Editorial

Atezolizumab plus bevacizumab for patients with Child-Pugh-B in hepatocellular carcinoma

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Atezolizumab plus bevacizumab is currently the main choice of first-line treatment for unresectable hepatocellular carcinoma (HCC), which has been proven superior to sorafenib for overall survival (OS) and progression-free survival (PFS) in the phase III IMbrave150 trial (1). Updata analysis from IMbrave150 showed that the median OS was 19.2 months for atezolizumab plus bevacizumab and 13.4 months for sorafenib [hazard ratio (HR) =0.66; 95% confidence interval (CI): 0.52–0.85; P=0.0009], and the median PFS was 6.9 and 4.3 months (HR =0.65; 95% CI: 0.53–0.81; P=0.0001) (2).

We read the article by D'Alessio *et al.* (3) recently published in *Hepatology* titled "*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*", with great interest. The authors evaluated the safety and efficacy of atezolizumab plus bevacizumab in patients with varying degree of liver dysfunction by a multicenter worldwide retrospective study. Baseline liver function was categorized by Child-Pugh (CP) score: 154 patients (76%) were in CP-A and 48 (24%) were CP-B. The incidences for any grade of atezolizumab-related adverse events (AEs) in CP-A and CP-B were 53% and 40%, respectively, whereas the proportions for grade ≥3 of atezolizumab-related AEs in CP-A and CP-B were 15% and 4%, respectively. Particularly, there were grade ≥3 hepatitis in 12 patients with CP-A (8%) and none with CP-B. On the other hand, the percentages for ant grade of bevacizumab-related AEs in CP-A and CP-B were 48% and 46%, respectively, whereas the percentages for grade ≥3 of bevacizumab-related AEs in CP-A and CP-B were 16% and 15%, respectively. the frequency of grade ≥3 GI bleeding was similar in patients with CP-A (4%) and CP-B (10%). In regard with the safety, there was no significant difference between the two groups. The objective response rate (ORR) was 26% for CP-A and 21% for CP-B. The disease control rate (DCR) for CP-A and CP-B was 74% and 68%, respectively. These responses were comparable between two groups. In 48 patients with CP-B, the median OS (95% CI) and median PFS (95% CI) was 6.7 (4.3–15.6) months and 3.4 (2.6–4.2) months.

According to a prospective global observational registry study for unresectable HCC patients treated sorafenib (GIDEON) study, 21% of patients (n=666) had CP-B status, and the median OS (95% CI) was 5.2 (4.6–6.3) months (4). There are few treatment options and limited data on safety and efficacy for patients with HCC who had CP-B and impaired liver function. Additionally, patients with CP-B status are typically not allowed to participate clinical trials of novel therapies because of their poor prognosis. Kudo *et al.* (5) conducted a phase I/II trial of nivolumab in 49 patients with advanced HCC and CP-B status to determine its safe and effectiveness in comparison to patients with CP-A in

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other cohorts of the CheckMate 040 study. According to CP-A and CP-B, the percentages for any grade of AEs were 79% and 51%, respectively, whereas the percentages for grade ≥3 of AEs in CP-A and CP-B were 23% and 24%, respectively. For CP-A status, the ORR was 20%, while for CP-B, it was 12%. The DCR for CP-A and CP-B was 61% and 55%, respectively. Nivolumab was equally as safe and effective for patients with CP-B as it was for those with CP-A. The median OS (95% CI) was 7.6 (4.4–10.5) months. A retrospective study to examine the outcomes and safety of patients treated atezolizumab plus bevacizumab between CP-A (n=427) and CP-B (n=30) status has just been published (6). In terms of AEs, patients with CP-B significantly more frequently experienced appetite loss and edema/ascites than those with CP-A. The ORR and DCR did not significantly differ between the two groups. For patients who were categorized as CP-B, the median OS and PFS were 6.4 months (95% CI: 4.3–11.0) and 6.0 months (95% CI: 2.4–8.0). When considered collectively, these results imply that atezolizumab plus bevacizumab may be provided in a manner that is safe even when it is not in compliance with the rigorous inclusion criteria of the IMbrave150 research.

Despite of limitations in this paper due to its retrospective design, which requires careful consideration when evaluating median OS or comparisons between CP-A and CP-B groups, this study offers a useful description of the safety and tolerability of atezolizumab plus bevacizumab in patients with CP-B status treated in routine clinical practice. It needs to be validated with real-world data on CP-B cases in prospective observational studies for systemic therapy in patients with unresected HCC, such as the GIDEON trial, and with results from phase II trials of atezolizumab plus bevacizumab for CP-B patients with HCC. In Japan, prospective observational study in real-world data of systemic therapy for unresectable HCC (PRISM—UMIN000040488) and phase II prospective trial for the use of atezolizumab plus bevacizumab exclusively in patients with CP-B status (CHALLENGE—jRCTs031210355) are investigating.

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Footnote

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References

1. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
2. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-73.
3. 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;76:1000-12.
4. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol 2016;65:1140-7.
5. Kudo M, Matilla A, Santoro A, et al. CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B

cirrhosis. J Hepatol 2021;75:600-9.
6. Tanaka T, Hiraoka A, Tada T, et al. Therapeutic efficacy of atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma in patients with Child-Pugh class A or B liver function in real-world clinical practice. Hepatol Res 2022;52:773-83.

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