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A Phase 3 Study of Pembrolizumab versus Placebo for Previously Treated Patients from Asia with Hepatocellular Carcinoma: Health-Related Quality of Life Analysis from KEYNOTE-394

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Keywords
Health-related quality of life · Patient-reported outcomes · KEYNOTE-394 · PD-1 inhibitor · Previously treated patients

Abstract
Introduction: KEYNOTE-394 showed pembrolizumab significantly improved overall survival, progression-free survival, and objective response rate with manageable safety versus placebo for patients from Asia with previously treated advanced hepatocellular carcinoma. We present results on health-related quality of life (HRQoL). ***Methods:*** HRQoL was evaluated using the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQol-5D-3L (EQ-5D-3L) questionnaires. Key HRQoL endpoints were least squares mean (LSM) score changes from baseline to week 12 and time to deterioration (TTD) for EORTC QLQ-C30 global health status (GHS)/QoL. *p* values were one-sided and nominal without adjustment for multiplicity. ***Results:*** The HRQoL population included patients randomly assigned to pembrolizumab (*n* = 298) and placebo (*n* = 152). From baseline to week 12, a greater decline in EORTC QLQ-C30 GHS/QoL score was observed with placebo (LSM, −8.4; 95% CI: −11.7 to −5.1) versus pembrolizumab (−4.0; 95% CI: −6.4 to −1.6;

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difference vs. placebo: 4.4; 95% CI: 0.5–8.4; nominal p = 0.0142). Similarly, a greater decline in the EQ-5D-3L visual analog scale score was observed with placebo (−6.9; 95% CI: −9.4 to −4.5) versus pembrolizumab (−2.7; 95% CI: −4.5 to −1.0; difference vs. placebo: 4.2; 95% CI: 1.2–7.2; nominal p = 0.0030). TTD in EORTC QLQ-C30 GHS/QoL score was similar between arms (hazard ratio, 0.85; 95% CI: 0.58–1.25; nominal p = 0.1993). ***Conclusion:*** Patients receiving placebo showed a greater decline in HRQoL than those receiving pembrolizumab. Combined with efficacy and safety data from KEYNOTE-394 and the global KEYNOTE-240 and KEYNOTE-224 trials, our data support the clinically meaningful benefit and manageable tolerability of pembrolizumab as second-line therapy for patients with advanced hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancer [1] and is often diagnosed at advanced stages [2]. Patients with advanced HCC generally have chronic cirrhosis, decreased liver function, compromised functional status, and impaired health-related quality of life (HRQoL), especially in physical, psychological, and functional well-being, and hepatobiliary symptoms [3–5]. Therefore, toxicity/tolerability and impact on HRQoL associated with HCC treatment are key considerations for treating patients, and HRQoL outcomes in patients with advanced HCC included in clinical trials could result in better physician decision-making for treatment selection and sequencing.

Despite recent progress in expanding treatment options, including targeted therapies and immunotherapies for advanced HCC [6–10], there remains an unmet medical need for treatment options that can prolong survival with HRQoL benefit. Pembrolizumab is a programmed death 1 (PD-1) inhibitor that received accelerated approval from the US Food and Drug Administration for patients with advanced HCC previously treated with sorafenib [11] based on findings from the global phase 2 KEYNOTE-224 study [10]. Although pembrolizumab narrowly missed prespecified statistical significance criteria for overall survival (OS) and progression-free survival (PFS) in the global second-line phase 3 KEYNOTE-240 study, pembrolizumab added to best supportive care (BSC) versus placebo plus BSC demonstrated a favorable benefit-to-risk profile [7] and preserved HRQoL during treatment [12].

KEYNOTE-394 is a randomized, double-blind, phase 3 trial of pembrolizumab plus BSC versus placebo plus BSC as second-line therapy in patients in Asia with advanced HCC and progression on or intolerance to sorafenib or oxaliplatin-based chemotherapy [13]. This study met its primary endpoint of OS as well as key secondary endpoints: pembrolizumab significantly reduced the risk of death by 21% (hazard ratio [HR], 0.79; 95% CI: 0.63–0.99; p = 0.0180), prolonged PFS (HR, 0.74; 95% CI: 0.60–0.92; p = 0.0032), and improved objective response rate (ORR; estimated difference, 11.4%; 95% CI: 6.7–16.0; $p < 0.0001$), with a manageable safety profile. As in other second-line trials (KEYNOTE-240 [7] and KEYNOTE-224 [10]), durable responses with pembrolizumab were also seen in KEYNOTE-394 [13], highlighting an important benefit of PD-1/programmed death ligand 1 (PD-L1) inhibitors in HCC. We report the results of the prespecified exploratory HRQoL analyses of this study.

Materials and Methods

Study Design and Patients

The study design and inclusion/exclusion criteria for KEYNOTE-394 (NCT03062358) were described previously [13]. Briefly, eligible patients were adults with either pathologically or radiographically confirmed HCC, radiographic progression of disease during or after treatment with or intolerance to sorafenib or oxaliplatin-based chemotherapy, Barcelona Clinic Liver Cancer stage C disease or stage B disease not amenable to or refractory to locoregional therapy and not amenable to curative treatment, Child-Pugh class A liver function, Eastern Cooperative Oncology Group performance status of 0 or 1, and ≥1 measurable lesion per investigator-assessed Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1). The study was conducted in accordance with standards of good clinical practice and the Declaration of Helsinki. The study protocol was approved by the appropriate Institutional Review Board/Ethics Review Committee at each site, and the name of each Ethics Committee/Institutional Review Board at each site is shown in online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000535338). All patients provided written informed consent.

Patients were randomly assigned 2:1 to receive pembrolizumab (200 mg) or saline placebo intravenously every 3 weeks for up to 35 cycles (approximately 2 years). Patients were allowed to receive BSC as per local guidelines. Randomization was stratified by prior treatment (sorafenib vs. chemotherapy), macrovascular invasion (yes vs. no), and HCC etiology (hepatitis B virus vs. others [hepatitis C virus or noninfection]). Treatment was discontinued on disease progression, unacceptable toxicity, intercurrent illness that prevented further treatment, withdrawal by investigator or patient, noncompliance with treatment/procedure, pregnancy, or receipt of 35 cycles of study treatment.

HRQoL Assessments

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQoL-5-Dimensions, 3-Level (EQ-5D-3L) questionnaires

Table 1. Completion and compliance rates* for HRQoL assessments from baseline to week 12

	Pembrolizumab (*n* = 298)	Placebo (*n* = 152)
EORTC QLQ-C30		
Baseline, *n* (%)	298 (100)	152 (100)
Week 3		
Completion, *n* (%)	280 (94.0)	147 (96.7)
Compliance, *n/N* (%)	280/284 (98.6)	147/148 (99.3)
Week 6		
Completion, *n* (%)	266 (89.3)	131 (86.2)
Compliance, *n/N* (%)	266/280 (95.0)	131/139 (94.2)
Week 9		
Completion, *n* (%)	216 (72.5)	106 (69.7)
Compliance, *n/N* (%)	216/225 (96.0)	106/111 (95.5)
Week 12		
Completion, *n* (%)	199 (66.8)	101 (66.4)
Compliance, *n/N* (%)	199/208 (95.7)	101/107 (94.4)
EQ-5D-3L		
Baseline, *n* (%)	298 (100)	151 (99.3)
Week 3		
Completion, *n* (%)	281 (94.3)	147 (96.7)
Compliance, *n/N* (%)	281/284 (98.9)	147/148 (99.3)
Week 6		
Completion, *n* (%)	266 (89.3)	132 (86.8)
Compliance, *n/N* (%)	266/280 (95.0)	132/139 (95.0)
Week 9		
Completion, *n* (%)	216 (72.5)	106 (69.7)
Compliance, *n/N* (%)	216/226 (95.6)	106/111 (95.5)
Week 12		
Completion, *n* (%)	199 (66.8)	102 (67.1)
Compliance, *n/N* (%)	199/208 (95.7)	102/107 (95.3)

*Completion rate was defined as the percentage of patients who completed ≥1 HRQoL assessment at each time point. Compliance with HRQoL assessment was defined as the percentage of patients who completed ≥1 item over those who were expected to complete the questionnaires (not including patients missing by design, such as death, discontinuation, translation not available). The primary time point for the analyses of HRQoL endpoints, week 12, was selected as the latest time point at which completion rate was ≥60% and compliance rate was ≥80% based on blinded data review. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-3L, EuroQol-5-Dimension, 3-Level; HRQoL, health-related quality of life; PRO, patient-reported outcomes.

were administered at baseline; weeks 3, 6, 9, 12, and 18; every 9 weeks thereafter for up to 1 year or till the end of treatment; treatment discontinuation; and the 30-day safety follow-up visit. EQ-5D-3L was assessed, followed by EORTC QLQ-C30, both before drug administration, adverse event evaluation, and disease status notification.

Endpoints

The primary endpoint was OS. Key secondary endpoints included PFS, ORR (both assessed per RECIST v1.1 by blinded independent central review), and safety and tolerability. HRQoL outcomes were prespecified exploratory endpoints. Key HRQoL endpoints included mean score changes from baseline to week 12 evaluated by EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) scale and subscales/items and EQ-5D-3L. The primary time point for the analyses of HRQoL endpoints, week 12, was selected as the latest time point at which the completion rate was ≥60% and the compliance rate was ≥80% based on blinded data review (Table 1). Other HRQoL endpoints were time to deterioration (TTD) for EORTC QLQ-C30 GHS/QoL and the number/proportions of patients with improved, stable, or deteriorated QLQ-C30 subscales/items. TTD was defined as time to the first onset of ≥10-point decline from

baseline and confirmed by a second adjacent ≥10-point decline from baseline. A score change of ≥10 points from baseline was used to classify the change as improved or deteriorated; this magnitude is generally perceived by patients as being clinically meaningful [14]. The EORTC QLQ-C30 includes five functional dimensions (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), and six single-item measures (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties). The EQ-5D-3L comprises five health state dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with each dimension rated on three severity levels [15].

Statistical Analyses

HRQoL endpoints were analyzed in all randomly assigned patients who received ≥1 dose of study treatment and completed ≥1 HRQoL assessment. Completion rate was defined as the percentage of patients who completed ≥1 HRQoL assessment at each time point. Compliance with HRQoL assessment was defined as the percentage of patients who completed ≥1 item over those who were expected to complete the questionnaires (not including patients missing by design, such as death, discontinuation, translation not available).

Least squares mean (LSM) score changes from baseline to week 12 were compared using a constrained longitudinal data analysis model. Treatment by study visit interaction and stratification factors were used as covariates. The Kaplan-Meier method was used to estimate TTD for EORTC QLQ-C30 GHS/QoL. Patients receiving study treatment or who discontinued the study without deterioration were censored at the time of the last assessment, and patients without baseline EORTC QLQ-C30 assessments were censored at the treatment start date. A stratified Cox proportional hazards model was used to assess the magnitude of the treatment difference (HR) between treatment arms in TTD. p values for all HRQoL analyses were one-sided and nominal. There was no adjustment for multiplicity.

Proportions of patients with improved, stable, or deteriorated scores for EORTC QLQ-C30 GHS/QoL and subscales/items at week 12 were summarized by treatment group and at the prior analysis visit, with multiple imputations based on the missing-at-randomization assumption. A linear transformation was applied to standardize each scale or item score as between 0 and 100, with a higher value indicating a better level of functioning for GHS/QoL scales/functioning but a worse severity of symptoms for symptom scales/items [16]. The EQ-5D-3L included a graded (0–100) vertical visual analog scale (VAS) on which patients rated their overall health state at the time of the assessment.

Results

Patients

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 (Fig. 1). Median time from randomization to data cutoff (June 30, 2021) was 33.8 months (range, 18.7–49.0). As reported previously, baseline characteristics were generally balanced across treatment arms [13]. With the exception of 1 patient in the pembrolizumab arm, all randomly assigned patients received ≥1 dose of assigned study treatment. Among these, the HRQoL analysis population included 298 patients in the pembrolizumab arm and 152 patients in the placebo arm. Two patients in the pembrolizumab group were excluded from HRQoL analyses because one did not receive study treatment and one did not complete ≥1 HRQoL assessment, and 1 patient in the placebo group was excluded because he/she did not complete ≥1 HRQoL assessment. Mean baseline EORTC QLQ-C30 GHS/QoL and EQ-5D VAS scores were similar between the arms (Fig. 2 and Table 2).

Compliance with EORTC QLQ-C30 at week 12 was 95.7% for pembrolizumab and 94.4% for placebo. Completion with EORTC QLQ-C30 at week 12 was 66.8% for pembrolizumab and 66.4% for placebo. Compliance with EQ-5D-3L at week 12 was 95.7% for pembrolizumab and 95.3% for placebo. Completion with EQ-5D-3L at week 12 was 66.8% for pembrolizumab and 67.1% for placebo (Table 1). The decline in completion rates at week 12 was associated with an increase in the number of patients who discontinued because of an adverse event, clinical progression, noncompliance with study drug, disease progression, patient withdrawal, or because they had no scheduled visit.

Key HRQoL Endpoints

For the EORTC QLQ-C30 GHS/QoL score, greater decline in LSM change from baseline to week 12 was observed in the placebo arm (LSM, −8.4; 95% CI: −11.7 to −5.1) versus the pembrolizumab arm (−4.0; 95% CI: −6.4 to −1.6; difference vs. placebo: 4.4; 95% CI: 0.5–8.4; nominal p = 0.0142) (Table 2). EORTC QLQ-C30 GHS/QoL mean scores generally remained stable over time in the pembrolizumab arm (Table 2; Fig. 2a, b). From baseline to week 12, LSM scores showed a larger decrease in all functional domains and an increase in all symptom domains (Fig. 3a, b) in the placebo arm, demonstrating deterioration in functioning and symptoms, as compared with the pembrolizumab arm. From baseline to week 12, LSM scores showed improvement in emotional functioning and symptoms of diarrhea and financial difficulty in the pembrolizumab arm. For the EQ-5D VAS score, greater decline was observed in the placebo arm (−6.9; 95% CI: −9.4 to −4.5) compared with the pembrolizumab arm (−2.7; 95% CI: −4.5 to −1.0; difference vs. placebo: 4.2; 95% CI: 1.2–7.2; nominal p = 0.0030) (Table 2).

Supportive HRQoL Endpoints

Generally, there were higher proportions of patients whose HRQoL functions and symptoms improved or remained stable in the pembrolizumab arm versus those in the placebo arm according to EORTC QLQ-C30 GHS/

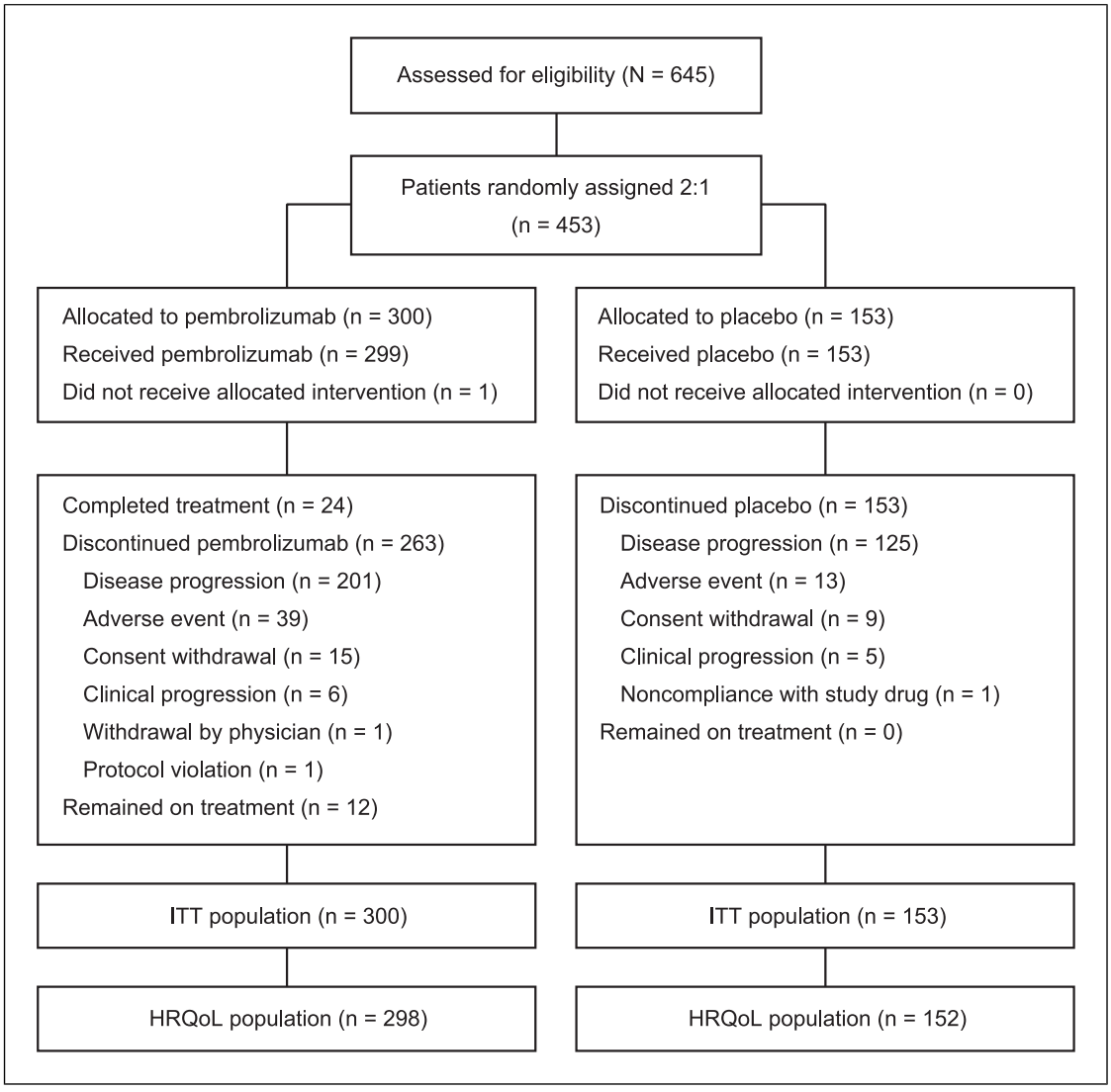

Fig. 1. Patient disposition in KEYNOTE-394 (CONSORT diagram). ITT, intention-to-treat; HRQoL, health-related quality of life.

QoL and domain scores (Fig. 4). A total of 72 patients (24.2%) in the pembrolizumab arm and 41 patients (27.0%) in the placebo arm experienced confirmed deterioration in EORTC QLQ-C30 GHS/QoL. Median TTD was not reached in either arm (HR, 0.85; 95% CI: 0.58–1.25; nominal $p = 0.1993$; Fig. 5).

Discussion

In prespecified exploratory HRQoL analyses from KEYNOTE-394, second-line pembrolizumab showed favorable HRQoL outcomes compared with placebo, both given with BSC for patients in Asia with advanced HCC. The benefit of pembrolizumab on HRQoL versus placebo, along with its clinically meaningful and statistically significant improvement in OS, PFS, and ORR, and manageable safety profile [13], supports a positive benefit-risk profile for pembrolizumab.

In our study, EORTC QLQ-C30 GHS/QoL mean scores generally remained stable over time in patients treated with pembrolizumab plus BSC. When we compared the LSM score change in EORTC QLQ-C30 GHS/QoL from baseline to week 12 between the two arms, we observed a greater decline in the placebo arm (pembrolizumab vs. placebo, 4.4; 95% CI: 0.5–8.4;

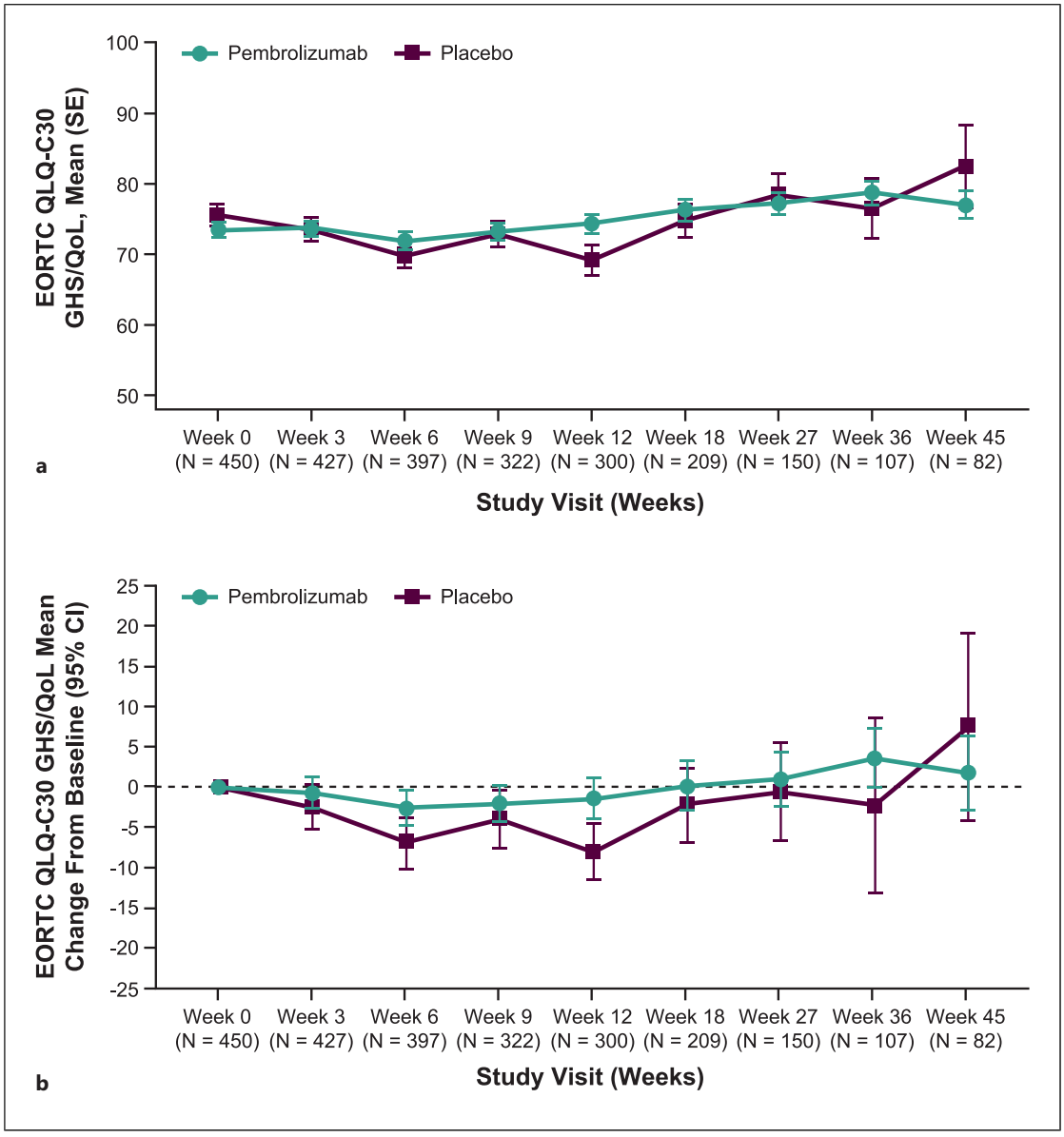

Fig. 2. EORTC QLQ-C30 mean (SE) GHS/QoL scores (**a**) and mean score changes from baseline (95% CI) over time (**b**). EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; QoL, quality of life.

nominal $p = 0.0142$). From baseline to week 12, results in EORTC QLQ-C30 functional and symptom domain scores consistently demonstrated more deterioration in HRQoL in the placebo arm compared with the pembrolizumab arm. Furthermore, consistent and favorable EQ-5D-3L outcomes were observed with pembrolizumab compared with placebo at week 12. Together, these findings suggest that adding pembrolizumab to BSC decreased the level of HRQoL deterioration compared with placebo plus BSC.

For supportive HRQoL endpoints, a score change of ≥10 points from baseline for EORTC QLQ-C30 was used to characterize the change as improved or deteriorated because this magnitude is generally considered clinically meaningful [14]. From baseline to week 12, higher proportions of patients reported improved or stable HRQoL functions and symptoms in the pembrolizumab arm versus those in the placebo arm according to EORTC QLQ-C30 GHS/QoL and domain scores. In addition, TTD was similar between the two arms. Less

Table 2. Change from baseline to week 12 in EORTC QLQ-C30 GHS/QoL and EQ-5D VAS scores

	Pembrolizumab	Placebo
EORTC QLQ-C30 GHS/QoL		
Baseline, mean (SD)	73.5 (18.8); *n* = 298	75.7 (17.9); *n* = 152
Week 12, mean (SD)	74.4 (18.1); *n* = 199	69.2 (20.8); *n* = 101
Change from baseline to week 12, LSM (95% CI)	−4.0 (−6.4 to −1.6); *n* = 298	−8.4 (−11.7 to −5.1); *n* = 152
Difference in LSM change from baseline to week 12 (95% CI)	4.4 (0.5–8.4) *p* = 0.0142	
EQ-5D VAS		
Baseline, mean (SD)	82.5 (13.8); *n* = 298	82.9 (13.3); *n* = 151
Week 12, mean (SD)	83.7 (12.5); *n* = 199	79.0 (17.1); *n* = 102
Change from baseline to week 12, LSM (95% CI)	−2.7 (−4.5 to −1.0); *n* = 298	−6.9 (−9.4 to −4.5); *n* = 152
Difference in LSM change from baseline to week 12 (95% CI)	4.2 (1.2–7.2) *p* = 0.0030	

EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D VAS, EuroQol-5-Dimension visual analog scale; GHS, global health status; LSM, least squares mean; QoL, quality of life.

than one-third of patients experienced confirmed deterioration for EORTC QLQ-C30 GHS/QoL; thus, median TTD was not reached in either arm.

The benefit of pembrolizumab on HRQoL in patients with advanced HCC is generally consistent with findings from studies of pembrolizumab in HCC [12] and other therapeutic areas that included HRQoL assessments [17–23]. In the global second-line, double-blind, phase 3 KEYNOTE-240 trial, pembrolizumab preserved HRQoL during treatment for advanced HCC. HRQoL was generally stable over time and was comparable between the pembrolizumab and placebo arms in KEYNOTE-240 [12].

HRQoL for other second-line treatment options for HCC (e.g., regorafenib, cabozantinib, and ramucirumab) has also been reported in phase 3 trials. In the double-blind phase 3 RESORCE trial in patients with HCC whose disease progressed on sorafenib, no clinically meaningful differences in HRQoL were noted between the regorafenib and placebo groups [24]. In the double-blind phase 3 CELESTIAL trial in patients with advanced HCC previously treated with sorafenib, cabozantinib was associated with an initial significant worsening in mean health utility scores for cabozantinib until week 33. At weeks 33, 49, and 65, health utility scores improved and favored cabozantinib, although this trend was not consistent up to week 81 [25, 26]. In a pooled analysis of 2 phase 3 studies, REACH and REACH-2, in previously treated patients with advanced HCC and α-fetoprotein levels ≥400 ng/mL, ramucirumab significantly delayed deterioration in disease-related symptoms compared with placebo based on total Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index scores and individual symptoms of back pain, weight loss, and pain [27]. In our study, HRQoL results generally favored pembrolizumab over placebo because patients treated with pembrolizumab showed less pronounced deterioration in HRQoL.

Despite the recent broadening of the HCC therapeutic landscape, the optimal treatment strategy remains unknown. Recently, the combination of atezolizumab (a PD-L1 inhibitor) and bevacizumab (an anti-vascular endothelial growth factor antibody) demonstrated a significant survival benefit versus sorafenib in patients with unresectable HCC in the front-line setting in the open-label phase 3 IMbrave150 study and is considered a new standard of care in the front-line setting [6]. Additionally, analysis of prespecified patient-reported outcomes from IMbrave150 showed clinically meaningful benefit in QoL, functioning, and key symptoms with atezolizumab plus bevacizumab compared with sorafenib [28]. Although efficacy, the adverse event profile, and HRQoL outcomes demonstrated a positive benefit-to-risk profile for atezolizumab plus bevacizumab, the IMbrave150 study excluded patients such as those with significant cardiovascular disease, unstable arrhythmia/angina, or anticoagulant use. Patients who are not candidates for atezolizumab plus bevacizumab may receive tremelimumab plus durvalumab (STRIDE regimen) [29] or first-line tyrosine kinase inhibitors (TKIs) such as sorafenib [30, 31] and lenvatinib [8]. The STRIDE regimen was associated with a manageable adverse event profile. A total of 35.8% of patients (139/388) had immune-mediated adverse events, with 20.1% (78/388) requiring high-dose steroid [29]. Both lenvatinib and sorafenib remain in clinical use, especially for patients

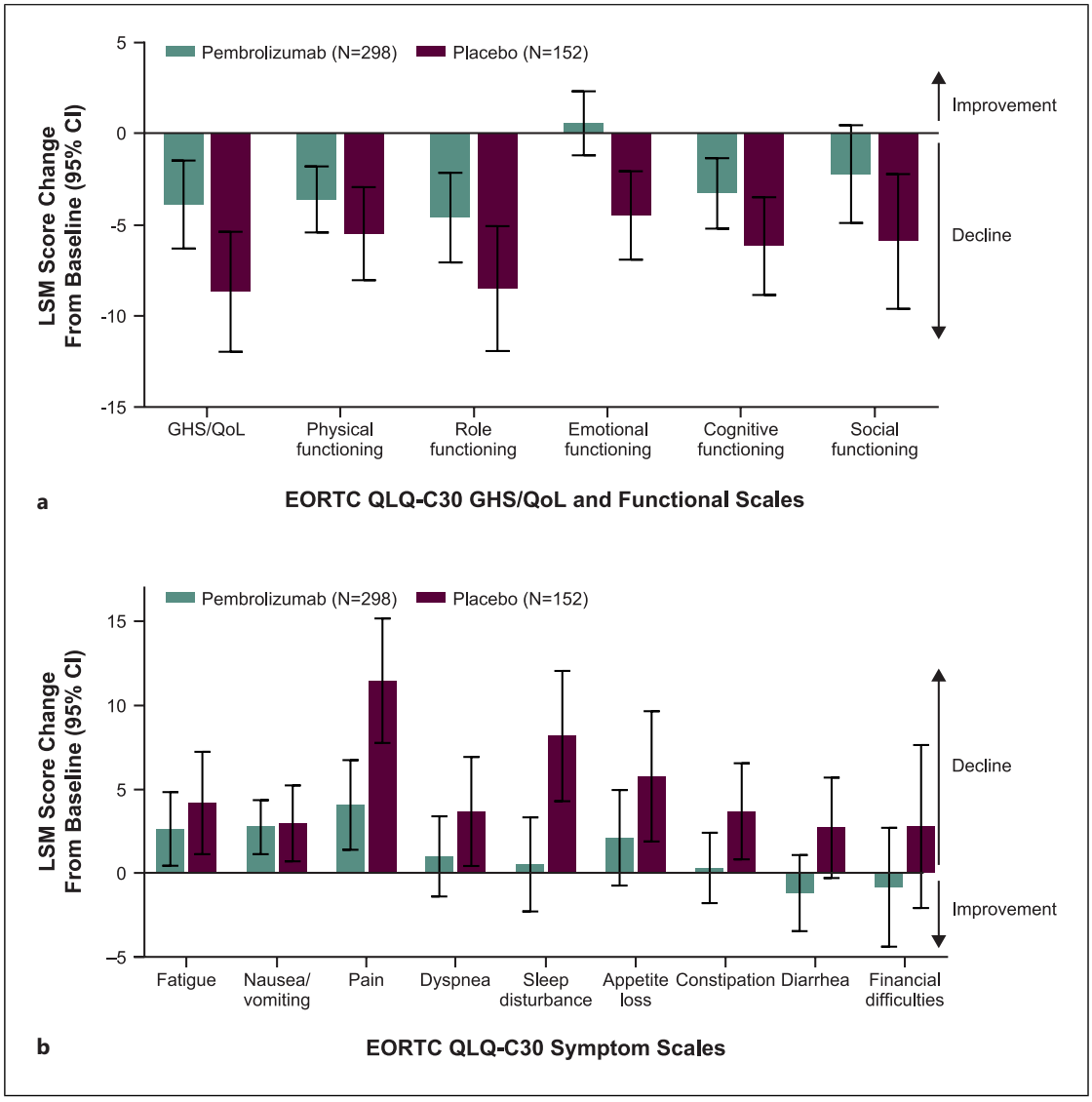

Fig. 3. Least squares mean (95% CI) score change from baseline to week 12 in EORTC QLQ-C30 GHS/QoL and functional domain scores (**a**) and EORTC QLQ-C30 symptom domain scores (**b**). EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; LSM, least squares mean; QoL, quality of life.

who are unable to tolerate, are ineligible for, or decline either atezolizumab plus bevacizumab or the STRIDE regimen. In this context, subsequent immunotherapy, including pembrolizumab and the combination of nivolumab plus ipilimumab, may fulfill the unmet medical need among patients with advanced HCC treated with first-line TKIs.

Patients with HCC generally have worse HRQoL than the general population. Patients often experience pain, fatigue, sleep disturbance, distress, and loss of appetite [5, 32, 33]. Therefore, treatment toxicity/tolerability and impact on HRQoL are important considerations and should influence decision-making processes regarding HCC management. In the phase 3 KEYNOTE-394 trial, pembrolizumab not only significantly reduced the risk of death by 21% (median OS with pembrolizumab vs. placebo, 14.6 vs. 13.0 months; HR, 0.79; 95% CI: 0.63–0.99; p = 0.0180) and provided durable responses (median duration of response, 23.9 vs. 5.6 months), but also demonstrated a manageable safety profile (grade 3–5 treatment-related adverse events, 14.4% with pembrolizumab) [13]. In the phase 2 CheckMate 040 study of

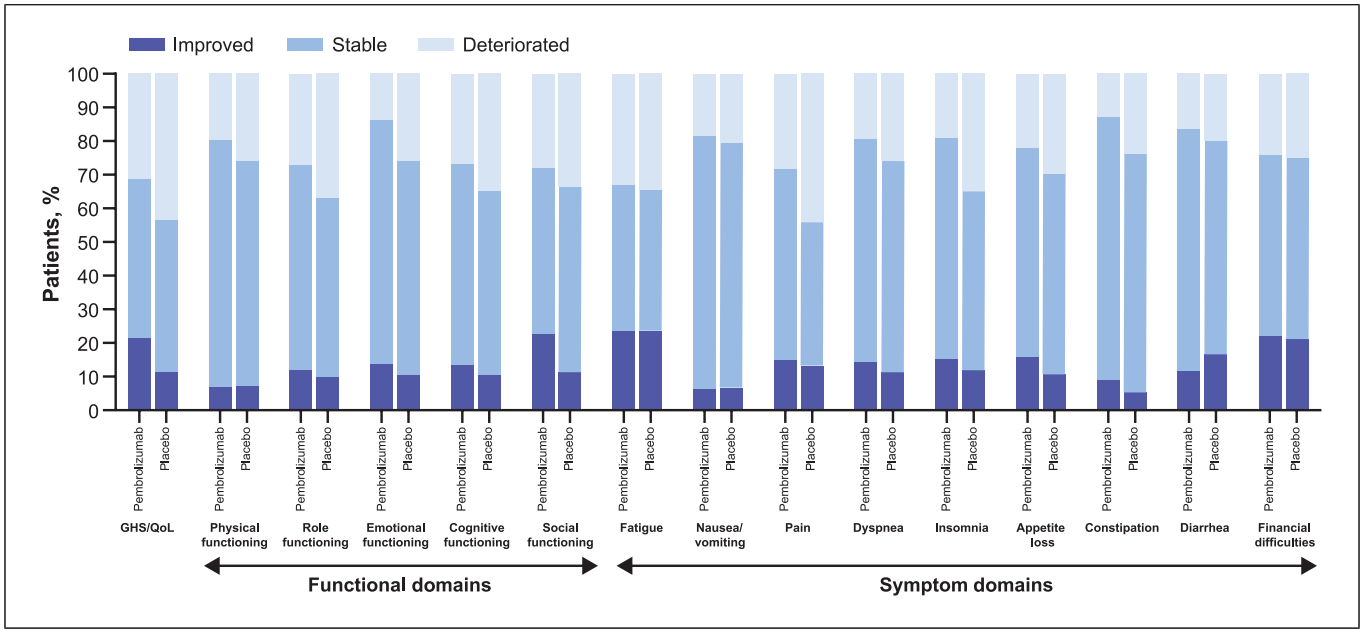

Fig. 4. Proportions of patients reporting improved, stable, or deteriorated EORTC QLQ-C30 scores at week 12. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; QoL, quality of life.

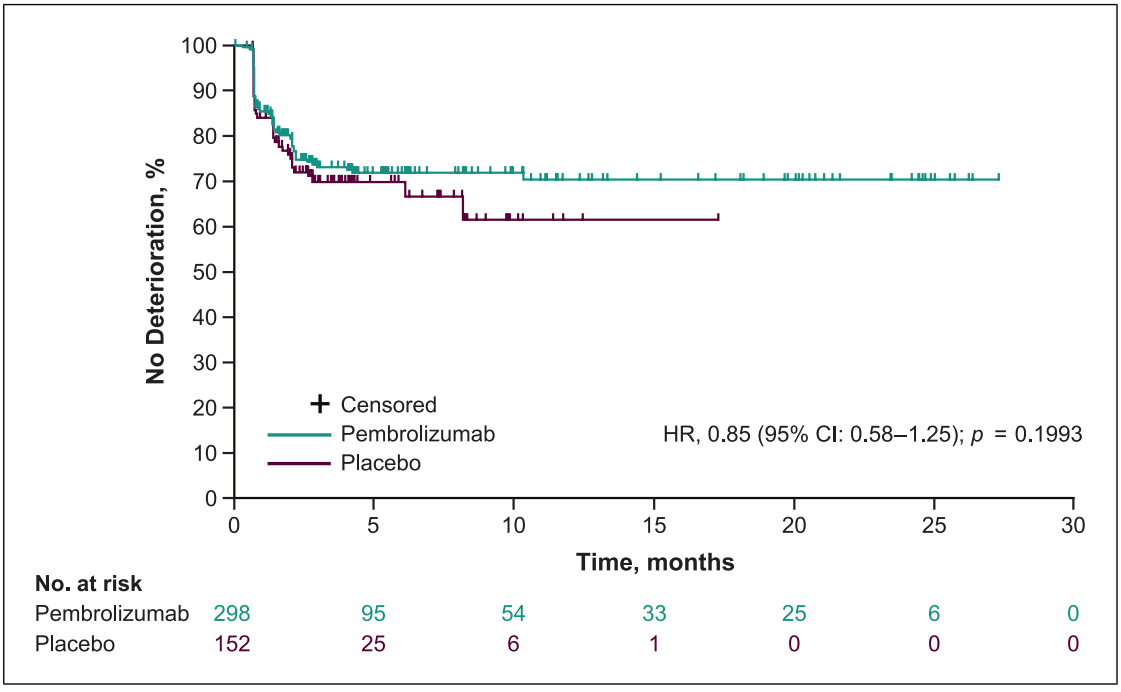

Fig. 5. Kaplan-Meier estimates of time to deterioration in EORTC QLQ-C30 GHS/QoL. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; HR, hazard ratio; QoL, quality of life.

nivolumab plus ipilimumab in patients with advanced HCC previously treated with sorafenib, nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) was associated with a median OS of 22.2 months and durable responses (median duration of response, 17.5 months). However, this regimen also led to grade 3 or 4 treatment-related adverse events in 53% of patients and the need for high-dose glucocorticoid therapy in more than half of patients who had a hepatic immune-mediated adverse event [34]. In this regard, the HRQoL benefit of pembrolizumab, along with its clinically meaningful and statistically significant benefit on OS, PFS, ORR, meaningful tumor shrinkage, long-term disease control, and manageable safety [13], highlights the overall clinical benefit of pembrolizumab among other treatment options in the second-line setting for advanced HCC.

Our study was a randomized, double-blind, placebo-controlled, phase 3 trial; thus, the risk of bias was decreased relative to an open-label study design. Additionally, the compliance rates through our primary time point (week 12) were high (>90%), reducing the effect of missing data on interpretation of the results. The main limitations of our study were that it recruited only patients from Asia, >90% of patients had Barcelona Clinic Liver Cancer stage C HCC (advanced stage), and all patients had Child-Pugh class A liver function. However, pembrolizumab has demonstrated consistent benefit on HRQoL across various indications, including diverse populations that include patients with HCC [12, 17–23]. In addition, BSC varied as per local guidelines and may have confounded the impact of pembrolizumab on HRQoL. Furthermore, placebo plus BSC as a comparator in this study is another limitation. When the study was initiated, there were no approved therapies in the second-line treatment setting for advanced HCC. However, over time, the treatment landscape has evolved; therefore, the results should be interpreted in this context. Finally, another limitation was that HRQoL endpoints were exploratory and not included in the formal statistical hypotheses testing with an overall controlled alpha, and therefore, the *p* values reported here were nominal.

In conclusion, pembrolizumab plus BSC demonstrated benefit for HRQoL versus placebo plus BSC in patients in Asia with previously treated advanced HCC. Greater decline in HRQoL with placebo versus pembrolizumab was observed. TTD was similar between the two arms. Combined with the efficacy and safety results from KEYNOTE-394, as well as other global second-line trials with pembrolizumab, including KEYNOTE-240 and KEYNOTE-224, our data support the benefit of pembrolizumab as second-line therapy for patients with advanced HCC.

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Statement of Ethics

The study was conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the appropriate Institutional Review Board/Ethics Review Committee at each site, and the name of each Ethics Committee/Institutional Review Board at each site is shown in online suppl. Table S1. All patients provided written informed consent.

Conflict of Interest Statement

Shukui Qin, Weijia Fang, Shuangyan Ou, Feng Zhang, Kin Chung Lee, Hye Jin Choi, Jiandong Tong, Min Tao, Aibing Xu, Ashley Cheng, Chang-Hsien Lu, Chang-Fang Chiu, Mohamed Ibrahim Abdul Wahid, and Zhendong Chen report no conflicts of interest. Ho Yeong Lim reports serving in an advisory role for Bayer, Eisai, AstraZeneca, Roche, and Ipsen. Zhenggang Ren reports serving in a consulting or advisory role for AstraZeneca, Merck Sharp & Dohme, and Roche. Shital Kamble and Josephine M. Norquist are full-time employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and hold stock in Merck & Co., Inc., Rahway, NJ, USA. Wenyan Zhong and Chen Li are full-time employees of MSD China. The idea for this study originated with the study sponsor, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Author Contributions

Concept and design: Shukui Qin and Zhenggang Ren. Acquisition of data: Shukui Qin, Weijia Fang, Zhenggang Ren, Shuangyan Ou, Ho Yeong Lim, Feng Zhang, Kin Chung Lee, Hye Jin Choi, Jiandong Tong, Min Tao, Aibing Xu, Ashley Cheng, Chang-Hsien Lu, Chang-Fang Chiu, Mohamed Ibrahim Abdul Wahid, and Zhendong Chen. Analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published, access to all the data, and responsibility for the integrity of the data and the accuracy of the data analysis: Shukui Qin, Weijia Fang, Zhenggang Ren, Shuangyan Ou, Ho Yeong Lim, Feng Zhang, Kin Chung Lee, Hye Jin Choi, Jiandong Tong, Min Tao, Aibing Xu, Ashley Cheng, Chang-Hsien Lu, Chang-Fang Chiu, Mohamed Ibrahim Abdul Wahid, Shital Kamble, Josephine M. Norquist, Wenyan Zhong, Chen Li, and Zhendong Chen.

Data Availability Statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (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 USA and EU 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. Further inquiries regarding the data and the manuscript can be directed to the corresponding author, Shukui Qin, via email (qinsk@csco.org.cn).

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