# Colorectal cancer and immunotherapy.

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## Abstract

**Through immunotherapy, a person's immune system is supported in finding and killing cancer cells more efficiently. Immunotherapy may help patients with advanced Colorectal cancer (CR). Immunotherapy has changed the course of several cancers with dismal prognoses in the past, including advanced lung, melanoma, bladder, head, neck and tumours. Immunotherapy has shown significant promise in recent years for subsets of Colorectal Cancer (CRC) with Microsatellite Instability (MSI), for which newer therapies such Programmed Death-1 (PD-1) inhibitors are beneficial. All CRC patients may benefit from these immunotherapeutics, even though other immunotherapeutics are still in the early stages of development.**

**Keywords:** Cancer, Immune system, Programmed death, Immunotherapeutic, Checkpoint inhibitors

## Introduction

Through immunotherapy, a person's immune system is assisted in identifying and eliminating cancer cells more effectively. Patients with advanced stage Colorectal cancer (CR) may benefit from immunotherapy. Numerous cancers with poor prognoses in the past, such as advanced lung, melanoma, bladder, head, neck and tumours, have turned course because to immunotherapy [1,2]. For subsets of Colorectal Cancer (CRC) with Microsatellite Instability (MSI), for which newer treatments like Programmed Death-1 (PD-1) inhibitors are effective, immunotherapy has shown increased promise during the past few years. These immunotherapeutics may be used for all CRC patients, although other immunotherapeutics are still in the early stages of development.

## Description

**Immune checkpoint inhibitors:** The immune system's capacity to restrain itself from attacking healthy cells in the body is a crucial component. In order to activate an immune response, "checkpoints," which are proteins on immune cells, must be turned on or off. These checkpoints are sometimes used by colorectal cancer cells to fend off immune system attacks. The immune response against colorectal cancer cells is restored with the aid of medications that target these checkpoints.

People, whose colorectal cancer cells have tested positive for particular gene modifications, such as a high level of Microsatellite Instability (MSI-H) or changes in one of the Mismatch Repair (MMR) genes, can take medications known as checkpoint inhibitors. Patients who have cancer that cannot be surgically removed, has returned (recurred) after treatment or has spread to other parts of the body may be treated with these medications (metastasized).

**PD-1 inhibitors:** Drugs that target PD-1, a protein on immune system cells called T cells that typically aids in preventing these cells from attacking other cells in the body, include pembrolizumab and nivolumab. These medications enhance the immune response against cancer cells by inhibiting PD-1.

**CTLA-4 inhibitor:** Another medication that stimulates the immune system is apilimumab; however it targets a different condition. The B7 ligands on APCs are bound by CTLA-4, which is found on the surface of CD4 and CD8 T cells. This prevents B7 from binding to CD28 receptors on T cells, which inhibits immunological activation.

**LAG-3:** T-cell function is impacted in a number of different ways by LAG-3, which is expressed on activated T-cells. The main ligand is MHC class II and LAG-3 and MHC class II interact to reduce the activation of antigen dependent $CD4^+$ T cells [3]. Additionally, it results in the negative control of T cell homeostasis, activation and proliferation as well as the suppression of T regulatory cells (Tregs) [4]. By directly affecting $CD8^+$ T cells and creating a tolerogenic state, LAG-3 maintains tolerance to self and tumour antigens. It also works in concert with PD-1 to cause $CD8^+$ T cell exhaustion [5,6].

**TIM-3:** Similar to PD-1 and CTLA-4, TIM-3 also performs a coinhibitory role in the immune system and promotes $CD8^+$ T cell fatigue [7]. TIM-3 expression is higher in colon cancer tissues than in healthy tissues and it is correlated with lymphatic metastasis and TNM. When TIM-3 is expressed on $CD8^+$ T cells in the mouse colon tumour model, this results in more effector cytokine release and death than when TIM-3 is not expressed [8]. Tumor infiltrating $CD8^+$ T lymphocytes undergo apoptosis as a result of tumour cells secreting galectin-9. By interfering with the galectin-9/TIM-3 signalling system, anti-TIM-3 antibodies reduce apoptosis, slow tumour

development, and improve the therapeutic effectiveness of chemotherapy.

**IDO:** IDO is an intracellular enzyme that causes tryptophan depletion, which suppresses the immune system and allows malignancies to evade the immune system [9]. IDO achieves this through boosting tumour angiogenesis, inducing immunological tolerance to tumour antigens, inhibiting T and NK cells, activating Tregs and MDSCs and promoting tumour microenvironment inflammation [10]. Colon adenocarcinoma cells are positive for IDO expression [11]. However, in this study, this did not correspond with tumour shrinkage. Inhibition of IDO expression affects the immune response in the colon tumour microenvironment in mice by boosting expression of pro inflammatory cytokines and a reducing Foxp3 positive Tregs [12]. To show effectiveness, IMO might need to be used along with another immunomodulating medication.

**Expected side effects of immunotherapy:** Fatigue, coughing, nausea, diarrhoea, skin rashes, appetite loss, constipation, joint pain and itching are a few of these medications' side effects. Rarely, other, more severe adverse effects may develop.

**Infusion reactions:** While receiving these medications, some patients may experience an infusion reaction which symptoms like an allergic reaction including fever, rashes, chills, itchy skin, facial flushing, wheezing and breathing difficulties.

**Autoimmune reactions:** These medications essentially disable one of the body's immune system's defences. The lungs, intestines, liver, hormone producing glands, nerves, skin, kidney and other organs can all experience serious or even life threatening issues when the immune system begins fighting other sections of the body.

## Conclusion

It's crucial to inform your medical team as soon as any new side effects develop during or following treatment with any of these medications. You might need to quit the medication and take high doses of corticosteroids to suppress your immune system if major adverse effects do emerge.

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