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Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

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ABSTRACT

BACKGROUND

Mismatch repair–deficient (dMMR) tumors can be found in 10 to 15% of patients with nonmetastatic colon cancer. In these patients, the efficacy of chemotherapy is limited. The use of neoadjuvant immunotherapy has shown promising results, but data from studies of this approach are limited.

METHODS

We conducted a phase 2 study in which patients with nonmetastatic, locally advanced, previously untreated dMMR colon cancer were treated with neoadjuvant nivolumab plus ipilimumab. The two primary end points were safety, defined by timely surgery (i.e., ≤2-week delay of planned surgery owing to treatment-related toxic events), and 3-year disease-free survival. Secondary end points included pathological response and results of genomic analyses.

RESULTS

Of 115 enrolled patients, 113 (98%; 97.5% confidence interval [CI], 93 to 100) underwent timely surgery; 2 patients had surgery delayed by more than 2 weeks. Grade 3 or 4 immune-related adverse events occurred in 5 patients (4%), and none of the patients discontinued treatment because of adverse events. Among the 111 patients included in the efficacy analysis, a pathological response was observed in 109 (98%; 95% CI, 94 to 100), including 105 (95%) with a major pathological response (defined as ≤10% residual viable tumor) and 75 (68%) with a pathological complete response (0% residual viable tumor). With a median follow-up of 26 months (range, 9 to 65), no patients have had recurrence of disease.

CONCLUSIONS

In patients with locally advanced dMMR colon cancer, neoadjuvant nivolumab plus ipilimumab had an acceptable safety profile and led to a pathological response in a high proportion of patients. (Funded by Bristol Myers Squibb; NICHE-2 ClinicalTrials.gov number, NCT03026140.)

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CME

Mismatch repair deficiency (dMMR) is found in up to 15% of nonmetastatic colon cancers,[1,2] and dMMR tumors are, at present, managed similarly to the way mismatch repair–proficient (pMMR) tumors are managed. Defects in the DNA mismatch repair machinery can be identified by detection of the loss of MMR protein expression with the use of immunohistochemical analysis or by detection of microsatellite instability with the use of polymerase-chain-reaction assays. Currently, patients with stage III dMMR colon cancer are treated with surgery, followed by adjuvant chemotherapy that consists of fluorouracil plus oxaliplatin.[3-5]

Recent data from the FOxTROT (Fluorouracil, Oxaliplatin and Targeted Receptor Pre-Operative Therapy) study support the use of neoadjuvant chemotherapy in patients with locally advanced colon cancer on the basis of improved 2-year disease control.[6] However, the efficacy of neoadjuvant chemotherapy was strongly associated with MMR status, and pathological responses were observed in only 7% of dMMR tumors.[6] Conversely, immune checkpoint blockade is highly effective in patients with dMMR metastatic colorectal cancers, significantly improving progression-free survival.[7-9] In addition, recent data strongly support the use of neoadjuvant immunotherapy in nonmetastatic dMMR tumors, with clinical and pathological responses observed in high proportions of patients.[10-12]

The NICHE (Neoadjuvant Immune Checkpoint Inhibition and Novel IO Combinations in Early-Stage Colon Cancer) study evaluated neoadjuvant immunotherapy in a small cohort of patients with dMMR colon cancer.[10,11] On the basis of data from this study, we hypothesized that cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade (a single dose of the CTLA-4 inhibitor ipilimumab) and programmed cell death 1 (PD-1) blockade (two doses of the PD-1 inhibitor nivolumab) would be safe and beneficial in a larger cohort of patients with locally advanced dMMR colon cancer. To test this hypothesis, we initiated the phase 2 NICHE-2 study to assess the safety and efficacy of neoadjuvant nivolumab plus ipilimumab in patients with locally advanced dMMR colon cancer.

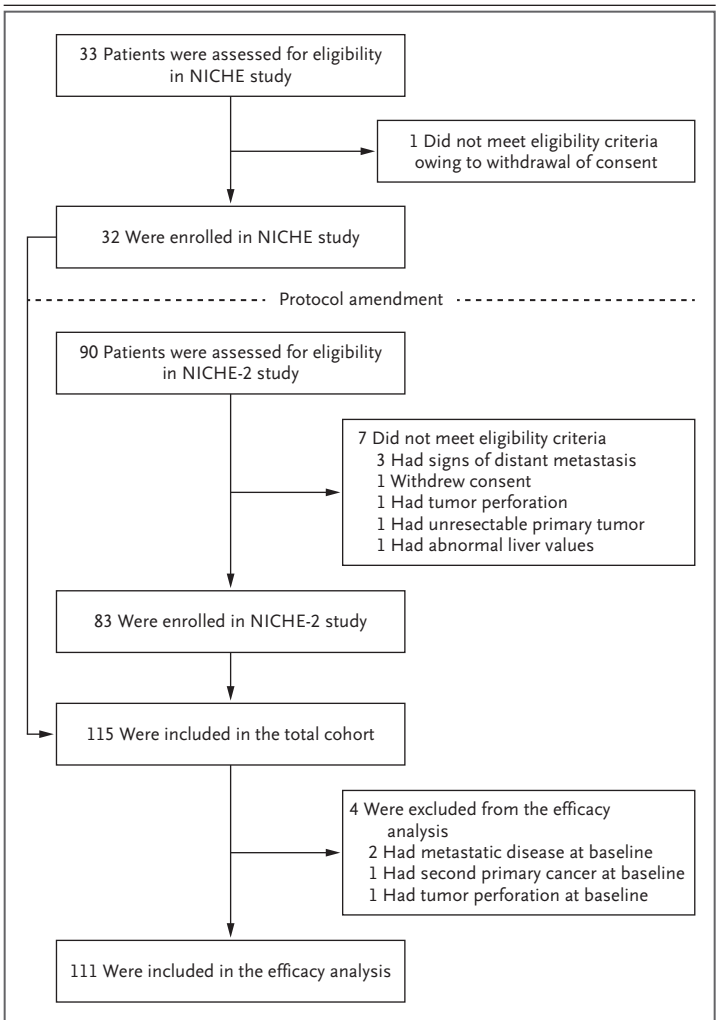

Figure 1. Screening and Enrollment, before and after Protocol Amendment.
A total of 115 patients with mismatch repair–deficient colon cancer were enrolled. A total of 32 patients were enrolled in the NICHE cohort. A protocol amendment in October 2020 then led to the enrollment of 83 patients in the NICHE-2 cohort, in which patients were eligible if they had disease classified by radiographic assessment as cT3 or higher, N+, or both according to the American Joint Committee on Cancer tumor–node–metastasis (TNM) staging system, version 8, in which T refers to the size and extent of the tumor (with higher numbers indicating greater advancement) and N+ indicates that cancer is present in the lymph nodes.

METHODS

PATIENTS

Full eligibility criteria are detailed in the protocol, available with the full text of this article at NEJM.org. Patients were eligible for inclusion if they were at least 18 years of age and had previously untreated, dMMR, clinical stage II or III colon adenocarcinoma that was deemed to be resectable and showed no signs of distant metastases. In the original protocol, safety was the primary end point, with a planned sample size

of 30 patients with clinical stage I, II, or III dMMR colon cancer. Revision of the protocol in October 2020 led to the addition of a second primary end point — 3-year disease-free survival — and to the enrollment of a new cohort of patients with disease classified as T3 or higher, N+, or both by radiographic assessment, in order to enrich for high-risk disease, stage III disease, or both. Radiographic assessment was performed according to the American Joint Committee on Cancer tumor–node–metastasis (TNM) cancer staging system, version 8, in which T refers to the size and extent of the tumor (with higher numbers indicating a more advanced tumor) and N refers to the spread of cancer to the lymph nodes (with N+ indicating that spreading has occurred). In the present report, we combine data from both the original NICHE dMMR cohort (32 patients)[10,11] and the new NICHE-2 dMMR cohort (83 patients) (Fig. 1).

Mismatch repair status was determined with the use of immunohistochemical analysis for MLH1, PMS2, MSH2, and MSH6 proteins, and deficiency was specified as the absence of staining of one or more proteins. Patients were required to have a World Health Organization performance-status score of 0 or 1 (range, 0 to 5, with higher numbers indicating greater disability).[13] Key exclusion criteria were clinical obstruction, previous immunotherapy, and active autoimmune disease requiring immunosuppressive therapy.

STUDY DESIGN

In this phase 2, multicenter, single-group study, patients received two doses of nivolumab at a dose of 3 mg per kilogram of body weight, with the first dose administered on day 1 and the second on day 15, and one dose of ipilimumab at a dose of 1 mg per kilogram on day 1. Surgery was scheduled to be performed at one of six participating centers in the Netherlands within 6 weeks after study enrollment. Tumor response was determined by central pathological assessment of residual viable tumor in the resection specimen.

STUDY OVERSIGHT

NICHE-2 is an investigator-initiated study. The study protocol was approved by the institutional review board at the Netherlands Cancer Institute, and the study was conducted in accordance with the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. In addition, the study was approved by the individual ethics board at each participating center. All patients provided written informed consent.

The Netherlands Cancer Institute conducted the study. The first author designed and coordinated the study, interpreted clinical and translational data, and wrote the manuscript. All data were treated confidentially. Bristol Myers Squibb funded the study but had no role in designing or executing the study, analyzing the data, or writing the manuscript. All the authors reviewed and edited the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

END POINTS

NICHE-2 was designed to have two separate primary end points: a safety end point and an efficacy end point. The safety end point was timely surgery, which was specified as the performance of planned surgery with a delay of no more than 2 weeks beyond the prespecified 6 weeks after study enrollment owing to treatment-related toxic effects. Delays due to logistic reasons or pandemic-related or other non–treatment-related serious adverse events were not considered to be treatment-related complications. The relationship of an adverse event to treatment was determined by the treating physician or, if the physician was uncertain, by consensus among the study investigators. The primary efficacy end point was 3-year disease-free survival. Secondary end points included pathological response and results of translational genomic analyses. In this report, we present data for the primary safety end point and for the secondary end points; in addition, since data on 3-year disease-free survival are not mature, we report the incidence of disease recurrence as of the latest follow-up.

PATHOLOGICAL ASSESSMENT

Formalin-fixed, paraffin-embedded sections were obtained from both pretreatment biopsy specimens and resection specimens. Slides of resection specimens were counterstained with hematoxylin and eosin and centrally reviewed by an experienced gastrointestinal pathologist, who assessed the percentage of residual viable tumor

in each sample.[14] A pathological response was specified as no more than 50% residual viable tumor in the resection specimen, whereas a major pathological response was specified as no more than 10% residual viable tumor and a pathological complete response as no residual viable tumor in either the tumor bed or the lymph nodes.[14,15] The American Joint Committee on Cancer staging protocol, version 8, was used for post–neoadjuvant therapy TNM staging.[16]

GENOMIC ANALYSES

Tumor and germline genomic analyses were performed by whole-exome sequencing of pretreatment tumor samples and matched germline DNA (details are provided in the Methods section in the Supplementary Appendix, available at NEJM.org). Whole-exome sequencing data were used to identify driver mutations and mutations in the gene encoding beta$_2$ microglobulin and to assess the tumor mutational burden.

STATISTICAL ANALYSIS

NICHE-2 was designed with two primary end points and a planned enrollment of 100 patients. To preserve the overall type I error rate at 5%, the alpha was split to test each primary end point at an equal level of 2.5%. For the safety end point, we calculated that a sample size of 95 patients would provide the study with 80% power to test the null hypothesis — that the percentage of patients undergoing timely surgery would be 85% — against an alternative hypothesis — that the percentage would be 95% — with the use of a binomial test for one proportion at a two-sided alpha of 2.5%.

For binary end points, two-sided confidence intervals were constructed with the Clopper–Pearson method; safety is reported with a 97.5% confidence interval, and secondary end points with a 95% confidence interval. To assess whether the pathological response differed in association with variables of interest, exploratory and post hoc subgroup analyses were conducted; no adjustment for multiplicity was performed, and confidence intervals cannot be used in place of hypothesis tests. Statistical analyses were performed with R software, version 4.3.0, and analyses related to whole-exome sequencing were performed with R software, version 4.2.0.[17,18] Details are provided in the Supplementary Appendix and in the protocol.

RESULTS

PATIENTS

From July 4, 2017, to July 18, 2022, a total of 115 patients with locally advanced and previously untreated dMMR colon cancers were enrolled and treated. The demographic and disease characteristics of the patients are summarized in Table 1.

All 115 patients were included in the safety analyses. The median age was 60 years (range, 20 to 82), and 58% were women. The patient population was representative of the general Dutch population and of patients with dMMR tumors in previous studies (Table S1). Of the 115 patients, 77 (67%) had stage III disease according to radiographic assessment and 74 (64%) had a cT4 tumor (defined as a tumor that has invaded the serosal surface [cT4a] or that has invaded or adhered to adjacent organs or structures [cT4b]). Four patients received a diverting stoma owing to obstructive disease before study enrollment. Among all enrolled patients, 111 met the eligibility criteria and were included in efficacy analyses. The patients who did not meet eligibility criteria were excluded for the following reasons: the presence of metastatic disease at baseline (2 patients), the presence of a second primary cancer at baseline (1 patient), and tumor perforation at baseline (1 patient) (Fig. 1).

TUMOR CHARACTERISTICS

A total of 37 patients had the Lynch syndrome, a hereditary condition affecting DNA mismatch repair, which had been newly diagnosed in 31 of these patients (Table 1 and Table S2). Another 76 patients had a sporadic dMMR tumor, which was attributed to *MLH1* promoter hypermethylation in 57 patients and to somatic MMR mutations in 19 patients. In 2 patients, the underlying cause of dMMR remained unexplained.[1]

SAFETY

The criteria to deem the primary safety end point successful were met. All patients completed both cycles of immunotherapy, and all patients underwent surgery, with an R0 resection (no tumor in the margins of the resected tissue) performed in 100% of the patients. The percentage of patients who underwent timely surgery according to protocol definitions was 98% (97.5% confidence interval [CI], 93 to 100);

only 2 patients (2%) had treatment-related adverse events that led to delay of surgery. Both delays were due to myositis (grade 2 and grade 3) that resolved with immunosuppressive treatment, which allowed surgery to be performed after a total delay of 10.0 weeks and 27.8 weeks, respectively, beyond the prespecified 6 weeks after study enrollment. No other surgical delays were noted.

Immune-related adverse events of any grade were observed in 73 patients (63%; 95% CI, 54 to 72), and most were grade 1 or 2 events. The most common grade 1 or 2 adverse events included infusion-related reactions (37 patients; 32%), thyroid function disorders (14 patients; 12%), and dry mouth (10 patients; 9%). Nine patients (8%) with thyroid function disorders and 4 patients (3%) with adrenal insufficiency received long-term replacement therapy. Five patients (4%; 95% CI, 1 to 10) had grade 3 or 4 adverse events, which included rash (1 patient), asymptomatic increase in amylase and lipase levels (1 patient), myositis (1 patient), hepatitis (1 patient), and hyponatremia (1 patient) (Table S3). Surgery-related adverse events of any grade were observed in 22 patients (19%; 95% CI, 12 to 28) (Table S4), and surgery-related grade 3 events occurred in 12 patients (10%; 95% CI, 6 to 18). Anastomotic leakage occurred in 4 patients (3%).

Table 1. Demographic and Disease Characteristics of the Patients.

Characteristic	Patients (N=115)
Female sex — no. (%)	67 (58)
Median age (range) — yr	60 (20–82)
WHO performance-status score — no. (%)*	
0	100 (87)
1	15 (13)
Race or ethnic group — no. (%)†	
White	97 (84)
Asian	6 (5)
Black	5 (4)
Other	7 (6)
Tumor stage — no. (%)‡	
cT2	17 (15)
cT3 or cT3–T4a	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status — no. (%)§	
cN–	38 (33)
cN+	77 (67)
Primary tumor location — no. (%)	
Right	78 (68)
Transverse	17 (15)
Left	20 (17)
Lynch syndrome — no. (%)	37 (32)
Unexplained dMMR — no. (%)¶	2 (2)
Non–Lynch syndrome dMMR — no. (%)	76 (66)

* The World Health Organization (WHO) performance-status score ranges from 0 to 5, with higher scores indicating greater disability.
† Race or ethnic group was reported by the patients or inferred on the basis of the country of birth if patient-reported data were unavailable. The category "Other" includes patients of Hispanic, Middle Eastern, and North African descent.
‡ Tumor stage was classified according to the American Joint Committee on Cancer staging system, version 8, with higher numbers indicating a more advanced tumor.
§ Nodal status indicates the presence (cN+) or absence (cN–) of cancer cells in the lymph nodes.
¶ Unexplained mismatch repair deficiency (dMMR) was specified as dMMR that could not be explained by characteristic germline alterations, biallelic somatic inactivation of the MMR protein, or *MLH1* promoter hypermethylation.

EFFICACY

A pathological response was observed in 109 of 111 patients (98%; 95% CI, 94 to 100), including 105 patients (95%; 95% CI, 89 to 98) with a major pathological response and 75 (68%; 95% CI, 58 to 76) with a pathological complete response (Fig. 2 and Table 2). These responses were observed within a median time from the first dose of immunotherapy to surgery of 5.4 weeks (range, 4.0 to 33.6). Furthermore, 4 patients had a partial response, with 18 to 35% residual viable tumor. Only 1 patient, with 60% residual viable tumor, was considered to have had no response. In the 5 patients with a partial response or no pathological response, dMMR was confirmed by immunohistochemical analysis in post-treatment resection samples. One patient with a time to surgery of 33.6 weeks owing to myositis could not be evaluated because the tumor bed could not be determined, which prevented the calculation of residual viable tumor. Of the 75 patients with a pathological complete response for whom radiographic response assessment was available, only 2 had a radiographic complete response.

A pathological complete response was observed in a higher percentage of patients with the Lynch syndrome than of those without (79% vs. 61%) (Fig. 3 and Fig. S1). Five patients, all

Table 2. Pathological Responses among Patients in the Efficacy Analysis.*

Residual Viable Tumor	Patients (N = 111)
	no. (%)
≤50% Residual viable tumor	109 (98)
≤10% Residual viable tumor: major pathological response	105 (95)
0% Residual viable tumor: complete pathological response	75 (68)
11–49% Residual viable tumor: partial pathological response	4 (4)
≥50% Residual viable tumor, indicating lack of pathological response	1 (1)
Unable to be evaluated†	1 (1)

* For patients with a synchronous second tumor in the colon, the response observed in the tumor with the highest baseline stage is shown.
† In one patient, the tumor bed could not be determined, and therefore, the percentage of residual viable tumor could not be calculated.

with the Lynch syndrome, had a synchronous second dMMR colon tumor. A pathological complete response was observed in both tumors in 4 of these patients (Table S5). Fourteen patients (13%) had resection specimens with tumor-positive lymph nodes (Table S6), and 3 of these patients received adjuvant chemotherapy, including the only patient who did not have a response to immunotherapy. When all treated patients (a total of 115) are included in the analysis (Table S7), the percentages of patients with any pathological response, a major pathological response, and a pathological complete response are similar to those in the efficacy analysis: 97% (95% CI, 93 to 99), 92% (95% CI, 86 to 96), and 66% (95% CI, 57 to 75), respectively.

With a median follow-up of 26.2 months (range, 9.1 to 65.3), no disease recurrences have been observed. All 37 patients with a follow-up of longer than 36 months remain disease-free.

WHOLE-EXOME SEQUENCING

Whole-exome sequencing data were available for 107 patients included in the efficacy analyses and revealed a tumor mutational burden ranging from 3.46 to 138.7 mutations per megabase (median, 42.5) (Fig. S2). The baseline tumor mutational burden was not associated with the occurrence of a pathological complete response (median, 41.8 mutations per megabase among patients with a pathological complete response vs. 43.6 mutations per megabase among patients without a pathological complete response). Furthermore, the tumor mutational burden did not differ between Lynch syndrome–associated and non–Lynch syndrome–associated tumors (median, 42.9 mutations per megabase in both groups). No associations were noted between the tumor mutational burden and the clinical T or N stage in the TNM staging system or between the tumor mutational burden and the MMR proteins affected (Fig. S3). The four patients with either a low tumor mutational burden (2 patients) or unexplained dMMR (2 patients) had a major pathological response (1 patient with a low tumor mutational burden) or a pathological complete response (3 patients) (Table S8).

A *BRAF* V600E mutation was detected in 41 of 72 non–Lynch syndrome–associated tumors (57%), all with *MLH1* promoter hypermethylation, and in 1 Lynch syndrome–associated tumor. A pathological complete response was observed in a higher percentage of patients with *BRAF* V600 wild-type tumors than in those with *BRAF* V600E mutant tumors (75% vs. 57%), yet the difference between these groups was not notable when only patients with non–Lynch syndrome–associated tumors were considered (65% vs. 59%). Furthermore, the percentage of patients with a pathological complete response was higher among those with *RAS* mutations than among those with *RAS* wild-type tumors (79% vs. 64%) (Fig. S4). A pathological complete response was also observed in 23 of the 33 patients (70%) with tumors that had a mutation in the gene encoding beta$_2$ microglobulin.

DISCUSSION

In a previous small study that included 32 patients, neoadjuvant immunotherapy led to pathological responses in 100% of patients with dMMR colon cancer.[10,11] In the present study, treatment with neoadjuvant PD-1 plus CTLA-4 blockade in patients with locally advanced dMMR colon cancer had an acceptable safety profile and resulted in pathological responses in 98% of patients after only 4 weeks of treatment, with a major pathological response observed in 95% of patients and a pathological complete response observed in 68%. NICHE-2 is a large study involving patients with nonmetastatic dMMR colon cancers that includes pathological assessment of both the complete tumor bed and lymph nodes in all patients.

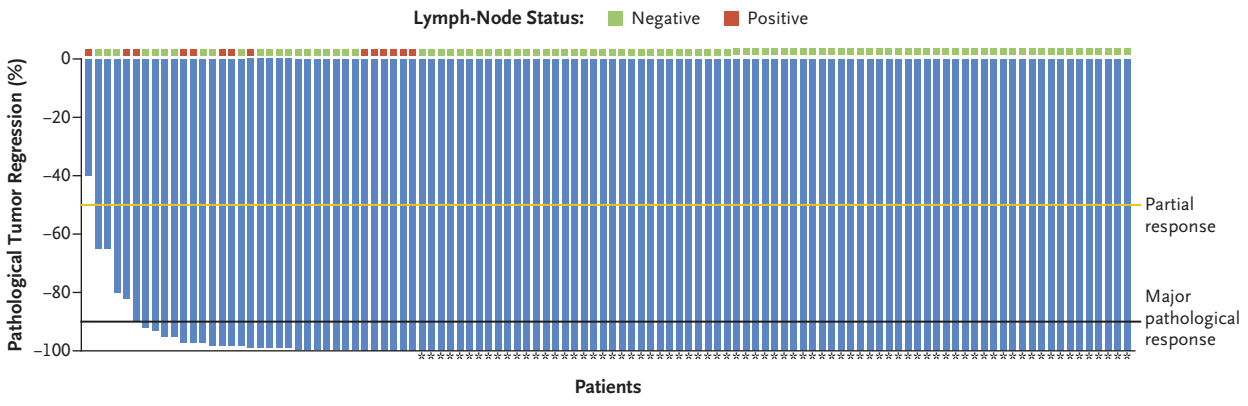

Figure 2. Pathological Responses among Patients in the Efficacy Analysis.

The waterfall plot shows the percentage of pathological tumor regression per tumor among the 110 tumors that could be evaluated for a pathological response. Boxes above each bar indicate the corresponding pathological lymph-node status. Patients with a pathological complete response in both the primary tumor and the lymph nodes are indicated by an asterisk. The black horizontal line indicates the threshold for a major pathological response, specified as at least 90% tumor regression. The yellow line indicates the threshold for a partial response, specified as at least a 50% regression.

Currently, patients with stage III dMMR colon cancer are treated with adjuvant chemotherapy consisting of fluorouracil plus oxaliplatin. Although the International Duration of Adjuvant Chemotherapy (IDEA) trial has led to a decrease in the duration of this adjuvant treatment from 6 to 3 months, thereby decreasing toxic effects,[19-21] 3-year risks of recurrence of stage III dMMR tumors remain high at approximately 35% for patients with either T4 or N2 disease, and most of these recurrences occur within 2 years.[22,23]

In our study, we aimed to include patients with disease classified as high risk on the basis of radiographic assessment — 64% of patients enrolled had cT4 tumors — and we observed a major pathological response and a pathological complete response in high proportions of patients regardless of tumor staging. Furthermore, only three patients received adjuvant chemotherapy. Despite the high percentage of high-risk tumors and the omission of chemotherapy in most patients in our study, no patient has had disease recurrence to date.

Randomized trials are often preferred to establish the efficacy of new treatments; however, in the case of nonmetastatic dMMR colon cancers, the substantial gap between response to neoadjuvant chemotherapy and response to neoadjuvant immunotherapy, in our opinion, renders a randomized trial comparing these treatments unethical. Specifically, even the lower bound of the 95% confidence interval from an intention-to-treat analysis of pathological response in our study, at 93%, would still be superior to the pathological response of 7% with neoadjuvant chemotherapy.[6] On the basis of these data, the treatment regimen from this study would provide substantial improvement in the treatment of patients with dMMR tumors, by limiting treatment duration while achieving a response in a high proportion of patients and maintaining a manageable safety profile.

Although neoadjuvant treatment is considered to be the standard of care in patients with rectal cancer and many other tumor types, neoadjuvant treatment for colon cancer is often reserved for patients in whom induction strategies are indicated, often to improve surgical outcomes. The FOxTROT study was the first to show the safety and feasibility of neoadjuvant chemotherapy in patients with colon cancer. In that study, pathological responses to neoadjuvant chemotherapy were observed in only 7% of dMMR tumors.[6] Neoadjuvant immunotherapy has been tested across tumor types,[24-26] with compelling data on the superiority of neoadjuvant to adjuvant immunotherapy in melanoma and, importantly, a strong association between a major pathological response or a pathological complete response to neoadjuvant immunotherapy and a lower risk of disease recurrence.[27,28]

Given the limited data on neoadjuvant immunotherapy in dMMR colon cancer, we opted in

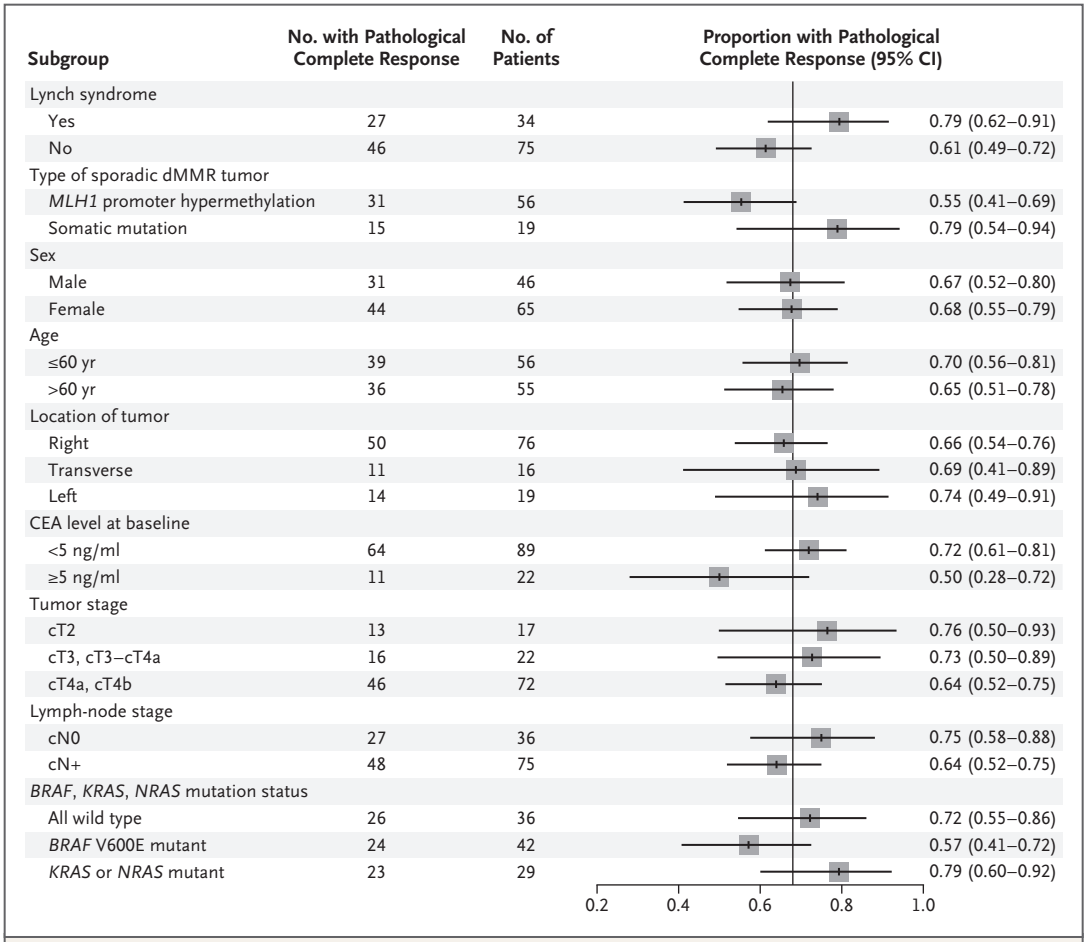

Figure 3. Pathological Complete Response According to Subgroups.

The response data are stratified according to characteristics of the 111 patients included in the efficacy analysis. Carcinoembryonic antigen (CEA) is a biomarker that is normally present in the blood at levels of 5.0 ng per milliliter or below. Levels above the normal range are associated with the presence of various cancers, with higher levels often indicating greater extent of disease. Tumor and lymph-node staging is according to the American Joint Committee on Cancer TNM staging system, with cT and cN indicating clinical stages. Lymph-node stage cN0 indicates the absence of cancer cells in the lymph nodes. The vertical line at 0.68 represents the proportion of patients in the efficacy analysis with a pathological complete response. The notation dMMR denotes deficient mismatch repair.

NICHE-2 for a short, 4-week neoadjuvant treatment period (two cycles of 2 weeks, with treatment administered at the beginning of each cycle) to avoid prolonging the time to surgery and to reduce the risks of toxic effects of treatment and disease progression during the treatment period. We observed that neoadjuvant immunotherapy did not lead to higher-than-expected surgical complications and that all but two patients underwent surgery without treatment-related delays. Furthermore, no patients had disease progression during treatment, and despite the high percentage of patients with cT4 tumors, none of these patients had surgical specimens that showed tumor involvement at the tissue margins.

In metastatic dMMR colorectal cancer, the percentages of patients who have a response to first-line anti–PD-1 monotherapy and anti–PD-1 plus anti–CTLA-4 combination therapy are approximately 45%[7] and 70%[9], respectively. Although data on the direct comparison of monotherapy with combination treatment are not yet available,[29] it is plausible that the addition of anti–CTLA-4 therapy increases efficacy in patients with dMMR tumors.

Small studies have shown a pathological complete response to neoadjuvant anti–PD-1 monotherapy in high percentages of patients with dMMR colorectal cancer.[12,30] In these studies, patients had a longer period of neoadjuvant treatment and a longer time to surgery or clinical assessment of response than those in the present study.[12,30] Since the majority of patients without a pathological complete response in our study had only 1 to 10% residual viable tumor, we may have observed a pathological complete response in a higher proportion of patients after a longer period between the end of treatment and surgery. Whether a pathological complete response is an aim of neoadjuvant treatment depends mainly on the treatment goals. Specifically, if the goal is organ preservation, a longer duration of treatment, an increased time to response assessment, or both may help achieve this goal in a higher proportion of patients. Although organ preservation is a well-established goal in the treatment of rectal cancer, there are notable differences from colon cancer. First, surgery for colon cancer carries a lower risk of colostomy and has less effect on long-term quality of life than surgery for rectal cancer. Second, although the follow-up for rectal cancer is fairly standardized, this is not the case for colon cancer. In our study, radiographic assessment rarely provided an accurate prediction of a pathological complete response. Additional factors, such as clearance of circulating tumor DNA, may be needed to enable organ preservation in patients with dMMR colon cancer after neoadjuvant immunotherapy.

One of the major limitations of our study is the often inaccurate radiographic staging of colon cancers, which can lead to possible overtreatment. Although overstaging is often assumed, we did observe a pathological complete response in lymph nodes from patients who were assessed as lymph-node–negative at baseline. Furthermore, although lymph-node involvement is often misclassified, cT staging, particularly when a cT4 tumor is assumed, has a high positive predictive value.[31,32] In NICHE-2, 64% of patients had cT4 tumors, and 67% of tumors were centrally assessed as lymph-node–positive. Finally, when designing the study, we took into consideration the caveat of inaccurate radiographic staging in calculations of the primary end point of disease-free survival. In our calculations, we aimed at inclusion of at least 80% of patients with radiographically assessed lymph-node involvement and assumed overstaging in 25% of these cases.

Nevertheless, a subgroup of patients with a low risk of recurrence and thus good prognosis may have received neoadjuvant immunotherapy. Although a risk of overtreatment is a factor in all studies of neoadjuvant therapies in colon cancer, many patients currently receiving adjuvant chemotherapy are overtreated, and in the case of dMMR tumors, most probably receive little to no benefit from this treatment. The high proportion of patients with a pathological response observed after only 4 weeks of treatment in our study, together with the safety profile, may provide sufficient justification to provide immunotherapy to patients with radiographically assessed high-risk disease, especially if 3-year disease-free survival data from this study are positive. With the high incidence of disease recurrence in patients with dMMR tumors that are stage T4, have spread to the lymph nodes, or both, despite adjuvant chemotherapy, improved systemic treatment is needed.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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