Editorial Commentary

The importance of not only living longer but also better in the setting of advanced urothelial cancer

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Cancer treatment that can prolong life and improve quality of life remains the ideal goal in cancer research. Patients with advanced urothelial cancer (UC) have poor prognosis and experience significant impairment in their health-related quality-of-life (HRQoL) during their course (1). Platinum-based chemotherapy has been the standard treatment for these patients for decades. Patients who had progressed on platinum-based chemotherapy had limited and modest treatment options until the approval of immune checkpoint inhibitors (ICI). Pembrolizumab has shown improved overall survival (OS), higher response rate and more favorable safety profile compared to single agent taxane or vinflunine chemotherapy in patients with platinum-refractory advanced UC, as demonstrated in the open-label randomized phase III KEYNOTE-045 trial (2). That trial met its primary endpoint demonstrating longer OS with pembrolizumab over chemotherapy [hazard ratio (HR) for death 0.73; 95%CI, 0.59–0.91; P=0.002]. There were fewer treatment-related adverse events (60.9% *vs.* 90.2%), including fewer ≥ grade 3 events (15.0% *vs.* 49.4%), with pembrolizumab compared to chemotherapy. There are four other FDA-approved ICI for platinum-refractory advanced UC (3-7). Two of those ICI, atezolizumab and pembrolizumab, are FDA-approved for the first line treatment of cisplatin-unfit patients whose tumors are PD-L1-high based on a companion assay, or patients who are also unfit for carboplatin (8,9).

Vaughn *et al.* reported patient-reported outcomes (PRO) from the Keynote 045 clinical trial (10). These PROs were exploratory objectives and assessed using well characterized instruments, the EuroQol five-dimensions questionnaire (EQ-5D) and the European Organization for Research and Treatment of Cancer QoL Questionnaire C30 (EORTC QLQ-C30). The QLQ-C30 is a reliable and validated measure of QoL, which includes nine multi-item scales; five functional scales (physical, role, cognitive, emotional, social); three symptom scales (fatigue, pain, nausea and vomiting); and a global health and QoL scale (11). Similarly, EQ-5D is a standardized instrument with a descriptive system comprising of dimensions that include mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This instrument also has a Visual Analog Scale (VAS), which records self-rated health on grade ranging from 0 to 100 (the latter is the best possible health status) (12). The key HRQoL endpoints were time to deterioration (TTD) and mean change from baseline to week 15 in the EORTC QLQ-C30 global health status/QoL score. Scores with <10-point change from baseline were considered stable, an increase of ≥10 points improved, whereas a decrease of ≥10 points deteriorated.

Treatment with pembrolizumab prolonged median TTD in global health status/QoL score compared to chemotherapy (3.5 *vs.* 2.3 months with pembrolizumab *vs.* chemotherapy, respectively). Similarly, EORTC QLQ-C30 global health status/QoL score was stable over time with pembrolizumab but worsened over time with chemotherapy. Progression was associated with worse scores in both groups, but patients on pembrolizumab experienced less

worsening compared to those on chemotherapy. The investigators also compared individual EORTC QLQ-C30 functional and symptom domains between the arms. Patients on pembrolizumab had minimal changes in these subscales as opposed to patients on chemotherapy, who had significant deterioration.

These findings are significant and clinically relevant showing that ICI in that setting not only prolonged OS but also improved QoL. The analyses were performed as part of a large randomized controlled phase III trial, using reliable and validated instruments, which are key strengths. The findings are consistent with reports from other solid tumors, where treatment with ICI have shown improved QoL compared to chemotherapy or targeted therapy (13,14).

However, there are certain limitations as rightly pointed out by the authors. This was an open-label trial, which could introduce bias in the interpretation of the results. Similarly, these HRQoL endpoints were exploratory in nature without predefined primary statistical-based hypotheses. An arbitrary cut-off of 15-week was selected as a primary analysis time point, which may limit the extrapolation of the findings beyond this time point. Patient reporting and recall biases are almost unavoidable and inherent to any trial. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, which could introduce selection bias. However, the results are very meaningful overall and corroborate the robust clinical benefit seen with the anti-PD1 agent in this trial. Meaningful, rapid and durable responses with the same agent were also noted in the Keynote 052 trial in the first line setting in cisplatin-unfit patients with advanced UC; the benefit was notable also in the subset of more senior patients enrolled in that trial (15).

A possible explanation of the QoL findings is the favorable toxicity profile with ICI compared to conventional cytotoxic chemotherapy. However, it is very important to educate patients and providers about the unique immune-related adverse events (irAEs) associated with ICI that should be captured and treated as early as possible to avoid potential ICI-related morbidity and mortality. These AEs may be under-reported since patients may not want to discontinue presumed "life-saving" therapy and/or be taken off trial. Patient-directed materials and continuous education by the medical team are essential for the optimal diagnosis and evidence-based management of irAEs. Such management may include the presence of multidisciplinary teams in the inpatient and/or outpatient setting, as well as tumor boards (16). Moreover, clinical trials, in the most part, may exclude patients with baseline autoimmune conditions and solid organ transplant, which renders the utilization of ICI in the "real world" clinical practice challenging when it comes to decision making for patients with those conditions. A recent review article attempted to address in part that question and made suggestions for consideration for ICI use based on the available data; this discussion is relevant since development of irAEs and/or exacerbation of autoimmune conditions may impact QoL (17). However, many patients with those conditions may still benefit from ICI, without notable irAEs, and still maintain a good QoL; PRO data is needed to help those discussions. Last, but not least, patient selection for a particular therapy should take into account PS and other major medical comorbidities, which may be exclusionary in most clinical trials. A recent study demonstrated that patients with advanced UC and ECOG PS ≥2 receiving ICI may have comparable response rates with those with ECOG PS 0–1, but with poor outcomes overall, that may also impact end of life healthcare utilization (18). Measurement of QoL and PRO with validated instruments in those populations can be the objective of "real world" pragmatic, comparative effectiveness studies and multisite registries.

QoL is a very important endpoint from all stakeholders' perspective. The availability of HRQoL data along with the primary results of a trial allows timely evaluation of the risk-benefit ratio and the value of treatment being considered. Therefore, oncology societies have formally included HRQoL and PRO data as parameters to determine the value added with cancer therapies (19,20). Similarly, a patient-centered approach to AEs reporting has also been initiated to complement clinician reporting. PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed by multidisciplinary investigators and patient representatives to assess symptomatic AEs from a patient's perspective (21). However, measurement of PRO and HRQoL can be time- and effort- consuming, costly and logistically challenging. Therefore, historically, such data may not have been included and/or reported in clinical trials (22). Vaughn *et al.* are to be praised for the important reported work in that regard. Ensuring early incorporation, proper collection and reporting, as well as timely availability of standardized HRQoL and PRO data from clinical trials should be a common goal for the entire cancer research community.

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Footnote

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