Review of: "First-line Immune Checkpoint Inhibitor-based Sequential Therapies for Advanced Hepatocellular Carcinoma: Rationale for Future Trials"

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the author tried to predict efficacy of second-line treatment using lenvatinib or sorafenib, or regorafenib, ramucirumab, cabozantinib after progression on Atezo+Beva treatment in patients with advanced or unresectable, un-TACEable patients, based on the available data from several RCTs, but not data from real-world study on the above scenario. I think it is an interesting study, and provides a rationale basis when we choose second-line treatment after AtezoBeva, or design a control trials, although I am quite familiar with the statistical analysis used in this study. There are several concerns as follows.

1. In the Reflect trial or Sharp trials, the treatment choices on progression after lenvatinib or sorafenib could be very different from the real-world scenario when using lenvatinib or sorafenib treatment as second-line treatment after Atezo+Beva, because when lenvatinib or sorafenib used as a first line treatment, second-line treatment using PD-1 antibody is still a choice, therefore, the expected efficacy is higher than progression after lenvatinib or sorafenib used after Atezo+Beva.

3. patients in the imbrave150 trial have no severe varices, therefore, favoring a long-term survival, and favoring second-line treatment using lenvatinib or sorafenib, as compared with other trials in which severe varices was not excluded.

4. Although there is no data so far, I believe the second-line treatment will more likely be Atezo+Beva+lenvatinib, TKI+PD-1 antibody or PD-1+CTLA-4 antibody, but not TKI monotherapy.