

Treatment options after PD-1/PDL-1 inhibitors in dMMR/MSI-H colorectal cancer: A systematic review

Michelle Trisya¹, Aileen A Suryohusodo¹, Findy Prasetyawaty²



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Authors' affiliations:

¹Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Pluit Raya, Jakarta Utara, Daerah Khusus Ibukota Jakarta, 14440, Indonesia

²Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo Hospital, Pangeran Diponegoro, Jakarta Pusat, Daerah Khusus Ibukota Jakarta, 10430, Indonesia

Corresponding author:
E-mail: michelletrisya@gmail.com

Abstract

Background: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality. Approximately 13% of CRCs are microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR), resulting in high tumor mutational burden and immunogenicity. These tumors are particularly responsive to programmed cell death protein 1 (PD-1) or programmed death-ligand 1 inhibitors (PD-L1). However, despite the durable responses, up to one-third experience progression due to primary or acquired resistance. The optimal management strategy following progression on PD-1/PD-L1 inhibitors remains undefined.

Results: A total of 504 studies were identified, one retrospective cohort study and eight case reports met inclusion criteria, comprising 38 patients with metastatic MSI-H/dMMR CRC. All studies demonstrated a low risk of bias. The cohort study reported limited efficacy of chemotherapy (ORR 13%, median PFS 2.9

Objective: This systematic review summarizes current and emerging treatment options in this setting.

Methods: A systematic search was performed. Eligible studies included case reports and observational studies of MSI-H/dMMR CRC patients who progressed on PD-1/PD-L1 blockade and received subsequent chemotherapy, targeted therapy, or combination immunotherapy. Risk of bias was assessed using the Joanna Briggs Institute checklist for case reports and the Newcastle–Ottawa Scale for cohort studies.

months, OS 7.4 months), whereas combination regimens especially PD-1 with bevacizumab or CTLA-4 blockade yielded durable responses up to 12–36 months. Most adverse events were manageable.

Conclusion: Following progression on PD-1/PD-L1 inhibitors, conventional chemotherapy offers modest benefit, whereas combination strategies integrating immunotherapy or anti-angiogenic agents show greater and durable efficacy.

Keywords: MSI-H/dMMR colorectal cancer, PD-1/PD-L1 inhibitor, post-PD-1 progression, treatment options

Abstrak

Latar Belakang: Kanker kolorektal (*colorectal cancer*/CRC) masih menjadi salah satu penyebab utama kematian terkait kanker. Sekitar 13% kasus CRC memiliki *microsatellite instability-high* (MSI-H) atau *mismatch repair-deficient* (dMMR), yang menyebabkan tingginya beban mutasi tumor dan imunogenisitas. Tumor ini sangat responsif terhadap inhibitor *programmed cell death protein 1* (PD-1) atau *programmed death-ligand 1* (PD-L1). Meskipun respons yang dihasilkan dapat bertahan lama, hingga sepertiga pasien mengalami progresi akibat resistensi primer maupun didapat. Strategi tata laksana optimal setelah progresi dengan inhibitor PD-1/PD-L1 masih belum ditetapkan.

Tujuan: Tinjauan sistematis ini merangkum pilihan terapi terkini dan terapi yang sedang berkembang pada kondisi tersebut.

Metode: Penelusuran sistematis dilakukan untuk mengidentifikasi penelitian yang relevan. Studi yang memenuhi kriteria meliputi laporan kasus dan studi observasional pada pasien CRC MSI-H/dMMR yang mengalami progresi setelah terapi penghambatan PD-1/PD-L1 dan selanjutnya mendapatkan kemoterapi, terapi target, atau imunoterapi kombinasi. Risiko bias dinilai menggunakan Joanna Briggs Institute checklist untuk laporan kasus dan Newcastle–Ottawa Scale untuk studi kohort.

Hasil: Sebanyak 504 studi teridentifikasi, dan satu studi kohort retrospektif serta delapan laporan kasus memenuhi kriteria inklusi, dengan total 38 pasien CRC metastatik MSI-H/dMMR. Seluruh studi menunjukkan risiko bias yang rendah. Studi kohort melaporkan efektivitas kemoterapi yang terbatas (ORR 13%, median PFS 2,9 bulan, OS 7,4 bulan), sedangkan regimen kombinasi, terutama PD-1 dengan bevacizumab atau penghambatan CTLA-4, menghasilkan respons yang bertahan lama hingga 12–36 bulan. Sebagian besar efek samping dapat ditangani.

Kesimpulan: Setelah terjadi progresi dengan inhibitor PD-1/PD-L1, kemoterapi konvensional memberikan manfaat yang terbatas, sedangkan strategi kombinasi yang mengintegrasikan imunoterapi atau agen antiangiogenik menunjukkan efektivitas yang lebih baik dan respons yang lebih bertahan lama.

Kata kunci: inhibitor PD-1/PD-L1, kanker kolorektal MSI-H/dMMR, pilihan terapi, progresi pasca-PD-1

Background

Colorectal cancer (CRC) is one of the most common malignancies worldwide, ranking third in incidence and a leading cause of cancer-related mortality.¹ Approximately 13% of CRCs exhibit microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), resulting from inactivation of mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*.² These defects lead to an accumulation of DNA replication errors and a hypermutated phenotype, which generates a high neoantigen load and increases tumor immunogenicity.³ As a result, MSI-H/dMMR tumors are particularly responsive to immune checkpoint blockade targeting the PD-1/PD-L1 pathway.

Pembrolizumab, an immunotherapy targeting PD-1, became the first-line standard of care (SOC) for patients with unresectable or metastatic MSI-H/dMMR CRC following the results of the phase III KEYNOTE-177 trial. In this study, pembrolizumab demonstrated a median progression-free survival (PFS) of 16.5 months compared to 8.2 months with chemotherapy (HR 0.60, 95% CI: 0.45–0.80; $p = 0.0004$), and durable overall survival (OS) benefits with more than five years of follow-up. Importantly, median OS was over twice as long for patients treated with pembrolizumab, despite a 62% cross-over rate from chemotherapy. Pembrolizumab also showed a favorable safety profile, with fewer grade 3–4 adverse events compared to standard chemotherapy regimens.^{4,5}

Despite the remarkable efficacy of pembrolizumab in patients with dMMR/MSI-H metastatic colorectal cancer, a subset of patients still experiences disease progression, suggesting that intrinsic or acquired resistance mechanisms may occur even in this highly immunogenic tumor subtype. In the phase III KEYNOTE-177 trial, approximately 29% of patients experienced primary disease progression, highlighting that not all dMMR/MSI-H CRCs respond to PD-1 blockade and that a proportion may harbor resistance to anti-PD-1 monotherapy.⁵ The CheckMate 142 study investigated combination immunotherapy with nivolumab and ipilimumab and demonstrated improved outcomes compared with PD-1 inhibition alone. In the first-line treatment cohort, only 13% of patients experienced direct progression on the combination, while in previously treated cohorts, the rate of progression was 12% with nivolumab plus ipilimumab compared to 26% with nivolumab monotherapy. These results suggest that dual

checkpoint blockade may help overcome some mechanisms of resistance seen with single-agent PD-1 therapy.⁶ However, these studies largely included immunotherapy-naïve patients, limiting their applicability to those progressing after pembrolizumab.

Currently, no established treatment guidelines exist for patients who progress following pembrolizumab or other PD-1/PD-L1 inhibitors. Ongoing clinical trials such as NIPIRESCUE (NCT05310643), and those evaluating novel bispecific antibodies like cadonilimab are investigating new strategies to overcome resistance and improve outcomes in this challenging clinical setting. Therefore, this systematic review aims to summarize current and emerging treatment options for patients with dMMR/MSI-H CRC after progression on pembrolizumab, focusing on efficacy, safety, and reported adverse events to guide future therapeutic directions.

Materials and Methods

This systematic review was registered in the PROSPERO database (registration number: [CRD420251-175508](#)) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed between September and October 2025 with no restriction on publication date.

Search Strategy

Electronic databases including PubMed, ProQuest, ScienceDirect, and ClinicalTrials.gov were systematically searched. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to microsatellite instability-high or mismatch repair-deficient colorectal cancer and treatment resistance after pembrolizumab. The main search keywords were: ("MSI-H COLORECTAL CANCER" OR "dMMR COLORECTAL CANCER") AND ("pembrolizumab") AND ("progression" OR "resistance" OR "refractory") AND ("nivolumab" OR "pembrolizumab" OR "PD-1/PDL-1 Inhibitors" OR "chemotherapy" OR "treatment options" OR "clinical trial" OR "FOLFIRI" OR "FOLFOX" OR "CAPEOX" OR "irinotecan" OR "Trifluridine/tipiracil" OR "Targeted Therapy" OR "Encorafenib" OR "Trastuzumab" OR "pertuzumab" OR "Sotorasib" OR "Larotrectinib" OR "lenvatinib"). Additional searches were performed using the following terms to ensure comprehensive coverage: ("MSI-H COLORECTAL CANCER" OR

"dMMR COLORECTAL CANCER") AND ("pembrolizumab") AND ("progression") AND ("IMMUNOTHERAPY" OR "chemotherapy" OR "treatment options" OR "clinical trial" OR "SECOND LINE").

Inclusion and Exclusion Criteria

Studies were included if they involved patients with dMMR or MSI-H CRC who had previously received pembrolizumab or another PD-1/PD-L1 inhibitor or Ipilimumab or another Anti-CTLA-4 and reported outcomes, safety, or adverse events of subsequent systemic therapies such as chemotherapy, immunotherapy, or targeted therapy. Eligible study designs included randomized controlled trials (RCTs), retrospective cohorts, case series, case reports, and conference abstracts published in English. Studies were excluded if they specifically excluded patients with prior PD-1 or PD-L1 blockade, were preclinical or non-human studies, or did not provide original data such as reviews or commentaries.

Study Selection and Data Extraction

Three independent authors performed data extraction from all the included studies into a pre-piloted data extraction form in Microsoft Excel. The following was extracted from each study:

- General study information: author and year of publication, study design, and country or study location.
- Participant characteristics: patient age, sex, comorbidities, family history or hereditary cancer syndrome, and primary tumor location.
- Disease characteristics: stage at diagnosis, sites of metastasis, and molecular profiles including *BRAF*, *KRAS/NRAS* mutations, HER2 status, PD-L1 expression, and tumor mutational burden (TMB).
- Treatment history: prior lines of therapy (e.g., FOLFOX, FOLFIRI, CAPEOX, PD-1/PDL-1 inhibitors), treatment response to previous regimens, and time to progression on PD-1/PDL-1 inhibitors.
- Subsequent therapy and outcomes: type and duration of subsequent therapy, response to subsequent therapy, time to response, progression-free survival (PFS), overall survival (OS), and disease status at last follow-up.
- Safety outcomes: occurrence, grade, and management of adverse events.

Results

A total of 504 records were retrieved across databases (PubMed: 14; ProQuest: 293; ScienceDirect: 185; ClinicalTrials.gov: 12). After removing duplicates and screening titles and abstracts, studies that did not include patients with prior PD-1/PD-L1 exposure were excluded. Ultimately, 9 studies met the eligibility criteria and were included in the final analysis. The included studies consisted of eight case reports and one retrospective cohort study, representing approximately 38 patients with dMMR/MSI-H metastatic colorectal cancer (mCRC) who progressed after PD-1/PD-L1 inhibitor therapy. (Figure 1)

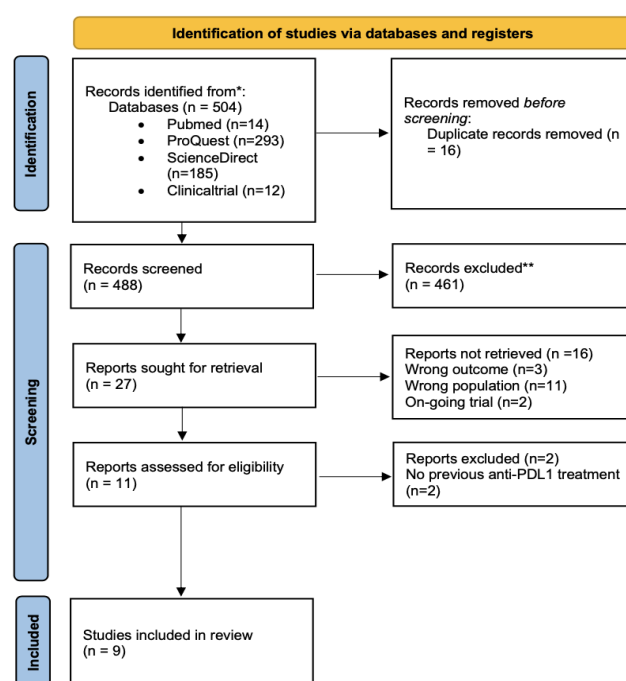


Figure 1: PRISMA flowchart outlining study search

Study Characteristics

Most of the studies included in this review were individual case reports, with one retrospective cohort study, highlighting the limited yet detailed clinical evidence available for MSI-H/dMMR colorectal cancer (CRC). The reported patient ages ranged from 39 to 84 years. The majority of cases presented with advanced-stage disease, most commonly Stage IV, and tumors were predominantly located in the right-sided or sigmoid colon, consistent with the proximal predilection typically observed in MSI-

H/dMMR CRC. Several cases demonstrated underlying hereditary cancer syndromes, particularly Lynch syndrome, or carried germline alterations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), reinforcing the established link between MMR gene dysfunction and microsatellite instability.

Across the included studies, molecular analyses revealed that BRAF V600E and RAS mutations were among the most frequently reported alterations. Additional mutations, including *PTEN*, *TP53*, *CDH1*, and *BRCA1*, were also identified, reflecting the genetic heterogeneity of this subgroup (Table 1).⁷⁻¹⁵

Synthesis of Result

The majority of included studies described patients who had previously received PD-1 or PD-L1 inhibitors, either as monotherapy or in combination with CTLA-4 blockade, typically following first-line fluoropyrimidine-based chemotherapy. The time to progression after initial immune checkpoint inhibition (ICI) varied considerably, ranging from 1.5 to 24 months. Subsequent treatment approaches included chemotherapy rechallenge (FOLFIRI, FOLFOX, or trifluridine/tipiracil-based regimens), targeted agents such as encorafenib or trastuzumab-based combinations, and dual immune checkpoint blockade in select cases.

Chemotherapy remained the most frequently adopted approach after ICI progression. In the largest cohort by Bui et al. (2021), standard regimens such as FOLFOX, FOLFIRI, or trifluridine–tipiracil, often combined with bevacizumab or cetuximab, yielded modest efficacy outcomes (ORR 13%, DCR 45%, median PFS 2.9 months, and OS 7.4 months). Nevertheless, a small proportion of patients (13%) achieved durable disease control beyond 16 months, suggesting possible residual chemosensitivity or immune-mediated enhancement of response. Similarly, Hamre et al. (2021) described temporary disease stabilization with FOLFIRI plus bevacizumab before transitioning to dual ICI, indicating that cytotoxic therapy may still provide transient benefit in this context.¹²

Rechallenge with immunotherapy represented a notable strategy in several reports. Das et al. (2020), Chow et al. (2023), and Hamre et al. (2021) observed renewed tumour control following nivolumab and ipilimumab after PD-1/PDL-1 inhibitor failure, achieving partial or durable responses lasting 9 to 20 months.^{11,12,14} In Geusens et al. (2024), pembrolizumab rechallenge after resolution of immune-related haemophagocytic lymphohistiocytosis (HLH) demonstrated feasibility and transient benefit without recurrence of severe toxicity.⁹ These findings support the rationale for ICI rechallenge or combination blockade in selected patients with manageable prior immune toxicity and preserved performance status.

Encouraging results were also reported with immunotherapy–anti-angiogenic combinations, suggesting potential synergy. Huang et al. (2025) documented a complete and sustained response exceeding three years with camrelizumab plus bevacizumab, while Maggadottir et al. (2024) reported radiological necrosis and disease stabilization with Radium-223 TCR T-cell therapy, underscoring the promise of cellular immunotherapy in post-ICI settings.^{7,10} Overall, treatment responses across studies were heterogeneous but tended to be durable in-patient receiving combination or dual-ICI regimens. Adverse events, including arthralgia, pneumonitis, and HLH, were reported but were generally manageable with corticosteroids or treatment interruption, and no fatal toxicities occurred upon rechallenge. These collective findings highlight the need for prospective evaluation of optimal sequencing and combination strategies in MSI-H/dMMR CRC following ICI progression.

Risk of Bias

All included studies demonstrated a low risk of bias. However, four case reports provided insufficient details on immune-related adverse events (irAEs), merely stating that treatment was well tolerated without clear documentation of monitoring or adverse-event grading. Table 1 and 2 summarize the overall risk of bias of all included studies. (Table 3 & Table 4)

Table 1. Patient Characteristics

First Author	Study Design	Age	Family History/ Hereditary Syndrome	Primary Tumor Location	Stage at Diagnosis	Mutations
Huang 2025 ⁷	Case Report	40	MLH-1 and PMS-2 deficient	Sigmoid colon	Stage IV	KRAS mutation
Li. 2025 ⁸	Case Report	84	MLH1 (-), PMS2 (-), MSH2 (+), and MSH6 (+)	Right side colon	Stage IV	mutations in PTEN, TP53, and CDH1
Geusens 2024 ⁹	Case Report	48	MSI-H / dMMR (loss of MSH6)	Sigmoid colon	Stage IV	RAS/BRAF wild type
Maggadottir 2024 ¹⁰	Case Report	42	Lynch Syndrome	Colon	Stage IV	N/A
Chow 2023 ¹¹	Case Report	45	MLH1(-) and PMS2 expression	Ascending colon right side	Stage IIIB	N/A
Hamre 2021 ¹²	Case Report	53	N/A	Colon	Stage IV	BRAF V600E mutation
Schuler 2021 ¹³	Case Report	N/A	MLH1 (-)& PMS2 (-)	Right sided colon	Stage IIIC	BRAF V600E mutation
Das 2020 ¹⁴	Case Report	39	MSI-H with loss of MSH2 and MSH6	Colon	Stage IV	BRCA1 mutation reported
Bui 2021 ¹⁵	Cohort Retrospective	Median 56	Lynch syndrome 39%, Sporadic 29%	colon and rectum	Stage IV	RAS-mutated = 8 (26%) BRAF-mutated = 8 (26%) RAS&BRAF = 1 (3%) RAS/BRAF wild-type = 14 (45%).

Table 2. Treatment after PD-1/PDL-1 Progression

First Author	Prior Lines of Therapy	Time to Progression After PD-1/PDL-1 Inhibitors	Subsequent treatment	Response to subsequent treatment	Results	Adverse Events
Huang 2025 ⁷	Chemotherapy (Oxaliplatin/ capecitabine), Immunotherapy (PD-1 inhibitor)	1.5 months	Immunotherapy (PD-1 Inhibitor) + Anti-VEGF antibody	6 months to PR	PFS 3 years and ongoing OS: Alive at last report	N/A
Li. 2025 ⁸	Chemotherapy (Capecitabine), Anti-VEGF antibody, immunotherapy (PD-1 Inhibitor)	Immediately	Palliative	N/A	OS: 9 months.	N/A
Geusens 2024 ⁹	Immunotherapy (PD-1 Inhibitor)	9 months	Chemotherapy (FOLFOX, FOLFIRI) + Anti-EGFR antibody	PR initially after pembrolizumab rechallenge	PFS : 9 months from pembrolizumab initiation OS: Alive at last report	Grade 4 (life-threatening immune-related event)
Maggadottir 2024 ¹⁰	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), , Immunotherapy (PD-1 inhibitor)	24 months	Radium-1 TCR T-cell therapy	10 weeks post-treatment completion (radiologic evidence of necrosis)	Stable disease for 4 months post-treatment OS: 6 months (190 days) after completion of T-cell therapy	Grade 1 Low-grade fever and chills post-infusion; mild transient cholestasis and pruritus due to tumor compression
Chow 2023 ¹¹	Chemotherapy (FOLFOX/FOLFIRI), Anti-VEGF antibody, Immunotherapy (PD-1 inhibitor)	2 months	Immunotherapy Combination (PD-1 + CTLA-4 inhibitor)	2 months	PFS: ≥20 months OS: Alive at last report	N/A
Hamre 2021 ¹²	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI) Immunotherapy (PD-1 inhibitor)	15 months	Chemotherapy (FOLFIRI) + Anti-VEGF antibody + Immunotherapy combination (PD-1 and CTLA-4 inhibitor)	Approximately 2 months (early symptomatic and biochemical improvement)	PFS: ≥18 months (ongoing) OS: ≥52 months since initial diagnosis; alive at last follow-up	Grade 1 (rash), Grade 2–3 (pneumonitis)
Schuler 2021 ¹³	Chemotherapy (Oxaliplatin/ capecitabine), Immunotherapy (PD-1 inhibitor)	After 3 doses of pembrolizumab	Chemotherapy (FOLFIRI)	After 2 courses SD	PFS: Ongoing complete remission as of last reported OS: Alive at last report	N/A
Das 2020 ¹⁴	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), , Immunotherapy (PD-1 inhibitor)	9,5 months	Immunotherapy combination (PD-1 and CTLA-4 inhibitor)	First radiologic improvement (20% reduction) at first post-combo scan (3 months after starting combo) and confirmed PR by 5 months	At least ≥5 months (time from start of combo to last reported follow-up with PR) and exact PFS not matured in report. OS: Alive at last report	Grade 2 (arthralgias on pembrolizumab).
Bui 2021 ¹⁵	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), Anti-VEGF antibody, Anti-EGFR antibody, Immunotherapy (PD1/PDL1 inhibitors)	Median duration: 5.6 months	Chemotherapy (FOLFOX, FOLFIRI 29 %, Trifluridine–tipiracil 16 %) + Anti-VEGF antibody 39 % + Anti-EGFR antibody 19 %	NR (within first 2–3 months for PD)	PFS: Median 2.9 months OS: Median 7.4 months	N/A

Table 3. Risk of Bias Assessment using Joanna Briggs Institute Critical Appraisal for Case Reports

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Risk of Bias
Huang 2025	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Li. 2025	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Geusens 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Maggadottir 2024	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Chow 2023	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Hamre 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schuler 2021	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Das 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 4. Risk of Bias Assessment using Newcastle-Ottawa Scale for Cohort Studies

Study	Selection				Comparability	Outcome			Risk of Bias
	#1	#2	#3	#4	#5	#6	#7	#8	
Bui 2021	**	N/A	**	**	*	**	**	**	Low

Discussion

The advent of immune checkpoint inhibitors (ICIs) targeting PD-1 and PD-L1 has substantially altered the therapeutic landscape of MSI-H or dMMR CRC. Despite the remarkable and durable responses observed in a subset of patients, a proportion eventually experiences disease progression, either due to primary resistance or acquired immune escape. The optimal management strategy following progression on pembrolizumab or other PD-1/PD-L1 inhibitors remains poorly defined. Several pieces of evidence will highlight the diversity of post-immunotherapy treatment approaches and their associated outcomes.

Standard Chemotherapy

Among the identified studies, the most frequently employed treatment strategies after progression on PD-1 blockade included cytotoxic chemotherapy, immune-based combination regimens, and targeted or experimental therapies. Chemotherapy may enhance the effects of prior immunotherapy by

increasing tumor antigen presentation, upregulating co-stimulatory molecules (e.g., B7-1), downregulating inhibitory checkpoints (e.g., PD-L1, B7-H4), and rendering tumor cells more susceptible to T-cell-mediated cytotoxicity. Prior exposure to anti-PD-1 therapy could therefore prime T cells and transiently improve responsiveness to subsequent chemotherapy, although this effect remains inconsistent in real-world settings.¹⁶ In a retrospective cohort by Bui et al. (2021), patients treated with standard regimens such as FOLFOX, FOLFIRI, or trifluridine–tipiracil achieved a disease control rate (DCR) of 45%, with median progression-free survival (PFS) and overall survival (OS) of 2.9 and 7.4 months, respectively. Similarly, another study reported a DCR of 58%, median PFS of 3.8 months, and OS of 8 months following chemotherapy post-ICI exposure.¹⁷ Collectively, these findings suggest that while chemotherapy retains modest antitumor activity after immune-therapy failure, its clinical benefits are generally limited and short-lived in this molecular setting.

Rechallenge of Immunotherapy

The findings in this study suggest that dual immune checkpoint blockade may reinduce antitumor immunity in selected patients. Several case reports and retrospective analyses have highlighted the potential benefit of combining or sequencing immunotherapeutic agents after resistance to ICI. Rechallenge strategies may involve single-agent or combination approaches, though no dedicated clinical trials have yet evaluated this in CRC. Evidence from other malignancies, such as melanoma and non-small cell lung cancer (NSCLC), shows mixed outcomes with immunotherapy rechallenge. Reuse of the same anti-CTLA-4 or anti-PD-1/PD-L1 agents yields modest efficacy (ORR 11–53%, DCR 47–83%), while switching between PD-1/PD-L1 inhibitors produces inconsistent results, likely due to small cohorts. Cross-class rechallenge appears more favorable, as patients previously treated with anti-CTLA-4 therapy achieved higher response rates (22–36%) to subsequent anti-PD-1/PD-L1 therapy than the reverse sequence ($\leq 22\%$), suggesting that overcoming tumor microenvironmental immunosuppression is key. Combination rechallenge using anti-PD-1 plus anti-CTLA-4 has shown improved responses and survival in some settings, though results remain heterogeneous.¹⁸ Another study found that single-agent rechallenge achieved comparable ORR and DCR to initial therapy but yielded longer PFS and OS than in patients who permanently discontinued ICIs across NSCLC, melanoma, and renal cell carcinoma.¹⁹

Several case reports further support these findings. Re-challenge with dual checkpoint blockade (e.g., nivolumab plus ipilimumab) or switching between anti-PD-1 agents was associated with disease stabilization or partial responses in selected cases.¹⁴ Another case report reported in which the combination of camrelizumab and bevacizumab resulted in a complete and durable response exceeding three years.⁷ These outcomes suggest that modulation of the tumor microenvironment through anti-angiogenic agents may restore or enhance immune responsiveness in dMMR/MSI-H tumors previously resistant to PD-1 blockade.

Similarly, the case described by Hamre et al. (2021) demonstrated that subsequent chemotherapy with FOLFIRI and bevacizumab achieved prolonged disease stability exceeding 18 months, potentially reflecting immune priming or “chemosensitization” induced by

prior immunotherapy exposure. Collectively, these observations indicate that the integration of ICIs with agents targeting angiogenesis or cytotoxic mechanisms warrants further investigation in this setting.

Targeted therapy

Targeted therapies used in CRC include anti-VEGF agents, anti-EGFR agent, BRAF and MEK pathway inhibitor, and Her2-targeted therapy. This review showed a combination of immunotherapy with anti-angiogenic therapy reported a complete and sustained response exceeding three years with camrelizumab plus bevacizumab. Anti-VEGF agents help restore normal tumor vasculature, improve oxygen delivery, facilitate immune-cell entry, and convert the immunosuppressive tumor milieu into one more favorable for immunotherapy.²⁰ Studies that investigate this combination have been shown to be favorable in other types of cancer, including lung cancer, hepatocellular carcinoma, gastric cancer, and cervical cancer.²¹

EGFR-TKIs indirectly strengthen anti-tumor immune responses and counteract immunosuppression in the tumor microenvironment, creating a rationale for combining targeted agents with immunotherapies. However, the combination of anti-EGFR and immunotherapy in CRC is yet to be explored. This combination has also been explored in NSCLC, which showed favorable results, though associated with serious adverse events and lack of definitive studies.²²

BRAF and MEK inhibitors exert potent antitumor effects by suppressing tumor cell proliferation and inducing apoptosis while enhancing tumor immunogenicity, providing a biological rationale for their combination with immunotherapy. However, no clinical evidence currently supports this strategy in colorectal cancer.²³ Preliminary studies in melanoma suggest that combining BRAF/MEK inhibitors with ICIs may yield durable responses in anti-PD-1–refractory cases, although outcomes appear comparable to those achieved with dual ICI therapy as subsequent therapy.^{24,25}

Combining HER2-targeted therapy with PD-1/PD-L1 inhibitors leverages HER2 blockade–induced immune activation and prevents PD-L1–mediated adaptive resistance, resulting in a more sustained and potent anti-tumor immune response.²⁶ This combination has been shown in the KEYNOTE-811 study, which showed improved ORR in gastric cancer.²⁷

Cellular Immunotherapy

Beyond conventional therapies, adoptive cellular immunotherapy has emerged as a promising modality for patients with ICI-refractory MSI-H/dMMR CRC. Maggadottir et al. (2024) reported temporary disease stabilization following treatment with TCR-engineered T-cell therapy, highlighting the potential of personalized T-cell-based strategies to overcome immune escape. Although such therapies remain investigational, they underscore the growing emphasis on individualized and mechanistically guided immunotherapeutic interventions for this subset.

Beyond conventional therapies, adoptive cellular immunotherapy has emerged as a promising modality for patients with ICI-refractory MSI-H/dMMR colorectal cancer. Genetically engineered T-cell receptor (TCR)-T therapies leverage patient-derived T cells re-programmed to recognize neo-antigen peptides presented on MHC, offering the potential to overcome immune-escape mechanisms inherent in these high-mutation-burden tumours. Early clinical experience in MSI-H CRC demonstrates feasibility and safety of TCR-T approaches, albeit with limited durability of response. Reviews of engineered T cells in colorectal cancer highlight the mechanistic rationale and key challenges (e.g., antigen heterogeneity, tumour microenvironment suppression) of translating this modality into meaningful outcomes in solid tumours.²⁸

Although still investigational, TCR-T therapy underscores the growing emphasis on individualized and mechanistically guided immunotherapeutic interventions for this subset of CRC. Continued development of neoantigen-specific TCRs, improved T-cell persistence, and combination strategies to optimize the tumour environment may help unlock its full potential in the post-PD-1/PD-L1 inhibitor setting.

Clinical and Safety Outcomes

Clinical outcomes following post-ICI treatment were heterogeneous across studies. Objective response rates ranged from 13% in the larger retrospective series to complete and durable responses in isolated cases. PFS varied widely, from approximately three months to several years, reflecting the diversity of interventions and patient populations. Notably, durable responses were more frequently observed in those receiving immune-based or anti-angiogenic combinations rather than cytotoxic chemotherapy alone.

Treatment-related adverse events were generally mild to moderate (Grade 1–2) and manageable with supportive measures and corticosteroids. Immune-related toxicities, including rash, arthralgia, and pneumonitis, were infrequent and did not preclude continued therapy in most cases, supporting the feasibility of combination or sequential approaches following prior ICI exposure.

Clinical Implication

The limited and variable activity of chemotherapy following PD-1 blockade raises the possibility that the immunologic landscape of dMMR/MSI-H CRC changes after ICI resistance. Mechanisms such as antigenic loss, mutations in interferon signaling pathways, or T-cell exclusion may contribute to therapeutic failure. Consequently, strategies aiming to reverse immune resistance through reactivation of exhausted T cells, modulation of the tumor vasculature, or recruitment of innate immunity represent a rational next step in the evolution of treatment paradigms for this population.

Limitations

The current body of evidence remains constrained by small sample sizes, retrospective designs, and the predominance of anecdotal reports. The heterogeneity in treatment regimens and reporting standards further limits the comparability of outcomes. Nevertheless, the collective findings emphasize that chemotherapy retains modest activity, while immunotherapy-based combinations and emerging cellular approaches hold promise for achieving durable control after PD-1 inhibitor failure.

Future prospective studies should aim to stratify patients by molecular mechanisms of resistance, incorporate translational endpoints, and evaluate rational combinations of immunotherapy, targeted agents, and cytotoxic chemotherapy. Such efforts will be essential to optimize post-ICI therapeutic sequencing and to extend survival for patients with dMMR/MSI-H metastatic CRC.

Conclusion

This systematic review highlights the paucity of evidence and absence of standardized treatment strategies for patients with MSI-H/dMMR colorectal cancer who progress following PD-1/PD-L1 inhibitor therapy. Across available studies, chemotherapy provides only modest and short-lived benefits,

whereas combination strategies integrating checkpoint blockade, anti-angiogenic agents, or targeted therapies yield more durable responses in selected cases. Rechallenge with immunotherapy particularly dual checkpoint inhibition appears feasible and may restore anti-tumour activity in a subset of patients, although robust predictive markers remain undefined. Emerging evidence also supports the potential of adoptive cellular immunotherapies, such as TCR-engineered T-cell therapy, as novel approaches to overcome immune resistance in this setting. However, their clinical application remains experimental and confined to early-phase studies. Collectively, these findings underscore the need for prospective, biomarker-driven trials to elucidate mechanisms of ICI resistance and to establish optimized therapeutic sequencing following PD-1/PD-L1 inhibitor failure in MSI-H/dMMR colorectal cancer.

Author Contributions

MT, ALS, FP contributed to the study design, data collection, data extraction, and analysis. MT, ALS, FP wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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