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ORIGINAL ARTICLE

Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study

M. Maio[1*], P. A. Ascierto[2], L. Manzyuk[3], D. Motola-Kuba[4], N. Penel[5], P. A. Cassier[6], G. M. Bariani[7], A. De Jesus Acosta[8], T. Doi[9], F. Longo[10], W. H. Miller, Jr[11,12], D.-Y. Oh[13,14,15], M. Gottfried[16], L. Xu[17], F. Jin[17], K. Norwood[17] & A. Marabelle[18]

[1]University of Siena and Center for Immuno-Oncology, Department of Oncology, University Hospital, Siena; [2]Unit of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Pascale, Naples, Italy; [3]Outpatient Medical Treatment Department, NN Blokhin National Medical Research Center of Oncology, Moscow, Russia; [4]COMOP A.C., Clinical Investigation, Mexico City, Mexico; [5]Medical Oncology Department, Centre Oscar Lambret and Lille University, Lille; [6]Department of Medical Oncology, Centre Léon Bérard, Lyon, France; [7]Department of Radiology and Oncology, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; [8]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, USA; [9]Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan; [10]Medical Oncology Department, Ramon y Cajal University Hospital, IRYCIS, CIBERONC, Madrid, Spain; [11]Segal Cancer Centre, Jewish General Hospital, Montréal; [12]Department of Medicine, McGill University, Montréal, Canada; [13]Department of Internal Medicine, Seoul National University Hospital, Seoul; [14]Cancer Research Institute, Seoul National University College of Medicine, Seoul; [15]Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, South Korea; [16]Department of Medical Oncology, Meir Medical Center, Kfar Saba, Israel; [17]Merck & Co., Inc., Rahway, USA; [18]Department of Therapeutic Innovation and Early Trials, Gustave Roussy, Institut National de la Santé et de la Recherche Médicale U1015/CIC1428, Université Paris Saclay, Villejuif, France

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Background: Pembrolizumab demonstrated durable antitumor activity in 233 patients with previously treated advanced microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) advanced solid tumors in the phase II multicohort KEYNOTE-158 (NCT02628067) study. Herein, we report safety and efficacy outcomes with longer follow-up for more patients with previously treated advanced MSI-H/dMMR noncolorectal cancers who were included in cohort K of the KEYNOTE-158 (NCT02628067) study.

Patients and methods: Eligible patients with previously treated advanced noncolorectal MSI-H/dMMR solid tumors, measurable disease as per RECIST v1.1, and Eastern Cooperative Oncology Group performance status of 0 or 1 received pembrolizumab 200 mg Q3W for 35 cycles or until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) as per RECIST v1.1 by independent central radiologic review.

Results: Three hundred and fifty-one patients with various tumor types were enrolled in KEYNOTE-158 cohort K. The most common tumor types were endometrial (22.5%), gastric (14.5%), and small intestine (7.4%). Median time from first dose to database cut-off (5 October 2020) was 37.5 months (range, 0.2-55.6 months). ORR among 321 patients in the efficacy population (patients who received $\geq$1 dose of pembrolizumab enrolled $\geq$6 months before the data cut-off date) was 30.8% [95% confidence interval (CI) 25.8% to 36.2%]. Median duration of response was 47.5 months (range, 2.1+ to 51.1+ months; '+' indicates no progressive disease by the time of last disease assessment). Median progression-free survival was 3.5 months (95% CI 2.3-4.2 months) and median overall survival was 20.1 months (95% CI 14.1-27.1 months). Treatment-related adverse events (AEs) occurred in 227 patients (64.7%). Grade 3-4 treatment-related AEs occurred in 39 patients (11.1%); 3 (0.9%) had grade 5 treatment-related AEs (myocarditis, pneumonia, and Guillain–Barre syndrome, $n = 1$ each).

Conclusions: Pembrolizumab demonstrated clinically meaningful and durable benefit, with a high ORR of 30.8%, long median duration of response of 47.5 months, and manageable safety across a range of heavily pretreated, advanced MSI-H/dMMR noncolorectal cancers, providing support for use of pembrolizumab in this setting.

Key words: microsatellite instability, mismatch repair deficiency, tumor-agnostic, cancer, immunotherapy, biomarker

INTRODUCTION

Tumors with mismatch repair deficiency (dMMR), either due to an inherited mutation or sporadic mutation, have a defect in one of the MMR genes (*MLH1*, *PMS2*, *MSH2*, and *MSH6*), resulting in failure to repair errors in DNA replication.[1,2] These errors are particularly prevalent in regions of repetitive DNA sequences known as microsatellites, resulting in high levels of microsatellite instability (MSI-H).[3] Approximately 2%-4% of

*Correspondence to: Dr Michele Maio, University of Siena and Center for Immuno-Oncology, Department of Oncology, University Hospital of Siena, Viale Bracci 14, 53100, Siena, Italy. Tel: +39-0577-586336
E-mail: maio@unisi.it (M. Maio).

cancers have MSI-H/dMMR.[4-7] These tumors have a marked increase in somatic mutations in comparison to non-MSI-H/dMMR tumors,[3] resulting in a higher neoantigen load. Moreover, tumors with MSI-H/dMMR have been associated with higher levels of CD8-positive tumor-infiltrating lymphocytes[8] and express higher levels of immune checkpoint proteins, including programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1),[1] cytotoxic T-lymphocyte antigen 4, and lymphocyte activation gene 3 than microsatellite stable tumors.[9]

Several studies have demonstrated the antitumor activity of immune checkpoint inhibitors targeting PD-1 or PD-L1 in patients with MSI-H/dMMR tumors.[3,10-15] The humanized IgG4 anti-PD-1 monoclonal antibody pembrolizumab has demonstrated antitumor activity in patients with MSI-H/dMMR solid tumors following disease progression on prior therapy.[3,11] In a phase II study of patients with dMMR and MMR-proficient colorectal cancer and dMMR noncolorectal cancers, objective responses for pembrolizumab were observed in 5 of 7 (71%) patients with dMMR noncolorectal cancers and 4 of 10 (40%) patients with dMMR colorectal cancer.[3] Results from a subsequent analysis including more patients ($n = 86$) across 12 tumor types with dMMR reported an objective response rate (ORR) of 53%.[12] In the nonrandomized, open-label, multicohort, phase II KEYNOTE-158 study, which enrolled patients with any of 10 solid tumor types (cohorts A to J) and patients with any solid tumor except colorectal tumors that were MSI-H/dMMR (cohort K), pembrolizumab demonstrated an ORR of 34.3%.[11] Median progression-free survival (PFS) was 4.1 months and median overall survival (OS) was 23.5 months.[11]

Pembrolizumab was granted accelerated approval by the United States Food and Drug Administration (FDA) for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H/dMMR solid tumors with disease progression following prior treatment and with no satisfactory alternative treatment options in May 2017, based in part on results from the KEYNOTE-158 study.[16,17] This approval, and the data on which it was based, established MSI-H/dMMR as a tumor-agnostic biomarker for pembrolizumab monotherapy.[17] Pembrolizumab has subsequently received tumor-agnostic approval for patients with advanced/recurrent MSI-H/dMMR solid tumors that have progressed after chemotherapy in other countries.[16,18,19]

Herein, we report the safety and efficacy outcomes from an analysis of patients with a wide range of MSI-H/dMMR solid tumors enrolled in cohort K of KEYNOTE-158 (ClinicalTrials.gov, NCT02628067). Cohort K enrolled patients with any advanced MSI-H/dMMR solid tumor (with the exception of colorectal cancers) irrespective of tumor origin, thereby representing a prospective tumor-agnostic, biomarker-driven approach to patient selection.

METHODS

Patients and study design

In KEYNOTE-158, cohorts A to J enrolled patients with 1 of 10 prespecified advanced tumor types regardless of biomarker status. Cohort K enrolled patients with any advanced MSI-H/dMMR solid tumor, with the exception of colorectal carcinoma.

Eligibility criteria for enrollment in KEYNOTE-158 have been previously described.[11] Briefly, eligible patients enrolled in cohort K were ≥18 years old with a histologically or cytologically confirmed incurable advanced (metastatic and/or unresectable) solid tumor that was MSI-H/dMMR (excluding colorectal cancer) with central confirmation of MSI status; with treatment failure on or intolerance to standard first-line therapies; who had provided a tissue sample for biomarker analysis from a tumor lesion not previously irradiated; who had measurable disease as per RECIST version 1.1 as assessed by independent central radiologic review; with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and who had adequate organ function. Patients were ineligible if they had received an investigational agent/device or prior anticancer monoclonal antibody within 4 weeks of the first dose; had immunodeficiency or received systemic steroid therapy or immunosuppressive therapy within 7 days of the first dose; had active autoimmune disease requiring systemic treatment within 2 years (replacement therapy, i.e. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, was permitted); had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks; had active central nervous system metastases and/or carcinomatous meningitis (patients with previously treated brain metastases that were stable were allowed); had current or history of noninfectious pneumonitis; or had an active infection requiring systemic therapy.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and with local and/or national regulations. The study protocol and its amendments were approved by an independent institutional review board or ethics committee at each site. Patients provided written informed consent before enrollment.

Study treatments

Pembrolizumab 200 mg was administered intravenously every 3 weeks for 35 cycles (~2 years) or until disease progression, unacceptable adverse events (AEs), intercurrent illness, investigator decision, or withdrawal of consent. Patients who stopped treatment with pembrolizumab after attaining a complete response (CR), partial response (PR), or stable disease (SD) were eligible for up to 17 cycles (~1 year) of re-treatment (second course) with pembrolizumab following disease progression if criteria were met.

Assessments

Tumor imaging was carried out by computed tomography (preferred modality) or magnetic resonance imaging at baseline, every 9 weeks during treatment for the first year, and every 12 weeks thereafter. Survival status was assessed

every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurred first.

MSI/MMR status was assessed prospectively at local laboratories from tumor tissue samples by PCR or by immunohistochemistry (IHC). MSI/MMR status was determined by examining either the loss of protein expression by IHC of four MMR enzymes (MLH1/MSH2/MSH6/PMS2) or analysis of five tumor microsatellite loci using PCR-based assays [either the five mononucleotide loci (BAT25, BAT26, NR21, NR24, Mono27) or the five mixed mononucleotide and dinucleotide loci (BAT25, BAT26, Di 5S346, Di 2S123, Di 17S250)], respectively. MSI-H/dMMR was defined as the absence of $\geq$1 of 4 MMR proteins by IHC or $\geq$2 allelic loci size shifts among the five microsatellite markers by PCR.

AEs were assessed throughout the study and for 30 days after the last dose of pembrolizumab (90 days for serious AEs) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Endpoints

The primary endpoint was ORR, defined as the proportion of patients with a CR or PR as per RECIST version 1.1 as assessed by independent central radiologic review. Secondary endpoints included duration of response (DOR, time from the first documented evidence of CR or PR until the sign of first documented disease progression or death, whichever occurred first) and PFS (time from first dose to the first documented disease progression or death, whichever occurred first) as per RECIST version 1.1 as assessed by independent central radiologic review; OS (time from first dose to the date of death due to any cause); and safety.

Statistical analysis

Efficacy was assessed in all patients who received $\geq$1 dose of pembrolizumab and had $\geq$6 months of follow-up (in order to allow sufficient time for responses to occur and be assessed). Safety was assessed in all patients who received $\geq$1 dose of pembrolizumab. As previously described,[11] the point estimate and exact Clopper—Pearson confidence interval (CI) were provided for ORR and the Kaplan—Meier method was used to estimate DOR, PFS, and OS along with 95% CIs.

RESULTS

Patients and treatment

A total of 351 patients across 28 tumor types were enrolled in cohort K of KEYNOTE-158 from 54 sites in 18 countries between 19 February 2016 and 1 October 2020. At the time of data cut-off (5 October 2020), 321 (91.5%) patients had received $\geq$1 dose of pembrolizumab and had $\geq$6 months of follow-up and were included in the efficacy population. Among all enrolled patients, the most common tumor types were endometrial (22.5%), gastric (14.5%), small intestine (7.4%), ovarian (7.1%), cholangiocarcinoma/biliary tract cancer (6.3%), pancreatic (6.3%), and brain (6.0%). Although assessment of PD-L1 status was not required for enrollment in cohort K, 9.4% of patients were assessed as having a PD-L1-positive tumor and 9.7% were assessed as having a PD-L1-negative tumor; the remainder were not evaluable or not assessed (Table 1). Median age was 60 years (range, 20-89 years), 59.0% of patients were women, 55.3% had an ECOG performance status of 1, 41.0% had received 1 prior line of therapy, and 55.6% had received $\geq$2 prior lines of therapy.

Median time from first dose to database cut-off was 37.5 months (range, 0.2-55.6 months). Median duration of treatment was 4.9 months (range, 0.03-29.7 months). At the time of data cut-off, 56 patients (16.0%) were continuing study treatment, 58 (16.5%) had completed 35 cycles of pembrolizumab, and 237 (67.5%) had discontinued treatment; the majority of patients [179 (51.0%)] discontinued owing to disease progression (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.05.519).

Efficacy outcomes

Among 321 patients in the efficacy population, the ORR by independent central radiologic review was 30.8% (95% CI 25.8% to 36.2%), including 27 patients (8.4%) with a CR and 72 (22.4%) with a PR (Table 2). An additional 61 patients (19.0%) had SD. Among patients who had at least one post-baseline assessment of tumor response, 178 of 287 (62.0%) had a decrease in target lesion size from baseline (Figure 1A; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.05.519). Median DOR was 47.5 months (range, 2.1+ to 51.1+ months). Kaplan—Meier estimate of the proportion of patients with a response duration of $\geq$1 year was 88.0%, $\geq$2 years was 74.1%, and $\geq$3 years was 70.1% (Figure 1B). At the time of data cut-off, 52 patients (52.5%) had an ongoing response. Among patients with a CR, 19 of 27 (70.4%) had an ongoing response.

Responses were observed across a broad range of tumor types. Among the most frequently occurring tumor types, the ORR was 48.5% (95% CI 36.2% to 61.0%) in endometrial cancer, 31.0% (95% CI 17.6% to 47.1%) in gastric cancer, 48.0% (95% CI 27.8% to 68.7%) in small intestine cancer, 33.3% (95% CI 15.6% to 55.3%) in ovarian cancer, 40.9% (95% CI 20.7% to 63.6%) in cholangiocarcinoma/biliary tract cancer, and 18.2% (95% CI 5.2% to 40.3%) in pancreatic cancer (Table 3). The ORR was 41.3% (95% CI, 32.6% to 50.4%) among the 126 patients who had received 1 line of prior therapy, 23.4% (95% CI, 17.5% to 30.2%) among the 184 patients who had received $\geq$2 lines of prior therapy, and 36.4% (95% CI, 10.9% to 69.2%) among the 11 patients who had not received prior systemic therapy. Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.05.519, shows ORR in subgroups defined by patient demographics and baseline disease characteristics.

As of data cut-off, 231 patients (72.0%) experienced events of disease progression or death (Figure 2A). Median PFS was 3.5 months (95% CI 2.3-4.2 months). Kaplan—Meier estimates of PFS rates were 33.9% at 1 year, 27.4% at 2 years, and 24.0% at years 3 and 4. At data cut-off, 180

Table 1. Patient demographics and baseline characteristics

	All patients[a] N = 351
Age, median (range), years	60 (20-89)
Sex, *n* (%)	
Men	144 (41.0)
Women	207 (59.0)
ECOG performance status, *n* (%)	
0	157 (44.7)
1	194 (55.3)
Metastasis stage, *n* (%)	
MX	20 (5.7)
M0	12 (3.4)
M1	319 (90.9)
Brain metastases, *n* (%)	6 (1.7)
Prior radiation therapy, *n* (%)	163 (46.4)
Number of prior lines of therapy, *n* (%)	
0	9 (2.6)
Adjuvant/neoadjuvant/definitive	3 (0.9)
1	144 (41.0)
2	87 (24.8)
3	56 (16.0)
4	22 (6.3)
≥5	30 (8.5)
Sum of target lesions measurable at baseline (mm), median (range)	72.4 (10.2-557.1)
Tumor type, *n* (%)	
Endometrial	79 (22.5)
Gastric	51 (14.5)
Small intestine	26 (7.4)
Ovarian	25 (7.1)
Cholangiocarcinoma/biliary tract	22 (6.3)
Pancreatic	22 (6.3)
Brain	21 (6.0)
Sarcoma	14 (4.0)
Breast	13 (3.7)
Neuroendocrine	12 (3.4)
Cervical	9 (2.6)
Prostate	8 (2.3)
Adrenocortical	7 (2.0)
Mesothelioma	6 (1.7)
SCLC	6 (1.7)
Thyroid	6 (1.7)
Urothelial	6 (1.7)
Renal	4 (1.1)
Salivary	4 (1.1)
Anal	2 (0.6)
Appendiceal adenocarcinoma	1 (0.3)
Hepatocellular carcinoma	1 (0.3)
HNSCC	1 (0.3)
Nasopharyngeal	1 (0.3)
Retroperitoneal adenocarcinoma	1 (0.3)
Testicular	1 (0.3)
Carcinoma of unknown origin	1 (0.3)
Vaginal	1 (0.3)
PD-L1 status[b], *n* (%)	
Positive[c]	33 (9.4)
Negative[d]	34 (9.7)
Not evaluable	3 (0.9)
Missing	281 (80.1)

ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; PD-L1, programmed death ligand 1; SCLC, small-cell lung cancer.
[a]Includes all patients who received ≥1 dose of pembrolizumab.
[b]Assessment of PD-L1 expression was not required for enrollment in cohort K.
[c]Defined as PD-L1 combined positive score ≥1.
[d]Defined as PD-L1 combined positive score <1.

Table 2. Confirmed objective response in the efficacy analysis population[a]

Response	N = 321
ORR, % (95% CI)	30.8 (25.8-36.2)
Best objective response, *n* (%)	
CR	27 (8.4)
PR	72 (22.4)
SD	61 (19.0)
PD	131 (40.8)
Not evaluable	3 (0.9)
No assessment[b]	27 (8.4)
Time to response, median (range), months	2.1 (1.3-12.9)
DOR, median (range), months	47.5 (2.1+ to 51.1+)
Kaplan–Meier estimate of patients with extended response duration, %	
≥1 year	88.0
≥2 years	74.1
≥3 years	70.1

'+' indicates no progressive disease by the time of last disease assessment.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Based on RECIST version 1.1 by independent central radiologic review.
[b]Patients with baseline assessment evaluated by the central radiology assessment but no post-baseline assessment at data cut-off including missing, discontinuing, or death before the first post-baseline scan.

patients (56.1%) had died (Figure 2B). Median OS was 20.1 months (95% CI 14.1-27.1 months). Kaplan–Meier estimates of OS rates were 58.6% at 1 year, 45.7% at 2 years, and 39.1% at both 3 and 4 years. PFS and OS outcomes among patients with the most frequently occurring tumor types are summarized in Table 3.

Safety

Among all 351 patients who received ≥1 dose of pembrolizumab, treatment-related AEs occurred in 227 patients (64.7%), including 42 patients (12.0%) who experienced grade 3-5 treatment-related AEs. Three patients (0.9%) died due to a treatment-related AE: myocarditis, pneumonia, and Guillain–Barre syndrome ($n = 1$ each; 0.3%). Twenty-three patients (6.6%) discontinued study treatment owing to a treatment-related AE. The most frequently occurring treatment-related AEs of any grade were pruritus (14.5%), fatigue (12.3%), and diarrhea (11.7%; Table 4). The most frequently occurring grade 3-5 treatment-related AEs were increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, hyperglycemia, and pneumonitis (all $n = 3$; 0.9%).

Immune-mediated AEs, regardless of attribution to study treatment or immune relatedness by the investigator, occurred in 69 patients (19.7%); 17 patients (4.8%) experienced grade 3-5 immune-mediated AEs; 10 patients (2.8%) discontinued due to an immune-mediated AE. The most frequently occurring immune-mediated AEs were hypothyroidism (9.7%), hyperthyroidism (4.3%), and pneumonitis (2.6%). Two patients (0.6%) had immune-mediated AEs that led to death with no other contributing factors: myocarditis and Guillain–Barre syndrome ($n = 1$ each; 0.3%). Infusion reactions occurred in four patients (1.1%). There were no grade 3-5 infusion reactions.

DISCUSSION

Among patients with a range of heavily pretreated advanced solid tumors with prospectively assessed MSI-H/dMMR status who were enrolled in cohort K of the KEYNOTE-158 study,

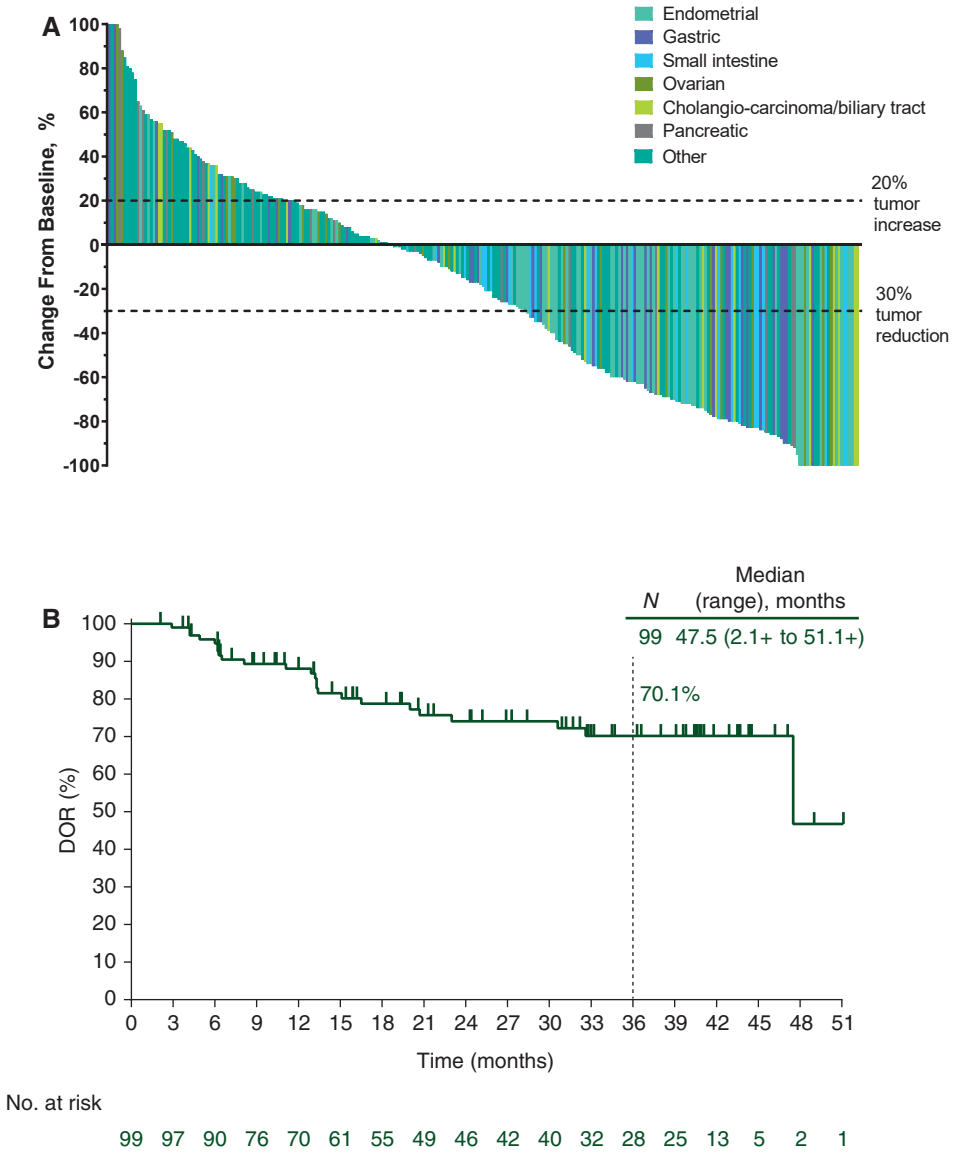

Figure 1. Antitumor activity. (A) Best percentage change from baseline in target lesion size. (B) Kaplan–Meier analysis of DOR per RECIST version 1.1 by independent central review.
DOR, duration of response.

pembrolizumab continued to demonstrate durable and clinically meaningful benefit with additional patients and longer follow-up. The ORR was 30.8% (95% CI 25.8% to 36.2%), including 8.4% of patients with a CR. CRs occurred in patients with a wide range of tumor types including those with small intestine, endometrial, gastric, ovarian, and cholangiocarcinoma/biliary tract carcinoma. Responses were durable, with median DOR of 47.5 months (range, 2.1+ to 51.1+ months), indicating that many responses were maintained even after stopping pembrolizumab (for which there was a 2-year treatment period); 52.5% of patients with a response had ongoing responses at the time of data cut-off (including 19 of 27 patients with confirmed CR). Assessment of OS and PFS outcomes in this study is challenging given the broad range of tumor types in the enrolled patient population, with consequent variation in prognosis, and use of a single-arm study design (owing to the lack of a standard comparator). Nonetheless, pembrolizumab demonstrated encouraging outcomes with a median OS of 20.1 months and median PFS of 3.5 months among patients with heavily pretreated advanced MSI-H/dMMR noncolorectal cancers. Taking into account of censoring, the estimated OS rate was 39.1% at 3 years with a plateau beyond that time. Toxicity was manageable, and no new safety signals were identified. Overall, these results from a population of patients who were selected for enrollment based on their MSI/MMR status support the use of pembrolizumab in this setting. These results provide further evidence for the utility of MSI-H/dMMR (assessed at a local laboratory using a standard technique consistent with current recommendations for MSI-H/dMMR testing[20]) as a tumor-agnostic biomarker for pembrolizumab monotherapy.

Results from the current analysis confirm and extend the findings from the prior analysis of patients with MSI-H/dMMR tumors enrolled in KEYNOTE-158.[11] In the prior analysis, MSI-H/dMMR status was determined retrospectively for patients

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Table 3. Summary of efficacy outcomes by tumor types with the highest number of enrolled patients

	Endometrial $n = 68$	Gastric $n = 42$	Small intestine $n = 25$	Ovarian $n = 24$	Cholangiocarcinoma/ biliary tract $n = 22$	Pancreatic $n = 22$
ORR, % (95% CI)	48.5 (36.2-61.0)	31.0 (17.6-47.1)	48.0 (27.8-68.7)	33.3 (15.6-55.3)	40.9 (20.7-63.6)	18.2 (5.2-40.3)
Best objective response, *n* (%)						
CR	10 (14.7)	4 (9.5)	4 (16.0)	3 (12.5)	3 (13.6)	1 (4.5)
PR	23 (33.8)	9 (21.4)	8 (32.0)	5 (20.8)	6 (27.3)	3 (13.6)
SD	13 (19.1)	7 (16.7)	7 (28.0)	2 (8.3)	3 (13.6)	3 (13.6)
PD	19 (27.9)	15 (35.7)	5 (20.0)	12 (50.0)	8 (36.4)	8 (36.4)
Not evaluable	1 (1.5)	1 (2.4)	—	—	—	—
No assessment	2 (2.9)	6 (14.3)	1 (4.0)	2 (8.3)	2 (9.1)	7 (31.8)
DOR, median (range), months	NR (2.9 to 47.1+)	NR (6.3 to 51.1+)	NR (2.1+ to 41.8+)	NR (4.2 to 43.5+)	30.6 (6.2 to 40.5+)	NR (8.1 to 24.3+)
Median PFS, months (95% CI)	13.1 (4.9-34.4)	3.2 (2.1-12.9)	23.4 (4.3-NR)	2.2 (2.0-6.2)	4.2 (2.1-24.9)	2.1 (1.9-3.4)
PFS rate $\geq$3 years[a], %	33.9	28.5	49.1	29.2	12.7	NR
Median OS, months (95% CI)	NR (32.4-NR)	11.0 (5.8-31.5)	NR (16.2-NR)	33.6 (11.0-NR)	19.4 (6.5-NR)	3.7 (2.1-9.8)
OS rate $\geq$3 years[a], %	62.1	34.5	58.7	42.6	30.3	22.7

'+' indicates no progressive disease by the time of last disease assessment.
CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]As per Kaplan–Meier method for censored data.

enrolled in cohorts A to J of KEYNOTE-158 and was determined prospectively for patients enrolled in cohort K.[11] Furthermore, the current analysis included a larger number of patients (351 patients versus 233 patients in prior analysis) with longer median follow-up (37.5 months versus 13.4 months in prior analysis[11]). Notably, the ORR was consistent with that previously reported (34.3%),[11] and clinically meaningful antitumor activity was observed across a range of tumor types including in the most frequently enrolled tumor types (endometrial, gastric, small intestine, ovarian, cholangiocarcinoma/biliary tract, pancreatic) for which there is currently a significant unmet need. Although lower response rates were observed in patients with pancreatic cancer (18.2%) than in the overall cohort, the DOR in that indication was not reached at median time from first dose to database cut-off of 37.5 months. While caution must be taken when interpreting OS in a single-arm study, the Kaplan–Meier estimate of the OS rate of 39.1% at 3 years was encouraging. To the best of our knowledge, these results represent the largest dataset of patients with MSI-H/dMMR noncolorectal cancers treated with an anti-PD-1 therapy.

Patients with a wide range of tumor types were enrolled, with the most common including endometrial, gastric, and small intestine, as well as tumor types that are known to have lower frequencies of MSI-H/dMMR.[5] Response rates were particularly high among patients with endometrial cancer and small intestine cancer, with approximately half of the patients experiencing an objective response. This analysis also included patients who had received varying numbers of prior lines of therapy. The ORR was higher in patients who had received 1 line of prior therapy than those with $\geq$2 prior lines of therapy (41.3% versus 23.4%), suggesting earlier administration of pembrolizumab may provide clinical benefit in this setting, and pembrolizumab should be offered as an earlier line of therapy. Of note, assessment of PD-L1 status was not planned for cohort K and no further data or tumor tissue are available for further evaluation.

Pembrolizumab has also demonstrated efficacy in the phase II KEYNOTE-164 study in patients with previously treated, advanced or metastatic MSI-H/dMMR colorectal cancer.[21] Tumor response in our study was similar to that from a recent update from KEYNOTE-164, which reported an ORR of 33% for pembrolizumab with a median follow-up of 31.3 months in cohort A (comprising patients with $\geq$2 prior lines of standard therapy) and 24.2 months in cohort B (patients with $\geq$1 prior line of systemic therapy).[21] Together, these data support the use of pembrolizumab in patients with previously treated MSI-H/dMMR tumors irrespective of tumor type. In the phase III KEYNOTE-177 study, first-line pembrolizumab significantly improved PFS versus 5-fluorouracil-based chemotherapy with/without bevacizumab or cetuximab [hazard ratio, 0.60 (95% CI 0.45-0.80); $P = 0.0002$] in patients with MSI-H/dMMR metastatic colorectal cancer.[22] Other anti-PD-1 inhibitors have demonstrated antitumor activity in patients with advanced MSI-H/dMMR noncolorectal cancers. In a phase II study evaluating nivolumab in patients with dMMR noncolorectal cancer ($N = 42$), the ORR was 36% with a median follow-up time of 17.3 months.[14] In a single-arm phase II study

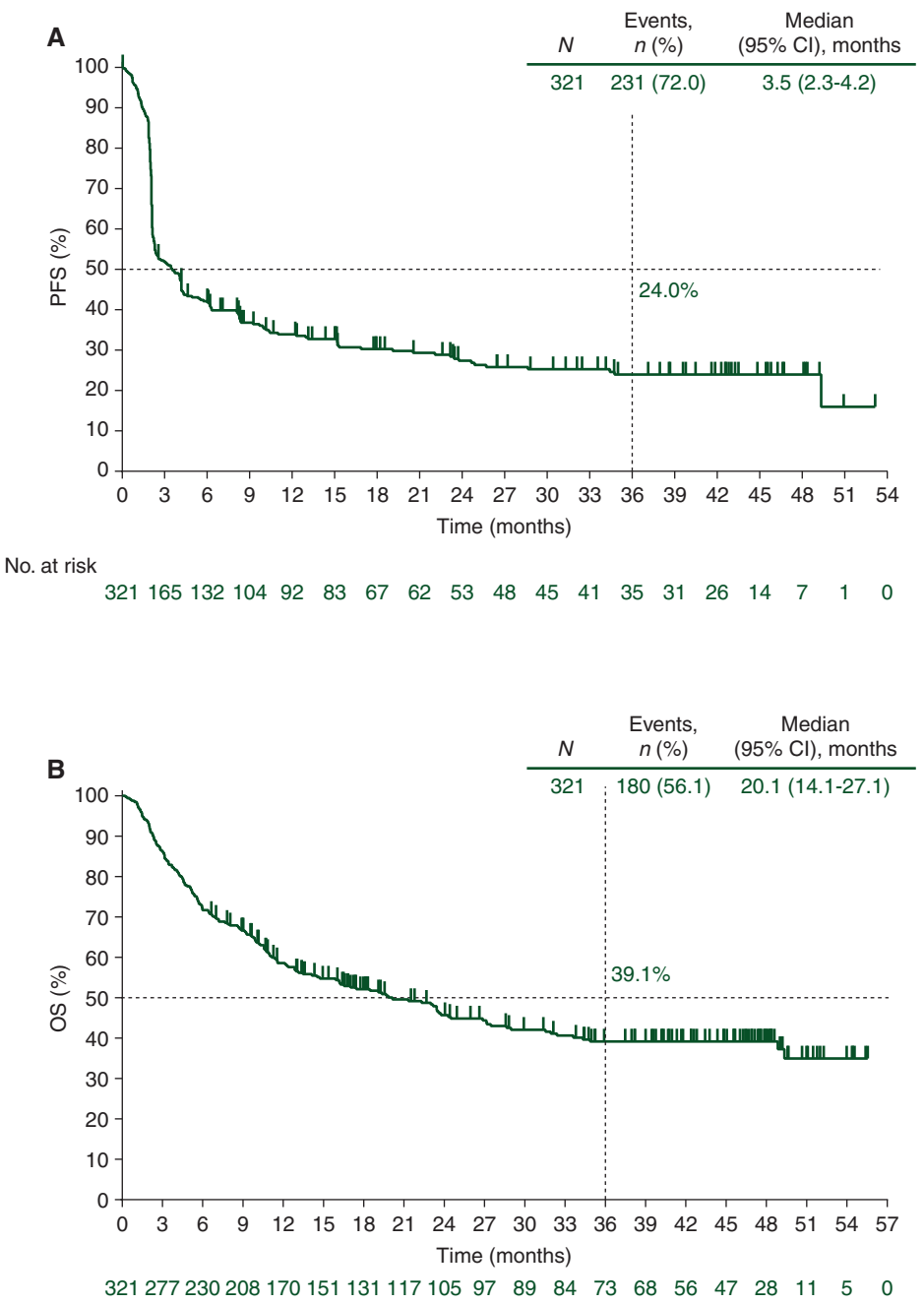

Figure 2. Kaplan–Meier estimates of PFS and OS. (A) PFS per RECIST version 1.1 by independent central radiologic review in the efficacy analysis population and (B) OS in the efficacy analysis population.
Q3W, every 3 weeks. OS, overall survival; PFS, progression-free survival.

evaluating the anti-PD-1 antibody tislelizumab in patients with previously treated, locally advanced unresectable or metastatic MSI-H/dMMR solid tumors ($N = 28$), ORR was 57.1% in patients with noncolorectal tumors after a median follow-up of 11.8 months.[23]

Pembrolizumab had a manageable safety profile, and no new safety signals were identified with long-term follow-up. As previously observed in patients with MSI-H/dMMR advanced tumors in KEYNOTE-158,[11] the most common treatment-related AEs were pruritus, fatigue, and diarrhea, the majority of which were grade 1 or 2. Overall, grade 3-5 treatment-related AEs occurred in 12.0% of patients, 6.6% of patients discontinued due to a treatment-related AE, and 0.9% died as a result of a treatment-related AE. Similarly, the proportion of patients with immune-mediated AEs and infusion reactions was consistent with that previously reported,[11] demonstrating there was no increase in toxicity with long-term follow-up. The safety findings were consistent with the established toxicity profile for pembrolizumab monotherapy in various advanced solid tumor types.[12,24-28]

In conclusion, pembrolizumab continued to demonstrate durable and clinically meaningful benefit with manageable toxicity in patients with heavily pretreated advanced MSI-H/dMMR noncolorectal cancers. These results support the

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Table 4. Summary of adverse events

AE	All patients $N = 351$	
Treatment-related AE, *n* (%)	227 (64.7)	
Grade 3-5	42 (12.0)	
Led to death[a]	3 (0.9)	
Led to discontinuation	23 (6.6)	
Treatment-related AEs occurring in ≥5% of patients, *n* (%)	**Any grade**	**Grade 3**[b]
Pruritus	51 (14.5)	0
Fatigue	43 (12.3)	2 (0.6)
Diarrhea	41 (11.7)	2 (0.6)
Arthralgia	33 (9.4)	0
Asthenia	32 (9.1)	1 (0.3)
Hypothyroidism	31 (8.8)	0
Rash	25 (7.1)	2 (0.6)
Nausea	22 (6.3)	0
Immune-mediated AEs, *n* (%)	**Any grade**	**Grade 3-5**[c]
Any	69 (19.7)	17 (4.8)
Hypothyroidism	34 (9.7)	0
Hyperthyroidism	15 (4.3)	1 (0.3)
Pneumonitis	9 (2.6)	3 (0.9)
Colitis	8 (2.3)	1 (0.3)
Severe skin reactions	5 (1.4)	5 (1.4)
Infusion reactions	4 (1.1)	0
Hepatitis	3 (0.9)	1 (0.3)
Myositis	3 (0.9)	0
Guillain–Barre syndrome	2 (0.6)	2 (0.6)
Nephritis	2 (0.6)	0
Pancreatitis	2 (0.6)	2 (0.6)
Type 1 diabetes mellitus	2 (0.6)	1 (0.3)
Myocarditis	1 (0.3)	1 (0.3)
Uveitis	1 (0.3)	0
Infusion reactions, *n* (%)	4 (1.1)	0

AE, adverse event.
[a]Due to Guillain–Barre syndrome, myocarditis, and pneumonia ($n = 1$ each).
[b]There were no grade 4 or 5 treatment-related AEs for these preferred terms.
[c]Two grade 5 immune-mediated AEs of Guillain–Barre syndrome and myocarditis.

tumor-agnostic efficacy of pembrolizumab for patients with MSI-H/dMMR solid tumors that have progressed following prior treatment, irrespective of tumor histology.

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DATA SHARING

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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