Editorial Commentary

Contemporary role of avelumab first-line maintenance in advanced urothelial carcinoma with consideration of the JAVELIN Bladder 100 comprehensive clinical subgroup analyses

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Urothelial carcinoma (UC) is an aggressive malignancy which has historically been associated with a poor prognosis. There are an estimated 82,290 diagnoses of advanced UC and 16,710 related deaths in the United States (US) in 2023 (1). Unfortunately, treatment of localized disease with curative intent has a high rate of early recurrence. Moreover, treatment of localized and locally-advanced disease often entails intensive therapies including cisplatin-based chemotherapy and radical cystectomy which are both associated with morbidity and long-term sequelae which may be of detriment to quality of life in survivors. The mainstay of therapy for advanced disease for nearly three decades has entailed front-line platinum-based chemotherapy, with cisplatin favored for those eligible.

Immune-oncology (IO) and the integration of immune checkpoint inhibitors (ICIs) lagged in the bladder disease space compared to other malignancies where the advent of ICIs had near immediate practice changing impact. Several studies evaluated the role of combination ICIs with platinum-based chemotherapy, or the role of ICIs alone in treatment-naïve patients with advanced UC. KEYNOTE-361 was an open-label randomized three-arm study employing pembrolizumab monotherapy, pembrolizumab with platinum-doublet, or platinum-doublet chemotherapy alone. The addition of pembrolizumab to chemotherapy did not significantly improve survival (2). The similarly designed IMvigor130 trial employing atezolizumab with chemotherapy also failed to demonstrate any added overall survival (OS) benefit with IO for the intention-to-treat (ITT) population (3). The phase III DANUBE trial investigating durvalumab alone or durvalumab plus tremelimumab versus chemotherapy similarly demonstrated no added benefit with IO (4). Although ICI monotherapy with atezolizumab or pembrolizumab had initially gained US regulatory approval for cisplatin-ineligible patients with programmed cell death ligand-1 (PD-L1) (+) tumors, mature OS data shows limited benefit and these approvals were subsequently withdrawn leaving pembrolizumab as an option only for those patients who are chemotherapy-ineligible.

The Phase III JAVELIN Bladder 100 study demonstrated unequivocal, although limited, survival advantage with switch maintenance avelumab over best supportive care (BSC) for patients with unresectable, locally-advanced or metastatic UC (mUC) who have not progressed with first-line platinum-based chemotherapy. In this study,

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700 patients with who did not have disease progression with four to six cycles of first-line gemcitabine plus cisplatin or carboplatin were randomized to receive BSC with or without maintenance avelumab (5). The primary endpoint was OS. The addition of avelumab significantly prolonged OS (21.4 *vs.* 14.3 months; HR, 0.69; 95% CI: 0.56–0.86) and median progression-free survival (PFS) (3.7 *vs.* 2.0 months; HR, 0.62; 95% CI: 0.52–0.75). Based on these results, avelumab rapidly gained regulatory approval and was integrated into guideline recommendations with maintenance therapy becoming a new standard-of-care.

In the April 2023 issue of *European Urology*, Grivas *et al.* present protocol-specified and post-hoc subgroup analyses from JAVELIN Bladder 100. Median follow-up was >19 months in both arms (6). Results from the subgroup analyses are consistent with the initial report for the ITT population, and HR's were <1 in all clinical subgroups examined, in favor of maintenance avelumab. Of note, the trial was not sufficiently powered nor designed to demonstrate differences in the unplanned subgroups and statistical significance favoring maintenance avelumab was not achieved for all subgroups analyzed. Of the patients treated with gemcitabine/carboplatin, baseline characteristics included a greater proportion of patients with poor renal function, poorer performance status, and advanced age—typically predictive of worse prognosis. Remarkably, patients treated with gemcitabine/carboplatin followed by switch maintenance avelumab had impressive durability to their response, and survival differences between populations treated with cisplatin and carboplatin-based doublet were minimal. Survival differences were even less discrete in the PD-L1(+) tumors. No significant treatment-by-subgroup interactions were observed between 1L chemotherapy subgroups. These data are hypothesis generating, and suggest that there are subgroups of patients in which the delineation between cisplatin and carboplatin may be less important, as outcomes are more comparable in the era of maintenance IO—at least compared to survival differences from historical standards. Subgroup analysis of patients with upper tract and lower tract disease demonstrates limited benefit with maintenance IO in the upper tract population (OS HR 0.90; 95% CI: 0.59–1.39), supporting the established notion that upper tract disease harbors different underlying tumor biology compared to lower tract disease, and reinforces the unmet need for novel approaches for this patient population. The study is limited in its analysis of potential predictive biomarkers outside PD-L1, nor is there data on underlying molecular subtype (i.e., basal, luminal) and correlating response. This study and future studies will benefit for integration of biomarkers.

Placing these results in context with the recently emerging body of literature will however significantly dampen enthusiasm for switch maintenance avelumab as the optimal utilization of IO within the mUC treatment paradigm. At the 2023 European Society for Medical Oncology congress, the results from two phase III studies were presented which directly impact the relevance of maintenance avelumab after front-line chemotherapy in mUC. The CheckMate-901 trial evaluated gemcitabine/cisplatin with or without nivolumab versus gemcitabine/cisplatin in cisplatin-eligible patients with previously untreated unresectable or mUC. Nivolumab plus gemcitabine/cisplatin demonstrated statistically significant improvements in OS (HR 0.78, 95% CI: 0.63–0.96) and PFS (HR 0.72, 95% CI: 0.59–0.88). Notably, 60% of patients in the control arm received a maintenance or subsequent-line ICI after disease progression (7). Cross-trial comparison between JAVELIN Bladder 100 and CheckMate-901 shows more similarity in efficacy data than differences and it remains unclear if the benefits of nivolumab therapy are due to combination with chemotherapy, or if the clinical benefits are derived from maintenance immunotherapy, as is the case with avelumab. Nivolumab-combination therapy demonstrated an objective response rate (ORR) of 57.6%, including a remarkable 21.7% complete response (CR) rate. Patients achieving a CR had an impressive duration of response of 37.1 months, speaking to the depth of responses observed. These data suggest synergy between IO and cisplatin, which has been demonstrated pre-clinically in the past, and support a combination as opposed to a switch-maintenance approach (8). The phase III EV-302/KEYNOTE-A39 trial evaluated enfortumab vedotin (EV) with pembrolizumab versus platinum-doublet chemotherapy in a similarly designed trial. Nearly 59% of patients treated with chemotherapy went on to receive an ICI in the maintenance or subsequent-line setting. EV with pembrolizumab demonstrated a staggering survival advantage over patients treated with chemotherapy, nearly doubling PFS (HR 0.45, 95% CI: 0.38–0.54) and OS (HR 0.47, 95% CI: 0.38–0.58). The benefits were universal across the study patient subgroups, and were irrespective of PD-L1 expression, primary disease site, or cisplatin-eligibility (9). In our view, the JAVELIN Bladder 100 subgroup analyses presented by Grivas *et al.* continue to highlight the efficacy of maintenance avelumab, and reinforce the benefits that were

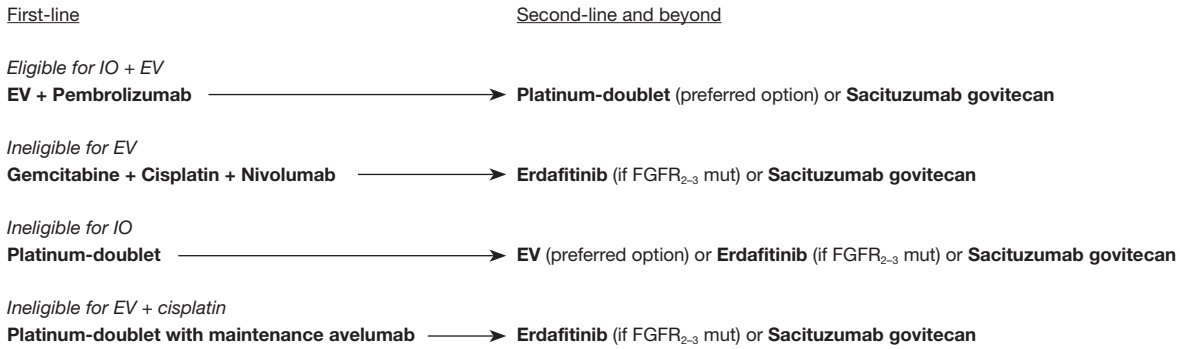

Figure 1 Proposed schema for treatment of metastatic urothelial carcinoma. IO, immuno-oncology; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor.

initially reported in the original data presentation which led to regulatory approval. However, the CheckMate-901 and EV-302 results are compelling enough to be considered the optimal 1L regimens for patients with locally advanced or mUC (*Figure 1*). Immunotherapy is now ideally situated in the front-line setting. Even further, we favor the combination of EV and pembrolizumab based on efficacy data, and unless a patient is ineligible or does not have access to EV therapy, platinum-based chemotherapy will likely be reserved for refractory disease, without any utility for maintenance IO.

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