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Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study

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Drafting or critical review of the manuscript: all authors

All authors had access to the data, which was verified by WYZ, LAD, Jr, DF, TA.

Declaration of Interests

LAD, Jr reports membership on the board of directors of Personal Genome Diagnostics (PGDx) and Jounce Therapeutics, honoraria for consulting/advisory role to PGDx, 4Paws and Neophore, uncompensated advisory/consulting role for MSD, research funding to the institution for clinical trials from MSD, patents for circulating tumor DNA analyses and mismatch repair deficiency for diagnosis and therapy with checkpoint blockade from Johns Hopkins University, the latter licensed to PGDx and Qiagen. Some licenses and relationships are associated with equity or royalty payments directly to Johns Hopkins and LAD. Equity in 4Paws, PGDx, Jounce Therapeutics, Thrive Earlier Detection and Neophore. His spouse holds equity in Amgen. The terms of all these arrangements are being managed by Johns Hopkins and Memorial Sloan Kettering in accordance with their conflict of interest policies; KKS reports consulting/advisory role and/or honoraria including compensation for travel, accommodation, and expenses from Bayer, Bristol Myers Squibb, Guardant Health, Daiichi-Sankyo, Innovent Biologics, Merck KGaA, MSD, Mirati Therapeutics, Roche, Servier, and Institutional Funding for Research from Adaptimmune Therapeutics, AstraZeneca, Merck KGaA, MSD and Roche; TWK reports research funding to the institution for clinical trials from MSD, and Merck Serono; BVJ, DS, MB, PG report research funding to the institution for clinical trials from MSD; LHJ reports research funding to the institution from MSD, 2cureX, Incyte, BMS; CP reports research funding to the institution from MSD, consulting /advisory role to Bayer, Nordic Pharma, and Servier; RGC reports research funding to the institution for clinical trials from MSD, BMS, Ipsen Pharma, Roche Pharma, Servier, Novartis, Pfizer, Merck, Bayer, Pharma Mar, honoraria from Roche Pharma, Sanofi Aventis, Servier, Novartis, Pfizer, Merck, Bayer, Pharma Mar, AAA, Advandz Pharma, Midatech Pharma, Pierre Fabre; CdlF reports research funding to the institution for clinical trials from MSD, consulting/advisory role for MSD, 2019 ESMO meeting invitation; FR reports research funding to the institution for clinical trials for MSD, Roche, Merck-Serono, Amgen, Pierre-Fabre, Sanofi-Aventis, Bayer, Servier, Lilly; consulting/advisory role for Roche, Merck-Serono, Amgen, Pierre Fabre, Sanofi-Aventis, Bayer, Servier, Lilly, Astra-Zeneca, Bristol-Myers Squibb, honoraria from MSD, Roche, Merck-Serono, Amgen, Pierre-Fabre, Sanofi-Aventis, Bayer, Servier, Lilly, Astra-Zeneca, Pfizer, Bristol-Myers Squibb, non-financial support from MSD, Roche, Merck-Serono, Amgen, Pierre-Fabre, Sanofi-Aventis, Bayer, Servier; EE reports research funding to the institution for clinical trials from MSD, Sanofi, honoraria from Amgen, Sanofi, Servier, MSD, Pierre Fabre, Hoffman La Roche, non-financial support from Amgen, Sanofi, MSD, Hoffman La Roche; DTL serves on advisory boards for Merck, Bristol Myers Squibb, and Janssen and has received research funding from Merck, Bristol Myers Squibb, Aduro Biotech, Curegenix, Medivir, Nouscom, and Abbvie. She has received speaking honoraria from Merck and is an inventor of licensed intellectual property related to technology for mismatch repair deficiency for diagnosis and therapy (WO2016077553A1) from Johns Hopkins University. The terms of these arrangements are being managed by Johns Hopkins; TY reports grants from MSD for the submitted work; grants from Ono, Sanofi, Daiichi Sankyo, Chugai, Parexel International, Taiho, Amgen and Sumitomo Dainippon, outside the submitted work; WYZ, DF, PM are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and hold stock in Merck & Co., Inc., Kenilworth, NJ, USA; TA reports consulting/advisory role and/or honoraria from Amgen, Astellas Pharma, Astra-Zeneca, Bristol-Myers Squibb, Chugai, Clovis, Gritstone Oncology, GlaxoSmithKline, Haliodx, Kaleido Biosciences, Merck & Co., Inc., Pierre Fabre, Roche/Ventana, Sanofi, Transgene, Seagen, Servier and compensation for travel, accommodation, and expenses from Roche/Genentech, MSD & Co., Inc, and Bristol-Myers Squibb.

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Summary

Background: Pembrolizumab has demonstrated superior progression-free survival (PFS) versus chemotherapy in newly-diagnosed MSI-H/dMMR metastatic colorectal cancer (mCRC). However, its impact on overall survival (OS) in this cohort of patients was unknown. Here we present the final OS analysis of KEYNOTE-177.

Methods: The phase 3, open-label study involved 193 sites in 23 countries. Patients aged at least 18 years, with Eastern Cooperative Oncology Group performance status of 0 or 1, and

who had newly-diagnosed MSI-H/dMMR mCRC were randomized 1:1 in blocks of four per stratum using an interactive voice response system /integrated web response system to intravenous pembrolizumab 200 mg every 3 weeks or to investigator's choice of intravenous mFOLFOX6 or FOLFIRI every 2 weeks with or without intravenous bevacizumab 5 mg/kg every 2 weeks or intravenous cetuximab (first dose 400 mg/m^2, then 250 mg/m^2 for every subsequent dose) weekly. Patients receiving chemotherapy could cross over to pembrolizumab for 35 treatments after progression. Dual-primary endpoints were OS and PFS in the intention-to-treat population. KEYNOTE-177 is registered at ClinicalTrials.gov NCT02563002 and is no longer enrolling patients.

Findings: Between February 11, 2016 and February 19, 2018, 307 patients were randomized to pembrolizumab (n = 153) or chemotherapy (n = 154). Sixty percent of patients crossed over from chemotherapy to anti-PD-1/anti-PD-L1 therapy (56 patients to on-study pembrolizumab, 37 patients to off-study therapy). At final analysis (median follow-up of 44.5 months [IQR, 39.7–49.8]), the hazard ratio [HR] for OS was 0.74 (95% confidence interval [CI] 0.53–1.03; *P*=0.0359; median not reached [95% CI 49.2-not reached] versus 36.7 months [95% CI, 27.6-not reached]) with pembrolizumab versus chemotherapy. Superiority of pembrolizumab versus chemotherapy for OS was not demonstrated as the prespecified α of 0.0246 needed for statistical significance was not achieved. The updated HR for PFS was 0.59 (95% CI 0.45–0.79; median 16.5 [95% CI 5.4–38.1] versus 8.2 months [95% CI 6.1–10.2]). Serious adverse events occurred in 62 of 153 (41%) patients who received pembrolizumab and 75 of 143 (52%) patients who received chemotherapy. Grade ≥3 treatment-related adverse events occurred in 33 of 153 (22%) versus 95 of 143 (66%) patients, respectively. Common grade ≥3 adverse events attributed to pembrolizumab were increased alanine aminotransferase, colitis, diarrhea, and fatigue in 3 of 153 (2%) patients each, and to chemotherapy were decreased neutrophil count (24 of 143 [17%] patients), neutropenia (22 of 143 [15%]), diarrhea (14 of 143 [10%]), and fatigue (13 of 143 [9%]). No deaths attributed to pembrolizumab occurred; one death due to intestinal perforation was attributed to chemotherapy.

Interpretation: Pembrolizumab versus chemotherapy continued to provide durable antitumor activity, with no significant difference in OS, and fewer treatment-related events. These findings support pembrolizumab as effective first-line therapy in patients with MSI-H/dMMR mCRC.

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Keywords

metastatic colorectal cancer; MSI-H; dMMR; PD-1 inhibitor

Introduction

Mismatch repair deficiency (dMMR) occurs in approximately 4–5% of all metastatic colorectal cancers (mCRC).[1,2] These dMMR tumors are unable to repair certain classes of mutations, resulting in tumors with a high mutational burden (TMB) and microsatellite instability (MSI-H).[3,4]

In metastatic colorectal cancer, PD-1 blockade with pembrolizumab or nivolumab in individuals with MSI-H/dMMR mCRC has provided an effective treatment option in the chemotherapy refractory setting.[5,6] Treatment with the anti-PD-1 therapies pembrolizumab or nivolumab provided durable antitumor responses in patients with previously treated MSI-H/dMMR mCRC leading to the Food and Drug Administration (FDA) approval of these therapies in patients with previously treated MSI-H/dMMR mCRC.[5,6] Recently, initial data from the randomized, phase 3 KEYNOTE-177 study of pembrolizumab versus standard-of-care chemotherapy in patients with previously untreated MSI-H/dMMR mCRC showed that pembrolizumab provided superior progression-free survival as frontline therapy and a better health-related quality of life.[7,8] These data supported the FDA and European Medicines Agency approval of pembrolizumab for frontline treatment of patients with MSI-H/dMMR mCRC.[9,10] Currently, guidelines recommend testing for MSI-H/dMMR status in patients diagnosed with mCRC.[11,12] Immunotherapy-based regimens have not yet demonstrated definitive evidence of clinical efficacy in patients with mismatch repair proficient/microsatellite stable mCRC.[13,14]

To our knowledge, the KEYNOTE-177 study was the first randomized study to have demonstrated the clinical benefit of PD-1 blockade in metastatic MSI-H/dMMR CRC in the first-line setting.[7] Before the results of KEYNOTE-177, the standard-of-care for newly diagnosed mCRC involved chemotherapy regardless of the molecular genotype with or without targeted therapy. This standard approach has included chemotherapy with 5-fluorouracil (5-FU) based regimens such as FOLFOX (5-FU, oxaliplatin, leucovorin), FOLFIRI (5-FU, irinotecan, leucovorin) with or without anti-epidermal growth factor receptor (EGFR) or anti-vascular endothelial growth factor (VEGF) therapies, and FOLFOXIRI (5-FU, oxaliplatin, and irinotecan) with or without anti-VEGF therapies.[15]

Here, we report the results of overall survival at the final analysis of the phase 3 KEYNOTE-177 study of front-line pembrolizumab versus chemotherapy (with or without the VEGF inhibitor bevacizumab or EGFR inhibitor cetuximab) in patients with MSI-H/dMMR mCRC.

Methods

Study design and participants

KEYNOTE-177 is an international, randomized, open-label phase 3 study of pembrolizumab versus investigator choice chemotherapy in patients with previously untreated MSI-H and or dMMR mCRC. Eligible patients were aged ≥18 years with locally confirmed MSI-H or dMMR stage IV CRC with measurable disease per Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST v1.1) by local investigator/radiology assessment, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Patients who were not eligible included those who received prior systemic therapy for stage IV CRC, although patients may have received adjuvant therapy for CRC if completed at least 6 months before randomization, patients with an active autoimmune disease that required systemic treatment within the previous 2 years, and those with a diagnosis of immunodeficiency or receiving systemic steroid therapy or other immunosuppressive therapy at least 7 days before randomization. Patients had to have

adequate hematological function (an absolute neutrophil count of at least 1,500/μL, platelet count of at least 100,000/μL, and haemoglobin of at least 9 g/dL or at least 5.6 mmol/L), renal function (creatinine levels of up to 1.5 times the upper limit of normal [ULN] or creatinine clearance of at least 60 mL/min if creatinine levels were higher than 1.5 times the ULN), and hepatic function (defined as total bilirubin levels of up to 1.5 times the ULN or direct bilirubin levels up to the ULN if total bilirubin levels were higher than 1.5 times the ULN; alanine and aspartate aminotransferase levels of up to 2.5 times the ULN or up to 5 times the ULN for patients with liver metastases; and albumin levels of at least 2.5 g/dL). Full eligibility criteria are listed in the study protocol (Appendix). The protocol and all amendments were approved by the appropriate institutional review boards or ethics committee at each participating institution. All patients provided written informed consent.

Randomization and masking

Treatment allocation and randomization occurred centrally, and patients were randomly allocated 1:1 using an interactive voice response system (IVRS)/integrated web response system (Almac Clinical Technologies, Souderton, PA, USA) in a block size of four per stratum. There was no stratification. The randomized allocation schedule for study medication was generated by the study sponsor and implemented in IVRS. Patients, investigators, and site staff were not masked to study treatment.

Procedures

Patients received intravenous pembrolizumab 200 mg every three weeks or investigator's choice of chemotherapy (chosen at least 3 days before randomization) with mFOLFOX (intravenous oxaliplatin 85 mg/m^2 on day 1, intravenous leucovorin 400 mg/m^2 on day 1, and intravenous 5-fluorouracil [5-FU] 400 mg/m^2 bolus on day 1 followed by 1200 mg/m^2/day continuous infusion for 2 days) every 2 weeks or FOLFIRI (intravenous irinotecan 180 mg/m^2 on day 1, intravenous leucovorin 400 mg/m^2 on day 1, and intravenous 5-FU 400 mg/m^2 bolus on day 1 followed by 1200 mg/m^2/day continuous infusion for 2 days) every 2 weeks with or without intravenous bevacizumab (5 mg/kg on day 1) every 2 weeks or intravenous cetuximab (400 mg/m^2 in week 1 followed by 250 mg/m^2 weekly thereafter), as previously published.[8] Dose modifications for all chemotherapy agents, bevacizumab, and cetuximab were permitted only due to toxicity and had to follow local guidelines. Oxaliplatin could be interrupted to prevent neuropathy and had to be resumed after 12 cycles of leucovorin and 5-FU. Dose interruption and discontinuation, but not reduction, was permitted for pembrolizumab to manage adverse events as described in the protocol.

Treatment was continued until disease progression, unacceptable toxicity, illness, or physician/patient decision to withdraw, or after completing the maximum of 35 treatments with pembrolizumab. There was no limit on the number of standard-of-care chemotherapy administrations. Patients randomized to chemotherapy had the option to cross over and receive 35 treatments with pembrolizumab after disease progression confirmed by blinded independent central review. MMR or MSI status was determined locally by either immunohistochemical (IHC) analysis of MLH1/MSH2/MSH6/PMS2 mismatch proteins or PCR-based analysis of 3–5 tumor microsatellite loci. Tumors were classified as MSI-H

when at least 2 allele shifts among the 3–5 analyzed were detected by PCR, or in the absence of at least 1 of 4 MMR proteins detected by IHC. Tumor imaging was acquired by computed tomography and had to include the chest, abdomen, and pelvis. Magnetic resonance imaging was permitted for imaging in the brain or for patients for whom computed tomography was contraindicated. Tumor response was assessed per RECIST v1.1 by blinded independent central review at week 9 and every 9 weeks thereafter. During follow-up, survival was assessed every 9 weeks. Adverse events were evaluated throughout the study and at 30 days (90 days for serious adverse events and events of interest to pembrolizumab) after treatment discontinuation and were graded according to the National Cancer Institute CTCAE, version 4.0.[16] Laboratory analyses, plus prothrombin time and activated partial thromboplastin clotting time, were performed during screening within 10 days prior to the first dose of study treatment. Pregnancy tests (if applicable; by serum β-human chorionic gonadotropin), hematology analyses (hematocrit, haemoglobin, platelet count, white blood cell count, absolute neutrophil and lymphocyte counts) and chemistry analyses (albumin, alkaline phosphatase, lactate dehydrogenase, alanine and aspartate aminotransferases, bicarbonate or carbon dioxide, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, nitrogen, and blood urea nitrogen or urea) were performed every 2 weeks, up to 72 hours prior to study treatment dose. Urinalysis (specific gravity, microscopic exam, protein, glucose, blood) and other laboratory tests (thyroid stimulating hormone, total or free triiodothyronine, free thyroxine) were performed every 4 weeks, up to 72 hours prior to study treatment dose. Serum tumour markers were analyzed on week 1, and then once every 8 weeks. These analyses were repeated at the time of study treatment discontinuation and at the 30-day follow-up visit. Additional study and treatment details are provided in the protocol (Appendix).

Important protocol deviations occurred in 33 patients (17 of 153 [11%] treated with pembrolizumab and 16 of 143 [10%] treated with chemotherapy) and included deviations from the study treatment discontinuation criteria (5 patients [3%] and 1 patient [1%], respectively), deviations from inclusion and exclusion criteria (1 patient [1%] and 1 patient [1%], respectively), and deviations in safety event reporting or safety follow-up (10 patients [7%] and 14 patients [9%], respectively).

Outcomes

The dual primary endpoints were progression-free survival per RECIST v1.1 by central review (randomization to first disease progression or death of any cause) and overall survival (randomization to death of any cause) in the intent-to-treat population (ITT). Secondary endpoints included objective response per RECIST v1.1 by central review in the ITT, safety and tolerability in all patients as treated. Exploratory endpoints included progression-free survival 2 (randomization to progression or any cause death on next line of therapy), progression-free survival per irRECIST by central review using Nishino's methodology,[17] duration of response (first complete or partial response until first disease progression or death of any cause) per RECIST v1.1 by central review, and health-related quality of life (previously reported).[8] A full list of exploratory endpoints is included in the protocol (Appendix).

Statistical analyses

The protocol specified two interim analyses and a final analysis. The overall type-1 error was strongly controlled at a one-sided alpha of 2.5% using the graphical method of Maurer and Bretz.[7] The Lan-DeMets O'Brien alpha spending function was used to construct group sequential boundaries to control the type-1 error rate.

The protocol-specified final analysis of overall survival was to be performed 12 months after the second interim analysis (IA2). This would allow comparison of superiority of pembrolizumab versus chemotherapy to have 85% power to show a hazard ratio of 0.62 for overall survival at the one-sided alpha level of 1.25% with a planned sample size of approximately 300 patients. The proportional hazards assumption for overall survival was examined by both graphical and analytic methods. If the curves were not parallel, supportive analyses such as restricted mean survival time were conducted to account for the non-proportional hazards effect. Due to the allowed cross over from chemotherapy to pembrolizumab, the actual power could be lower. Adjustment for the effect of crossover on overall survival was performed as a sensitivity analysis based on the rank preserving structural failure time model, and two-stage model based on an examination of the appropriateness of the data to the assumptions required by the methods; no p-values are available for these comparisons.[18] As the threshold for superiority of pembrolizumab versus chemotherapy for progression-free survival was met at IA2 (final analysis for progression-free survival), the alpha initially allocated for the progression-free survival endpoint was passed to the overall survival endpoint with a 0.99 transfer weight, allowing the boundary for superiority of pembrolizumab versus chemotherapy for overall survival to occur at the one-sided alpha of 0.0246 with 140 overall survival events, at 12 months after IA2. The primary hypotheses that pembrolizumab prolongs progression-free and overall survival versus standard-of-care chemotherapies were evaluated using a Log-rank test. Hazard ratios were estimated with a Cox regression model and event rates over time were estimated using the Kaplan-Meier method. The ORR analysis was conducted only if the progression-free and overall survival null hypotheses were rejected. Patients with no postbaseline assessment were defined as not assessable. Post-hoc assessment of survival and response at the 36-month landmark timepoint[19] are reported as the final analysis was conducted at least 3 years after the last patient was randomized. The study had 92% power to show superiority of pembrolizumab versus chemotherapy at a one-sided alpha of 2.5% with a difference in ORR of 19%. SAS version 9.4 was used for all statistical analyses. Overall survival, progression-free survival, ORR, and DOR were assessed in the intention-to-treat population. Safety analyses were performed in the population of all patients who received at least one dose of study treatment. Prespecified subgroup categories for overall survival analysis included age, geographic region, recurrent versus new-diagnosed, BRAF wildtype versus BRAF V600E, and site of the primary tumor. Post hoc subgroups included sex, ECOG performance status, and presence of KRAS mutation. Formal statistical testing was not prespecified for overall survival by subgroups, and P values were nominal. The full statistical analysis plan is available in section 8 of the protocol.

Role of the funding source

The sponsor funded the study, participated in study design, data interpretation, and the writing of this report. The sponsor maintained the study database. All authors had full access to the study data, were involved in the writing or reviewing and editing drafts of the manuscript and approved the decision to submit for publication. Assistance in the preparation of the manuscript was provided by a medical writer employed by the sponsor.

Results

A total of 852 patients were screened for the study, of whom 545 failed to meet the inclusion and exclusion criteria and were not eligible for enrollment (Figure 1). Between February 11, 2016 and February 19, 2018, 307 patients were randomized to receive pembrolizumab (n = 153) or chemotherapy (n = 154). Demographics and participant baseline characteristics were previously reported[7] and were generally well balanced between treatment groups. Briefly, patients had a median age of 63 years (interquartile range [IQR], 50–73), 209 (68.1%) of 307 had right-sided tumors, 125 (40.7%) had hepatic metastases, 72 (23.5%) had KRAS/NRAS mutant tumors, and 81 (26.4%) had $BRAF^{V600E}$ mutant tumors (Table 1). At the data cut-off date of February 19, 2021, the median time from randomization to data cut-off was 44.5 months (IQR, 39.7–49.8). At final analysis, 59 patients in the pembrolizumab group had completed 35 treatments according to protocol; no patients in the pembrolizumab group and 2 in the chemotherapy group were still receiving first-line treatment.

A total of 296 patients received at least one dose of study treatment, 153 of 153 (100%) in the pembrolizumab group and 143 of 154 (93%) in the chemotherapy group. The median (IQR) duration of treatment exposure was 11.1 months (2.8–23.8) in the pembrolizumab group and 5.7 months (2.7–11.2) in the chemotherapy group. In the intention-to-treat population, 52 (34%) of 153 patients in the pembrolizumab group and 121 (79%) of 154 in the chemotherapy group received subsequent anticancer therapy, including 56 (36.4%) of 154 patients in the chemotherapy group who crossed over to receive pembrolizumab (Appendix, page 7).

At final analysis, overall survival with pembrolizumab (median not reached [NR], 95% confidence interval [CI], 49.2 to NR) versus chemotherapy (median 36.7 months, 95% CI, 27.6 to NR) did not meet the one-sided α boundary of 0.0246 required for superiority (hazard ratio [HR] 0.74, 95% CI, 0.53–1.03; P = 0.0359) (Figure 2). A total of 140 (45.6%) of 307 patients died, 62 (40.5%) of 153 in the pembrolizumab group and 78 (50.6%) of 154 in the chemotherapy group. The estimated 36-month overall survival rates for pembrolizumab versus chemotherapy were 61.4% (95% CI, 53.2%–68.6%) versus 50.3% (95% CI, 42.0%–58.0%). At data cut-off, 56 (36%) of 154 patients had crossed over on study to pembrolizumab from the chemotherapy group following progression, and an additional 37 (24%) had received anti-PD-1 or anti-PD-L1 therapies outside of the study for a proportion of 60% in the intention-to-treat population. The cross over population included 6 of 11 patients assigned to receive chemotherapy who withdrew before receiving treatment. The estimated restricted mean survival time for overall survival after 36 months of follow-up, calculated because the proportional hazards assumption was violated, was 26.6 (95% CI 24.4–28.7) in the pembrolizumab group versus 25.0 (95% CI 22.8–27.1) in the

chemotherapy group, for a difference of 1.6 (95% –1.4 to 4.6). Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed HR for overall survival of 0.66 (95% CI 0.42–1.04) and 0.77 (95% CI 0.44–1.38), respectively. Overall survival was generally consistent across most pre-specified subgroups (Figure 3).

Pembrolizumab versus chemotherapy met the criteria for superiority for progression-free survival at second interim analysis.[7] Similarly, at final analysis, progression-free survival was longer with pembrolizumab (median 16.5 months, 95% CI 5.4–38.1) versus chemotherapy (median 8.2 months, 95% CI 6.1–10.2); however, as superiority was met at the second interim analysis, it was not formally tested at final analysis (HR 0.59, 95% CI 0.45–0.79). A total of 203 (66.1%) patients had a progression event or died, 86 (56.2%) of 153 in the pembrolizumab group and 117 (76.0%) of 154 in the chemotherapy group. The estimated 36-month progression-free survival for pembrolizumab versus chemotherapy was 42.3% (95% CI 34.0–50.4) versus 11.1% (95% CI 6.1–17.9) (Table 2), respectively. An analysis of time from randomization to progression on next line therapy (progression-free survival 2) showed that progression-free survival 2 was longer with pembrolizumab (median 54.0 months, 95% CI 44.4 to NR) versus chemotherapy (median 24.9 months, 95% CI 16.6–32.6); HR 0.61, 95% CI 0.44–0.83; P = 0.0008. A total of 163 (53.1%) patients had a progression event during the next line of therapy or died, 68 (44.4%) of 153 in the pembrolizumab group and 95 (61.7%) of 154 in the chemotherapy group. Estimated 36-month progression-free survival 2 was 60% (95% CI 51.3–66.8) versus 39% (95% CI 30.6–46.3), respectively (Figure 4A). Among 84 patients in the pembrolizumab group and 117 in the chemotherapy group, median progression-free survival by irRECIST criteria was 21.9 months (95% CI 9.1–41.7) with pembrolizumab and 8.6 months (95% CI 6.3–10.6) with chemotherapy.

The proportion of patients with an objective response was 45.1% (69 of 153 [95% CI 37.1–53.3]) with pembrolizumab versus 33.1% (51 of 154 [95% CI 25.8–41.1]) with chemotherapy (Appendix, page 8). At final analysis, 20 (13.1%) versus 6 (3.9%) complete responses (CRs) were observed with pembrolizumab versus chemotherapy compared with 17 (11.1%) versus 6 (3.9%) CRs observed at previous interim analysis. The median duration of response was not reached (IQR, 36.1 to not reached) with pembrolizumab versus 10.6 months (IQR, 8.1–28.8) with chemotherapy (Figure 4B). After 36 months, approximately 76% (95% CI 62%–85%) of patients in the pembrolizumab group versus 24% (95% CI 12%–38%) in the chemotherapy group had an ongoing response (Appendix, page 8).

The safety profile of pembrolizumab versus chemotherapy in KEYNOTE-177 study was previously published.[7] At final analysis, in the all patients as-treated population, adverse events due to any cause occurred in 149 (97%) of 153 patients in the pembrolizumab group and 142 (99%) of 143 patients in the chemotherapy group. Grade ≥3 events occurred in 86 (56%) of 153 versus 112 (78%) of 143 patients in the pembrolizumab and chemotherapy groups. Any cause grade 5 adverse events regardless of attribution observed in 6 (3.9%) of 153 patients in the pembrolizumab group (1 of 153 [1%] patient each due to abdominal sepsis, death, diarrhea, duodenal perforation, failure to thrive, and pseudobulbar palsy) and 7 (4.9%) of 143 patients in the chemotherapy group (1 of 143 [1%] patient each due to

aortic dissection, aspiration, cardiac arrest, cholangitis, intestinal perforation, pulmonary embolism, and upper gastrointestinal haemorrhage) (Table 2). Adverse events attributed to drug by investigator occurred in 122 (80%) of 153 patients in the pembrolizumab group and 141 (99%) of 143 patients in the chemotherapy group (Table 2). Grade ≥3 treatment-related adverse events occurred in 33 (22%) of 153 patients in the pembrolizumab group and 95 (66%) of 143 patients in the chemotherapy group, including one death in the latter. Discontinuation of pembrolizumab due to a treatment-related adverse event occurred in 15 (10%) of 153 patients, due to increased alanine aminotransferase, autoimmune colitis, colitis, or hepatitis (2 of 153 [1%] patients each) or acute kidney injury, increased aspartate aminotransferase, autoimmune hepatitis, hypophysitis, immune-mediated hepatitis, pneumonitis, or psoriasis (1 of 153 [1%] patient each). Discontinuation of chemotherapy due to a treatment-related adverse event occurred in 10 (7%) of 143 patients, due to asthenia (2 of 143 [1%] patients) or acute myocardial infarction, cerebrovascular accident, diarrhea, fatigue, febrile neutropenia, intestinal perforation, palmar-plantar erythrodysaesthesia syndrome, or stomatitis (1 of 143 [1%] patient each). Serious adverse events attributed to study treatment occurred in 25 (16%) of 153 patients in the pembrolizumab group (most commonly colitis in 3 of 153 [2%] patients) and in 41 (29%) of 143 patients in the chemotherapy group (most commonly diarrhea in 9 of 143 [6%] patients and febrile neutropenia in 5 of 143 [4%] patients). No deaths attributed to pembrolizumab occurred; one death due to intestinal perforation was attributed to chemotherapy. Immune-mediated adverse events and infusion reactions occurred in 47 (31%) of 153 patients in the pembrolizumab group and 21 (15%) of 143 patients in the chemotherapy group. Grade ≥3 immune-mediated events and infusion reactions occurred in 14 (9%) of 153 patients versus 3 (2%) of 143 patients, respectively. The most common events were colitis in 5 of 153 (3%) and hepatitis in 4 of 153 (3%) patients in the pembrolizumab group and infusion reactions in 1 of 143 (1%) and severe skin reactions in 2 of 143 (1%) patients in the chemotherapy group. Approximately 10 (7%) of 153 patients in the pembrolizumab group and 1 (1%) of 143 patients in the chemotherapy group discontinued due to an immune-mediated adverse event or infusion reaction. There were no deaths associated with immune-mediated adverse events or infusion reactions (Table 2).

Discussion

At the final analysis of the randomized, phase 3 KEYNOTE-177 study, first-line treatment with pembrolizumab versus chemotherapy did not provide a statistically significant difference in overall survival (NR versus 36.7 months, respectively) in patients with MSI-H/dMMR mCRC.

The progression-free survival benefit of pembrolizumab versus chemotherapy observed at the second interim analysis[7] was also confirmed at final analysis with 42.3% versus 11.1% of patients, respectively, alive and progression-free at 36 months. As observed at prior interim analysis, after an initial crossing of the progression-free survival Kaplan-Meier curves which may reflect a mixture of primary resistance,[20] misdiagnosed pMMR/MSS disease, and pseudoprogression,[21] there was a pronounced separation of the curves in favor of pembrolizumab versus chemotherapy indicating a long-term benefit with pembrolizumab over time. Responses to pembrolizumab continued to be durable with increased incidence

of complete and partial response observed with pembrolizumab versus chemotherapy. These data support the FDA and EMA approvals of pembrolizumab as first-line therapy in MSI-H/dMMR mCRC.

The lack of statistically significant overall survival benefit may be related to the cross over design of KEYNOTE-177. At final analysis, only 2 patients remained on chemotherapy, and 56 (36%) of 154 patients randomized to chemotherapy had met the cross over criteria and were treated with pembrolizumab. In addition, 37 (24%) patients received off-study anti-PD-1/PD-L1 therapies, for an effective cross over of 60%. This high cross over likely contributed to an improvement in overall survival in the chemotherapy group. This population also included 6 of 11 patients initially assigned to receive chemotherapy who refused randomized treatment, and crossed over to anti-PD1 therapies, outside the study.

Several potential limitations of the study may have had an impact on the observed results, such as the local testing of dMMR/MSI-H status prior to randomisation without central confirmation. The heterogeneity of chemotherapy regimens and targeted agents permitted by the protocol may have contributed to variable results for the standard-of-care chemotherapy-based treatment group. In addition, RECIST1.1 evaluation can fail to take pseudoprogression into consideration.[21] Finally, the high overall cross over in the study (60% of patients), with 24% of the patients who received subsequent anti-PD-1 or anti-PD-L1 therapy having done so outside the study, may have affected the power to interpret the overall survival results.

Prior studies have shown that, typically, overall survival with front-line 5-FU-based regimens, with or without anti-EGFR or anti- VEGF therapies, was a median of 13.6 months in patients with dMMR mCRC.[2] After adjusting for cross over, the HR for overall survival still trended toward a benefit for pembrolizumab versus chemotherapy. The complementary restricted mean survival time analysis performed when the proportional hazards assumption is violated also favored pembrolizumab, again suggesting a survival benefit with pembrolizumab versus chemotherapy. This survival benefit was generally consistent across most pre-specified subgroups. However, the study was not powered to address any differences among subgroups, including among patients with RAS/BRAF mutations as demonstrated by the wide confidence intervals that cross 1.0. Overall, these data provide evidence of the benefit of PD-1 inhibitors in first-line dMMR/MSI-H mCRC. Multiple ongoing studies are examining the benefit of addition of chemotherapy or CTLA-4 blockade to PD-1/PD-L1 inhibitors for patients with dMMR/MSI-H mCRC including the COMMIT (NCT02997228), CA209–8HW (NCT04008030), and MK-1308A-008 (NCT04895722) studies.

The survival benefit with pembrolizumab versus chemotherapy was supported by the significantly longer progression-free survival and durable responses observed at final analysis. In addition, many objective responses deepened and were more durable with pembrolizumab versus chemotherapy. With an additional 12 months of follow-up after the interim analysis, the proportion of patients with an objective response with pembrolizumab improved from 43.8% to 45.1% at final analysis versus 33.1% (no change from IA2) with chemotherapy, with duration of response not reached versus 10.6 months, respectively. Evaluation of the time from randomization to progression on next line of therapy or

any cause death (progression-free survival 2) for the 52 patients in the pembrolizumab group versus 121 in the chemotherapy group who received subsequent therapy showed that progression-free survival 2 was at least twice as long with pembrolizumab versus chemotherapy (54.0 versus 24.9 months), indicating that pembrolizumab offers greatest benefit in the first-line treatment of these patients. This improvement is not likely due to immunotherapy-related pseudoprogression, as a significant incidence of pseudoprogression would have diminished the benefit as these patients would have stopped therapy. In addition, as previously published, pembrolizumab monotherapy led to clinically meaningful improvements in health-related quality of life compared with chemotherapy in patients with MSI-H/dMMR mCRC.[8]

The safety profile observed at final analysis was consistent with that previously published at the initial analysis,[7] and with that observed with pembrolizumab across multiple tumor types.[22–25] Treatment with chemotherapy was associated with a higher proportion of any cause, treatment-related, and grade ≥3 treatment-related adverse events, while patients receiving pembrolizumab reported a higher proportion of immune-mediated adverse events and infusion reactions.

These data confirm the durable antitumor benefit of pembrolizumab monotherapy with longer progression-free survival, higher objective response and complete response, and fewer treatment related adverse events compared with chemotherapy as first-line therapy in patients with MSI-H/dMMR mCRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, 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 patients 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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Research in Context

Evidence before the study

We conducted a PubMed search on December 9, 2021 using the terms PD-1 OR PD-L1 OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq OR durvalumab OR Imfinzi OR avelumab OR Bavencio AND MSI-H/dMMR metastatic colorectal cancer. No limits were applied to the search. We also searched the 2020 and 2021 abstract records of the American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the World Congress on Gastrointestinal Cancer, and the European Society for Medical Oncology Congress using the same search terms to identify results of clinical studies that were not yet published in the peer-reviewed literature.

We identified three published clinical studies of anti-PD-1 or anti-PD-L1 therapy for MSI-H/dMMR mCRC: the phase 3, open-label KEYNOTE-177 interim analysis of first-line pembrolizumab versus chemotherapy, the phase 2 open-label KEYNOTE-164 study of pembrolizumab as second-line or greater therapy, and the phase 2, open-label CheckMate 142 study of nivolumab as second-line or greater therapy in patients with MSI-H/dMMR mCRC.

Added value of this study

Data from the final analysis of KEYNOTE-177 confirm the results observed at the previously published interim analysis, which were the first from a phase 3 randomized study of an anti-PD-1 inhibitor in first-line MSI-H/dMMR mCRC versus an active comparator. These data show that progression-free survival is superior with pembrolizumab versus chemotherapy. There was no statistically significant difference in overall survival. The overall survival analysis may have been impacted by the high proportion (60%) of patients who crossed over from chemotherapy to second-line anti-PD-1/anti-PD-L1 therapy. Responses were durable and continued to deepen with pembrolizumab versus chemotherapy. The safety profile remained favorable at final analysis with fewer high-grade treatment-related adverse events observed with pembrolizumab versus chemotherapy.

Implications of the available evidence

These data show that pembrolizumab continues to have a durable antitumor response with fewer treatment-related adverse events in patients with MSI-H/dMMR mCRC in the first-line setting compared with chemotherapy, and support pembrolizumab as a standard first-line treatment in this population.

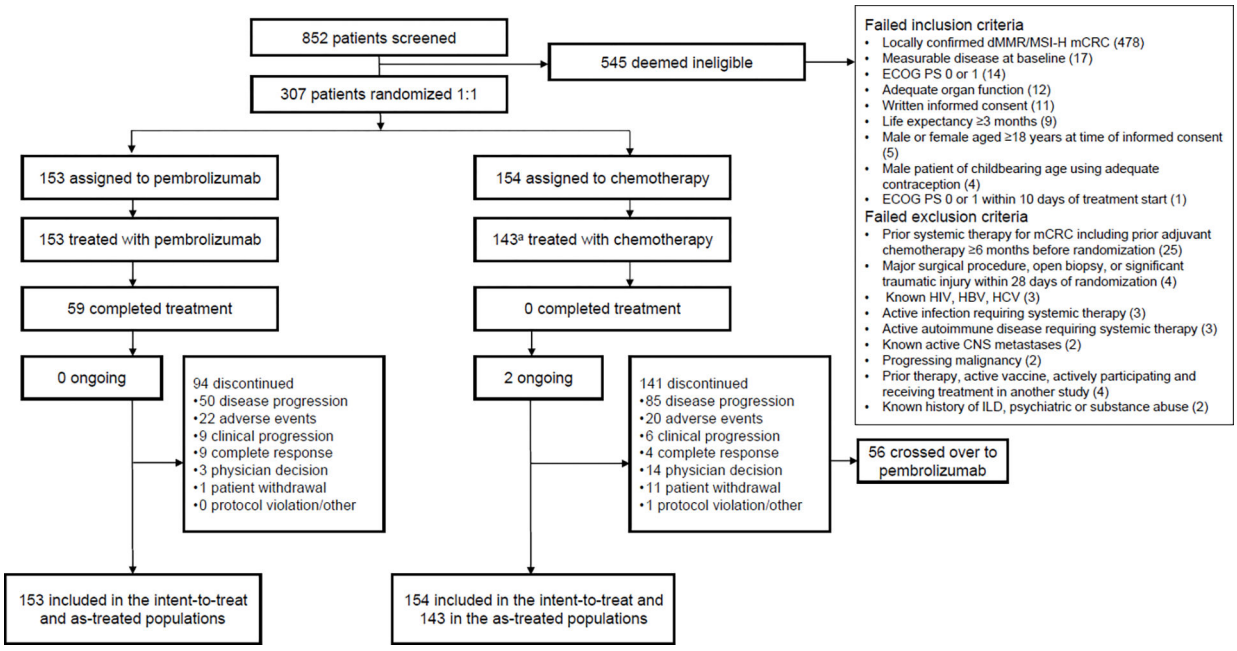

Figure 1.

Study profile. Summary of patients who were screened for enrollment and randomized to pembrolizumab or chemotherapy.[a]11 patients randomized to the chemotherapy group subsequently withdrew consent and did not receive treatment.

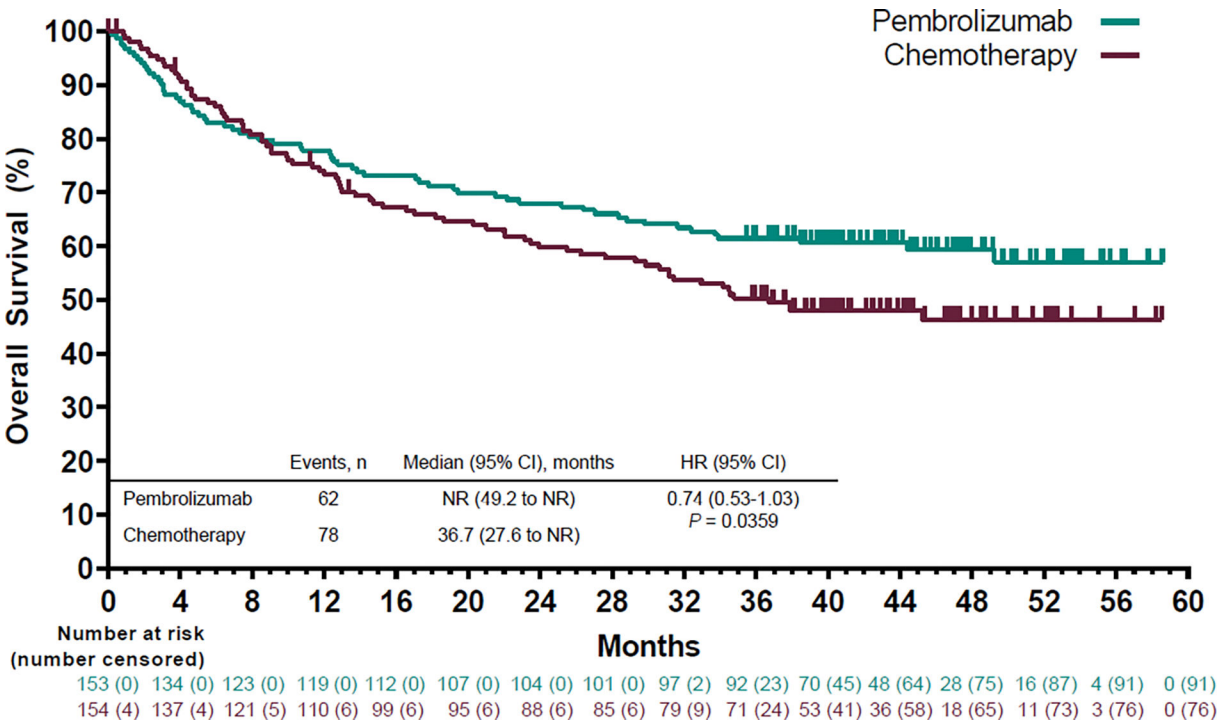

Figure 2.
Kaplan-Meier estimates of overall survival in patients with MSI-H/dMMR mCRC

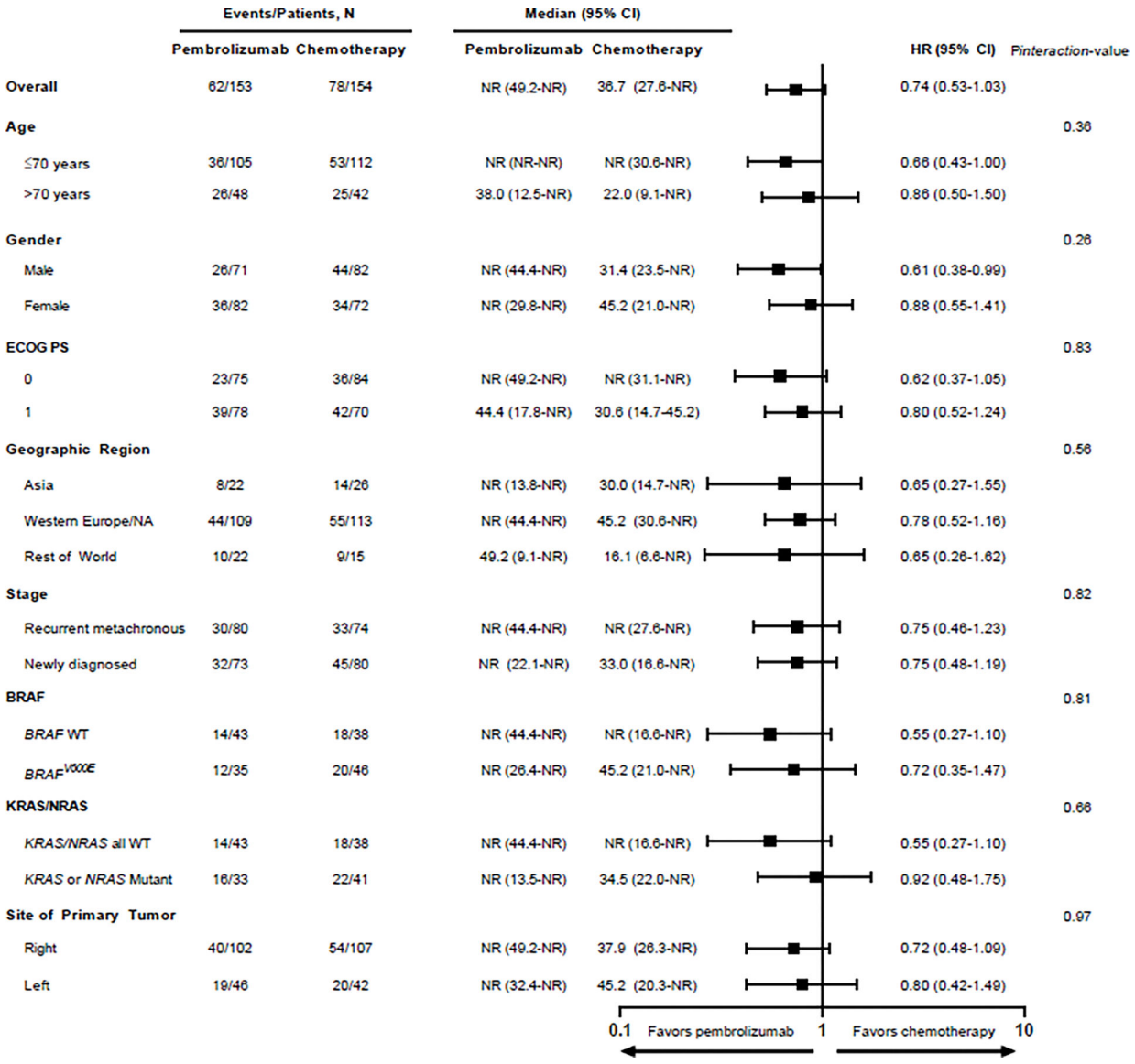

Figure 3.

Overall survival in key subgroups of patients with MSI-H/dMMR mCRC. All subgroups were prespecified except for sex, ECOG performance status, and KRAS mutation. Prespecified categories were age, geographic region, recurrent versus new-diagnosed, BRAF wildtype vs BRAF V600E, site of primary tumor. The hazard ratios for death for the comparison of pembrolizumab versus standard-of-care therapy in all subgroups was calculated based on a Cox proportional regression model with Efron's method of tie handling with treatment as a covariate. Two-sided interaction p-values are provided based on a multivariate Cox regression model with treatment, age, sex, ECOG performance status, geographic region, recurrent versus new-diagnosed, BRAF/KRAS/NRAS all wild type versus BRAF V600E, BRAF/KRAS/NRAS all wildtype versus KRAS or NRAS mutant, site of primary tumor and their interactions with treatment as covariates. The joint testing was done as a post-hoc exploratory analysis and P values are not adjusted for multiplicity and are nominal only. The dashed line indicates the overall OS HR for the study.

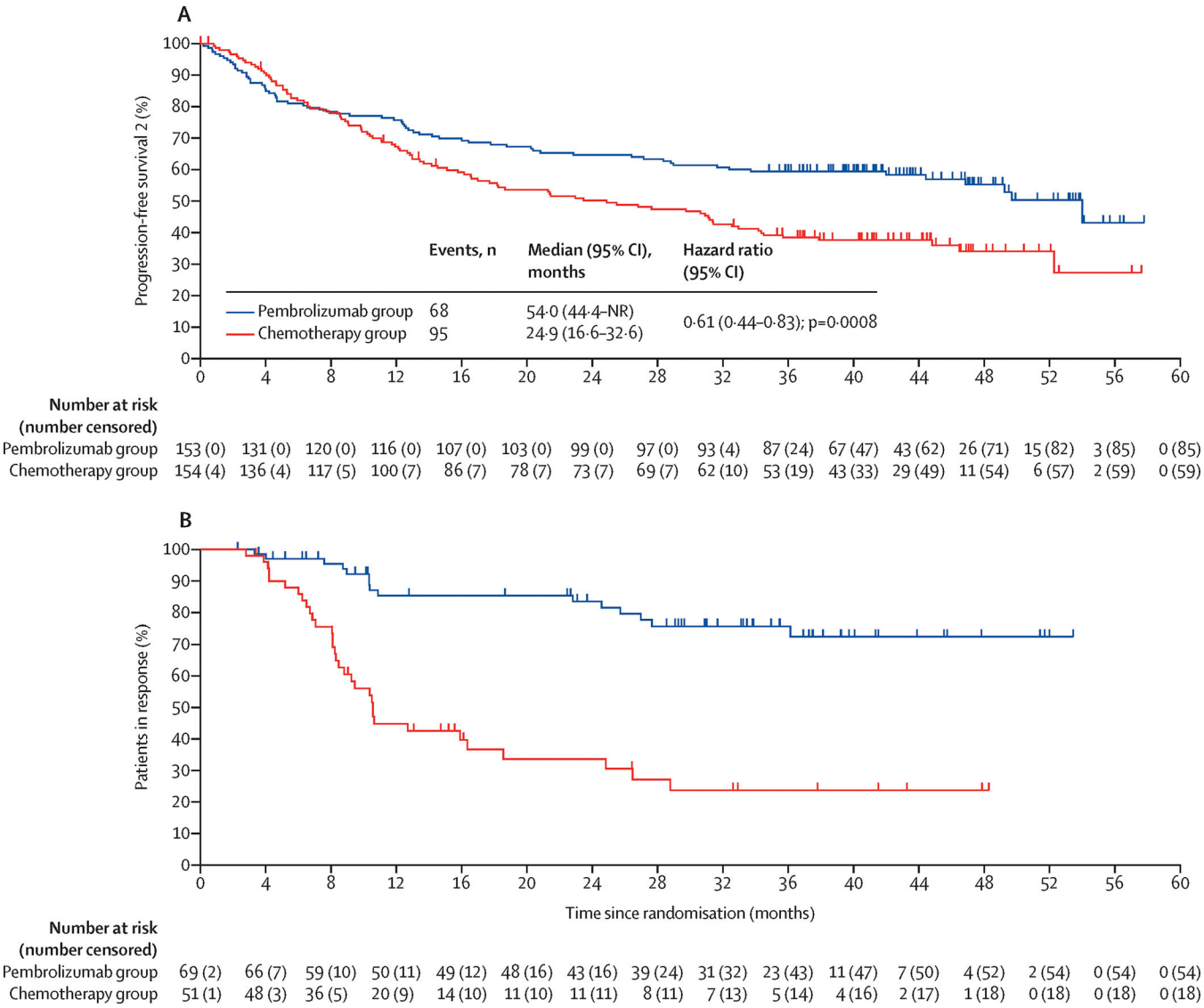

Figure 4.

Kaplan-Meier estimate of (A) time from randomization to progression on next line of therapy or any cause death in patients with MSI-H/dMMR mCRC. (B) Median duration of response in patients with MSI-H/dMMR mCRC

Table 1.

Baseline patient and disease characteristics in the intention-to-treat population

Characteristic, n (%)	Pembrolizumab N = 153	Chemotherapy N = 154
Age, median (range), years	63.0 (24–93)	62.5 (26–90)
Male	71 (46.4)	82 (53.2)
ECOG PS 0	75 (49.0)	84 (54.5)
Recurrent disease	80 (52.3)	74 (48.1)
Liver Metastasis	71 (46.0)	54 (35.0)
Asia region	22 (14.4)	26 (16.9)
Western Europe/North America region	109 (71.2)	113 (73.4)
Rest of World	22 (14.4)	15 (9.7)
White	113 (73.9)	116 (75.3)
Asian	24 (15.7)	26 (16.9)
Black	9 (5.9)	5 (3.2)
Race not reported/missing	7 (4.6)	7 (4.5)
Not Hispanic/Latino	128 (83.7)	131 (85.1)
Hispanic/Latino	11 (7.2)	10 (6.5)
Ethnicity not reported/missing/unknown	14 (9.2)	13 (8.4)
Right-sided tumor	102 (66.7)	107 (69.5)
Left-sided tumor	46 (30.1)	42 (27.3)
Other/unknown tumor location	5 (3.2)	5 (3.2)
Prior adjuvant therapy only	33 (21.6)	37 (24.0)
Prior neoadjuvant therapy (perioperative)	5 (3.2)	8 (5.2)
No prior therapy	115 (75.2)	109 (70.8)
BRAF, KRAS, NRAS all wildtype	43 (28.1)	38 (24.7)
KRAS or NRAS mutant	33 (21.6)	39 (25.3)
$BRAF^{V600E}$ mutant and KRAS/NRAS not mutant	35 (22.9)	44 (28.6)
$BRAF^{V600E}$ mutant and KRAS/NRAS mutant	0	2 (1.3)
Unknown[a]	42 (27.5)	31 (20.1)

[a]Defined as when KRAS/NRAS or $BRAF^{V600E}$ one or two or all are missing or if only one or two are missing and the other is WT.

Table 2.

Adverse events in all treated patients[a] with MSI-H or dMMR mCRC

Events, n (%)	**Pembrolizumab N =153**				**Chemotherapy N = 143**			
Any adverse event	**149 (97)**				**142 (99)**			
Grade ≥3[b]	**86 (56)**				**112 (78)**			
Treatment-related events ≥10%[c]	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhea	35 (23)	3 (2)	0	0	62 (43)	13 (9)	1 (1)	0
Fatigue	28 (18)	3 (2)	0	0	50 (35)	13 (9)	0	0
Pruritus	21 (14)	0	0	0	6 (4)	1 (1)	0	0
Arthralgia	17 (11)	0	0	0	1 (1)	0	0	0
AST increased	14 (9)	2 (1)	0	0	6 (4)	1 (1)	0	0
Hypothroidism	16 (10)	0	0	0	0	0	0	0
Nausea	19 (12)	0	0	0	76 (53)	3 (2)	0	0
Decreased appetite	12 (8)	0	0	0	46 (32)	3 (2)	0	0
Asthenia	11 (7)	0	0	0	20 (14)	5 (3)	0	0
Anemia	7 (5)	2 (1)	0	0	12 (8)	7 (5)	0	0
Stomatitis	8 (5)	0	0	0	37 (26)	6 (4)	0	0
Alopecia	5 (3)	0	0	0	28 (20)	0	0	0
Vomiting	5 (3)	0	0	0	35 (24)	5 (3)	0	0
Dizziness	4 (3)	0	0	0	15 (10)	0	0	0
Mucosal inflammation	4 (3)	0	0	0	24 (17)	1 (1)	0	0
Peripheral neuropathy	1 (1)	0	0	0	24 (17)	1 (1)	0	0
Neutrophil count decreased	1 (1)	0	0	0	9 (6)	16 (11)	8 (6)	0
White blood cell count decreased	1 (1)	0	0	0	11 (8)	4 (3)	2 (1)	0
Neutropenia[d]	0	0	0	0	8 (6)	17 (12)	5 (3)	0
Peripheral sensory neuropathy	0	0	0	0	26 (20)	3 (2)	0	0
Epistaxis	0	0	0	0	20 (14)	0	0	0
PPE syndrome	0	0	0	0	23 (16)	2 (1)	0	0

Events, n (%)	**Pembrolizumab N =153**				**Chemotherapy N = 143**			
Any adverse event	**149 (97)**				**142 (99)**			
Grade ≥3[b]	**86 (56)**				**112 (78)**			
Adverse events of interest[e], n (%)	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All events	33 (22)	12 (8)	2 (1)	0	18 (13)	3 (2)	0	0
Hypothyroidism	19 (12)	0	0	0	4 (3)	0	0	0
Colitis	5 (3)	3 (2)	2 (1)	0	1 (1)	0	0	0
Hyperthyroidism	6 (4)	0	0	0	0	0	0	0
Pneumonitis	6 (4)	0	0	0	2 (1)	0	0	0
Adrenal insufficiency	2 (1)	2 (1)	0	0	0	0	0	0
Hepatitis	0	4 (3)	0	0	0	0	0	0
Infusion reactions	3 (2)	0	0	0	10 (7)	1 (1)	0	0
Severe skin reactions	0	2 (1)	0	0	0	2 (1)	0	0
Thyroiditis	2 (1)	0	0	0	0	0	0	0

[a]The all treated population included all patients who were randomized and received at least one study treatment.

[b]Grade 5 any cause events occurred in 6 patients in the pembrolizumab group (diarrhea, duodenal perforation, death from unknown cause, abdominal sepsis, failure to thrive in the setting of cachexia, and pseudobulbar palsy in 1 patient each), and 7 patients in the chemotherapy group (cardiac arrest, intestinal perforation, upper gastrointestinal hemorrhage, aspiration, pulmonary embolism, aortic dissection, and cholangitis in 1 patient each).

[c]Treatment-related adverse events were attributed to study treatment by investigator. Reported are treatment-related adverse events that occurred in at least 10% of patients in any group.

[d]Neutropenia is the clinical diagnosis resulting from decreased neutrophil count. Both are reported here.

[e]Adverse events of interest (Immune-mediated adverse events and infusion reactions) were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators. Reported are adverse events of interest in at least 2 patients in any group.

Abbreviations: AST, aspartate aminotransferase increased; PPE, Palmar plantar erythrodysaesthesia