Editorial Commentary

CheckMate 9ER patient-reported outcomes: the patient is not willing to give up

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Clinical decisions, in addition to be supported by research evidence, should accommodate patients' preferences (1). Before choosing a treatment, we as clinicians should ask ourselves how much the patient is ready and willing to accept in exchange for an uncertain benefit.

Therefore, we must first offer patients clear and accurate information about the potential benefits and harms of the recommended treatment, and secondly we must use valid tools to assess patients' perceptions of their general health and cancer symptoms over time.

In the phase 3, open label, Checkmate 9ER trial, a total of 651 patients with advanced renal cell carcinoma (RCC) systemic treatment naïve were randomized 1:1 to the combination of nivolumab—a PD-L1 inhibitor—and cabozantinib—a VEGFR inhibitor—or sunitinib—another VEGFR inhibitor.

At a median follow-up of 18.1 months, the combination of nivolumab and cabozantinib yielded a relevant benefit over sunitinib in terms of progression-free survival (PFS) [24 PFS events lower every 100 patients treated—number needed to treat (NNT) 4], overall survival (OS) (10 OS events lower every 100 patients treated—NNT 10) and objective response rate (29 responses more every 100 patients treated—NNT 3). Remarkably, responses were rapid and durable, with 3 complete remissions more every 100 patients treated (2).

However, we must not divert attention from the potential harms associated with such a combined treatment which includes two agents endowed by a completely different mechanism of action and with a not overlapping safety profile.

Indeed, patients receiving nivolumab plus cabozantinib experienced an absolute increase of 10% in grade ≥3 drug-related adverse events (DRAEs), and an absolute increase of 7% in DRAEs leading to treatment discontinuation, as compared to sunitinib alone (2).

Patient-reported outcomes (PROs) are a powerful tool for providing optimal care.

PROs reflect the patient's perception of his/her general health status and cancer symptoms influenced by the toxicities and efficacy of drugs over time without the coding of the patient's response by healthcare professionals.

Prof. Cella and colleagues analyzed PROs in the phase 3 CheckMate 9ER study (3). PROs were assessed with a cancer-specific instrument—FKSI-19 (Functional Assessment of Cancer Therapy - Kidney Symptom Index-19) (4)—and a cancer-generic instrument—EQ-5D-3L (EuroQoL-five dimension-three level) (5)—as exploratory endpoints. The FKSI-19 measures disease-related emotional, physical and general symptoms, ability to work, as well as Health Related Quality of Life (HRQOL); higher scores identify better health state and impacts on HRQoL. The EQ-5D-3L collects data on motility, self-care, daily activities, stress, pain, depression and the patient's self-assessment health; higher scores indicate better health state. PRO instruments (FKSI-19 and EQ-5D-3L) were dispensed before the start of therapy, before each treatment cycle (every 2 weeks for nivolumab plus cabozantinib, every

6 weeks for sunitinib), and during follow-up visits (30 and 100 days from last dose). Although PROs are administered more frequently in the nivolumab plus cabozantinib arm, the analysis included only those assessment timepoints that were common to both treatment arms (before starting therapy and every 6 weeks until week 115). PROs completion rates in both treatment arms remained high in both treatment arms through week 115. Even though the differences in FKSI-19 and EQ-5D-3L scores between the two treatments were nominally significant, they did not overcome the threshold values [minimal important differences (MIDs)] established for individual change during the validation process (3). However, these within-patient thresholds are not validated to establish change in FKSI-19 scores as clinically significant at the group level. Indeed, when the thresholds were applied to define deterioration of quality of life (QoL) at the individual level, the combination of nivolumab and cabozantinib successfully decreased the risk of clinically meaningful deterioration in both all scores of the FKSI-19 (including disease-related symptoms) and in EQ-5D-3L VAS compared with sunitinib irrespective of the definition used (first, confirmed, or definitive deterioration).

Although PROs were assessed at the start of each treatment cycle (after 2 weeks without sunitinib *vs.* 1 week without nivolumab, and no break for cabozantinib), analysis of the GP5 item ("*I am bothered by side effects of treatment*" rated on a 5-point Likert scale) until week 55 showed a lower proportion of patients bothered by treatment side effects in the nivolumab plus cabozantinib arm (6). Patients in the nivolumab plus cabozantinib arm showed a decreased risk (48% less) of being notably bothered by DRAEs than patients in sunitinib arm [odds ratio (OR), 0.52; 95% CI: 0.35–0.77]. At nearly 3 years of follow-up, patients continued to report improved HRQoL with nivolumab plus cabozantinib compared with sunitinib (7).

Thus, we believe that the effectiveness of nivolumab plus cabozantinib as first-line treatment of advanced RCC is associated with clinically meaningful improvements in patients' quality of life and disease-related symptoms.

A recent analysis by Servetto and colleagues indicated that for a proportion of recent cancer treatments, regulatory approval has occurred without published QoL results or with delayed publications of QoL data (8). Information on QoL assessment should be described in detail in study protocols and methods sections of manuscripts, and QoL results should be reported in the main publication in order to fully explain to the patient the benefit/harm ratio of a new treatment.

The use of PROs in research and clinical practice has been limited by: (I) variability of measurements, (II) complexity and length of assessments, (III) lack of group-level thresholds, as well as (IV) inability to compare results. These limitations have been partially overcome with the creation of the Patient-Reported Outcome Measurement Information System (PROMIS), which states common measures, decreases the response burden on the patient, and simplifies scoring using item response theory and computer technology (9). Furthermore, we are confident that future studies will establish clinically meaningful minimum thresholds also for group-level differences and changes.

Ultimately, analysis of PROs in the Checkmate 9ER trial confirms how much the patient is willing to accept in terms of short- and long-term side effects… because the patient is not willing to give up living longer.

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