# Exploring the Potential of Immunotherapy in Small Bowel Adenocarcinoma

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Cancer is a class of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. The immune system is the body's defense line against any infection with its network of cells, tissue, organs, and molecules. There are two main parts of the immune system: innate immunity, which is a rapid, non-specific response to foreign molecules, and adaptive immunity, which is a delayed and targeted response to invaders. These mechanisms allow the immune system to fight cancer, such as when NK cells detect and kill early cancer cells and T cells recognize tumor-specific antigens or cancer cells and destroy them. However, cancer can evade these defenses by reducing antigen expression to avoid detection of T cells, secreting immunosuppressive factors like cytokines that inhibit immune cell function, and upregulating immune checkpoint proteins like PD-L1 to induce T cell exhaustion. Immunotherapy is a type of cancer treatment that improves the anti-tumor response. It is an attractive option to overcome cancer immune evasion, as it harnesses the immune system to recognize and eliminate cancer cells specifically. In this review, we will discuss small-bowel adenocarcinoma with the treatment of immune checkpoint inhibitors (ICIs) and its potential as a wide approach through the exploration of its effectiveness.

Small Bowel Adenocarcinoma is a relatively rare malignant tumor of the gastrointestinal tract that requires focused attention due to limited treatment options, underscoring the importance of understanding the disease for improved patient outcomes. With its incidence steadily increasing in recent years and comprising about 40% of all small bowel cancers, the majority of SBAs originate in the duodenum. This is the first stretch of the small intestine connecting to the stomach, though it can manifest in other parts such as the jejunum or the ileum. (Galsomino, 2022). Early symptoms of this cancer typically include abdominal pain, unexplained weight loss, and gastrointestinal bleeding. Several factors contribute to the development of small intestine tumors, including dietary habits such as consuming red meat, smoked foods, and cured foods. Additionally, chronic inflammatory bowel involvement, including Crohn's disease, malabsorptive immune disorders, celiac sprue, and hereditary intestinal disorders, nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome, are considered factors contributing to the development of the tumors in the small intestine. (Ocasio Quinones, 2024). People who are diagnosed with cancer are usually around the ages of 50 to 70, and it particularly occurs in males. According to an article from the National Library of Medicine, small bowel cancer is mainly diagnosed in blacks and Asian-Pacific islanders, with a rate of 42% and 34% among patients who are identified with the cancer (Goodman, 2013). On the other hand, cancer syndrome is a type of inherited disorder in which there is a higher-than-normal risk of certain types of cancer. Examples of such syndromes include familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC/Lynch syndrome), Peutz-Jeghers syndrome (PJS), MUTYH-associated polyposis, as well as cystic fibrosis. All of the syndromes noted above carry an increased risk of adenocarcinoma (Kohsla, 2022). In terms of survival rate, early detection and intervention improve survival outcomes for patients. About 85% of people who have localized small intestine adenocarcinomas survive 5

years or more. However, for those who have metastatic small intestine adenocarcinomas, the 5-year survival rate drops to 42% (Yale Medicine).

Various treatments effectively address adenocarcinoma, depending on its stages. Localized small bowel adenocarcinoma is primarily managed with wide-segmental surgical resection. The involved mesentery is removed at the time of the surgical removal of the tumor. At the time of surgical resection, nodes are also resected, as this helps determine the need for adjuvant chemotherapy as well as radiation therapy after surgery to try to kill any cancer cells that may have been left behind but were undetectable.

Small bowel adenocarcinoma (SBA) can impact the immune system through various mechanisms, leading to immune dysregulation. The dysregulation often involves lymphocyte dysfunction, which can contribute to immune evasion in SBA. Specifically, the dysfunction of lymphocytes can cause celiac disease activity, potentially creating an immune evasion aspect of the disease. (Christodoulidis, 2024) In SBA, dysplasia, which is an abnormal cell, can develop due to inflammation triggered by cytokines, promoting cell growth while damaging the epithelial surface. This damage can directly cause dysplasia and allow carcinogens to pass through intercellular junctions, affecting the cell microenvironment. In SBA, dysplasia tends to gather mutations in important genes like *KRAS, p53*, and mismatch repair proteins as they progress from precancerous stages to cancer, playing a significant role in the development and advancement of the diseases and impacting the immune response within the tumor microenvironment. (Khan, 2019) The immunotherapy used in small bowel adenocarcinoma (SBA) includes various types of treatments, such as cancer vaccines that aim to stimulate the immune system to recognize and attack tumor-specific antigens on SBA cells, and immune checkpoint inhibitors work to remove the inhibitory signals and allow the T cells to remain active and mount a stronger anti-tumor immune response against the SBA cells. Specifically, for patients with SBA who have a molecular feature called high microsatellite instability (MSI-H) or mismatch repair, immune checkpoint inhibitors like Pembrolizumab (Keytruda), Nivolumab (Opdivo), Ipilimumab (Yervoy), and Dostarlimab (Jemperli) are utilized as a type of immunotherapy to target the disease. (Vitello, 2023) (Cancer Net, 2012) These immune checkpoint inhibitors enhance the immune system's ability to recognize and attack cancer cells, offering a promising treatment approach for SBA patients. PD-1 is an immunoinhibitory receptor expressed on the surface of CD4 and CD8 T cells, B cells, natural killer cells, and monocytes. T cells are our main body’s defense against pathogens and play a crucial role in the immune response against cancer. Immunotherapy aims to activate and enhance the function of these T-cells to recognize and attack cancer in SBA by binding to PD-L1 for inhibition of immune suppression in these cells (Christodoulidis, 2024). Moreover, immunotherapy has demonstrated efficacy in patients with defective mismatch repair tumors, with a 50% overall response rate observed in previously treated cases, which supports the promise of immunotherapy in small bowel adenocarcinoma (Tim de Back, 2023). However, the evidence from the Vita-Salute University San Raffaele has noted that only a subset of patients with specific molecular features, such as microsatellite instability-high (MSI-H) and high tumor mutational burden (TMB-H), seem to respond effectively to immune checkpoint inhibitors with the presence of these biomarkers at frequencies of 7.6% for MSI-H and 9.5% for TMB-H (Vitiello, 2023). The limitations of retrospective studies with diverse patient populations and small phase II studies that were stopped due to low enrollment affect the evidence supporting the role of immunotherapy in SBA.

To establish the efficacy of immunotherapy in advanced SBAs, large randomized trials are needed. On the other hand, there are several FDA-approved immunotherapies for small bowel adenocarcinoma, including pembrolizumab and nivolumab as immune checkpoint inhibitors that work by blocking the PD-1/PD-L1 pathway, which cancer cells exploit to induce T cell exhaustion and evade immune destruction. By disrupting this checkpoint, these drugs reinvigorate cytotoxic T cells to mount an enhanced anti-tumor response against small bowel adenocarcinoma, especially in cases with high mutational burden and increased tumor antigen expression. They are both neoadjuvant therapies that are combined with chemotherapy, in which nivolumab is followed by surgery for early-stage small bowel adenocarcinoma. (Phillips, 2023) These immunotherapies offer a new approach for patients facing such challenging cancer with their promises.

A few ongoing clinical trials explore immunotherapy's role in treating small bowel adenocarcinoma. One of the ongoing clinical trials is a phase II study on how well ramucirumab (an immunotherapy drug) combined with paclitaxel (a chemotherapy drug) or the FOLFIRI regimen works in treating patients with small bowel cancers that have spread extensively to other anatomic sites or are no longer responding to treatment. The trial is in phase II, in which SBA patients are being tested and healthy participants are not accepted. The inclusion criteria for patients to be enrolled are that they must have confirmed small bowel adenocarcinoma, excluding ampullary adenocarcinomas, with metastatic or locally advanced unresectable disease. Brain metastases are allowed if they are stable for at least 30 days post-treatment. They should be neurologically asymptomatic, without recent corticosteroid use, and have measurable or non-measurable disease assessed within specific timeframes. Prior treatment with fluoropyrimidine and/or oxaliplatin within the past 12 months is required. The exclusion criteria are that the patient must not have received prior treatment with irinotecan, taxane, or ramucirumab for small bowel adenocarcinoma. Major surgery within 28 days, minor surgery within 7 days before registration, or planned elective major surgery during protocol treatment is not allowed. Patients must not also be enrolled in or have discontinued within the last 28 days a clinical trial involving an investigational product or non-approved drug use. The study is tested randomly with Arm I containing ramucirumab and paclitaxel and Arm II with irinotecan, leucovorin, and fluorouracil. The outcomes are being measured to support the insight that these drugs work through various mechanisms to impede tumor cell growth and spread, such as killing cells, halting cell division, or preventing metastasis. Moreover, this combination treatment aims to treat advanced or refractory small bowel cancers, potentially extending patients' survival. (NCT04205968) Another ongoing trial studies how well pembrolizumab, which is a type of immune checkpoint inhibitor (ICT), works in treating patients with small bowel adenocarcinoma that has spread to other places in the body or that cannot be removed by surgery. This is a Phase II trial in which patients need to be diagnosed with SBA, and they need to be 18 years of age and older to be eligible. Also,  all sexes are accepted for the trial. The inclusion criteria for the patients are that they must have biopsy-proven small bowel adenocarcinoma, excluding ampullary and appendiceal tumors, with locally advanced or metastatic disease. They should provide written informed consent, have measurable disease per RECIST 1.1, and have received at least one prior line of systemic chemotherapy for metastatic disease. Patients must be willing to provide blood and tissue samples for research, have an ECOG performance status of 0 or 1, and meet specific laboratory criteria. Specifically, female participants who have the potential for pregnancy must have a negative pregnancy test and commit to using contraception during the

study and for a set time after treatment. The patients ineligible for the trial include those with non-adenocarcinoma histology, adenocarcinoma from the ampulla or appendix, recent investigational therapy use, active tuberculosis, hypersensitivity to pembrolizumab, and recent major surgery. The study researches the treatment pembrolizumab IV received by the patient to show the overall response rate, progression-free survival, and overall survival rate, proving that the treatment interferes with the ability of tumor cells to grow and spread. (NCT02949219) Both ongoing clinical trials are still in the investment stage, and further experiments and exploration are needed to support immunotherapy as an effective treatment for patients who suffer from SBA.

Small bowel adenocarcinoma (SBA) is a rare and aggressive type of cancer that originates from the glandular cells lining the small intestine and is characterized by a poor outlook and molecular uniqueness compared to colorectal and gastric cancers. Immunotherapy has shown promising results in treating SBA, particularly in cases with specific molecular features like high microsatellite instability (MSI-H) or high tumor mutational burden (TMB-H). Drugs such as pembrolizumab and nivolumab, which are immune checkpoint inhibitors, work by blocking the PD-1/PD-L1 pathway, allowing T cells to mount a stronger anti-tumor response against SBA cells. Additionally, cancer vaccines that stimulate the immune system to target tumor-specific antigens on SBA cells have been investigated, which have demonstrated efficiency. However, not all patients respond equally to these treatments, and further research is needed to identify biomarkers that can predict treatment response and optimize patient selection for immunotherapy. Currently, the field is working on biomarker identification to predict the treatment response to immunotherapy in SBA and combination therapies, with ongoing clinical trials combining immunotherapy drugs and chemotherapy to enhance treatment efficiency. On the other hand, determining the optimal combination of immunotherapy agents with other treatment modalities and the sequencing of these therapies is an ongoing challenge to achieve maximal therapeutic benefit while minimizing toxicity. Overall, immunotherapy is still a potential option for addressing the demands of treatments, and it needs the efforts of continued research and clinical trials to unlock its full potential.

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