Original paper

Diagnostic consistency of programmed death-ligand 1 immunohistochemistry – comparative analysis of SP142 and 22C3 clones in non-small cell lung cancer

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Programmed death-ligand 1 (PD-L1) expression is a critical predictive biomarker for immune checkpoint inhibitor therapies in non-small cell lung cancer (NSCLC). Although various antibody clones are used for immunohistochemical (IHC) detection, differences in platforms and scoring algorithms raise concerns regarding analytical agreement at clinically relevant thresholds. This study evaluated the analytical concordance between VENTANA SP142, VENTANA 22C3, and DAKO 22C3 PD-L1 IHC assays in NSCLC, focusing on therapeutic decision-making thresholds.
Non-small cell lung cancer samples from 205 patients were stained using VENTANA SP142, VENTANA 22C3, and DAKO 22C3 assays. Programmed death-ligand 1 expression was assessed in tumor cells using predefined thresholds (< 1%, 1–49%, ≥ 50%). Inter-assay agreement was evaluated using intraclass correlation coefficients (ICC).
Strong analytical agreement (ICC > 0.90) was observed between SP142 and both DAKO and VENTANA 22C3 assays in the < 1% and 1–49% expression groups. Agreement decreased between VENTANA SP142 and DAKO 22C3 at the ≥ 50% threshold (ICC = 0.704). Conversely, concordance between VENTANA and DAKO 22C3 was high across all thresholds, particularly in the < 1% and ≥ 50% subgroups (ICC = 1.0 and 0.867, respectively).
VENTANA and DAKO 22C3 assays demonstrate high analytical agreement. While SP142 is comparable at low expression levels, its reliability declines at higher thresholds. These findings underscore the necessity of standardized assay selection for accurate immunotherapy stratification in NSCLC.

Key words: PD-L1, NSCLC, SP142, 22C3, assay concordance, immune checkpoint inhibitors, DAKO, VENTANA.

Introduction

With a steadily increasing incidence in every location, lung cancer continues to be the primary cause of cancer-related death globally [1]. Over 50% of patients with lung cancer receive their diagnosis at an advanced stage, where their chances of survival are greatly reduced [2]. Lung malignancies are very diverse both histologically and molecularly, with non-small cell lung cancer (NSCLC) accounting for over 85% of all cases [3]. The identification of EGFR, BRAF, and MET mutations as well as ALK, ROS1, and RET rearrangements are examples of molecular profiling that has been essential to the diagnosis and treatment planning of NSCLC in recent years [3]. In addition to these genetic changes, programmed

death-ligand 1 (PD-L1) protein expression analysis has become a vital indicator for directing immune checkpoint inhibitor treatment.

One important immune checkpoint route that cancers use to avoid cytotoxic T-cell-mediated response is the PD-1/PD-L1 axis. A member of the B7 superfamily, PD-L1 is expressed by tumor cells in a number of cancers, including glioblastoma, lung, breast, ovarian, and head and neck cancers, in addition to activated immune cells [4, 5]. Tumor growth is made possible by PD-L1's interaction with its receptor PD-1, which reduces T-cell activation, cytokine generation, and immune response. Antitumor immunity has been demonstrated to be restored by therapeutic antibodies that target PD-1 or PD-L1, with PD-L1 expression acting as a predictive and prognostic biomarker for immunotherapy responsiveness [6].

The main technique for identifying PD-L1 expression is immunohistochemistry (IHC), which is commonly expressed as the proportion of tumor cells that show membranous staining (tumor proportion score – TPS). Using different monoclonal antibody clones and diagnostic platforms, such as 22C3 (DAKO), SP142 (VENTANA), SP263 (VENTANA), and 28-8 (DAKO), several PD-L1 IHC assays have been created. These assays vary in sensitivity and intended therapeutic pairings. In patients with TPS ≥ 1%, the Food and Drug Administration has approved the 22C3 test as a companion diagnostic for pembrolizumab; those with TPS ≥ 50% showed better results [7, 8]. However, SP142 has demonstrated decreased sensitivity in detecting tumor cell PD-L1 positivity [9]. SP142 was created primarily to evaluate PD-L1 expression on immune cells for atezolizumab treatment [10, 11].

The Blueprint project is one of several comparative investigations that have shown analytical differences between these assays. High concordance is shown by 22C3, 28-8, and SP263, although SP142 tends to underestimate PD-L1 positivity, particularly at low expression levels [9, 12, 13]. This variability affects test interchangeability and could influence clinical decision-making. It is caused by variations in staining platforms, scoring algorithms, and antibody affinity. Furthermore, the requirement for standardized evaluation techniques is further highlighted by the fact that inter-observer agreement is typically higher for tumor cell labeling than for immune cell assessment.

Assessing the analytical concordance between commonly used PD-L1 IHC assays in NSCLC is crucial in light of these difficulties. In a cohort of NSCLC specimens, this study attempts to evaluate the comparability of the VENTANA SP142 and 22C3 assays with the DAKO 22C3 assay across clinically relevant expression thresholds. Our goal is to clarify how assay-specific variations may affect treatment stratification and therapy results in standard pathology practice by looking at staining patterns and inter-assay agreement.

Here, we systematically assess the analytical concordance and inter-assay reliability of three clinically implemented PD-L1 IHC assays (VENTANA SP142, VENTANA 22C3, and DAKO 22C3) in a large retrospective cohort of non-small cell lung cancer, with particular emphasis on clinically relevant tumor proportion score thresholds.

Material and methods

To find appropriate NSCLC cases, a retrospective evaluation of digital pathology data from the Department of Pathology at Istanbul University's Cerrahpa'a Faculty of Medicine was conducted. Two hundred and five NSCLC cases were chosen from among lung resections carried out between 2000 and 2012 on the basis of the accessibility of formalin-fixed paraffin-embedded blocks and the availability of adequate tumor tissue. Each of the chosen patients had had a pneumonectomy, lobectomy, or segmentectomy performed in the same institution's Department of Thoracic Surgery.

Tissue construction

Blocks of tumors that were sufficiently preserved were chosen for IHC examination. To identify the ideal antibody dilutions and incubation conditions, pilot testing was conducted on control blocks and representative cases prior to IHC operations. After reviewing slides stained with hematoxylin and eosin, similar tumor-rich regions on the donor blocks were found. Areas of bleeding, necrosis, calcification, or anthracosis were avoided when choosing tumor cores. Areas with dense inflammatory infiltrates at the tumor interface were prioritized. The use of tissue microarrays enabled a standardized comparative assessment across assays while minimizing pre-analytical and platform-related variability.

Immunohistochemistry

Programmed death-ligand 1 expression was examined using IHC on 4-μm slices taken from tissue microarray blocks. The VENTANA Benchmark XT automated staining system (VENTANA Medical Systems, Tucson, AZ, USA) was used for all staining operations, and the manufacturer's instructions for each antibody were followed. The SP142 clone (VENTANA), 22C3 pharmDx (VENTANA), and 22C3 pharmDx (DAKO, Heverlee, Belgium) were among the antibodies employed in this investigation. Prior to full-scale implementation, pilot testing was used to identify the ideal antibody dilutions and incubation conditions. Cytoplasmic or immune cell staining was not graded for any of the three assays; only

Table I. Demographic and clinical characteristics

Characteristic	*n* (%)
Non-smokers	12 (6)
Male	183 (89)
Female	22 (11)
Mean age (range)	60 (39–80)
Smokers	193 (94)
Total patients	205 (100)

full or partial membranous staining of tumor cells was regarded as positive. Three skilled pathologists independently assessed each slide while being blinded to the clinical information and antibody identity to reduce interpretation heterogeneity.

Three predetermined thresholds were used to semi-quantitatively evaluate PD-L1 expression: ≥ 50% (high expression), 1–49% (low expression), and < 1% (negative). Current clinical guidelines state that a tumor proportion score of ≥1% indicates PD-L1 positivity [14]. Analyzing the analytical concordance of PD-L1 expression in a cohort of 205 NSCLC specimens using the three antibody-platform combinations – VENTANA SP142, VENTANA 22C3, and DAKO 22C3 – was the main goal of the IHC analysis.

Statistical analysis

Programmed death-ligand 1 expression was semi-quantitatively assessed using three preset thresholds: ≥ 50% (high expression), 1–49% (low expression), and < 1% (negative). According to current clinical standards, PD-L1 positive is indicated by a tumor proportion score of ≥ 1% [14]. The primary objective of the IHC investigation was to examine the analytical concordance of PD-L1 expression in a cohort of 205 NSCLC specimens utilizing the three antibody-platform combinations: VENTANA SP142, VENTANA 22C3, and DAKO 22C3. Intraclass correlation coefficient (ICC) was calculated using a two-way mixed-effects model based on single measurements (absolute agreement). Intraclass correlation coefficient values were reported together with their 95% confidence intervals. Subgroups with fewer than 10 cases were excluded from ICC analysis to avoid unstable variance estimations. Statistical analyses were performed using IBM SPSS v26 and JASP v0.19.3.0.

Results

Patient characteristics

A total of 205 patients were included in the study. The majority were male (n = 183, 89%), while 22 patients (11%) were female. The age range was 39–80 years, with a mean age of 60 years. A history of smoking was present in 193 patients (94%), whereas only 12 patients (6%) were never-smokers; notably, 11 of these non-smoking patients were female. Detailed demographic and clinical characteristics are summarized in Table I.

Table II. Histological subtype distribution of non-small cell lung cancer

Subtype	*N*
Squamous cell carcinoma	107
Adenocarcinoma	72
Other NSCLC	26
Large cell carcinoma	4
Adenosquamous carcinoma	8
Large cell neuroendocrine carcinoma	5
Pleomorphic carcinoma	5
Mucoepidermoid carcinoma	4
Total patients	205

NSCLC – non-small cell lung cancer

Distribution of non-small cell lung cancer histological subtypes

The distribution of NSCLC histological subtypes among the 205 cases is presented in Table II. Squamous cell carcinoma and adenocarcinoma were the most frequent subtypes, while other histological variants were less prevalent.

Programmed death-ligand 1 expression across non-small cell lung cancer subtypes

Programmed death-ligand 1 expression was evaluated using three immunohistochemical assays: VENTANA SP142, DAKO 22C3, and VENTANA 22C3. Programmed death-ligand 1 positivity varied according to both histological subtype and antibody clone.

Using the DAKO 22C3 assay, PD-L1 positivity was lower in squamous cell carcinoma (6/107) compared to adenocarcinoma (22/72). Conversely, the VENTANA SP142 and VENTANA 22C3 assays demonstrated more comparable positivity rates across histological subtypes (Table III). Statistically significant differences in PD-L1 expression between subtypes were observed with DAKO 22C3 (p = 0.001) and VENTANA 22C3 (p = 0.019), whereas no significant difference was detected with VENTANA SP142 (p = 0.468).

Inter-assay concordance of programmed death-ligand 1 expression

General concordance

Inter-assay concordance was evaluated across predefined PD-L1 expression categories (< 1%, 1–49%,

Table III. Programmed death-ligand 1 positivity results of three different immunohistochemistry tests according to non-small cell lung cancer subtypes

Antibody clone	NSCLC			Total positive cases, n = 205 (%)	p-value
	Squamous cell carcinoma, n = 107	Adenocarcinoma, n = 72	Other, n = 26		
VENTANA SP142	12	15	5	32 (15.6)	0.468
DAKO 22C3	6	22	7	35 (17.1)	0.001
VENTANA 22C3	4	14	3	21 (10.2)	0.019

NSCLC – non-small cell lung cancer

Table IV. Intraclass correlation coefficients analysis of programmed death-ligand 1 immunohistochemistry tests at different expression levels

Comparison	Expression (%)	ICC (95% CI)	n
VENTANA SP142 vs. DAKO 22C3	< 1	100	158
VENTANA SP142 vs. VENTANA 22C3	< 1	100	165
DAKO 22C3 vs. VENTANA 22C3	< 1	100	173
VENTANA SP142 vs. DAKO 22C3	> 50	70.4	6
DAKO 22C3 vs. VENTANA 22C3	> 50	86.7	4

ICC – intraclass correlation coefficients

and ≥ 50%). Near-perfect concordance was consistently observed in the < 1% PD-L1 expression category across all assay pairs (Table IV). In contrast, concordance decreased in the ≥ 50% expression category.

Inter-assay reliability (intraclass correlation coefficients analysis)

Inter-assay reliability was assessed using ICC (Figure 1). Reliability interpretation thresholds were defined as follows: < 0.50 (poor), 0.50–0.75 (moderate), 0.75–0.90 (good), and > 0.90 (excellent).

Most comparisons demonstrated good to excellent reliability (ICC > 0.75). The highest reliability was observed between DAKO 22C3 and VENTANA 22C3 in the < 1% expression category (ICC = 0.91). Additionally, VENTANA SP142 (< 1%) showed good to excellent agreement with all DAKO 22C3 categories. In the ≥ 50% expression category, only the comparison between VENTANA SP142 and DAKO 22C3 showed moderate reliability (ICC = 0.704).

Correlation between programmed death-ligand 1 assays

A positive correlation was identified between VENTANA and DAKO measurements (Figure 2). VENTANA 22C3 levels frequently rose in tandem with PD-L1 expression determined by SP142, indicating a strong correlation (Figure 3). Nevertheless, discrepancies persisted. Although PD-L1 measurements from DAKO and VENTANA using the same 22C3 clone were significantly concordant (Figure 4), occasional inconsistencies were observed. For instance, in one case (Case 22689), SP142 showed low expression (20%), while DAKO 22C3 (90%) and VENTANA 22C3 (1%) yielded markedly different results, highlighting significant inter-assay variability (Figure 5).

Discussion

The majority of patients are diagnosed with NSCLC at an advanced stage, and despite therapeutic advancements, the prognosis remains poor. Globally, NSCLC continues to be a leading cause of cancer-related mortality [12]. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have become a widely utilized treatment option for NSCLC, demonstrating durable responses in a subset of patients. Consequently, accurate measurement of PD-L1 expression *via* IHC serves as a vital biomarker for treatment stratification. Clinical decision-making is heavily influenced by significant variations in antibody clones, platforms, staining procedures, and scoring criteria among PD-L1 assays [3, 13, 14].

Despite recent progress in targeted therapies, long-term survival remains inadequate, particularly for patients lacking actionable mutations. Extensive research has been dedicated to developing novel therapeutic approaches for this population. Immunotherapy, bolstered by an evolving understanding of the tumor-immune system interface, has emerged as an effective treatment for various malignancies [2, 10, 11]. Studies elucidating how tumor cells exploit the PD-1/PD-L1 axis to suppress anti-tumor immunity have paved the way for monoclonal antibody development [15, 16]. However, identifying

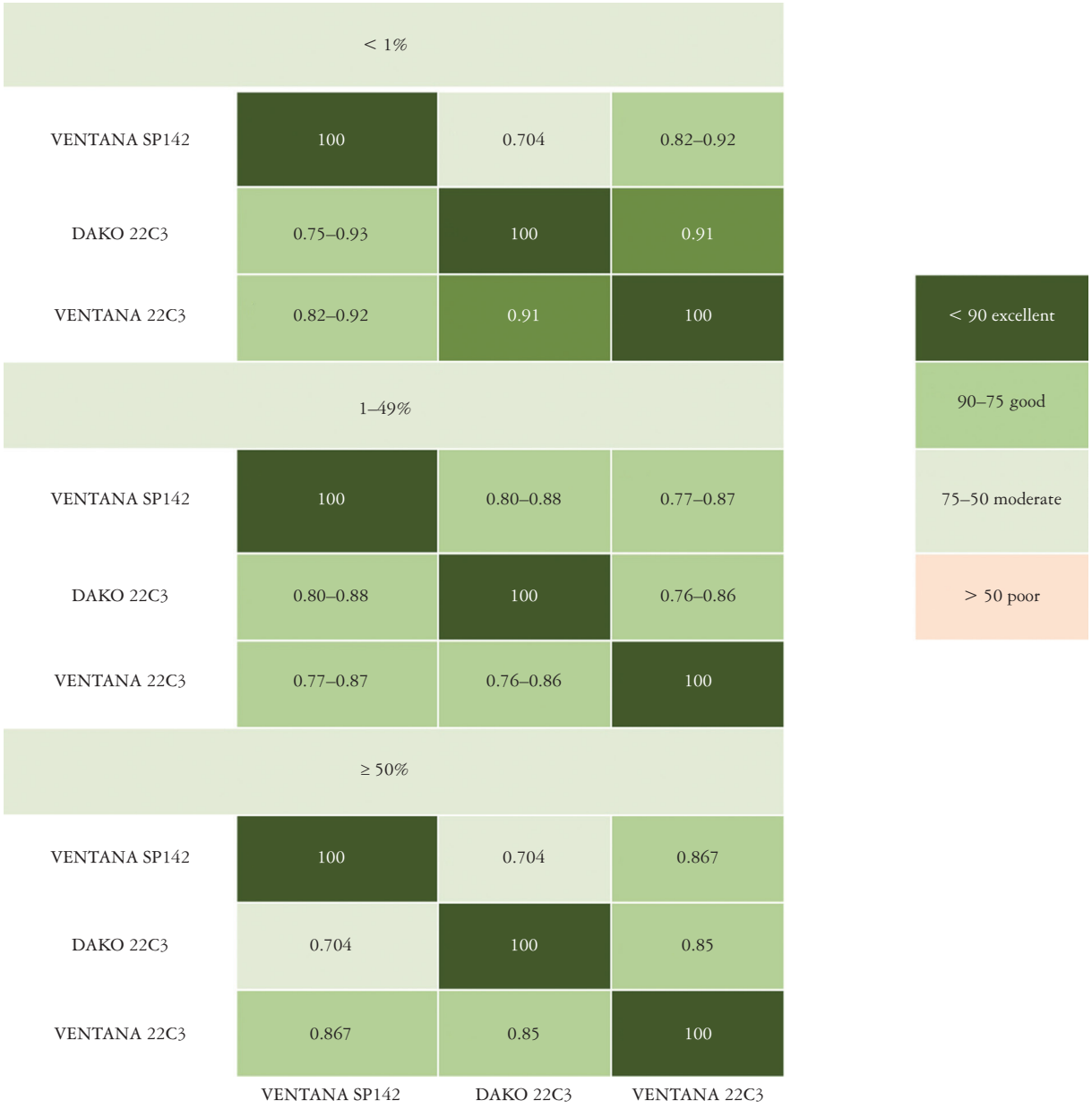

Figure 1. Intraclass correlation coefficients and concordance of programmed death-ligand 1 immunohistochemistry assays across different expression thresholds (< 1%, 1–49%, and ≥ 50%)

which patients will derive the most benefit from these therapies remains a significant clinical challenge.

In this study, we evaluated the analytical concordance between three commonly used PD-L1 assays: VENTANA SP142, VENTANA 22C3, and DAKO 22C3. Overall, the study demonstrates good concordance and inter-assay reliability across multiple PD-L1 testing platforms. Subgroups with low PD-L1 expression (< 1%) exhibited excellent agreement, suggesting potential interchangeability in clinical practice [9, 13]. While high analytical concordance suggests potential technical interchangeability at low tumor proportion score thresholds, clinical interchangeability should not be assumed, particularly for assays linked to distinct therapeutic indications.

However, concordance decreased at the ≥ 50% cutoff, particularly between SP142 and DAKO 22C3 (ICC = 0.70). This decline may be partly attributed to the limited sample sizes within high-expression subgroups. Furthermore, despite positive correlations, none of the assays achieved perfect alignment, indicating inherent potential for variability across different testing methods.

SP142 demonstrated a more restricted dynamic range for tumor-cell PD-L1 staining, which may limit its concordance with other assays at higher tumor proportion score thresholds. Previous studies have shown that the SP142 assay is consistently less sensitive in determining tumor cell PD-L1 expression [2]. Our findings indicate that SP142 showed lower concordance in

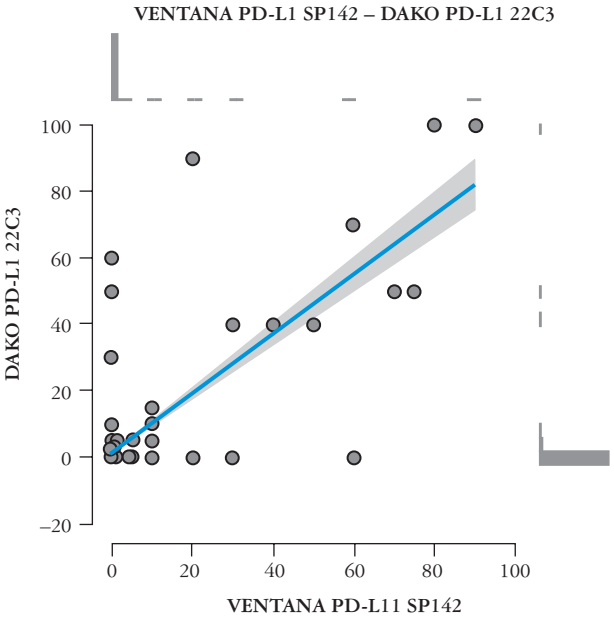

Figure 2. Correlation between VENTANA PD-L1 SP142 – DAKO PD-L1 22C3 markers positive association expressed by {R^2} value and especially concentration in low expression (< ~ 20%) area

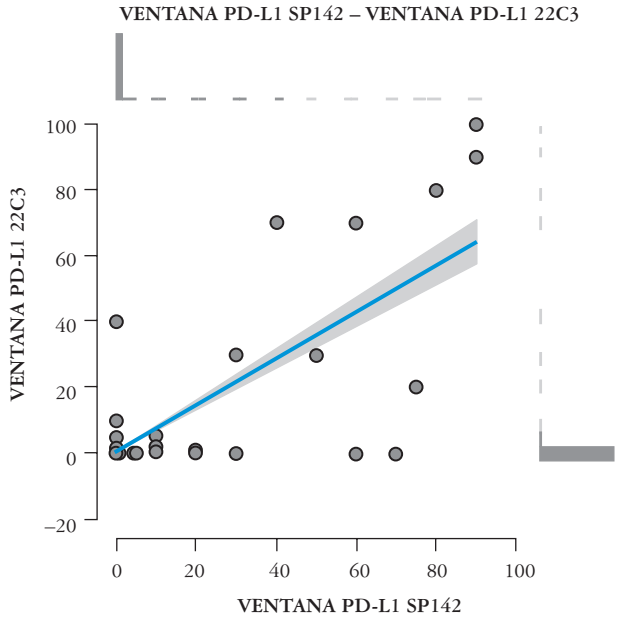

Figure 3. Correlation between VENTANA PD-L1 SP142 and VENTANA PD-L1 22C3 markers distribution showing strong positive concordance of different clones from the same manufacturer, but inconsistent points at high expressions

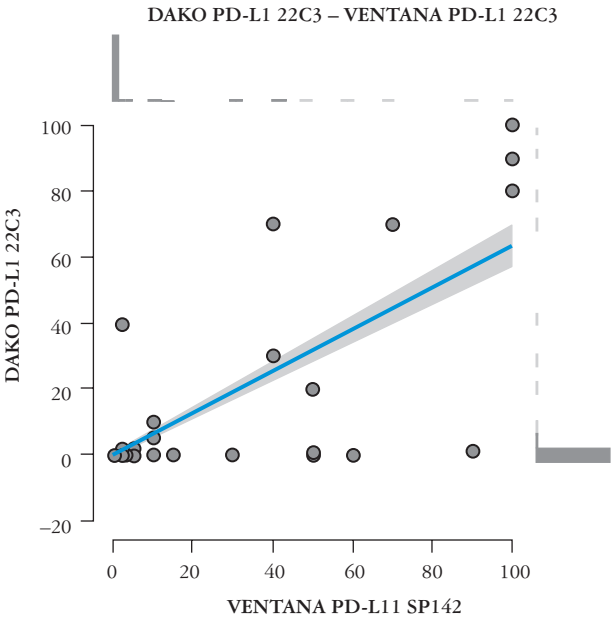

Figure 4. Correlation between DAKO PD-L1 22C3 – VENTANA PD-L1 22C3 markers excellent concordance of the same antibody clone on different platforms, with slight deviations seen in recognitions

the ≥ 50% expression subgroup, especially when compared to DAKO 22C3. In contrast, the VENTANA and DAKO 22C3 assays maintained strong concordance at high TPS cutoffs (ICC > 0.85). Technical and biological factors, such as the SP142 antibody's primary targeting of cytoplasmic domains and its tendency to show less membrane staining, likely account for this discrepancy. These results underscore the need for caution when evaluating inter-assay concordance with SP142 at high expression levels [3, 9, 13]. Due to discordant cases, accurate ICC calculations became difficult or impossible in certain categories.

Variations in PD-L1 assessment directly impact therapeutic outcomes. Pembrolizumab efficacy is strongly correlated with the 50% TPS threshold in the 22C3 assay [4, 5]. Despite positive correlations, the lack of perfect concordance among PD-L1 assays supports the urgent need for standardization in routine clinical practice.

Consequently, due to differences in assay performance and assay-specific cutoffs, potential variability must be considered when interpreting results in high-expression categories. Since PD-L1 positivity thresholds directly determine therapeutic indications, discrepancies between assays can lead to significant clinical consequences. Therefore, assay selection must be a key consideration in clinical decisions, and cases analyzed across various platforms should be evaluated with care [9, 12, 13, 17, 18].

The SP142 antibody demonstrated limited utility in differentiating between NSCLC histological subtypes, suggesting low sensitivity for tumor cell staining. The 22C3 antibodies, particularly the DAKO clone, showed more distinct variability between squamous cell carcinoma and adenocarcinoma, with PD-L1 positivity being more prevalent in adenocarcinoma cases [19]. Although digital image analysis was not employed, our analysis indicated that immune cell scoring remains challenging and less reliable than tumor cell scoring [9]. Although the cohort predates routine clinical implementation of immune checkpoint inhibitors, the biological determinants of PD-L1

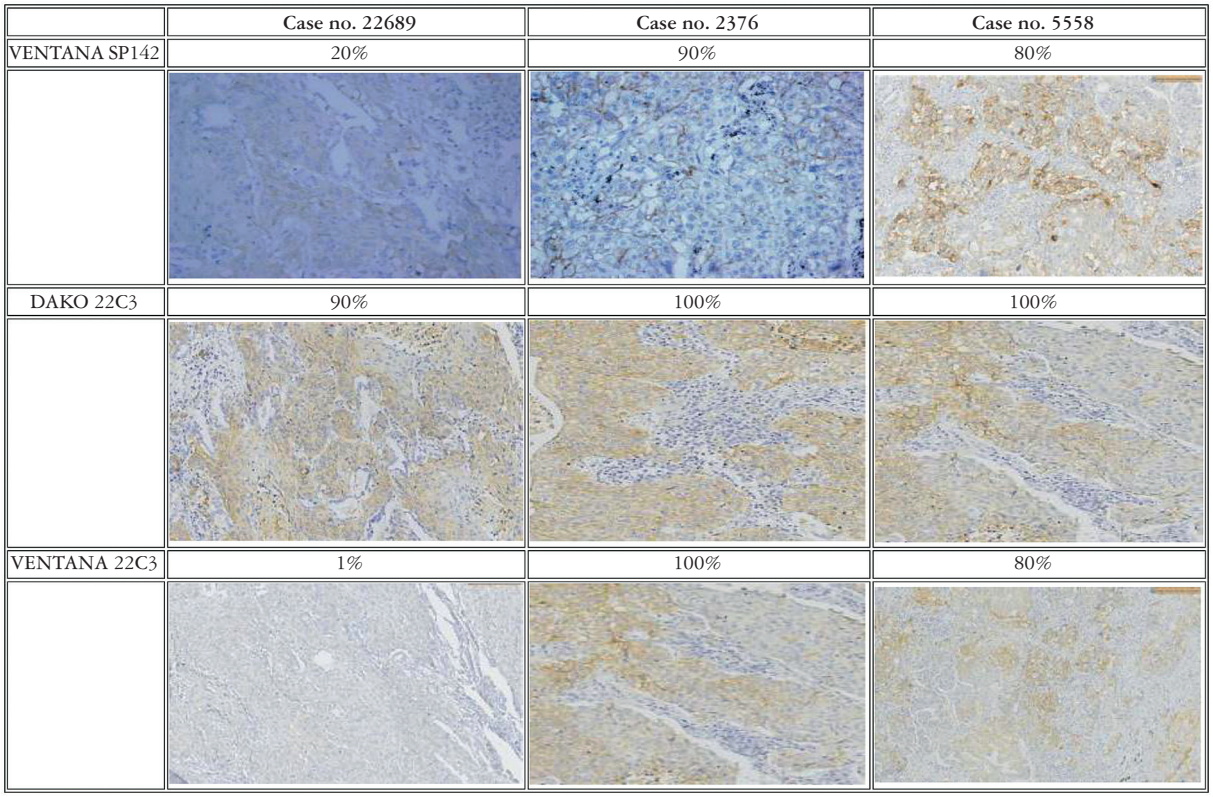

Figure 5. Comparison of programmed death-ligand 1 immunohistochemistry test results in three representative non-small cell lung cancer cases

The images illustrate staining patterns and inter-assay concordance using three different antibody clones (VENTANA SP142, DAKO 22C3, and VENTANA 22C3). Case 22689 demonstrates extreme variability, where DAKO 22C3 shows 90% positivity compared to markedly lower results in others. Case 2376 shows high concordance with strong positivity (90–100%) across all platforms, while Case 5558 exhibits moderate concordance (80–100%). Case 22689, in particular, provides a striking example of significant inter-assay discrepancy.

expression and assay-specific performance remain directly applicable to contemporary diagnostic practice.

Conclusions

Our study confirms a strong analytical concordance between the VENTANA 22C3 and DAKO 22C3 assays while highlighting the specific limitations of SP142 in high-expression scenarios. These findings are critical for ensuring accurate biomarker-based patient selection and optimizing therapeutic outcomes in NSCLC. From a practical pathology perspective, these findings underscore the importance of assay-specific interpretation when PD-L1 expression is used to guide immunotherapy selection.

Disclosures

1.Institutional review board statement: Written consent was acquired from the patients for use in our study following the completion of their biopsy blocks, diagnosis, and treatment procedures. The Çankırı Karatekin University Health Ethics Committee authorized the study protocol (10-04-2025 No. ce55d6ad80cd40d1).
2.Assistance with the article: None.
3.Financial support and sponsorship: None.
4.Conflicts of interest: None.

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