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Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

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abstract

PURPOSE Pembrolizumab demonstrated antitumor activity and safety in the phase II KEYNOTE-224 trial in previously treated patients with advanced hepatocellular carcinoma (HCC). KEYNOTE-240 evaluated the efficacy and safety of pembrolizumab in this population.

PATIENTS AND METHODS This randomized, double-blind, phase III study was conducted at 119 medical centers in 27 countries. Eligible patients with advanced HCC, previously treated with sorafenib, were randomly assigned at a two-to-one ratio to receive pembrolizumab plus best supportive care (BSC) or placebo plus BSC. Primary end points were overall survival (OS) and progression-free survival (PFS; one-sided significance thresholds, $P = .0174$ [final analysis] and $P = .002$ [first interim analysis], respectively). Safety was assessed in all patients who received ≥ 1 dose of study drug.

RESULTS Between May 31, 2016, and November 23, 2017, 413 patients were randomly assigned. As of January 2, 2019, median follow-up was 13.8 months for pembrolizumab and 10.6 months for placebo. Median OS was 13.9 months (95% CI, 11.6 to 16.0 months) for pembrolizumab versus 10.6 months (95% CI, 8.3 to 13.5 months) for placebo (hazard ratio [HR], 0.781; 95% CI, 0.611 to 0.998; $P = .0238$). Median PFS for pembrolizumab was 3.0 months (95% CI, 2.8 to 4.1 months) versus 2.8 months (95% CI, 2.5 to 4.1 months) for placebo at the first interim analysis (HR, 0.775; 95% CI, 0.609 to 0.987; $P = .0186$) and 3.0 months (95% CI, 2.8 to 4.1 months) versus 2.8 months (95% CI, 1.6 to 3.0 months) at final analysis (HR, 0.718; 95% CI, 0.570 to 0.904; $P = .0022$). Grade 3 or higher adverse events occurred in 147 (52.7%) and 62 patients (46.3%) for pembrolizumab versus placebo; those that were treatment related occurred in 52 (18.6%) and 10 patients (7.5%), respectively. No hepatitis C or B flares were identified.

CONCLUSION In this study, OS and PFS did not reach statistical significance per specified criteria. The results are consistent with those of KEYNOTE-224, supporting a favorable risk-to-benefit ratio for pembrolizumab in this population.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and a leading cause of cancer-related death worldwide.[1] For more than a decade, sorafenib, an antiangiogenic multikinase inhibitor, was the only systemic agent available with a survival benefit for the treatment of advanced HCC.[2] Over the past 2 years, a number of new agents have demonstrated activity in advanced HCC in phase III studies. All of these are antiangiogenic agents, including tyrosine kinase inhibitors lenvatinib in the first-line setting and regorafenib, cabozantinib, and the monoclonal antibody ramucirumab in the second-line setting after prior sorafenib therapy.[3-6]

Pembrolizumab and nivolumab, both anti–programmed death-1 (PD-1) monoclonal antibodies, have demonstrated promising clinical efficacy and safety in patients with advanced HCC who were previously treated with sorafenib and have both received accelerated approval in the United States for this population.[7-10] KEYNOTE-240 is a randomized, double-blind, placebo-controlled, phase III trial designed to confirm the efficacy and safety of pembrolizumab plus best supportive care (BSC) versus

placebo plus BSC in patients with previously treated advanced HCC.

PATIENTS AND METHODS

Study Design

This randomized, double-blind, phase III study was conducted at 119 medical centers in 27 countries (Data Supplement, online only). The trial protocol and amendments were approved by the appropriate ethics committees at all centers. All patients provided written informed consent.

Eligible patients were age 18 years or older with a radiographic or pathologic diagnosis of HCC, radiographic progression during or intolerance to sorafenib treatment, and Barcelona Clinic Liver Cancer stage C disease or stage B disease[11] not amenable to or refractory to locoregional therapy. Patients had Child-Pugh liver class A disease,[12] an Eastern Cooperative Oncology Group performance score of 0 or 1, and otherwise adequate organ function.

Patients who had received prior immunotherapy, including anti–PD-1, anti–PD-1 ligand (PD-L1), or anti–PD-L2 agents, or previous systemic therapy for HCC in the advanced setting other than sorafenib were excluded, as were those with clinically apparent ascites on physical examination, main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging, or clinically diagnosed hepatic encephalopathy within the past 6 months. Full eligibility criteria are provided in the protocol (Data Supplement).

Patients were randomly assigned at a ratio of two to one to receive either 200 mg of pembrolizumab or saline placebo intravenously every 3 weeks for at least 35 cycles (approximately 2 years). Both arms received BSC at the discretion of the investigator in accordance with local practices. Randomization was performed using an interactive voice-response/integrated Web-response system, with stratification by geographic region (Asia excluding Japan *v* non-Asia including Japan), macrovascular invasion (MVI; yes *v* no), and α-fetoprotein level (< 200 *v* ≥ 200 ng/mL). The treatment period was from the first dose received until progressive disease (PD) according to RECIST (version 1.1),[13] unacceptable toxicity, patient withdrawal of consent, investigator decision to withdraw the patient, or 35 cycles of study drug received.

Assessments

Tumor imaging (computed tomography, magnetic resonance imaging, or both) was performed 21 days or earlier before random assignment and repeated at 6 weeks after random assignment and then every 6 weeks thereafter until progression. Response was assessed according to RECIST (version 1.1)[13] by blinded, independent, central radiologic review. Patients were contacted approximately every 12 weeks for survival assessment during follow-up. Adverse events (AEs) and laboratory abnormalities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Potential immune-related hepatitis resulting from treatment was assessed as described in the protocol.

End Points

The primary end points were overall survival (OS; defined as time from random assignment to death resulting from any cause) and progression-free survival (PFS; defined as time from random assignment to first documented PD per RECIST [version 1.1] or death resulting from any cause, whichever occurred first). Secondary end points were objective response rate (ORR; defined as proportion of patients with confirmed complete response [CR] or partial response [PR]), disease control rate (DCR; defined as proportion of patients who achieved CR, PR, or stable disease [SD] with duration of ≥ 5 weeks), duration of response (DOR; defined as time from first documented CR or PR to PD or death), time to progression (defined as time from random assignment to first documented PD), and safety and tolerability.

Statistical Analysis

Efficacy was assessed in the intention-to-treat population, which included all randomly assigned patients. The Kaplan-Meier method was used to estimate OS and PFS, time to progression, and DOR. For OS, patients who were alive at data cutoff or were lost to follow-up were censored at the time of last known survival. For PFS, patients who were alive and without PD or who stopped scans without progression were censored at the last imaging assessment; patients who experienced progression or death after a gap of more than 141 days (representing $\geq$ two scheduled imaging assessments) after the last non-PD scan or started new anticancer therapy without prior progression were censored at the last non-PD scan date before the gap or start of new anticancer therapy, whichever was earlier. Treatment differences in OS and PFS and time to progression were tested by the stratified log-rank test using a stratified Cox proportional hazards model with Efron's method of tie handling to estimate hazard ratios (HRs) and 95% CIs (95% CIs for HRs are descriptive and do not imply superiority when 1 is excluded). Differences in ORR and DCR were assessed by the stratified Miettinen and Nurminen[14] method. Stratification factors for randomization were applied to all stratified analyses, with all patients with MVI combined into one stratum because of their small number. Safety was assessed in the as-treated population (all randomly assigned patients who received $\geq$ one dose of study treatment), and summary statistics for baseline, during treatment, and change from baseline were provided by treatment group.

Two interim efficacy analyses and a final efficacy analysis of OS were specified in the protocol. The primary analyses of PFS and ORR were prespecified at the first interim analysis of OS. The overall type I error rate (one-sided $\alpha = 2.5\%$) was

controlled across the testing of OS and for both PFS and ORR at the first interim analysis using the graphical method of Maurer and Bretz.[15] An initial α of 2.3% was assigned for OS and 0.2% for PFS; α was to be redistributed per the prespecified multiplicity strategy (Data Supplement). The type I error was controlled across the two interim analyses and final OS analysis using a group-sequential design with O'Brien-Fleming superiority boundaries.[16] With an enrollment of 408 patients, the study would have 92% power for the OS analysis with 273 deaths, assuming a true HR of 0.65 at an α of 2.3% and 94% power for the PFS analysis with approximately 331 PFS events, assuming a true HR of 0.60 at an α of 0.2%.

The first interim analysis was conducted when approximately 183 deaths were anticipated (data cutoff, March 26, 2018); 190 deaths and 312 PFS events were actually observed. At this time, the first interim analysis of OS and analyses of PFS and ORR were performed. The second interim analysis of OS was conducted when approximately 232 deaths were expected (data cutoff, July 30, 2018); 238 deaths were actually observed. The final analysis was performed after 284 OS events (data cutoff, January 2, 2019).

To address the use of subsequent anticancer therapies after discontinuation of study medication, two post hoc sensitivity analyses of OS were performed, adjusted for treatment switches to anticancer therapies in both arms. One analysis used the inverse probability of censoring weighting method (IPCW), and the other used a two-stage survival analysis model.[17-20]

RESULTS

From May 31, 2016, to November 23, 2017, a total of 413 patients at 119 sites from 27 countries were randomly

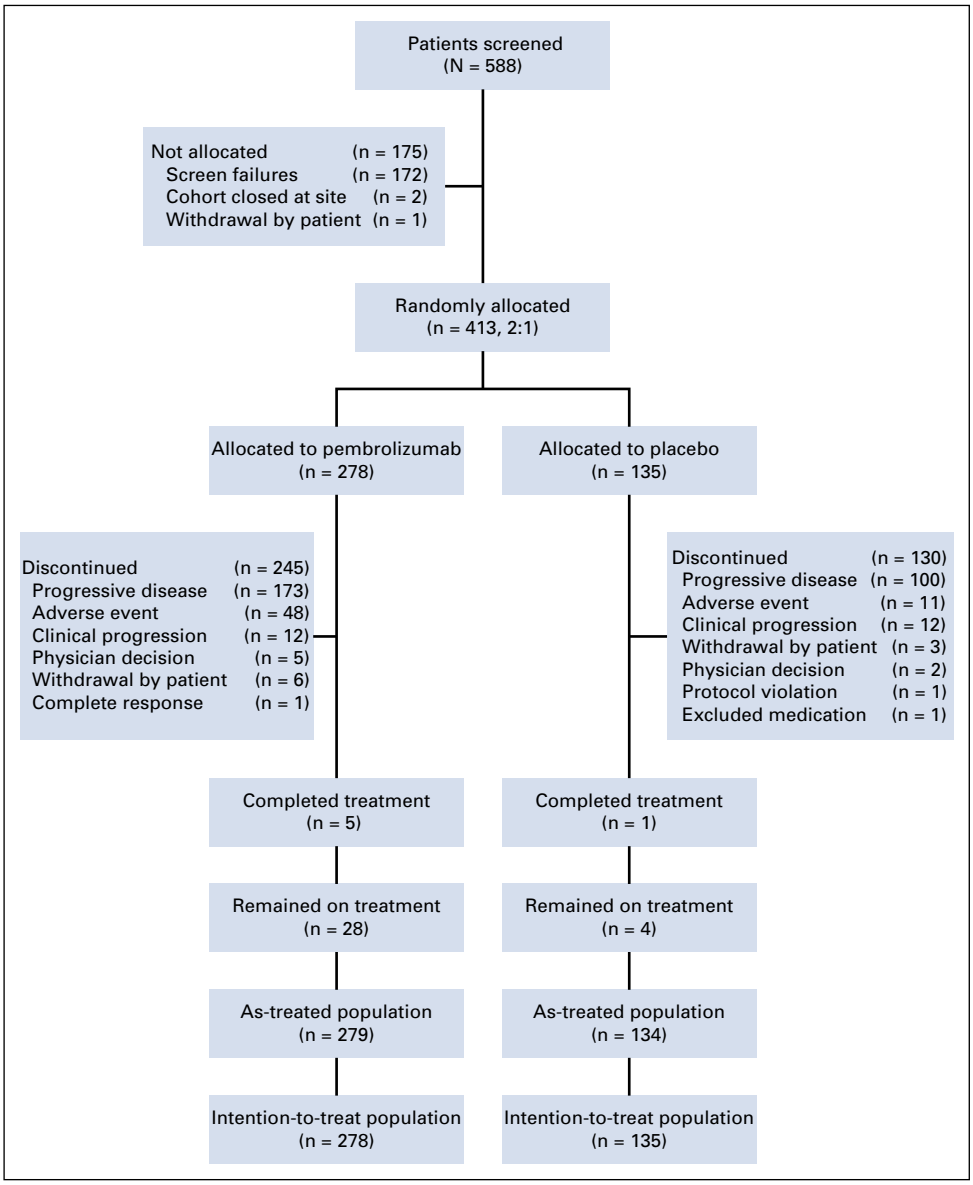

FIG 1. Trial profile. All randomly assigned patients received study treatment or placebo.

assigned at a two-to-one ratio to the pembrolizumab (n = 278) or placebo group (n = 135; Fig 1). Baseline patient characteristics were generally well balanced between the two treatment groups (Table 1). Median duration of prior sorafenib use was 4.6 months (range, 0.1-56.6 months) in the pembrolizumab group and 4.9 months (range, 0.3-101.4 months) in the placebo group. Median time from stopping sorafenib until the first dose of study treatment was 1.2 months (range, 0.2-19.5 months) for pembrolizumab and 1.1 months (range, 0.5-81.3 months) for placebo; median time from progression or recurrence until the first dose of study treatment was 1.5 months (range, 0.0-20.9 months) and 1.4 months (range, 0.4-40.4 months), respectively.

By the data cutoff date for the final analysis (January 2, 2019), there were 284 deaths, 28 patients (10.1%) were still receiving pembrolizumab, and four patients (3.0%) were receiving placebo. Of the 413 patients enrolled, all received ≥ one dose of study drug. The most common reason for permanent discontinuation of study treatment was PD, which occurred in 173 patients (62.2%) in the pembrolizumab group and 100 (74.1%) in the placebo group. Median duration of follow-up was 13.8 months (range, 0.9-30.4 months) for pembrolizumab and 10.6 months (range, 0.9-29.5 months) for placebo; median duration of treatment was 3.5 months (range, 0.0-24.4 months) and 2.8 months (range, 0.0-24.2 months), respectively.

As of January 2, 2019, 180 patients (64.7%) in the pembrolizumab group and 101 patients (74.8%) on placebo had died. Median OS was 13.9 months (95% CI, 11.6 to 16.0 months) in the pembrolizumab group and 10.6 months (95% CI, 8.3 to 13.5 months) in the placebo group (HR, 0.781; 95% CI, 0.611 to 0.998; $P = .0238$; Fig 2A). Median PFS was 3.0 months (95% CI, 2.8 to 4.1 months) for pembrolizumab and 2.8 months (95% CI, 1.6 to 3.0 months) for placebo (HR, 0.718; 95% CI, 0.570 to 0.904; $P = .0022$) at final analysis (Fig 2B). Median PFS at the first interim analysis was similar (3.0 months; 95% CI, 2.8 to 4.1 months and 2.8 months; 95% CI, 2.5 to 4.1 months, respectively; HR, 0.775; 95% CI, 0.609 to 0.987; $P = .0186$). Kaplan-Meier estimates of PFS rates at 12 months were 19.4% (95% CI, 14.6% to 24.9%) for pembrolizumab and 6.7% (95% CI, 3.0% to 12.4%) for placebo. Median time to progression was 3.8 months (range, 2.8-4.4 months) in the pembrolizumab group and 2.8 months (range, 1.6-2.9 months) for placebo (HR, 0.688; 95% CI, 0.540 to 0.877; $P = .0011$; Data Supplement). Results for OS and PFS were generally consistent in all subgroups (Fig 3). Although OS and PFS improved compared with placebo, they did not meet the prespecified boundaries of $P = .0174$ for OS (final analysis) and $P = .002$ for PFS (at the first interim analysis).

ORR was 18.3% (95% CI, 14.0% to 23.4%) for pembrolizumab and 4.4% (95% CI, 1.6% to 9.4%) for placebo

TABLE 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	No. (%) Pembrolizumab (n = 278)	Placebo (n = 135)
Age, years		
Median	67	65
Range	18-91	23-89
Male sex	226 (81.3)	112 (83)
Region of enrollment		
Asia without Japan	67 (24.1)	31 (23.0)
European Union	96 (34.5)	43 (31.9)
Japan	40 (14.4)	19 (14.1)
United States	21 (7.6)	16 (11.9)
Other*	54 (19.4)	26 (19.3)
ECOG performance status		
0	162 (58.3)	71 (52.6)
1	116 (41.7)	64 (47.4)
Child-Pugh score		
A5	176 (63.3)	86 (63.7)
A6	101 (36.3)	47 (34.8)
B7	1 (0.4)	2 (1.5)
BCLC stage		
B	56 (20.1)	29 (21.5)
C	222 (79.9)	106 (78.5)
Alcohol use	159 (57.2)	79 (58.5)
Viral status†		
HBV	72 (25.9)	29 (21.5)
HCV	43 (15.5)	21 (15.6)
Uninfected	163 (58.6)	85 (63.0)
Prior treatment with sorafenib		
Intolerance	36 (12.9)	18 (13.3)
PD	242 (87.1)	117 (86.7)
Extrahepatic disease	195 (70.1)	93 (68.9)
MVI	36 (12.9)	16 (11.9)
Baseline AFP, ng/mL		
≥ 200	129 (46.4)	58 (43.0)
< 200	149 (53.6)	77 (57.0)

NOTE. Data cutoff, January 2, 2019.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PD, progressive disease.

*Includes Argentina, Australia, Canada, Chile, Colombia, Israel, Mexico, Norway, Russian Federation, and Turkey.

†HBV infection defined as hepatitis B surface antigen positive and/or detectable HBV DNA; HCV infection defined as anti–hepatitis C antibody positive and detectable HCV RNA.

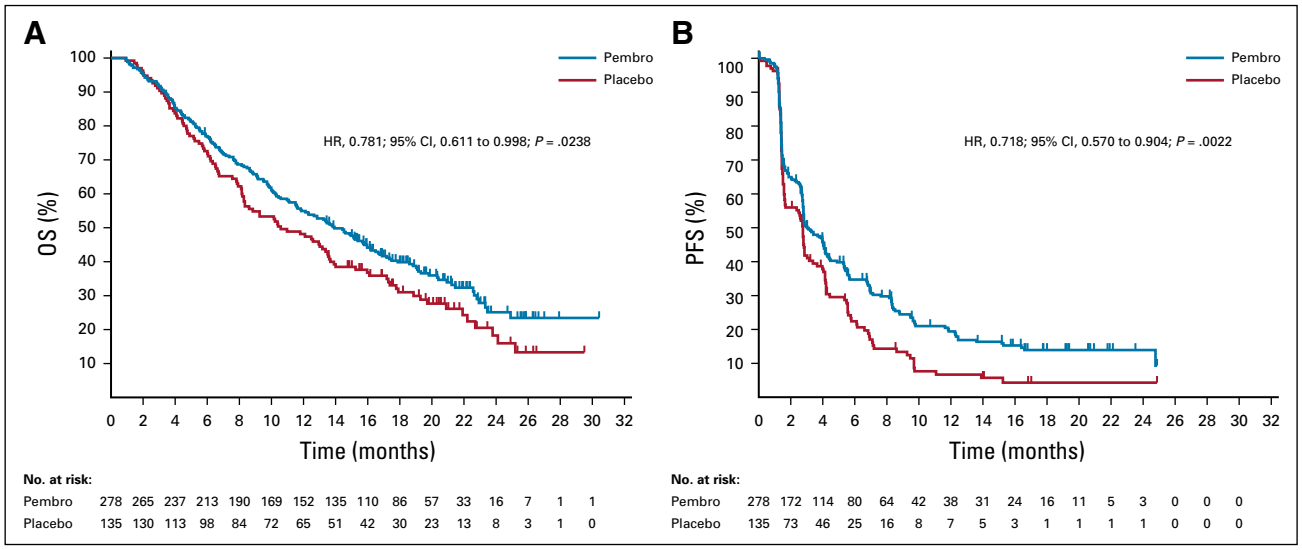

FIG 2. Overall survival (OS) and progression-free survival (PFS) in intention-to-treat population at final analysis. Kaplan-Meier estimates of (A) OS and (B) PFS per RECIST (version 1.1; blinded central imaging review) at final analysis in the trial groups. Tick marks indicate censored observations. The 12-month survival rates were estimated from the Kaplan-Meier curve time point. Pembro, pembrolizumab.

at final analysis (nominal one-sided $P = .00007$; Table 2). DCRs were 62.2% (95% CI, 56.2% to 68.0%) and 53.3% (95% CI, 44.6% to 62.0%), respectively (nominal one-sided $P = .03807$). Best overall responses were six CRs (2.2%) and 45 PRs (16.2%); 122 patients (43.9%) had SD, and 90 (32.4%) PD in the pembrolizumab group. In the placebo group, there were no CRs; six patients (4.4%) had PRs, 66 (48.9%) had SD, and 57 (42.2%) had PD. Reductions from baseline in the sum of the longest diameters of target lesions are shown in the data supplement. Median time to response was 2.7 months (range, 1.2-16.9 months) in the pembrolizumab group and 2.9 months (range, 1.1-6.9 months) in the placebo group. Median DOR by the Kaplan-Meier method was 13.8 months (range, 1.5+-23.6+ months) for pembrolizumab and not reached (range, 2.8-20.4+) for the six responding patients on placebo (+ indicates no PD at last disease assessment).

AEs resulting from any cause occurred in 269 patients (96.4%) receiving pembrolizumab and 121 (90.3%) receiving placebo (Table 3). Grade 3 or higher adverse events occurred in 147 (52.7%) and 62 patients (46.3%) in the pembrolizumab and placebo groups, respectively. Discontinuation of treatment because of AEs occurred in 48 patients (17.2%) in the pembrolizumab group and 12 (9.0%) in the placebo group. The most common reasons were ascites in 12 patients (4.3%) in the pembrolizumab group and three (2.2%) in the placebo group and increased AST and blood bilirubin in four patients (1.4%) and one (0.7%) in each of these groups, respectively. AEs leading to treatment interruption occurred in 84 patients (30.1%) for pembrolizumab and 21 (15.7%) for placebo. These were most commonly attributed to increased blood bilirubin and AST levels for pembrolizumab (15 [5.4%] and 13 patients [4.7%], respectively) and placebo (five [3.7%] and four patients [3.0%], respectively). AEs leading to death occurred in seven patients (2.5%) with pembrolizumab and four (3.0%) with placebo. Events attributed to study treatment that led to death occurred in one patient (0.4%) in the pembrolizumab group and none in the placebo group.

The most common AEs reported in 10% of patients or more were increased AST and blood bilirubin levels in either treatment group, fatigue and pruritus for pembrolizumab, and fatigue, cough, and increased AST level for placebo (Table 3). Of those, the only grade 3 or higher adverse AE experienced in 10% of patients or more was increased AST level in 37 patients (13.3%) in the pembrolizumab group and 10 (7.5%) for placebo. Grade 3 or higher adverse events that occurred more frequently with pembrolizumab than placebo were increased AST level (37 [13.3%] *v* 10 patients [7.5%]), blood bilirubin level (21 [7.5%] *v* seven patients [5.2%]), and increased ALT (17 [6.1%] *v* four patients [3.0%]); those that occurred more frequently in the placebo than pembrolizumab arm included anemia (12 [9.0%] *v* 11 patients [3.9%]) and diarrhea (three [2.2%] *v* four patients [1.4%]). The percentages of patients with events attributed to treatment by the investigator were 60.9% in the pembrolizumab group and 48.5% in the placebo group (Data Supplement). The incidence of any treatment-related grade 3 or higher adverse event was low, with increased AST and ALT levels being most common in the pembrolizumab (5.4% and 3.6%, respectively) and placebo (1.5% and 1.5%, respectively) groups.

Immune-mediated AEs prespecified by the sponsor regardless of treatment attribution occurred in 51 patients (18.3%) in the pembrolizumab group and 11 (8.2%) in the

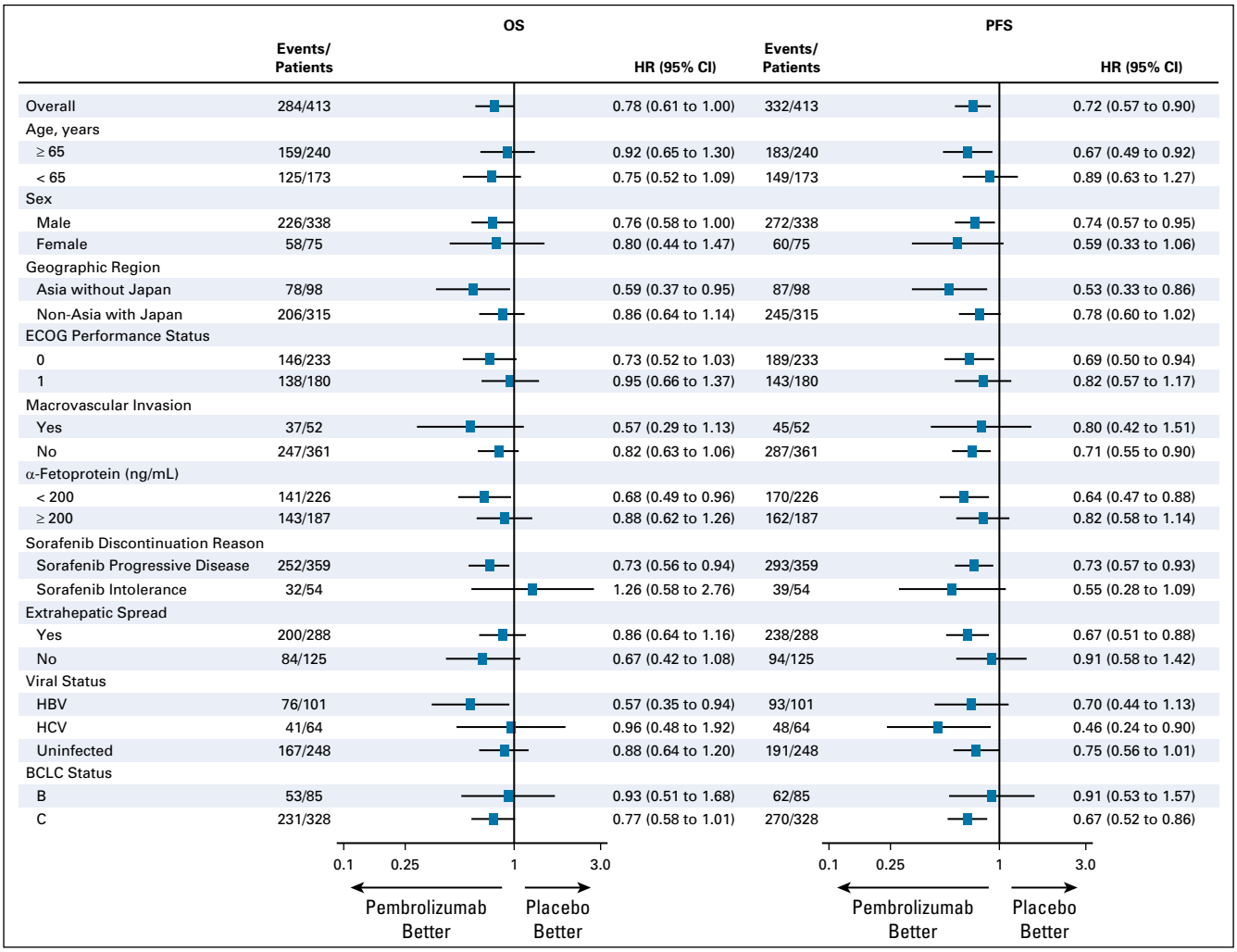

FIG 3. Subgroup analysis of overall survival (OS) and progression-free survival (PFS) in intention-to-treat population at final analysis. Analyses of OS and PFS assessed per RECIST (version 1.1; blinded central imaging review) in key prespecified subgroups. BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

placebo group, of which the most common were hypothyroidism, hyperthyroidism, and pneumonitis (Table 3). These events were grade 3 or higher in 20 patients (7.2%) in the pembrolizumab group and one (0.7%) in the placebo group. On the basis of sponsor assessment, immune-mediated hepatitis events were seen in 10 patients (3.6%) in the pembrolizumab group, approximately 90% of which resolved, and none in the placebo group, and no identified cases of hepatitis B or C viral flares were observed. There were 23 patients (8.2%) in the pembrolizumab group and one (0.7%) in the placebo group who received steroids for possible immune-mediated AEs.

At progression during study treatment, systemic anticancer therapies were used by 116 patients (41.7%) in the pembrolizumab group and 64 (47.4%) in the placebo group (Data Supplement); at any given time after random assignment, the percentage of patients who received poststudy therapy was higher in the placebo arm (Data Supplement). Two post hoc sensitivity analyses of OS accounting for the use of subsequent anticancer therapies resulted in similarly lower HRs for the treatment differences (range, 0.67-0.68; Data Supplement). Median OS was longer in the pembrolizumab group versus placebo when survival was adjusted for treatment switches to subsequent anticancer therapies in both arms using the IPCW model (13.9 *v* 9.3 months; HR, 0.67; 95% CI, 0.48 to 0.92; nominal one-sided $P = .0066$) and a two-stage survival analysis model (10.6 *v* 7.6 months; HR, 0.68; 95% CI, 0.53 to 0.86; nominal one-sided $P = .0011$).

DISCUSSION

KEYNOTE-240 did not meet its prespecified statistical dual end points of improving PFS and OS with pembrolizumab in the second-line treatment of advanced HCC. The improvements seen in OS, PFS, ORR, and DOR with pembrolizumab in this randomized phase III study

TABLE 2. Summary of Response in Intention-to-Treat Population by Central Radiology Review per RECIST (version 1.1)

Parameter	No. (%)	
	Pembrolizumab (n = 278)	Placebo (n = 135)
Objective response*	51 (18.3)	6 (4.4)
95% CI	14.0 to 23.4	1.6 to 9.4
Estimated treatment difference†	13.8	
95% CI	7.7 to 19.5	
P‡	.00007	
Best overall response§		
CR	6 (2.2)	0 (0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
≥ 23 weeks‖	37 (13.3)	20 (14.8)
PD	90 (32.4)	57 (42.2)
Not evaluable	7 (2.5)	3 (2.2)
Not assessable¶	8 (2.9)	3 (2.2)
DCR#	173 (62.2)	72 (53.3)

Data cutoff, January 2, 2019; final analysis.

Abbreviations: CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

*Includes CR and PR.

†Difference in percentage for pembrolizumab versus placebo; 95% CI based on Miettinen and Nurminen method stratified by geographic region (Asia without Japan *v* non-Asia with Japan), macrovascular invasion (yes *v* no), and α-fetoprotein (< 200 *v* ≥ 200 ng/mL).

‡One-sided *P* value for testing difference.

§Confirmed by independent central review per RECIST (version 1.1).

‖SD within 24-week scan window or later.

¶Patients who had baseline assessment by investigator review or central radiology but no postbaseline assessment by data cutoff date, including discontinuation or death before first postbaseline scan.

#Includes CR, PR, and SD (≥ 5 weeks).

were consistent with those of the single-arm KEYNOTE-224 study, a phase II trial conducted in a similar population.[9]

Several factors related to study design may have affected the results of KEYNOTE-240. For one, the prespecified multiplicity strategy for testing the OS and PFS hypotheses required efficacy boundaries for the dual end points of α = 0.0174 for OS at final analysis and 0.002 for PFS at primary analyses and resulted in HRs of 0.781 (95% CI, 0.611 to 0.998; *P* = .0238) and 0.775 (95% CI, 0.609 to 0.987; *P* = .0186) for OS and PFS, respectively. Thus, neither of the primary end points reached statistical significance at required levels. The study was powered for an OS HR of 0.65, with an expected initial improvement of 4.1 months in median OS, from 7.6 months for placebo to 11.7 months with pembrolizumab. The OS for the placebo group in this study was better than predicted compared with other second-line studies, likely in part because of the impact of the unanticipated availability of effective poststudy therapies. At the time of study initiation, no drugs had been approved for the treatment of HCC after progression with sorafenib. During the course of the trial, several drugs, including regorafenib and nivolumab, were approved in this setting.[7,21] The use of these and other agents at progression likely influenced postprogression survival and trial outcomes. Consistent with this, HRs resulting from the two exploratory sensitivity analyses, which evaluated OS while adjusting for the use of subsequent anticancer therapy (range, 0.67-0.68), were closer to the 0.65 HR for OS on which the trial was originally powered. The statistical methodology used in these analyses relied on certain assumptions, and although plausible in this study setting, these should be taken into consideration when interpreting the results of the sensitivity analyses. A lower rate of MVI attributed to the exclusion of patients with main portal vein invasion[3,4,6] may also have affected outcomes.

Although estimates of PFS medians in the two groups were relatively close, the greater separation at later time points in the Kaplan-Meier curves demonstrated that some patients derived long-term benefit from pembrolizumab. As such, more than 19% of the patients receiving pembrolizumab remained progression free for more than 1 year, in line with improvements seen in PFS and Kaplan-Meier curves for immunotherapies, where medians tend to be less reflective of this durable benefit.[22]

The pembrolizumab ORR was substantially higher than that of placebo (18.3% *v* 4.4%) and was comparable to those ORRs observed in previous immunotherapy trials for nivolumab (14.3%) and pembrolizumab (17.0%).[8,9,23,24] Pembrolizumab also led to a shift toward better categories of best overall response compared with placebo; 10% fewer patients in the pembrolizumab arm had PD, and 14% more had an objective response.

In this patient population selected for well-preserved liver function, there were no new or unexpected toxicities. Pembrolizumab was well tolerated, with a similar incidence and severity of AEs as seen in other tumor types, including immune-mediated hepatic events.[24] There were no reported cases of viral hepatitis flares.

To date, biomarkers that enrich for a patient population more likely to benefit from pembrolizumab have not been validated in HCC.[9] In addition, the clinical benefit in this study was consistent across clinical subgroups and etiologies of underlying liver disease. Ongoing efforts are aimed at identifying predictive markers of benefit and development of novel combinations to improve overall clinical outcomes.

This study, the first phase III randomized trial to our knowledge to report the use of checkpoint inhibitors in advanced HCC, did not meet its predetermined level of

TABLE 3. AEs Resulting From Any Cause in As-Treated Population

	No. (%)			
	Pembrolizumab (n = 279)		Placebo (n = 134)	
AE	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any	269 (96.4)*	145 (52.0)	121 (90.3)*	62 (46.3)
Leading to discontinuation of treatment	48 (17.2)	40 (14.3)	12 (9.0)	7 (5.2)
Leading to death	7 (2.5)	0 (0)	4 (3.0)	0 (0)
Leading to death attributed to treatment†	1 (0.4)‡	0 (0)	0 (0)	0 (0)
Occurring in ≥ 10% of patients in either group§				
AST increased	63 (22.6)	37 (13.3)	22 (16.4)	10 (7.5)
Blood bilirubin increased	52 (18.6)	21 (7.5)	17 (12.7)	7 (5.2)
Fatigue	52 (18.6)	7 (2.5)	31 (23.1)	2 (1.5)
Pruritus	51 (18.3)	1 (0.4)	16 (11.9)	0 (0)
ALT increased	49 (17.6)	17 (6.1)	13 (9.7)	4 (3.0)
Decreased appetite	48 (17.2)	3 (1.1)	21 (15.7)	0 (0)
Diarrhea	48 (17.2)	4 (1.4)	21 (15.7)	3 (2.2)
Abdominal pain	40 (14.3)	4 (1.4)	9 (6.7)	0 (0)
Nausea	32 (11.5)	2 (0.7)	20 (14.9)	1 (0.7)
Edema peripheral	32 (11.5)	0 (0)	17 (12.7)	0 (0)
Rash	32 (11.5)	2 (0.7)	7 (5.2)	0 (0)
Anemia	27 (9.7)	11 (3.9)	14 (10.4)	12 (9.0)
Back pain	27 (9.7)	4 (1.4)	14 (10.4)	0 (0)
Constipation	26 (9.3)	1 (0.4)	15 (11.2)	0 (0)
Pyrexia	26 (9.3)	2 (0.7)	15 (11.2)	0 (0)
Asthenia	25 (9.0)	0 (0.0)	15 (11.2)	0 (0)
Cough	24 (8.6)	0 (0.0)	24 (17.9)	0 (0)
Arthralgia	20 (7.2)	1 (0.4)	14 (10.4)	1 (0.7)
Dyspnea	18 (6.5)	0 (0)	15 (11.2)	2 (1.5)
Events of interest‖				
Any	51 (18.3)	20 (7.2)	11 (8.2)	1 (0.7)
Hypothyroidism	14 (5.0)	1 (0.4)	7 (5.2)	0 (0)
Hyperthyroidism	9 (3.2)	0 (0)	0 (0)	0 (0)
Pneumonitis	10 (3.6)	4 (1.4)	1 (0.7)	0 (0)
Severe skin reaction	8 (2.9)	6 (2.2)	0 (0)	0 (0)
Hepatitis	5 (1.8)	4 (1.4)	0 (0)	0 (0)
Colitis	4 (1.4)	2 (0.7)	2 (1.5)	0 (0)
Infusion reaction	3 (1.1)	0 (0)	0 (0)	0 (0)
Adrenal insufficiency	2 (0.7)	0 (0)	0 (0)	0 (0)
Hypophysitis	2 (0.7)	1 (0.4)	0 (0)	0 (0)
Myasthenia syndrome	1 (0.4)	0 (0)	0 (0)	0 (0)
Myositis	2 (0.7)	1 (0.4)	0 (0)	0 (0)
Thyroiditis	1 (0.4)	0 (0)	0 (0)	0 (0)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.7)	1 (0.7)

Abbreviation: AE, adverse event.

*There were 11 grade 5 events, all leading to death, including seven (2.5%) in pembrolizumab arm (AE terms: myocardial infarction, n = 1; esophageal variceal hemorrhage, n = 1; upper GI hemorrhages, n = 2; death, n = 1; hepatic cirrhosis, n = 1; and malignant neoplasm progression, n = 1) and four (3.0%) in placebo arm (AE terms: myocardial ischemia, n = 1; death, n = 1; hepatic failure, n = 1; and peritonitis, n = 1).

†Attributed to treatment by investigator.

‡Death attributed to malignant neoplasm progression, possibly related to study treatment, by investigator. No grade 5 events occurred in ≥ 10% of patients in either group.

§Events listed in descending order of frequency in pembrolizumab group.

‖Events of interest are those with immune-related cause considered regardless of attribution to study treatment by investigator; listed in decreasing frequency in pembrolizumab group.

statistical significance. The findings in KEYNOTE-240 reinforce the clinical activity of pembrolizumab as demonstrated in the KEYNOTE-224 trial in HCC patients previously treated with sorafenib, which supported its accelerated approval by the US Food and Drug Administration with a favorable disease control and toxicity profile. Data will be available according to the data-sharing policy of Merck Sharp & Dohme, which, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via e-mail to dataaccess@merck.com.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-E386, 2015
2. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008
3. Abou-Alfa GK, Meyer T, Cheng AL, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 379:54-63, 2018
4. Bruix J, Qin S, Merle P, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389:56-66, 2017
5. Kudo M, Finn RS, Qin S, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018
6. Zhu AX, Kang YK, Yen CJ, et al: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20:282-296, 2019
7. US Food & Drug Administration. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib
8. El-Khoueiry AB, Sangro B, Yau T, et al: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389:2492-2502, 2017

9. Zhu AX, Finn RS, Edeline J, et al: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 19:940-952, 2018
10. US Food and Drug Administration: FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma. https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma
11. Llovet JM, Brú C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
12. Pugh RN, Murray-Lyon IM, Dawson JL, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60:646-649, 1973
13. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
14. Miettinen O, Nurminen M: Comparative analysis of two rates. Stat Med 4:213-226, 1985
15. Maurer W, Bretz F: Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 5:311-320, 2013
16. Lan KKG, Demets DL: Discrete sequential boundaries for clinical-trials. Biometrika 70:659-663, 1983
17. Robins JM, Finkelstein DM: Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 56:779-788, 2000
18. Latimer NR, Abrams KR, Lambert PC, et al: Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: Methods, limitations, and recommendations. Med Decis Making 34:387-402, 2014
19. Skaltsa K, Ivanescu C, Naidoo S, et al: Adjusting overall survival estimates after treatment switching: A case study in metastatic castration-resistant prostate cancer. Target Oncol 12:111-121, 2017
20. Latimer NR, Abrams KR, Lambert PC, et al: Adjusting for treatment switching in randomised controlled trials: A simulation study and a simplified two-stage method. Stat Methods Med Res 26:724-751, 2017
21. US Food and Drug Administration: FDA expands approved use of Stivarga to treat liver cancer. https://www.fda.gov/news-events/press-announcements/fda-expands-approved-use-stivarga-treat-liver-cancer
22. Hellmann MD, Kris MG, Rudin CM: Medians and milestones in describing the path to cancer cures: Telling "tails". JAMA Oncol 2:167-168, 2016
23. Opdivo (nivolumab) prescribing information. Princeton, NJ, Bristol-Meyers Squibb, 2018
24. Keytruda (pembrolizumab) prescribing information. Whitehouse Station, NJ, Merck, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

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