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Letter to the Editor

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Letter regarding "Impact of Bevacizumab Being Skipped due to Adverse Events of Special Interest for Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab: An Exploratory Analysis of the Phase III IMbrave150 Study"

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We read with great interest the article written by Kudo et al. [1] on "Impact of Bevacizumab Being Skipped due to Adverse Events of Special Interest for Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab: An Exploratory Analysis of the Phase III IMbrave150 Study." They analyzed the effects of bevacizumab being skipped due to adverse events (AEs) on the clinical outcomes of atezolizumab and bevacizumab (Atez/Bev) in hepatocellular carcinoma patients who were enrolled in Imbrave150 trial. They divided the patients into two groups based on whether or not bevacizumab had ever been skipped due to AEs associated with bevacizumab. To minimize immortal time bias, they conducted a 6-month landmark analysis, demonstrating no significant meaningful differences in progression-free survival and overall survival between the two groups.

First, we congratulate the authors on their insightful analysis of impact of bevacizumab being skipped using the Imbrave150 cohort. Our real-world data indicated that early interruption of bevacizumab (within the first 9 weeks) led to a decrease in the efficacy of Atez/Bev [2], which was inconsistent with the authors' findings [1]. We would like to highlight the reasons for this discrepancy. First, there were differences in the types of AEs leading to bevacizumab interruption. The most frequent AEs leading to bevacizumab interruption in the authors' cohort were proteinuria (n = 34, 49%), followed by hypertension (n = 16, 23%) [1], while proteinuria (n = 19, 29.7%) is the most frequent AE, followed by appetite loss (n = 10, 15.6%) in our real-world data [2]. While the development of elevated blood pressure and proteinuria was associated with favorable outcome of Atez/Bev [3], a cautious interpretation is required due to potential inclusion of lead-time bias when the relationship between AEs and clinical outcome was analyzed. Second, there is a difference in the evaluation method regarding the impact of bevacizumab being skipped. We evaluated early bevacizumab interruption within the first 9 weeks, whereas the authors assessed bevacizumab interruption during the entire treatment period, focusing only on patients who received Atez/Bev for more than 6 months. Additionally, the number of early bevacizumab interruption in our cohort might be greater than in the authors' cohort because half of the patients in our cohort were treated as later-line settings and had a history of tyrosine kinase

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inhibitors, which act as multikinase inhibitors including blocking vascular endothelial growth factor. Third, the authors included 210 patients who received Atez/Bev for more than 6 months, accounting for 64% (210/329) in arm A of the Imbrave150 trial. Given that these patients can continue to receive many treatment cycles, Atez/Bev might exhibit a better tumor response compared to those who received Atez/Bev for less than 6 months. Indeed, approximately 50% of tumor response was observed according to the swimmer plot in the authors' manuscript and median progression-free survival of 15.5 months was achieved. Accordingly, these patients can benefit from immune checkpoint inhibitors and the impact of bevacizumab being skipped might be limited. The authors' findings may not be applicable to cases with a treatment duration of less than 6 months. Fourth, the discrepancy in the authors' and our results is associated not only with whether bevacizumab was ever skipped or not but also with the period of bevacizumab interruption. In our cohort, the patients were older and had non-viral-related chronic liver disease. Hepatocellular carcinoma patients with non-viral etiology were likely to be accompanied with metabolic comorbidities, including hypertension and diabetes mellitus. A longer period of bevacizumab interruption might be required to manage the bevacizumab-related AEs in these patients.

The authors' results suggest that skipping bevacizumab due to bevacizumab-related AEs did not considerably impact the efficacy and safety of Atez/Bev. However, the impact of skipping bevacizumab in real-world cohorts remains controversial. It is crucial to ensure a cautious and judicious management of AEs, such as proteinuria, to maintain adherence to bevacizumab during the initial treatment period, especially within the first 6 months.

Conflict of Interest Statement

The authors report no conflict of interest with regard to this article.

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References

1 Kudo M, Tsuchiya K, Shao Y-Y, Finn RS, Galle PR, Ducreux M, et al. Impact of bevacizumab being skipped due to adverse events of special interest for bevacizumab in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab: an exploratory analysis of the phase III IMbrave150 study. Liver Cancer. 2023:1–12. doi: 10.1159/000535501.

2 Hatanaka T, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, et al. Association of early bevacizumab interruption with efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma: a landmark analysis. Hepatol Res. 2022;52(5):462–70. doi: 10.1111/hepr.13748.

3 Han JW, Chang HS, Yang JY, Choi HS, Park HS, Jun HO, et al. Intravitreal administration of retinal organoids-derived exosomes alleviates photoreceptor degeneration in royal college of surgeons rats by targeting the mitogen-activated protein kinase pathway. Int J Mol Sci. 2023;24(15):12068. doi: 10.3390/ijms241512068.