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Clinicopathological Correlates and Prognostic Impact of PD-L1 and ALK Expression in Stage III–IV Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a malignancy with a high propensity for returning after treatment. Ongoing investigations are exploring effective therapeutic avenues for individuals diagnosed with CRC. This study set out to compare the detection of programmed death-ligand 1 (PD-L1) and anaplastic lymphoma kinase (ALK) across stage III and IV CRC cases, and to assess the clinicopathological relevance of their detection. A sample set of 169 stage III and IV CRC tissues underwent immunohistochemical testing for ALK (D5F3) and PD-L1 (SP142 and SP263) on formalin-fixed paraffin-embedded material. Clinicopathological parameters were collected from medical charts and by reassessing hematoxylin and eosin slides. Detection of PD-L1 SP142 and PD-L1 SP263 was recorded in 17.8% and 28.4% of CRC cases, respectively. ALK D5F3 detection was documented in 4 instances. A significant relationship emerged between PD-L1 SP142 detection and both tumor location and serum carcinoembryonic antigen (CEA) concentration. PD-L1 SP263 detection was tied to serum tumor marker levels and the presence of tumor-infiltrating lymphocytes. Univariate analysis revealed an association between PD-L1 detection and reduced overall survival in CRC patients. In multivariate analysis, PD-L1 SP263 detection emerged as an independent marker of shorter survival. PD-L1 detection was associated with indicators of poor clinical outcome, including shortened survival time. Subsequent studies are warranted to elucidate the pathways mediating the association between PD-L1 detection and an unfavorable prognosis in CRC.

Keywords: Colorectal cancer, Therapeutic avenues, Programmed death-ligand 1 (PD-L1), Anaplastic lymphoma kinase (ALK)

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Introduction

Globally, colorectal cancer (CRC) stands as the third most frequently diagnosed malignancy and the second most common contributor to cancer-related death. For the year 2022, the number of newly recorded CRC diagnoses approached 2 million, while fatalities were estimated at 903,859. CRC incidence is not uniformly distributed across nations. Wealthier nations exhibit higher CRC incidence, while less affluent nations exhibit lower figures [1]. Numerous factors, including environmental and molecular determinants, gut microbial populations, and metabolic byproducts, drive this variation in incidence [2]. For stage I and II CRC, surgical removal remains the cornerstone of management given the lower likelihood of recurrence. In contrast, the National Comprehensive Cancer Network guidelines endorse individually tailored treatment plans for stage III and IV disease. Current research underscores a multimodal treatment paradigm incorporating chemotherapy, targeted agents, radiotherapy, and immunotherapy [3, 4].

Therapeutic blockade of the programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis with immunotherapy has arisen as a groundbreaking modality

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for solid tumors, including non-small cell lung carcinoma (NSCLC) and malignant melanoma. More recent studies have also confirmed the disease-controlling potential of immunotherapy in metastatic CRC [5]. PD-L1, which binds to PD-1, is a widely recognized biomarker measured by immunohistochemistry to predict responsiveness to these treatments. Earlier research suggests that elevated PD-L1 expression is associated with therapeutic gains from immunotherapy. The exact nature of the relationship between PD-L1 detection and treatment response, specifically in CRC, is not yet completely understood [5, 6].

Anaplastic lymphoma kinase (ALK), the kinase associated with anaplastic lymphoma, is a well-studied biomarker analyzed by molecular techniques and immunohistochemistry. ALK-targeted inhibitors are currently approved for the treatment of NSCLC and neoplasms harboring ALK fusions [7]. Immunohistochemical assessment for ALK has proven useful as an initial screen for identifying tumors harboring ALK fusions. Although the frequency of ALK-positive CRC remains low, ALK inhibitors may offer a future targeted option based on ALK status evaluation. Earlier publications demonstrate how genomic alterations can shape the tumor immune landscape. Specifically, EML4-ALK fusions appear to stimulate the PD-1/PD-L1 pathway by upregulating PD-L1 [8]. We posited that PD-L1 and ALK detection in CRC patients are functionally linked. The present work evaluated ALK and PD-L1 status in 169 stage III and IV CRC tissue samples and examined their relationship with clinicopathological variables.

Materials and Methods

Patients and tissue samples

An initial pool of 224 CRC patients who had resectional surgery at Jeonbuk National University Hospital from April 2019 through August 2020 was assembled. Elimination of candidates who received neoadjuvant chemotherapy or radiotherapy (n = 55) yielded a definitive study population of 169. For patients presenting with clinical stages I-III CRC, surgical removal was the initial therapeutic measure. Subjects with stage IV CRC underwent surgery with palliative intent followed by adjuvant chemotherapy. The entry requirements for the investigation focused on stages III and IV CRC patients, given that those with advanced disease (stages III and IV) require further therapeutic measures postoperatively. This cohort was not administered any supplementary therapy, including chemotherapy, radiotherapy, or immunotherapy. Two pathologists (KYJ and ARA), masked to the clinical background, re-evaluated the CRC tissue from the 169 cases. The hematoxylin and eosin (H&E) slides from all formalin-fixed, paraffin-embedded (FFPE) tissue blocks of CRC cases were reassessed according to the WHO classification for digestive system tumors. Tumor-Node-Metastasis staging followed the American Joint Committee on Cancer (AJCC) 8th edition guidelines. The evaluation of tumor-infiltrating lymphocytes (TILs) adhered to the methodology outlined by the International TIL Working Group (ITWG). For comparative purposes, TIL levels were divided into low and high categories, with a demarcation point of 55%. Circulating levels of preoperative cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were recorded, applying thresholds of 37 kU/L and 5.0 ng/mL, respectively. The entire large bowel was bisected into right and left anatomical segments for analysis. The right-sided segment was defined as the region encompassing the cecum, the ascending colon, and the proximal two-thirds of the transverse colon. The left-sided segment comprised the distal one-third of the transverse colon, along with the descending colon, sigmoid colon, and rectum. Surveillance following surgery involved abdominal computed tomography (CT) scanning every 3 months to screen for recurrent or metastatic disease. All procedures were consistent with the Declaration of Helsinki, and the protocol received Institutional Review Board clearance from Jeonbuk National University Hospital (IRB No. 2024-05-019). Obtaining informed consent was deemed unnecessary.

Immunohistochemical staining for ALK and PD-L1

All specimens underwent immunohistochemical processing to evaluate ALK and PD-L1 status. For the immunohistochemical workup, tissue microarrays (TMA) were assembled, each containing 2-mm-diameter cores extracted from FFPE donor blocks. Three ready-to-use commercial antibody clones were used: ALK (clone D5F3; Roche), PD-L1 (clone SP142; Roche), and PD-L1 (clone SP263; Roche). The staining procedure for FFPE sections was carried out on a Ventana BenchMark ULTRA automated platform (Roche Diagnostics, Mannheim, Germany).

Evaluation of ALK and PD-L1 expression

Two pathologists (JKY and ARA), blinded to all clinical and pathological data, interpreted the ALK- and PD-L1-stained slides. For every case, the assessment of ALK (D5F3), PD-L1 (SP142), and PD-L1 (SP263) relied on the manufacturer's Ventana interpretation guide. ALK (D5F3) was deemed positive when strong granular cytoplasmic reactivity was observed in tumor cells (TCs), regardless of the percentage involved. PD-L1 (SP142) scoring followed the Ventana guide and encompassed both TC and immune cell (IC) compartments. Positivity for PD-L1 (SP142) was assigned to cases meeting the threshold of ≥ 50% TC

staining or ≥ 10% IC staining. A cutoff of ≥ 1% TC defined PD-L1 (SP263) positivity **(Figure 1)**.

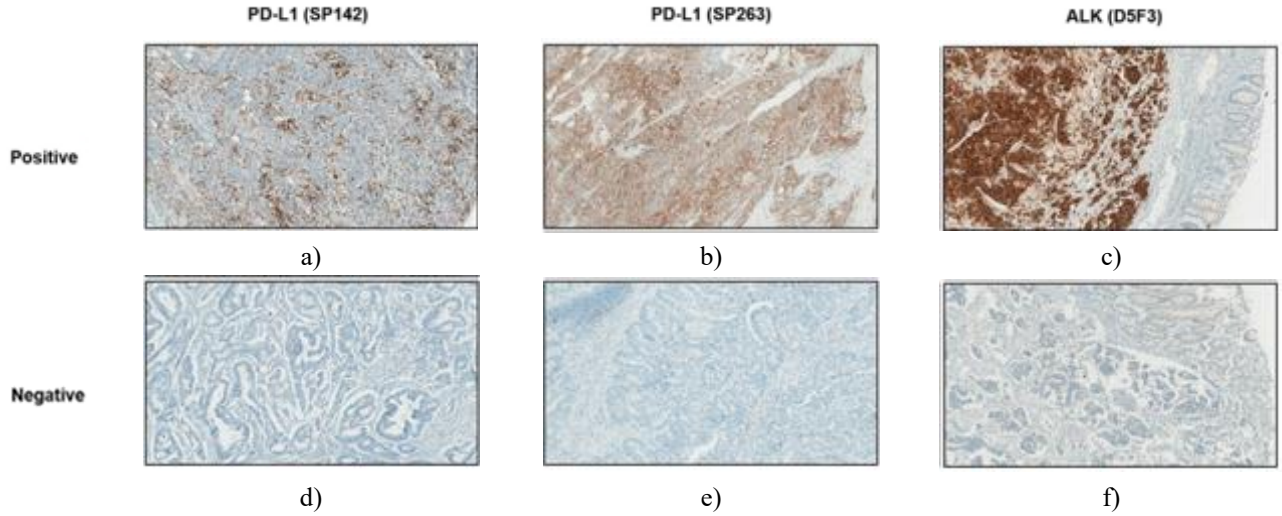


Figure 1. Positive and negative expression patterns of PD-L1 (SP142), PD-L1 (SP263), and ALK (D5F3) antibodies. Abbreviations: ALK = anaplastic lymphoma kinase, PD-L1 = programmed death-ligand 1.

Statistical analysis

Relationships between clinicopathological variables and patient outcomes in CRC were examined by chi-square testing and Cox proportional hazards regression. The prognostic endpoints, comprising overall survival (OS) and relapse-free survival (RFS), were tracked through December 2022. Death from CRC served as the defining event in OS analysis. The OS interval was calculated from the date of pathological diagnosis to either the date of death or the last known follow-up visit. RFS was defined as the interval from the pathological diagnosis to relapse, death, or the last follow-up contact. The Kaplan–Meier method was applied to generate survival curves, and differences were assessed with the log-rank test. All data processing was executed in SPSS version 29.0 (IBM Corp., Armonk, NY, USA). A two-tailed P-value falling below 0.05 was accepted as statistically significant.

Results and Discussion

Immunohistochemical staining and the correlations with clinicopathological characteristics in stages III and IV CRC patients

The study population had a mean age of 70.26 years, with 45.0% of participants being female. Over the course of monitoring, relapse was documented for 62 patients (36.7%), while 42 patients (24.9%) died. The cutoff for the last follow-up was fixed either at the final patient encounter or at the date of death, up to December 2022. The length of follow-up approximated 3 years. PD-L1 (SP142) positivity was recorded in 30 of the 169 tumors (17.8%). A significant clustering of PD-L1 (SP142)-positive cases was observed among right-sided colon primaries (P = .024), cases with CEA elevation (P < .001), and those with ALK (D5F3) positivity (P = .002) **(Table 1)**. PD-L1 (SP263) positivity was present in 48 of the 169 tumors (28.4%). Statistically significant associations were noted between PD-L1 (SP263) expression and both CEA elevation (P < .001) and CA19-9 elevation (P = .023); meanwhile, an inverse link was found with high TIL counts (P = .030) **(Table 2)**. ALK (D5F3) positivity was observed in only 4 of 169 cases (2.4%), with no meaningful clinicopathological associations. Additionally, a strong positive relationship between PD-L1 (SP142) and PD-L1 (SP263) expression was confirmed (P < .001).

Table 1. Association between patterns of PD-L1 (SP142) expression and clinicopathological characteristics.

Clinicopathological characteristics	Category	P-value	PD-L1 positive (n = 30)	PD-L1 negative (n = 139)	No
Age (years)	≤ 70	.680	13 (16.5%)	66 (83.5%)	79
	> 70		17 (18.9%)	73 (81.1%)	90
Sex	Male	.310	14 (15.1%)	79 (84.9%)	93
	Female		16 (21.1%)	60 (78.9%)	76
Tumor location*	Right	.024	16 (26.7%)	44 (73.3%)	60
	Left		14 (12.8%)	95 (87.2%)	109
Serum CEA level	Normal	<.001	6 (7.3%)	76 (92.7%)	82

Serum CA19-9 level	Elevated		24 (27.6%)	63 (72.4%)	87
	Normal	.152	29 (19.2%)	122 (80.8%)	151
	Elevated		1 (5.6%)	17 (94.4%)	18
TNM stage	III	.349	19 (20.2%)	75 (79.8%)	94
	IV		11 (14.7%)	64 (85.3%)	75
Tumor-infiltrating lymphocytes (TIL)	Low	.991	27 (17.8%)	125 (82.2%)	152
	High		3 (17.6%)	14 (82.4%)	17
ALK (D5F3) status	Negative	.002	27 (16.4%)	138 (83.6%)	165
	Positive		3 (75.0%)	1 (25.0%)	4
Survival status (Death)	Absent	<.001	10 (7.9%)	117 (92.1%)	127
	Present		20 (47.6%)	22 (52.4%)	42
Relapse status	Absent	<.001	7 (6.5%)	100 (93.5%)	107
	Present		23 (37.1%)	39 (62.9%)	62

Left colon: defined as the segment from the distal one-third of the transverse colon to the rectum. Right colon: defined as the segment from the cecum to the proximal two-thirds of the transverse colon. Abbreviations: ALK = anaplastic lymphoma kinase, CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, PD-L1 = programmed death-ligand 1, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

Table 2. Correlation between PD-L1 (SP263) expression subtypes and clinicopathological features.

Clinical characteristics	Subgroup	P value	PD-L1 positive (n = 48)	PD-L1 negative (n = 121)	No
Age (years)	≤ 70	.848	23 (29.1%)	56 (70.9%)	79
	> 70		25 (27.8%)	65 (72.2%)	90
Sex	Male	.628	25 (26.9%)	68 (73.1%)	93
	Female		23 (30.3%)	53 (69.7%)	76
Tumor location*	Right	.292	20 (33.3%)	40 (66.7%)	60
	Left		28 (25.7%)	81 (74.3%)	109
Serum CEA level	Normal	< .001	6 (7.3%)	76 (92.7%)	82
	Elevated		42 (48.3%)	45 (51.7%)	87
Serum CA19-9 level	Normal	.023	47 (31.1%)	104 (68.9%)	151
	Elevated		1 (5.6%)	17 (94.4%)	18
TNM stage	III	.140	31 (33.0%)	63 (67.0%)	94
	IV		17 (22.7%)	58 (77.3%)	75
Tumor-infiltrating lymphocytes (TIL)	Low	.030	47 (30.9%)	105 (69.1%)	152
	High		1 (5.9%)	16 (94.1%)	17
PD-L1 (SP142) status	Negative	< .001	27 (19.4%)	112 (80.6%)	139
	Positive		21 (70.0%)	9 (30.0%)	30
ALK (D5F3) status	Negative	.879	47 (28.5%)	118 (71.5%)	165
	Positive		1 (25.0%)	3 (75.0%)	4
Death status	Absent	< .001	18 (14.2%)	109 (85.8%)	127
	Present		30 (71.4%)	12 (28.6%)	42
Relapse status	Absent	< .001	3 (2.8%)	104 (97.2%)	107
	Present		45 (72.6%)	17 (27.4%)	62

Left colon: refers to the anatomical region extending from the distal one-third of the transverse colon through to the rectum. Right colon: refers to the anatomical region spanning from the cecum through to the proximal two-thirds of the transverse colon. Abbreviations: ALK = anaplastic lymphoma kinase, CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, PD-L1 = programmed death-ligand 1, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

Relationship between PD-L1 expression and the prognostic impact of patients with stages III and IV CRC

To determine whether PD-L1 expression carries prognostic significance in advanced CRC, we divided the stage III and IV cohort by PD-L1 status and generated comparative OS and RFS curves. As illustrated in **Figure 2**, the Kaplan–Meier analyses revealed that patients whose tumors stained positive for either PD-L1 (SP142) or PD-L1 (SP263) experienced a statistically significant decline in both OS and RFS. **Table 3** summarizes the univariate Cox regression outputs for the entire stage III and IV group. Among the factors that emerged as significantly detrimental to OS were advancing age (hazard ratio [HR], 2.192; 95% confidence interval [CI], 1.139–4.217; P = .019), a raised preoperative serum CEA value (HR, 3.458; 95% CI, 1.699–7.039; P < .001), PD-L1 (SP142) positivity (HR, 6.417; 95% CI, 3.472–11.861; P < .001), and PD-L1

(SP263) positivity (HR, 8.896; 95% CI, 4.532–17.460; P < .001). When the endpoint was RFS, the set of adverse influences comprised elevated preoperative CEA (HR, 3.353; 95% CI, 1.895–5.933; P < .001), PD-L1 (SP142) positivity (HR, 4.284; 95% CI, 2.539–7.229; P < .001), and PD-L1 (SP263) positivity (HR, 15.655; 95% CI, 8.703–28.162; P < .001). Multivariable models were subsequently formulated for both outcomes **(Table 4)**. In the OS model, the effects of older age (HR, 2.433; 95% CI, 1.256–4.712; P = .008), PD-L1 (SP142) expression (HR, 2.996; 95% CI, 1.536–5.847; P = .001), and PD-L1 (SP263) expression (HR, 6.841; 95% CI, 3.259–14.206; P < .001) all persisted as independently significant. RFS was independently predicted to be shorter by the presence of PD-L1 (SP263) expression alone (HR, 15.655; 95% CI, 8.703–28.162; P < .001).

Table 3. Univariate Cox proportional hazards regression analysis for the overall survival and relapse-free survival of stages III and IV CRC patients.

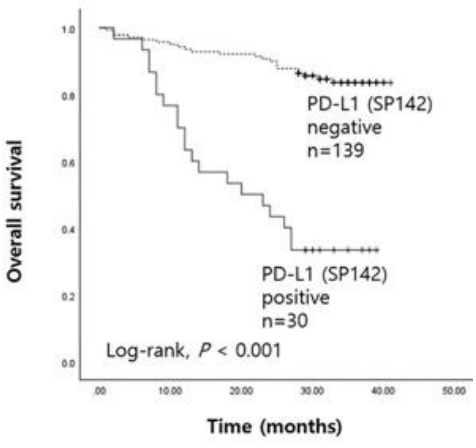
Clinical characteristics	No.	RFS HR (95% CI)	P-value	OS HR (95% CI)	P-value
Age (years) > 70 (vs ≤ 70)	90/169	1.216 (0.736–2.010)	.445	2.192 (1.139–4.217)	.019
Female (vs male)	76/169	1.055 (0.639–1.741)	.833	1.371 (0.748–2.514)	.307
Left colon tumor (vs right colon)	109/169	0.888 (0.530–1.488)	.652	0.637 (0.347–1.170)	.146
Serum CEA elevation (vs normal)	87/169	3.353 (1.895–5.933)	< .001	3.458 (1.699–7.039)	< .001
Serum CA19-9 elevation (vs normal)	18/169	0.494 (0.179–1.365)	.174	0.391 (0.094–1.617)	.195
TNM stage IV (vs III)	75/169	0.747 (0.448–1.246)	.264	0.739 (0.396–1.378)	.341
High TIL (vs low)	17/169	0.397 (0.124–1.268)	.119	0.415 (0.100–1.718)	.225
PD-L1 (SP142) positive (vs negative)	30/169	4.284 (2.539–7.229)	< .001	6.417 (3.472–11.861)	< .001
PD-L1 (SP263) positive (vs negative)	48/169	15.655 (8.703–28.162)	< .001	8.896 (4.532–17.460)	< .001

Abbreviations: CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, OS = overall survival, PD-L1 = programmed death-ligand 1, RFS = relapse-free survival, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

Table 4. Multivariable Cox proportional hazards modeling evaluates overall survival and relapse-free survival among individuals with stage III and IV CRC.

Clinical characteristics	RFS HR (95% CI)	P value	OS HR (95% CI)	P-value
Age (years) > 70 (vs ≤ 70)	—	—	2.433 (1.256–4.712)	.008
PD-L1 (SP142) positive (vs negative)	—	—	2.996 (1.536–5.847)	.001
PD-L1 (SP263) positive (vs negative)	15.655 (8.703–28.162)	< .001	6.841 (3.259–14.206)	< .001

Covariates entered into the multivariable model for overall survival comprised age, sex, tumor location, elevated CEA, elevated CA19-9, Tumor-Node-Metastasis stage, tumor-infiltrating lymphocytes, PD-L1 (SP142) positivity, and PD-L1 (SP263) positivity. Abbreviations: CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, OS = overall survival, PD-L1 = programmed death-ligand 1, RFS = relapse-free survival.



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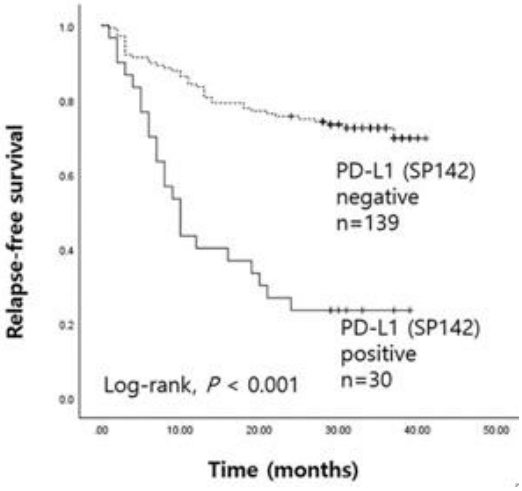

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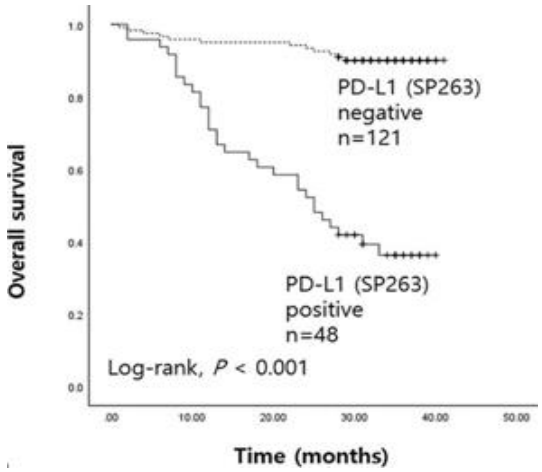

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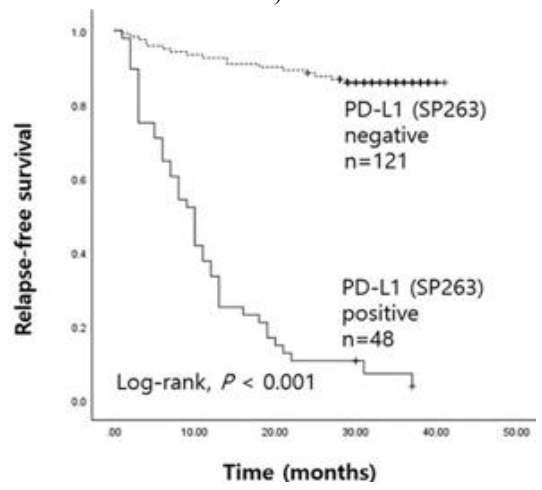

d)

Figure 2. Kaplan–Meier survival plots depicting overall survival (OS) and relapse-free survival (RFS): (a) OS Kaplan–Meier plots stratified according to PD-L1 (SP142) status in stage III and IV colorectal cancers, (b) RFS Kaplan–Meier plots stratified according to PD-L1 (SP142) status in stage III and IV colorectal cancers, (c) OS Kaplan–Meier plots stratified according to PD-L1 (SP263) status in stage III and IV colorectal cancers and (d) RFS Kaplan–Meier plots stratified according to PD-L1 (SP263) status in stage III and IV colorectal cancers. Abbreviation: PD-L1 = programmed death-ligand 1.

Characterizing the expression patterns of ALK and PD-L1, along with their associations with clinicopathological parameters, in individuals diagnosed with stage III or IV CRC can inform the development of personalized treatment regimens. The ALK gene encodes a receptor kinase protein that is fundamentally implicated in the pathogenesis of malignant neoplasms. Within the spectrum of solid tumors, ALK genetic aberrations are predominantly identified in pulmonary carcinomas and occur only sporadically in CRC [9, 10]. In the cohort presented here, ALK staining was observed in only 4 of 169 tumor specimens examined—a finding that aligns with the low frequencies reported in prior literature. With positivity limited to 4 cases, the small number of events inevitably restricts the statistical weight and interpretability of any association. As such, ALK immunohistochemistry offers negligible prognostic information in this setting. One limitation of the present work is that ALK alterations were interrogated exclusively by immunohistochemistry, and the resulting data lack the depth required to draw a robust conclusion.

In this research, we systematically evaluated the immunohistochemical detection of PD-L1 utilizing two separate clones, namely SP142 and SP263, across a series of human CRC tissues. Our analyses yielded positivity frequencies of 17.8% (30/169) for PD-L1 (SP142) and 28.4% (48/169) for PD-L1 (SP263) within the stage III and IV CRC study population. Specimens scored as PD-L1 (SP142)-positive showed a predilection for right-sided colonic location, concurrent CEA elevation, and co-expression of ALK (D5F3). Cases registering as PD-L1 (SP263)-positive displayed associations with elevated serum levels of both CEA and CA19-9. When subjected to univariate analysis, both PD-L1 (SP142) and PD-L1 (SP263) positivity were linked to abbreviated OS and RFS intervals. Upon multivariate adjustment, PD-L1 (SP142) emerged as an independent correlate of reduced OS, whereas PD-L1 (SP263) independently predicted both worse OS and worse RFS.

PD-L1, which binds PD-1, localizes to both the tumor immune microenvironment and the surface of neoplastic cells. The PD-1 receptor itself functions as an immunosuppressive coreceptor expressed on activated T lymphocytes, B lymphocytes, and myeloid cells. Cancer immunotherapy has risen to prominence as an innovative pillar of oncological treatment. Therapeutic antibodies that disrupt the PD-1/PD-L1 signaling axis have achieved remarkable response rates in NSCLC, malignant melanoma, and urothelial carcinoma. Whether CRC patients derive meaningful clinical benefit from immune checkpoint blockade remains a matter of ongoing debate, and the precise mechanistic underpinnings of these agents within the CRC milieu remain inadequately characterized. So far, only CRC cases with microsatellite instability have demonstrated a notable response to the PD-1 inhibitors pembrolizumab and nivolumab, as shown by the CheckMate 142 and KEYNOTE-177 trials. These landmark clinical investigations have also highlighted the diagnostic role of PD-L1 as a biomarker for predicting the therapeutic effectiveness of pembrolizumab or nivolumab in advanced CRC, while acknowledging that harmonized antibody clones and scoring criteria are needed [11].

Whether PD-L1 expression carries prognostic significance in CRC remains a contested issue. Some lines of evidence have suggested that PD-L1 positivity denotes a marker of aggressive disease biology, including poor tumor differentiation and lymphatic vessel infiltration, and heralds an unfavorable outcome [12]. Yet other studies

have contradicted this, reporting that PD-L1 expression is an indicator of a more favorable prognosis in CRC [13]. The divergent findings render the clinical interpretation of PD-L1 status ambiguous. Data from the current study indicate that PD-L1 expression correlates with adverse clinicopathological features and with curtailed OS and RFS durations among stage III and IV CRC patients. These results raise the possibility that individuals with stage III or IV CRC whose tumors display PD-L1 positivity could be prime candidates for immunotherapeutic intervention, including PD-1/PD-L1 checkpoint blockade, potentially offering a strategy to improve outcomes in a subgroup characterized by poor prognosis.

Conclusion

Several caveats must be considered when interpreting this study. TMA-based evaluation carries an inherent risk of underestimating PD-L1 prevalence when compared against whole-tissue section analysis. Even though each TMA block included duplicate 2-mm cores from each donor specimen, the well-documented intratumoral heterogeneity in PD-L1 expression may still lead to sampling bias. In addition, the degree of concordance between PD-L1 (SP142) and PD-L1 (SP263) clones, when identical thresholds and scoring methodologies were applied, was not formally assessed. Furthermore, information regarding the actual clinical responses of enrolled patients to immune checkpoint inhibitors was not captured. Consequently, additional investigations are warranted to define the therapeutic impact of immunotherapy within the CRC population and to ascertain the equivalence and interchangeability of these two antibody clones in colorectal cancer tissue.

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Conflict of interest: None

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Ethics statement: None

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