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107

Effect of pembrolizumab on hepatitis B viral load and aminotransferase levels in patients with advanced hepatocellular carcinoma in KEYNOTE-224 and KEYNOTE-240

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INTRODUCTION

- Limited data are available regarding the impact of immune checkpoint inhibitors on patients with hepatocellular carcinoma (HCC) and underlying viral hepatitis
- Patients with cancer with hepatitis B virus (HBV) infection are often excluded from clinical trials; however, published case reports have shown that HBV viral load increases with treatment with immune checkpoint inhibitors[1-3]
- The phase 2 KEYNOTE-224 (NCT02702414) study and phase 3 KEYNOTE-240 (NCT02702401) study of the PD-1 inhibitor pembrolizumab have demonstrated a favorable benefit–risk ratio in the second-line treatment setting for patients with advanced HCC[4,5]
  - Patients receiving nucleos(t)ide analogs with controlled HBV infection at baseline were eligible

AIM

- To evaluate HBV viral load and transaminase levels in patients with HBV infection in the KEYNOTE-224 and KEYNOTE-240 pembrolizumab clinical trials in HCC

METHOD

- The KEYNOTE-224 and KEYNOTE-240 studies assessed the safety and efficacy of pembrolizumab (200 mg every 3 weeks [Q3W]) in patients with advanced HCC following progression during or after treatment with sorafenib or intolerance to sorafenib[4,5]
- Patients with active HBV infection (hepatitis B surface antigen [HBsAg] positive and/or HBV DNA detectable) and inactive HBV infection (antihepatitis B core antigen [HBc] positive, HBsAg negative, and HBV DNA not detectable) at baseline were eligible for both studies
  - Patients with active HBV infection were required to have received antiviral therapy for ≥12 weeks and have an HBV viral load <100 IU/mL prior to first dose of study drug
- HBV viral load and liver transaminases were evaluated Q3W during treatment, at 30 days after last dose, and in all patients with Hepatic Events of Clinical Interest, which were criteria prespecified in the protocols to trigger additional assessment
- The criteria defining potential HBV viral flare were as follows: >1 log increase and 1000 IU/mL viral load with concurrent alanine transaminase (ALT) elevation classified according to 1 of the following 3 criteria occurring within 7 days of time of the viral load increase (baseline ALT <2× upper limit of normal [ULN] and postbaseline ALT ≥5× ULN; baseline ALT ≥2× ULN and postbaseline ALT >3× baseline level; ALT >500 U/L regardless of baseline level)
- Data cutoff dates: February 13, 2018 (KEYNOTE-224), and January 2, 2019 (KEYNOTE-240)

RESULTS

Table 1. Patient Characteristics With HBV Baseline Serology (active and inactive positive)

n (%)	Active HBV Infection[a] KEYNOTE-224 Pembrolizumab n = 8	Active HBV Infection[a] KEYNOTE-240 Pembrolizumab n = 72	Active HBV Infection[a] KEYNOTE-240 Placebo n = 29	Inactive HBV Infection[b] KEYNOTE-224 Pembrolizumab n = 13	Inactive HBV Infection[b] KEYNOTE-240 Pembrolizumab n = 73	Inactive HBV Infection[b] KEYNOTE-240 Placebo n = 29
Sex						
Male	8 (100)	59 (81.9)	25 (86.2)	13 (100)	59 (80.8)	24 (82.8)
Female	0 (0)	13 (18.1)	4 (13.8)	0 (0)	14 (19.2)	5 (17.2)
Age, years (median, range)						
	66 (57-77)	62 (21-85)	58 (45-82)	65 (43-80)	68 (46-84)	67 (51-89)
Race						
Asian	3 (37.5)	58 (80.6)	25 (86.2)	4 (30.8)	36 (49.3)	12 (41.4)
Black/African American	1 (12.5)	6 (8.3)	2 (6.9)	1 (7.7)	6 (8.2)	2 (6.9)
White	3 (37.5)	8 (11.1)	2 (6.9)	8 (61.5)	30 (41.1)	13 (44.8)
Other	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (1.4)	2 (6.8)
Ethnicity						
Hispanic/Latino	0 (0)	0 (0)	0 (0)	0 (0)	4 (5.5)	3 (10.3)
Not Hispanic/Latino	8 (100)	66 (91.7)	28 (96.6)	12 (92.3)	66 (90.4)	26 (89.7)
Not reported/unknown	0 (0)	6 (8.3)	1 (3.4)	1 (7.7)	3 (4.1)	0 (0)
Geographic region						
Asia (excluding Japan)	—	42 (58.3)	19 (65.5)	—	21 (28.8)	8 (27.6)
European Union	5 (62.5)	11 (15.3)	1 (3.4)	5 (38.5)	15 (20.5)	4 (13.8)
Japan	2 (25)	13 (18.1)	6 (20.7)	2 (15.4)	13 (17.8)	4 (13.8)
United States	0 (0)	0 (0)	1 (3.4)	6 (46.2)	11 (15.1)	6 (20.7)
Other	1 (12.5)	6 (8.3)	2 (6.9)	0 (0)	13 (17.8)	7 (24.1)
Child-Pugh Class						
A	7 (87.5)	72 (100)	29 (100)	12 (92.3)	72 (98.6)	29 (100)
B	1 (12.5)	0 (0)	0 (0)	1 (7.7)	1 (1.4)	0 (0)
HBV Antigen						
Positive	0 (0)	11 (15.3)	6 (20.7)	0 (0)	0 (0)	0 (0)
Negative	7 (87.5)	59 (81.9)	23 (79.3)	6 (46.2)	67 (91.8)	21 (72.4)
Not available	1 (12.5)	2 (2.8)	0	7 (53.8)	6 (8.2)	8 (27.6)

[a]Defined as being HBsAg positive and/or HBV DNA detectable.
[b]Defined as being anti-HBc positive, HBsAg negative, and HBV DNA not detectable.

Table 2. Median Durations of Follow-Up and Exposure to Pembrolizumab

	Active HBV Infection[a] KEYNOTE-224 Pembrolizumab n = 8	Active HBV Infection[a] KEYNOTE-240 Pembrolizumab n = 72	Active HBV Infection[a] KEYNOTE-240 Placebo n = 29	Inactive HBV Infection[b] KEYNOTE-224 Pembrolizumab n = 13	Inactive HBV Infection[b] KEYNOTE-240 Pembrolizumab n = 73	Inactive HBV Infection[b] KEYNOTE-240 Placebo n = 29
Median (range) time from first dose to data cutoff, months	14.5 (11.8-19.1)	23.2 (15-28.6)	22.6 (15-29.0)	14.8 (11.9-18.7)	20.7 (13.8-29.5)	21.9 (13.3-27.2)
Median (range) time on therapy, months	5.0 (1.4-13.0)	2.7 (0-23.4)	2.1 (0-9.0)	4.2 (0-12.6)	4.2 (0-24.4)	2.1 (0.7-18.8)

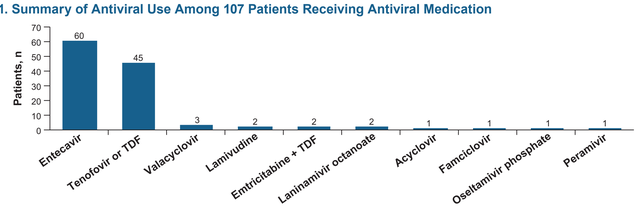
[a]Defined as being HBsAg positive and/or HBV DNA detectable.
[b]Defined as being anti-HBc positive, HBsAg negative, and HBV DNA not detectable.

Table 3. Changes in HBV Viral Load and ALT Levels During Treatment in Patients With Active and Inactive HBV Infection Status

Patients with HBV, n (%)	Active HBV Infection[a] KEYNOTE-224 Pembrolizumab n = 8	Active HBV Infection[a] KEYNOTE-240 Pembrolizumab n = 72	Active HBV Infection[a] KEYNOTE-240 Placebo n = 29	Inactive HBV Infection[b] KEYNOTE-224 Pembrolizumab n = 13	Inactive HBV Infection[b] KEYNOTE-240 Pembrolizumab n = 73	Inactive HBV Infection[b] KEYNOTE-240 Placebo n = 29
>1 log decrease	0 (0)	28 (38.9)	8 (27.6)	0 (0)	1 (1.4)	0 (0)
>1 log increase + 1000 IU/mL	0 (0)	2 (2.8)	1 (3.4)	0 (0)	0 (0)	0 (0)
>2 log increase	0 (0)	3 (4.2)	1 (3.4)	0 (0)	1 (1.4)	0 (0)
>3 log increase	0 (0)	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)
ALT ≥3× BL + >100 U/L post-BL	1 (12.5)	6 (8.3)	3 (10.3)	1 (7.7)	15 (20.6)	2 (6.9)
ALT and AST to >5× ULN and/or >3× BL	1 (12.5)	6 (8.3)	3 (10.3)	0 (0)	12 (16.4)	5 (17.2)
Viral flare[c]	0 (0)	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)
2 log increase + ALT ≥3× BL + >100 U/L post-BL	0 (0)	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)

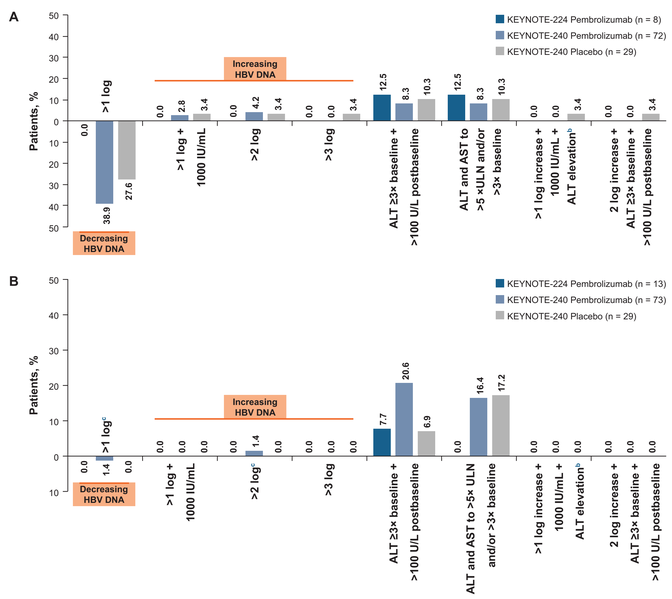
AST, aspartate aminotransferase; BL, baseline.
[a]Defined as being HBsAg positive and/or HBV DNA detectable.
[b]Defined as being anti-HBc positive, HBsAg negative, and HBV DNA not detectable.
[c]Viral flare defined as >1 log increase and 1000 IU/mL viral load with concurrent ALT elevation classified according to 1 of the following 3 criteria within 7 days of time of the viral load increase: 1) BL ALT <2× ULN and post-BL ALT ≥5× ULN, 2) BL ALT ≥2× ULN and post-BL ALT >3× BL level, and 3) ALT >500 U/L regardless of BL level.

Figure 1. Summary of Antiviral Use Among 107 Patients Receiving Antiviral Medication



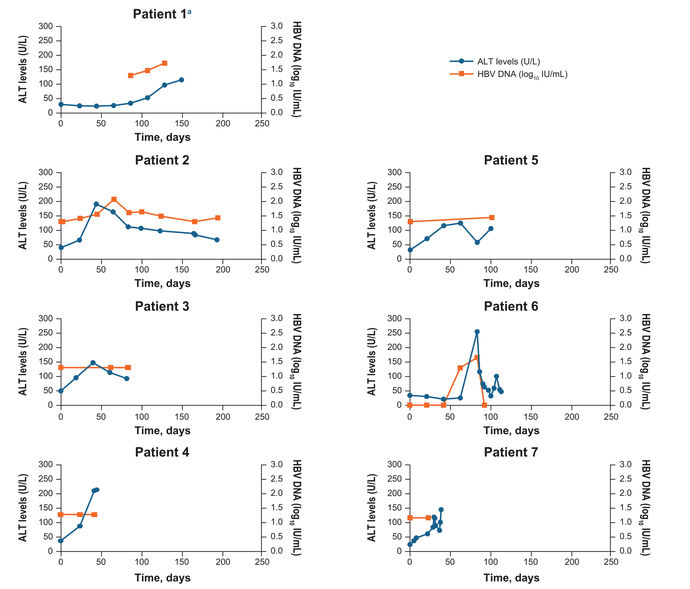
TDF, tenofovir disoproxil fumarate.

Figure 2. Changes in HBV Viral Load and ALT Levels During Treatment in Patients With Active (A) and Inactive (B) HBV Infection Status[a]



[a]Active HBV infection is defined as HBsAg positive and/or HBV DNA detectable. Inactive HBV is defined as anti-HBc positive, HBsAg negative, and HBV DNA not detectable.
[b]ALT elevation was classified according to 1 of 3 criteria ≥ 7 days of time of the viral load increase (baseline ALT <2× ULN and postbaseline ALT ≥5× ULN; baseline ALT ≥2× ULN and postbaseline ALT >3× baseline level; ALT >500 U/L regardless of baseline level).
[c]Among patients with inactive HBV infection, >1 log decrease and >2 log increase in HBV DNA were each reported in separate patients (n = 1 each).

Figure 3. Time Course of ALT and Viral Load Variations for 7 Patients With Active Positive HBV Infection Receiving Pembrolizumab and With ALT ≥3× Baseline and >100 U/L Postbaseline



[a]Patient discontinued therapy due to immune-mediated colitis and had no additional follow-up. At the time of ALT increase, this patient had low-level HBV viremia (20 IU/mL with increase to 50 IU/mL).

CONCLUSIONS

- In the present study, viral load increases and decreases were observed in patients with advanced HCC treated with pembrolizumab
- Few patients with advanced HCC and HBV infection had viral load increases during therapy; however, HBV viral flares were not observed in patients receiving pembrolizumab
- No pembrolizumab discontinuation was observed due to HBV viral load increase or flare
- These data suggest that pembrolizumab is unlikely to significantly affect underlying HBV infection in patients with advanced HCC receiving HBV antiviral therapy

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