Editorial Commentary

ORIENT-32 trial: sintilimab + bevacizumab biosimilar as a promising combination therapy in advanced hepatocellular carcinoma

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Although the incidence of hepatocellular carcinoma (HCC) has increased over the past several decades, therapeutic advances have largely remained stagnant and clinical outcomes have historically remained poor. More recently, as the biology and molecular landscape of these tumors has been better characterized and as the applicability of molecularly targeted agents and immunotherapies has expanded, there has been an exciting and long overdue shift in the treatment paradigm of HCC (1).

The use of immune checkpoint inhibitors combined with antiangiogenic agents has gained traction and recently evolved into a standard of care treatment for patients with advanced HCC (2). Notably, the phase 3 IMbrave150 study demonstrated a superior response rate and survival advantage with the combination of atezolizumab, a PD-L1 inhibitor, and bevacizumab, a VEGF inhibitor, when compared to sorafenib in the first-line setting (3).

Similarly, the results of the randomized, open-label phase 2/3 ORIENT-32 study reported by Ren *et al.*, which is the focus of this commentary, revealed that sintilimab, an anti-PD-1 antibody, in combination with IBI305, a bevacizumab biosimilar, had a significant progression-free and overall survival advantage versus sorafenib in treatment-naïve Chinese patients with advanced, hepatitis B virus (HBV)-associated HCC. Median progression-free survival increased to 4.6 months with sintilimab plus IBI305, as compared to 2.8 months with sorafenib. An interim analysis of overall survival showed a median of 10.4 months with sorafenib, although the median had not yet been reached in the combination arm. The difference was associated with a statistically significant 43% reduction in the survival hazard favoring the investigational combination regimen (4). Importantly, the safety profile of the combination regimen used in this trial was similar to that previously reported, without any new safety signals identified. The trial was designed with an appropriate control arm, comparing the investigational agents to current standard of care multikinase inhibitor.

In comparison to the IMbrave150 study, patients enrolled in the ORIENT-32 trial may in fact more accurately represent the real-world population of HCC patients. For example, subjects enrolled in the ORIENT-32 trial had a higher rate of extrahepatic metastatic disease burden, more commonly had received prior local therapy, and had a relatively poorer baseline Eastern Cooperative Oncology Group (ECOG) performance status. As opposed to IMbrave150, ORIENT-32 included Child-Pugh class B patients, suggesting some enrollees had more severe baseline hepatic impairment (3,4). Collectively, the more inclusive eligibility criteria in ORIENT-32 creates a more broadly applicable and clinically meaningful study.

The synergy between combined immune checkpoint and VEGF inhibition can be explained by emerging data suggesting that antiangiogenic agents, through a variety

of mechanisms, have an immunostimulatory effect on the tumor microenvironment that can then be harnessed by the co-administration of immunotherapy, ultimately leading to increased antitumor effects (5,6). Although mechanistically similar, the distinct immunotherapy agents used in these studies (PD-L1 inhibitor in IMbrave150 and PD-1 inhibitor in ORIENT-32) may have intrinsic and clinically relevant differences that can account for variations in the outcomes of patients with HCC treated with these partner drugs (7).

Although the investigational combination regimen employed in OREINT-32 met its predefined survival endpoints, we have identified several shortcomings in this study. Some of the baseline characteristics in the intention-to-treat population, including exclusively Chinese participants with primarily HBV-associated HCC, may limit the generalizability of these findings on a global scale. HBV remains the leading risk factor for HCC worldwide, however other etiologies of chronic liver disease, including hepatitis C virus (HCV), chronic alcoholic hepatitis and non-alcoholic fatty liver disease, also commonly contribute to hepatocarcinogenesis (8,9). Such distinctive pathogenic mechanisms underlying the development of HCC can in part explain the heterogeneity of these tumors, and therefore the response to therapies among HCC subtypes may vary considerably (10,11). Another study limitation lies in the relatively short duration of follow-up, with a median follow-up period of 10 months. Results from the first interim overall survival analysis are likely too premature to confidently declare a meaningful survival advantage.

Overall, the ORIENT-32 trial is the first large-scale phase 3 study evaluating a PD-1 inhibitor-based combination therapy for advanced HCC in the first-line setting that has met its primary endpoint. It represents a promising new, safe and efficacious treatment option amid the ever-growing landscape of novel immune checkpoint inhibitor combination therapies.

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