

ORIGINAL ARTICLE

Nonoperative Management of Mismatch Repair–Deficient Tumors

A. Cercek,¹ M.B. Foote,¹ B. Rousseau,¹ J.J. Smith,² J. Shia,³ J. Sinopoli,¹ J. Weiss,¹ M. Lumish,⁴ L. Temple,¹ M. Patel,¹ C. Wilde,¹ L.B. Saltz,¹ G. Argiles,¹ Z. Stadler,¹ O. Artz,¹ S. Maron,¹ G. Ku,¹ P. Gu,¹ Y.Y. Janjigian,¹ D. Molena,² G. Iyer,¹ J. Coleman,² W. Abida,¹ S. Cohen,¹ K. Soares,² M. Schattner,¹ V.E. Strong,² R. Yaeger,¹ P. Paty,² M. Shcherba,¹ R. Sugarman,¹ P.B. Romesser,⁵ A. Zervoudakis,¹ A. Desai,¹ N.H. Segal,¹ I. El Dika,¹ M. Widmar,² I. Wei,² E. Pappou,² G. Fumo,⁶ S. Aparo,⁷ M. Gonen,⁸ M. Gollub,⁹ V.S. Jayaprakasam,⁹ T.-H. Kim,⁹ J. Garcia Aguilar,² M. Weiser,² and L.A. Diaz, Jr.¹

ABSTRACT

BACKGROUND

Among patients with mismatch repair–deficient (dMMR), locally advanced rectal cancer, neoadjuvant checkpoint blockade eliminated the need for surgery in a high proportion of patients. Whether this approach can be extended to all early-stage dMMR solid tumors, regardless of tumor site, is unknown.

METHODS

We conducted a phase 2 study in which patients with stage I, II, or III dMMR solid tumors that were amenable to curative-intent surgery were treated with neoadjuvant dostarlimab, a programmed cell death 1 (PD-1) blocking agent, for 6 months. The response to treatment was assessed in two cohorts: patients in cohort 1 had dMMR, locally advanced rectal cancer, and patients in cohort 2 had dMMR nonrectal solid tumors. Patients with a clinical complete response could elect to proceed with nonoperative management; those with residual disease were to undergo resection. In this analysis, the primary end point, assessed in cohort 1, was a sustained clinical complete response at 12 months. Recurrence-free survival and safety were evaluated.

RESULTS

A total of 117 patients were included in the analysis. In cohort 1, all 49 patients who completed treatment had a clinical complete response and elected to proceed with nonoperative management. A total of 37 patients had a sustained clinical complete response at 12 months, a finding that met the criterion for efficacy. In cohort 2, a total of 35 of 54 patients who completed treatment had a clinical complete response, and 33 elected to proceed with nonoperative management. Among the 103 patients who completed treatment across both cohorts, 84 had a clinical complete response, and 82 did not undergo surgery. Among the 117 total patients, recurrence-free survival at 2 years was 92% (95% confidence interval, 86 to 99); the median follow-up for recurrence was 20.0 months (range, 0 to 60.8). The majority of patients (95%) had reversible, grade 1 or 2 adverse events (60%) or had no adverse events (35%). The option for curative resection was not compromised during or after treatment in any of the patients.

CONCLUSIONS

Among patients with early-stage dMMR solid tumors that were amenable to curative-intent surgery, neoadjuvant PD-1 blockade led to organ preservation in a high proportion of patients. (Funded by Swim Across America and others; ClinicalTrials.gov number, NCT04165772.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Cercek can be contacted at cerceka@mskcc.org, and Dr. Diaz at diaz15@mskcc.org; Drs. Cercek and Diaz can be contacted at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

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COMplete surgical resection is the predominant curative option for early-stage solid tumors.¹ Nonoperative management that consists of radiation therapy combined with chemotherapy has been successfully implemented for several types of cancer, including anal, bladder, rectal, and head and neck cancers.²⁻⁷ In addition, for small lung tumors, stereotactic radiation therapy can result in outcomes similar to those observed with surgery.⁸

Mismatch repair–deficient (dMMR) tumors are highly sensitive to immune checkpoint blockade, and in the context of metastatic disease, a substantial clinical benefit has been seen with this treatment across tumor types. This finding resulted in the first tumor-agnostic approval by the Food and Drug Administration, with immune checkpoint blockade indicated for all metastatic dMMR cancers, regardless of tumor site.⁹⁻¹² As neoadjuvant therapy, immune checkpoint blockade has resulted in elimination of the primary tumor in patients with colorectal cancers, and for rectal cancer specifically, data from our earlier study suggested that surgery can be averted when a clinical complete response is attained.¹³⁻¹⁶

The complete elimination of dMMR primary tumors with the use of programmed cell death 1 (PD-1) blockade alone in patients with rectal cancer has led to the question of whether this approach could be extended beyond rectal cancer to all early-stage dMMR solid tumors, regardless of tumor site — mirroring the benefit of immune checkpoint blockade across metastatic dMMR cancers. The potential effect is substantial, given that 2 to 3% of all early-stage solid tumors have an dMMR phenotype.⁹ Despite data supporting the efficacy of this treatment for metastatic disease, a concern with neoadjuvant therapy is that the “window of opportunity” for curative resection may lapse if the tumor progresses and becomes unresectable during the course of treatment with an immune checkpoint inhibitor.

To test the premise of nonoperative management of early-stage dMMR solid tumors, we expanded on our findings in patients with rectal cancer and enrolled patients with early-stage dMMR solid tumors at any site that were amenable to curative-intent surgery. The patients were treated with neoadjuvant dostarlimab, a PD-1 blocking agent, for 6 months and were monitored for response, progression, or recurrence.

METHODS

PATIENTS

Patients underwent screening at Memorial Sloan Kettering Cancer Center, Hartford HealthCare, and Baptist Health Miami Cancer Institute. Patients were referred for enrollment in the study if they had a newly diagnosed stage I, II, or III solid tumor that was amenable to curative-intent surgery and was dMMR, with loss of expression of MLH1, MSH2, MSH6, or PMS2 on immunohistochemical staining. Additional eligibility criteria are described in the protocol, available with the full text of this article at NEJM.org.

STUDY DESIGN

This phase 2 study was designed to evaluate the response to neoadjuvant dostarlimab, which was administered intravenously at a dose of 500 mg every 3 weeks for 6 months (nine cycles), in two cohorts: patients in cohort 1 had dMMR, locally advanced rectal cancer, and patients in cohort 2 had dMMR nonrectal solid tumors. Clinical response assessments were performed up to 8 weeks after completion of dostarlimab therapy with the use of tumor-specific imaging and endoscopy; all feasible assessments were performed. Patients with residual disease were to be treated with standard neoadjuvant therapy and surgery. Those with a clinical complete response could elect to proceed with nonoperative management, without receiving additional therapy or surgery. A clinical complete response was defined as no evidence of residual disease on tumor-specific imaging and on endoscopy when feasible.⁶ Details regarding the response assessments are provided in the Supplementary Appendix, available at NEJM.org.

STUDY OVERSIGHT

The institutional review board at Memorial Sloan Kettering Cancer Center approved the protocol and subsequent amendments. All the patients provided written informed consent. The manuscript was written solely by the authors, who collected the data and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

END POINTS

Two primary end points were assessed in cohort 1 (patients with dMMR rectal cancer). The first pri-

mary end point was overall response. The second primary end point was a sustained clinical complete response at 12 months after completion of dostarlimab therapy, with or without chemoradiotherapy, in patients who had not undergone surgery or had proceeded to surgery and had a pathological complete response. The analyses performed in cohort 2 (patients with dMMR nonrectal solid tumors) were exploratory. Recurrence-free survival and safety were evaluated, and genomic analyses were performed. A comparison of response assessments was performed in an exploratory analysis.

TUMOR GENOMIC ANALYSES

Genomic sequencing was performed on DNA from tumor tissue and matched normal blood samples for the detection of somatic and germline genomic alterations.¹⁷ All the samples were obtained in accordance with an institutional review board–approved protocol. Mutational profile similarity scores range from 0.4% to 99.9%, with higher scores indicating a higher likelihood that samples share a common somatic genetic ancestry.¹⁸ Microsatellite instability sensor scores are continuous starting at zero, with higher scores indicating a higher degree of microsatellite instability.

Circulating tumor DNA was measured with the use of a tumor-informed approach. For this approach, somatic mutations were identified with exome sequencing of DNA from tumor tissue and matched normal whole blood that assessed up to 50 tumor-specific mutations in cell-free DNA isolated from plasma. Details regarding the genomic analyses are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We previously reported the results for the first primary end point, which was assessed in cohort 1.¹⁵ The null hypothesis was rejected; an overall response of greater than 25% occurred when 12 consecutive patients had a clinical complete response.

We now report the results for the second primary end point, which was assessed in cohort 1. The analysis was based on data obtained from December 2019 through April 2025. We estimated that the study would have 80% power to show an improvement in the sustained clinical complete response from 27.5% (unacceptable) to 50% (acceptable) at a type I error of 0.05.

The study was conducted in accordance with Simon's two-stage minimax design. In the first stage, we planned to enroll 15 patients. If 4 or fewer patients had a clinical complete response for at least 12 months after completion of dostarlimab therapy, the study was to be discontinued owing to futility. If 13 or more patients had a clinical complete response for at least 12 months after completion of dostarlimab therapy, the study was to be discontinued owing to efficacy. Given the high efficacy noted in the first stage, the study was discontinued; the second stage was not needed.

The analyses performed in cohort 2 were exploratory. The widths of all confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. All statistical analyses were performed with the use of R software, version 4.3.2 (R Foundation for Statistical Computing). Details regarding the statistical analysis are provided in the Supplementary Appendix.

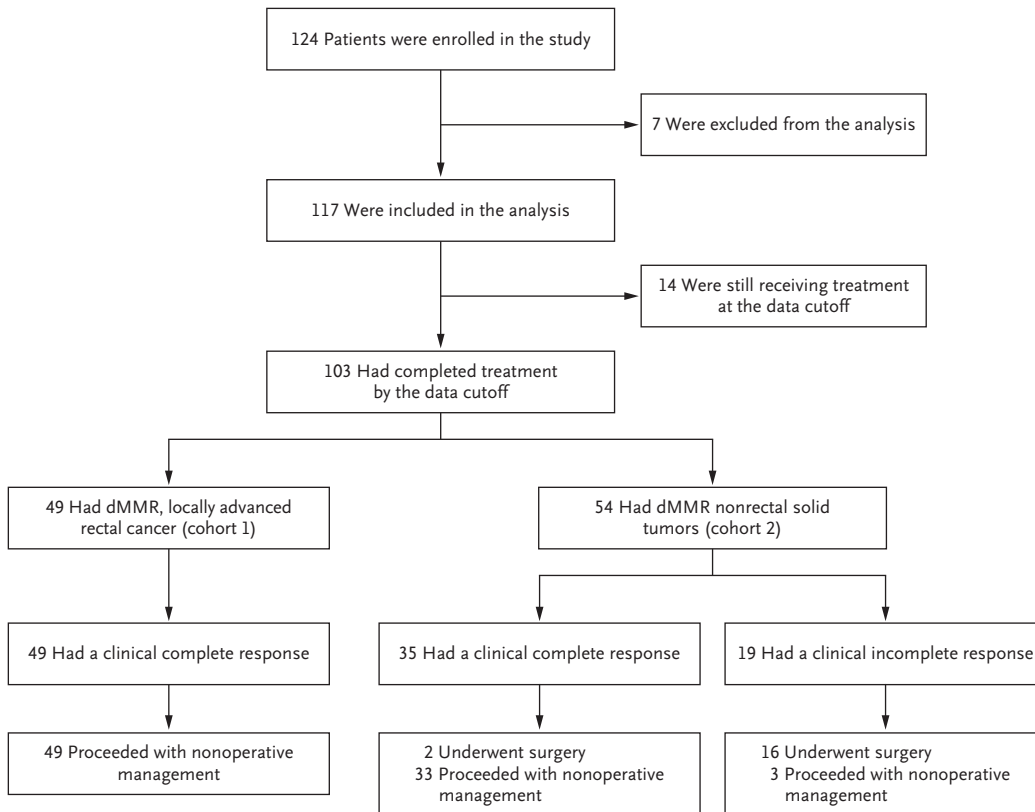
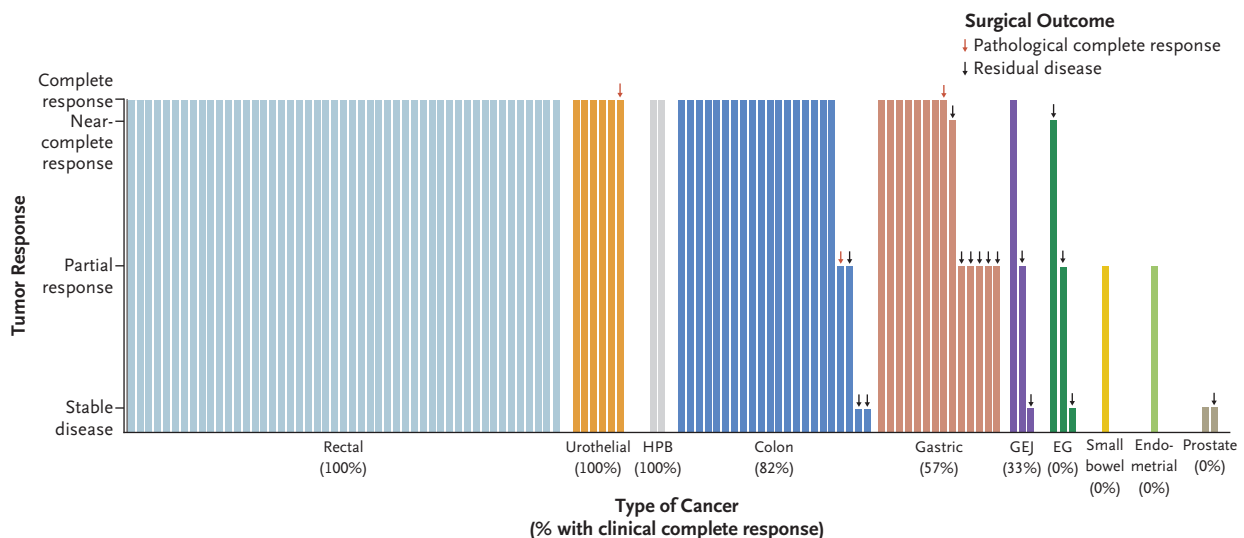
RESULTS

PATIENT AND TUMOR CHARACTERISTICS

A total of 124 patients were enrolled in the study. Seven patients were excluded from the analysis: 3 were found to have metastases or second cancers before treatment and withdrew from the study, 2 opted to discontinue therapy after one dose of dostarlimab, 1 discontinued therapy after four doses, and 1 was lost to follow-up.

By the data cutoff, 103 patients had completed treatment, and 14 were still receiving treatment (Fig. 1A). In cohort 1, a total of 49 patients completed treatment, with 48 patients completing all nine cycles. One patient chose to discontinue therapy after eight cycles because of an unrelated asthma exacerbation. In cohort 2, a total of 54 patients completed treatment, with 49 patients completing all nine cycles. Three patients discontinued therapy before they had a clinical complete response owing to concern about a lack of response, and 2 discontinued therapy after they had a clinical complete response owing to adverse events that were determined by the investigator to be related to treatment.

Patients in cohort 1 had only dMMR rectal cancers. Patients in cohort 2 had dMMR nonrectal solid tumors, including esophagogastric, colon, hepatobiliary, genitourinary, and gynecologic

A Enrollment, Treatment, and Response Assessment**B Clinical Response****Figure 1. Enrollment, Treatment, and Response Assessment.**

Panel A shows the distribution of patients after enrollment, treatment, and response assessment. Panel B shows the clinical response for each patient according to tumor type. Hepatobiliary (HPB) cancers consist of periampullary cancer and cholangiocarcinoma. EG denotes esophageal and GEJ gastroesophageal junction.

tumors. Across both cohorts, 64% of the patients had evidence of lymph-node involvement on imaging. All the patients had tumors with loss of expression of mismatch-repair proteins; loss of both MLH1 and PMS2 was the most common finding. Pathogenic germline variants in a mismatch-repair gene were noted in 44% of the patients (Table 1, and Table S1 in the Supplementary Appendix).

CLINICAL COMPLETE RESPONSE AND NONOPERATIVE MANAGEMENT

In cohort 1 (among patients with dMMR rectal cancer), all 49 patients who completed treatment had a clinical complete response and elected to proceed with nonoperative management (Fig. 1B). A total of 37 patients in cohort 1 had a sustained clinical complete response at 12 months after completion of treatment, a finding that satisfied the criterion for efficacy with respect to the second primary end point.

In cohort 2 (among patients with dMMR non-rectal solid tumors), 35 of the 54 patients (65%) who completed treatment had a clinical complete response, and 33 (61%) elected to proceed with nonoperative management. Two patients (1 with gastric cancer and 1 with urothelial cancer) who had a clinical complete response elected to undergo surgical resection. In both patients, no evidence of cancer was found in the resection specimen.

Among the 103 patients who completed treatment across both cohorts, 84 (82%; 95% confidence interval [CI], 72 to 88) had a clinical complete response, and 82 (80%; 95% CI, 70 to 87) did not undergo surgery. The primary tumor did not progress or become unresectable during or after treatment in any of the patients.

CLINICAL INCOMPLETE RESPONSE

In cohort 1, no patients had a clinical incomplete response (Fig. 1B). In cohort 2, a total of 19 of the 54 patients (35%) who completed treatment had a clinical incomplete response. Sixteen of these patients underwent surgical resection of the primary tumor, and 3 patients deferred surgery. Of the 16 patients who underwent surgery, 13 had evidence of tumor regression in the resection specimen. Of note, 3 had evidence of a pathological complete response in the primary tumor but had residual tumor in the lymph nodes (Table S2).

In 18 of the 19 patients who had a clinical incomplete response, the tumors had had a high degree of microsatellite instability at baseline. In the 1 other patient, the tumor had had subclonal loss of MLH1 and PMS2 and had been microsatellite stable.

Genomic data were available for 17 patients who had a clinical incomplete response, and sequences were compared between tumor tissue obtained at baseline and remnant tumor tissue obtained after treatment. Overall, the pre- and post-treatment tumors had a high likelihood of genomic relatedness (99.6%; 95% CI, 97.43 to 99.97).¹⁸ However, in two patients (Patients 51 and 90), the tumors had a low likelihood of genomic relatedness, with a mutational profile similarity score of less than 0.4%. In these two patients, the remnant tumors were not dMMR and did not have a high degree of microsatellite instability (Fig. S2); these were probably new primary tumors. Beyond these two cases, no meaningful differences were noted between the pre- and post-treatment tumors in the median tumor mutational burden among 14 patients (43 vs. 34 mutations per megabase), in the median microsatellite instability sensor score among 12 patients (15 vs. 16), or in loss of mismatch-repair proteins.

DURABILITY OF RESPONSE AND DISEASE RECURRENCE

Among the 117 total patients included in the analysis across both cohorts, recurrence-free survival at 2 years was 92% (95% CI, 86 to 99) (Fig. 2A and Fig. S3). The median follow-up for recurrence was 20.0 months (range, 0 to 60.8). Among 50 patients in cohort 1, recurrence-free survival at 2 years was 96% (95% CI, 90 to 100); the median follow-up for recurrence was 30.2 months (range, 5.8 to 60.8). Among 67 patients in cohort 2, recurrence-free survival at 2 years was 85% (95% CI, 70 to 100); the median follow-up for recurrence was 14.9 months (range, 0 to 32.7).

Disease recurrence developed in only 5 patients across both cohorts. One patient had tumor regrowth at the primary tumor site (the rectum), and 4 patients had recurrence solely in the lymph nodes. No patients underwent resection of the primary tumor after recurrence. One patient underwent resection of an isolated lymph node and had no evidence of disease at the data

Table 1. Characteristics of the Patients and the Tumors at Baseline.*

Characteristic	Cohorts 1 and 2 (N=117)	Cohort 1 (N=50)	Cohort 2 (N=67)
Sex — no. (%)			
Female	57 (49)	28 (56)	29 (43)
Male	60 (51)	22 (44)	38 (57)
Median age (range) — yr	57.0 (26–87)	51.0 (26–78)	67.0 (28–87)
ECOG performance-status score — no. (%)†			
0	88 (75)	40 (80)	48 (72)
1	29 (25)	10 (20)	19 (28)
Tumor type — no. (%)			
Rectal cancer	50 (43)	50 (100)	0
Colon cancer	33 (28)	0	33 (49)
Esophageal cancer	3 (3)	0	3 (4)
Gastroesophageal junction cancer	3 (3)	0	3 (4)
Gastric cancer	15 (13)	0	15 (22)
Urothelial cancer	7 (6)	0	7 (10)
Prostate cancer	2 (2)	0	2 (3)
Periampullary cancer	1 (1)	0	1 (1)
Cholangiocarcinoma	1 (1)	0	1 (1)
Small-bowel cancer	1 (1)	0	1 (1)
Endometrial cancer	1 (1)	0	1 (1)
Clinical tumor stage — no. (%)			
T0	1 (1)	1 (2)	0
T1–2	27 (23)	10 (20)	17 (25)
T3	65 (56)	23 (46)	42 (63)
T4	24 (21)	16 (32)	8 (12)
Clinical nodal stage — no. (%)			
Node-positive	75 (64)	42 (84)	33 (49)
Node-negative	42 (36)	8 (16)	34 (51)
Mismatch-repair gene with pathogenic Lynch syndrome–associated germline variants — no. (%)			
MLH1	16 (14)	7 (14)	9 (13)
MSH2	23 (20)	9 (18)	14 (21)
MSH6	12 (10)	8 (16)	4 (6)
None	60 (51)	23 (46)	37 (55)
Unknown	6 (5)	3 (6)	3 (4)
Deficient mismatch-repair proteins on immuno-histochemical staining — no. (%)			
MLH1 and PMS2	61 (52)	21 (42)	40 (60)
MSH2 and MSH6	37 (32)	16 (32)	21 (31)
MLH1 and MSH6	1 (1)	0	1 (1)
MSH2 alone	3 (3)	3 (6)	0
MSH6 alone	9 (8)	5 (10)	4 (6)

Table 1. (Continued.)

Characteristic	Cohorts 1 and 2 (N=117)	Cohort 1 (N=50)	Cohort 2 (N=67)
PMS2 alone	6 (5)	5 (10)	1 (1)
Median microsatellite instability sensor score (range) [‡]	18.8 (0.2–39.4)	19.3 (2.2–37.6)	18.7 (0.2–39.4)
Median tumor mutational burden (range) — mutations per megabase [§]	53.2 (4.9–145.0)	62.3 (27.2–106.3)	50.3 (4.9–145.0)

* A total of 124 patients were enrolled in the study; 7 patients were excluded from the analysis. Patients in cohort 1 had mismatch repair–deficient (dMMR), locally advanced rectal cancer, and patients in cohort 2 had dMMR nonrectal solid tumors. Percentages may not total 100 because of rounding.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

‡ Microsatellite instability sensor scores are continuous starting at zero, with higher scores indicating a higher degree of microsatellite instability. The score was unknown for 12 patients (3 in cohort 1; 9 in cohort 2).

§ The value was unknown for 9 patients (3 in cohort 1; 6 in cohort 2).

cutoff. PD-1 blockade was restarted in 4 patients, and 3 of these patients had no evidence of disease at the data cutoff.

Mismatch-repair deficiency with high genomic relatedness was seen consistently across the original and recurrent tumors, and no meaningful differences in the tumor mutational burden or the microsatellite instability sensor score were noted between the original and recurrent tumors that could be evaluated (Fig. S4). Among 4 patients, the median disease-free interval after recurrence was 6.6 months (range, 3.1 to 14.9). One patient was not included in the analysis because data were available from only one assessment performed during treatment, which showed a partial response.

No deaths occurred in either cohort. Across both cohorts, the median follow-up for survival was 21.5 months (range, 0 to 60.8; 95% CI, 19.4 to 23.6).

ADVERSE EVENTS

Adverse events occurred in 65% of the patients who received at least one dose of dostarlimab (Table 2). Reversible, grade 1 or 2 adverse events occurred in 60%. The most common grade 1 or 2 adverse events were fatigue (occurring in 23% of the patients across both cohorts), rash or dermatitis (in 21%), and pruritus (in 19%). The following grade 3 adverse events occurred in one patient each: diabetes, lung infection, hypothyroidism, encephalitis, and neutropenia. Grade 4 febrile neutropenia occurred in one patient.

COMPARISON OF RESPONSE ASSESSMENTS

We compared various techniques for response assessment by measuring the timing of response

among patients in both cohorts who had a clinical complete response and did not undergo surgery. On either imaging-based assessment or endoscopic assessment when feasible, the median time to a complete response was 6.2 months (range, 2.6 to 10.0) (Fig. S5). On imaging-based assessment (Fig. 2B), the median time to a complete response was 6.1 months (range, 1.2 to 12.5). On endoscopic assessment, the median time to a complete response was 6.1 months (range, 1.2 to 9.8).

Tumor biopsies were performed in both cohorts. The median time to a negative biopsy was 1.5 months (range, 1.1 to 9.8). Testing for circulating tumor DNA was also performed in both cohorts; such testing was positive in 70 of the 74 patients (95%) who were tested at baseline. Among the 52 patients who could be evaluated and also had a clinical complete response, the median time to clearance of circulating tumor DNA was 1.4 months (range, 1.3 to 8.3).

A total of 343 biopsies were performed during the study. A comparison of results from testing for circulating tumor DNA (a surrogate for the presence of tumor) with results from these biopsies showed substantial concordance (Kappa coefficient, 0.76; 95% CI, 0.68 to 0.83), with 307 observed agreements accounting for 89.50% of the total results.

The clearance of circulating tumor DNA varied according to the clinical response to treatment (Fig. 3). Among patients with a clinical complete response, circulating tumor DNA became undetectable during therapy, and testing remained negative at the end of treatment. Among

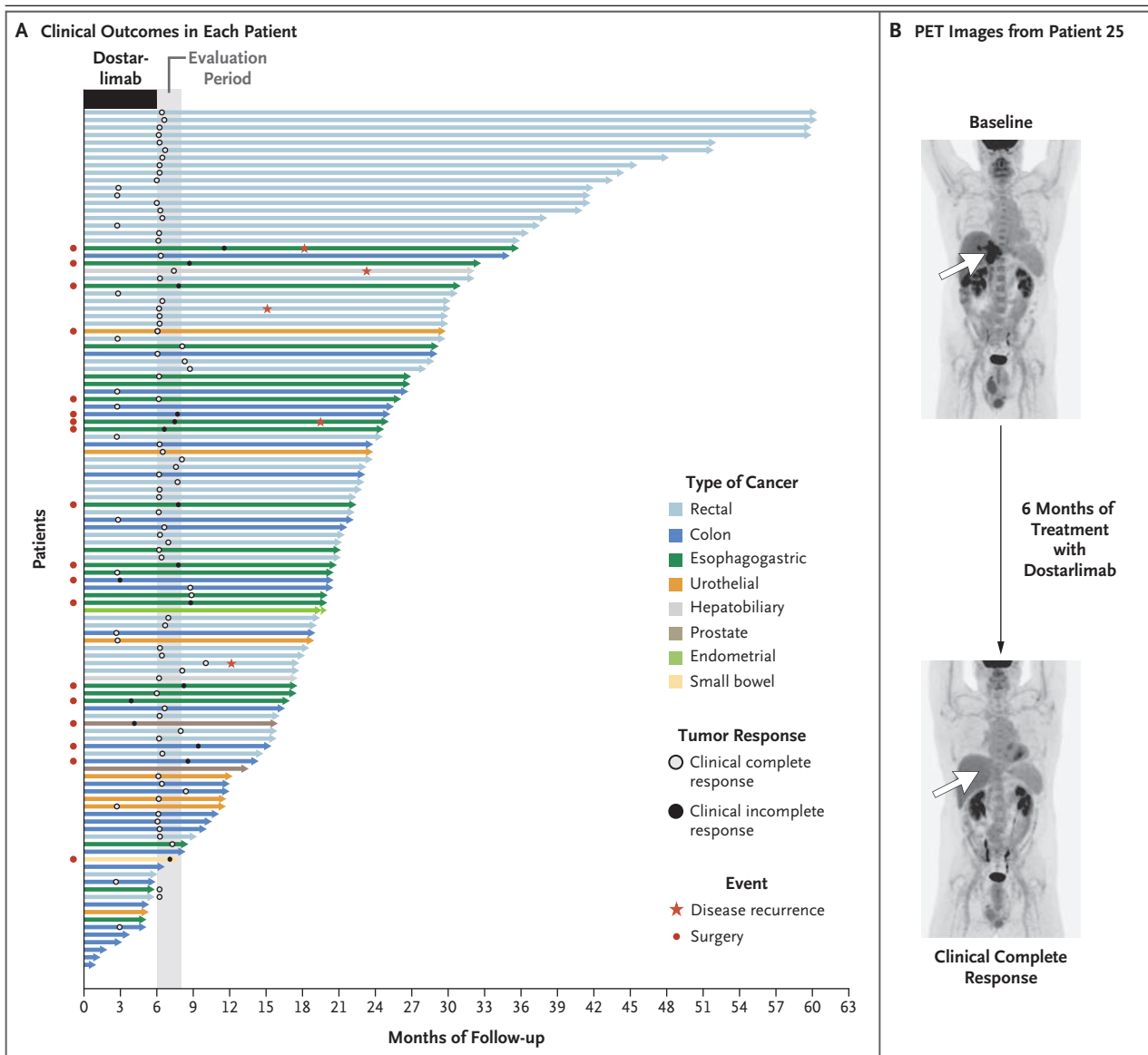


Figure 2. Clinical Outcomes.

Panel A shows a swimmer plot of clinical outcomes for each patient according to tumor type. Esophagogastric cancers consist of esophageal, gastroesophageal junction, and gastric cancers; hepatobiliary cancers consist of periampullary cancer and cholangiocarcinoma. Panel B shows axial positron-emission tomographic (PET) images from Patient 25, who had mismatch repair–deficient, localized intrahepatic cholangiocarcinoma. The top image shows the tumor at baseline, and the bottom image shows a clinical complete response after the administration of dostarlimab therapy for 6 months.

patients with a clinical incomplete response, circulating tumor DNA remained detectable during therapy and at the end of treatment. Among patients who had a recurrence, circulating tumor DNA remained detectable during therapy, and clearance was slower than that observed among those who had a clinical complete response.

DISCUSSION

The data from this study, which were obtained from a small group of patients with stage I, II, or III dMMR solid tumors, showed that neoadjuvant PD-1 blockade enabled a nonoperative management strategy in a high proportion of patients. As seen in the context of metastatic

disease, the efficacy of immune checkpoint blockade appeared to be relatively tumor-agnostic, driven primarily by the dMMR phenotype rather than the tumor site of origin.

Among patients with dMMR solid tumors that were amenable to curative-intent surgery, the use of neoadjuvant PD-1 blockade for 6 months was associated with few adverse events. The option for curative resection was not compromised in any of the patients, although the course of treatment was longer than that in other studies of neoadjuvant therapy. A major concern with neoadjuvant therapy is that the “window of opportunity” for resection may lapse if the tumor grows and spreads to the point of no longer being amenable to curative-intent surgery. Therefore, the duration of treatment is often limited to a few cycles. To maximize the clinical response, we administered immune checkpoint blockade for 6 months — a duration of treatment that in previous studies appeared to result in a higher clinical complete response rate than shorter durations.^{10,19,20}

In all the patients who had a clinical complete response, organs were preserved without additional therapy. Three patients who had rectal cancer were subsequently able to conceive and deliver healthy children, which would not have been possible with standard treatment for rectal cancer.²¹

Among patients who did not have a clinical complete response, the most common tumor types were prostate and gastroesophageal tumors. Beyond these cases, the reason that different sites of primary disease were associated with different results for clinical complete response is unclear. The microbiome and other cellular components of the tumor microenvironment, such as myeloid cells, and the underlying tumor heterogeneity probably contributed to these outcomes. It is possible that a longer duration of treatment or the administration of combination immune checkpoint blockade would have led to a complete response in these patients.²⁰

It is notable that disease recurrence developed in only five patients. In four of these patients, the recurrence was restricted to the lymph nodes; one patient underwent resection of an isolated lymph node and remained free of disease. The four other patients resumed PD-1 blockade, with three having complete disease regression, which suggests that resistance to the preexisting neoantigens

Table 2. Adverse Events.*

Event	Cohorts 1 and 2 (N = 124)	
	Grade 1 or 2†	Grade 3 or 4
	number of patients (percent)	
Dermatologic		
Rash or dermatitis	26 (21)	0
Flushing	2 (2)	0
Pruritus	24 (19)	0
Dry skin	5 (4)	0
Gastrointestinal		
Colitis	2 (2)	0
Constipation	4 (3)	0
Diarrhea	11 (9)	0
Nausea	8 (6)	0
Dry mouth	8 (6)	0
Constitutional		
Fatigue	28 (23)	0
Chills	4 (3)	0
Fever	3 (2)	0
Myalgia	3 (2)	0
Hot flashes	2 (2)	0
Arthralgia	9 (7)	0
Arthritis	2 (2)	0
Neurologic		
Headache	4 (3)	0
Encephalitis	0	1 (1)
Endocrine		
Diabetes	0	1 (1)
Hyperthyroidism	4 (3)	0
Hypothyroidism	16 (13)	1 (1)
Respiratory		
Cough	2 (2)	0
Lung infection	0	1 (1)
Renal, hydration, or nutrition		
Increased creatinine level	2 (2)	0
Ophthalmologic		
Dry eye	3 (2)	0
Other		
Decreased neutrophil count	0	1 (1)
Febrile neutropenia	0	1 (1)
Infusion-related reaction	3 (2)	0

* Adverse events were assessed in the patients who received at least one dose of dostarlimab.

† Shown are grade 1 or 2 adverse events that occurred in at least two patients.

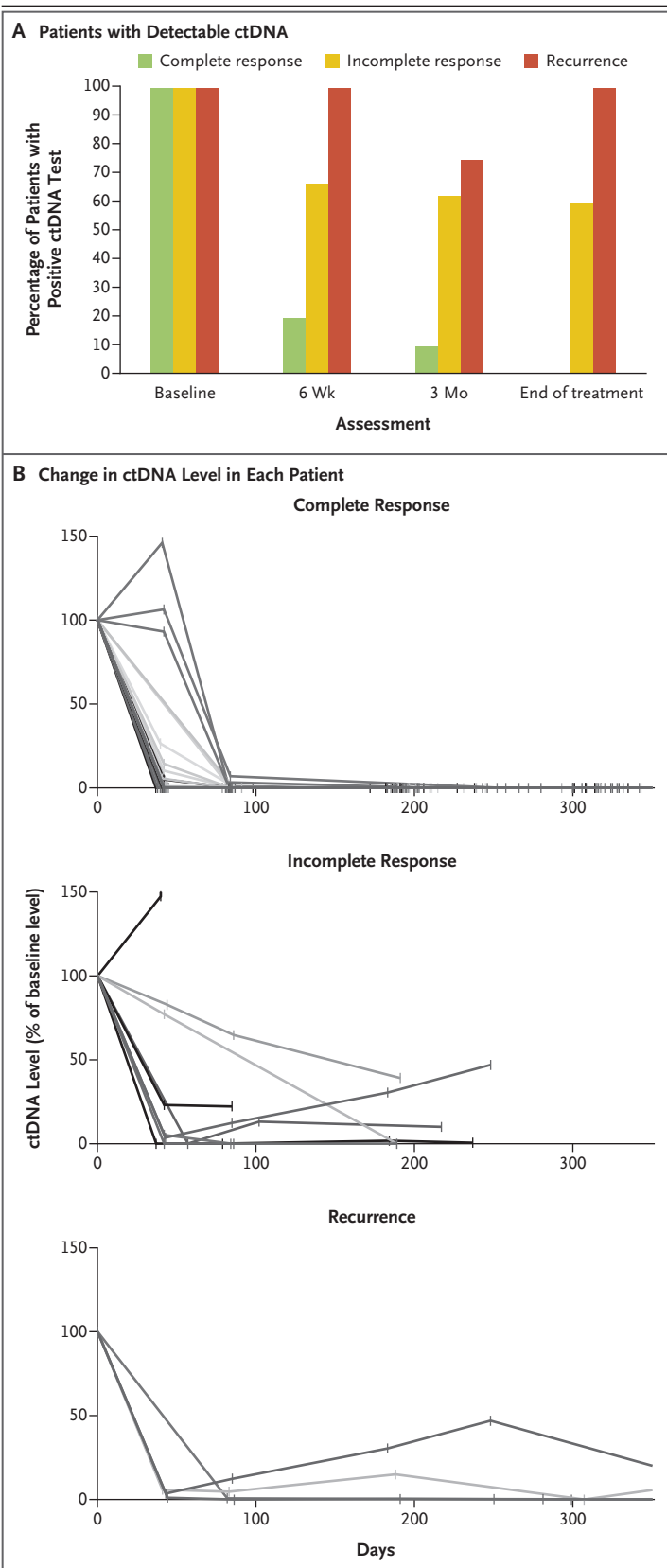


Figure 3. Clearance of Circulating Tumor DNA According to Clinical Response.

Panel A shows the percentage of patients who had detectable circulating tumor DNA (ctDNA) over time according to clinical response. Panel B shows the change in the ctDNA level in each patient over time according to clinical response.

had not developed or new neoantigens that were sufficient to trigger an immunotherapeutic response had emerged.²²⁻²⁴

A substantial challenge moving forward is determining the best approach to monitoring tumor responses. We used tumor-specific imaging and endoscopy with biopsy when feasible. Most of these approaches could be used for gastrointestinal tumors, but for tumors at sites that were not accessible by means of endoscopy, monitoring relied completely on imaging. Imaging-based monitoring was successful in most cases. However, findings on imaging are not as definitive as those seen in tissue.

The analysis of circulating tumor DNA provided a unique window onto the dynamic response to PD-1 blockade. Use of a tumor-informed approach, in which mutations in the tumor are used to design probes that analyze circulating cell-free DNA, was first described in mice and later studied in humans for the purposes of tracking tumor burden and measuring minimal residual disease.^{25,26} Circulating tumor DNA can be used to detect active disease in real time, in part because it has a short plasma half-life of less than 2 hours.²⁶

In our study, we used a new assay that has very high sensitivity and specificity for detecting circulating tumor DNA, owing to its ability to simultaneously assess up to 50 tumor-defined mutations in cell-free DNA and its ability to discard sequencing-induced artifactual mutations by requiring detected genomic alterations to be present on the forward and reverse strands of a cell-free DNA fragment.²⁷⁻²⁹ More than 90% of the early-stage tumors were detected at baseline with this assay, and it also allowed us to reliably monitor the therapeutic response in real time.

In all the patients with a clinical complete response, circulating tumor DNA had cleared by the end of treatment. In patients with a clinical incomplete response and in those with a recurrence, circulating tumor DNA cleared more slowly, with levels remaining elevated throughout

treatment in many cases. Furthermore, when circulating tumor DNA levels were compared with matched biopsy results, the concordance was high, a finding suggesting that circulating tumor DNA is in fact a reliable “liquid biopsy” surrogate. Testing for circulating tumor DNA may become an important addition to the response assessment performed after neoadjuvant therapy, especially when endoscopy and biopsy of the tumor are not feasible.

Although the data from this study are encouraging, larger studies are needed to confirm the long-term benefit of this treatment, especially among patients with nonrectal tumors, who had a shorter median follow-up for recurrence of 14.9 months. Whether these studies enroll patients with various tumor types or focus on those with a single tumor type will be an important consideration. The necessity of a randomized trial for confirmation of these findings should also be considered. For tumors that can be surgically resected without severe complications and without severe effects on quality of life (e.g., colon cancer), a randomized trial designed to measure overall survival would be prudent. However, for tumors that cannot be surgically resected without life-altering effects (e.g., cancer involving the esophagus, stomach, pancreas, bladder, or rectum), a randomized trial may be less feasible, and results from a single-group study may be sufficient to modify clinical practice, especially when there is a high likelihood of complete response.

This study provides a foundation for altering the traditional therapeutic paradigm for early-

stage dMMR solid tumors and eliminating the need for surgery and other therapies in most patients.

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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.

AUTHOR INFORMATION

Andrea Cercek, M.D.,¹ Michael B. Foote, M.D.,¹ Benoit Rousseau, M.D., Ph.D.,¹ J. Joshua Smith, M.D., Ph.D.,² Jinru Shia, M.D.,³ Jenna Sinopoli, N.P.,¹ Jill Weiss, B.S.,¹ Melissa Lumish, M.D.,⁴ Lindsay Temple, B.A.,¹ Miteshkumar Patel, M.S.,¹ Callahan Wilde, B.A.,¹ Leonard B. Saltz, M.D.,¹ Guillem Argiles, M.D.,¹ Zsafia Stadler, M.D.,¹ Oliver Artz, Ph.D.,¹ Steven Maron, M.D.,¹ Geoffrey Ku, M.D.,¹ Ping Gu, M.D.,¹ Yelena Y. Janjigian, M.D.,¹ Daniela Molena, M.D.,² Gopa Iyer, M.D.,¹ Jonathan Coleman, M.D.,² Wassim Abida, M.D.,¹ Seth Cohen, M.D.,¹ Kevin Soares, M.D.,² Mark Schattner, M.D.,¹ Vivian E. Strong, M.D.,² Rona Yaeger, M.D.,¹ Philip Paty, M.D.,² Marina Shcherba, M.D.,¹ Ryan Sugarman, M.D.,¹ Paul B. Romesser, M.D.,⁵ Alice Zervoudakis, M.D.,¹ Avni Desai, M.D.,¹ Neil H. Segal, M.D., Ph.D.,¹ Imane El Dika, M.D.,¹ Maria Widmar, M.D.,² Iris Wei, M.D.,² Emmanouil Pappou, M.D., Ph.D.,² Gerard Fumo, M.D.,⁶ Santiago Aparo, M.D.,⁷ Mithat Gonen, M.D.,⁸ Marc Gollub, M.D.,⁹ Vetri S. Jayaprakasam, M.B., B.S.,⁹ Tae-Hyung Kim, M.D.,⁹ Julio Garcia Aguilar, M.D., Ph.D.,² Martin Weiser, M.D.,² and Luis A. Diaz, Jr., M.D.¹

¹Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York; ²Department of Surgery, Memorial Sloan Kettering Cancer Center, New York; ³Department of Pathology, Memorial Sloan Kettering Cancer Center, New York; ⁴Department of Oncology, Case Comprehensive Cancer Center, Cleveland; ⁵Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York; ⁶Department of Oncology, Hartford HealthCare, Hartford, CT; ⁷Department of Oncology, Baptist Health Miami Cancer Institute, Miami; ⁸Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York; ⁹Department of Radiology, Memorial Sloan Kettering Cancer Center, New York.

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