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Nivolumab plus relatlimab in patients with previously treated microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study

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ABSTRACT

Background Programmed death-1 (PD-1) inhibitors, including nivolumab, have demonstrated long-term survival benefit in previously treated patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (CRC). PD-1 and lymphocyte-activation gene 3 (LAG-3) are distinct immune checkpoints that are often co-expressed on tumor-infiltrating lymphocytes and contribute to tumor-mediated T-cell dysfunction. Relatlimab is a LAG-3 inhibitor that has demonstrated efficacy in combination with nivolumab in patients with melanoma. Here, we present the results from patients with MSI-H/dMMR metastatic CRC treated with nivolumab plus relatlimab in the CheckMate 142 study.

Methods In this open-label, phase II study, previously treated patients with MSI-H/dMMR metastatic CRC received nivolumab 240 mg plus relatlimab 160 mg intravenously every 2 weeks. The primary end point was investigator-assessed objective response rate (ORR).

Results A total of 50 previously treated patients received nivolumab plus relatlimab. With median follow-up of 47.4 (range 43.9–49.2) months, investigator-assessed ORR was 50% (95% CI 36% to 65%) and disease control rate was 70% (95% CI 55% to 82%). The median time to response per investigator was 2.8 (range 1.3–33.1) months, and median duration of response was 42.7 (range 2.8–47.0+) months. The median progression-free survival per investigator was 27.5 (95% CI 5.3 to 43.7) months with a progression-free survival rate at 3 years of 38%, and median overall survival was not reached (95% CI 17.2 months to not estimable), with a 56% overall survival rate at 3 years. The most common any-grade treatment-related adverse events (TRAEs) were diarrhea (24%), asthenia (16%), and hypothyroidism (12%). Grade 3 or 4 TRAEs were reported in 14% of patients, and TRAEs of any grade leading to discontinuation were observed in 8% of patients. No treatment-related deaths were reported.

Conclusions Nivolumab plus relatlimab provided durable clinical benefit and was well tolerated in previously treated patients with MSI-H/dMMR metastatic CRC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nivolumab has demonstrated clinical benefit in previously treated patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (CRC).

⇒ Elevated lymphocyte-activation gene 3 (LAG-3) expression in patients with MSI-H/dMMR CRC suggests that dual inhibition of programmed death-1 and LAG-3 with nivolumab and relatlimab combination therapy may provide improved efficacy in these patients.

WHAT THIS STUDY ADDS

⇒ Nivolumab plus relatlimab demonstrated durable clinical benefit and manageable safety in previously treated patients with MSI-H/dMMR metastatic CRC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These encouraging results warrant further investigation of nivolumab plus relatlimab for the treatment of MSI-H/dMMR metastatic CRC.

Trial registration number NCT02060188.

BACKGROUND

Colorectal cancer (CRC) is the third most commonly diagnosed cancer with almost 2 million new cases annually and is the second leading cause of cancer-related death with almost 1 million deaths worldwide in 2020.[1] Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR)

adenocarcinoma is identified in approximately 5% of metastatic CRC.[2–4]

Novel immunotherapeutic agents have demonstrated clinical benefit in patients with MSI-H/dMMR metastatic CRC across lines of therapy.[5–8] Programmed death-1 (PD-1) checkpoint inhibition by nivolumab has demonstrated durable responses with acceptable safety in previously treated patients with MSI-H/dMMR metastatic CRC.[7] Nivolumab in combination with ipilimumab, a cytotoxic T lymphocyte antigen-4 inhibitor, mediates antitumor immune responses by distinct but complementary pathways and has demonstrated durable responses and long-term survival benefit with a manageable safety profile in previously untreated and treated patients with MSI-H/dMMR metastatic CRC.[5 6 8]

Lymphocyte-activation gene 3 (LAG-3) is an inhibitory immune checkpoint and binds to major histocompatibility complex II. LAG-3 and PD-1 are distinct immune checkpoints that are often co-expressed on tumor-infiltrating T cells, contributing to tumor-mediated T-cell dysfunction.[9] Dual immune checkpoint inhibition with nivolumab and relatlimab, a LAG-3-blocking antibody, demonstrated significant progression-free survival (PFS) benefit compared with nivolumab alone with a manageable safety profile in patients with previously untreated metastatic or unresectable melanoma. Based on these results, a fixed-dose combination of nivolumab plus relatlimab was granted approval by the Food and Drug Administration for the treatment of unresectable or metastatic melanoma.[10 11] The clinical benefit of nivolumab in multiple tumors, in combination with data showing increased LAG-3 expression in patients with MSI-H/dMMR CRC,[12] suggests that dual inhibition of PD-1 and LAG-3 may enhance efficacy.

CheckMate 142 (NCT02060188) is a phase II, multicohort, non-randomized study of nivolumab-based therapies in patients with metastatic CRC. Here, we report the first results of the nivolumab plus relatlimab cohort in previously treated patients with MSI-H/dMMR metastatic CRC from the CheckMate 142 study.

METHODS

Study design and participants

CheckMate 142 is an ongoing, open-label, multicenter phase II study. Eligible patients were ≥18 years of age with histologically confirmed recurrent or metastatic CRC locally assessed as MSI-H or dMMR, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST V.1.1). Patients must have progressed on, been intolerant to, or refused at least one line of previous treatment for their metastatic or recurrent disease, which must have included a fluoropyrimidine and either oxaliplatin or irinotecan. Patients who received oxaliplatin in an adjuvant setting must have progressed within 6 months of completion of adjuvant therapy in order for adjuvant oxaliplatin to have counted as a prior therapy needed for study entry.

Patients were ineligible for the study if they had active brain metastases, leptomeningeal metastases, prior active malignancies within the last 3 years (except for locally curable cancers which have been cured), known or suspected autoimmune disease, or any condition requiring systemic treatment with corticosteroids or immunosuppressive medications (≤14 days before the first dose of study treatment). Patients were also ineligible if their prior treatments included any immunotherapy or drug which specifically targets T-cell co-stimulation or immune checkpoint pathways (such as anti-PD-ligand (L)1 therapy).

Patients received nivolumab 240 mg and relatlimab 160 mg intravenously (30 min and 60 min infusions, respectively) every 2 weeks until disease progression, death, unacceptable drug toxicity, withdrawal of consent, or study end. Dose delays were permitted at the discretion of the investigator, but dose modifications were not allowed. Treatment beyond initial progressive disease (per RECIST V.1.1) was permitted if the patient tolerated the study drug and benefited from study treatment, per investigator assessment.

End points and assessments

The primary end point was objective response rate (ORR) (best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated patients) as determined by investigator assessment per RECIST V.1.1. BOR was defined as the best response designation recorded between first dose and initial objectively documented progression or subsequent therapy, whichever occurred first. Where there was no documented progression or subsequent therapy, all available response designations contributed to BOR determination. Duration of response (DOR) was defined as the time from first response date to the date of the first documented tumor progression or death of any cause. The secondary end points were ORR and DOR as determined by blinded independent central review (BICR) and disease control rate (DCR; best overall response of CR, PR, or stable disease of at least 12 weeks divided by the number of treated patients). Other key end points included PFS (time from first dose to first documented progression, or death due to any cause, whichever occurred first), determined by both investigator and BICR, and overall survival (OS; time from first dose to death), safety, and analysis of association between efficacy and the tumor LAG-3 and PD-L1 expression.

Imaging assessments were performed within 28 days prior to the first dose, every 6 weeks for 24 weeks, and then every 12 weeks thereafter until progression or discontinuation, using CT or MRI. For patients with disease control for 3 years after the first dose, tumor assessments could be modified to every 24 weeks or could remain the same on investigator discretion. Tumor imaging assessments were completed using RECIST V.1.1 criteria. Confirmation of

PR and CR was required after at least 4 weeks from the initial scan reporting a response.

Adverse events were evaluated at baseline, at each study visit, continuously throughout treatment, and a minimum of 100 days after treatment discontinuation using the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0.[13] The causal relationship to study drug was determined by the investigator. Treatment-related adverse events (TRAEs) with potential immunological etiology that require frequent monitoring or intervention were grouped by category (endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin).[14] Immune-modulating medications, including corticosteroids and immunosuppressive agents, were used to manage TRAEs with potential immunological etiology per protocol-specified algorithms.[15]

Baseline tumor biopsies or archival tissues were analyzed for LAG-3 and PD-L1 levels. Tumor cell PD-L1 expression was determined using the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay (Dako, Santa Clara, California, USA). Tumor cell PD-L1 expression was defined as complete circumferential or partial linear plasma membrane staining in a minimal of 100 viable tumor cells. LAG-3 expression was determined using an IHC assay. LAG-3 expression was reported as percent LAG-3-positive cells resembling lymphocytes relative to all nucleated cells within the tumor region.

Statistical analysis

The sample size was not based on power consideration but was determined to provide precision on the estimation of ORR. With 40 patients, the 95% CI for 16 responders was expected to be between 25% and 57%.

A response rate estimate and corresponding two-sided 95% exact CI was provided. The Clopper-Pearson method was used to calculate the exact CI. DOR was summarized for patients who achieved confirmed PR or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CIs (based on the log-log transformation), were also calculated. ORR based on BICR assessment was summarized similarly as investigator-assessed ORR. The Kaplan-Meier method was also used for PFS and OS determination with corresponding 95% CIs calculated using log-log transformation.

Safety analyses were performed in all treated patients. Descriptive statistics of safety are presented using National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0, tabulated using worst grade by system organ class and Medical Dictionary for Regulatory Activities preferred term.

RESULTS

Patients

Enrollment into the nivolumab plus relatlimab cohort of this study occurred from May 2017 to December 2017. A total of 50 patients from 13 sites in 7 countries with previously treated MSI-H/dMMR metastatic CRC were treated with nivolumab plus relatlimab.

At data cut-off (September 2021), minimum duration of follow-up (time from first dose to data cut-off) was 43.9 months, and median duration of follow-up was 47.4 (range 43.9–49.2) months. The median age was 60.0 (range 18–80) years, 56% of patients were male, and 80% had received treatment for metastatic disease (table 1). Fifteen (30%) patients were both *BRAF* and *KRAS* wild type, 12 (24%) had *BRAF* mutations, and 17 (34%) had *KRAS* mutations. Eight (16%) patients had confirmed history of Lynch syndrome (although Lynch syndrome status was unknown in 52% of patients). As of clinical data cut-off, 40 (80%) patients had discontinued and 10 (20%) were still receiving treatment. Reasons for treatment discontinuation included disease progression (19 patients (38%)), maximum clinical benefit (8 patients (16%)), study drug toxicity (5 patients (10%)), adverse events unrelated to study drug (5 patients (10%)), other (2 patients (4%)), and patient request (1 patient (2%)).

Patients received a median of 35 doses of nivolumab (range 1–104) and 34.5 doses of relatlimab (range 1–104); 88% of patients had a relative dose intensity of at least 90% for both nivolumab and relatlimab. The median treatment duration was 16.2 (range 0–49) months for both nivolumab and relatlimab, with 26 (52%) patients and 21 (42%) patients having a treatment duration of >1 and >2 years, respectively. Sixteen (32%) patients underwent subsequent treatment, including systemic therapy (10 patients, 20%) and surgery (6 patients, 12%).

Efficacy

Objective response was achieved in 50% of patients (95% CI 36% to 65%) per investigator assessment (table 2). The DCR per investigator was 70% (95% CI 55% to 82%). The median time to response per investigator was 2.8 (range 1.3–33.1) months with 96% (95% CI 75% to 99%) of responders remaining in response at 6 months. Most of the responses were within 24 weeks of first dose (21/25; 84%), although a small number of responders experienced onset of response after 24 weeks (4/25; 16%). The median DOR was 42.7 months (95% CI 27.7 to not estimable). Overall, 10% of patients had a CR, 40% had a PR, 24% had stable disease, and 26% had progressive disease as best response. Responses per investigator assessment were 90% concordant with BICR results; ORR per BICR was 48% (95% CI 34% to 63%). Among evaluable patients, 35 (71%) of the 49 patients had a reduction in tumor burden from baseline per investigator assessment (figure 1A). There was a rapid reduction in tumor burden, sustained over time in most patients (figure 1B).

ORR benefit was observed across evaluated subgroups, including age, sex, *KRAS/BRAF* mutation status, baseline ECOG performance status, history of Lynch syndrome, number of prior systemic regimens received, presence of liver metastases, and neutrophil-to-lymphocyte ratio (online supplemental table 1).

Table 1 Baseline patient demographics and clinical characteristics

Characteristic	NIVO+RELA (n=50)
Median age (range), years	60 (18–80)
<65	34 (68)
≥65	16 (32)
Sex	
Male	28 (56)
Female	22 (44)
Race	
White	49 (98)
Black or African-American	1 (2)
ECOG performance status	
0	35 (70)
1	15 (30)
Disease stage at diagnosis*	
I–III	29 (58)
IV	21 (42)
Primary tumor location	
Right colon	34 (68)
Rectum	6 (12)
Left colon	4 (8)
Colon NOS	3 (6)
Transverse colon	1 (2)
Presence of liver metastases	
Yes	18 (36)
No	32 (64)
Clinical history of Lynch syndrome†	
Yes	8 (16)
No	16 (32)
Unknown	26 (52)
Mutation status	
KRAS/*BRAF* wild type	15 (30)
BRAF mutation	12 (24)
KRAS mutation	17 (34)
KRAS/*BRAF* mutation	1 (2)
Unknown	5 (10)
PD-L1 expression status	
≥1%	3 (6)
<1%	24 (48)
Unknown	23 (46)
LAG-3 expression status	
≥1%	8 (16)
<1%	14 (28)
Unknown	28 (76)
Neutrophil-to-lymphocyte ratio‡	
<3	22 (44)
≥3	28 (56)
Number of prior systemic regimens§,¶	
0	4 (8)
1	11 (22)
2	16 (32)
3	15 (30)
≥4	4 (8)
Regimen setting	
Adjuvant	25 (50)
Metastatic disease	40 (80)
Type of prior systemic therapy received	
5-FU (fluorouracil, capecitabine)	46 (92)
Oxaliplatin	43 (86)
Irinotecan	31 (62)
VEGF inhibitors (bevacizumab, aflibercept, ramucirumab)	27 (54)
EGFR inhibitors (cetuximab, panitumumab)	14 (28)
Regorafenib	5 (10)
Other chemotherapy	2 (4)
Primary reason for discontinuation of last prior systemic therapy	
Disease progression	34 (68)
Drug toxicity	9 (18)
Completed treatment	2 (4)
Other**	1 (2)

Data are n (%) unless otherwise noted.
*All patients had stage IV disease at study entry.
†Lynch syndrome designation was based on the clinical records of patients at sites in countries where this reporting was permitted.
‡Neutrophil-to-lymphocyte ratio was derived by dividing absolute neutrophil count by absolute lymphocyte count.
§Some patients may have been treated with more than one type of therapy.
¶All four patients who received 0 prior systemic treatments for metastatic disease received adjuvant therapy and progressed within 6 months.
**Investigator discretion.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LAG-3, lymphocyte-activation gene 3; NIVO, nivolumab; NOS, not otherwise specified; PD-L1, programmed death ligand 1; RELA, relatlimab; VEGF, vascular endothelial growth factor.

At the data cut-off date, 30 (60%) of 50 treated patients experienced disease progression, including 17 (34%) whose disease progressed after achieving disease control (stable disease, n=7; partial response, n=10). No patients with CR subsequently progressed during follow-up. Clinical characteristics for the 17 patients with progression

Table 2 Response, disease control rate, and durability of response

	NIVO+RELA (n=50)	
	Investigator assessed	**BICR assessed**
Objective response rate, n (%)	25 (50)	24 (48)
95% CI	35.5 to 64.5	33.7 to 62.6
Best overall response, n (%)		
Complete response	5 (10)	8 (16)
Partial response	20 (40)	16 (32)
Stable disease	12 (24)	11 (22)
Progressive disease	13 (26)	14 (28)
Unable to determine	0	1 (2)
Disease control rate,* n (%)	35 (70)	32 (64)
95% CI	55.4 to 82.1	49.2 to 77.1
Median time to response (range),† months	2.8 (1.3–33.1)	2.7 (1.4–19.4)
Median duration of response (95% CI),† months	42.7 (27.7 to not estimable)	Not reached (21.9 to not estimable)

*CR+PR+SD (for at least 12 weeks); 95% CI based on the Clopper-Pearson method.
†Evaluated in patients who had an objective response.
BICR, blinded independent central review; CR, complete response; NIVO, nivolumab; PR, partial response; RELA, relatlimab; SD, stable disease.

following disease control are shown in online supplemental table 2.

The median PFS was 27.5 (95% CI 5.3 to 43.7) months, and PFS rates at 12, 24, and 36 months were 58.0%, 51.4%, and 38.0%, respectively (figure 2A). Median OS was not reached (95% CI 17.2 months to not estimable), and OS rates at 12, 24, and 36 months were 70%, 58%, and 56%, respectively (figure 2B).

Twenty-two patients had a quantifiable LAG-3 expression status; 14 (64%) had expression <1% and 8 (36%) had expression ≥1%. ORR per investigator in patients whose tumors had LAG-3 expression ≥1% was 63% (95% CI 24.5% to 91.5%) and in patients with LAG-3 expression <1% was 36% (95% CI 12.8% to 64.9%). Twenty-three patients had a quantifiable tumor cell PD-L1 expression status; 24 (89%) had expression <1%, and 3 (11%) had expression ≥1%. ORR per investigator in patients with tumor cell PD-L1 expression ≥1% was 33% (95% CI 0.8% to 90.6%) and in patients with tumor cell PD-L1 expression <1% was 63% (95% CI 40.6% to 81.2%) (online supplemental table 3). PFS and OS based on LAG-3 or PD-L1 expression were difficult to interpret due to the small sample size (online supplemental figures 1 and 2).

Safety

Any-grade TRAEs were reported in 70% of patients and grade 3 or 4 TRAEs were reported in 14% of patients (table 3). There were no grade 5 events. The most common TRAEs of any grade were diarrhea (24% of patients), asthenia (16% of patients), and hypothyroidism (12% of patients). Four (8%) patients discontinued treatment due to TRAEs of any grade, which included ocular myasthenia, colitis, arthralgia, and encephalopathy.

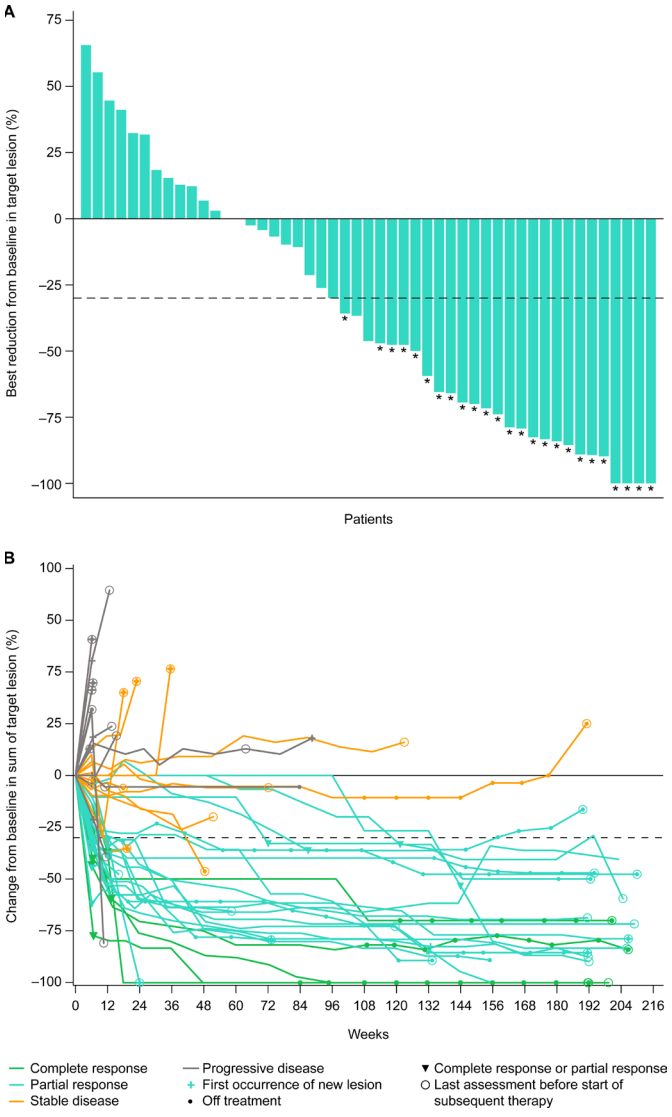

Figure 1 Antitumor activity. (A) Waterfall plot depicting change from baseline in evaluable patients per investigator. Patients with target lesion at baseline and at least one on-treatment tumor assessment. Best reduction is maximum reduction in sum of diameters of target lesions. Horizontal reference line indicates the 30% reduction consistent with a RECIST V.1.1 response. Asterisk symbol represents responders. (B) Tumor burden change over time per investigator. Patients with target lesion at baseline and at least one postbaseline tumor assessment are included. Assessments are per investigator using RECIST V.1.1, confirmation of response required. Horizontal reference line indicates the 30% reduction consistent with a RECIST V.1.1 response. CR, complete response; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability-high; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UTD, up to date.

Treatment-related serious adverse events occurred in 3 (6%) patients (ocular myasthenia, colitis, and encephalopathy). Of the 22 deaths during the study, 18 were due to disease progression, 1 to sudden death, 1 to myocardial infarction, 1 to sepsis, and 1 for unknown reasons.

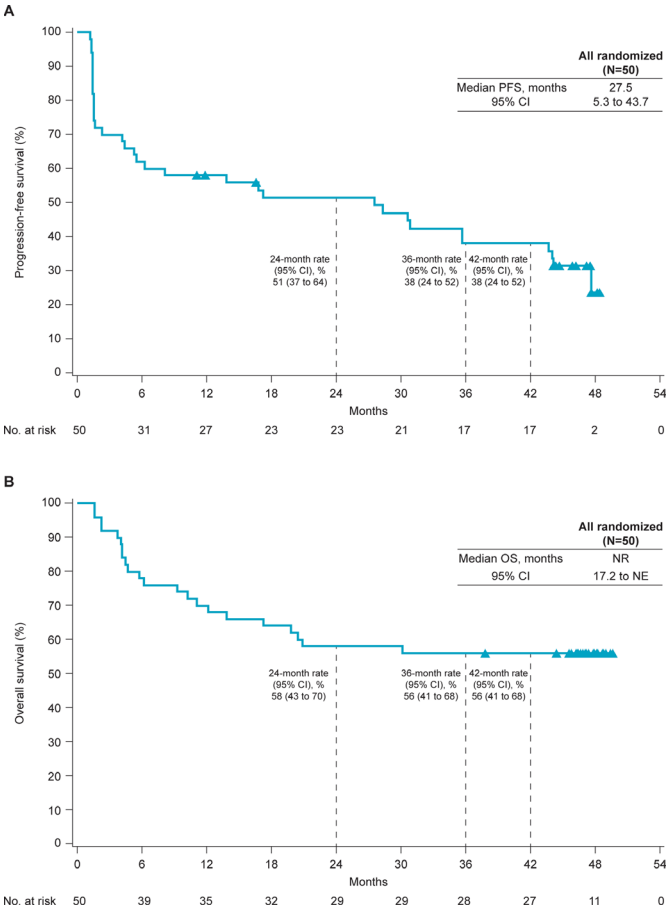

Figure 2 Kaplan-Meier plot of survival. (A) Progression-free survival per investigator. (B) Overall survival in all patients. Symbols represent censored observations.

Table 3 Summary of treatment-related adverse events in all treated patients

	NIVO+RELA (n=50)*	
	Any grade	**Grade 3–4†**
All TRAEs	35 (70)	7 (14)
Serious TRAEs	3 (6)	1 (2)
TRAEs leading to discontinuation‡	4 (8)	2 (4)
Events in 10% or more of treated patients		
Diarrhea	12 (24)	0 (0)
Asthenia	8 (16)	0 (0)
Hypothyroidism	6 (12)	0 (0)
Pruritus	5 (10)	0 (0)
Rash	5 (10)	0 (0)
Arthralgia	5 (10)	1 (2)

Data are n (%).
*Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of study therapy according to the Common Terminology Criteria for Adverse Events, V.4.0, and Medical Dictionary for Regulatory Activities, V.24.1.
†There were no grade 5 events.
‡Reasons for discontinuation were ocular myasthenia (grade 3), colitis, arthralgia (grade 3), and encephalopathy, each in one patient.
NIVO, nivolumab; RELA, relatlimab; TRAE, treatment-related adverse event.

Table 4 Summary of treatment-related adverse events with potential immunological etiology

	NIVO+RELA (n=50)*	
	Any grade	**Grade 3–4**
Endocrine	11 (22)	0 (0)
Gastrointestinal	12 (24)	0 (0)
Hepatic	2 (4)	1 (2)
Pulmonary	0 (0)	0 (0)
Renal	0 (0)	0 (0)
Skin	11 (22)	0 (0)

Data are n (%).
*Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of study therapy. Common Terminology Criteria for Adverse Events, V.4.0, and Medical Dictionary for Regulatory Activities, V.24.1.
NIVO, nivolumab; RELA, relatlimab.

No deaths were related to study drug toxicity. Of the any-grade TRAEs with potential immunological etiology, 11 (22%) patients had endocrine events, 12 (24%) patients had gastrointestinal events, 11 (22%) patients had dermatological events, and 2 (4%) patients had hepatic events (table 4). There was one grade 3 or 4 adverse event with potential immunological etiology, which was hepatic.

DISCUSSION

Nivolumab plus relatlimab demonstrated durable responses and survival benefit with a well-tolerated safety profile at 47.2-month median follow-up in previously treated patients with MSI-H/dMMR metastatic CRC. Treatment with nivolumab plus relatlimab resulted in an investigator-assessed ORR of 50% that was characterized by long durability, with a median DOR of 42.7 months. The investigator-assessed PD rate was 26%. Median PFS was 27.5 months, with a 2-year PFS rate of 51%. Median OS was not reached, with a 2-year OS rate of 58%.

ORR and DCR were broadly similar across baseline demographics and disease characteristics such as age, sex, and ECOG performance status. ORR was also similar between patients with neutrophil-to-lymphocyte ratio of ≥3 and <3 (cut-off based on previous studies[16 17]). Conversely, there were certain subgroups where differences in ORR were observed. ORR in patients with *KRAS* mutations was numerically lower than in those with *BRAF* mutations and with *KRAS/BRAF* wild-type tumors, although sample sizes were small; likewise, patients with liver metastases had a numerically lower ORR than those without, similar to results of nivolumab-based therapies in other indications, although CIs overlapped, limiting interpretation.[18] Patients whose tumors expressed LAG-3 ≥1% had numerically higher ORR than those with LAG-3 expression <1%, although CIs overlapped, and the sample size was small for patients with LAG-3 expression ≥1%. CIs for ORR in patients with tumor cell PD-L1 expression ≥1% and <1% also overlapped, although there were only three patients who had tumor cell PD-L1 expression ≥1%.

Nivolumab in combination with relatlimab has already been demonstrated to provide added benefit in comparison to nivolumab monotherapy in patients with untreated melanoma.[10] The CheckMate 142 study was not designed for cross-cohort comparisons and cannot be used for cross-trial comparison as there may be differences in patient baseline demographics and disease characteristics. In an indirect comparison, investigator-assessed ORR with nivolumab 240 mg plus relatlimab 160 mg every 2 weeks was numerically higher than rates observed with anti-PD-1 monotherapies in patients with MSI-H/dMMR metastatic CRC (pembrolizumab ORR 33%[19]; nivolumab ORR 31%[7]). The investigator-assessed PFS was also numerically higher with nivolumab plus relatlimab than nivolumab monotherapy[7] in previously treated patients with MSI-H/dMMR metastatic CRC but lower than nivolumab plus ipilimumab.[6]

Nivolumab plus relatlimab was well tolerated, with no new safety signals observed. TRAEs of any grade were reported in 70% of patients, with grade 3–4 TRAEs reported in 14% of patients. Although the frequency of any-grade TRAEs was similar to nivolumab monotherapy, pembrolizumab monotherapy, and nivolumab plus ipilimumab, in which 70%, 80%, and 73% of patients experienced a TRAE, respectively, grade 3–4 TRAEs in this trial were less frequent compared with those regimens, reported in 20%, 22%, and 32% of patients, respectively.[7 19 20] Treatment discontinuation occurred due to all-cause adverse events in 16% of patients and TRAEs in 10% of patients.

A limitation of this study was the small sample size. Additionally, the lack of a comparator group and non-randomized study design make it difficult to compare the efficacy of nivolumab plus relatlimab with other treatments.

In conclusion, nivolumab plus relatlimab demonstrated durable clinical benefit and was well tolerated in patients with MSI-H/dMMR metastatic CRC. These findings further reflect the clinical benefit of dual checkpoint inhibition as a treatment strategy for MSI-H/dMMR metastatic CRC. The Neoadjuvant Immune Checkpoint Inhibition and Novel IO Combinations in Early-Stage Colon Cancer (NICHE-3) study is currently assessing neoadjuvant nivolumab plus relatlimab for the treatment of locally advanced dMMR colon cancer.[21]

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Contributors MJO conceptualized and designed the study in collaboration with Bristol Myers Squibb, and acts is responsible for the research as guarantor. FG, MA, MW, MLLM, GL, PG-A, AGH, ACG, EVC, SMMcC, ML, and SL recruited and/or treated patients and gathered clinical data on efficacy and safety. SMMcC, BH, and ML analyzed the clinical data. All authors interpreted the data, had access to all the data in the study, participated in developing or reviewing the manuscript, and provided final approval to submit the manuscript for publication.

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Ethics approval The protocol was approved by the institutional review board or independent ethics committee at each site. The study was conducted according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the study protocol. All patients provided written informed consent per Declaration of Helsinki principles. A complete site and investigator list is provided in the online supplement file of this article. Additionally, institution details for each site are available at the CheckMate 142 clinicaltrials.gov trial page: https://clinicaltrials.gov/study/NCT02060188#contacts-and-locations

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