Peer Review File

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Reviewer A

This editorial commentary nicely summarized several recent trial results in 1L advanced/metastatic urothelial cancer; however, it lacks authors' perspective.
Response: Thank you for your comments. Authors' perspectives follow the summary of the updated analysis, especially in the context of data surrounding EV-302 and CheckMate 901.

In the sentence "In summary, the updated results of JAVELIN Bladder 100 continues to establish the benefits of chemotherapy followed by avelumab maintenance as the standard of care.", "chemotherapy followed by avelumab maintenance" is inaccurate. Maintenance avelumab can only be given among advanced/metastatic urothelial cancer patients who did not progress after platinum-based chemotherapy.
Response: Thank you for this comment, added the words "…standard of care in patients who have not progressed on chemotherapy" though this has been alluded to all throughout the paper since that is the essence of the JAVELIN Bladder 100 trial, that is switch maintenance avelumab in patients who have not progressed (ie., achieved stable disease, CR and PR).

Reviewer B

1. Background- needs to reference and update with survival follow up data from the Powles et al JCO 2023 paper on Javelin-Bladder-100- this showed the median OS was 23.8 months (95% CI, 19.9 to 28.8) versus 15.0 months (95% CI, 13.5 to 18.2), respectively (hazard ratio [HR], 0.76 [95% CI, 0.63 to 0.91]; 2-sided P = .0036).
Response: Thank you for this comment, added on the updated OS findings.
2. It is unclear how the updated analysis is different from the prior analysis by Grivas et al. Was there any difference in outcomes compared to the prior subgroup analysis by Grivas et al? Was the follow-up longer and what was the median follow-up?
Response: This particular Powles Eur Urol paper discusses the clinical subgroups including response to chemotherapy, performance status, visceral metastases, creatinine clearance, etc. which showed response regardless of receipt of cisplatin vs carboplatin and other subgroups or sites of tumor. On the other hand, the JCO 2023 was an update on patients who received > 2 years of maintenance avelumab.

3. Discussion needs to update since EV+pembrolizumab is now approved in the US for all patients with advanced UC.

Response: Thanks for this comment. Added a section to further discuss the results of EV-302 that showed improvement in OS and PFS and response rates that changes the standard of care in the US.

4. Based on this subgroup analysis, is there any group that might be offered the Javelin paradigm vs the EV-pembro or gem-cis-nivo regimen or is this impossible to know currently. Eg if response to platinum-based chemo can be reliably predicted, will the paradigm of platinum-based chemo followed by avelumab be more tolerable especially in PS=2 or frail patients?

Response: Thank you very much to the Reviewer for this comment. I went ahead and rendered further editorial comments on this since EV + pembro while approved in the US, may not be available in every other country outside of the US. Toxicity management is also key since neuropathy occurred in 63% of patients, rash in 66.8% and hyperglycemia in 13%. While efficacy and outcomes (OS and PFS) are clearly superior, it was compared to chemotherapy alone though 30% did receive avelumab maintenance. In addition, there is conceivably a small minority of population of patients (perhaps the lymph node positive disease) that might be cured with cisplatin-based chemotherapy which would make the JAVELIN Bladder 100 trial paradigm still relevant.