original reports

Pembrolizumab Versus Placebo as Second-Line Therapy in Patients From Asia With Advanced Hepatocellular Carcinoma: A Randomized, Double-Blind, Phase III Trial

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abstract

PURPOSE We evaluated the efficacy and safety of pembrolizumab in patients from Asia with previously treated advanced hepatocellular carcinoma (HCC).

METHODS In a double-blind, phase III trial, 453 patients with advanced HCC and progression during or after treatment with or intolerance to sorafenib or oxaliplatin-based chemotherapy were randomly assigned in a 2:1 ratio to receive pembrolizumab (200 mg) or placebo once every 3 weeks for ≤ 35 cycles plus best supportive care. The primary end point was overall survival (one-sided significance threshold, $P = .0193$ [final analysis]). Secondary end points included progression-free survival (PFS) and objective response rate (ORR; one-sided significance threshold, $P = .0134$ and .0091, respectively [second interim analysis]; RECIST version 1.1, by blinded independent central review).

RESULTS Median overall survival was longer in the pembrolizumab group than in the placebo group (14.6 *v* 13.0 months; hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; $P = .0180$). Median PFS was also longer in the pembrolizumab group than in the placebo group (2.6 *v* 2.3 months; hazard ratio for progression or death, 0.74; 95% CI, 0.60 to 0.92; $P = .0032$). ORR was greater in the pembrolizumab group (12.7% [95% CI, 9.1 to 17.0]) than in the placebo group (1.3% [95% CI, 0.2 to 4.6]; $P < .0001$). Treatment-related adverse events occurred in 66.9% of patients (grade 3, 12.0%; grade 4, 1.3%; grade 5, 1.0%) in the pembrolizumab group and 49.7% of patients (grade 3, 5.9%; grade 4, 0%; grade 5, 0%) in the placebo group.

CONCLUSION In patients from Asia with previously treated advanced HCC, pembrolizumab significantly prolonged overall survival and PFS, and ORR was greater versus placebo.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Primary liver cancer is a leading type of cancer and a cause of cancer-related mortality worldwide. It was the sixth most common type of cancer and third most common cause of cancer-related death in 2020, with 905,677 new cases and 830,180 deaths reported.[1] The incidence and mortality are especially high in Eastern Asia, where 491,687 new cases and 449,534 deaths were reported in that same year.[1] Disease burden is also high in Northern America, with 46,599 new cases and 34,818 deaths reported in 2020.[1] Hepatocellular carcinoma (HCC) is the main histologic type of primary liver cancer,[2] and patients are often diagnosed with advanced-stage disease not amenable to curative treatment approaches in most regions of the world.[3] Although advances in antiangiogenic therapy and immunotherapy have improved clinical outcomes in the first- and second-line treatment setting,[4-9] availability differs across the globe and there is a paucity of data from phase III clinical studies supporting single-agent second-line immune checkpoint inhibitors.[10-12] There is high unmet medical need for treatment options that are tolerable and prolong survival.

The programmed death 1 (PD-1) inhibitor pembrolizumab received accelerated approval from the US Food and Drug Administration in November 2018 on the basis of the global phase II KEYNOTE-224 study in patients with advanced HCC previously treated with sorafenib.[7] In this study, pembrolizumab demonstrated antitumor activity and a manageable adverse event profile. A similar favorable benefit-to-risk profile

CONTEXT

Key Objective

KEYNOTE-394 evaluated the efficacy and safety of pembrolizumab plus best supportive care versus placebo plus best supportive care in patients from Asia with previously treated advanced hepatocellular carcinoma (HCC).

Knowledge Generated

Pembrolizumab showed statistically significant and clinically meaningful improvement in overall survival, progression-free survival, and objective response rate compared with placebo in patients from Asia with advanced HCC and disease progression or intolerance to sorafenib or oxaliplatin-based chemotherapy. Adverse events were manageable and consistent with the known safety profile of pembrolizumab in previously treated patients with advanced HCC.

Relevance *(E.M. O'Reilly)*

This study adds to the body of evidence pertaining to the role of immune checkpoint blockade in HCC.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

for pembrolizumab when added to best supportive care (BSC) compared with placebo when added to BSC was observed in the global phase III KEYNOTE-240 study; however, the study narrowly missed prespecified statistical significance criteria for overall survival (OS) or progression-free survival (PFS).[8] We conducted the KEYNOTE-394 study to determine whether pembrolizumab plus BSC would improve efficacy compared with placebo plus BSC in patients from Asia with advanced HCC who were previously treated with sorafenib or oxaliplatin-based chemotherapy (ClinicalTrials.gov identifier: NCT03062358).

METHODS

Patients

Eligible patients were adults with confirmed HCC, radiographic progression during or after treatment with or intolerance to sorafenib or oxaliplatin-based chemotherapy, Barcelona Clinic Liver Cancer (BCLC) stage C or B[13] disease not amenable to or refractory to locoregional therapy and not amenable to curative treatment, Child-Pugh A liver score, Eastern Cooperative Oncology Group performance status of 0 or 1,[14] $\geq$ 1 measurable lesion per investigator-assessed RECIST version 1.1, and adequate organ function (Data Supplement, online only). Patients with past or ongoing hepatitis C virus (HCV) or controlled hepatitis B virus (HBV) infection were eligible if protocol-defined criteria were met. HCV infection was defined as antihepatitis C antibody–positive and detectable HCV RNA, and HBV infection was defined as hepatitis B surface antigen–positive and/or detectable HBV DNA. Full eligibility criteria are provided in the Protocol (online only).

An independent external data monitoring committee assessed safety and efficacy throughout the study and at interim analyses. The study protocol and all amendments were approved by the relevant ethics committee or institutional review board at each participating center, and the study was conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Study Design and Treatments

This randomized, double-blind, phase III study was conducted in mainland China, Hong Kong, Republic of Korea, Malaysia, and Taiwan. Patients were randomly assigned in a 2:1 ratio to receive pembrolizumab (200 mg) or saline placebo intravenously once every 3 weeks. Random assignment was performed centrally using an interactive voice response system/integrated web-response system and was stratified by prior treatment (sorafenib *v* chemotherapy), macrovascular invasion (yes *v* no), and HCC etiology (HBV *v* other [HCV or noninfected]). Patients were permitted to receive BSC per local guidelines. Full details regarding treatment and adverse event management are provided in the Data Supplement and Protocol.

Assessments and End Points

The primary end point was OS. Secondary end points were PFS, the objective response (confirmed complete or partial response) rate (ORR), duration of response, disease control rate, and time to progression, all assessed per RECIST version 1.1 by blinded independent central review, and safety and tolerability. Additional details on assessments and end points are provided in the Data Supplement.

Statistical Analysis

The statistical analysis plan is provided in the protocol. Efficacy was assessed in all randomly assigned patients. Safety was assessed in all randomly assigned patients who received $\geq$ 1 dose of study treatment. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. The comparison of treatment groups was performed using the stratified log-rank test (OS and PFS) and the stratified Miettinen and Nurminen method[15] (ORR). Estimation of the hazard ratio was done

using a stratified Cox regression model and Efron's method of handling ties. Random assignment was initially stratified by prior treatment, macrovascular invasion, and HCC etiology; however, during enrollment, it was noted that a small proportion of patients had prior chemotherapy use and were not HBV-positive. Therefore, stratifying analyses by prior treatment and HCC etiology was no longer useful. Thus, stratification factors for stratified analyses were changed to macrovascular invasion (yes *v* no), α-fetoprotein (< 200 *v* ≥ 200 ng/mL), and region (China *v* ex-China), with all cells corresponding to macrovascular invasion yes combined. Sensitivity analysis with the strata per the original protocol was not performed because some strata were prohibitively small, but a post hoc sensitivity analysis using an unstratified log-rank test was performed.

The overall type I error across the OS, PFS, and ORR hypotheses was strongly controlled at a one-sided alpha level of 0.025 by the graphical approach of Maurer and Bretz[16] (Data Supplement). The second interim analysis was the final analysis time point for testing superiority of PFS and ORR.

RESULTS

Patients and Treatment

Between May 31, 2017, and December 11, 2019, 453 patients were randomly assigned to pembrolizumab (n = 300) or placebo (n = 153), both given with BSC. One patient assigned to pembrolizumab did not receive treatment (Fig 1). Median follow-up at final analysis, defined as the time from random assignment to data cutoff (June 30, 2021), was 33.8 months (range, 18.7-49.0 months). At final analysis, 24 of 299 patients (8.0%) in the pembrolizumab group completed 35 cycles of treatment, and 12 of 299 (4.0%) were still receiving treatment; no patient in the placebo group completed 35 cycles of treatment and all 153 patients discontinued treatment. The most common reason for treatment discontinuation in both groups was progressive disease (pembrolizumab, 67.2%; placebo, 81.7%).

Baseline demographic and disease characteristics were generally balanced in the pembrolizumab and placebo groups (Table 1). Across both treatment groups, median age was 54.0 years, 84.5% were male, 100.0% had Child-Pugh liver classification A, and 93.4% had BCLC stage C disease. Most patients had previously been treated with sorafenib (pembrolizumab, 90.7%; placebo, 90.8%) compared with oxaliplatin-based chemotherapy (pembrolizumab, 9.3%; placebo, 9.2%). There were 78.7% and 81.0% of patients in the pembrolizumab and placebo groups who were positive for HBV (hepatitis B surface antigen–positive and/or detectable HBV DNA), respectively.

Efficacy

At the final analysis, 222 patients (74.0%) in the pembrolizumab group and 128 patients (83.7%) in the placebo group had died. OS was significantly improved in the pembrolizumab group compared with the placebo group (median, 14.6 months [95% CI, 12.6 to 18.0] *v* 13.0 months

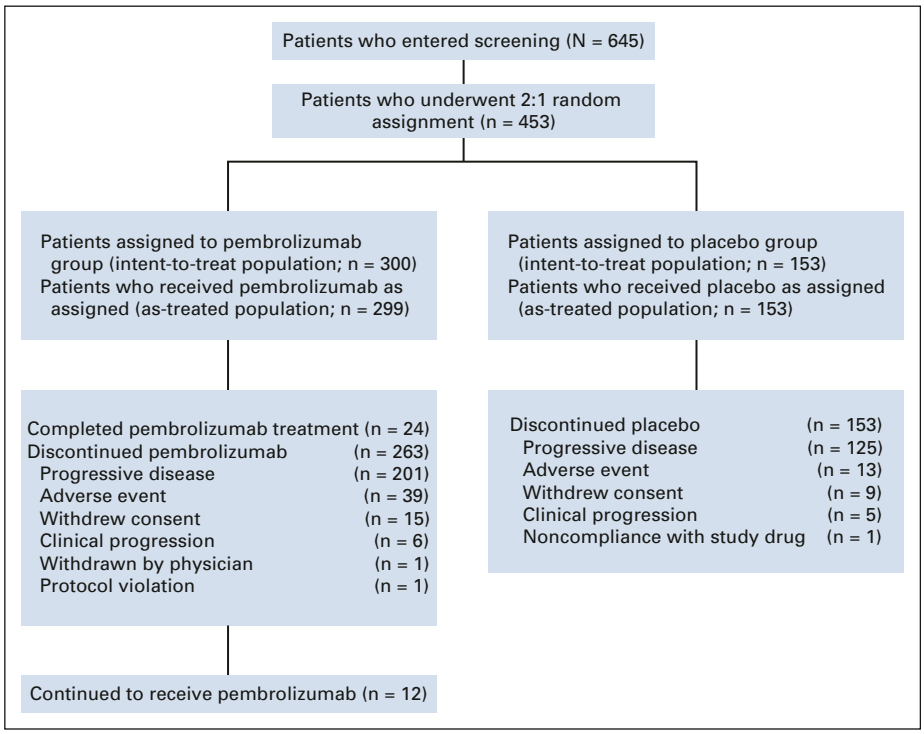

FIG 1. CONSORT diagram.

TABLE 1. Demographic and Disease Characteristics of the Patients at Baseline (intention-to-treat population)[a]

Characteristic	Pembrolizumab + Best Supportive Care (n = 300)	Placebo + Best Supportive Care (n = 153)
Age, years, median (range)	54 (22-82)	54 (22-78)
≥ 65 years	69 (23.0)	29 (19.0)
Male	257 (85.7)	126 (82.4)
Region[b]		
China	255 (85.0)	132 (86.3)
Ex-China	45 (15.0)	21 (13.7)
Eastern Cooperative Oncology Group performance status score[c]		
0	124 (41.3)	60 (39.2)
1	176 (58.7)	93 (60.8)
Child-Pugh classification A	300 (100.0)	153 (100.0)
α-Fetoprotein level, ng/mL		
< 200	131 (43.7)	75 (49.0)
≥ 200	169 (56.3)	78 (51.0)
Extrahepatic spread	232 (77.3)	120 (78.4)
Macrovascular invasion	33 (11.0)	17 (11.1)
Hepatitis B status		
Positive[d]	236 (78.7)	124 (81.0)
Negative	64 (21.3)	29 (19.0)
Hepatitis C status		
Positive[e]	5 (1.7)	1 (0.7)
Negative	295 (98.3)	152 (99.3)
Current disease overall Barcelona Clinic Liver Cancer stage[f]		
B	23 (7.7)	7 (4.6)
C	277 (92.3)	146 (95.4)
Prior first-line treatment		
Sorafenib	272 (90.7)	139 (90.8)
Oxaliplatin-based chemotherapy	28 (9.3)	14 (9.2)
Prior treatment intolerant/progressed		
Oxaliplatin-based chemotherapy progressive disease	25 (8.3)	14 (9.2)
Oxaliplatin-based chemotherapy intolerance	3 (1.0)	0 (0.0)
Sorafenib progressive disease	243 (81.0)	132 (86.3)
Sorafenib intolerance	29 (9.7)	7 (4.6)
Prior locoregional therapy	234 (78.0)	125 (81.7)
Prior treatment surgery	199 (66.3)	106 (69.3)
Prior treatment radiation	66 (22.0)	39 (25.5)

NOTE. Data are No. (%) unless otherwise indicated.

[a]The intention-to-treat population includes all randomly assigned patients. Percentages may not equal 100 because of rounding.

[b]Region for China includes mainland China, Hong Kong, and Taiwan; region for ex-China includes Republic of Korea and Malaysia.

[c]The Eastern Cooperative Oncology Group performance status classification uses a 5-point scale, with 0 indicating no symptoms and higher scores indicating increasing disability.[14]

[d]Hepatitis B status was collected from the electronic case report form and positive was defined as hepatitis B surface antigen–positive and/or detectable hepatitis B virus DNA on the basis of investigator assessment.

[e]Hepatitis C was collected from the electronic case report form and positive was defined as antihepatitis C antibody positive and detectable hepatitis C virus RNA on the basis of investigator assessment.

[f]The Barcelona Clinic Liver Cancer staging system is based on a 5-stage scale, with 0 indicating very early disease and consecutive letters indicating more advanced-stage disease.[13]

[95% CI, 10.5 to 15.1]; hazard ratio for death, 0.79 [95% CI, 0.63 to 0.99]; $P = .0180$, which was below the prespecified P value boundary of .0193 for OS at the final analysis; Fig 2A). A post hoc sensitivity analysis that evaluated OS without adjusting for stratification factors in log-rank test yielded results similar to the primary analysis (hazard ratio for death, 0.79 [95% CI, 0.63 to 0.98]; nominal $P = .0156$). The estimated percentage of patients alive at 12, 24, and 36 months was 57.0% (95% CI, 51.2 to 62.4), 34.3% (95% CI, 28.8 to 39.8), and 23.4% (95% CI, 18.0 to 29.3) in the pembrolizumab group and 52.9% (95% CI, 44.7 to 60.5), 24.9% (95% CI, 18.3 to 32.1), and 11.0% (95% CI, 5.9 to 17.9) in the placebo group. Subgroup analyses showed that the treatment effect on OS was generally consistent across major subgroups (Data Supplement).

At the second interim analysis, which had a data cutoff date of June 30, 2020, PFS was significantly improved in the pembrolizumab group compared with the placebo group (median, 2.6 months [95% CI, 1.5 to 2.8] *v* 2.3 months [95% CI, 1.4 to 2.8]; hazard ratio for progression or death, 0.74 [95% CI, 0.60 to 0.92]; $P = .0032$, which was below the prespecified P value boundary of .0134 for PFS at the second interim analysis; Fig 2B). The estimated percentage of patients who were alive without disease progression at 12 and 18 months was 15.9% (95% CI, 11.6 to 20.9) and 11.8% (95% CI, 7.8 to 16.7) in the pembrolizumab group and 1.4% (95% CI, 0.1 to 6.4) and 0% (95% CI, not estimable [NE] to NE) in the placebo group, respectively. The effect of pembrolizumab on PFS was generally consistent across protocol-specified subgroups (Data Supplement).

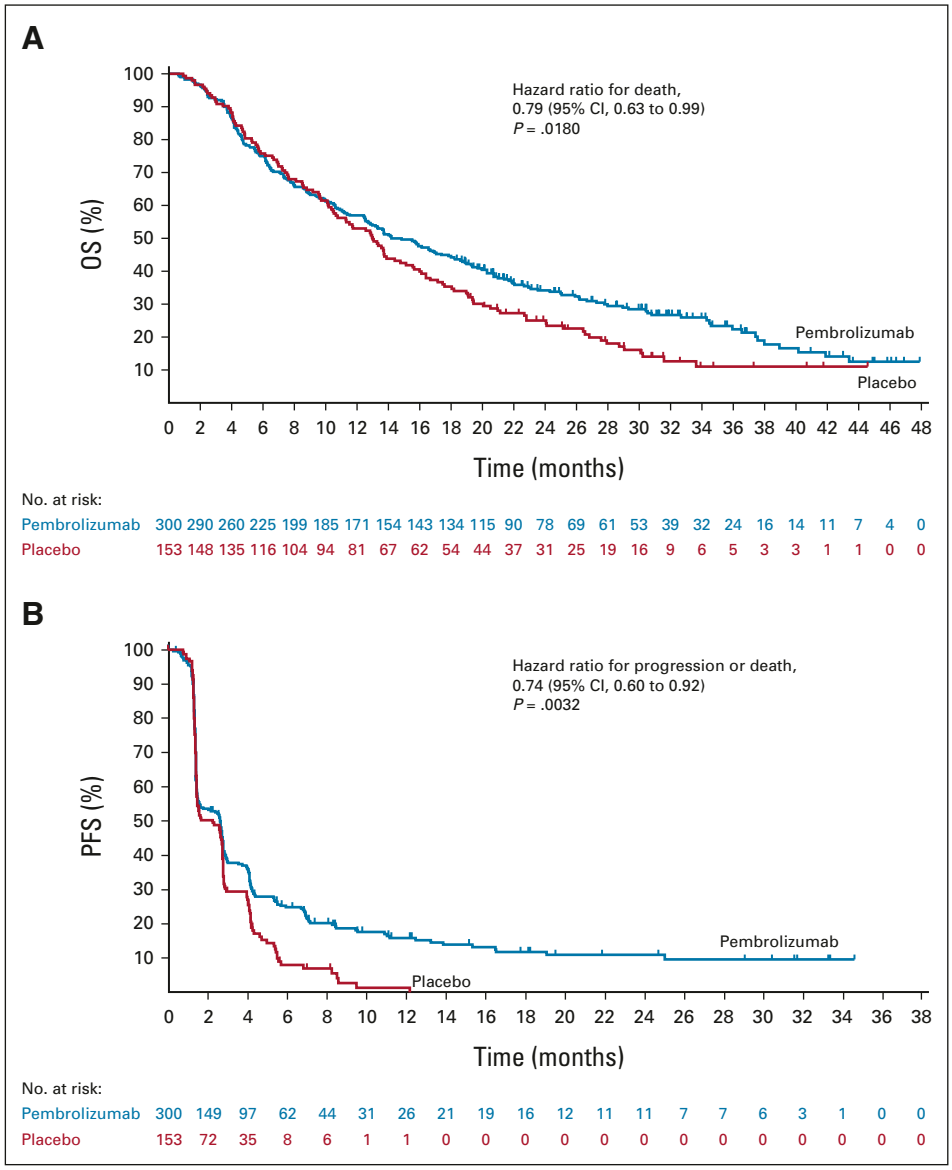

FIG 2. Kaplan-Meier analysis of (A) OS at final analysis and (B) PFS at the second interim analysis. OS, overall survival; PFS, progression-free survival.

Improvement in PFS with pembrolizumab was maintained at final analysis (hazard ratio for progression or death, 0.74; 95% CI, 0.59 to 0.92; Data Supplement). The estimated percentage of patients who were alive without disease progression at 24 months was 11.2% (95% CI, 7.6 to 15.6) in the pembrolizumab group and 0% (95% CI, NE to NE) in the placebo group. The median time to progression was 2.7 months (95% CI, 1.5 to 2.8) in the pembrolizumab group and 1.7 months (95% CI, 1.4 to 2.8) in the placebo group at the final analysis (hazard ratio for progression, 0.72 [95% CI, 0.58 to 0.90]; Data Supplement).

The ORR at the second interim analysis was significantly higher in the pembrolizumab group (12.7% [95% CI, 9.1 to 17.0]) than in the placebo group (1.3% [95% CI, 0.2 to 4.6]; estimated treatment difference, 11.4% [95% CI, 6.7 to 16.0]; $P < .0001$, which was below the prespecified P value boundary of .0091 for ORR at the second interim analysis; Table 2). At the time of the final analysis, the ORR was 13.7% (95% CI, 10.0 to 18.1) in the pembrolizumab group and 1.3% (95% CI, 0.2 to 4.6) in the placebo group (estimated treatment difference, 12.3% [95% CI, 7.5 to 17.1]; Data Supplement). The disease control rate was 52.7% (95% CI, 46.8 to 58.4) in the pembrolizumab group and 47.7% (95% CI, 39.6 to 55.9) in the placebo group at the final analysis. In the pembrolizumab group, the number of complete responders increased from six at the second interim analysis to nine at final analysis; there was one complete responder in the placebo group at both analyses.

Median duration of response was longer for the 41 responders in the pembrolizumab group (23.9 months) than the two responders in the placebo group (5.6 months) at final analysis (Data Supplement).

After discontinuation of study treatment, 152 patients (50.7%) in the pembrolizumab group and 102 patients (66.7%) in the placebo group received systemic anticancer therapy; 62 patients (20.7%) and 43 patients (28.1%), respectively, received PD-1/programmed death ligand 1 (PD-L1) inhibitors (Data Supplement).

Safety

The median treatment duration was 3.3 months (range, 0.03-27.3 months) for the pembrolizumab group and 2.2 months (range, 0.03-15.5 months) for the placebo group. Adverse events occurred in 283 patients (94.6%; grade 3, n = 122 [40.8%]; grade 4, n = 25 [8.4%]; grade 5, n = 10 [3.3%]) in the pembrolizumab group and 147 patients (96.1%; grade 3, n = 41 [26.8%]; grade 4, n = 7 [4.6%]; grade 5, n = 2 [1.3%]) in the placebo group. Adverse events leading to discontinuation occurred in 38 patients (12.7%) in the pembrolizumab group and 12 patients (7.8%) in the placebo group. The most frequent adverse events leading to discontinuation were ascites (pembrolizumab n = 7 [2.3%]; placebo n = 1 [0.7%]), increased blood bilirubin (pembrolizumab n = 4 [1.3%]; placebo n = 2 [1.3%]), and hepatic encephalopathy (pembrolizumab n = 3 [1.0%]; placebo n = 0). Adverse

TABLE 2. Confirmed Response at the Second Interim Analysis (intention-to-treat population)[a]

Confirmed Response	Pembrolizumab + Best Supportive Care (n = 300)	Placebo + Best Supportive Care (n = 153)
Objective response rate, % (95% CI)	12.7 (9.1 to 17.0)	1.3 (0.2 to 4.6)
Estimated treatment difference (95% CI)	11.4 (6.7 to 16.0)[b]	
P[c]	< .0001	
Disease control, No. (%)	153 (51.0)	72 (47.1)
Best overall response, No. (%)		
Complete response	6 (2.0)	1 (0.7)
Partial response	32 (10.7)	1 (0.7)
Stable disease	115 (38.3)	70 (45.8)
Sustained stable disease[d]	26 (8.7)	8 (5.2)
Progressive disease	129 (43.0)	72 (47.1)
Not evaluable	10 (3.3)	1 (0.7)
No assessment[e]	8 (2.7)	8 (5.2)
Duration of response, months, median (range)[f]	23.9 (2.8 to 32.0+)	5.6 (3.0+ to 5.6)

[a]The intention-to-treat population includes all randomly assigned patients.

[b]On the basis of Miettinen and Nurminen method stratified by macrovascular invasion (yes *v* no), α-fetoprotein level (ng/mL) (< 200 *v* ≥ 200), and region (China *v* ex-China), with all cells that correspond to macrovascular invasion (defined as yes) combined.

[c]One-sided P for testing difference.

[d]Duration of stable disease ≥ 23 weeks (stable disease within 24-week scan window or later).

[e]Includes patients with a baseline assessment (by investigator or blinded independent central review) but no postbaseline assessment on the data cutoff date, including discontinuation or death before the first postbaseline scan.

[f]Calculated in the 38 patients in the pembrolizumab group and two patients in the placebo group who had a confirmed complete response or partial response.

events leading to death occurred in 10 patients (3.3%) in the pembrolizumab group and two patients (1.3%) in the placebo group.

Two hundred patients (66.9%) in the pembrolizumab group and 76 patients (49.7%) in the placebo group experienced treatment-related adverse events (Table 3). In the pembrolizumab group, the most common treatment-related adverse events were increased aspartate aminotransferase levels (12.0%), increased alanine aminotransferase levels (11.7%), and rash (11.7%). In the placebo group, the most common treatment-related adverse events were increased aspartate aminotransferase levels (11.1%), increased alanine aminotransferase levels (9.2%), and pyrexia (5.9%). Treatment-related adverse events leading to discontinuation occurred in 12 patients (4.0%) in the pembrolizumab group and one patient (0.7%) in the placebo group. Three grade 5 treatment-related adverse events according to investigators occurred in the pembrolizumab group (one each for gastrointestinal hemorrhage, immune-mediated hepatitis [confounded by metastasis to both lungs and lymphatic metastasis with chylous ascites resulting in circulatory failure], and soft tissue infection); no grade 5 treatment-related adverse events occurred in the placebo group.

All-cause immune-mediated adverse events and infusion reactions, based on a list of terms prepared by the sponsor regardless of attribution to study treatment by the investigator, occurred in 54 patients (18.1%; grade 3, n = 6 [2.0%]; grade 4, n = 2 [0.7%]; grade 5, n = 1 [0.3%]) in the pembrolizumab group and 16 patients (10.5%; all grade 1 or 2) in the placebo group (Data Supplement). There were nine patients (16.7%) in the pembrolizumab group and two patients (12.5%) in the placebo group who received corticosteroid for immune-mediated adverse events. In the pembrolizumab group, four patients received corticosteroid for immune-mediated hepatitis, two patients for severe skin reactions, and one patient each for hypophysitis, nephritis, and pneumonitis. In the placebo group, one patient received corticosteroid for infusion reaction and one patient for hypothyroidism and hyperthyroidism. Immune-mediated hepatitis prespecified by the sponsor occurred in five patients (1.7%) in the pembrolizumab group, and one patient (0.3%) died of immune-mediated hepatitis. No patient in the placebo group experienced immune-mediated hepatitis by sponsor review. Infusion reactions occurred in one patient (0.3%) in the pembrolizumab group and two patients (1.3%) in the placebo group; all were grade 1 or 2.

DISCUSSION

In the phase III KEYNOTE-394 study, pembrolizumab plus BSC showed a statistically significant and clinically meaningful improvement in OS compared with placebo plus BSC in patients from Asia with advanced HCC and disease progression or intolerance to sorafenib or oxaliplatin-based chemotherapy. Additionally, statistically significant improvements in PFS and ORR were observed with pembrolizumab compared with placebo. Pembrolizumab plus BSC was associated with a manageable adverse event profile, with adverse events consistent with the known safety profile in previously treated patients with advanced HCC.

The results from the current study involving patients from Asia are generally comparable with the results reported for pembrolizumab monotherapy in the second-line treatment of advanced HCC in global patient populations.[7,8] Of note, in the phase III global KEYNOTE-240 study and the current study, the OS hazard ratios were similar (0.78 [95% CI, 0.61 to 1.0] and 0.79 [95% CI, 0.63 to 0.99], respectively).[8] PFS hazard ratios in each study were also comparable (KEYNOTE-240 [final analysis]: 0.72 [95% CI, 0.57 to 0.90] and KEYNOTE-394 [second interim analysis]: 0.74 [95% CI, 0.60 to 0.92]). A similar trend for ORR with pembrolizumab versus placebo was seen in both studies (KEYNOTE-240, 13.8%; KEYNOTE-394, 11.4%). Interpretation of these results should consider differences in baseline demographic and disease characteristics. Compared with the KEYNOTE-240 study, more patients in the current study in the pembrolizumab group were younger (median age, 54 *v* 67 years), had BCLC stage C disease (92.3% *v* 79.9%), an α-fetoprotein level $\geq$ 200 ng/mL (56.3% *v* 46.4%), HBV-positive (78.7% *v* 25.9%), and received PD-1/L1 inhibitors after discontinuation of study treatment (20.7% *v* 6.8%).[8] Although the current study comprised a large proportion of patients with HBV-related HCC, patients in the pembrolizumab group did not achieve higher response rates compared with the KEYNOTE-240 study, which comprised a small proportion of patients with HBV-related HCC. In addition to comparable efficacy between the current study and KEYNOTE-240 study, the safety profile for pembrolizumab was similar in both studies. The results observed in the current study expand on previous findings from KEYNOTE-240, a globally conducted study of similar design, inclusion/exclusion criteria, and end points, and on findings from KEYNOTE-224, a globally conducted phase II study in a similar patient population.[7] Collectively, these observations support the favorable benefit-to-risk profile of pembrolizumab in patients globally with previously treated advanced HCC.

Morbidity and mortality of HCC are high, especially in Eastern Asia,[1] and there is a high unmet need for treatment options that prolong survival and have manageable adverse events. Despite advances in the first-line treatment setting, including approval of atezolizumab plus bevacizumab (IMbrave150)[4] and durvalumab plus tremelimumab (HIMALAYA),[9] data from phase III clinical studies supporting single-agent second-line immune checkpoint inhibitors are limited. In the current study, pembrolizumab plus BSC improved survival outcomes for patients with advanced HCC, with some patients experiencing longer-term benefit evidenced by

TABLE 3. Any Grade Treatment-Related Adverse Events Occurring in 5% or More Patients in Either Group or Grade 3-5 Treatment-Related Adverse Events Occurring in All Patients (as-treated population)[a,b]

Treatment-Related Adverse Events	Pembrolizumab + Best Supportive Care (n = 299)			Placebo + Best Supportive Care (n = 153)		
Event	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any treatment-related adverse event	200 (66.9)	36 (12.0)	4 (1.3)	76 (49.7)	9 (5.9)	0 (0.0)
Increased aspartate aminotransferase	36 (12.0)	7 (2.3)	0 (0.0)	17 (11.1)	3 (2.0)	0 (0.0)
Increased alanine aminotransferase	35 (11.7)	5 (1.7)	1 (0.3)	14 (9.2)	2 (1.3)	0 (0.0)
Rash	35 (11.7)	1 (0.3)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)
Pruritus	32 (10.7)	0 (0.0)	0 (0.0)	4 (2.6)	0 (0.0)	0 (0.0)
Increased blood bilirubin	27 (9.0)	2 (0.7)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)
Hypothyroidism	25 (8.4)	0 (0.0)	0 (0.0)	8 (5.2)	0 (0.0)	0 (0.0)
Decreased white blood cell count	25 (8.4)	1 (0.3)	0 (0.0)	8 (5.2)	0 (0.0)	0 (0.0)
Diarrhea	22 (7.4)	2 (0.7)	0 (0.0)	6 (3.9)	0 (0.0)	0 (0.0)
Decreased platelet count	22 (7.4)	4 (1.3)	0 (0.0)	6 (3.9)	1 (0.7)	0 (0.0)
Pyrexia	21 (7.0)	1 (0.3)	0 (0.0)	9 (5.9)	0 (0.0)	0 (0.0)
Proteinuria	19 (6.4)	2 (0.7)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)
Decreased neutrophil count	16 (5.4)	5 (1.7)	2 (0.7)	8 (5.2)	0 (0.0)	0 (0.0)
Hyperthyroidism	15 (5.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Increased blood alkaline phosphatase	10 (3.3)	0 (0.0)	0 (0.0)	2 (1.3)	1 (0.7)	0 (0.0)
Increased gamma-glutamyltransferase	10 (3.3)	5 (1.7)	0 (0.0)	5 (3.3)	3 (2.0)	0 (0.0)
Decreased lymphocyte count	8 (2.7)	1 (0.3)	0 (0.0)	2 (1.3)	1 (0.7)	0 (0.0)
Increased bilirubin conjugated	5 (1.7)	2 (0.7)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Pneumonitis	5 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated hepatitis	4 (1.3)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Chest discomfort	4 (1.3)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Hepatic function abnormal	4 (1.3)	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypophosphatemia	4 (1.3)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Increased blood lactate dehydrogenase	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protein urine present	3 (1.0)	1 (0.3)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Decreased weight	2 (0.7)	1 (0.3)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Hyponatremia	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Neutropenia	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Stress urinary incontinence	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute hepatic failure	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ascites	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypercholesterolemia	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated nephritis	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis bullous	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile infection	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophysitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. Data are No. (%).

[a]The as-treated population includes all randomly assigned patients who received at least one dose of study treatment.

[b]Three grade 5 treatment-related adverse events occurred in the pembrolizumab group (gastrointestinal hemorrhage, n = 1; immune-mediated hepatitis [confounded by metastasis to both lungs and lymphatic metastasis with chylous ascites resulting in circulatory failure], n = 1; soft tissue infection, n = 1). No grade 5 treatment-related adverse events occurred in the placebo group.

greater estimated proportions of patients who were alive in the pembrolizumab group compared with the placebo group at 12 (57.0% *v* 52.9%), 24 (34.3% *v* 24.9%), and 36 (23.4% *v* 11.0%) months, and greater estimated proportions of patients who were alive and progression-free in the pembrolizumab group compared with the placebo group at 12 (15.9% *v* 1.4%) and 18 (11.8% *v* 0%) months. Pembrolizumab offers patients a treatment option with a different safety profile than currently available treatments and is also an important option for patients with contraindications to vascular endothelial growth factor inhibitors or those who are not able to tolerate combination immunotherapy.

The KEYNOTE-394 study allowed inclusion of patients who received prior first-line treatment with oxaliplatin-based chemotherapy, which is not a globally approved first-line standard-of-care treatment but is a treatment option in some Asian countries. Although < 10% of patients were previously treated with oxaliplatin-based chemotherapy, this is a limitation of the current study. Another limitation is the small sample sizes of some protocol-specified subgroups, specifically those with HCV and nonviral etiologies of HCC. However, a primary risk factor for HCC in East Asian countries is HBV infection: approximately 80% of newly diagnosed HCC is attributed to chronic infection with HBV.[17,18] Therefore, the present study, which included a large majority of patients from China, is consistent with published reports on the geographic variability of risk factors for HCC.[17,18] Approximately 80% of patients were HBV-positive and six patients (< 2% of patients) were HCV-positive; two of these six patients were also HBV-positive. Therefore, the number of patients whose HCC had an HCV etiology is too small for a meaningful subgroup analysis. The effect of poststudy therapies on postprogression survival is also another limitation as this may have attenuated the observed treatment effect. The proportion of patients who received poststudy PD-1/L1 inhibitors following progression (pembrolizumab, 20.7%; placebo, 28.1%) was primarily driven by availability of treatment options in Asia at the time of the study. In mainland China, where approximately 80% of patients were enrolled, few PD-1/L1 inhibitors were approved in the second-line treatment setting of advanced HCC. Camrelizumab[12] was approved in 2020 and tislelizumab[10,11] was approved in 2021; the last patient was enrolled in the KEYNOTE-394 study in December 2019. Pembrolizumab is not approved in mainland China for the treatment of advanced HCC.

In conclusion, pembrolizumab plus BSC significantly improved OS, PFS, and ORR compared with placebo plus BSC in patients from Asia with advanced HCC and progression on or intolerance to sorafenib or oxaliplatin-based chemotherapy. The data in this study reinforce observations in globally conducted studies for pembrolizumab in the second-line treatment of advanced HCC, and support its use as a single agent in this setting.

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[5]Hunan Cancer Hospital, Changsha, China
[6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[7]Fudan University Shanghai Cancer Center, Shanghai, China
[8]Harbin Medical University Cancer Hospital, Harbin, China
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CLINICAL TRIAL INFORMATION

KEYNOTE-394 (NCT03062358)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the

scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab Versus Placebo as Second-Line Therapy in Patients From Asia With Advanced Hepatocellular Carcinoma: A Randomized, Double-Blind, Phase III Trial

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Travel, Accommodations, Expenses: Merck

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Investigators

Country/Region	Site Name	Principal Investigator
China	The First Hospital of Jilin University	Li, Wei
	Jilin Cancer Hospital	Cheng, Ying
	Jiangsu Cancer Hospital	Zhu, Liangjun
	The First Affiliated Hospital of Anhui Medical University	Gu, Kangsheng
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	Bengbu Medical College First Affiliated Hospital	Wang, Zishu
	Wuhan Tongji Hospital	Yuan, Xianglin
	The First Affiliated Hospital of Dalian Medical University	Liu, Jiwei
	Yangzhou No. 1 People's Hospital	Tong, Jiandong
	Fudan University Shanghai Cancer Center	Meng, Zhiqiang
	The First Affiliated Hospital of Soochow University	Tao, Min
	The Third Xiangya Hospital of Central South University	Cao, Peiguo
	Hunan Cancer Hospital	Xu, Ruocai
	Nantong Tumor Hospital	Xu, Aibing
	West China Hospital of Sichuan University	Wang, Xin
	Anhui Provincial Hospital	Pan, Yueyin
	The First People's Hospital of Foshan	Wang, Wei
	The First Affiliated Hospital Zhejing University	Fang, Weijia
	Hubei Cancer Hospital	Zhang, Feng

(continued on following page)

TABLE A1. List of Investigators (continued)

Country/Region	Site Name	Principal Investigator
Hong Kong	Princess Margaret Hospital	Cheng, Ashley
	Pamela Youde Nethersole Eastern Hospital	WaiMan, Sarah
	Hong Kong Sanatorium Hospital	Chua, Tsin Tien Daniel
Malaysia	University Malaya Medical Center	Ho, Gwo Fuang
	Beacon Hospital Sdn Bhd	Abdul Wahid, Mohamed Ibrahim
	Hospital Universiti Kebangsaan	Ismail, Fuad
South Korea	Samsung Medical Center	Lim, Ho Yeong
	Asan Medical Center	Ryoo, Baek-Yeol
	Severance Hospital Yonsei University Health System	Kim, Han Sang
	Seoul National University Hospital	Lee, Dae-Won
Taiwan	China Medical University Hospital	Chiu, Chang-Fang
	National Cheng Kung University Hospital	Chang, Ting-Tsung
	Chia-Yi Chang Gung Memorial Hospital	Lu, Chang-Hsien