rapid communications

Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability–High/Mismatch Repair–Deficient Metastatic Colorectal Cancer: KEYNOTE-164

Dung T. Le, MD[1]; Tae Won Kim, MD[2]; Eric Van Cutsem, MD, PhD[3]; Ravit Geva, MD[4]; Dirk Jäger, MD[5]; Hiroki Hara, MD[6]; Matthew Burge, MBChB, FRACP[7]; Bert O'Neil, MD[8]; Petr Kavan, MD, PhD[9]; Takayuki Yoshino, MD[10]; Rosine Guimbaud, MD, PhD[11]; Hiroya Taniguchi, MD, PhD[12]; Elena Elez, MD, PhD[13]; Salah-Eddin Al-Batran, MD[14]; Patrick M. Boland, MD[15]; Todd Crocenzi, MD[16]; Chloe E. Atreya, MD, PhD[17]; Yi Cui, PhD[18]; Tong Dai, MD, PhD[19]; Patricia Marinello, PharmD[19]; Luis A. Diaz Jr, MD[20]; and Thierry André, MD[21]

abstract

PURPOSE KEYNOTE-164 (NCT02460198) evaluated the antitumor activity of pembrolizumab in previously treated, metastatic, microsatellite instability–high/mismatch repair–deficient (MSI-H/dMMR) colorectal cancer (CRC).

METHODS This phase II open-label study involved 128 centers worldwide. Eligible patients were age ≥ 18 years and had metastatic MSI-H/dMMR CRC treated with ≥ 2 prior lines of standard therapy, including fluoropyrimidine, oxaliplatin, and irinotecan with or without anti–vascular endothelial growth factor/epidermal growth factor receptor monoclonal antibody (cohort A) or ≥ 1 prior line of therapy (cohort B). MSI-H/dMMR status was assessed locally. Patients received pembrolizumab 200 mg every 3 weeks for up to 2 years until progression, unacceptable toxicity, or withdrawal. The primary end point was objective response rate by RECIST version 1.1 by independent central review. Secondary end points were duration of response, progression-free survival (PFS), overall survival, safety, and tolerability.

RESULTS A total of 124 patients with MSI-H/dMMR CRC (61 in cohort A, 63 in cohort B) enrolled. At data cutoff, median follow-up was 31.3 months (range, 0.2-35.6 months) for cohort A and 24.2 months (range, 0.1-27.1 months) for cohort B. Objective response rate was 33% (95% CI, 21% to 46%) and 33% (95% CI, 22% to 46%), respectively, with median duration of response not reached in either cohort. Median PFS was 2.3 months (95% CI, 2.1 to 8.1 months) and 4.1 months (95% CI, 2.1 to 18.9 months). Median overall survival was 31.4 months (95% CI, 21.4 months to not reached) and not reached (95% CI, 19.2 months to not reached). Treatment-related grade 3-4 adverse events occurred in 10 patients (16%) in cohort A and 8 (13%) in cohort B, with the most common occurring in ≥ 2 patients being pancreatitis, fatigue, increased alanine aminotransferase, and increased lipase (2 patients each; 3%) in cohort A.

CONCLUSION Pembrolizumab is effective with a manageable safety profile in patients with MSI-H/dMMR CRC.

J Clin Oncol 38:11-19. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying article on page 1

Appendix

Protocol

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

Accepted on October 16, 2019 and published at ascopubs.org/journal/jco on November 14, 2019: DOI https://doi.org/10.1200/JCO.19.02107

Clinical trial information: NCT02460198.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer death, with an estimated 881,000 deaths worldwide.[1] In the United States, 145,600 new cases and 51,020 deaths are estimated to occur in 2019.[2] Approximately 5% of stage IV CRC is microsatellite instability-high (MSI-H) and results from accumulations of high levels of single-base mismatches or short insertions and deletions in repetitive DNA tracts as a result of deficiencies in DNA mismatch repair (dMMR).[3] MSI-H/dMMR metastatic CRC often originates on the right side of the colon, is poorly differentiated, and is more closely associated with mutation in the *BRAF* gene than microsatellite-stable (MSS) CRC, all factors associated with poor outcomes.[4,5] Typically, patients with MSI-H/dMMR metastatic CRC are less responsive to conventional chemotherapy and have a poorer prognosis than patients with mismatch repair-proficient or MSS CRC.[6,7]

Evidence has shown that MSI-H/dMMR tumors achieve durable responses to single-agent programmed death 1 (PD-1) blockade, regardless of tumor type, or in combination with cytotoxic T-lymphocyte–associated antigen-4 inhibitor in MSI-H/dMMR CRC.[6-9] In an initial study of 41 patients

with heavily pretreated MSI-H/dMMR CRC, MSI-H non-CRC, and MSS cancers, treatment with the PD-1 inhibitor pembrolizumab resulted in objective response rates (ORRs) of 40%, 71%, and 0% respectively.[6] In an updated analysis in 78 evaluable patients, pembrolizumab provided an ORR of 52% in patients with MSI-H/dMMR CRC and 54% in patients with MSI-H non-CRC.[7] Nivolumab has also demonstrated antitumor activity in MSI-H/dMMR CRC. In a phase II study, nivolumab provided a response rate of 31% and a 12-month overall survival (OS) rate of 73% in heavily pretreated patients with metastatic MSI-H/dMMR CRC, while its combination with the cytotoxic T-lymphocyte–associated antigen-4 inhibitor ipilimumab demonstrated a response rate of 55% and 12-month OS rate of 85%.[8,9] Pembrolizumab is approved by the US Food and Drug Administration for the treatment of patients with MSI-H/dMMR solid tumors who experienced progression on prior treatment and had no satisfactory alternative treatment options, regardless of tumor site or histology, and for patients with MSI-H CRC who experienced progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[10] Nivolumab (with or without ipilimumab) is currently approved for the treatment of patients with MSI-H/dMMR CRC tumors who experienced progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[11] Here, we present data from the KEYNOTE-164 study that evaluated the antitumor activity of pembrolizumab after ≥ 2 (cohort A) or ≥ 1 (cohort B) prior lines of therapy in patients with MSI-H/dMMR CRC.

METHODS

Study Design and Patients

KEYNOTE-164 is an international, phase II, open-label, nonrandomized, multicenter study of pembrolizumab in patients with previously treated, unresectable, locally advanced or metastatic MSI-H and/or dMMR CRC. MSI-H and/or dMMR status was verified by local polymerase chain reaction or immunohistochemistry testing. Eligible patients were age ≥ 18 years with previously treated, histologically proven, locally advanced, unresectable or metastatic MSI-H CRC who had undergone ≥ 2 prior lines of standard therapy that included fluoropyrimidine, oxaliplatin, and irinotecan with or without anti–vascular endothelial growth factor or epidermal growth factor receptor monoclonal antibodies (cohort A) and ≥ 1 prior line of systematic therapy (cohort B). Patients who withdrew from standard treatment and were ineligible for retreatment with the same therapies were eligible. In both cohorts, patients with prior adjuvant therapy were counted as having 1 prior line of therapy if that patient's disease had progressed within 6 months after treatment. In addition, patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy > 3 months, ≥ 1 measurable lesion per RECIST version 1.1 (v1.1), and adequate organ function. Patients were excluded if they had prior monoclonal antibody, chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks of study start; prior anti-PD-1, programmed death ligand 1 (PD-L1), or PD-L2 therapy; active autoimmune disease; active malignancy requiring treatment; active infection requiring systemic treatment; known history of HIV, interstitial lung disease, or active noninfectious pneumonitis; and active hepatitis B or C virus infection. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The protocol and all amendments were approved by the institutional review board or ethics committee at each participating institution.

Procedures

All enrolled patients received intravenous pembrolizumab 200 mg every 3 weeks for up to 35 cycles (approximately 2 years) or until disease progression, unacceptable toxicity, or study withdrawal. Patients who discontinued treatment for reasons other than progression were followed until progression, initiation of a new anticancer therapy, withdrawal of consent, or loss to follow-up.

Tumor response was assessed every 9 weeks per RECIST v1.1 by independent central review. During follow-up, survival was assessed every 9 weeks. Patients who achieved a confirmed complete response (CR) and had received at least 8 cycles of pembrolizumab with ≥ 2 cycles beyond the date of CR had the option of discontinuing pembrolizumab or continuing study therapy. Eligible patients who stopped pembrolizumab after 35 cycles or who stopped after attaining a CR could resume pembrolizumab, at the discretion of the investigator, for an additional 17 cycles (approximately 1 year) after they had experienced radiographic progression. Adverse events (AEs), including serious and predefined AEs of clinical interest, were monitored throughout the study and for 30 days (90 days for serious AEs) after pembrolizumab discontinuation and were graded by investigators according to the National Cancer Institute CTCAE (version 4).

Outcomes

The primary end point was ORR (the proportion of patients with CR or partial response [PR]) as assessed by independent central radiology review per RECIST v1.1. Secondary end points were duration of response (DOR; time from first documented CR or PR until disease progression [PD] or death as a result of any cause, whichever occurred first), disease control rate (DCR; proportion of patients with CR + PR plus stable disease [SD] for ≥ 24 weeks before PD), progression-free survival (PFS; time from first study treatment to first documented PD or death, whichever occurred first), OS (time from first study treatment to death as a result of any cause), safety, and tolerability. Patients without documented death at data cutoff were censored at the date of last follow-up.

Statistical Analyses

Cohorts A and B were evaluated independently. In cohort A, for ORR (RECIST v1.1 by central review), with a sample size of 60 patients and assuming a true response rate of 35% with pembrolizumab, the study had a 93% power to reject the null hypothesis of a response rate of 15% with pembrolizumab, with a one-sided α of 2.5% at final analysis. The boundary for statistical success corresponded to an observed response rate of at least 26.7% with a one-sided α of 2.5%. In cohort B, with a sample size of 60 patients and at least 19 responders observed, the lower bound of the 95% CI would be $>$ 20%. Point estimates and exact Clopper-Pearson CIs were provided for response rate and DCR (per RECIST v1.1 by central review) in both cohorts. Kaplan-Meier estimates were provided for DOR and PFS (per RECIST v1.1 by central review) and OS. Safety was assessed by descriptive analyses. The efficacy and safety analysis populations included all patients who received $\geq$ 1 dose of pembrolizumab. Statistical analyses were done using SAS 9.4 software (SAS Institute, Cary, NC).

Data Availability

Merck Sharp & Dohme's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone Web site or through e-mail to dataaccess@merck.com.

RESULTS

Patients

Between September 14, 2015, and September 12, 2017, 61 patients with advanced, metastatic MSI-H/dMMR CRC who received $\geq$ 2 prior therapies (cohort A) and 63 who received $\geq$ 1 prior therapy (cohort B) from 128 sites in 7 countries were enrolled. The median duration of follow-up was 31.3 months (range, 0.2-35.6 months) for patients in cohort A and 24.2 months (range, 0.1-27.1 months) for patients in cohort B. The patient characteristics in each cohort were consistent with those of a stage IV MSI-H/dMMR CRC population (Table 1). Of the 61 patients in cohort A and 63 patients in cohort B, all patients in cohort A and 59 (94%) in cohort B had stage M1 disease, and 27 (44%) patients in cohort A and 19 (30%) in cohort B had $\geq$ 3 prior therapies. As of the data cutoff date of September 4, 2018, all patients in cohort A had completed treatment, and treatment was ongoing in 10 patients (16%) in cohort B. A total of 40 patients

TABLE 1. Baseline Characteristics in Patients With Microsatellite Instability–High/Mismatch Repair–Deficient Colorectal Cancer

Characteristic	Cohort A (n = 61), No. (%)	Cohort B (n = 63), No. (%)
Median age, years (range)	53 (21-84)	59 (23-83)
Age > 65 years	17 (28)	24 (38)
Male	36 (59)	33 (52)
Race		
Asian	19 (31)	14 (22)
Black/African American	0 (0)	7 (11)
White	42 (69)	42 (67)
ECOG performance status		
0	29 (48)	22 (35)
1	32 (52)	41 (65)
Stage M1	61 (100)	59 (94)
Mutation status		
KRAS/*BRAF*/*NRAS* wild type	11 (18)	6 (9)
KRAS mutated	16 (26)	22 (35)
BRAF mutated	9 (15)	5 (8)
NRAS mutated	3 (5)	5 (8)
Median tumor size, mm (range)	99 (11-408)	60 (10-307)
Prior (neo)adjuvant therapy	21 (34)	17 (27)
Prior lines of therapy		
1	6 (10)*	24 (38)
2	28 (46)	20 (32)
≥ 3	27 (44)	19 (30)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Patients with prior adjuvant therapy for advanced disease were counted as having 1 prior line of therapy.

(66%) in cohort A and 42 (67%) in cohort B discontinued treatment largely because of PD (Appendix Table A1, online only).

Efficacy

In cohort A, 20 (33%; 95% CI, 21% to 46%) of the 61 patients had a confirmed objective response (2 CRs and 18 PRs) per RECIST v1.1 by central review (Table 2). Eleven patients (18%; 95% CI, 9% to 30%) had SD with a DCR of 51% (95% CI, 38% to 64%). The median time to response was 4.3 months (range, 1.8-24.9 months), with the median DOR not reached (range, 6.2 to 31.3+ months). Eighty-five percent of responses were ongoing at analysis, and an estimated 95% of patients had a DOR of ≥ 12 months. Similarly, in cohort B, 21 (33%; 95% CI, 22% to 46%) of the 63 patients had a confirmed response (5 CRs and 16 PRs) per RECIST v1.1 by central review (Table 2), and 15 (24%; 95% CI, 14% to 36%) had prolonged SD (Appendix Fig A1, online only) with a DCR of 57% (95% CI, 44% to 70%). The median time to response was 3.9 months (range, 1.8-12.5 months), with the median DOR not reached (range, 4.4 to 23.6+ months). Seventy-six percent of responses were ongoing at time of analysis, and an estimated 95% of patients had a DOR of ≥ 12 months. Thirty-four (56%) of the 61 patients in cohort A and 39 (62%) of the 63 in cohort B had a reduction from baseline in target lesion size (Fig 1). Changes from baseline in tumor size showed a general reduction in tumor burden over time, including in some patients with SD (Appendix Fig A1).

In the 61 patients of cohort A, there were 42 (69%) PFS events (RECIST v1.1 by central review) at data cutoff. The median PFS was 2.3 months (95% CI, 2.1 to 8.1 months) with estimated 12- and 24-month PFS rates of 34% and 31%, respectively (Fig 2A). In the 63 patients in cohort B, there were 39 (62%) PFS events at data cutoff. The median PFS was 4.1 months (95% CI, 2.1 to 18.9 months) with estimated 12- and 24-month PFS rates of 41% and 37%, respectively (Fig 2B). In cohort A, the median OS was 31.4 months (95% CI, 21.4 months to not reached) with estimated 12- and 24-month OS rates of 72% and 55%, respectively (Fig 3A). In cohort B, the median OS was not reached (95% CI, 19.2 months to not reached) with 12- and 24-month OS rates of 76% and 63%, respectively (Fig 3B).

Response Rate by Prior Lines of Therapy

In cohort A, 6 patients (10%) had 1 prior therapy, 28 (46%) had 2 prior therapies, and 27 (44%) had ≥ 3 prior therapies (Table 1). Patients experienced a reduction from baseline in target lesion size regardless of number of prior therapies (Fig 1). In cohort A, responses were observed in 2 (33%) of 6 patients with 1 prior therapy, 11 (39%) of 28 with 2 prior therapies, and 7 (26%) of 27 with ≥ 3 prior therapies (Appendix Table A2, online only). In cohort B, 24 (38%), 20 (32%), and 19 (30%) patients had 1, 2, or ≥ 3 prior therapies, respectively, and patients experienced a reduction from baseline in target lesion size regardless of number of prior therapies. In cohort B, responses were observed in 7 (29%) of 24 patients with 1 therapy, 9 (45%) of 20 with 2 prior therapies, and 5 (26%) of 19 with ≥ 3 prior therapies (Appendix Table A2).

Response Rate by Mutation Status

Eleven patients (18%) in cohort A and 7 (11%) in cohort B had *KRAS*/*BRAF*/*NRAS* wild-type tumors. Nine patients (15%) in cohort A and 5 (8%) in cohort B had *BRAF*-mutant tumors, and 16 (26%) in cohort A and 22 (35%) in cohort B had *KRAS*-mutant tumors (Table 1). In cohort A, responses were observed in 5 (55%) of 9 patients with *BRAF*-mutant tumors and in 7 (37%) of 19 with *KRAS*/*NRAS*-mutant tumors (Appendix Table A2; Appendix Fig A2 and A3 online only). In cohort B, responses were observed in 1 (20%) of 5 patients with

TABLE 2. Best Response (RECIST Version 1.1 by Central Review) in Patients With Microsatellite Instability–High/Mismatch Repair–Deficient Colorectal Cancer

	Cohort A (n = 61)		Cohort B (n = 63)	
Best Response	**No. (%)**	**95% CI**	**No. (%)**	**95% CI**
Objective response rate*	20 (33)	21 to 46	21 (33)	22 to 46
Complete response	2 (3)	0 to 11	5 (8)	3 to 18
Partial response	18 (30)	19 to 43	16 (25)	15 to 38
Stable disease	11 (18)	9 to 30	15 (24)	14 to 36
Disease progression	28 (46)	33 to 59	25 (40)	28 to 53
Nonevaluable	2 (3)	0 to 11	2 (3)	0 to 11
Disease control rate	31 (51)	38 to 64	36 (57)	44 to 70
Median time to response, months (range)	4.3 (1.8-24.9)		3.9 (1.8-12.5)	
Median duration of response, months (range)	NR (6.2 to 31.3+)†		NR (4.4 to 23.6+)†	

Abbreviation: NR, not reached.

*Objective response rate by investigator was 31.1% in cohort A and 38.1% in cohort B.

†"+" indicates no PD at the time of last assessment.

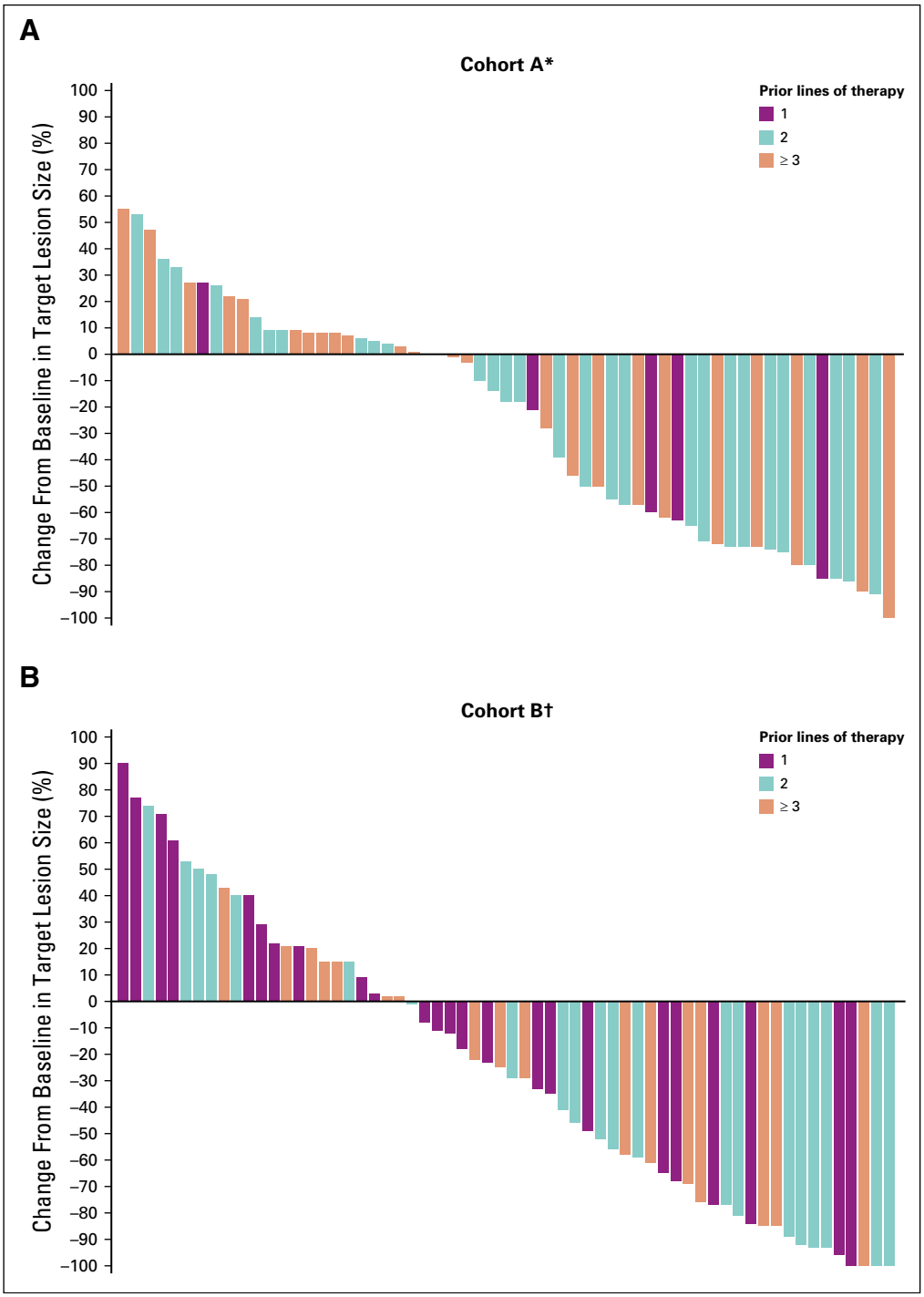

FIG 1. Best percent change from baseline in target lesion size (RECIST version 1.1 by central review) by prior lines of therapy in patients with microsatellite instability–high colorectal cancer in (A) cohort A and (B) cohort B. (*) Two patients in cohort A did not have postbaseline assessments and are not included. (†) One patient in cohort B did not have postbaseline assessments and is not included.

a *BRAF*-mutant tumor and in 9 (36%) of 25 with *KRAS/NRAS*-mutant tumors (Appendix Table A2; Appendix Fig A2 and A3).

Safety

In cohort A, 38 (62%) of 61 patients had any-grade treatment-related AEs, with 10 (16%) having a grade 3-4 treatment-related AE (Table 3). Two patients (3%) discontinued because of treatment-related AEs of increased alanine aminotransferase and pneumonitis in 1 patient each. Treatment-related AEs with incidence of ≥ 10% were arthralgia and nausea in 10 patients (16%) each; diarrhea, asthenia, and pruritus in 8 patients (13%) each; and fatigue in 6 patients (10%). The most

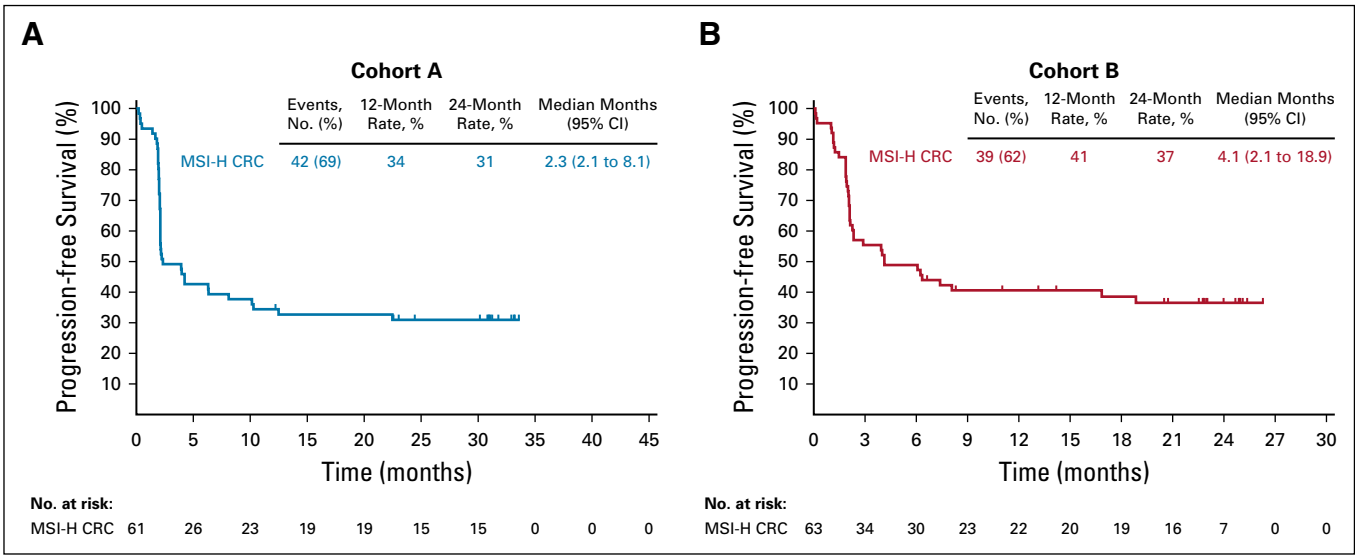

FIG 2. Kaplan-Meier estimates of progression-free survival (RECIST version 1.1 by central review) in patients with microsatellite instability–high colorectal cancer (MSI-H CRC) in (A) cohort A and (B) cohort B.

common grade 3-4 treatment-related AEs among these patients were fatigue in 2 (3%) and asthenia in 1 (2%). In cohort B, 44 (70%) of 63 patients had any-grade treatment-related AEs, with 8 (13%) having a grade 3-4 treatment-related AE. Two patients (3%) discontinued because of a treatment-related AE of pneumonitis. Treatment-related AEs with incidence of ≥ 10% were fatigue and hypothyroidism in 11 patients (17%) each and hyperthyroidism, arthralgia, and diarrhea in 7 patients (11%) each. There were no grade 3-4 treatment-related AEs among these patients. No grade 5 treatment-related AEs occurred in either cohort (Table 3).

Immune-mediated AEs or infusion reactions occurred in 13 (21%) of the 61 patients in cohort A (Table 3). Most events were grade 1-2 in severity, with 4 patients (7%) having a grade 3-4 immune-mediated AE. Grade 3-4 immune-mediated AEs were pancreatitis in 2 patients (3%) and hepatitis, pneumonitis, and severe skin toxicity in 1 patient (2%) each. Twenty-three (37%) of the 63 patients in cohort B had immune-mediated AEs or infusion reactions, with 2 patients (3%) having a grade 3-4 immune-mediated AE. Grade 3-4 immune-mediated AEs were colitis and pneumonitis in 1 patient (2%) each (Table 3). One patient (2%) in each cohort discontinued because of

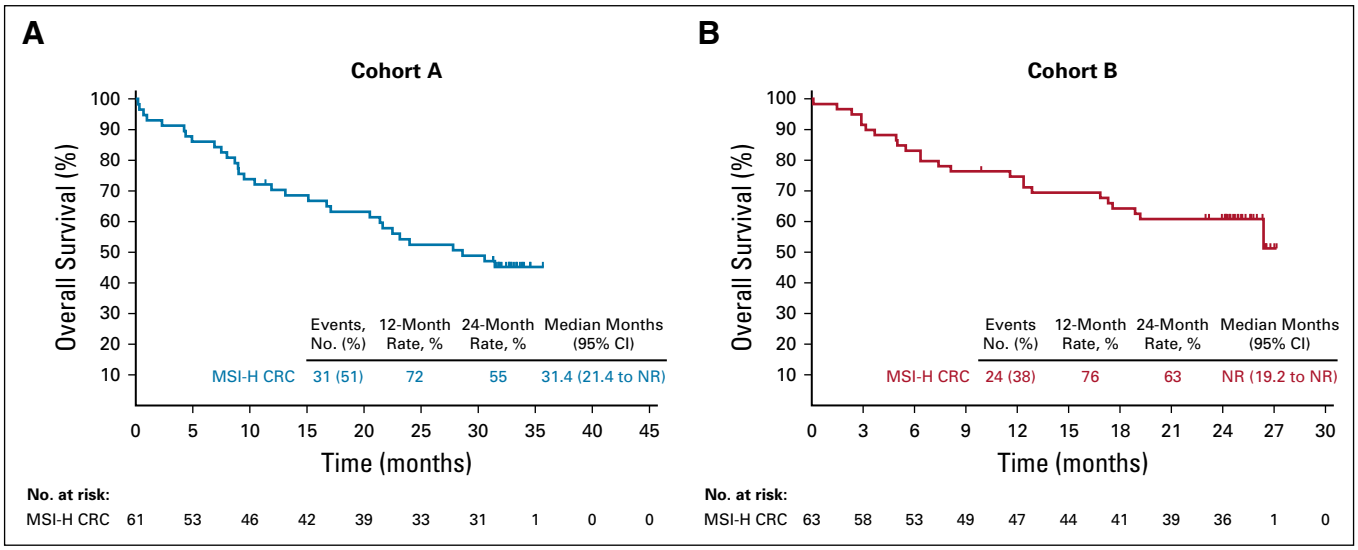

FIG 3. Kaplan-Meier estimates of overall survival in patients with microsatellite instability–high colorectal cancer (MSI-H CRC) in (A) cohort A and (B) cohort B. NR, not reached.

TABLE 3. Treatment-Related AEs in Patients With Microsatellite Instability–High/Mismatch Repair–Deficient Colorectal Cancer

AE	Cohort A (n = 61), No. (%)		Cohort B (n = 63), No. (%)	
Treatment-related AE				
All	38 (62)		44 (70)	
Grade 3-4	10 (16)		8 (13)	
Led to discontinuation	2 (3)*		2 (3)*	
Led to death	0 (0)		0 (0)	
Events ≥ 10% in any group	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Arthralgia	10 (16)	1 (2)	7 (11)	0 (0)
Nausea	10 (16)	0 (0)	5 (8)	0 (0)
Diarrhea	8 (13)	0 (0)	7 (11)	0 (0)
Asthenia	8 (13)	1 (2)	2 (3)	0 (0)
Pruritus	8 (13)	0 (0)	5 (8)	0 (0)
Fatigue	6 (10)	2 (3)	11 (17)	0 (0)
Hypothyroidism	3 (5)	0 (0)	11 (17)	0 (0)
Hyperthyroidism	2 (3)	0 (0)	7 (11)	0 (0)
Immune-mediated AEs and infusion reactions†				
All	13 (21)		23 (37)	
Grade 3-4	4 (7)		2 (3)	
Led to discontinuation	1 (2)‡		2 (3)‡	
Led to death	0 (0)		0 (0)	
All events	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism	6 (10)	0 (0)	13 (21)	0 (0)
Hyperthyroidism	3 (5)	0 (0)	7 (11)	0 (0)
Pancreatitis	3 (5)	2 (3)	0 (0)	0 (0)
Colitis	1 (2)	0 (0)	1 (2)	1 (2)
Hepatitis	1 (2)	1 (2)	0 (0)	0 (0)
Myositis	1 (2)	0 (0)	1 (2)	0 (0)
Pneumonitis	3 (5)	1 (2)	3 (5)	1 (2)
Severe skin toxicity	1 (2)	1 (2)	0 (0)	0 (0)
Infusion-related reactions	1 (2)	0 (0)	1 (2)	0 (0)

Abbreviation: AE, adverse event.

*Increased alanine aminotransferase and pneumonitis in 1 patient each in cohort A and pneumonitis in 2 patients in cohort B.

†On the basis of a list specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by investigator.

‡Pneumonitis in 1 patient in cohort A and 2 in cohort B.

an immune-mediated AE of pneumonitis. No grade 5 immune-mediated AEs occurred in either cohort.

DISCUSSION

The data from the KEYNOTE-164 study confirm that pembrolizumab provides durable responses with a manageable safety profile in patients with previously treated MSI-H/dMMR advanced or metastatic CRC. Pembrolizumab is approved for patients with previously treated MSI-H/dMMR CRC after fluoropyrimidine, oxaliplatin, and irinotecan, and for patients with MSI-H/dMMR non-CRC solid tumors after ≥ 1 prior therapy, regardless of tumor type or origin. This first US Food and Drug Administration approval of a tumor-agnostic anticancer therapy was based on data that showed an ORR of 39.6% and evidence of durable clinical benefit in 149 patients with MSI-H/dMMR cancers across 5 clinical studies, including 61 from cohort A of the phase II KEYNOTE-164 study and 19 from the KEYNOTE-158 study of pembrolizumab in patients with MSI-H/dMMR CRC and non-CRC, respectively.[10,12] The current updated analysis provides data from both cohort A (MSI-H/dMMR CRC after ≥ 2 prior therapies) and cohort B (MSI-H/dMMR CRC after ≥ 1 prior therapy) of KEYNOTE-164 with longer follow-up. A companion article by Marabelle et al[13] presents data from KEYNOTE-158

(ClinicalTrials.gov identifier: NCT02628067), which studied pembrolizumab in patients with previously treated metastatic MSI-H/dMMR non-CRC solid tumors.

With a median duration of follow-up of 31 months in cohort A, pembrolizumab provided an ORR of 33%, including 2 CRs, in patients with MSI-H/dMMR CRC and prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Similarly, in cohort B, with a median duration of follow-up of 24 months, the ORR was 33%, including 5 CRs. The median DOR was not reached in either cohort, and the median OS was 31 months in cohort A and not reached in cohort B, which supports the durability of the clinical benefit of pembrolizumab in some patients with MSI-H/dMMR CRC. While the lines of therapy for cohorts A and B are largely overlapping, cohort B was composed of 38% of patients receiving pembrolizumab after 1 line of therapy and, therefore, represented tumors earlier in the disease course. Our observations are in line with data from the neoadjuvant setting suggesting that treatment with PD-1 blockade earlier or even treatment of naïve tumors can be more effective than treatment of more advanced and refractory cases.[14] The phase III KEYNOTE-177 study (ClinicalTrials.gov identifier: NCT02563002) is evaluating the antitumor activity of first-line pembrolizumab compared with standard chemotherapy for patients with MSI-H/dMMR metastatic CRC and should help to further refine this observation.

In the current study, 46% of patients in cohort A and 49% in cohort B had *BRAF*- or *RAS*-mutant tumors. Although the numbers of patients with MSI-H/dMMR CRC *BRAF*- or *RAS*-mutant tumors were small, responses in 19 of these patients were still ongoing at the time of analysis. These data compare favorably with response rates historically observed with *EGFR* inhibitors (approximately 7-8%) and chemotherapy in patients with *KRAS*-, *RAS*-, or *BRAF*-mutant metastatic CRC.[15,16] The demonstration of durability of responses with pembrolizumab in MSI-H/dMMR CRC in various disease subsets supports the use of pembrolizumab in patients with MSI-H/dMMR CRC regardless of mutation status and 1, 2, or ≥ 3 prior lines of treatment. Furthermore, the safety profile is consistent with that observed with pembrolizumab across multiple tumor types.[12] No new safety signals were identified.

Limitations of the current study include the small subgroup size, which impairs interpretation of subgroup analyses, and lack of a comparator. In addition, MSI-H or dMMR status was assessed locally because availability and collection of tissue samples limited central confirmation. These tissue limitations precluded identification of potential biomarkers, such as baseline immune cell infiltrate, PD-L1 expression, and tumor mutation burden, that may correlate with efficacy. Nonetheless, an understanding of the response to PD-1 blockade in MSI/dMMR tumors is of high interest and may highlight novel mechanisms of response that may affect the field of immunotherapy. Tumor intrinsic (ie, mutation spectra, heterogeneity) and extrinsic (ie, tumor microenvironment, HLA restriction) properties will be important factors to evaluate in future cohorts.

In summary, data from KEYNOTE-164 confirm the durable clinical benefit of pembrolizumab in patients with previously treated MSI-H/dMMR metastatic CRC. Pembrolizumab is an important addition to the treatment options for these patients.

AFFILIATIONS

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[2]Asan Medical Center, Seoul, Republic of Korea
[3]University Hospitals Gasthuisberg Leuven, KU Leuven, Leuven, Belgium
[4]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[5]Nationales Centrum Tumorerkrankungen, Heidelberg, Germany
[6]Saitama Cancer Center, Saitama, Japan
[7]Royal Brisbane and Women's Hospital, Herston, QLD, Australia
[8]Indiana University Health University Hospital, Indianapolis, IN
[9]McGill University Health Centre, Montréal, Québec, Canada
[10]National Cancer Center Hospital East, Chiba, Japan
[11]Centre Hospitalier Universitaire de Toulouse, Toulouse, France
[12]Aichi Cancer Center Hospital, Aichi, Japan
[13]Vall d'Hebron Institute of Oncology, Barcelona, Spain
[14]Krankenhaus Nordwest, Frankfurt, Germany
[15]Roswell Park Comprehensive Cancer Center, Buffalo, NY
[16]Providence Cancer Center, Portland, OR
[17]University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA
[18]MSD China, Beijing, People's Republic of China
[19]Merck & Co Inc, Kenilworth, NJ
[20]Memorial Sloan Kettering Cancer Center, New York, NY
[21]Sorbonne Université, Paris, France

CORRESPONDING AUTHOR

Dung T. Le, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans St, Room 410, Baltimore, MD 21287; e-mail: dle@jhmi.edu.

PRIOR PRESENTATION

Presented at the American Society of Clinical Oncology 2017 Annual Meeting, Chicago, IL, June 2-6, 2017; the European Society of Medical Oncology (ESMO) Congress 2017, Madrid, Spain, September 8-12, 2017; the ESMO World Congress on Gastrointestinal Cancer 2018, Barcelona, Spain, June 20-23, 2018; and ESMO Congress 2019, Barcelona, Spain, September 27-October 1, 2018.

SUPPORT

Supported by Merck Sharp & Dohme, a subsidiary of Merck & Co Inc., Kenilworth, NJ, USA. Academic advisors and representatives of the sponsor participated in designing the study. Data collected by investigators and their site personnel were analyzed and interpreted by senior academic authors and representatives of the sponsor.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02107.

AUTHOR CONTRIBUTIONS

Conception and design: Dung T. Le, Takayuki Yoshino, Petr Kavan, Todd Crocenzi, Luis A. Diaz Jr

Provision of study material or patients: Dung T. Le, Tae-Won Kim, Eric Van Cutsem, Ravit Geva, Matthew Burge, Bert O'Neil, Petr Kavan, Takayuki Yoshino, Rosine Guimbaud, Hiroya Taniguichi, Elena Elez, Patrick M. Boland, Todd Crocenzi, Chloe E. Atreya, Luis A. Diaz Jr, Thierry André

Collection and assembly of data: Dung T. Le, Eric Van Cutsem, Dirk Jäger, Petr Kavan, Takayuki Yoshino, Salah-Eddin Al-Batran, Todd Crocenzi, Chloe E. Atreya, Luis A. Diaz Jr

Data analysis and interpretation: Dung T. Le, Tae Won Kim, Eric Van Cutsem, Dirk Jäger, Hiroki Hara, Matthew Burge, Petr Kavan, Takayuki Yoshino, Chloe E. Atreya, Patrick M. Boland, Todd Crocenzi, Yi Cui, Tong Dai, Patricia Marinello, Luis A. Diaz Jr, Thierry André

Manuscript writing: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients and their families and caregivers and all investigators and their site personnel, Ruixue Wang and Jiao Nan Li (MSD China, Beijing, China) for statistical analysis support, Luana Atherly-Henderson (Merck Sharp & Dohme, a subsidiary of Merck & Co Inc., Kenilworth, NJ, USA (MSD)) for medical writing assistance, Jonathan Cheng (MSD) for critical review of the manuscript, and Conrad Messam (MSD) for critical clinical study support.

REFERENCES

1. International Agency for Research on Cancer: Cancer Fact Sheet, March 2019. https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf
2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
3. Koopman M, Kortman GA, Mekenkamp L, et al: Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer 100: 266-273, 2009
4. Goldstein J, Tran B, Ensor J, et al: Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). Ann Oncol 25:1032-1038, 2014
5. 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 20:5322-5330, 2014
6. Le DT, Uram JN, Wang H, et al: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015
7. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017
8. 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 18:1182-1191, 2017
9. Overman MJ, Lonardi S, Wong KYM, et al: Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 36:773-779, 2018
10. Lemery S, Keegan P, Pazdur R: First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 377:1409-1412, 2017
11. Bristol-Myers Squibb, Princeton, NJ, USA: OPDIVO (nivolumab): US prescribing information, 2018
12. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA: Keytruda (pembrolizumab): US prescribing information, 2019
13. 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 38:1-10, 2020
14. Forde PM, Chaft JE, Smith KN, et al: Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 378:1976-1986, 2018
15. De Roock W, Claes B, Bernasconi D, et al: Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: A retrospective consortium analysis. Lancet Oncol 11:753-762, 2010
16. Di Nicolantonio F, Martini M, Molinari F, et al: Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 26:5705-5712, 2008

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability–High/Mismatch Repair–Deficient Metastatic Colorectal Cancer: KEYNOTE-164

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Dung T. Le
Honoraria: Merck
Consulting or Advisory Role: Merck, Bristol-Myers Squibb
Research Funding: Merck, Bristol-Myers Squibb, Aduro Biotech, Curegenix, Medivir
Patents, Royalties, Other Intellectual Property: Inventor of technology, "Microsatellite Instability as a Pharmacogenomic Marker of Therapeutic Response to Immune Checkpoint Inhibition"

Tae Won Kim
Employment: Asan Medical Center
Research Funding: Sanofi (Inst)

Eric Van Cutsem
Consulting or Advisory Role: Bayer AG, Eli Lilly, Roche, Servier, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Halozyme, Array BioPharma
Research Funding: Amgen (Inst), Bayer AG (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Ipsen (Inst), Merck (Inst), Merck KGaA (Inst), Servier (Inst), Bristol-Myers Squibb (Inst)

Ravit Geva
Leadership: Pyxis
Honoraria: Bristol-Myers Squibb, MSD, Medison, Roche, Novartis, Janssen Pharmaceuticals, Pfizer, Takeda Pharmaceuticals
Consulting or Advisory Role: Bayer AG, Novartis, MSD, BOL Pharma
Patents, Royalties, Other Intellectual Property: Options, BOL Pharma
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Merck Serono, Bayer AG, Medison

Dirk Jäger
Consulting or Advisory Role: Roche (Inst), Genentech (Inst), Bristol-Myers Squibb (Inst), BioNTech AG (Inst), Amgen (Inst)

Hiroki Hara
Honoraria: Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Eli Lilly, Ono Pharmaceutical, Takeda Pharmaceuticals, Bristol-Myers Squibb, Sanofi, MSD, Daiichi Sankyo, Kyowa Hakko Kirin
Consulting or Advisory Role: Ono Pharmaceutical, MSD
Research Funding: AstraZeneca (Inst), Chugai Pharma (Inst), Merck Serono (Inst), MSD (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Boehringer Ingelheim (Inst), Dainippon Sumitomo Pharma (Inst), Daiichi Sankyo (Inst), Pfizer (Inst), LSK BioPharma (Inst), Eisai (Inst), Incyte (Inst), BeiGene (Inst)

Matthew Burge
Stock and Other Ownership Interests: Bristol-Myers Squibb, Pfizer, Gilead Sciences, CSL Limited, Coclear
Honoraria: Roche, Amgen, Merck KGaA, Servier, Merck Sharp & Dohme
Consulting or Advisory Role: Amgen, Roche, Ipsen
Patents, Royalties, Other Intellectual Property: Funding for an investigator-initiated prospective trial (Inst)
Travel, Accommodations, Expenses: Amgen, Roche

Bert O'Neil
Employment: Eli Lilly
Consulting or Advisory Role: Bristol-Myers Squibb, Merck

Petr Kavan
Honoraria: Amgen, Ipsen, Novartis, Bayer AG
Consulting or Advisory Role: Novartis, Pfizer, Amgen, Celgene, Taiho Pharmaceutical, LEO Pharma
Travel, Accommodations, Expenses: Pfizer, Ipsen, Taiho Pharmaceutical, Novartis

Takayuki Yoshino
Research Funding: Chugai Pharma (Inst), Sanofi (Inst), Sumitomo Dainippon (Inst), GlaxoSmithKline (Inst), Novartis (Inst), MSD (Inst), Daiichi Sankyo (Inst), PAREXEL International (Inst), Ono Pharmaceutical (Inst)

Rosine Guimbaud
Consulting or Advisory Role: Servier, MSD Oncology, Roche, Pierre Fabre, AstraZeneca
Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb

Hiroya Taniguchi
Honoraria: Takeda Pharmaceuticals, Chugai Pharmaceutical, Merck Serono, Taiho Pharmaceutical, Bayer AG, Eli Lilly Japan, Yakult Honsha, Sanofi

Elena Elez
Consulting or Advisory Role: Amgen, Roche, Merck Serono, Sanofi, Servier, Bayer AG, Pierre Fabre
Research Funding: Merck Serono, Sanofi (Inst)
Travel, Accommodations, Expenses: Roche, Merck Serono, Sanofi, Amgen

Salah-Eddin Al-Batran
Stock and Other Ownership Interests: IKF Klinische Krebsforschung GmbH
Consulting or Advisory Role: Roche, Celgene, Eli Lilly, Bristol-Myers Squibb, Merck, Nordic Bioscience, Merck Sharp & Dohme
Speakers' Bureau: Eli Lilly, Roche, Celgene, AIO GmbH, Forum für Medizinische Fortbildung, MCI Group, Nordic Bioscience, Promedior
Research Funding: Celgene, Eli Lilly, Medac, Hospira, Sanofi, German Cancer Aid, German Research Foundation, Federal Ministry of Education and Research of Germany, Merck, Roche, Vifor Pharma

Patrick M. Boland
Honoraria: Boston Biomedical
Consulting or Advisory Role: Sirtex Medical, Merrimack
Research Funding: Boehringer Ingelheim (Inst), Merck (Inst), Theradiag (Inst), Advaxis (Inst), Bayer AG (Inst), Genentech (Inst), Roche (Inst), Boston Biomedical (Inst), Ipsen (Inst), Merrimack (Inst), Athenex (Inst),

Todd Crocenzi
Research Funding: Bristol-Myers Squibb (Inst), AstraZeneca (Inst), MedImmune (Inst)

Chloe E. Atreya
Consulting or Advisory Role: Array BioPharma, Pionyr Immunotherapeutics
Research Funding: Novartis, Merck, Bristol-Myers Squibb, Guardant Health, Genentech (Inst)
Travel, Accommodations, Expenses: Roche

Tong Dai
Stock and Other Ownership Interests: Merck

Yi Cui
Employment: MSD China
Stock and Other Ownership Interest: Merck Sharp & Dohme

Patricia Marinello
Employment: Merck Sharp & Dohme
Stock and Other Ownership Interests: Merck Sharp & Dohme

Luis A. Diaz Jr
Leadership: Personal Genome Diagnostics, Jounce Therapeutics
Stock and Other Ownership Interests: PapGene, Personal Genome Diagnostics, Jounce Therapeutics, Zydecom Corporation, Thrive Detect, Neophore, Amgen (I)
Consulting or Advisory Role: Merck, Personal Genome Diagnostics, Cell Design Labs, Lyndra, Caris Life Sciences, Genocea Biosciences, Zydecom, Neophore
Research Funding: Merck (Inst)
Patents, Royalties, Other Intellectual Property: US-2010041048-A1: Circulating Mutant DNA to Assess Tumor Dynamics, US-2015344970-A1: Personalized Tumor Biomarkers, WO-2010118016-A2: Digital Quantification of DNA Methylation, US-2005202465-A1: Thymidylate Synthase Gene and Metastasis, US-2014227271-A1: Somatic Mutations in Atrx in Brain Cancer, WO-2012094401-A2: Genes Frequently Altered in Pancreatic Neuroendocrine Tumors, US-2013323167-A1: Detecting and Treating Solid Tumors Through Selective Disruption of Tumor Vasculature, EP-2912468-B1: Papanicolaou Test for Ovarian and Endometrial Cancers, US-9976184-B2: Mutations in Pancreatic Neoplasms, US-2017267760-A1: Checkpoint Blockade and Microsatellite Instability, US-2018171413-A1: Head and Neck Squamous Cell Carcinoma Assays, US-2018171413-A1: Head and Neck Squamous Cell Carcinoma

Assays, US-2018171413-A1: Head and Neck Squamous Cell Carcinoma Assays, US-2018086832-A1: HLA-Restricted Epitopes Encoded by Somatically Mutated Genes, US-2018258490-A1: Assaying Ovarian Cyst Fluid, US-2016208340-A1: TERT Promoter Mutations in Urothelial Neoplasia, US-2015252415-A1: Arid1b and Neuroblastoma, WO-2018071796-A2: Compositions and Methods for Identifying Functional Anti-Tumor T-Cell Responses, EP-3322824-A1: Detection of Tumor-Derived DNA in Cerebrospinal Fluid, US-2016273049-A1: Systems and Methods for Analyzing Nucleic Acid (Inst), US-2018135044-A1: Non-Unique Barcodes in a Genotyping Assay (Inst), US-2017016075-A1: Neoantigen Analysis (Inst)
Travel, Accommodations, Expenses: Merck

Thierry André
Honoraria: Roche, Genentech, Bristol-Myers Squibb, Servier, Xbiotech, Bayer AG, Sanofi, Amgen, PRMA Consulting, Pierre Fabre, Vantana
Consulting or Advisory Role: Roche, Genentech, Amgen, Bristol-Myers Squibb, Mundipharma, HalioDX, MSD Oncology, Servier, Guardant Health, Bayer AG, AstraZeneca, MedImmune, Tesaro, Clovis Oncology
Travel, Accommodations, Expenses: Roche, Genentech, Amgen, Bristol-Myers Squibb, MSD Oncology, Vantana

No other potential conflicts of interest were reported.

APPENDIX

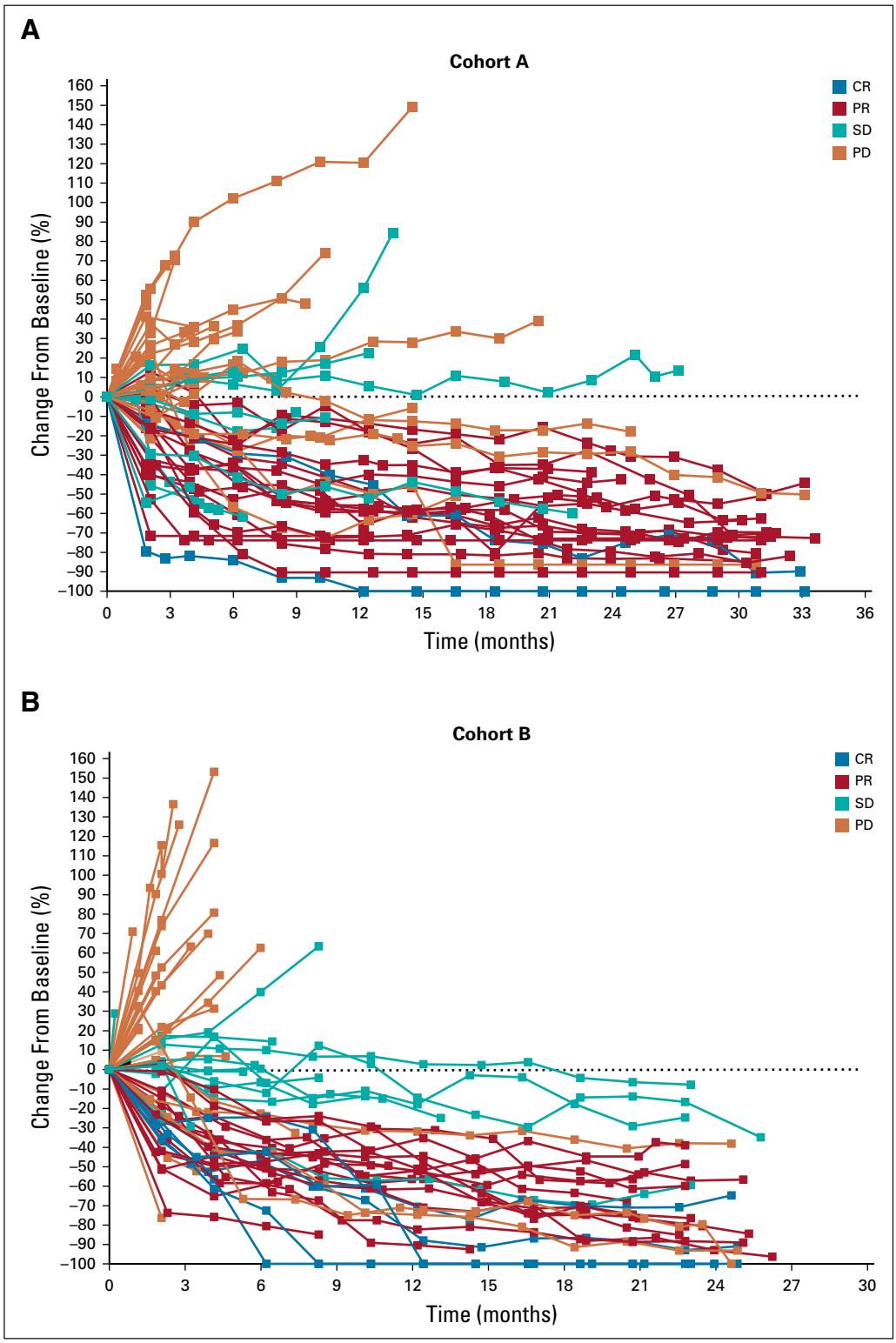

FIG A1. Percent change from baseline in target lesion size (RECIST v1.1) with time in patients with microsatellite instability–high/mismatch repair–deficient colorectal cancer in (A) Cohort A and (B) Cohort B. CR, complete response; PD, disease progression; PR, partial response; SD, stable disease.

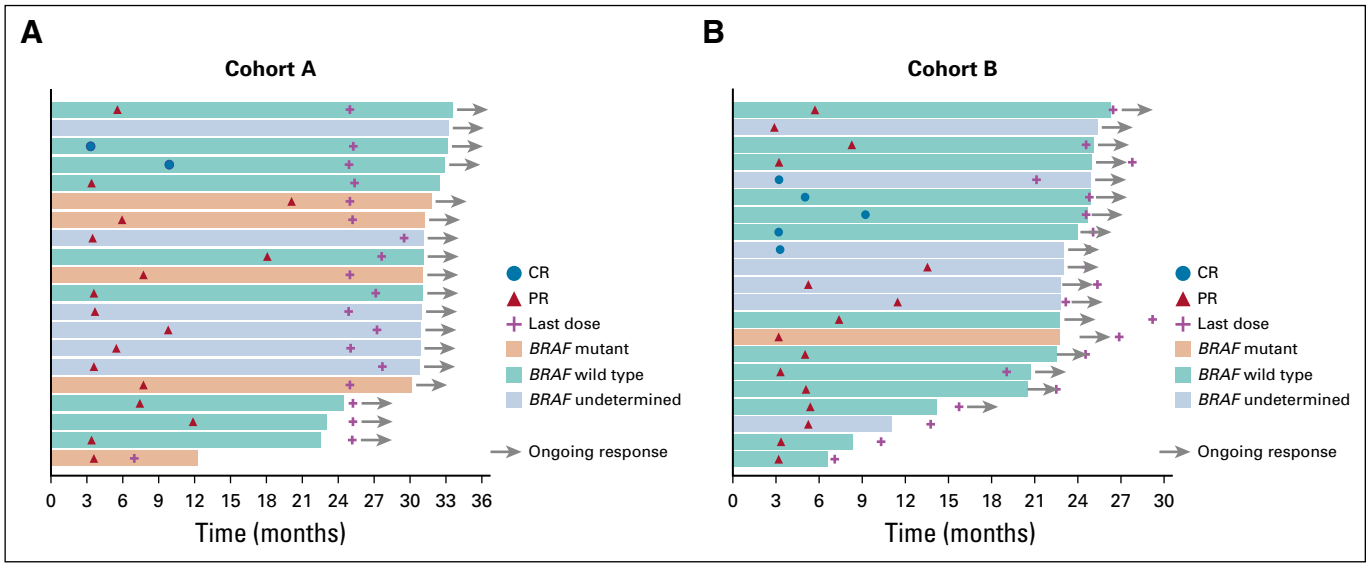

FIG A2. Treatment exposure and duration of response by BRAF status in patients with microsatellite instability–high/mismatch repair–deficient colorectal cancer in (A) Cohort A and (B) Cohort B. CR, complete response; PR, partial response.

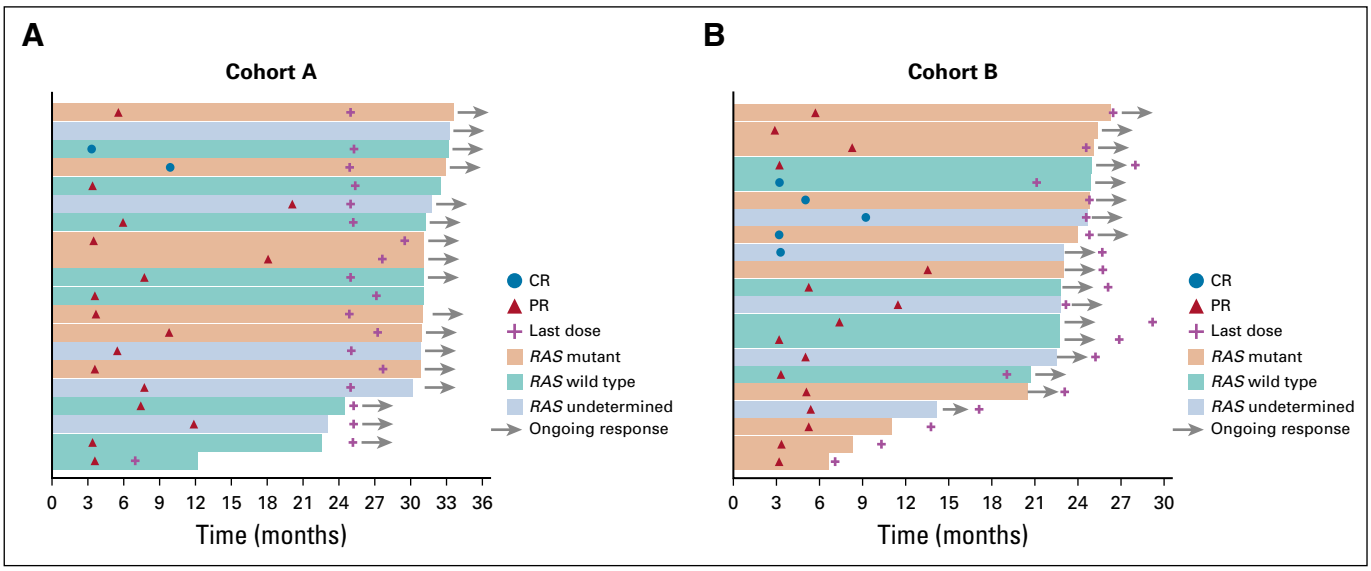

FIG A3. Treatment exposure and duration of response by RAS status in patients with microsatellite instability–high/mismatch repair–deficient colorectal cancer in (A) Cohort A and (B) Cohort B. CR, complete response; PR, partial response.

TABLE A1. Treatment Disposition

Disposition	Cohort A (n = 61), No. (%)	Cohort B (n = 63), No. (%)
Completed	21 (34)	11 (17)
Treatment ongoing	0 (0)	10 (16)
Discontinued	40 (66)	42 (67)
Disease progression	29 (48)	27 (43)
Adverse event	5 (8)	4 (6)
Patient/physician decision/noncompliance	6 (10)	11 (17)

TABLE A2. Overall Response in Subgroups of Patients With Microsatellite Instability–High/Mismatch Repair–Deficient Colorectal Cancer

Response	Cohort A (n = 61), No. (%)	Cohort B (n = 63), No. (%)
Prior line of therapy		
1	2 (33)	7 (29)
2	11 (39)	9 (45)
≥ 3	7 (26)	5 (26)
BRAF/*RAS** mutant status, No. of total No. (%)		
BRAF wild type	9 of 28 (32)	13 of 29 (45)
BRAF mutant	5 of 9 (55)	1 of 5 (20)
BRAF undetermined	6 of 24 (25)	7 of 29 (24)
RAS wild type	8 of 19 (42)	7 of 16 (44)
RAS mutant	7 of 19 (37)	9 of 25 (36)
RAS undetermined	5 of 23 (22)	5 of 22 (23)

**RAS* group includes *KRAS*/*NRAS* status.