Peer Review File

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Reviewer A

Comment 1: I've read the manuscript with interest. I recommend rejection for this article, because it is unclear which literature hiatus it is filling (the manuscript does not specify an objective), the overview of combination therapies is incomplete (not a systematic assessment) and it is unclear why there is substantial focus on LEAP and not for instance on EV+P study. For these reasons, I do not have very specific improvement points for the authors.

Reply 1: Thanks for your time to review my paper. I appreciate the comment. This work is an invited Editorial Commentary paper from the Editorial team of 'The Translational Andrology and Urology'. I have accepted the invitation with pleasure and written the comment on: Matsubara N,et al. Pembrolizumab with or Without Lenvatinib as First-line Therapy for Patients with Advanced Urothelial Carcinoma (LEAP-011): A Phase 3, Randomized, Double-Blind Trial. Eur Urol. 2023:S0302-2838(23)03064-6. Exactly, recent clinical trials such as EV-302 and CM-901 would be epoch making and may more worth looking at. However, highlighting the clinical trials with negative data such as LEAP-011 might be important to interpret the positive results. I have overviewed ongoing randomized control trials of combination therapy for 1L aUC including other TKI plus IO and put them a table together (I understand this is not a systematic assessment). We are able to know at a glance, what kind of trials are ongoing and situation and brief results of the clinical trials. I have responded comments of Reviewer B, and now, the paper has got better, I believe. Again, I really appreciate your time reviewing the manuscript. The reviewer's understanding would be appreciated.

Change in the text: N/A

Reviewer B

Comment 1: Design of LEAP011 trial- please mention dose and schedule of Lenvatinib and pembrolizumab. The population can be characterized as unfit and mostly platinum-ineligible, which may have compromised tolerability of this high dose of Lenvatinib (20 mg once daily). This will assist with interpreting and enhancing discussion of dose intensity and tolerability.

Reply 1: I appreciate the reviewer's comment. Description regarding dose and schedule of trial drugs is vital because this clinical trial included cisplatin-ineligible patients who are likely to be less tolerable to intensified treatment.

Change in the text: I added a couple of sentences in Page 4, line 4–10, as shown below: 'Lenvatinib 20 mg as the initial dose or placebo was administered orally once daily. Patients in both treatment arms received pembrolizumab 200 mg intravenously once every 3 weeks for up to 35 doses, corresponding to approximately 24 months, until radiographic disease progression according to RECIST v1.1, intolerable adverse events, or physician or patient decision to withdraw from the clinical trial. If one drug in the combination group was discontinued, the other drug could be continued.'

Comment 2: The authors have chosen to highlight combinations in general, but this is an opportunity to highlight the activity of VEGF inhibitors and whether they may play a role in therapy. Recently, cabozantinib+pembrolizumab was active with a high ORR and CR and DOR in the firstline setting (Jain RK et al GU ASCO January 2024). Could there be a more optimal VEGFR TKI? If cabozantinib combines better, could zanzalintinib be even more optimal?

Reply 2: I really appreciate the reviewer's comment and recommendation. Exactly, both cabozantinib and zanzalintinib are promising drugs for future clinical investigation to improve the therapeutic index.

Change in the text: I added a section in Page 8, line 2–18, as shown below:
Heading 'Emerging 1L combination therapy of TKI plus IO for cisplatin-ineligible aUC'
Treatment options for cisplatin-ineligible and, particularly, platinum-ineligible patients with aUC are limited. The result of PemCab phase II trial 'Cabozantinib plus Pembrolizumab as First-line Therapy for Cisplatin-ineligible Advanced Urothelial Carcinoma' as presented by in the 2024 American Society of Clinical Oncology Genitourinary (ASCO GU) cancers symposium. In 36 patients with aUC who were cisplatin-ineligible or who refused cisplatin, a promising ORR of 45.7%, CR rate of 14.2%, and median duration of response of 14.7 months

was observed for pembrolizumab plus cabozantinib as 1L therapy. The median number of cycles received were 10 cycles of pembrolizumab and 7.5 cycles of cabozantinib. With a median follow-up of 14.3 months, the median PFS and OS were 7.6 and 17.1 months, respectively. Moreover, zanzalintinib is a next-generation TKI that inhibits cancer growth and spread through including VEGF receptors, MET, AXL and MER, which are similar to cabozantinib. Thus, zanzalintinib might be a vital direction of clinical investigation to improve the therapeutic index. The potential of combination of cabozantinib/zanzalintinib and pembrolizumab should be further evaluated.

I have added two citation papers for this change.

24. Jain RK, Swami U, Bilen MA, et al. Cabozantinib plus pembrolizumab as first-line therapy for cisplatin-ineligible advanced urothelial carcinoma (PemCab). Paper presented at: 2024 ASCO Genitourinary Cancers Symposium; January 25–27, 2024; San Francisco, CA. Abstract 539.

25. Hsu J, Chong C, Serrill J, et al. Preclinical Characterization of XL092, a Novel Receptor Tyrosine Kinase Inhibitor of MET, VEGFR2, AXL, and MER. Mol Cancer Ther. 2023;22:179-191.

Comment 3: Regarding CHECKMATE901, authors should highlight the long duration of CR. This was the major highlight of extremely durable benefit in a subgroup and potential cures.

Reply 3: I totally agree this comment. Of note, the median duration of complete response was 37.1 months with nivolumab-combination therapy and 13.2 months with gemcitabine–cisplatin alone. This is a huge difference.

Change in the text: I added a couple of sentences in Page 6, line 7–10, as shown below: 'The median duration of complete response was 37.1 months with nivolumab-combination therapy and 13.2 months with gemcitabine–cisplatin alone.'

Comment 4: Authors should take the opportunity to discuss if a potential role for the Javelin paradigm exists now following EV302 and CHECKMATE901 trial.

Reply 4: This is a great comment. EV plus pembrolizumab and GC plus nivolumab would be widely accepted as the gold standard 1L treatment for patients with aUC in near future. Two clinical trials showed positive result in the clinical trial setting. However, in the real-world setting, various types of patients such as elderly patients, vulnerable patients, or those with

comorbidities. I do not think all the patients should be treated with these novel combination treatments.

Change in the text: I added a couple of sentences in Page 7, line 17–25, as shown below: '1L chemotherapy with GC, GCarbo, or DD-MVAC, followed by switch maintenance avelumab or second-line pembrolizumab has been recommended in clinical practice guidelines for years. Based on the positive result of clinical trials, EV plus pembrolizumab and/or GC plus nivolumab would be widely accepted as the gold standard 1L treatment for patients with aUC in near future. However, treatment options should be selected with caution on a case-by-case basis. For example, elderly patients, vulnerable patients, or those with comorbidities are generally intolerant to intensified treatments and have high risk of treatment-related death. Still, vintage sequential therapy (chemotherapy followed by ICI) could play important roles in the real clinical setting.'

Comment 5. It should be highlighted that cure is still not possible for the vast majority and trials and translational studies are important.

Reply 5: Thanks for the comment. This will be a great massage to physicians and researchers who are making significant efforts for improving the management of aUC.

Change in the text: I added a couple of sentences in Page 8, line 23–25, as shown below: 'Still, radical cure is not possible in the vast majority of patients with aUC, thus, further translational researches and clinical trials are definitely needed.'