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CORRESPONDENCE

Response to: Atezolizumab plus bevacizumab in unresectable HCC: insights from the AMETHISTA trial interim analysis

On behalf of our co-authors, we respond to the letter by Drs Zhu, Fan, Qin, and Zhou[1] regarding our publication on the interim analysis of the phase IIIb AMETHISTA trial.[2] AMETHISTA was designed to evaluate the findings of the phase III IMbrave150 study in an Italian population and was not intended for generalizability.

STRENGTHS AND LIMITATIONS OF INCLUSION CRITERIA

At the time of study design, atezolizumab plus bevacizumab was not yet approved in Europe or reimbursed in Italy and could only be administered within a trial. Thus, inclusion and exclusion criteria closely mirrored IMbrave150 to ensure relevance. Patients with viral coinfection, Child–Pugh B cirrhosis, or prior systemic therapy were excluded by design. Unlike most subsequent real-world studies, which were retrospective,[3,4] AMETHISTA was a prospective phase IIIb trial, necessitating strict inclusion criteria.

Cirrhosis was not an exclusion criterion; rather, the enrolled population included a limited but significant proportion of patients with cirrhosis. It is also noteworthy that, a decade after the introduction of direct antiviral agents for hepatitis C virus, the proportion of hepatocellular carcinoma (HCC) cases arising from cirrhosis has declined, aligning our cohort with contemporary populations. As expected, hepatitis B virus (HBV)-positive patients were underrepresented due to the lower prevalence of HBV infection in Italy, precluding separate subgroup analyses.

Zhu et al. raised concerns regarding the characterization of patients with metabolic dysfunction-associated steatotic liver disease (MASLD). We acknowledge this as an ongoing issue; however, at the time of study design (2020), the current MASLD definition[5] was not established, and such data were not collected.

INTERPRETATION OF EFFICACY AND SAFETY RESULTS

Extrahepatic disease was not an exclusion criterion, and almost half the patients had extrahepatic spread. Regarding pre-treatment esophagogastroduodenoscopy, variceal management, grade $\geq$3 bleeding, and insufficient current prophylaxis, we would like to remark that given the lack of a comparator group and the small sample size of this subgroup of patients at risk (11 in total, 6 of which experienced bleeding), it is impossible to draw any conclusion about whether bevacizumab has any effect or whether such patients would have bled regardless of treatment. We agree that this issue deserves further investigation from real-world data, as patients with high-risk varices are at risk of bleeding regardless of treatment.[6] Therefore, head-to-head comparisons in similar patients are needed before any definitive conclusion can be drawn. Of course, the multidisciplinary approach is standard of care for patients with HCC.

SOCIOECONOMIC AND MULTIDISCIPLINARY PERSPECTIVES

The cost of bevacizumab was beyond the scope of our study. However, we note that bevacizumab originator is already off-patent and biosimilars are available. The cost of atezolizumab is higher than bevacizumab but in line with other immunotherapy options used in various cancer types.

In addition to the points discussed above, Zhu and colleagues highlighted some characteristics of our study that may be worthy of attention, reported their general point of view, for instance on the utility of a multidisciplinary board (which is standard of care, as mentioned above), and provided recommendations for future research. However, these aspects were not related to the AMETHISTA trial.

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REFERENCES

1. Zhu W, Fan C, Quin J, et al. Comment on: Atezolizumab plus bevacizumab in unresecatble HCC: insights from the AMETHISTA trial interim analysis. *ESMO Open*. 2025;10:104546.
2. Piscaglia F, Masi G, Martinelli E, et al. Atezolizumab plus bevacizumab as first-line treatment of unresectable hepatocellular carcinoma: interim analysis results from the phase IIIb AMETHISTA trial. *ESMO Open*. 2025;10:104110.
3. Casadei-Gardini A, Rimini M, Tada T, et al. Atezolizumab plus bevacizumab versus lenvatinib for unresectable hepatocellular carcinoma: a large real-life worldwide population. *Eur J Cancer.* 2023;180:9-20.
4. D'Alessio A, Fulgenzi CAM, Nishida N, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: a real-world study. *Hepatology.* 2022;76:1000-1012.
5. Rinella ME, Lazarus JV, Ratziu V, et al., NAFLD Nomenclature Consensus Group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79:1542-1556.
6. Iavarone M, Alimenti E, Tada T, et al. Incidence and predictors of esophagogastric varices bleeding in patients with hepatocellular carcinoma in lenvatinib. *Liver Cancer.* 2023;13:215-226.