Letter

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Overshadowed prospect of programmed cell death protein-1 (PD-1) inhibitor as monotherapy for patients with advanced hepatocellular carcinoma

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Summary **Hepatocellular carcinoma (HCC) is a prevalent and refractory cancer in the world and very few drugs are available for the disease treatment currently. Programmed cell death protein-1 (PD-1) monoclonal antibodies including nivolumab and pembrolizumab has received accelerated approval for treatment of advanced HCC based on phase 1/2 clinical trials. However, the recently disclosed results of phase 3 clinical trials showed that both nivolumab and pembrolizumab as monotherapy failed to meet the primary objectives, which might overshadow the prospect of PD-1 inhibitors as monotherapy in treatment of advanced and unresectable HCC. The feasibility of PD-1 inhibitors in combination with other therapies or in other HCC settings requires further verification in the future.**

Keywords: HCC, PD-1, immune checkpoint inhibitor, sorafenib, lenvatinib

Hepatocellular carcinoma (HCC) is a common and deadly cancer with limited treatment options. The vast majority of HCC occurs in Asian and sub-Saharan African countries and the incidence of HCC in the United States and other developing countries is increasing (*1,2*). Surgical removal of the tumor is associated with better cancer prognosis, but only 10-15% of patients are suitable for surgical resection due to the extent of disease or poor liver function (*3,4*). For more advanced disease, including spread of cancer beyond the liver or in persons who may not tolerate surgery, molecular targeted drugs including sorafenib, lenvatinib, regorafenib, and cabozantinib might be employed to decrease symptoms of disease and maximize duration of survival (*5*). Two programmed cell death protein-1 (PD-1) inhibitors, nivolumab and pembrolizumab, have received accelerated approval for HCC treatment based on the promising results of phase 1/2 clinical trials. However, the recently disclosed outcomes of phase 3 clinical trials of both drugs might overshadow the application of PD-1 inhibitors as monotherapy in advanced HCC patients (*5-7*).

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Nivolumab is the first PD-1 monoclonal antibody approved for the second-line treatment of HCC. This approval was based on an open-label, non-comparative, phase 1/2 dose escalation and expansion trial (CheckMate 040). In this trial, the safety and efficacy of nivolumab was evaluated as a first-line treatment in patients who had not previously received sorafenib and as a second-line treatment in those with previous disease progression on sorafenib (*8*). In the study, nivolumab showed an objective response rate of 20% at a dose of 3 mg/kg in the expansion stage. Since the start of this study, nivolumab has been approved for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, *etc*., no new safety signals were observed in HCC patients (*8*). Supported by the results of CheckMate 040, a phase 3 randomized, multi-center study (CheckMate 459) was performed to evaluate nivolumab versus sorafenib as a first-line treatment in patients with advanced and unresectable HCC. On June 24, 2019, Bristol-Myers Squibb announced the topline results of this study. Although the trial showed a clear trend towards improvement in overall survival (OS) for patients treated with nivolumab compared to sorafenib, it did not achieve statistical significance for its primary endpoint of OS per the pre-specified analysis (HR = 0.85 [95% CI: 0.72-1.02]; p = 0.0752) (*6*). Results of this study demonstrated limited benefits of PD-1 antibody as a first-line drug for patients with advanced HCC.

Pembrolizumab is another approved PD-1 monoclonal antibody for advanced HCC patients. In the non-randomized, open-label phase 2 trial (KEYNOTE-224), pembrolizumab displayed potential for patients whose disease progressed on previous sorafenib treatment (*9*). Overall, pembrolizumab was tolerable and showed an objective response of 17% and stable disease of 44% in 104 patients (*9*). The results accelerated the approval of pembrolizumab as a second-line treatment option for advanced HCC patients and promoted the initiation of phase 3, randomized trials for comprehensively evaluating the drug as a second-line treatment in advanced HCC patients. The trial of KEYNOTE-240 aimed to test the safety and efficacy of pembrolizumab versus best supportive care in participants with previously systemically treated advanced HCC. The complete results of this trial, published on May 26, 2019, showed that pembrolizumab improved OS (HR: 0.78; $p = 0.0238$) and progression free survival (PFS) (HR: 0.78; $p = 0.0209$) versus placebo, however, these differences did not meet significance per the prespecified statistical plan (*7*). Although the objective response rate (ORR) of pembrolizumab group is significantly higher than that of placebo group (16.9% versus 2.2%) (*7*), which is consistent with that of KEYNOTE-224, the OS and PFS data might compromise the confidence of pembrolizumab as a second-line monotherapy for advanced HCC given several second-line molecular targeted drugs are available in the market.

The treatment of HCC remains a huge challenge in the current stage. There have been no significant advances over sorafenib, which was approved in 2007, in more than a decade until the recent successes of lenvatinib, regorafenib, and cabozantinib as first- or second-line drugs. Immune checkpoint inhibitor brings new breakthrough for controlling cancers and has been introduced in HCC treatment with high expectations. Currently, various clinical trials are being carried out to evaluate the safety and efficacy of PD-1 or PD-L1 monoclonal antibodies alone or in combination of other drugs (*e.g.*, lenvatinib and apatinib), adoptive T-cell therapy (*e.g.*, CAR-GPC3 T cells), locoregional therapies (*e.g.*, transhepatic arterial chemotherapy), or curative surgery for HCC treatment (*10*). The recently disclosed results of phase 3 clinical trials of nivolumab and pembrolizumab might be a setback for PD-1 monoclonal antibody as monotherapy in treatment of advanced HCC. The feasibility of PD-1/PD-L1 inhibitors in combination with other therapies or in other HCC settings requires further verification in the future.

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