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PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

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ABSTRACT

BACKGROUND

Neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum is a standard treatment for locally advanced rectal cancer. A subset of rectal cancer is caused by a deficiency in mismatch repair. Because mismatch repair–deficient colorectal cancer is responsive to programmed death 1 (PD-1) blockade in the context of metastatic disease, it was hypothesized that checkpoint blockade could be effective in patients with mismatch repair–deficient, locally advanced rectal cancer.

METHODS

We initiated a prospective phase 2 study in which single-agent dostarlimab, an anti–PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemoradiotherapy and surgery. Patients who had a clinical complete response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery. The primary end points are sustained clinical complete response 12 months after completion of dostarlimab therapy or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

RESULTS

A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

CONCLUSIONS

Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade. Longer follow-up is needed to assess the duration of response. (Funded by the Simon and Eve Colin Foundation and others; ClinicalTrials.gov number, NCT04165772.)

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Locally advanced rectal cancer is typically managed with multimodal therapy, including chemotherapy, radiation, and surgery. Current evidence supports a strategy involving the use of neoadjuvant therapy, in which induction chemotherapy with a fluoropyrimidine in combination with oxaliplatin is followed by chemoradiotherapy and then surgery.[1-3] This approach results in a pathological complete response in up to a quarter of patients, but it is associated with marked complications and toxic effects — including bowel, urinary, and sexual dysfunction; infertility; and altered quality of life — in a substantial proportion of patients.[4-6] In patients undergoing surgery, resection of the rectum is life-altering and often warrants a permanent diverting colostomy.[6,7] Owing to the complications of surgery and the high frequency of pathological complete response, interest in organ-sparing nonoperative management is increasing. The use of clinical complete response that is achieved with neoadjuvant treatment as a surrogate for pathological complete response provides patients with a nonoperative option that results in a survival benefit that is similar to that in patients undergoing surgical resection.[8-11]

Approximately 5 to 10% of rectal adenocarcinomas are mismatch-repair deficient, and these tumors have been shown to respond poorly to standard chemotherapy regimens, including neoadjuvant chemotherapy in locally advanced rectal cancer.[12-14] Immune checkpoint blockade alone has been shown to be highly effective as first-line treatment for patients with mismatch repair–deficient metastatic colorectal cancer, as well as for patients with treatment-refractory disease, with objective response rates of 33 to 55%, clinically significant durability of response, and prolonged overall survival.[15-17]

On the basis of the benefits seen in the context of metastatic disease, we hypothesized that single-agent programmed death 1 (PD-1) blockade alone might be beneficial in mismatch repair–deficient, locally advanced rectal cancer. To test this hypothesis, we initiated a phase 2 study to investigate the overall response and frequency of sustained clinical complete response to neoadjuvant treatment with dostarlimab, a PD-1 inhibitor, in this patient population.

Methods

Patients

Patients were eligible for enrollment if they were 18 years of age or older and had mismatch repair–deficient stage II or stage III rectal cancer that had been diagnosed on the basis of standard clinical criteria. Mismatch-repair status was determined with the use of a chromogenic immunohistochemical assay for the detection of loss of expression of MLH1, MSH1, MSH6, and PMS2. Staging was confirmed by standard magnetic resonance imaging (MRI), which was performed according to a specified protocol for rectal cancer; computed tomography (CT) of the chest, abdomen, and pelvis; and colonoscopy. Positron-emission tomography (PET) was performed according to the current study protocol, available with the full text of this article at NEJM.org. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability) and no evidence of distant metastases. Other key eligibility criteria included no previous receipt of immunotherapy, chemotherapy, or radiation for the rectal tumor and no active autoimmune disease, active infectious disease, or recent receipt (within the previous 7 days) of immunosuppressive therapy.

Study Design

In this single-group, prospective phase 2 study, neoadjuvant dostarlimab administered intravenously at a dose of 500 mg every 3 weeks for 6 months (nine cycles) was to be followed by standard radiation therapy (total dose of 5040 cGy given in 28 fractions) with concurrent administration of capecitabine at standard doses and then total mesorectal excision. Patients who had a clinical complete response (as defined below) after completion of either induction anti–PD-1 therapy or chemoradiotherapy subsequently underwent nonoperative follow-up (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

Patients were assessed for clinical response with the use of endoscopic and digital rectal examinations at baseline (before treatment), at 6 weeks, at 3 months, and at 6 months and then every 4 months after the start of treatment. T2-weighted and diffusion-weighted MRI of the rectum,[18] ^{18}F-fluorodeoxyglucose (FDG)–PET, and CT

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of the chest, abdomen, and pelvis were performed at baseline, at 3 months, and at 6 months and then every 4 months after the start of treatment. Tumor biopsies were performed at the time of each endoscopy. All assessments were to be performed early if patients had clinical symptoms of progression.

Tumor response was determined on the basis of T2-weighted and diffusion-weighted MRI of the rectum, endoscopic evaluation, and digital rectal examination.[19] A clinical complete response was defined as the absence of residual disease on digital and endoscopic rectal examination, as well as the absence of residual disease on rectal MRI, with no restricted diffusion on T2-weighted imaging.

STUDY OVERSIGHT

This is an investigator-initiated study. The protocol was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. All the patients provided written informed consent before study enrollment in accordance with the principles of the Declaration of Helsinki. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

END POINTS

The study is evaluating two primary end points, with a planned enrollment of 30 patients. One end point is sustained clinical complete response 12 months after completion of dostarlimab therapy (in patients who do not undergo surgery) or pathological complete response (in patients who undergo surgery) after completion of dostarlimab therapy with or without chemoradiotherapy. Pathological complete response was defined in the protocol as the absence of residual cancer on the histologic examination of surgical specimens. The other end point is overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy. Only the second end point is reported here. Overall response was determined on the basis of T2-weighted and diffusion-weighted MRI of the rectum, endoscopic visualization, and digital rectal examination. Overall response was defined in the protocol as progressive disease, stable disease, partial response, near-complete response, or complete response (additional details are provided in the protocol).

PATHOLOGICAL AND GENOMIC ANALYSES

Formalin-fixed, paraffin-embedded tumor samples obtained from biopsies that were performed during the study were stained with hematoxylin and eosin and reviewed by a trained pathologist, who visually assessed the samples to confirm the diagnosis, identify the general histologic features, and estimate the percentage of viable tumor cells in each tumor sample. Mismatch-repair status was determined with the use of a chromogenic immunohistochemical assay for the detection of loss of expression of MLH1, MSH1, MSH6, and PMS2.

Tumor-specific and germline comprehensive genomic analyses were performed with the use of Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT), a next-generation sequencing assay. This assay, which has been approved by the Food and Drug Administration, detects somatic and germline genomic alterations in more than 400 genes and assesses tumor mutational burden. All the patients undergoing comprehensive molecular analysis for somatic tumor-specific alterations or analysis of known hereditary alterations provided additional written informed consent specific to those analyses.

Formalin-fixed, paraffin-embedded biopsy sections were also evaluated with the use of quantitative immunofluorescence analysis that was standardized for simultaneous measurement of DAPI (4′,6-diamidine-2-phenylindole) for all cells, cytokeratin for tumor and normal gut epithelial cells (clone AE1/AE3, Dako), CD20+ B lymphocytes (clone L26, M0755; Dako), programmed death ligand 1 (PD-L1) (clone E1L3N, CST), and CD8+ T lymphocytes (clone C8/144B, M7103; Dako). The marker levels were measured in selected tissue compartments and expressed as quantitative immunofluorescence scores on the basis of arbitrary units of fluorescence. Details are provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

We assessed the overall response rate using a one-sample hypothesis; the null hypothesis to be tested was that the percentage of patients with an overall response would be less than 25%. Successful rejection of the null hypothesis would require 6 or more patients with an overall response by the end of the first stage (after 15

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Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	
White	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic or Latinx ethnic group — no. (%)*	1 (6)
ECOG performance-status score — no. (%)†	
0	12 (75)
1	4 (25)
Tumor stage — no. (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status — no. (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge (range) — cm	5 (0.9–8.9)

* Race and ethnic group were reported by the patient.
† The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

patients had been enrolled) and 11 or more patients with an overall response by the end of the second stage (after 30 patients had been enrolled). This decision rule would result in a type I error rate of 6% if 25% of the patients had an overall response and would provide the study with 84% power if 50% had an overall response. The null hypothesis was established on the basis of a study by Seligmann et al., in which the observed response to chemotherapy among patients with mismatch repair–deficient rectal cancers was 7% (8 of 115 patients).[20] We are reporting the results without awaiting full enrollment, because the second criterion for the decision rule (≥11 patients having an overall response) has already been met.

Binomial proportions are reported with a 95% exact confidence interval. Quantitative immunofluorescence scores for pathological samples obtained at baseline, during treatment, and during follow-up were compared with the use of the Mann–Whitney test. The statistical analysis and graphical representation were performed with GraphPad Prism software, version 9.0.2 (GraphPad Software). P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

A total of 16 patients have been enrolled and treated (Table 1). Of these patients, 12 have been enrolled for longer than 6 months and have completed the nine planned cycles (6 months) of dostarlimab. The median follow-up time from study enrollment to the clinical data cutoff for the 12 patients is 12 months (range, 6 to 25). The remaining 4 patients have received at least one dose of dostarlimab and continue to receive treatment. The median age of all the enrolled patients is 54 years (range, 26 to 78), and 62% are women. All 16 patients met the eligibility criteria, and no patients have withdrawn from the study. Of the 16 patients, 15 have clinical stage III disease, and 1 has clinical stage II disease. The most common presenting symptoms were rectal bleeding (in 88% of the patients), constipation (in 31%), and abdominal pain (in 25%) (Table S1).

TUMOR CHARACTERISTICS

Mutational analysis of the tumor specimens by next-generation sequencing confirmed microsatellite instability in all 14 patients for whom testing was performed and revealed a high tumor mutational burden, ranging from 37.9 to 103.0 mutations per megabase (mean, 60.0). The *BRAF* V600E mutation was absent in all 14 patients (Tables 2 and S2).

None of the patients have a known family history of the Lynch syndrome. Germline analysis identified pathogenic genomic alterations in 57% of the patients (8 of 14 patients); all the alternations are associated with the Lynch syndrome. Alterations in *MSH2* were most common, occurring in 4 of the 8 patients; pathogenic alterations in *MSH6*, *MLH1*, and *PMS2* were also present (Table 2).

EFFICACY

The criteria for the primary end point of overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy have been met.

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The percentage of patients with a clinical complete response was 100% (95% confidence interval [CI], 74 to 100) in 12 consecutive patients who have completed 6 months of therapy (Fig. 1, Table 2, and Fig. S2). After completion of therapy at 6 months, the median time to rectal MRI was 16 days (range, 8 to 26), and the median time to endoscopy was 20 days (range, 14 to 28).

During the median follow-up period of 12 months, no patients have received chemoradiotherapy, and no patients have undergone surgical resection. Because none of the 12 patients who completed 6 months of dostarlimab therapy have undergone surgery, evaluation of pathological complete response will not be possible. No patients have had disease progression or recurrence, and all 16 enrolled patients are alive (Tables 2 and S2).

The primary end point involving the durability of response (sustained clinical complete response at 12 months) is not reported in its finality. To date, 4 patients have had 1 year of sustained clinical complete response after completion of dostarlimab alone (Table S2).

Therapeutic responses were rapid, with resolution of symptoms within 9 weeks after initiation of dostarlimab in 81% of the patients. At the time of the 3-month assessment, 5 patients had had an endoscopic complete response, but only 2 patients had had a radiographic complete response (Fig. S3 and Tables S1 and S2).

SAFETY

Adverse events of any grade occurred in 12 of the 16 patients (75%; 95% CI, 48 to 92). No adverse events of grade 3 or higher were reported. The most common adverse events of grade 1 or 2 included rash or dermatitis (in 31% of the patients), pruritus (in 25%), fatigue (in 25%), and nausea (in 19%). Thyroid-function abnormalities occurred in 1 patient (6%) (Table S3).

BIOMARKERS OF LONGITUDINAL RESPONSE

Endoscopic biopsies were performed at baseline and during visual inspection of tumor response at 6 weeks, at 3 months, and at 6 months and then every 4 months. Patients who had a clinical complete response after 6 months of dostarlimab therapy and had tissue that could be evaluated also had no evidence of tumor on endoscopic biopsy, with a majority of patients having no evidence of viable tumor as early as 6 weeks after initiation of therapy (Fig. 2). Longitudinal endoscopic, pathological, and radiographic data for each patient are depicted in Figure S4.

Tumor samples evaluated by multiplex quantitative immunofluorescence analysis showed variable PD-L1 protein expression with higher levels in cytokeratin-negative stromal cells than in cytokeratin-expressing cancer cells, as well as lymphocytic infiltration enriched for cells expressing CD8 or CD20. PD-L1 protein and CD8+ T lymphocytes were present at baseline; the levels of both increased 6 weeks after administration of dostarlimab in the tumor and normal epithelial tissue compartment as well as in the stromal tissue compartment but decreased transiently from 3 to 6 months during treatment and then returned to higher levels in the tumor-free rectal mucosa after 6 months. CD20+ B lymphocytes formed nodular aggregates, predominantly in the stromal areas, that were consistent with tertiary lymphoid structures. The levels of these aggregates gradually increased after 6 weeks of therapy to levels that were 6 to 10 times as high as the baseline levels 6 months after completion of dostarlimab therapy (Fig. 3).

Serial FDG-PET scans, which were obtained at baseline, at 3 months, and at 6 months and then every 4 months to further evaluate tumor response to PD-1 blockade, showed an evolution of tumor eradication that was similar to that seen on pathological examination and genomic analysis. Maximum standardized uptake values were reduced to background levels in all the patients as early as 3 months after the start of dostarlimab therapy. All the patients who completed 6 months of treatment had complete tumor resolution on FDG-PET (Fig. S5).

DISCUSSION

In this study involving patients with mismatch repair–deficient, locally advanced rectal cancer, treatment with neoadjuvant PD-1 blockade alone resulted in a clinical complete response — as measured by the combination of rectal MRI, visual endoscopic inspection, and digital rectal examination — in all 12 patients who had at least 6 months of follow-up. The completeness of these responses is further supported by the absence of residual tumor on serial endoscopic biopsies and the resolution of FDG uptake on PET scans.

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Table 2. Individual Patient Data.*

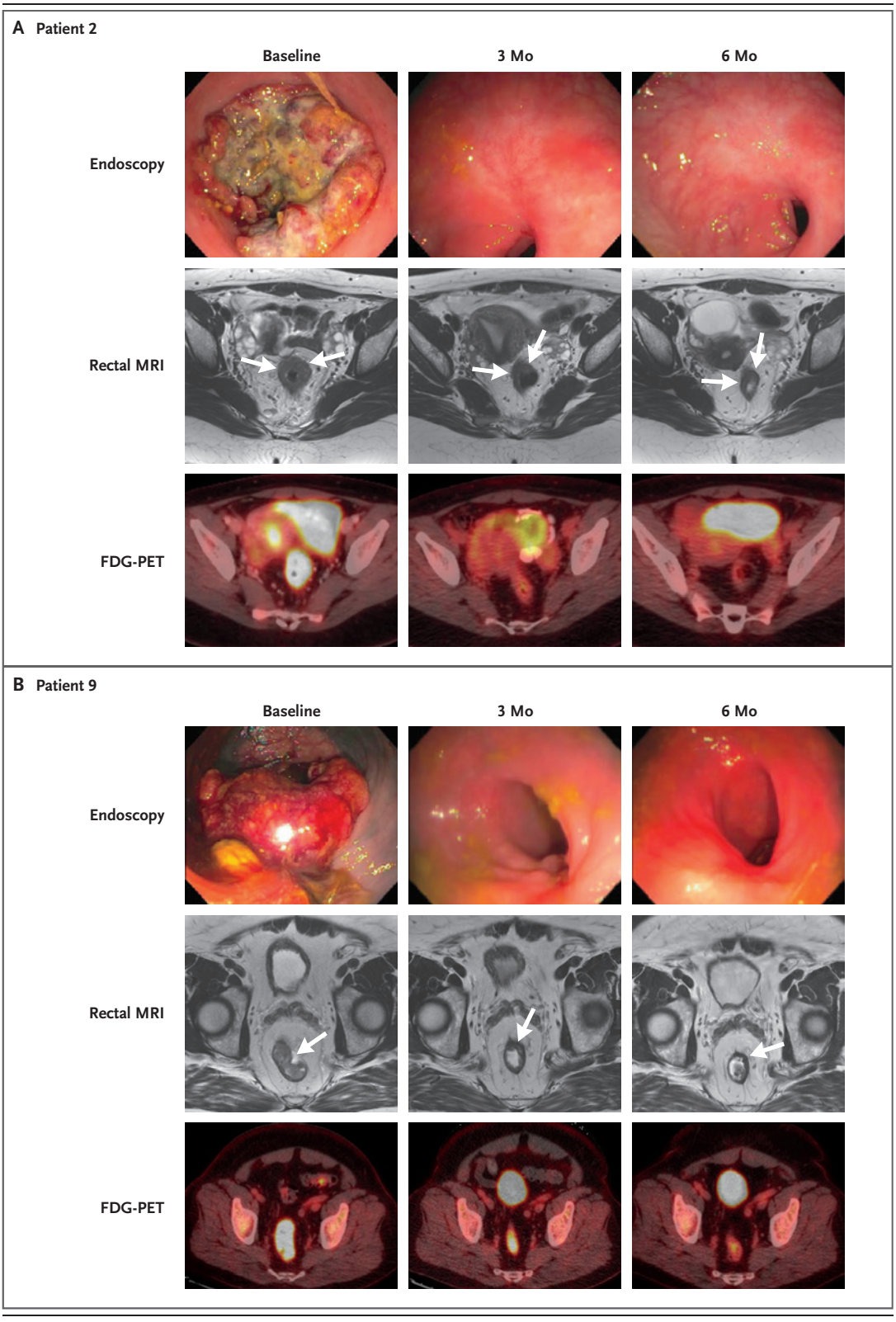
Patient No. (Sex, Age)	Tumor Stage; Nodal Status	Germline Pathogenic Variant†	Mismatch-Repair Status, Chromogenic IHC Assay	PD-L1 Level	TIL Level	*BRAF* V600E Mutation	Tumor Mutational Burden‡	Completed 6 mo of Dostarlimab Therapy	CRT or Surgery	Response on Endoscopic Visualization	Digital Examination; Endoscopic Biopsy	Response on Rectal MRI	Response on FDG-PET
1 (F, 38 yr)	T4; positive	*MSH2* (c.687delA)	MSH2 and MSH6 absent	+	+++	No	88.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
2 (F, 30 yr)	T3; positive	*MSH2* (c.8942+3A→T)	MSH2 and MSH6 absent	++	+	No	45.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
3 (F, 61 yr)	T1 to T2; positive	None	MSH2 and MSH6 absent	+++	+++	No	62.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
4 (F, 28 yr)	T4; positive	None	MSH2 and MSH6 absent	+	++	No	65.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
5 (F, 53 yr)	T1 to T2; positive	*MSH2* (c.942+3A→T)	MSH2 absent	+	+	No	103.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
6 (F, 77 yr)	T1 to T2; positive	*MSH6* (c.1969delC)	MSH6 absent	+++	+++	No	93.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
7 (F, 77 yr)	T1 to T2; positive	None	MLH1 and PMS2 absent	++	++	No	75.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
8 (F, 55 yr)	T3; positive	*MSH2* (c.1784T→G)	MSH2 absent	++	+	No	78.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR

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9 (M, 68 yr)	T3; positive	None	MSH2 and MSH6 absent	+++	++	No	62.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
10 (F, 78 yr)	T3; negative	None	MLH1 and PMS2 absent	+	+	No	37.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
11 (F, 55 yr)	T3; positive	*PMS2* (c.2500_2501delinsG)	MSH2 and MSH6 absent	++	++	No	52.7	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
12 (M, 27 yr)	T3; positive	None	PMS2 absent	+++	+++	No	54.4	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
13 (M, 26 yr)	T3; positive	*MLH1* (c.1489dupC)	MLH1 and PMS2 absent	NA	NA	No	47.8	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	CR at 3 mo	CR
14 (M, 43 yr)	T3; positive	*MSH6* (c.3476dupA)	MSH6 absent	NA	NA	No	74.1	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	Near-CR at 3 mo	CR
15 (M, 59 yr)	T3; positive	NA	PMS2 absent	NA	NA	NA	NA	No; ongoing, 5 wk	No	NE	NE; NE	NE	NE
16 (M, 51 yr)	T4b; positive	NA	MSH2 absent	NA	NA	NA	NA	No; ongoing, 3 wk	No	NE	NE; NE	NE	NE

* CR denotes complete response, CRT chemoradiotherapy, FDG-PET ^{18}F-fluorodeoxyglucose–positron-emission tomography, IHC immunohistochemical, NA not available, NE not able to be evaluated, PD-L1 programmed death ligand 1, and TIL tumor-infiltrating lymphocyte.
† All alterations identified are associated with the Lynch syndrome.
‡ Units are reported in mutations per megabase.

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Figure 1 (facing page). Evolution of Endoscopic and Radiographic Response in Representative Patients Treated with Dostarlimab.

Shown are the results of endoscopic evaluations, T2-weighted MRI of the rectum, and ^{18}F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) for two representative patients at baseline and at 3 months and 6 months. Panel A (Patient 2) shows an endoscopic complete response and a near-complete response on T2-weighted rectal MRI at 3 months and a clinical complete response at 6 months. Panel B (Patient 9) shows an endoscopic complete response and a radiographic complete response at 3 months. Arrows identify the tumor at each time point. Diffusion-weighted images of the rectum for these two patients are provided in Figure S2 in the Supplementary Appendix.

In our study, the elimination of tumors after 6 months of therapy with PD-1 blockade enabled us to omit both chemoradiotherapy and surgery and to proceed with observation alone. Surgery and radiation can have permanent effects on fertility, sexual health, and bowel and bladder function.[4-7,21] The implications for quality of life are substantial, especially among patients in whom standard treatment would affect childbearing potential. Given that the incidence of rectal cancer is rising among young adults of childbearing age, the use of PD-1 blockade to eliminate the need for chemoradiotherapy and surgery may confer a particular benefit in that age group.[22]

Neoadjuvant immunotherapy has been tested in several solid tumors,[23-26] including those known to be sensitive to checkpoint blockade in the context of metastatic disease, such as non–small-cell lung cancer (NSCLC), urothelial carcinoma, and melanoma. The levels of activity seen with those tumor types have not been nearly as high as the extent of activity we observed in patients with mismatch repair–deficient rectal cancer. One contributing factor might be that we administered 6 months of immunotherapy, whereas the other studies investigated shorter exposures to checkpoint blockade. Responses to immunotherapy have been shown to evolve over a period of months rather than weeks in mismatch repair–deficient tumors.[27] However, we have observed at least a near-complete response in many of the patients in our study after only 3 months of treatment. In a study involving patients with NSCLC, two doses of PD-1 blockade resulted in a 10% response rate, and in a study involving patients with melanoma, 52% had a response with immunotherapy alone.[24,28] In a pilot study in which patients with mismatch repair–deficient colon cancer received a single dose of ipilimumab and two doses of nivolumab before surgery, 50% of the patients had a response.[29] In a study in which patients with early-stage treatment-refractory mismatch repair–deficient colorectal cancer were treated with either toripalimab (a PD-1–blocking antibody) plus celecoxib or toripalimab monotherapy for 3 months, an imaging-based response occurred in approximately 55% of the patients.[30] In all these studies, however, all the patients proceeded to surgical resection, thereby incurring the long-term complications associated with that procedure.

An important question is why these localized mismatch repair–deficient rectal tumors respond so much more robustly than metastatic colorectal tumors. In a study involving patients with metastatic disease who had not previously received any treatment, the rate of imaging-based complete response of mismatch repair–deficient colorectal tumors was 11.1% despite the presence of molecular features at baseline that were similar to those of the tumors evaluated in our study.[15] One explanation that lends itself to tumors of the gastrointestinal tract is the potential influence of the gut microbiome. A growing literature supports the immunomodulatory role of certain bacterial species in augmenting the antitumor immune response potentiated by checkpoint blockade.[31-33] A study of neoadjuvant checkpoint blockade in NSCLC showed that an abundance of gut ruminococcus and akkermansia species was associated with major pathological response.[34] *Fusobacterium nucleatum* has been found to be associated with an immunoresponsive tumor microenvironment in mismatch repair–deficient tumors.[35] We speculate that, in addition to the tumor cell–intrinsic factor driving the response to PD-1 blockade (namely, the extremely high tumor mutational burden associated with mismatch-repair deficiency), a tumor cell–extrinsic factor, such as the microbiome, may be driving this exceptionally good response. Tumor cell–intrinsic features beyond tumor mutational

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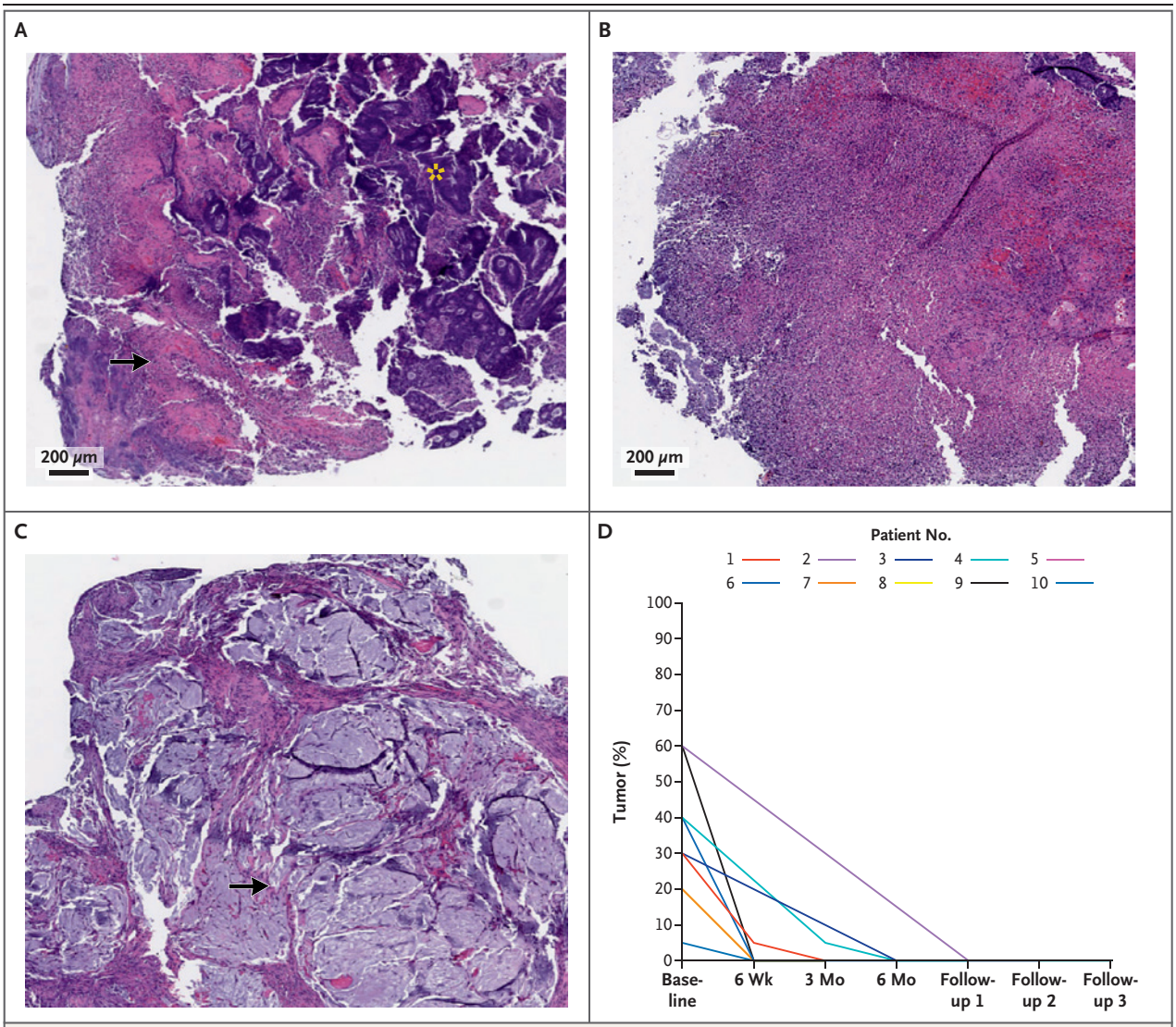


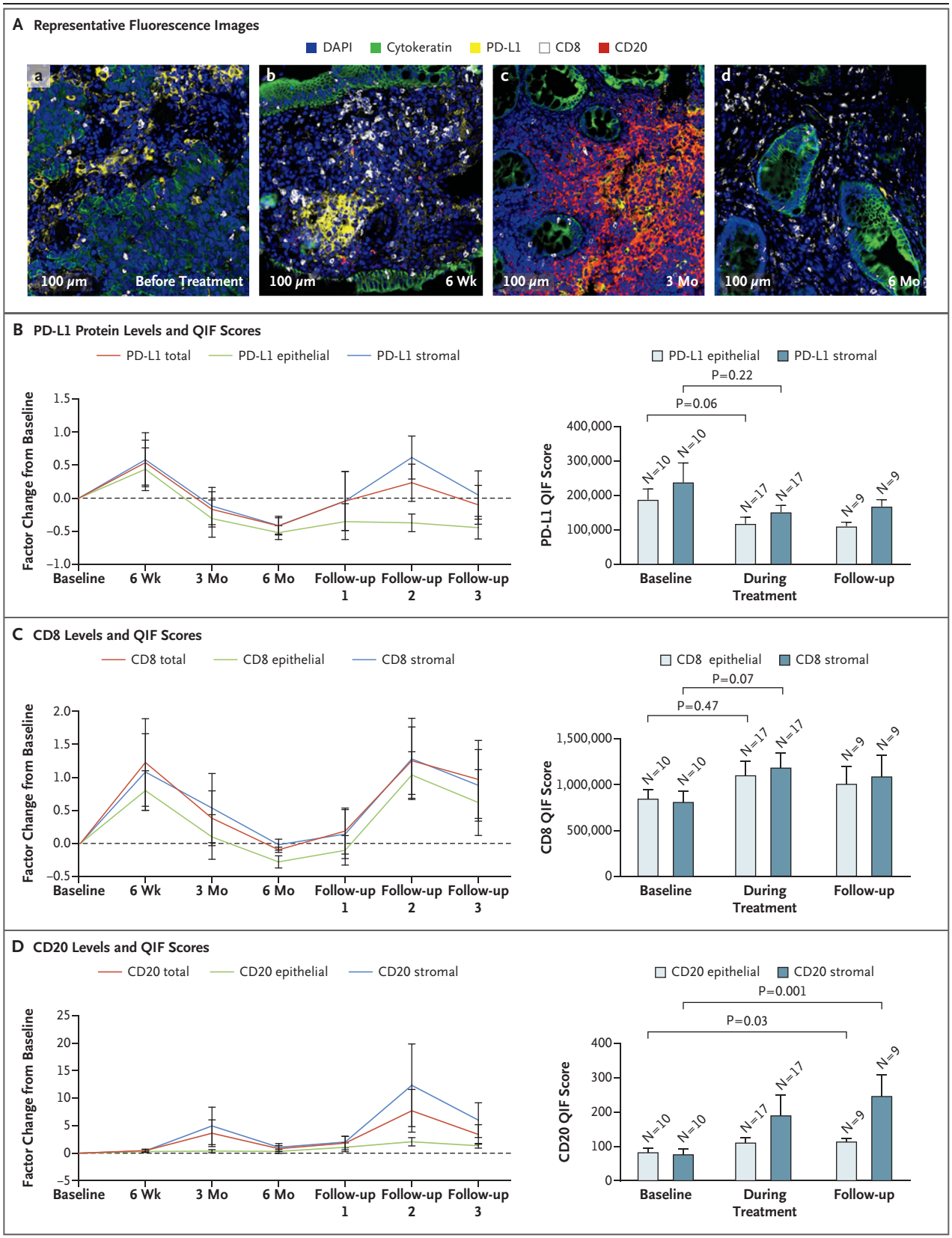
Figure 2. Biopsy Specimens of the Rectum before and after PD-1 Blockade and Viable Tumor Cell Content.

Hematoxylin and eosin staining of representative biopsy specimens obtained at baseline (Panels A and B) shows examples of viable tumor cells (Panel A, asterisk) surrounded by necrosis (Panel A, arrow) and extensive necrosis and inflammation with scant viable tumor cells (Panel B). Staining of representative biopsy specimens obtained at 3 months after initiation of treatment (Panel C) shows the presence of acellular residual mucin pools (arrow). Also shown (Panel D) are the estimated percentages of viable tumor cells on pathological examination of specimens obtained before treatment (baseline), during treatment (6 weeks through 6 months), and during follow-up in 10 patients. PD-1 denotes programmed death 1.

Figure 3 (facing page). Immune Contexture Changes after PD-1 Blockade in Rectal Tumors and Mucosa.

Representative multicolor fluorescence images (Panel A) show tumor and normal epithelial cells that are positive for cytokeratin, programmed death ligand 1 (PD-L1) protein, CD8+ T lymphocytes, and CD20+ B lymphocytes in rectal biopsy samples that were obtained at baseline and after 6 weeks, 3 months, and 6 months of PD-1 blockade. Changes in the levels of PD-L1 protein (Panel B), CD8+ T lymphocytes (Panel C), and CD20+ B lymphocytes (Panel D) that were selectively measured in the total tissue areas, in the cytokeratin-positive tumor and normal epithelial cell areas (labeled as "epithelial"), and in the cytokeratin-negative stromal tissue compartment are shown across multiple biopsy time points before and after initiation of treatment. Also shown are the mean factor change ±SE (I bars) of each marker relative to baseline levels in each patient for whom tissue samples could be evaluated. In addition, mean ±SE (T bars) quantitative immunofluorescence (QIF) scores of PD-L1 protein (Panel B), CD8+ T lymphocytes (Panel C), and CD20+ B lymphocytes (Panel D) that were selectively measured in tumor and normal epithelial cells and in stromal cells in biopsy samples obtained at baseline, during treatment (week 6 through month 6), and after treatment are shown. The number of individual samples included in each group is indicated above each bar. P values were calculated with the use of the Mann–Whitney test. DAPI denotes 4′,6-diamidine-2-phenylindole.

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burden — such as clonality, aneuploidy, and mutation class,[36-38] which have been shown to influence response to immunotherapy — may affect the differences in response between localized and metastatic disease.

The evolution of the local immune response showed a substantial initial expansion of PD-L1–positive and CD8+ T lymphocytes, followed by a decrease to below pretreatment levels in the same time frame that complete response was achieved. After treatment was completed, a repopulation with PD-L1–positive cells was noted, primarily in the stroma, in conjunction with CD8+ T-lymphocyte expansion and a prominent increase in CD20+ B lymphocytes within tertiary lymphoid structures (data not shown). In melanomas, the coexistence of CD8+ T lymphocytes and CD20+ B lymphocytes and the development of tertiary lymphoid structure has been associated with an improved clinical benefit from checkpoint blockade.[39]

Although the results of our study are promising, especially given that 12 consecutive patients all had a clinical complete response, the study is small and represents the experience of a single institution. These findings must be reproduced in a larger prospective cohort that balances academic and community practices and ensures the participation of patients from a diverse set of racial and ethnic backgrounds.

Once available, data on the duration of complete response — the other primary end point of the study — will address the question of whether this approach will, in the long term, spare all or most patients from surgical resection. To date, 4 of the 13 patients who were needed to meet our prespecified criteria for the end point regarding the duration of response have had a sustained clinical complete response for more than 1 year after completion of dostarlimab therapy. In a study involving patients with metastatic mismatch repair–deficient tumors who had an objective response after treatment with single-agent PD-1 blockade, the durability of response exceeded 75% at 30 months[40]; such results make us optimistic that disease remission will be durable in the context of neoadjuvant therapy. As these data mature, we envision that PD-1 blockade will be evaluated in other mismatch repair–deficient tumors, such as localized pancreatic, gastric, and prostate cancers, in the context of neoadjuvant treatment; this could open the door for an immunoablative approach involving a variety of tumor types akin to mismatch-repair deficiency in patients with metastatic disease. In the event that local or distant recurrence is observed, combination chemotherapy or radiation may be warranted in addition to checkpoint blockade.

In our study, single-agent dostarlimab was remarkably effective in mismatch repair–deficient, locally advanced rectal cancer, providing a clinical complete response in all 12 patients who have completed treatment to date. The study also provides a framework for evaluation of highly active anticancer therapies in the neoadjuvant context, wherein patients would potentially be spared from chemoradiotherapy and surgery while their tumor is treated when it is most likely to respond — namely, before exposure to other agents that might select for cells with a resistant phenotype.

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APPENDIX

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