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CheckMate 214 patient-reported outcomes: listening to our patients

In *The Lancet Oncology*, David Cella and colleagues[1] assessed the patient-reported outcomes (PROs) of 847 patients at intermediate or poor risk with advanced or metastatic renal cell carcinoma randomly assigned (1:1) to sunitinib or nivolumab plus ipilimumab in the phase 3 randomised CheckMate 214 trial.[1,2]

The primary endpoints of the trial have been reported previously,[2] and PROs were an exploratory endpoint. The investigators assessed PROs using the Functional Assessment of Cancer Therapy-General (FACT-G), FACT-Kidney Symptom Index-19 (FKSI-19), and EuroQoL five dimension three level (EQ-5D-3L) instruments, each of which collects data on different domains. FKSI-19 collects data about functional wellbeing, treatment side-effects, and emotional, physical, and overall disease-related symptoms; FACT-G collects data about functional, physical, social and family, and emotional wellbeing; and EQ-5D-3L collects data about mobility, self-care, usual activity, pain and discomfort, and depression and anxiety, and subjective perception of wellbeing through an analogue visual rating scale (VAS).

Comparison of PRO scores at baseline with those later in the treatment regimen showed improved PROs for participants in the nivolumab and ipilimumab group compared with the sunitinib group, except for emotional symptoms (collected in FKSI-19) and emotional and social and family wellbeing (collected by FACT-G) for which no statistical difference emerged. In brief, risk of deterioration in PRO scores was lower for patients who were given nivolumab plus ipilimumab than for those given sunitinib (FKSI-19 deterioration hazard ratio [HR] 0·54, 95% CI 0·46–0·63; FACT-G deterioration HR 0·63, 0·52–0·75; and EQ-5D UK utility score HR 0·67, 0·57–0·80). Moreover, improvement in FKSI-19 and FACT-G scores were associated with decreased risk of death and disease progression.

These results could have been influenced by a number of factors, first, the difference in the toxicity profile of nivolumab plus ipilimumab immunotherapy compared with the tyrosine kinase inhibitor sunitinib.[3] Nivolumab and ipilimumab are both immune checkpoint inhibitor antibodies and endocrine and auto-immune adverse events often lead to laboratory anomalies as the first presentation of toxicity; thus, even if patients have severe toxicity, clinicians can stop treatment before the development of physical symptoms and so physical symptoms might not have been reported as they were prevented before they occurred. Additionally, such an early interuption of treatment could affect the effectivness of the treatment. However, the benefit of treatment on quality of life noticeably emerged in the PROs during the first 25 weeks of treatment—ie, not just during nivolumab administration. This observation suggests that even if the addition of ipilimumab to nivolumab led to increased immune-related adverse events,

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See **Articles** page 297

the comparison of PROs between the combination and sunitinib still favoured the combination immunotherapy.

Notably, the mean score of some PRO domains that were assessed favoured sunitinib after week 103—such as the EQ-5D-3L VAS score in which the median difference between the treatment groups lost its signficance. The different methods of treatment administration (intravenously for the combination *vs* orally for sunitinib) could have affected the PROs after long-term administration, outweighing the initial health-related quality of life (HRQoL) benefits.

Immune-checkpoint inhibitors are changing the management of advanced renal cell carcinoma and perhaps also other stages of the disease.[4–6] In this evolving field, evidence provided by the study by Cella and colleagues will be of great importance. Quality of life is a key endpoint of clinical studies that is often not properly investigated in large trials. For instance, Marandino and colleagues[7] systematically reviewed 446 publications of randomised phase 3 trials in oncology and showed that assessment of quality of life was often not reported or not considered as a secondary or exploratory endpoint.[7] In view of the fact that the aim of creating more effective treatments for metastatic renal cell carcinoma is to increase patient survival, the assessment of PROs should be an essential endpoint that clinicians consider during treatment planning.

Another aspect that must be considered is the effect of this study on clinical practice. On July 26, 2018, the Committee for Medicinal Products for Human Use (CHMP) expressed a negative opinion on the use of nivolumab plus ipilimumab as first-line therapy in advance renal cell carcinoma.[8] This decision was mainly because nivolumab alone resulted in better clinical benefits (ie, overall survival, progression-free survival, and the proportion of patients with a response) in a previous trial[9] in patients with advanced or metastatic renal cell carcinoma than in CheckMate 214,[9] and whether the addition of ipilimumab is associated with an effective benefit or higher toxicity without clinical improvement is not known. Bex and colleagues[8] have since expressed their perplexity about this negative option. Indeed, they remarked on the non-negligible superiority of the combination of nivolumab plus ipilimumab over sunitinib in terms of improved overall survival and the proportion of patients who had an objective response (42% *vs* 27%).[2] We agree that nivolumab plus ipilimumab could be an important treatment option for patients at intermediate or poor risk with advanced or metastatic renal cell carcinoma and we think that the results of this study reinforce this issue because an important outcome such as quality of life and PROs favoured the use of the immune checkpoint inhibitor antibody combination.

In conclusion, this study is of particular interest because quality of life is often not investigated in clinical trials. Correlation between toxicity profile and assessment of quality of life provide important information that will aid in clinical decision making. Finally, the subjective improved tolerability profile of the immune checkpoint inhibitor combination that emerged from CheckMate 214 reinforces the value of treatment using immune checkpoint inhibitor antibodies in the first-line setting as a favourable treatment option in patients at intermediate or poor risk with advanced or metastatic renal cell carcinoma.

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