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Editorial Commentary

Pembrolizumab for second line treatment of advanced hepatocellular carcinoma—who would benefit?

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In the study "*Pembrolizumab versus placebo as second-line therapy in patients from Asia with advanced hepatocellular carcinoma*: *a randomized*, *double-blind*, *phase III trial*", recently published in *J Clin Oncol* (1), Qin *et al.* reports on the final progression-free survival (PFS) and overall survival (OS) results of the KEYNOTE-394 trial. The trial included 453 Asian patients in Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 with preserved liver function and advanced hepatocellular carcinoma (HCC), progressing or being intolerable to first line treatment with sorafenib or (for 9%) oxaliplatin-based chemotherapy. Patients were randomized 2:1 to either treatment with programmed death-ligand 1 (PD-L1) inhibitor pembrolizumab or placebo. Biomarker enrichment was not attempted. The primary endpoint was met with a modest but statistically significant improvement in median OS from 13.0 to 14.6 months [hazard ratio (HR) 0.79 (95% confidence interval: 0.63–0.99)]. In addition, PFS and objective response rate (ORR) were better with pembrolizumab than placebo.

This trial began inclusion of patients, while the similarly designed KEYNOTE-240 study was still recruiting worldwide. In that study, published in 2019 (2), a nominal improvement of outcome was observed, but statistically the primary endpoints of OS and PFS were not met and the trial was negative. However, a significant reduction in HR's for PFS and OS was shown in a subgroup analysis of 176 patients included from Asia. Although the two studies are similar in size, randomization, treatment and major inclusion criteria, there are some differences apart from geography. Among others, KEYNOTE-240 was not placebo controlled and in KEYNOTE-394 statistics of long-term results are better as median follow-up is approximately 3 times longer (33.8 months).

As expected from demography (3), disease biology of the two study populations is different. Patients were on average 12 years younger in KEYNOTE-394 and 80% were infected with hepatitis B virus (HBV), while in KEYNOTE-240 only 40% were infected with hepatitis and 58% had a history of alcohol. Prognostic factors of patients in KEYNOTE-394 are less favorable with more patients being in PS 1 rather than 0, in Barcelona Clinic Liver Cancer (BCLC) stage C rather than B, and with more patients with high alpha-fetoprotein (AFP) and extrahepatic disease. Despite this, the median OS of patients in the placebo group is at least on par with multikinase inhibitor-treated patients in first line studies (4-6), suggesting selective inclusion.

The HR's for OS are similar in the two KEYNOTE studies showing a 21–22% reduction in risk of death for the pembrolizumab-treated patients. The median PFS is short (≤3.0 months), but what is most striking is the effect

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on long-term survival that in KEYNOTE-394 is driven by a median duration of response of almost 2 years among the 13% who had an objective response. Hence, PFS was 16% at 12 months and 12% at 18 months, which compares favorably with currently approved second line treatments for unselected HCC populations (7,8). The effect on PFS resulted in a doubling of survivors at 3 years with pembrolizumab (23%) compared to placebo (11%), despite that 28% in the placebo group crossed over to treatment with an PD-L1 inhibitor.

Safety data were consistent with other studies demonstrating the tolerability of single-drug treatment with check point inhibitors in advanced HCC (9). Adverse effects (AEs) were frequent but often related to consequences of disease rather than treatment. AEs leading to treatment abortion were reported in only 4% in the KEYNOTE-394 study, and treatment-related death occurred in only 0.7% in the two KEYNOTE studies combined.

Within recent years, randomized studies have shown that antiangiogenic therapy and immunotherapy improve outcomes compared to sorafenib in the first-line setting, both in Asian populations (10,11) and in rest of the world (6), and these treatments have become standard of care for patients with advanced HCC in good PS without contraindications (12). The population of patients eligible for immunotherapy in second line is today therefore limited. The study by Qin *et al.* shows that in Asian HCC patients in PS 0–1 with preserved liver function and BCLC stage B and C disease, pembrolizumab is an active and tolerable second-line treatment after sorafenib, providing a modest, but statistically significant OS benefit. The long follow-up of patients in the KEYNOTE-349 allowed for disclosure of a striking long-term impact of pembrolizumab on PFS and OS in a minority of patients. These patients unfortunately cannot at present be identified *a priori*.

Other evidence-based, second-line options after progression on sorafenib or lenvatinib (5) are available, including cabozantinib (7), regorafenib (8), and ramucirumab (13). Antiangiogenic therapy combined with immunotherapy may also be considered for check-point inhibitor naïve patients, although side-effects may restrict its use in a fragile population (12). Both KEYNOTE studies of pembrolizumab in second line suffer from lack of assessments of predictive biomarkers (9). These are especially needed in the current context indicating a large benefit achieved by a minority, while the average impact is modest. In lack of predictive biomarkers for immunotherapy in HCC, close monitoring of treatment efficacy or resistance, e.g., using circulating tumor DNA (ctDNA) (14), could possibly facilitate a more personalized treatment approach and improve prognosis.

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