



Retrospective Study

Efficacy and safety of preoperative immunotherapy in patients with mismatch repair-deficient or microsatellite instability-high gastrointestinal malignancies

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Abstract

BACKGROUND

Programmed death protein (PD)-1 blockade immunotherapy significantly prolongs survival in patients with metastatic mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal malignancies such as gastric and colorectal cancer. However, the data on preoperative immunotherapy are limited.

AIM

To evaluate the short-term efficacy and toxicity of preoperative PD-1 blockade immunotherapy.

METHODS

In this retrospective study, we enrolled 36 patients with dMMR/MSI-H gastrointestinal malignancies. All the patients received PD-1 blockade with or without chemotherapy of CapOx regime preoperatively. PD1 blockade 200 mg was given intravenously over 30 min on day 1 of each 21-d cycle.

RESULTS

Three patients with locally advanced gastric cancer achieved pathological complete response (pCR). Three patients with locally advanced duodenal carcinoma achieved clinical complete response (cCR), followed by watch and wait. Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastasis from colon cancer reached CR, including three with pCR and one with cCR. pCR was achieved in two of five patients with non-liver metastatic colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. cCR was achieved in seven of 36 cases, among which, six were selected for watch and wait strategy. No cCR was observed in gastric or colon cancer.

CONCLUSION

Preoperative PD-1 blockade immunotherapy in dMMR/MSI-H gastrointestinal malignancies can achieve a high CR, especially in patients with duodenal or low rectal cancer, and can achieve high organ function protection.

Key Words: Preoperative; PD-1 blockade; dMMR/MSI-H; Gastrointestinal malignancies

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Core Tip: To the best of our knowledge, this retrospective study is one of the few to summarize mismatch repair-deficient/microsatellite instability-high gastric, duodenal, and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis that only one patient was excluded from the cohort because symptoms disappeared after programmed death protein 1 therapy and she refused to examination and further treatment.

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INTRODUCTION

Many solid tumors have a mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) ratio, and dMMR/MSI-H subtype, as a unique type of tumor, accounts for 5%-15% of solid tumor patients[1]. However, the proportion of dMMR/MSI-H varies significantly among different tumor types, with a high incidence in colorectal, gastric and endometrial cancer, as well as breast cancer, liver cancer, cholangiocarcinoma, pancreatic cancer and other solid tumors[2]. As a distinguished biomarker, dMMR/MSI-H status can accurately predict the efficacy of immunotherapy for many solid tumors[3,4].

MSI-H subtype is one of the molecular subtypes of gastric or colorectal cancer[5,6]. MSI-H is an independent prognostic factor in gastrointestinal tumors, with good prognosis and resistance to conventional chemoradiotherapy[7,8]. Locally advanced gastrointestinal malignancies or surgically resectable metastatic colorectal cancer require preoperative treatment to improve R0 resection rate. However, many studies[9,10] on locally advanced gastric cancer suggest that the pathological complete response (pCR) rate of conventional preoperative neoadjuvant chemotherapy is not high, and dMMR/MSI-H gastric cancer has a worse response to conventional chemotherapy. As with gastric cancer, pancreaticoduodenectomy (Whipple's procedure) for duodenal cancer is a major, invasive procedure that needs to be performed even after preoperative chemotherapy. MSI-H colorectal cancer is resistant to conventional chemotherapy[11] and radiotherapy[12], and low advanced rectal cancer requires R0 resection and organ preservation.

In 2015[13] and 2017, Le *et al*[14] revealed that pembrolizumab [programmed death protein (PD) 1 blockade] achieved a high objective response rate for metastatic dMMR/MSI-H solid malignant tumors, and some patients achieved complete response (CR). In 2017, for the first time, the United States FDA approved pembrolizumab (for immunotherapy of all unresectable, metastatic dMMR/MSI-H solid tumors based on biomarkers instead of tumor types). A series of studies[15-18] on advanced or metastatic dMMR/MSI-h gastrointestinal malignancies such as gastric and colorectal cancer showed that PD1 blockade achieved better therapeutic effects.

This study aimed to evaluate the efficacy and safety of preoperative PD-1 blockade immunotherapy in patients with dMMR/MSI-H locally advanced or metastatic gastrointestinal malignancies.

MATERIALS AND METHODS

Patients

We retrospectively analyzed clinical data of all patients with dMMR/MSI-H gastrointestinal malignancies who received preoperative PD1 blockade immunotherapy with or without chemotherapy in Ward 3, Gastrointestinal Cancer Center, Peking University Cancer Hospital from January 1, 2020 to September 30, 2022. Preoperative PD-1 blockade immunotherapy is recommended for patients with dMMR/MSI-H detected by molecular detection before treatment. This cohort was a series of sequential cases.

The inclusion criteria were: (1) Age ≥ 18 and ≤ 90 years; (2) Eastern Collaborative Oncology Group performance status score 0–2; (3) gastrointestinal malignancies: gastric cancer, duodenal carcinoma, or colorectal cancer; (4) adenocarcinoma or mucous adenocarcinoma confirmed by endoscopic biopsy; (5) clinical stage II–IV according to imaging examinations [spiral computed tomography, magnetic resonance imaging, positron emission tomography–computed tomography (PET-CT) or ultrasound colonoscopy]; and (6) MSI and MMR status confirmed by immunohistochemical staining, polymerase chain reaction (PCR) and next-generation sequencing (NGS). The exclusion criteria included: (1) Initially unresectable metastasis lesion; and (2) diseases of the immune system. This study was approved by the Ethics Committee of Peking University Cancer Hospital (2022YJZ39) and it conformed to the provisions of the Declaration of Helsinki.

Treatment and evaluation

All patients were discussed in a multidisciplinary team conference. All patients received PD1 blockade (PD1 blockade 200 mg intravenously over 30 min on day 1 of each 21-d cycle) preoperative immunotherapy with or without CapOx chemotherapy (oxaliplatin 130 mg/m² on day 1 and capecitabine 1000 mg/m² twice daily on d 1–14, repeated every 3 wk).

The primary tumor response was assessed according to the iRECIST criteria[19]. Acute toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events 4.0[20]. After every one or two cycles of neoadjuvant immunotherapy, all patients had complete assessment including computed tomography (CT), magnetic resonance imaging, PET-CT, blood counts, renal biochemistry, hepatobiliary function, thyroid function, cardiac function, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) to evaluate the general condition and treatment response. The determination of clinical complete response (cCR) was based on Memorial Sloan Kettering Cancer Center standard[21] and International Watch & Wait Database[22]. The cCR was defined as no evidence of residual tumor determined by rectum MRI, abdomen/pelvis CT and chest CT, endoscopic physical examination, normal CEA and/or digital rectal exam. Pathological staging was based on the 8th edition of the American Joint Committee on Cancer TNM staging system[23]. Post-treatment response was assessed by NCCN grading: 0 = complete response (ypCR) with no detectable cancer cells; 1 = major response with few residual cancer cells; 2 = partial response; 3 = no or very little response[24].

Postoperative complications were classified according to the Clavien–Dindo classification[24].

Follow-up and statistical analysis

After initial treatment, all patients were re-examined every 3 mo for the first 2 years, 6-mo intervals for the next 3 years, and yearly thereafter. Clinical data were obtained by laboratory examination records, imaging examination records, pathological examination records, and medical records review. Survival data were obtained from outpatient clinical visit or telephone interview. Analyses were conducted using SPSS for Windows version 19.0. Frequencies and percentages were calculated for categorical variables, and means and standard deviations for continuous variables.

RESULTS

Patient characteristics

From January 1, 2020 to September 30, 2022, 37 patients with dMMR/MSI-H gastrointestinal malignancies finished preoperative PD1 blockade immunotherapy, and one patient with locally advanced colon cancer refused re-examination and treatment after symptom resolution. By September 30, 2022, 36 patients completed PD1 blockade immunotherapy and the treatment results were analyzed.

The clinical features are shown in Tables 1 and 2. Twenty-six men (26/36, 72.2%) and 10 women (10/36, 27.8%) were enrolled and the median age was 52 (26–87) years. Lynch syndrome was diagnosed in 16 patients. Three patients were diagnosed with initially unresectable locally advanced gastric cancer, three with locally advanced duodenal carcinoma, and 30 with colorectal cancer. Among the 30 cases of colorectal cancer, 21 were locally advanced and nine were surgically resectable metastatic colorectal cancer. Twenty-seven patients received single PD-1 blockade as preoperative therapy, and nine with PD1 blockade and CapOx regimen. Of these patients, nine were initially treated with CapOx and two with radiotherapy, which was ineffective and switched to immunotherapy.

Table 1 Patient, tumor and treatment characteristics

All cases	N (%)
Sex, n (%)	
Male	26 (72.2)
Female	10 (27.8)
Age, yr (median)	52.0
ECOG	
0	2 (5.6)
1	30 (83.3)
2	4 (11.1)
Tumor location, n (%)	
Stomach	3 (8.3)
Duodenum	3 (8.3)
Colorectal cancer	30 (83.3)
Clinical TNM stage, n (%)	
II-III	27(75.0)
IV	9 (25.0)
Lynch syndrome	
Yes	16 (44.4)
No	20 (55.6)
No clear	0 (0.0)
MMR and MSI status	
Consistent	30 (83.3)
Inconsistent	6 (16.7)

ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch repair; MSI: Microsatellite instability; TNM: Tumor-node-metastasis.

Efficacy

With a median interval of 2 wk after neoadjuvant immunotherapy (range: 1–4 wk), all patients received imaging evaluation (Table 2). cCR was achieved in seven patients (patient 4, 5, 6, 23, 26, 27, 30), among which six (patient 4, 5, 6, 23, 26, 30) were selected for wait and watch strategy. No cCR was observed in gastric or colon cancer. Thirty patients underwent surgery, including nine laparoscopic operations and 21 Laparotomies. Twenty-nine patients achieved R0 resection according to the postoperative pathological diagnosis (Table 2).

Three patients with locally advanced gastric cancer achieved pathological CR (pCR). Three patients with locally advanced duodenal carcinoma achieved cCR and then watch and wait (Video 1). Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastasis from colon cancer achieved CR, including three pCR and one cCR. pCR was achieved in two of five patients with non-liver metastases from colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. The CR (cCR and pCR) rate was 58.3% (21/36).

No adjuvant therapy was performed after pCR was achieved. Six patients received 2–10 cycles of adjuvant mono-immunotherapy after reaching cCR. The median follow-up was 9.4 (1–29) mo, and final follow-up time was September 30, 2022. pCR and cCR patients had no recurrence during follow-up. No patient died during follow-up.

Safety

Preoperative immunotherapy was well tolerated and there was no interruption caused by immunotherapy-related toxicity. Two patients had grade 3 toxicity that presented as hypothyroidism and hematochezia, and eight patients had grade 1 or 2 toxicity including hypothyroidism, thyroid toxicity, rash, fatigue, reactive cutaneous capillary endothelial proliferation (Table 3). No surgery was delayed, but four patients experienced emergency surgery, of which two had perforated tumor, and two had

Table 2 Details of the 36 patients with neoadjuvant programmed death protein 1 blockade immunotherapy

No.	Tumor location	Clinical stage	MMR status	MSI status	Courses of ICB	Combined treatment	Surgery	Pathological stage
1	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 6	CapeOX	Total gastrectomy	PCR
2	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 5	CapeOX	Total gastrectomy	PCR
3	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 3	CapeOX	Total gastrectomy	PCR
4	Duodenum	T3N0M0	dMMR	MSI-H	Pembrolizumab × 4	-	cCR	-
5	Duodenum	T3N0M0	dMMR	MSI-H	Pembrolizumab × 6	-	cCR	-
6	Duodenum	T4aN0M0	dMMR	MSI-L	Sintilimab × 8	CapeOX	cCR	-
7	LACC	T4aN+M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
8	LACC	T3N+M0	dMMR	MSI-H	Sintilimab × 2	-	Colectomy	ypT3N0
9	LACC	T4bN2M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
10	LACC	T3N+M0	dMMR	MSI-H	Camrelizumab × 4	CapeOX	Colectomy	PCR
11	LACC	T4bN+M0	dMMR	MSI-H	Pembrolizumab × 1	-	Colectomy	ypT3N0
12	LACC	T3N+M0	dMMR	MSI-H	Camrelizumab × 3	-	Colectomy	ypT2N0
13	LACC	T4bN2bM0	dMMR	MSI-H	Sintilimab × 4	-	Colectomy	ypT1N1b
14	LACC	T4bN+M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
15	LACC	T4aN+M0	dMMR	MSS	Sintilimab × 3	CapeOX	Colectomy	ypT3N0
16	LACC	T4aN+M0	dMMR	MSI-H	Toripalimab × 8	-	Colectomy	ypT2N0
17	LACC	T3N0M0	dMMR	MSI-H	Pembrolizumab × 4	-	Colectomy	ypT3N0
18	LACC	T4bN2aM0	dMMR	MSI-H	Sintilimab × 5	-	Colectomy	PCR
19	LACC	T4bN2bM0	dMMR	MSI-H	Sintilimab × 3	-	Colectomy	PCR
20	LACC	T4aN2bM0	dMMR	MSS	Pembrolizumab × 3	-	Colectomy	ypT3N1a
21	LACC	T3N2aM0	pMMR	MSI-H	Pembrolizumab × 3	-	Colectomy	PCR
22	LACC	cT4aN2M0	dMMR	MSI-H	Pembrolizumab × 4	-	Colectomy	PCR
23	Low rectum	T3N1M0	dMMR	MSI-H	Pembrolizumab × 1	-	CCR	-
24	Low rectum	T3N2M0	dMMR	MSI-H	Nivolumab × 3	CapeOX	LAR	PCR
25	Low rectum	T3N+M0	pMMR	MSI-H	Sintilimab × 4	-	LAR	ypT3N0
26	Low rectum	T3N+M0	dMMR	MSI-H	Pembrolizumab × 2	-	CCR	-
27	Low rectum	T3N2M0	pMMR	MSI-H	Camrelizumab × 3	CapeOX	CCR	PCR
28	CLM	M1a	dMMR	MSI-H	Sintilimab × 6	CapeOX	Hepatectomy	PCR
29	CLM	T4bN2M1a	dMMR	MSI-H	Sintilimab × 4	CapeOX	ColectomyHepatectomy	ypT4bN1aM0
30	CLM	M1a	dMMR	MSI-H	Sintilimab × 26	-	CCR	-
31	CLM	T4aN2M1a	dMMR	MSI-H	Pembrolizumab × 4	-	ColectomyHepatectomy	PCR
32	Rectum	T4bN2M1c	dMMR	MSI-H	Pembrolizumab × 1	-	Colectomy	ypT4bN2aM1c
33	Rectum	T4bN2M1a	dMMR	MSI-H	Sintilimab × 6	-	Hartmann	PCR

34	Colon	T4bN2M1c	dMMR	MSI-H	Tislelizumab × 8	-	Colectomy	ypT0N0M1c
35	Colon	T4bN2M1c	dMMR	MSI-H	Sintilimab × 5	CapeOX	Colectomy	ypT3N0M1c
36	Colon	T4aN1M1c	dMMR	MSI-H	Sintilimab × 5	-	Colectomy	PCR

cCR: Clinical complete response; LACC: Locally Advanced Colon Cancer; pMMR: Proficient mismatch repair; dMMR: Different mismatch repair; ICB: Immune checkpoint inhibitor; CLM: Colorectal Liver Metastases; LAR: Low Anterior Resection; PCR: Polymerase chain reaction.

Table 3 Adverse events

Adverse events	No. of patients (%)		
	Grade 1	Grade 2	Grade 3
Immuno-related			
Any	4 (11.1)	4 (11.1)	2 (5.6)
Dermatologic			
Rash	2 (5.6)	0 (0)	0 (0)
RCCEP	1 (2.80)	0 (0)	0 (0)
Endocrine			
Hypothyroidism	2 (5.6)	2 (5.6)	1 (2.80)
Hyperglycemia	0 (0)	0 (0)	0 (0)
Fatigue	3 (8.3)	4(11.1)	0 (0)
Surgery-related			
Any	1 (2.80)	4(11.1)	1 (2.80)
Chylous fistula	0 (0)	2 (5.6)	0 (0)
Anastomosis leakage	0 (0)	2 (5.6)	0 (0)
Fever	1 (2.80)	0 (0)	0 (0)
Intra-abdominal hemorrhage	0 (0)	0 (0)	1 (2.80)

RCCEP: Reactive cutaneous capillary endothelial proliferation.

colonic obstruction. There was no 30-d mortality. Four patients had grade 1 or 2 postoperative complications, including two grade 2 chylous fistula, two grade 2 anastomotic leak, and one grade 1 fever. One patient (case 24) underwent emergency surgery for intestinal obstruction, and received a second operation for postoperative abdominal bleeding (grade 3). All patients recovered well after conservative treatment and only one (anastomotic leak) stayed in hospital > 2 wk after surgery.

DISCUSSION

This retrospective study is one of the few to summarize dMMR/MSI-H gastric, duodenal and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis and only one patient was excluded because her symptoms disappeared after PD1 therapy and she refused further examination and treatment.

The GERCOR NEONIPIGA study[25] reported neoadjuvant nivolumab plus ipilimumab in patients with localized dMMR/MSI-H esophagogastric adenocarcinoma showed a pCR rate of 58.6%. The NICHE study[26] and PICC study[27] of dMMR/MSI-H colon cancer showed a pCR rate of 60% and 65%, respectively. Cercek *et al*[28] reported 14 patients with dMMR/MSI-H rectal cancer using dostarlimab (PD1 blockade); all of whom achieved cCR and avoided surgical treatment.

MSI-H/dMMR tumors are currently the best predictive markers for cancer immunotherapy, but MSI-H tumors are also heterogeneous, and show different incidence, differences in clinical and radiographic responses to immunotherapy in different solid tumors, primary immunotherapy resistance in some patients, and heterogeneity of different stages of the same tumor[1,29-31]. In our cohort three patients with locally advanced gastric cancer achieved pCR. Three patients with locally advanced duodenal carcinoma evaluated as cCR received the watch and wait strategy. Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastatic lesions from colon cancer

reached CR. pCR was achieved in two of five patients with non-liver metastatic colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. No cCR was observed in gastric or colon cancer. Duodenal and low rectal cancers have a high cCR rate, and do not require surgery and achieve organ preservation. Based on such high pCR and cCR rates, some patients can avoid surgery. Eleven of 36 patients in our study underwent routine preoperative chemotherapy and/or radiotherapy, which was unnecessary. Neoadjuvant therapy should be effective, moderate and accurate based on the treatment target. It is necessary to determine the molecular status of patients before treatment.

Different from the prospective clinical study, patients in our cohort underwent surgery and achieved R0 resection on imaging examination. Five patients achieved cCR or pCR within one or two cycles, and 15 patients who achieved pCR did not receive postoperative adjuvant therapy. None of the patients with pCR or cCR had recurrence or metastasis during follow-up. The Keynote 016[13], Keynote 177[2] and CHECKMATE 142[16] studies showed that if MSI-H tumors were highly sensitive to PD1 inhibitors or CTLA4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4) antibody, the response was rapid, and there was a significant tail effect of immunotherapy after long follow-up. Because of the inaccuracy of conventional imaging in the assessment of immunotherapy, the development of new tests that reflect the pathological response (*e.g.*, metabolic imaging) or molecular features (*e.g.*, liquid biopsy) is needed to better assess the response to treatment[32]. For MSI-H tumors sensitive to PD1 immunotherapy, early and short-term PD1 treatment can achieve a curative effect. It is necessary to clarify the characteristics and immune microenvironment of MSI-H tumors.

Our study and others have shown that preoperative immunotherapy is safe for most patients[33,34]. However, we have seen that there are some hidden dangers in the use of immunotherapy for such patients before surgery, such as stenosis, obstruction and perforation during the treatment of colon cancer. Previous studies[35,36] of neoadjuvant chemotherapy have suggested that obstruction and perforation reflect the poor effect of neoadjuvant therapy and are associated with tumor progression and poor prognosis. Due to immune cell infiltration and other reasons, many patients did not observe tumor remission on imaging-maintained stability or even some enlargement, but pathological examination will find a large number of necrosis tumors and inflammatory immune response[37]. Our study also observed this phenomenon. Our cohort reported four patients with MSI-H colon cancer with obstruction and perforation during PD1 treatment; all of whom had some tumor pathological response after emergency surgery, including one who achieved pCR and three with pathological ratings of TRG2-3. We also observed five patients with regional lymph node enlargement during treatment. Although no trace of metastasis was found after lymph node dissection, it increased the difficulty of surgery and was prone to complications of lymphatic leakage. The incidence of thyroid dysfunction was 22% and three patients required long-term oral thyroxine replacement therapy.

Many studies[2,3,14-18] have reported that 10%-40% of patients with dMMR/MSI-H colorectal cancer developed primary drug resistance when receiving immunotherapy. Cohen *et al*[38] suggested that primary resistance to PD-1 blockades in dMMR/MSI-H metastatic colorectal cancer can largely be attributed to misdiagnosis of MMR/MSI status. In our cohort, 16.7% (6/36) of patients had MMR and MSI discordance[39,40]. We found that this discordance was test related and in some patients it was related to examination methods, tissue volume, tumor heterogeneity, and examination quality control. Six patients were re-diagnosed with MMR and MSI status, and three were found to be consistent (Table 4). Our study and many others have found that intrinsic resistance exists even when MSI is consistent with MMR status[39,40]. Wang *et al*[41] found that combination of AKT1 and CDH1 mutations predicted primary resistance to immunotherapy in dMMR/MSI-H gastrointestinal cancer.

The limitations of this study included its small sample size, retrospective design, short follow-up time, and different neoadjuvant regimens and cycles. However, our study was a real-world clinical study in patients who required preoperative immunotherapy, and the group was a continuous case cohort, with the exception of one patient who declined to be enrolled because of resolution of symptoms. This study compared preoperative immunotherapy for dMMR/MSI-H in different gastrointestinal tumors, and showed that specific treatment strategies could be used for different tumor sites. It was encouraging to find that a high proportion of dMMR/MSI-H duodenal and low rectal cancers did not require surgery after preoperative immunotherapy, and this treatment strategy deserves further investigation.

CONCLUSION

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy achieved significant results and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies. Some low cases of low rectal cancer or duodenal cancer can achieve cCR and avoid surgery and achieve organ preservation. Larger clinical trials are needed to conform our results.

Table 4 Details of the 6 patients with inconsistency of dMMR and MSI-H

No.	Tumor location	Clinical stage	Heredity	MMR (IHC)biopsy	MMR (NGS) biopsy	MSI (PCR) biopsy	MSI (NGS) biopsy	MMR (IHC) surgery	MMR (NGS) surgery	MMR (PCR) surgery	MMR (NGS) surgery	Reason
6	Duodenum	T4aN+M0	Lynch	dMMR	dMMR	MSI-L	MSI-L					-
15	Colon	T4aN+M0	No	dMMR	pMMR	MSS	MSS	pMMR	pMMR	MSS	MSS	Tumor heterogeneity
20	Colon	T4aN2bM0	No	dMMR	dMMR	MSS	MSS	dMMR	dMMR	MSI-H	MSI-H	Low tumor content
21.	Colon	T3N2aM0	No	pMMR	dMMR	MSI-H	MSI-H					Only MSH3 mt
25	Rectum	T3N+M0	No	pMMR	pMMR	MSS	MSI-H	pMMR	pMMR	MSS	MSI-H	DDR mt
27	Rectum	T3N2M0	No	pMMR	pMMR	MSS	MSI-H					DDR mt

IHC: Immunohistochemistry; PCR: Polymerase chain reaction; NGS: Next-generation sequencing; MSI-L: Microsatellite instability-low; pMMR: Proficient mismatch repair; dMMR: Different mismatch repair; WT: Wild type; MT: Mutant type.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant programmed death protein (PD)-1 blockade immunotherapy has been sufficiently applied in a variety of cancers, but was rare in metastatic mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal malignancies. Since the NICHE Study have showed their inspiring results that neoadjuvant immunotherapy was an efficient and safe method to improve colon cancer patients' outcome, NCCN guideline then recommend immune checkpoint inhibitors to cT4b gastric or colorectal cancer. However, whether preoperative immunotherapy can expand to other stage gastrointestinal malignancies is still unknown.

Research motivation

We performed this study among 36 initially surgical resected difficult dMMR/MSI-H gastrointestinal malignancies such gastric cancer, duodenal cancer and colorectal cancer patients who received preoperative PD-1 blockade immunotherapy followed by surgery in order to investigate if the indication of preoperative immunotherapy can expand to initially surgical resected difficult dMMR/MSI-H gastrointestinal malignancies and evaluate the safety and efficacy.

Research objectives

To the best of our knowledge, this retrospective study is one of the few to summarize dMMR/MSI-H gastric, duodenal, and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis that only one patient was excluded from the cohort because symptoms disappeared after PD1 therapy and she refused to examination and further treatment.

Research methods

The limitations of this study included its small sample size, retrospective design, short follow-up time, and different neoadjuvant regimens and cycles. However, our study was a real-world clinical study in patients who required preoperative immunotherapy, and the group was a continuous case cohort, with the exception of one patient who declined to be enrolled because of resolution of symptoms.

Research results

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy could achieve significant effect and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies.

Research conclusions

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy could achieve significant effect and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies. Some low rectal cancer or duodenal cancer can achieve clinical complete response and avoid surgery to achieve organ preservation. Large sample clinical trials are needed.

Research perspectives

This study compared preoperative immunotherapy for dMMR/MSI-H in different gastrointestinal tumors, and showed that specific treatment strategies could be used for different tumor sites. It was encouraging to find that a high proportion of dMMR/MSI-H duodenal and low rectal cancers did not require surgery after preoperative immunotherapy, and this treatment strategy deserves further investigation.

FOOTNOTES

Author contributions: Wu AW contributed to conception and design of the study, draft and final approval of the manuscript; Li YJ contributed to collection of the data, draft the manuscript, study design and statistical analysis; Wu AW, Li YJ, Liu XZ and Yao YF, Li ZW, Zhang XY, Lin XF contributed to quality control of the study especially the surgery part, acquisition of data; All authors approved the final manuscript.

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Institutional review board statement: This study was approved by the ethics committee of Peking University cancer hospital (approval no. 2022YJZ39).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at drwuaw@sina.com.

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REFERENCES

- 1 **Lorenzi M**, Amonkar M, Zhang J, Mehta S, Liaw KL. Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review. *J Oncol* 2020; 2020 [DOI: [10.1155/2020/1807929](https://doi.org/10.1155/2020/1807929)]
- 2 **Hause RJ**, Pritchard CC, Shendure J, Salipante SJ. Classification and characterization of microsatellite instability across 18 cancer types. *Nat Med* 2016; **22**: 1342-1350 [PMID: [27694933](https://pubmed.ncbi.nlm.nih.gov/27694933/) DOI: [10.1038/nm.4191](https://doi.org/10.1038/nm.4191)]
- 3 **André T**, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020; **383**: 2207-2218 [PMID: [33264544](https://pubmed.ncbi.nlm.nih.gov/33264544/) DOI: [10.1056/NEJMoa2017699](https://doi.org/10.1056/NEJMoa2017699)]
- 4 **Marabelle A**, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghorri R, Joe AK, Pruitt SK, Diaz LA Jr. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol* 2020; **38**: 1-10 [PMID: [31682550](https://pubmed.ncbi.nlm.nih.gov/31682550/) DOI: [10.1200/JCO.19.02105](https://doi.org/10.1200/JCO.19.02105)]
- 5 **Guinney J**, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L, Tejpar S. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015; **21**: 1350-1356 [PMID: [26457759](https://pubmed.ncbi.nlm.nih.gov/26457759/) DOI: [10.1038/nm.3967](https://doi.org/10.1038/nm.3967)]
- 6 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: [25079317](https://pubmed.ncbi.nlm.nih.gov/25079317/) DOI: [10.1038/nature13480](https://doi.org/10.1038/nature13480)]
- 7 **Yang G**, Zheng RY, Jin ZS. Correlations between microsatellite instability and the biological behaviour of tumours. *J Cancer Res Clin Oncol* 2019; **145**: 2891-2899 [PMID: [31617076](https://pubmed.ncbi.nlm.nih.gov/31617076/) DOI: [10.1007/s00432-019-03053-4](https://doi.org/10.1007/s00432-019-03053-4)]
- 8 **Popat S**, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005; **23**: 609-618 [PMID: [15659508](https://pubmed.ncbi.nlm.nih.gov/15659508/) DOI: [10.1200/JCO.2005.01.086](https://doi.org/10.1200/JCO.2005.01.086)]
- 9 **Kim SY**, Choi YY, An JY, Shin HB, Jo A, Choi H, Seo SH, Bang HJ, Cheong JH, Hyung WJ, Noh SH. The benefit of microsatellite instability is attenuated by chemotherapy in stage II and stage III gastric cancer: Results from a large cohort with subgroup analyses. *Int J Cancer* 2015; **137**: 819-825 [PMID: [25614197](https://pubmed.ncbi.nlm.nih.gov/25614197/) DOI: [10.1002/ijc.29449](https://doi.org/10.1002/ijc.29449)]
- 10 **Pietrantonio F**, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, Choi YY, Kim KM, Nankivell MG, Morano F, Wotherspoon A, Valeri N, Kook MC, An JY, Grabsch HI, Fucà G, Noh SH, Sohn TS, Kim S, Di Bartolomeo M, Cunningham D, Lee J, Cheong JH, Smyth EC. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer. *J Clin Oncol* 2019; **37**: 3392-3400 [PMID: [31513484](https://pubmed.ncbi.nlm.nih.gov/31513484/) DOI: [10.1200/JCO.19.01124](https://doi.org/10.1200/JCO.19.01124)]
- 11 **Seymour MT**, Morton D. FOXTROT: An international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. *J Clin Oncol* 2019; **37**: 3504 [DOI: [10.1200/JCO.2019.37.15_suppl.3504](https://doi.org/10.1200/JCO.2019.37.15_suppl.3504)]
- 12 **Hasan S**, Renz P, Wegner RE, Finley G, Raj M, Monga D, McCormick J, Kirichenko A. Microsatellite Instability (MSI) as an Independent Predictor of Pathologic Complete Response (PCR) in Locally Advanced Rectal Cancer: A National Cancer Database (NCDB) Analysis. *Ann Surg* 2020; **271**: 716-723 [PMID: [30216221](https://pubmed.ncbi.nlm.nih.gov/30216221/) DOI: [10.1097/SLA.0000000000003051](https://doi.org/10.1097/SLA.0000000000003051)]
- 13 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhajee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: [26028255](https://pubmed.ncbi.nlm.nih.gov/26028255/) DOI: [10.1056/NEJMoa1500596](https://doi.org/10.1056/NEJMoa1500596)]
- 14 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: [28596308](https://pubmed.ncbi.nlm.nih.gov/28596308/) DOI: [10.1126/science.aan6733](https://doi.org/10.1126/science.aan6733)]
- 15 **Le DT**, Kim TW, Van Cutsem E, Geva R, Jäger D, Hara H, Burge M, O'Neil B, Kavan P, Yoshino T, Guimbaud R, Taniguchi H, Elez E, Al-Batran SE, Boland PM, Crocenzi T, Atreya CE, Cui Y, Dai T, Marinello P, Diaz LA Jr, André T. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol* 2020; **38**: 11-19 [PMID: [31725351](https://pubmed.ncbi.nlm.nih.gov/31725351/) DOI: [10.1200/JCO.19.02107](https://doi.org/10.1200/JCO.19.02107)]
- 16 **Overman MJ**, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, Desai J, Hill A, Axelson M, Moss RA, Goldberg MV, Cao ZA, Ledezne JM, Maglinte GA, Kopetz S, André T. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017; **18**: 1182-1191 [PMID: [28734759](https://pubmed.ncbi.nlm.nih.gov/28734759/) DOI: [10.1016/S1470-2045\(17\)30422-9](https://doi.org/10.1016/S1470-2045(17)30422-9)]
- 17 **Diaz LA Jr**, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Le DT, Yoshino T, Zhong WY, Fogelman D, Marinello P, Andre T; KEYNOTE-177 Investigators. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* 2022; **23**: 659-670 [PMID: [35427471](https://pubmed.ncbi.nlm.nih.gov/35427471/) DOI: [10.1016/S1470-2045\(22\)00197-8](https://doi.org/10.1016/S1470-2045(22)00197-8)]
- 18 **Janjigian YY**, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzian MV, Bruges R, Zander T, Pazo-Cid R,

- Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; **398**: 27-40 [PMID: 34102137 DOI: 10.1016/S0140-6736(21)00797-2]
- 19 Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancy J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE; RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017; **18**: e143-e152 [PMID: 28271869 DOI: 10.1016/S1470-2045(17)30074-8]
- 20 Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC, Lacouture ME. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. *J Am Acad Dermatol* 2012; **67**: 1025-1039 [PMID: 22502948 DOI: 10.1016/j.jaad.2012.02.010]
- 21 Smith JJ, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A, Widmar M, Ganesh K, Yaeger R, Cercek A, Weiser MR, Nash GM, Guillem JG, Temple LKF, Chalasani SB, Fuqua JL, Petkovska I, Wu AJ, Reingold M, Vakiani E, Shia J, Segal NH, Smith JD, Crane C, Gollub MJ, Gonen M, Saltz LB, Garcia-Aguilar J, Paty PB. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. *JAMA Oncol* 2019; **5**: e185896 [PMID: 30629084 DOI: 10.1001/jamaoncol.2018.5896]
- 22 van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, Habr-Gama A, Perez RO, Renehan AG, van de Velde CJH; IWW Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWW): an international multicentre registry study. *Lancet* 2018; **391**: 2537-2545 [PMID: 29976470 DOI: 10.1016/S0140-6736(18)31078-X]
- 23 Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Gurski L, Freedman-Cass DA. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 874-901 [PMID: 30006429 DOI: 10.6004/jnccn.2018.0061]
- 24 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]
- 25 André T, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, Jary M, Tournigand C, Aparicio T, Desrame J, Lièvre A, Garcia-Larnicol ML, Pudlzar T, Cohen R, Memmi S, Vernerey D, Henriques J, Lefevre JH, Svrcek M. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. *J Clin Oncol* 2023; **41**: 255-265 [PMID: 35969830 DOI: 10.1200/JCO.22.00686]
- 26 Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, Lopez-Yurda M, Grootsholten C, Beets GL, Snaebjornsson P, Maas M, Mertz M, Veninga V, Bounova G, Broeks A, Beets-Tan RG, de Wijkerslooth TR, van Lent AU, Marsman HA, Nuijten E, Kok NF, Kuiper M, Verbeek WH, Kok M, Van Leerdam ME, Schumacher TN, Voest EE, Haanen JB. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020; **26**: 566-576 [PMID: 32251400 DOI: 10.1038/s41591-020-0805-8]
- 27 Hu H, Kang L, Zhang J, Wu Z, Wang H, Huang M, Lan P, Wu X, Wang C, Cao W, Hu J, Huang Y, Huang L, Shi L, Cai Y, Shen C, Ling J, Xie X, He X, Dou R, Zhou J, Ma T, Zhang X, Luo S, Deng W, Ling L, Liu H, Deng Y. Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 38-48 [PMID: 34688374 DOI: 10.1016/S2468-1253(21)00348-4]
- 28 Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, Stadler Z, Yaeger R, Smith JJ, Rousseau B, Argiles G, Patel M, Desai A, Saltz LB, Widmar M, Iyer K, Zhang J, Gianino N, Crane C, Romesser PB, Pappou EP, Paty P, Garcia-Aguilar J, Gonen M, Gollub M, Weiser MR, Schalper KA, Diaz LA Jr. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med* 2022; **386**: 2363-2376 [PMID: 35660797 DOI: 10.1056/NEJMoa2201445]
- 29 Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. *Nat Rev Clin Oncol* 2010; **7**: 153-162 [PMID: 20142816 DOI: 10.1038/nrclinonc.2009.237]
- 30 Lee MKC, Loree JM. Current and emerging biomarkers in metastatic colorectal cancer. *Curr Oncol* 2019; **26**: S7-S15 [PMID: 31819705 DOI: 10.3747/co.26.5719]
- 31 Li SKH, Martin A. Mismatch Repair and Colon Cancer: Mechanisms and Therapies Explored. *Trends Mol Med* 2016; **22**: 274-289 [PMID: 26970951 DOI: 10.1016/j.molmed.2016.02.003]
- 32 Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou V, Rektman N, Anders RA, Cuda JD, Illei PB, Gabrielson E, Askin FB, Niknafs N, Smith KN, Velez MJ, Sauter JL, Isbell JM, Jones DR, Battafarano RJ, Yang SC, Danilova L, Wolchok JD, Topalian SL, Velculescu VE, Pardoll DM, Brahmer JR, Hellmann MD, Chaft JE, Cimino-Mathews A, Taube JM. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). *Ann Oncol* 2018; **29**: 1853-1860 [PMID: 29982279 DOI: 10.1093/annonc/mdy218]
- 33 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa1200690]
- 34 Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, Shen C, Duma N, Vera Aguilera J, Chintakuntlawar A, Price KA, Molina JR, Pagliaro LC, Halfdanarson TR, Grothey A, Markovic SN, Nowakowski GS, Ansell SM, Wang ML. Treatment-

- Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-analysis. *JAMA Oncol* 2019; **5**: 1008-1019 [PMID: 31021376 DOI: 10.1001/jamaoncol.2019.0393]
- 35 **Wolmark N**, Wieand HS, Rockette HE, Fisher B, Glass A, Lawrence W, Lerner H, Cruz AB, Volk H, Shibata H. The prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. Findings from the NSABP clinical trials. *Ann Surg* 1983; **198**: 743-752 [PMID: 6357118 DOI: 10.1097/0000658-198312000-00013]
- 36 **Chen HS**, Sheen-Chen SM. Obstruction and perforation in colorectal adenocarcinoma: an analysis of prognosis and current trends. *Surgery* 2000; **127**: 370-376 [PMID: 10776426 DOI: 10.1067/msy.2000.104674]
- 37 **Wang Q**, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. *Int Immunopharmacol* 2018; **58**: 125-135 [PMID: 29579717 DOI: 10.1016/j.intimp.2018.03.018]
- 38 **Cohen R**, Hain E, Buhard O, Guilloux A, Bardier A, Kaci R, Bertheau P, Renaud F, Bibeau F, Fléjou JF, André T, Svrcek M, Duval A. Association of Primary Resistance to Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer With Misdiagnosis of Microsatellite Instability or Mismatch Repair Deficiency Status. *JAMA Oncol* 2019; **5**: 551-555 [PMID: 30452494 DOI: 10.1001/jamaoncol.2018.4942]
- 39 **Amodio V**, Mauri G, Reilly NM, Sartore-Bianchi A, Siena S, Bardelli A, Germano G. Mechanisms of Immune Escape and Resistance to Checkpoint Inhibitor Therapies in Mismatch Repair Deficient Metastatic Colorectal Cancers. *Cancers (Basel)* 2021; **13** [PMID: 34072037 DOI: 10.3390/cancers13112638]
- 40 **Sahin IH**, Akce M, Alese O, Shaib W, Lesinski GB, El-Rayes B, Wu C. Immune checkpoint inhibitors for the treatment of MSI-H/MMR-D colorectal cancer and a perspective on resistance mechanisms. *Br J Cancer* 2019; **121**: 809-818 [PMID: 31607751 DOI: 10.1038/s41416-019-0599-y]
- 41 **Wang Z**, Zhang Q, Qi C, Bai Y, Zhao F, Chen H, Li Z, Wang X, Chen M, Gong J, Peng Z, Zhang X, Cai J, Chen S, Zhao X, Shen L, Li J. Combination of AKT1 and CDH1 mutations predicts primary resistance to immunotherapy in dMMR/MSI-H gastrointestinal cancer. *J Immunother Cancer* 2022; **10** [PMID: 35705314 DOI: 10.1136/jitc-2022-004703]



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