Neoadjuvant Immunotherapy Leads to Major Response and Low Recurrence in Localized Mismatch Repair–Deficient Colorectal Cancer

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ABSTRACT

Background: Our study aimed to evaluate the efficacy and feasibility of neoadjuvant anti–PD-1 treatment for localized mismatch repair–deficient (dMMR) colorectal cancer (CRC). **Patients and Methods:** The study cohort included patients with localized dMMR CRC who received PD-1 inhibitors as neoadjuvant therapy from 3 medical centers in Southern China. Main eligibility criteria included age between 18 and 75 years, ECOG performance status of 0 or 1, and receipt of ≥2 doses of PD-1 inhibitors. **Results:** A total of 73 patients were included. Most of the tumors were locally advanced, including 19 (26.0%) T4a and 29 (39.7%) T4b. Most patients (79.5%) received PD-1 inhibitor monotherapy. Objective response per radiologic assessment was achieved in 62 (84.9%) patients, including 17 (23.3%) with complete response (CR) and 45 (61.6%) with partial response, with a median time to response of 9.6 weeks. Patients with T4a/4b disease had a similar response rate as those with T2–3 disease (84.0% vs 85.4%; *P*=.999). As of writing, a total of 50 patients have undergone surgery. Pathologic CR was achieved in most (57.1%) patients and remained high (59.5%) even among the 38 patients with T4a/4b disease. The 17 patients with CR did not undergo surgery and adopted a watch-and-wait strategy. After a median follow-up of 17.2 months (range, 3.4–45.1 months), the overall median recurrence-free and overall survivals were not reached. Among patients undergoing surgery or achieving CR, the 2-year tumor-specific disease-free and overall survival rates were both 100%. During neoadjuvant treatment, grade 3–4 adverse events occurred in 8 patients; 4 required acute intervention. Severe postoperative complications were recorded in 4 patients, 3 of whom required a second surgery. **Conclusions:** Neoadjuvant therapy with PD-1 blockade is highly effective for localized dMMR CRC, with an acceptable safety profile and low recurrence rate. This treatment holds promise for becoming the new standard of care for localized dMMR CRCs.

J Natl Compr Canc Netw 2023;21(1):60–66.e5
doi: 10.6004/jnccn.2022.7060

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Background

Mismatch repair–deficient (dMMR) or microsatellite instability–high (MSI-H) colorectal cancer (CRC) represents a special CRC subtype characterized by a higher tumor mutational burden (TMB), more tumor neoantigens, and a higher density of tumor infiltrating lymphocytes.[1–3] These immunogenic features render dMMR CRC a "hot tumor" that is highly responsive to treatment with PD-1 blockade. For patients with dMMR metastatic CRC (mCRC), anti–PD-1 treatment has been proven to be strikingly effective, resulting in a high response rate and sustained progression-free survival,[4–7] and thus has become the new standard of care.[8]

For nonmetastatic dMMR CRC, which often exhibits an expansile growth pattern and is prone to develop into a bulky tumor,[9] efforts have been made to assess the feasibility of neoadjuvant treatment. Unfortunately, neoadjuvant therapy with cytotoxic agents, although resulting in significant tumor downstaging in mismatch repair–proficient CRC, fails to bring benefits for dMMR CRC. The FOxTROT trial showed that nearly three-fourths of the dMMR CRC had no regression after 6 weeks of chemotherapy, and the 2-year relapse-free survival did not improve compared with the postoperative chemotherapy group.[10] Even worse, in a study evaluating MMR status and chemosensitivity, more than one-fourth of dMMR rectal cancers were found to progress after neoadjuvant chemotherapy.[11]

The success of PD-1 blockade for dMMR mCRC has prompted attempts to validate its efficacy in the neoadjuvant setting, but so far data are limited. NICHE is the first trial evaluating PD-1 blockade (+ ipilimumab) for localized dMMR CRC.[12] Preliminary results show that PD-1 inhibitors are highly effective, with nearly all of the patients achieving objective response and 60% achieving pathologic complete response (pCR). A recent study by Cercek et al[13] reports

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even more striking results, showing that 100% of patients with localized dMMR rectal cancer achieved a CR after 6 months of treatment with PD-1 blockade. There are also some retrospective studies reporting major tumor regression in localized dMMR CRC after treatment with PD-1 blockade.[14,15]

However, these studies are subject to some common limitations, such as a small sample size and a lack of long-term follow-up. Whether neoadjuvant anti–PD-1 treatment could reduce tumor recurrence and prolong survival for patients with dMMR CRC remains unknown. Our study aimed to evaluate the efficacy and feasibility of neoadjuvant PD-1 inhibitors for dMMR CRC and report the long-term survival of this population with a considerably large sample size.

Patients and Methods

Patient Selection

We retrospectively reviewed patients with dMMR/MSI-H CRC who received PD-1 inhibitors as neoadjuvant therapy between October 1, 2017, and December 31, 2021, at Sun Yat-sen University Cancer Center, the Sixth Affiliated Hospital of Sun Yet-sen University, and Yunnan Cancer Center. Eligible patients were those with histopathologically confirmed dMMR/MSI-H CRC, with unresected primary CRC, aged between 18 and 75 years, with an ECOG performance status of 0 or 1, and who received ≥2 doses of PD-1 inhibitors. Patients who received previous chemotherapy were allowed, and those with multiple CRC were also included. Patients suspected of metastatic disease and those without radiographic assessment of treatment response were excluded. The STROBE guideline was used to guide the reporting of this retrospective study.[16]

This study was performed in accordance with the Declaration of Helsinki and approved to waive informed patient consent by the Institutional Review Board of Sun Yat-sen University Cancer Center (approval number B2020-064-01) due to the observational and noninterventional study.

Data Collection

Demographic and clinicopathologic data of patients were collected, including ECOG performance status, tumor staging, MMR/MSI status, TMB, *RAS* status, serum CEA level, tumor response, tumor regression grade (TRG), treatment-related adverse effects, surgical complications, and postoperative treatments, follow-up, and disease-free and overall survival. The status of dMMR/MSI-H was determined by either immunohistochemistry, PCR, or next-generation sequencing with biopsy tissue, as per the clinical routine of the participating centers.

Treatment and Follow-Up

The decisions to treat patients with PD-1 inhibitors instead of surgery were made by the primary surgeons of the participating centers, with the most common reason being to avoid multivisceral resection and sphincter dysfunction. Most of the CRCs were locally advanced (cT4a/4b), although a few low-lying rectal cancers were at an early stage. Because there was no guideline recommending PD-1 inhibitors as neoadjuvant treatment of CRC, the decisions were made based on empirical experience, and thus the regimens were not unanimous (either PD-1 blockade monotherapy or combined with chemotherapy, targeted therapy, or radiotherapy). Of note, several kinds of PD-1 inhibitors were used in the study, including pembrolizumab, nivolumab, sintilimab, toripalimab, camrelizumab, and tislelizumab. Although belonging to the same genre of PD-1 blockade, some were used off-label.

Radiographic assessment of response was generally performed after 2 cycles of treatment, and every 2 to 3 months afterward before surgery (if performed), according to the revised RECIST guideline (version 1.1).[17] Surgery was recommended when R0 resection and organ preservation were deemed achievable, but prolonged immunotherapy was usually prescribed when there was continuing tumor shrinkage on radiology. For patients whose tumor had achieved clinical CR (cCR; defined as the absence of tumor on radiologic and endoscopic findings), a watch-and-wait approach was offered according to clinical practice, especially for those who would otherwise experience organ dysfunction or multivisceral resection. Assessment of TRG was performed for all resected tumors, as per the 4-tier grading system recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer.[18] Postoperative treatment was not stipulated, but for patients achieving TRG 0/1, PD-1 blockade was recommended for at least 6 months, and for patients achieving TRG 2/3, oxaliplatin-based chemotherapy was recommended.

Statistics

Overall survival (OS) was defined as the time from start of PD-1 blockade to death from any cause. Disease-free survival (DFS) was defined as the time from tumor resection or cCR to tumor recurrence or death. Associations between categorical variables were assessed by chi-square test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate. Kaplan-Meier method was used to estimate OS and progression-free survival. All *P* values were 2-sided, and $P<.05$ was considered statistically significant. All analyses were performed in R version 4.1.0 (R Foundation for Statistical Computing).

Results

Clinicopathologic Description

A total of 73 patients were included in the study, 29 (39.7%) of whom were female (Table 1). Median age at treatment was 48 years. The most common locations of the primary

Table 1. Baseline Characteristics

Characteristic	n (%)
Total, n	73
Age, median (range), y	48 (19–78)
Sex	
Female	29 (39.7)
Male	44 (60.3)
Primary tumor site	
Ascending colon	18 (24.7)
Transverse colon	14 (19.2)
Descending colon	2 (2.7)
Sigmoid colon	14 (19.2)
Rectum	18 (24.7)
Multiple	7 (9.6)
Clinical T stage	
T2	3 (4.1)
T3	22 (30.1)
T4a	19 (26.0)
T4b	29 (39.7)
RAS status	
Mutant-type	25 (34.2)
Wild-type	16 (21.9)
Unknown	32 (43.8)
Lynch syndrome	
Yes	27 (37.0)
No	15 (20.5)
Unknown	31 (42.5)
Positive nodal status	66 (90.4)
Prior chemotherapy	24 (32.9)
Combined therapy	15 (20.5)

tumor were the rectum (24.7%) and ascending colon (24.7%); 7 (9.6%) patients had multiple CRCs. Most of the tumors were locally advanced, with 19 (26.0%) being cT4a and 29 (39.7%) being cT4b. Most patients (79.5%) received PD-1 inhibitor monotherapy, whereas the others received concurrent therapies, either with ipilimumab (4.1%) or cytotoxic chemotherapy (16.4%, 2 with concurrent radiation); 24 (32.9%) patients had received prior chemotherapy before the initiation of PD-1 blockade.

Response to PD-1 Blockade

Response data are shown in Table 2. Of the 73 patients, 62 (84.9%) achieved an objective response per radiologic assessment, including 17 (23.3%) with CR and 45 (61.6%) with partial response (PR). The median time to response was 9.6 weeks (range, 3.7–17.3 weeks). Patients with cT4a/4b disease had a similar response rate to those with cT2–3 disease (85.4% vs 84.0%, respectively), and the objective response rate remained high among patients with cT4b disease (27/29; 93.1%). Patients with cT2–3 disease were more likely to achieve CR than those with cT4a/4b disease (52% vs 8.3%; $P<.001$) (Figure 1A). Progressive disease (PD) and stable disease (SD) were observed in 1 and 10 patients, respectively (supplemental eTable 1, available with this article at JNCCN.org). Responses were observed irrespective of tumor location, *RAS* mutation status, the presence of Lynch syndrome, and whether there were combinatory therapies (supplemental eTable 2).

Table 2. Objective and Overall Response

Characteristic	n (%)
Objective response	62 (84.9)
Time to response, median (range), wk	9.6 (3.7–17.3)
Radiographic response	
Complete response	17 (23.3)
Partial response	45 (61.6)
Stable disease	10 (13.7)
Progressive disease	1 (1.4)

Surgery After Neoadjuvant Therapy

As of writing, surgery had been performed on 50 patients; 40 with PR, 9 with SD, and 1 with PD (Table 3). Median time from initiation of PD-1 blockade to surgery was 4.0 months (range, 1.4–12.2 months). All of these patients, except one who received ostomy due to unresectable tumor, underwent R0 resection for the primary tumor. pCR (TRG 0) was observed in patients with PR (accounting for 62.2%) but not in those with SD or PD (Figure 1B). The rate of pCR + cCR was 61.6%.

A good tumor regression (TRG 0/1) was associated with a better radiologic response and higher TMB, but not with tumor location, *RAS* status, or receipt of combined therapies (supplemental eTable 3). Positive lymph nodes were found in 2 (4.1%) patients, both of whom had a poor regression. A total of 23 patients did not undergo surgery: 17 with CR, 5 with PR, and 1 with SD. Of the 6 patients with PR/SD, 2 were deemed resectable but still under treatment, 1 was deemed unresectable, and 3 refused surgery for unspecified reasons.

Outcomes of Patients With Locally Advanced (cT4a/4b) Disease

A total of 48 patients had locally advanced disease, with CR and PR observed in 4 (8.3%) and 37 (77.1%) of them, respectively; the median time to response was 9.1 weeks (range, 4.1–22 weeks) (Table 4). As of writing, surgery had been performed on 38 (80.9%) of these patients, and the median time from neoadjuvant treatment to surgery was

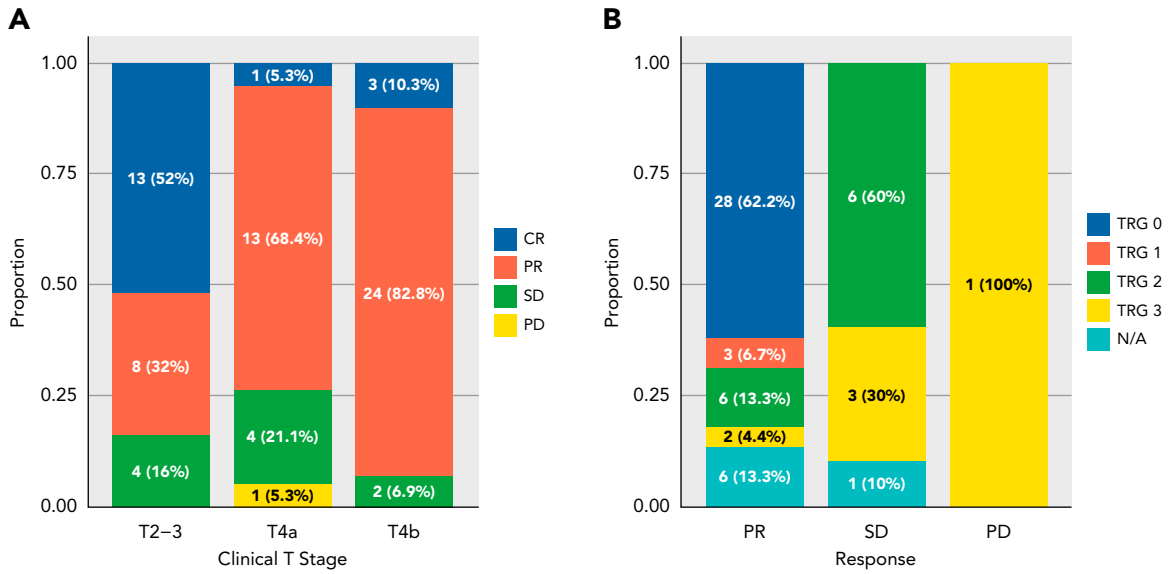

Figure 1. Radiologic response, TRG, and clinical T stage. **(A)** Radiologic response among patients with different clinical T stage; patients with cT2–3 disease were more likely to achieve CR. **(B)** TRG among patients with different responses; most patients with PR achieved a pathologic CR (TRG 0).

Abbreviations: CR, complete response; N/A, TRG not available because surgery was not performed or the tumor was unresectable; PD, progressive disease; PR, partial response; SD, stable disease; TRG, tumor regression grade.

4.0 months (range, 1.4–12.2 months). All of the surgery achieved R0 resection, and 22 (59.5%) patients achieved a pCR (TRG 0).

Among the 29 patients with cT4b tumors, the most common affected sites were the abdominal wall (44.8%), duodenum (20.7%), and bladder (17.3%). Surgery was performed on 16 patients, 9 with routine colectomy, 6 with multivisceral resection, and 1 with ostomy (supplemental eTable 4). Pathologic reports showed that most (66.7%) of the resected tumors achieved pCR. Even among the 6 patients receiving multivisceral resection for suspected invasion, 4 achieved a pCR.

Table 3. Characteristics of Patients Undergoing Surgery

Characteristic	n (%)
Time to surgery, median (range), mo	4 (1.4–12.2)
Radiologic response	
Complete response	0 (0.0)
Partial response	40 (80.0)
Stable disease	9 (18.0)
Progressive disease	1 (2.0)
Resection margin	
R0	49 (98.0)
Unresectable	1 (2.0)
Tumor regression grade (TRG)	
TRG 0	28 (57.1)
TRG 1	3 (6.1)
TRG 2	12 (24.5)
TRG 3	6 (12.2)
Nodal status	
Positive	2 (4.1)
Negative	47 (95.9)

Long-Term Survival

After a median follow-up of 17.2 months (range, 3.4–45.1 months), 1 patient died of cardiovascular disease (not treatment-related) and 1 patient with unresectable tumor experienced progression. The latter patient was a 66-year-old male whose tumor was deemed unresectable after 6 cycles of PD-1 blockade (despite achieving PR); he discontinued the treatment for unknown reasons and reported lung metastasis 16.6 months later.

As of writing, none of the patients undergoing surgery had experienced recurrence, including 16 who did not receive any treatment after the surgery (median postoperative follow-up of 9.3 months) and 18 who had a poor TRG (median postoperative follow-up of 12.0 months). None of the patients achieving cCR experienced tumor relapse. Overall median DFS and OS were not reached (supplemental eFigure 1). The 2-year rates of tumor-specific OS and DFS were both 100%. Of note, the only patient with PD underwent R0 surgery and remained disease-free after 13.4 months of follow-up.

Safety Profiles

During neoadjuvant treatment, 8 severe (grade 3–4) drug-related adverse events were reported (supplemental

Table 4. Outcomes of Patients With T4a/4b Disease

Characteristic	n (%)
Total, n	48
Time to response, median (range), mo	9.1 (4.1–22)
Time to surgery, median (range), mo	4.0 (1.4–12.2)
Clinical T stage	
T4a	19 (39.6)
T4b	29 (60.4)
Radiologic response	
Complete response	4 (8.3)
Partial response	37 (77.1)
Stable disease	6 (12.5)
Progressive disease	1 (2.1)
Surgery after PD-1 blockade	
Yes	38 (79.2)
No/Not yet	10 (20.8)
Tumor regression grade (TRG)	
TRG 0	22 (59.5)
TRG 1	1 (2.7)
TRG 2	9 (24.3)
TRG 3	5 (13.5)

eTable 5). Bowel obstruction was the most common, observed in 3 patients; all required acute intervention (2 underwent ostomy and 1 underwent endoscopic stenting). One patient underwent resection with preventive ostomy due to perforation. No deaths were observed among the 8 patients. Immune-related toxicities occurred in 10 patients; the most common toxicity was hypothyroidism (n=6), followed by hypoadrenocorticism (n=2), pneumonitis (n=2), and encephalitis (n=1). All these events except pneumonia were grade 1–2.

Postoperative complications were analyzed among the 51 patients undergoing surgery. Severe complications were observed in 4 patients: adhesive intestinal obstruction (n=1), abdominal infection (n=1), anastomotic leak (n=1), and abdominal bleeding (n=1); 3 of these 4 patients required a second surgery. No deaths occurred within 1 month after the surgery.

Discussion

Our study confirms that neoadjuvant immunotherapy results in a strikingly high response rate (84.9%) for patients with nonmetastatic dMMR/MSI-H CRC, even those with locally advanced disease. Nearly one-fourth of the patients achieved cCR after the treatment. There was no recurrence among patients undergoing surgery or achieving CR. Neoadjuvant immunotherapy is well-tolerated with few grade 3–4 adverse events and postoperative complications.

Although PD-1 inhibitors have been proven highly effective for dMMR/MSI-H CRC, more than half of the patients with mCRC did not experience response.[4–6] In KEYNOTE-177, treatment failure led to the initial crossing of the Kaplan-Meier curves, suggesting that primary resistance to PD-1 blockade can cause rapid progression.[7] In the neoadjuvant scenario, however, nearly all dMMR/MSI-H CRCs are shown to respond to PD-1 blockade.[12] In the present study, we confirmed that neoadjuvant treatment with PD-1 blockade led to strikingly high rates of response (84.9%) and pCR/cCR (61.6%) for localized dMMR/MSI-H CRC. Moreover, response rate remained comparably high (85.4%) even among patients with bulky tumor (cT4a/4b), suggesting that tumor burden alone was not a predictor of response. However, among the 17 patients with CR, most (82.4%) had an early cT stage (cT2–3). Therefore, although tumor burden does not predict response, it may be able to predict cCR. The phenomenon that early-stage tumors tend to have a higher degree of response is also seen in glioblastoma and melanoma,[19,20] and is assumed to result from stronger T-cell infiltration and less immunosuppression in early-stage tumors.

In the CheckMate 142 trial, combination nivolumab + ipilimumab resulted in a higher response rate than nivolumab monotherapy (55% vs 31%) among patients with metastatic dMMR/MSI-H CRC.[5,6] In the neoadjuvant setting, in contrast, a recent phase II trial showed that PD-1 blockade monotherapy led to a high pCR rate that was comparable to that of the NICHE trial (65.4% vs 60%), which used nivolumab + ipilimumab.[12,21] In our study, 58 patients received PD-1 blockade monotherapy, with rates of response and pCR/cCR of 87.9% and 60.3%, respectively, displaying no difference to combination therapy. These results suggest that neoadjuvant therapy with PD-1 blockade alone is sufficient to achieve a high response rate for localized dMMR/MSI-H CRC and is probably as effective as the combination therapy. A recent study by Cercek et al[13] also supported PD-1 blockade monotherapy for dMMR/MSI-H rectal cancer, with 100% of the patients achieving complete regression after 6 months of the treatment.

For neoadjuvant immunotherapy, correlation was poor between radiologic assessment and pathologic results, because tumors achieving major pathologic response or pCR were often evaluated as gross residual on CT scan.[12] In our study, 68.3% (28/41) of patients with PR who underwent surgery were found to have achieved pathologic CR. This finding is echoed by a recent study, in which pCR was observed in 4 patients undergoing multivisceral resection for residual tumor after anti–PD-1 treatment.[22] Therefore, gross tumor residue on radiologic imaging after immunotherapy

does not signify viable tumor cells. The actual response of PD-1 blockade therapy tends to be underestimated in the neoadjuvant setting.

Whether the high response rate of neoadjuvant therapy can translate into long-term survival benefits remain a focus of interest. In the FOxTROT trial, cytotoxic chemotherapy induced significant downstaging, but long-term follow-up demonstrated no survival benefits, especially for the dMMR subset.[10] The NICHE trial has not yet reported the long-term results of neoadjuvant immunotherapy. Our study had a median follow-up of 17.2 months, with 16 patients being followed for >24 months. There was no recurrence or tumor-related death among patients undergoing surgery or achieving cCR (including 18 with poor TRG and 15 not receiving postoperative PD-1 blockade). The 2-year recurrence rate (0%) in our study was markedly lower than that in the FOxTROT trial (15.1% for the dMMR subset).[10] In view of this disparity, we believe that neoadjuvant immunotherapy is likely to provide long-term benefits for patients with localized dMMR/MSI-H CRC.

Overtreatment remains a concern for neoadjuvant treatment. In the FOxTROT trial, among patients undergoing surgery without chemotherapy, 44% of the patients found to have node-positive disease on radiologic assessment were found to be node-negative on pathologic assessment,[23] suggesting that nearly half of the patients with stage I/II CRC would be overtreated should they receive neoadjuvant therapy. This problem is even more alarming for nonmetastatic dMMR/MSI-H CRCs, because for one thing, their nodal status is more likely to be overstaged on radiologic assessment,[24] and for another, immunotherapy may cause permanent organ damage.[25] In our study, 12 of the 25 patients with cT2–3 disease underwent surgery, and 11 (91.7%) had node-negative disease. It remained unknown whether the lymph nodes were negative at baseline or downstaged by immunotherapy. Overtreatment cannot be ruled out, but it should be noted that 13 of these 25 patients, including 9 with low-lying rectal cancer and 3 with multiple CRCs, achieved CR and thus avoided potentially organ-damaging surgery.

With cytotoxic chemotherapy, FOxTROT showed that neoadjuvant chemotherapy did not increase postoperative complications, with comparable rates of stoma and anastomotic complication.[23] For PD-1 blockade, similar results were found in both clinical trials and retrospective reports.[12,15,21] In our study, severe postoperative complications were observed in 4 (7.8%) patients, which seemed comparable to observations in previous reports.[26,27] However, during neoadjuvant treatment, 5 (6.8%) severe events were noted (3 obstruction, 1 perforation, 1 abdominal infection), 3 of which required emergency surgery. Therefore, for bulky tumors, the threat of acute abdomen persists even when apparent response is achieved. Close monitoring should be exercised during neoadjuvant treatment.

Our study has several limitations. First, due to its retrospective nature, the regimens used varied. Although most patients received PD-1 blockade monotherapy, approximately 20% received concurrent therapies. Furthermore, a variety of PD-1 inhibitors were used, and some were used off-label in CRC. In addition, the number of treatment cycles varied between patients, with 6 patients receiving ≤3 cycles of the treatment, which might be insufficient to achieve the best response and thus may cause underestimation of efficacy. Last, although our study had a relatively long follow-up, it is still insufficient to establish the survival benefits of neoadjuvant anti–PD-1 treatment. Longer follow-up is needed.

Conclusions

Our study demonstrates that neoadjuvant therapy with PD-1 blockade is highly effective for localized dMMR/MSI-H CRC, with an acceptable safety profile and low recurrence rate. Although longer follow-up is need to validate its survival benefits, neoadjuvant immunotherapy has shown great promise as the new standard of care for locally advanced dMMR/MSI-H CRC.

Submitted June 11, 2022; final revision received August 1, 2022; accepted for publication August 1, 2022.

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Data availability statement: The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2022876429.

Disclosures: The authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

Funding: Research reported in this publication was supported by the National Natural Science Foundation of China under award numbers 81871971 and 82073159 (P.R. Ding), as well as the Chinese Society of Clinical Oncology under award numbers T-XD2019-073 and Y-Genecast-055 (P.R. Ding).

Disclaimer: This retrospective study was performed in accordance with the Declaration of Helsinki and the Institutional Review Board of Sun Yat-sen University Cancer Center approved to waive informed patient consent due to the observational and noninterventional study (approval number B2020-064-01).

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Neoadjuvant Immunotherapy Leads to Major Response and Low Recurrence in Localized Mismatch Repair–Deficient Colorectal Cancer

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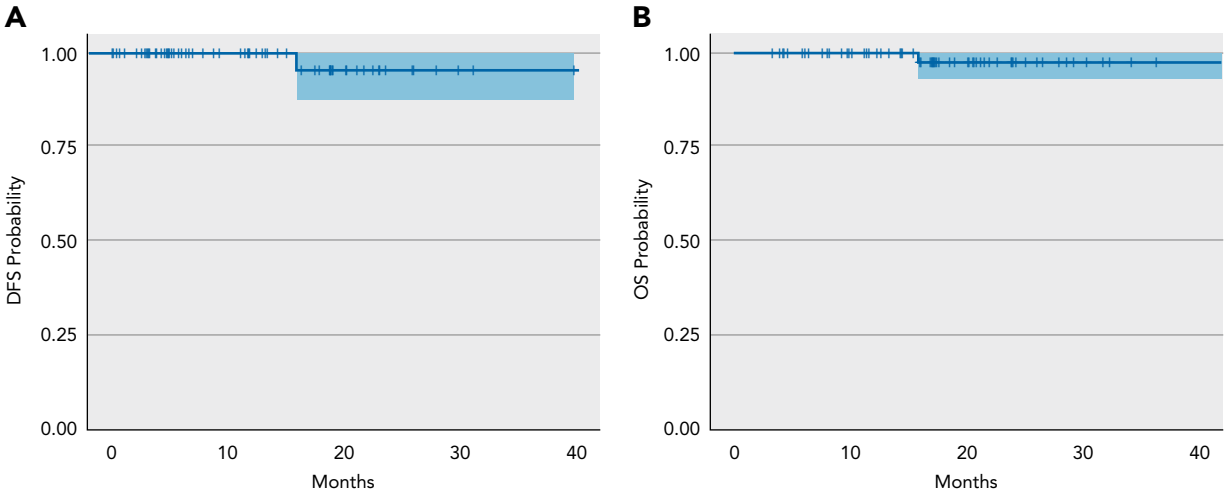
J Natl Compr Canc Netw 2023;21(1):60–66.e5



eFigure 1. Kaplan-Meier curves for **(A)** DFS, analyzed among patients undergoing tumor resection or achieving complete response (n=66), and **(B)** OS, analyzed among all the study patients (n=73).
Abbreviations: DFS, disease-free survival; OS, overall survival.

eTable 1. Characteristics of Patients With Stable/Progressive Disease

Patient ID	Sex	Age, y	Primary Site	Clinical Staging	Lynch Syndrome	Prior Chemotherapy	Drug	Cycles Used	Extent of Surgery	TRG
1	F	34	Transverse	cT4bN1M0	Yes	XELOX*5	Toripalimab	3	R0	TRG 2
2	M	32	Sigmoid	cT4bN1M0	Yes	No	Pembrolizumab	4	R0	TRG 2
3	F	30	Rectal	cT2–3N2M0	Yes	XELOX*1	Pembrolizumab	7	R0	TRG 3
4[a]	M	73	Descending	cT4aN1M0	No	No	Pembrolizumab	2	R0	TRG 3
5	F	53	Ascending	cT4aN1M0	No	FOLFOXIRI*1	Sintilimab	3	R0	TRG 3
6	F	36	Transverse	cT2–3N1M0	Yes	No	Sintilimab	6	R0	TRG 2
7	F	72	Transverse	cT4aN2M0	Unknown	No	Toripalimab	2	R0	TRG 2
8	M	63	Transverse	cT2–3N1M0	Unknown	No	Toripalimab	5	R0	TRG 2
9	M	50	Sigmoid	cT2–3N1M0	No	No	Pembrolizumab	4	R0	TRG 2
10	F	30	Sigmoid	cT4aN2M0	Unknown	No	Toripalimab	23	—	—
11	M	58	Sigmoid	cT4aNxM0	Unknown	No	Tislelizumab	6	R0	TRG 3

Abbreviations: F, female; FOLFOXIRI, folinic acid/5-FU/oxaliplatin/irinotecan; M, male; TRG, tumor regression grade; XELOX, capecitabine/oxaliplatin.
[a]Patient with progressive disease.

eTable 2. Comparisons Between Responders and Nonresponders

Characteristic	CR/PR n (%)	SD/PD n (%)	*P* Value
Total, n	62	11	
Age, median (range), y	48 (19–78)	50 (30–73)	.890
TMB, median (range), muts/Mb	78.7 (40.3–622.1)	56.6 (21.1–77)	.036
Sex			.327
Male	39 (62.9)	5 (45.5)	
Female	23 (37.1)	6 (54.5)	
Primary tumor site[a]			.147
Rectum	17 (30.9)	1 (9.1)	
Colon, right-sided	26 (47.3)	5 (45.5)	
Colon, left-sided	12 (21.8)	5 (45.5)	
Clinical T stage			.154
T2–3	21 (33.9)	4 (36.4)	
T4a	14 (22.6)	5 (45.5)	
T4b	27 (43.5)	2 (18.2)	
RAS status			.685
Mutant-type	20 (58.8)	5 (71.4)	
Wild-type	14 (41.2)	2 (28.6)	
Lynch syndrome			.686
Yes	23 (65.7)	4 (57.1)	
No	12 (34.3)	3 (42.9)	
Prior chemotherapy			.999
No	42 (67.7)	7 (63.6)	
Yes	20 (32.3)	4 (36.4)	
PD-1 blockade alone			.221
Yes	11 (17.7)	4 (36.4)	
No	51 (82.3)	7 (63.6)	

Abbreviations: CR, complete response; muts, mutations; PD, progressive disease; PR, partial response; SD, stable disease; TMB, tumor mutational burden.
[a]7 patients with multiple colorectal cancers were excluded.

eTable 3. Comparisons Between TRG 0/1 and TRG 2/3

Characteristic	TRG 2/3 n (%)	TRG 0/1 n (%)	*P* Value
Total, n	18	31	
Age, median (range), y	48.5 (30–73)	48 (27–74)	.670
TMB, median (range), muts/Mb	56.6 (21.1–84.5)	91.7 (66.2–622.1)	.004
Sex			.394
Male	10 (55.6)	21 (67.7)	
Female	8 (44.4)	10 (32.3)	
Primary tumor site[a]			.154
Colon, right-sided	8 (50.0)	17 (58.6)	
Colon, left-sided	7 (43.8)	8 (27.6)	
Rectum	1 (6.2)	4 (13.8)	
Clinical T stage			.392
T2–3	4 (22.2)	8 (25.8)	
T4a	8 (44.4)	8 (25.8)	
T4b	6 (33.3)	15 (48.4)	
Radiologic response			<.001
PR	8 (44.4)	31 (100.0)	
SD	9 (50.0)	0 (0)	
PD	1 (5.6)	0 (0)	
RAS status			.230
Mutant-type	8 (80.0)	9 (52.9)	
Wild-type	2 (20.0)	8 (47.1)	
Lynch syndrome			.999
Yes	6 (66.7)	12 (60.0)	
No	3 (33.3)	8 (40.0)	
Prior chemotherapy			.753
Yes	6 (33.3)	9 (29.0)	
No	12 (66.7)	22 (71.0)	
PD-1 blockade alone			.999
Yes	15 (83.3)	25 (80.6)	
No	3 (16.7)	6 (19.4)	

Abbreviations: muts, mutations; PD, progressive disease; PR, partial response; SD, stable disease; TMB, tumor mutational burden; TRG, tumor regression grade.
[a]4 patients with multiple colorectal cancers were excluded.

eTable 4. Outcomes of Patients With T4b Tumors

Characteristic	n (%)
Total, n	29
T4b involved site	
Abdominal wall	13 (44.8)
Duodenum	6 (20.7)
Bladder	5 (17.2)
Psoas major muscle	2 (6.9)
Liver	1 (3.4)
Rectum	1 (3.4)
Stomach	1 (3.4)
Radiologic response	
Complete response	3 (10.3)
Partial response	24 (82.8)
Stable disease	2 (6.9)
Surgical procedure	
Right hemicolectomy	9 (42.9)
Anterior resection	2 (9.5)
Left hemicolectomy	2 (9.5)
Subtotal colectomy	1 (4.8)
Anterior resection + partial cystectomy	3 (14.3)
Anterior resection + radical hysterectomy + ostomy	1 (4.8)
Right hemicolectomy + partial duodenal resection	1 (4.8)
Left hemicolectomy + left nephrectomy	1 (4.8)
Transverse colectomy + partial gastrectomy	1 (4.8)
Tumor regression grade (TRG)	
TRG 0	14 (66.7)
TRG 1	1 (4.8)
TRG 2	5 (23.8)
TRG 3	1 (4.8)

eTable 5. Severe AEs During Neoadjuvant Treatment

Severe AE	Events	Sex	Age, y	Primary Tumor Site	Regimen	Invasive Treatment
NT1	Neutropenia	F	34	Transverse colon	Toripalimab + FOLFOX + radiation	Not required
NT2	Pancreatitis	M	73	Descending colon	Pembrolizumab	Not required
NT3	Bowel obstruction	F	72	Transverse colon	Toripalimab + XELOX + radiation	Ostomy
NT4	Bowel obstruction	M	50	Sigmoid colon	Pembrolizumab	Endoscopic stenting
NT5	Peritonitis	M	40	Ascending colon	Pembrolizumab + FOLFIRI	Not required
NT6	Bowel obstruction	M	23	Rectum	Serplulimab	Ostomy
NT7	Pneumonia	M	40	Sigmoid colon	QL1604	Not required
NT8	Bowel obstruction	M	59	Sigmoid colon	Sintilimab	Colectomy + ostomy
SC1	Bowel obstruction	M	52	Transverse colon-hepatic	Sintilimab	Second surgery
SC2	Abdominal infection	F	72	Transverse colon	Toripalimab + XELOX + radiation	Not required
SC3	Anastomotic leak	M	62	Rectum	Tislelizumab	Second surgery
SC4	Abdominal bleeding	M	48	Transverse colon-hepatic	Sintilimab	Second surgery

Abbreviations: AE, adverse event; F, female; FOLFIRI, folinic acid/5-FU/irinotecan; FOLFOX, folinic acid/5-FU/oxaliplatin; M, male; NT, neoadjuvant therapy; SC, surgical complications; XELOX, capecitabine/oxaliplatin.