Editorial

The role of avelumab in advanced urothelial carcinoma in the context of a dynamic treatment landscape

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Urothelial carcinoma is a very common malignancy and the 6th most common in the US (1). Patients may either present with or, most commonly, progress to advanced disease, at which point the cancer is considered incurable and treatment options aim for life prolongation, tumor response and delay of progression, as well as palliation. Over the past three decades, the standard regimens for advanced urothelial cancer (aUC) have included platinum-based chemotherapy. Specifically, cisplatin-based regimens provide reasonable anti-tumor activity (about 50% response rates) but limited probability of long-term remission (10–15% of patients mostly with lymph node-only metastases are alive and disease-free at five years). Most patients inevitably progress and the median overall survival (OS) is about 15 months (2). Cisplatin-ineligible patients have been treated with carboplatin-based chemotherapy regimens with relatively inferior outcomes compared to cisplatin-fit patients (3,4).

The rapid development of immune checkpoint inhibitors (ICI) against PD-L1 or PD-1 has led to a revolution in the treatment landscape of aUC. Since May 2016, five ICI, including atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab have received FDA approval for aUC refractory to platinum-based chemotherapy, mostly based on data from phase I/II clinical trials (5-9). Among these agents, pembrolizumab has shown OS benefit compared to salvage chemotherapy (taxane or vinflunine) in a randomized phase III trial (6). A similar phase III trial of atezolizumab *vs.* chemotherapy showed OS benefit favoring atezolizumab in the entire trial population, but not in the subset of patients with "higher PD-L1 expression", which was the primary endpoint (10). Moreover, in the frontline cisplatin-ineligible setting, both pembrolizumab and atezolizumab have received accelerated approval based on encouraging results from large single arm phase II trials (11,12). The FDA recently updated the label for pembrolizumab and atezolizumab in the frontline cisplatin-unfit patient setting, requiring the use of a specific companion diagnostic assay to determine PD-L1 status and indicating either pembrolizumab or atezolizumab only for patients whose tumors express high PD-L1 based on the established cutoff of each corresponding assay (13). However, patients who are considered either unfit also for carboplatin-based chemotherapy in this frontline setting or platinum-refractory do not require PD-L1 testing in US based on the FDA label. Overall, these recent developments have generated significant excitement for the use of ICI in aUC.

With that context in mind, data regarding individual ICI are of very high interest: the study by Patel *et al.* presented updated results of the safety and efficacy of one of those ICIs, avelumab, from two pooled cohorts of a phase I trial (NCT01772004) (14). Overall, that study enrolled patients from 80 centers in US, Europe and Asia with at least one measurable lesion, life expectancy of at least 3 months and ECOG performance status 0–1. Overall, 249 patients were eligible and received avelumab 10 mg/kg IV over 1 hour every 2 weeks until disease progression, unacceptable toxicity or withdrawal. The primary efficacy endpoint was overall response rate (ORR) by RECIST (v1.1) criteria as

assessed by independent review. Median age was 68 years, 65% were current or former smokers, 23% had upper urinary tract as the primary tumor site, 84% had visceral metastases, and 50% had at least two prior lines of therapy. Median treatment duration was 12 weeks and median follow-up was 9.9 months. Among 161 patients with prior platinum-based chemotherapy and at least 6 months of follow-up, ORR (complete and partial response) was 17% (27 patients), which included 6% complete responses. Another 23% (37 patients) had stable disease as best response. Responses occurred in both "PD-L1 positive" (24%) and "PD-L1 negative" (14%) patients, based on immunohistochemistry using the Dako assay with the 73-10 PD-L1 antibody and predefined cut-off level based on percentage of positively stained cells. The median time to response was 11.4 weeks and median duration of response was not reached at the time of data cutoff; most responses appeared durable. Median OS in the entire cohort was estimated at 6.5 months; therapy was generally well tolerated. Among all patients, treatment-related adverse events (TRAEs) grade 3 or higher were observed in 8% of patients and included one treatment-related death from pneumonitis. Most common any grade TRAEs included infusion reaction (29%) and fatigue (16%).

This clinical trial added important and relevant additional data to our understanding of both efficacy and tolerability of ICI in aUC. The patient population included in the trial was fairly representative of the real-world setting and included many patients with adverse characteristics, e.g., high Bellmunt risk score, visceral metastasis, and multiple prior lines of therapy. For the most part, efficacy and safety data with avelumab in aUC presented in this study was congruent with other ICI in the platinum-refractory setting with 15–21% ORR and durable responses. Longer follow up from this trial can help report OS data; however, OS data need to be interpreted with extreme caution, esp. in single arm phase I and II trials, with unavoidable selection and confounding biases. Aside from a slightly higher observed rate of infusion reactions when indirectly compared to other ICI, the toxicity profile was comparable to other ICI trials including (but not limited to) fatigue, rash, asthenia and hypothyroidism. Similarly to other ICI trials in aUC, higher PD-L1 expression correlated with higher ORR, but responses were noted regardless of PD-L1 status; therefore, the clinical utility of PD-L1 expression in tumor tissue remains to be further defined in aUC. There are inherent challenges to define the predictive *vs.* prognostic role of a putative biomarker, e.g., PD-L1, in a single arm study. Notably, there remains considerable variability in the assessment of tumor tissue PD-L1 expression in aUC across assays.

While the above-mentioned study findings confirm the significant activity of avelumab in aUC, they do not distinguish avelumab significantly from other ICI in this space, esp. in the context of a phase III trial that showed OS benefit with pembrolizumab *vs.* salvage chemotherapy as a primary endpoint in platinum-refractory aUC patients (providing level I evidence). Additional factors that can be relevant to decision making in clinical practice may include frequency of administration, cost and cost-effectiveness, patient preferences, and insurance coverage.

The role of avelumab in UC has to be further defined based on relevant factors described below. Despite the generally perceived similarity in the mechanism of action across ICI, avelumab has the unique feature that it can also induce antibody-dependent cellular cytotoxicity (ADCC) unlike the other ICI approved in aUC. The clinical relevance of this mechanism needs to be clearly demonstrated in future trials. Moreover, the specific treatment setting, selected patient population, as well as trial design are very critical aspects. One consideration is utilization of avelumab in a relatively novel space in aUC, where no other ICI is currently approved. An ongoing phase III clinical trial (NCT02603432; Javelin Bladder 100) is comparing the efficacy (measured by overall and progression-free survival) of avelumab plus best supportive care to the current standard of best supportive care alone in patients with aUC whose disease has not progressed following completion of 4–6 cycles of first-line platinum-based chemotherapy. There is only another (phase II) trial, to our best knowledge, in that space (NCT02500121). The results of those two "switch maintenance" clinical trials are anticipated with very high interest, esp. in the context of four ongoing large randomized clinical trials in the frontline setting of chemotherapy-naïve aUC patients. Moreover, avelumab has been successfully combined with other agents in other tumor types, e.g., with anti-angiogenic agents in advanced renal cell carcinoma, therefore, evaluation of several combinations can be of potential benefit and are worth pursuing in aUC. Last, but not least, the discovery and validation of prognostic and predictive biomarkers can help enrichment strategies to select patients with higher chance of clinical benefit. The several ongoing clinical trials in aUC provide the appropriate platform to evaluate the potential clinical utility of biomarkers that may be relevant to avelumab activity.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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