Editorial Commentary

Important caveats of KEYNOTE-045: relevance of these findings in the current and future therapeutic paradigm

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Urothelial carcinoma of bladder is the fourth most common cancer in men in United States and ninth most common cancer worldwide (1). It is estimated that in 2018, there will be 81,190 new cases and 17,240 deaths due to bladder cancer in United States (US) (2). Although most patients (70%) have non-muscle invasive bladder cancer (NMIBC) (T0–T1), 30–40% have muscle invasive bladder cancer (MIBC) (T2–T4a) and around 5% have metastatic urothelial carcinoma (MUC) at presentation (3). MUC has a high mortality rate with therapeutic options for those with advanced disease being up until recently limited. The standard platinum-based chemotherapy has for the most part remained the first line option for patients exhibiting this unfortunate diagnosis but, if and once platinum-based regimen fail, there is no largely accepted consensus about which treatment should be offered next. Vinflunine was approved as a treatment option for post-platinum recurrent disease in Europe (4,5). However, in US, patients were receiving single-agent chemotherapy regimens (e.g., taxanes) with response rates of around 10% and median survival of 6 to 8 months (6,7).

Recent advances have improved our understanding of the role of immune system in cancer. The treatment landscape of MUC is rapidly changing with the demonstration of clinical benefits of immunotherapy and promise of targeted therapies. Between May 2016 to May 2017 FDA has granted accelerated approval to 5 PD-1/PD-L1 agents (atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab) for patients with post-platinum locally advanced or MUC. Atezolizumab and pembrolizumab are also approved as first-line treatment for cisplatin-ineligible MUC patients (8).

In 2017, results were reported from the phase III, KEYNOTE-045 trial (9), where patients that either recurred or progressed following platinum-based chemotherapy were treated with pembrolizumab, a humanized monoclonal IgG4k isotype antibody, compared to chemotherapy. A total of 542 patients were enrolled and randomized to receive either pembrolizumab or investigator choice chemotherapy (paclitaxel, docetaxel, and vinflunine). The co-primary endpoints were OS and PFS. Irrespective of PD-L1 expression there was an improvement in OS with pembrolizumab 10.3 months (95% CI, 8–11.8) compared to chemotherapy 7.4 months (95% CI, 6.1–8.3) (HR 0.73, 95% CI, 0.59–0.91, P=0.002). The ORR was 21.1% *vs.* 11.4% in the pembrolizumab versus the chemotherapy group respectively. The noted improvement in overall survival fostered significant excitement within the genitourinary oncology community and became the only checkpoint inhibitor with full US FDA approval for treatment of post-platinum treated MUC patients (9). Of note, the toxicity profile was much favorable for pembrolizumab as compared to chemotherapy. Pembrolizumab was better tolerated with 60.9% of patients experiencing any grade treatment-related adverse events (TRAEs) compared to 90.2% of those in the chemotherapy group. The most common TRAEs in the pembrolizumab group includes pruritus (19.5%), fatigue (13.9%), and nausea (10.9%). Immune-related adverse

events (AEs) were observed in 16.9% of patients in the pembrolizumab group with hypothyroidism being most common (6.4%).

In the past decade, patient-focused care is becoming a critical component of quality health care. Studies have shown that early integration of patient related outcomes (PROs) improves quality of life (QOL), emergency room utilization and survival outcomes in patients (10). In 2018, Vaughn and colleagues reported exploratory results from KEYNOTE-045 described above in *Journal of Clinical Oncology* comparing patient-reported outcomes including quality of life between pembrolizumab and chemotherapy groups (11), demonstrating that the quality of life in patients administered pembrolizumab were significantly better. Clinical scholars have also devised systems to measure this essential facet of the study, in order to compare different regimens of. The far-reaching article by Vaughn and the KEYNOTE-045 collaboration group (11) reflected exactly this important concern, with perhaps the largest ever group of patients having this information scrutinized. Despite the large number of studies contrasting these different second-line chemotherapy options for MUC, they provided a limited amount of information on health-related quality-of-life (HRQoL) outcomes with more information related to this endpoint clearly necessary. Fortunately, highlighting the timeliness of this study to answer this important study question. In the present editorial, we will focus our attention on detailing the pertinent caveats of this article.

The PROs instruments used by authors in this study were detailed and validated in prior peer reviewed publications: the EuroQoL five-dimensions questionnaire (EQ-5D) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). The PRO data was collected at baseline and at weeks 3, 6 and 9, then every 6 weeks up to 1 year or at the end of treatment. The primary end-point was set up at 15 weeks of treatment. Definitions of deterioration and improvement (ten points increase or decrease on the EORTC QLQ-C30 protocol) were previously validated and already used in other studies, not only within the urological field. Even though a significant number of patients did not complete the questionnaires (EORTC QLQ-C30 completion rate was of 59% in the pembrolizumab group versus 46.2% in the chemotherapy group), with these results reported at the median follow-up of 18.5 months.

The most compelling result from this study was the prolonged time to deterioration (TTD) in global health status and HRQoL score: 3.5 months for the pembrolizumab versus 2.3 months for the chemotherapy group (HR 0.72, P=0.004). This is more significant when we place this in the context of the overall survival of these treatment options. The global health status observed at week 15 and baseline remained stable on pembrolizumab (0.69 points of difference) but were significantly worse in the chemotherapy group (8.36 points); with a mean difference of 9.05 points (95% CI, 4.61–13.5 points, P<0.001) between two groups. This is perhaps the great take-home message in regard to patients having almost the same HRQoL assessment before starting pembrolizumab and within the middle of their treatment course whereby providing appealing facets to the tolerability and minimal impact of treatment on important determinants of patient quality of life. In many ways, this could provide an increasing impetus for patients to seek this systemic treatment versus others and potentially receive a more prolonged course of treatment if clinically indicated. This is clearly in addition to the favorable survival endpoints offered by this treatment modality.

Another notable finding of this study was that a larger proportion of patients treated with pembrolizumab achieved improved HRQoL measures at week 15 (31.2% versus 21.7%, respectively) in addition to fewer patients experiencing deterioration of health status (28.9% versus 40.3%, respectively). The primary study end-point was set-up to be measured at an objective timepoint of 15 weeks but, as the current data shows, the improvement in quality of life parameters were sustained for even longer. It is true that the number of patients that properly completed longer follow-up was smaller nevertheless the important concept of maintaining an adequate HRQoL status throughout longer treatment courses, which is needed in MUC particularly in treatment responders, bringing heightened excitement about these results.

A similar improvement in QOL has been reported in other studies with checkpoint inhibitors. CheckMate 275 evaluated the role of nivolumab in platinum refractory patients with MUC and Necchi *et al.* showed that its use exhibited stable, or in some cases significant improvement in HRQoL as measured by EORTC QLQ-C30 and EQ-5D-3L (12). Similarly, KEYNOTE-010, comparing the efficacy of pembrolizumab with chemotherapy in prior platinum progressed metastatic NSCLC patients, showed improvement in global QOL by 8.3 points (13). In KEYNOTE-024, treatment-naïve, advanced NSCLC, global QOL for pembrolizumab was significantly high compared to chemotherapy by 7.8 points (14). Another

topic of relevance is the side effect profiles of these different immunotherapy agents as possible explanation to improvement in QOL. All regimens were analyzed and compared, revealing a safer profile within the monoclonal antibody group. For obvious reasons, systemic regimens with less significant and a lower incidence of side effects will in all likelihood result in better quality of life, and this was nicely depicted within this study. A symbolic example is fatigue: one of the most common symptoms of MUC, fatigue had a significantly lower incidence in the pembrolizumab group, and this was sustained throughout the treatment course.

Some critiques of this study would raise a few pertinent details. One of them being the 9.05-point difference in the EORTC QLQ-C30 score observed between the pembrolizumab and the chemotherapy groups. Even though a 10-point difference is used in defining a significant improvement or deterioration, no one can nevertheless contest that this was a significant improvement. Prior studies proved that even smaller differences on such questionnaires can dramatically impact patient's quality of life (15). Yet questionnaires and parameters are useful for comparisons and academic studies, physicians caring for such patients are well aware that even minimal improvements in quality of life, for patients with advanced cancer this can be extremely significant and gratifying. As health professionals working with patients facing such a diagnosis and are undergoing such intense and life altering treatment, we appreciate the merit in quality of life improvement.

Other critiques bring relevance to this discussion is the cost-effectiveness of these treatment modalities. This is a challenging topic, since financial costs may vary within different regions of the world with the financial impact challenging to accurately contrast. On a very interesting international study published on the *European Urology* (16), a Markov model was developed to compare cost efficacy of pembrolizumab versus chemotherapy, comparing prices in the USA, UK, Canada and Australia. Pembrolizumab revealed an increase of 0.36 quality-adjusted life-years compared to chemotherapy and showed an incremental cost-effectiveness ratio of $122.557 in the USA, $91.995 in the UK, $90.099 in Canada and $99.966 in Australia. However, pembrolizumab was found to be cost effective on the USA only. Since there is a higher willingness-to-pay threshold per quality-adjusted life-years on this country in comparison to the others (100–150 K is the USA *vs.* 32–60 K in Australia, for example). Unfortunately, data from other European and Asian countries, especially those with a socialized medicine, was not evaluated.

In regard to cost-effectiveness, another point of consideration is the different access of this medication, outside the scope of clinical trials. Drug approval and distribution is often determinate by a national health agency and this also influence the costs. Different health models around the world will approach this discussion in different forms. With current data, it is known that there is a potential increase in costs of treatment when using these specific monoclonal antibodies but, since there is no current standard of care regimen and, most importantly, the other options seem to be less effective, the real answer to this question is still open for discussion.

Over the years, more light has been shed on the quality of life during cancer treatment, especially among patients with metastatic and advanced disease. When we contrast studies solely based on survival endpoints, we may draw unidimensional conclusion as depicted in the simple example of a drug that increases overall survival but also causes horrible side-effects, creating a very stressful treatment course. Timely and multifaceted studies such as KEYNOTE-045 bring a more granular and realistic expectation of the merit of a given systemic therapeutic modality.

We congratulate the efforts of the KEYNOTE-045 group, not only to demonstrate the overall survival and improved side-effect profile of pembrolizumab over multi-agent systemic chemotherapy (paclitaxel, docetaxel and vinflunine), but also to clearly reveal that quality of life parameters for the most part was preserved and significantly improved with this novel checkpoint inhibitor in patients with MUC. This information provides an impetus in supporting pembrolizumab as a new standard of care for platinum-refractory advanced MUC and also brings more enthusiasm to the rapidly-developing and exciting immunotherapies within our therapeutic armamentarium (8).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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