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ORIGINAL REPORT

# Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

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## ABSTRACT

### Purpose

Nivolumab provides clinical benefit (objective response rate [ORR], 31%; 95% CI, 20.8 to 42.9; disease control rate, 69%; 12-month overall survival [OS], 73%) in previously treated patients with DNA mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) metastatic colorectal cancer (mCRC); nivolumab plus ipilimumab may improve these outcomes. Efficacy and safety results for the nivolumab plus ipilimumab cohort of CheckMate-142, the largest single-study report of an immunotherapy combination in dMMR/MSI-H mCRC, are reported.

### Patients and Methods

Patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks. Primary end point was investigator-assessed ORR.

### Results

Of 119 patients, 76% had received ≥ two prior systemic therapies. At median follow-up of 13.4 months, investigator-assessed ORR was 55% (95% CI, 45.2 to 63.8), and disease control rate for ≥ 12 weeks was 80%. Median duration of response was not reached; most responses (94%) were ongoing at data cutoff. Progression-free survival rates were 76% (9 months) and 71% (12 months); respective OS rates were 87% and 85%. Statistically significant and clinically meaningful improvements were observed in patient-reported outcomes, including functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related adverse events (AEs) occurred in 32% of patients and were manageable. Patients (13%) who discontinued treatment because of study drug-related AEs had an ORR (63%) consistent with that of the overall population.

### Conclusion

Nivolumab plus ipilimumab demonstrated high response rates, encouraging progression-free survival and OS at 12 months, manageable safety, and meaningful improvements in key patient-reported outcomes. Indirect comparisons suggest combination therapy provides improved efficacy relative to anti–programmed death-1 monotherapy and has a favorable benefit-risk profile. Nivolumab plus ipilimumab provides a promising new treatment option for patients with dMMR/MSI-H mCRC.

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## INTRODUCTION

Colorectal cancer (CRC) remains a leading cause of cancer-related death worldwide, with a 5-year survival rate of 14% in patients with metastatic CRC (mCRC).[1,2] Patients with DNA mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) mCRC (approximately 4% of patients)[3-5] are a distinct biomarker-defined population that benefits less from conventional chemotherapy; evolving data show poorer outcomes in key clinical parameters in these patients compared with those with MMR-proficient/microsatellite stable mCRC.[4-9]

Evidence from recent studies of anti–programmed death-1 (PD-1) checkpoint inhibitors has demonstrated that dMMR/MSI-H status is a biomarker predictive of response to

ASSOCIATED CONTENT

Appendix
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anti–PD-1 therapy[3,10-13]; thus, universal dMMR/MSI-H testing is recommended for patients with mCRC.[14-16] In the monotherapy cohort of CheckMate-142, nivolumab, the fully human immunoglobulin G4 monoclonal antibody inhibitor of PD-1, provided durable responses (investigator-assessed objective response rate [ORR], 31%; median duration of response [DOR], not yet reached with median follow-up of 12.0 months), sustained disease control (disease control rate [DCR] ≥ 12 weeks, 69%), progression-free survival (PFS) rates of 54% (9 months) and 50% (12 months), and overall survival (OS) rates of 78% (9 months) and 73% (12 months) in previously treated patients with dMMR/MSI-H mCRC.[11] Nivolumab is approved in the United States for the treatment of adult and pediatric (age ≥ 12 years) patients with dMMR/MSI-H mCRC who had disease progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[17] Ipilimumab is a fully human immunoglobulin G1 monoclonal antibody that targets the cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) checkpoint receptor.[18] In preclinical and clinical settings, the combination of nivolumab plus ipilimumab has provided enhanced activity over nivolumab monotherapy,[19-21] and the combination is approved for the treatment of metastatic melanoma using specific dosing (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for four doses followed by nivolumab 3 mg/kg once every 2 weeks).[17]

Presented here are efficacy, safety, biomarker, and patient-reported outcome (PRO) analyses from the complete population of patients in the nivolumab plus ipilimumab cohort of CheckMate-142, which, to our knowledge, is the largest single-study report of combination immunotherapies in patients with dMMR/MSI-H mCRC.

## PATIENTS AND METHODS

### Study Design and Participants

CheckMate-142 is an ongoing, multicenter, open-label, phase II trial. Patients in the nivolumab plus ipilimumab cohort were treated at 28 sites in eight countries. Eligible patients were age ≥ 18 years and had histologically confirmed recurrent CRC or mCRC assessed as dMMR and/or MSI-H per local guidelines. Patients had disease progression on or after or were intolerant of ≥ one prior systemic treatment that included a fluoropyrimidine and oxaliplatin or irinotecan; however, patients who refused chemotherapy were eligible. Any chemotherapy, curative-intent radiotherapy, or biologic or investigational therapy must have been completed > 28 days before treatment initiation; focal palliative radiotherapy must have been completed ≥ 2 weeks before starting treatment. Eligible patients had an Eastern Cooperative Oncology Group performance status of ≤ 1 and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).[22,23] Patients were excluded for active, known, or suspected autoimmune disease; conditions requiring corticosteroids (prednisone equivalents > 10 mg per day) or other immunosuppressive medication ≤ 14 days before starting treatment; other serious or uncontrolled medical disorders; active brain or leptomeningeal metastases; or prior malignancy within the previous 3 years except for cured select localized cancers. Additional exclusion criteria included prior treatment with an anti–PD-1, anti–programmed death-ligand 1/2 (PD-L1/PD-L2), anti–CTLA-4, or other agent targeting T-cell costimulation or immune checkpoint pathways.

Patients received nivolumab 3 mg/kg (60-minute intravenous [IV] infusion) and ipilimumab 1 mg/kg (90-minute IV infusion) once every 3 weeks for four doses and then nivolumab 3 mg/kg IV once every 2 weeks (Appendix Fig A1, online only) until disease progression, discontinuation because of toxicity, death, withdrawal of consent, or study end. Dose modifications were not permitted. Dose interruptions for treatment-related adverse events (TRAEs) were allowed (Appendix, online only). Treatment beyond initial progression was permitted if the patient tolerated and benefited from study treatment per investigator assessment.

Study protocol and amendments were approved by the institutional review board or independent ethics committee at each participating center. CheckMate-142 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and patients provided written informed consent before enrollment.

### Outcomes

The primary end point was investigator-assessed ORR (patients with best response of complete response [CR] or partial response [PR] divided by the number of treated patients) per RECIST (version 1.1). Secondary end points included ORR per blinded independent central review (BICR) and DCR (patients with best response of CR, PR, or stable disease for ≥ 12 weeks divided by the number of treated patients). Other end points included safety and tolerability, PFS (time from first dose to first documented progression or death resulting from any cause, whichever occurred first) per investigator assessment and BICR, OS (time from the first dose to death), association between biomarker expression and efficacy, and changes from baseline in PROs.

### Assessments

Tumors were assessed using computed tomography or magnetic resonance imaging per RECIST (version 1.1) ≤ 28 days before the first dose (baseline), followed by every 6 weeks for 24 weeks and every 12 weeks thereafter until the time of disease progression or discontinuation. All responses had to be confirmed by another scan ≥ 4 weeks later. Safety was assessed per Common Terminology Criteria for Adverse Events (version 4.0) continuously throughout treatment and for ≥ 100 days after treatment discontinuation.[24] Patients were then observed for survival every 3 months. PRO analyses were performed before the first dose of study treatment and every 6 weeks thereafter using the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and three-level five-dimensional EuroQol instrument (EQ-5D).[25,26] EORTC QLQ-C30 assesses symptoms, functioning, and quality of life (QOL) using scales from 0 to 100, with higher scores indicating better functioning and QOL or worse symptoms. For each scale, a ≥ 10-point change from baseline was regarded as clinically meaningful.[27] EQ-5D assesses problems (none, some, or extreme) in five health dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). EQ-5D also has a visual analog scale, which allows patients to rate their health; scores range from 0 to 100 (higher values indicate better perceived health), and changes from baseline of ≥ 7 points were deemed clinically meaningful.[28]

Tumor MMR and/or MSI status was evaluated before screening per local guidelines using immunohistochemistry and/or polymerase chain reaction (PCR). Samples with loss of expression of ≥ one mismatch repair protein per immunohistochemistry were identified as dMMR. Tumor samples were identified as MSI-H using PCR if instability was found in ≥ two markers when five loci were tested, in ≥ three of four markers when one PCR failed, or ≥ 30% of markers when > five loci were tested. Additional MMR/MSI testing criteria are provided in the Appendix. Tumor PD-L1 expression (≥ 1% or < 1%) was determined using archival or pretreatment biopsy tissue with the Dako 28-8 pharmDx immunohistochemistry assay (Dako North America, Carpinteria, CA). Positive PD-L1 staining was defined as complete circumferential or partial linear plasma membrane staining. *BRAF*/*KRAS* mutation status was determined at the time of screening per local guidelines. Lynch syndrome status was characterized as positive or negative by investigators based on medical history collected from clinical records; genetic testing for Lynch syndrome was not mandated in the protocol.

  

### Statistical Analyses

Patients were enrolled using a Simon two-stage study design. Per the protocol, only patients confirmed as MSI-H by a central laboratory were used to determine the number of responders necessary to progress from stage one to stage two. If ≤ six of the first 19 patients confirmed as MSI-H by a central laboratory had an objective response (CR or PR) in stage one, enrollment would end; however, if ≥ seven of these patients had a response in stage one, additional patients would be enrolled in stage two. Efficacy and safety were analyzed in all patients (dMMR/MSI-H per local laboratory) who received ≥ one dose of study treatment. Response-evaluable patients had baseline and ≥ one on-study tumor assessment. The 95% CI for ORR was estimated using the Clopper and Pearson method. The Kaplan-Meier product-limit method was used to determine medians for DOR, PFS, and OS; corresponding 95% CIs were calculated based on log-log transformation. Descriptive statistics were used to characterize patient characteristics, PRO analyses, and safety. Missing PRO data were treated as indicated by the scoring manuals.[25] For inferential PRO analyses, changes in mean scores over time were analyzed using linear mixed models adjusted for baseline score.[29] Statistical analyses were performed using SAS software (version 9.02; SAS Institute, Cary, NC).

## RESULTS

### Baseline Characteristics and Patient Disposition

Patients were enrolled in the nivolumab plus ipilimumab combination cohort of CheckMate-142 from May 2015 through September 2016. Twenty-seven patients were enrolled in stage one, of whom 19 were confirmed as MSI-H per central laboratory. A sufficient number of confirmed investigator-assessed responses were reported in these 19 patients, and additional patients (n = 92) were enrolled in stage two per the protocol. At data cutoff (July 2017), 119 patients with dMMR/MSI-H mCRC were treated in stages one and two. Median duration of follow-up (potential time on study from first dose to data cutoff) was 13.4 months (range, 9 to 25 months). Most patients (68%) were age < 65 years, and 76% had received ≥ two prior lines of systemic therapy (Table 1); 69% of patients received prior chemotherapy with oxaliplatin, irinotecan, and a fluoropyrimidine. *BRAF* and *KRAS* mutations were identified in 24% and 37% of patients, respectively.

Most patients (n = 75; 63%) were still receiving treatment at data cutoff. Among patients (n = 44) who discontinued therapy, the primary reasons were disease progression (n = 23; 19%), AEs related to study drug (n = 16; 13%), and AEs unrelated to study drug (n = 2; 2%); additional reasons included loss to follow-up, death, and patient did not present for restaging (each n = 1; 1%). A median of 24 doses of nivolumab (range, one to 55 doses) and four of ipilimumab (range, one to four doses) were received; 76% and 85% of patients had a relative dose intensity ≥ 90% for nivolumab and ipilimumab, respectively.

**Table 1.** Baseline Patient Demographic and Clinical Characteristics (N = 119)

| Characteristic | No. (%) |
|---|---|
| Age, years | |
| Median | 58.0 |
| Range | 21-88 |
| < 65 | 81 (68) |
| Male sex | 70 (59) |
| Race | |
| White | 109 (92) |
| Black | 2 (2) |
| Asian | 3 (3) |
| Other | 5 (4) |
| ECOG performance status | |
| 0 | 54 (45) |
| 1 | 65 (55) |
| Disease stage at diagnosis | |
| II | 14 (12) |
| III | 52 (44) |
| IV | 53 (45) |
| Primary tumor location | |
| Right colon | 65 (55) |
| Left and sigmoid colon | 30 (25) |
| Transverse colon | 15 (13) |
| Rectum | 6 (5) |
| Colon, NOS | 3 (3) |
| No. of prior systemic treatments | |
| 0 | 1 (1) |
| 1 | 27 (23) |
| 2 | 43 (36) |
| ≥ 3 | 48 (40) |
| Prior therapies received | |
| Fluoropyrimidines (5-fluorouracil or capecitabine) | 118 (99) |
| Oxaliplatin | 111 (93) |
| Irinotecan | 87 (73) |
| VEGF inhibitors* | 68 (57) |
| EGFR inhibitors† | 35 (29) |
| Regorafenib | 11 (9) |
| Trifluridine/tipiracil | 2 (2) |
| Other experimental drugs | 3 (3) |
| Other chemotherapy | 8 (7) |
| Prior radiotherapy | 20 (17) |
| Mutation status | |
| *BRAF*/*KRAS* wild type | 31 (26) |
| *BRAF* mutation | 29 (24) |
| *KRAS* mutation | 44 (37) |
| Unknown | 15 (13) |
| Tumor PD-L1 expression quantifiable at baseline | |
| ≥ 1% | 26 (22) |
| < 1% | 65 (55) |
| Unknown | 28 (24) |
| Clinical history of Lynch syndrome‡ | |
| Yes | 35 (29) |
| No | 31 (26) |
| Unknown | 53 (45) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.
*VEGF inhibitors included bevacizumab, aflibercept, and ramucirumab.
†EGFR inhibitors included cetuximab and panitumumab.
‡Lynch syndrome designation was based on the clinical records of patients at sites in countries where this reporting was permitted (excluded Italy).

### Efficacy

Of 119 patients, 54.6% (95% CI, 45.2 to 63.8) achieved an objective response per investigator assessment, including 3.4% with CRs and 51.3% with PRs (Table 2). Disease control for ≥ 12 weeks was achieved in 80% (95% CI, 71.5 to 86.6) of patients. Outcomes per investigator assessment were 91% concordant with BICR results. The ORR per BICR was 49% (95% CI, 39.5 to 58.1), including 4% of patients with CRs and 45% with PRs; DCR for ≥ 12 weeks was observed in 79% (95% CI, 70.6 to 85.9) of patients (Appendix Table A1, online only). Additional efficacy outcomes per BICR are presented in Appendix Figures A2 and A3 (online only). Investigator-assessed responses were observed irrespective of tumor *BRAF* or *KRAS* mutation status, tumor PD-L1 expression,

**Table 2.** ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

| Response | No. (%) | 95% CI |
|---|---|---|
| ORR | 65 (55) | 45.2 to 63.8 |
| Best overall response | | |
| Complete response | 4 (3) | |
| Partial response | 61 (51) | |
| Stable disease | 37 (31) | |
| Progressive disease | 14 (12) | |
| Not determined | 3 (3) | |
| Disease control for ≥ 12 weeks | 95 (80) | 71.5 to 86.6 |

Abbreviations: DCR, disease control rate; ORR, objective response rate.

or clinical history of Lynch syndrome (Appendix Table A2, online only). The ORR and DCR in patients with a *BRAF* mutation were 55% and 79%, respectively.

Among evaluable patients (n = 115), 78% had a reduction in tumor burden from baseline per investigator assessment (Fig 1A). Median time to response was 2.8 months (range, 1 to 14 months). Responses were durable, with 94% of responders having ongoing responses at data cutoff, and 83% had responses lasting ≥ 6 months (Fig 1B). The median DOR was not reached (95% CI, not estimable). Median PFS per investigator assessment was not reached after 33 PFS events; 9- and 12-month PFS rates were 76% (95% CI, 67.0 to 82.7) and 71% (95% CI, 61.4 to 78.7), respectively (Fig 2A). The median OS was not reached (95% CI, not estimable), and the 9- and 12-month OS rates were 87% (95% CI, 80.0 to 92.2) and 85% (95% CI, 77.0 to 90.2), respectively (Fig 2B).

### *PROs*

PRO questionnaire completion rates ranged from 80% to 100% through week 91, after which < 10 patients were eligible for on-treatment assessment (Appendix Table A3, online only). While on study, most patients (≥ 60%) maintained functioning and global health status/QOL without worsening of symptoms per EORTC QLQ-C30 (Appendix Table A4, online only). After adjustment for baseline score, statistically significant and clinically meaningful improvements (mean change from baseline ≥ 10 points) were reported in key PROs, including symptoms, functioning, and global health status/QOL by week 13 or earlier, and these improvements were largely maintained in patients receiving treatment (Appendix Fig A4A to Fig A4H, online only). Although not demonstrating a mean change from baseline ≥ 10 points at most on-treatment time points, statistically significant improvements were reported for nausea or vomiting, dyspnea, diarrhea, cognitive functioning, and physical functioning (Appendix Fig A4I to Fig A4M). Per EQ-5D, 6% (self-care) to 63% (pain) of patients reported health problems at baseline; notable (> 10%) reductions in patients reporting health problems were observed as early as week 13 for all dimensions (Appendix Table A5, online only). After adjustment for baseline score, statistically significant and clinically meaningful improvements in the visual analog scale of EQ-5D were observed by week 19, and these improvements were maintained in patients continuing treatment (Appendix Fig A5, online only).

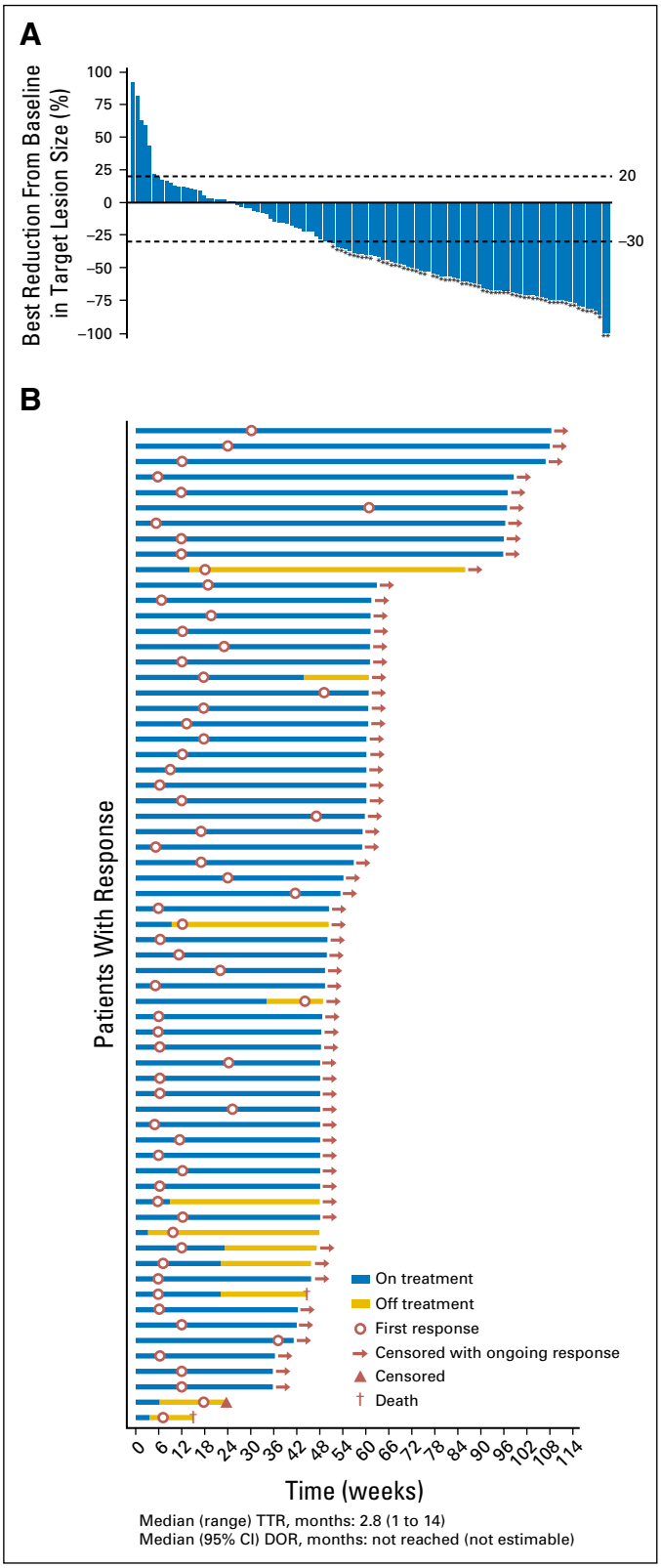


**Fig 1.** (A) Waterfall plot depicting the best change from baseline in target lesion size per investigator assessment. (B) Characteristics of patients with a response per investigator assessment. Bars indicate the duration of progression-free survival (PFS). DOR, duration of response; TTR, time to response. (*) Patient with confirmed response.

  

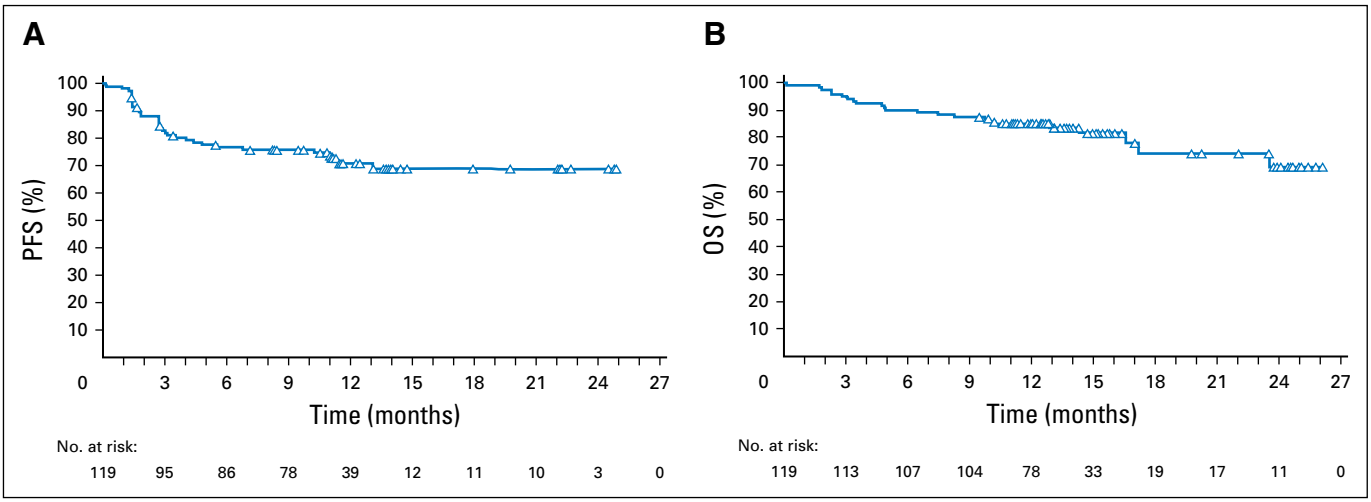


**Fig 2.** Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in all patients.

### *Safety*

Any-grade TRAEs were reported in 73% of patients, with the most common being diarrhea (22%), fatigue (18%), and pruritus (17%; Table 3). Thirty-two percent of patients experienced a grade 3 (27%) or 4 (5%) TRAE, with elevated AST and/or ALT (11%), elevated lipase (4%), anemia (3%), and colitis (3%) occurring in > two patients. Serious TRAEs were reported in 23% (any grade) and 20% (grade 3 to 4) of patients. TRAEs led to discontinuation in 13% (any grade) and 10% (grade 3 to 4) of patients; the only events leading to discontinuation in > one patient were autoimmune hepatitis and acute kidney injury (2% each). Among patients (n = 16) whose primary reason for discontinuing treatment was an AE related to study drug, the ORR was 63%, DCR for ≥ 12 weeks was 81%, and median DOR was not reached, consistent with efficacy results in the overall population. Any-grade select TRAEs (events with potential immunologic etiology) analyzed by organ category occurred in 29% (skin), 25% (endocrine), 23% (GI), 19% (hepatic), and 5% (pulmonary, renal) of patients; the median time to onset ranged from 5.2 to 12.6 weeks (Appendix Table A6, online only). Some patients (range, 22% to 56%) received immune-modulating medication to manage their select TRAEs. With the use of protocol-specified management algorithms, select TRAEs resolved in most patients (range, 71% to 96%), except for endocrine TRAEs, which resolved in 40% of patients. The median time to resolution of nonendocrine select TRAEs ranged from 1.5 to 9.0 weeks; the median time to resolution of endocrine TRAEs was not reached. No treatment-related deaths were reported.

**Table 3.** Summary of TRAEs With Nivolumab in Combination With Ipilimumab (N = 119)

| TRAE | No. (%) | | |
|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 |
| Any TRAE | 49 (41) | 32 (27) | 6 (5) |
| Diarrhea* | 24 (20) | 2 (2) | 0 |
| Fatigue* | 19 (16) | 2 (2) | 0 |
| Pruritus* | 18 (15) | 2 (2) | 0 |
| Pyrexia* | 18 (15) | 0 | 0 |
| Increased AST* | 8 (7) | 9 (8) | 0 |
| Hypothyroidism* | 15 (13) | 1 (1) | 0 |
| Nausea* | 14 (12) | 1 (1) | 0 |
| Increased ALT* | 6 (5) | 8 (7) | 0 |
| Rash* | 11 (9) | 2 (2) | 0 |
| Hyperthyroidism* | 13 (11) | 0 | 0 |

NOTE. TRAEs were assessed during treatment and for up to 30 days after the last dose of study treatment according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).
Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
*Reported in > 10% of patients.

## DISCUSSION

Although the development of PD-1 inhibitors provided an important advance in the treatment of patients with dMMR/MSI-H mCRC,[3,10-12] an opportunity remains to explore rational combinations to further improve these results. Nivolumab and ipilimumab act synergistically to promote T-cell antitumor activity through complementary mechanisms of action.[17,18,20,21] Results of the nivolumab plus ipilimumab cohort reported here demonstrate a manageable safety profile and robust clinical activity, with an ORR of 55%, DCR for ≥ 12 weeks of 80%, PFS rates of 76% (9 months) and 71% (12 months), and OS rates of 87% (9 months) and 85% (12 months); responses in patients with dMMR/MSI-H mCRC were observed irrespective of tumor PD-L1 expression, *BRAF*/*KRAS* mutation status, or clinical history of Lynch syndrome. The favorable benefit-risk profile seen in this cohort suggests a role for combination checkpoint inhibitor therapy in the treatment of patients with dMMR/MSI-H mCRC.

In CheckMate-142, monotherapy and combination therapy cohorts were neither randomly assigned nor designed for formal comparison; however, considering the limitations of an indirect comparison, nivolumab plus ipilimumab provided a numerically higher response rate (55%; 95% CI, 45 to 64) relative to the response rate (31%; 95% CI, 21 to 43) with nivolumab monotherapy in a similar population of patients (n = 74) with a comparable median follow-up time.[11] Likewise, with the limitations of cross-trial comparisons in mind, the response rate with nivolumab plus ipilimumab in CheckMate-142 was numerically higher relative to

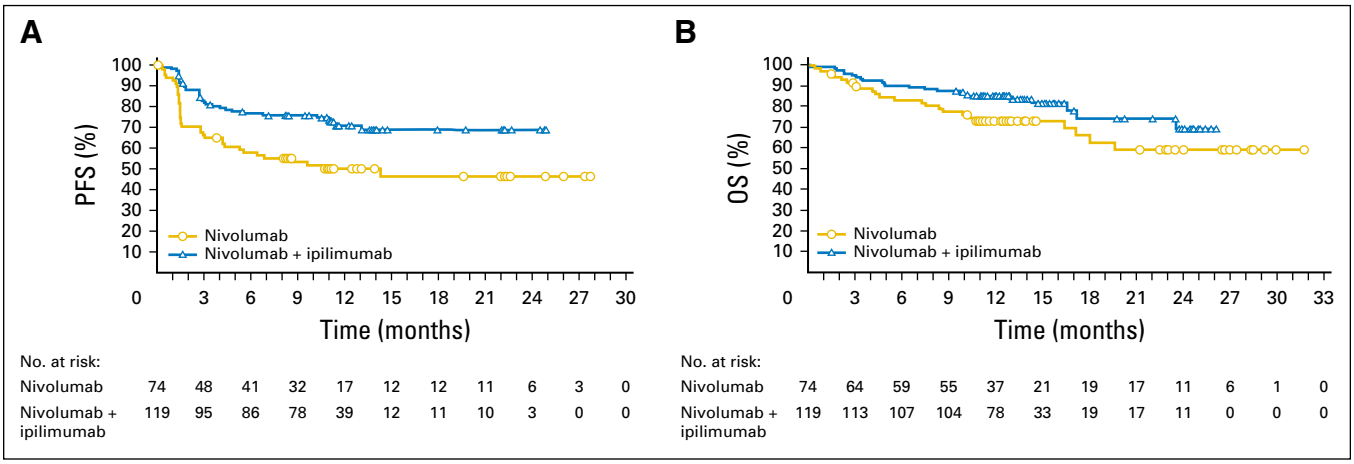


**Fig 3.** Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in patients treated with nivolumab plus ipilimumab in the analyses presented herein or nivolumab in the monotherapy cohort of CheckMate-142 from an analysis that had a similar median follow-up (potential time on study from first dose to data cutoff: 13.4 months).[11]

the rate (28%; 95% CI, 17 to 41) reported with pembrolizumab monotherapy in previously treated patients (n = 61) with MSI-H mCRC in KEYNOTE-164, of whom 15% had *BRAF* mutations and 90% had received ≥ two prior lines of therapy.[12,13] Although results with pembrolizumab monotherapy in KEYNOTE-016 showed numerically higher response rates (57%; 95% CI, 39 to 73), the limited number of patients (n = 28) and sites (n = 6; United States only) as well as a high rate of Lynch syndrome (54%) may have biased findings in this study.[10,30,31] In an indirect comparison of PFS and OS, estimated 12-month PFS (71%) and OS (85%) rates with nivolumab plus ipilimumab were numerically higher relative to those observed with anti–PD-1 monotherapies (nivolumab [CheckMate-142]: PFS, 50% and OS, 73%; pembrolizumab [KEYNOTE-164]: PFS, 34% and OS, 72%).[11-13] Despite the caveats associated with indirect comparisons, Kaplan-Meier plots of PFS and OS with nivolumab monotherapy and nivolumab plus ipilimumab combination therapy in CheckMate-142 suggest that the addition of ipilimumab may improve the long-term clinical benefit of nivolumab (Fig 3)[11]; additional investigation is warranted.

Nivolumab plus ipilimumab combination therapy has been investigated using different doses and schedules in other tumor types, and the safety profile has been found to be influenced by the ipilimumab dose.[20,21,32] In mCRC, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks was selected based on the safety cohort of CheckMate-142.[33] At this dose, a majority of patients received all four doses of ipilimumab, and the safety profile was manageable. Importantly, the incidence of diarrhea and colitis with combination therapy did not seem elevated in this population compared with that in patients with other solid tumors.[20,21,32] The rate of any-grade and grade 3 to 4 TRAEs was 73% and 32%, respectively, and efficacy was maintained (ORR, 63%; DCR, 81%) in patients who discontinued treatment because of study drug–related AEs.[11] Nonendocrine select TRAEs resolved in most patients (range, 71% to 96%) in a median of 1.5 to 9.0 weeks with the use of protocol-specified management algorithms; endocrine TRAEs resolved in 40% of patients. Of note, the overall rate of any-grade TRAEs in the combination therapy cohort was comparable to that in the nivolumab monotherapy cohort (70%), and the rates of discontinuation because of study drug-related AEs (13% and 7%, respectively) were modest in each cohort.[11] Importantly, patients exhibited statistically significant and clinically meaningful on-treatment improvements with combination therapy in key PROs, including symptoms, functioning, and QOL.

In conclusion, the results presented here demonstrate that nivolumab in combination with ipilimumab provided durable responses, high DCR, encouraging survival rates, manageable safety, and meaningful improvements in key PROs in previously treated patients with dMMR/MSI-H mCRC. Considering the indirect comparisons that suggest numerically higher response rates and an improved long-term clinical benefit with nivolumab plus ipilimumab relative to anti–PD-1 monotherapy, and the favorable benefit-risk profile of combination therapy, nivolumab plus ipilimumab represents a promising new treatment option in these patients. Evaluation of nivolumab plus ipilimumab as a first-line therapy (phase II) in patients with dMMR/MSI-H mCRC is ongoing.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

  

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer**

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## Appendix

### Dose Interruptions for Treatment-Related Adverse Events

Dose interruptions for treatment-related adverse events (TRAEs) were allowed until resolution of these events or for ≤ 6 weeks from the last treatment. Patients could resume treatment at the next scheduled dose after TRAE resolution; however, patients were not to skip administration of nivolumab plus ipilimumab (if toxicity allowed) to ensure that each patient received four doses of combination therapy. Patients with interruptions lasting > 6 weeks were discontinued from the study, except when dosing was interrupted for prolonged steroid tapers to manage TRAEs or for non-TRAEs (required approval).

### Local Laboratory Criteria for Determining Mismatch Repair–Proficient and Microsatellite Instability Status

DNA mismatch repair deficiency determined by immunohistochemistry refers to the loss of expression of ≥ one mismatch repair protein (ie, MLH1, MSH2, MSH6, or PMS2).

Microsatellite instability–high (MSI-H) is most frequently determined by polymerase chain reaction. MSI-H in tumors refers to changes in ≥ two of the five National Cancer Institute–recommended panels of microsatellite markers in tumor tissue. The original Bethesda guidelines proposed a panel of five microsatellite markers for the uniform analysis of MSI in Lynch syndrome (Umar A, et al: J Nat Cancer Inst 96:261-268, 2004). Individual testing sites may use a slightly different panel of markers incorporating alternative mononucleotide and/or dinucleotide markers. Regardless of the panel of markers, samples with instability in ≥ 30% of these markers are defined as MSI-H, whereas those with < 30% unstable markers are designated as MSI-low. Samples with no detectable alterations are microsatellite stable.

### Central Laboratory Criteria for Determining Microsatellite Instability in Combination Stage One

In combination stage one of the two-stage Simon design, a central laboratory was used to confirm the MSI-H status of tumor tissue collected at baseline by polymerase chain reaction using modified Bethesda criteria. This panel included two mononucleotide (BAT-25 and BAT-26) and three dinucleotide (D5S346, D2S123, and D17S250) repeats (Umar A, et al: J Nat Cancer Inst 96:261-268, 2004). Samples with instability in ≥ two of these markers were defined as MSI-H, whereas those with one unstable marker were designated as MSI-low. Samples with no detectable alterations were identified as microsatellite stable.

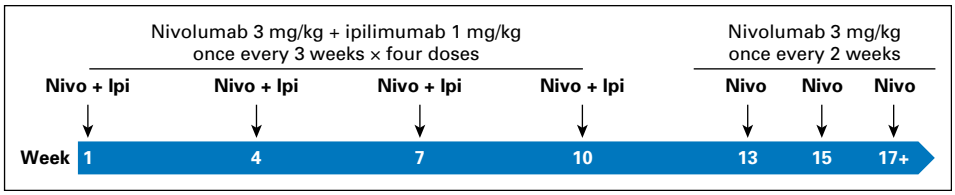


**Fig A1.** Nivolumab (Nivo) plus ipilimumab (Ipi) dosing schedule in CheckMate-142.

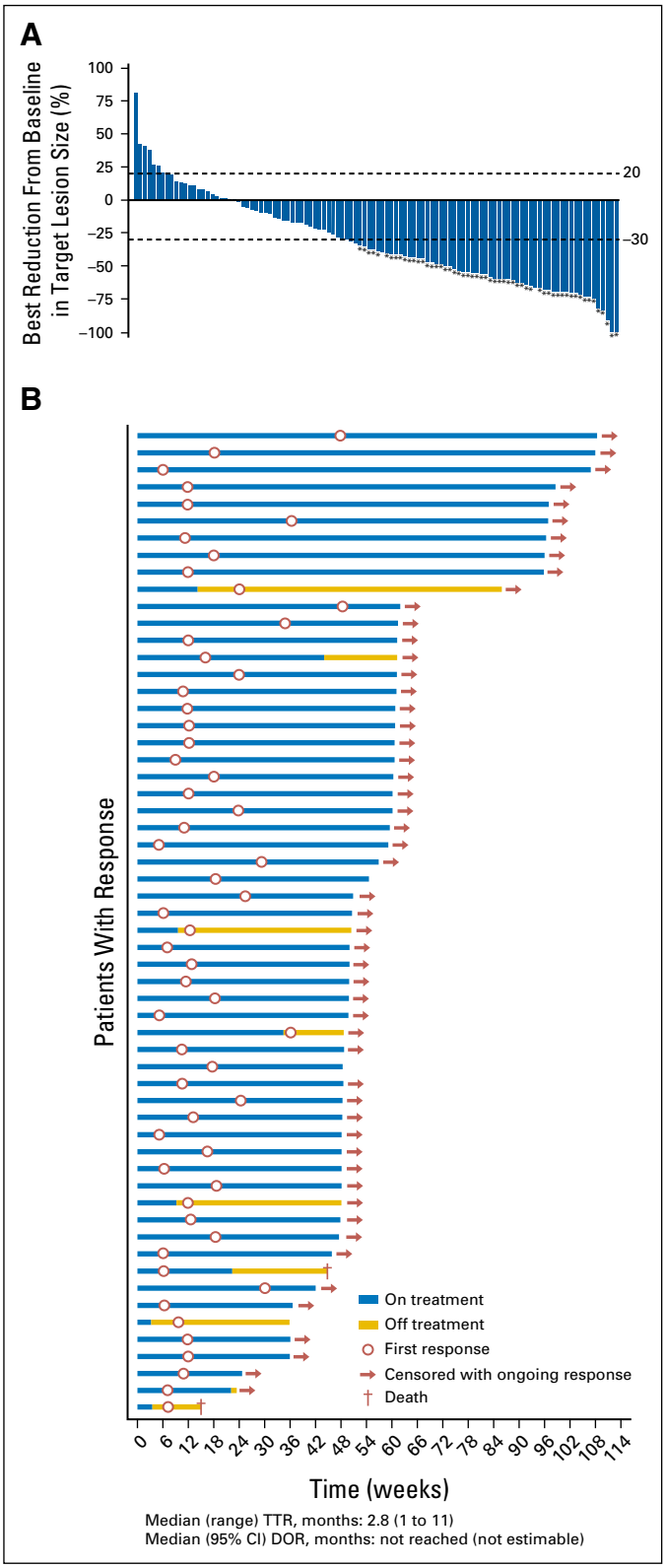


**Fig A2.** (A) Best reduction from baseline in target lesion size, and (B) characteristics of response per blinded independent central review. DOR, duration of response; TTR, time to response. (*) Patient with confirmed response

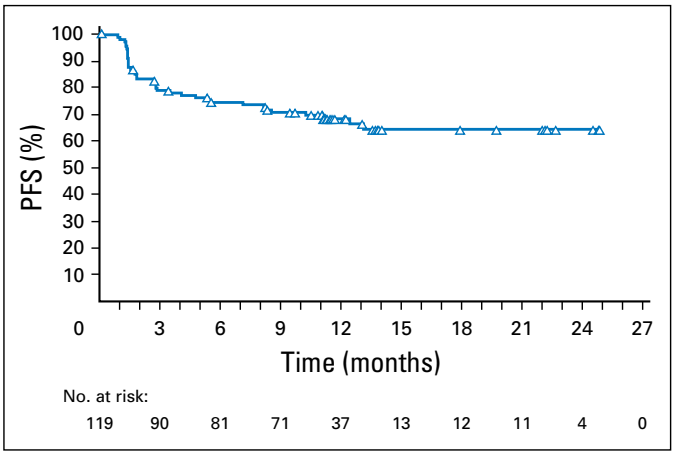


**Fig A3.** Progression-free survival (PFS) per blinded independent central review.

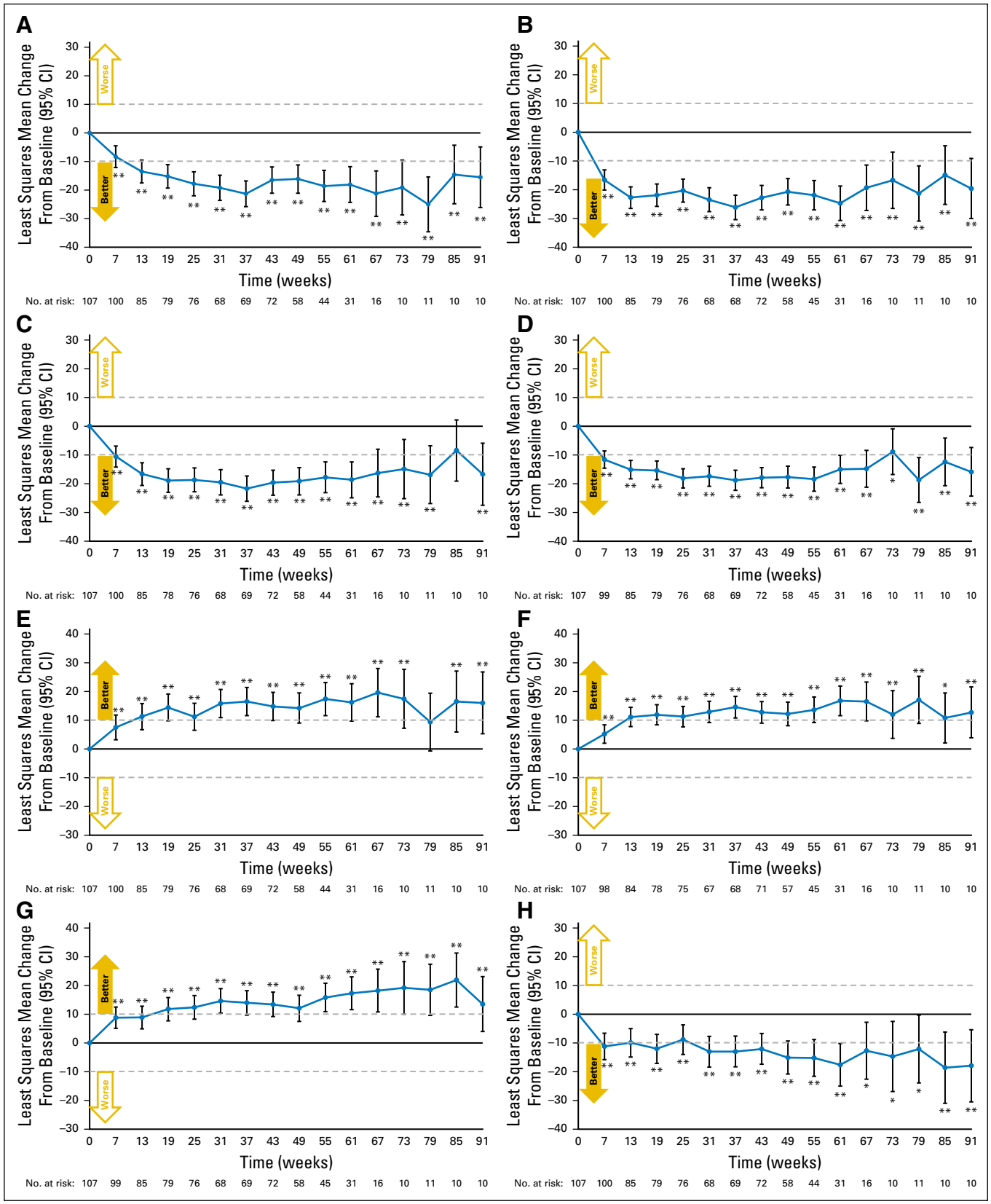


**Fig A4.** Patient-reported outcomes: mean change from baseline per the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire. (A) Fatigue, (B), pain, (C) appetite loss, (D) constipation, (E) role functioning, (F) global health status/quality of life, (G) social functioning, (H) insomnia, (I) nausea/vomiting, (J) dyspnea, (K) diarrhea, (L) cognitive functioning, and (M) physical functioning. (*) $P < .05$. (**) $P < .01$.

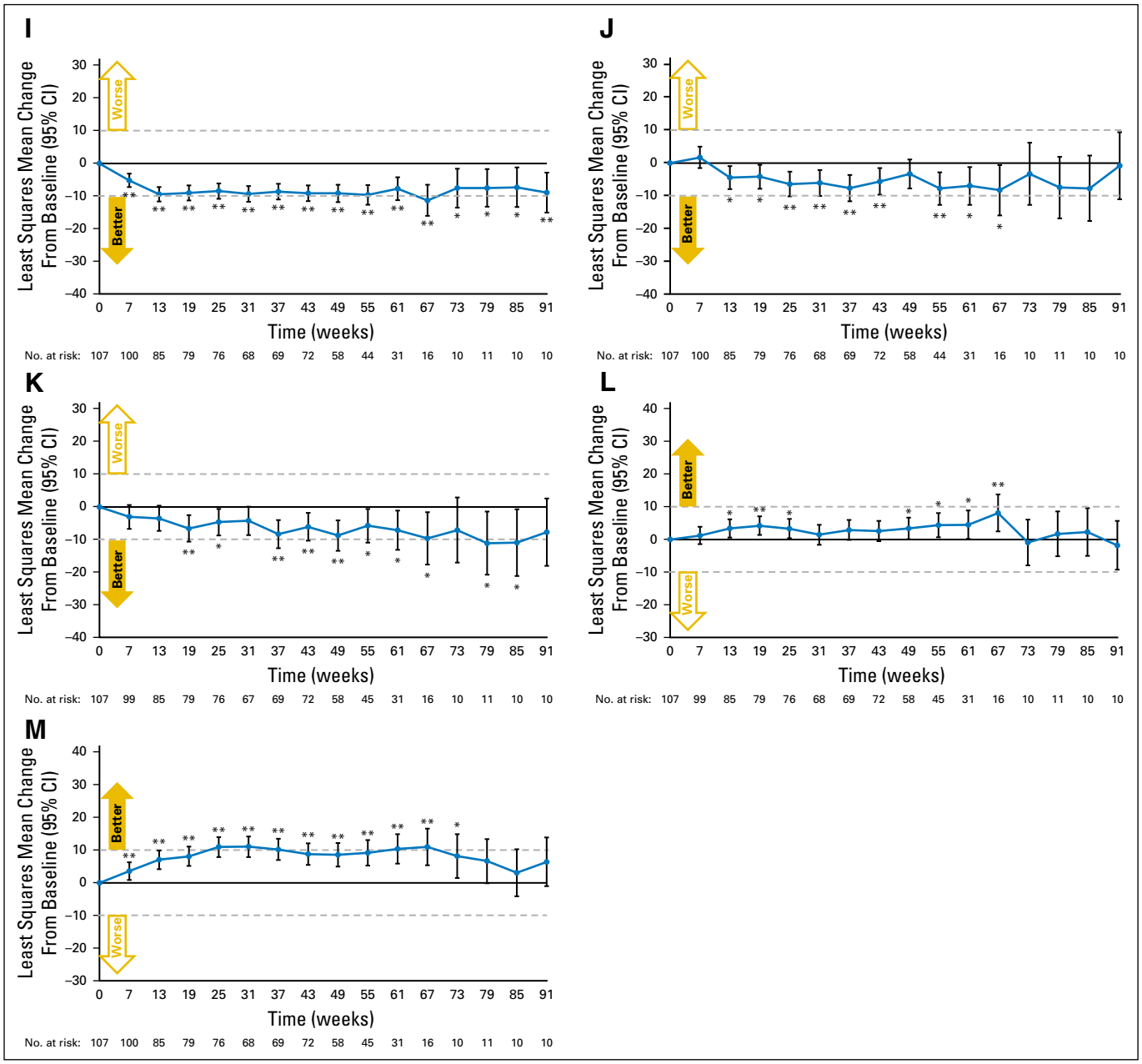


**Fig A4.** (Continued).

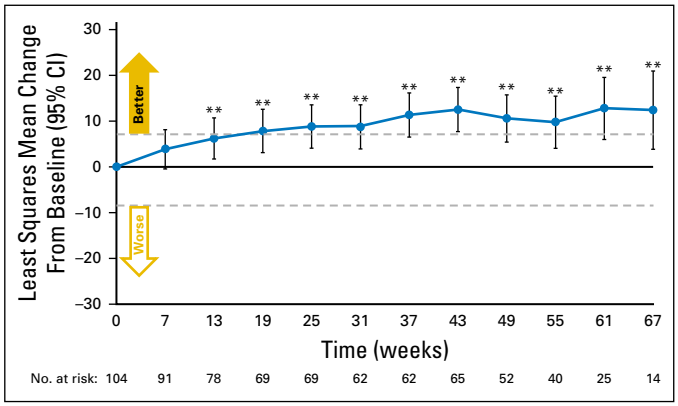


**Fig A5.** Patient-reported outcomes: mean change from baseline per three-level five-dimensional EuroQol instrument visual analog scale. (**) $P < .01$.

**Table A1.** ORR, Best Overall Response, and DCR per BICR (N = 119)

| Response | No. (%) | 95% CI |
|---|---|---|
| ORR | 58 (49) | 39.5 to 58.1 |
| Best overall response | | |
| Complete response | 5 (4) | |
| Partial response | 53 (45) | |
| Stable disease | 39 (33) | |
| Progressive disease | 17 (14) | |
| Not determined | 4 (3) | |
| Not reported | 1 (1) | |
| Disease control for ≥ 12 weeks | 94 (79) | 70.6 to 85.9 |

Abbreviations: BICR, blinded independent central review; DCR, disease control rate; ORR, objective response rate.

**Table A2.** ORR and DCR in Biomarker-Defined Patient Populations per Investigator Assessment (N = 119)

| Biomarker | No. (%) | |
|---|---|---|
| | ORR | Disease Control for ≥ 12 Weeks |
| Tumor PD-L1 expression | | |
| ≥ 1% (n = 26) | 14 (54) | 20 (77) |
| < 1% (n = 65) | 34 (52) | 51 (78) |
| Unknown (n = 28) | 17 (61) | 24 (86) |
| Mutation status | | |
| *BRAF*/*KRAS* wild type (n = 31) | 17 (55) | 24 (77) |
| *BRAF* mutant (n = 29) | 16 (55) | 23 (79) |
| *KRAS* mutant (n = 44) | 25 (57) | 37 (84) |
| Unknown (n = 15) | 7 (47) | 11 (73) |
| Clinical history of Lynch syndrome* | | |
| Yes (n = 35) | 25 (71) | 30 (86) |
| No (n = 31) | 15 (48) | 25 (81) |
| Unknown (n = 53) | 25 (47) | 40 (75) |

Abbreviations: DCR, disease control rate; ORR, objective response rate; PD-L1, programmed death-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 A3.** Completion Rates for PRO Measures

| Measure | Week (No. of patients) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (n = 119) | 7 (n = 110) | 13 (n = 97) | 19 (n = 90) | 25 (n = 85) | 31 (n = 82) | 37 (n = 81) | 43 (n = 79) | 49 (n = 71) | 55 (n = 52) | 61 (n = 34) | 67 (n = 20) | 73 (n = 12) | 79 (n = 11) | 85 (n = 11) | 91* (n = 10) |
| EORTC QLQ-C30 | 115 (97) | 102 (93) | 87 (90) | 80 (89) | 78 (92) | 69 (84) | 70 (86) | 73 (92) | 59 (83) | 46 (88) | 31 (91) | 16 (80) | 10 (83) | 11 (100) | 10 (91) | 10 (100) |
| EQ-5D | 112 (94) | 99 (90) | 85 (88) | 78 (87) | 77 (92) of 84** | 69 (84) | 69 (85) | 72 (91) | 59 (83) | 46 (88) | 30 (88) | 16 (80) | 10 (83) | 11 (100) | 10 (91) | 10 (100) |

NOTE. Data presented as No. (%) of patients who completed questionnaire (%) of No. of patients in the study.
Abbreviations: EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D, three-level five-dimensional EuroQol instrument; PRO, patient-reported outcome.
*Beyond week 91, < 10 patients had completed questionnaires; therefore, the results for these patients were not included in the analyses.
**The number of patients completing the assessment differed from the patient number indicated in the column header.

**Table A4.** EORTC QLQ-C30: Patients With ≥ 10-Point Deterioration From Baseline

| Dimension | Week (No. of patients) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 (n = 100) | 13 (n = 85) | 19 (n = 79) | 25 (n = 76) | 31 (n = 68) | 37 (n = 69) | 43 (n = 72) | 49 (n = 58) | 55 (n = 45) | 61 (n = 31) | 67 (n = 16) | 73 (n = 10) | 79 (n = 11) | 85 (n = 10) | 91 (n = 10) |
| Physical functioning | 14 (14) | 7 (8) | 9 (11) | 5 (7) | 3 (4) | 4 (6) | 5 (7) | 8 (14) | 3 (7) | 2 (6) | 1 (6) | 2 (20) | 1 (9) | 1 (10) | 0 |
| Role functioning | 28 (28) | 13 (15) | 12 (15) | 19 (25) | 10 (15) | 7 (10) | 11 (15) | 7 (12) | 4 (9) | 3 (10) | 2 (13) | 2 (20) | 2 (18) | 2 (20) | 2 (20) |
| Emotional functioning | 17 (17) | 10 (12) | 9 (11) | 7 (9) | 7 (10) | 7 (10) | 4 (6) | 4 (7) | 3 (7) | 1 (3) | 3 (19) | 2 (20) | 1 (9) | 1 (10) | 1 (10) |
| Cognitive functioning | 22 (22) | 10 (12) | 14 (18) | 13 (17) | 19 (28) | 12 (17) | 11 (15) | 10 (17) | 6 (13) | 6 (19) | 2 (13) | 4 (40) | 2 (18) | 2 (20) | 2 (20) |
| Social functioning | 20 (20) | 15 (18) | 10 (13) | 6 (8) | 7 (10) | 8 (12) | 8 (11) | 5 (9) | 3 (7) | 1 (3) | 2 (13) | 1 (10) | 0 | 0 | 1 (10) |
| Fatigue | 22 (22) | 14 (16) | 14 (18) | 13 (17) | 10 (15) | 10 (14) | 12 (17) | 8 (14) | 2 (4) | 3 (10) | 2 (13) | 2 (20) | 1 (9) | 1 (10) | 1 (10) |
| Nausea and vomiting | 12 (12) | 3 (4) | 4 (5) | 6 (8) | 4 (6) | 2 (3) | 3 (4) | 2 (3) | 1 (2) | 1 (3) | 0 | 0 | 0 | 1 (10) | 0 |
| Pain | 13 (13) | 10 (12) | 10 (13) | 7 (9) | 3 (4) | 3 (4) | 5 (7) | 4 (7) | 4 (9) | 2 (6) | 1 (6) | 2 (20) | 1 (9) | 2 (20) | 1 (10) |
| Dyspnea | 15 (15) | 7 (8) | 11 (14) | 8 (11) | 6 (9) | 5 (7) | 8 (11) | 7 (12) | 2 (4) | 3 (10) | 1 (6) | 1 (10) | 0 | 0 | 0 |
| Insomnia | 15 (15) | 15 (18) | 13 (16) | 14 (18) | 11 (16) | 9 (13) | 9 (13) | 6 (10) | 6 (13) | 4 (13) | 4 (25) | 0 | 1 (9) | 0 | 1 (10) |
| Appetite loss | 15 (15) | 9 (11) | 6 (8) | 4 (5) | 3 (4) | 2 (3) | 3 (4) | 3 (5) | 4 (9) | 2 (6) | 2 (13) | 2 (20) | 0 | 2 (20) | 0 |
| Constipation | 11 (11) | 2 (2) | 1 (1) | 1 (1) | 2 (3) | 0 | 2 (3) | 2 (3) | 1 (2) | 2 (6) | 1 (6) | 1 (10) | 0 | 1 (10) | 1 (10) |
| Diarrhea | 14 (14) | 12 (14) | 6 (8) | 7 (9) | 8 (12) | 6 (9) | 10 (14) | 7 (12) | 6 (13) | 3 (10) | 0 | 1 (10) | 0 | 0 | 1 (10) |
| Financial difficulties | 8 (8) of 98* | 10 (12) of 83* | 5 (6) of 77* | 9 (12) of 74* | 6 (9) of 66* | 7 (10) of 67* | 9 (13) of 70* | 6 (11) of 56* | 7 (16) of 44* | 4 (13) of 30* | 2 (13) | 1 (10) | 0 | 0 | 0 |
| Global health status | 18 (18) of 99* | 6 (7) of 84* | 8 (10) of 78* | 7 (9) of 75* | 5 (7) of 67* | 4 (6) of 68* | 6 (8) of 71* | 4 (7) of 57* | 4 (9) | 2 (6) | 1 (6) | 1 (10) | 0 | 1 (10) | 0 |

NOTE: Data presented as No. (%) unless otherwise indicated.
Abbreviation: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire.
*The number of patients completing the assessment differed from the patient number indicated in the column header; therefore, data are presented as No. of patients with ≥ 10-point deterioration (%) of No. of patients completing the assessment.

**Table A5.** EQ-5D: Patients Reporting Some Health Problems

| Dimension | Week (No. of patients) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (n = 112) | 7 (n = 99) | 13 (n = 85) | 19 (n = 78) | 25 (n = 77) | 31 (n = 69) | 37 (n = 69) | 43 (n = 71) | 49 (n = 58) | 55 (n = 46) | 61 (n = 30) | 67 (n = 16) | 73 (n = 10) | 79 (n = 11) | 85 (n = 10) | 91 (n = 10) |
| Mobility | 31 (28) | 21 (21) | 15 (18) | 13 (17) | 7 (9) | 8 (12) | 7 (10) | 13 (18) | 8 (14) | 8 (17) | 5 (17) | 0 | 3 (30) | 1 (9) | 1 (10) | 1 (10) |
| Self-care | 7 (6) | 7 (7) | 3 (4) | 2 (3) | 2 (3) | 3 (4) | 1 (1) | 3 (4) | 3 (5) | 1 (2) | 2 (7) | 2 (13) | 1 (10) | 0 | 0 | 1 (10) |
| Usual activities | 52 (46) | 31 (31) | 26 (31) | 21 (27) | 26 (34) of 76* | 17 (25) | 16 (23) | 14 (20) | 12 (21) | 11 (24) | 8 (27) | 5 (31) | 3 (30) | 3 (27) | 4 (40) | 3 (30) |
| Pain | 71 (63) | 57 (58) | 32 (38) | 33 (42) | 30 (39) | 28 (41) | 20 (29) | 28 (39) | 16 (28) | 14 (30) | 13 (43) | 6 (38) | 7 (70) | 5 (45) | 3 (30) | 3 (30) |
| Anxiety | 54 (48) | 37 (37) | 21 (25) | 21 (27) | 21 (27) | 16 (23) | 14 (20) | 21 (30) | 16 (28) | 13 (28) | 8 (27) | 4 (25) | 5 (50) | 2 (18) | 4 (40) | 4 (40) |

NOTE: Data presented as No. (%) unless otherwise indicated.
Abbreviation: EQ-5D, three-level five-dimensional EuroQol instrument.
*The number of patients completing the assessment differed from the patient number indicated in the column header; therefore, data are presented as No. of patients with ≥ 10-point deterioration (%) of No. of patients completing the assessment.

**Table A6.** Summary of Select Treatment-Related Adverse Events

| | Patients With Event No. (%) | | Time to Onset (weeks) Median (range) | | Patients With Resolution No. (%) | | Time to Resolution Median (range) | | Patients Who Received Immune-Modulating Medication No. (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Organ System | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| Skin | 34 (29) | 5 (4) | 5.2 (0.3-38) | 2.1 (1-23) | 24 (71) | 5 (100) | 9.0 (0.4-106) | 2.6 (1-13) | 19 (56) | 4 (80) |
| Endocrine | 30 (25) | 6 (5) | 9.1 (3-42) | 13.1 (8-20) | 12 (40) | 3 (50) | Not reached (2-93) | Not reached (2-48) | 11 (37) | 4 (67) |
| GI | 27 (23) | 4 (3) | 9.1 (0.3-41) | 16.1 (4-38) | 25 (96) | 4 (100) | 1.5 (0.1-28) | 1.1 (1-3) | 6 (22) | 3 (75) |
| Hepatic | 23 (19) | 13 (11) | 7.0 (1-42) | 10.0 (3-42) | 17 (74) | 11 (85) | 5.0 (0.3-66) | 3.3 (1-57) | 10 (43) | 9 (69) |
| Pulmonary | 6 (5) | 1 (1) | 10.5 (4-15) | 6.0 (6-6) | 5 (83) | 1 (100) | 4.5 (1-49) | 1.0 (1-1) | 2 (33) | 0 |
| Renal | 6 (5) | 2 (2) | 12.6 (1-36) | 15.6 (7-24) | 5 (83) | 1 (50) | 6.3 (3-21) | Not reached (4-21) | 2 (33) | 2 (100) |

NOTE. Treatment-related adverse events were assessed during treatment and for up to 30 days after the last dose of study treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).