


# Colorectal Cancer: Insights Into Biomarkers, Therapeutic Agents, And Monoclonal Antibodies

Kritika Saini <sup>1</sup> , Sushmita Uniyal <sup>1,\*</sup> 

<sup>1</sup> Department of Pharmacology, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun-248001, Uttarakhand, India; [sainikittu13@gmail.com](mailto:sainikittu13@gmail.com) (K.S.); [sushmitauniyal@sgrru.ac.in](mailto:sushmitauniyal@sgrru.ac.in) (S.U.);

\* Correspondence: [sushmitauniyal@sgrru.ac.in](mailto:sushmitauniyal@sgrru.ac.in);

Received: 27.04.2024; Accepted: 10.01.2025; Published: 25.11.2025

**Abstract:** Colorectal cancer (CRC) requires a multifaceted strategy for optimal care because it continues to be a worldwide health concern. An extensive summary of the roles of monoclonal antibodies, conventional medications, and biomarkers in diagnosing and treating CRC is presented herein. The methodology used for this review included searching articles indexed in PubMed, Google Scholar, Wiley, and Scopus. Biomarkers are crucial for CRC because they aid in early identification, prognosis, and treatment selection. With targeted and immunotherapeutic techniques, monoclonal antibodies (mAbs) are a paradigm change in the treatment of CRC. Integrating biomarkers, traditional medications, and monoclonal antibodies, healthcare providers can tailor treatment plans to individual patients, enhancing both the precision and effectiveness of therapy. Biomarkers help identify specific tumor characteristics, guiding the selection of appropriate medications, including traditional chemotherapy and targeted therapies like monoclonal antibodies. This combination approach can optimize treatment outcomes by leveraging the latest advancements in personalized medicine and immunotherapy, ultimately improving patient care and prognosis.

**Keywords:** colorectal cancer; monoclonal antibodies; biomarkers; therapeutic agents.

© 2025 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The authors retain copyright of their work, and no permission is required from the authors or the publisher to reuse or distribute this article, as long as proper attribution is given to the original source.

## 1. Introduction

Colorectal carcinogenesis is gaining increased recognition due to its widespread occurrence and profound personal impact. Various genetic abnormalities have been identified in colorectal malignancies, with distinct patterns observed between different regions of the colon. Notably, distal colon cancer often exhibits specific chromosomal instability (CIN), while proximal colon cancer is frequently associated with microsatellite instability (MSI). This understanding of the genetic landscape informs both diagnosis and treatment strategies, facilitating more targeted and effective approaches to managing colorectal cancer (CRC) [1]. The distinct characteristics of rectal cancer growth may be attributed to distinct embryological development and physiological conditions. Environmental factors like diet and alcohol intake also play a role in tumor development. Survival rates are higher when excluding rectal cancers, emphasizing the different segments of CRC [1,2]. The colon and rectum make up the last section of the human digestive tract. It measures approximately one yard in length and begins at the ileocecal valve, which signifies the end of the small intestine, and concludes at the anus [3].

### *1.1. Epidemiology*

One to two million new instances of CRC are identified each year, making it one of the most prevalent diseases in the world. With 700,000 cancer-related fatalities a year, CRC ranks third overall in terms of cancer incidence and is the fourth leading cause of cancer-related mortality [4].

In affluent nations, CRC primarily affects the elderly population, while its occurrence among younger people is on the rise despite the disease's general decline. On the other hand, in India, a nation with low rates of CRC, the incidence is on the rise across all age categories, even the younger ones. The review of the literature shows a higher proportion of patients under 40 years old with colon cancer in industrialized nations. However, there has been no significant change in this proportion from 2014 to 2021. This age group (less than 40) accounts for nearly three out of four cases, underscoring the need for early detection and appropriate treatment. The survival rate depends on the stage of disease, with about 92% for stage I and nearly 10% for stage IV [5-9].

### *1.2. Prevalence of colorectal cancer*

After China and the United States of America, India came in third. According to GLOBOCAN's prediction, India's cancer case count is predicted to increase to 2.08 million, representing a 57.5 percent increase from 2020 to 2040. Reported colon cancer cases in India were 21595 in 2022 [10,11].

### *1.3. Gender differentiation*

A retrospective cohort study of 3314 CRC patients (including 1999 men and 1315 women) found that age at diagnosis did not differ substantially between men and women. Males were more likely to be diagnosed than females during check-ups (48.9% males and 42.0% women,  $p < .001$ ). The sex differences in CRC among both sexes can be due to biological and behavioral variations [12].

### *1.4. Causes of CRC*

CRC stems from genetic, environmental, and lifestyle factors. Genetic mutations, whether inherited (like in familial adenomatous polyposis or Lynch syndrome) or acquired, disrupt normal cell growth, leading to cancer [13]. Dietary elements, including elevated red meat consumption and diminished fiber intake, coupled with lifestyle practices such as smoking and inactivity, augment the risk of CRC. Chronic inflammation in illnesses such as ulcerative colitis and Crohn's disease increases risk. Comprehending these aspects is essential for the prevention and management of CRC [14,15].

### *1.5. Diagnosis of CRC by location.*

37% of tumor localizations occur in the rectum, while less prevalent sites include the hepatic angle (4%), splenic angle (2%), cecum (8%), ascending colon (9%), descending colon (5%), transverse colon (4%), and sigmoidal tumors (31%). About 65% of colon cancers are distal to the splenic angle and readily identifiable with sigmoidoscopy, whereas 35% of colon cancers are proximal to the sigmoid and remain undiagnosed by flex sigmoidoscopy. Elevated

blood levels of carcinoembryonic antigen (CEA) are associated with a recurrence of the illness in 60–70% of cases; this is assumed to be a poor prognostic factor [16,17].

### *1.6. Risk factors associated with CRC.*

Multiple factors have been associated with the onset of CRC. Research has demonstrated that those with a history of cancer, colon polyps, inflammatory bowel diseases, diabetes mellitus, or cholecystectomy, as well as those with familial connections to such ailments, have an increased risk of getting CRC. Moreover, lifestyle factors significantly influence development [18]. According to studies, unhealthy eating habits (a diet heavy in red and processed meat and low in fruits, vegetables, fiber, calcium, and nutritious foods), alcohol use, cigarette smoking, being overweight, and physical inactivity all raise the risk of CRC [19]. In addition, the risk of CRC is known to be influenced by the gut microbiome, age, gender, race, and socioeconomic status [20,21].

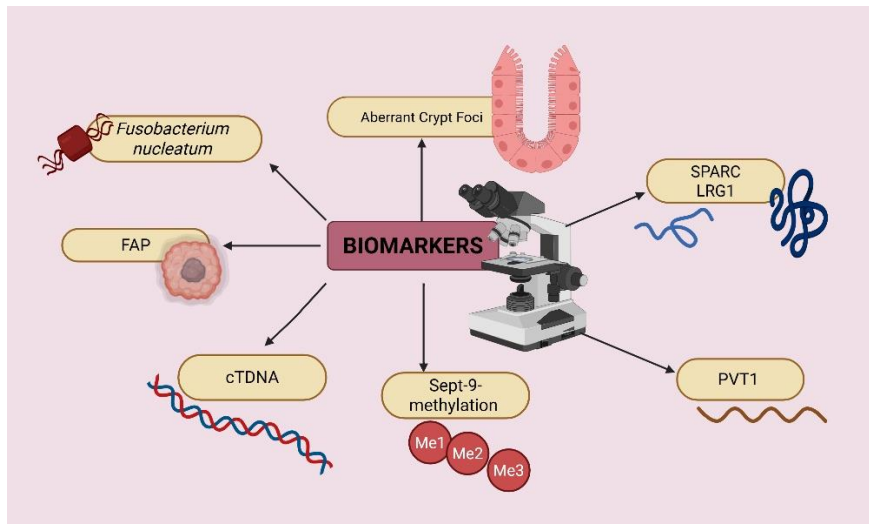
## **2. Screening of CRC**

In theory, removing premalignant colon adenomas could prevent the majority of colon malignancies. Similarly, early colon cancer detection, when the disease is treatable with surgical excision, is anticipated to yield significant benefits. These characteristics have led to recommendations for mass screening, which start earlier for those at higher risk due to family history or other predisposing factors, and around age 50 for the adult population at average risk [22]. The available screening modalities include sigmoidoscopy, colonoscopy, and occult blood testing. The sigmoidoscopy and colonoscopy have varying sensitivities for detecting cancer (15–30%, 60%, and 90%, respectively). The costs of the operation and post-anesthesia recovery for both the pre-test and post-test have limited the widespread adoption of colonoscopic screening. Recently, the detection of colon cancer-specific mutated DNA in the faces of colon cancer patients has paved the path for the advancement of molecularly based screening [3,23].

### *2.1. Biomarkers to identify colon cancer*

Indicators of pathogenic processes, normal biological processes, or reactions to an exposure or intervention are commonly referred to as biomarkers. These measurable traits can take various forms, derived from molecular, histologic, radiographic, or physiologic data. Traditional screening methods such as colonoscopy, fecal occult blood tests, and imaging techniques have been effective but may have limitations, including invasiveness, cost, and patient discomfort. In recent years, there has been growing interest in identifying biomarkers for colon cancer detection, prognosis, and treatment response. Biomarkers are measurable indicators of biological processes, disease states, or treatment effects within the body [22,24]. They can be found in various bodily fluids, such as blood, urine, and stool, as well as in tissue samples. Biomarker-based approaches offer the potential for non-invasive, cost-effective, and precise detection methods, facilitating early diagnosis and personalized treatment strategies for colon cancer patients [25]. Progress in molecular subtypes of colon cancer, DNA methylation, and microRNA biogenesis has led to the identification of novel colorectal biomarkers that may facilitate early diagnosis, tailored treatment selection, and CRC prognosis [26]. CRC, a slow-developing cancer, can be detected early through regular health examinations. Colonoscopy

improves detection but is expensive and inconvenient. Novel non-invasive biomarkers are needed to detect CRC early. Advances in genomics and proteomics could lead to the discovery of biomarkers useful for CRC [27]. This review aims to provide an overview of the current landscape of biomarkers used to identify colon cancer. The types of biomarkers being investigated, their potential utility in clinical practice, and the challenges associated with their implementation are discussed in Figure 1. An overview of recent advancements in biomarker research and their implications for improving the management of colon cancer is also provided.



**Figure 1.** Different biomarkers used to identify colorectal cancer: SPARC – Secreted Protein Acidic and Rich in Cysteine, LRG1 – Leucine Rich alpha-2 Glycoprotein, FAP- Fibroblast Activating Protein, PVT1- Plasmacytoma Variant Translocation, ctDNA- Circulating Tumor DNA.

Table 1 outlines various biomarkers utilized in the identification and assessment of CRC. These biomarkers include SPARC and LRG1, which are found in serum-derived extracellular vesicles and are associated with CRC metastasis. Aberrant Crypt Foci (ACF) show promise as early indicators of CRC, sharing molecular defects with colon tumors. *Fusobacterium nucleatum*, abundantly found in CRC patients' stool samples, plays a role in tumor development. Fibroblast Activation Protein (FAP) in CRC stroma is linked to angiogenesis and poor prognosis. PVT1, a lncRNA near the oncogene C-MYC, influences cancer development and prognosis. Circulating tumor DNA (ctDNA) assays targeting SEPT9 methylation offer non-invasive CRC screening. Lastly, the SEPT9 methylated DNA assay is a blood marker showing promise for early-stage CRC detection. These biomarkers have the potential to improve CRC diagnosis, prognosis, and treatment strategies.

**Table 1.** Biomarkers are used to identify colorectal cancer.

Biomarkers	Inference	Ref.
<b>SPARC</b> (Secreted Protein Acidic and Rich in Cysteine) <b>LRG1</b> (Leucine Rich alpha-2-Glycoprotein)	Serum-derived extracellular vesicles (EVs) from right-sided colon cancer (RCC) exhibit distinct protein profiles compared to those from left-sided colon cancer (LCC). Specifically, EVs from RCC patients may promote metastasis through the upregulation of extracellular matrix (ECM)-related proteins, notably SPARC and LRG1.	[28-30]
<b>Aberrant Crypt Foci</b>	Experimental evidence strongly supports the hypothesis that aberrant crypt foci (ACF) are relevant biomarkers for colon cancer. ACF exhibits histological similarities to colon adenomas and adenocarcinomas. However, evidence for ACF in people is more subjective, considering the limited ability to monitor their growth and alterations throughout the progression of cancer. The advent of cancer stem cells holds the potential to replicate ACF formation from single stem cells, possibly enabling monitoring of their growth as they form tumors.	[31-33]
<i>Fusobacterium nucleatum</i>	<i>Fusobacterium nucleatum</i> is found abundantly in stool samples of individuals with adenomas and CRC and is linked to CRC development. It promotes inflammation, modulates immune response, alters the gut microbiome, and directly interacts with tumor cells, fostering tumor growth and progression. This suggests its potential as a diagnostic or therapeutic target for CRC.	[34,35]
<b>FAP</b> (Fibroblast Activating Protein)	In CRC, high levels of Fibroblast Activation Protein (FAP) in the tumor stroma stimulate the growth of new blood vessels (angiogenesis), promoting tumor progression. Additionally, FAP overexpression leads to the breakdown of collagen in the stroma, increasing the risk of metastasis and disease recurrence. It also weakens the immune system in the CRC microenvironment, contributing to poor prognosis and overall survival for patients. Therefore, FAP serves as a key factor in CRC aggressiveness and may be a potential therapeutic target.	[36,37]
<b>PVT1-Plasmacytoma Variant Translocation 1</b>	PVT1, located near the oncogene C-MYC on chromosome 8q24.21, influences cancer development through transcriptional regulation by p53, acting as a border element for tumor-suppressor DNA, impacting cell development and proliferation, promoting chemoresistance, and contributing to carcinogenesis. Elevated PVT1 expression correlates with decreased overall survival in cancer patients, indicating its potential as a prognostic marker. Overall, targeting PVT1 may offer therapeutic potential in cancer treatment.	[36,38]
<b>ctDNA- Circulating tumor DNA</b>	Blood-based ctDNA assays, particularly those targeting SEPT9 methylation, show promise for CRC screening and diagnosis. However, to improve their sensitivity and specificity, larger sample sizes are needed for robust statistical analysis. This allows for a better assessment of the assay's performance across different patient demographics and disease stages, as well as addressing potential sources of variability. Overall, optimizing ctDNA assays could offer non-invasive and accurate CRC detection methods.	[39-41]
<b>Sept 9 Methylation</b>	The SEPT9 methylated DNA assay is a prominent blood marker used for CRC detection. It detects methylation of the SEPT9 promoter region in tumor-derived DNA found in plasma. This method has shown detection rates ranging from 57% to 64% in individuals with CRC stages 0–I. Methylation of SEPT9 is hypothesized to be a specific biomarker for early-stage CRC. The SEPT9 methylated DNA assay provides a non-invasive means of detecting CRC, particularly in its early stages, by analyzing blood samples.	[39,42,43]

### 3. Therapeutic Agents Used in Colorectal Cancer Treatment

#### 3.1. Oxaliplatin.

Oxaliplatin (L-OHP) has significant therapeutic importance in colon cancer treatment due to its broad-spectrum activity across various cancer cell lines and its lack of cross-resistance with other platinum-based drugs, such as cisplatin. The antiproliferative efficacy of oxaliplatin is enhanced when used in combination with 5-Fluorouracil (5-FU), thereby improving the chemotherapy regimen [44]. Clinical data show that oxaliplatin is effective and well-tolerated when used alone or with folinic acid and 5-FU in the treatment of metastatic colorectal cancer (mCRC). Despite the possibility of peripheral sensory neuropathy, oxaliplatin has a generally good safety profile with tolerable side effects. Its significance as an important

component of current treatment approaches for mCRC is highlighted by its capacity to overcome resistance and offer significant therapeutic advantages [44,45].

### 3.2. Irinotecan.

Irinotecan hydrochloride is a topoisomerase I inhibitor used to treat multiple cancer types, including mCRC. It is a prodrug that is converted to its active metabolite (SN-38) in the body by carboxylesterases. In clinical settings, irinotecan significantly improves survival, particularly when combined with targeted therapy and other chemotherapeutic agents such as oxaliplatin [46]. Despite its efficacy, irinotecan has the potential to cause serious toxicity, which can occasionally lead to treatment failure. Due to a complex interplay of genetic, environmental, and physiological factors, systemic exposure to SN-38 varies. However, because of its ability to prolong life, especially when combined with 5-FU, oxaliplatin, and targeted therapies, irinotecan is crucial in cancer therapy. Although irinotecan is predominantly excreted via the liver, patients with significant renal impairment and UGT1A1 polymorphisms may require dose modifications to reduce the risk of side effects. In conclusion, irinotecan's adaptability and effectiveness make it a fundamental therapeutic agent in oncology, notwithstanding the need for careful monitoring and dosage adjustments to enhance therapeutic outcomes and reduce toxicity [46,47].

### 3.3. Capecitabine.

Capecitabine, a prodrug of 5-FU extensively studied in CRC treatment, was initially granted FDA approval for adjuvant therapy in stage III disease. However, the most comprehensive data on the drug comes from the metastatic setting. Despite increasing off-label use, particularly in adjuvant and neoadjuvant settings pending ongoing clinical investigations, the efficacy of capecitabine in mCRC is well established [39,48]. Clinical findings demonstrate that capecitabine, administered alone or in combination with oxaliplatin, is comparable to 5-FU, a traditional chemotherapy medication for CRC. This suggests that capecitabine is as effective as traditional chemotherapy regimens for treating mCRC, providing a viable alternative. Posing convenience as an oral medication and a favorable side-effect profile further enhance its attractiveness in clinical practice. Therefore, capecitabine's versatility and efficacy make it a valuable option in the management of mCRC [49].

### 3.4. Oral fluoropyrimidine UFT (Tegafur-uracil) and leucovorin.

Phase II studies have demonstrated the efficacy and tolerability of combining UFT (a prodrug of 5-FU and LV (leucovorin) in the initial treatment of mCRC. Furthermore, two phase III studies have shown comparable effectiveness and improved acceptability of UFT with LV compared to intravenous bolus 5-FU, a standard chemotherapy regimen for mCRC [50]. Importantly, UFT with LV has been associated with low rates of hand-foot syndrome (HFS), a common side effect of chemotherapy. Indirect comparisons between capecitabine, another oral fluoropyrimidine, and UFT suggest similar survival rates. In both first- and second-line therapies for individuals with mCRC, this data indicates that UFT is a suitable substitute for intravenous 5-FU. Its efficacy, tolerability, and lower HFS incidence make UFT with LV an attractive option for managing mCRC, providing patients with an oral alternative to intravenous chemotherapy while maintaining comparable outcomes [51].

### 3.5. KP1339.

The ruthenium complex sodium trans-[tetrachloridobis(1H-indazole)-ruthenate (III)] (KP1339/IT-139) has demonstrated preclinical efficacy in various in vivo tumor models, including those predictive of colon cancer [52]. Clinical investigations have shown disease stabilization with minimal side effects. KP1339 induces cell death by disrupting endoplasmic reticulum (ER) homeostasis through its inhibition of GRP78. This disruption leads to immunogenic cell death (ICD), which is primarily dependent on the PERK/eIF2 $\alpha$  branch of the ER. ICD is significant as it triggers an immune response against cancer cells, strengthening long-lasting immunological effects. Metal-based chemotherapy agents like oxaliplatin also induce ICD. In a three-dimensional colon cancer spheroid model, KP1339 therapy induced an ICD signature characterized by increased mobility group release, ATP secretion, calreticulin exposure, and PERK/eIF2 $\alpha$  phosphorylation. This mechanism highlights the potential of KP1339 as an effective and immunogenic treatment for colon cancer, offering a promising avenue for further clinical exploration [53].

### 3.6. 5-Fluorouracil (standard drug).

5-FU is a cornerstone drug for various stages of CRC and is commonly used as an adjuvant drug after surgery, particularly in stage II colon cancer. Now, as a combination of three drugs: folinic acid (leucovorin), 5-FU, and oxaliplatin, named as FOLFOX, is administered as a standard regimen for advanced CRC [50, 55].

In mCRC, 5-FU is frequently used in combination with oxaliplatin or irinotecan, with specific regimens such as FOLFIRI tailored to each patient's needs. Depending on treatment regimen and patient characteristics, 5-FU can be administered as a bolus injection or a continuous infusion [56]. Despite its efficacy, 5-FU can cause adverse effects such as myelosuppression, nausea, vomiting, and diarrhea, which require close observation and control during the course of treatment [57].

## 4. Drugs that potentiate the effect of 5-FU on colon cancer

### 4.1. Chloroquine.

Chloroquine (CQ), which was first administered as an anti-malarial drug, has drawn interest due to its potential use in cancer treatment. It has demonstrated the ability to suppress cell growth and induce cell death in a variety of cancer types, including CRC. Findings from CRC studies have been encouraging when CQ is combined with the anti-cancer drug 5-FU. This combination enhances the inhibitory effects on CRC cell proliferation, primarily by inducing cell cycle arrest in the G0/G1 phase and promoting apoptosis. The downregulation of CDK2 and the overexpression of p21Cip1 and p27Kip1 enhance the efficacy of 5-FU when combined with CQ. CQ also enhances its anti-cancer effects by inhibiting the autophagy induced by 5-FU in CRC cells. Chloroquine is readily accessible for further research into CRC treatment plans, given its current therapeutic use in conditions such as rheumatoid arthritis and lupus erythematosus. Therefore, managing CRC with a combination therapy of chloroquine and 5-FU offers a potential strategy, as it could help patients in clinical settings [15].

#### 4.2. Acriflavine.

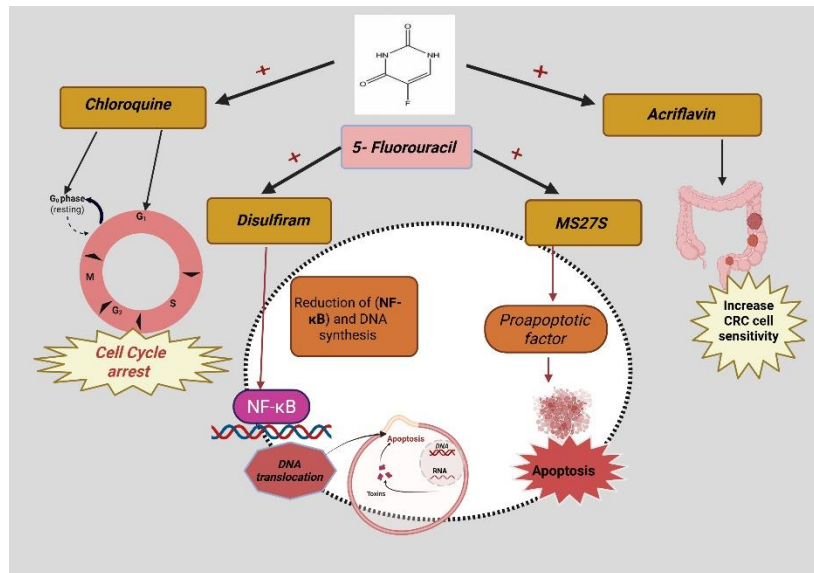
Acriflavine (Acf), composed of 3,6-diamino-10-methylacridinium chloride (tryptaflavin) and 3,6-diaminoacridine (proflavine), has been used in medicine for a long time. Recent research demonstrates that it has potential anticancer effects. Studies suggest it works effectively against a number of cancers, such as breast cancer, osteosarcoma, and hepatocellular carcinoma. Notably, Acf has shown inhibitory effects on hypoxia-inducible factors, which hinder tumor growth and progression, particularly in murine CRC models. Investigation into its combination with 5-FU revealed that simultaneous treatment with Acf did not affect CRC cells' resistance to 5-FU. However, pre-treatment with ACF significantly increased the sensitivity of CRC cells to the cytotoxic effects of 5-FU. Interestingly, ACF did not influence levels of topoisomerase 2 or HIF-1 $\alpha$  mRNA. A novel finding: pre-treatment with Acf, regardless of cell p53 status, significantly enhances the cytotoxicity of 5-FU in CRC cells. These findings suggest promising synergistic potential between Acf and 5-FU in the treatment of CRC, warranting further exploration and clinical investigation [58].

#### 4.3. Disulfiram.

Disulfiram (DS), a clinically utilized anti-alcohol medication, has exhibited a robust dose-dependent suppression of 5-FU-induced and constitutive NF- $\kappa$ B activity. Although it did not affect 5-FU-induced I $\kappa$ B $\alpha$  degradation, DS reduced NF- $\kappa$ B nuclear translocation and DNA-binding activity. When DS was combined with 5-FU, a synergistic increase in 5-FU cytotoxicity was observed in both cell lines. Furthermore, this combination has been shown to markedly increase the apoptotic effect of 5-FU on DLD-1 and RKOWT cell lines. In vitro studies have also demonstrated that DS effectively eradicated 5-FU chemoresistance in the H6305-FU cell line. Both 5-FU and DS independently exhibited the ability to induce apoptosis. The combination of these two medications demonstrated a remarkable enhancement in apoptotic impact. This suggests a promising synergistic potential between 5-FU and DS, providing a potential avenue to improve 5-FU efficacy and overcome chemoresistance in certain cell lines [59].

#### 4.4. MS275.

MS275, an HDAC inhibitor, has attracted attention for its potential to induce apoptosis, particularly in combination with 5-FU. Its proapoptotic effects vary depending on factors such as incubation duration, dosage, and the cell type involved. Notably, the intrinsic apoptotic pathway is activated, especially when MS275 is combined with 5-FU, possibly due to increased reactive oxygen species (ROS) generation. MS275 induces a significant increase in ROS formation at concentrations of 1 or 5  $\mu$ M, consistent with the notion that oxidative stress-induced mitochondrial dysfunction triggers apoptosis. This strongly suggests that MS275 enhances 5-FU cytotoxicity against CRC cells. The observed synergistic interaction between MS275 and 5-FU presents a promising strategy to augment the efficacy of 5-FU in the treatment of CRC, highlighting areas for further research and potential therapeutic use [60]. The mechanism of potentiating activity of 5-FU in different combinations when used to treat colon cancer is illustrated in Figure 2.



**Figure 2.** Illustration showing the mechanism of activity potentiation of 5-FU with various drug combinations.

## 5. Monoclonal antibody (mAb) therapy in cancer

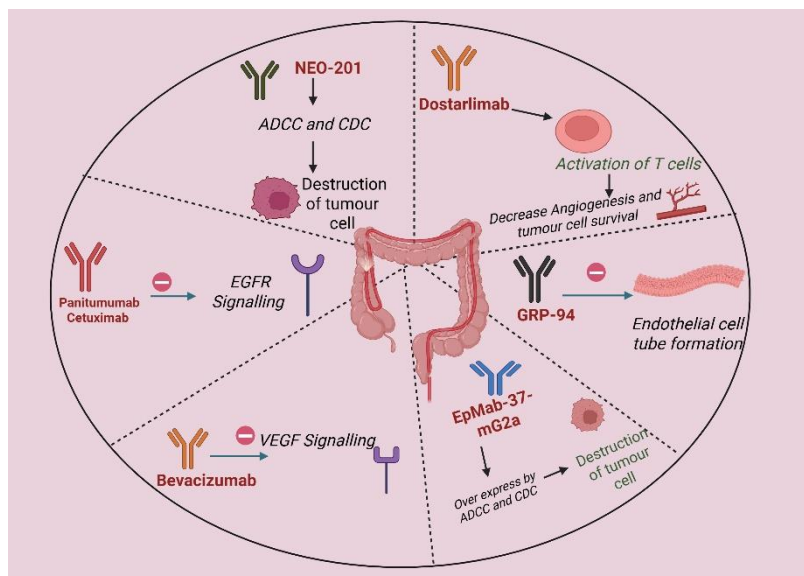
In cancer treatment, monoclonal antibody-based immunotherapy has become a crucial element that enhances more conventional approaches, including chemotherapy, radiation, and surgery. These antibodies have important therapeutic implications and different mechanisms of action [61]. Their capacity to target tumor cells precisely and promote the establishment of long-lasting immune responses against tumors is noteworthy. Owing to this attribute, antibodies block the major signaling pathway linked to the development of cancer or aid the immune system in eliminating tumor cells through processes such as complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). Furthermore, monoclonal antibodies can minimize systemic toxicity by serving as carriers that deliver radioisotopes or cytotoxic chemicals directly to cancer cells. Chimeric antigen receptor (CAR) T-cell therapy and immune checkpoint inhibitors are two novel cancer therapies that have transformed cancer care by leveraging the adaptability of antibodies as a therapeutic platform. These advances have the potential to improve outcomes and quality of life for patients with a variety of cancer types, as well as provide advanced or resistant cancer patients with additional therapeutic options. Monoclonal antibody-based immunotherapy is set to become increasingly important in the overall management of cancer as research continues to identify new targets and improve therapeutic approaches, ushering in a new era in oncology where accuracy and individualised treatment are crucial [62,63].

Monoclonal antibody-based adjuvant therapy has proven effective in the treatment of CRC, and ongoing international trials continue to refine and expand its utility. One notable advancement in this field is the emergence of new molecules, such as chimeric antibodies, which offer enhanced targeting capabilities while simultaneously reducing toxicity. Chimeric antibodies are engineered to combine specific regions from both human and non-human antibodies, optimizing their ability to bind to tumor cells with high affinity. By leveraging this increased targeting precision, chimeric antibodies can selectively recognize and neutralize cancer cells while minimizing off-target effects on healthy tissues. This targeted approach not only enhances the efficacy of adjuvant therapy but also mitigates the adverse side effects commonly associated with traditional chemotherapy or radiation. As a result, chimeric

antibodies represent a promising avenue for improving the safety and efficacy of adjuvant therapy in CRC patients, ultimately leading to better clinical outcomes and quality of life for those undergoing treatment [64].

5.1. Mechanism of monoclonal antibody

Monoclonal antibodies can be used to fight various diseases, including cancer, autoimmune disorders, and infectious diseases. They work in different ways, such as binding to antigens on cells or pathogens, blocking signaling pathways, activating the immune system, and inducing cell death. They can also be engineered to deliver cytotoxic drugs or radioisotopes to diseased cells while minimizing toxicity to healthy cells. These mechanisms demonstrate the versatility and effectiveness of monoclonal antibodies in providing personalized therapeutic interventions for patients with diverse diseases [65] (Figure 3).



**Figure 3.** Illustration showing mechanism of action of monoclonal antibodies in colon cancer treatment: EGFR-epidermal growth factor, VEGF -vascular endothelial growth factor, ADCC-antibody-dependent cell-mediated cytotoxicity, CDC- complement-dependent cytotoxicity.

Table 2 provides a comprehensive overview of antibodies utilized in the treatment of CRC, highlighting their targets, indications, and mechanisms of action. Bevacizumab, Panitumumab, and Cetuximab target VEGF and EGFR signaling pathways, respectively, to inhibit tumor growth. EpMab 37 mG2a f and NEO-201 target EpCAM overexpression and CEACAM-5/6, respectively, employing ADCC and CDC mechanisms to destroy tumor cells. GRP94 antibody inhibits tumor angiogenesis by targeting GRP94-mediated pathways. Dostarlimab, currently under clinical trial, activates T cells to combat CRC by reducing angiogenesis and tumor cell survival. These antibodies represent diverse therapeutic strategies, including targeting tumor-specific antigens, inhibiting signaling pathways, and modulating immune responses, underscoring their significance in CRC treatment and emphasizing the potential for improved patient outcomes.

**Table 2.** Different antibodies are used for CRC treatment, with their mechanism of action.

Antibody	Target	Mechanism of action	Reference
Bevacizumab (Avastin) Humanized IgG1	VEGF	Inhibition of VEGF signaling	[65,66]

Antibody	Target	Mechanism of action	Reference
Panitumumab (Vectibix) Human IgG2	EGFR	Inhibition of EGFR signaling	[63,66,67]
Cetuximab (Erbix) Chimeric murine/murine IgG1	EGFR	Inhibition of EGFR signaling	[65,66]
EpMab-37-mG2a-f (mouse IgG1, kappa)	EpCAM-overexpressing CHO-K1	EpCAM-overexpressing CHO-K1 antibody- dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)	[68,69]
NEO-201 IgG1 humanized	(CEACAM)-5 and CEACAM-6	antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and enhance immune tumor-killing	[68,70,71]
GRP94 Human-specific	GRP94-mediated tumor angiogenesis	Inhibit endothelial cell tube formation via concomitant downregulation of GRP-94.	[72-74]
Dostarlimab Under the Phase 2 clinical trial End of trial in 2025	T cells	Activation of T cells- decreased angiogenesis and tumor cell survival	[75]

## 6. Conclusions

In summary, tailored and effective methods to treat colorectal cancer have been enabled by the development of biomarkers, targeted drugs, and monoclonal antibodies. Tailored therapy is guided by key indicators such as KRAS and BRAF mutations, and treatment options are expanded to include regorafenib, oxaliplatin, irinotecan, capecitabine, and KP1339. Monoclonal antibodies are useful for stimulating the immune system or specifically attacking cancer cells. Despite obstacles such as resistance to therapy, research continues to identify additional biomarkers to improve outcomes. By combining these developments, customized treatment for colorectal cancer enters a new era, offering the promise of improved survival and quality of life. It is anticipated that more studies will reveal developments in the knowledge and management of this illness.

## Author Contributions

Conceptualization, K.S. and S.U.; methodology, K.S. and S.U.; resources, K.S. and S.U.; data curation, S.U.; writing—original draft preparation, K.S.; writing—review and editing, K.S. and S.U.; visualization, K.S.; supervision, S.U.; All authors have read and agreed to the published version of the manuscript.

## Institutional Review Board Statement

Not applicable.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

## Funding

This research received no external funding.

## Acknowledgments

The writers are grateful to Shri Guru Ram Rai University for the necessary data and literature access facilities to enable them to produce this review paper. The images and figures were created using BioRender.

## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Favoriti, P.; Carbone, G.; Greco, M.; Pirozzi, F.; Pirozzi, R.E.M.; Corcione, F. Worldwide burden of colorectal cancer: a review. *Updates Surg.* **2016**, *68*, 7–11, <https://doi.org/10.1007/s13304-016-0359-y>.
2. Li, F.Y.; Lai, M. De. Colorectal cancer, one entity or three. *J Zhejiang Univ Sci B.* **2009**, *10*, 219–29, <https://doi.org/10.1631/jzus.B0820273>.
3. Markowitz, S.D.; Dawson, D.M.; Willis, J.; Willson, J.K.V. Focus on colon cancer. *Cancer Cell* **2002**, *1*, 233–236, [https://doi.org/10.1016/s1535-6108\(02\)00053-3](https://doi.org/10.1016/s1535-6108(02)00053-3).
4. Mármol, I.; Sánchez-de-Diego, C.; Dieste, A.P.; Cerrada, E.; Yoldi, M.J.R. Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. *Int. J. Mol. Sci.* **2017**, *18*, 197, <https://doi.org/10.3390/ijms18010197>.
5. Yusoff, A.A.M.; Khair, S.Z.M.; Abdullah, W.S.W.; Abd Radzak, S.M.; Abdullah, J.M. Somatic mitochondrial DNA D-loop mutations in meningioma discovered: a preliminary data. *Journal of Cancer Research and Therapeutics.* **2020**, *16*, 1517–1521, [http://dx.doi.org/10.4103/jcrt.JCRT\\_1132\\_16](http://dx.doi.org/10.4103/jcrt.JCRT_1132_16).
6. Boyle, P.; Leon, M.E. Epidemiology of colorectal cancer. *Br Med Bull.* **2002**, *64*, 1-25, <https://doi.org/10.1093/bmb/64.1.1>.
7. Rawla, P.; Sunkara, T.; Barsouk, A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Przegląd gastroenterologiczny* **2019**, *14*, 89–103, <https://doi.org/10.5114/pg.2018.81072>.
8. Baidoun, F.; Elshiy, K.; Elkeraie, Y.; Merjaneh, Z.; Khoudari, G.; Sarmini, M.T.; Gad, M.; Al-Husseini, M.; Saad, A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr. Drug Targets* **2021**, *22*, 998-1009, <https://doi.org/10.2174/1389450121999201117115717>.
9. Ogunwobi, O.O.; Mahmood, F.; Akingboye, A. Biomarkers in Colorectal Cancer: Current Research and Future Prospects. *Int. J. Mol. Sci.* **2020**, *21*, 5311, <https://doi.org/10.3390/ijms21155311>.
10. Solowey, E.; Lichtenstein, M.; Sallon, S.; Paavilainen, H.; Solowey, E.; Lorberboum-Galski, H. Evaluating medicinal plants for anticancer activity. *Sci. World J.* **2014**, *2014*, 721402, <https://doi.org/10.1155/2014/721402>.
11. Wong, M.C.S.; Ding, H.; Wang, J.; Chan, P.S.F.; Huang, J. Prevalence and risk factors of colorectal cancer in Asia. *Intest Res.* **2019**, *17*, 317–29, <https://doi.org/10.5217/ir.2019.00021>.
12. Joo, H.J.; Lee, H.S.; Jang, B.I.; Kim, D.B.; Kim, J.H.; Park, J.J.; Kim, H.G.; Baek, I.H.; Lee, J.; Kim, B. Sex-specific differences in colorectal cancer: A multicenter retrospective cohort study. *Cancer reports (Hoboken, N.J.)* **2023**, *6*, e1845, <https://doi.org/10.1002/cnr2.1845>.
13. Ponz de Leon, M.; Roncucci, L. The cause of colorectal cancer. *Dig Liver Dis.* **2000**, *32*, 426–39, [https://doi.org/10.1016/s1590-8658\(00\)80265-0](https://doi.org/10.1016/s1590-8658(00)80265-0).
14. Bardelčíková, A.; Šoltys, J.; Mojžiš, J. Oxidative Stress, Inflammation and Colorectal Cancer: An Overview. *Antioxidants* **2023**, *12*, 901, <https://doi.org/10.3390/antiox12040901>.
15. Cappell, M.S. Pathophysiology, Clinical Presentation, and Management of Colon Cancer. *Gastroenterol Clin North Am.* **2008**, *37*, 1–24, <https://doi.org/10.1016/j.gtc.2007.12.002>.
16. Granados-Romero, J.J.; Valderrama-Treviño, A.I.; Contreras-Flores, E.H.; Barrera-Mera, B.; Herrera Enríquez, M.; Uriarte-Ruíz, K.; Ceballos-Villalba, J.C.; Estrada-Mata, A.G.; Alvarado Rodríguez, C.; Arauz-Peña, G. Colorectal cancer: a review. *Int. J. Res. Med. Sci.* **2017**, *5*, 4667-4676, <https://doi.org/10.18203/2320-6012.ijrms20174914>.
17. Świdarska, M.; Choromańska, B.; Dąbrowska, E.; Konarzewska-Duchnowska, E.; Choromańska, K.; Szczurko, G.; Myśliwiec, P.; Dadan, J.; Ładny, J.; Zwierz, K. The diagnostics of colorectal cancer. *Contemporary Oncology/Współczesna Onkologia* **2014**, *18*, 1-6, <https://doi.org/10.5114/wo.2013.39995>.

18. Rasool, S.; Kadla, S.A.; Rasool, V.; Ganai, B.A. A comparative overview of general risk factors associated with the incidence of colorectal cancer. *Tumor Biol.* **2013**, *34*, 2469–76, <https://doi.org/10.1007/s13277-013-0876-y>.
19. Hua, H.; Jiang, Q.; Sun, P.; Xu, X. Risk factors for early-onset colorectal cancer: systematic review and meta-analysis. *Front. Oncol.* **2023**, *13*, 1132306, <https://doi.org/10.3389/fonc.2023.1132306>.
20. Gausman, V.; Dornblaser, D.; Anand, S.; Hayes, R.B.; O’Connell, K.; Du, M.; Liang, P.S. Risk Factors Associated With Early-Onset Colorectal Cancer. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 2752-2759.e2, <https://doi.org/10.1016/j.cgh.2019.10.009>.
21. Sawicki, T.; Ruskowska, M.; Danielewicz, A.; Niedźwiedzka, E.; Arłukowicz, T.; Przybyłowicz, K.E. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. *Cancers* **2021**, *13*, 2025, <https://doi.org/10.3390/cancers13092025>.
22. Negrut, R.L.; Cote, A.; Maghiar, A.M. Exploring the Potential of Oral Microbiome Biomarkers for Colorectal Cancer Diagnosis and Prognosis: A Systematic Review. *Microorganisms* **2023**, *11*, 1586, <https://doi.org/10.3390/microorganisms11061586>.
23. Simon, K.; Balchen, V. Colorectal cancer development and advances in screening. *Clin Interv Aging.* **2016**, *11*, 967-976, <https://doi.org/10.2147/CIA.S109285>.
24. Alfano, C.; Farina, L.; Petti, M. Networks as Biomarkers: Uses and Purposes. *Genes* **2023**, *14*, 429, <https://doi.org/10.3390/genes14020429>.
25. Pellino, G.; Gallo, G.; Pallante, P.; Capasso, R.; De Stefano, A.; Maretto, I.; Malapelle, U.; Qiu, S.; Nikolaou, S.; Barina, A.; Clerico, G.; Reginelli, A.; Giuliani, A.; Sciaudone, G.; Kontovounisios, C.; Brunese, L.; Trompetto, M.; Selvaggi, F. Noninvasive Biomarkers of Colorectal Cancer: Role in Diagnosis and Personalised Treatment Perspectives. *Gastroenterology research and practice* **2018**, *2018*, 2397863, <https://doi.org/10.1155/2018/2397863>.
26. Yiu, A.J.; Yiu, C.Y. Biomarkers in Colorectal Cancer. *Anticancer Res.* **2016**, *36I*, 1093-1102, .
27. Tanaka, T.; Tanaka, M.; Tanaka, T.; Ishigamori, R. Biomarkers for Colorectal Cancer. *Int. J. Mol. Sci.* **2010**, *11*, 3209-3225, <https://doi.org/10.3390/ijms11093209>.
28. Zhong, M. E.; Chen, Y.; Xiao, Y.; Xu, L.; Zhang, G.; Lu, J.; Qiu, H.; Ge, W.; Wu, B. Serum extracellular vesicles contain SPARC and LRG1 as biomarkers of colon cancer and differ by tumour primary location. *EBioMedicine* **2019**, *50*, 211–223, <https://doi.org/10.1016/j.ebiom.2019.11.003>.
29. Kurtul, N.; Taşdemir, E.A.; Ünal, D.; İzmirlir, M; Eroglu, C. SPARC: As a prognostic biomarker in rectal cancer patients treated with chemo-radiotherapy. *Cancer biomarkers: section A of Disease markers* **2017**, *18*, 459–466, <https://doi.org/10.3233/CBM-161733>.
30. Drev, D.; Harpain, F.; Beer, A.; Stift, A.; Gruber, E.S.; Klimpfinger, M.; Thalhammer, S.; Reti, A.; Kenner, L.; Bergmann, M.; Marian, B. Impact of Fibroblast-Derived SPARC on Invasiveness of Colorectal Cancer Cells. *Cancers* **2019**, *11*, 1421, <https://doi.org/10.3390/cancers11101421>.
31. Wargovich, M.J.; Brown, V.R.; Morris, J. Aberrant crypt foci: the case for inclusion as a biomarker for colon cancer. *Cancers* **2010**, *2*, 1705–1716, <https://doi.org/10.3390/cancers2031705>.
32. Clapper, M.L.; Chang, W.-C.L.; Cooper, H.S. Dysplastic Aberrant Crypt Foci: Biomarkers of Early Colorectal Neoplasia and Response to Preventive Intervention. *Cancer Prev. Res.* **2020**, *13*, 229–240, <https://doi.org/10.1158/1940-6207.CAPR-19-0316>.
33. Bird, R.P.; Good, C. K. The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Toxicology letters* **2000**, *112-113*, 395–402, [https://doi.org/10.1016/s0378-4274\(99\)00261-1](https://doi.org/10.1016/s0378-4274(99)00261-1).
34. Keenan, J.I.; Frizelle, F.A. Biomarkers to Detect Early-Stage Colorectal Cancer. *Biomedicines* **2022**, *10*, 255, <https://doi.org/10.3390/biomedicines10020255>.
35. Wang, N.; Fang, J. Y. *Fusobacterium nucleatum*, a key pathogenic factor and microbial biomarker for colorectal cancer. *Trends in microbiology* **2023**, *31*, 159–172, <https://doi.org/10.1016/j.tim.2022.08.010>.
36. Kalaei, Z.; Manafi-Farid, R.; Rashidi, B.; Kiani, F.K.; Zarei, A.; Fathi, M.; Jadidi-Niaragh, F. The Prognostic and therapeutic value and clinical implications of fibroblast activation protein- $\alpha$  as a novel biomarker in colorectal cancer. *Cell communication and signaling: CCS* **2023**, *21*, 139, <https://doi.org/10.1186/s12964-023-01151-y>.
37. Coto-Llerena, M.; Ercan, C.; Kancherla, V.; Taha-Mehlitz, S.; Eppenberger-Castori, S.; Soysal, S.D.; Ng, C.K.Y.; Bolli, M.; von Flüe, M.; Nicolas, G.P.; Terracciano, L.M.; Fani, M.; Piscuoglio, S. High Expression of FAP in Colorectal Cancer Is Associated With Angiogenesis and Immunoregulation Processes. *Frontiers in oncology* **2020**, *10*, 979, <https://doi.org/10.3389/fonc.2020.00979>.

38. Fan, H.; Zhu, J.H.; Yao, X.Q. Long non-coding RNA PVT1 as a novel potential biomarker for predicting the prognosis of colorectal cancer. *The International journal of biological markers* **2018**, *33*, 415–422, <https://doi.org/10.1177/1724600818777242>.
39. Min, L.; Chen, J.; Yu, M.; Liu, D. Using Circulating Tumor DNA as a Novel Biomarker to Screen and Diagnose Colorectal Cancer: A Meta-Analysis. *Journal of clinical medicine* **2023**, *12*, 408, <https://doi.org/10.3390/jcm12020408>.
40. Khakoo, S.; Georgiou, A.; Gerlinger, M.; Cunningham, D.; Starling, N. Circulating tumour DNA, a promising biomarker for the management of colorectal cancer. *Critical reviews in oncology/hematology* **2018**, *122*, 72–82, <https://doi.org/10.1016/j.critrevonc.2017.12.002>.
41. Tie, J.; Kinde, I.; Wang, Y.; Wong, H.L.; Roebert, J.; Christie, M.; Tacey, M.; Wong, R.; Singh, M.; Karapetis, C.S.; Desai, J.; Tran, B.; Strausberg, R.L.; Diaz, L.A.; Jr, Papadopoulos, N.; Kinzler, K.W.; Vogelstein, B.; Gibbs, P. Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer. *Annals of oncology: official journal of the European Society for Medical Oncology* **2015**, *26*, 1715–1722, <https://doi.org/10.1093/annonc/mdv177>.
42. Ma, Z.; Williams, M.; Cheng, Y.Y.; Leung, W.K. Roles of Methylated DNA Biomarkers in Patients with Colorectal Cancer. *Disease markers* **2019**, *2019*, 2673543, <https://doi.org/10.1155/2019/2673543>.
43. Xie, L.; Jiang, X.; Li, Q.; Sun, Z.; Quan, W.; Duan, Y.; Li, D.; Chen, T. Diagnostic Value of Methylated *Septin9* for Colorectal Cancer Detection. *Frontiers in oncology* **2018**, *8*, 247, <https://doi.org/10.3389/fonc.2018.00247>.
44. Bleiberg, H. Oxaliplatin (L-OHP): a new reality in colorectal cancer. *British journal of cancer* **1998**, *77*, 1–3, <https://doi.org/10.1038/bjc.1998.427>.
45. Arango, D.; Wilson, A.J.; Shi, Q.; Corner, G.A.; Arañes, M.J.; Nicholas, C.; Lesser, M.; Mariadason, J.M.; Augenlicht, L.H. Molecular mechanisms of action and prediction of response to oxaliplatin in colorectal cancer cells. *British journal of cancer* **2004**, *91*, 1931–1946, <https://doi.org/10.1038/sj.bjc.6602215>.
46. Fujita, K.; Kubota, Y.; Ishida, H.; Sasaki, Y. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. *World J. Gastroenterol.* **2015**, *21*, 12234–12248, <https://doi.org/10.3748/wjg.v21.i43.12234>.
47. Jang, H.J.; Hong, E.M.; Jang, J.; Choi, J.E.; Park, S.W.; Byun, H.W.; Koh, D.H.; Choi, M.H.; Kae, S.H.; Lee, J. Synergistic Effects of Simvastatin and Irinotecan against Colon Cancer Cells with or without Irinotecan Resistance. *Gastroenterol. Res. Pract.* **2016**, *2016*, 7891374, <https://doi.org/10.1155/2016/7891374>.
48. Ge, C.; Huang, X.; Zhang, S.; Yuan, M.; Tan, Z.; Xu, C.; Jie, Q.; Zhang, J.; Zou, J.; Zhu, Y.; Feng, D.; Zhang, Y.; Aa, J. In vitro co-culture systems of hepatic and intestinal cells for cellular pharmacokinetic and pharmacodynamic studies of capecitabine against colorectal cancer. *Cancer Cell Int.* **2023**, *23*, 14, <https://doi.org/10.1186/s12935-023-02853-6>.
49. Hameed, H.; Cassidy, J. Use of capecitabine in management of early colon cancer. *Cancer management and research* **2011**, *3*, 295–299, <https://doi.org/10.2147/CMR.S12704>.
50. González-Barón, M.; Feliu, J.; de la Gándara, I.; Espinosa, E.; Colmenarejo, A.; Martínez-Martínez, B.; Blanco, E.; García-Girón, C.; Juárez, F.; Garrido, P. Efficacy of oral tegafur modulation by uracil and leucovorin in advanced colorectal cancer. A phase II study. *European journal of cancer (Oxford, England : 1990)* **1995**, *31A*, 2215–2219, [https://doi.org/10.1016/0959-8049\(95\)00487-4](https://doi.org/10.1016/0959-8049(95)00487-4).
51. Bennouna, J.; Saunders, M.; Douillard, J.Y. The role of UFT in metastatic colorectal cancer. *Oncology* **2009**, *76*, 301–310, <https://doi.org/10.1159/000209334>.
52. Schoenhacker-Alte, B.; Mohr, T.; Pirker, C.; Kryeziu, K.; Kuhn, P.S.; Buck, A.; Hofmann, T.; Gerner, C.; Hermann, G.; Koellensperger, G.; Keppler, B.K.; Berger, W.; Heffeter, P. Sensitivity towards the GRP78 inhibitor KP1339/IT-139 is characterized by apoptosis induction via caspase 8 upon disruption of ER homeostasis. *Cancer letters* **2017**, *404*, 79–88, <https://doi.org/10.1016/j.canlet.2017.07.009>.
53. Wernitznig, D.; Kiakos, K.; Del Favero, G.; Harrer, N.; Machat, H.; Osswald, A.; Jakupec, M.A.; Wernitznig, A.; Sommergruber, W.; Keppler, B.K. First-in-class ruthenium anticancer drug (KP1339/IT-139) induces an immunogenic cell death signature in colorectal spheroids in vitro. *Metallomics* **2019**, *11*, 1044–1048, <https://doi.org/10.1039/c9mt00051h>.
54. Sharma, S.; Saltz, L.B. Oral chemotherapeutic agents for colorectal cancer. *The oncologist* **2000**, *5*, 99–107, <https://doi.org/10.1634/theoncologist.5-2-99>.

55. Azwar, S.; Seow, H.F.; Abdullah, M.; Jabar, M.F.; Mohtarrudin, N. Recent Updates on Mechanisms of Resistance to 5-Fluorouracil and Reversal Strategies in Colon Cancer Treatment. *Biology* **2021**, *10*, 854, <https://doi.org/10.3390/biology10090854>.
56. Rivory, L.P.; Lecturer, C.S. New drugs for colorectal cancer - mechanisms of action. *Aust Prescr.* **2002**, *25*, 108-10, <https://doi.org/10.18773/austprescr.2002.110>.
57. García-Alfonso, P.; Muñoz Martín, A.J.; Ortega Morán, L.; Soto Alsar, J.; Torres Pérez-Solero, G.; Blanco Codesido, M.; Calvo Ferrandiz, P.A.; Grasso Cicala, S. Oral drugs in the treatment of metastatic colorectal cancer. *Therapeutic advances in medical oncology* **2021**, *13*, 17588359211009001, <https://doi.org/10.1177/17588359211009001>.
58. Zargar, P.; Ghani, E.; Jalali Mashayekhi, F.; Ramezani, A.; Eftekhari, E. Acriflavine Enhances the Antitumor Activity of the Chemotherapeutic Drug 5-Fluorouracil in Colorectal Cancer Cells. *Oncol. Lett.* **2018**, *15*, 10084–10090, <https://doi.org/10.3892/ol.2018.8569>.
59. Wang, W.; McLeod, H.L.; Cassidy, J. Disulfiram-mediated inhibition of NF- $\kappa$ B activity enhances cytotoxicity of 5-fluorouracil in human colorectal cancer cell lines. *Int. J. Cancer* **2003**, *104*, 504–511, <https://doi.org/10.1002/ijc.10972>.
60. Flis, S.; Gnyszka, A.; Flis, K.; Sławiniński, J. MS275 enhances cytotoxicity induced by 5-fluorouracil in the colorectal cancer cells. *European journal of pharmacology* **2010**, *627*, 26–32, <https://doi.org/10.1016/j.ejphar.2009.10.033>.
61. Arsene, D.; Galais, M.P.; Bouhier-Leporrier, K.; Reimund, J.M. Recent developments in colorectal cancer treatment by monoclonal antibodies. *Expert opinion on biological therapy* **2006**, *6*, 1175–1192, <https://doi.org/10.1517/14712598.6.11.1175>.
62. Tol, J.; Punt, C.J. Monoclonal antibodies in the treatment of metastatic colorectal cancer: a review. *Clinical therapeutics* **2010**, *32*, 437–453, <https://doi.org/10.1016/j.clinthera.2010.03.012>.
63. Cheng, J.; Chen, G.; Lv, H.; Xu, L.; Liu, H.; Chen, T.; Qu, L.; Wang, J.; Cheng, L.; Hu, S.; Wang, Y. CD4-Targeted T Cells Rapidly Induce Remissions in Mice with T Cell Lymphoma. *BioMed research international* **2021**, *2021*, 6614784, <https://doi.org/10.1155/2021/6614784>.
64. Pullyblank, A.M.; Monson, J.R. Monoclonal antibody treatment of colorectal cancer. *The British journal of surgery* **1997**, *84*, 1511–1517.
65. Adams, G.; Weiner, L. Monoclonal antibody therapy of cancer. *Nat. Biotechnol.* **2005**, *23*, 1147–1157, <https://doi.org/10.1038/nbt1137>.
66. Grimsley, A.; Shah, K.S.; McKibbin, T. Monoclonal Antibodies in Cancer. In *Pharmaceutical Biotechnology: Fundamentals and Applications*, Crommelin, D.J.A., Sindelar, R.D., Meibohm, B., Eds.; Springer New York: New York, NY, **2013**; pp. 337-359, [https://doi.org/10.1007/978-1-4614-6486-0\\_17](https://doi.org/10.1007/978-1-4614-6486-0_17).
67. Hwang, K.; Yoon, J.H.; Lee, J.H.; Lee, S. Recent Advances in Monoclonal Antibody Therapy for Colorectal Cancers. *Biomedicines* **2021**, *9*, 39, <https://doi.org/10.3390/biomedicines9010039>.
68. Li, G.; Suzuki, H.; Ohishi, T.; Asano, T.; Tanaka, T.; Yanaka, M.; Nakamura, T.; Yoshikawa, T.; Kawada, M.; Kaneko, M.K.; Kato, Y. Antitumor activities of a defucosylated anti-EpCAM monoclonal antibody in colorectal carcinoma xenograft models. *Int. J. Mol. Med.* **2023**, *51*, 1–14, <https://doi.org/10.3892/ijmm.2023.5221>.
69. Veronese, M.L.; O'Dwyer, P.J. Monoclonal antibodies in the treatment of colorectal cancer. *Eur J Cancer* **2004**, *40*, 1292–301, <https://doi.org/10.1016/j.ejca.2004.02.014>.
70. Arlen, P.M.; Morelli, M.P. Rationale, discovery and clinical development of NEO-201. *Expert Opin Biol Ther* **2020**, *20*, 105–8, <https://doi.org/10.1080/14712598.2020.1696767>.
71. Fantini, M.; David, J.M.; Saric, O.; Dubeykovskiy, A.; Cui, Y.; Mavroukakis, S.A.; Bristol, A.; Annunziata, C.M.; Tsang, K.Y.; Arlen, P.M. Preclinical Characterization of a Novel Monoclonal Antibody NEO-201 for the Treatment of Human Carcinomas. *Frontiers in immunology* **2018**, *8*, 1899, <https://doi.org/10.3389/fimmu.2017.01899>.
72. Tsang, K.y.; Fantini, M.; Mavroukakis, S.A.; Zaki, A.; Annunziata, C.M.; Arlen, P.M. Development and Characterization of an Anti-Cancer Monoclonal Antibody for Treatment of Human Carcinomas. *Cancers* **2022**, *14*, 3037, <https://doi.org/10.3390/cancers14133037>.
73. Yun, S.; Lee, S.; Lee, H.-Y.; Oh, H.J.; Kwak, Y.; Lee, H.S. Clinicopathologic and Prognostic Association of GRP94 Expression in Colorectal Cancer with Synchronous and Metachronous Metastases. *Int. J. Mol. Sci.* **2021**, *22*, 7042, <https://doi.org/10.3390/ijms22137042>.

74. Lee, J.S.; Roh, M.S.; Lee, H.W.; Lee, E.H.; Pak, M.G.; Kim, K.; Nam, H.Y.; Kim, K.M.; Jung, S.B. Prognostic significance of glucose-related protein 94 in colorectal cancer. *Pathology, research and practice* **2020**, *216*, 153013, <https://doi.org/10.1016/j.prp.2020.153013>.
75. Singh, V.; Sheikh, A.; Abourehab, M.A.S.; Kesharwani, P. Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. *Biosensors* **2022**, *12*, 617, <https://doi.org/10.3390/bios12080617>.

### **Publisher's Note & Disclaimer**

The statements, opinions, and data presented in this publication are solely those of the individual author(s) and contributor(s) and do not necessarily reflect the views of the publisher and/or the editor(s). The publisher and/or the editor(s) disclaim any responsibility for the accuracy, completeness, or reliability of the content. Neither the publisher nor the editor(s) assume any legal liability for any errors, omissions, or consequences arising from the use of the information presented in this publication. Furthermore, the publisher and/or the editor(s) disclaim any liability for any injury, damage, or loss to persons or property that may result from the use of any ideas, methods, instructions, or products mentioned in the content. Readers are encouraged to independently verify any information before relying on it, and the publisher assumes no responsibility for any consequences arising from the use of materials contained in this publication.