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Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study

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Summary

Background—Metastatic DNA mismatch repair–deficient/microsatellite instability–high (dMMR/MSI-H) colorectal cancer (mCRC) has a poor prognosis following conventional chemotherapy and exhibits high levels of tumour neoantigens, tumour-infiltrating lymphocytes, and checkpoint regulators, all features that correspond with response to programmed cell death receptor-1 (PD-1) blockade in other tumour types. Thus, nivolumab, a PD-1 immune checkpoint inhibitor, was evaluated in this population.

Methods—In this is ongoing, multicentre, open-label, nonrandomised, phase 2 trial, adult patients (aged ≥18 years) with histologically confirmed recurrent or mCRC locally assessed as dMMR/MSI-H who had progressed on/after or been intolerant of at least one prior line of treatment, including a fluoropyrimidine and oxaliplatin or irinotecan, were enrolled. Patients were given nivolumab 3 mg/kg every 2 weeks until disease progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint was investigator-assessed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors v1·1. All patients who received at least one dose of study drug were included in the primary and safety analysis. This trial is registered with ClinicalTrials.gov, number NCT02060188.

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Findings—Among the 74 patients who were enrolled between March 12, 2014, and March 16, 2016, most (54·1%) had received ≥3 prior therapies. At a median follow-up of 12·0 months (interquartile range 8·57–18·00 months), 23 of 74 patients (31·1% [95% CI 20·8%–42·9%]) achieved an investigator-assessed objective response; 68·9% (95% CI 57·1%–79·2%) of patients had disease control for ≥12 weeks. Median duration of response was not yet reached; all responders were alive, and 8 (34·8%) had responses of ≥12 months. The most common (≥10% of patients) drug-related adverse events was fatigue (n=16 [21·6%]), diarrhoea (n=15 [20·3%]), pruritus (n=10 [13·5%]) and rash (n=8 [10·8%]). The most common grade 3 or 4 drug-related adverse events were increased lipase (n=6 [8·1%]) and amylase (n=2 [2·7%]) levels. Five patients (6·8%) discontinued treatment because of increased alanine aminotransferase, colitis, duodenal ulcer, acute kidney injury, and stomatitis (n=1 each). Twenty-three patients (31·1%) died during the study; none of these deaths was considered to be treatment related by the investigator.

Interpretation—Nivolumab provided durable responses and disease control, as well as long-term survival in pre-treated patients with dMMR/MSI-H mCRC, and is a new treatment option for these patients.

Keywords

PD-1; nivolumab; colorectal cancer; microsatellite instability; immune-checkpoint inhibitor

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death.[1] Standard of care for patients with metastatic CRC (mCRC) who are not surgical candidates is palliative fluorouracil-based chemotherapy regimens combined with agents targeting angiogenesis or the epidermal growth factor receptor.[2] Despite a number of available systemic therapies for patients with metastatic disease, the 5-year survival rate is only 13·5%.[3]

Emerging evidence suggests patients with DNA mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) mCRC (≈4% to 5% of patients) are a distinct biomarker-defined population who benefit less from conventional chemotherapy and have a shorter overall survival (OS) than patients with proficient MMR (pMMR) mCRC.[4–7] Compared with pMMR/microsatellite-stable tumours, dMMR/MSI-H CRCs are associated with a higher mutational burden and tumour neoantigen load and dense immune cell infiltration.[8–11] In a pooled analysis of four phase 3 studies in the first-line setting, patients with dMMR mCRC had significantly worse outcomes compared with those with pMMR mCRC (median OS 13·6 vs 16·8 months; hazard ratio 1·35 [95% CI 1·13–1·61]; p=0·001).[6] In this analysis, the presence of *BRAF* mutation was found to confer a poor prognosis, suggesting that the poor prognosis of sporadic dMMR mCRC may be driven in part by the *BRAF* mutation status.

dMMR/MSI-H mCRCs are currently treated with the same systemic agents used for all mCRCs.[12–14] The potential of programmed death receptor-1 (PD-1) inhibitors in patients with dMMR metastatic tumours was first demonstrated in a phase 1 trial of nivolumab in 39 patients with refractory solid tumours, 14 of whom had mCRC.[13] One patient with dMMR mCRC received 5 doses of nivolumab 3 mg/kg and achieved a durable complete response

persisting for >21 months at the time of publication.[13] Long-term follow-up demonstrated clinical and radiological compete response (CR) >3 years later, at which time the patient had not received any anti-neoplastic therapy for 3 years and had no evidence of disease recurrence. The clinical benefit of PD-1 blockade in dMMR mCRC has also been reported in a phase 2 study of pembrolizumab.[12] Among patients (n=11) with dMMR mCRC in that study, 4 achieved partial responses (PRs) and 5 had stable disease. Based on activity of PD-1 inhibitors in patients with dMMR/MSI-H mCRC, CheckMate 142 was designed as a phase 2 trial to investigate the activity and safety of nivolumab monotherapy or nivolumab in combination with ipilimumab in patients with MSI-H and non-MSI-H mCRC. Here we report the efficacy, safety, and biomarker analyses for the nivolumab monotherapy in patients with MSI-H mCRC.

Methods

Study design and participants

This is an ongoing multicentre, open-label, nonrandomised, multi-cohort phase 2 trial. In this Article, we report results from nivolumab monotherapy cohort that enrolled patients with MSI-H mCRC at 31 sites (academic centre and hospitals) in 8 countries (Australia, Belgium, Canada, France, Ireland, Italy, Spain, and United States; table S1). Eligible patients had histologically confirmed metastatic/recurrent CRC with tumours locally assessed as dMMR and/or MSI-H. Patients were ≥18 years old with an Eastern Cooperative Oncology Group performance status of ≤1 and measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1·1.[15] Patients must have progressed on/after or been intolerant of at least one prior line of treatment, including a fluoropyrimidine and oxaliplatin or irinotecan; patients who refused chemotherapy were permitted on protocol.

Baseline laboratory tests required to assess eligibility included white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), lipase, and amylase. Patients with the following concurrent conditions were excluded from the study: active brain metastases or leptomeningeal metastases; any serious or uncontrolled medical disorder that might have resulted in an increased risk associated with participation in the study or study drug administration, that impaired the ability of the patient to receive nivolumab, or that interfered with the interpretation of study results; a prior malignancy active within the previous 3 years; active, known, or suspected autoimmune disease (except for vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition requiring only hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger); the need for immunosuppressive doses of systemic corticosteroids or other immunosuppressive drugs 2 weeks before nivolumab administration; and previous treatment with other therapy targeting T-cell costimulation or immune checkpoint pathways. Patients were also excluded if they had an acute or chronic hepatitis B or hepatitis C virus infection or history of positive testing for human immunodeficiency virus or known AIDS. Prior palliative radiotherapy was allowed if completed ≥2 weeks prior to study drug administration per the protocol.

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrolment. The protocol, amendments, and patient informed consent received appropriate approval by the Institutional Review Board and the Independent Ethics Committee before study initiation at each site.

Procedures

Patients received intravenous nivolumab monotherapy 3 mg/kg every 2 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or study end. Dose reductions were not allowed; dose interruptions were allowed for all drug-related adverse events (AEs) until the resolution of these events or ≤6 weeks from the last dose. Patients who had interruptions lasting >6 weeks were permanently discontinued from the study, except when dosing was interrupted to allow for prolonged steroid tapers to manage drug-related AEs or when such interruptions for non–drug-related reasons were approved by the study's medical monitor. Criteria for discontinuation of study drug are summarised in the appendix (appendix p 1). Treatment beyond initial disease progression was permitted if the patient tolerated and benefited from study therapy based on investigator assessment; these patients had to discontinue treatment if their tumour burden volume increased by ≥10% from the time of initial progression.

Patients were assessed for tumour responses performed within 28 days prior to the first dose using computed tomography or magnetic resonance imaging. Tumour imaging assessments for ongoing study treatment decisions were conducted by the investigator per RECIST v1·1[15] at baseline, every 6 weeks for 24 weeks, and every 12 weeks thereafter until disease progression or discontinuation.

Patient-reported outcomes were evaluated by the European Organisation for Research and Treatment of Cancer QLQ-Core 30 (EORTC QLQ-30) and the 3-level EQ-5D.[17,18] The EORTC QLQ-C30 assesses functioning, symptoms, and quality of life on scales ranging from 0 to 100, with higher scores indicating better functioning, quality of life, or worsening symptoms. For the EORTC QLQ-C30, a 10-point change in score was considered clinically meaningful.[19] The EQ-5D assesses the proportion of patients reporting health problems and has a visual analogue scale (VAS) evaluating self-reported health on a scale from 0 to 100, with higher scores indicating better health status.

Tumour MMR/MSI was assessed per local guidelines (immunohistochemistry and/or polymerase chain reaction [PCR]) prior to screening. MSI was subsequently evaluated on mandatory fresh tumour biopsies collected at enrolment per central laboratory using PCR (modified Bethesda panel including transforming growth factor β type 2 receptor); tumour samples with instability in 0, 1, or ≥2 markers were identified as microsatellite-stable, MSI-low, and MSI-H, respectively. Exploratory biomarker analysis of tumour PD-L1 expression (≥1% or <1%) was performed on either archival or pre-treatment study biopsy samples by immunohistochemistry using the Dako 28–8 pharmDx assay (Dako North America, Carpinteria, CA, USA); positive staining was defined as complete circumferential or partial linear plasma membrane staining. The abundance (rare, intermediate, or numerous) of tumour-associated immune cells expressing PD-L1 was determined by a pathologist. The level of PD-L1 expression was determined by pathologist's qualitative analysis with the

presence of easily detected mononuclear cells in the field characterised as “numerous” and few cells identified in the field as “rare”. “Intermediate” was subjectively defined as anything between “numerous” and “rare” by the pathologist. *BRAF* and *KRAS* mutation status was determined per local guidelines. Characterisation of Lynch syndrome as positive or negative was determined by investigators based on past medical history collected from clinical records; genetic testing for Lynch syndrome was not mandated by the study protocol. The change from baseline in carcinoembryonic antigen (CEA) levels was evaluated on day 1 of week 7.

On-treatment local laboratory assessments were done ≤72 hours prior to each dose through week 23 and every alternate dose thereafter. Extended assessments were complete blood count with differential and platelet count, liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), creatinine, BUN or serum urea concentrations, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, and thyroid-stimulating hormone with reflex to free T4 and free T3. Toxicity assessments were done continuously during the treatment phase and for ≥100 days following discontinuation per Common Terminology Criteria for Adverse Events (CTCAE) v4·03.[16] Survival follow-up was performed every 3 months for ≤3 years.

Outcomes

The primary endpoint was objective response rate (ORR) per investigator assessment in dMMR/MSI-H mCRC according to RECIST v1·1 criteria. Best overall response was defined as the best response between the date of first dose and progression or subsequent therapy, whichever occurred first. The investigator-assessed ORR was further characterised by the investigator-assessed duration of response (DOR) and rate of CR. DOR was defined as the time from first confirmed response (CR or PR) to the date of tumour progression or death due to any cause, whichever occurred first. The secondary endpoint was blinded independent central review (BICR)–assessed ORR (defined as the number of patients with a best overall response of confirmed CR or PR, according to RECIST v1·1 criteria, divided by the number of those treated). Exploratory endpoints included safety and tolerability of nivolumab monotherapy, progression-free survival (PFS) based on investigator and BICR assessments (defined as the time from first dosing date to the date of the first documented progression, or death due to any cause, whichever occurred first), and OS (defined as the time from first dosing date to the date of death). Additionally, the association between biomarkers other than dMMR/MSI-H, efficacy, and patient-reported outcomes was assessed. Post hoc analysis of disease control ≥ 12 weeks defined as no progressive disease between the time from the first dose of study therapy and last day of week 12 was also performed.

Statistical analysis

Using a two-stage Simon study design: if fewer than seven of the first 19 patients with centrally confirmed MSI-H CRC had an objective response (CR or PR) with nivolumab, enrolment would end; however, if seven or more patients had a response, 29 additional centrally confirmed patients would be treated in stage 2. All patients were locally assessed as dMMR/MSI-H, but in some cases, these results could not be confirmed by a central laboratory; therefore, additional patients were enrolled into stage 2 to ensure that 48 patients

with centrally confirmed MSI-H CRC received study therapy. The 95% CI for ORR were estimated using the Clopper and Pearson method. Descriptive statistics were used to characterise baseline patient characteristics and safety analyses performed in all treated patients per CTCAE v4·03.[16] Kaplan-Meier methodology was used to determine medians and 95% CI (based on log-log transformation) for DOR, PFS, and OS. Descriptive statistics were used to analyse patient-reported outcomes.

Role of the funding source

The sponsor of the study (Bristol-Myers Squibb) provided the study drug and worked with the investigators to design the study and to collect, analyse, and interpret the data. All authors made the decision to submit the report for publication, and all drafts of the report were prepared by the corresponding author with input from coauthors and editorial assistance from professional medical writers (Chrysalis Medical Communications, Inc, US), funded by the sponsor. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

Between March 12, 2014, and March 16, 2016, 74 patients with locally determined dMMR/MSI-H CRC were recruited and enrolled into stages 1 and 2 of the trial, all of whom were given treatment and included in the analyses. An adequate number of objective responses (n=7) were achieved in the first 19 patients with centrally confirmed dMMR/MSI-H CRC treated with nivolumab 3 mg/kg every 2 weeks in stage 1; therefore, enrolment into stage 2 was initiated and is now complete. As of the February 6, 2017 data cut-off, 74 patients with locally determined dMMR/MSI-H mCRC had received nivolumab in stages 1 and 2 combined with median follow-up of 12·0 months (IQR 8·57–18·00 months). Most patients were <65 years old and had received ≥3 prior systemic therapies; 4 patients had received prior adjuvant therapy without treatment for metastatic disease (table 1). Of note 39·0% of the patients with locally determined dMMR/MSI-H CRC were *BRAF/KRAS* wild type and 16·0% had tumours harbouring a *BRAF* mutation.

Among the 74 patients with locally determined dMMR/MSI-H CRC, 53 patients (71·6%) were centrally identified as having MSI-H tumours and 14 (18·9%) as having non–MSI-H (microsatellite-stable/MSI-low) tumours; due to a lack of adequate tumour tissue/DNA, seven patients (9·5%) had no central results (table S2). Among the 14 patients who did not have agreement between local and central laboratories, ten were assessed locally by immunohistochemistry only and four had discordant PCR results (table S2); in each case, biopsy specimens collected at different time points were used for local and central testing. Also among the 14 patients who were not confirmed five patients with a clinical history of Lynch syndrome who were identified locally as dMMR using immunohistochemistry and centrally as microsatellite stable using PCR (table S3).

At data cut-off 36 of the 74 patients (48·6%) were still receiving treatment; discontinuations occurred in 38 patients (51·4%) due to disease progression (n=27 [36·5%]), treatment-related toxicity (n=6 [8·1%]), AE unrelated to study drug (n=1 [1·4%]), maximum clinical benefit (n=1 [1·4%]), patient decision (n=1 [1·4%]), withdrawal of consent (n=1 [1·4%]) or

other (n=1 [1·4%]). Of note, one of the patients who reported at least one AE leading to discontinuation discontinued because of disease progression. The median number of doses received was 22 (IQR 6–29 doses).

Among the 74 patients with locally determined dMMR/MSI-H CRC, 23 patients achieved PRs per investigator assessment and the ORR was 31·1% (95% CI 20·8%–42·9%; table 2); disease control for ≥12 weeks occurred in 51 patients (68·9% [95% CI 57·1%–79·2%]). Per BICR, two patients (2·7%) had CRs, and 22 patients (29·7%) had PRs, for an ORR of 32·4% (95% CI 22·0%–44·3%); 47 patients (63·5% [95% CI 51·5%–74·4%]) had disease control for ≥12 weeks (table 2). The rate of concordance for assessments of response per investigator and BICR was 87·8%. Among the 53 patients who were centrally confirmed as MSI-H, the ORR per investigator was 35·8% (95% CI 23·1%–50·2%) and the rate of disease control lasting ≥12 weeks was 73·6% (95% CI 59·7–84·7; table 2). Per BICR, one patient (1·9%) had a CR, and 18 patients (34·0%) had PRs, for an ORR of 35·8% (95% CI 23·1%–50·2%).

Per investigator assessment, patients with locally determined dMMR/MSI-H CRC had a median time to response of 2·8 months (IQR 1·38–3·15 months). Responses and stable disease appeared durable, with only three responders experiencing progression (figure 1A). Median DOR was not yet reached (95% CI not estimable [NE]–NE) and all responders were alive at the time of analyses, with 8 of these patients (34·8%) having responses lasting ≥12 months (figure 1B). At 12 months, the investigator-assessed PFS was 50·4 % (95% CI 38·1%–61·4%; figure 2A) and investigator-assessed OS was 73·4% (95% CI 61·5%–82·1%). At the time of this analysis, 23 events were reported, and the median was not yet reached (95% CI 18·0–NE; figure 2B). BICR-assessed efficacy results are reported in tables 2, S4, and S5 and figures S1 and S2.

Efficacy was also assessed per investigator in biomarker-defined subpopulations of patients with locally determined dMMR/MSI-H CRC. ORRs and disease control were observed patient subgroups including those with (≥1%) and without (<1%) tumour PD-L1 expression, tumour *BRAF* or *KRAS* mutations, and a clinical history of Lynch syndrome (tables 3 and S6). Change in CEA levels (based on September database lock) from baseline to day 1 of week 7 were similar in responders and those with stable disease for ≥12 weeks (figure S3); patients with disease control for ≥12 weeks had a greater decrease in CEA levels versus patients with stable for <12 weeks or progressive disease (p=0·038).

Patient-reported outcome analyses were conducted through week 97, with questionnaire completion rates at each time point ranging from 68·3% to 100·0% (table S7). Per EORTC QLQ-C30 assessment, ≥50% of patients experienced no meaningful (≥10-point change) deterioration in functioning or worsening of symptoms. As early as week 13, clinically meaningful improvements were reported in functioning (emotional, role, and social), symptoms (fatigue, pain, insomnia, appetite loss, constipation, and diarrhoea), and quality of life, with some outcomes being maintained through week 37 or beyond (figure S4). No meaningful improvements in physical functioning, nausea and vomiting, or dyspnoea were observed, and clinically relevant worsening in cognitive functioning was observed at week 67. The percentage of patients reporting some health problems at baseline on the EQ-5D

ranged from 11·9% (self-care) to 56·7% (pain), with notable (>10%) reductions in health problems observed as early as week 13 for all dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The mean EQ-5D VAS score at baseline was 51·1 (SD 33·7), and patients who continued treatment for 19 weeks achieved mean VAS scores between 68·0 and 87·7 (figure S5).

All-cause AEs were reported in 73 (98·6%) of 74 patients: 29 (39·2%) had grade 1 or 2 events, 30 (40·5%) had grade 3 events, 10 (13·5%) had grade 4 events, and 4 (5·4%) had grade 5 events. A total of 52 patients (70·3%) had drug-related AEs: 36 (48·6%) had grade 1 or 2 events, 13 (17·6%) had grade 3 events, 2 (2·7%) had grade 4 events, and 1 (1·4%) had a grade 5 event. The most common (≥10% of patients) drug-related AEs was fatigue (n=16 [21·6%]), diarrhoea (n=15 [20·3%]), pruritus (n=10 [13·5%]), and rash (n=8 [10·8%]; table 4, table S8). Grade 3 or 4 drug-related AEs were reported in 15 patients (20·3%); increased lipase (n=6 [8·1%]) and increased amylase (n=2 [2·7%]) were the only grade 3 or 4 events that occurred in more than one patient. AEs were manageable, with five (6·8%) patients discontinuing treatment due to drug-related AEs, including increased ALT, colitis, duodenal ulcer, acute kidney injury, and stomatitis (n=1 each). Drug-related serious AEs occurred in 9 patients (12·2%) and included adrenal insufficiency, increased ALT levels, colitis, diarrhoea, gastritis, stomatitis, acute kidney injury, pain, and arthritis (n=1 [1·4%] each); all were grade 3 or 4. One grade 5 serious AE of sudden death of unknown cause was also reported; this patient died 10 days after their last dose while on a steroid taper as treatment for grade 3 colitis; cause of death was not determined at autopsy and was not attributed to drug-related toxicity. A total of 23 patients (31·1%) died due to disease progression (n=20 [27·0%]) or unknown cause (n=3 [4·1%]); 12 (13·5%) patients died ≤100 days after their last dose, including five (6·8%) of whom died ≤30 days after their last dose; no deaths were reported due to study drug toxicity.

Discussion

CheckMate 142 is a multicentre international study investigating the efficacy and safety of nivolumab in the largest cohort of patients with dMMR/MSI-H mCRC ever treated with an immune checkpoint inhibitor. In this study, nivolumab demonstrated encouraging efficacy in patients with dMMR/MSI-H tumours. Among patients with locally determined dMMR/MSI-H mCRC, the investigator-assessed ORR by RECIST v1·1 criteria was 31·1% and the rate of disease control lasting ≥12 weeks was 68·9%. Responses were observed across all atient subgroups including those with (≥1%) and without (<1%) tumour PD-L1 expression, suggesting that PD-L1 is not a predictive biomarker in these patients. In addition, responses were reported in patients with and without a clinical history of Lynch syndrome, or *KRAS* or *BRAF* mutations. *BRAF* V600E mutations are associated with sporadic dMMR/MSI mCRC and are rarely found in patients with Lynch syndrome[20,21] In this study, an ORR of 25% (investigator-assessed) was observed in patients with *BRAF*-mutant tumors, which is higher than historical rates reported with chemotherapy (<10%)[22,23] or combination therapy including BRAF or EGFR or MEK inhibitors (10%–16%)[24,25] in patients with mCRC who have *BRAF* mutations. These findings suggest that nivolumab may exhibit greater activity than traditional therapy in these patients who typically have a poor prognosis as compared with patients with *BRAF* wild-type mCRC. Importantly, both responses and stable disease

proved to be durable with DOR not yet reached in the overall population. The plateaus in the Kaplan-Meier plots of PFS, OS rate of 73·4% at 1 year, and median OS not yet reached further speak to the durability of clinical benefit in some patients. Patient-reported outcome analyses showed clinically meaningful improvements in functioning, symptoms, and quality of life, and patients who continued treatment for ≥19 weeks attained a level of health per the EQ-5D VAS that would be regarded as equal to or exceeding the general health of many populations.[26] Nivolumab was well tolerated in patients with dMMR/MSI-H mCRC, with the exclusion of minor fraction of patients who experienced elevated lipase and amylase levels, which is consistent with the known safety profile for nivolumab reported in other solid tumours,[27–29] most AEs were manageable and resolved, and no new safety signals were observed. The incidence of diarrhoea and colitis did not appear elevated in this population of patients compared with those with other solid tumours.[29] The findings of the CheckMate 142 study suggest that nivolumab is a promising therapeutic option for patients with previously treated dMMR/MSI-H mCRC. CheckMate 142 is also evaluating combination therapy with nivolumab plus ipilimumab in patients with dMMR/MSI-H mCRC; this combination was well tolerated and demonstrated promising preliminary efficacy in dMMR/MSI-H CRC.[30] Ongoing studies are evaluating the combination of nivolumab with other immunotherapies in dMMR/MSI-H mCRC. In addition, the safety and efficacy of rational combinations of nivolumab with other anti-cancer therapies is being investigated in pMMR mCRC.

The population of patients in the current study provides additional insight regarding the activity of anti-PD-1 therapy in dMMR/MSI-H mCRC. The clinical activity of anti-PD-1 therapy was initially reported by Le et al in a small cohort (n=11) of patients with dMMR/MSI-H mCRC that had a high proportion of Lynch syndrome; 8 patients (73%) had *BRAF* wildtype tumours and none of the patients had *BRAF* mutated tumours.[14] In contrast, approximately one third of the patients in Checkmate 142 had Lynch syndrome and 16% of patients had tumour harbouring a *BRAF* mutation making this a more heterogeneous population. Of note, the patient population of CheckMate 142 also represents a young mCRC population, given an estimated median age is approximately 70 years for patients with mCRC, and may be reflective of the inclusion of patients with Lynch syndrome who are generally diagnosed at an earlier age and/or the younger age of patients enrolled in clinical trials.

Exploratory biomarker analysis to evaluate the relationship between dMMR/MSI-H status and known biomarkers for anti-PD-1 immunotherapy (ie, PD-L1) and CRC (ie, BRAF and KRAS) did not identify these biomarkers as predictive of response to nivolumab in this patient population. However, evidence from this study suggests that MMR/MSI status can be used to identify patients who will benefit from immunotherapy with nivolumab.[30] Similarly, following treatment with pembrolizumab no responses were observed in patients with pMMR mCRC.[14] These findings strongly suggest dMMR/MSI-H is a marker for response to PD-1 checkpoint inhibition in mCRC. These findings are in line with the recent amendment to the National Comprehensive Cancer Network guidelines, which recommend universal testing for dMMR/MSI-H in all patients with mCRC.[2] Additional biomarker studies are actively ongoing to identity possible biomarker correlatives for clinical outcome with nivolumab. Preliminary analysis of CEA changes suggests a possible correlation between

CEA reduction and durable clinical response (≥12 weeks) to nivolumab, although the reduction of CEA levels was not predictive of response to nivolumab. More correlative studies are warranted to strengthen this observation.

In this study, dMMR/MSI-H status was determined locally before inclusion based on archival tissue using PCR or immunohistochemistry and assessed centrally by PCR (modified Bethesda criteria) using tumour tissue collected at baseline. Twenty-one patients locally assessed as dMMR/MSI-H were not centrally confirmed as MSI-H. This discrepancy appeared to be primarily due to inadequate tumour cellularity or DNA from pre-treatment biopsy tissue, different methods/criteria used, and/or differences in the tumour samples, which were biopsied at different time points for central versus local testing. This highlights the real-word challenges associated with gathering adequate tissue from metastatic sites for correlative studies as well as the importance of utilizing testing methodologies for dMMR/MSI-H that are aligned with the amount of tumour tissue available. Although discrepancies were observed between local and central assessments, ORRs were similar at 31·1% and 35·8%, respectively. Additionally, three of the 14 patients (21·4%) not centrally confirmed as MSI-H had confirmed responses to treatment, suggesting that local testing adequately identified a dMMR/MSI-H population that derived benefit from nivolumab.

A limitation of this study is that patient subgroups were relatively small, which may limit the interpretation of the subgroup analyses. The lack of a comparator arm is another limitation of the study; however, the level of clinical benefit observed as confirmed responses in this study is remarkable in the historical context of other clinical trials conducted in heavily pre-treated patients with mCRC.[31–33]

In conclusion, nivolumab provided promising and durable responses rates with prolonged survival relative to the anticipated median survival in patients with dMMR/MSI-H mCRC. Clinically meaningful improvements were observed in patient-reported outcomes, and the safety profile of nivolumab was similar to experiences in other tumour types, with no new safety signals observed. These results suggest that nivolumab is a new treatment option in patients with dMMR/MSI-H mCRC, as reflected by the recent inclusion of nivolumab in the National Comprehensive Cancer Network treatment guidelines for this population.[2] Based on these observations further investigation of nivolumab with ipilimumab or other novel combinations with the potential to build on the benefit of nivolumab is warranted

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We searched PubMed for articles published between January 1, 2012, and January 1, 2017, with no language restrictions, reporting on the use of a programmed cell death receptor-1 (PD-1) immune checkpoint inhibitor for the treatment of patients with DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) using the search terms ("DNA mismatch repair" or "microsatellite instability") and "programmed cell death receptor-1 inhibitor" and "colorectal cancer", filtering for articles describing clinical trials.

We also searched abstracts of the annual meeting of the American Society of Clinical Oncology using the search term "DNA mismatch repair" or "microsatellite instability" and "programmed death-1 inhibitor" and "metastatic CRC", limiting the results to clinical trials published or presented during the past 2 years. Trials in progress were excluded from the search results.

The search yielded one article and three abstracts that reported the results of a phase 2 study that evaluated the clinical activity of pembrolizumab, an anti–PD-1 immune checkpoint inhibitor, in 35 patients with progressive metastatic carcinoma with or without mismatch repair deficiency. In this study, mismatch repair status was predictive of clinical benefit with pembrolizumab in ten patients with dMMR metastatic CRC; no responses were noted in patients (n=18) with proficient MMR (pMMR) metastatic CRC. An updated analysis of this study presented at the Gastrointestinal Symposium Congress in 2016 included 53 patients (dMMR n=28; pMMR n=25).

Added value of this study

CheckMate 142 is the largest phase 2 study to date to evaluate the efficacy and safety of PD-1 inhibitor therapy in patients with dMMR/MSI-H metastatic CRC(mCRC). The results from CheckMate 142 demonstrated that nivolumab monotherapy was well tolerated, provided durable responses and disease control with all responders alive at the time of analysis, and long-term survival in a population of pre-treated patients with dMMR/MSI-H mCRC. Responses and disease control were observed in patients with dMMR/MSI-H mCRC across all subgroups including patients with tumours that were positive (≥1%) or negative (<1%) tumour PD-1 ligand 1 (PD-L1) expression, tumours harbouring *BRAF* or *KRAS* mutations, and those with and without a clinical history of Lynch syndrome. Additionally, nivolumab was associated with clinically meaningful improvements in patient-reported functioning, symptoms, and quality of life in patients with dMMR/MSI-H mCRC.

Implications of all the available evidence

Patients with dMMR/MSI-H mCRC are traditionally treated with conventional chemotherapy ± targeted therapies and may have significantly worse outcomes compared with those with pMMR mCRC. The results from this phase 2 study confirm the clinical benefit of PD-1 inhibitor therapy in dMMR/MSI-H mCRC and suggest that nivolumab is a new treatment option for patients with previously treated dMMR/MSI-H metastatic

CRC. Ongoing studies are exploring the combination of nivolumab with other immunotherapies in patients with dMMR/MSI-H mCRC.

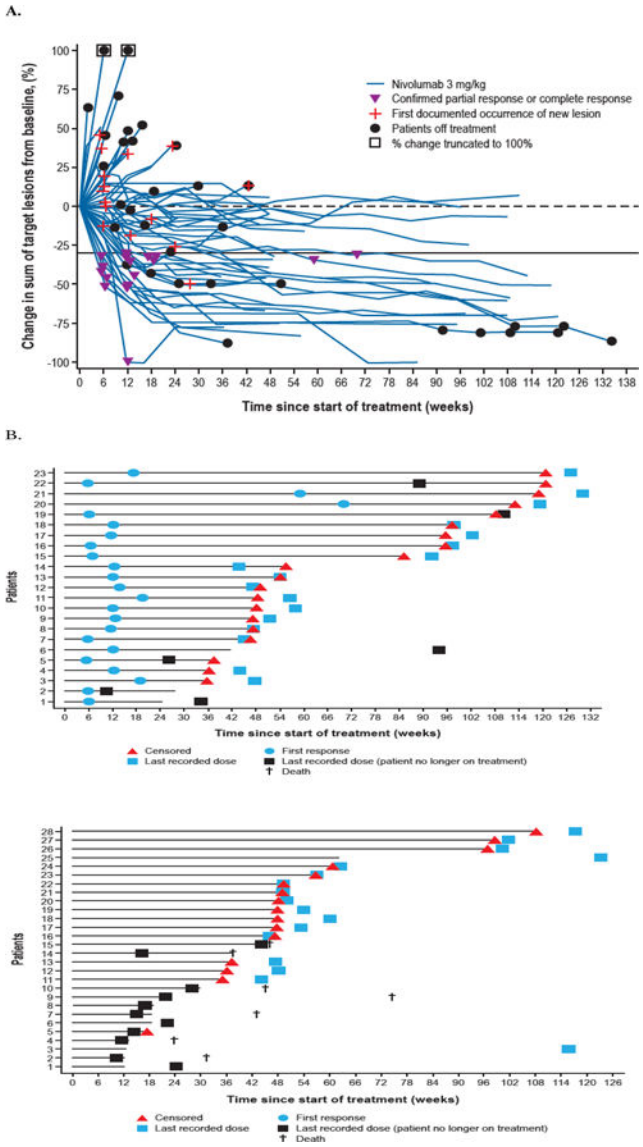

Figure 1: Plots of change from baseline in target lesion size over time in patients with metastatic or recurrent colorectal cancer locally assessed as dMMR/MSI-H

(A) Percentage change from baseline in the sum of the tumour burden for target lesions over time per investigator assessment for evaluable patients treated with nivolumab. Triangles indicate complete response or partial response per Response Evaluation Criteria In Solid Tumors v1·1; plus signs indicate the first occurrence of a new lesion; solid circle indicate patient who were off treatment; squares indicate percentage change truncated to 100%. (B) Characteristics of response (top panel) or stable disease (bottom panel) evaluated per investigator assessment per Response Evaluation Criteria In Solid Tumors v1·1. The lines represent length of progression-free survival. Triangles indicate censored observations; solid circle indicate the first response; solid black square indicate the last dose when the patient was off treatment; dagger signs indicate death. dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high.

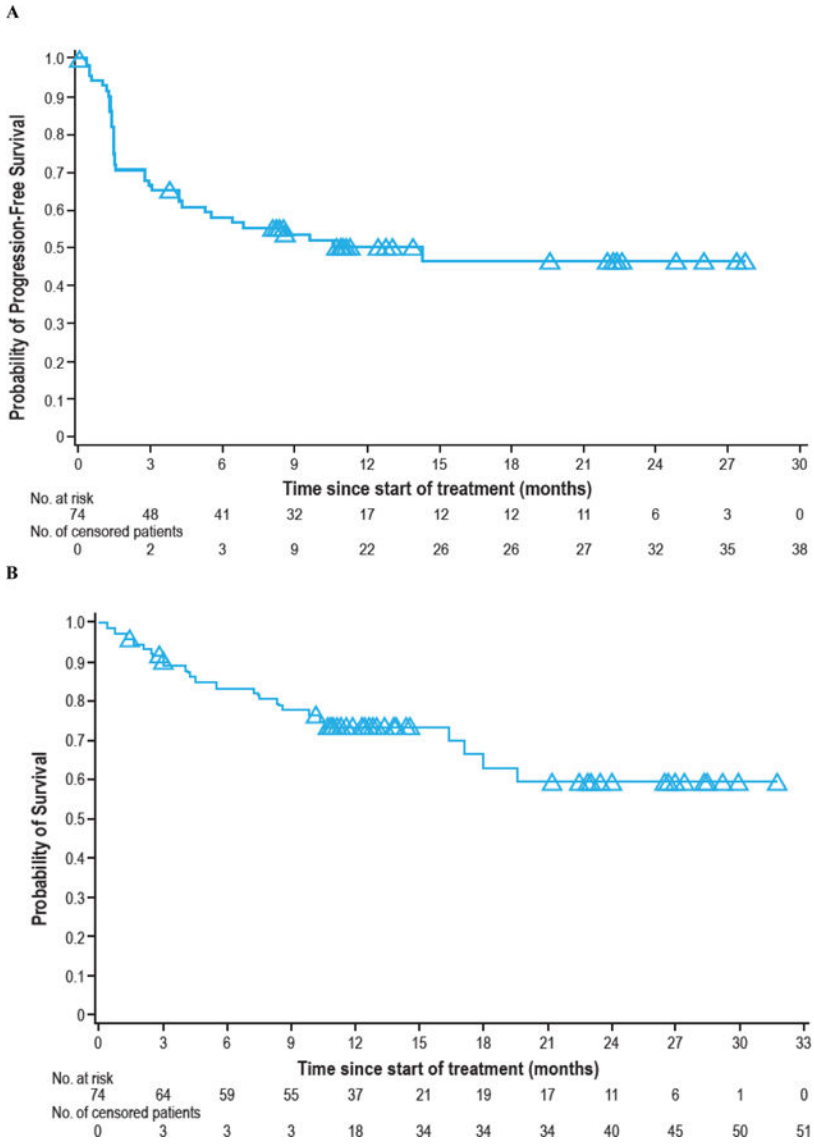

Figure 2: Plots of progression-free survival per investigator assessment and overall survival in patients with metastatic or recurrent colorectal cancer locally assessed as dMMR/MSI-H

(A) Kaplan-Meier curve for progression-free survival per investigator assessment in patients treated with nivolumab. Triangles indicate censored observations. (B) Kaplan-Meier curve for overall survival in all patients treated with nivolumab. Triangles indicate censored observations. dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high; NE=not estimable.

Table 1:

Demographics, baseline patient characteristics, and prior therapies

	dMMR/MSI-H per local assessment (N=74)
Age	
Median (IQR), years	52·5 (44·0–64·0)
<65 years, n (%)	57 (77)
Male, n (%)	44 (59)
Race, n (%)	
White	65 (88)
Black	7 (9)
Asian	1 (1)
Other	1 (1)
ECOG performance status, n (%)*	
0	32 (43)
1	42 (57)
Disease stage at diagnosis, n (%)	
I–II	15 (20)
III	26 (35)
IV	33 (45)
Prior systemic treatments, n (%)	
0	1 (1)
1	11 (15)
2	22 (30)
≥3	40 (54)
Prior therapies received, n (%)	
Fluoropyrimidines (5-fluorouracil or capecitabine)	73 (99)
Oxaliplatin	71 (96)
VEGF inhibitors†	57 (77)
Irinotecan	55 (74)
EGFR inhibitors‡	31 (42)
Regorafenib	12 (16)
Other	11 (15)
Prior radiotherapy, n (%)	27 (36)
Mutation status, n (%)	
BRAF/KRAS wild type	29 (39)
BRAF mutation	12 (16)
KRAS mutation	26 (35)
Unknown	7 (9)
Tumour PD-L1 expression quantifiable at baseline, n (%)	
≥1%	21 (28)

	dMMR/MSI-H per local assessment (N=74)
<1%	47 (64)
Unknown	6 (8)
Clinical history of Lynch syndrome, n (%)[§]	
Yes	27 (36)
No	28 (38)
Unknown	19 (26)

dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; PD-L1, programmed death-1 ligand 1; VEGF=vascular endothelial growth factor.

[*] One patient had an ECOG performance status of 1 at randomisation that deteriorated to 3 by the time of treatment initiation.

[†] VEGF inhibitors included bevacizumab, aflibercept, and ramucirumab.

[‡] EGFR inhibitors included cetuximab and panitumumab.

[§] Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).

Table 2:

Objective response rate, best overall response, and disease control rate per investigator and BICR assessments in patients with metastatic or recurrent colorectal cancer locally assessed as dMMR/MSI-H

	dMMR/MSI-H per local assessment (N=74)		dMMR/MSI-H per central assessment (N=53)	
Patients, n (%)	**Investigator**	**BICR**	**Investigator**	**BICR**
			19 (35·8)	19 (35·8)
Objective response rate	23 (31·1)	24 (32·4)		
[95% CI]	[20·8–42·9]	[22·0–44·3]		
			[23·1–50·2]	[23·1–50·2]
Best overall response				
Complete response	0	2 (2.7)	0	1 (1·9)
Partial response	23 (31·1)	22 (29·7)	19 (35·8)	18 (34·0)
Stable disease	28 (37·8)	25 (33·8)	20 (37·0)	19 (35·8)
Progressive disease	19 (25·7)	21 (28·4)	11 (20·8)	12 (22·6)
Not determined	4 (5·4)	4 (5·4)	3 (5·7)	3 (5·7)
Disease control for ≥12				
	51 (68·9)	47 (63·5)	39 (73·6)	37 (69·8)
weeks				
	[57·1–79·2]	[51·5–74·4]		
[95% CI]				
			[59·7–84·7]	[55·7–81·7]

BICR=blinded independent central review; dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high.

Table 3:

Investigator-assessed objective response rate and disease control rate in biomarker-defined patient populations

Patients, n (%)	dMMR/MSI-H per local assessment (N=74)	
	Objective response rate	**Disease control for ≥12 weeks**
Tumour PD-L1 expression		
≥1% (n=21)	6 (28·6)	11 (52·4)
<1% (n=47)	13 (27·7)	35 (74·5)
Immune cell PD-L1 expression		
Rare (n=24)	5 (20·8)	14 (58·3)
Intermediate (n=21)	5 (23·8)	17 (81·0)
Numerous (n=23)	9 (39·1)	15 (65·2)
Mutation status		
BRAF mutant (n=12)	3 (25·0)	9 (75·0)
KRAS mutant (n=26)	7 (26·9)	16 (61·5)
BRAF/*KRAS* wild type (n=29)	12 (41·4)	23 (79.3)
Clinical history of Lynch syndrome*		
Yes (n=27)	9 (33·3)	19 (70·4)
No (n=28)	8 (28·6)	21 (75·0)

dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high; PD-L1=programmed death-1 ligand 1.

* Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).

Table 4:

Treatment-Related Adverse Events

	dMMR/MSI-H per local assessment (N=74)*		
	Grade 1–2	**Grade 3**	**Grade 4**
Any Event	36 (48·6)	13 (17·6)	2 (2·7)
Fatigue	16 (21·6)	1 (1·4)	0
Diarrhoea	15 (20·3)	1 (1·4)	0
Pruritus	10 (13·5)	0	0
Rash	8 (10·8)	0	0
Nausea	7 (9·5)	0	0
Hypothyroidism	7 (9·5)	0	0
Asthenia	5 (6·8)	0	0
Aspartate aminotransferase increase	5 (6·8)	0	0
Arthralgia	4 (5·4)	0	0
Pyrexia	4 (5·4)	0	0
Dry skin	4 (5·4)	0	0
Maculopapular rash	4 (5·4)	1 (1·4)	0
Alanine aminotransferase increase	3 (4·1)	1 (1·4)	0
Lipase increase	3 (4·1)	4 (5·4)	2 (2·7)
Amylase increase	2 (2·7)	2 (2·7)	0
Stomatitis	2 (2·7)	1 (1·4)	0
Abdominal pain	1 (1·4)	1 (1·4)	0
Creatinine increased	1 (1·4)	1 (1·4)	0
Lymphocyte count decreased	1 (1·4)	1 (1·4)	0
Colitis	0	1 (1·4)	0
Acute kidney injury	0	1 (1·4)	0
Adrenal insufficiency	0	1 (1·4)	0
Oesophagitis	0	1 (1·4)	0
Gamma-glutamyltransferase increased	0	1 (1·4)	0
Gastritis	0	1 (1·4)	0
Pain	0	1 (1·4)	0

Data presented as n (%). This table reports grade 1–2 treatment-related events in ≥10% of patients in any treatment cohort and all grade 3–4 events.

*One grade 5 event of sudden death was reported.