Correspondence on editorial regarding “Atezolizumab and bevacizumab for hepatocellular carcinoma: how to approach salvage therapy for non-responders?”

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Dear Editor

We are so grateful to receive the informative comments from Professor Naoshi Nishida on our publication. We would like to describe two additional issues to think about further. Because Professor Nishida explained in detail the scientific background of using tyrosine kinase inhibitor (TKI) use after ATE/BEV failure and the ongoing phase II trial regarding TKI treatment, we tried to focus on other options such as immune check point inhibitor (ICI)-based treatment and radiation after ATE/BEV failure. In addition, we described the clinical outcomes of lenvatinib treatment in patients with decreased liver function, which is commonly encountered during second- or higher-line treatment.

**ICI-based treatment after atezolizumab/bevacizumab (ATE/BEV) failure**

Although there are only a few retrospective reports on ICI-based treatment after ATE/BEV failure, the most frequently studied regimen is combination of anti-cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitor (ipilimumab) with anti-PD-1 monoclonal antibody (nivolumab). Data of 47 hepatocellular carcinoma (HCC) patients who were treated with nivolumab plus ipilimumab after ATE/BEV failure from our institute showed overall response rate (ORR) of 25.5% and disease control rate (DCR) of 42.6%, the median progression-free survival (PFS) of 1.4 months (95% CI, 1.1–1.7), and the median overall survival (OS) was not reached.¹ Wong et al. reported ORR of 16% and median OS of 10.9 months among 25 HCC patients treated with ipilimumab and nivolumab/pembrolizumab after progression on prior anti-PD-1/L1 (prior ATE/BEV 14%), and three (12%) patients achieved CR.² In a study by Roessler et al., among 10 patients who were treated with nivolumab plus ipilimumab after progression from ICI-based treatment (prior ATE/BEV 70%), median PFS and OS were 2.9 months and 7.4 months, respectively.³ Combination of CTLA-4 and PD-1 blockade works synergistically with longer-lasting immune effects. Additionally, CTLA-4/PD-1 blockade combination
has been shown to increase the CD8+ T cell to myeloid-derived suppressor cells, and decrease the fraction of regulatory T cells which can reverse the tumor immune escape in patients with primary resistance to PD-1 inhibitors.2,4

Combination of ICI plus TKI or antiangiogenic agents after ATE/BEV failure (ICI failure) has been also investigated. In a phase II study by Li et al., tislelizumab (PD-1 monoclonal antibody) plus regorafenib treatment achieved 28.6% ORR and 71.4% DCR, with a median PFS of 6.8 months among 28 pretreated patients (21.4% had prior PD1-inhibitor and TKI combination).5 Another combination of suvencitug (VEGF-A inhibitor) plus envafolimab (PD-L1 inhibitor) for 18 HCC patients (40.0% had prior PD-1/PD-L1 antibody) showed 11.1% ORR and 72.2% DCR, with the median PFS of 4.3 months.6

In fact, several studies have demonstrated that combination therapies involving ICIs and TKIs offer significant advantages over monotherapies. The combination of lenvatinib, a multi-kinase inhibitor, with pembrolizumab, an anti-PD-1 antibody, demonstrated promising efficacy in advanced HCC. The phase Ib KEYNOTE-524 study reported an objective response rate ORR of 36.0%, which is significantly higher than the ORR observed with pembrolizumab alone in the KEYNOTE-224 study7,8. Similarly, the combination of cabozantinib, another multi-kinase inhibitor, with atezolizumab has been investigated. The phase III COSMIC-312 trial revealed a statistically significant improvement in PFS compared to sorafenib, although the OS benefit did not reach statistical significance9. Another promising combination involves the use of sintilimab (anti-PD-1) with the bevacizumab biosimilar IBI305, which showed significant benefits in overall survival and PFS in the ORIENT-32 trial conducted in China10. Furthermore, research into the combination of ICIs with other novel agents, such as fibroblast growth factor receptor 4 (FGFR4) and MET inhibitors, is ongoing. These inhibitors have shown potential in modulating the tumor microenvironment and enhancing immune responses. For example, targeting FGFR4 was found to decrease PD-L1 expression and reduce regulatory T cell infiltration, thereby potentiating the immune-mediated killing of tumor cells11.

Overall, while these combination strategies represent significant advancements in the
treatment landscape of HCC, their specific efficacy after ATE/BEV failure needs further detailed investigation. Continued research into these combinations and their underlying mechanisms will be crucial in optimizing therapeutic outcomes and expanding treatment options for advanced HCC after ATE/BEV failure.

**Radiation therapy after ATE/BEV failure**

Radiation therapy converting tumor microenvironments into more immunogenic condition by releasing tumor antigen, effectively activates circulating cytotoxic T-cells, which can enhance immunogenic cell death through modulated immunity in HCC.\textsuperscript{12,13} Radiotherapy can be considered for oligoprogression or newly developed vascular invasion during ICI therapy in advanced HCC patients. Sindhu et al. analyzed 16 patients with HCC who received stereotactic body radiation therapy (SBRT) after oligoprogression during ICI therapy.\textsuperscript{14} PFS after SBRT was 7.1 months, with 1-year OS was 96.3%. There’s an ongoing phase II study of sintilimab plus bevacizumab combined with radiotherapy as first-line treatment for HCC having malignant portal vein thrombi. ORR and DRR was 58.7% and 100%, and the median OS and PFS were 24.0 months and 13.8 months, respectively.\textsuperscript{15} Theoretically, SBRT can also be extrapolated to cases with vascular invasion after progression with prior ICI-based therapy.

**Clinical outcomes of second-line lenvatinib treatment in Child-Pugh Class B patients**

Because the relative dose intensity of lenvatinib has a significant impact on its effectiveness, authors from editorial concerned about a sufficient dose would not be administered when using lenvatinib as a second-line treatment where many of Child-Pugh class B patients may be involved in the real world. According to the study by Singal et al., among Child-Pugh class B who were treated with lenvatinib in a second- or higher line setting showed 50.6% of ORR, median PFS and OS were 11.9 months, and
13.5 month, respectively.\textsuperscript{16} However, another study by Muto et al. demonstrated the numerically lower clinical outcomes of OS 6.7 month, and PFS 3.6 month in Child-Pugh class B patients (n=4) treated with second-line lenvatinib.\textsuperscript{17} We previously demonstrated that our study showed low ORR (7.5\% in unmatched, 5.6\% in PS-matched) and low OS (10.3 month) and PFS (3.5 month) than expectation in the lenvatinib second-line with cohort.\textsuperscript{18} The OS and PFS was lower at 6.5 month and PFS 2.2 month, respectively, with Child-Pugh Class B patients in our study, but the patient number (n=3) was too small to draw any conclusion regarding clinical outcomes. Considering that Child-Pugh class B patients receiving second or higher-line systemic therapy will be common in clinical practice, lenvatinib can be a good alternative if liver function and adverse events are well monitored and managed as there is few treatment option. Future studies with real-world data in with Child-Pugh Class B patients are anticipated.

In conclusion, there are several options for second-line treatment after ATE/BEV failure, such as TKI, ICI-based treatment, locoregional therapy such as SBRT in case of oligoprogression or newly developed vessel invasion. Currently, selection is based on consideration of serious adverse events or contraindications from previous treatment. We will be able to predict and adjust customized treatment for each individual patient by accumulating real world data from multiple cases. Since liver function is the most important predictor of OS in second-line treatment or higher, it will be necessary to accumulate data on the outcomes of lenvatinib and other regimens especially in patients with Child-Pugh class B patients, preferably by dividing groups into Child-Pugh score 7, and 8.
References


