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Reply

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# Reply to the 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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**Keywords**
Atezolizumab · Bevacizumab · Unresectable hepatocellular carcinoma · Adverse events of special interest · Skipped bevacizumab

Dear Editor,

We thank Hatanaka et al. for their interest and valuable comments on our article [1]. They pointed out several reasons for the discrepancy between our study and their results [2].

First, the types of adverse events (AEs) leading to bevacizumab interruption differed between the two studies [3]. In our analysis, we reported the AEs of special interest for bevacizumab that led to bevacizumab interruption, which did not include appetite loss [1]. This may have resulted in the difference in AEs leading to bevacizumab interruption between the two studies. As they mentioned, the immortal time bias should be considered when analyzing the relationship between AEs and clinical outcomes. Several previous studies reporting the relationship between bevacizumab-related AEs and clinical outcomes had not performed analyses that account for the immortal time bias [4]. Thus, it remains unclear whether the development of hypertension and proteinuria due to bevacizumab is associated with improved clinical outcomes.

Second, the two studies used different methods to consider the association between clinical outcomes and bevacizumab interruption. We did not perform an analysis focusing on patients who skipped bevacizumab early, so the impact of early bevacizumab interruption on clinical outcomes and the number of patients who interrupted bevacizumab early were not evaluated. Our

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study only included patients who had not previously received systemic treatment, and we found no obvious differences between groups that were observed in the distribution of major baseline characteristics. A stratified Cox proportional hazards model was used to reduce the confounding bias. On the other hand, Hatanaka et al. only examined the impact of early bevacizumab interruption on clinical outcomes, which may have been affected by bias due to imbalanced baseline characteristics and patient selection. Their study included patients who had previously received systemic treatment, and their results showed that modified albumin-bilirubin grade 2b, which is a prognostic factor, and later-line settings were more common in the group of patients who interrupted bevacizumab within 9 weeks than in the control group. However, since they did not evaluate the impact of these factors on overall survival and progression-free survival in the multivariate analysis, it is controversial to argue that the interruption of bevacizumab within 9 weeks worsens prognosis. In addition, the validity of the 9-week landmark analysis for evaluating early bevacizumab interruption is unclear as the robustness of the 9-week time period was not evaluated. In summary, the difference in the clinical question, study population and statistical analysis method could contribute to the discrepancy between the results of Hatanaka et al. and our study.

Third, as mentioned in a separate analysis in the efficacy section of our article (page 6) [1], we performed a landmark analysis in patients who received atezolizumab + bevacizumab for at least 3 months and observed similar trends as those seen in the 6-month landmark analysis. Furthermore, time-dependent analyses, in which the first occurrence of bevacizumab AEs of special interest leading to bevacizumab interruption was included as the time-dependent variable, in the overall population also supported the results of the 6-month landmark analysis. Therefore, we believe that the main conclusion of our study is not limited to patients who received atezolizumab + bevacizumab for at least 6 months.

Fourth, we agree with Hatanaka et al. on the importance of considering the duration of bevacizumab interruption. To our knowledge, no study has investigated the relationship between the duration of bevacizumab interruption and prognosis, which does not invalidate our conclusion at this point. Future studies are needed to address this question.

In conclusion, the insightful comments from Hatanaka et al. contribute to our understanding of the impact of bevacizumab interruption due to AEs in patients with hepatocellular carcinoma treated with atezolizumab + bevacizumab. Our comprehensive analysis, which accounted for immortal time bias and ensured comparability through landmark and time-dependent covariate analyses, strengthened the generalizability of our findings. We remain confident in the validity of our conclusions.


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## Conflict of Interest Statement

Masatoshi Kudo reports the following conflicts of interest: honoraria payment to self from Bayer, Chugai Pharmaceutical Co. Ltd., Eli Lilly, Eisai, and Takeda; research funding to institution from AbbVie, Chugai Pharmaceutical Co. Ltd., EA Pharma, Eisai, F. Hoffmann-La Roche Ltd, GE HealthCare, Gilead Sciences, Otsuka, Sumitomo Dainippon Pharma, Taiho, and Takeda; and Editor-in-Chief of Liver Cancer. Kaoru Tsuchiya reports the following conflicts of interest: advisory/consultancy fees to self from Chugai Pharmaceutical Co. Ltd. and Eisai; speakers bureau participation for Chugai Pharmaceutical Co. Ltd., Eisai, Eli Lilly, and Takeda; and research funding to institution from F. Hoffmann-La Roche Ltd. Tatsuya Yamashita reports the following conflicts of interest: speakers bureau participation for Bayer and Chugai Pharmaceutical Co. Ltd. and research funding to institution from F. Hoffmann-La Roche Ltd. Hironori Koga reports the following conflicts of interest: research funding to institution from AbbVie, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo, and F. Hoffmann-La Roche Ltd. Yuki Nakagawa reports the following conflicts of interest: employment by Chugai Pharmaceutical Co. Ltd. Masafumi Ikeda reports the following conflicts of interest: honoraria to self from Bayer, Chugai Pharmaceutical Co. Ltd., Eisai, Eli Lilly, and Takeda; advisory/consulting fees to self from Chugai Pharmaceutical Co. Ltd., Eisai, Eli Lilly, Merck Sharp and Dohme, and Takeda; and research funding to institution from Bayer, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eisai, Eli Lilly, F. Hoffmann-La Roche Ltd., Merck Sharp and Dohme, and Takeda.


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## Author Contributions

Masatoshi Kudo, Tatsuya Yamashita, Hironori Koga, Yuki Nakagawa, Masafumi Ikeda, and Kaoru Tsuchiya contributed to writing – review and editing.

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