

Adjuvant Immunotherapy in Microsatellite Instability-High Colon Cancer: A Literature Review on Efficacy, Challenges, and Future Directions

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Colon cancer accounts for nearly 10% of all cancer diagnoses annually. Microsatellite instability-high (MSI-H) colon cancer is a particularly aggressive subtype of colon cancer that is known to have a significant number of genetic mutations. Microsatellite instability (MSI) refers to genetic hypermutability caused by the dysfunction of the DNA mismatch repair (*MMR*) system, which leads to errors in repetitive DNA sequences and is a hallmark of certain cancers, including MSI-H colon cancer. MSI-H colon cancer acts on the DNA mismatch repair system causing an accumulation of mutations in microsatellite regions of the DNA. These mutations have been linked with increased tumorigenesis and decreased response to conventional forms of chemotherapy for colon cancer. However, this increased tumor burden results in significant production of neoantigens which makes these tumors immunogenic and therefore perfect candidates for pairing with immunotherapy. As a result, adjuvant immunotherapy in MSI-H colon cancer has become a burgeoning field of research, and synthesizing information regarding the efficacy of these immunotherapies is the goal of this literature review. Pembrolizumab, a monoclonal antibody targeting programmed cell death protein 1 (*PD-1*), was among the first to receive approval for the treatment of MSI-H colon cancer and was observed to have significant efficacy versus traditional chemotherapy with statistically significant improvements in metrics such as progression-free survival (PFS), overall response (OR), and disease-free survival (DFS). Similarly, Nivolumab, another *PD-1* inhibitor, and the combination of nivolumab and ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*) inhibitor) were granted Food and Drug Administration (FDA) approval for the treatment of MSI-H colon cancer and have also shown the ability to outperform traditional chemotherapy with a higher overall response rate (ORR), mean PFS, and overall survival rates. Off-label uses of existing adjuvant immunotherapies such as Atezolizumab (a programmed death-ligand 1 (*PD-L1*) inhibitor) and Durvalumab (a *PD-L1* inhibitor) have shown promise with preliminary results showing higher DFS and recurrence-free survival but need further data collection. Emerging immunotherapy targets such as lymphocyte activation gene 3 (*LAG-3*) and T-cell immunoreceptor with immunoglobulin and Immunoreceptor Tyrosine-based Inhibitory Motif domains (*TIGIT*) inhibitors show preliminary promise and may one day become a part of the approach to the treatment of MSI-H colon cancer. This review highlights current advancements, challenges, and emerging trends in the application of immunotherapy for MSI-H colon cancer, with a focus on improving patient outcomes.

Keywords: MSI-H; colon cancer; immune checkpoint inhibitors; adjuvant immunotherapy; emerging immunotherapies; tumor microenvironment; translational oncology

Introduction

Colon cancer is the 3rd most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide, accounting for nearly 10% of all cancer diagnoses annually [1]. Colon cancer, also known as colorectal cancer (CRC) when including the rectum, typically arises from the epithelial cells lining the colon or rectum, often developing from precursor lesions such as adenomatous polyps. The disease spectrum ranges from early-stage localized cancer, which is often curable with surgical resection, to advanced or metastatic disease, which poses

significant therapeutic challenges [2]. The prognosis of colon cancer varies significantly by stage, with early detection and surgical resection offering a 5-year survival rate of over 90% in stage I disease. However, this rate drops dramatically to approximately 14% in metastatic cases [3]. Risk factors include advanced age, a diet high in red or processed meats, physical inactivity, obesity, smoking, and alcohol consumption, with approximately 25% of cases attributed to hereditary syndromes such as Lynch syndrome or familial adenomatous polyposis [2].

Colon cancer symptoms vary by stage and tumor location. Early-stage colon cancer is frequently asymptomatic,

with diagnosis often occurring incidentally during routine screenings. When symptoms appear, they may include rectal bleeding, changes in bowel habits (diarrhea or constipation), unexplained weight loss, fatigue, and abdominal discomfort. Advanced disease can present with bowel obstruction, perforation, or metastatic symptoms such as liver dysfunction or respiratory issues if the lungs are involved [3].

The etiology of colon cancer is multifactorial, with genetic, environmental, and lifestyle components playing critical roles. Certain lifestyle factors such as diets high in red and processed meats, obesity, smoking, and excessive alcohol consumption increase the risk of colon cancer [2]. In addition, genetic predispositions and hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis (FAP) contribute to approximately 5–10% of cases. Lynch syndrome, characterized by a mismatch repair (*MMR*) gene mutation, is closely linked to microsatellite instability-high (MSI-H) tumors [4]. Conditions such as inflammatory bowel disease (IBD) are also associated with increased CRC risk due to chronic epithelial injury and inflammation [3]. Colon cancer prevention relies on lifestyle modifications and regular screenings. High-fiber diets, physical activity, reduced consumption of red and processed meats, and cessation of smoking can decrease risk. Screening methods such as colonoscopy, stool-based tests, and sigmoidoscopy are instrumental in detecting precancerous polyps or early-stage cancers and improving survival rates [1].

MSI-H colon cancer is a subset of colorectal cancers characterized by defects in the *MMR* system, which is responsible for correcting DNA replication errors. Deficient *MMR* leads to the accumulation of mutations in microsatellite regions, contributing to tumorigenesis [4]. MSI-H tumors represent approximately 15% of all CRCs, with 3–5% arising sporadically due to hypermethylation of the MutL homolog 1 (*MLH1*) promoter and 12% associated with Lynch syndrome [2]. MSI-H tumors are associated with high tumor mutational burden (*TMB*), resulting in the production of neoantigens that make these tumors immunogenic and more susceptible to immune checkpoint blockade [5,6].

Over the last decade, personalized therapies targeting specific molecular characteristics of tumors have become increasingly relevant. MSI-H colon cancer, characterized by a high frequency of mutations in short, repeated sequences of DNA due to *MMR* deficiency, has unique clinical and immunologic properties that make it an intriguing candidate for immunotherapy. This feature highlights their responsiveness to immune checkpoint inhibitors (ICIs), as neoantigens attract cytotoxic T-cell infiltration [5,6]. Additionally, MSI-H tumors exhibit lower expression of immune evasion mechanisms such as programmed cell death protein 1 (*PD-1*) compared to microsatellite-stable (*MSS*) CRCs, further enhancing ICI efficacy [7].

Traditionally, MSI-H colon cancers are treated with surgery followed by chemotherapy for higher stages. The current standard of care for resected high-risk stage II and stage III colon cancer is adjuvant chemotherapy, often using fluoropyrimidine-based regimens like 5-fluorouracil (5-FU) with or without oxaliplatin [2]. However, MSI-H tumors are relatively resistant to these therapies due to their unique molecular profile. This resistance has prompted the exploration of immunotherapy, which leverages the immune system's ability to target MSI-H tumors effectively. While adjuvant chemotherapy has been the standard of care for resected high-risk stage II and stage III colon cancers, its benefit is limited in MSI-H tumors due to inherent resistance to fluoropyrimidine-based regimens [7].

However, recent studies have raised questions about the efficacy of chemotherapy in MSI-H cases, as these tumors tend to be less responsive to 5-FU-based regimens compared to *MSS* tumors. Given the poor response to traditional adjuvant chemotherapy and the heightened immunogenic potential of MSI-H tumors, immunotherapy, particularly in the adjuvant setting, has become a promising area of investigation. Recent advances in immunotherapy have transformed the treatment regimen, particularly for patients with MSI-H colon cancer, who exhibit favorable responses to ICIs targeting the *PD-1*/programmed death-ligand 1 (*PD-L1*) axis and cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*) [8]. Immune checkpoint inhibitors targeting the *PD-1/PD-L1* and *CTLA-4* pathways are of particular interest, as they may help stimulate a sustained immune response that could prevent recurrence in MSI-H colon cancer patients post-surgery.

Adjuvant immunotherapy in MSI-H colon cancer has emerged as a promising approach to reduce recurrence risk and improve long-term survival. This review will not cover immunotherapy in *MSS* colon cancers, as these tumors lack the same immunogenic profile and have shown lower response rates to ICIs. However, we will focus specifically on non-metastatic MSI-H colon cancer in the adjuvant (post-surgical) setting, rather than in metastatic or neoadjuvant (pre-surgical) scenarios, as the intent is to explore immunotherapy's potential to reduce recurrence after curative-intent surgery. This review focuses on evaluating the benefits of adjuvant immunotherapy in MSI-H colon cancer compared to standard chemotherapy. By analyzing clinical trial data and real-world outcomes, the review aims to assess whether incorporating ICIs into adjuvant therapy can enhance radiographic response, disease-free survival (DFS), and overall survival, reduce recurrence, minimize treatment-related toxicities, and optimize therapeutic outcomes. As the understanding of tumor immunology deepens, ongoing studies aim to refine therapeutic strategies, maximize efficacy, and minimize toxicity, ultimately improving survival outcomes for patients with MSI-H colon cancer.

Navigating Treatment Pathways: Chemotherapy and Immunotherapy in MSI-H Colon Cancer

Chemotherapy for MSI-H Colon Cancer

Standard chemotherapy has been the backbone of adjuvant treatment for colon cancer, though its efficacy is reduced in MSI-H subtypes due to inherent resistance. Some of the common chemotherapy regimens include: FOLFOX (folinic acid + fluorouracil + oxaliplatin), Capecitabine monotherapy, and 5-FU monotherapy. With the FOLFOX regimen, the DFS is approximately 74% at 3 years in stage III *non*-MSI-H colon cancer [9]. The DFS in MSI-H demonstrates less benefit observed compared to *non*-MSI-H colon cancer with DFS rates approximately 60–65% [10]. The adverse events (AEs) of this chemotherapy include the following: Peripheral neuropathy (30%), neutropenia (35%), and diarrhea (20%) [11]. Capecitabine is effective as monotherapy but has limited efficacy in MSI-H cancers. The DFS in MSI-H was approximately 60% [12]. The AEs include the following: Hand-foot syndrome (15%), diarrhea (20%), and fatigue (25%) [13]. The 5-FU Alone chemotherapy shows minimal benefit in MSI-H cancers compared to other regimens, with a DFS in MSI-H observed to be below 50% [10].

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs), including pembrolizumab and nivolumab, have revolutionized cancer treatment by enhancing the immune system's ability to recognize and attack tumor cells. These agents target immune checkpoints such as programmed cell death protein 1 (*PD-1*)/programmed death-ligand 1 (*PD-L1*) or cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*), effectively “releasing the brakes” on the immune system. While they have shown remarkable efficacy in treating cancers such as melanoma, non-small cell lung cancer, and MSI-H colorectal cancer, their use is frequently associated with immune-related adverse events (irAEs) due to immune system overactivation such as immune-mediated colitis, hepatitis, and skin rash [14]. Immune-mediated colitis occurs due to inflammation of the colon and is most commonly associated with *CTLA-4* inhibitors but can also occur with *PD-1/PD-L1* inhibitors like pembrolizumab and nivolumab [15]. These symptoms include diarrhea, abdominal pain, and sometimes severe complications like perforation or sepsis. Mild cases can often be managed with antidiarrheal agents and increased hydration. Moderate to severe colitis requires corticosteroids (e.g., prednisone 1–2 mg/kg daily). For refractory cases, immunosuppressants like infliximab or vedolizumab are recommended [16]. Other adverse events such as immune-mediated hepatitis and skin rash can also be managed with corticosteroids and adequate monitoring of the event. While pembrolizumab and nivolumab have revolutionized cancer treatment, early recognition and prompt management of these adverse events are critical to maximizing patient outcomes while minimizing adverse

impacts on quality of life. A personalized approach to balancing efficacy and safety is essential in this evolving therapeutic landscape.

While programmed cell death protein 1 (*PD-1*)/programmed death-ligand 1 (*PD-L1*) inhibitors have transformed cancer treatment, their efficacy is often limited by primary or acquired resistance. Understanding these resistance mechanisms is essential to improving therapeutic outcomes and designing next-generation immunotherapy strategies. Resistance stems from a combination of tumor-intrinsic and tumor-extrinsic factors that enable cancer cells to evade immune detection or dampen immune activation. The tumor microenvironment (TME) plays a pivotal role in mediating resistance to *PD-1/PD-L1* inhibitors. The tumor microenvironment plays a pivotal role in mediating the efficacy of immune checkpoint inhibitors by modulating innate and adaptive immune cell responses, which are critical for tumor control [17]. Tumors can create an immunosuppressive TME by recruiting regulatory immune cells and secreting suppressive cytokines. Tumors can promote the recruitment of regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs), which inhibit the activation and proliferation of cytotoxic regulatory T cells (Tregs) [18]. In addition, tumors can also upregulate *PD-L1* expression in response to inflammation, further suppressing T-cell-mediated killing. Major histocompatibility complex class I (*MHC-I*) molecules are critical for presenting tumor antigens to CD8+ T cells. Tumors can evade immune detection by silencing *MHC-I* expression through genetic mutations or epigenetic changes, preventing antigen presentation to cytotoxic T cells [11]. Defects in antigen processing pathways also contribute to resistance. Tumors can inhibit proteasome function, leading to reduced generation of peptide fragments necessary for *MHC-I* presentation. Mutations in the transporter associated with antigen processing 1 (TAP1) and transporter associated with antigen processing 2 (TAP2), responsible for loading antigens onto *MHC-I*, have also been implicated in resistance [18]. To overcome these resistance mechanisms, combination therapies targeting multiple immune pathways are being explored such as dual checkpoint blockade, targeting the TME, and other personalized approaches. Dual checkpoint blockade through combining *PD-1/PD-L1* inhibitors with *CTLA-4*, lymphocyte activation gene 3 (*LAG-3*), or T-cell immunoreceptor with immunoglobulin and Immunoreceptor Tyrosine-based Inhibitory Motif domains (*TIGIT*) inhibitors can restore T-cell function and broaden immune activation [19]. Furthermore, agents targeting transforming growth factor-beta (*TGF-β*) or MDSCs aim to reprogram the TME and mitigate its immunosuppressive effects. Lastly, personalized approaches such as neoantigen vaccines and adoptive T-cell therapies are promising strategies to enhance tumor immunogenicity and counteract antigen loss [19].

Pembrolizumab

Pembrolizumab, a *PD-1* inhibitor, is among the most studied ICIs for MSI-H colon cancer and has been approved for metastatic MSI-H colon cancer and is under investigation for adjuvant use [20]. Full approval was based on the KEYNOTE-177 (NCT02563002) trial. This trial had 307 patients with MSI-H or *dMMR* gene mutation colorectal cancer that was untreated, unresectable, or metastatic.

This trial primarily utilized the efficacy outcomes of progression-free survival (PFS) and overall survival (OS). Median PFS was 16.5 months (95% confidence interval (CI): 5.4, 32.4) in the pembrolizumab arm and 8.2 months (95% CI: 6.1, 10.2) with chemotherapy. Radiographic response in the pembrolizumab group was also reported, as compared to the chemotherapy group. The overall response (complete and partial response) in the pembrolizumab group was 43.8% (95% CI: 35.8, 52.0), and in the chemotherapy group, it was 33.1% (95% CI: 25.8, 41.1). Pembrolizumab also had a 7% higher complete response rate (11% vs 4%) [21].

Subsequent clinical trials have demonstrated its efficacy in both metastatic and non-metastatic settings. In the adjuvant setting, pembrolizumab showed significant improvement in DFS, with DFS rates of 83% at 12 months compared to 68% for standard chemotherapy [22]. The overall response rate (ORR) demonstrated 55% for pembrolizumab vs. 42% for conventional chemotherapy [22].

Adverse events occurred in 97% of the pembrolizumab group and 99% of the chemotherapy group. The most common of these were decreased neutrophil count, neutropenia, and diarrhea. Each of these adverse events occurred at a lower frequency in the immunotherapy group vs the chemotherapy group [21]. Other common adverse events (AEs) include fatigue (20%), and immune-mediated colitis (5%) [8].

Nivolumab and Ipilimumab

Nivolumab is another *PD-1* inhibitor that gained Food and Drug Administration (FDA) approval for single-agent use in patients with *dMMR* and MSI-H colorectal cancer. This approval was because of the CHECKMATE 142 trial (NCT 02060188) which was conducted in 53 patients determined to have *dMMR* or MSI-H colon cancer and had failed fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Nivolumab therapy showed single agent efficacy with an ORR of 35.8% (95% CI: 23.1, 50.2), disease control at 12 weeks of 73.6% (95% CI: 59.7, 84.7), and showed high levels of durable responses at 12.0 and 13.4 months [8,23].

As the trial expanded, Nivolumab efficacy in combination with ipilimumab (a *CTLA-4* inhibitor) was explored and also showed efficacy and was approved for the treatment of metastatic MSI-H CRC. Trials reported a DFS benefit of 75% at 2 years compared to 59% with chemotherapy alone [8]. The ORR was 60% for nivolumab in combina-

tion with ipilimumab [8]. Mean progression-free survival and median overall survival rates of 74% and 79% overall were not reached [24].

A phase 3 study, CHECKMATE 8HW (NCT04008030) was initiated to expand on these results. In this study, 303 patients were randomized to either nivolumab (nivo) + ipilimumab (ipi) or chemotherapy. Preliminary results released in 2024 show a 79% reduction in the risk of disease progression or death in the experimental group along with a statistically significant improvement in PFS in comparison to the control group of just chemotherapy [25].

The combination therapy increased the rate of immune-related adverse events, with Grade 3 or 4 AEs such as hepatitis (10%) and diarrhea (8%) observed in 20% of patients [8].

Atezolizumab

Atezolizumab, a *PD-L1* inhibitor, currently under investigation for MSI-H colon cancer in the adjuvant setting, demonstrated efficacy in reducing recurrence risk in stage II and III MSI-H colon cancer [21]. Trial data showed recurrence-free survival (*RFS*) rates of 78% at 18 months compared to 65% in the standard chemotherapy arm [22]. The ORR for Atezolizumab was reported to be 50% [22]. The AEs included infusion-related reactions (12%) and hypothyroidism (5%) [22].

Durvalumab

Durvalumab has been investigated in combination with chemotherapy in early-phase trials and is currently being evaluated in combination with chemotherapy [26]. The DFS for Durvalumab was 70% at 12 months with combination vs. 60% for chemotherapy only [27]. The ORR was 40% [27]. Adverse events include fatigue (15%), rash (10%), and pneumonitis (5%) [27].

Emerging Treatments for MSI-H Colon Cancer

LAG-3 Inhibitors

There are several emerging treatments for MSI-H Colon cancer that are under investigation. Lymphocyte activation gene 3 (*LAG-3*) is an immune checkpoint receptor that negatively regulates T cell activity. *LAG-3* is expressed in activated T cells, regulatory T cells (Tregs), and natural killer (NK) cells. It binds to major histocompatibility complex (*MHC*) class I molecules, exerting a negative regulatory effect by inhibiting T-cell proliferation, cytokine secretion, and immune activation [19]. This suppression helps maintain immune homeostasis but is co-opted by tumor cells to evade immune surveillance. Dual blockade of *LAG-3* and *PD-1* has shown synergistic effects, as these checkpoints function through non-overlapping pathways to inhibit T-cell activity.

Tumors with MSI-H often exhibit high levels of immune cell infiltration, including T cells, making them prime

Table 1. Comparative summary of cancer therapies: efficacy, survival, and adverse events.

Therapy	Drug class	Experimental arm	DFS/PFS	OS	ORR	Grade 3/4 AEs	Most common AEs
FOLFOX	Chemotherapy	FOLFOX vs. no chemotherapy	12–15 vs. Not available	35–40 vs. Not available	~35	30	Neuropathy, neutropenia, diarrhea
Capecitabine	Chemotherapy	Capecitabine vs. no chemotherapy	11–13 vs. Not available	Not available	~30	20	Hand-foot syndrome, diarrhea, fatigue
Pembrolizumab	<i>PD-1</i> Inhibitor	Pembrolizumab vs. chemotherapy	18.2 vs. 12.4	Not reached	55	12	Fatigue, colitis, diarrhea
Nivolumab	<i>PD-1</i> Inhibitor	Nivolumab + ipilimumab vs. chemo	20.1 vs. 14.6	24.3 vs. 18.5	60	20	Diarrhea, hepatitis, rash
Atezolizumab	<i>PD-1</i> Inhibitor	Atezolizumab vs. chemotherapy	16.3 vs. 9.8	30.2 vs. 22.8	50	18	Infusion reactions, hypothyroidism
Durvalumab	<i>PD-1</i> Inhibitor	Durvalumab + chemotherapy vs. chemotherapy alone	15.8 vs. 11.0	Not reported	40	15	Fatigue, rash, pneumonitis
<i>LAG-3</i> Inhibitors	Emerging Therapy	<i>LAG-3</i> inhibitor + <i>PD-1</i> inhibitor	Not reported	Not reported	40–50	20–25	Rash, fatigue
<i>TIGIT</i> Inhibitors	Emerging Therapy	<i>TIGIT</i> inhibitor + <i>PD-L1</i> inhibitor	Not reported	Not reported	30–50	15–20	Immune-related adverse events

DFS, disease-free survival (months); PFS, progression-free survival (months); OS, overall survival (months); ORR, overall response rate (percentage); AEs, adverse events; FOLFOX, folinic acid + fluorouracil + oxaliplatin; *PD-1*, programmed cell death protein 1; *LAG-3*, lymphocyte activation gene 3; *TIGIT*, T-cell immunoreceptor with immunoglobulin and Immunoreceptor Tyrosine-based Inhibitory Motif domains; *PD-L1*, programmed death-ligand 1.

candidates for immune-based therapies [28]. However, tumors can evade immune responses through the upregulation of multiple checkpoint receptors, including *LAG-3*. Targeting *LAG-3* can help overcome this immune suppression and enhance the effectiveness of *PD-1* inhibitors like pembrolizumab (Keytruda) [28]. *LAG-3* Inhibitors work by targeting *LAG-3* to enhance T-cell activity [29].

Preliminary studies indicate an ORR of 40–50% in combination with *PD-1* inhibitors [8]. One promising *LAG-3* inhibitor, favezelimab, is a monoclonal antibody that blocks the interaction between *LAG-3* and its ligand, *MHC* Class I molecules, which is crucial for down-regulating T cell responses. In combination with *PD-1* inhibitors, favezelimab has shown encouraging results in clinical trials. For example, in patients with MSI-H CRC who had failed prior treatments, this combination was associated with a 6.3% tumor response rate, with median progression-free survival of 2.1 months and overall survival of 8.3 months [30]. The combination therapy worked particularly well in patients with high *PD-L1* expression [30]. Relatlimab, a *LAG-3* inhibitor, combined with nivolumab, showed promise in a Phase 2/3 trial (RELATIVITY-047) for advanced melanoma. The combination demonstrated a 25% reduction in risk of disease progression compared to nivolumab alone, with manageable toxicity profiles [31].

As with other immune checkpoint inhibitors, *LAG-3* inhibitors can trigger immune-related adverse events where the immune system attacks normal tissues. In clinical tri-

als, the most common side effects observed with favezelimab, both alone and in combination with pembrolizumab, were fatigue, nausea, and mild to moderate gastrointestinal symptoms [30]. Serious adverse events occurred in 20% of patients receiving the combination therapy, which is consistent with other immunotherapies [30].

TIGIT Inhibitors

TIGIT inhibitors are emerging as a promising therapeutic approach for cancers, including MSI-H colorectal cancer. *TIGIT* is an inhibitory checkpoint receptor that can dampen immune responses by binding to its ligand, the poliovirus receptor (*PVR*), which is expressed in tumor cells [32]. *TIGIT* is expressed on T cells and NK cells and competes with the costimulatory receptor CD226 for binding to CD112 and CD155 on antigen-presenting cells and tumor cells. When *TIGIT* binds these ligands, it transmits inhibitory signals that dampen T-cell and NK cell function [33]. *TIGIT* also promotes immune tolerance by enhancing Treg function, which is particularly advantageous to tumors. By blocking *TIGIT*, these inhibitors aim to enhance T-cell activation and improve anti-tumor immunity.

Initial trials of *TIGIT* inhibitors in combination with *PD-1* inhibitors, such as tiragolumab (anti-*TIGIT*) and atezolizumab (anti-*PD-L1*), have demonstrated encouraging results [32]. In patients with advanced MSI-H colorectal cancer, the combination has shown potential in overcoming resistance mechanisms, leading to higher response rates

compared to monotherapies. For example, early-phase trials have indicated ORRs of 30–50% in MSI-H tumors [32]. Emerging evidence suggests improved DFS when combined with *PD-L1* inhibitors [29]. However, while these results are promising, the exact benefit of *TIGIT* inhibition in MSI-H colon cancer is still under investigation. The combination therapy seems most effective when used in patients who are not fully responsive to traditional *PD-1/PD-L1* inhibitors, offering a possible route to improving outcomes in this group [34]. Tiragolumab, a *TIGIT* inhibitor, in combination with atezolizumab (*PD-L1* inhibitor), exhibited promising Phase 2 results in non-small cell lung cancer (NSCLC). The combination improved PFS and overall response rates (ORR) compared to atezolizumab monotherapy, although ongoing trials are needed to confirm efficacy [33]. In the *PD-1/PD-L1* pathway, these inhibitors unleash T-cell activity by blocking interactions that suppress T-cell responses in the tumor microenvironment. While highly effective, a significant subset of patients exhibits primary or acquired resistance to *PD-1/PD-L1* blockade. However, regarding *LAG-3* and *TIGIT*, these checkpoints modulate T-cell function through distinct and often complementary pathways, unlike the *PD-1/PD-L1* therapies. Dual checkpoint blockade strategies (e.g., *PD-1 + LAG-3* or *PD-L1 + TIGIT*) could enhance efficacy by addressing multiple mechanisms of immune evasion simultaneously.

Table 1 highlights the progression from chemotherapy to established immune checkpoint inhibitors and emerging therapies, showcasing their efficacy, safety profiles, and potential to address resistance mechanisms in cancer treatment.

Clinical trials, such as the landmark KEYNOTE-177 study, demonstrated that pembrolizumab, a *PD-1* inhibitor, significantly improved progression-free survival compared to standard chemotherapy in metastatic MSI-H colon cancer [21]. Additionally, adjuvant use of ICIs is being explored in resected, high-risk MSI-H colon cancer, leveraging the hypermutated tumor environment to sustain durable immune responses [35]. These findings have catalyzed a shift toward personalized treatment strategies, aiming to optimize outcomes for patients with MSI-H colon cancer by integrating immunotherapy into the adjuvant setting.

Other agents have gained favor as well. The CHECKMATE trials have shown the efficacy of Nivo as a single agent and Nivo + ipo as well. Phase 2 trials have shown an ORR that is higher than the existing chemotherapy with durable results [8]. The preliminary results of the Phase 3 trials also show the Median *PFS* and *OS* showing a statistically significant benefit from the standard chemotherapy [25]. Although not FDA-approved for use in MSI-H colorectal cancer, Atezolizumab and Durvalumab have also had promising preliminary results that show some efficacy in treatment.

While adjuvant immunotherapy does appear to show promising levels of efficacy in the treatment of MSI-H col-

orectal cancer, several challenges remain. Some of these include the identification of biomarkers predictive of response, management of immune-related adverse events, and the high cost of therapy, which may limit accessibility [17]. Furthermore, the use of adjuvant immunotherapy in non-metastatic and surgically resected MSI-H colon cancer remains under evaluation, with growing evidence from both clinical practice and trials indicating its potential role.

Conclusion

This literature review seeks to explain current trends with regard to adjuvant immunotherapy in the treatment of MSI-H colon cancer treatment and explores the efficacy of these treatments. The most popular immunotherapies in MSI-H colon cancer treatment were determined from the literature, their mechanism of action was explained and the data from their clinical trials was extracted, analyzed, and reported. As this avenue of treatment becomes more popular, this literature review will become important as a source to evaluate the efficacy of these treatments so that clinicians can determine if the utilization of these immunotherapies is efficacious in their specific patient encounters and at larger populations as well.

Author Contributions

VK: Developed the initial idea and hypothesis for the research, designed the study objectives and overall approach, and conducted most of the methodology, data collection, data analysis, and interpretation. VK also prepared the table, wrote the first draft, critically reviewed and edited the manuscript multiple times, and handled the majority of the project administration responsibilities. SN: Contributed to data collection, data analysis, and interpretation. Additionally, SN assisted with drafting sections of the manuscript and contributed to its critical review and editing. SD: Did formal analysis and validation, also provided supervision for the project, critically reviewed and edited the manuscript, and secured the journal for the paper submission. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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