Peer Review File

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Reviewer A

The authors provide an editorial commentary on the recently published subgroup analysis from the JAVELIN 100 trial. The authors of the commentary provide an excellent overview of the landscape of IO trials in advanced urothelial cancer and place the JAVELIN results in a broader context. Importantly, the authors provide context of this study in light of the recently reported EV-302/Keynote-A39 which showed drastic survival benefit which likely will become standard of care even with another positive CheckMate 901 trial. The authors provide a well written and thoughtful commentary and there are no major corrections or comments.

There is one very minor comment:
Page 1, line 15 - change "early-stage" to "localized and locally advanced." This language is more accurate as early stage can include non-muscle invasive disease which does not require suggested therapies

Reply 1: Thank you for the suggestion. We agree with your recommended language and nomenclature for disease characterization and have changed the text accordingly.
Changes in the text: "early-stage" has been changed to "localized and locally advanced" (see Page 1, line 14-15)".

Reviewer B

The reviewer does not have any concerns about the manuscript.

Reply 1: Thank you for your review.

Reviewer C

The advent of immune checkpoint inhibitors (ICIs) has remarkably changed the treatment of advanced UC in the last few years. The majority of patients with advanced UC tend to progress after platinum-based chemotherapy and only few patients can achieve a long-term disease control. In 2020, the anti-PD-L1 antibody avelumab as first-line maintenance therapy for patients without disease progression after 4 to 6 cycles of platinum-based chemotherapy has improved the survival outcomes.
This is an important article addressing an area of need where more information is urgently needed.
If additional consideration of following revisions, we would appreciate it.

1. How about the effectiveness of avelumab for irAE?

Reply 1: Thank you for highlighting this important point. We agree that the exploration of the predictive value of an immune related toxicity on efficacy/survival is warranted. Unfortunately, the published subgroup analysis by Grivas et al. does not provide any data or commentary on irAE's.

2. Could the authors describe concerning some biomarkers other than PD-L1?

Reply 2: Thank you for the suggestion. We agree with the importance of biomarkers in the urothelial cancer disease space. Lack of predictive biomarkers outside of PD-L1 remains an unmet need. Unfortunately, the subgroup analysis reviewed in this editorial only provides data on PD-L1. As such, the scope of this editorial is limited. However, we have noted that moving forward, this and other trials should continue to work on developing biomarkers.

3. Are there any correlations between the response to avelumab and molecular subtypes (basal/luminal, etc).

Reply 3: Unfortunately, the JAVELIN study does not provide data on the molecular subtypes and correlations to response. We appreciate the suggestion, and agree that the data would be interesting. We have noted this in the text.

4. The authors need to add in the end of text their proposal on therapeutic scheme for advanced UC patients in a straight-forward manner including late-line.

Reply 4: We appreciate the reviewer's recommendation for incorporating a therapeutic scheme within this editorial. We created a flow diagram accordingly for front-line and second line/refractory disease.
Changes in the text: Please see figure 1 at the end of the text.