Editorial Commentary

Positivity of the KEYNOTE-394 but negativity of the KEYNOTE-240: differences in efficacy between Eastern and Western populations?

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The first randomized studies of anti-PD-1 drugs as single agents have been disappointing (1,2) in the management of patients treated for advanced hepatocellular carcinoma (HCC). As first-line treatment, nivolumab failed to improved results over sorafenib in the Checkmate-459 study (2). In second line, after sorafenib, in a global study, pembrolizumab failed to improve outcomes versus best supportive care (BSC) in the KEYNOTE-240 trial (1). However, this failure was frequently interpreted as being at least partly due to imperfections of the trial design (3). The results of the KEYNOTE-394, with a similar comparison but conducted only in Asia and with specific inclusion criteria, were thus eagerly awaited.

KEYNOTE-394 was a double-blind randomized phase III Asian study evaluating pembrolizumab (200 mg) administered every 3 weeks versus placebo in second-line treatment HCC, after sorafenib or oxaliplatin-based chemotherapy, for patients with unresectable HCC not eligible for a locoregional treatment. The primary endpoint was overall survival (OS) and the secondary endpoints were progression-free survival (PFS), the objective response rate (ORR), duration of response, disease control rate and time to progression. Four hundred and fifty-three patients were randomized, 300 in the pembrolizumab group and 153 in the placebo group.

Patients were all with a good performance status (0 or 1), with mainly the Barcelona Clinic Liver Cancer (BCLC) stage C (423 patients, 93%), only 30 patients (7%) were BCLC stage B; all patients had a Child-Pugh A liver score. Three hundred and sixty-six patients (81%) had a viral hepatitis, most of them hepatitis B (360 patients, 79%). Most patients (411, 91%) received sorafenib as first-line treatment, and 42 patients received oxaliplatin-based chemotherapy.

Median OS was significantly improved in the pembrolizumab arm as compared with the placebo arm, 14.6 months (95% CI: 12.6 to 18.0) versus 13.0 months (95% CI: 10.5 to 15.1), respectively; hazard ratio (HR) =0.79 (95% CI: 0.63 to 0.99); P=0.0180. Median PFS was also significantly improved with 2.6 months (95% CI: 1.5 to 2.8) in the pembrolizumab group versus 2.3 months in the placebo group (95% CI: 1.4 to 2.8), HR =0.74 (95% CI: 0.60 to 0.92; P=0.0032). The ORR was 13.7% (95% CI: 10.0% to 18.1%) in the pembrolizumab group versus 1.3% (95% CI: 0.2% to 4.6%) in the placebo group. The safety was manageable, most of adverse events (AE) were due to disease progression, 54 patients (18.1%) experimented grade 3 immune-related toxicities, only 9 patients received corticosteroids for immune-related AE.

KEYNOTE-394 was a positive Asian study validating pembrolizumab as second-line treatment for patients with an unresectable HCC previously pretreated with sorafenib or oxaliplatin-based chemotherapy. In contrast, KEYNOTE-240, evaluating pembrolizumab in the same indication with a majority of Western patients, was a negative study. What could explain the different outcomes

Table 1 Main characteristics from KEYNOTE-240 and KEYNOTE-394

Characteristics	KEYNOTE-240 (n=413)	KEYNOTE-394 (n=453)
Population		
Asian	157 (38%)	453 (100%)
Non-Asian	256 (62%)	
Viral status		
HBV	101 (24%)	360 (79%)
HCV	64 (15%)	6 (1%)
Barcelona Clinic Liver Cancer stage		
B	85 (21%)	30 (7%)
C	328 (79%)	423 (93%)

HBV, hepatitis B virus; HCV, hepatitis C virus.

between these two similar studies?

KEYNOTE-240 was a randomized phase III trial; 413 patients were randomized, 278 in the pembrolizumab arm and 135 in the placebo arm. In the KEYNOTE-394, the median age was 54 years old, almost 13 years earlier than in the KEYNOTE-240 (median age was 67 years in the pembrolizumab group versus 65 years in the placebo group). In the KEYNOTE-240, most patients were non-Asian (256/413, 62%), whereas KEYNOTE-394 was exclusively Asian. In the KEYNOTE-240, 328 patients (79%) had a stage BCLC C compared to KEYNOTE-394 with 423 patients (93%). In the KEYNOTE-240, most patients had no viral hepatitis (248, 60%). And finally, in the KEYNOTE-394, 42 patients (9%) could receive oxaliplatin-based chemotherapy whereas in the KEYNOTE-240, all patients received previous sorafenib (*Table 1*).

The main results from the KEYNOTE-240 and the KEYNOTE-294 are presented on *Table 2*. In the KEYNOTE-240, two co-primary endpoints were defined: OS and PFS, and two interim analyses were scheduled. Due to the co-primary endpoints and these interim analyses, there is a consumption of alpha risk. Median overall survival (mOS) was 13.9 months (95% CI: 11.6 to 16.0) in the pembrolizumab group and 10.6 months (95% CI: 8.3 to 13.5) in the placebo group (HR =0.781; 95% CI: 0.611 to 0.998; P=0.0238), and median progression free survival (mPFS) was 3.0 months (95% CI: 2.8 to 4.1) for pembrolizumab and 2.8 months (95% CI: 1.6 to 3.0) for placebo (HR =0.718; 95% CI: 0.570 to 0.904; P=0.0022). Indeed, the HR were similar, even a bit better in the KEYNOTE-240 trial as compared to the KEYNOTE-394, and the difference in statistical positivity was only related to the split of the alpha risk. This is reinforced by the meta-analysis of both trial, which suggest consistent results with pembrolizumab in both trials, and a superiority over BSC (4).

One other explanation for the better results in the Asian population, could be the different of etiologies of HCC. In Asia population, the main etiology is viral (hepatitis C or B), whereas in occidental world, the main causes are alcohol and nonalcoholic steatohepatitis (NASH). There has been a debate about better results of immunotherapy in viral hepatitis (5), albeit more recent data with the HIMALAYA and LEAP-02 trials have not confirmed the hypothesis (6,7).

HCC is a global concern, but practices vary greatly worldwide, for example as regard to the relative role of loco-regional therapies and systemic therapies (8-10). Some of the differences between the guidelines can be related to differences in the populations: for example, Asian patients have more frequently hepatitis B virus (HBV) infection, with the possibility to develop HCC without cirrhosis, which is much less frequent in the Western world where hepatitis C virus (HCV) and non-viral etiologies (alcohol and NASH) are predominant. Some of the differences might arise from differences of less well-defined criteria, for example in the definition of which tumor burden can still be treated with TACE or not. Some of the differences might be driven by access to drugs, with different healthcare systems having different criteria for approval and reimbursement of drugs. All these factors make it very important to properly assess the results of treatment in the different populations.

However, in the example of pembrolizumab, the differences of the positivity of the KEYNOTE-240 and KEYNOTE-394 studies seems more related to differences of statistical design than differences of efficacy.

Finally, of course the results of the KEYNOTE-394 should be interpreted in the current context of immune-based combination (3). Since the results of the IMbrave-150 trial were released (11), the first-line treatment for HCC is a combination of an anti-PD-L1 with an anti-VEGF, atezolizumab-bevacizumab, improving mPFS (6.9 versus 4.3 months, HR =0.65, P=0.0001) and mOS (19.2 versus 13.4 months, HR 0.66, P<0.0009) versus sorafenib which was the unique molecule in first-line treatment during more than 10 years (12). More recently, a doublet of immunotherapy with an anti PD-L1 and anti-CTLA-4: durvalumab and tremelimumab, could be used in first line with the positive results of the HIMALAYA study (6).

The potential role for single-agent anti-PD-1 has been

Table 2 Main results from KEYNOTE-240 and KEYNOTE-394

Clinical outcomes	KEYNOTE-240			KEYNOTE-394		
	Pembrolizumab	Placebo	HR	Pembrolizumab	Placebo	HR
mOS	13.9 (95% CI: 11.6 to 16.0) months	10.6 (95% CI: 8.3 to 13.5) months	HR =0.781; 95% CI: 0.611 to 0.998; P=0.0238	14.6 (95% CI: 12.6 to 18.0) months	13.0 (95% CI: 10.5 to 15.1) months	HR =0.79; 95% CI: 0.63 to 0.99; P=0.0180
mPFS	3.0 (95% CI: 2.8 to 4.1) months	2.8 (95% CI: 1.6 to 3.0) months	HR =0.718; 95% CI: 0.570 to 0.904; P=0.0022	2.6 (95% CI: 1.5 to 2.8) months	2.3 (95% CI: 1.4 to 2.8) months	HR =0.74 95% CI: 0.60 to 0.92; P=0.0032
ORR	13.7% (95% CI: 10.0% to 18.1%)	1.3% (95% CI: 0.2% to 4.6%)	–	18.3% (95% CI: 14.0% to 23.4%)	4.4% (95% CI: 1.6% to 9.4%)	–

HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate.

greatly diminished by the validation of these combinations as first-line treatment. Here again, we have differences between Western world and Asia: while the Western countries have positive results only with atezolizumab-bevacizumab and durvalumab-tremelimumab, the Asian investigators also validated two additional combinations: the sintilimab-IBI305 (a bevacizumab biosimilar) (13) and the camrelizumab-rivoceranib (14) combinations. Furthermore, single-agent durvalumab and tislelizumab (6,14) have been demonstrated as non-inferior to sorafenib. It would only be differences of access to the drugs that could justify the sorafenib then pembrolizumab sequence, while other combinations or sequences appear more suitable for most patients.

In conclusion, the success of the KEYNOTE-394 illustrates the major importance of conducting research in every parts of the world, to ensure that results of treatment are generalizable; however, the failure of KEYNOTE-240 illustrates that complicating the statistics might have deleterious effects. But both trials illustrate the increasing role of immunotherapy in HCC.

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Footnote

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