TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

REVIEW

Colorectal Cancers and Microsatellite Instability

Sahra ESMKHANI,[1,2] Mustafa EMREM,[2] Ali ŞAHİN,[3] Hüseyn BABAYEV,[4] Can ZEYNELOĞLU,[4] Sena ARDIÇLI,[4] Hilal YAZICI,[2] Hülya YAZICI[5]

[1]Division of Cancer Genetics, Department of Basic Oncology, İstanbul University, Institute of Health Sciences, İstanbul-*Türkiye*
[2]TÜBİTAK Marmara Research Center, Climate Change and Life Sciences, Biotechnology Research Group, Kocaeli-*Türkiye*
[3]Department of Emergency Service, Dr. Vefa Tanır Ilgın City Hospital, Konya-*Türkiye*
[4]Swiss Institute of Allergy and Asthma Research, University of Zurich, Davos-*Switzerland*
[5]Department of Medical Biology and Genetics, İstanbul Health and Technology University Faculty of Medicine, İstanbul-*Türkiye*

SUMMARY

Colorectal cancer (CRC) is a multifactorial disease arising from the complex interplay between genetic predisposition and environmental influences. Despite its widespread incidence globally, CRC demonstrates favorable prognostic outcomes when detected at an early stage. Microsatellite instability (MSI) is a common molecular abnormality associated with colorectal tumorigenesis. This review provides a comprehensive analysis of the molecular mechanisms, clinical implications, therapeutic approaches, and immune system interactions in MSI-associated CRC (MSI-CRC). Molecular changes include DNA slippage, dysfunction in the DNA mismatch repair (dMMR) system, and genetic/epigenetic factors that contribute to MSI. Clinically, MSI-CRC is characterized by distinct phenotypic features, including associations with Lynch syndrome, specific diagnostic methodologies, and prognostic relevance. The therapeutic landscape highlights the promising efficacy of immunotherapies and targeted treatments, particularly in dMMR–MSI-H-CRC. Immune dynamics within the tumor microenvironment (TME) reveal patterns of immune infiltration, immune evasion strategies, and opportunities to enhance the effectiveness of immunotherapy. Understanding these interrelated aspects is critical for developing tailored therapeutic strategies and improving patient outcomes in MSI-CRC.

Keywords: Biomarkers; colon carcinoma; instability; microsatellite; stability.

INTRODUCTION

Colorectal cancer (CRC) presents a significant global public health burden, ranking as the third most common cancer and the second leading cause of cancer-related mortality.[1] The complexity of CRC stems from its diverse molecular pathways and clinical heterogeneity. Among the key factors driving CRC pathogenesis, microsatellite instability (MSI) has emerged as a crucial biomarker, offering profound insights into tumorigenesis and therapeutic strategies. MSI results from defects in the DNA mismatch repair (MMR) system and disrupts the fidelity of DNA replication, leading to widespread genomic instability and the accumulation of mutations across the genome, resulting in a mutator phenotype. These mutations can target critical cancer-related genes, leading to the activation of oncogenic pathways and promoting tumorigenesis.[2] Moreover, MSI is a hallmark of approximately 80% of Lynch syndrome cases and is also observed in 20% of sporadic

Received: November 04, 2024
Accepted: November 26, 2024
Online: December 17, 2024

Accessible online at:
www.onkder.org

Dr. Hülya YAZICI
İstanbul Sağlık ve Teknoloji Üniversitesi Tıp Fakültesi,
Tıbbi Biyoloji ve Genetik Anabilim Dalı,
İstanbul-Türkiye
E-mail: hulyayazici67@gmail.com

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

CRC cases, highlighting its importance in both hereditary and sporadic forms of the disease. MSI is further prevalent in around 20% of early-stage sporadic CRC cases (stages I and II) and 12% in stage III disease. Conversely, its incidence is lower in metastatic CRC settings, where it is found in only 4–5% of cases.[3,4]

In 1993, Aaltonen et al.[5] first described MSI in Lynch syndrome, utilizing an arbitrarily primed PCR (AP-PCR) approach. Subsequent studies have highlighted MSI's prevalence in CRC, particularly in endometrial, gastric, breast, prostate, and bladder cancers. With the FDA's approval of immune checkpoint inhibitors for dMMR–MSI-H advanced cancers, MSI has gained attention as a key molecular signature, driving interest in its diagnostic and therapeutic potential. Clinically, MSI is associated with a favorable prognosis in CRC, as patients with MSI-high tumors generally experience better outcomes compared to those with microsatellite-stable (MSS) tumors.[6] MSI tumors tend to be less responsive to conventional chemotherapy but demonstrate heightened sensitivity to immune checkpoint inhibitors targeting PD-1, offering a promising therapeutic avenue.[7]

Looking ahead, the incorporation of MSI testing into clinical practice requires rigorous validation, including assessments of analytical validity, clinical validity, and clinical utility.[8] Current methods for detecting MSI, such as immunohistochemistry (IHC) and polymerase chain reaction (PCR), are well-established, while emerging techniques like next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) analysis offer non-invasive alternatives with potential clinical relevance.[9,10]

Further research is necessary to fully elucidate the clinical implications of MSI in CRC, particularly regarding its role in Lynch syndrome screening, prognostic stratification, and therapeutic decision-making. Understanding the complex interplay between MSI and CRC biology may pave the way for more personalized treatment approaches, particularly in leveraging immune interactions within the tumor microenvironment (TME) for therapeutic benefit.

Molecular Mechanisms of MSI in CRC

DNA Slippage and Mismatch Repair (MMR) System Dysfunction

The integrity of genomic stability hinges upon the intricate machinery of DNA mismatch repair (MMR), a system designed to rectify errors that arise during DNA replication.[11] MMR operates through a meticulous process, represented in Figure 1, involving the detection and correction of base mismatches and small loops, thereby ensuring replication fidelity and preventing the accumulation of mutations.[12] Crucial to this process are key components of the MMR pathway, notably MutS and MutL complexes. In human cells, MutSα and MutSβ complexes, comprising various combinations of MSH proteins, detect mismatches and short loops, while MutLα, MutLβ, and MutLγ, formed by different pairs of MLH proteins, orchestrate the subsequent repair process.[13] However, when the MMR system malfunctions, the consequences can be dire, leading to genomic instability and predisposition to cancer. Deficiencies in essential MMR proteins, particularly MSH2 and MLH1, result in severe phenotypes, underscoring the indispensability of these factors in maintaining genomic integrity.[14]

Genetic and Epigenetic Factors Contributing to MSI

The three major molecular pathways of colorectal cancer (CRC) are the conventional chromosomal instability (CIN) pathway, the serrated pathway, and the microsatellite instability (MSI) pathway (Table 1). The CIN pathway is initiated by APC mutation, followed by mutations in *KRAS, PIK3CA*, and *SMAD4*, and loss of heterozygosity of *TP53*, commonly associated with low CpG island methylation, high CIN, and microsatellite stability.[15] The serrated pathway can be subdivided into CIMP-low-MSS tumors with KRAS mutations, *BRAF* mutant CIMP-high-MSS tumors, and BRAF mutant CIMP-high-MSI tumors, often involving the silencing of *MGMT, CDKN2A*, or *MLH1*. Lastly, the MSI pathway results from the dysfunction of DNA mismatch repair genes encoding MLH or MSH proteins, leading to high levels of microsatellite instability.[16]

Genetic factors play a significant role in the development of MSI in colorectal cancer. Lynch syndrome (OMIM#120435), which is caused by mono-allelic germline MMR pathogenic variants, stemming from mutations in MMR genes such as *MLH1, MSH2, MSH6,* and *PMS2*, stands as a prominent genetic cause of MSI.[17] Specifically, inactivation of the *MLH1* or *PMS2* alleles is the most frequent cause of Lynch syndrome and is associated with approximately 80% of cases.[17] Mutations in MMR genes associated with Lynch syndrome frequently precipitate the onset of cancer at earlier ages, typically between 40 and 60 years. These mutations are implicated in a diverse spectrum of cancers, predominantly found in the gastrointestinal and genitourinary tracts, most frequently colorectal cancer and endometrial cancer.[3]

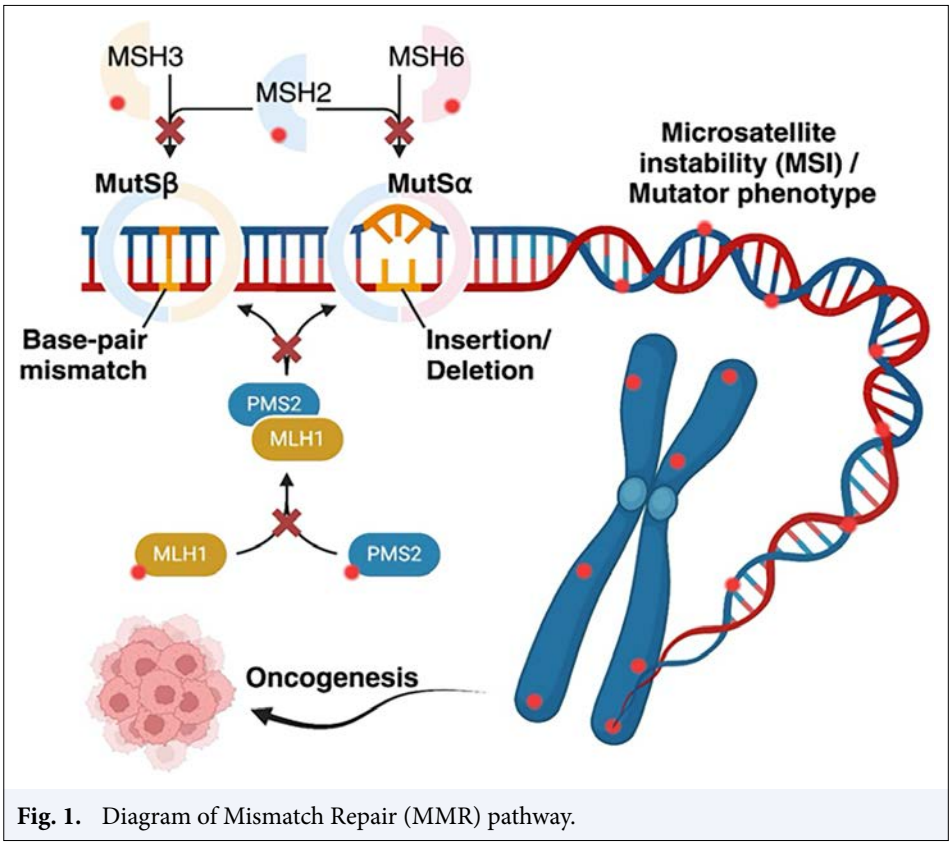

Fig. 1. Diagram of Mismatch Repair (MMR) pathway.

On the other hand, constitutional mismatch repair deficiency (CMMRD), a rare condition compared to Lynch syndrome, is caused by bi-allelic germline pathogenic variants in MMR genes.[18] It has an estimated birth incidence of one in a million. Typically, CMMRD manifests with hematological, brain, and intestinal cancers during childhood or adolescence, with a median age of onset under 10 years.[19] MSI-H tumors frequently harbor mutations in key CRC-related genes like *APC, KRAS*, and *TP53*, signifying a convergence of genetic alterations in these malignancies.[20] Additionally, RNF43 mutations, a negative feedback regulator of the Wnt/β-catenin pathway, have been observed in CRCs with a high prevalence of MSI-H, suggesting their potential involvement in MSI development.[21]

On the other hand, epigenetic factors also play a significant role in MSI, where the CpG island methylator phenotype (CIMP) is characterized by hypermethylation in tumor suppressor gene promoters, leading to functional loss.[22] A recently identified subgroup of patients with MSI tumors is referred to as having "Lynch-like syndrome" (LLS). These patients were diagnosed with cancers related to Lynch syndrome, with their tumors showing an MSI phenotype and/or loss of MMR gene expression. Cases with loss of MLH1 expression were confirmed to lack MLH1 promoter hypermethyl-

Table 1 The three major molecular pathways of colorectal cancer

Pathway	Key Mutations/Alterations	Features	Notes
CIN pathway	*APC, KRAS, PIK3CA, SMAD4, TP53*	High chromosomal instability, low CpG island methylation	Observed in 65%–70% of sporadic CRCs, develops slowly over decades
Serrated pathway	*BRAF, KRAS, MGMT, CDKN2A, MLH1*	Subdivided into CIMP-low-MSS, CIMP-high-MSS and CIMP-high-MSI	Involves epigenetic silencing, prevalent in 15% of CRCs
MSI pathway	*MLH1, MSH2, MSH6, PMS2*	High microsatellite instability hypermutation	Common in Lynch syndrome, MSI-H tumors often hypermutated

CIN: Conventional chromosomal instability; CRC: Colorectal cancer; CIMP: Island methylator phenotype; MSS: Microsatellite-stable; MSI: Microsatellite instability

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

ation. However, no germline mutations in MMR genes were detected. Compared to LS patients, individuals with LLS exhibit a lower standardized incidence ratio of LS-related tumors. The mechanisms behind LLS remain unclear, but it is known that acquired MMR deficiency accounts for a significant portion of these cases.[23,24]

CIMP-positive CRCs, often arising via a serrated pathway, exhibit frequent association with MSI-H tumors, emphasizing the interplay between genetic and epigenetic alterations in CRC development.[25]

Detecting MMR Dysfunction: Microsatellite Instability Analysis

In clinical settings, the diagnosis of dysfunctional MMR is often achieved by assessing microsatellite instability (MSI), a hallmark of MMR failure.[26] MSI is characterized by alterations in the lengths of microsatellite loci, serving as an indirect indicator of MMR deficiency. Typically, this is detected through PCR-based assays targeting specific microsatellite repeats.[27] The Bethesda panel, comprising mononucleotide and dinucleotide repeats, is commonly employed for MSI assessment, with instability at multiple loci indicative of MSI-high status.[12] Currently, the standard diagnostic methods for MSI and MMR deficiency include pentaplex PCR-based methods, incorporating five mononucleotide and quasi-monomorphic microsatellite regions (such as *BAT-25* and *BAT-26*), and MMR immunohistochemistry on tumor tissue samples.[27] Advances in alternative systems, such as next-generation sequencing (NGS) and real-time PCR-based methods, offer improved accuracy and efficiency for MSI detection.[28]

Notably, the development of liquid biopsy techniques allows for the determination of MSI from cell-free DNA (cfDNA) in plasma, facilitating non-invasive testing and real-time monitoring of disease progression. These assays are often developed based on whole-genome sequencing (WGS) or whole-exome sequencing (WES) data from tumor tissue samples, which can be refined to large and customized gene panels.[27] A well-validated example is the FDA-authorized Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) gene panel, developed at the Memorial Sloan Kettering Cancer Center. Initially designed as a hybrid capture-based NGS assay for targeted deep sequencing of key cancer genes in formalin-fixed paraffin-embedded (FFPE) tumor specimens, this assay was used to study DNA from over 10,000 tumor specimens and patient-matched germline DNA from peripheral blood, identifying clinically relevant mutations and mutation signatures.[29] The panel has since expanded to interrogate 468 cancer-related genes, analyzing tumor-derived and matched germline DNA samples in a CLIA-certified laboratory. It is FDA-approved as a tumor profiling test to provide information on somatic alterations and MSI for use by qualified healthcare professionals.[30]

One significant advantage of these newer techniques is their ability to analyze multiple microsatellite loci simultaneously, enhancing the sensitivity and specificity of MSI detection. For instance, the Promega MSI analysis system employs a panel of five mononucleotide markers and two pentanucleotide markers to detect MSI with high precision. Additionally, the Idylla MSI assay, a fully automated PCR-based system, delivers rapid and reliable results with minimal hands-on time, providing automated interpretation of MSI status.[31] These advancements in MSI analysis not only facilitate the diagnosis of MMR dysfunction but also offer insights into the mutational landscape of tumors, guiding therapeutic strategies and prognostic assessments. The importance of MSI testing has increased in personalized medicine, helping identify patients who might benefit from specific treatments like immune checkpoint inhibitors and informing decisions about adjuvant chemotherapy.

Clinical Implications of MSI in CRC

Clinical Features and Prognosis of MSI-CRC

MSI-CRCs exhibit distinct clinical features and prognosis compared to microsatellite stable (MSS) tumors. Patients with MSI-CRCs tend to belong to specific demographic groups, such as females and the elderly, and are commonly located in the proximal colon.[32] Previous studies indicated that colorectal cancer (CRC) with microsatellite instability (MSI) in elderly patients (aged 60–70 years and over 87 years) is often linked to MLH1 inactivation and MLH1 promoter methylation.[33] In contrast, tumors in younger patients (under 45 years) are typically associated with MSH2 inactivation.[34] This study revealed that patients aged 50 years and older showed a lower propensity for having MSH2 and/or MSH6-MSI.[35] Notably, CRC associated with MSH2-MSI commonly occurs at a younger age.[36] MSI-CRCs are also associated with mucinous histology and poor differentiation (Table 2).[37]

Although MSI-CRCs typically exhibit aggressive histopathological features, they often show a lower response to 5-fluorouracil (5-FU) chemotherapy compared to MSS tumors,[6] which has led to the exploration of other therapeutic avenues for these patients. Later it was discovered that MSI-H CRCs are notably more responsive to immune checkpoint inhibitors, such as pembrolizumab or other PD-1 inhibitors, compared to their MSS counterparts. Despite their aggressive his-

Table 2 Clinical features and prognosis of MSI-CRC

Feature	MSI-CRC	MSS-CRC
Demographic groups	Females, Elderly	Varies
Tumor location	Proximal colon	Distal colon, Rectum
Histology	Mucinous, Poor differentiation	Non-mucinous, Well-differentiated
Response to 5-FU treatment	Favorable	Variable
Response to immunotherapy	Enhanced sensitivity	Limited response
Prognosis	Better overall prognosis	Worse prognosis (advanced stages)

MSI: Microsatellite instability; CRC: Colorectal cancer; MSS: Microsatellite-stable

topathological features, MSI-CRCs have been linked to better overall prognosis, particularly in early-stage disease.[38] This improved prognosis is attributed to the enhanced immune response against the high number of neoantigens present in MSI-H tumors, leading to an immunogenic tumor microenvironment.[39] Importantly, MSI status serves as a predictive biomarker for response to immunotherapy, which has resulted in FDA approval of pembrolizumab and nivolumab for treatments targeting MSI-H and MMR-deficient CRCs.[40]

Immune Interactions in the Tumor Microenvironment

Role of Immune Infiltration in MSI-CRC

In colorectal cancer, the tumor microenvironment (TME) orchestrates disease progression and therapeutic responses. Particularly in MSI-H CRCs, the TME is characterized by dense immune infiltration owing to the high mutational burden resulting from somatic hypermethylation of MMR genes.[41] This leads to the generation of numerous immunogenic neopeptide antigens, attracting various immune cell populations, including CD8+ T cells, B cells, and macrophages. This influx creates an immunologically active milieu that influences disease behavior and therapeutic outcomes.[42] Recent studies have uncovered significant heterogeneity within MSI-H CRCs. While MSI-H tumors generally exhibit better overall survival compared to MSS CRCs, subgroups within MSI-H CRCs demonstrate distinct immune profiles and clinical behaviors.[43]

The molecular classifications primarily designed to predict colorectal cancer prognosis and recurrence risk have been proposed. The most well-known of these is the "consensus molecular subtype (CMS) classification," which has enhanced the understanding of the genomic and epigenomic landscapes of colorectal cancer, aiding in better patient management. This classification divides colorectal cancer into four CMS categories (CMS1–4), each with different prognoses. This manuscript places the CMS classification in various contexts, exploring its relationships with precursor lesions, tumor immunophenotype, and gut microbiota. It also examines the CMS classification's role in predicting prognosis and/or response to pharmacological treatments, marking a crucial step toward precision medicine.[44] Some MSI-H tumors display heightened T-cell activity, associated with improved prognosis (classified as CMS1 subtype), while others exhibit diminished T-cell activity and poorer prognosis (classified as MSI-H in CMS3 and CMS4 subtypes). The differential presence of specific immune cell subpopulations, such as memory $CD4^+/CD8^+$ cells, γδ T cells, and regulatory T cells, contributes to this heterogeneity, influencing overall immune dynamics and disease outcomes.[45,46]

Mechanisms of Immune Evasion and Checkpoint Inhibitor Resistance

Despite robust immune infiltration in MSI-H CRCs, certain tumors develop sophisticated mechanisms to evade immune surveillance and resist checkpoint inhibitor therapy. Common strategies involve alterations in the human leukocyte antigen (HLA) complex and antigen-processing machinery (APM), critical for effective antigen presentation and T-cell recognition.[47] Mutations in genes encoding components of the HLA complex and APM machinery, such as beta-2-microglobulin (*B2M*) and HSPA5, are prevalent in MSI-H CRCs, impairing tumor antigen presentation, hampering T-cell recognition, and enabling tumors to evade immune detection and elimination.[48] Moreover, emerging evidence implicates the gut microbiota, particularly Fusobacterium nucleatum, in CRC pathogenesis and treatment response. F. nucleatum, frequently associated

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

with MSI-H CRCs, exerts profound effects on the TME and immune response. It can induce pro-inflammatory environments, foster immunosuppression, and inhibit T-cell activity, thereby promoting tumor progression and conferring resistance to immunotherapy.[49,50]

Therapeutic Landscape of MSI-CRC

Immunotherapy and Targeted Therapies for MSI-H CRC

Immunotherapy has emerged as a promising approach for the treatment of mismatch repair-deficient MSI-H colorectal cancer (CRC). Initial studies exploring immune checkpoint inhibitors (ICIs) in CRC demonstrated limited clinical activity in unselected patients. However, subsequent investigations focusing on dMMR–MSI-H CRC revealed remarkable responses to PD-1 inhibitors. The CheckMate 142 trial investigated nivolumab, a PD-1 inhibitor, in patients with dMMR–MSI-H metastatic CRC. The study reported an objective response rate of 31% and a disease control rate of 69%, with promising progression-free survival (PFS) and overall survival outcomes.[51] In the phase II CheckMate 142 study, nivolumab plus low-dose ipilimumab as first-line therapy for patients with dMMR–MSI-H metastatic colorectal cancer (mCRC) demonstrated a 69% objective response rate and an 84% disease control rate, with a 13% complete response rate. The treatment showed robust and durable clinical benefit, with a median progression-free survival and median overall survival not reached at the median follow-up of 29.0 months. Additionally, 74% of responders had ongoing responses at data cut-off, and the treatment was well tolerated, with grade 3–4 treatment-related adverse events occurring in 22% of patients.[52] Based on these promising results, further randomized studies are warranted.

Similarly, in the phase III KEYNOTE 177 trial, pembrolizumab, an anti-PD-1 antibody, demonstrated superiority over chemotherapy in first-line treatment of dMMR–MSI-H mCRC, with significantly improved PFS and OS. The trial highlighted a 45.1% objective response rate in the pembrolizumab arm compared to 33.1% in the chemotherapy arm, leading to its approval as the new standard of care.[53]

Ongoing studies are evaluating PD-1 or PD-L1 inhibition in various settings, including first-line therapy, with the aim of further improving outcomes for patients with dMMR–MSI-H CRC. In another study, which aimed to evaluate the safety and efficacy of neoadjuvant PD-1 blockade immunotherapy with sintilimab, another PD-1 inhibitor, for locally advanced dMMR–MSI-H CRC, researchers focused on patients treated at the Sixth Affiliated Hospital of Sun Yat-sen University from June 2020 to June 2022, aiming to provide insights into the clinical and pathological responses to this treatment. By retrospectively analyzing the clinical data of 11 patients who received six injections of sintilimab before radical laparoscopic resection, the study sought to determine the pathological complete response (pCR) rates and the occurrence of immunotherapy-related adverse events. Their findings suggest that single-agent neoadjuvant PD-1 antibody immunotherapy could be a promising treatment approach for locally advanced dMMR–MSI-H CRC, warranting further validation in phase II and III clinical trials.[54]

In contrast, patients with proficient mismatch repair/microsatellite stable (pMMR–MSI-L) CRC have not benefited significantly from immunotherapy alone. Limited responses were observed in patients with pMMR–MSI-L CRC treated with immune checkpoint inhibitors.[55]

The study investigated in 2023 showed the efficacy of combining PD-1, BRAF, and MEK inhibitors in treating BRAFV600E-CRC, given the limited success of BRAF inhibitor combinations alone. Conducted as a single-arm phase II trial, 37 patients received the PD-1 inhibitor spartalizumab and kinase inhibitors designed for BRAF V600E mutations, dabrafenib and trametinib. The primary endpoint, overall response rate (ORR), was met with a 24.3% response rate overall and 25% in MSS patients. Notably, MSI patients exhibited better and more durable responses, with approximately one-third showing responses lasting over a year. These results suggest that BRAF pathway inhibition may enhance the immune response in BRAFV600E CRC, particularly in MSI patients,[56] although further research is needed to optimize treatment strategies for this subtype.

FDA-Approved Treatments for MSI-H/MMR CRC Patients

Recognizing the immunological landscape within dMMR–MSI-H colorectal cancer tumors is crucial for therapeutic success. These tumors are characterized by elevated immune cell infiltration and upregulated immune checkpoints such as PD-1, PD-L1, and CTLA4.[55] This understanding has paved the way for the development and FDA approval of pioneering immunotherapy agents like pembrolizumab and nivolumab, significantly reshaping treatment paradigms and providing new hope for patients who were previously difficult to treat. Key trials such as KEYNOTE-177 and CheckMate-142 have demonstrated remarkable improvements in PFS and ORR with these agents, both as monotherapy and in combination regimens.[51–53] Further-

more, neoadjuvant immunotherapy approaches show promise for curative interventions in select cases, while ongoing research into tumor-specific antigens, DNA polymerase mutations (POLD1/POLE), and immune evasion mechanisms seeks to refine treatment selection and overcome resistance.[40,57–59] Biomarkers like tumor mutational burden (TMB), immunoscore, and PD-L1 expression are under scrutiny to tailor treatment decisions and predict response to immunotherapy. The identification of predictive markers and elucidation of underlying mechanisms are vital for optimizing patient outcomes in dMMR–MSI-H CRC.

Challenges and Future Directions in MSI-Targeted Therapy

While the advent of FDA-approved treatments has propelled MSI-targeted therapy into the spotlight, significant challenges persist, necessitating a multifaceted approach to optimize patient outcomes. One pressing concern is the heterogeneity within dMMR–MSI-H CRC, underscored by variations in treatment response and resistance mechanisms.[60] Despite promising clinical trial results, identifying robust predictive biomarkers remains elusive. BRAF status and PD-L1 expression, once thought to hold predictive value, have shown inconsistent correlations, highlighting the complex interplay of molecular factors influencing treatment response.[61,62] Additionally, the clinical history of Lynch syndrome has emerged as a potential modifier of treatment outcomes, emphasizing the need for comprehensive patient stratification strategies.[63]

The management of immune-related adverse events (IRAEs) poses another challenge, particularly in patients with pre-existing autoimmune disorders. While immunotherapy offers unprecedented therapeutic potential, the risk of exacerbating autoimmune conditions necessitates vigilant monitoring and a multidisciplinary approach to IRAE management.[64] Looking ahead, elucidating alternative actionable genes and exploring combination therapies represent promising avenues for enhancing treatment efficacy and overcoming resistance. Molecular profiling, coupled with advances in gut microbiome modulation, holds potential for refining patient stratification and optimizing treatment selection in dMMR–MSI-H CRC.[65] Moreover, neoadjuvant immunotherapy strategies offer the possibility of curative interventions in select cases, highlighting the evolving landscape of MSI-targeted therapy beyond conventional approaches.[40] Harnessing the synergy between immunotherapy and other treatment modalities, such as targeted therapies and chemotherapy, presents an opportunity for personalized treatment regimens tailored to individual patient profiles. As research continues to unravel the intricacies of MSI-targeted therapy, collaboration across disciplines and innovative trial designs will be crucial for translating scientific insights into clinical practice.

Potential Strategies to Enhance Immunotherapy Efficacy in MSI-CRC

To augment the efficacy of immunotherapy in MSI-H CRCs, several innovative strategies have been proposed:

- Targeting Immune Evasion Mechanisms: Therapeutic interventions aimed at restoring HLA expression or enhancing antigen presentation hold promise for improving T-cell recognition and response to immunotherapy.[66]
- Modulating the Gut Microbiota: Interventions targeting specific microbial populations, such as F. nucleatum, have the potential to enhance treatment response by reshaping the TME and fostering antitumor immune responses.[67]
- Combination Therapies: Combinations of checkpoint inhibitors with agents targeting alternate immune checkpoints or pathways involved in immune evasion could synergistically overcome resistance mechanisms and bolster anti-tumor immunity.[68]
- Patient Stratification: Precision medicine approaches, including subtyping CRCs based on their genetic characteristics and immune landscape, may enable the identification of patients most likely to benefit from immunotherapy, guiding personalized treatment strategies for optimal outcomes.[69]

Recent Insights into Genetic Factors

Werner Syndrome Helicase as a Synthetic Lethal Target in MSI-CRC

Recent studies have broadened our knowledge of the genetic factors involved in the development of microsatellite instability (MSI) in CRC, in addition to well-established mechanisms such as DNA slippage and dysfunction in the MMR system. Among these factors, the WRN gene, encoding the Werner syndrome ATP-dependent helicase, has emerged as a significant player.[70] *WRN*, a multifunctional enzyme with helicase and exonuclease activities, plays essential roles in multiple cellular processes vital for genome stability, such as DNA replication, transcription, DNA repair, and telomere maintenance. Depletion of WRN leads to cell cycle arrest, DNA damage, mitotic anomalies, chromosome fragmentation, and apoptosis. The frequent loss of heterozygosity at the WRN loci on chromosome

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

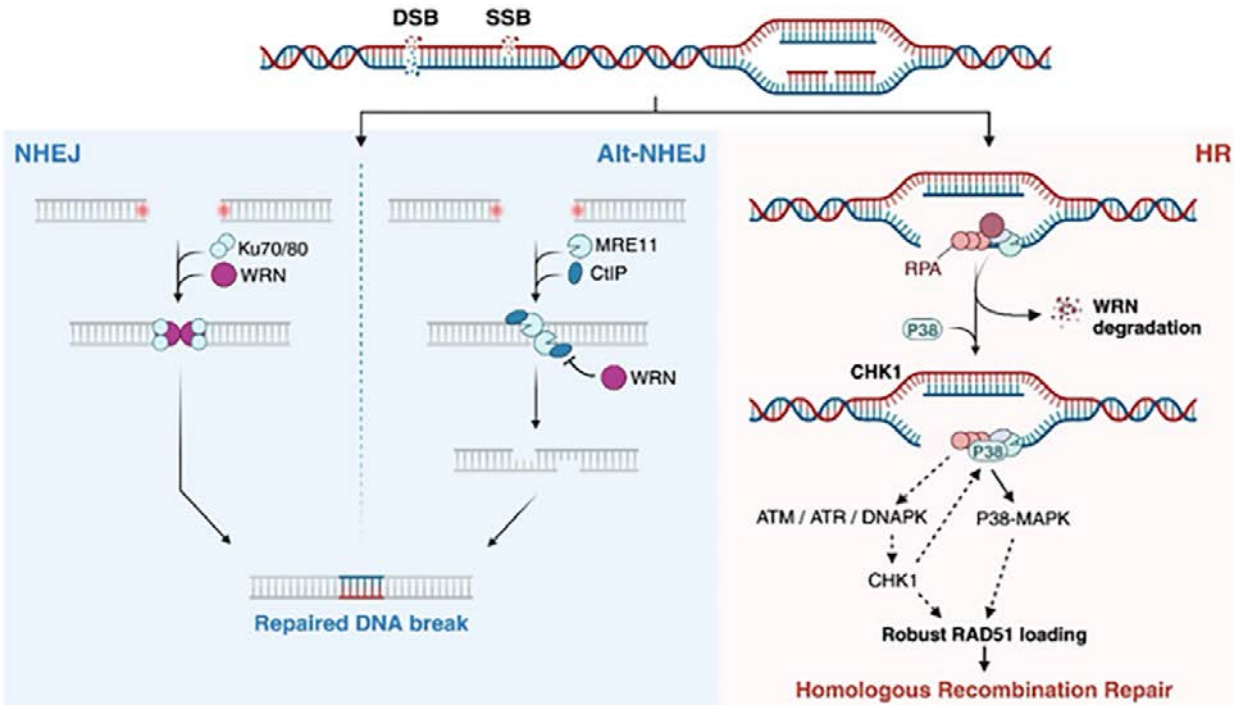

Fig. 2. The WRN RECQL helicase influences the choice of double-strand break (DSB) repair pathways. WRN is essential for promoting canonical nonhomologous end joining (c-NHEJ) and inhibiting alternative NHEJ (alt-NHEJ). In homologous recombination repair (HRR), WRN is vital for late-stage DSB resection and for CHK1-driven RAD51 loading. When WRN is absent, control shifts to p38-MAPK-mediated RAD51 loading during HRR in cancer cells. Key terms: DSB (double-strand break), SSB (single-strand break), NHEJ (nonhomologous end joining), alt-NHEJ (alternative NHEJ), HRR (homologous recombination repair), CHK (checkpoint kinase 1), RAD51 (DNA repair protein RAD51 homolog 1), MRE (meiotic recombination 11), CTIP (CtBP-interacting protein), ATM (ataxia-telangiectasia mutated), and ATR (ataxia-telangiectasia and Rad3-related).

8p11.2-p12 in various cancers underscores its function as a tumor suppressor gene.[71,72]

This factor is a synthetic lethal target in microsatellite unstable cancers. Synthetic lethality is a phenomenon where the simultaneous occurrence of two genetic events results in cell death, whereas each event alone does not have this effect.[73] WRN deficiency has been associated with the promotion of MSI-H phenotypes, exacerbating replication stress and DNA damage, particularly in cells already harboring MMR defects.[74] The concept of synthetic lethality in MSI-H CRC has gained traction, with emerging experimental data highlighting a synthetic lethal phenomenon driven by expansion mutations in numerous $(TA)_n$ dinucleotide repeats. The elongation of $(TA)_n$ repeats increases the likelihood of secondary DNA structure formation, requiring WRN intervention for resolution. However, in the absence of functional WRN helicase activity, these unresolved DNA structures impede the progression of DNA replication forks, resulting in substantial DNA damage (Fig. 2).[75]

In another investigation, it was discovered that WRN loss in MMR-deficient cells triggers DNA double-strand breaks (DSBs), leading to the activation of ATM and CHK2 signaling kinases. This activation induces the tumor suppressor p53 and the pro-apoptotic protein PUMA, thereby promoting mitochondria-mediated apoptosis. The study identifies PUMA as a crucial mediator of apoptosis following WRN loss. Specifically, inhibition of WRN results in the activation of PUMA, which is essential for inducing cell death in MMR-deficient CRC cells.[76] Moreover, in MMR-deficient cells, the genome relies more on alternative DNA repair mechanisms to avoid exceeding the tolerable mutation threshold, which would otherwise lead to cell death. Consequently, any loss of function in the WRN gene disrupts these compensatory repair mechanisms, such as homologous recombination (HR) and non-homologous end joining (NHEJ), ultimately causing programmed cell death in the cancerous cell.[77]

The discovery of WRN's role in MSI-H cancers has opened exciting avenues for targeted therapy. Researchers are developing specific WRN inhibitors and employing gene-editing techniques such as CRISPR-Cas9 to selectively kill MSI-H cancer cells while leaving healthy cells unharmed.[78–80] Understanding the interplay between WRN and MSI-H in CRC provides valuable insights into potential therapeutic targets and strategies for personalized treatment approaches.

CONCLUSION

The multifaceted landscape of microsatellite instability (MSI) in colorectal cancer (CRC) presents a rich tapestry of clinical implications, therapeutic opportunities, and challenges. Through this comprehensive review, we have explored the clinical features and prognostic significance of MSI CRCs, delved into the intricate mechanisms underlying immune interactions within the tumor microenvironment, and discussed the evolving therapeutic landscape of MSI-targeted therapy.

MSI CRCs exhibit distinct clinical behaviors and responses to treatment, driven by their unique molecular characteristics and immune microenvironment. MSI-H tumors demonstrate heightened immune infiltration and favorable responses to immunotherapy. However, challenges such as tumor heterogeneity and immune evasion mechanisms underscore the need for precision medicine approaches and innovative therapeutic strategies.

The advent of immunotherapy, particularly immune checkpoint inhibitors, has revolutionized the treatment paradigm for MSI-H CRCs, offering newfound hope and improved outcomes for patients previously considered therapeutically challenging. FDA-approved agents like pembrolizumab and nivolumab have reshaped clinical practice, with ongoing research exploring novel combinations and neoadjuvant approaches to further enhance treatment efficacy.

Significant challenges remain, including the heterogeneity within MSI-H CRCs, the complexity of immune evasion mechanisms, and the management of immune-related adverse events. Addressing these challenges will require collaborative efforts across disciplines, innovative trial designs, and the integration of emerging technologies and biomarkers into clinical practice.

As we navigate the complexities of MSI CRCs, fueled by advancements in understanding tumor biology and immunology, the future holds promise for personalized and precise therapeutic interventions tailored to individual patient profiles. By unraveling the intricacies of immune interactions in the TME and leveraging the power of targeted therapy, we can strive toward improved outcomes and a paradigm shift in CRC management.

In essence, the journey towards optimizing MSI-targeted therapy is multifaceted. However, with collaboration and innovation, we can continue to push the boundaries of possibility, reshaping the standard of care and improving the lives of patients affected by colorectal cancer.

Conflict of Interest: All authors declared no conflict of interest.

Use of AI for Writing Assistance: No AI technologies utilized.

Financial Support: Not applicable.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin 2023;73(3):233–54.
2. Gian LdA, Lorena B, Cinzia A, Gioacchino L, Federica G, Francesca N. Microsatellite instability in colorectal cancer. Acta Bio Med 2018;89(Suppl 9):97.
3. Roudko V, Cimen Bozkus C, Greenbaum B, Lucas A, Samstein R, Bhardwaj N. Lynch syndrome and MSI-H cancers: From mechanisms to "off-the-shelf" cancer vaccines. Front Immunol 2021;12:757804.
4. Battaglin F, Naseem M, Lenz HJ, Salem ME. Microsatellite instability in colorectal cancer: Overview of its clinical significance and novel perspectives. Clin Adv Hematol Oncol 2018;16(11):735.
5. Peltomaki P, Aaltonen LA, Sistonen P, et al. Genetic mapping of a locus predisposing to human colorectal cancer. Science. 1993;260(5109):810–812.
6. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Curr Treat Options Oncol 2015;16:1–15.
7. Borelli B, Antoniotti C, Carullo M, Germani MM, Conca V, Masi G. Immune-checkpoint inhibitors (ICIs) in metastatic colorectal cancer (mCRC) patients beyond microsatellite instability. Cancers 2022;14(20):4974.
8. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken J, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27(8):1386–422.
9. Baudrin LG, Deleuze JF, How-Kit A. Molecular and computational methods for the detection of microsatellite instability in cancer. Front Oncol 2018;8:621.
10. Willis J, Lefterova MI, Artyomenko A, Kasi PM, Nakamura Y, Mody K, et al. Validation of microsatellite instability detection using a comprehensive

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

plasma-based genotyping panel. Clin Cancer Res 2019;25(23):7035–45.
11. Li Z, Pearlman AH, Hsieh P. DNA mismatch repair and the DNA damage response. DNA Repair 2016;38:94–101.
12. Baretti M, Le DT. DNA mismatch repair in cancer. Pharmacol Ther 2018;189:45–62.
13. Zhang X, Li J. Era of universal testing of microsatellite instability in colorectal cancer. World J Gastrointest Oncol 2013;5(2):12.
14. Richman S. Deficient mismatch repair: Read all about it. Int J Oncol 2015;47(4):1189–202.
15. Nguyen LH, Goel A, Chung DC. Pathways of colorectal carcinogenesis. Gastroenterology 2020;158(2):291–302.
16. Huang Z, Yang M. Molecular network of colorectal cancer and current therapeutic options. Front Oncol 2022;12:852927.
17. Peltomäki P, Nyström M, Mecklin JP, Seppälä TT. Lynch syndrome genetics and clinical implications. Gastroenterology 2023;164(5):783–99.
18. Tamura K, Kaneda M, Futagawa M, Takeshita M, Kim S, Nakama M, et al. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. Int J Clin Oncol 2019;24:999–1011.
19. Gallon R, Brekelmans C, Martin M, Bours V, Schamschula E, Amberger A, et al. Constitutional mismatch repair deficiency mimicking Lynch syndrome is associated with hypomorphic mismatch repair gene variants. NPJ Precis Oncol 2024;8(1):119.
20. Lin EI, Tseng LH, Gocke CD, Reil S, Le DT, Azad NS, et al. Mutational profiling of colorectal cancers with microsatellite instability. Oncotarget 2015;6(39):42334.
21. Elez E, Ros J, Fernández J, Villacampa G, Moreno-Cárdenas AB, Arenillas C, et al. RNF43 mutations predict response to anti-BRAF/EGFR combinatory therapies in BRAF V600E metastatic colorectal cancer. Nat Med 2022;28(10):2162–70.
22. Mojarad EN, Kuppen PJ, Aghdaei HA, Zali MR. The CpG island methylator phenotype (CIMP) in colorectal cancer. Gastroenterol Hepatol Bed Bench 2013;6(3):120.
23. Thibodeau SN, French AJ, Cunningham JM, Tester D, Burgart LJ, Roche PC, et al. Microsatellite instability in colorectal cancer: Different mutator phenotypes and the principal involvement of hMLH1. Cancer Res 1998;58(8):1713–8.
24. Porkka N, Lahtinen L, Ahtiainen M, Böhm JP, Kuopio T, Eldfors S, et al. Epidemiological, clinical and molecular characterization of Lynch-like syndrome: A population-based study. Int J Cancer 2019;145(1):87–98.
25. Jasmine F, Haq Z, Kamal M, Raza M, da Silva G, Gorospe K, et al. Interaction between microsatellite instability (MSI) and tumor DNA methylation in the pathogenesis of colorectal carcinoma. Cancers 2021;13(19):4956.
26. Suraweera N, Duval A, Reperant M, Vaury C, Furlan D, Leroy K, et al. Evaluation of tumor microsatellite instability using five quasimonomorphic mononucleotide repeats and pentaplex PCR. Gastroenterology 2002;123(6):1804–11.
27. Gilson P, Merlin JL, Harlé A. Detection of microsatellite instability: State of the art and future applications in circulating tumour DNA (ctDNA). Cancers 2021;13(7):1491.
28. Tieng FYF, Abu N, Lee LH, Ab Mutalib NS. Microsatellite instability in colorectal cancer liquid biopsy—current updates on its potential in non-invasive detection, prognosis and as a predictive marker. Diagnostics 2021;11(3):544.
29. Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic—implementation issues and future challenges. Nat Rev Clin Oncol 2021;18(5):297–312.
30. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23(6):703–13.
31. Velasco A, Tokat F, Bonde J, Trim N, Bauer E, Meeney A, et al. Multi-center real-world comparison of the fully automated Idylla microsatellite instability assay with routine molecular methods and immunohistochemistry on formalin-fixed paraffin-embedded tissue of colorectal cancer. Virchows Arch 2021;478:851–63.
32. Cesana N. A Comparative study regarding the morphologic implications of microsatellite instability in malignant colorectal neoplasia. Lietuvos Sveikatos Mokslu Universitetas 2022.
33. Kim HG, Lee S, Kim DY, Ryu SY, Joo JK, Kim JC, et al. Aberrant methylation of DNA mismatch repair genes in elderly patients with sporadic gastric carcinoma: A comparison with younger patients. J Surg Oncol 2010;101(1):28–35.
34. Salem ME, Bodor JN, Puccini A, Xiu J, Goldberg RM, Grothey A, et al. Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors. Int J Cancer 2020;147(10):2948–56.
35. Yiu R, Qiu H, Lee SH, García-Aguilar J. Mechanisms of microsatellite instability in colorectal cancer patients in different age groups. Dis Colon Rectum 2005;48:2061–9.
36. Coggins R, Cawkwell L, Bell S, Crockford G, Quirke P, Finan P, et al. Association between family history and mismatch repair in colorectal cancer. Gut 2005;54(5):636–42.
37. Khan M, Loree JM, Advani SM, Ning J, Li W, Pereira AA, et al. Prognostic implications of mucinous differentiation in metastatic colorectal carcinoma can be explained by distinct molecular and clinicopathologic characteristics. Clin Colorectal Cancer 2018;17(4):e699–709.

38. Lizardo DY, Kuang C, Hao S, Yu J, Huang Y, Zhang L. Immunotherapy efficacy on mismatch repair-deficient colorectal cancer: From bench to bedside. Biochim Biophys Acta Rev Cancer 2020;1874(2):188447.
39. Mulet-Margalef N, Linares J, Badia-Ramentol J, Jimeno M, Sanz Monte C, Manzano Mozo JL, et al. Challenges and therapeutic opportunities in the dMMR/MSI-H colorectal cancer landscape. Cancers 2023;15(4):1022.
40. Zhang X, Wu T, Cai X, Dong J, Xia C, Zhou Y, et al. Neoadjuvant immunotherapy for MSI-H/dMMR locally advanced colorectal cancer: New strategies and unveiled opportunities. Front Immunol 2022;13:795972.
41. Cohen R, Rousseau B, Vidal J, Colle R, Diaz LA, André T. Immune checkpoint inhibition in colorectal cancer: Microsatellite instability and beyond. Target Oncol 2020;15:11–24.
42. Lin A, Zhang J, Luo P. Crosstalk between the MSI status and tumor microenvironment in colorectal cancer. Front Immunol 2020;11:552467.
43. Gupta R, Sinha S, Paul RN. The impact of microsatellite stability status in colorectal cancer. Curr Probl Cancer 2018;42(6):548–59.
44. Guinney J, Dienstmann R, Wang X, De Reynies A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21(11):1350–6.
45. Toor SM, Sasidharan Nair V, Murshed K, Abu Nada M, Elkord E. Tumor-infiltrating lymphoid cells in colorectal cancer patients with varying disease stages and microsatellite instability-high/stable tumors. Vaccines 2021;9(1):64.
46. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, Segal NH, et al. Immunotherapy in colorectal cancer: Rationale, challenges and potential. Nat Rev Gastroenterol Hepatol 2019;16(6):361–75.
47. Heregger R, Huemer F, Steiner M, Gonzalez-Martinez A, Greil R, Weiss L. Unraveling resistance to immunotherapy in MSI-high colorectal cancer. Cancers 2023;15(20):5090.
48. Koi M, Carethers JM. The colorectal cancer immune microenvironment and approach to immunotherapies. Future Oncol 2017;13(18):1633–47.
49. Sun CH, Li BB, Wang B, Zhao J, Zhang XY, Li TT, et al. The role of fusobacterium nucleatum in colorectal cancer: From carcinogenesis to clinical management. Chronic Dis Transl Med 2019;5(3):178–87.
50. Wu J, Li Q, Fu X. Fusobacterium nucleatum contributes to the carcinogenesis of colorectal cancer by inducing inflammation and suppressing host immunity. Transl Oncol 2019;12(6):846–51.
51. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. 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(9):1182–91.
52. Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: The phase II CheckMate 142 study. J Clin Oncol 2022;40(2):161–70.
53. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt CJ, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 Study. J Clin Oncol 2020;38(18):2163–72.
54. Pei F, Wu J, Zhao Y, He W, Yao Q, Huang M, et al. Single-agent neoadjuvant immunotherapy with a PD-1 antibody in locally advanced mismatch repair-deficient or microsatellite instability-high colorectal cancer. Clin Colorectal Cancer 2023;22(1):85–91.
55. He R, Lao Y, Yu W, Zhang X, Jiang M, Zhu C. Progress in the application of immune checkpoint inhibitor-based immunotherapy for targeting different types of colorectal cancer. Front Oncol 2021;11:764618.
56. Tian J, Chen JH, Chao SX, Pelka K, Giannakis M, Hess J, et al. Combined PD-1, BRAF and MEK inhibition in BRAFV600E colorectal cancer: A phase 2 trial. Nat Med 2023;29(2):458–66.
57. Rus Bakarurraini NAA, Ab Mutalib NS, Jamal R, Abu N. The landscape of tumor-specific antigens in colorectal cancer. Vaccines 2020;8(3):371.
58. Ma X, Dong L, Liu X, Ou K, Yang L. POLE/POLD1 mutation and tumor immunotherapy. J Exp Clin Cancer Res 2022;41(1):216.
59. Ozcan M, Janikovits J, von Knebel Doeberitz M, Kloor M. Complex pattern of immune evasion in MSI colorectal cancer. Oncoimmunology 2018;7(7):e1445453.
60. Huang Q, Yu T, Li L, Zhang Q, Zhang S, Li B, et al. Intraindividual tumor heterogeneity of mismatch repair status in metastatic colorectal cancer. Appl Immunohistochem Mol Morphol 2023;31(2):84–93.
61. Chung BS, Liao IC, Lin PC, Wu SY, Kang JW, Lin BW, et al. PD-L1 expression in high-risk early-stage colorectal cancer—its clinical and biological significance in immune microenvironment. Int J Mol Sci 2022;23(21):13277.
62. Twomey JD, Zhang B. Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. AAPS J 2021;23:1–11.
63. Scott RJ. Modifier genes and Lynch syndrome: Some considerations. Hered Cancer Clin Pract 2022;20(1):35.
64. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers 2020;6(1):38.
65. Temraz S, Nassar F, Nasr R, Charafeddine M, Mukherji D, Shamseddine A. Gut microbiome: A promising biomarker for immunotherapy in colorectal cancer. Int J Mol Sci 2019;20(17):4155.

Turk J Oncol 2025;40(1):83–94
doi: 10.5505/tjo.2024.4477

66. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: Insights into tumour immunogenicity and immune evasion. Nat Rev Cancer 2021;21(5):298–312.
67. Perillo F, Amoroso C, Strati F, Giuffrè MR, Díaz-Basabe A, Lattanzi G, et al. Gut microbiota manipulation as a tool for colorectal cancer management: Recent advances in its use for therapeutic purposes. Int J Mol Sci 2020;21(15):5389.
68. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. Cell 2015;161(2):205–14.
69. Molinari C, Marisi G, Passardi A, Matteucci L, De Maio G, Ulivi P. Heterogeneity in colorectal cancer: A challenge for personalized medicine? Int J Mol Sci 2018;19(12):3733.
70. Chan EM, Shibue T, McFarland JM, Gaeta B, Ghandi M, Dumont N, et al. WRN helicase is a synthetic lethal target in microsatellite unstable cancers. Nature 2019;568(7753):551–6.
71. Brosh Jr RM, Opresko PL, Bohr VA. Enzymatic mechanism of the WRN helicase/nuclease. Methods Enzymol 2006;409:52–85.
72. Jacinto FV, Esteller M. Mutator pathways unleashed by epigenetic silencing in human cancer. Mutagenesis 2007;22(4):247–53.
73. Huang A, Garraway LA, Ashworth A, Weber B. Synthetic lethality as an engine for cancer drug target discovery. Nat Rev Drug Discov 2020;19(1):23–38.
74. Lieb S, Blaha-Ostermann S, Kamper E, Rippka J, Schwarz C, Ehrenhöfer-Wölfer K, et al. Werner syndrome helicase is a selective vulnerability of microsatellite instability-high tumor cells. Elife 2019;8:e43333.
75. van Wietmarschen N, Nathan WJ, Nussenzweig A. The WRN helicase: Resolving a new target in microsatellite unstable cancers. Curr Opin Genet Dev 2021;71:34–8.
76. Sobol RW. WRN suppresses p53/PUMA-induced apoptosis in colorectal cancer with microsatellite instability/mismatch repair deficiency. Proc Natl Acad Sci U S A 2023;120(2):e2219963120.
77. Zhou J, Zhou XA, Zhang N, Wang J. Evolving insights: How DNA repair pathways impact cancer evolution. Cancer Biol Med 2020;17(4):805.
78. Zhou F, Yang G, Liu Y, Xue L, Guo Y, Li Z, et al. Discovery of a novel WRN inhibitor, ZM-3329 that efficiently inhibits MSI-H tumor growth. Cancer Res 2024;84(6_Suppl):7278.
79. Ferretti S, Hamon J, de Kanter R, Scheufler C, Andraos-Rey R, Barbe S, et al. Discovery of WRN inhibitor HRO761 with synthetic lethality in MSI cancers. Nature 2024:1–7.
80. Picco G, Cattaneo CM, van Vliet EJ, Crisafulli G, Rospo G, Consonni S, et al. Werner helicase is a synthetic-lethal vulnerability in mismatch repair–deficient colorectal cancer refractory to targeted therapies, chemotherapy, and immunotherapy. Cancer Discov 2021;11(8):1923–37.