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Management of portal hypertension in patients treated with atezolizumab and bevacizumab for hepatocellular carcinoma

To the Editor:

Management of portal hypertension in the setting of advanced hepatocellular carcinoma (HCC) was not raised by Baveno VII renewing consensus in portal hypertension.[1] The "Club Francophone pour l'Etude de l'Hypertension Portale" would like to take the opportunity to discuss this issue.

The combination of atezolizumab and bevacizumab which is the current first-line therapy for advanced HCC[2] may expose patients to bleeding complications related to portal hypertension. Phase II studies of bevacizumab monotherapy in HCC have shown a 10% rate of variceal bleeding.[3] This risk was lower in the IMbrave150 study, with only 3.65% of hemorrhages secondary to gastric or oesophageal varices in the atezolizumab + bevacizumab arm compared to 1.28% in the sorafenib arm (https://clinicaltrials.gov/ct2/show/results/NCT03434379; last update posted: December 30, 2021), but similar to other phase III data.[2,4] In IMbrave 150, patients were excluded in case of bleeding related to portal hypertension in the last 6 months or in the absence of efficient prophylaxis. Therefore in « real life », a meticulous evaluation of bleeding risk secondary to portal hypertension is needed and primary prophylaxis is essential when indicated before starting combination therapy.[5]

The recent Baveno VII consensus for portal hypertension recommends non-selective beta blockers (NSBBs) in compensated cirrhosis with clinically significant portal hypertension (CSPH) defined by the presence of either gastroesophageal varices, or ascites, or portosystemic collateral vessels or liver stiffness measurement (LSM) ≥25 kPa or hepatic venous pressure gradient ≥10 mmHg.[1] In patients without CSPH, screening endoscopy is indicated either if platelets ≤150,000/mm^3 or LSM ≥20 kPa. Other patients can be followed by yearly repetition of LSM and platelet count. If varices are present, primary NSBB prophylaxis is indicated in first line whatever the size. In case of NSBB contraindication or intolerance, endoscopic band ligation (EBL) must be alternatively performed for high-risk varices.

However, in case of advanced HCC, with or without portal obstruction, Baveno VII criteria are not applicable since LSM and platelet count may be modified by the tumor and portal hypertension may rapidly worsen so that the annual rhythm of follow-up by LSM and platelets is not appropriate.[4] Therefore, before starting bevacizumab, a screening endoscopy in the 6 previous months is mandatory.[5] Likewise, when primary prophylaxis is not indicated, screening endoscopy should be considered yearly.

One other concern is primary prophylaxis in case of NSBB contraindication or intolerance. In patients treated with bevacizumab, EBL is the alternative to NSBBs, but we have to keep in mind that it may not be so safe. Indeed 10 to 12 days after EBL, ulcer bleeding occurs in 4.6%, with an increased risk in patients with HCC (hazard ratio 8.84; 95% CI 2.85-27.02).[6] Bevacizumab could further delay post-EBL ulcer healing as well as bleeding control. Given this potential side effect, a 4-week interval is usually recommended after surgery before starting bevacizumab, which can be reduced to 7 to 14 days for less invasive procedures.[7,8] Moreover, varices eradication requires 3 to 4 EBL sessions repeated at intervals of 2 or 3 weeks,[9] which may impact HCC treatment initiation. In our expert opinion, atezolizumab + bevacizumab treatment should not be delayed until complete eradication, and combination therapy can be started 2 weeks after a first EBL session in the absence of post-EBL ulcer bleeding.

The last concern is that, if acute bleeding occurs during atezolizumab + bevacizumab treatment, secondary prophylaxis with NSBBs and EBL must be started and HCC treatment may be modified. In patients who maintained an ECOG performance status 0/1 and remained compensated after bleeding, it is not clear for how long bevacizumab should be interrupted due to the risk of slower healing of ulcers and bleeding recurrence. Other questions are still pending. Should atezolizumab be continued in monotherapy until variceal eradication? Is there a definitive contraindication to this combination therapy? Should other anti-VEGF therapy such as tyrosine kinases inhibitors (TKIs) be preferred as this treatment was associated with a decrease in portal hypertension in preclinical models[4]? To date, strong clinical evidence is lacking to consider that TKIs would be safer than continuing atezolizumab + bevacizumab in this situation. Moreover, other combination therapies will probably be available soon. Tremelimumab + durvalumab recently showed promising results (Gastrointestinal Cancer Symposium of the American Society of Clinical Oncology, January 2022) and the results of pembrolizumab + lenvatinib are still pending. The

Keywords: Baveno VII; Variceal Bleeding; Hepatocarcinoma; Immunotherapy; Prophylaxis.
Received 24 January 2022; received in revised form 5 February 2022; accepted 9 February 2022; available online 17 February 2022
https://doi.org/10.1016/j.jhep.2022.02.004

decision should obviously take into account, case by case, the initial response to immunotherapy.

Financial support
The authors received no financial support to produce this manuscript.

Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions
Guarantor of the article: Isabelle Ollivier-Hourmand. Isabelle Ollivier-Hourmand drafted the manuscript. Manon Allaire contributed to the critical revision of the manuscript. Jean Paul Cervoni contributed to the critical revision of the manuscript.

Acknowledgements
Governing Board members of the "Club Francophone pour l'Etude de l'Hypertension Portale":

Delphine Weil, Violaine Ozenne, Pierre Emmanuel Rautou, Charlotte Bouzbib, Sabrina Sidali, Frédéric Oberti, Maeva Guillaume, Paul Castellani, Paul Calame, Sandrine Barge, and Christophe Bureau.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.02.004.

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Reply to: 'Management of portal hypertension in patients treated with atezolizumab and bevacizumab for hepatocellular carcinoma'

To the Editor:
We read with interest the comments of Drs. Ollivier-Hourmand, Alaire and Cervoni, who wrote a letter on behalf of the 'Club Francophone pour l'Etude de l'Hypertension Portale' commenting on the management of portal hypertension in the specific group of patients with hepatocellular carcinoma (HCC) treated with atezolizumab and bevacizumab (Ate/Beva).[1]

Underlying cirrhosis is present in over 90% of patients with HCC[2] and thus, the issue of management of portal hypertension (PH) in patients with cirrhosis and HCC is very relevant. To date, there are no studies evaluating whether patients with cirrhosis and HCC require different clinical strategies for screening, treatment, and follow-up of PH-related complications compared to those without HCC. Therefore, we strongly suggest following Baveno VII recommendations[3] in patients with cirrhosis and HCC. Importantly, it has been shown that, in patients with HCC who experienced variceal bleeding, survival was improved in those who undergo secondary prophylaxis

Received 27 April 2022; accepted 28 April 2022; available online 5 May 2022
https://doi.org/10.1016/j.jhep.2022.04.029