**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 90126

**Manuscript Type:** EDITORIAL

**Immune signature of small bowel adenocarcinoma and the role of tumor microenvironment**

Christodoulidis G *et al*. Immune status of small bowel adenocarcinoma

Grigorios Christodoulidis, Marina Nektaria Kouliou, Konstantinos Eleftherios Koumarelas

**Grigorios Christodoulidis, Marina Nektaria Kouliou, Konstantinos Eleftherios Koumarelas,** Department of General Surgery, University Hospital of Larissa, Larissa 41110, Greece

**Author contributions:** Christodoulidis G, Kouliou MN and Koumarelas KE contributed to this paper; Christodoulidis G designed the overall concept and outline of the manuscript; Christodoulidis G, Kouliou MN and Koumarelas KE contributed to the discussion and design of the manuscript; Christodoulidis G, Koumarelas KE and Kouliou MN contributed to the writing, editing the manuscript, and review of literature.

**Corresponding author: Grigorios Christodoulidis, PhD, Doctor, Editor-in-Chief,** Department of General Surgery, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. gregsurg09@gmail.com

**Received:** November 23, 2023

**Revised:** January 13, 2024

**Accepted:** January 30, 2024

**Published online:**

**Abstract**

In this editorial we comment on the article published “Clinical significance of programmed cell death-ligand expression in small bowel adenocarcinoma is determined by the tumor microenvironment”. Small bowel adenocarcinoma (SBA) is a rare gastrointestinal neoplasm and despite the small intestine's significant surface area, SBA accounts for less than 3% of such tumors. Early detection is challenging and the reason arises from its asymptomatic nature, often leading to late-stage discovery and poor prognosis. Treatment involves platinum-based chemotherapy with a 5-fluorouracil combination, but the lack of effective chemotherapy contributes to a generally poor prognosis. SBAs are linked to genetic disorders and risk factors, including chronic inflammatory conditions. The unique characteristics of the small bowel, such as rapid cell renewal and an active immune system, contributes to the rarity of these tumors as well as the high intratumoral infiltration of immune cells is associated with a favorable prognosis. Programmed cell death-ligand 1 (PD-L1) expression varies across different cancers, with potential discrepancies in its prognostic value. Microsatellite instability (MSI) in SBA is associated with a high tumor mutational burden, affecting the prognosis and response to immunotherapy. The presence of PD-L1 and programmed cell death 1, along with tumor-infiltrating lymphocytes, plays a crucial role in the complex microenvironment of SBA and contributes to a more favorable prognosis, especially in the context of high MSI tumors. Stromal tumor-infiltrating lymphocytes are identified as independent prognostic indicators and the association between MSI status and a favorable prognosis, emphasizes the importance of evaluating the immune status of tumors for treatment decisions.

**Key Words:** Programmed cell death 1; Programmed cell death-ligand 1; Programmed death ligand; Small bowel adenocarcinoma; Tumor infiltrating lymphocytes; Tumor microenvironment; Microsatellite instability

Christodoulidis G, Kouliou MN, Koumarelas KE. Immune signature of small bowel adenocarcinoma and the role of tumor microenvironment. *World J Gastroenterol* 2024; In press

**Core Tip:** Small bowel adenocarcinoma (SBA) is an uncommon gastrointestinal tumor, accounting for fewer than 3% of all cases, even though it constitutes 95% of the gastrointestinal tract. SBA, which is mostly located in the duodenum, typically goes undetected for a long period of time, resulting to a late-stage discovery and a dismal prognosis. The immunological response, consisting of CD4+ and CD8+ T-lymphocytes, is critical in determining the prognosis. Programmed cell death 1/programmed cell death-ligand 1 (PD-L1) pathway, which is known to be involved in immune evasion in cancer, is implicated in SBA, with PD-L1 expression to a variety of prognostic consequences. The complicated interaction of immunological components, including as TILs and regulatory T cells, emphasizes the complexities of SBA.

**INTRODUCTION**

Small bowel adenocarcinoma (SBA) is an uncommon condition, accounting for less than 3% of all gastrointestinal neoplasms. Its rarity comes in contrast with the facts that small intestine constitutes 95% of the surface area of the entire gastrointestinal tract. Adenocarcinomas, constituting around 40% of malignant small bowel tumors, predominantly manifest in the duodenum, with a notable prevalence of 50%–55%[1–4]. SBA presents a challenge in terms of early detection, as it is frequently asymptomatic for an extended period (2 to 8 months), leading to late-stage discovery and poor prognosis. Its detection often arises from complications such as intestinal perforation, ileus, and unbridled gastrointestinal hemorrhaging and by the time of the diagnosis, nearly one-third of individuals are presented with distant metastasis and an advances stage[1,2,5–7]. However, the advanced stage of the diagnosis and the lack of effective chemotherapy lead to a poor prognosis. In terms of treatment options, platinum-based combination chemotherapy with 5-fluorouracil is commonly used and mostly palliatively, and five-year overall survival (OS) rate reaches as high as 30% for locally advanced tumors[3,8].

Malignant small bowel tumors, are often associated with genetic disorders such as familial adenomatous polyposis, Lynch syndrome, Peutz–Jeghers syndrome, and juvenile polyposis, or risk factors including chronic inflammatory conditions like Crohn’s disease and coeliac disease, along with environmental factors like smoking, alcohol, and certain dietary habits[2,9–11]. The tumorigenesis of SBAs is believed to align with colorectal cancer (CRC), although chronic inflammation may lead to a distinct sequence of inflammation–dysplasia–adenocarcinoma in some cases[2,12]. The small bowel's unique characteristics, including rapid epithelial cell renewal, preventing the accumulation of genetic damage, an active immune surveillance as it is the largest organ of the immune system, contribute to the rarity of these tumors. High intratumoral infiltration of CD3+ and CD8+ cytotoxic T-lymphocytes, along with the presence of tertiary lymphoid structures, is associated with a favorable prognosis[1,2]. Moreover, microsatellite instability (MSI) in SBA, varies between 5% and 35%, exhibiting a high tumor mutational burden, potentially contributing to the unique characteristics of these cancers[2,3,9].

Evading immune surveillance through the Programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway is a hallmark of cancer. PD-L1, a key player in modulating the tumor microenvironment (TME), is upregulated in various solid tumors, including gastrointestinal cancers[1,2]. Studies have shown the efficacy of blocking the PD-1/PD-L1 signaling pathway in gastrointestinal cancers with high MSI (MSI-H), establishing a significant association between MSI-H and PD-L1 expression in SBA[1]. Interestingly, the relationship between PD-L1 expression and prognosis in gastric and CRC remains contentious. While some studies suggest a favorable prognosis associated with PD-L1 expression, others indicate a poorer prognosis in these cancers, with the effectiveness of anti-PD-L1/PD-1 therapy relying on tumor-infiltrating lymphocytes (TILs), mainly composed of CD8+ T cells[1,2]. The abundance of TILs has been linked to improved survival, emphasizing the crucial role of the immune system in combating small bowel cancers[2]. However, the presence of regulatory T cells, characterized by the expression of FoxP3, within TILs introduces an immunosuppressive element, potentially hindering the efficacy of therapy. A high ratio of FoxP3+ to CD8+ T cells is correlated with poor clinical outcomes in digestive system cancers[1]. In this Editorial we elaborate on the TME, the infiltration of immune cells and the immune status of the tumor, stromal and immune cells.

**The role of PD-1, PD-L1 and TILs in Small Bowel Adenocarcinoma**

PD-1 is an immunoinhibitory receptor expressed on the surface of CD4+ and CD8+ T cells, B cells, natural killer cells, and monocytes. Its binding to PD-L1 Leads to the inhibition of immune suppression in these cells. Tumors expressing PD-L1 are considered immune-active, generating an immunosuppressive microenvironment. Consequently, PD-L1-positive tumors may be associated with a poor prognosis[1,13].

Given that the PD-1/PD-L1 pathway provides a potential immune escape route for tumors, an increase in PD-L1 expression is anticipated in advanced disease. Although PD-1/PD-L1 expression is expected to suppress the immune reaction against tumors, reports on the prognostic value of PD-L1 expression vary across different cancer types[2,3]. PD-L1 expression has been shown to correlate with a poor prognosis in esophageal cancer, pancreatic carcinoma, hepatocellular carcinoma, renal cell carcinoma, and ovarian cancer. However, in breast cancer and Merkel cell carcinoma, PD-L1 has been found to correlate with a better patient outcome. For lung cancer, melanoma, gastric cancer, and CRC, both positive and negative prediction values have been reported[2,13,14]. One potential reason for this discrepancy in results may be attributed to the wide variation in the definition of PD-L1 positivity, with the cutoff for positive staining ranging from 1% to 50%. Nevertheless, the mere existence of PD-1/PD-L1 factors allows for the possibility of utilizing targeted immunotherapy in the context of precision medicine.

Microsatellite unstable tumors are characterized by an extensive mutational load, resulting in truncating mutations identified by immune surveillance due to misfolded proteins serving as neoantigens[2,15,16]. This leads to an enhanced antitumoral immune reaction and, consequently, improved survival. MSI status is linked to a high number of PD-1 positive immune cells and PD-L1 expression in immune cells[2,3].

PD-L1 can be expressed by tumor cells (PD-L1TC) or peritumoral inflammatory cells, predominantly histiocytes. PD-L1 expression in tumor cells ranges from 25% to 43%, while in tumor-infiltrating immune cells, it can reach as high as 54%[1,3,9,13]. PD-L1 expression is also increased in MSI tumors (86%) compared to those with microsatellite stable (MSS, 21%). Furthermore, PD-L1 expression is associated with the underlying cause of the tumor. Giuffrida *et al*[17] observed that when SBA is associated with coeliac disease or Crohn's disease, the expression is around 35%, while in sporadic cases of SBA, the expression is only 5%. Increased PD-L1TC is associated with a deeper depth of invasion (*P* < 0.005), increased infiltration of T-lymphocytes (CD3+, CD4+, and CD8+), and a 5-year OS of 74%, compared with PD-L1 negative SBAs[1,3,13]. The appearance of PD-L1 in tumor-infiltrating immune cells leads to a better prognosis, reducing the probability of peritoneal metastasis (*P* < 0.05), increasing the 5-year Disease-Specific Survival to 81%, compared to 33%, and the OS to 74% *vs* 27% in PD-L1 negative cases[2]. Thota *et al*[3] observed that 72% of patients with PD-L1 expression in immune cells had necrosis in the invasion border[3]. Moreover, Klose *et al*[13] support that the absence of PD-L1 in SBAs is correlated with female gender, increased tumor recurrence, metastasis, higher staging, and higher rates of postoperative administration of chemotherapy[13].

PD-1 expression is also increased in SBAs, especially in MSI-H tumors. According to Wirta *et al*[2] and Thota *et al*[3], all MSI-H tumors showed increased expression of PD-1, whereas only 75% of MSS tumors did[2,3]. This is directly related to a smaller tumor-node-metastasis (TNM) staging, with only 9% of patients in stage IV and 42% reported to have stage I or II, positively affecting the OS of the patients[2,9]. However, MSI is present in around 32% of SBA patients, and MSI-H varies from 10% to 21.7%, altering the appearance of PD-1, as MSI, in general, is related to PD-1 expression only in 37.5% of cases[13,18,19]. The 5-year OS in patients with MSI is 60%, while in patients with MSS, it is 54%. Pedersen *et al*[19] in the second phase of their multicenter study, using Pembrolizumab in patients with advanced SBA, observed that 2 patients with MSI-H had a confirmed partial response (50%), while only one (3%) from the MSS/MSI-Low group had a confirmed partial response, and 1 had an unconfirmed response. The responders had an average duration of response of 28.5 months in the MSI-H group and 17.5% in the MSS/MSI-Low group[19]. MSI status, along with PD-1 and PD-L1 expression, may be a helpful predictor for the prognosis of patients and for treatment selection.

TILs play a crucial role in the complex microenvironment of SBA. These specialized immune cells are found within the tumor tissue and are integral components of the host's anti-tumor response. In SBA, the presence and activity of TILs are of particular interest, as they are implicated in both the progression and potential control of the disease. In particular, the appearance of CD8+ TILs in the tumor or the stroma is correlated with less lymph node (LN) metastasis, fewer distant metastases, less peritoneal seeding, and an earlier TNM stage (*P* < 0.005)[1]. Increased percentages of TILs are also correlated with the infiltration of B cells, dendritic cells, and natural killer cells, enhancing the immune response. Along those lines, T-reg and T-helper cells might also be present, regulating the immune response and leading to a worse prognosis[5,20,21]. FoxP3 T-reg cells are associated with deeper depth of invasion, but this association is not significant. However, the increased ratio of FoxP3 to CD8+ cells is significantly associated with a worse prognosis, peritoneal, LN, and distant metastasis (*P* < 0.005)[1]. Moreover, low percentages of CD8+ cells lead to peritoneal seeding (*P* = 0.003), worsening the prognosis[9]. Parkes *et al*[14] observed that infiltration of CD3+, CD4+, and CD8+ T-cells leads to a better progression-free survival rate (*P* < 0.005), and CD8+ cells are also associated with increased OS, although the *P*-value was more than 0.05[14]. According to the multicenter cohort of Noh *et al*[9], the best prognosis was observed in patients with high PD-L1 and high CD8+ TILs in SBA[9].

**CONCLUSION**

The presence of PD-L1 and PD-1 in SBAs, in contrast to other cancer types, contributes to a more favorable prognosis. Patients with SBA and MSI-H tumors exhibit superior OS rates compared to those with MSS tumors. Similarly, individuals with elevated stromal tumor-infiltrating lymphocyte (sTIL) levels in SBA demonstrate extended OS times, establishing sTIL as a robust independent prognostic indicator. Furthermore, MSI status is closely associated with a favorable prognosis, particularly in the context of MSI-H tumors, and is directly correlated with PD-1 expression. The calculation of a Combined Positive Score is pivotal for evaluating the immune status of tumors and establishing a pertinent cut-off value for the treatment of patients with anti-PD-1/PD-L1 factors.

**REFERENCES**

1 **Hoshimoto A**, Tatsuguchi A, Hamakubo R, Nishimoto T, Omori J, Akimoto N, Tanaka S, Fujimori S, Hatori T, Shimizu A, Iwakiri K. Clinical significance of programmed cell death-ligand expression in small bowel adenocarcinoma is determined by the tumor microenvironment. *World J Gastroenterol* 2023; **29**: 5566-5581 [PMID: 37970475 DOI: 10.3748/wjg.v29.i40.5566]

2 **Wirta EV**, Szeto S, Hänninen U, Ahtiainen M, Böhm J, Mecklin JP, Aaltonen LA, Seppälä TT. Prognostic Value of Immune Environment Analysis in Small Bowel Adenocarcinomas with Verified Mutational Landscape and Predisposing Conditions. *Cancers (Basel)* 2020; **12** [PMID: 32718028 DOI: 10.3390/cancers12082018]

3 **Thota R**, Gonzalez RS, Berlin J, Cardin DB, Shi C. Could the PD-1 Pathway Be a Potential Target for Treating Small Intestinal Adenocarcinoma? *Am J Clin Pathol* 2017; **148**: 208-214 [PMID: 28821192 DOI: 10.1093/AJCP/AQX070]

4 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]

5 **Feng J**, Tang X, Song L, Zhou Z, Jiang Y, Huang Y. Potential biomarkers and immune characteristics of small bowel adenocarcinoma. *Sci Rep* 2022; **12**: 16204 [PMID: 36171259 DOI: 10.1038/s41598-022-20599-5]

6 **Aparicio T**, Pachev A, Laurent-Puig P, Svrcek M. Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma. *Cancers (Basel)* 2022; **14** [PMID: 35565398 DOI: 10.3390/cancers14092268]

7 **Lech G**, Korcz W, Kowalczyk E, Słotwiński R, Słodkowski M. Primary small bowel adenocarcinoma: current view on clinical features, risk and prognostic factors, treatment and outcome. *Scand J Gastroenterol* 2017; **52**: 1194-1202 [PMID: 28737049 DOI: 10.1080/00365521.2017.1356932]

8 **Gelsomino F**, Balsano R, De Lorenzo S, Garajová I. Small Bowel Adenocarcinoma: From Molecular Insights to Clinical Management. *Curr Oncol* 2022; **29**: 1223-1236 [PMID: 35200603 DOI: 10.3390/curroncol29020104]

9 **Noh BJ**, Hong SM, Jun SY, Eom DW. Prognostic implications of immune classification in a multicentre cohort of patients with small intestinal adenocarcinoma. *Pathology* 2020; **52**: 228-235 [PMID: 31685233 DOI: 10.1016/j.pathol.2019.09.004]

10 **Shenoy S**. Genetic risks and familial associations of small bowel carcinoma. *World J Gastrointest Oncol* 2016; **8**: 509-519 [PMID: 27326320 DOI: 10.4251/wjgo.v8.i6.509]

11 **Bennett CM**, Coleman HG, Veal PG, Cantwell MM, Lau CC, Murray LJ. Lifestyle factors and small intestine adenocarcinoma risk: A systematic review and meta-analysis. *Cancer Epidemiol* 2015; **39**: 265-273 [PMID: 25736860 DOI: 10.1016/j.canep.2015.02.001]

12 **Maguire A**, Sheahan K. Primary small bowel adenomas and adenocarcinomas-recent advances. *Virchows Arch* 2018; **473**: 265-273 [PMID: 29998424 DOI: 10.1007/s00428-018-2400-7]

13 **Klose J**, Lasitschka F, Horsch C, Strowitzki MJ, Bruckner T, Volz C, Schmidt T, Schneider M. Prognostic relevance of programmed death-ligand 1 expression and microsatellite status in small bowel adenocarcinoma. *Scand J Gastroenterol* 2020; **55**: 321-329 [PMID: 32191146 DOI: 10.1080/00365521.2020.1734073]

14 **Parkes EE**, Savage KI, Lioe T, Boyd C, Halliday S, Walker SM, Lowry K, Knight L, Buckley NE, Grogan A, Logan GE, Clayton A, Hurwitz J, Kirk SJ, Xu J, Sidi FA, Humphries MP, Bingham V; Neo-DDIR Investigators, James JA, James CR, Paul Harkin D, Kennedy RD, McIntosh SA. Activation of a cGAS-STING-mediated immune response predicts response to neoadjuvant chemotherapy in early breast cancer. *Br J Cancer* 2022; **126**: 247-258 [PMID: 34728791 DOI: 10.1038/s41416-021-01599-0]

15 **Tran E**, Ahmadzadeh M, Lu YC, Gros A, Turcotte S, Robbins PF, Gartner JJ, Zheng Z, Li YF, Ray S, Wunderlich JR, Somerville RP, Rosenberg SA. Immunogenicity of somatic mutations in human gastrointestinal cancers. *Science* 2015; **350**: 1387-1390 [PMID: 26516200 DOI: 10.1126/science.aad1253]

16 **Schrock AB**, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, Ross JS, Wilson R, Miller VA, Ali SM, Overman MJ. Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol* 2017; **3**: 1546-1553 [PMID: 28617917 DOI: 10.1001/jamaoncol.2017.1051]

17 **Giuffrida P**, Arpa G, Grillo F, Klersy C, Sampietro G, Ardizzone S, Fociani P, Fiocca R, Latella G, Sessa F, D'Errico A, Malvi D, Mescoli C, Rugge M, Nesi G, Ferrero S, Furlan D, Poggioli G, Rizzello F, Macciomei MC, Santini D, Volta U, De Giorgio R, Caio G, Calabrò A, Ciacci C, D'Armiento M, Rizzo A, Solina G, Martino M, Tonelli F, Villanacci V, Cannizzaro R, Canzonieri V, Florena AM, Biancone L, Monteleone G, Caronna R, Ciardi A, Elli L, Caprioli F, Vecchi M, D'Incà R, Zingone F, D'Odorico A, Lenti MV, Oreggia B, Reggiani Bonetti L, Astegiano M, Biletta E, Cantoro L, Giannone AG, Orlandi A, Papi C, Perfetti V, Quaquarini E, Sandri G, Silano M, Usai P, Barresi V, Ciccocioppo R, Luinetti O, Pedrazzoli P, Pietrabissa A, Viglio A, Paulli M, Corazza GR, Solcia E, Vanoli A, Di Sabatino A. PD-L1 in small bowel adenocarcinoma is associated with etiology and tumor-infiltrating lymphocytes, in addition to microsatellite instability. *Mod Pathol* 2020; **33**: 1398-1409 [PMID: 32066859 DOI: 10.1038/s41379-020-0497-0]

18 **Jun SY**, Park ES, Lee JJ, Chang HK, Jung ES, Oh YH, Hong SM. Prognostic Significance of Stromal and Intraepithelial Tumor-Infiltrating Lymphocytes in Small Intestinal Adenocarcinoma. *Am J Clin Pathol* 2020; **153**: 105-118 [PMID: 31576398 DOI: 10.1093/ajcp/aqz136]

19 **Pedersen KS**, Foster NR, Overman MJ, Boland PM, Kim SS, Arrambide KA, Jaszewski BL, Bekaii-Saab T, Graham RP, Welch J, Wilson RH, McWilliams RR. ZEBRA: A Multicenter Phase II Study of Pembrolizumab in Patients with Advanced Small-Bowel Adenocarcinoma. *Clin Cancer Res* 2021; **27**: 3641-3648 [PMID: 33883178 DOI: 10.1158/1078-0432.CCR-21-0159]

20 **Aristin Revilla S**, Kranenburg O, Coffer PJ. Colorectal Cancer-Infiltrating Regulatory T Cells: Functional Heterogeneity, Metabolic Adaptation, and Therapeutic Targeting. *Front Immunol* 2022; **13**: 903564 [PMID: 35874729 DOI: 10.3389/fimmu.2022.903564]

21 **Saleh R**, Elkord E. FoxP3(+) T regulatory cells in cancer: Prognostic biomarkers and therapeutic targets. *Cancer Lett* 2020; **490**: 174-185 [PMID: 32721551 DOI: 10.1016/j.canlet.2020.07.022]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 23, 2023

**First decision:** January 5, 2024

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Stan FG, Romania **S-Editor:** Li L **L-Editor:** A **P-Editor:**