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Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

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ABSTRACT

BACKGROUND

Programmed death 1 (PD-1) blockade has clinical benefit in microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) tumors after previous therapy. The efficacy of PD-1 blockade as compared with chemotherapy as first-line therapy for MSI-H–dMMR advanced or metastatic colorectal cancer is unknown.

METHODS

In this phase 3, open-label trial, 307 patients with metastatic MSI-H–dMMR colorectal cancer who had not previously received treatment were randomly assigned, in a 1:1 ratio, to receive pembrolizumab at a dose of 200 mg every 3 weeks or chemotherapy (5-fluorouracil–based therapy with or without bevacizumab or cetuximab) every 2 weeks. Patients receiving chemotherapy could cross over to pembrolizumab therapy after disease progression. The two primary end points were progression-free survival and overall survival.

RESULTS

At the second interim analysis, after a median follow-up (from randomization to data cutoff) of 32.4 months (range, 24.0 to 48.3), pembrolizumab was superior to chemotherapy with respect to progression-free survival (median, 16.5 vs. 8.2 months; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.80; P=0.0002). The estimated restricted mean survival after 24 months of follow-up was 13.7 months (range, 12.0 to 15.4) as compared with 10.8 months (range, 9.4 to 12.2). As of the data cutoff date, 56 patients in the pembrolizumab group and 69 in the chemotherapy group had died. Data on overall survival were still evolving (66% of required events had occurred) and remain blinded until the final analysis. An overall response (complete or partial response), as evaluated with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was observed in 43.8% of the patients in the pembrolizumab group and 33.1% in the chemotherapy group. Among patients with an overall response, 83% in the pembrolizumab group, as compared with 35% of patients in the chemotherapy group, had ongoing responses at 24 months. Treatment-related adverse events of grade 3 or higher occurred in 22% of the patients in the pembrolizumab group, as compared with 66% (including one patient who died) in the chemotherapy group.

CONCLUSIONS

Pembrolizumab led to significantly longer progression-free survival than chemotherapy when received as first-line therapy for MSI-H–dMMR metastatic colorectal cancer, with fewer treatment-related adverse events. (Funded by Merck Sharp and Dohme and by Stand Up to Cancer; KEYNOTE-177 ClinicalTrials.gov number, NCT02563002.)

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*A complete list of investigators in the KEYNOTE-177 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Colorectal cancer is clinically defined by its tissue of origin in the colon or rectum, but it is a heterogeneous disease classified by its genetics.[1-3] Despite well-known genetic differences in the disease, chemotherapy treatment of colorectal cancer is largely uniform. Patients with newly diagnosed metastatic colorectal cancer are treated with 5-fluorouracil (5-FU)–based regimens, such as FOLFOX (5-FU, oxaliplatin, and leucovorin) or FOLFIRI (5-FU, irinotecan, and leucovorin) alone or in combination with therapies that block epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) signaling.[4-6]

One well-described genetic subset of colorectal cancer is tumors with mismatch-repair deficiency (dMMR), which are found in 15% of all patients with colorectal cancer (12% of whom have sporadic cases, and 3% hereditary cases). The majority (approximately 80%) of cases of sporadic dMMR colorectal cancer are caused by methylation of the *MLH1* gene promoter, whereas more than 70% of hereditary cases are associated with germline mutations in the *MLH1* and *MSH2* genes.[7-11] Both forms result in the inability of cells to recognize and repair spontaneous mutations, resulting in a very high tumor mutation burden as well as altered microsatellite sequences that render these tumors high in microsatellite instability (MSI-H).[10] Mounting evidence suggests that MSI-H–dMMR tumors are less responsive to conventional chemotherapy, but the literature to date has been inconclusive, and chemotherapy remains the standard of care for patients with MSI-H–dMMR colorectal cancer.[12-14]

Programmed death 1 (PD-1) blockade has emerged as highly effective therapy for patients with MSI-H–dMMR metastatic colorectal cancer that is refractory to standard chemotherapy combinations.[15-18] The PD-1 inhibitors pembrolizumab and nivolumab led to durable response in some patients with previously treated MSI-H–dMMR metastatic colorectal cancer, a finding that contributed to Food and Drug Administration approvals of pembrolizumab and nivolumab for patients with MSI-H–dMMR metastatic colorectal cancer that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[15-18]

We conducted the randomized, phase 3, open-label KEYNOTE-177 trial to evaluate the efficacy and safety of PD-1 blockade with pembrolizumab as compared with standard-of-care chemotherapy as first-line treatment for MSI-H–dMMR metastatic colorectal cancer.

Methods

Patients

Eligible patients were 18 years of age or older and had MSI-H–dMMR stage IV colorectal cancer with measurable disease according to Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1, as confirmed with radiologic assessment by local investigators; an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 6-point scale, with higher scores reflecting greater disability); and adequate organ function. Patients could have received previous adjuvant chemotherapy for colorectal cancer if the earlier treatment had been completed at least 6 months before randomization.

Trial Design and Treatment

This multicenter, international, open-label, phase 3 trial was conducted at 192 sites in 23 countries. Patients were randomly assigned in a 1:1 ratio to pembrolizumab at a dose of 200 mg every 3 weeks intravenously or to the investigator's choice of chemotherapy determined within 3 days before randomization. The choices of chemotherapy were as follows: mFOLFOX6, administered intravenously, consisting of oxaliplatin (85 mg per square meter of body-surface area delivered as a 2-hour infusion on day 1), leucovorin (400 mg per square meter administered as a 2-hour infusion on day 1), and 5-fluoropyrimidine (400 mg per square meter on day 1, followed by 1200 mg per square meter for 2 days for a total of 2400 mg per square meter delivered by continuous infusion over 46 to 48 hours); mFOLFOX6 plus bevacizumab (5 mg per kilogram of body weight administered intravenously on day 1); mFOLFOX6 plus cetuximab (400 mg per square meter administered intravenously over 2 hours [first infusion] followed by 250 mg per square meter administered as one 1-hour infusion weekly); FOLFIRI, administered intravenously, consisting of irinotecan (180 mg per square meter delivered over 30 to 90 minutes on day 1), leucovorin (400 mg per square meter delivered by infusion over 30 to 90 minutes on day 1), and 5-fluoropyrimidine (400 mg per square meter administered as a bolus on day 1, followed by 1200 mg per square meter per day for 2 days for a total of 2400 mg per square meter delivered

by continuous infusion over 46 to 48 hours); FOLFIRI plus bevacizumab; or FOLFIRI plus cetuximab (with bevacizumab and cetuximab administered at the same doses as those listed above with mFOLFOX6). All the chemotherapy regimens were repeated every 2 weeks. The investigator's choice of chemotherapy combination was determined before randomization. Treatment was continued for a maximum of 35 treatments with pembrolizumab or until disease progression, development of unacceptable toxic effects, illness, or a decision by the physician or patient to withdraw from the trial.

Randomization was performed centrally with the use of an interactive voice-response system and integrated Web-response system. Patients randomly assigned to chemotherapy could cross over to pembrolizumab (to receive a maximum of 35 treatments) after disease progression (defined according to RECIST, version 1.1, and confirmed by independent central reviewers who were unaware of the treatment assignments), at the discretion of the investigator. Metastasectomy with curative intent, with or without resection of the primary tumor (if resection was not previously performed), was permitted at the discretion of the investigator.

ASSESSMENTS

Mismatch repair status was determined locally by immunohistochemical analysis of the DNA mismatch repair proteins MLH1, MSH2, MSH6, and PMS2 and was classified as dMMR by the absence of expression of MMR proteins. MSI-H status was determined locally by polymerase-chain-reaction–based analysis of three to five tumor microsatellite loci. Tumors were classified as MSI-H when at least two allele shifts among the three to five analyzed were detected. Tumor response was assessed according to RECIST, version 1.1, by blinded independent central review at week 9 and then every 9 weeks. Disease progression was verified by imaging, performed at a central location. During follow-up, survival was assessed every 9 weeks. Adverse events were evaluated throughout the trial and at 30 days (and at 90 days for serious adverse events) after treatment discontinuation and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

END POINTS

The two primary end points were progression-free survival (the time from randomization to first disease progression, as assessed by central review according to RECIST, version 1.1, or death from any cause) and overall survival (the time from randomization to death from any cause). Secondary end points included overall response (complete or partial response) as determined by central review according to RECIST, version 1.1, and safety. Exploratory end points included the duration of response (the time from first complete or partial response to first disease progression) as determined by central review according to RECIST, version 1.1.

TRIAL OVERSIGHT

The trial was designed by academic investigators and employees of the sponsor (Merck Sharp and Dohme). An external, independent data monitoring committee reviewed interim trial results to ensure patient safety and to assess efficacy at prespecified interim analyses. The protocol (available with the full text of this article at NEJM.org) and all amendments were approved by the appropriate institutional review board or ethics committee at each participating institution. All patients provided written informed consent before entering the trial.

All the authors attest that the trial was conducted in accordance with standards of Good Clinical Practice. All the authors had access to the data, were involved in the writing or critical review and editing of the manuscript, and vouch for the accuracy and completeness of the data reported and for the fidelity of the trial to the protocol. The first draft was written by the lead author and senior author with assistance from a medical writer employed by the sponsor.

STATISTICAL ANALYSIS

Efficacy was assessed in the intention-to-treat population, which consisted of all patients who underwent randomization. Safety was assessed in the as-treated population, which included patients who underwent randomization and received at least one dose of trial medication. The Kaplan–Meier method was used to estimate progression-free survival and duration of response. In the analysis of progression-free survival, data for patients who were alive without disease progression were censored as of the time of the last imaging assessment; data for patients who had surgery with curative intent were censored as of the date of surgery. Deaths that occurred without disease progression were included as events in the evalu-

Table 1. Demographic and Patient Characteristics at Baseline.*

Characteristic	Pembrolizumab (N=153)	Chemotherapy† (N=154)
Median age (range) — yr	63.0 (24–93)	62.5 (26–90)
≥65 years of age — no. (%)	73 (48)	71 (46)
Male sex — no. (%)	71 (46)	82 (53)
ECOG performance-status score of 0 — no. (%)‡	75 (49)	84 (55)
MSI-H§ — no. (%)	153 (100)	153 (99)
Region — no. (%)		
Asia	22 (14)	26 (17)
Western Europe or North America	109 (71)	113 (73)
Rest of world	22 (14)	15 (10)
Primary tumor location — no. (%)		
Right side	102 (67)	107 (69)
Left side	46 (30)	42 (27)
Other site or site missing¶	5 (3)	5 (3)
Stage — no. (%)		
Recurrent metachronous‖	80 (52)	74 (48)
Newly diagnosed with metastatic disease	73 (48)	80 (52)
Prior systemic therapy — no. (%)		
Adjuvant	33 (22)	37 (24)
Neoadjuvant with or without adjuvant systemic therapy	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status — no. (%)		
BRAF, *KRAS*, *NRAS* all wild type	34 (22)	35 (23)
KRAS or *NRAS* mutant	33 (22)	41 (27)**
$BRAF^{V600E}$ mutant	34 (22)	43 (28)**
Could not be evaluated for *BRAF*, *KRAS*, or *NRAS*††	52 (34)	38 (25)

* Data shown are for the intention-to-treat population. Percentages may not total 100 because of rounding.

† Eleven patients received mFOLFOX6 (5-FU, oxaliplatin, and leucovorin) only, 64 received mFOLFOX6 plus bevacizumab, 5 received mFOLFOX6 plus cetuximab, 16 received FOLFIRI (5-FU, irinotecan, and leucovorin) alone, 36 received FOLFIRI plus bevacizumab, and 11 received FOLFIRI plus cetuximab.

‡ An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates fully active.

§ Microsatellite-instability–high (MSI-H) status was determined locally by means of a polymerase-chain-reaction or immunohistochemical test.

¶ The tumor site was classified as other if primary tumors were located on both the left and right sides.

‖ Recurrence was defined as a secondary colorectal cancer occurring 6 months or more after the index cancer.

** Three patients who had both a $BRAF^{V600E}$ mutation and a *KRAS* or *NRAS* mutation are included.

†† Patients could not be evaluated for *BRAF*, *KRAS*, or *NRAS* if no $BRAF^{V600E}$, *KRAS*, or *NRAS* mutation was present and if at least one of the mutation statuses was undetermined or missing or the type of *BRAF* mutation was not $BRAF^{V600E}$.

ation of progression-free survival. For the analysis of overall survival, data for patients without documented death at data cutoff were censored as of the last known date the patients were alive. We used a log-rank test to assess between-group differences in progression-free survival. Hazard ratios and associated 95% confidence intervals were calculated with the use of a Cox proportional-hazards model with Efron's method of handling ties. The proportional-hazards assumption of progression-free survival was examined by both graphical and analytic methods. If the curves were not parallel, violation of the proportional-hazards assumption would be examined by complementary analyses such as an analysis that uses restricted mean survival time (the area under the survival curve up to the specific time point). Differences in response rates were assessed with the method of Miettinen and Nurminen.

The graphical method of Maurer and Bretz was used to strictly control the type I error rate across both primary end points and interim analyses at a one-sided alpha level of 2.5%. The Lan–DeMets (O'Brien) alpha spending function was used to construct group sequential boundaries to control the type I error rate. Two interim analyses and a final analysis were planned. The first interim analysis (interim progression-free survival and overall survival analyses) was planned to occur after 162 patients had disease progression or died and 6 months after the last patient underwent randomization. The current second interim analysis (final analysis of progression-free survival and interim analysis of overall survival) was planned to take place after 209 patients had disease progression or died or 24 months after the last patient underwent randomization, whichever occurred first; we calculated that the study would then have approximately 98% power to detect a hazard ratio of 0.55 for progression-free survival in the analysis of superiority of pembrolizumab over chemotherapy, at a one-sided alpha level of 1.25%. The prespecified P-value boundary for superiority of pembrolizumab over chemotherapy with respect to progression-free survival was P=0.0117. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS AND TREATMENT

Between February 11, 2016, and February 19, 2018, a total of 852 patients at 192 sites in 23 countries

were screened, and 307 were randomly assigned to receive pembrolizumab (153 patients) or chemotherapy (154 patients) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Eleven patients randomly assigned to the chemotherapy group did not begin trial treatment. Demographic and baseline characteristics, including previous receipt of adjuvant or neoadjuvant therapy, were generally well balanced between groups. The median age of the patients was 63 years (range, 24 to 93); 209 patients (68%) had tumors on the right side, 153 (50%) had new diagnoses of colorectal cancer, and 77 (25%) had *BRAF*^{V600E} mutant tumors (Table 1). At the data cutoff date of February 19, 2020, the median trial follow-up (the time from randomization to data cutoff) was 32.4 months (range, 24.0 to 48.3). A total of 153 patients in the pembrolizumab group and 143 in the chemotherapy group received at least one dose of trial treatment (as-treated population). The median duration of treatment exposure was 11.1 months (range, 0.0 to 30.6) in the pembrolizumab group and 5.7 months (range, 0.1 to 39.6) in the chemotherapy group. A total of 57 patients in the pembrolizumab group completed 35 treatments; 2 patients in the pembrolizumab group and 6 in the chemotherapy group were still receiving treatment (Fig. S1).

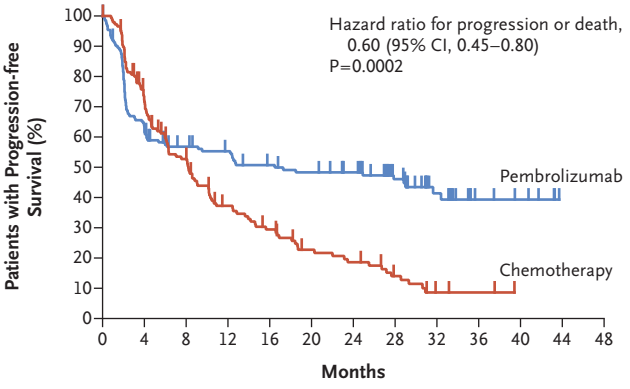

Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

Shown are Kaplan–Meier estimates of progression-free survival among patients with microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) colorectal cancer. The analysis was performed in the intention-to-treat population. Tick marks represent data censored at the time of the last imaging assessment. Progression-free survival was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by independent central reviewers who were unaware of the group assignments. The P value shown met the prespecified statistical criterion (P=0.0117) for superiority of pembrolizumab over chemotherapy.

PRIMARY END POINT

The median progression-free survival was 16.5 months (95% confidence interval [CI], 5.4 to 32.4) with pembrolizumab and 8.2 months (95% CI, 6.1 to 10.2) with chemotherapy. The prespecified statistical criteria for superiority of pembrolizumab over chemotherapy were met (hazard ratio, 0.60; 95% CI, 0.45 to 0.80; P=0.0002) (Fig. 1). The estimated percentages of patients alive and progression-free at 12 months and at 24 months were 55.3% (95% CI, 47.0 to 62.9) and 48.3% (95% CI, 39.9 to 56.2), respectively, in the pembrolizumab group and 37.3% (95% CI, 29.0 to 45.5) and 18.6% (95% CI, 12.1 to 26.3), respectively, in the chemotherapy group. Because the proportional-hazards assumption was violated, an analysis of restricted mean survival time was performed. The estimated restricted mean survival time for progression-free survival after 24 months of follow-up was 13.7 months (95% CI, 12.0 to 15.4) in the pembrolizumab group as compared with 10.8 months (95% CI, 9.4 to 12.2) in the chemotherapy group. Progression-free survival was consistently longer with pembrolizumab than with chemotherapy across key prespecified subgroups tested (Fig. 2).

RADIOGRAPHIC RESPONSE

An overall response (complete or partial response) was observed in 43.8% (95% CI, 35.8 to 52.0) of the patients in the pembrolizumab group as compared with 33.1% (95% CI, 25.8 to 41.1) in the chemotherapy group, with complete responses in 11% and 4%, respectively (Table 2 and Fig. S2). The percentage of patients with progressive disease was higher in the pembrolizumab group than in the chemotherapy group (29.4% vs. 12.3%). Nine patients in the pembrolizumab group and 19 in the chemotherapy group could not be evaluated for best response or a radiographic assessment was not performed.

DURATION OF RESPONSE

Of patients with a complete or partial response at 24 months, 83% in the pembrolizumab group had ongoing responses, as compared with 35% in the chemotherapy group (Table S2). The median duration of response was not reached (range, 2.3+ to 41.4+, with the plus sign indicating no progressive disease at the time of the last assessment) in the pembrolizumab group and was 10.6 months (range, 2.8 to 37.5+) in the chemotherapy group

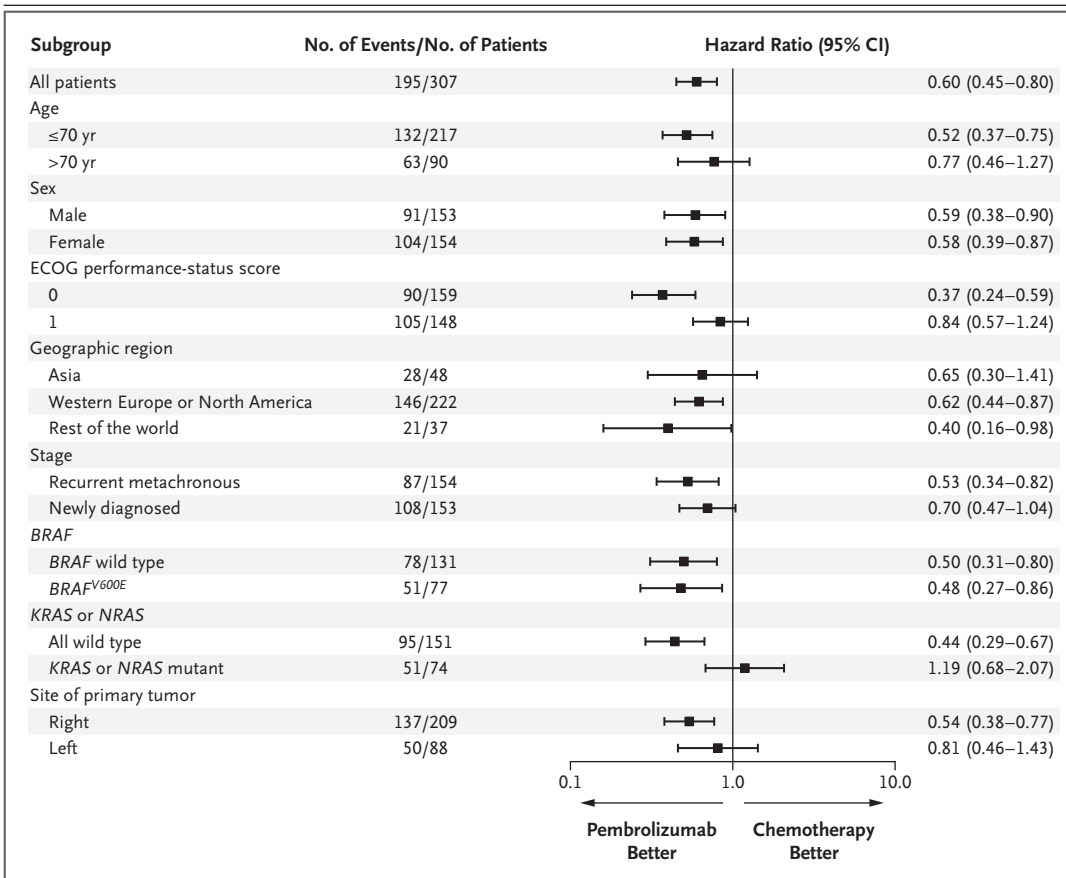

Figure 2. Progression-free Survival in Key Subgroups of Patients with MSI-H–dMMR Metastatic Colorectal Cancer.
Shown are hazard ratios for progression-free survival with pembrolizumab as compared with chemotherapy in prespecified subgroups in the intention-to-treat population. The Cox proportional-hazards model with Efron's method of handling ties was used to assess the magnitude of the treatment difference between groups. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability.

(Fig. S3). Fourteen patients (9%) in the pembrolizumab group and 13 (8%) in the chemotherapy group had surgery with curative intent during the initial treatment phase.

OVERALL SURVIVAL

At the time of data cutoff, data on overall survival were still evolving, with 125 of the required 190 events for the final analysis of overall survival having occurred. As of the data cutoff date, 56 patients in the pembrolizumab group and 69 in the chemotherapy group had died. The independent data monitoring committee recommended that the trial continue without changes to the final analysis for assessment of overall survival until 190 overall deaths have occurred or until 12 months after the second interim analysis. Crossover will be a factor in the assessment of overall survival. At the time of data cutoff, 56 of 154 patients (36%) randomly assigned to the chemotherapy group had crossed over to the pembrolizumab group after disease progression was confirmed. An additional 35 patients in the chemotherapy group received anti–PD-1 or anti–programmed death ligand 1 (anti–PD-L1) therapies outside the trial, for an effective crossover rate to anti–PD-1 or anti–PD-L1 therapy of 59% in the intention-to-treat population.

SAFETY

Adverse events occurred in 149 of 153 patients (97%) in the pembrolizumab group and in 142 of 143 patients (99%) in the chemotherapy group (Table 3). Adverse events of grade 3 or higher occurred in 86 patients (56%) in the pembrolizumab group as compared with 111 (78%) in the chemo-

Table 2. Antitumor Activity in the Intention-to-Treat Population.

Variable	Pembrolizumab (N=153)	Chemotherapy (N=154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3

* Overall response was defined as a confirmed complete response or partial response. The denominators for the percentages are patients in the intention-to-treat population, which included all patients who underwent randomization. Patients who could not be evaluated, who had no assessment available, or who did not start either therapy (11 patients in the chemotherapy group) were not excluded from this analysis.
† Percentages may not total 100 because of rounding.
‡ This category includes patients for whom no postbaseline imaging was performed.
§ The Kaplan–Meier method for censored data was used to calculate duration. A plus sign indicates no progressive disease by the time of the last assessment. NR denotes not reached.

therapy group; the most common of these events were decreased neutrophil count (0% vs. 17%), neutropenia (0% vs. 15%), and diarrhea (6% vs. 11%). A total of 21 patients (14%) in the pembrolizumab group and 17 (12%) in the chemotherapy group discontinued treatment owing to adverse events. Grade 5 adverse events occurred in 6 patients (4%) in the pembrolizumab group and in 7 patients (5%) in the chemotherapy group. Adverse events attributed by the investigator to treatment occurred in 122 patients (80%) in the pembrolizumab group as compared with 141 (99%) in the chemotherapy group. Treatment-related events of grade 3 or higher occurred in 33 patients (22%) and 94 patients (66%), respectively, including one death in the chemotherapy group (Table S2).

Immune-mediated adverse events and infusion reactions occurred in 47 patients (31%) in the pembrolizumab group as compared with 18 (13%) in the chemotherapy group. Grade 3 or 4 events of interest occurred in 14 patients (9%) and 3 patients (2%), respectively (Table 3), with colitis (3%) and hepatitis (3%) most common in the pembrolizumab group and infusion reactions (1%) and severe skin reactions (1%) most common in the chemotherapy group. No grade 5 immune-mediated adverse events were observed.

DISCUSSION

This randomized phase 3 trial showed that frontline pembrolizumab was superior to chemotherapy with respect to progression-free survival in patients with MSI-H–dMMR metastatic colorectal cancer. The beneficial effect was observed generally across key patient subgroups and supports previous data showing the benefit of pembrolizumab monotherapy in MSI-H–dMMR solid tumors.[15-17,19]

This trial also provides prospective data on progression-free survival with chemotherapy alone or in combination with bevacizumab or cetuximab in patients with MSI-H–dMMR metastatic colorectal cancer as first-line treatment. The median progression-free survival of 8.2 months and the overall response of 33.1% observed with chemotherapy are consistent with data suggesting limited efficacy of chemotherapy in patients with MSI-H–dMMR metastatic colorectal cancer.[12-14]

The radiographic response was consistent with the results in previous studies of MSI-H–dMMR tumors that showed higher complete response rates with pembrolizumab or other immune checkpoint inhibitors than with chemotherapy.[16-21] In contrast, more patients had progressive disease

Table 3. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab (N=153)		Chemotherapy (N=143)	
	Any	Grade ≥3	Any	Grade ≥3
	number of patients (percent)			
Any adverse event†	149 (97)	86 (56)	142 (99)	111 (78)
Diarrhea	68 (44)	9 (6)	89 (62)	16 (11)
Fatigue	58 (38)	6 (4)	72 (50)	13 (9)
Nausea	47 (31)	4 (3)	85 (59)	6 (4)
Abdominal pain	37 (24)	8 (5)	42 (29)	8 (6)
Decreased appetite	36 (24)	0	58 (41)	7 (5)
Vomiting	33 (22)	2 (1)	53 (37)	7 (5)
Arthralgia	28 (18)	1 (1)	7 (5)	0
Pyrexia	28 (18)	1 (1)	20 (14)	0
Anemia	27 (18)	8 (5)	32 (22)	15 (10)
Pruritus	25 (16)	0	12 (8)	1 (1)
Back pain	26 (17)	2 (1)	24 (17)	1 (1)
Constipation	26 (17)	0	45 (31)	0
Cough	26 (17)	0	23 (16)	0
Aspartate aminotransferase increase	24 (16)	4 (3)	12 (8)	3 (2)
Dizziness	24 (16)	0	27 (19)	0
Alanine aminotransferase increase	22 (14)	4 (3)	16 (11)	3 (2)
Blood alkaline phosphatase increase	22 (14)	4 (3)	6 (4)	2 (1)
Dyspnea	21 (14)	1 (1)	15 (10)	0
Headache	21 (14)	0	22 (15)	0
Rash	20 (13)	1 (1)	16 (11)	1 (1)
Upper abdominal pain	20 (13)	2 (1)	11 (8)	1 (1)
Nasopharyngitis	20 (13)	0	10 (7)	0
Asthenia	19 (12)	3 (2)	31 (22)	6 (4)
Dry skin	19 (12)	0	13 (9)	0
Hypertension	19 (12)	11 (7)	16 (11)	7 (5)
Hypothyroidism	19 (12)	0	3 (2)	0
Pain in extremity	18 (12)	0	11 (8)	1 (1)
Peripheral edema	18 (12)	0	12 (8)	2 (1)
Dry mouth	17 (11)	0	9 (6)	0
Upper respiratory tract infection	16 (10)	0	8 (6)	0
Urinary tract infection	14 (9)	1 (1)	16 (11)	4 (3)
Hypokalemia	13 (8)	2 (1)	24 (17)	9(6)
Alopecia	11 (7)	0	29 (20)	0
Stomatitis	10 (7)	0	43 (30)	6 (4)
Dyspepsia	9 (6)	0	16 (11)	0
Mucosal inflammation	7 (5)	0	27 (19)	1 (1)
Weight decreased	7 (5)	1 (1)	17 (12)	1 (1)

Table 3. (Continued.)

Event	Pembrolizumab (N=153)		Chemotherapy (N=143)	
	Any	Grade ≥3	Any	Grade ≥3
	number of patients (percent)			
Peripheral sensory neuropathy	3 (2)	0	31 (22)	3 (2)
Neutrophil count decrease	2 (1)	0	33 (23)	24 (17)
Neutropenia‡	3 (2)	0	30 (21)	22 (15)
Epistaxis	2 (1)	0	23 (16)	0
Peripheral neuropathy	1 (1)	0	27 (19)	1 (1)
PPE syndrome	1 (1)	0	25 (17)	1 (1)
White-cell count decrease	1 (1)	0	17 (12)	6 (4)
Adverse events of interest§	47 (31)	14 (9)	18 (13)	3 (2)
Hypothyroidism	19 (12)	0	3 (2)	0
Colitis	10 (7)	5 (3)	0	0
Hyperthyroidism	6 (4)	0	0	0
Pneumonitis	6 (4)	0	1 (1)	0
Adrenal insufficiency	4 (3)	2 (1)	0	0
Hepatitis	4 (3)	4 (3)	0	0
Infusion reactions	3 (2)	0	11 (8)	1 (1)
Severe skin reactions	2 (1)	2 (1)	2 (1)	2 (1)
Thyroiditis	2 (1)	0	0	0
Hypophysitis	2 (1)	0	0	0
Myocarditis	0	0	1 (1)	0
Nephritis	1 (1)	0	0	0
Pancreatitis	1 (1)	1 (1)	0	0
Type 1 diabetes mellitus	1 (1)	1 (1)	0	0
Myositis	1 (1)	0	0	0

* The as-treated population included all patients who underwent randomization and received at least one trial treatment. PPE denotes palmar–plantar erythrodysesthesia syndrome.
† Reported are adverse events that occurred in at least 10% of patients in any group. Grade 3 or higher events among these events are reported.
‡ Neutropenia is the clinical diagnosis resulting from decreased neutrophil count.
§ Adverse events of interest (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 adverse events of interest are reported.

as the best response with pembrolizumab than with chemotherapy (29.4% vs. 12.3%). After an initial crossing of the progression-free survival Kaplan–Meier curves, a pronounced separation of the curves for pembrolizumab and chemotherapy was observed, which indicated a meaningful long-term benefit with pembrolizumab. In addition, the difference in restricted mean survival time, a complementary analysis for progression-free survival performed when the proportional-hazards assumption is violated, favored pembrolizumab. Because the treatment effect can change over time when the proportional-hazards assumption is violated, evaluation of the treatment effect must consider multiple factors, including the hazard ratios for progression-free survival, the median progression-free survival time, progression-free survival rates over time, and the restricted mean survival time, to reflect the totality of the data. Differences in these factors were consis-

tently favorable for pembrolizumab as compared with chemotherapy in the KEYNOTE-177 trial. These data support the benefit of pembrolizumab in patients with MSI-H–dMMR metastatic colorectal cancer.

Many markers of progressive disease during the first months of PD-1 blockade therapy have been proposed for MSI-H–dMMR tumors, including low tumor mutation burden, Janus kinase mutations, loss of beta-2-microglobulin that could impair antigen presentation by major histocompatibility complex I, misdiagnosed MSI-H–dMMR, and pseudoprogression, but these data remain inconclusive.[15,16,22-24] With respect to the biomarkers in our data set, tumors containing hot-spot mutations in *RAS* genes did not have a progression-free survival benefit with PD-1 blockade therapy, although the small sample size and high percentage of missing information on mutation status limit this interpretation. Although the mechanism of resistance is unknown, it is reasonable to postulate that adding chemotherapy or anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) to PD-1 blockade could overcome this apparent resistance in the subgroup of patients whose cancer does not respond to pembrolizumab alone. However, the added toxic effects of these combinations must be carefully considered given the prolonged clinical benefit from pembrolizumab alone for the majority of patients. Randomized phase 3 studies evaluating first-line chemotherapy with or without atezolizumab (ClinicalTrials.gov number, NCT02997228) or nivolumab with or without ipilimumab (NCT04008030) in MSI-H–dMMR metastatic colorectal cancer are ongoing.

Additional observations in this data set included the finding that approximately one third of patients had tumors on the left side, highlighting the importance of testing for MSI-H–dMMR in all colorectal cancers, not just tumors on the right side. Second, although a substantial proportion of MSI-H–dMMR tumors are hereditary, the effect of hereditary as compared with sporadic tumors on the response to PD-1 blockade could not be determined because consent for germline testing was not obtained. However, $BRAF^{V600E}$ mutations in MSI-H–dMMR tumors can be considered a surrogate for sporadic disease, and we observed that patients with $BRAF^{V600E}$ mutant tumors and those with wild-type MSI-H–dMMR tumors benefitted equally from PD-1 blockade. Future studies are needed to evaluate the influence of hereditary dMMR on the response to PD-1 blockade in this patient population.

The safety profile of pembrolizumab in the current trial is consistent with that observed with pembrolizumab across multiple tumor types.[25-27] With the exception of immune-mediated or infusion-related adverse events, chemotherapy was associated with more grade 3 or higher adverse events, including one treatment-related death.

Although the trial met the prespecified statistical criteria for the superiority of pembrolizumab over chemotherapy, overall survival is not reported. The independent data monitoring committee recommended the continued masking of overall survival data until 190 deaths for the final analysis of overall survival have been observed or 12 months have elapsed since the last data review. The trial was considered to be successful if pembrolizumab was superior to chemotherapy with respect to either primary end point.

These data represent another step forward for biomarker-driven studies targeting MSI-H–dMMR colorectal cancers. Treatment with pembrolizumab led to significantly longer progression-free survival and fewer treatment-related adverse events than chemotherapy. As a result, pembrolizumab should be considered an option for initial therapy for patients with MSI-H–dMMR metastatic colorectal cancer.

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REFERENCES

1. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138(6):2073-2087.e3.
2. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993;363:558-61.
3. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology 2010;138:2059-72.
4. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
5. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018;29:44-70.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: rectal cancer, version 3. 2020 (https://www.nccn.org/professionals/physician_gls/default.aspx).
7. Koopman M, Kortman GAM, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer 2009;100:266-73.
8. Zlobec I, Kovac M, Erzberger P, et al. Combined analysis of specific KRAS mutation, BRAF and microsatellite instability identifies prognostic subgroups of sporadic and hereditary colorectal cancer. Int J Cancer 2010;127:2569-75.
9. Arnold CN, Goel A, Compton C, et al. Evaluation of microsatellite instability, hMLH1 expression and hMLH1 promoter hypermethylation in defining the MSI phenotype of colorectal cancer. Cancer Biol Ther 2004;3:73-8.
10. Goel A, Boland CR. Epigenetics of colorectal cancer. Gastroenterology 2012;143(6):1442-1460.e1.
11. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. J Clin Oncol 2019;37:286-95.
12. Innocenti F, Ou F-S, Qu X, et al. Mutational analysis of patients with colorectal cancer in CALGB/SWOG 80405 identifies new roles of microsatellite instability and tumor mutational burden for patient outcome. J Clin Oncol 2019;37:1217-27.
13. Tougeron D, Sueur B, Zaanan A, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: an AGEO retrospective multicenter study. Int J Cancer 2020;147:285-96.
14. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322-30.
15. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
16. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
17. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer: KEYNOTE-164. J Clin Oncol 2020;38:11-9.
18. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
19. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
20. Ludford K, Cohen R, Svrcek M, et al. Pathological tumor response following immune checkpoint blockade for deficient mismatch repair advanced colorectal cancer. J Natl Cancer Inst 2020 April 15 (Epub ahead of print).
21. Lenz H-J, Lonardi S, Zagonel V, et al. Nivolumab plus low-dose ipilimumab as first-line therapy in microsatellite instability-high/DNA mismatch repair deficient metastatic colorectal cancer: clinical update. J Clin Oncol 2020;38:4 Suppl:11. abstract.
22. Middha S, Yaeger R, Shia J, et al. Majority of *B2M*-mutant and -deficient colorectal carcinomas achieve clinical benefit from immune checkpoint inhibitor therapy and are microsatellite instability-high. JCO Precis Oncol 2019;3:PO.18.00321.
23. Cohen R, Hain E, Buhard O, et al. Association of primary resistance to immune checkpoint inhibitors in metastatic colorectal cancer with misdiagnosis of microsatellite instability or mismatch repair deficiency status. JAMA Oncol 2019;5:551-5.
24. Martin-Romano P, Castanon E, Ammari S, et al. Evidence of pseudoprogression in patients treated with PD1/PDL1 antibodies across tumor types. Cancer Med 2020;9:2643-52.
25. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823-33.
26. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2020;382:810-21.
27. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789-801.