JHEP|Reports

Response to: "Anticoagulation is not associated with an increased risk of variceal bleeding under systemic therapy for advanced HCC"

To the Editor:

We are grateful to Allaire *et al.* for their letter.[1] The authors report the occurrence of acute variceal bleeding (AVB) in a large series of patients with hepatocellular carcinoma (HCC) treated with atezolizumab/bevacizumab (atezo/bev).[2] All patients received a gastroscopy before starting systemic therapy and most had adequate AVB prophylaxis. The slightly higher occurrence of AVB in their cohort compared to ours could be due to the differences in baseline characteristics of both studies.[3] There was a higher frequency of patients with esophageal varices at baseline and previous episodes of AVB in their study. More individuals with splenomegaly >12 cm, and a lower median platelet count indicate a higher number of patients with significant portal hypertension. The presence of varices, previous AVB, and spleen size could be identified as predictive factors for gastrointestinal bleeding in our cohort. Another possible reason for the higher AVB occurrence is the longer follow-up period.

Of relevance is the comparison of bleeding episodes in patients treated with atezo/bev *vs*. sorafenib, which was recently published by the authors.[2] The Imbrave150 study reported a slightly higher occurrence of AVB with atezo/bev as compared to sorafenib (2.4% *vs.* 0.6%),[4] but this highly selected cohort is limited in representing real-world conditions. One example is the exclusion of patients with therapeutic anticoagulation. The colleagues' study confirms that no higher frequency of bleeding was observed with atezo/bev compared to sorafenib under real-world conditions. Anticoagulation did not increase the risk of AVB bleeding in their study or our cohort. A prerequisite is the systematic endoscopic screening combined with consequent management of portal hypertension and its complications to assure the safety of these treatments in patients with HCC.[5] We agree with the authors that non-selective beta-blockers should be the mainstay of primary and secondary prophylaxis of variceal bleeding. Non-selective beta-blockers reduce portal hypertension as a disease driver. They not only prevent gastrointestinal (re)bleeding but can also reduce overall hepatic decompensation events.[6–8]

Based on the findings of both studies we conclude that (1) AVB bleeding episodes are not significantly more frequent in patients treated with atezo/bev *vs*. the alternative first-line agents lenvatinib and sorafenib and (2) therapeutic anticoagulation does not seem to represent a contraindication to atezo/bev. Future studies should aim at assessing the safety of the VEGF-inhibition-free regimen durvalumab/tremelimumab and its impact on portal hypertension in patients with HCC.

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Conflict of interest

NBK has received reimbursement of meeting attendance fees and travel expenses from EISAI and lecture honoraria from the Falk Foundation and AstraZeneca. ENDT has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, MSD, Mallinckrodt, Omega, Pfizer, IPSEN, Terumo and Roche. He has received reimbursement of meeting attendance fees and travel expenses from Arqule, Astrazeneca, BMS, Bayer, Celsion and Roche, and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and IPSEN and Roche and is currently employed at Boehringer-Ingelheim. AG is an advisory board or steering committee member to AbbVie, Alexion, Bayer, BMS, CSL Behring, Eisai, Falk, Gilead, Heel, Intercept, Ipsen, Merz, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, and Sequana and a speaker for Advanz. FPR has received honoraria for lectures, consulting activities, and travel support from the Falk Foundation, AbbVie, Gilead, Ipsen, AstraZeneca, Roche and Novartis. All other authors report no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

FPR and NBK designed the study and wrote the manuscript; FPR and NBK conducted data analyses and wrote the manuscript; all co-authors were involved in the data collection and preparation of the manuscript.

Data availability statement

Data is available upon request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101146.

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Author names in bold designate shared co-first authorship

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