Received: 19 August 2022 | Revised: 24 October 2022 | Accepted: 7 November 2022

DOI: 10.1111/cas.15650

ORIGINAL ARTICLE

Cancer Science WILEY

Pembrolizumab in Asian patients with microsatellite-instability-high/mismatch-repair-deficient colorectal cancer

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Funding information
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Abstract

The phase 3 KEYNOTE-177 study evaluated pembrolizumab versus chemotherapy with or without bevacizumab or cetuximab in patients with newly diagnosed, microsatellite-instability-high (MSI-H)/mismatch-repair-deficient (dMMR) metastatic colorectal cancer (mCRC). Primary endpoints were progression-free survival (PFS) per RECIST v1.1 by blinded independent central review (BICR) and overall survival (OS). Secondary endpoints were overall response rate (ORR) per RECIST v1.1 by BICR and safety. Here, we report results from the post hoc analysis of patients who were enrolled in Asia from the final analysis (FA) of KEYNOTE-177. A total of 48 patients from

Japan, Korea, Singapore, and Taiwan (pembrolizumab, $n = 22$; chemotherapy, $n = 26$) were included. At FA, median time from randomization to data cutoff (February 19, 2021) was 45.3 (range 38.1–57.8) months with pembrolizumab and 43.9 (range 36.6–55.1) months with chemotherapy. Median PFS was not reached (NR; 95% confidence interval [CI] 1.9 months–NR) with pembrolizumab versus 10.4 (95% CI 6.3–22.0) months with chemotherapy (hazard ratio [HR] 0.56, 95% CI 0.26–1.20). Median OS was NR (range 13.8 months–NR) versus 30.0 (14.7–NR) months (HR 0.65, 95% CI 0.27–1.55) and ORR was 50% (95% CI 28–72) versus 46% (95% CI 27–67). Grade 3/4 treatment-related adverse events (TRAEs) were reported by two patients (9%) in the pembrolizumab arm and 20 (80%) in the chemotherapy arm. Immune-mediated adverse events or infusion reactions were reported by six patients (27%) and 10 patients (40%), respectively. No deaths due to TRAEs occurred. These data support first-line pembrolizumab as a standard of care for patients from Asia with MSI-H/dMMR mCRC. ClinicalTrials.gov identifier: NCT02563002.

KEYWORDS
Asia, colorectal cancer, microsatellite instability, mismatch-repair deficiency, pembrolizumab

1 | INTRODUCTION

Colorectal cancer (CRC) was the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related mortality in 2020.[1] Although outcomes have improved with early detection and advances in treatment, the 5-year overall survival (OS) rate for patients with metastatic CRC (mCRC) remains less than 15%.[2,3] The incidence of CRC has risen in most countries over the last three decades, with a substantial increase observed in Asia.[4] Particularly high rates of CRC have been reported in high-income countries in East and Southeast Asia, suggested to be largely attributable to the adoption of a Westernized lifestyle, the prevalence of smoking, and the aging population.[5] In 2017, the age-standardized incidence rate of CRC (per 100,000 person-years) was 48.0 in Taiwan, 45.0 in Japan, 34.9 in Singapore, and 32.5 in South Korea compared with a global rate of 23.2.[4] Therefore, there is substantial interest in the effectiveness of emerging treatments for CRC in patients from Asia.

Treatment options for patients with unresectable CRC worldwide have until recently been limited to chemotherapy and targeted agents.[6,7] Evidence from a number of clinical trials has shown that CRC tumors characterized by DNA mismatch-repair deficiency (dMMR) and a high degree of microsatellite instability (MSI-H) are susceptible to treatment with immune checkpoint inhibitors (ICIs).[8–11] Tumors that are MSI-H/dMMR have an increased tumor mutational burden that leads to the production of neoantigens, resulting in MSI-H/dMMR tumors being more immunogenic than those with proficient DNA mismatch repair.[12] As a result, MSI-H/dMMR tumors are associated with high numbers of tumor-infiltrating lymphocytes, whose activity can be enhanced by ICI.[12] The programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab have both demonstrated substantial antitumor activity in patients with previously treated MSI-H/dMMR mCRC.[8–11] As a consequence, treatment guidelines for Asia were updated to recommend routine MMR testing because of the strong predictive value of MMR status for the use of ICIs in mCRC.[6] Recent data from the phase 3 KEYNOTE-177 study showed that pembrolizumab has robust and durable antitumor activity as first-line therapy in patients with MSI-H/dMMR mCRC.[13,14] Pembrolizumab provided significantly longer median progression-free survival (PFS) compared with chemotherapy (16.5 vs. 8.2 months, hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.45–0.80, $P = 0.0002$) at the second interim analysis and a nonstatistically significant but clinically meaningful improvement in OS at final analysis (FA; median not reached [NR] vs. 36.7 months, HR 0.74, 95% CI 0.53–1.03, $P = 0.036$).[13,14] Fewer treatment-related adverse events (TRAEs) were reported with pembrolizumab compared with chemotherapy, with clinically meaningful improvement in health-related quality of life.[14,15] However, data are limited on the efficacy of ICIs in Asian patients with MSI-H/dMMR mCRC. Here, we report results from the FA of the KEYNOTE-177 study for patients who were enrolled in Asia.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

KEYNOTE-177 (NCT02563002) was an international, multicenter, open-label, phase 3 study. Details of the study were previously published.[13] In brief, eligible patients were aged at least 18 years and had MSI-H/dMMR stage IV CRC. Patients had measurable disease per RECIST v1.1, an ECOG performance status of 0 or 1, and

adequate organ function. Patients must not have received prior systemic therapy for stage IV CRC but may have received prior adjuvant chemotherapy for CRC completed at least 6 months before randomization.

Patients were randomly assigned (1:1) to receive pembrolizumab 200 mg i.v. every 3 weeks or the investigator's choice of chemotherapy with or without bevacizumab or cetuximab every 2 weeks. No stratification factors were used for randomization. The choice of chemotherapeutic regimen was determined prior to randomization. Chemotherapy options included modified FOLFOX6 (mFOLFOX6; oxaliplatin 85 mg/m^2 i.v. over 2 h, day 1; leucovorin 400 mg/m^2 i.v. over 2 h, day 1; 5-fluoropyrimidine 400 mg/m^2 i.v. bolus, day 1, then 1200 mg/m^2/day for 2 days for a total of 2400 mg/m^2 delivered by continuous infusion over 46–48 h), mFOLFOX6 plus bevacizumab (5 mg/kg i.v., day 1), mFOLFOX6 plus cetuximab (400 mg/m^2 i.v. over 2 h, then 250 mg/m^2 i.v. over 1 h, weekly), FOLFIRI (irinotecan 180 mg/m^2 i.v. over 30–90 min, day 1; leucovorin 400 mg/m^2 i.v. infusion to match irinotecan, day 1; 5-fluoropyrimidine 400 mg/m^2 i.v. bolus, day 1, then 1200 mg/m^2/day for 2 days for a total of 2400 mg/m^2 delivered by continuous infusion over 46–48 h), FOLFIRI plus bevacizumab (5 mg/kg i.v., day 1), and FOLFIRI plus cetuximab (400 mg/m^2 i.v. over 2 h, then 250 mg/m^2 i.v. over 1 h, weekly). Treatment with pembrolizumab was continued for ≤2 years (~35 cycles) or until progressive disease (PD), unacceptable toxicity, or physician or patient decision to withdraw. Eligible patients randomly assigned to chemotherapy who experienced PD per RECIST v1.1 as assessed by the investigator and confirmed by blinded independent central review (BICR) could cross over to receive pembrolizumab for ≤35 cycles at the investigator's discretion.

2.2 | Efficacy and safety assessments

MMR or MSI status was determined locally. MMR status was determined by immunohistochemical analysis, with tumors classified as dMMR by the absence of at least one of four MMR enzymes (MLH1, MSH2, MSH6, and PMS2). Polymerase chain reaction-based analysis of tumor microsatellite loci was also undertaken locally, with MSI-H status defined as the detection of at least two allele shifts among the three to five allele shifts analyzed. Imaging by computed tomography or magnetic resonance imaging was performed every 9 weeks. Tumor response was assessed per RECIST v1.1 by BICR. Adverse events (AEs) were evaluated throughout the study and for 30 days after treatment discontinuation (90 days for serious AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

2.3 | Outcomes

The primary endpoints were PFS per RECIST v1.1 by BICR and OS. Secondary endpoints included overall response rate (ORR; complete response [CR] or partial response [PR]) per RECIST v1.1 by BICR and safety. Duration of response (DOR) per RECIST v1.1 by BICR was included as an exploratory endpoint.

2.4 | Statistical analyses

This unplanned post hoc subgroup analysis included only patients enrolled in KEYNOTE-177 from the Asian region, defined as Japan, Korea, Singapore, and Taiwan. Efficacy was assessed in the intention-to-treat (ITT) population, comprising all patients enrolled in Asia who were randomly assigned to treatment. Safety was assessed in the as-treated population, comprising all patients enrolled in Asia who were randomly assigned to treatment and received at least one dose of study treatment.

PFS, OS, and DOR were estimated using the Kaplan–Meier method. For the PFS analysis, data for patients who were alive with no PD were censored at the time of the last imaging assessment, and data for patients who underwent surgery with curative intent were censored at the surgical date. For the OS analysis, missing data for patients were censored at the date of last known contact. A Cox proportional-hazards model with Efron's method of tie handling was used to estimate HRs and associated 95% CIs.

Two interim analyses and a FA were prespecified in the protocol for the global population.[14] The FA was planned to be performed after 190 OS events had occurred across both arms or 12 months after the second interim analysis, whichever occurred first. Additional details are provided in Appendix S1 (Additional Statistical Analyses Methods, Data Availability Statement; Table S1). SAS version 9.4 was used for all statistical analyses.

2.5 | Ethics approval

Written informed consent was obtained from all patients prior to enrollment. The study protocol and all amendments were reviewed and approved by the appropriate institutional review board or ethics committee at each study center, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

3 | RESULTS

Between February 11, 2016, and February 19, 2018, of the 307 patients randomly assigned to treatment in KEYNOTE-177, 48 were from Asia (Japan [n = 22], Korea [n = 14], Singapore [n = 5], or Taiwan [n = 7]), of whom 22 received pembrolizumab and 26 received chemotherapy (Figure 1). At data cutoff (February 19, 2021), of the 22 patients who were assigned to receive pembrolizumab, all received ≤1 dose of study treatment, 10 (45%) completed study treatment, and 12 (55%) discontinued study treatment. Reasons for discontinuation in the pembrolizumab arm were radiologic PD (n = 7), AEs (n = 2), clinical progression (without radiologic

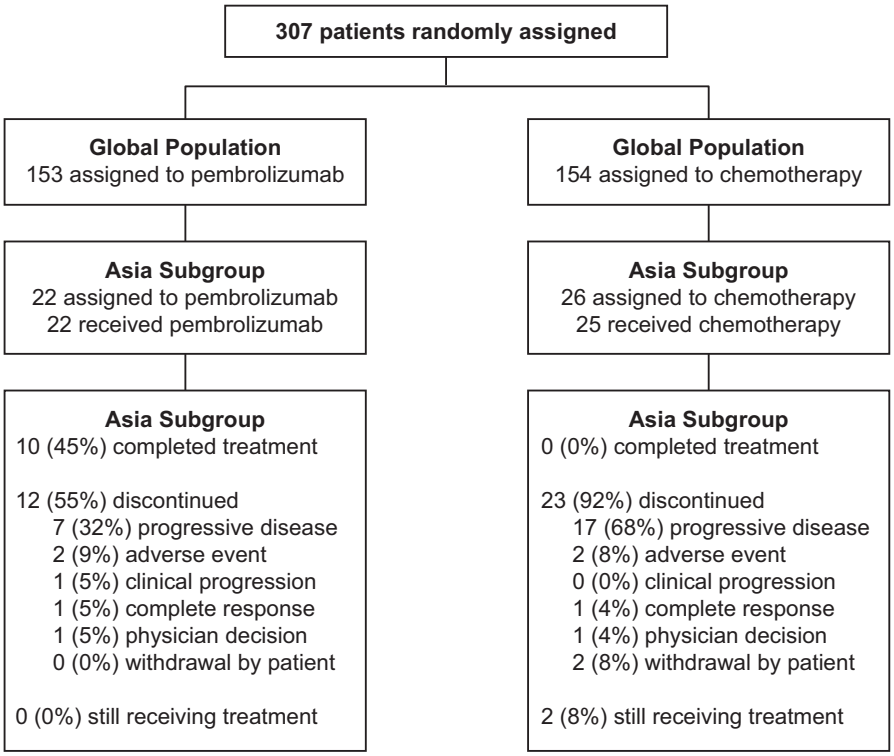

FIGURE 1 Patient disposition in the Asia subgroup

evidence) (n = 1), CR (n = 1), and physician decision (n = 1). Of the 26 patients who were assigned to receive chemotherapy, 25 received ≤1 dose of study treatment, two (8%) were continuing to receive study treatment, and 23 (92%) had discontinued study treatment. Reasons for study discontinuation in the chemotherapy arm were PD (n = 17), AEs (n = 2), withdrawal by the patient or physician (n = 3), and CR (n = 1).

The median time from randomization to data cutoff was 45.3 (range 38.1–57.8) months in the pembrolizumab arm and 43.9 (range 36.6–55.1) months in the chemotherapy arm.

3.1 | Demographics and baseline characteristics

Demographics and baseline characteristics were generally balanced between treatment arms (Table 1). The median (range) age was 65.5 (24–83) years in the pembrolizumab arm and 64.0 (31–90) years in the chemotherapy arm. Compared with chemotherapy, a higher proportion of patients receiving pembrolizumab had an ECOG performance status of 0 (13 [59%] vs. 10 [38%]), had right-sided tumors (14 [64%] vs. 13 [50%]), and had received prior (neo)adjuvant therapy (8 [36%] vs. 5 [19%]) (Table 1).

At data cutoff, two patients (9%) in the pembrolizumab arm received subsequent anti-PD-1/L1 therapies. A total of 10 patients (38%) assigned to chemotherapy had crossed over to pembrolizumab after PD was confirmed, and an additional four patients (15%) received subsequent anti-PD-1/L1 therapies outside the study, for an effective crossover rate of 54% among patients initially randomly assigned to chemotherapy (Table 2). A total of eight patients (36%) in the pembrolizumab group and six patients (23%) in the chemotherapy group received subsequent therapies other than an anti-PD-1/L1 therapy.

3.2 | Progression-free survival

At data cutoff, the median PFS was NR (95% CI 1.9 months–NR) in the pembrolizumab arm and 10.4 (6.3–22.0) months in the chemotherapy arm (HR 0.56, 95% CI 0.26–1.20) (Figure 2). The 12-month PFS rate was 62% (95% CI 38–79) in the pembrolizumab arm compared with 46% (95% CI 25–64) in the chemotherapy arm. The 24-month PFS rates were 52% (95% CI 29–71) and 28% (95% CI 11–46), respectively.

3.3 | Overall survival

The median OS was NR (95% CI 13.8 months-NR) in the pembrolizumab arm and 30.0 (14.7–NR) months in the chemotherapy arm (HR 0.65, 95% CI 0.27–1.55) (Figure 3). The 12-month OS rate was 77% (95% CI 54–90) in the pembrolizumab arm compared with 73% (95% CI 52–86) in the chemotherapy arm. The 24-month OS rates were 68% (95% CI 45–83) and 50% (95% CI 30–67), respectively.

3.4 | Radiographic response

The ORR was 50% (95% CI 28–72) in the pembrolizumab arm and 46% (95% CI 27–67) in the chemotherapy arm (Table 3). In the pembrolizumab arm, four patients (18%) had CR, seven patients (32%)

TABLE 1 Baseline characteristics of the Asia subgroup

	Pembrolizumab vs. chemotherapy	
	Pembrolizumab, *n* = 22	Chemotherapy, *n* = 26
Age, median (range), years	65.5 (24–83)	64.0 (31–90)
≥65 years	11 (50)	11 (42)
<65 years	11 (50)	15 (58)
Sex, *n* (%)		
Male	9 (41)	14 (54)
Female	13 (59)	12 (46)
Race, *n* (%)		
Asian	22 (100)	25 (96)
White	0 (0)	1 (4)
ECOG performance status, *n* (%)		
0	13 (59)	10 (38)
1	9 (41)	16 (62)
Stage, *n* (%)		
Recurrent metachronous[a]	12 (55)	11 (42)
Newly diagnosed	10 (45)	15 (58)
Metastases location, *n* (%)		
Hepatic and/or pulmonary	9 (41)	11 (42)
Other	13 (59)	15 (58)
Site of primary tumor, *n* (%)		
Right	14 (64)	13 (50)
Left	7 (32)	10 (38)
Other/missing[b]	1 (5)	3 (12)
Prior systemic therapy, *n* (%)		
Adjuvant only	6 (27)	2 (8)
Neoadjuvant with or without adjuvant	2 (9)	3 (12)
None	14 (64)	21 (81)
Mutation status, *n* (%)		
BRAF/KRAS/NRAS all wild type	4 (18)	5 (19)
KRAS/NRAS mutant and $BRAF^{V600E}$ not mutant	5 (23)	8 (31)
$BRAF^{V600E}$ mutant and *KRAS/NRAS* not mutant	5 (23)	5 (19)
Could not be evaluated for *BRAF*, *KRAS*, *NRAS*[c]	8 (36)	8 (31)
MSI-high[d]	22 (100)	26 (100)

Abbreviations: *BRAF*, v-RAF murine sarcoma viral oncogene homolog; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI, microsatellite instability; *NRAS*, neuroblastoma RAS viral oncogene homolog.

[a]Recurrence was defined as a secondary colorectal cancer occurring at least 6 months after the index cancer.

[b]The tumor site was classified as 'Other' if primary tumors were located on both the left and right sides.

[c]Patients could not be evaluated for *BRAF*, *KRAS*, or *NRAS*, if no $BRAF^{V600E}$, *KRAS*, or *NRAS* mutation was present, and if ≥1 mutation status was undetermined or missing or the type of *BRAF* mutation was not $BRAF^{V600E}$.

[d]MSI-high status was determined locally by means of a polymerase chain reaction or immunohistochemical testing.

TABLE 2 Subsequent anticancer therapy in the Asia subgroup

	Pembrolizumab, *n* = 22	Chemotherapy, *n* = 26
Any anti-PD-1/PD-L1 therapy, *n* (%)	2 (9)	14 (54)
On-protocol therapy – pembrolizumab[a]	1 (5)	10 (38)
Off-protocol therapies	1 (5)	4 (15)
Any non-anti-PD-1/PD-L1 therapy, *n* (%)	8 (36)	6 (23)
Chemotherapy	7 (32)	4 (15)
Folic acid derivative	4 (18)	2 (8)
VEGF inhibitor	4 (18)	3 (12)
EGFR inhibitor	3 (14)	1 (4)
TIM3 inhibitor	1 (5)	1 (4)

Abbreviations: EGFR, epithelial growth factor receptor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TIM3, T-cell immunoglobulin and mucin-domain containing molecule 3; VEGF, vascular endothelial growth factor.

[a]Including a second course of treatment for patients randomly assigned to the pembrolizumab arm.

had PR, and two patients (9%) had stable disease. In the chemotherapy arm, three patients (12%) had CR, nine patients (35%) had PR, and nine patients (35%) had stable disease. More patients in the pembrolizumab arm had PD compared with the chemotherapy arm (eight [36%] vs. four [15%]).

3.5 | Duration of response

The median time to response (CR or PR) was 2.1 (range 1.9–33.2) months in the pembrolizumab arm and 2.1 (range 1.9–24.9) months in the chemotherapy arm (Table 3). The median DOR was NR (range 4.4+ to 45.7+; + indicates there was no PD by the time of the last disease assessment) in the pembrolizumab arm and 18.6 (range 3.4+ to 47.9+) months in the chemotherapy arm (Figure 4 and Table 3). Seven patients (88%) in the pembrolizumab arm and four (44%) in the chemotherapy arm had an estimated DOR of at least 24 months.

3.6 | Safety

The median duration of treatment exposure was 20.7 (range 0.0–25.3) months in the pembrolizumab arm and 8.4 (range 1.6–49.2) months in the chemotherapy arm. AEs occurred in 22 patients (100%) in the pembrolizumab arm and 25 patients (100%) in the chemotherapy arm. Grade 3–5 AEs were reported in 10 patients (46%) receiving pembrolizumab and 22 (88%) receiving chemotherapy. Grade 3–5 AEs occurring in at least 10% of patients were increased gamma-glutamyl transferase levels in three patients (14%) in the pembrolizumab arm and decreased neutrophil count in 10 patients (40%), decreased white blood cell count in four patients (16%),

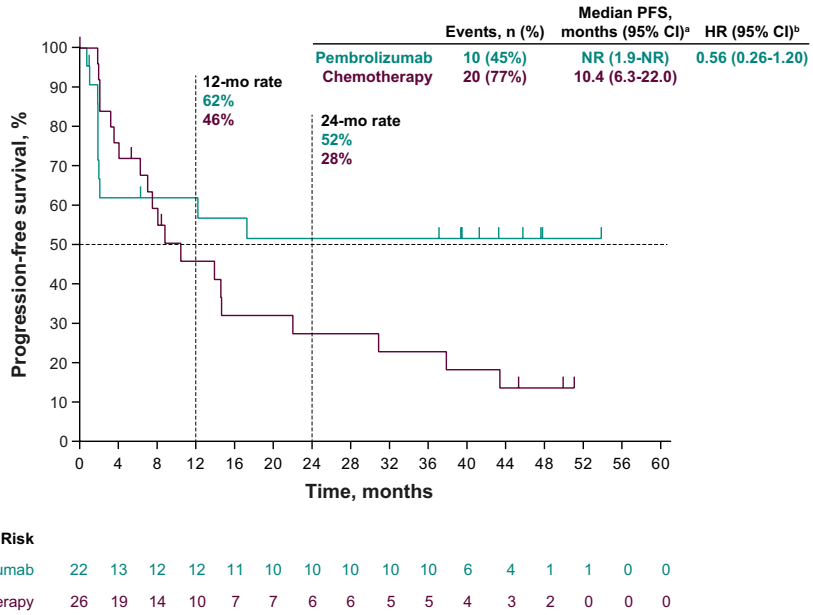

FIGURE 2 Kaplan–Meier estimates of progression-free survival (PFS) in the Asia subgroup ($n = 48$). [a]From the product-limit (Kaplan–Meier) method for censored data. [b]Based on the Cox regression model with Efron's method of tie handling with treatment as a covariate. CI, confidence interval; HR, hazard ratio; mo, month; NR, not reached

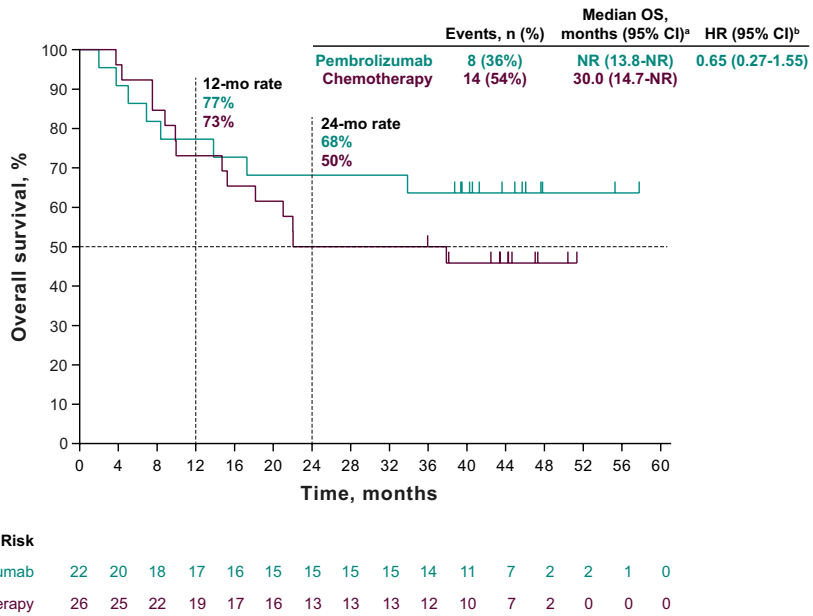

FIGURE 3 Kaplan–Meier estimates of overall survival (OS) in the Asia subgroup ($n = 48$). [a]From the product-limit (Kaplan–Meier) method for censored data. [b]Based on the Cox regression model with Efron's method of tie handling with treatment as a covariate. CI, confidence interval; HR, hazard ratio; mo, month; NR, not reached

and decreased appetite in three patients (12%) in the chemotherapy arm. TRAEs occurred in 14 patients (64%) in the pembrolizumab arm compared with 25 patients (100%) in the chemotherapy arm. Grade 3/4 TRAEs were reported for two patients (9%) and 20 patients (80%) in the pembrolizumab and chemotherapy arms, respectively; there were no grade 5 TRAEs (Tables 4 and S1). Two patients (9%) in the pembrolizumab arm and one patient (4%) in the chemotherapy arm discontinued treatment due to TRAEs (increased alanine aminotransferase levels and psoriasis in the pembrolizumab arm, and pneumonitis in the chemotherapy arm).

Immune-mediated AEs or infusion reactions occurred in six patients (27%) in the pembrolizumab arm and 10 patients (40%) in the chemotherapy arm (Table 5). These included hypothyroidism in three patients (14%), hyperthyroidism in two (9%), adrenal insufficiency in one (5%), and pneumonitis in one (5%) in the pembrolizumab arm, and hypothyroidism in two patients (8%), pneumonitis in two (8%), and colitis in one (4%) in the chemotherapy arm. Infusion reactions occurred in one patient (5%) in the pembrolizumab arm and five patients (20%) in the chemotherapy arm (all grade 1/2).

4 | DISCUSSION

In this post hoc subgroup analysis of patients from Asia with MSI-H/dMMR mCRC enrolled in KEYNOTE-177, first-line treatment with pembrolizumab provided numerically longer PFS, OS, and DOR compared with chemotherapy. The ORR was similar between the two arms. These results are generally consistent with those observed in the global population evaluated in KEYNOTE-177.[13,14] In the global population, first-line treatment with pembrolizumab

TABLE 3 Summary of antitumor responses in the Asia subgroup

	Pembrolizumab, *n* = 22	Chemotherapy, *n* = 26
Overall response[a]		
No. of patients	11	12
% (95% CI)	50.0 (28.2–71.8)	46.2 (26.6–66.6)
Best overall response, *n* (%)		
Complete response	4 (18)	3 (12)
Partial response	7 (32)	9 (35)
Stable disease	2 (9)	9 (35)
Progressive disease	8 (36)	4 (15)
Not evaluable/no assessment[b]	1 (5)	1 (4)
Time to response, median (range), months	2.1 (1.9–33.2)	2.1 (1.9–24.9)
Duration of response[c] median (range), months	NR (4.4+ to 45.7+)	18.6 (3.4+ to 47.9+)
Response duration of ≥24 months, *n* (%)[c]	7 (88)	4 (44)

Note: + Indicates there was no progressive disease by the time of the last disease assessment.
Abbreviations: CI, confidence interval; NR, not reached.
[a]Overall response was defined as a confirmed complete response or partial response.
[b]Patients for whom no postbaseline imaging was available.
[c]The Kaplan–Meier method for censored data was used to calculate median of duration.

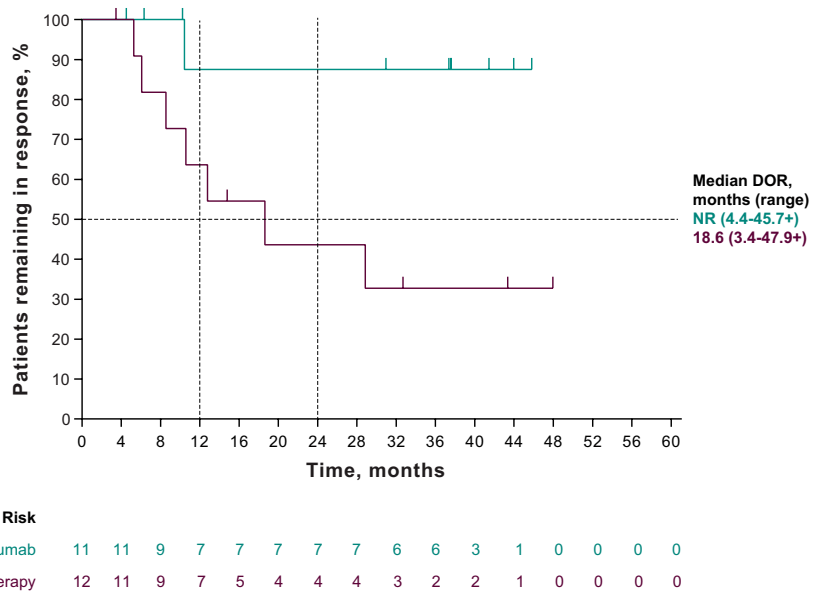

FIGURE 4 Kaplan–Meier estimates for duration of response (DOR) in patients from the Asia subgroup with a confirmed response (*n* = 23). + indicates there was no progressive disease by the time of last disease assessment. NR, not reached

provided a significantly longer PFS, higher ORR, and prolonged response duration compared with chemotherapy. OS was also longer with pembrolizumab versus chemotherapy in the global population; however, this difference was not statistically significant. This result is partially due to the number of deaths observed at FA. The protocol-specified FA of OS was planned after 190 deaths had occurred across both arms or 12 months after the second interim analysis. As the latter cutoff was reached first, the analysis was conducted when only 140 deaths were observed.[13] It might also be related to the high effective crossover rate (60%) of patients in the chemotherapy arm who received off-study anti-PD-1/L1 therapy leading to improved survival and a nonsignificant difference in OS between the two arms.[13]

Among patients in the Asia subgroup, the Kaplan–Meier curves of PFS with pembrolizumab and chemotherapy cross shortly after treatment initiation and continue to diverge, with higher PFS rates observed with pembrolizumab compared with chemotherapy (52% vs. 28%) at 24 months. PFS improvement was clinically meaningful for pembrolizumab compared with chemotherapy (HR 0.56, 95% CI 0.26–1.20), which was consistent with the HR benefit seen in the global population (HR 0.59, 95% CI 0.45–0.79).[14]

Similarly, in the Asia subgroup, the Kaplan–Meier curves for OS with pembrolizumab and chemotherapy cross each other and then continue to diverge. OS in the Asia subgroup was numerically longer for pembrolizumab compared with chemotherapy (HR 0.65, 95% CI 0.27–1.55), which was also consistent with findings from the global

TABLE 4 Treatment-related adverse events of any grade that occurred in at least 10% of patients in either treatment arm in the Asia subgroup

Treatment-related adverse event	Pembrolizumab, $n = 22$		Chemotherapy, $n = 25$	
	Any grade[a] *n* (%)	Grade 3–5[a] *n* (%)	Any grade[a] *n* (%)	Grade 3–5[a] *n* (%)
Any	14 (64)	2 (9)	25 (100)	20 (80)
Malaise	4 (18)	0	4 (16)	0
Diarrhea	3 (14)	0	11 (44)	2 (8)
Hypothyroidism	3 (14)	0	0	0
Pyrexia	3 (14)	0	3 (12)	0
ALT level increased	2 (9)	1 (5)	5 (20)	0
AST level increased	2 (9)	1 (5)	5 (20)	1 (4)
Decreased appetite	2 (9)	0	13 (52)	2 (8)
Fatigue	2 (9)	0	13 (52)	2 (8)
Alopecia	1 (5)	0	9 (36)	0
Anemia	1 (5)	0	3 (12)	1 (4)
Rash	1 (5)	0	3 (12)	0
Nausea	0	0	15 (60)	0
Neutrophil count decreased	0	0	15 (60)	10 (40)
Peripheral sensory neuropathy	0	0	14 (56)	1 (4)
Stomatitis	0	0	11 (44)	0
WBC count decreased	0	0	11 (44)	4 (16)
Vomiting	0	0	9 (36)	0
PPE syndrome	0	0	6 (24)	0
Epistaxis	0	0	5 (20)	0
Hypersensitivity	0	0	5 (20)	0
Platelet count decreased	0	0	4 (16)	0
Proteinuria	0	0	4 (16)	1 (4)
Skin hyperpigmentation	0	0	4 (16)	0
Hypoesthesia	0	0	4 (16)	0
Dermatitis acneiform	0	0	3 (12)	0
Hypertension	0	0	3 (12)	2 (8)
Neutropenia	0	0	3 (12)	2 (8)
Paronychia	0	0	3 (12)	1 (4)
Urticaria	0	0	3 (12)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; WBC, white blood cell.

[a]Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

population (HR 0.74, 95% CI 0.53–1.03, $P = 0.036$).[14] Similar effective crossover rates were also observed between the Asia subgroup and the global population (54% and 60%), which likely contributed to the lack of statistical significance in OS. At FA, 10 of 26 patients (38%) in the Asia subgroup who were randomly assigned to chemotherapy met crossover criteria and were treated with pembrolizumab. A total of four additional patients (15%) received anti-PD-1/L1 therapies outside the study, for an effective crossover rate of 54%.

In the Asian subgroup, the ORR was similar between the pembrolizumab and chemotherapy treatment arms (50% vs. 46%, respectively), whereas the ORR was improved with pembrolizumab in the global population (45% vs. 33%). CR rates in the Asian subpopulation for pembrolizumab- and chemotherapy-treated patients (18% vs. 12%, respectively) were somewhat greater than in the global study (13% vs. 4%, respectively). However, comparisons between the Asia subgroup and the global population should be viewed with caution given the small number of patients in the Asia subgroup. As we observed in the global population (29% vs. 12%), there was a trend toward a greater number of patients in the pembrolizumab versus chemotherapy arm who experienced PD as best response (36% vs. 15%).[14] In the Asia subgroup, pembrolizumab treatment led to longer-lasting responses than chemotherapy,

TABLE 5 Immune-mediated adverse events and infusion reactions of any grade that occurred in at least one patient in any treatment arm in the Asia subgroup[a]

Immune-mediated adverse event	Pembrolizumab, *n* = 22 *n* (%)	Chemotherapy, *n* = 25 *n* (%)
Any	6 (27)	10 (40)
Adrenal insufficiency	1 (5)	0
Colitis	0	1 (4)
Hyperthyroidism	2 (9)	0
Hypothyroidism	3 (14)	2 (8)
Infusion reactions	1 (5)	5 (20)
Pneumonitis	1 (5)	2 (8)

[a]Immune-mediated adverse events and infusion reactions were derived from a list of terms specified by the sponsor, regardless of attribution to any trial treatment by investigators. All events were reported.

which was consistent with the results of the global population and durable responses documented with pembrolizumab across several tumor types.[14,16]

The safety profile of pembrolizumab was favorable compared with chemotherapy in the Asia subgroup, as was observed in the global population. The difference in the incidence of grade 3–5 TRAEs was particularly notable (9% with pembrolizumab vs. 80% with chemotherapy). The most common immune-mediated AEs in the pembrolizumab arm were hypothyroidism (14%) and hyperthyroidism (9%), which are well-documented AEs associated with checkpoint inhibitors.[17] Infusion reactions were less common with pembrolizumab (5%) compared with chemotherapy (20%).

To date, limited data are available regarding the efficacy and safety of ICIs among patients of Asian descent with MSI-H/dMMR mCRC. A subgroup analysis of Japanese patients in the KEYNOTE-164 study showed that pembrolizumab provided durable antitumor activity and an acceptable safety profile in patients with previously treated MSI-H/dMMR advanced CRC.[18] The ORR among Japanese patients was 29% (2/7) for patients who had received ≤2 prior lines of standard therapy and 67% (4/6) for patients who had received ≤1 prior line of therapy. Median DOR was NR in either group. It was also reported that TRAEs tended to occur more frequently in the Japanese subgroup compared with the global population. No data are available for nivolumab because only one patient of Asian descent was included in the CheckMate 142 study that investigated nivolumab in patients with previously treated MSI-H/dMMR CRC.[11]

The current subgroup analysis is limited by the post hoc nature of the analysis and the lack of statistical power to show differences in outcome between the treatment arms among patients enrolled from Asia. The number of patients in each arm was also small, which limits definitive conclusions. The high crossover rate seen in the chemotherapy arm may have contributed to the antitumor activity seen in the chemotherapy arm in the survival analyses, as in the case of the global population. Differences in baseline characteristics between the Asia subgroup and the global population may also have influenced results. A higher proportion of patients receiving pembrolizumab in the Asia subgroup had an ECOG performance status of 0 compared with the global population (59% vs. 49%). Similarly, a higher proportion of patients receiving chemotherapy in the Asia subgroup had left-sided tumors, which are generally associated with a better prognosis, compared with the global population (38% vs. 27%). However, given the small number of patients in the Asian subgroup, these data should be interpreted with caution.

The results from the global population of KEYNOTE-177 have led to a paradigm shift in the treatment of patients with MSI-H/dMMR mCRC, and pembrolizumab is now approved by the Japan Pharmaceuticals and Medical Devices Agency as monotherapy for the treatment of patients with unresectable, advanced, or recurrent MSI-H CRC, by the US Food and Drug Administration for the treatment of unresectable or metastatic MSI-H/dMMR CRC, and by the European Medicines Agency for the first-line treatment of metastatic MSI-H/dMMR CRC.[19–21] The current analysis is the only report of the efficacy and safety of a first-line checkpoint inhibitor in Asian patients with MSI-H/dMMR mCRC. The results show that first-line pembrolizumab provides longer PFS, more durable responses, and improved safety compared with chemotherapy, supporting the use of pembrolizumab monotherapy for MSI-H/dMMR mCRC in Asian patients.

AUTHOR CONTRIBUTIONS

Conception, design, or planning of the study: T.Y., B.V.J., C.D.L.F., D.T.L., P.M., and L.A.D. Acquisition of the data: T.Y., T.A., W.P.Y., K.K.S., B.V.J., L.H.J., D.S., R.G.C., J.A.G., C.D.L.F., F.R., E.E., and D.T.L. Analysis of the data: T.Y., T.A., B.V.J., D.S., C.D.L.F., D.T.L., N.A., D.F., and L.A.D. Interpretation of the results: T.Y., T.A., T.W.K., K.K.S., B.V.J., C.J.A.P., R.G.C., J.A.G., P.G., C.D.L.F., F.R., E.E., D.T.L., N.A., D.F., and L.A.D. Drafting of the manuscript: T.Y., T.A., B.V.J., J.A.G., C.D.L.F., and D.T.L. Critically reviewing or revising the manuscript for important intellectual content: T.Y., T.A., T.W.K., W.P.Y., K.K.S., B.V.J., L.H.J., C.J.A.P., D.S., R.G.C., J.A.G., P.G., C.D.L.F., F.R., E.E., D.T.L., N.A., D.F., P.M., and L.A.D.

ACKNOWLEDGMENTS

This work was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. We thank the patients and their families and caregivers for participating in this trial, and all investigators and site personnel. Medical writing and editorial assistance were provided by Jemimah Walker, PhD, Mehak Aggarwal, PharmD, and Doyel Mitra, PhD, CMPP, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

FUNDING INFORMATION

The study was designed under the responsibility of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in conjunction with the steering committee. The study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Pembrolizumab was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. All

authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST

B.V.J., C.J.A.P., D.S., J.A.-G., L.H.J., P.G., T.W.K., and W.P.Y have no conflicts of interest. T.Y. has received lecture fees and/or honoraria from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Merck Biopharma Co., Ltd., Bayer Yakuhin, Ltd., Ono Pharmaceutical Co., Ltd., and MSD K.K.; and has also received research funds from Ono Pharmaceutical Co., Ltd., Sanofi K.K., Daiichi Sankyo Co., Ltd., PAREXEL International Inc., Pfizer Japan Inc., Taiho Pharmaceutical Co., Ltd., MSD K.K., Amgen K.K., Genomedia Inc., Sysmex Corporation, Chugai Pharmaceutical Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. T.A. reports attending advisory board meetings and receiving consulting fees from AstraZeneca, Astellas, Bristol Myers Squibb, Gritstone Oncology, GamaMabs Pharma Sa, GlaxoSmithKline, Merck & Co. Inc., Nordic Oncology, Pierre Fabre, Seagen, Servier and Transgène; honoraria from AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Merck & Co. Inc., Pierre Fabre, Roche/Ventana, Sanofi, Seagen and Servier; and travel expenses of US$500 or more from Bristol Myers Squibb and Merck & Co and Servier. K.K.S. has received lecture fees and/or honoraria from Daiichi Sankyo, Merck KGaA, MSD, Mirati Therapeutics, Roche, and Servier; and has received research funds from MSD, Roche, AstraZeneca, and Adaptimmune Therapeutics. R.G.C. has received annual remuneration of US$500 or more from AAA, Ipsen, BMS, MSD, Novartis, Ph MAR, Merck, and Roche; and a family member has received annual remuneration of US$500 or more from Amgen, AstraZeneca, Bayer, BMS, Glaxo, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi, Takeda, and US$10,000 or more from MSD, Lilly, and Genomics. C.D.L.F. has received lecture fees, honoraria, or other fees from MSD and BMS and has received research funds from MSD. F.R. has received lecture fees and/or honoraria from MSD, BMS, Roche, Lilly, Servier, Sanofi, Astra-Zeneca; research funds from MSD; and annual remuneration of US$500 or more from MSD. E.E. has received personal financial interest for consulting/advisory role and/or honoraria, travel grants and research grants from Amgen, Bayer, Hoffman-La Roche, Merck Serono, Sanofi, Pierre Fabre, MSD, Organon, Novartis, and Servier. She has received institutional financial interest in the form of financial support for clinical trials or contracted research from Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm International SA, F. Hoffmann-La Roche Ltd., Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Janssen-Cilag SA, MedImmune, Menarini, Merck Health KGAA, Merck Sharp & Dohme, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Pharma Mar, Sanofi, Aventis Recherche & Développement, Servier, and Taiho Pharma USA Inc. D.T.L. has received research funding to run clinical trials. D.F., N.A., and P.M. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. D.F. and P.M. are stockholders of Merck & Co., Inc., Rahway, NJ, USA. L.A.D. has served as a consultant for PetDx, Innovatus CP, Se'er, Delfi, Kinnate, and Neophore; holds equity in Epitope, Jounce Therapeutics, PetDx, Se'er, Delfi, Kinnate, and Neophore; has a family member who holds equity in Amgen; holds a patent; and is a member of the board of directors of Jounce Therapeutics and Epitope.

ETHICAL APPOROVAL

The KEYNOTE-177 trial is registered on ClinicalTrials.gov (NCT02563002). The study protocol and all amendments were reviewed and approved by the appropriate institutional review board or ethics committee at each study center, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yoshino T, Andre T, Kim TW, et al. Pembrolizumab in Asian patients with microsatellite-instability-high/mismatch-repair-deficient colorectal cancer. *Cancer Sci*. 2023;114:1026-1036. doi:10.1111/cas.15650