Editorial Commentary

Refining the subgroup analyses and optimal patient population in the JAVELIN Bladder 100 trial

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The phase III JAVELIN Bladder 100 trial (1,2) was the landmark trial that investigated the role of switch maintenance therapy with avelumab, a programmed death-ligand 1 (PD-L1) checkpoint inhibitor, in patients who have not progressed after receiving platinum-based chemotherapy in patients with metastatic or locally advanced urothelial cancer. The results of the updated trial showed maintained efficacy with a median overall survival (OS) for avelumab maintenance with best supportive care (BSC) compared to BSC alone at 23.8 months [95% confidence interval (CI): 19.9–28.8] versus 15.0 months (95% CI: 13.5–18.2), respectively with a [hazard ratio (HR) of 0.76 (95% CI: 0.63–0.91); two-sided P=0.003]. This trial led to the standard of care in the United States in 2020 of a switch maintenance avelumab therapy approach with the United States Food and Drug Administration (US FDA) approval on June 20, 2020, as well as in several other countries worldwide. The update by Grivas *et al.* [2023] in *Eur Urol* (3) presented the pre-specified and post-hoc analyses of the clinical subgroups using the Kaplan-Meier method and Cox proportional hazards models with data cut-off on October 21, 2019. The subgroups that were evaluated included those who received gemcitabine and cisplatin (gem/cis) or those who received gemcitabine and carboplatin (gem/carbo) and PD-L1 positive population.

The JAVELIN Bladder 100 trial was an international trial that enrolled 350 patients that were randomly assigned to avelumab plus BSC versus BSC alone. The primary OS analysis showed better OS at 1 year which was 71.3% in the avelumab group and 58.4% in the control group which translated to a median OS of 21.4 months compared to 14.3 months for the BSC group, HR for death was 0.69; with a 95% CI: 0.56–0.86; P=0.001. All the other endpoints were statistically significantly different in favor of avelumab with prolonged OS in the PD-L1-positive population with an OS at one year at 79.1% in the avelumab group compared to 60.4% in the control group (HR, 0.56; 95% CI: 0.40–0.79; P<0.001).

This updated analysis seeks to understand the differences between the patients who received gem/cis (n=389) and gem/carbo (n=269). Gem/carbo was received by 128 patients with PD-L1+ patients. Different factors including age ≥65 years, differences via performance status as defined by the Eastern Cooperative Oncology Group (ECOG) of ≥1, visceral metastasis at baseline, creatinine clearance ≥60 mL/min, PD-L1 status, first line chemotherapy with gem/cis and complete response (CR) or partial response (PR) as best response to first line chemotherapy were further evaluated. Results of this updated analysis showed no difference whether one received gem/cis or gem/carbo. This includes HRs for OS with avelumab and BSC compared to BSC alone which

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was consistently <1.0 amongst the parameters examined, and that includes patients treated with either first-line gemcitabine with cisplatin or gemcitabine with carboplatin (spanning HRs of 0.89 and 0.64, respectively), which all suggests lack of difference and evidence of benefit regardless of clinical characteristics or presentation. Similarly, patients with PD-L1+ tumors treated with gemcitabine and carboplatin had a HR of 0.67, 95% CI: 0.39–1.14) and those whose best response was either PR or SD equally benefited, with HR of 0.62 and 0.7, respectively. In the patients who achieved CR (n=179), the HR for avelumab with BSC was 0.8 (95% CI: 0.46–1.37) and median OS was not yet reached with a wide CI and data is likely immature. In addition, the HR for progression-free survival (PFS) was 0.65 (95% CI: 0.44–0.95) with a median PFS was 7.4 months compared to 3.8 months in the BSC arm (95% CI: 2.1–5.6). In the PR subgroup of 326 patients, the HR for OS was 0.62 (95% CI: 0.46–0.84). PFS for the avelumab and BSC group yielded similar results as long as non-progression is achieved after first-line chemotherapy.

The JAVELIN Bladder 100 trial update suggests beneficial response from almost all subgroups regardless of receipt of gem/cis or gem/carbo, PD-L1 status, or achievement of response, and was the key design of the trial (i.e., achieving response or stable disease before proceeding on avelumab maintenance. There was also a companion manuscript that outlined the quality of life and patient reported outcomes (4) as well as the interval of time from chemotherapy until beginning of avelumab maintenance (5), which showed no difference. There are limitations to this particular dataset including the smaller numbers and post-hoc analyses and same data cut-off as the original publication with the same median follow-up of over 19 months. However, the relevance of this dataset also comes on the heels of positive results from first-line therapy use in cisplatin-ineligible patients with pembrolizumab and enfortumab vedotin (EV) combination based on the EV-103 cohort A (6) and cohort K (7). In addition, EV-302/Keynote A39 which is the phase III confirmatory registrational trial comparing EV plus pembrolizumab compared to gem/cis or gem/carbo chemotherapy has been presented showing OS, PFS and response advantage over chemotherapy alone. EV-302 revealed that PFS was significantly prolonged with combination of EV with pembrolizumab at a median PFS of 12.5 months versus chemotherapy at 6.3 months, with a HR 0.45 (95% CI: 0.38–0.54); P<0.001, reducing the risk of progression or death by 55%. OS was also significantly prolonged with EV and pembrolizumab with a median OS of 31.5 months compared to chemotherapy with a median OS of 16.1 months, with a HR 0.47 (95% CI: 0.38–0.58) translating to a reduction in the risk of death by 53% (8). This is especially relevant given the superior results of a non-chemotherapy combination compared to a chemotherapy-containing regimen, though further analysis showed up to 30% of such patients enrolled in the EV-302 trial did receive switch maintenance avelumab therapy in the chemotherapy control arm. Therefore, while this is not a trial that directly compares EV and pembrolizumab with chemotherapy followed by avelumab maintenance, it is difficult not to compare the two different approaches. On the other hand, the phase III CheckMate 901 trial which examined concurrent chemotherapy with another programmed cell death 1 (PD-1) inhibitor drug nivolumab (9), while showing negative primary OS endpoint results for the front-line therapy of stage IV patients with urothelial carcinoma whose tumors express PD-L1 ≥1%, conversely showed positive OS and PFS findings in the sub-study of nivolumab with cisplatin-based chemotherapy compared to chemotherapy in the cisplatin-eligible patient population. It remains to be seen why the other two large randomized trials using combination of chemotherapy and checkpoint inhibitor trials of IMvigor130 (10) and Keynote 361 (11) did not show benefit, while the CheckMate 901 trial did. Perhaps priming or inducing an anti-cancer immune response from the use of cisplatin that promotes ferroptosis may be key (12).

In summary, the updated results of JAVELIN Bladder 100 continue to establish the benefits of chemotherapy followed by avelumab maintenance as the standard of care in patients who have not progressed on chemotherapy. However, the front-line systemic therapy is rapidly changing with the US FDA approval of the combination of a non-chemotherapy containing regimen with EV and pembrolizumab in all-comers based on the EV-302 trial showing improved OS and PFS over chemotherapy. However, adoption for all patients still require careful consideration since toxicity occurs in a substantial number of patients who receive EV and pembrolizumab and comorbidities or frailty commonly afflicts a predominantly elderly patient population of metastatic urothelial carcinoma. In addition, the chemotherapy with nivolumab sub-study of the CheckMate 901, given recent US FDA approval, will likely change the landscape of treatment for cisplatin-eligible patients. Conceivably, there is still a minority of patients who achieve CR to cisplatin-based chemotherapy who have potential to be cured. Therefore,

identifying the right population of patients who are the best fit for each regimen would be of paramount importance given high attrition rates and the odds of not surviving beyond first-line therapy. On the other hand, clinicians need to be cognizant of toxicity management (since common toxicity with the EV and pembrolizumab like neuropathy occurred in 63% of patients, rash in 66.8% and hyperglycemia in 13%), appropriate patient population selection (i.e., those with high body mass index, hyperglycemia or poorly controlled diabetes, neuropathy) fit for each type of therapy, and de-escalation strategies. In addition, this new combination therapy of EV + pembrolizumab may not be available yet to patients all over the world, such that treatment that follows the JAVELIN Bladder 100 protocol remains relevant for a substantial population of metastatic urothelial cancer patients.

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Footnote

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