL scores might help in the assessment of potential overall survival benefit in patients with advanced renal cell carcinoma. In this treatment setting, relative to everolimus, the use of nivolumab is associated with both improved survival and improved HRQoL. Furthermore, HRQoL and overall survival appear to be linked, as baseline HRQoL was associated with survival. Patients with high HRQoL at baseline survived longer than those with low HRQoL. Future research with the FKSI-DRS in clinical practice is warranted.

treatment-related adverse events were less frequent with nivolumab than with everolimus.[2] Furthermore, an analysis of HRQoL scores according to the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) questionnaire (a subscale of the 15-item FKSI-15) showed that median change from baseline increased over time with nivolumab treatment. This change differed significantly from the change from baseline scores with everolimus treatment at each assessment point through to week 104, representing an improvement in HRQoL ($p<0·05$) with nivolumab.[2] In this study, we report the complete HRQoL analysis from CheckMate 025, including results from mixed model analyses. We used the FKSI-DRS and European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) assessments to evaluate changes in HRQoL over time between and within treatment groups in patients with advanced renal cell carcinoma who received nivolumab or everolimus. Additionally, we explored the association between baseline HRQoL scores and overall survival for the entire study cohort.

## Methods

### Study design and participants

CheckMate 025 was a phase 3, randomised, open-label study of nivolumab versus everolimus in patients with advanced renal cell carcinoma. Patients were randomly assigned to treatment from Oct 22, 2012, to March 11, 2014, at 146 sites in 24 countries in North America, Europe, Australia, South America, and Asia (appendix pp 4–7). Full details of the study design have been reported previously.[2] The study was approved by the institutional review board or independent ethics committee at each centre and was conducted in accordance with Good Clinical Practice guidelines defined by the International Conference on Harmonisation. Nivolumab was provided by the sponsor (Bristol-Myers Squibb, Princeton, NJ, USA), whereas everolimus was provided by the sponsor for sites outside the USA and by AcariaHealth (Hawthorne, NY, USA) for sites within the USA.

Adults aged 18 years or older with histological confirmation of advanced renal cell carcinoma with a clear-cell component, measurable disease (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), Karnofsky performance status of at least 70% at the time of study entry, and who had received one or two anti-angiogenic therapies for advanced renal cell carcinoma were eligible to participate. 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. Patients underwent a washout period of at least 14 days for previous anticancer therapy or palliative focal radiation therapy and 28 days for previous bevacizumab therapy before the first dose of study drug. Key exclusion criteria were previous treatment with an mTOR inhibitor, a disorder requiring treatment with glucocorticoids (equivalent to >10 mg of prednisone

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